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Cobalt-Catalyzed Hydrofluorination of Unactivated Olefins: A Radical Approach of Fluorine Transfer

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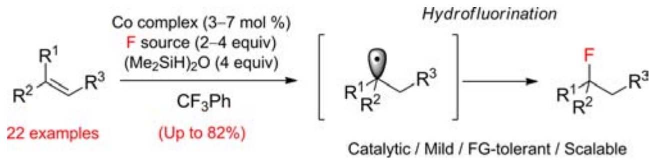
ABSTRACT



Catalytic hydrofluorination of olefins using a cobalt catalyst was developed. The exclusive Markovnikov selectivity, functional group tolerance, and scalability of this reaction make it an attractive protocol for the hydrofluorination of olefins. A preliminary mechanistic experiment showed the involvement of a radical intermediate.

Given the growing number of functional fluorinated molecules in their products, the demand for an efficient and regioselective fluorination method is increasing in the pharmaceutical and agrochemical industries.[1] Hydrofluorination of olefins, i.e., net addition of hydrogen fluoride to olefins, is a fundamentally important transformation with a broad spectrum of applications, as olefins are a commonly used functional group in organic chemistry.

Olah et al. first studied hydrofluorination of olefins using HF/pyridine.[2] More recently, Thibaudeau et al. reported a modified method using a superacid (HF/SbF_5) to prepare β-fluoroamines.[3] However, these two acidic conditions face problems with substrate scope and functional group tolerance. Very recently, Boger et al. originally developed a powerful $Fe^{III}/NaBH_4$-mediated process for the hydrofluorination of olefins via a free-radical intermediate, which shows outstanding substrate scope and functional group tolerance.[4] However, there is still room for improvement in the hydrofluorination of olefins, especially in terms of the use of metal catalysts. Herein, we report the development of a mild, functional group tolerant, and scalable hydrofluorination of unactivated olefins catalyzed by a cobalt complex. Moreover, the results of a mechanistic probe suggest the involvement of a carbon radical intermediate.

Seminal work by Mukaiyama and Isayama provided evidence of Markovnikov selectivity of olefin hydration using a cobalt catalyst and phenylsilane in an O_2 atmosphere (Scheme 1).[5] Inspired by this work, Carreira et al. demonstrated cobalt-catalyzed hydrohydrazination,[6,7b] hydroazidation,[7] hydrocyanation,[8] hydrochlorination,[9] and hydrooximation.[10] Girijavallabhan et al. independently reported hydrothiolation.[11] In a previous study on

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Scheme 1. Cobalt Catalysis in Mukaiyama and Carreira, Boger's Fluorination, and in this Work

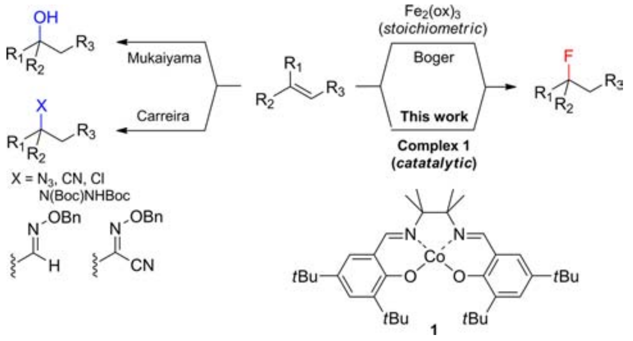
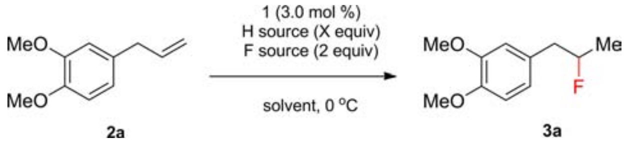
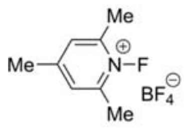


Table 1. Optimization of Reaction Parameters[a]

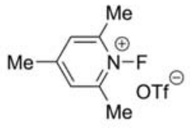


entry	H source	F source	solvent	yield (%)
1	$(Me_2SiH)_2O$	**F1**	THF	0
2	$(Me_2SiH)_2O$	**F1**	CH_3CN	<10
3	$(Me_2SiH)_2O$	**F1**	CH_3Ph	<10
4	$(Me_2SiH)_2O$	**F1**	AcOEt	<10
5	$(Me_2SiH)_2O$	**F1**	CH_2Cl_2	57
6	$(Me_2SiH)_2O$	**F1**	CF_3Ph	81
7	$(Me_2SiH)_2O$	**F2**	CF_3Ph	0
8	$(Me_2SiH)_2O$	**F3**	CF_3Ph	0
9	$(Me_2SiH)_2O$	**F4**	CF_3Ph	0
10	$(Me_2SiH)_2O$	**F5**	CF_3Ph	0
11	$(Me_2SiH)_2O$	**F6**	CF_3Ph	10−20
12	$PhSiH_3$[b]	**F1**	CF_3Ph	68

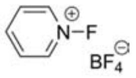
[a] Olefin (0.56 mmol), **1** (3.0 mol %), H source (4.0 equiv), F source (2.0 equiv), solvent (3.3 mL), 0 °C (2.0 h). [b] 3.0 equiv.



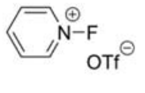
F1



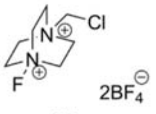
F2



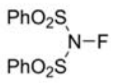
F3



F4



F5



F6

olefin functionalization, it was proposed that the radical intermediate reacts with a radical trap reagent.[12] However, to the best of our knowledge, cobalt-catalyzed hydrofluorination of olefins has not yet been demonstrated, despite the significant progress made in the field of cobalt catalysis and the high demand for fluorinated compounds.[13] Based on the recent progress in the approaches of free-radical fluorination, we believe that C−F bond formation could be realized using a common electrophilic fluorinating agent.[14,15] Notably, we found that the use of an alcoholic solvent led to the incorporation of alcohol into olefins, i.e., hydroalkoxylation of olefins with excellent Markovnikov selectivity and functional group tolerance.[16]

Based on this consideration and our experimental result, we initiated our study on the hydrofluorination of 4-allyl-1,2-dimethoxybenzene (**2a**) by conducting a systematic screening of nonalcoholic solvents in the presence of a cobalt catalyst **1** (Table 1, entries 1−6). We found that the use of CF_3Ph as a solvent was essential to obtain a high yield (entry 6). Encouraged by this result, we evaluated a series of various F sources and identified *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**F1**, 233,500 jpy/kg, TOSOH F-TECH, INC.) as an optimal F source (entries 6−11). Considering the previously reported radical fluorination reactions using **F5** or **F6**, **F1** is a rare radical fluorine source.[14] Replacing 1,1,3,3-tetramethyldisiloxane [$(Me_2SiH)_2O$] with phenylsilane gave an unsatisfactory result (entry 12). An undesired hydration product was constantly obtained in moderate yield when the reactions were performed without the degassing operation. This observation suggests the incorporation of molecular oxygen, which is similar to the reaction originally reported by Mukaiyama and Isayama.[5] In these optimizations, the anti-Markovnikov product was not observed.

After establishing the optimized reaction conditions, we explored the scope of the hydrofluorination protocol with various monosubstituted olefins, **2b**−**2s** (Scheme 2). A wide range of substrates and functional groups were tolerated, including ethers (**3b**, **3c**, **3f**), alcohols (**3e**), fluoroanion-sensitive silyl ethers (**3c**, **3g**), acid-sensitive groups

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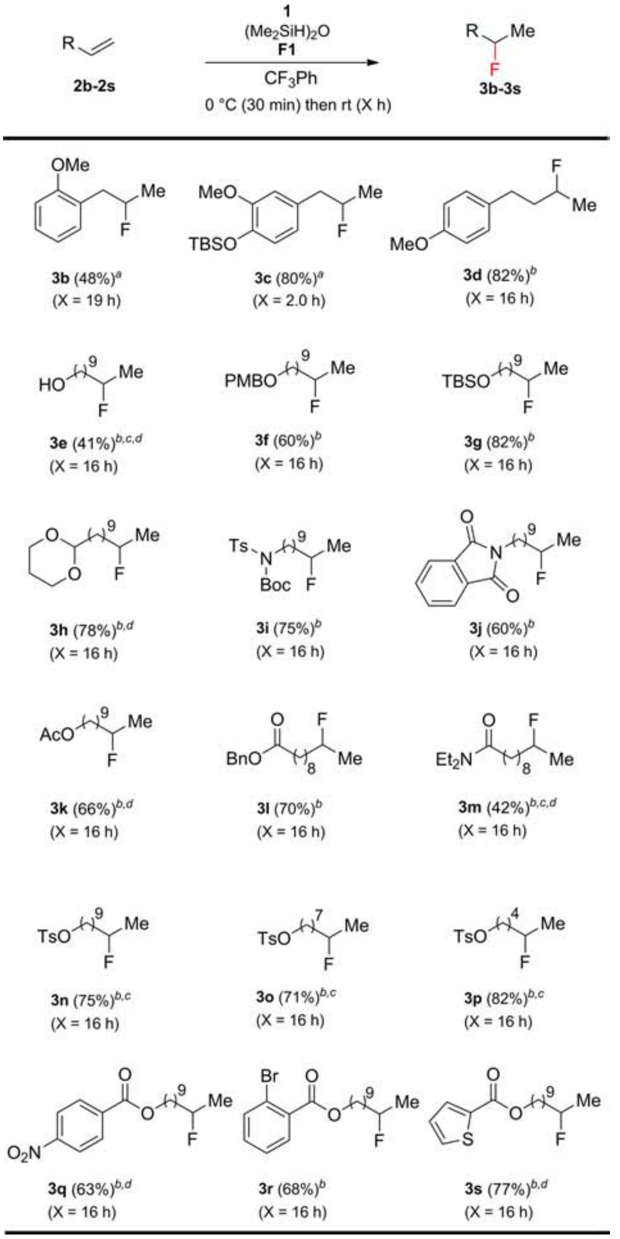
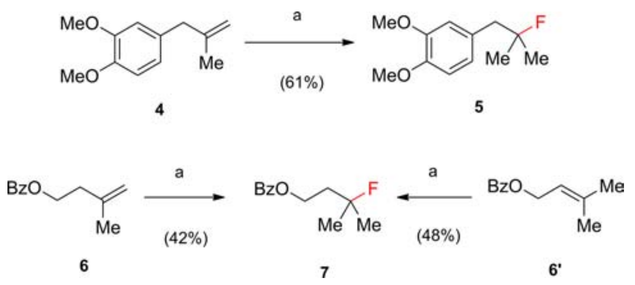
Scheme 2. Scope and Limitation of Monosubstituted Olefins



[a] Olefin (0.56 mmol), **1** (3.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F1** (2.0 equiv), CF_3Ph (0.17 M), X = 19 h (**3b**) or X = 2 h (**3c**). [b] Olefin (0.56 mmol), **1** (7.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F1** (3.0 equiv), CF_3Ph (0.17 M), X = 16 h. [c] **F1** (4.0 equiv). [d] Yield was calculated based on NMR data.

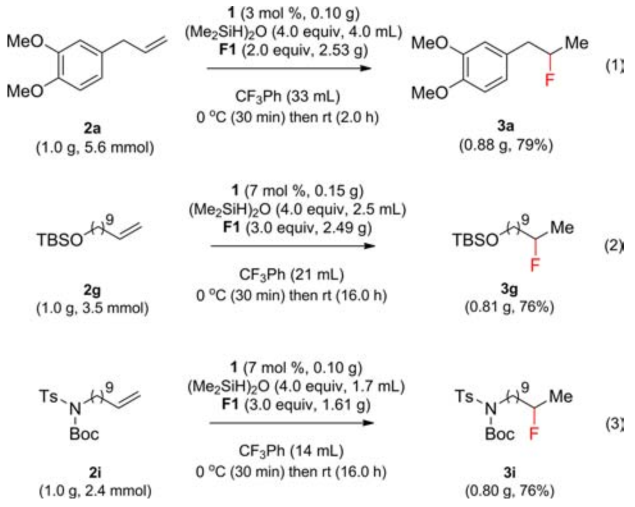
Scheme 3. Substrate Scope and Limitation with Di- and Trisubstituted Olefins[a]



[a] Olefin (0.56 mmol), **1** (7.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F1** (3.0 equiv), CF_3Ph (0.17 M), 0 °C (2 h).

(PMB **3f**, acetal **3h**), esters (**3k**, **3l**), amides (**3m**), tosylates (**3n**, **3o**, **3p**), nitro group (**3q**), bromo (**3r**), and thiophene (**3s**). Amino surrogates **3i** and **3j** were also obtained in good yields. Undesired olefin isomerization resulted in a lower yield in hydrofluorination, especially in the case of **3e** and **3m**. In addition, we analyzed the substrate scope with di- and trisubstituted olefins (Scheme 3). Geminally disubstituted olefins **4** and **6** gave corresponding fluorinated compounds **5** and **7**.[17] The sterically hindered trisubstituted olefin **6′** was also fluorinated in 48% yield.[18] At this stage, the method was found to be ineffective for compounds, including amino, carboxylic acid, phenol, and alkyne, for which Boger's method provided satisfactory yields.[4a,19]

In contrast to the Boger's method, which requires a low concentration of the reaction mixture (0.0125 M), this method offers the advantage of scalability.[4a] Using 1.0 g of **2a**, **2g**, and **2i** as the substrate, the hydrofluorination products **3a**, **3g**, and **3i** were obtained in reasonable yield respectively (eqs 1−3).



The mechanistic implications of the hydrofluorination of olefins merit discussion. To probe whether a radical intermediate was involved in the reaction, hydrofluorination of **8**[4a] was conducted under optimized conditions, and the fluorinated pyrrolidine **9** (*cis*) and **10** (*trans*) were afforded (Scheme 4). This suggests that the involvement of a radical intermediate is possible under the current reaction conditions. The aforementioned formation of a hydration product, which was observed without the degassing operation, further supports the mechanism involving a radical intermediate.[12]

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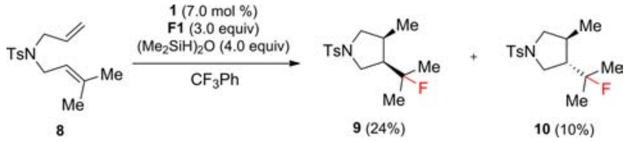
(17) Compound **5** was obtained together with the undesired olefin isomer. Compound **7** (from **6**) was obtained together with the undesired hydrated product despite the degassing operation.

(18) Compound **7** (from **6′**) was obtained together with the undesired hydrated product despite the degassing operation.

(19) Aminos and alkynes were found to inhibit this reaction. Phenols and carboxylic acids gave a complex product mixture.

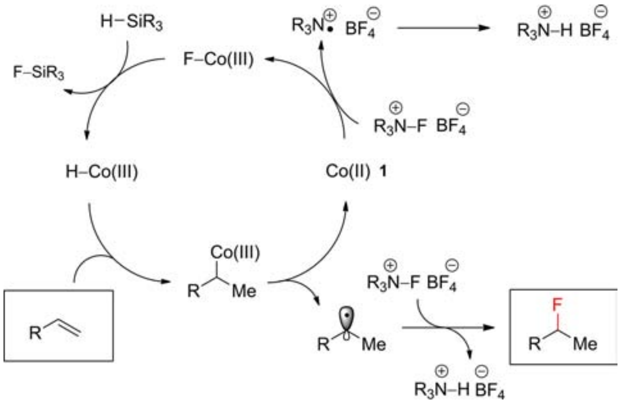
Scheme 4. Mechanistic Experiment[a]



[a] Olefin (0.56 mmol), **1** (7.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F1** (3.0 equiv), CF_3Ph (0.17 M), 0 °C, 30 min, then rt, 16 h.

A plausible mechanism is shown in Scheme 5. The catalytic cycle begins with the generation of the Co–F complex together with the amino cation radical.[20–22] The amino cation radical is quenched to afford 2,4,6-trimethylpyridinium tetrafluoroborate.[23] Next, transformation of the Co–F complex to the Co–H complex occurs.[24] The driving force of this process is the strong F–Si bonding energy. As Carreira et al. previously proposed, the Co–H complex inserts into the olefin[25] and the resultant Co–alkyl species then releases complex **1** to generate the key radical intermediate. Finally, the radical intermediate reacts with **F1** to form the desired fluorinated product.

Scheme 5. Plausible Mechanism



In summary, we developed the catalytic hydrofluorination of olefins using a cobalt catalyst. The exclusive Markovnikov selectivity, functional group tolerance, and scalability make this reaction an attractive protocol for the hydrofluorination of olefins. A preliminary mechanistic experiment showed the involvement of a radical intermediate. We are currently developing the asymmetric variant of this reaction.

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Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The CF_3Ph solution of complex **1** is bright red. The solution becomes olive green upon addition of **F1**. The addition of XeF_2 also makes the solution olive green. NMR analysis of these solution did not provide any useful results because of the paramagnetic cobalt.

(21) For examples of the metal–fluoride complex with *N*-fluoropyridinium salts, see: "Cu" (a) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552. (b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4648. "Pd" (c) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (d) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (e) Kaspi, A. W.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2010**, *132*, 10626. (f) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. (g) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414.

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(23) 2,4,6-Trimethylpyridinium tetrafluoroborate was isolated as an off-white solid.

(24) The reaction of Co–F complexes and silane to provide a Co–H complex has been reported by Holland et al. For examples of Co–fluoride complexes, see: (a) Ding, K.; Dugan, T. R.; Brennessel, W. W.; Bill, E.; Holland, P. L. *Organometallics* **2009**, *28*, 6650. (b) Dugan, T. R.; Goldberg, J. M.; Brennessel, W. W.; Holland, P. L. *Organometallics* **2012**, *31*, 1349.

(25) Although the author did not observe any evidence of Co–C bond formation, insertion of the Co–H complex into the olefins commonly accounts for cobalt catalysis.

The authors declare no competing financial interest.