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Functionalized analogues of Tröger's base: scope and limitations of a general synthetic procedure and facile, predictable method for the separation of enantiomers

Delphine Didier [a], Benoît Tylleman [a], Natacha Lambert [a], Christophe M.L. Vande Velde [a], Frank Blockhuys [b], Alain Collas [b], Sergey Sergeyev [a,*]

[a] Université Libre de Bruxelles (ULB), Laboratoire de Chimie des Polymères, CP 206/01, Boulevard du Triomphe, 1050 Bruxelles, Belgium
[b] Department of Chemistry, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

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ABSTRACT

A major stumbling block in the applications of enantiomerically pure Tröger's base analogues is their poor availability. We have therefore developed a facile method for the enantioseparation of functionalized Tröger's base analogues possessing various substitution patterns. The systematic separation of a library comprising 36 representatives on the commercially available Whelk O1 chiral stationary phase provided valuable information on structure–enantioselectivity relationships. A mechanistic explanation of observed relationships allows one to predict whether or not enantioseparation of a given, perhaps yet unknown derivative of Tröger's base will be feasible. In addition, we provide a detailed report on the scope and limitations of the general synthetic protocol employing anilines and paraformaldehyde in CF_3COOH, as well as some considerations concerning the mechanism of formation of Tröger's base analogues.

1. Introduction

Tröger's base, (±)-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-**1a**, Fig. 1), was first synthesized in 1887 by the condensation of *para*-methylaniline with formaldehyde. Tröger's base is a chiral diamine with two stereogenic bridgehead nitrogen atoms. The unique set of structural features (C_2-symmetry and a rigid V-shape geometry with the two aromatic rings nearly perpendicular to each other) makes derivatives of Tröger's base very attractive for applications in supramolecular chemistry and molecular recognition.[1,2] For instance, various functional groups capable of forming hydrogen bonds were installed at the extremities of the V-shaped skeleton of Tröger's base to create synthetic receptors for the recognition of adenine, pyrimidine, biotin derivatives,[3] and dicarboxylic acids.[4] The rigid scaffold of Tröger's base was used in 'molecular torsion balances' for the quantification of weak molecular forces,[5] in the templated synthesis of fullerene derivatives,[6–8] and in the synthesis of self-assembled metallohelicates[9,10] or metallomacrocycles.[11] However, many of these applications explore only the geometry of Tröger's base skeleton, and deal with racemates. The advantages of Tröger's base chirality thus remain largely unexploited.

A major stumbling block in the applications of enantiomerically pure Tröger's base analogues is their poor availability. The resolution of Tröger's base derivatives with the aid of chiral acids was for a long time considered as unfeasible due to the acid-promoted racemization via the formation of an iminium intermediate. There are a few notable exceptions to this rule,[12] and recent publications reveal considerable controversy in this issue. Thus, Tröger's base was successfully resolved with the aid of (−)-(*R*,*R*)-dibenzoyltartaric acid in acetone to give (−)-(*R*,*R*)-**1a** with 91% ee.[13] Kostyanovsky and co-workers,[14] as well as Wärnmark and co-workers[15] reported a considerable increase in the stability toward racemization of Tröger's base analogues bearing substituents in the *ortho*-positions relative to the nitrogen atoms, though the resolution of

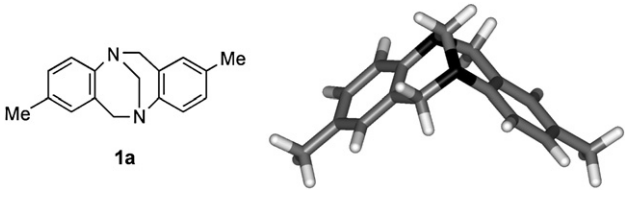

Figure 1. Tröger's base: structural formula (left) and optimized geometry of (*S*,*S*)-enantiomer (right).

* Corresponding author. Tel.: +32 2 6505392; fax: +32 2 6505410.
E-mail address: sserguee@ulb.ac.be (S. Sergeyev).

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such derivatives with the aid of chiral acids was not demonstrated. Overall, the resolution of Tröger's base and its analogues via diastereoisomeric salts does not appear impossible, but it certainly requires a careful choice of resolving agents and experimental conditions on a case-to-case basis, and therefore lacks generality. Crystallization of racemic conglomerates followed by manual separation of crystals of enantiopure Tröger's base analogues[16,17] is fundamentally important, but is of limited practical utility.

As early as in 1944 Prelog and Wieland have separated enantiomers of Tröger's base by column chromatography on lactose.[18] Later on, Tröger's base became a popular model substance for various chiral chromatography techniques.[19] Currently, both enantiomers of Tröger's base are commercially available. However, enantioseparations of Tröger's base analogues are rather scattered and have never been performed on a systematic basis.[16,20,21] In support of our own studies on asymmetric organocatalysis, we became interested in enantiopure Tröger's base analogues bearing various functional groups in different positions of the methanodibenzo[*b*,*f*][1,5]diazocine system. Here, we describe a facile and predictable method for the enantioseparation of Tröger's base analogues by chromatography on the commercially available chiral stationary phase (CSP) Whelk O1. As the thorough evaluation of such a method necessitated a relatively large library of racemic compounds, we also investigated in detail the scope and limitations of a general procedure for the synthesis of Tröger's base analogues from the corresponding anilines.

2. Results and discussion

2.1. Preparation of Tröger's base analogues from anilines

For our studies on the enantioseparation of Tröger's base analogues, we needed a relatively large library of racemates. Therefore, we were interested in a general method, with very clearly established scope and limitations, which would permit easy synthesis of as many as possible Tröger's base analogues according to a standard, operationally simple recipe, with minimal, if any, variation of reaction conditions.

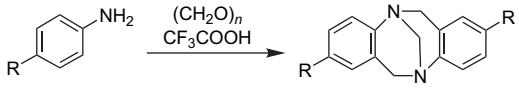
The most used general approach for the synthesis of Tröger's base derivatives is the condensation of anilines with formaldehyde or its synthetic equivalent in the presence of a Brønsted acid. However, a variety of conditions were applied with very uneven success. Various sources of reactive formaldehydes were used, as were different acidic reaction media. Very recent reports on the Lewis acid catalysis in the synthesis of Tröger's base,[13] or on the preparation of heteroaromatic Tröger's base analogues in ionic liquids[22] evidence that there is still an ongoing search for improved synthetic protocols.

To the best of our knowledge, two procedures for the synthesis of Tröger's base analogues were rigorously examined for their scope and limitations on a relatively large number of molecules. Wilcox and co-workers found that only anilines with electron-donating substituents afford Tröger's base analogues in the condensation with CH_2O in HCl/EtOH/H_2O.[23,24] On the contrary, a method that uses DMSO in AcOH/HCl as an unusual equivalent of formaldehyde tolerates a range of functional groups, including strongly electron-withdrawing substituents. However, yields are often low, and the use of corrosive gaseous HCl (in some instances, at elevated temperatures) renders this method rather impractical.[25]

It was accepted that non-aqueous, highly ionizable reaction media are in general beneficial for the condensation of anilines with formaldehyde. Performing condensation of some anilines in AcOH/HCl instead of EtOH/H_2O/HCl considerably improved yields of a few Tröger's base analogues.[26] Later on, the paraformaldehyde/CF_3COOH method introduced by Wärnmark became popular for the synthesis of synthetically valuable halogen derivatives of Tröger's base.[27–30] A few other reported examples, in which this protocol was successfully applied for the condensations of some other aromatic amines,[9,31,32] prompted us to choose it for our work and to investigate systematically its scope and limitations. We therefore performed condensations of anilines **4–6** bearing various functional groups and having different substitution patterns of the aromatic ring. The outcomes of these reactions are summarized in Tables 1–3. All reported yields of Tröger's base analogues **1–3** are those of analytically pure products after purification by column chromatography (see Section 4).

For 4-substituted and 2,4-disubstituted anilines with moderately electron-donating alkyl substituents we obtained yields of the corresponding Tröger's base analogues (±)-**1a**,**c–f** and (±)-**2a**, which are superior to those for any alternative methods. 4-Methoxy- and 4-methylsulfanyl anilines **4g**,**h** also gave high yields of the expected products. A notable contrast was 4-methoxy-2-methylaniline **5d**: an additional methyl group resulted in the dramatic drop of yield of the corresponding Tröger's base analogue (from 66% for (±)-**1g** to 10% for (±)-**2d**). This is in agreement with the earlier reported 14% yield of (±)-**2d** from **5d** and formaldehyde in EtOH/H_2O/HCl.[24] Presumably, when the aromatic ring is too much activated by electron-donating groups, it becomes prone to hydroxymethylation via the attack of protonated formaldehyde, which finally leads to polymeric products in a process that closely resembles the acid-catalyzed formation of phenol–formaldehyde

Table 1
Condensation of 4-substituted anilines with $(CH_2O)_n$ in CF_3COOH



4a–t (±)-**1a–t**

Tröger's base analogue	R	Yield,[a] %	Previously reported yields,[b] %
(±)-**1a**	Me	89	60 (A),[24] 77 (B),[26] 55 (D)[25]
(±)-**1b**	H	70[c]	0 (A),[24] 53 (D)[25]
(±)-**1c**	Et	86	
(±)-**1d**	*i*-Pr	86	
(±)-**1e**	*t*-Bu	88	
(±)-**1f**	*n*-Hexyl	79	
(±)-**1g**	MeO	66	19.5 (A),[33] 53 (B),[26] 60 (D)[25]
(±)-**1h**	MeS	69	59 (B)[26]
(±)-**1i**	Me_2N	<10[d]	0 (B)[26]
(±)-**1j**	CH_2CH_2OH	54	46 (A)[24]
(±)-**1k**	CH_2OH	22	0 (A)[24]
(±)-**1l**	F	69[c]	0 (A),[26] 5–10 (B),[26] 29–61 (C),[27,29] 61 (D)[25]
(±)-**1m**	Cl	57[c]	0 (A,B),[26] 63–67 (C),[27,29] 45 (D)[25]
(±)-**1n**	Br	55[c]	0 (A,B),[26] 55–65 (C)[27,29]
(±)-**1o**	I	56[c]	37–64 (C)[6,27,29]
(±)-**1p**	COOEt	74	23[4] (E), 37 (D)[25]
(±)-**1q**	CF_3	54, 42[e]	20 (D)[25]
(±)-**1r**	4-CN-C_6H_4	43[f]	
(±)-**1s**	CN	0	21 (D)[25]
(±)-**1t**	NO_2	0	23 (D)[25]

[a] If not stated otherwise: aniline **4a–t** (5 mmol) and then $(CH_2O)_n$ (10 mmol) were added to CF_3COOH (10 mL) at −15 °C and then allowed to react at rt for 24 h.

[b] Reactions of anilines with the following combinations of reactants and solvents: A: CH_2O/H_2O/EtOH/HCl; B: $(CH_2O)_n$/AcOH/HCl; C: $(CH_2O)_n$/CF_3COOH; D: DMSO/AcOH/HCl; E: $(CH_2)_6N_4$ in CF_3COOH.

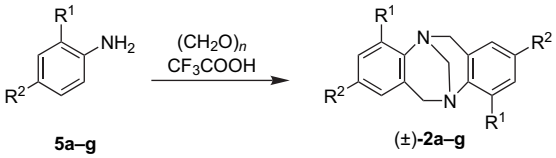
[c] Compounds (±)-**1b**,**l–o** were synthesized by this method previously under various conditions.[27,29,32] However, the yields of halogen derivatives (±)-**1l–o** were shown to be significantly dependent on the temperature, the scale of reaction, and the order of the addition of reactants.[29] We therefore preferred to reproduce these syntheses in exactly the same conditions as for the other derivatives.

[d] Estimated yield, only impure material was obtained.

[e] Addition of reactants to CF_3COOH at −15 °C followed by heating to reflux for 15 h.

[f] Prepared from 2.5 mmol of **4r** and 5 mmol of $(CH_2O)_n$.

Table 2
Condensation of 2,4-disubstituted anilines with $(CH_2O)_n$ in CF_3COOH

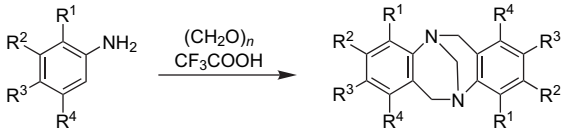


5a–g (±)-**2a–g**

Tröger's base analogue	R^1	R^2	Yield,[a] %	Previously reported yields,[b] %
(±)-**2a**	Me	Me	87	32–40 (A),[24] 40 (B),[26] 57 (D)[25]
(±)-**2b**	Br	Me	98[c]	
(±)-**2c**	Br	CF_3	34[d]	
(±)-**2d**	Me	MeO	10	14 (A)[24]
(±)-**2e**	Me	NO_2	18, 22,[e] 81[f,g]	80 (C)[9]
(±)-**2f**	NO_2	Me	0[e,h]	
(±)-**2g**	Br	Br	20, 27,[i] 33[g]	60[j] (C)[34]

[a] If not stated otherwise: aniline **5a–g** (5 mmol) and then $(CH_2O)_n$ (10 mmol) were added to CF_3COOH (10 mL) at −15 °C and then allowed to react at rt for 24 h.
[b] Reactions of anilines with the following combinations of reactants and solvents: A: CH_2O/H_2O/EtOH/HCl; B: $(CH_2O)_n$/AcOH/HCl; C: $(CH_2O)_n/CF_3COOH$; D: DMSO/AcOH/HCl.
[c] Yield from Ref. 20.
[d] Prepared from 2 mmol of **5c** and 4 mmol of $(CH_2O)_n$.
[e] Addition of reactants to CF_3COOH at −15 °C followed by heating to reflux for 24 h.
[f] Compound (±)-**2e** was synthesized by this method previously. In this paper we discuss some variations of the reaction conditions. For the sake of unambiguous comparison, we have also reproduced the original procedure as published.[9]
[g] Addition of reactants to CF_3COOH at rt followed by reaction at rt for 24 h.
[h] Formamide derivative **9** (39%) was isolated, see Scheme 3.
[i] Reaction at rt for 21 days.
[j] We are unable to reproduce the recently published 60% yield of (±)-**2g**. Although the molecular structure of (±)-**2g** was unambiguously proven by Try and co-workers with the aid of X-ray diffraction, no other analytical data were published.[34] This raises doubts about either the homogeneity of the material isolated by authors, or the accuracy of the published yield.

Table 3
Condensation of variously substituted anilines with $(CH_2O)_n$ in CF_3COOH



6a–g (±)-**3a–g**

Tröger's base analogue	R^1	R^2	R^3	R^4	Yield,[a] %
(±)-**3a**	Br	H	H	Br	61, 67[b]
(±)-**3b**	F	F	F	F	37[c]
(±)-**3c**	Me	H	H	H	75
(±)-**3d**	Me	Me	H	H	94
(±)-**3e**	H	Me	H	Me	71
(±)-**3f**	Me	H	H	Me	47
(±)-**3g**	MeO	H	H	H	0

[a] If not stated otherwise: aniline **6a–g** (5 mmol) and then $(CH_2O)_n$ (10 mmol) were added to CF_3COOH (10 mL) at −15 °C and then allowed to react at rt for 24 h.
[b] Addition of reactants to CF_3COOH at rt followed by reaction at rt for 24 h.
[c] Prepared from 2 mmol of **6b** and 4 mmol of $(CH_2O)_n$, yield from Ref. 35.

resins (see Scheme 1). In accord with this was also the outcome of the reaction with **4i** that bears a very strong electron-donating Me_2N group. In this case, a complex mixture of products was formed, which did apparently contain some amount of Tröger's base analogue (±)-**1i**, according to the spectral data of the reaction mixture after work up.[36] Column chromatography afforded a fraction considerably enriched in this material, but all attempts to isolate pure (±)-**1i** failed.

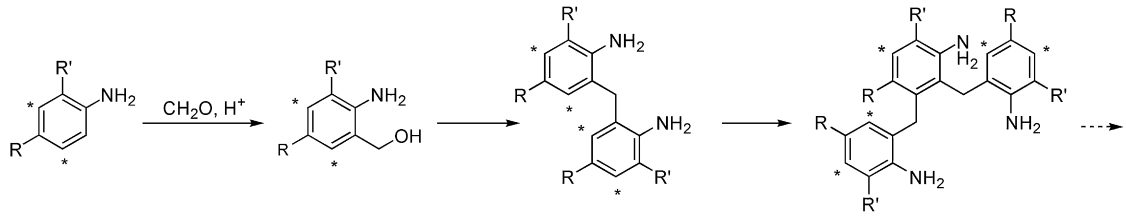
An unprotected hydroxyl group is compatible with the reaction conditions: thus, diol (±)-**1j** was prepared from 4-(2-hydroxyethyl)aniline **4j** in approximately the same yield as by the condensation in EtOH/H_2O/HCl.[24] Notably, we succeeded also in the preparation, albeit in modest yield (22%), of diol (±)-**1k**, which was reported to be inaccessible by condensation in aqueous medium, probably due to the easy formation of a benzyl-type cation that then attacks another aniline molecule to finally afford polymeric products in a sequence of electrophilic substitutions similar to that depicted in Scheme 1.[24] This observation is of a certain practical value, considering the synthetic versatility of the hydroxyl function. Despite the modest yield, the one-step synthesis of (±)-**1k** from inexpensive 4-aminobenzylalcohol **4k** appears competitive with the known multi-step procedure.[6,8]

Next to anilines **4l–o**,[27] also anilines **4p**,**q** bearing stronger electron-withdrawing groups (CF_3, COOEt) gave good yields of the corresponding Tröger's base analogues (±)-**1p**,**q**. However, yields of Tröger's base analogues with two electron-withdrawing groups per ring were somewhat lower. Thus, having either CF_3 and bromine or two bromines on the aromatic ring of anilines **5c**,**g**, respectively, considerably lowered yields of the corresponding Tröger's base analogues (±)-**2c**,**g** compared to (±)-**1n**. At the same time, 2,5-dibromoaniline **6a** gave 61–67% of the corresponding Tröger's base analogue (±)-**3a**. Higher yield of (±)-**3a** compared to its isomer (±)-**2g** is likely due to the cooperative orienting effect of NH_2 and 5-bromo substituents in **6a**.

X-ray diffraction analysis of (±)-**3a** revealed the angles between the two planes of the aromatic rings to be 106.4° and 105.2°, respectively, for the two crystallographically independent molecules (Fig. 2; see Supplementary data for detailed discussion of the crystal structure of (±)-**3a**). These values are comparatively large, but not unique for multiply substituted Tröger's base analogues.[2,34]

Also an unprecedented octafluoro analogue of Tröger's base (±)-**3b** was synthesized from 1,2,3,4-tetrafluoroaniline **6b**, although in a modest yield (37%). Considering current interest in 'oligo-Tröger's bases' as concave aromatic receptors (molecular clips or tweezers),[2,15,37] (±)-**3b** can be viewed as an initial entry to a new generation of concave molecules with highly fluorinated aromatic rings.

Tetrabromides (±)-**2g** and (±)-**3a** are interesting intermediates for metal-catalyzed cross-coupling reactions, which were extensively used earlier for the transformation of dibromo and diiodo analogues of Tröger's base into variety of complex derivatives.[38,39] We attempted to optimize the yield of tetrabromide (±)-**2g**. However, even very long reaction times improved the yield only slightly. The best, even if still rather modest yield of (±)-**2g** (33%) was



Scheme 1. Formation of polymeric products from strongly activated anilines. Positions designated with '*' are also highly activated toward electrophilic substitution when R and/or R′ are very strong electron-donating groups such as MeO, Me_2N.

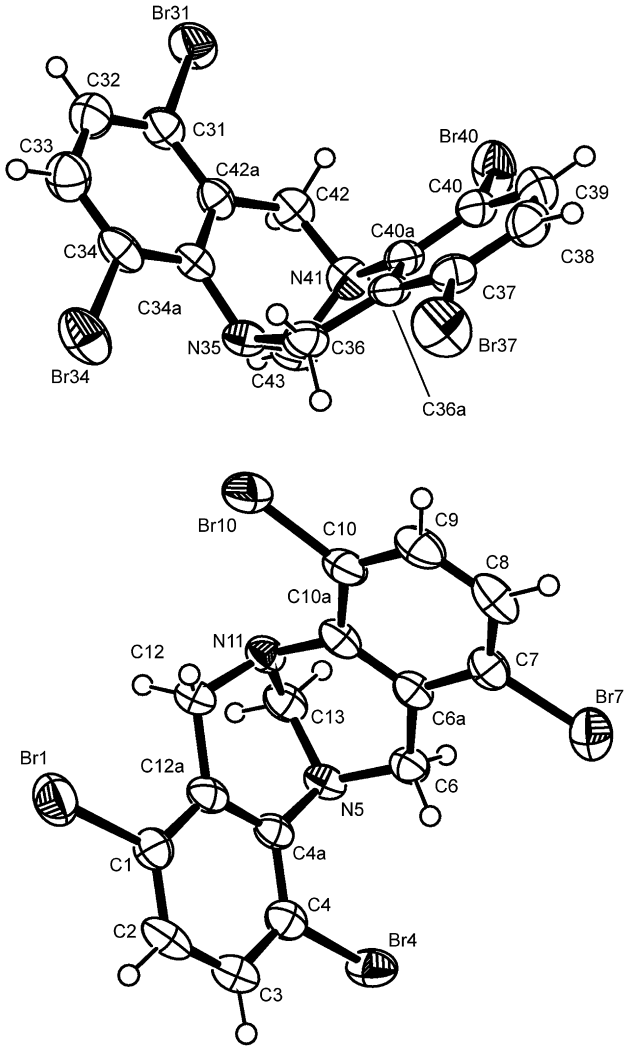


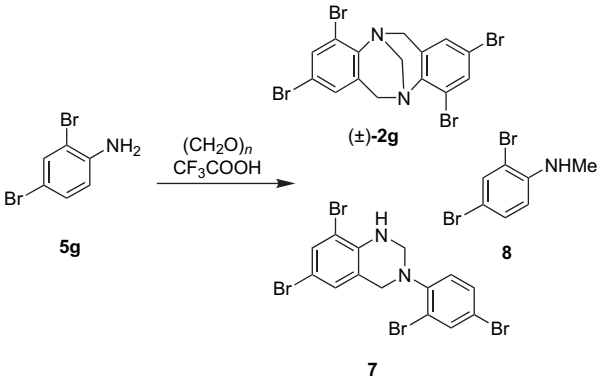
Figure 2. ORTEP plot of the asymmetric unit of (±)-**3a** with the displacement ellipsoids drawn at the 50% probability level.

obtained when the reactants were added to CF_3COOH in one portion at rt. In an attempt to rationalize the rather low yields of Tröger's base analogue (±)-**2g**, we decided to carefully isolate side products and intermediates of this reaction (Table 4). The only isolable products were tetrahydroquinazoline **7** and *N*-methyl-2,4-dibromoaniline **8**. Structure of **7** was unambiguously confirmed by X-ray diffraction analysis (Fig. 3). To the best of our knowledge, no X-ray structure of tetrahydroquinazolines has so far been reported, possibly due to the instability of such compounds toward oxidation (see discussion below).

The accepted mechanism for the formation of Tröger's base analogues from anilines and formaldehyde involves the following key steps: (1) the transformation of aniline **A** into the iminium intermediate **B** that may exist in equilibrium with unstable methylene imine **C** and diarylaminomethane **D**; (2) the electrophilic attack of **B** at the *ortho*-position of aniline **A** to give *ortho*-aminobenzylamine **E**; (3) the cyclization of **E** to give tetrahydroquinazoline **F**; (4) the formation of iminium intermediate **G** from **F** and finally, the intramolecular electrophilic substitution in **G** to give a Tröger's base analogue (±)-**H** (Scheme 2).

Previously, convincing evidence was obtained that the rate-limiting steps in the formation of Tröger's base derivatives are the conversion of tetrahydroquinazoline derivative **F** to the reactive intermediate **G** and the intramolecular electrophilic substitution in the latter. When aromatic rings bear activating substituents, these

Table 4
Products from the condensation of 2,4-dibromoaniline with $(CH_2O)_n$ in CF_3COOH



Temperature[a] (°C)	Time	(±)-**2g**,[b] %	**7**,[b] %	**8**,[b] %
−15 °C	24 h	20	51	4.5
rt.	48 h	33	28	6
−15 °C	21 days	27	0	18

[a] Temperature at which the reaction was initiated.
[b] Yields of isolated, analytically pure substances.

steps still proceed relatively easily. However, when the starting aniline bears electron-withdrawing groups, they reduce the nucleophilicity of the secondary amine nitrogen in **F** and slow down the intramolecular electrophilic substitution in **G**. An important side reaction of a relatively unstable **F** is an oxidation to the dihydroquinazoline **I** that was in some instances isolated earlier.[26,40]

The following explanation of why analogues of Tröger's base bearing moderately electron-withdrawing substituents (e.g., halogens) can easily be prepared in CF_3COOH, but not in HCl/H_2O, was suggested by Wärnmark and co-workers:[27] in CF_3COOH, the concentration of the reactive protonated formaldehyde, which is necessary for the transformation of tetrahydroquinazoline **F** into the cationic intermediate **G** is higher than in aqueous HCl, and it substantially accelerates the rate-limiting step.

We provide somewhat different rationalization based on the data from Table 4. Isolation of 51% of tetrahydroquinazoline **7** undoubtedly confirms that its further conversion is indeed the rate-limiting step. However, prolonged reaction times only cause marginal increase in the yield of Tröger's base analogue (±)-**2g** ((±)-**H**, R=R′=Br), while tetrahydroquinazoline **7** (**F**, R=R′=Br) was completely consumed. Considering that formaldehyde is taken in excess (2 equiv per 1 equiv of aniline, while 1.5 equiv is required for the formation of Tröger's base framework), and that the formation of tetrahydroquinazoline **F** only requires 1:1 stoichiometry aniline/CH_2O, there should be sufficient formaldehyde during the entire course of the reaction. This suggests the participation of a different

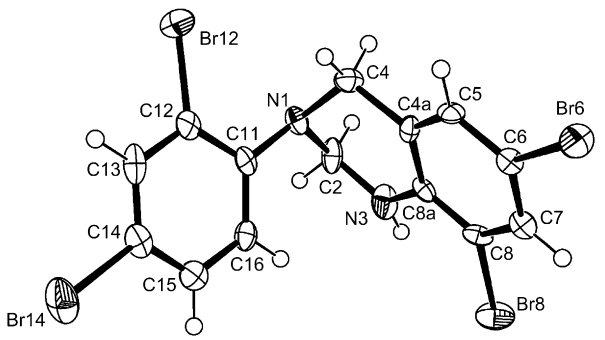
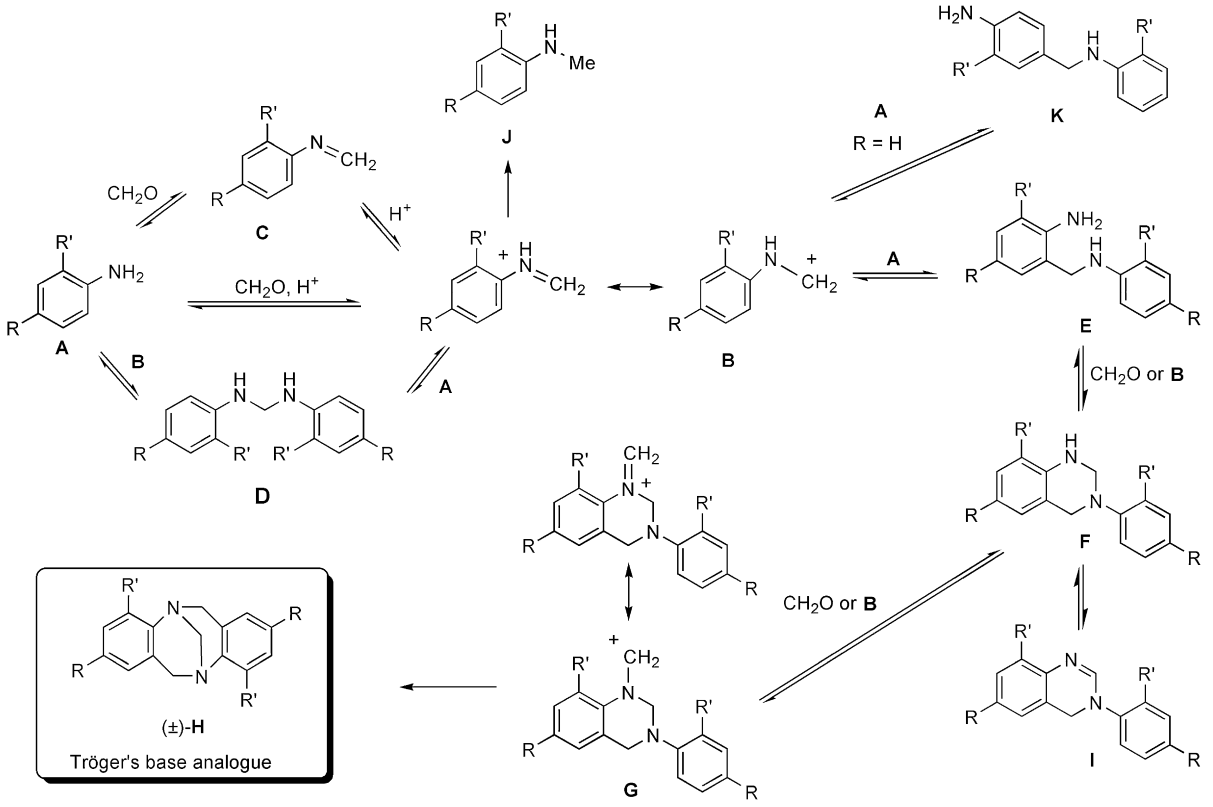


Figure 3. ORTEP plot of **7** with the displacement ellipsoids drawn at the 50% probability level.



Scheme 2. Accepted mechanism for the formation of Tröger's base analogues from anilines and some possible side processes.

electrophile, namely, iminium cation **B** in the conversion of **F** to **G**. The possibility of this process was clearly demonstrated by Wagner in his comprehensive study of reactions between aromatic amines and formaldehyde.[41] In the early stages of the reaction, there are sufficient amounts of both tetrahydroquinazoline **F** and iminium cation **B**, therefore the reactive intermediate **G** is formed relatively quickly and then easily cyclizes to give the final Tröger's base analogue. Later on, the only source of **B** is the reverse reactions of intermediates **E** and **F** (reversibility of the formation of **E** and **F** was demonstrated earlier).[41] As these reverse reactions are apparently rather slow, the concentration of the reactive cation **B** becomes low. Hence, formation of the intermediate **G** proceeds only sluggishly. Instead, a considerable amount of **B** is reduced to *N*-methylaniline **8** (**J**, R=R′=Br) in a hydride-transfer process, well known as Eschweiler–Clarke methylation, in which CH_2O serves as a hydrogen donor. When **F** is completely consumed, *N*-methylaniline **J** becomes the second major product of the reaction. The fact that after 21 days only 45% of total material can be isolated (vs ca. 76% after 24 h) clearly indicates also the formation of non-isolable, probably polymeric products.

It should be noted that *N*-methyl derivatives of the starting anilines were observed in virtually all reactions. Thus, in the course of syntheses of (±)-**1o** and (±)-**1q** we have isolated 4% of *N*-methyl-4-iodoaniline and 4% of *N*-methyl-4-(trifluoromethyl)aniline, respectively. In other cases, *N*-methylanilines were not isolated, but their formation was evidenced by TLC (relatively unpolar spots with R_f close to that of the corresponding starting aniline) and by ^{1}H NMR (characteristic signals of MeN at ca. 3.0 ppm).

The fact that the best yield of (±)-**2g** from **5g** was obtained upon mixing the reactants at rt is also in good agreement with our speculations. In this case, the highest concentrations of both **B** and **F**, which are involved in the rate-limiting step, are probably achieved soon after the start of the reaction. Also in line with this rationalization, condensation of 2-methyl-4-nitroaniline **5e** gave the best result when reactants were added to CF_3COOH in one portion at rt. When reactants were carefully added to CF_3COOH upon cooling to −15 °C, and the reaction was allowed to proceed either at rt or at reflux of CF_3COOH, the yield of Tröger's base analogue (±)-**2e** was much lower.[42] Thus, high concentrations of reactive intermediates at the earlier stages of reaction appear to be vitally important in the case of deactivated anilines.[43]

It is remarkable that the electron-donating methyl group in aniline **5e** counterbalances the presence of the very strong electron-withdrawing NO_2 group, and the formation of Tröger's base analogue proceeds efficiently. When strong electron acceptors such as CN or NO_2 are present alone (anilines **4s**,**t**), they deactivate the aromatic ring to such an extent that no Tröger's base analogue is formed. However, 4-methyl-2-nitroaniline (**5f**) also gave no Tröger's base analogue in any of the discussed modifications of conditions. Instead, the formamide derivative **9** was unexpectedly isolated when the reaction was conducted upon heating. The structure of **9** was unambiguously confirmed by X-ray diffraction analysis (Fig. 4), by NMR, and by ESIMS data. The formation of **9**

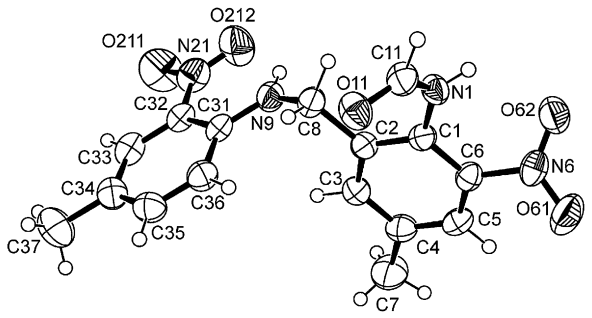
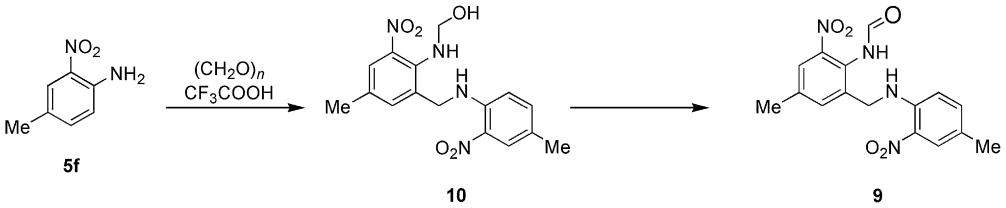


Figure 4. ORTEP plot of **9** with the displacement ellipsoids drawn at the 50% probability level.



Scheme 3. Formation of an unexpected product **9** from aniline **5f**.

could be explained by the reaction of the initially formed *ortho*-aminobenzylamine (Scheme 2, **E**, R=Me, R′=NO_2) with formaldehyde to give an unstable *N*-hydroxymethyl derivative **10**, which then undergoes formal dehydrogenation to give the formamide **9**. *N*-Hydroxymethyl amines such as **10** are probable intermediates in the formation of tetrahydroquinazolines **F**. However, we never observed formamides such as **9** in reactions with other anilines. Hence, stabilization of **10** and **9** by intramolecular H-bonding with the neighboring nitro group might account for the unusual course of this reaction (Scheme 3).

The final interesting point is the condensation of 4-unsubstituted anilines, the simplest being aniline itself (**4b**). Earlier studies have shown that the reaction between aniline and CH_2O in EtOH/H_2O/HCl does not produce the corresponding analogue of Tröger's base and leads only to polymeric products.[2] However, we have recently synthesized (±)-**1b** in very good yield in CF_3COOH.[32] Furthermore, it has been shown that 3-halo-2-methyl anilines produce Tröger's base analogues in 32–59% yield, though some polymerization apparently occurs, which possibly accounts for the modest yields.[28] The above-mentioned condensations of 2,5-dibromoaniline **6a** to give up to 67% of (±)-**3a** is in line with this observation. It thus appears clear that at least relatively electron-poor 4-unsubstituted anilines do give analogues of Tröger's base upon condensation with paraformaldehyde in CF_3COOH.

We were therefore keen to examine the possibility to perform this reaction with 4-unsubstituted anilines bearing electron-donating substituents. Gratifyingly, 2-methyl- as well as 2,3-, 2,5-, and 3,5-dimethylanilines **6c**–**f** afforded the corresponding Tröger's base derivatives in yields up to 94% (Table 3). However, 2-methoxyaniline (**6g**) indeed gave only products of polymerization. One can thus conclude that an unsubstituted position 4 poses a problem only in anilines that are strongly activated toward electrophilic substitution, while moderately activated or non-activated anilines react smoothly. Analogues of Tröger's base with free 2,8-positions are interesting substrates for the synthetic approach based on regioselective electrophilic substitutions, which was recently introduced by us.[32,44]

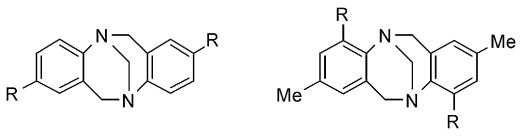
We believe that seemingly contradictory findings on the behavior of 4-unsubstituted anilines in the reaction with formaldehyde in various media may be satisfactorily explained as follows. The first unwanted process that will lead to polymeric products is the attack of the protonated formaldehyde at the most reactive *para*-position of the starting aniline. As discussed above, this process is slowed down in CF_3COOH compared to HCl/H_2O due to lower concentration of protonated formaldehyde. Another side reaction that would prevent formation of Tröger's base is the attack of the electrophile **B** at the *para*-position of the aniline to give *para*-aminobenzylamine **K**. The latter cannot undergo further transformation to give Tröger's base analogue. The formation of **K** is likely even favored over the formation of its isomer *ortho*-aminobenzylamine **E**, for steric reasons. However, the formation of **K**, as well as of its isomer **E**, is reversible (see above), and reverse process generates back the reactive iminium cation **B**.[41] Thus, the overall process produces a Tröger's base analogue (±)-**H**, the formation of which is irreversible. Rather widely varied yields (47–94%) of Tröger's base analogues (±)-**3d**–**f** from the corresponding isomeric dimethylanilines **6d**–**f** might indicate that the *para*-aminobenzylamine **K** also undergoes further transformations, that do not lead to isolable products.

To recapitulate this section, yields of Tröger's base analogues from anilines bearing electron-donating substituents were good to excellent in the standardized conditions (addition of reactants to CF_3COOH at −15 °C followed by reaction at rt for 24 h). Outcomes of reactions with anilines bearing electron-withdrawing groups vary considerably. In some cases, initiating reactions at rt improved yields, but in no case it provided Tröger's base analogues that would otherwise be inaccessible in the standard conditions. Other variations of reaction conditions, such as elevated temperatures or prolonged reaction times, had only minor effects. An unsubstituted *para*-position in aniline derivatives only presents a problem in combination with very strong electron-donating groups (e.g., MeO) in other positions. Anilines with free *para*-position and moderately electron-donating or electron-withdrawing groups in other positions do produce Tröger's base analogues with yields up to 94%.

2.2. Enantioseparation of Tröger's base analogues

With a number of functionalized Tröger's base analogues in hand, we turned to the study of their enantioseparation. In order to have a more representative library of compounds, we added a few more functionalized derivatives (±)-**1u**–**w** and (±)-**2h**–**k** that are unavailable via the condensation of anilines with formaldehyde. They were synthesized by alternative methods according to published procedures (see Fig. 5 for structures and Section 4 for references).

For the separations, we have chosen the commercial 'brush-type' chiral stationary phase (CSP) Whelk O1 with covalently bound chiral selector derived from 3,4-disubstituted 1,2,3,4-tetrahydrophenanthrene (Fig. 6).[45] From a practical standpoint, brush-type CSPs are compatible with a wider range of mobile phases including highly polar and chlorinated solvents and are more stable than polysaccharide-coated CSPs, which can leach off with use. This is important as some analogues of Tröger's base showed very strong retention on the cellulose-based CSP Chiralcel OJ, thus rendering separation rather lengthy.[20] Among other brush-type CSPs, Whelk O1 became popular because of its broad versatility combined with



1u: R = NH_2
1v: R = CHO
1w: R = Ph

2h: R = CN
2i: R = CHO
2j: R = NH_2
2k: R = CH_2OH

Figure 5.

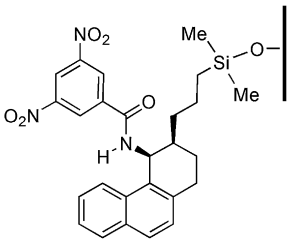


Figure 6. (3*R*,4*S*)-Whelk O1 CSP used in this study. This CSP is marketed by Regis Technologies, Inc under the name (*S*,*S*)-Whelk O1. The absolute configuration of the chiral selector is thus incorrectly designated. This should not lead to confusion. Incorrect designation results from the fact that the original version of this CSP had an 11-carbon linker, but substitution of it by the 3-carbon linker results in the inversion of Cahn–Ingold–Prelog priorities.

excellent efficiency. A considerable amount of data on enantioseparations of various analytes have been accumulated and rationalized.[46] Importantly, a small well-defined chiral selector appears beneficial for the understanding of structure–enantioselectivity relationship.

Due to conformational preferences of the saturated ring in 1,2,3,4-tetrahydrophenanthrene (half-chair with the pseudoaxial amide group), the chiral selector of Whelk O1 has a cleft-like shape. Preferential binding of the more retained enantiomer of a chiral analyte in the cleft is provided through simultaneous face-to-face π–π interactions with the π-acidic 3,5-dinitrobenzoyl moiety, face-to-edge π–π binding with the π-basic naphthalene system and H-bonding with the hydrogen of the amide group. The less retained enantiomer is incapable of all these interactions without inducing a deviation from the lowest-energy conformation. This model is supported by systematic separations of various analytes, as well as by crystallization of homo- and heterochiral complexes of the chiral selector and an analyte, by analysis of ^{1}H NMR spectra of homo- and heterochiral complexes, and by computational studies.[47] Thus, a typical good analyte for Whelk O1 CSP is an aromatic system with an additional H-bond acceptor in the proximity of the chiral center.

Since the tertiary nitrogen atoms in the molecule of Tröger's base are asymmetric centers and can act as H-bond acceptors, Tröger's base certainly appears a promising analyte for separation on Whelk O1. This is confirmed by the efficient separation of Tröger's base on Whelk O1 reported by the manufacturer (k_1=2.52, α=1.80 in hexane/EtOH 96:4).[48] In order to gain insight into the structure–enantioselectivity relationship, we proceeded with the separation of variously functionalized analogues of Tröger's base. Experimental data are summarized in Tables 5 and 6 as retention factors of the two enantiomers k_1, k_2, separation factors $\alpha=k_2/k_1$, and base line resolutions R_s. As long as it was practical, we used hexane/*i*-PrOH (95:5) as a mobile phase, for the purpose of better direct comparison between different analytes.

From the experiments on the enantioseparation of derivatives (±)-**1a**–**w** (bearing substituents only in the *para*-position relative to the nitrogen), a few trends became apparent. As expected, the electron-withdrawing substituents reduce separation factors and increase retention times. In this case two cooperative factors ruin the separation: firstly, the face-to-face π–π binding between the electron-poor aromatic ring and the electron-poor part of the chiral selector is not favored, and secondly, the 'achiral retention' due to dipole–dipole interactions with the underlying silica support is increased. In case of electron-donating substituents in the analytes, these effects become competitive: the favored binding of the analyte with the π-acidic 3,5-dinitrobenzoyl moiety of the chiral selector is beneficial for enantioselectivity, but at the same time a polar substituent increases achiral retention and has a negative impact on the enantioselectivity. Subtle interplay between these two effects is clearly illustrated by the comparison between (±)-**1g** and (±)-**1h** substituted with electron-donating MeO and MeS groups, respectively. In the former case, retention times of both enantiomers are longer, the separation factor is smaller, the resolution is poorer, and the tailing of peaks is considerable—all this because of the stronger interactions of the more polar MeO group with the underlying SiO_2 support. Hydrogen bond donors (CH_2CH_2OH, NH_2, (±)-**1j**,**u**) at the *para*-position strongly increase retention and decrease enantioselectivity due to pronounced interactions with SiO_2.

Alkyl substituents increase the separation factors (cf. (±)-**1a**,**c**–**f** vs (±)-**1b**). Moreover, both the increase of length of alkyl substituents (from Me to hexyl) and the increase of their volume (from Et to *t*-Bu) progressively decreases retention of both enantiomers, but at the same time enhances enantioselectivity. The same trend has been observed previously for 3-alkyl-5-methyl-5-arylhydantoins bearing alkyl substituents of various lengths.[49] Phenyl group in the *para*-position improves the enantioselectivity compared to the unsubstituted parent molecule (cf. (±)-**1w** vs (±)-**1b**) and only slightly diminishes it compared to the methyl group (cf. (±)-**1w** vs (±)-**1a**). One can conclude that a bulky substituent does

Table 5
Enantioseparations of 2,8-disubstituted Tröger's base analogues

Tröger's base analogue	Mobile phase (hexane/*i*-PrOH, v/v)	k_1	k_2	α	R_s
(±)-**1b**	95:5	1.33	2.17	1.63	2.23
(±)-**1a**	95:5	1.35	3.16	2.34	4.57
(±)-**1c**	95:5	0.99	2.42	2.46	3.51
(±)-**1d**	95:5	0.74	1.83	2.49	3.67
(±)-**1e**	95:5	0.41	1.41	3.41	3.82
(±)-**1f**	95:5	0.53	1.95	3.65	4.16
(±)-**1g**	95:5	6.90	10.5	1.51	2.21
(±)-**1h**	95:5	5.06	9.07	1.79	4.07
(±)-**1j**	80:20	5.67	7.40	1.30	1.33
(±)-**1l**	95:5	1.10	1.46	1.32	1.21
(±)-**1m**	95:5	1.09	1.62	1.49	2.08
(±)-**1n**	95:5	1.37	2.11	1.54	2.60
(±)-**1o**	95:5	1.56	2.53	1.62	3.02
(±)-**1p**	95:5	22.6	24.1	1.07	0.55
(±)-**1q**	95:5	0.49	0.70	1.45	1.01
(±)-**1r**	50:50	8.46	10.5	1.24	0.72
(±)-**1s**	80:20	12.0		1.00	N.S.[a]
(±)-**1u**	50:50	8.5		1.00	N.S.[a]
(±)-**1v**	80:20	13.5		1.00	N.S.[a]
(±)-**1w**	95:5	3.87	7.91	2.05	5.79

[a] N.S.=no separation.

Table 6
Enantioseparations of Tröger's base analogues bearing substituents in positions other than 2 and 8

Tröger's base analogue	Mobile phase (hexane/*i*-PrOH, v/v)	k_1	k_2	α	R_s
(±)-**2a**	98:2	0.49	0.61	1.24	0.53
(±)-**2b**	98:2	1.18	1.55	1.31	1.79
(±)-**2c**	98:2	0.58		1.00	N.S.[a]
(±)-**2d**	95:5	2.95	3.17	1.07	0.32
(±)-**2e**	90:10	10.4		1.00	N.S.[a]
(±)-**2g**	98:2	1.43	1.73	1.21	1.43
(±)-**2h**	95:5	14.6	16.6	1.14	0.88
(±)-**2i**	95:5	4.88	8.28	1.70	3.77
(±)-**2j**	80:20	6.51		1.00	N.S.[a]
(±)-**2k**	80:20	3.93	5.30	1.35	2.31
(±)-**3a**	98:2	1.05	1.21	1.14	0.89
(±)-**3b**	100:0	1.41		1.00	N.S.[a]
(±)-**3c**	99:1	0.72		1.00	N.S.[a]
(±)-**3d**	98:2	0.75	0.90	1.20	0.58
(±)-**3e**	95:5	1.42		1.00	N.S.[a]
(±)-**3f**	98:2	0.69	0.97	1.41	2.12

[a] N.S.=no separation.

not alter the conformational preference of the analyte, while achiral interactions with underlying silica support are reduced.

For the series of halogen derivatives (±)-**1l**–**o**, there is a constant increase in enantioselectivity with the increase of the polarizability of the halogen (from F to I). This is in perfect agreement with the observations of Pirkle and co-workers on the separations of amide derivatives of 1-(4-halophenyl)ethylamine on Whelk O1. Our finding also supports the generalized prediction of Pirkle and co-workers that polarizable halogens will increase enantioselectivity, as long as the halogen-substituted aromatic ring is π-basic and the inductive effect of the substituent does not affect the strength of the hydrogen bond involved in the chiral recognition.[50] The fact that derivatives with Br or I in different positions ((±)-**1n**,**o**, (±)-**2b**,**g**) can be satisfactorily separated is rather valuable, in view of possibilities to carry out various cross-coupling reactions with these intermediates.[38,39] When performed in non-acidic conditions, transformations of these derivatives are unlikely to be accompanied by racemization.

In the series of derivatives (±)-**2** and (±)-**3** bearing substituents in positions other than *para* relative to the nitrogen, there is a general drastic decrease of separation factors compared to the unsubstituted parent molecule (±)-**1b**, regardless of the nature of the substituents (Table 6). In agreement with the rationalization given above, both strong electron-donating and electron-withdrawing groups were particularly detrimental for enantioselectivity. Notable exceptions are derivatives with H-bond donor groups in *ortho*-position respective to the nitrogen atom, such as (±)-**2i**,**k**, which demonstrated relatively good separation. This suggests additional hydrogen bonding, presumably, with NO_2 groups of the chiral selector as hydrogen bond acceptors.

Remarkably, all di- and tetramethyl derivatives (±)-**2a**,**3c**–**f** with substituents in positions other than *para* respective to the nitrogen showed smaller separation factors than Tröger's base (±)-**1a**. This is clearly indicative of the steric hindrance, which prevents efficient π–π interactions between the aromatic rings of Tröger's base framework and the chiral selector. Finally, octafluoride (±)-**3b** predictably showed very poor retention even with hexane as a mobile phase and no enantioseparation was achieved.

Overall, it appears that 2,8-disubstituted Tröger's base analogues are the easiest to separate by the described method, while 4,10-positions (*ortho* to the nitrogen atoms) should either remain unsubstituted or bear a hydrogen bond donor. This consideration should probably be kept in mind in the design of studies that rely on enantiomerically pure Tröger's base analogues.

3. Conclusion

Firstly, we studied the scope and limitations of a general procedure for the synthesis of Tröger's base analogues from anilines and paraformaldehyde in CF_3COOH. It appears to be a method of choice for all anilines since it provides better yields compared to any other known protocol. The scope is broad and the reaction conditions are identical for most anilines, though in a few cases minor modifications of the general procedure may be useful. The notable limitations are the presence of very strong electron-donating groups (Me_2N) and very strong acceptors, such as NO_2 and CN, when not counterbalanced with electron-donating groups. A number of Tröger's base analogues prepared in the course of the present study can serve as useful intermediates for various synthetic transformations.

Secondly, we systematically studied separations of Tröger's base analogues on the commercially available CSP Whelk O1. Structure–enantioselectivity relationships were established in terms of the substitution pattern of the aromatic rings and the nature of substituents. This mechanistic explanation can be used to predict whether or not enantioseparation of a given, perhaps yet unknown derivative of Tröger's base will be feasible with the aid of the described method.

Perspectives of the reported study are numerous and include: (1) further variations of the structure of Tröger's base analogues, in order to prove predictive capacity of the method; (2) getting an insight into the quantitative structure–enantioselectivity relationship through a combination of various techniques: further chromatographic data, including correlations between elution order and absolute configurations of analytes, ^{1}H NMR and crystallographic studies of homo- and heterochiral diasteroisomeric complexes of analytes and the chiral selector, and computer modeling may prove useful; (3) expanding the scope of separation through the use of other commercial CSPs. All these studies are currently in progress and their results will be reported in due course.

4. Experimental section

4.1. General

All chemicals were purchased from Aldrich, Acros or TCI Europe and used without further purification unless stated otherwise. Column chromatography: SiO_2 Kieselgel 60 (Macherey-Nagel, particle size 0.04–0.063 mm). TLC: precoated SiO_2 plates Kieselgel $60F_{254}$ (Merck). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Brucker Avance 300 spectrometer; chemical shifts (δ) are given in parts per million relative to Me_4Si; coupling constants (J) are given in hertz. Electron impact mass spectra (EIMS) were recorded on a Waters AutoSpec 6F instrument and electrospray ionization mass spectra (ESIMS) on a Waters QToF 2 instrument; m/z with the lowest isotopic mass are reported. The following derivatives were synthesized according to published methods: (±)-**1s**,**u**,[39] (±)-**1v**,[6] (±)-**1w**,[51] (±)-**2b**,[20] (±)-**2h**,**i**,[39] (±)-**2j**,**k**.[20]

HPLC separations were performed at ambient temperature on an Agilent 1100 instrument equipped with the Rheodyne 7725 manual injector. The solvents were of HPLC grade. Column (*S*,*S*)-Whelk-O1 (250×4.6 mm) was purchased from Regis Technologies (USA). Injection: 20 μL of analyte solution in CH_2Cl_2, ca. 1 mg mL^{-1}; mobile phase: hexane/*i*-PrOH, nominal flow rate: 2.0 mL min^{-1}; detection: UV at fixed wavelength 254 or 230 nm. Void volume was detected from the injection of 1,3,5-tri-*tert*-butylbenzene. Separation parameters were calculated as follows: $k_1=(t_1-t_0)/t_0$, $k_2=(t_2-t_0)/t_0$, $\alpha=k_2/k_1$, $R_s=2(t_2-t_1)/(w_2+w_1)$, where t_1, t_2 are retention times of the two enantiomers, t_0 is the void time, k_1, k_2 are retention factors of the two enantiomers, α is the separation factor, w_1, w_2 are widths of peaks at the base line, R_s is the resolution at the base line.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 681274 ((±)-**3a**), CCDC 685743 (**7**), and CCDC 682620 (**9**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)12233 36033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Synthesis of Tröger's base analogues (±)-1–3 from anilines 4–6

Anilines **4**–**6** (5 mmol) and then paraformaldehyde (300 mg, 10 mmol) were added in portions under vigorous stirring to CF_3COOH (10 mL) at −15 °C. The resulting mixture was allowed to reach rt and stirred for 24 h, then slowly added to a stirred mixture of ice and 30% aqueous NH_3 (17 mL). If necessary, pH value of the resulting mixture was adjusted to 9–10 by the addition of 30% aqueous NH_3. Extraction with CH_2Cl_2 (3×50 mL), drying of the organic layer over $MgSO_4$, and removal of the solvent in vacuum gave

a crude product, which was purified by column chromatography on SiO_2 (details are specified below for individual compounds). In some cases reaction conditions were varied as specified in Tables 1–3, but the work up and purification procedures were always the same for a given compound.

For the following Tröger's base analogues spectral data were identical with those published before: (±)-**1a**,[24] (±)-**1b**,[32] (±)-**1j**,[24] (±)-**1k**,[6] (±)-**1l**–**o**,[27] (±)-**1p**,[4] (±)-**1q**,[25] (±)-**2a**,**d**,[24] (±)-**2e**,[9] and (±)-**3b**.[35] The following compounds have been reported before, but without spectral characterization: (±)-**1g**,**h**,[25] and (±)-**2g**.[34] We therefore give below their ^1H and ^{13}C spectra. For all other Tröger's base analogues we report full analytical details below.

4.2.1. (±)-2,8-Diethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]-diazocine ((±)-**1c**)

Prepared according to the general procedure from 4-ethylaniline **4c** (605 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 5:1) to afford pure (±)-**1c** (597 mg, 86%) as a colorless oil, which partially solidified upon standing for a few weeks, but did not produce a material with a distinct mp. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.15 (t, $^3J_{H,H}$=7.7 Hz, 6H), 2.51 (q, $^3J_{H,H}$=7.7 Hz, 4H), 4.13 (d, $^2J_{H,H}$=16.7 Hz, 2H), 4.29 (s, 2H), 4.66 (d, $^2J_{H,H}$=16.7 Hz, 2H), 6.72 (d, $^4J_{H,H}$=1.8 Hz, 2H), 6.98 (dd, $^3J_{H,H}$=8.1 Hz, $^4J_{H,H}$=1.8 Hz, 2H), 7.05 (d, $^3J_{H,H}$=8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=15.4, 28.2, 58.6, 66.9, 124.9, 126.0, 126.8, 127.6, 139.7, 145.7. HREIMS: *m*/*z*: calcd for $C_{19}H_{22}N_2$ ($[M]^+$) 278.1783; found: 278.1788.

4.2.2. (±)-2,8-Di(iso-propyl)-6H,12H-5,11-methanodibenzo[b,f]-[1,5]diazocine ((±)-**1d**)

Prepared according to the general procedure from 4-(*iso*-propyl)aniline **4d** (675 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 5:1) to afford pure (±)-**1d** (655 mg, 86%) as a white solid; mp 109–110.5 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.16 (d, $^3J_{H,H}$=6.9 Hz, 12H), 2.78 (sept, $^3J_{H,H}$=6.9 Hz, 2H), 4.14 (d, $^2J_{H,H}$=16.7 Hz, 2H), 4.29 (s, 2H), 4.68 (d, $^2J_{H,H}$=16.7 Hz, 2H), 6.74 (d, $^4J_{H,H}$=1.8 Hz, 2H), 7.02 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=1.8 Hz, 2H), 7.07 (d, $^3J_{H,H}$=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=23.9, 33.5, 58.5, 66.8, 124.5, 124.9, 125.4, 127.5, 144.3, 145.8. HREIMS: *m*/*z*: calcd for $C_{21}H_{26}N_2$ ($[M]^+$) 306.2096; found: 306.2091.

4.2.3. (±)-2,8-Di(tert-butyl)-6H,12H-5,11-methanodibenzo[b,f]-[1,5]diazocine ((±)-**1e**)

Prepared according to the general procedure from 4-(*tert*-butyl)aniline **4e** (745 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 5:1) to afford pure (±)-**1e** (733 mg, 88%) as a white solid; mp 207–209 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.24 (s, 18H), 4.15 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.28 (s, 2H), 4.69 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.90 (d, $^4J_{H,H}$=1.8 Hz, 2H), 7.07 (d, $^3J_{H,H}$=8.4 Hz, 2H), 7.18 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=31.3, 34.2, 58.5, 66.8, 123.4, 124.3, 124.6, 127.1, 145.6, 146.6. HREIMS: *m*/*z*: calcd for $C_{23}H_{30}N_2$ ($[M]^+$) 334.2409; found: 334.2404.

4.2.4. (±)-2,8-Dihexyl-6H,12H-5,11-methanodibenzo[b,f][1,5]-diazocine ((±)-**1f**)

Prepared according to the general procedure from 4-hexylaniline **4f** (885 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 5:1) to afford pure (±)-**1f** (770 mg, 79%) as a white solid; mp 61–63 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.87 (t, $^3J_{H,H}$=6.7 Hz, 6H), 1.20–1.35 (m, 12H), 1.52 (quint, $^3J_{H,H}$=6.7 Hz, 4H), 2.46 (t, $^3J_{H,H}$=7.8 Hz, 4H), 4.12 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.29 (s, 2H), 4.66 (d, $^2J_{H,H}$=16.8 Hz, 2H), 6.70 (d, $^4J_{H,H}$=1.8 Hz, 2H), 6.96 (dd, $^3J_{H,H}$=8.2 Hz, $^4J_{H,H}$=1.8 Hz, 2H), 7.03 (d, $^3J_{H,H}$=8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=14.1, 22.6, 29.1, 31.4, 31.7, 35.4, 58.6, 66.9, 124.8, 126.5, 127.3, 127.5, 138.6, 145.7. HREIMS: *m*/*z*: calcd for $C_{27}H_{38}N_2$ ($[M]^+$) 390.3035; found: 390.3025.

4.2.5. (±)-2,8-Dimethoxy-6H,12H-5,11-methanodibenzo[b,f][1,5]-diazocine ((±)-**1g**)

Prepared according to the general procedure from 4-methoxyaniline **4g** (615 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 4:1) to afford pure (±)-**1g** (469 mg, 66%) as a white solid; mp 171–173 °C (lit.[26] mp 172–173 °C). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.70 (s, 6H), 4.08 (d, $^2J_{H,H}$=17.8 Hz, 2H), 4.29 (s, 2H), 4.65 (d, $^2J_{H,H}$=17.8 Hz, 2H), 6.42 (d, $^4J_{H,H}$=3.0 Hz, 2H), 6.74 (dd, $^3J_{H,H}$=8.7 Hz, $^4J_{H,H}$=3.0 Hz, 2H), 7.06 (d, $^3J_{H,H}$=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=55.3, 58.9, 67.2, 110.9, 114.0, 125.9, 128.6, 140.9, 156.1.

4.2.6. (±)-2,8-Bis(methylsulfanyl)-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine ((±)-**1h**)

Prepared according to the general procedure from amine **4h** (695 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 4:1, then 1:1) to afford pure (±)-**1h** (527 mg, 69%) as an off-white solid; mp 186–187 °C (lit.[26] mp 184–185 °C). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.40 (s, 6H), 4.10 (d, $^2J_{H,H}$=16.9 Hz, 2H), 4.28 (s, 2H), 4.64 (d, $^2J_{H,H}$=16.9 Hz, 2H), 6.82 (d, $^4J_{H,H}$=2.2 Hz, 2H), 7.05 (d, $^3J_{H,H}$=8.4 Hz, 2H), 7.10 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=2.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=16.6, 58.6, 66.9, 125.5, 125.7, 126.8, 128.4, 133.1, 145.6. HREIMS: *m*/*z*: calcd for $C_{17}H_{18}N_2S_2$ ($[M]^+$) 314.0911; found: 314.0908.

4.2.7. (±)-[(6H,12H-5,11-Methanodibenzo[b,f][1,5]diazocin-2,8-diyl)bis(4,1-phenylene)]dicarbonitrile ((±)-**1r**)

Prepared according to the general procedure from amine **4r** (487 mg, 2.50 mmol), paraformaldehyde (150 mg, 5.00 mmol), and CF_3COOH (5 mL). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 9:1) to afford pure (±)-**1r** (0.231 g, 43%) as a white solid; mp 109–110.5 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.30 (d, $^2J_{H,H}$=16.8 Hz, 2H), 4.38 (s, 2H), 4.81 (d, $^2J_{H,H}$=16.8 Hz, 2H), 7.17 (d, $^4J_{H,H}$=2.1 Hz, 2H), 7.26 (d, $^3J_{H,H}$=8.4 Hz, 2H), 7.42 (dd, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=2.1 Hz, 2H), 7.57 (d, $^3J_{H,H}$=8.7 Hz, 4H), 7.66 (d, $^3J_{H,H}$=8.7 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=58.8, 66.9, 110.6, 118.9, 125.8, 125.8, 126.4, 127.3, 128.4, 132.6, 135.0, 145.0, 148.7; HRESIMS: *m*/*z*: calcd for $C_{29}H_{20}N_4Na$ ($[M+Na]^+$) 447.1586; found: 447.1581.

4.2.8. (±)-4,10-Dibromo-2,8-bis(trifluoromethyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine ((±)-**2c**)

Prepared according to the general procedure from amine **5c** (502 mg, 2.1 mmol), paraformaldehyde (130 mg, 4.30 mmol), and CF_3COOH (4 mL). The crude product was purified by column chromatography (hexane/CH_2Cl_2 85:15) to afford pure (±)-**2c** (0.181 g, 34%) as a white solid; mp 115–116 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.37 (s, 2H), 4.43 (d, $^2J_{H,H}$=17.6 Hz, 2H), 4.67 (d, $^2J_{H,H}$=17.6 Hz, 2H), 7.24 (d, $^4J_{H,H}$=1.1 Hz, 2H), 7.73 (d, $^4J_{H,H}$=1.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=55.2, 67.2, 120.4, 123.0 (q, $^1J_{C,F}$=272.4 Hz, CF_3), 123.5 (q, $^3J_{C,F}$=3.6 Hz), 127.9 (q, $^2J_{C,F}$=33.1 Hz, CCF_3), 127.9 (q, $^3J_{C,F}$=3.6 Hz), 130.9, 147.8. HRESIMS: *m*/*z*: calcd for $C_{17}H_{11}^{79}Br_2F_6N_2$ ($[M+H]^+$) 514.9193; found: 514.9209.

4.2.9. (±)-2,4,8,10-Tetrabromo-6H,12H-5,11-methanodibenzo[b,f]-[1,5]diazocine ((±)-**2g**)

Prepared according to the general procedure from amine **5g** (1.255 g, 5 mmol). The crude product was purified by column chromatography (CH_2Cl_2) to afford pure (±)-**2g** (269 mg, 20%) together with 6,8-dibromo-3-(2,4-dibromophenyl)-1,2,3,4-tetrahydroquinazoline (**7**, 671 mg, 51%) and *N*-methyl-2,4-dibromoaniline (**8**, 60 mg, 4.5%).

Analytical data of (±)-**2g**: white solid, mp 222–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.23–4.33 (m, 4H), 4.55 (d, $^2J_{H,H}$=17.8 Hz, 2H), 7.09 (d, $^4J_{H,H}$=2.1 Hz, 2H), 7.59 (d, $^4J_{H,H}$=2.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=55.0, 67.4, 117.7, 120.7, 129.1, 132.1, 134.0, 143.6. ESIMS: *m*/*z*: 535 ($[C_{15}H_{11}^{79}Br_4N_2]^+$, $[M+H]^+$).

Analytical data of **7**: off-white solid, mp 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.39 (s, 2H, $ArCH_2N$), 4.51 (br, 1H, NH), 4.67 (br, 2H, NCH_2N), 6.90 (d, $^3J_{H,H}$=8.6 Hz, 1H), 7.07 (d, $^4J_{H,H}$=2.2 Hz, 1H), 7.27 (dd, $^3J_{H,H}$=8.6 Hz, $^4J_{H,H}$=2.3 Hz, 1H), 7.45 (d, $^4J_{H,H}$=2.2 Hz, 1H), 7.72 (d, $^4J_{H,H}$=2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=52.1, 61.9, 109.6, 109.9, 117.0, 120.3, 122.8, 123.9, 128.3, 131.3, 132.8, 136.0, 139.7, 147.0. EIMS: *m*/*z*: 522 ($[C_{14}H_{10}^{79}Br_4N_2]^+$, $[M]^+$).

Analytical data of **8** were identical to those published earlier.[52]

4.2.10. (±)-1,4,7,10-Tetrabromo-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine ((±)-**3a**)

Prepared according to the general procedure from amine **6a** (1.255 g, 5 mmol). The crude product was purified by column chromatography (CH_2Cl_2) to afford pure (±)-**3a** (820 mg, 61%) as a white solid; mp 232–234 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=4.27 (s, 2H), 4.34 (d, $^2J_{H,H}$=17.8 Hz, 2H), 4.41 (d, $^2J_{H,H}$=17.8 Hz, 2H), 7.18 (d, $^3J_{H,H}$=8.6 Hz, 2H), 7.37 (d, $^3J_{H,H}$=8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=56.9, 66.6, 119.5, 122.1, 129.5, 130.2, 132.4, 146.5. HRESIMS: *m*/*z*: calcd for $C_{15}H_{11}^{79}Br_4N_2$ ($[M+H]^+$) 534.7656; found: 534.7657.

4.2.11. (±)-4,10-Dimethyl-6H,12H-5,11-methanodibenzo[b,f]-[1,5]diazocine ((±)-**3c**)

Prepared according to the general procedure from *o*-toluidine **6c** (536 mg, 5.00 mmol). The crude product was purified by column chromatography (hexane/AcOEt 95:05) to afford pure (±)-**3c** (474 mg, 75%) as a white solid; mp 96–97 °C (lit.[16] mp 96–98 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): nearly identical to published data of (±)-**3c** prepared by reductive dehalogenation of the corresponding dibromo derivative.[16] ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=18.0, 55.9, 68.3, 124.6, 125.3, 128.9, 129.7, 133.8, 147.0.

4.2.12. (±)-3,4,9,10-Tetramethyl-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine ((±)-**3d**)

Prepared according to the general procedure from 2,3-dimethylaniline **6d** (606 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2) to afford pure (±)-**3d** (653 mg, 94%) as a white solid; mp 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.22 (s, 6H), 2.31 (s, 6H), 3.91 (d, $^2J_{H,H}$=16.5 Hz, 2H), 4.33 (s, 2H), 4.58 (d, $^2J_{H,H}$=16.5 Hz, 2H), 6.66 (d, $^3J_{H,H}$=7.6 Hz, 2H), 6.82 (d, $^3J_{H,H}$=7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=13.2, 20.2, 55.4, 67.6, 123.8, 125.3 (2C), 131.1, 135.8, 145.8. HRESIMS: *m*/*z*: calcd for $C_{19}H_{23}N_2$ ($[M+H]^+$) 279.1861; found: 279.1855.

4.2.13. (±)-1,3,7,9-Tetramethyl-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine ((±)-**3e**)

Prepared according to the general procedure from 3,5-dimethylaniline **6e** (606 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 5:1) to afford pure (±)-**3e** (492 mg, 71%) as a white solid; mp 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.06 (s, 6H), 2.24 (s, 6H), 4.10 (d, $^2J_{H,H}$=16.7 Hz, 2H), 4.24 (s, 2H), 4.49 (d, $^2J_{H,H}$=16.7 Hz, 2H), 6.65 (s, 2H), 6.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=18.0, 21.0, 57.1, 66.0, 123.18, 123.22, 126.4, 135.3, 136.5, 148.3. HREIMS: *m*/*z*: calcd for $C_{19}H_{22}N_2$ ($[M]^+$) 278.1783; found: 278.1786.

4.2.14. (±)-1,4,7,10-Tetramethyl-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine ((±)-**3f**)

Prepared according to the general procedure from 2,5-dimethylaniline **6f** (606 mg, 5.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2/AcOEt 98:2) to afford pure (±)-**3f** (326 mg, 47%) as a white solid; mp 195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.06 (s, 6H), 2.40 (s, 6H), 3.93 (d, $^2J_{H,H}$=16.9 Hz, 2H), 4.27 (s, 2H), 4.41 (d, $^2J_{H,H}$=16.9 Hz, 2H), 6.76 (d, $^3J_{H,H}$=7.5 Hz, 2H), 6.97 (d, $^3J_{H,H}$=7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=17.0, 17.8, 53.6, 66.3, 125.1, 126.5, 128.5, 130.3, 132.8, 146.4; HREIMS: *m*/*z*: calcd for $C_{19}H_{22}N_2$ ($[M]^+$) 278.1783; found: 278.1783.

4.2.15. N-[4-Methyl-2-[(4-methyl-2-nitro-phenylamino)methyl]-6-nitrophenyl]-formamide (**9**)

Reaction between 4-methyl-2-nitroaniline **5f** and paraformaldehyde was carried out according to the general procedure with the following amendment: after addition of the reactants to CF_3COOH, the reaction mixture was heated to reflux for 24 h. Column chromatography (CH_2Cl_2/AcOEt 8:2) afforded **9** (337 mg, 39%) as an orange solid; mp 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.27 (s, 3H), 2.38 (s, 3H), 4.54 (d, $^3J_{H,H}$=6.0 Hz, 2H, CH_2N), 6.59 (d, $^3J_{H,H}$=8.6 Hz, 1H), 7.22 (dd, $^3J_{H,H}$=8.6 Hz, $^4J_{H,H}$=2.0 Hz, 1H), 7.49 (s, 1H), 7.81 (s, 1H), 8.02 (d, $^4J_{H,H}$=2.0 Hz, 1H), 8.35 (t, $^3J_{H,H}$=6.0 Hz, 1H, CH_2NH), 8.44 (s, 1H, CH═O), 8.66 (br, 1H, NHCH═O). ^{13}C NMR (75 MHz, $(CD_3)_2CO$, 25 °C; assignments from DEPT experiments): δ=20.8 (CH_3), 21.8 (CH_3), 44.9 (CH_2), 116.5 (CH), 125.7 (CH), 126.7 (C), 127.3 (C), 127.5 (CH), 134.2 (CH), 139.4 (CH), 139.7 (C), 140.0 (C), 144.9 (C), 145.0 (C), 148.6 (C), 161.9 (CH). HRESIMS: *m*/*z*: calcd for $C_{16}H_{16}N_4NaO_5$ ($[M+Na]^+$) 367.1018; found: 367.1015.

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Supplementary data

Additional X-ray diffraction data, including experimental details, for (±)-**3a**, **7**, and **9**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.111.

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36. ESIMS of the reaction mixture after work up displayed the corresponding $[M+H]^+$ pseudomolecular ion, and ^1H NMR spectrum revealed typical features of the methanodiazocine bicycle, that is, an AB system ($^2J_{Hendo,Hexo}$=16.5 Hz) at 4.60 and 4.05 ppm, and a singlet of the NCH_2N bridge at 4.25 ppm. In the acidic medium, protonation converts Me_2N group into a very strong acceptor, which would deactivate the aromatic ring toward electrophilic substitutions. However, there is always some free amine in equilibrium with an ammonium cation.
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42. The synthesis of (±)-**2e** was very recently reported by Lützen and co-workers, Ref. 9. We thank Prof. A. Lützen and Dr. U. Kiehne for the helpful discussion concerning the variation of conditions in this reaction.
43. It should be noted that in most cases the addition of reactants should be performed slowly and upon cooling. An attempt to initiate the reaction between 4-iodoaniline and paraformaldehyde by addition of reactants to CF_3COOH in one portion without cooling resulted in an exothermic reaction that produced a tarry, dark material and only traces of the desired Tröger's base analogue.
44. Di- or tetramethyl derivatives (±)-**3c**–**f** should be more reactive toward electrophilic substitution than (±)-**1b**. In a preliminary experiment, we confirmed a much higher reactivity of (±)-**3c** compared to (±)-**1b** in the electrophilic bromination. This study is currently in progress and will be published in due course.
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