



## Mg–Cu bimetal system for selective C–F bond activation

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### ABSTRACT

Bimetal system of Mg–CuCl in DMI for selective C–F and C–Cl bonds activation has been examined. This article involves (1) a short overview of bimetal system of Mg–metals for selective C–F bond activation, (2) C–F bond activation of alkyl trifluoroacetates leading to alkyl difluoro(trimethylsilyl)acetates via difluoroketene silyl acetal, (3) selective C–Cl bond activation of 3- and 4-chloropentafluoroethylbenzenes, (4) C–F bond activation of substituted benzotrifluorides and (5) microscopic observation of an active site of magnesium surface formed in Mg–CuCl system and elucidation of reaction mechanism of C–Cl and C–F bond activation at the active site.

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### 1. Introduction

C–F bond activation has been one of the current active subjects, which has been utilized for an effective transformation of trifluoromethyl or perfluoroalkyl groups to difluoro or monofluoroalkyl moieties. Even though the C–F bond activation is not easy in general due to the C–F bond strength, mechanism-based rational C–F bond activations have been proposed and actually utilized successfully [1]. Among them, metal magnesium can highly promote the C–F bond activation since it has a reduction potential feasible for C–F bond cleavage as shown in Table 1. And also metal magnesium is easily handled and its use is economically feasible and environmentally friendly [2].

Some of the successful Mg–metal promoted transformations of trifluoromethyl building blocks are shown in Fig. 1 [3].

Meanwhile, metallic Mg possesses potentially unfavorable property for reduction and Grignard reagent preparation, which results in limited reductive power and unfavorable induction period, respectively. To access this problem, some kinds of activations such as elevated reaction temperature, use of an activator such as iodine and 1,2-dibromoethane, ultrasonic irradiation, and vigorous mechanical stirring have been employed for smooth initiation of the desired reaction. The major unfavorable property arises from oxide layer of the Mg metal surface. The activation described above would be dependent on either removal of the oxide layer or cooperation of Lewis acidic self-catalysis by

the generated Mg(II). It is needed for us to devise reaction conditions so as to overcome this unfavorable property.

Another factor for controlling the Mg-promoted defluorination is how to match the LUMO level of a substrate with practical reducing power of metal Mg. The reactivity of trifluoromethyl(CF<sub>3</sub>)-bearing substrates for Mg(0)-promoted reductive defluorination can be explained by LUMO energy levels of the substrates as shown in Supplementary Figs. 2 and 3. The reactivities of the substrates are deduced by reaction times, conversion of the substrates, and product yields and they are lined with the order of LUMO energy levels which are calculated by AM1 geometry optimization of substrates with MacSpartan plus. Supplementary Figs. 2 and 3 indicate that lower LUMO level of  $\pi$ -system of the substrate enables smooth electron transfer from metal Mg and thus gives the defluorinated compounds in higher yields; in the case of higher LUMO level of the  $\pi$ -system, reductive defluorination does not occur or gives products in low yields. The consistency of the product yields of Mg-promoted defluorination-silylation reactions with the order of LUMO energy levels of the substrates seems to be reasonable within the same type of trifluoromethyl and pentafluoroethyl compounds. Meanwhile, whether the defluorination occurs or not is not necessarily consistent with the calculated LUMO energy levels on comparing the reactions of different types of the substrates. For example, defluorination of (pentafluoroethyl)benzene (LUMO = –0.48 eV) does not occur, in contrast, that of trifluoromethyl alkyl ketone (LUMO = –0.29 eV) does under the examined experimental conditions. Thus, the reactivity of the substrates in Mg(0)-promoted defluorination reactions can not be explained only by the LUMO energy levels of the substrates. Other factors such as interactions between substrates and the surface of metal Mg and cooperative

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**Table 1**Reduction potential of metals.  $M^{n+} + ne^- \rightleftharpoons M(0) E^{\circ}[V]$ .

M	Li	K	Na	Mg	Al	Mn	Zn	Ni	H	Cu
$-E^{\circ}$	3.0	2.9	2.7	2.4	1.7	1.2	0.8	0.3	0	-0.3

action of the Mg(II) ion with functional group of substrates may affect feasibility of the substrate reaction.

As shown in Supplementary Figs. 2 and 3, Mg-promoted defluorination of alkyl trifluoroacetates and benzotrifluoride does not proceed under the conventional reaction conditions ever examined in our laboratory. Question is how to activate metal magnesium reduction system so as to realize defluorination of these unreactive substrates.

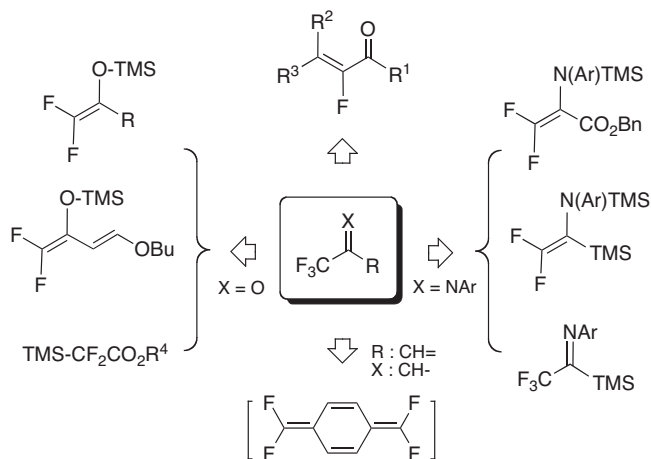
The surface of commercially available magnesium metal is mostly corroded so that freshly generated magnesium like Rieke Mg and Mg-metal alloys have been sometimes used for promoting Grignard reaction of unreactive substrates. Rieke magnesium generated by  $MgCl_2$ -K-I in THF enabled Grignard reaction of 4-fluorotoluene [4]. The Mg-Cu alloy for Grignard reagent generations from *n*-butyl chloride [5], fluorobenzene [6], bromoalkenes [7], and aryl bromides [8] was reported. Benzeneselenenyl copper generated by the reaction of diphenyl diselenide with Mg-Cu bimetals was used for selenation of iodobenzene [9]. A bimetallic system of Mg-MgCl<sub>2</sub>-FeCl<sub>2</sub> in THF was also found to be effective for Grignard reagent generation of aryl chlorides [10].

Keeping in mind the scope and limitation of the Mg-promoted reductive reactions and the activation of metal magnesium ever studied, we have examined Mg-CuCl system in detail so as to enable (1) defluorinative silylation of alkyl trifluoroacetates, (2) chemoselective either defluorination or dechlorination of 4-chloro- and 3-chloro(pentafluoroethyl)benzenes, (3) defluorinative silylation of substituted benzotrifluorides, and finally tried (4) the rational explanation for the mechanism of the defluorination based on the microscopic observation of the Cu-deposited metal magnesium surface. This short account has been written on the bases of doctor thesis of Dr. Shinya Utsumi, Okayama University, Japan (March, 2012) and the summarized results of C-F bond activation over fifteen years in our laboratory.

## 2. Results and discussion

### 2.1. Defluorinative silylation of alkyl trifluoroacetates

$\alpha,\alpha$ -Difluoroacyl moieties ( $RCF_2COX$ ) are important key units for inhibitory activity in pharmaceuticals [11]. And polyfluoroalkyl



**Fig. 1.** Partially fluorinated building blocks prepared by Mg-promoted defluorination of  $CF_3$ -building blocks; TMS =  $SiMe_3$ .

silanes [12] are building blocks useful for nucleophilic polyfluoroalkylation like Ruppert-Prakash reagents [13]. Among them alkyl difluoro(trimethylsilyl)acetates are useful for nucleophilic introduction of difluoroacetate unit and are alternatives for the corresponding Reformatsky and Ullmann reagents [14,15]. They can be prepared by electrochemical reductive [14] or  $SmI_2$ -promoted [16] silylation of alkyl trifluoroacetates **1**. However, more accessible Mg-promoted defluorination protocol is not applicable for the purpose although it works for the corresponding phenyl trifluoroacetate **1** ( $R = Ph$ ) [17]. The LUMO of phenyl trifluoroacetate is lower than those of alkyl trifluoroacetates, which thus enables Mg-promoted reductive defluorination of phenyl trifluoroacetate. The problem which must be solved is how to activate the Mg-system so as to make defluorinative silylation of alkyl trifluoroacetates **1** possible.

We tried Mg/CuCl/TMS-Cl bimetallic system for defluorinative silylation since the conventional Mg/TMS-Cl system ever used successfully for defluorination of trifluoromethyl ketones did not work for the purpose. Metal Mg powder was pretreated with CuCl in the presence of TMS-Cl in DMI at room temperature under Ar atmosphere for 15 min and then alkyl trifluoroacetates **1** were added to the suspension of Mg/CuCl/TMS-Cl in DMI. The reaction mixture was stirred at room temperature for 4 h (Ref. [18] for experimental details of removal of silyl acetal **3** and isolation of the desired ethyl 2, 2-difluoro-(2-trimethylsilyl)acetates **2**. Among Mg metal, Mg powder was found to be more useful than Mg turning and Mg ribbon.

The sole use of metal Mg was totally ineffective. In contrast, the combined use of metal Mg with CuCl (0.5 eq) induced the desired reaction dramatically. Any other combinations of  $FeCl_3$ ,  $NiCl_2$ , and Zn dust with metal Mg were useless. Interestingly, metal Cu instead of CuCl was also ineffective, suggesting freshly generated Cu(0) on metal Mg may act effectively for reductive defluorination. The microscopic observation of Mg-Cu bimetallic system is discussed in Section 2.4.

The solvent DMI was found to be the best for both conversion and yield of **2** so far as examined; solvent (Conv. %, yield of **2**, %) DMI (100%, 62%), DMF (30%, 8%), NMP (64%, 14%), DMI/THF (22%, 5%), THF (24%, 2%), MeCN (14%, 4%). Optimization of the reaction conditions resulted in the best conditions for defluorinative silylation of alkyl trifluoroacetates [Mg (4 eq)/CuCl (0.5 eq)/LiCl (8 eq)/TMS-Cl (8 eq) in DMI, room temperature for 4 h] [18,19]. The desired products **2**, 2-difluoro-2-(trimethylsilyl)acetates **2** were obtained under the optimized conditions in the range of 60–68% isolated yields as shown in Supplementary Table 2 [20]. The proposed reaction mechanism is shown in Scheme 1 [18]. Stepwise reaction sequence; first electron transfer  $\rightarrow$  trapping anion radical with TMS-Cl  $\rightarrow$  second electron transfer leads to the formation of intermediate **5** which undergoes either defluorination or trapping with TMS-Cl [21] resulting in formation of **2** or **3**, respectively (Scheme 2).

### 2.2. Selective defluorination and dechlorination of 3- and 4-chloro(pentafluoro-ethyl)benzenes

Defluorinative silylation of 3-chloro(pentafluoroethyl)benzene **6** proceeds smoothly and quantitatively at 0 °C, affording 3-chloro-[(1'-trimethylsilyl)tetrafluoroethyl]benzene **9** under the conventional Mg/TMS-Cl/DMPU system, in which no dechlorination was observed [22]. Meanwhile, the corresponding 4-chloro-substrate

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