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Hydroalkoxylation of Unactivated Olefins with Carbon Radicals and Carbocation Species as Key Intermediates

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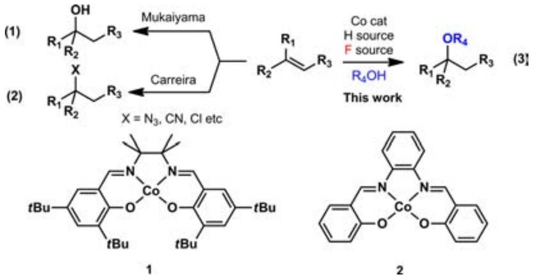
Ⓢ *Supporting Information*

ABSTRACT: A unique Markovnikov hydroalkoxylation of unactivated olefins with a cobalt complex, silane, and *N*-fluoropyridinium salt is reported. Further optimization of reaction conditions yielded high functional group tolerance and versatility of alcoholic solvent employed, including methanol, *i*-propanol, and *t*-butanol. Use of trifluorotoluene as a solvent made the use of alcohol in stoichiometric amount possible. Mechanistic insight into this novel catalytic system is also discussed. Experimental results suggest that catalysis involves both carbon radical and carbocation intermediates.

Scheme 1. Co-Catalyzed Hydroalkoxylation: Mukaiyama, Carreira, and this work



Markovnikov hydroalkoxylation of olefins—the coupling of olefins with alcohols—is a pivotal C−O bond-forming reaction in organic chemistry.[1,2] The conventional oxymercuration−reduction process is well-known; however, the stepwise nature of the reaction as well as the need for stoichiometric amounts of toxic reagents are notable drawbacks associated with the method.[3] Because of this, catalytic processes, particularly those involving a metal catalyst, have been sought after for decades.[4,5] Previously reported approaches have relied on nucleophilic attack on a metal-coordinated olefin and protonation of the metal−carbon bond.[6] Recently, aerobic hydroalkoxylations have also been reported by Sigman,[7] Sakurai,[8] and Hartung.[9] Although various reports of inter- and intramolecular Markovnikov hydroalkoxylations exist, there remains considerable room for improvement in terms of functional group tolerance, which could enable a methodology ideal for use in the field of complex molecule synthesis.[10] Herein, we report a unique intermolecular Markovnikov hydroalkoxylation of unactivated olefins using a cobalt catalyst, a hydrogen source, an electrophilic fluorine reagent, and an alcoholic solvent. It is important to note that the cobalt catalytic systems described here show exceptional functional group tolerance and high reactivities at low temperatures, encompassing a remarkably wide substrate scope, including sterically demanding nucleophilic alcohols. In addition, our hydroalkoxylation method is distinguished from earlier reports in terms of the proposed reaction mechanism.

In 1989, Mukaiyama and Isayama reported the hydration of olefins using $Co(acac)_2$, $PhSiH_3$, and molecular oxygen (eq 1, Scheme 1).[11] Since then, this powerful reaction and its modifications have been applied to complex natural product synthesis.[12] Independent to this, Carreira et al. developed various functional group tolerant transformations, such as hydrohydrazination,[13,14b] hydroazidation,[14] hydrocyanation,[15] hydrochlorination,[16] and hydrooximation[17] using a cobalt salen catalyst (eq 2, Scheme 1). Inspired by this versatile cobalt catalyst system, we aimed to develop a hydrofluorination reaction to afford fluorinated compounds, which are being intensely investigated because of their high demand in pharmaceutical and agricultural industries.[18] Surprisingly, when subjecting 4-allyl-1,2-dimethoxybenzene (**3a**) to a catalytic amount of catalyst **1** in ethanol in the presence of phenylsilane and *N*-fluorobenzenesulfonimide (NFSI, **F1**) (Table 1, entry 1), the unexpected hydroalkoxylated product **4ab** was obtained in 93% yield. This led us to explore functional group tolerance of the reaction after condition optimization and mechanistic studies. Initial examinations of catalyst effects revealed that the presence of catalyst **1** is required for the hydroalkoxylation to take place (Table 1, entries 1−4). In the absence of phenylsilane, desired products were not obtained. Next, we evaluated a series of various F sources (**F2**−**F6**) and found that, while all of them facilitated the hydroalkoxylation of **3a**, reactions conducted with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**F6**) provided higher yields than those conducted with **F1**, **F2** (Selectfluor), **F3** (*N*-fluoropyridinium triflate), **F4** (*N*-fluoropyridinium tetrafluorobrate), and **F5** (*N*-fluoro-2,4,6-trimethylpyridinium triflate) (Table 1, entries 1, 5−10).

Encouraged by this result, we evaluated a series of different alcohol solvents, including methanol, *i*-propanol, and *t*-butanol (Scheme 2). This hydroalkoxylation of olefins was amenable to all solvents examined. Of particular note is the high reactivity of *t*-butanol; among the hydroalkoxylations reported in literature, few examples of *t*-butanol addition to olefins exist.[19,20]

Experiments probing the substrate scope of monosubstituted olefins are summarized in Scheme 3. We found that the

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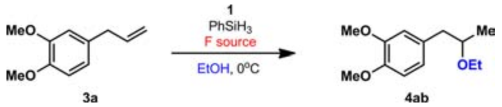
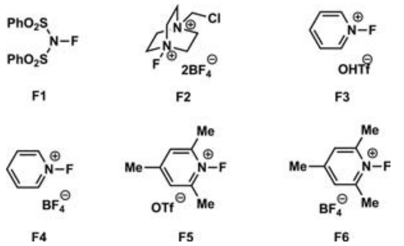
Table 1. Optimization of Reaction Parameters[a]

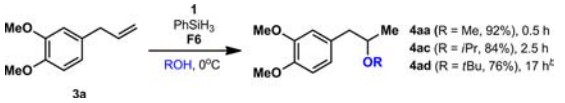


entry	Co cat	F source	time (h)	yield (%)
1	**1**	**F1**	0.5	93
2	**2**	**F1**	22	<5
3	Co(acac)$_2$	**F1**	22	
4	–	**F1**	22	0
5	**1**	–	22	<5
6	**1**	**F2**	22	21
7	**1**	**F3**	22	45
8	**1**	**F4**	22	56
9	**1**	**F5**	22	78
10	**1**	**F6**	0.5	96

[a]Procedure (A): **3a** (0.56 mmol), Co cat. (1.0 mol %), PhSiH$_3$ (1.0 equiv), F source (1.1 equiv), EtOH (0.17 M), 0 °C, under air, 0.5–22 h.

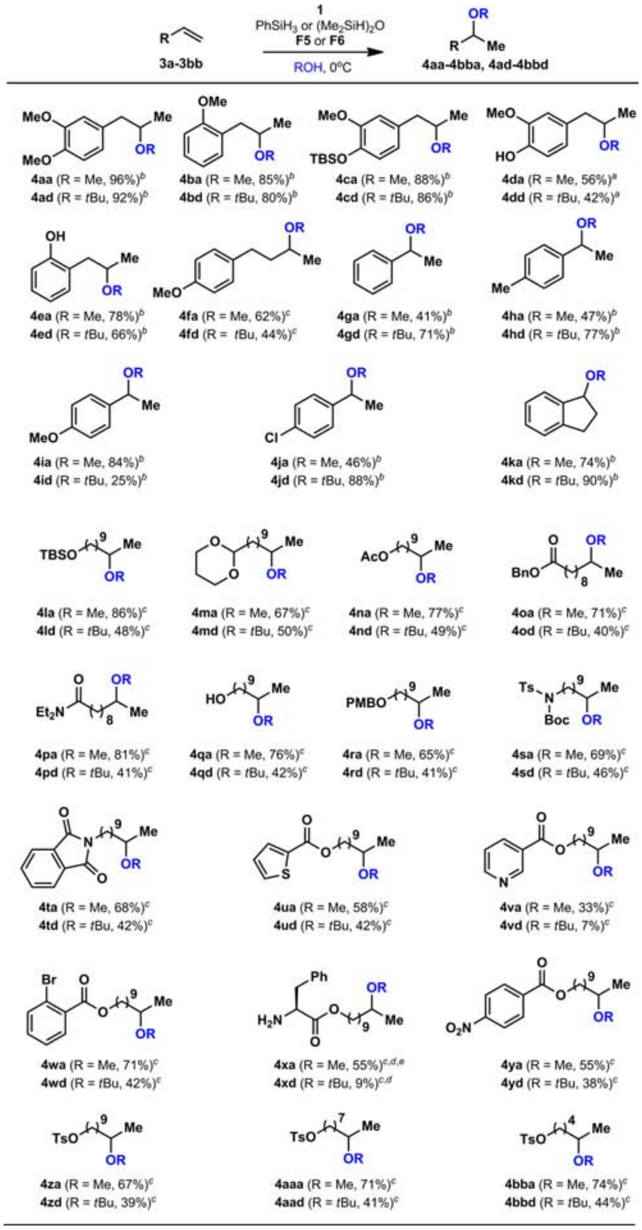


Scheme 2. Solvent Scope[a]



[a]Procedure (A): **3a** (0.56 mmol), **1** (1.0 mol %), PhSiH$_3$ (1.0 equiv), **F6** (1.1 equiv), ROH (0.17 M), 0 °C, under air, 0.5–17 h. [b] Mixed solvent (t-BuOH:CF$_3$Ph = 3:2) was used.

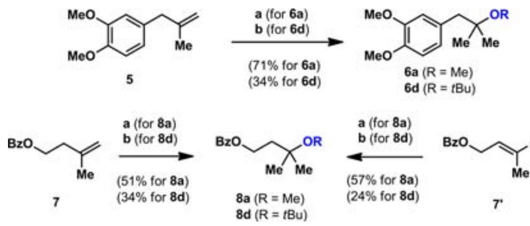
Scheme 3. Scope and Limitation for Monosubstituted Olefins[a]



[a](a) Procedure (A): olefin **3**, **1** (1.0 mol %), PhSiH$_3$ (1.0 equiv), **F6** (1.1 equiv), MeOH, or mixed solvent (t-BuOH:CF$_3$Ph = 3:2) (0.17 M), 0 °C, under air, 1.5 h for **4da** or 4.5 h for **4dd.** (b) Procedure (B): olefin **3**, **1** (3.0 mol %), (Me$_2$SiH)$_2$O (2.0 equiv), **F6** (2.0 equiv, **4aa–4ea**, **4ad–4ed**, **4ga–4ga**, or **F5** (2.0 equiv, **4hd–4ld**), MeOH, or mixed solvent (t-BuOH:CF$_3$Ph = 3:2) (0.10 M), 0 °C, under Ar, 17 h. (c) Procedure (C): olefin **3**, **1** (5.0 mol %), (Me$_2$SiH)$_2$O (4.0 equiv), **F6** (2.0 equiv, **4fa**, **4la–4bba**), or **F5** (2.0 equiv, **4fd**, **4ld–4bbd**), MeOH (0.10 M), 0 °C, under Ar, 17 h. (d) Calculated yield after purification and Boc protection. (e) 3 equiv of **F6**

optimum reaction conditions for **3a** were not always ideal for other substrates owing to differing reactivities and formation of hydration products (OH instead of OR). Generally, electron-donating group substituted phenylpropanoids (**3a–3e**) gave better results than the other substrates (**3f–3bb**). Accordingly, a more versatile reaction protocol using complex **1**, **F5**, or **F6** and 1,1,3,3-tetramethyldisiloxane [(Me$_2$SiH)$_2$O] under argon with subsequent degassing was identified, which was able to tolerate a wide range of functional groups, and applicable to substrates including sp^2 and sp^3 substituted olefins. Notably, **F5** was superior to **F6** in the addition of t-butanol to long-chain substrates in particular. However, undesired olefin isomerization resulted in lower yields for most cases of t-butanol addition. 1-Allyl-4-chlorobenzene gave α-hydroalkoxylated product in both methanol and t-butanol, which should be generated via isomerization and hydroalkoxylation. Substrates **3d**, **3e**, and **3q**, which possess a potentially reactive hydroxyl group under typical hydroalkoxylation conditions, remained intact in this transformation. No cyclized product was detected in the formation of **4ea** and **4ed**. Various hydroalkoxylated products were obtained in useful yields from terminal olefins featuring fluoroanion-sensitive silyl ethers (TBS), acid-sensitive groups (PMB, acetal), esters, amides, bromo, nitro, tosylates, heterocycles, including sulfur atoms, and amino surrogates. Note that the amino group (**3x**), which has strongly coordinative and nucleophilic features, was also tolerated. The shorter carbon chain substrates with tosyl group were also examined and show that there is no significant difference among C6–C11. Geminally disubstituted and trisubstituted olefins also gave corresponding hydroalkoxylated products (Scheme 4). Although yield can be further improved, the sterically challenging t-butanol addition to a trisubstituted sp^2

Scheme 4. Hydroalkoxylation of Di- and Trisubstituted Olefins[a]

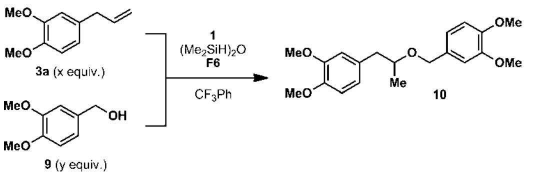


[a](a) Procedure (B): olefin, **1** (3.0 mol %), $(Me_2SiH)_2O$ (2.0 equiv), **F6** (2.0 equiv), MeOH (0.17 M), 0 °C, under Ar, 17 h. (b) Procedure (C): olefin, **1** (5.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F5** (2.0 equiv), mixed solvent (*t*-BuOH:CF_3Ph = 3:2) (0.10 M), 0 °C, under Ar, 17 h.

carbon, which leads to bis *tert*-alkyl ether, was achieved. At this stage, this method was found to be ineffective for reactions of alkynes.

We extended to use of stoichiometric amount of alcohol in an inert solvent. We found that use of trifluorotoluene as a solvent was essential for obtaining a reasonable yield (Table 2). Moreover, the conditions using less alcohol **9** than olefin **3a** afforded desired product in high yield (entry 3).

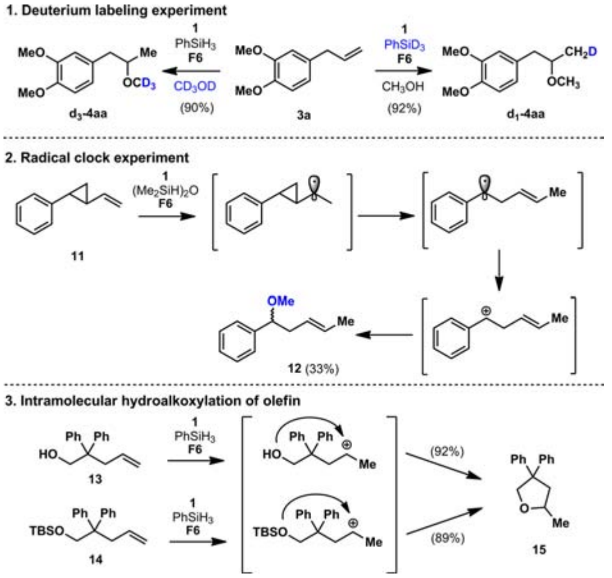
Table 2. Stoichiometric Amount of Alcohol[a]



entry	*x*	*y*	**10** (%)
1	1	2	79[b]
2	1	1	67
3	2	1	80[c]

[a]Procedure (B): **3a** (1 or 2 equiv), **9** (1 or 2 equiv), **1** (3.0 mol %), $(Me_2SiH)_2O$ (2.0 equiv), **F6** (2.0 equiv), CF_3Ph (0.17 M), 0 °C, under Ar, 17 h. [b]Yield was calculated based on **3a**. [c]Yield was calculated based on **9**.

Scheme 5. Mechanistic Study[a]

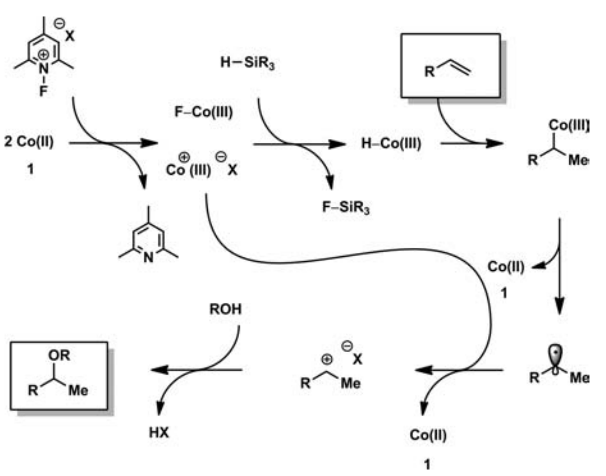


[a](1) Deuterium labeling experiment: Procedure (A): olefin **3a**, **1** (1.0 mol %), $PhSiH_3$ or $PhSiD_3$ (1.0 equiv), **F6** (1.1 equiv), CH_3OH or CD_3OD (0.10 M), 0 °C, under air, 30 min. (2) Radical clock experiment: Procedure (C): olefin **11**, **1** (5.0 mol %), $(Me_2SiH)_2O$ (4.0 equiv), **F6** (2.0 equiv), MeOH (0.10 M), 0 °C, under Ar, 17 h. (3) Intramolecular hydroalkoxylation of olefins: Procedure (A): olefin (**13** or **14**), **1** (1.0 mol %), $PhSiH_3$ (1.0 equiv), **F6** (1.1 equiv), MeOH (0.10 M), 0 °C, under air, 20 min.

The mechanistic implications of this olefin hydroalkoxylation merit discussion. Deuterium-labeling experiments, as shown in Scheme 5(1), resulted in complete deuterium incorporation at the terminal position from $PhSiD_3$ and not from CD_3OD. This suggested that protonation of the metal−carbon bond involved in conventional hydroalkoxylation[4,5] is not likely and that there is similarity with Carreira's methodology involving the presence of Co-hydrides and carbon radical intermediates. Furthermore, given the results of C−O bond formation using alcohol solvents, this hydroalkoxylation implicated not only a carbon radical but also a carbocation intermediate. First, to probe whether a carbon radical intermediate was involved in the reaction, hydroalkoxylation of **11**, a radical clock,[21] was conducted under optimized conditions; product **12** was obtained in which the cyclopropane ring was cleaved (Scheme 5(2)). Furthermore, it should be noted that hydration products were obtained without degassing, particularly in the case of long-chain substrates (e.g., **3l**), which would be due to the incorporation of molecular oxygen into a carbon radical intermediate, followed by reduction to hydroxyl. These two observations provided further evidence for a carbon radical intermediate. Second, experimental observations supporting a carbocation intermediate were as follows: the hydroxyl group in compound **13** and TBS ether in compound **14** trapped the resultant cationic carbons to form the identical cyclic ether **15** (Scheme Scheme 5(2)). Because of the inertness of TBS ethers in the reaction of **3l** (Scheme 3), the driving force for Si−O bond cleavage was thought to be provided by the proximally generated carbocation. Thus, the mechanism can be presumably distinguished from previously reported conventional and aerobic hydroalkoxylation.

A proposed mechanism that is consistent with the experimental data and literature is provided (Scheme 6). Initially, the catalytic cycle begins with formation of a Co−fluoride complex together with a cationic Co complex in the presence of a pyridinium salt (2,4,6-collidine in the optimized

Scheme 6. Proposed Mechanism



reaction) and next transformation of Co−fluoride to the Co−hydride complex occurs, the driving force of which is the strong F−Si bonding energy. The reaction of Co−fluoride complexes and silane to provide a Co−hydride complex has been reported by Holland et al.[22] The remaining steps from Co−hydride complex to carbon radical intermediate should be identical to the mechanism proposed by Carreira: hydrocobaltation of the olefins leads to a Co−alkyl complex, followed by the generation of the carbon radical intermediate with the release of cobalt complex **1**.[14a] The key carbocation intermediate could then be generated by the oxidation of the carbon radical with the remaining cationic cobalt complex, which releases the second cobalt complex **1**. Previously, the oxidation of an alkyl radical by a cationic cobalt complex has been reported by Kochi et al.[23] Finally, the carbocation intermediate is quenched by alcoholic solvent to form the hydroalkoxylated product and acid, which is then neutralized by the pyridine base.

In summary, we developed a cobalt-catalyzed hydroalkoxylation of olefins using silane and *N*-fluoropyridinium salt. This serendipitously discovered reaction is found to be functional group tolerant and applicable to even bulky alcohol reactants. A preliminary mechanistic investigation suggests an unprecedented mechanism involving carbon radical and carbocation intermediates to effect the transformation. Further investigations are focused on expanding the nucleophile scope (other than alcohol) as well as the application to natural product synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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