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p-Toluenesulfonic acid catalysed fluorination of α-branched ketones for the construction of fluorinated quaternary carbon centres†

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A *p*-toluenesulfonic acid catalyzed fluorination of α-branched ketones for the construction of fluorinated quaternary carbon centers has been developed, featuring a broad substrate scope, environmentally benign reaction conditions, and operational simplicity.

The structural motif bearing a quaternary C–F centre is seldom found in natural products but widely present in clinical drugs, agrochemicals, organocatalysts, and functional materials.[1,2] For example, nucleocidin (**1a**)[1r] is one of the five fluorine-containing natural products that have been isolated to date, while fluticasone (**1b**)[2b] has been used for the treatment of asthma as a clinical drug. Other representative compounds containing a quaternary C–F center include the insecticide flubendiamide (**1c**),[1n] maxipost (**1d**), which is used as a potent opener of maxi-K channels and an activator of KCNQ4 potassium channels,[1n,p] compound **1e** and its analogues with potential neuroprotective activity,[1h] and organocatalysts **1f** and **1g** (Fig. 1).[1o,q] Because of the dramatic change in the physical, chemical, biological, and structural properties of the parent compounds by fluorine substitution, the introduction of a fluorine atom to organic molecules is of great importance in modern medical chemistry, pharmaceutical industry, chemical biology, and materials science.[1,2] However, due to the rather limited presence of fluorine-containing organic molecules in nature, achieving these fluorine-containing functional molecules relies mainly on various fluorination reactions. Consequently, diverse fluorinating reagents and fluorinating methodologies for the construction of various C–F bonds have been discovered and developed.[3]

Compared with other classic C–F bonds, the construction of quaternary C–F carbon centres is a more challenging topic in modern fluorination chemistry, therefore certain functional groups have been used to address this problem.[4] Among them, the carbonyl group is usually used for this propose because of not only its wide presence in many functional organic molecules but also its diverse transformations into other functionalities. Although its enolized intermediate has usually been applied to introduce the quaternary C–F bond,[2] from the synthetic viewpoint, the direct fluorination of ketones is much more efficient and should receive the attention from synthetic chemists. Despite the extensive investigation of the fluorination, even the asymmetric fluorination of the 1,3-dicarbonyl compound and its variants (Scheme 1a),[2b] the α-fluorination of α-branched ketones remained underexplored.[5] Very recently, Toste and coworkers have developed an efficient asymmetric approach for the construction an α-fluorinated α-branched ketone scaffold, but some shortcomings still existed in their procedure, such as moderate to good chemical yields, the use of 2.0 equiv. of ketones, and the relatively narrow substrate scope (alkyl substituted substrates are not compatible) (Scheme 1b).[5a] Therefore, the development of new synthetic approaches toward this valuable scaffold is still in high demand. In continuation of our research interest for the construction of aza-quaternary carbon centres,[6] herein, we reported an efficient approach for the preparation of α-fluorinated α-branched ketones through a *p*-toluenesulfonic acid (PTSA) catalysed fluorination.

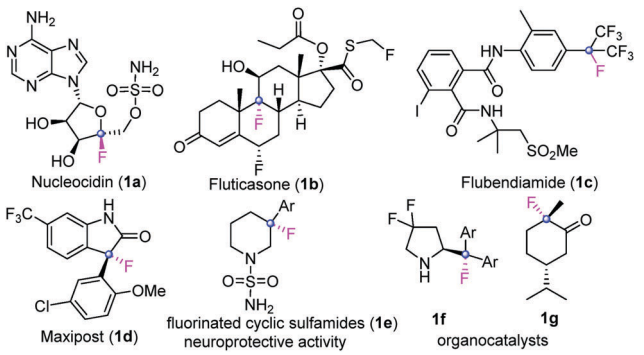

Fig. 1 The representative functional molecules bearing a C–F quaternary stereogenic centre.

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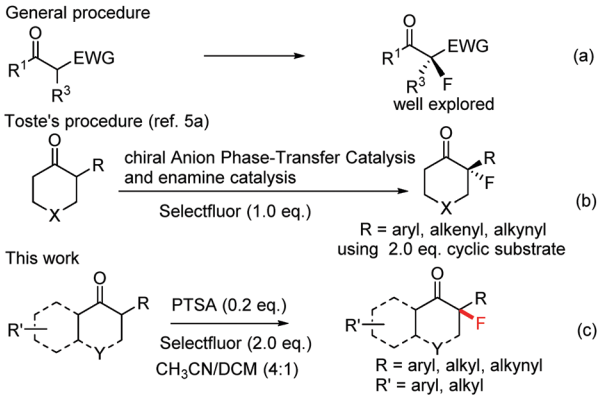
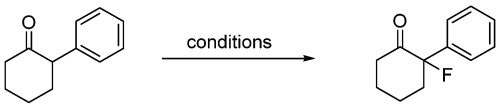


Scheme 1 An overview of construction of the quaternary C–F bond from ketone derivatives.

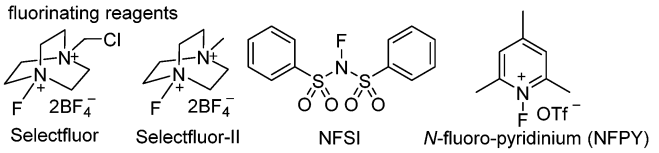
Initially, we selected 2-phenylcyclohexanone (**2a**) as a model substrate and Selectfluor as the fluoride source to investigate the fluorination reaction. When PTSA was used as the catalyst to promote the fluorination in 1,2-dichloroethane (DCE) at room temperature for 48 hours, the desired product **3a** was isolated in 23% yield with the recovery of 66% starting material **2a** (entry 1, Table 1). Further solvent screening showed that CH_3CN was the most suitable solvent for the reaction, but trace unknown by-products was observed.[7] In order to reduce these undesired by-products, the replacement of PTSA with other protonic acids was then evaluated, *albeit* with only inferior results obtained (entries 3–7, Table 1). Next, some mixed solvents were further tested, and CH_3CN/DCM (v/v = 4/1) was found to be the best choice, which reduced the undesired side-reactions and increased the isolated yield of product **3a** to 84% (entries 8–11, Table 1). Subsequently, the screening of the amount of Selectfluor revealed that increasing the Selectfluor content to 2.5 equivalents slightly improved the yield of product **3a** (entries 12–14, Table 1), while decreasing the amount of catalyst PTSA led to the observation of unknown by-products and the need of a relatively longer reaction time.[7] Finally, other fluorinating reagents were evaluated; however, no better results were obtained (entries 15–17, Table 1). Therefore, 1.0 equiv. of ketone, 2.0 equiv. of Selectfluor, and 0.2 equiv. of PTSA in 1 mL CH_3CN/DCM at room temperature were selected as the optimal reaction conditions for the next investigation.

We then investigated the substrate scope of this fluorination reaction under the optimal conditions. As summarized in Table 2, 2-arylcyclohexanones with a range of arene substituents were first evaluated, and substrates with either aryl electron-withdrawing groups (such as F, Cl, and Br, and even NO_2 and CF_3) or electron-donating groups (such as Me, ^{t}Bu, and OMe) all performed well, producing the desired products **3a–3n** in good to excellent yields. Moreover, the position of the substituent could slightly affect the yields of the products (**3b–3d**), and the bis-substituted aryl ring product **3o** could be isolated in 81% yield. These results indicated that the substituents on arene had a slight influence on the reaction outcomes. 2-(2-Naphthyl)cyclohexanone was also proved to be a viable substrate, providing the corresponding product **3p** in satisfactory yield. It should be noted that the mono-fluorinated

Table 1 The screening of optimal conditions[a]



Entry	F reagent	Acid	Solvent	Yield[b] (%)
1	Selectfluor (2.0)	PTSA	DCE	23[c]
2	Selectfluor (2.0)	PTSA	CH_3CN	82[d]
3	Selectfluor (2.0)	—	CH_3CN	NR[e]
4	Selectfluor (2.0)	HCl	CH_3CN	79
5	Selectfluor (2.0)	H_2SO_4	CH_3CN	78[d]
6	Selectfluor (2.0)	H_3PO_4	CH_3CN	37[d]
7	Selectfluor (2.0)	HBF_4	CH_3CN	77[d]
8	Selectfluor (2.0)	PTSA	CH_3CN/DCM	84
9	Selectfluor (2.0)	PTSA	CH_3CN/DMSO	0[e]
10	Selectfluor (2.0)	PTSA	CH_3CN/THF	82[d]
11	Selectfluor (2.0)	PTSA	CH_3CN/hexane	80[d]
12	Selectfluor (2.5)	PTSA	CH_3CN/DCM	85
13	Selectfluor (1.5)	PTSA	CH_3CN/DCM	78
14	Selectfluor (1.0)	PTSA	CH_3CN/DCM	74
15	Selectfluor-II (2.0)	PTSA	CH_3CN/DCM	80
16	NFSI (2.0)	PTSA	CH_3CN/DCM	23
17	NFPY (2.0)	PTSA	CH_3CN/DCM	0[e]

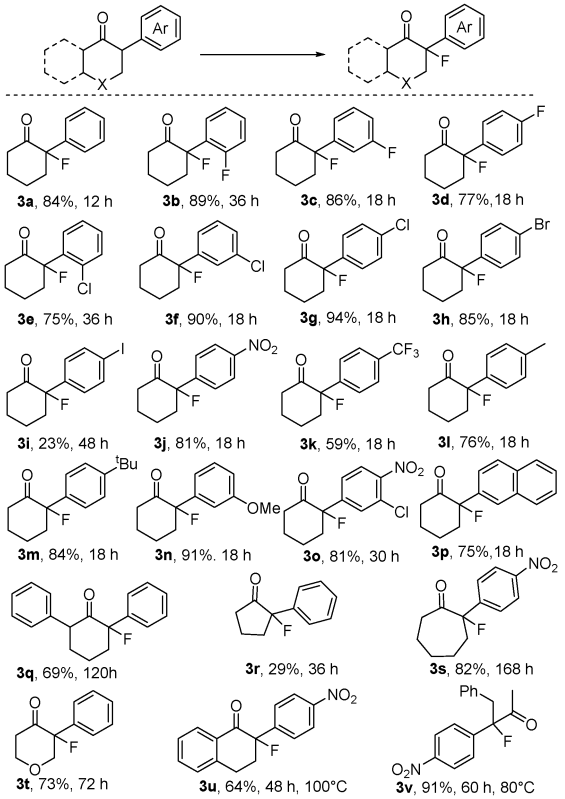


[a] Reactions were performed using 2-phenylcyclohexanone (**2a**, 0.20 mmol) and fluorinating reagents (0.40 mmol) in 1.0 mL solvent at room temperature under an argon atmosphere. [b] Isolated yield. [c] Recovery of 66% starting material. [d] Trace impurity was observed in the isolated product **3a**. [e] Recovery of the starting material.

product **3q** was obtained in 69% yield without the isolation of the disubstituted product. Then, substrates with different ring sizes were investigated. Cyclopentanone, cycloheptanone, oxa-cyclohexanone, and benzocyclic ketones were all tolerated in the current fluorination, affording the corresponding products **3r–3u** in acceptable to good yields. Finally, in contrast to Toste's procedure, which is not compatible with linear substrates, when linear substrate **2v** was subjected to the optimal conditions, the reaction performed well and generated **3v** in 91% yield with excellent selectivity. These results demonstrated that the current fluorination is a complementary fluorination methodology to Toste's procedure. Notably, the substituents (Cl, Br, OMe, Me, and NO_2 groups) on arene could be further transformed into other functionalities and thus afford more sophisticated fluorine-containing molecules.

Next, we turned our attention to α-alkyl substituted ketones, which are not compatible under Toste's fluorination conditions and thus more challenging to fluorinate. To our pleasure, these ketones are viable substrates under the current fluorination conditions (Table 3). For example, either linear *n*-hexyl-, benzyl- or cyclohexyl-substituted substrates performed well, producing the corresponding products **3w–3y** in good to excellent yields. Moreover, an alkyl group bearing other terminal functionalities such as ether or nitrile also reacted smoothly, and the expected products **3z** and **3aa** could be obtained in 67% and 82% yields, respectively. Specifically, symmetric dialkylketones could be mono-fluorinated in high chemoselectivity, affording the expected

Table 2 The scope of α-aryl substituted ketones[a]



[a] Reactions were performed using substrates (0.20 mmol) and Selectfluor (0.40 mmol) in 1.0 mL CH_3CN/DCM (4/1) at noted temperature under an argon atmosphere, and the isolated yields are listed.

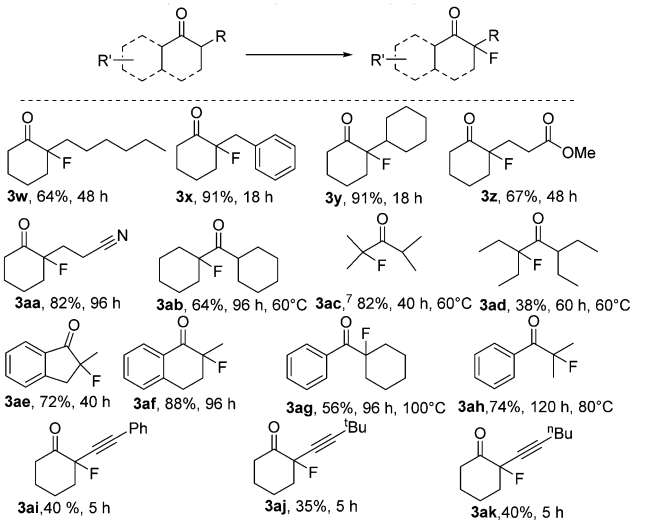
products **3ab–3ad** in good yields without isolation of difluorination products.[7] Finally, other types of alkyl substituted ketones were further evaluated. Benzocyclic ketones could provide products **3ae** and **3af** in 72% and 88% yields, respectively. Remarkably, similar to the aryl substituted linear substrate **2v**, alkyl substituted linear ketones were also amenable to the fluorination, and the desired products **3ag–3ah** could be obtained after a prolonged reaction time at higher temperature. These reaction results again indicated that our fluorination methodology provided an alternative approach for the synthesis of challenging α-alkyl substituted ketones, either cyclic or linear.

The current fluorination was further expanded to α-alkynyl and α-alkenyl substituted ketones (Table 3). The expected alkynyl ketones **3ai–3ak** could be isolated in moderated yields, while 2-(1-cyclohexenyl)cyclohexanone gave complex mixtures.

A practical application of this fluorination was next studied. The gram-scale reactions of **2a** and **2y** were conducted, which produced the expected products **3a** and **3y** in 91% and 81% yields, respectively. These results demonstrated that the current fluorination procedure could be applied for the gram-scale synthesis of either aryl substituted or alkyl substituted fluorine-containing ketones (Scheme 2a).

Late-stage fluorination of small molecules, especially natural products, is one of the valuable synthetic strategies for the design, preparation, and discovery of fluoride-containing

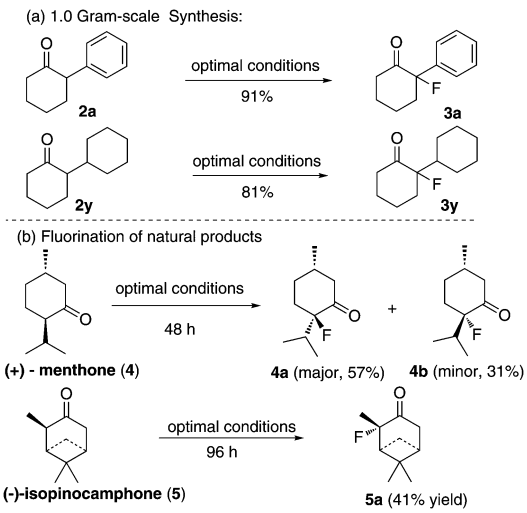
Table 3 The scope of α-alkyl and α-alkynyl substituted ketones[a]



[a] Reactions were performed using substrates (0.20 mmol) and Selectfluor (0.40 mmol) in 1.0 mL CH_3CN/DCM (4/1) at noted temperature under an argon atmosphere, and the isolated yields are listed.

functional molecules.[8] Therefore, some natural monoterpenes were subjected to the optimal conditions, and the expected products were isolated in acceptable yields (Scheme 2b). For (+)-methone (**4**), two diastereoisomers (−)-(2*S*,5*R*)-2-fluoro-2-isopropyl-5-methylcyclohexanone (**4a**) and (+)-(2*R*,5*R*)-2-fluoro-2-isopropyl-5-methylcyclohexanone (**4b**) could be isolated in 57% and 31% yields, respectively.[7,9] In comparison, (−)-isopinocamphone (**5**) would produce a single diastereoisomer **5a** under the optimal conditions but in a relatively low yield (41%) presumably due to the volatility of product **5a**.[7] These chiral products possess the similar skeleton to the organocatalyst **1g**.

In conclusion, an efficient fluorination of ketones for the construction of the challenging quaternary C–F bond has been achieved. The current catalytic transformation features a broad substrate scope, good to excellent yields, and environmentally



Scheme 2 Some synthetic applications of fluorination.

benign reaction conditions, obviating the use of transition metals. Late-stage fluorination of natural products has also been realized. The development of a corresponding asymmetric transformation is underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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