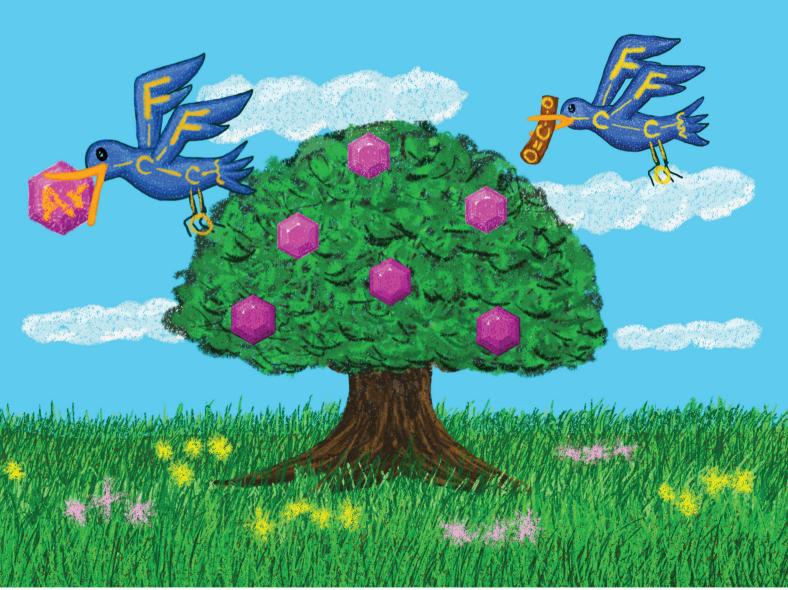
Volume 25 Number 5 7 March 2023 Pages 1693-2030

Green Chemistry

Cutting-edge research for a greener sustainable future

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ISSN 1463-9262



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Kotaro Kikushima, Yasuyuki Kita, Toshifumi Dohi *et al.* Decarboxylative arylation with diaryliodonium(III) salts: alternative approach for catalyst-free difluoroenolate coupling to aryldifluoromethyl ketones

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Cite this: *Green Chem.*, 2023, **25**, 1790

Received 24th November 2022, Accepted 18th January 2023

DOI: 10.1039/d2gc04445e

rsc.li/greenchem

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

Catalyst-free access to aryldifluoromethyl ketones has been achieved through decarboxylative arylation of α,α -difluoro- β -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.¹ 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,^{2a} FKB12 inhibitor,^{2b} fungal CYP51 inhibitor,^{2c} and BACE 1 inhibitor^{2d} (Fig. 1). Furthermore, the difluoromethylene (-CF₂-) groups serve as bioisosteres for carbonyl compounds and oxygen and sulfur atoms.^{3,4}

Difluoromethylene units have been introduced by α -fluorination or deoxofluorination of the corresponding carbonyl compounds using electrophilic fluorination reagents or aminosulfur trifluorides. 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. Aryldifluoroacetates have been synthesized νia transition metal-catalyzed coupling reactions of commercially available bromodifluoroacetate and aryl

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

Fig. 1 Biologically active compounds containing difluoromethylene

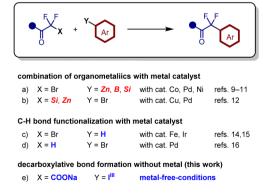


Fig. 2 Various approaches to α -aryl- α , α -difluorinated carbonyl compounds.

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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, ¹⁴ photocatalysts, ¹⁵ or palladium catalysts can generate aryldifluoromethyl carbonyl compounds. ¹⁶ 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. Decarboxylative fluoroalkylation using α-fluorinated carboxylate can produce the corresponding organofluorines, although these reactions require transition metals, heat, or photoirradiation in most cases. Fluorine-containing activated methylene derivatives undergo decarboxylative C-C bond formation under relatively mild conditions, although the generation of aryldifluoromethyl ketones *via* decarboxylative arylation is unprecedented so far. 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 (Ar¹Ar²I⁺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.²¹ Our group has developed an efficient method for the arylation of carboxylic acids,²²²a phenols,²²²b and hydroxyamines²²²c using easily accessible trimethoxyphenyl (TMP) iodonium salts (Ar(TMP) I⁺X⁻).²³,²⁴ 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 α , α -difluoroβ-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 Na₂CO₃ 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 H₂O as the proton source (entry 3). In fact, the reaction of 1a-Na with 2a-OTs-TMP in the presence of H2O 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^a

Ph F ONa +	+ TMP L 100 °C, 20 h	Ph NO2
1a-Na	2a-L-Ar	3aa

Entry	L	Ar	Solvent	NMR Yield
1	OTs	TMP	Toluene	86%
2^b	OTs	TMP	Toluene	34%
3^c	OTs	TMP	Toluene	48%
4	$OCOCF_3$	TMP	Toluene	83%
5	OTf	TMP	Toluene	26%
6	OAc	TMP	Toluene	15%
7	BF_4	TMP	Toluene	60%
8	OTs	TMP	$PhCF_3$	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%) ^d
15	OTs	DMP	4-MeTHP	87%
16	OTs	Mes	4-MeTHP	45%
17	OTs	DCP	4-MeTHP	35%
	TMP = OMe DM	P = OMe	Mes = Me DCI	P = CI

^a 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: ¹⁹F NMR yield. ^b Conducted at 70 °C. ^c The corresponding acid **1a-H** (0.30 mmol) and Na₂CO₃ (0.30 mmol) were used instead of **1a-Na**. ^d 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, 25 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-methyltetrahydropyrane (4-MeTHP)²⁶ 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 vields (entries 16 and 17).

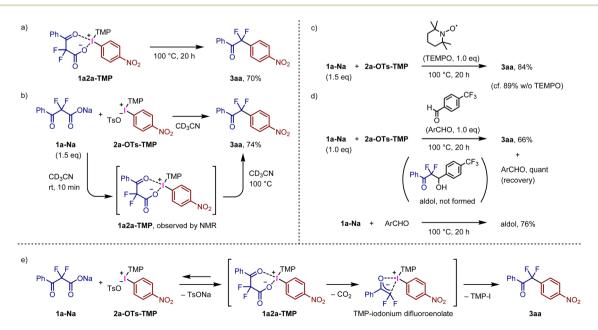
We speculated that the present reaction proceeded *via* the initial ligand exchange of fluorinated carboxylate **1a-Na** with the tosylate anion of **2a-OTs**, followed by decarboxylative C–C bond formation. The expected intermediate **1a2a-TMP** was prepared *via* the general synthetic method for TMP-iodonium

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salts from 4-nitoroiodobenzene with α,α-difluoro-β-keto acid **1a-H** using mCPBA as an oxidant (Fig. S2 \dagger). 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 CD₃CN 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 171,27 and/or single-electron-transfer (SET) process. 12f,28 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 β-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 β-hydroxy ketone in 76% yield. 19c,d,e 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.²⁹

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. 13 Alternatively, concerted decarboxylative ligand coupling could also be a possible reaction mechanism for the present system.

The decarboxylative arylation of benzovlacetate derivatives is limited to a few examples, which require copper catalysts. 20a,c Therefore, the present reaction is a complementary method for accessing difluoromethyl aryl ketones. The limited examples prompted us to examine various combinations of α,α-difluoro-β-ketoacid sodium salts 1-Na and TMPiodonium 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. α,α-Difluoro-β-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



Mechanistic studies for decarboxylative ligand coupling.

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Synthesis of various aryldifluoromethyl ketones using α, α -difluoro- β -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 difluoroenolate 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 α,α -difluoro- β -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 20-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. 30,31 In fact, 20-OTs-DCP was prepared by the reaction of N,N-dimethyluracil and 2,6-dichloroiodobenzene (DCP-I) in the pres-

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

ence of mCPBA 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 20-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 40 in 64% yield. Aryl difluoromethyl ketone 3ae was reacted with organomagnesium reagents to afford the corresponding tertiary alcohols 5aea $(85\%)^{16b}$ and **5aeb** (61%). Treatment of **3bk** with mCPBA in a

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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 α,α -difluoro- β -keto acid ester with diaryliodonium salts to afford the corresponding α,α-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 α,α -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

K. K. and T. D. acknowledge support from JSPS KAKENHI grant number 18H02014 (K. K.) and 19K05466 (T. D.), JST CREST grant number JPMJCR20R1, and the Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

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