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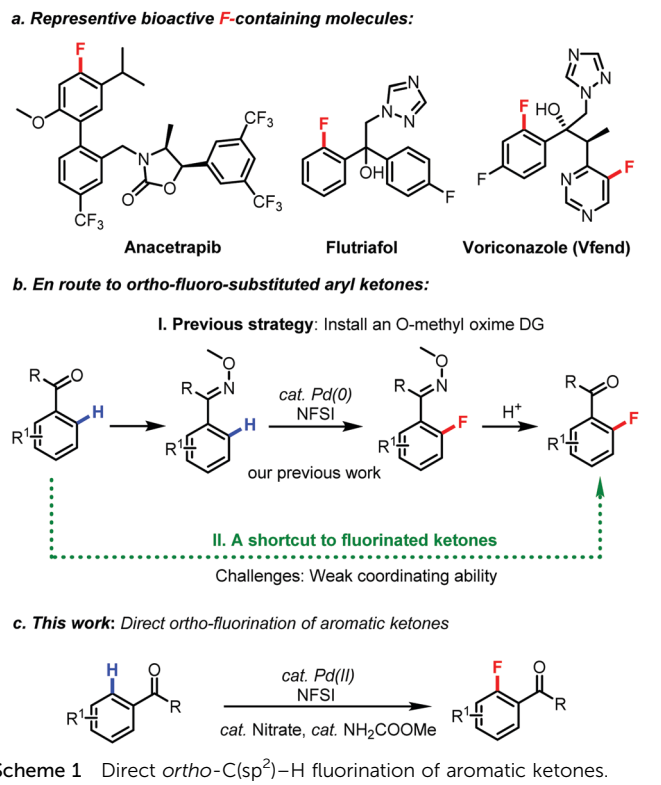
Pd-Catalysed direct C(sp^2)–H fluorination of aromatic ketones: concise access to anacetrapib†

Qiuzi Wu,‡ Yang-Jie Mao,‡ Kun Zhou, Shuang Wang, Lei Chen, Zhen-Yuan Xu, Shao-Jie Lou* and Dan-Qian Xu*

The Pd-cataylsed direct *ortho*-C(sp^2)–H fluorination of aromatic ketones has been developed for the first time. The reaction features good regioselectivity and simple operations, constituting an alternative shortcut to access fluorinated ketones. A concise synthesis of anacetrapib has also been achieved by using late-stage C–H fluorination as a key step.

Aromatic ketones are the fundamental structural moieties in organic chemistry due to their abundance, ubiquity, and transformational versatility.[1] Therefore, the selective introduction of the fluorine atom into aromatic ketones is of great interest and importance since the fluorinated ketones can be easily transformed to more elaborate fluorine-containing pharmaceutical or agrochemical molecules, which may possess improved bioactivity, metabolic stability and lipophilicity (Scheme 1a).[2] However, the weak coordinating ability of the ketone group makes the direct C–H bond fluorination of aryl ketones a longstanding challenge.[3–6] Usually, pre-installed oximes or imines were used as ketone surrogates in C–H bond functionalization.[7,8] For instance, we have previously developed an oxime directed fluorination of aromatic ketone derivatives in the presence of a catalytic nitrate promoter.[8a] Despite the mild reaction conditions, the additional two steps of installation and removal of the directing group significantly attenuate the practical use of this strategy (Scheme 1b).

To overcome this limitation, several C–H functionalizations of aromatic carbonyls enabled by transient directing groups were developed.[9,10] For instance, in the study by Sorensen and co-workers, the *ortho*-C(sp^2)–H fluorination of benzaldehydes enabled by orthanilic acids has been achieved.[10a] Yu *et al.* also reported an enantioselective benzylic C(sp^3)–H fluorination of 2-alkyl benzaldehyde in the presence of a chiral amino acid.[10b] Nevertheless, the analogous C–H bond fluorination of aromatic ketones has not been reported so far, probably due to the slower interaction between ketones and transient directing groups.[11] In this context, we herein described the first example of the Pd-catalysed direct *ortho* C–H bond fluorination of aromatic ketones. The key to the success of this transformation is the catalytical utilization of carbamates and nitrates as



Scheme 1 Direct *ortho*-C(sp^2)–H fluorination of aromatic ketones.

Catalytic Hydrogenation Research Center, State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Key Laboratory of Green Pesticides and Cleaner Production Technology of Zhejiang Province, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: chrc@zjut.edu.cn, loushaojie@zjut.edu.cn

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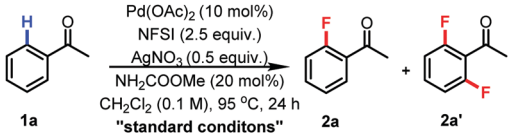
‡ These authors contributed equally.

additives (Scheme 1c). An alternative synthesis of anacetrapib has also been achieved through late-stage C–H bond fluorination and subsequent transformation of ketones.

A simple acetophenone **1a** was selected as the template substrate at the outset of this project (Table 1). After modifying various reaction conditions,[12,13] we found that the desired product *O*-fluoroacetophenone **2a** could be obtained in a good yield of 85% under the following reaction conditions: $Pd(OAc)_2$ (10 mol%), *N*-fluorobenzenesulfonimide (NFSI) (2.5 equiv.), $AgNO_3$ (0.5 equiv.), NH_2COOMe (20 mol%), and heating at 95 °C for 24 hours (Table 1, entry 1). Control experiments showed that the presence of $AgNO_3$ and NH_2COOMe is crucial (entries 2–4). The amount of these additives is also responsible for the reaction efficiency. Neither a higher loading nor a lower loading of these key additives gave a better result than the standard conditions (entries 5–9). Benzyl carbamate could also promote the reaction (entry 10). However, a more sterically demanding *tert*-butyl carbamate was much less effective (entry 11). In addition, nitrite additives also gave positive results, albeit in lower yields (entries 12 and 13).[13e] The replacement of $AgNO_3$ with other silver salts resulted in lower yields, indicating that nitrate is the actual promoter in this transformation (entry 14).[13] As expected, the reaction shuts down in the absence of a Pd catalyst (entry 15). $Pd(OAc)_2$ performed the best among the catalysts tested (entries 16–19). Changing the solvent did not improve the yield (entries 20 and 21).

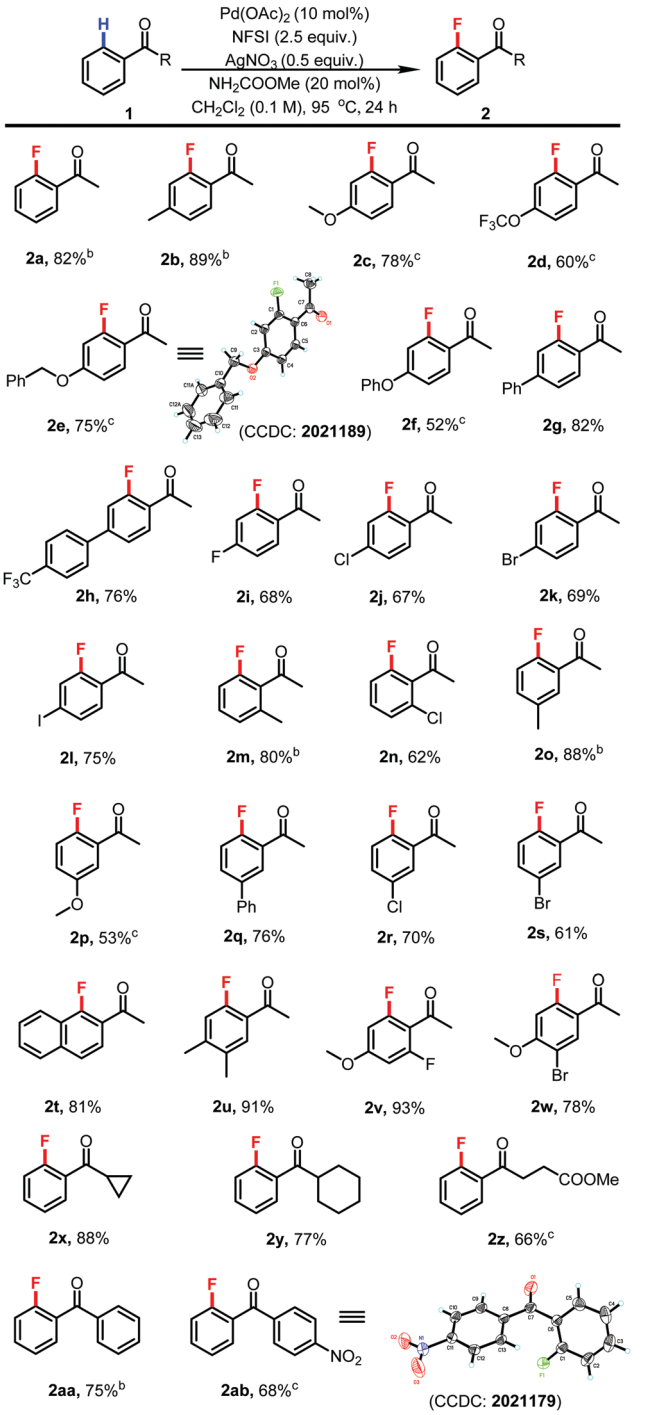
Table 1 Optimization of the reaction conditions[a]



Entry	Variations from "standard conditions"	2a[a] [%]	2a'[a] [%]
1	None	**85**	**Trace**
2	$AgNO_3$ (0), NH_2COOMe (0)	5	0
3	$AgNO_3$ (0), NH_2COOMe (40 mol%)	14	0
4	$AgNO_3$ (0.3 equiv.), NH_2COOMe (0)	15	0
5	$AgNO_3$ (0.3 equiv.)	55	0
6	$AgNO_3$ (0.75 equiv.)	83	5
7	$AgNO_3$ (1.0 equiv.)	69	5
8	NH_2COOMe (40 mol%)	44	2
9	NH_2COOMe (80 mol%)	32	12
10	NH_2COOBn instead of NH_2COOMe	68	3
11	NH_2COO^tBu instead of NH_2COOMe	10	0
12	$AgNO_2$ instead of $AgNO_3$	59	0
13	KNO_3 instead of $AgNO_3$	56	0
14	Ag_2CO_3 instead of $AgNO_3$	12	0
15	Without $Pd(OAc)_2$	0	0
16	$PdCl_2$ instead of $Pd(OAc)_2$	79	3
17	$Pd(dba)_2$ instead of $Pd(OAc)_2$	56	6
18	$Pd(PPh_3)_4$ instead of $Pd(OAc)_2$	49	0
19	$[Pd(Cl)(C_3H_5)]_2$ instead of $Pd(OAc)_2$	13	0
20	DCE instead of CH_2Cl_2	57	2
21	EtOAc instead of CH_2Cl_2	15	0

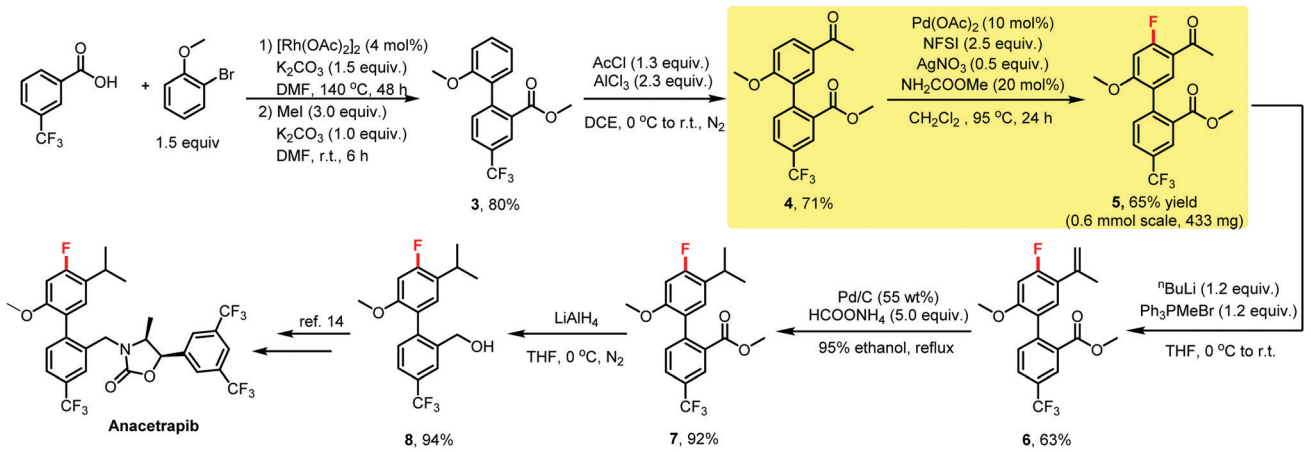
[a] Standard conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), NFSI = *N*-fluorobenzenesulfonimide (0.25 mmol), $AgNO_3$ (0.05 mmol), NH_2COOMe (0.02 mmol), CH_2Cl_2 (1.0 mL), 95 °C, 24 h. Yields were determined by using GC analysis using dodecane as an internal standard.

Table 2 Substrate scope of ketones[a,b,c]



[a] Standard conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), NFSI = *N*-fluorobenzenesulfonimide (0.5 mmol), $AgNO_3$ (0.1 mmol), NH_2COOMe (0.04 mmol) and CH_2Cl_2 (2.0 mL), 95 °C, 24 h, under air, and isolated yields. [b] $AgNO_3$ (0.15 mmol), 12 h. [c] $AgNO_3$ (0.15 mmol).

Having established the optimized conditions for the direct *ortho*-C(sp^2)–H fluorination of acetophenone, we then examined the substrate scope of this transformation (Table 2). In general, both electron-donating groups and electron-withdrawing groups were well tolerated. Functional groups



Scheme 2 The application of the *ortho*-C(sp^2)–H bond fluorination of ketone **4** in the synthesis of anacetrapib.

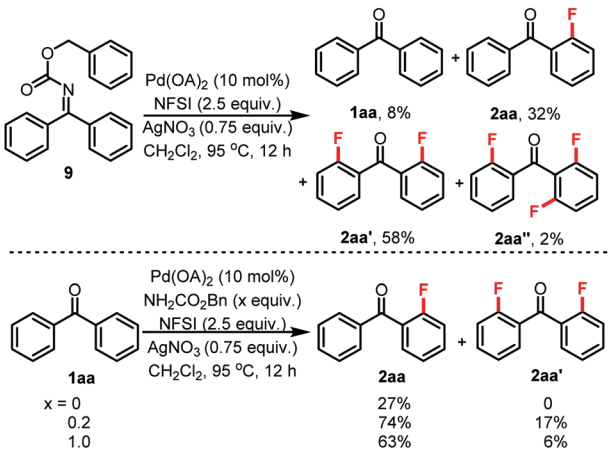
such as methoxyl (**2c** and **2p**), trifluoromethoxyl (**2d**), benzoxyl (**2e**), phenoxyl (**2f**), phenyl (**2g** and **2q**), trifluoromethyl (**2h**), halo (**2i–2l**, **2n**, **2r**, and **2s**), and nitro (**2ab**) groups were all compatible under the reaction conditions. Substituents tethered at the *ortho* position of the ketone did not hamper the reaction (**2m**, **2n**, and **2v**). The *ortho* C–H bond fluorination of *meta*-substituted aromatic ketones took place at the less sterically demanding site (**2o–2s**, **2u**, and **2w**). However, fluorination selectively occurred at the electronically favoured but sterically disfavoured α-position of 2-acetylnaphthalene (**2t**). Other alkyl aromatic ketones were also accommodated in this transformation. Strained cyclopropyl (**2x**), cyclohexyl (**2y**), and carboxyl (**2z**) groups were well tolerated. In addition, the C–H bond fluorination of diaryl ketones also took place smoothly and selectively at the more electron-rich aromatic ring (**2aa** and **2ab**). However, the fluorination of challenging substrates such as the ketones bearing strong electron-withdrawing groups, heteroaryl ketones, and the flexible α,β-unsaturated ketones was less efficient (see the ESI† for more details).

Encouraged by the substrate scope of the present protocol, we envisioned that this fluorination platform might enable the late-stage incorporation of fluorine atoms in the total synthesis of complicated fluorine-containing molecules and improve their traditional synthetic routines.

Anacetrapib is a fluorine-containing cholesteryl ester transfer protein (CETP) inhibitor developed by Merck for the treatment of hypercholesterolemia.[14] Given the challenging fluorine incorporation, the fluorine atom of anacetrapib is usually introduced at a very early-stage of the synthetic pathway, which requires different fluorinated starting materials. Herein, we presented a concise access towards anacetrapib through late-stage C–H fluorination (Scheme 2). The biaryl precursor **3** was obtained in good yields *via* a selective Rh-catalysed C–H arylation of 3-trifluoromethyl benzoic acid with 2-bromoanisole. The aromatic ketone **4** was synthesized by traditional Friedel–Crafts acylation of **3**. Treating **4** with the standard fluorination conditions (0.6 mmol scale) gave the fluorinated ketone **5** in a decent yield of 65%, 433 mg. Then, a key precursor **8** was finally obtained in good yields after several well developed transformations (witting reaction, reduction and hydrogenation) from compound **5**.[15] This synthetic application further demonstrated the potential of the present fluorination protocol in the preparation of fluorine-containing complexes and pharmaceutical molecules.[16]

Next, several control experiments were carried out to better understand the role of the carbamate additive in this reaction (Scheme 3). The C–H fluorination of complex **9** in the absence of carbamate additive resulted in diverse fluorinated diphenyl ketone products (Scheme 3, top). In contrast, the yield of fluorination of ketone **1aa** decreased sharply in the absence of benzyl carbamate (Scheme 3, bottom). These results suggested that this imine species **9** might be *in situ* generated during the reaction and promote fluorination. However, the exact mechanism of this reaction is still not clear and the ligand effect of the carbamate additive could not be ruled out at this stage.[17]

In conclusion, we have developed the palladium-catalysed *ortho*-C(sp^2)–H fluorination of aromatic ketones in the presence of carbamate and nitrate. The reaction features good regioselectivity and simple operations, constituting a new method for the direct incorporation of fluorine atoms into synthetically



Scheme 3 Experimental studies on the role of carbamate.

useful aromatic ketones. Moreover, the synthesis of an anacetrapib precursor has also been achieved by using the late-stage C–H bond fluorination of ketone **4** as a key step.

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Conflicts of interest

There are no conflicts to declare.

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