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A new synthesis of trifluorinated compounds via 1,1-dichloro-1-alkenes in superacid

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Abstract—A two step process for converting ketone or aldehyde via 1,1-dichloro-1-alkenes to the corresponding 1,1,1-trifluoro-derivatives is described, based on HF addition and chlorine–fluorine exchange under superacidic conditions.

The unusual reactivity of functionalized organic substrates, especially natural products, in HF–SbF_5 system is of great interest. Under these superacidic conditions, such compounds are (poly)protonated and their reactivity is dramatically modified compared to conventional acidic media. Novel and selective reactions as long-range functionalization of unactivated C–H bonds,[1] dearomatization,[2] isomerization of saturated or unsaturated substrates,[3] regioselective electrophilic trifluoromethylation of substituted aromatics,[4] and difluorination of various compounds,[5] have been discovered first using simple substrates as model compounds, then applied to polyfunctional products. For example, under these highly acidic conditions, it has been demonstrated that the *Vinca* alkaloids such as vinorelbine afforded vinflunine,[6] a new difluoroderivative selected for its promising antitumor activity (phase III clinical trials).

In search for new reactions, we have recently described a novel access to trifluorinated compounds starting from 3-bromopropargyl amines in superacid.[7] Taking into account the proposed mechanism (Scheme 1) and postulated intermediate ion **C**, extension to the readily available 1,1-dichloro-1-alkenes seemed worthwhile.

Such substrates are anticipated to be C-protonated to give carbenium ion **E**, which is trapped by a fluoride ion (SbF_6^-, $Sb_2F_{11}^-$ ...) to afford a monofluoro intermediate (Scheme 2). Halogen exchange should then lead to the trifluorinated derivatives.

The preparation of a set of 1,1-dichloro-1-alkenes (**1**–**8**) was carried out from various aldehydes or ketones according to the known procedure.[8] The chain extension by one carbon to form dichloroolefins **2**, **3**, **5**, **6**, and **7** was accomplished by reaction of the aldehydes or ketones with the carbontetrachloride–triphenylphosphine reagent in tetrahydrofuran at 60 °C.[9,10] Supplementary addition of activated magnesium at room temperature was done to afford **3**.[11] While 3-fluorene **7**, 2-quinoline **6**, and alkyl derivative **3** are prepared in good yield (respectively, 81%, 62%, 97%), the desired dichloroolefins **2** and **5** were isolated in lower yield (20%) together with unreacted starting material. Substrates **1**, **4**, and **8** are commercially available (Fig. 1).

All 1,1-dichloro-1-alkenes **1**–**8** were then submitted to acidic conditions. Preliminary experiments were performed using HF alone (0 °C, 5 h). In all cases, starting material was recovered. The use of more acidic conditions (HF–SbF_5) was then considered.[12]

In the present study, the reactions were carried out in HF–SbF_5 (molar ratio 7/1) at low temperature (−20 °C to −40 °C). Starting materials were completely transformed within 10–20 min of reaction time. In some cases, subsequent treatment with HF–pyridine 70/30 (v/v 1 mL)[13] was required (Table 1, entries 2, 5, and 6) at −78 °C. Then, the resulting mixture was quenched with iced water and sodium carbonate. After extraction

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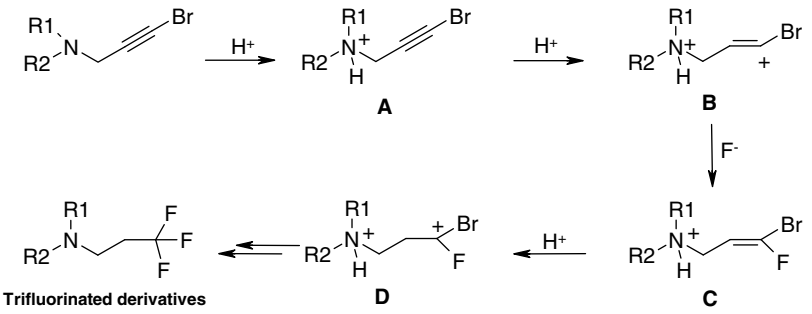
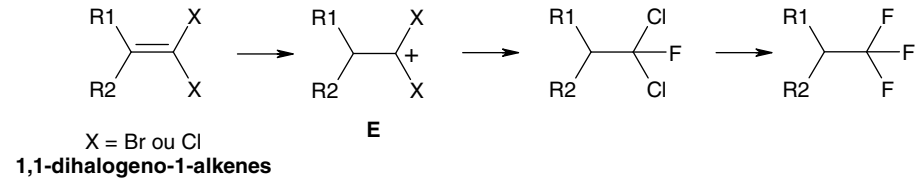


Scheme 1. Proposed mechanism for the formation of trifluorinated compounds.



Scheme 2. Dihalogeno alkenes as precursor of trifluorinated compounds.

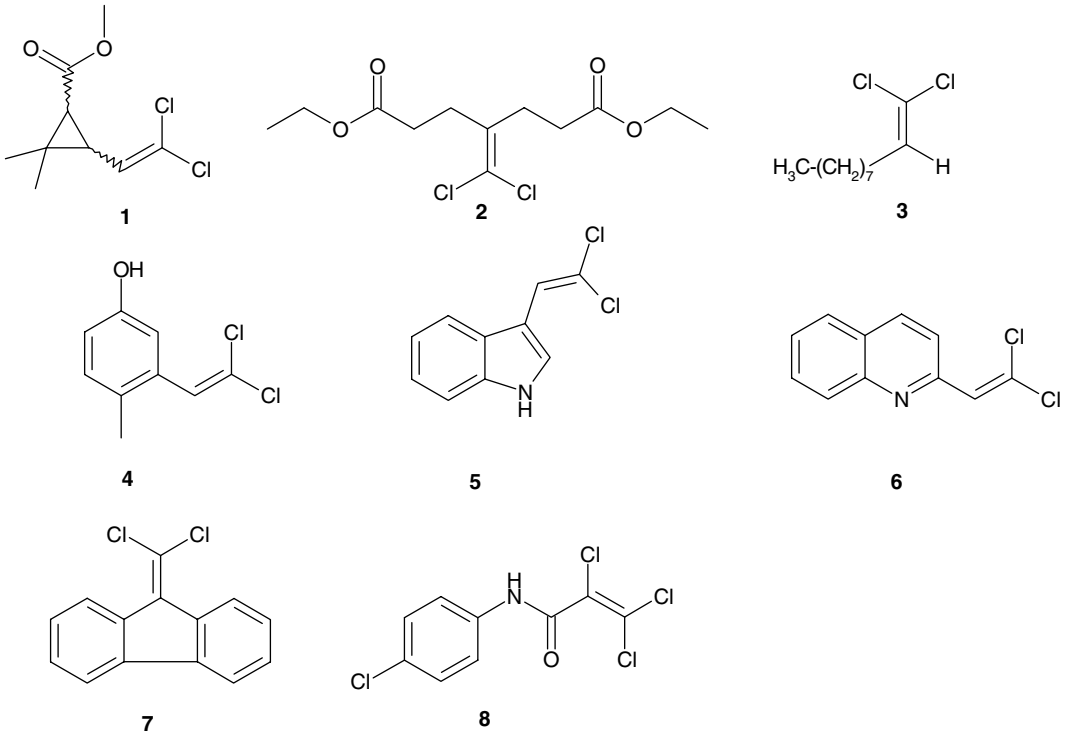


Figure 1. Starting materials.

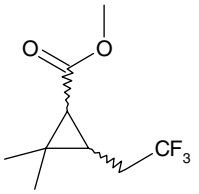
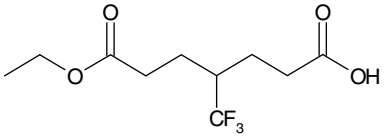
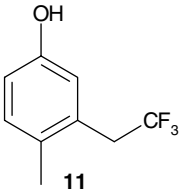
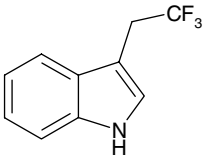
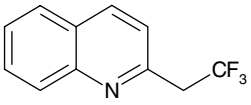
with dichloromethane and usual work-up, the products were purified by column chromatography over SiO_2.

The isolated yields reported in Table 1 were obtained after complete consumption of starting material.

It should be noticed that compounds **1**, **2**, **4**, **5**, and **6** afford the trifluorinated derivatives as the sole product. Reaction yields are modest with diester **2** but fair to good with the other substrates.

Only a short reaction time is needed to give the expected trifluorinated compound from **1** (*Z*/*E* ratio 25/75). The same experimental procedure furnished an inseparable mixture of $CClF_2/CF_3$ for phenol **4** or $CCl_2F/CClF_2/CF_3$ derivatives for compounds **2**, **5**, and **6** (as determined by ^{19}F NMR). Complete exchange to afford CF_3 compounds required longer reaction times (phenol **4**) and/or the use of more fluorinating reagent HF–pyridine (**2**, **5**, and **6**). In addition, alkyl substrate **3** did not afford the corresponding trifluoroderivative but an

Table 1. Reactivity of 1,1-dichloro-1-alkenes derivatives in HF–SbF_5

Entry	Starting material	T (°C), time (min)	Yield (%)	Product
1	**1**	−40, 10	59	 **9**
2	**2**	−40,[a] 15	35	 **10**
3	**3**	−40, 10	—	Complex mixture
4	**4**	−40, 15	72	 **11**
5	**5**	−20,[a] 20	50	 **12**
6	**6**	−20,[a] 20	71	 **13**
7	**7**	−40, 10	—	No reaction
8	**8**	−40, 10	—	No reaction

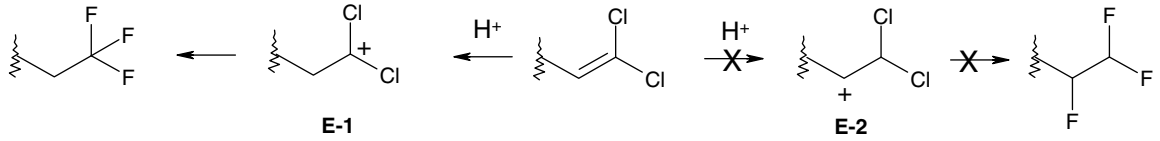
[a] Followed by treatment with HF–pyridine.

inseparable complex mixture. Finally, aromatic substrate **7** and amide derivative **8** remained unchanged under these acidic conditions.

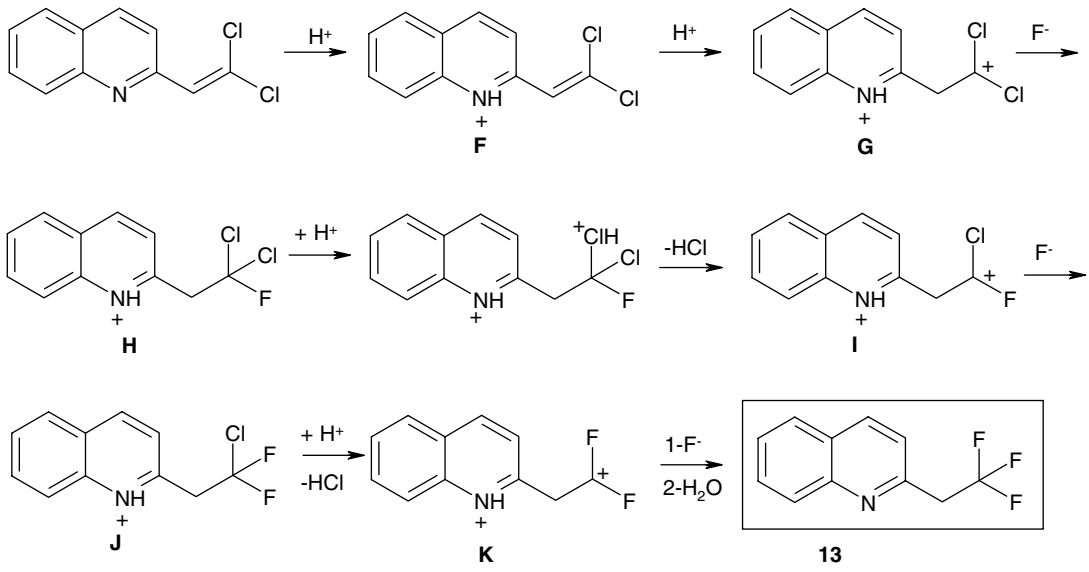
For all trifluorinated compounds, structure assignment was made by ^{1}H, ^{13}C, and ^{19}F NMR. As expected, ^{19}F NMR spectrum exhibits specific signals (**9**, **11**, **12**, **13**: $\delta = -65.3$ to -69 ppm, t, $J = 11$ Hz; **10**, −71.1, d, $J = 9$ Hz)[14] in agreement with the trifluoro moiety.

For all substrates, we observed the sole formation of 1,1,1-trifluorinated compounds. This result can be explained by assuming the initial regioselective protonation of the double bond to afford the more stabilized α-dichlorocarbenium ion **E-1**, precursor of the 1,1,1-trifluorinated compounds (Scheme 3). This result is in agreement with the known stabilization of α-chloronium ions by chlorine atom which becomes both a π donor and a σ donor.[15,5]

The postulated mechanism is outlined in Scheme 4 (quinoline derivative). In HF–SbF_5, this substrate is N-protonated. Further regioselective protonation of dichloroalkene **F** affords carbenium ion **G**, which is



Scheme 3.



Scheme 4. Proposed mechanism for the formation of trifluorinated compounds.

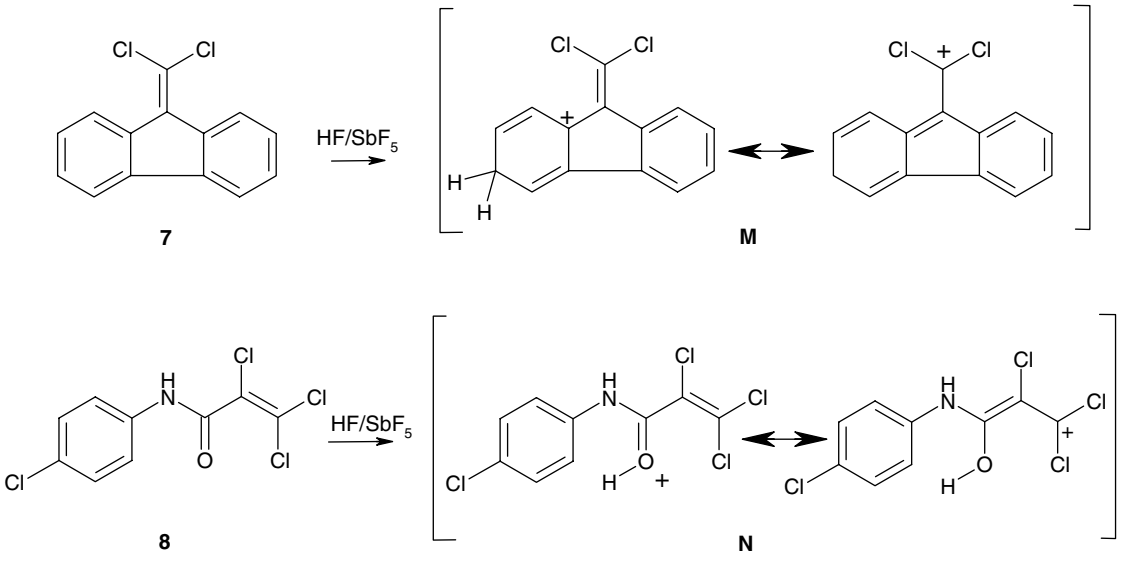
trapped by a fluoride ion (SbF_6^-, $Sb_2F_{11}^-$) to give ion **H**. Protonation of one of the chlorines followed by elimination of HCl yields the more stabilized ion **I**, which can react with a fluoride ion leading to ion **J**. The same sequence of protonation–elimination of HCl affords α-fluoronium ion **K**, precursor of the trifluorinated compound **13** (Scheme 4). Halogen exchange is observed in $HF–SbF_5$ alone (entries 1, 4) but may necessitate a more fluorinating reagent[13,4] (HF–pyridine) to reach completion (entries 2, 5, and 6).

Such mechanism can be ruled out for iminium ion of indole **5**,[16] O-protonated phenolic compound **4**,[17] and di-O-protonated esters **1** and **2**.[18] For diester **2**, cleavage of one ester function is observed leading to a lower isolated yield (35%). As previously described by Olah under such superacidic conditions, the ethyl esters are cleaved via acyl-oxygen fission to afford the corresponding carboxylic acid.[19]

Particular behavior was observed for compounds **3**, **7**, and **8**. For the alkyl derivative **3**, a rearranged and inseparable mixture of compounds is observed. This unexpected reactivity may be due to isomerization of the alkyl chain under superacidic conditions. Similar behavior of alkyl derivatives has been already observed in $HF–SbF_5$.[20–22]

The lack of reactivity of substrates **7** and **8** could be explained by strong mesomeric stabilization of a positive charge as outlined in Scheme 5.

In superacids, the C-protonated aromatic substrate **7** and the O-protonated amide **8** should lead, respectively, to the highly stabilized ions **M** and **N** (Scheme 5). The low reactivity of ions **M** and **N** did not allow the expected trapping by fluorine ion, the poor nucleophilic nature of fluoride ion (SbF_6^-, $Sb_2F_{11}^-$) accounting for this result.[23–25]



Scheme 5.

In conclusion, this new reaction appears to be a very interesting way to prepare 1,1,1-trifluorinated compounds in two steps, starting from aldehyde or ketone via the corresponding 1,1-dichloroalkenes. This process may be limited in the case of substrates leading to highly stabilized carbenium ions.

Extension of this novel reaction to polyfunctional bioactive products will be reported in a near future.

Acknowledgments

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12. The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangement in place. In a typical experiment, to a stirred solution of HF (6 mL) and SbF_5 (3 mL) at low temperature (see Table 1) in a 50 mL Teflon reactor was added the substrate (1.6 mmol). The mixture was maintained at a given temperature for 10–20 min., according to the substrate. In some cases (compounds **2**, **5**, **7**), the mixture was then cooled to −78 °C and HF–pyridine (1 mL, 70/30 (v/v)) was added. The reaction was kept at 0 °C overnight, then very carefully poured into a vigorously stirred mixture of Na_2CO_3, H_2O and ice. After extraction with dichloromethane and usual work-up, the reaction mixture was evaporated to dryness and purified on SiO_2.
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14. Compound **9** (*Z*/*E* ratio: 25/75): ^{1}H NMR (300 MHz, $CDCl_3$ TMS as internal standard): δ 3.69–3.66 (2s, 3H, OC*H*$_3$t, OC*H*$_3$c), 2.52–2.17 (m, 2H, C*H*$_2$-CF$_3$c, C*H*$_2$-CF$_3$t), 1.61–1.54 (m, 1H, H-3t, H-3c), 1.36–1.30 (m, 1H, H-1t, H-1c), 1.24–1.22 (2s, 3H, C*H*$_3$t, C*H*$_3$c), 1.21–1.18 (2s, 3H, C*H*$'_3$c, C*H*$'_3$t). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (C=Ot), 171.7 (C=Oc), 126.6 (q, $^1J_{CF} = 277$ Hz, *C*F$_3$t and *C*F$_3$c), 51.7 (OC*H*$_3$t), 51.4 (OC*H*$_3$c), 32.8 (q, $^2J_{CF} = 28.9$ Hz, *C*H$_2$–CF$_3$t), 31.8 (C-1t), 28.44 (*C*H$'_3$c), 28.4 (q, $^2J_{CF} = 29.1$ Hz, *C*H$_2$–CF$_3$c), 27.7 (C-3c); 26.4 (C-2t), 25.3 (q, $^3J_{CF} = 3.7$ Hz, C-3t), 24.8 (C-2c), 21.4 (*C*H$'_3$t), 20.2 (*C*H$_3$t), 14.1 (*C*H$_3$c). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −67.6 (t, $J = 10.4$ Hz, C*F*$_3$t), −67.7 (t, $J = 11.0$ Hz, C*F*$_3$c). Calcd HRMS ($C_8H_{10}O_3F_3$): $[M-OCH_3]^+$ 179.06837; found 179.0692.
Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$ TMS as internal standard): δ 4.15 (q, $J = 7.2$ Hz, 2H, C*H*$_2$CH$_3$), 2.52 (t, $J = 7.8$ Hz, 2H, H-6), 2.45 (t, $J = 7.5$ Hz, 2H, H-2), 2.23 (m, $J_{H-F} = 9.0$ Hz, 1H, H-4), 1.95 (m, 2H, H-5), 1.78 (m, 2H, H-3), 1.26 (t, $J = 7.2$ Hz, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4 (C-7), 172.8 (C-1), 127.9 (q, $^1J_{CF} = 280$ Hz, *C*F$_3$), 60.8 (*C*H$_2$CH$_3$), 41.1 (q, $^2J_{CF} = 25.4$ Hz, C-4), 31.2 (C-2), 30.9 (C-6), 23.0 (q, $^3J_{CF} = 2.5$ Hz, C-5), 22.7 (q, $^3J_{CF} = 2.4$ Hz, C-3), 14.2 (CH$_2$*C*H$_3$). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −71.1 (t, $J = 9.0$ Hz). Calcd HRMS ($C_8H_{10}O_3F_3$): $[M-OC_2H_5]^+$ 211.05820; found, 211.0583.
Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$ TMS as internal standard): δ 7.07 (d, $J = 8.0$ Hz, 1H, H-2), 6.72 (m, 2H, H-5 and H-6), 4.71 (s, 1H, O*H*), 3.34 (q, $J = 10.8$ Hz, 2H, H-1′), 2.27 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5 (C-1), 131.7 (C-5), 129.8 (q, $^3J_{CF} = 2.7$ Hz, C-3), 129.7 (C-4), 126.0 (q, $^1J_{CF} = 277$ Hz, C-2′), 117.9 (C-2), 115.2 (C-6), 37.1 (q, $^2J_{CF} = 29.7$ Hz, C-1′), 18.7 (*C*H$_3$). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −66.4 (t, $J = 11.0$ Hz).
Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$ TMS as internal standard): δ 8.10 (s, 1H, N*H*), 7.61 (d, $J = 7.7$ Hz, 1H, H-4), 7.36 (d, $J = 7.6$ Hz, 1H, H-7), 7.23–7.14 (m, 3H, H-2, H-5 and H-6), 3.53 (q, $J = 11.1$ Hz, 2H, H-1′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9 (C-7a), 127.3 (C-3a), 126.2 (q, $^1J_{CF} = 277$ Hz, C-2′), 124.2 (C-2), 122.5 (C-6), 120.1 (C-5), 118.7 (C-4), 111.3 (C-7), 104.8 (q, $^3J_{CF} = 3.3$ Hz, C-3), 30.5 (q, $^2J_{CF} = 31.4$ Hz, C-1′). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −67.3 (*t*, $J = 11.0$ Hz). Calcd HRMS ($C_{10}H_8NF_3$): 199.06088; found, 199.0608.
Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$ TMS as internal standard): δ 8.18 (d, $J = 8.4$ Hz, 1H, H-4) 8.10 (d, $J = 8.5$ Hz, 1H, H-8), 7.84 (d, $J = 8.2$ Hz, 1H, H-5), 7.75 (m, 1H, H-7), 7.57 (m, 1H, H-6), 7.46 (d, $J = 8.4$ Hz, 1H, H-3), 3.81 (q, $J = 10.8$ Hz, 2H, H-1′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5 (q, $^3J_{CF} = 3.4$ Hz, C-2), 148.4 (C-8a), 137.3 (C-4), 130.3 (C-7), 129.7 (C-8), 127.9 (C-5), 127.7 (C-4a), 127.3 (C-6), 125.9 (q, $^1J_{CF} = 277$ Hz, C-2′), 122.0 (C-3), 44.0 (q, $^2J_{CF} = 29.1$ Hz, C-1′). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −65.3 (t, $J = 10{,}7$ Hz). Calcd HRMS ($C_{11}H_8NF_3$) 211.06088; found, 211.0603.
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25. In the case of **7**, one cannot rule out the possibility of alternative protonation on the CCl_2 carbon, leading to a highly stabilized bis-benzylic carbenium ion which should be unreactive and will afford back **7** upon deprotonation.