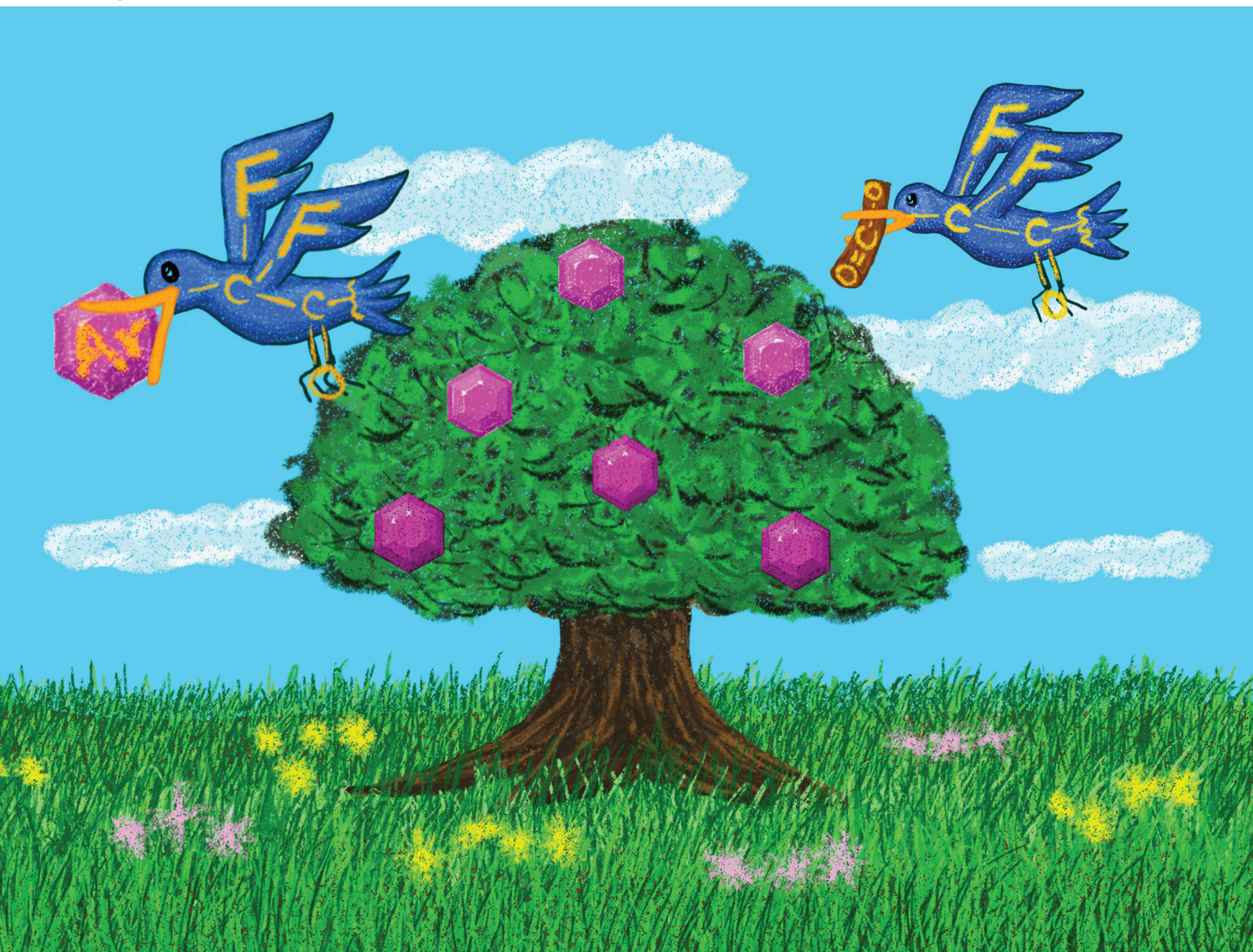


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## COMMUNICATION

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alternative approach for catalyst-free difluoroenolate  
coupling to aryl difluoromethyl ketones



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# Decarboxylative arylation with diaryliodonium(III) salts: alternative approach for catalyst-free difluoroenolate coupling to aryldifluoromethyl ketones†

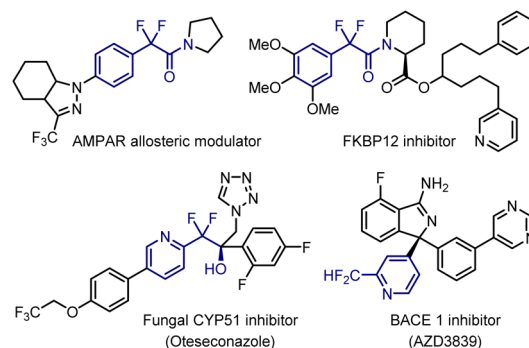
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**Catalyst-free access to aryldifluoromethyl ketones has been achieved through decarboxylative arylation of  $\alpha,\alpha$ -difluoro- $\beta$ -ketoacid salts using diaryliodonium(III) salts. The products were successfully transformed into the corresponding esters, amides, and difluoromethyl compounds. This strategy provides access to fluorine-containing drugs, thus contributing to drug design.**

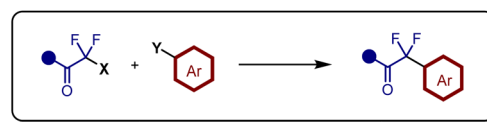
Introduction of fluorine atoms into small molecules is a widely accepted strategy in medicinal chemistry for enhancing the lipophilicity, metabolic stability, and bioavailability relative to those of non-fluorinated parent compounds.<sup>1</sup> Considerable efforts have been devoted to constructing fluorine-containing molecules. Aryldifluoromethyl carbonyls are attractive synthetic intermediates for the corresponding esters, amides, alcohols, and difluoromethyl compounds. These units are present in biologically active compounds, such as the AMPAR allosteric modulator,<sup>2a</sup> FKB12 inhibitor,<sup>2b</sup> fungal CYP51 inhibitor,<sup>2c</sup> and BACE 1 inhibitor<sup>2d</sup> (Fig. 1). Furthermore, the difluoromethylene ( $-\text{CF}_2-$ ) groups serve as bioisosteres for carbonyl compounds and oxygen and sulfur atoms.<sup>3,4</sup>

Difluoromethylene units have been introduced by  $\alpha$ -fluorination or deoxofluorination of the corresponding carbonyl compounds using electrophilic fluorination reagents<sup>5</sup> or aminosulfur trifluorides.<sup>6</sup> However, these reagents are expensive and unstable in water, generating toxic compounds such as HF. In contrast, transformation of fluorine-containing building blocks is an efficient approach as it does not require hazardous fluorination reagents.<sup>7,8</sup> Aryldifluoroacetates have been synthesized *via* transition metal-catalyzed coupling reactions of commercially available bromodifluoroacetate and aryl

metal species containing zinc,<sup>9</sup> boron,<sup>10</sup> or silicon (Fig. 2a).<sup>11</sup> The combination of aryl halides with metal enolates of  $\alpha,\alpha$ -difluoroacetates or  $\alpha,\alpha$ -difluoroamides is also an effective approach for accessing  $\alpha,\alpha$ -difluorinated carbonyl compounds (Fig. 2b).<sup>12,13</sup> These methods require the use of organometallic



**Fig. 1** Biologically active compounds containing difluoromethylene units.



## combination of organometallics with metal catalyst

- a) X = Br Y = Zn, B, Si with cat. Co, Pd, Ni refs. 9–11  
b) X = Si, Zn Y = Br with cat. Cu, Pd refs. 12

## C-H bond functionalization with metal catalyst

- c) X = Br Y = H with cat. Fe, Ir refs. 14, 15  
d) X = H Y = Br with cat. Pd refs. 16

## decarboxylative bond formation without metal (this work)

- e) X = COONa Y = I<sup>III</sup> metal-free conditions

**Fig. 2** Various approaches to  $\alpha$ -aryl- $\alpha,\alpha$ -difluorinated carbonyl compounds.

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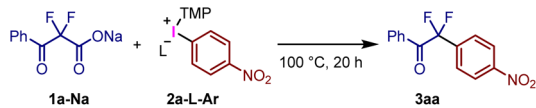
species and transition metal catalysts, which increases costs and generates stoichiometric amounts of metallic byproducts containing zinc, boron, or silicon salts. Direct C–H bond functionalization of arenes (Fig. 2c) or difluoroacetophenone (Fig. 2d) using Fenton reagents,<sup>14</sup> photocatalysts,<sup>15</sup> or palladium catalysts can generate aryldifluoromethyl carbonyl compounds.<sup>16</sup> Nevertheless, these methods require metal catalysts and/or organometallic species.

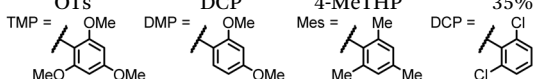
As an alternative approach to avoid chemical wastes, decarboxylative coupling reactions are an attractive strategy because they generate only carbon dioxide as the byproduct during bond formation.<sup>17</sup> Decarboxylative fluoroalkylation using  $\alpha$ -fluorinated carboxylate can produce the corresponding organofluorines, although these reactions require transition metals, heat, or photoirradiation in most cases.<sup>17j,18</sup> Fluorine-containing activated methylene derivatives undergo decarboxylative C–C bond formation under relatively mild conditions,<sup>19</sup> although the generation of aryldifluoromethyl ketones *via* decarboxylative arylation is unprecedented so far.<sup>20</sup> Given these circumstances, the development of catalyst-free arylation of fluorinated carboxylates, without chemical waste, would be an economical and environmentally friendly method for the synthesis of fluorine-containing biologically active compounds.

To achieve catalyst-free decarboxylative fluoroalkylation, we focused on the use of diaryliodonium(III) salts ( $\text{Ar}^1\text{Ar}^2\text{I}^+\text{X}^-$ ) as arylation reagents. This will offer an alternative approach to transition metal-free arylations of various nucleophiles forming aryl–heteroatom and aryl–carbon bonds.<sup>21</sup> Our group has developed an efficient method for the arylation of carboxylic acids,<sup>22a</sup> phenols,<sup>22b</sup> and hydroxyamines<sup>22c</sup> using easily accessible trimethoxyphenyl (TMP) iodonium salts ( $\text{Ar}(\text{TMP})\text{I}^+\text{X}^-$ ).<sup>23,24</sup> Herein, we describe the first example of the decarboxylative arylation of difluoroacetate derivatives using TMP-iodonium tosylates to afford aryldifluoromethyl carbonyl compounds (Fig. 2e). The selective C–H bond functionalization of uracil through the present strategy to incorporate fluorine-containing functional groups was also demonstrated.

Initially, we examined the reaction of  $\alpha,\alpha$ -difluoro- $\beta$ -ketoacid sodium salt **1a-Na** with (4-nitrophenyl)(TMP)iodonium tosylate **2a-OTs-TMP** in toluene at 100 °C to afford the desired decarboxylative coupling product **3aa** in 86% yield (Table 1, entry 1). In this reaction, formation of the corresponding aryl ester *via* a direct coupling reaction was not observed. When the reaction was carried out at 70 °C, the yield dropped to 34% (entry 2). Combining acid **1a-H**, instead of **1a-Na**, with  $\text{Na}_2\text{CO}_3$  decreased the yield to 48%, and a large quantity of the decarboxylative protonation product was generated as a side product presumably reacting with the *in situ* generated  $\text{H}_2\text{O}$  as the proton source (entry 3). In fact, the reaction of **1a-Na** with **2a-OTs-TMP** in the presence of  $\text{H}_2\text{O}$  increased the yield of the protonation product (Fig. S1†). Thus, sodium salt **1a-Na** was employed as the starting material for subsequent examinations. The use of TMP-iodonium trifluoroacetate afforded a comparable yield of **3aa** (entry 4). In contrast, the yield decreased when TMP-iodonium salts bearing triflate, acetate, and tetrafluoroborate were used (entries 5–7). Next, we

**Table 1** Optimization of reaction conditions for decarboxylative coupling<sup>a</sup>

|  |                    |     |                   |                        |
|--|--------------------|-----|-------------------|------------------------|
| Entry  | L                  | Ar  | Solvent           | NMR Yield              |
| 1  | OTs                | TMP | Toluene           | 86%                    |
| 2 <sup>b</sup>   | OTs                | TMP | Toluene           | 34%                    |
| 3 <sup>c</sup>   | OTs                | TMP | Toluene           | 48%                    |
| 4  | OCOCF <sub>3</sub> | TMP | Toluene           | 83%                    |
| 5  | OTf                | TMP | Toluene           | 26%                    |
| 6  | OAc                | TMP | Toluene           | 15%                    |
| 7  | BF <sub>4</sub>    | TMP | Toluene           | 60%                    |
| 8  | OTs                | TMP | PhCF <sub>3</sub> | 85%                    |
| 9  | OTs                | TMP | DMF               | 23%                    |
| 10   | OTs                | TMP | MeCN              | 67%                    |
| 11   | OTs                | TMP | i-BuOAc           | 76%                    |
| 12   | OTs                | TMP | i-BuOH            | 11%                    |
| 13   | OTs                | TMP | 1,4-Dioxane       | 65%                    |
| 14   | OTs                | TMP | 4-MeTHP           | 89% (85%) <sup>d</sup> |
| 15   | OTs                | DMP | 4-MeTHP           | 87%                    |
| 16   | OTs                | Mes | 4-MeTHP           | 45%                    |
| 17   | OTs                | DCP | 4-MeTHP           | 35%                    |



<sup>a</sup> Reaction conditions: **1a-Na** (0.30 mmol) and **2a-L-Ar** (0.20 mmol) in solvent (1.0 mL) at 100 °C for 20 h: <sup>19</sup>F NMR yield. <sup>b</sup> Conducted at 70 °C. <sup>c</sup> The corresponding acid **1a-H** (0.30 mmol) and  $\text{Na}_2\text{CO}_3$  (0.30 mmol) were used instead of **1a-Na**. <sup>d</sup> Isolated yield.

screened the solvents using **2a-OTs-TMP**. The use of benzotrifluoride was comparable to that of toluene (entry 8).

The reactivity in *N,N*-dimethylformamide (DMF), in which both starting materials were highly soluble, was low, affording the product in 23% yield (entry 9). Using acetonitrile and isobutyl acetate, which are recommended solvents in the CHEM21 selection guide,<sup>25</sup> acceptable yields of **3aa** (entries 10 and 11) were obtained, whereas the yield was low in isobutyl alcohol (entry 12). The present reaction proceeded in THF at 100 °C to afford **3aa** in high yield (not shown in the Table), albeit with low reproducibility, presumably because of the incompatibility of the reaction with the boiling point of THF. Thus, we tested cyclic ethers with high boiling points. Consequently, the reaction in 1,4-dioxane afforded a moderate yield of 65% (entry 13), whereas the reaction in 4-methyltetrahydropyran (4-MeTHP)<sup>26</sup> afforded **3aa** in good yields (89%; entry 14). The dimethoxyphenyl (DMP) group was also employed as a dummy aryl ligand instead of the TMP group to afford the desired product **3aa** in a comparable yield (entry 15). In addition, the mesityl (Mes) and dichlorophenyl (DCP) groups allowed selective bond formation, albeit with decreased yields (entries 16 and 17).

We speculated that the present reaction proceeded *via* the initial ligand exchange of fluorinated carboxylate **1a-Na** with the tosylate anion of **2a-OTs**, followed by decarboxylative C–C bond formation. The expected intermediate **1a2a-TMP** was prepared *via* the general synthetic method for TMP-iodonium

salts from 4-nitroiodobenzene with  $\alpha,\alpha$ -difluoro- $\beta$ -keto acid **1a-H** using *m*CPBA as an oxidant (Fig. S2†). Treatment of isolated iodonium salt **1a2a-TMP** in toluene at 100 °C afforded the decarboxylative arylation product **3aa** in 70% yield (Fig. 3a). The reaction of **1a-Na** with **2a-OTs-TMP** in CD<sub>3</sub>CN at room temperature was monitored by NMR spectroscopy to confirm the generation of **1a2a-TMP** (Fig. 3b and Fig. S3†). Decarboxylative ligand coupling of **1a2a-TMP** proceeded continuously at 100 °C to afford the coupling product **3aa** in 74% yield (Fig. S4†). The reaction of **1a-Na** and **2a-OTs-TMP** in the presence of TEMPO produced **3aa** in 84% yield (Fig. 3c), indicating that the present reaction does not involve radical species generated by Hunsdiecker-type decarboxylation<sup>17i,27</sup> and/or single-electron-transfer (SET) process.<sup>12f,28</sup> When the reaction of **1a-Na** and **2a-OTs-TMP** was carried out with 4-(trifluoromethyl)benzaldehyde, the decarboxylative arylation reaction preferentially proceeded to afford **3aa** in 66% yield, along with quantitative recovery of the added aldehyde (Fig. 3d); formation of a  $\beta$ -hydroxy ketone *via* decarboxylative aldol reaction was not observed. In contrast, **1a-Na** reacted with the aldehyde in the absence of **2a-OTs-TMP** to produce the corresponding  $\beta$ -hydroxy ketone in 76% yield.<sup>19c,d,e</sup> We assume that sodium difluoroenolate is not a major intermediate for the present decarboxylative bond formation. Based on these results, a plausible reaction mechanism involving decarboxylative arylation is outlined in Fig. 3e. Initially, the ligand exchange of **1a-Na** with tosylate anion of **2a-OTs-TMP** preferentially proceeds before the decarboxylation, generating intermediate **1a2a-TMP** along with the release of TsONa. The precipitation of TsONa can promote this step if nonpolar solvents are used. We envisioned that the decarboxylation of **1a2a-TMP** proceeded to form the corresponding iodonium difluoroenolate salt, containing *O*-bound and/or *C*-bound difluoroenolates.<sup>29</sup>

Subsequent ligand coupling generates the arylation product **3aa**. The heating is presumably required for the decarboxylation step; silyl difluoroenolates react with diaryliodonium salts at room temperature to afford the corresponding arylation products.<sup>13</sup> Alternatively, concerted decarboxylative ligand coupling could also be a possible reaction mechanism for the present system.

The decarboxylative arylation of benzoylacetate derivatives is limited to a few examples, which require copper catalysts.<sup>20a,c</sup> Therefore, the present reaction is a complementary method for accessing difluoromethyl aryl ketones. The limited examples prompted us to examine various combinations of  $\alpha,\alpha$ -difluoro- $\beta$ -ketoacid sodium salts **1-Na** and TMP-iodonium tosylate salts **2-OTs-TMP** (Fig. 4). Functionalized aryl rings bearing nitro, cyano, ester, acetyl, and trifluoromethyl groups were introduced *via* decarboxylative arylation reactions to afford **3aa–3ae**. The ester group was not hydrolysed and survived during the reaction, indicating that the present reaction proceeds under mild conditions at least below pH 10. The introduction of an aryl group bearing an *ortho*-substituent showed a low reactivity (**3af**, 36%) due to steric hindrance. The use of TMP-iodonium tosylates bearing electron-rich aromatic rings proved challenging under standard conditions. Reaction monitoring by NMR spectroscopy suggested that the decarboxylative coupling step was influenced by the low electrophilicity of aryl groups (Fig. S5†). Additional optimization of the reaction conditions (Fig. S6†) revealed that aryl rings bearing methyl and methoxy groups could be successfully introduced at a higher temperature (130 °C) in toluene to afford **3ag–3ai** in moderate yields.  $\alpha,\alpha$ -Difluoro- $\beta$ -ketoacid sodium salts bearing electron-donating groups, such as methoxy, *tert*-butyl, and methyl groups, were employed to afford the corresponding products **3ba**, **3bb**, **3bj**, **3ca**, **3da**, **3ej** and **3bk**. The reactivity

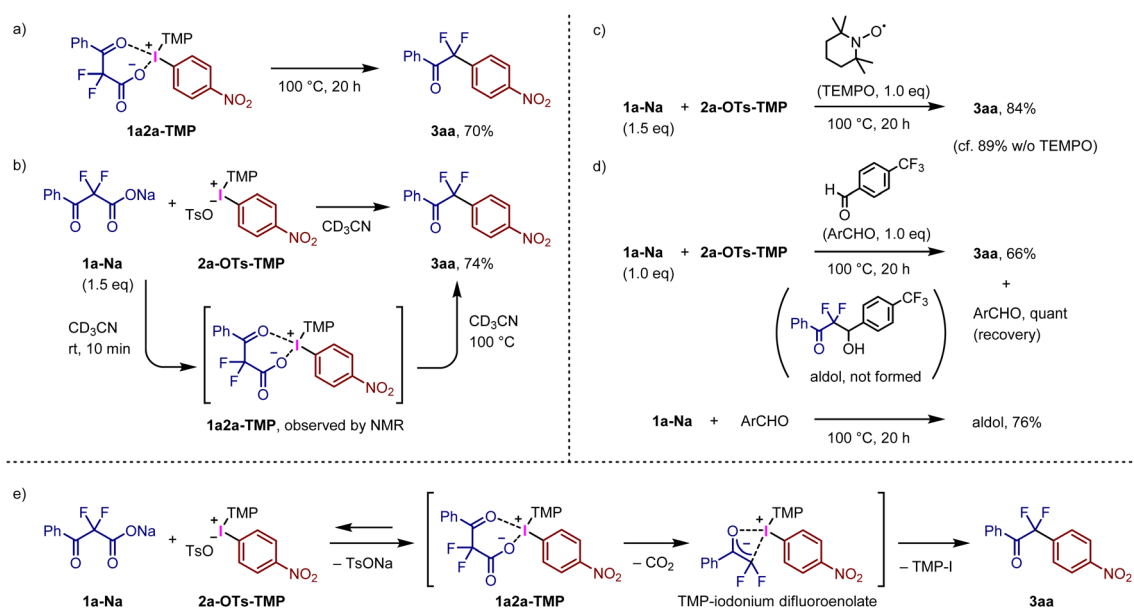


Fig. 3 Mechanistic studies for decarboxylative ligand coupling.

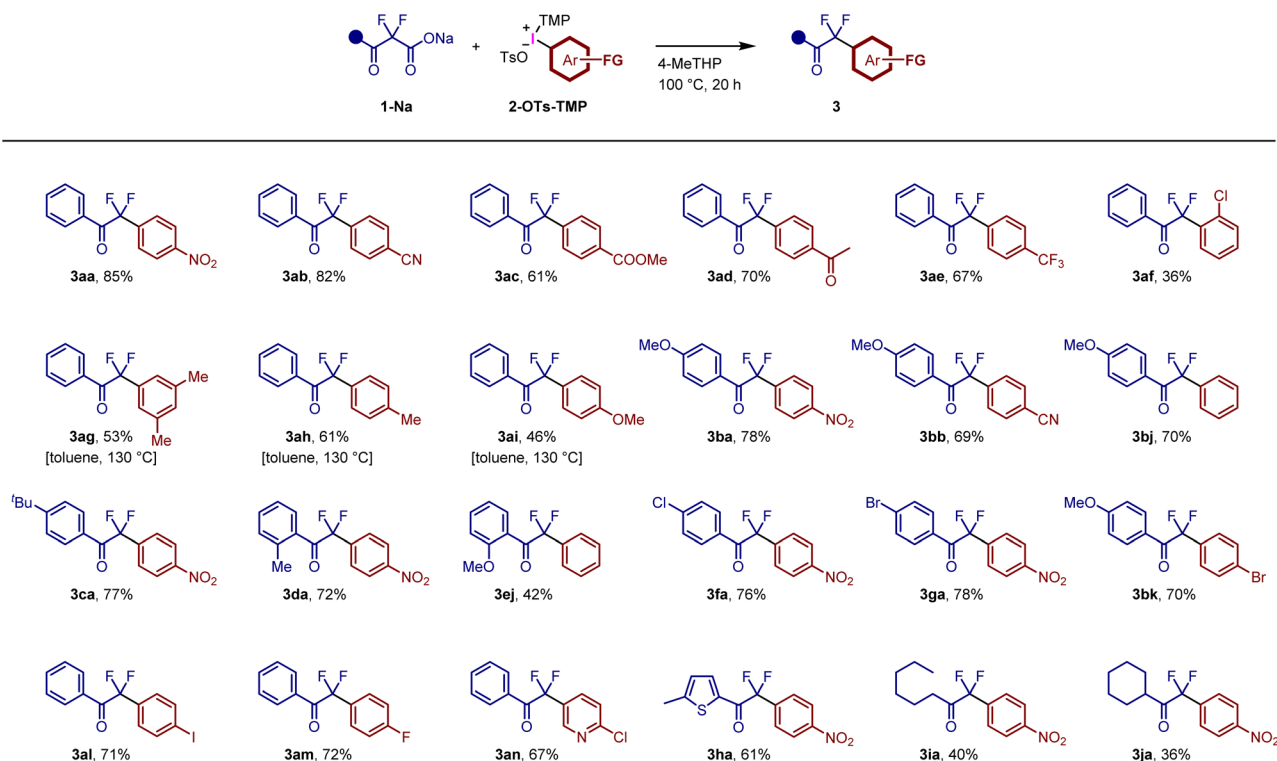


Fig. 4 Synthesis of various aryl difluoromethyl ketones using  $\alpha,\alpha$ -difluoro- $\beta$ -ketoacid sodium salts and TMP-iodonium tosylates.

was unaffected by *ortho*-methyl group to afford **3da** in 72% yield. In contrast, *ortho*-methoxy group decreased the yield (**3ej**: 42%), presumably because the corresponding difluoro-enolate intermediate is hardly generated due to the steric hindrance. The metal-free conditions enable the preparation of reactive aryl halide-bearing products **3af**, **3fa**, **3ga**, **3bk**, **3al** and **3am**. Heteroarenes, such as pyridine and thiophene groups, were incorporated as aryl groups to obtain **3an** and **3ha**. Notably, the nucleophilic aromatic substitution of fluorine and chlorine atoms did not proceed under our conditions (see **3am** and **3an**). Aryl halides **3af**, **3fa**, **3ga**, **3bk**, **3al**, **3am**, and **3an** can be used as starting materials for transition metal-catalyzed coupling or nucleophilic aromatic substitutions. In addition to the aryl ketones, alkyl ketones **3ia** and **3ja** were synthesized from the corresponding  $\alpha,\alpha$ -difluoro- $\beta$ -ketoacid sodium salts, albeit in moderate yields. In all the cases depicted in Fig. 4, arylation products bearing the TMP group were not observed.

The reaction of *N,N*-dimethyluracil(DCP)iodonium tosylate **2o-OTs-DCP** with **1a-Na** resulted in uracil-selective C–C bond formation, affording the corresponding difluoromethyl ketone **3ao** in 65% yield (Fig. 5a). Notably, a C–C bond was formed at the 6-position of *N,N*-dimethyluracil instead of the 5-position, wherein 1,4-addition presumably occurred in the conjugated enone system of the uracil derivative. *N,N*-Dimethyluracil iodonium salts can be synthesized *via* the direct introduction of iodonium moieties, starting from *N,N*-dimethyluracil.<sup>30,31</sup> In fact, **2o-OTs-DCP** was prepared by the reaction of *N,N*-dimethyluracil and 2,6-dichloriodobenzene (DCP-I) in the pres-

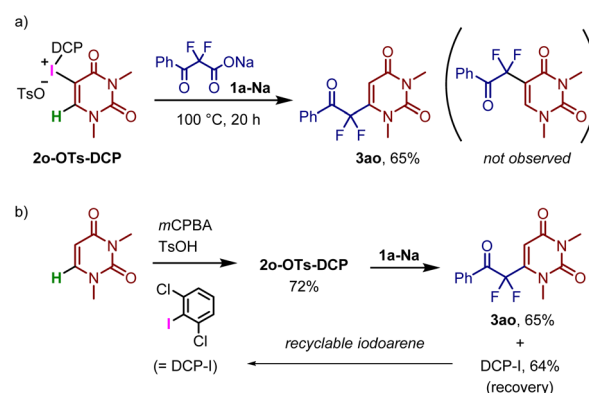
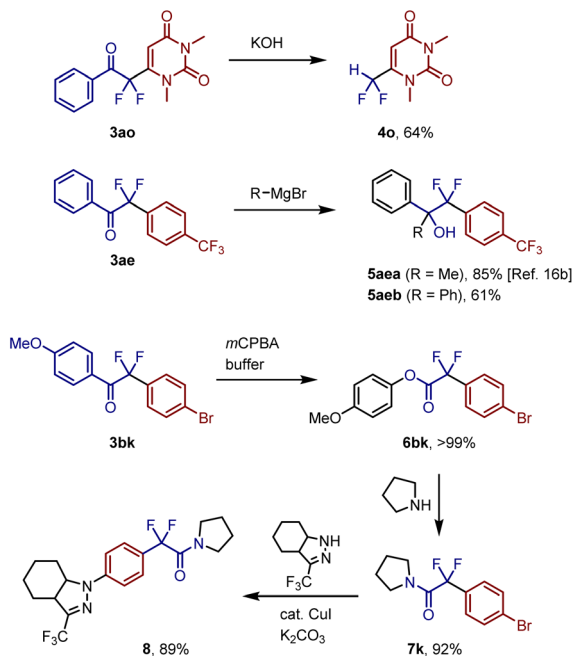


Fig. 5 C–H functionalization of uracil using recyclable iodoarene.

ence of *m*CPBA and *p*-TsOH (Fig. 5b). After the decarboxylative coupling with **1a-Na**, DCP-I was successfully recovered in its pure form, which could be recycled as the starting material for **2o-OTs-DCP**. This strategy enables the selective C–H bond functionalization of uracil using renewable iodonium salt.

Next, we examined the further transformation of the decarboxylative coupling products (Fig. 6). The aryl carbonyl unit of coupling product **3ao** was removed *via* treatment with KOH to generate difluoromethyluracil **4o** in 64% yield. Aryl difluoromethyl ketone **3ae** was reacted with organomagnesium reagents to afford the corresponding tertiary alcohols **5aea** (85%)<sup>16b</sup> and **5aeb** (61%). Treatment of **3bk** with *m*CPBA in a



**Fig. 6** Transformation of aryldifluoromethyl ketones.

mixed solvent of dichloromethane and 1,1,1,3,3,3-hexafluoro-2-propyl alcohol (HFIP) afforded quantitative yield of aryl ester **6bk**, which reacted with pyrrolidine to generate the corresponding difluoroacetamide **7k** in 92% yield. This sequential transformation was successfully applied to a gram-scale reaction to obtain **7k** in 80% yield (1.2 g) without the isolation of the ester intermediate. Functionalized difluoroacetamide **7k** was converted to the AMPAR allosteric inhibitor **8** in 89% yield *via* a copper-catalyzed coupling reaction.

## Conclusions

We have developed the decarboxylative arylation of an  $\alpha,\alpha$ -difluoro- $\beta$ -keto acid ester with diaryliodonium salts to afford the corresponding  $\alpha,\alpha$ -difluoroketones. The reaction involves sequential ligand exchange, followed by decarboxylative ligand coupling. Two fluorine atoms were successfully incorporated at the benzyl position in the absence of hazardous fluorination reagents, organometallic compounds, and transition metal catalysts. The resulting  $\alpha,\alpha$ -difluoromethyl ketone group could be converted into the corresponding ester, amide, and difluoromethyl groups, which are found in biologically active compounds. The present reaction offers an environmentally friendly synthetic approach to fluorine-containing drugs and is expected to contribute to drug design and discovery.

## Author contributions

K. K. and T. D. conceived and designed the experiments and directed the project. K. Y., N. U. and N. Y. performed the

experiments. K. K., K. Y. and N. U. analyzed the data and checked the experimental details. K. K., Y. K. and T. D. wrote the paper. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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