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Nucleophilic Tetrafluoroethylation Employing in Situ Formed Organomagnesium Reagents

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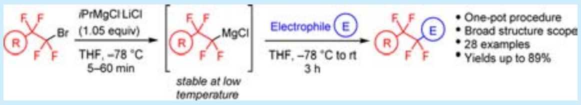
Ⓢ *Supporting Information*

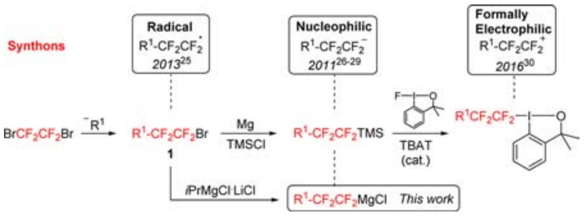
ABSTRACT: Tetrafluoroalkyl bromides are metalated with equimolar *i*PrMgCl·LiCl (Turbo Grignard) to form organomagnesium compounds which are stable at low temperatures and react with various electrophiles (aldehydes, ketones, CO_2, cyclic sulfate and sulfamidate, *N*-sulfonylimines, nitrone, chlorophosphate, nonaflyl azide) to afford novel functionalized tetrafluoroethylene-containing products. Ease of operation, excellent selectivity, high nucleophilicity, and enhanced stability of the reactive species together with a broad substrate scope comprise a highly attractive nucleophilic tetrafluoroethylation protocol affording unique synthetic building blocks.



The incorporation of a difluoromethylene (CF_2) group or perfluoroalkylidene groups [$(CF_2)_n$] into organic molecules is a popular strategy for modification of various properties of molecules in life science and material science applications.[1−6] For instance, the difluoromethylene group can act as a bioisostere of ethereal oxygen, carbonyl, or CHOH groups, and the difluoromethyl group can also serve as a lipophilic hydrogen bond donor.[5,7−9] In carbohydrates, the replacement of CHOH groups with CF_2 units causes only minimal steric and ring conformation perturbation, but because of attractive dipolar interactions of C−F bonds and hydrophobic desolvation, there is, in some cases, such as in a hexafluorinated sugar derivative, a dramatic improvement of transmembrane transport observed.[10,11] In addition, tetrafluorinated sugar analogues are currently being investigated as enzyme inhibitors.[12−14] For these reasons, there is a high demand for new synthetic methods enabling the incorporation of CF_2CF_2 groups.

Approaches to tetrafluoroethylene-containing compounds can be divided into fluorination methods, such as deoxofluorination of 1,2-dicarbonyl compounds,[15,16] and fluoroalkyl-transfer methods.[17−22] The latter approach is based on functionalization of suitable CF_2CF_2 precursors including tetrafluoroethylene or 1,2-dihalotetrafluoroethanes.[23,24] We have recently reported heteroatom-substituted radical,[25] nucleophilic,[26−29] and electrophilic[30] tetrafluoroethylene synthons starting from $BrCF_2CF_2Br$ (Scheme 1). However, the preparation of the nucleophilic reagent silane from the bromide required an extra synthetic step and displayed limited reaction scope.[26−29] The strategy used for the preparation of tetrafluorinated sugars and azasugars employed metal−halogen exchange followed by intramolecular cyclization.[31−36] One report described metalation of 4-bromo-3,3,4,4-tetrafluorobut-1-ene with an excess of MeLi and addition to carbonyl compounds under Barbier conditions.[37] Given the considerable body of literature on perfluoroalkyl organometallics,[38−43] we were curious to see whether metalation of $R^1CF_2CF_2Br$ provides stable metalated species and to explore their reactivity with electrophiles in a one-pot fashion. If successful, this methodology could serve as a tool for the synthesis of a variety of CF_2CF_2-containing compounds.

Scheme 1. Reagents for Radical, Nucleophilic, and Electrophilic Tetrafluoroethylene Group Transfer



Commercially available **1a** was selected for the initial screening aimed at identification of a suitable metalation reagent R^2M (Table 1). The in situ produced organometallic species underwent reaction with the subsequently added electrophile (4-nitrobenzaldehyde, **2a**) to provide **3aa**. Side reactions included protonation to **4a**, fluoride elimination to **5a**, and reaction with R^2Br to give **6a**. It was found that MeLi and *n*-BuLi metalated **1a** rapidly at −78 °C; however, the main products were **6a** and **5a**, respectively (Table 1, entries 1 and 2). Under Barbier conditions the formation of **3aa** increased dramatically. Unfortunately, adduct **7a** arising from the reaction of R^2 M with **2a** formed in about 10% yield, and some unreacted **1a** was still present in the crude reaction mixture (Table 1, entries 3 and 4).

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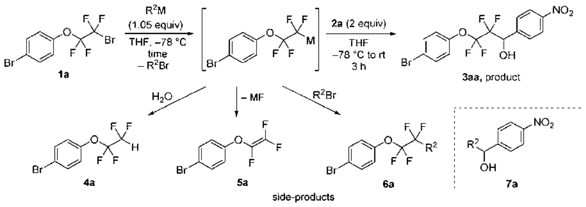
Table 1. Metalation of 1a and Addition of the in Situ Formed Organometallic Species to 4-Nitrobenzaldehyde (2a)[a]



entry	R² M	time (min)	yield[b] (%)				
			1a	**3aa**	**4a**	**5a**	**6a**
1	MeLi	2	0	5	6	1	82
2	*n*BuLi	2	0	traces	0	50	0
3	MeLi	[c]	11	59	19	0	9
4	*n*BuLi	[c]	15	65	17	1	0
5	*i*PrMgCl	10	0	64	15	12	0
6	*i*PrMgCl·LiCl	45	0	85 (80)	12	0	0

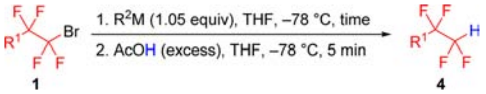
[a] Reaction conditions: **1a** (0.1 mmol), *c*(**1a**) = 0.2 M, R² M (1.05 equiv), THF, −78 °C, time; then **2a** (2 equiv), THF, −78 °C to rt, 3 h. [b] ^{19}F NMR yield using $PhCF_3$ as an internal standard, isolated yield in parentheses. [c] Barbier conditions (R² M added at −78 °C to the mixture of **1a** and **2a**).

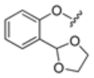
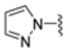
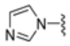
With *i*PrMgCl and its LiCl complex, known as the Turbo Grignard reagent, the metalation required a longer time than with organolithiums. On the other hand, fewer side products were formed, and the best result was obtained using Turbo Grignard (Table 1, entry 6). The organomagnesium formed from **1a** and the Turbo Grignard reagent was stable for 4 h at −78 °C, at −50 °C decomposed to **5a** with a half-life of 1.5 h, and fully decomposed within 50 min at −40 °C. Thus, *i*PrMgCl·LiCl outperformed other metalation reagents in terms of stability of the resulting fluorinated metalated species while maintaining their good nucleophilicity.

The observed differences in metalation times for **1a** prompted us to investigate in more detail the effect of structure of **1** on metalation rates at −78 °C in THF using *i*PrMgCl·LiCl. ^{19}F NMR analyses of the reaction mixture after addition of acetic acid at different reaction times allowed us to determine the minimal metalation times needed for complete conversion of **1** to **4** (Table 2). In general, metalation using LiCl-free Grignard reagent was faster than with the Turbo Grignard reagent, which is surprising since LiCl is known to break aggregates and make the organomagnesium species more reactive.[44,45] With Turbo Grignard, the metalation times varied from <5 min for **1f** and aliphatic bromides **1h**−**j** to 1 h for some of the aryloxy derivatives. Sulfone **1g** quickly eliminated phenylsulfinate to give tetrafluoroethylene and was thus excluded from further reactions with electrophiles. Bromide **1i** and **1i** reacted with the Turbo Grignard reagent regioselectively on the CF_2 group bearing the bromine atom. Metalated species derived from bromide **1i** and tosylate **1j** mostly eliminated fluoride to form the trifluorovinyl compounds **5**; however, at −90 °C this side reaction was reasonably suppressed. In the case of **1l**, further experiments with D_2O and **2a** revealed a rearrangement of the metal species due to appreciable acidity of the hydrogen atom on the imidazole ring, affording a mixture of products **3la**, **3l′a**, and **4l** as shown in Scheme 2.

Having identified suitable metalation conditions, reactions of bromides **1** with a range of electrophiles leading to tetrafluoroethylene-containing products **3** were examined (Table 3).

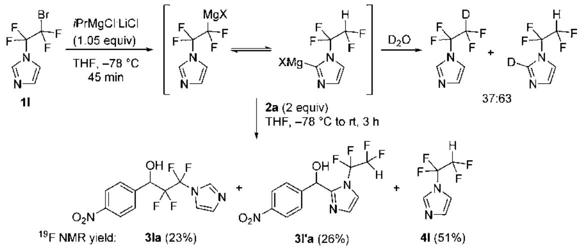
Table 2. Metalation Times of 1 with Grignard Reagents[a]



entry	1	R¹	R²M	time (min)[b]
1	**1a**	4-BrC_6H_4O	*i*PrMgCl	<10
2	**1a**	4-BrC_6H_4O	*i*PrMgCl·LiCl	45
3	**1b**	4-(EtOOC)C_6H_4O	*i*PrMgCl	<10
4	**1b**	4-(EtOOC)C_6H_4O	*i*PrMgClLiCl	60
5	**1c**		*i*PrMgClLiCl	60
6	**1d**	4-(MeO)C_6H_4O	*i*PrMgCl·LiCl	30
7	**1e**	4-FC_6H_4O	*i*PrMgCl·LiCl	45
8	**1f**	PhS	*i*PrMgCl·LiCl	<5
9[c]	**1g**	$PhSO_2$	*i*PrMgCl·LiCl	<5
10	**1h**	$N_3CH_2CH_2$	*i*PrMgCl·LiCl	<5
11[d]	**1i**	$BrCH_2CH_2$	*i*PrMgCl·LiCl	<5
12[d]	**1j**	$TsOCH_2CH_2$	*i*PrMgCl·LiCl	<5
13	**1k**		*i*PrMgCl·LiCl	30
14	**1l**		*i*PrMgCl·LiCl	45

[a] Reaction conditions: **1** (0.03 mmol), R² M (1.05 equiv), THF, *c*(**1**) = 0.2 M, −78 °C, time; then 10% AcOH in THF (1 mL), −78 °C, 5 min. [b] Time to reach >95% conversion of **1** to **4**, determined by ^{19}F NMR. [c] Tetrafluoroethylene formed instead of **4g**. [d] Metalation was conducted at −90 °C.

Scheme 2. Metalation of 1l and the Reaction with D_2O or 2a



Metalation times corresponded to values shown in Table 2 (5 min for **1f**,**h**−**j**). Reactions of a random selection of bromides **1** with electron-rich or electron-poor aromatic aldehydes, enolizable aliphatic aldehyde, or *α*,*β*-unsaturated aldehyde provided adducts in high yields (Table 3, entries 1−9). Addition to ketones also proceeded with good efficiency (Table 3, entries 10−14), which implies that the organomagnesium species derived from **1** are more nucleophilic than the previously reported $PhSCF_2CF_2TMS$ with fluoride initiators.[26] With CO_2, novel tetrafluoropropionic acids were synthesized (Table 3, entries 15−17). Following a failed addition to unactivated imine (*N*-(4-(trifluoromethyl)benzylidene)aniline), *N*-sulfonylaldimine and cyclic ketimine yielded sulfonamides (Table 3, entries 18 and 19). Similarly, whereas reactions with epoxides (2-ethyloxirane and 7-oxabicyclo[4.1.0]heptane) were unproductive, the ring opening of cyclic sulfate **2r** and cyclic sulfamidate **2s** provided 2-fluoroalkyl-substituted ethanols and amines, respec-

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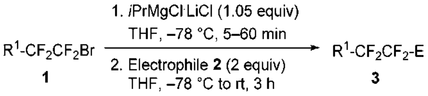
Table 3. One-Pot Nucleophilic Tetrafluoroethylation Starting from Bromides 1a−k[a]



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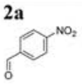
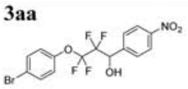
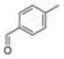
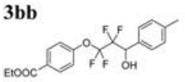
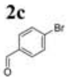
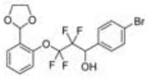
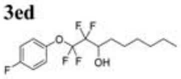
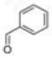
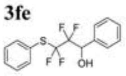
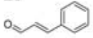
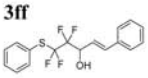
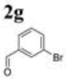
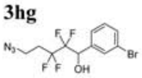
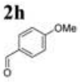
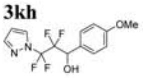
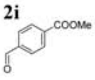
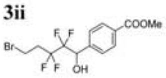
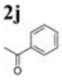
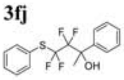
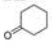
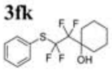
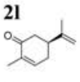
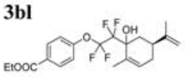
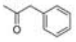
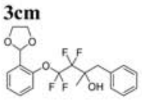
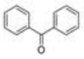
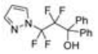
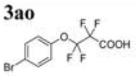
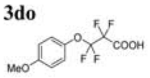
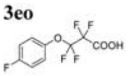
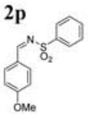
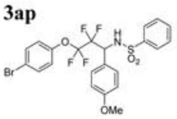
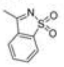
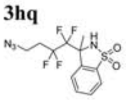
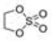
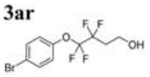
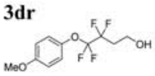
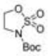
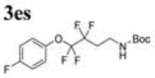
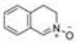
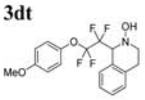
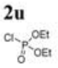
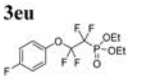
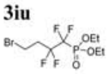
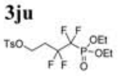
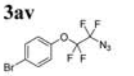
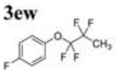
1	1a	2a 	3aa 	80
2	1b	2b 	3bb 	75
3	1c	2c 	3cc 	87
4	1e	2d 	3ed 	76
5	1f	2e 	3fe 	73
6	1f	2f 	3ff 	71
7	1h	2g 	3hg 	82
8	1k	2h 	3kh 	89
9[c]	1i	2i 	3ii 	52
10[d]	1f	2j 	3fj 	53
11[d]	1f	2k 	3fk 	73
12	1b	2l 	3bl 	68[e]
13	1c	2m 	3cm 	85
14	1k	2n 	3kn 	67
15	1a	2o CO$_2$	3ao 	72
16	1d	2o	3do 	80
17	1e	2o	3eo 	78
18	1a	2p 	3ap 	62
19	1h	2q 	3hq 	27
20[f]	1a	2r 	3ar 	86[g]
21[f]	1d	2r	3dr 	76[g]
22[h]	1e	2s 	3es 	76[i]
23	1d	2t 	3dt 	61
24	1e	2u 	3eu 	78
25	1i	2u	3iu 	37
26[c]	1j	2u	3ju 	48
27	1a	2v nC$_4$F$_9$SO$_2$N$_3$	3av 	71
28[j]	1e	2w CH$_3$I	3ew 	66[k]

[a]Reaction conditions: **1** (0.43−4.0 mmol), *i*PrMgCl·LiCl (1.05 equiv), THF, *c*(**1**) = 0.2 M, −78 °C, 5−60 min (see Table 2 for metalation times); then **2** (2 equiv), THF, −78 °C to rt, 3 h. [b]Isolated yield. [c]Metalation was conducted at −90 °C. [d]Using 1.05 equiv of **1** and 1 equiv of **2**. [e]dr 95:5 (HPLC). [f]Using 1.2 equiv of **2**. [g]After treatment with 16% aqueous H_2SO_4, reflux, overnight. [h]Using 0.95 equiv of **2**. [i]After treatment with 10% aqueous H_2SO_4, rt, 1 h. [j]Using 4 equiv of **2**. [k]^{19}F NMR yield using internal standard ($PhCF_3$); **3ew** was obtained together with **4e** (24%) as an inseparable mixture.

tively in high yields after acidic hydrolysis (Table 3, entries 20−22).[46]

Reaction with 3,4-dihydroisoquinoline 2-oxide (**2t**) resulted in the formation of the respective products (Table 3, entry 23) and with diethyl chlorophosphate (**2u**), moderate to good yields of the corresponding fluoroalkyl phosphonates were obtained (Table 3, entries 24−26). In the two latter cases, the reactions with **1i** and **1j** led to considerable elimination to trifluorovinyl compounds **5i** and **5j** both at −78 and −90 °C, causing reduced yields of the products. A highly electrophilic azide **2v** afforded the corresponding fluoroalkyl azide **3av** in good yield (Table 3, entry 27). Lastly, the formation of side product **6** in the metalation experiments shown in Table 1 prompted us to investigate alkyl halides as electrophiles. However, the reaction was only partially successful with MeI where the methylated product **3ew** was obtained in good ^{19}F NMR yield (Table 3, entry 28) in an inseparable mixture with **4e**, and no alkylated product could be detected in the reaction with allyl bromide.

In conclusion, metalation of structurally diverse 1-bromo-1,1,2,2-tetrafluoroalkanes with the Turbo Grignard reagent provided regioselective organomagnesium compounds which were found to be stable at low temperature and displayed excellent reactivity with a broad range of functionalized electrophiles, including carbonyl compounds, CO_2, cyclic sulfate and sulfamidate, *N*-sulfonylimines, nitrone, chlorophosphate, and an electrophilic azide. This approach toward nucleophilic tetrafluoroalkylation thus showed a favorable combination of reactivity and selectivity, surpassing the previously used fluoroalkyl silanes or organolithium compounds in terms of the scope of both nucleophiles and electrophiles and the yields of corresponding products. Many of the described products are inaccessible via other methods, and as all of them contain diverse functional groups allowing functionalization, they can serve as potentially promising building blocks for the design of drugs, pesticides, and advanced materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02890.

Experimental procedures, product characterization, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): CF Plus Chemicals s.r.o. (www.cfplus.cz) company, an ETHZ spin-off, commercializes the CF_2CF_2 building blocks used in this publication.

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