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Rh-catalyzed novel α-fluoroalkylation of α,β-unsaturated ketones and its mechanism

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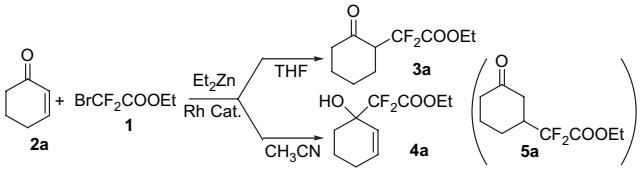
Abstract—Treatment of α,β-unsaturated ketones and fluoroalkyl halides with Et_2Zn in the presence of $RhCl(PPh_3)_3$ gave novel reductive fluoroalkylation products at the α-position of α,β-unsaturated ketones in moderate to good yields. The rhodium hydride complex derived from Et_2Zn and Rh catalyst seems to have played an important role in this reaction.

1. Introduction

Since fluorinated compounds have significantly interesting properties, they attract much attention in the fields of medicines, agricultural chemicals, and other valuable materials.[1] Therefore, the method for introducing a fluorine functional group to an organic compound has been actively investigated.[2] Among the methods for the synthesis of fluorine compounds, there are many reactions using halodifluoroacetates such as their Reformatsky reaction,[3] aldol reaction of their enolate or acetal,[4] and their radical addition reaction.[5] We have reported new cross-coupling reaction,[6] Michael-type reaction,[7] and radical reaction[8] of ethyl bromodifluoroacetate (**1**) in the presence of active copper powder.

For further expansion, we examined a new type of Michael reaction of **1** with α,β-unsaturated ketones (**2**) using diethylzinc (Et_2Zn) in the presence of a rhodium catalyst. Interestingly, the reaction of 2-cyclohexen-1-one (**2a**) and **1** with Et_2Zn in the presence of rhodium catalyst in THF gave an unexpected product (ethyl 2,2-difluoro-2-(2-oxocyclohexyl)-acetate, **3a**) with a small amount of the Reformatsky type product (**4a**), while the Michael-type product (**5a**) was not obtained at all. When the above reaction was carried out in acetonitrile, **4a** was obtained selectively in high yields (Scheme 1).[9]



Scheme 1. Reaction of **2a** with **1**.

The unexpected product (**3a**) attracted our interest, since it has a CF_2COOEt group on the α-carbon of α,β-unsaturated carbonyl group. Therefore, we examined the reaction of other unsaturated ketones with **1** or other fluoroalkyl halides (R_f–X), and found that this reaction has a wide applicability.

In this paper, first we will show the scope of this reaction with several α,β-unsaturated ketones (**2**). Next, the application of this reaction to various fluoroalkyl halides (R_f–X) will be presented. Here, our preliminary results of α-trifluoromethylation reaction will be also involved. Finally, some experiments carried out to clarify the mechanism of this interesting reaction will be discussed.

2. Results and discussion

As shown in the previous communication,[9] we examined the reaction of several α,β-unsaturated ketones (**2**) and **1** with Et_2Zn in the presence of $RhCl(PPh_3)_3$ in THF at 0 °C. The results are shown in Table 1. As mentioned above, **3a** was obtained in a good yield by reaction with **2a** (entry 1). However, **2b** that has a methyl group on the β-carbon did not afford the same type of product (**3b**), but the 1,2-addition product (**4b**) in a good yield as shown in entry 2. In acyclic enones, **2c** that does not have any substituents on the

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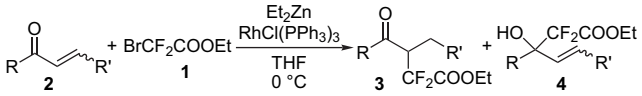
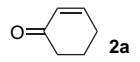
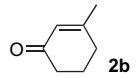
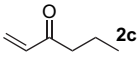
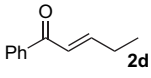
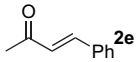
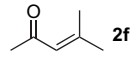
Table 1. Reaction of **1** with several enones



Entry	2	Time (h)	Yield of **3**[a,b] (%)	Yield of **4**[a,b] (%)
1	 **2a**	0.5	71	4
2	 **2b**	4	0	63
3	 **2c**	3	25	0
4	 **2d**	3	18	32
5	 **2e**	4	38	12
6	 **2f**	4	0	45

[a] Isolated yield.
[b] Purified by ODS column chromatography (MeOH/H_2O=7:3).

β-carbon afforded **3c** selectively, although the yield was lower than **2a** (entry 3). Using the β-monosubstituted ketones such as **2d** or **2e** (entries 4 and 5) lead to the generation of the objective products (**3d** or **3e**) in low to moderate yields, although the selectivity was low. On the other hand, **2f** did not give **3f** at all. Thus, presence of two carbon substituents on the β-position seems to inhibit the formation of **3** (entries 2 and 6).

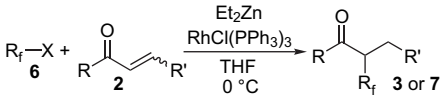
We expected that this reaction will provide a new methodology for the synthesis of fluorine compounds, if other fluoroalkyl halides could be used for this reaction.

Recently, we have reported that the same Rh-catalyzed novel α-trifluoromethylation of α,β-unsaturated ketones proceeded, and the α-CF_3 ketones were obtained in good yields.[10] As the next step, we examined the similar reaction using other fluoroalkyl halides (R_f–X, **6**) to afford the α-fluoroalkylated products (**7**). The results are shown in Table 2.

In entries 3–6, C_3F_7–I (**6b**) or $C_{10}F_{21}$–I (**6c**) reacted with **2** to give the corresponding products (**7c**–**f**) in moderate to good yields. Thus, this reaction was found to be applied to common perfluoroalkyl halides. So, we examined the reaction of α,α-difluoro halogen compounds (**1** and **6d**–**f**) as shown in entries 7–10. The acetylenic compound (**6d**) did not give **7g** but the 1,2-addition product (**8g**) in a low yield. Next, we examined the effect of halogens (entries 8–10). Although we detected the formation of cyclohexanone which might be derived from **2a** on GLC, the corresponding product (**7h**) was not obtained with the chloride (**6e**) (entry 8). On the other hand, the bromide (**1**) or the iodide (**6f**) gave **3a** in good yields.

In the previous report,[10] we speculated the reaction mechanism of the α-trifluoromethylation as shown in outer circle of Figure 1. The above result shows that the ease of oxidative addition of R_f–X to **11** and/or reductive elimination from **12** would be largely concerned with the formation of **3** or **7** (Table 2).

Table 2. Reaction with various fluoroalkyl halides



Entry	R_f–X	2	Time (h)	Yield[a] (%)	Product
1	CF_3–I **6a**	**2a**	0.5	55	**7a**
2	CF_3–I **6a**	**2e**	0.5	77	**7b**
3	C_3F_7–I **6b**	**2a**	2	52	**7c**
4	C_3F_7–I **6b**	**2e**	1	62	**7d**
5	$C_{10}F_{21}$–I **6c**	**2a**	3	41	**7e**
6	$C_{10}F_{21}$–I **6c**	**2e**	1	46	**7f**
7	Ph—≡—CF_2–Br **6d**	**2a**	22	0[b]	**7g**
8	CI–CF_2COOMe **6e**	**2a**	5	0	**7h**
9	Br–CF_2COOEt **1**	**2a**	0.5	71[c]	**3a**
10	I–CF_2COOEt **6f**	**2a**	0.5	68	**3a**

[a] Isolated yield.
[b] The 1,2-adduct (**8g**) was obtained in 19% yield.
[c] The 1,2-adduct (**4a**) was obtained in 4% yield with **3a**.

On the other hand, if the rhodium hydride complex (**10**) could be generated by other alkylmetals or metal hydrides, the catalytic cycle would be performed as shown by the bold line in the circle in Figure 1. Therefore, we examined the reaction of $C_{10}F_{21}$–I (**6c**) with **2e** by using some alkylmetals or metal hydrides instead of Et_2Zn to clarify the reaction mechanism. Furthermore, we expected that if the rhodium hydride complex (**10**) was formed efficiently, improvement of the yields or expansion of scope of the reaction could be attained.

Unfortunately, we could not obtain the product (**7f**) at all, when we examined some alkylmetals or metal hydrides such as Et_3Al, Et_3B, NaH, DIBAL-H or Et_3SiH. Furthermore, use of EtMgBr or Et_2Mg[11] leads only to the formation of 1,2-addition product (**8f**).

On the other hand, we could obtain the objective product (**7f**) by using EtMgBr with $ZnCl_2$,[12] although the yield was low (19%). So, we examined the reaction by using

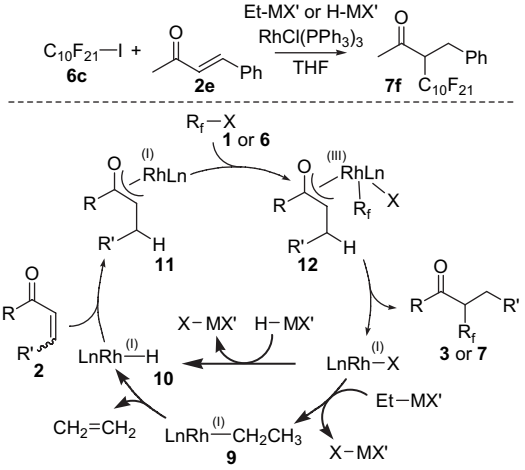
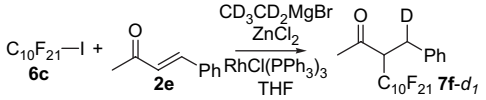


Figure 1. Tentative reaction mechanism of α-fluoroalkylation.

CD_3CD_2MgBr with $ZnCl_2$ for confirmation of the reaction mechanism. As expected, we obtained the product (**7f**-d_1) that a deuterium atom was introduced at the β-position of **2e** (Scheme 2). This means that the reaction proceeded via our proposed mechanism as shown in Figure 1, and the transmetalation of a deuterated alkylzinc and rhodium catalyst induced the formation of the rhodium deuteride complex (**10**-d_1).



Scheme 2. Certification of the reaction mechanism.

3. Conclusion

In conclusion, we found that various fluoroalkyl groups could be introduced at the α-position of α,β-unsaturated ketones (**2**) by using a new rhodium catalyzed reaction, although presence of two carbon substituents on the β-position of **2** seems to inhibit the formation of **3**. Furthermore, we could obtain the information supporting our proposed mechanism of the α-fluoroalkylation reaction of **2**. The rhodium hydride complex (**10**) which was easily generated by the transmetalation of alkylzinc with rhodium catalyst played an important role, since the reaction was induced by Et_2Zn. The α-fluoroalkylation reaction of α,β-unsaturated ketones has never been reported, and we expect that this reaction will be useful as a new methodology for introduction of a fluorine group to organic compounds.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded on JNM-GX400 spectrometer. Tetramethylsilane (TMS) was used as an internal standard. ^{19}F NMR spectra were recorded on Hitachi FT-NMR R-1500 and JEOL-ECA-600SN spectrometers. Benzotrifluoride (BTF) was used as an internal standard. Mass spectra were obtained on JEOL JMS-700T spectrometer. IR spectra were recorded on Hitachi 270-30 Infrared spectrophotometer. Gas–liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column: 5% SE-30 3 mm×2 m, carrier: N_2 at 30 mL/min). Peak areas were calculated on a Hitachi D-2000 Chromato-Integrator. Melting points were measured on Yanagimoto micro melting point apparatus MP-S3. All the solvents were purified by standard procedure under Ar atmosphere, and other commercially available reagents were used without further purification.

4.2. Synthesis of α,α-difluoro-γ-keto esters (3)

4.2.1. Typical procedure. Under Ar atmosphere, **1** (0.38 mL, 3 mmol) and **2a** (0.19 mL, 2 mmol) were added to the solution of $RhCl(PPh_3)_3$ (37 mg, 2 mol %) in THF (8 mL) at 0 °C and the mixture was stirred for 0.5 h. Then 1.0 M Et_2Zn in hexane (3.0 mL, 3 mmol) was gradually added to the mixture, and the mixture was stirred at same temperature for 1 h. The solution was quenched with 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with satd NaCl and dried with $MgSO_4$. The solvent was removed in vacuo and ODS column chromatographic purification ($MeOH/H_2O$=7:3) to give **3a** (312 mg, 71%) and **4a** (16 mg, 4%).

4.2.2. Spectral data.

4.2.2.1. Ethyl 2,2-difluoro-2-(2-oxocyclohexyl)acetate (3a). A colorless oil; ^1H NMR ($CDCl_3$) δ: 1.35 (t, 3H, *J*=7.2 Hz), 1.69 (m, 2H), 1.86 (m, 1H), 2.08 (m, 2H), 2.35 (m, 2H), 2.45 (m, 1H), 3.33 (m, 1H), 4.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 13.8, 23.9, 25.3 (m), 26.5, 41.6 (m), 54.4 (m), 62.7, 114.1 (m), 163.6 (m), 206.4 (m); ^{19}F NMR ($CDCl_3$) δ: −46.2 (dd, 1F, *J*=273.8, 7.6 Hz), −55.3 (dd, 1F, *J*=273.8, 19.3 Hz); MS *m/z*: 220 (M^+); HRMS calcd $C_{10}H_{14}O_3F_2$: 220.09 (M^+), found: 220.09; IR (neat) cm^{-1}: 1778, 1760, 1720, 1318, 1222, 1140.

4.2.2.2. Ethyl 2,2-difluoro-3-methyl-4-oxoheptanoate (3c). A colorless oil; ^1H NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.3 Hz), 1.35 (d, 3H, *J*=7.5 Hz), 1.35 (t, 3H, *J*=7.2 Hz), 1.61 (sextet, 2H, *J*=7.3 Hz), 2.52 (m, 2H), 3.39 (m, 1H), 4.33 (q, 2H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 9.8 (m), 13.5, 13.9, 16.7, 43.4 (m), 50.7 (m), 62.9, 114.8 (m), 163.3 (m), 207.1 (m); ^{19}F NMR ($CDCl_3$) δ: −43.7 (dd, 1F, *J*=268.3, 12.5 Hz), −50.5 (dd, 1F, *J*=268.3, 15.2 Hz); MS *m/z*: 222 (M^+); HRMS calcd $C_{10}H_{16}O_3F_2$: 222.11 (M^+), found: 222.11; IR (neat) cm^{-1}: 2968, 1776, 1720.

4.2.2.3. Ethyl 3-benzoyl-2,2-difluorohexanoate (3d). A colorless oil; ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, *J*=7.3 Hz), 1.27 (t, 3H, *J*=7.2 Hz), 1.35 (m, 2H), 1.85 (m, 1H), 1.99 (m, 1H), 4.22–4.34 (m, 3H), 7.50 (m, 2H), 7.62 (m, 1H), 7.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 13.8, 14.1, 20.8, 29.0 (m), 50.3 (m), 63.0, 115.1 (dd, *J*=259.1, 252.0 Hz), 128.4, 128.7, 133.7, 136.8, 163.3 (m), 197.3 (m); ^{19}F NMR ($CDCl_3$) δ: −40.1 (dd, 1F, *J*=265.5, 13.1 Hz), −46.2 (dd, 1F, *J*=265.5, 13.8 Hz); MS *m/z*: 284 (M^+); HRMS calcd $C_{15}H_{18}O_3F_2$: 284.12 (M^+), found: 284.12; IR (neat) cm^{-1}: 1770, 1692, 1240.

4.2.2.4. Ethyl 3-benzyl-2,2-difluoro-4-oxopentanoate (3e). A colorless oil; ^1H NMR ($CDCl_3$) δ: 1.35 (t, 3H, *J*=7.2 Hz), 2.01 (s, 3H), 3.08 (d, 2H, *J*=7.8 Hz), 3.66 (m, 1H), 4.31 (q, 2H, *J*=7.2 Hz), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 13.9, 31.8 (t, *J*=4.6 Hz), 31.9 (t, *J*=2.6 Hz), 58.1 (t, *J*=20.8 Hz), 63.3, 114.4 (t, *J*=255.0 Hz), 127.0, 128.7, 128.8, 137.0, 162.9 (t, *J*=31.6 Hz), 204.2 (t, *J*=3.7 Hz); ^{19}F NMR ($CDCl_3$) δ: −44.2 (d, 2F, *J*=13.1 Hz); MS *m/z*: 270 (M^+); HRMS calcd $C_{14}H_{16}O_3F_2$: 270.11 (M^+), found: 270.11; IR (neat) cm^{-1}: 1772, 1726.

4.2.2.5. Ethyl 2,2-difluoro-2-(1-hydroxycyclohex-2-enyl)acetate (4a). A colorless oil; ^1H NMR ($CDCl_3$) δ: 1.37 (t, 3H, *J*=7.1 Hz), 1.73–1.92 (m, 4H), 1.96–2.16 (m, 2H), 2.40 (br s, 1H), 4.36 (dq, 2H, *J*=7.1, 0.9 Hz), 5.84 (d, 1H, *J*=9.8 Hz), 6.14 (m, 1H); ^{19}F NMR ($CDCl_3$) δ: −54.9 (s, 1F), −54.9 (s, 1F); MS *m/z*: 203 (M^+−OH), 175 (M^+−OEt); HRMS calcd $C_{10}H_{14}O_3F_2$: 220.09 (M^+), $C_{10}H_{13}F_2O_2$: 203.09 (M^+−OH), $C_8H_9F_2O_2$: 175.06 (M^+−OEt), found: 203.09 (M^+−OH), 175.06 (M^+−OEt).

4.2.2.6. Ethyl 2,2-difluoro-(1-hydroxy-3-methylcyclohex-2-enyl)acetate (4b). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.36 (t, 3H, J=7.3 Hz), 1.76 (s, 3H), 1.75–1.82 (m, 4H), 1.94–2.00 (m, 2H), 2.35 (br s, 1H), 4.35 (m, 2H), 5.57 (s, 1H); ^{19}F NMR ($CDCl_3$) δ: −54.7 (s, 1F), −54.9 (s, 1F); MS m/z: 234 (M^+); HRMS calcd $C_{11}H_{16}F_2O_3$: 234.11 (M^+), found: 234.11.

4.2.2.7. Ethyl (*E*)-2,2-difluoro-3-hydroxy-3-phenylhept-4-enoate (4d). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.5 Hz), 1.16 (t, 3H, J=7.2 Hz), 2.13 (m, 2H), 3.35 (br s, 1H), 4.19 (q, 2H, J=7.2 Hz), 5.99 (dt, 1H, J=15.2, 6.2 Hz), 6.10 (d, 1H, J=15.2 Hz), 7.30–7.38 (m, 3H), 7.56–7.58 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: −51.5 (s, 2F); MS m/z: 284 (M^+); HRMS calcd $C_{15}H_{18}O_3F_2$: 284.12 (M^+), found: 284.12.

4.2.2.8. Ethyl (*E*)-2,2-difluoro-3-hydroxy-3-methyl-5-phenylpent-4-enoate (4e). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, J=7.2 Hz), 1.54 (t, 3H, J=1.6 Hz), 2.86 (br s, 1H), 4.31 (q, 2H, J=7.2 Hz), 6.30 (dd, 1H, J=16.5, 1.6 Hz), 6.80 (d, 1H, J=16.5 Hz), 7.25–7.41 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: −54.3 (s, 1F), −54.4 (s, 1F); MS m/z: 270 (M^+); HRMS calcd $C_{14}H_{16}O_3F_2$: 270.11 (M^+), found: 270.11.

4.2.2.9. Ethyl 2,2-difluoro-3-hydroxy-3,5-dimethylhex-4-enoate (4f). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, J=7.2 Hz), 1.47 (t, 3H, J=1.5 Hz), 1.74 (d, 3H, J=1.2 Hz), 1.89 (d, 3H, J=1.5 Hz), 2.63 (br s, 1H), 4.35 (m, 2H), 5.34 (m, 1H); ^{19}F NMR ($CDCl_3$) δ: −55.1 (s, 2F); MS m/z: 222 (M^+); HRMS calcd $C_{10}H_{16}F_2O_3$: 222.11 (M^+), found: 222.11.

4.3. Synthesis of α-trifluoromethylated ketones (7)[10]

4.3.1. Typical procedure. Under Ar atmosphere, a solution of **6a** (ca. 1 mL) in THF (2 mL) was added to a solution of **2e** (292 mg, 2 mmol) and $RhCl(PPh_3)_3$ (37 mg, 2 mol %) in THF (6 mL) at −30 °C. Et_2Zn of 1.0 M in hexane (3.0 mL, 3 mmol) was gradually added to the solution at 0 °C, and then the solution was stirred at rt for 0.5 h. The solution was quenched with 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with satd NaCl and dried with $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (AcOEt/hexane=1:9) to give **7b** (332 mg, 77%).

4.3.2. Spectral data.

4.3.2.1. 2-Trifluoromethylcyclohexanone (7a). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.67–1.88 (m, 3H), 1.99–2.03 (m, 1H), 2.07–2.15 (m, 1H), 2.31–2.39 (m, 2H), 2.48–2.53 (m, 1H), 3.08 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 23.8, 27.1, 27.6 (q, J=2.5 Hz), 42.2 (q, J=1.6 Hz), 53.7 (q, J=25.5 Hz), 124.6 (q, J=278.6 Hz), 202.9; ^{19}F NMR ($CDCl_3$) δ: −6.02 (d, 3F, J=8.3 Hz); MS m/z: 166 (M^+); HRMS calcd $C_7H_9OF_3$: 166.06 (M^+), found: 166.06; IR (neat) cm^{-1}: 2956, 2880, 1730, 1394, 1274.

4.3.2.2. 3-Trifluoromethyl-4-phenylbutan-2-one (7b). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 2.07 (s, 3H), 3.06 (dd, 1H, J=13.9, 4.2 Hz), 3.18 (dd, 1H, J=13.9, 10.9 Hz), 3.56 (dqd, 1H, J=10.9, 8.3, 4.2 Hz), 7.12–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 31.8 (q, J=1.6 Hz), 31.9 (q, J=2.7 Hz), 57.6 (q, J=24.9 Hz), 124.4 (q, J=280.3 Hz), 127.1, 128.7, 128.8, 136.4, 201.3 (q, J=1.9 Hz); ^{19}F NMR ($CDCl_3$) δ: −4.42 (d, 3F, J=8.3 Hz); MS m/z: 216 (M^+); HRMS calcd $C_{11}H_{11}OF_3$: 216.08 (M^+), found: 216.08; IR (neat) cm^{-1}: 1734, 1264.

4.4. Synthesis of other α-fluoroalkylated ketones (7)

4.4.1. Typical procedure. Under Ar atmosphere, **6b** (0.43 mL, 3 mmol) and **2e** (292 mg, 2 mmol) were added to the solution of $RhCl(PPh_3)_3$ (37 mg, 2 mol %) in THF (8 mL) at 0 °C and the mixture was stirred for 0.5 h. Et_2Zn of 1.0 M in hexane (3.0 mL, 3 mmol) was gradually added to the solution at 0 °C, and then the solution was stirred at rt for 1 h. The solution was quenched with 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with satd NaCl and dried with $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (AcOEt/hexane=1:9) to give **7d** (394 mg, 62%).

4.4.2. Spectral data.

4.4.2.1. 2-Heptafluoropropylcyclohexanone (7c). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.69–1.80 (m, 1H), 1.84–1.93 (m, 1H), 2.01 (m, 3H), 2.26 (m, 1H), 2.40–2.59 (m, 2H), 3.13–3.24 (m, 1H); ^{19}F NMR ($CDCl_3$) δ: −17.9 (t, 3F, J=11.0 Hz), −51.0 (m, 2F), −61.3 (m, 2F); MS m/z: 266 (M^+); HRMS calcd $C_9H_9OF_7$: 266.05 (M^+), found: 266.05; IR (neat) cm^{-1}: 1732, 1226.

4.4.2.2. 3-Heptafluoropropyl-4-phenylbutan-2-one (7d). A colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.96 (s, 3H), 3.16 (m, 2H), 3.62 (m, 1H), 7.14–7.33 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: −17.57 (m, 3F), −51.40 (m, 2F), −61.61 (m, 2F); MS m/z: 316 (M^+); HRMS calcd $C_{13}H_{11}OF_7$: 316.07 (M^+), found: 316.07; IR (neat) cm^{-1}: 1736, 1354, 1228, 1178, 1122, 1082.

4.4.2.3. 2-Perfluorodecylcyclohexanone (7e). A colorless solid; mp=73.5–74.0 °C; ^{1}H NMR ($CDCl_3$) δ: 1.69–2.09 (m, 5H), 2.26 (m, 1H), 2.49 (m, 2H), 3.20 (m, 1H); ^{19}F NMR ($CDCl_3$) δ: −18.0 (m, 3F), −49.4 (m, 1F), −51.1 (m, 1F), −57.2 (m, 2F), −58.9 (m, 8F), −59.1 (m, 2F), −59.9 (m, 2F), −63.3 (m, 2F); MS m/z: 616 (M^+); HRMS calcd $C_{16}H_9OF_{21}$: 616.03 (M^+), found: 616.03; IR (neat) cm^{-1}: 1724, 1216, 1154.

4.4.2.4. 3-Perfluorodecyl-4-phenylbutan-2-one (7f). A colorless solid; mp=63.8–64.2 °C; ^{1}H NMR ($CDCl_3$) δ: 1.96 (s, 3H), 3.17 (m, 2H), 3.63 (m, 1H), 7.15–7.17 (m, 2H), 7.25–7.33 (m, 3H); ^{19}F NMR ($CDCl_3$) δ: −18.0 (m, 3F), −49.4 (m, 1F), −52.0 (m, 1F), −57.4 (m, 2F), −58.9 (m, 10F), −59.9 (m, 2F), −63.3 (m, 2F); MS m/z: 666 (M^+); HRMS calcd $C_{20}H_{11}OF_{21}$: 666.05 (M^+), found: 666.05; IR (neat) cm^{-1}: 1726, 1222, 1154.

4.4.2.5. (*E*)-2-Perfluorodecyl-4-phenylbut-3-en-2-ol (8f). A colorless solid; mp=88.0–90.0 °C; ^{1}H NMR ($CDCl_3$) δ: 1.62 (s, 3H), 2.29 (s, 1H), 6.33 (d, 1H, J=16.2 Hz), 6.86 (d, 1H, J=16.2 Hz), 7.25–7.43 (m, 5H); ^{19}F NMR ($CDCl_3$) δ: −18.0 (m, 3F), −55.4 to −56.7 (m, 3F), −58.2 to −59.1 (m, 11F), −59.9 (s, 2F), −63.3 (m,

2F); MS *m/z*: 666 (M^+); HRMS calcd $C_{20}H_{11}OF_{21}$: 666.05 (M^+), found: 666.05; IR (neat) cm^{-1}: 3616, 1346, 1148.

4.4.2.6. 1-(1,1-Difluoro-3-phenylprop-2-ynyl)cyclohex-2-enol (8g). A pale yellow oil; ^1H NMR ($CDCl_3$) δ: 1.77–1.84 (m, 2H), 1.94–1.97 (m, 2H), 2.04–2.19 (m, 2H), 2.15 (br s, 1H), 5.86 (m, 1H), 6.16 (m, 1H), 7.33–7.43 (m, 3H), 7.50–7.53 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: −35.4 (s, 1F), −35.5 (s, 1F); MS *m/z*: 248 (M^+); HRMS calcd $C_{15}H_{14}OF_2$: 248.10 (M^+), found: 248.10; IR (neat) cm^{-1}: 3464, 2948, 2244, 1294, 1138, 1052.

4.5. Reaction by using deuterated alkylzinc reagent

4.5.1. Typical procedure. Under Ar atmosphere, a solution of 1.0 M $ZnCl_2$ in Et_2O (3.0 mL, 3 mmol) was added to a solution of 2.0 M CD_3CD_2MgBr in Et_2O (3.0 mL, 6 mmol). The resulting suspension was stirred overnight at rt. To the solution of $RhCl(PPh_3)_3$ (9 mg, 2 mol %), **2e** (73 mg, 0.5 mmol), and **6c** (484 mg, 0.75 mmol) was gradually added the clear supernatant portion of the Zn reagent (1.5 mL, 0.75 mmol) at 0 °C, and then the solution was stirred at rt for 1 h. The solution was quenched with 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with satd NaCl and dried with $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (AcOEt/hexane=1:9) to give **7f**-d_1 (62 mg, 19%).

4.5.2. Spectral data.

4.5.2.1. 4-Deutero-3-perfluorodecyl-4-phenylbutan-2-one (7f-d_1). A colorless solid; ^1H NMR ($CDCl_3$) δ: 1.96 (s, 3H), 3.17 (m, 1H), 3.63 (m, 1H), 7.15–7.17 (m, 2H), 7.25–7.33 (m, 3H); ^{19}F NMR ($CDCl_3$) δ: −18.0 (m, 3F), −49.4 (m, 1F), −51.9 (m, 1F), −57.4 (m, 2F), −58.9 (m, 10F), −59.9 (m, 2F), −63.3 (m, 2F); MS *m/z*: 667 (M^+); HRMS calcd $C_{20}H_{10}DOF_{21}$: 667.05 (M^+), found: 667.05.

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