HAL open science

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

Maurizio Mastropasqua Talamo, Flavia Pop, Narcis Avarvari

▶ **To cite this version:**

Maurizio Mastropasqua Talamo, Flavia Pop, Narcis Avarvari. Straightforward N -alkylation of diketopyrrolopyrroles through the Mitsunobu reaction with benzyl, α-branched, and chiral alcohols. Chemical Communications, 2021, 57 (53), pp.6514-6517. 10.1039/d1cc02472h . hal-03452266

HAL Id: hal-03452266

https://univ-angers.hal.science/hal-03452266v1

Submitted on 26 Nov 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

ChemComm

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

Journal:	*ChemComm*
Manuscript ID	Draft
Article Type:	Communication

SCHOLARONE™
Manuscripts

Chemical Communications May 10th, 2021

Statement

Dear Editor,

Please find attached a manuscript entitled: ***Straightforward N-alkylation of diketopyrrolopyrroles through Mitsunobu reaction with benzyl, α-branched, and chiral alcohols***, by Maurizio Mastropasqua Talamo, Flavia Pop and Narcis Avarvari, to be considered for publication in *Chemical Communications* as a Communication. I submit this manuscript in name of the other authors who are aware of and have approved the content and agree with the submission decision. None of the material has been published or is under consideration elsewhere, including the Internet.

Diketopyrrolopyrrole (DPP) and derivatives are versatile emissive dyes, provided with excellent stability. Their electronic and spectroscopic properties can be tuned through chemical synthesis by modifying the nature of the flanking aromatic units and the extension of the π-conjugated system. Their chemical versatility is further influenced by the nature of the N-alkyl units that play a crucial role in the improvement of the solubility, can also affect the structural, conformational, and solid-state organization through intra- and intermolecular interactions and have strong consequences on the electronic and photophysical properties. These class of derivatives have received much attention in recent years for applications in various areas such as molecular imaging, sensing, and, especially, organic electronics. N-alkylation of DPPs proceeds smoothly with primary alkyl halides but with secondary alkyl halides the yields dramatically drop to ~2% due to competitive elimination reactions. Secondary alkyl or benzyl groups on the N atoms of DPPs have a huge influence on the solid state organization, and hence on the photophysical properties and charge mobility, and also allow the introduction of stereogenic centres close to the DPP core, thereby the development of efficient methods for the introduction of such substituents is of paramount interest.

Here we report our comprehensive study on the use of primary, secondary aliphatic and benzyl-type alcohols as alkylating agents for the N-alkylation of DPPs under mild Mitsunobu conditions, enabling unprecedented convenient access to N-alkylated DPPs with α-branched side chains and with α-stereogenic carbons. The Mitsunobu strategy has never been adapted before to the N-alkylation of DPPs. The broad scope of the method is demonstrated for three aromatic flanking groups, namely thiophene, *para*-Br-benzene and pyridine. The influence of the solvent on the O-/N-alkylation ratio is emphasized as well. The use of enantiopure (*S*)-1-phenylethanol allowed the preparation of enantiopure DPP. The X-ray single crystal analysis of one DPP-thiophene and one DPP-pyridine N,N-substituted with indanyl and *sec*-butyl groups, respectively, represent the first examples of DPP bearing secondary carbon atoms linked to the N atoms of the lactam core characterized in the solid state.

We are convinced therefore that our work is suitable for publication in *Chemical Communications* since it presents the degree of novelty and originality required by the journal, and spans areas of general interest such as organic synthesis, precursors for organic electronics, crystal engineering, chirality, meeting the criteria of urgency to be submitted to *Chem. Commun.*

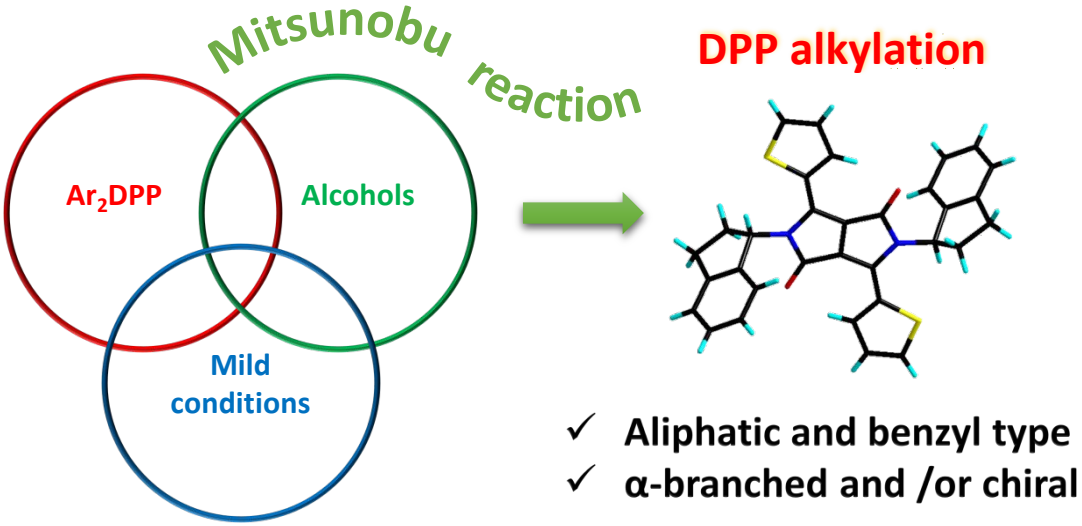
We look forward to hearing from you regarding the progress of our submission.

Thank you in advance for your time.

With best regards,
Maurizio Mastropasqua Talamo and Flavia Pop

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

Table of Contents Entry



Diketopyrrolopyroles are N-alkylated in mild conditions using secondary aliphatic and benzyl type alcohols.

COMMUNICATION

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

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Maurizio Mastropasqua Talamo,*[a] Flavia Pop*[a] and Narcis Avarvari[a]

The N-alkylation of diketopyrrolopyrroles (DPPs) represents a fundamental step to ensure solubility and further processability. Commonly used nucleophilic subtitution on halogenated derivatives is replaced in this work by Mitsunobu reaction affording unprecedented DPPs with α-branched and chiral chains.

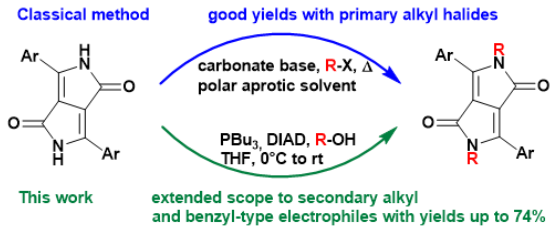
Diketopyrrolopyrrole (DPP) based compounds have triggered a remarkable attention in the research field of materials for optoelectronic applications,[1-3] fluorescent probes[4,5] and pigments.[6] The versatility of DPP derivatives in developing organic semiconductors consists in the adjustability, through chemical synthesis, of their electronic and spectroscopic properties by modifying the nature of the flanking aromatic units and the extension of the π-conjugated systems.[3,7] DPP derivatives are commonly synthesized by first forming the bilactam core through a condensation reaction between aromatic nitriles and succinic esters in the presence of tertiary alkoxides.[7] Asymmetrical DPPs, decorated with different aromatic units, can be equally obtained by forming the two lactam rings stepwise.[8] These synthetic routes, although being practical and cost-effective, afford secondary bilactams that result hardly soluble due to extended intermolecular hydrogen bonding.[9] For this reason a step of N-derivatization with alkyl chains[10] (more recently also with aryl groups[11,12] and cleavable *tert*-butoxycarbonyl groups[13-15]) is generally needed to ensure a satisfactory solubility for processing or further derivatization reactions. The symmetry of the DPP derivatives can be broken by using two different alkyl chains, method that has proven efficient to tune the planarity of the corresponding polymers and improve their charge mobility,[16] whereas fully asymmetric DPPs *via* both the nature of the aromatic units and of the alkyl chains has been reported only recently.[17]

[a] *Univ Angers, CNRS, MOLTECH-Anjou, SFR MATRIX, F-49000 Angers, France.*
E-mail: maurizio.mastropasquatalamo@univ-angers.fr; flavia.pop@univ-angers.fr

Electronic Supplementary Information (ESI) available: Experimental section, synthesis and characterization, X-ray crystallographic data. CCDC 2056004–2056005 and 2082406. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

The N-alkyl groups on DPP derivatives play a crucial role not only in the improvement of the solubility but, depending on their nature, they can also affect the structural, conformational, and solid-state organization through intra- and intermolecular interactions with strong consequences on the electronic and photophysical properties.[18-22] For instance, the π-π stacking interactions (which often determine a quenching of the photoluminescence in the solid state for DPP-based fluorophores) can be considerably reduced by using sterically demanding side chains such as benzyl groups[23-25] or α-branched alkyl groups.[19,26] This latter class of N-alkyl substituents should be regarded as a practical expedient for introducing stereogenic centres close to the DPP core, opening the way towards a cutting-edge class of chiral fluorophores with enhanced chiroptical properties.[27-30]

N-alkylation of DPPs is typically performed by bimolecular nucleophilic substitution reaction with alkyl halides, after deprotonation with non-nucleophilic bases, such as carbonate salts, in polar aprotic solvents upon heating (Scheme 1).[10] Under such conditions, N-alkylation proceeds smoothly with primary alkyl halides, but when secondary alkyl halides are used as alkylating agents the yields dramatically drop to ~2% due to competitive elimination reactions.[19] Moreover, the stereoselectivity of the S_N2 reactions, with typical Walden inversion, could be impaired in case of the use of secondary halides due to concomitant substitution reactions following a S_N1 mechanism. It appears thus evident that the N-alkylation step may become a bottleneck in the overall synthetic process, therefore any improvement in term of reaction yield is highly desirable.



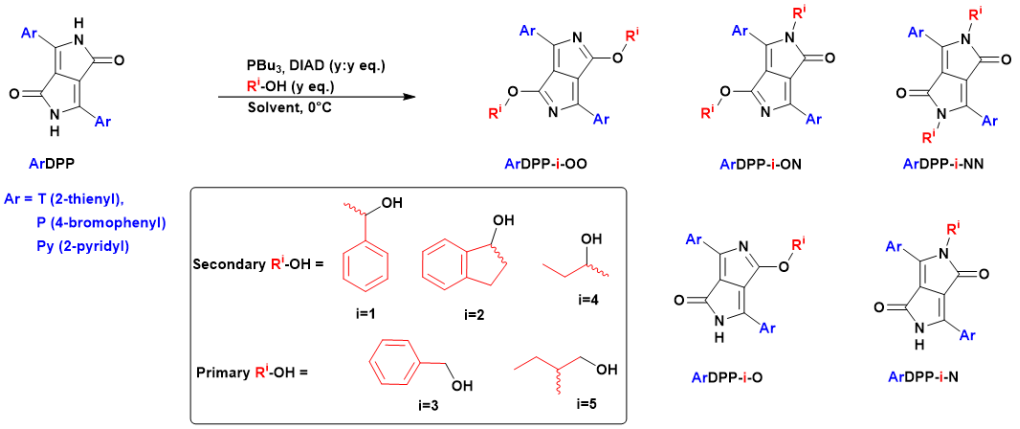
Scheme 1 Routes for N-alkylation of DDP derivatives.

In an attempt to overcome the severe limitations concerning the use of secondary halides, we decided to explore alternative methods for DPP N-alkylation, and therefore focused on the Mitsunobu reaction, which generally allows the formation of carbon-carbon and carbon-heteroatom bonds with stereoselective outcome. The Mitsunobu reaction involves the use of pro-nucleophiles (in the form Nu-H) and electrophiles derived from alcohols (R-OH, with R being a primary, secondary, sometimes tertiary alkyl group), in the presence of stoichiometric amounts of tertiary phosphines and azadicarboxylates.[31,32] Noteworthy, catalytic versions of the Mitsunobu reaction are recently emerging as a new synthetic tool with a more sustainable impact and with less troublesome purification issues.[33,34] The mechanism of the classic Mitsunobu reaction implies the synergistic action of phosphine and azadicarboxylate as a reactive adduct which allows the conversion of the pro-nucleophile into the nucleophile and the activation of the alcohol into the more reactive oxyphosphonium ion. The final step of the reaction consists in the nucleophilic attack on the oxyphosphonium, leading to the formation of the product Nu-R, with phosphine oxide and reduced azadicarboxylate as by-products (**Erreur ! Source du renvoi introuvable.**, SI).[31]

Here we report our study on the use of primary, secondary aliphatic and benzyl-type alcohols as alkylating agents for the N-alkylation of DPPs under mild Mitsunobu conditions, enabling unprecedented convenient access to N-alkylated DPPs with α-branched side chains and with α-stereogenic carbons.

In order to investigate the viability of the Mitsunobu reaction for the N-alkylation of bis-aryl-diketopyrrolopyrroles, three readily available DPP substrates were employed in our study, namely the 3,6-di(thiophen-2-yl)pyrrolo[3,4-*c*]pyrrole-1,4(2*H*,5*H*)-dione (**TDPP**), the 3,6-bis(4-bromophenyl)pyrrolo[3,4-*c*]pyrrole-1,4(2*H*,5*H*)-dione (**PDPP**) and 3,6-di(pyridin-2-yl)pyrrolo[3,4-*c*]pyrrole-1,4(2*H*,5*H*)-dione (**PyDPP**). As electrophilic counterpart, both primary alcohols (2-methyl-butan-1-ol, benzyl alcohol) and secondary alcohols (butan-2-ol, 1-phenyl-ethanol, 1-indanol) racemic and enantiopure (for 1-phenyl-ethanol) were employed (Scheme 2). To the best of our knowledge, the use of the Mitsunobu strategy has never been reported for DPP N-alkylation before. Yu et al.[35] confirmed the difficulties in the N-alkylation of lactams with secondary alkyl bromides, proposing instead the use of secondary heterobenzyl bromides as effective electrophiles. Jung and Fletcher[36] reported a study on the use of the Mitsunobu reaction for the selective N-alkylation of 1,4-benzodiazepines at the anilide site, which can be considered somehow similar to the N-H group of the DPP in terms of pK_a and reactivity. Their experiments gave good yields in chloroform at room temperature, with 2.5 eq. of R-OH/PBu_3/DIAD (diisopropyl-azadicarboxylate). Therefore, we chose to apply these conditions (except the use of 5 eq. due to the twofold reactivity of DPP bilactams) as a starting point in our investigation (Table 1). However, in our first attempts the starting material was largely recovered with only few traces of soluble coloured products (alkylated DPPs). We supposed that, due to the poor solubility of the DPP substrates in chloroform, side reactions (such as the alkylation of the azadicarboxylate) occurred at a much higher rate than the desired one. Based on this assumption, we changed the solvent for THF (which is a typical solvent for the Mitsunobu reaction) as it showed a better solubilisation of DPP substrates. This modification resulted in slightly higher but still unsatisfactory yields. A further improvement was obtained by changing the order of addition of the reagents: instead of adding the DIAD dropwise to the mixture containing all the other reagents, we first preformed the DIAD/PBu_3 complex, then we transferred the DIAD/PBu_3 complex to the DPP/THF mixture causing the effective deprotonation and solubilisation of the dye (witnessed by the appearance of a bright purple colour in solution), and finally we added dropwise the alcohol. After further adjustments, it was thus possible to attain good-to-excellent conversions in the case of primary alcohols such as benzyl alcohol (i=3) and 2-methyl-butan-1-ol (i=5), with a conversion of ca. 50% (probably limited by the very efficient DIAD-alkylation side reaction), whereas secondary alcohols racemic (i=1, i=2) and chiral (i=1) led to a much higher conversion, from 77% up to quantitative.

Alkylation with benzyl-type alcohols (i=3) gave NN-products with yields (based on the converted starting material) ranging from 46% to 73%.



Scheme 2 Synthesis of alkylated DPP derivatives **TDPP-1**, **TDPP-2**, **TDPP-3**, **TDPP-5**, **PDPP-1** and **PyDPP-4**, with the structures of all the possible products of mono-O-alkylation, mono-N-alkylation, bis-OO-alkylation, bis-ON-alkylation, and bis-NN-alkylation.

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

COMMUNICATION

Table 1 Reaction conditions of TDPP, PDPP and PyDPP alkylation with corresponding conversion rate and molar composition of the products.

Ar	i	R^i-OH	y (eq.)	solvent	Conversion[a]	molar composition of the products[b]			
						ArDPP-i-O	ArDPP-i-N	ArDPP-i-OO	ArDPP-i-NN
T	1	*rac*-1-PhEtOH	2.5[c]	THF	50%	/	63%	/	28%
			5[c]	THF	55%	/	46%	/	26%
			5	THF	85%	Traces[d]	52%	/	46%
	2	*rac*-1-indanol	5	THF	100%	/	24%	/	73%
	3	BnOH	5	THF	52%	Traces[d]	30%	Traces[d]	65%
	5	*rac*-2-Me-1-BuOH	5	THF	50%	24%	23%	34%	12%
			5	$CHCl_3$	30%	Traces[d]	23%	13%	57%
P	1	(*S*)-1-PhEtOH	5	THF	77%	/	14%	/	46%
Py	4	*rac-sec*-BuOH	5	THF	40%	/	Traces	/	70%

[a] Conversion based on recovered starting material. [b] Remainder to 100% consisting of unidentified by-products. [c] Alcohol added all at once instead than dropwise. [d] Visible on column chromatography, with slightly larger RF than the N-alkylated counterpart, but not present in quantifiable amount.

Even considering a yield based on the starting material, the new method afforded the product of bis-NN-benzylation of **TDPP** in a 34% yield (52% conversion × 65% yield based on converted started material) which is much larger than the 7% previously reported for the nucleophilic substitution with benzyl bromide.[37]

As mentioned by Jung and Fletcher,[36] we found that the selectivity between O- and N-alkylation is sensibly reduced in case of the use of aliphatic alcohols, with detectable amounts of O-alkylated products in the case of 2-methyl-butan-1-ol (i=5), whereas in the case of benzyl type alcohols (i=1-3) the alkylation proceeded almost exclusively at the nitrogen site. Following their argument about the beneficial role of chloroform as solvent, we tested again the N-alkylation of **TDPP** with 2-methyl-butan-1-ol (i=5) in $CHCl_3$, implementing our new conditions regarding the order of addition of the reagents. Despite a conversion of only 30%, this latter modification resulted indeed in an improvement of chemoselectivity (N- vs O-alkylation), with a yield of bis-NN-alkylation based on the converted started material of 57%, which exceeds the 34% previously reported for N-alkylation with the corresponding alkyl bromide.[38]

The DPP derivatives with α-branched alkyls obtained with the new method described herein have never been characterized before. Besides the possibility of having the ramification of the alkyl chain next to the N-atom of the DPP core, this new method can render them chiral if enantiopure alcohols are used as demonstrated by the use of (*S*)-1-phenylethanol (i=1). The position of the ramification on the alkyl chain plays an important role in the stacking in the solid state of the corresponding DPPs. As previously shown, the displacement of the neighbouring molecules in the packing of **TDPP** molecules is highly dependent of the nature and bulkiness of the substituents.[18] **TDPP-2-NN** (i=2) and **PyDPP-4-NN** (i=4), which could be obtained as suitable single crystals for X-ray diffraction analysis, represent the first examples of DPP bearing secondary carbon atom linked to the N of the lactam core that have ever been characterized in the solid state. The effect of the bulky indanyl and *sec*-butyl can be rationalized from the π-π stacking interactions which can be appreciated from the molecular displacement and interplanar distances (Table S2, SI). The interplanar distance of 4.01 Å observed for compound **TDPP-2-NN** is superior to the one observed in the crystal of **TDPP-5-NN** (i=5, racemic and (*S,S*) enantiomer[18]) which was highest reported to date amongst similar bis-N,N-alkylated **TDPP**s (Fig.

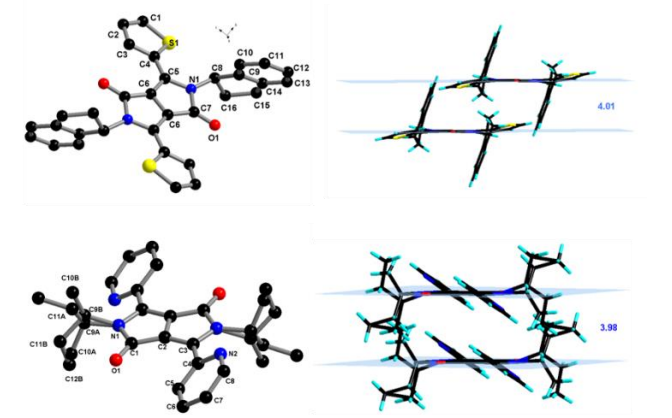


Fig. 1 View of the molecular structure with atom labels (left; hydrogen atoms have been omitted for clarity) and side view of the crystal packing together with the plane to plane distance given in Å (right) of **TDPP-2-NN** (i=2) (top) and **PyDPP-4-NN** (i=4) (bottom). The *sec*-butyl group is disordered in **PyDPP-4-NN**.

Please do not adjust margins

1 and Table S2, ESI). Similarly, the overall molecular displacement in compound **TDPP-2-NN** is more significant than in other **TDPP**s reflecting the effect of the substituent bulkiness. Ultimately, the reaction conditions were not optimized for maximizing the yields of bis-N,N-alkylation, since mono-N-alkylated DPP also have synthetic interest towards the preparation of unsymmetrically dialkylated DPP. Nonetheless, we believe that improvements in terms of substrate conversion and completeness of the reaction could be achieved by further adjustments of the reagents stoichiometry.

In conclusion, the use of the Mitsunobu reaction for the N-alkylation of DPP with alcohols as electrophilic agents, shows promising features regarding the enhanced access to soluble DPP derivatives. Beyond the use of mild conditions and the possibility to recycle the starting material, the advantages of this method comprise also the introduction of secondary and stereogenic carbon directly connected to the DPP core through C–N bonds with unprecedented straightforwardness. Moreover, since alcohols are usually employed as starting material for the synthesis of the corresponding alkyl halides, this new approach benefits of the use of cheaper and less hazardous alkylating agents. These synthetic improvements are expected to significantly boost the research in the field of functional DPP-based materials for optoelectronics and chiroptical applications.

This work was supported in France by the CNRS, the University of Angers, the Région Pays de la Loire and the RFI LUMOMAT (HEROES Project). Coraline Clochard (MOLTECH-Anjou) is warmly thanked for help with the synthesis of compound **TDPP-5**. Magali Allain (MOLTECH-Anjou) is deeply acknowledged for help with the refinement of the crystal structures.

There are no conflicts to declare.

Notes and references

1 S. Ghosh, S. Shankar, D. S. Philips and A. Ajayaghosh, *Mater. Today Chem.*, 2020, **16**, 100242.
2 Q. Liu, S. E. Bottle and P. Sonar, *Adv. Mater.*, 2020, **32**, 1903882-1–46.
3 A. Ruiz-Carretero, N. R. Ávila Rovelo, S. Militzer and P. J. Mésini, *J. Mater. Chem. A*, 2019, **7**, 23451-23475.
4 W. Li, L. Wang, H. Tang and D. Cao, *Dyes Pigm.*, 2019, **162**, 934–950.
5 M. Kaur and D. H. Choi, *Chem. Soc. Rev.*, 2015, **44**, 58–77.
6 M. Casutt, B. Dittmar, H. Makowska, T. Marszalek, S. Kushida, U. H. F. Bunz, J. Freudenberg, D. Jänsch and K. Müllen, *Chem. Eur. J.*, 2019, **25**, 2723–2728.
7 M. Grzybowski and D. T. Gryko, *Adv. Opt. Mater.*, 2015, **3**, 280–320.
8 S. Stas, J.-Y. Balandier, V. Lemaur, O. Fenwick, G. Tregnago, F. Quist, F. Cacialli, J. Cornil and Y. H. Geerts, *Dyes Pigm.*, 2013, **97**, 198–208.
9 A. Iqbal, M. Jost, R. Kirchmayr, J. Pfenninger, A. Rochat and O. Wallquist, *Bull. Soc. Chim. Belg.*, 1988, **97**, 615–644.
10 F. Pop, J. Humphreys, J. Schwarz, L. Brown, A. van den Berg and D. B. Amabilino, *New J. Chem.*, 2019, **43**, 5783–5790.
11 K. Gutkowski, K. Skonieczny, M. Bugaj, D. Jacquemin and D. T. Gryko, *Chem. Asian J.*, 2020, **15**, 1369–1375.
12 W. Jiang, Z. Liu, D. Zhu, W. Zheng, L. Chen, X. Zhang, G. Zhang, Y. Yi, L. Jiang and D. Zhang, *Angew. Chem. Int. Ed.*, 2021, **60**, 10700–10708.
13 A. Punzi, E. Maiorano, F. Nicoletta, D. Blasi, A. Ardizzone, N. Ventosa, I. Ratera, J. Veciana and G. M. Farinola, *Eur. J. Org. Chem.*, 2016, **2016**, 2617–2627.
14 M. Rooney, S. Mattiello, R. Stara, A. Sanzone, P. Brazzo, M. Sassi and L. Beverina, *Dyes Pigm.*, 2018, **149**, 893–901.
15 S. Mula, T. Han, T. Heiser, P. Lévêque, N. Leclerc, A. P. Srivastava, A. Ruiz-Carretero and G. Ulrich, *Chem. Eur. J.*, 2019, **25**, 8304–8312.
16 Z. Wang, Z. Liu, L. Ning, M. Xiao, Y. Yi, Z. Cai, A. Sadhanala, G. Zhang, W. Chen, H. Sirringhaus and D. Zhang, *Chem. Mater.*, 2018, **30**, 3090–3100.
17 L. Sharma and H. Bronstein, *RSC Adv.*, 2021, **11**, 5276–5283.
18 F. Pop, W. Lewis and D. B. Amabilino, *CrystEngComm*, 2016, **18**, 8933–8943.
19 B. W. H. Saes, M. M. Wienk and R. A. J. Janssen, *Chem. Eur. J.*, 2020, **26**, 14221–14228.
20 M. Cigánek, P. Heinrichová, A. Kovalenko, J. Kučerík, M. Vala, M. Weiter and J. Krajčovič, *Dyes Pigm.*, 2020, **175**, 108141.
21 B. W. H. Saes, M. Lutz, M. M. Wienk, S. C. J. Meskers and R. A. J. Janssen, *J. Phys. Chem. C*, 2020, **124**, 25229–25238.
22 S. Militzer, N. Nishimura, N. R. Ávila-Rovelo, W. Matsuda, D. Schwaller, P. J. Mésini, S. Seki and A. Ruiz-Carretero, *Chem. Eur. J.*, 2020, **26**, 9998–10004.
23 Y. Jin, Y. Xu, Y. Liu, L. Wang, H. Jiang, X. Li and D. Cao, *Dyes Pigm.*, 2011, **90**, 311–318.
24 A. S. Murphy, C. E. Killalea, J. Humphreys, P. A. Hume, M. J. Cliffe, G. J. Murray, E. S. Davies, W. Lewis and D. B. Amabilino, *ChemPlusChem*, 2019, **84**, 1413–1422.
25 J. Kuwabara, T. Yamagata and T. Kanbara, *Tetrahedron*, 2010, **66**, 3736–3741.
26 I. Meager, R. S. Ashraf, S. Mollinger, B. C. Schroeder, H. Bronstein, D. Beatrup, M. S. Vezie, T. Kirchartz, A. Salleo, J. Nelson and I. McCulloch, *J. Am. Chem. Soc.*, 2013, **135**, 11537–11540.
27 C. Ye, J. Zhang, X. Lin, T. Zhang, B. Wang, and T. He, *Opt. Mater. Express*, 2017, **7**, 3529–3537.
28 T. Gao, Z. Jiang, B. Chen, Q. Sun, Y. Orooji, L. Huang and Z. Liu, *Dyes Pigm.*, 2020, **173**, 107998.
29 K. Dhbaibi, L. Favereau, M. Srebro-Hooper, M. Jean, N. Vanthuyne, F. Zinna, B. Jamoussi, L. Di Bari, J. Autschbach and J. Crassous, *Chem. Sci.*, 2018, **9**, 735–742.
30 K. Dhbaibi, C. Shen, M. Jean, N. Vanthuyne, T. Roisnel, M. Górecki, B. Jamoussi, L. Favereau and J. Crassous, *Front. Chem.*, 2020, **8**, 237.
31 S. Fletcher, *Org. Chem. Front.*, 2015, **2**, 739–752.
32 O. Mitsunobu, *Synthesis*, 1981, 1-28.
33 R. H. Beddoe, H. F. Sneddon and R. M. Denton, *Org. Biomol. Chem.*, 2018, **16**, 7774–7781.
34 R. H. Beddoe, K. G. Andrews, V. Magné, J. D. Cuthbertson, J. Saska, A. L. Shannon-Little, S. E. Shanahan, H. F. Sneddon and R. M. Denton, *Science*, 2019, **365**, 910–914.
35 M. Yu, K. Stevenson and G. Zhou, *Tetrahedron Lett.*, 2014, **55**, 5591–5594.
36 K.-Y. Jung and S. Fletcher, *MedChemComm*, 2012, **3**, 1160–1163.
37 J. Calvo-Castro, S. Maczka, C. Thomson, G. Morris, A. R. Kennedy and C. J. McHugh, *CrystEngComm*, 2016, **18**, 9382–9390.
38 M. Kirkus, L. Wang, S. Mothy, D. Beljonne, J. Cornil, R. A. J. Janssen and S. C. J. Meskers, *J. Phys. Chem. A*, 2012, **116**, 7927–7936.

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

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

Maurizio Mastropasqua Talamo,*[a] Flavia Pop*[a] and Narcis Avarvari[a]

[a] *Univ Angers, CNRS, MOLTECH-Anjou, SFR MATRIX, F-49000 Angers, France. E-mail: maurizio.mastropasquatalamo@univ-angers.fr; flavia.pop@univ-angers.fr*

Table of contents

Straightforward N-alkylation of diketopyrrolopyrroles through Mitsunobu reaction with benzyl, α-branched, and chiral alcohols 1
General methods and materials 1
Synthesis and characterization 2
TDPP-1 3
TDPP-2 4
TDPP-3 5
TDPP-5 6
PDPP-1 7
PyDPP-4 8
Mechanism of Mitsunobu reaction 9
X-ray crystallography 9

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.

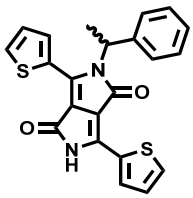
The mixture was quenched with a splash of water, concentrated under vacuum, diluted into CH_2Cl_2, filtered through a PTFE membrane to collect the insoluble unreacted ArDPP. The filtrate was washed with 1M HCl, then water, the organic layer was dried over $MgSO_4$ and the solvent removed under reduced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

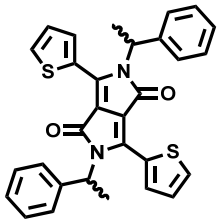


TDPP-1-N
(*R* + *S*)

^{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*)

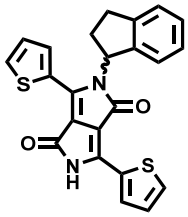
^{1}H NMR (499 MHz, 50 °C, $CDCl_3$) δ = 8.13 (dd, J = 3.8, 1.0 Hz, 2H), 7.53 (dd, J = 5.0, 1.0 Hz, 2H), 7.39 (d, J = 7.3 Hz, 4H), 7.36 – 7.32 (m, 4H), 7.26 – 7.23 (m, 2H), 7.15 (dd, J = 5.0, 3.9 Hz, 2H), 5.84 (qd, J = 7.1, 4.3 Hz, 2H), 1.98 (dd, J = 7.1, 2.3 Hz, 6H) ppm.

^{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.

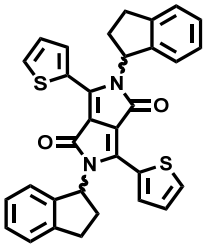


TDPP-2-N
(*R* + *S*)

^{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*)

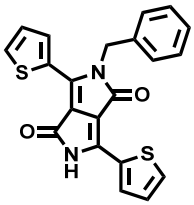
^{1}H NMR (499 MHz, 50 °C, $CDCl_3$) δ = 8.21 (s, 2H), 7.51 (d, J = 4.8 Hz, 2H), 7.28 – 7.11 (m, 10H), 3.29 – 3.20 (m, 2H), 3.02 – 2.94 (m, 2H), 2.70 (td, J = 21.8, 9.6 Hz, 2H), 2.55 (dtt, J = 12.1, 8.9, 3.0 Hz, 2H) ppm.

^{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.

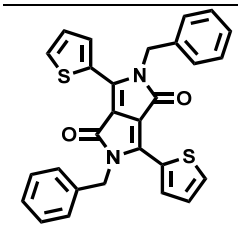


TDPP-3-N

^{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.

^{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

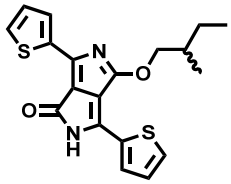
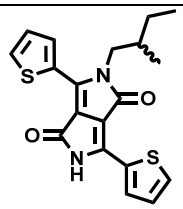
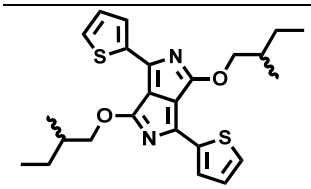
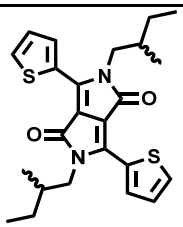


TDPP-3-NN

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

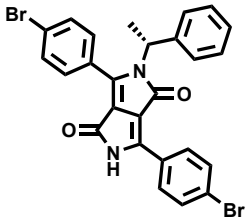
TDPP-5

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.

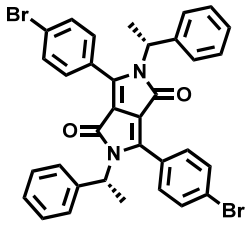


(*R*)-PDPP-1-N

^{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

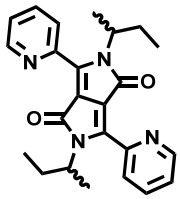
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.60 – 7.54 (m, 4H), 7.47 – 7.42 (m, 4H), 7.36 – 7.27 (m, 10H), 5.30 (q, J = 7.0 Hz, 2H), 1.85 (d, J = 7.2 Hz, 6H) ppm.

^{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.



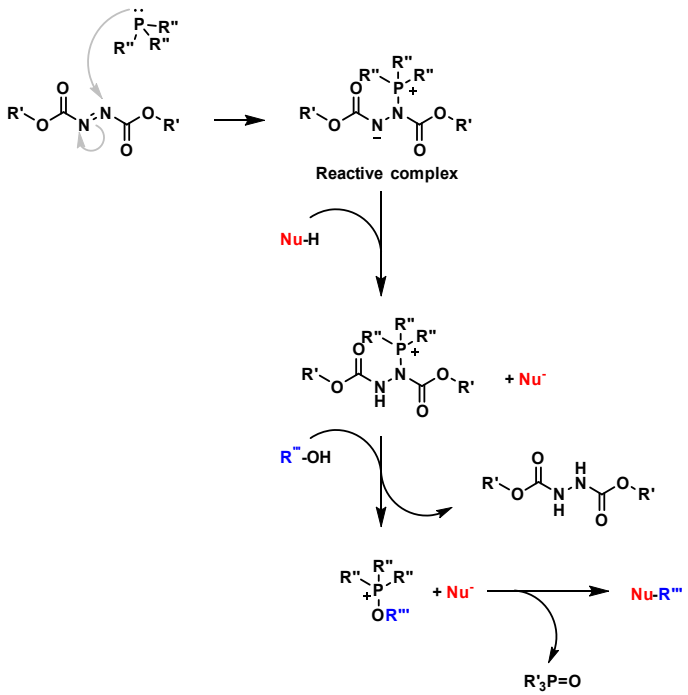
PyDPP-4-NN
(*R,R* + *S,S* + *meso*)

^{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).

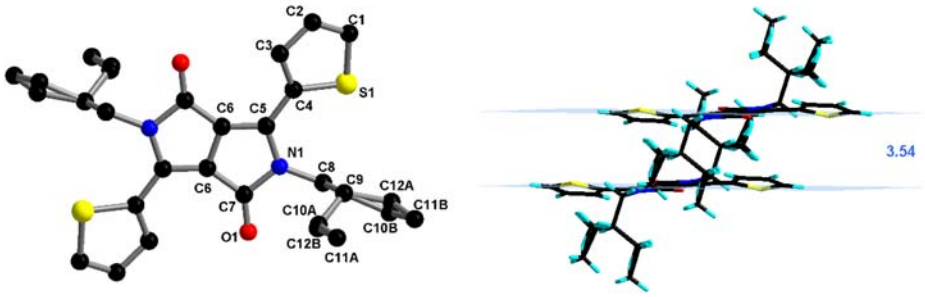


Fig. S1 View of the molecular structure with atom labels (left; hydrogen atoms have been omitted for clarity) and side view of the crystal packing together with the plane to plane distance given in Å (right) of TDPP-5-NN (i=5).

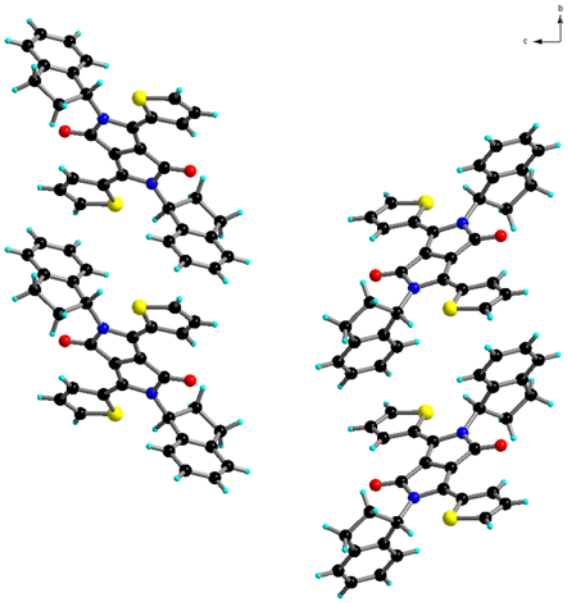


Fig. S2 Molecular packing of **TDPP-2-NN** (i=2) in the *bc* plane.

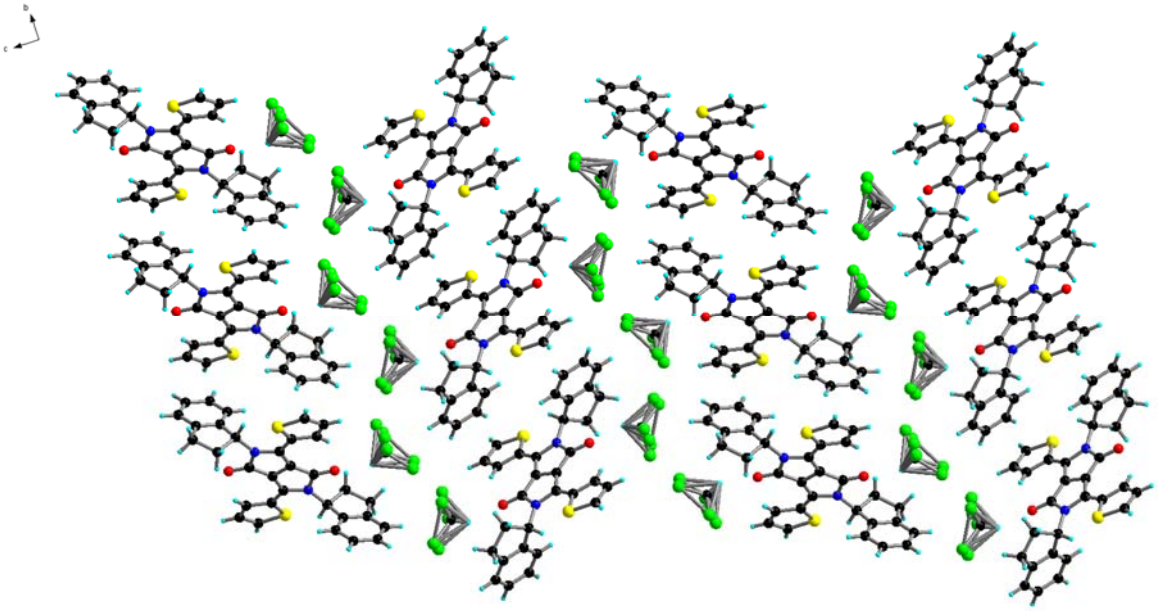


Fig. S3 Molecular packing of **TDPP-2-NN** (i=2) in the *bc* plane, showing a layer packing separated by solvent molecules.

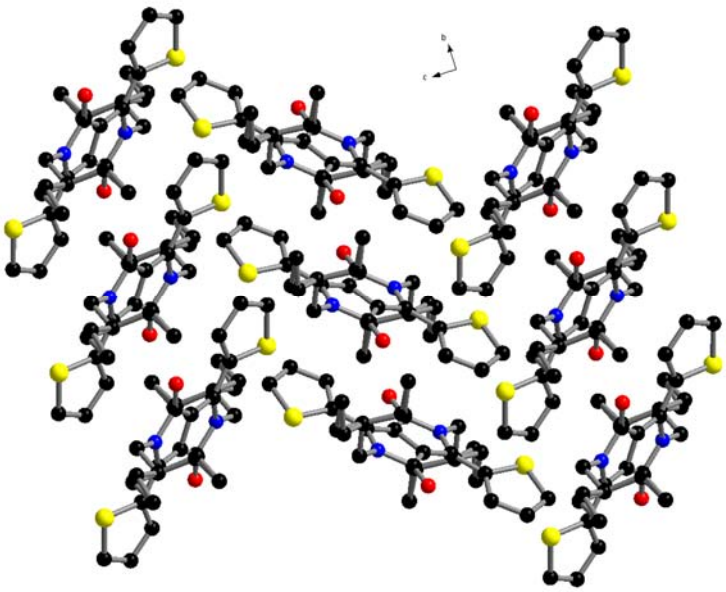


Fig. S4 Molecular packing of **TDPP-5-NN** (i=5, racemic) in the *bc* plane, showing the edge-to-face disposition of the molecules between the parallel layers.

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]

1. J. Calvo-Castro, S. Maczka, C. Thomson, G. Morris, A. R. Kennedy and C. J. McHugh, *CrystEngComm*, 2016, **18**, 9382–9390.
2. T. G. Hwang, J. Y. Kim, J. W. Namgoong, J. M. Lee, S. B. Yuk, S. H. Kim and J. P. Kim, *Photochem. Photobiol. Sci.*, 2019, **18**, 1064–1074.
3. E. H. Ghazvini Zadeh, M. V. Bondar, I. A. Mikhailov and K. D. Belfield, *J. Phys. Chem. C*, 2015, **119**, 8864–8875.
4. F. Pop, W. Lewis and D. B. Amabilino, *CrystEngComm*, 2016, **18**, 8933–8943.
5. S. Rieth, Z. Li, C. E. Hinkle, C. X. Guzman, J. J. Lee, S. I. Nehme and A. B. Braunschweig, *J. Phys. Chem. C*, 2013, **117**, 11347–11356.
6. Y. Zhou, C. X. Guzman, L. C. Helguero-Kelley, C. Liu, S. R. Peurifoy, B. Captain and A. B. Braunschweig, *J. Phys. Org. Chem.*, 2016, **29**, 689–699.