# The Direct β-C(sp$^3$)–H Fluorination of Carboxylic Acids

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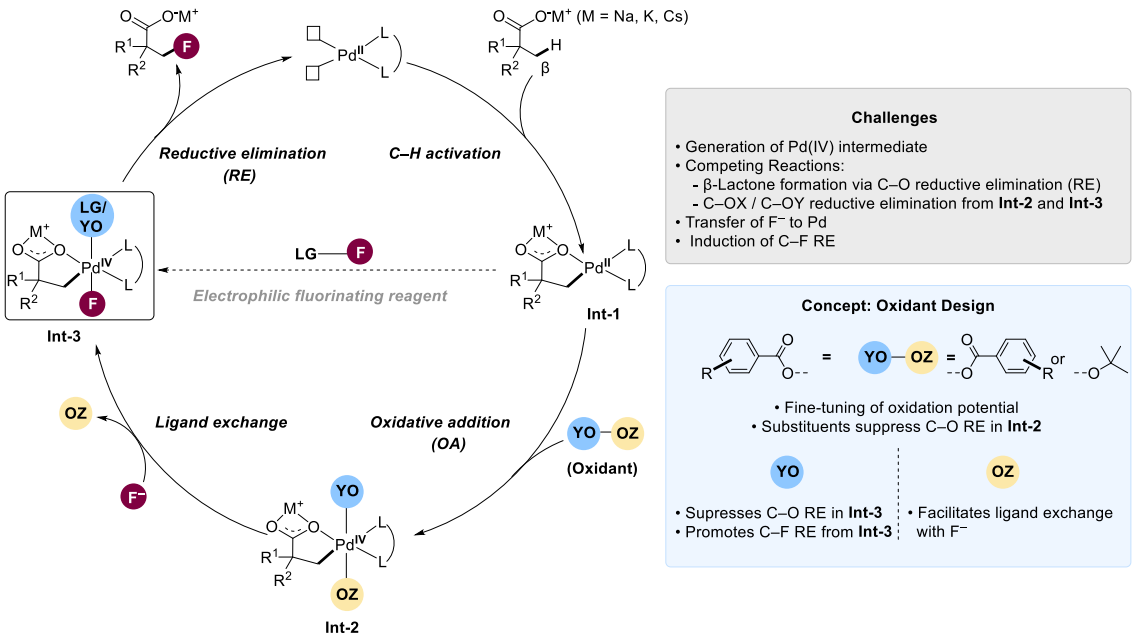
**Abstract: Due to their widespread applications fluorine-containing compounds have become indispensable in various areas of our everyday lives. The ever-increasing demand for complex fluorinated molecules has raised a significant interest to develop new synthetic methodologies that selectively introduce fluorine into molecular scaffolds. While functional group interconversion approaches are well-established in this regard, their reliance on pre-installed reactive handles has encouraged organic chemists to investigate new strategies to enable a direct conversion of inert C–H bonds into C–F bonds. Transition-metal-catalyzed fluorination reactions have been recognized as a promising tool in this context, but fundamental challenges, such as the very high energetic barriers associated with the formation of C–F bonds by reductive elimination, amongst other reasons, remain to be addressed systematically. Arguably, research towards new concepts in fluorination chemistry should be conducted with substrates that are of immediate utility and imply a generalizability of the respective strategies. Carboxylic acids, owing to their versatile synthetic utility in organic synthesis and their comparably challenging use in C–H activation ideally fulfill these criteria. Herein, we here report a protocol that for the first time enables the β-C(sp$^3$)–H fluorination of free carboxylic acids. The rational design of the oxidizing reagent proved to be crucial in establishing the protocol and introduces a new dimension to the rational design of synthetic methods in the field of C–H activation. The reported protocol gives access to a wide range of fluorinated carboxylic acids without the need to introduce an exogenous directing group.**

Fluorine, owing to its small size and high electronegativity can markedly influence chemical, physical, and biological properties, such as lipophilicity, solubility, conformational flexibility, and metabolic stability of organic molecules. Therefore, the incorporation of fluorine into molecular scaffolds is of great interest in various fields, such as medicinal chemistry, [1, 2] agricultural chemistry, [3, 4] material science, [5] and positron emission tomography (PET). [6, 7] Generally, two fundamentally distinct classes of fluorination reagents exist in the chemical toolbox: electrophilic ($F^+$ or $F^{\cdot}$) and nucleophilic ($F^-$) fluorine sources that offer the possibility of forging C–F bonds with orthogonal applicability profiles (substrate structures, functional group compatibilities, etc.). Nucleophilic sources of fluorine which are often readily accessible, inexpensive, and bench-stable, have been widely exploited to construct C–F bonds using functional group interconversion approaches. [8-10] However, these methods heavily rely on the availability of pre-installed reactive handles or native functional groups which limits the applications of such protocols and implies the need to develop complementary synthetic methods that enable the direct conversion of inert C–H bonds to C–F bonds. In this regard, amongst other existing strategies, [11-13] transition-metal-catalyzed fluorination reactions emerged as a very promising technique to synthesize fluorinated building blocks in an atom- and step-economical manner. Despite the importance of C(sp$^3$)–F motifs in various fields, transition-metal-catalyzed C(sp$^3$)–H fluorination reactions remain underdeveloped in comparison to analogous C(sp$^2$)–H fluorinations. [11, 12] The development of transition-metal-catalyzed C(sp$^3$)–H fluorination reactions faces several intrinsic challenges —The formation of C–F bonds by reductive elimination (RE) from low-valent transition metal centers, such as Pd(II) complexes is very challenging. [14, 15] Consequently, oxidants with a very high oxidation potential are used, to generate high valent transition-metal species, from which the RE becomes relatively facile. The RE thus constitutes the main obstacle to C–F bond formation. Additional challenges arise from the poor reactivity of inert C(sp$^3$)–H bonds, caused by their low acidity, high bond energies, and increased entropic penalty for cyclopalladation resulting from the larger conformational flexibility in the starting material (compared to arene ortho-C–H activation). [16, 17] To circumvent the challenging RE from Pd(II), a limited number of transition metal catalyzed C(sp$^3$)–H fluorination reactions has been reported for carboxylic acid derivatives using strongly oxidizing

electrophilic fluorinating reagents capable of generating Pd(IV), all of which required the covalent attachment of strongly coordinating exogenous directing groups[18] on the substrate. [19-22] Commercially available electrophilic fluorinating reagents often feature N–F bonds which besides serving as a stoichiometric oxidant to produce Pd (IV), also transfer the required fluorine atom to palladium alongside the nitrogen-based fragment. From a conceptual point of view, the presence of this (sometimes strongly coordinating) N-containing moiety on palladium may be detrimental for the activation/functionalization of substrates where the entire catalytic cycle relies on designed external ligands. In such cases the identification of suitable electrophilic fluorinating reagents by structural fine-tuning may not be feasible. In 2012, Sanford and co-workers established the first example of a transition-metal-catalyzed C($sp^3$)–H fluorination reaction using a nucleophilic fluoride source in combination with an exogenous oxidant and accomplished a benzylic C($sp^3$)–H fluorination. [23] Despite this seminal work showing the potential of this strategy as an alternative to electrophilic fluorination reagents, this approach has not been exploited for the fluorination of other substrate classes to date. The transition-metal-catalyzed direct C($sp^3$)–H activation/functionalization of free carboxylic acids constitutes a highly attractive goal, as the carboxylic acid moiety is one of the most fundamental and synthetically versatile functional groups in organic chemistry that occurs in the plethora of natural products and pharmacologically relevant compounds. [24, 25] However, the development of such methods remains very challenging due to the low directing ability of carboxylate unit and prevalence of competing coordination modes between palladium and carboxylate moiety amongst other reasons. [26] Over the last years, the area of palladium-catalyzed-C($sp^3$)–H activation/functionalization of free carboxylic acids has witnessed significant advancements through contributions by various research groups including our laboratory. Most of these studies focused on developing new C–C bond forming reactions. [26-28] Amongst the C-heteroatom bond forming reactions, the C–O bond formation received significant attention. [29-32] Very recently, Yu and co-workers have reported the bromination and chlorination of free carboxylic acids. [33] Despite the significant progress in this field, the particularly attractive fluorination of free carboxylic acids has remained out of reach. When aiming to develop such a transformation, several important factors have been taken into account. Due to the weak directing ability of the carboxylate moiety, the use of designed external ligands has proven crucial to accelerate the rate of C–H activation/functionalization reaction, influencing not only the challenging C–H activation step but also the other steps of a catalytic cycle. [34-36] Consequently, progress in this field have hitherto always relied on the extensive screening of ligands, in some cases including the design of novel ligand motifs, to identify a suitable ligand scaffold, followed by extensive structural fine-tuning of the ligand structure and the reaction conditions. In this study, we set out to develop a direct C($sp^3$)–H fluorination of carboxylic acids using a nucleophilic fluoride source. As discussed above, the C–F bond formation should rely on a Pd (II)/Pd (IV) catalytic cycle and require the use of a strong external oxidant. To date, studies relying on a Pd (II)/Pd (IV) catalytic cycle have tested a limited number of commercially available oxidants and, after discovering initial promising reactivity, focused on optimizing the remaining reaction parameters, a strategy that proved insufficient for the envisaged reaction. We realized that the typically employed oxidants transfer organic species onto the catalyst during the oxidation process that remain on the catalyst during critical steps of the catalytic cycle. We envisioned that the design of a suitable oxidant (**YOOZ**) might be key to enable the desired reactivity (**Scheme 1**). Such peroxide-based oxidants would transfer two components (**YO** and **OZ**) onto the catalyst during oxidation, each of them having different roles in the catalytic cycle.




**Scheme 1.** Catalytic cycle for the β-C($sp^3$)–H fluorination of free carboxylic acids with possible associated challenges and concept of oxidant design.

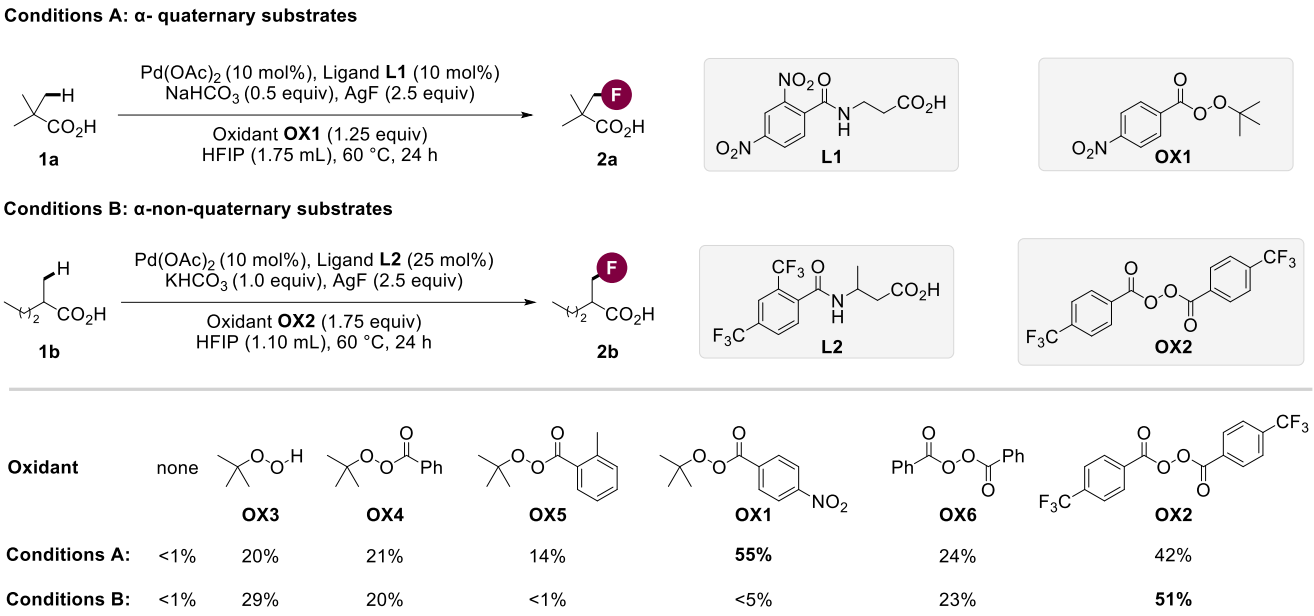
The C–H activated palladacycle **Int-1** formed via C–H activation of the carboxylic acid would first undergo oxidative addition (OA) with the oxidant to generate **Int-2**. The generation of this Pd(IV)-species is expected to be influenced heavily by the groups (**OY** and **OZ**), which define the redox potential of the reagent. Within **Int-2** the properties of the oxidant's component (**OZ**) have to ensure it undergoes fast ligand exchange with the incoming fluoride thereby enabling the generation of **Int-3**. The other component of the oxidant (**OY**), together with the external ligand is expected to influence the C–F RE process from **Int-3.** Furthermore, both groups **OY** and **OZ** would have to be chosen such as to suppress undesired side reactions in **Int-2** or **Int-3,** in particular the possible C–O RE to give C–**OY**, C–**OZ**, or a β-lactone. We thus envisaged that the design of oxidants could serve as a new dimension in reaction optimization to complement ligand design and the choice of reaction conditions and enable highly challenging transformations such as the direct C($sp^3$)–H fluorination of carboxylic acids reported herein.

## Results and Discussion

### Reaction design and optimization

With this design element in hand, we initiated our optimization studies with pivalic acid (**1a**) as a model substrate and silver fluoride as a fluorine source. To gain initial information regarding the optimal oxidant structure, we evaluated common organic peroxides owing to their well-known ability of oxidizing Pd(II) to Pd(IV).[37-39] Initially, BzOO*t*-Bu showed an encouraging reactivity with 20% yield (see supporting information for more details). Due to the propensity of *t*-$BuO^-$ to undergo facile ligand exchange with the incoming nucleophile,[40] we expected that a structural fine-tuning of the benzoyl-motif would influence the steric and electronic properties of Pd(IV) in both **Int-2** and **Int-3**. After an extensive systematic structural variation of the oxidant (for detailed yields of various oxidants see supporting information), the oxidant **OX1** in **Conditions A** (**Scheme 2**) provided the desired product in 55% yield, while the commercially available oxidants (**OX3**, **OX4**, and **OX6**) performed significantly worse, highlighting that ligand design alone was not sufficient to unlock the desired reactivity. Notably, the presence of an electron donating methyl group in **OX5** turned out be detrimental for the reaction suggesting that the electronic properties of the benzoyl-group play a crucial role in this process. We also observed that the reaction benefitted from strong electron-withdrawing groups, such as -$CF_3$, or -$NO_2$, on the oxidant and was sensitive to the position of the substituent on the arene ring, with a substitution at the para position giving maximal yields. Although the

commercially available ligand Ac-β-Ala-OH gave considerable reactivity, a further optimization of ligand structure revealed **L1** to be the best performing ligand under **Conditions A.** With these conditions in hand, we became interested in expanding our protocol to α-non-quaternary substrates, which are considered to be inherently more challenging substrates due to the lack of a favorable Thorpe-Ingold effect and the reduced stability of the intermediately formed palladacycle. As commercially available oxidants (**OX3**, **OX4**, and **OX6**) offered little reactivity, a structural fine-tuning of the oxidant led us to discover the benzoyl peroxide-based oxidant **OX2** with a providing 51% yield of our desired product **2b** under **Conditions B** (**Scheme 2**). Once more, an extensive structural fine-tuning of the Ac-β-Ala-OH motif led us to identify **L2** as a suitable ligand. It is important to note that the commercially available oxidants performed significantly worse than **OX2** even under the optimized conditions (**Scheme 2**), which again highlights how crucial the strategy of oxidant design was in developing this transformation.

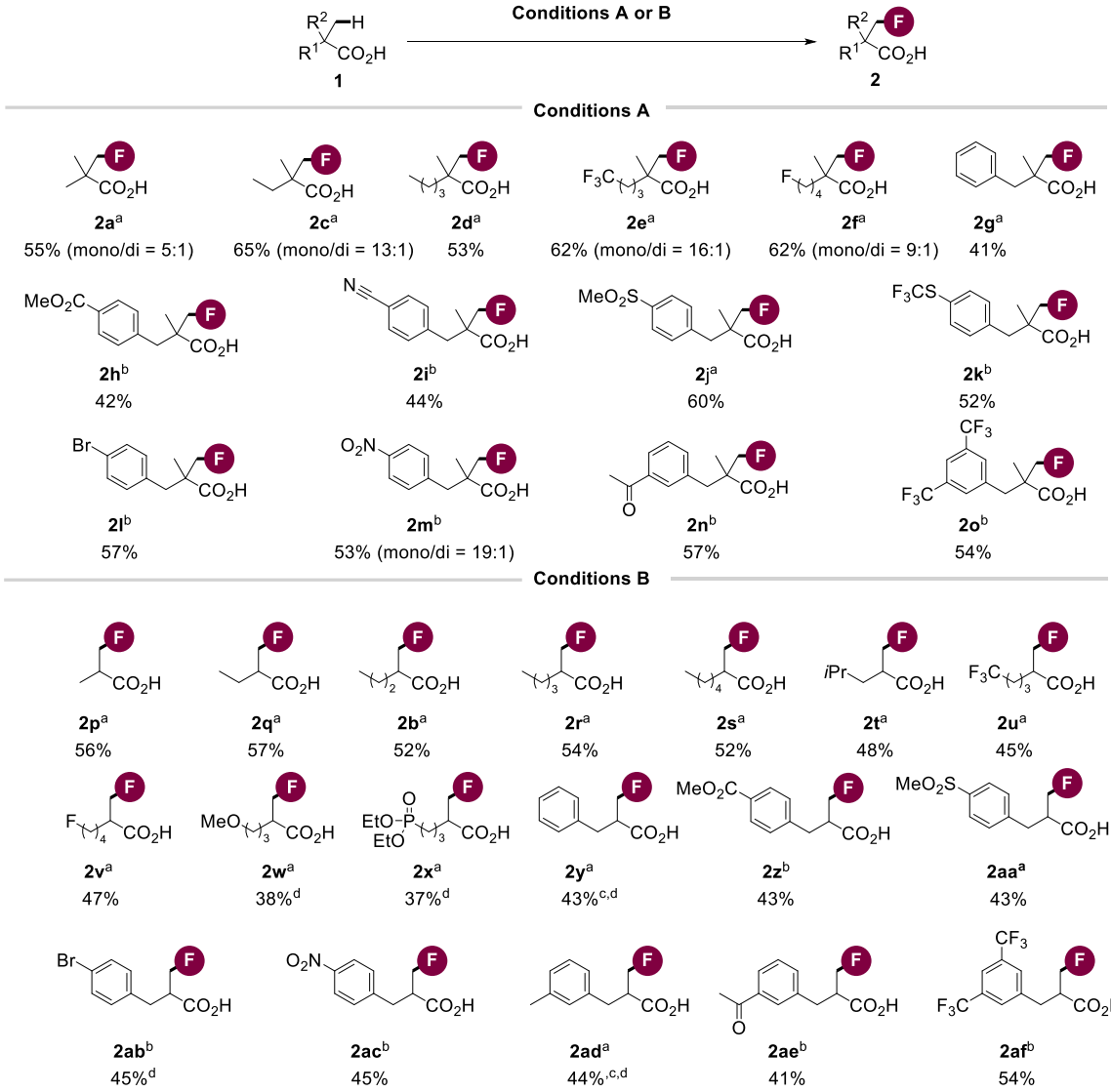



| Oxidant | none | OX3 | OX4 | OX5 | OX1 | OX6 | OX2 |
|---|---|---|---|---|---|---|---|
| Conditions A: | <1% | 20% | 21% | 14% | **55%** | 24% | 42% |
| Conditions B: | <1% | 29% | 20% | <1% | <5% | 23% | **51%** |

**Scheme 2:** Comparison of (designed) oxidants under the two sets of optimized reaction conditions. Reactions were conducted on a 0.1 mmol scale. Yields were determined by $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

### Scope studies of fluorination reaction

Having identified the suitable reaction conditions, we proceeded to study the scope of our transformation. The substrate scope of α-quaternary substrates was evaluated first. As expected from the optimization studies, the product **2a** derived from pivalic acid **1a** was obtained in 55% yield and a mono/di-ratio of 5:1 under **Conditions A** (Scheme 3). Variation in the aliphatic chain length provided satisfactory yields for **2c** (65%, mono/di-ratio of 13:1) and **2d** (53%). Substrates having trifluoromethyl substituent **2e** (62%, mono/di-ratio of 16:1) as well as fluorine substituent **2f** (62%, mono/di-ratio of 9:1) on the side chain were well-tolerated. We were furthermore interested in examining various aryl-containing substrates to check whether the highly reactive benzylic C–H bonds present in these substrates are compatible in our reaction conditions. A range of functional groups was well-tolerated, such as an ester **2h** (42%), nitrile **2i** (44%), sulfur-containing motifs in **2j** (60%) and **2k** (52%), a halogen-substituent in **2l** (57%), a nitro group in **2m** (53%, mono/di-ratio of 19:1), a ketone in **2n** (57%), and a trifluoromethyl group in **2o** (54%). In order to further probe the synthetic utility of our protocol, a representative reaction was performed on a 1 mmol scale giving **2c** in 55% yield, demonstrating that our protocol can be conducted on a preparatively useful scale.

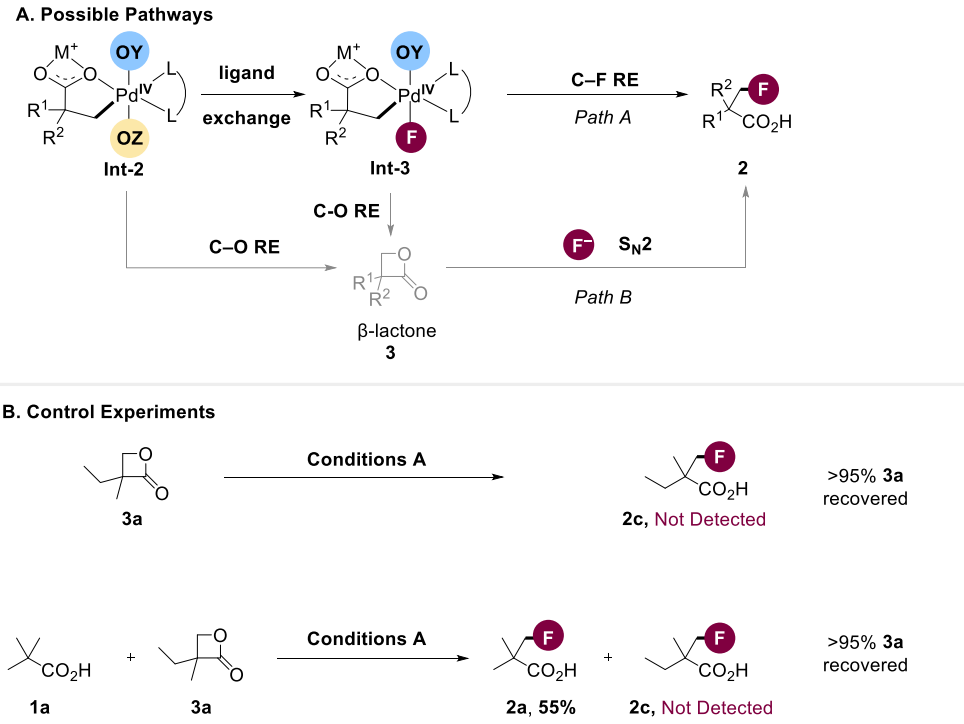



**Scheme 3.** Scope of the direct fluorination of carboxylic acids. Reactions were conducted on a 0.2 mmol scale. mono/di ratios larger than 20:1 are not reported. [a] Isolated after conversion to naphthyl ester. [b] Isolated after conversion to the benzyl ester. [c] $^1$H NMR yield using $CH_2Br_2$ as internal standard. [d] 2.25 equivalents of **OX2** were used.

We proceeded to explore the scope of α-non-quaternary substrates under **Conditions B**. Substrates with gradual increase in the chain length (**2p, 2b, 2q, 2r, 2s**) as well as a branched-chain **2t** provided satisfactory yields. A series of substrates bearing heteroatom containing functional groups (**2u**–**2x**) afforded the respective fluorinated products in moderate to good yield. Electron-poor arene groups, such as in ester **2z** (43%), sulfonate **2aa** (43%), haloarene **2ab** (43%), nitro-substituted **2ac** (45%), ketone **2ae** (41%), and trifluoromethyl-substituted **2af** (41%) were well tolerated under our reaction conditions. Electron-rich arenes on the other hand, gave poor yields under our optimized reaction conditions, presumably due to the aforementioned competing benzylic C($sp^3$)–H functionalization reactions. Considering that such side reactions would consume some of the oxidant, we reasoned that a slight increase in the oxidant loading could help to drive our desired reaction to completion. To our delight, this proved to be effective allowing us to obtain good yield for substrates bearing electron-rich arenes. Overall, a considerable functional group tolerance could once more be demonstrated even for the challenging α-non-quaternary substrates.

### Mechanistic Insights

Considering the challenges associated with the key C–F RE, we became interested in gaining initial mechanistic insights, in particular concerning this part of the reaction mechanism. As depicted in **Scheme 4A**, there are two plausible pathways that could lead to the product formation — **Int-2** could first undergo ligand exchange with the incoming nucleophile $F^-$ to give **Int-3**, from where a C–F RE would form the desired product (*Path A, cf. Scheme 1*)**.** Alternatively, either **Int-2** and/or **Int-3** could undergo a C–O RE to form a β-lactone, which would then undergo a subsequent $S_N2$ reaction with $F^-$ to afford **2** (*Path B*).




**Scheme 4.** Preliminary mechanistic experiments to probe the involvement of a C–F RE. Yields were determined by $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Interestingly, during the scope investigations we could in some cases detect traces of β-lactone (< 3% NMR-Yield), which could either constitute a side product formed by a competing RE from **Int-2** and **Int-3** (*Path A*), or a reaction intermediate (*Path B*). We thus performed control experiments to elucidate, which one of these pathways is operative. When β-lactone **3a** was subjected to **Conditions A**, the corresponding fluorinated product **2c** was not detected in $^1$H NMR and $^{19}$F NMR, while more than 95% of **3a** could still be detected after the reaction, implying that the $S_N2$ reaction of β-lactone with $F^-$ does not occur to a relevant degree under our reaction conditions. To further corroborate this result, we considered the scenario that a reactive intermediate formed during the course of our C–H fluorination reactions could be necessary to trigger the ring opening process of β-lactone. To probe this, **1a** and **3a** were subjected to **Conditions A** together, which resulted in the formation of **2a** in 55% yield (proving that the β-lactone has no detrimental effect on the reaction) while **2c** was not detected. Again, more than 95% of β-lactone **3a** were recovered after the reaction. Overall, these results allow us to rule out *Path B* and thus constitute strong support for the involvement of a C–F RE in the direct fluorination of carboxylic acids.

## Conclusion

In summary, we have developed a protocol that for the first time, enables a direct β-C($sp^3$)–H fluorination of free carboxylic acids. The reaction constitutes a rare example in C–H fluorination, where a nucleophilic fluoride source is combined with an external oxidant. The reported synthetic method employs the free carboxylic acids as limiting

reagents and uses an operationally simple source of fluoride. It was shown to be suitable for challenging α-non-quaternary carboxylic acids and displays considerable functional group tolerance, giving the access to a broad range of fluorinated compounds. The key to success in this study has been the rational design of the oxidants. We identify oxidant-design as a new design dimension that complements ligand-design and can be adopted broadly in organic synthesis to develop synthetic methods which require high valent transition metal species. The further use of these new oxidants to unlock new reactivities is currently ongoing in our laboratory.

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## Methods

### Fluorination of α-Quaternary Carboxylic Acids

An oven dried 10 mL Schlenk tube was charged with $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), **L1** (5.7 mg, 0.020 mmol, 10 mol%), $NaHCO_3$ (8.4 mg, 0.10 mmol, 0.5 equiv), **OX1** (59.8 mg, 0.250 mmol, 1.25 equiv), AgF (63.4 mg, 0.500 mmol, 2.5 equiv), carboxylic acid (0.2 mmol, 1.0 equiv) and HFIP (3.5 mL). The reaction mixture was stirred (stirring speed = 900 rpm) at 60 °C for 24 h in a preheated metal block. The reaction mixture was allowed to cool to rt and formic acid (0.2 mL) was added. The mixture was filtered through a pad of Celite® using $CH_2Cl_2$ (35 mL) to complete the elution and the volatiles were removed under reduced pressure. $K_2CO_3$ (138 mg, 1.00 mmol, 5.0 equiv), NaI (4.5 mg, 0.060 mmol, 0.3 equiv), 2-(Bromomethyl)naphthalene (220 mg, 1.00 mmol, 5.0 equiv) or benzyl bromide (118 µL, 1.00 mmol, 5.0 equiv) and acetone (5 mL) were added and the resulting mixture was stirred at rt for 24 h. The mixture was filtered through a pad of Celite® using $CH_2Cl_2$ (25 mL) to complete the elution, all volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography.

### Fluorination of α-Non-Quaternary Carboxylic Acids

An oven dried 10 mL Schlenk tube was charged with $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol%), **L2** (17.2 mg, 50.0 µmol, 25 mol%), $KHCO_3$ (20 mg, 0.20 mmol, 1.0 equiv), **OX2** (132.4 mg, 350.0 µmol, 1.75 equiv), AgF (63.4 mg, 0.500 mmol, 2.5 equiv), carboxylic acid (0.2 mmol, 1.0 equiv) and HFIP (2.2 mL). The reaction mixture was stirred (stirring speed = 900 rpm) at 60 °C for 24 h in a preheated metal block. The reaction mixture was allowed to cool to rt and formic acid (0.2 mL) was added. The mixture was filtered through a pad of Celite® using $CH_2Cl_2$ (35 mL) to complete the elution and the volatiles were removed under reduced pressure. $Cs_2CO_3$ (325 mg, 1.00 mmol, 5.0 equiv), NaI (75 mg, 0.050 mmol, 2.5 equiv), 2-(Bromomethyl)naphthalene (220 mg, 1.00 mmol, 5.0 equiv) or benzyl bromide (118 µL, 1.00 mmol, 5.0 equiv) and acetone (5 mL) were added and the resulting mixture was stirred at rt for 24 h. The mixture was filtered through a pad of Celite® using $CH_2Cl_2$ (25 mL) to complete the elution, all volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography.