HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2020 March 28.

Published in final edited form as:

J Am Chem Soc. 2020 March 11; 142(10): 4793–4799. doi:10.1021/jacs.9b13757.

Catalyzing the Hydrodefluorination of CF_3-Substituted Alkenes by $PhSiH_3$. $H^{\cdot}$ Transfer from a Nickel Hydride

Chengbo Yao,
Department of Chemistry, Columbia University, New York 10027, United States

Shuai Wang,
Department of Chemistry, Columbia University, New York 10027, United States

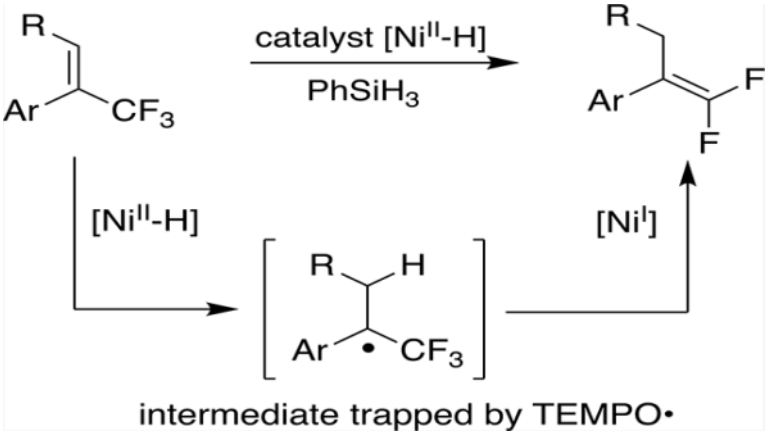
Jack Norton,
Department of Chemistry, Columbia University, New York 10027, United States

Matthew Hammond
Department of Chemistry, Columbia University, New York 10027, United States

Abstract

The hydrodefluorination of CF_3-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 $H^{\bullet}$ transfer from the nickel hydride. The relative reactivity of various substrates supports the proposed mechanism, as does a TEMPO trapping experiment.

Graphical Abstract



Corresponding Author: Jack Norton – Department of Chemistry, Columbia University, New York 10027, United States, jrn11@columbia.edu.

The authors declare no competing financial interest.

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)

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 CF_3 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 defluorination of CF_3 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 CF_3 alkene, producing a new radical which is then quenched by the formation of a Ni–C bond; β-F elimination gives the final 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]

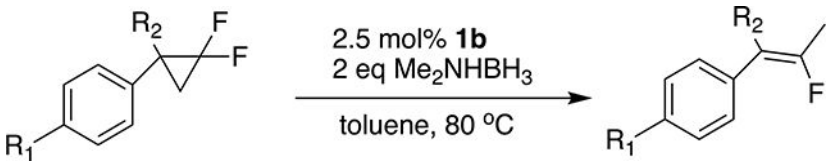
While investigating hydrogen atom transfer (HAT) from **1a**, we found that it carried out the hydrodefluorination of α-CF_3 styrene **2a** (Scheme 2). During that reaction, the characteristic ^{19}F NMR resonance of the Ni(II)-F complex **1b** was observed at δ −444.3.[49] Moreover, the disappearance 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 ^1H NMR peak of **1a** reappeared. (Et_3SiH 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_N2' -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 (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** 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 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.

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_6D_6) was distilled from molten potassium and benzophenone ketyl. Benzene (C_6D_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_3CN, 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_6D_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_6D_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_6D_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 $C_{18}H_{27}F_3NO$ $[M+H]^+$: 330.2045, found: 330.2025.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank Rebecca Wiles and Gary Molander for providing some of the CF_3 alkenes (**2b–2h** in Table 1). Lutz Gade and Chris Lorenc are acknowledged for helpful discussions. Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award R01GM124295.

REFERENCES

(1). Kirsch P Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications. Wiley-VCH: Weinhelm, Germany, 2004.

(2). Müller K; Faeh C; Diederich F Fluorine in Pharmaceuticals: Looking Beyond Intuition. Science 2007, 317 (5846), 1881. [PubMed: 17901324]

(3). Hagmann WK The Many Roles for Fluorine in Medicinal Chemistry. J. Med. Chem 2008, 51 (15), 4359–4369. [PubMed: 18570365]

(4). Purser S; Moore PR; Swallow S; Gouverneur V Fluorine in medicinal chemistry. Chem. Soc. Rev 2008, 37 (2), 320–330. [PubMed: 18197348]

(5). Zhou Y; Wang J; Gu Z; Wang S; Zhu W; Aceña JL; Soloshonok VA; Izawa K; Liu H Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. Chem. Rev 2016, 116 (2), 422–518. [PubMed: 26756377]

(6). Wang J; Sánchez-Roselló M; Aceña JL; del Pozo C; Sorochinsky AE; Fustero S; Soloshonok VA; Liu H Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). Chem. Rev 2014, 114 (4), 2432–2506. [PubMed: 24299176]

(7). Pan Y; Qiu J; Silverman RB Design, Synthesis, and Biological Activity of a Difluoro-Substituted, Conformationally Rigid Vigabatrin Analogue as a Potent γ-Aminobutyric Acid Aminotransferase Inhibitor. J. Med. Chem 2003, 46 (25), 5292–5293. [PubMed: 14640537]

(8). Altenburger J-M; Lassalle GY; Matrougui M; Galtier D; Jetha J-C; Bocskei Z; Berry CN; Lunven C; Lorrain J; Herault J-P; Schaeffer P; O'Connor SE; Herbert J-M SSR182289A, a selective and potent orally active thrombin inhibitor. Bioorg. Med. Chem 2004, 12 (7), 1713–1730. [PubMed: 15028263]

(9). Messaoudi S; Tréguier B; Hamze A; Provot O; Peyrat J-F; De Losada JR; Liu J-M; Bignon J; Wdzieczak-Bakala J; Thoret S; Dubois J; Brion J-D; Alami M Isocombretastatins A versus Combretastatins A: The Forgotten isoCA-4 Isomer as a Highly Promising Cytotoxic and Antitubulin Agent. J. Med. Chem 2009, 52 (14), 4538–4542. [PubMed: 19530698]

(10). Bobek M; Kavai I; De Clercq E Synthesis and biological activity of 5-(2,2-difluorovinyl)-2'-deoxyuridine. J. Med. Chem 1987, 30 (8), 1494–1497. [PubMed: 3039140]

(11). Meanwell NA Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. J. Med. Chem 2011, 54 (8), 2529–2591. [PubMed: 21413808]

(12). Magueur G; Crousse B; Ourévitch M; Bonnet-Delpon D; Bégué J-P Fluoro-artemisinins: When a gem-difluoroethylene replaces a carbonyl group. J. Fluorine Chem 2006, 127 (4), 637–642.

(13). Leriche C; He X; Chang C.-w. T.; Liu H.-w. Reversal of the Apparent Regiospecificity of NAD(P)H-Dependent Hydride Transfer: The Properties of the Difluoromethylene Group, A Carbonyl Mimic. J. Am. Chem. Soc 2003, 125 (21), 6348–6349. [PubMed: 12785757]

(14). Zhao Z; Liu H-w. Synthesis of a Deoxysugar Dinucleotide Containing an exo-Difluoromethylene Moiety As a Mechanistic Probe for Studying Enzymes Involved in Unusual Sugar Biosynthesis. J. Org. Chem 2001, 66 (20), 6810–6815. [PubMed: 11578241]

(15). Fujita T; Fuchibe K; Ichikawa J Transition-Metal-Mediated and -Catalyzed C–F Bond Activation by Fluorine Elimination. Angew. Chem., Int. Ed 2019, 58 (2), 390–402.

(16). Zhang X; Cao S Recent advances in the synthesis and CF functionalization of gem-difluoroalkenes. Tetrahedron Lett. 2017, 58 (5), 375–392.

(17). Chelucci G Synthesis and Metal-Catalyzed Reactions of gem-Dihalovinyl Systems. Chem. Rev 2012, 112 (3), 1344–1462. [PubMed: 22085400]

(18). Hu J; Han X; Yuan Y; Shi Z Stereoselective Synthesis of Z Fluoroalkenes through Copper-Catalyzed Hydrodefluorination of gem-Difluoroalkenes with Water. Angew. Chem., Int. Ed 2017, 56 (43), 13342–13346.

(19). Hu J; Zhao Y; Shi Z Highly tunable multi-borylation of gem-difluoroalkenes via copper catalysis. Nat. Catal 2018, 1 (11), 860–869.

(20). Yoo W-J; Kondo J; Rodríguez-Santamaría JA; Nguyen TVQ; Kobayashi S Efficient Synthesis of α-Trifluoromethyl Carboxylic Acids and Esters through Fluorocarboxylation of gem-Difluoroalkenes. Angew. Chem., Int. Ed 2019, 58 (20), 6772–6775.

(21). Hamlin TA; Kelly CB; Cywar RM; Leadbeater NE Methylenation of Perfluoroalkyl Ketones using a Peterson Olefination Approach. J. Org. Chem 2014, 79 (3), 1145–1155. [PubMed: 24410210]

(22). Jiang B; Xu Y Trifluoroisopropenylzinc reagent as a useful α-(trifluoromethyl)ethenyl carbanion synthetic equivalent. Preparation and palladium-catalyzed coupling with aryl halides. J. Org. Chem 1991, 56 (26), 7336–7340.

(23). Kobayashi O; Uraguchi D; Yamakawa T Synthesis of α-trifluoromethylstyrene derivatives via Ni-catalyzed cross-coupling of 2-bromo-3,3,3-trifluoropropene and aryl Grignard reagents. J. Fluorine Chem 2009, 130 (6), 591–594.

(24). Phelan JP; Wiles RJ; Lang SB; Kelly CB; Molander GA Rapid access to diverse, trifluoromethyl-substituted alkenes using complementary strategies. Chem. Sci 2018, 9 (12), 3215–3220. [PubMed: 29732105]

(25). Trost BM; Debien L Palladium-Catalyzed Trimethylene-methane Cycloaddition of Olefins Activated by the σ-Electron-Withdrawing Trifluoromethyl Group. J. Am. Chem. Soc 2015, 137 (36), 11606–11609. [PubMed: 26291872]

(26). Lang SB; Wiles RJ; Kelly CB; Molander GA Photoredox Generation of Carbon-Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. Angew. Chem. Int. Ed 2017, 56 (47), 15073–15077.

(27). Phelan JP; Lang SB; Sim J; Berritt S; Peat AJ; Billings K; Fan L; Molander GA Open-Air Alkylation Reactions in Photoredox-Catalyzed DNA-Encoded Library Synthesis. J. Am. Chem. Soc 2019, 141 (8), 3723–3732. [PubMed: 30753065]

(28). He Y; Anand D; Sun Z; Zhou L Visible-Light-Promoted Redox Neutral γ,γ-Difluoroallylation of Cycloketone Oxime Ethers with Trifluoromethyl Alkenes via C–C and C–F Bond Cleavage. Org. Lett 2019, 21 (10), 3769–3773. [PubMed: 31063391]

(29). Xia P-J; Ye Z-P; Hu Y-Z; Song D; Xiang H-Y; Chen X-Q; Yang H Photocatalytic, Phosphoranyl Radical-Mediated N–O Cleavage of Strained Cycloketone Oximes. Org. Lett 2019, 21 (8), 2658–2662. [PubMed: 30942601]

(30). Ding D; Lan Y; Lin Z; Wang C Synthesis of gem-Difluoroalkenes by Merging Ni-Catalyzed C–F and C–C Bond Activation in Cross-Electrophile Coupling. Org. Lett 2019, 21 (8), 2723–2730. [PubMed: 30924666]

(31). Lu X; Wang X-X; Gong T-J; Pi J-J; He S-J; Fu Y Nickel-catalyzed allylic defluorinative alkylation of trifluoromethyl alkenes with reductive decarboxylation of redox-active esters. Chem. Sci 2019, 10 (3), 809–814. [PubMed: 30774875]

(32). Lin Z; Lan Y; Wang C Synthesis of gem-Difluoroalkenes via Nickel-Catalyzed Reductive C–F and C–O Bond Cleavage. ACS Catal. 2019, 9 (1), 775–780.

(33). Lan Y; Yang F; Wang C Synthesis of gem-Difluoroalkenes via Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Coupling. ACS Catal. 2018, 8 (10), 9245–9251.

(34). Xiao T; Li L; Zhou L Synthesis of Functionalized gem-Difluoroalkenes via a Photocatalytic Decarboxylative/Defluorinative Reaction. J. Org. Chem. 2016, 81 (17), 7908–7916. [PubMed: 27467781]

(35). Chen H; Anand D; Zhou L Photoredox Defluorinative Alkylation of 1-Trifluoromethyl Alkenes and 1,3-Butadienes with 1,4-Dihydropyridines as Alkylation Reagents. Asian J. Org. Chem 2019, 8 (5), 661–664.

(36). Wiles RJ; Phelan JP; Molander GA Metal-free defluorinative arylation of trifluoromethyl alkenes via photoredox catalysis. Chem. Commun 2019, 55 (53), 7599–7602.

(37). Ichitsuka T; Fujita T; Ichikawa J Nickel-Catalyzed Allylic C(sp3)–F Bond Activation of Trifluoromethyl Groups via β-Fluorine Elimination: Synthesis of Difluoro-1,4-dienes. ACS Catal. 2015, 5 (10), 5947–5950.

(38). Huang Y; Hayashi T Rhodium-Catalyzed Asymmetric Arylation/Defluorination of 1-(Trifluoromethyl)alkenes Forming Enantioenriched 1,1-Difluoroalkenes. J. Am. Chem. Soc 2016, 138 (38), 12340–12343. [PubMed: 27627581]

(39). Liu Y; Zhou Y; Zhao Y; Qu J Synthesis of gem-Difluoroallylboronates via FeCl2-Catalyzed Boration/β-Fluorine Elimination of Trifluoromethyl Alkenes. Org. Lett 2017, 19 (4), 946–949. [PubMed: 28139930]

(40). Ahrens T; Kohlmann J; Ahrens M; Braun T Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation To Access Fluorinated Building Blocks. Chem. Rev 2015, 115 (2), 931–972. [PubMed: 25347593]

(41). Amii H; Uneyama K C–F Bond Activation in Organic Synthesis. Chem. Rev 2009, 109 (5), 2119–2183. [PubMed: 19331346]

(42). Whittlesey MK; Peris E Catalytic Hydrodefluorination with Late Transition Metal Complexes. ACS Catal. 2014, 4 (9), 3152–3159.

(43). Kuehnel MF; Lentz D; Braun T Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated Hydrodefluorination Reactions. Angew. Chem. Int. Ed 2013, 52 (12), 3328–3348.

(44). Hu J-Y; Zhang J-L, Hydrodefluorination Reactions Catalyzed by Transition-Metal Complexes. In Organometallic Fluorine Chemistry, Braun T, Hughes RP, Eds.; Springer International Publishing: Cham, 2015; pp 143–196.

(45). Andrella NO; Xu N; Gabidullin BM; Ehm C; Baker RT Selective Copper Complex-Catalyzed Hydrodefluorination of Fluoroalkenes and Allyl Fluorides: A Tale of Two Mechanisms. J. Am. Chem. Soc 2019, 141 (29), 11506–11521. [PubMed: 31305996]

(46). Tian H; Shimakoshi H; Imamura K; Shiota Y; Yoshizawa K; Hisaeda Y Photocatalytic alkene reduction by a B_{12}–TiO_2 hybrid catalyst coupled with C–F bond cleavage for gem-difluoroolefin synthesis. Chem. Commun 2017, 53 (68), 9478–9481.

(47). Wu X; Xie F; Gridnev ID; Zhang W A Copper-Catalyzed Reductive Defluorination of β-Trifluoromethylated Enones via Oxidative Homocoupling of Grignard Reagents. Org. Lett 2018, 20 (6), 1638–1642. [PubMed: 29513540]

(48). Rettenmeier C; Wadepohl H; Gade LH Stereoselective Hydrodehalogenation via a Radical-Based Mechanism Involving T-Shaped Chiral Nickel(I) Pincer Complexes. Chem. - Eur. J 2014, 20 (31), 9657–9665. [PubMed: 25042356]

(49). Wenz J; Rettenmeier CA; Wadepohl H; Gade LH Catalytic C–F bond activation of geminal difluorocyclopropanes by nickel(I) complexes via a radical mechanism. Chem. Commun 2016, 52 (1), 202–205.

(50). Rettenmeier CA; Wenz J; Wadepohl H; Gade LH Activation of Aryl Halides by Nickel(I) Pincer Complexes: Reaction Pathways of Stoichiometric and Catalytic Dehalogenations. Inorg. Chem 2016, 55 (16), 8214–8224. [PubMed: 27483018]

(51). Wenz J; Kochan A; Wadepohl H; Gade LH A Readily Accessible Chiral NNN Pincer Ligand with a Pyrrole Backbone and Its Ni(II) Chemistry: Syntheses, Structural Chemistry, and Bond Activations. Inorg. Chem 2017, 56 (6), 3631–3643. [PubMed: 28276677]

(52). Wenz J; Wadepohl H; Gade LH Regioselective hydrosilylation of epoxides catalysed by nickel(II) hydrido complexes. Chem. Commun. 2017, 53 (31), 4308–4311.

(53). This difference in reactivity is probably due to a steric effect on the initial HAT step (see the mechanism we propose in the bottom half of Scheme 3).

(54). When substrate 2a is treated with 20 mol% CpCr(CO)3H at 70 °C for 24 h, the hydrogenation product is obtained in 23% yield; no hydrodefluorination product is observed. The difference in results between CpCr(CO)3H and 1a is probably due to steric effects: the Ni complex 1a has a bulky ligand environment and thus cannot transfer a second hydrogen atom to 5. In contrast, CpCr(CO)3H is able to transfer a second hydrogen atom to give the hydrogenation product. The bulkiness of the Ni hydride 1a is also demonstrated by the HAT experiments in footnote 59.

(55). Li G; Kuo JL; Han A; Abuyuan JM; Young LC; Norton JR; Palmer JH Radical Isomerization and Cycloisomerization Initiated by $H^{\bullet}$ Transfer. J. Am. Chem. Soc 2016, 138 (24), 7698–7704. [PubMed: 27167594]

(56). Kuo JL; Hartung J; Han A; Norton JR Direct Generation of Oxygen-Stabilized Radicals by $H^{\bullet}$ Transfer from Transition Metal Hydrides. J. Am. Chem. Soc 2015, 137 (3), 1036–1039. [PubMed: 25569214]

(57). Kuo JL; Lorenc C; Abuyuan JM; Norton JR Catalysis of Radical Cyclizations from Alkyl Iodides under H2: Evidence for Electron Transfer from [CpV(CO)3H]−. J. Am. Chem. Soc 2018, 140 (13), 4512–4516. [PubMed: 29543448]

(58). Hartung J; Pulling ME; Smith DM; Yang DX; Norton JR Initiating radical cyclizations by H transfer from transition metals. Tetrahedron 2008, 64 (52), 11822–11830.

(59). Compound 1a is able to catalyze the hydrogenation of styrene or methyl methacrylate in C6D6 at 60 °C under 70 psig H2. H/D exchange is observed when α-methylstyrene is treated with 1a under 70 psig D2.

(60). Choi J; Tang L; Norton JR Kinetics of Hydrogen Atom Transfer from (η5-C5H5)Cr(CO)3H to Various Olefins: Influence of Olefin Structure. J. Am. Chem. Soc 2007, 129 (1), 234–240. [PubMed: 17199304]

(61). At this stage we are not sure if the Ni(I) metalloradical 1c recombines with the carbon-centered radical and then undergoes β-fluorine elimination.

(62). Henry DJ; Parkinson CJ; Mayer PM; Radom L Bond Dissociation Energies and Radical Stabilization Energies Associated with Substituted Methyl Radicals. J. Phys. Chem. A 2001, 105 (27), 6750–6756.

(63). Hioe J; Zipse H Radical Stability—Thermochemical Aspects. Encyclopedia of Radicals in Chemistry, Biology and Materials; Wiley, 2012 DOI: 10.1002/9781119953678.rad012.

(64). Estes DP; Norton JR; Jockusch S; Sattler W Mechanisms by which Alkynes React with CpCr(CO)3H. Application to Radical Cyclization. J. Am. Chem. Soc 2012, 134 (37), 15512–15518. [PubMed: 22900920]

(65). Yao C; Dahmen T; Gansäuer A; Norton JAnti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis. Science 2019, 364 (6442), 764–767. [PubMed: 31123133]

(66). Choi J; Pulling ME; Smith DM; Norton JR Unusually Weak Metal–Hydrogen Bonds in HV(CO)4(P–P) and Their Effectiveness as $H^{\bullet}$ Donors. J. Am. Chem. Soc 2008, 130 (13), 4250–4252. [PubMed: 18335937]

(67). Estes DP; Grills DC; Norton JR The Reaction of Cobaloximes with Hydrogen: Products and Thermodynamics. J. Am. Chem. Soc 2014, 136 (50), 17362–17365. [PubMed: 25427140]

(68). Sheldrick GM A short history of SHELX. Acta Crystallogr., Sect. A: Found. Crystallogr 2008, 64, 112–122.

(69). Sheldrick GM SHELXTL, An Integrated System for Solving, Refining, and Displaying Crystal Structures from Diffraction Data; University of Göttingen: Göttingen, Federal Republic of Germany, 1981.

(70). Sheldrick GM Crystal structure refinement with SHELXL. Acta Crystallogr., Sect. C: Struct. Chem 2015, 71 (1), 3–8. [PubMed: 25567568]

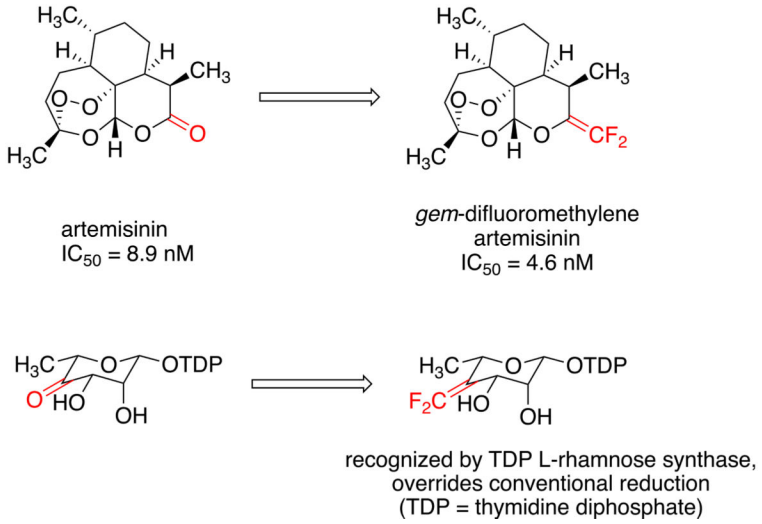


Figure 1.
Representative applications of *gem*-difluoroalkenes.

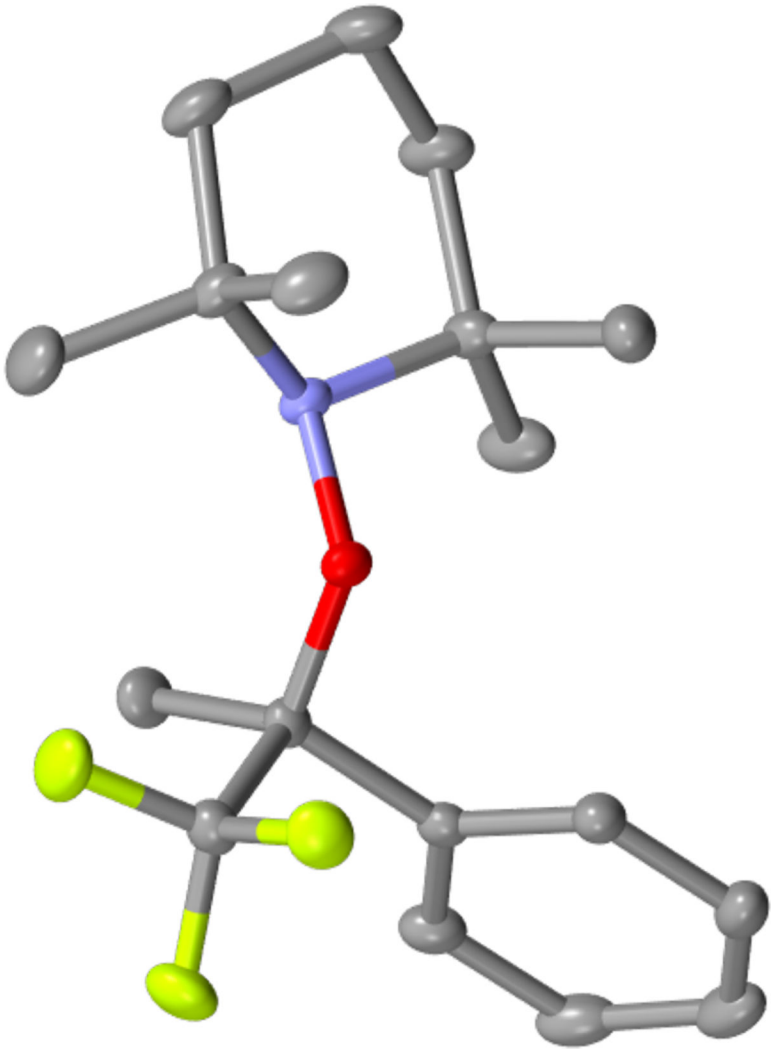
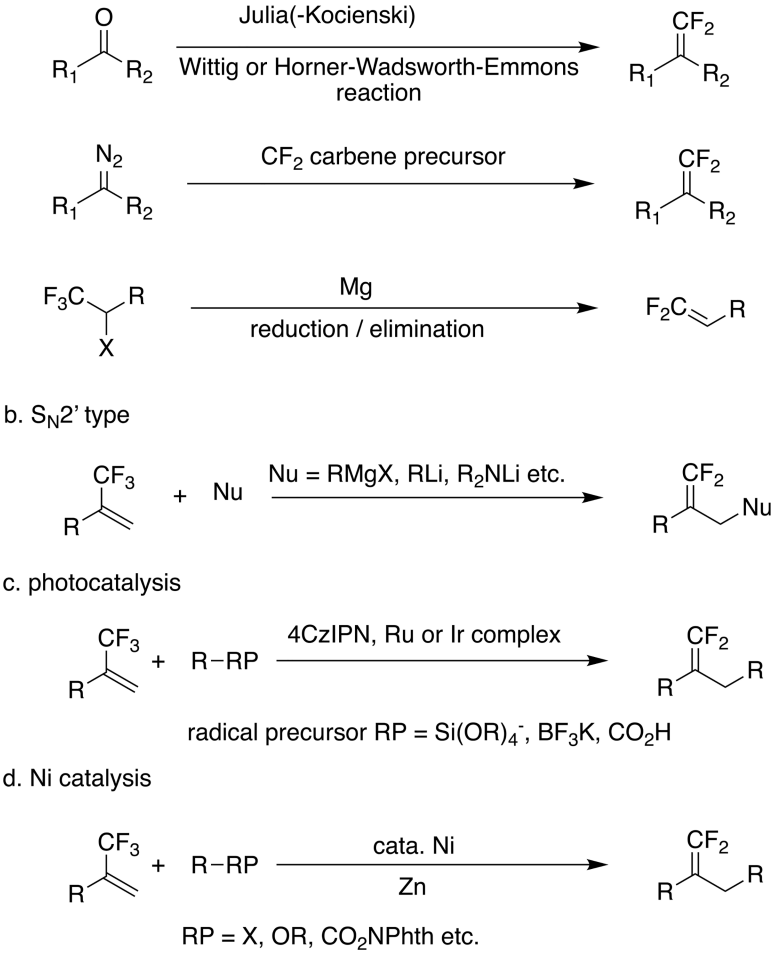
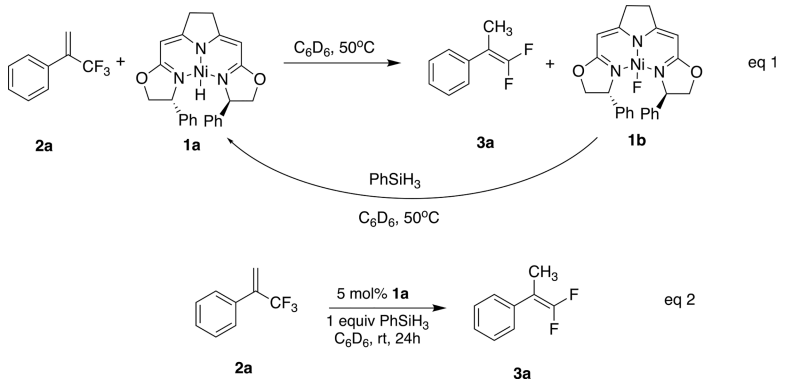


Figure 2.
Molecular structure of TEMPO-adduct **6**. Hydrogen atoms are omitted for clarity.



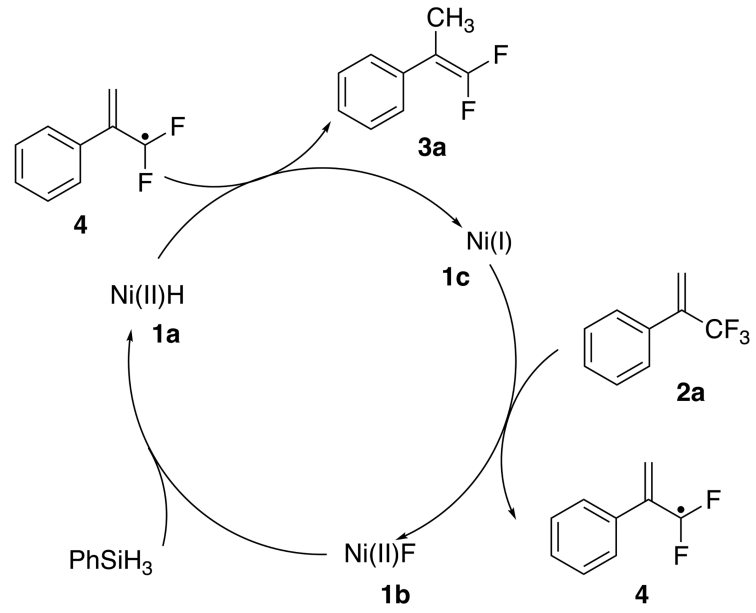
Scheme 1.

Typical Synthetic Routes to *gem*-Difluoroalkenes

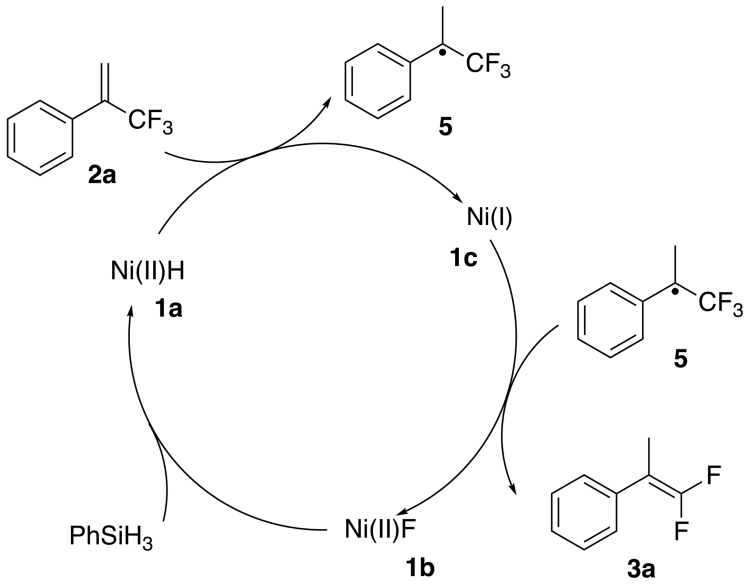


Scheme 2.

Hydrodefluorination by $PhSiH_3$ of α-CF_3 Styrene 2a by isoPmBox Ni(II)-H 1a in a Stoichiometric and a Catalytic Manner

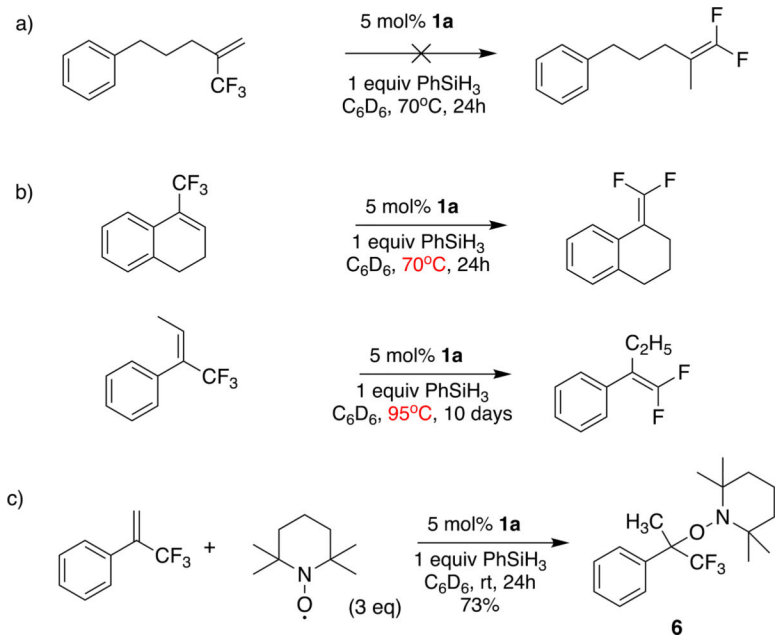


Hydrogen Atom Transfer Initiation



Scheme 3.

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

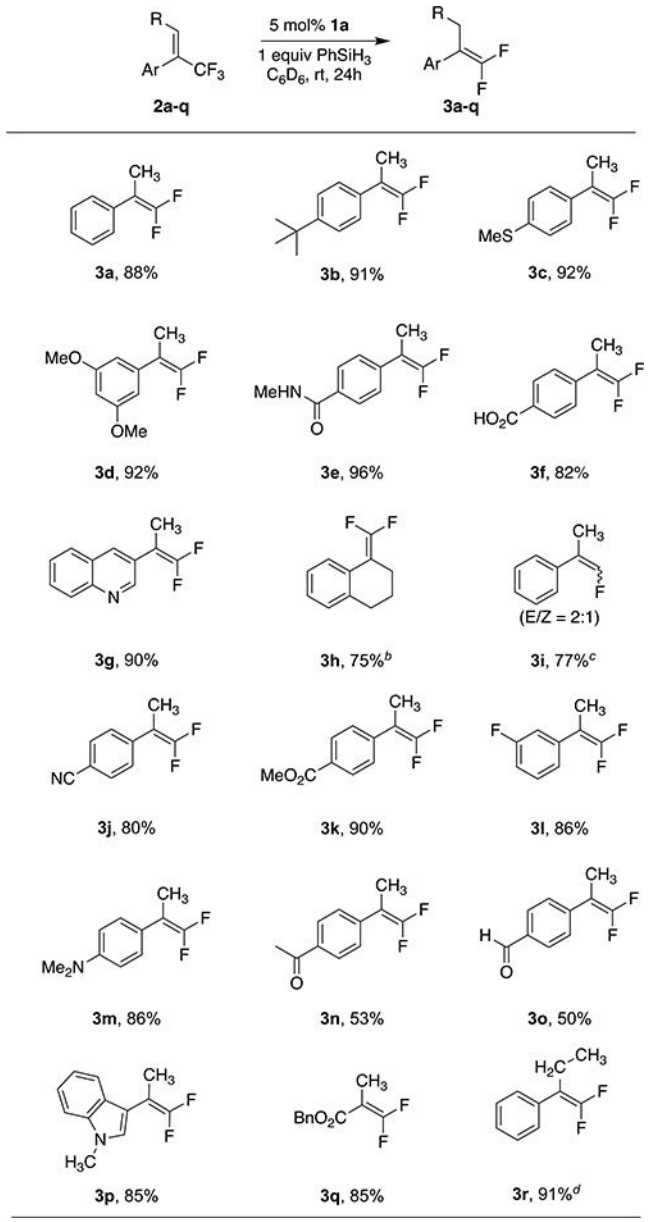


Scheme 4. Evidence in Favor of HAT-Initiating Mechanism[a]

[a]The structure of **6** has been confirmed by single-crystal X-ray diffraction (Figure 2).

Table 1.

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



[a]Isolated yields, unless otherwise noted.

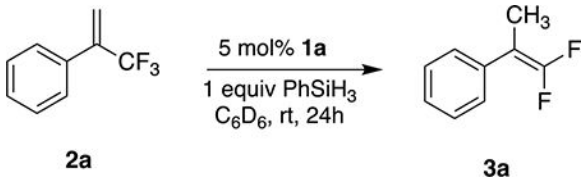
[b]70 °C.

[c]50 °C.

[d]95 °C, 10 days, only from the *E* isomer of starting material. The yield is determined by ^{19}F NMR.

Table 2.

Control Experiments[a]



2a **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.