

Pd-Catalyzed α -Arylation of Trimethylsilyl Enolates of α,α -Difluoroacetamides

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S Supporting Information

ABSTRACT: We report the arylation and heteroarylation of α,α -difluoro- α -(trimethylsilyl)acetamides with aryl and heteroaryl bromides catalyzed by an air- and moisture-stable palladacyclic complex containing $P(t\text{-Bu})_2\text{Cy}$ as ligand. A broad range of electronically varied aryl and heteroaryl bromides underwent this transformation to afford α -aryl- α,α -difluoroacetamides in high yields. Due to the electrophilicity of the fluorinated amide, this palladium-catalyzed cross-coupling reaction provides a versatile platform to generate a range of α,α -difluoro carbonyl compounds, such as α -aryl- α,α -difluoro ketones, -acetaldehydes, -acetates, and acetic acids, and difluoroalkyl derivatives, such as 2-aryl-2,2-difluoroethanols and -ethylamines, under mild conditions.

Fluorine-containing aromatic compounds are widespread in medicinal chemistry and material sciences due to their unique stability, reactivity, and biological properties.¹ Compounds containing a fluorinated aromatic ring or trifluoromethyl group have been studied extensively.² Molecules containing an α,α -difluorobenzyl unit ($\text{ArCF}_2\text{-}$) are particularly desirable building blocks for medical chemistry because they contain two fluorine atoms at a metabolically labile benzylic position.³ However, methods for the introduction of functionalized α,α -difluoroalkyl groups onto arenes are limited.

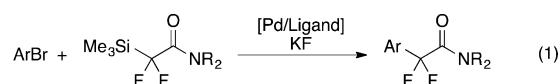
Classic methods to prepare these α,α -difluorobenzyl compounds rely on *gem*-deoxodifluorination of benzoyl derivatives with sulfur tetrafluoride and *N,N*-diethylaminosulfur trifluoride derivatives.⁴ Oxidative desulfurization-difluorination of 1-aryl-1,3-dithiolanes with the combination of oxidant and Olah's reagent also provides such compounds.⁴ However, these reactions occur with limited scope. In addition, the fluorinating reagents for these reactions are highly sensitive toward moisture and may undergo explosive decomposition upon heating. Alternatively, *gem*-difluorination of benzylic C–H bonds could be conducted, but this reaction occurred with limited scope.⁵

Cross-coupling reactions could be envisioned to form products containing fluorine in the benzylic position. The cross-coupling of α,α -difluoroalkyl halides (XCF_2R , X = Cl, Br, or I) with arylboronic acids catalyzed by transition metal complexes is one approach to α,α -difluorobenzyl compounds that has been reported recently.⁶ However, boronic acids are not as accessible and widely available a partner for cross coupling as are aryl halides, and the coupling of α,α -difluoroalkyl halides with heteroaryl boronates was not reported.

Thus, the coupling of aryl and heteroaryl halides with difluoroalkyl nucleophiles would be a valuable reaction for the synthesis of fluoroalkylarenes. However, the coupling reaction between an aryl electrophile and a difluoroalkyl nucleophile occurs with limited scope. For example, the Pd-catalyzed coupling of aryl halides with difluorinated enolates of carbonyl compounds has been reported with only 1,1-difluoroacetophenone derivatives.⁷ These reactions occur, in part, because difluoroacetophenones are more acidic than their non-fluorinated congeners⁸ and can be deprotonated with insoluble inorganic bases. The copper-catalyzed coupling of aryl halides with the silyl enolate of 1,1-difluoroacetate has been reported, but it requires aryl iodides as the coupling partner.⁹

The Pd-catalyzed coupling of an aryl bromide with the enolate of a 1,1-difluorocarboxylic acid derivative could provide a general route to a variety of functionalized α,α -difluoroalkylarenes due to the versatile reactivity of carboxylic acid derivatives. However, the couplings of aryl halides with α,α -difluorocarboxylic acid derivatives are distinct from those of a difluoroacetophenone because the fluorinated carboxylic acid derivatives are less acidic than their non-fluorinated analogues,¹⁰ and they are not stable to soluble strong bases. Thus, the generation of the difluoroenolate of a carboxylic acid derivative by deprotonation is challenging. In addition, the rate of reductive elimination of fluoroalkylpalladium complexes is slower than that of their non-fluorinated analogues,¹¹ and this slow rate of reductive elimination could cause the catalytic reaction to require temperatures at which the enolates of difluorocarboxylic acid derivatives are unstable.

We show that these challenges can be met by conducting the coupling of aryl and heteroaryl bromides with the silicon enolates of α,α -difluoroacetamides in the presence of a highly active palladium catalyst. The reactions of the silicon enolates of α,α -difluoroacetamides with a range of aryl and heteroaryl bromides occur when catalyzed by an air- and moisture-stable palladacyclic complex containing the sterically hindered $P(t\text{-Bu})_2\text{Cy}$ as ligand and KF as activator of the enolate (eq 1). The



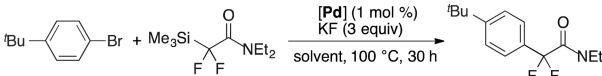
carbonyl unit in these products is more electrophilic than that of a non-fluorinated amide; this property can be exploited to convert the coupled products to a variety of α,α -difluorobenzyl compounds.

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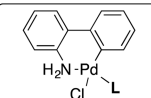
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We initiated our studies of Pd-catalyzed α -arylation of α,α -difluoroacetamides by evaluating reactions of an aryl bromide with the silicon enolate of the amide. We tested a variety of single-component palladacyclic catalyst precursors containing simple trialkyl phosphine ligands¹² and various solvents for the coupling reaction of 1-bromo-4-*tert*-butylbenzene with *N,N*-diethyl- α,α -difluoro- α -(trimethylsilyl)acetamide. The results of these experiments are summarized in Table 1.

Table 1. Evaluation of Pd-Catalyst Precursors and Solvents for the Model Arylation of a Difluoroacetamide^a



entry	[Pd]	solvent	conv. ^b	yield ^b
1	[Pd1]	1,4-dioxane	23%	13%
2	[Pd2]	1,4-dioxane	65%	62%
3	[Pd3]	1,4-dioxane	full	87%
4	[Pd4]	1,4-dioxane	7%	4%
5	[Pd3]	toluene	28%	27%
6	[Pd3]	DMF	full	<5%
7	[Pd3]	THF	full	81%
8	[Pd3]	DMSO	<5%	<5%
9	[Pd3]	1,4-dioxane/toluene (1:1)	full	98%



L = PCy₃, [Pd1]
 L = PCy₂(*t*-Bu), [Pd2]
 L = PCy(*t*-Bu)₂, [Pd3]
 L = P(*t*-Bu)₃, [Pd4]

^aConditions: aryl bromide (0.400 mmol), α,α -difluoro- α -(trimethylsilyl)acetamide (0.800 mmol), KF (1.20 mmol), [Pd] (4.0 μ mol), solvent (1 mL), 100 °C, 30 h. ^bDetermined by GC analysis with dodecane as internal standard.

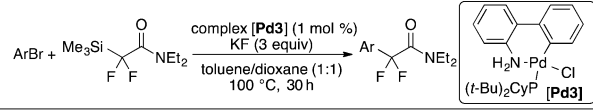
The reactions were conducted with 1-bromo-4-*tert*-butylbenzene as the limiting reagent and 1 mol % Pd precatalyst in the presence of KF at 100 °C. They were conducted in 1,4-dioxane with palladacyclic complexes [Pd1]–[Pd4] containing trialkylphosphines possessing different steric properties (PCy₃, PCy₂(*t*-Bu), PCy(*t*-Bu)₂, and P(*t*-Bu)₃; entries 1–4). Reactions catalyzed by the PCy₃- and P(*t*-Bu)₃-ligated Pd-complexes occurred to low conversion of aryl bromide and afforded the coupled product in low yields (entries 1 and 4). The reaction conducted with [Pd2] ligated by PCy₂(*t*-Bu) occurred to modest conversion of aryl bromide and gave the coupled product in modest yield (entry 2). However, the reaction catalyzed by [Pd3] containing PCy(*t*-Bu)₂ as ligand occurred to full conversion and afforded the coupled product in 87% yield (entry 3).

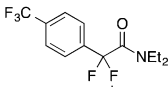
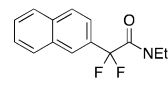
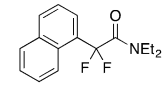
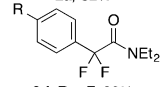
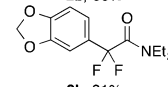
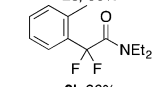
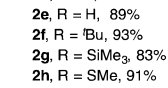
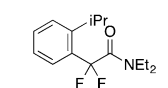
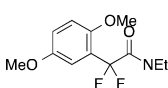
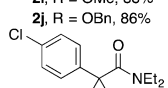
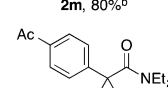
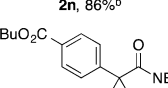
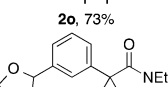
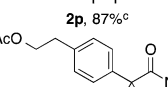
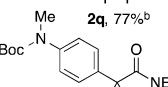
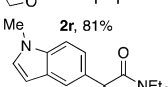
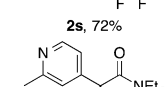
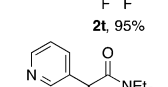
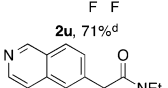
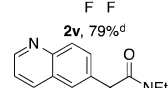
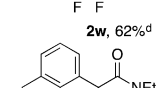
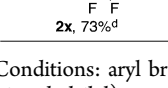
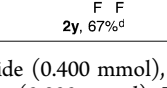
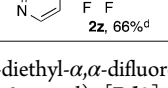
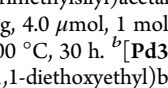
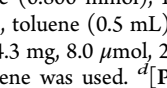
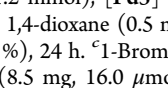
The solvent effect on this reaction was pronounced. The reaction catalyzed by 1 mol % of [Pd3] in toluene occurred to low conversion of the aryl bromide (28%), but with good mass balance (entry 5). The reaction in DMF led to full conversion of the aryl bromide, but formed predominantly the hydrodehalogenation product *tert*-butylbenzene and less than 5% of the coupled product (entry 6). The reaction conducted in DMSO proceeded to both low conversion and low yield (<5%, entry 8). The reaction in THF (entry 7) occurred similarly to the reaction in 1,4-dioxane (entry 3). Analysis of the conversion of the trimethylsilyl enolate of α,α -difluoroacetamide showed that it was fully consumed during the reactions in 1,4-dioxane, DMF, THF, and DMSO (entries 3 and 6–8), but that the mass balance was not as high as it was for the reaction in toluene (entry 5). Given the high yield of the reaction in 1,4-dioxane, but the higher mass balance of the reaction in toluene, we tested the reaction in a mixture of 1,4-dioxane and toluene (v/v 1:1, entry 9). In this solvent system, full conversion of the aryl

bromide occurred, and the coupled product formed in nearly quantitative yield.

With an active catalyst in hand and reliable conditions identified for this Pd-catalyzed arylation reaction, we studied the scope of aryl bromides that undergo this cross-coupling reaction. These results are summarized in Table 2. In general, a wide range of electronically varied aryl bromides reacted to give the corresponding coupled products in high yields (68–93%) with 1 mol % of [Pd3].

Table 2. Pd-Catalyzed Coupling of *N,N*-Diethyl- α,α -difluoro- α -(trimethylsilyl)acetamide with Aryl Bromides^a



		
2a, 82% ^b	2b, 86%	2c, 90%
		
2d, R = F, 80%	2k, 81%	2l, 86%
		
2e, R = H, 89%	2m, 80% ^b	2n, 86% ^b
		
2f, R = <i>t</i> -Bu, 93%	2o, 73%	2q, 77% ^b
		
2g, R = SiMe ₃ , 83%	2p, 87% ^c	2r, 81%
		
2h, R = SiMe ₂ , 91%	2s, 72%	2t, 95%
		
2i, R = OMe, 88%	2v, 79% ^d	2w, 62% ^d
		
2j, R = OBn, 86%	2x, 73% ^d	2y, 67% ^d
		
		2z, 66% ^d

^aConditions: aryl bromide (0.400 mmol), *N,N*-diethyl- α,α -difluoro- α -(trimethylsilyl)acetamide (0.800 mmol), KF (1.2 mmol), [Pd3] (2.2 mg, 4.0 μ mol, 1 mol %), toluene (0.5 mL), and 1,4-dioxane (0.5 mL), 100 °C, 30 h. ^b[Pd3] (4.3 mg, 8.0 μ mol, 2 mol %), 24 h. ^c1-Bromo-4-(1,1-diethoxyethyl)benzene was used. ^d[Pd3] (8.5 mg, 16.0 μ mol, 4 mol %), 24 h.

The data in Table 2 show that the electronic properties of the aryl bromides have little influence on the yields of this cross-coupling process. Products formed from the reactions of electron-deficient (2a–2c) and electron-rich (2f–2k) aryl bromides were isolated in yields as high as those from reactions of electron-neutral aryl bromides (2d and 2e). However, the reaction of the most electron-deficient 1-bromo-4-benzotrifluoride was slower than the reactions of the more electron-rich aryl bromides when conducted in the presence of 1 mol % [Pd3] and afforded the coupled product (2a) in only a modest yield (53%). The same reaction catalyzed by 2 mol % [Pd3] gave the desired product in high yield (82%).

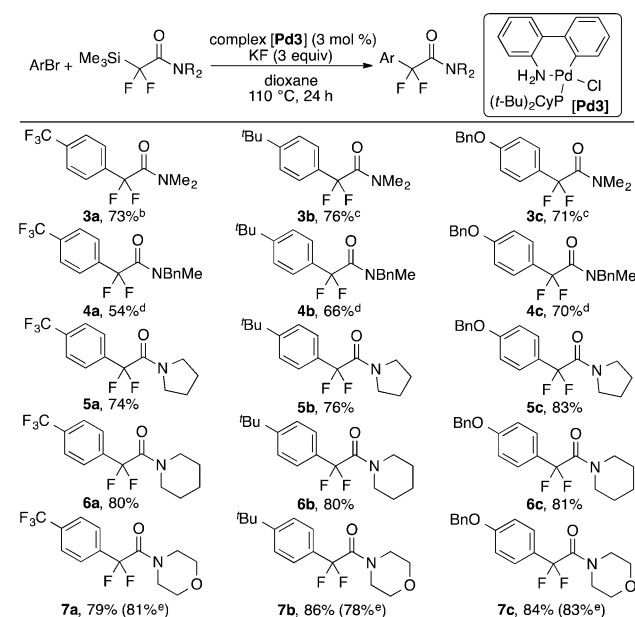
This coupling reaction tolerates a range of functionalities, including thioether (2h), ether (2i, 2j, and 2n), ester (2q and 2s), and carbamate (2t) moieties. Reactions of aryl halides

bearing both bromo and chloro substituents occurred selectively at the bromide (**2o**) under standard conditions, leaving the C–Cl bond intact. Enolizable ketone, aldehyde, free hydroxyl, and arylamino groups are not compatible with the reaction conditions. However, aryl bromides containing an enolizable ketone (**2p**, the protecting group was removed upon workup under acidic conditions) or aldehyde (**2r**) protected as the diethyl acetal, an alcohol protected as the acetyl ester (**2s**), and aniline protected as the Boc carbamate (**2t**) afforded the corresponding coupled products in high yields.

This arylation reaction also occurred with brominated nitrogen-containing heterocycles, such as bromopyridines, bromoquinolines, and bromoisquinolines (**2u–2z**). For these reactions of nitrogen-containing heterocycles, a higher catalyst loading (4 mol %) was required to obtain the coupled products in good yields.

The scope of α,α -difluoro- α -(trimethyl)silylacetamides that undergo this coupling reaction is summarized in Table 3. For

Table 3. Pd-Catalyzed Coupling of α,α -Difluoro- α -(trimethylsilyl)acetamides and Aryl Bromides^a



^aConditions: aryl bromide (0.400 mmol), α,α -difluoro- α -(trimethylsilyl)acetamide (0.800 mmol), KF (1.2 mmol), [Pd3] (6.5 mg, 12 μmol), 1,4-dioxane (1.0 mL), 110 $^\circ\text{C}$, 24 h. ^b100 $^\circ\text{C}$. ^cToluene (1.0 mL), 1,4-dioxane (1.0 mL), 100 $^\circ\text{C}$. ^d[Pd3] (8.6 mg, 16 μmol), toluene (0.5 mL), 1,4-dioxane (0.5 mL), 100 $^\circ\text{C}$, 48 h. ^eThe corresponding aryl chloride (0.400 mmol) was used.

each amide, we studied the arylation with three electronically varied aryl bromides (4-bromobenzotrifluoride, 1-bromo-4-(*tert*-butyl)benzene, and 1-(benzyloxy)-4-bromobenzene). The α,α -difluoro- α -(trimethylsilyl)acetamides that undergo this reaction include acyclic *N,N*-dialkyl amides (**3a–3c**) and alkyl benzyl amides (**4a–4c**). They also include a series of cyclic amides, such as the pyrrolidinyl (**5a–5c**), piperidinyl (**6a–6c**), and morpholinyl (**7a–7c**) amides. These amides reacted with the selected electronically varied aryl bromides to afford the coupled products in 54–89% yield.

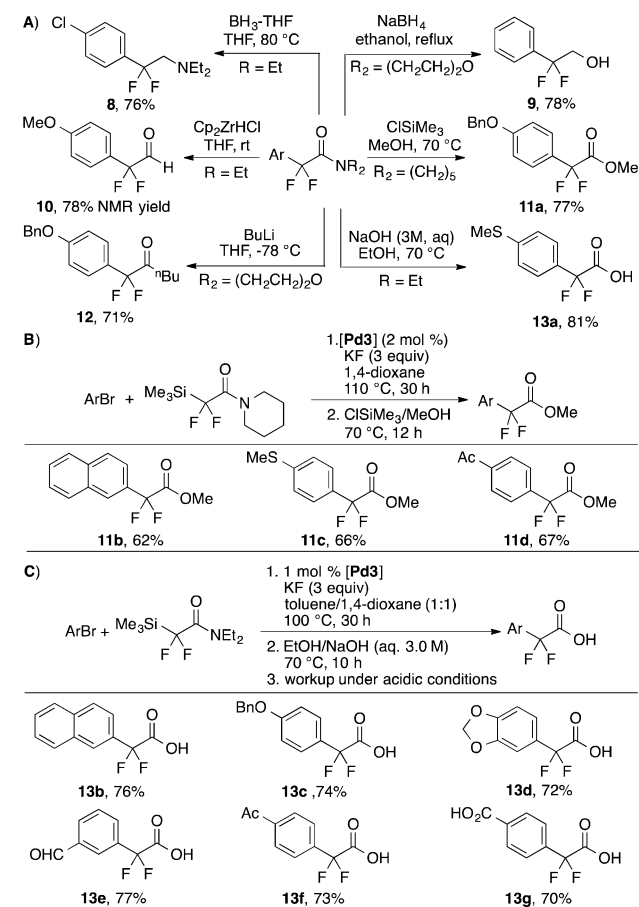
These coupling reactions can be conducted on a larger scale and without a drybox. The reaction of 1-bromo-4-(1,1-diethoxyethyl)benzene with *N,N*-diethyl- α,α -difluoro- α -

(trimethyl)silylacetamide conducted outside a drybox on 4.0 mmol scale catalyzed by 1 mol % of [Pd3] occurred in a yield (90%) that was similar to that of the reaction assembled in a drybox on a smaller scale (0.400 mmol, Table 2, **2p**). Thus, these coupling reactions can be conveniently conducted on a scale that would allow practical applications in medicinal and likely process chemistry.

An important feature of carboxylic acid derivatives is the ability to convert one of the functional groups to another and to reduce them to the corresponding alcohols and amines. However, the amide is typically the most stable carboxylic acid derivative and, therefore, is not the preferred synthetic intermediate to form other products in this class. We considered that the two fluorine atoms on the α carbon of the coupled products could cause the carbonyl group in α,α -difluoroacetamides to be more electrophilic than the carbonyl group of their non-fluorinated congeners and the amides prepared in this work to be more reactive toward nucleophiles than typical amides. At the same time, conditions for reducing the amide could lead to hydrodefluorination. Thus, we conducted studies to evaluate the reactivity of the α -aryl- α,α -difluoroacetamide products of this coupling process toward reactions that would form a range of α,α -difluoroalkylarenes.

The results in Scheme 1 show that the α -aryl- α,α -difluoroacetamides undergo a series of transformations under conditions more typical of the reactions of esters than of the reactions of amides. These difluoroamides can be reduced (A, Scheme 1) to tertiary amines (**8**), primary alcohols (**9**), or

Scheme 1. Transformations of α -Aryl- α,α -difluoroacetamides



aldehydes (**10**) without hydrodefluorination. Morpholine amides are known to act as surrogates for Weinreb amides, which can be converted selectively to ketones,¹³ and the difluoromorpholine amide **7c** reacted with *n*-butyllithium to form difluorobenzyl alkyl ketone **12**. This ketone product is not accessible by the Pd-catalyzed α -arylation of difluoromethyl butyl ketone.¹⁴ Piperidinyl difluoroamide **6** was transformed to the corresponding methyl ester (**11a**) by reaction with methanol and Me₃SiCl (12 h at 70 °C). In addition, *N,N*-diethyl difluoroamides underwent hydrolysis more readily to afford α -aryl- α,α -difluoroacetic acid (**13a**) than the corresponding non-fluorinated amides.

The silicon enolates of difluoro esters, so far, do not undergo the same coupling as the amides, but we developed a simple one-pot method to form the 1-aryl-1,1-difluoro esters via the palladium-catalyzed coupling of difluoroamides. The reaction sequence comprising Pd-catalyzed arylation of piperidinyl α,α -difluoroacetamide and methanolysis of the resulting amide products (**B**, Scheme 1) formed methyl α -aryl- α,α -difluoroacetates **13b–13d**.

A similar protocol was developed for the transformation of aryl bromides to α -aryl- α,α -difluoroacetic acids. As shown in part C of Scheme 1, a series of α -aryl- α,α -difluoroacetic acids containing electron-rich, electron-poor, and functionalized aryl groups were prepared in good to excellent yields by a sequence comprising Pd-catalyzed α -arylation of piperidinyl α,α -difluoroacetamide and hydrolysis of the resulting amide products to the acids at 70 °C.

In summary, we have developed a convenient and efficient protocol for the α -arylation and heteroarylation of the trimethylsilyl enolates of α,α -difluoroacetamides with aryl and heteroaryl bromides catalyzed by a single-component air- and moisture-stable palladacyclic precatalyst [**Pd3**]. A broad range of aryl and heteroaryl bromides, including those of basic nitrogen heterocycles, were coupled with α,α -difluoro- α -(trimethylsilyl)acetamides in high isolated yields. The α -aryl- α,α -difluoroacetamide products of these coupling reactions can be converted to 2-aryl-2,2-difluoroethanols and -ethylamines, as well as α -aryl- α,α -difluoroketones, -acetaldehydes, -acetates, and -acetic acids. Therefore, this Pd-catalyzed cross-coupling of aryl halides with α,α -difluoro- α -(trimethylsilyl)acetamides provides a method to prepare a variety of valuable building blocks containing fluorine atoms at the metabolically labile benzylic position for medicinal chemistry.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedures, and characterization of all compounds, including ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): A patent application has been filed by the University of California. J.F.H. is a founder of Catylix; he and the company may benefit financially from the expected results of the PHS-funded research conducted in his laboratory.

■ ACKNOWLEDGMENTS

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