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Palladium-Catalyzed C8-Fluoroalkylation and C8-Fluoroalkenylation of Naphthalenes by C–H Activation

Hugo Amistadi-Revol,^[a] Julie Tremblais,^[a] Nicolas Casaretto,^[b] and Sébastien Prévost*^[a]

[a] H. Amistadi-Revol, J. Tremblais, Dr S. Prévost
Laboratoire de Synthèse Organique (LSO – UMR 7652)
CNRS, Ecole Polytechnique, ENSTA Paris, Institut Polytechnique de Paris
828 boulevard des Maréchaux, 91120 Palaiseau, France
E-mail: sebastien.prevost@ensta-paris.fr

[b] Dr N. Casaretto
Laboratoire de Chimie Moléculaire (LCM – UMR 9168)
CNRS, Ecole Polytechnique, Institut Polytechnique de Paris
Route de Saclay, 91120 Palaiseau, France

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Abstract: In this study, two novel C8-functionalization methods of 1-carbonylnaphthalenes are detailed. Leveraging iodonium triflate as coupling partners, we disclosed palladium-catalyzed C8-fluoroalkylation and C8-fluoroalkenylation processes. These protocols exhibit broad applicability across diverse naphthalene derivatives, thanks to carbonyl directing groups at C1 position which can be retained for subsequent applications or selectively removed, enhancing the versatility of the developed methodologies.

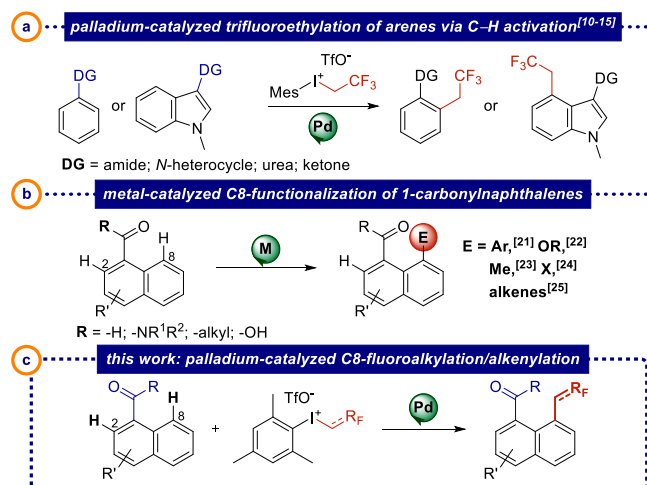
Introduction

The introduction of a fluorine atom into organic compounds holds great significance in chemistry due to the manifold benefits derived from its presence. Indeed, the incorporation of fluorine atoms onto various scaffold can profoundly alter the biological, physical or chemical properties of a compound.^[1] Consequently, these compounds find extensive applications in drug discovery,^[2] agrochemistry^[3] or materials science.^[4] Among the various fluorinated groups that can be introduced, the trifluoromethyl group is probably the most extensively studied.^[5] However, certain research groups have shown interest in the trifluoroethyl group (CF₃CH₂), considering it as a bioisoster of an ethyl substituent.^[6] While CF₃CH₂I remains one of the most popular trifluoroethylating agent, utilized in cross-coupling or radical reactions,^[7] other trifluoroethyl agents have been developed, leading to significant advancements in the field. In particular, aryl(trifluoroethyl)iodonium salts have been employed in palladium-catalyzed C–H functionalization.^[8] Since the initial synthesis of 2,2,2-trifluoroethyl(aryl)iodonium triflate,^[9] these salts have served as crucial coupling partners in C–H activation reactions (Scheme 1.a). Notably, in 2016, the group of Novák reported the first palladium-catalyzed C–H trifluoroethylation on aniline derivatives using these iodonium salts.^[10] Subsequent to this pioneering work, several C–H trifluoroethylation reactions have been documented on diverse scaffolds such as aromatic ureas,^[11] indols,^[12] aromatic amides,^[13] quinazolinones,^[14] benzo[h]quinolines^[15] or acrylamides.^[16] Concurrently,

mechanistic studies, such as those conducted by Li's group, have been undertaken to comprehend the role of the acid in the transformation.^[17] Interestingly, other (fluorinated)iodonium salts have recently found application, such as a (chlorodifluoroethyl)iodonium salt by Chen and co-workers,^[18] as well as (fluoroalkenylated)iodonium salts employed by the Novák's group.^[19]

Significant advancements have been made in recent years regarding the direct C–H functionalization of naphthalene skeletons.^[20] Initially, the focus was primarily on functionalizing the C2 position, employing direct *ortho*-C–H activation methods of arenes. However, a shift in interest has been observed, with several research groups now exploring functionalization at other positions. Notably, with respect to the C8–H bond involving carbonyl as directing group, substantial improvements have been realized by our research group and others. Presently, employing palladium catalysis, it is feasible to introduce aryls,^[21] oxygenated groups,^[22] methyl,^[23] halogen atoms^[24] or alkenes^[25] into this position (Scheme 1.b). In this context, our interest led us to embark on the development of a novel C8-functionalization method for 1-carbonylnaphthalenes, specifically targeting the introduction of fluorinated groups, with the objective to facilitate the synthesis of polysubstituted naphthalenes featuring fluorinated substituents (Scheme 1.c).

Herein we describe a palladium-catalyzed C8-fluoroalkylation and -fluoroalkenylation of naphthalenes, employing amides or ketones as directing groups.

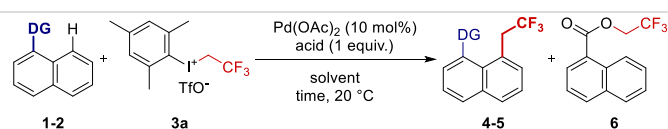


Scheme 1. C-H fluoroalkylation and metal-catalyzed C8-functionalization of 1-carbonylnaphthalenes.

Results and Discussion

At the outset of our investigations, our focus centered on the directing group within the C8-trifluoroethylation reaction (Table 1). Following established literature precedents, we initially employed palladium diacetate ($\text{Pd}(\text{OAc})_2$) as catalyst, 2,2,2-trifluoroethyl(mesityl)iodonium triflate **3a** as trifluoroethylating agent and trifluoroacetic acid (TFA) as additive in 1,2-dichloroethane (DCE) as solvent. These conditions were applied to different 1-carbonylnaphthalenes (see the Supporting Information) and, amide **1a** and ketone **2a** emerged from this screening. Indeed, when methylamide **1a** was used as directing group, C8-trifluoroethylated naphthalene **4a** was observed in 65% NMR yield (Table 1, entry 1), whereas, when pyrrolidine amide **1'a** was the directing group, no desired product was observed (Table 1, entry 2). Instead, known trifluoroethylated ester **6** was isolated in substantial amount. Further exploration of various carbonyl derivatives as directing groups revealed the most promising outcome with methyl ketone **2a**, resulting in a 41% NMR yield of trifluoroethylated product **5a** (Table 1, entry 3). Given these observations, methyl amide was identified as the most suitable directing group, prompting a comprehensive optimization. Notably, to address a slight product degradation, the reaction time was reduced to 2 hours and dichloromethane (DCM) was selected as solvent (Table 1, entry 5). Under these conditions, trifluoroethylated naphthalene **4a** was obtained in a very good 84% NMR yield. Concerning methylketone **2a**, an optimization was also undertaken, revealing that tribromoacetic acid served as the most effective acid additive (Table 1, entries 7-9). A final enhancement was achieved by conducting the reaction in DCE at lower concentration for 4 hours, resulting in a noteworthy 78% NMR yield (Table 1, entry 10).

Table 1. Selected optimization results of the C8-fluoroalkylation reaction.^[a]

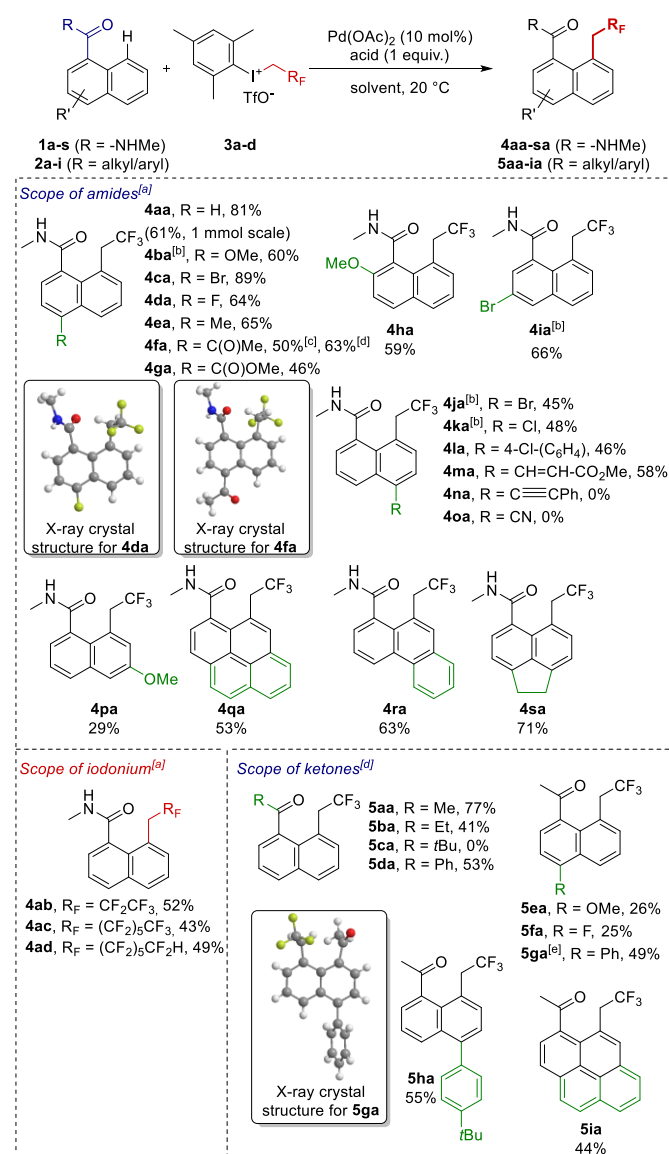


Entry	DG	Time [h]	Solvent [mol.L ⁻¹]	Acid	Yield ^[b] of 4 or 5 [%]
1		24	DCE (0.2)	TFA	65
2		24	DCE (0.2)	TFA	0 ^[d]
3		24	DCE (0.2)	TFA	41
4		24	DCM (0.2)	TFA	67
5		2	DCM (0.2)	TFA	84
6 ^[c]		2	DCM (0.2)	TFA	0
7		2	DCE (0.2)	TFA	59
8		2	DCE (0.2)	TCA	57
9		2	DCE (0.2)	TBA	62
10		4	DCE (0.1)	TBA	78

[a] General reaction conditions: **1** or **2** (0.1 mmol), $\text{Pd}(\text{OAc})_2$ (0.1 equiv.), $\text{MesI}^+\text{CH}_2\text{CF}_3\text{TfO}^-$ (1.1 equiv.), acid (1 equiv.), solvent, 20 °C, time. [b] NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [c] No palladium source. [d] Formation of ester **6** in 25% NMR yield. TFA = trifluoroacetic acid; TCA = trichloroacetic acid; TBA = tribromoacetic acid.

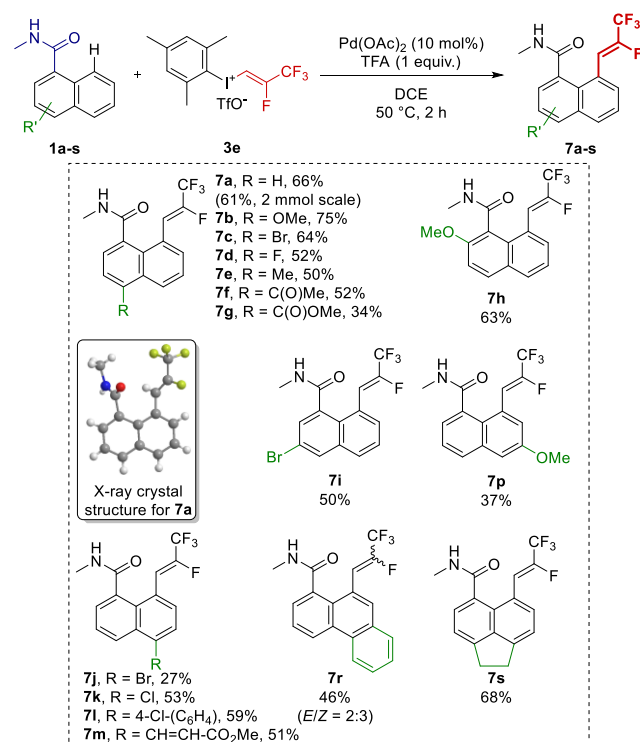
With the optimized conditions in hand, we began to investigate the scope of the C8-trifluoroethylation of 1-methylamide naphthalenes (Scheme 2). First, *N*-methyl-8-(trifluoroethyl)-1-naphthamide **4aa** was isolated in 81% yield, consistent with the previous NMR yield. Subsequently, a wide variety of 4- and 5-substituted *N*-methyl-1-naphthamides (**1ba-1ga** and **1ja-1oa**) were tested and, pleasingly, the reaction exhibited compatibility with a myriad of functional groups, encompassing methoxy group, halogen atoms (Br, Cl, F), alkyls, aryls, carbonyls (ketone, ester) and acrylate. Corresponding products were obtained in moderate to excellent yields (45-89%). Crucially, the C8-selectivity of the reaction was validated by single-crystal X-ray analysis of **4da**.^[26] Interestingly, the utilization of 4-acetyl-*N*-methyl-1-naphthamide **1fa** as starting material resulted in the observation of only mono-trifluoroethylation in 63% yield. As expected, the enhanced efficiency of amide as directing group was affirmed thanks to the single-crystal X-ray analysis of product **4fa** (competitive experiment between **1a** and **2a** was also carried out: see Supporting information 8.d).^[26] It should also be mentioned that no reactivity was detected with naphthalenes **1na-1oa** bearing alkyne or nitrile groups in position 5. Subsequent evaluation of the substituent's position revealed that C8-trifluoroethylated naphthalenes substituted at positions 2, 3 and 6 (**4ha**, **4ia** and **4pa**) were successfully synthesized under our conditions, despite a moderate yield of 29% with a methoxy group in position 6. Finally, the reaction was extended to more complex polycyclic aromatic skeletons such as pyrene, anthracene or 1,2-dihydroaceneaphthylene. In order to enlarge the scope of the reaction, different fluoroalkylethyl(mesityl)iodonium triflate were synthesized and employed to deliver corresponding 8-fluoroalkylated naphthalenes **4ab-4ad** with acceptable yields (43-52%). As seen during the optimization, methyl ketone also

emerged as a suitable directing group for this transformation. The conditions closely parallel those employed for amides, using tribromoacetic acid as the acid and DCE as the solvent. So, several 1-ketonaphthalenes **2a-i** were subjected to the reaction conditions, revealing that steric hindrance of the ketone played an important role in reactivity. For instance, methylketone delivered corresponding product **5aa** in 77% yield, while the yield was decreased to 41% with ethylketone **2ba** and no reactivity was observed with *tert*-butylketone **2ca**. Phenylketone **2da** was also tested, and only trifluoroethylated naphthalene **5da** was observed, leaving the phenyl ring untouched. Expanding the exploration to substituted 1-methylketone naphthalenes, a slightly reduced reactivity was observed compare to amides. Yet trifluoroethylated ketones **5ea-5ha** were isolated in moderate to good yields (25-55%). Similar to amides, C8-regioselectivity was confirmed through single-crystal X-ray analysis of naphthalene **5ga**.^[26] Lastly, the pyrene skeleton was successfully used, leading to the isolation of desired trifluoroethylated pyrene **5ia** in 44% yield.



[d] Reactions were carried out using **2** (0.3 mmol), MesI⁺CH₂CF₃TfO⁻ (0.33 mmol), TBA (0.3 mmol), Pd(OAc)₂ (0.03 mmol) in DCE (3 mL) for 4 h at 20 °C.
 [e] 6 h at 20 °C.

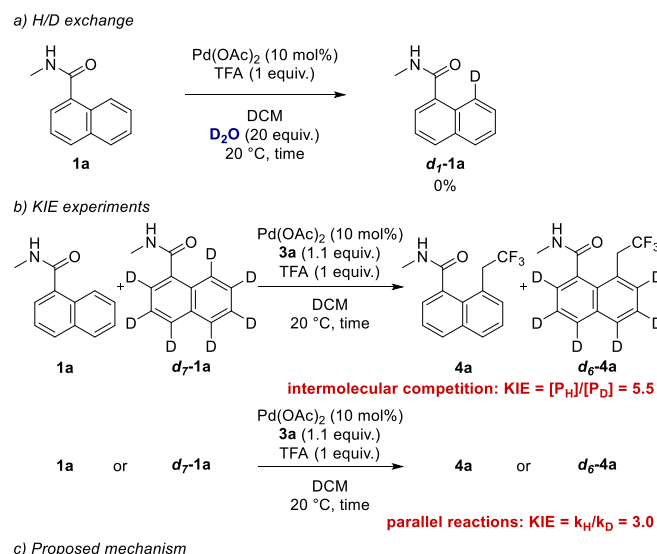
The Novák's group recently disclosed a palladium-catalyzed fluoroalkenylation employing this time (*Z*)-fluoroalkenyl-(mesityl)iodonium salts.^[19] Motivated by this, we explored the feasibility of a C8-fluoroalkenylation of 1-carbonylnaphthalenes. After evaluating various carbonyl derivatives, it was discovered that methyl amide proved to be the optimal directing group for the transformation. Intriguingly, the use of an ethyl ester as directing group resulted in a substantial yield (51%) of desired product, but predominantly exhibiting a *E* selectivity (see the Supporting Information). After a brief optimization on amide **1a** as model substrate, suitable conditions were identified using mesityl(tetrafluoro-propenyl)iodonium triflate **3e** as coupling partner at 50 °C in DCE as solvent, and applied to explore the scope of the reaction (Scheme 3). First, our model substrate **1a** underwent conversion into desired (*Z*)-*N*-methyl-8-(2,3,3,3-tetrafluoroprop-1-en-1-yl)-1-naphthamide **7a** with a 66% isolated yield. Once again, the C8-regioselectivity of the reaction was confirmed through single-crystal X-ray analysis of compound **7a**.^[26] Then, a diverse array of 1-methylamide naphthalenes **1** were transformed into corresponding C8-fluoroalkenylated naphthalenes **7**. The reaction exhibited broad generality, tolerating various functional groups, including methoxy, halogen atoms (Br, Cl, F), methyl, carbonyl derivatives (ketone, ester), aryl or activated alkene, with isolated yields ranging from 27 and 75%. Notably, a good reactivity was consistently observed across diverse substituent positions. Moreover, polycyclic amides **1r** and **1s** were successfully engaged in the reaction, yielding desired products in 46% and 68% respectively, although fluoroalkene **7r** was isolated as a *E/Z* mixture.



Scheme 2. Scope of the C8-fluoroalkylation. [a] Reactions were carried out using **1** (0.3 mmol), MesI⁺CH₂R_FTfO⁻ (0.33 mmol), TFA (0.3 mmol), Pd(OAc)₂ (0.03 mmol) in DCM (1.5 mL) for 2 h at 20 °C. [b] 1 h at 20 °C. [c] 4 h at 20 °C.

Scheme 3. Scope of the C8-fluoroalkenylation. [a] Reactions were carried out using **1** (0.2 mmol), MesI⁺CH₂CF₃TfO⁻ (0.24 mmol), TFA (0.2 mmol), Pd(OAc)₂ (0.02 mmol) in DCE (0.2 mL) for 2 h at 50 °C.

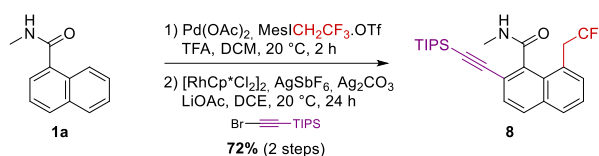
After successfully developed these C8-fluoroalkenylation and C8-fluoroalkenylation reactions, we conducted some experiments to gain a deeper understanding of the reaction mechanism (Scheme 4). First, the addition of D₂O to the reaction mixture revealed no H/D exchange at C8–H, suggesting an irreversible cyclopalladation (Scheme 4.a). Subsequently, kinetic isotopic effect (KIE) experiments were carried out (Scheme 4.b), with both, intermolecular and parallel KIE calculated at 5.5 and 3.0 respectively. These values strongly indicate the involvement of the C–H bond cleavage in the rate-determining step. Based on these mechanistic findings and drawing from previous reports,^[11,17] a plausible mechanism was proposed (Scheme 4.c). Upon activation of the palladium (II) catalyst through ligand exchange with TFA (Pd(TFA)₂) was found to be an efficient catalyst even in the absence of additional TFA, see Table S1.5), the carbonyl group directed the palladium catalyst approach towards the C8-position, facilitating the formation of palladacycle **B**. It is noteworthy that the mechanism might also involve a dimeric palladium species.^[11] Then, oxidative addition by the iodonium salt could form palladium (IV) complex **C**, followed by reductive elimination to deliver desired C8-functionalized product and regenerate active palladium (II) catalyst.



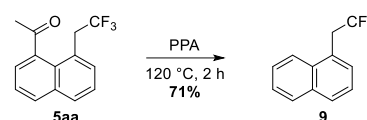
Scheme 4. Mechanism investigations.

In order to show the utility of our methodologies, synthetic transformations were performed. First, sequential C–H functionalizations of 1-methylnaphthalene **1a** were achieved (Scheme 5.a). Trifunctionalized naphthalene **8** was obtained in 72% yield over two step thanks to a C8-fluoroalkenylation followed by a rhodium-catalyzed C2-alkynylation developed by the Echavarren's group.^[27] In a second time, the ketone directing group was successfully removed thanks to polyphosphoric acid at 120 °C to deliver naphthalene **9** in 71% yield (Scheme 5.b).^[28]

a) Sequential C-H functionalizations



b) Directing group removal



Scheme 5. Synthetic transformations.

Conclusion

In conclusion, we propose an innovative palladium-catalyzed C8-fluoroalkenylation reaction, alongside a C8-fluoroalkenylation of 1-carbonylnaphthalenes, utilizing different iodonium salts as coupling partners. Notably, methyl amide and ketones emerged as the most effective directing groups and a very good functional group tolerance was observed. These methodologies offer an efficient pathway to access polysubstituted fluoronaphthalenes and hold promise for facilitating late-stage functionalization of bioactive compounds featuring a naphthalene scaffold. Further explorations of C–H functionalizations of naphthalene derivatives are currently in progress in our laboratory.

Experimental Section

Trifluoroalkylation of amides: In a tube, to a solution of naphthamide **1a-s** (1 equiv.) in DCM (0.2 M) was added Pd(OAc)₂ (10 mol%) and MesI⁺CH₂R_FTfO⁻ **3** (1.1 equiv.). Then, trifluoroacetic acid (1 equiv.) was added dropwise and the mixture was stirred at r.t. for 1-2 h. At r.t., the mixture was filtered through celite and washed with DCM. Then, a saturated NaHCO₃ aqueous solution was added, the aqueous phase was extracted three times with DCM. The combined organic phases were subsequently washed with brine, dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography.

Trifluoroalkylation of ketones: In a tube, to a solution of ketonaphthalene **2a-i** (1 equiv.) in DCE (0.1 M) was added Pd(OAc)₂ (10 mol%) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate **3a** (1.1 equiv.). Then, tribromoacetic acid (1 equiv.) was added dropwise and the mixture was stirred at r.t. for 4 h. At r.t., the mixture was filtered through celite and washed with DCM. Then, a saturated NaHCO₃ aqueous solution was added, the aqueous phase was extracted three times with DCM. The combined organic phases were subsequently washed with brine, dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography.

Fluoroalkenylation of amides: In a tube, to a solution of naphthamide **1a-s** (1 equiv.) in DCE (1 M) was added Pd(OAc)₂ (10 mol%) and (*Z*)-mesityl(2,3,3,3-tetrafluoroprop-1-en-1-yl)iodonium trifluoromethanesulfonate **3e** (1.2 equiv.). Then trifluoroacetic acid (1 equiv.) was added dropwise and the mixture was stirred at 50 °C for 2 h. At r.t., the mixture was filtered through celite and washed with DCM. Then, a saturated NaHCO₃ aqueous solution was added, the aqueous phase was extracted three times with DCM. The combined organic phases were subsequently washed with brine, dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography.

Supporting Information

The authors have cited additional references within the Supporting Information.^[29-32]

Acknowledgements

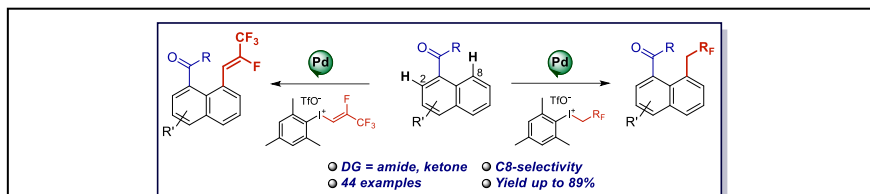
This work was supported by the ANR JCJC grant NaFMETS (ANR-20-CE07-0017). The CNRS, ENSTA Paris and Ecole Polytechnique are acknowledged for financial supports. We thank Sophie Bourcier and Marianne Guillard for HRMS analyses and Dr Lucas Pagès for his help with ¹⁹F NMR.

Keywords: C–H activation • naphthalene • fluoroalkylation • fluoroalkenylation • iodonium salts

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The successful realization of direct palladium-catalyzed C8-fluoroalkylation and C8-fluoroalkenylation of naphthalene derivatives has been accomplished, employing iodonium salts as coupling partners. The reactions exhibited complete C8-regioselectivity, and diverse carbonyl groups were identified as effective directing groups.

Institute and/or researcher Twitter usernames: @LSOpolytech