Organocatalyzed Asymmetric Reactions via Microwave Activation

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Supporting Information

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General Remarks. Concerning $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra, chemical shift ($\delta$) are given in ppm relative to tetramethylsilane (0 ppm). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants are reported in Hz. Optical rotations were measured at 25°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10$^{-1}$ deg.cm$^2$ g$^{-1}$ (concentration c given as g/100 mL). Enantiomeric excesses were determined by chiral Super Fluid Chromatography (SFC), with appropriated program using a gradient of methanol or by chiral Gas Chromatography (GC), with appropriated program using a gradient of temperature. Temperature programs are described as follows: initial temperature (°C) – initial time (min) – temperature gradient (°C/min) – final temperature (°C); retention times (R$_T$) are given in min. Flash chromatography was performed using silicagel 32-63 µm, 60 Å. Evolution of reaction was followed by TLC. Benzaldehyde 2c and isobutyraldehyde 4c were freshly distilled before using. Cyclopentadiene monomer 7 was freshly used after cracking. (S,S)-N-Isopropyl-2,2'-bipyrolidine (iPBP) was prepared as described in literature procedure.¹ (S,S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride 9 was prepared as

described in literature. All other reagents and solvents were purchased from commercial suppliers and used as received.

**Microwave irradiation experiments.**

Microwave-assisted reactions were carried out using a focused microwave unit (Biotage Initiator™). The instrument consists of a continuous focused microwave power delivery system with operator selectable power output from 0-300 W. In all experiments, a constant power was applied to ensure reproducibility. Reactions were performed in glass vessels (2-5 mL) sealed with a septum. Pressure measurement is accomplished by a non-invasive sensor integrated into the cavity lid, which measures the deformation of the Teflon seal of the vessels (maximum 20 bar). Temperature controlled is achieved by means of an IR sensor and the indicated temperature corresponds to the maximal temperature reached during each experiment. The specified reaction time corresponds to the total irradiation time. Efficient cooling is accomplished by means of a pressurized air (with a pressure of 5 bar) during the entire experiment.

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I. Aldol reactions

**General procedure 1 under microwave irradiation.** In a 2-5 mL vessel were introduced L-proline, DMSO (2.4 mL) and finally acetone 1 (20 vol %, 0.6 mL) and the mixture was stirred for 15 min under argon. Aldehyde was added (0.3 mmol) and the vessel was sealed with a septum and placed into the microwave cavity. The microwave source was then turned on. Constant microwave irradiation as well as simultaneous air-cooling (5 bar) were used during the entire reaction time. The evolution of the reaction was monitored by TLC. After cooling to room temperature, the mixture was quenched as described in literature procedure 3 using NH₄Cl aq. sat. and extracted with EtOAc (2x). The combined organic layers were washed successively with water and brine, dried over MgSO₄, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate.

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(R)-4-hydroxy-4-(4-nitrophenyl)butan-2-one 3a (Table 2, entry 1): From 4-nitrobenzaldehyde 2a (1 eq., 0.3 mmol, 45.3 mg) and L-proline (0.2 eq., 0.06 mmol, 6.9 mg) according to general procedure I (15 W, 0 bar, 35 °C) to give complete conversion after 15 min and to afford aldol product 3a (43.3 mg, 69%). The enantiomeric excess was determined by chiral SFC (AS-H column, 2 mL/min, 200 bar, methanol 10%-2-1-25%, 30°C, Rt: 3.03 (R), 3.89 (S)). \([\alpha]_D^{20} = +42.6 \) (c 1.035, ee= 70%, CHCl₃).

\(^1\)H NMR (400 MHz, CDCl₃) : \(\delta = 8.22-8.20 \) (d, J= 8.60 Hz, 2H), 7.55-7.52 (d, J= 8.84 Hz, 2H), 5.28-5.24 (m, 1H), 3.56-3.55 (m, 1H), 2.86-2.84 (d, 2H), 2.22 (s, 3H). Other spectroscopic data are in agreement with published data.\(^3\)
(R)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)butan-2-one 3b (Table 2, entry 2): From α,α,α-trifluoro-p-tolualdehyde 2b (1 eq., 0.3 mmol, 52.23 mg) and L-proline (0.2 eq., 0.06 mmol, 6.9 mg) according to general procedure 1 (15 W, 0 bar, 32 °C) to give complete conversion after 15 min and to afford aldol product 3b (48.5 mg, 70%). The enantiomeric excess was determined by chiral SFC (AS-H column, 2 mL/min, 200 bar, methanol 2%-2-1-15%, 30°C, R: 2.95 (R), 3.43 (S)). [α]D²⁰ = +32.6 (c 1.14, ee= 70%, CHCl₃).

¹H NMR (400 MHz, CDCl₃) : δ = 7.62-7.60 (d, J= 8.08 Hz, 2H), 7.49-7.47 (d, J= 8.08 Hz, 2H), 5.23-5.20 (m, 1H), 3.44-3.43 (m, 1H), 2.85-2.84 (d, 2H), 2.21 (s, 3H). Other spectroscopic data are in agreement with published data. ⁴

(R)-4-hydroxy-4-phenylbutan-2-one 3c (Table 2, entry 3): From benzaldehyde 2c (1 eq., 0.3 mmol, 30 µL) and L-proline (0.3 eq., 0.09 mmol, 10.3 mg) according to general procedure 1 (15 W, 0 bar, 31 °C) to give 89% conversion after 1 h and to afford aldol product 3c (34.2 mg, 70%). The enantiomeric excess was determined by chiral SFC (OD-H column, 2 mL/min, 200 bar, methanol 10%-2-1-25%, 30°C, R t: 6.60 (R), 6.98 (S)). [α]D^20 = +37.2 (c 0.575, ee= 68%, CHCl₃).

^1H NMR (400 MHz, CDCl₃) : δ = 7.36-7.30 (m, 4H), 7.29-7.26 (m, 1H), 5.17-5.14 (m, 1H), 3.29 (br, 1H), 2.92-2.79 (m, 2H), 2.19 (s, 3H). Other spectroscopic data are in agreement with published data.³
(R)-4-hydroxy-4-(naphthalen-2-yl)butan-2-one 3d (Table 2, entry 4): From 2-naphtaldehyde 2d (1 eq., 0.3 mmol, 46.9 mg) and L-proline (0.3 eq., 0.09 mmol, 10.3 mg) according to general procedure 1 (15 W, 0 bar, 31 °C) to give 79% conversion after 1 h and to afford aldol product 3d (35.9 mg, 56%). The enantiomeric excess was determined by chiral SFC (AD column, 2 mL/min, 200 bar, methanol 10%-2-1-25%, 30°C, R: 6.94 (R), 7.61 (S)). [α]D20 = +34.8 (c 0.525, ee= 74%, CHCl3).

1H NMR (400 MHz, CDCl3) : δ = 7.85-7.83 (m, 4H), 7.50-7.45 (m, 3H), 5.35-5.31 (m, 1H), 3.39-3.38 (m, 1H), 2.96-2.93 (m, 2H), 2.21 (s, 3H). Other spectroscopic data are in agreement with published data.3
(R)-4-hydroxy-4-p-tolybutan-2-one 3e (Table 2, entry 5): From p-tolualdehyde 2e (1 eq., 0.3 mmol, 35 µL) and L-proline (0.3 eq., 0.09 mmol, 10.3 mg) according to general procedure 1 (15 W, 0 bar, 32 °C) to give 82% conversion (with 1:1 ratio of aldol product 3e and α,β-unsaturated ketone derived from aldol product 3e) after 1 h and to afford aldol product 3d (20.3 mg, 38%). The enantiomeric excess was determined by chiral SFC (AS-H column, 2 mL/min, 200 bar, methanol 10%-2-1-25%, 30°C, R: 2.92 (R), 3.24 (S)). [α]D^20 = +21.4 (c 0.41, ee= 64%, CHCl₃).

^1H NMR (400 MHz, CDCl₃) : δ = 7.25-7.23 (m, 2H), 7.17-7.15 (m, 2H), 5.13-5.11 (m, 1H), 3.17 (br, 1H), 2.92-2.77 (m, 2H), 2.33 (s, 3H), 2.19 (s, 3H). Other spectroscopic data are in agreement with published data.5

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II. Conjugate Additions

General procedure 2 under microwave irradiation. In a 2-5 mL vessel were introduced $(R,R)$-iPBP (0.15 eq. 0.05 mmol, 9.1 mg), CHCl$_3$ (2.5 mL), $\beta$-nitrostyrene (1 eq., 0.335 mmol, 50 mg) and finally the aldehyde or the ketone (10 eq., 3.35 mmol) and the vessel was sealed with a septum and placed into the microwave cavity. The microwave source was then turned on. Constant microwave irradiation as well as simultaneous air-cooling (5 bar) were used during the entire reaction time. The evolution of the reaction was monitored by TLC. After cooling to room temperature, the mixture was then hydrolyzed as described in literature procedure$^1$ using 1N HCl (2 mL). The layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography on silica gel using a mixture of cyclohexane and ethyl acetate.

$^{(3S,4S)}$-3-hydroxy-5-nitro-4-phenylpentan-2-one 6a (Table 3, entry 2) : From hydroxyketone 4a (10 eq., 3.35 mmol, 0.23 mL) according to general procedure 2 (15 W, 0 bar, 28°C) to give complete conversion after 4 h and to afford Michael adduct 6a as a mixture of two inseparable diastereoisomers (syn/anti 11:89) (62.3 mg, 83%). The enantiomeric excess was determined by chiral SFC (OJ column, 2 mL/min, 200 bar, methanol 5%-2-1-15%, 30°C, $R_t$: 4.7 ($S,S$), 5.5 ($R,R$)).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ = 7.41-7.23 (m, 5H), 4.84-4.79 (dd, $J_1$=6.04, $J_2$=13.36 Hz, 1H), 4.67-4.62 (dd, $J_1$=8.32, $J_2$=13.64 Hz, 1H), 4.40-4.39 (m, 1H), 3.83 (dt, $J_1$=6.04, $J_2$=8.32 Hz, 1H), 3.80-3.73 (m, 1H), 2.07 (s, 3H). Other spectroscopic data are in agreement with published data.$^1$
(2S,3R)-2-isopropyl-4-nitro-3-phenylbutanal 6b (Table 3, entry 4): From 3-methylbutyraldehyde 4b (10 eq., 3.35 mmol, 0.36 mL) according to general procedure 2 (15 W, 0 bar, 27°C) to give complete conversion after 1 h and to afford Michael adduct 6b (76.4 mg, 97%).

The enantiomeric excess was determined by chiral GC (Hydrodex-B-3P, iso 150°C, R: 38.48 (R,S), 39.61 (S,R)). [α]D20 = -51.6 (c 1.0, ee= 78%, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 9.93 (d, 1H, J = 2.2 Hz), 7.36-7.29 (m, 3H), 7.20-7.17 (m, 2H), 4.69-4.64 (dd, 1H, J = 4.32 Hz, J = 12.64 Hz), 4.60-4.54 (m, 1H), 3.92-3.86 (m, 1H), 2.79-2.75 (m, 1H), 1.75-1.67 (m, 1H), 1.10-1.09 (d, 3H, J = 7.08 Hz), 0.89-0.87 (d, 3H, J = 7.08 Hz). Other spectroscopic data are in agreement with published data.

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**Table 3:**

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**Figure 1:**

- **Signal 1:** FID 10,
  - Peak Multiplicity: 1
  - Area: 1.655
  - Height: 1.055
  - Integrated Area: 2.085

- **Signal 2:** FID 20,
  - Peak Multiplicity: 2
  - Area: 1.385
  - Height: 1.055
  - Integrated Area: 2.115

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S10
(S)-2,2-dimethyl-4-nitro-3-phenylbutanal 6c (Table 3, entry 6): From isobutyraldehyde 4c (10 eq., 3.35 mmol, 0.30 mL) and according to general procedure 2 (15 W, 0 bar, 27°C) to give 80% conversion after 2 h and to afford Michael adduct 6c (56.7 mg, 76%). The enantiomeric excess was determined by chiral GC (Hydrodex-B-3P, iso 140°C, R: 47.39 (R), 48.44 (S)). $[\alpha]_D^{20} = -6.7$ (c 1.0, ee = 77%, CHCl3).

$^1$H NMR (400 MHz, CDCl3) : δ = 9.53 (s, 1H), 7.33-7.29 (m, 3H), 7.20-7.18 (m, 2H), 4.88-4.82 (m, 1H), 4.71-4.66 (m, 1H), 3.80 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H). Other spectroscopic data are in agreement with published data.1

### III. Diels-Alder reaction

**General procedure 3 under microwave irradiation.** In a 2-5 mL vessel were introduced (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride 9 (0.05 eq. 0.095 mmol, 25 mg), MeOH/H2O (95/5 v/v 2 mL), and (E)-cinnamaldehyde 8 (1 eq., 1.915 mmol, 0.25 mL). The solution was stirred 2 minutes under argon before addition of cyclopentadiene monomer 7 (3 eq., 5.745 mmol, 0.48 mL) and the vessel was sealed with a septum and placed into the microwave cavity. The microwave source was then turned on. Constant microwave irradiation as well as simultaneous air-cooling (5 bar) were used during the entire reaction time. The evolution of the reaction was monitored by TLC. After cooling to room temperature, the mixture was then quenched as described in literature procedure5 diluting with Et2O and washed successively with H2O and brine. The organic layer was dried over Na2SO4, filtered,
concentrated under reduced pressure. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA:H₂O:CHCl₃ (1:1:2, 12 mL) for 2 h at room temperature, followed by neutralization with sat. aq. NaHCO₃ and extraction with Et₂O. Purification of the Diels-Alder adduct was accomplished by silica gel chromatography using a mixture of cyclohexane and ethyl acetate.

(1S,2S,3S,4R)-3-phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde endo-10 and (1R,2S,3S,4S)-3-phenylbicyclo[2.2.1]hex-5-ene-2-carboxaldehyde exo-10 (Table 4, entry 3) : Prepared according to general procedure 3 (50 W, 1 bar, 65 °C) to give 84% conversion after 1 h and to afford 1:1.2 endo-10/exo-10 mixture as a pale yellow oil. Product ratio was determined by ¹H NMR on the crude material. The enantiomeric excess of each diastereoisomer was determined on the primary alcohols coming from the reduction of the aldehydes endo-10/exo-10 mixture by SFC (chiralpak AD column, 2 mL/min, 200 bar, MeOH 10%-2-1-25%, 30°C, R: exo : 4.80 (R), 4.5.51 (S), and endo : 6.64 (R), 7.90 (S)).

Endo-10 : ¹H NMR (400 MHz, CDCl₃) : δ = 9.61 (d, 1H, J=), 7.14-7.33 (m, 5H), 6.62-6.43 (m, 1H), 6.17-6.15 (m, 1H), 3.34 (br, 1H), 3.13 (br, 1H), 3.09 (m, 1H), 2.99 (m, 1H), 1.79-1.84 (m, 1H), 1.65-1.59 (m, 1H). Other spectroscopic data are in agreement with published data.⁶

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1H Spectrum of aldol product 3a (400 MHz, CDCl3)

1H Spectrum of aldol product 3b (400 MHz, CDCl3)
1H Spectrum of aldol product 3e (400 MHz, CDCl3)

1H Spectrum of Michael adduct 6a (400 MHz, CDCl3)
1H Spectrum of endo-10/exo-10 mixture (400 MHz, CDCl3)
Temperature, pressure and microwave power profiles for the reaction mixture corresponding to Table 1, entry 10 (constant microwave power of 15 W during 15 min, using simultaneous cooling).

Status: OK
Absorption Level: Very High
Vial: 2.0-5.0 ml
Pre-stirring: 0
Initial power: 0

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<th>bar</th>
<th>W</th>
<th>FHT</th>
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Temperature (°C)  
Pressure (bar)  
Power (W)
Temperature, pressure and microwave power profiles for the reaction mixture corresponding to Table 2, entry 1 (constant microwave power of 15 W during 15 min, using simultaneous cooling).

Status: OK
Absorption Level: Very High
Vial: 2.0-5.0 ml
Pre-stirring: 0
Initial power: 0

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Temperature (°C)

Pressure (bar)

Power (W)
Temperature, pressure and microwave power profiles for the reaction mixture corresponding to Table 2, entry 3 (constant microwave power of 15 W during 1 h, using simultaneous cooling).

Status: OK  
Absorption Level: Very High  
Vial: 2.0-5.0 ml  
Pre-stirring: 0  
Initial power: 0

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<th>bar</th>
<th>W</th>
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![Graph of Temperature (°C)](image1)

![Graph of Pressure (bar)](image2)

![Graph of Power (W)](image3)