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 R2Zn, 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 alkylation has been recognized as one of the most important organic reactions. In the last decade, numerous synthetic methodologies have been developed for this transformation. Especially, the transition-metal-catalyzed 1,4-conjugated addition has been intensively investigated and applied for enantioselective versions in several successful examples. Among these developments, the metal nucleophile also has been studied for expanding substrate scopes under the milder reaction condition. The organozinc reagents (i.e., RZnX, R2Zn, and R3ZnMet) are known as unique nucleophiles compared to other common organometallic reagents, that is, the softer nucleophilicity of organozinc reagents shows higher functional-group tolerance. However, organozinc reagents often require the assistance of transition metals or Lewis acids in order to react as expected.

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. For example, trifluoromethyl-bearing olefins, such as 1 in Scheme 1, shows very interesting LUMO-lowering effect on its β-carbon. We and Yamazaki et al. 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. 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.

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 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, 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-Bu)3ZnLi, 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 R2Zn were used for further reactions. Dialkylzinc reagents were found to be the most effective, 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-
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 |
|-----------------|-------------------|-----------------|-----------------|
| Entry | Organozinc reagent | Equiv | Method* | Product Yield (%) |
| 1 | Et$_2$Zn | 3.0 | A | 8 | 2aa | 57 (54) |
| 2 | Et$_2$Zn | 1.2 | B | 1 | 2aa | 83 (82) |
| 3 | n-Bu$_2$Zn | 3.0 | A | 8 | 2ab | 62 (37) |
| 4 | (n-Bu)$_2$Zn | 2.4 | B | 2 | 2ab | 81 (56) |
| 5 | (n-Bu)$_2$ZnLi | 3.0 | C | 2 | 2ab | 27$^d$ |
| 6 | (n-Hex)$_2$Zn | 2.4 | B | 2 | 2ac | 66 (61) |
| 7 | c-HexZn | 2.4 | A | 8 | 2ad | 50$^e$ |
| 8 | (i-Pr)$_2$Zn | 1.2 | B | 1 | 2ae | 86 (62) |
| 9 | (i-Bu)$_2$Zn | 2.4 | B | 2 | 2af | 50$^e$ |
| 10 | Et$_2$O(C$_2$H$_5$)$_2$Zn | 3.0 | A | 8 | 2ag | 54$^e$ |
| 11 | NC(CH$_2$)$_3$ZnI | 3.0 | A | 8 | 2ah | 49$^e$ |

*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.

Yields were determined by $^1$H NMR spectroscopy, and the values in parentheses are isolated yields.

$^a$The commercially available salt-free organozinc reagents were used.

$^b$The 1,2-adduct was isolated as the major product in 69%.

$^c$The pure products were inseparable from impurities.

Based on the known reactivity of organozinc reagents, Et$_2$Zn 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$_2$H) group also reacted smoothly to give the product in (Table 2, entries 1–4). The olefin with a difluoromethyl groups (EWDs) can survive under the given reaction conditions at –78 °C.

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.

$^1$H and $^13$C NMR spectra were recorded on a Bruker DRX-500 (500.13 MHz for $^1$H and 125.75 MHz for $^13$C) spectrometer on samples dissolved in CDCl$_3$ with Me$_2$Si 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 Avant-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 (Merk, Silica gel 60 F$_{254}$). All reactions were carried out under an atmosphere of argon. Anhyd THF and Et$_2$O 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.

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1.4-Conjugated Alkylation of RZn to 4,4,4-Trifluoro-1-phenylbut-2-ene (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) in THF at 0 °C. The reaction was quenched with sat. aq NH4Cl (3 mL), and the combined organic layers were dried (Na2SO4). 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 R2Zn to 4,4,4-Trifluoro-1-phenylbut-2-ene (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 R2Zn (0.3 mL, 1.2 equiv) [in case of in situ generation of R2Zn; 0.6 mL of ZnCl2 (1.0 M, Et2O solution) was added to 0.75 mL of RLi (1.6 M, hexane solution) at 0 °C, and the mixture was stirred for 30 min at 0 °C] at −8 °C, and stirred for 1 h at −8 °C. The reaction was quenched with sat. aq NH4Cl (10 mL), extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na2SO4). The organic solvents were removed, and the residue was purified by silica gel column chromatography to give the corresponding product.

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

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

IR (neat): 3063, 2959, 2874, 1692, 1598, 1450, 1422, 1394, 1349, 1326, 1307, 1257, 1219 cm−1.

19F NMR (CDCl3): δ = 34.33 (q, J = 2.2 Hz), 42.87 (q, J = 24.6 Hz), 128.37 (q, J = 280.8 Hz), 128.08, 127.82, 133.39, 136.52, 196.67.

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): 2961, 2880, 1684, 1598, 1473, 1452, 1396, 1326, 1271, 1211, 1169, 1137, 1070 cm−1.

19F NMR (CDCl3): δ = −67.49 (d, J = 9.8 Hz, 3 F).

HRMS: m/z calcd for C16H13F3O (M + H): 270.1118; found: 269.1117.

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.

HRMS: m/z calcd for C16H13F3O (M + H): 259.1310; found: 259.1307.

4-Methyl-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, 1473, 1452, 1396, 1326, 1271, 1211, 1169, 1137, 1070 cm−1.

19F NMR (CDCl3): δ = −71.27 (d, J = 9.8 Hz, 3 F).

HRMS: m/z calcd for C17H16F3O (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): 2961, 2880, 1684, 1598, 1473, 1452, 1396, 1326, 1271, 1211, 1169, 1137, 1070 cm−1.

19F NMR (CDCl3): δ = −67.49 (d, J = 9.8 Hz, 3 F).

HRMS: m/z calcd for C16H20F3O3 (M + H): 317.1365; found: 317.1367.

19F NMR (CDCl3): δ = −71.27 (d, J = 9.8 Hz, 3 F).

HRMS: m/z calcd for C16H22F3O (M + H): 287.1623; found: 287.1621.

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.

19F NMR (CDCl3): 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).

1H NMR (CDCl3): 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).

13C NMR (CDCl3): δ = 34.33 (q, J = 2.2 Hz), 42.87 (q, J = 24.6 Hz), 128.37 (q, J = 280.8 Hz), 128.08, 127.82, 133.39, 136.52, 196.67.

19F NMR (CDCl3): δ = −67.49 (d, J = 9.8 Hz, 3 F).

HRMS: m/z calcd for C16H13F3O (M + H): 270.1116; found: 270.1103.

Ethyl 7-Oxa-7-phenyl-5-trifluoromethylheptanoate (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, 1473, 1452, 1396, 1326, 1271, 1211, 1169, 1137, 1070 cm−1.

1H NMR (CDCl3): δ = 1.06 (s, 9 H), 3.02 (dd, J = 18.1, 3.9 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).

13C NMR (CDCl3): 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.

19F NMR (CDCl3): δ = −64.13 (d, J = 10.5 Hz, 3 F).

HRMS: m/z calcd for C16H21F3O2 (M + H): 259.1310; found: 259.1314.

19F NMR (CDCl3): δ = −71.31 (d, J = 7.1 Hz, 3 F).

HRMS: m/z calcd for C16H17F3O2 (M + H): 270.1106; found: 270.1103.
N,N-Dibenzy1-3-trifluoromethylpentanamide (2ba)
Method B; yield: 65 mg (0.17 mmol, 68%); yellow oil.
IR (neat): 3068, 2977, 2945, 2889, 1586, 1465, 1448, 1414, 1383, 1326, 1253, 1151, 1084, 1044, 1025 cm⁻¹.
1H NMR (CDCl₃); δ = 1.05 (t, J = 7.5 Hz, 3 H), 1.33 (t, J = 7.0 Hz, 6 H), 1.70–1.90 (m, 3 H), 2.03 (dd, J = 21.2, 15.7, 3.4 Hz, 1 H), 2.40–2.55 (m, 1 H), 4.04–4.17 (m, 4 H).
19F NMR (CDCl₃); δ = 10.68, 16.31, 16.41, 17.70–20.75 (m, 1 C), 24.00 (dd, J = 146.2, 2.7 Hz), 39.32 (d, J = 26.5, 2.7 Hz), 61.86 (d, J = 6.5 Hz), 61.95 (d, J = 6.9 Hz), 127.77 (d, J = 279.2, 18.5 Hz).
13C NMR (CDCl₃); δ = −67.40 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C₁₄H₁₄F₄O₆S (M + H): 267.0667; found: 267.0661.

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, 1084, 1044, 1025 cm⁻¹.
1H NMR (CDCl₃); 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 (dd, J = 21.2, 15.7, 3.4 Hz, 1 H), 2.40–2.55 (m, 1 H), 4.04–4.17 (m, 4 H).
19F NMR (CDCl₃); δ = 10.68, 16.31, 16.41, 17.70–20.75 (m, 1 C), 24.00 (dd, J = 146.2, 2.7 Hz), 39.32 (d, J = 26.5, 2.7 Hz), 61.86 (d, J = 6.5 Hz), 61.95 (d, J = 6.9 Hz), 127.77 (d, J = 279.2, 18.5 Hz).
13C NMR (CDCl₃); δ = −67.40 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C₁₄H₁₄F₄O₆S (M + H): 263.1024; found: 263.1029.

Diethyl [2-(Trifluoromethyl)butyl]phosphonate (2da)
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, 1084, 1044, 1025 cm⁻¹.
1H NMR (CDCl₃); 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 (dd, J = 21.2, 15.7, 3.4 Hz, 1 H), 2.40–2.55 (m, 1 H), 4.04–4.17 (m, 4 H).
19F NMR (CDCl₃); δ = 10.68, 16.31, 16.41, 17.70–20.75 (m, 1 C), 24.00 (dd, J = 146.2, 2.7 Hz), 39.32 (d, J = 26.5, 2.7 Hz), 61.86 (d, J = 6.5 Hz), 61.95 (d, J = 6.9 Hz), 127.77 (d, J = 279.2, 18.5 Hz).
13C NMR (CDCl₃); δ = −67.40 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C₁₄H₁₄F₄O₆S (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, 2966, 2940, 2882, 1688, 1598, 1581, 1463, 1449, 1380, 1359, 1320, 1260 cm⁻¹.
1H NMR (CDCl₃); δ = 0.99 (t, J = 7.5 Hz, 3 H), 1.49 (dd, J = 14.7, 7.3, 7.3 Hz, 1 H), 1.65 (dd, J = 14.7, 7.4, 7.1 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 (dd, 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).
13C NMR (CDCl₃); δ = 11.33, 21.08 (d, 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.
19F NMR (CDCl₃); δ = −123.81 (d, J = 275.3, 56.5, 14.1 Hz, 1 F), −125.17 (d, J = 275.3, 56.5, 19.8 Hz, 1 F).
HRMS: m/z calcd for C₁₄H₁₄F₂O (M + H): 213.1090; found: 213.1084.

(5)-3-[3-(Trifluoromethyl)pentanoyl]-4-phenylazolidin-2-one (2fa)
Method B.
$^{13}$C NMR (CDCl$_3$): $\delta = 11.24, 21.54$ (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$_3$): $\delta = -70.17$ (d, $J = 9.8$ Hz, 3 F).

HRMS: $m/z$ calculated for C$_{16}$H$_{19}$F$_3$NO$_3$ (M + H): 330.1317; found: 330.1325.

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

References


(8) The alkylzinc halides, RZnX, 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-Bu)ZnLi, was prepared by mixing 3 equiv of n-BuLi (1.6 M hexane solution) and 1 equiv of ZnCl$_2$ (1.0 M, Et$_2$O solution) at 0 °C for 30 min.

(11) The reactivity of dialkylzinc reagents is: salt-free R$_2$Zn > in situ generated R$_2$Zn.

(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$_2$Zn 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).