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Generating Diversity in Difluoromethyl Ketone Derivatives

Gareth A. DeBoos,[†] Jeremy J. Fullbrook,[‡] and Jonathan M. Percy*[,‡]

School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom, and Avecia Ltd., PO Box 42, Hexagon House, Blackley, Manchester M9 8ZS, United Kingdom

jmpercy@chemistry.bham.ac.uk

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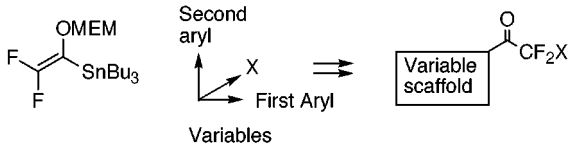
ABSTRACT

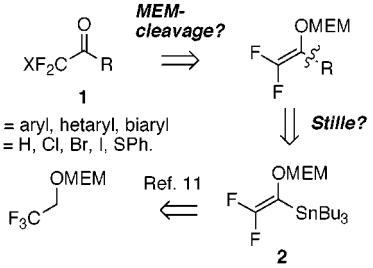


Two consecutive palladium-catalyzed coupling reactions from a readily available difluoroenol stannane set the stage for the synthesis of a range of difluoro- and halodifluoromethyl ketones upon a variable aryl template.

Though numerous methods exist for the synthesis of trifluoromethyl ketones (useful inhibitors of protease[1] and other enzymes[2]) and chlorodifluoromethyl ketones, there are few methods suitable for the rapid generation of molecular diversity in molecules of class **1**. For example, the classical reaction between chlorodifluoro- or trifluoroacetic acid derivatives[3] and σ-organometallic reagents requires that a separate organometallic nucleophile is generated for each variation of the aryl group, and the high reactivity or availability of organolithium and Grignard reagents may limit the range of compatible functional groups. Recently, Liebeskind and Srogl[4] showed that couplings were possible between *S*-phenyl trifluorothioacetate and boronic acids, affording a valuable entry to aryl trifluoromethyl ketones. The recent reductive defluorination method of Uneyama[5] (which complements Ishihara's reduction of chlorodifluoromethyl ketones[6]) then enables a link to be made to difluoroenol derivatives. Other routes to difluoroenol silanes were described by Portella[7] (who converted acyl silanes to difluoroenol silyl ethers by reaction with Ruppert's reagent), Fleming,[8] and Xu.[9]

We anticipated a different approach in which we would use transition-metal-catalyzed coupling chemistry to combine a relatively stable difluoroenol fragment, obtained from trifluoroethanol,[10] with a range of functionalized aryl species. Subsequent coupling reactions would begin to generate diversity only if the difluoroenol derivative was able to withstand the reaction conditions required. Finally, we would release the latent difluoroketones under mild electrophilic conditions to afford some novel and potentially useful species (Scheme 1).

Scheme 1. Retrosynthetic Analysis



[†] Avecia Ltd.
[‡] School of Chemistry, University of Birmingham.

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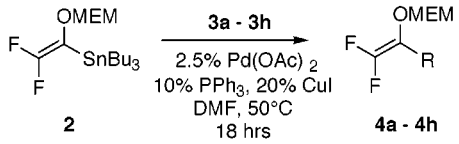
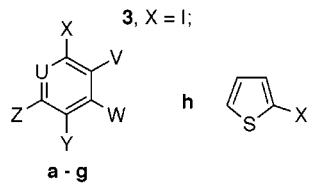
The only stoichiometric organometallic reaction required in such a sequence would be for the synthesis of stannane **2** following our published procedure,[11] a reaction we have performed routinely on a 0.2 mol scale. We have described Stille and Suzuki−Miyaura couplings of the corresponding enol *N*,*N*-diethylcarbamate[12] but were anxious, lest cleavage of the MEM group should occur under Stille couplings. We then prepared iodotriflates **3a**−**c** (in 94%, 95%, and 93% yield, respectively) following a standard procedure[13] and attempted the Stille couplings under modified Farina−Liebeskind conditions (Scheme 2). We were able to use

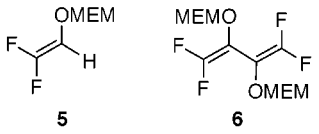
Scheme 2. Stille Couplings to Stannane **2**





	U	V	W	Y	Z	Yield (%)	
a	CH	OTf	H	H	H	33 [a]	21[b]
b	CH	H	OTf	H	H	100	86
c	CH	H	H	OTf	H	100	96
d	CH	H	CO_2Bn	OTf	H	100	70
e	CH	H	H	OMe	H	94	(-)
f	CH	H	CHO	OBn	I	(-)	25
g	N	H	H	Br	H	39	30
h	-	-	-	-	-	95	(-)

All reactions were run to 100% conversion of starting material. [a]Yield by ^{19}F NMR. [b]Isolated yield.



palladium(II) acetate directly in the reactions at a low loading (2.5%), which reduced the cost and simplified the workup relative to procedures that deploy Pd_2dba_3 complexes.

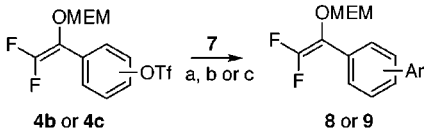
The *meta*- and *para*-congeners coupled efficiently (86% for **4b** and 96% for **4c**), whereas as expected, a poor yield was obtained for *ortho*-isomer **4a** as a result of steric hindrance caused by the TfO substituent.[14] The presence of Cu(I) salt was critical to minimize the coformation of enol acetal **5**, a significant byproduct when the cocatalyst was omitted. Functionalized iodotriflate **3d** also coupled efficiently. With diiodide **3f**, we observed the formation of a major coupling product **4f** by ^{19}F NMR, though the isolated yield was low and a significant amount of **5** was formed also. Coupling with bromobenzene failed, however, and we recovered **5** and diene **6** only from the reaction.

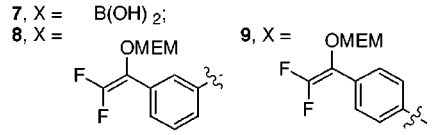
Generally, slow oxidative addition of the halide to the palladium catalyst leads to the formation of byproducts **5** and **6**. However, attempted coupling with 2,5-dibromopyridine (in which the heteroaryl C−Br bond is more labile) did lead to some product formation (according to ^{19}F NMR spectra of crude reaction mixtures) though the reaction was very slow (20% product after 18 h).

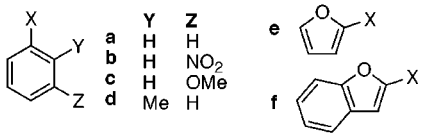
With 5-bromo-2-iodopyridine,[15] we were able to isolate **4g** in 30% yield. Except for **4h**, all of the coupling products were sufficiently stable to be characterized fully. Stille and Suzuki−Miyaura couplings were then attempted for **4b** and **4c** to determine the stability of the enol acetal under the more forcing conditions required for coupling with the less reactive aryl triflates.

Suzuki−Miyaura couplings[16] to **4c** were successful, particularly under the conditions described by Oh-e and coworkers,[17] and a range of biarylethenes were isolated in moderate to good yield (Scheme 3, Table 1).

Scheme 3. Suzuki Couplings to Triflates **4b** and **4c**







[a] 5% $PdCl_2(PPh_3)_2$, 4.0 eq. Et_3N, 2.0 eq. **7**, DMF, 90 °C. [b] 1% $Pd(OAc)_2$, 1.2% PCy_3, 3.3 eq. KF, 2.0 eq. **7**, THF, 65 °C. [c] 2.5% Pd_2dba_3·$CHCl_3$, 20% PPh_3, 1.5 eq. K_3PO_4, 2.0 eq. **7**, 1.4-dioxane, 85 °C.

The lower limit of boronic acid reactivity was reached at the 3-nitrophenylboronic acid, which reacted very slowly indeed with **4b** and **4c**; in fact, it was not possible to isolate

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Table 1. Outcomes of Suzuki Coupling Reactions

reactants		conditions	time (h)	conversion (%)	product	yield (%)[a]
7a	**4b**	a	16	45		0
		a	48	87	**8a**	48
	4c	b	20	0		0
		c	16	100	**9a**	67
7c	**4c**	a	90	15		0
		c	72	100	**9c**	40
7d	**4c**	a	90	100	**9d**	84
7e	**4c**	a	90	100	**9e**	49
7f	**4c**	a	90	100	**9f**	51

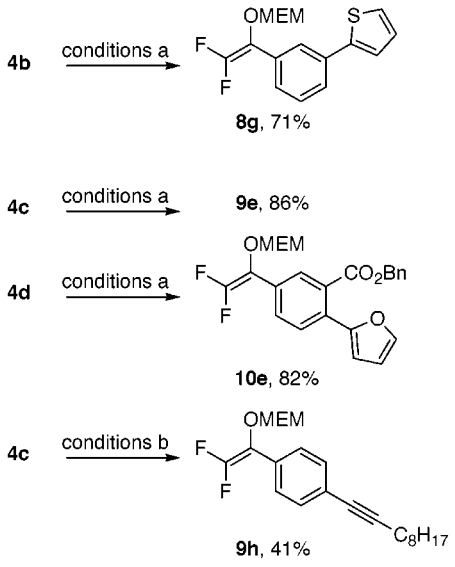
[a] Isolated yields. All reactions were run on 0.5 mmol scale. All single runs.

any coupled product. We did not explore *meta*-substituted **4b** under Suzuki−Miyaura conditions fully, but a slow though moderately successful coupling was executed with phenylboronic acid. There is clear scope here for optimization and generalization. In Stille couplings,[18] **4a** was unreactive but **4b** and **4c** were coupled successfully with reactive stannanes, even though lithium chloride was absent. Functionalized triflate **4d** underwent an extremely rapid coupling (3−5 min) under identical conditions.

In a solitary and unoptimized example, a Sonogashira reaction between 1-decyne and **4c** delivered the alkyne **9h** in 41% yield.[19] (Scheme 4).

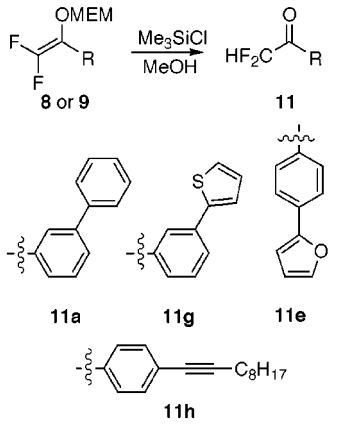
We then examined cleavage of the enol acetal which had been shown to occur under mild conditions. Cleavage occurred in methanol containing chlorotrimethylsilane,[20] and direct removal of the methanol from the reaction afforded the pure difluoromethyl ketones **11** after filtration through a short silica plug (Scheme 5). In a series of NMR experiments,

Scheme 4. Stille and Sonogashira Couplings of Triflates **4b**, **4c**, or **4d**



[a] 5% $PdCl_2(PPh_3)_2$, DMF, 85 °C, $RSnBu_3$. [b] 5% $PdCl_2(PPh_3)_2$, DMF, 4.0 Et_3N, 90 °C, 1-decyne.

Scheme 5. Protic Cleavage of MEM Enol Ethers **8** or **9**



enol acetal	ketone	yield/%
8a	**11a**	53
8g	**11g**	82
9e	**11e**	60
9h	**11h**	78

[a] Isolated yields; all reactions run to 100% conversion.

we also showed that **4c** reacted cleanly and quantitatively with Br_2 in dioxane, NCS, or I_2 in THF and PhSCl in DCM to afford products with ^{19}F NMR spectra consistent with the formation of the respective difluoroketones. This final result suggests that we have a very flexible method for the synthesis of XCF_2COAr in which we can vary the X substituent and the Ar scaffold from aryl to heteroaryl and biaryl, through which molecular diversity can be generated, though some optimization of coupling chemistry is clearly required.

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Supporting Information Available: ^{19}F NMR and R_f data for all compounds and experimental procedures for the synthesis of **4c**, **9e** (via Suzuki), and **11e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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