2-Carboxythioester-1,3-dithiane: a Functionalized Masked Carbonyl Nucleophile for the Organocatalytic Enantioselective Michael Addition to Enones

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General Methods
Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F$_{254}$ pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300) or at 500 MHz (Bruker Advance 500). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl$_3$ δ = 7.26 ppm). $^{13}$C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, or on 500 MHz spectrometers (Bruker Advance 500) operating at 125 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl$_3$, δ = 77.0 ppm). $^{19}$F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Fluorine chemical shifts are reported in ppm (δ) relative to CF$_3$Cl. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell with a length of 1 dm.

Substrate 1 and catalysts were prepared according to literature procedures.$^{1}$

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**General procedure for organocatalytic reactions**

![Chemical reaction diagram]

**GENERAL PROCEDURE FOR “IN FLASK” REACTIONS**

To a solution of dithianilthioester (0.15 mmol), catalyst (0.015 mmol) and co-catalyst in dry toluene (1.5 mL), cyclohexenone (0.23 mmol) was added. The resulting mixture was stirred under inert atmosphere for 20 hours at room temperature. After this reaction time, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (eluent: Hexane/EtOAC = 8/2). The enantiomeric excess was determined by HPLC on chiral stationary phase.

**GENERAL PROCEDURE FOR THE MICROWAVE-ASSISTED REACTIONS**

The primary amine catalyst, the co-catalytic acid and the dithianilthioester (0.15 mmol) were dissolved in dry toluene; then, the \( \alpha,\beta \)-unsaturated ketone was added. The stirred reaction mixture was heated to the desired temperature under constant microwave irradiation for the desired time, typically at 40°C with power set up at 200MW. After this period, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 8/2). The enantiomeric excess was determined by HPLC on chiral stationary phase.
**Products characterization**

\[
S-(2,2,2\text{-trifluoroethyl})\ 2\text{-}(3\text{-oxocyclohexyl})\text{-1,3-dithiane-2-carbothioate (2)}
\]

The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

\[R_f = 0.25\ \text{(8:2 hexane/EtOAc).}\]

\[1^\text{H} \text{NMR (300 MHz, CDCl}_3\text{): } \delta: 3.61 \text{ (t, J=8 Hz, 2H), 2.92 (q, J = 8 Hz, 1H), 2.62 (d, J=8 Hz), 2.51 (t, J = 8 Hz), 2.37 (t, J=8 Hz), 2.25 (q, J= 8 Hz), 2.12 (t, J=8 Hz), 1.9 (q, J=8 Hz).}\]

\[1^9\text{F} \text{NMR (282 MHz, CDCl}_3\text{): } \delta: -66.46 \text{ (t, J = 8 Hz).}\]

\[13^\text{C} \text{NMR (75 MHz, CDCl}_3\text{): } \delta: 209.10 \text{ (s), 196.61 (s), 124.85 (t, J=276 Hz), 123.02 (s), 69.17 (s) 53.40 (s), 46.92 (s), 42.97 (s), 40.98 (s), 32.17 (q, J=30 Hz), 30.91 (s), 28.22 (s), 26.53 (s), 24.33 (s), 23.93 (s).}\]

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; (-) enantiomer, obtained with 9-amino-9-\text{-epi-quinine (catalyst B)}: \text{tr} 12.21 min (major), \text{tr} 14.44 min (minor); (+) enantiomer, obtained with 9-amino-9-\text{-epi-quinidine (catalyst A)}: \text{tr} 12.15 min (minor), \text{tr} 14.15 min (major).

HRMS: \text{m/z calc. for C}_{13}\text{H}_{17}\text{S}_{3}\text{O}_{2}\text{F}_{3}\text{Na}_{1} = 381.02350; \text{found = 381.02376.}\]

\[\alpha \text{D}^23 = -3.79^\circ \ \text{(c: 0.73, CHCl}_3, \text{ ee 93% obtained with 9-amino-9-\text{-epi-quinine - cat B}).}\]

\[\alpha \text{D}^23 = +4.52^\circ \ \text{(c: 0.39, CHCl}_3, \text{ ee 93% obtained with 9-amino-9-\text{-epi-quinidine - cat A).}\]

Melting point: 70-73°C
**S-(2,2,2-trifluoroethyl) 2-(3-oxocyclopentyl)-1,3-dithiane-2-carbothioate (3)**

The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a white solid.

\[ R_f = 0.21 \text{ (8:2 hexane/EtOAc).} \]

1H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \): 3.65 (q, J=8 Hz, 2H), 3.01-2.89 (m, 2H), 2.84-2.76 (m, 2H), 2.63-2.53 (m, 1H), 2.47-2.35 (m, 2H), 2.27-2.20 (m, 1H), 2.15-2.11 (m, 2H), 1.89-1.94 (m, 3H).

19F NMR (282 MHz, CDCl\textsubscript{3}) \( \delta \): -66.51 (t, J = 8 Hz).

13C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \): 214.96 (s), 196.45 (s), 124.09 (t, J=250 Hz), 67.40 (s), 44.94 (s), 39.53 (s), 37.86 (s), 32.63 (q, J=30 Hz), 27.77 (s), 27.60 (s), 23.66 (s), 23.41 (s).

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-epi-quinine (catalyst B): \( t_R \) 19.09 min (major), \( t_R \) 17.7 min (minor); enantiomer obtained with 9-amino-9-epi-quinidine (catalyst A): \( t_R \) 17.70 min (minor), \( t_R \) 16.37 min (major).

HRMS: m/z calc. for C\textsubscript{12}H\textsubscript{15}S\textsubscript{3}O\textsubscript{2}F\textsubscript{3}Na\textsubscript{1} = 367.00785; found = 367.00857.
**S-(2,2,2-trifluoroethyl) 2-(3-oxo-1,3-diphenylpropyl)-1,3-dithiane-2-carbothioate (6)**

The product was purified by flash column chromatography on silica gel with an 8:2 hexane/ethyl acetate mixture as eluent. The product appears as a light yellow oil.

$$R_f = 0.30 \text{ (8:2 hexane:EtOAc).}$$

$$^1H \text{ NMR (300 MHz, CDCl}_3\text{):} \delta: 7.93 (d, J=8 \text{ Hz, 2H}), 7.55-7.50 (m, 1H), 7.45-7.37 (m, 5H), 7.25-7.22 (m, 2H), 4.18 (dd, J = 8.1, 5.1 \text{ Hz, 1H}), 3.84-3.82 (m, 2H), 3.45 (qd, J = 10.1, 3.7 \text{ Hz, 2H}), 2.97-2.84 (m, 2H), 2.79-2.72 (m, 2H), 2.08-2.01 (m, 1H), 1.93-1.79 (m, 1H).$$

$$^{13}C \text{ NMR (75 MHz, CDCl}_3\text{):} \delta: 133.09 (s), 129.78 (s), 128.53 (s), 128.03 (s), 127.94 (s), 49.63 (s), 40.47 (s), 33.44 (q, J = 33.3 \text{ Hz}), 28.68 (s), 28.28 (s), 23.44 (s). C=O \text{ and } CF_3 \text{ are not visible}$$

$$^{19}F \text{ NMR (282 MHz, CDCl}_3\text{):} \delta: -65.95 (t, J = 8 \text{ Hz}).$$

HRMS: m/z calc. for C_{22}H_{21}S_3O_2F_3Na = 493.05480; found = 493.05469.

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-epi-quinidine (catalyst A): $$t_R$$ 15.63 min (minor), $$t_R$$ 9.67 min (major).

**S-(2,2,2-trifluoroethyl) 2-(3-oxo-1-phenylbutyl)-1,3-dithiane-2-carbothioate (7)**

The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as a light yellow oil.

$$R_f = 0.25 \text{ (9:1 hexane:EtOAc).}$$

$$^1H \text{ NMR (300 MHz, CDCl}_3\text{):} \delta: 7.32-7.29 \text{ (m, 2H), 7.26-7.24 \text{ (m, 3H), 3.91 (dd, J = 9.6, 3.9 Hz, 1H), 3.44 (qd, J = 10.0, 2.4 Hz, 2H), 3.32-3.15 \text{ (m, 2H), 2.94-2.80 \text{ (m, 2H), 2.77-2.67 \text{ (m, 2H), 2.03 \text{ (s, 3H), 2.00-1.97 \text{ (m, 1H), 1.89-1.77 \text{ (m, 1H).}}}}$$

$$^{19}F \text{ NMR (282 MHz, CDCl}_3\text{):} \delta: -65.99 (t, J = 8 \text{ Hz}).$$

$$^{13}C \text{ NMR (75 MHz, CDCl}_3\text{):} \delta: 205.10 (s), 197.10 (s), 136.84 (s), 129.72 (s), 128.00 (s), 127.36 (q, J = 276 \text{ Hz}), 69.75 (s), 49.39 (s), 45.10 (s), 33.39 (q, J = 33.0 \text{ Hz}), 28.62 (s), 28.27 (s), 23.43 (s). HRMS: m/z calc. for C_{17}H_{19}S_3O_2F_3Na = 431.04048; found = 431.04041.$$ The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-epi-quinidine (catalyst A): $$t_R$$ 14.42 min (minor), $$t_R$$ 15.53 min (major).
S-(2,2,2-trifluoroethyl) 2-(3-oxo-1-phenylbutyl)-1,3-dithiane-2-carbothioate (8)

The product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The product appears as a light solid oil. 

\[ R_f = 0.30 \text{ (9:1 hexane:EtOAc).} \]

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \delta: 7.56-7.53 (d, 2H), 7.40-7.48 (m, 3H), 3.91 (dd, J = 9.6, 3.9 Hz, 1H), 3.44 (qd, J = 10.0, 2.4 Hz, 2H), 3.32-3.15 (m, 2H), 2.94-2.80 (m, 2H), 2.77-2.67 (m, 2H), 2.03 (s, 3H), 2.00-1.97 (m, 1H), 1.89-1.77 (m, 1H). \]

\[ \text{19F NMR (282 MHz, CDCl}_3\text{)} \delta: -65.99 (t, J = 8 Hz). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)} \delta: 206.10 (s), 197.10 (s), 188.05 (s), 142.05 (s), 136.84 (s), 131.06 (s), 129.27 (s), 125.73 (s), 69.58 (s), 49.03 (s), 45.05 (s), 33.20 (q, J = 33.0 Hz), 29.69 (s), 28.58 (s), 28.27 (s), 23.37 (s). \]

HRMS: m/z calc. for C_{17}H_{18}S_3F_3O_2Cl_1Na_1 = 465.00018; found = 465.00113.

The enantiomeric excess was obtained by HPLC with Daicel Chiralpack OD-H column; eluent: 9:1 Hex/IPA; flow rate: 0.8 mL/min; detection: 210 nm; enantiomer obtained with 9-amino-9-epi-cinchonine (catalyst C): \( t_R 21.21 \text{ min (minor), } t_R 29.37 \text{ min (major).} \)
**Procedure for the synthesis of the methyl δ-ketothioester 10: determination of the absolute configuration**

Raney-Ni (wet, 1.5g) was washed with H2O till almost neutral pH and subsequently three times with MeOH, a solution of the thioester 2 (0.2 mmol) in MeOH (2 m was added to the suspension of washed Raney-Ni in MeOH; the reaction mixture was stirred for 20 hours at room temperature. After this period, the reaction mixture filtered over a celite pad; the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: pentane/Et2O = 9/1). The desired product was obtained in 21 % yield.

Rf = 0.21 (7:3 hexane:EtOAc).

1H NMR (300 MHz, CDCl3) δ: 3.70 (s, 3H), 2.27-2.50 (m, 6H), 2.07-2.16 (m, 2H), 1.95-1.99 (m, 1H), 1.69-1.74 (m, 1H), 1.42-1.50 (m, 1H).

13C NMR (75 MHz, CDCl3) δ: 51.57 (s), 47.42 (s), 41.03 (s), 40.69 (s), 35.51 (s), 30.86 (s), 24.73 (s). C=O are not visible due to the small amount.

MS Mass (ESI+) m/z calc. for C8H14O3: 170.21, found: 171.0 [M + H]; 193.0 [M + Na].

[α]25D = -19.8° (c: 0.53, CHCl3) – compound derived from 2 (ee: 97%) obtained with 9-amino-9-epi-quinidine (cat A).

Analytical data are in agreement with literature ones.2

By comparing the sign of the optical rotatory power of compound 6 with literature data, the configuration of compound 2 obtained with catalyst A (9-amino-9-epi-quinidine ) was established to be (S).2

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**Procedure for the synthesis of the α-ketothioesters 11**

A solution of thioester 2 (1 eq., 0.33 mmol) in CH$_2$CN:H$_2$O (8:2) (1 mL) was added to a stirred solution of N-bromosucinimide (10 eq.) in CH$_2$CN:H$_2$O (8:2) (5 mL) at 0 °C. The solution turned yellow to limpid orange. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. After this period, the reaction mixture was treated with Na$_2$SO$_4$ and extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. $^1$H NMR analysis of the crude showed compound 7 as unique product formed; succinimide was precipitated from EtOAc while concentrating the crude. The crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 1/1). The desired product was obtained in 20% yield.

$^1$H NMR (300 MHz, CDCl$_3$) δ: 3.72-3.54 (m, 3H), 2.65-2.28 (m, 4H), 2.19-2.06 (m, 2H), 1.92-1.79 (m, 1H), 1.73 (ddd, J = 13.1, 10.3, 2.5 Hz, 1H).

$^{19}$F NMR (282 MHz, CDCl$_3$) δ: -66.48 (t, J = 9.6 Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 207.92 (s), 193.70 (s), 187.61 (s), 124.41 (d, J = 276.4 Hz), 43.92 (s), 41.06 (s), 40.81 (s), 30.49 (q, J = 34.3 Hz), 26.74 (s), 24.57 (s).

HRMS: m/z calc. for C$_{10}$H$_{11}$SO$_3$F$_3$Na$_1$ = 291.02732; found = 291.02763.

$[\alpha]_D^{25} = +10.9^o$ (c: 0.4, CHCl$_3$) – compound derived from 2 (ee: 98%) obtained with 9-amino-9-epí-quinidine (cat A).
Procedure for the synthesis of the methyl δ-ketoester 12

AgCO₂CF₃ (2 eq., 53 mmol) and Et₃N (1 eq., 0.12 mmol) were added to a solution of the thioester 2 in methanol (43 mmol in 210 µL); the reaction mixture was stirred for 2 hours at room temperature. After this period, the reaction mixture was treated with H₂O and extracted with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 9/1). The desired product was obtained in 60 % yield.

Rf = 0.57 (9:1 hexane:EtOAc).

HRMS: m/z calc. for C₁₁H₁₁S₂O₂F₂Na₁ = 297.05896; found = 297.05924.

¹H NMR (300 MHz, CDCl₃) δ: 3.84 (s, 3H), 3.29-3.17 (m, 2H), 2.78-2.71 (m, 2H), 2.64-2.49 (m, 3H), 2.44-2.39 (m, 1H), 2.33-2.22 (m, 1H), 2.17-2.07 (m, 3H), 1.94-1.74 (m, 2H), 1.69-1.54 (m, 1H)

¹³C NMR (75 MHz, CDCl₃) δ: 210.05 (s), 170.79 (s), 58.67 (s, 1C), 53.10 (s), 45.26 (s), 43.13 (s), 41.09 (s), 27.88 (s), 26.66 (s), 24.64 (s), 24.55 (s).

[α]D²⁵ = -7.29° (c: 0.96, CHCl₃) – compound derived from 2 obtained with 9-amino-9-epi-quinidine (cat A).
**C.I.G.A.**
Centro Interdipartimentale Grandi Apparecchiature
via C. Golgi 19  20133 MILANO  tel 02 503 14587  fax 02 503 14139  e-mail : ciga@unimi.it  web : http://users.unimi.it/ciga

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**REPORT ANALISI**
**SPETTROMETRIA DI MASSA**

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**STRUMENTAZIONE**

Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) - 4.7 T Magnet (Magnet)

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**SORGENTE**
ESI

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CAMPIONE
ME615
SORGENTE
ESI

m/z sperimentale errore (ppm)
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Molecular Formula: C 12 H 15 F 3 O 2 S 3 Na 1 (+1)

Monoisotopic Mass: 367.00785
REPORT ANALISI
SPETTROMETRIA DI MASSA

STRUMENTAZIONE
Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) - 4 T Magnet (Magnex)

CAMPIONE
ME632
SORGENTE
ESI

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Monoisotopic Mass: 493.05480

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**Molecular Formula:** C_{12}H_{18}O_{3}S_{2}Na_{1} (+1)

**Monoisotopic Mass:** 297.05896

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# Report Analisi

**Spettrometria di Massa**

**Strumentazione:**
Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APFEX II & Xmass software (Bruker Daltonics) - 4 T T Magnet (Magnex)

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**Sorgente:**
ESI

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**Molecolare Formula:** $C_{17}H_{18}O_{2}S_{3}F_{3}Cl_{1}Na_{1}(+1)$

**Monoisotopic Mass:** 465.00018
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra