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One-pot facile synthesis of 4-amino-1,8-naphthalimide derived Tröger's bases *via* a nucleophilic displacement approach

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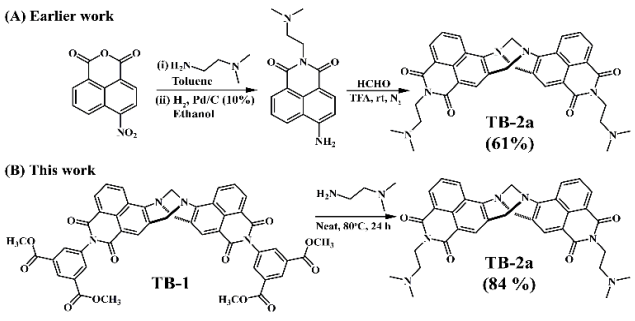
We report here a novel one-pot synthetic strategy for the synthesis of a family of *N*-alkyl-1,8-naphthalimide based Tröger's bases *via* a nucleophilic substitution reaction of a common 'precursor' (or a 'synthon') *N*-aryl-1,8-naphthalimide Tröger's base heated at 80ºC in neat aliphatic primary amine, in overall yield of 65-96 %. This methodology provides an efficient and one-step facile rout to design 1,8-naphthalimide derived Tröger's base structures in analytically pure form without the use of column chromatography purification, that can be used in medicinal chemistry and as supramolecular scaffolds. We also report the formation of the corresponding anhydride, and the crystallographic analysis of two of the resulting products, that of the *N*-phenyl-4-amino-1,8-naphthalimide and the anhydride derived Tröger's bases.

Introduction

Tröger's base (TB), was first synthesised by Julius Tröger in 1887 from the reaction of *p*-toluidine and formaldehyde in aqueous hydrochloric acid.[1] This motif gives rises to a fascinating chiral cleft-shaped molecule containing a methano-1,5-diazocine ring fused with two aromatic molecules, that has been employed in numerous systems.[2-3] The intrinsic chirality with a C_2 axis of symmetry of the TB structure is provided by the presence of the two configurationally stable bridgehead stereogenic nitrogen atoms of the diazocine ring.[4] X-ray crystallographic analysis has shown that the methano-1,5-diazocine ring (N-CH_2-N) places the two aromatic moieties almost orthogonal to each other, with dihedral angles ranging from 90 to 104º, thus engendering a unique V-shaped geometry possessing a hydrophobic cavity.[5-7] The TB structure was one of the very early heterocyclic ring systems to be isolated with stereogenic "N" atoms and has been used as racemates within the field of supramolecular chemistry.[8-9] The ease of synthesis and its unique chiral cleft-shaped geometry has made TB an attractive supramolecular scaffold for the design of molecular receptors for anions, cations and biologically relevant small molecules including nucleic acid.[10] The TB structure has also been used in the development of "torsion-balance,[11] water soluble cyclophanes,[9, 12] chiral solvating agents[6] and molecular tweezers,[3, 7, 13-14] optoelectronic devices[3, 14] selective catalysis[15] and in the formation of various hydrogen- and metal-mediated self-assembled structures.[16]

The 4-amino-1,8-naphthalimide derivatives belong to an important class of heterocyclic fluorophores, which absorb and emit within the visible region, with high fluorescence quantum yield and large Stokes shift, which is solvent dependent.[17-18] The strong emission characteristics of 4-amino-1,8-naphthalimides in various organic and aqueous media, is due to their internal charge-transfer (ICT) excited state transition, which is caused by the "push–pull" character of the electron-withdrawing imide and the electron donating amino moiety.[19-20] The 1,8-naphthalimide fluorophores have been used in a variety of applications including the development of colorimetric and luminescent sensors for biologically relevant ions and molecules,[18-19, 21] fluorescent logic gates and molecular switches.[22] They have also been used as luminescent probes for selective staining of live cells,[23] as potential DNA targeting agents,[24] stimuli responsive hydrogel[25] and in photochemical welding of tissues.[26]



Scheme 1. Synthesis of 4-amino-1,8-naphthalimide derived Tröger's base **TB-2a**. (A) The earlier reported procedure from the Gunnlaugsson research group. (B) The newly developed one-pot synthetic procedure described herein.

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† Electronic Supplementary Information (ESI) available: ^{1}H NMR of **TB-1**, ^{1}H, ^{13}C NMR and HRMS spectra of **TB-**(**2a-2k**) and **TB-3**. Crystallographic details for **TB-2k** (CCDC = 1563998) and **TB-3** (CCDC = 1564000). See DOI: 10.1039/x0xx00000x

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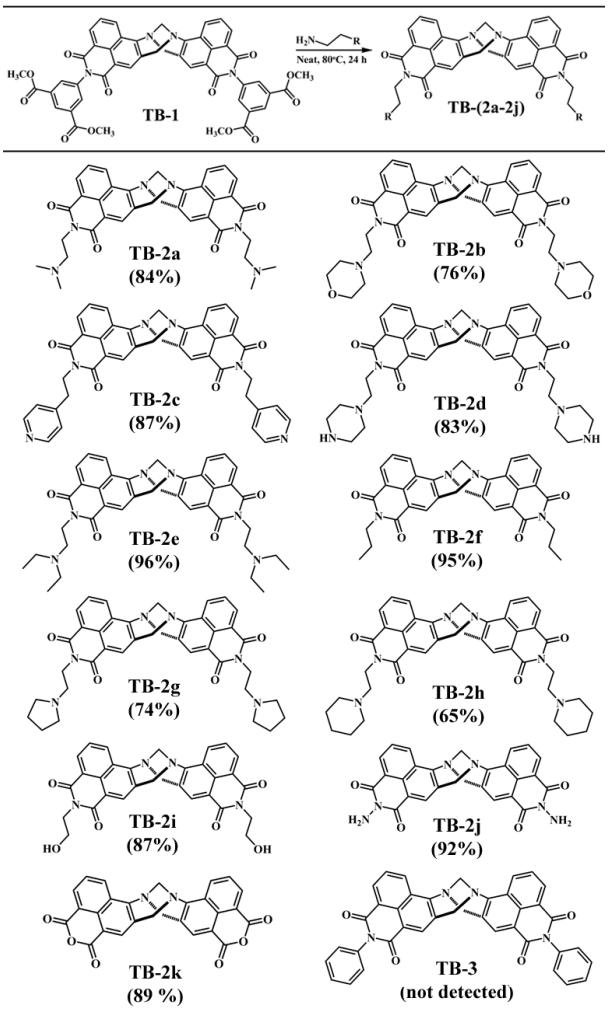
Over the past few years, we have developed several examples of 3- and 4-amino-1,8-naphthalimide fluorophore derived Tröger's base structural motifs (*c.f.* Scheme 1). We have employed these as novel bifunctional luminescent supramolecular scaffolds for self-assembly to create hierarchical supramolecular functional materials for applications within the supramolecular and medicinal chemistry fields.[27, 28-31] Prior to our work, Lewis *et al*. synthesized a series of 4-amino-1,8-naphthalimde-derived Tröger's bases and demonstrated some of their photophysical characteristics.[32]

In general, these naphthalimide TB derivatives are synthesised in three steps from 3/4-nitro-1,8-naphthalic anhydride as shown in Scheme 1A.[27, 32] As part of our on-going research in the development of new synthetic methodology, we report herein a novel one-pot expedient synthetic method for the design and synthesis of a family of *N*-alkyl-1,8-naphthalimide based Tröger's bases **TB-(2a-2k)** from a common precursor **TB-1**, in neat amine as *via* a nucleophilic displacement approach, Scheme 1B. We were also able to treat **TB-1** in aqueous KOH, which gave the corresponding anhydride, which opens up the possibility of further derivatisations. This methodology provides a convenient entry into the synthesis of 4-amino-1,8-naphthalimide derivatives in one-pot, with higher yielding and high purity end products, which makes **TB-1**, an ideal 'synthon' for the formation of large range of such TBs for applications in variety of research areas.

Results and discussion

Until 2013, it was believed that the heterocyclic ring of *N*-aryl-1,8-naphthalimides, once formed, was chemically stable and unreactive towards nucleophilic substitution.[26] During the synthesis of Lucifer Yellow anhydride from Brilliant Sulfofalvin, Stewart *et al.* stated that the heterocyclic ring of *N*-aryl-1,8-naphthalimides was inert to nucleophilic substitution, except in the condition of unusual electron deficiency at the imide site, and resistance to acid/base hydrolysis.[33] Contrary to this statement, Lewis and co-workers demonstrated that the heterocyclic ring of such *N*-aryl-4-chloro-1,8-naphthalimide was not inert and underwent a facile nucleophilic substitution with aliphatic primary amines.[26] Based on these investigations, it was established that for efficient nucleophilic substitution reactions to occur, *i*) the *N*-aryl group, carrying the electron withdrawing substituent, must be attached at the imide site,[26] and the presence of an electron withdrawing substituent (*i.e.* -Cl, -NO_2) at the 4-position of the heterocyclic ring enhances the nucleophilic displacement of *N*-aryl groups at the imide site.[26] In contrast, electron donating substituents (*i.e.* -NH_2, -$N(CH_3)_2$) that delocalize electronically with the imide carbonyl groups were found to suppress nucleophilic displacement.[26] Keeping these structural requirements in mind, we set out to investigate if *N*-aryl-1,8-naphthalimide Tröger's base (such as **TB-1**)[31] carrying a pair of electron-withdrawing ester groups (-$COOCH_3$) on *N*-aryl moiety, could also be used as a 'common' starting material or a 'synthon' to synthesis a family of *N*-alkyl-1,8-naphthalimide Tröger's base fluorophores **TB-(2a-2k)** (Scheme 2) in such systems the methano-1,5-diazocine ring reduced the ICT character making them perhaps more likely to facilitate such a nucleophilic displacement.[27-29] We foresaw that one or more -$COOCH_3$ substituent on *N*-phenyl group may cause sufficient electrophilicity at the imide site for nucleophilic displacement to take place, and this was our initial 'synthon' employed in our investigation, being formed and used as a racemic mixture.



Scheme 2. Substrate scope for the reaction of aliphatic primary amines with **TB-1** precursor to generate **TB-(2a-2j)**. The anhydride **TB-2k** was obtained in pure form the reaction of **TB-1** and aqueous KOH.

Our investigation began with the reaction of **TB-1** in neat *N,N*-dimethylethylenediamine, which we had previously developed as potential anticancer agent (tested in K562 chronic myeloid leukaemia cells),[27,30] as a model substrate, at ambient temperature in air. This resulted in the formation of the desired product **TB-2a** in 17 % isolated yield. To our delight, the yield of **TB-2a** was enhanced significantly to 84 % upon increasing the reaction temperature to 80ºC (*c.f.* Scheme 1B). ^{1}H NMR spectroscopy was used to monitor the progress of the reaction. After 24 hours of heating at 80ºC, the resonances corresponding to -$COOCH_3$ (at 3.93 ppm) and *N*-aryl moiety (at 8.16 and 8.79 ppm) of **TB-1** disappeared, being replaced with three new sets of resonances in the range of 4.28 to 2.31 ppm, corresponding to the *N,N*-dimethylethylenediamine moiety, confirming the complete conversion of **TB-1** to **TB-2a** (Fig. S1-S2, ESI). High-resolution mass spectrometry (HRMS) analysis further supported the formation of **TB-2a** (Fig. S4, ESI). Under this reaction condition, nucleophilic substitution reactions of **TB-1** with a series of aliphatic primary amine substrates, carrying different functionality, were further explored, as summarized in Scheme 2.

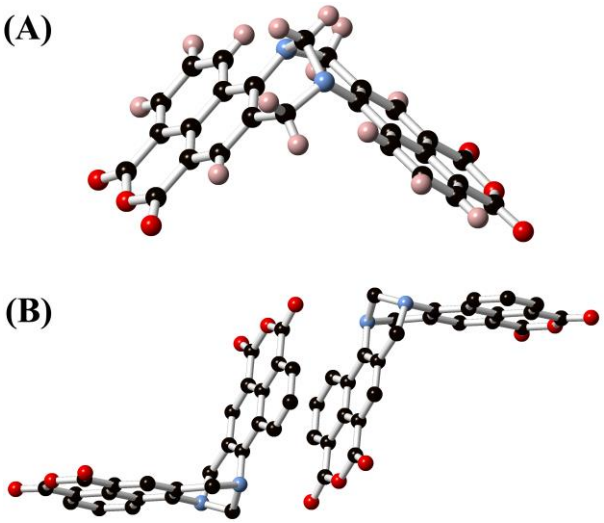


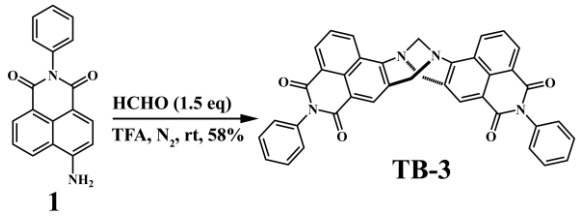
Fig 1. (A) Molecular structure of **TB-2k**, showing the orthogonal nature of the two 1,8-naphthalic anhydride moieties forced by the Tröger's base moiety. (B) Intermolecular π-π stacking interactions between two neighbouring naphthalic anhydride moieties. Lattice solvent molecules and hydrogen atoms are omitted for clarity.

In general, the reactions were clean and yielded the target products **TB-(2a-2j)**, which were isolated in analytically pure form, by a simple solvent extraction in dichloromethane without the need of further purifications using column chromatography. The overall yield of the desired products did not vary widely with respect to the primary amine substrates and the isolated yields were all in good to excellent range (Scheme 2), and in most cases greatly enhanced compare to the more traditional way of making those products in two to three steps, previously developed in our laboratory. The isolated products were fully characterised using various spectroscopic techniques (see the experimental section and Fig. S2-S31 in ESI). Gratifyingly, the reactions with acyclic-tertiary amine substrates (*N,N*-dimethylethylenediamine and *N,N*-diethylethylenediamine) furnished the corresponding products **TB-2a** (84 %) and **TB-2e** (96 %) in very high yields; while the substrates (4-(2-aminoethyl)morpholine, 1-(2-aminoethyl)piperazine, 1-(2-aminoethyl)pyrrolidine and 1-(2-aminoethyl)piperidine) carrying cyclic-tertiary amine group gave the target product (**TB-2b, TB-2g, TB-2h**) in moderate yields (65-76 %) (Scheme 2). Furthermore, the reactions were also very smooth, with aromatic pyridyl (4-(2-aminoethyl)pyridine) and hydroxyl amine (2-aminoethanol) substrates and both furnished the desired products (**TB-2c** and **TB-2i**) in 87 % yield (Scheme 2).

It is also interesting to note that the reaction of **TB-1** and hydrazine hydrate (NH_2-$NH_2.H_2O$) provided the target product **TB-2j** in 92% yield, albeit the possibility to form the oligomeric product, which we found to be the only product upon attempting to form this product using the more traditional three step route (Scheme 2). Moreover, the reaction of **TB-1** with simple aqueous KOH underwent smoothly to yield the target anhydride **TB-2k** in 89 % yield (Scheme 2). The NMR (^{1}H and ^{13}C) and HRMS analysis supported the formation of **TB-2k** in pure form (Fig. S32-S34, ESI).

The structure of **TB-2k** was further confirmed using X-ray diffraction analysis. Yellow crystals of **TB-2k** were grown by slow evaporation of a DMSO solution at ambient temperature. Crystallographic details are summarized in Table S1 (ESI). Single crystal X-ray analysis provided a structural model in the monoclinic space group *C*2/*c*. The asymmetric unit contains half of one molecule of **TB-2k** and one associated DMSO molecule, disordered over three overlapping orientations. The complete molecule of **TB-2k** contains a two-fold rotation axis intersecting the central methylene carbon atom C13. The mean interplanar angle between the two naphthyl groups within the molecule is 97.8° (Figure 1A). The geometry of the anhydride group includes lengthened C-C bonds between the carbonyl carbon atoms and the carbon atoms of position 1 and 8 of the naphthyl ring (1.468(4) and 1.475(4) Å for C10-C11 and C1-C2, respectively) consistent with partial bond localisation, while the carbonyl C=O distances of 1.202(3) and 1.195(4) Å and C-O distances of 1.387(4) and 1.398(4) are typical for cyclic anhydride species. Intermolecular interactions in the structure of **TB-2k** are dominated by face-to-face π-π stacking interactions between adjacent naphthalic anhydride moieties, with a parallel head-to-tail interaction of this type exhibiting a mean interplanar distance of 3.49 Å (Figure 1B). The Interaction between π systems can also be implicated in an edge-to-edge contact between the anhydride groups of two adjacent species, with both groups oriented parallel and a minimum C···O distance of 3.058(5) Å. Similar contacts are commonly observed in various cyclic anhydride species.[34] In contract to **TB-3** and other TB structures,[28] the typical C-H hydrogen bond donation from the bridgehead carbon atom is not involved in C-H···π interactions, but rather undergoes a C-H···O interaction with the carbonyl oxygen atoms of adjacent anhydride groups, with a C···O distance of 3.288(3) Å and C-H···O angle of 150.9° (Fig. S38, ESI).

To further extend this methodology, the precursor **TB-1** was reacted with aromatic primary amine aniline, under similar reaction conditions, to generate the *N*-phenyl-1,8-naphthalimide Tröger's base **TB-3**. However, no product was isolated from this reaction (*c.f.* Scheme 2). This might be attributed to the effect of steric hindrance, but more likely due to the fact that the aromatic primary amines are weaker nucleophiles than the aliphatic amines[35] and thus it is clear that aromatic primary amine is not sufficient to displace the *N*-aryl moiety from the imide site.



Scheme 3. Synthesis of *N*-phenyl-4-amino-1,8-naphthalimide derived Tröger's base **TB-3** from *N*-(phenyl)-4-amino-1,8-naphthalimide precursor **1**.

To evaluate the need of electron-withdrawing ester (-$COOCH_3$) substituents on the *N*-aryl moiety and the level of electrophilicity required for the complete displacement of the *N*-aryl moiety, we designed an unsubstituted *N*-phenyl-1,8-naphthalimide derived Tröger's base **TB-3** as a precursor from **1**, which was formed in two steps. **TB-3** was prepared, as before, as a racemic mixture as shown in Scheme 3.[36] Compound **1** was converted into the desired Tröger's base **TB-3**, by using 1.5 equiv. of paraformaldehyde in neat

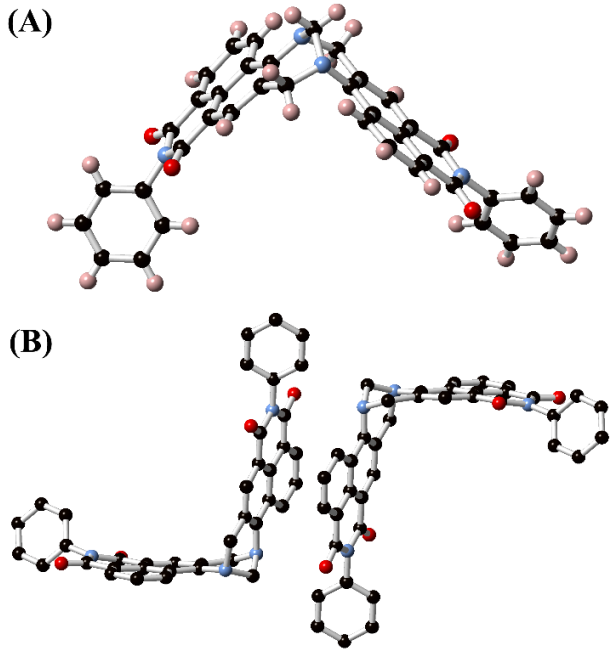
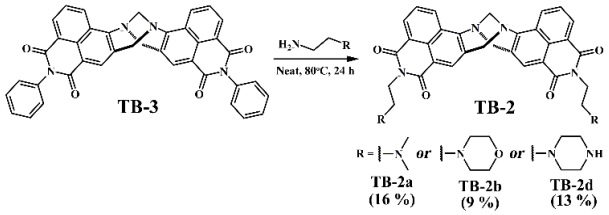


Fig 2. (A) X-ray crystal structure of **TB-3**, showing the orthogonal nature of the two 1,8-naphthalimide moieties forced by the Tröger's base moiety. (B) Intermolecular π-π stacking interactions between two neighbouring naphthalimide moieties. Lattice solvent molecules and hydrogen atoms are omitted for clarity.

trifluoroacetic acid under an inert atmosphere over 12 hours at room temperature. The resulting reaction mixture was basified (pH>10) using aq.NH_3 and extracted with CH_2Cl_2 to give **TB-3** as a bright yellow solid in 58% yield. The formation and purity of **TB-3** was fully investigated by various spectroscopic techniques (all syntheses and full spectroscopic characterizations are described in detail in the experimental section and also see Fig S35-S37 in ESI).

The formation of **TB-3** was unambiguously proved by single crystal X-ray diffraction analysis. Suitable single crystals were grown by slow evaporation of a dichloromethane-methanol (2:1, v/v) solution of **TB-3** at ambient temperature. **TB-3** crystallised in a triclinic system, in the centrosymmetric space group *P*-1. Crystallographic data and refinement parameters are summarized in Table S1 (ESI). The diffraction analysis of **TB-3** clearly show that the methano-1,5-diazocine ring (N-CH_2-N bridgehead angle is 111.79°) places the two 1,8-naphthalimide moieties almost orthogonal to each other (with a mean interplanar angle of 90.12°) giving rise to the unique V-shaped geometry (Fig. 1A). The **TB-3** molecules pack through intermolecular π-π stacking interactions ($d_{centroid}$-$d_{centroid}$ = 3.65 Å) between two adjacent naphthalimide moieties resulting in head-to-tail arrangements of the naphthalimide molecules (Figure 1B). Furthermore, extensive intermolecular C-H…O hydrogen bonding and C-H…π interactions can also be observed in the solid-state packing of **TB-3**, governed primarily by interactions between π-deficient naphthalimide moiety and the CH_2 groups of the N–CH_2–N bridgehead and the *N*-phenyl group from another neighbouring molecule of **TB-3** (Fig. S39, ESI).



Scheme 4. Synthesis of 4-amino-1,8-naphthalimide derived Tröger's bases **TB-2** from **TB-3**.

The reaction of **TB-3** with different aliphatic amine substrates (*N,N*-Dimethylethylenediamine, 4-(2-aminoethyl)morpholine and 1-(2-aminoethyl)piperazine), under standard reaction conditions, indeed gave the desired products (**TB-(2a-2b**) and **TB-2d)** in pure form. However, unlike that seen for **TB-3**, these were formed in significantly lower yield, as demonstrated in Scheme 4. This confirms that the electron-withdrawing -$COOCH_3$ substituent on the *N*-aryl moiety is essential to generate sufficient electron-deficiency at the imide carbonyl group for the complete heterocyclic ring cleavage to occur by aliphatic primary amine nucleophiles.[17, 26]

Conclusions

Herein we have successfully developed and demonstrated a novel one-pot synthetic procedure for the facile synthesis of a family of structurally fascinating *N*-alkyl-1,8-naphthalimide Tröger's bases **TB-(2a-2k)** *via* nucleophilic substitution reaction from a single common 'synthon'. This structure, *N*-aryl-1,8-naphthalimide Tröger's base **TB-1**, carries electron-withdrawing ester (-$COOCH_3$) groups, which in the presence of aliphatic primary amine in a neat form or aqueous KOH, give the desired products with good purity and high yield. This strategy is both efficient and highly feasible for practical use, as the target products can be isolated in high yields and in analytically pure form without the use of chromatography purifications. We also demonstrate that the corresponding anhydride can be formed. Therefore, this methodology is easily adoptable and more beneficial in terms of broad substrate scope and good tolerance of functional groups. Furthermore, work is in progress to uncover the synthetic utility of this new strategy to develop structurally interesting supramolecular scaffolds, which will be further explored to generate various self-assembled structures and supramolecular functional materials.

Experimental

Materials and methods: All reagents, solvents, and starting materials were purchased from Sigma-Aldrich, Merck, or Fisher Scientific, were of reagent grade and were used as received. Solvents used were HPLC grade unless otherwise stated. Deuterated solvents [$(CD_3)_2SO$ and $CDCl_3$] used for NMR analyses were purchased from Sigma-Aldrich or Apollo Scientific. Bis-[*N*-(5-dimethyl-isophthalate)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (**TB-1**)[31] and *N*-(phenyl)-4-amino-1,8-naphthalimide (**1**)[36] were synthesized following

procedure reported in the literature. Melting point was determined using an Electrochemical IA9000 digital melting point apparatus in an unsealed capillary tube.

FT-IR spectra were recorded in the range 4000–400 cm^{-1} on a Perkin-Elmer spectrometer equipped with a universal ATR sampling accessory.

All NMR spectra were recorded on a Bruker-DPX-Avance spectrometer operating at 400/600 MHz for ^1H NMR and 100/150 MHz for ^{13}C NMR in commercially available deuterated solvent. Chemical shifts are reported in parts-per million (ppm) relative to the internal solvent ($(CD_3)_2SO$ = 2.5 ppm or $CDCl_3$ = 7.26 ppm) signal. All NMR data were processed with Bruker Win-NMR 5.0, Topspin and MestReNova softwares. Multiplicities were abbreviated as follows: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m).

APCI-ESI mass spectra were acquired on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. The *m/z* values were recorded over a range of 100-1600. MicroTOF control and HyStar software were used to carry out the analysis. HPLC-grade CH_3CN or CH_3OH or DMSO were used as carrier solvents.

X-ray crystallography: Diffraction data for **TB-2k** were collected using a Bruker APEX-II Duo dual-source instrument using Cu Kα (λ = 1.54178 Å) radiation. The data were collected using ω and ϕ scans with the crystal immersed in oil and maintained at a constant temperature of 100 K using a Cobra cryostream. The data were reduced and processed using the Bruker APEX suite of programs.[37] A multi-scan absorption correction was applied using SADABS.[38] The X-ray diffraction data of **TB-3** were collected at 100.15 K on a Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn 724+ detector mounted at the window of an FR-E+ Super bright Mo-Kα rotating anode generator (λ = 0.71073 Å) with HF or VHF varimax optics. Unit cell parameters were refined against all data and an empirical absorption correction applied in CrystalClear-SM 1.4.0 software. All datasets were solved using SHELXS[39] structure solution program using Direct Methods and refined by full-matrix least squares procedures using SHELXL-2015[40] within the OLEX-2 GUI.[41] The hydrogen atom positions were included in the model by electronic density or were geometrically calculated and refined using a riding model.

General procedure for the synthesis of Tröger's bases TB-(2a-2j) from TB-1

Tröger's base **TB-1** (10 mg, 0.012 mmol) was mixed with the appropriate neat primary aliphatic amines (0.5 mL) and the mixture was stirred at 80 °C for 24 h and then allowed to cool to room temperature. The solution was poured onto ice and a precipitate formed immediately. The resultant precipitate was stirred vigorously at room temperature for 2 h and then collected by centrifugation. The product was extracted into dichloromethane and the organic layer was isolated, dried over $MgSO_4$ and stripped under reduced pressure to isolate the expected product **TB-(2a-2j)** as an orange/bright yellow solid.

Bis-[*N*-(1-dimethylaminoethyl)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2a)[2]. Compound **TB-2a** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat *N,N*-dimethylethylenediamine (0.5 mL) to yield the product as an orange powder (6 mg, 0.010 mmol, 84 %). HRMS (APCI) m/z: calcd for $C_{35}H_{35}N_6O_4$ [M+H$^+$] 603.2720, found 603.2720; ^1H NMR (400 MHz, ($CDCl_3$) δ 8.59 (2H, d, *J* = 8.0 Hz, Ar-H), 8.57 (2H, d, *J* = 8.0 Hz, Ar-H), 8.09 (2H, s, Ar-H), 7.85-7.83 (2H, dd, *J* = 4.0 Hz, *J* = 4.0 Hz, Ar-H), 5.14-5.10 (2H, d, *J* = 16.8 Hz, NCH_2), 4.66 (2H, s, N-CH_2-N), 4.59-4.55 (2H, d, *J* = 16.8 Hz, NCH_2), 4.27-4.24 (4H, t, *J* = 6.8 Hz, $NCH_2CH_2N(CH_3)_2$), 2.61-2.57 (4H, t, *J* = 6.8 Hz, $NCH_2CH_2N(CH_3)_2$), 2.31 (12H, s, $N(CH_3)_2$); ^{13}C NMR (100 MHz, ($CDCl_3$) δ 164.20, 163.65, 149.16, 131.03, 130.52, 128.78, 128.38, 127.32, 127.14, 125.27, 123.16, 118.91, 57.12, 56.87, 45.63, 37.92.

Bis-[*N*-(1-morpholinoethyl)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2b)[2] Compound **TB-2b** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat 4-(2-aminoethyl)morpholine (0.5 mL) to yield the product as a yellow powder (6.2 mg, 0.010 mmol, 76 %). HRMS (APCI) m/z: calcd for $C_{39}H_{39}N_6O_6$ [M+H$^+$] 687.2931, found 687.2941; ^1H NMR (600 MHz, ($CDCl_3$) δ 8.69 (2H, d, *J* = 7.8 Hz, Ar-H), 8.59 (2H, d, *J* = 6.0 Hz, Ar-H), 8.09 (2H, s, Ar-H), 7.87-7.85 (2H, t, *J* = 8.4 Hz, Ar-H), 5.15-5.12 (2H, d, *J* = 16.8 Hz, NCH_2), 4.66 (2H, s, N-CH_2-N), 4.60-4.57 (2H, d, *J* = 17.4 Hz, NCH_2), 4.27-4.25 (4H, t, *J* = 6.6 Hz, NCH_2CH_2N) 3.62 (4H, s-br, $N(CH_2CH_2)_2O$), 2.64-2.63 (2H, t, *J* = 6.6 Hz, NCH_2CH_2N, 2.62 (4H, s-br, $N(CH_2CH_2)_2O$); ^{13}C NMR (150 MHz, ($CDCl_3$) δ 164.15, 163.62, 149.19, 130.99, 130.47, 128.81, 128.36, 127.37, 127.19, 125.29, 123.16, 118.19.

Bis-[*N*-(2-(pyridine-4-yl)ethyl]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2c)[3] Compound **TB-2c** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat 4-(2-aminoethyl)pyridine (0.5 mL) to yield the product as a yellow powder (7.0 mg, 0.010 mmol, 87 %). HRMS (APCI) m/z: calcd for $C_{41}H_{31}N_6O_4$ [M+H$^+$] 671.2407, found 671.2376; ^1H NMR (600 MHz, ($CDCl_3$) δ 8.71 (2H, d, *J* = 7.8 Hz, Ar-H), 8.59 (2H, d, *J* = 7.2 Hz, Ar-H), 8.45 (4H, d, *J* = 6.0 Hz Py-H), 8.06 (2H, s, Ar-H), 7.88-7.86 (2H, t, *J* = 7.8 Hz, Ar-H), 7.24-7.23 (4H, d, *J* = 5.4 Hz, Py-H), 5.15-5.12 (2H, d, *J* = 16.8 Hz, NCH_2), 4.67 (2H, s, N-CH_2-N), 4.60-4.56 (2H, d, *J* = 17.4 Hz, NCH_2), 4.41-4.34 (4H, m, NCH_2CH_2), 3.01-2.98 (4H, t, *J* = 7.2 Hz, NCH_2CH_2); ^{13}C NMR (150 MHz, ($CDCl_3$) δ 163.82, 163.24, 149.26, 148.91, 130.98, 130.49, 128.89, 128.16, 127.25, 127.09, 125.20, 124.42, 122.73, 118.41, 66.87, 56.96, 40.10, 33.37.

Bis-[*N*-(1-(2-aminoethyl)piperazine)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2d). Compound **TB-2a** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat 1-(2-aminoethyl)piperazine (0.5 mL) to yield the product as an orange powder (6.8 mg, 0.010 mmol, 83 %). Melting point 275–280 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{39}H_{41}N_8O_4$ [M+H$^+$] 685.3251, found 685.3256; ^1H NMR (400 MHz, ($CDCl_3$) δ 8.69 (2H, d, *J* = 8.0 Hz, Ar-H), 8.58 (2H, d, *J* = 7.2 Hz, Ar-H), 8.07 (2H, s, Ar-H), 7.87-7.84 (2H, t, *J* = 8.0 Hz, Ar-H), 5.15-5.11 (2H,

d, *J* = 16.8 Hz, NCH_2), 4.67 (2H, s, N-CH_2-N), 4.61-4.56 (2H, d, *J* = 17.2 Hz, NCH_2), 4.27-4.24 (4H, t, *J* = 6.4 Hz, NCH_2CH_2N), 2.81 (4H, d, *J* = 4.4 Hz, $N(CH_2CH_2)_2NH$), 2.63-2.61 (4H, t, *J* = 6.8 Hz, $N(CH_2CH_2)_2NH$), 2.59 (4H, s-br, $N(CH_2CH_2)_2NH$); ^{13}C NMR (100 MHz, ($CDCl_3$) *δ* 164.14, 163.59, 149.15, 130.97, 130.51, 128.80, 128.35, 127.34, 127.19, 125.28, 123.15, 118.87, 67.07, 65.89, 57.13, 56.02, 53.92, 45.69, 37.15, 30.97; IR υ_{max} (neat sample, cm^{-1}) 3362, 2922, 2848, 1690, 1650, 1594, 1454, 1374, 1346, 1234, 1168, 1122, 1052, 1006, 920, 784, 690, 582.

Bis-[*N*-(1-diethylaminoethyl)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2e). Compound **TB-2e** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat *N,N*-diethylethylenediamine (0.5 mL) to yield the product as an orange powder (7.6 mg, 0.011 mmol, 96 %). Melting point 230–232 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{39}H_{43}N_6O_4$ [M+H$^+$] 659.3346, found 689.3343; ^{1}H NMR (400 MHz, ($CDCl_3$) *δ* 8.68 (2H, d, *J* = 8.4 Hz, Ar-H), 8.58 (2H, d, *J* = 6.4 Hz, Ar-H), 8.08 (2H, s, Ar-H), 7.87-7.83 (2H, t, *J* = 8.0 Hz, Ar-H), 5.14-5.10 (2H, d, *J* = 16.8 Hz, NCH_2), 4.66 (2H, s, N-CH_2-N), 4.59-4.55 (2H, d, *J* = 17.2 Hz, NCH_2), 4.23-4.19 (4H, t, *J* = 7.6 Hz, NCH_2CH_2N), 2.71-2.69 (4H, t, *J* = 7.6 Hz, NCH_2CH_2N), 2.63-2.57 (8H, m, $NCH_2CH_2N(CH_2CH_3)_2$), 1.04-1.01 (12H, t, *J* = 6.8 Hz, $NCH_2CH_2N(CH_2CH_3)_2$); ^{13}C NMR (100 MHz, ($CDCl_3$) *δ* 164.12, 163.58, 149.12, 130.92, 130.41, 128.73, 128.31, 127.32, 127.16, 125.27, 123.19, 118.94, 67.06, 57.10, 49.80, 47.55, 37.88, 12.23; IR υ_{max} (neat sample, cm^{-1}) 2968, 2814, 1696, 1654, 1618, 1598, 1571, 1511, 1458, 1405, 1374, 1352, 1299, 1256, 1233, 1210, 1167, 1148, 1118, 1100, 1055, 963, 919, 786, 759, 690, 660, 585.

Bis-[*N*-(1-propylamine)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2f). Compound **TB-2f** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) neat 1-propylamine (0.5 mL) to yield the product as a bright yellow powder (6.2 mg, 0.011 mmol, 95 %). Melting point 314–316 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{33}H_{29}N_4O_4$ [M+H$^+$] 545.2189, found 545.2178; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.68 (2H, d, *J* = 8.0 Hz, Ar-H), 8.59 (2H, d, *J* = 6.4 Hz, Ar-H), 8.09 (2H, s, Ar-H), 7.87-7.83 (2H, t, *J* = 7.6 Hz, Ar-H), 5.15-5.11 (2H, d, *J* = 17.2 Hz, NCH_2), 4.67 (2H, s, N-CH_2-N), 4.61-4.56 (2H, d, *J* = 17.2 Hz, NCH_2), 4.08-4.05 (4H, t, *J* = 7.6 Hz, $NCH_2CH_2CH_3$), 1.72-1.62 (4H, m, $NCH_2CH_2CH_3$), 0.96-0.92 (6H, t, *J* = 7.6 Hz, $NCH_2CH_2CH_3$); ^{13}C NMR (100 MHz, ($CDCl_3$) *δ* 164.16, 163.64, 149.06, 130.94, 130.44, 128.69, 128.31, 127.29, 127.14, 125.27, 123.23, 118.98, 67.10, 57.15, 41.81, 21.34, 11.44; IR υ_{max} (neat sample, cm^{-1}) 2954, 2872, 1696, 1655, 1618, 1596 1571, 1508, 1458, 1404,1367, 1348, 1299, 1255, 1232, 1111, 1060, 1017, 965, 953, 926, 919, 890, 806, 786, 761, 738, 699, 588, 576, 555.

Bis-[*N*-(1-(2-aminoethyl)pyrrolidine)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2g). Compound **TB-2g** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat 1-(2-aminoethyl)pyrrolidine (0.5 mL) to yield the product as an orange powder (5.8 mg, 0.009 mmol, 74 %). Melting point 285–287 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{39}H_{39}N_6O_4$ [M+H$^+$] 655.3033, found 655.3024; ^{1}H NMR (400 MHz, ($CDCl_3$) *δ* 8.67 (2H, d, *J* = 7.2 Hz, Ar-H), 8.59 (2H, d, *J* = 6.4 Hz, Ar-H), 8.08 (2H, s, Ar-H), 7.87-7.83 (2H, t, *J* = 8.0 Hz, Ar-H), 5.14-5.09 (2H, d, *J* = 17.2 Hz, NCH_2), 4.66 (2H, s, N-CH_2-N), 4.59-4.56 (2H, d, *J* = 17.2 Hz, NCH_2), 4.31-4.28 (4H, t, *J* = 6.8 Hz, $NCH_2CH_2N(CH_2)_4$), 2.75-2.71 (4H, t, *J* = 7.2 Hz, $NCH_2CH_2N(CH_2)_4$), 2.61 (4H, s-br, $N(CH_2)_4$), 1.76-1.73 (4H, m, $N(CH_2)_4$); ^{13}C NMR (100 MHz, ($CDCl_3$) *δ* 164.12, 163.56, 149.12, 130.97, 130.47, 128.74, 128.34, 127.31, 127.14, 125.26, 123.20, 118.95, 67.12, 57.10, 54.34, 53.59, 39.08, 23.56; IR υ_{max} (neat sample, cm^{-1}) 2966, 2785, 2169, 1697, 1655, 1619, 1596, 1572, 1511, 1456, 1404, 1374, 1354, 1335, 1302, 1256, 1231, 1169, 1118, 1055, 922, 814, 787, 761, 736, 720, 694, 639.

Bis-[*N*-(1-(2-aminoethyl)piperidine)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2h). Compound **TB-2h** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat 1-(2-aminoethyl)piperidine (0.5 mL) to yield the product as an orange powder (5.3 mg, 0.008 mmol, 65 %). Melting point 287–289 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{41}H_{43}N_6O_4$ [M+H$^+$] 683.3346, found 683.3340; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.58 (2H, d, *J* = 8.0 Hz, Ar-H), 8.56 (2H, d, *J* = 7.2 Hz, Ar-H), 8.08 (2H, s, Ar-H), 7.87-7.85 (2H, t, *J* = 7.6 Hz, Ar-H), 5.14-5.10 (2H, d, *J* = 16.8 Hz, NCH_2), 4.65 (2H, s, N-CH_2-N), 4.59-4.55 (2H, d, *J* = 17.2 Hz, NCH_2), 4.43 (4H, s-br, $NCH_2CH_2N(CH_2)_5$), 2.96 (4H, s-br, $NCH_2CH_2N(CH_2)_5$), 1.81 (4H, s-br, $N(CH_2)_5$), 1.51 (6H, s-br, $N(CH_2)_5$); ^{13}C NMR (100 MHz, ($CDCl_3$) *δ* 164.24, 163.66, 149.45, 131.13, 130.73, 129.07, 128.44, 127.40, 127.15, 125.36, 122.94, 118.69, 67.00, 65.87, 57.09, 53.95, 37.62, 25.91, 24.30; IR υ_{max} (neat sample, cm^{-1}) 3385, 2935, 1695, 1654, 1594, 1510, 1458, 1404, 1375, 1351, 1302, 1255, 1233, 1169, 1099, 1055, 918, 784, 757, 692, 575.

Bis-[*N*-(2-aminoethanol)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2i). Compound **TB-2i** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in 2-aminoethanol (0.5 mL) to yield the product as a yellow powder (5.7 mg, 0.01 mmol, 87 %). Melting point 365–368 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{31}H_{25}N_4O_6$ [M+H$^+$] 549.1774, found 549.1768; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) *δ* 8.72 (2H, d, *J* = 8.0 Hz, Ar-H), 8.49 (2H, d, *J* = 8.0 Hz, Ar-H), 8.12 (2H, s, Ar-H), 7.98-7.97 (2H, t, *J* = 8.0 Hz, Ar-H), 5.19-5.16 (2H, d, *J* = 17.4 Hz, NCH_2), 4.73 (2H, s, N-CH_2-N), 4.69-4.66 (2H, d, *J* = 17.4 Hz, NCH_2), 4.09-4.07 (4H, t, *J* = 7.2 Hz, NCH_2CH_2OH), 3.35-3.352 (4H, t, *J* = 7.8 Hz, NCH_2CH_2OH); ^{13}C NMR (150 MHz, $(CD_3)_2SO$)) *δ* 163.54, 162.93, 148.93, 130.58, 130.13, 129.01, 127.51, 127.12, 126.67, 126.11, 122.60, 117.82, 66.08, 57.71, 56.75, 41.60, 28.98; IR υ_{max} (neat sample, cm^{-1}) 3260, 2968, 2882, 1695, 1648, 1616, 1596, 1568, 1509, 1456, 1402, 1378, 1340, 1325, 1290, 1252, 1232, 1211, 1170, 1154, 1099, 1073, 1054, 1030, 1008, 984, 931, 880, 838, 785, 759, 692, 588.

Bis-[*N*-(hydrazine)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-2j). Compound **TB-2j** was synthesized by reacting **TB-1** (10 mg, 0.012 mmol) in neat hydrazine hydrate (0.5 mL) to yield the product as a bright yellow powder (5.4 mg, 0.011 mmol, 92 %). Melting point 370–372 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{27}H_{19}N_6O_4$ [M+H$^+$] 491.1468, found

491.1452; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 8.74 (2H, d, J = 8.4 Hz, Ar-H), 8.50 (2H, d, J = 7.2 Hz, Ar-H), 8.13 (2H, s, Ar-H), 7.99-7.96 (2H, t, J = 7.8 Hz, Ar-H), 5.73 (4H, s, N-NH_2), 5.17-5.16 (2H, d, J = 17.4 Hz, NCH_2), 4.72 (2H, s, N-CH_2-N), 4.71-4.69 (2H, d, J = 9.6 Hz, NCH_2); ^{13}C NMR (150 MHz, $(CD_3)_2SO$)) δ 160.45, 159.96, 149.30, 130.76, 130.23, 129.23, 127.26, 126.81, 126.30, 126.10, 122.12, 117.32, 65.93, 64.93, 56.75, 54.93; IR υ_{max} (neat sample, cm^{-1}) 3046, 2953, 2871, 1697, 1655, 1595, 1570, 1508, 1459, 1404, 1367, 1348, 1299, 1255, 1232, 1111, 1059, 1018, 965, 889, 806, 786, 761, 736, 698, 677, 661, 588, 576, 556.

Synthesis and Characterization of TB-2k. Compound **TB-1** (50 mg, 0.059 mmol, 1 eq.), was dissolved in THF:MeOH (4:1, 10 mL) and stirred for 10 min. KOH (aq.) (40 mg, 0.708 mmol, 10 mL, 12 eq.) was added and the solution was refluxed at 80 °C for 24 h. Solvents removed under reduced pressure, leaving water. The aqueous solution was acidified using HCl (1 M) until pH= ~1 as achieved. The acidic solution was left to stir for 2 h and was filtered, washed with water, dried with diethyl ether and isolated as a yellow powder (24 mg, 0.052 mmol, 89 %). Melting point 289–291 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{27}H_{14}N_2O_6$ [M-H$^-$] 462.0852, found 462.0865; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 8.79 (2H, d, J = 8.4 Hz, Ar-H), 8.51 (2H, d, J = 7.8 Hz, Ar-H), 8.15 (2H, s, Ar-H), 8.01-7.99 (2H, t, J = 7.2 Hz, Ar-H), 5.19-5.16 (2H, d, J = 16.8 Hz, NCH_2), 4.73 (2H, s, N-CH_2-N), 4.71 (2H, d, J = 17.4 Hz, NCH_2); ^{13}C NMR (150 MHz, $(CD_3)_2SO$)) δ 161.34, 160.57, 150.46, 132.96, 132.45, 130.68, 130.34, 128.01, 127.26, 127.01, 119.91, 114.80, 66.37, 57.10; IR υ_{max} (neat sample, cm^{-1})2978, 1766, 1726, 1598, 1572, 1460, 1406, 1288, 1238, 1194, 1148, 1088, 1038, 996, 922, 780, 756, 676, 576.

Bis-[N-(phenyl)]-9,18-methano-1,8-naphthalimide-[*b,f*][1,5]diazocine (TB-3). A mixture of *N*-(phenyl)-4-amino-1,8-naphthalimide (**1**; 150 mg, 0.47 mmol, 1.0 eq.) and paraformaldehyde (21.2 mg, 0.71 mmol, 1.5 eq.) in neat trifluoroacetic acid (4 mL) were stirred at room temperature for 12 hours under a nitrogen atmosphere. The reaction mixture was then neutralized and further basified to pH = ~12 by the slow addition of aqueous ammonia. The aqueous solution was extracted several times with dichloromethane and the organic extract was washed with saturated $NaHCO_3$ (1 × 50 mL), brine solution (1 × 50 mL) followed by H_2O (1 × 100 mL). The combined filtrates were passed over $MgSO_4$ and solvents removed under reduced pressure to get the expected product **TB-3** as bright yellow solid (168 mg, 0.27 mmol, 58 %) after triturating with cold-diethyl ether. %). Melting point 363–365 ºC (decomp.). HRMS (APCI) m/z: calcd for $C_{39}H_{25}N_4O_4$ [M+H$^+$] 613.1876, found 613.1869; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 8.80 (2H, d, J = 8.4 Hz, Ar-H), 8.50 (2H, d, J = 7.2 Hz, Ar-H), 8.15 (2H, s, Ar-H), 8.01-7.99 (2H, t, J = 7.8 Hz, Ar-H), 7.71 (4H, d, J = 9.0 Hz, Ar_{phenyl}-H), 7.51-7.48 (4H, t, J = 7.8 Hz, Ar_{phenyl}-H), 7.45-7.43 (2H, t, J = 14.4 Hz, Ar_{phenyl}-H), 7.29 (2H, s, Ar_{phenyl}-H), 5.23 (2H, d, J = 17.4 Hz, NCH_2), 4.79 (2H, s, N-CH_2-N), 4.73 (2H, d, J = 16.8 Hz, NCH_2); ^{13}C NMR (150 MHz, $(CD_3)_2SO$)) δ 164.16, 163.57, 149.63, 136.44, 135.84, 132.33, 131.86, 131.11, 130.73, 129.72, 129.51, 129.30, 128.59, 128.45, 127.66, 123.49, 121.77, 118.69, 66.66, 65.38, 57.36; IR υ_{max} (neat sample, cm^{-1}) 2981, 1703, 1662, 1594, 1574, 1509, 1487, 1458, 1403, 1372, 1345, 1303, 1242, 1184, 1128, 1087, 1070, 1037, 1012, 958, 928, 845, 781, 739, 695, 661, 600, 582.

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Notes and references

1. J. H. Reed, *J. Prakt. Chem.*, 1886, **34**, 160; L. Mosca, J. Cejka, B. Dolensky, M. Havlik, M. Jakubek, R. Kaplanek, V. Kral and P. Anzenbacher, *Chem. Commun.*, 2016, **52**, 10664; M. Valík, R. M. Strongin and V. Král, *Supramol. Chem.*, 2005, **17**, 347.
2. B. Dolensky, M. Havlik and V. Kral, *Chem. Soc. Rev.*, 2012, **41**, 3839; B. Dolenský, J. Elguero, V. Král, C. Pardo and M. Valík, *Adv. Heterocycl. Chem.*, 2007, **93**, 1.
3. Ö. V. Rúnarsson, J. Artacho and K. Wärnmark, *Eur. J. Org. Chem.*, 2012, **2012**, 7015.
4. M. A. Spielman, *J. Am. Chem. Soc.*, 1935, **57**, 583; E. C. Wagner, *J. Am. Chem. Soc.*, 1935, **57**, 1296; V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1944, **27**, 1127.
5. S. B. Larson and C. S. Wilcox, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1986, **42**, 224; C. Pardo, E. Sesmilo, E. Gutiérrez-Puebla, A. Monge, J. Elguero and A. Fruchier, *J. Org. Chem.*, 2001, **66**, 1607.
6. S. H. Wilen, J. Z. Qi and P. G. Williard, *J. Org. Chem.*, 1991, **56**, 485.
7. M. Havlík, V. Král, R. Kaplánek and B. Dolenský, *Org. Lett.*, 2008, **10**, 4767.
8. A. Hansson, J. Jensen, Ola F. Wendt and K. Wärnmark, *Eur. J. Org. Chem.*, 2003, **2003**, 3179; J. Jensen, M. Strozyk and K. Warnmark, *J. Heterocycl. Chem.*, 2003, **40**, 373.
9. C. S. Wilcox and M. D. Cowart, *Tetrahedron Lett.*, 1986, **27**, 5563.
10. A. Manjula and M. Nagarajan, *Tetrahedron*, 1997, **53**, 11859; E. M. Boyle, S. Comby, J. K. Molloy and T. Gunnlaugsson, *J. Org. Chem.*, 2013, **78**, 8312; S. Satishkumar and M. Periasamy, *Tetrahedron: Asymmetry*, 2009, **20**, 2257; T. Kobayashi and T. Moriwaki, *heterocycles*, 2004, **62**, 399 ; S. Goswami, K. Ghosh and S. Dasgupta, *J. Org. Chem.*, 2000, **65**, 1907; K.-H. Kim and J.-I. Choe, *Bull. Korean Chem. Soc*, 2006, **27**, 1737; M. Valík, J. Malina, L. Palivec, J. Foltýnová, M. Tkadlecová, M. Urbanová, V. Brabec and V. Král, *Tetrahedron*, 2006, **62**, 8591; C. Bailly, W. Laine, M. Demeunynck and J. Lhomme, *Biochem. Biophys. Res. Commun.*, 2000, **273**, 681; A. Tatibouet, M. Demeunynck, C. Andraud, A. Collet and J.

Lhomme, *Chem. Commun.*, 1999, 161; R. M. Duke, J. E. O'Brien, T. McCabe and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2008, **6**, 4089.

11. H. Gardarsson, W. B. Schweizer, N. Trapp and F. Diederich, *Chem. Eur. J.*, 2014, **20**, 4608; S. Paliwal, S. Geib and C. S. Wilcox, *J. Am. Chem. Soc.*, 1994, **116**, 4497; F. R. Fischer, W. B. Schweizer and F. Diederich, *Angew. Chem. Int. Ed.*, 2007, **46**, 8270; F. Hof, D. M. Scofield, W. B. Schweizer and F. Diederich, *Angew. Chem. Int. Ed.*, 2004, **43**, 5056.
12. T. H. Webb, H. Suh and C. S. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 8554; C. S. Wilcox, *Tetrahedron Lett.*, 1985, **26**, 5749; M. D. Cowart, I. Sucholeiki, R. R. Bukownik and C. S. Wilcox, *J. Am. Chem. Soc.*, 1988, **110**, 6204.
13. J. N. H. Reek, M. J. Crossley, J. N. H. Reek, A. P. H. J. Schenning, A. W. Bosman and E. W. Meijer, *Chem. Commun.*, 1998, 11; V. Parchaňský, P. Matějka, B. Dolenský, M. Havlík and P. Bouř, *J. Mol. Struct.*, 2009, **934**, 117.
14. C. Yuan, Q. Xin, H. Liu, L. Wang, M. Jiang and X. Tao, *Sci. China. Chem*, 2011, **54**, 587.
15. Y. Goldberg and H. Alper, *Tetrahedron Lett.*, 1995, **36**, 369; B. Minder, M. Schürch, T. Mallat and A. Baiker, *Catal. Lett.*, 1995, **31**, 143; Y.-M. Shen, M.-X. Zhao, J. Xu and Y. Shi, *Angew. Chem. Int. Ed.*, 2006, **45**, 8005; F. Xu, R. D. Tillyer, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *Tetrahedron: Asymmetry*, 1998, **9**, 1651.
16. C. S. Hawes, C. M. Fitchett, S. R. Batten and P. E. Kruger, *Inorg. Chim. Acta*, 2012, **389**, 112; T. Weilandt, U. Kiehne, J. Bunzen, G. Schnakenburg and A. Lützen, *Chem. Eur. J.*, 2010, **16**, 2418; B. M. Rosen, M. Peterca, C. Huang, X. Zeng, G. Ungar and V. Percec, *Angew. Chem. Int. Ed.*, 2010, **49**, 7002; T. Weilandt, U. Kiehne, G. Schnakenburg and A. Lutzen, *Chem. Commun.*, 2009, 2320; U. Kiehne, T. Weilandt and A. Lützen, *Eur. J. Org. Chem.*, 2008, **2008**, 2056; U. Kiehne, T. Weilandt and A. Lützen, *Org. Lett.*, 2007, **9**, 1283; M. S. Khoshbin, M. V. Ovchinnikov, C. A. Mirkin, J. A. Golen and A. L. Rheingold, *Inorg. Chem.*, 2006, **45**, 2603; Y.-M. Jeon, G. S. Armatas, D. Kim, M. G. Kanatzidis and C. A. Mirkin, *Small*, 2009, **5**, 46.
17. S. Banerjee, E. B. Veale, C. M. Phelan, S. A. Murphy, G. M. Tocci, L. J. Gillespie, D. O. Frimannsson, J. M. Kelly and T. Gunnlaugsson, *Chem. Soc. Rev.*, 2013, **42**, 1601; H. D. P. Ali, P. E. Kruger and T. Gunnlaugsson, *New J. Chem.*, 2008, **32**, 1153; E. B. Veale and T. Gunnlaugsson, *J. Org. Chem.*, 2008, **73**, 8073.
18. R. M. Duke, E. B. Veale, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Chem. Soc. Rev.*, 2010, **39**, 3936; R. Parkesh, T. Clive Lee and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2007, **5**, 310.
19. T. Gunnlaugsson, T. C. Lee and R. Parkesh, *Org. Biomol. Chem.*, 2003, **1**, 3265.
20. E. B. Veale, G. M. Tocci, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2009, **7**, 3447.
21. F. Lupo, S. Gentile, F. P. Ballistreri, G. A. Tomaselli, M. E. Fragala and A. Gulino, *Analyst*, 2010, **135**, 2273; K. A. Mitchell, R. G. Brown, D. Yuan, S.-C. Chang, R. E. Utecht and D. E. Lewis, *J. Photochem. Photobiol.*, 1998, **115**, 157; T. Gunnlaugsson, M. Glynn, G. M. Tocci, P. E. Kruger and F. M. Pfeffer, *Coord. Chem. Rev*, 2006, **250**, 3094; E. B. Veale and T. Gunnlaugsson, *Ann. Rep. Progr. Chem.*, 2010, **106**, 376; H. D. P. Ali, P. E. Kruger and T. Gunnlaugsson, *New J. Chem.*, 2008, **32**, 1153; R. M. Duke and T. Gunnlaugsson, *Tetrahedron Lett.*, 2007, **48**, 8043; E. B. Veale, J. A. Kitchen and T. Gunnlaugsson, *Supramol. Chem.*, 2013, **25**, 101; T. Gunnlaugsson, M. Nieuwenhuyzen, L. Richard and V. Thoss, *Tetrahedron Lett.*, 2001, **42**, 4725; T. Gunnlaugsson, B. Bichell and C. Nolan, *Tetrahedron Lett.*, 2002, **43**, 4989; R. M. Duke and T. Gunnlaugsson, *Tetrahedron Lett.*, 2011, **52**, 1503.
22. H. Wang, H. Wu, L. Xue, Y. Shi and X. Li, *Org. Biomol. Chem.*, 2011, **9**, 5436; S. Zheng, P. L. M. Lynch, T. E. Rice, T. S. Moody, H. Q. N. Gunaratne and A. P. de Silva, *Photochem. Photobiol.*, 2012, **11**, 1675.
23. X. Qian, Y. Xiao, Y. Xu, X. Guo, J. Qian and W. Zhu, *Chem. Commun.*, 2010, **46**, 6418; R. Parkesh, T. Clive Lee and T. Gunnlaugsson, *Tetrahedron Lett.*, 2009, **50**, 4114; E. Calatrava-Perez, S. A. Bright, S. Achermann, C. Moylan, M. O. Senge, E. B. Veale, D. C. Williams, T. Gunnlaugsson and E. M. Scanlan, *Chem. Commun.*, 2016, **52**, 13086.
24. G. J. Ryan, S. Quinn and T. Gunnlaugsson, *Inorg. Chem*, 2008, **47**, 401; S. Banerjee, J. A. Kitchen, S. A. Bright, J. E. O'Brien, D. C. Williams, J. M. Kelly and T. Gunnlaugsson, *Chem. Commun.*, 2013, **49**, 8522; S. Banerjee, J. A. Kitchen, T. Gunnlaugsson and J. M. Kelly, *Org. Biomol. Chem.*, 2012, **10**, 3033; S. Banerjee, J. A. Kitchen, T. Gunnlaugsson and J. M. Kelly, *Org. Biomol. Chem.*, 2013, **11**, 5642.
25. Z. Guan, L. Yang, W. Wang, J. Zhang, J. Liu, C. Ren, S. Wang, Y. Gao and P. Huang, *RSC Adv.*, 2017, **7**, 34755; J. I. Lovitt, C. S. Hawes, A. D. Lynes, B. Haffner, M. E. Mobius and T. Gunnlaugsson, *Inorg. Chem. Front*, 2017, **4**, 296; J. A. Kitchen, P. N. Martinho, G. G. Morgan and T. Gunnlaugsson, *Dalton Trans.*, 2014, **43**, 6468; C. S. Hawes, A. D. Lynes, K. Byrne, W. Schmitt, G. Ryan, M. E. Mobius and T. Gunnlaugsson, *Chem. Commun.*, 2017, **53**, 5989.
26. R. K. McKenney, L. L. Groess, K. M. Kopidlansky, K. L. Dunkle and D. E. Lewis, *Org. Biomol. Chem.*, 2013, **11**, 4390; S. M. Anderson, S. D. Mitchell, K. A. LaPlante, R. K. McKenney and D. E. Lewis, *J. Heterocyclic Chem.*, 2017, **54**, 2029.
27. E. B. Veale and T. Gunnlaugsson, *J. Org. Chem.*, 2010, **75**, 5513; E. B. Veale, D. O. Frimannsson, M. Lawler and T. Gunnlaugsson, *Org. Lett.*, 2009, **11**, 4040.
28. S. Banerjee, S. A. Bright, J. A. Smith, J. Burgeat, M. Martinez-Calvo, D. C. Williams, J. M. Kelly and T. Gunnlaugsson, *J. Org. Chem.*, 2014, **79**, 9272.
29. R. B. P. Elmes, M. Erby, S. A. Bright, D. C. Williams and T. Gunnlaugsson, *Chem. Commun.*, 2012, **48**, 2588.
30. S. Murphy, S. A. Bright, F. E. Poynton, T. McCabe, J. A. Kitchen, E. B. Veale, D. C. Williams and T. Gunnlaugsson, *Org. Biomol. Chem.*, 2014, **12**, 6610.
31. S. Shanmugaraju, C. Dabadie, K. Byrne, A. J. Savyasachi, D. Umadevi, W. Schmitt, J. A. Kitchen and T. Gunnlaugsson, *Chem. Sci.*, 2017, **8**, 1535.
32. N. R. Deprez, K. A. McNitt, M. E. Petersen, R. G. Brown and D. E. Lewis, *Tetrahedron Lett.*, 2005, **46**, 2149.
33. W. W. Stewart, *J. Am. Chem. Soc.*, 1981, **103**, 7615.
34. R. D. Rieke, G. O. Page, P. M. Hudnall, R. W. Arhart and T. W. Bouldin, *J. Chem. Soc., Chem. Commun.*, 1990, 38.
35. J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 1958, **80**, 4337.
36. P. A. Panchenko, Y. V. Fedorov, O. A. Fedorova, V. P. Perevalov and G. Jonusauskas, *Russ. Chem. Bull.*, 2009, **58**, 1233.
37. *Bruker APEX-3,* Bruker-AXS Inc., Madison, WI, 2016.

38. B.-A. I. SADABS, Madison, WI, 2016.
39. G. Sheldrick, *Acta Crystallogr. Sect. A*, 2008, **64**, 112.
40. G. Sheldrick, *Acta Crystallogr. Sect. A*, 2015, **71**, 3.
41. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.