

Article

Urea Activation by an External Brønsted Acid: Breaking Self-Association and Tuning Catalytic Performance

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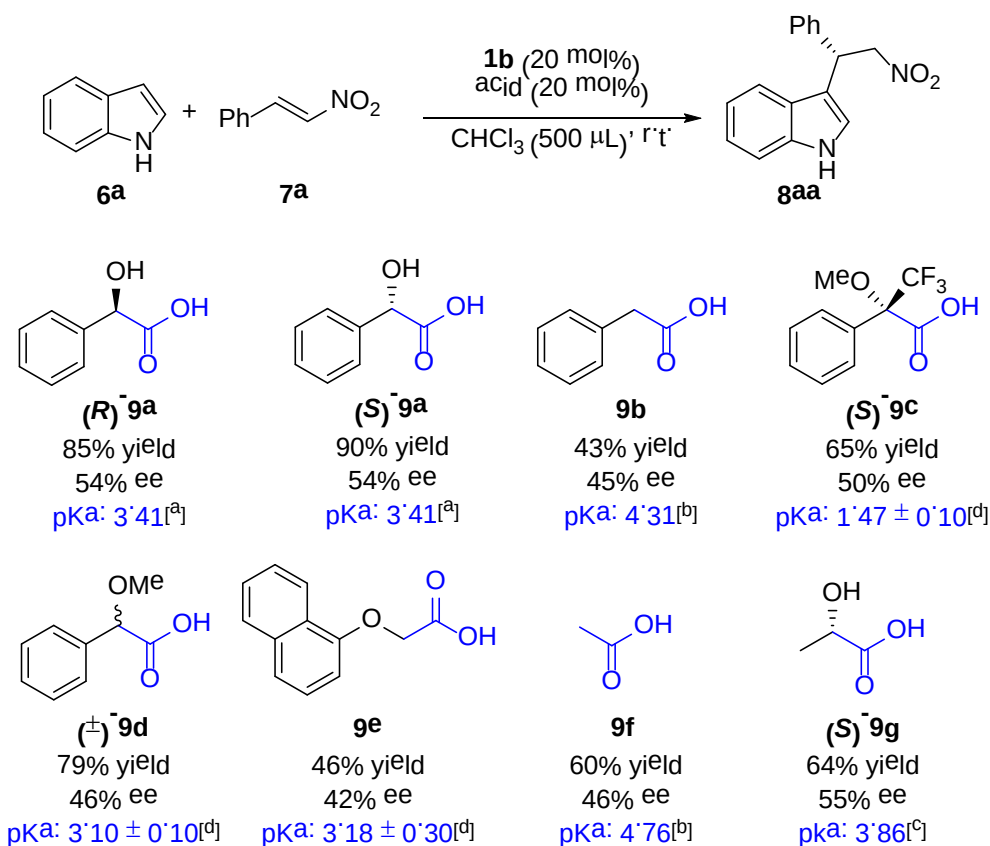
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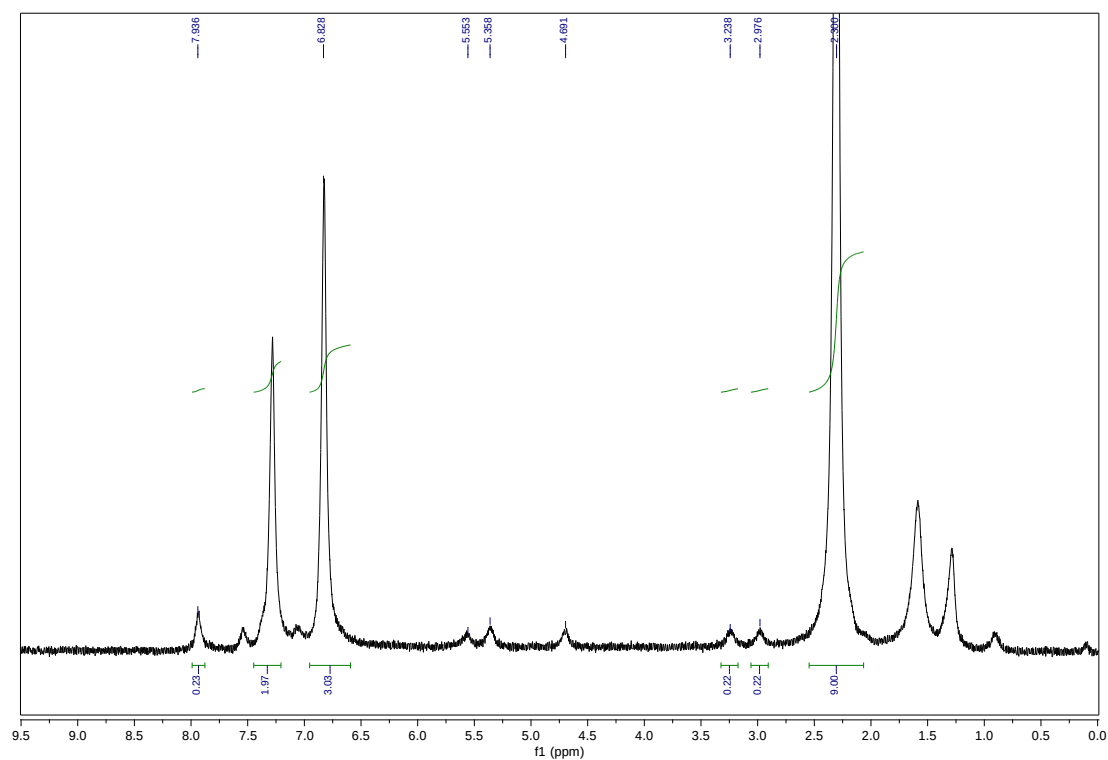
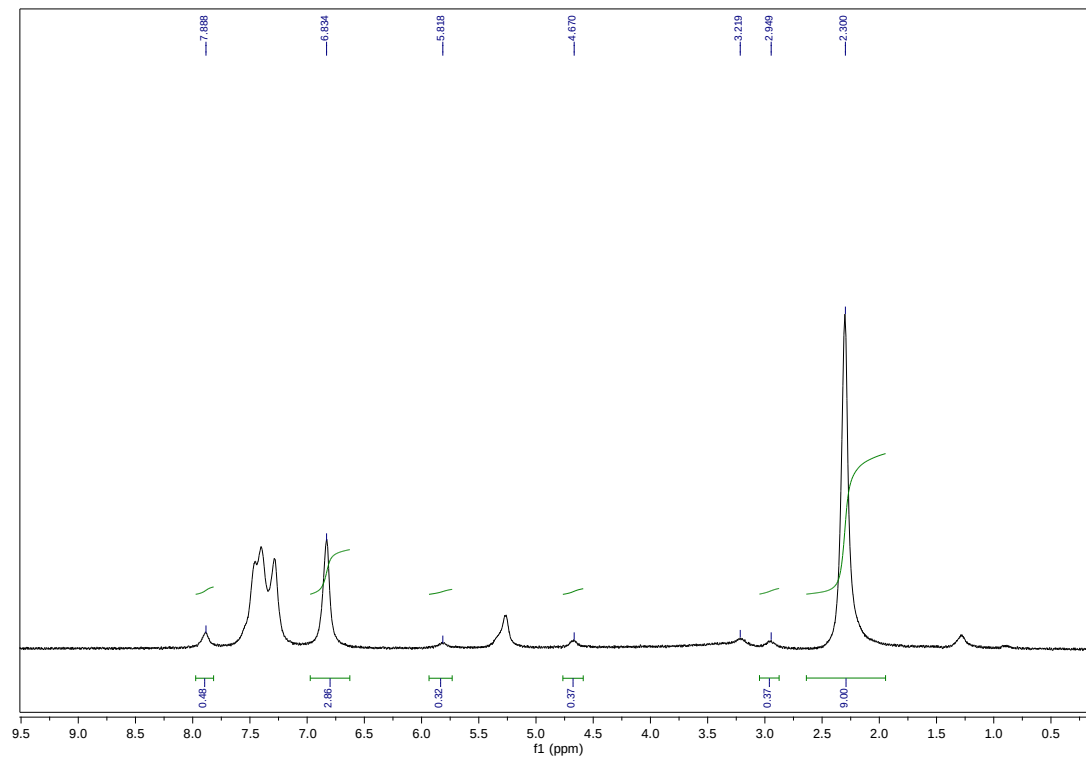
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Electronic Supplementary Information (ESI)



Scheme S1. pK_a values in waters. ^[a] Bjerrum, J., et al. Stability Constants, Chemical Society, London, 1958. ^[b] Dippy, J.F.J.; Hughes, S.R.C.; Rozanski, A. J. Chem. Soc. 1959, 2492. ^[c] Dawson, R.M.C. et al., Data for Biochemical Research, Oxford, Clarendon Press, 1959. ^[d] Stimated value reported in Scifinder with the employed softward: Advanced Chemistry Development (ACD/Labs) Software VII.02.

Effect of the acid in the ^1H NMR signals of the urea catalysts (500 MHz)**Figure S1.** Urea **1b** (0.02 mmol) and acid ($\pm$)-**9a** (0 mmol) in CDCl_3 (0.5 mL).**Figure S2.** Urea **1b** (0.02 mmol) and acid ($\pm$)-**9a** (0.01 mmol) in CDCl_3 (0.5 mL).

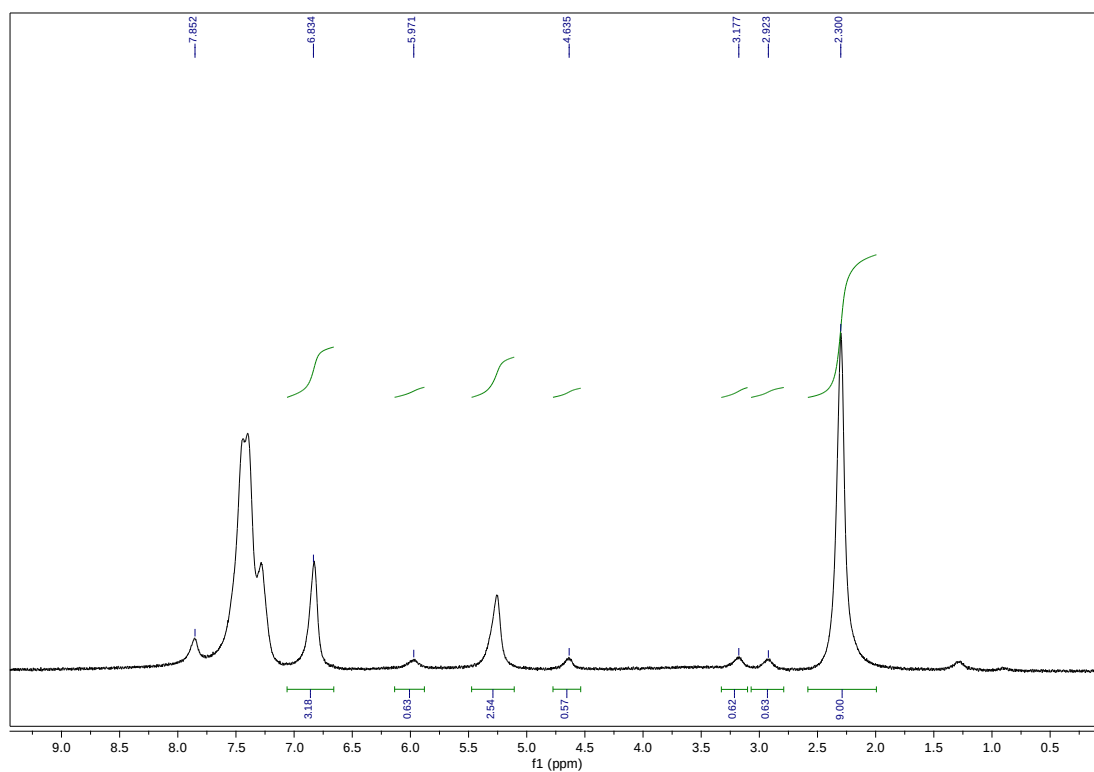


Figure S3. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.02 mmol) in CDCl₃ (0.5 mL).

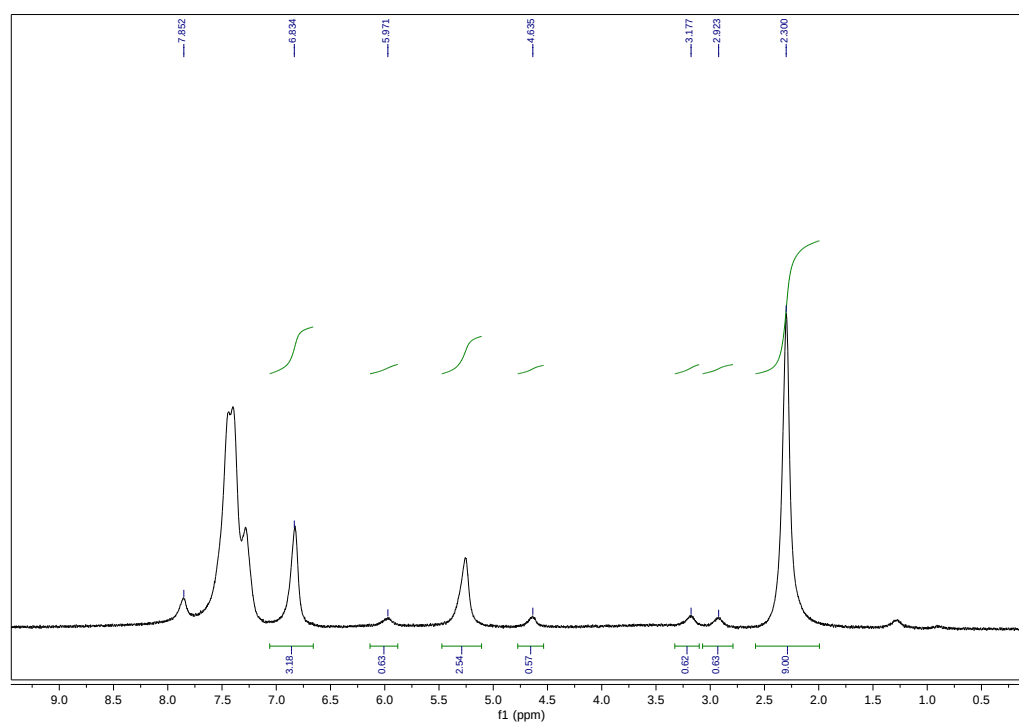


Figure S3. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.02 mmol) in CDCl₃ (0.5 mL).

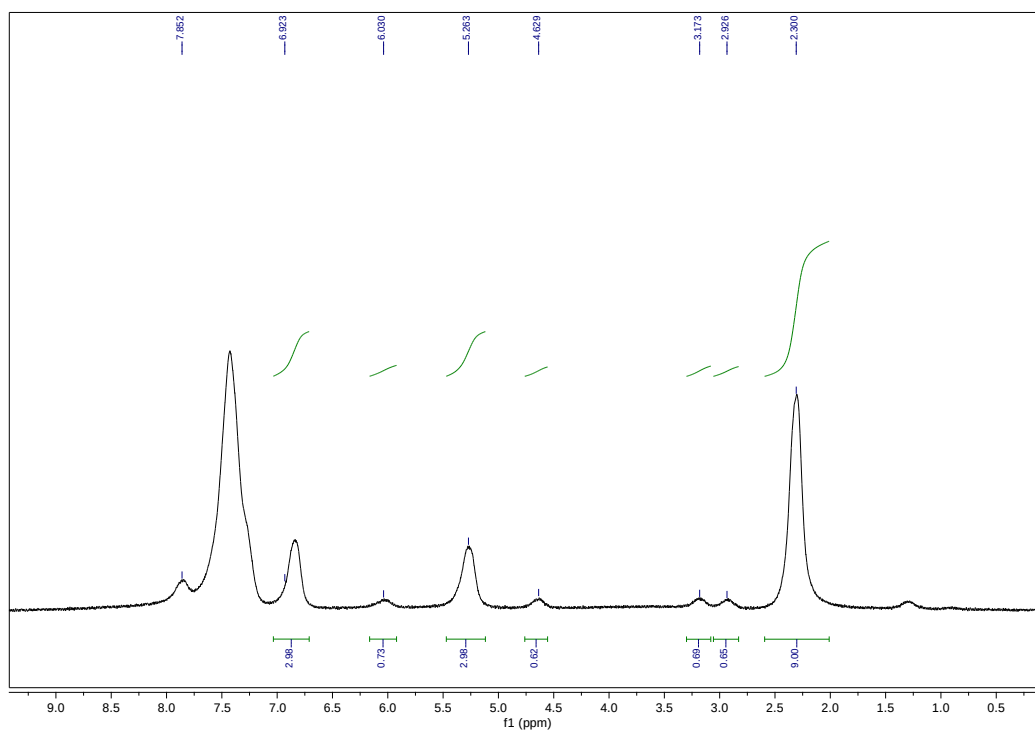


Figure S4. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.03 mmol) in CDCl₃ (0.5 mL).

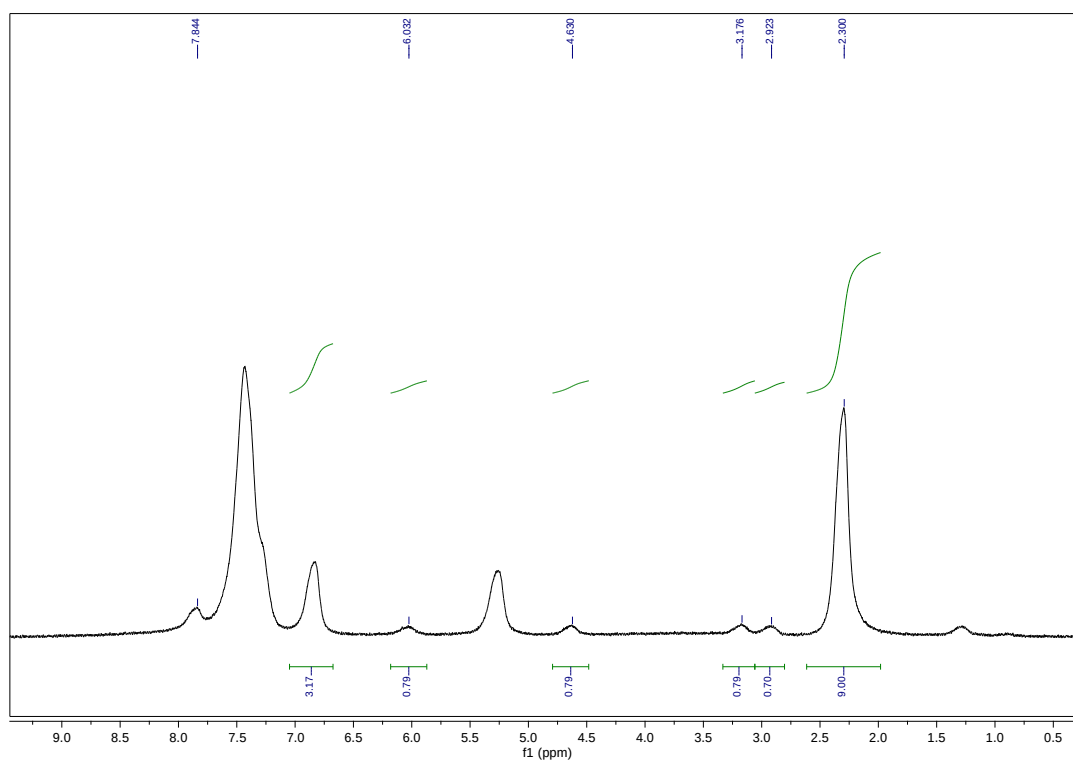


Figure S5. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.04 mmol) in CDCl₃ (0.5 mL).

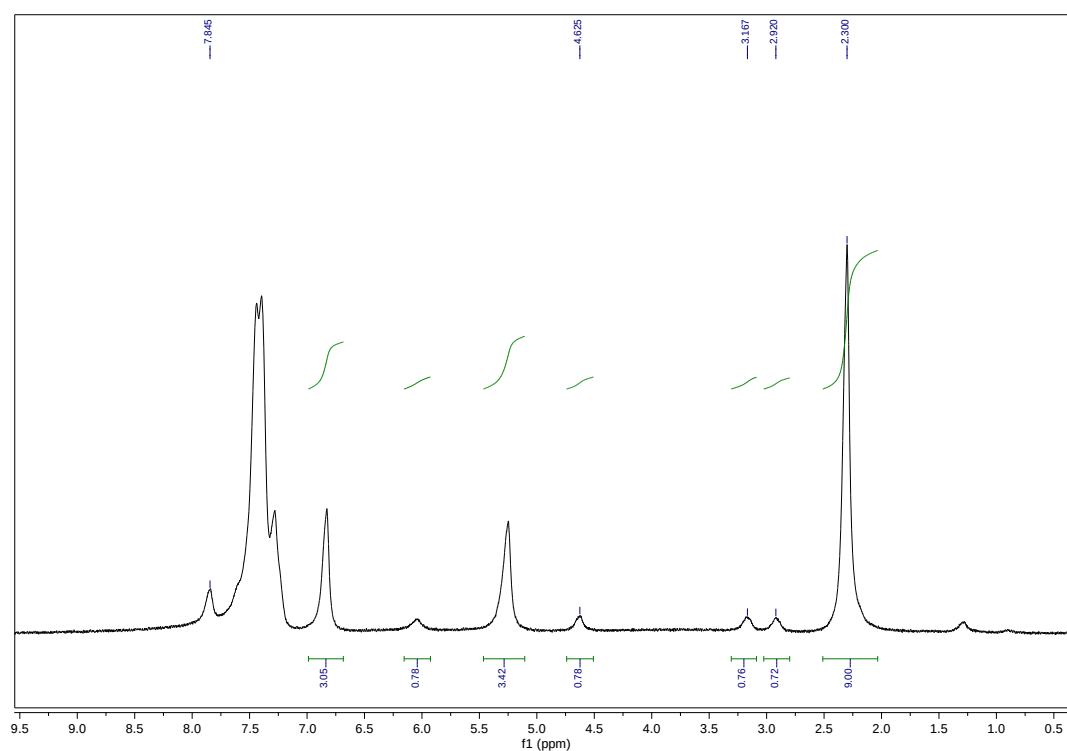


Figure S6. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.06 mmol) in CDCl₃ (0.5 mL).

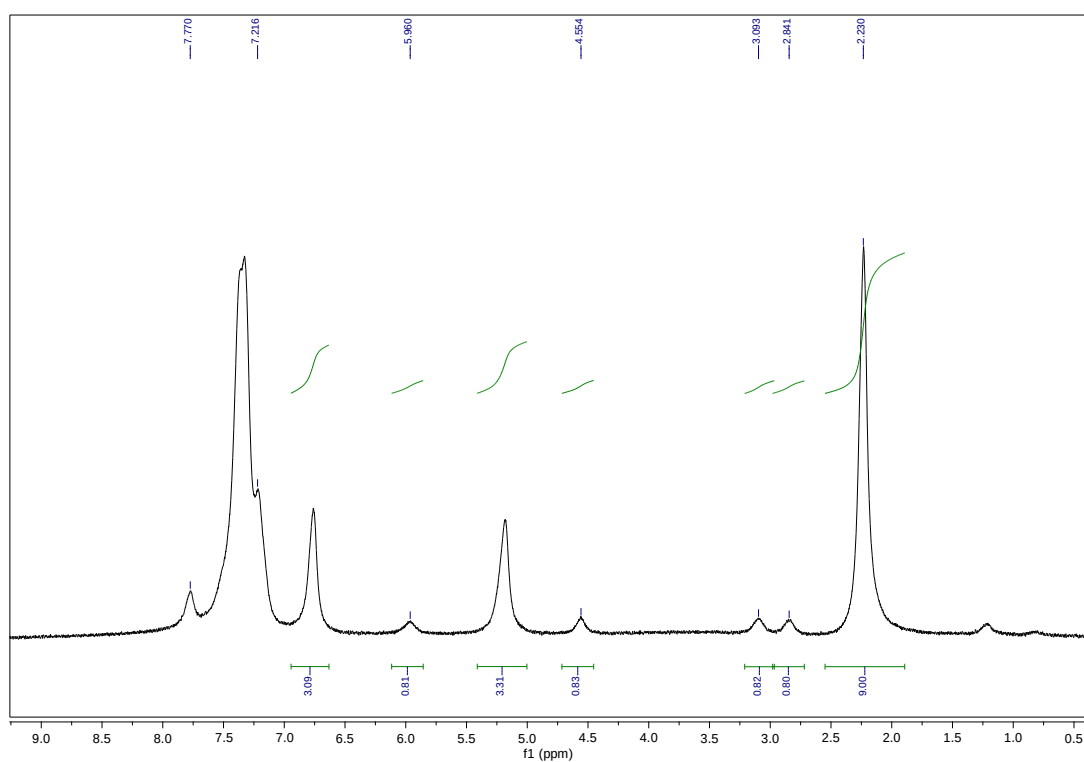


Figure S7. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.08 mmol) in CDCl₃ (0.5 mL).

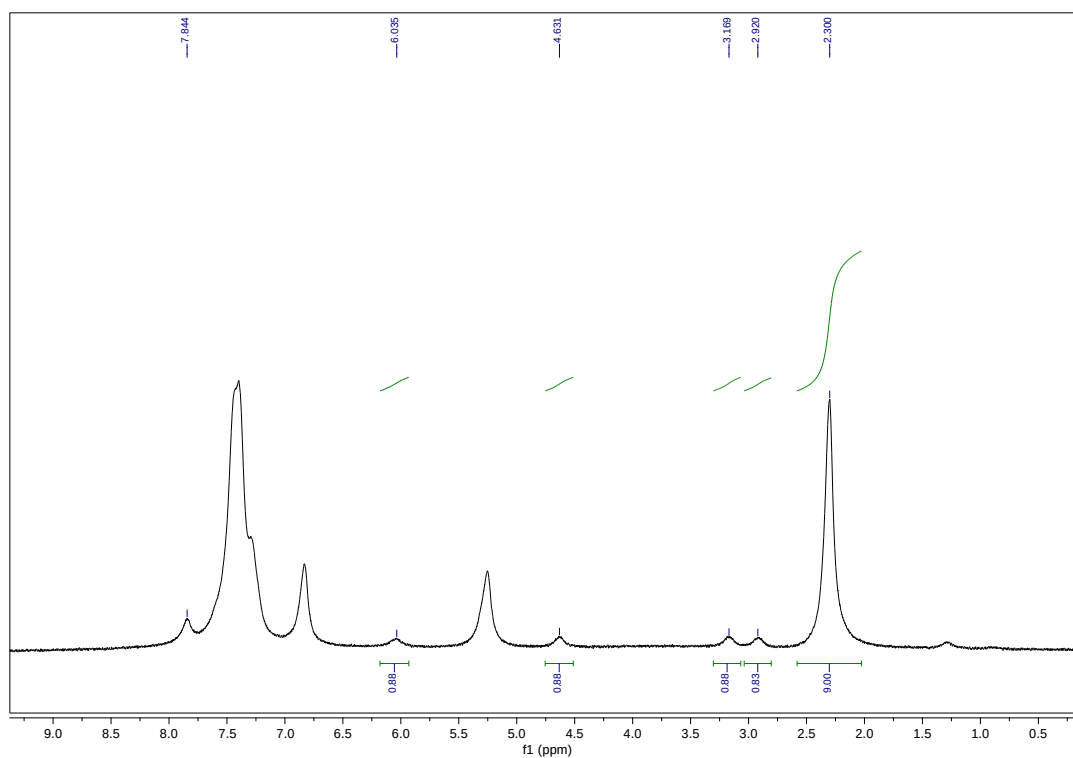
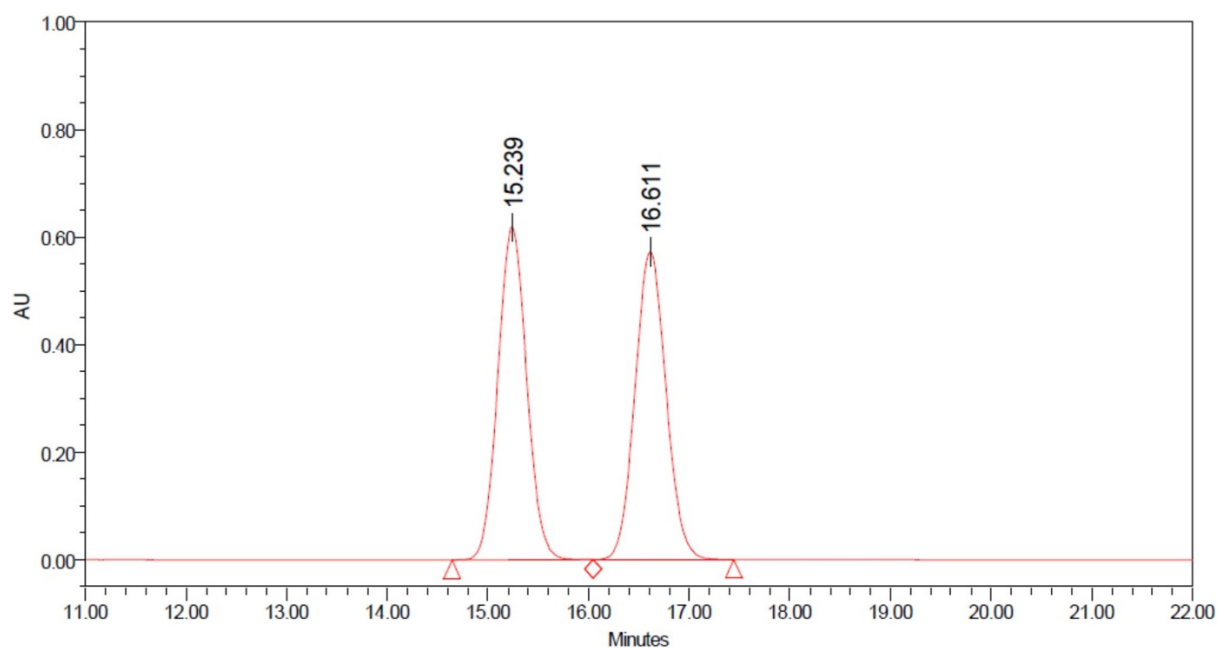


Figure S8. Urea **1b** (0.02 mmol) and acid (±)-**9a** (0.1 mmol) in CDCl_3 (0.5 mL).

HPLC ANALYSIS OF COMPOUNDS **8**



Processed Channel: PDA 254.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	15.239	12306311	49.97	619767
2	PDA 254.0 nm	16.611	12319344	50.03	572872

Figure S9. Racemic mixture of **8aa**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).

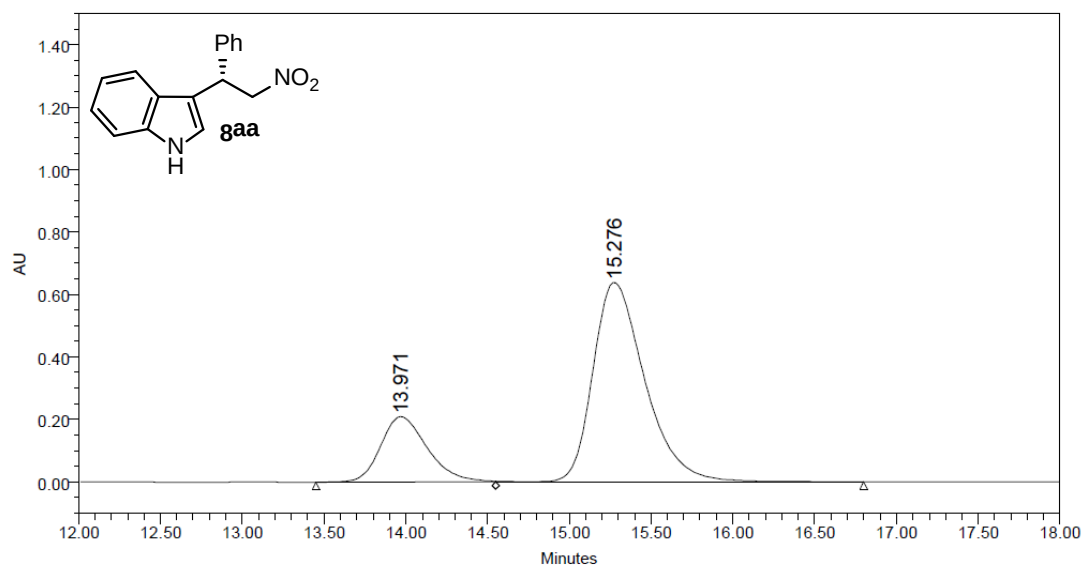


Figure S10. Chiral sample of (S)-3-(2-nitro-1-phenylethyl)-1H-indole (8aa) using urea·HA (1b·(±)-9a).

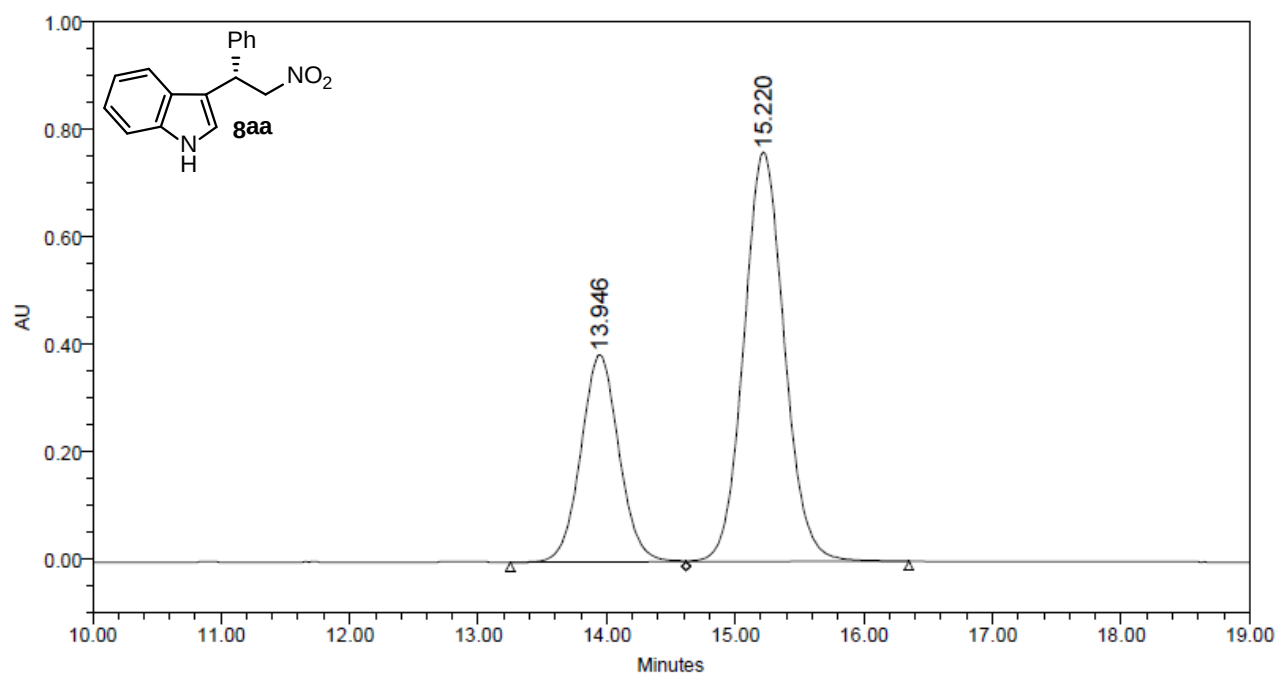
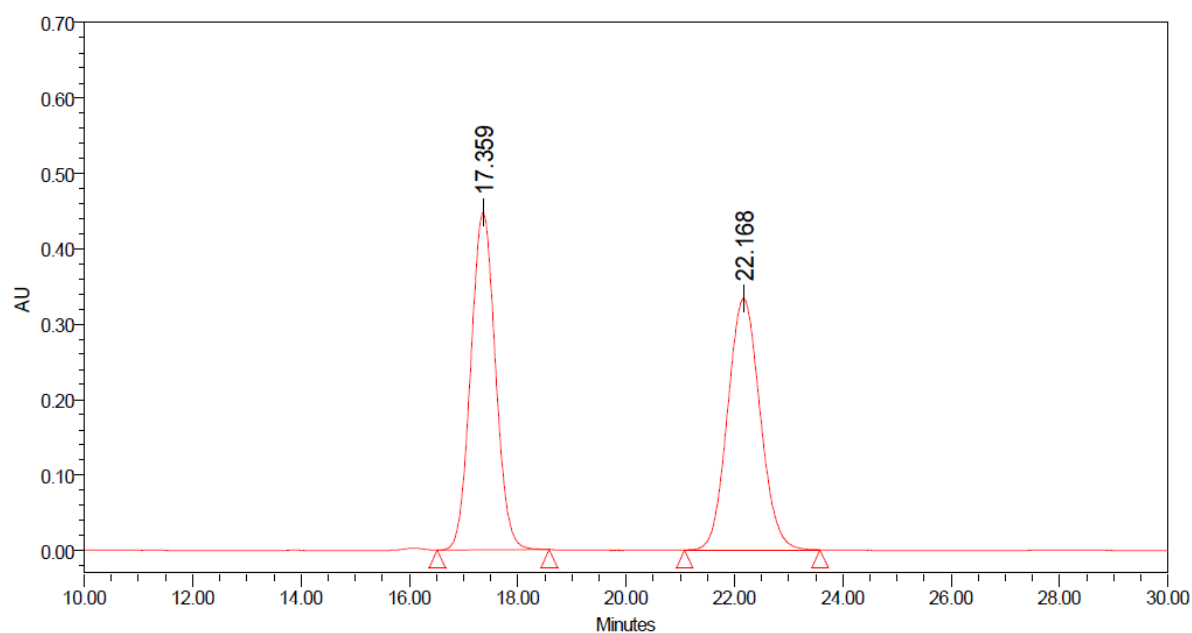


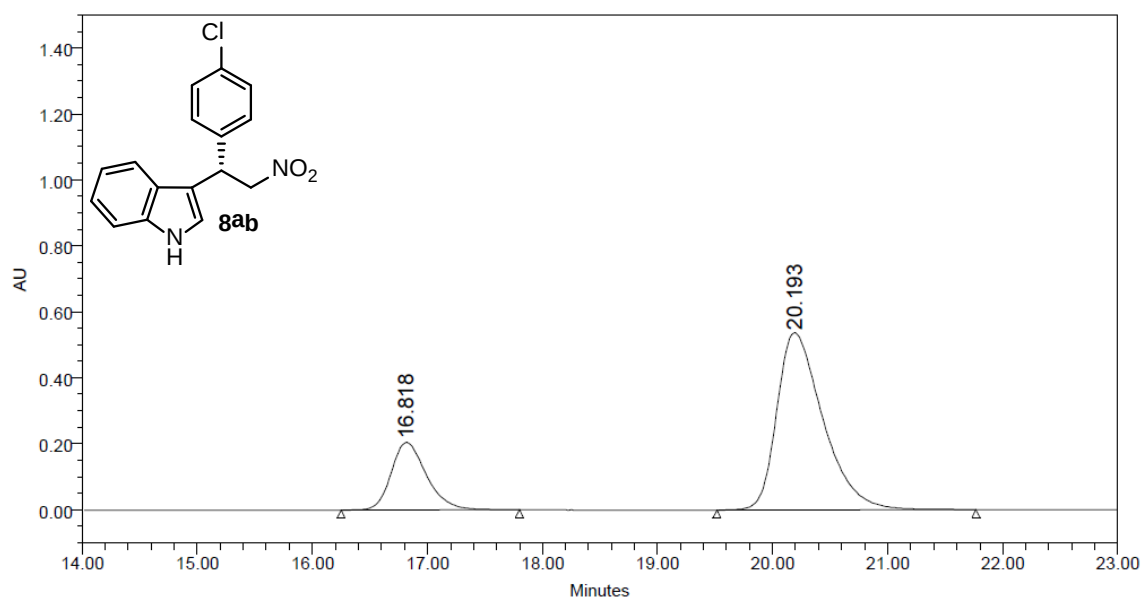
Figure S11. Chiral sample of (S)-3-(2-nitro-1-phenylethyl)-1H-indole (8aa) using urea 1b only.



Processed Channel: PDA 254.0 nm

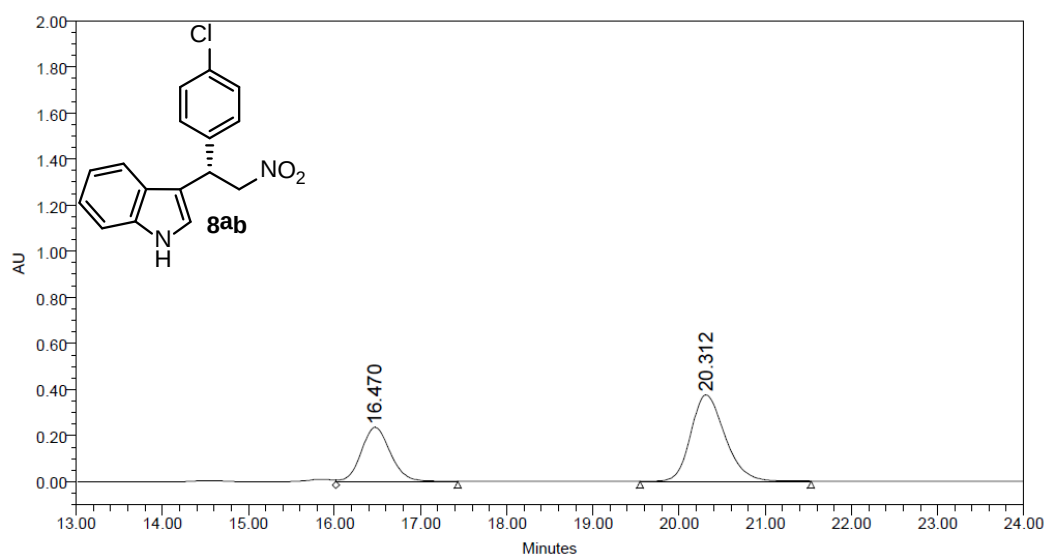
	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	17.359	14157054	50.57	447551
2	PDA 254.0 nm	22.168	13840118	49.43	333279

Figure S12. Racemic mixture of **8ab**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).



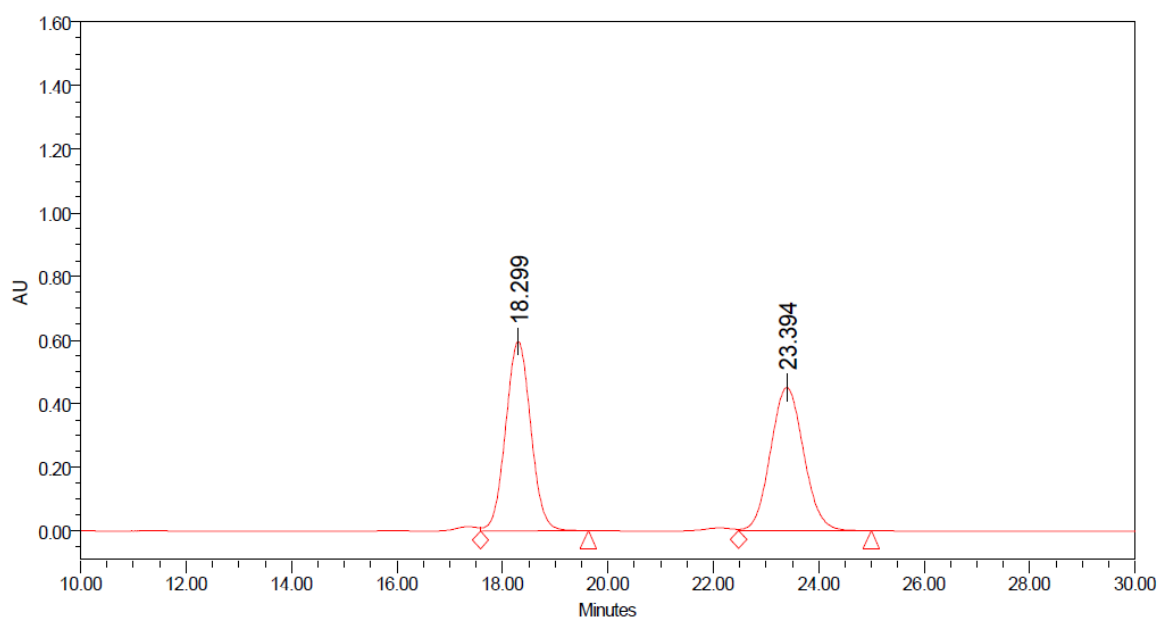
	RT	Area	% Area	Height
1	16.818	4350626	22.50	204049
2	20.193	14984915	77.50	537104

Figure S13. Chiral sample of (*S*)-3-(1-(4-chlorophenyl)-2-nitroethyl)-1*H*-indole (**8ab**) using urea-HA (**1b**(±)-**9a**).



	RT	Area	% Area	Height
1	16.470	5511957	34.85	235320
2	20.312	10305258	65.15	375595

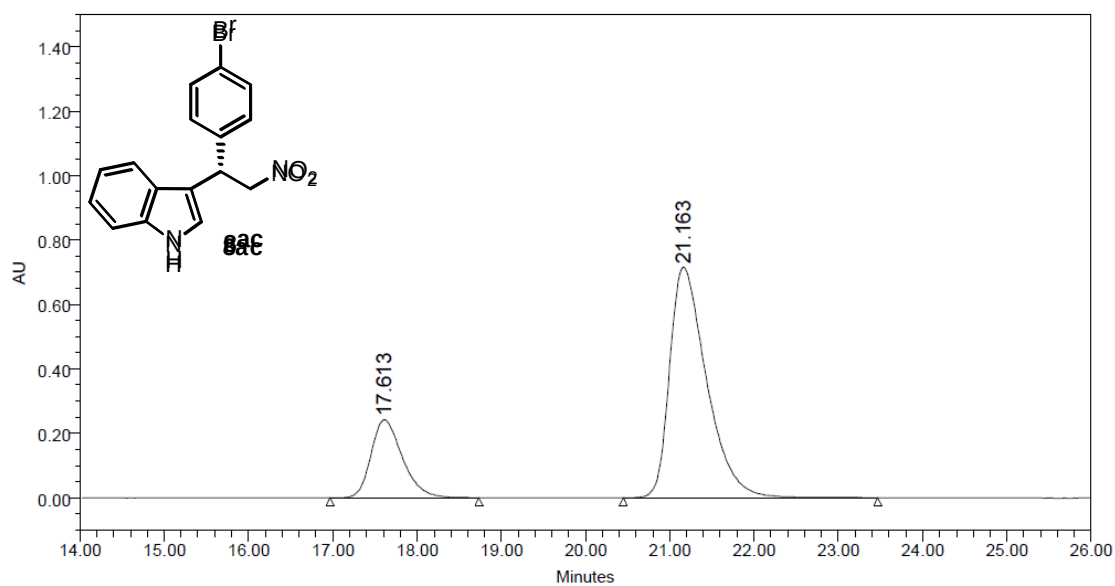
Figure S14. Chiral sample of (S)-3-(1-(4-chlorophenyl)-2-nitroethyl)-1H-indole (8ab) using urea 1b only.



Processed Channel: PDA 236.7 nm

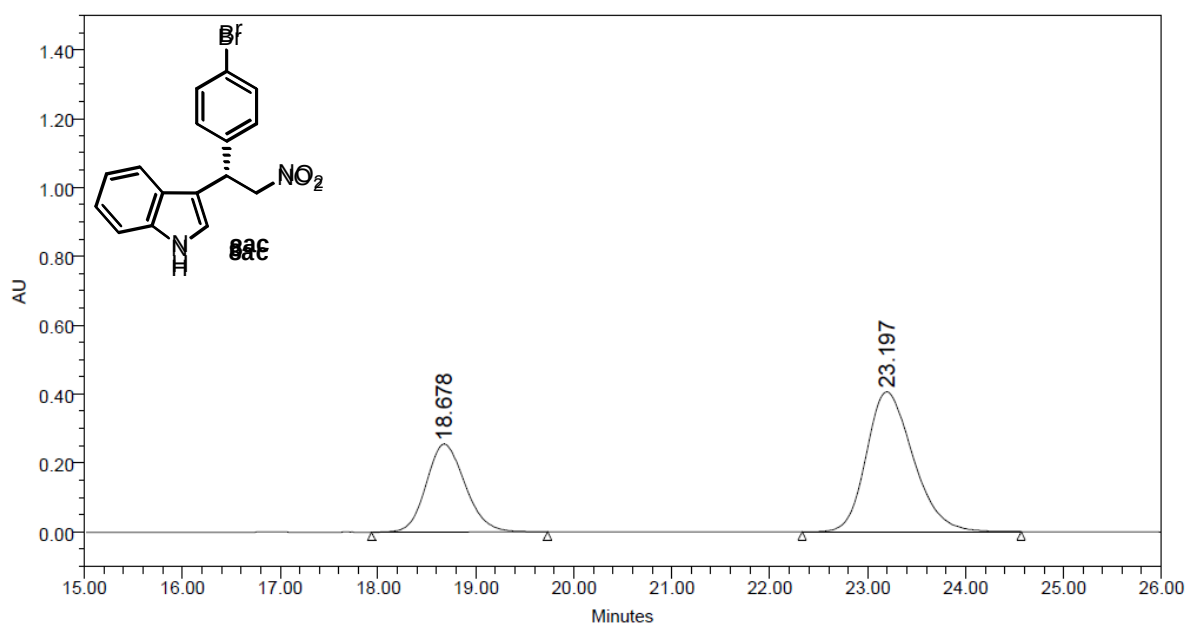
	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 236.7 nm	18.299	19691082	50.00	595626
2	PDA 236.7 nm	23.394	19689266	50.00	450404

Figure S15. Racemic mixture of 8ac. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).



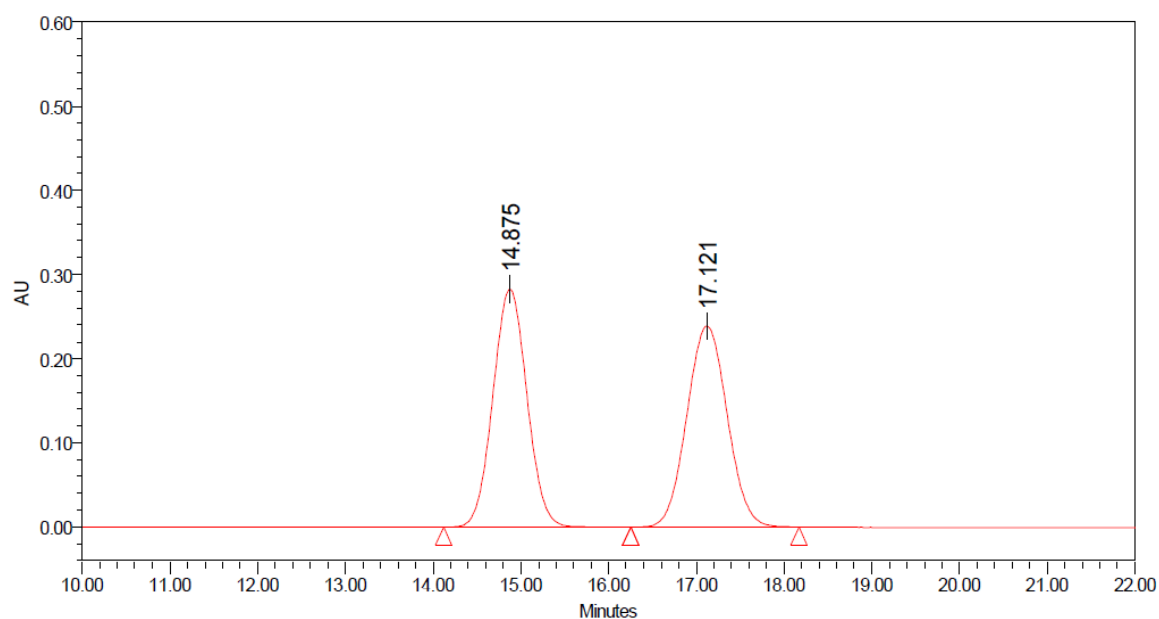
	RT	Area	% Area	Height
1	17.613	6269894	22.34	241758
2	21.163	21793879	77.66	715428

Figure S16. Chiral sample of (S)-3-(1-(4-bromophenyl)-2-nitroethyl)-1H-indole (8ac) using urea-HA (1b(±)-9a).



	RT	Area	% Area	Height
1	18.678	7037041	34.24	255022
2	23.197	13513282	65.76	406287

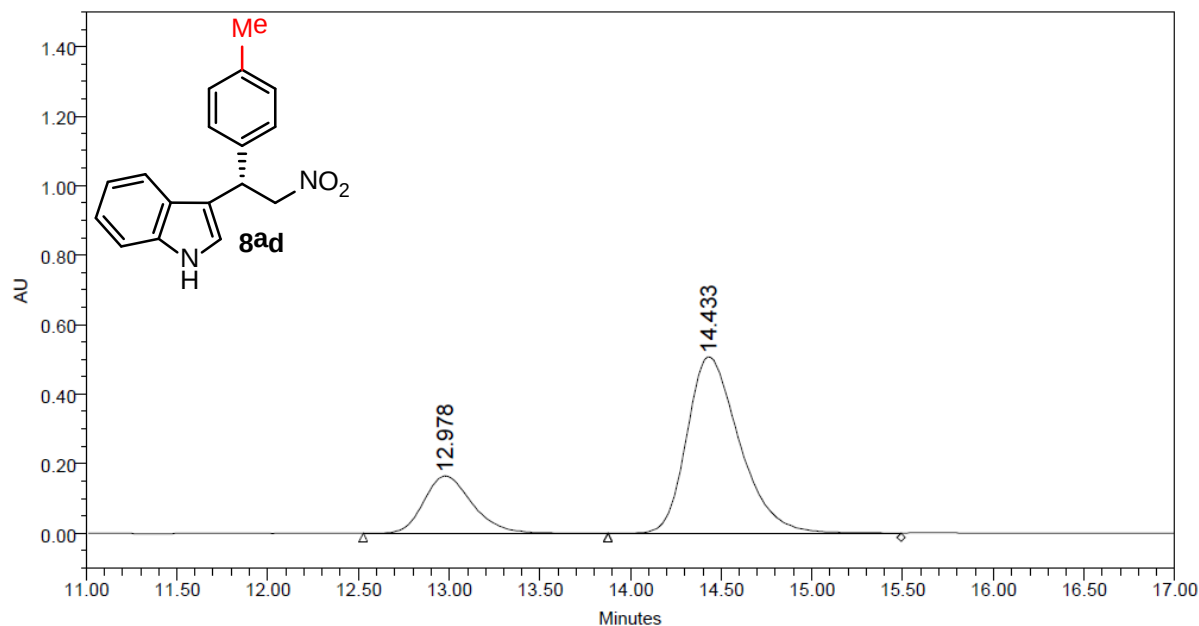
Figure S17. Chiral sample of (S)-3-(1-(4-bromophenyl)-2-nitroethyl)-1H-indole (8ac) using urea 1b only.



Processed Channel: PDA 254.0 nm

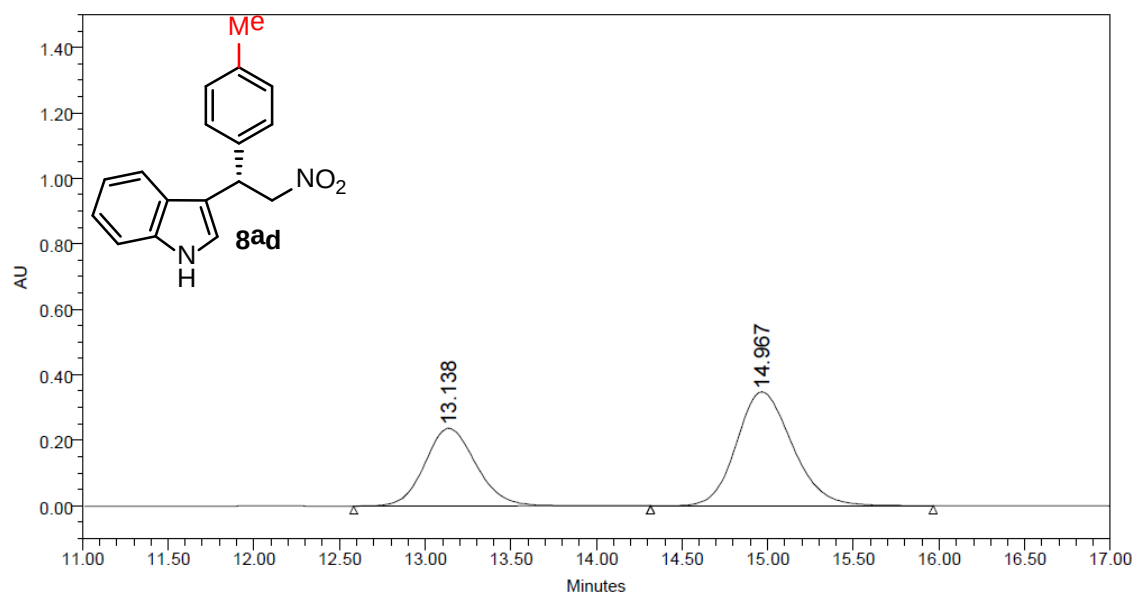
	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	14.875	7658569	50.03	283205
2	PDA 254.0 nm	17.121	7649169	49.97	239101

Figure S18. Racemic mixture of **8ad**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).



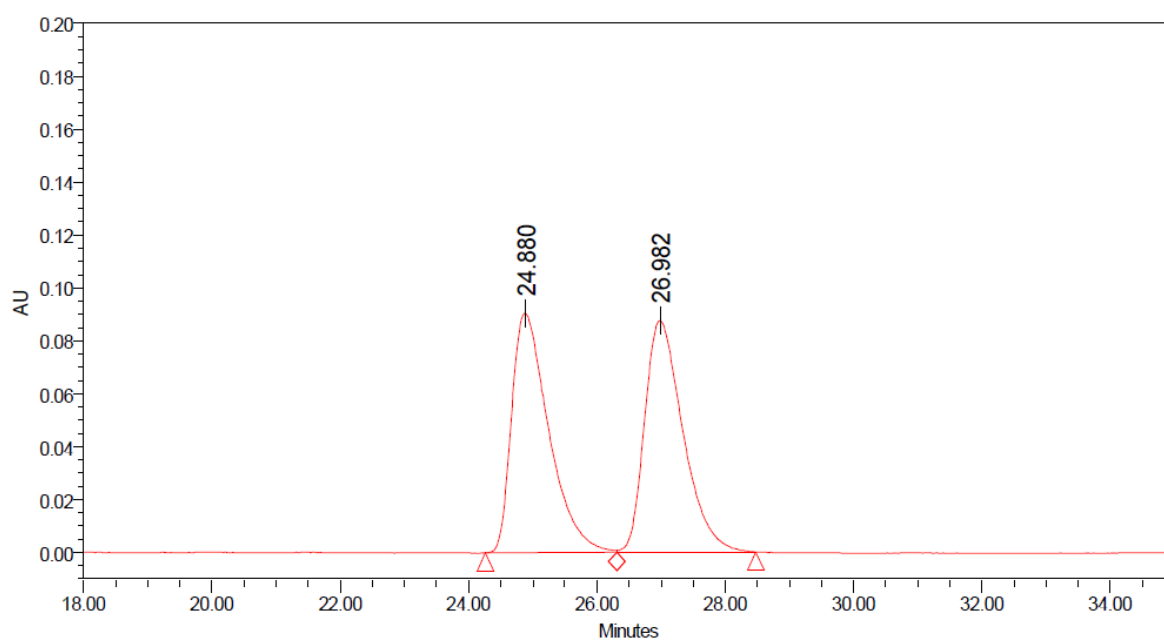
	RT	Area	% Area	Height
1	12.978	3061150	23.00	165026
2	14.433	10245387	77.00	507780

Figure S19. Chiral sample of (*S*)-3-(2-nitro-1-*p*-tolylethyl)-1*H*-indole (**8ad**) using urea-HA (**1b**(±)-**9a**).



	RT	Area	% Area	Height
1	13.138	4925932	38.44	237122
2	14.967	7887706	61.56	347726

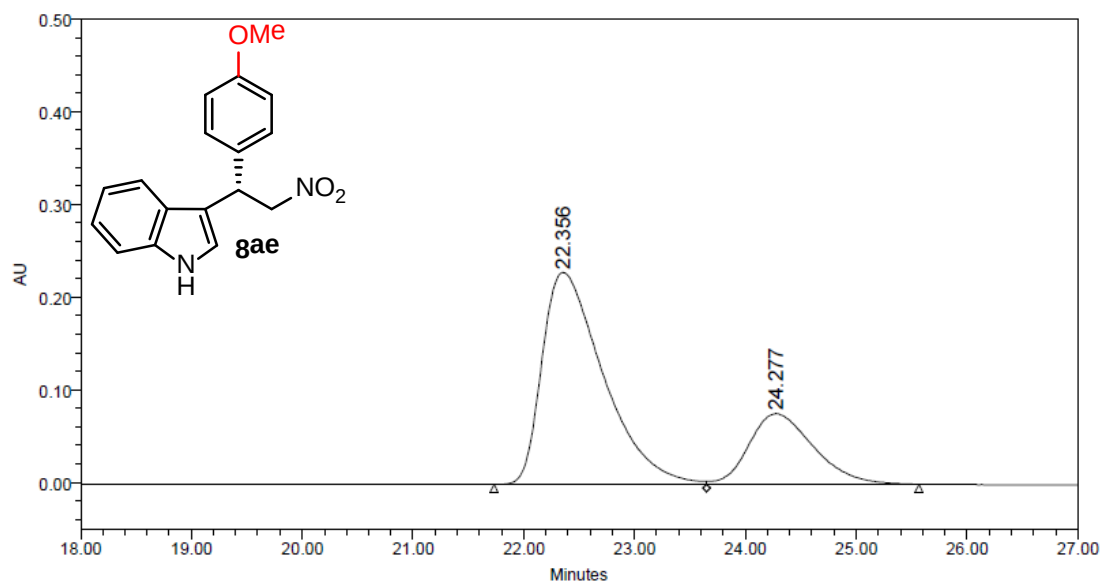
Figure S20. Chiral sample of (S)-3-(2-nitro-1-p-tolyethyl)-1H-indole (8ad) using urea 1b only.



Processed Channel: PDA 254.0 nm

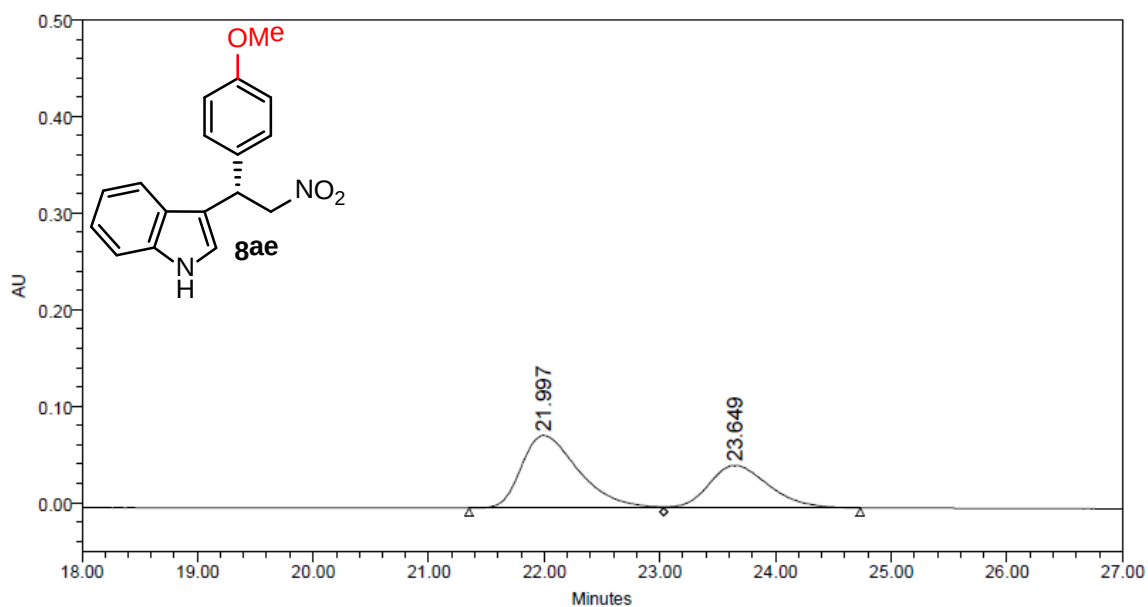
	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	24.880	3648989	50.03	90622
2	PDA 254.0 nm	26.982	3644486	49.97	87594

Figure S21. Racemic mixture of 8ae. Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL/min).



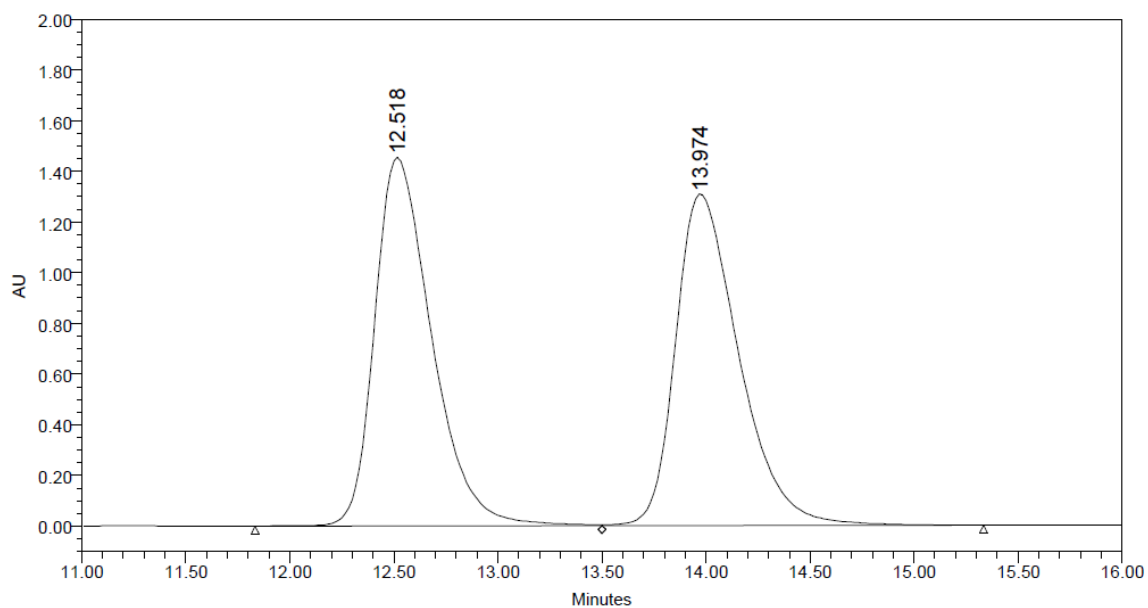
	RT	Area	% Area	Height
1	22.356	8820147	74.08	228768
2	24.277	3085521	25.92	75997

Figure S22. Chiral sample of (S)-3-(1-(4-methoxyphenyl)-2-nitroethyl)-1H-indole (8ae) using urea-HA (1b·(±)-9a).



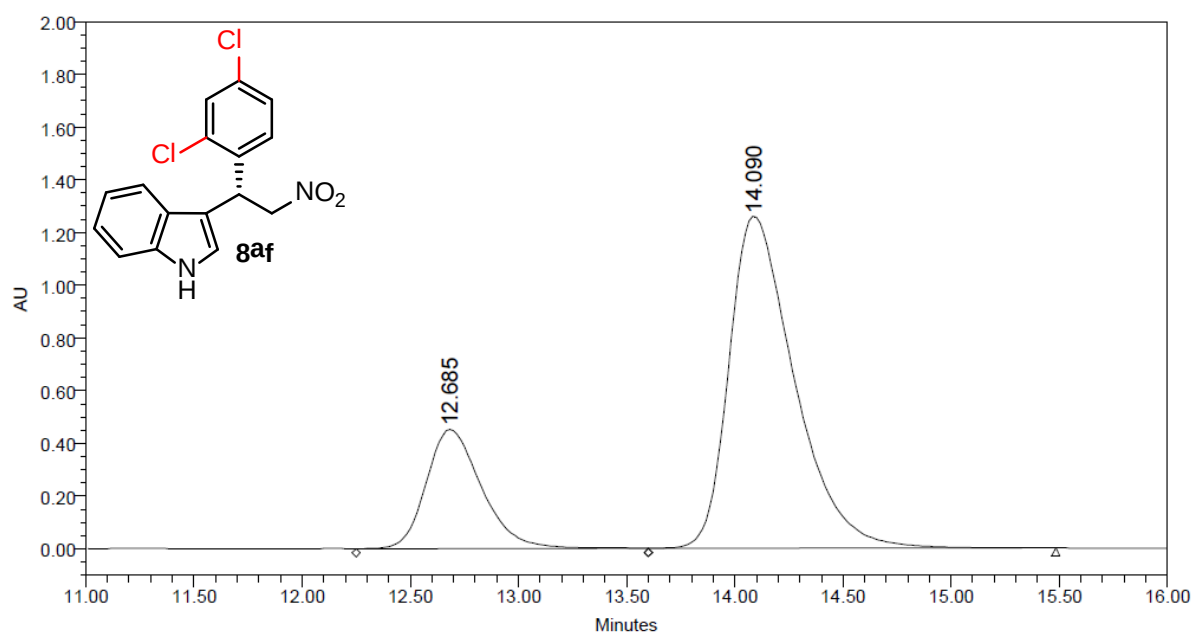
	RT	Area	% Area	Height
1	21.997	2577616	61.92	75065
2	23.649	1584964	38.08	44002

Figure S23. Chiral sample of (S)-3-(1-(4-methoxyphenyl)-2-nitroethyl)-1H-indole (8ae) using urea 1b.



	RT	Area	% Area	Height
1	12.518	27661131	50.00	1455165
2	13.974	27665770	50.00	1310171

Figure S24. Racemic mixture of **8af**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min), λ = 254 nm.



	RT	Area	% Area	Height
1	12.685	8043703	23.28	452597
2	14.090	26503853	76.72	1262108

Figure S25. Chiral sample of (*R*)-3-(1-(2,4-dichlorophenyl)-2-nitroethyl)-1*H*-indole (**8af**) using urea-HA (1b-(±)-9a).

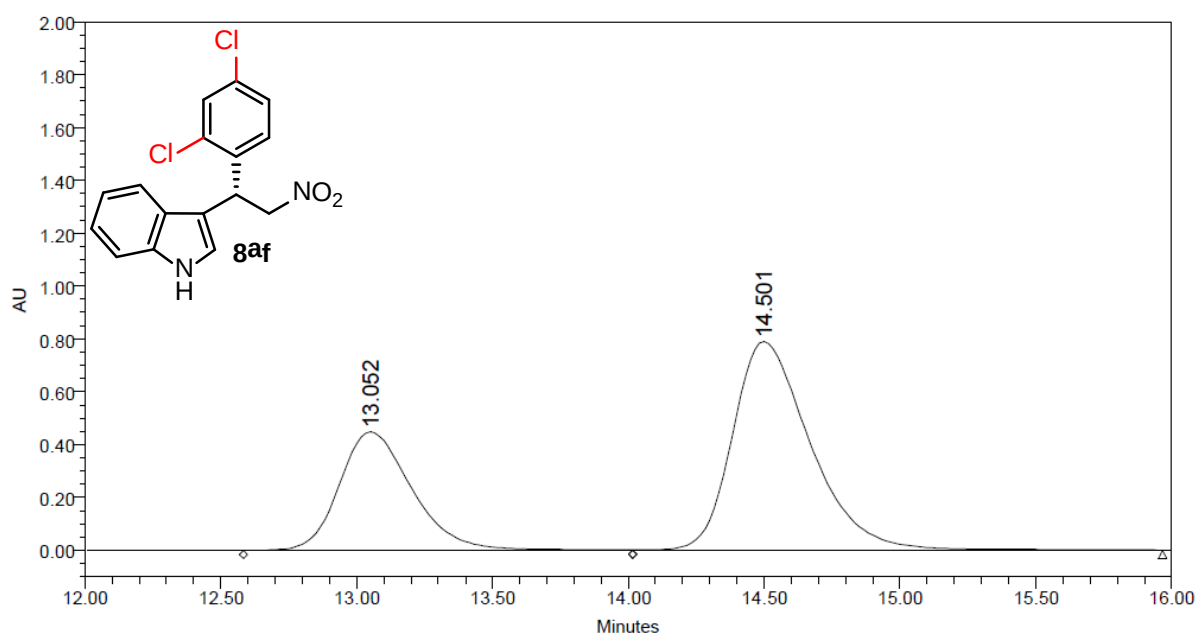


Figure S26. Chiral sample of (*R*)-3-(1-(2,4-dichlorophenyl)-2-nitroethyl)-1*H*-indole (8af) using urea 1b only.

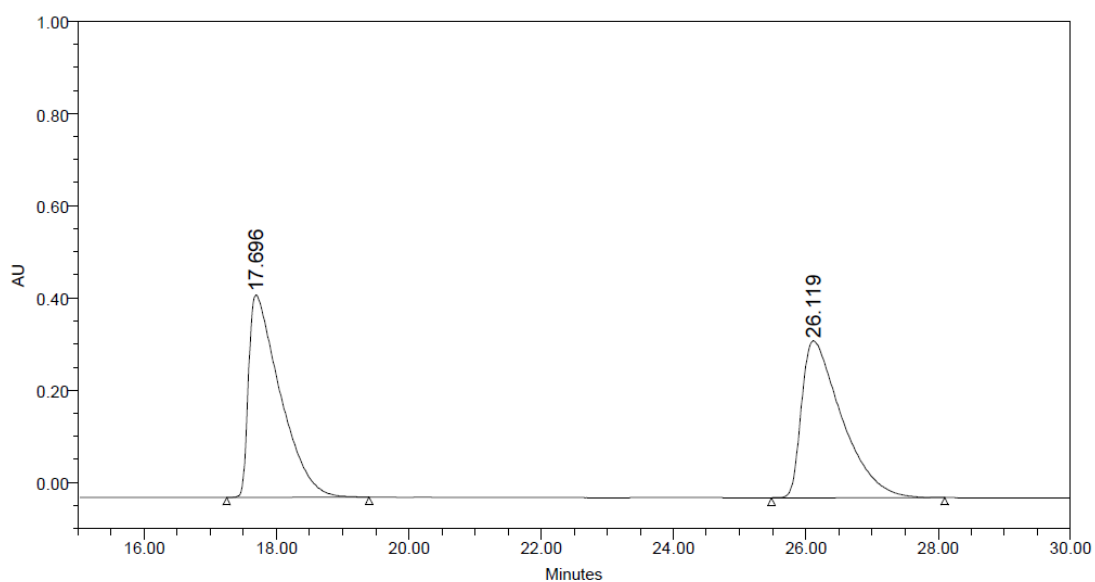
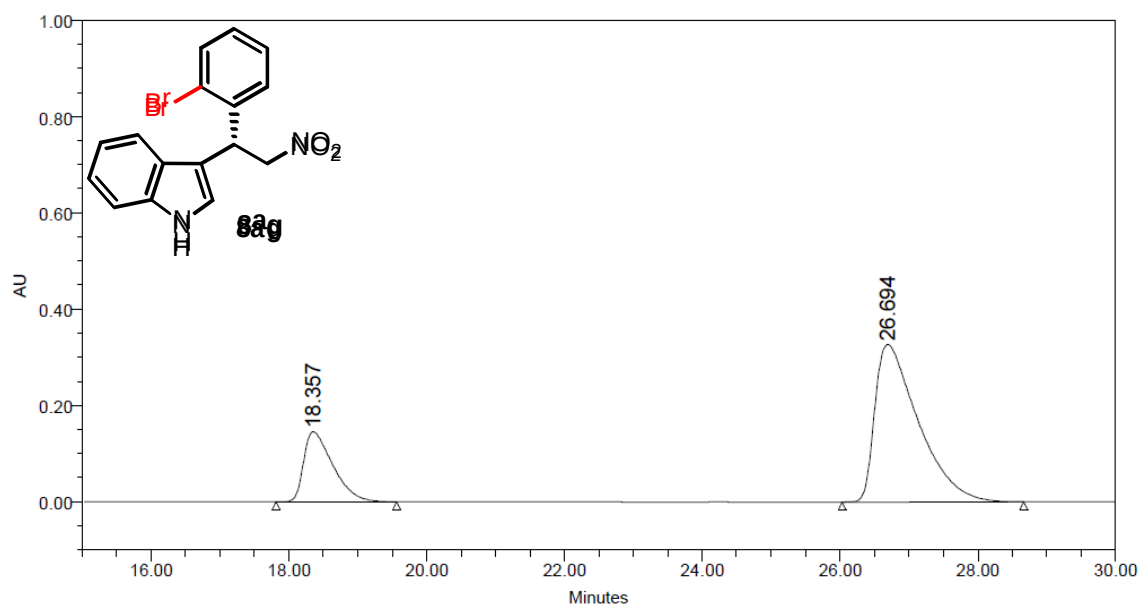
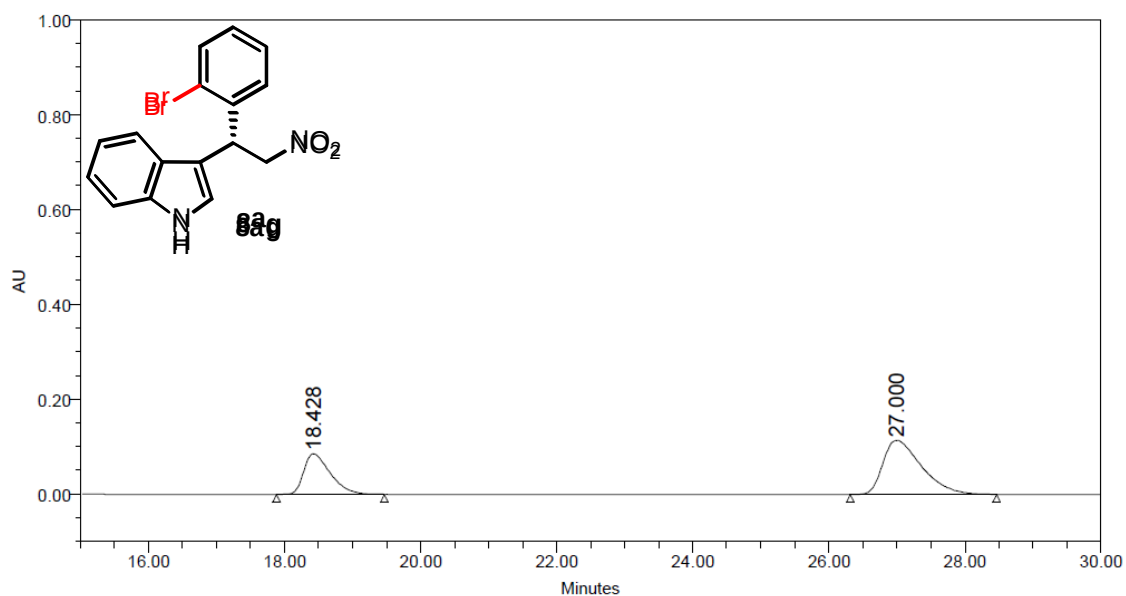


Figure S27. Racemic mixture of 8ag. Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL/min), λ = 254 nm.



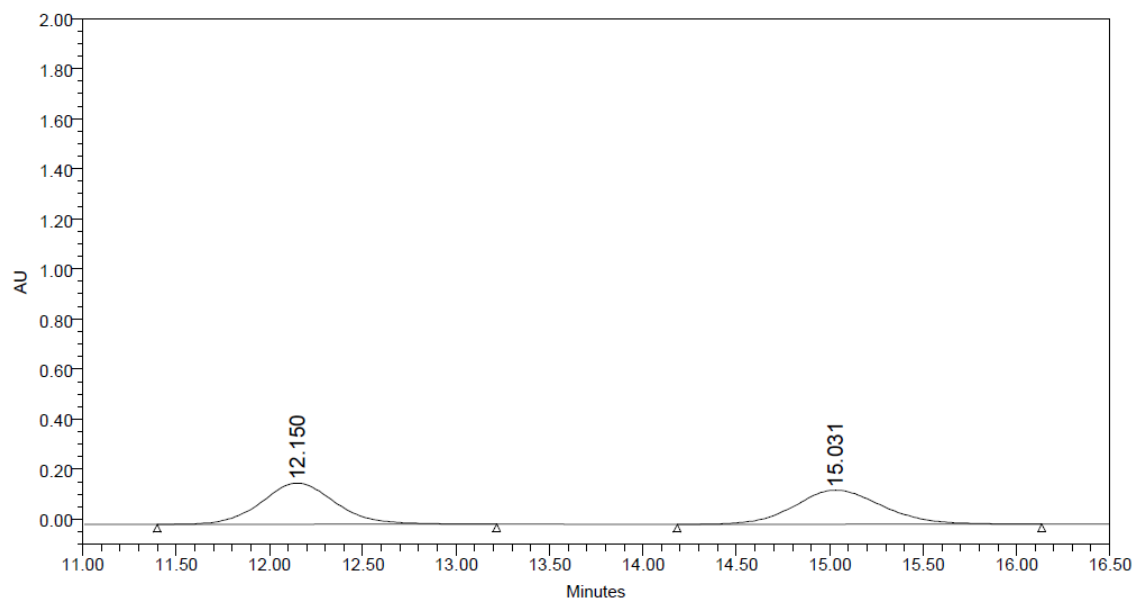
	RT	Area	% Area	Height
1	18.357	4284078	22.97	145860
2	26.694	14367925	77.03	327798

Figure S28. Chiral sample of (R)-3-(1-(2-bromophenyl)-2-nitroethyl)-1H-indole (8ag) using urea-HA (1b(±)-9a).



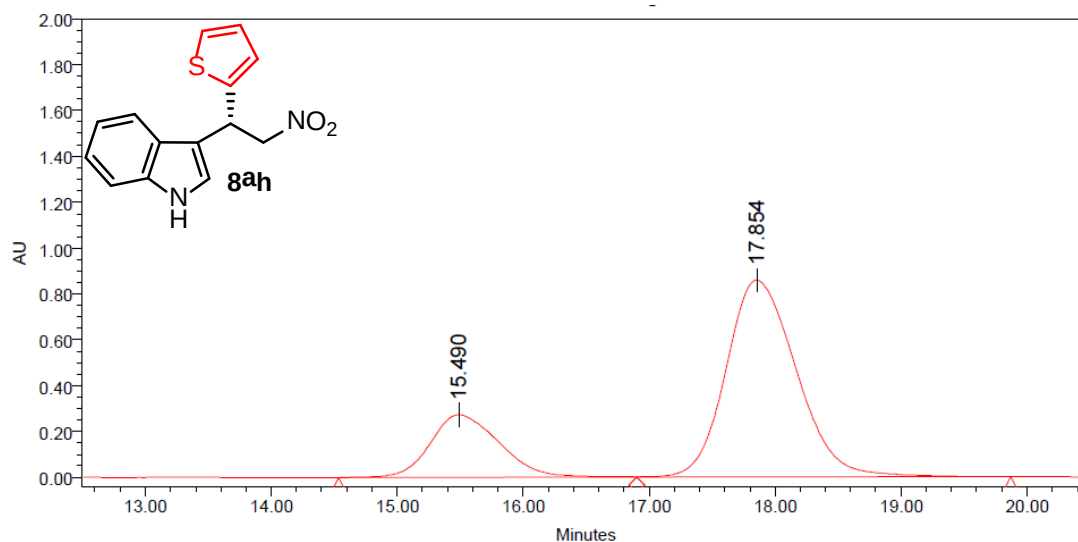
	RT	Area	% Area	Height
1	18.428	2330951	33.84	85747
2	27.000	4556508	66.16	114939

Figure S29. Chiral sample of (R)-3-(1-(2-bromophenyl)-2-nitroethyl)-1H-indole (8ag) using urea 1b only.



	RT	Area	% Area	Height
1	12.150	4528607	50.47	164291
2	15.031	4443523	49.53	135942

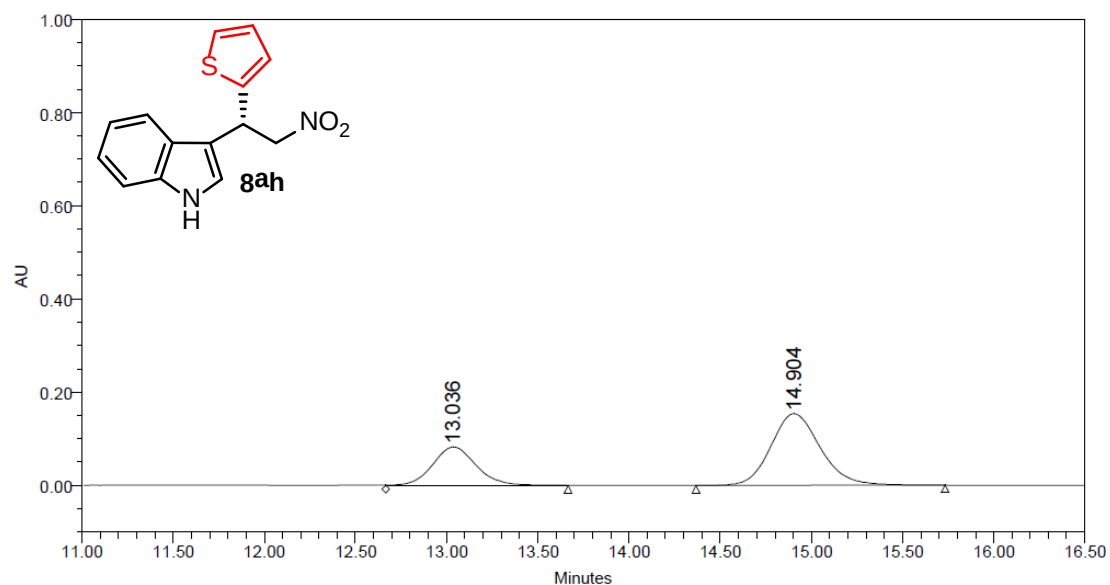
Figure S30. Racemic mixture of **8ah**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min), λ = 254 nm.



Processed Channel: PDA 254.0 nm

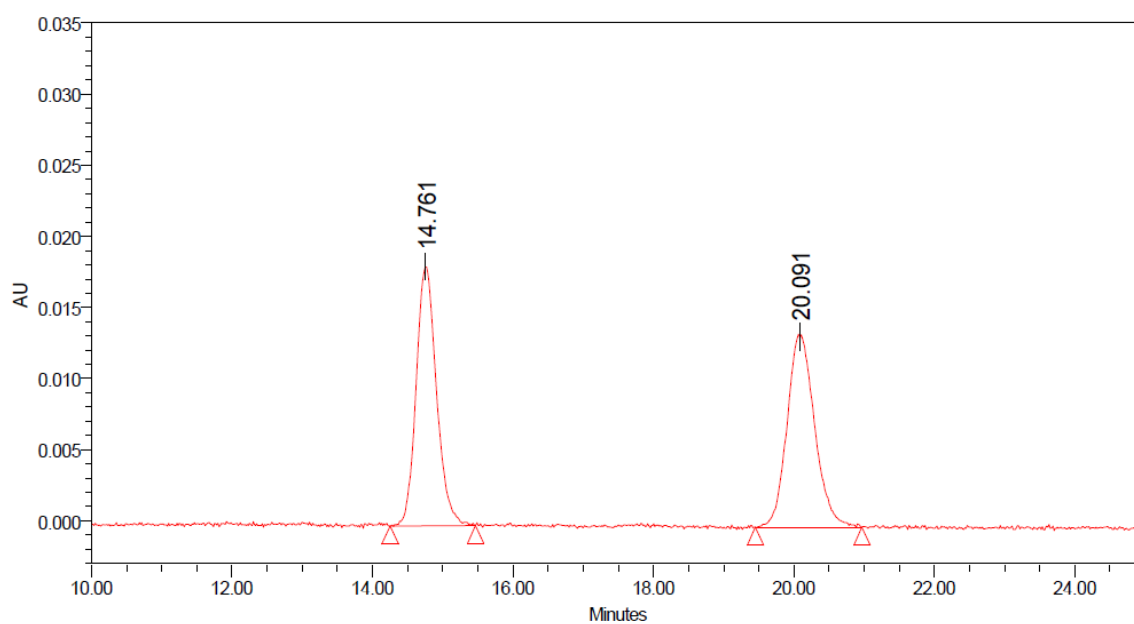
	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	15.490	10366918	23.76	272684
2	PDA 254.0 nm	17.854	33269531	76.24	858519

Figure S31. Chiral sample of (*S*)-3-(2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-indole (**8ah**) using urea-HA (**1b**·($\pm$)-**9a**).



	RT	Area	% Area	Height
1	13.036	1354834	31.80	82250
2	14.904	2905834	68.20	154166

Figure S32. Chiral sample of (S)-3-(2-nitro-1-(thiophen-2-yl)ethyl)-1H-indole (8ah) using urea 1b only.



Processed Channel: PDA 219.9 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 219.9 nm	14.761	368948	50.04	18269
2	PDA 219.9 nm	20.091	368339	49.96	13491

Figure S33. Racemic mixture of 8ai. Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL/min).

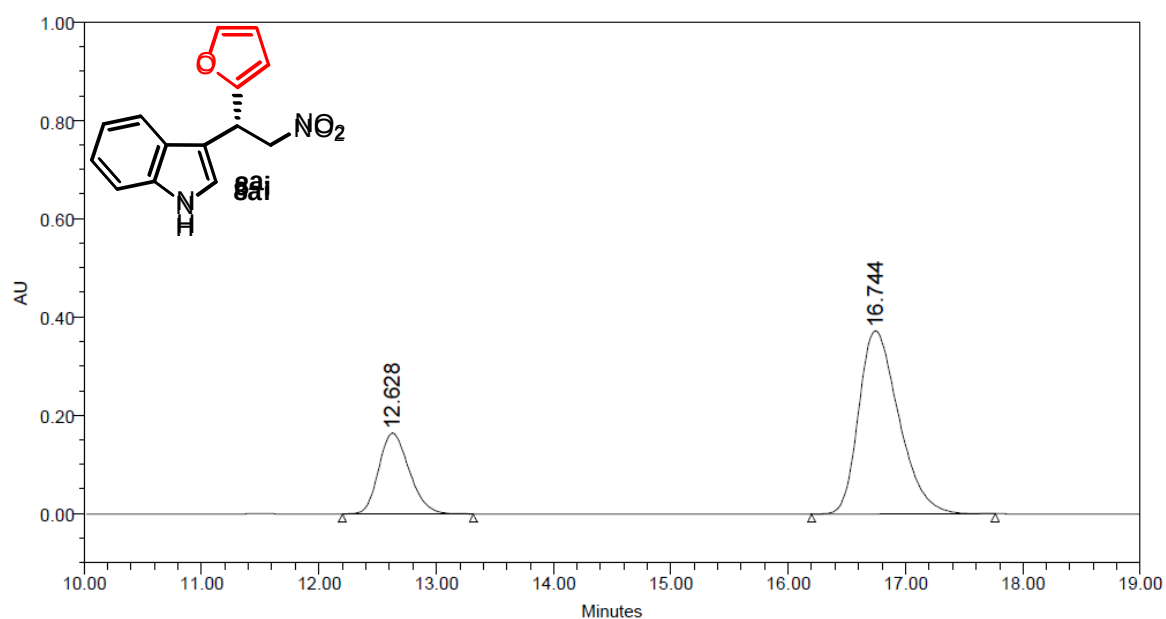


Figure S34. Chiral sample of (S)-3-(1-(furan-2-yl)-2-nitroethyl)-1H-indole (8ai) using urea·HA (1b·(±)-9a).

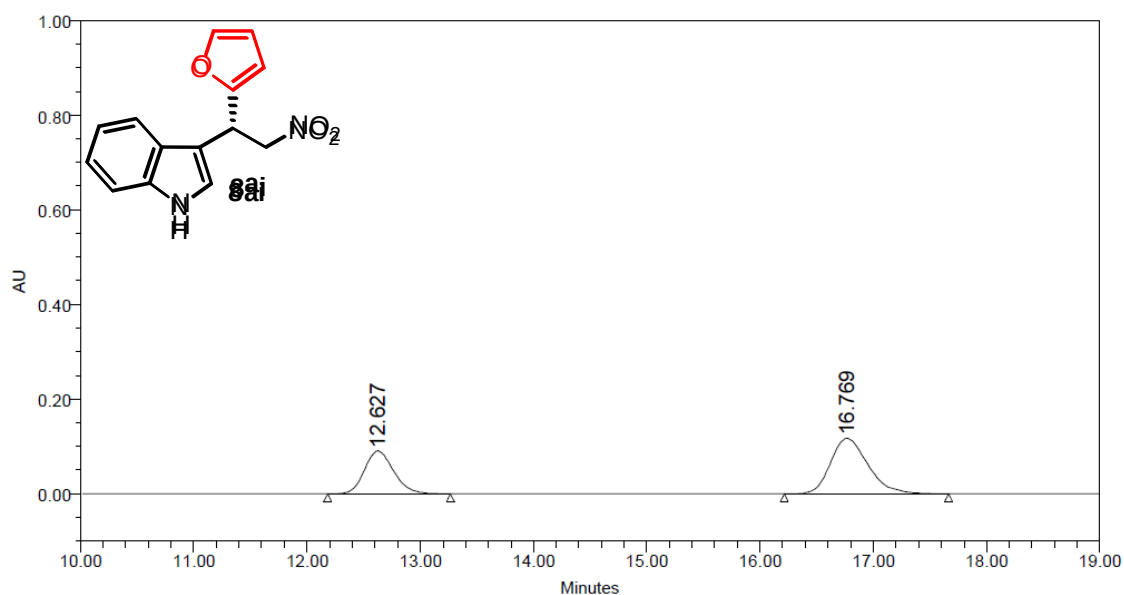
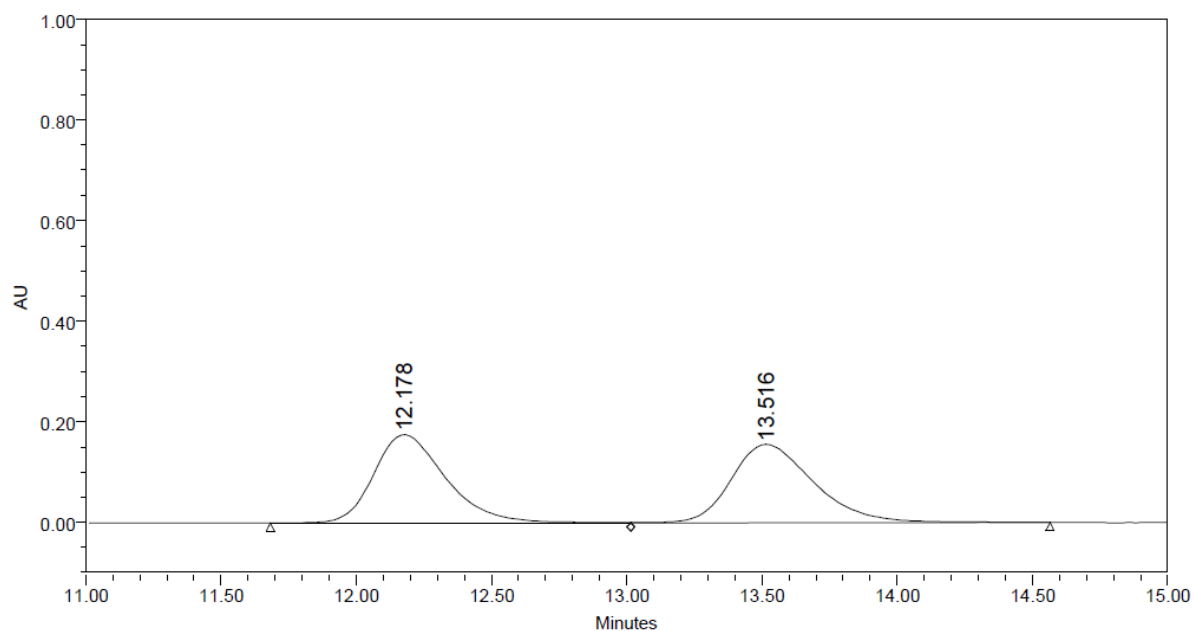
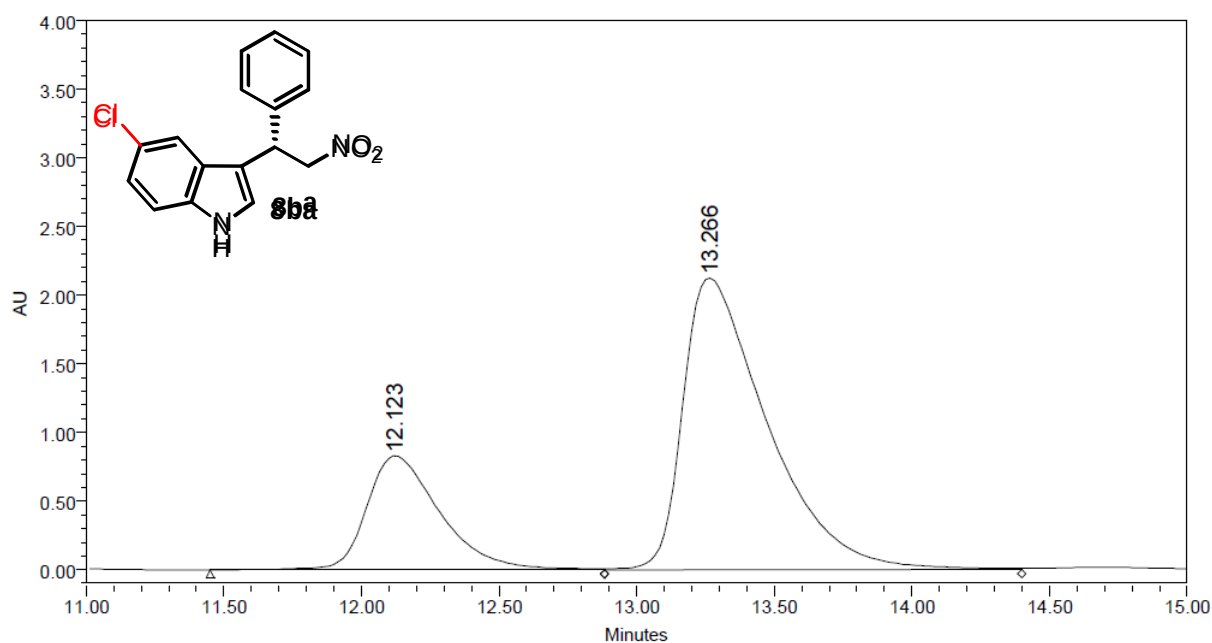


Figure S35. Chiral sample of (S)-3-(1-(furan-2-yl)-2-nitroethyl)-1H-indole (8ai) using urea 1b only.



	RT	Area	% Area	Height
1	12.178	3237841	49.49	175366
2	13.516	3304279	50.51	155674

Figure S36. Racemic mixture of **8ba** Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min), λ = 254 nm.



	RT	Area	% Area	Height
1	12.123	15260483	25.20	828761
2	13.266	45307505	74.80	2125081

Figure S37. Chiral sample of (S)-5-chloro-3-(2-nitro-1-phenylethyl)-1H-indole (**8ba**) using urea-HA (**1b**($\pm$)-**9a**).

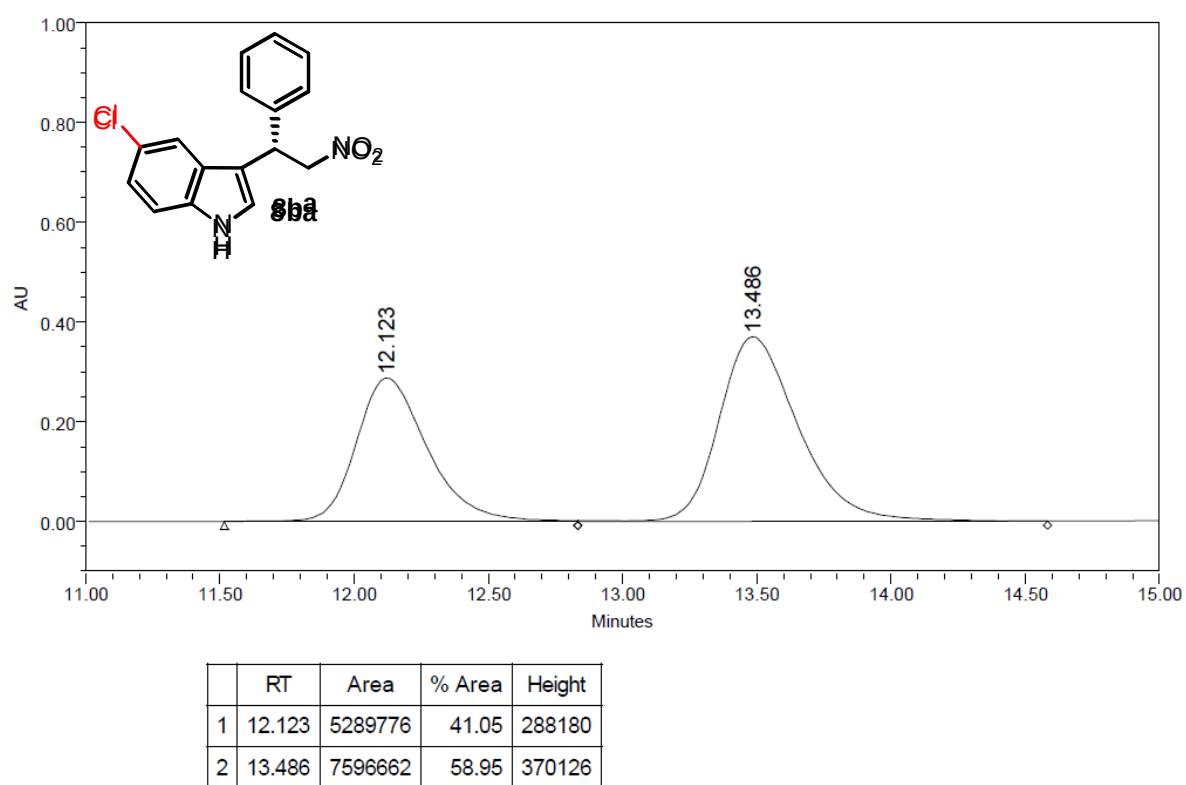


Figure S38. Chiral sample of (S)-5-chloro-3-(2-nitro-1-phenylethyl)-1H-indole (8ba) using urea 1b only.

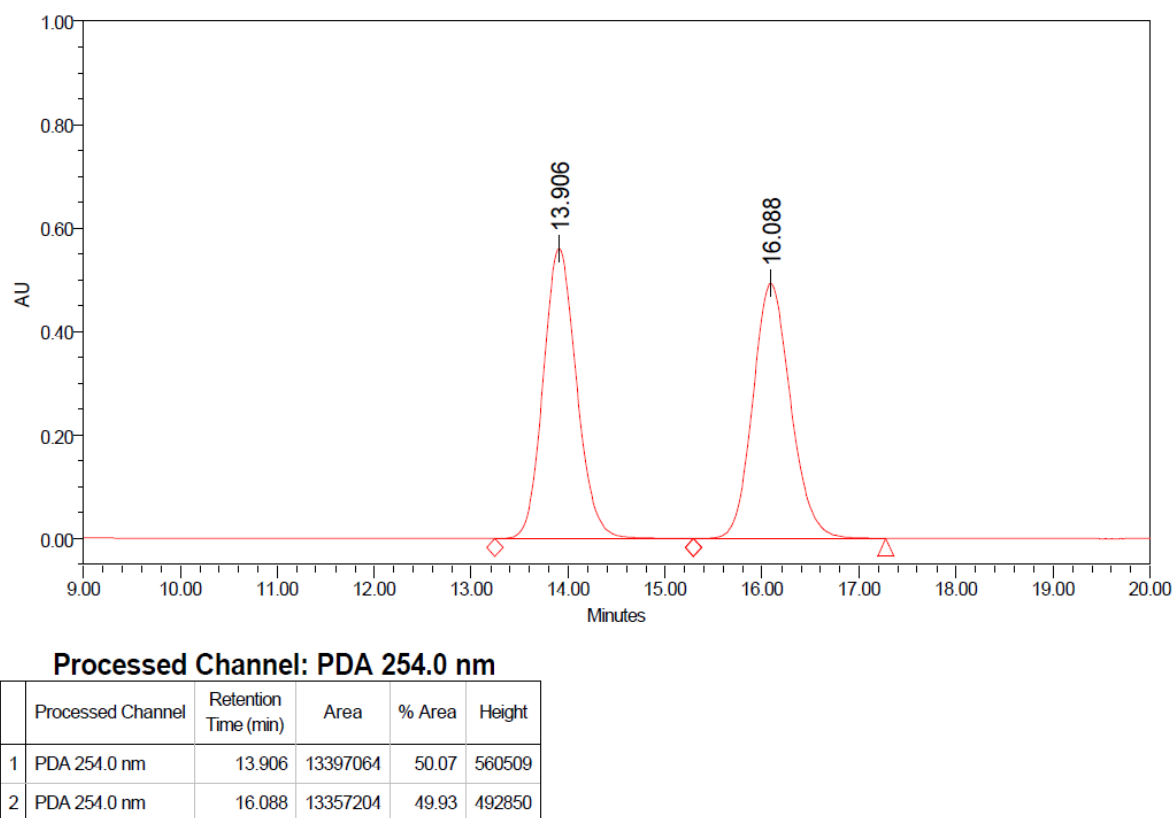


Figure S39. Racemic mixture of 8ca. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).

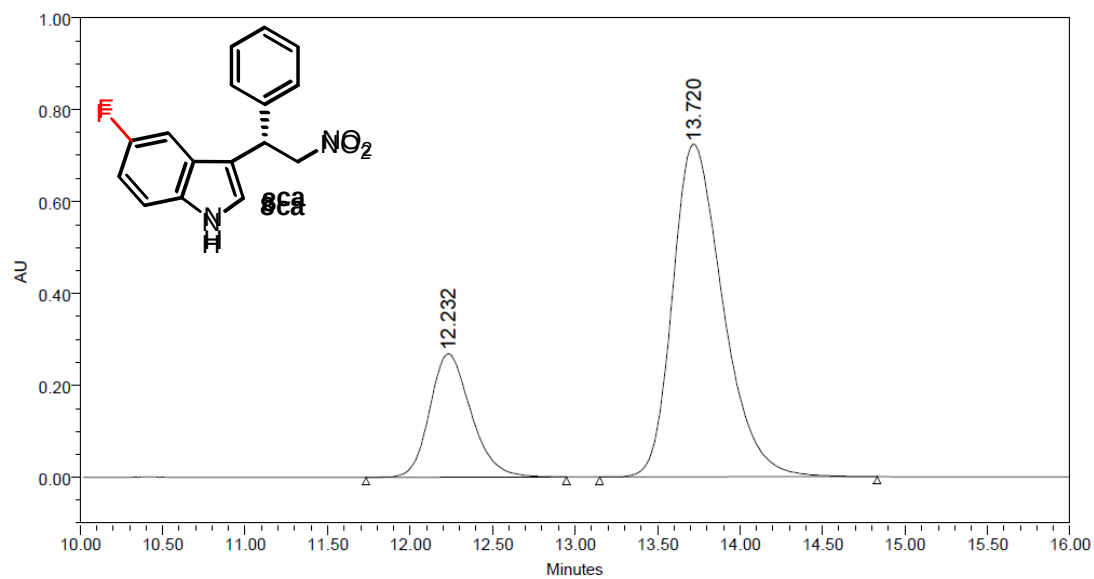


Figure S40. Chiral sample of (S)-5-fluoro-3-(2-nitro-1-phenylethyl)-1H-indole (8ca) using urea-HA (1b(±)-9a).

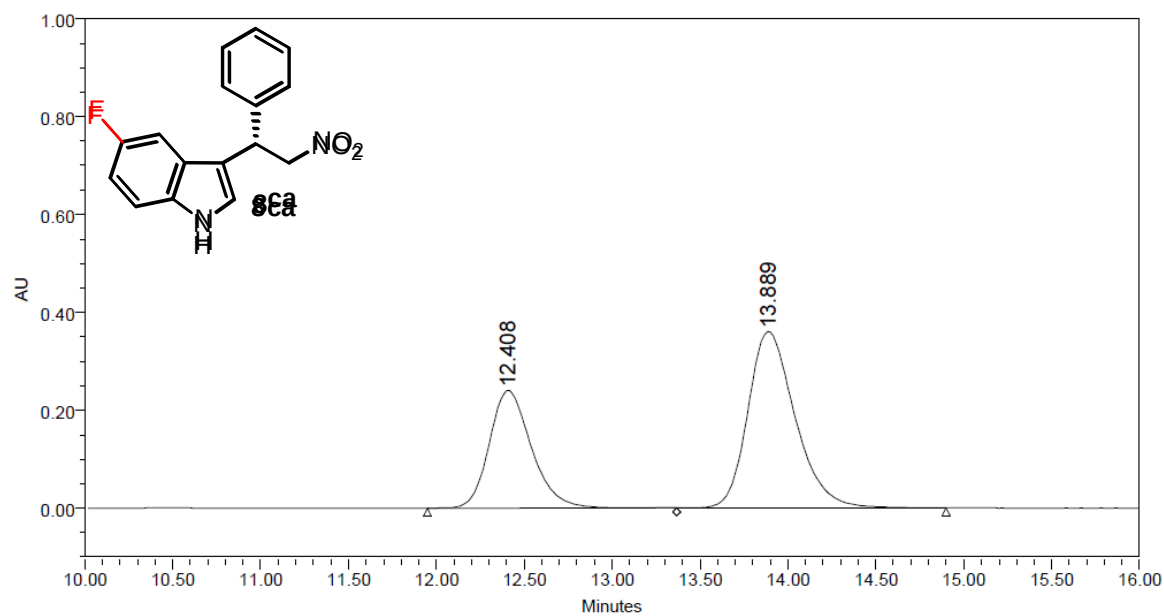
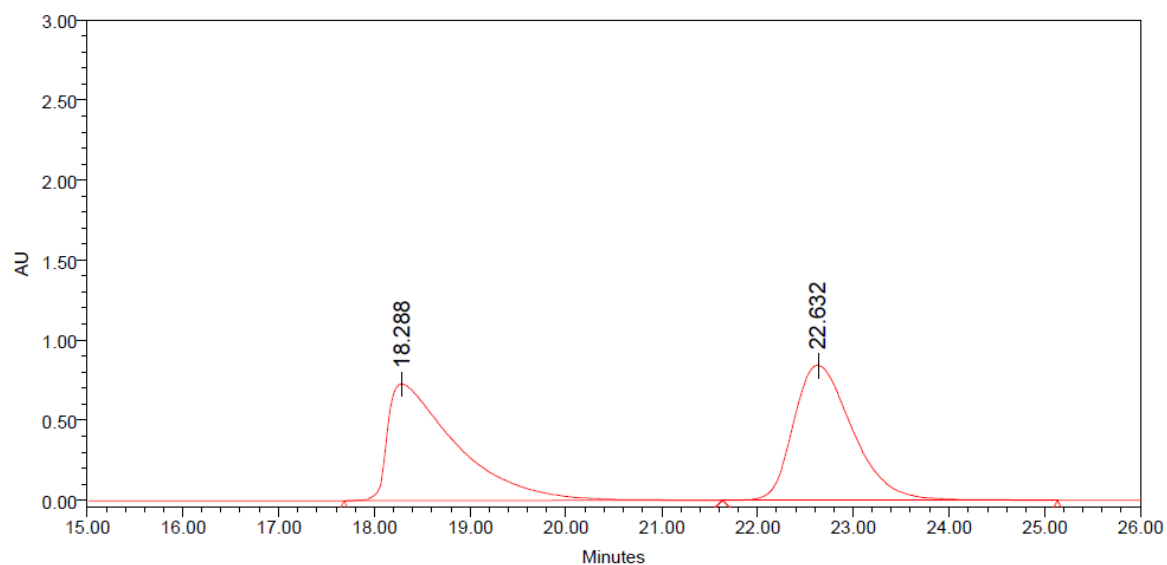


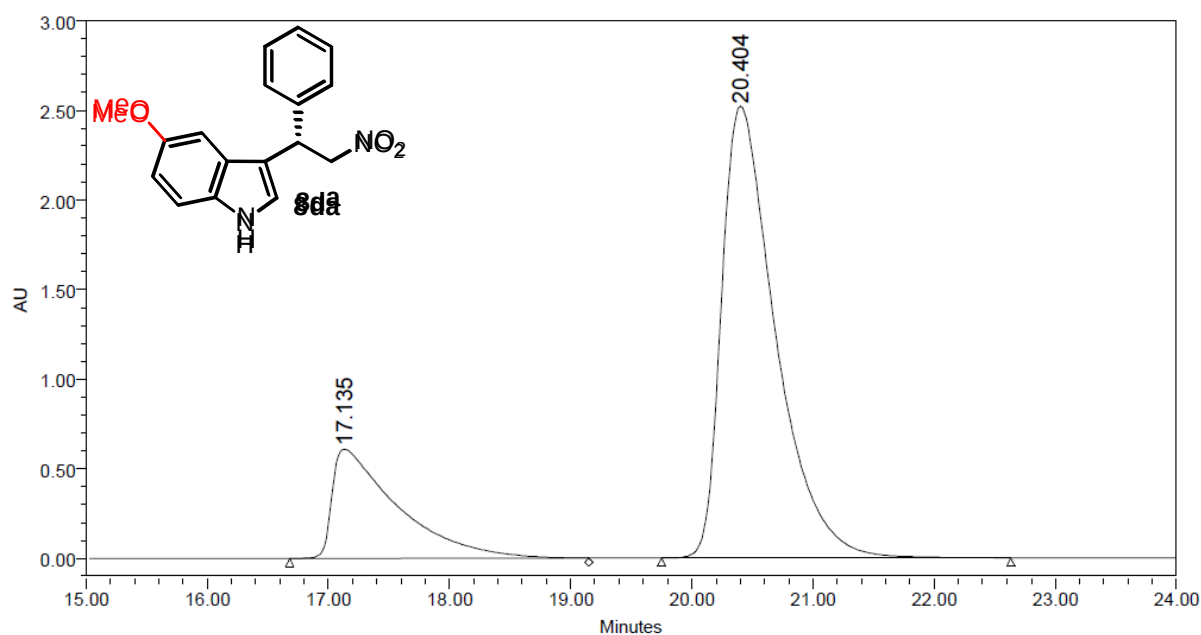
Figure S41. Chiral sample of (S)-5-fluoro-3-(2-nitro-1-phenylethyl)-1H-indole (8ca) using urea 1b only.



Processed Channel: PDA 254.0 nm

	Processed Channel	Retention Time (min)	Area	% Area	Height
1	PDA 254.0 nm	18.288	36075245	50.00	728232
2	PDA 254.0 nm	22.632	36080531	50.00	843167

Figure S42. Racemic mixture of **8da**. Daicel Chiralpak IA column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min).



	RT	Area	% Area	Height
1	17.135	22846810	22.65	610172
2	20.404	78007944	77.35	2522436

Figure S43. Chiral sample of (*S*)-5-methoxy-3-(2-nitro-1-phenylethyl)-1*H*-indole (**8da**) using urea-HA (**1b**-(±)-**9a**).

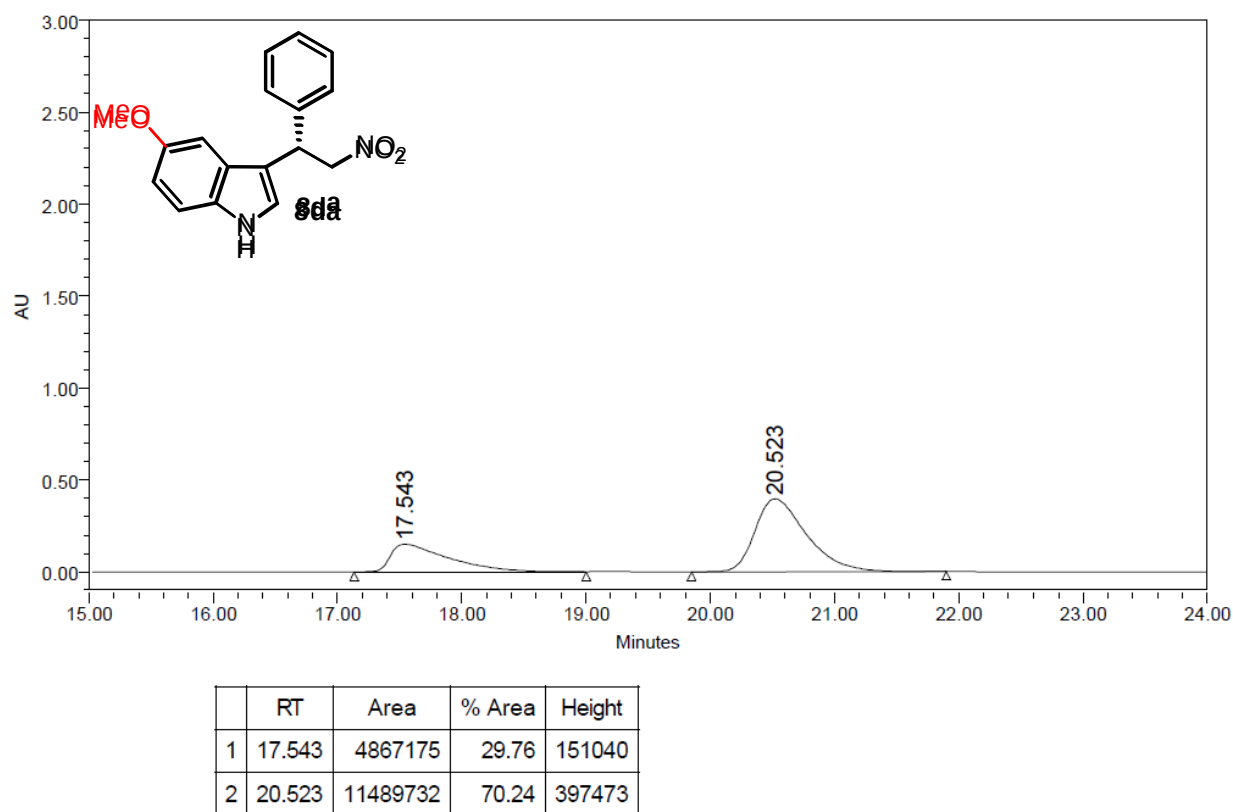


Figure S44. Chiral sample of (S)-5-methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (8da) using urea 1b only.

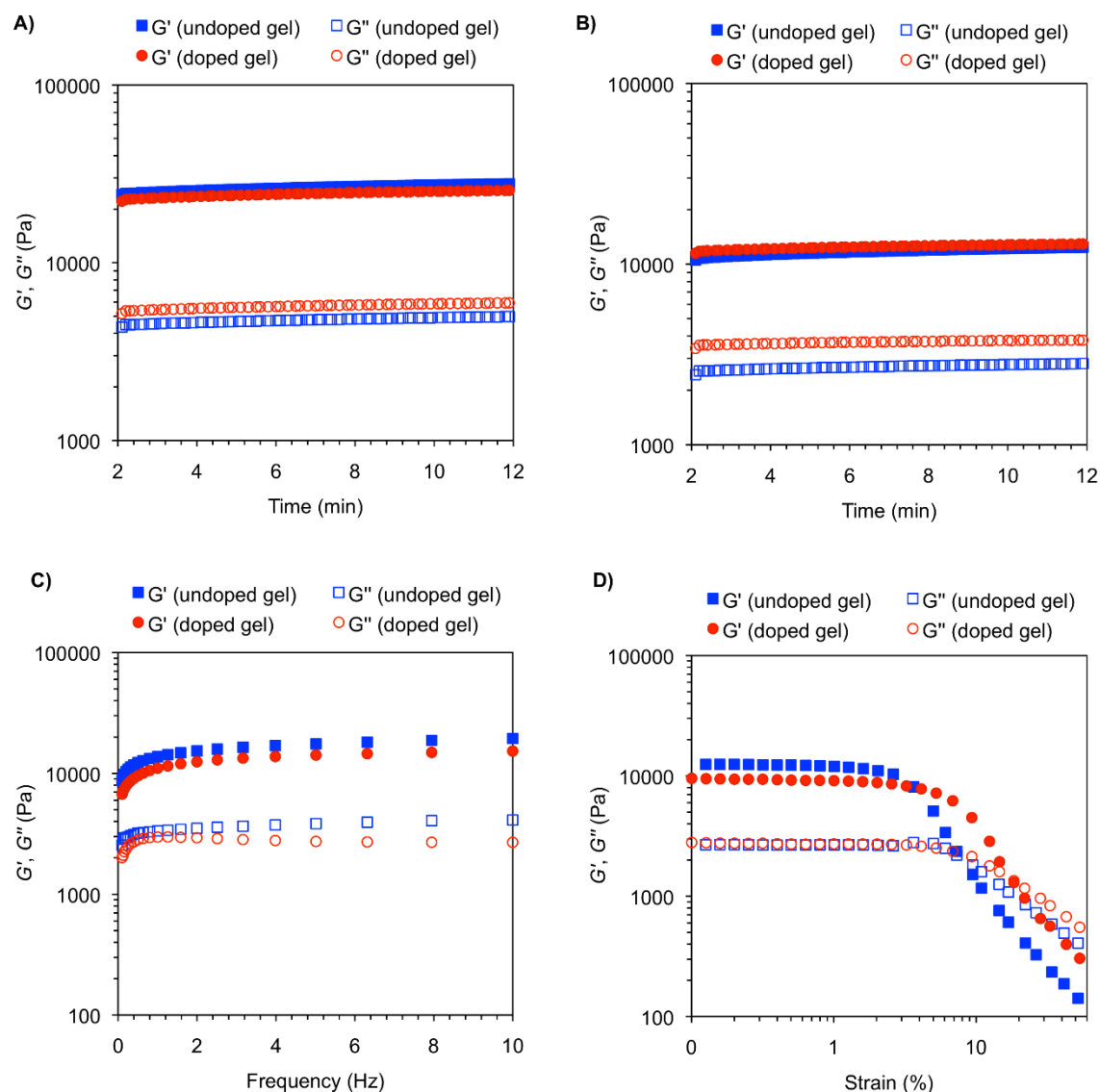


Figure S45. A) DTS measurements of undoped gel made of **1b** in CHCl_3 ($c = 14$ g/L), and doped gel made of **1b** ($c = 14$ g/L) and mandelic acid (molar ratio **1b**:acid = 0.1) in CHCl_3 . B-D) Rheological measurements for the undoped gel made of **1b** in toluene ($c = 12$ g/L), and doped gel made of **1b** ($c = 12$ g/L) and mandelic acid (molar ratio **1b**:acid = 0.1) in toluene: B) DTS, C) DFS, D) DSS.

Table S1. Effects of the addition of different additives on the aspect, gelation time and T_{gel} with respect to the pristine gels prepared in $CHCl_3$ and in toluene.^a

$CHCl_3$					
Additive	Molar Ratio 1b:Additive	Aspect ^b	Gelation Time	T_{gel} (± 2 °C) (After One Night)	Amount of Liquid Expelled
-	-	Colorless, translucent gel ^b	6 min	57	-
AA	0.1	Colorless, translucent gel ^b	8 min	61	-
AA	0.3	Colorless, translucent gel ^b	13 min	42	-
AA	0.9	Colorless, translucent gel ^b	8 min	48	-
PAA	0.1	Colorless translucent partial gel	25 min	50	≈ 100 μ L
PAA	0.3	Colorless translucent partial gel	>overnight	46	≈ 300 μ L
PAA	0.9	Colorless translucent partial gel	30 min	50	≈ 100 μ L
BA	0.3	Colorless translucent partial gel	>7 h	47	≈ 300 μ L
BA	0.6	Colorless translucent partial gel	>7 h	45	≈ 400 μ L
BA	0.9	Colorless translucent partial gel	>7 h	45	≈ 500 μ L
LA (racemic)	0.1	Colorless translucent partial gel	>overnight	41	≈ 100 μ L
LA (racemic)	0.3	Colorless translucent partial gel	>overnight	31	≈ 500 μ L
LA (racemic)	0.9	Stable colorless translucent weak gel	<overnight	31	-
MA (racemic)	0.1	Colorless translucent partial gel	12 min	42	nd
MA (racemic)	0.3	Colorless translucent partial gel	>overnight	40	nd
MA (racemic)	0.9	Colorless translucent partial gel	>overnight	nd	nd
MAE (racemic)	0.1	Colorless translucent partial gel	>overnight	39	≈ 100 μ L
MAE (racemic)	0.3	Colorless translucent partial gel	>overnight	39	≈ 300 μ L
MAE (racemic)	0.9	Colorless, translucent gel ^b	<overnight	44	< 50 μ L
Toluene					
Additive	Molar Ratio 1b:Additive	Aspect ^b	Gelation Time	T_{gel} (± 2 °C) (After One Night)	Amount of Liquid Expelled
-	-	Stable colorless, transparent gel	>1 h 15 min 50 min	35	-
AA	0.1	Colorless, transparent gel ^b	<overnight	34	-
AA	0.3	Colorless, transparent gel ^b	<3 h 15 min	34	-
AA	0.9	Stable colorless transparent gel	2 h	34	-
PAA	0.1	Stable colorless transparent gel	<overnight	33	-
PAA	0.3	Stable colorless transparent weak gel	<overnight	nd	-
PAA	0.9	Colorless, transparent gel ^b	<overnight	33	< 50 μ L
LA (racemic)	0.1	Stable colorless transparent gel	<overnight	29	-
LA (racemic)	0.3	Colorless transparent partial gel	>overnight	nd	≈ 700 μ L
LA (racemic)	0.9	Colorless transparent partial gel	>overnight	nd	≈ 500 μ L
MA (racemic)	0.1	Colorless, transparent gel ^b	22 min	36	< 50 μ L
MA (racemic)	0.3	Stable colorless transparent gel	>overnight	33-36	-
MA (racemic)	0.9	Stable colorless transparent gel	2 h 20 min	35	-
MAE (racemic)	0.1	Colorless transparent partial gel	>overnight	nd	≈ 600 μ L
MAE (racemic)	0.3	Colorless transparent partial gel	>overnight	nd	≈ 500 μ L
MAE (racemic)	0.9	Stable colorless transparent gel	<overnight	31	-

^a Abbreviations: AA = acetic acid; PAA = phenylacetic acid; BA = benzoic acid; LA = lactic acid; MA = mandelic acid; MAE = mandelic acid methyl ester; nd = not determined. ^b A small drop of liquid was observed, albeit it could not be quantified.