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Transition Metal-Free Trifluoromethylation of *N*-Allylamides with Sodium Trifluoromethanesulfinate: Synthesis of Trifluoromethyl-Containing Oxazolines

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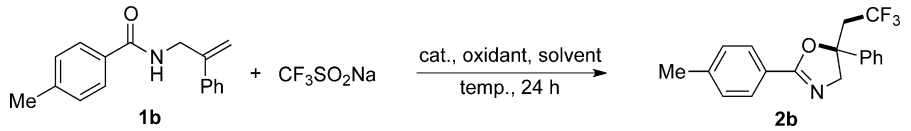
Abstract: A transition metal-free method for the trifluoromethylation of *N*-allylamides has been developed, and the corresponding trifluoromethyl-containing oxazolines were prepared in moderate to good yields. The protocol uses readily available substituted *N*-allylamides as the starting materials, inexpensive and easily stored sodium trifluoromethanesulfinate as the trifluoromethyl source, iodobenzene diacetate as the oxidant, and the procedure involves sequential intermolecular trifluoromethylation of alkenes with sodium trifluoromethanesulfinate and intramolecular cyclization. This is the first example to prepare CF_3-containing oxazolines. Therefore, the present method should afford an efficient and practical strategy for synthesis of other CF_3-containing cyclic compounds.

Keywords: difunctionalization; oxazoles; sodium trifluoromethanesulfinate; transition metal-free procedure; trifluoromethylation

Introduction

The oxazole motif is an important nitrogen heterocycle that widely occurs in many natural products, as well as biologically and pharmaceutically active molecules.[1] Furthermore, 2,5-substituted oxazoles are useful building blocks and intermediates in organic synthesis.[2] The traditional methods for the synthesis of oxazoles mainly include both dehydration of an amido alcohol and condensation of a nitrile with an amino alcohol.[3] However, they usually need extended reaction times and elevated temperatures, and the dehydration method requires stoichiometric amounts of dehydrating agent in which the product purification is tedious. The oxidative cyclization of readily available *N*-allylamides to oxazoles is an attractive alternative to traditional processes,[4] and the use of transition metals such as Au,[5] Pd,[6] Ag,[7] Cu,[8] and Mo[9] greatly promotes the synthesis of various oxazole derivatives. On the other hand, the CF_3-containing molecules exhibit unique properties including elevated electronegativity, hydrophobicity, metabolic stability, and bioavailability, so they often find use in pharmaceuticals, agrochemicals and functional materials.[10,11] Recently, the introduction of the trifluoromethyl group to various organic molecules has attracted wide attention,[12] and there has been great progress in transition metal-mediated or catalyzed functionalizations of alkenes.[13] Inspiringly, the methods for transition metal-free trifluoromethylation have recently been developed. Baran and co-workers have reported an efficient transition metal-free C–H trifluoromethylation of heterocycles,[14] and Nicewicz's group has developed a novel transition metal-free hydrotrifluoromethylation of alkenes with *N*-Me-9-mesitylacridinium as a photoredox catalyst.[15] Nevado and co-workers have explored a transition metal-free aryltrifluoromethylation of activated alkenes with Togni′s reagent.[16] We have developed an efficient transition metal-free trifluoromethylation and arylation of alkenes to yield 3-(trifluoromethyl)-indolin-2-one derivatives with sodium trifluoromethanesulfinate.[17] To the best of our knowledge, the synthesis of CF_3-containing oxazole derivatives has not been reported thus far. Herein, we report an efficient transition metal-free trifluoromethylation of *N*-allylamides leading to CF_3-containing oxazole derivatives by using inexpensive, readily available and easily stored sodium trifluoromethanesulfinate (Langlois's reagent[18]) as the trifluoromethyl source.

Table 1. Optimization of conditions on trifluoromethylation of 4-methyl-*N*-(2-phenylallyl)benzamide (**1b**) with CF_3SO_2Na leading to 2-5-phenyl-2-*para*-tolyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole (**2b**).[a]



Entry	Cat.	Oxidant	Solvent	Temp. [°C]	Yield [%][b]
1	–	*m*-CPBA	DCE	90	trace
2	–	*t*-BuOOH	DCE	90	28
3	**–**	**$PhI(OAc)_2$**	**DCE**	**90**	**72**
4	–	$K_2S_2O_8$	DCE	90	trace
5	–	–	DCE	90	0
6	–	$PhI(OAc)_2$	CH_2Cl_2	90	68
7	–	$PhI(OAc)_2$	toluene	90	19
8	–	$PhI(OAc)_2$	MeCN	90	57
9	–	$PhI(OAc)_2$	EtOAc	90	54
10	–	$PhI(OAc)_2$	DCE	60	58
11	CuI	$PhI(OAc)_2$	DCE	90	53
12	$Pd(OAc)_2$	$PhI(OAc)_2$	DCE	90	40
13	$FeCl_3$	$PhI(OAc)_2$	DCE	90	54
14	$NiCl_2$	$PhI(OAc)_2$	DCE	90	63

[a] *Reaction conditions:* 4-methyl-*N*-(2-phenylallyl)benzamide (**1b**) (0.2 mmol), CF_3SO_2Na (0.5 mmol), oxidant (0.5 mmol), catalyst (0.02 mmol), solvent (2 mL), temperature (60 or 90 °C), reaction time (24 h) under nitrogen atmosphere.
[b] Isolated yield.

Results and Discussion

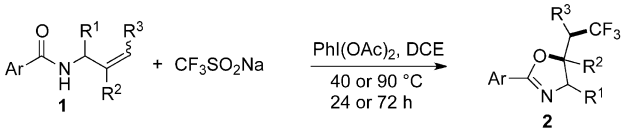
As shown in Table 1, our search for optimized reaction conditions began by treating 4-methyl-*N*-(2-phenylallyl)benzamide (**1b**) with CF_3SO_2Na in the presence of different oxidants in dichloroethane (DCE) at 90 °C under a nitrogen atmosphere (entries 1–4), and $PhI(OAc)_2$ gave the highest yield (entry 3). No target product was observed in the absence of oxidant (entry 5). Other solvents were attempted (entries 6–9), and 1,2-dichloroethane (DCE) provided the best result (compare entries 3, 6–9). When the temperature was decreased to 60 °C, the yield was reduced (entry 10). Four common catalysts were added to the reaction system, and the reactivity was obviously decreased (entries 11–14). The results showed that the transition metals did not catalyze this reaction (*on the contrary, they inhibited the reactivity of the substrates*), so the transition metal-free trifluoromethylation of *N*-allylamides is suitable under following conditions: $PhI(OAc)_2$ as the oxidant, DCE as the solvent at 90 °C under a nitrogen atmosphere.

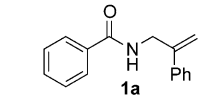
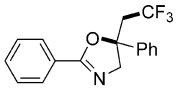
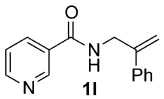
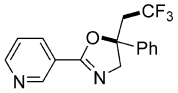
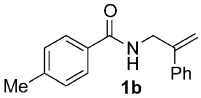
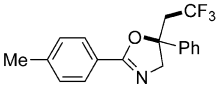
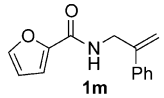
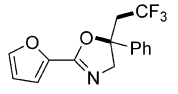
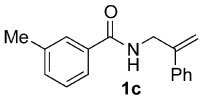
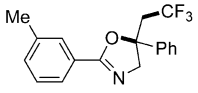
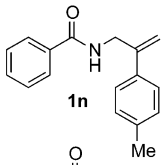
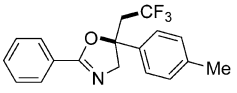
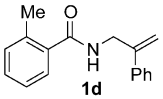
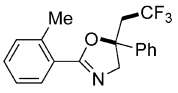
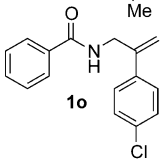
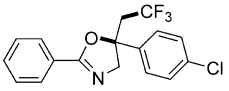
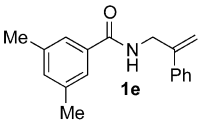
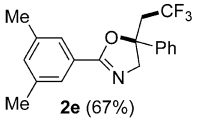
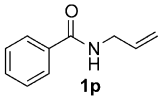
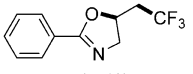
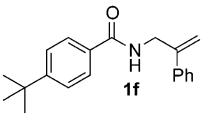
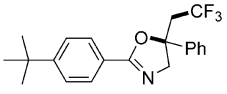
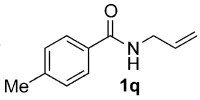
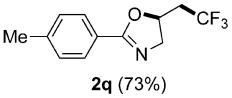
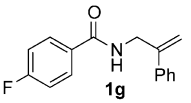
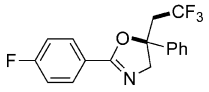
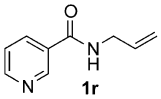
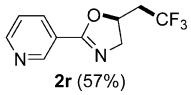
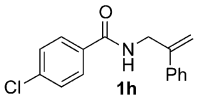
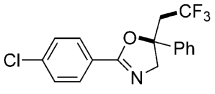
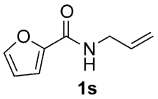
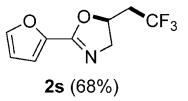
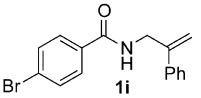
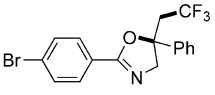
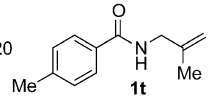
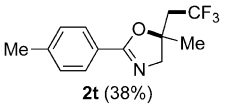
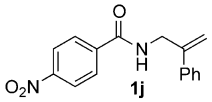
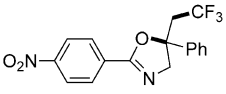
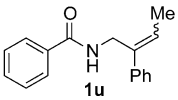
After getting the optimum reaction conditions, we investigated the scope for the trifluoromethylation of *N*-allylamides (**1**) with CF_3SO_2Na leading to CF_3-containing oxazole derivatives. As shown in Table 2, the tested substrates provided moderate to good yields. For substituents on the Ar of *N*-allylamides (**1**), those substrates containing electron-donating groups showed slightly higher reactivity than those with electron-withdrawing groups, and substrate **1d** gave a lower yield due to steric hindrance of the *ortho*-methyl (entry 4). The substrates with R^2 = aryl or hydrogen provided higher yields than **1t** with R^2 = methyl (entry 20), and **1u** with an internal alkene gave 41% yield (entry 21). A lower temperature and longer time were required for **1v** containing R^1 = methyl (entry 22). The trifluoromethylation leading to CF_3-containing oxazolines (**2**) could tolerate various functional groups including C–F bond (entry 7), C–Cl bond (entries 8 and 15), C–Br bond (entry 9), nitro (entries 10 and 11), nitrogen heterocycles (entries 12 and 18) and oxygen heterocycle (entries 13 and 19) in the substrates.

Inspired by the results above, we prepared spirocyclic compound **2w** by using the present method. As shown in Scheme 1, 3,4-dihydronaphthalen-1(2*H*)-one (**3**) underwent the three-step reaction (addition of TMSCN to ketone, reduction and formation of ammonium) to provide (1,2-dihydronaphthalen-4-yl)methanamine hydrochloride (**4**) in 31% total yield, and then reaction of **4** with 4-methylbenzoyl chloride in the presence of triethylamine gave **1w** in 80% yield. Finally, trifluoromethylation of **1w** with CF_3SO_2Na under the standard conditions afforded the target product (**2w**) in 43% yield.

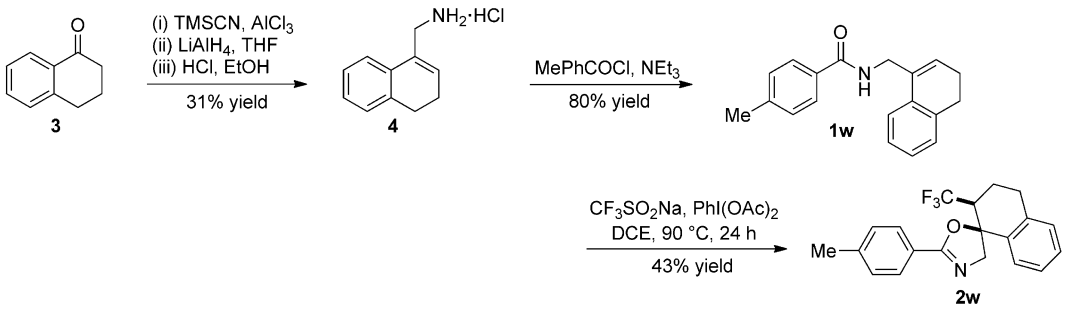
We attempted the synthesis of chiral oxazolines containing CF_3 groups. As shown in Scheme 2, trifluoromethylation of (*R*)-*N*-(1-phenylallyl)benzamide with CF_3SO_2Na was performed under the standard conditions, a pair of diastereoisomers of **2x** and **2x′**

Table 2. Trifluoromethylation of *N*-allylamides (**1**) with CF_3SO_2Na leading to CF_3-containing oxazolines (**2**).[a]

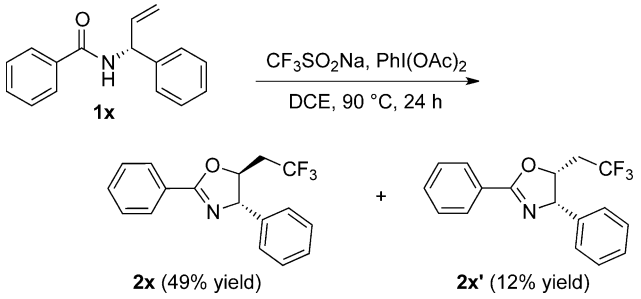


Entry	1	2 (Yield[b])	Entry	1	2 (Yield[b])
1	 **1a**	 **2a** (63%)	12	 **1l**	 **2l** (68%)
2	 **1b**	 **2b** (72%)	13	 **1m**	 **2m** (61%)
3	 **1c**	 **2c** (55%)	14	 **1n**	 **2n** (71%)
4	 **1d**	 **2d** (48%)	15	 **1o**	 **2o** (80%)
5	 **1e**	 **2e** (67%)	16	 **1p**	 **2p** (66%)
6	 **1f**	 **2f** (73%)	17	 **1q**	 **2q** (73%)
7	 **1g**	 **2g** (59%)	18	 **1r**	 **2r** (57%)
8	 **1h**	 **2h** (65%)	19	 **1s**	 **2s** (68%)
9	 **1i**	 **2i** (61%)	20	 **1t**	 **2t** (38%)
10	 **1j**	 **2j** (51%)	21	 **1u**	**2u** (41%)
11	**1k**	**2k** (65%)	22[c]	**1v**	**2v** (65%)

[a] *Reaction conditions: N*-allylamide (**1**) (0.2 mmol), CF_3SO_2Na (0.5 mmol), $PhI(OAc)_2$ (0.5 mmol), DCE (2 mL), temperature (90 °C), reaction time (24 h) under nitrogen atmosphere.
[b] Isolated yield.
[c] Temperature (40 °C), reaction time (72 h).



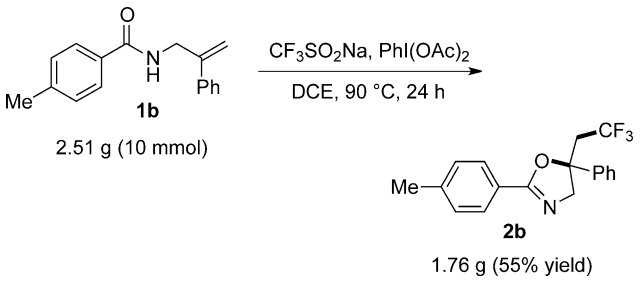
Scheme 1. Synthesis of compound **2w** by using the present method.



Scheme 2. Synthesis of chiral oxazolines **2x** and **2x′**.

($dr = 4:1$) was observed, and pure products **2x** and **2x′** were obtained after isolation by a preparative TLC.

A scale-up experiment was investigated by using the trifluoromethylation of **1b** as an example (Scheme 3). Reaction of 10 mmol (2.51 g) of **1b** with 25 mmol (4.90 g) of CF_3SO_2Na under the standard conditions provided **2b** in 55% yield (1.76 g). Therefore, the present method is effective for the scaled-up synthesis of CF_3-containing oxazolines.

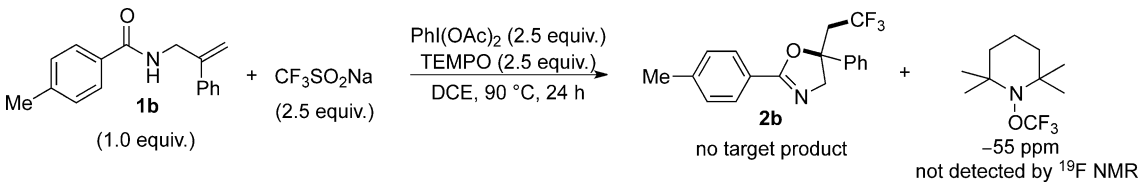


Scheme 3. Synthesis of **2b** on a gram scale under the standard conditions.

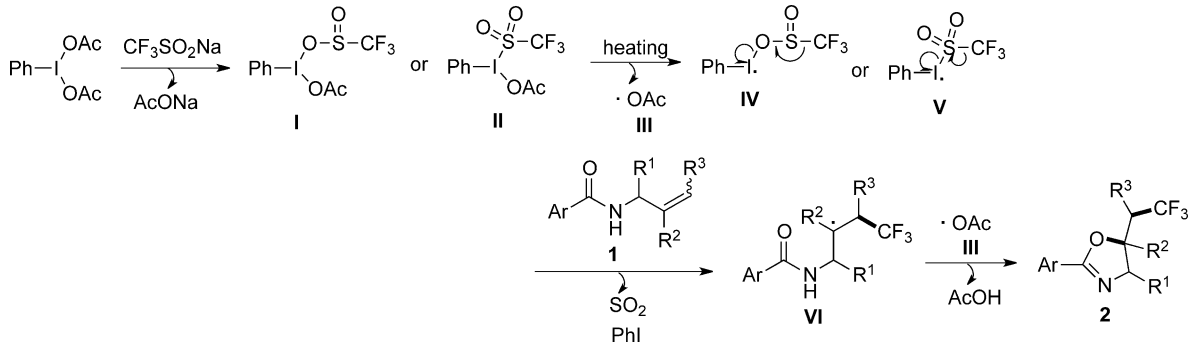
We explored the possible reaction mechanism for the transition metal-free trifluoromethylation of *N*-allylamides. As shown in Scheme 4, the radical scavenger, 2.5 equiv. of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), was added to the reaction system of 4-methyl-*N*-(2-phenylallyl)benzamide (**1b**) and CF_3SO_2Na, and the mixture was treated under the standard conditions. No target product was found, and the result showed that the reaction could involve a free radical intermediate process. Further, TEMPO-CF_3 at ^{19}F NMR −55 ppm was not observed by ^{19}F NMR, which implied that other free radicals rather than $\cdot CF_3$ occurred at the beginning of the process.[19] Therefore, a possible mechanism for the transition metal-free trifluoromethylation of *N*-allylamides is proposed in Scheme 5 according to the results above and the previous references.[19,20] First, reaction of $PhI(OAc)_2$ with CF_3SO_2Na provides **I** or **II** leaving NaOAc, and desorption of **I** or **II** gives free radicals **III** and **IV** or **V** under the conditions of heating.[19] Treatment of **IV** or **V** with *N*-allylamide (**1**) affords **VI** freeing SO_2 and PhI, and intramolecular cyclization of **VI** in the presence of **III** yields the target product (**2**) freeing AcOH.

Conclusions

We have developed a simple, efficient and practical transition metal-free trifluoromethylation of *N*-allylamides. The protocol uses readily available *N*-allylamides as the starting materials, inexpensive, stable



Scheme 4. Treatment of 4-methyl-*N*-(2-phenylallyl)benzamide (**1b**) with CF_3SO_2Na in the presence of TEMPO under the standard conditions.



Scheme 5. Possible mechanism for the trifluoromethylation of *N*-allylamides with CF_3SO_2Na.

and easily stored CF_3SO_2Na as the trifluoromethyl source, $PhI(OAc)_2$ as the oxidant, and no transition metal, ligand and additive were required. The procedure avoided contamination of transition metals to the products, and it is economical and environment friendly chemistry. The reactions comprise intermolecular trifluoromethylation of alkenes and intramolecular cyclization, and the corresponding CF_3-containing oxazolines were obtained in moderate to good yields. This is the first example to prepare CF_3-containing oxazole derivatives *via* difunctionalization of alkenes. We believe that the present strategy will find wide application in the synthesis of other CF_3-containing cyclic compounds.

Experimental Section

General Procedure for the Synthesis of Compounds 2a–w

A 25-mL Schlenk tube was charged with a magnetic stirrer and 1,2-dichloroethane (2.0 mL). Substituted *N*-allylamide (**1**) (0.2 mmol), CF_3SO_2Na (0.5 mmol, 78 mg), $PhI(OAc)_2$ (0.5 mmol, 160 mg) were added to the tube under a nitrogen atmosphere. The tube was sealed, and the mixture was stirred at 90 °C for 24 h under a nitrogen atmosphere. The resulting mixture was cooled to room temperature, the solvent was removed by a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired target product.

Three representative examples are shown below.

2,5-Diphenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole (2a): Eluent: petroleum ether/ethyl acetate (5:1); isolated yield: 38 mg (63%); colorless film. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (d, $J = 7.2$ Hz, 2H), 7.52 (t, $J = 7.3$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.41–7.36 (m, 4H), 7.33–7.30 (m, 1H), 4.39 (d, $J = 4.9$ Hz, 1H), 4.22 (d, $J = 4.9$ Hz, 1H), 2.90 (dq, $J = 13.5$ Hz, $J = 10.2$ Hz, 2×1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 163.0$, 142.7, 131.8, 128.8, 128.6, 128.4, 128.1, 127.4, 125.0 (q, $J = 278.7$ Hz), 124.4, 84.8, 68.3, 44.3 (q, $J = 27.3$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -65.87$ (s, 3F); ESI-MS: $m/z = 306.6$ $[M+H]^+$.

5-(4-Chlorophenyl)-2-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole (2o): Eluent: petroleum ether/ethyl acetate (3:1); isolated yield: 48 mg (71%); colorless film. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (d, $J = 7.7$ Hz, 2H), 7.53 (t, $J = 7.0$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.38–7.33 (m, 4H), 4.36 (d, $J = 14.9$ Hz, 1H), 4.18 (d, $J = 14.8$ Hz, 1H), 2.88 (dq, $J = 11.1$ Hz, $J = 10.0$ Hz, 2×1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.9$, 141.0, 134.0, 132.0, 129.0, 128.6, 128.4, 127.1, 126.0, 124.8 (q, $J = 278.6$ Hz), 84.4, 68.4, 44.3 (q, $J = 27.3$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -62.19$ (s, 3F); ESI-MS: $m/z = 340.5$ $[M+H]^+$.

2-(Furan-2-yl)-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole (2s): Eluent: petroleum ether/ethyl acetate (5:1); isolated yield: 30 mg (68%); colorless film. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 3.3$ Hz, 1H), 7.47 (d, $J = 4.9$ Hz, 1H), 7.10–7.07 (m, 1H), 5.01–4.93 (m, 1H), 4.25 (dd, $J = 14.8$ Hz, $J = 9.9$ Hz, 1H), 3.78 (dd, $J = 14.8$ Hz, $J = 7.1$ Hz, 1H), 2.71–2.62 (m, 1H), 2.47–2.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.4$, 130.6, 130.2, 129.6, 127.6, 125.2 (q, $J = 277.0$ Hz), 73.6, 60.3, 39.3 (q, $J = 28.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -62.30$ (s, 3F); ESI-MS: $m/z = 220.2$ $[M+H]^+$.

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