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Tandem Metal and Organocatalysis in Sequential Hydroformylation and Enantioselective Mannich Reactions

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Abstract: Metal-catalysed hydroformylation is successfully combined with an organocatalysed stereoselective Mannich reaction in a tandem reaction sequence. This novel type of "tandem catalysis" allows access to complex molecular systems with high levels of enantioselectivity, using simple starting materials and an amino acid as the chiral catalyst.

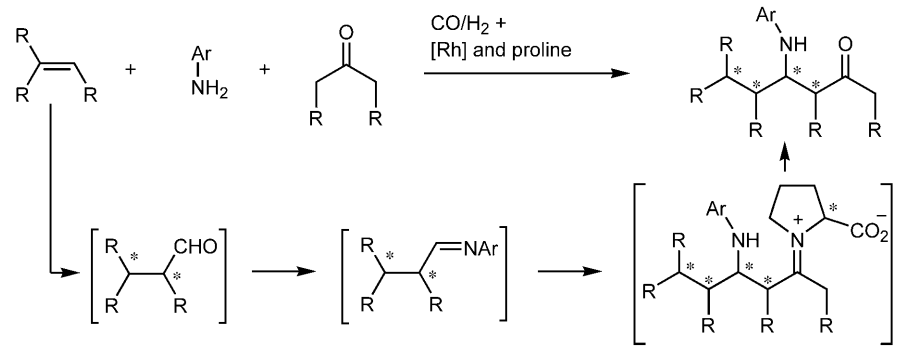
Keywords: hydroformylation; Mannich reaction; organocatalysis; tandem reactions

Recent syntheses of natural and drug-like compounds have clearly revealed the advantages of combining several reactions into a tandem reaction sequence to provide complex molecules in a clean and efficient manner.[1] We and others have demonstrated that tandem reactions under hydroformylation conditions are a useful strategy for the synthesis of complex molecular systems.[2] More recent attention has been focused on "tandem catalysis"[3] where a metal catalyst works together with a chiral organocatalyst affording highly functionalised molecules with excellent levels of enantioselectivity.[4] Here we now report the first use of this methodology in sequential hydroformylation and asymmetric Mannich reactions.

The proposed sequential transformation involves hydroformylation of an alkene mediated by a triphenyl phosphite-modified Rh catalyst and L-proline-catalysed enantioselective Mannich reaction of the aldehyde formed *in situ*, an aromatic amine and a ketone (Scheme 1). Like the related tandem hydroformylation/enantioselective aldol reactions,[4d,e] this process leads to the generation of up to four new adjacent stereogenic centres in the product, and clearly, when high levels of control are observed, these approaches are of considerable importance.

The synthetic plan relied on finding optimal conditions for both hydroformylation and enantioselective Mannich reactions and then combining these reactions into a tandem sequence.

The hydroformylation reactions were performed using the previously reported protocol.[4d] The catalyst was readily prepared *in situ* from $[Rh(acac)(CO)_2]$ and an excess of triphenyl phosphite. Cyclic olefins were used as substrates in order to avoid the regioselectivity problems of hydroformylation reactions. The hydroformylation experiments were performed in acetone, since in subsequent Mannich reactions acetone will serve both as the enamine component and as solvent (Table 1). As shown in Table 1, excellent conver-



Scheme 1. Hydroformylation/enantioselective Mannich reactions.

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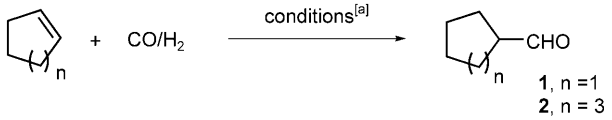
Table 1. Rh-catalysed hydroformylation of cyclic olefins.



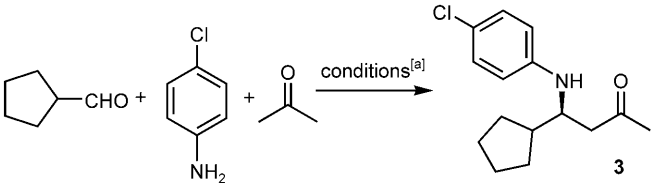
Entry	Substrate	*T* [°C]	*t* [h]	Conversion [%][b]	Aldehyde yield [%][b]
1	cyclopentene	25	72	94	94
2	cyclopentene	40	72	>99	>99
3	cycloheptene	25	120	>99	>99
4	cycloheptene	40	72	>99	>99

[a] *Conditions:* 20/20 bar CO/H_2, 0.5 mol% [$Rh(acac)(CO)_2$], 2 mol% $P(OPh)_3$, acetone (0.78 M alkene).
[b] Determined by GC using dodecane as an internal standard.

sions were obtained. As was expected, at 25 °C the hydroformylation rate was lower than at 40 °C. In order to have full cycloheptene conversion at room temperature, the reaction time was increased to 120 h (Table 1, entry 3). According to GC and ^1H NMR analyses of the crude mixtures, only aldehydes are formed during the hydroformylation reaction.

After conditions for the hydroformylation of cyclic olefins in acetone were optimised, we focused our attention on the enantioselective organocatalysed Mannich reaction. L-Proline was selected as the first candidate as it is usually a highly stereoselective organocatalyst in the direct catalytic Mannich reaction.[5] The L-proline-catalysed reaction of cyclopentanecarbaldehyde, *p*-chloroaniline and acetone was chosen as a representative example (Table 2).

Table 2. L-Proline-catalysed enantioselective Mannich reaction.



Entry	Solvent	Isolated yield **3** [%]	*ee* **3** [%][b]
1	$CHCl_3$/acetone 4:1	50	16
2	toluene/acetone 4:1	25	45
3	DMSO/acetone 4:1	8	13
4	DMF/acetone 4:1	9	17
5	CH_2Cl_2/acetone 4:1	52	72
6	acetone	55	65

[a] *Conditions:* 30 mol% L-proline, room temperature, 72 h, solvent (0.1 M aldehyde).
[b] Determined by chiral HPLC.

Chlorinated co-solvents and acetone gave moderate yields (50–55%) of the desired product **3** (Table 2, entries 1, 5 and 6). However, good enantioselectivity (65–72% *ee*) was obtained only in dichloromethane (DCM) and acetone. Changing the solvent to dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) led to decreases in both enantioselectivity and yield of the Mannich product. The stereochemical outcome of the reaction was assigned by analogy with the known β-amino ketone obtained from the L-proline-catalysed reaction of cyclohexanecarbaldehyde, 4-methoxyaniline and acetone.[6] In order to enforce the equilibrium favouring the Mannich product a 30-fold excess of acetone is normally required, therefore the aldehyde concentration was kept at 0.1 M (Table 2).[5g,7]

We next investigated sequential hydroformylation and Mannich reactions under optimised conditions (Table 3). In contrast to the hydroformylation experiments from Table 1, in the sequential reaction we had to use a more dilute solution in order to keep a 30-fold excess of acetone. According to the GC analysis, at this low Rh catalyst concentration the hydroformylation did not proceed at room temperature (Table 3, entry 1). At 40 °C, however, cyclopentene was fully converted within 72 h (entries 2, 3 and 4). Using acetone as the reaction solvent, the product was generated in moderate yield; however, the stereoselectivity was very low. Chloroform/acetone led to an almost complete loss of the enantioselectivity (Table 3, entry 3). Efforts to improve the enantioselectivity by using DCM as co-solvent with acetone led to a considerable improvement, affording the Mannich product in 52% yield and 71% *ee* (Table 3, entry 4). Based on these results, we judged DCM/acetone to be the most promising solvent system for further investigations.

Hayashi's group has previously reported that high pressure (2000 bar) accelerates the L-proline-catalysed Mannich reaction of various aldehydes, *p*-anisidine and acetone, giving both better yields and better enantioselectivities.[6]

We wondered if the pressure used for the hydroformylation (20–80 bar) would have some effect on the reaction yields and stereoselectivities. Various CO and H_2 partial pressures were studied to ascertain the effects of pressure on tandem hydroformylation and enantioselective Mannich reactions.

The reaction between cyclopentene, *p*-chloroaniline and acetone was performed at 10/10, 20/20, 30/30 and 40/40 bar pressures of CO/H_2 (Table 4).

The total pressure was found to have an impact not only on the product yield, but also on the enantioselectivity. Reaction at 10/10 bar pressure generated the desired product in reasonable yield and reasonable *ee* (Table 4, entry 1). Increasing the pressure to 20/20 or 30/30 bar provided the product in similar yields, but

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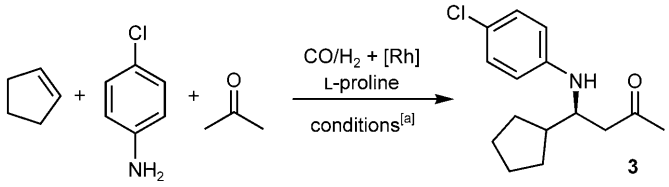
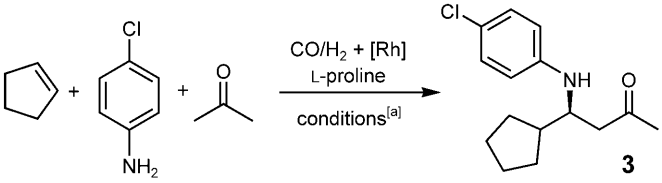
Table 3. Sequential hydroformylation/enantioselective Mannich reactions.



Entry	Solvent	T [°C]	Alkene conversion [%][b]	Isolated yield **3** [%]	*ee* **3** [%][c]
1	CH_2Cl_2/acetone 4:1	25	<5	–	–
2	acetone	40	>99	53	19
3	$CHCl_3$/acetone 4:1	40	>99	49	1
4	CH_2Cl_2/acetone 4:1	40	>99	52	71

[a] *Conditions:* 20/20 bar CO/H_2, 0.5 mol% [Rh(acac)$(CO)_2$], 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, solvent (0.1 M alkene).
[b] Determined by GC using dodecane as an internal standard.
[c] Determined by chiral HPLC.

Table 4. Influence of CO and H_2 partial pressures on sequential hydroformylation/Mannich reaction.



Entry	P_{CO} [bar]	P_{H_2} [bar]	Cyclopentene conversion [%][b]	Isolated yield **3** [%]	*ee* **3** [%][c]
1	10	10	>99	51	54
2	20	20	>99	52	71
3	30	30	>99	48	74
4	40	40	>99	23	77

[a] *Conditions:* 0.5 mol% [Rh(acac)$(CO)_2$], 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, CH_2Cl_2/acetone 4:1 (0.1 M alkene).
[b] Determined by GC using dodecane as an internal standard.
[c] Determined by chiral HPLC.

higher enantioselectivities (entries 2 and 3). Further increasing the pressure to 40/40 bar resulted in improved enantioselectivity, but diminished yield (entry 4). Thus, the original pressure choice (20/20 bar CO/H_2) was found to be optimal.

Next, tandem reactions of cyclic olefins with aromatic amines and acetone were examined (Table 5).

Again, excellent alkene conversions were obtained using the triphenyl phosphite-modified Rh catalyst. The tandem reaction with an amine bearing an electron-donating substituent (OMe) on the phenyl ring provided products in modest yields and poor enantioselectivities (Table 5, entries 1 and 2). In contrast, an amine bearing an electron-withdrawing substituent (F, Cl) on the phenyl ring gave better enantioselectivities although in some cases yields were lower (Table 5, entries 3–6).

In conclusion, for the first time, we could successfully combine metal-catalysed hydroformylation with the organocatalysed, stereoselective Mannich reaction in a tandem reaction sequence. This is a powerful approach for the generation of optically active nitrogen-containing molecules. The yields and enantioselectivities of the process were found to be highly dependent on the substrates and conditions used. We are currently investigating the tandem reaction of more complex starting materials, including prochiral olefins and prochiral ketones using proline and other organocatalysts.

Experimental Section

General Remarks

Hydroformylation experiments were carried out in a Berghof HR-200 high pressure reactor with magnetic stirring and electrical heating. The inside part of the cover was made from Teflon® to protect the solution from direct contact with the stainless steel. All reactions were carried out in freshly distilled solvents. Dichloromethane was distilled from calcium hydride. Acetone was stirred over boric anhydride for 24 h and then distilled. Commercial reagents were used as received. Column chromatography was carried out using MN Kieselgel 60 (0.063–0.2 mm/70–230 mesh). TLC was performed on Merck Silica gel 60 F_{254} plates. Visualisation of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or by anisaldehyde stain. For gas chromatographic analyses, a Carlo Erba HRGC Mega2 Series MFC 800 chromatograph with a Carlo Erba EL 580 flame ionisation detector (FID) was used. Separations were performed on the column CHROMPACK DB-1701 (25 m × 0.32 mm × 1.0 μm). ^{1}H NMR spectra were recorded on a

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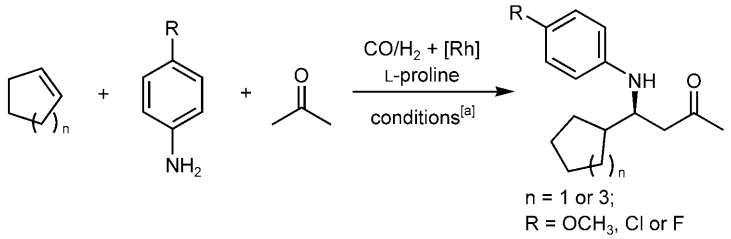
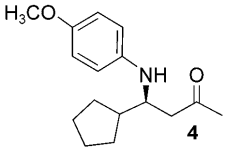
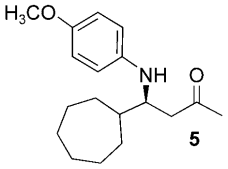
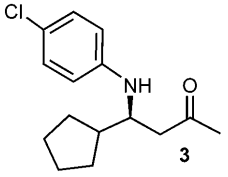
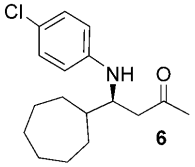
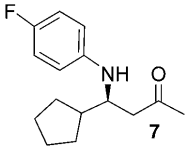
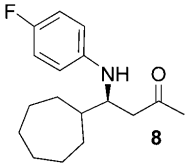
Table 5. Investigation of different alkenes and aromatic amines.



Entry	Alkene	R	Alkene conversion [%][b]	Product	Isolated yield [%]	*ee* [%][c]
1		OCH_3	>99	 **4**	53	32
2		OCH_3	>99	 **5**	50	42
3		Cl	>99	 **3**	52	71
4		Cl	>99	 **6**	25	74
5		F	>99	 **7**	44	72
6		F	>99	 **8**	21	51

[a] *Conditions:* 20/20 bar CO/H_2, 0.5 mol% $[Rh(acac)(CO)_2]$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, CH_2Cl_2/acetone 4:1 (0.1 M alkene).
[b] Determined by GC using dodecane as an internal standard.
[c] Determined by chiral HPLC.

Bruker 400 spectrometer, with residual proton signal of the deuterated solvent as the internal reference ($\delta_H = 7.26$ ppm for $CDCl_3$). ^{13}C NMR spectra were recorded on the same spectrometer and referenced to solvent signals ($\delta_c = 77$ ppm for $CDCl_3$). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows δ/ppm (multiplicity, number of protons, coupling constant *J* in Hz). Semipreparative HPLC was performed using a SUPELCOSIL™ LC-SI 5 μm (25 cm × 21.2 mm) column. Analytical HPLC was performed on a Hewlett–Packard 1050 Series chromatographs using a CHIRALCEL OJ-H (250 × 4.6 mm), CHIRALPAK AD (250 × 4.6 mm) and CHIRALCEL OD-H (250 × 4.6 mm) columns as noted.

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General Procedure for Rh-Catalysed Hydroformylation of Cyclic Olefins (Table 1)

To a solution of $[Rh(acac)(CO)_2]$ (5 mg, 0.019 mmol, 0.005 equiv.) in 5 mL of acetone in a vial, was added $P(OPh)_3$ (24 mg, 0.078 mmol, 0.02 equiv.). The solution was stirred with a magnetic stirrer for 5 min and then charged with olefin (3.9 mmol, 1 equiv.) and dodecane (199 mg, 1.17 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurised to 20/20 bar CO/H_2 and heated to given temperature. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. The carrier gas was 40 kPa He, temperature programme of 30 °C for 10 min, then 15 °C/min to 260 °C; retention times: 4.57 min for cyclopentene, 14.20 min for cycloheptene, 17.60 min for cyclopentanecarbaldehyde, 21.23 min for dodecane, 22.39 min for cycloheptanecarbaldehyde.

L-Proline-Catalysed Mannich Reaction under Atmospheric Pressure (Table 2)

To a stirred suspension of L-proline (35 mg, 0.3 mmol, 0.3 equiv.) in 10 mL of solvent were added 4-chloroaniline (140 mg, 1.1 mmol, 1.1 equiv.) and cyclopentanecarbaldehyde (98 mg, 1 mmol, 1 equiv.). The resulting mixture was stirred at room temperature for 72 h. Two different work-up procedures were used: a) when DMSO and DMF were used as solvents (Table 2, entries 3 and 4) the reaction mixture was quenched with 5 mL 0.5 M phosphate buffer (pH 7) and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to give the crude product; b) when chloroform, toluene, DCM or acetone (Table 2, entries 1, 2, 5 and 6) were used, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum to give the crude product. In both cases the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4, $R_f = 0.40$) to afford (*S*)-4-(4-chlorophenylamino)-4-cyclopentylbutan-2-one **3** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$–7.06 (m, 2H), 6.53–6.51 (m, 2H), 3.76 (br. s., 1H), 3.70–3.64 (m, 1H), 2.67 (dd, 1H, $J =$ 16.7, 5.1 Hz), 2.61 (dd, 1H, $J = 16.7$, 5.4 Hz), 2.12 (s, 3H), 2.11–2.02 (m, 1H), 1.82–1.48 (m, 6H), 1.28–1.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.2$, 29.6, 31.0, 35.7, 45.2, 46.8, 54.3, 114.2, 121.6, 129.1, 146.2, 208.1; ESI-MS: *m/z* 266.13064, calcd. for $[M+H]^+$ ($C_{15}H_{21}ClNO$): 266.13117, elemental analysis (%), calcd. for $C_{15}H_{20}ClNO$: C 67.79, H 7.58; found: C 67.48, H 7.86; IR (film): $\nu_{max} = 3386$, 2952, 2866, 1708, 1598, 1500 cm^{-1}; $[\alpha]_D^{20}$: +25.8 (*c* 0.51, *n*-heptane). HPLC: CHIRALCEL OD-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 72%: t_R (major) = 6.6 min; t_R (minor) = 5.4 min.

Sequential Hydroformylation and Enantioselective Mannich Reactions (Table 3, entry 4)

To a solution of $[Rh(acac)(CO)_2]$ (1.3 mg, 0.005 mmol, 0.005 equiv.) in 10 mL of solvent in a vial, was added triphenyl phosphite (6.2 mg, 0.02 mmol, 0.02 equiv.). The solution was stirred with a magnetic stirrer for 5 min and then charged with alkene (1.0 mmol, 1 equiv.), aromatic amine (1.1 mmol, 1.1 equiv.) and L-proline (35 mg, 0.3 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurised with CO and H_2 and heated. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography.

(*S*)-4-Cyclopentyl-4-(4-methoxyphenylamino)butan-2-one (4): Purified using column chromatography (EtOAc/cyclohexane 1:5, $R_f = 0.50$) to afford the title compound as a brown oil; yield: 138 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.75$–6.72 (m, 2H, $J = 8.7$ Hz), 6.58–6.55 (m, 2H, $J = 8.7$ Hz), 3.72 (s, 3H), 3.65–3.60 (m, 1H), 3.44 (br. s, 1H), 2.66–2.56 (m, 2H), 2.10 (s, 3H), 2.07–2.03 (m, 1H), 1.80–1.53 (m, 6H), 1.26–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.2$, 29.6, 30.9, 35.4, 45.1, 46.9, 55.3, 55.6, 114.8, 141.7, 151.9, 208.5; ESI-MS: $m/z = 262.18002$, calcd. for $[M+H]^+$ ($C_{16}H_{24}NO_2$: 262.18070; elemental analysis (%), calcd. for $C_{16}H_{23}NO_2$: C 73.53, H 8.87; found: C 73.14, H 8.98; IR (film/NaCl): $\nu_{max} = 3381$, 2949, 2831, 2359, 1715, 1618, 1512 cm^{-1}; $[\alpha]_D^{20}$: +6.2 (*c* 0.50, *n*-heptane); HPLC: CHIRALCEL OJ-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 32%: t_R (major) = 16.4 min; t_R (minor) = 14.6 min.

(*S*)-4-Cycloheptyl-4-(4-methoxyphenylamino)butan-2-one (5): Purified using column chromatography (EtOAc/cyclohexane 1:5, $R_f = 0.30$) to afford the title compound as a brown oil; yield: 145 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.75$–6.73 (m, 2H, $J = 8.7$ Hz), 6.56–6.54 (m, 2H, $J = 8.7$ Hz), 3.72 (s, 3H), 3.70–3.67 (m, 1H), 3.41 (br. s, 1H), 2.60–2.46 (m, 2H), 2.13 (s, 3H), 1.71–1.20 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.9$, 27.0, 28.2, 30.1, 30.5, 42.1, 45.3, 55.7, 56.3, 114.9, 141.4, 152.0, 208.5; ESI-MS: $m/z = 290.21151$, calcd. for $[M+H]^+$ ($C_{18}H_{28}NO_2$): 290.21200; elemental analysis (%), calcd. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40; found: C 74.29, H 10.03; IR (film/NaCl): $\nu_{max} = 3369$, 2919, 2853, 2359, 1704, 1590, 1505 cm^{-1}; $[\alpha]_D^{20}$: +5.9 (*c* 0.50, *n*-heptane); HPLC: CHIRALCEL OJ-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 42%: t_R (major) = 19.9 min; t_R (minor) = 17.6 min.

(*S*)-4-(4-Chlorophenylamino)-4-cycloheptylbutan-2-one (6): Purified using column chromatography (EtOAc/cyclohexane 1:5, $R_f = 0.29$) to afford the title compound as a light yellow oil; yield: 76 mg (26%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.09$–7.06 (m, 2H, $J = 8.7$ Hz), 6.51–6.49 (m, 2H, $J =$ 8.7 Hz), 3.71 (br. s., 2H), 2.63–2.48 (m, 2H), 2.13 (s, 3H), 1.74–1.24 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.9$, 27.8, 28.2, 30.3, 36.3, 42.3, 45.2, 55.2, 114.3, 129.1, 145.9, 208.1; ESI-MS: *m/z* 294.16205, calcd. for $[M+H]^+$ ($C_{17}H_{25}ClNO$): 294.16247; elemental analysis (%), calcd. for $C_{17}H_{24}ClNO$: C 69.49, H 8.23; found: C 69.09, H 8.50; IR (film/NaCl): $\nu_{max} = 3367$, 2923, 2852, 1712, 1598, 1489 cm^{-1}; $[\alpha]_D^{20}$: +26.2 (*c* 0.50, *n*-heptane); HPLC: CHIRALCEL OD-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 74%: t_R (major) = 6.4 min; t_R (minor) = 8.0 min.

(*S*)-4-Cyclopentyl-4-(4-fluorophenylamino)butan-2-one (7): Purified using column chromatography (EtOAc/cyclohexane 1:5) to afford the title compound as a yellow oil; yield: 111 mg (44%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.85$–

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6.80 (m, 2H), 6.52–6.50 (m, 2H), 3.63–3.60 (m, 2H), 2.62-2.60 (m, 2H), 2.10 (s, 3H), 2.06–2.02 (m, 1H), 1.62–1.59 (m, 7H), 1.25–1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 29.7, 31.0, 36.3, 45.2, 46.8, 55.0, 114.3, 115.5, 115.7, 120.1, 125.5, 129.8, 143.9, 156.8, 208.3; ESI-MS: m/z = 250.16017, calcd. for $[M+H]^+$ ($C_{15}H_{21}FNO$): 250.16072; elemental analysis (%), calcd. for $C_{15}H_{21}FNO$: C 71.97, H 8.46; found: C 71.83, H 8.59; IR (film/NaCl): ν_{max} = 3389, 2952, 2867, 2365, 1712, 1612, 1514 cm^{-1}; $[\alpha]_D^{20}$: +26.8 (*c* 0.48, *n*-heptane); HPLC: CHIRALCEL OD-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 72%: t_R (major) = 10.8 min; t_R (minor) = 10.0 min.

(*S*)-4-Cycloheptyl-4-(4-fluorophenylamino)butan-2-one (8): Purified using column chromatography (EtOAc/cyclohexane 1:5, R_f = 0.29) to afford the title compound as a yellow oil; yield: 60 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.82 (m, 2H), 6.53–6.50 (m, 2H), 3.72–3.68 (m, 1H), 2.61–2.47 (m, 2H), 2.13 (s, 3H), 1.74–1.36 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 27.9, 28.3, 30.3, 30.5, 30.6, 42.3, 45.3, 56.0, 114.4, 115.7, 143.8, 154.6, 154.9, 208.4; ESI-MS: m/z = 278.19147, calcd. for $[M+H]^+$ ($C_{17}H_{25}FNO$): 278.19202; elemental analysis (%), calcd. for $C_{15}H_{24}FNO$: C 73.61, H 8.72; found: C 73.28, H 8.90; IR (film/NaCl): ν_{max} = 3389, 2928, 2854, 2365, 1711, 1612, 1513 cm^{-1}; $[\alpha]_D^{20}$: +21.9 (*c* 0.50, *n*-heptane); HPLC: CHIRALCEL OD-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL × min^{-1}, 254 nm, *ee* = 72%: t_R (major) = 6.4 min; t_R (minor) = 5.1 min.

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