Copper-Catalyzed Cross-Coupling of Organozincs with Carboxylic Acids via Acyloxyphosphonium Ions: Direct Access to (fluoro)Ketones

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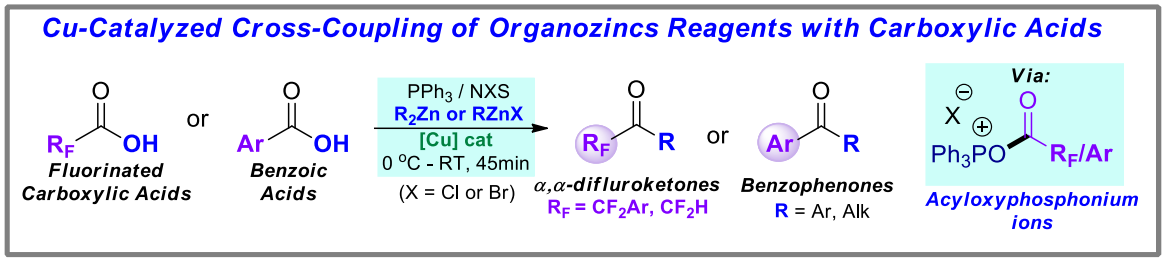
Graphical Abstract:



ABSTRACT: Acyloxyphosphonium ions readily and conveniently prepared *in-situ* from parent α,α-difluorinated carboxylic acids and commodity chemicals are established as convenient acyl electrophiles that to be used in a copper-catalyzed cross-coupling protocol with organozinc reagents as carbon nucleophiles to smoothly afford α,α-difluoroketones. Several carboxylic acids can be employed efficiently using this copper-catalyzed protocol. In the case of CF_2H- and CF_3-ketones di- and trifluoroacetic acid can be employed under copper-free conditions. The transformations proceed under mild reaction conditions (0 °C-RT), produce the target compounds in short reaction times (45 min) and exhibit good chemoselectivity and functional group compatibility. Notably, this methodology was also demonstrated useful for the synthesis of non-fluorinated ketones (benzophenones) directly from benzoic acids.

Ketones play a focal role in organic chemistry, and they are present in many naturally occurring compounds and active pharmaceutical ingredients (APIs). [1] Furthermore, their role in organic chemistry is further highlighted by their utility in a wide variety of chemical elaborations.[1b] Conventionally, ketones can be accessed via direct uncatalyzed or transition-metal-catalyzed acylation using acyl electrophiles such as acyl halides,[2] (thio)esters,[3] activated amides,[4] or anhydrides. [5] However, these protocols require preparation/isolation of these substrates, usually from the parent carboxylic acids. Thus, streamlined, and direct access to ketones from readily available carboxylic acids or through their *in-situ* (pre)activation is still highly sought-after.[6]

On the other hand, even though fluorine is 13th most abundant element in the earth's crust [7] only a handful of naturally occurring organofluorine compounds have been identified.[7c] Accordingly, access to organofluorine compounds rely on synthetic methodologies to incorporate fluorine or fluorinated motifs into organic molecules. Thus, development of streamlined methods to access organofluorine compounds represents a highly desirable and worthwhile endeavor.

Because of their enhanced lipophilicity, membrane permeability and increased metabolically stability, organofluorine compounds including α,α,-difluoroketones have increasingly found widespread applications in pharmaceuticals, material science, and agrochemicals.[8] (Figure 1).

Accordingly, considerable efforts have been devoted to developing methods for accessing RCF_2-ketones (R = H, Ar, Alkyl). Along these lines, optimal synthetic methods toward these targets should be designed with the fluorine atom supply chain in mind.[9] Historically, most synthetic methods to access α,α-difluoro ketones rely on electrophilic α-difluorination of (di)carbonyl compounds or derivatives (imines/enamines),[10] electrophilic fluorination of alkynes,[11] transition-metal-catalyzed,[12a-d] metal-free,[12e-f] or visible photoredox-catalyzed[13] functionalization of gem-difluorinated (silyl)enolates, amongst other methods.[14]

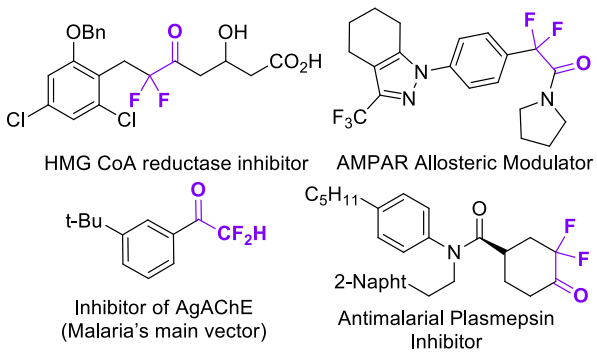
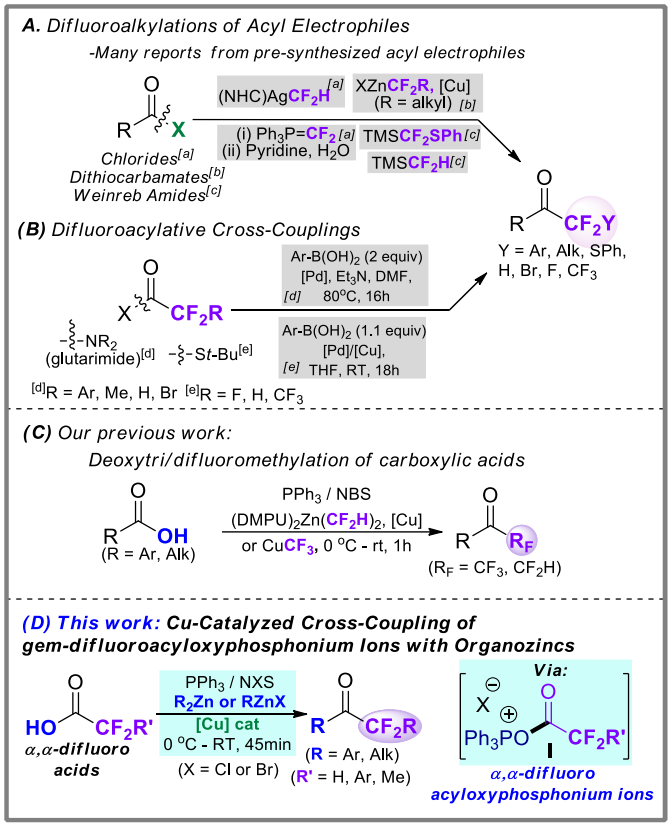


Figure 1. Biologically relevant α,α-difluoroketones.

Despite the availability of the above-mentioned strategies, the development of a synthetic strategy that directly utilized α,α-difluorinated acids under mild and practical conditions would bring significant advantages into the synthetic chemist toolbox. However, although conceptually simple, current reports following this strategy present serious drawbacks. For example, 2.4 equiv. of BuLi must be added to difluoroacetic acid (DFA) at -78 °C over a period of 3 h to obtain only 48% of the target CF_2H ketone.[15a] Similar cryogenic conditions must be used in the case of RLi or RMgX addition to α,α-difluoro esters[15b] or amides.[15c-e] The high reactivity of these organometallic reagents calls for a strict control of the reaction conditions in order to prevent double addition by-products, and in most cases, the use of cryogenic conditions is required, thereby hampering the method's synthetic utility, particularly for large scale applications. To circumvent these limitations, considerable efforts have been made in recent years that rely on difluoroalkylation of acyl electrophiles. For example, Dilman and coworkers reported a Cu-catalyzed cross-coupling between dithiocarbamates with gem-difluorinated organozinc reagents[16a] as well as the reaction of acyl chlorides with $Ph_3P{=}CF_2$[16b]. Similarly, (NHC)AgCF_2H,[16c] PhSCF_2TMS[16d] and TMSCF_2H[16e] have been employed for difluoromethylation of acyl chlorides or Weinreb amides. However, these processes necessitate the preparation and isolation of acyl electrophiles and/or the use of expensive nucleophilic difluoroalkylation reagents (Scheme 1A).

Scheme 1. Representative routes to α,α-Difluoro ketones from acyl electrophiles and our work from carboxylic acids.



An important breakthrough was recently disclosed by Amgoune and coworkers where a Pd-catalyzed cross-coupling of *N*-difluoroacyl glutarimides with $ArB(OH)_2$ afforded the target products after 16 h at 80 °C.[17a] This work stands as the first report on direct installation of the $RCF_2C(O)$- (R = Ar, H) motif into carbon nucleophiles through a catalytic process.[17b] However, it still presents some limitations as the required *N*-difluoroacyl electrophiles must be prepared from the parent α,α-difluoro carboxylic acids and are obtained in low to moderate (44-75%) yields. A similar strategy was recently disclosed by Ban, Dai

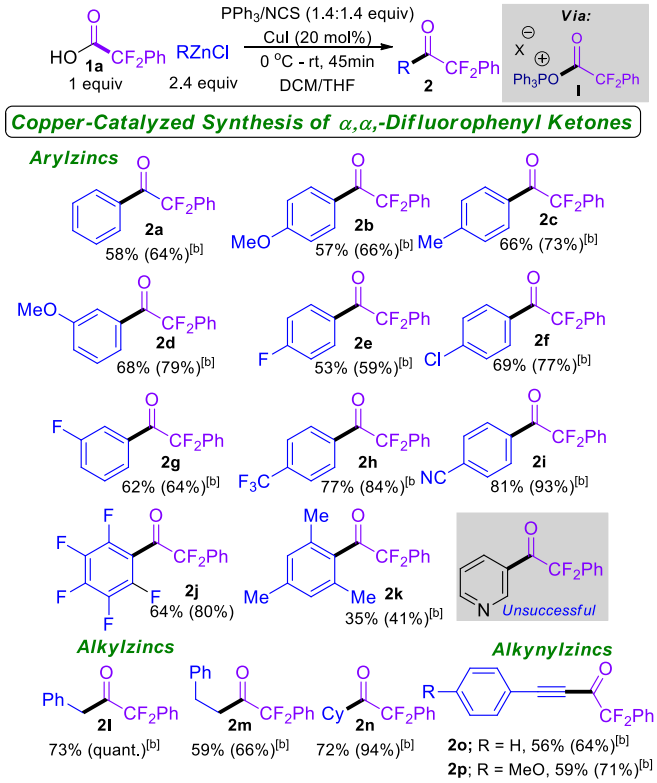
and coworkers[17c] using fluorinated thioesters under Liebeskind-Strogl coupling conditions.[3b] In this fashion CF_2H-, CF_3- and CF_2CF_3-ketones were accessed under Pd/Cu co-catalyzed conditions from $ArB(OH)_2$ at room temperature after 18 h of reaction time. In this case, no information of the yield of required thioester electrophiles was provided (Scheme-1B).

Stemming from our interest in organofluorine chemistry[18] and inspired by our recent report on deoxygenative di/trifluoromethylation of carboxylic acids via copper-mediated coupling of acyloxyphosphonium ions[19] and $(DMPU)_2Zn(CF2H)_2$[20a] (Scheme 1C) we set out to develop an improved protocol to access α,α-difluoro (as well as non-fluorinated) ketones directly the parent carboxylic acids.

In pursuit of a synthetic protocol of practical utility, several factors had to be addressed: (i) avoid any isolation of acyl electrophiles, (ii) take advantage of the widespread availability of α,α-difluoro acids (and carboxylic acids in general), and (iii) capitalize on the enhanced stability, balanced reactivity and low cost of non-fluorinated organozinc reagents.[20b-d] Accordingly, we envisioned that acyloxyphosphonium ions **I** derived from inexpensive gem-difluoro acids and formed in-situ upon the reaction with PPh_3/NXS (X = Cl or Br) reagent system, would be suitable electrophilic coupling partners to achieve a facile difluoroacylation of organozinc reagents as carbon nucleophiles. (Scheme 1D). Despite the development of several synthetic methodologies in recent years, to the best of our knowledge, the synthesis of CF_2H- or CF_2Ar-ketones directly from α,α-difluoro carboxylic acids under practical conditions (0 °C-RT) remains elusive.[19g] In this work, we delineate our results in the development of such a protocol.

Initial investigations were performed using commercially available α,α-difluorophenylacetic acid **1a** under our previously optimized conditions for deoxydifluoromethylation of benzoic acids (PPh_3/NBS; 1.4 equiv each). The α,α-difluoroacyloxyphosphonium ion generated under this conditions, delivered ketone **2a** in only 39% yield (^{19}F NMR) upon reaction with Ph_2Zn (1.2 equiv) in the absence of Cu-catalyst. After extensive optimization studies,[21] optimal results were obtained by treatment of **1a** with N-chlorosuccinimide (PPh_3/NCS; 1.4 equiv each) and PhZnCl (2.4 equiv) under catalytic amounts of CuI (20 mol%). In this case, **2a** was smoothly generated in 64% yield as determined by ^{19}F NMR spectroscopy in only 45 min. With these conditions in hand we explored the generality and scope of different organozinc halides, and the results of this Cu-catalyzed procedure are shown in Scheme 2.

Scheme 2. Cu-Catalyzed Synthesis of α,α-Difluorophenyl Ketones[a]



[a] Conditions: 0.25mmol of **1a** (1 equiv), PPh_3 (1.4 equiv), NCS (1.4 equiv), RZnCl (2.4 equiv) and CuI (0.05 mmol); isolated yields. [b] Yields in parenthesis as determined by ^{19}F NMR using $PhOCF_3$ as internal standard. See *Supporting Information* for full experimental details.

First, the scope of arylzinc chlorides was studied using **1a** as the model substrate. ArZnCl nucleophiles bearing electron-donating, electron-neutral and electron-withdrawing groups all afforded the target ketones **2a-2k** in satisfactory yields in fast reaction times. Methyl and methoxy substituents afforded **2b-2d** in good yields. Chloro- and Fluoro-substituted ArZnCl at different positions all cleanly afforded the corresponding ketones **2e-2g** in good yields. Electron-deficient arylzincs were also

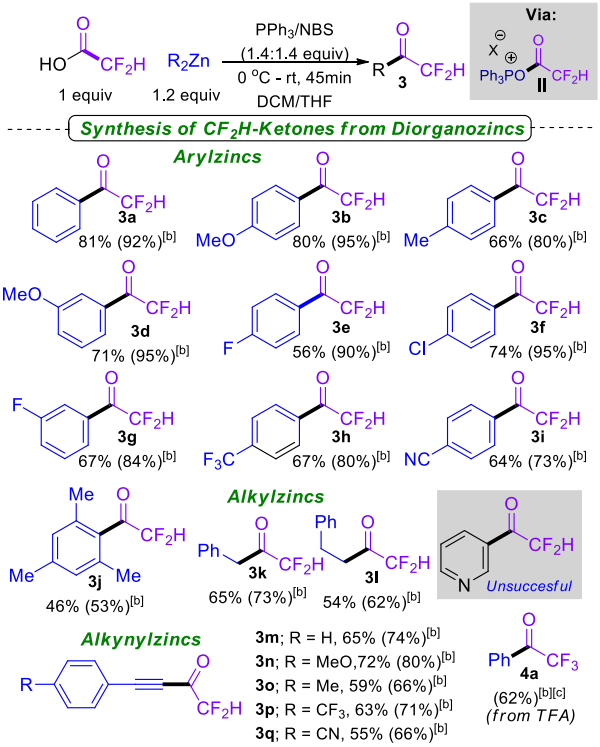
well tolerated and 4–CN-, 4–CF_3 and pentaflurophenylzinc halides gave the target products **2i**, **2j** and **2k** in 80-93% yields as determined by ^{19}F NMR. In some cases, product loss during purification could not be avoided (**2j**, 64% isolated yield). Though a modest isolated yield of **2j** was obtained, this result is notable as it is in stark contrast with the results described by Amgoune in which attempts to prepare **2j** using *N*-difluoroacyl glutarimide and C_6F_5-$B(OH)_2$ were unsuccessful.[17a] As expected, the bulkier mesityl group led to low yields of **2k**. Gratifyingly, alkylzinc halides (benzyl, phenethyl and cyclohexyl) were also well tolerated under our reaction conditions and in these cases, excellent yields of **2l** and **2n** were obtained, albeit phenethyl derivative **2m** was obtained in slightly lower yield (59%). At the present stage, our method does not tolerate the 3-pyridyl functionality which represents some limitations. Current investigations are underway to overcome these limitations.

Motivated by the success of different types of aryl- and alkylzinc nucleophiles, we were eager to explore the generality or our protocol using zinc acetylides as nucleophilic coupling partners. Alkynes are a versatile functional group for the synthesis of valuable organic compounds[22] and the corresponding propargylic ketones would represent valuable handles for further chemical elaborations affording products containing a gem-difluoro tag. In this context, propargyl ketones (**2o-2p**) were isolated upon reaction with the corresponding alkynylzinc halides. The parent phenylethynylzinc chloride as well as the 4-OMe substituted organozinc nucleophile afforded **2o** and **2p** in synthetically useful isolated yields (56% and 59%, respectively).

Implementation of this strategy using widely available difluoroacetic acid (DFA) as the engender of difluoroacetyl functionality enabled us to access valuable difluromethyl ketones **3** in a practical and expedient fashion (Scheme-3). Notably, in this case, the reaction proceeds well in the absence of Cu catalyst, likely due to the high electrophilicity of the α,α-difluoroacyloxyphosphonium species **II**. This contrasts with the need of Cu-catalysis for smooth preparation of products **2**. Furthermore, in this case, PPh_3/NBS in combination with diorganozinc reagents (1.2 equiv) was found to provide the best results under otherwise identical conditions to those used for α,α-difluoro acids **1**.[21]

Aromatic diorganozinc reagents (Ar_2Zn) bearing electron-neutral (**3a**) and electron-donating groups such as 4-OMe and 4-Me (**3b-3c**) smoothly afforded the target CF_2H ketones in high yields. Similarly, diorganozincs with 3-OMe, Fluoro-, Chloro- and electron-withdrawing groups such as 4-CN and 4-CF_3 were equally effective to achieve this transformation (**3d-3i**). Despite the excellent yields as determined by ^{19}F NMR spectroscopy, in some cases, the high volatility of the CF_2H ketone product precluded us from obtaining high isolated yields (**3e**). As expected, sterically encumbered mesityl-substituted CF_2H ketone **3j** could be obtained only in modest isolated yield (46%). However, it should be noted that the previously reported route to **3j** relies on a multistep sequence of reductive difluoroalkylation of Mesityl-CHO with $BrCF_2CO_2Et$/Et_2Zn, oxidation, and decarboxylation (78% over three steps).[23] Even though a modest yield of **3j** was obtained here, our method can certainly be considered complementary given its operational simplicity (single step, 45 min) and the ready availability and low cost of the starting materials.

Scheme 3. Synthesis of Difluoromethyl Ketones[a]



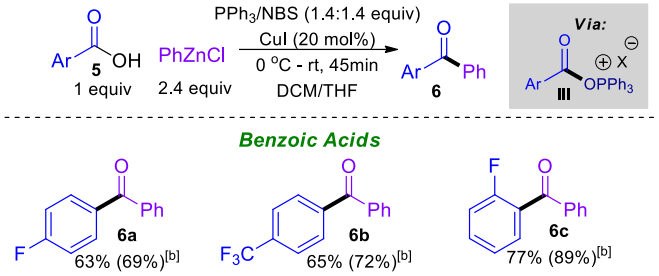
[a] Conditions: 0.25mmol of DFA, PPh_3 (1.4 equiv), NBS (1.4 equiv) and R_2Zn (1.2 equiv); isolated yields shown. [b] Yields in parenthesis as determined by ^{19}F NMR using $PhOCF_3$ as internal standard. [c] Unoptimized results; from PhZnCl and TFA. See *Supporting Information* for full experimental details.

More reactive dialkylzinc reagents pleasingly afforded the target products **3k** and **3l** without double addition by-products being detected, a common side reaction commonly encountered with electrophilic fluoroketones and carbon nucleophiles.[14g] Similarly to the synthetic protocol towards products **2**, this protocol currently has a limitation and 3-Pyridyl organozincs failed to deliver the corresponding products. The reasons for these unsatisfactory results are yet unclear. On the other hand, dialkynylzinc reagents cleanly afforded propargyl CF_2H ketones **3m-3q** in good isolated yields. Interestingly, electron-deficient zinc acetylides afforded **3p** and **3q** cleanly. This contrast to the results obtained with α,α-difluorophenylacetic acid **1a**, which heralds to the enhanced electrophilic power of α,α-difluoroacyloxyphosphonium ion **II** derived from DFA. This is further highlighted by the fact that reaction of **II** with organozinc nucleophiles, proceed smoothly in the absence of Cu or other transition-metal catalysts. To our delight, the use of trifluoroacetic acid under otherwise identical conditions (Cu-free) afforded trifluoromethyl ketone **4a** in 62% yield by ^{19}F NMR (unoptimized conditions).

In pursuit of a simple strategy for ketone synthesis and spurred by the success in the synthesis of fluoroketones **2**-**4** from fluorocarboxylic acids, we were prompted to interrogate the hypothesis of whether benzoic acids **5** would also be amenable substrates under the current strategy. If successful, the corresponding ketones would be rapidly accessible and this transformation would represent a complimentary approach to the well-established Pd-catalyzed Fukuyama ketone synthesis, Weinreb ketone synthesis, Liebeskind-Srogl coupling as well as the other previously established methods for ketone synthesis from acyl electrophiles[2,3,4,5,6]. Importantly, we have previously unambiguously demonstrated that under these conditions, acyl bromides are not generated from benzoic acids, but instead, acyloxyphosphonium species **III** is the active electrophile.[20a]

The preliminary results of our investigations in this context are shown in Scheme 4. Gratifyingly, acyloxyphosphonium ions **III** derived from 4-fluoro, 4-trifluoromethyl and 2-fluorobenzoic acids (**5a-5c**) all gave rise to the target benzophenones products **6** in high yields after 45 min. As it was expected, in this case, Cu-catalysis was required to smoothly achieve the transformation with PhZnCl as the nucleophilic coupling partner and control experiments showed that in the absence of Cu catalyst, no ketone could be obtained.[24]

Scheme 4. Direct Synthesis of Benzophenones from Benzoic Acids



[a] Conditions: 0.25mmol of benzoic acids **5**, PPh_3 (1.4 equiv), NBS (1.4 equiv), PhZnCl (2.4 equiv) and CuI (0.05 mmol); isolated yields shown. [b] Yields in parenthesis as determined by ^{19}F NMR using $PhOCF_3$ as internal standard. See *Supporting Information* for full experimental details.

In conclusion, a novel process to generate $ArCF_2$-, CF_2H-, CF_3- and aryl ketones (benzophenones) directly from the parent carboxylic acids has been developed. The protocol delineated herein represents an expedient and efficient method for ketone synthesis that complements previously reported methods using other acyl electrophiles. Implementation of this process, with di- and trifluoroacetic acid, enabled a Cu-free direct di/trifluoroacetylation of organozinc reagents using inexpensive di- and trifluoroacetic acid. The key reactive intermediates, acyloxyphosphonium ions **I-III** are expediently prepared *in-situ* from the parent carboxylic acids and commodity chemicals (PPh_3, NXS). An additionally important feature of these protocols include the fast reaction times (30-45 min) and the mild reaction conditions. More importantly, the use of organozinc reagents which have much greater functional group compatibility than other reactive organometallics (RMgX, RLi) allows for an overall enhanced practicality and functional group compatibility. We foresee that utilization of these protocols will be a useful addition to the synthetic chemist toolbox. Mechanistic investigations and further implementation of this versatile strategy for utilization of carboxylic acids in catalysis are currently underway in our laboratory.

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[23] A very recent report synthesizing sterically encumbered **3j** relies on a three-step sequence of reductive alkylation of Mesityl-CHO with $BrCF_2CO_2Et/Et_2Zn$, alcohol oxidation, followed by decarboxylation (78% over three steps; >48h total reaction time) see: Messara, A.; Panossian, A.; Mikami, K.; Hanquet, G.; Leroux, F. R. Direct Deprotonative Functionalization of α,α-Difluoromethyl Ketones Using a Catalytic Organosuperbase. *Angew. Chem. Int. Ed.* **2023**, *62* (10) e2022158. https://doi.org/10.1002/anie.202215899.

[24] (a) Protodemetallation products were the main products detected in the absence of Cu-catalyst. (b) The substrate scope presented here is preliminary; a full substrate scope study of benzoic acids and organozinc reagents is currently underway in our laboratory. Furthermore, mechanistic studies and DFT computational investigations are also being conducted.