Article

Catalyzing the Hydrodefluorination of CF₃-Substituted Alkenes by PhSiH₃. H• Transfer from a Nickel Hydride

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ABSTRACT: The hydrodefluorination of CF₃-substituted alkenes can be catalyzed by a nickel(II) hydride bearing a pincer ligand. The catalyst loading can be as low as 1 mol%. *gem*-Difluoroalkenes containing a number of functional groups can be formed in good to excellent yields by a radical mechanism initiated by H• transfer from the nickel hydride. The relative reactivity of various substrates supports the proposed mechanism, as does a TEMPO trapping experiment.
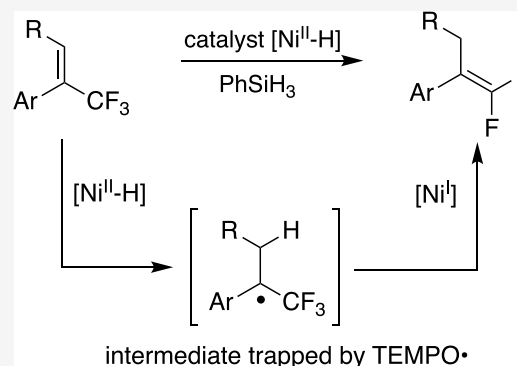
■ INTRODUCTION

Fluorine chemistry is gaining increasing attention because of the importance of fluorine-containing compounds in medicinal chemistry and agrochemistry.[1−6] Among fluorine-containing functional groups, *gem*-difluoroalkenes are intriguing, contained in a series of biologically active compounds,[7−10] and well established as a bioisostere of carbonyl compounds with increased metabolic stability and thus improved pharmaceutical performance.[11−14] In the case of artemisinin, the replacement of a carbonyl with a *gem*-difluoralkene gives enhanced antimalarial activity. In some cases, the *gem*-difluoroalkene moiety reverses the regioselectivity of enzyme-catalyzed hydride reduction (Figure 1). *gem*-Difluoroalkenes can also serve as versatile building blocks for the synthesis of other fluorine-containing molecules.[15−20]

The growing interest in the *gem*-difluoroalkene moiety has led to a number of strategies for its preparation (Scheme 1). The conventional approach relies on functional group interconversion, i.e., the difluoromethylenation of carbonyl or diazo compounds (Scheme 1a).[16,17] However, these functional group interconversion strategies typically involve highly reactive intermediates or harsh reaction conditions, limiting their substrate scope.

There are several ways in which *gem*-difluoroalkenes can be prepared from the readily available[21−25] trifluoromethyl-substituted alkenes. In one convergent approach, nucleophilic attack on a CF₃ can lead to fluoride loss, but an S_N2′ reaction with strong nucleophiles, such as Grignard reagents or organolithium reagents, will suffer from poor functional group tolerance (Scheme 1b). Recently, radical chemistry has been used for the synthesis of *gem*-difluoroalkenes, with defluorina-
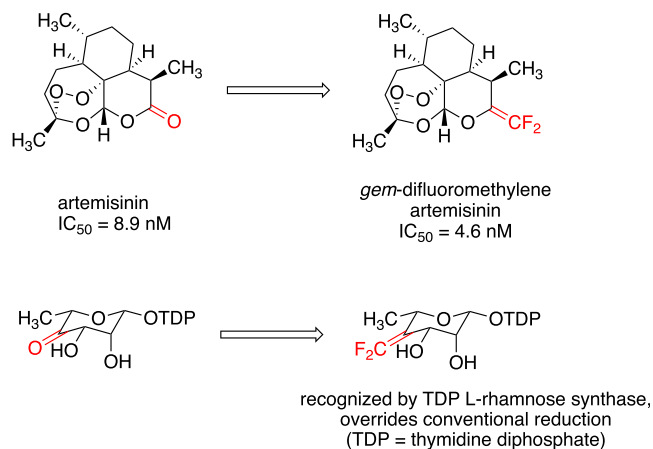

Figure 1. Representative applications of *gem*-difluoroalkenes.

tion of CF₃ by either photocatalysis or Ni catalysis (Scheme 1c,d).[26−36]

Typical Ni-catalyzed defluorinations of trifluoromethyl alkenes for the synthesis of *gem*-difluoroalkenes begin with single electron transfer from the nickel to an alkyl radical precursor. The resulting alkyl radical adds to another CF₃ alkene, producing a new radical which is then quenched by the formation of a Ni−C bond; β-F elimination gives the final

Scheme 1. Typical Synthetic Routes to *gem*-Difluoroalkenes

a. function group interconversion
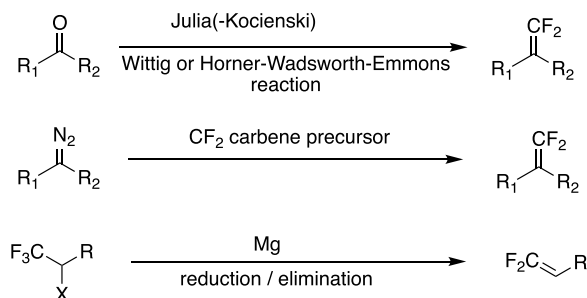
b. S$_N$2' type
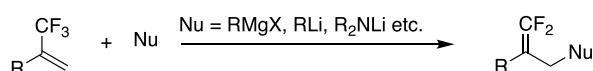
c. photocatalysis

d. Ni catalysis

Scheme 2. Hydrodefluorination by PhSiH$_3$ of α-CF$_3$ Styrene 2a by isoPmBox Ni(II)-H 1a in a Stoichiometric and a Catalytic Manner
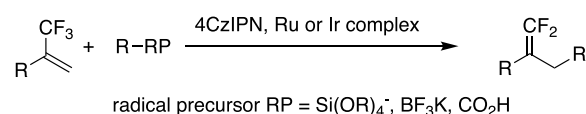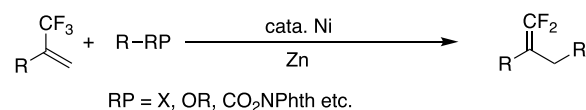

product. Other routes to functionalized *gem*-difluoroalkenes, such as alkenylation,[37] arylation,[38] and borylation,[39] have also been reported.

In general, C−F bond activation provides an easy approach to the synthesis of partially fluorinated compounds from readily available polyfluorinated species.[15,40,41] The simplest transformation of this sort, hydrodefluorination, has attracted much attention and features a unique mechanistic diversity.[42−45] However, most hydrodefluorination reactions promoted by transition metals are limited to aromatic or olefinic C−F bonds and show little selectivity among such bonds. The Hisaeda group has reported a (Co)B$_{12}$−TiO$_2$ hybrid catalyst for the photochemical hydrodefluorination of substituted α-CF$_3$ styrenes,[46] although a hydrogenation byproduct is always generated along with the *gem*-difluoroalkene. Zhang and co-workers reported a copper-catalyzed reductive defluorination of β-trifluoromethylated enones.[47] However, the use of Grignard reagents limited its functional group tolerance. Herein, we report that the iso-PmBox Ni(II) hydride 1a can catalyze the synthesis of *gem*-difluoroalkenes by the hydrodefluorination of trifluoromethyl-substituted alkenes with silanes.

■ RESULTS AND DISCUSSION

The iso-PmBox nickel hydride system 1a was developed by, and has been studied by, the Gade group.[48] It is well established that the Ni(II) hydride is in dynamic equilibrium with Ni(I) metalloradical. The Ni(I) can abstract halides from organic compounds and make Ni(II) halides, from which Ni(II)-H can be regenerated with silanes and boron hydrides.[49−52]

While investigating hydrogen atom transfer (HAT) from 1a, we found that it carried out the hydrodefluorination of α-CF$_3$ styrene 2a (Scheme 2). During that reaction, the characteristic
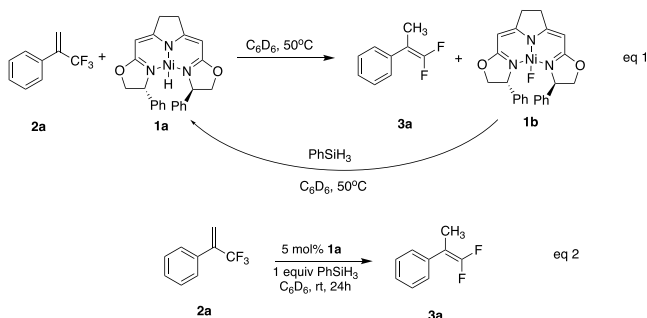
^{19}F NMR resonance of the Ni(II)-F complex 1b was observed at δ −444.3.[49] Moreover, the disappearance of 2a (a ^{19}F singlet at δ −64.50) was accompanied by the appearance of an ABX$_3$ pattern centered at δ −90.69 ($^2J_{F,F}$ = 44.1 Hz, $^4J_{H,F}$ = 3.3 Hz), belonging to the *gem*-difluoroalkene 3a. After the addition of PhSiH$_3$, the ^{19}F peak of 1b disappeared and the ^{1}H NMR peak of 1a reappeared. (Et$_3$SiH did not regenerate 1a.) Indeed, 1a was able to catalyze, in quantitative yield (as determined by ^{19}F NMR) at room temperature, the dehydrofluorination of 2a with a stoichiometric amount of PhSiH$_3$.

Table 1 displays the scope of our reaction. Various substituents, either electron-donating or electron-withdrawing, and different substitution patterns on the aromatic ring are well tolerated. All the substrates give yields ranging from good to near quantitative. No substantial amount of hydrogenation products was observed for any of the substrates, demonstrating a satisfying chemoselectivity. A thioether 3c, an ether 3d, a tertiary amine 3m, and the heteroaromatic rings in 3g and 3p remain intact. Even the acidic protons of an amide 3e or the carboxylic acid 3f do not interfere with the reaction. An exocyclic *gem*-difluoroalkene 3h, and the 2,2-difluorostyrene 3r, can be obtained from trisubstituted alkenes bearing a CF$_3$ substituent, although an elevated temperature is required. Interestingly, only the E isomer of the starting material 2r gives product, with elevated temperature and extended reaction time, while the Z isomer remains unreacted.[53] A monofluoroalkene 3i can be obtained from an alkene bearing a difluoromethyl substituent. Nitrile 3j, ester 3k, ketone 3n, and aldehyde 3o, which are not compatible with Wittig or Julia-type olefinations or with strong nucleophiles in S$_N$2'-type reactions, are all well tolerated by our method. Product 3l shows that our reaction can achieve chemoselective activation of the C−F bonds in trifluoromethyl alkenes without attacking an aryl fluoride C−F bond. Other radical stabilizing groups, like a carboalkoxy substituent, can also facilitate the reaction, as shown by the formation of product 3q. Unfortunately, the reaction does not work on CF$_3$ alkenes with aliphatic substituents, even at elevated temperatures—a result that is to be expected from the mechanism we propose below.

The control experiment in Table 2 (entry 2) shows that the nickel hydride 1a is required for the reaction. Attempts at replacing 1a with metal hydrides previously used in our lab (entry 3), such as HCpCr(CO)$_3$ and HV(CO)$_4$(dppe) (dppe = 1,2-bis(diphenylphosphino)ethane), have been unsuccessful,[54] so the reactivity of 1a is unique. The catalyst loading can be reduced (entry 4) to 1 mol% without diminishing the yield, although a longer reaction time is necessary. The number of equivalents of PhSiH$_3$ can be reduced without affecting the yield

Table 1. Substrate Scope of the Nickel-Hydride-Catalyzed Hydrodefluorination of Trifluoromethyl-Substituted Alkenes[a]

3a, 88%
3b, 91%
3c, 92%
3d, 92%
3e, 96%
3f, 82%
3g, 90%
3h, 75%[b]
3i, 77%[c] (E/Z = 2:1)
3j, 80%
3k, 90%
3l, 86%
3m, 86%
3n, 53%
3o, 50%
3p, 85%
3q, 85%
3r, 91%[d]

[a]Isolated yields, unless otherwise noted. [b]70 °C. [c]50 °C. [d]95 °C, 10 days, only from the *E* isomer of starting material. The yield is determined by ^{19}F NMR.

(entry 5), which suggests that all three silane hydrides can be used.

Two mechanisms for this reaction seem worth considering. One (shown in the top of Scheme 3) is similar to Gade's proposal for the hydrodefluorination (eq 3) of geminal difluorocyclopropanes.[49] The Ni(I) (complex **1c**) may abstract

eq 3
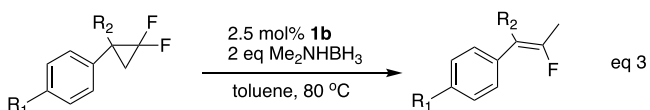
an F atom from the substrate **2a** to form the Ni(II) fluoride **1b** and the organic radical **4**; H• transfer from the Ni(II) hydride **1a**

Table 2. Control Experiments[a]

2a   5 mol% **1a** / 1 equiv PhSiH$_3$ / C$_6$D$_6$, rt, 24h   **3a**

entry	deviation from "standard conditions"	yield[b] (%)
1	none	>95
2	no **1a**	<5
3	20 mol% HCpCr(CO)$_3$ or 20 mol% HV(CO)$_4$(dppe) instead of **1a**	<5
4	1 mol% **1a**, 72 h	>95
5	0.4 equiv PhSiH$_3$	>95

[a]All reactions are performed on 0.5 mmol scale. [b]Determined by ^{19}F NMR.

Scheme 3. Two Possible Mechanisms Initiated by Fluorine Atom Abstraction and Hydrogen Atom Transfer, Respectively

Fluorine Atom Abstration Initiation
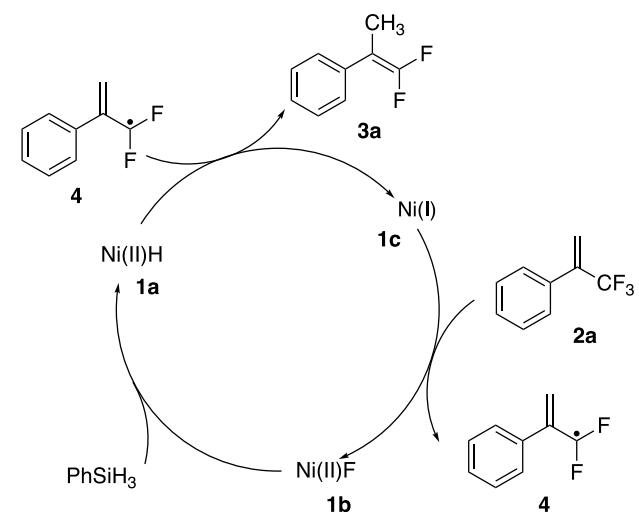
Hydrogen Atom Transfer Initiation

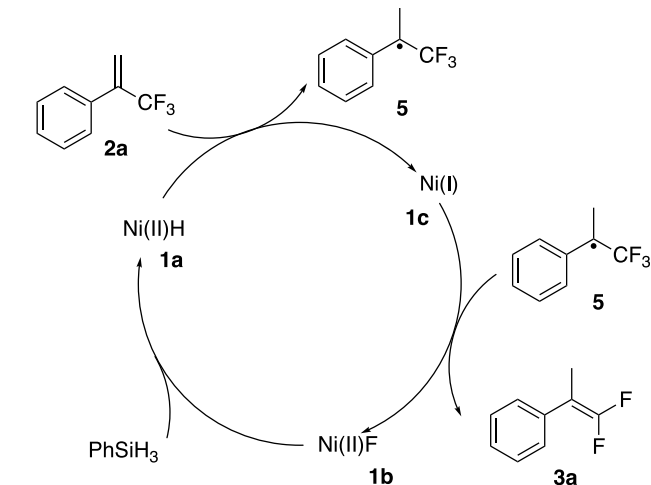will then give the product **3a** and regenerate **1c**, while the silane will reduce the fluoride **1b** back to the hydride **1a**. The other possible mechanism (shown at the bottom of Scheme 3) involves the sort of H• transfer to olefins that we have used to generate radicals for cyclization and isomerization.[55−58] Transfer to the methylene of **2a** from the hydride **1a** is expected,[59,60] generating the organic radical **5** while leaving the Ni(I) complex **1c**. Abstraction of an F atom from **5** by **1c** gives the product **3a** and yields the Ni fluoride **1b**,[61] which can be reduced by the silane back to **1a**.

The second mechanism is supported by several lines of evidence. First, it explains why aliphatic alkenes do not work (Scheme 4a), even at an elevated temperature. The aryl group is

Scheme 4. Evidence in Favor of HAT-Initiating Mechanism[a]
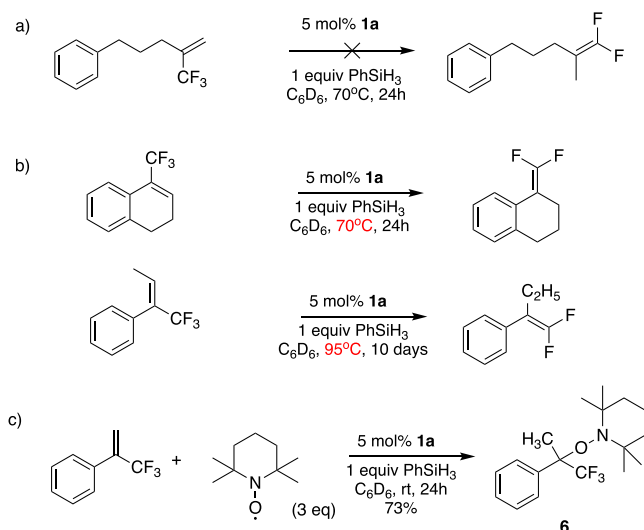
[a]The structure of **6** has been confirmed by single-crystal X-ray diffraction (Figure 2).

essential for stabilizing the organic radical resulting from HAT, given that CF$_3$ is a radical destabilizing group;[62,63] however, the fluorine atom abstraction in the first mechanism would not require an aryl substituent. Second, the slow reaction of trisubstituted alkenes (in Scheme 4b) is more easily explained by the second mechanism—using the established[60,64] effects of olefin substitution on the rate of HAT to an olefin from a metal hydride. A methyl substituent on the carbon receiving the H• (in the second mechanism) is known to slow HAT by about 3 orders of magnitude, while the rate of fluorine atom abstraction (in the first mechanism) should not change much with the extra substituent on carbon. Third, and the most conclusive, is the successful trapping of the radical **5** by TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; Scheme 4c). The addition of 3 equiv of TEMPO to the reaction results in the formation of the TEMPO adduct **6** (Figure 2) in 73% isolated yield.

CONCLUSION

gem-Difluoroalkenes with a variety of functional groups can be generated by the nickel-hydride-catalyzed hydrodefluorination of CF$_3$ alkenes. The reaction is initiated by H• transfer from Ni to the substrate. Trapping of the radical **5** with TEMPO demonstrates a new mechanism for the previously reported[48] NNN-pincer nickel(I/II) system.
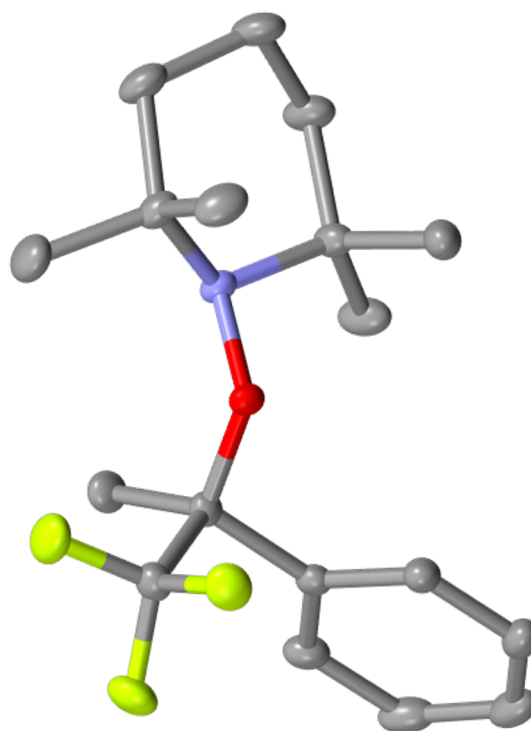

Figure 2. Molecular structure of TEMPO-adduct **6**. Hydrogen atoms are omitted for clarity.

EXPERIMENTAL SECTION

General Procedures. All manipulations were carried out in an inert atmosphere box (O$_2$ < 1 ppm) or under Ar by standard Schlenk techniques unless otherwise noted. Glassware was oven-dried or flame-dried prior to use. All commercial reagents were used as received without further purification unless specified. Deuterated benzene (C$_6$D$_6$) was distilled from molten potassium and benzophenone ketyl. Benzene (C$_6$H$_6$) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl. isoPmbox-Ni(II)-H **1a**,[48] CpCr-(CO)$_3$H,[65] HV(CO)$_4$(dppe),[66] and Co(dmgBF$_2$)$_2$(THF)$_2$[67] were synthesized according to the literature procedures and stored in an argon atmosphere glovebox (O$_2$ < 1 ppm). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded using a Bruker 500 Ascend, DRX 500, DRX 400, or DRX 300 spectrometer. Peaks are referenced relative to solvent residual peaks in benzene-d^6, THF-d^8, CD$_3$CN, and CDCl$_3$. The data are reported as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz). High-resolution mass spectra were acquired on a Waters XEVO G2-XS QToF mass spectrometer equipped with a UPC2 SFC inlet and a LockSpray source with one of three probes: electrospray ionization (ESI) probe, atmospheric pressure chemical ionization (APCI) probe, or atmospheric pressure solids analysis probe (ASAP). X-ray diffraction data were collected on a Bruker Apex II diffractometer. Crystal data, data collection and refinement parameters are summarized in Table S1. The structure was solved using direct methods and standard difference map techniques, and was refined by full-matrix least-squares procedures on F^2 with SHELXTL (Version 2013/4).[68−70]

General Procedure of NiH-Catalyzed Hydrodefluorination. In an inert atmosphere glovebox, CF$_3$ substituted alkenes (0.25 or 0.5 mmol), PhSiH$_3$ (1 equiv), and isoPmbox Ni(II)-H **1a** (0.05 equiv) were weighed in a glass vial and transferred to a J-Young tube using 1 mL of dry and degassed C$_6$D$_6$. The reaction was carried out at room temperature for 24 h unless otherwise noted. The crude reaction mixture was directly subjected to flash column chromatography for purification. Spectroscopic details of all the reaction products can be found in the Supporting Information.

Reaction with Other Metal Hydrides. In an inert atmosphere glovebox, (1,1-difluoroprop-1-en-2-yl)benzene **2a** (0.25 mmol), PhSiH$_3$ (0.25 mmol, 1 equiv), and HCpCr(CO)$_3$ (10 mg, 0.05 mmol, 0.2 equiv), Co(dmgBF$_2$)$_2$(THF)$_2$ (27 mg, 0.05 mmol, 0.2 equiv), or HV(CO)$_4$(dppe) (28 mg, 0.05 mmol, 0.2 equiv) were weighed in a glass vial and transferred to a J-Young tube using 1 mL of dry and degassed C$_6$D$_6$. The reaction was carried out at room temperature for 24 h. Crude ^{1}H NMR and ^{19}F NMR were taken directly or after silica plug.

TEMPO Trapping Experiment. In an inert atmosphere glovebox, (1,1-difluoroprop-1-en-2-yl)benzene **2a** (0.5 mmol), PhSiH$_3$ (0.5 mmol, 1 equiv), TEMPO (1.5 mmol, 3 equiv), and isoPmbox Ni(II)-H **1a** (0.025 mmol, 0.05 equiv) were weighed in a glass vial and transferred to a J-Young tube using 1 mL of dry and degassed C$_6$D$_6$. The reaction was carried out at room temperature for 144 h. The reaction conversion was 56%, 77%, and 89% at 3, 17, and 144 h, respectively. The crude reaction mixture was directly subjected to flash column chromatography for purification. Flash column chromatography was done using pure hexane. Product was obtained with 73% yield.

2,2,6,6-Tetramethyl-1-((1,1,1-trifluoro-2-phenylpropan-2-yl)oxy)piperidine (6). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.68–7.62 (m, 2H), 7.46–7.34 (m, 3H), 1.95 (q, *J* = 1.2 Hz, 3H), 1.69–1.50 (m, 3H), 1.47–1.41 (m, 2H), 1.29–1.36 (m, 7H), 1.13 (s, 3H), 0.43 (s, 3H). ^{19}F NMR (376 MHz, chloroform-*d*) δ −74.83. ^{13}C NMR (101 MHz, chloroform-*d*): δ 140.86, 128.27, 127.76, 127.68, 126.00 (q, *J* = 287.6 Hz), 82.54 (q, *J* = 26.4 Hz), 60.98, 60.26, 41.68, 41.56, 33.13, 33.08 (q, *J* = 4.1 Hz), 20.89, 20.80, 16.92, 16.35 (q, *J* = 1.7 Hz). HRMS-ASAP+ (*m/z*): calcd for C$_{18}$H$_{27}$F$_3$NO [M+H]$^+$: 330.2045, found: 330.2025.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13757.

Starting material preparation, NMR spectra of substrates and products, and 2D NMR characterization of compound **6** (PDF)

X-ray crystallographic data for **6** (CIF)

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Notes
The authors declare no competing financial interest.

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