

Note

Markovnikov-Selective Addition of Fluorous Solvents to Unactivated Olefins Using a Co Catalyst

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We developed an addition reaction of fluorous solvents to olefins using salen–cobalt (Co) complex, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, and 1,1,3,3-tetramethyldisiloxane. This reaction condition was found to activate olefins, which enabled them to be attacked by 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), both of which are electronically weak nucleophiles.

Key words hydroalkoxylation; cobalt (Co); fluorous solvent; olefin

Markovnikov-selective hydroalkoxylation of unactivated olefins is a fundamental process of ether formation in organic chemistry. Many research groups have investigated catalytic versions of this reaction to date.^{1–3} In 2013, we also reported a unique Markovnikov-selective hydroalkoxylation of unactivated olefins with a cobalt (Co) complex, silane, and *N*-fluoropyridinium salt (Chart 1). This reaction condition enabled unactivated olefins to connect with a wide range of alcoholic solvents, including methanol, ethanol, *i*-propanol, and *t*-butanol.^{4–6} Furthermore, detailed investigation of this reaction revealed excellent functional group tolerance. From the perspective of the mechanism, this catalysis involves both a putative carbon radical species and carbocationic species, and the formation of C–O bonds should occur between the cationic species and alcoholic solvent. Given this working hypothesis, we envisioned that poor nucleophilic fluorous alcoholic solvents would attack carbocationic species to produce hydroalkoxylated compounds. This reaction is of value in terms of the high demand for fluorinated molecules in the pharmaceutical and agrochemical industries. The incorporation of 2,2,2-trifluoroethanol (TFE), which is an extensively used solvent, into simple hydrocarbon alkenes has been previously reported; for example, Chapman reported addition of TFE to olefins using $\text{BF}_3 \cdot \text{Et}_2\text{O}$.⁷ Tokunaga and colleagues reported gold-catalyzed addition of TFE to 1-octene.⁸ Matsuoka *et al.* reported palladium-catalyzed addition of fluorous alcohol to hexafluoropropene.⁹ Photochemical addition of TFE has also reported.^{10–13} However, the yields and substrate scope reported in these results still remain to be improved. Herein, we report on incorporation of fluorous solvents into unactivated olefins using a Co(salen) complex, an *N*-fluoropyridinium salt, and a disiloxane reagent in good yields.

Results and Discussion

Based on the consideration, we initiated the optimization of the reaction conditions. As we expected, when 4-allyl-1,2-dimethoxybenzene (**2a**) was subjected to a catalytic amount of catalyst **1** in TFE in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($\text{Me}_3\text{NFPY} \cdot \text{BF}_4$) and 1,1,3,3-tetramethyldisiloxane $[(\text{Me}_2\text{SiH})_2\text{O}]$ under argon, desired product **3a** was obtained in 81% yield without anti-Markovnikov adducts (Table 1, entry 4). In the absence of catalyst **1**, *N*-fluoro-2,4,6-trimethylpyridinium salt, or $(\text{Me}_2\text{SiH})_2\text{O}$, no reaction

took place (entries 1–3). This result supported that **3a** was probably produced *via* the same reaction mechanism as that of our previous hydroalkoxylation reaction. The tetrafluoroborate anion of the *N*-fluoropyridinium salt was slightly better than the trifluoromethanesulfonate anion (OTf) in terms of yield (entries 4, 5). When TFE was replaced with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which has weaker nucleophilicity, using $\text{Me}_3\text{NFPY} \cdot \text{BF}_4$ gave a complex product mixture including the hydrogenated compound (33%) and hydrofluorinated compound¹⁴ (36%) without HFIP adduct **3a'** (Chart 2). On the other hand, in the case of $\text{Me}_3\text{NFPY} \cdot \text{OTf}$, desired product **3a'** was obtained in 12% yield together with some byproducts. To the best of our knowledge, this is the first example of hydroalkoxylation of unactivated olefins to afford the HFIP adduct.

Encouraged by this result, the scope of monosubstituted olefins was next investigated (Table 2). As expected, a fluoroanion-sensitive silyl ether (**3b**) and product containing an acid-sensitive acetal (**3c**) were successfully isolated in acceptable yields from phenylpropanoids (**2b**, **c**). *o*-Allylanisole (**2d**) also underwent addition reaction to afford the corresponding product (**3d**) together with a complex mixture of byproducts. In the case of styrene substrates (**2e–g**), electronically poor, neutral, and rich aromatic rings were applicable in this reaction, whereas methoxy-group-substituted styrene gave a complex product mixture. Geminally disubstituted olefin **4** gave corresponding product **5** in 63% yield together with recovered **4** (5%) and an isomer (10%, β, β' -dimethylstyrene, Chart 3).

In contrast to our previous results of hydroalkoxylation of unactivated olefins,⁴ the scope of this TFE addition reaction is rather limited. For example, homoallylanisole **6** gave recovered **6** and a complex mixture of byproducts without desired product **7**, whereas hydroalkoxylation using methanol or *t*-butanol took place efficiently according to our previous report⁴ (Chart 4). Long-chain substrate **8** also did not give desired product **9**, and resulted in recovery of **8** (26%) and a complex product mixture.

In summary, we developed an addition reaction of fluorous solvents to olefins using salen–Co complex **1**, $\text{Me}_3\text{NFPY} \cdot \text{BF}_4$, and $(\text{Me}_2\text{SiH})_2\text{O}$. This reaction condition was found to activate olefins, which enabled them to be attacked by TFE and HFIP, both of which are electronically weak nucleophiles. Phenylpropanoids and styrene substrates successfully gave TFE ad-

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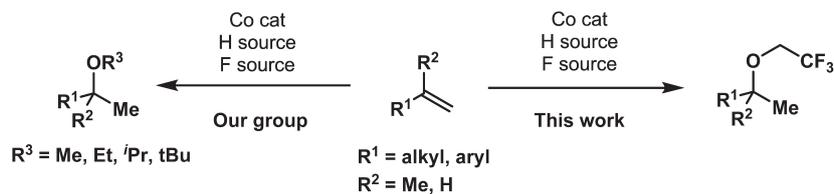


Chart 1. Our Previous Report and This Work of Hydroalkoxylation

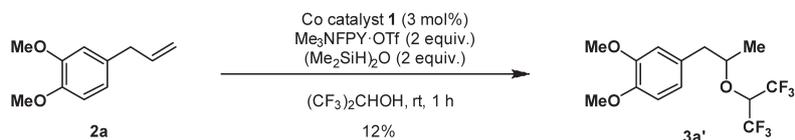


Chart 2. Cobalt-Catalyzed HFIP Addition to Unactivated Olefins

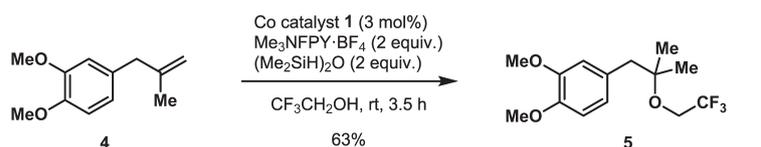


Chart 3. TFE Addition to Geminally Disubstituted Olefin

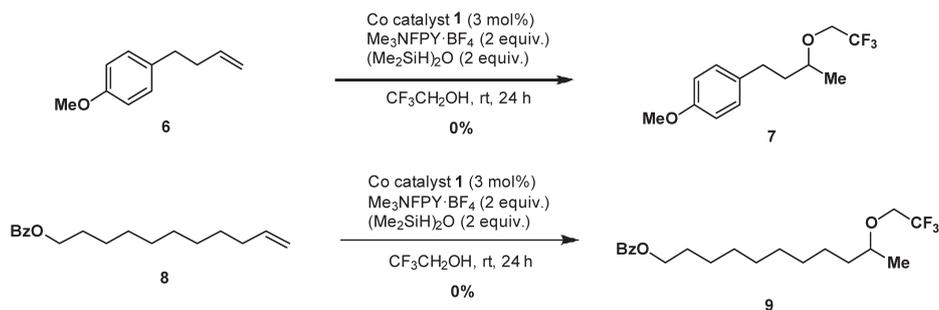
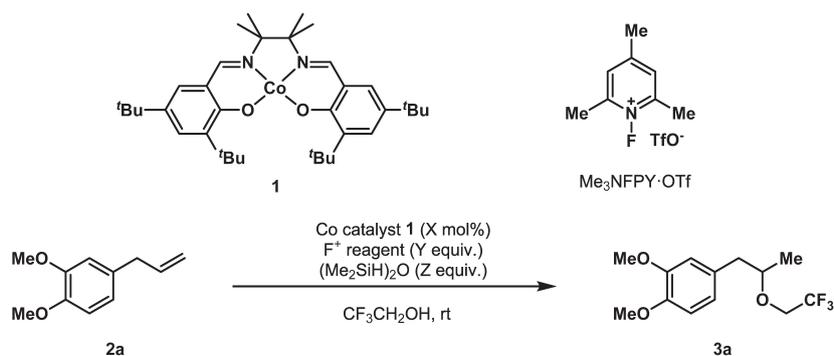
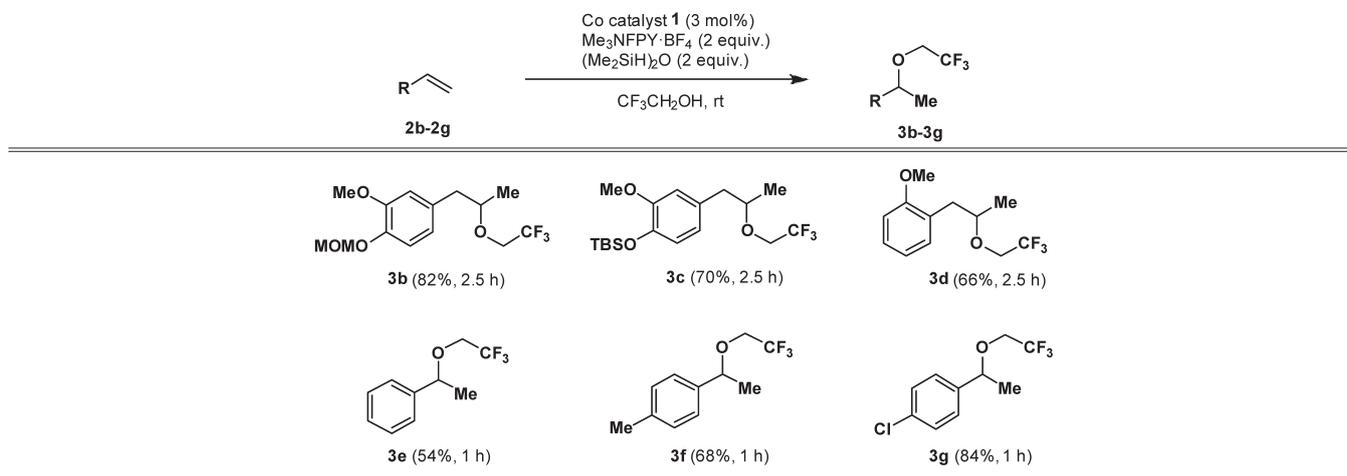


Chart 4. Unsuccessful Results of TFE Addition

Table 1. Optimization of Reaction Conditions^{a)}

Entry	Co catalyst (X mol%)	F^+ reagent (Y eq)	$(\text{Me}_2\text{SiH})_2\text{O}$ (Z eq)	Time (h)	Yield (%) ^{b)}
1	—	$\text{Me}_3\text{NFPY} \cdot \text{OTf}$ (2 eq)	2 eq	3.5	0
2	3 mol%	—	2 eq	3.5	0
3	3 mol%	$\text{Me}_3\text{NFPY} \cdot \text{OTf}$ (2 eq)	—	3.5	0
4	3 mol%	$\text{Me}_3\text{NFPY} \cdot \text{OTf}$ (2 eq)	2 eq	3.5	77
5	3 mol%	$\text{Me}_3\text{NFPY} \cdot \text{BF}_4$ (2 eq)	2 eq	3.5	81

^{a)} Conditions: **2a**, 0.25 mmol; **1**, 3 mol%; $\text{Me}_3\text{NFPY} \cdot \text{X}$, 2 eq; $(\text{Me}_2\text{SiH})_2\text{O}$, 2 eq; and $\text{CF}_3\text{CH}_2\text{OH}$, 0.10 M under Ar. ^{b)} Yield (%)=isolation yield.

Table 2. Substrate Scope of Olefins^{a)}

^{a)} Yield (%)=isolation yield.

ducts. This mild and neutral condition offers the advantage of functional group tolerance. For now, there is room to improve in terms of substrate scope. The results show that the stabilization of the carbocationic intermediate is required toward TFE addition. In the case of styrene substrates, the plausible benzyl cation species should be stabilized by the neighboring aromatic ring. In the case of phenylpropanoids, there is a non-classical interaction between the homobenzyl carbocationic species and aromatic ring.¹⁵⁾ On the other hand, loss of these contributions in substrates **6** or **8** is the reason for the failure of the desired reaction. Further investigation will focus on expanding the substrate scope and optimizing the reaction conditions.

Experimental

General All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated. Reactions were monitored by TLC carried out on Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde and ceric ammonium molybdate, and heat as developing agents. Kanto Chemical Silica gel 60N (spherical, neutral 0.040–0.050 mm) was used for flash column chromatography and Yamazen EPCLC-AI-580S. NMR spectra were recorded on JEOL ECX-400 and calibrated using residual undeuterated solvent as an internal reference (CHCl₃@7.26 ppm ¹H-NMR, 77.0 ppm ¹³C-NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sext=sextet, sept=septet, m=multiplet, br=broad. High-resolution (HR)-MS were recorded on JEOL AccuTOF. IR spectra were recorded on a JASCO FT/IR-4100. Melting points were recorded on a JASCO P-1020 melting point apparatus. Optical rotations were measured on a JASCO P-2000 digital polarimeter with a sodium lamp. **1**, **2c**, **4**, **6** and **8** are prepared according to a previously reported literature.⁴⁾ **2a**, **d-g** are commercially available and used as received.

General Procedure of Co-Catalyzed Hydrotrifluoroethoxylation of Olefins To a solution of **2a** (44.5 mg, 0.250 mmol, 1 eq) in 2,2,2-trifluoroethanol (1.5 mL) was added complex **1** (4.5 mg, 0.00750 mmol, 3 mol%) and *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (114 mg, 0.50 mmol, 2.0 eq), followed by another portion of 2,2,2-trifluoroethanol (1.0 mL). The solution was bubbled with Ar for 10 min, after which 1,1,3,3-tetramethyldisiloxane (0.088 mL, 0.50 mmol, 2.0 eq) was added over 30 s at 0°C under Ar. The resulting mixture was stirred at room temperature (rt.) and the reaction was monitored by TLC. After completion, the solvent was evaporated and the residue was purified by flash column chromatography to give **3a** (56.5 mg, 81%) as pale yellow oil.

Compound **3a**

Pale yellow oil, IR (attenuated total reflectance (ATR)) ν_{\max} =2636, 1515, 1263, 1138 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ : 6.71–6.80 (m, 3H), 3.861 (s, 3H), 3.854 (s, 3H), 3.68–3.80 (m, 3H), 2.83 (dd, 1H, *J*=14.0, 6.8 Hz), 2.65 (dd, 1H, *J*=13.6, 5.2 Hz), 1.19 (d, 3H, *J*=6.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ : 148.7, 147.6, 130.8, 124.0 (*J*=277 Hz), 121.3, 112.8, 111.1, 79.2, 66.6 (*J*=34.3 Hz), 55.8, 55.7, 42.6, 19.4; HR-MS [direct analysis in real time (DART)(+)] Calcd for C₁₃H₁₈F₃O₃ (M+H⁺): 279.1203. Found 279.1203.

Compound **3a'**

Pale yellow oil, IR (ATR) ν_{\max} =2939, 1516, 1191 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ : 6.79 (d, 1H, *J*=8.0 Hz), 6.70–6.73 (m, 2H), 4.10 (sept, 1H, *J*=6.0 Hz), 3.98 (sext, 1H, *J*=6.0 Hz), 3.87 (s, 6H), 2.92 (dd, 1H, *J*=13.6, 6.0 Hz), 2.72 (dd, 1H, *J*=13.6, 6.4 Hz), 1.21 (d, 3H, *J*=6.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ : 148.7, 147.7, 129.6, 121.5, 112.7, 111.0, 81.7, 74.3 (*J*=32.4 Hz), 55.8, 55.7, 42.4, 18.9; HR-MS [DART(+)] Calcd for C₁₄H₁₇F₆O₃ (M+H⁺): 347.1076. Found 347.1076.

Compound **3b**

Pale yellow oil, IR (ATR) ν_{\max} =2935, 1513, 1268, 1155 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ : 7.05 (d, 1H, *J*=8.0 Hz), 6.78 (d, 1H, *J*=1.6 Hz), 6.70 (dd, 1H, *J*=8.0, 1.6 Hz), 5.20 (s, 3H), 3.86 (s, 3H), 3.69–3.80 (m, 3H), 3.51 (s, 3H), 2.84 (dd, 1H, *J*=13.6, 6.8 Hz), 2.64 (dd, 1H, *J*=13.6, 5.6 Hz), 1.19 (d, 3H, *J*=6.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ : 149.5, 145.0, 132.5, 124.0 (*J*=277 Hz), 121.5, 116.3, 113.1, 95.6, 79.1, 66.5

($J=33.4$ Hz), 56.1, 55.7, 42.6, 19.4; HR-MS [DART(+)] Calcd for $C_{14}H_{23}F_3NO_4$ ($M+NH_4^+$): 326.1574. Found 326.1577.

Compound 3c

Pale yellow oil, IR (ATR) $\nu_{\max}=2932, 1513, 1278, 1157$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 6.77 (d, 1H, $J=8.0$ Hz), 6.72 (d, 1H, $J=1.6$ Hz), 6.63 (dd, 1H, $J=8.0, 1.6$ Hz), 3.79 (s, 3H), 3.65–3.74 (m, 3H), 2.81 (dd, 1H, $J=14.0, 7.2$ Hz), 2.62 (dd, 1H, $J=14.0, 5.6$ Hz), 1.19 (d, 3H, $J=6.4$ Hz), 1.00 (s, 9H), 0.15 (s, 6H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 150.7, 143.6, 131.7, 124.0 ($J=277$ Hz), 121.5, 120.7, 113.5, 79.4, 66.6 ($J=34.4$ Hz), 55.4, 42.8, 25.7, 19.6, 18.4, -4.72 ; HR-MS [DART(+)] Calcd for $C_{18}H_{30}F_3O_3Si$ ($M+H^+$): 379.1911. Found 379.1909.

Compound 3d

Pale yellow oil, IR (ATR) $\nu_{\max}=2934, 1495, 1278, 1245, 1157$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 7.22 (td, 1H, $J=8.0, 1.8$ Hz), 7.14 (dd, 1H, $J=8.0, 1.8$ Hz), 6.89 (t, 1H, $J=8.0$ Hz), 6.85 (d, 1H, $J=8.0$ Hz), 3.83 (s, 3H), 3.73–3.87 (m, 3H), 2.98 (dd, 1H, $J=13.0, 6.0$ Hz), 2.67 (dd, 1H, $J=13.0, 6.8$ Hz), 1.18 (d, 3H, $J=6.4$ Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 150.7, 143.6, 131.7, 124.0 ($J=277$ Hz), 121.5, 120.7, 113.5, 79.4, 66.6 ($J=34.4$ Hz), 55.4, 42.8, 25.7, 19.6, 18.4, -4.72 ; ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 157.4, 131.4, 127.8, 126.4, 124.1 ($J=278$ Hz), 120.4, 110.2, 77.8, 66.5 ($J=33.4$ Hz), 55.2, 37.5, 19.7; HR-MS [DART(+)] Calcd for $C_{12}H_{16}F_3O_2$ ($M+H^+$): 249.1097. Found 249.1101.

Compound 3e

Colorless oil, IR (ATR) $\nu_{\max}=2930, 1279, 1162$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 7.31–7.41 (m, 5H), 4.58 (q, 1H, $J=6.4$ Hz), 3.58–3.74 (m, 2H), 1.52 (d, 3H, $J=6.4$ Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 141.8, 128.7, 128.1, 126.2, 124.1 ($J=278$ Hz), 79.5, 65.7 ($J=33.3$ Hz), 23.8; HR-MS [DART(+)] Calcd for C_8H_9 [$M-CF_3CH_2O$] $^+$: 105.0699. Found 105.0700.

Compound 3f

Colorless oil, IR (ATR) $\nu_{\max}=2981, 1277, 1158$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 7.16–7.22 (m, 4H), 4.53 (q, 1H, $J=6.4$ Hz), 3.55–3.70 (m, 2H), 2.35 (s, 3H), 1.48 (d, 3H, $J=6.4$ Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 138.7, 137.9, 129.4, 126.3, 124.1 ($J=278$ Hz), 79.3, 65.6 ($J=33.4$ Hz), 23.8, 21.1; HR-MS [DART(+)] Calcd for C_9H_{11} [$M-CF_3CH_2O$] $^+$: 119.0855. Found 119.0859.

Compound 3g

Colorless oil, IR (ATR) $\nu_{\max}=2982, 1278, 1161$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 7.35 (d, 2H, $J=8.2$ Hz), 7.26 (d, 2H, $J=8.2$ Hz), 4.55 (q, 1H, $J=6.4$ Hz), 3.57–3.72 (m, 2H), 1.48 (d, 2H, $J=6.4$ Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 140.3, 133.8, 128.9, 127.6, 123.9 ($J=277$ Hz), 78.8, 77.2, 65.8

($J=34.3$ Hz), 23.7; HR-MS [DART(+)] Calcd for C_8H_8Cl [$M-CF_3CH_2O$] $^+$: 139.0309. Found 139.0312.

Compound 5

Pale yellow oil, IR (ATR) $\nu_{\max}=2937, 1515, 1267, 1148$ cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ : 6.83 (d, 1H, $J=2.0$ Hz), 6.77 (d, 1H, $J=7.8$ Hz), 6.70 (dd, 1H, $J=7.8, 2.0$ Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.75 (q, 2H, $J=8.4$ Hz), 2.75 (s, 2H), 1.17 (s, 6H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 148.3, 147.5, 130.1, 124.3 ($J=277$ Hz), 122.4, 113.7, 110.4, 60.5 ($J=34.4$ Hz), 55.8, 55.6, 47.1, 24.5; HR-MS [DART(+)] Calcd for $C_{12}H_{17}O_2$ [$M-CF_3CH_2O$] $^+$: 193.1223. Found 193.1225.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Material The online version of this article contains supplementary materials.

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