Effect of fluorine on palladium-catalyzed cross-coupling reactions of aryl bromides with trifluoromethyl aryl ketones *via* difluoroenol silyl or monofluoroenol silyl ethers†

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Palladium-catalyzed cross-coupling reactions of α-aryl-β,β-difluoroenol silyl and α-aryl-β-fluoroenol silyl ethers with aryl bromides proceed smoothly with good functional compatibility.

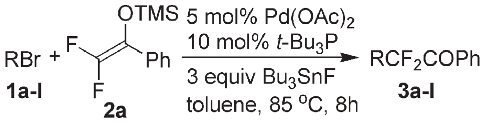
A variety of difluoromethylene compounds, which have been less explored relative to trifluoromethylated and monofluorinated compounds, are useful in medicinal science research.[1,2] Previously, 2,2-difluoro-2-phenylacetophenone was synthesized by electrophilic fluorination.[3] However, most electrophilic reagents tend to be expensive and/or difficult to prepare, and often the functional group is incompatible with the reactive reagents. A useful alternative approach to the synthesis of α,α-difluoroketones involves carbon–carbon bond forming reactions of difluoro enol silanes, including Mukaiyama aldol reactions,[4] Michael additions,[5] cycloadditions[6] and halogenations.[7]

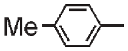
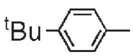
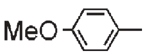
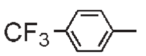
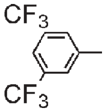
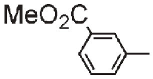
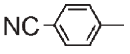
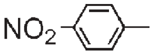
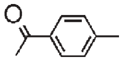
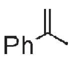
Our approach to the synthesis of difluorinated ketones involves the first examples of cross-coupling reactions of difluoro enol ethers. Even after more than twenty years since the discovery of the Pd-catalyzed cross-coupling reactions of non-fluorinated enol silyl ethers,[8] the reactions have never been extended to fluorinated analogues.

Recent progress in the study of coupling reactions of substituted enol silyl ethers[9,10] encouraged us to examine the analogous palladium-catalyzed cross-coupling reactions of difluoroenol silyl ethers (monofluoroenol silyl ether) with aryl halides. The method described in this work provides a mild and extensive method for difluoroacetophenone synthesis. Utilization of a bromo-containing precursor allows control of the positional outcome based on the initial position of the bromine substituent in contrast to the specific electronics of the aryl system that are normally required in an oxidative cross-coupling reaction.[11]

Magnesium-promoted selective defluorination of aryl trifluoromethyl ketones provides a straightforward route to difluoroenol silyl ethers.[12,13] Tri(*tert*-butyl)phosphine is a bulky and electron-rich ligand that serves very well in Pd-catalyzed coupling with enol silyl ethers. Monobromobenzene **1a** was reacted with two equivalents of silyl enol ether **2a** in the presence of 5 mol% of palladium acetate and 10 mol% tri(*tert*-butyl)phosphine with three equivalents of tributyltin fluoride in toluene at 85 °C (oil bath) under a nitrogen atmosphere for 8 h to give 2,2-difluoro-2-phenylacetophenone (**3a**) in 91% isolated yield.† In the ^{19}F NMR spectrum of the product, a singlet is observed at δ −97.5 ppm. The range of aryl halides used in these reactions is depicted in Table 1. Reactions of various halides, which contain either an electron-withdrawing group or an electron-donating group attached to the phenyl ring of **1**, proceeded efficiently under

Table 1 Pd-catalyzed arylation of trimethylsilyl β,β-difluoroenol ether with various halides[a]



No.	Halide	R	Product	Yield (%)[b]
1	**1a**	Ph–	**3a**	91
2	**1b**		**3b**	86
3	**1c**		**3c**	82
4	**1d**		**3d**	84
5	**1e**		**3e**	81
6	**1f**		**3f**	70
7	**1g**		**3g**	89
8	**1h**		**3h**	90
9	**1i**		**3i**	76
10	**1j**		**3j**	82
11	**1k**		**3k**	82
12	**1l**		**3l**	20[c]

[a] Reactions were conducted with 1 equiv. of the halide **1** (0.67 M) and 2 equiv. of silyl enol ether **2**. [b] Isolated yield is based on the halide. [c] Yield based on ^{19}F NMR spectrum, by using benzotrifluoride as an internal standard.

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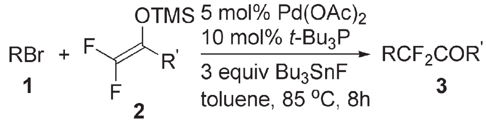
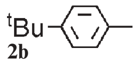
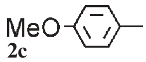
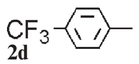
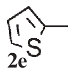
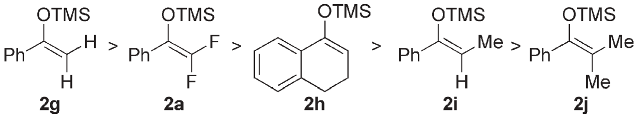
† Electronic supplementary information (ESI) available: Experimental procedures, characterization, and proton, carbon, and fluorine NMR data. See DOI: 10.1039/b705137a

Table 2 Pd-catalyzed arylation of different trimethylsilyl difluoroenol ethers with various halides[a]

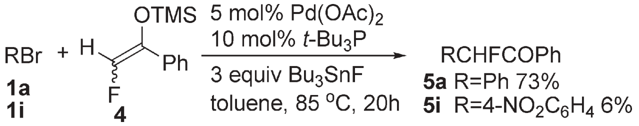


No.	Halide	R′	Product	Yield (%)[b]
1	**1g**	 **2b**	**3m**	94
2	**1k**		**3n**	75
3	**1h**	 **2c**	**3o**	75
4	**1i**		**3p**	68
5	**1a**	 **2d**	**3q**	45
6	**1a**	 **2e**	**3r**	75
7	**1a**	Hexyl **2f**	**3s**	6[c]

[a] Reactions were conducted with 1 equiv. of the halide **1** (0.67 M) and 2 equiv. of TMS enol ether **2**. [b] Isolated yield is based on the halide. [c] ^{19}F NMR yield.



Scheme 1 Relative rate of reaction for silyl enol ethers in Pd-catalyzed cross-coupling with bromobenzene.



Scheme 2 Pd-catalyzed arylation of trimethylsilyl α-phenyl-β-monofluoroenol ether with aryl halides.

standard conditions to give good to excellent product yields. It is worthwhile noting that many base-sensitive functional groups, such as cyano, nitro, ester and carbonyl, were stable during the reactions.

When 2-bromothiophene was employed, a heteroaryl group was introduced into the final difluoroketone. However, when α-bromostyrene was the reactant, the yield of the product (^{19}F NMR chemical shift at δ −96.7 ppm) was 20% based on the ^{19}F NMR analysis (benzotrifluoride as internal standard).

The general arylation procedure was applied to additional silyl enol ethers (Table 2). The cross-coupling reactions of the enol ethers with a *tert*-butyl or methoxy group attached to the phenyl rings also resulted in high product yields. However, when the substituent was trifluoromethyl, the yield of product was <50%, probably arising from the instability of the enol ether. When a silyl enol ether that contained a thienyl group was used, the reaction also proceeded smoothly. This kind of phenyldifluoromethyl heteroaryl ketone has not been synthesized previously. Starting from 1,1,1-trifluoro-2-octanone, [1-(difluoromethylene)heptyl]oxy trimethylsilane **2f** was synthesized[12] and extracted into hexane. The hexane layer was separated and the hexane was pumped off. The crude product was dissolved into toluene and subjected to the reaction. But only 6% of the product **3s** was detected by ^{19}F NMR spectroscopy. Pure **3s** was difficult to separate from the impurities and the major product was 1,1-difluoro-2-octanone.

To discover the extent to which the substituted fluorines influence the reactivity, a non-fluorinated silyl enol ether and an equivalent of **2a** were added to the reaction system and reacted with **1a** for 1 h. Analysis of the products gave the relative rate. Approximately, **2g** reacted twice as fast as **2a**; **2a** reacted twice as fast as **2h**, and five times faster than **2i**; **2j** was slowest (Scheme 1).

In order to obtain additional information about the effect of fluorine, we also tried the cross-coupling reaction of monofluoroenol silyl ether **4** (Scheme 2). The reaction proceeded sluggishly compared with the difluoro analogues **2**. After 8 h under the same reaction conditions, the conversion of monofluoroenol silyl ether was about 70%. Therefore, the reaction time was prolonged to 20 h. Using ^{19}F NMR spectroscopy, a chemical shift at δ −176.5 ppm (d, J = 48.4 Hz) was observed for one product (**5a**) in 73% yield. The other major product was 2-fluoroacetophenone. However, when 4-nitrobromobenzene was the reactant, the yield was only 6% based on fluorine NMR analysis. The chemical shift was at −179.2 ppm (d, J = 48 Hz). It was reported previously that **5a** could be synthesized by either fluorination of a secondary alcohol by a perfluoro-1-butanesulfonyl fluoride–iPr$_2$NEt(HF)$_3$–iPr$_2$NEt system[14] or fluorination of the enol ether by trifluoromethyl hypofluorite (CF$_3$OF).[15] The coupling reactions of monofluoroenol ether have not yet been studied, although its Mukaiyama aldol reaction has been observed.[16] These mild reaction conditions make the synthesis of an enantioselective monofluoroketone possible if a suitable chiral ligand is used.[17]

Although the mechanism is not clear, a mechanism for the Pd-catalyzed arylation of difluoro enol ether has been proposed.[9] Based on the latter, the starting silyl enol ether reacted with Bu$_3$SnF to generate the tin enolate, which is in equilibrium with an α-stannyl ketone intermediate. Reaction of the tin enolate with Ar–Pd–X produces the Pd-enolate as the transmetalation product. Reductive elimination of the Pd-enolate to form a C–C bond then gives the arylated product and regenerates Pd^0. However, the intermediacy of (tBu$_3$P)$_n$Pd(Ar)F complexes cannot be ruled out.[18,19]

In summary, Pd-catalyzed arylations of difluoro or fluoro enol silyl ethers were achieved by use of Pd(OAc)$_2$ and tBu$_3$P in the presence of Bu$_3$SnF, participated by electron-poor and electron-rich aryl bromides with a good functional tolerance. The similar bulk of fluorine to hydrogen and its nature as an electrostatic surrogate of oxygen mean that the substituted fluorine contributes significantly to the reactivity of α-aryl-β,β-difluoroenol trimethylsilyl ethers. The reactions with additional fluorinated silyl enol ethers, expansion to halides other than aromatic, and a mechanistic study will be reported in due course.

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