Supplementary information

Investigation of the chiral recognition role of cyclodextrin hydroxyl moieties via high performance liquid chromatography

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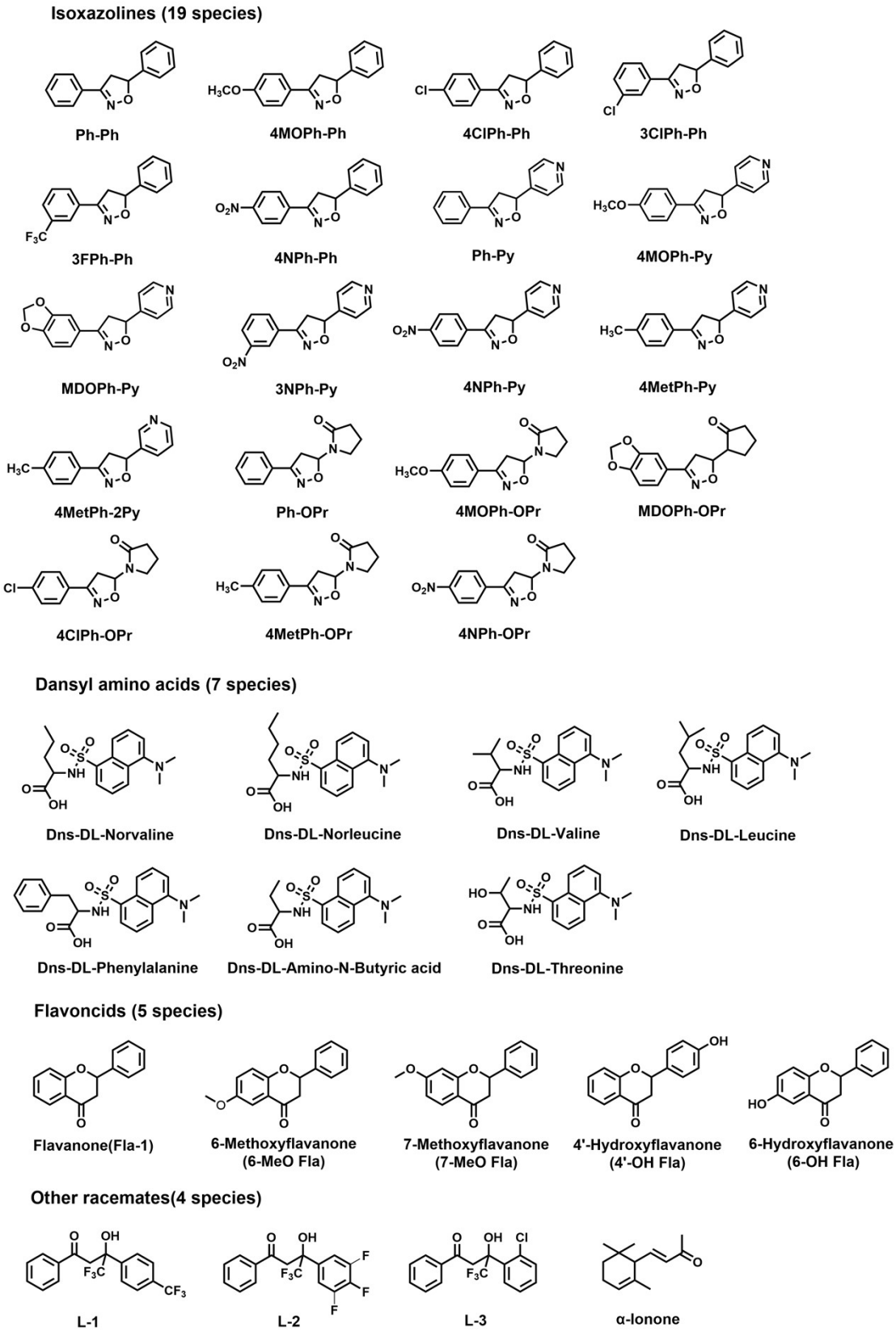


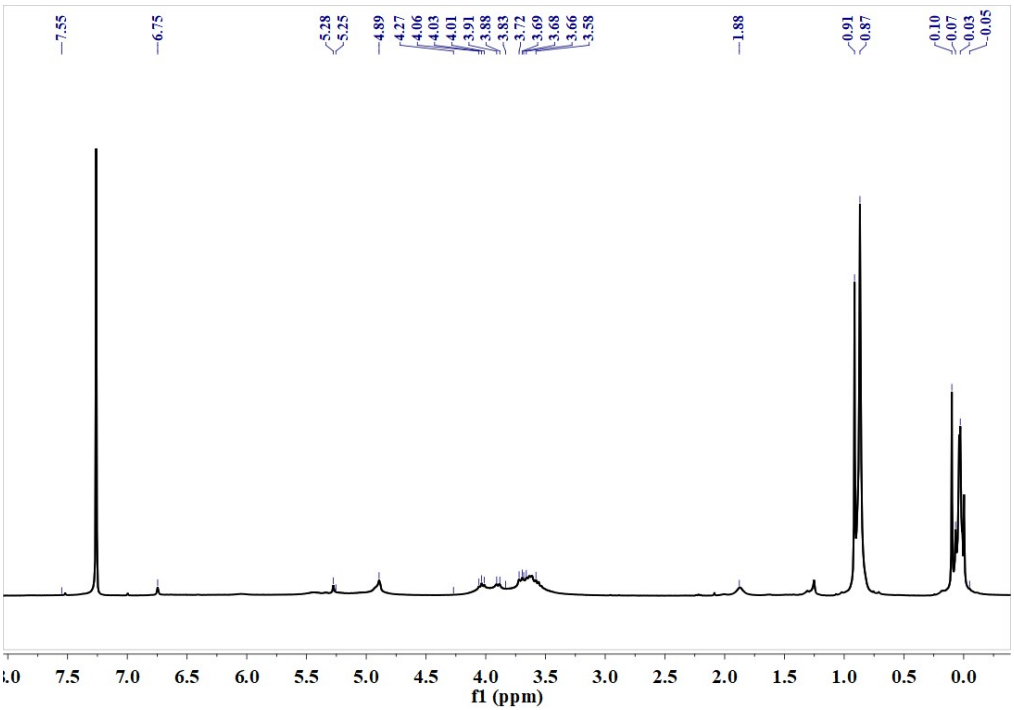
Fig. S1 Structures of analytes.

Synthesis of selectively substituted allylimidazole CD

Mono-6^{A}-deoxy-(p-tolylsulfonyl)-β-CD (TsO-CD), Mono-6^{A}-deoxy-6-(1-allylimidazolium)-β-CD chloride and thiol functionalized silica (SiO_2-SH) were synthesized according to previously approaches.[1-3]

Synthesis of hexakis (6-O-tert-butyldimethylsilyl)-deoxy-AICD (6-TBDMAICD)

Dried 1-allylimidazole-β-CD (3.90 g, 3 mmol) was dissolved in anhydrous pyridine (25 mL) and cooled to 0 ℃. A solution of TBDMSCl (5.43 g, 36 mmol) dissolved in pyridine (20 mL) was added dropwise. After 3 h, the reaction was raised to room temperature and continued to react for 18 h. The solvent was removed by vacuum distillation and washed with DCM (120 mL). The organic layer was washed with saturated salt water and dried with anhydrous Na_2SO_4. The crude product was concentrated under vacuum and purified by column chromatography (dichloromethane: methanol: water: 80:19:1) to give the pure product (4.07 g, yield: 67%).



^{1}H NMR (400 MHz, $CDCl_3$): 0.05-0.10 (36H, Si (CH_3)), 0.81-0.91 (54H, Si(C (CH_3)$_3$), 3.58-4.02 (36H), 5.26 (7H, H-1), 4.27-3.58 (63H), 1.88(3H).

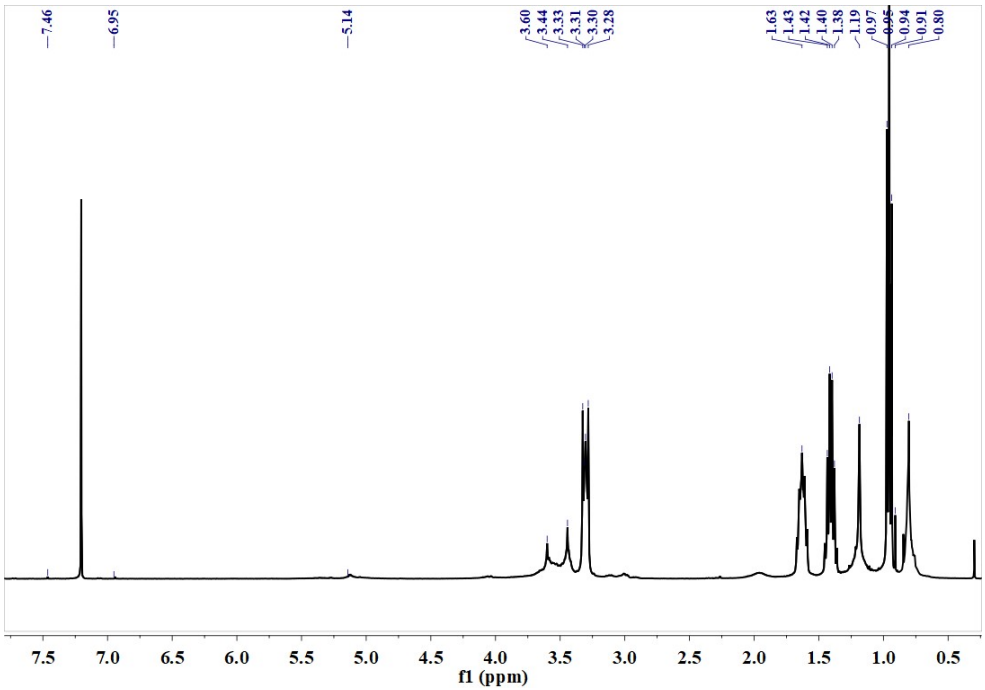
ESI–MS (m/z): 1911.70 (calculated) and 1908.59 (found) for [M+]

Synthesis of hexakis (6-O-tert-butyldimethylsilyl) - hexakis (2, 3-di-O-methyl) -deoxy-AICD

NaH 60% in oil (2.08 g, 52.0 mmol) was washed with hexane (3·20 mL) to obtain oil-free NaH. Per-6-(tert-butyldimethylsilyl)-β-CD (1.91 g, 1.0 mmol) was dissolved in anhydrous THF (25 mL) after NaH was added slowly under N_2 atmosphere and stirred for 2 h until no gas produced. MeI (3.24 mL, 52 mmol) was added dropwise to the cooled reaction system. The mixture was stirred under N_2 atmosphere and protected from light for 2 h, then the solution was heated to room temperature and the reaction for 18 h. Afterwards, the unreacted NaH and MeI were quenched by slowly adding MeOH to the system. The solvent was removed under vacuum evaporation and the residue was taken up in DCM (50 mL). The organic layer was washed with H_2O (30 mL) and brine (2·30 mL) followed by drying with Na_2SO_4 and concentrated to a solid, then dried under vacuum at 50 ℃ to obtain the desired solid.

Synthesis of hexakis(2,3-di-O-methyl)-deoxy-AICD (2,3-MeAICD)

Heptakis-(6-O-tert-butyldimethylsilyl)-hexakis (2, 3-di-O-methyl)-deoxy-6-(1-allylimidazolium)-β-CD (7.35 g, 3.5 mmol) and TBAF (5.53 g, 21 mmol) were dissolved in anhydrous THF (140 mL) and stirred at 60 °C under reflux and N_2 atmosphere for 4 h. After the reaction, THF was removed by vacuum distillation and the residue was taken up in DCM (350 mL), washed with water (100 mL×2) then dried with anhydrous Na_2SO_4 and concentrated. The product was obtained by purification of the crude product by column chromatography (SiO_2, $CHCl_3$-MeOH, 8:1 → 4:1). (2.66 g, yield: 54%)

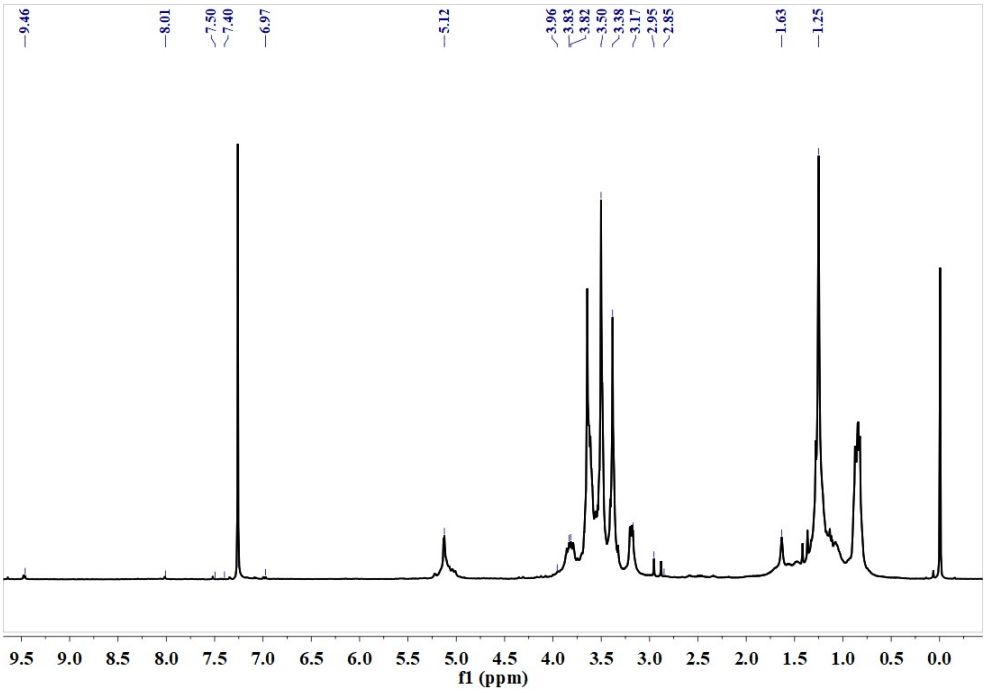


^{1}H-NMR (400Mz, $CDCl_3$): 9.47(1H), 7.46(1H), 6.95(1H), 5.14 (7H, C(1)H), 3.31-3.60 (49H), 3.30 (21H, OCH_3), 3.28 (21H, OCH_3), 1.91(3H).

ESI–MS (m/z): 1477.48 (calculated) and 1476.78 (found) for [M+]

Synthesis of heptakis-(Per-O-methyl)-deoxy-AICD (Per-MeAICD)

The dried 1-allylimidazole-β-CD (1.56 g, 1.2 mmol) was dissolved in anhydrous DMF (20 mL), stirred and cooled to 0 ℃ after adding NaH (2.64 g containing 60% oil, 90 mmol) and stirred for 2 h. MeI (8.9 mL, 360 mmol) was added slowly at 0 ℃ and stirred for 1 h. The reaction was slowly heated to room temperature and continued for 16 h. The unreacted NaH was decomposed by the addition of methanol (20 mL). The reaction mixture was extracted with $CHCl_3$ (2×30 mL) to collect the organic layer and washed with water to neutral (3×20 mL). After that, dried with Na_2SO_4, extraction and filtration, and the crude product was concentrated and then purified by silica gel column chromatography (n-hexane: acetone = 2:1). (1.51g, yield: 77.7%)



^{1}H-NMR (400Mz, $CDCl_3$): 9.46(1H), 8.01(1H), 7.50(1H), 5.13 (7H, C(1)H), 3.96-3.78 (21H, C(5)H, C(6)H), 3.64 (21H, O(3')CH_3), 3.63-3.56 (14H, C(3)H C(4)H), 3.48-3.52 (21H, O(2')CH_3), 3.38 (18H, O(6')CH_3), 2.95 (7H, C(2)H), 1.63(3H).

ESI–MS (m/z): 1561.48(calculated) and 1561.80 (found) for [M+].

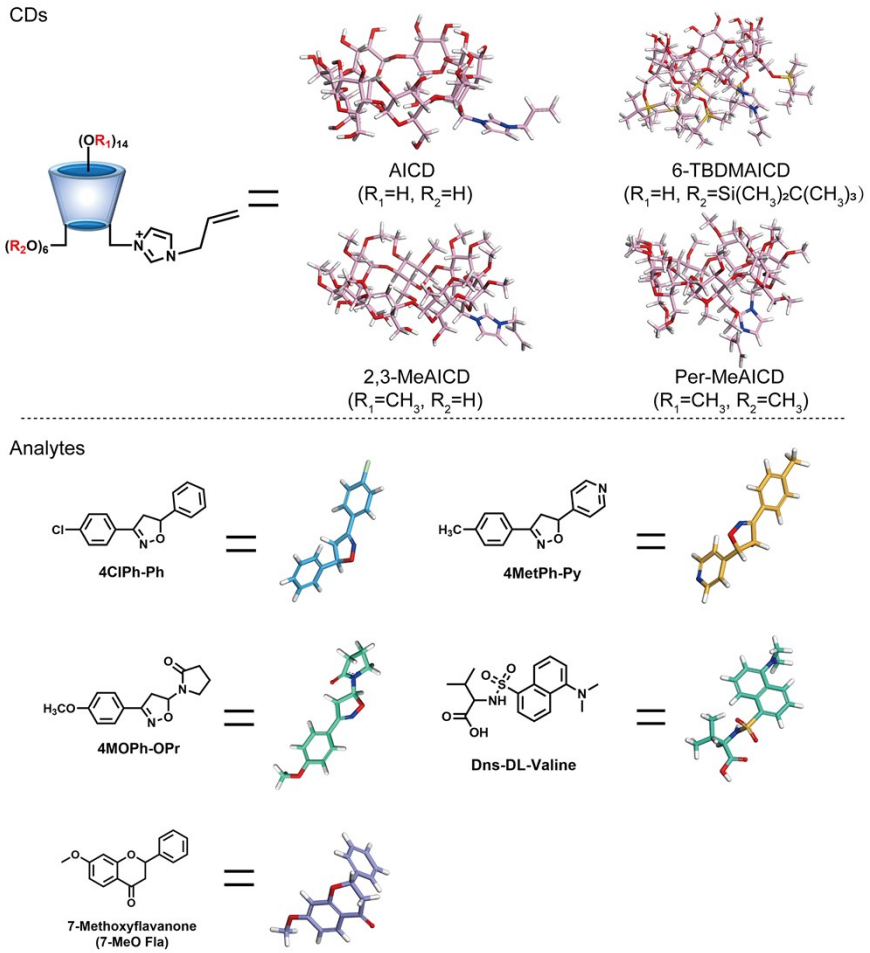


Fig. S2 Chemical structures and geometries of AICDs and analytes obtained through Autodock.

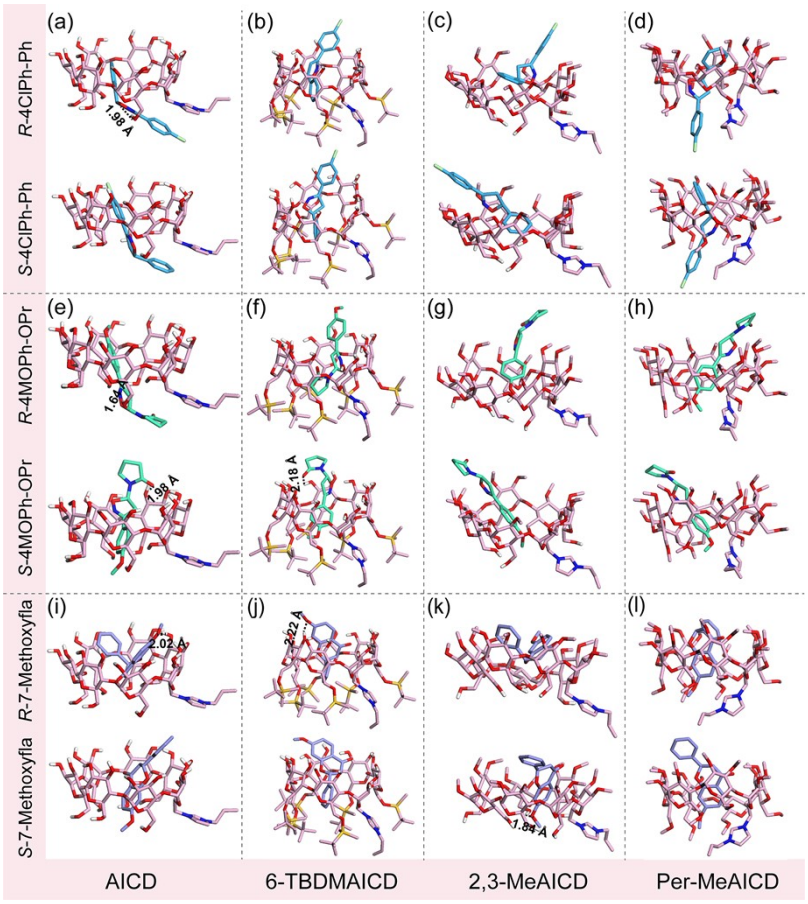


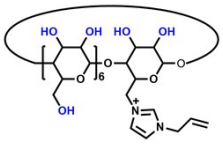
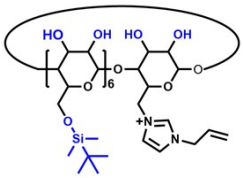
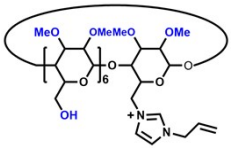
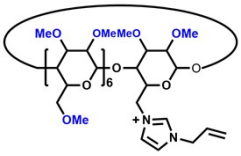
Fig. S3 Molecular docking results. (a-d): 4ClPh-Ph and CSPs; (e-h): 4MOPh-OPr and CSPs; (i-l): 7-Methoxyfla and CSPs. The hydrogen bonding is labeled by black line. O red, N dark blue, H white, C pink of CD, S yellow , C blue of 4ClPh-Ph, C green of 4MOPh-OPr, C purple of 7-Methoxyfla.

Table S1 Elemental analysis of the thiol silica and CDCSPs

CDCSPs	Average EA			
	N (%)	C (%)	H (%)	S (%)
Thiol silica	0.03	3.54	1.41	1.48
AICDCSP	0.55	10.74	2.25	0.98

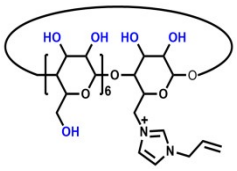
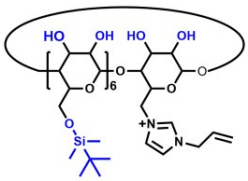
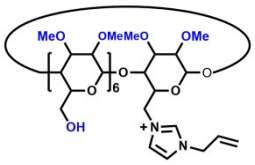
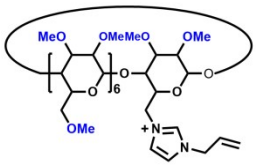
6- TBDMAICDCSP	0.35	14.13	2.79	1.18
2, 3-MeAICDCSP	0.14	5.57	1.63	1.46
Per-MeAICDCSP	0.19	6.70	1.73	0.98

Table S2 Separation of racemic analytes on CDCSPs with ACN/H_2O as mobile phase

Types	Analytes												
		AICDCSP			6- TBDMAICDCSP			2, 3-MeAICDCSP			Per-MeAICDCSP		
		k_1	Rs	α	k_1	Rs	α	k_1	Rs	α	k_1	Rs	α
Ar-Phs (i)	Ph-Ph	4.01	1.83	1.04	-	-	-	5.17	0.00	1.00	2.65	0.00	1.00
	4MOPh-Ph	3.53	1.55	1.08	-	-	-	5.52	0.00	1.00	3.68	0.00	1.00
	4ClPh-Ph	4.45	1.68	1.12	11.19	0.00	1.00	8.19	0.00	1.00	3.92	<0.5	1.03
	3ClPh-Ph	5.12	0.00	1.00	-	-	-	8.73	0.00	1.00	4.11	<0.5	1.02
	3FPh-Ph	2.34	0.00	1.00	-	-	-	9.97	0.00	1.00	3.91	<0.5	1.04
	4NPh-Ph	8.49	0.00	1.14	-	-	-	6.26	0.00	1.00	3.14	<0.5	1.04
Ar-Pys (ii)	Ph-Py	7.94	0.46	1.07	16.96	0.00	1.00	8.75	0.00	1.00	4.16	0.00	1.00
	4MOPh-Py	10.07	1.27	1.10	16.22	0.35	1.06	10.82	0.00	1.00	4.80	0.00	1.00
	MDOPh-Py	13.35	2.17	1.17	17.80	0.12	1.05	10.95	0.00	1.00	5.10	0.00	1.00
	4MetPh-Py	12.64	1.28	1.10	12.24	0.00	1.00	13.39	0.00	1.00	5.19	0.00	1.00
	4MetPh-2Py	10.58	1.44	1.11	7.30	1.22	1.50	9.73	0.00	1.00	5.70	0.00	1.00
	3NPh-Py	6.01	0.00	1.00	24.71	0.00	1.00	11.32	0.00	1.00	4.53	0.00	1.00
	4NPh-Py	10.67	0.00	1.00	15.30	0.00	1.00	11.05	0.00	1.00	5.56	0.00	1.00
Flavonoids (i)	Flavanone	2.08	1.44	1.15	6.86	0.11	1.02	3.93	0.00	1.00	5.61	0.00	1.00
	6-MeO flavanone	1.46	0.00	1.00	7.84	0.00	1.00	3.93	0.00	1.00	6.72	0.00	1.00
	7-MeO flavanone	1.42	0.00	1.00	8.20	0.00	1.00	3.89	0.00	1.00	6.67	0.00	1.00
	4'-OH flavanone	2.26	3.13	1.33	5.16	0.00	1.00	1.94	0.00	1.00	3.80	0.00	1.00
	6-OH flavanone	1.80	0.00	1.00	5.04	0.00	1.00	2.07	0.00	1.00	4.15	0.00	1.00

Conditions: (i): ACN: H_2O=30:70, rate=1.0 mL/min, T=30℃; (ii): ACN: H_2O=20:80, rate=1.0 mL/min, T=30℃. "-": no peaks.

Table S3 Separation of racemic analytes on CDCSPs in PO modes

Types	Analytes												
		AICDCSP			6- TBDMAICDCSP			2, 3-MeAICDCSP			Per-MeAICDCSP		
		k_1	R_s	α	k_1	R_s	α	k_1	R_s	α	k_1	R_s	α
Ar-Phs	Ph-Ph	0.88	0.00	1.00	0.76	0.00	1.00	0.65	0.00	1.00	0.78	0.00	1.00
	4MOPh-Ph	1.00	0.00	1.00	0.89	0.00	1.00	0.52	0.00	1.00	0.53	0.00	1.00
	4ClPh-Ph	0.81	0.00	1.00	0.99	0.00	1.00	0.61	0.00	1.00	0.73	0.00	1.00
	3ClPh-Ph	0.83	0.00	1.00	0.74	0.00	1.00	0.64	0.00	1.00	0.80	0.00	1.00
	3FPh-Ph	0.68	0.00	1.00	0.56	0.00	1.00	0.51	0.00	1.00	0.68	0.00	1.00
	4NPh-Ph	1.05	0.00	1.00	1.37	1.41	1.35	0.71	0.00	1.00	0.93	0.00	1.00
Ar-Pys	Ph-Py	1.60	0.00	1.00	1.16	0.00	1.00	1.76	0.00	1.00	1.17	0.00	1.00
	4MOPh-Py	1.95	0.00	1.00	1.16	0.00	1.00	1.90	0.00	1.00	1.40	0.00	1.00
	MDOPh-Py	1.97	0.00	1.00	1.42	0.00	1.00	2.00	0.00	1.00	1.42	0.00	1.00
	4MetPh-Py	1.45	0.00	1.00	1.06	0.00	1.00	1.60	0.00	1.00	1.08	0.00	1.00
	4MetPh-2Py	1.20	0.00	1.00	0.91	0.00	1.00	0.99	0.00	1.00	0.92	0.00	1.00
	3NPh-Py	2.57	0.00	1.00	1.61	0.00	1.00	2.06	0.00	1.00	2.06	0.00	1.00
	4NPh-Py	2.23	0.00	1.00	2.48	0.00	1.00	1.94	0.00	1.00	1.67	0.00	1.00
Ar-OPrs	Ph-OPr	1.47	0.00	1.00	1.11	0.00	1.00	1.04	0.00	1.00	1.03	0.00	1.00
	4MOPh-OPr	1.80	0.00	1.00	1.40	0.00	1.00	0.52	0.00	1.00	1.23	0.00	1.00
	MDOPh-OPr	1.90	0.00	1.00	1.61	0.00	1.00	1.22	0.00	1.00	1.26	0.00	1.00
	4ClPh-OPr	1.37	0.00	1.00	1.13	0.22	1.12	0.98	0.00	1.00	0.96	0.00	1.00
	4MetPh-OPr	1.38	0.00	1.00	1.07	0.00	1.00	1.03	0.00	1.00	0.97	0.00	1.00
	4NPh-OPr	2.17	0.00	1.00	2.63	0.00	1.00	1.17	0.00	1.00	1.30	0.00	1.00
Dns-Amino acids	Dns-Nva	1.31	0.00	1.00	0.97	0.00	1.00	1.06	0.00	1.00	1.05	0.00	1.00
	Dns-NIe	1.97	0.00	1.00	0.41	0.00	1.00	0.52	0.00	1.00	0.53	0.00	1.00
	Dns-Val	2.57	0.00	1.00	2.53	0.00	1.00	1.25	0.00	1.00	1.96	0.00	1.00
	Dns-Leu	2.73	0.00	1.00	2.56	0.00	1.00	1.91	0.00	1.00	2.11	0.00	1.00
	Dns-Phe	1.55	0.00	1.00	1.14	0.00	1.00	1.16	0.00	1.00	1.13	0.00	1.00
	Dns-Aba	1.65	0.00	1.00	1.79	0.00	1.00	1.10	0.00	1.00	1.26	0.00	1.00
Flavonoids	Flavanone	0.73	0.00	1.00	0.53	0.00	1.00	0.64	0.00	1.00	0.69	0.00	1.00
	6-MeO flavanone	0.83	0.00	1.00	0.56	0.00	1.00	0.87	0.00	1.00	0.72	0.00	1.00
	7-MeO flavanone	0.91	0.00	1.00	0.39	0.47	1.66	0.52	0.00	1.00	0.53	0.00	1.00
	4’-OH flavanone	1.53	0.00	1.00	1.44	0.00	1.00	0.51	0.00	1.00	0.80	0.00	1.00

	6-OH flavanone	1.21	0.00	1.00	1.64	0.00	1.00	0.48	0.00	1.00	0.76	0.00	1.00
	L-1	0.48	0.00	1.00	0.17	0.17	1.59	0.34	0.00	1.00	0.51	0.00	1.00
Other analytes	L-2	0.51	0.00	1.00	0.28	0.00	1.00	0.34	0.00	1.00	0.51	0.00	1.00
	L-3	0.70	0.00	1.00	0.37	0.00	1.00	0.45	0.00	1.00	0.61	0.00	1.00
	α-lonone	0.61	0.00	1.00	0.49	0.00	1.00	0.46	0.00	1.00	0.44	0.00	1.00

Conditions: MeOH:IPA=10:90(v:v), rate=1.0 mL/min, T=30 °C.

Table S4 Modeling binding free energy (ΔG) of analytes and CDs with Autodock.

Analytes	AICD				6- TBDMAICD				2,3-MeAICD				Per-MeAICD			
	$\Delta G_{R/D}$[a]	$\Delta G_{S/L}$[a]	$\lvert\Delta\Delta G\rvert$[ab]	α	$\Delta G_{R/D}$[a]	$\Delta G_{S/L}$[a]	$\lvert\Delta\Delta G\rvert$[ab]	α	$\Delta G_{R/D}$[a]	$\Delta G_{S/L}$[a]	$\lvert\Delta\Delta G\rvert$[ab]	α	$\Delta G_{R/D}$[a]	$\Delta G_{S/L}$[a]	$\lvert\Delta\Delta G\rvert$[ab]	α
4ClPh-Ph	-5.84	-6.22	0.38	1.12	-6.57	-6.18	0.01	1.11	-5.84	-6.00	0.16	1.00	-7.99	-7.60	0.39	1.08
4MetPh-Py	-5.31	-5.61	0.30	1.10	-5.93	-5.64	0.29	1.15	-5.46	-5.65	0.19	1.00	-7.20	-6.98	0.22	1.00
4MOPh-OPr	-5.08	-5.25	0.17	1.15	-5.03	-5.09	0.06	1.00	-5.32	-5.21	0.10	1.00	-6.95	-7.10	0.15	1.00
Dns-Val	-4.87	-4.52	0.35	1.15	-4.29	-4.68	0.39	1.14	-5.72	-5.74	0.02	1.00	-6.41	-6.22	0.19	1.00
7-MeO flavanone	-6.18	-5.68	0.50	1.13	-6.39	-6.16	0.23	1.00	-6.52	-6.39	0.13	1.00	-8.27	-7.98	0.29	1.00

References

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3 X.X. Li, X. Jin, X.B. Yao, X.F. Ma, Y. Wang, *J. Chromatogr. A*, 2016, **1467**, 279-287.