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Electronic Supplementary Information

Selective Cocrystallization Separation Method Based on Noncovalent Interactions and Its Application

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S1. Experimental Section

S1.1 Materials

Three isomers of cresol, *o*-, *m*- and *p*-cresol, (mass fraction: w% > 99.0%, Abbreviated as OC, MC and PC in the context, respectively) were commercially purchased from Tianjin Yuanli Chemical Co., Ltd., of China. The piperazine coformer (PP, w% >99.0%) and toluene solvent were in-sourced in the Tianjin Guangfu Fine Chemical Research Institute. The urea coformer (U, w% > 99.0%) was obtained from the XiLONG SCIENTIFIC Co., Ltd., of China, and the oxalic acid coformer (OXA, w% >99.0%) was obtained from Meryer (Shanghai) Chemical Technology Co., Ltd. All the cocrystal formers and solvents in analytical-grade were used as received without further purification. The toluene-d8 (toluene-d8, 99.9 atom % D, contains 0.03% (v/v) TMS) and dimethyl sulfoxide-d6 (DMSO-d6, 99.9 atom % D, contains 0.03% (v/v) TMS) were purchased from SIGMA-ALORICH Company of USA. The molecular structures of the compounds are shown in Figure S1.



Figure S1. Molecular structures of isomers and coformers.

S1.2 Analytical methods & equipments

X-ray powder diffraction (PXRD). The PXRD analyses were carried on a powder diffractometer (Rigaku D/MAX 2500) using Cu K α (1.54 Å) radiation. The tube voltage and amperage were set to 40 kV and 100mA, respectively. And data were collected at room temperature in the range of $2\theta = 2-50^{\circ}$, with a step size of 0.02°. Samples were packed into silicon sample holders.

Differential scanning calorimetry (DSC). The DSC measurements were carried out with Mettler-Toledo DSC 1/500 instrument. Samples of approximately 5-10 mg were placed into pans and were analyzed in the temperature range of 25-150 °C (the highest measured temperature) with heating rate of 5 °C/min and using 50 mL/min nitrogen as insert gas purge.

Fourier transformed infrared spectrometer (FTIR). FTIR spectra have been recorded on the Bruker Alpha FTIR-ATR instrument with 4 cm⁻¹ resolution and 32 scans per spectrum and 4000-400 cm⁻¹ range. And the temperature-dependent IR data were collected by **attenuated total reflectance Fourier transformed infrared spectroscopy (ATR-FTIR,** Mettler Toledo, Switzerland).

Raman spectroscopy (Raman). Raman spectra were recorded on the *RamanRXN2*TM *HYBRID* analyzer (Kaiser Optical Systems, Inc. USA) using *PhAT* probe with a range of 1890-300 cm⁻¹.

¹**H-nuclear magnetic resonance (**¹**H NMR)**. ¹H NMR analyses were carried out on a Varian Inova 500 MHz Spectrometer (Palo Alto, CA, USA). Samples of different qualities were dissolved into 0.6 ml of DMSO-d6. All spectra were collected at room temperature. And the chemical shifts are referenced to internal TMS (0.00 ppm).

Gas chromatography (GC). The GC analyses were performed with BRUKER (SCION 456-GC) and equipped with an FID (Flame Ionization Detector). An HP-INNOWax column (0-260 (270): $30 \text{ m} \times 250 \text{ \mu}\text{m} \times 0.25 \text{ \mu}\text{m}$, 19091N-133, Agilent) was used to separate the components. Ethyl benzoate was selected as internal standard, and the concentrations of the substance were determined by internal standard method (ISTD).

S1.3. Single cocrystals preparation

MC_U cocrystal: Urea and *m*-cresol were dissolved in toluene in a certain stoichiometric ratio. The suitable single crystal was grown from solution in toluene by slow solvent evaporation at room temperature. Another way for obtaining the single MC_U cocrystal is recrystallization: (1) Dissolve certain amount of MC_U cocrystal in MC solution at higher temperature to form a saturated solution; (2) Add MC_U cocrystal seeds to the saturated solution; and (3) slowly cool down to room temperature. Regular hexagonal transparent single MC_U crystals can be obtained.

OC_U cocrystal: The methods of obtaining **OC_U** cocrystals suitable for single crystal X-ray analysis are the same as the preparation method of **MC_U** single crystal. Rectangular and transparent single **OC_U** crystals can be obtained.

PC_OXA cocrystal: Crystals suitable for single crystal X-ray analysis were obtained by allowing a saturated toluene solution with PC and OXA mixture to evaporate slowly in a desiccator at room temperature. After several months, regular and transparent diamond-shaped single crystals were obtained.

MC_PP cocrystal: Piperazine and *m*-cresol were dissolved in toluene in a certain stoichiometric ratio at higher temperature to form saturated solution. Crystals suitable for single crystal X-ray analysis were obtained when slowly cool down to room temperature. Another way to obtain the single **MC_PP** cocrystal is by evaporating slowly in ether solution and atmosphere at room temperature.

OC_PP cocrystal: The methods of obtaining **OC_PP** cocrystals suitable for single crystal X-ray analysis are the same with the preparation method of **MC_PP** single crystal.

PC_PP cocrystal: Piperazine and *p*-cresol were dissolved in toluene in a certain stoichiometric ratio. Crystals suitable for single crystal X-ray analysis were obtained by slowly cooling down toluene solution to room temperature.

S1.4. Grinding experiments

In order to confirm that PC with U and MC/OC with OXA cannot form cocrystal, NG and LAG milling reactions were performed. For the NG, the two components were mixed in various molar ratios (0.5:1, 1:1 and 2:1, respectively), and the mixtures were ground using an agate mortar and pestle for 20-30 min, respectively. While for the LAG, selected solvents (such as toluene, *n*-heptane, methanol, ethanol and dichloromethane, respectively, about 50 µl) were added dropwise over the course of grinding. Complexes formation were confirmed by PXRD.

Moreover, to test the generality of selective cocrystallization based on H-bonding, some CCFs, such as thiourea, imidazole, malonic acid and succinic acid, which have similar structures with those that have selectivity mentioned above were applied to cocrystallize with MC and/or PC. And the milling reaction methods are the same as the method mentioned above.

S2. Results & Discussions

S2.1. Analyses of cocrystals.



Figure S2. Morphologies of the cocrystals obtained by screening experiments, a) MC_U, b) OC_U, c) MC_PP, d) OC_PP, e) PC_PP and f) PC_OXA, respectively.

The melting points of cocrystals are as follows (Peak values): 71.7 °C (MC_U cocrystal), 61.9 °C (OC_U cocrystal), 78.4 °C (PC_OXA cocrystal), 61.7 °C (MC_PP cocrystal), 60.7 °C (OC_PP cocrystal), 92.6 °C (PC_PP cocrystal), 72.4 °C (MC_IMZ cocrystal), and 32.5 °C (PC_IMZ cocrystal), respectively. The melting points of all cocrystals are between those of their corresponding coformers, and the endothermic peaks are very sharp, which means that the crystallinity and purity of these cocrystals are high. Moreover, it can also be found that the melting points of MC_U and OC_U cocrystals, MC_PP and OC_PP cocrystals are very close, while the melting point of PC_PP cocrystal are quite different from those of MC_PP and OC_PP cocrystals.



Figure S3. The DSC curves of new solids: a) Cresols-U, b) Cresols-PP, c) Cresols-OXA and d) Cresols-IMZ, respectively.

PXRD pattern of U shows characteristic peaks (2θ) at 21.96°, 22.34°, 35.59°, 45.06° and 45.46°.

PXRD pattern of MC_U cocrystal shows characteristic peaks (2θ) at 7.89°, 11.06°, 15.56°, 17.74°, 22.14°, 24.08°, 24.62°, 25.34°, 25.88° and 32.34°.

PXRD pattern of OC_U cocrystal shows characteristic peaks (2 θ) at 6.64°, 13.36°,

6

18.32°, 18.90°, 24.08° and 26.92°.



Figure S4. The PXRD patterns of cocrystals: a) Cresols-U, b) Cresols-PP, c) Cresols-OXA and d) Cresols-IMZ, respectively.

PXRD pattern of OXA shows characteristic peaks (2θ) at 14.72°, 18.60°, 22.76°, 27.06°, 28.84°, 30.80°, 35.53°, 38.52° and 40.20°.

PXRD pattern of PC_OXA cocrystal shows characteristic peaks (2 θ) at 4.92°, 9.96° and 15.04°.

PXRD pattern of PP shows characteristic peaks (2θ) at 15.84°, 17.38°, 20.12°, 22.78° and 37.58°.

PXRD pattern of MC_PP cocrystal shows characteristic peaks (2 θ) at 7.00°, 14.18°, 14.66°, 15.92°, 17.80°, 20.18°, 21.36° and 26.62°.

PXRD pattern of OC_PP cocrystal shows characteristic peaks (2 θ) at 9.98°, 15.00°, 20.18°, 23.50° and 24.96°.

PXRD pattern of PC_PP cocrystal shows characteristic peaks (2 θ) at 8.08°, 16.42°, 26.76° and 33.14°.

PXRD pattern of IMZ shows characteristic peaks (2θ) at 12.90°, 20.42°, 20.84°, 25.98°,

28.28° and 30.78°.

PXRD pattern of MC_IMZ cocrystal shows characteristic peaks (2θ) at 14.12°, 16.28°, 16.86°, 19.10°, 20.18°, 20.76°, 21.52°, 21.96°, 22.78°, 24.20°, 25.38°, 26.66° and 28.60°.

PXRD pattern of PC_IMZ cocrystal shows characteristic peaks (2*θ*) at 13.06°, 16.92°, 17.22°, 17.82°, 18.50°, 19.30°, 19.78°, 24.44°, 24.96°, 28.02°, 29.14° and 37.66°.

And the PXRD patterns of these cocrystals were also calculated by using single crystal X-ray crystallography and the data are given in Figure S5. It can be seen that the calculated PXRD data of single crystal crystallography are consistent with the experiment data, except that the intensity of some diffraction peaks is slightly different, which confirms the accuracy and reliability of the single crystal structure data.



Figure S5. Comparison of the PXRD patterns of cocrystals (CCDC) simulated by single crystal crystallography and the PXRD patterns of cocrystals obtained by experiments. a) MC_U, b) OC_U, c) MC_PP, d) OC_PP, e) PC_PP and f) PC_OXA, respectively.



Figure S6. The FTIR spectra of cocrystals, a) MC_U, b) OC_U, c) PC_OXA, d) MC_PP, e) OC_PP and f) PC_PP, respectively.



Figure S7. The Raman spectra of cocrystals, a) MC_U, b) OC_U, c) MC_PP, d) OC PP, e) PC PP, and f) PC OXA, respectively.

Figure S6 and Figure S7 display the solid FTIR spectra and Raman spectra of cocrystals and monomers, respectively. And the formation of neutral H-bonding between isomers and coformers in cocrystals can be confirmed by both FTIR and Raman data. Taking FTIR data as an example, there is obvious H-bonding in the cocrystals formed by cresols and coformers. Under the influence of H-bonding, the O-H stretching vibration (v(O-H)) of MC/OC in MC_U cocrystal and OC_U cocrystal red shift from 3312 cm⁻¹ and 3314 cm⁻¹ to 3210 cm⁻¹ and 3199 cm⁻¹, respectively. While, the N-H stretching vibration (v(N-H)) of U in MC_U cocrystal blue shift from 3435 cm⁻¹ to 3442 cm⁻¹,

respectively. The C=O stretching vibration (v(C=O)) of U in OC_U cocrystal red shift from 1679 cm⁻¹ to 1653 cm⁻¹. And in the PC_OXA cocrystal, the O-H bending vibration (δ (O-H)) of OXA red shift from 1393 cm⁻¹ to 1378 cm⁻¹, while the O-H bending vibration (δ (O-H)) of PC blue shift from 1434 cm⁻¹ to 1445 cm⁻¹. In the MC_PP/OC_PP/PC_PP cocrystals, the N-H stretching vibration (v(N-H)) of PP blue shift from 3123 cm⁻¹ to 3279/3278/3280 cm⁻¹, respectively, while the O-H stretching vibration (v(O-H)) of MC/OC/PC red shift from 3312/3314/3309 cm⁻¹ to 3279/3278/3280 cm⁻¹, respectively.

Because of the complementarity between Raman spectrum and IR spectrum, there is no further discussion on Raman data.



S2.2. 2D Long-range synthon Aufbau modules (LSAMs (2D))

Figure S8. Asymmetric unit and atom numbering scheme of MC_U (1:1), OC_U (2:2), MC_PP (2:1), OC_PP (2:1), PC_PP (1:1) and PC_OXA (2:1) cocrystals, respectively, showing the intermolecular H-bonding (light blue dashed line). (C: grey; H: white; O: red; N: blue)



Figure S9. 2D LSAMs of cocrystals, a) MC_U, b) OC_U, c) MC2_PP, d) OC2_PP, e) PC_PP and f) PC_OXA, respectively. The molecules are coloured by symmetry equivalence.

S2.3.	Crystal	lograph	ic in	formation	tables
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	MC_U	OC_U	PC_OXA	
Chemical formula	$CH_4N_2O \cdot C_7H_8O$	CH ₄ N ₂ O·C ₇ H ₈ O	C ₇ H ₈ O·CHO ₂	
Mr	168.20	168.20	153.15	
Crystal system, space group	Orthorhombic, Pbca	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	
Temperature (K)	123	200	160	
a, b, c (Å)	11.2502 (5) 7.1880 (4) 21.7868 (15)	7.4001 (1) 26.1446 (6) 10.7253 (2)	17.4483 (6) 6.0743 (2) 7.2533 (2)	
eta (°)		93.977 (1)	96.229 (3)	
$V(\text{\AA}^3)$	1761.81 (17)	2070.06 (7)	764.21 (4)	
Ζ	8	8	4	
Radiation type	Μο <i>Κ</i> α	Cu Ka	Cu Ka	
$\mu (mm^{-1})$	0.09	0.65	0.86	
Crystal size (mm)	$0.2\times0.15\times0.15$	$0.05\times0.05\times0.05$	0.2 imes 0.2 imes 0.04	
Data collection				
Diffractometer	SuperNova, Single source at offset, Eos	ROD, Synergy Custom system, HyPix		
Absorption correction		Multi-scan		
T_{\min}, T_{\max}	0.382, 1.000	0.818, 1.000	0.593, 1.000	
No. of measured, independent and observed reflections	4033, 1552, 1214	20209, 4152, 2714	6955, 1491, 1301	
$R_{\rm int}$	0.030	0.048	0.043	
$(\sin \theta / \lambda)_{max} (\text{\AA}^{-1})$	0.595	0.633	0.625	
Refinement				
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.055, 0.147, 1.10	0.052, 0.165, 1.04	0.045, 0.104, 1.05	
No. of reflections	1552	4152	1491	
No. of parameters	111	259	122	
H-atom treatment	constrained	independent and con	strained refinement	
$\Delta \rho_{max}, \Delta \rho_{min} (e \text{ Å}^{-3})$	0.21, -0.22	0.33, -0.25	0.26, -0.20	
CCDC number	1541360			

Table S1. Crystallographic information for the cocrystals

	MC_PP	OC_PP	PC_PP		
Chemical formula	$C_{18}H_{26}N_2O_2$	$C_{18}H_{26}N_2O_2$	$C_{11}H_{18}N_2O$		
Mr	302.41	302.41	194.27		
Crystal system, space group	Orthorhombic, Pbca	Monoclinic, $P2_1/n$	Orthorhombic, $P2_12_12_1$		
Temperature (K)	113	133	113		
	5.5482 (17)	5.6352 (8)	5.9035 (10)		
<i>a</i> , <i>b</i> , <i>c</i> (Å)	12.167 (3)	13.4281 (17)	8.3771 (16)		
	24.556 (6)	11.2825 (15)	21.980 (4)		
β (°)		93.703 (3)			
$V(Å^3)$	1657.6 (8)	852.0 (2)	1087.0 (3)		
Ζ	4	2	4		
Radiation type	Μο <i>Κ</i> α	Μο Κα	Μο <i>Κ</i> α		
μ (mm ⁻¹)	0.08	0.08	0.08		
Crystal size (mm)	$0.20\times0.18\times0.12$	$0.20\times0.18\times0.12$	$0.20\times0.18\times0.12$		
Data collection					
Diffractometer	Rigaku XtaLAB P200				
Absorption correction	Multi-scan REQAB (Rigaku, 1998)				
T_{\min}, T_{\max}	0.984, 0.991	0.985, 0.991	0.985, 0.991		
No. of measured, independent and observed reflections	14815, 1882, 1509	8549, 1950, 1756	13953, 2501, 2450		
$R_{\rm int}$	0.053	0.038	0.015		
$(\sin \theta / \lambda)_{max} (\text{\AA}^{-1})$	0.651	0.651	0.650		
Refinement					
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.044, 0.124, 1.06	0.041, 0.126, 1.07	0.027, 0.076, 1.07		
No. of reflections	1882	1950	2501		
No. of parameters	105	106	140		
H-atom treatment	independe	ent and constrained ref	inement		
$\Delta \rho_{max}, \Delta \rho_{min} (e \text{ Å}^{-3})$	0.27, -0.19	0.26, -0.24	0.19, -0.17		
CCDC number	1906693	1907006	1907017		

 Table S1. Crystallographic information for the cocrystals (continuation)

	D-H…A	<i>d</i> (D-H)	<i>d</i> (H…A)	$d(D \cdots A)$	∠(DHA)	symop_for_A
MC_U	O(11)-H(11)····O(1)	0.82	1.91	2.710(2)	164	1/2+x,y,1/2-z
	N(3)-H(3A)···O(1)	0.86	2.07	2.929(2)	172.5	1/2+x,y,1/2-z
	N(4)-H(4A)…O(1)	0.86	2.09	2.946(2)	171.5	1-x,1/2+y,1/2-z
	N(3)-H(3B)…O(11)	0.86	2.20	2.969(2)	148.5	x,y,z
	N(4)-H(4B)…O(11)	0.86	2.26	3.009(2)	146	x,y,z
OC_U	O(1)-H(1)····O(2)	0.89(3)	1.83(3)	2.721(2)	174(3)	x,y,z
	O(4)-H(4)····O(3)	0.90(3)	1.82(3)	2.717(2)	177(3)	x,1.5-y,1/2+z
	N(3)-H(3B)…O(1)	0.92(2)	2.16(2)	3.002(2)	152(2)	x,1.5-y,-1/2+z
	N(4)-H(4B)…O(1)	0.92(2)	2.24(2)	3.070(2)	149(2)	x,1.5-y,-1/2+z
	N(1)-H(1A)····O(4)	0.88(3)	2.29(3)	3.077(2)	149(2)	x,1.5-y,1/2+z
	N(2)-H(2B)…O(4)	0.93(2)	2.17(2)	3.009(2)	150(2)	x,1.5-y,1/2+z
	N(3)-H(3A)····O(3)	0.91(2)	2.08(2)	2.985(2)	174(2)	x,y,z
	N(4)-H(4C)O(3)	0.91(2)	2.10(2)	3.010(2)	173(2)	x,y,z
	N(2)-H(2A)····O(2)	0.90(2)	2.08(2)	2.978(2)	176(2)	x,y,z
	N(1)-H(1B)O(2)	0.88(3)	2.14(3)	3.013(2)	176(2)	1+x,y,z
MC_PP	O(1)-H(1D)…N(1)	0.84	1.86	2.679(2)	164.5	x,y,z
	N(1)-H(1)…π	0.89(1)	2.46	-	-	-
OC_PP	O(1)-H(1A)…N(1)	0.84	1.89	2.715(1)	168.7	1+x,y,z
	N(1)-H(1)…π	0.88(1)	2.44	-	-	-
PC_PP	O(1)-H(1D)…N(1)	0.87(1)	1.83(2)	2.684(1)	167(1)	x,y,z
	$N(1)-H(1)\cdots N(2)$	0.90(1)	2.15(1)	3.038(1)	170(1)	x,y,z
	N(2)-H(2)…π	0.89(1)	2.43	-	-	-
PC_OXA	O(1)-H(1)····O(3)	0.88(2)	1.85(2)	2.733(1)	175(2)	x,-1+y,z
	O(2)-H(2A)····O(1)	0.96(2)	1.68(2)	2.633(2)	170(2)	x,y,z

Table S2. H-bonding information for these cocrystals

S2.4. Structure consistency



Figure S10. Structure consistency of MC_U (left) ^[S1] and OC_U (right). a)/A) 3D supramolecular crossed layers. b)/B) H-bonding interactions between adjacent and crossed layers. c)/C) Two molecular channels. d)/D) The corrugated urea layers. e)/E) Some weak intermolecular interactions.

S2.5. Binding studies in solution

¹H NMR (MC, 500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 9.23 (s, 1H; OH), 7.03 (dd, 1H; =CH-), δ = 6.56 (mm, 3H; =CH-), 2.21 ppm (s, 3H; CH₃).

¹H NMR (OC, 500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 9.22 (s, 1H; OH), 6.98 (m, 2H; =CH-), δ = 6.76 (dd, 1H; =CH-), δ = 6.67 (td, 1H; =CH-), 2.11 ppm (s, 3H; CH₃).

¹H NMR (PC, 500 MHz, [D₆]DMSO, 25 °C, TMS): *δ* = 9.09 (s, 1H; OH), 7.00 (mm, 2H; =CH-), *δ* = 6.59 (mm, 2H; =CH-), 2.18 ppm (m, 3H; CH₃).

¹H NMR (Urea, 500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 5.42 ppm (s, 4H; NH₂).

¹H NMR (OXA, 500 MHz, [D₆]DMSO, 25 °C, TMS): $\delta = 11 \sim 16$ ppm (s, 2H; COOH). The peak of H (active H) in carboxyl group was broadened, and the shape of peak was gentle and was even extended to the baseline of the spectrum.



Figure S11. The concentration-dependent ¹H NMR data in DMSO-d6. a) MCU cocrystals, b) OCU cocrystals, c) PC+U, d) MC+OXA, e) OC+OXA and f) PCOXA coceystals, respectively.

¹H NMR (MC_U, 500 MHz, [D₆]DMSO, 25 °C, TMS): *δ* = 9.21~9.27 (s, 1H; OH), 7.03 (t, 1H; =CH-), *δ* = 6.56 (dt, 3H; =CH-), *δ* = 5.42 (s, 4H; NH₂),2.21 ppm (s, 3H; CH₃).

¹H NMR (OC_U, 500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 9.23~9.26 (s, 1H; OH), 6.84 (m, 4H; =CH-), δ = 5.40 (s, 4H; NH₂), 2.14 ppm (s, 3H; CH₃).

¹H NMR (PC+U, 500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 9.10~9.12 (s, 1H; OH), 7.01 (m, 2H; =CH-), δ = 6.57 (m, 2H; =CH-), δ = 5.50 (s, 4H; NH₂), 2.14 ppm (s, 3H; CH₃). Because "MC+OXA", "OC+OXA" and "PC_OXA" contain active hydrogen, and the peak of active hydrogen is extended, it is not easy to perform quantitative analysis.



Figure S12. The concentration-dependent ¹H NMR data of MC in DMSO-d6.

S2.6. Selective cocrystallization of cresol mixtures with CCFs



Figure S13. PXRD patterns of cocrystal products. a) MC_U cocrystals, and b) PC_OXA cocrystals.



Figure S14. Micrographs of cocrystal products' morphology. a) MC_U, and b) PC_OXA, respectively.





Figure S15. GC results of the cocrystals obtained from cresol mixtures by using different selective CCFs (U or OXA). The purity of MC (a) MC_U-1, b) MC_U-3) and/or PC (c) PC_OXA) is above 99.5%. However, due to the smaller crystal size of PC_OXA cocrystals, MC in mother liquor is usually contained, which reduces the purity of PC.





Figure S16. PXRD patterns of solid of Cresol+U (a)) and Cresol+OXA (b)) obtained from milling reaction, respectively. The selective cocrystallization in solid state was confirmed.

S2.8. Additional CCFs



Figure S17. PXRD patterns of solids of a) Cresol+TU, b) Cresol+MAA, and c) Cresol+OXA obtained from milling reaction, respectively. No cocrystals formed.

S2.9. Additional selective cocrystals



Figure S18. PXRD patterns of solids of (2, 3, 4-) pyridinecarboxamide isomers and IMZ obtained from NG and/or LAG reaction, respectively. a) 2PCAD can form cocrystals with IMZ, while b) 3PCAD with IMZ and c) 4PCAD with IMZ are both physical mixtures. Namely, IMZ can selectively cocrystalize with 2PCAD. ($\mathbf{0}$: New peaks of cocrystal different from raw compounds, \blacklozenge : Peaks of coformer IMZ, and \aleph : Peaks of (2, 3, 4-) pyridinecarboxamide isomers, respectively.)

Figure S18 shows the PXRD patterns of solids of (2, 3, 4-) pyridinecarboxamide isomers and IMZ obtained from NG and/or LAG reaction, respectively. It can be seen that the black curves shown in b) and c) are the sum of the red and blue curves, which means that IMZ and 3PCAD or 4PCAD formed a physical mixture after grinding, respectively. On the other hand, new different peaks from raw compounds appear on the black curve shown in Figure S18a), located at (2θ) 8.84°, 11.78°, 15.48°,17.70°, 19.40°, 23.74°, 28.11°, respectively, as shown on the black curve by the mark " \mathbf{O} ".



Figure S19. The DSC curves of solids of (2, 3, 4-) pyridinecarboxamide isomers and IMZ obtained from NG and/or LAG reaction, respectively. Different endothermic peaks correspond to different physical processes: Peaks 1 to 7 represent the melting of IMZ+2PCAD cocrystal, IMZ+3PCAD eutectic, IMZ+4PCAD eutectic, IMZ monomer, 2PCAD monomer, 3PCAD monomer and 4PCAD monomer, respectively.



Figure S20. PXRD patterns of solids of *cis-/trans-* buteneic acid and TU obtained from NG and/or LAG reaction, respectively. a) ML can form cocrystals with TU, while b) FM with TU is physical mixture. Namely, TU can selectively cocrystalize with ML. (\mathbf{O} : New peaks of cocrystal different from raw compounds, $\mathbf{\diamond}$: Peaks of coformer TU, and $\mathbf{\kappa}$: Peaks of *cis-/trans-* buteneic acid, respectively.)

Figure S20 shows the PXRD patterns of solids of *cis-/trans-* buteneic acid and TU obtained from NG and/or LAG reaction, respectively. It can be seen that the black curve shown in Figure S20b) is the sum of the red and blue curves, which means that TU and FM formed a physical mixture after grinding. Although compared with the blue curve, the black curve in Figure S20b) shows a deviation to the high diffraction angle, no new diffraction peak appears. This is caused by the reduction of the TU unit cell due to grinding. On the other hand, new different peaks from raw compounds appear on the

black curve shown in Figure S20a), located at (2θ) 14.37°, 14.84°, 16.21°,18.78°, 24.19°, 37.68°, respectively, as shown on the black curve by the mark " \mathbf{O} ".



Figure S21. The DSC curves of solids of *cis-/trans-* buteneic acid and TU obtained from NG and/or LAG reaction, respectively. Different endothermic peaks correspond to different physical processes: Peaks 1 to 3 represent the melting of TU+ML cocrystal, TU monomer and TU in TU+FM mixture; Peaks 3 to 6 represent the decomposition process of TU in TU+FM mixture, ML monomer, ML in TU+ML cocrystal, and FM in TU+FM mixture, respectively. And the exothermic peak 7 to 10 represent the decomposition process of TU in TU+ML cocrystal, TU monomer, respectively.

	Table S3. The lattice parameters of the monomers					
Monomers	Crystal system, pace group	<i>a</i> , <i>b</i> , <i>c</i> (Å)	β (°)			
	Manaalinia	16.42 (3)				
2PCAD	P2 / a	7.11 (2)	100.2 (2)			
	$\Gamma \Sigma_1/a$	5.19 (2)				
		3.975 (5)				
3PCAD	Monoclinic	15.632 (8)	99.03 (7)			
	$P2_1/c$	9.422 (4)				
		9.8880 (12)				
4PCAD	Orthorhombic	7.9929 (9)				
	$Pca2_1$	15.1620 (18)				
		7.732 (4)				
IMZ	Monoclinic	5.458 (2)	117.26 (3)			
	$P2_1/c$	9.779 (4)				
		7.619				
FM	Monoclinic	15.014	112.0			
	$P2_{1}/c$	6.686				
		7.47(1)				
ML	Monoclinic	10.15 (1)	123.5			
	$P2_{1}/c$	7.65 (1)				
		7.5791 (9)				
TU	Orthorhombic	8.533 (8)				
	Pnma	5.4655 (4)				



Figure S22. Comparison of the PXRD patterns of monomers (CCDC) simulated by single crystal crystallography and the PXRD patterns of products obtained by experiments. a) 2PCAD and IMZ+2PCAD, b) 3PCAD and IMZ+3PCAD, c) 4PCAD and IMZ+4PCAD, and d) IMZ, respectively.



Figure S23. Comparison of the PXRD patterns of monomers (CCDC) simulated by single crystal crystallography and the PXRD patterns of products obtained by experiments. a) ML and TU+ML, b) FM and TU+FM, and c) TU, respectively.

From Figure S22 and S23, it can be seen that the PXRD patters of monomers simulated by single crystal crystallography are basically the same as the experimental PXRD patterns. And compared with the simulated PXRD patterns, the grinding products have new characteristic diffraction peaks. Therefore, we can conclude that new products different from the starting monomers are formed.

CCDC numbers

MC_U cocrystal: 1541360

OC_U cocrystal: 2024768

PC_OXA cocrystal: 2024770

MC_PP cocrystal: 1906693

OC_PP cocrystal: 1907006

PC_PP cocrystal: 1907017

References

[S1] N. Wang, H. Hao, H. Lu, R. Xu, CrystEngComm 2017, 19, 3746-3752.