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Selective C(sp^3)-H and C(sp^2)-H Fluorination of Alcohols Using Practical Auxiliaries

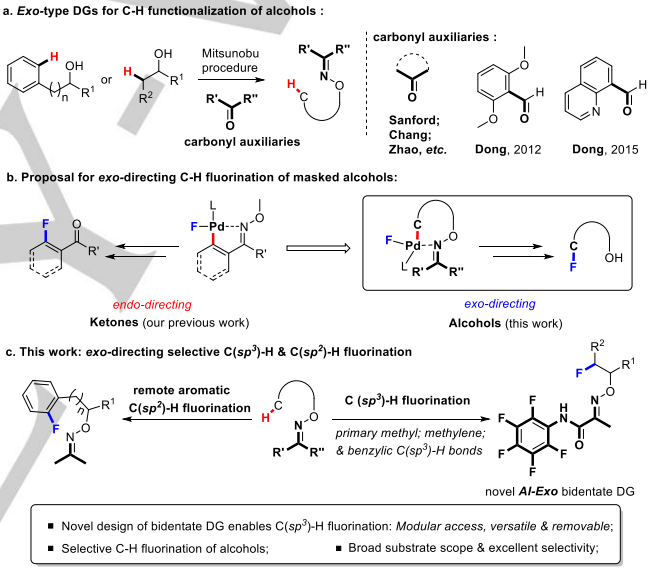
Yang-Jie Mao, Shao-Jie Lou*, Hong-Yan Hao and Dan-Qian Xu*

Dedicated to Professor Zhen-Yuan Xu on the occasion of his 80th birthday

Abstract: Selective introduction of fluorine into molecules *via* the cleavage of inert C-H bonds is of central academic and synthetic interest, yet remains challenging. Given the central role of alcohols in organic chemistry as the most ubiquitous building blocks, a versatile and selective C(sp^3)-H and C(sp^2)-H fluorination of simple alcohols enabled by novel designed *exo*-directing groups was developed for the first time. C(sp^2)-H bond fluorination was achieved by using simple acetone oxime as auxiliary, whereas a new, modular and easily accessible bidentate auxiliary was developed for the efficient and site-selective fluorination of various primary methyl, methylene and benzylic C(sp^3)-H bonds. Fluorinated alcohols can readily be accessed by the removal of auxiliaries, which significantly expands the synthetic prospect of the present protocol.

Alcohols are considered to be among the most important and ubiquitous building blocks in organic chemistry. The hydroxy groups can readily be transformed into various functional groups such as alkenes, haloalkanes, aldehydes, ketones, carboxylic acids, and esters, which are described as basic reactions in many textbooks in organic chemistry. Thus, the direct C-H bond transformation of alcohols is undoubtedly of great interest to the chemists.

On the other hand, organic fluorides are linchpin in pharmaceuticals, agrochemicals and materials.[1] Thus, C-F bond construction has been of great interest as well as a long-standing challenge to the chemical society.[2] Among the established fluorination protocols, direct replacement of simple and inert C-H bonds to the corresponding C-F bonds not only retains the molecular size, but dramatically enhances the lipophilicity, bioavailability and metabolic stability in comparison with their non-fluorinated analogues. In the recent years, substantial efforts have been devoted to the chelation-assisted aromatic C(sp^2)-H bond fluorination of aryl heterocycles,[3] masked amines,[4] carboxylic acids,[5] aldehydes,[6] ketones[7] and phenols,[8] *etc*. In addition, Pd(II)-catalyzed direct electrophilic aromatic C(sp^2)-H fluorination was also realized by Ritter.[9] However, the selective catalytic fluorination of the inert C(sp^3)-H bonds remains challenging[10] and mainly focused on the β-fluorination of masked carboxylic acids.[11] Very recently, Yu's group developed a Pd(II)-catalyzed enantioselective C(sp^3)-H fluorination of 2-alkyl benzaldehyde derivatives using a chiral bidentate transient directing group.[12] To the best of our knowledge, neither C(sp^2)-H nor C(sp^3)-H fluorination of alcohols has been reported due to the underdeveloped C-H transformation of alcohols and the challenging formation of C-F bonds. Given the central role of alcohols in organic chemistry, new strategies for the site-selective C-H fluorination of simple alcohols are highly desirable.



Scheme 1. Selective C(sp^2)-H and C(sp^3)-H fluorination of alcohols enabled by *exo*-directing strategies

The last decade has witnessed the emergence of transition metal catalyzed C-H functionalization using directing groups as intramolecular ligands.[13] The design of novel directing groups enriches the scope of C-H functionalization by improving the reactivity as well as selectivity. For instance, hydroxyl itself as an *O*-donor ligand directing group was less efficient due to the weakly coordinating ability to the transition metals, thus novel strategies using masked alcohols as auxiliaries were developed for the C-H bond functionalization of alcohols.[13c, 14] Among these, Dong[15] and Sanford[16] developed an elegant *exo*-directing strategy to enable the selective C-H bond functionalization of oximes on the oxygen side. Very recently, several C-H bond transformations including the C(sp^3)-H sulfonyloxylation,[17] intramolecular alkoxylation,[18] amidation[19] and the C(sp^2)-H bond acetoxylation,[20] olefination[21] were developed by using this strategy. However, the structural modifications of the previous auxiliaries (simple ketones, aryl

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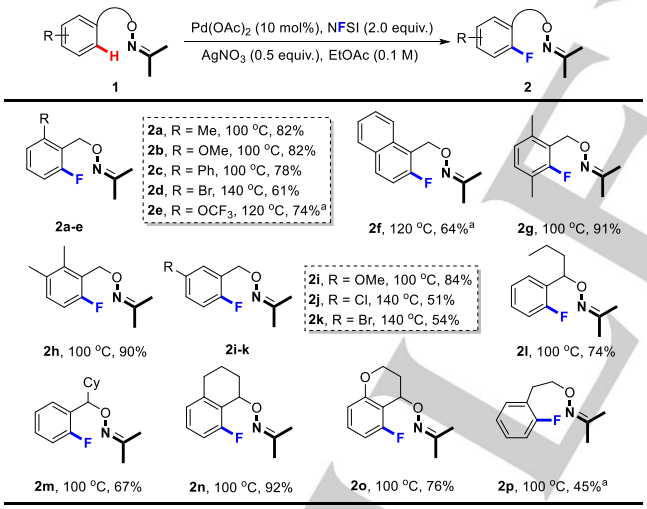
aldehydes) are difficult to realize in a modular fashion, which may limit the diversity of C-H transformations, such as the challenging C-H bond fluorination of alcohols (Scheme 1, a). In the context of these limitations, we became intrigued in establishing a novel family of highly modular *exo*-type bidentate auxiliaries for various C-H functionalization. Herein, as part of our continuous interest in the C-H bond fluorination of diverse fundamental compounds,[7-8] we report a selective C(sp^2)-H and C(sp^3)-H fluorination of alcohols by using the *exo-directing* catalytic mode for the first time (Scheme 1, b). A simple acetone oxime ether enabled the remote aromatic C(sp^2)-H bond fluorination under a Pd-nitrate catalysis, whereas a newly developed bidentate auxiliary derived from pyruvamide enabled the selective fluorination of more challenging inert C(sp^3)-H bonds (Scheme 1, c).

Aromatic C-H bond functionalization of alcohols has remained underdeveloped due to the lack of suitable auxiliaries to stabilize the transition metals. Oximes were recently found as *exo*-directing groups for the C-H bond functionalization of alcohols. However, in comparison with their *endo* counterparts, relatively lower efficiency as well as limited reaction types was observed due to the flexible and remote coordinating / directing mode between the substrates and catalysts. Encouraged by our recent nitrate-promoted aromatic C-H bond fluorination of oximes[7], we envisioned that the C-H fluorination of the challenging aromatic alcohols might be feasible with a more electrophilic palladium-nitrate catalysis.

Table 1. Aromatic C-H bond fluorination of alcohols



Conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), NFSI = N-fluorobenzenesulfonimide (0.6 mmol), $AgNO_3$ (0.15 mmol) and EtOAc (3.0 mL) were added to a test tube, the mixture was stirred at the indicated temperature for 12 h. [a] NFSI (3.0 equiv.) was used.

At the outset of this fluorination project, *O*-(2-methylbenzyl)-acetoxime (**1a**) was treated with Pd catalyst, nitrate promoter and NFSI in various solvents. To our delight, *ortho* C-H bond fluorinated product **2a** was obtained in 82% isolated yield in EtOAc. As anticipated, nitrate additives were indispensable in this transformation, and only 44% yield of **2a** was detected in the absence of $AgNO_3$ (see the SI for details).[22]

The scope of the reaction was next explored under the optimized conditions. Generally, the reaction tolerated various functional groups such as alkyls, halogens, phenyl and alkoxyls (Table 1, **2a**-**2k**). The *ortho* bromo-substituted substrate was selectively fluorinated at the C-H bond with the bromo group intact (Table 1, **2d**). Moreover, α-substituted benzyl alcohols also underwent mono-fluorination smoothly (Table 1, **2l**-**2o**). Notably, fluorination of masked phenethyl alcohol also occurred at the remote *ortho* position *via* a 7-membered palladacycle intermediate (Table 1, **2p**).

Having established the C(sp^2)-H bond fluorination of alcohols, we turned our attention to the more challenging fluorination of the inert C(sp^3)-H bonds. In principle, C-F bond formation is usually more sluggish in the competing reductive eliminations from high-valent Pd^{IV} species due to the poor nucleophilicity of fluorine anion. Indeed, fluorinating reagent NFSI was mainly used as a bystanding oxidant[23] for the formation of other chemical bonds such as C-O bond and C-N bond in the previous C(sp^3)-H bond functionalization of alcohols.[17, 19b] Only cyclic methylene C(sp^3)-H were fluorinated in moderate yields as side reactions. No efficient C(sp^3)-H bond fluorination of alcohols has been developed to date. We started our C(sp^3)-H fluorination with the cyclohexanone oxime[19] and Dong's bidentate quinolin-8-carbonyl oximes.[17, 24] Though they showed good compatibility in the previous C(sp^3)-H transformations,[25] no desired fluorinated products were detected when these neutral monodentate (L-type) or bidentate (L, L-type) oxime auxiliaries were used (Table 2, **DG 1**, **2** and **2'**). We envisioned that modifying the oxime auxiliaries might be able to control the Pd^{IV} reductive elimination pathway towards C-F bond formation. Given the advantage and successful application of bidentate, monoanionic auxiliaries (L, X-type) in the C(sp^3)-H bond functionalizations,[26] we proposed to replace one neutral *N*-donor ligand by an anionic motif to stabilize the high-valent palladium complexes and facilitate the C−F bond formation.[27]

Pyruvic acid is a simple, readily available skeleton and perfectly matches our proposal for the auxiliary design.[28] Various pyruvamides derived from pyruvic acid and amines were prepared and investigated for the β-fluorination of isoamyl alcohol. As shown in Table 2, the Weinreb-type amide gave no fluorinated product (**DG 3**). An attempt to utilize a tridentate auxiliary also failed (**DG 4**). To our delight, simple N-cyclohexyl pyruvamide and pyruvanilide gave promising results and the desired products were detected in 10% and 21% yield respectively (**DG 5** and **6**). Encouraged by this result, various pyruvanilides were next surveyed (**DG 7-9** and **DG^{Al}**). Gratefully, though electron-donating amides were less efficient, electron-withdrawing amides exhibited good reactivity towards β-fluorination. Especially when the N-pentafluorophenyl pyruvamide was used as the bidentate auxiliary, 95% yield of the desired product was observed. The weakly coordinating nature of the electron-withdrawing pyruvamide is likely responsible for the dramatic increase of the reactivity in C-F bond formation according to the previous reports.[13c, 29] Finally, the negative results of using pentafluorophenol pyruvate (**DG 10**) and N-methyl-N-pentafluorophenyl pyruvamide (**DG 11**) as auxiliaries confirmed the necessity and superiority of this bidentate, monoanionic auxiliary in the C(sp^3)-H bond fluorination of alcohols. In comparison with the previous report, our auxiliary is highly modular and easily accessible through simple amidation of pyruvic acid with diverse amines, and may thus find application in various C-H bond functionalizations with different transition metals by adjusting the electronic nature of the bidentate auxiliaries.

With the optimized conditions in hand, the substrate scope of the β-fluorination was then investigated (Table 3). Methyl C-H bonds in the β-position of primary, secondary, and tertiary

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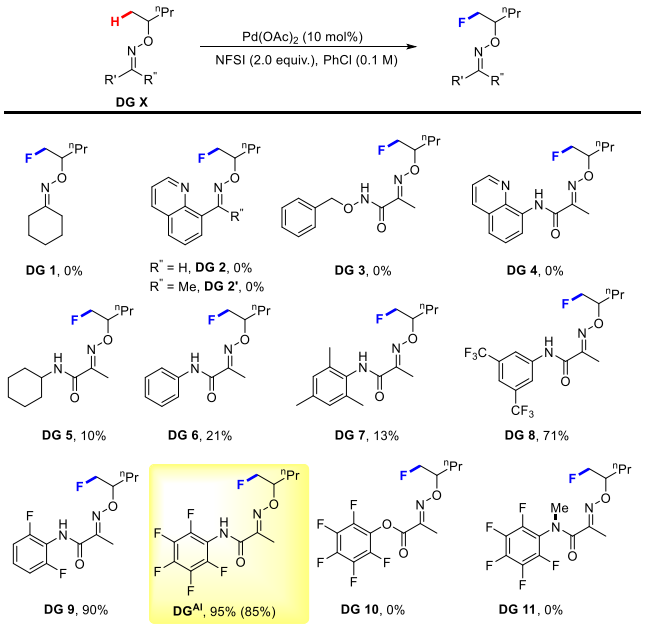
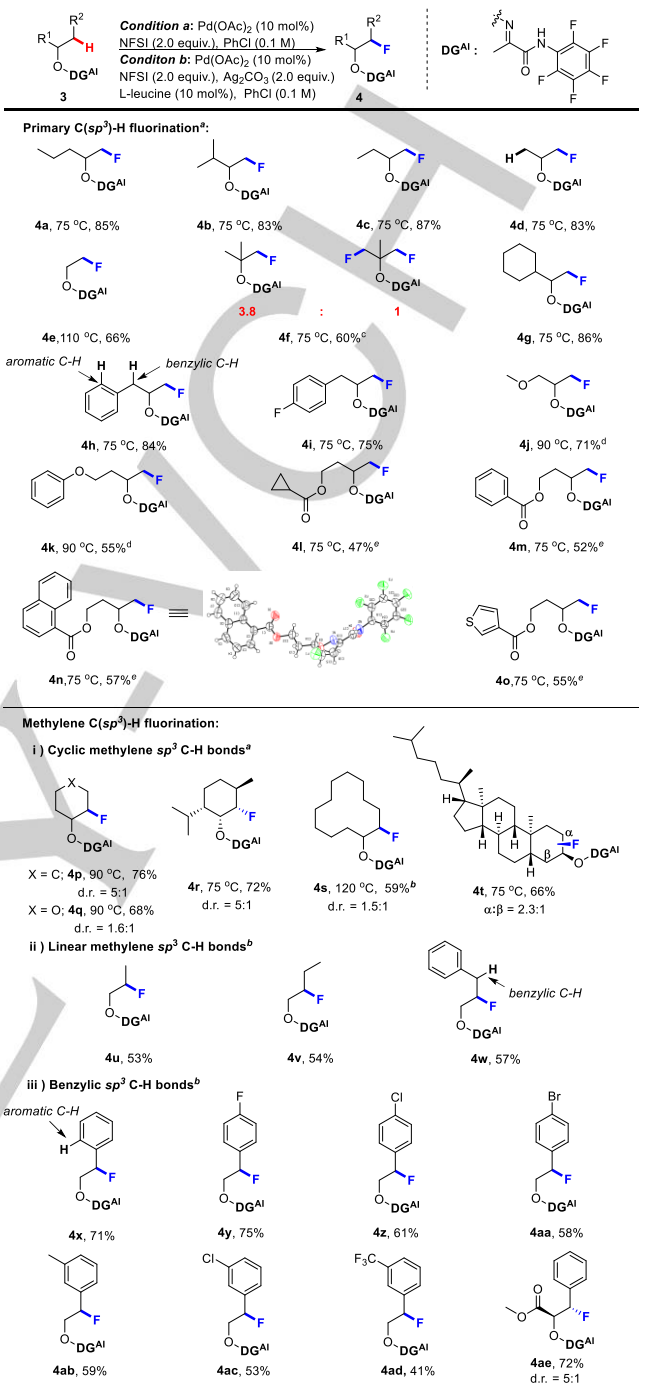
Table 2. Screening of auxiliaries for C(sp^3)-H bond fluorination of alcohols.



Standard conditions: **DG X** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), NFSI = N-fluorobenzenesulfonimide (0.2 mmol.), and PhCl (1.0 mL) were added to a test tube, the mixture was stirred at 75 °C for 24 h. Yields were determined by GC-MS analysis using dodecane as internal standard. The isolated yield is given in parenthesis.

alcohols were fluorinated smoothly in moderate to excellent yields (Table 3, **4a-4f**). Difluorination was observed for the *tert*-butanol derived substrate bearing three available methyls C-H bonds (Table 3, **4f**), whereas mono-fluorination was detected in excellent selectivity for the *iso*-propanol derived substrate (Table 3, **4d**). Various functional groups such as aryls, ethers, cyclopropane, esters and thiophene were well tolerated (Table 3, **4g-4o**). In addition, β-fluorination selectivity was further confirmed by the X-ray crystal structure of product **4n**. To our delight, less reactive methylene C(sp^3)-H bonds were also accommodated in this transformation. Fluorination of cyclic methylene C-H bonds even in more complex structures was also feasible, giving the mono-fluorinated products in good yields (Table 3, **4p-4r & 4t**). However, the methylene C-H bonds in cyclododecanol-derived substrate exhibited similar reactivity to the more challenging acyclic methylene C-H bonds, which required elevated reaction temperature to achieve comparable yields (Table 3, **4s** & **4u-4w**). In addition, due to its flexible 12-membered-ring, the stereoselectivity of **4s** was insufficient in comparison with the substrates bearing more rigid 6-membered ring. Next, the benzylic C(sp^3)-H bond fluorination of phenylethyl alcohols was investigated (Table 3, **4x-4ae**). Notably, the reactions gave excellent β-fluorination selectivity at the benzylic position, even when aromatic C(sp^2)-H bonds were available in the same molecules. The selectivity was thus complementary to the aforementioned aromatic C(sp^2)-H bond fluorination of acetone oxime-based phenylethyl alcohol (Table 1, **2p**). It is noteworthy that functionalization of acyclic methylene C-H bonds or benzylic C-H bonds was much less efficient in the previous *exo*-directing reports, which further demonstrated the superiority of our new auxiliary. Moreover, remarkably high chemo- and site-selectivity were observed by using the new *exo*-amide-imine (**DG**^{AI}) auxiliary even when multiple reactive C–H bonds are presented in a single molecule (*e.g.* **4h**, **4w**, **4x**), which is of great importance in the selective late-stage C-H fluorination of complex alcohols.

Table 3. Scope of C(sp^3)-H bond fluorination of alcohols



Standard conditions a: **3** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), NFSI = N-fluorobenzenesulfonimide (0.6 mmol, 2.0 equiv.), and PhCl (3.0 mL) were added to a test tube, the mixture was stirred at indicated temperatures for 24 h. Conditions b: **3** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), NFSI (0.6 mmol), Ag_2CO_3 (0.6 mmol), L-leucine (0.03 mmol), and PhCl (3.0 mL) were added to a test tube, the mixture was stirred at 120 °C for 24 h. [c] $Pd(OAc)_2$ (20 mol%), NFSI = (3.0 equiv.). [d] DCE (3.0 mL) was used instead of PhCl (3.0 mL). [e] Reactions were performed under N_2 atmosphere and extra dry solvent was used.

Furthermore, the removal of the directing group can be readily achieved by the Raney Ni catalyzed reduction or molybdenum hexacarbonyl mediated cleavage of the N-O bond, giving the corresponding fluorinated alcohols in high yields[21] (Scheme 2).

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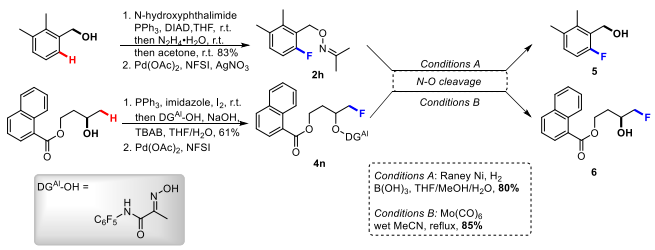
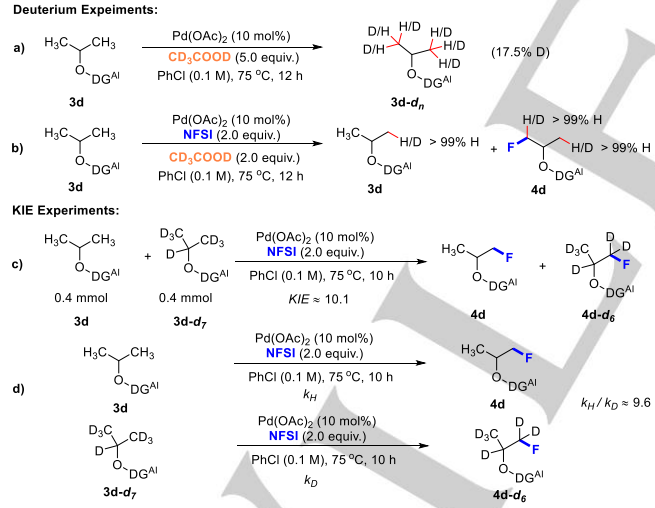


Scheme 2. Installation and removal of DGs.

With the intriguing bidentate auxiliary assisted C(sp^3)-H fluorination established, several mechanistic experiments were conducted to get further insight into the reaction. Firstly, a dimer palladium complex was obtained to further establish the proposed mode of interaction between the bidentate auxiliary and the palladium (see the SI for details). For better understanding the nature of C(sp^3)-H cleavage, several deuterium-labeling experiments were carried out. The results indicated that the C-H cleavage step was reversible in the absence of NFSI (Scheme 3, a) but irreversible under the present catalytic condition (Scheme 3, b). Next, a large KIE value around 10 was obtained by the one-pot intermolecular competition experiment or two side-by-side reactions between **3d** and deuterated **3d**-d_7 (Scheme 3, c & d), which suggested that the C-H cleavage was likely to occur in the turnover-limiting step. Based on the above observations and previous literature,[24, 30-31] a plausible mechanism involving a Pd(II/IV) catalytic cycle is proposed (see the SI for details).



Scheme 3. Preliminary mechanism studies.

In conclusion, we have developed a general and selective C(sp^2)-H and C(sp^3)-H fluorination of simple alcohols. Various C-H bonds including aromatic C-H bonds, methyl C-H bonds, methylene C-H bonds as well as benzylic C-H bonds were selectively fluorinated enabled by *exo*-directing groups, providing a general method to incorporate fluorine into simple alcohols. Moreover, the auxiliaries can readily be removed by the cleavage of the N-O bond to furnish fluorinated alcohols. Notably, the newly developed bidentate auxiliaries are modular, easily accessible and removable, which might have broad application prospect in various challenging C-H bond functionalization in the near future. Further explorations on the development of new reactions with the novel modified pyruvamide auxiliaries are ongoing in our lab.

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Keywords: C(sp^3)-H fluorination • C(sp^2)-H fluorination • alcohol • *exo*-directing • bidentate auxiliary

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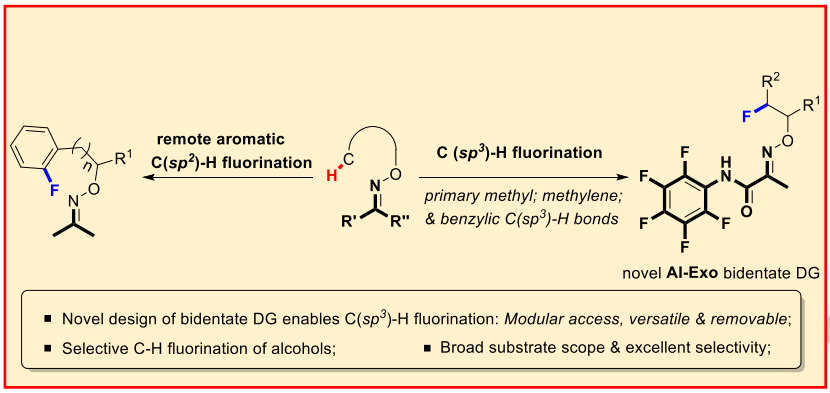

A versatile and selective C(sp^3)-H and C(sp^2)-H fluorination of simple alcohols enabled by a novel design of *exo*-directing groups was developed for the first time. C(sp^2)-H bond fluorination was achieved by using simple acetone oxime as auxiliary, whereas a new and modularly accessible bidentate auxiliary was developed for the efficient and site-selective fluorination of more challenging C(sp^3)-H bonds of diverse primary methyl, methylene and benzylic C-H bonds.

Yang-Jie Mao, Shao-Jie Lou, Hong-Yan Hao and Dan-Qian Xu**

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Selective C(sp^3)-H and C(sp^2)-H Fluorination of Alcohols Using Practical Auxiliaries