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Fluorination Hot Paper

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Mild and Versatile Nitrate-Promoted C–H Bond Fluorination**

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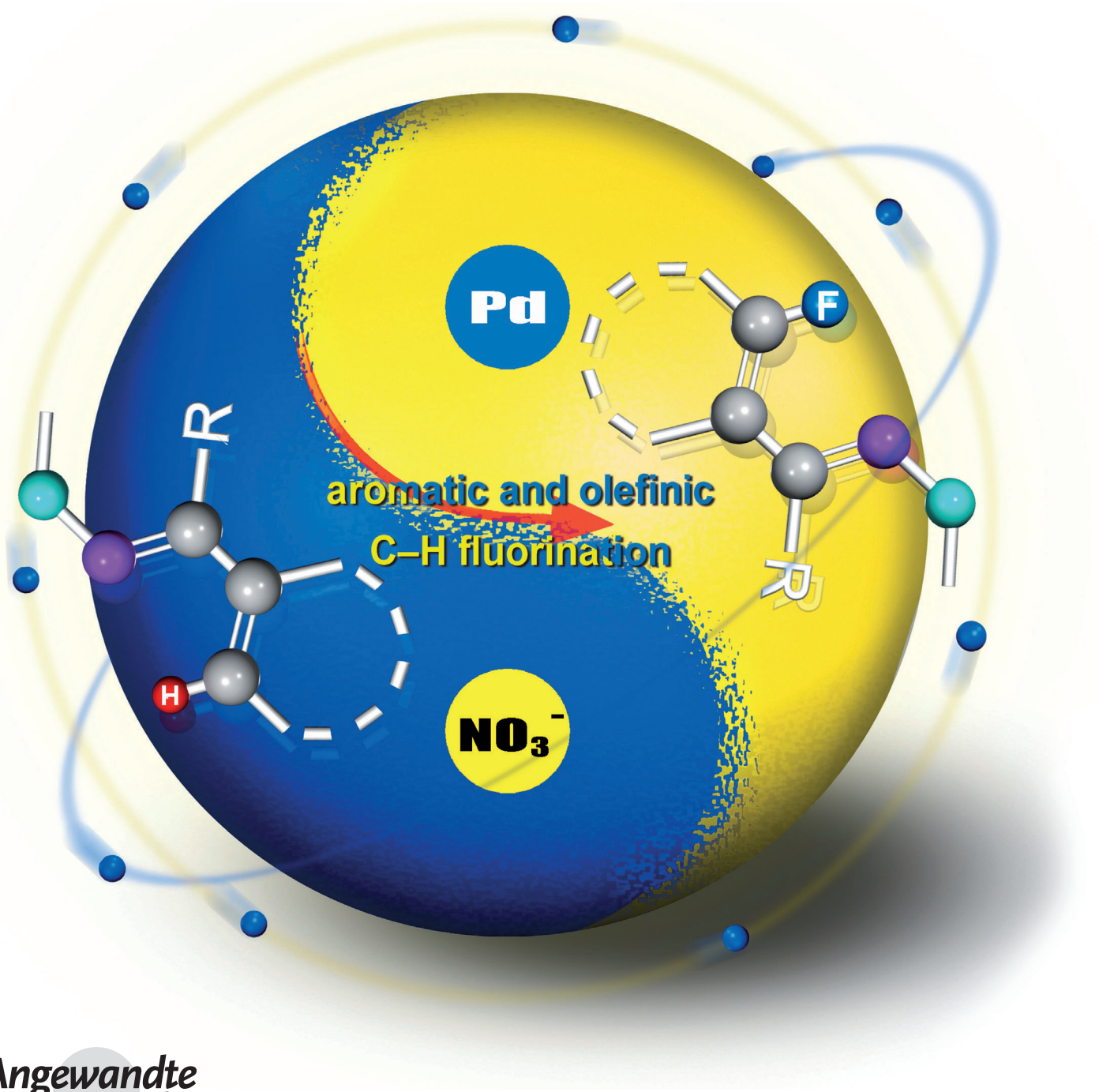

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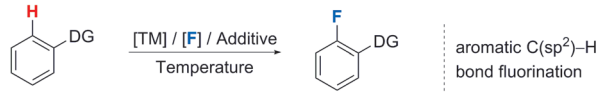
Abstract: *A novel and facile C–H bond fluorination proceeds under remarkably mild conditions (close to room temperature in most cases). Both aromatic and olefinic C(sp^2)–H bonds with a wide range of electronic properties are selectively fluorinated in the presence of a catalytic amount of simple, cheap, and nontoxic nitrate as the promoter. A Pd^{II}/Pd^{IV} catalytic cycle that is initiated by an in situ generated cationic $[Pd(NO_3)]^+$ species was proposed based on preliminary mechanistic studies.*

Fluorinated scaffolds are prevalent in biologically active compounds, pharmaceuticals, agrochemicals, and materials. Because of the drastically increased lipophilicity, bioavailability, and metabolic stability of the fluorinated molecules, the introduction of fluorine substituents has always been of great interest to chemists.[1] Nevertheless, the unique nature of the fluorine atom renders the construction of C–F bonds under mild conditions a great challenge. This issue applies in particular to the selective late-stage fluorination of simple C–H bonds.[2]

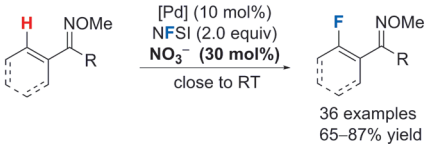
Despite the classical pyrolytic conversion of aryl diazonium salts into aryl fluorides (Balz–Schiemann reaction), which was discovered in the early 1920s,[3] many methods for C–F bond formation protocols have only been described during the past few decades.[4] Several efficient procedures have been developed to transform phenols,[5] aryl magnesium species,[6] aryl halides,[7] triflates,[8] silanes,[9] or stannanes,[10,11c] aryl boron species,[11] and iodonium salts[12] into the corresponding aryl fluorides by using nucleophilic or electrophilic fluorinating agents. However, the utilization of prefunctionalized starting materials as well as the relatively harsh reaction conditions still limit the application of these procedures. A method for mild and selective C–H bond fluorination appears to be an attractive and practical alternative for the construction of C–F bonds. Over the past few years, several examples of directed C–H bond fluorination have been described (Scheme 1).[13] Sanford and co-workers pioneered chelation-assisted C–H bond fluorination;[14] however, poor selectivity with respect to mono-/difluorination was observed for the fluorination of aromatic C–H bonds because of the strong coordination ability of the pyridine directing group. More recently, Yu et al. reported a triflamide-directed *ortho* fluorination of aromatic C–H bonds in the presence of $Pd(OTf)_2{\cdot}2H_2O$ (OTf = trifluoromethanesulfonate) and *N*-methyl-2-pyrrolidone (NMP), which did not suffer from C–H bond acetoxylation, but still displayed a poor mono-/difluorination selectivity.[15] In 2011, the Yu group developed a modified strategy that features a weakly coordinating amide as the directing group, which significantly improved the mono-/difluorination selectivity.[16] Aside from the electrophilic fluorinating agents, the nucleophilic fluorine source AgF was also employed in such transformations. Sanford and co-workers developed the first benzylic C–H bond fluorination of 8-methylquinoline derivatives with a nucleophilic fluorinating agent.[17] Daugulis et al. described a copper-catalyzed aromatic C–H bond fluorination using an excess of *N*-methylmorpholine-*N*-oxide (NMO) as a sacrificial oxidant.[18] Our group recently reported a selective aromatic C–H bond fluorination that is promoted by trifluoroacetic acid (TFA) and features diverse *N*-aryl-substituted N-heterocycles as the directing groups.[19] However, among all of the methods that have been described for directed C–H bond fluorination, none could be carried out under mild reaction conditions (e.g., at room temperature) because of the high strengths of both the C–H and the C–F bond. As part of our search for novel catalytic systems for C–H bond fluorination,[19] we intended to develop a mild and versatile method for selective C–H bond fluorination (Scheme 1).

1) Previous work:



	DG	[F]	Additive	*T* [°C]
Sanford	pyridine	*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1.5–2.0 equiv)	–	110 (microwave)
Yu	triflamide or *N*-arylbenzamide	*N*-fluoro-2,4,6-trimethylpyridinium triflate (1.5–3.0 equiv)	NMP (0.5 equiv)	120
Daugulis	8-aminoquinoline benzamide	AgF (3.5–6.0 equiv)	NMO (4.5-8.0 equiv)	50–125
Our group	*N*-aryl N-heterocycle	NFSI (1.5 equiv)	TFA (2.0 equiv)	110

2) This work: mild C–H bond fluorination:



Scheme 1. Previous reports on C–H bond fluorination. DG = directing group, NFSI = *N*-fluorobenzenesulfonimide.

Inspired by encouraging achievements in versatile C–H bond activation/functionalization as well as in C–F bond formation under mild conditions,[10b,11c,20] we hypothesized that a mild C–H bond fluorination could be accomplished in the presence of specific additives. *O*-Methyl oxime ethers[21]

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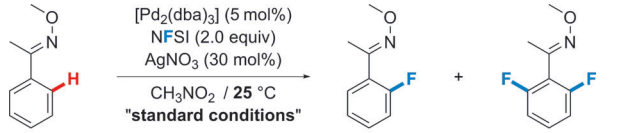
were selected as the model substrates because of their readily removable oxime groups and extensive derivatization potential. Having investigated various additives,[22] we were delighted to find that in the presence of $Pd(OAc)_2$ (10 mol%) and a catalytic amount of silver nitrate (30 mol%), acetophenone *O*-methyl oxime (**1a**) was successfully *ortho*-monofluorinated to give **2a** in 78% yield, along with 10% of the *ortho*-acetoxylated side product even at room temperature. Gratefully, after a thorough screen of other catalysts, including Pd^0 and Pd^{II} precursors, the formation of the *ortho*-acetoxylation side product was eventually avoided when $[Pd_2(dba)_3]$ was utilized to afford *ortho*-monofluorinated **2a** in 90% yield (Table 1, entry 1). On the other hand, *ortho*-difluorinated **2aa** was formed as the sole product with full consumption of substrate **1a** under more forcing conditions (110°C; entry 2), thus the mono-/difluorination selectivity could readily be altered by a change in reaction temperature.

However, the reaction did not proceed in the absence of a palladium catalyst or $AgNO_3$ (entries 3 and 4). As $AgNO_3$ was imperative to the present transformation, various silver salts were next investigated. To our surprise, only silver nitrate and silver nitrite could successfully promote the reaction, whereas other silver salts were ineffective. The unique counteranion effect led us to presume that the nitrate anion might be the pivotal promoter. Various combinations of nitrate anions and silver cations were investigated to verify their respective roles in this fluorination system. Interestingly, although various silver additives, such as Ag_2SO_4, Ag_2O, or AgOTf, responded poorly when used on their own, the fluorination proceeded smoothly with additional KNO_3 (1.0 equiv; entries 5–8). Remarkably, when KNO_3 was used as the sole additive, the reaction proceeded even more efficiently than with $AgNO_3$ as only 2% of difluorinated **2aa** was detected (entry 9). Furthermore, attempts to use other nitrates, such as $NaNO_3$ or even hydrous $Cu(NO_3)_2{\cdot}2H_2O$, provided comparable results (entries 10 and 11). Nitrites could also promote the transformation, albeit in lower yields (entries 12 and 13). The function of the nitrate is still not clear; Sanford et al. have developed a nitrate-promoted $C(sp^3)$–H bond acetoxylation, and the nitrates were proposed to act as a redox co-catalyst, meanwhile, a nitrate ligand effect cannot be excluded.[23] In various previously reported mild C–H activation/functionalization processes,[20] the reactivity of the electrophilic palladium catalyst was dramatically enhanced when specific anions, including CF_3COO^-, BF_4^-, and OTs^-, were coordinated to the transition metal, thus lowering the activation barrier for aromatic C–H bond metalation, which enables the reactions to take place under mild conditions. We hypothesize that a highly reactive cationic $[Pd(NO_3)]^+$ species that is generated in situ from the Pd precatalyst and nitrate initiates the C–H bond activation. To test this hypothesis, the reaction was carried out with $Pd(NO_3)_2{\cdot}2H_2O$ (10 mol%) in the absence of external nitrate additives. Pleasingly, a result similar to that with the $[Pd_2(dba)_3]/AgNO_3$ catalytic system was obtained (entry 14), which indicated that the nitrate anion was the crucial promoter of this transformation. Thus, a novel nitrate-promoted selective C–H bond fluorination under mild conditions has been developed.

Table 1: Optimization of the reaction conditions.[a]



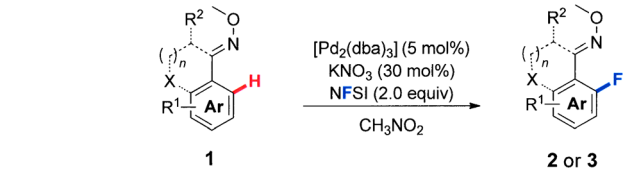
1a **2a** **2aa**

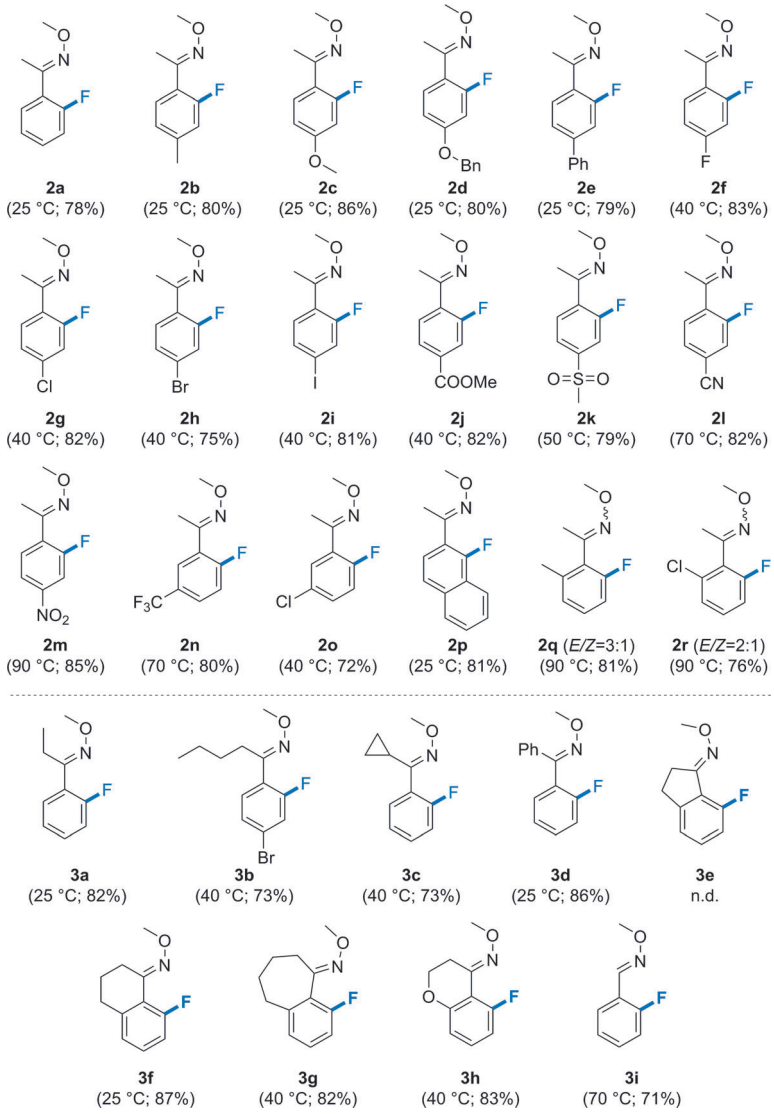
Entry	Variation from the "standard conditions"	Conv. of **1a**[b] [%]	**2a**[c] [%]	**2aa**[c] [%]
1	–	97	90	5
2[d]	110°C instead of 25°C	99	trace	98
3	without $[Pd_2(dba)_3]$	0	0	0
4	without $AgNO_3$	6	6	0
5	Ag_2SO_4, AgOTf, or Ag_2O instead of $AgNO_3$	trace	trace	0
6	Ag_2SO_4 andKNO_3 instead of $AgNO_3$	83	80	2
7	AgOTf and KNO_3 instead of $AgNO_3$	82	79	2
8	Ag_2O and KNO_3 instead of $AgNO_3$	82	79	2
9	**KNO_3 instead of $AgNO_3$**	**93**	**90**	**2**
10	$NaNO_3$ instead of $AgNO_3$	90	87	2
11	$Cu(NO_3)_2{\cdot}2H_2O$ instead of $AgNO_3$	84	78	2
12	KNO_2 instead of $AgNO_3$	45	44	trace
13	$NaNO_2$ instead of $AgNO_3$	44	43	trace
14	$Pd(NO_3)_2{\cdot}2H_2O$ instead of $[Pd_2(dba)_3]$ and $AgNO_3$	96	86	7

[a] Standard reaction conditions: **1a** (0.1 mmol), $[Pd_2(dba)_3]$ (5 mol%), NFSI (2.0 equiv), additive (30 mol%), CH_3NO_2 (1.0 mL), RT, 24 h. [b] Determined by GC-MS. [c] Determined by GC-MS using dodecane as an internal standard. [d] $Pd(OAc)_2$ (10 mol%) instead of $[Pd_2(dba)_3]$ (5 mol%), NFSI (2.5 equiv). dba = dibenzylideneacetone.

With the optimized conditions for mild C–H bond fluorination established, various acetophenone *O*-methyl oximes were employed as substrates to examine the scope of this transformation (Table 2, **2a–r**). Substrates bearing electron-donating groups, such as methoxy, methyl, or benzyloxy substituents, were smoothly *ortho*-monofluorinated in good yields under the optimized reaction conditions at 25°C (**2a–2e**). In contrast, substrates with electron-withdrawing substituents were less reactive. With more electron-poor substrates, harsher conditions were thus required. As shown in Table 2, the fluorination of substrates with halogen, carboxyl, methylsulfonyl, cyano, nitro, or trifluoromethyl substituents proceeded at temperatures ranging from 40°C to 90°C in good yields (**2f–o**). *Meta*-substituted substrates were selectively fluorinated at the *para* position relative to this substituent because of steric effects (**2n**, **2o**). Interestingly, electronic effects were more significant than steric effects owing to the small size of the fluorine atom. When (naphthalen-2-yl)ethanone *O*-methyl oxime was used as the substrate, the electronically favored 1-position of the naphthalene ring was fluorinated with the less sterically hindered C–H bond at the 2-position remaining intact (**2p**). The fluorination of *ortho*-substituted substrates was more difficult because of the increase in steric hindrance between the *ortho*

Table 2: Mild fluorination of aromatic C–H bonds.[a]





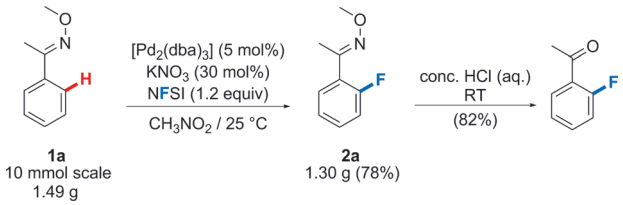
[a] Reaction conditions: **1** (0.3 mmol), $[Pd_2(dba)_3]$ (5 mol%), NFSI (2.0 equiv), KNO_3 (30 mol%), CH_3NO_2 (3.0 mL). Yields of isolated products are given.

substituent and the *O*-methyl oxime directing group, which is unfavorable for the cyclopalladation step (**2q**, **2r**).

Ortho-monofluorination of model substrate **1a** was also carried out on gram scale to evaluate the applicability of this method. No obstacles were encountered when the reaction was conducted under modified conditions at room temperature for 24 hours (Scheme 2). The removal of the *O*-methyl oxime directing group could be readily achieved by treatment with acid according to previous reports (Scheme 2).

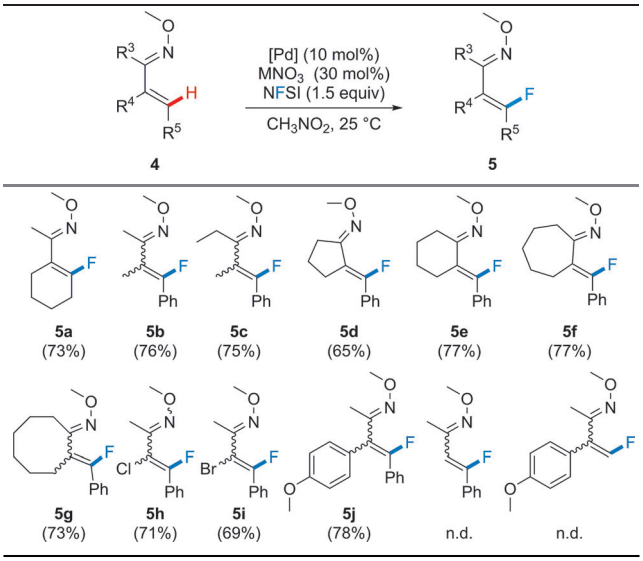
Other carbonyl *O*-methyl oximes were also investigated to evaluate the generality of this method (**3a–i**). A variety of alkyl/aryl aryl ketones were successfully *ortho*-monofluorinated at room temperature or close to room temperature (**3a–d**). The reaction tolerates linear alkyl chains (**3a**, **3b**) and a cyclopropyl group (**3c**). With benzophenone *O*-methyl oxime, mono-fluorinated **3d** was selectively furnished in good yield. 1-Tetralone *O*-methyl oxime, 1-benzosuberanone oxime, and chroman-4-one *O*-methyl oxime were also smoothly fluorinated at the *ortho* position (**3f–h**). However, the reaction of 1-indanone *O*-methyl oxime failed because of ring strain in the indanone (**3e**). Aside from the oxime ethers of ketones, less reactive aldehyde *O*-methyl oxime ethers could also be fluorinated, but a slightly elevated reaction temperature of 70 °C was require to obtain **3i** in good yield. Thus, the present system enables the regioselective aromatic C(sp^2)–H bond fluorination of diverse carbonyl *O*-methyl oximes under mild conditions, which substantially enhances the applicability of this directed C–H bond fluorination method.

With a highly effective procedure for aromatic C(sp^2)–H bond fluorination established, we turned our attention to the more challenging fluorination of olefinic C(sp^2)–H bonds (Table 3). To our delight, 1-cyclohexenylethanone *O*-methyl oxime (**4a**) could be converted into the corresponding fluorinated product **5a** in 73% yield under the standard reaction conditions. To the best of our knowledge, this is the first example of chelation-assisted olefinic C(sp^2)–H bond fluorination. Encouraged by this result, more α,β-unsaturated oximes were subjected to the present fluorination procedure. Pleasingly, α,β-



Scheme 2. Gram-scale C–H bond fluorination of **1a**.

Table 3: Fluorination of olefinic C(sp^2)–H bonds at room temperature.[a]



[a] Reaction conditions: **4** (0.3 mmol), $[Pd_2(dba)_3]$ (5 mol%) or $Pd(OAc)_2$ (10 mol%), NFSI (1.5 equiv), KNO_3 or $AgNO_3$ (30 mol%), CH_3NO_2 (3.0 mL), RT. $[Pd_2(dba)_3]$ (5 mol%)and KNO_3 (30 mol%) were used for **4a**, whereas $Pd(OAc)_2$ (10 mol%) and $AgNO_3$ (30 mol%) were used for all other substrates **4**. Yields of isolated products are given.

unsaturated oximes with various substituents, such as alkyl chains, halide substituents, or aryl rings, furnished the β-fluorinated products in good yields at room temperature (**5b–j**). Notably, even a substrate with a five-membered cyclopentanone oxime ring, which was unreactive when embedded in an indole moiety for aromatic C(sp^2)–H bond fluorination, worked in this case (**5d**). Even cyclooctanone oxime could direct the β-selective C–H bond fluorination (**5g**). However, reactions of α- or β-unsubstituted oximes did not proceed, presumably because formation of the s-*cis* isomer, which is required for directed C–H bond activation, was sterically disfavored.

ESI-MS analysis was utilized as a powerful means to obtain insights into this highly efficient C–H bond fluorination. To our delight, a clear spectrum was obtained when the reaction mixture was subjected to ESI-MS;[22] palladacycle **B**, [aryl–Pd^{IV}–F] intermediate **C**, which is formed after oxidative addition, as well as the product of reductive elimination, Pd^{II} intermediate **D**, were detected at *m*/*z* values of 403, 718, and 550, respectively. Furthermore, the ^{19}F NMR spectrum of a stoichiometric reaction entailed a signal at −189 ppm, which increased in intensity with reaction time.[22] We speculate that this signal corresponds to the fluorine resonance of the key [aryl–Pd^{IV}–F] intermediate **C**.[24] Based on the above observations and previous reports,[25] we propose a reaction mechanism that involves a Pd^{II}/Pd^{IV} catalytic cycle initiated by an in situ generated cationic $[Pd(NO_3)]^+$ species (Figure 1).[22]

In summary, we have described a novel nitrate-promoted mild selective fluorination of aromatic and olefinic C(sp^2)–H bonds. The present fluorination method features 1) mild reaction conditions (generally close to room temperature), 2) the use of a catalytic amount of non-toxic and inexpensive potassium nitrate as a highly efficient promoter, and 3) a

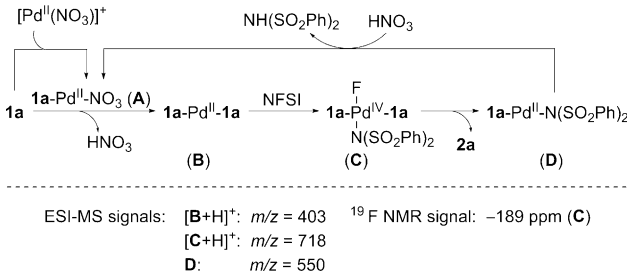


Figure 1. Proposed mechanism.

remarkably broad substrate scope for both aromatic and olefinic C(sp^2)–H fluorination. Furthermore, analysis by ESI-MS and ^{19}F NMR spectroscopy showed that a highly reactive [aryl–Pd^{IV}–F] intermediate was generated during the reaction. A Pd^{II}/Pd^{IV} catalytic cycle that is initiated by a cationic $[Pd(NO_3)]^+$ species was proposed. Further studies to expand the applicability of the present catalytic system are currently in process.

Experimental Section

Oxime ether **1** or **4** (0.3 mmol), palladium catalyst (10 mol%), nitrate salt (30 mol%), NFSI (2.0 equiv), and CH_3NO_2 (3.0 mL) were successively added to a test tube. Then, the tube was sealed, and the reaction mixture stirred at the indicated temperature for 12–24 h (monitored by TLC). Upon completion, the resulting mixture was diluted with Et_2O (10 mL), filtered through a celite pad, and washed with an additional 10 mL of Et_2O. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/EtOAc as the eluent to give the fluorinated product **2**, **3**, or **5**.

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