Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2419–2424
Tetrahedron
www.elsevier.com/locate/tet

Unusual reactions of Grignard reagents toward fluoroalkylated esters

Takashi Yamazaki*, Tsukasa Terajima, Tomoko Kawasaki-Taskasuka

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei 184-8588, Japan

Received 7 November 2007; received in revised form 27 December 2007; accepted 2 January 2008
Available online 6 January 2008

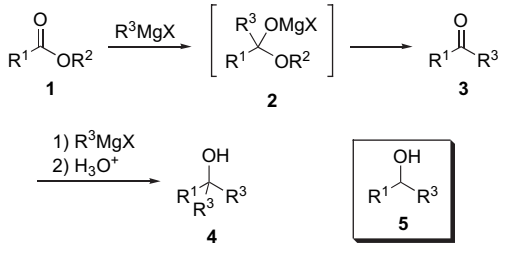
Abstract

Fluorine-containing esters were demonstrated to be convenient substrates for construction of the corresponding ketones by low temperature reaction with Grignard reagents followed by warming up to 0 °C, while heating the mixture up to 80 °C readily promoted the reduction of the ketones obtained by the generated magnesium alkoxides whose mechanism was speculated as Meerwein–Ponndorf–Verley type reduction by computational technique.

Keywords: Grignard reagents; Fluoroalkyl groups; Meerwein–Ponndorf–Verley reductions

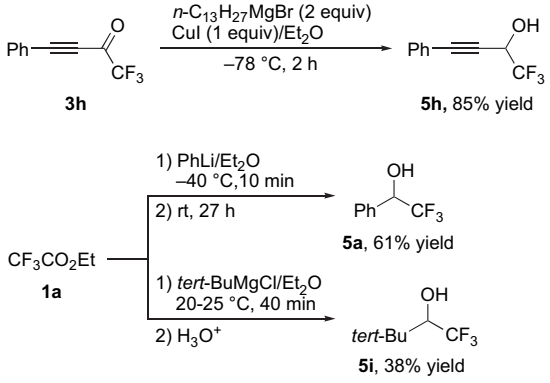
1. Introduction

Elaboration from simple substrates is usually required for the construction of desired fluorinated molecules because of their structurally limited availability from commercial suppliers, especially in the case of aliphatic materials.[1] Grignard reactions with readily obtained perfluorinated esters **1** are one of the widely employed methods for the preparation of the corresponding ketones **3** as convenient synthetic intermediates (Scheme 1). This interesting and convenient process can be utilized since the strong electron-withdrawing nature of perfluoroalkyl moieties significantly contributes to the stabilization of the tetrahedral intermediates **2**, which removes a chance to accept further attack of the second Grignard molecule. In fact, Creary has already demonstrated that ethyl trifluoroacetate **1a** (R^1=CF_3, R^2=C_2H_5) afforded trifluoroacetophenone **3a** (R^1=CF_3, R^3=Ph) in 86% yield on reaction with PhMgBr without formation of the tertiary alcohol **4a** (R^1=CF_3, R^2=R^3=Ph).[2]



Scheme 1.

In spite of such easy and convenient process,[3] it has been reported that this type of method sometimes did not work properly and the product was contaminated with unexpected secondary alcohols **5**.[4] For example, as shown in Scheme 2,



Scheme 2.

* Corresponding author. Tel./fax: +81 42 388 7038.
E-mail address: tyamazak@cc.tuat.ac.jp (T. Yamazaki).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.015

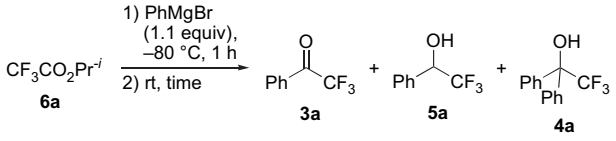
Linderman found out that the propargyl ketone **3h** with a CF_3 group was reduced to the corresponding alcohol **5h** whose mechanism was experimentally proved to be by way of the β-hydride elimination of the Grignard reagent, *n*-$C_{13}H_{27}MgBr$, by capture of the resultant 1-tridecene.[4c] However, similar alcohol **5a** or **5i** was also obtained by treatment of ethyl trifluoroacetate **1a** with PhLi[4a] or *tert*-BuMgCl,[4c] respectively, while none of these organometallic species possessed appropriate hydrogen atoms β to the metals.

When we recently tried the reaction of PhMgBr and isopropyl trifluoroacetate **6a** in a THF solvent, 2,2,2-trifluoro-1-phenyl-ethanol **5a** was isolated as the major product in 42% yield. However, as long as we concerned, no literature has disclosed why and how such secondary alcohols are formed in the reaction of fluorinated esters and Grignard reagents without requisite β-hydride, which prompted us to start our basic study for clarification of this unanswered process.

2. Results and discussions

At first, we have investigated in detail the model reaction using isopropyl trifluoroacetate **6a** and PhMgBr under various conditions after addition of the latter at −80 °C and stirring for 1 h at the same temperature (Table 1). It is readily understood that involvement of THF as the reaction medium (entries 1–4) was apparently inappropriate for the clean construction of the desired 2,2,2-trifluoroacetophenone **3a**. It is interesting to note that THF even as the Grignard solvent (shown in parentheses in Table 1) was quite effective in alteration of the reaction course (for example, entry 2 vs 5 and 3 vs 8) although only about 1 mL of a Grignard solution was added to 5 mL of the reaction solvent. Thus, exclusion of THF was crucial for the selective preparation of either the ketone **3a** or the alcohol **5a**. The lower temperature with shorter reaction time seemed to lead to preferential ketone formation as the result of suppressive production of both alcohols **4a** and **5a** (entry 6 vs 7 and 10 vs 12). On the other hand, extension of the reaction time drastically changed the product distribution and the reduced material **5a** became the major component (entry 5 vs 6 and 8 vs 9 and 10). The present investigation eventually allowed us to select the conditions in entry 7 or 12 for the effective construction of fluorinated ketones **3** and the one in entry 9 for the one-pot formation of the corresponding secondary alcohols **5**. When the desired ketones **3** are expected to possess relatively lower boiling points, entry 7 would be the route of choice. On the other hand, because heating the reaction mixture was found to facilitate the in situ reduction of the ketones **3** (vide infra), utilization of toluene would be recommended for selective construction of secondary alcohols **5**.

Table 1
Investigation of reaction conditions[a]

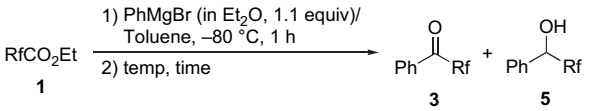


Entry	Solvent[b,c]	Time (h)	^{19}F NMR yield (%)		
			3a	**5a**	**4a**
1	THF (THF)	1	4	19	21
2	Et_2O (THF)	1	4	24	22
3	Tol (THF)	1	0	51	12
4	THF (Et_2O)	1	10	56	19
5	Et_2O (Et_2O)	1	69	8	6
6	Et_2O (Et_2O)	5	2	58	1
7[d]	Et_2O (Et_2O)	1	93[e]	0	11
8	Tol (Et_2O)	1	63	13	9
9	Tol (Et_2O)	2	10	88[f]	0
10	Tol (Et_2O)	5	0	77	<1
11[d]	Tol (Et_2O)	1	80	1	1
12[d]	Tol (Et_2O)	5	94[g]	6	1

[a] Grignard reagent (ca. 1 mol/L) solution was used after titration.
[b] In the parenthesis was shown the solvent for the Grignard reagent.
[c] Tol: toluene.
[d] Reaction temperature of 0 °C was maintained for the second step.
[e] Yield of 81% was attained after Kugelröhr distillation.
[f] Isolated yield of 83% was attained after chromatographic separation.
[g] Yield of 78% was attained after chromatographic separation.

For validation of these two independent reaction conditions, various types of fluorine-containing esters were employed as the substrates whose results are summarized in Table 2. Employment of less expensive and more easily available ethyl trifluoroacetate **1a** instead of the corresponding isopropyl ester **6a** and stirring the mixture for 1 h at −80 °C followed by additional 1 h at 0 °C furnished the ketone **3a** in 76% isolated yield along with only a trace amount of the further reduced material **5a** (entry 1). On the other hand, elongation of the reaction time to 24 h at ambient temperature affected the composition of the products dramatically and the secondary alcohol **5a** became predominant (75% yield, entry 2). Total disappearance of the ketone **3a** was accomplished only in 1 h at the elevated temperature (entry 3). Although these reactions were carried out in dehydrated toluene, entries 4 and 5 described the examples using the usual solvent: thus, the cheapest toluene (>99.0%, see the footnote of Table 2) was employed for this transformation without any pretreatment, which attained almost identical results in the same 1 mmol (entry 4) and even 50 mmol (entry 5) scale. Entries 6–8 demonstrated effectiveness of the present procedure: when $PhCH_2CH_2MgBr$ was employed as the representative sp^3-type Grignard reagent instead of PhMgBr with the sp^2-hybridized reaction center, basically the same results were recorded and the selective preparation of the ketone **7a** or alcohol **8a** was realized in a similar fashion, just by changing the reaction temperature and/or time. Ethyl chlorodifluoroacetate **1b** was found to work well and stirring at 0 °C for a short time (ca. 5 min) allowed to produce the ketone **3b** while the higher temperature was required for the reductive transformation into the corresponding alcohol **5b** (entries 9–11). On the other hand, the lower halogen content of an Rf group changed the situation. Thus, chlorofluoroacetate **1c** participated nicely in the ketone construction by brief stirring at 0 °C after its mixing with the Grignard reagent at −80 °C for 1 h, while increasing the temperature to 80 °C did not affect the reduction at all with partial decomposition of the initially obtained ketone **3c** (entries 12–14). Reactions of trichloroacetate **1d**[5]

Table 2
Reaction of phenylmagnesium bromide with a variety of fluorine-containing esters



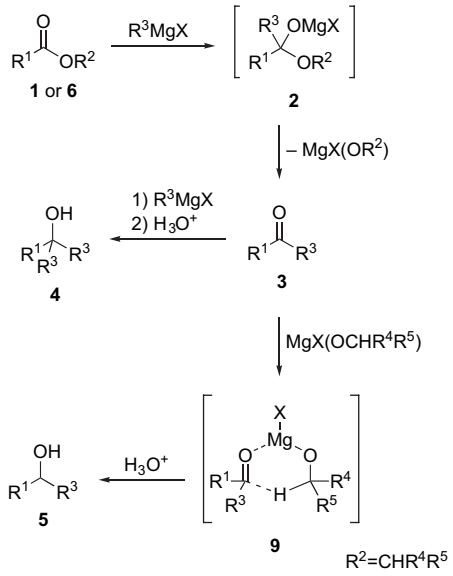
a: Rf=CF_3, b: Rf=$CClF_2$, c: Rf=CHClF
d: Rf=CCl_3, e: Rf=CH_3, f: Rf=CF_3CF_2

Entry	Rf	Temp (°C)	Time (h)	^{19}F NMR yield[a] (%)	
				3	**5**
1	CF_3	0	1	96 [76]	1
2		rt	24	3	84 [75]
3		80	1	0	84 [79]
4[b]		80	1	0	80 [79]
5[b,c]		80	1	0	[70]
6[d]		0	5	82 [75]	2
7[d]		rt	24	2	79 [82]
8[d]		80	0.5	0	79 [78]
9	CF_2Cl	0	0.1	62 [59]	0
10		rt	24	16	60
11		80	1	7	73 [71]
12	CHClF	0	0.1	87 [82]	0
13		rt	24	34	13
14		80	1	48	0
15	CCl_3	0	1	[10][e]	0
16	CH_3	0	1	0	[56][f]
17	CF_3CF_2	rt	5	9	11
18[g]		rt	3	0	68 [69]
19		−80	4	29	0
20[h]		−80	2	57 [46]	1

[a] In the bracket was shown the isolated yield.
[b] Toluene (>99.0%), the cheapest (extra pure) grade purchased from Kanto Chemical Co., Inc., Japan, was used instead of the corresponding dehydrated toluene.
[c] The reaction was performed in a 50 mmol scale.
[d] CF_3CO_2i-Pr **6a** was used as the substrate and reacted with $PhCH_2CH_2MgBr$. The products obtained were **7a** and **8a** instead of **3a** and **5a**, respectively.
[e] A complex mixture was obtained along with this ketone.
[f] Isolated yield of 1,1-diphenylethanol.
[g] PhMgBr (2 equiv) was employed with stirring for 3 h at the first step, and then warming up to rt after addition of 2.2 equiv of *i*-PrOH.
[h] PhMgBr (3 equiv) was employed.

(entry 15) was found to proceed sluggishly affording a large amount of unidentified mixtures, and nonfluorinated ethyl acetate **1e** (entry 16) only furnished the tertiary alcohol **4e** by the way of the second nucleophilic attack of PhMgBr to the in situ generated ketone **3e**.[6] The present method was also applicable to ethyl pentafluoropropionate **1f**, which showed slight decrease in reactivity. This system seemed to require an excess amount of PhMgBr for attainment of higher conversion, for example, addition of threefold excess of the Grignard reagent realized the formation of the ketone **3f** in an acceptable yield (entry 20), while this yield diminished to half by using a standard amount (1.1 equiv) of the nucleophile (entry 19). This ester **1f** also led to the straightforward synthesis of the corresponding secondary alcohol **5f** with the aid of *i*-PrOH as the effectively accelerating additive (entry 18).

At this point, we have postulated the present reaction mechanism as described in Scheme 3. Thus, as expected, Grignard

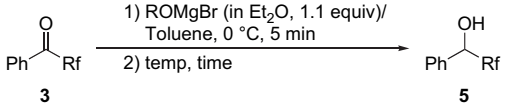


Scheme 3. Possible reaction mechanism.

reagents R^3MgX would initiate this transformation by nucleophilically attacking at the ester carbonyl carbon atom to furnish the tetrahedral intermediates **2**. When ethyl acetate **1e** was employed as the substrate and reacted with PhMgBr, the electron-donating methyl group as R^1 should destabilize **2** (R^2=Et) to smoothly yield acetophenone **3e** with releasing MgBr(OEt). Thus, this ketone **3e** is exposed to other PhMgBr molecules at an earlier stage and, as a result, readily transformed into 1,1-diphenylethanol **4e** by reaction with the second Grignard molecule (entry 14 in Table 2). In quite sharp contrast, attachment of strongly electron-withdrawing fluorinated moieties as R^1 should render such ester **1** or **6** more electrophilic and the life-time of the intermediates **2** longer at low temperature. Thus, when these ester **1** or **6** would be quickly transformed into **2** at −80 °C, a large portion of the Grignard reagents has been consumed, and slow decomposition of **2** by raising the temperature liberated the electrophilically sensitive **3** to which $MgX(OR_2)$ would start the hydride delivery by way of the Meerwein–Ponndorf–Verley (MPV) type reduction mechanism[7] to eventually produce the unexpected secondary alcohols **5**. However, a stronger Lewis basic solvent THF would coordinatively weaken the Mg–O bond in **2** affecting its collapse into the corresponding ketones **3**, which consistently explained the experimental results on the formation of approximately 20% of the undesired tertiary alcohol **4a** in entries 1–4 in Table 1. On the other hand, utilization of ether or toluene with lower Lewis basicity improved the situation and the yield of the byproduct **4a** was effectively suppressed to at most 10%.

For validation of this hypothesis, the phenyl ketones **3** were independently subjected to a toluene solution containing magnesium alkoxides[7a] freshly prepared by simple mixing of PhMgBr and appropriate alcohols at 0 °C (Table 3). In the case of 2,2,2-trifluoroacetophenone **3a**, magnesium ethoxide was not found quite effective for realization of a high level of conversion at room temperature, while *i*-PrOMgBr

Table 3
Reduction of fluorinated ketones **3** with appropriate magnesium alkoxides



3 **5**

Entry	Rf	R	Temp (°C)	Time (h)	^{19}F NMR yield[a]	
					5	**3**
1	CF_3	Et	rt	5	49	37
2		Et	80	1	[66]	0
3		*i*-Pr	rt	1	[80]	0
4		*n*-C_6H_{13}	rt	5	[78]	1
5		*tert*-C_4H_9	rt	5	5	70
6	CF_3CF_2	*i*-Pr	rt	1	[76]	0
7	CH_3	*i*-Pr	Reflux	5	[80]	[20]

[a] In the bracket was shown the yield after isolation.

promoted the hydride delivery significantly smoothly (entry 1 vs 3). Similar trend was also observed for pentafluoropropiophenone **3f** (entry 6). Comparison of entries 3 and 6 with 7 unambiguously indicated how easily ketone **3a** or **3f** with perfluorinated moieties were converted into the corresponding alcohol **5a** or **5f**, respectively; although nonfluorinated acetophenone **3e** was reduced to 1-phenylethanol **5e** in 80% yield, refluxing in toluene for 5 h seemed not enough to reach to completion which was in sharp contrast to the case of the fluorine-containing substrates **3a** and **3f**, only 1 h at room temperature being sufficient. Magnesium isopropoxide was demonstrated to be the reagent with the highest reactivity among other alkoxides tested, and no reaction was basically occurred by *tert*-butoxide without containing any appropriate β-hydride to magnesium.[8]

These experimental data led to assumption that success of this MPV transformation would be primarily related to the electron-withdrawing characteristics of the ester substituent R^1 (Scheme 3), leading to lowering the LUMO energy level[9] which resulted in increase of accepting ability of Grignard reagents as well as hydride from the magnesium alkoxide species. In Table 4 was described computational information including the charges at the C=O groups and the LUMO energy levels for phenyl ketones **3** with various fluorinated alkyl groups.[9] First of all, as reported previously[10] it is apparent from the NBO charge of the carbonyl carbon atom that the stronger electron-withdrawing group activated the carbonyl moiety toward nucleophilic attack by lowering the LUMO energy level, not by making the C=O carbon more positive.[11] In addition, the LUMO energy gap at least in part adequately explained distinct reactivity difference of *i*-PrOMgBr toward **3a** and **3e** with CF_3 and CH_3 groups, respectively (Table 3, entry 3 vs 7). Although the ketones **3a**, **3b**, and **3d** possessed the similar LUMO values, unlike chlorodifluorinated ester **1b** showing analogous trend to the trifluorinated **1a**, trichloroacetate **1d** only afforded a complex mixture of chlorinated materials with the yield of the desired ketone **3d** extremely low (entry 13 in Table 2). For gaining some insight into this strikingly contrasting outcome, we have carried out computation of the stationary points for the anion radical species both derived from **3a** and **3d** because the single electron transfer (SET) process is known to be one of the major side reactions of Grignard reagents[12] (Table 5). The most distinguishing point is the appreciable 102 pm elongation of the C^2–Cl^3 bond in **10d** when compared with the corresponding neutral species **3d**, while only as short as 3 pm difference was observed between the trifluorinated **10a** and **3a**. The fact that the C^1–C^2 bond of **10d** was contracted by 13 pm and the sum of the angles around the C^2 atom (Cl^1–C^2–C^1, Cl^2–C^2-C^1, and Cl^1–C^2–Cl^2) was 353.3° led to speculation that the **10d** structure has significantly changed to the one analogous to enolate by SET mechanism. This would elucidate at least in part why the reaction between trichloroacetate **1d** and PhMgBr proceeded sluggishly, which would be attributed to the possible aldol type sequence by way of the enolates directly from **1d** and/or from the in situ obtained 2,2,2-trichloroacetophenone **3d**.[13]

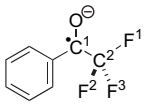
The present MPV reduction was also computationally analyzed[9] by using the model reaction system of isopropoxy magnesium chloride and acetone or 1,1,1-trifluoroacetone with dimethyl ether coordinating to magnesium so as to fill its vacant site since the authors could not find out the theoretical consideration of this MPV system after the pioneering work by the Houk's group.[14] Transition states **13a** and **13e** (TSs), confirmed by a single imaginary frequency,[15] were found to possess the six-membered chair-like structure. In spite of their similar appearance, the relatively large difference was noticed between their activation energies of 14.17 and 5.12 kcal/mol for the non- (**13e**) and trifluorinated (**13a**) TSs, respectively. The earlier TS of the latter was specifically characterized by the cleaving $C^1\cdots H$ and forming $C^2\cdots H$ bond lengths of

Table 4
NBO charges of C=O groups and LUMO energy levels[9]

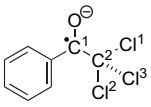
R^3 in **3**[a]	NBO charge		Energy level of LUMO (eV)
	C=O	C=*O*	
CH_3 (**e**)	0.559	−0.557	−1.929
CHClF (**c**)	0.514	−0.509	−2.568
$CClF_2$ (**b**)	0.493	−0.502	−2.771
CF_3 (**a**)	0.481	−0.500	−2.768
CCl_3 (**d**)	0.525	−0.509	−2.690

[a] R^1=Ph.

Table 5
Representative parameters for **3a**, **3d**, **10a**, and **10d** obtained by ab initio calculation[9]



10a



10d

	Bond length (pm)					Angles around C^2 (°)[a]
	C^1–C^2	C^1–O	C^2–X^1	C^2–X^2	C^2–X^3	
10a	152.0	127.0	134.8	138.4	138.4	341.3
3a	156.4	120.7	133.0	135.4	135.4	333.3
10d	145.3	123.3	174.7	173.2	282.6	353.3
3d	158.3	120.4	178.0	180.6	180.6	329.1

[a] Sum of the angles of X^1–C^2–C^1, X^2–C^2–C^1, and X^1–C^2–X^2 (X: F or Cl).

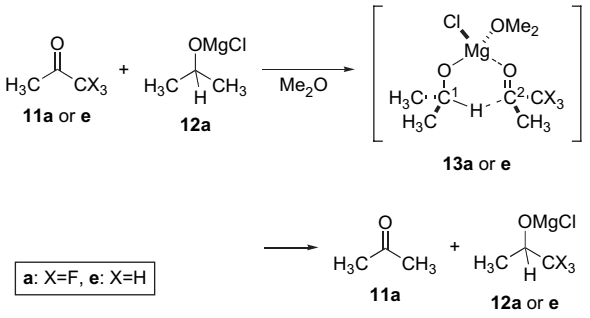


Figure 1. Transition state structure of **11**.

121.9 and 161.6 pm, which were calculated to be 10 and 46% longer than the ones of the corresponding substrate **12e** and product **12a**. On the other hand, the same bonds in the non-fluorinated TS **13e** were 134.4 and 136.4 pm in length, which explained 21 and 23% elongation. This small discrepancy would stem from a slight distortion from the expected C_s symmetry due to the Me_2O molecule. Such nature allowed **13a** to possess 10 pm longer distance between the two methyl groups attached to the upper side of both C^1 and C^2, which should result in the less steric hindrance and eventually contribute to decrease the activation energy. In addition to the lower activation energy already shown above, the strong energetic stabilization of the product combination in the fluorinated case by 20.66 kcal/mol relative to the substrate system would be, of course, one of the most important driving force of the present reaction on the basis of the thermodynamically controlled nature due to the low activation energy (Fig. 1).

3. Conclusion

As described above, the present study offers the product selective preparation of either ketones **3** or their reduced forms **5** where trifluorinated esters **1a** and **6a** were found to be the most potent substrates among other fluorinated esters tested.[16] It is worthwhile to note that transformation to the latter alcohols **5**, following to the well-known MPV reduction of the former ketones **3** as suggested by the present computation, is the quite convenient and economical route because it proceeded in a one-pot manner without addition of any other reducing agents.

4. Experimental

*4.1. Preparation of secondary alcohols **5***

Reaction of PhMgBr and isopropyl trifluoroacetate **6a** was described as the representative example.

Method 1: To a 30 mL two-necked flask under an argon atmosphere containing isopropyl trifluoroacetate **6a** (0.14 mL, 1.0 mmol) and anhydrous toluene (5 mL) at −80 °C was added 1.1 mL of PhMgBr (1.0 mol/L in Et_2O, 1.1 mmol) and stirring was continued for 1 h at that temperature. After 2 h stirring at room temperature and quenching the mixture with 2 mL of a 1 mol/L HCl aqueous solution and usual workup furnished a crude material, which was purified by distillation to give 0.155 g of 2,2,2-trifluoro-1-phenylethanol **5a** (0.880 mmol) in 88% yield.

Method 2: To a 30 mL two-necked flask under an argon atmosphere containing 2-propanol (91.8 μL, 1.2 mmol) and anhydrous toluene (5 mL) at 0 °C was added 1.1 mL of PhMgBr (1.0 mol/L in Et_2O, 1.1 mmol) and stirring was continued at the same temperature for 0.5 h. To this solution was added 2,2,2-trifluoroacetophenone **3a** (0.174 g, 1.0 mmol) in toluene (1 mL) and the whole mixture was stirred for 1 h at 0 °C. After quenching the mixture with 2 mL of a 1 mol/L HCl aqueous solution and usual workup furnished a crude material, which was purified by distillation. 2,2,2-Trifluoro-1-phenylethanol **5a** (0.140 g, 0.795 mmol) was obtained in 80% yield.

*4.1.1. 2,2,2-Trifluoro-1-phenylethanol (**5a**)*[17]

R_f=0.45 (*n*-hex/AcOEt=3:1); ^{1}H NMR δ 2.82 (1H, s), 5.01 (1H, q, J=7.2 Hz), 7.40−7.47 (5H, m); ^{19}F NMR δ −79.55 (d, J=7.2 Hz); bp 85 °C (2.0 kPa).

*4.1.2. 2-Chloro-2,2-difluoro-1-phenylethanol (**5b**)*[18]

Yield: 71%; R_f=0.48 (CH_2Cl_2); ^{1}H NMR δ 3.20 (1H, s), 5.04 (1H, q, J=8.1 Hz), 7.38−7.42 (3H, m), 7.47−7.48 (2H, m); ^{19}F NMR: δ −66.03 (1F, dd, J=9.6, 176.9 Hz), −64.04 (1F, dd, J=7.2, 174.5 Hz).

*4.1.3. 2-Chloro-2-fluoro-1-phenylethanol (**5c**)*[19]

NMR yield: 7 and 6% as an inseparable diastereomer mixture. R_f=0.31 (*n*-hex/Acetone=3:1); ^{1}H NMR δ 2.76 (1H, s), 4.91 (1H, dd, J=5.4, 12.9 Hz) and 4.94 (1H, dd, J=5.4, 9.0 Hz), 6.15 (1H, dd, J=5.4, 51.1 Hz) and 6.15 (1H, dd, J=5.4, 49.6 Hz), 7.37−7.40 (5H, m); ^{19}F NMR: δ −145.26 (dd, J=14.7, 53.5 Hz) and −141.58 (dd, J=9.6, 53.2 Hz).

*4.1.4. 2,2,3,3,3-Pentafluoropropiophenone (**5f**)*[20]

Yield: 69%; R_f=0.52 (*n*-hex/AcOEt=3:1); ^{1}H NMR δ 2.54 (1H, d, J=4.8 Hz), 5.12 (1H, ddd, J=5.1, 7.5, 16.8 Hz), 7.41−7.46 (5H, m); ^{19}F NMR δ −131.11 (1F, dd, J=19.5, 293.2 Hz), −123.11 (1F, dd, J=7.2, 293.2 Hz), −82.46 (3F, s); bp 120 °C (2.0 kPa).

*4.1.5. 1,1,1,-Trifluoro-4-phenyl-2-butanol (**8a**)*[21]

Yield: 78%; R_f=0.27 (*n*-hex/AcOEt=3:1); ^{1}H NMR δ 1.87−2.08 (2H, m), 2.10 (1H, d, J=6.9 Hz), 2.69−2.80 (1H, m), 2.86−2.94 (1H, m), 3.83−3.96 (1H, m), 7.19−7.33 (5H, m); ^{19}F NMR δ −81.12 (d, J=7.2 Hz).

References and notes

1. (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006; (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3; (c) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, Germany, 2000; (d) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha Scientific: Tokyo, Japan, 1998.
2. Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.
3. (a) Dishart, K. T.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 2268; (b) Wagner, P. J.; Truman, R. J.; Puchalski, A. E.; Wake, R. *J. Am. Chem.*

Soc. **1986**, *108*, 7727; (c) Lin, J.-T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem*. **1987**, *52*, 3211; (d) Hamada, H.; Shiromoto, M.; Funahashi, M.; Itoh, T.; Nakamura, K. *J. Org. Chem*. **1996**, *61*, 2332.

4. (a) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Fluorine Chem*. **1981**, *18*, 117; (b) Roberts, D.; Hall, E. W. *J. Org. Chem*. **1988**, *53*, 2573; (c) Linderman, R.; Lonikar, M. S. *J. Org. Chem*. **1988**, *53*, 6013; (d) Gorbunova, M. G.; Gerus, I. I.; Kukhar, V. P. *J. Fluorine Chem*. **1993**, *65*, 25.
5. When ethyl trichloroacetate was added to an ethereal solution of PhMgBr (4 equiv) at 0 °C and then refluxing for 1.5 h furnished an almost quantitative amount of PhCl, see: Kaluszyner, A.; Reuter, S. *J. Am. Chem. Soc*. **1953**, *75*, 5126.
6. In Ref. 2, Creary reported basically identical result for the reaction of PhMgBr and ethyl acetate in ether at −78 °C, followed by warming to rt leading to the exclusive formation of the tertiary alcohol 1,1-diphenylethanol in 96% yield.
7. For the MPV reductions using fluorine-containing substrates, see: Kellogg, R. M. *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M., Eds.; Pargamon: Oxford, 1991; p 88; (a) Nasipuri, D.; Bhattacharya, P. K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 576; (b) Sokeirik, Y. S.; Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem*. **2006**, *127*, 150; (c) Sokeirik, Y. S.; Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett*. **2006**, *47*, 2821.
8. Although this yield should be theoretically zero, a small amount of contaminant might cause this reaction.
9. Computation was carried out by Gaussian 03W using B3LYP/6-311++G** (except for the TS **13** as well as the substrates and products (**11** and **12**) in Figure 1 using B3LYP/6-31+G*) level of theory. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision B.03*; Gaussian: Wallingford, CT, 2004.
10. Linderman, R. J.; Jamois, E. A. *J. Fluorine Chem*. **1991**, *53*, 79.
11. This result would be supported by the ^{13}C NMR chemical shifts of **3a** (δ 179.59 (q, J=34 Hz)) and **3e** (δ 197.94), clearly indicating more deshielded circumstance of the carbonyl carbon atom of **3e**, see: Asao, N.; Asano, T.; Yamamoto, Y. *Angew. Chem., Int. Ed*. **2001**, *40*, 3206.
12. For example, Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic: New York, NY, 1995; Chapter 6.
13. A small amount of the aldol product (ca. 5% yield) was also detected in the case of trifluorinated case. The similar situation was occurred for the related system in Ref. 7b.
14. Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc*. **1987**, *109*, 906.
15. Imaginary frequencies for these TSs were obtained as $-201.28\ cm^{-1}$ for **13a** and $-525.17\ cm^{-1}$ for **13e**.
16. Very recently, the similar type of reaction was appeared using a combination of RfMgBr and Ti(O*i*-Pr)$_4$, see: Mikami, K.; Murase, T.; Itoh, Y. *J. Am. Chem. Soc*. **2007**, *129*, 11686. Moreover, Oppenauer oxidation by using the high electrophilicity of trifluoroacetone was also reported. Mello, R.; Martínez-Ferrer, J.; Asensio, G.; González-Núñez, M. E. *J. Org. Chem*. **2007**, *72*, 9376.
17. Sibille, S.; Mcharek, S.; Perichon, J. *Tetrahedron* **1989**, *45*, 1423.
18. Kitazume, T.; Asai, M.; Tsukamoto, T.; Yamazaki, T. *J. Fluorine Chem*. **1992**, *56*, 271.
19. Kitazume, T.; Takeda, M. Jpn. Kokai Tokkyo Koho JP 01233244, 1989.
20. Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem*. **1987**, *52*, 2481.
21. Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayaka, C. H. *Org. Lett*. **2005**, *7*, 2193.