A Convenient Route to Trifluoromethyl-Substituted Cyclopropane Derivatives

Pavel K. Mykhailiuk, Sergii Afonin, Anne S. Ulrich, Igor V. Komarov

Abstract: A range of alkenes have been converted in a single step into the corresponding trifluoromethyl-substituted cyclopropanes by treatment with 2-diazo-l,l,l-trifluoroethane over metal catalysts. Application of the Gaspar–Roth procedure allowed the preparation of target compounds on a multi-gram scale. The practical utility of this reaction has been demonstrated by the synthesis of both diastereoisomers of the non-natural amino acid trifluoronorcoramic acid in two steps.

Key words: fluorine, alkenes, amino acids, catalysts, diazo compounds

The cyclopropane ring is a vital structural unit in many naturally occurring and biologically active molecules. Cyclopropanes containing trifluoromethyl substituents are especially attractive moieties, because fluorination (e.g. incorporation of a CF₃-group) often imparts unique chemical and biological properties to organic compounds. Several methods for the synthesis of trifluoromethyl-substituted cyclopropanes are known: transformation of cyclopropane carbonylaxic acids by treatment with sulfur tetrafluoride (SF₄), reaction of active methylene groups with 2-bromo-3,3,3-trifluoropropene, and intramolecular cyclization of trifluoromethyl-substituted cyanohydrins, amongst others. The addition of photolytically generated trifluoromethylcarbene to alkenes has also been described in the literature. However, in the latter report, the products – trifluoromethyl-substituted cyclopropanes – were not isolated and the reaction mixtures were only analyzed by gas chromatography. Surprisingly, catalytic decomposition of 2-diazo-l,l,l-trifluoroethane for the generation of trifluoromethylcarbene has hardly received any attention so far, even though the transition-metal-catalyzed generation of other carbenes and their subsequent reactions are widely applied. Recently, Simonneaux and co-workers described the first example of catalytic trifluoromethylcarbene generation and its stereoselective addition to styrene derivatives. Here, we have extended the application of this methodology to the trifluoromethyl-cyclopropanation of diverse classes of alkenes by 2-diazo-l,l,l-trifluoroethane over metal catalysts, and outline the scope of the reaction.

The procedure reported in the original work required isolation of highly toxic, gaseous CF₃CHN₂. Obviously, it is desirable to avoid this hazardous step, especially when working on a large scale. Therefore, for the trifluoromethyl-cyclopropanation of alkenes 1–5 (Scheme 1), we have applied the Gaspar–Roth procedure, which was initially used for methylene generation. This safe method does not involve diazomethane isolation and easily allows the preparation of target compounds on gram scales.

Scheme 1  Trifluoromethyl-cyclopropanation of alkenes 1–5 with 2-diazol,l,l,l-trifluoroethane over metal catalysts

As can be seen from Table 1, the electron-rich olefins 1–3 smoothly underwent cyclopropanation in the presence of dirhodium(II) tetracetae as catalyst. In contrast, the cyclopropanation of cyclohexene 4 was not productive with this catalyst; the cyclopropanes (±)-4a and (±)-4b were obtained in moderate yield only when copper(I) trifluoromethanesulfonate (CuOTf) was used as a catalyst. To demonstrate the advantages of this approach, we have synthesized both diastereoisomers of trifluoronorcoramic acid analogues of naturally occurring norcoronamic acid (Figure 1), which is a building block of the toxin norcoronatine from Pseudomonas syringae.

Figure 1  Norcoronamic acid

Cyclopropanation of the corresponding unsaturated precursor 5 led to the desired products (±)-5a and (±)-5b in the presence of Rh₂(OAc)₄. Notably, the choice of catalyst...
was crucial, as the use of CuCl yielded compound 6 as the major product (Scheme 2).

Treating (±)-5a in 6N HCl at 80 °C for 30 hours afforded the amino acid (±)-7a, with spectral characteristics identical to those described in the literature for the trans-trifluoronorcoronamic acid.15 The cis-trifluoronorcoronamic acid (±)-7b was obtained from (±)-5b following the same procedure used for the preparation of (±)-7a (Scheme 3).

In summary, the addition of the catalytically generated trifluoromethylcarbene to electron-rich C=C double bonds goes smoothly with most catalysts; in other cases, a careful selection of the catalysts is needed.

Solvents were purified according to standard procedures. All starting materials were purchased from Acros, Merck or Fluka. Melting points are uncorrected. Analytical TLC was performed using Polygram SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase.1H, 13C and 19F NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 400, 101 and 377 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS (1H, 13C) or CF3C6H4 (19F) as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument using chemical ionization (CI). Elemental analysis was performed at the Mikroanalytisches Labor, Institute of Organic Chemistry, University of Karlsruhe.

**Trifluoromethyl-Cyclopropanation; General Procedure**
2-Diazo-1,1-trifluoroethane was obtained in a generator flask in the following manner; a concentrated aqueous solution of 2,2,2-trifluoroethyamine hydrochloride was slowly added dropwise to a concentrated aqueous solution of sodium nitrite under stirring at 0 °C. The diazotrifluoroethene formed was gradually blown off the generator flask by an inert gas (Ar) through a drying tube (MgSO4) into a vessel equipped with a condenser. The vessel contained a stirring mixture of the neat alkene and the catalyst (10 mol%) listed in Table 1 (in the case of 5, the solvent CH2Cl2 was used). The mixture of the inert gas and CF3CHN2 was blown through an inlet in such a way that it passed through the stirring reaction mixture. When the reaction was complete (NMR, HPLC; usually 5–10 equivalents of the 2,2,2-trifluoroethylamine hydrochloride was consumed in 5–12 h), the reaction mixture was dissolved in Et2O and filtered. The filtrate was triturated by the addition of 5% aqueous KMnO4 (Caution! The reaction is exothermic!) to remove traces of unreacted alkene, washed with H2O (2 ×), dried over MgSO4 and evaporated. The isomeric CF3-substituted cyclopropanes were isolated by either distillation or column chromatography. TLC (Silufol; pentane–Et2O) or pentane–MeOH] of all diastereomeric mixtures clearly showed two spots, thus proving the possibility of preparative separation of the diastereomers. Indeed, the cyclopropanes 1a/1b, 3a/3b and 5a/5b were easily separated by flash chromatography. However, the high volatility of 2a/2b and 4a/4b hindered their preparative separation: evaporation of the eluent led to co-evaporation of the products.

**Table 1** Trifluoromethyl-cyclopropanation of 1–5

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Catalysta</th>
<th>Products</th>
<th>Yield (%)b</th>
<th>Ratio a/b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh2(OAc)4</td>
<td><img src="image1" alt="image" /></td>
<td>91</td>
<td>2.0:1.0</td>
</tr>
<tr>
<td>2</td>
<td>Rh2(OAc)4</td>
<td><img src="image2" alt="image" /></td>
<td>63</td>
<td>1.8:1.0</td>
</tr>
<tr>
<td>3</td>
<td>Rh2(OAc)4</td>
<td><img src="image3" alt="image" /></td>
<td>82</td>
<td>2.1:1.0</td>
</tr>
<tr>
<td>4</td>
<td>CuOTf</td>
<td><img src="image4" alt="image" /></td>
<td>45</td>
<td>2.0:1.0</td>
</tr>
<tr>
<td>5</td>
<td>Rh2(OAc)4</td>
<td><img src="image5" alt="image" /></td>
<td>23</td>
<td>1.0:1.0</td>
</tr>
</tbody>
</table>

a 10 mol% of catalyst was used in each experiment.
b Isolated yield after distillation.

![Scheme 2](image6) Trifluoromethyl-cyclopropanation of 5 over CuCl yielded the unexpected product 6.

![Scheme 3](image7) Synthesis of trifluoronorcoronamic acid 7a and its stereoisomer 7b.

(1RS,6SR,7RS)-7-(Trifluoromethyl)-2-oxabicyclo[4.1.0]heptane (1a)
Bp (mixture 1a/1b) 50–55 °C (20 mmHg); Rf = 0.8 (pentane–Et2O, 2:1).

**Synthesis of trifluoronorcoronamic acid 7a**

\[
\begin{align*}
\text{AcHN} & \quad \text{CO}_2\text{Me} \\
\text{CF}_3\text{CHN}_2 & \quad \text{CuCl} \\
\text{CH}_2\text{Cl}_2 & \quad \text{AcHN} \\
\text{CO}_2\text{Me} & \quad \text{AcHN} \\
\text{CO}_2\text{Me} & \quad \text{H}_2\text{N} \\
\text{CF}_3 & \quad \text{H}_2\text{N} \\
\text{COOH} & \quad \text{COOH} \\
\text{HCl} & \quad \text{HCl} \\
\text{F}_3 & \quad \text{F}_3 \\
\text{H}_2 & \quad \text{H}_2 \\
\text{N} & \quad \text{N} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{F} & \quad \text{F} \\
\end{align*}
\]

Synthesis 2008, No. 11, 1757–1760 © Thieme Stuttgart · New York
1H NMR (400 MHz, CDCl3): δ = 3.70 (m, 2 H, 1-CH and 3-CH), 3.29 (dd, J = 11.4, 2.0 Hz, 1 H, 3-CH), 2.06 (m, 2 H, 5-CH), 1.73 (m, 1 H, 4-CH), 1.46 (m, 1 H, 4-CH), 1.28 (m, 2 H, 6-CH and 7-CH).

13C NMR (101 MHz, CDCl3): δ = 128.82 (s, Ph), 128.35 (s, Ph), 123.68 (q, 1 C–F = 35.2 Hz, 7-CH), 20.25 (s, 5-CH), 14.17 (s, 4-CH2), 12.94 (s, 6-CH).


2-(Trifluoromethyl)cyclopropyl Acetate (2a and 2b)

Bp 60–70 °C (200 mmHg).

1H NMR (400 MHz, CDCl3): δ = 4.40 (m, 1 H, 1-CH), 2.13 (s, 1 H, CH of 2b), 2.10 (s, 1.9 H, CH of 2a), 1.90 (m, 0.6 H, 2-CH of 2a), 1.76 (m, 0.4 H, 2-CH of 2b), 1.45–1.20 (m, 2 H, 3-CH2).

13C NMR (101 MHz, CDCl3): δ = 100.84 (d, JCF = 7.5 Hz, 1.0 F, HF of 2b), 95.84 (d, JHF = 7.5 Hz, 1.8 F, CF3 of 2a).

C NMR (101 MHz, CDCl3): δ = 170.09 (s, CH2CO2 of 2b), 169.59 (s, CH2CO2 of 2a), 125.12 (q, JCF = 271.1 Hz, CF1 of 2b), 124.76 (q, JCF = 270.5 Hz, CF1 of 2a), 49.07–48.96 (2 overlapped q, JCF = 4.0 Hz, OCH), 20.10 (s, CH2 of 2a), 20.09 (s, CH2 of 2b), 19.95 (q, JCF = 37.1 Hz, CCF2 of 2a), 18.37 (q, JCF = 36.1 Hz, CCF of 2b), 9.06 (q, JCF = 3.1 Hz, CH2 of 2a), 8.07 (q, JCF = 3.1 Hz, CH2 of 2b).


Methyl 2-[Acetyl(2,2,2-trifluoroethyl)amino]acrylate (6)

Compound 6 was obtained in 15% yield as a viscous oil using CuCl as a catalyst.

1H NMR (400 MHz, CDCl3): δ = 5.62 (s, 1 H), 4.85 (s, 1 H), 4.46 (q, J = 8.4 Hz, 2 H), 3.72 (s, 3 H), 1.92 (s, 3 H).

13C NMR (377 MHz, CDCl3): δ = 88.5 (t, J = 7.5 Hz, CF3).

Methyl (1RS,2SR)-1-(Acetamido)-2-(trifluoromethyl)cyclopropene carbonate (5a)

Rf = 0.4 (CH2Cl2–MeOH, 5:1).

1H NMR (400 MHz, CDCl3): δ (rotamers) = 6.31 (2 × br s, 1 H, NH), 3.70 (2 × s, 3 H, CO2CH3), 2.12 (m, 1 H, CF2CH), 1.92 (2 × s, 3 H, CH2CO), 1.61 (m, 1 H, CH=CH), 1.42 (m, 1 H, CHH).

13C NMR (377 MHz, CDCl3): δ = 101.41 (d, JHF = 7.5 Hz, CF3).

MS: m/z = 184 [M + 1]*. Anal. Calcd for C7H12F3NO3: C, 42.65; H, 4.48; N, 6.22. Found: C, 42.61; H, 4.43; N, 7.66.

Methyl (1RS,2RS)-1-(Acetamido)-2-(trifluoromethyl)cyclopropene carbonate (5b)

Rf = 0.35 (CH2Cl2–MeOH, 5:1).

1H NMR (400 MHz, CDCl3): δ (rotamers) = 5.86 (2 × br s, 1 H, NH), 3.68 (3 s, 3 H, CO2CH3), 2.40 (m, 1 H, CF2CH), 1.97 (br s, 4 H of CH2CO and CHH), 1.68 (t, J = 6.8 Hz, 1 H, CHH).

13C NMR (377 MHz, CDCl3): δ = 100.07 (d, JHF = 7.5 Hz, CF3).

MS: m/z = 184 [M + 1]*. Anal. Calcd for C7H12F3NO3: C, 42.65; H, 4.48; N, 6.22. Found: C, 42.61; H, 4.43; N, 7.66.

(1S,2S,3R,4S,5R)-2-(Trifluoromethyl)cyclopropyl benzene (3a)

Rf = 0.5 (pentane–EtO, 2:1).

1H NMR (400 MHz, CDCl3): δ = 7.32 (t, J = 7.6 Hz, 2 H, Ph), 7.25 (t, J = 7.6 Hz, 1 H, Ph), 7.16 (s, J = 7.6 Hz, 2 H, Ph), 2.44 (dt, J = 9.2, 5.6 Hz, 1 H, PhCH3), 1.87 (m, 1 H, CF2CH), 1.46 (dt, J = 9.6, 5.6 Hz, 1 H, CHH), 1.35 (m, 1 H, CHH).

13C NMR (101 MHz, CDCl3): δ = 139.24 (s, Ph), 129.64 (s, Ph), 128.82 (s, Ph), 128.35 (s, Ph), 126.68 (q, JCF = 240.5 Hz, CF3), 23.14 (q, JCF = 37.3 Hz, CF2CH), 19.78 (q, JCF = 3.2 Hz, PhCH), 11.06 (q, JCF = 3.2 Hz, CH2).

MS: m/z = 186 [M+]*. Anal. Calcd for C15H16F3: C, 64.51; H, 4.87. Found: C, 64.22; H, 4.50.

(1S,2S,3R,4S,5R)-2-(Trifluoromethyl)cyclopropyl benzene (3b)

Rf = 0.5 (pentane–EtO, 2:1).

1H NMR (400 MHz, CDCl3): δ = 7.33 (d, J = 4.4 Hz, 4 H, Ph), 7.27 (m, 1 H, Ph), 2.54 (dt, J = 8.4, 8.0 Hz, 1 H, PhCH3), 1.91 (m, 1 H, CF2CH), 1.51 (dd, J = 7.2, 5.6 Hz, 1 H, CHH), 1.35 (m, 1 H, CHH).

13C NMR (377 MHz, CDCl3): δ = 100.59 (d, JHF = 7.5 Hz, CF3).

1H NMR (101 MHz, CDCl3): δ = 135.49 (s, Ph), 133.10 (q, JCF = 221.5 Hz, CF3), 127.14 (s, Ph), 126.99 (s, Ph), 126.71 (s, Ph), 20.71 (q, JCF = 3.2 Hz, PhCH), 20.45 (q, JCF = 35.2 Hz, CF2CH), 6.63 (q, JCF = 3.2 Hz, CH3).

MS: m/z = 186 [M+]*. Anal. Calcd for C15H16F3: C, 64.51; H, 4.87. Found: C, 64.22; H, 4.50.
Mp >200 °C (dec).  

$^1$H NMR (400 MHz, D$_2$O): $\delta = 2.75$ (m, 1 H, CF$_3$CH), 1.93 (t, $J = 9.2$ Hz, 1 H, CH$_2$), 1.87 (t, $J = 9.2$ Hz, 1 H, CH$_2$).

$^{19}$F NMR (377 MHz, CD$_3$OD): $\delta = 102.33$ (d, $^3J_{HF} = 7.5$ Hz, CF$_3$).

MS: $m/z = 170$ [M – Cl]$^+$.  

Anal. Calcd for C$_5$H$_7$ClF$_3$NO$_2$: C, 29.21; H, 3.43; N, 6.81. Found: C, 29.01; H, 3.14; N, 6.43.

Acknowledgment  

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References  


(b) Doering, W. E.; Roth, W. R. Tetrahedron 1963, 19, 715; and references therein.

(11) Notably, Simonneaux and co-workers observed the stereoselective formation of only the trans-isomer 3a, while performing the trifluoromethyl-cyclopropanation of 3 over chiral metalloporphyrins (reference 9).


