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# Mg$^0$-promoted selective C–F bond cleavage of trifluoromethyl ketones: a convenient method for the synthesis of 2,2-difluoro enol silanes

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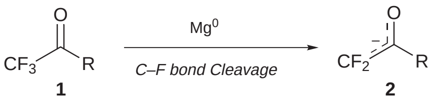
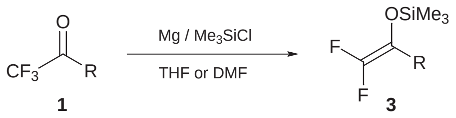
**2,2-Difluoro enol silyl ethers were readily prepared by Mg$^0$ promoted selective defluorination of trifluoromethyl ketones in the presence of TMSCl, which involves C–F bond cleavage.**

Difluoro enol silyl ethers are synthetic equivalents of enolates of α,α-difluoro ketones and useful synthons for difluoro compounds, which provide a wide repertoire of bioactive fluorinated compounds.[1] One of the well-established methods for preparing difluoro enol silyl ethers is dehalogenation from halodifluoromethyl groups.[2] Selective defluorination of the trifluoromethyl group is a promising method for preparing difluoro compounds due to the broad and easy availability of trifluoromethylated compounds. However, there are very few successful cases of the selective demonofluorination from a trifluoromethyl group.[3–7] Recently, we have reported electroreductive methods for difluoro enol silyl ethers[8] and difluoro enamines[9] using trifluoromethyl ketones and imines as starting materials. A key feature of these methodologies is the selectivity of defluorination which derives from the higher reduction potentials of the product enols and enamines than those of the parent keto systems.[8] Here, we report the first successful Mg$^0$-promoted selective defluorination of trifluoromethyl ketones **1** in the presence of TMSCl by means of a process involving C–F bond cleavage [eqn. (1)],[10] which provides a highly efficient access to a variety of 2,2-difluoro enol silyl ethers.



(1)

The reaction procedure is very simple. The mixture of **1a** (6.0 mmol), TMSCl and Mg[11] (12 mmol) in 2.4 ml of anhydrous THF was stirred at 0 °C for 20 min [eqn. (2)].† After filtration, the difluoro enol silyl ether **3a** was obtained in 91% NMR yield.



(2)

Compared to previously available methods, this methodology has several advantages: (i) the starting trifluoromethylated materials are readily available directly from trifluoroacetates; (ii) Mg as a reducing agent is cheap and easy to handle; and (iii) selective formation of 2,2-difluoro enol silyl ethers is achieved in a short reaction time.

As shown in Table 1, the same procedure for the selective formation of **3** works well for a diverse group of aromatic, heteroaromatic and aliphatic ketones, and the over-reduction products were not detected.

In the cases of aromatic and heteroaromatic ketones **1a–f**, the reactions were completed within 25 min at 0 °C in THF (entries 1–6), as compared with the case of aliphatic ketones (**1g** and **1h**) which required DMF as a solvent (entries 7 and 8).[12] Also, aromatic and heteroaromatic ketones **1a–f** generally gave good yields, and the presence of electron-withdrawing and -donating groups had little effect on the yields. Notably, CF$_3$-arene and Cl-arene functionalities were compatible with the present reaction conditions; the reductive cleavage of the benzylic C–F bond[13] or aromatic C–Cl bond[14] did not occur (entries 3 and 4).

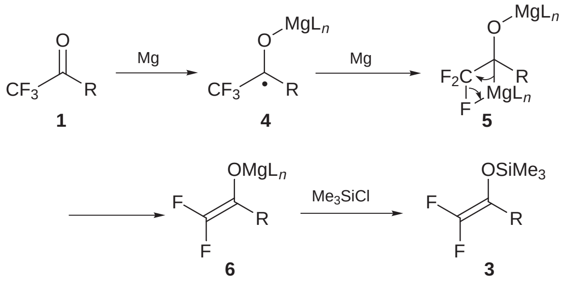
**Table 1** Mg$^0$-promoted defluorinative silylation of trifluoromethyl ketones **1**[a]

| Entry | **1** | R | *T*/°C | *t*/min | Product **3** | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | 0 | 20 | **3a** | 91 |
| 2 | **1b** | 4-MeOC$_6$H$_4$ | 0 | 20 | **3b** | 89 |
| 3 | **1c** | 4-CF$_3$C$_6$H$_4$ | 0 | 20 | **3c** | 87 |
| 4 | **1d** | 4-ClC$_6$H$_4$ | 0 | 20 | **3d** | 98 |
| 5 | **1e** | 2-furyl | 0 | 25 | **3e** | 97 |
| 6 | **1f** | 2-thienyl | 0 | 25 | **3f** | 97 |
| 7[c] | **1g** | C$_6$H$_{13}$ | 0 | 30 | **3g** | 56 |
| 8[c] | **1h** | Cy | 0 | 30 | **3h** | 62 |

[a] Unless otherwise stated, the reactions were performed on a 0.6 mmol scale in THF. [b] NMR yield, which was calculated by $^{19}$F NMR integration of product **3** relative to 1,3-bis(trifluoromethyl)benzene internal standard. [c] DMF was used as solvent, and 8 equiv. of Mg was used.

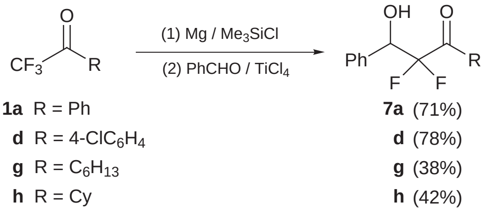
The formation of **3** can be explained by assuming the pathway pictured in Scheme 1. Initially, the intermediate ketyl species **4** is generated in the reaction of Mg$^0$ with a ketone **1**, which is further reduced to anion species **5** by Mg. The resultant β-fluorinated organomagnesium species **5** readily undergoes β-elimination to form **2**. In general, the cleavage of a C–F bond is not easy due to the large bond energy (*ca.* 552 kJ mol$^{-1}$). However, the bond breaking does occur rather easily when the CF$_3$ group is attached to a π-system because electron acceptance into the carbonyl group and subsequent extrusion of the fluoride ion may make large contributions to the driving force of the reaction. The reduction potential of aromatic ketones (**1a–f**) is more negative than that of aliphatic ones (**1g** and **1h**). Therefore, the difference in reactivity between aromatic ketones and aliphatic ones may derive from the tendency to form ketyl anion species **3**.

In particular, utilization of 2,2-difluoro enol silanes **3** is made in aldol reactions.[7] After simple filtration of the metal waste, the crude products **3** were used directly in the next reaction without



**Scheme 1**

purification due to the instability of **3**. When benzaldehyde was added to a solution of **3a** and $TiCl_4$ at −78 °C, the aldol adduct **7a** was formed [eqn. (3)] in 71% isolated yield (from **1a**).



(3)

In conclusion, $Mg^0$-promoted selective defluorination of a series of trifluoromethyl ketones provides a promising route to difluoro enol silanes.

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## Notes and references

† *Typical procedure* for **3a**: To TMSCl (2.6 g, 24 mmol) in freshly distilled THF (24 ml) and Mg (290 mg, 12 mmol) cooled down to 0 °C under an argon atmosphere, trifluoroacetophenone (1.04 g, 6.0 mmol) was added dropwise and then stirred for an additional 20 min. After evaporation of most of the THF, hexane (20 ml) was added to the residue, and the resulting salt was filtered and the filtrate concentrated to give 1.21 g (*ca.* 0.53 mmol) of crude product (the crude product **3a** had purity > 95%).

To a solution of crude **3a** and benzaldehyde (1.27 g, 12 mmol) in $CH_2Cl_2$ (10 ml) cooled down to −78 °C, was added dropwise a solution of $TiCl_4$ (6 mmol) in $CH_2Cl_2$ (10 ml). Then the reaction mixture was quenched with aq. $NH_4Cl$, and the organic layer was washed with brine and dried over $Mg_2SO_4$. Purification of the products by chromatography on silica gel (hexane–EtOAc 5 : 1) provided **7a** (1.18 g, 71% from **1a**) as a colorless oil. *Selected data* for **7d**: 3512 cm$^{-1}$ ($\nu_{OH}$), 1696 cm$^{-1}$ ($\nu_{CO}$); $\delta_H$($CDCl_3$, 200 MHz) 3.05 (d, *J* 3.6, 1 H), 5.35 (ddd, $J_{HF}$ 18.6, 7.6, 3.6, 1 H), 7.2–7.5 (m, 7 H), 7.9–8.0 (m, 2 H); $\delta_F$($CDCl_3$, 188 MHz, $C_6F_6$ as an internal standard) 45.2 (dd, $J_{FF}$ 290.7, $J_{HF}$ 18.6, 1 F), 56.9 (dd, $J_{FF}$ 290.7, $J_{HF}$ 7.6, 1 F).

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