

ELECTRONIC SUPPLEMENTARY INFORMATION for:

Halogen-Bonded Cocrystals via Resonant Acoustic Mixing

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Table S1. $^{13}\text{C}[^1\text{H}]$ CPMAS solid-state NMR experimental conditions. S22

1: **1a(i)**, (*p*-DITFB)₂(TMP)¹:

1-1: RAM mechanochemistry synthesis

241 mg (0.5 mmol) 1,4-diiidotetrafluorobenzene (*p*-DITFB) as halogen bond donor, 82 mg (0.5 mmol) 2,3,5,6-tetramethylpyrazine (TMP) as an acceptor, and 260 μ L chloroform were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

1.2: Ball milling preparation

The halogen bond donor, *p*-DITFB (241 mg, 0.5 mmol), and the halogen bond acceptor, TMP (82 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, with 50 μ L of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

1.3: PXRD results

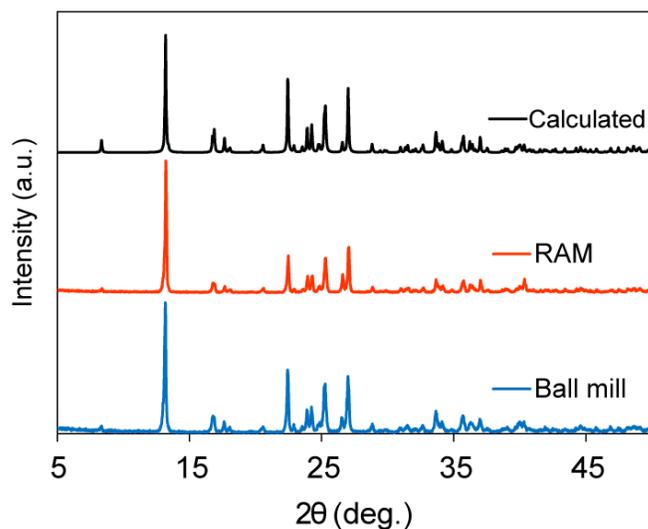


Figure S1. Experimental diffractograms for ball milled and RAM products, and calculated diffractogram for cocystal **1a(i)**, (*p*-DITFB)₂(TMP).

1-3: ^{13}C CP/MAS SSNMR results

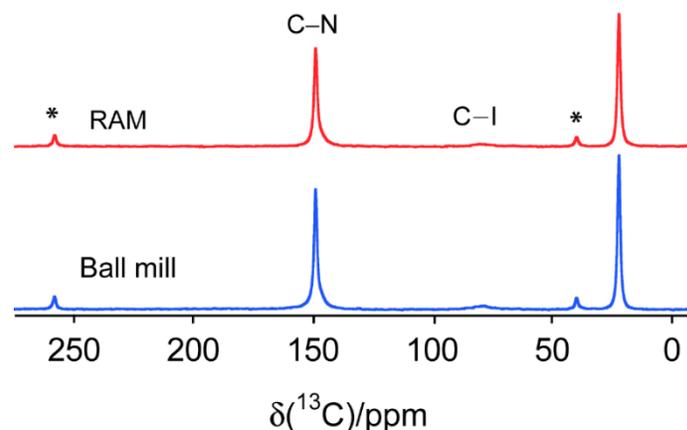


Figure S2. ^{13}C solid-state NMR spectra of cocrystal **1a(i)**, (*p*-DITFB).2(TMP): the ball mill product is depicted in blue (lower); RAM product in red (upper). The labels denote the C-N and C-I carbons of TMP and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

2: **1a(ii)**, 4(*p*-DITFB)·1.5(TMP)²

2.1: RAM mechanochemistry synthesis

402 mg (1 mmol) 1,4-diodotetrafluorobenzene (*p*-DITFB) as halogen bond donor and 68 mg (0.5 mmol) 2,3,5,6-tetramethylpyrazine (TMP) as an acceptor were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 45 minutes at an acceleration of 80g.

2.2: PXRD results

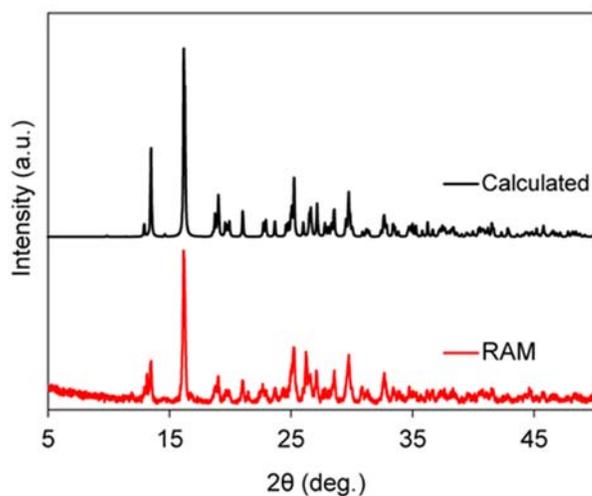


Figure S3. Diffractogram for the RAM product, and calculated diffractogram for cocrystal **1a(ii)**, 4(*p*-DITFB)·1.5(TMP).

2.3: ^{13}C CP/MAS SSNMR results

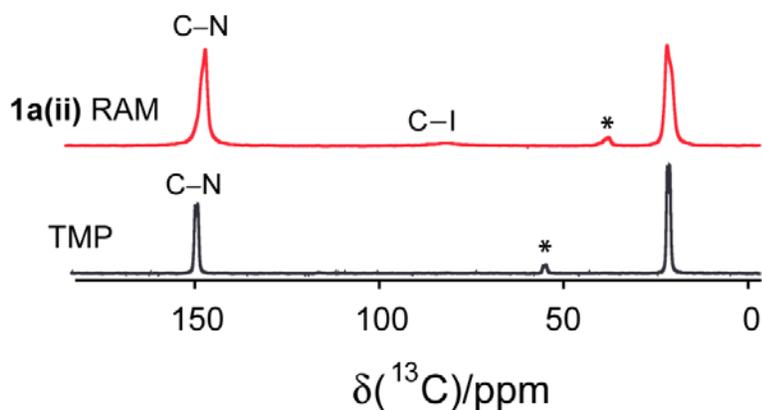


Figure S4. ^{13}C solid-state NMR spectra of XB acceptor TMP in black (lower) and cocrystal **1a(ii)**, 4(*p*-DITFB):1.5(TMP), prepared by RAM in red (upper). The labels denote the C-N and C-I carbons of TMP and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

3: **2a**, (*sym*-TFTIB):(TMP)³

3.1: RAM mechanochemistry synthesis

357 mg (0.7 mmol) 1,3,5-trifluoro-2,4,6-triiodobenzene (*sym*-FTIB) as halogen bond donor, 95 mg (0.7 mmol) 2,3,5,6-tetramethylpyrazine (TMP) as an acceptor, and 45 μL THF were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

3.2: Ball milling preparation

The halogen bond donor, *sym*-TFTIB (357 mg, 0.7 mmol), and the halogen bond acceptor, TMP (95 mg, 0.7 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 23 μL of THF as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 40 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

3.3: PXRD results

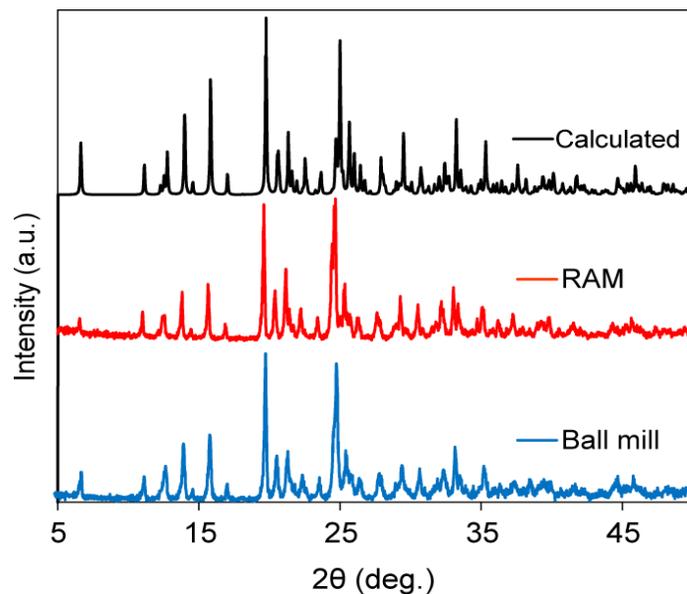


Figure S5. Diffractograms for ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **2a**, (*sym*-TFTIB)(TMP).

3.4: ^{13}C CP/MAS SSNMR results

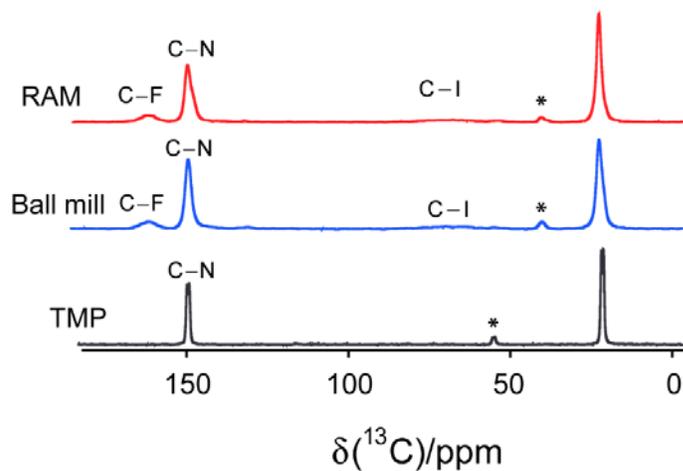


Figure S6. ^{13}C solid-state NMR spectra of XB acceptor TMP in black (lower) and cocrystal **2a**, (*sym*-TFTIB)(TMP), prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N carbons of TMP, and C-I and C-F carbons of *sym*-TFTIB. The asterisks denote spinning sidebands.

4: **1b**, (*p*-DITFB) \cdot 2(DMAP)⁴

4.1: RAM mechanochemistry synthesis

321 mg (0.8 mmol) 1,4-diodotetrafluorobenzene (*p*-DITFB) as halogen bond donor and 196 mg (1.6 mmol) 4-dimethylaminopyridine (DMAP) as an acceptor were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 45 minutes at an acceleration of 80g.

4.2: Ball milling preparation

The halogen bond donor, *p*-DITFB (321 mg, 0.8 mmol), and the halogen bond acceptor, DMAP (196 mg, 1.6 mmol), were combined in a 10 mL stainless steel milling jar. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 30 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

4.3: PXRD results

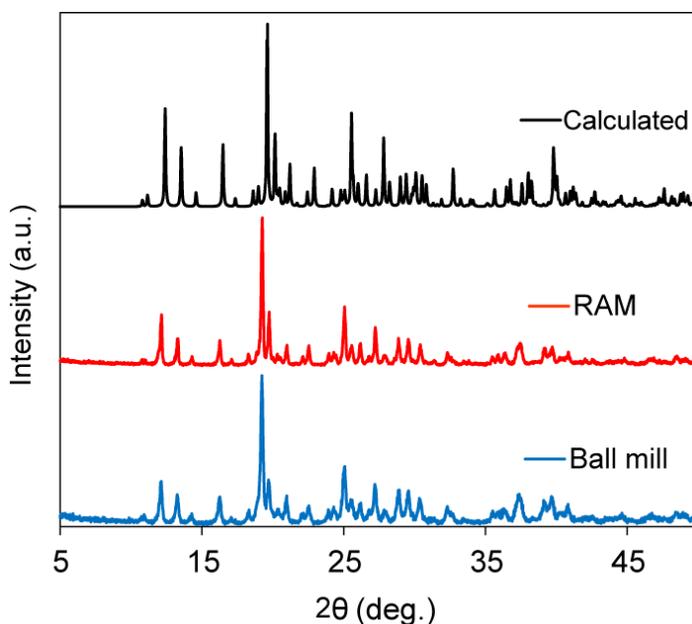


Figure S7. Diffractograms for ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **1b**, (*p*-DITFB) \cdot 2(DMAP).

4.4: ^{13}C CP/MAS SSNMR results

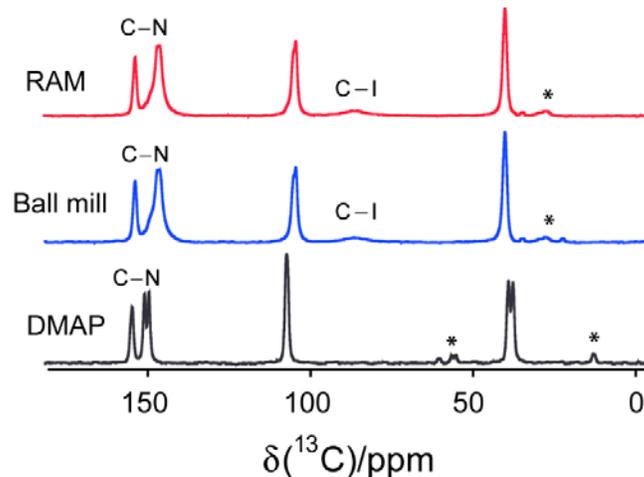


Figure S8. ^{13}C solid-state NMR spectra of XB acceptor DMAP in black (lower) and cocrystal **1b**, (*p*-DITFB)₂(DMAP) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N and C-I carbons of DMAP and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

5: **2b**, (*sym*-TFTIB)₃(DMAP)⁵

5.1: RAM mechanochemistry synthesis

255 mg (0.5 mmol) 1,3,5-trifluoro-2,4,6-triiodobenzene (*sym*-TFTIB) as halogen bond donor and 183 mg (1.5 mmol) 4-dimethylaminopyridine (DMAP) as an acceptor were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

5.2: Ball milling preparation

The halogen bond donor, *sym*-TFTIB (255 mg, 0.5 mmol), and the halogen bond acceptor, DMAP (183 mg, 1.5 mmol), were added to a 10 mL stainless steel milling jar. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

5.3: PXRD results

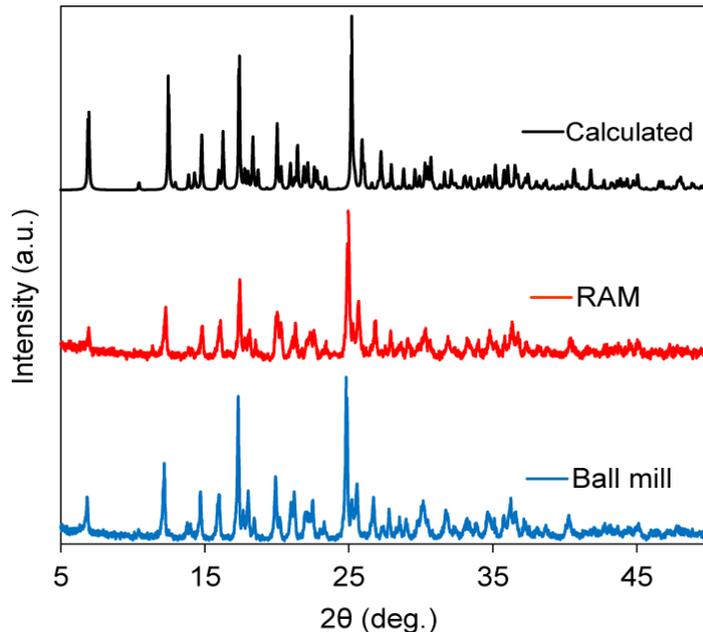


Figure S9. Diffractograms for ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **2b**, (*sym*-TFTIB)₃(DMAP).

5.4: ¹³C CP/MAS SSNMR results

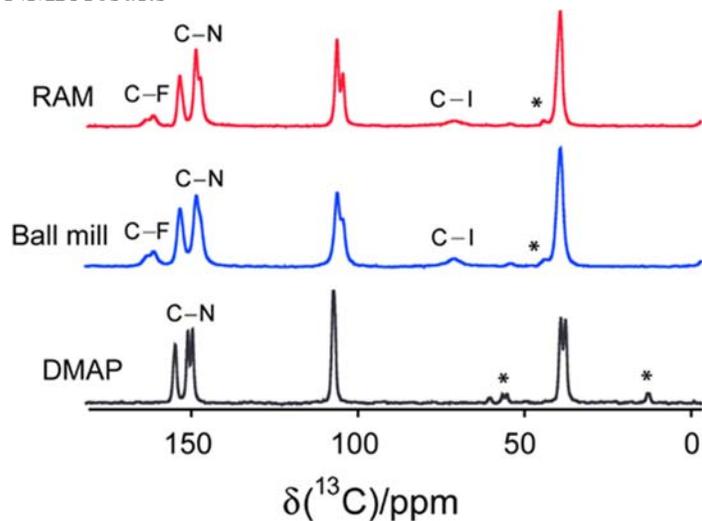


Figure S10. ¹³C solid-state NMR spectra of XB acceptor DMAP in black (lower) and cocrystal **2b**, (*sym*-TFTIB)₃(DMAP) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N carbons of DMAP, and C-I and C-F carbons of *sym*-TFTIB. The asterisks denote spinning sidebands.

6: **1c**, **2**(*p*-DITFB).(o-Phe)¹

6.1: RAM mechanochemistry synthesis

321 mg (0.8 mmol) 1,4-diiodotetrafluorobenzene (*p*-DITFB) as halogen bond donor, 196 mg (1.6 mmol) 1,10-phenanthroline (o-Ph) as acceptor, and 35 μ L chloroform were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

6.2: Ball milling preparation

The halogen bond donor, *p*-DITFB (241 mg, 0.6 mmol), and the halogen bond acceptor, o-Ph (108 mg, 0.6 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 18 μ L of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

6.3: PXRD results

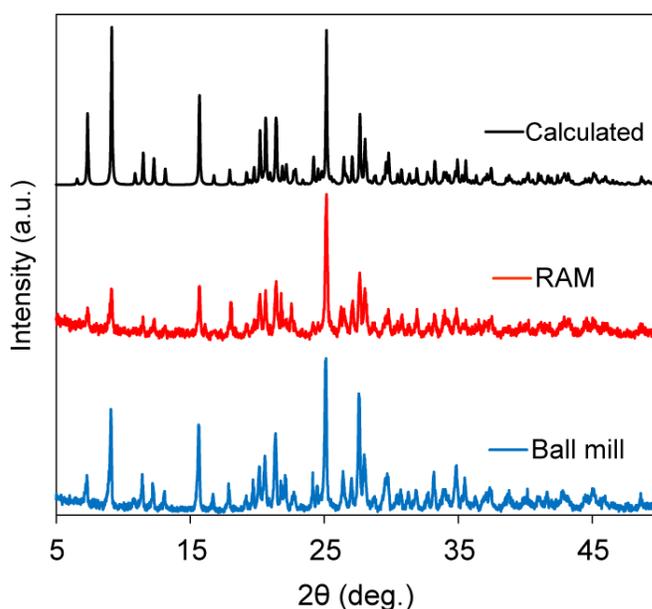


Figure S11. Diffractograms of ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **1c**, **2**(*p*-DITFB).(o-Phe).

6.4: ^{13}C CP/MAS SSNMR results

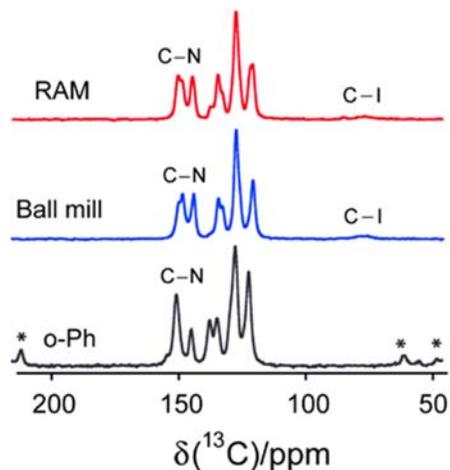


Figure S12. ^{13}C solid-state NMR spectra of XB acceptor o-Phe in black (lower) and cocrystal **1c**, 2(*p*-DITFB):(o-Phe) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N and C-I carbons of o-Phe and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

7: **2c**, (*sym*-TFTIB):(o-Phe)³

7.1: RAM mechanochemistry synthesis

255 mg (0.5 mmol) 1,3,5-trifluoro-2,4,6-triiodobenzene (*sym*-TFTIB) as halogen bond donor, 90 mg (0.5 mmol) 1,10-phenanthroline (o-Ph) as acceptor, and 35 μL THF were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

7.2: Ball milling preparation

The halogen bond donor, *sym*-TFTIB (255 mg, 0.5 mmol), and the halogen bond acceptor, o-Ph (90 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 18 μL of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

7.3: PXRD results

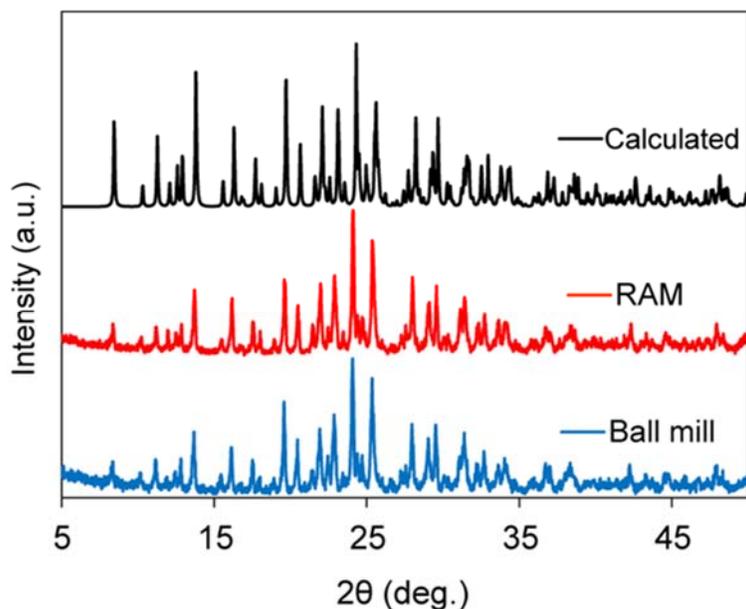


Figure S13. Diffractograms of ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **2c**, (*sym*-TFTIB) \cdot (*o*-Phe).

7.4: ^{13}C CP/MAS SSNMR results

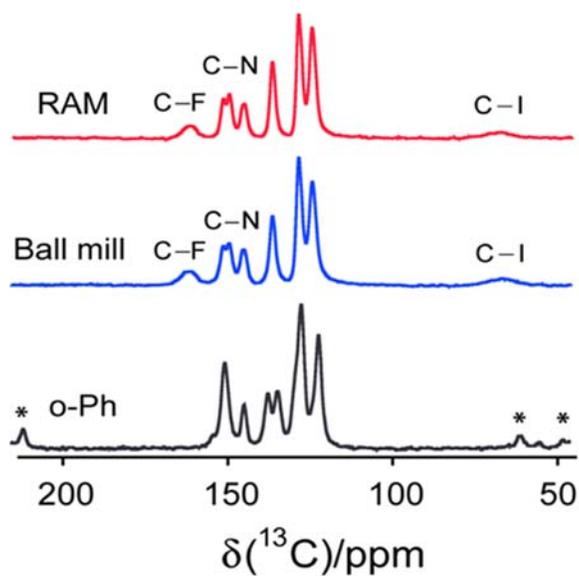


Figure S14. ^{13}C solid-state NMR spectra of XB acceptor *o*-Phe in black (lower) and cocrystal **2c**, (*sym*-TFTIB) \cdot (*o*-Phe) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N carbons of *o*-Phe, and C-I and C-F carbons of *sym*-TFTIB. The asterisks denote spinning sidebands.

8: **1d**, (*p*-DITFB)(PheDON)⁶

8.1: RAM mechanochemistry synthesis

205 mg (0.5 mmol) 1,4-diiodotetrafluorobenzene (*p*-DITFB) as halogen bond donor, 105 mg (0.5 mmol) 1,10-phenanthroline-5,6-dione (PheDON) as acceptor, and 155 μ L chloroform were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

8.2: Ball milling preparation

The halogen bond donor, *p*-DITFB (205 mg, 0.5 mmol), and the halogen bond acceptor, PheDON (105 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 31 μ L of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 30 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

8.3: PXRD results

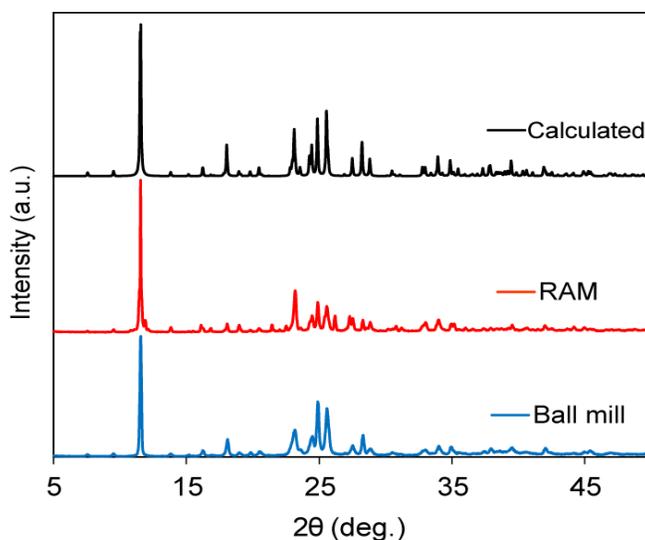


Figure S15. Diffractograms of ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **1d**, (*p*-DITFB)(PheDON).

8.4: ^{13}C CP/MAS SSNMR results

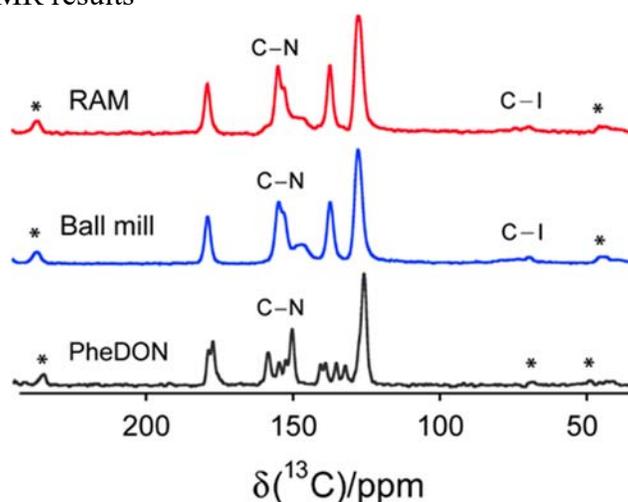


Figure S16. ^{13}C solid-state NMR spectra of XB acceptor o-Phe in black (lower) and cocrystal **1d**, (*p*-DITFB):(PheDON) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N and C-I carbons of PheDON and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

9: **2d**, (*sym*-TFTIB):(PheDON)

9.1: RAM mechanochemistry synthesis

205 mg (0.5 mmol) 1,3,5-trifluoro-2,4,6-triiodobenzene (*sym*-TFTIB) as halogen bond donor, 105 mg (0.5 mmol) 1,10-phenanthroline-5,6-dione (PheDON) as acceptor, and 250 μL chloroform were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

9.2: Ball milling preparation

The halogen bond donor, *sym*-TFTIB (205 mg, 0.5 mmol), and the halogen bond acceptor, PheDON (105 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 31 μL of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

9.3: Crystal preparation by slow evaporation:

The halogen bond donor, *sym*-TFTIB (76 mg, 0.15 mmol), was dissolved in 2 mL of chloroform. The halogen bond acceptor, PheDON (32 mg, 0.15 mmol), was dissolved in 2 mL of chloroform. The donor solution was added dropwise to the halogen bond acceptor solution. The solvent was allowed to gradually evaporate at room temperature, resulting in the formation of orange cocrystals of **2d**. The vial was tightly sealed as soon as single cocrystals were observed by eye.

9.4: PXRD results

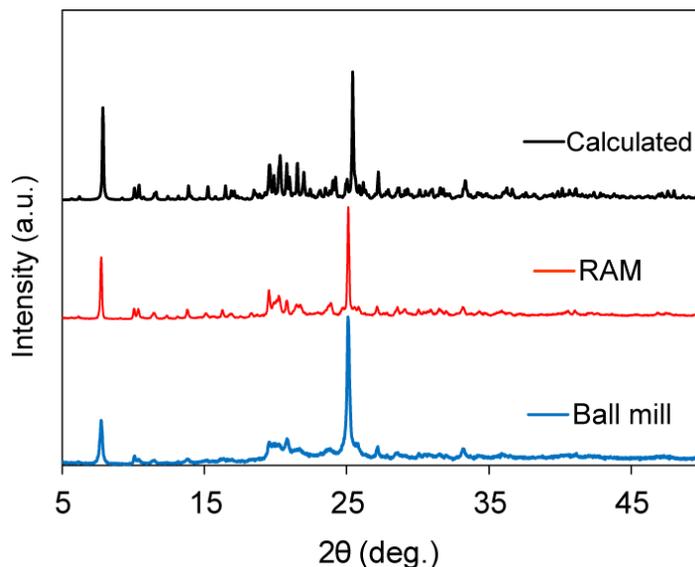


Figure S17. Diffractograms of ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **2d**, (*sym*-TFTIB)(PheDON).

9.5: ^{13}C CP/MAS SSNMR results

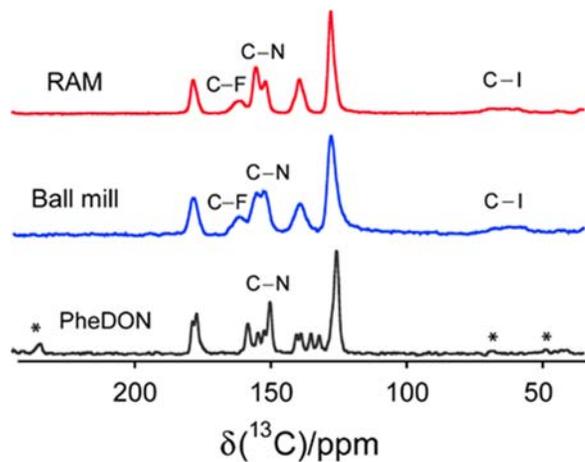


Figure S18. ^{13}C solid-state NMR spectra of XB acceptor o-Phe in black (lower) and cocrystal **2d**, (*sym*-TFTIB)(PheDON) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N carbons of PheDON, and C-I and C-F carbons of *sym*-TFTIB. The asterisks denote spinning sidebands.

10: **1e**, (*p*-DITFB)·(DIZFON)⁶

10.1: RAM mechanochemistry synthesis:

205 mg (0.5 mmol) 1,4-diiodotetrafluorobenzene (*p*-DITFB) as halogen bond donor, 91 mg (0.5 mmol) 4,5-diazafluoren-9-one (DIZFON) as acceptor, and 150 μ L THF were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

10.2: Ball milling preparation

The halogen bond donor, *p*-DITFB (205 mg, 0.5 mmol), and the halogen bond acceptor, DIZFON (91 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 30 μ L of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 30 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

10.3: PXRD results

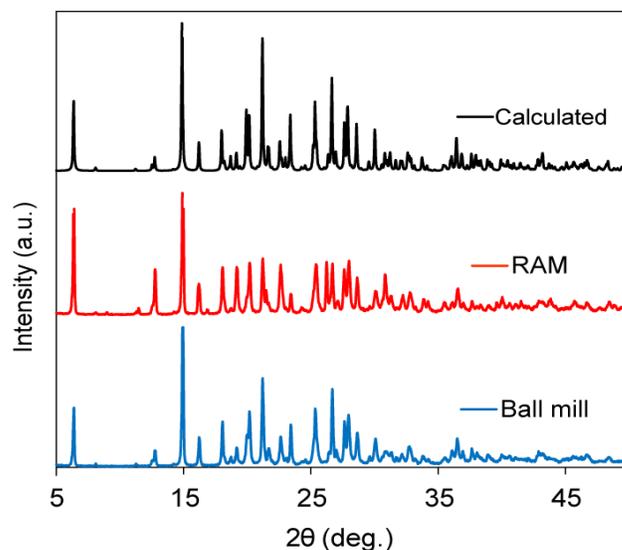


Figure S19. Diffractograms of ball mill and RAM products and calculated powder X-ray diffraction pattern for cocrystal **1e**, (*p*-DITFB)·(DIZFON).

10.4: ^{13}C CP/MAS SSNMR results

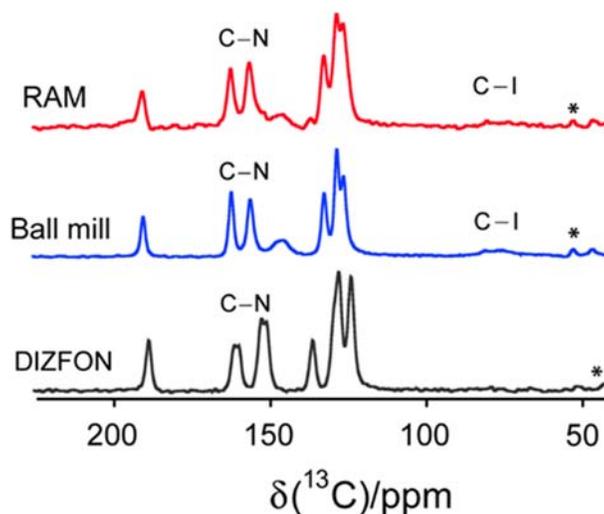


Figure S20. ^{13}C solid-state NMR spectra of XB acceptor o-Phe in black (lower) and cocrystal **1e**, (*p*-DITFB):(DIZFON) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N and C-I carbons of DIZFON and *p*-DITFB, respectively. The asterisks denote spinning sidebands.

11: **2e**, (*sym*-TFTIB):(DIZFON)

11.1: RAM mechanochemistry synthesis

255 mg (0.5 mmol) 1,3,5-trifluoro-2,4,6-triiodobenzene (*sym*-TFTIB) as halogen bond donor, 94 mg (0.5 mmol) 4,5-diazafluoren-9-one (DIZFON) as acceptor, and 223 μL THF were added to a 1-dram glass vial and securely mounted within a lab-built sample holder and positioned on the PharmaRAM 1 resonant acoustic mixer. The sample was oscillated for 50 minutes at an acceleration of 80g.

11.2: Ball milling preparation

The halogen bond donor, *sym*-TFTIB (255 mg, 0.5 mmol), and the halogen bond acceptor, DIZFON (94 mg, 0.5 mmol), were combined in a 10 mL stainless steel milling jar, supplemented with 32 μL of chloroform as a liquid additive. Subsequently, ball milling was conducted using a Retsch MM 400 ball mill at a frequency of 30 Hz for 45 minutes at room temperature. The milling process employed two stainless steel grinding balls with a diameter of 5 mm.

11.3: Crystal preparation by slow evaporation

The halogen bond donor, *sym*-TFTIB (76 mg), was dissolved in 2 mL of chloroform. The halogen bond acceptor, DIZFON (27 mg), was dissolved in 2 mL of chloroform. The donor solution was added dropwise to the acceptor solution. The solvent was allowed to gradually evaporate at room temperature, resulting in the formation of yellow cocrystals of **2e**. The vial was tightly sealed as soon as single cocrystals were observed by eye.

11.4: PXRD results

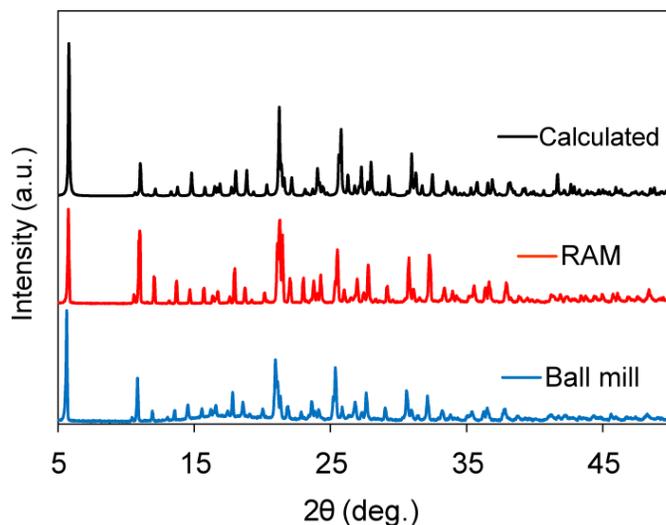


Figure S21. Diffractograms for ball mill and RAM products, and calculated powder X-ray diffraction pattern for cocrystal **2e**, (*sym*-TFTIB):(DIZFON).

11.5: ^{13}C CP/MAS SSNMR results

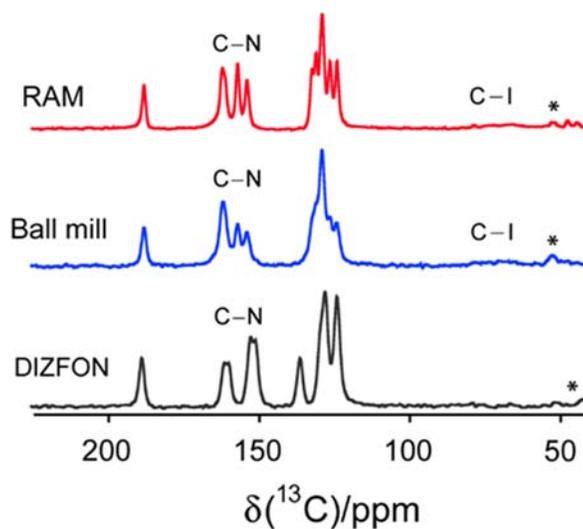


Figure S22. ^{13}C solid-state NMR spectra of XB acceptor DIZFON in black (lower) and cocrystal **2e**, (*sym*-TFTIB):(DIZFON) prepared by ball milling in blue (middle), and by RAM in red (upper). The labels denote the C-N carbons of, and C-I carbons of *sym*-TFTIB. The asterisks denote spinning sidebands.

Table S1. $^{13}\text{C}[^1\text{H}]$ CPMAS solid-state NMR experimental conditions.

compound	number of scans	recycle delay / s	MAS frequency / kHz
a	2048	2	10
1a(i)	1024	30	11
1a(ii)	1024	30	11
2a	1024	30	11
b	2048	30	10
1b	1024	30	12
2b	1024	40	11
c	1024	60	4.5
1c	1024	60	12
2c	1024	90	12
d	512	100	11
1d	2048	30	11
2d	2048	40	12
e	1024	120	11
1e	1024	120	11
2e	1024	80	11

Additional Details on Single-Crystal X-Ray Diffraction for 2d and 2e

Raw data collection and processing were executed utilizing the ApexIII software package developed by Bruker.⁷ Initial unit cell parameters were deduced from 36 data frames obtained from specific ω scans. Semi-empirical absorption corrections, based on equivalent reflections, were applied as part of the data processing.⁸ The systematic absences observed in the diffraction dataset and the unit cell parameters were in line with the assigned space group.

Initial structural solutions were established employing ShelXT direct methods⁹ and subsequently refined using full-matrix least-squares procedures based on F^2 with the assistance of ShelXL and ShelXle software.¹⁰ Hydrogen atom positions were determined based on geometric considerations and further refined using a riding model.

The structure of **2d** (which contains 8 sets of crystallographically unique molecule pairs stacked in layers) is noteworthy as the difference map shows the presence of whole molecule disorder among some of the layers over a mirror plane. Attempts were made to model this behaviour both from a twinning or supercell standpoint, and through modelling of the disorder directly. In the former case, use of RLatt, cell_now, and other twin detection tools did not convincingly show the presence of any twinning. When disorder was modelled directly, the R value and general quality of the structure did not improve, the disorder fraction remained small, and it served only to muddy the interpretation of the structure. Thus the potential disorder was not included in the final model.

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