Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Yuan, S. Liu and W. Mai, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01739A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB01739A

Journal Name

RSCPublishing

PAPER

Copper-catalysed difluoroalkylation of aromatic aldehydes via decarboxylation/aldol reaction

Cite this: DOI: 10.1039/xoxxoooooox

Jin-Wei Yuan, Shuai-Nan Liu, Wen-Peng Mai*

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Copper-catalysed a tandem decarboxylation/aldol reaction of simple aromatic aldehydes with 2,2-difluoro-3-oxo-3-arylpropanoic acid has been developed under mild conditions. This method provides a new route for the direct one-pot synthesis of difluorinated aldols in moderate to good yields from simple substrates.

Introduction

Organic compounds containing a fluorine atom often show unique bioactivities in medicinal chemistry or excellent properties in material science.[1] It is well known that many pharmaceuticals have the effectiveness due to their possessing some fluorine atoms.[2] Therefore, various organic fluorinated compounds have been developed for application in these areas. For example, the preparation of α,α-difluoro-β-hydroxy ketones has been received considerable attention due to their potency serving as renin inhibitors.[3] Recently, Colby and co-workers reported the *in vivo* studies of difluoromethyl ketones as γ-Aminobutyric acid (GABA) agonists, in which, structure-activity investigations indicated that replacing the fluorines of the difluoromethyl ketone with hydrogens resulted in an inactive analogue (Fig 1).[4] However, the simple synthetic routes of difluoromethyl ketone scaffold remain very rare.[5] In 2013, Wolf et al developed copper-catalyzed bond scission of pentafluorobutane-1,3-diones and then reacted with aldehydes to produce α,α-difluoro-β-hydroxy ketones (Scheme 1, eq. 1).[5a] In 2016, Leclerc reported a Brook/Elimination/Aldol reaction sequence for one-pot preparation of difluoromethyl ketones using tetrabutylamm

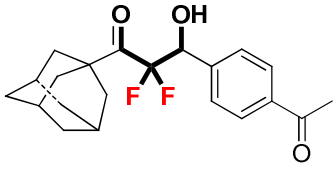
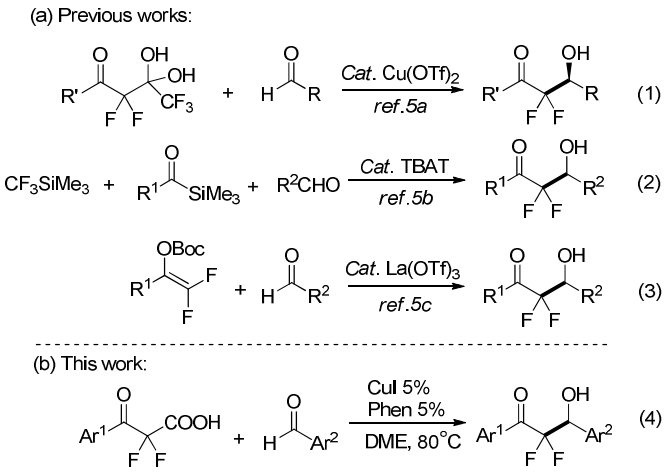


Fig. 1 The GABA agonist α,α-difluoro-β-hydroxy ketone.

[a] *School of Chemical Engineering And Environment, Henan University of Technology, Lianhua Street, Zhengzhou 450001, China. E-mail: maiwp@yahoo.com. Fax: +86-371-67756715; Tel: +86-371-67756718*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

-onium difluorotriphenylsilicate as the catalyst at -40 ºC (Scheme 1, eq. 2).[5b] Very recently, Sasaki also reported a $La(OTf)_3$-catalyzed aldol reaction between difluoroenol *O*-Boc esters and carbonyl compounds to construct α,α-difluoro-β-hydroxy ketones (Scheme 1, eq. 3).[5c] Even so, the formation of α,α-difluoro-β-hydroxy ketones from difluoroenolates and aldehydes is still complicated due to the precursor of the difluoroenolate should be prepared *via* multi-steps under -78 ºC using LDA or *n*-BuLi and the Ruppert–Prakash reagent ($TMSCF_3$) is highly dependent in this transformation.[5-6] Herein, as a part of our efforts on decarboxylative reactions,[7] we wish to report a copper-catalysed novel tandem decarboxylation/aldol reaction toward the difluoromethyl ketone scaffold using 2,2-difluoro-3-oxo-3-arylpropanoic acid as substrates which could be prepared easily based on Zhang's or Song's works.[8]

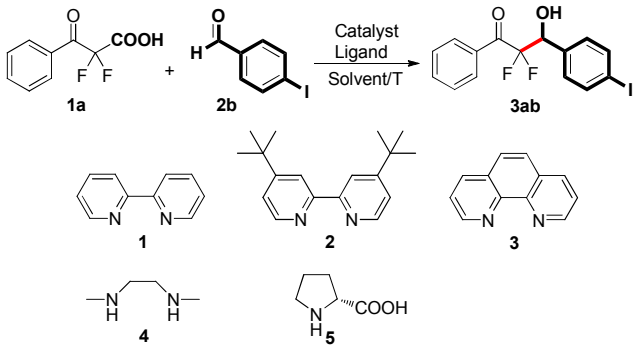


Scheme 1 The synthesis of α,α-difluoro-β-hydroxy ketones.

Results and discussion

PAPER View Article Online DOI: 10.1039/C7OB01739A Journal Name

Table 1 Optimization of reaction conditions[a]

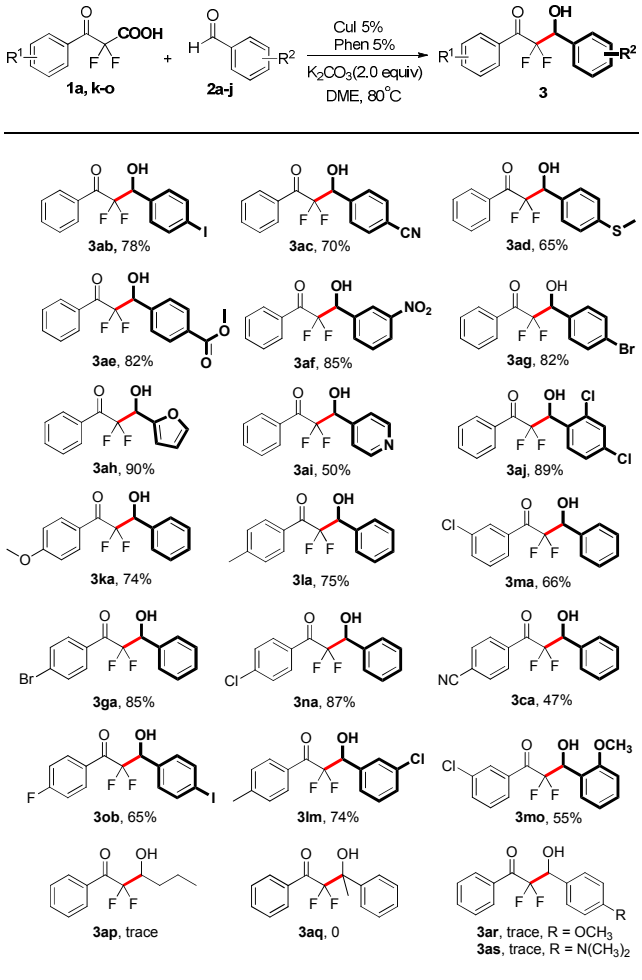


Entry	Catalyst (equiv.)	Ligand(equiv.)	Solvent/T(℃)	Yield[b](%)
1	$Cu(OAc)_2$(0.1)	**L1** (0.1)	DMSO/80	28
2	$Cu(OAc)_2$(0.1)	**L2** (0.1)	DMSO/80	37
3	$Cu(OAc)_2$(0.1)	**L3** (0.1)	DMSO/80	50
4	$Cu(OAc)_2$(0.1)	**L4** (0.1)	DMSO/80	trace
5	$Cu(OAc)_2$(0.1)	**L5** (0.1)	DMSO/80	trace
6	CuCl(0.1)	**L3** (0.1)	DMSO/80	63
7	CuBr(0.1)	**L3** (0.1)	DMSO/80	60
8	CuI(0.1)	**L3** (0.1)	DMSO/80	71
9	CuO(0.1)	**L3** (0.1)	DMSO/80	0
10	Cu_2O(0.1)	**L3** (0.1)	DMSO/80	0
11	CuI(0.1)	**L3** (0.1)	DME/80	76
12	CuI(0.1)	**L3** (0.1)	Diglyme/80	71
13	CuI(0.1)	**L3** (0.1)	Dioxane/80	39
14	CuI(0.1)	**L3** (0.1)	Toluene/80	trace
15	CuI(0.1)	**L3** (0.1)	CH_3CN/80	65
16	CuI(0.05)	**L3** (0.05)	DME/80	78
17	CuI(0.05)	**L3** (0.05)	DME/50	39
18	CuI(0.05)	**L3** (0.05)	DME/28	trace
19[c]	CuI(0.05)	-	DME/80	30
20[d]	-	**L3** (0.05)	DME/80	trace

[a] Reaction conditions: **1a** (1.0 mmol), **2b** (1.5 mmol), catalyst (0.05 or 0.1 equiv), Ligand (0.05 or 0.1 equiv), K_2CO_3 (2.0 equiv), solvent (5 mL) in 50 mL round-bottom flask at 80℃ under N_2 for 10 h. [b] Isolated yield. [c] under air and without Ligand. [d] Without catalyst.

At the beginning, based on our assumption, copper catalyzed direct α-arylation of α,α-difluoroketone acid with aryl iodide *via* decarboxylation process was investigated.[9] Unfortunately, no coupling product was found using 2,2-difluoro-3-oxo-3-phenylpropanoic acid (**1a**) and 4-iodobenzaldehyde (**2b**) as the substrates. Another C-C bond formation through aldol reaction was observed unexpectedly. Thus, we simply continue to use the two substrates for the optimal conditions of the "unexpected reaction". Firstly, the reaction was performed in the presence of 10 % $Cu(OAc)_2$ and 10 % 2,2'-bipyridine in DMSO at 80 ℃. The unexpected product α,α-difluoro-β-hydroxy ketone (**3ab**) was isolated in 28% yield (Table 1, entry 1). Changing the ligand from **L2** to **L5**, the best result was achieved when 1,10-phenanthroline (**L3**) as ligand using $Cu(OAc)_2$ as catalyst in DMSO (Table 1, entry 3). Using **L3** as ligand, other Cu salts such as CuCl, CuBr and CuI showed better catalytic effect than $Cu(OAc)_2$ under the same conditions (Table 1, entries 6-8). 71% isolated yield was obtained when CuI was explored as the catalyst (Table 1, entry 8). On the contrary, CuO or Cu_2O serving as catalyst displayed no effect in this transfromation (Table 1, entries 9-10). Further screening of solvents revealed that the solvents were also crucial for this reaction. No desired product was found when the reaction proceeded in toluene (table 1, entry 14) and only 39% product **3ab** was obtained when performing the reaction in dioxane (Table 1, entry 13). Diglyme or CH_3CN as the solvent, the reaction gave the desired product in moderate yields (Table 1, entries 12 and 15). However, reaction conducted with CuI as the catalys and **L3** ligand formed the desired product in 76% yield in DME (Table 1, entry 11).

Table 2 Reaction of aromatic aldehydes with different 2,2-difluoro-3-oxo-3-arylpropanoic acid[a,b]



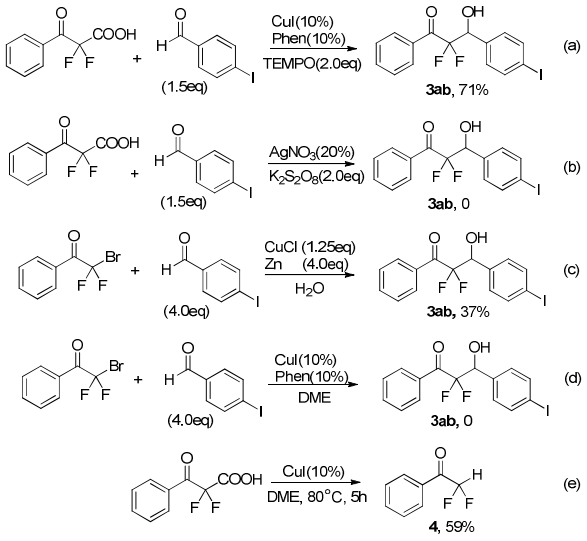
[a] Reaction conditions: **1** (1.0 mmol), aromatic aldehydes (1.5 mmol), CuI (0.05 mmol), Phen (0.05 mmol), DME (5 mL), 80℃, 10 h. [b] Isolated yield.

Journal Name

View Article Online
DOI: 10.1039/C7OB01759A PAPER

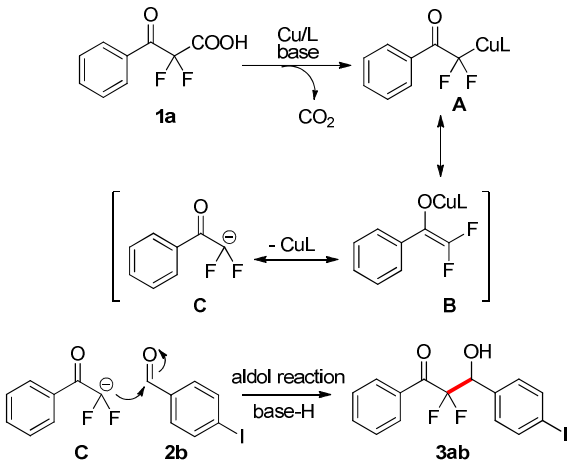
Reducing the amount of the catalyst system did not delay the reaction (Table 1, entry 16). Nevertheless, the temperature influenced the results of this transformation obviously, no reaction occur at room temperature (Table 1, entries 17-18). The reaction did not occur in the absence of CuI at all or produced low yield without ligand, it displayed that both of the catalyst and ligand were important for the transformation (Table 1, entries 19-20).

After investigating the reaction conditions, the substrates testing were carried out subsequently. As shown in Table 2, various aromatic aldehydes reacted with 2,2-difluoro-3-oxo-3-phenylpropanoic acid (**1a)**, the decarboxylation/aldol-adduct products were isolated in moderate to good yields. **1a** with aromatic aldehydes such as methyl 4-formylbenzoate and 3-nitrobenzaldehyde, the α,α-difluoro-β-hydroxy ketones were obtained in 82% and 85% yield respectively (Table 2, **3ae** and **3af**). Even in the presence of copper salt, aromatic aldehydes containing halides (I, Br, Cl) could take part in this transformation smoothly without dehalogenation. The corresponding products were obtained in moderate yields (Table 2, **3ab**, **3ag** and **3aj**). We further examined heteroaromatic aldehydes, for furan-2-carbaldehyde, the desired product was obtained in 90% (Table 2, **3ah**), for 4-pyridinecarboxaldehyde, only 50% product was obtained (Table 2, **3ai**). Then the scope of 2,2-difluoro-3-oxo-3-arylpropanoic acid was also tested. Both electron-withdrawing groups (CN, F, Br) and electron-donating groups (CH_3O, CH_3) on the phenyl ring of the substrate **1** were well tolerated in the decarboxylatio/aldol processes. CN and F on the *para*-position of the phenyl ring of the substrate **1**, produced the corresponding products in 47% and 65% respectively (Table 2, **3ca** and **3ob**). At the same position, Cl and Br group did not influence the reactivity and the desired products were obtained in high yields (Table 2, **3ga** and **3na**). 2,2-difluoro-3-oxo-3-arylpropanoic acid with electron-donating groups (CH_3O, CH_3) underwent efficient decarboxylation to provide the expected products in 75% yield (Table 2, **3ka** and **3la**). Nevertheless, for alphatic aldehyde (**2p**) or acetophenone (**2q**), the reaction did not occur and no product was obtained (Table 2, **3ap** and **3aq**). The reason for this result is not clear at present. Moreover, the aryl aldehydes which have strong electron-donating groups at *para*-position were not tolerated under the current conditions (Table 2, **3ar** and **3as**). It could be due to the decrease of the formyl group's electrophilicity in 4-methoxybenzaldehyde (**2r**) and 4-(dimethylamino)benzaldehyde (**2s**).



Scheme 2 Control experiments

Radical trapping experiment was subsequently performed in order to understand the mechanism of copper catalysed decarboxylation/aldol reaction (**Scheme 2**, a). The desired product **3ab** was still obtained in 71% yield when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added. This result displayed the decarboxylation process is not through radical route. Moreover, classic radical decarboxylative process catalysed by $AgNO_3$ was not effective in this transformation **(Scheme 2,** b**).** Stoichiometric metal-mediate Reformatsky reaction of bromodifluoromethyl ketone with 4-iodobenzaldehyde (**2b**) could gave the desired product in low yield using a known procedure (**Scheme 2**, c).[10] But the same reaction did not occur under the current catalytic conditions (**Scheme 2**, d). This result demonstrates the current protocol is a Reformatsky-type reaction of catalytic version using 2,2-difluoro-3-oxo-3-arylpropanoic acid as substrate. In addition, decarboxylic reaction of **1a** could occur in the presence of catalytic copper iodide which provided some evidence of the formation of enolate anion (**Scheme 2**, e).



Scheme 3 Proposed mechanism for the reaction

Based on the previous works on the synthesis of α,α-difluoro-β-hydroxy ketones,[5] a primary mechanism for the decarboxylation/aldol reaction of 2,2-difluoro-3-oxo-3-phenylpropanoic acid **1a** with 4-iodobenzaldehyde **2b** has been proposed (Scheme 3). At first, by the assistance of Cu(I) catalyst, the intermediate **A** was formed through decarboxylation. After keto-enol tautomerism, the intermediates **B** or **C** were formed. Then, the nucleophilic addition of the intermediate **B** or **C** to aromatic aldehyde **2b**, leads to the product **3ab**.

Conclusions

View Article Online
DOI: 10.1039/C7OB01739A
Journal Name

In summary, we have developed a practical method for the synthesis of α,α-difluoro-β-hydroxy ketones owning biological activity *via* catalytic decarboxylation/aldol reaction using 2,2-difluoro-3-oxo-3-arylpropanoic acids as substrates which can be easily prepared in some simple steps. The novel method is catalysed by simple copper salt and used cheap ligand under mild conditions. Comparing with the previous methods, the substrates used in this reaction are moisture- and air-stable, moreover, the reaction does not need low temperature (stabilizing enol anion) or high temperature (decarboxylation＞150℃).

Experimental section

General experimental procedure for the synthesis of 3

To a mixture of 2,2-difluoro-3-oxo-3-arylpropanoic acids **1** (1.0 mmol) and aromatic aldehydes **2** (1.5 mmol) and CuI (5% mmol, 9.5 mg), 1,10-phenanthroline (5.0 mmol, 9.0 mg) was added Dimethoxyethane (DME) (5.0 mL). The mixture was stirred at 80 ºC under N_2 for 10 hours. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (20 mL), washed with saturated brine and $NaHCO_3$, and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3.**

2,2-difluoro-3-hydroxy-3-(4-iodophenyl)-1-phenylpropan-1-one (3ab). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.38 (dd, *J* = 20.0, 4.0 Hz, 1H), 3.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.68 (t, J_{C-F} = 32.0 Hz), 137.42, 134.84, 134.31, 132.11, 130.30, 130.00, 128.76, 115.26 (t, J_{C-F} = 256 Hz), 95.08, 72.75 (dd, J_{C-F} = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.83 (d, *J* = 297.04 Hz), -116.34 (d, *J* = 297.04 Hz); HRMS: cacld for $C_{15}H_{11}F_2IO_2$ $[M+H]^+$ 387.9772; found 387.9766.

4-(2,2-difluoro-1-hydroxy-3-oxo-3-phenylpropyl)benzonitrile (3ac). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.28 (q, *J* = 8.0 Hz, 5H), 7.49 (t, *J* = 8.0 Hz, 2H), 5.47 (dd, *J* = 20.0, 4.0 Hz, 1H), 3.49 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 190.68 (t, J_{C-F} = 32.0 Hz), 140.04, 135.00, 131.95, 130.31, 130.28, 128.95, 128.81, 118.54, 115.33 (t, J_{C-F} = 256 Hz), 112.70, 72.42 (dd, J_{C-F} = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.28 (d, *J* = 297.04 Hz), -116.16 (d, *J* = 297.04 Hz); HRMS: calcd for $C_{16}H_{12}F_2NO_2$ $[M+H]^+$ 288.0836; found 288.0839.

2,2-difluoro-3-hydroxy-3-(4-(methylthio)phenyl)-1-phenylpropan-1-one (3ad). Yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.35 (dt, *J* = 20.0, 4.0 Hz, 1H), 3.01 (s, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.88 (t, J_{C-F} = 32.0 Hz), 139.75, 134.64, 132.38, 131.35, 130.26, 128.69, 128.55, 126.14, 115.68 (t, J_{C-F} = 256 Hz), 72.96 (dd, J_{C-F} = 28, 23 Hz), 15.58; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -104.34 (d, *J* = 289.52 Hz), -116.10 (d, *J* = 289.52 Hz); HRMS: calcd for $C_{16}H_{15}F_2O_2S$ $[M+H]^+$ 309.0761; found 309.0770.

Methyl-4-(2,2-difluoro-1-hydroxy-3-oxo-3-phenylpropyl)-benzoate (3ae). White solid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04-8.07 (m, 4H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 5.44 (dt, *J* = 20.0, 4.0 Hz, 1H), 3.92 (s, 3H), 3.33 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.63 (t, J_{C-F} = 29.0 Hz), 139.66, 134.81, 132.16, 130.32, 130.26, 129.46, 128.75, 128.19, 115.42 (t, J_{C-F} = 256 Hz), 72.86 (dd, J_{C-F} = 28, 23 Hz), 52.23; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.67 (d, *J* = 297.04 Hz), -116.06 (d, *J* = 297.04 Hz).

2,2-difluoro-3-hydroxy-3-(3-nitrophenyl)-1-phenylpropan-1-one (3af). Colorless liquid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 5.55 (dt, *J* = 20.0, 4.0 Hz, 1H), 3.39 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.34 (t, J_{C-F} = 29.0 Hz), 136.76, 135.12, 134.26, 131.78, 130.36, 129.19, 128.86, 123.88, 123.35, 114.90 (t, J_{C-F} = 256 Hz), 72.17 (dd, J_{C-F} = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.80 (d, *J* = 300.80 Hz), -117.33 (d, *J* = 300.80 Hz).

3-(4-bromophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (3ag). White solid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.47-7.54 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.37 (dt, *J* = 20.0, 4.0 Hz, 1H), 3.39 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.68 (t, J_{C-F} = 32.0 Hz), 134.84, 133.64, 132.11, 131.46, 130.30, 130.26, 129.83, 128.76, 115.11 (t, J_{C-F} = 266 Hz), 72.67 (dd, J_{C-F} = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.87 (d, *J* = 297.04 Hz), -117.11 (d, *J* = 297.04 Hz).

2,2-difluoro-3-(furan-2-yl)-3-hydroxy-1-phenylpropan-1-one (3ah). Pale yellow liquid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 6.50 (s, 1H), 6.38 (s, 1H), 5.43 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.02 (t, J_{C-F} = 29.0 Hz), 148.41, 143.29, 134.68, 130.20, 130.17, 128.74, 115.52 (t, J_{C-F} = 256 Hz), 110.71, 110.20, 68.15 (dd, J_{C-F} = 25.0 Hz, 4.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -105.90 (d, *J* = 289.52 Hz), -113.58 (d, *J* = 289.52 Hz).

2,2-difluoro-3-hydroxy-1-phenyl-3-(pyridin-4-yl)propan-1-one (3ai). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 4H), 5.41 (dd, *J* = 20.0, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.68 (J_{C-F} = 32.0 Hz), 148.95, 145.58, 134.63, 132.54, 130.25, 128.70, 123.28, 115.90 (t, J_{C-F} = 266 Hz), 71.57 (dd, J_{C-F} = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.36 (d, *J* = 289.52 Hz), -116.10 (d, *J* = 289.52 Hz); HRMS: calcd for $C_{14}H_{12}F_2NO_2$ $[M+H]^+$ 264.0836; found 264.0838.

3-(2,4-dichlorophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (3aj). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.63-7.68 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 5.96 (dd, *J* = 20.0, 4.0 Hz, 1H), 3.18 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.45 (t, J_{C-F} = 29.0 Hz), 135.47, 134.94, 134.65, 131.84, 131.45, 131.09, 130.35, 129.17, 128.81, 127.39, 115.50 (t, J_{C-F} = 265 Hz), 68.52 (dd, J_{C-F} = 29, 22 Hz). ^{19}F NMR ($CDCl_3$, 376MHz): δ -103.19 (d, *J* = 300.80 Hz), -117.56 (d, *J* = 300.80 Hz); HRMS: calcd for $C_{15}H_{11}Cl_2F_2O_2$ $[M+H]^+$ 331.0104; found 331.0106.

2,2-difluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (3ka). White solid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.49-7.50 (m, 2H), 7.34-7.40

View Article Online
DOI: 10.1039/C7OB01759A PAPER

(m,3H), 6.91 (d, J = 12.0 Hz, 2H), 5.36 (dt, J = 20.0, 4.0 Hz, 1H), 3.87 (s, 3H), 3.22 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.13 (t, $J_{C\text{-}F}$ = 29.0 Hz), 164.81, 134.85, 133.00, 132.96, 132.93, 128.17, 125.17, 115.86 (t, $J_{C\text{-}F}$ = 263 Hz), 114.02, 73.40 (dd, $J_{C\text{-}F}$ = 28.0 Hz, 23.0 Hz), 55.60; ^{19}F NMR ($CDCl_3$, 376MHz): δ -103.68 (d, J = 293.28 Hz), -115.50 (d, J = 293.28 Hz).

2,2-difluoro-3-hydroxy-3-phenyl-1-(p-tolyl)propan-1-one (3la). White solid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, J = 8.0 Hz, 2H), 7.52-7.53 (m, 2H), 7.42-7.43 (s, 3H), 7.31 (d, J = 8.0 Hz, 2H), 5.42 (dd, J = 20.0, 4.0 Hz, 1H), 3.14 (s, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.46 (t, J = 32.0 Hz), 145.99, 134.76, 130.45 (t, J = 3.0 Hz), 129.81, 129.43, 128.99, 128.29, 128.16, 115.76 (t, $J_{C\text{-}F}$ = 255 Hz), 73.37 (dd, $J_{C\text{-}F}$ = 28.0 Hz, 23.0 Hz), 21.87; ^{19}F NMR ($CDCl_3$, 376MHz): δ -104.12 (d, J = 293.28 Hz), -115.92 (d, J = 293.28 Hz).

1-(3-chlorophenyl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (3ma). Colorless thick liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.50 ((d, J = 8.0 Hz, 1H), 7.42 (s, 2H), 7.38-7.40 (m, 4H), 5.37 (dd, J = 20.0, 4.0 Hz, 1H), 3.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.95 ($J_{C\text{-}F}$ = 29.0 Hz), 134.95, 134.52, 134.44, 134.03, 130.14, 129.96, 129.22, 128.40, 128.28, 128.07, 115.76 ($J_{C\text{-}F}$ = 256 Hz), 73.30 (dd, $J_{C\text{-}F}$ = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376MHz): δ -104.69 (d, J = 289.52 Hz), -116.10 (d, J = 289.52 Hz); HRMS: calcd for $C_{15}H_{12}ClF_2O_2$ $[M+H]^+$, 297.0494; found 297.0487.

1-(4-bromophenyl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (3ga). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, J = 8.0 Hz, 2H), 7.39-7.49 (m, 7H), 6.92-6.98 (m, 3H), 5.37 (dt, J = 20.0, 4.0 Hz, 1H), 2.97 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.95 ($J_{C\text{-}F}$ = 29.0 Hz), 141.35, 134.55, 131.65, 130.80, 129.16, 129.07, 128.38, 128.08, 115.83 (t, $J_{C\text{-}F}$ = 262 Hz), 73.35 (dd, $J_{C\text{-}F}$ = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376MHz): δ -104.48 (d, J = 293.28 Hz), -116.02 (d, J = 293.28 Hz); HRMS: calcd for $C_{15}H_{12}BrF_2O_2$ $[M+H]^+$, 340.9989; found 340.9984.

1-(4-chlorophenyl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (3na). White solid (known compound), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.48 (s, 2H), 7.39-7.41 (m, 3H), 5.37 (dt, J = 20.0, 4.0 Hz, 1H), 2.97 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.14 (t, $J_{C\text{-}F}$ = 32.0 Hz), 134.52, 132.08, 131.62, 131.20, 130.07, 129.18, 128.39, 128.08, 115.70 (t, $J_{C\text{-}F}$ = 262 Hz), 73.33 (dd, $J_{C\text{-}F}$ = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -104.55 (d, J = 289.52 Hz), -116.09 (d, J = 289.52 Hz).

4-(2,2-difluoro-3-hydroxy-3-phenylpropanoyl)benzonitrile (3ca). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.0 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.48-7.50 (m, 3H), 7.39-7.40 (m, 3H), 5.40 (dd, J = 20.0, 4.0 Hz, 1H), 3.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 190.14 (t, $J_{C\text{-}F}$ = 32.0 Hz), 134.69, 134.61, 132.40, 130.25, 129.06, 128.67, 128.32, 128.13, 118.30, 115.75 (t, $J_{C\text{-}F}$ = 265 Hz) 73.37 (dd, $J_{C\text{-}F}$ = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -104.37 (d, J = 293.28 Hz), -116.04 (d, J = 293.28 Hz). HRMS: calcd for $C_{16}H_{12}F_2NO_2$ $[M+H]^+$ 288.0836; found 288.0836.

2,2-difluoro-1-(4-fluorophenyl)-3-hydroxy-3-(4-iodophenyl)-propan-1-one (3ob). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09-8.12 (m, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.33 (dt, J = 20.0, 4.0 Hz, 1H), 3.11 (d, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.82 (t, $J_{C\text{-}F}$ = 32.0 Hz), 167.99 (d, $J_{C\text{-}F}$ = 257 Hz), 137.45, 134.21, 133.36, 129.97, 128.51, 116.25 (d, $J_{C\text{-}F}$ = 23 Hz), 115.33 (t, $J_{C\text{-}F}$ = 260 Hz), 95.41, 72.69 (dd, $J_{C\text{-}F}$ = 28, 23 Hz); ^{19}F NMR ($CDCl_3$, 376MHz): δ -101.01, -103.63 (d, J = 297.04 Hz), -116.19 (d, J = 297.04 Hz); HRMS: calcd for $C_{15}H_{11}F_3IO_2$ $[M+H]^+$, 406.9756; found 406.9755.

3-(3-chlorophenyl)-2,2-difluoro-3-hydroxy-1-(p-tolyl)propan-1-one (3lm). Colorless thick liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.29-7.36 (m, 5H), 5.36 (d, J = 16.0 Hz, 1H), 3.23 (s, 1H), 2.42 (s 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.49 (t, $J_{C\text{-}F}$ = 30.0 Hz), 146.25, 136.74, 134.28, 130.48, 129.50, 129.45, 129.09, 128.35, 126.38, 115.33 (t, $J_{C\text{-}F}$ = 260 Hz), 72.66 (dd, $J_{C\text{-}F}$ = 28, 23 Hz), 21.88; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -103.44 (d, J = 297.04 Hz), -116.28 (d, J = 297.04 Hz); HRMS: calcd for $C_{16}H_{14}ClF_2O_2$ $[M+H]^+$, 311.0650; found 311.0657.

1-(3-chlorophenyl)-2,2-difluoro-3-hydroxy-3-(2-methoxyphenyl) propan-1-one (3mo). Colorless thick liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.63 (dd, J = 16.0, 8.0 Hz, 1H), 3.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.37 (t, $J_{C\text{-}F}$ = 28.0 Hz), 157.32, 134.81, 134.42, 134.06, 130.34, 130.06, 129.86, 129.59, 128.14, 122.57, 121.08, 116.76 (t, $J_{C\text{-}F}$ = 265 Hz), 114.27, 70.37 (dd, $J_{C\text{-}F}$ = 28.0 Hz, 23.0 Hz), 55.35; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -106.78 (d, J = 270.72 Hz), -114.67 (d, J = 270.72 Hz); HRMS: calcd for $C_{16}H_{13}ClF_2O_3$ $[M+H]^+$, 326.0521; found 326.0528.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China No. 21302042 and the Department of Henan Province Natural Science and Technology Foundation (No. 172102210225), Natural Science Foundation in Henan Province Department of Education (No. 17A150005), the Program for Innovative Research Team from Zhengzhou (No. 131PCXTD605) and Project of Youth Backbone Teachers of Henan University of Technology (2016003).

Notes and references

1 (a) S. Purser, P. R. Moore, S. Swallow, V. Gouveneur, *Chem. Soc. Rev*., 2008, 37, 320; (b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, H. *Chem. Rev*. 2014, **114**, 2432; (c) I. Ojima, J. R. McCarthy, J. T. Welch, *Biomedical Frontiers of Fluorine Chemistry*, ACS Editions, Washington, DC, 1996; (d) M. Schlosser, *Angew. Chem., Int. Ed*., 2006, **45**, 5432; (e) K. Müller, C. Faeh, F. Diederich, *Science*. 2007, **317**, 1881.

2 (a) H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S. H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem*., 2004, **12**, 979. (b) J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson, S. K. Erickson-Viitanen, *J. Med. Chem*., 2000, **43**, 2019.

View Article Online
DOI: 10.1039/C7OB01739A Journal Name

3 (a) A. M. Doherty, I. Sircar, B. E. Kornberg, J. Quin III, R. T. Winters, J. S. Kaltenbronn, M. D. Taylor, B. L. Batley, S. R. Rapundalo, M. J. Ryan, C. A. Painchaud, *J. Med. Chem*., 1992, **35**, 2. (b) M. Eda, A. Ashimori, F. Akahoshi, T. Yoshimura, Y. Inoue, C. Fukaya, M. Nakajima, H. Fukuyama, T. Imada, N. Nakamura, *Bioorg. Med. Chem. Lett*., 1998, **8**, 913; (c) J. W. Skiles, C. Miao, R. Sorek, S. Jacober, P. W. Mui, G. Chow, S. W. Weldon, G. Possanza, M. Skoog, J. Keirns, G. Letts, A. S. Rosenthal, *J. Med. Chem*., 1992, **35**, 4795.

4 C. Han, A. E. Salyer, E. H. Kim, X. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchhoff, T. K. Salvador, J. A. Chester, G. H. Hockerman, D. A. Colbry, *J. Med. Chem*., 2013, **56**, 2456.

5 (a) P. Zhang, C. Wolf, *Angew. Chem., Int. Ed*., 2013, **52**, 7869; (b) M. Decostanzi, J. Godemert, S. Oudeyer, V. Levacher, J. M. Campagne, E. Leclerc, *Adv. Synth. Catal*., 2016, **358**, 526 (c) S. Sasaki, T. Suzuki, T. Uchiya, S. Toyota, A. Hirano, M. Tanemura, H. Teramoto, T. Yamauchi, K. Higashiyama, *J. Fluorine Chem*., 2016, **92**, 78.

6 (a) O. Lefebvre, T. Brigaud, C. Portella, *J. Org. Chem*., 2001, **66**, 1941; (b) H. Hata, T. Kobayashi, H. Amii, K. Uneyama, J .T. Welch, *Tetrahedron Lett*, 2002, **43** 6099; (c) Z. L. Yuan, Y. Wei, M. Shi, *Tetrahedron*, 2010, **66**, 7361; (d) J. S. Yu, Y. L. Liu, J. Tang, X. Wang, J. Zhou, *Angew. Chem. Int. Ed*., 2014, **53**, 9512; (e) C. R. Burkholder, W. R. Dolbier Jr, M. Médebielle *J. Fluorine Chem*., 2001, **109**, 39; (f) C. R. Cao, M. Jiang, J. T. Liu, *Eur. J. Org. Chem*., 2015, 1144; (g) F. M. Liao, Y. L. Liu, J. S. Yu, F. Zhou, J. Zhou, *Org. Biomol. Chem*., 2015, **13**, 8906; (h) Y. L. Liu, J. Zhou, *Chem. Commun*., 2012, **48**, 1919; (i) L. Wu, *J. Fluorine Chem*., 2011, **132**, 367; (j) G. Blond, T. Billard, B. R. Langlois, *Chem. Eur. J*.; 2002, **8**, 2917.

7 (a) W. P. Mai, B. Sun, L. Q. You, L. R. Yang, P. Mao, J. W. Yuan, Y. M. Xiao, L. B. Qu, *Org. Biomol. Chem*., 2015, **13**, 2750; (b) W. P. Mai, J. T. Wang, L. R. Yang, J. W. Yuan, Y. M. Xiao, P. Mao and L. B. Qu, *Org. Lett*., 2014, **16**, 204; (c) W. M. Zhao, X. L. Chen, J. W. Yuan, L. B. Qu, L. K. Duan and Y. F. Zhao, *Chem. Commun*., 2014, **50**, 2018; (d) W. P. Mai, G. C. Sun, J. T. Wang, G. Song, P. Mao, L. R. Yang, J. W. Yuan, Y. M. Xiao and L. B. Qu, *J. Org. Chem*., 2014, **79**, 8094. (e) W. P. Mai, G. Song, G. C. Sun, L. R. Yang, J. W. Yuan,Y. M. Xiao, P. Mao and L. B. Qu, *RSC Adv*., 2013, **3**, 19264.

8 (a) H. Y. Zhao, Z. Feng, Z. Luo, X. G. Zhang, *Angew. Chem. Int. Ed*., 2016, **55,** 10401; (b) M. Ke, Q. Song, *J. Org. Chem*., 2016, 81, 3654; (c) Z. Feng, Q. Q. Ming, Y. L. Xiao, B. Zhang, X. G. Zhang, *Angew. Chem. Int. Ed*., 2014, **53,** 1669; (d) Y. L. Xiao, W. H. Guo, G. Z. He, Q. Pan, X. G. Zhang, *Angew. Chem. Int. Ed*., 2014, **53,** 9909.

9 (a) S. I. Arlow, J. F. Hartwig, *Angew. Chem. Int. Ed*., 2016, **55**, 4567; (b) S. Ge, W. Chaładaj, J. F. Hartwig, *J. Am. Chem. Soc*., 2014, **136**, 4149; (c) S. Ge, S. I. Arlow, M. G. Mormino, J. F. Hartwig, *J. Am. Chem. Soc*., 2014, **136**, 14401.

10 H. Yao, C. R. Cao, M. Jiang, J. T. Liu, *J. Fluorine Chem*., 2013, **156**, 45.