Synthetic Methods

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Palladium Catalysis Enables Benzylation of α,α-Difluoroketone Enolates

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Abstract: *A palladium-catalyzed decarboxylative benzylation reaction of α,α-difluoroketone enolates is reported, in which the key C(α)–C(sp³) bond is generated by reductive elimination from a palladium intermediate. The transformation provides convergent access to α-benzyl-α,α-difluoroketone-based products, and should be useful for accessing biological probes.*

The α,α-difluoroketone is a privileged substructure in medicinal chemistry.[1] For this substructure, the electron-withdrawing fluorine atoms encourage rehybridization of the sp²-hybridized C=O to form sp³-hybridized hydrates or hemihydrates,[2] which can then interact with aspartyl proteases through noncovalent hydrogen-bonding networks involving water molecules, and with serine proteases through reversible covalent interactions.[1] In addition, a subset of α-benzyl-α,α-difluoroketone derivatives also have demonstrated cholesterol-lowering,[3] analgesic,[4] anxiolytic,[5] and pro-inflammatory[6] activities (Figure 1). Thus, convergent and mild strategies for accessing α-benzyl-α,α-difluoroketone-based substructures should be useful for developing new therapeutic candidates and biological probes.

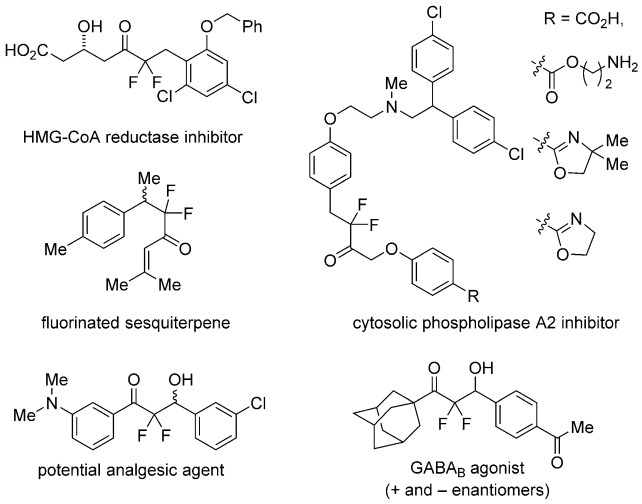

Figure 1. α-Benzyl-α,α-difluoroketone motifs in bioactive molecules.

A convergent preparation of this substructure would involve a transformation capable of generating a C(α)–C(sp³) bond, presumably by reacting a nucleophilic α,α-difluoroketone enolate with an sp³-hybridized benzylic electrophile (Figure 2a). Alkylation of ketone enolates with sp³-based electrophiles is a fundamental transformation for accessing a broad spectrum of α-functionalized ketones.[7] However, nucleophilic substitution reactions of α,α-difluorinated enolates with sp³-based electrophiles have not been generally developed, because of two problems. First, chemoselective formation of α,α-difluoroketone enolates presents challenges, because deprotonation of α,α-difluoromethyl ketones produces enolates at the nonfluorinated position under both thermodynamic and kinetic conditions (Figure 2b),[8] and upon trapping, cannot afford α-functionalized-α,α-difluoroketones. Second, α,α-difluoroenolates possess unique physicochemical properties that preclude formation of the C(α)–C(sp³) bond. Specifically, the strong inductive effect of the two fluorine atoms[9a] decreases the charge density of an enolate at the α-position,[9b] and thus reduces the nucleophilicity of the anion and disfavors reactions with sp³-based electrophiles (Figure 2c). As a result, α,α-difluoroketone enolates react by S_N2 reactions at the O to generate difluorovinyl ethers, instead of at C(α) (Figure 2d).[10] Because of these two factors, only two manuscripts describe S_N1- or S_N2-like alkylation reactions of α,α-difluoroketones, and both require stoichiometric amounts of metal reagents to promote the reactions (Figure 2e).[11]

Because of this intrinsically poor reactivity, several alternative strategies for accessing α-benzyl-α,α-difluoroketones have been developed, including: 1) deoxyfluorination of α-ketoesters using strong fluorinating reagents, followed by addition of organolithium or Grignard reagents to the resulting α,α-difluoroester, for which the strong bases and harsh reagents destroy many functional groups;[3] 2) 1,2-addition of α-lithio-β,β-difluorovinyl ethers to aldehydes followed by deoxygenation (or cyclization) of the resulting alcohol, which only accesses a small subset of products;[12] 3) a single radical addition reaction of an aldehyde to a (2,2-difluorovinyl)benzene;[13] and 4) a late-stage electrophilic difluorination of prefunctionalized imines using Selectfluor/NFSI followed by acid-mediated hydrolysis—not a convergent strategy, which also generates a mixture of fluorinated products for substrates bearing two sites capable of undergoing imine-enamine isomerization.[14] However, none of

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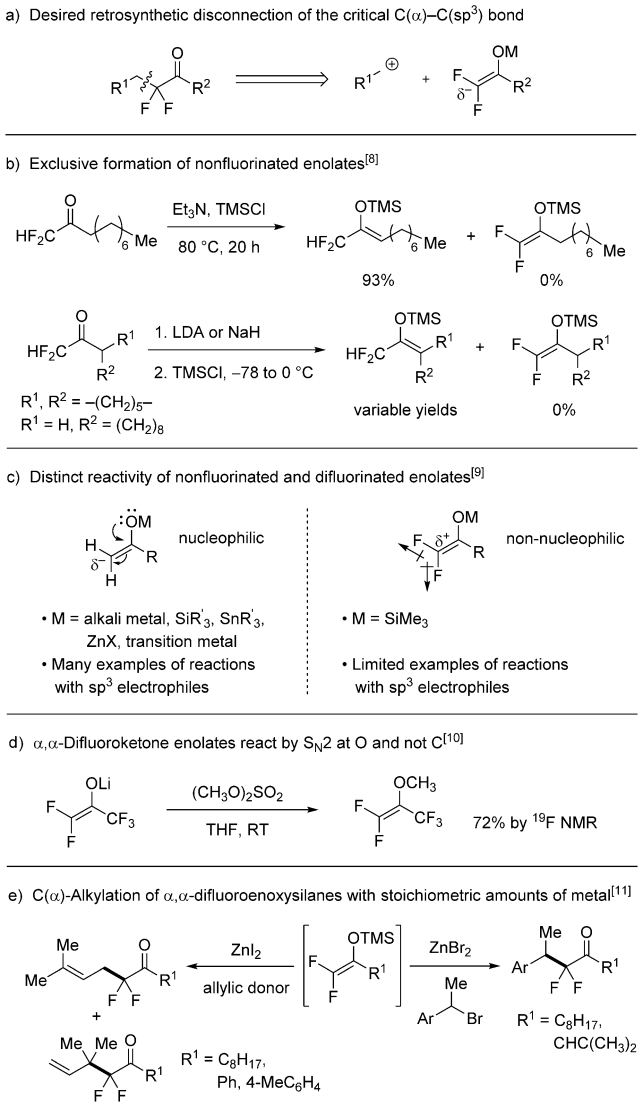
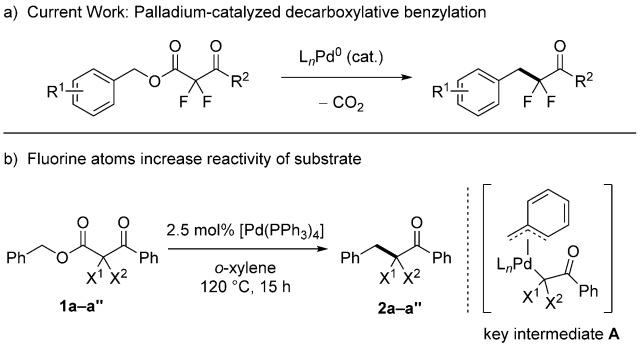


Figure 2. Underdeveloped reactions of α,α-difluoroketone enolates with sp^3-hybridized electrophiles. LDA = lithium diisopropylamide, THF = tetrahydrofuran, TMS = trimethylsilyl.

these reactions convergently generates the key C(α)–C(sp^3) bond.

To complement these known strategies, a desirable and convergent alternative for accessing α-benzyl-α,α-difluoroketones involves the net reaction of an α,α-difluoroketone enolate with an sp^3-based electrophile (Figure 2a). Although recently reported reactions have coupled α,α-difluoroketone enolates with aryl[15] and allyl electrophiles,[16] never has a palladium-based catalytic system effectively promoted the benzylation reaction of α,α-difluoroketone enolates (Table 1a). In this reaction, a decarboxylative strategy would chemoselectively generate the appropriate α,α-difluoroenolate, and the critical C(α)–C(sp^3) bond would form by reductive elimination from a high-energy [L_nPd(benzyl)(α,α-difluoroenolate)] intermediate (Table 1b, **A**). Herein, we report such a palladium-catalyzed process which accomplishes a net benzylation of α,α-difluoroketone enolates to provide α-benzyl-α,α-difluoroketones.

Table 1: Palladium-catalyst promotes decarboxylative benzylation reaction of α,α-difluoroenolates.[a]



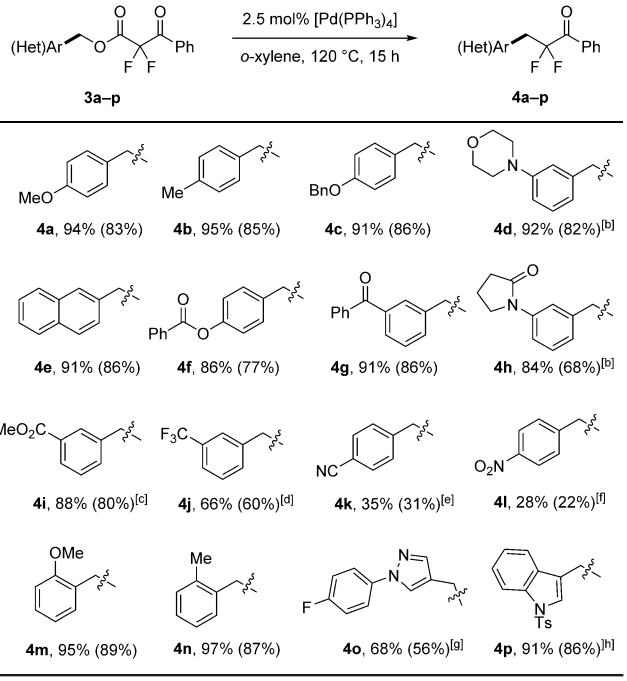
Entry	X^1, X^2	Conv. [%]	Yield [%][b]	Yield [%][c]
1	F, F (**1a**)	100	90	80
2	H, F (**1a'**)	8	0	0
3	H, H (**1a''**)	0	0	0

[a] Standard reaction conditions: **1a**–**1a''** (1.0 equiv), [Pd(PPh$_3$)$_4$] (2.5 mol%), *o*-xylene (0.05 M), 120 °C, 15 h. The reported data represents an average of two independent experiments. [b] The yields were determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene and fluorobenzene (**1a** and **1a'**) and by ^{1}H NMR spectroscopy using CH_2Br_2 (**1a''**) as an internal standard. [c] Yield of isolated product.

Thorough and systematic screening of palladium-based catalysts and precatalysts, and P-based ligands identified [Pd(PPh$_3$)$_4$] as an efficient catalyst for the present reaction.[17] Additionally, certain biarylmonophosphine-based ligands derived from S-Phos, X-Phos, and Ru-Phos scaffolds[18] also generated the coupled product.[17] After optimization, the final system (2.5 mol% [Pd(PPh$_3$)$_4$]/*o*-xylene/120 °C) readily generated the desired α-benzyl-α,α-difluoroketone (Table 1b, entry 1), thus confirming our hypothesis that transition-metal catalysis should form the critical C(α)–C(sp^3) bond.

However, this catalyst system only coupled the α,α-difluorinated substrate, while the mono- and nonfluorinated substrates did not provide the expected products (entries 2 and 3). This dramatic fluorine effect facilitated the present reaction with neutral and even electron-deficient benzyl esters, while some other transformations involving oxidative addition of [Pd(PPh$_3$)$_4$] into nofluorinated benzyl esters typically require an extended conjugated system or an electron-rich benzylic moiety.[19] This phenomenon likely reflects the strong σ-withdrawing inductive effect of the two fluorine atoms, which increases the electrophilicity of the substrate, and accelerates the oxidative addition step to generate the high-energy dearomatized π-benzyl intermediate (**A**).[20] In contrast, we believe that the fluorine substituents likely do not accelerate the decarboxylation step of the reaction. Despite the increased stability of the α,α-difluorinated enolate (ketone-CF_2H pK_a = 20.2; ketone-CFH_2 pK_a = 21.7; ketone-CH_3 pK_a = 24.7),[21] rehybridization of α,α-difluorinated enolate carbanions from C(sp^3) to C(sp^2) actually occurs more slowly than for nonfluorinated enolates,[22] which contradicts the trend observed (Table 1b).

Table 2: Decarboxylative difluorobenzylation of substrates bearing distinct benzyl moieties.[a]

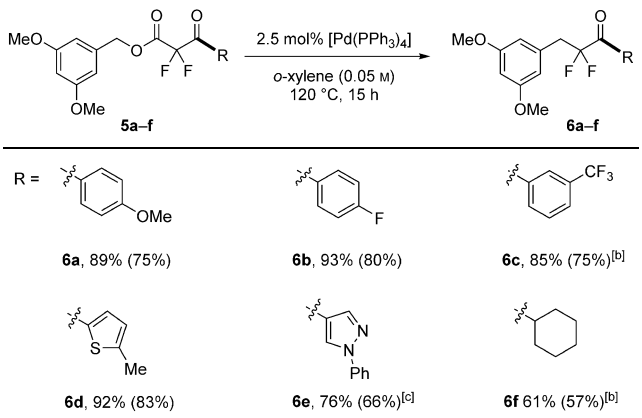


[a] Standard reaction conditions: **3a–p** (1.0 equiv), [Pd(PPh$_3$)$_4$] (2.5 mol%), *o*-xylene (0.05 M), 120°C, 15 h. ^{19}F NMR Yields were determined using α,α,α-trifluorotoluene as an internal standard. The value within parentheses indicates the yield of the isolated product. [b] 24 h. [c] [Pd(PPh$_3$)$_4$] (5.0 mol%). [d] [Pd(PPh$_3$)$_4$] (5.0 mol%), 140°C. [e] [Pd(PPh$_3$)$_4$] (20 mol%), 140°C, *o*-xylene (0.01 M), 24 h. [f] [Pd(PPh$_3$)$_4$] (5.0 mol%), 140°C, 24 h. [g] 140°C, 16 h. [h] [PdCp(η^3-1-Ph-C$_3$H$_4$)] (2.0 mol%), PhXPhos (4.0 mol%), 155°C, 15 h. Ts = 4-toluenesulfonyl.

A variety of substrates bearing electron-rich, electron-neutral, and electron-deficient benzylic moieties underwent the decarboxylative reaction to generate α-benzyl-α,α-difluoroketones (Table 2). Generally, the optimized reaction conditions converted electron-rich, electron-neutral, and weakly electron-deficient substrates into the products **4a–h** in high yields. However, moderately electron-deficient substrates required higher catalyst loading and/or reaction temperatures to provide good yields of the products **4i**,**j**. Further, substrates bearing strong electron-withdrawing groups were less active, and generated the products **4k**,**l** in lower yields, even after optimization. This trend implicates the intermediacy of [Pd(π-benzyl)(α,α-difluoroenolate)] (**A**),[20] as electron-donating groups stabilize the intermediate and facilitate the reaction, and electron-withdrawing groups destabilize the intermediate and retard the reaction. While the electronic nature of the substrates affected the outcome of the reaction, steric effects did not impede the reaction. Reactions of *ortho*-substituted benzyl esters afforded products in comparably high yields relative to the analogous *para*-substituted substrates (**4m**,**n** versus **4a**,**b**). Further, N-containing heterobenzyl substrates also tolerated the present reaction conditions, and provided the corresponding products in modest-to-high yields (**4o**,**p**).

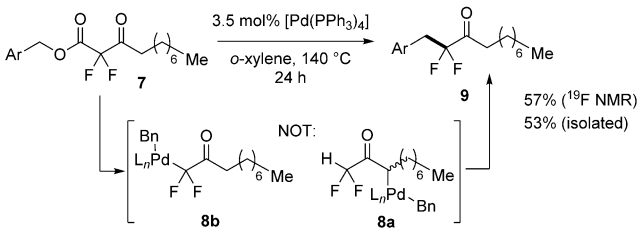
The decarboxylative reaction also successfully produced products bearing a variety of aryl and alkyl α,α-difluoroketone moieties (Table 3). Reactions of substrates bearing electron-rich, electron-neutral, and electron-withdrawing aryl α,α-difluoroketones provided the corresponding products **6a–c** in high yields under the standard reaction conditions. Further, both S- and N-containing heteroaryl α,α-difluoroketone moieties were tolerated (**6d**,**e**), and at an increased temperature, the reaction of an aliphatic α,α-difluoroketone substrate afforded the product **6f** in reasonable yield.

Table 3: Decarboxylative difluorobenzylation of substrates bearing distinct ketone moieties.[a]



[a] Standard reaction conditions: **5a–f** (1.0 equiv), [Pd(PPh$_3$)$_4$] (2.5 mol%), *o*-xylene (0.05 M), 120°C, 15 h. Yield was determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. The value within parentheses indicates the yield of the isolated product. [b] 130°C, 24 h. [c] 24 h.

As previously noted, alkylation reactions of α,α-difluoroketone enolates suffer from two classical problems, namely, generation of the appropriate enolate[8] and alkylation at C(α) instead of at O.[10] Although examples **4a–p** and **6a–f** confirm the ability of the palladium-catalyzed system to generate the C(α)–C(sp^3) bond, most of the substrates do not bear enolizable hydrogen atoms at the nonfluorinated α-position of the ketone, and therefore cannot form a nonfluorinated enolate. As such, these substrates do not confirm whether the palladium-catalyzed decarboxylative protocol would selectively generate the fluorinated enolate. To address this concern, we explored the reaction of aliphatic substrate **7**, which could theoretically decarboxylate and isomerize to generate the undesired enolate **8a** at a nonfluorinated position (Scheme 1). Subjection of **7** to [Pd(PPh$_3$)$_4$] at 140°C, generated the product **9** in 53% yield upon isolation,



Scheme 1. Decarboxylative strategy chemoselectively generates the desired enolate.

with no detectable products arising from alkylation at the nonfluorinated position. This reaction, combined with the reaction of **6f**, likely proceeds by exclusive participation of the palladium-bound external enolate **8b**, and does not isomerize to generate the internal enolate **8a**. Thus, the present decarboxylative reaction overcomes both previously presented challenges associated with alkylation reactions of α,α-difluoroketone enolates.

In conclusion, a palladium-catalyzed decarboxylative coupling reaction generated an unfavorable enolate and formed a key C(α)–C(sp^3) bond. This method facilitates the preparation of α-benzyl-α,α-difluoroketones under neutral conditions, and provides access to molecules bearing sensitive functional groups and N-containing heterocycles. We envision that this strategy should not only provide a straightforward route to access biologically important α-benzyl-α,α-difluoroketone-based compounds, but also enable the development of additional transition metal catalyzed coupling reactions of functionalized fluoroalkyl anions with sp^3-based electrophiles.

Acknowledgments

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