Organocatalytic Domino Michael–Aldol Reaction of Ketones and α,β-Unsaturated Trifluoromethyl Ketones

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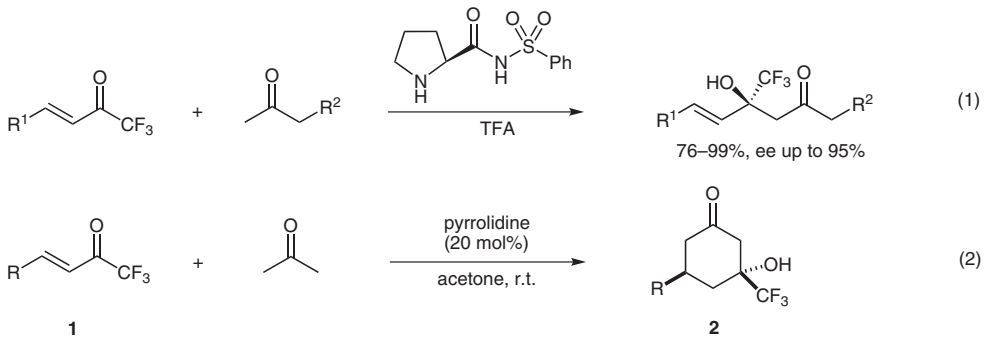
Abstract: Pyrrolidine-catalyzed domino Michael–aldol reaction of α,β-unsaturated trifluoromethyl ketones and ketones was achieved under mild conditions; β-hydroxy-β-trifluoromethyl cyclohexanones were obtained in high yields with good diastereoselectivities.

Key words: bicyclic compounds, cyclizations, domino reactions, organocatalytic, trifluoromethyl

The importance of fluorine-containing compounds in the fields of agricultural, medicinal and material chemistry is well known.[1] Among various organofluorine compounds, α-trifluoromethyl tertiary alcohols have attracted much attention recently because they could serve as liquid crystals[2a] and drugs such as Efavirenz (anti-HIV).[2b,c] On the other hand, since cyclic compounds form the backbone of many bioactive compounds, the development of synthetic methods for cyclic α-trifluoromethyl tertiary alcohols would be very valuable in the field of pharmaceutical research.[3]

Except for the direct trifluoromethylation of ketones,[4] most methods for the synthesis of α-trifluoromethyl tertiary alcohols utilize α-trifluoromethyl ketones as precursors and the aldol reaction of such ketones takes an important place in those synthetic methodologies.[5] However, preformed enol or enolate derivatives are involved in those reactions, which is not atom efficient. Recently, a direct organocatalytic aldol reaction pioneered by List, Barbas and co-workers has achieved great success.[6] The proline-catalyzed asymmetric aldol reaction between methyl ketones and aryl trifluoromethyl ketones was realized by Zhang and co-workers, although only moderate enantioselectivities were obtained.[7a] During the course of our studies on the reaction of trifluoromethyl substituted ketones, it was found that the regioselectivity of the reaction of ketones and α,β-unsaturated trifluoromethyl ketones could be controlled by choosing an appropriate organocatalyst; unsaturated α-trifluoromethyl tertiary alcohols were synthesized with good enantioselectivities from the aldol reaction of methyl ketones and α,β-unsaturated trifluoromethyl ketones under the catalysis of proline-derived *N*-sulfonylamide (Scheme 1, equation 1).[7b] When pyrrolidine was used as the catalyst, however, 3-hydroxy-3-(trifluoromethyl)cyclohexanones were obtained through an organocatalyzed Michael–aldol reaction (Scheme 1, equation 2). A few methods could be found in the literature concerning access to this kind of structure. The reaction of fluoroalkyl-containing 1,3-dicarbonyl compounds with enones suffered from low yields.[8a,b] The Michael–aldol reaction of cyclic enamines with α,β-unsaturated trifluoromethyl ketones affording hydroxy- and trifluoromethyl-containing bicyclic ketones was reported recently, but only cyclic enamines worked well in such cases and the preformation of enamines was not atom-economic.[8c,d] Herein we report the detailed results of pyrrolidine-catalyzed domino Michael–aldol reaction of ketones and α,β-unsaturated trifluoromethyl ketones, which provides a practical method for the synthesis of β-hydroxy-β-trifluoromethyl cyclohexanones.



Scheme 1

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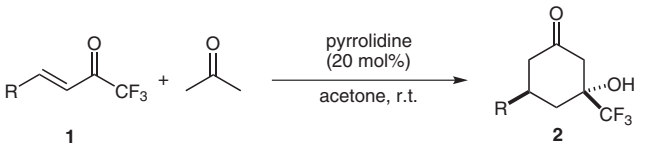
To some extent, the domino reaction[9] reported herein is similar to the proline-catalyzed Robinson annulation pioneered by Hajos, Eder and co-workers thirty years ago,[9a,b] and the domino Michael–aldol reaction of acyclic β-keto esters and unsaturated ketones recently reported by Jørgensen et al.[9d,e] However, instead of simple ketones, reactive ketones such as 1,3-diketones and β-keto esters were necessary in both cases. Recently, Tang and co-workers also reported an annulation reaction of cyclic ketones with enone esters,[9h] but only acetone gave the aldol product in their reaction.

In our case, acetone and α,β-unsaturated trifluoromethyl ketones underwent a domino Michael–aldol reaction smoothly to give the corresponding β-hydroxy-β-trifluoromethyl cyclohexanones in good yields and with high diastereoselectivities using pyrrolidine as the catalyst. The results are summarized in Table 1. The reaction showed a wide scope for the structural variation of unsaturated ketone **1**. Good yields were obtained not only with aryl unsaturated ketones (Table 1, entries 1–6), but alkynyl-, alkenyl- and alkyl-substituted unsaturated ketones were also found to be suitable substrates (Table 1, entries 7–9).

Table 1 Domino Michael–Aldol Reaction of Acetone and α,β-Unsaturated Trifluoromethyl Ketones[a]



1 2

Entry	1	R	Time (h)	Product	d.r.[b]	Yield (%)[c]
1	**1a**	Ph	6	**2a**	>95:5	72
2	**1b**	4-ClC_6H_4	5	**2b**	>95:5	87
3	**1d**	4-$MeOC_6H_4$	10	**2d**	>95:5	67
4	**1e**	4-MeC_6H_4	10	**2e**	>95:5	75
5	**1f**	1-naphthyl	10	**2f**	>95:5	72
6	**1g**	2-furyl	5	**2g**	>95:5	71
7	**1h**	PhC≡C	10	**2h**	>95:5	71
8	**1i**	PhCH=CH	4	**2i**	>95:5	61
9	**1k**	*n*-C_8H_{17}	5	**2k**	>95:5	71

[a] Reaction conditions: Unsaturated ketone **1** (0.5 mmol), pyrrolidine (20 mol%), acetone (5 mL), stirring.
[b] Determined by ^1H NMR analysis of crude product.
[c] Isolated yield.

The relative stereochemistry of cyclohexanones **2** was determined by X-ray crystallographic analysis of **2a** (Figure 1).[10] The bulky phenyl and trifluoromethyl groups were found to be in equatorial positions.

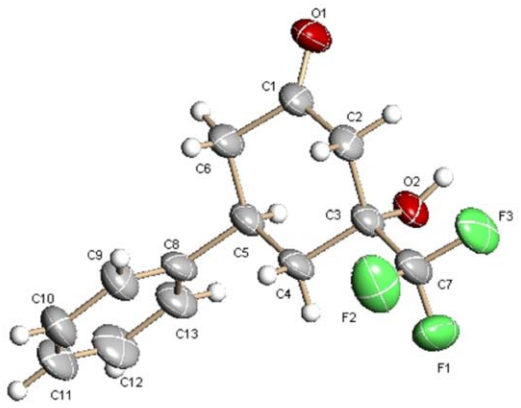
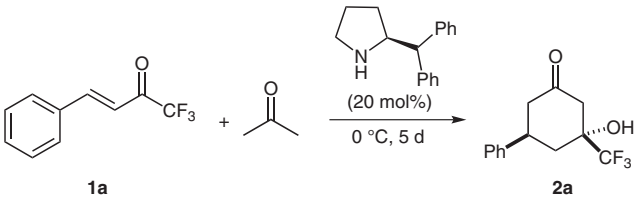


Figure 1 ORTEP representation of the crystal structure of **2a**

To investigate the potential for a catalytic asymmetric process, we tried the reaction with various chiral secondary amine catalysts. Unfortunately, the asymmetric reaction suffered from poor reactivity and enantioselectivity. The best result was obtained with the catalysis of 2-(diphenylmethyl)pyrrolidine (Scheme 2).

Taking acetone as an example, a possible mechanism for the above domino Michael–aldol reaction was proposed as shown in Scheme 3 referring to the reaction of enamines with unsaturated ketones **1**.[8c,d] The addition of the enamine, formed from the reaction of pyrrolidine and acetone, to **1** gave an iminium intermediate, which subsequently tautomerized to the corresponding enamine **3**. The intramolecular aldol reaction may proceed via the chair transition-state to give the final product **2** after hydrolytic release of the catalyst.

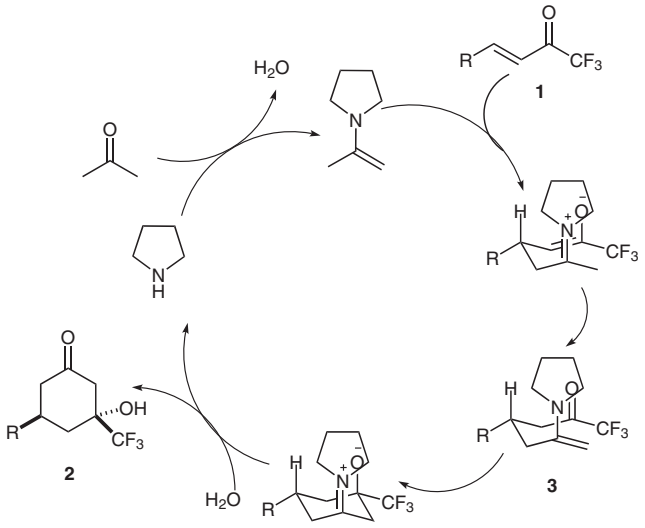
Like the reported reaction of cyclic enamines and unsaturated trifluoromethyl ketones, cyclic ketones could also undergo the domino Michael–aldol reaction with **1** under the catalysis of pyrrolidine. As shown in Table 2, various six-membered cyclic ketones reacted well with **1** and gave only one bicyclic hydroxy ketone isomer with good yields (Entries 1–3). The electronic properties of the substituent had little effect on the reaction (Entries 3, 4 and 5). However, the orientation of the substituents in the bicyclic products was different from that found in the cyclohexanones obtained from acetone. Based on X-ray diffraction analysis of **2m**, the phenyl substituent is in the axial position, whereas the trifluoromethyl group is equatorial (Figure 2).[10]



1a 2a

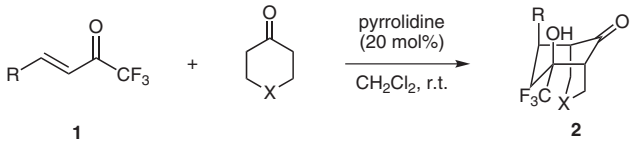
79%, 58% ee

Scheme 2



Scheme 3

Table 2 Domino Michael–Aldol Reaction of α,β-Unsaturated Trifluoromethyl Ketones and Cycloketones[a]



1 2

Entry	R	X	Time (h)	d.r.[b]	Product	Yield (%)[c]
1	Ph	CH_2	10	>95:5	**2m**	70
2	Ph	N(Me)	14	>95:5	**2n**	87
3	Ph	O	36	>95:5	**2o**	96
4	4-$MeOC_6H_4$	CH_2	10	>95:5	**2p**	80
5	4-ClC_6H_4	CH_2	10	>95:5	**2q**	83

[a] Reaction conditions: Unsaturated ketone **1** (0.25 mmol), cycloketone (2.5 mmol), pyrrolidine (20 mol%), CH_2Cl_2 (5 mL), stirring.
[b] Determined by ^1H NMR analysis of crude product.
[c] Isolated yield.

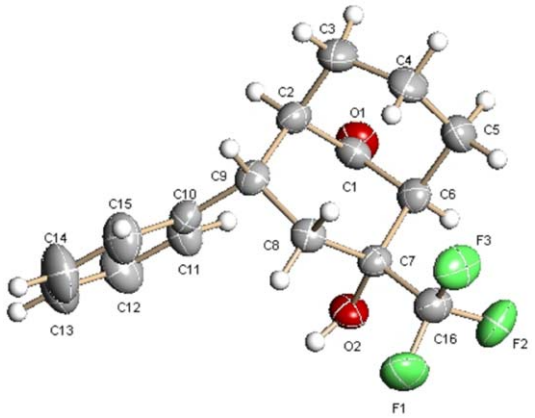
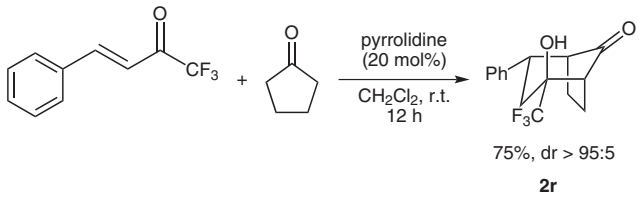


Figure 2 ORTEP representation of the crystal structure of **2m**



Scheme 4

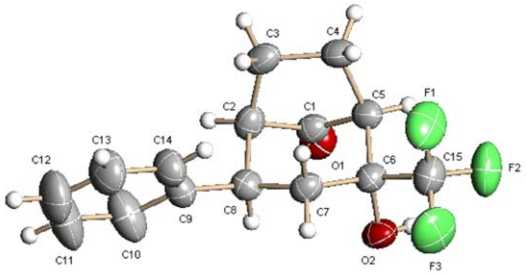


Figure 3 ORTEP representation of the crystal structure of **2r**

In contrast, the configuration of bicyclic product **2r** from the reaction of **1a** and cyclopentanone, differs with that of **2m** (Scheme 4, Figure 3).[10] Both phenyl and trifluoromethyl groups are in equatorial positions as indicated by its X-ray crystallographic analysis.

The different stereochemical outcomes for the reactions of cyclohexanone and cyclopentanone might be caused by steric effects in the Michael addition step. Two possible transition states have been proposed as shown in Figure 4.[8c,d] In the case of cyclohexanone, the addition might proceed through transition state A in order to minimize steric interaction between the cyclohexenyl and the phenyl groups. The reaction is kinetically controlled and gives the less energetically favored addition product with the phenyl substituent in the axial position. When cyclopentanone is used as reactant, the less bulky cyclopentenyl group makes it possible to adopt transition state B, which affords the more stable addition product with the phenyl group in the equatorial position. Different reaction stereochemistry for cyclopentanone and cylcohexanone has also been observed in the organocatalytic Michael addition reaction of cycloketones with chalcones.[11] The high diastereoselectivity for cyclohexanone (d.r. >50:1) is in sharp contrast to the low diastereomeric ratio (3:1) for cyclopentanone.

In addition, similar results have also been reported for a number of oganocatalytic reactions proceeding via enamine intermediates,[12] especially in the proline-derived tetrazole-catalyzed aldol reaction of chloral and ketones, in which the *syn*-selectivity (80% de) for cyclopentanone was changed to *anti*-selectivity (92% de) for cyclohexanone.[12a] The reason for this change is still unknown and has not been addressed in the literature.

In summary, we have developed a facile method for the preparation of β-hydroxy-β-trifluoromethyl cyclohexan-

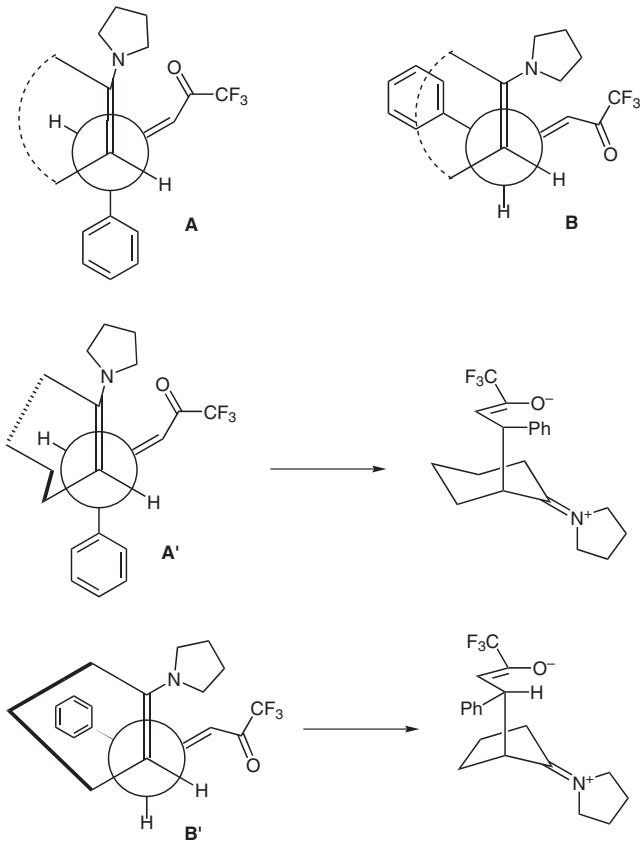


Figure 4

ones. Using pyrrolidine as the catalyst, domino Michael–aldol reaction between α,β-unsaturated trifluoromethyl ketones and ketones took place readily under mild conditions to give the corresponding addition products in high yields and diastereoselectivities.

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Acetone was distilled from K_2CO_3 before use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra and high-resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 and a Finnigan MAT-8430 spectrometer, respectively. Petroleum ether (PE), used for column chromatography on silica gel (300–400 mesh), was the fraction boiling in the range 60–90 °C.

Domino Michael–Aldol Reaction of Unsaturated Ketone 1 and Acetone; General Procedure

Unsaturated ketone **1** (1 mmol) and pyrrolidine (14 mg, 0.2 mmol) were added to acetone (5 mL). The reaction mixture was stirred at r.t. for the time indicated in Table 1. After removal of the solvent, the crude reaction product was directly charged onto the chromatography column and purified on silica gel (PE–EtOAc, 5:1) to afford compound **2**.

3-Hydroxy-5-phenyl-3-(trifluoromethyl)cyclohexanone (2a)

White solid; mp 140–141 °C.

IR (film): 3290, 1720, 1192, 1170 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 5 H), 3.49 (tt, J_1 = 12.9, 3.9 Hz, 1 H), 2.81–2.44 (m, 5 H), 2.30–2.04 (m, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.1 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 36.2, 37.6, 45.0, 47.3, 75.1 (q, J = 28.6 Hz), 125.8 (q, J = 283.4 Hz), 126.9, 127.0, 128.8, 143.5, 205.0.

MS (70 eV): m/z (%) = 258 (37.65) [M^+], 104 (100).

Anal. Calcd for $C_{13}H_{13}F_3O_2$: C, 60.46; H, 5.07. Found: C, 60.73; H, 5.28.

Compound **2a** was also prepared through an asymmetric domino Michael–aldol reaction as follows: Unsaturated ketone **1a** (48 mg, 0.24 mmol) and (*S*)-2-(diphenylmethyl)pyrrolidine (11 mg, 0.048 mmol) were added to a mixture of acetone (0.2 mL) and Et_2O (5 mL) at 0 °C. The reaction mixture was stirred for 5 d at 0 °C. After removal of the solvent, the crude reaction product was directly charged onto the chromatography column and purified on silica gel (PE–EtOAc, 10:1) to afford compound **2a**.

Yield: 49 mg (79%); $[\alpha]_D^{20}$ +7.7 (c = 0.52, $CHCl_3$); chiral HPLC (chiralpak OD column; detected at 214 nm; *n*-hexane–*i*-PrOH, 70:30) retention times: 7.8 min (major), 11.2 min (minor).

5-(4-Chlorophenyl)-3-hydroxy-3-(trifluoromethyl)cyclohexanone (2b)

White solid; mp 158–159 °C.

IR (film): 3332, 1727, 1168 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.46–7.36 (m, 4 H), 3.48 (tt, J = 12.9, 3.9 Hz, 1 H), 2.91–2.79 (m, 2 H), 2.58–2.18 (m, 4 H).

^{19}F NMR (282 MHz, acetone-d_6): δ = –84.0 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 36.0, 37.0, 44.9, 47.0, 75.0 (q, J = 29.7 Hz), 125.8 (q, J = 282.8 Hz), 128.7, 128.8, 132.1, 142.5, 204.4.

MS (70 eV): m/z (%) = 292 (10.53) [M^+], 44 (100).

Anal. Calcd for $C_{13}H_{12}F_3O_2$: C, 53.35; H, 4.13. Found: C, 53.31; H, 4.33.

3-Hydroxy-5-(4-methoxyphenyl)-3-(trifluoromethyl)cyclohexanone (2d)

White solid; mp 147–148 °C.

IR (film): 3337, 1725, 1260, 1162 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.31 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8.1 Hz, 2 H), 3.40 (tt, J = 12.9, 3.9 Hz, 1 H), 3.28 (s, 3 H), 2.82 (dd, J = 13.5 Hz, 2 H), 2.56–2.41 (m, 2 H), 2.28–2.15 (m, 2 H).

^{19}F NMR (282 MHz, acetone-d_6): δ = –84.0 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 36.4, 36.8, 43.1, 47.6, 54.6, 75.0 (q, J = 28.8 Hz), 114.0, 125.8 (q, J = 282.9 Hz), 127.8, 135.5, 158.7, 204.8.

MS (70 eV): m/z (%) = 288 (78.59) [M^+], 134 (100).

Anal. Calcd for $C_{14}H_{15}F_3O_2$: C, 58.33; H, 5.24. Found: C, 58.44; H, 5.35.

3-Hydroxy-5-(4-methylphenyl)-3-(trifluoromethyl)cyclohexanone (2e)

White solid; mp 116–117 °C.

IR (film): 3369, 1721, 1168 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.11 (m, 4 H), 3.44 (tt, J = 12.9, 3.9 Hz, 1 H), 2.79–2.43 (m, 5 H), 2.34 (s, 3 H), 2.30–2.03 (m, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.0 (s, 3 F).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 36.4, 37.3, 45.8, 48.1, 76.0 (q, *J* = 29.6 Hz), 125.0 (q, *J* = 282.9 Hz), 126.6, 129.6, 136.9, 139.4, 206.9.

MS (70 eV): *m*/*z* (%) = 272 (17.02) [M$^+$], 43 (100).

Anal. Calcd for $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.97; H, 5.61.

3-Hydroxy-5-(naphthalen-1-yl)-3-(trifluoromethyl)cyclohexanone (2f)
White solid; mp 173–174 °C.

IR (film): 3343, 1712, 1178 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.59–7.40 (m, 4 H), 4.37 (tt, *J* = 12.9, 3.9 Hz, 1 H), 2.89–2.68 (m, 5 H), 2.47–2.22 (m, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.9 (s, 3 F).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.3, 36.2, 46.3, 47.5, 75.9 (q, *J* = 29.7 Hz), 122.4, 122.5, 125.0 (q, *J* = 282.3 Hz), 125.9, 126.6, 127.7, 127.9, 129.1, 130.9, 134.1, 138.1, 206.2.

MS (70 eV): *m*/*z* (%) = 308 (88.59) [M$^+$], 153 (100).

Anal. Calcd for $C_{17}H_{15}F_3O_2$: C, 66.23; H, 4.90. Found: C, 66.27; H, 4.94.

5-(Furan-2-yl)-3-hydroxy-3-(trifluoromethyl)cyclohexanone (2g)
White solid; mp 104–105 °C.

IR (film): 3325, 1722, 1267, 1184 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 1 H), 6.33–6.31 (m, 1 H), 6.09 (d, *J* = 2.7 Hz, 1 H), 3.58 (tt, *J* = 12.9, 4.5 Hz, 1 H), 2.80–2.58 (m, 4 H), 2.40–2.35 (m, 1 H), 2.22–2.12 (m, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.1 (s, 3 F).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6, 33.8, 45.1, 45.8, 75.0 (q, *J* = 29.7 Hz), 104.8, 110.2, 124.9 (q, *J* = 282.7 Hz), 141.8, 155.5, 206.3.

MS (70 eV): *m*/*z* (%) = 248 (29.67) [M$^+$], 94 (100).

Anal. Calcd for $C_{11}H_{11}F_3O_3$: C, 53.23; H, 4.47. Found: C, 53.22; H, 4.33.

3-Hydroxy-5-(2-phenylethynyl)-3-(trifluoromethyl)cyclohexanone (2h)
White solid; mp 102–103 °C.

IR (film): 3337, 1720, 1195, 1168, 1115 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5 H), 3.40 (tt, *J* = 12.6, 4.2 Hz, 1 H), 2.85–2.42 (m, 6 H), 2.16 (t, *J* = 13.2 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.0 (s, 3 F).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 35.1, 45.7, 46.1, 75.0 (q, *J* = 30.1 Hz), 82.7, 89.2, 122.8, 124.7 (q, *J* = 282.4 Hz), 128.28, 128.32, 131.3, 204.3.

MS (70 eV): *m*/*z* (%) = 282 (29.85) [M$^+$], 128 (100).

Anal. Calcd for $C_{15}H_{13}F_3O_2$: C, 63.83; H, 4.64. Found: C, 63.97; H, 4.62.

3-Hydroxy-5-styryl-3-(trifluoromethyl)cyclohexanone (2i)
White solid; mp 122–123 °C.

IR (film): 3333, 1719, 1191, 1142 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 5 H), 6.47 (d, *J* = 15.9 Hz, 1 H), 6.14 (dd, *J* = 15.9, 7.2 Hz, 1 H), 3.13–3.05 (m, 1 H), 2.93 (s, 1 H), 2.72–2.58 (m, 3 H), 2.36–2.20 (m, 2 H), 1.92 (t, *J* = 12.9 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.0 (s, 3 F).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.0, 35.4, 45.8, 46.5, 75.6 (q, *J* = 29.8 Hz), 125.0 (q, *J* = 282.7 Hz), 126.2, 127.7, 128.6, 130.3, 131.0, 136.6, 206.2.

MS (70 eV): *m*/*z* (%) = 284 (10.79) [M$^+$], 91 (100).

Anal. Calcd for $C_{15}H_{15}F_3O_2$: C, 63.38; H, 5.32. Found: C, 63.40; H, 5.17.

3-Hydroxy-5-octyl-3-(trifluoromethyl)cyclohexanone (2k)
White solid; mp 86–87 °C.

IR (film): 3332, 2921, 1720, 1134 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66–2.51 (m, 3 H), 2.20–1.96 (m, 4 H), 1.64 (t, *J* = 13.2 Hz, 1 H), 1.39–1.27 (m, 14 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –84.2 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 13.5, 22.4, 26.3, 29.1, 29.3, 31.7, 31.8, 34.89, 34.91, 36.2, 45.2, 45.5, 75.1 (q, *J* = 29.5 Hz), 125.9 (q, *J* = 282.3 Hz), 205.2.

MS (70 eV): *m*/*z* (%) = 294 (2.04) [M$^+$], 43 (100).

Anal. Calcd for $C_{15}H_{25}F_3O_2$: C, 61.21; H, 8.56. Found: C, 61.12; H, 8.64.

Domino Michael–Aldol Reaction of Unsaturated Ketone 1 and Cyclic Ketones; General Procedure
Unsaturated ketone **1** (0.25 mmol), cyclic ketones (2.5 mmol) and pyrrolidine (3 mg, 0.05 mmol) were added to CH_2Cl_2 (5 mL). The reaction mixture was stirred at r.t. for the time indicated in Table 2. After removal of the solvent, the crude reaction product was directly charged onto the chromatography column and purified on silica gel (PE–EtOAc, 5:1) to afford compound **2**.

2-Hydroxy-4-phenyl-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (2m)
White solid; mp 184–186 °C.

IR (film): 3310, 1705, 1283, 1165, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.69 (m, 1 H), 1.86 (s, 1 H), 2.03–2.40 (m, 6 H), 2.74 (s, 1 H), 3.02–3.11 (m, 2 H), 3.62 (d, *J* = 7.8 Hz, 1 H), 7.18–7.29 (m, 5 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.81 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 18.7, 30.4, 34.1, 37.3, 45.7, 50.7, 52.3, 79.6 (q, *J* = 27.3 Hz), 125.7, 127.1, 127.6 (q, *J* = 284.9 Hz), 127.9, 147.5, 213.8.

MS (70 eV): *m*/*z* (%) = 298 (9.76) [M$^+$], 98 (100.00).

Anal. Calcd for $C_{16}H_{17}F_3O_2$: C, 64.42; H, 5.74. Found: C, 64.25; H, 5.89.

6-Hydroxy-3-methyl-8-phenyl-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (2n)
White solid; mp 145–147 °C.

IR (film): 3338, 2951, 1714, 1177, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (s, 1 H), 2.06 (d, *J* = 13.8 Hz, 1 H), 2.29 (s, 3 H), 2.46 (d, *J* = 11.4 Hz, 1 H), 2.66 (dd, *J* = 10.8, 3 Hz, 2 H), 2.94 (s, 1 H), 3.28 (tt, *J* = 13.2, 2.7 Hz, 2 H), 3.81 (m, 2 H), 7.15–7.31 (m, 5 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.73 (s, 3 F).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.68, 44.39, 46.02, 51.02, 52.75, 58.13, 65.04, 80.13 (q, *J* = 28.1 Hz), 126.32, 126.66 (q, *J* = 284.4 Hz), 127.56, 128.54, 145.94, 213.12.

MS (70 eV): *m*/*z* (%) = 313 (21.42) [M$^+$], 58 (100.00).

Anal. Calcd for $C_{16}H_{18}F_3NO_2$: C, 61.33; H, 5.79; N, 4.47. Found: C, 61.36; H, 5.89; N, 4.20.

6-Hydroxy-8-phenyl-6-trifluoromethyl-3-oxabicyclo[3.3.1]nonan-9-one (2o)
White solid; mp 168–169 °C.

IR (film): 3327, 1716, 1170, 1008, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.25 (d, *J* = 14.4 Hz, 1 H), 2.70 (s, 1 H), 2.84 (s, 1 H), 3.28 (dd, *J* = 14.4, 8.9 Hz, 1 H), 3.76 (d, *J* = 12.2 Hz, 1 H), 3.89 (d, *J* = 8.9 Hz, 1 H), 3.92 (dd, *J* = 11.2, 2 Hz, 1 H), 4.41–4.47 (m, 2 H), 5.07 (s, 1 H), 7.13 (t, *J* = 7.3 Hz, 1 H), 7.22 (t, *J* = 7.4 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.46 (s, 3 F).

^{13}C NMR (125 MHz, acetone-d_6): δ = 34.95, 46.26, 54.53, 56.18, 71.30, 78.29, 80.14 (q, *J* = 27.4 Hz), 126.27 (q, *J* = 285.0 Hz), 126.53, 128.66, 128.85, 147.02, 209.78.

MS (70 eV): *m*/*z* (%) = 300 (68.31) [M^+], 55 (100.00).

Anal. Calcd for $C_{15}H_{15}F_3O_3$: C, 60.00; H, 5.04. Found: C, 59.83; H, 5.13.

2-Hydroxy-4-(4-methoxyphenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (2p)
White solid; mp 131–133 °C.

IR (film): 3306, 2942, 1708, 1516, 1160, 830 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.62 (s, 1 H), 2.01–2.33 (m, 7 H), 2.72 (d, *J* = 1.8 Hz, 1 H), 2.97–3.06 (m, 2 H), 3.56 (d, *J* = 9 Hz, 1 H), 3.75 (s, 3 H), 6.80 (d, *J* = 9.0 Hz, 2 H), 7.20 (d, *J* = 9.0 Hz, 2 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.65 (s, 3 F).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.81, 30.49, 35.14, 37.41, 44.96, 50.27, 52.26, 55.23, 80.11 (q, *J* = 28.1 Hz), 113.84, 126.73 (q, *J* = 284.7 Hz), 128.64, 138.62, 157.91, 216.11.

MS (70 eV): *m*/*z* (%) = 328 (17.18) [M^+], 231 (100.00).

Anal. Calcd for $C_{17}H_{19}F_3O_3$: C, 62.19; H, 5.83. Found: C, 62.05; H, 5.84.

2-Hydroxy-4-(4-chlorophenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (2q)
White solid; mp 194–195 °C.

IR (film): 3325, 1705, 1283, 1172, 1106 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.69 (m, 1 H), 1.99–2.39 (m, 7 H), 2.72 (br s, 1 H), 2.94–3.06 (m, 2 H), 3.58 (d, *J* = 9 Hz, 1 H), 7.23 (d, *J* = 2.1 Hz, 4 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.79 (s, 3 F).

^{13}C NMR (75 MHz, acetone-d_6): δ = 18.66, 30.36, 34.03, 37.14, 44.99, 50.49, 52.10, 79.40 (q, *J* = 27.5 Hz), 127.46 (q, *J* = 285.5 Hz), 127.82, 129.62, 130.96, 146.46, 213.83.

MS (70 eV): *m*/*z* (%) = 332 (27.03) [M^+], 98 (100.00).

Anal. Calcd for $C_{16}H_{16}ClF_3O_2$: C, 57.75; H, 4.85. Found: C, 57.90; H, 4.58.

2-Hydroxy-4-phenyl-2-trifluoromethylbicyclo[3.2.1]octan-8-one (2r)
White solid; mp 114–115 °C.

IR (film): 3340, 1746, 1164, 1093, 705 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.70–2.15 (m, 5 H), 2.35 (t, *J* = 13.2 Hz, 1 H), 2.53 (d, *J* = 6 Hz, 1 H), 2.60 (d, *J* = 6.3, 1 H), 3.65–3.72 (m, 1 H), 3.75 (s, 1 H), 7.23–7.38 (m, 5 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.86, 19.54, 27.70, 42.67, 49.02, 50.37, 78.70 (q, *J* = 28.7 Hz), 123.32 (q, *J* = 284.0 Hz), 127.16, 127.45, 140.18, 213.81.

^{19}F NMR ($CDCl_3$, 282 MHz): δ = –79.66 (s, 3 F).

MS (EI, 70 eV): *m*/*z* (%) = 284 (9.56) [M^+], 55 (100.00).

Anal. Calcd for $C_{15}H_{15}F_3O_2$: C, 63.38; H, 5.32. Found: C, 63.32; H, 5.32.

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(10) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 619907 (**2a**), CCDC 665816 (**2m**) and CCDC 665817 (**2r**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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