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Supporting Information

A Halogen-Bond Donor Amino Acid for Organocatalysis in Water

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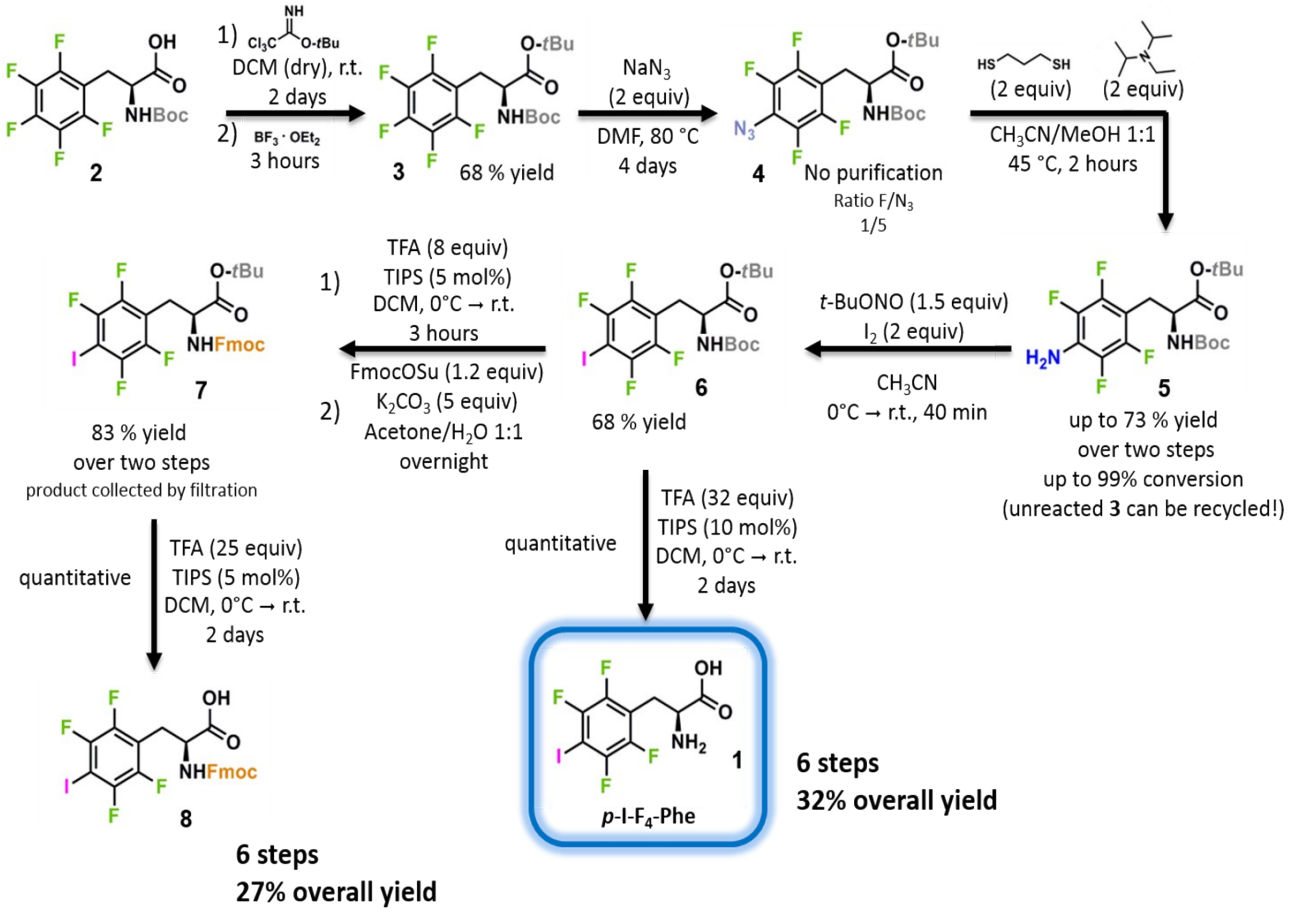
S1. Materials and methods

All reagents were purchased from commercial suppliers (Alfa-Aesar, Sigma-Aldrich, Apollo, Fluorochem) and used without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker ADVANCE 400 spectrometer operating at 9.37 T (400 MHz). ^{19}F chemical shifts are reported in ppm from the haxafluoroisopropanol (–77.3 ppm) resonance as the external standard. DSC analyses were performed using a Mettler Toledo DSC600 instrument. IR spectra were obtained using a Nicolet Nexus FTIR spectrometer equipment with U-ATR device. The product conversions were determined by high-performance liquid chromatography (HPLC), which was performed on a Tri Rotar-VI HPLC, MD-910 multichannel detector (JASCO) using a Phenomenex Jupiter column (90Å, C-18, 1mL/min flow rate). Buffer A composition: 97.5% water, 2.5% acetonitrile, 0.07% TFA. Buffer B composition: 30% water, 70% acetonitrile, 0.07% TFA.

S2. Synthetic procedures

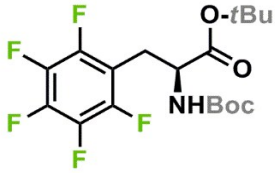
S2.1 Synthesis of the amino acid F(F_4I)

For the synthesis of the unnatural amino acid **F(F_4I)**, we modified the procedure already reported in literature [1], improving the overall yield.



Scheme S.1. Synthetic procedure for **F(F_4I)**.

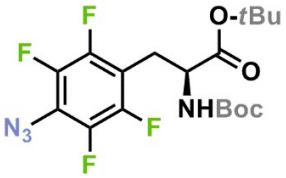
Synthesis of *N*-Boc-pentafluoro-L-phenylalanine tert-butyl ester (3).



Commercially available *N*-Boc-pentafluoro-L-phenylalanine **2** (1500 mg, 4.22 mmol, 1 equiv) was dissolved in dichloromethane (DCM) to have a ≈ 0.1 M solution. To the solution tert-butyl 2,2,2-trichloroacetimidate (1844 mg, 8.44 mmol, 1.510 mL, d= 1.221 g/mL, 2 equiv) was slowly added. The mixture was stirred at r.t. for 2 days and monitored by TLC; the formation of a white solid occurred. Subsequently, $BF_3{\cdot}OEt_2$ was added (90 mg, 0.633 mmol, 78 µL, 1.15 g/mL, 0.15 equiv), and the mixture was stirred for further two hours. Then, the reaction was quenched by adding a $NaHCO_3$ saturated solution (50 mL) and the resulting mixture was extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (Hexane/AcOEt 10:1), yielding 1180 mg of desired compound (68% yield) as a pale thick oil that solidifies to give a white solid (R_f = 0.35 in Hex/AcOEt 10:1, permanganate staining solution).
The synthesis can be scaled up to 3 or 5 g, with a poor drop in yield (62 % vs 68 %). In these cases, it was possible to recover also the unreacted starting material, even in a small extent (≈ 500 mg on the 5g scaled reaction).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.12 (m, 1H, N*H*), 4.44 (m, 1H, C*H*NH), 3.22 (dd, 1H, ^3J = 4.0 Hz, $^2J_{gem}$= 13.5 Hz, PhC*H*H), 3.03 (dd, 1H, ^3J = 7.0 Hz, $^2J_{gem}$= 13.5 Hz, PhCH*H*), 1.45 (s, 9H, COOCCH_3), 1.39 (s, 9H, NCOOCCH_3) ppm; ^{19}F-NMR (475 MHz, $CDCl_3$): δ = -142.9 (dd, 2F, $^3J_{2,3}$ = 22.3 Hz, $^5J_{2,5}$ = 7.6 Hz), -157.1 (t, 1F, $^3J_{4,3}$ = 20.4 Hz), -173.8 (td, 2F, $^3J_{3,4}$ = 20.4 Hz, $^3J_{3,2}$ = 22.3 Hz, $^5J_{3,6}$ = 7.6 Hz) ppm.

Synthesis of *N*-Boc-(4-azido-2,3,5,6-tetrafluoro)-L-phenylalanine tert-butyl ester (4).



In a pyrex tube, dry DMF was purged by nitrogen flux for 15 minutes. Then, compound **3** (4353 mg, 10.6 mmol, 1 equiv, 0.7 M in AA) was dissolved. After complete dissolution, NaN_3 (1378 mg, 21.2 mmol, 2 equiv) was added and the tube was sealed. The resulting solution was immerged in an 80 °C pre-heated bath and stirred at the same temperature for two days; slowly the mixture turns to a brownish colour. The reaction was then poured into water (200 mL) and extracted with chloroform (3 x 100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting waxy brownish solid was used for the next step without any further purification. (R_f = 0.64 in Hex/AcOEt 6:1, permanganate staining solution). Product **4** can be isolated from the reaction mixture to yield c.a. a 78 % yield of white solid, by flash column chromatography eluting with Hex/AcOEt 10:1.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.04 (m, 1H, N*H*), 4.43 (m, 1H, C*H*NH), 3.21 (dd, 1H, ^{3}J = 6.3 Hz, $^{2}J_{gem}$= 14.0 Hz, PhC*H*H), 3.03 (dd, 1H, ^{3}J = 7.8 Hz, $^{2}J_{gem}$= 14.0 Hz, PhCH*H*), 1.46 (s, 9H, COOCCH_3), 1.41 (s, 9H, NCOOCCH_3) ppm; ^{19}F-NMR (475 MHz, $CDCl_3$): δ = -143.2 (dd, 2F, $^{3}J_{2,3}$ = 21.1 Hz, $^{5}J_{2,5}$ = 10.2 Hz), -153.6 (bs, 2F) ppm; IR (ATR): ν = 3390 (w), 3325 (w), 2981 (m), 2937 (w), 2121 (s, diagnostic for N_3 group), 1729 (m), 1656 (w), 1520 (m), 1503 (s), 1492 (s), 1394 (w), 1369 (m), 1283 (w), 1236 (m), 1151 (s), 1123 (m), 1006 (m), 978 (m), 934 (w), 843 (m), 746 (w) cm^{-1}.

SAFETY WARNINGS: Compound **4** is an azide. Organic azides are known to be potentially explosive compounds, whose explosions are caused by frictions, and their handling requires careful consideration of the risks. [2] Please use the following equation for safe organic azide:

$$(N_C+N_O)/N_N > 3$$

where N_C N_O and N_N are respectively the number of carbon, oxygen and nitrogen atoms present in the molecule. In our case compound **4** has a value > 3; nevertheless, since the reaction scale was increased up to a 4.3 g scale, the reaction mixture was treated with special precautions: proper gloves were worn during flask manipulation that may involve frictions (insertion/removal from the rotavapor, use of glass stoppers, connectors or joints…), protective screen during evaporation or extraction step were used. We want to underline that in our laboratory we did not experience any problem in several repeated syntheses.

Synthesis of *N*-Boc-(4-ammino-2,3,5,6-tetrafluoro)-L-phenylalanine tert-butyl ester (5).

The crude compound **4** was dissolved in a 1:1 mixture of MeOH/CH_3CN to have a ≈ 0.15 M solution. To the resulting mixture 1,3-propanedithiol (2294 mg, 21.2 mmol, 2.13 mL, d = 1.076 g/mL, 2 equiv) and *N*,*N*-diisopropylethylamine (2740 mg, 21.2 mmol, 3.69 mL, d = 0.742 g/mL, 2 equiv) were added. A slight effervescence was observed. The reaction was immerged in a 45 °C preheated bath and stirred for two hours. Then the mixture was concentrated, poured in 100 ml of saturated NH_4Cl solution and extracted with DCM (3 x 80 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting waxy brownish solid was purified by flash column chromatography, eluting with a polarity gradient starting from Hexane/AcOEt 15:1 to Hexane/AcOEt 3:1, to give the desired product as a white solid with a 73 % yield (99 % conversion, with possible recovery of unreacted **3**).

(R_f = 0.22 in Hex/AcOEt 5:1, permanganate staining solution). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.07 (d, 1H, ^{3}J = 8.8 Hz N*H*), 4.41 (pq, 1H, C*H*NH), 3.92 (bs, 2H, NH_2), 3.14 (dd, 1H, ^{3}J = 5.8 Hz, $^{2}J_{gem}$= 14.0 Hz, PhC*H*H), 2.97 (dd, 1H, ^{3}J = 7.6 Hz, $^{2}J_{gem}$= 14.0 Hz, PhCH*H*), 1.44 (s, 9H, COOCCH_3), 1.40 (s, 9H, NCOOCCH_3) ppm; ^{19}F-NMR (475 MHz, $CDCl_3$): δ = -146.0 (m, 2F), -163.6 (m, 2F) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3 (s, 1C, *C*OOtBu), 155.9 (s, 1C, NH*C*OOtBu), 145.5 (s, dddd, 2C, $^{1}J_{C\text{-}F}$ = 240 Hz, *J* = 16 Hz, *J* = 8.6 Hz , *J* = 4.3 Hz, *C*F), 136.7 (s, dddd, 2C, $^{1}J_{C\text{-}F}$= 230 Hz, *J* = 17 Hz, *J* = 5.5 Hz , *J* = 4.0 Hz, *C*F), 125.3 (s, tt, 1C, $^{3}J_{C\text{-}F}$ = 14 Hz, *J* = 17 Hz, *J* = 4.0 Hz, *C*NH_2), 102.2 (s, t, 1C, $^{3}J_{C\text{-}F}$ = 19 Hz, *C*CH_2), 82.4 (s, 1C, *C*(CH_3)$_3$), 79.7 (s, 1C, *C*(CH_3)$_3$), 53.6 (d, 1C,

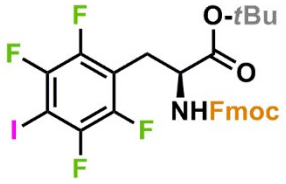
*C*HNH), 28.1 (q, 3C, *C*H_3), 27.8 (q, 3C, *C*H_3), 25.7 (t, 1C, *C*H_2) ppm; IR (ATR): ν = 3504 (w), 3394 (m), 3010 (w), 2978 (w), 2937 (w), 1743 (m), 1697 (s), 1670 (m), 1608 (w), 1521 (m), 1502 (s), 1451 (w), 1370 (m), 1347 (m), 1279 (w), 1217 (w), 1143 (s), 1092 (m), 1055 (m), 1021 (w), 981 (w), 960 (w), 935 (m), 853 (m), cm^{-1}; MS (ESI): m/z (%) = 409 (4) $[M+H]^+$, 431 (100) $[M+Na]^+$; Calculated mass for the benzylic cation $C_7H_4F_4N^{\cdot}$ = 178.027370; Found = 178.027987; 3.5 ppm, 0.6 mDa.

Synthesis of *N*-Boc-(4-iodo-2,3,5,6-tetrafluoro)-L-phenylalanine tert-butyl ester (6).

To a 0 °C cooled solution of **5** (1105 mg, 2.71 mmol) in freshly distilled CH_3CN (0.1 M in **5**) protected from light, iodine (1376 mg, 5.42 mmol, 2 eqv) was added. After complete dissolution, *t*-BuONO (420 mg, 4.07 mmol, 484 µL, d= 0.867 g/mL, 1.5 equiv) was added dropwise over a period of 5 min. The resulting solution was allowed to return at r.t. and stirred further for 2 h. Then it was concentrated to reduced volume avoiding the use of heat and subsequently poured into 100 mL of a 2 M $NaHSO_3$ solution. The aqueous mixture was extracted with DCM (80 mL x 4). The collected organic layers were then washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified via flash column chromatography eluting with a polarity gradient starting with DCM/Hexane 1:1, to yield a white solid with a 68% yield.

(R_f = 0.71 in Hex/AcOEt 5:1, permanganate staining solution, blue spot in *p*-anisaldehyde staining solution). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.05 (bs, 1H, N*H*), 4.46 (bs, 1H, C*H*NH), 3.23 (dd, 1H, ^3J = 5.0 Hz, $^2J_{gem}$= 13.5 Hz, PhC*H*H), 3.08 (dd, 1H, ^3J = 7.5 Hz, $^2J_{gem}$= 13.5 Hz, PhCH*H*), 1.45 (s, 9H, COOCC*H*$_3$), 1.39 (s, 9H, NCOOCC*H*$_3$) ppm; ^{19}F-NMR (475 MHz, $CDCl_3$): δ = -122.3 (bs, 2F), -141.1 (pq, 2F) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.8 (s, 1C, *C*OOtBu), 154.9 (s, 1C, NH*C*OOtBu), 147.0 (s, ddt, 2C, $^1J_{C\text{-}F}$ = 240 Hz, *J* = 16 Hz, *J* = 4.3 Hz, *C*F), 145.0 (s, dm, 2C, $^1J_{C\text{-}F}$= 230 Hz, *C*F), 116.8 (s, t, 1C, $^3J_{C\text{-}F}$ = 18.4 Hz, *C*CH$_2$), 82.9 (s, 1C, *C*(CH$_3$)$_3$), 80.1 (s, 1C, *C*(CH$_3$)$_3$), 70.4 (s, t, 1C, $^3J_{C\text{-}F}$ = 27.4 Hz, *C*I), 53.1 (d, 1C, *C*HNH), 28.2 (q, 3C, *C*H$_3$), 27.9 (q, 3C, *C*H$_3$), 27.0 (t, 1C, *C*H$_2$) ppm; IR (ATR): ν = 3412 (m), 2990 (m), 2980 (m), 2936 (m), 1732 (m), 1692 (s), 1524 (m), 1476 (s), 1370 (m), 1328 (w), 1293 (m), 1427 (m), 1155 (s), 1063 (m), 1031 (m), 952 (s), 882 (w), 845 (m), 819 (m), 794 (w), 774 (w), 742 (w), 614 (m), 485 (m) cm^{-1} ; MS (ESI): m/z (%) = 519 (4) $[M+H]^+$, 542 (100) $[M+Na]^+$; Calculated mass for the cation $C_8H_5F_4NI^{\cdot}$ = 317.941530; Found = 317.940289; -3.9 ppm, -1.2 mDa.

Synthesis of *N*-Fmoc-(4-iodo-2,3,5,6-tetrafluoro)-L-phenylalanine tert-butyl ester (7).



To a 0 °C cooled solution of **6** (800 mg, 1.54 mmol, 1 equiv) in DCM (0.13 M in **6**) protected from light, TFA (1406 mg, 12.33 mmol, 944 µL, d= 1.49 g/mL, 8 equiv) and TIPS (12 mg, 0.077 mmol, 16 µL, d= 0.773 g/mL,

5 mol%) were added. The resulting solution was allowed to return at r.t. and stirred further for 3 h. Then the mixture was added with toluene (10 mL) and reduced to dryness. The resulting crude was checked by TLC and by NMR to verify the full removal of Boc protecting group, and it was pure enough to be used directly in the next synthetic step. The crude was then dissolved in a 1:1 acetone/water mixture (0.1 M in starting material), added with K_2CO_3 (1063 mg, 7.7 mmol, 5 equiv) and FmocOSu (623 mg, 1.85 mmol, 1.2 equiv) and stirred at r.t. overnight protecting it from light. The resulting suspension was then filtered to get the final product as a white solid (83 % yield over two steps).

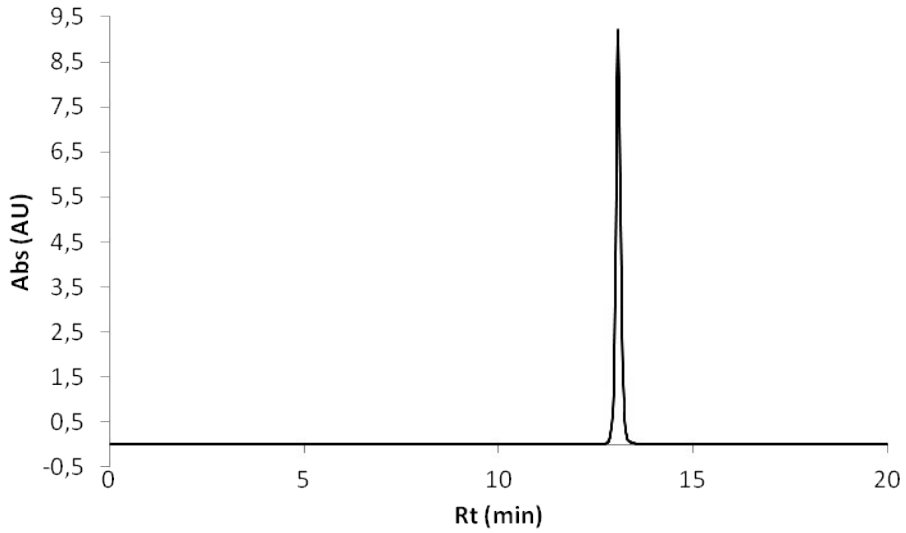
(R_f = 0.66 in $CHCl_3$, permanganate staining solution, strongly fluorescent at 365 nm). ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.75 (pd, 2H, C*H*), 7.56 (pt, 2H, C*H*), 7.40 (pt, 2H, C*H*), 7.31 (pt, 2H, C*H*), 5.46 (bs, 1H, N*H*), 4.57 (pt, 1H, C*H*NH), 4.40 (dd, 1H, ^3J = 7.2 Hz, $^2J_{gem}$= 10.4 Hz, OCH_2), 4.30 (dd, 1H, ^3J = 7.2 Hz, $^2J_{gem}$= 10.4 Hz, OCH_2), 4.19 (pt, 1H, ^3J = 7.2 Hz, OCH_2CH), 3.29 (dd, 1H, ^3J = 6.8 Hz, $^2J_{gem}$= 13.6 Hz, PhC*H*H), 3.15 (dd, 1H, ^3J = 6.8 Hz, $^2J_{gem}$= 13.6 Hz, PhCH*H*), 1.44 (s, 9H, $COOCCH_3$) ppm; ^{19}FNMR (475 MHz, $CDCl_3$): δ = -120.7 (pq, 2F), -139.8 (pq, 2F) ppm; ^{13}CNMR (100 MHz, $CDCl_3$): δ = 169.6 (s, 1C, *C*OOtBu), 155.6 (s, 1C, NH*C*OOFmoc), 148.2 (s, ddt, 2C, $^1J_{C\text{-}F}$ = 244 Hz, *J* = 16 Hz, *J* = 4.3 Hz, *C*F), 145.0 (s, dm, 2C, $^1J_{C\text{-}F}$= 248 Hz, *C*F), 143.7 (s, 2C), 141.2 (s, 2C), 127.6 (d, 2C), 127.0 (d, 2C), 125.0 (d, 2C), 119.9 (d, 2C), 116.8 (s, t, 1C, $^3J_{C\text{-}F}$ = 18.3 Hz, *C*CH_2), 83.2 (s, 1C, *C*(CH_3)$_3$), 70.7 (s, t, 1C, $^3J_{C\text{-}F}$ = 27.4 Hz, *C*I), 67.2 (t, 1C, O*C*H_2), 53.3 (d, 1C, *C*HNH), 47.1 (d, 1C, OCH_2CH), 27.7 (q, 3C, *C*H_3), 26.6 (t, 1C, *C*H_2) ppm; IR (ATR): ν = 3425 (w), 3160 (w, broad), 3061 (w), 2989 (w), 1793 (w), 1720 (m), 1696 (m), 1507 (m), 1475 (s), 1449 (w), 1412 (m), 1340 (w), 1250 (w), 1204 (w), 1176 (m), 1156 (m), 1060 (m), 1042 (s), 1025 (m), 928 (w), 889 (m), 760 (s), 742 (s), 727 (m), 690 (w) cm^{-1} ; MS (ESI): m/z (%) = 586 (6) $[M\text{-}tBu+H]^+$, 664 (100) $[M+Na]^+$, 680 (4) $[M+K]^+$; Calculated mass for $C_{28}H_{24}F_4NO_4I$ = 641.066890; Found = 641.068624; 2.7 ppm, 1.7 mDa.

Synthesis of *N*-Fmoc-(4-iodo-2,3,5,6-tetrafluoro)-L-phenylalanine (8).

To a 0 °C cooled solution of **7** (519 mg, 0.81 mmol, 1 equiv) in DCM (0.13 M in **7**) protected from light, TFA (2306 mg, 20.22 mmol, 1548 µL, d= 1.49 g/mL, 25 equiv) and TIPS (12.8 mg, 0.081 mmol, 17 µL, d= 0.773 g/mL, 10 mol%) were added. The resulting solution was allowed to return at r.t. and stirred further for 2 days. Then the mixture was added with toluene (10 mL) and reduced to dryness. The resulting crude was checked by TLC and by NMR to verify the full removal of Boc protecting group, and it was pure enough to be used directly in the solid phase synthesis of peptides, otherwise it can be purified by RP-HPLC (see chromatogram below).

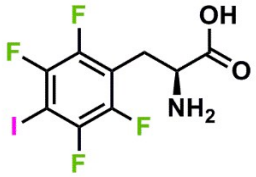
(Rf = 0.16 in $CHCl_3$/AcOEt 2:1 +0.5 % v/v CH_3COOH, permanganate staining solution, strongly fluorescent at 365 nm). ^{1}HNMR (400 MHz, methanol-d_4): δ = 7.76 (pd, 2H, C*H*), 7.58 (pd, 2H, C*H*), 7.52 (bs, 1H, COO*H*), 7.37 (pt, 2H, C*H*), 7.28 (pt, 2H, C*H*), 4.51 (dd, 1H, ^3J = 9.4 Hz, ^3J = 5.4 Hz, C*H*NH), 4.40 (bs, 1H, N*H*), 4.31 (dd, 1H, ^3J = 7.2 Hz, ^2Jgem= 10.4 Hz, OCH_2), 4.22 (dd, 1H, ^3J = 6.8 Hz, $^2J_{gem}$= 10.4 Hz, OCH_2), 4.12 (pt, 1H, OCH_2CH), 3.36 (dd, 1H, ^3J = 5.4 Hz, $^2J_{gem}$= 13.8 Hz, PhC*H*H), 3.19 (dd, 1H, ^3J = 9.4 Hz, $^2J_{gem}$= 13.8 Hz, PhC*H*H) ppm;

^{19}FNMR (475 MHz, $CDCl_3$): δ = -123.6 (m, 2F), -141.8 (m, 2F) ppm; ^{13}CNMR (100 MHz, methanol-d_4): δ = 173.6 (s, 1C, *C*OOH), 158.4 (s, 1C, NH*C*OOFmoc), 148.3 (s, dm, 2C, $^1J_{C\text{-}F}$ = 257 Hz, *C*F), 146.1 (s, dm, 2C, $^1J_{C\text{-}F}$= 250 Hz, *C*F), 145.1 (s, 2C), 142.1 (s, 2C), 128.7 (d, 2C), 128.2 (d, 2C), 126.1 (d, 2C), 120.9 (d, 2C), 118.4 (s, t, 1C, $^3J_{C\text{-}F}$ = 18.3 Hz, *C*CH_2), 72.3 (s, t, 1C, $^3J_{C\text{-}F}$ = 28.1 Hz, *C*I), 68.2 (t, 1C, O*C*H_2), 54.2 (d, 1C, *C*HNH), 48.3 (d, 1C, OCH_2*C*H), 26.8 (t, 1C, *C*H_2) ppm; IR (ATR): ν = 3307 (w), 3065 (w), 3020 (w), 2950 (w), 2925 (w), 1696 (s), 1535 (m), 1473 (s), 1449 (m), 1340 (w), 1266 (m), 1250 (m), 1228 (m), 1105 (w), 1086(w), 1050 (w), 1019 (m), 950 (m), 871 (w), 800 (m), 757 (m), 738 (s) cm^{-1} , MS (ESI): m/z (%) = 608 (100) $[M+Na]^+$, 625 (40) $[M+K]^+$; Calculated mass for $C_{24}H_{16}F_4NO_4I$ = 585.008610; Found = 585.006023; -4.4 ppm, -2.6 mDa.



RP-HPLC analytical trace of amino acid **8**.

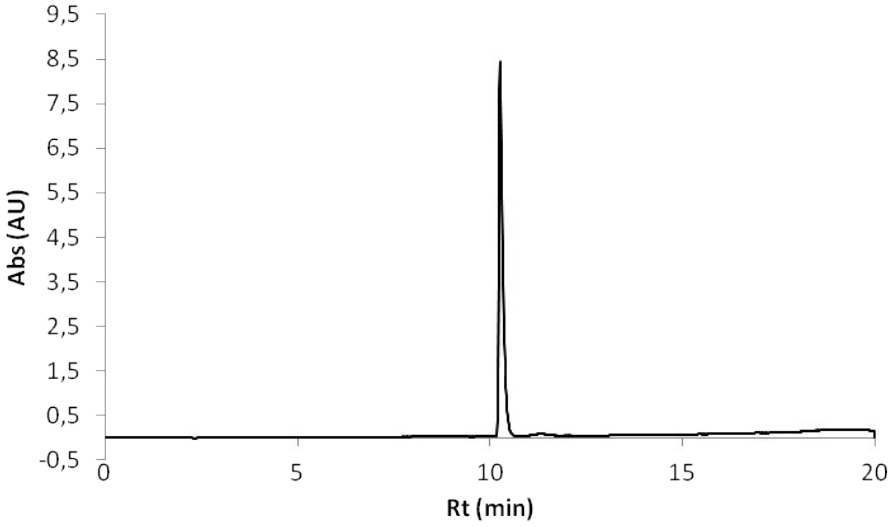
Synthesis of 4-iodo-2,3,5,6-tetrafluoro-L-phenylalanine (1, F(F_4I)).



To a 0 °C cooled solution of **6** (582 mg, 1.06 mmol, 1 equiv) in DCM (0.13 M in **6**) protected from light, TFA (3868 mg, 33.92 mmol, 2596 µL, d= 1.49 g/mL, 32 equiv) and TIPS (17.4 mg, 0.11 mmol, 23 µL, d= 0.773 g/mL, 10 mol%) were added. The resulting solution was allowed to return at r.t. and stirred for 2 days. Then the mixture was added with toluene (10 mL) and reduced to dryness. The resulting crude was checked by TLC and purified by RP-HPLC (see chromatogram below).

^{1}H-NMR (500 MHz, methanol-d_4): δ = 4.04 (pt, 1H, ^3J = 7.0 Hz, C*H*NH), 3.42 (dd, 1H, ^3J = 7.0 Hz, $^2J_{gem}$= 14.0 Hz, PhC*H*H), 3.26 (dd, 1H, ^3J = 7.0 Hz, $^2J_{gem}$= 14.0 Hz, PhCH*H*) ppm; ^{19}F-NMR (475 MHz, $CDCl_3$): δ = -124.5 (m, 2F), -143.6 (m, 2F), -77.96 (TFA) ppm; ^{13}C-NMR (100 MHz, methanol-d_4): δ = 171.1 (s, 1C, *C*OOH), 148.7 (s, dd, 2C, $^1J_{C\text{-}F}$ = 241 Hz, *J* = 15.5 Hz, *C*F), 146.1 (s, dd, 2C, $^1J_{C\text{-}F}$= 247 Hz, *J* = 15.5 Hz, *C*F), 116.4 (s, t, 1C, $^3J_{C\text{-}F}$ =

18.4 Hz, *C*CH_2), 73.4 (s, t, 1C, $^3J_{C-F}$ = 28.3 Hz, *C*I), 53.8 (d, 1C, *C*HNH), 25.7 (t, 1C, *C*H_2) ppm ; IR (ATR): ν = 3520 (w), 3159 (w), 2919 (w, broad), 2753 (w), 1741 (m), 1671 (m), 1643 (m), 1611 (m), 1596 (m), 1561 (m), 1531 (m), 1472 (s), 1435 (m), 1416 (w), 1244 (m), 1191 (s), 1146 (s), 1090 (w), 1066 (w), 993 (m), 940 (m), 911 (m), 850 (m), 799 (s), 728 (m) cm^{-1} ; MS (ESI): m/z (%) = 364 (100) $[M+H]^+$, 386 (70) $[M+Na]^+$; Calculated mass for fragment $C_8H_5F_4NI$ = 317.940582; Found = 317.940289; -0.9 ppm, -0.3 mDa.



RP-HPLC analytical trace of amino acid **1**.

S2.2 General procedure for the catalytic activity synthesis of products 3 a-d.

In a screw cap vial, aldehyde **1a**-**1d** (0.1 M), 4 hydroxycoumarin (0.2 M) and catalyst (0.2%-10%) were suspended in 0.5 mL of pure water. The resulting mixture was stirred at the chosen temperature and time conditions. The resulting reaction mixture was fully dissolved by addition of DMSO (2 mL) prior to HPLC analysis (90%A to 0%A over 30 min binary gradient). The product formation was quantified by peaks area integration at 310 nm, as a mean of 3 independent measurements. Biscoumarin methanes products **3a-3d** characterization is in accordance to previously reported literature[3], and here below summarized.

3a ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.11 (1H, s, CH), 7.41-7.23 (9H, m), 7.63 (2H, t), 8.04 (2H, d br), 11.29 (1H, s, OH), 11.52 (1H, s, OH) ppm. ^{13}C (100MHz, $CDCl_3$): δ= 36.3, 104.0, 105.8, 116.4, 116.7, 124.5, 125.0, 126.6, 127.0, 128.7, 133, 135.3, 152.4, 152.6, 164.7, 165.8, 167.0, 169.3. ESI-MS, MeOH (m/z): 413.0 $[M+H]^+$, 425.0 $[M+Na]^+$. HPLC Rt: 29.21 min

3b ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.20 (6H, s, CH_3), 6.07 (1H, s, CH), 7.39 -7.49 (8H, m), 7.66 (2H, t), 8.03 (2H, d br), 11.53 (1H, s, OH). ^{13}C (100MHz, $CDCl_3$): δ= 36.2, 46.3, 103.5, 105.0, 116.7, 116.9, 120.5, 124.6, 125.3, 129.0, 133.4, 137.4, 142.4, 152.5, 152.7, 164.9, 166.5, 167.1, 169.3. ESI-MS, MeOH (m/z): 456.0 $[M+H]^+$, 478.0 $[M+Na]^+$. HPLC Rt: 18.28

3c ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.04 (1H, s, CH), 7.16 (2H, d), 7.29 (2H, t), 7.42 (4H, d), 7.64 (2H, t), 8.04 (2H, d), 11.29 (1H, s, OH), 11.53 (1H, s, OH). ^{13}C (100MHz, $CDCl_3$): δ= 36.0, 103.9, 105.4, 116.5, 116.8, 124.6, 125.1, 128.1, 129.0, 132.9, 133.1, 134.0, 152.5, 152.7, 164.8, 166.1, 167.0, 169.4. ESI-MS, MeOH (m/z): 446.9 $[M+H]^+$, 468.9 $[M+Na]^+$. HPLC Rt: 29.9 min

3d ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.12 (1H, s, CH), 7.42 (6H, m), 7.67 (2H, t), 8.05 (2H, dd), 8.19 (2H, d), 11.35 (1H, s, OH), 11.56 (1H, s, OH) ppm. ^{13}C (100MHz, $CDCl_3$): δ= 36.7, 103.5, 105.0, 116.4, 116.9, 124.0,

124.6, 125.3, 127.7, 133.5, 143.6, 147.1, 152.5, 152.7, 165.0, 166.6, 167.1, 169.3. ESI-MS, MeOH (m/z): 457.9 $[M+H]^+$, 480.0 $[M+Na]^+$. HPLC Rt: 26.48 min

S2.3 Co-crystals synthesis

1,4-DITFB and aldehyde (**1b**-**1d**) were dissolved in a 1:1 molar ratio in 1 mL of $CHCl_3$ or MeOH/$CHCl_3$ 1/1 mixture. Precipitation occurred by slow evaporation of the solvent (24 h).

S2.4 Amino acid F(F_4I) stability

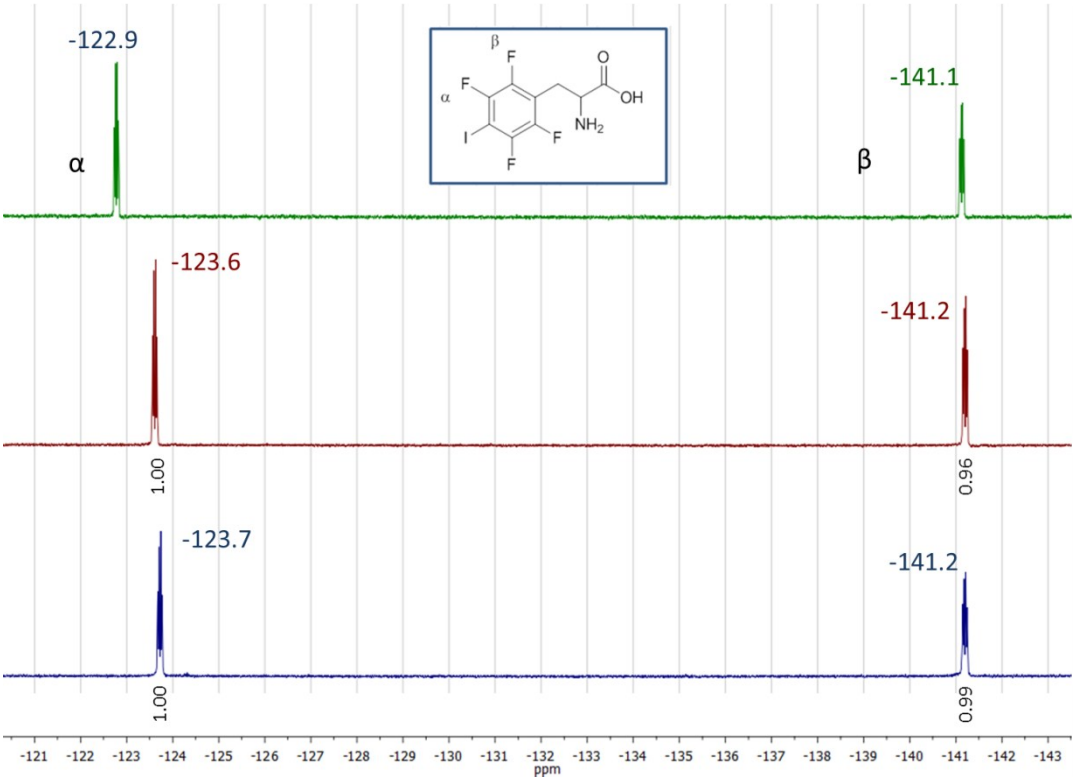
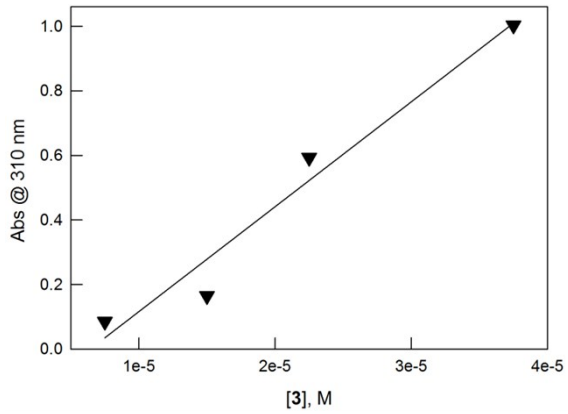


Figure S1. ^{19}F-NMR spectra of: F(F_4I) (green line); reaction mixture (0.1M of **1a**, 0.2 M of 4-hydroxycoumarine and 10 % of F(F_4I)) after 1 h at 100 °C (red line); 0.1 M of **1a** and 10 % of F(F_4I). Solvent: H_2O containing 20% of DMSO-d^6.

After stirring the reaction mixture containing 10 mol% of **F(F_4I)** at 100 °C for 1 h no significant change could be observed in the amino acid spectrum. A slight up-field shift of fluorine atoms in *ortho* position with the C-I fragment has been observed, suggesting an increased electron density felt by the fluorine atoms. This behavior could be probably due to the carbonyl coordination that induces the polarization of the C–I fragment involved in the binding. [4]

S2.4 Calibration curve of product **3**



S3. Conversion Tables

Table S1. Optimization of catalytic reaction conditions.

Entry	Catalyst (% mol)	$T^{[a]}$	t	Yield [%][b]
1	$F(F_4I)$ (0.2)	100	20 min	97 (3)
2	I_2 (0.2)	100	20 min	85 (4)
3	no cat.	100	20 min	56 (4)
4	$F(F_4I)$ (0.2)	60	1h	97 (3)
5	I_2 (0.2)	60	1h	76 (4)
6	no cat	60	1h	46 (5)

[a] Temperature (°C). [b] Reaction conditions: **1** (0.1M), **2** (0.2 M), and catalyst in H_2O 0.5 mL; the reaction yields were determined by HPLC. Standards deviation in parentheses.

Table S2. Reaction of benzaldehyde (1) with 4-hydroxycoumarine (2) in the presence of various catalysts.

Catalyst	Yield [%][b]
//	46 (5)
Phe	47 (5)
F_5-Phe	50 (5)
Br-Phe	47 (6)
Tyr	50 (5)
I-Phe	69 (5)
I_2	76 (4)
$F(F_4I)$	97 (3)
Fmoc-$F(F_4I)$	99 (5)

[a] **1** (0.1M), **2** (0.2 M), and $F(F_4I)$ (0.2 mM) in H_2O 0.5 mL at 60 °C for 1h. The reaction yields were determined by

HPLC, standard deviations in parentheses.

Table S3. Reaction of different aromatic aldehydes (**1a-d**) with 4-hydroxycoumarine (**2**) in the presence of 0.2 mol % of **F(F_4I)**.

Entry	**1**	R	Yield [%] [a]	Yield [%] [b]
1	1a	-H	97 (3)	46 (5)
2	1b	-$N(CH_3)_2$	53 (4)	23 (3)
3	1c	-Cl	75 (3)	45 (3)
4	1d	-NO_2	100 (2)	47 (4)

[a] **1a-1d** (0.1M), **2** (0.2 M), and **F(F_4I)** (0.2 mM) in H_2O 0.5 mL at 60 °C for 1h, [b] reaction performed in the absence of catalyst; The reaction yields were determined by HPLC, standard deviations in parentheses.

S4. Kinetics profiles

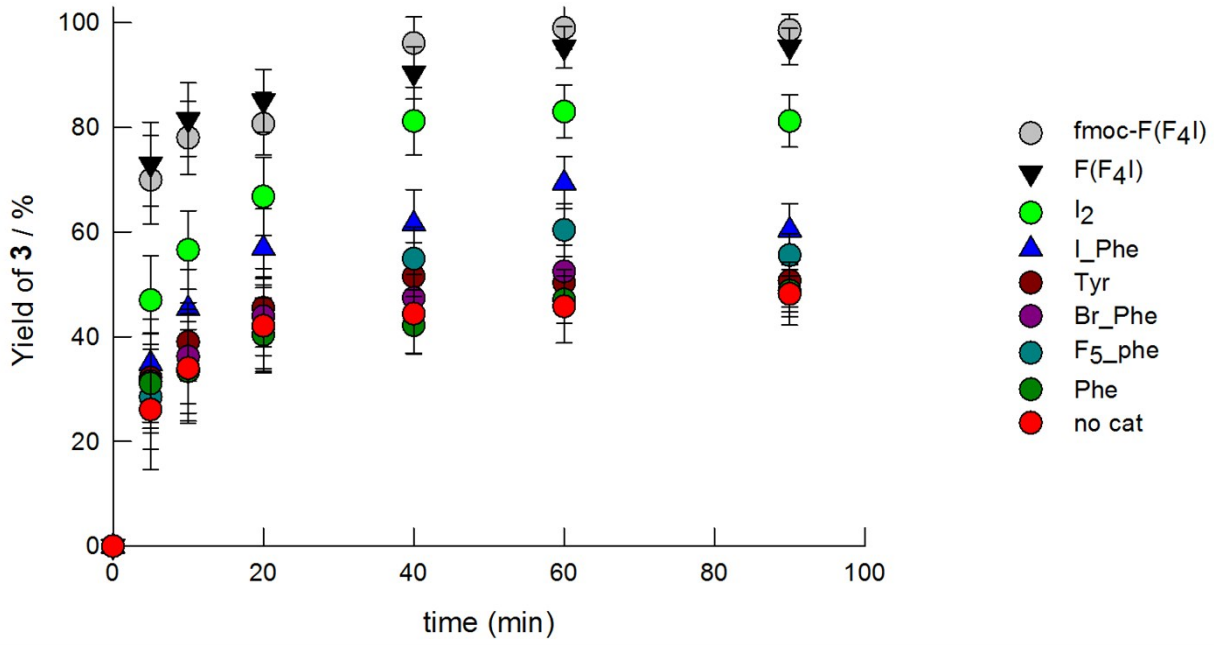


Figure S2. Conversion *vs*. time curves for the benchmark reaction performed at 60 °C with different catalysts.

S5. Differential scanning calorimetry (DSC) experiments

DSC analyses were performed using a Mettler Toledo DSC600 instrument. 15-20 mg of sample were measured in a closed aluminum pan with heating/cooling rates of 10 °C/min. All the mixtures melted with single peaks at temperatures higher than both pure precursors indicating co-crystal formation.

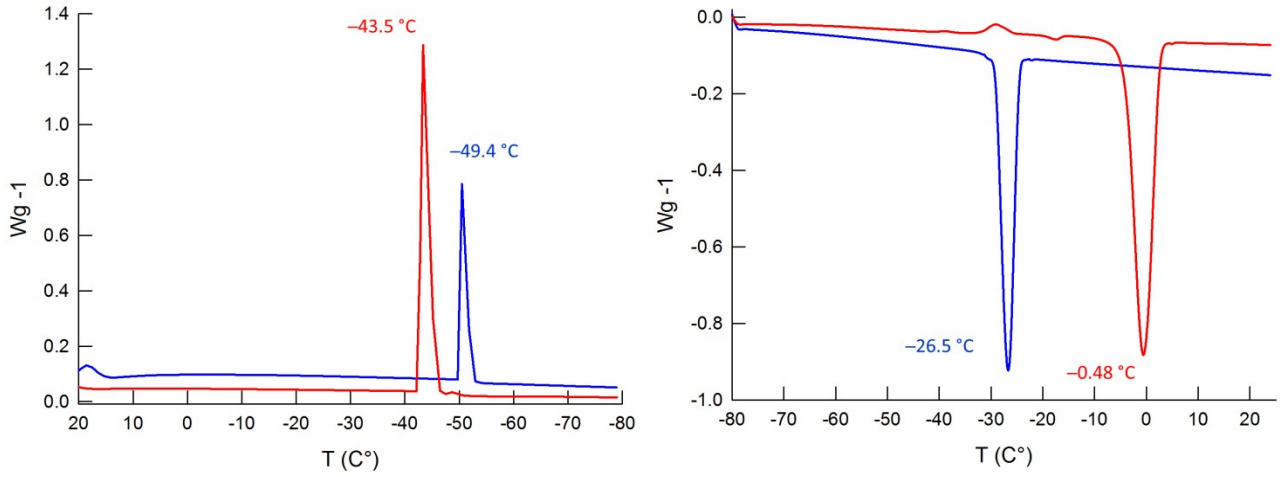


Figure S3. DSC thermograms of pure **IPFB** (red lines) and co-crystal with **1a** (blue line). Experiments were performed with heating/cooling rates of 10 °C/min.

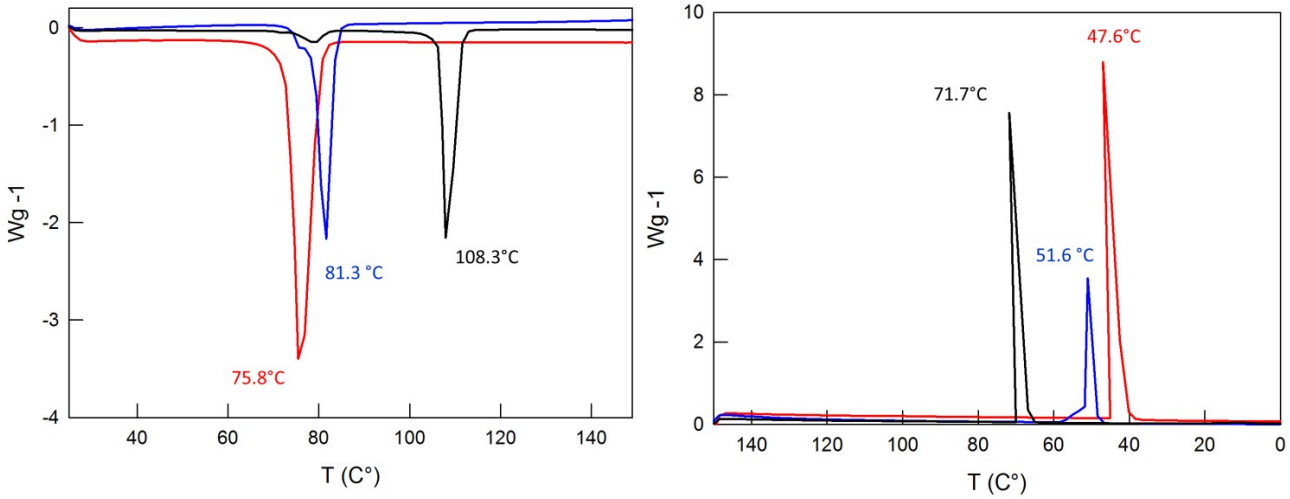


Figure S4. DSC thermograms of **1,4-DITFB** (red lines), **1b** (black lines) and co-crystal (blue line). Experiments were performed with heating/cooling rates of 10 °C/min.

Table S4. Experimental melting points (m.p.) and crystallization points (c.p.) of the starting compounds and the obtained co-crystals. Onset values are reported.

Compound/co-crystal	c.p. (°C)	m.p. (°C)
IPFB	-49.4	-26.5
1a	-79.6	
IPFB:1a (1:1)	-43.5	-0.48
1,4-DITFB	71.7	108.3
1b	47.6	75.8
1,4-DITFB:**1b** (1:1)	51.6	81.3

S6. ATR-FTIR experiments

For each sample, spectra were collected (128 scans) using solid-state substrate beam splitter. Selected bands for the spectra of the starting compounds **1,4-DIFTB** and **1b**-**c** and of corresponding co-crystals measured at r.t. are reported.

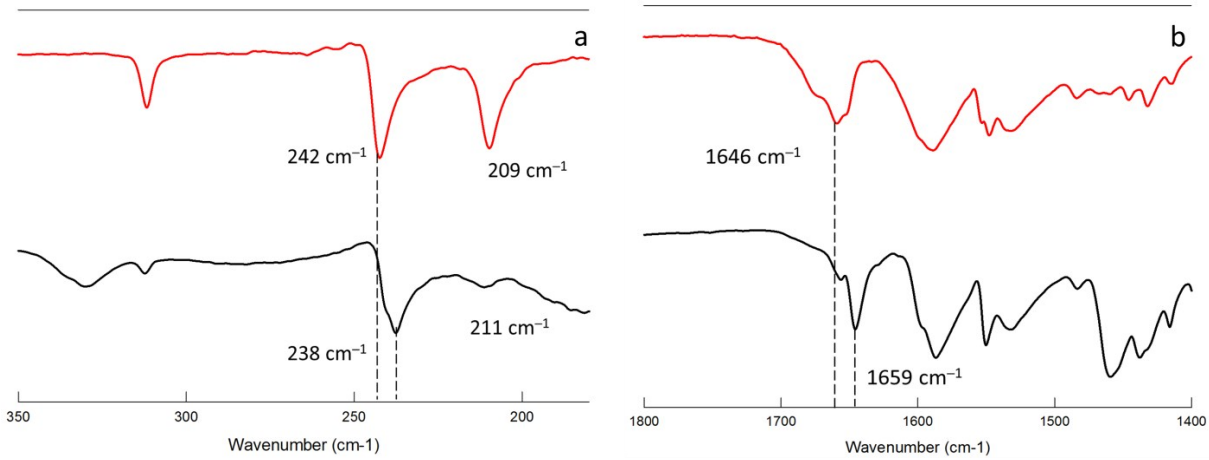


Figure S5. IR spectroscopy of 1,4-DIFTB (red line) and co-crystal with **1b** (black line).

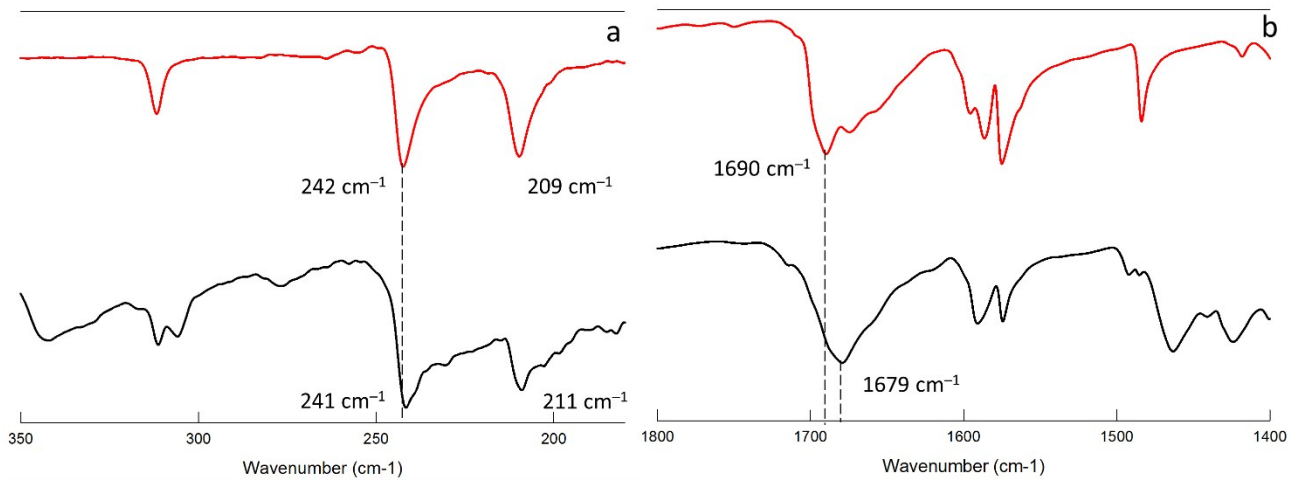


Figure S6. Far-IR (a) and IR (b) spectra of 1,4-DIFTB (red line) and co-crystal with **1c** (black line).

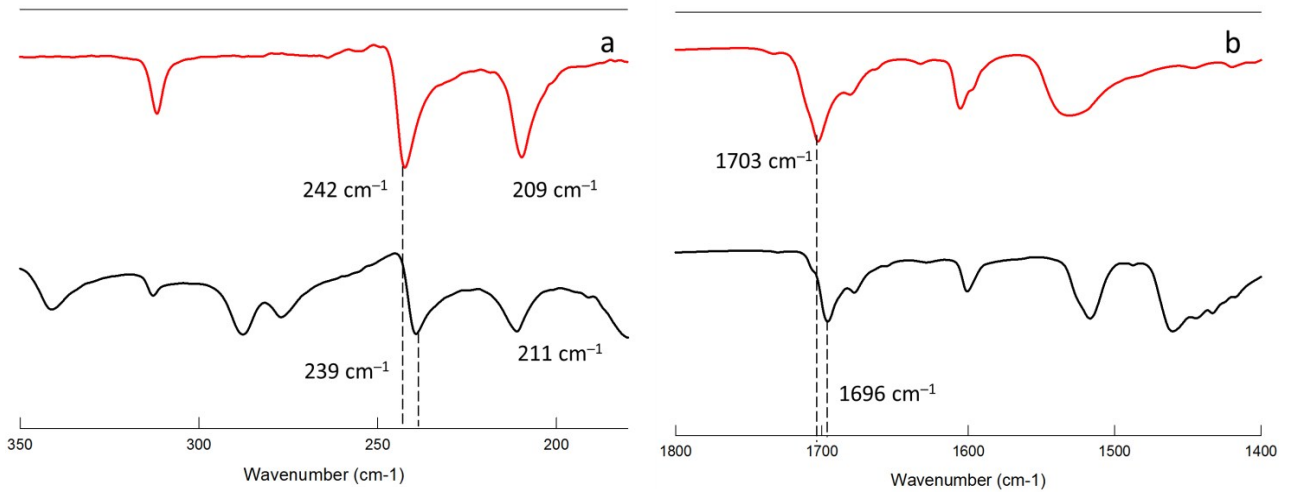


Figure S7. Far-IR (a) and IR (b) spectra of 1,4-DIFTB (red line) and co-crystal with **1d** (black line).

A red shift of C-I stretching vibration bands of 1,4-DITFB (red lines, Figures *a*) occurred in the co-crystal spectra with XB acceptors **1b**-**1d**. Moreover, spectra of aldehydes show a broad band (ν C=O) that undergoes a red shift in the FTIR spectrum of the co-crystal. As expected, the halogen bond perturbs the electron density of the carbonyl group and this results in a reduced electron density on C=O with respect to the pure aromatic aldehyde.[5] Similar behaviors have been observed in FT-IR spectra of the co-crystals with **1c** and **1d** (See Figure S6 and S7).

S7. X-ray diffraction analysis

CCDC 1840351 and 1841117 contain the supplementary crystallographic data for compound **F(F_4I)** and **1-4-DITFB/1b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

Structural characterization of F(F_4I) amino acid.

Data collections of **F(F_4I)** were performed at the X-ray diffraction beamline (XRD1) of the Elettra Synchrotron, Trieste (Italy).[6] The crystals were dipped in perfluoropolyether Fomblin oil (Sigma Aldrich, Saint Louis, USA) and mounted on the goniometer head with kapton loops (MiTeGen, Ithaca, USA). Complete datasets were collected at 100 K (nitrogen stream supplied through an Oxford Cryostream 700 - Oxford Cryosystems Ltd., Oxford, United Kingdom) through the rotating crystal method. Data were acquired using a monochromatic wavelength of 0.700 Å, on a Pilatus 2M hybrid-pixel area detector (DECTRIS Ltd., Baden-Daettwil, Switzerland). The diffraction data were indexed, integrated and scaled using XDS.[7] Crystals appear as thin colorless rods prone to radiation damage, as previously reported for other halogenated molecules.[8, 9] The structures were solved by the dual space algorithm implemented in the SHELXT code.[10] Fourier analysis and refinement were performed by the full-matrix least-squares methods based on F2 implemented in SHELXL (Version 2017/1).[11] The Coot program was used for modeling.[12] Anisotropic thermal motion refinement have been used for all atoms. Limited thermal motion parameters restrains (SIMU) have been used to prevent phenyl ring carbons of one residue, to become non-positive definite (NPD). Radiation damage is responsible for electron density maps distortions, close to heavy atoms, and give rise to quite high model e.s.d. Hydrogen atoms were included at calculated positions with isotropic Ufactors = 1.2·Ueq or Ufactors = 1.5·Ueq for water hydrogens, methyl and protonated amino groups (Ueq being the equivalent isotropic thermal factor of the bonded non hydrogen atom). The **F(F_4I)** amino acid crystallized in a chiral monoclinic unit cell (*P* 2_1 space group). The model has been fully refined as a 2-component non-merohedral twin. Crystal showed two domains related by a 180° rotation around *a** reciprocal lattice direction (twin fraction refined to 29%). Refined Flack parameters[13] confirm the expected amino acids Cα configurations. Pictures were prepared using CCDC Mercury [14]. Essential crystal and refinement data are reported below (Table S2).

Three crystallographically independent **F(F_4I)** amino acid molecules have been found in the asymmetric unit (ASU; Figure S8). Salt bridges links negatively charged carboxylates, with protonated N-terminal primary amine of flanked molecules (shortest $O^{-}\cdots N^{+}$ distance is 2.65(3) Å). Molecules are packed through hydrogen bonds that give rise to channels aligned with crystallographic b direction filled by water molecules (H-bonds details in Table S2; Figure S9). Polar tails are oriented towards this channels, while hydrophobic side chains define complementary channels, with the same orientations, where hydrophobic and halogen bond interactions are present and with acetone molecules trapped in. Solvent voids represent 14% of the cell volume (266 $Å^3$) equally distributed among polar and apolar vacancies.

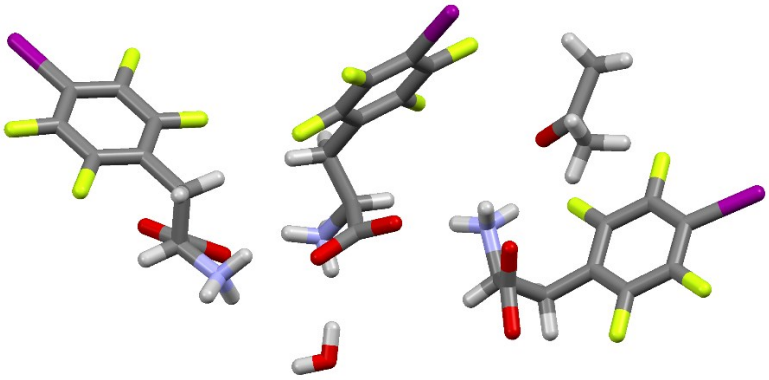


Figure S.8. ASU content for **F(F_4I)**.

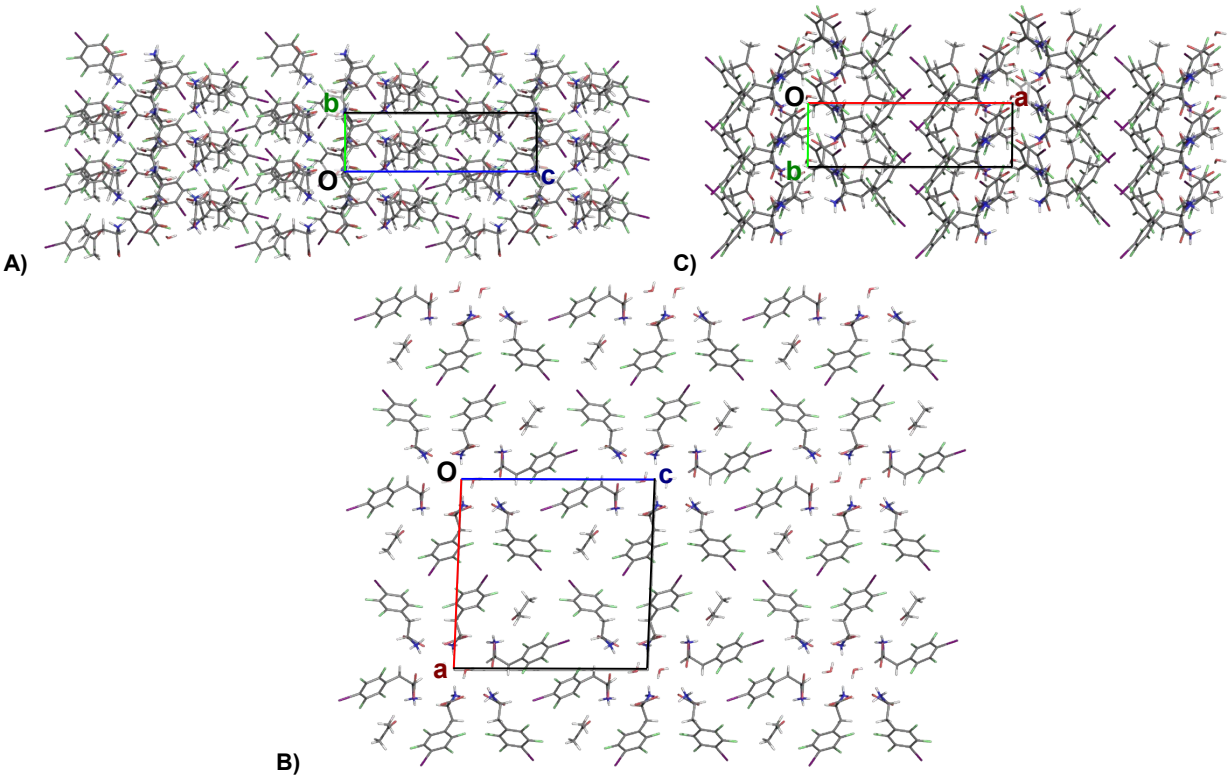


Figure S.9. F(F_4I). Crystal packing views along crystallographic *a*, *c* and *b* axis.

As already reported in literature [15], halogen bonding occurs orthogonally to the hydrogen bond involving amide carbonyl oxygen and amine group with an angle I···O···N of 106.6°.

Table S.5. Crystallographic data and refinement details for **F(F$_4$I)**.

	F(F$_4$I)·$^1/_3$C$_3$H$_6$O·$^1/_3$H$_2$O [C$_9$H$_6$F$_4$INO$_2$·$^1/_3$C$_3$H$_6$O·$^1/_3$H$_2$O]
CCDC Number	1840351
Chemical Formula	$C_{10}H_{8.67}F_4INO_{2.67}$
Formula weight (g/mol)	388.41
Temperature (K)	100(2)
Wavelength (Å)	0.700
Crystal system	Monoclinic
Space Group	$P\,2_1$
Unit cell dimensions	a = 18.049(4) Å b = 5.593(1) Å c = 18.384(4) Å α = 90° β = 92.36(3)° γ = 90°
Volume (Å^3)	1854.3(6)
Z	6
Density (calculated) (g·cm^{-3})	2.087
Absorption coefficient (mm^{-1})	2.503
F(000)	1116
Crystal size (mm^3)	0.10 x 0.04 x 0.04
Crystal habit	Colorless thin rods
Theta range for data collection	1.09° to 29.08°
Resolution (Å)	0.72
Index ranges	-25 ≤ h ≤ 25 -7 ≤ k ≤ 7 -25 ≤ l ≤ 25
Reflections collected	12396
Independent reflections (data with I>2σ(I))	8997 (6660)
Data multiplicity (max resltn)	2.17 (2.09)
I/σ(I) (max resltn)	11.10 (3.53)
R_{merge} (max resltn)	0.0680 (0.2721)
Data completeness (max resltn)	95.9% (94.8%)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	481 / 13 / 8997
Goodness-of-fit on F^2	1.039
Δ/σ_{max}	0.010
Final R indices [I>2σ(I)][a]	R_1 = 0.0983, wR_2 = 0.2614
R indices (all data)[a]	R_1 = 0.1259, wR_2 = 0.2826
Flack x parameter	0.04(4)
Largest diff. peak and hole (e·Å^{-3})	3.967 and -2.556
R.M.S. deviation from mean (e·Å^{-3})	0.295

[a] $R_1 = \Sigma\, ||Fo|-|Fc|| \,/\, \Sigma\, |Fo|$, $wR_2 = \{\Sigma\, [w(Fo^2 - Fc^2)^2] \,/\, \Sigma\, [w(Fo^2)^2]\}^{½}$

Table S6. Geometrical parameters of hydrogen bonds found in **F(F_4I)** crystal packing.

D-H···A	d(D-H) (Å)	d(H···A) (Å)	d(D···A) (Å)	<(DHA) (°)
(CA-HA)_1···O_3#1	1.00	2.51	3.48(3)	163.2
(N-H0A)_1···O_1#1	0.91	2.41	3.09(3)	131.6
(N-H0A)_1···OXT_1#1	0.91	2.04	2.89(3)	155.0
(N-H0B)_1···O_2	0.91	1.88	2.74(2)	156.1
(N-H0C)_1···O_4#2	0.91	1.94	2.76(3)	149.1
(N-H0A)_2···OXT_3#2	0.91	2.14	2.75(3)	123.6
(N-H0B)_2···O_2#3	0.91	2.64	3.08(3)	110.5
(N-H0B)_2···OXT_2#3	0.91	2.11	2.74(3)	125.6
(N-H0C)_2···O_1	0.91	2.15	2.75(2)	122.6
(CB-HB1)_2···FD2_1	0.99	2.62	3.54(3)	155.0
(CB-HB2)_2···OXT_2#3	0.99	2.59	3.32(3)	131.0
(N-H0A)_3···O_3	0.91	2.12	2.65(3)	116.1
(N-H0B)_3···O_3#1	0.91	2.45	2.95(3)	114.8
(N-H0C)_3···FD2_3	0.91	2.12	2.99(2)	159.5
(N-H0C)_3···O_5	0.91	2.36	2.81(3)	110.1
(CB-HB2)_3···OXT_3#1	0.99	2.58	3.41(3)	141.5
(O-H1)_4···OXT_3#2	0.8(4)	2.0(4)	2.76(3)	174(46)
(O-H2)_4···O_1	0.8(4)	2.1(4)	2.82(3)	158(44)
(C2-H2A)_5···O_3	0.98	2.58	3.52(4)	159.8
(C2-H2A)_5···FD2_3#3	0.98	2.57	3.20(5)	122.1
Symmetry transformations used to generate equivalent atoms: #1 = x, y+1, z ; #2 = -x+2, y+1/2, -z ; #3 = x, y-1, z				

Structural characterization of co-crystal 1-4-DITFB/1b.

X-ray diffraction data were collected at Bruker APEX-II diffractometer equipped with sealed-tube and CCD detector, using Mo-Kα radiation (λ = 0.71073 Å). Data collection was performed at room temperature (296 K). The diffraction data were indexed, integrated and scaled using SAINT. [16] The structure was solved by SHELXS[17] and refinements were carried out by full-matrix least-squares on F^2 using the SHELXL program. [11] The main crystallographic data for co-crystal 1-4-DITFB/**1b** are reported in Table S5 and detailed in the following paragraphs. 1-4-DITFB/1b crystals were pale yellow plates. The number of collected reflections was 10820; the number of parameters used for the refinement was 413. No restraints were used. Hydrogen atoms were included at calculated positions through HFIX instruction. The asymmetric unit contains two molecules of 1-4-DITFB and two molecules of aldehyde **1b** (Figure S.10).

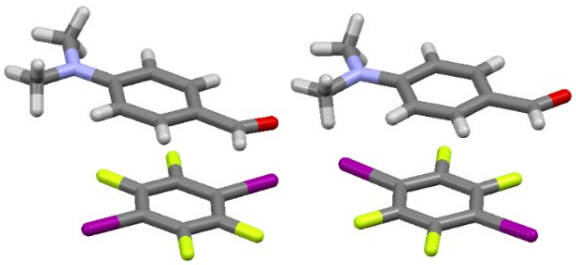


Figure S10. ASU content for co-crystal 1-4-DITFB/**1b**

One molecule of 1,4-DITFB acts as di-topic halogen bond donor (I1···O5 2.916(7) Å ; I2···O4 2.931(4) Å), while the other one forms a XB (I4···O4 3.033(4) Å) and a short I···F contact (I3···F3 3.299(3) Å) with the

fluorine atom of a nearby 1,4-DITFB unit (Figure S.11). Besides I···O contacts, leading to the formation of infinite chains along the crystallographic axis *a*, the structure develops along the other directions through a network of weak H···F interactions involving both aromatic and methyl hydrogens of 1b molecules (Figure S.12).

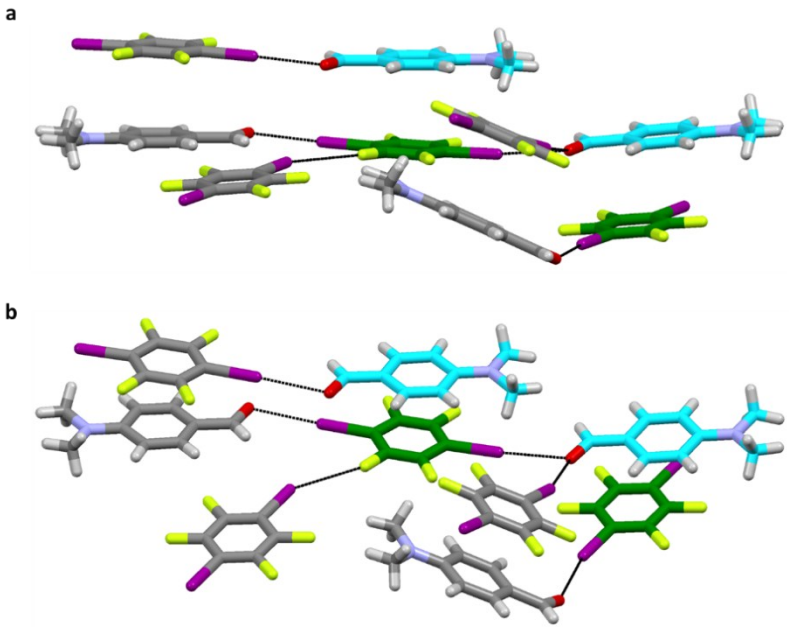


Figure S11. Co-crystal formed between 1,4-DITFB and 1b. Lateral view (a) and top view (b) of the interaction pattern related to the asymmetric unit, represented at the center and consisting in two 1,4-DITFB and two **1b** molecules. Color code: Carbon: grey, blue and green; Iodine: purple; Fluorine: yellow; Oxygen: red, Hydrogen: white.

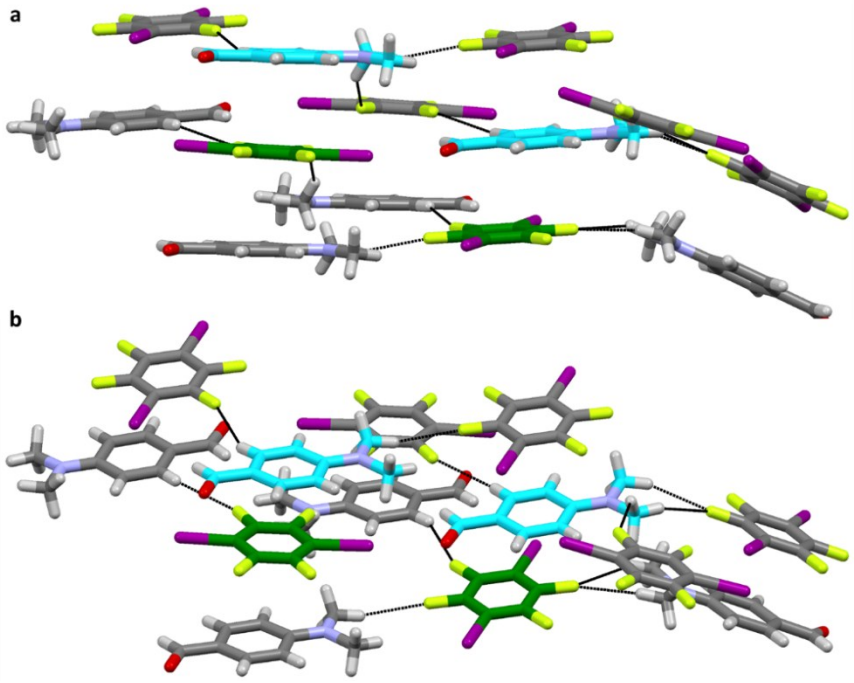


Figure S12. Co-crystal formed between 1,4-DITFB and **1b**. Lateral view (a) and top view (b) of the network of weak H···F interactions involving both aromatic and methyl hydrogens of **1b**. Colored carbon atoms relate to the asymmetric unit content. Color code: Carbon: grey, light blue and green; Iodine: purple; Fluorine: yellow; Oxygen: red, Hydrogen: white.

Table S.7. Contacts list for 1-4-DITFB/1b co-crystal.

Contact	Length (Å)
C1···F4	3.481(4)
C7···I2	3.580(4)
C8···F1	3.299(5)
C8···F5	3.487(6)
C9···F5	3.512(5)
C22···F2	3.393(5)
C22···F8	3.577(6)
C26···F7	3.299(4)
C28···I1	3.486(5)
I1···O2	2.924(4)
I2···O1	2.918(3)
I3···F3	3.299(2)
I4···O1	3.042(3)
F1···H8A	2.649
F2···H22A	2.645
F4···H1	2.639
F5···H8B	2.598
F5···H9B	2.592
F7···H26	2.449
F8···H22B	2.652

Table S8. Crystallographic data and refinement details for 1-4-DITFB/1b co-crystal.

	1-4-DITFB/1b
CCDC Number	1841117
Chemical Formula (Formula weight)	$C_{12}F_8I_4 \cdot C_{18}H_{22}N_2O_2$ (1102.09 g/mol)
Temperature (K)	296
Wavelength (Å)	0.71073
Crystal system and Space Group	Monoclinic $P\,2_1/c$
Unit cell dimensions	a = 16.6735 (4) Å b = 7.2738 (2) Å c = 29.1480 (7) Å β = 96.230 (1)°
Volume (Å^3)	3514.18 (15)
Z	4
Absorption coefficient (mm^{-1})	3.62
Crystal size (mm^3)	0.30 × 0.25 × 0.10
Crystal habit	Pale yellow plates
Theta range for data collection	2.89° to 28.14

Reflections collected	41129
Independent reflections (data with I>2σ(I))	10820 (6633)
Refinement method	Full-matrix least-squares on F^2
Number of parameters	413
R_{int}	0.047
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.720
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.035, 0.086, 1.00
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.74, −1.13

S8. Calculation and plot of the molecular electrostatic potential (MEP)

The calculation of MEP has been carried out by employing Density Functional Theory (DFT) by means of Gaussian09 code.[18] The hybrid exchange-correlation functional B3LYP and 6-311G(d,p) basis set have been used for all the atoms except I. In the case of I atom, fully relativistic ECP28MDF (I) effective core potential have been used together with aug-cc-pVTZ basis set.[19] First, an optimization run has been carried out to obtain the equilibrium geometry of the molecule followed by the computation run for the generation of MEP. Molden visualization program [20] has been employed to compute and plot the MEP map on the 0.001 a.u. contour for the isodensity surface, as suggested in Refs.[21] Color ranges adopted in the plot are (in kcal/mol): red lower than -18.8; yellow -6.3; green 0.0; light blue +6.3; blue larger than +21.5.

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