SUPPORTING INFORMATION

Ternary and quaternary Phase Diagrams: Key Tools for Chiral Resolution through solution Cocrystallization.

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Here, we present all the data used to create the diagrams presented in the main text (Tables 1 – 5), as well as a schematic representation of a quaternary phase diagram wherein a diastereomeric pair of cocrystals is formed involving both enantiomers of the target molecule and the chiral conformer. In this case the overall resolution system is no longer enantiospecific.

TABLE 1. Data used to create the cross-section " fixed solvent molar percentage" at 9°C. (Figure 6)

Ternary Phase Diagrams at 9°C for a given amount of acetonitrile (89 mol%).										
	Initial system composition			Final solid state in suspension	Final solution composition					
				XRPD analysis[1]	Reverse HPLC		Chiral HPLC			
	%mol **S-2**	%mol **R-1**	%mol **S-1**		mg/l **S-2**	mg/l **RS-1**	% **R-1**	%mol **S-2**	%mol **R-1**	%mol **S-1**
1	96.96	1.52	1.52	I	269.62	26.69	49.96	90.99	4.50	4.51
2	95.53	2.23	2.23	I	323.98	38.74	48.38	89.32	5.17	5.51
3	93.12	3.44	3.44	I	314.36	55.01	53.17	85.11	7.92	6.97
4	86.08	6.96	6.96	I	370.58	99.73	50.94	78.79	10.80	10.40
5	79.51	10.24	10.24	I	453.24	149.30	49.06	75.22	12.16	12.62
6	73.68	13.16	13.16	-	447.43	180.97	48.9	71.20	14.08	14.72
7	68.17	15.91	15.91	-	452.83	239.03	49.73	65.45	17.18	17.37
8	63.22	18.39	18.39	-	321.89	206.73	49.05	60.89	19.18	19.93
9	60.40	19.80	19.80	-	347.01	251.84	50.21	57.95	21.12	20.94
10	58.50	20.75	20.75	-	331.92	259.28	51.82	56.14	22.73	21.13
11	68.02	13.33	18.65	-	352.74	184.67	39.58	65.64	13.60	20.76
12	68.15	10.58	21.27	-	382.66	134.59	24.67	73.98	6.42	19.60
13	68.07	8.00	23.94	II	338.78	148.40	32.12	69.54	9.78	20.68
14	64.33	13.69	21.97	II	319.90	180.34	46.28	63.95	16.68	19.37
15	64.32	10.95	24.73	II	292.30	154.56	41.49	65.41	14.35	20.24
16	64.40	8.22	27.39	II	304.68	150.91	35.76	66.88	11.84	21.28
17	60.41	14.14	25.45	II	265.44	172.63	46.63	60.59	18.38	21.03
18	60.31	11.37	28.32	II	263.10	162.10	41.6	61.88	15.86	22.26
19	60.33	8.50	31.18	II	237.73	136.26	36.89	63.57	13.44	22.99
20	64.37	15.74	19.89	-	339.12	208.11	42.91	61.97	16.32	21.71

[1] I= S-2 ; II= S-1-S2 co-crystal ; IV= RS-1 ; - = Liquid

21	60.28	15.61	24.11	II	296.14	197.94	49.96	59.94	20.02	20.05
22	60.41	18.40	21.19	-	329.06	238.24	46.26	58.00	19.43	22.57
23	57.45	15.22	27.33	II	255.83	189.40	48.76	57.46	20.74	21.80
24	57.40	16.71	25.89	II	277.76	211.54	49.58	56.77	21.43	21.80
25	57.48	19.72	22.80	II	280.62	219.07	51.56	56.16	22.60	21.24
26	74.16	6.46	19.38	II	392.17	158.47	24.22	71.22	6.97	21.81
27	83.25	5.29	11.46	I	415.72	121.52	32.88	77.38	7.44	15.18
28	79.61	5.07	15.32	I	428.96	158.21	22.44	73.06	6.05	20.90
29	35.69	13.39	50.92	II + IV	100.72	182.96	14.63	35.50	9.44	55.06
30	36.18	15.93	47.89	II + IV	90.81	141.89	22.47	39.03	13.70	47.27
31	41.69	13.26	45.05	II + IV	130.25	167.25	27.82	43.78	15.64	40.58
32	57.33	21.33	21.33	II	311.98	271.75	53.96	53.45	25.12	21.43
33	54.37	22.82	22.82	-	287.81	282.92	48.97	50.43	24.28	25.30
34	79.61	3.70	16.68	I +II	320.96	109.33	27.67	74.59	7.03	18.38
35	77.02	3.85	19.13	I + II	399.73	139.25	23.6	74.16	6.10	19.74
36	74.36	3.85	21.79	I + II	306.51	104.42	20.28	74.59	5.15	20.26

TABLE 2. Data used to create the cross-section " fixed solvent molar percentage" at -10°C. (Figure 6)

Ternary Phase Diagrams at -10°C and appointed molar percentage of 89 mol% of acetonitrile.										
	Initial composition			Final solid state in suspension	Final liquid composition					
				XRPD analysis[2]	Reverse HPLC		Chiral HPLC			
	%mol **S-2**	%mol **R-1**	%mol **S-1**		mg/l **S-2**	mg/l **RS-1**	% **R-1**	%mol **S-2**	%mol **R-1**	%mol **S-1**
1	93.03	3.48	3.48	I	213.37	62.47	50.05	79.26	10.38	10.36
2	86.16	6.92	6.92	I	282.37	114.90	44.52	73.33	11.87	14.80
3	79.55	10.22	10.22	I + II	248.70	106.53	65.6	72.31	18.16	9.52
4	73.51	13.24	13.24	I + II	303.96	141.92	71.58	70.55	21.08	8.37
5	67.91	16.05	16.05	I + II	355.66	180.66	72.69	68.77	22.70	8.53
6	63.23	18.38	18.38	II	411.99	226.43	75.93	67.06	25.01	7.93
7	67.78	13.40	18.83	I + II	328.50	156.77	73.31	70.10	21.92	7.98
8	60.16	19.92	19.92	II	296.02	175.27	75.15	65.39	26.01	8.60
9	58.56	20.72	20.72	II	315.06	204.97	74.69	63.23	27.46	9.31
10	86.96	1.29	11.75	I + II	167.48	74.80	68.95	71.47	19.67	8.86
11	68.00	5.34	26.65	I + II	243.03	80.44	56.84	77.17	12.98	9.85
12	64.28	13.74	21.98	II	306.62	132.04	71.64	72.21	19.91	7.88
13	64.05	8.37	27.58	II	286.50	99.93	60.23	76.23	14.32	9.45
14	60.00	11.52	28.48	II	231.67	113.55	68.85	69.53	20.98	9.49
15	59.99	8.59	31.42	II	228.66	97.01	66.1	72.50	18.18	9.32
16	60.25	15.56	24.19	II	293.45	157.53	73.05	67.57	23.69	8.74

[2] I33= S-2 ; II= S-1 :S-2 co-crystal ; IV= RS-1 ; V= R-1 ; -=Liquid

17	57.26	15.22	27.52	II	146.85	94.59	74.2	63.46	27.11	9.43
18	57.47	19.70	22.84	II	272.96	179.96	75.63	62.92	28.04	9.04
19	74.27	6.39	19.34	I + II	221.68	78.73	57.66	75.90	13.89	10.20
20	83.50	5.49	11.01	I + II	214.18	72.25	55.85	76.83	12.94	10.23
21	79.55	5.09	15.36	I + II	215.12	70.97	55.99	77.23	12.75	10.02
22	35.90	13.49	50.61	II + IV	82.76	128.60	13.03	41.86	7.58	50.57
23	35.64	16.07	48.29	II + IV	33.57	40.92	47.62	47.86	24.83	27.31
24	41.53	13.30	45.17	II + IV	112.10	97.11	23.1	56.36	10.08	33.56
25	49.95	25.03	25.03	II + IV	262.49	165.48	76.71	63.96	27.65	8.39
26	47.31	13.12	39.57	II + IV	183.05	134.45	32.12	60.37	12.73	26.90
27	48.09	17.21	34.70	II + IV	196.02	134.32	54.3	62.01	20.63	17.36
28	41.96	20.37	37.67	II + IV	159.46	104.69	68.67	63.02	25.40	11.59
29	38.07	24.78	37.15	II + IV	131.54	83.71	62.82	63.74	22.78	13.48
30	57.73	21.13	21.13	II	304.23	187.35	76.69	64.50	27.23	8.28
31	54.33	22.84	22.84	II	250.06	200.54	76.33	58.25	31.87	9.88
32	68.45	18.49	13.06	I + II						
33	68.07	21.23	10.70	-						
34	68.41	26.36	5.23	-						
35	64.41	21.95	13.64	II						
36	64.14	27.48	8.38	-						
37	59.86	28.69	11.44	IV						
38	59.99	31.52	8.49	IV						
39	60.24	24.10	15.67	II						
40	60.21	19.89	19.89	II						
41	58.57	20.72	20.72	II						
42	86.96	11.76	1.29	I						
43	56.81	23.86	19.33	II + IV						
44	74.64	19.01	6.35	I						
45	83.22	11.25	5.53	I						
46	79.41	15.47	5.12	I						
47	35.97	50.69	13.34	IV + V						
48	36.19	47.78	16.03	IV + V						
49	41.66	45.13	13.21	IV + V						
50	47.42	39.43	13.15	IV + V						
51	46.53	36.40	17.07	IV						
52	41.30	38.46	20.24	IV						
53	38.26	37.13	24.61	IV						
54	57.52	21.24	21.24	II						
55	53.90	23.05	23.05	II						

- For points 32 up to 55 HPLC analysis was not performed. For these points, only the information on the nature of the Solid state phases was used.

TABLE 3. Data used to create the cross-section "Racemic composition plane" at -10°C. (Figure 7)

Racemic composition cross-section at -10°C												
	Initial composition				Final solid state in suspension	Final liquid composition						
					XRPD analysis[3]	Reverse HPLC		Chiral HPLC				
	%mol **S-2**	%mol **R-1**	%mol **S-1**	%mol Acetonitrile		mg/ml **S-2**	mg/ml **RS-1**	% **R-1**	%mol **S-2**	%mol **R-1**	%mol **S-1**	%mol ACN
1	6.80	0.09	0.096	93	I	55.88	0.96	44.32	1.88	0.02	0.01	98.09
2	6.64	0.17	0.17	93	I	40.14	3.49	53.02	1.36	0.05	0.06	98.54
3	6.34	0.32	0.32	93	I	75.32	16.23	52.25	2.51	0.23	0.25	97.01
4	6.13	0.43	0.43	93	I	85.38	23.70	48.95	2.83	0.36	0.34	96.47
5	5.82	0.58	0.58	93	I	101.63	33.58	51.66	3.34	0.48	0.51	95.68
6	5.50	0.74	0.74	93	I	112.62	42.45	49.42	3.68	0.63	0.61	95.09
7	4.90	1.04	1.04	93	-	106.95	56.44	61.21	3.48	0.64	1.01	94.87
8	4.55	1.22	1.22	93	II	88.71	57.06	66.17	2.91	0.57	1.11	95.42
9	4.25	1.37	1.37	93	II	86.09	53.13	52.05	2.83	0.75	0.81	95.62
10	3.69	1.65	1.65	93	IV	84.85	52.40	49.44	2.79	0.78	0.76	95.68
11	3.36	1.81	1.81	93	IV	67.61	42.27	50.26	2.24	0.62	0.63	96.51
12	3.05	1.97	1.97	93	IV	70.57	50.13	48.86	2.33	0.76	0.72	96.19
13	2.74	2.12	2.12	93	IV	49.54	32.99	51.81	1.66	0.47	0.51	97.36
14	2.07	2.46	2.46	93	IV	29.79	23.25	49.5	1.01	0.35	0.35	0.98
15	1.44	2.77	2.77	93	IV	55.88	0.96	61.21	1.88	0.02	0.01	98.09
16	10.23	0.38	0.38	89	I	106.69	31.24	50.05	3.50	0.46	0.46	95.58
17	9.48	0.76	0.76	89	I	141.18	57.45	44.52	4.55	0.74	0.92	93.80
18	8.75	1.12	1.12	89	I + II	124.35	53.27	65.6	4.03	1.01	0.53	94.43
19	8.09	1.46	1.46	89	I + II	151.98	70.96	71.58	4.86	1.45	0.58	93.11
20	7.47	1.77	1.77	89	I + II	177.83	90.33	72.69	5.61	1.85	0.70	91.85
21	6.96	2.02	2.02	89	II	205.99	113.22	75.93	6.40	2.39	0.76	90.46
22	6.62	2.19	2.19	89	II	148.01	87.63	75.15	4.71	1.88	0.62	92.79
23	6.44	2.28	2.28	89	II	157.53	102.48	74.69	4.98	2.16	0.73	92.12
24	6.35	2.32	2.32	89	II	131.24	82.74	76.71	4.21	1.82	0.55	93.42
25	5.98	2.51	2.51	89	II	152.11	93.68	76.69	4.83	2.04	0.62	92.51
26	5.49	2.75	2.75	89	IV + II	125.03	100.27	76.33	4.00	2.19	0.68	93.14
27	14.34	0.33	0.33	85	I	77.25	18.79	49.92	2.57	0.28	0.28	96.87
28	14.00	0.50	0.50	85	I	82.11	26.37	53.63	2.72	0.42	0.36	96.50
29	12.98	1.01	1.01	85	I	128.09	59.57	50.27	4.14	0.87	0.86	94.14
30	11.91	1.54	1.54	85	I +II	137.48	66.11	72.35	4.42	1.37	0.53	93.68
31	11.04	1.98	1.98	85	I +II	155.93	80.95	74.79	4.96	1.72	0.58	92.73
32	10.28	2.36	2.36	85	I +II	169.43	45.50	75.95	5.42	0.99	0.31	93.27

[3] I= S-2 ; II= S-1 :S-2 co-crystal ; IV= RS-1

33	9.02	2.99	2.99	85	II	163.57	99.18	77.92	5.17	2.18	0.62	92.03
34	8.54	3.23	3.23	85	II	170.37	124.97	78.93	5.33	2.76	0.74	91.17
35	7.87	3.57	3.57	85	II	146.04	103.23	77.25	4.63	2.26	0.67	92.44
36	6.72	4.14	4.14	85	II + IV	133.88	97.39	73.47	4.27	2.04	0.74	92.95
37	5.95	4.53	4.53	85	IV	154.91	93.60	49	4.92	1.30	1.35	92.43

TABLE 4. Data used to create ternary phase diagrams of tetrahedron sides

Ternary Phase Diagrams, Tertahedron Sides at 9°C												
	Initial composition				Final solid state in suspension	Final liquid composition						
					XRPD analysis[4]	Reverse HPLC		Chiral HPLC				
	mg **S-2**	mg **R-1**	mg **S-1**	ml Acetonitrile		mg/ml **S-2**	mg/ml **RS-1**	% **R-1**	%mol **S-2**	%mol **R-1**	%mol **S-1**	%mol ACN
Ternary phase diagram of chiral API (front side, Figure 3)												
1		0.00	68.93	1	III		23.762	50		0	0.72	99.28
2		33.91	33.91	1	IV		20.001	49.52		0.30	0.31	99.39
3		36.60	41.46	1	IV		19.992	37.45		0.24	0.37	99.39
4		34.65	44.60	1	IV		21.382	30.12		0.22	0.43	99.35
5		35.39	56.83	1	IV		30.433	14.62		0.16	0.76	99.07
6		6.05	72.73	1	IV		32.429	12.58		0.17	0.81	99.01
7		22.30	67.17	1	IV		25.893	12.75		0.19	0.59	99.21
8		35.17	50.96	1	III		36.299	19.75		0.11	0.99	98.90
9		1.38	72.01	1	III		38.660	4.66		0.16	1.01	98.83
10		2.43	72.81	1	IV		34.870	9.38		0.18	0.88	98.94
Ternary phase diagram of cocrystal system (rigth side, Figure 4)												
11	254.99		0.00	1	I	72.72	0.00		2.44		0	97.56
12	0.00		68.93	1	III	0.00	23.76		0		0.72	99.28
13	231.63		105.20	1	II	120.77	34.87		3.94		1.02	95.04
14	201.66		99.39	1	II	107.12	33.25		3.51		0.97	95.51
15	231.62		81.72	1	II	110.67	31.49		3.63		0.92	95.45
16	230.85		109.78	1	II	105.75	31.49		3.47		0.92	95.61
17	10.38		67.69	1	III	11.09	26.06		0.38		0.79	98.83
18	250.80		14.18	1	I	94.88	12.11		3.14		0.36	96.50
19	226.45		99.60	1	II	124.27	35.69		4.05		1.04	94.91
20	257.06		38.16	1	I	154.66	60.77		4.95		1.74	93.31
21	229.45		79.54	1	II	101.35	33.39		3.33		0.98	95.69
22	219.76		92.47	1	II	91.67	29.07		3.02		0.86	96.12
23	212.07		102.66	1	II	85.60	29.44		2.83		0.87	96.30
24	198.55		109.98	1	III	102.31	50.07		3.34		1.46	95.19
25	220.33		109.35	1	III	114.47	54.71		3.72		1.59	94.69

[4] I= S-2 ; II= S-1 :S-2 co-crystal ; III=S-1 ; IV= RS-1 ; V=R-1

26	227.61		101.03	1	II	129.06	40.97		4.19		1.19	94.62
Ternary phase diagram ofa non-cocrystal forming system (back side, Figure 5)												
27	254.99	0.00		1	I	72.72	0.00		2.44	0.00		97.56
28	0.00	68.93		1	V	0.00	23.76		0.00	0.72		99.28
29	253.61	83.78		1	I	147.90	54.00		4.76	1.55		93.69
30	252.35	24.39		1	I	101.21	19.02		3.34	0.56		96.10
31	252.18	11.54		1	I	93.65	10.45		3.10	0.31		96.59
32	253.86	33.28		1	I	116.32	25.74		3.81	0.75		95.44
33	251.66	40.48		1	I	123.59	30.86		4.03	0.90		95.07
34	13.61	82.25		1	V	15.09	32.07		0.51	0.97		98.52

TABLE 5. Data used to create ternary phase diagrams of tetrahedron sides

Ternary Phase Diagrams, Tertahedron Sides at -10°C												
	Initial composition				Final solid state in suspension	Final liquid composition						
					XRPD analysis[5]	Reverse HPLC		Chiral HPLC				
	mg **S-2**	mg **R-1**	mg **S-1**	ml Acetonitrile		mg/ml **S-2**	mg/ml **RS-1**	% **R-1**	%mol **S-2**	%mol **R-1**	%mol **S-1**	%mol ACN
Ternary phase diagram of chiral API (front side, Figure 3)												
1		0	66.32	1	III		15.01	0		0	0.46	99.54
2		30.58	30.58	1	IV		9.92	50		0.15	0.15	99.70
3		2.65	64.22	1	III + IV		14.38	14.87		0.07	0.37	99.56
4		7.6	57.67	1	IV		13.57	11.79		0.05	0.37	99.59
5		12.84	57.71	1	IV		13.71	10.59		0.04	0.37	99.58
6		15.11	47.23	1	IV		16.63	11.21		0.06	0.45	99.49
7		25.01	41.67	1	IV		17.57	10.72		0.06	0.48	99.46
8		30.00	36.31	1	IV		9.36	24.35		0.07	0.22	99.71
Ternary phase diagram of cocrystal system (rigth side, Figure 4)												
9	253.23		0	1	I	55.60	0		1.87		0	98.13
10	0		66.32	1	III	0	15.01		0		0.46	99.54
11	231.66		95.92	1	II	83.59	16.98		2.78		0.50	96.72
12	193.84		100.86	1	II	68.06	14.70		2.27		0.44	97.29
13	232.17		82.84	1	II	66.52	13.27		2.22		0.40	97.38
14	227.6		112.13	1	II	83.68	17.32		2.78		0.51	96.71
15	9.27		68.82	1	III	12.28	16.68		0.42		0.51	99.08
16	245.8		11.37	1	I	63.50	11.33		2.13		0.34	97.54
17	219.92		98.2	1	II	105.91	22.10		3.49		0.65	95.86
18	252.36		38.375	1	I + II	61.63	12.42		2.06		0.37	97.56
19	32.24		70.77	1	II + III	0.08	16.67		0.003		0.51	99.49
20	73.53		71.74	1	II	27.62	27.35		0.93		0.82	98.24

[5] I= S-2 ; II= S-1 :S-2 co-crystal ; III=S-1 ; IV= RS-1 ; V=R-1

21	124.44		70.82	1	II	61.91	7.47		2.08		0.22	97.70
Ternary phase diagram of a non-cocrystal forming system (back side, Figure 5)												
22	253.23	0		1	I	55.60	0		1.87	0		98.13
23	0	66.32		1	III	0	15.01		0	0.46		99.54
24	243.45	81.86		1	I + V	125.74	63.55		4.06	1.84		94.10
25	246.70	24.09		1	I	80.44	21.92		2.67	0.65		96.68
26	247.88	10.14		1	I	62.62	10.21		2.10	0.31		97.60
27	254.78	32.38		1	I	77.37	25.30		2.57	0.75		96.68
28	249.96	36.81		1	I	87.48	30.25		2.89	0.89		96.22
29	12.64	82.89		1	V	14.55	21.45		0.49	0.65		98.86
30	42.73	87.98		1	V	25.88	29.34		0.87	0.88		98.24

In the main text, we focused on an enantiospecific cocrystal system, as this is novel with respect to salts. Nevertheless, resolution through cocrystallization in solution remains possible even if a diastereomeric pair of cocrystals is formed. In this case, the ternary phase diagram located on the back side of a tetrahedral diagram, as represented on Figure 1 in the supporting information, has the shape of a ternary phase diagram of a cocrystal system. As the two diastereomeric cocrystals have different physico-chemical properties, in particular solubility, the overall diagram is still assymetric and the conditions for an effective resolution, listed in the main text , can still be satisfied. On the figure below, ternary phase diagrams represent projections of the sides oft he tetrahedron quaternary phase diagram for both cases, clearly indicating the difference.

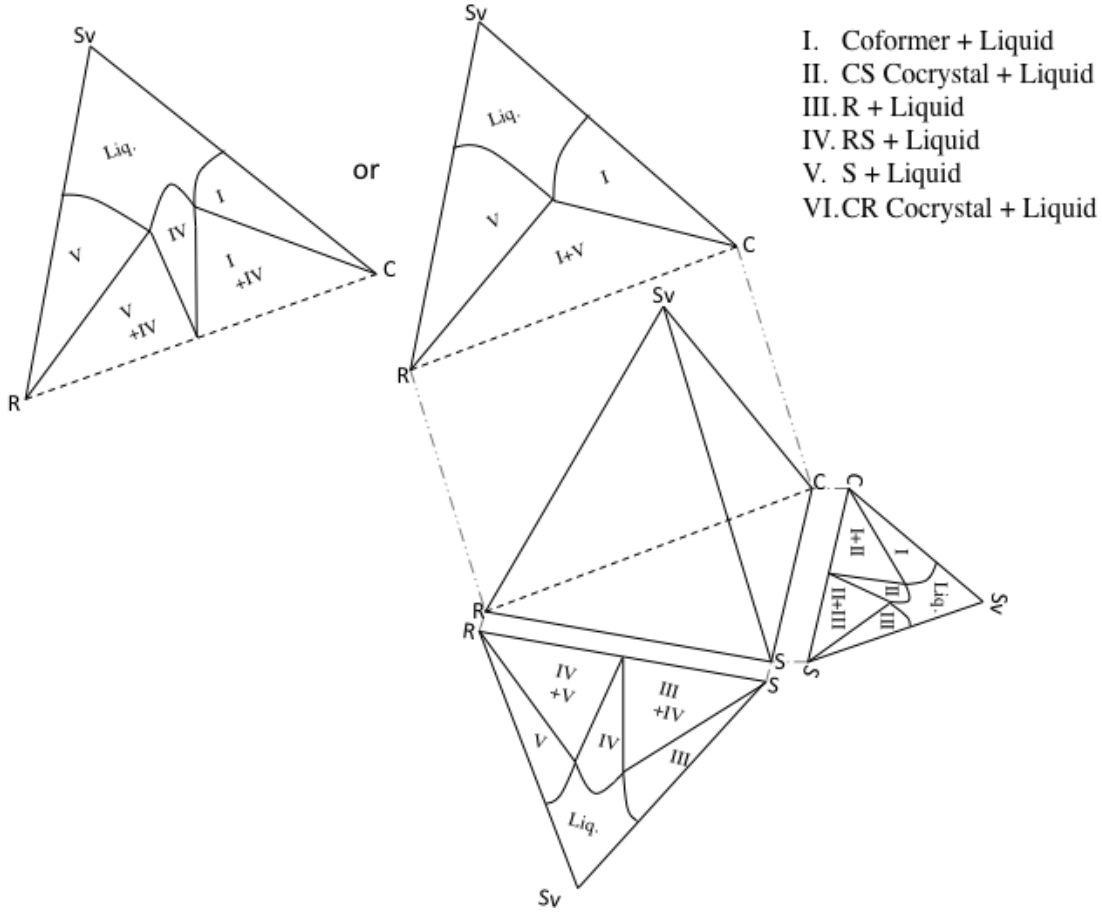

FIGURE 1. Schematic representation of a quaternary phase diagram, which can be used for a resolution through cocrystallization in solution. Both the enantiospecific, as well as the non-enantiospecific cases are represented.