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Cobalt-catalyzed decarboxylative difluoroalkylation of nitrophenylacetic acid salts†

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The selective installation of fluorine-containing groups into biologically relevant molecules has been used as a common strategy for the development of pharmaceutically active molecules. However, the selective incorporation of *gem*-difluoromethylene groups next to sterically demanding secondary and tertiary alkyl groups remains a challenge. Herein, we report the first cobalt-catalyzed regioselective difluoroalkylation of carboxylic acid salts. The reaction allows for the facile construction of various difluoroalkylated products in good yields tolerating a wide range of functionalities on either reaction partner. The potential of the method is illustrated by the late-stage functionalization of molecules of biological relevance. Mechanistic studies support the *in situ* formation of a cobalt(I) species and the intermediacy of difluoroalkyl radicals, thus suggesting a Co(I)/Co(II)/Co(III) catalytic cycle.

Introduction

The incorporation of fluorine into organic substructures is one of the most widely studied areas of synthetic organic chemistry due to the numerous applications that fluorinated compounds possess.[1] The *gem*-difluoromethylene unit is an important therapeutic moiety because of its ability to increase metabolic stability[2] or improve the pharmacokinetic properties of molecules.[3] The significance of this structural motif in drug discovery is further illustrated by the large variety of difluoroalkane-containing pharmaceutical compounds such as HIV-1 therapeutic agents,[4] and chemotherapy drugs (Fig. 1).[5] However, the incorporation of these fluorinated linkages remains a significant synthetic challenge and still relies on traditional methods such as the use of nucleophilic or electrophilic fluoride sources (*e.g.*, DAST or Selectfluor).[6]

In recent years, transition metal-catalyzed cross-couplings have emerged as convenient strategies for the construction of fluorine-containing organic compounds.[6h,7–12] Recent efforts have led to the construction of various C(sp^2 or sp)–CF_2R bonds where the fluorinated alkane is often connected to the aryl,[13] vinylic,[12f,14] or propargylic[9f,11b,15] positions. In contrast, the selective installation of the difluoromethylene group adjacent to aliphatic all carbon quaternary C(sp^3)-centers remains innately challenging and sparsely reported (Scheme 1).[11c,12b,16,17]

Nonetheless, integrating quaternary carbon centers has the potential to impart conformational rigidity and metabolic stability, leading to improved pharmacokinetic properties of

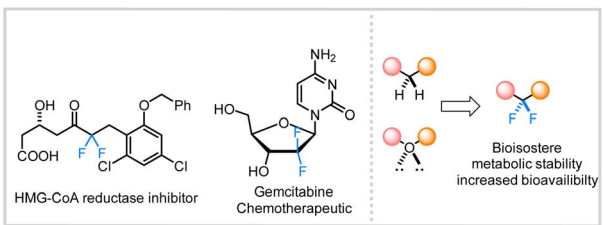
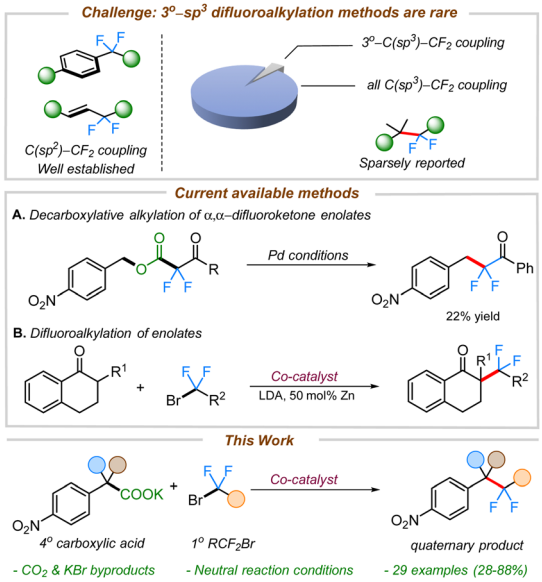


Fig. 1 Select fluorine-containing therapeutics.



Scheme 1 Decarboxylative difluoroalkylations.

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molecules.[18] With this in mind, we set out to develop difluoroalkylation of quaternary benzyl nucleophiles for the facile construction of all carbon quaternary C(sp^3)–CF_2 bonds.

We envisioned leveraging decarboxylation as an efficient strategy for the generation of benzylic nucleophiles from organic acids.[19] There are a few reports on decarboxylative difluoroalkylations known in the literature.[20,20d,21,22] Altman and co-workers have previously developed decarboxylative electrophilic benzylations of difluoroenolate nucleophiles (Scheme 1A).[23] Although the chemistry proved highly effective for the difluoroalkylation of primary electron-rich benzyl electrophiles, the outcomes were substantially worse with electron-deficient benzyl electrophiles. Furthermore, coupling of 2° or 3° benzyl electrophiles was not possible. To address the challenge of difluoroalkylation of sterically-demanding benzyl moieties, we posited an alternate strategy involving umpolung of the reactive intermediates (*i.e.* using benzyl nucleophiles with α,α-difluorocarbonyl electrophiles).

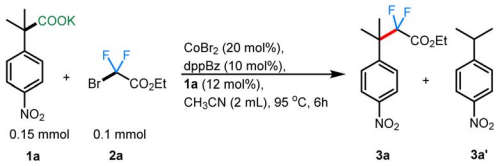
Results and discussion

To begin, we took inspiration from Wang's cobalt-catalyzed *gem*-difluoroalkylation of α-tertiary aryl ketones (Scheme 1B).[12b] While that chemistry required the use of stoichiometric LDA and 50 mol% Zn reductant, it was anticipated that a decarboxylative coupling strategy would allow additive-free synthesis under more neutral conditions.[24]

We initiated our studies by optimizing the conditions for the cobalt-catalyzed difluoroalkylation of 2-methyl-2-(4-nitrophenyl)propanoic acid potassium salt (**1a**) with bromodifluoroacetate (**2a**) using the conditions adapted from a related allylation study.[24] Interestingly, with 10 mol% $CoBr_2$ and 10 mol% of dppBz, we observed the corresponding difluoroalkylated (**3a**) in reasonable yields along with 30% of the protonated product **3a′** (Table 1, entry 4). Gratifyingly, when the cobalt loading was increased to 20 mol%, we observed the highest yield (81%) for the difluoroalkylated product **3a** and decreased amount of the protonated byproduct **3a′** (Table 1, entry 1). Control studies confirmed the necessity of both cobalt and the ligand for efficient reactivity (Table 1, entries 2 & 3). Replacing $CoBr_2$ with other cobalt sources such as $Co(BF_4)_2$ or CoI_2 gave decreased yields of **3a** (Table 1, entries 6 & 7). The initial solvent of choice, MeCN, was found to be the best for the reaction (Table 1, entry 8). Various bis-phosphine and diamine-containing ligands were screened; however, all of them failed to give an improvement in yield compared to that of dppBz (Table 1, entries 10–12). After additional screenings (see ESI† for more details), it was determined that $CoBr_2$ (20 mol%), dppBz (10 mol%), and **1a** (12 mol%) in CH_3CN at 95 °C were optimal for this reaction, producing the desired product **3a** in 77% isolated yield.

With the optimized conditions in hand, we sought to expand the protocol to accommodate other fluoroalkylating reagents and carboxylate salts, enabling the construction of a unique range difluoroalkyl groups. Remarkably, in all cases, the product formation was regiospecific, with the C–CF_2 bond formation occurring at the site where decarboxylation had

Table 1 Initial optimization results

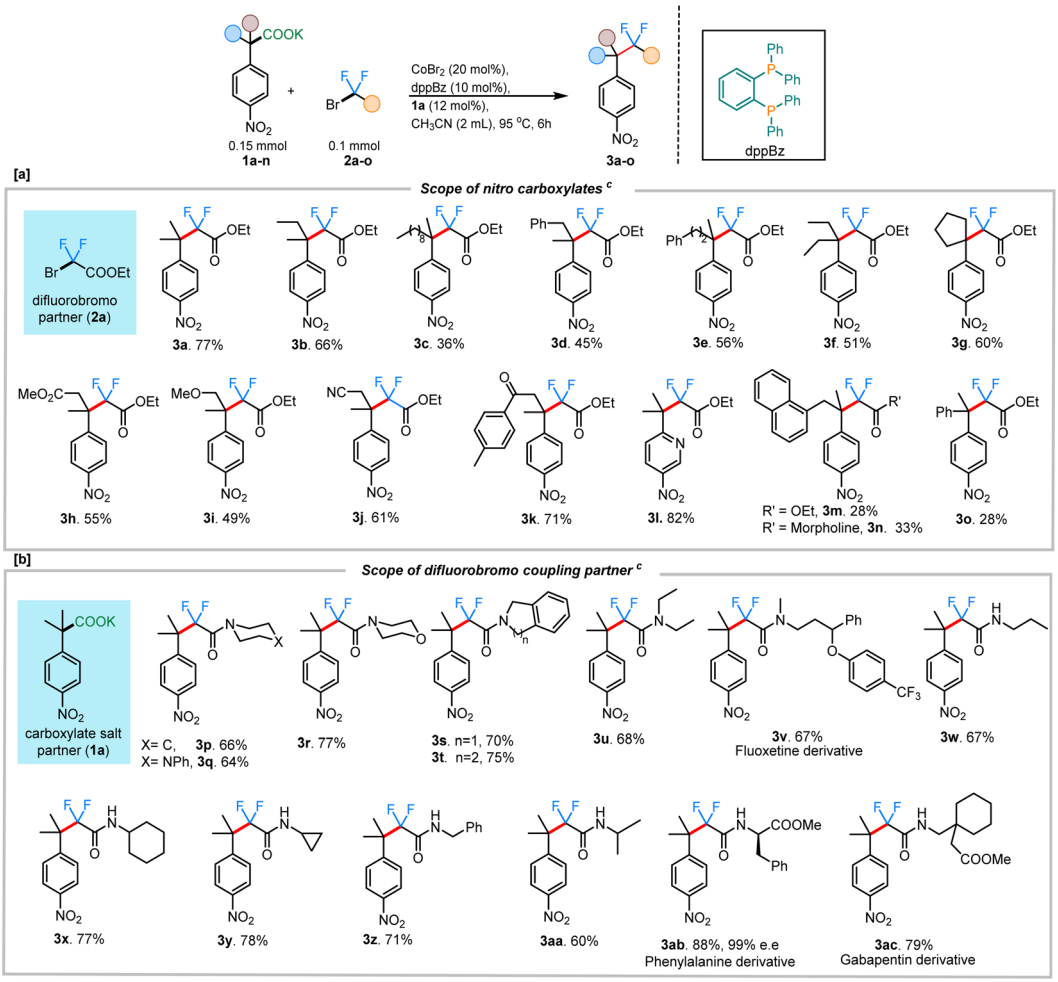


Entry	Variations in conditions	Yield[a] **3a** : **3a′** [%]
1	—	84(77) : 16
2	No cobalt	—
3	No ligand	—
4	10 mol% of $CoBr_2$	15 : 30
5	15 mol% of $CoBr_2$	24 : 36
6	$Co(BF_4)_2$ instead of $CoBr_2$	40 : 80
7	CoI_2 instead of $CoBr_2$	54 : 19
8	DMF, DMSO, THF instead of MeCN	<25
9	60 °C instead of 95 °C	40 : 18
10	dppe instead of dppBz	31 : 52
11	dppf instead of dppBz	45 : 50
12	dtbbpy instead of dppBz	42 : 28

[a] Yields determined by quantitative ^{1}H NMR analysis. Numbers in parentheses are isolated yields.

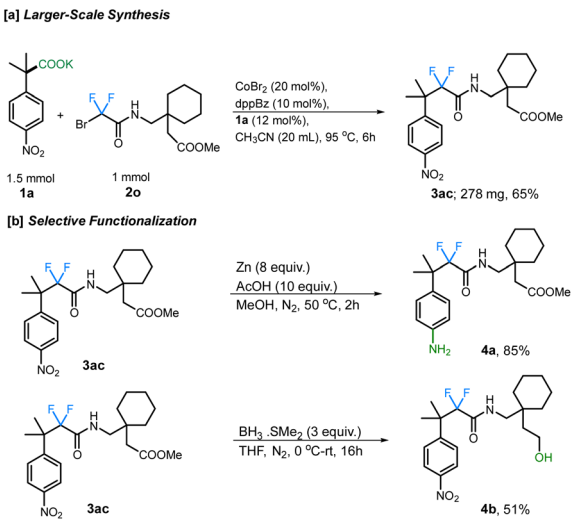
occurred (**3h** & **3j–k**). A wide range of potassium salts of various substituted 4-nitrophenyl acetic acids were found to be tolerant to the reaction conditions, providing the coupled products in moderate to good yields (Scheme 2). In addition to a simple methyl substituent (**3a**; 77%), the alkyl chain was extended to accommodate other longer alkyl chains (**3b**; 66% and **3c**; 36%), albeit with lower yields. Both benzylic- and homobenzylic-substituted carboxylate salts gave reasonable yields for the corresponding fluoroalkylated product (**3d**; 45% and **3e**; 56%). A carboxylate salt containing a cyclopentyl group at the alpha position gave the subsequent fluoroalkyated product in 60% yield (**3g**). Carboxylate salts bearing other important functional groups such as ester (**3h**; 55%), ether (**3i**; 49%), nitrile (**3j**; 61%), and ketone groups (**3k**; 71%) were all tolerated under the reaction conditions. Owing to the biological importance of heterocyclic compounds, the pyridine-containing carboxylate salt **1l** was tested under our reaction conditions. We were delighted to find that **1l** also underwent the transformation to deliver the corresponding difluoroalkylated product **3l** in 82% yield. While many couplings occurred to provide products in moderate to good yield, it was noted that, as the steric hindrance around the quaternary carbon increased, the yields of coupling were adversely affected. This was especially clear with the naphthyl-substituted salt giving only 28% of the corresponding difluoroalkylated product (**3m**). Similar results were obtained with the α-phenyl carboxylate salt, giving only 28% of the corresponding difluoroalkylated product **3o**. In instances with lower yields for the product, the mass balance was always accounted for by the amount of the protonated byproduct isolated.

Additionally, the scope of different difluorobromo coupling partners was explored. Various acetamides, both cyclic and acyclic, were found to be well-tolerated during this



Scheme 2 Scope of decarboxylative difluoroalkylations. [a] Scope of nitro carboxylates. [b] Scope of difluorobromo alkanes. [c] All reactions were run on a 0.1 mmol scale. Yields reported are isolated yields. Reaction conditions: $CoBr_2$ (20 mol%), dppBz (10 mol%), **1a** (12 mol%), CH_3CN (2 mL), 95 °C.

transformation. Cyclic piperidine (**3p**; 66%), piperazine (**3q**; 64%), morpholine (**3r**; 77%), indoline (**3s**; 70%), and tetrahydroisoquinoline (**3t**; 75%) derived acetamides gave the corresponding fluoroalkylated product in good yields. The reaction was even successful with a fluoxetine-derived difluorobromoacetamide providing the corresponding cross-coupled product in 67% yield (**3v**). Simple alkyl substituted difluoroacetamides such as *N*-propyl (**3w**), *N*-cyclohexyl (**3x**), *N*-cyclopropyl (**3y**), *N*-benzyl (**3z**), and *N*-isopropyl (**3aa**) were also found to undergo the transformation efficiently, with the cyclopropyl ring staying intact under the reaction conditions. Importantly, a difluorobromoacetamide derived from L-phenylalanine also gave the cross-coupled product **3ab** in 88% yield, without any observable racemization of the existing stereocenter (see ESI† for more details). This highlights the utility of decarboxylative couplings that obviate strong-base additives.[12b] The reaction with a gabapentin-derived difluorobromoacetamide likewise proceeded in good yield, and could be scaled up to a 1 mmol scale without large reduction in the yield (Scheme 3a).



Scheme 3 (a) Larger-scale reaction. (b) Synthetic utility.

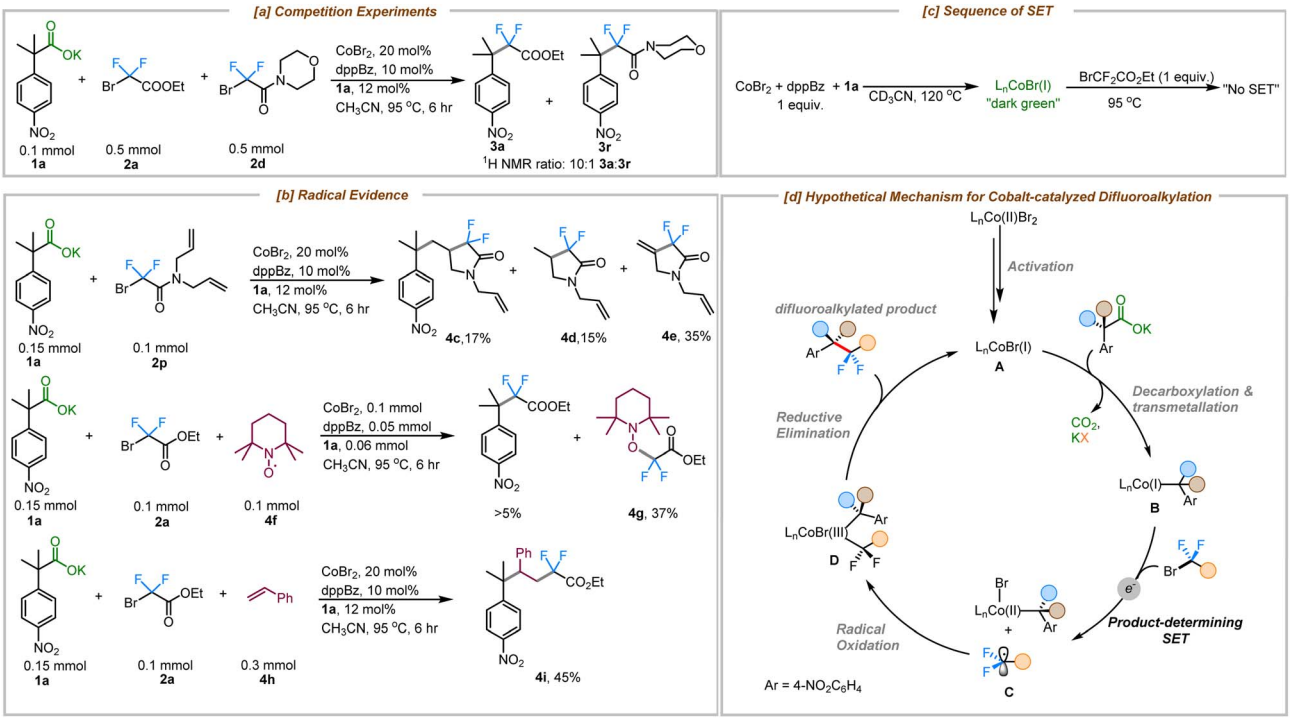


Fig. 2 Mechanistic insights. (a) Competition experiment (b) radical evidence (c) sequence of SET (d) hypothetical difluoroalkylation mechanism.

Finally, we further demonstrated the synthetic potential of this cobalt-catalyzed decarboxylative difluoroalkylation method through the synthetic modification of the difluoroalkylated products. For example, the resulting gabapentin-derived product **2m** can be selectively reduced under Zn/AcOH conditions to the aniline derivative **4a.** Moreover, the reduction of the ester group using $BH_3 \cdot SMe_2$ provides the corresponding alcohol **4b** which can undergo further derivatizations (Scheme 3b).

To gain more insight into the mechanism of this cobalt-catalyzed decarboxylative difluoroalkylation reaction, a series of different experiments was performed. A competition experiment between bromodifluoroacetate (**2a**) and bromodifluoroacetamide (**2d**) showed that **2a** reacted 10× faster than the related amide (**2d**) (Fig. 2a). This rate difference could result either from the more favorable oxidative addition of the bromodifluoroacetate to Co(I) or preferential single electron transfer from Co(I). Expectedly, the more electron deficient bromodifluoroacetates are easier to reduce than bromodifluoroacetamides.[25] Importantly, concerted oxidative addition *vs.* single electron transfer pathways are distinguished by the intermediacy of a difluoroalkyl radical in the latter pathway.

With this in mind, a radical clock experiment was performed with substrate **2p**, which delivered the cyclized product **4c** in 17% yield along with protocyclized product **4d** and the dehydrocyclized product **4e** in 15% and 35% respectively. Beyond that, a TEMPO trapping experiment showed the formation of adduct **4g** in 37% yield and produced less than 5% of the coupled product (**3a**). Furthermore, the use of an external radical trap such as styrene delivered the corresponding three-component coupled product *via* a regioselective radical trapping pathway that furnished the product **4i** exclusively (Fig. 2b). Based on our previous mechanistic studies for the cobalt-catalyzed decarboxylative allylation reaction, we have proposed the formation of an $L_1Co(I)$ species as the active catalytic species under these reaction conditions (see ESI for details; Fig. S10†).[24] Furthermore, since the addition of the fluoroalkylating agent (**2a**) to the active Co–Br catalyst didn't show any evidence for irreversible bond scission products while being monitored using ^{19}F NMR, we propose that decarboxylative metalation to form the more electron-rich alkyl-Co species might occur prior to SET (Fig. 2c, see ESI† for details).

Taken together, we propose the following mechanism for the cobalt-catalyzed decarboxylative difluoroalkylation reaction (Fig. 2d). The reduction of the $CoBr_2$/dppBz complex by the carboxylate **1a** generates the catalytically active Co(I) species (**A**).[24] Decarboxylative metalation generates species **B**,[19] which in turn reduces the difluoro alkyl bromide *via* SET, generating the difluoroalkyl radical **C**. Radical **C** undergoes subsequent radical oxidation and trapping by the cobalt complex to form species **D**. Reductive elimination from complex **D** delivers the difluoroalkyated product and regenerates the active cobalt(I) species.

Conclusions

In summary, we have developed a simple and efficient method for the regioselective difluoroalkylation of potassium salts of carboxylic acids. This cobalt-catalyzed decarboxylative approach allows for the facile construction of quaternary $C(sp^3)$–CF_2 bonds in a fully regio- and chemoselective fashion in moderate

to good yields. The reaction proceeds with moderate to good efficacy, modest functional group tolerance, as well as a broad substrate scope, producing molecular CO_2 and KBr as the only waste by-products. Mechanistic studies demonstrated a single electron transfer to the difluoroalkyl halides from a Co(I) species leading to the formation of a discrete difluoroalkyl radical.

Data availability

The data underlying this study are available in the published article and its ESI.†

Author contributions

J. T. and E. J. conceptualized and initiated the project. E. J. and I. S. performed the experiments and analyzed the data. J. T. and E. J. co-wrote the paper.

Conflicts of interest

The authors declare no conflict of interest.

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