Straightforward N-alkylation of diketopyrrolopyrroles through Mitsunobu reaction with benzyl, α-branched, and chiral alcohols

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General methods and materials

All commercially available reagents and solvents were used as received unless otherwise noted. Dry tetrahydrofuran was directly used from the purification machines. Chloroform as solvent for synthesis was distilled over calcium hydride prior to use. **TDPP** (3,6-di(thiophen-2-yl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione)[1], **PDPP** (3,6-bis(4-bromophenyl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione)[2] and **PyDPP** (3,6-di(pyridin-2-yl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione)[3] were synthesized according to previously reported procedures. Chromatography purifications were performed on silica gel Sorbent Technologies Silica Gel (60 Å, 65 x 250 mesh) and thin layer chromatography (TLC) was carried out using aluminum sheets precoated with silica gel 60 (EMD 40−60 mm, 230−400 mesh with 254 nm dye). All reactions were carried out in Schlenk tubes under argon atmosphere. Dropwise additions were

done with a programmable syringe pump. NMR spectra were acquired on a Bruker Avance DRX 300 and 500 spectrometers operating at 300 and 500 MHz for ^{1}H and 75 and 125 MHz for ^{13}C, respectively, at room temperature in CDCl3 solutions. ^{1}H and ^{13}C NMR spectra were referenced to the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are expressed in parts per million (ppm) downfield from external tetramethylsilane (TMS), using the solvent residual signal as an internal standard and the coupling constant values (J) are reported in Hertz (Hz). The following abbreviations have been used: s, singlet; dd, doublet of doublets; m, multiplet. Mass spectrometry MALDI–TOF MS spectra were recorded on Bruker Biflex-IIITM apparatus, equipped with a 337-nm N2 laser.

Details about data collection and solution refinement are given in Table S1. Single crystals of the compounds were mounted on glass fibre loops using a viscous hydrocarbon oil to coat the crystal and then transferred directly to cold nitrogen stream for data collection. X-ray data collection were performed at 150 K on an Agilent Supernova with CuKα (λ = 1.54184 Å). The structures were solved by direct methods with the SHELXS-97 and SIR92 programs and refined against all F2 values with the SHELXL-97 program1 using the WinGX graphical user interface.2. All non-H atoms were refined anisotropically. Hydrogen atoms were introduced at calculated positions (riding model), included in structure factor calculations but not refined. Crystallographic data for the two structures obtained at 150 K have been deposited with the Cambridge Crystallographic Data Centre, deposition numbers CCDC 2056004 (**TDPP-2-NN**), CCDC 2082406 (**PyDPP-4-NN**) and CCDC 2056005 (**(*rac*)-TDPP-5-NN**). These data can be obtained free of charge from CCDC, 12 Union road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Synthesis and characterization

Under argon atmosphere, tributylphosphine (394 µL, 1.60 mmol) was dissolved in dry THF (6 mL) and the mixture cooled at 0 °C, then DIAD (314 µL, 1.60 mmol) was added dropwise, resulting in a rapid loss of DIAD's bright yellow tint upon formation of a complex with the phosphine. In a separate Schlenk tube, under argon atmosphere, **ArDPP** (0.32 mmol) was dispersed in dry THF (6 mL) and the mixture cooled at 0°C. The mixture containing the Bu_3P/DIAD complex was added dropwise into the second Schlenk tube resulting in a bright purple solution. At this point, R-OH (1.60 mmol) dissolved in THF (1 mL) was injected dropwise to the mixture over 2h. The mixture was then allowed to reach r.t. and kept under stirring overnight.

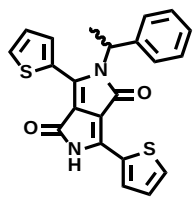
The mixture was quenched with a splash of water, concentrated under vacuum, diluted into CH_2Cl_2, filtered through a PTFE membrane to collect the insoluble unreacted ArDPP. The filtrate was washed with 1M HCl, then water, the organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure.

The compound was purified by column chromatography on silica gel with mixtures of AcOEt/DCM/PE as the elution system.

Note: Due to several factors (contamination of the products with alkylated and/or reduced DIAD by-products, close RF values between O-alkylated and N-alkylated derivatives, waxy consistency of the O-alkylated derivatives precluding reprecipitation) in some cases the purification of O-alkylated derivatives was not accomplished, therefore the characterization of such products was not achieved.

TDPP-1

Following the general procedure, from 96 mg of TDPP and 194 µL of *rac*-1-phenylethanol, 14 mg of solid TDPP were recovered (85% conversion). After column chromatography (eluent polarity gradient from DCM:PE = 3:7, to DCM 100%, to AcOEt:DCM = 2:98), and subsequent reprecipitation in MeCN, **TDPP-1-N** (57 mg, 52% yield on reacted substrate) and **TDPP-1-NN** (64 mg, 46% yield on reacted substrate) were obtained as bright red solids.

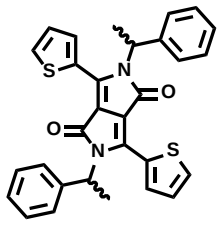


TDPP-1-N
(*R* + *S*)

^{1}H NMR (499 MHz, 50 °C, $CDCl_3$) δ = 8.33 (dd, J = 3.8, 0.8 Hz, 1H), 8.13 (d, J = 3.3 Hz, 1H), 7.93 (s, 1H), 7.57 (d, J = 5.0 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.28 – 7.24 (m, 1H), 7.20 (dd, J = 4.9, 4.0 Hz, 2H), 5.87 (q, J = 7.2 Hz, 1H), 2.01 (d, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.94, 141.18, 140.94, 136.80, 133.99, 132.74, 130.86, 130.79, 130.65, 129.47, 129.44, 128.75, 128.46, 127.41, 126.63, 109.16, 53.77, 29.87, 18.57 ppm.

HRMS: calcd for $[C_{22}H_{15}N_2O_2S_2]^-$ = 403.0693 , found = 403.05804



TDPP-1-NN
(*R,R* + *S,S* + *meso*)

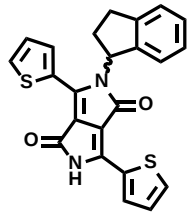
^{1}H NMR (499 MHz, 50 °C, $CDCl_3$) δ = 8.13 (dd, J = 3.8, 1.0 Hz, 2H), 7.53 (dd, J = 5.0, 1.0 Hz, 2H), 7.39 (d, J = 7.3 Hz, 4H), 7.36 – 7.32 (m, 4H), 7.26 – 7.23 (m, 2H), 7.15 (dd, J = 5.0, 3.9 Hz, 2H), 5.84 (qd, J = 7.1, 4.3 Hz, 2H), 1.98 (dd, J = 7.1, 2.3 Hz, 6H) ppm.

^{13}C NMR (126 MHz, 50 °C, $CDCl_3$) δ = 162.09, 141.29, 141.28, 141.26, 141.23, 134.19, 134.15, 130.75, 130.73, 129.38, 128.68, 128.41, 128.40, 127.34, 127.32, 126.74, 126.70, 109.93, 109.90, 53.73, 53.62, 29.87, 18.59, 18.52, 18.45 ppm.

HRMS: calcd for $C_{30}H_{24}N_2O_2S_2$ = 508.1279 , found = 508.1284

TDPP-2

Following the general procedure, from 96 mg of TDPP and 214 mg of *rac*-1-indanol,any traces of solid starting material TDPP did not remain in the mixture (100% conversion). After column chromatography (polarity gradient from DCM:PE = 3:7, to DCM 100%, to AcOEt:DCM = 2:98), and subsequent reprecipitation in MeCN, **TDPP-2-N** (32 mg, 24% yield) and **TDPP-2-NN** (124 mg, 73% yield on reacted substrate) were obtained as bright red solids.

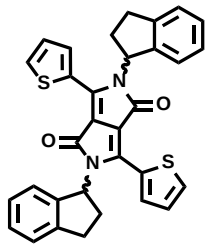


TDPP-2-N
(***R*** + ***S***)

^{1}H NMR (499 MHz, 50 °C, CDCl3) δ = 8.23 (d, J = 3.7 Hz, 1H), 8.16 (s, 1H), 7.68 (s, 1H), 7.49 (d, J = 4.6 Hz, 1H), 7.47 (d, J = 5.0 Hz, 1H), 7.22 – 7.08 (m, 5H), 6.17 – 6.11 (m, 1H), 3.23 – 3.15 (m, 1H), 2.96 – 2.88 (m, 1H), 2.67 – 2.59 (m, 1H), 2.51 (dtd, J = 12.4, 8.9, 3.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, 50 °C, CDCl3) δ = 161.53, 143.30, 141.61, 141.14, 136.66, 134.19, 132.82, 130.89, 130.64, 130.58, 129.55, 129.48, 128.51, 128.12, 126.85, 125.24, 123.39, 109.17, 53.49, 30.89, 30.43, 29.86 ppm.

HRMS: calcd for $[C_{23}H_{15}N_2O_2S_2]^-$ = 416.0583 , found = 415.0580



TDPP-2-NN
(***R,R*** + ***S,S*** + ***meso***)

^{1}H NMR (499 MHz, 50 °C, $CDCl_3$) δ = 8.21 (s, 2H), 7.51 (d, J = 4.8 Hz, 2H), 7.28 – 7.11 (m, 10H), 3.29 – 3.20 (m, 2H), 3.02 – 2.94 (m, 2H), 2.70 (td, J = 21.8, 9.6 Hz, 2H), 2.55 (dtt, J = 12.1, 8.9, 3.0 Hz, 2H) ppm.

^{13}C NMR (126 MHz, 50 °C, $CDCl_3$) δ = 161.69, 161.67, 143.25, 141.77, 141.66, 141.43, 141.41, 134.39, 134.33, 130.73, 130.67, 129.45, 129.43, 128.44, 128.02, 128.00, 126.78, 126.78, 125.20, 125.19, 123.39, 123.38, 109.75, 109.73, 60.07, 30.87, 30.86, 30.33, 29.86 ppm.

HRMS: calcd for $[C_{32}H_{23}N_2O_2S_2]^-$ = 531.1213, found = 531.1206

TDPP-3

Following the general procedure, from 96 mg of TDPP and 166 µL of benzyl alcohol, 46 mg of solid TDPP were recovered (52% conversion). After column chromatography (polarity gradient from DCM:PE = 3:7, to DCM 100%, to AcOEt:DCM = 2:98), and subsequent reprecipitation in MeCN, **TDPP-3-N** (19 mg, 30% yield on reacted substrate) and **TDPP-3-NN** (52 mg, 65% yield on reacted substrate) were obtained as dark red solids.

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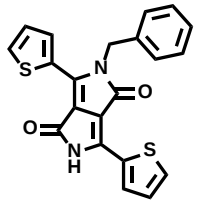
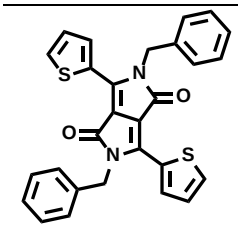
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.60 (s, 1H), 8.39 (s, 1H), 8.02 (s, 1H), 7.63 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H), 7.38 – 7.27 (m, 6H), 5.36 (s, J = 6.4 Hz, 2H) ppm.



TDPP-3-N

^{13}C NMR not available due to poor solubility in common deuterated solvents.

HRMS: calcd for $[C_{21}H_{13}N_2O_2S_2]^-$ = 389.0437 , found = 389.0424

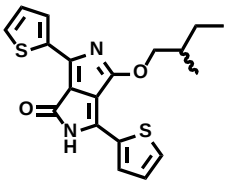


TDPP-3-NN

The spectrometric data match those previously reported in literature for this compound.[1]

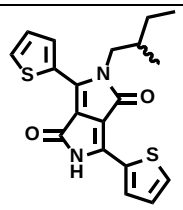
TDPP-5

Following the general procedure, from 96 mg of TDPP and 173 µL of *rac*-2-methyl-butanol, 48 mg of solid TDPP were recovered (50% conversion). After column chromatography (polarity gradient from DCM:PE = 3:7, to DCM 100%, to AcOEt:DCM = 2:98), **TDPP-5-O** (14 mg, 24% yield on reacted substrate), **TDPP-5-N** (13.6 mg, 23% yield on reacted substrate), a mixture of **TDPP-5-OO/TDPP-5-ON** (25 mg, 35% yield on reacted substrate) and **TDPP-5-NN** (8.5 mg, 12% yield on reacted substrate) were obtained as dark purple solids.



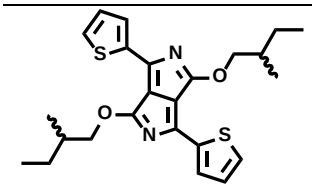
TDPP-5-O
(*R* + *S*)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.99 (s, 2H), 8.44 (d, J = 2.9 Hz, 2H), 8.03 (d, J = 3.5 Hz, 2H), 7.69 (d, J = 4.5 Hz, 2H), 7.53 (dd, J = 5.0, 1.0 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.22 (dd, J = 5.0, 3.8 Hz, 2H), 5.37 (d, J = 5.1 Hz, 2H), 1.98 – 1.75 (m, 4H), 1.50 (d, J = 6.2 Hz, 6H), 1.06 (t, J = 7.5 Hz, 6H) ppm.



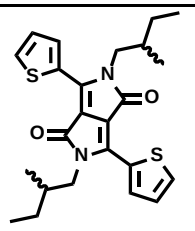
TDPP-5-N
(*R* + *S*)

The spectrometric data match those previously reported in literature for this compound.[4]



TDPP-5-OO
(*R,R* + *S,S* + *meso*)

^{1}H NMR (300 MHz, CDCl3) δ = 8.03 (d, J = 3.6 Hz, 2H), 7.54 (d, J = 5.1 Hz, 2H), 7.19 (dd, J = 4.9, 3.9 Hz, 2H), 5.33 (dd, J = 12.4, 6.1 Hz, 4H), 1.91 – 1.75 (m, 6H), 1.47 (d, J = 6.2 Hz, 6H), 1.04 (t, J = 7.4 Hz, 6H). ppm.

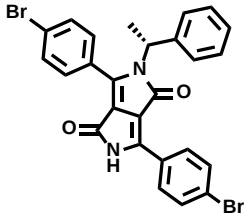


TDPP-5-NN
(*R,R* + *S,S* + *meso*)

The spectrometric data match those previously reported in literature for this compound.[5]

PDPP-1

Following the general procedure, from 96 mg of PDPP and 194 µL of (*S*)-1-phenylethanol, 22 mg of solid PDPP were recovered (77% conversion). After column chromatography (eluent polarity gradient from DCM:PE = 1:9, to DCM 100%, to AcOEt:DCM = 2:98), **PDPP-1-N** (19 mg, 14% yield on reacted substrate) and **PDPP-1-NN** (74 mg, 46% yield on reacted substrate) were obtained as bright orange solids.

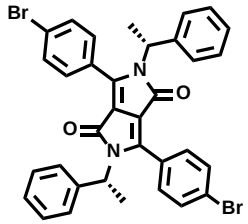


(*R*)-PDPP-1-N

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.70 (s, 1H), 8.15 (d, J = 8.7 Hz, 2H), 7.61 (dd, J = 12.9, 8.6 Hz, 4H), 7.49 (d, J = 8.6 Hz, 2H), 7.39 – 7.27 (m, 5H), 5.38 (q, J = 7.0 Hz, 1H), 1.92 (d, J = 7.2 Hz, 3H).

^{13}C NMR (76 MHz, $CDCl_3$) δ = 163.22, 162.66, 148.21, 144.24, 141.02, 132.63, 132.33, 130.68, 129.47, 128.88, 127.61, 127.10, 126.89, 126.44, 126.41, 126.13, 111.92, 110.27, 53.69, 18.74 ppm.

HRMS: calcd for $[C_{26}H_{17}Br_2N_2O_2]^-$ = 546.9675 , found = 546.9662



(*R*'*R*)-PDPP-1-NN

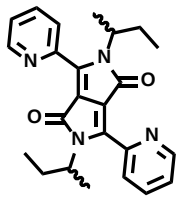
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60 – 7.54 (m, 4H), 7.47 – 7.42 (m, 4H), 7.36 – 7.27 (m, 10H), 5.30 (q, J = 7.0 Hz, 2H), 1.85 (d, J = 7.2 Hz, 6H) ppm.

^{13}C NMR (76 MHz, $CDCl_3$) δ = 162.67, 148.52, 141.13, 132.26, 130.60, 128.73, 127.49, 126.96, 126.60, 125.93, 110.84, 53.56, 13.71 ppm.

HRMS: calcd for $C_{34}H_{26}Br_2N_2O_2$ = 652.0345 , found = 652.0356

PyDPP-4

Following the general procedure, from 50 mg of PyDPP and 194 µL of (*S*)-1-phenylethanol, 30 mg of solid PDPP were recovered (40% conversion). After column chromatography (eluent polarity gradient from DCM:PE = 1:9, to DCM 100%), **PyDPP-4-N** (20 mg, 70% yield on reacted substrate) was obtained as a bright orange solid.



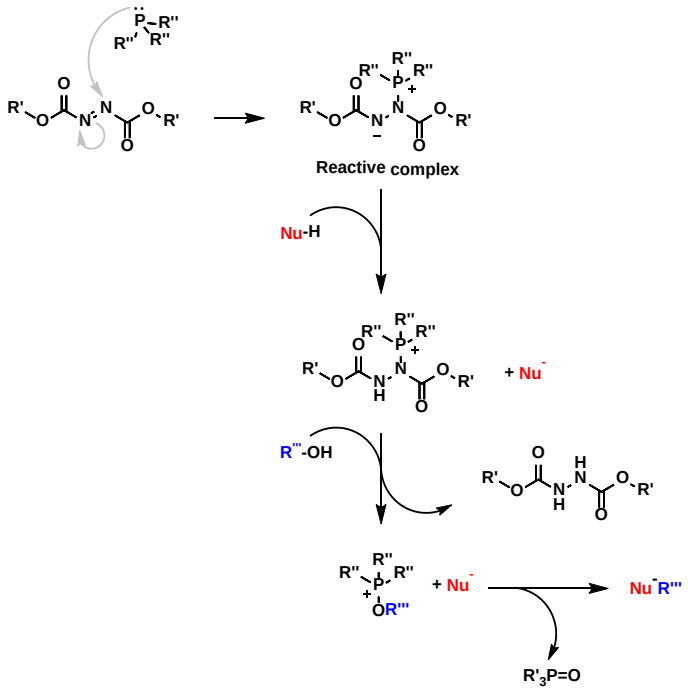
PyDPP-4-NN
(*R,R* + *S,S* + *meso*)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.72 (ddd, J = 4.7, 1.6, 0.7 Hz, 2H), 8.49 (dd, J = 8.0, 0.7 Hz, 2H), 7.89 (td, J = 7.8, 1.8 Hz, 2H), 7.34 (ddd, J = 7.6, 4.8, 1.1 Hz, 2H), 4.92 – 4.78 (m, 2H), 2.30 – 2.12 (m, 2H), 1.84 – 1.67 (m, 2H), 1.56 (dd, J = 6.8, 4.4 Hz, 6H), 0.84 (td, J = 7.4, 3.5 Hz, 6H) ppm.

^{13}C NMR (76 MHz, $CDCl_3$) δ = 163.13, 163.11, 149.27, 147.86, 147.85, 147.55, 147.45, 136.99, 127.41, 127.39, 124.79, 111.59, 111.55, 54.09, 54.04, 27.29, 18.91, 11.72, 11.67 ppm.

HRMS: calcd for $C_{24}H_{26}N_4O_2$ = 402.2056 , found = 402.2052

Mechanism of Mitsunobu reaction



Scheme S1 Simplified mechanism of the Mitsunobu reaction.

X-ray crystallography

Red, bright prismatic single crystals of racemic of **TDPP-5-NN** (i=5) have been obtained by evaporation from chloroform solution. Compound **TDPP-5-NN** (i=5) crystallized in the monoclinic system, centrosymmetric space group $P2_1/n$ with half of independent molecule in the asymmetric unit (Figure S1).

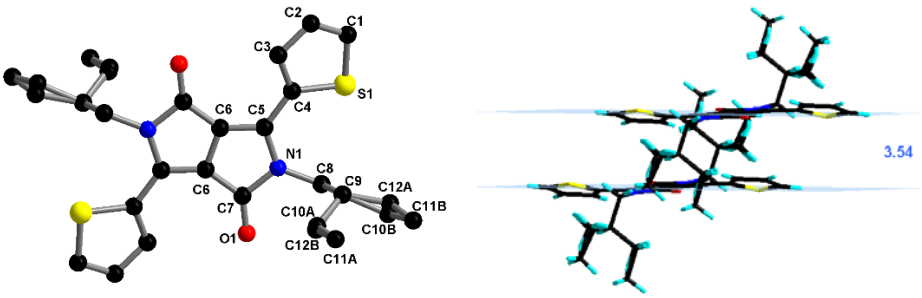


Fig. S1 View of the molecular structure with atom labels (left; hydrogen atoms have been omitted for clarity) and side view of the crystal packing together with the plane to plane distance given in Å (right) of TDPP-5-NN (i=5).

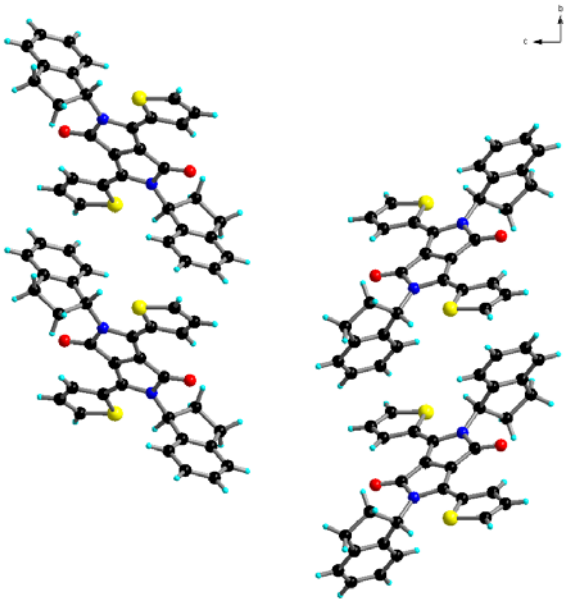


Fig. S2 Molecular packing of **TDPP-2-NN** (i=2) in the *bc* plane.

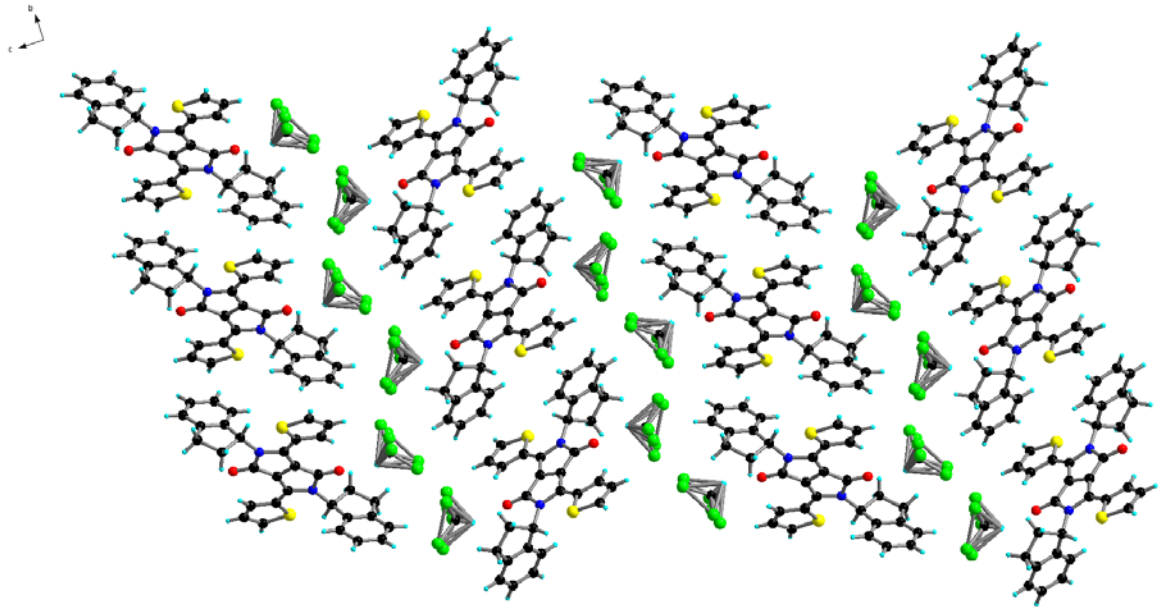


Fig. S3 Molecular packing of **TDPP-2-NN** (i=2) in the *bc* plane, showing a layer packing separated by solvent molecules.

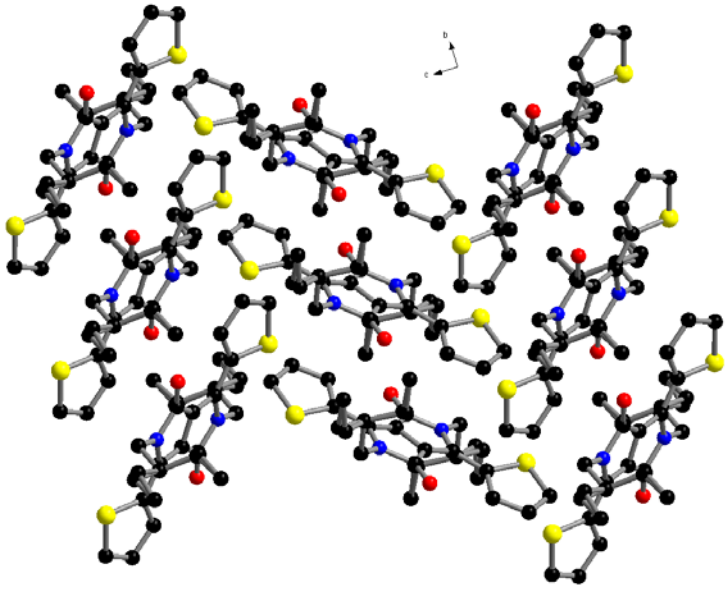


Fig. S4 Molecular packing of **TDPP-5-NN** (i=5, racemic) in the *bc* plane, showing the edge-to-face disposition of the molecules between the parallel layers.

Table S1 Detailed crystallographic data.

	TDPP-2-NN (i=2, racemic)	PyDPP-4-NN (i=4, racemic)	TDPP-5-NN (i=5, racemic)	TDPP-5-NN (i=5, *S,S*) (ref.14)
Chemical formula	$C_{34}H_{26}Cl_6N_2O_2S_2$	$C_{24}H_{26}N_4O_2$	$C_{24}H_{28}N_2O_2S_2$	$C_{24}H_{28}N_2O_2S_2$
M_r	771.39	402.49	440.60	440.60
Crystal system, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1$
Temperature (K)	150.0 (1)	200.4(6)	150.0 (1)	120
a, *b*, *c* (Å)	6.5241 (2), 9.3333 (3), 27.7177 (9)	11.5078(9, 5.6097(4, 16.8043(11)	13.0653 (11), 5.5363 (3), 16.2264 (10)	16.0248 (4), 5.61472 (12), 25.7171 (6)
β (°)	90.516 (3)	106.234(8)	109.093 (8)	106.106 (3)
V (Å^3)	1687.70 (9)	1041.55(14)	1109.14 (14)	2223.07 (10)
Z	2	2	2	4
ρ_{calc} (g.cm^{-3})	1.518	1.283	1.319	Cu $K\alpha$
μ (Cu $K\alpha$) (mm^{-1})	6.092	0.667	2.357	2.35
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7224, 3435, 3050	4206, 2096, 1789	4034, 2123, 1807	24225, 8553, 7909
R_{int}	0.0279	0.0204	0.0227	0.034
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0439, 0.1180, 1.042	0.0548, 0.1430, 1.074	0.0455, 0.1312, 1.050	0.036, 0.099, 1.05
CCDC number	2056004	2082406	2056005	

Table S2 Measured values (Å) of the aryl•••lactam centroids, inter-planar distances and overall plane to plane shift (ArDPP-ArDPP) together with dihedral angles (˚) between the planes of DPP and the adjacent aryl groups (DPP-Ar) and the planes of lactam unit and C_{Lactam}-N-C(R) of the substituent.

TDPP	Ar•••lactam centroids (Å)	Inter-planar distance (Å)	ArDPP plane to plane shift (Å)	DPP-Ar (˚)	Lactam-[C_{Lactam}-N-C(R)] (˚)
TDPP-2-NN (i=2, racemic)	3.82	4.01	5.39	13.85	7.46
TDPP-5-NN (i=5, racemic)	3.77	3.54	4.44	17.96	4.23
TDPP-5-NN (i=5, *S,S*)[6]	**a**: 3.69; 3.74 **b**: 3.69; 3.72	**a**: 3.58 **b**: 3.35	**a**: 4.54 **b**: 4.49	**a**: 18.24 and 14.57 **b**: 20.70 and 16.84	**a**: 3.43 and 4.35 **b**: 3.98 and 4.39
Py-DPP-4-NN (i=4, racemic)	-	3.98	4.10	34.21	

The X-ray structure of **TDPP-5-NN** (i=5, *S,S*) has already been reported as (*S,S*) enantiomer.[6]

Circular dichroism

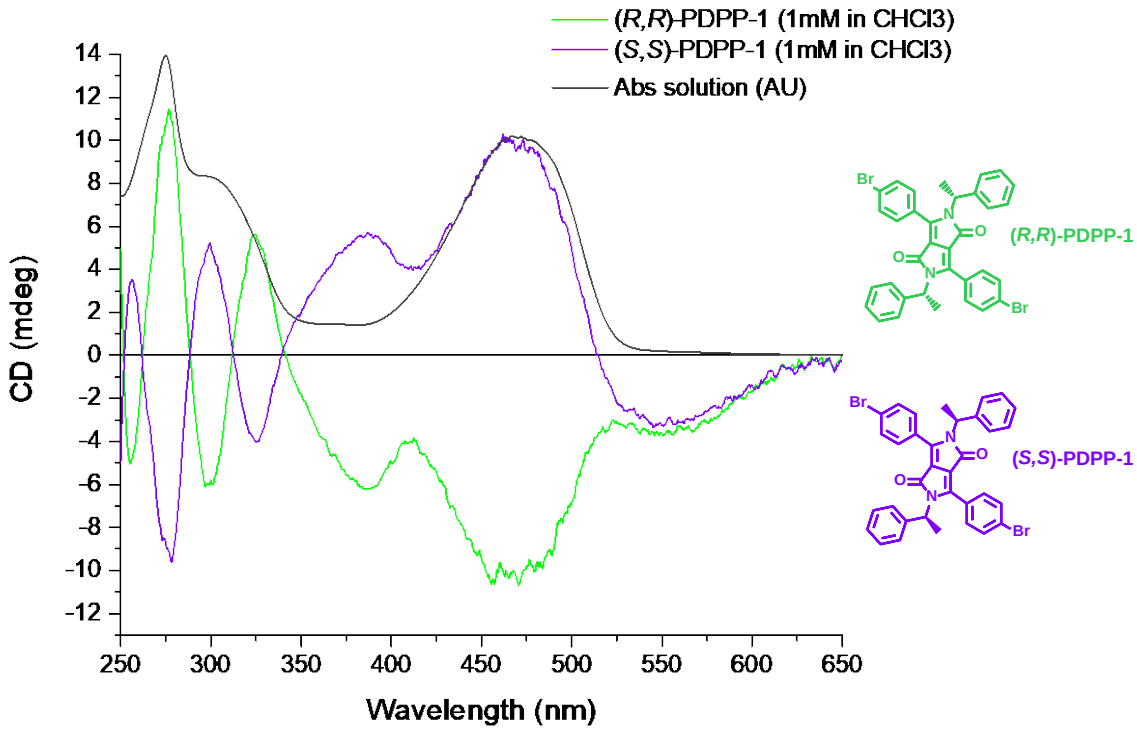


Fig. S5 Absorption and CD spectra of **PDPP-1-NN** (i=1) (*S,S*) and (*R,R*) enantiomers 1mM in chloroform solutions. (*S,S*) **PDPP-1-NN** (i=1) has been obtained in similar conditions and yields as the (*R,R*) **PDPP-1-NN** (i=1) described above.

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