

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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**Synthesis and Evaluation of Guanidinyl Pyrrolidines as Bifunctional Catalysts for
Enantioselective Conjugate Additions to Cyclic Enones**

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Supplementary Information

General procedure for the guanidine catalyzed conjugate addition reactions:

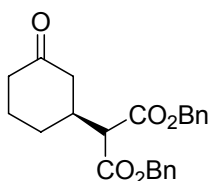
All reactions were performed in closed vials without the exclusion of air or moisture.

To a solution of the catalyst in an appropriate solvent was added the enone followed by the nucleophile. The solution was stirred at ambient temperature for the specified time and the reaction was monitored by TLC. The mixture was diluted with solvent and the resulting solution was washed once with aqueous HCl (0.5 N), dried (Na₂SO₄) and concentrated under reduced pressure to provide the crude product which was purified by flash chromatography on silica gel.

All conjugate addition products displayed spectral data in agreement with that reported in the literature.²⁻⁷

The enantiomeric excess and absolute configuration of **4a**, **4b** and **7** were assigned by comparison of the HPLC retention times with those reported in the literature.² The configuration of **4c** was assigned by analogy to the retention times for **4a** and **4b**. The enantiomeric excess of nitroketones **5a,b,c,d** and **5f** were determined by chiral HPLC comparison with racemic samples. The enantiomeric excess of **5e** was determined by conversion to diastereomeric ketals with (2*R*,3*R*)-2,3-butanediol. The absolute configurations of **5a-f** were determined by comparison of the sign of the observed optical rotations with that reported in the literature.⁷

Dibenzyl 2-((*S*)-3-oxocyclohexyl)malonate (**4a**):^{2,3}



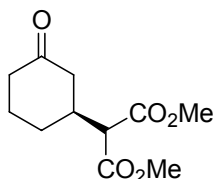
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), dibenzyl malonate (152 μ L, 0.6 mmol) and **2** (9.5 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (3 mL) for 139 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 125 mg (64%) of **4a** as a colourless solid.

¹H NMR (500 MHz, CDCl₃): 7.36-7.34 (m, 6H, ArH), 7.30-7.27 (m, 4H, ArH), 5.16 (AB system, 4H, OCH₂), 3.42 (d, 1H, *J* = 8.3, CH(CO₂Bn)₂), 2.62-2.52 (m, 1H, CHCH₂), 2.47-2.41 (m, 1H, CH₂), 2.41-2.36 (m, 1H, CH₂), 2.28-2.18 (m, 2H, CH₂), 2.16-2.00 (m, 1H, CH₂), 1.95-1.88 (m, 1H, CH₂), 1.7-1.6 (m, 1H, CH₂), 1.52-1.44 (m, 1H, CH₂); MS (APCI): *m/z* 381.1 (M+1); IR (neat): 2928, 1729, 1712, 1257, 1226, 1148 cm⁻¹.

Enantiomeric excess: 86.3%

*t*_{major}: 49.1 min; *t*_{minor}: 41.6 min (Chiralpak AS-H, 230 nm, hexanes/*i*PrOH, 95/5, 1 mL/min).

Dimethyl 2-((S)-3-oxocyclohexyl)malonate (4b):^{2,4}



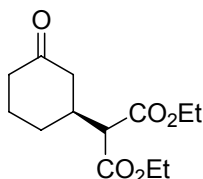
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), dimethyl malonate (71 μ L, 0.6 mmol) and **2** (14 mg, 15 mol%), according to the general procedure, in dichloromethane (1 mL) for 92 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 110 mg (94%) of **4b** as a white solid.

¹H NMR (500 MHz, CDCl₃): 3.76 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.47 (d, 1H, *J* = 8.5, CH(CO₂Me)₂), 2.59-2.50 (m, 1H, CHCH₂), 2.47-2.41 (m, 1H, CH₂), 2.41-2.36 (m, 1H, CH₂), 2.28-2.18 (m, 2H, CH₂), 2.16-2.00 (m, 1H, CH₂), 1.95-1.88 (m, 1H, CH₂), 1.7-1.6 (m, 1H, CH₂), 1.52-1.44 (m, 1H, CH₂); MS (APCI): *m/z* 229.1 (M+1); IR (neat): 2923, 1732, 1711, 1436, 1257, 1228, 1153 cm⁻¹.

Enantiomeric excess: 59%

*t*_{major}: 26.2 min; *t*_{minor}: 21.6 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

Diethyl 2-((S)-3-oxocyclohexyl)malonate (4c):^{2,4}



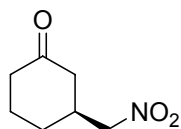
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), diethyl malonate (94 μ L, 0.6 mmol) and **2** (14 mg, 15 mol%), according to the general procedure, in dichloromethane (1 mL) for 92 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 111 mg (90%) of **4c** as a white solid.

¹H NMR (500 MHz, CDCl₃): 4.24-4.18 (2 q, 4H, CH₂CH₃), 3.29 (d, 1H, *J* = 7.4, CH(CO₂Et)₂), 2.59-2.50 (m, 1H, CHCH₂), 2.49-2.38 (m, 2H, CH₂), 2.31-2.22 (m, 2H, CH₂), 2.11-2.03 (m, 1H, CH₂), 1.99-1.94 (m, 1H, CH₂), 1.73-1.64 (m, 1H, CH₂), 1.56-1.47 (m, 1H, CH₂), 1.29-1.26 (2 t, 6H, CH₃); MS (APCI): *m/z* 257.1 (M+1); IR (neat): 2936, 1727, 1713, 1255, 1227, 1152, 1096, 1028 cm⁻¹.

Enantiomeric excess: 52%

*t*_{major}: 13.5 min; *t*_{minor}: 11.9 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

(S)-3-(Nitromethyl)cyclohexanone (5a):⁵



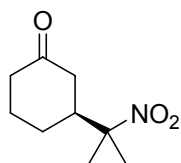
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), nitromethane (140 μ L, 2.5 mmol) and **2** (14 mg, 15 mol%), according to the general procedure, in dichloromethane (2 mL) for 120 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 25 mg (31%) of **5a** as a colourless oil.

¹H NMR (500 MHz, CDCl₃): 4.41-4.35 (d of AB, 4H, $J = 7.4, 12.1$, CH₂NO₂), 2.71-2.61 (m, 1H, CHCH₂), 2.54-2.44 (m, 2H, CH₂), 2.84-2.27 (m, 1H, CH₂), 2.21-2.10 (m, 2H, CH₂), 2.03-1.96 (m, 1H, CH₂), 1.80-1.70 (m, 1H, CH₂), 1.59-1.48 (m, 1H, CH₂); MS (EI, 70 eV): m/z 157 (M⁺); IR (neat): 2923, 2853, 1710, 1544, 1383, 1229 cm⁻¹.

Enantiomeric excess: 72%

t_{major} : 36.1 min; t_{minor} : 64.1 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

(S)-3-(2-Nitropropan-2-yl)cyclohexanone (5b):⁶



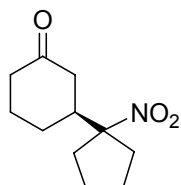
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), 2-nitropropane (93 μ L, 1.0 mmol) and **2** (9.5 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (4 mL) for 156 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 42 mg (43%) of **5b** as a colourless solid.

¹H NMR (500 MHz, CDCl₃): 2.47-2.35 (m, 3H, CHCH₂, CH₂), 2.28-2.20 (m, 1H, CH₂), 2.16-2.08 (m, 2H, CH₂), 1.83-1.77 (m, 1H, CH₂), 1.67-1.6 (m, 1H, CH₂), 1.57 (s, 3H, CH₃), 1.55 (s, 3H, CH₃), 1.47-1.38 (m, 1H, CH₂); MS (EI, 70 eV): m/z 185 (M⁺); IR (neat): 2924, 1711, 1531, 1401, 1314, 1234, 1140 cm⁻¹; $[\alpha]_{\text{D}}^{23} = -27$ (c 1, CHCl₃).

Enantiomeric excess: 65%

t_{major} : 43.3 min; t_{minor} : 40.5 min (Chiralpak AS-H, 230 nm, hexanes/iPrOH, 95/5, 1 mL/min).

(S)-3-(1-Nitrocyclopentyl)cyclohexanone (5c):⁴



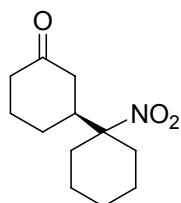
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), nitrocyclopentane (274 μ L, 2.5 mmol) and **2** (9.5 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (4 mL) for 240 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 47 mg (44%) of **5c** as a colourless oil.

¹H NMR (500 MHz, CDCl₃): 2.74-2.64 (m, 2H, CHCH₂, CH₂), 2.49-2.46 (m, 1H, CH₂), 2.42-2.35 (m, 1H, CH₂), 2.32-2.16 (m, 3H, CH₂), 2.15-2.08 (m, 1H, CH₂), 1.97-1.91 (m, 1H, CH₂), 1.83-1.66 (m, 6H, CH₂), 1.65-1.55 (m, 1H, CH₂), 1.45-1.36 (m, 1H, CH₂); MS (EI, 70 eV): m/z 211 (M⁺); IR (neat): 2957, 1713, 1530, 1449, 1434, 1351 cm⁻¹; [α]_D²³ = + 6.1 (c 1, CHCl₃).

Enantiomeric excess: 41%

*t*_{major}: 28.7 min; *t*_{minor}: 14.6 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

(S)-3-(1-Nitrocyclohexyl)cyclohexanone (5d):⁴



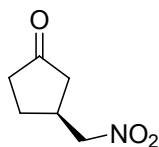
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), nitrocyclohexane (126 μ L, 1.0 mmol) and **2** (9.5 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (4 mL) for 192 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 49 mg (42%) of **5d** as a white solid.

¹H NMR (500 MHz, CDCl₃): 2.54-2.45 (m, 3H, CHCH₂, CH₂), 2.43-2.38 (m, 1H, CH₂), 2.25-2.14 (m, 1H, CH₂), 2.14-2.02 (m, 2H, CH₂), 1.96-1.91 (m, 1H, CH₂), 1.73-1.62 (m, 3H, CH₂), 1.53-1.49 (m, 2H, CH₂), 1.40-1.18 (m, 6H, CH₂); MS (EI, 70 eV): m/z 225 (M⁺); IR (neat): 2925, 2856, 1711, 1677, 1546, 1530, 1346, 1149 cm⁻¹; [α]_D²³ = - 0.3 (c 1, CHCl₃).

Enantiomeric excess: 45%

*t*_{major}: 25.6 min; *t*_{minor}: 13.1 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

(S)-3-(Nitromethyl)cyclopentanone (5e):⁷

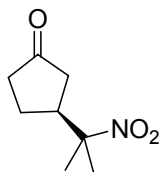


The reaction of cyclopentanone (50 μL , (0.6 mmol)), nitromethane (161 μL , 3.0 mmol) and **2** (16 mg, 15 mol%), according to the general procedure, in dichloromethane (2 mL) for 96 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 60/40) 40 mg (49%) of **5e** as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ 4.56-4.45 (m, 2H, CH₂NO₂), 3.06-2.97 (m, 1H, CHCH₂), 2.54 (dd, 1H, $J = 7.3, 18.2$, CH₂), 2.44-2.35 (m, 1H, CH₂), 2.33-2.21 (m, 2H, CH₂), 2.02 (dd, 1H, $J = 9.6, 18.2$, CH₂) 1.76-1.67 (m, 1H, CH₂); MS (APCI): m/z 142.1 (M-1); IR (neat): 1738, 1544, 1403, 1383, 1161 cm^{-1} .

Enantiomeric excess: 50% (based on ¹³C spectra of ketal with (2*R*,3*R*)-2,3-butanediol⁶).

(S)-3-(2-Nitropropan-2-yl)cyclopentanone (5f):⁷



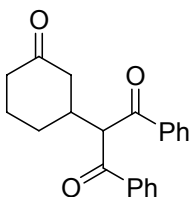
The reaction of cyclopentanone (50 μL , (0.6 mmol)), 2-nitropropane (276 μL , 1.2 mmol) and **2** (11 mg, 10 mol%), according to the general procedure, in 1,2-dichloroethane (4 mL) for 96 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 85 mg (88%) of **5f** as a colourless gum.

¹H NMR (500 MHz, CDCl₃): δ 2.89-2.81 (m, 1H, CHCH₂), 2.45-2.32 (m, 2H, CH₂), 2.28-2.20 (m, 1H, CH₂), 2.14-2.03 (m, 2H, CH₂), 1.73-1.65 (m, 1H, CH₂), 1.64 (s, 3H, CH₃), 1.62 (s, 3H, CH₃); MS (EI, 70 eV): m/z 171 (M⁺); IR (neat): 2926, 1743, 1533, 1375, 1348, 1278, 1164, 1148 cm^{-1} ; $[\alpha]_{\text{D}}^{23} = -13.3$ (c 1, CHCl₃).

Enantiomeric excess: 26%

t_{major} : 39.3 min; t_{minor} : 58.8 min (Chiralpak AS-H, 210 nm, hexanes/*i*PrOH, 85/15, 1 mL/min).

3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)cyclohexanone (**6**):⁸



The reaction of cyclohexenone (50 μ L, (0.5 mmol)), dibenzoylmethane (127 mg, 0.6 mmol) and **2** (1 mg, \sim 1 mol%), according to the general procedure, in 1,2-dichloroethane (3 mL) for 120 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 75/25) 20 mg (12%) of **6** as a white solid.

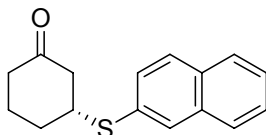
¹H NMR (500 MHz, CDCl₃): δ 8.0-7.96 (m, 4H, ArH), 7.59-7.55 (m, 2H, ArH), 7.47-7.43 (m, 4H, ArH), 5.25 (d, 1H, J = 8.1, CH(COPh)₂), 3.08-3.00 (m, 1H, CHCH₂), 2.46-2.40 (m, 2H, CH₂), 2.31-2.24 (m, 2H, CH₂), 2.07-2.02 (m, 1H, CH₂), 1.98-1.93 (m, 1H, CH₂), 1.75-1.66 (m, 1H, CH₂), 1.61-1.52 (m, 1H, CH₂); MS (APCI): m/z 319.2 (M-1); IR (neat): 2926, 1693, 1664, 1447, 1258, 1229, 1179 cm⁻¹.

Enantiomeric excess: 80%

t_{major} : 36.1 min; t_{minor} : 31.9 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

A similar reaction of cyclohexenone (50 μ L, (0.5 mmol)), dibenzoylmethane (244 mg, 1 mmol) and **2** (14 mg, 15 mol%) in dichloromethane (2 mL) for 48 h gave 167 mg (99%) of **6** with 39% ee.

(*R*)-3-(Naphthalen-2-ylthio)cyclohexanone (**7**):⁹



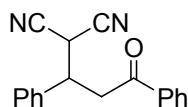
The reaction of cyclohexenone (50 μ L, (0.5 mmol)), naphthalene-2-thiol (83 mg, 0.5 mmol) and **2** (1 mg, 1 mol%), according to the general procedure, in 1,2-dichloroethane (3 mL) at -20 °C for 48 h gave after purification by flash column chromatography on silica gel (hexanes/ethylacetate 80/20) 88 mg (66%) of **6** as a colourless gum.

¹H NMR (500 MHz, CDCl₃): δ 7.92 (br s, 1H, ArH), 7.83-7.78 (m, 3H, ArH), 7.52-7.48 (m, 3H, ArH), 3.58-3.52 (m, 1H, CHCH₂), 2.76-2.72 (m, 1H, CH₂), 2.46-2.29 (m, 3H, CH₂), 2.22-2.13 (m, 2H, CH₂), 1.83-1.68 (m, 2H, CH₂); MS (EI, 70eV): m/z 256 (M⁺); IR (neat): 2929, 1709, 1418, 1220 cm⁻¹.

Enantiomeric excess: 20%

t_{major} : 16.9 min; t_{minor} : 10.9 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

2-(3-Oxo-1,3-diphenylpropyl)malononitrile (**8**):¹⁰



The reaction of *trans*-chalcone (100 mg, (0.5 mmol)), malononitrile (38 mg, 0.6 mmol) and **2** (4.5 mg, 5 mol%), according to the general procedure, in dichloromethane (1 mL) for 20 h gave 132 mg (quant.) of **9** as a solid that was pure by ¹H NMR.

¹H NMR (500 MHz, CDCl₃): δ 7.98-7.96 (m, 2H, ArH), 7.66-7.62 (m, 1H, ArH), 7.52-7.41 (m, 7H, ArH), 4.66 (d, 1H, CH(CN)₂), 3.98-3.96 (m, 1H, CHCH₂), 3.75-3.67 (m, 2H, CH₂); MS (APCI): m/z 273.1 (M-1); IR (neat): 2257, 1681, 1450, 1313, 1235 cm⁻¹.

Enantiomeric excess: 2%

*t*_{major}: 20.9 min; *t*_{minor}: 18.9 min (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 70/30, 1 mL/min).

References:

- 1) Prepared from Boc-(*S*)-prolinol by conversion to the corresponding azide *via* the mesylate and subsequent hydrogenation of the azide to the amine. For representative procedures, see: E. Bellis, K. Vasilatou, G. Kokotos *Synthesis* 2005, 2407.
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