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Facile one-pot preparation of allylic alcohols with a fluorine-containing alkyl group at the γ-position

Takashi Yamazaki *, Masashi Ichikawa, Tomoko Kawasaki-Takasuka, Shigeyuki Yamada

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

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ABSTRACT

A useful one-pot preparation method of allylic alcohols with fluorinated alkyl groups at the γ position was developed from the corresponding enoates by way of the DIBAL-mediated half reduction, followed by nucleophilic attack of Grignard reagents to aldehydes equilibrating with aluminium acetals.

1. Introduction

In the field of synthetic chemistry, allylic alcohols have been regarded as one of the most important class of compounds and widely employed as versatile substrates for Claisen rearrangement [1], Sharpless epoxidation [2], Diels–Alder reactions [3], and so forth [4]. This is also the case for fluorine-containing counterparts, and for example, redox isomerization [5], palladium-catalyzed S_N2' reactions [6], osmium-catalyzed diol formation [7] have been published in this decade starting from allylic alcohols with a γ-CF_3 substituent [8]. In our hand, because of ready availability of 4,4,4-trifluorobut-2-enoates by way of Horner–Wadsworth–Emmons reactions using such commercially available aldehyde equivalents as trifluoroacetaldehyde hydrate or hemiacetals [9], our initial plan to construct such allylic alcohols were to synthesize α,β-unsaturated ketones by nucleophilic 1,2-addition of appropriate Grignard reagents at low temperature [10], followed by $NaBH_4$ reduction, but this route was found not to give any fruitful results. Then we have started our investigation to develop a new and efficient pathway to get access to the title compounds from fluorinated enoates as substrates, whose results are reported below.

2. Results and discussion

Our fundamental concept was based on the consideration that the intermediary aluminium acetal **Int-A** obtained by the DIBAL reduction of enoates **1** at −80 °C would afford, with release of an aluminium alkoxide molecule, the corresponding aldehydes **3** which would be then conveniently trapped *in situ* by such representative nucleophiles like Grignard or lithium reagents (Scheme 1) [11]. This method should be superior to the previously reported procedure due to no requirement of isolation of reactive and tough-to-handle intermediary aldehydes **3** [12]. Following to this scheme, a small excess amount of DIBAL (1.1 equiv.) was subjected to a THF solution containing benzyl (*E*)-4,4,4-trifluorobut-2-enoate **1aa** at −80 °C, and the whole mixture was stirred for 1 h at the same temperature. At this point, disappearance of the substrate **1aa** was noticed by TLC analysis with observation of the resultant benzyl alcohol, which was the clear proof of complete consumption of **1aa** and formation of **Int-A**. To this flask was added PhMgBr, and the reaction was continued further 1 h with keeping the temperature at −80 °C, but this protocol afforded only a small amount of the desired product **4aa** (Table 1, entry 1). Increase of the amount of the Grignard reagent to 1.5 equiv. did not affect the outcome at all (entry 2), and only a complex mixture was formed by raising the reaction temperature from −80 to 0 °C after addition of PhMgBr (entry 3). However, alteration of the solvent from THF to Et_2O apparently affected the present system and 1.5 equiv. loading of PhMgBr led to isolation of **4aa** in 59% yield, but unfortunately with low reproducibility (entry 6). Interesting to note was the deteriorating effect of THF, leading to failure of the reaction even in

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

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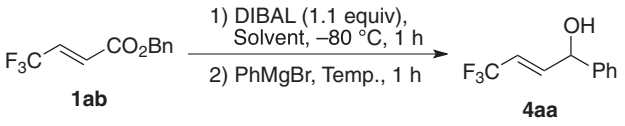
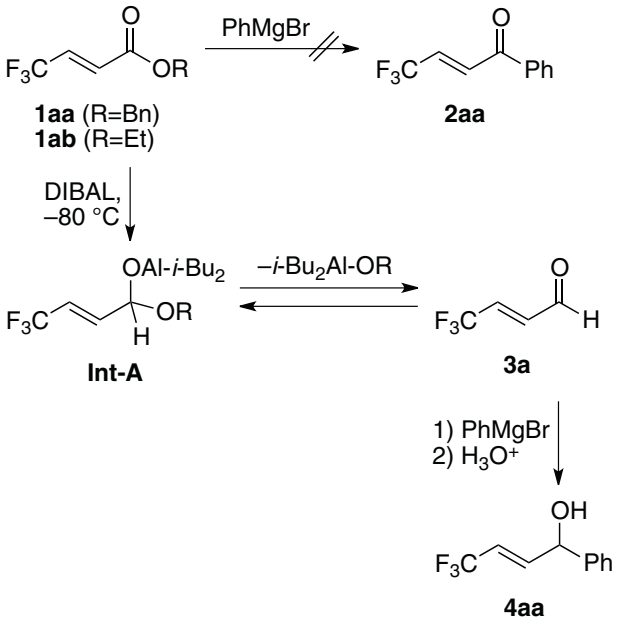
Table 1
Investigation of reaction conditions



Entry	Solvent	PhMgBr (equiv.)	Temp. (°C)	Yield of **4aa**[a] (%)
1	THF	1.1	−80	(5)
2	THF	1.5	−80	(5)
3	THF	1.1	−80 to 0	Complex
4[b]	Et_2O	1.1	−80	Trace
5	Et_2O	1.1	−80	(14)
6	Et_2O	1.5	−80	59 (66)
7	Et_2O	2.0	−80	(12)
8	Et_2O	3.0	−80	(17)
9	Et_2O	1.5	−80 to 0	56 (59)
10	Et_2O	1.5	−80 to rt	60 (64)
11[c]	Et_2O	1.5	−80 to rt	72

[a] Isolated yields, and in the parenthesis were shown the yields determined by ^{19}F NMR.
[b] PhMgBr prepared in THF was used.
[c] The corresponding ethyl ester **1aa** was employed as the substrate.

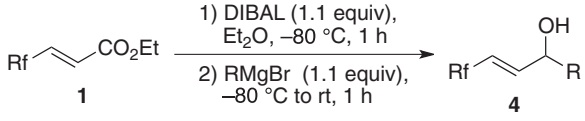


Scheme 1.

an Et_2O solvent as long as the Grignard reagent was prepared in THF (entry 4). Further increase of the quantity of this nucleophile was ineffective and the yields decreased significantly. Warming up the reaction mixture either to 0 °C or rt after addition of PhMgBr at −80 °C resulted in better consequence, and the desired allylic alcohol **4aa** was isolated in an acceptable level of 56 and 60% yields (entries 9 and 10, respectively). Because of easy preparation and handling in terms of its boiling point, the benzyl ester **1ab** was used as the starting material, while the resultant benzyl alcohol was found to cause troublesome situation at the chromatographic isolation step due to its close polarity to the product **4aa**. Eventually, this problem was solved by employment of the corresponding ethyl ester **1ab**, and this protocol in 10 mmol scale was found to attain 72% isolated yield.

At the next stage, optimized reaction conditions thus determined were applied to a variety of α,β-unsaturated esters **1** (Table 2). As described in entry 11 in Table 1, trifluorinated α,β-unsaturated ester **1aa** afforded **4aa** in 72% yield, which was in sharp contrast to the case of non-fluorinated crotonate **1fa**, only affording a complex mixture (entry 2). This would be understood on the basis of the instability of the corresponding intermediary aluminium acetal, smoothly giving crotonaldehyde which would further reacted with PhMgBr. On the other hand, the present protocol was applicable to other fluorine-containing enoates **1ba** to **1ea**, allowing to construct the corresponding allylic alcohols **4ba** to **4ea** in good to excellent yields (entries 3–6). However, switch of the nucleophile from PhMgBr to $PhCH_2CH_2MgBr$ gave the disappointing result (entry 7), but the low yield of **4ab** was nicely improved to an acceptable level just by alteration of the solvent from Et_2O to CH_2Cl_2 which attained 51% isolated yield (entry 8). This nucleophile was also subjected to a solution of enoates **1da** and **1ea** with C_2F_5 as well as C_6F_{13} groups, respectively, and the desired product was obtained in good yield in the case of **1 da** (entry 10), while only 26% yield was recorded by **1ea** probably due to lower solubility of this substrate in CH_2Cl_2 (entry 11). Steric bulkiness of nucleophiles seemed to affect the reaction severely, and 26% yield was obtained by the action of *c*-$C_6H_{11}MgBr$ (entry 9).

Table 2
Reactions of various enoates **1** with Grignard reagents



Entry	Rf	R	Product	Yield[a] (%)
1	CF_3 (**1aa**)	Ph–	**4aa**	72
2	CH_3 (**1fa**)	Ph–	–	Complex
3	CHF_2 (**1ba**)	Ph–	**4ba**	62
4	$CClF_2$ (**1ca**)	Ph–	**4ca**	85
5	C_2F_5 (**1da**)	Ph–	**4da**	81
6	C_6F_{13} (**1ea**)	Ph–	**4ea**	89
7	CF_3 (**1aa**)	$PhCH_2CH_2$–	**4ab**	17
8[b]	CF_3 (**1aa**)	$PhCH_2CH_2$–	**4ab**	51
9[b]	CF_3 (**1aa**)	*c*-C_6H_{11}–	**4ac**	26
10[b]	C_2F_5 (**1da**)	$PhCH_2CH_2$–	**4db**	58
11[b]	C_6F_{13} (**1ea**)	$PhCH_2CH_2$–	**4eb**	26

[a] Isolated yields.
[b] CH_2Cl_2 was used as a solvent instead of Et_2O.

3. Conclusion

As mentioned above, we have successfully developed a useful one-pot preparation method of allylic alcohols **4** with fluorinated alkyl groups at the γ position, starting from the corresponding fluorinated α,β-unsaturated esters **1** by way of the DIBAL-mediated half reduction, followed by nucleophilic attack of Grignard reagents to aldehydes equilibrating with aluminium acetals. Further improvement of this method is in progress in this laboratory.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in dried glassware with magnetic stirring. Anhydrous Et_2O, THF and CH_2Cl_2 were purchased and were used without further purification. Analytical thin-layer chromatography (TLC) was routinely used for monitoring reactions by generally using a mixture of hexane and AcOEt (v/v). Spherical neutral silica gel (63–210 μm)

was employed for column chromatography. ^{1}H (300.40 MHz), ^{13}C (75.45 Hz), and ^{19}F (282.65 Hz) NMR spectra were recorded on a JEOL AL 300 spectrometer in $CDCl_3$ and chemical shifts were recorded in parts per million (ppm), downfield from internal tetramethylsilane (Me_4Si: δ 0.00, for ^{1}H and ^{13}C) or hexafluorobenzene (C_6F_6: δ −163.00 for ^{19}F). Data were tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; m, multiplet; b, broad peak), coupling constants in Hertz. Infrared (IR) spectra were obtained on a JASCO A-302 spectrometer and reported in wave numbers (cm^{-1}).

4.2. General procedure for the preparation of **4**

4.2.1. (E)-4,4,4-Trifluoro-1-phenylbut-2-en-1-ol (**(E)-4aa**) [13]

To a solution of ethyl (*E*)-4,4,4-trifluorobut-2-enoate **1aa** 1.690 g (10.1 mmol) in Et_2O (20 mL) was added a hexane solution (1.02 M) of DIBAL 10.3 mL (10.5 mmol) at −80 °C and after 1 h stirring at that temperature, PhMgBr 12.0 mL (1.21 M in Et_2O, 14.5 mmol) was added. The whole mixture was stirred at −80 °C for 15 min, then rt for 1 h where 1 M HCl (15 mL) was added. Extraction with Et_2O three times, and the obtained organic layer was dried over anhydrous $MgSO_4$. Filtration and evaporation of the volatiles furnished oily materials which was chromatographed on silica gel (hexane:AcOEt = 4:1) to afford 1.463 g (7.24 mmol) of (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-ol **(E)-4aa** as a colourless oil in 72% yield. Rf = 0.41 (hexane:AcOEt = 4:1). ^{1}H NMR δ 2.09 (1H, dd, *J* = 3.9, 0.6 Hz), 5.34 (1H, m), 6.05 (1H, dqd, *J* = 15.5, 6.6, 2.0 Hz), 6.53 (1H, ddq, *J* = 15.6, 3.7, 1.5 Hz), 7.28–7.44 (5H, m). ^{19}F NMR δ −65.28 (d, *J* = 6.0 Hz).

4.2.2. (E)-6,6,6-Trifluoro-1-phenylhex-4-en-3-ol (**(E)-4ab**) [8b]

CH_2Cl_2 was employed as a solvent instead of Et_2O. Yield 51%, Rf = 0.44 (hexane:AcOEt = 4:1). ^{1}H NMR δ 1.67 (1H, d, *J* = 4.8 Hz), 1.90 (2H, m), 2.76 (2H, m), 4.29 (1H, m), 5.90 (1H, dqd, *J* = 15.6, 6.6, 1.8 Hz), 6.42 (1H, ddq, *J* = 15.6, 4.2, 2.1 Hz), 7.14–7.33 (5H, m). ^{13}C NMR δ 31.2, 37.7, 69.4, 117.8 (q, *J* = 34.1 Hz), 123.1 (q, *J* = 268.6 Hz), 126.1, 128.3, 128.5, 141.0, 142.1 (q, *J* = 6.2 Hz). ^{19}F NMR δ −65.36 (d, *J* = 6.9 Hz).

4.2.3. (E)-1-Cyclohexyl-4,4,4-trifluorobut-2-en-1-ol (**(E)-4ac**) [14]

CH_2Cl_2 was employed as a solvent instead of Et_2O. Yield 26%, Rf = 0.43 (hexane:AcOEt = 4:1). ^{1}H NMR δ 1.00–1.27 (5H, m), 1.46–1.50 (1H, m), 1.60 (1H, d, *J* = 4.8 Hz), 1.61–1.80 (5H, m), 4.06 (1H, m), 5.88 (1H, dqd, *J* = 15.8, 6.4, 1.8 Hz), 6.41 (1H, ddq, 15.8, 5.0, 2.0 Hz). ^{13}C NMR δ 25.9, 26.0, 26.2, 27.8, 28.7, 43.4, 74.7, 118.5 (q, *J* = 33.6 Hz), 123.2 (q, *J* = 268.5 Hz), 141.1 (q, *J* = 6.2 Hz). ^{19}F NMR δ −65.15 (d, *J* = 6.8 Hz).

4.2.4. (E)-4,4-Difluoro-1-phenylbut-2-en-1-ol (**(E)-4ba**)

Yield 62%, Rf = 0.17 (hexane:AcOEt = 4:1). ^{1}H NMR δ 2.10 (1H, bs), 5.31 (1H, m), 6.00 (1H, m), 6.12 (1H, m), 6.25 (1H, ddt, *J* = 15.6, 4.5, 3.3 Hz), 7.26–7.41 (5H, m). ^{13}C NMR δ 73.2, 114.5 (t, *J* = 234.5 Hz), 122.6 (t, *J* = 24.2 Hz), 125.4, 126.4, 128.3, 128.5, 128.8, 140.2 (t, *J* = 11.2 Hz), 141.1. ^{19}F NMR δ −112.47 (1F, m), −112.67 (1F, m). IR ν (neat) 3360, 3032, 2881, 2327, 1737, 1682, 1494, 1455, 1387, 1295, 1143, 1019, 972, 764, 701 cm^{-1}. Anal. Calcd for $C_{10}H_{10}F_2O$: C,65.21; H, 5.47. Found C, 65.02; H, 5.57.

4.2.5. (E)-4-Chloro-4,4-difluoro-1-phenylbut-2-en-1-ol (**(E)-4ca**)

Yield 85%, Rf = 0.56 (hexane:AcOEt = 5:1). ^{1}H NMR δ 2.06 (1H, d, *J* = 3.9 Hz), 5.35 (1H, m), 6.22 (1H, dtd, *J* = 15.6, 8.7, 1.5 Hz), 6.42 (1H, ddt, *J* = 15.6, 4.2, 2.1 Hz), 7.32–7.42 (5H, m). ^{13}C NMR δ 72.7, 123.9 (t, *J* = 27.2 Hz), 125.0 (t, *J* = 286.3 Hz), 126.6, 128.6, 129.0, 138.0 (t, *J* = 6.8 Hz), 140.6. ^{19}F NMR δ −51.44 (d, *J* = 9.3 Hz). IR ν (neat) 3350, 2360, 2341, 1674, 1494, 1456, 1233, 1069, 964, 764, 700 cm^{-1}. Anal. Calcd for $C_{10}H_9ClF_2O$: C,54.94; H, 4.15. Found C, 54.85; H, 4.17.

4.2.6. (E)-4,4,5,5,5-Pentafluoro-1-phenylpent-2-en-1-ol (**(E)-4 da**)

Yield 81%, Rf = 0.54 (hexane:AcOEt = 3:1). ^{1}H NMR δ 2.09 (1H, d, *J* = 3.6 Hz), 5.37 (1H, q, *J* = 13.3 Hz), 6.07 (1H, d, *J* = 15.6 Hz), 6.57 (1H, ddt, *J* = 15.6, 4.2, 2.2 Hz), 7.12–7.38 (5H, m). ^{13}C NMR δ 72.9, 112.4 (tq, *J* = 249.3, 38.5 Hz), 116.0 (t, *J* = 23.5 Hz), 119.2 (qt, *J* = 284.7, 37.8 Hz), 126.7, 128.7, 129.0, 140.3, 143.2 (t, *J* = 8.1 Hz). ^{19}F NMR δ −116.72 (2F, d, *J* = 11.4 Hz), −86.46 (3F, s). IR ν (neat) 3360, 2360, 2341, 1683, 1342, 1203, 1039, 979, 764, 700 cm^{-1}. Anal. Calcd for $C_{11}H_9F_5O$: C, 52.39; H, 3.60. Found C, 52.42; H, 3.53.

4.2.7. (E)-6,6,7,7,7-Pentafluoro-1-phenylhept-4-en-3-ol (**(E)-4db**)

CH_2Cl_2 was employed as a solvent instead of Et_2O. Yield 45%, Rf = 0.32 (hexane:AcOEt = 4:1). ^{1}H NMR δ 1.71 (1H, d, *J* = 4.8 Hz), 1.91 (2H, m), 2.76 (2H, m), 4.33 (1H, m), 5.90 (1H, dt, *J* = 15.3, 12.0 Hz), 6.47 (1H, ddt, *J* = 15.3, 4.5, 2.4 Hz), 7.19–7.33 (5H, m). ^{13}C NMR δ 31.3, 37.9, 69.8, 112.3 (tq, *J* = 250.0, 38.5 Hz), 116.2 (t, *J* = 23.5 Hz), 118.9 (qt, *J* = 285.4, 37.8 Hz), 126.5, 128.4, 128.6, 140.9, 144.4 (t, *J* = 8.1 Hz). ^{19}F NMR δ –116.73 (2F, d, *J* = 13.8 Hz), –86.56 (3F, s). Anal. Calcd for $C_{13}H_{13}F_5O$: C, 55.72; H, 4.68. Found C, 55.82; H, 4.70.

4.2.8. (E)-4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-1-phenylnon-2-en-1-ol (**(E)-4ea**)

Yield 89%, Rf = 0.49 (hexane:AcOEt = 3:1). ^{1}H NMR δ 1.62 (1H, bs), 5.39 (1H, m), 6.10 (1H, dt, *J* = 15.8, 10.2 Hz), 6.56 (1H, ddt, *J* = 15.8, 4.2, 2.2 Hz), 7.30–7.43 (5H, m). ^{13}C NMR δ 73.1, 116.3 (t, *J* = 23.5 Hz), 126.6, 128.7, 129.0, 140.4, 143.2 (t, *J* = 8.7 Hz). ^{19}F NMR δ −127.41 (2F, m), −124.55 (2F, m), −124.14 (2F, brs), −122.88 (2F, brs), −112.90 (2F, quint, *J* = 15.0 Hz), −82.1 (3F, t, *J* = 10.3 Hz). IR ν (neat) 3351, 2360, 2342, 1683, 1240, 1202, 1145, 980, 700 cm^{-1}. Anal. Calcd for $C_{15}H_9F_{13}O$: C, 39.84; H, 2.01. Found C, 39.82; H, 2.01.

4.2.9. (E)-6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecafluoro-1-phenylundec-4-en-3-ol (**(E)-4eb**)

CH_2Cl_2 was employed as a solvent instead of Et_2O. Yield 26%, Rf = 0.38 (hexane:AcOEt = 4:1). ^{1}H NMR δ 1.70 (1H, d, *J* = 4.8 Hz), 1.91 (2H, m), 2.76 (2H, m), 4.35 (1H, br), 5.93 (1H, dt, *J* = 15.3, 12.9 Hz), 6.46 (1H, ddt, *J* = 15.3, 4.2, 2.4 Hz), 7.19–7.33 (5H, m). ^{13}C NMR δ 31.3, 38.0, 69.9, 116.5 (t, *J* = 23.5 Hz), 126.2, 128.4, 128.6, 140.9, 144.5 (t, *J* = 8.0 Hz). ^{19}F NMR δ −127.46 (2F, m), −124.70 (2F, m), −124.21 (2F, m), −122.92 (2F, m), −112.85 (q, *J* = 13.8 Hz), −82.07 (3F, t, *J* = 9.0 Hz). IR ν (neat) 3368, 2931, 2349, 1675, 1364, 1240, 1203, 1145, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{13}F_{13}O$: C, 42.51; H, 2.73. Found C, 42.68; H, 2.65.

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