REVIEW

Recent Developments in Synthetic Chemistry, Chiral Separations, and Applications of *Tröger*'s Base Analogues

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Tröger's base is a well-known chiral molecule with a few unusual structural features. The chemistry of *Tröger*'s base analogues has been greatly developed over the last 20 years, and numerous interesting applications in supramolecular chemistry and in molecular recognition have emerged. This Review gives a short overview of the chemistry of *Tröger*'s base and its analogues, with particular focus on recent achievements in synthesis, enantiomer separations, and applications.

Introduction. – The history of *Tröger*'s base goes back to 1887, when a young German chemist, *Julius Tröger* (born 1862 in Leipzig, died 1942 in Braunschweig), published a study on the condensation of some aromatic amines with formaldehyde [1]. In the course of his research towards a doctoral degree at the University of Leipzig, *Tröger* studied a reaction between methylal $CH_2(MeO)_2$ and *para*-toluidine (=4-methylbenzenamine) in aqueous HCl. He isolated an unwanted product, which he described as a 'base $C_{17}H_{18}N_2$', but failed to assign a plausible structure to it. Since those very early days, the history of *Tröger*'s base was fraught with controversies. Largely due to his failure to properly describe the base isolated by him, *Tröger* was given only a modest grade for his Ph.D. thesis. It likely brought him to move from Leipzig to the University of Braunschweig in 1888, where he built up a successful scientific career, until his retirement in 1928 [2].

Meanwhile, *Tröger*'s base kept on puzzling chemists, and several more structural misassignments were published before its correct chemical structure came to light in 1935 [3]. *Tröger*'s base eventually turned out to be racemic 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-**1**; *Fig. 1*). It features a central bicyclic aliphatic unit fused with the two benzene rings. Curiously, only in 1986, this structure was unambiguously confirmed with the aid of single-crystal X-ray-diffraction (XRD) analysis [4] – a surprisingly long gap for an air-stable, soluble, very easily available compound with a molecular weight of only 250. The two tertiary bridgehead N-atoms of this C_2-symmetrical molecule are stereogenic centers. In general, enantiomers of chiral tertiary amines with stereogenic N-atom cannot be resolved because of a rapid inversion at room temperature. However, inversion of the bridgehead N-atoms in the molecule of *Tröger*'s base is greatly hindered since it would impose a very high ring strain. It was the later *Nobel*-Prize winner *Vladimir Prelog* who has recognized the chiral nature of *Tröger*'s base and performed the chromatographic separation of the

enantiomers on specially prepared lactose in 1944 [5]. This was truly pioneering work, representing not only the first separation of a chiral amine with a stereogenic N-atom, but at the same time the first preparatively useful application of chromatography on a chiral stationary phase.

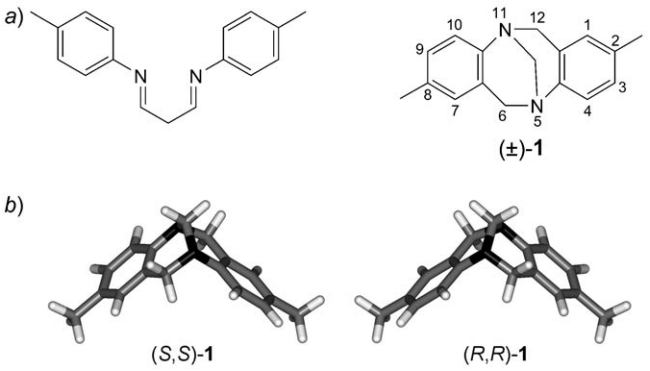


Fig. 1. a) *Structure tentatively assigned to* Tröger*'s base* [1] (left) *and the correct structural formula including the numbering according to its systematic name 6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine* (right). b) *PM3-Optimized geometry of the two enantiomers of* Tröger*'s base.*

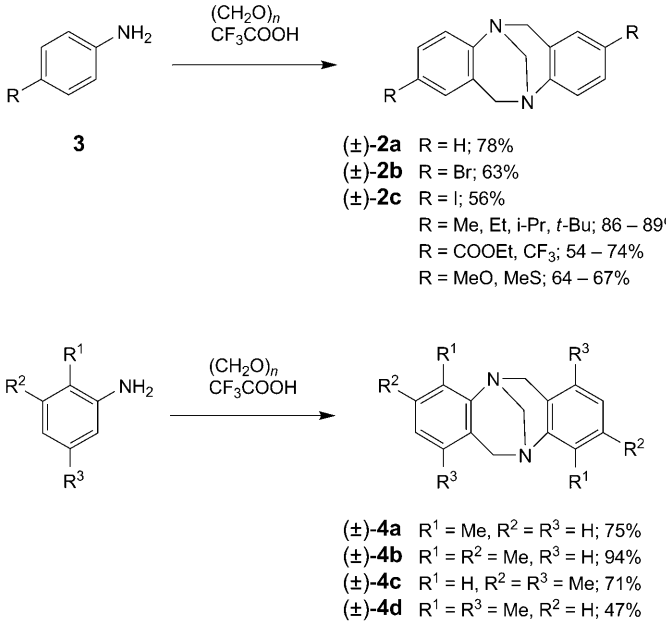
Since the pioneering work of *Prelog*, *Tröger*'s base became a classical example of a molecule with an 'unusual' type of chirality, and it has found its place in many stereochemistry textbooks. It also became a popular model substance for the evaluation of chiral chromatography processes. However, only in the late 1980s, interest in the functionalized analogues of *Tröger*'s base emerged, due to the fact that the two aromatic rings fused to the central bicyclic framework are nearly perpendicular to each other, creating a rigid, V-shaped molecular scaffold with a distance of *ca.* 1 nm between the two extremities. Hence, *Tröger*'s base offers itself as a unique, nanometer-sized building block for unusual molecular designs. For instance, various functional groups capable of H-bond formation were installed at the extremities of the V-shaped skeleton of *Tröger*'s base to create synthetic receptors for the recognition of adenine derivatives [6] or dicarboxylic acids [7]. Water-soluble cyclophane-like analogues of *Tröger*'s base have been suggested as chiral receptors for small, neutral organic molecules [8].

It should be mentioned that several reviews and book chapters have thoroughly covered various aspects of *Tröger*'s base chemistry [9][10]. The author of the present review has recently published in a national, non-peer-reviewed journal a brief account on selected recent developments in the field [11]. The purpose of the present review (which might be viewed as an extension of the previous brief account) is to highlight the most recent achievements in the chemistry of this 'fascinating molecule' [12], as well as future perspectives, while citing all the important original works published in 2006–2008. On the contrary, the citation of earlier literature, which is covered by the comprehensive review of *Dolenský et al.* [10], is limited to selected significant articles.

Synthetic Chemistry of *Tröger*'s Base and Its Analogues. – The most general approach to *Tröger*'s base analogues **2**, that is, derivatives of 6*H*,12*H*-5,11-methano-

dibenzo[*b*,*f*][1,5]diazocine bearing various substituents at different positions of the aromatic rings[1]), comprises variations of the original *Tröger* synthesis, namely, the *Brønsted* acid catalyzed condensation of formaldehyde with suitably substituted anilines (= benzenamines) **3** (*Scheme 1*). Formaldehyde is either used as a commercial aqueous solution (formaline) or generated *in situ* from a suitable precursor, such as $(MeO)_2CH_2$, $(CH_2)_6N_4$, or paraformaldehyde. Different reagents and reaction media (aqueous or ethanolic HCl solutions, acetic, trifluoroacetic, or methanesulfonic acids) were tried with highly variable success. Recent reports on the use of DMSO as an unusual equivalent of formaldehyde [14], on the *Lewis* acid catalysis in the synthesis of *Tröger*'s base [15], or on the preparation of heteroaromatic *Tröger*'s base analogues in ionic liquids [16] evidence that there is still an ongoing search for improved synthetic protocols.

Scheme 1. *Synthesis of Symmetrical* Tröger*'s Base Analogues from Anilines*



[1]) Derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine are often referred to as 'derivatives of *Tröger*'s base'. Strictly speaking, this is often not correct since many of these molecules lack the Me group at the 2- and 8-positions. The parent structure is therefore 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, which is sometimes rather unluckily termed, following traditions of natural-product nomenclatures, '*nor-Tröger*'s base'. However, the systematic name is rather complex while the term 'derivatives of *Tröger*'s base' is intuitively clear and has, therefore, been widely accepted throughout the chemical literature. '*Tröger*'s base analogues' appears as a somewhat better description since it can be extended to the molecules with other carbo- or heterocyclic rings instead of benzene rings. On the other hand, this may include also some other polycyclic systems, resembling the shape of *Tröger*'s base (see, *e.g.*, [13]). Within this account, the terms 'derivatives of *Tröger*'s base' and '*Tröger*'s base analogues' are used in an interchangeable sense.

Many procedures based on this general approach have the following common and important limitation: the substituents at the aromatic ring should have an electron-donating nature to allow electrophilic substitutions that represent key steps in the formation of the *Tröger*'s base framework (see [10][17] for detailed discussions of the mechanism). This obstacle has been efficiently overcome by the paraformaldehyde/CF_3COOH protocol, introduced by *Jensen* and *Wärnmark* for the synthesis of halogen derivatives of *Tröger*'s base such as (±)-**2b**,**c** (*Scheme 1*) [18]. This method was also extended to the synthesis of *Tröger*'s base derivatives with halogen atoms at other positions of the aromatic rings [19–21], including polyhalogenated derivatives [22][23]. A study in our laboratory has shown that a number of *Tröger*'s base analogues with both electron-donating (*e.g.*, alkyl, MeO, MeS) and electron-withdrawing (*e.g.*, COOEt, CF_3) substituents can be prepared in fair to excellent yields from the corresponding anilines and paraformaldehyde in CF_3COOH [23]. This protocol thus appears to be the most general among all known variations. As to limitations, some very electron-rich anilines (*e.g.*, 4-(dimethylamino)aniline) gave very poor yields due to extensive formation of polymeric products, while anilines bearing very strong acceptor groups (such as 4-cyano- and 4-nitroanilines) did not react[2]). At the same time, when NO_2 and electron-donating group(s) (Me and/or MeO) are both present, they counterbalance each other, and the aromatic ring becomes sufficiently activated for the formation of *Tröger*'s base derivatives [24][25].

The halogen-substituted analogues of *Tröger*'s base, first introduced by *Jensen* and *Wärnmark* in 2001 [18], are particularly important synthetic intermediates since they provide access to many other functional derivatives *via* transition-metal-catalyzed cross-coupling reactions, including *Kumada* [18], *Suzuki–Miyaura* [26][27], and *Sonogashira* [28][29] coupling, *Buchwald* amination [30], and Cu- or Pd-catalyzed cyanation [27][30]. Other synthetically valuable derivatives can be prepared *via* a double halogen-lithium exchange with BuLi followed by the reaction of the lithium intermediate with a range of electrophiles (*Scheme 2*) [31]. Many other transformations of functional groups attached to the aromatic rings of *Tröger*'s base analogues have been explored. These are standard synthetic operations, which are rather common for various aromatic derivatives. They will not be discussed here, but it is noteworthy that the *Tröger*'s base skeleton demonstrates stability towards various reagents and conditions, including $LiAlH_4$, Na in boiling EtOH, BBr_3 in CH_2Cl_2, MnO_2 and $KMnO_4$ at temperatures up to 80°, and catalytic heterogeneous reduction [10].

It is worth mentioning that the reaction between unsubstituted aniline and paraformaldehyde in CF_3COOH smoothly provides 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine ((±)-**2a**) in 78% yield [32]. We have also demonstrated that 2-methyl, as well as 2,3-, 2,5- and 3,5-dimethylanilines gave the corresponding analogues (±)-**4a–d** of *Tröger*'s base in up to 94% yield (*Scheme 1*). These findings clearly show that the absence of a substituent in the *para*-position of the starting aniline does not necessarily lead to polymerization, as was widely accepted earlier [10]. The easy

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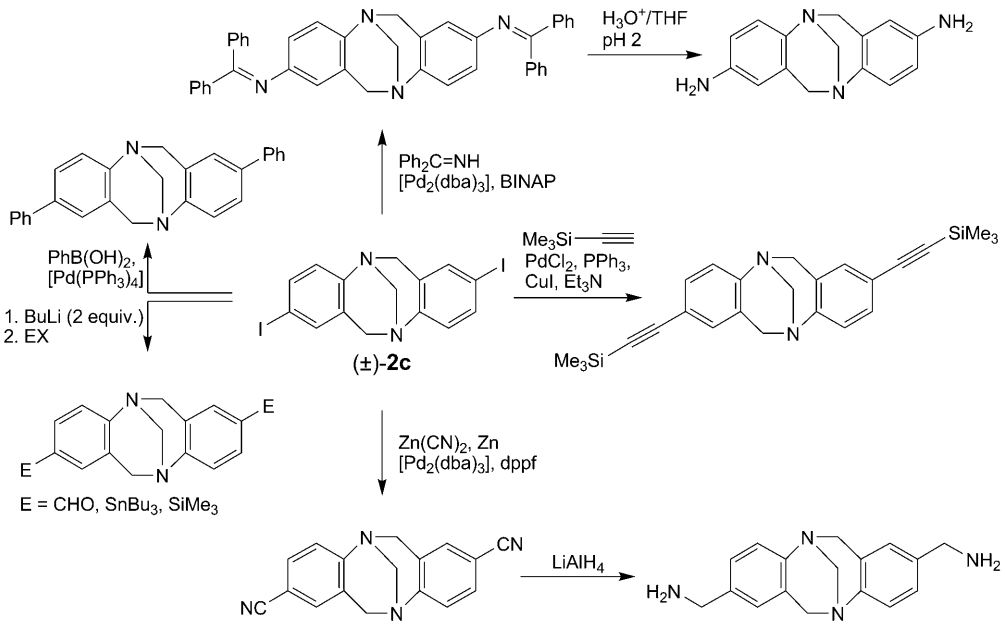
[2]) Anilines with strongly electron-withdrawing *para*-substituents (including 4-cyanoaniline (=4-aminobenzonitrile) and 4-nitroaniline) do give the corresponding *Tröger*'s base derivatives upon the action of DMSO in HCl/AcOH as an unusual synthetic equivalent of formaldehyde, although the yields are generally low [14].

Scheme 2. *Examples of Synthetic Transformations Starting from Diiodide (±)-***2c**. dba = dibenzylideneacetone (= 1,5-diphenylpenta-1,4-dien-3-one); BINAP = (±)-[1,1′-binaphthalene]-2,2′-diylbis[diphenylphosphine], dppf = 1,1′-bis(diphenylphosphino)ferrocene.

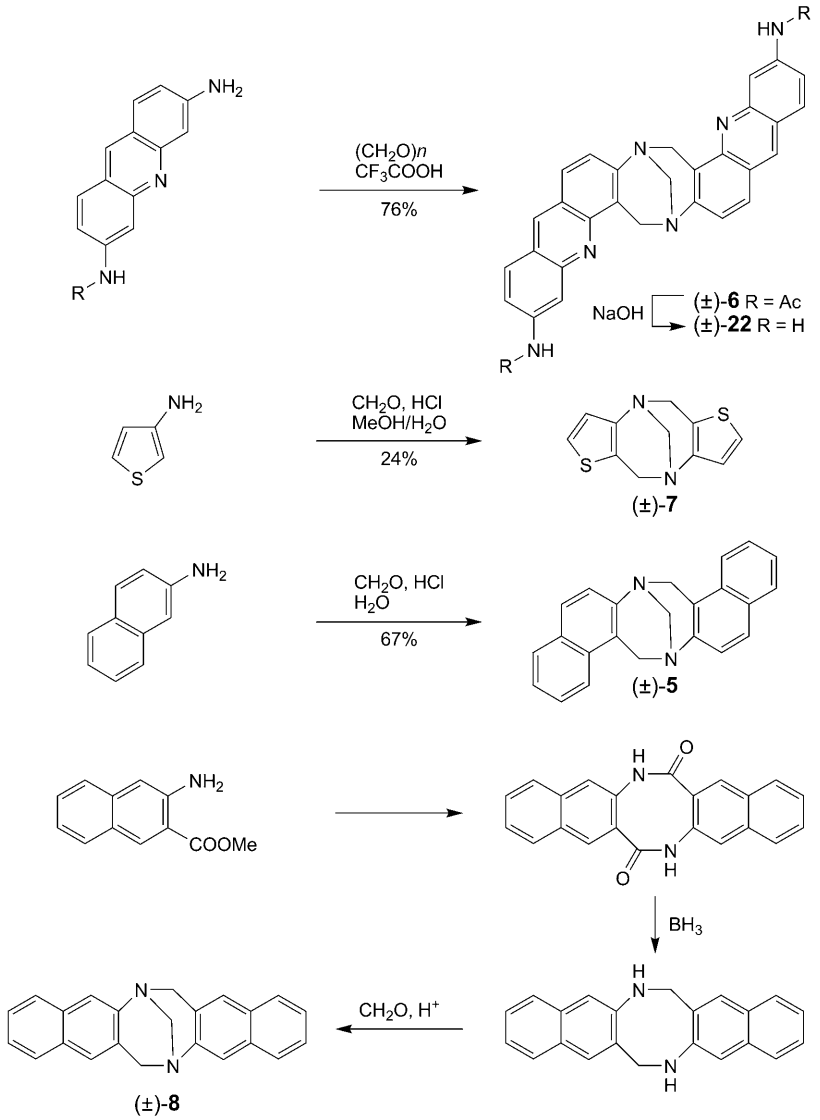


accessibility of (±)-**4a**–**d** makes them attractive intermediates for the synthesis of unsymmetrical derivatives of *Tröger*'s base *via* electrophilic substitutions (see below).

Next to substituted anilines, a number of nonbenzenoid aromatic and heteroaromatic amines, including derivatives of naphthalene, acridine, phenanthroline, pyrrole, thiophene, and porphyrins give *Tröger*'s base derivatives *via* the condensation with CH_2O, though yields vary considerably. For many of nonbenzenoid systems, the formation of several regioisomeric products is *a priori* possible. However, these condensations are typically highly regioselective, mirroring the usual reactivity of nonbenzenoid aromatics towards electrophiles. Thus, naphthalen-2-amine [33] and a protected acridin-2-amine [34] give exclusively analogues (±)-**5** and (±)-**6** of *Tröger*'s base, respectively, resulting from the substitution at position 1, while thiophen-3-amine [35] undergoes exclusively substitution at position 2 to give (±)-**7**. Such preferences in reactivity may pose a problem in the synthesis of certain analogues of *Tröger*'s base. Thus, a naphthalene analog (±)-**8** of *Tröger*'s base is inaccessible *via* the condensation of naphthalen-2-amine with formaldehyde due to lower reactivity of position 3 *vs.* position 1. However, (±)-**8** was successfully synthesized in three steps by sequential build-up of the central methanodiazocine moiety starting from the methyl ester of 3-aminonaphthalene-2-carboxylic acid (*Scheme 3*) [36].

The direct condensation of anilines with formaldehyde gives access only to symmetric derivatives of *Tröger*'s base. At the same time, diamines **9**, which are assumed to be key intermediates in the synthesis of *Tröger*'s base analogues from

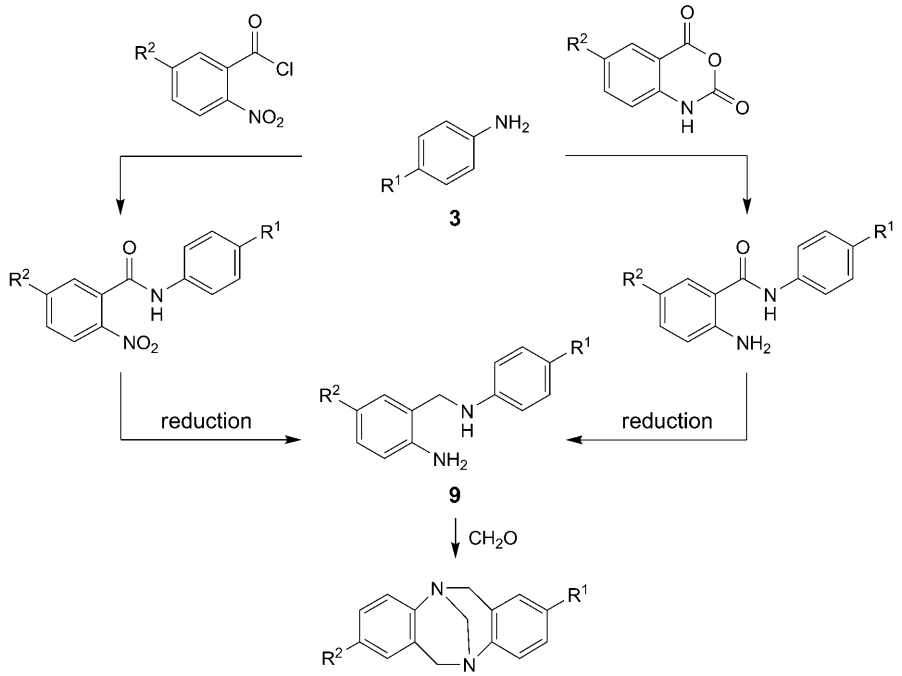
Scheme 3. *Synthesis of* Tröger*'s Base Analogues from (Hetero)aromatic Amines*



anilines [10][17], can be prepared by independent methods, *e.g.*, starting from anilines **3** and derivatives of either isatoic anhydride (=2*H*-3,1-benzoxazine-2,4(1*H*)-dione) or of 2-nitrobenzoyl chloride (*Scheme 4*). Subsequent treatment of **9** with formaldehyde in $HCl/H_2O/EtOH$ afforded (in case of $R^1 \neq R^2$) the corresponding nonsymmetric analogues (±)-**10** of *Tröger*'s base. Similar to the synthesis of symmetric analogues of *Tröger*'s base from anilines, this condensation tolerates only electron-donating substituents R^1 [37]. This methodology is nevertheless very valuable, since it provides

access to complex unsymmetrical derivatives of *Tröger*'s base, such as precursors for 'molecular torsion balances' (see *Scheme 13* below) [38–40].

Scheme 4. Wilcox *Synthesis of Nonsymmetrical* Tröger*'s Base Analogues*

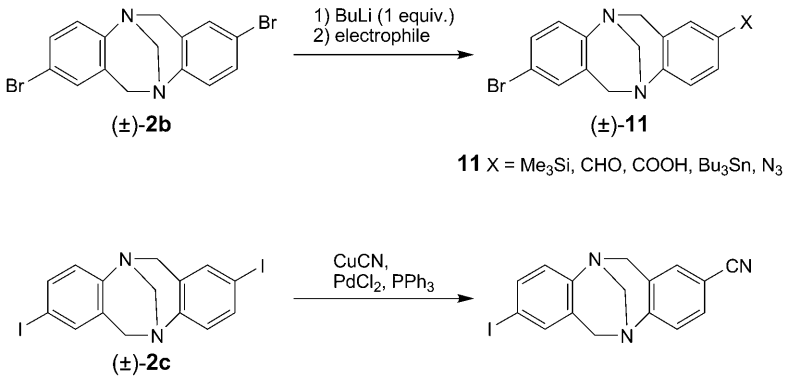


(±)-**10** R^1 = Me, MeO; R^2 = H, Me, Cl, Br, NO_2

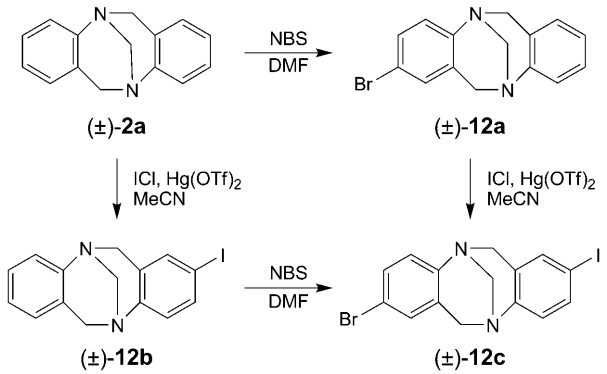
An alternative approach to nonsymmetrical derivatives of *Tröger*'s base involves desymmetrization of dihalo derivatives, *e.g.*, of (±)-**2b**,**c**, *via* a single halogen-lithium exchange. Subsequent reaction with an electrophilic reagent afforded unsymmetrical derivatives (±)-**11** [31]. The remaining halogen atom in (±)-**11** can again be used for the generation of an organolithium derivative followed by reaction with a different electrophile. A nonselective substitution of only one I-atom in diiodide (±)-**2c** *via* Pd-catalyzed amination or cyanation represents yet another entry to valuable unsymmetrical derivatives, albeit the yields are modest (*Scheme 5*) [27].

Finally, the recently reported electrophilic substitution in 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (±)-**2c** upon action of NBS or ICl provides unsymmetrical halogen derivatives (±)-**12a**–**c** (*Scheme 6*) [32]. Unprecedented (±)-**12c** bearing a Br- and an I-atom at the two different aromatic rings is particularly interesting, since it can serve as a substrate for *selective* substitution of the more reactive I-atom *via* various cross-coupling reactions, leaving the Br-atom intact for further transformations. Obviously, the various approaches discussed are complementary and altogether constitute a powerful methodology for the synthesis of complex unsymmetrical derivatives of *Tröger*'s base.

Scheme 5. *Desymmetrization of 2,8-Dihalogeno-Substituted 6*H,*12*H-*5,11-Methanodibenzo[*b,f*][1,5]-diazocines*



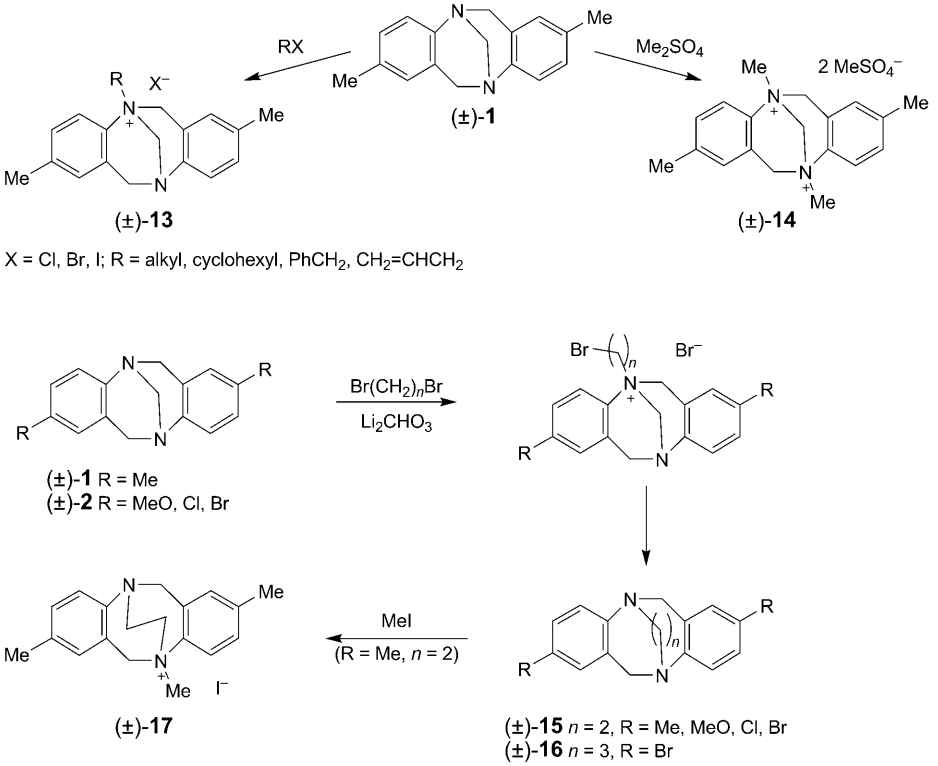
Scheme 6. *Desymmetrization of 6*H,*12*H-*5,11-Methanodibenzo[*b,f*][1,5]diazocine.* NBS = *N*-Bromosuccinimide; DMF = *N*,*N*-dimethylformamide, TfO = trifluoromethanesulfonate.



To conclude the section devoted to the synthetic chemistry of *Tröger*'s base analogues, we will mention selected transformations involving the central, aliphatic bicyclic system of 6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine. First of all, the preparation of quaternary salts of *Tröger*'s base (±)-**1** was studied, and the outcome is controversial. Several independent studies [41] have shown that monocationic derivatives such as (±)-**13** can easily be prepared upon the action of a suitable alkylating agent (*Scheme 7*). At the same time, quaternization of the two N-atoms was reported to be unfeasible. This may be explained by the strongly negative inductive effect of the quaternary N-atom in (±)-**13** that greatly reduces the nucleophilicity of the tertiary N-atom. However, *Kostyanovsky* and co-workers have recently reported the preparation of the dicationic derivative (±)-**14** in nearly quantitative yield by the reaction of (±)-**1** with dimethyl sulfate [42].

Formation of a quaternary salt probably represents the first step in the interesting reaction between *Tröger*'s base analogues and 1,2-dibromoethane. Subsequent

Scheme 7. *Transformations Involving the Central Aliphatic Bicyclic System of 6H,12H-5,11-Methanodibenzo[b,f][1,5]diazocine*



cleavage of the NCH_2N bridge followed by the intramolecular nucleophilic substitution of the second Br-atom results in the unusual 'bridge-replacement' transformation to give (±)-**15**, an analogue of *Tröger*'s base featuring an NCH_2CH_2N bridge. A series of molecules bearing different substituents at the 2- and 8-positions was prepared by this method (*Scheme 7*) [43–45]. The analogous reaction with 1,3-dibromopropane proceeds only sluggishly (10% of (±)-**16**), and 1,4-dibromobutane gives no bridged product at all, which is in accord with thermodynamic preferences for the formation of a seven-, eight-, or nine-membered ring.

Derivatives (±)-**15** with an NCH_2CH_2N bridge maintain the V-shape similar to that of *Tröger*'s base, while (±)-**16** with a longer bridge adopts 'flattened' conformations with two aromatic rings in a propeller-like orientation with respect to each other [43]. Molecular-geometry optimization predicts the dihedral angle between the planes of the two aromatic rings for NCH_2CH_2N-bridged molecules to decrease by *ca.* 20° compared to NCH_2N analogues [46]. This is in agreement with the values of dihedral angles obtained from single-crystal XRD studies (*Table*). It should be kept in mind that the *Tröger*'s base framework possesses a certain conformational flexibility, and packing effects can apparently account for at least 10° differences in the dihedral angle between

the planes of the aromatic ring, as evidenced by the example of racemic and enantiomerically pure *Tröger*'s base **1**. However, the angle is always smaller for an NCH_2CH_2N-bridged analogue *vs.* an NCH_2N-bridged one for each pair of derivatives bearing identical substituents at the aromatic rings. The largest encountered difference of *ca.* 20° (for R = H) exactly corresponds to the geometry-optimization results. Furthermore, the smallest angle for the NCH_2CH_2N-bridged molecule (*i.e.*, R = H) is *ca.* 76°, while angles smaller than *ca.* 85° are not known for 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine derivatives [10]. Easy-to-perform 'bridge replacement' in *Tröger*'s base analogues can therefore be considered as an efficient approach to the 'fine tuning' of molecular geometry.

Table. *Experimental Dihedral Angles* (XRD data) *between the Planes of the Two Aromatic Rings of* NCH_2CH_2N*-Bridged* Tröger*'s Base Analogues* (±)-**15**, *together with the Reference Values of the Corresponding* NCH_2N*-Bridged Derivatives Featuring Identical Substituents.* See *Scheme 7* for structures.

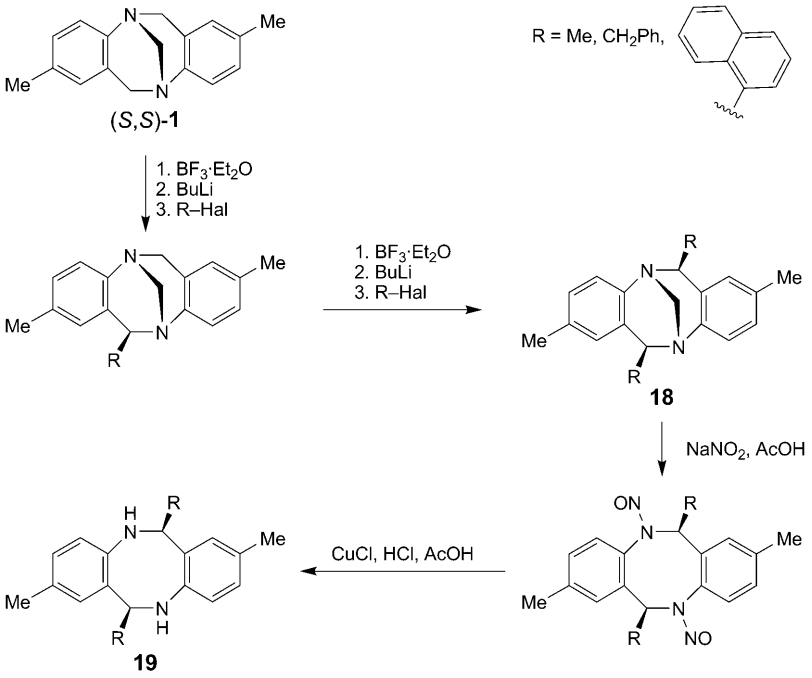
R	**1** or **2** (NCH_2N)[a])	(±)-**15** (NCH_2CH_2N)
H	95.4° [47]	75.9° [44]
Cl	95.6° [48]	87.0° [45]
Br	94.5° [49]	87.0° [43]
Me	92.9° and 97.4° [50][b])	89.0° [42]
	102.2° [50][c])	

[a]) Racemates, unless indicated otherwise. [b]) Two crystallographically independent molecules per unit cell. [c]) (+)-(*S*,*S*)-Enantiomer.

Another interesting aspect of NCH_2CH_2N-bridged analogues of *Tröger*'s base is their stability towards the acid-catalyzed racemization (see below). Reaction of enantiomerically pure (−)-**15** (R = Me) also produces the corresponding quaternary salt (−)-**17** in nearly quantitative yield and without racemization. Furthermore, the heating of (−)-**17** in DMF results in quantitative recovery of enantiomerically pure (−)-**15**. Due to the presence of a heavy atom (I^- ion), the determination of the *Flack* parameter [51] from the single-crystal XRD analysis of enantiomerically pure (+)-**17** allowed for the assignment of its absolute configuration as (+)-(*R*,*R*)-**17**. By chemical correlation, the absolute configuration of **15** can, therefore, be unambiguously assigned as (−)-(*S*,*S*)-**15** and (+)-(*R*,*R*)-**15** [42].

Harmata and co-workers demonstrated deprotonation at the benzylic CH_2 of (*S*,*S*)-**1** with BuLi in the presence of $BF_3 \cdot Et_2O$ followed by stereoselective reaction of the carbanion with various electrophiles (see [52] and ref. cit. therein; *Scheme 8*). Sequential alkylation of the two benzylic CH_2 groups can be performed without affecting the configuration of the *Tröger*'s base skeleton to give **18**. Subsequent cleavage of the methylene bridge between two N-atoms gives access to C_2-symmetrical chiral cyclic secondary diamines **19** that may be useful in metal-catalyzed or organocatalytic reactions. Hence, the transformation of (*S*,*S*)-**1** to **19** illustrates the synthetic utility of *Tröger*'s base as an entry to further, otherwise hardly accessible chiral molecules. Recent progress in enantiomer separations of *Tröger*'s base analogues (see below) greatly increases the number of such analogues to which this useful methodology could be applied.

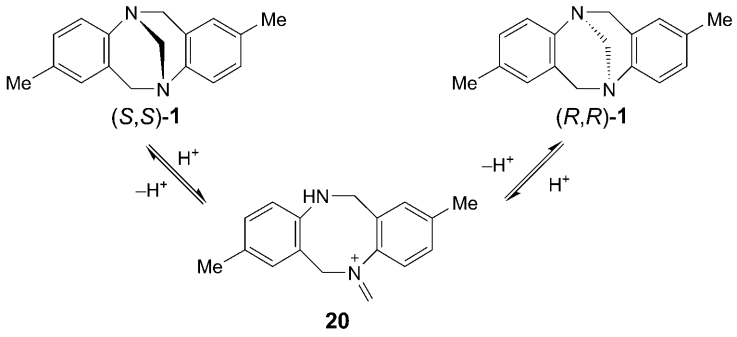
Scheme 8. *Transformations of* Tröger*'s Base into Other C_2-Symmetrical Chiral Diamines*



To conclude this section, we will mention the very recently published reactions between *Tröger*'s base and some activated alkenes and alkynes. Interesting and unusual products were reported by two different research groups, but the results of these two studies are controversial [53]. This issue might require further clarifications and will not be discussed here.

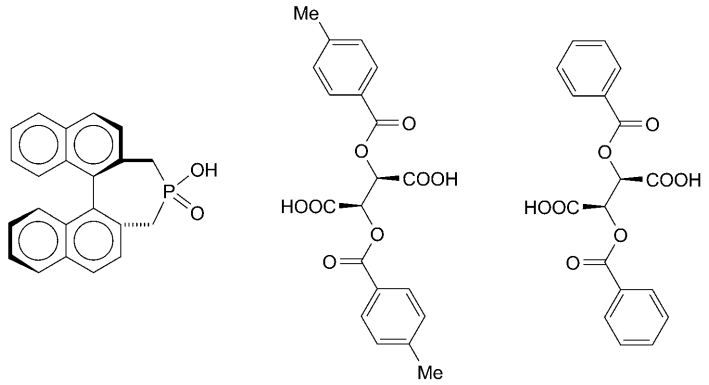
Enantiomer Separations of *Tröger*'s Base and Its Analogues. – Perhaps the most controversial chapter in the history of *Tröger*'s base is related to separations of its enantiomers. As mentioned above, as early as 1944 *Prelog* and *Wieland* have separated two enantiomers of *Tröger*'s base by chromatography on lactose [5]. It was also *Prelog* who reported on the slow acid-catalyzed racemization of *Tröger*'s base. It was postulated later that the inversion of configuration occurs *via* a reversible formation of an achiral iminium intermediate **20** that can with equal probability close back to either of the two enantiomers (*Scheme 9*). Although this racemization model appears very plausible, no spectroscopic evidence of iminium intermediate **20** was obtained [54]. The intermediate **20** is therefore suggested to be present in concentrations too low to be detected spectroscopically. This is also consistent with the fairly slow rate of the interconversion of enantiomers in solution: the racemization half-life of *Tröger*'s base **1** at 25° and pH 1 was found to be 6.4 h [55]. An indirect confirmation of this mechanism is the stability towards racemization of *Tröger*'s base analogues **15**, featuring the

Scheme 9. *Racemization of* Tröger*'s Base via Iminium Intermediate* **20**



NCH_2CH_2N bridge [56]. Indeed, in this case, the formation of a stabilized iminium intermediate is not possible.

In accordance with the observed acid-promoted racemization, it was postulated that chiral resolution of *Tröger*'s base *via* crystallization of diastereoisomeric salts with chiral acids is not feasible. Some unsuccessful attempts were indeed documented to confirm this assertion. However, a few important exceptions have been reported too. An important 'special case' is the isolation of enantiomerically pure (ee > 98%) *Tröger*'s base (+)-**1** with the aid of (−)-[1,1′-binaphthalene]-2,2′-diyl hydrogen phosphate (=(−)-4,5-dihydro-4-hydroxy-3*H*-dinaphtho[2.1-*c*:1′,2′-*e*]phosphepin 4-oxide; **21**; *Fig. 2*) described by *Wilen* and co-workers [57]. Under these special circumstances, a strongly acidic resolving agent does induce the racemization *in solution*, but only one enantiomer of *Tröger*'s base *crystallizes* from the solution as a stable salt. A *strongly acidic* resolving agent has been deliberately chosen to facilitate salt formation. Furthermore, the yield of (+)-**1** from (±)-**1** was 93%, that is, 186% based on the amount of (+)-**1** initially present in the racemate. This clearly implies that



(–)-**21** (*R*,*R*)-**23a** (*R*,*R*)-**23b**

Fig. 2. *Chiral acids used for enantiomer separations of* Tröger*'s base*

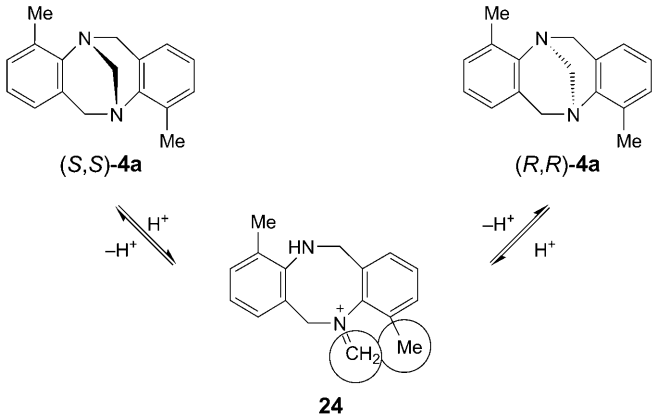
essentially all (−)-**1** initially present in the racemate has been isomerized to (+)-**1**. Hence, this experiment cannot really be considered as a separation of enantiomers but rather as a crystallization-induced asymmetric transformation (CIAT) of one enantiomer into another. Another, relatively recent efficient CIAT of a *Tröger*'s base analogue in the *absence* of chiral acids is driven by the presence of homochiral (*S*)- or (*R*)-1-phenylethyl groups in the molecule [58]. In one more particular case, an acridinamine analogue of *Tröger*'s base, (±)-**22** (see *Scheme 3* above), was resolved by crystallization of its 2,3-di-*O*-benzoyltartrate salts [34]. This separation was only possible because protonation of the more basic N-atoms of the acridine rings prevented racemization *via* the formation of an iminium intermediate similar to **20**.

However, some other reported cases of successful resolution do not fit into the picture described above. Thus, the naphthalene analogue (±)-**5** of *Tröger*'s base (see *Scheme 3* above) has been successfully resolved with the aid of either (+)- or (−)-2,3-di-*O*-(*p*-toluoyl)tartaric acid (**23a**; *Fig. 2*) [33]. However, there should be no considerable difference in the stability towards racemization between *Tröger*'s base **1** and its naphthalene analogue **5**. Indeed, recently, the resolution of **1** with the aid of (−)-(*R*,*R*)-2,3-di-*O*-benzoyltartaric acid ((−)-(*R*,*R*)-**23b**) has been revisited [15]. Quite surprisingly, a salt (−)-(*R*,*R*)-**1**·(−)-(*R*,*R*)-**23b** was obtained after precipitation from acetone, and its neutralization afforded (−)-(*R*,*R*)-**1** with 91% ee (98% ee after a single crystallization). The structure of (−)-(*R*,*R*)-**1**·(−)-(*R*,*R*)-**23b** was confirmed by single-crystal X-ray-diffraction analysis. The bond lengths of the carboxylic acid groups and OH−N distances clearly indicate nondissociated COOH groups and an efficient H-bond O−H···N. Hence, (−)-(*R*,*R*)-**1**·(−)-(*R*,*R*)-**23b** is not an actual salt, but rather a H-bonded aggregate.

In another recent work, *Kostyanovsky* and co-workers reported considerable increase in the racemization energy barrier of *Tröger*'s base analogues upon substitution in the *ortho*-positions relative to the N-atoms ($\Delta G^{\ddagger}$ of enantiomerization was found to be 130.4 kJ mol^{-1} for (*S*,*S*)-**4a** *vs.* 101.4 kJ mol^{-1} for *Tröger*'s base (*S*,*S*)-**1**) [55]. For the isomerization of (*S*,*S*)-**4a** to (*R*,*R*)-**4a** (or *vice versa*) to happen, the methylene group of the iminium intermediate **24** has to pass through the plane of the aromatic ring followed by ring closure on the opposite side (*Scheme 10*). For this, a rotation around the C(4a)−N (or C(10a)−N) bond should occur. It is therefore predictable that the substitution of *ortho* H-atoms (in positions 4 and 10) by bulkier groups should increase the energy barrier of this process and, consequently, slow down the racemization. Although the resolution of racemic **4a** with the aid of chiral acids was not reported, it is reasonable to suggest that derivatives with substituents in the *ortho* position relative to the N-atoms should be good candidates to test this approach.

The examples discussed should prompt us to reconsider the (un)feasibility of the resolution of *Tröger*'s base derivatives with the aid of chiral, optically pure acids. An up-to-date statement concerning such a resolution should probably be moderated to the following one: '*Resolution of* Tröger*'s base and its analogues via diastereoisomeric salts is feasible in some cases, but requires the careful choice of resolving agents and of experimental conditions. In addition, the stability of* Tröger*'s base analogues towards racemization in acidic medium considerably depends on the substitution pattern of the aromatic rings*'. Nonetheless, crystallization of diastereoisomeric salts appears to be of limited scope as enantiomer-separation method, taking into account reports on

Scheme 10. *Racemization of* Tröger*'s Base Analogue* **4a** via *Iminium Intermediate* **24**. Circles denote steric hindrance in the transition state.



unsuccessful attempts to resolve *Tröger*'s base analogues with the aid of chiral acids [59].

The reported separations of several *Tröger*'s base analogues *via* crystallization of conglomerates followed by manual separation are interesting but are of limited practical utility [60]. Furthermore, many *Tröger*'s base analogues tend to form racemic crystals rather than conglomerates.

Taking the above into account, HPLC on chiral stationary phases (CSP) appears very attractive as an enantiomer-separation method for functionalized *Tröger*'s base analogues. Curiously, in spite of the popularity of *Tröger*'s base itself as a standard probe for the evaluation of various newly designed CSPs, enantiomer separations of functionalized *Tröger*'s base analogues were not known for a long time. However, in recent years, several enantiomer separations on both commercial and tailor-made CSP were published [20][59][61]. Very recently, we reported the systematic separation of variously functionalized analogues of *Tröger*'s base on commercial CSP *Whelk O1* featuring a covalently bound tetrahydronaphthalene derivative as a chiral selector. Screening of the library composed of 36 derivatives has shown that the separation on this phase is not only facile but also predictable: based on the molecular recognition model, structure – selectivity relationships were established. One can therefore forecast whether or not the enantiomer separation of a given, perhaps yet unsynthesized *Tröger*'s base analogue will be feasible [23]. Considering the general advantages of chiral HPLC (various CSP are commercially available, recovery of purified material is extremely easy, and materials with *ca.* 100% ee are often directly available from a single run), it currently appears to be the method of choice to access enantiomerically pure derivatives of *Tröger*'s base on a preparative scale.

Finally, a very special example of enantiomer separation concerns the phenanthroline analogue (±)-**25** of *Tröger*'s base that was used to prepare complexes $[Ru(phen)_2 \cdot \mathbf{25}]^{2+}$ (phen = phenanthroline) with an octahedral hexacoordinated Ru^{II} center (*Fig. 3*). This creates an interesting configurational situation where stereogenic units

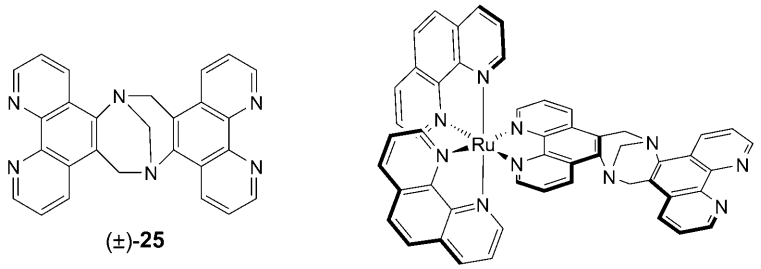


Fig. 3. *Phenathroline analogue (±)-***25** *of* Tröger*'s base and its complex [Ru(phen)$_2$·***25***]$^{2+}$* (the *Λ*-(*R*,*R*)-diastereoisomer is shown)

originating from (±)-**25** and from the Ru^{II} center are combined in one molecular entity. When the enantiomerically pure Ru^{II} precursor complex *Λ-cis*-[Ru(phen)$_2$(py)$_2$]$^{2+}$ (py = pyridine) was used, the resulting diastereoisomeric complexes *Λ*-(*R*,*R*)-[Ru(phen)$_2$·**25**]$^{2+}$ and *Λ*-(*S*,*S*)-[Ru(phen)$_2$·**25**]$^{2+}$ were isolated by fractional crystallization [62].

Assignment of the Absolute Configuration of *Tröger*'s Base and Its Analogues. – Determination of the absolute configuration of a chiral molecule is a common issue chemists have to tackle. Unless single-crystal XRD data (either anomalous scattering of heavy atoms or the relative configuration *vs.* an internal reference with known absolute configuration) are available, such assignments are not infallible. Determination of the absolute configuration of *Tröger*'s base enantiomers serves as an excellent illustration of this problem, since it has proven rather controversial. The first tentative assignment was based on the comparison of chiroptical properties of *Tröger*'s base and those of the structurally somewhat similar alkaloid argemonine, and (+)-**1** was determined to have (*S*,*S*) absolute configuration [63]. Shortly after, *Mason et al.* reassigned (+)-**1** as (*R*,*R*)-configured based on the analysis of circular dichroism (CD) data by the exciton chirality method [64]. The assignment of *Mason et al.* has been cited in the literature until 1991, before *Wilen* and co-workers unequivocally established by XRD analysis of the salt (+)-**1**·(−)-**21** that it was incorrect and that the assignment should be inverted to (+)-(*S*,*S*)-**1** and (−)-(*R*,*R*)-**1** [57]. Recent XRD data of (−)-**1**·(−)-**23b** [15] reconfirm the assignment of *Wilen* and co-workers[3]). Finally, the calculated and measured vibrational-circular-dichroism (VCD) spectra of **1** were also in accord with this assignment [65].

Based on the unambiguously determined absolute configuration of **1**, absolute configurations of selected *Tröger*'s base analogues were assigned by comparison of their CD spectra with those of **1** [19][66]. However, in general, this method should be used with care. On the one hand, *Kostyanovsky* and co-workers have confirmed by XRD data a correlation between the absolute configuration of three variously substituted *Tröger*'s base analogues and the sign of the lowest-energy *Cotton* effect in

[3]) Rather confusingly, the dextrorotatory enantiomer of *Tröger*'s base is still listed as (*R*,*R*) in the *Fluka* catalog.

their CD spectra [60]. On the other hand, *Lützen* and co-workers have clearly shown that the sign and the magnitude of different *Cotton* effects may change greatly between various *Tröger*'s base analogues, rendering direct comparison of CD spectra unreliable [59]. Therefore, particular caution is advised in comparing CD spectra of *Tröger*'s base analogues having different substitution patterns of the aromatic rings.

Uses and Applications of *Tröger*'s Base and Its Analogues. – Since the beginning of the 'renaissance' of *Tröger*'s base in the 1980s, its framework has been extensively used, first by *Wilcox* and then by others in the design of synthetic H-bonding receptors with various recognition elements for functionalized molecules (*Fig. 4*; see review [10] for examples and leading references). In a recent work, *Crossley* and co-workers demonstrated preferential ditopic binding of dicarboxylic acids in the internal cavity of the *Tröger*'s base analogue (±)-**26** featuring two dihydroxy(porphyrinato)tin(IV) moieties and possessing two different binding sites (inside and outside the V-shaped cavity) (*Fig. 4*). It was shown that the initial ditopic H-bonding of $HOOC(CH_2)_n$-COOH with the two $Sn(OH)_2$ functions facilitates the subsequent ligand exchange to produce a stable carboxylate featuring two ester-like $COO-Sn^{IV}$ bonds, thus producing quantitative intra-cavity binding. An interesting extension of this study will be the *enantioselective* intra-cavity binding of α-amino acids [67]. Another recent work of *Crossley*'s group deals with the synthesis of an unsymmetrical V-shaped receptor with four nonequivalent tin(IV) binding sites. This design allows better identification of the factors which control the ligand exchange at (porphyrinato)tin(IV), expanding their utility in supramolecular chemistry [68].

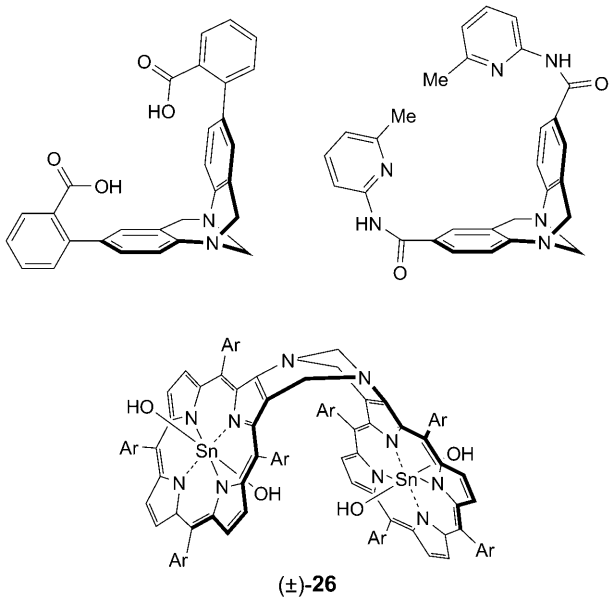
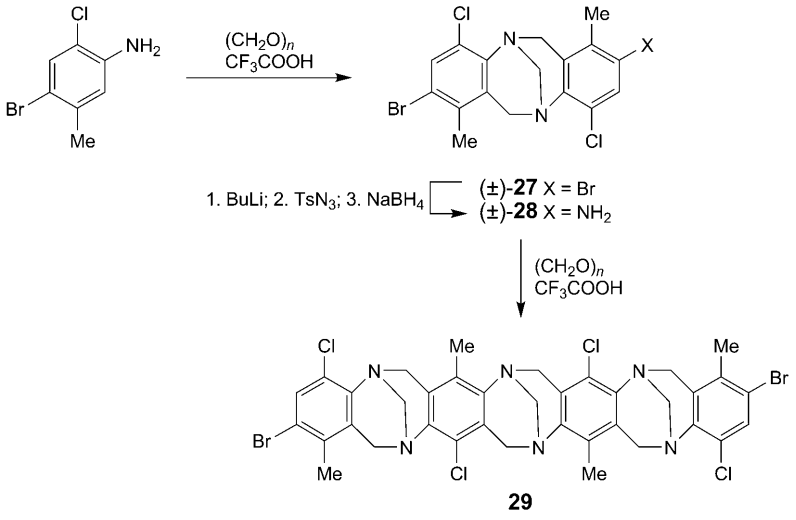


Fig. 4. Tröger*'s base analogues as H-bonding receptors*

Relatively recently, a great deal of attention has been given to 'bis-, tris-, and oligo-*Tröger*'s bases', that is, molecules comprising two, three, or more methanodibenzodiazocine units fused in such a way that an aromatic ring of one methanodibenzodiazocine unit constitutes a part of a neighboring one. This is due to the challenge to create relatively unfunctionalized molecular tweezers or clefts with extended concave surfaces. These molecular shapes are important for the understanding of recognition processes on concave surfaces that are governed largely by nondirectional solvophobic effects and *van der Waals* interactions, as well as, in relevant cases, by π-stacking and cation–π interactions.

For 'oligo-*Tröger*'s bases', multiple regioisomers are *a priori* possible, depending on the pattern in which the benzene rings and the methanodiazocine moieties are fused. Various synthetic methodologies have been developed to overcome regio- an diastereoselectivity issues, which are becoming increasingly complex when the number of fused methanodibenzodiazocine cores grows. This subject was extensively covered by the excellent review of *Dolenský et al.* [10] (see also the most recent works from some of the authors of this review [69]). The recently published synthesis of a 'linear tris-*Tröger*'s base' (*Scheme 11*) may serve as an illustrative example of an efficient approach towards selective construction of a single regioisomer [70]. The key steps are desymmetrization of dibromide (±)-**27** according to the lithiation methodology of *Wärnmark* and co-workers [31] (see above) to give amine (±)-**28**, and the assembly of the central methanodiazocine unit in the 'linear tris-*Tröger*'s base' **29** by the condensation of (±)-**28** with paraformaldehyde. Since **29** has a Br-atom in each terminal benzene ring, successive desymmetrization/condensation can in principle be repeated to synthesize higher generations of 'linear oligo *Tröger*'s bases'.

Scheme 11. *Synthesis of 'Linear Tris-*Tröger*'s Base'* **29**



29

anti,*anti*, *anti*,*syn*, and *syn*,*syn* diastereoisomers

'Tris-*Tröger*'s base' **29** was obtained as a mixture of three diastereoisomers, which differ in the mutual orientation of methanodiazocine bridges. All three were isolated and two of them (*syn*,*syn* and *anti*,*syn*) were unambiguously identified by XRD. A molecule of (±)-*syn*,*syn*-**29** has a cleft-like shape with distances of 8.5–9.0 Å between the planes of the aromatic rings, while (±)-*anti*,*syn*-**29** features a cleft of a smaller size (*Fig. 5*). Interestingly, addition of NH_4Cl to the reaction mixture during the synthesis of **29** resulted in the increase of the ratio of cleft-shaped *syn*,*syn* and *anti*,*syn* isomers to the *anti-anti* isomer, suggesting a template effect of NH_4^+.

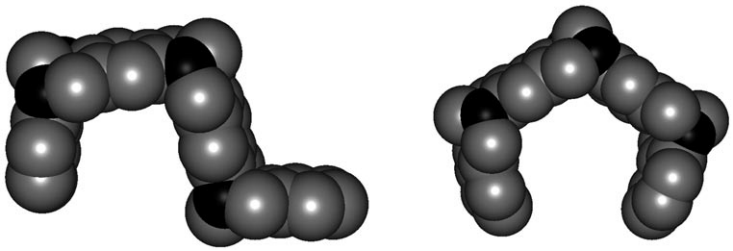


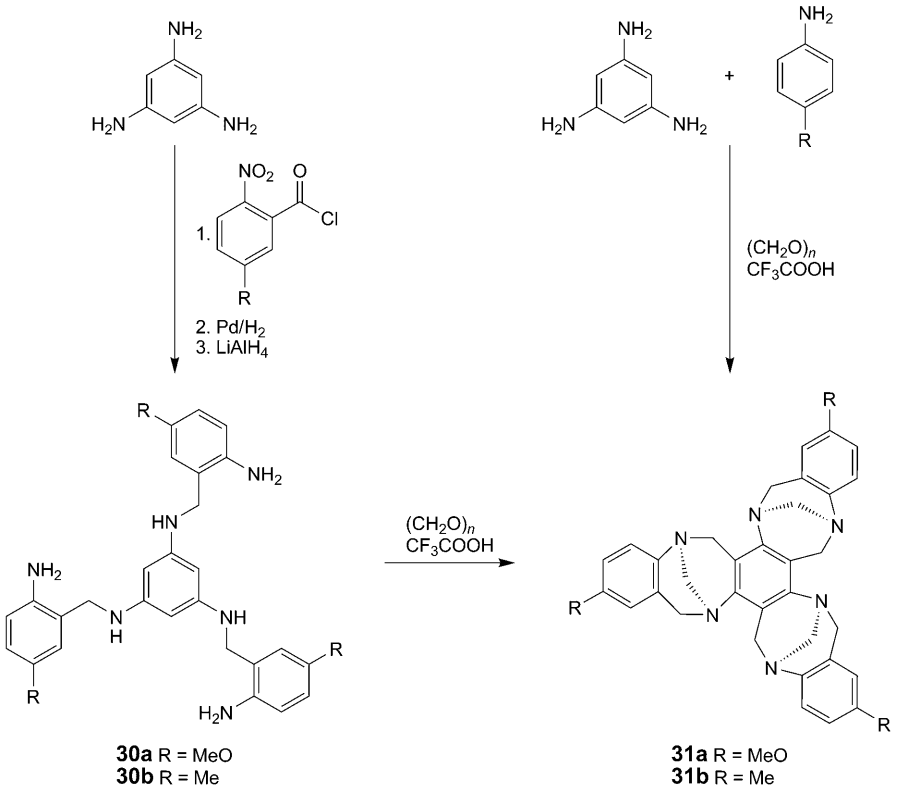
Fig. 5. *Space-filling presentations of* anti,syn-**29** (left) *and* syn,syn-**29** (right). Images generated based on the atom coordinates deposited with the *Cambridge Crystallographic Data Centre* (*CCDC*) as structures No. 284529 and 284530 [70]. H-Atoms as well as Cl, Br, and Me substituents are omitted for clarity.

It is worth mentioning that Cl-atoms primarily served to block one of the *ortho*-positions and, therefore, to exclude formation of other possible regioisomers. However, it turned out that these substituents also bring configurational stability: little or no interconversion was observed for all three diastereoisomers of **29** upon treatment with 3M HCl at temperatures up to 95° for 6 days. This is in striking contrast with the general ease of racemization of *Tröger*'s base derivatives, as well as with the facile interconversion of diastereoisomers of some other 'oligo *Tröger*'s bases' lacking substituents in *ortho* positions relative to the N-atom (see ref. cit. in [70]). At the same time, configurational stability of **29** is in perfect agreement with the high racemization barrier for **4a** bearing *o*-methyl substituents (see above).

Recently, an unprecedented 'tris-*Tröger*'s base' system with all three methanodibenzodiazocine units sharing a single benzene ring was reported (*Scheme 12*). In the crucial synthetic step, the treatment of a precursor **30a**,**b** (prepared from benzene-1,3,5-triamine in a three-step synthesis) afforded 'tris-*Tröger*'s bases' **31a**,**b** in 8–18% yield [71]. Rather strikingly, **31b** was also prepared by a direct one-step condensation between benzene-1,3,5-triamine and 4-methylaniline. In spite of the low yield (2% of **31b** isolated), this transformation is remarkable as a spectacular multicomponent reaction with a total of 13 participating molecules and 18 C–C and C–N bonds formed in a single synthetic step (*Scheme 12*).

In acidic solution, **31a** exists as an equilibrium mixture of *calix*-**31a** and *throne*-**31a** (3:97). Under neutral conditions, both diastereoisomers are stable: they were separated by column chromatography and identified with the aid of single-crystal XRD analysis (*Fig. 6*). *Calix*-**31a** is particularly attractive since it can be viewed as a chiral cavitand with an estimated cavity volume of *ca.* 78 $Å^3$ and should be capable to accommodate small guest molecules.

Scheme 12. *Synthesis of 'Tris-*Tröger*'s Bases'* **31a**,**b**



Perhaps the most elegant and at the same time the most fundamentally important molecular design using *Tröger*'s base motif is the 'molecular torsion balance' (*Scheme 13*) originally designed by *Wilcox* and co-workers [38] and further developed by *Diederich* and co-workers [72]. Small differences in free energy between 'folded' and 'unfolded' conformers of (±)-**32** (*Scheme 13*) can be measured by NMR experiments and used for the quantification of weak forces such as aromatic edge-to-face interactions [38], CH–π interactions [38], or weak attractions between 'organic' F-atoms and an amide group [72]. Characterization of such forces is of primary importance for the understanding of protein folding and for the rational design of enzyme inhibitors. It is therefore unsurprising that the groups of *Wilcox* and *Diederich* have revisited this concept very recently. An improved design of *Wilcox*'s molecular balance offers solubility in H_2O and allows to avoid corrections for the change of dipole moment between folded and unfolded conformers [40]. The last generation of *Diederich*'s molecular balance, (±)-**33**–(±)-**36** (*Scheme 14*), comprising an indole fragment required considerable efforts (up to 21 synthetic steps from commercially available materials) but in return provided a convincing evidence for the existence of attractive orthogonal dipolar interactions between a C_{sp^2}–F bond and an amide C=O

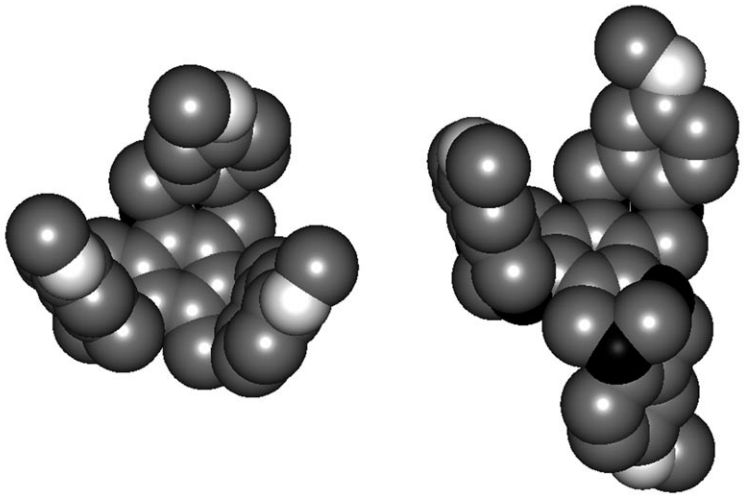
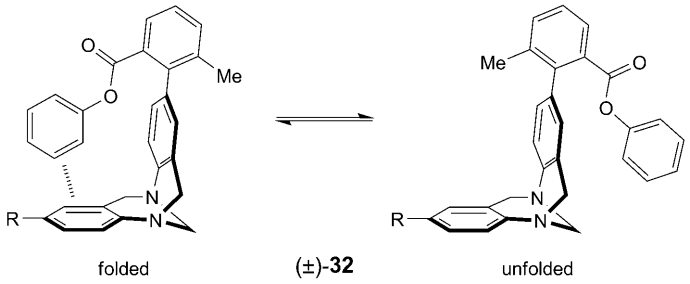


Fig. 6. *Space-filling presentations of* calix-**31a** (left) *and* throne-**31a** (right). Images generated based on the atom coordinates deposited with the *CCDC* as structures No. 640697 and 640698 [71]. H-Atoms are omitted for clarity.

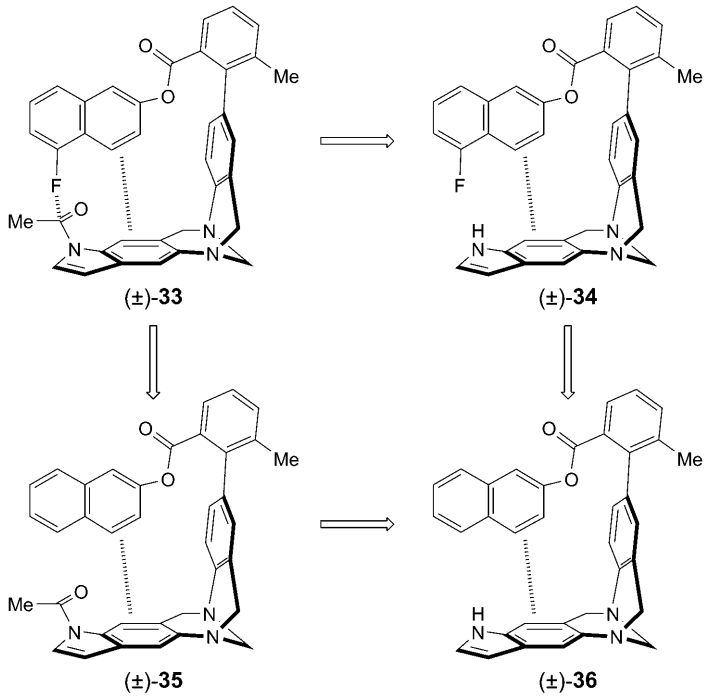
group [73]. Since F-atoms have become widespread and important components of many drugs and drug candidates, this type of interactions represents an important tool to tune protein–ligand interactions in medicinal-chemistry research [74].

Scheme 13. *Concept of the Molecular Torsion Balance Introduced by* Wilcox *for the Quantification of Aromatic Face-to-Edge Interactions*



New ideas exploring the unusual V-shaped geometry of *Tröger*'s base framework continue to emerge. Thus, *Bew et al.* have suggested it as a conformationally restricted scaffold to induce a *ca.* 90° turn in synthetic peptides [29]. The structural motif of *Tröger*'s base was incorporated into a phosphine/thioether chelating ligand (±)-**37** that was reacted with $[Cu(MeCN)_4]PF_6$ to quantitatively produce a dimeric metallomacrocycle **38** with tetrahedrally coordinated Cu^I. Upon addition of pyridine, the weaker coordination bond between Cu and S was cleaved, while the stronger Cu–P bond was retained to give an expanded dimeric macrocycle **39** (*Scheme 15*). In a reaction between (±)-**37** and a Rh^I complex with preferred square planar geometry, a more

Scheme 14. *Double-Mutant Cycle of* Diederich *Molecular Torsion Balances for the Determination of the Free Energy of Interactions between an F-Atom and an Amido Group*

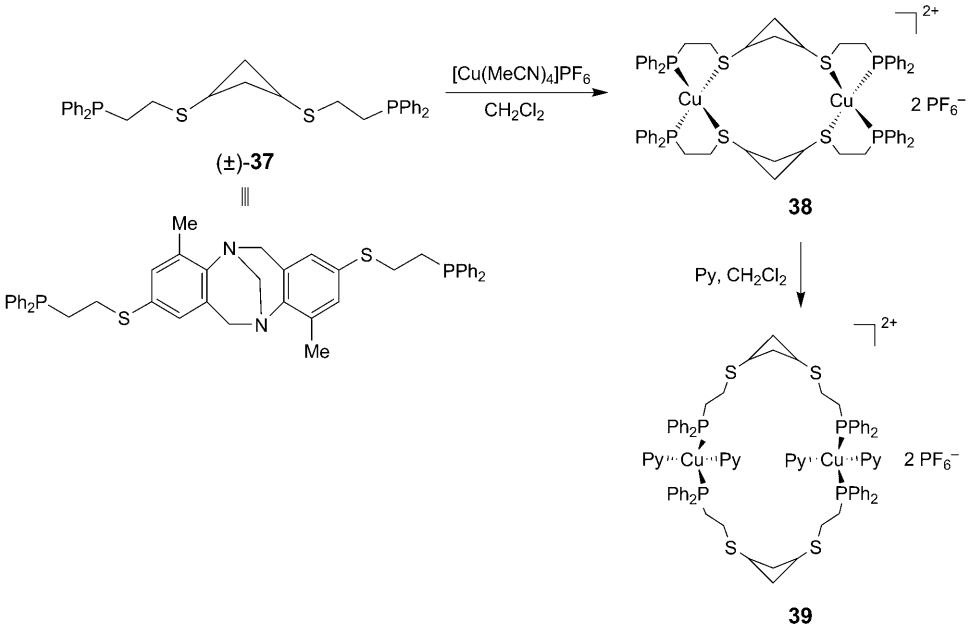


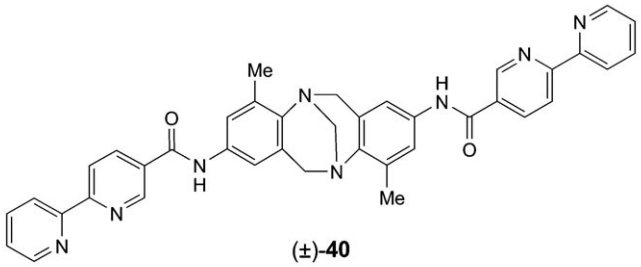
complicated behavior was observed, namely, the formation of a mixture of di- and trimeric metallomacrocycles [75].

Another class of conceptually new ligands for the metal-mediated self-assembly comprise the *Tröger*'s base scaffold expanded with 2,2′-bipyridine fragments [24][76]. Upon the coordination of two bis(bipyridine) ligands (±)-**40** around Ag^+ cations, self-assembly of a double-stranded helical complex $[Ag_2(\mathbf{40})_2]^{2+}$ was observed, as confirmed by ESI-MS. Interestingly, the use of *racemic* rather than enantiomerically pure ligands allows one to take more advantage of the chirality of the *Tröger*'s base core and gain deeper insight into the self-assembly process. As the example of $[Ag_2(\mathbf{40})_2]^{2+}$ shows (*Fig. 7*), formation of different homoleptic complexes is possible even from the enantiomerically pure ligand. Starting from the racemic ligand, also heteroleptic complexes (combining ligands with opposite configuration within one and the same complex) must be considered. However, self-assembly of (±)-**40** with Ag^+ gave a single, homoleptic complex. Its relative configuration was tentatively assigned as *Λ*,*Λ*-$[Ag_2\{(S,S)\text{-}\mathbf{40}\}_2]^{2+}$/*Δ*,*Δ*-$[Ag_2\{(S,S)\text{-}\mathbf{40}\}_2]^{2+}$ on the basis of ROESY NMR experiments and energies of PM3-optimized diastereoisomers but was not unambiguously confirmed [76].

In the case of Fe^{2+} cations with preferred octahedral coordination, triple-stranded homoleptic helicates $[Fe_2(\mathbf{41})_3]^{4+}$ were formed from the ligand (±)-**41**, although their relative configuration was not assigned (*Fig. 8*). Interestingly, self-assembly proved to

Scheme 15. *Formation of Metallomacrocycles from the Ligand (±)-***37**





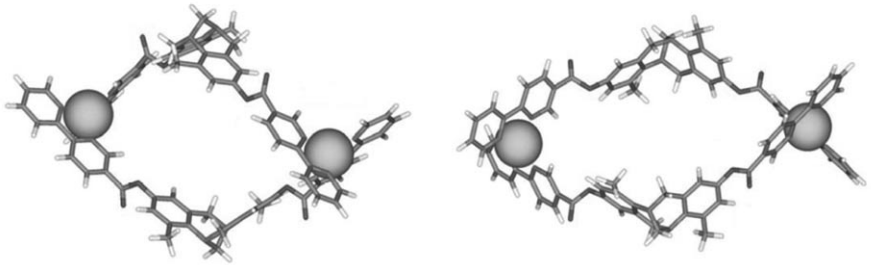


Fig. 7. *Structure of the ligand (±)-***40** *and PM3-optimized geometry of double-stranded diastereoisomeric complexes Δ,Δ-[Ag2{(S,S)-***40***}2]2+* (left) *and Λ,Λ-[Ag2{(S,S)-***40***}2]2+* (right). Reproduced from [76].

be very sensitive to the electronic structure of the coordinating metal cation. Thus, self-assembly of triple-stranded helicates from (±)-**41** and Zn^{2+} was not diastereoselective, and neither was self-assembly of similar ligands bearing catechol (= benzene-1,2-diol) end groups around Ti^{IV} ions [77]. Furthermore, the formation of metallohelicates from (±)-**40** and (±)-**41** is interesting from at least two standpoints. Firstly, this self-assembly shows great preference for a single stereoisomer in an *a priori* very complex situation. Secondly, double- and in particular triple-stranded helicates form a relatively large, chiral cavity that makes them attractive 'molecular containers'.

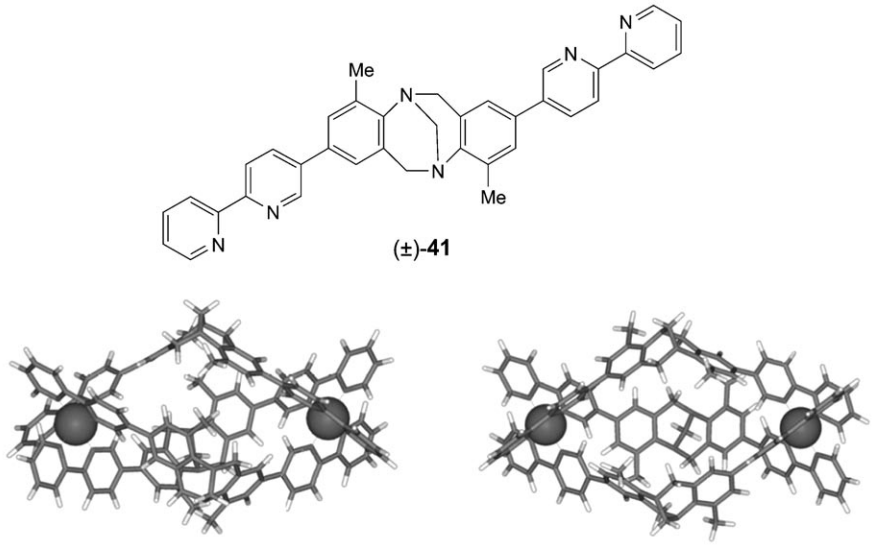


Fig. 8. *Structure of the ligand (±)-***41** *and PM3-optimized geometry of triple-stranded diastereoisomeric complexes Δ,Δ-[Fe$_2${(S,S)-***41***}$_3$]$^{4+}$* (left) *and Λ,Λ-[Fe$_2${(S,S)-***41***}$_3$]$^{4+}$* (right). Reproduced from [76].

Very recently, the first examples of *Tröger*'s base derivatives designed as materials for optical and optoelectronic applications have been suggested. Thus, bis-pyridinium derivative (±)-**42** demonstrated unusually efficient aggregation-induced light emission in the solid state, while luminescence in solution was quenched [78]. This behavior is strikingly different to that of the planar analog **43** in which the V-shaped *Tröger*'s base scaffold is replaced with a flat 1,4-phenylene moiety. The solid-state fluorescence was thus attributed to the crystal-packing features that result from the V-shape of (±)-**42**. In addition, we have recently reported on the synthesis and optical properties of similarly designed bi-chromophoric systems with two *para*-nitrophenyl or benzothiazolium acceptors, *i.e.*, of (±)-**44** and (±)-**45** (*Fig. 9*) [79]. The combination of donor–π-acceptor design and the inherent chirality of the molecule may prove promising in the design of novel noncentrosymmetric materials for NLO (nonlinear optics) applications. In preliminary studies of quadratic (second-order) NLO properties, (±)-**44** and (±)-**45** showed encouraging values of first molecular hyperpolarizability (β) in solution [80]. Very recently, fluorene derivatives such as (±)-**46** were reported to show efficient photo- and electroluminescence. Organic light-emitting diodes (OLED) fabricated

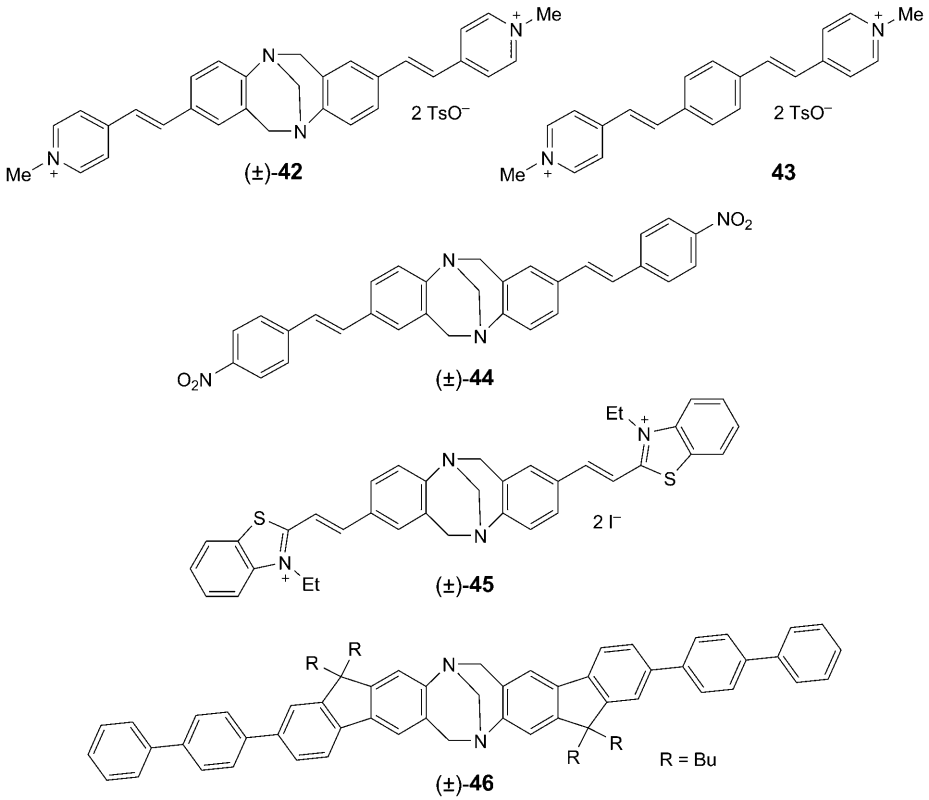


Fig. 9. Tröger*'s base analogues comprising two chromophore moieties*

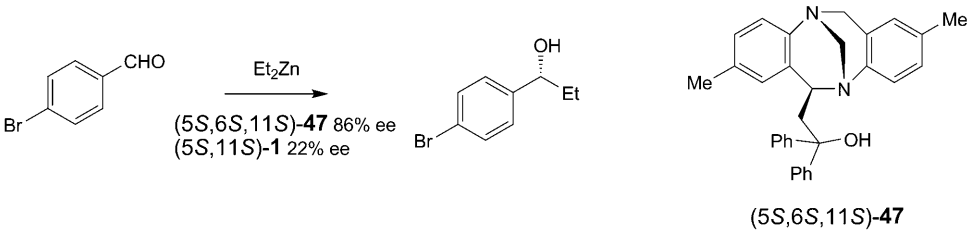
with (±)-**46** as emitters demonstrated high brightness, high efficiency, and low turn-on voltage [81].

Chirality is an important property of *Tröger*'s base, but most of the reported studies deal with racemic derivatives. It does not necessarily mean that chirality is not explored, as is clearly demonstrated by the example of diastereoselective self-assembly of metallohelicates (see above) or by the use of racemic *Tröger*'s base as a standard probe for the efficiency of newly designed CSP and for various chromatography processes (for representative recent examples, see [82]). Nonetheless, enantiomerically pure *Tröger*'s base analogues have many potential applications, which are only scarcely explored. Thus, *Wilen* and co-workers have used enantiomerically pure *Tröger*'s base (+)-(*S*,*S*)-**1** as a chiral solvating agent and observed enantiomer discrimination in the ^{1}H-NMR spectra of racemic alcohols [57]. *Demeunynck* and co-workers reported on a remarkable enantioselective interaction of the acridine analogue (+)-**22** of *Tröger*'s base (see *Scheme 3*) with calf-thymus DNA, presumably, *via* minor-groove binding of the V-shaped motif rather than by the intercalation of the planar acridine moiety [34].

Intuitively, one would expect considerable interest to *Tröger*'s base analogues in the field of asymmetric catalysis, but in fact such applications are rather limited. Thus,

enantiomerically pure *Tröger*'s base demonstrated moderate asymmetric induction as an additive in the 1,4-addition of aryllithium reagents to α,β-unsaturated esters (57% ee) [83], in heterogeneous hydrogenation of ethyl pyruvate (65% ee) [84], and more recently, in the aziridination of chalcones (up to 67% ee) [85]. In spite of relatively modest asymmetric induction, the results of these scattered studies should be viewed as a promising initial lead, rather than as an ultimate limit. In fact, there is no reason why *Tröger*'s base should be the best candidate for applications in asymmetric catalysis since it is an arbitrarily chosen (due to its commercial availability in the enantiomerically pure form) derivative of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine lacking any additional functional group. Actually, the only documented attempt to build a rationally designed ligand for catalytic applications, *i.e.*, (5*S*,6*S*,11*S*)-**47**, resulted in a rather encouraging (up to 86% ee) asymmetric induction in the addition of Et_2Zn to aromatic aldehydes (*Scheme 16*; *cf.* 22% ee with (*S*,*S*)-**1**) [86].

Scheme 16. Tröger*'s Base Derivatives Catalyze the Addition of Et_2Zn to Aromatic Aldehydes*



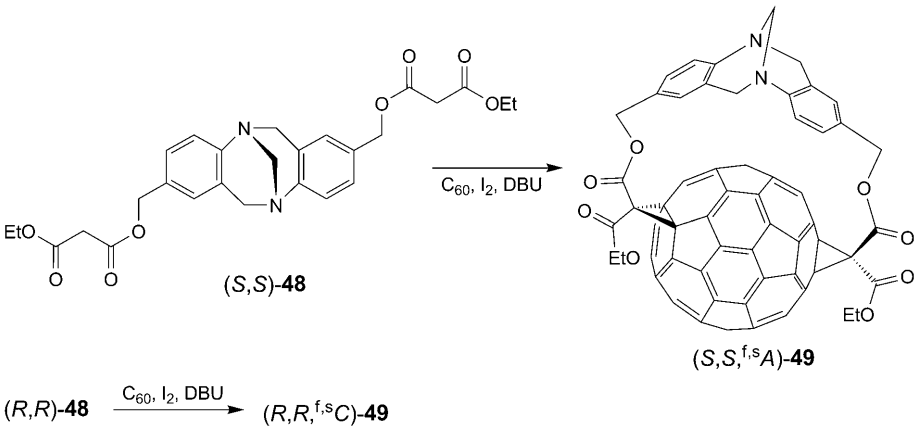
(5*S*,6*S*,11*S*)-**47**

An elegant application of *Tröger*'s base as a covalent template in the functionalization of fullerenes has been reported by the group of *Diederich* [19][66]. Two reactive malonate groups were installed at different positions of the rigid *Tröger*'s base scaffold that was acting as a 'tether'. In a subsequent 'tether-directed' double *Bingel* cyclopropanation of C_{60}, regio- and stereoselectivity is governed by the length and the geometry of the relatively rigid tether. Depending on the distance between reactive groups, bis-adducts of C_{60} with different addition patterns were prepared, and each time only one out of the multiple, theoretically possible regioisomers was obtained. Even more remarkably, addition of enantiomerically pure bis-malonates to C_{60} proceeds with perfect diastereoselectivity and afforded enantiomerically pure fullerene derivatives with inherently chiral *trans*-2 addition patterns: (*R*,*R*)-**48** gave exclusively (*R*,*R*,^{f,s}*C*)-**49**, and (*S*,*S*)-**48** produced exclusively (*S*,*S*,^{f,s}*A*)-**49** (*Scheme 17*)[4]). This very high asymmetric induction is particularly noteworthy taking into account the very large distance between the two reactive centers spanned by a chiral tether. An interesting aspect of the described functionalization of fullerenes is an efficient chirality transfer from the *Tröger*'s base framework to the extended helix-shaped fullerene chromophores that display *Cotton* effect over a remarkable range of wavelengths (up to 750 nm; *Fig. 10*). A similar strategy allowed the regioselective preparation of bis- and tetrakis-cyclopropanated adducts of C_{70} [88]. Independently, tether-directed double

[4]) Configurational descriptors $^{f,s}C/^{f,s}A$ (f = fullerene, s = systematic (numbering), *C* = clockwise, *A* = anticlockwise) are used to express the chirality sense of fullerenes and their derivatives, similarly to descriptors *R*/*S* for a stereogenic center, or *P*/*M* for a helix. For detailed explanation, see [87].

Bingel cyclopropanation of C_{60} with various *Tröger*'s base analogues was studied by the group of *Saigo* [46]. However, only racemic tethers were used in this study.

Scheme 17. Tröger's *Base Analogues in the 'Tether-Directed' Functionalization of* C_{60}. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.



There are few reports on the attempted applications of *Tröger*'s base for chiral separations. Thus, molecularly imprinted polymers (MIP) were prepared by copolymerization of methacrylic acid (=2-methylprop-2-enoic acid) and ethylene glycol dimethacrylate (=ethane-1,2-diyl bis(2-methylprop-2-enoate) in the presence of enantiomerically pure *Tröger*'s base followed by removal of template. The resulting MIP showed high enantioselectivity in the separation of *Tröger*'s base by HPLC [89] or capillary liquid chromatography/electrochromatography [90]. Chiral recognition of an analyte by MIP takes place in chiral cavities created during the polymerization process and featuring the shape of the template used for the imprinting. Since the general shape of the molecule remains similar for different *Tröger*'s base analogues, one may expect considerable cross-selectivity of so prepared MIP towards other *Tröger*'s base analogues. This can be a viable alternative to HPLC on chiral stationary phases for the separation of synthetically valuable *Tröger*'s base derivatives, and possibly of other chiral molecules.

Conclusions and Perspectives. – Personally, I am captivated by the historical progress of *Tröger*'s base from an ill-defined, accidentally prepared substance through an academic curiosity to a 'fascinating molecule' that shows a true renaissance in recent years. Review of the recent literature devoted to the chemistry of *Tröger*'s base analogues shows a number of remarkable developments. Advances in synthetic methods provide access to rather sophisticated *Tröger*'s base analogues, such as V-shaped synthetic receptors or 'molecular torsion balances' for the quantification of weak molecular forces. It is almost certain that a growing number of applications and uses of this unique molecular scaffold will arise.

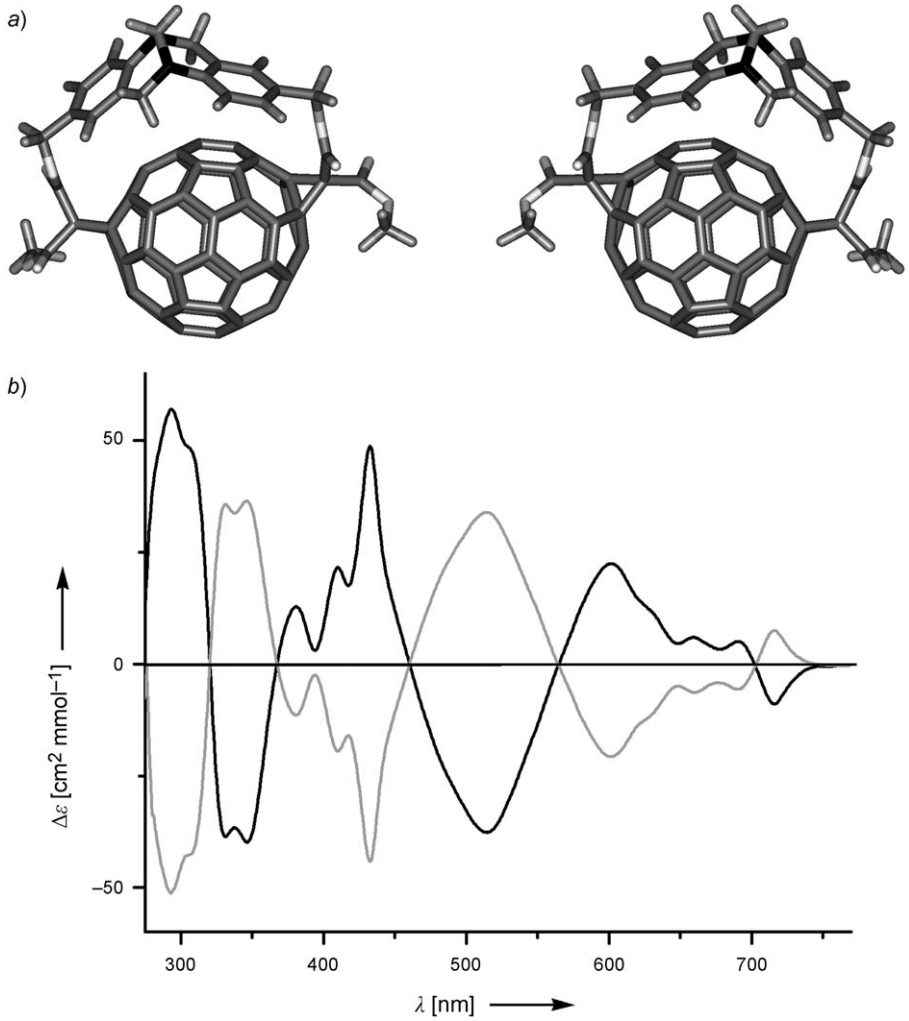


Fig. 10. a) *PM3-Optimized geometries of two enantiomeric fullerene bis-adducts with inherently chiral* trans*-2 addition pattern: (*S,S,^{fs}A*)*-**49** (left) *and (*R,R,^{fs}C*)*-**49** (right). b) *CD Spectra of (*S,S,^{fs}A*)*-**49** (black) *and (*R,R,^{fs}C*)*-**49** (grey). Reproduced from [66].

Thus – in view of emerging examples of metallomacrocycles and metallohelicates – self-assembly of even more complex supramolecular structures, such as capsules, cages, synthetic nanotubes, or three-dimensional metalorganic frameworks appears to be a promising field. Recently pioneered applications of the *Tröger*'s base skeleton in charge-transfer push-pull chromophores will likely result in novel solid-state fluorescent or NLO-active materials. Current interest in 'oligo *Tröger*'s bases' is catalyzed by the possibility to create molecular clips and clefts with expanded concave surfaces, and the first examples of chiral cavitands will probably be followed by further ones.

Enantiomerically pure derivatives of *Tröger*'s base deserve particular attention, since they will allow to fully explore the chirality of this molecule. A stumbling block in this research was the poor availability of the optical antipodes. However, efficient methods for the enantiomer separation of functionalized *Tröger*'s base analogues are becoming available. On the other hand, configurationally stable *Tröger*'s base derivatives were recently discovered, and the origin of their stability towards the acid-promoted racemization is well understood. Easier availability of enantiomerically pure *Tröger*'s base analogues, in combination with powerful synthetic methodologies for many sophisticated derivatives, will likely promote their application in asymmetric catalysis and organocatalysis. *Tröger*'s base has already been tried as a chiral solvating agent, but derivatives bearing further functional groups capable of more efficient recognition of analytes appear even more promising. And what about their uses as chiral derivatization agents for analysis and/or separations of other racemic mixtures? Finally, self-assembly of enantiomerically pure *Tröger*'s base analogues into container-like molecules might open, in the long term, perspectives for new chiral separation techniques. The old molecule keeps on searching for a new job.

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