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Quantum chemical calculation of ^{19}F NMR chemical shifts of trifluoromethyl diazirine photoproducts and precursors

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ABSTRACT

Irradiation of aryl(trifluoromethyl)diazirines may result in a multitude of products, which are difficult to assign in the ^{19}F NMR spectrum. In this article, it is demonstrated that an average accuracy of 2.9 ppm (standard deviation) can be achieved by quantum chemical calculations at the B3LYP 6-311G++(2d,2p) level of theory, followed by a Boltzmann weighting of the optimized conformers. A set of 30 compounds was investigated both experimentally and theoretically. ^{19}F NMR chemical shifts of precursor *Z*-oximes and *Z*-tosyloximes ranged from δ_F −62.9 to −61.8 ppm, whereas their *E* counterparts showed shifts between δ_F −67.2 and −66.2 ppm. Stereochemical assignments were confirmed by two X-ray analyses. Quantum chemical calculation also allowed the assignment of the configuration of an (*E*,*E*) azine. Trifluoromethyl diazirines exhibited a δ_F between −66.1 and −65.6, diaziridines between −76.2 and −75.9 ppm. The smallest δ_F values were observed for α-oxygenated trifluoromethyl compounds (δ_F −78.9 to −77.4 ppm). The average deviation of the calculated from the experimental values corresponds to only about 1% of the standard ^{19}F NMR chemical shift range.

1. Introduction

^{19}F NMR spectra of organofluorine compounds cover a chemical shift range of more than 300 ppm [1]. In principle, that large dispersion should allow distinction of very similar fluorinated compounds. There is considerable interest in predicting ^{19}F NMR shifts [2], because fluorine is very important for the development of pharmaceuticals [3]. Recent work has analyzed the ^{19}F NMR chemical shifts of trifluoroacetylated molecules [4]. When studying the chemistry of photoaffinity labeling [5] employing trifluoromethylated diazirines, we became aware of the possible complexity of mixtures of trifluoromethylated products. Fig. 1 shows a typical ^{19}F NMR spectrum obtained in our laboratory by irradiation of (*p*-methoxyphenyl)(trifluoromethyl)diazirine (**1**) in the presence of phenol. Only after preparative isolation of the compounds could the major signals at −66.21, −66.83, −77.37, and −78.93 ppm be assigned to compounds **17**, **18**, **30** (Fig. 2), and **32** (Fig. 4), respectively [6]. We were not able to identify the compound causing the signal at −73.91 ppm. It would be of advantage to be able to rapidly estimate on the components of such a crude reaction mixture without the need to isolate each of them.

There are several reports on quantum mechanical calculations of ^{19}F NMR chemical shifts. Maximal accuracy of about 2 ppm was achieved when electron correlation and perturbative corrections were taken into account in high-level CCSD(T) calculations with large basis sets [7]. Here, calculation times are proportional to N^6 to N^7 (where N is the number of basis functions), which, at least currently, limits broad applicability of such approaches for larger systems [8]. Other quantum chemical approaches are faster, because they scale only as N^3 to N^4. There are also semiempirical MNDO approaches for larger systems employing NMR-specific parameters [9].

Our synthetic work has provided us with several CF_3-containing compounds, together with their experimental ^{19}F NMR chemical shifts [10]. We felt it would be interesting to analyze which combination of functional and basis set would give the best quantum chemical prediction of NMR chemical shifts of CF_3 groups, which cover the rather small area between −60 and −90 ppm, corresponding to about 10% of the total chemical shift range in ^{19}F NMR spectroscopy.

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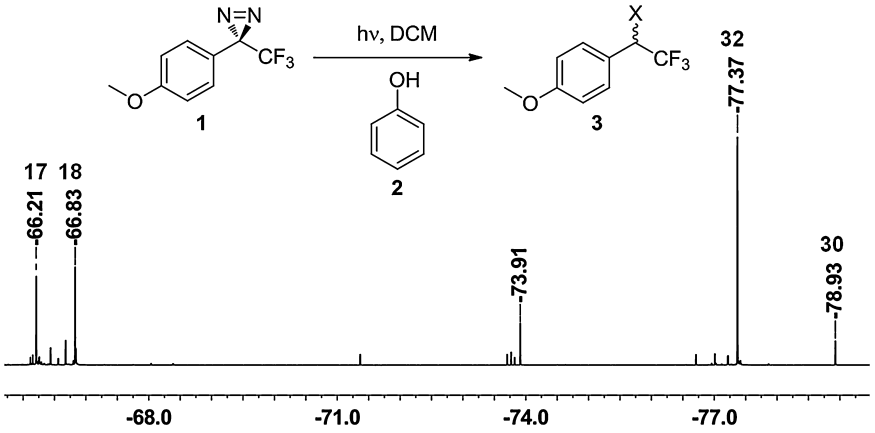


Fig. 1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$, referenced to $CFCl_3$, δ_F = 0.0 ppm) after irradiation (350 nm) of diazirine **1** in the presence of phenol (**2**).

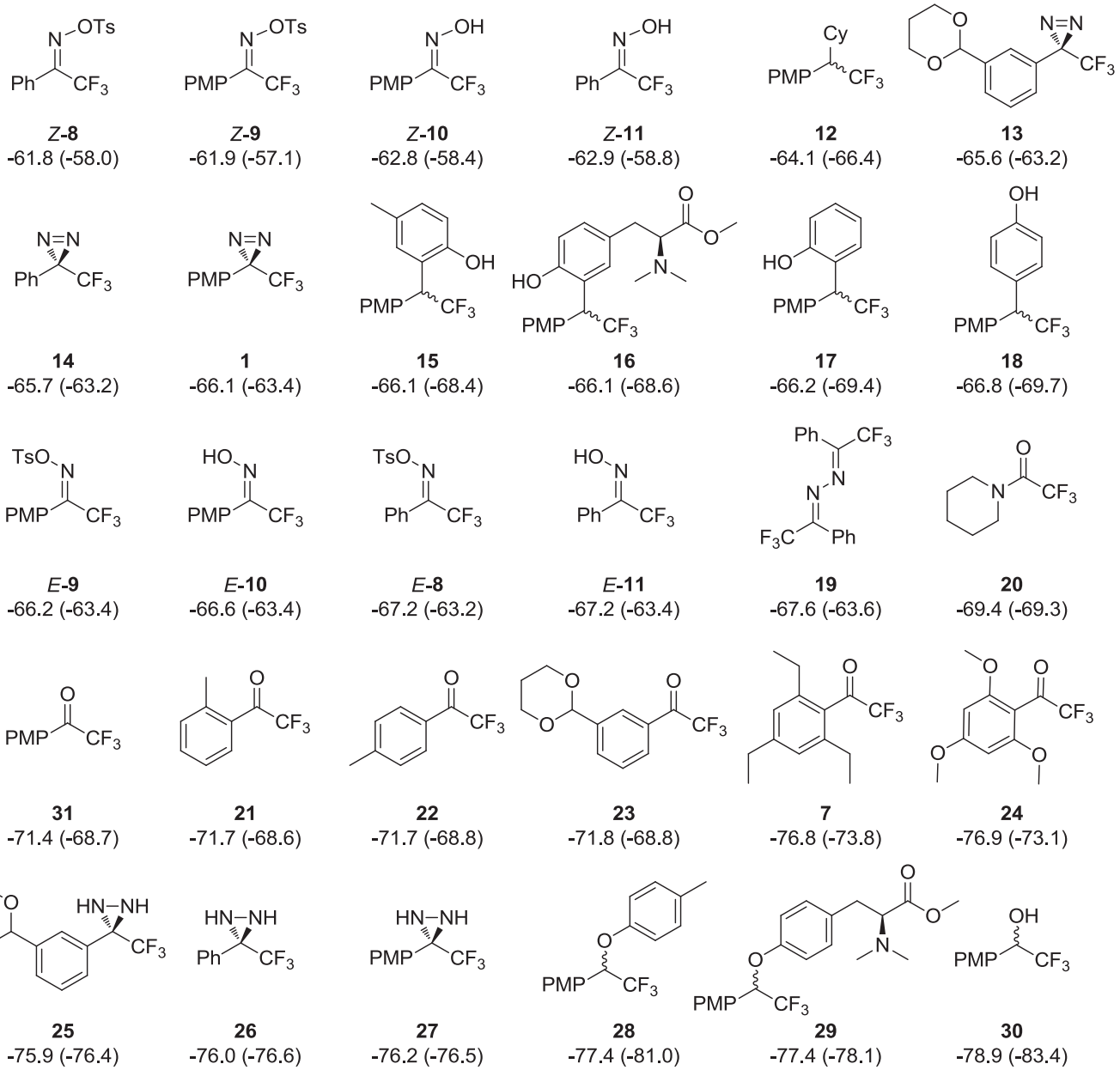


Fig. 2. Investigated molecules, grouped by decreasing experimental ^{19}F NMR chemical shifts ($CDCl_3$, referenced to $CFCl_3$, δ_{ref} 0 ppm, PMP = *p*-methoxyphenyl). Values in brackets were calculated by GIAO NMR calculations on the B3LYP PCM ($CHCl_3$) 6-311G++(2d,2p) level of theory and are referenced to hexafluorobenzene (δ_{ref} −164.9 ppm).

2. Results and discussion

2.1. Experimental ^{19}F NMR data

Fig. 2 shows the 30 molecules that we analyzed, all of which share a 2,2,2-trifluoroethylbenzene core unit. References are given in the footnotes of Table 1. The only hitherto undescribed compounds in the list are ketones **6** and **7**. Ketone **6** was synthesized from 4-bromo-3,5-dimethylanisole (**4**) by bromine/lithium exchange (*n*BuLi) and quenching with CF_3CO_2Et (79%, Scheme 1). Use of *N*-trifluoroacetylpiperidine as electrophile led to replacement of the CF_3 group of product **6** by piperidide via haloform reaction (27%) [11,12]. Sterically hindered ketone **7** was obtained in rather low yield (36%) from 2-bromo-1,3,5-triethylbenzene (**5**) after treatment with *t*BuLi and quenching with *N*-trifluoroacetylpiperidine.

^{19}F NMR spectra were taken in $CDCl_3$, referenced to $CFCl_3$ (δ_F = 0.0 ppm). A rather narrow range of chemical shifts between δ_F −78.9 and −61.8 ppm was observed, with the shift interval between δ_F −65.5 and −67.5 ppm being particularly crowded. Still, shifts can in part be sorted according to functional groups. ^{19}F NMR chemical shifts of *Z*-oximes (*Z*-**11**, *Z*-**10**) and *Z*-tosyloximes (*Z*-**8**, *Z*-**9**) range from δ_F −62.9 to −61.8 ppm, whereas their *E* counterparts (*E*-**11**, *E*-**8**, *E*-**9**, *E*-**10**) show shifts between δ_F −67.2 and −66.2 ppm. Diazirines (**1**, **13**, **14**) show a δ_F between −66.1 and −65.6, diaziridines (**25**, **26**, **27**) between −76.2 and −75.9 ppm. ^{19}F NMR chemical shifts of disubstituted trifluoroacetyl benzenes **21**, **22**, **23** and **31** (δ_F −71.8 to −71.4) differ from those of tetrasubstituted **6** and **24** (δ_F −76.9 to −76.8). The smallest δ_F values were observed for α-oxysubstituted compounds **28**, **29**, and **30** (δ_F −78.9 to −77.4 ppm). Aryl adducts **15**, **16**, **17**, and **18** showed δ_F values between −66.8 and −66.1 ppm. Fig. 3 gives a helpful overview over the ^{19}F NMR chemical shifts to be expected for the groups of the CF_3- containing compounds discussed herein.

An interesting case is represented by azine **19**, for which only one signal was observed in the ^{19}F NMR spectrum (δ_F −67.6). This could be caused by an overwhelming predominance of one of the symmetrical diastereomers (*E*,*E* or *Z*,*Z*) or by accidental isochrony in case of the non-symmetrical diastereomer (*E*,*Z*) or mixtures. The stereochemical assignment was unclear and, thus, azine **19** represented a suitable test case for ^{19}F NMR chemical shift calculation.

2.2. Quantum chemical calculations

At the beginning, a suitable combination of functional and basis set had to be chosen. Therefore, the geometry of a set of five arbitrarily chosen molecules (**6**, *E*-**11**, *Z*-**11**, **32**, **33**, Fig. 4) was optimized on the B97D 6-31G(d) level of theory and the obtained structures were submitted to GIAO NMR calculations [13] employing the B3LYP [14] and the B97D [15] functionals. The B97D functional includes dispersion contributions, which are important for the description of sterically demanding compounds.

Both functionals were used with and without modeling the effects of chloroform employing the PCM model [16]. As LCAO basis we used three different basis sets of increasing flexibility (6-31G(d), 6-311G++(2d,2p) and 6-311G+(3df,3dp)) as implemented in Gaussian09 [17]. The ^{19}F NMR chemical shift of a given compound was calculated from the isotropic shielding σ as $\delta = \sigma_{ref} - \sigma + \delta_{ref}$, using C_6F_6 as reference (calculated σ_{ref} = 333.6 ppm, tabulated δ_{ref} −164.9 ppm). Fig. 5 gives the average deviations of GIAO NMR calculation results obtained for molecules *E*-**11**, *Z*-**11**, **32**, **33**, and **6** employing twelve combinations of four functionals and three basis sets (chloroform, PCM). The combination of the B3LYP (PCM) functional and the

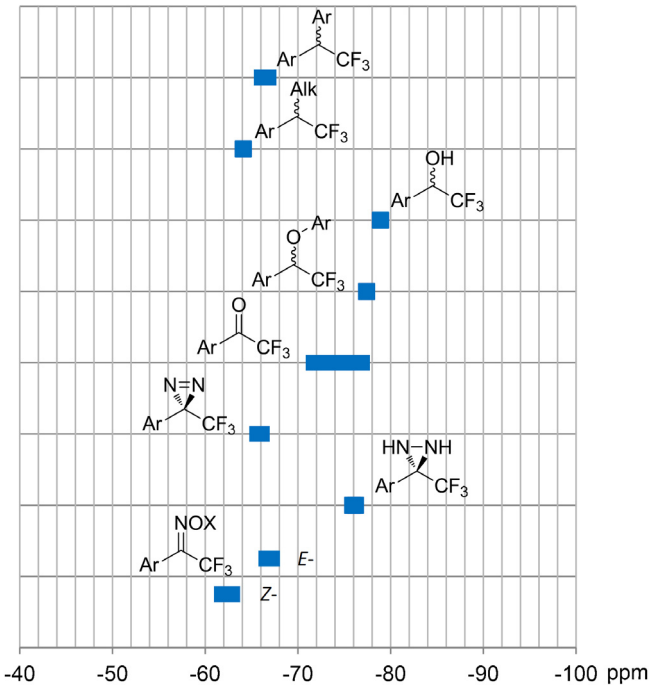
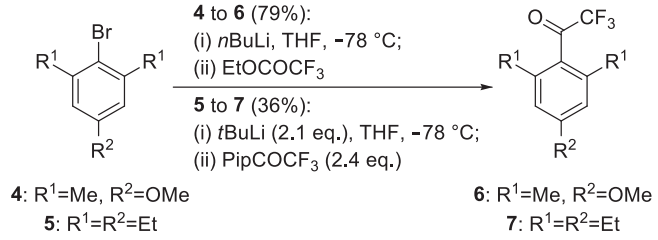


Fig. 3. Experimental ^{19}F NMR chemical shift ranges observed for the investigated structural types.

Table 1
Calculated and experimental ^{19}F NMR chemical shifts ($CDCl_3$) of the 30 compounds shown in Figure 2.

Compound	δ_{calc}	δ_{exp}	$\delta_{calc} - \delta_{exp}$	Compound	δ_{calc}	δ_{exp}	$\delta_{calc} - \delta_{exp}$
E-**11** [21]	−63.4	−67.1	3.7	**22** [22]	−68.8	−71.7	2.9
Z-**11** [21]	−58.8	−62.9	4.1	**24** [23]	−73.1	−76.9	3.8
E-**10** [6]	−63.4	−66.6	3.2	**7**	−73.8	−76.8	3.0
Z-**10** [6]	−58.4	−62.8	4.4	**23** [10]	−68.8	−71.8	3.0
E-**8** [21]	−63.2	−67.2	4.0	**17** [6]	−69.4	−66.2	−3.2
Z-**8** [21]	−58.0	−61.8	3.8	**18** [6]	−69.7	−66.8	−2.9
E-**9** [6]	−63.4	−66.2	2.8	**28** [6]	−81.0	−77.4	−3.6
Z-**9** [6]	−57.1	−61.9	4.8	**15** [6]	−68.4	−66.1	−2.3
13 [10]	−63.2	−65.6	2.4	**30** [6]	−83.4	−78.9	−4.5
26 [21]	−76.6	−76.0	−0.6	**12** [6]	−66.4	−64.1	−2.3
27 [6]	−76.5	−76.2	0.3	**20** [6]	−69.3	−69.4	0.1
14 [21]	−63.2	−65.7	2.5	**29** [6]	−78.1	−77.4	−0.7
1 [6]	−63.4	−66.1	2.7	**16** [6]	−68.6	−66.1	−2.5
25 [10]	−76.4	−75.9	−0.5	**19** [25]	−63.6	−67.6	4.0
21 [24]	−68.6	−71.7	−3.1	**31** [6]	−68.7	−71.4	2.7



Scheme 1. Synthesis of ketones **6** and **7**.

6-311G++(2d,2p) basis set proved to be the most accurate, with an average absolute error of 1.9 ppm. We observed an advantage of the B3LYP over the B97D functional.

For the larger set of 30 compounds (structures shown in Fig. 2), conformers with the lowest energy were determined employing the MMFF force field [18]. Each conformer was optimized at the B97D 6-31G(d) level of theory, followed by GIAO NMR calculations at the B3LYP PCM ($CHCl_3$) 6-311G++(2d,2p) level of theory. The conformer distribution was calculated using standard Monte Carlo methods, as implemented in Spartan 08, leading to global minimum geometries for the subsequent quantum chemical optimizations [19]. The calculated ^{19}F NMR chemical shifts of the energetically different, optimized conformers were Boltzmann-weighted (298 K).

Deviations of the calculated values ($\delta_{calc} - \delta_{exp}$, B3LYP (PCM) 6-311G++(2d,2p)) vary between −4.5 and +4.8 ppm (Table 1). Calculated and experimental values are plotted against each other in Fig. 6. The standard deviation was 2.9 ppm and did not increase greatly when considering only the energetically most favored conformer of each compound (3.2 ppm). Small absolute deviations of less than 1 ppm were observed for the diaziridines **25**–**27**, and for *N*-trifluoroacetylpiperidine (**20**). For the regioisomeric photoadducts **16** and **29** of L-*N*,*N*-dimethyl tyrosine methyl ester we obtained $\Delta\delta_F$ values of 0.7 (**29**) and 2.5 ppm (**16**).

Higher absolute deviations between 4.0 and 4.8 ppm were obtained for oxime derivatives *Z*-**11**, *Z*-**10**, *Z*-**9**, *E*-**8**, and for benzylic alcohol **30**. Fortunately, we were able to obtain X-ray analyses of oxime *E*-**11** and the *O*-tosylated analog *E*-**8** (Fig. 7) [20]. Thus, unambiguous assignment of the experimental ^{19}F NMR chemical shifts of both pairs of oximes became possible.

For all oxime diastereomers, the chemical shift deviation between calculation and experiment ($\Delta\delta_F = \delta_{calc} - \delta_{exp}$) was positive (+2.8 to +4.1 ppm), which cannot currently be explained. Choosing a more advanced basis set appears to help. After re-optimization of *E*-**9** employing a higher basis set [6-311G (2d,2p)] than used previously for geometry optimization [6-31G*] we observed a decrease of the shift deviation from 2.8 to 0.9 ppm. However, the ^{19}F NMR chemical shift difference of *Z*- and *E*-oximes is already predicted accurately (5 ppm) by the employed standard calculation procedure.

What remained to be assigned was the configuration of azine **19**. Quantum chemical calculation predicts ^{19}F NMR chemical shifts of the three possible diastereomers of −63.6 ppm (*E*,*E*), −64.3/ − 59.8 (*E*,*Z*), and −57.7 ppm (*Z*,*Z*) if calculated as described by modeling $CHCl_3$ (PCM). Thus, accidental isochrony of the ^{19}F NMR chemical shifts of the two diastereotopic CF_3 groups of an (*E*,*Z*) isomer can be excluded. In the experiment, we observed only one signal at δ_F −67.6 ppm, which clearly indicates the presence of the (*E*,*E*) diastereomer, which is also the thermodynamically most stable. The difference of calculated and experimental ^{19}F NMR chemical shifts ($\Delta\delta_F$ = 4.0 ppm) is of the same sign and magnitude as in the case of the structurally related oxime derivatives (Fig. 7)

3. Conclusion

In summary, we could show that GIAO NMR calculations, combined with geometry optimization with the B97D functional and a 6-31G* basis set followed by Boltzmann weighting of the NMR shifts, constitute an interesting and useful tool to support

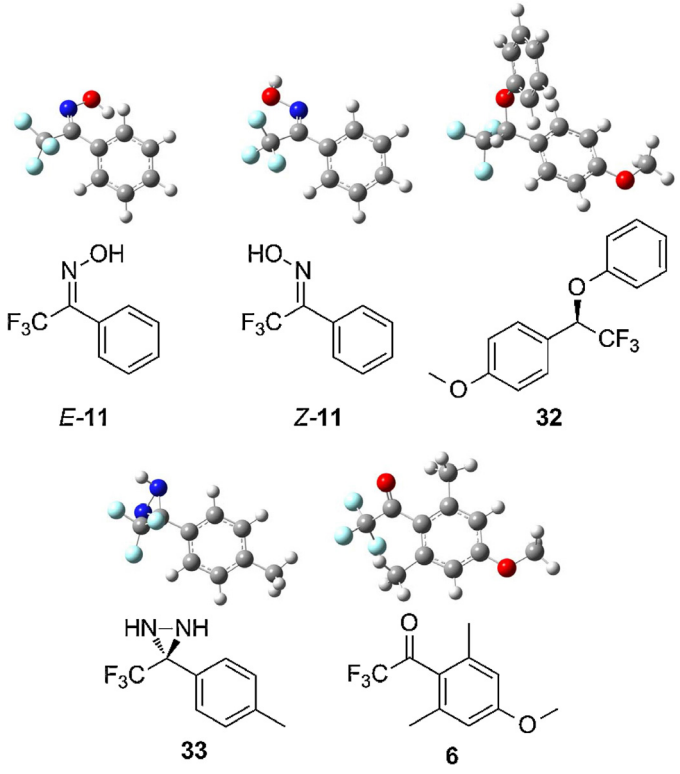


Fig. 4. Optimized geometries of compounds *E*-**11**, *Z*-**11**, **32**, **33**, and **6** on the B97D 6-31G(d) level of theory.

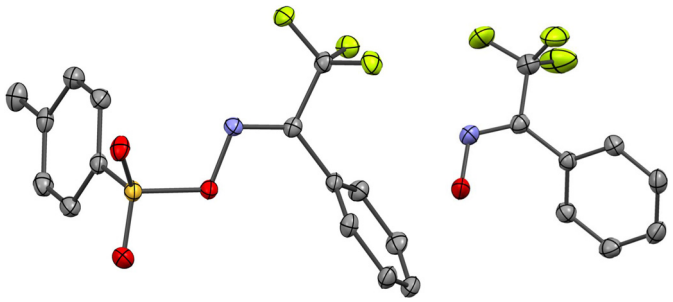


Fig. 5. Average absolute deviations of GIAO NMR calculation results obtained for molecules *E*-**11**, *Z*-**11**, **32**, **33**, and **6** employing the 12 combinations of 4 functionals and 3 basis sets (chloroform, PCM). Average $\Delta\delta_F$ was calculated via the sum of $\Delta\delta_F$ of the chosen molecules for each combination divided by the number of molecules.

users by providing structural information about CF_3-containing molecules. We were able to identify a suitable combination of basis set and density functional for the calculation of CF_3 ^{19}F NMR chemical shifts [B3LYP/6-311G++(2d,2p), PCM = $CHCl_3$]. The calculations took between 2 h and 2 days on a DELL Power Edge T110 PC with 8x Intel(R)Xeon(R) CPU X3470@2.93 GHz and 8192 MB memory, and can be conducted on an everyday basis in a standard laboratory. We were pleased by the accuracy of prediction. Frequent problems such as the assignment of *E*/*Z* configuration to trifluoromethylated oximes can be solved. Our results should encourage researchers dealing with mixtures of CF_3- containing compounds to use quantum mechanical calculation for analysis. This will be interesting for analyzing photoaffinity labeling with aryl(trifluoromethyl)diazirines with chemical accuracy.

Quantum chemical calculations of ^1H NMR chemical shifts [26] provided an average deviation of 0.12 ppm (GIAO/B3LYP/aug-cc-pVDZ) [27], corresponding to an error of about 1%. The ^{19}F NMR chemical shift calculations presented in this article delivered an average absolute deviation of only 2.9 ppm, also corresponding to about 1% of the standard chemical shift range of ^{19}F NMR spectroscopy of 300 ppm.

4. Experimental

4.1. General methods

NMR spectra were taken with a Bruker DPX-200 (200.1 MHz for ^1H, 188.3 MHz for ^{19}F), Bruker AV II-300 (300.1 MHz for ^1H, 75.5 MHz for ^{13}C), Bruker DRX-400 (400.1 MHz for ^1H, 100.6 MHz for ^{13}C, 376.3 MHz for ^{19}F) and a Bruker AV III-400 (400.1 MHz for ^1H, 100.6 MHz for ^{13}C), ^1H and ^{13}C NMR signals were referenced to the solvent signal or TMS. Experimental ^{19}F NMR signals were referenced to $CFCl_3$ (δ_{ref} −0 ppm, virtual internal referencing). Calculated ^{19}F NMR shifts were referenced to C_6F_6 (σ_{ref} = 333.6 ppm, δ_{ref} −164.9 ppm). All measurements were performed at 300 K. Mass spectra were obtained with a Thermo-Finnigan MAT (MAT95XL) spectrometer and a ThermoFisher Scientific (LTQ-Orbitrap Velos) spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer. UV/Vis spectra were measured with a Varian Cary 100 Bio UV/Vis-spectrometer. Melting points were measured with a Büchi 530 melting point apparatus. Chemicals were purchased from commercial suppliers and used without further purification. Silica gel 60 (40–63 μm, Merck) was used for column chromatography. Petroleum ether had a boiling range from 40 to 60 °C.

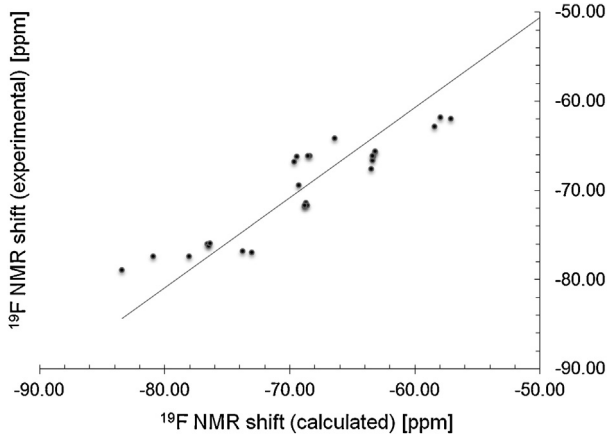


Fig. 6. Experimental ^{19}F NMR chemical shifts of 30 trifluoromethyl compounds (structures see Fig. 2) plotted against the calculated values (standard deviation 2.9 ppm).

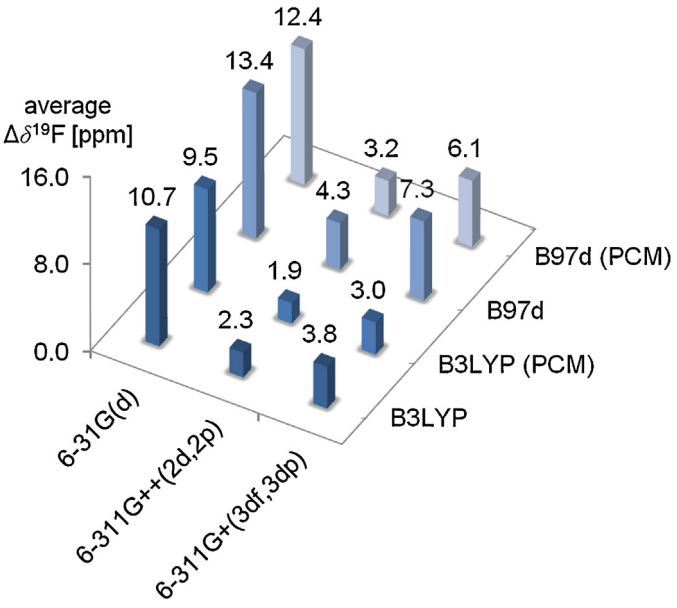


Fig. 7. X-ray analyses of *E*-**8** (left) and *E*-**11** (right). Hydrogen atoms have been omitted for clarity.

4.1.1. (E)-2,2,2-trifluoro-1-phenylethanonoxime (E-***11***)

The synthesis of 11 was described earlier [21]. We observed the isomerization of the originally *E*/*Z* mixture to pure *E* in the solid state within 3 years at rt. X-ray analysis confirmed the configuration of the oxime double bond. TLC: R_f = 0.6 [PE/EtOAc (5/1)]; m.p. 88 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, br), 1H, O-*H*), 7.55–7.52 (m, 2H, *oCH*), 7.49–7.46 (m, 3H, *mCH*, *pCH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1 (q, $^2J_{CF}$ = 32.4 Hz, *C*N), 130.8 (1C, *pC*H), 128.7 (2C, *mC*H), 128.6 (2C, *oC*H), 125.9 (1C, ipso*C*), 120.7 (q, $^1J_{CF}$ = 274.8 Hz, 1C, *C*F_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −67.1. IR (ATR): $\tilde{\nu}$ = 3265 cm^{-1} (m, br), 3072 (w), 2911 (w), 1722 (w), 1460 (m), 1439 (m), 1335 (m), 1280 (w), 1205 (s), 1183 (s), 1130 (s), 1039 (m), 1013 (s), 959 (s), 925 (m), 772 (m), 745 (m), 707 (s), 691 (s), 611 (m). UV–vis ($CHCl_3$): λ_{max} (log ε) = 240 (3.82) nm. MS (EI, 70 eV): *m*/*z* (%) = 189.0 (71), 173.0 (17), 104.0 (77), 103.0 (73), 77.0 (100).

4.1.2. (E)-2,2,2-trifluoro-1-phenylethanon-O-tosyloxime (E-***8***)

The synthesis of **8** was described earlier [21]. The *E* isomer was isolated via column chromatography (silica, PE/EA = 30/1). X-ray analysis confirmed the configuration of the double bond. TLC: R_f = 0.2 [PE/EA (30/1)]; m.p. 86–88 °C. ^1H NMR (400 MHz, $CDCl_3$):

δ = 7.90–7.87 (m, 2H, *o*C*H*$_{tosyl}$), 7.55–7.45 (m, 3H, *o*C*H*, *p*C*H*), 7.39–7.37 (m, 4H, *m*C*H*, *m*C*H*$_{tosyl}$), 2.48 (s, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (q, $^2J_{CF}$ = 33.4 Hz, 1C, *C*N), 146.2 (1C, *p*CH_{tosyl}), 131.7 (1C, *p*CH), 131.3 (1C, *ipso*CH_{tosyl}), 129.9 (2C, *m*CH_{tosyl}), 129.3 (2C, *o*CH_{tosyl}), 128.8 (2C, *o*CH), 128.4 (2C, *m*CH), 124.7 (1C, *ipso*CH), 119.6 (q, $^1J_{CF}$ = 277.6 Hz, 1C, *C*-1), 21.8 (1C, *C*H$_3$). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −67.2. IR (ATR): $\tilde{\nu}$ = 3061 cm^{-1} (w), 2924 (w), 2853 (w), 1596 (m), 1492 (w), 1450 (w), 1386 (s), 1344 (m), 1305 (w), 1215 (m), 1193 (s), 1141 (s), 1090 (m), 1036 (w), 1004 (m), 891 (s), 805 (s), 767 (s), 752 (s), 703 (s), 676 (s), 649 (s), 545 (s). UV–vis ($CHCl_3$): λ_{max} (log ε) = 242 (4.01) nm. MS (EI, 70 eV): *m*/*z* (%) = 343.1 (2), 249.1 (2), 173.0 (16), 155.0 (100), 104.0 (75), 91.0 (86), 77.0 (39).

4.1.3. 2,2,2-Trifluoro-1-(2,4,6-triethylphenyl)ethanone (**7**)

Under N_2 atmosphere at −78 °C, 2-bromo-1,3,5-triethylbenzene (**5**, 0.78 mL, 4.2 mmol, 1.0 equiv.) was dissolved in dry THF (11 mL). At −78 °C, *t*BuLi (1.9 M in pentane, 4.6 mL, 8.7 mmol, 2.1 equiv.) was added dropwise and the mixture was stirred for 30 min. 1-Trifluoroacetylpiperidine (**20**, 1.80 g, 10.0 mmol, 2.4 equiv.) was added and the solution was stirred for 30 min at −78 °C. The reaction was stopped by addition of saturated aqueous NH_4Cl (5 mL) at −78 °C and warmed to rt. The layers were separated and the organic phase was dried over $MgSO_4$. Subsequent removal of the solvent under reduced pressure gave the crude product, which was purified over silica (pentane). Ketone **7** (389 mg, 1.5 mmol, 36%) was obtained as a colorless oil. TLC: R_f = 0.7 [Hex/EA (2/1)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 2H, *m*C*H*), 2.65 (q, $^3J_{HH}$ = 7.5 Hz, 2H, *p*CC*H*$_2$), 2.49 (q, $^3J_{HH}$ = 7.5 Hz, 4H, *o*CC*H*$_2$), 1.25 (t, $^3J_{HH}$ = 7.6 Hz, 3H, *p*CCH$_2$C*H*$_3$), 1.19 (t, $^3J_{HH}$ = .5 Hz, 6H, *o*CCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9 (q, $^2J_{CF}$ = 36.5 Hz, 1C, *C*O), 147.3 (1C, *p*C), 141.3 (2C, *o*C), 130.6 (1C, *ipso*C), 125.8 (2C, *m*CH), 115.6 (q, $^1J_{CF}$ = 293.0 Hz, 1C, *C*F$_3$), 28.8 (1C, *p*CCH$_2$), 26.5 (2C, *o*CCH$_2$), 15.5 (2C, *o*CCH$_2$C*H*$_3$), 15.2 (1C, *p*CCH$_2$C*H*$_3$). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −76.8. IR (ATR): $\tilde{\nu}$ = 2972 cm^{-1} (m), 2939 (w), 2880 (w), 1739 (m), 1607 (m), 1571 (w), 1460 (m), 1379 (w), 1305 (w), 1253 (w), 1194 (s), 1150 (s), 1077 (w), 935 (s), 874 (m), 737 (m), 654 (w), 619 (w). UV–vis ($CHCl_3$): λ_{max} (log ε) = 274 (3.22), 234 (3.06), 231 (3.06) nm. MS (EI, 70 eV): *m*/*z* (%) = 258.1 (22), 189.1 (100), 161.1 (8), 133.1 (14), 115.1 (14), 105.1 (26), 91.1 (16). HRGCMS (EI): *m*/*z* calc. for $C_{14}H_{17}F_3O$ 258.12315; found 258.12341 (1.0 ppm).

4.2. (Piperidin-1-yl)(2,4,6-triethylphenyl)methanone (**34**)

Under N_2 atmosphere, 1-bromo-2,4,6-triethylbenzene (1.50 g, 6.22 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL). At −78 °C, *n*BuLi (1.6 M in hexane, 4.3 mL, 6.84 mmol, 1.1 equiv.) was added dropwise and the solution was stirred for 30 min. At −78 °C, 1-trifluoroacetylpiperidine (**20**, 0.97 mL, 6.53 mmol, 1.05 equiv.) was added and the mixture was stirred for 30 min at −78 °C. The cooling bath was removed and the solution was warmed to rt, then stirred for a further 30 min. The solution was cooled to 0 °C and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The solvent was removed under reduced pressure and the resulting emulsion was suspended in EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified over silica [PE/10/1→5/1→EA] affording amide **34** (624 mg, 2.28 mmol, 37%) and ketone **7** (226 mg, 880 μmol, 14%) as yellowish oils. TLC: R_f = 0.2 [PE/EA (4/1)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 2H, *m*C*H*), 3.78–3.76 (m, 2H, NC*H*$_2$), 3.14–3.11 (m, 2H, NC*H*$_2$), 2.64–2.48 (m, 6H, *o*CC*H*$_2$, *p*CC*H*$_2$), 1.68–1.64 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$), 1.46–1.45 (m, 2H, NCH$_2$C*H*$_2$CH$_2$), 1.22 (t, $^3J_{HH}$ = .6 Hz, 9H, *o*CCH$_2$C*H*$_3$, *p*CCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (1C, *C*O), 144.3 (1C. *ipso*C), 139.5 (2C, *o*C), 133.0 (1C, *p*C), 125.1 (2C, *m*C), 47.4 (1C, NCH$_2$), 41.9 (1C, NCH$_2$), 28.8 (1C, *p*CCH$_2$), 26.4 (1C, NCH$_2$CH$_2$), 25.9 (2C, *o*CCH$_2$), 25.7 (1C, NCH$_2$CH$_2$), 24.6 (1C, NCH$_2$CH$_2$CH$_2$), 15.5 (1C, *p*CCH$_2$CH$_3$), 15.1 (2C, *o*CCH$_2$CH$_3$). IR (ATR): $\tilde{\nu}$ = 3233 cm^{-1} (w), 2964 (m), 2934 (m), 2857 (m), 1628 (s), 1427 (s), 1371 (m), 1278 (s), 1238 (m), 1182 (m), 1098 (m), 1028 (m), 999 (m), 955 (m), 899 (w), 873 (m), 853 (m), 781 (m), 749 (m), 702 (m), 591 (w), 535 (m). UV–vis ($CHCl_3$): λ_{max} (log ε) = 231 (2.74), 240 (3.24) nm. GCMS (EI, 70 eV): *m*/*z* (%) = 273.2 (20), 244.2 (12), 189.1 (100), 105.1 (16). HRGCMS (EI): *m*/*z* calc. for $C_{14}H_{17}F_3O$ 273.20926; found 273.20827 (3.6 ppm).

4.2.1. 2,2,2-Trifluoro-1-(4-methoxy-2,6-dimethylphenyl)ethanone (**6**)

Under N_2 atmosphere, 4-bromo-3,5-dimethylanisole (**7**, 1.0 g, 4.6 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL) and cooled to −78 °C. *n*BuLi (1.6 M in hexane, 3.5 mL, 5.6 mmol, 1.2 equiv.) was added and the solution was stirred for 30 min. Afterwards $F_3CCOOEt$ (796 mg, 5.6 mmol, 1.2 equiv.) was added and the solution was stirred for 4 h. The reaction was stopped by addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with TBME (10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified over silica [PE/EA = 40/1→20/1→4/1] and ketone **6** was obtained as a colorless oil (845 mg, 2.6 mmol, 79%). TLC: R_f = 0.8 [PE/EA (4/1)]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.61 (s, 2H, *m*C*H*), 3.81 (s, 3H, OC*H*$_3$), 2.24 (s, 6H, C*H*3). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.0 (q, $^2J_{CF}$ = 36.1 Hz, 1C, *C*O), 161.0 (1C, *p*C), 137.4 (2C, *o*C), 115.7 (q, $^1J_{CF}$ = 291.8 Hz, 1C, *C*F$_3$), 112.8 (2C, *m*CH), 55.2 (1C, OCH$_3$), 19.7 (2C, *C*H$_3$). ^{19}F NMR (376 MHz, $CDCl_3$): δ = 77.0. IR (ATR): $\tilde{\nu}$ = 2967 cm^{-1} (w), 2944 (w), 2843 (w), 1735 (m), 1603 (m), 1467 (m), 1324 (m), 1189 (s), 1138 (s), 1065 (w), 1034 (w), 1001 (w), 949 (m), 906 (s), 859 (m), 841 (m), 776 (w), 741 (m), 637 (m), 607 (m), 575 (m), 534 (w). UV–vis ($CHCl_3$): λ_{max} (log ε) = 295 (3.37), 239 (3.42) nm. MS (EI, 70 eV): *m*/*z* (%) = 232.1 (18), 163.1 (100), 135.1 (25), 103.1 (8), 91.1 (18). HRGCMS (EI): *m*/*z* calc. for $C_{14}H_{17}F_3O$ 232.07111; found 232.07131 (0.9 ppm).

4.2.2. (4-Methoxy-2,6-dimethylphenyl)(piperidin-1-yl)methanone (**35**)

Under N_2 atmosphere, 4-bromo-3,5-dimethylanisole (**7**, 2.0 g, 9.2 mmol, 1.0 equiv.) was dissolved in dry THF (40 mL) and cooled to −78 °C. Subsequently *n*BuLi (1.6 m, 6.39 mL, 10.2 mmol, 1.1 equiv.) was added and the solution was stirred for 2 h. At −78 °C 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone (**20**, 1.83 g, 10.1 mmol, 1.1 equiv.) was added and the solution was stirred for a further 1.5 h at −78 °C. Afterwards the reaction was stopped by the addition of saturated aqueous NH_4Cl (30 mL). The phases were separated and the organic layer was washed with NH_4Cl (aq., 3 × 15 mL). The combined aqueous layers were extracted with TBME (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified over silica [PE/EA: 20/1→10/1→4/1] and the amide **35** was obtained as a yellowish oil (571 mg, 2.3 mmol, 27%). TLC: R_f = 0.4 (PE/EA 2/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.56 (s, 2H, *m*C*H*), 3.80–3.76 (m, 5H, NC*H*$_2$, OC*H*$_3$), 3.16–3.13 (m, 2H, NC*H*$_2$), 2.23 (s, 6H, C*H*$_3$), 1.67–1.64 (1.67–1.64, 4H, NCH$_2$C*H*$_2$C*H*$_2$), 1.49–1.43 (m, 2H, NCH$_2$C*H*$_2$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (1C, *C*O), 159.2 (1C, *p*C), 135.3 (2C, *o*C), 129.4 (1C, *ipso*C), 112.9 (2C, *m*C), 55.1 (1C, OCH$_3$), 47.1 (1C, NCH$_2$), 42.1 (1C, NCH$_2$), 26.7 (1C, NCH$_2$CH$_2$), 25.8 (1C, NCH$_2$CH$_2$), 24.6 (1C, NCH$_2$CH$_2$CH$_2$), 19.4 (2C, *C*H$_3$). IR (ATR): $\tilde{\nu}$ = 2991 cm^{-1} (w), 2935 (w, br), 2854 (w), 1626 (s), 1605 (s), 1439 (m), 1316 (m), 1217 (m). 1146 (s), 852 (m). UV–vis ($CHCl_3$): λ_{max} (log ε) = 232 (3.19), 240 (3.64), 276 (3.08), 283 (3.01) nm. MS (EI, 70 eV): *m*/*z*

(%) = 247.2 (22), 232.2 (15), 163.1 (100), 135.1 (14), 103.1 (6), 91.1 (11). HRGCMS (EI): m/z calc. for $C_{14}H_{17}F_3O$ 247.15723; found 247.15592 (5.3 ppm).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.06.027.

References

[1] G. Saielli, R. Bini, A. Bagno, Theor. Chem. Acc. 131 (2012) 1140–1150.
[2] F.J. Weigert, K.J. Karel, J. Fluorine Chem. 37 (1987) 125–149.
[3] J.-P. Bégué, D.B. Delpon, J. Fluorine Chem. 127 (2006) 992–1012.
[4] J.C. Sloop, Rep. Org. Chem. 3 (2013) 1–12.
[5] M. Hashimoto, Y. Hatanaka, Eur. J. Org. Chem. (2008) 2513–2523.
[6] B. Raimer, T. Lindel, Chem. Eur. J. 19 (2013) 6551–6555.
[7] M.E. Harding, M. Lenhart, A.A. Auer, J. Gauss, J. Chem. Phys. 128 (2008) 244111 (and references cited therein).
[8] M. Kobayashi, H. Nakai, J. Chem. Phys. 131 (2009) 114108.
[9] D.E. Williams, M.B. Peters, B. Wang, K.M. Merz Jr., J. Phys. Chem. A (2008) 8829–8838.
[10] F. Hentschel, B. Raimer, G. Kelter, H.-H. Fiebig, F. Sasse, T. Lindel, Eur. J. Org. Chem. (2014) 2120–2127.
[11] H.L. Hassinger, R.M. Soll, G.W. Gribble, Tetrahedron Lett. 39 (1998) 3095–3098.
[12] G.W. Gribble, H.L. Fraser, J.C. Badenock, Chem. Commun. (2001) 805–806.
[13] R. Ditchfield, Mol. Phys. 27 (1974) 789–807.
[14] (a) A.D. Becke, Phys. Rev. A 38 (1988) 3098–3100;
(b) A.D. Becke, J. Chem. Phys 98 (1993) 5648–5652;
(c) C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785–789;
(d) S.H. Vosko, L. Wilk, M. Nusair, Can. J. Phys. 58 (1980) 1200–1211.
[15] S.J. Grimme, Comput. Chem. 27 (2006) 1787–1799.
[16] J. Tomasi, M. Persico, Chem. Rev. 94 (1994) 2027–2094.
[17] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision A.1, Gaussian, Inc., Wallingford, CT, 2009.
[18] T.A. Halgren, J. Comp. Chem. 17 (1996) 490–519.
[19] Y. Shao, L.F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S.T. Brown, A.T.B. Gilbert, L.V. Slipchenko, S.V. Levchenko, D.P. O'Neill, R.A. DiStasio Jr., R.C. Lochan, T. Wang, G.J.O. Beran, N.A. Besley, J.M. Herbert, C.Y. Lin, T. Van Voorhis, S.H. Chien, A. Sodt, R.P. Steele, V.A. Rassolov, P.E. Maslen, P.P. Korambath, R.D. Adamson, B. Austin, J. Baker, E.F.C. Byrd, H. Dachsel, R.J. Doerksen, A. Dreuw, B.D. Dunietz, A.D. Dutoi, T.R. Furlani, S.R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R.Z. Khalliulin, P. Klunzinger, A.M. Lee, M.S. Lee, W.Z. Liang, I. Lotan, N. Nair, B. Peters, E.I. Proynov, P.A. Pieniazek, Y.M. Rhee, J. Ritchie, E. Rosta, C.D. Sherrill, A.C. Simmonett, J.E. Subotnik, H.L. Woodcock III, W. Zhang, A.T. Bell, A.K. Chakraborty, D.M. Chipman, F.J. Keil, A. Warshel, W.J. Hehre, H.F. Schaefer, J. Kong, A.I. Krylov, P.M.W. Gill, M. Head-Gordon, Phys. Chem. Chem. Phys 8 (2006) 3172.
[20] CCDC-997871 and -997872 contain the supplementary crystallographic data for compounds **8** and **11** respectively, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif (12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.
[21] J. Brunner, H. Senn, F.H. Richards, J. Biol. Chem. 8 (1980) 3313–3318.
[22] K. Strømgaard, D.R. Saito, H. Shindou, S. Ishii, T. Shimizu, K. Nakanishi, J. Med. Chem. 45 (2002) 4038–4046.
[23] R.K. Mackie, S. Mhatre, J.M. Tedder, J. Fluorine Chem. 20 (1977) 437–445.
[24] J.M. Chong, E.K. Mar, J. Org. Chem. 56 (1991) 893–896.
[25] D. Bell, A.O.A. Eltoum, N.J. O'Reilly, A.E. Tipping, J. Fluorine Chem. 64 (1993) 151–166.
[26] B. Wang, A.T. Dossy, S.S. Walse, A.S. Edison, K.M. Merz, J. Nat. Prod. 72 (2009) 709–713.
[27] R. Jain, T. Bally, P.R. Rablen, J. Org. Chem. 74 (2009) 4017–4023.