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Article

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

Chengbo Yao, Shuai Wang, Jack R. Norton, and Matthew Hammond

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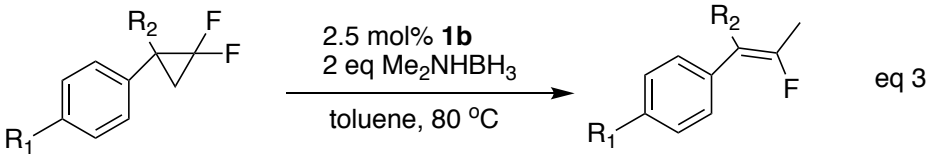
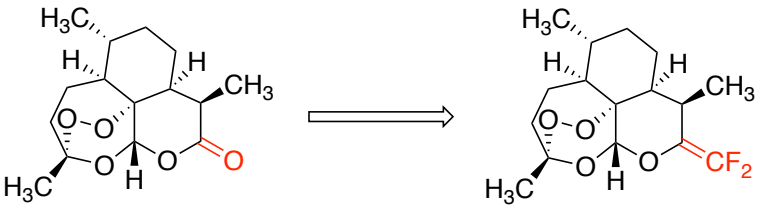
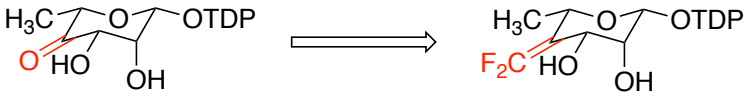


eq 3

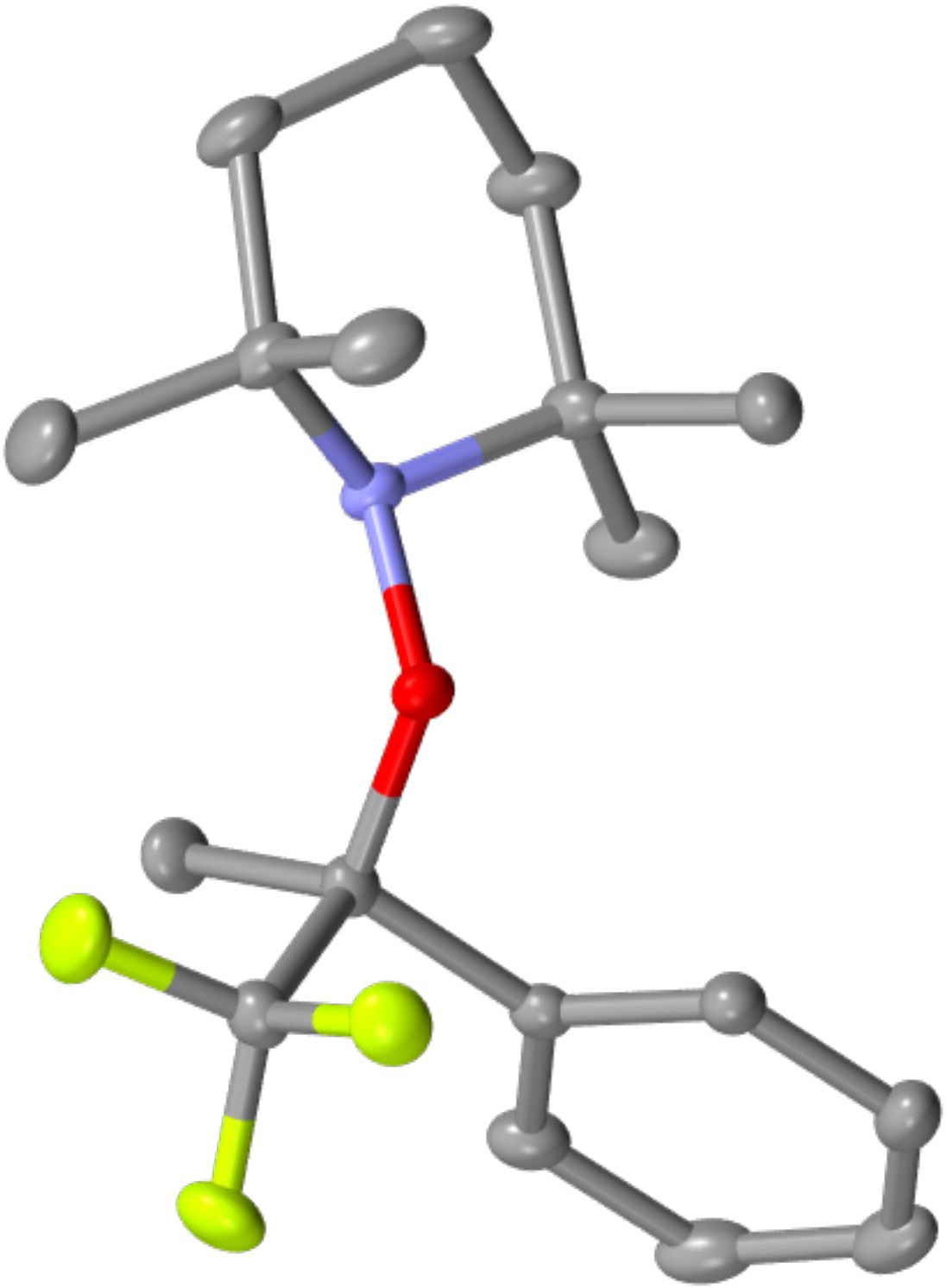


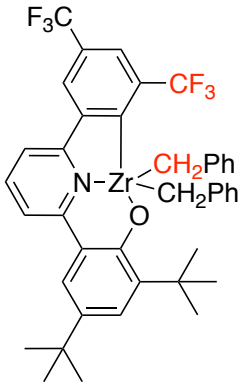
artemisinin
IC_{50} = 8.9 nM

gem-difluoromethylene
artemisinin
IC_{50} = 4.6 nM

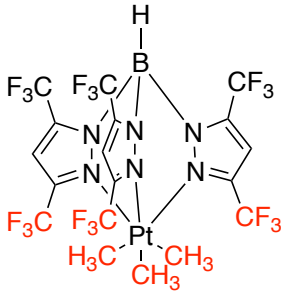


recognized by TDP L-rhamnose synthase,
overrides conventional reduction
(TDP = thymidine diphosphate)



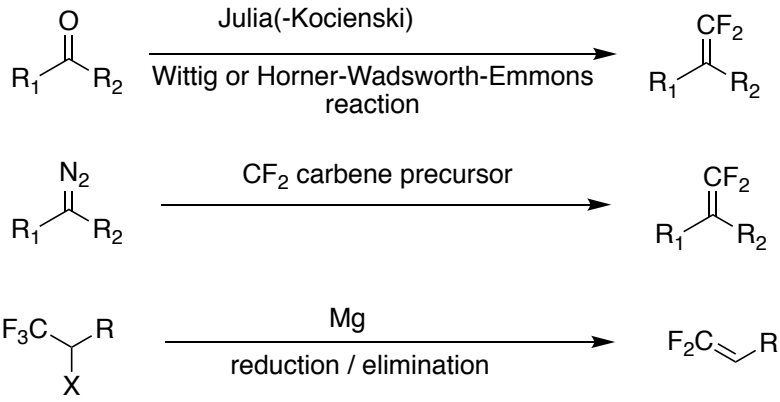

F3C
CF3
N
Zr
CH2Ph
CH2Ph
O

7

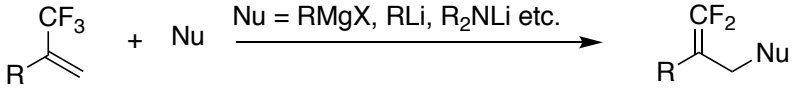

H
B
F3C
F3C
CF3
N
N
N
N
N
N
F3C
F3C
CF3
Pt
H3C
CH3
CH3

8

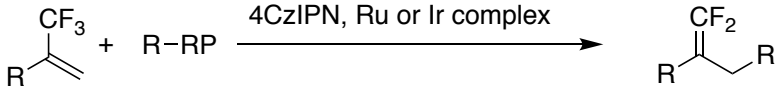
a. function group interconversion



b. S_N2' type

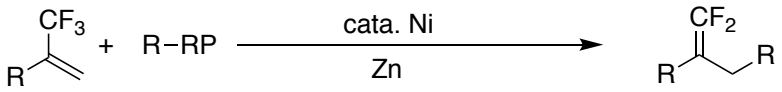


c. photocatalysis

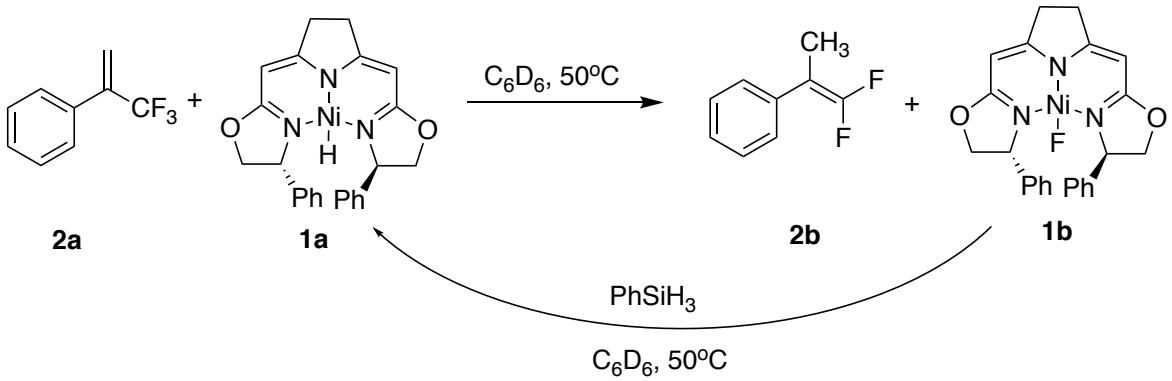


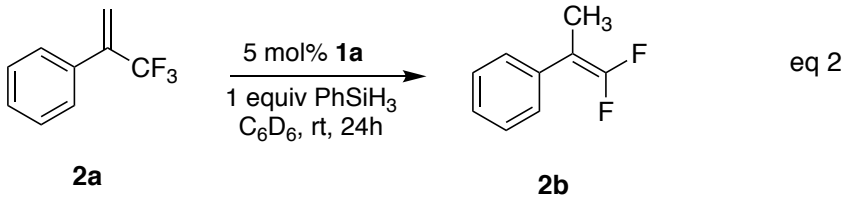
radical precursor RP = $Si(OR)_4^-$, BF_3K, CO_2H

d. Ni catalysis

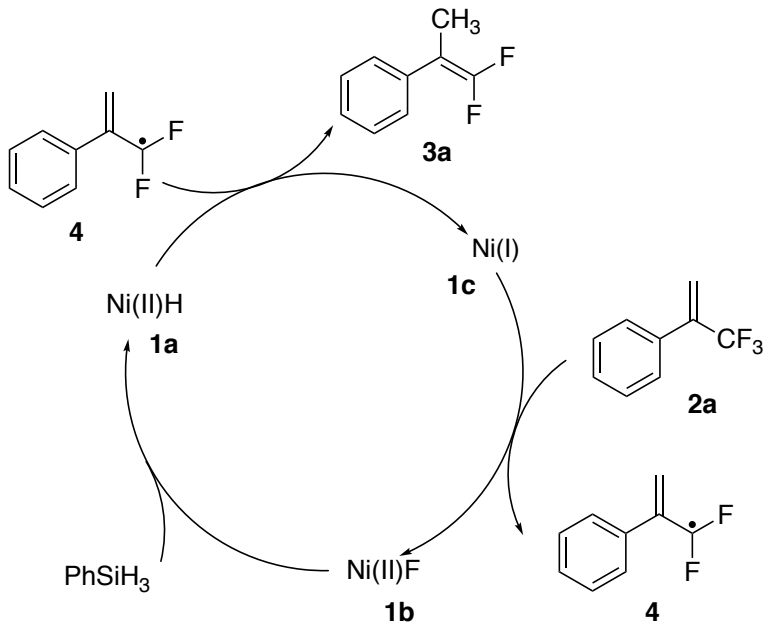


RP = X, OR, CO_2NPhth etc.

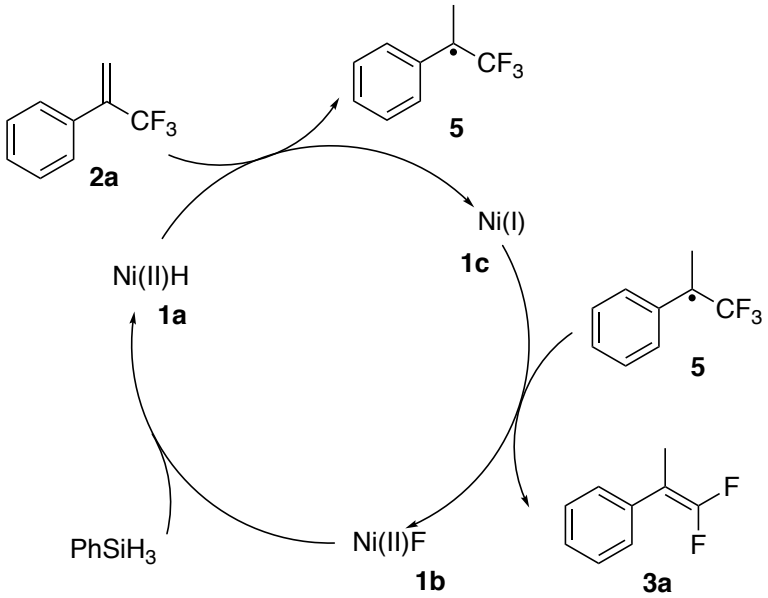

CF3
+
N
O
N
Ni
N
O
H
Ph Ph
C6D6, 50°C
CH3
F
F
+
N
O
N
Ni
N
O
F
Ph Ph
eq 1
2a
1a
2b
1b
PhSiH3
C6D6, 50°C


CF3
5 mol% 1a
1 equiv PhSiH3
C6D6, rt, 24h
CH3
F
F
eq 2
2a
2b

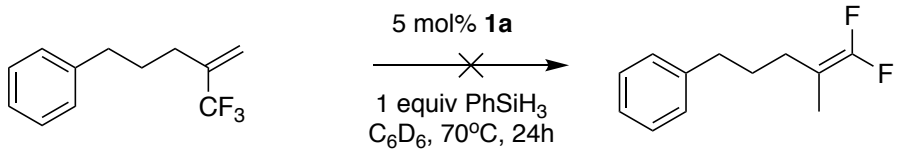
Fluorine Atom Abstration Initiation



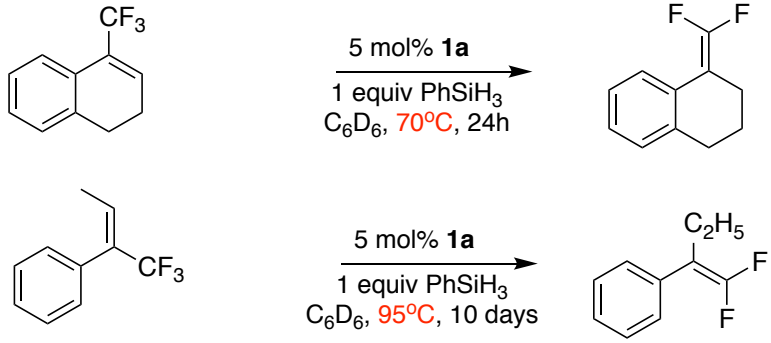
Hydrogen Atom Transfer Initiation



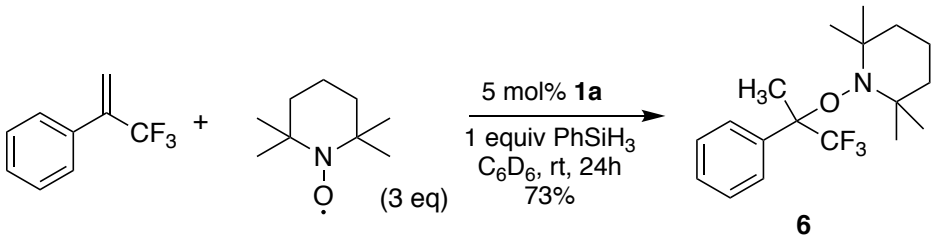
a)


CF3
5 mol% 1a
1 equiv PhSiH3
C6D6, 70°C, 24h
F
F

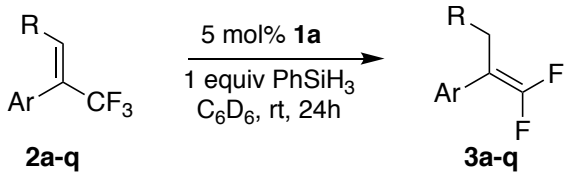
b)


CF3
5 mol% 1a
1 equiv PhSiH3
C6D6, 70°C, 24h
F
F
CF3
5 mol% 1a
1 equiv PhSiH3
C6D6, 95°C, 10 days
C2H5
F
F

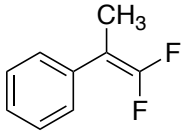
c)


CF3
+
N
O
(3 eq)
5 mol% 1a
1 equiv PhSiH3
C6D6, rt, 24h
73%
H3C
O
N
CF3

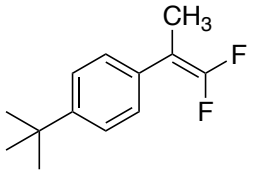
6



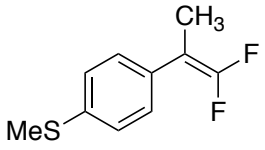
2a-q **3a-q**



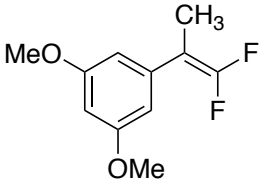
3a, 88%



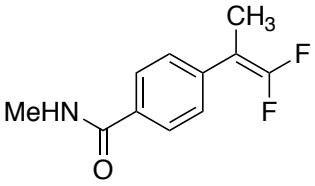
3b, 91%



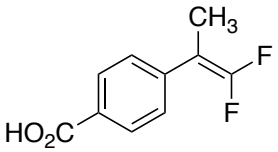
3c, 92%



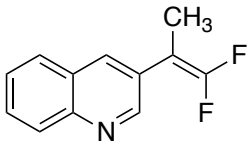
3d, 92%



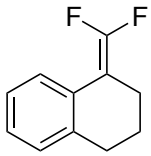
3e, 96%



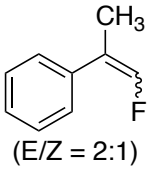
3f, 82%



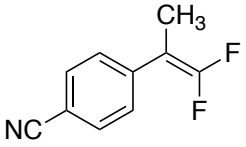
3g, 90%



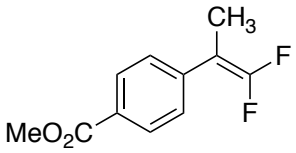
3h, 75%[b]



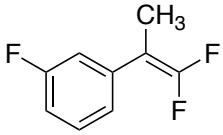
3i, 77%[c]



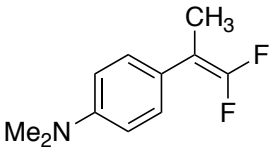
3j, 80%



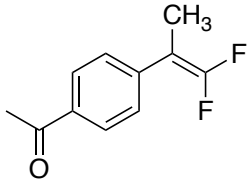
3k, 90%



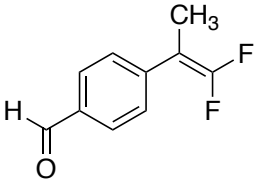
3l, 86%



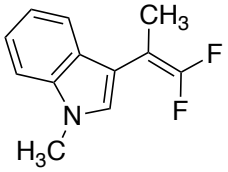
3m, 86%



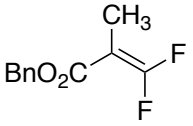
3n, 53%



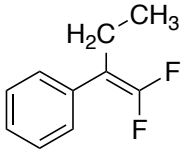
3o, 50%



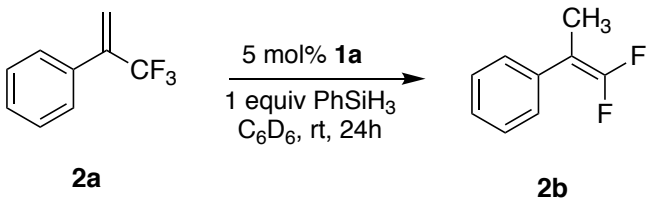
3p, 85%



3q, 85%



3r, 91%[d]



2a **2b**

Catalyzing the Hydrodefluorination of CF_3-substituted Alkenes by $PhSiH_3$. H• Transfer from a Nickel Hydride

Chengbo Yao[1], Shuai Wang[1†], Jack Norton[1*], Matthew Hammond[1]

[1]Department of Chemistry, Columbia University, 3000 Broadway, New York, 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• 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]

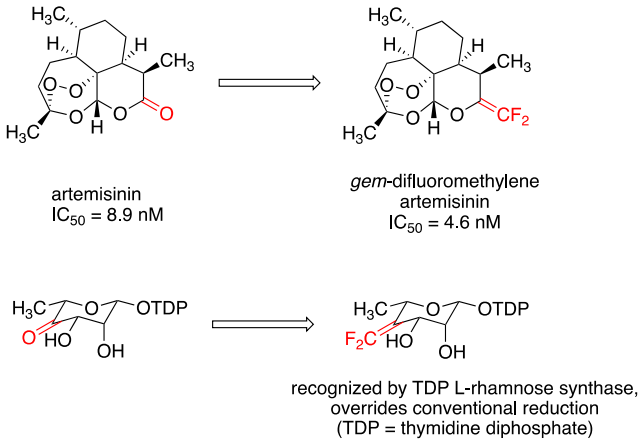
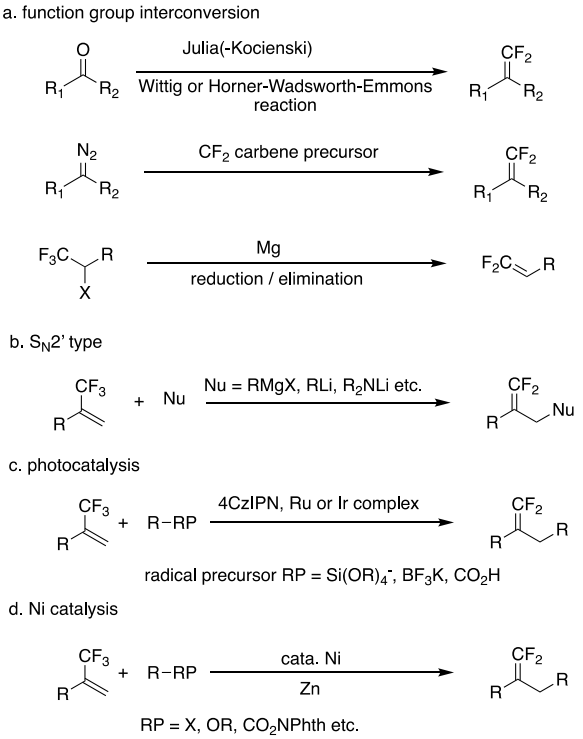


Figure 1. Representative applications of *gem*-difluoroalkenes.

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]



Scheme 1. Typical synthetic routes to *gem*-difluoroalkenes.

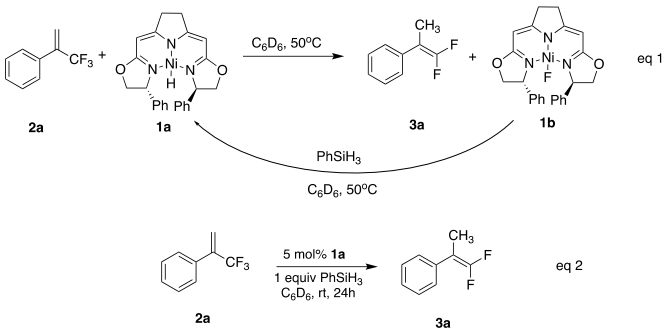
Typical Ni-catalyzed defluorinations of trifluoromethyl alkenes for the synthesis of *gem*-difluoroalkenes begin with single electron transfer from the nickel to an alkyl radical precursor. The resulting alkyl radical adds to another CF_3 alkene, producing a new radical which is then quenched by the 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 his coworkers 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]

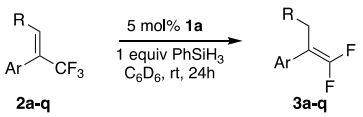
While investigating hydrogen atom transfer (HAT) from **1a**, we found that it carried out the hydrodefluorination of α-CF_3 styrene **2a** (Scheme 2). During that reaction the characteristic ^{19}F NMR resonance of the Ni(II)-F complex **1b** was observed at δ –444.3.[49] Moreover, the disappearance 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 ($^2J_{F,F}$ = 44.1Hz, $^4J_{H,F}$ = 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 $PhSiH_3$.



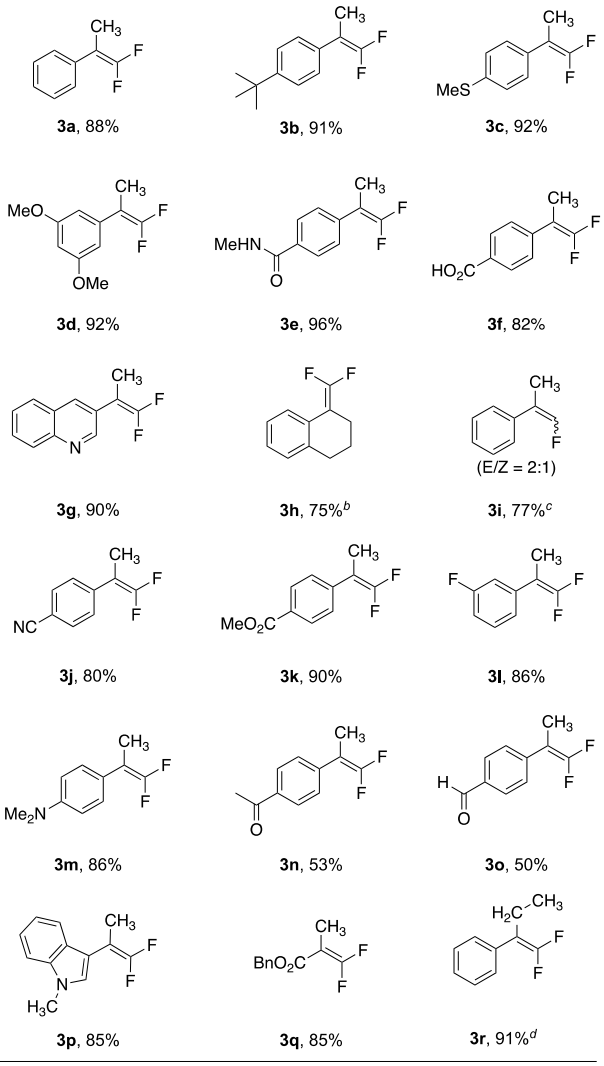
Scheme 2. Hydrodefluorination by $PhSiH_3$ of α-CF_3 styrene **2a** by isoPmBox Ni(II)-H **1a** in a stoichiometric and a catalytic manner.

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 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.

Table 1. Substrate scope of the nickel-hydride-catalyzed hydrodefluorination of trifluoromethyl-substituted alkenes.[a]



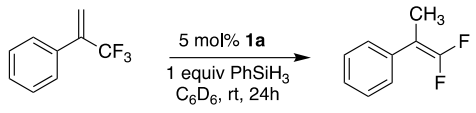
2a-q 3a-q



[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.

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.

Table 2. Control Experiments



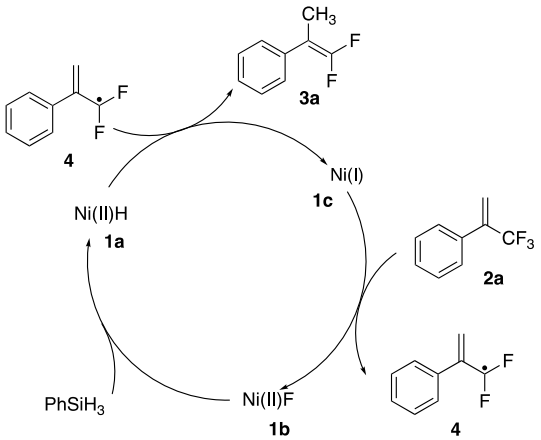
2a 3a

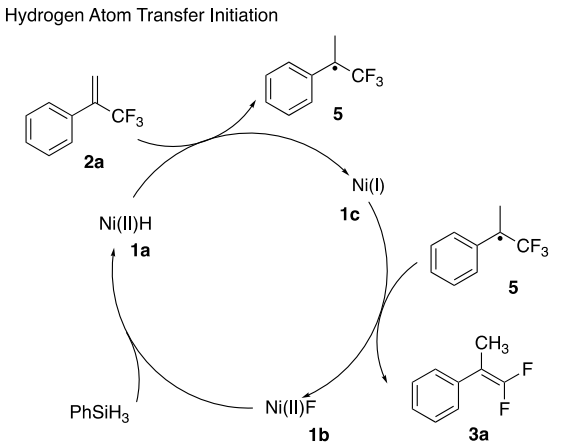
Entry	Deviation from "Standard Condition"	Yield[a]
1	None	>95%
2	No **1a**	< 5%
3	20 mol% $HCpCr(CO)_3$, or 20 mol% $HV(CO)_4$(dppe) instead of **1a**	< 5%
4	1 mol% **1a**, 72h	>95%
5	0.4 equiv $PhSiH_3$	>95%

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

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 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**.

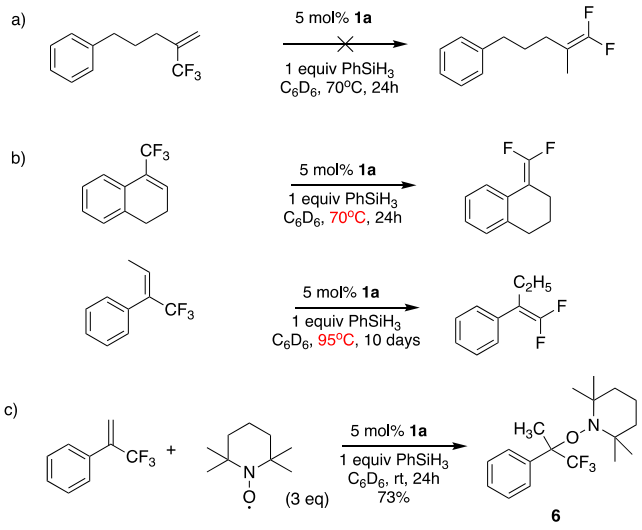
Fluorine Atom Abstraction Initiation





Scheme 3. Two possible mechanisms initiated by fluorine atom abstraction and hydrogen atom transfer respectively

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 three 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 (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** in 73% isolated yield.



Scheme 4. Evidences in favor of HAT-initiating mechanism

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

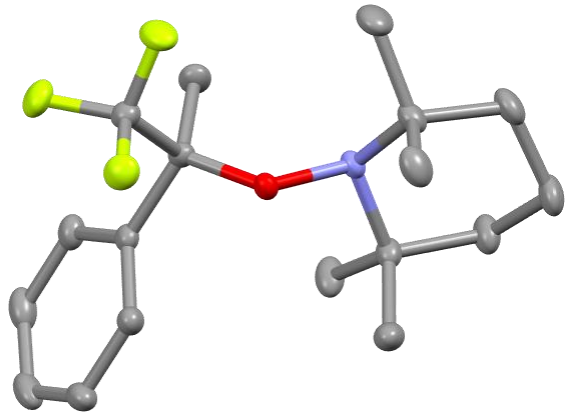


Figure 2. Molecular structure of TEMPO-adduct **6**. Hydrogen atoms are omitted for clarity.

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 & benzophenone ketyl. Benzene (C_6H_6) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl. isoPmbox-Ni(II)-H **1a**[48], $CpCr(CO)_3H$[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). ^1H 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 mmol 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 1ml of dry and degassed C_6D_6. The reaction was carried out at room temperature for 24 hours 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 1ml of dry and degassed C_6D_6. The reaction was carried out at room temperature for 24 hours. Crude ^1H 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 1ml of dry and degassed C_6D_6. The reaction was carried out at room temperature for 144 hours. The reaction conversion was 56%, 77% and 89% at 3 hours, 17 hours and 144 hours. 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 ^1H 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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 interests.

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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 hours, 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 and to give the hydrogenation product. The bulkiness of the Ni hydride **1a** is also demonstrated by the HAT experiments in footnote 59.
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