ELECTRONIC SUPPLEMENTARY INFORMATION

for

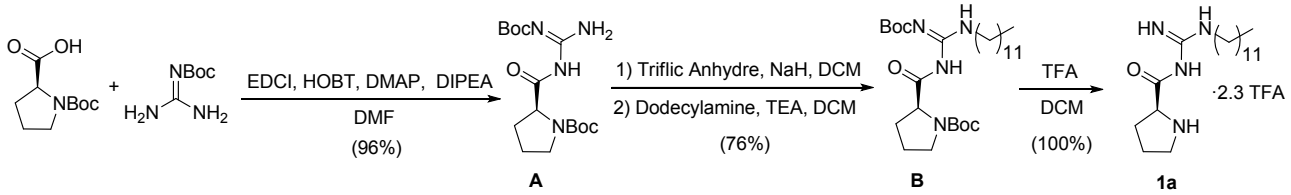
Intramolecular hydrogen bonding guides a cationic amphiphilic organocatalyst to highly stereoselective aldol reactions in water.

Ángel M. Valdivielso, Alba Catot, Ignacio Alfonso*, and Ciril Jimeno*.

Department of Biological Chemistry and Molecular Modelling. Institute of Chemical Research of Catalonia (IQAC-CSIC). c/Jordi Girona 18-26, E08034 Barcelona (Spain).

ignacio.alfonso@iqac.csic.es, ciril.jimeno@iqac.csic.es

1. Synthesis of acylguanidine 1a:



1.a) Synthesis of guanidyl-proline compound A

To a solution of Boc-Pro-OH (1.00 g, 4.65 mmol) in dry DMF (46.5 mL) at 0 ºC were added successively EDC·HCl (981 mg, 5.12 mmol), HOBt·12H_2O (942 mg, 6.98 mmol), DIPEA (870 µL, 5.12 mmol) and DMAP (57 mg, 0.47 mmol). After 30 min, Boc-guanidine (1.11 g, 6.97 mmol) was added and the mixture was stirred overnight at room temperature. The, the mixture was diluted with EtOAc (150 mL) and washed with saturated $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and solvent removed. The crude product was purified by column chromatography using a gradient of MeOH in DCM (0 to 4%) to give **A** (1.60 g, 96%) as a white foam.

IR (ATR) 3375, 2974, 1701, 1664, 1630, 1535 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.23-8.12 (m, 3H), 4.39-4.24 (m, 0.5H), 4.21-4.09 (m, 0.5H), 3.62-3.32 (m, 2H), 2.33-2.12 (m, 1H), 2.12-1.95 (m, 1H), 1.95-1.83 (m, 2H), 1.53-1.37 (m, 2H); **MS (ESI-TOF)** 357.2138 $(M+H)^+$, 713.4230 $(2M+H)^+$; calculated for $C_{16}H_{28}N_4O_5$: 357.2132 $(M+H)^+$, 713.4192 $(2M+H)^+$; $[\alpha]_D$ = -72.3 (c = 1.0, $CHCl_3$).

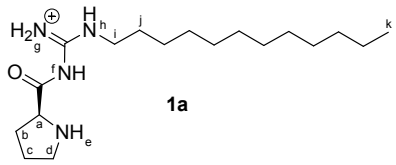
1.b) Synthesis of dodecyl-guanidyl proline compound B.

To a solution of the guanidyl proline **A** (1.49 g, 4.19 mmol) in dry DCM (40 mL) under nitrogen atmosphere at 0 ºC was added dry NaH (222 mg, 8.80 mmol) and the reaction mixture was stirred for one hour at 0 °C. After that, the slightly yellow solution was cooled to -60 °C and triflic acid anhydride (846 µL, 5.03 mmol) was added. The reaction mixture was stirred for three hours at -60 °C, warmed up to room temperature within two hours and was stirred overnight. Afterwards, water was added dropwise under vigorous stirring until no more gas evolved. Then, triethylamine (1.75 mL, 12.6 mmol) and dodecylamine (923 mg, 5.03 mmol) were added and the mixture was stirred over weekend at room temperature. The reaction mixture was diluted with DCM (100 mL) and washed with saturated $NaHCO_3$ (3 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and solvent removed. The crude product was purified by flash chromatography using hexane:EtOAc mixtures to give **B** (1.66 g, 76%) as a colorless oil.

IR (ATR) 3320, 2975, 2925, 2854, 1698, 1620, 1613, 1563 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 12.93-12.87 (m, 0.6H), 12.12-12-07 (m, 0.2H), 12.04-12.00 (m, 0.2H), 8.86-8.71 (m, 0.6H), 8.43-8.33 (m, 0.4H), 4.37-4.26 (m, 0.4H), 4.21-4.08 (m, 0.6H), 3.67-3.28 (m, 4H), 2.33-2.10 (m, 1H),

2.09-2.01 (m, 0.6H), 1.98-1.86 (m, 2H), 1.82-1.75 (m, 0.6H), 1.67-1.19 (m, 38H), 0.86 (t, 3H, *J* = 7 Hz); **MS (ESI-TOF)** 525.3859 $(M+H)^+$, 1049.7899 $(2M+H)^+$, 1071.7765 $(2M+Na)^+$; calculated for $C_{28}H_{52}N_4O_5$: 525.4010 $(M+H)^+$, 1049.7948 $(2M+H)^+$, 1071.7773 $(2M+Na)^+$; $[\alpha]_D$ = -44.8 (c = 1.0, $CHCl_3$).

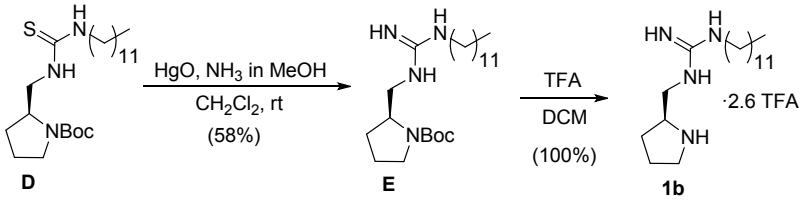
1.c) Boc-deprotection of B. Synthesis of catalyst 1a.



Compound **B** (1.39g, 2.65 mmol) was dissolved in 30% TFA in dry DCM (15 mL) and the mixture was stirred for 1 h. Then, the solvent was removed, the residue was dissolved in CH_3CN/H_2O (1:5) and was lyophilized to obtain the final catalyst **1a** as TFA salt, as a pale yellow waxy solid (**1a**·2.3TFA, 1.55 g, 100%).

IR (ATR) 3473, 3442, 2919, 2850, 1685, 1663, 1594 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 11.08-9.90 (m, 1H, f-NH), 9.35 (t, 1H, *J* = 4 Hz, h-NH), 9.27-8.92 (m, 1H, g-NH), 8.39-7.97 (m, 1H, g-NH), 4.26 (t, 1H, *J* = 7 Hz, a-H), 3.54-3.41 (m, 2H, d-H), 3.26 (q, 2H, *J* = 7 Hz, i-H), 2.59-2.49 (m, 1H, b-H), 2.18-2.06 (m, 3H, b-H and c-H), 1.62 (p, 2H, *J* = 7 Hz, j-H), 1.37-1.18 (m, 18H, $9CH_2$), 0.86 (t, 3H, *J* = 7 Hz, k-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.5 [CO], 162.1 [q, *J* = 37 Hz, CO (TFA)], 153.5 [guanidine], 116.0 [q, *J* = 291 Hz, CF_3 (TFA)], 60.5 [C_a], 46.7 [C_d], 42.0 [C_i], 31.9 [CH_2], 29.6 [CH_2], 29.5 [CH_2], 29.3 [C_b], 29.0 [CH_2], 27.7 [C_j], 26.5 [CH_2], 24.0 [C_c], 22.6 [CH_2], 14.0 [C_k]; **MS (ESI-TOF)** 325.2950 $(M+H)^+$, 649.5867 $(2M+H)^+$; calculated for $C_{18}H_{36}N_4O$: 325.2962 $(M+H)^+$, 649.5851 $(2M+H)^+$; $[\alpha]_D$ = -28.0 (c = 1.0, $CHCl_3$).

2. Synthesis of guanidine 1b:



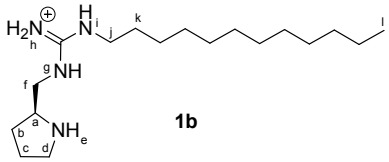
2.a) Transformation of thiourea D into Boc-protected guanidine E.[1]

To a solution of the thiourea **D** (800 mg, 1.87 mmol) in dry DCM (10 ml) were added HgO (567 mg, 2.62 mmol) and 7 M ammonia in MeOH (10 mL). The mixture was stirred overnight at 60ºC. After TLC check, more HgO (567 mg, 2.62 mmol) and 7 M ammonia in MeOH (10 mL) were added and the mixture was heated overnight at 70ºC. Finally, it was filtered through Celite, the solvent was evaporated and the crude product was purified by flash chromatography using of

DCM/MeOH mixtures with some drops of aqueous ammonia to give guanidine **E** as a brown waxy solid (448 mg, 58%).

IR (ATR) 2923, 2852, 1668, 1616 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.07-6.86 (m, 3H), 4.12-3.55 (m, 1H), 3.43-2.95 (m, 6H), 2.04-1.74 (m, 4H), 1.73-1.51 (m, 2H), 1.43 (s, 9H), 1.40-1.14 (m, 18H), 0.85 (t, 3H, *J* = 7 Hz); **MS (ESI-TOF)** 411.3612 $(M+H)^+$; calculated for $C_{23}H_{46}N_4O_2$: 411.3694 $(M+H)^+$; $[\alpha]_D$ = -10.7 (c = 1.1, $CHCl_3$).

2.b) Boc-deprotection of E. Synthesis of catalyst 1b.



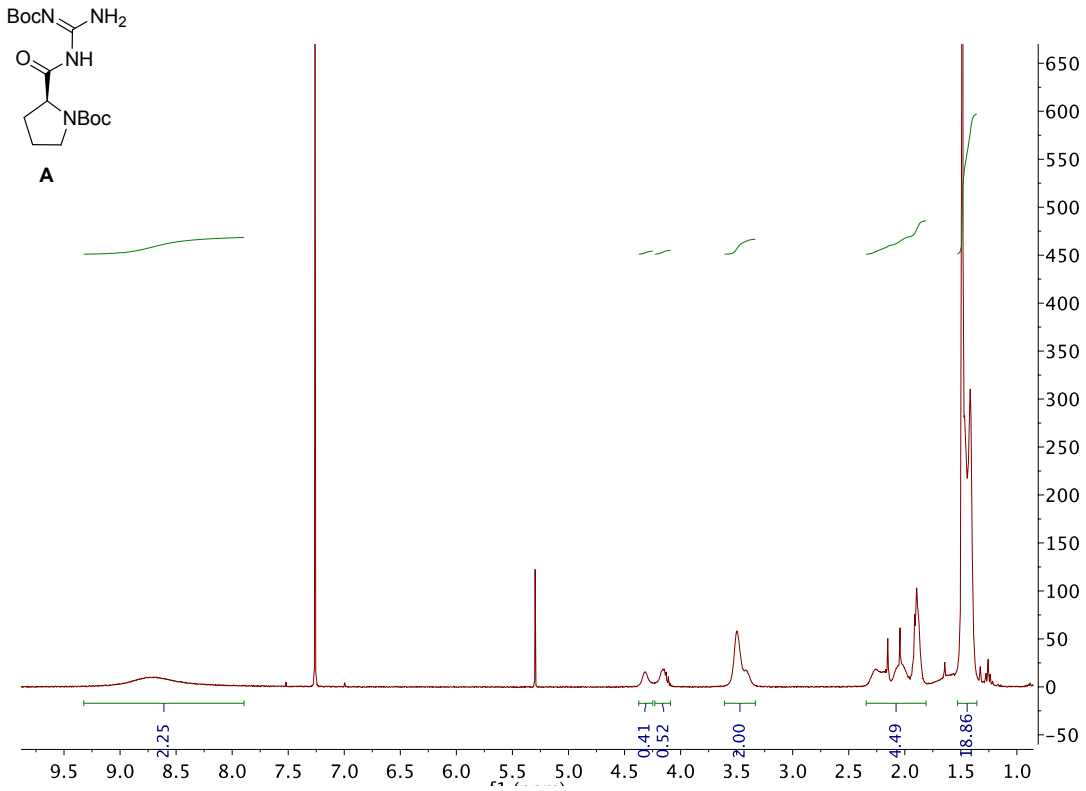
1b

Compound **E** (562 mg, 1.10 mmol) was dissolved in 30% TFA in dry DCM (6 mL) and the mixture was stirred for 1 h. Then, the solvent was removed in vacuo, the residue was dissolved in CH_3CN/H_2O (1:5) and was lyophilized to obtain the final catalyst **1b** as a TFA salt, as a brown oil (**1b**·2.6TFA, 668 mg, 100%).

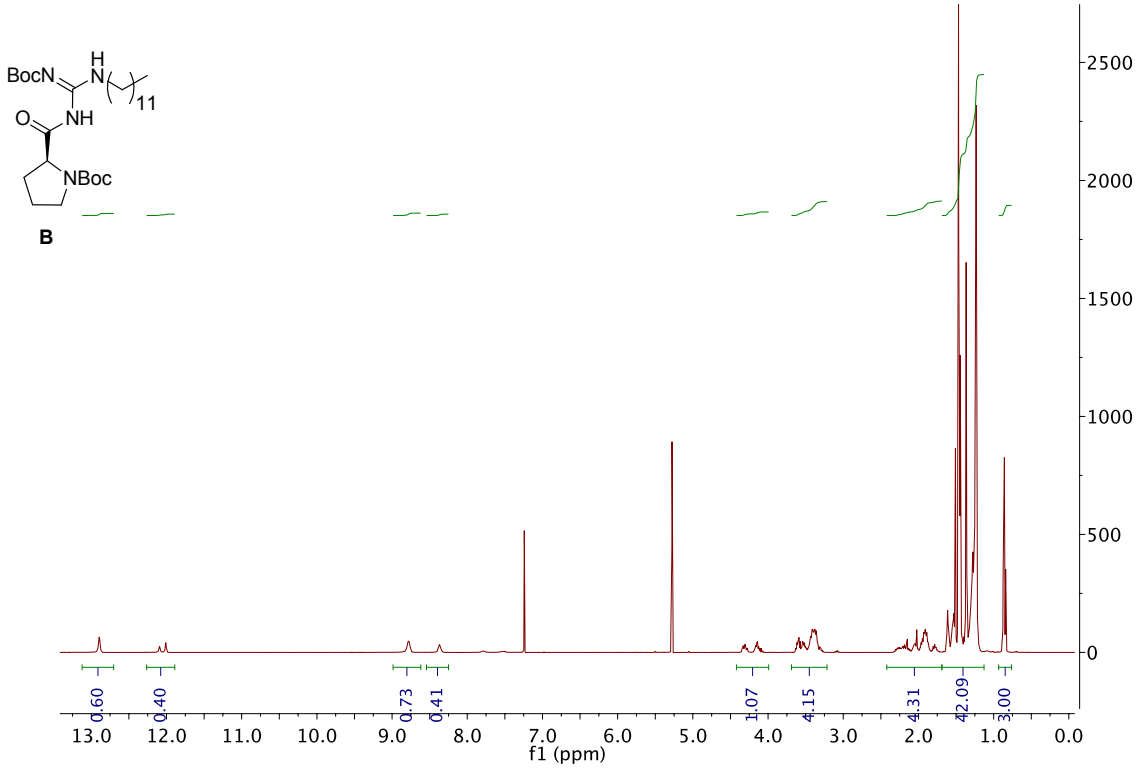
IR (ATR) 2925, 2855, 1664, 1629 cm^{-1}; **^{1}H-NMR** (400 MHz, DMSO-d6) δ 9.71-9.26 (m, 1H, h-NH), 9.15-8.79 (m, 1H, h-NH), 8.28-7.11 (m, 5H, e-NH, g-NH and i-NH), 3.81-3.56 (m, 1H, a-H), 3.55-3.38 (m, 2H, f-H), 3.29-3.01 (m, 4H, d-H and j-H), 2.12-2.00 (m, 1H, b-H), 1.99-1.83 (m, 2H, c-H), 1.69-1.54 (m, 1H, b-H), 1.51-1.44 (m, 2H, k-H), 1.32-1.18 (m, 18H, $9CH_2$), 0.89 (t, 3H, *J* = 7 Hz, l-H); **^{13}C-NMR** (100 MHz, DMSO-d6) δ 158.7 [q, *J* = 34.5 Hz, CO (TFA)], 157.7 [guanidine], 116.2 [q, *J* = 294 Hz, CF_3 (TFA)], 58.2 [C_a], 44.9 [C_d], 41.8 [C_f], 41.0 [C_i], 31.3 [CH_2], 29.1 [CH_2], 29.0 [CH_2], 28.7 [CH_2], 28.3 [C_k], 27.3 [C_b], 26.1 [CH_2], 22.9 [C_c], 22.1 [CH_2], 13.9 [C_l]; **MS (ESI-TOF)** 311.3164 $(M+H)^+$; calculated for $C_{18}H_{38}N_4$: 311.3169 $(M+H)^+$; $[\alpha]_D$ = +12.5 (c = 1.0, $CHCl_3$).

3. NMR spectra of compounds A, B, 1a, E, and 1b:

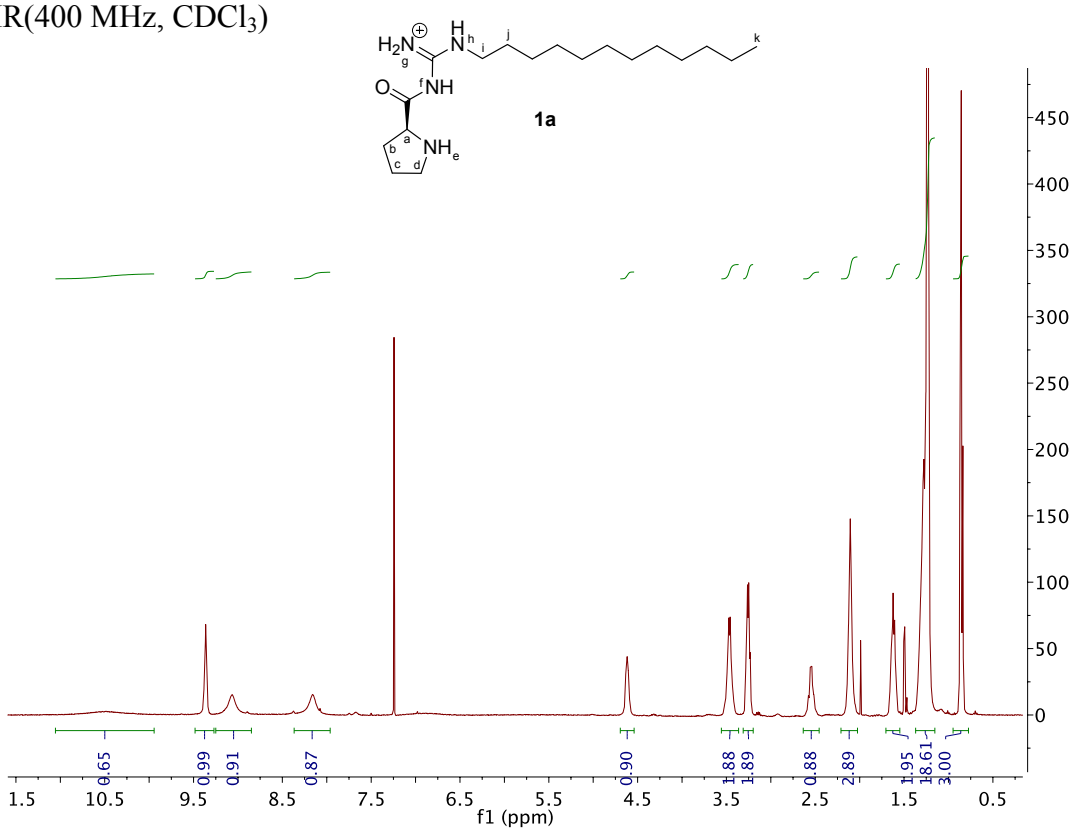
^{1}H NMR(400 MHz, $CDCl_3$)



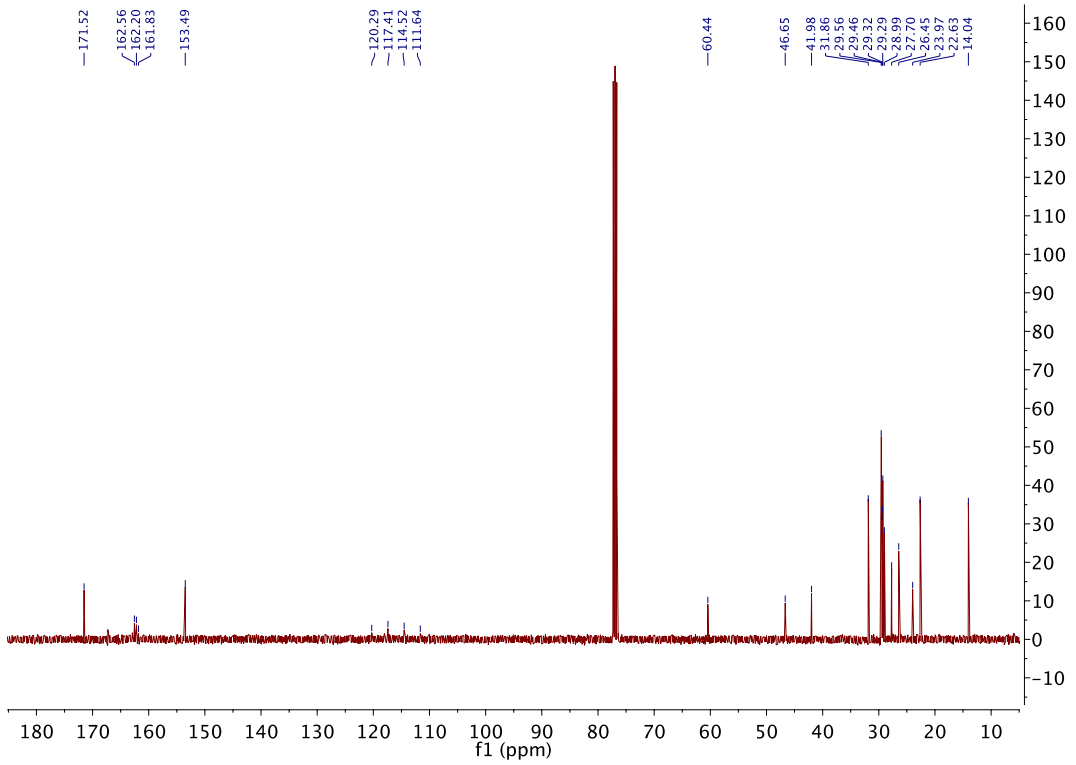
^{1}H NMR(400 MHz, $CDCl_3$)



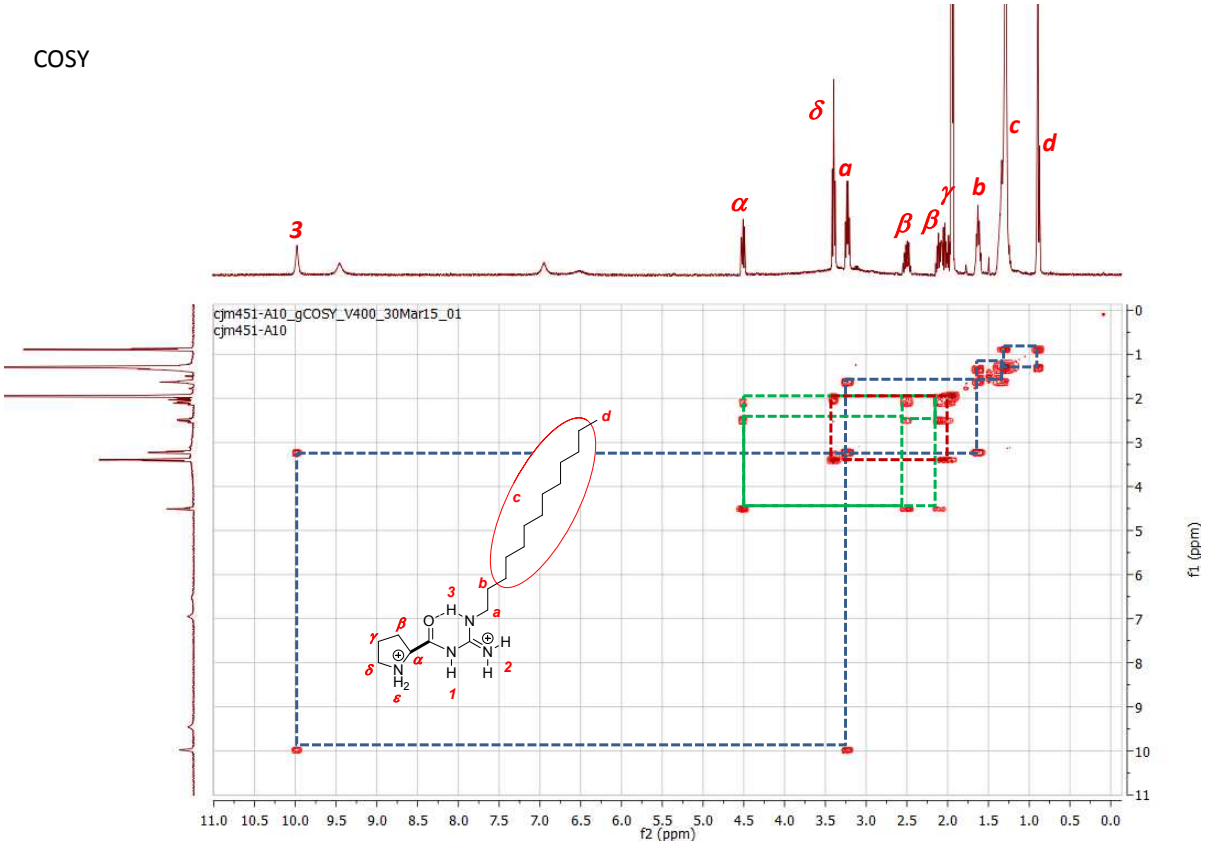
^{1}H NMR(400 MHz, $CDCl_3$)



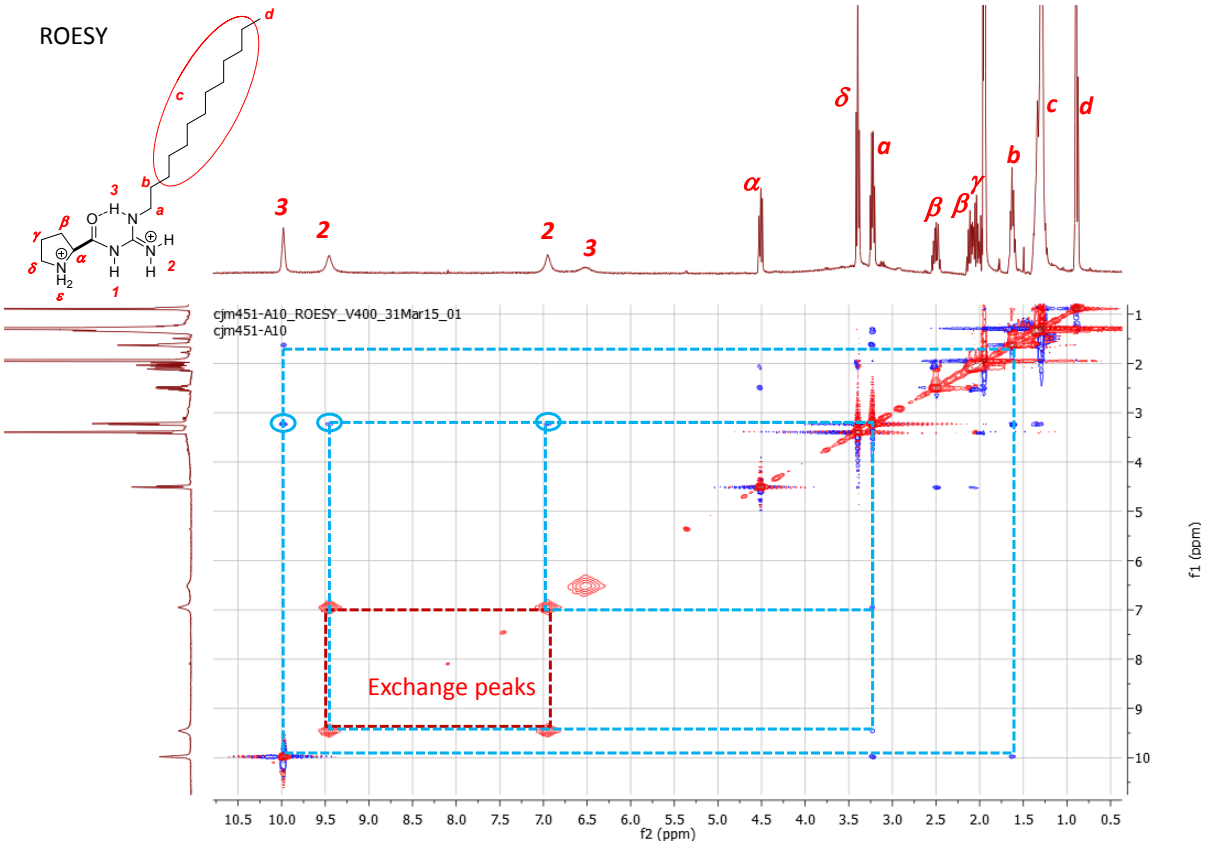
^{13}C NMR(100 MHz, $CDCl_3$)



^{1}H NMR(400 MHz, CD_3CN, COSY):

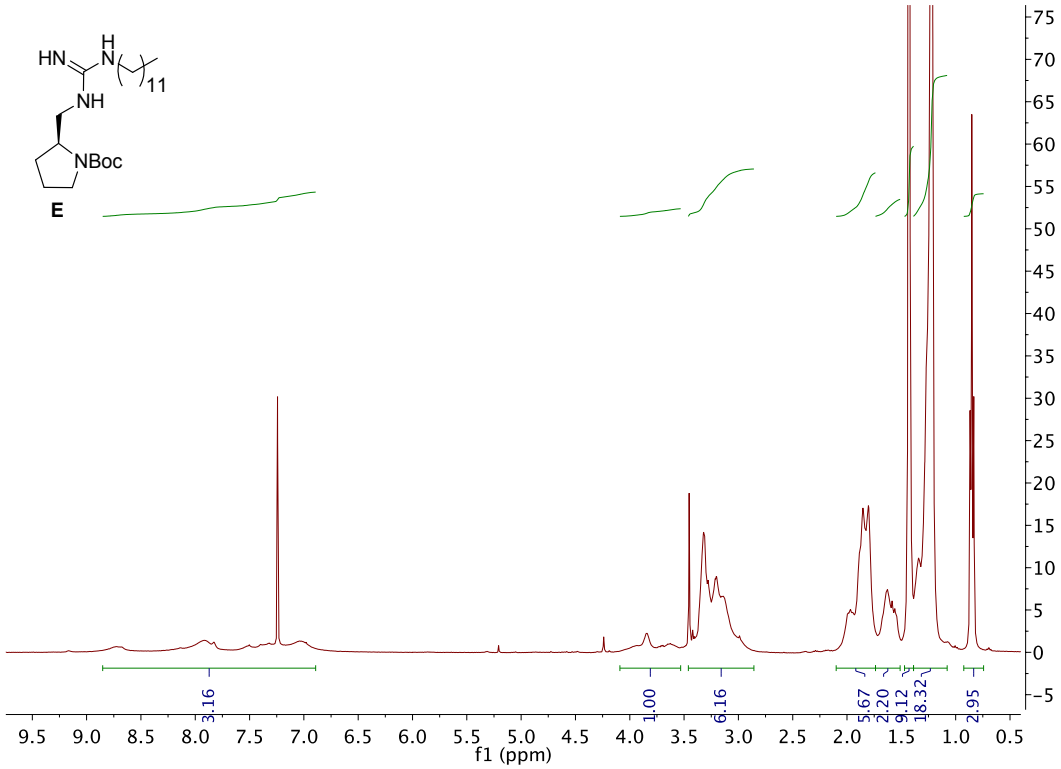


^{1}H NMR(400 MHz, CD_3CN, ROESY):

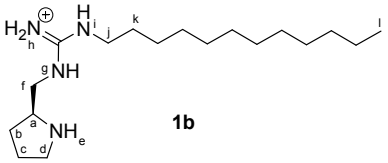


Catalyst **1a** is not soluble in water nor D_2O. Fast exchange of protons *1-3* takes place upon addition of some drops of D_2O. COSY and ROESY experiments were performed in CD_3CN rather than in $CDCl_3$ (dielectric constant 4.81) because its dielectric constant (37.5) lies between cyclohexanone (18.20) and water (80).

^{1}H NMR(400 MHz, $CDCl_3$):

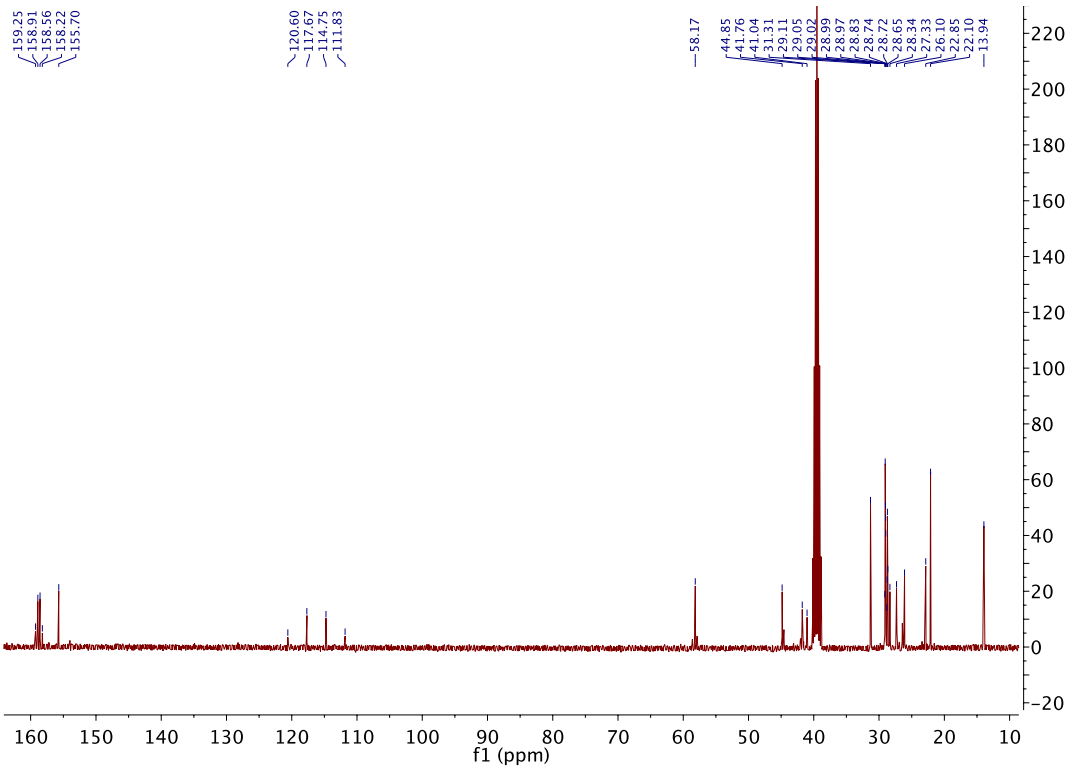


^{1}H NMR(400 MHz, DMSO-d^{6}):



1b

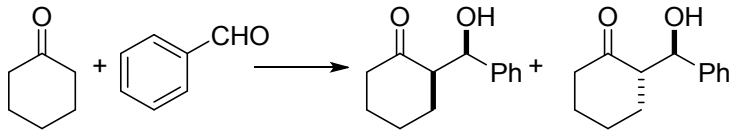
^{13}C NMR(100 MHz, DMSO-d^{6}):

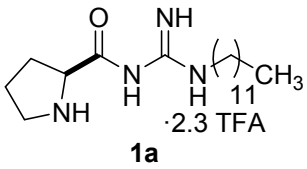


4. Typical procedure for the asymmetric aldol reaction in water catalyzed by 1a.

In a flask, catalyst **1a** (0.045 mmol, 26 mg) was weighed, and dissolved in cyclohexanone (0.47 ml, 4.50 mmol). Then, the aldehyde (0.450 mmol) and a pH 7 buffer solution (0.2 M Na_2HPO4 and 0.1 M citric acid) were added. The mixture was vigorously stirred for 48 hours (at 1000 rpm). Then, it was transferred to a separation funnel and diluted with water and dichloromethane. The organic layer was separated, and the aqueous layer extracted twice again with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with hexane:ethyl acetate mixtures of increasing polarity.

5. Effect of the amount of aqueous phase





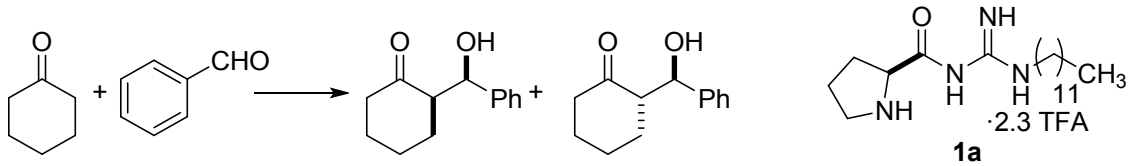
1a

10 mol% cat **1a**.

0.35 ml cyclohexanone + 35 μl benzaldehyde + citrate/phosphate pH 7 buffer

Added buffer pH 7 volume/ ml	Conversion/%	d.r. (anti/syn)	ee/% (anti)
0.65	73	12/1	88
0.33	88	8.6/1	88
0.16	69 (66 yield)	36/1	89
0.08	46	11/1	79

6. Effect of added surfactants.



10 mol% cat **1a**.

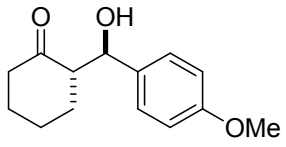
0.35 ml cyclohexanone + 35 µl benzaldehyde + 0.16 ml citrate/phosphate pH 7 buffer

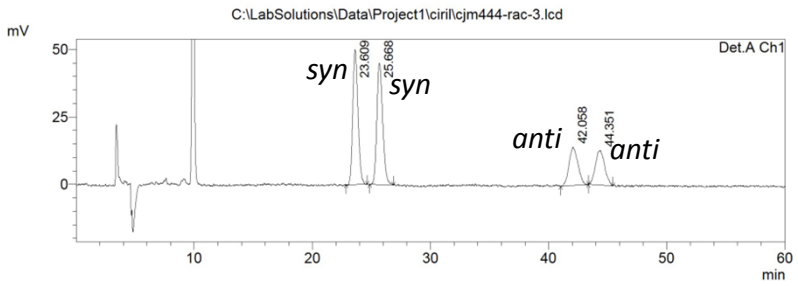
Amount of catalyst **1a** (mol%)	Amount of surfactant (mol%)	Conversion/%	d.r. (anti/syn)	ee/% (anti)
10	5% SDS	66	17	90
10	10% SDS	30	12	93
10	20% SDS	21	9.8	92
10	50% SDS	17	7.3	93
10[a]	10% 1-dodecanol	89	21/1	89
5[a]	10% 1-dodecanol	40	7/1	87
5[a]	20% 1-dodecanol	52	10/1	89

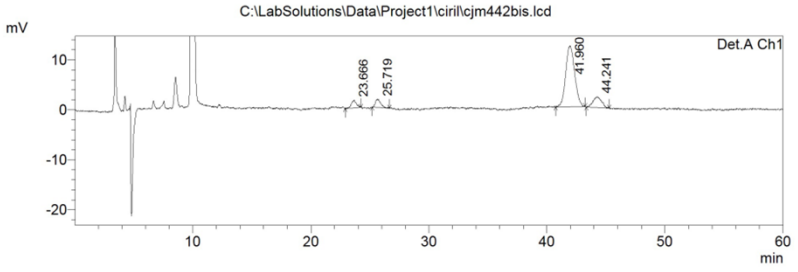
[a] Reaction performed on *p*-chlorobenzaldehyde as substrate.

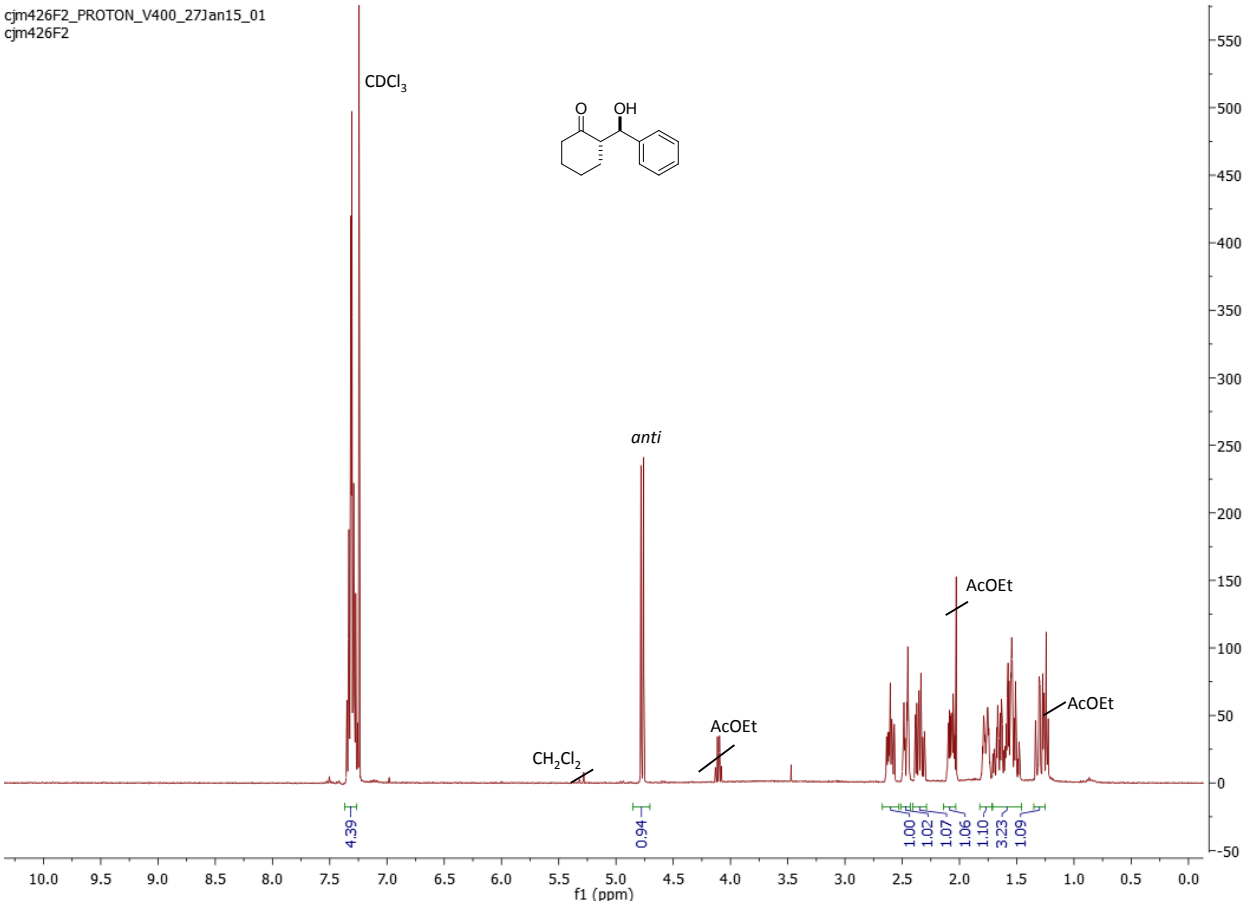
7. ^{1}H NMR and HPLC data of aldol products.

HPLC: ID column, 1 ml/min, 10% *iso*-propanol, 209 nm (Crude product, 13% conversion).



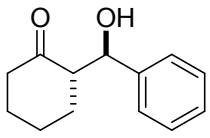


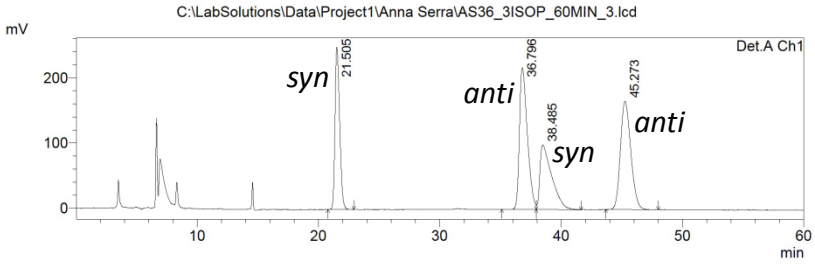


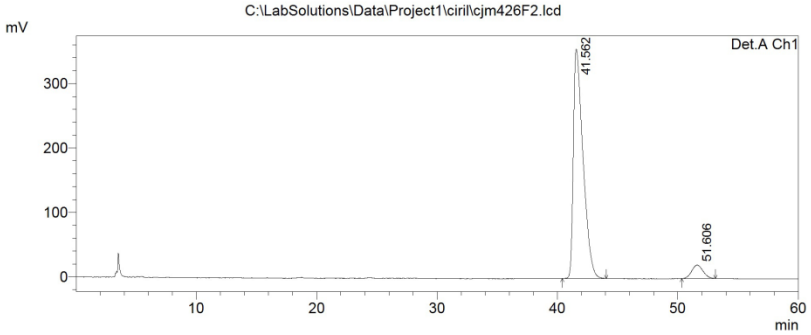


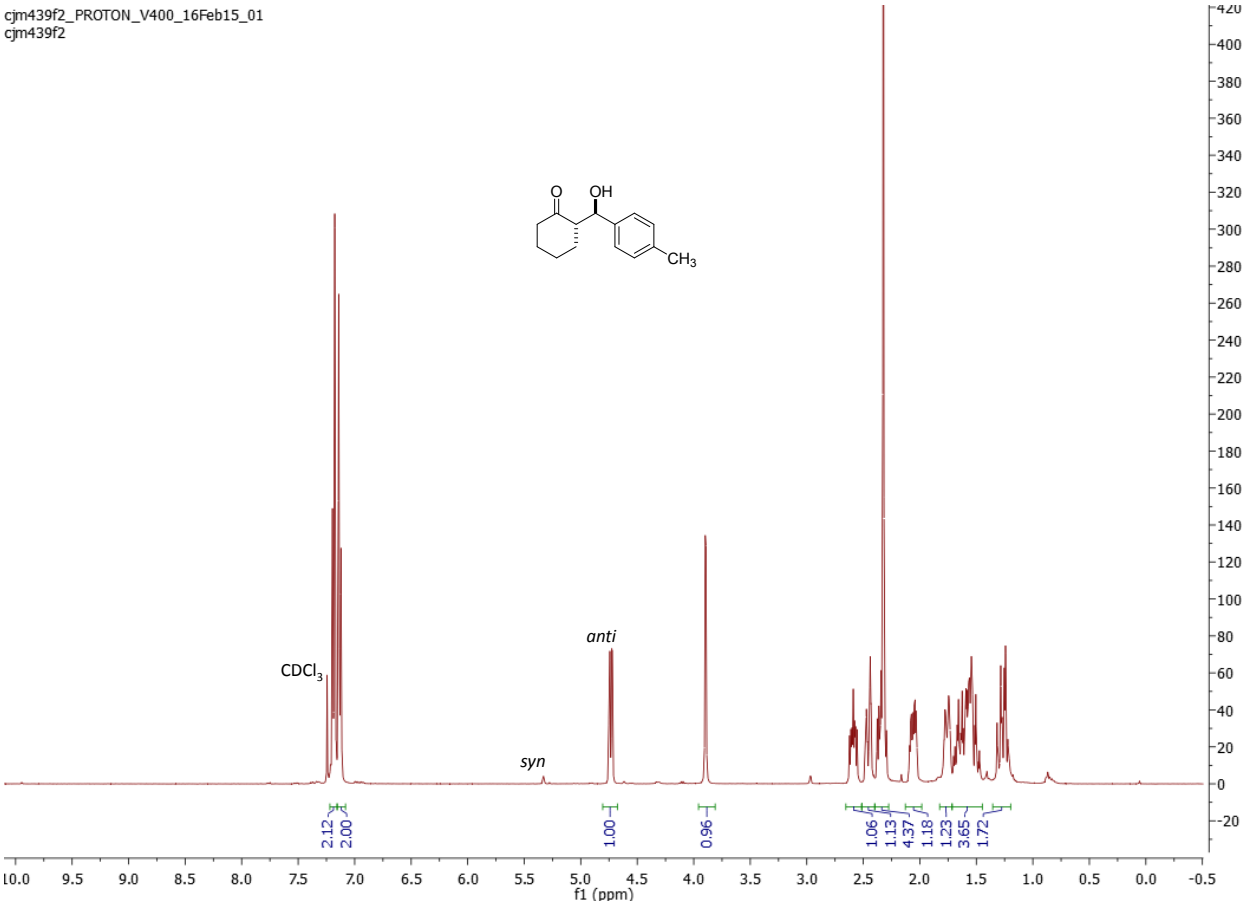
$[\alpha]_D$ = +22.4 (c = 1.0, $CHCl_3$, 89% ee), lit. $[\alpha]_D$ = +27.7(c = 0.85, $CHCl_3$, >99% ee)[2]

HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

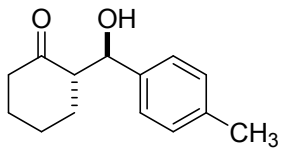


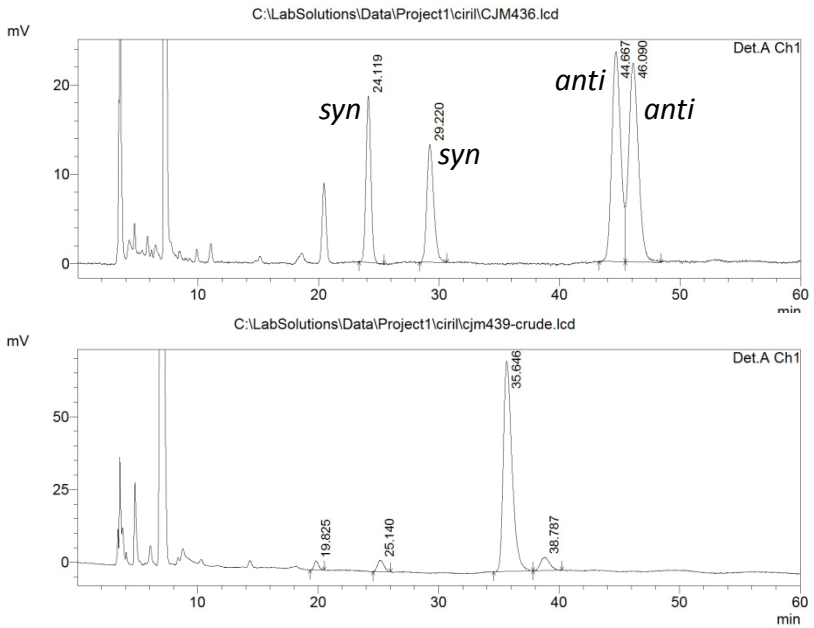


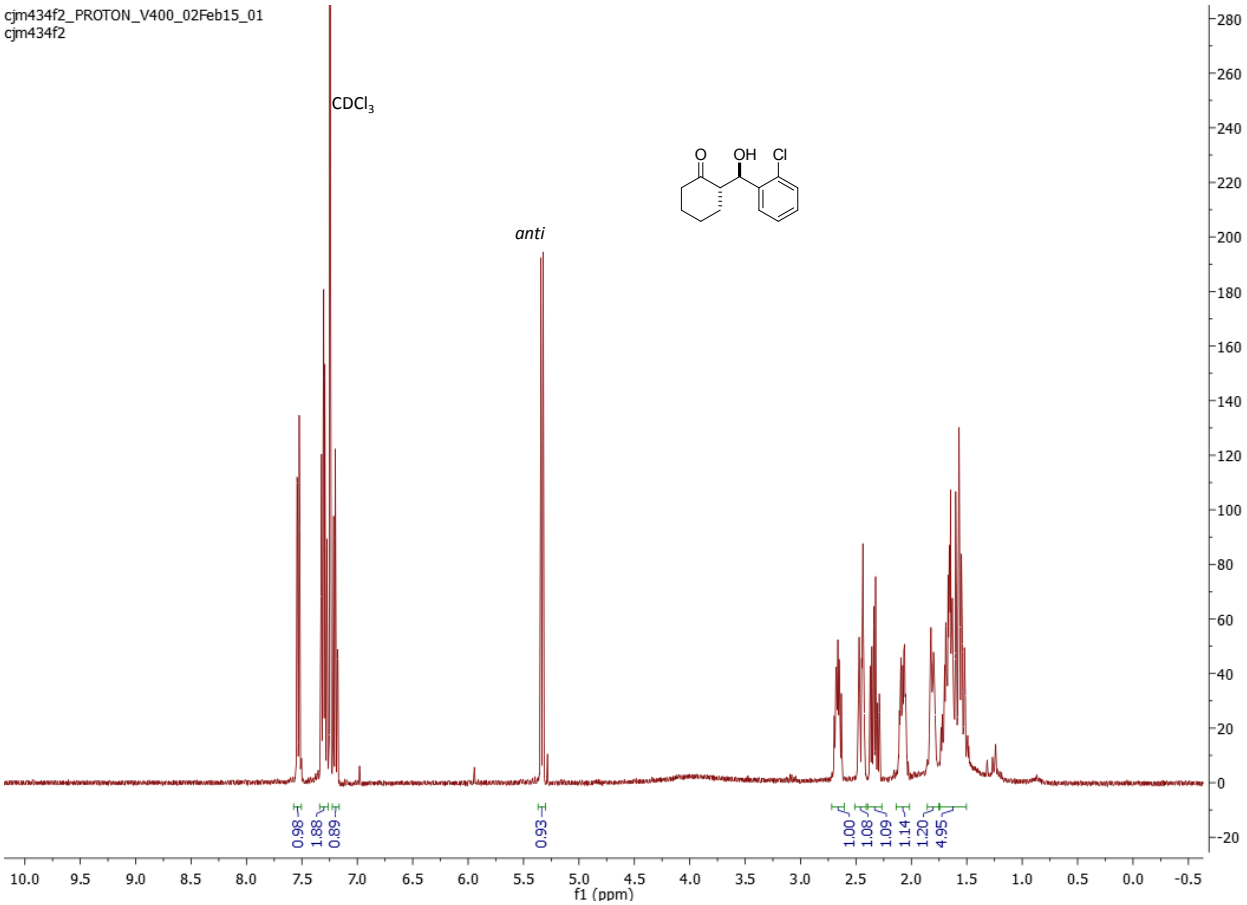




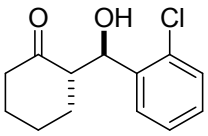
HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

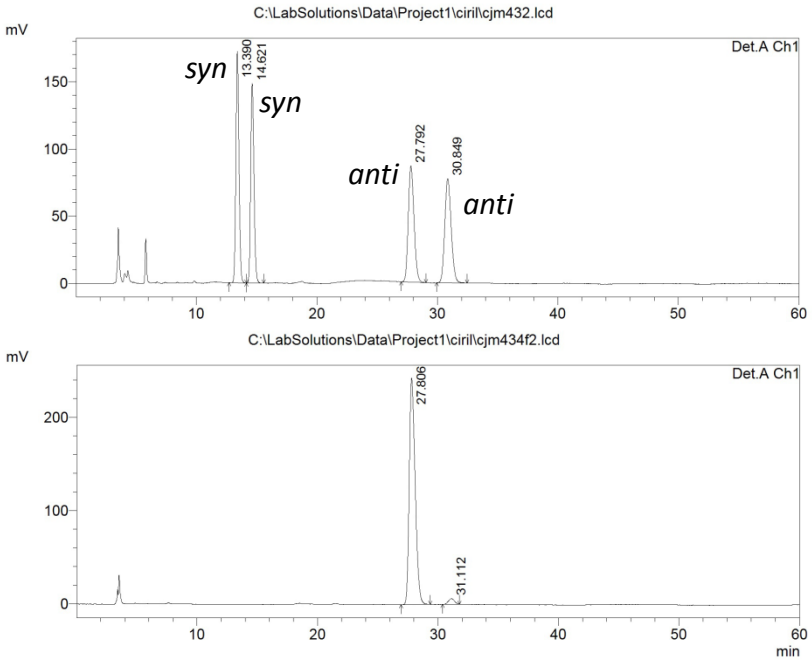


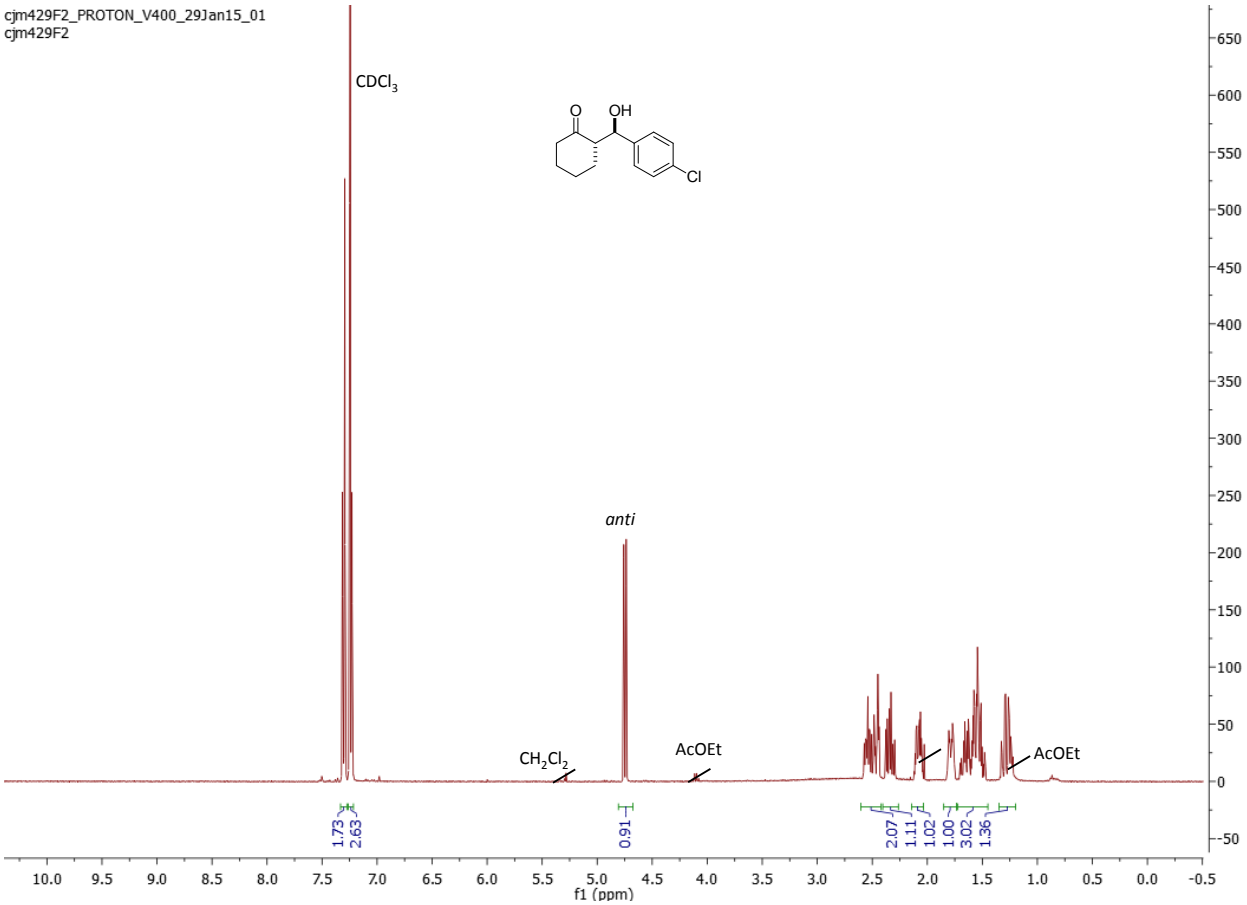




HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

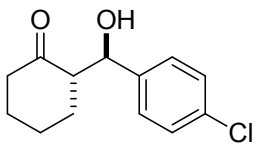


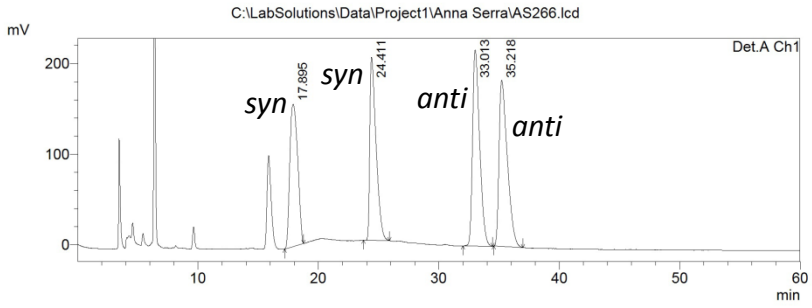


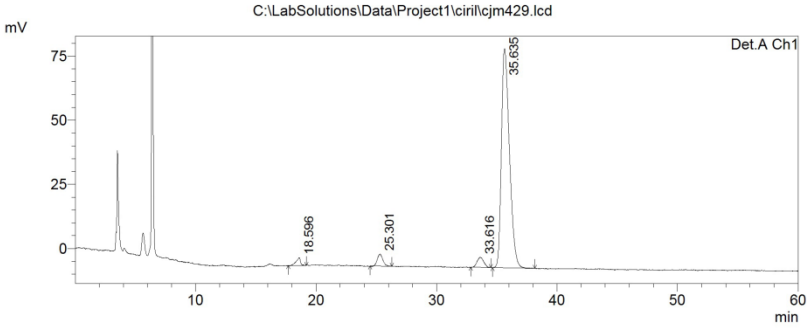


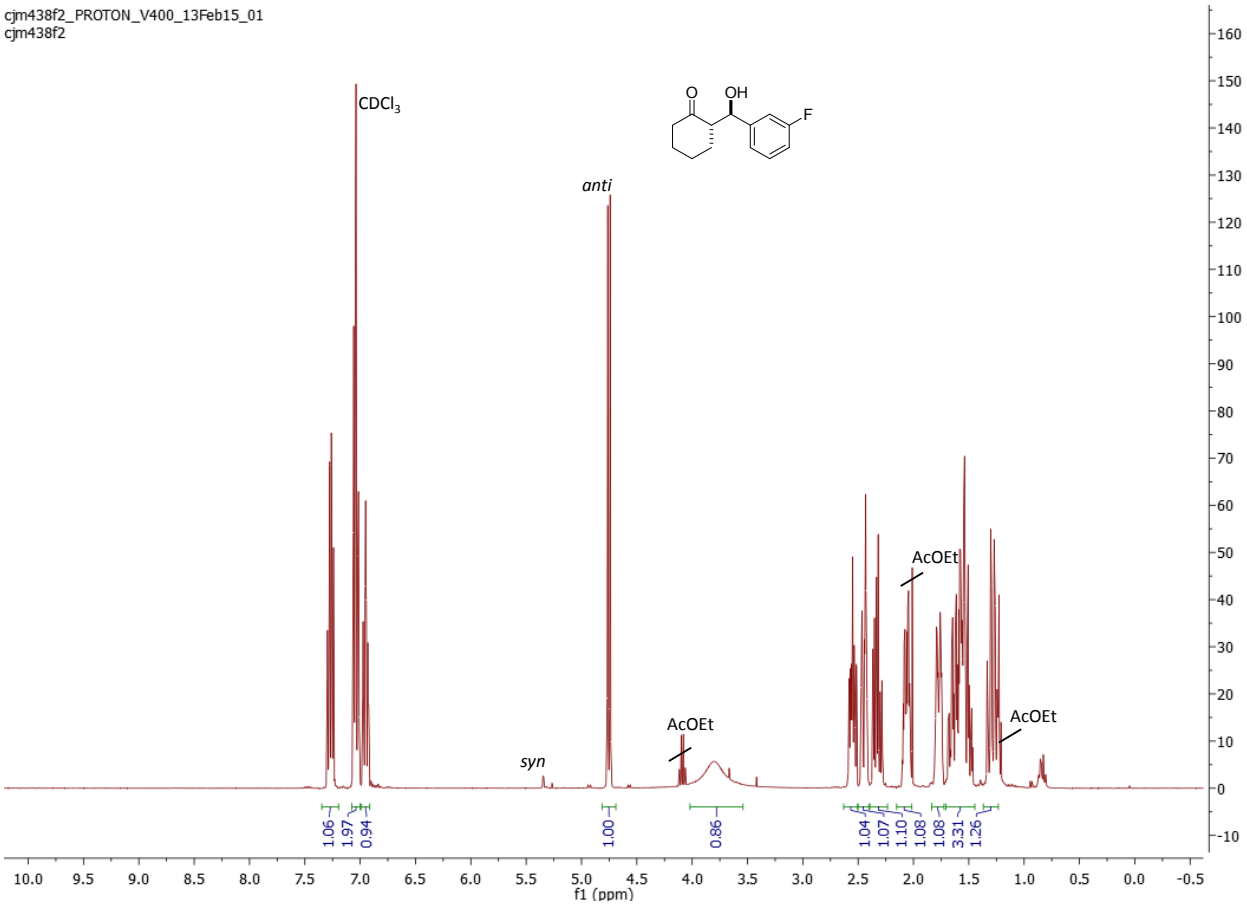
$[\alpha]_D$ = +23.4 (c = 1.0, $CHCl_3$, 93% ee), lit. $[\alpha]_D$ = +21.7(c = 1.0, $CHCl_3$, >99% ee)[3]

HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

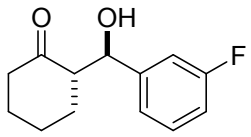


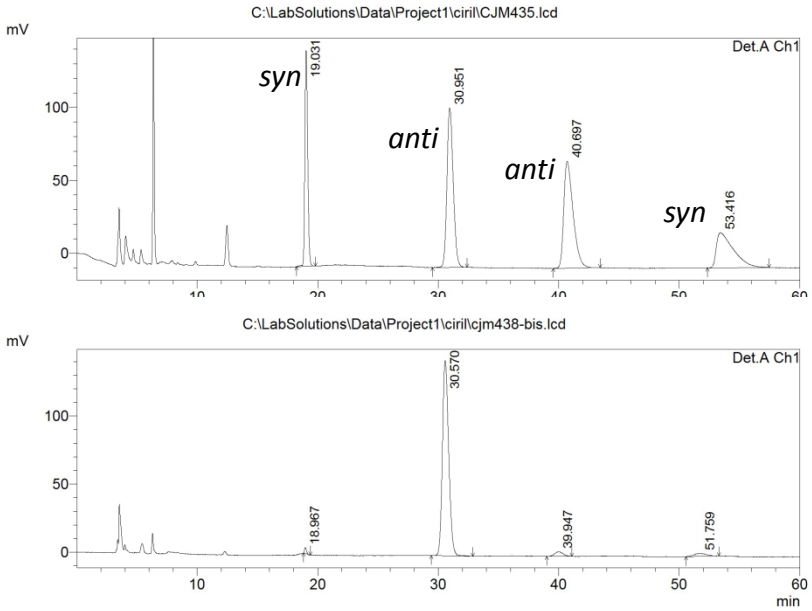


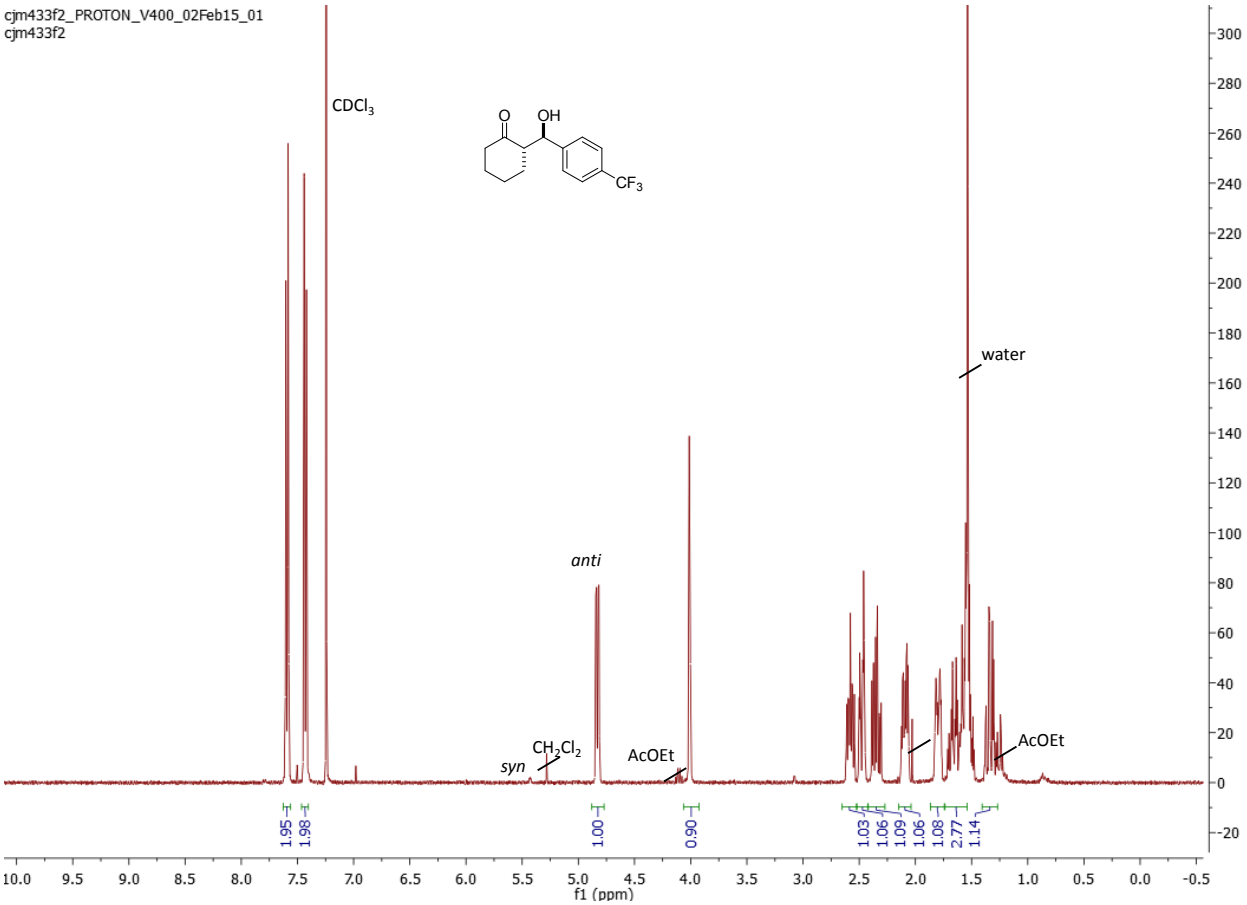




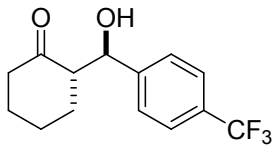
HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

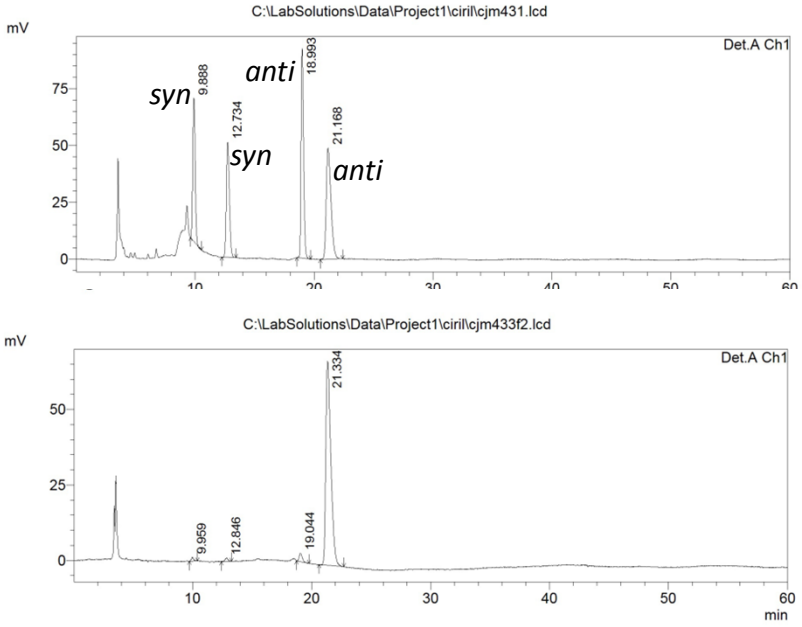


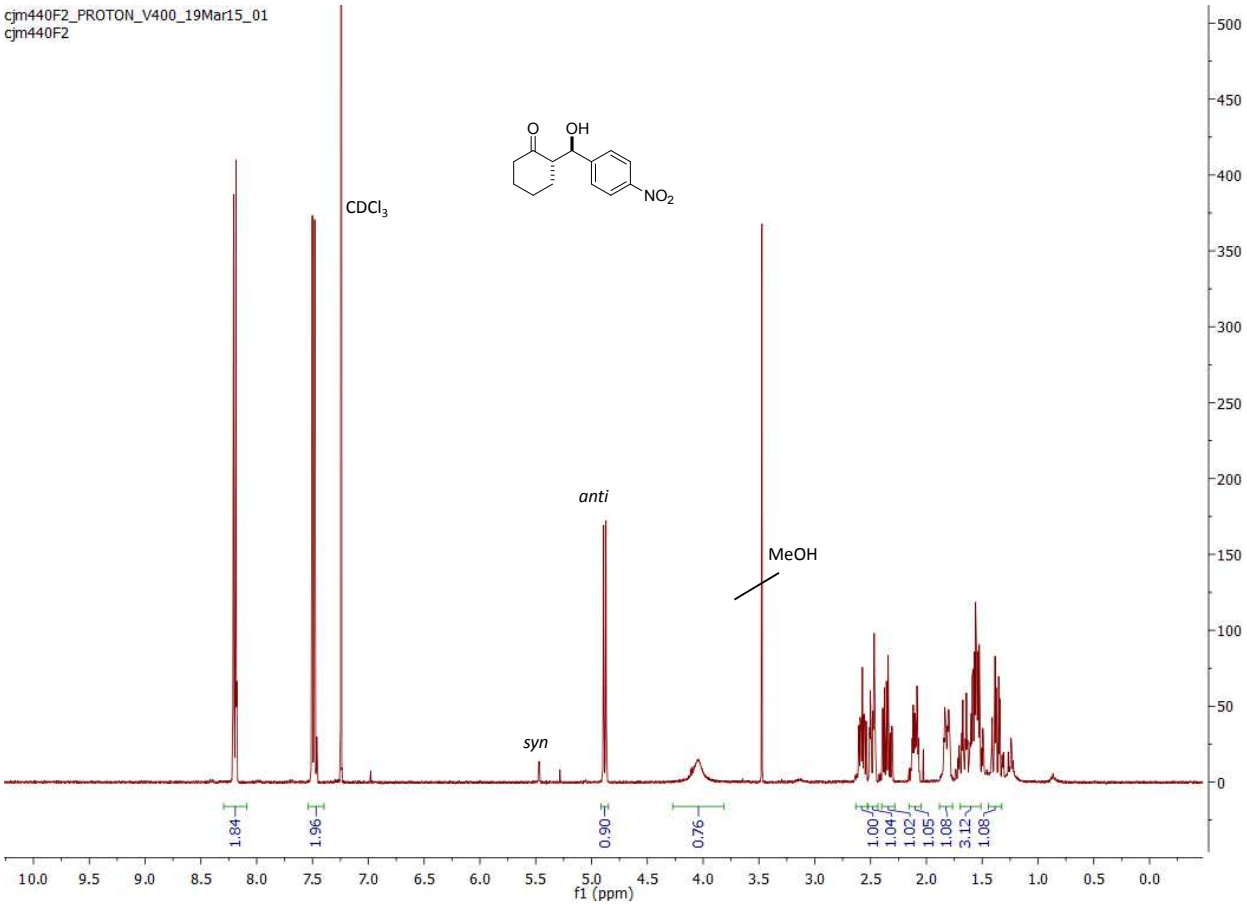




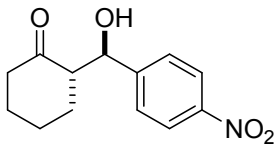
HPLC: ID column, 1 ml/min, 3% *iso*-propanol, 209 nm.

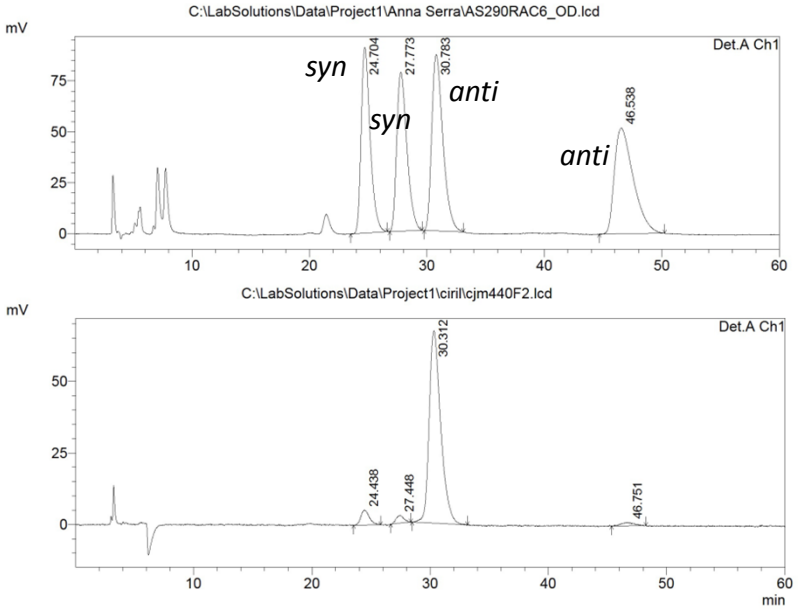


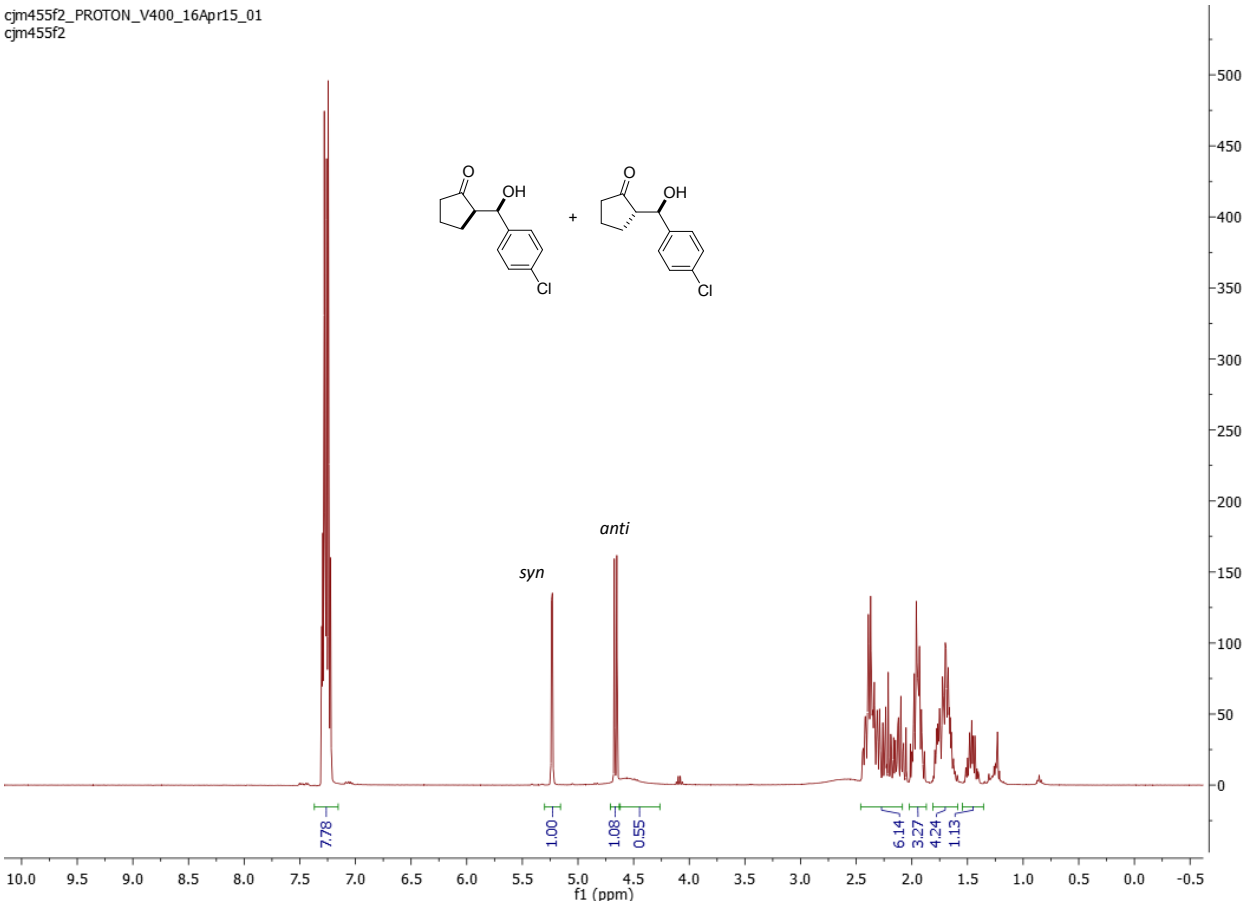




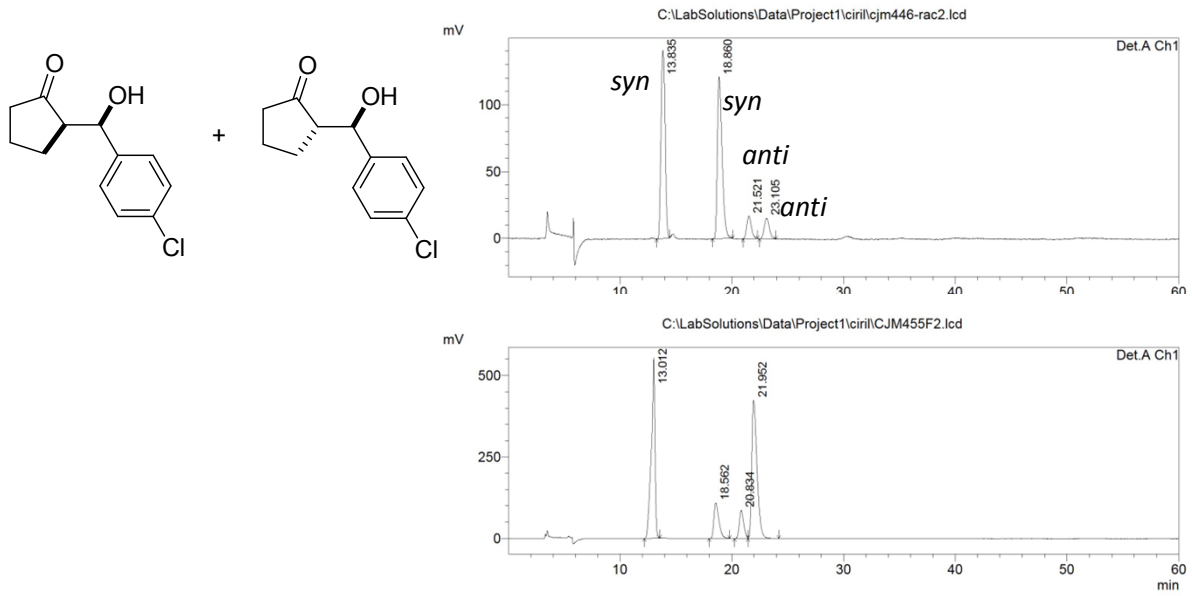
HPLC: OD column, 1 ml/min, 5% *iso*-propanol, 209 nm.

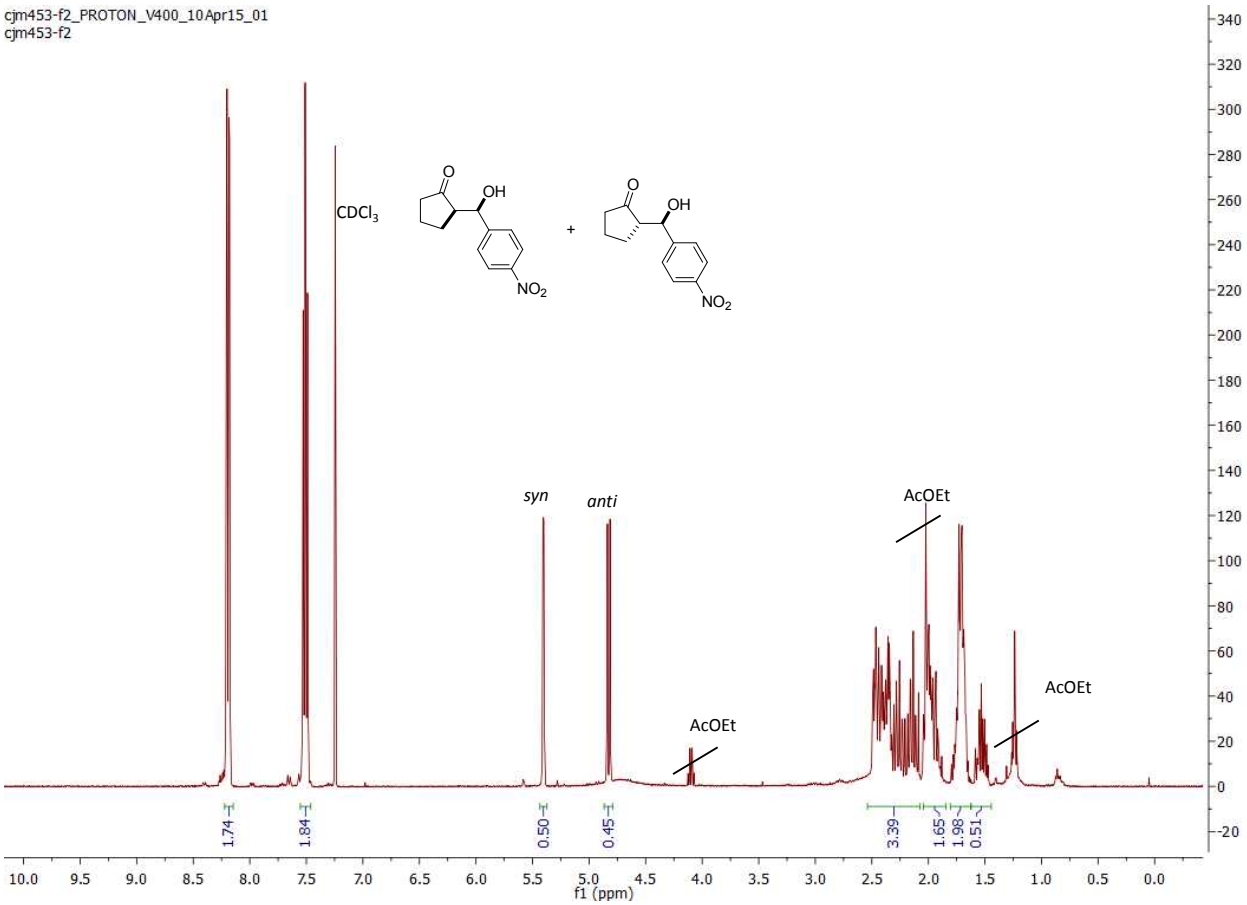




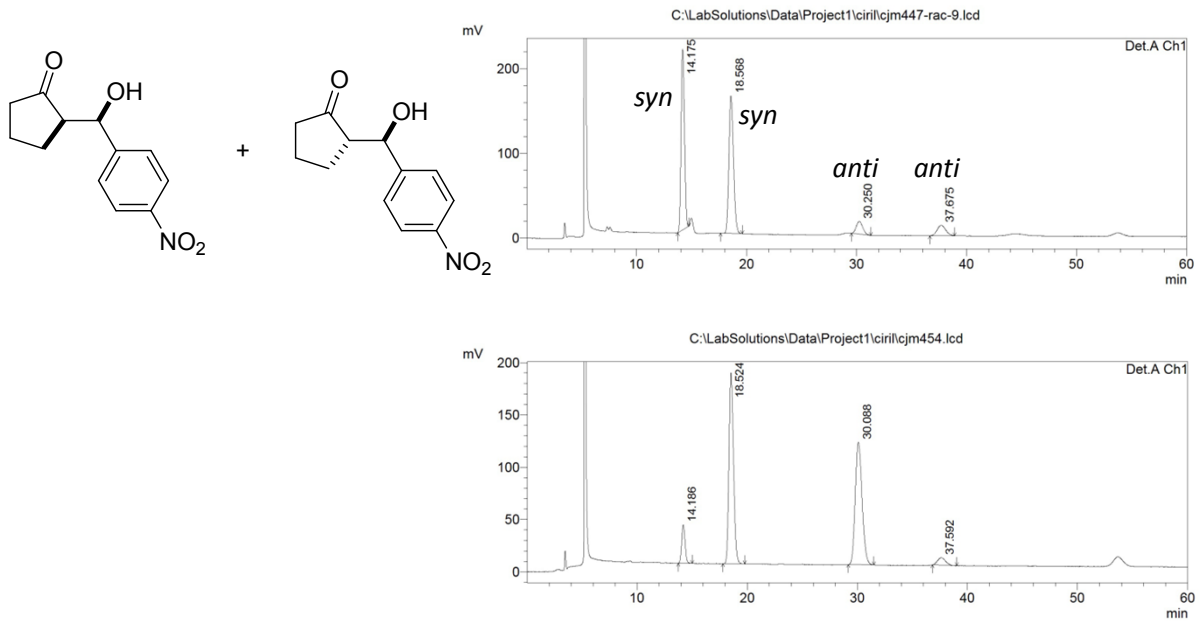


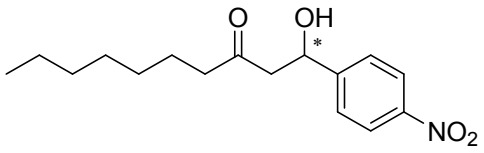
HPLC: ID column, 1 ml/min, 5% *iso*-propanol, 209 nm.



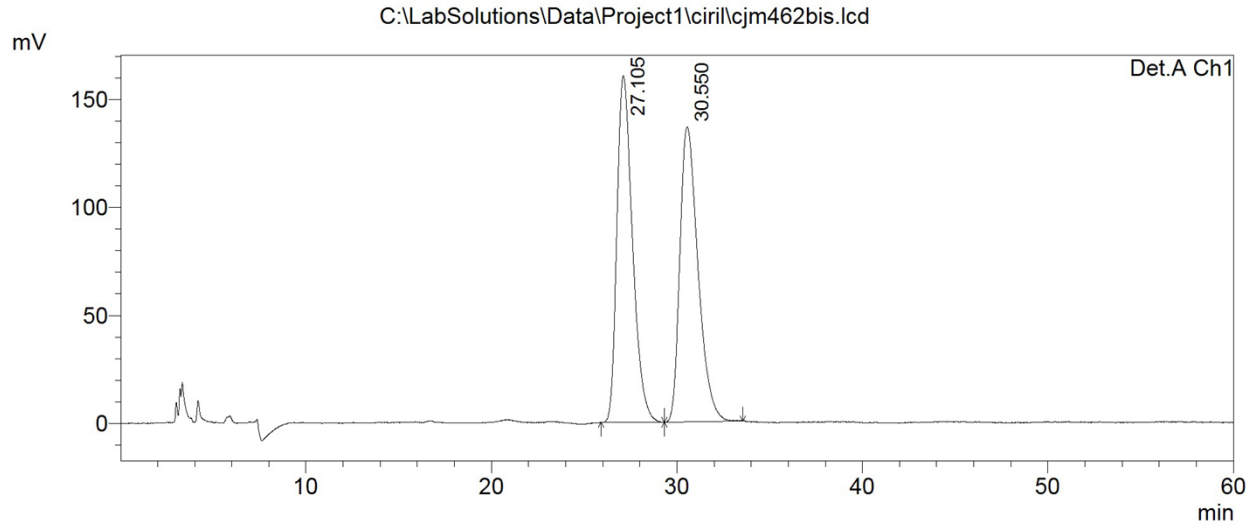


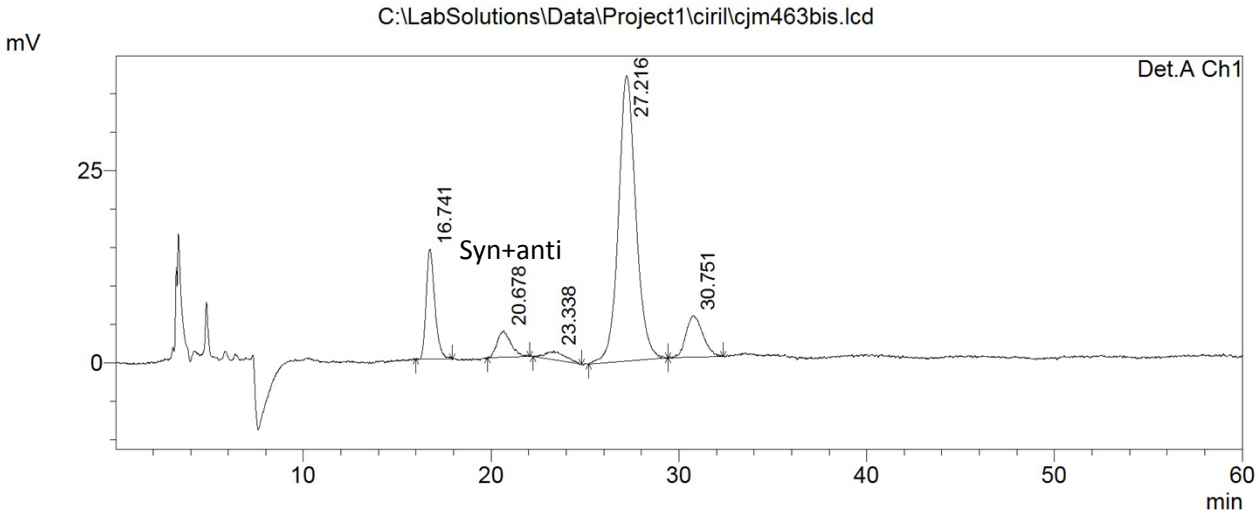
HPLC: IC column, 1 ml/min, 10% *iso*-propanol, 209 nm.





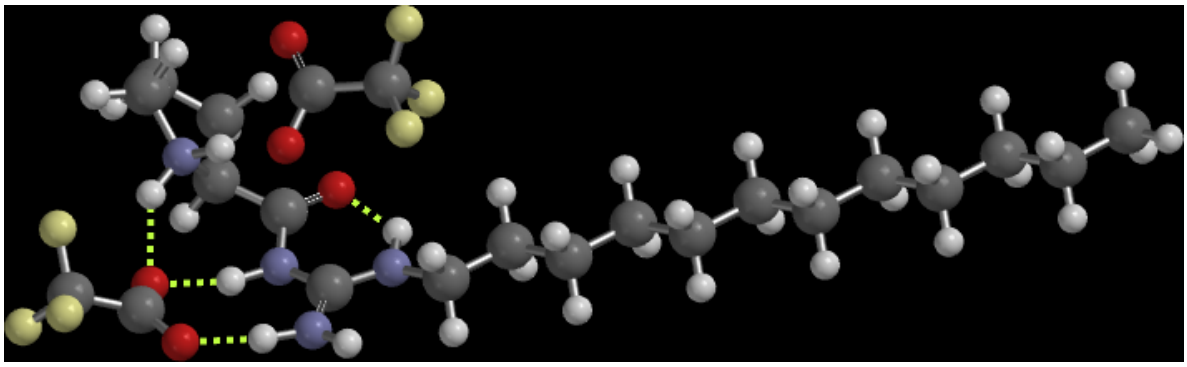
HPLC (ID, 1 ml/min, 3% IPA, 209 nm)



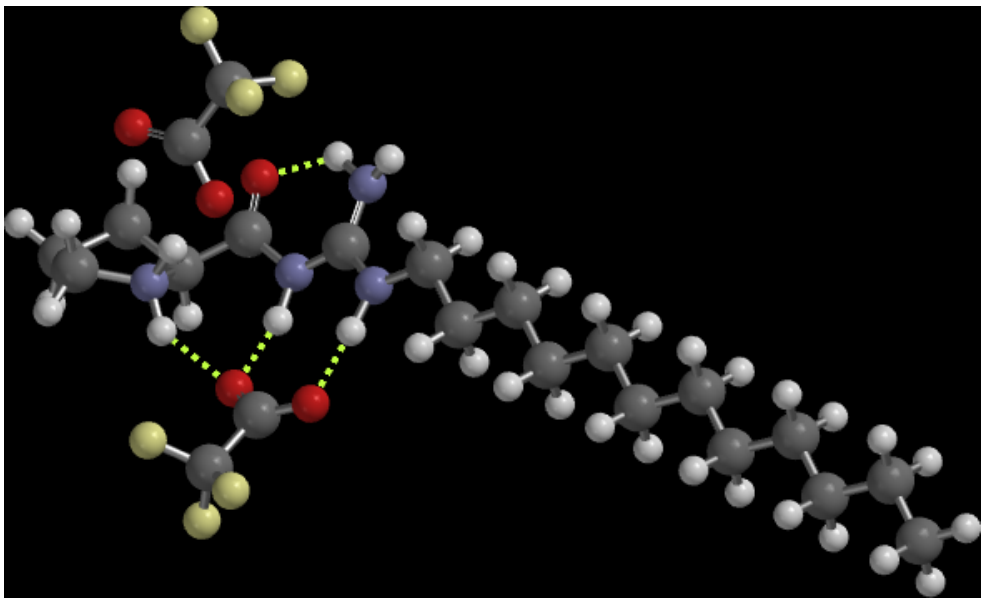


8 DFT (B3LYP/6-31G*) calculated more stable conformers with the full dodecyl chain.

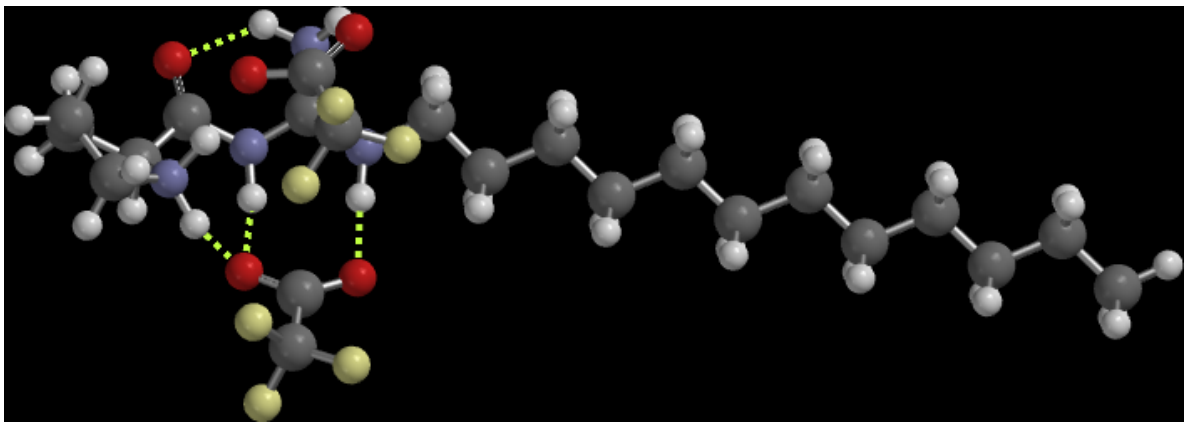
Calculation performed with Spartan'10, Wavefunction Inc., Irvine (CA).



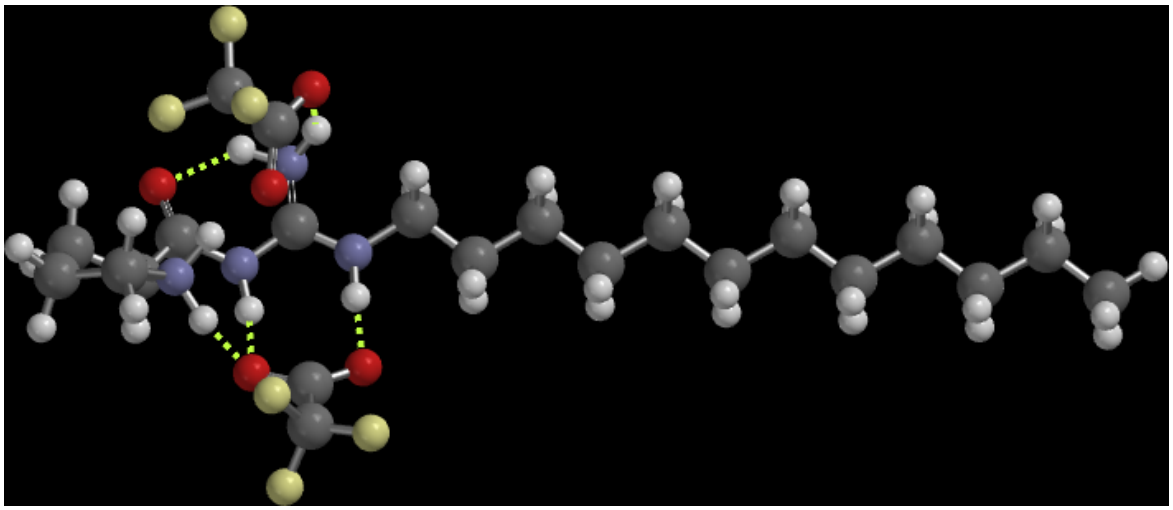
Rel. Energy = 0 Kcal/mol



Rel energy = +1.06 Kcal/mol



Rel. Energy = +1.97 Kcal/mol



Rel. Energy = +2.14 Kcal/mol

9. References

1. D. A. Leigh, C. C. Robertson, A. M. Z. Slawin, P. I. T. Thomson. *J. Am. Chem Soc.* **2013**, *135*, 9939-9943.

2. Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.*, **2006** , *45*, 958 – 961.

3. Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett*., **2006** , *8*, 4417 – 4420.