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 RZn, 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, RZn, and RZnMet) 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 narrower 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 RZn 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,8 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)2ZnLi,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, RZn and RZn were used for further reactions. Dialkylzinc reagents were found to be the most effective,11 and even sterically hindered alkyl groups, such as t-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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organozinc reagent</th>
<th>Equiv</th>
<th>Method</th>
<th>Time (h)</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂Zn</td>
<td>3.0</td>
<td>A</td>
<td>8</td>
<td>2aa 57 (54)</td>
</tr>
<tr>
<td>2</td>
<td>Et₂Zn</td>
<td>3.0</td>
<td>A</td>
<td>8</td>
<td>2ab 62 (37)</td>
</tr>
<tr>
<td>3</td>
<td>(n-Bu)₂Zn</td>
<td>2.4</td>
<td>B</td>
<td>2</td>
<td>2ab 81 (56)</td>
</tr>
<tr>
<td>4</td>
<td>(n-Bu)₂ZnLi</td>
<td>3.0</td>
<td>C</td>
<td>2</td>
<td>2ab 27d</td>
</tr>
<tr>
<td>5</td>
<td>(n-Hex)₂Zn</td>
<td>2.4</td>
<td>B</td>
<td>2</td>
<td>2ac 66 (61)</td>
</tr>
<tr>
<td>6</td>
<td>c-HexZn</td>
<td>2.4</td>
<td>A</td>
<td>8</td>
<td>2ad 50e</td>
</tr>
<tr>
<td>7</td>
<td>(i-Pr)₂Zn</td>
<td>1.2</td>
<td>B</td>
<td>1</td>
<td>2ae 86 (62)</td>
</tr>
<tr>
<td>8</td>
<td>(i-Bu)₂Zn</td>
<td>2.4</td>
<td>B</td>
<td>2</td>
<td>2af 50e</td>
</tr>
<tr>
<td>9</td>
<td>EtO₂C(CH₃)₂Zn</td>
<td>3.0</td>
<td>A</td>
<td>8</td>
<td>2ag 54e</td>
</tr>
<tr>
<td>10</td>
<td>NC(CH₂)₃Zn</td>
<td>3.0</td>
<td>A</td>
<td>8</td>
<td>2ah 49e</td>
</tr>
</tbody>
</table>

*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 ¹⁹F 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, Et₂Zn 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 (CF₂H) group also reacted smoothly to give the product in excellent yield (entry 5).

Table 2. 1,4-Conjugated Alkylation of Various Fluoroalkylated Electron-Deficient Olefins 1 with Et₂Zn

<table>
<thead>
<tr>
<th>Entry</th>
<th>EWD</th>
<th>R</th>
<th>Et₂Zn (equiv)</th>
<th>Temp (°C)</th>
<th>Product Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>Et₂Zn (3.6 equiv) at –20 °C, 24 h</td>
<td>2aa 83 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>Et₂Zn (3.6 equiv) at –40 °C, 24 h</td>
<td>2ab 80 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>Et₂Zn (3.6 equiv) at –20 °C, 24 h</td>
<td>2ca 75 (68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>Et₂Zn (3.6 equiv) at –20 °C, 24 h</td>
<td>2da 72 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>Et₂Zn (3.6 equiv) at –20 °C, 24 h</td>
<td>2ea 85 (85)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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.15 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.

Scheme 2 Preliminary results of the conjugated addition using chiral substrates

1H and 13C NMR spectra were recorded on a Bruker DRX-500 (500.13 MHz for ¹H and 125.75 MHz for ¹³C) spectrometer on samples dissolved in CDCl₃ with Me₆Si as an internal reference. A Jeol JNM-AL400 (376.05 MHz) spectrometer was used to record ¹⁹F NMR spectra in CDCl₃ using CFCl₃ as an internal standard. IR spectra were recorded as liquid film or KBr disk with an Avargas-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 F254). All reactions were carried out under an atmosphere of argon. Anhyd THF and Et₂O 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.

A. Morigaki et al.

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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-ene (1a; 50 mg, 0.25 mmol) in THF (1 mL) was added alkylzinc iodide (freshly prepared prior to the reaction from R and Zn dust) in THF at 0 °C. The mixture was then stirred for 8 h at 0 °C and quenched with saturated aqueous NH4Cl (5 mL). The mixture was then concentrated in vacuo. 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-ene (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 stirred for 30 min at 0 °C at –78 °C and then for 1 h at –78 °C. The reaction was quenched with saturated aqueous 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. For a detailed description, refer to the original paper.

1-Phenyl-3-trifluoromethylnonan-1-one (2ab)
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 (CDCl3): δ = 1.06 (s, 9 H), 3.02 (ddd, J = 10.5 Hz, 3 F).
19F NMR (CDCl3): δ = –71.09 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C16H13F3O (M + H): 259.1091; found: 259.1093.

1-Phenyl-3-trifluoromethylpentan-1-one (2ac)
Method A; the product was inseparable from impurities, therefore only the peaks that could be assigned are described. For IR, 1H NMR, and 19F NMR data, refer to the original paper.

3-Cyclohexyl-4,4,4-trifluoro-1-phenylbutan-1-one (2ad)
Method B; yield: 38 mg (0.16 mmol, 62%); white solid; mp 28–29 °C.
IR (KBr): 2935, 2974, 2947, 2921, 2889, 1684, 1598, 1473, 1452, 1396, 1322, 1271, 1211, 1169, 1137, 1070 cm–1.
1H NMR (CDCl3): δ = 0.99 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 2.13 (sept, 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).
13C NMR (CDCl3): 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.
19F NMR (CDCl3): δ = –67.69 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C16H13F3O (M + H): 245.1153; found: 245.1149.

1-Phenyl-3-trifluoromethylpentan-1-one (2ae)
Method B; yield: 38 mg (0.16 mmol, 62%); yellow oil.
IR (KBr): 2935, 2974, 2947, 2921, 2889, 1684, 1598, 1473, 1452, 1396, 1322, 1271, 1211, 1169, 1137, 1070 cm–1.
1H NMR (CDCl3): δ = 1.06 (s, 9 H), 3.02 (ddd, J = 10.5 Hz, 3 F).
19F NMR (CDCl3): δ = –71.37 (d, J = 9.8 Hz, 3 F).
HRMS: m/z calcd for C16H13F3O (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. For IR, 1H NMR, and 19F NMR data, refer to the original paper.

7-Oxo-7-phenyl-5-trifluoromethylheptane-1,1-diol (2ab)
Method B; the product was inseparable from impurities, and therefore only the peaks that could be assigned are described. For IR, 1H NMR, and 19F NMR data, refer to the original paper.

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Synthesis 2013, 45, 101–105
N,N-Dibenzyl-3-trifluoromethylpentanamide (2ha)
Method B; yield: 65 mg (0.19 mmol, 74%); yellow oil.

IR (neat): 3088, 3065, 3031, 2970, 2939, 2883, 1744, 1651, 1606, 1586, 1496, 1435, 1385, 1367, 1257 cm⁻¹.

1H NMR (CDCl₃): δ = 1.10 (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).

13C NMR (CDCl₃): 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.

19F NMR (CDCl₃): δ = –70.93 (d, J = 7.6 Hz, 3 F).

HRMS: m/z calecd for C₂₃H₂₅F₂NO (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, 1856, 1465, 1448, 1414, 1383, 1326, 1253, 1151, 1086, 1044, 1025 cm⁻¹.

1H NMR (CDCl₃): δ = 1.035 (d, J = 7.5, 0.81 Hz, 3 H), 1.78–1.88 (m, 2 H), 2.69–2.80 (m, 1 H), 3.14 (ddd, 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).

13C NMR (CDCl₃): 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.

19F NMR (CDCl₃): δ = –70.61 (d, J = 7.6 Hz, 3 F).

HRMS: m/z calecd for C₁₅H₁₇F₃NO₂S (M + H): 267.0667; found: 267.0661.

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

IR (neat): 3068, 3035, 2985, 2946, 2884, 1790, 1697, 1473, 1395, 1366, 1322, 1208, 1169, 1139, 1124, 1084, 1069, 1045, 1015 cm⁻¹.

1H NMR (CDCl₃): 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).

13C NMR (CDCl₃): 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.

19F NMR (CDCl₃): δ = –71.22 (d, J = 7.6 Hz, 3 F).

HRMS: m/z calecd for C₁₅H₁₇F₃NO₂ (M + H): 316.1161; found: 316.1154.

Minor Isomer

Major Isomer

Minor Isomer

Major Isomer

Minor Isomer

Major Isomer

Minor Isomer

Major Isomer

Minor Isomer

Minor Isomer
$^{13}$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: $m/z$ calcd for C$_{16}$H$_{19}$F$_3$NO$_3$ (M + H): 330.1317; found: 330.1325.

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References


(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, ($n$-Bu)$_3$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).

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