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Synthesis of new derivatives from a Tröger base via exchange of the methano bridge with carbonyl compounds

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ABSTRACT

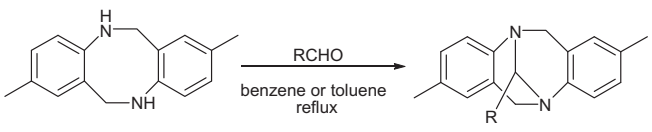
A simple one-pot method has been developed for the preparation of new Tröger base derivatives by an exchange reaction with the methano bridge of *rac*-Tröger base derivatives with carbonyl compounds in the presence of $TiCl_4$ or $POCl_3$. The use of chiral (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide as a carbonyl compound gave the corresponding methano Tröger base derivatives with the diastereomeric ratios of up to 77:23.

1. Introduction

Tröger base **1a**, a molecule with two bridgehead stereogenic nitrogen atoms is generally prepared by the condensation reaction of *p*-toludine and formaldehyde promoted by acids. Many structurally diverse Tröger base derivatives have been made with synthetic alterations on the aromatic core[1] as well as the saturated aliphatic core.[2] Tröger base derivatives are useful as ligand in asymmetric catalysis,[3] as a chiral solvating agent,[4] in molecular replication studies,[5] in biomimitic systems[6] and as DNA-interacting probes.[7] Recently, we have reported methods for the Lewis acid promoted synthesis, resolution, and applications of Tröger base and its derivatives.[8] Herein we report a Lewis acid promoted synthesis of new Tröger base derivatives by substitution of the methylene bridge with carbonyl compounds in a single pot operation.

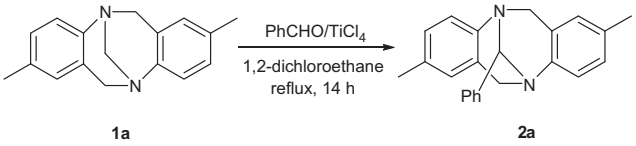
2. Result and discussion

Tröger base derivatives with substitution at the 5,11-methano position are generally synthesized by the reaction of cyclic secondary amines with carbonyl compounds, which in turn needs to be obtained from the corresponding Tröger base (Scheme 1).[9]



Scheme 1.

We have observed that the reaction of Tröger base with benzaldehyde in the presence of $TiCl_4$ under refluxing 1,2-dichloroethane (DCE) affords the 5,11-substituted derivative **2a** in a 59% yield (Schemes 2 and 3).



1a **2a**

Scheme 2.

Several other aldehydes and ketones can be exchanged with the methano group in the Tröger base in this manner to obtain the products in moderate to good yields. The results are summarized in Table 1. The spiro compound **2i** was obtained from the reaction with cyclopentanone. The structure of this compound was further confirmed by X-ray crystal structure analysis. The crystal structure of the compound **2i** is shown in Figure 1.[10]

We have also examined the reaction of the Tröger base with benzaldehyde in the presence of several Lewis acids. Whereas $BF_3{\cdot}OEt_2$ and $ZnBr_2$ were not effective in the reaction with benzaldehyde in the presence of $POCl_3$ in toluene at 80 °C, the 5,11-substituted Tröger base **2a** was obtained in moderate yields (Scheme 4). We observed that the reaction using 1,2-dichloroethane under refluxing conditions (i.e., 83 °C) for 3 h instead of using toluene solvent at 80 °C gave relatively lower yields (42%) in a run using benzaldehyde. The reaction also takes place with other aldehydes; the results are summarized in Table 2.

We have observed that the DMF can be used as a carbonyl partner in the reaction with $POCl_3$ to obtain the corresponding 5,11-substituted product **3a** in a 63% yield (Table 3, entry 1). The optimum results were obtained using CH_2Cl_2 as the solvent

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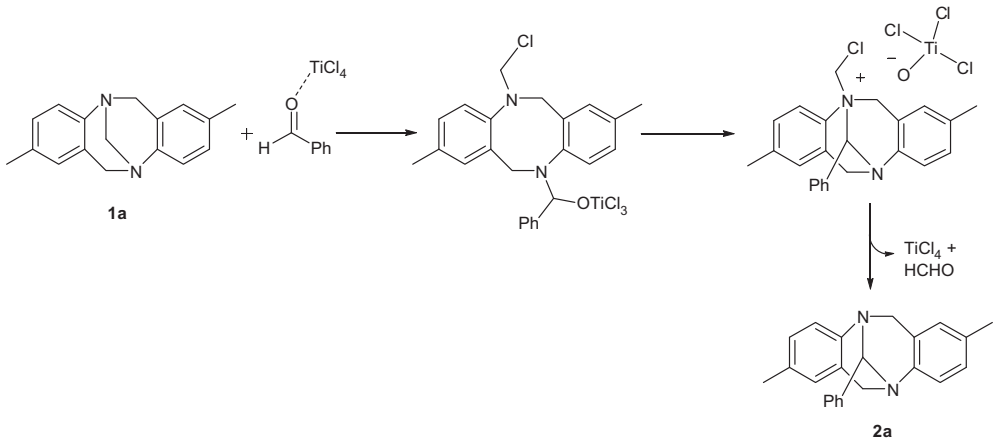
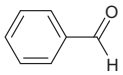
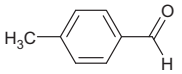
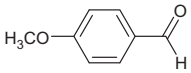
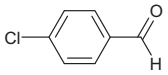
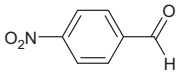
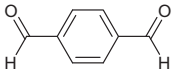
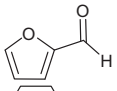
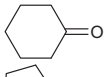


Scheme 3. Tentative mechanism for the formation of 5,11-substituted derivatives.

Table 1
Reaction of Tröger base **1a** with aldehydes and ketones in the presence of $TiCl_4$[a]

Entry	Aldehyde/ketone	Product	Yield[b,c] (%)
1		**2a**	59
2		**2b**	61
3		**2c**	62
4		**2d**	53
5		**2e**	35
6		**2f**	52
7		**2g**	61
8		**2h**	50
9		**2i**	41

[a] All reactions were carried out by using racemic Tröger base **1a** (5 mmol), carbonyl compounds (5.1 mmol) and $TiCl_4$ (10 mmol) in 1,2-dichloroethane (15 mL) at 25 °C and refluxed for 14 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).

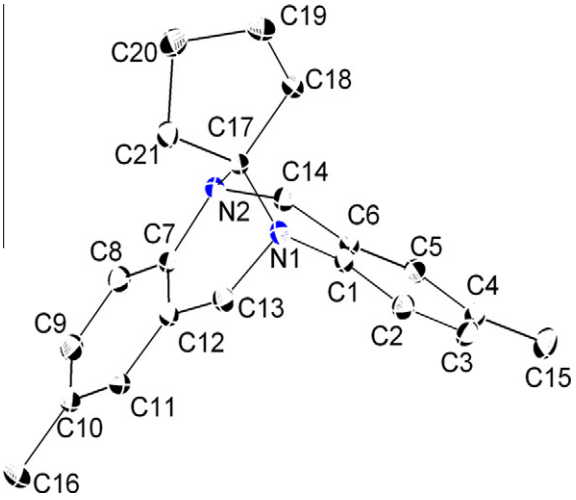
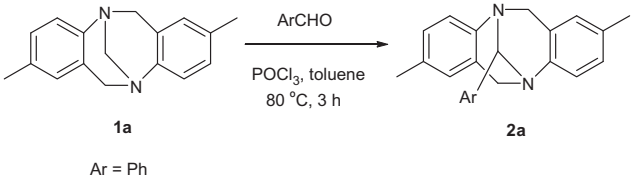


Figure 1. ORTEP representation of the crystal structure of compound **2i**. Thermal ellipsoids are drawn at 20% probability and all the hydrogen atoms are removed for clarity.



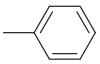
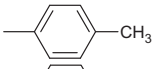
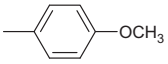
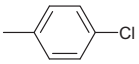
Scheme 4.

(Table 3). In addition to the 5,11-substituted derivative **3a**, the ring opened product **4** was also obtained in small amounts (Table 3, entries 2–9 and Scheme 5).

We have also examined the $POCl_3$ promoted reaction of other Tröger base derivatives with DMF. The results are summarized in Table 4. The reaction of methoxy Tröger base **1b** and DMF with $POCl_3$ gave the corresponding 5,11-substituted derivative **3b** in a 84% yield. In order to further examine the scope of this reaction, we prepared other Tröger base derivatives without any substitution at the *ortho* or *para* positions with respect to the nitrogens. The steric effect of the *ortho* substitution by a methyl group decreases the yield of the reaction significantly (Table 4, entry 5). A tentative mechanism was considered for this transformation involving Vilsmeier type iminium ion intermediates (Scheme 6).

We envisaged the possibility of the asymmetric synthesis of Tröger base derivatives using a chiral formamide instead of dimethyl formamide. Thus, we examined the reaction of *rac*-**1a** and (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide as formyl partner in the presence of $POCl_3$ at 25 °C. In this reaction, the corresponding 5,11-substituted Tröger base derivative was obtained in a 75% yield (Scheme 7). The ^{1}H NMR spectrum of the product showed that the product was a diastereomeric mixture with a 75:25 ratio. The reaction was carried out using various solvents. Optimum results were obtained in dichloromethane solvent (Table 5, entry 1). Lowering

Table 2
Reaction of Tröger base **1a** with various aldehydes in the presence of $POCl_3$[a]

Entry	Aromatic aldehyde Ar-CHO	Product	Yield[b,c] (%)
1	Ar = 	**2a**	60
2	Ar = 	**2b**	65
3	Ar = 	**2c**	68
4	Ar = 	**2d**	55
5	Ar = 	**2g**	60

[a] All reactions were carried out by using racemic Tröger base **1a** (5 mmol), then adding the aromatic aldehyde (5.1 mmol) and $POCl_3$ (8.75 mmol) in toluene (15 mL) at 0 °C, bringing the mixtures to 25 °C and then heating at 80 °C for 3 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).

Table 3
Reaction of Tröger base **1a** with DMF in the presence of $POCl_3$[a]

Entry	$POCl_3$ (equiv)	Solvent	Yield[b,c] (%) **3a**	Yield[b,c] (%) **4**
1	1.75	DMF[d]	63	0
2	1.75	DCM	93	Trace[e]
3	2.0	DCM	89	Trace[e]
3	1.5	DCM	91	5
4	1.25	DCM	74	12
5	1.0	DCM	70	19
6	1.75	$CHCl_3$	56	7
7	1.75	DCE	42	9
8	1.75	Toluene	52	9
9	1.75	Acetonitrile	35	11
10	1.75	MeOH	0[f]	0[f]

[a] Unless otherwise mentioned, all reactions were carried out using racemic Tröger base **1a** (2 mmol), DMF (2.1 mmol), solvent (15 mL) at 25 °C for 1 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).
[d] Reaction was carried out by using racemic Tröger base **1a** (5 mmol) and $POCl_3$ (8.75 mmol) in DMF (5 mL) at 0 °C and then heated at 80 °C for 3 h.
[e] Identified by ^{1}H NMR.
[f] No reaction.

the temperature to 0 °C did not improve the selectivity of the Tröger base formed (Table 5, entry 6). Further lowering of the temperature to −10 °C gave only a trace amount of the desired product (Table 5, entry 7). However, the diastereomers obtained could not be separated by chromatography or crystallization.

We also examined the $POCl_3$ promoted reaction of other Tröger base derivatives with (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide under the experimental conditions. The results are summarized in Table 6. The reaction of Tröger base derivative **1c** and (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide **5** with $POCl_3$ gave the corresponding 5,11-substituted derivative **8** in a 68% yield with a diastereomeric ratio of 75:25 (Table 6, entry 3). In this case, the diastereomeric mixture could not be isolated in pure form by column chromatography. However, crystallization of the product mixture **8** from acetone solvent gave the major diastereomer **8a** in pure form with a 51% chemical yield. The Tröger base derivative **1d** gave the corresponding 5,11-substituted product **9** in a 52% yield with a diastereomeric ratio of 58:42 (Table 6, entry 4). In this case, the major diastereomer **9a** was also isolated in pure form with a 50% chemical yield by crystallization of product mixture **9** from acetone solvent. The X-ray structural analysis of a single crystal of **9a** revealed that the product was a 5,11-substituted derivative with an (*R*,*R*)-configuration at the newly formed stereogenic nitrogen centers. The ORTEP diagram for the major product is shown in Figure 2.[11] The reaction of Tröger base derivative **1e** with (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide did not give the desired 5,11-substituted product (Table 6, entry 5); the starting materials were recovered under the reaction conditions. This is presumably because the *ortho* and *meta* methyl substituents greatly hinder this reaction.

The asymmetric induction in the formation of the major product in the diastereoselective synthesis of the Tröger base derivatives can be rationalized as outlined in Scheme 8. The reaction of racemic Tröger base **1a** with (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide in the presence of $POCl_3$ leads to iminium ion intermediates, which should be in equilibrium (Scheme 8). Invariance of the diastereomeric ratio (75:25) for the products (Table 6) obtained from the unhindered substrates **1a**, **1b,** and **1c** indicates the thermodynamic control of the reaction.[15]

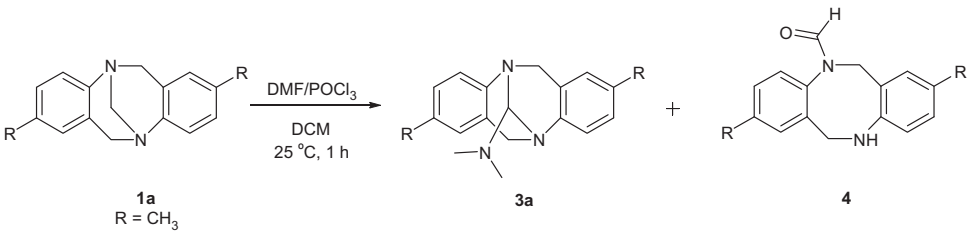
3. Conclusion

In conclusion, we have developed $TiCl_4$ or $POCl_3$ promoted one-pot methods to readily access 5,11-substituted Tröger base derivatives. During the preparation of this manuscript, reports have appeared describing the $POCl_3$ promoted exchange reaction of the methano bridge reported using achiral amides.[12] However, the methods described here are generally applicable for aldehydes, ketones, and amides. In addition, we have also devised a method for the diastereoselective synthesis of Tröger base derivatives using (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide as a carbonyl group partner. Furthermore, asymmetric induction in the synthesis of chiral Tröger base derivatives using a chiral reagent to exchange the 5,11 methano bridge has been reported for the first time. Since the chiral Tröger base derivatives **6**–**9** containing a reduced chiral guanidine moiety are readily accessible, the method described herein has considerable potential for further synthetic applications.

4. Experimental

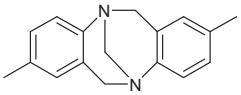
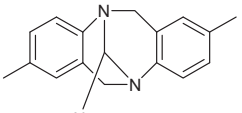
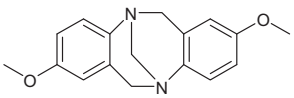
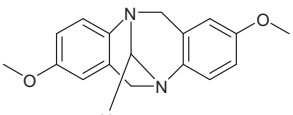
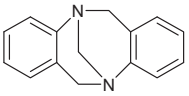
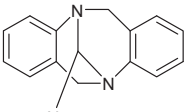
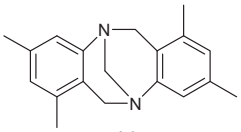
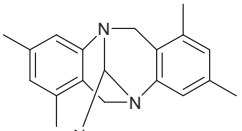
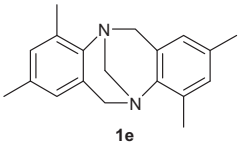
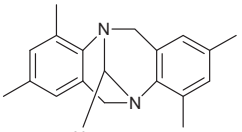
4.1. Materials and methods

Tröger base derivatives **1a**, **1b**, **1d**, **1e** were prepared by following the method reported from this laboratory. Tröger base **1c**[13] and

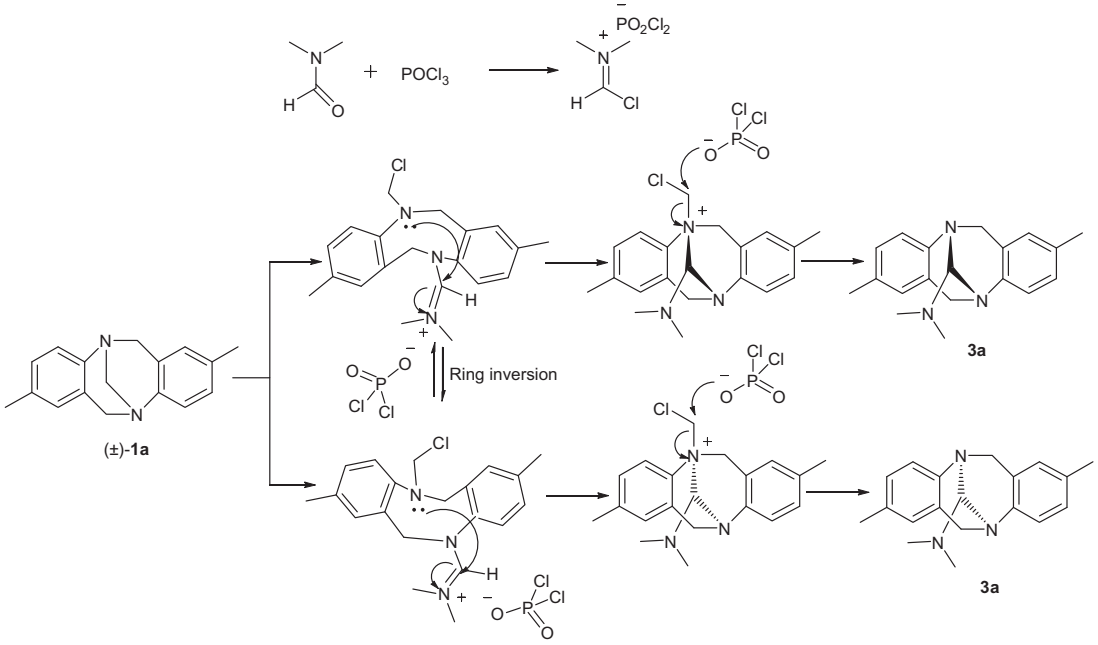


Scheme 5.

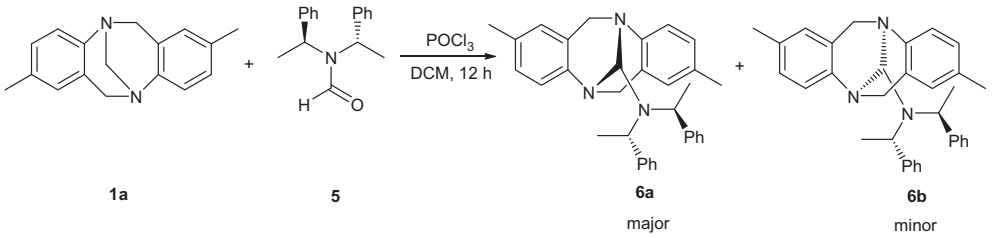
Table 4
Vilsmeier–Haack type reaction of Tröger base derivatives with DMF[a]

Entry	Substrate	Product	Yield[b,c] (%)
1	 **1a**	 **3a**	93
2	 **1b**	 **3b**	84
3	 **1c**	 **3c**	88
4	 **1d**	 **3d**	86
5	 **1e**	 **3e**	65

[a] All reactions were carried out using racemic Tröger base derivatives (2 mmol), DMF (2.1 mmol) and $POCl_3$ (3.5 mmol) in dry CH_2Cl_2 (15 mL) at 25 °C for 1 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^1H NMR, ^{13}C NMR).



Scheme 6. Tentative mechanism for the $POCl_3$ promoted reaction.



Scheme 7.

Table 5
Reaction of Tröger base with (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide **5** in the presence of $POCl_3$[a]

Entry	Solvent	Temperature (°C)	Yield[b,c] (%)	dr[d] (%)
1	DCM	25	75	75:25
2	$CHCl_3$	25	40	75:25
3	Toluene	25	38	75:25
4	DCE	25	47	75:25
5	CH_3CN	25	23	75:25
6	DCM	0	32	75:25
7	DCM	−10	Trace (<5%)[e]	—

[a] All reactions were carried out using racemic Tröger base **1a** (2 mmol), (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide **5** (2.1 mmol) and $POCl_3$ (3.5 mmol) in 15 mL DCM for 12 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).
[d] The diastereomeric ratios were estimated from ^{1}H NMR (400 MHz) data. The diastereomeric ratios 77:23 were also estimated by HPLC using chiral cell phenomenex cellulose-1 column.
[e] dr not estimated.

(*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)foramide[14] were prepared following a reported procedure. $POCl_3$ and DMF were purchased from commercial sources and used as received. Dichloromethane was distilled from calcium hydride under nitrogen. The melting points reported herein are uncorrected and were determined using a superfit capillary point apparatus. IR spectra were recorded on a JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance-400 MHz Spectrometer with chloroform-d as a solvent and TMS as reference. Optical rotations were measured in an AUTOPOL-IV digital polarimeter (readability ±0.001°). Liquid chromatography (LC) and mass analysis (LC–MS) were performed on SHIMADZU-LCMS-2010A. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and a Thermo Finnigan analyzer series Flash EA1112. HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. The dr values were determined from ^{1}H NMR signals and chiral cell phenomenex cellulose-1 column with eluents:hexane/2-propanol.

4.1.1. General procedure for the preparation of the 5,11-substituted derivatives 2a–2i of Tröger base using $TiCl_4$

To a reaction flask cooled under N_2, was added Tröger base (1.25 g, 5 mmol) in 1,2-dichloroethane (15 mL) and $TiCl_4$ (1.9 g, 1.1 mL, 10 mmol). Next, the carbonyl compound (5.1 mmol) was added at 25 °C and the reaction mixture was refluxed for 14 h. It was then cooled to 0 °C and quenched with saturated K_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed successively with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 2–5% ethyl acetate in hexane to give the desired 5,11-substituted derivative.

4.1.1.1. 2,8-Dimethyl-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 2a.

Yield: 0.96 g (59%); mp 180–182 °C (lit.[9a] mp 182–183 °C); IR (KBr) 3012, 2908, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 2H), 7.32–7.22 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.0–6.97 (m, 2H), 6.80 (s, 1H), 6.48 (s, 1H), 5.34 (s, 1H), 4.83 (d, *J* = 16.4 Hz, 1H), 4.35 (d, *J* = 16.4 Hz, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 3.91 (d, *J* = 16.8 Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 143.7, 138.5, 133.3, 132.9, 128.3, 128.2, 128.0, 127.7, 127.5, 127.3, 127.2, 126.9, 125.4, 125.0, 74.6, 60.8, 52.6, 20.9, 20.8; MS (EI): *m*/*z* 327.0 (M+1); Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.75; H, 6.72; N, 8.51.

4.1.1.2. 2,8-Dimethyl-13-(4-methylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 2b.

Yield: 1.03 g (61%); mp 168–170 °C; IR (KBr) 3011, 2993, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.13–7.09 (m, 3H), 7.0–6.97 (m, 2H), 6.79 (s, 1H), 6.47 (s, 1H), 5.31 (s, 1H), 4.80 (d, *J* = 16.4 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 3.90 (d, *J* = 16.8 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 143.8, 136.9, 135.5, 133.3, 132.9, 128.9, 128.3, 128.0, 127.8, 127.5, 127.3, 127.0, 125.4, 125.1, 74.5, 60.8, 52.6, 21.2, 21.0, 20.9; MS (EI): *m*/*z* 341.1 (M+1); Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23. Found: C, 84.51; H, 7.16; N, 8.12.

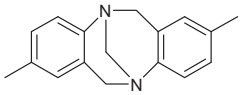
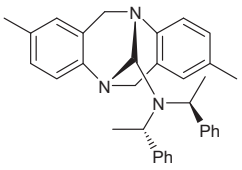
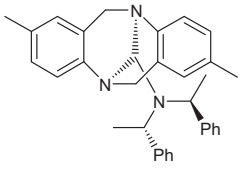
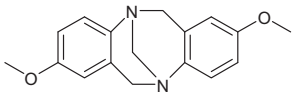
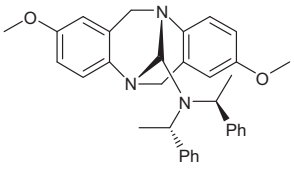
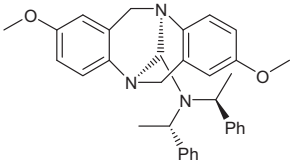
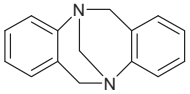
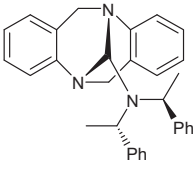
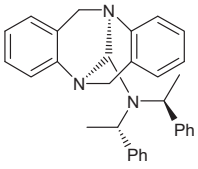
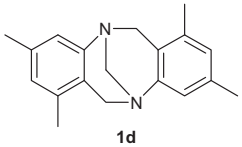
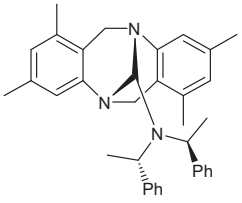
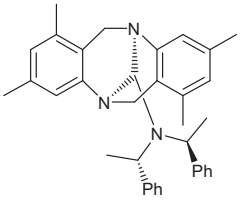
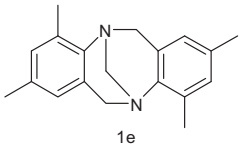
4.1.1.3. 2,8-Dimethyl-13-(4-methoxyphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 2c.

Yield: 1.1 g (62%); mp 152–154 °C (lit.[9a] mp 155–156 °C); IR (KBr) 3015, 2908, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.0–6.98 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 6.49 (s, 1H), 5.29 (s, 1H), 4.82 (d, *J* = 16.4 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 1H), 4.15 (d, *J* = 16.8 Hz, 1H), 3.90 (d, *J* = 16.8 Hz, 1H), 3.77 (s, 3H), 2.26 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 147.6, 143.7, 133.3, 132.9, 130.6, 128.7, 128.2, 128.0, 127.8, 127.3, 126.9, 125.4, 125.1, 113.6, 74.3, 60.8, 55.1, 52.4, 20.9, 20.8; MS (EI): *m*/*z* 357.35 (M+1); Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86; O, 4.49. Found: C, 80.68; H, 6.72; N, 7.95.

4.1.1.4. 2,8-Dimethyl-13-(4-chlorophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 2d.

Yield: 0.954 g (53%); mp 156–158 °C; IR (KBr) 3015, 2995, 1491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.0–6.98 (m, 2H), 6.79 (s, 1H), 6.48 (s, 1H), 5.28 (s, 1H), 4.80 (d, *J* = 16.4 Hz, 1H), 4.33 (d, *J* = 16.4 Hz, 1H), 4.10 (d, *J* = 16.8 Hz, 1H), 3.90 (d, *J* = 16.8 Hz, 1H), 2.26 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (l00 MHz, $CDCl_3$): δ 147.4, 143.4, 137.0, 133.5, 133.2, 130.0, 129.1, 128.4, 128.1, 127.5, 127.2, 126.9, 125.4, 125.1, 74.1, 60.6, 52.5, 20.9, 20.8; MS (EI): *m*/*z* 361 (M+1); Anal. Calcd for $C_{23}H_{21}ClN_2$: C, 76.55; H, 5.87; N, 7.76; Cl, 9.82. Found: C, 76.45; H, 5.81; N, 7.68.

Table 6
Diastereoselective synthesis of various 5,11-substituted methano bridged Tröger base derivatives[a]

Entry	Substrate	Products	Yield[b,c] (%)	dr[d] (%)
1	 **1a**	 **6a**  **6b**	75	75:25
2	 **1b**	 **7a**  **7b**	66	75:25
3	 **1c**	 **8a**  **8b**	68	75:25
4	 **1d**	 **9a**  **9b**	52	58:42
5	 1e	No reaction	—	—

[a] All reactions were carried out using racemic Tröger base derivatives (2 mmol), (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)foramide **5** (2.1 mmol) and $POCl_3$ (3.5 mmol) in 15 mL DCM at 25 °C for 12 h.
[b] The yields are of isolated products.
[c] The products were characterized by spectroscopic data (IR, ^1H NMR, ^{13}C NMR).
[d] The diastereomeric ratios were estimated from the ^1H NMR (400 MHz) data. The diastereomeric ratios were also estimated for **6** (77:23), **7** (77:23), and **9** (60:40) by HPLC using a chiral cell phenomenex cellulose-1 column.

4.1.1.5. 2,8-Dimethyl-13-(4-nitrophenyl)-6*H*,12*H*-5,11-methano dibenzo[*b*,*f*][1,5]diazocine 2e. Yield: 0.65 g (35%); mp 159–161 °C (lit.[9a] mp 160.5–161 °C); IR (KBr) 2920, 2852, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.0–6.99 (m, 2H), 6.80 (s, 1H), 6.48 (s, 1H), 5.34 (s, 1H), 4.82 (d, J = 16.4 Hz, 1H), 4.35 (d, J = 16.4 Hz, 1H), 4.06 (d, J = 17.2 Hz, 1H), 3.94 (d, J = 17.2 Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 147.1, 145.8, 143.0, 133.8, 133.6, 128.7, 128.6, 128.2, 127.9, 127.2, 127.0, 126.9, 125.5, 125.1, 123.5, 74.2, 60.5, 52.6, 20.9, 20.8; MS (EI): m/z 372.2 (M+1); Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31; O, 8.61. Found: C, 74.48; H, 5.63; N, 11.25.

4.1.1.6. 2,8-Dimethyl-13-(4-formylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 2f. Yield: 0.92 g (52%); mp 80–82 °C; IR (KBr) 3012, 2918, 2727, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.82 (s, 4H), 7.22 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.05–7.0 (m, 2H), 6.81 (s, 1H), 6.48 (s, 1H), 5.35 (s, 1H), 4.83 (d, J = 16.4 Hz, 1H), 4.36 (d, J = 16.4 Hz, 1H), 4.12 (d, J = 17.2 Hz, 1H), 3.94 (d, J = 17.2 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (l00 MHz, $CDCl_3$): δ 192.1, 147.4, 145.4, 143.3, 135.5, 133.7, 133.4, 129.7, 128.5, 128.3, 128.2, 128.0, 127.4, 127.3, 126.9, 125.4, 125.0, 74.5, 60.6, 52.7, 20.9, 20.8; MS (EI): m/z 355.2 (M+1); Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90; O, 4.51. Found: C, 81.23; H, 6.32; N, 7.83.

4.1.1.7. 2,8-Dimethyl-13-(2-furyl)-6*H*,12*H*-5,11-methanodibenzo [*b*,*f*][1,5]diazocine 2g. Yield: 0.96 g (61%); mp 133–135 °C (lit.[9a] mp 135–135.5 °C); IR (KBr) 3014, 2916, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.0–6.98 (m, 2H), 6.76 (s, 1H), 6.57 (s, 1H), 6.27–6.26 (m, 1H), 6.11–6.10 (m, 1H), 5.38 (s, 1H), 4.80 (d, J = 16.8 Hz, 1H), 4.25 (d, J = 16.4 Hz, 1H), 4.17 (d, J = 16.8 Hz, 1H), 3.99 (d, J = 16.8 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (l00 MHz, $CDCl_3$): δ 151.6, 146.2, 143.5, 142.3, 133.8, 133.4, 128.3, 128.2, 127.5, 127.4, 127.2,

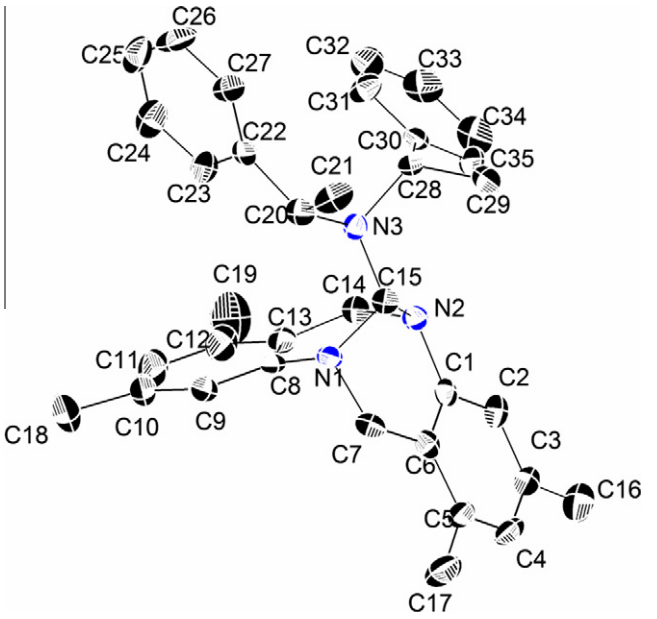


Figure 2. ORTEP representation of the crystal structure of compound **9a**. Thermal ellipsoids are drawn at 35% probability and all hydrogen atoms are removed for clarity.

126.9, 125.4, 125.1, 110.3, 109.1, 71.3, 60.6, 53.5, 20.9; MS (EI): *m*/*z* 317.2 (M+1); Calcd for $C_{21}H_{20}N_2O$: C 79.72, H 6.37, N 8.85, O 5.06. Found: C 79.62, H 6.41, N 8.76.

4.1.1.8. 2,8-Dimethyl-13-spiro[cyclohexane-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine] 2h. Yield: 0.79 g (50%); mp 192–194 °C (lit.[9a] mp 195–196 °C); IR (KBr) 2920, 2854, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04–6.98 (m, 4H), 6.66 (s, 2H), 4.57 (d, *J* = 16.8 Hz, 2H), 4.03 (d, *J* = 17.2 Hz, 2H), 2.21 (s, 6H), 1.82–1.47 (m, 10H); ^{13}C NMR (l00 MHz, $CDCl_3$): δ 146.0, 133.0, 128.4, 128.1, 126.6, 126.1, 70.2, 54.6, 33.3, 26.0, 22.1, 20.9; MS (EI): *m*/*z* 319.2 (M+1); Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.79; H, 8.28; N, 8.72.

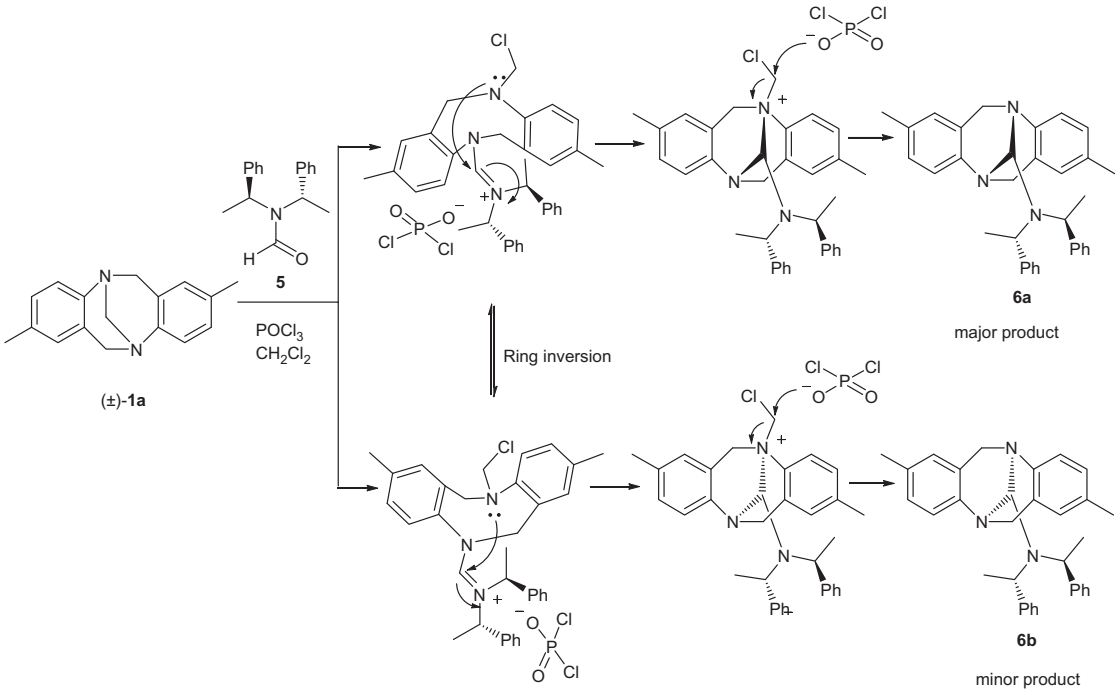
4.1.1.9. 2,8-Dimethyl-13-spiro[cyclopentane-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine] 2i. Yield: 0.62 g (41%); mp 182–184 °C; IR (KBr) 2922, 2854, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04–6.95 (m, 4H), 6.69 (s, 2H), 4.70 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 17.2 Hz, 2H), 2.22 (s, 6H), 2.04–1.99 (m, 2H), 1.83–1.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 133.1, 127.9, 127.8, 126.8, 125.8, 80.7, 55.6, 35.9, 23.9, 20.9; MS (EI): *m*/*z* 305.2 (M+1); Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.68; H, 7.89; N, 9.26.

4.1.2. General procedure for the preparation of 5,11-substituted derivatives of Tröger base using $POCl_3$

To a reaction flask cooled under N_2, was added Tröger base (1.25 g, 5 mmol) in toluene (15 mL) and $POCl_3$ (0.8 mL, 8.75 mmol) slowly at 0 °C under N_2. Next, the carbonyl compound (5.1 mmol) was added at 0 °C. The reaction mixture was brought to 25 °C and allowed to stir for 3 h at 80 °C. Then it was diluted with ethyl acetate and neutralized with a 10% aq NaOH solution. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 2–5% ethyl acetate in hexane to elute the desired 5,11-substituted derivatives of Tröger base. Following, this procedure Tröger base derivatives **2a**, **2b**, **2c**, **2d,** and **2g** were prepared (Table 2).

4.1.3. General procedure for the preparation of Tröger base derivatives 1d and 1e

To a solution of substituted anilines (10 mmol) and paraformaldehyde (0.60 g, 20 mmol) in CH_2Cl_2 (40 mL) was added $AlCl_3$ (1.33 g, 10 mmol) under an N_2 atmosphere. The reaction mixture was allowed to stir for 12 h at 25 °C and the reaction was quenched with cold water. The reaction mixture was extracted using CH_2Cl_2



Scheme 8.

and the combined organic extracts were successively washed with water, brine solution and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 2–5% ethyl acetate in hexane to give the desired Tröger base derivatives. For Tröger base derivatives **1d** and **1e**, the spectroscopic data were identical to the previously reported values.[13]

4.1.4. General procedure for the preparation of 5,11-substituted derivatives 3a–3e using $POCl_3$

To a solution of Tröger base derivatives **1a**–**1e** (2 mmol) and DMF (0.153 g, 0.16 mL, 2.1 mmol) in CH_2Cl_2 (15 mL) was added $POCl_3$ (0.535 g, 0.32 mL, 3.5 mmol) at 25 °C under an N_2 atmosphere and stirred for 1 h. It was then cooled to 0 °C and quenched with a 10% aq NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed successively with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 5–10% ethyl acetate in hexane to elute the desired Tröger base derivatives (Table 4).

4.1.4.1. 2,8-Dimethyl-13-(*N*,*N*-dimethylamino)-6*H*,12*H*-5,11-methano-dibenzo[*b*,*f*][1,5]diazocine 3a. Yield: 0.546 g (93%); White solid, mp 102–104 °C; IR (KBr) 2991, 1494, 1421, 1205, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04–6.92 (m, 4H), 6.73 (s, 1H), 6.69 (s, 1H), 4.62 (d, J = 8.8 Hz, 1H), 4.58 (d, J = 8.8 Hz, 1H), 4.18 (d, J = 16.4 Hz, 1H), 3.85 (m, 2H), 2.42 (s, 6H), 2.23 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 142.1, 133.2, 133.0, 128.2, 128.0, 127.8, 127.0, 126.9, 125.4, 125.2, 90.4, 59.5, 51.6, 41.6, 21.0, 20.9; MS (EI): m/z 294.25 (M+1); Anal. Calcd for $C_{19}H_{23}N_3$: C, 77.78; H, 7.90; N, 14.32. Found: C, 77.65; H, 7.93; N, 14.21.

4.1.4.2. 2,8-Dimethoxy-13-(*N*,*N*-dimethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 3b. Yield: 0.545 g (84%); White solid, mp 111–113 °C; IR (KBr) 2999, 1494, 1458, 1240, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.76–6.69 (m, 2H), 6.42 (d, J = 10.4 Hz, 2H), 4.61 (d, J = 9.6 Hz, 1H), 4.56 (d, J = 9.2 Hz, 1H), 4.14 (d, J = 16.8 Hz, 1H), 3.84–3.80 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 155.8, 141.9, 137.7, 129.3, 129.1, 126.5, 126.3, 113.9, 113.7, 110.7, 110.4, 90.5, 59.6, 55.4, 55.3, 51.9, 41.5; MS (EI): m/z 326 (M+1); Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.35; H, 7.16; N, 12.81.

4.1.4.3. 13-(*N*,*N*-Dimethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 3c. Yield: 0.464 g (88%); White solid, mp 141–143 °C; IR (KBr) 3063, 2945, 1481, 1448, 1275, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.07 (m, 4H), 6.97–6.86 (m, 4H), 4.68 (d, J = 9.2 Hz, 1H), 4.64 (d, J = 9.2 Hz, 1H), 4.25 (d, J = 16.4 Hz, 1H), 3.93 (d, J = 16.4 Hz, 1H), 3.88 (s, 1H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 144.8, 128.7, 128.4, 127.2, 127.0, 126.6, 126.5, 125.7, 125.4, 123.8, 123.7, 90.1, 59.5, 51.6, 41.6; MS (EI): m/z 266.2 (M+1); Anal.Calcd for $C_{17}H_{19}N_3$: C 76.95, H 7.22, N 15.84. Found: C 77.23, H 6.48, N 15.76.

4.1.4.4. 1,3,7,9-Tetramethyl-13-(*N*,*N*-dimethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5] diazocine 3d. Yield: 0.551 g (86%); White solid, mp 227–229 °C; IR (KBr) 2995, 2914, 1435, 1280, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 4.46 (d, J = 16.4 Hz, 1H), 4.39 (d, J = 16.4 Hz, 1H), 4.15 (d, J = 16.4 Hz, 1H), 3.87 (d, J = 16.4 Hz, 1H), 3.79 (s, 1H), 2.41 (s, 6H), 2.26 (s, 3H), 2.24 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 144.8, 136.5, 136.0, 135.0, 134.4, 126.4, 126.3, 124.0, 123.9, 123.8, 123.7, 89.8, 58.3, 50.3, 41.7, 21.1, 21.0, 18.1, 17.9; MS (EI): m/z 322.35 (M+1); Anal. Calcd for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.51; H, 8.52; N, 12.95.

4.1.4.5. 2,4,8,10-Tetramethyl-13-(*N*,*N*-dimethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5] diazocine 3e. Yield: 0.418 g (65%); white solid, mp 100–102 °C; IR (KBr) 2943, 1475, 1271, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.84 (s, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 4.49 (d, J = 16.8 Hz, 1H), 4.43 (d, J = 16.8 Hz, 1H), 3.97 (d, J = 16.8 Hz, 1H), 3.84 (s, 1H), 3.63 (d, J = 16.8 Hz, 1H), 2.40 (s, 6H), 2.36 (s, 6H), 2.20 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 139.8, 133.2, 132.9, 132.7, 129.6, 129.5, 128.3, 124.5, 124.4, 91.0, 56.0, 48.4, 41.6, 21.0, 20.9, 17.0, 16.9; MS (EI): m/z 322.35 (M+1); Anal. Calcd for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.31; H, 8.41; N, 13.16.

4.1.4.6. 2,8-Dimethyl-11,12-dihydro-6*H*-dibenzo[*b*,*f*] [1,5] diazocine-5-carbaldehyde 4. Yield: 0.102 g (19%); white solid, mp 159–162 °C; IR (KBr) 3346, 2966, 2932, 2887, 1655, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.07–7.02 (m, 3H), 6.94 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.83 (s, 2H), 4.28 (s, 2H), 3.96 (br s, 1H), 2.32 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 146.2, 138.5, 137.5, 134.7, 133.3, 130.9, 129.8, 129.5, 129.1, 125.4, 123.3, 119.3, 50.9, 50.2, 20.9, 20.4; MS (EI): m/z 267.20 (M+1); Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52; O, 6.01. Found: C, 76.51; H, 6.75; N, 10.45.

4.1.5. General procedure for the diastereoselective synthesis of Tröger base derivatives 6–9

To a solution of Tröger base derivatives **1a**–**1e** (2 mmol) and (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)foramide (0.531 g, 2.1 mmol) in CH_2Cl_2 (15 mL) was added $POCl_3$ (0.535 g, 0.32 mL, 3.5 mmol) at 25 °C under an N_2 atmosphere and stirred for 12 h. It was then cooled to 0 °C and quenched with 10% aq NaOH solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were successively washed with water, brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silica gel using 3–10% ethyl acetate in hexane to give the desired Tröger base derivatives (Table 6).

4.1.5.1. 2,8-Dimethyl-13-bis(1-phenylethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine. Data for a product mixture of **6**: yield: 0.712 g (75%); dr = 75:25; White solid, mp 81–83 °C. $[\alpha]_D^{25} = -97.6$ (c 0.38, $CHCl_3$). The diastereomeric ratio was calculated on the basis of ^1H NMR analysis of the $-CH_3$ protons of the (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl) moiety [for the major 1.51 (d, J = 8.0 Hz, 6H), and for the minor 1.63 (d, J = 8.0 Hz, 2H)]. Furthermore, dr = 77:23 was estimated by chiral HPLC analysis on Chiral cell phenomenex cellulose-1 column, hexane/2-propanol = 99.5:0.5, flow rate 1 mL/min; IR (KBr) 2924, 1493, 1450, 1209, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16–6.93 (m, 14H), 6.78–6.51 (m, 7H), 6.12 (d, J = 8.0 Hz, 0.3H), 5.05 (d, J = 16.0 Hz, 0.3H), 4.76 (m, 1H), 4.60 (m, 2.5H), 4.35 (d, J = 16.0 Hz, 1H), 4.10–3.94 (m, 1.7H), 3.73 (d, J = 16.0 Hz, 1H), 3.39 (d, J = 16.0 Hz, 1H), 2.24–218 (m, 8H), 1.63 (d, J = 8.0 Hz, 2H), 1.51 (d, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 146.7, 144.3, 142.7, 142.2, 133.1, 132.7, 129.2, 128.9, 128.0, 127.7, 127.6, 127.4, 127.2, 126.9, 126.5, 126.2, 125.8, 125.6, 125.4, 125.0, 83.5, 82.8, 59.9, 59.8, 52.5, 51.1, 51.0, 21.0, 20.9, 16.1; MS (EI): m/z 474.35 (M+1); Anal. Calcd for $C_{33}H_{35}N_3$: C, 83.68; H, 7.45; N, 8.87. Found: C, 83.49; H, 7.51; N, 8.95.

4.1.5.2. (2,8-Dimethyoxy-13-bis(1-phenylethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5] diazocine. Data for a product mixture of **7**: yield: 0.665 g (66%); dr = 75:25; White solid, mp 90–92 °C; $[\alpha]_D^{25} = -92$ (*c* 0.88, $CHCl_3$). The diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of the $-CH_3$ protons of the (*S*,*S*)-*N*,*N*-bis(α- methylbenzyl) moiety [For major 1.56 (d, *J* = 8.0 Hz, 6H), and for minor 1.67 (d, *J* = 8.0 Hz, 2H)]. Furthermore, dr = 77:23 was estimated by chiral HPLC analysis on Chiral cell phenomenex cellulose-1 column, hexane/2-propanol = 99.5:0.5, flow rate 1 mL/min; IR (KBr) 2932, 1493, 1450, 1209, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.06 (m, 11.5H), 6.82–6.75 (m, 6H), 6.48–6.44 (m, 1.6H), 6.35–6.34 (m, 1.3H), 6.18 (d, *J* = 8.0 Hz, 0.4H), 5.30 (s, 1H), 5.09 (d, *J* =16.0 Hz, 0.4H), 4.83–4.78 (m, 1.3H), 4.66–4.62 (m, 2.8H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.14–3.96 (m, 1.7H), 3.75–3.73 (m, 8.5H), 3.38 (d, *J* = 16.0 Hz, 1H), 1.67 (d, *J* = 8.0 Hz, 2H), 1.56 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 155.7, 155.1, 144.4, 142.4, 142.2, 138.3, 137.7, 130.5, 129.8, 129.7, 128.8, 128.4, 128.2, 127.9, 127.4, 126.7, 126.6, 126.5, 126.1, 125.8, 113.7, 113.3, 110.5, 110.4, 109.6, 83.7, 83.0, 60.0, 55.4, 52.5, 51.3, 16.0, 15.8; MS (EI): *m*/*z* 506.45 (M+1); Anal. Calcd for $C_{33}H_{35}N_3O_2$: C, 78.38; H, 6.98; N, 8.31; O, 6.33. Found: C, 78.51; H, 6.91; N, 8.25.

4.1.5.3. Product mixture 8. Yield: 0.605 g (68%); dr = 75:25; White solid, mp 169–161 °C; the diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of the $-CH_3$ protons of the (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl) moiety [For major 1.57 (d, *J* = 7.2 Hz, 6H), and for minor 1.69 (d, *J* = 7.2 Hz, 2H)]. The diastereomeric mixture was crystallized from acetone to obtain compound **8a** in pure form.

13-Bis(1-phenylethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine **8a** white solid, mp 161–163 °C; $[\alpha]_D^{25} = -189.4$ (*c* 0.32, $CHCl_3$); IR (KBr) 3024, 2928, 1496, 1449, 1212, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.15 (m, 10H), 7.05–7.01 (m, 2H), 6.96–6.94 (m, 1H), 6.82–6.79 (m, 5H), 4.88 (s, 1H), 4.64 (d, *J* = 8.0 Hz, 2H), 4.50 (d, *J* = 16.8 Hz, 1H), 4.22 (d, *J* = 16.4 Hz, 1H), 3.79 (d, *J* = 16.4 Hz, 1H), 3.49 (d, *J* = 16.8 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 144.9, 144.3, 129.8, 129.2, 128.8, 127.5, 126.9, 126.8, 126.6, 126.3, 126.1, 125.8, 125.7, 123.7, 123.6, 82.6, 59.8, 52.6, 51.2, 15.9; MS (EI): *m*/*z* 446.35 (M+1); Anal. Calcd for $C_{31}H_{31}N_3$: C, 83.56; H, 7.01; N, 9.43. Found: C, 83.65; H, 7.12; N, 9.36.

4.1.5.4. Product mixture 9

Yield: 0.525 g (52%); dr = 58:42; White solid, mp 220–221 °C; The diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of the $-CH_3$ protons of the (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl) moiety [For major 1.57 (d, *J* = 7.2 Hz, 6H), and for minor 1.69 (d, *J* = 7.2 Hz, 4.4H)]. Further, dr = 60:40 was estimated by chiral HPLC analysis on Chiral cell phenomenex cellulose-1 column, hexane/2-propanol = 99.5:0.5, flow rate 0.6 mL/min; The diastereomeric mixture was crystallized from acetone to obtain compound **9a** in pure form.

(1,3,7,9-Tetramethyl-13-bis(1-phenylethylamino)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine **9a**: White solid, mp 221–223 °C; $[\alpha]_D^{25} = -264$ (c 0.10, $CHCl_3$). IR (KBr) 3026, 2926, 1494, 1448, 1211, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.16 (m, 6H), 6.82–6.65 (m, 8H), 4.80 (s, 1H), 4.58 (d, *J* = 8.0 Hz, 2H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 3.29 (q, *J* = 16.0 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 2.07 (s, 3H), 1.85 (s, 3H), 1.52 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 144.6, 144.5, 136.2, 135.6, 134.9, 134.0, 128.8, 127.2, 126.0, 125.8, 125.1, 124.5, 123.8, 123.7, 81.8, 58.3, 52.3, 49.9, 21.0, 20.9, 17.9, 17.5, 15.4; MS (EI): *m*/*z* 502.45 (M+1). Anal. Calcd for $C_{35}H_{39}N_3$: C, 83.79; H, 7.84; N, 8.38. Found: C, 83.65; H, 7.78; N, 8.26.

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10. Compound **2i** was characterized by X-ray crystallography. Crystal data for the compound **2i** Molecular formula: $C_{21}H_{24}N_2$, MW = 304.42, monoclinic, space group: *C*2/*c*, *a* = 14.7341(11) Å, *b* = 8.3650(6) Å, *c* = 13.5544(10) Å, α = 90°, β = 91.7610(10), γ = 90°, *v* = 1669.8(2) Å^3, *Z* = 4, ρ_c = 1.211 mg m^{-3} μ = 0.071 mm^{-1}, *T* = 298(2) K. Of the 8679 reflections collected, 1639 reflections were unique (R_{int} = 0.0238). Refinement on all data converged at R1 = 0.0607, wR2 = 0.1399 (CCDC deposition number: 853836).
11. Compound **9a** was characterized by X-ray crystallography. Crystal data for the compound **9a** Molecular formula: $C_{35}H_{39}N_3$, MW = 501.69, orthorhombic, space group: *P*2(1)2(1)2(1), *a* = 9.3077(10) Å, *b* = 14.8229(16) Å, *c* = 20.866(2) Å, α = 90°, β = 90°, γ = 90°, *v* = 2878.9(5) Å^3, *Z* = 4, ρ_c = 1.158 mg m^{-3} μ = 0.067 mm^{-1}, *T* = 298(2) K. Of the 30439 reflections collected, 5069 reflections were unique (R_{int} = 0.0700). Refinement on all data converged at *R*1 = 0.1172, w*R*2 = 0.2165 (CCDC deposition number: 853835).
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