The First Practical Additive-Free 1,4-Conjugated Alkylation of Fluoroalkylated Electron-Deficient Olefins with Various Organozinc Reagents

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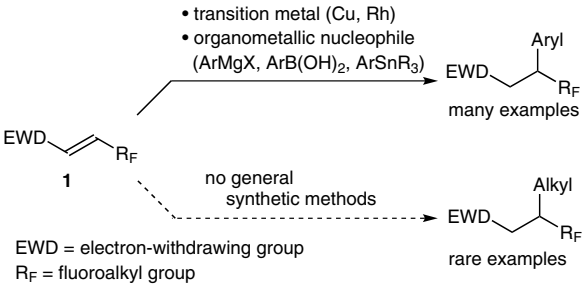
Abstract: 1,4-Conjugated alkylation of fluoroalkylated olefins with organozinc reagents, such as RZnI and R_2Zn, was conducted smoothly to give the corresponding products in moderate yields without the use of either transition metals or Lewis acids. This reaction protocol allows not only a wide range of alkyl groups but also electron-withdrawing groups to be incorporated as 1,4-conjugated adducts.

Key words: 1,4-conjugated alkylation, organozinc reagents, trifluoromethyl, electron-deficient olefin

The carbon–carbon bond formation through 1,4-conjugated addition has been recognized as one of the most important organic reactions. In the last decade, numerous synthetic methodologies have been developed for this transformation.[1] Especially the transition-metal-catalyzed 1,4-conjugated addition has been intensively investigated and applied for enantioselective versions in several successful examples.[2] Among these developments, the metal nucleophile also has been studied to search for expanding substrate scopes under the milder reaction condition. The organozinc reagents (i.e., RZnX, R_2Zn, and R_3ZnMet) are known as unique nucleophiles compared to other common organometallic reagents, that is, the softer nucleophilicity of organozinc reagents shows higher functional-group tolerance.[3] However, organozinc reagents often require the assistance of transition metals or Lewis acids in order to react as expected.[4]

Tremendous attention has been paid to fluorine-containing molecules because of their biological properties as well as their unique reactivities, which has led to new developments of synthetic methodologies.[5] For example, trifluoromethyl-bearing olefins, such as **1** in Scheme 1, shows very interesting LUMO-lowering effect on its β-carbon.[6] We and Yamazaki et al.[7] have demonstrated that the electron-deficient olefin **1** can serve as an excellent reaction partner for 1,4-conjugated addition, but incoming substrates for these reactions are to some extent limited. In fact, the introduction of simple alkyl substrates has been facing many difficulties, such as defluorination and a narrow range of the substrate scope.[7] To overcome this limitation, we revisited the basic nature of olefin **1**, and realized that it will be possible for even unreactive nucleophiles to react with olefin **1** without addition of any activators (i.e., transition metals and Lewis acids). Herein, we describe the first practical 1,4-conjugated alkylation of fluoroalkylated olefins **1** with organozinc reagents under the additive-free conditions.



Scheme 1 1,4-Conjugated addition to fluoroalkylated electron-deficient olefins **1** with organometallic reagents

Initially, the least reactive organozinc reagents, alkylzinc halides, were chosen for the 1,4-conjugated alkylation to (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (**1a**). Thus, the olefin **1a** was treated with 3.0 equivalents of freshly prepared RZnI[8] in THF at 0 °C and then the reaction mixture was stirred for eight hours at the same temperature. To our surprise, the reaction gave the corresponding 1,4-adduct in a moderate yield without extra additive (Table 1, entries 1 and 3). Next, the same reaction was tested with dialkylzinc reagents,[9] which gave a smoother reaction and higher yield of the product in only one hour at –78 °C (entries 2 and 4). Interestingly, when the organozincate, $(n\text{-Bu})_3ZnLi$,[10] was utilized in this reaction, its 1,2-adduct was obtained instead as the major product (entry 5). This reaction trend of organozinc reagents was observed similarly in other substrates; therefore, RZnI and R_2Zn were used for further reactions. Dialkylzinc reagents were found to be the most effective,[11] and even sterically hindered alkyl groups, such as *i*-Pr and *t*-Bu, could be introduced in moderate yields (entries 8 and 9). However, in contrast by taking full advantage of the mild reactivity of organozinc halides, the alkyl groups with labile function-

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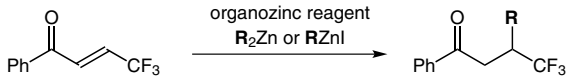
alities could also be installed into the desired structure (entries 10 and 11).

Table 1 1,4-Conjugated Alkylation of Olefin **1a** with Various Organozinc Reagents



1a **2**

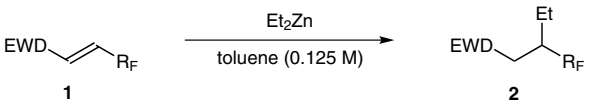
Entry	Organozinc reagent	Equiv	Method[a]	Time (h)	Product	Yield (%)[b]
1	EtZnI	3.0	A	8	**2aa**	57 (54)
2	Et_2Zn[c]	1.2	B	1	**2aa**	83 (82)
3	*n*-BuZnI	3.0	A	8	**2ab**	62 (37)
4	$(n\text{-Bu})_2Zn$	2.4	B	2	**2ab**	81 (56)
5	$(n\text{-Bu})_3ZnLi$	3.0	C	2	**2ab**	27[d]
6	$(n\text{-Hex})_2Zn$	2.4	B	2	**2ac**	66 (61)
7	*c*-HexZnI	2.4	A	8	**2ad**	50[e]
8	$(i\text{-Pr})_2Zn$[c]	1.2	B	1	**2ae**	86 (62)
9	$(t\text{-Bu})_2Zn$	2.4	B	2	**2af**	50[e]
10	$EtO_2C(CH_2)_3ZnI$	3.0	A	8	**2ag**	54[e]
11	$NC(CH_2)_3ZnI$	3.0	A	8	**2ah**	49[e]

[a] Method A: in THF (0.25 M) at 0 °C. Method B: in toluene (0.125 M) at –78 °C. Method C: in THF (0.25 M) at –78 °C.
[b] Yields were determined by ^{19}F NMR spectroscopy, and the values in parentheses are isolated yields.
[c] The commercially available salt-free organozinc reagents were used.
[d] The 1,2-adduct was isolated as the major product in 69%.
[e] The pure products were inseparable from impurities.

Based on the known reactivity of organozinc reagents, Et_2Zn was chosen for the 1,4-conjugated alkylation with various types of electron-deficient olefins, and these results are shown in Table 2. Although slight modifications were required from the original condition depending on the reactivity of olefins **1**, most electron-withdrawing groups (EWDs) can survive under the given reaction condition without formation of any noticeable by-products (Table 2, entries 1–4). The olefin with a difluoromethyl (CF_2H) group also reacted smoothly to give the product in excellent yield (entry 5).

Finally, preliminary work on the possibility of diastereoselective 1,4-conjugated alkylation using trifluoromethylated alkenes with Evan's chiral auxiliary was conducted (Scheme 2). Thus, treatment of **1f** or **1g** with 3.6 equivalents of Et_2Zn at –40 °C for 24 hours gave the corresponding 1,4-adducts in good yields; however, as diastereomeric mixtures in both cases. Further effort to attain higher diastereoselectivity is currently underway in our laboratory.

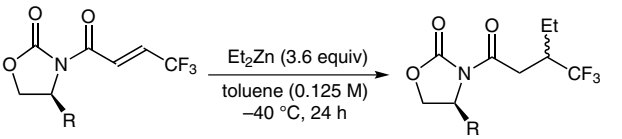
Table 2 1,4-Conjugated Alkylation of Various Fluoroalkylated Electron-Deficient Olefins **1** with Et_2Zn[a]



1 **2**

Entry	EWD	R_F	Et_2Zn (equiv)	Temp (°C)	Product	Yield (%)[b]
1[c]	C(O)Ph	CF_3	1.2	–78	**2aa**	83 (82)
2[d]	$C(O)NBn_2$	CF_3	3.6	–40	**2ba**	80 (74)
3[d]	SO_2Ph	CF_3	3.6	–20	**2ca**	75 (68)
4[d]	$P(O)(OEt)_2$	CF_3	3.6	–20	**2da**	72 (69)
5[c]	C(O)Ph	CF_2H	2.4	–78	**2ea**	92 (85)

[a] The reaction was conducted following method B of Table 1 but at different temperatures.
[b] Yields were determined by ^{19}F NMR spectroscopy, and the values in parentheses are isolated yields.
[c] The reaction time was 1 h.
[d] The reaction time was 24 h.



1f: R = Ph
1g: R = Bn

2fa: R = Ph, dr = 61:39
2ga: R = Bn, dr = 66:34

Scheme 2 Preliminary results of the conjugated addition using chiral substrates

In summary, we have examined the simple yet practical 1,4-conjugated alkylation of fluoroalkylated electron-deficient olefins with various unreactive organozinc reagents without any additives.[12] As a result, this reaction protocol can allow many labile alkyl groups to participate in 1,4-conjugated addition reaction; that is, our new methodology can compensate for the previously established 1,4-conjugated addition limited strictly to aromatic nucleophiles.

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 (500.13 MHz for ^1H and 125.75 MHz for ^{13}C) spectrometer on samples dissolved in $CDCl_3$ with Me_4Si as an internal reference. A Jeol JNM-AL400 (376.05 MHz) spectrometer was used to record ^{19}F NMR spectra in $CDCl_3$ using $CFCl_3$ as an internal standard. IR spectra were recorded as liquid film or KBr disk with an Avtar-370DTGS spectrometer (Thermo Electron) or an FT/IR-4100 (JASCO) spectrometer. High-resolution mass spectra were taken with a JEOL JMS-700 MS spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200) and TLC analysis was performed on silica gel TLC plates (Merck, Silica gel 60 F_{254}). All reactions were carried out under an atmosphere of argon. Anhyd THF and Et_2O were purchased from Wako Pure Chemical Industries, Ltd. *n*-BuLi (1.6 M hexane solution) was commercially available from Wako Pure Chemical Industries, Ltd. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use.

1,4-Conjugated Alkylation of RZnI to 4,4,4-Trifluoro-1-phenylbut-2-enone (1a); General Procedure for Method A

To a solution of 4,4,4-trifluoro-1-phenylbut-2-enone (**1a**; 50 mg, 0.25 mmol) in THF (1 mL) was added alkylzinc iodide (freshly prepared prior to the reaction from RI and Zn dust[8]) in THF at 0 °C. The mixture was then stirred for 8 h at 0 °C and quenched with sat. aq NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). The organic solvents were removed, and the residue was purified by silica gel column chromatography to give the corresponding product.

1,4-Conjugated Alkylation of R_2Zn to 4,4,4-Trifluoro-1-phenylbut-2-enone (1a); General Procedure for Method B

To a solution of 4,4,4-trifluoro-1-phenylbut-2-enone (**1a**; 50 mg, 0.25 mmol) in toluene (2 mL) was added a 1.0 M hexane solution of R_2Zn (0.3 mL, 1.2 equiv) [in case of in situ generation of R_2Zn; 0.6 mL of $ZnCl_2$ (1.0 M, Et_2O solution) was added to 0.75 mL of RLi (1.6 M, hexane solution) at 0 °C, and stirred for 30 min at 0 °C] at –78 °C, and stirred for 1 h at –78 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL), extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). The organic solvents were removed, and the residue was purified by silica gel column chromatography to give the corresponding product.

1-Phenyl-3-trifluoromethylpentan-1-one (2aa)

Method B; yield: 47 mg (0.21 mmol, 82%); yellow oil.

IR (neat): 3063, 2973, 2943, 2886, 1691, 1598, 1582, 1465, 1450, 1422, 1394, 1349, 1326, 1307, 1257, 1219 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.5 Hz, 3 H), 1.49–1.59 (m, 1 H), 1.73–1.81 (m, 1 H), 2.97–3.08 (m, 2 H), 3.22–3.28 (m, 1 H), 7.45–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 7.96–7.98 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 11.25, 21.73, 36.73 (q, *J* = 2.5 Hz), 39.43 (q, *J* = 25.8 Hz), 128.03, 128.37 (q, *J* = 279.6 Hz), 128.73, 133.45, 136.49, 196.50.

^{19}F NMR ($CDCl_3$): δ = –71.09 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{12}H_{13}F_3O$ (M^+): 230.0918; found: 230.0913.

1-Phenyl-3-trifluoromethylheptan-1-one (2ab)

Method B; yield: 36 mg (0.14 mmol, 56%); yellow oil.

IR (neat): 3063, 2959, 2874, 1692, 1598, 1582, 1450, 1421, 1395, 1352, 1328, 1268, 1221, 1165, 1130, 1096 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.27–1.40 (m, 4 H), 1.42–1.49 (m, 1 H), 1.69–1.76 (m, 1 H), 3.01–3.13 (m, 1 H), 3.03 (dd, *J* = 17.2, 7.1 Hz, 1 H), 3.27 (dd, *J* = 17.2, 3.6 Hz, 1 H), 7.46–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 7.95–7.98 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.71, 22.60, 28.50 (q, *J* = 1.8 Hz), 28.89, 37.23 (q, *J* = 2.5 Hz), 38.08 (q, *J* = 26.1 Hz), 128.02, 128.70, 128.37 (q, *J* = 279.6 Hz), 133.41, 136.49, 196.44.

^{19}F NMR ($CDCl_3$): δ = –71.32 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{14}H_{18}F_3O$ (M + H): 259.1310; found: 259.1304.

1-Phenyl-3-trifluoromethylnonan-1-one (2ac)

Method B; yield: 44 mg (0.15 mmol, 61%); yellow oil.

IR (neat): 3063, 2931, 2860, 1745, 1692, 1598, 1582, 1450, 1421, 1351, 1255, 1218, 1163, 1131, 1100, 1002 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.21–1.48 (m, 9 H), 1.68–1.75 (m, 1 H), 3.00–3.12 (m, 1 H), 3.02 (dd, *J* = 17.1, 7.3 Hz, 1 H), 3.27 (dd, *J* = 17.1, 3.6 Hz, 1 H), 7.46–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 7.95–7.98 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.99, 22.52, 26.74, 28.83 (q, *J* = 1.8 Hz), 29.22, 31.51, 37.27 (q, *J* = 2.1 Hz), 38.17 (q, *J* = 26.1 Hz), 128.05, 128.37 (q, *J* = 279.6 Hz), 128.73, 133.44, 136.52, 196.52.

^{19}F NMR ($CDCl_3$): δ = –71.31 (d, *J* = 7.1 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{22}F_3O$ (M + H): 287.1623; found: 287.1616**.**

3-Cyclohexyl-4,4,4-trifluoro-1-phenylbutan-1-one (2ad)

Method A; the product was inseparable from impurities, therefore only the peaks that could be assigned are described.

IR (neat): 3062, 2930, 2856, 1691, 1598, 1581, 1450, 1422, 1390, 1344, 1264, 1240, 1217, 1186, 1154, 1109, 1050, 1019, 1002 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.07–1.28 (m, 5 H), 1.61–1.80 (m, 6 H), 3.06–3.23 (m, 3 H), 7.46–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 7.97–7.99 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 34.33 (q, *J* = 2.2 Hz), 42.87 (q, *J* = 24.6 Hz), 128.37 (q, *J* = 280.8 Hz), 128.08, 128.72, 133.39, 136.52, 196.67.

^{19}F NMR ($CDCl_3$): δ = –67.40 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{17}H_{16}F_3O$ (M + H): 293.1153; found: 293.1146.

4-Methyl-1-phenyl-3-trifluoromethylpentan-1-one (2ae)

Method B; yield: 38 mg (0.16 mmol, 62%); white solid; mp 28–29 °C.

IR (KBr): 2993, 2974, 2947, 2921, 2889, 1684, 1598, 1473, 1452, 1396, 1322, 1271, 1221, 1169, 1137, 1070 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 2.13 (dsept, *J* = 7.0, 3.8 Hz, 1 H), 3.02 (dd, *J* = 17.6, 5.7 Hz, 1 H), 3.10–3.18 (m, 1 H), 3.22 (dd, *J* = 17.6, 5.3 Hz, 1 H), 7.48–7.51 (m, 2 H), 7.56–7.62 (m, 1 H), 7.97–8.00 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 19.03, 20.20, 27.15, 33.72 (q, *J* = 2.5 Hz), 42.84 (q, *J* = 24.7 Hz), 128.06, 128.34 (q, *J* = 281.1 Hz), 128.71, 133.39, 136.52, 196.62.

^{19}F NMR ($CDCl_3$); δ = –67.96 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{13}F_3O$ (M + H): 245.1153; found: 245.1149.

4,4-Dimethyl-1-phenyl-3-trifluoromethylpentan-1-one (2af)

Method B; the pure product was isolated as a white solid in very low yield; mp 39–40 °C.

IR (KBr): 2961, 2880, 1684, 1598, 1478, 1451, 1373, 1355, 1289, 1265, 1202, 1147, 1096, 1074, 1028 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.06 (s, 9 H), 3.02 (ddd, *J* = 18.1, 3.9, 1.0 Hz, 1 H), 3.13–3.21 (ddq, *J* = 3.9, 6.1, 10.5 Hz, 1 H), 3.25 (dd, *J* = 18.1, 6.1 Hz, 1 H), 7.46–7.51 (m, 2 H), 7.57–7.61 (m, 1 H), 7.96–7.99 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 28.26, 32.39, 34.89 (q, *J* = 2.8 Hz), 46.09 (q, *J* = 23.7 Hz), 128.51 (q, *J* = 282.2 Hz), 128.07, 128.70, 133.36, 136.49, 196.59.

^{19}F NMR ($CDCl_3$): δ = –64.13 (d, *J* = 10.5 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{13}F_3O$ (M + H): 259.1310; found: 259.1314.

Ethyl 7-Oxa-7-phenyl-5-trifluoromethylheptanoate (2ag)

Method A; the product was inseparable from impurities, and therefore only the peaks that could be assigned are described.

^{19}F NMR ($CDCl_3$): δ = –71.27 (d, *J* = 7.1 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{20}F_3O_3$ (M + H): 317.1365; found: 317.1367.

7-Oxo-7-phenyl-5-trifluoromethylheptanenitrile (2ah)

Method A; the product was inseparable from impurities, and therefore only the peaks that could be assigned are described.

^{19}F NMR ($CDCl_3$): δ = –70.96 (d, *J* = 7.1 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{14}H_{15}F_3NO$ (M + H): 270.1106; found: 270.1103.

_N_,_N_-Dibenzyl-3-trifluoromethylpentanamide (2ba)
Method B; yield: 65 mg (0.19 mmol, 74%); yellow oil.

IR (neat): 3088, 3065, 3031, 2970, 2939, 2883, 1744, 1651, 1606, 1586, 1496, 1453, 1385, 1361, 1327, 1257 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.5 Hz, 3 H), 1.21–1.29 (m, 1 H), 1.35–1.40 (m, 1 H), 2.43 (dd, *J* = 16.5, 7.3 Hz, 1 H), 2.71 (dd, *J* = 16.5, 4.8 Hz, 1 H), 2.90–3.10 (m, 1 H), 4.44 (d, *J* = 17.2 Hz, 1 H), 4.502 (d, *J* = 14.6 Hz, 1 H), 4.505 (d, *J* = 17.2 Hz, 1 H), 4.80 (d, *J* = 14.6 Hz, 1 H), 7.10–7.42 (m, 10 H).

^{13}C NMR ($CDCl_3$): δ = 11.25, 21.70, 31.48, 40.66 (q, *J* = 25.6 Hz), 48.69, 49.77, 126.18, 127.47 (q, *J* = 292.9 Hz), 127.51, 127.74, 128.24, 128.63, 129.04, 136.03, 137.05, 170.46.

^{19}F NMR ($CDCl_3$): δ = –70.93 (d, *J* = 7.6 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{20}H_{22}F_3NO$ (M + H): 350.1732; found: 350.1728.

2-Trifluoromethylbutyl Phenyl Sulfone (2ca)
Method B; yield: 45 mg (0.17 mmol, 68%); yellow oil.

IR (neat): 3068, 2977, 2945, 2889, 1586, 1465, 1448, 1414, 1383, 1326, 1253, 1151, 1086, 1044, 1025 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.03 (dt, *J* = 7.5, 0.81 Hz, 3 H), 1.78–1.88 (m, 2 H), 2.69–2.80 (m, 1 H), 3.14 (dd, *J* = 14.6, 8.3 Hz, 1 H), 3.33 (dd, *J* = 14.6, 2.9 Hz, 1 H), 7.59–7.62 (m, 2 H), 7.68–7.72 (m, 1 H), 7.93–7.95 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 10.54, 21.32, 39.52 (q, *J* = 27.3 Hz), 54.00, 126.81 (q, *J* = 280.8 Hz), 127.93, 129.52, 134.18, 139.02.

^{19}F NMR ($CDCl_3$): δ = –70.61 (d, *J* = 7.6 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{14}H_{18}F_3O_2S$ (M + H): 267.0667; found: 267.0661.

Diethyl [2-(Trifluoromethyl)butyl]phosphonate (2da)
Method B; yield: 45 mg (0.17 mmol, 68%); yellow oil.

^1H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 7.4 Hz, 3 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 1.70–1.90 (m, 3 H), 2.03 (ddd, *J* = 21.2, 15.7, 3.4 Hz, 1 H), 2.40–2.55 (m, 1 H), 4.04–4.17 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 10.68, 16.31, 16.41, 21.60–21.75 (m, 1 C), 24.00 (dq, *J* = 146.2, 2.7 Hz), 39.32 (qd, *J* = 26.5, 2.7 Hz), 61.86 (d, *J* = 6.5 Hz), 61.95 (d, *J* = 6.9 Hz), 127.77 (qd, *J* = 279.2, 18.5 Hz).

^{19}F NMR ($CDCl_3$): δ = –67.40 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_9H_{19}F_3O_3P$ (M + H): 263.1024; found: 263.1029.

3-Difluoromethyl-1-phenylpentan-1-one (2ea)
Method B; yield: 49 mg (0.21 mmol, 85%), yellow oil.

IR (neat) 3062, 2696, 2940, 2882, 1688, 1598, 1581, 1463, 1449, 1380, 1359, 1320, 1260 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.5 Hz, 3 H), 1.49 (ddq. *J* = 14.7, 7.3, 7.3 Hz, 1 H), 1.65 (ddq, *J* = 14.7, 7.4, 7.4 Hz, 1 H), 2.53–2.65 (m, 1 H), 2.99 (dd, *J* = 17.8, 6.9 Hz, 1 H), 3.21 (dd, *J* = 17.8, 5.6 Hz, 1 H), 5.94 (td, *J* = 57.5, 2.9 Hz, 1 H), 7.45–7.49 (m, 2 H), 7.54–7.60 (m, 1 H), 7.95–8.00 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 11.33, 21.08 (dd, *J* = 5.8, 3.5 Hz), 35.89 (t, *J* = 4.4 Hz), 39.39 (t, *J* = 19.1 Hz), 117.90 (t, *J* = 241.8 Hz), 127.99, 128.63, 133.25, 136.75, 197.99.

^{19}F NMR ($CDCl_3$): δ = –123.81 (ddd, *J* = 275.3, 56.5, 14.1 Hz, 1 F), –125.17 (ddd, *J* = 275.3, 56.5, 19.8 Hz, 1 F).

HRMS: *m*/*z* calcd for $C_{12}H_{15}F_2O$ (M + H): 213.1090; found: 213.1084.

(*S*)-3-[3-(Trifluoromethyl)pentanoyl]-4-phenyloxazolidin-2-one (2fa)
Method B.

Major Isomer
Yield: 45 mg (0.14 mmol, 29%); white solid; mp 96–97 °C.

IR (KBr) 3033, 2974, 2945, 2886, 1786, 1700, 1455, 1414, 1387, 1366, 1306, 1253, 1207, 1178, 1130, 1105, 1039 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 7.5 Hz, 3 H), 1.35–1.45 (m, 1 H), 1.62–1.71 (m, 1 H), 2.73–2.84 (m, 1 H), 3.01 (dd, *J* = 18.3, 6.4 Hz, 1 H), 3.29 (dd, *J* = 18.3, 6.0 Hz, 1 H), 4.31 (dd, *J* = 8.9, 3.7 Hz, 1 H), 4.72 (t, *J* = 8.9 Hz, 1 H), 5.44 (dd, *J* = 8.9, 3.7 Hz, 1 H), 7.29–7.31 (m, 2 H), 7.33–7.41 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 10.98, 21.42 (q, *J* = 2.3 Hz), 33.96 (q, *J* = 2.5 Hz), 39.66 (q, *J* = 26.0 Hz), 57.76, 70.11, 125.90, 127.86 (q, *J* = 279.8 Hz), 128.86, 129.21, 138.72, 153.61, 169.96.

^{19}F NMR ($CDCl_3$): δ = –71.30 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{15}H_{17}F_3NO_3$ (M + H): 316.1161; found: 316.1154.

Minor Isomer
Yield: 22 mg (0.07 mmol, 14%); white solid; mp 54–55 °C.

IR (KBr) 3068, 3035, 2985, 2946, 2884, 1790, 1697, 1473, 1395, 1336, 1232, 1208, 1169, 1139, 1124, 1084, 1069, 1045, 1015 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 3 H), 1.44–1.50 (m, 1 H), 1.67–1.72 (m, 1 H), 2.70–2.81 (m, 1 H), 3.05 (dd, *J* = 18.2, 7.2 Hz, 1 H), 3.27 (dd, *J* = 18.2, 5.3 Hz, 1 H), 4.30 (dd, *J* = 8.9, 4.0 Hz, 1 H), 4.72 (t, *J* = 8.9 Hz, 1 H), 5.43 (dd, *J* = 8.9, 4.0 Hz, 1 H), 7.27–7.30 (m, 2 H), 7.33–7.41 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 11.20, 21.44 (q, *J* = 2.0 Hz), 34.13 (q, *J* = 2.6 Hz), 39.70 (q, *J* = 26.0 Hz), 57.81, 70.11, 125.81, 127.83 (q, *J* = 278.2 Hz), 128.89, 129.25, 138.54, 153.59, 170.00.

^{19}F NMR ($CDCl_3$): δ = –71.22 (d, *J* = 7.5 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{15}H_{17}F_3NO_3$ (M + H): 316.1161; found: 316.1154.

(*S*)-3-[3-(Trifluoromethyl)pentanoyl]-4-benzyloxazolidin-2-one (2ga)
Method B.

Major Isomer
Yield: 35 mg (0.11 mmol, 31%); yellow oil.

IR (neat): 3088, 3065, 3030, 2974, 2944, 2886, 1778, 1701, 1605, 1498, 1482, 1455, 1390, 1327, 1257, 1212, 1169, 1134, 1049, 1030 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.04 (t, *J* = 7.5 Hz, 3 H), 1.49–1.58 (m, 1 H), 1.75–1.84 (m, 1 H), 2.76 (dd, *J* = 13.4, 9.7 Hz, 1 H), 2.86–2.95 (m, 1 H), 3.08 (dd, *J* = 18.1, 6.3 Hz, 1 H), 3.23 (dd, *J* = 18.1, 6.1 Hz, 1 H), 3.31 (dd, *J* = 13.4, 3.4 Hz, 1 H), 4.19 (dd, *J* = 9.1, 2.9 Hz, 1 H), 4.23 (dd, *J* = 9.1, 7.7 Hz, 2 H), 4.67–4.72 (m, 1 H), 7.20–7.22 (m, 2 H), 7.26–7.30 (m, 1 H), 7.31–7.36 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 11.19, 21.41 (q, *J* = 2.4 Hz), 34.00 (q, *J* = 2.2 Hz), 37.82, 39.77 (q, *J* = 26.2 Hz), 55.29, 66.40, 127.42, 127.91 (q, *J* = 279.8 Hz), 128.98, 129.34, 135.02, 153.34, 170.42.

^{19}F NMR ($CDCl_3$): δ = –71.19 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{19}F_3NO_3$ (M + H): 330.1317; found: 330.1309.

Minor Isomer
Yield: 30 mg (0.09 mmol, 27%); yellow oil.

IR (neat): 3029, 2967, 2943, 2881, 1786, 1703, 1455, 1391, 1257, 1213, 1170, 1134, 1104, 1030 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 7.5 Hz, 3 H), 1.48–1.57 (m, 1 H), 1.73–1.81 (m, 1 H), 2.77 (dd, *J* = 13.3, 9.6 Hz, 1 H), 2.87–2.96 (m, 1 H), 2.99 (dd, *J* = 18.1, 6.5 Hz, 1 H), 3.31 (dd, *J* = 13.3, 3.3 Hz, 1 H), 3.33 (dd, *J* = 18.1, 5.6 Hz, 1 H), 4.20 (dd, *J* = 9.1, 3.2 Hz, 1 H), 4.23 (dd, *J* = 9.1, 7.6 Hz, 1 H), 4.67–4.71 (m, 1 H), 7.19–7.22 (m, 2 H), 7.26–7.30 (m, 1 H), 7.33–7.35 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 11.24, 21.54 (q, *J* = 2.0 Hz), 34.04 (q, *J* = 2.5 Hz), 37.69, 39.78 (q, *J* = 26.1 Hz), 55.27, 66.33, 127.42, 127.94 (q, *J* = 279.8 Hz), 129.00, 129.35, 134.98, 153.31, 170.48.

^{19}F NMR ($CDCl_3$): δ = –70.17 (d, *J* = 9.8 Hz, 3 F).

HRMS: *m*/*z* calcd for $C_{16}H_{19}F_3NO_3$ (M + H): 330.1317; found: 330.1325.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(8) The alkylzinc halides, RZnI, were prepared according to the reported procedure; see ref. 4b.

(9) The prepared dialkylzinc reagents were used without the removal of LiCl. For the detailed preparation procedure, see the experimental section.

(10) The lithium zincate, $(n\text{-Bu})_3ZnLi$, was prepared by mixing 3 equiv of *n*-BuLi (1.6 M hexane solution) and 1 equiv of $ZnCl_2$ (1.0 M, Et_2O solution) at 0 °C for 30 min.

(11) The reactivity of dialkylzinc reagents is: salt-free R_2Zn > in situ generated R_2Zn.

(12) The control experiments were conducted as follows. The 1,4-conjugated additions to (*E*)-1-phenylbut-2-en-1-one or chalcone with Et_2Zn were attempted under the same conditions as given in Table 1, entry 2; however, a quantitative amount of the starting alkene was recovered in both cases (methods A and B).