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Regioselective Synthesis of Dimethylamino- or Arylalkylamino-"Crowned" Tröger's Base Analogues Under Vilsmeier–Haack Conditions

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Dedicated to Professor Madhavarao Nagarajan on the occasion of his 60th birthday

Keywords: Tröger's base / Amination / Regioselectivity

Under typical Vilsmeier–Haack conditions, Tröger's base undergoes regioselective dimethylamino or arylalkylamino substitution on the methano bridge of the dibenzo[*b*,*f*][1,5]diazocine system, revealing a hitherto unknown reactivity pattern. The regioselectivity of the reaction was established by NMR spectroscopy and X-ray crystallography. The key feature of this reaction is its generality; it is compatible with different substitution patterns on the Tröger's base and can be performed with DMF as well as with other formamides. The wide scope of the reaction has been applied in the synthesis of several uncommon Tröger's base analogues.

Introduction

Tröger's base[1] [Figure 1(a)] is a fascinating molecule with a unique concave conformation and C_2-symmetric chirality arising from its two stereogenic nitrogen centres.[2] Owing to its rigid V-shaped geometry, Tröger's base has become a valued building block for the creation of novel supramolecular frameworks[3] and exploration of molecular recognition phenomena.[4] Tröger's base analogues have also found applications in other fields such as in asymmetric catalysis,[5] in stereoselective synthesis as chiral solvating agents[6] and in bioorganic chemistry.[7] Given this background, there is an immense demand for the construction of unusual Tröger's base analogues.

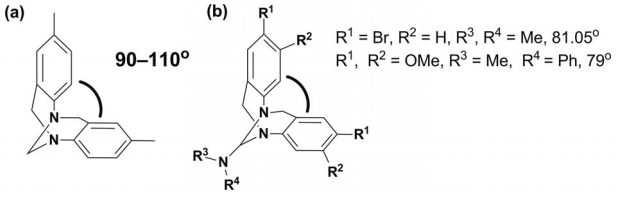

Figure 1. a) Tröger's base. b) Target dialkyl/arylalkyl-crowned Tröger's base analogues.

Classically, Tröger's base is produced by acid-catalysed condensation of 4-methylaniline with formaldehyde (or its equivalents).[8] For many years the presence of the electron-donating substituent on the aniline ring was thought to be a prerequisite for this condensation. However, Warnmark et al. reported that the presence of electron-withdrawing groups such as halogen atoms in almost any position on the aniline aromatic ring also resulted in good substrates for the synthesis of Tröger's base analogues.[9] This facilitates the introduction of any group by substitution of halogen on the aromatic core. The same group reported the lithiation of dihalogenated Tröger's base analogues followed by substitutions on the aromatic core,[10] as well as direct functionalization on the aromatic core of Tröger's base through Pd-catalysed cross-coupling reactions,[11] facilitating the introduction of acid-sensitive groups. Subsequently there were reports on the synthesis of Tröger's base analogues bearing other electron-withdrawing substituents such as ester[12] and nitro groups.[13] *C*-Alkylation of the Tröger's base-saturated component has been carried out through benzylic carbon lithiation.[14] The bicyclic methanodibenzodiazocene, which is known to racemize in the presence of dilute acids,[15] was restricted to *N*-alkylations, *N*-acylations, *N*-nitrosylations[16] and conversion into ethano-bridged Tröger's base analogues.[17]

Our interest in the utility of Tröger's base analogues as hosts in supramolecular chemistry[18] led us to design strategies for the general synthesis of Tröger's base analogues with variation of substitution both on the aromatic ring and

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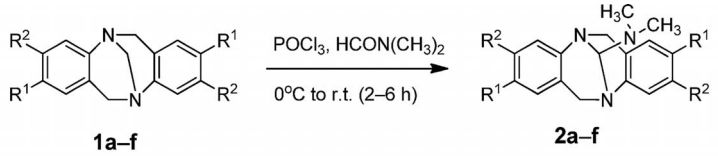
on the methylene bridge. In this context we were interested in electrophilic substitutions of Tröger's base and report here the reactions of Tröger's base and its analogues under Vilsmeier–Haack conditions[19] for the first time [Figure 1 (b)].

Results and Discussion

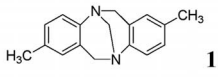
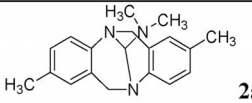
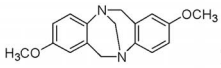
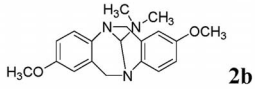
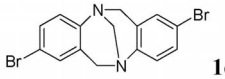
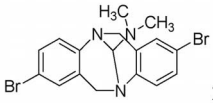
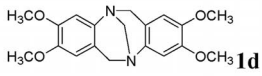
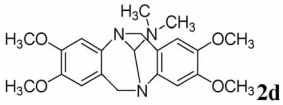
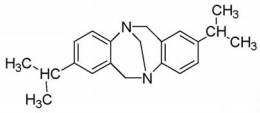
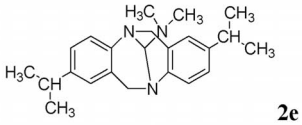
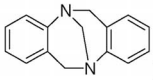
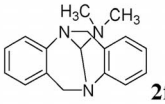
2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1a**) was subjected to classical Vilsmeier–Haack conditions with DMF and $POCl_3$. The product of this reaction was identified by ^1H NMR analysis as *N*,*N*,2,8-tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (**2a**, Table 1). The substitution had taken place not on the aromatic core of the Tröger's base but on the methano bridge of the saturated bicyclic component. A literature review revealed that similar methylene bridge substitutions occurred in triphenylcorroles,[20] with excess DMF believed to trigger the unusual substitution. In our reaction, it was further found that the substitution occurred only at the methylene bridge whether the reaction was carried out either with the optimum concentration of Vilsmeier–Haack reagent (3 equiv.) or with an excess (10 equiv.). The optimized Vilsmeier–Haack conditions were applied to the substituted Tröger's base analogues **1a**–**1f** in order to investigate the generality of the method for constructing new analogues. The reactions were regioselective in all cases and products were obtained in 53 to 72% yields. Various functionalities and multiple substitution patterns on the Tröger's base aromatic core appear to be compatible for substitution at the methano bridge under classic Vilsmeier–Haack conditions as shown in Table 1.

A thorough search for methylene bridge substitution on the Tröger's base diazocine unit revealed that a few "methano strap" modified Tröger's base analogues have been reported.[21] However, they were synthesized from a 5,6,11,12-tetrahydrodibenzodiazocine unit (cyclic diamine) generated by removing the methylene unit from the corresponding Tröger's base. An attempt to synthesize Tröger's base analogues containing spiro[4.5]lactone straps by direct substitution of the methano bridge were fruitful only when the aromatic core substituents were electron-donating.[22] Electron-withdrawing substituents were detrimental and the corresponding spiro[4.5]lactone analogues were synthesized from the cyclic diamines. Unusually modified Tröger's base analogues produced by Michael addition to dimethyl acetylenedicarboxylate and leading to methylene-bridged vinyl carboxylate derivatives have been described.[23] This work, however, has no such limitations. The methano bridge substitu-

Table 1. Synthesis of dimethylamine-crowned Tröger's base analogues under Vilsmeier–Haack conditions.[a]



1a–f **2a–f**

S.No	Tröger's base	Product	Time (h)	Yield [%][b]
1	 **1a**	 **2a**	2	72
2	 **1b**	 **2b**	2	69
3	 **1c**	 **2c**	3	66
4	 **1d**	 **2d**	2	70
5	 **1e**	 **2e**	6	53
6	 **1f**	 **2f**	2.5	64

[a] All the reactions were carried out with the Tröger's base or analogue (1 mmol), $POCl_3$ (3 mmol) and formamide (3 mmol). [b] Isolated yields.

tion under Vilsmeier–Haack conditions occurs both in substituted and in unsubstituted Tröger's base analogues **1a**–**1f**.

In order to establish the structures of the products unambiguously, the crystal structure of *N*-(2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)dimethylamine (**2c**, Table 1) was determined by X-ray crystallography. The compound crystallized in the chiral $P2_12_12_1$ space group, with one molecule in the asymmetric unit. Figure 2 (a) shows the molecular structure, with the expected overall V-shape and the crowning of the methano bridge with the dimethylamino functionality. Although the crystal contained only one enantiomer, a solution made from bulk solid showed no optical rotation: the reaction is not stereoselective and this crystallization of enantiomers into separate chiral crystals is an example of spontaneous resolution. The two bromine atoms in the crystal are in different environments. Together they form short, polarization-induced, type-II Br···Br contacts with the two bromine atoms separated by 3.70 Å.[24] An interesting feature of this structure is that one of the bromine atoms forms Br···π contacts with the aromatic ring such that the C–Br bond is pointing towards the carbon of another C–Br bond (C–Br···C angle is 170.6°; distance of 3.53 Å) as opposed to the centre of the aromatic ring (C–Br···π angle is 151.9°). Figure 2 (b) shows the network of Br···Br and C–Br···C contacts in the crystal. The angle between the planes of aromatic rings within the molecule is 81.05°.

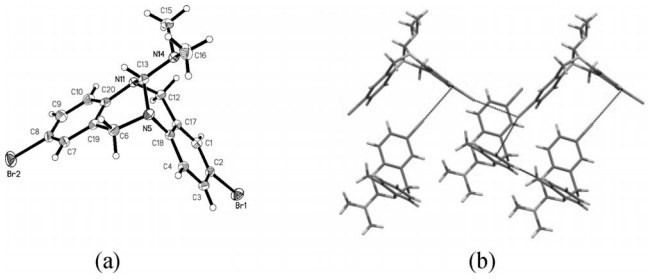
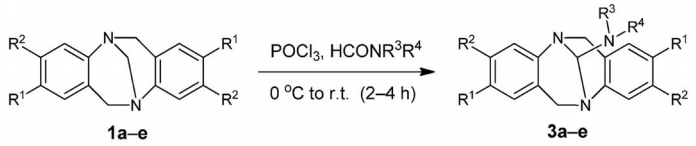
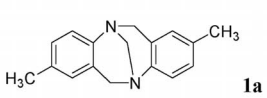
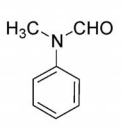
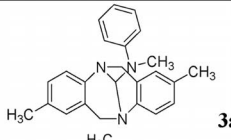
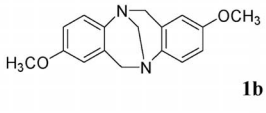
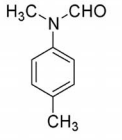
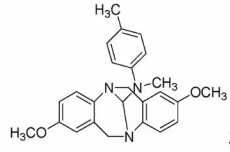
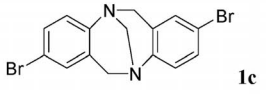
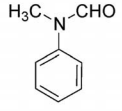
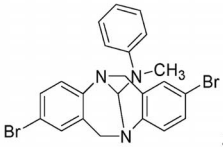
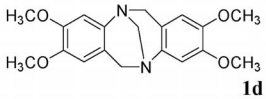
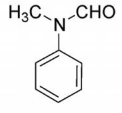
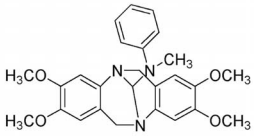
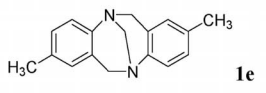
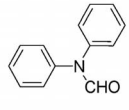
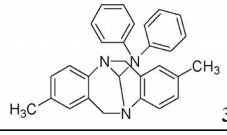


Figure 2. a) The molecular structure of **2c**, with the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. b) Crystal structure of **2c** showing a network of Br···Br and Br···C contacts.

A plausible mechanism based on the observed results is shown in Scheme 1. The nitrogen atoms are more nucleo-

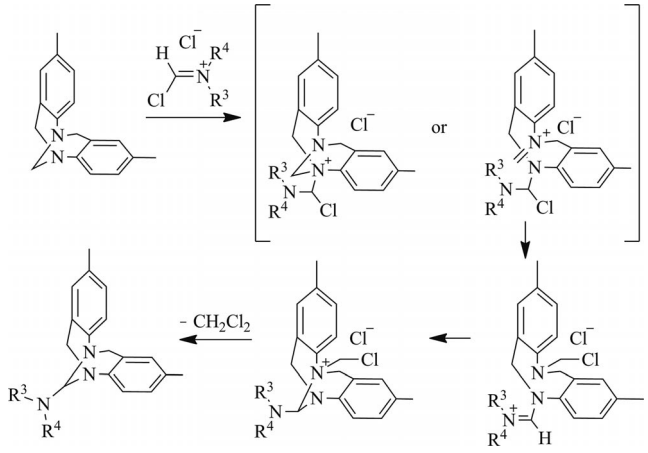
Table 2. Synthesis of arylalkyl-crowned Tröger's base analogues under typical Vilsmeier–Haack conditions.[a]



S. No	Tröger's base	Formamide	Product	Time (h)	Yield [%][b]
1	 **1a**		 **3a**	2.5	72
2	 **1b**		 **3b**	4	68
3	 **1c**		 **3c**	3	72
4	 **1d**		 **3d**	2	83
5	 **1e**		 **3e**	12	<5[c]

[a] All the reactions were carried out with the Tröger's base or analogue (1 mmol), $POCl_3$ (3 mmol) and the formamide derivative (3 mmol). [b] Isolated yields. [c] Only a trace of product was observed in the crude ^1H NMR spectrum.

philic than the aromatic ring, probably due to the fact that their lone pairs are not involved in conjugation, leading to substitution at the bridgehead. However, the other equally important driving force is the lability of the methano bridge. This is substantiated by the fact that the ethano-bridged Tröger's base analogue does not undergo formylation at all, neither at the bridgehead nor on the aromatic ring. Ethano-bridged Tröger's base analogues are known to be resistant to the conventional racemization via iminium ions that occurs in methano-bridged Tröger's base analogues. The mechanism involves nucleophilic attack by the bridgehead nitrogen on the Vilsmeier–Haack reagent and proceeds via an iminium intermediate. Closure of the methano bridge followed by elimination of dichloromethane leads to the formation of product.



Scheme 1. Plausible mechanism for the synthesis of dialkylamino/arylalkylamino-crowned Tröger's base analogues under typical Vilsmeier–Haack conditions.

Furthermore, the generality and scope of this reaction were investigated by replacing the DMF with other formylating agents such as *N*-phenylformamide, *N*,*N*-diphenylformamide, *N*-methyl-*N*-phenylformamide, piperidine-1-carbaldehyde, morpholine-1-carbaldehyde[25] and DCM as solvent. Whereas *N*-phenylformamide did not react as expected, *N*,*N*-diphenylformamide gave trace amounts of the corresponding products. Under Vilsmeier–Haack conditions, the reactions between various Tröger's base analogues and *N*-methyl-*N*-phenylformamide were facile, affording 68–83% yields of products (Table 2).

Interestingly, the X-ray crystal structure of *N*-(2,3,8,9-tetramethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)methylphenylamine (**3d**, Table 2), shown in Figure 3, was different from that of *N*-(2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-yl)dimethylamine (**2c**, Table 1). The compound crystallized in the centrosymmetric $P2_1/c$ space group with one molecule in the asymmetric unit. This is an example of a true racemate, with the two enantiomers forming a dimer across an inversion centre and lead to a staircase-like framework of molecules. The angle between the planes of aromatic rings within the molecule is 79°.

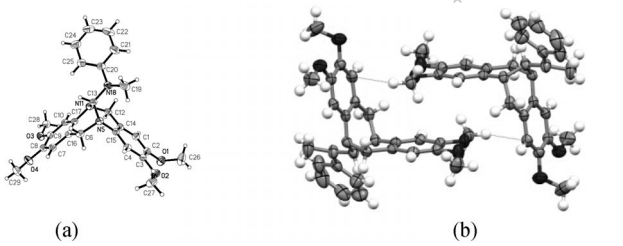
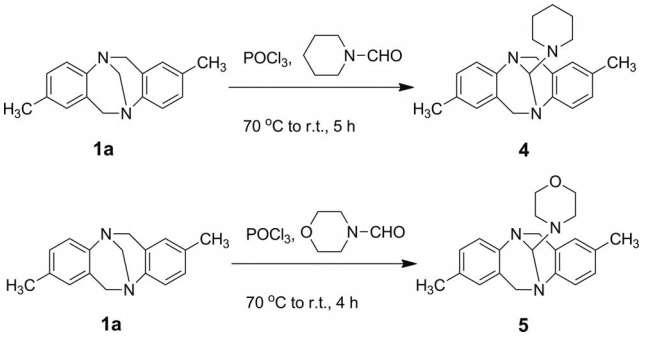


Figure 3. a) The molecular structure of **3d**, with the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius. b) Crystal structure of **3d** showing enantiomer dimer.

Treatment of **1a** with the heterocyclic formamides piperidine-1-carbaldehyde and morpholine-1-carbaldehyde (Scheme 2) under Vilsmeier–Haack conditions results in the formation of 2,8-dimethyl-13-piperidin-1-yl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**4**) and 13-(morpholin-4-yl)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**5**) in 81% and 72% yields, respectively. However, the Vilsmeier–Haack reagent had to be formed at 70 °C in this case.



Scheme 2. Treatment of 1a with heterocyclic formamides and $POCl_3$.

Conclusions

In summary, treatment of Tröger's base analogues under Vilsmeier–Haack conditions illustrates the distinctive reactivity pattern of the molecule. The wide scope and generality of the Vilsmeier reaction has been utilized to generate some unusual Tröger's base scaffolds. Normally, in the sharply folded V-shape geometry of Tröger's base analogues, the angle between two aromatic planes is in the range of 90–100°. The crowning of the methylene bridge results in the two aromatic planes in the molecule being brought closer, as evidenced by the smaller angles between the planes (81° and 79°). Methylene unit substitutions have been known to affect the overall geometries of Tröger's base analogues through variation of the dihedral angles. These findings are consistent with this. These structurally diverse Tröger's base analogues represent new building blocks for generation of supramolecular frameworks. Further studies on their applicability in recognition phenomena and catalysis are being actively pursued.

Experimental Section

General Methods: All starting materials were obtained from commercial sources and used without further purification. All reactions were carried out under anhydrous conditions. Organic fractions were dried with anhydrous Na_2SO_4. TLC analyses were performed on glass plates coated with silica gel (60 F_{254}). Plates were visualized with the aid of UV light (254 nm) and/or iodine. Column chromatography was performed on silica gel (60 × 120 mesh) on a glass column. Melting points (m.p.s) were determined in capillary tubes and are uncorrected.

^{1}H and ^{13}C NMR spectra (300 and 75 MHz, respectively) were recorded with use of TMS as an internal standard (δ = 0 ppm). Mass data (ESI) were recorded by quadruple mass spectrometry. HRMS data were obtained with the ESI ionization sources. IR spectra were recorded as KBr pellets or neat with a FTIR spectrometer. All Tröger's base analogues were synthesized by the method developed by Warnmark et al.[9] and were completely characterized before their subjection to Vilsmeier–Haack conditions.

Synthesis of Dimethylamino-Crowned Tröger's Base Analogues Under Vilsmeier–Haack Conditions. General Procedure 1: Dimethylformamide (3 mmol) was cooled in an ice bath and phosphorus oxychloride (3 mmol) was added dropwise. After formation of a yellow-coloured paste, the reaction mixture was allowed to warm to room temperature. Tröger's base or an analogue (1 mmol), dissolved in dry dimethylformamide (10 mL), was added and the reaction mixture was stirred at room temperature for 2–6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into cold saturated $NaHCO_3$ solution and stirred at room temperature for 1 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed with water (3 × 10 mL), dried and concentrated in vacuo. The crude product was purified by column chromatography with EtOAc/hexane as eluent.

(±)-*N*,*N*,2,8-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocin-13-amine (2a): 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1a**, 180 mg, 0.72 mmol) in DMF (4 mL) was added to Vilsmeier–Haack reagent prepared from DMF (168 μL, 2.16 mmol) and $POCl_3$ (202 μL, 2.16 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **2a** (151 mg, 72%) as a pale brown solid; m.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96–6.82 (m, 4 H), 6.62 (d, J = 13.6 Hz, 2 H), 4.53 (dd, J = 16.6, 6.8 Hz, 2 H), 4.09 (d, J = 16.6 Hz, 1 H), 3.75 (d, J = 15.9 Hz, 2 H), 2.36 (s, 6 H), 2.19 (s, 3 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.2, 142.0, 132.8, 132.6, 128.0, 127.8, 127.6, 126.7, 126.6, 125.1, 124.9, 90.1, 59.2, 51.4, 41.3, 20.7, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 2947, 1494 cm^{-1}. MS (ESI): m/z (%) = 294 (100) [M + H]. HRMS (ESI) calcd. for $C_{19}H_{24}N_3$ 294.1970; found 294.1969.

(±)-2,8-Dimethoxy-*N*,*N*-dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocin-13-amine (2b): 2,8-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1b**, 123 mg, 0.43 mmol) in DMF (4 mL) was added to Vilsmeier–Haack reagent prepared from DMF (101 μL, 1.3 mmol) and $POCl_3$ (120 μL, 1.3 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **2b** (98 mg, 69%) as a pale yellow solid; m.p. 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (dd, J = 14.9, 8.7 Hz, 2 H), 6.69 (td, J = 8.7, 2.6 Hz, 2 H), 6.35 (dd, J = 8.7, 2.6 Hz, 2 H), 4.53 (dd, J = 16.6, 10.0 Hz, 2 H), 4.08 (d, J = 16.6 Hz, 1 H), 3.79–3.63 (m, 8 H), 2.36 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 155.8, 141.9, 137.6, 129.3, 128.9, 126.5, 126.0, 113.9, 113.6, 110.6, 110.3, 90.4, 59.7, 55.0, 52.0, 41.6 ppm. IR (KBr): $\tilde{\nu}$ = 2937, 1494 cm^{-1}. MS (ESI): m/z (%) = 326 (100) [M + H]. HRMS (ESI) calcd. for $C_{19}H_{24}N_3O_2$ 326.1868; found 326.1882.

(±)-2,8-Dibromo-*N*,*N*-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocin-13-amine (2c): 2,8-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1c**, 200 mg, 0.52 mmol) in DMF (5 mL) was added to Vilsmeier–Haack reagent prepared from DMF (120 μL, 1.57 mmol) and $POCl_3$ (147 μL, 1.57 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **2c** (146 mg, 66%) as a white solid; m.p. 190–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 2 H), 7.03 (d, J = 2.1 Hz, 1 H), 6.99–6.85 (m, 3 H), 4.56 (dd, J = 16.6, 7.7 Hz, 2 H), 4.11 (d, J = 16.6 Hz, 1 H), 3.77 (t, J = 16.4 Hz, 2 H), 2.34 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 143.5, 130.6, 130.5, 130.3, 130.1, 129.3, 127.3, 127.0, 116.8, 116.6, 89.7, 59.0, 51.3, 41.3 ppm. IR (KBr): $\tilde{\nu}$ = 2950, 1473 cm^{-1}. MS (ESI): m/z (%) = 424 (100) [M + H]. HRMS (ESI) calcd. for $C_{17}H_{18}N_3Br_2$ 421.9867; found 421.9848.

Crystals were obtained from 100 mg of (±)-**2c** in dilute EtOAc (25 mL) at room temp. after 48 h. A well shaped crystal was picked for XRD studies.

(±)-2,3,8,9-Tetramethoxy-*N*,*N*-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (2d): 2,3,8,9-Tetramethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1d**, 300 mg, 0.87 mmol) in DMF (8 mL) was added to Vilsmeier–Haack reagent prepared from DMF (204 μL, 2.63 mmol) and $POCl_3$ (246 μL, 2.63 mmol). The crude product was purified by column chromatography with EtOAc in hexane (10%) as eluent to afford **2d** (236 mg, 70%) as a pale yellow solid; m.p. 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.55 (d, J = 9.1 Hz, 2 H), 6.31 (d, J = 6.4 Hz, 2 H), 4.47 (t, J = 15.9 Hz, 2 H), 4.06 (d, J = 16.2 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.77–3.67 (m, 8 H), 2.37 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.3, 148.1, 146.0, 145.8, 141.4, 137.0, 119.6, 119.2, 108.9, 108.6, 108.4, 90.3, 58.9, 55.8, 55.7, 51.0, 41.5 ppm. IR (KBr): $\tilde{\nu}$ = 2935, 1506 cm^{-1}. MS (ESI): m/z (%) = 385 (100) [M + H]. HRMS (ESI) calcd. for $C_{21}H_{28}N_3O_4$ 386.2079; found 386.2096.

(±)-2,8-Diisopropyl-*N*,*N*-dimethyl-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocin-13-amine (2e): 2,8-Diisopropyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1e**, 90 mg, 0.29 mmol) in DMF (4 mL) was added to Vilsmeier–Haack reagent prepared from DMF (68 μL, 0.88 mmol) and $POCl_3$ (82 μL, 0.88 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **2e** (54 mg, 53%) as a pale yellow gummy compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, J = 15.9 Hz, 4 H), 6.67 (d, J = 15.9 Hz, 2 H), 4.55 (dd, J = 16.6, 13.6 Hz, 2 H), 4.13 (d, J = 16.6 Hz, 1 H), 3.80 (d, J = 17.4 Hz, 2 H), 2.37 (s, 6 H), 1.25 (s, 2 H), 1.18 (s, 6 H), 1.15 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.8, 144.0, 143.6, 142.5, 128.1, 128.0, 125.5, 125.3, 125.1, 124.3, 124.1, 90.3, 59.6, 51.7, 41.7, 33.6, 29.8, 24.1 ppm. IR (neat): $\tilde{\nu}$ = 2955, 1493 cm^{-1}. MS (ESI): m/z (%) = 350 (100) [M + H]. HRMS (ESI) calcd. for $C_{23}H_{32}N_3$ 350.2596 found 350.2586.

(±)-*N*,*N*-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (2f): 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1f**, 250 mg, 1.12 mmol) in DMF (6 mL) was added to Vilsmeier–Haack reagent prepared from DMF (262 μL, 3.37 mmol) and $POCl_3$ (316 μL, 3.37 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **2f** (191 mg, 64%) as a white solid; m.p. 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14–6.78 (m, 8 H), 4.61 (dd, J = 16.6, 9.2 Hz, 2 H), 4.19 (d, J = 16.6 Hz, 1 H), 3.85 (d, J = 17.2 Hz,

2 H), 2.38 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.9, 144.7, 128.6, 128.3, 127.1, 126.9, 126.5, 126.4, 125.6, 125.3, 123.7, 123.6, 90.1, 59.4, 51.5, 41.5 ppm. IR (KBr): $\tilde{\nu}$ = 2939, 1444 cm^{-1}. MS (ESI): *m*/*z* (%) = 266 (100) [M + H]. HRMS (ESI) calcd. for $C_{17}H_{20}N_3$ 266.1657; found 266.1651.

Synthesis of Arylalkylamino-Crowned Tröger's Base Analogues Under Typical Vilsmeier–Haack Conditions. General Procedure 2: *N*-Methyl-*N*-phenylformamide (3 mmol) was cooled in an ice bath and phosphorus oxychloride (3 mmol) was added dropwise. After formation of a yellow coloured paste, the reaction mixture was allowed to warm to room temperature. Tröger's base (1 mmol) dissolved in dry dichloromethane (10 mL) was added to the Vilsmeier–Haack reagent and the reaction mixture was stirred at room temperature for 2–4 h. After completion of the reaction (monitoring by TLC), the reaction mixture was poured into saturated $NaHCO_3$ solution and stirred at room temperature for 1 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed with water (3 × 10 mL), dried and concentrated in vacuo. The crude product was purified by column chromatography with EtOAc/hexane as eluent.

(±)-*N*,2,8-Trimethyl-*N*-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (3a): 2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1a**, 250 mg, 1 mmol) in dry CH_2Cl_2 (8 mL) was added to the Vilsmeier–Haack reagent prepared from *N*-methyl-*N*-phenylformamide (405 mg, 3 mmol) and $POCl_3$ (280 μL, 3 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **3a** (255 mg, 72%) as a pale brown solid; m.p. 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 7.9 Hz, 2 H), 7.05–6.88 (m, 6 H), 6.84 (t, *J* = 7.2 Hz, 1 H), 6.69 (s, 1 H), 6.60 (s, 1 H), 5.09 (s, 1 H), 4.70 (d, *J* = 16.6 Hz, 1 H), 4.34 (d, *J* = 16.6 Hz, 1 H), 4.22 (d, *J* = 15.9 Hz, 1 H), 3.75 (d, *J* = 16.6 Hz, 1 H), 2.83 (s, 3 H), 2.22 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 145.6, 142.6, 133.3, 133.2, 128.4, 128.1, 128.0, 127.0, 126.8, 125.3, 124.8, 119.8, 118.1, 84.6, 60.5, 50.7, 36.5, 20.8 ppm. IR (KBr): $\tilde{\nu}$ = 2915, 1494 cm^{-1}. MS (ESI): *m*/*z* (%) = 356 (100) [M + H]. HRMS (ESI) calcd. for $C_{24}H_{26}N_3$ 356.2126; found 356.2122.

(±)-2,8-Dimethoxy-*N*,2,8-trimethyl-*N*-(*p*-tolyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (3b): 2,8-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1b**, 120 mg, 0.42 mmol) in CH_2Cl_2 (4 mL) was added to the Vilsmeier–Haack reagent prepared from *N*-methyl-*N*-*p*-tolylformamide (0.190 mg, 1.27 mmol) and $POCl_3$ (119 μL, 1.27 mmol). The crude product was purified by column chromatography with EtOAc in hexane (10%) as eluent to afford **3b** (115 mg, 68%) as a pale yellow gummy compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01–6.87 (m, 6 H), 6.67 (dt, *J* = 8.7, 2.6 Hz, 2 H), 6.39 (d, *J* = 2.6 Hz, 1 H), 6.32 (d, *J* = 2.8 Hz, 1 H), 4.96 (s, 1 H), 4.67 (d, *J* = 16.4 Hz, 1 H), 4.36 (d, *J* = 16.6 Hz, 1 H), 4.15 (d, *J* = 16.8 Hz, 1 H), 3.72–3.64 (m, 7 H) 2.79 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 155.8, 147.1, 141.2, 137.9, 130.1, 129.5, 129.0, 126.5, 126.1, 119.7, 113.9, 113.8, 110.5, 110.4, 85.2, 60.3, 55.3, 55.2, 51.2, 38.0, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 2922, 1496 cm^{-1}. MS (ESI): *m*/*z* (%) = 402 (100) [M + H]. HRMS (ESI) calcd. for $C_{25}H_{28}N_3O_2$ 402.2181; found 402.2196.

(±)-2,8-Dibromo-*N*,2,8-trimethyl-*N*-phenyl-6*H*,12*H*-5,11-methanodibenzo[b,f][1,5]diazocin-13-amine (3c): 2,8-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1c**, 138 mg, 0.36 mmol) in dry CH_2Cl_2 (8 mL) was added to the Vilsmeier–Haack reagent prepared from *N*-methyl-*N*-phenylformamide (147 mg, 1.08 mmol) and $POCl_3$ (101 μL, 1.08 mmol). The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **3c** (126 mg, 72%) as a white solid; m.p. 130–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 4 H), 7.08–6.89 (m, 7 H), 5.01 (s, 1 H), 4.71 (d, *J* = 16.6 Hz, 1 H), 4.40 (d, *J* = 16.6 Hz, 1 H), 4.21 (d, *J* = 16.6 Hz, 1 H), 3.74 (d, *J* = 16.6 Hz, 1 H), 2.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.9, 146.9, 143.7, 130.5, 130.0, 129.3, 128.5, 127.2, 126.8, 121.1, 119.6, 116.8, 116.7, 84.4, 59.6, 50.5, 37.8 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 1473 cm^{-1}. MS (ESI): *m*/*z* (%) = 486 (100) [M + H]. HRMS (ESI) calcd. for $C_{22}H_{20}N_3Br_2$ 484.0023; found 484.0012.

(±)-*N*-(2,3,8,9-Tetramethoxy-*N*,2,8-trimethyl-*N*-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocin-13-amine (3d): 2,3,8,9-Tetramethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1d**, 300 mg, 0.87 mmol) in dry CH_2Cl_2 (8 mL) was added to the Vilsmeier–Haack reagent prepared from *N*-methyl-*N*-phenylformamide (355 mg, 2.63 mmol) and $POCl_3$ (246 μL, 2.63 mmol). The crude product was purified by column chromatography with EtOAc in hexane (10%) as eluent to afford **3d** (325 mg, 83%) as a white solid; m.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 8.2 Hz, 2 H), 7.0 (d, *J* = 8.2 Hz, 2 H) 6.85 (t, *J* = 6.8 Hz, 1 H), 6.58 (d, *J* = 3.6 Hz, 2 H), 6.36 (s, 1 H), 6.29 (s, 1 H), 5.06 (s, 1 H), 4.65 (d, *J* = 15.5 Hz, 1 H), 4.28 (d, *J* = 15.5 Hz, 1 H), 4.17 (d, *J* = 16.4 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.70 (d, *J* = 16.4 Hz, 1 H), 2.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 148.4, 146.2, 146.0, 140.8, 137.4, 128.3, 120.0, 119.6, 119.1, 118.2, 108.7, 108.5, 108.4, 108.0, 84.7, 59.8, 55.8, 55.7, 55.6, 50.2, 36.6 ppm. IR (KBr): $\tilde{\nu}$ = 2908, 1503 cm^{-1}. MS (ESI): *m*/*z* (%) = 443 (100) [M + H]. HRMS (ESI) calcd. for $C_{26}H_{30}N_3O_4$ 448.2236; found 448.2256.

Crystals were obtained from 200 mg of (±)-**3d** in dilute EtOAc (40 mL) at room temp. after 72 h. A well shaped crystal was picked for XRD studies.

(±)-2,8-Dimethyl-13-(piperidin-1-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4): Piperidine-1-carbaldehyde (135 mg, 1.2 mmol) was cooled in an ice bath and phosphorus oxychloride (112 μL, 1.2 mmol) was added dropwise. The reaction mixture was then heated to 70 °C and stirred for 1 h to give a yellow coloured paste. It was then allowed to cool to room temperature, 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1a**, 100 mg, 0.4 mmol) in dry CH_2Cl_2 (5 mL) was added, and the mixture was stirred at room temperature for 3 h. After completion of the reaction (monitoring by TLC), the reaction mixture was poured into saturated $NaHCO_3$ solution and stirred at room temp. for 1 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed with water (3 × 10 mL), dried and concentrated in vacuo. The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **4** (108 mg, 81%) as a pale yellow gummy compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87–6.73 (m, 4 H), 6.53 (d, *J* = 16.0 Hz, 2 H), 4.44 (d, *J* = 16.2 Hz, 2 H), 4.01 (d, *J* = 16.4 Hz, 1 H), 3.83 (s, 1 H), 3.64 (d, *J* = 16.0 Hz, 1 H), 2.10 (s, 3 H), 2.01 (s, 3 H), 1.43–1.17 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 142.2, 132.6, 132.2, 128.5, 127.9, 127.7, 127.4, 126.6, 125.2, 124.7, 119.1, 88.7, 59.6, 51.5, 49.7, 29.6, 25.6, 24.9, 20.8, 20.7 ppm. IR (neat): $\tilde{\nu}$ = 2925, 1493 cm^{-1}. MS (ESI): *m*/*z* (%) = 334 (100) [M + H]. HRMS (ESI) calcd. for $C_{22}H_{28}N_3$ 334.2283; found 334.2295.

(±)-13-(Morpholin-4-yl)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (5): Morpholine-1-carbaldehyde (248 mg, 2.16 mmol) was cooled in an ice bath and phosphorus oxychloride (202 μL, 2.16 mmol) was added dropwise. The reaction mixture was then heated to 70 °C and stirred for 1 h to give a yellow coloured paste. It was cooled to room temperature, 2,8-dimethyl-6*H*,12*H*-

5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1a**, 180 mg, 0.72 mmol) in dry CH_2Cl_2 (6 mL) was then added, and the mixture was stirred at room temperature for 2 h. After completion of the reaction (monitoring by TLC), the reaction mixture was poured into saturated $NaHCO_3$ solution and stirred at room temp. for 1 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were washed with water (3 × 10 mL), dried and concentrated in vacuo. The crude product was purified by column chromatography with EtOAc in hexane (5%) as eluent to afford **5** (173 mg, 72%) as a pale yellow gummy compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88 (d, J = 13.8 Hz, 4 H), 6.63 (d, J = 15.3 Hz, 2 H), 4.52 (dd, J = 16.4, 11.1 Hz, 2 H), 4.37 (d, J = 16.4 Hz, 1 H), 3.96 (s, 1 H), 3.74 (d, J = 16.2 Hz, 1 H), 3.66–3.54 (m, 4 H), 2.85–2.60 (m, 4 H), 2.20 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 142.0, 133.3, 132.8, 128.5, 128.0, 127.7, 126.9, 126.7, 125.3, 124.9, 88.7, 66.9, 59.6, 51.5, 49.5, 20.9, 20.8 ppm. IR (neat): $\tilde{\nu}$ = 2913, 1494, 1178 cm^{-1}. MS (ESI): *m*/*z* (%) = 336 (100) [M + H]. HRMS (ESI) calcd. for $C_{21}H_{26}N_3O$ 336.2075; found 336.2082.

X-Ray Crystallography Data for 2c and 3d: X-ray data for compounds **2c** and **3d** were collected at room temperature with use of a Bruker Smart Apex CCD diffractometer and graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) by the ω-scan method.[26] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined by use of 7640 reflections for **2c** and 7047 for **3d**.

Integration and scaling of intensity data were accomplished by use of the SAINT program.[27] The structures were solved by direct methods with use of SHELXS97 and refinement was carried out by the full-matrix least-squares technique with SHELXL97.[28] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H distances of 0.93–0.96 Å and with U_{iso}(H) = 1.2 U_{eq} (C) or 1.5 U_{eq} for methyl atoms. For **2c**, the absolute configuration was confirmed by unambiguous refinement of the absolute structure parameters [0.018(13) for the *S* configuration of the C(13) atom].

Data for 2c: Formula $C_{17}H_{17}Br_2N_3$, M = 423.16, orthorhombic, space group $P2_12_12_1$, a = 8.6149(9) Å, b = 9.9174(10) Å, c = 19.7154(13) Å, V = 1644.9(3) Å^3, Z = 4, D_c = 1.709 g cm^{-3}, μ(Mo-K) = 4.928 mm^{-1}, F(000) = 840, T = 294(2) K, $R1(I > 2\sigma)$ = 0.0303, $wR2$(all data) = 0.0855 for 2893 independent reflections with a goodness-of-fit of 1.072.

Data for 3d: Formula $C_{26}H_{29}N_3O_4$, M = 447.52, monoclinic, space group $P2_1/c$, a = 9.9850(9) Å, b = 15.6080(14) Å, c = 15.4194(14) Å, β = 104.797(2)°, V = 2323.4(4) Å^3, Z = 4, Dc = 1.279 g cm^{-3}, μ(Mo-K) = 0.087 mm^{-1}, F(000) = 952, T = 294(2) K, $R1(I > 2\sigma)$ = 0.0486, $wR2$(all data) = 0.1263 for 4083 independent reflections with a goodness-of-fit of 1.079.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C spectra for all compounds, crystallographic data for **2c** and **3d** (CIF files).

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