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General Protocols for the Synthesis of C_2-Symmetric and Asymmetric 2,8-Disubstituted Analogues of Tröger's Base via Efficient Bromine−Lithium Exchanges of 2,8-Dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

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Methods for facile synthesis of symmetric and unsymmetric functionalized analogues of Tröger's base were developed with use of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) as the starting material. C_2-symmetric 2,8-disubstituted analogues of Tröger's base (**4a**−**f**) were synthesized via double bromine−lithium exchange of **2** followed by quench with electrophiles. Desymmetrization via single bromine−lithium exchange of **2**, followed by quench with electrophiles, afforded asymmetric analogues of Tröger's base (**6a**−**g**). Further reaction of 2-bromo-8-(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**6b**) produced **7a**−**c** via single bromine−lithium exchange and subsequent quench with electrophiles.

Introduction

Tröger's base,[1] 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**1**), is a chiral rigid molecule with a concave shape (Figure 1). Analogues of Tröger's base have been used as hosts in recognition phenomena,[2] DNA intercalation,[3] enzyme inhibition[4] and as ligands for asymmetric catalysis.[5,6] Although qualified for extensive usage in many fields of chemistry and related sciences, the number of synthesized analogues of Tröger's base has hitherto been limited. The Tröger's base condensation reaction of an aniline with formaldehyde, or its equivalent, under acidic conditions, precludes the presence of acid-sensitive functional groups. Anilines unsubstituted in the 4-position do not form analogues of Tröger's base in the condensation.[7] More importantly, the Tröger's base condensation reaction requires the aniline to be substituted with an electron-donating group.[8] Only a few exceptions to this latter prerequisite have been reported.[9,10] Therefore general strategies for the synthesis of analogues of Tröger's base are lacking.

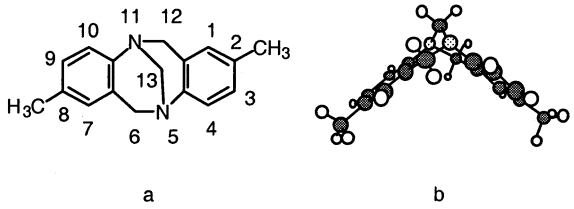

FIGURE 1. (a) ChemDraw representation of Tröger's base (**1**). (b) Chem 3D representation of the energy-minimized (Merck Molecular Force Field) Tröger's base.

Recently, we established conditions for anilines substituted with electron-withdrawing halogens in the 4-position to undergo the Tröger's base condensation reaction to afford 2,8-dihalo-substituted analogues of Tröger's base in good yields.[11] To gain access to otherwise inaccessible analogues of Tröger's base, we reckoned that bromine−lithium exchange would provide the most facile and general protocol for the preparation of substituted analogues of Tröger's base. By exploiting the already fixed positions of the bromines of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**, Scheme 1), functional groups could be regioselectively introduced into the 2- and 8-positions of **2** via double bromine−lithium exchange to the dilithiated analogue of Tröger's base **3** and subsequent quench with electrophiles. We herein report a highly general protocol for the preparation of C_2-symmetric 2,8-difunctionalized analogues of Tröger's base (**4a**−**f**) via efficient double bromine−lithium exchange of **2**. Single bromine−lithium exchange should, in addition, provide access to asymmetric functionalized analogues of Tröger's base by desymmetrization of the dissymmetric 2,8-dibromo analogue of Tröger's base **2**.

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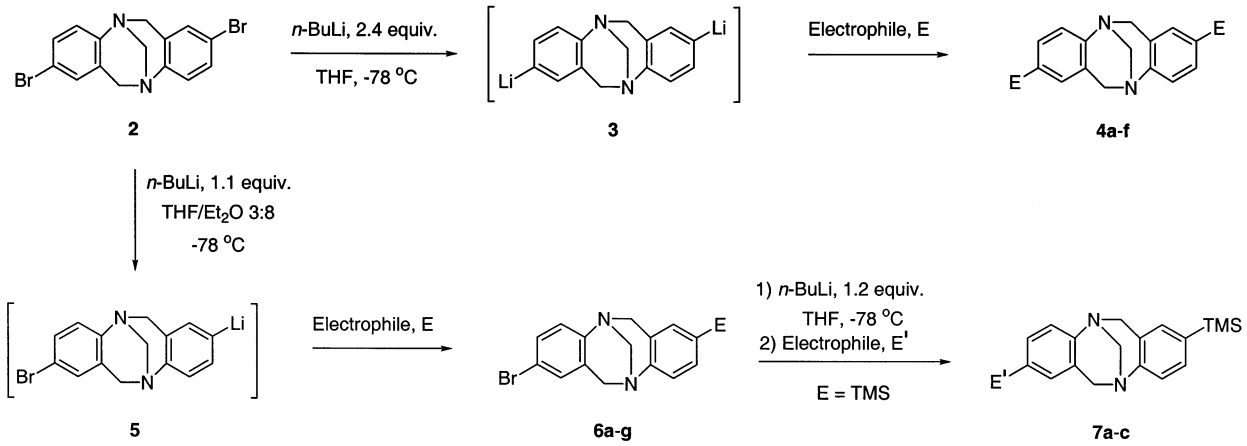
SCHEME 1. Overall Protocol for the Synthesis of C_2-Symmetric and Asymmetric Analogues of Tröger's Base



In general, when having access to C_2-symmetric starting materials, desymmetrization has proven an efficient means of synthesizing asymmetric compounds.[12,13] Asymmetric analogues are important because they would allow for the construction of even larger libraries of Tröger's base related building blocks with differentiated termini. Asymmetric analogues of Tröger's base have hitherto been almost inaccessible due to the lack of efficient synthetic methods. Attempts to prepare asymmetric analogues of Tröger's base by using two differently substituted anilines in the Tröger's base condensation reaction would give rise to a more or less statistical mixture of three different analogues. In special cases, however, asymmetrical analogues have been synthesized by condensing two different anilines tethered with one methylene unit.[8] This method allowed for the synthesis of asymmetric analogues of Tröger's base with an electron-withdrawing group in only one of the aniline rings.

Facile access to asymmetric analogues of Tröger's base would require efficient single bromine−lithium exchange of **2** without concomitant double bromine−lithium exchange. Controlling single bromine−lithium exchange of 2,5-dibromopyrrole has been reported to be trivial.[14,15] However, exclusive single bromine−lithium exchange of 2,6-dibromopyridine was only recently reported to proceed, by proper choice of solvent.[16] In the present case, the dilithiated compound **3** (Scheme 1) would carry one negative charge in each of two discrete aromatic ring systems. Hence, it might be expected that the balance of controlling exclusive formation of the monolithiated analogue of Tröger's base **5** (Scheme 1) would be rather delicate because of the relatively low difference in stability between **3** and **5**, at least compared to the di- and monoanion of the above-mentioned pyridine in which the two repulsive charges of the dianion are localized in proximity to each other. This would be expected to allow for a more efficient repulsive interaction between the charges, resulting in a larger difference in energy between the di- and monolithiated species.

TABLE 1. Optimization of the Double Bromine−Lithium Exchange of 2 According to the Reaction in Scheme 1 with H_2O as the Electrophile

reaction time[a] (min)	0	2	5	10	15	20	25	30
yield[b] (%) of **4a**	82	89	88	85	85	87	76	67

[a] In each case the *n*-BuLi was added over 5 min. [b] Isolated yield of chromatographically pure products.

Despite the anticipated difficulty in selectively generating the monolithiated species **5**, we herein report a highly general method for the synthesis of asymmetric functionalized analogues of Tröger's base (**6a**−**g**, **7a**−**c**) via efficient single bromine−lithium exchange of **2** (Scheme 1).

Results and Discussion

Optimization of the Double Bromine−Lithium Exchange. Initially the equivalents of *n*-BuLi required to obtain complete double bromine−lithium exchange of **2** were determined by isolating the products obtained after quenching the reaction with H_2O.

With use of 1.1 equiv of *n*-BuLi per bromo atom, 35% of the expected 2,8-dihydro analogue of Tröger's base, compound **4a** (Table 2), was isolated along with 15% of the 2-bromo-8-hydro analogue **6a** (Table 4), resulting from single lithiation, when using not optimized reaction conditions (Scheme 1). The use of 1.2 equiv of *n*-BuLi per bromo atom produced solely **4a** in 77% yield. Using additional amounts of *n*-BuLi was not considered as deprotonation, an undesired side reaction, of one of the benzylic protons of Tröger's base has been reported under comparable reaction conditions.[17] The reaction was optimized with respect to the reaction time of the double bromine−lithium exchange by isolating the products resulting from different reaction times (Table 1). In the interval 2−20 min the extent of the double bromine−lithium exchange seemed more or less equal as judged by the isolated yields of product. However, after 5 min of reaction time the yield by crude product NMR was above 98% and the isolated yield was 88% (corresponding to 94% for each bromine−lithium exchange). Using 2 min

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TABLE 2. Introduction of Electrophiles via Double Bromine−Lithium Exchange of 2 According to the Reaction in Scheme 1

entry	electrophile	E	product	yield[a] (%)
1	H_2O	H	**4a**	88
2	TMSCl	TMS	**4b**	89
3	DMF	CHO	**4c**	54[b]
4	PhCHO	PhCH(OH)	**4d**	58
5	CO_2	CO_2H	**4e**	65[c,d]
6	Bu_3SnCl	Bu_3Sn	**4f**	71
7	TsCN	CN		d,e
8	BnBr	Bn		f

[a] Isolated yields of analytically pure products. [b] Isolated yield of chromatographically pure product. [c] In 1 mmol scale, isolated as the mono-HCl salt. [d] Using reverse addition for the quench with the electrophile. [e] 7% of impure product (by NMR, HRMS, and IR) was isolated. [f] 85% of 1,2-diphenylethane was isolated.

TABLE 3. Optimization of the Single Bromine−Lithium Exchange of 2 According to the Reaction in Scheme 1 with H_2O as the Electrophile

solvent	equiv of *n*-BuLi	yield[a] (%) of **6a**
THF	1.3	57
THF	1.2	71
THF	1.05	59
dichloromethane	1.2	b
THF/Et_2O 3:8	1.2	82[c]
THF/Et_2O 3:8	1.1	82[c]

[a] Isolated yield of chromatographically pure products. [b] Unreacted starting material. [c] Isolated yields of analytically pure products.

of reaction time produced small amounts of **6a** resulting from incomplete dilithiation. Reaction times of 10 min and more invariably allowed for the isolation and characterization of different amounts of mono- and dibutylated analogues of Tröger's base, presumably resulting from Wurtz couplings between the formed *n*-butyl bromide and the correspondingly formed lithiated analogue of Tröger's base. In conclusion, using 5 min for the double bromine−lithium exchange was found to be the optimal conditions as lesser reaction times lead to incomplete dilithiation. Prolonged reaction times resulted in the formation of undesired byproducts by consumption of the formed dilithiated analogue **3**.

Synthesis of C_2-Symmetric Analogues. The optimized conditions for the double bromine−lithium exchange were applied with different electrophiles in order to investigate the generality of the method and to synthesize new, previously inaccessible, analogues of Tröger's base (Table 2).

The yields were generally good: 54%-89%, corresponding to 73%-94% for each bromine−lithium exchange, with the exceptions being entries 7 and 8. In some cases minute amounts of products resulting from monodebrominated products were observed, presumably resulting from monohydrolysis of the dilithiated **3** prior to the intended double quench with electrophiles. The 2,8-dihydro analogue of Tröger's base, compound **4a**, entry 1, was the only compound previously reported,[18] synthesized in four steps in an overall yield of ca. 19%. In comparison, the present methodology allowed for its synthesis in only two steps from 4-bromoaniline in an overall yield of 55%. The bis(trimethylsilyl) compound **4b** was formed in excellent yield and can be further derivatized by either ipso-displacement[19] or transition metal mediated cross-coupling[20] at a later stage if desired. In the least favorable yields, synthesis of the diformyl (**4c**) and the bis(hydroxyphenylmethyl) (**4d**) analogues, entries 3 and 4, no byproducts were produced in significant amounts. The mixture of diastereomers constituting **4d** was not separated by column chromatography. The 2,8-dicarboxyl analogue of Tröger's base **4e**, entry 5, was synthesized by adding the solution of **3** in THF to a saturated solution of CO_2 in THF at −78 °C; reverse addition. The 2,8-bis(tributylstannyl) analogue **4f**, entry 6, is seemingly quite stable to air, and might prove efficient for introducing aromatic and heteroaromatic substituents into the Tröger's base core via Stille cross-coupling. Attempts to synthesize the analogue with two cyano groups, entry 7, by the general procedure of adding the electrophile to the reaction mixture resulted in a complicated mixture. In situ generation of the dilithiated compound **3** in the presence of the electrophile by addition of *n*-BuLi to a solution of **2** and tosyl cyanide was also unsuccessful. Therefore reverse addition as described for the preparation of **4e** above was attempted, which nevertheless resulted in an unacceptable poor yield of 2,8-dicyano-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, the identity of which was established by NMR, HRMS, and IR. With benzyl bromide as an electrophile, entry 8, a complicated mixture resulted and the only major compound isolated was 1,2-diphenylethane (85% calculated from benzyl bromide). This compound was presumably formed by an initial bromine−lithium exchange of benzyl bromide and subsequent reaction (Wurtz coupling) of the benzyllithium with benzyl bromide that was in excess. In this case the bromine−lithium exchange occurs faster than the desired electrophilic reaction. Using benzyl chloride as the electrophile likewise failed to produce the desired compound. To prevent the bromine−lithium exchange from occurring prior to the electrophilic reaction, it was considered worthwhile examining the reaction with use of the corresponding organomagnesium analogue of Tröger's base. All attempts to form this compound by bromine−magnesium exchange with isopropylmagnesium chloride, oxidative addition with magnesium, and transmetallation of **3** with $MgBr_2$ failed in our hands.

Optimization of the Single Bromine−Lithium Exchange. To perform efficient single bromine−lithium exchange of **2**, the effects on the yield of varying the equivalents of *n*-BuLi and the solvent used were examined by isolating the 2-bromo-8-hydro analogue **6a** after quenching the reaction with H_2O (Table 3).

The optimal conditions for the single bromine−lithium exchange resulting in **6a** were obtained with 1.1 equiv of *n*-BuLi in a solvent mixture of THF/diethyl ether 3:8. Neither the starting material **2** nor **4a** resulting from dilithiation was produced upon quench with water. When 1.2 equiv were used, a minute amount of **4a** was produced. Compound **2** was poorly soluble in Et_2O, but

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TABLE 4. Introduction of Electrophiles via Single Bromine−Lithium Exchange of 2 According to the Reaction in Scheme 1

entry	electrophile	E	product	yield[a] (%)
1	H_2O	H	**6a**	82
2	TMSCl	TMS	**6b**	68
3	DMF	CHO	**6c**	71
4	PhCHO	PhCH(OH)	**6d**	62[b]
5	CO_2	CO_2H	**6e**	61[c]
6	Bu_3SnCl	Bu_3Sn	**6f**	70
7	TsCN	CN	**6g**	60
8	BnBr	Bn		d

[a] Isolated yield of analytically pure products. [b] Isolated yield of chromatographically pure product. [c] In 1 mmol scale, isolated as the mono-HCl salt. Using reverse addition for the quench with the electrophile. [d] 42% of **2** and 19% of **6a** was isolated along with unidentified components.

readily soluble in the more polar THF. Most likely, the dilithiated compound **3** was better solvated in THF than in Et_2O, because THF is a more strongly coordinating solvent. We suggest that these differences in solubilizing effects result in a larger difference in energy between **3**and **5** in the solvent mixture THF/Et_2O 3:8 than in THF.

Synthesis of Asymmetric Analogues. The optimized conditions for single bromine−lithium exchange were applied with different electrophiles in order to investigate the generality of the method and to synthesize new, previously inaccessible, analogues of Tröger's base (Table 4).

The same electrophiles as for the synthesis of C_2 symmetrically substituted analogues of Tröger's base above were used. The yields were generally good: 60−82%, except again when using benzyl bromide, entry 8. In all cases the yields were above the statistical distribution yield of 50%. The only previously reported method for the synthesis of asymmetric analogues of Tröger's base was a three-step synthetic sequence giving yields ranging from 31% to 43%.[8] The overall yields of the present two-step procedure from 4-bromoaniline were in the range of 38% to 52%, on comparable 1 mmol scale. When quenching with the first electrophile, trimethylsilyl chloride (Table 4, entry 2), the starting material **2** and the doubly quenched bis(trimethylsilyl) analogue **4b** were produced, if the electrophile was added swiftly. Using 1 min for the addition eliminated this phenomenon, resulting in the desired 2-bromo-8-(trimethylsilyl) analogue **6b**. Consequently, as a general procedure, 1 min of addition time of the electrophile was used for quenching **5** as opposed to the quenching of **3**, which was carried out without delay. In addition, the synthesis of **6b** was carried out in two different scales as it was later used as a starting material, thereby the effect of the scale on the yield was examined. The difference in yield was considered insignificant, as the yield with 2 mmol of **2** was 70% compared to 68% when 0.5 mmol of **2** was used. The mixture of diastereomers constituting **6d** was not separated by column chromatography. The monocarboxylic analogue **6e**, entry 5, was prepared in the same manner as the dicarboxylic acid **4e** (Table 2, entry 5), namely by reverse addition. With tosyl cyanide as the electrophile the reaction proceeded without any apparent concomitant formation of products resulting from nucleophilic attack on the cyanide group once the product **6g** was formed. This was seemingly a difference from the quench of the dilithio intermediate **3** with tosyl cyanide, which led to a complicated mixture under similar reaction conditions, indicating a higher reactivity of **3** compared to **5**. In entry 8, using benzyl bromide as the electrophile resulted in the same initial bromine−lithium exchange of benzyl bromide as observed for the attempted synthesis of the 2,8-dibenzyl analogue of Tröger's base.

TABLE 5. Introduction of Electrophiles via Bromine−Lithium Exchange of 6b

entry	electrophile	E	product	yield[a] (%)
1	DMF	CHO	**7a**	63
2	PhCHO	PhCH(OH)	**7b**	84[b]
3	Bu_3SnCl	Bu_3Sn	**7c**	66

[a] Isolated yield of analytically pure products. [b] Isolated yield of chromatographically pure product.

Synthesis of Analogues with Two Different Electrophiles. To further demonstrate the versatility of the synthetic methods developed, a second bromine−lithium exchange was performed on the trimethylsilyl-substituted compound **6b**. Subsequent quench with electrophiles afforded previously inaccessible analogues of Tröger's base **7a**−**c** (Table 5).

This is thus a means of sequential bromine−lithium exchange allowing for the introduction of two different substituents, not bromine, into the Tröger's base core. With this methodology the yields were good, and comparable to those of the formation of **4a**−**f** and **6a**−**g**. The trimethylsilyl group not only tolerates the conditions of *n*-BuLi, it also allows for further reaction as described above.

Conclusion

In conclusion, using **2** as the starting material for introducing electrophiles via the organolithium intermediates **3** and **5** allows for the facile preparation of C_2-symmetric and asymmetric 2,8-di- and monofunctionalized (apart from bromine) analogues of Tröger's base in good to high yields. The method of single lithiation is also a simple means of desymmetrization of an important synthetic building block, giving access to important asymmetric analogues of Tröger's base difficult to synthesize by other means. With the sequential introduction of electrophiles these protocols allow for a high degree of choice of functional groups and differentiation of the termini. Therefore this is a very versatile pathway to complicated asymmetric analogues of Tröger's base. Seemingly, there is a pronounced difference in stability of the two species: dilithiated **3** and monolithiated **5**. This was observed as quench with tosyl cyanide proved inefficient for **3** whereas **5** reacted in the anticipated way. In addition, prolonged exposure of **2** to *n*-BuLi consumes the formed **3** by reaction with the formed *n*-BuBr to afford di- and monobutylated analogues of Tröger's base, observable after approximately 10 min. This was not the case with **5** after exposure of 30 min. It should be possible to further derivatize the synthesized new analogues of Tröger's base to allow for the synthesis of highly complex molecules for future usage in fields such as catalysis and supramolecular chemistry.

Experimental Section

General Methods. All reactions were performed under argon atmosphere using syringe-septum cap techniques and flame drying all glassware prior to use. TLC -analyses (Merck

60 F_{254} sheets) were visualized under UV light (254 nm). Column chromatography (CC) was performed with silica gel (Matrex 0.063−0.200 mm): diameter 6−6.5 cm; length 3.5−10 cm; and fraction sizes 25 mL. Melting points (mp) were determined in capillary tubes and were verified or corrected with standard substances. Chemical shifts are given in ppm relative to TMS, using the residual $CHCl_3$ peaks at 7.26 (^{1}H NMR) and 77.16 (^{13}C NMR) in $CDCl_3$ and the residual MeOH peaks at 3.31 (^{1}H NMR) and 49.00 (^{13}C NMR) in MeOH-d_4 as internal standards.[21] For the numbering of atoms see Figure 1. Assignments were accomplished by coupling constants and integrals. Elemental analyses were performed after CC or after crystallization if required (according to NMR) by A. Kolbe, Mikroanalytisches Laboratorium, Germany.

Materials. All chemicals were used as received from commercial sources without further purification unless otherwise stated, except for benzaldehyde and DMF which were distilled prior to use. Anhydrous THF and Et_2O were dried and stored over 3 Å molecular sieves. *n*-BuLi was titrated prior to use.[22] Compound **2** was prepared in scales of 40−80 mmol in 20−30% yields as previously described,[11] with the exception that TFA was added to the reaction mixture at 0 or −15 °C. All compounds were colorless crystals unless otherwise stated.

Double Bromine−Lithium Exchange of 2 Followed by Reaction with an Electrophile: General Procedure I. To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (**2**) (190 mg, 0.5 mmol) in THF (2 mL) at −78 °C was added dropwise 1.6 M *n*-BuLi in hexane (750 μL, 1.2 mmol) over 5 min. After 5 min the electrophile (1.5 mmol) was added swiftly and the reaction mixture was allowed to reach room temperature over approximately 30 min. The reaction was continued for 15 min additionally before water (2 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo and the crude product was purified by CC with EtOAc/heptane as the eluent.

6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine (4a). **4a** was prepared following general procedure I, using **2** (187 mg, 0.49 mmol), 1.6 M *n*-BuLi (740 μL, 1.18 mmol), and H_2O (2 mL) as the electrophile. CC (EtOAc (30%) in heptane) gave 97 mg (88%) of **4a**: mp 136.5−137.0 °C (lit.[18] mp 138−139 °C); R_f 0.22 (EtOAc (40%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, J = 16.5 Hz, 2H), 4.34 (s, 2H, H-13), 4.71 (d, J = 16.6 Hz, 2H), 6.89−7.00 (m, 4H), 7.12−7.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.8 (2C, C-6 and C-12), 66.9 (1C, C-13), 124.1 (2C), 125.3 (2C), 127.1 (2C), 127.5 (2C), 128.0 (2C), 148.2 (2C); HRMS (EI+) calcd for $C_{15}H_{14}N_2$ 222.1157, found 222.1158. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.93; H, 6.35; N, 12.47.

2,8-Bis(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (4b). **4b** was prepared following general procedure I, using **2** (189 mg, 0.50 mmol), 1.6 M *n*-BuLi (745 μL, 1.19 mmol), and trimethylsilyl chloride (152 mg, 1.4 mmol), which was dried over CaH_2 and freshly distilled under argon, as the electrophile. CC (EtOAc (20%) in heptane) gave 152 mg (89%) of **4b**: mp 172.5−173.0 °C; R_f 0.24 (EtOAc (20%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 18H, 6 × CH_3), 4.22 (d, J = 16.7 Hz, 2H), 4.32 (s, 2H, H-13), 4.73 (d, J = 16.6 Hz, 2H), 7.06 (d, J = 0.8 Hz, 2H, H-1 and H-7), 7.14 (d, J = 7.9 Hz, 2H, H-4 and H-10), 7.32 (dd, J = 7.9, 0.8 Hz, 2H, H-3 and H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.9 (6C, 6 × CH_3), 58.6 (2C, C-6 and C-12), 66.8 (1C, C-13), 124.7 (2C), 127.4 (2C), 132.3 (2C), 132.4 (2C), 135.7 (2C), 149.0 (2C); HRMS (FAB+) calcd for $C_{21}H_{30}N_2Si_2$ 366.1948, found 366.1941. Anal. Calcd for $C_{21}H_{30}N_2Si_2$: C, 68.79; H, 8.25; N, 7.64. Found: C, 68.86; H,8.22; N, 7.69.

2,8-Diformyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (4c). **4c** was prepared following general procedure I, using **2** (188 mg, 0.50 mmol), 1.6 M *n*-BuLi (743 μL, 1.19 mmol), and DMF (109 mg, 1.49 mmol) as the electrophile. CC (EtOAc (50%) in heptane) gave 74 mg (54%) of **4c**: mp 160.0−161.0 °C (EtOAc); R_f 0.12 (EtOAc (50%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (d, J = 15.8 Hz, 2H), 4.35 (s, 2H, H-13), 4.81 (d, J = 17.0 Hz, 2H), 7.27 (d, J = 9.2 Hz, 2H, H-4 and H-10), 7.48 (d, J = 1.6 Hz, 2H, H-1 and H-7), 7. 07 (dd, J = 8.3 Hz, J = 1.9 Hz, 2H, H-3 and H-9), 9.84 (s, 2H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.8 (2C, C-6 and C-12), 66.6 (1C, C-13), 125.8 (2C), 128.2 (2C), 129.2 (2C), 129.2 (2C), 132.7 (2C), 154.1 (2C), 191.1 (2C, CHO);. IR (KBr) 1683 cm^{-1} (C=O); HRMS (FAB+) calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1068. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.31; H, 4.99; N, 9.89.

2,8-Bis(hydroxyphenylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (4d). **4d** was prepared following general procedure I, using **2** (192 mg, 0.50 mmol), 1.6 M *n*-BuLi (756 μL, 1.21 mmol), and benzaldehyde (161 mg, 1.51 mmol) as the electrophile. CC (EtOAc (80%) in heptane) gave 127 mg (58%) of **4d** as a mixture of diastereomers: mp 83.0−84.5 °C; R_f 0.17 (EtOAc (40%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (br s, 2H), 3.83−3.99 (m, 4H), 4.27−4.40 (m, 2H), 5.59−6.62 (m, 2H), 6.67−7.31 (m, 16H); HRMS (EI+) calcd for $C_{29}H_{26}N_2O_2$ 434.1994, found 434.2002. Anal. Calcd for $C_{29}H_{26}N_2O_2$: C, 80.16; H, 6.03; N, 6.45. Found: C, 80.08; H, 5.95; N, 6.27.

2,8-Dicarboxyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine Hydro chloride (4e). To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) (380 mg, 1.0 mmol) in THF (4 mL) at −78 °C was added dropwise 1.3 M *n*-BuLi in hexane (1.85 mL, 2.4 mmol) over 5 min. After 5 min the reaction mixture was transferred into a saturated solution of CO_2 in THF at −78 °C by means of a pipet at −78 °C. After filtration the solid was dissolved in methanol and treated with a commercial solution of 4 M HCl in 1,4-dioxane (1 mL). Concentration in vacuo and crystallization from 2-propanol (28 mL) gave 201 mg (65%) of **4e**: decomposition above 220 °C (2-propanol); ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.62 (d, J = 17.1 Hz, 2H), 4.91 (s, 2H, H-13), 5.06 (d, J = 16.8 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H, H-3 and H-9 or H-4 and H-10), 7.85 (s, 2H, H-1 and H-7), 7.99 (d, J = 8.4 Hz, 2H, H-3 and H-9 or H-4 and H-10); ^{13}C NMR (75 MHz, MeOH-d_4) δ 58.2 (2C, C-6 and C-12), 67.9 (1C, C-13), 125.8 (2C), 126.5 (2C), 130.5 (2C), 131.2 (2C), 131.5 (2C), 145.4 (2C), 168.1 (2C, CO_2H); IR (KBr) 2966 (br, O−H) 1697 (C=O) cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{14}N_2O_2$ 310.0954, found 310.0965. Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 58.88; H, 4.36; N, 8.08. Found: C, 59.04; H, 4.42; N, 7.97.

2,8-Bis(tributylstannyl)-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine (4f). **4f** was prepared following general procedure I with the addition that the crude product was redissolved in Et_2O (10 mL) and stirred for 1 h with a 10% aqueous solution of KF. The white solid was filtered off and after separation of the two layers the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo and the crude product was purified by CC. Using **2** (193 mg, 0.51 mmol), 1.6 M *n*-BuLi (762 μL, 1.22 mmol), and tributylstannyl chloride (410 μL, 1.52 mmol) as the electrophile. CC (EtOAc (0−20%) in heptane) gave 289 mg (71%) of **4f** as a colorless oil: R_f 0.42 (EtOAc (20%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−0.89 (m, 18H, 6 × CH_3), 0.96−1.01 (m, 12H, 6 × CH_2), 1.27−1.34 (m, 12H, 6 × CH_2), 1.45−1.53 (m, 12H, 6 × CH_2), 4.19 (d, J = 16.7 Hz, 2H), 4.31 (s, 2H, H-13), 4.71 (d, 2H, J = 16.6 Hz), 6.97 (s, 2H, H-1 and H-7), 7.10 (d, 2H, J = 7.8 Hz, H-3 and H-9 or H-4 and H-10), 7.24 (d, 2H, J = 7.9 Hz, H-3 and H-9 or H-4 and H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7 (6C), 13.8 (6C), 27.5 (6C), 29.2 (6C), 58.6 (2C, C-6 and C-12), 66.8 (1C, C-13), 124.9 (2C), 127.8 (2C), 135.1 (2C), 135.4 (2C), 136.8 (2C), 148.3 (2C); HRMS (FAB+) calcd for $C_{39}H_{67}N_2{}^{120}Sn_2$ (M + H$^+$) 803.3348, found 803.3349. Anal. Calcd for

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$C_{39}H_{66}N_2Sn_2$: C, 58.52; H, 8.31; N, 3.50. Found: C, 58.45; H, 8.22; N, 3.56.

Single Bromine−Lithium Exchange of 2 Followed by Reaction with an Electrophile: General Procedure II. To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) (190 mg, 0.5 mmol) in THF (1.5 mL) and Et_2O (4 mL) at −78 °C was added dropwise 1.6 M *n*-BuLi in hexane (344 μL, 0.55 mmol) over 2 min. After 5 min the electrophile (0.75 mmol) was added dropwise over 1 min and the reaction mixture was allowed to reach room temperature over approximately 30 min. The reaction was continued for 15 min additionally before water (2 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo and the crude product was purified by CC with EtOAc/heptane as the eluent.

2-Bromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (6a). 6a was prepared following general procedure II, using **2** (188 mg, 0.49 mmol), 1.3 M *n*-BuLi (419 μL, 0.54 mmol), and H_2O (2 mL) as the electrophile. CC (EtOAc (40%) in heptane) gave 141 mg (82%) of **6a**: mp 123.5−125.0 °C; R_f 0.20 (EtOAc (40%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10−4.18 (m, 2H), 4.23−4.34 (m, 2H), 4.62−4.72 (m, 2H), 6.92−7.26 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.5 (1C), 58.8 (1C), 66.9 (1C), 116.6 (1C), 124.3(1C), 125.2 (1C), 126.9 (1C), 127.1 (1C), 127.64 (1C), 127.65 (1C), 129.8 (1C), 130.2 (1C), 130.5 (1C), 147.3 (1C), 147.8 (1C); HRMS (FAB+) calcd for $C_{15}H_{13}{}^{79}BrN_2$ 300.0262, found 300.0264. Anal. Calcd for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.35; N, 9.30. Found: C, 59.70; H, 4.40; N, 9.22.

2-Bromo-8-(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6b). 6b was prepared following general procedure II, using **2** (187 mg, 0.49 mmol), 1.3 M *n*-BuLi (416 μL, 0.54 mmol), and trimethylsilyl chloride (93 μL, 0.74 mmol) as the electrophile. CC (EtOAc (20%) in heptane) gave 125 mg (68%) of **6b**: mp 140.0−141.0 °C; R_f 0.12 (EtOAc (20%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 9H, 3 × CH_3), 4.12−4.20 (m, 2H), 4.23−4.35 (m, 2H), 4.63−4.74 (m, 2H), 7.02−7.06 (m, 3H), 7.10−7.13 (m, 1H), 7.25−7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.0 (3C,-CH_3), 58.4 (1C), 58.8 (1C), 66.8 (1C), 116.6 (1C), 124.5 (1C), 126.9 (1C), 127.0 (1C), 129.8 (1C), 130.3 (1C), 130.5 (1C), 132.2 (1C), 132.6 (1C), 136.0 (1C),147.4 (1C), 148.6 (1C); HRMS (FAB+) calcd for $C_{18}H_{21}{}^{79}BrN_2Si$ 372.0657, found 372.0657. Anal. Calcd for $C_{18}H_{21}BrN_2Si$: C, 57.90; H, 5.67; N, 7.50. Found: C, 58.10; H, 5.62; N, 7.41.

2-Bromo-8-formyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocine (6c). 6c was prepared following general procedure II, using **2** (193 mg, 0.51 mmol), 1.3 M *n*-BuLi (430 μL, 0.56 mmol), and DMF (59 μL,0.76 mmol) as the electrophile. CC (EtOAc (50−60%) in heptane) gave 119 mg (71%) of **6c**: mp 204.0−205.5 °C; R_f 0.16 (EtOAc (50%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16−4.23 (m, 2H), 4.28 (s, 2H, H-13), 4.67−4.75 (m, 2H), 7.00−7.05 (m, 2H), 7.22−7.29 (m, 2H), 7.447−7.453 (m, 1H), 7.66−7.69 (m, 1H), 9.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.6 (1C), 58.6 (1C), 66.7 (1C), 117.0 (1C), 125.7 (1C), 126.9 (1C), 128.3 (1C), 128.9 (1C), 129.3 (1C), 129.7 (1C), 129.8 (1C), 130.9 (1C), 132.6 (1C), 146.8 (1C), 154.3 (1C), 191.1 (1C); IR (KBr) 1697, 1680, 1668 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{13}{}^{79}BrN_2O$ 328.0211, found 328.0214. Anal. Calcd for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.50; H, 4.11; N, 8.43.

2-Bromo-8-(hydroxyphenylmethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (6d). 6d was prepared following general procedure II, using **2** (189, 0.50 mmol), 1.3 M *n*-BuLi (421 μL, 0.55 mmol), and benzaldehyde (76 μL, 0.75 mmol) as the electrophile. CC (EtOAc (70−80%) in heptane) gave 125 mg (62%) of **6d** as a mixture of diastereomers: mp 98.5−100.0 °C (heptane); R_f 0.42 (EtOAc (80%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (br s, 1H), 3.99−4.17 (m, 4H), 4.52−4.57 (m, 2H), 5.66−5.67 (m, 1H), 6.84−7.32 (m, 11H); HRMS (FAB+) calcd for $C_{22}H_{19}{}^{79}BrN_2O$ 406.0681, found 406.0673. Anal. Calcd for $C_{22}H_{19}BrN_2O$: C, 64.87; H, 4.70; N, 6.98. Found: C, 64.94; H, 4.82; N, 6.79.

2-Bromo-8-carboxyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*]-[1,5]diazocine Hydrochloride (6e). To a stirred solution of 2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (**2**) (378 mg, 1.0 mmol) in THF (3 mL) and Et_2O (8 mL) at −78 °C was added dropwise 1.6 M *n*-BuLi in hexane (684 μL, 1.09 mmol) over 2 min. After 5 min the reaction mixture was transferred into a saturated solution of CO_2 in THF at −78 °C by means of a pipet at −78 °C. The reaction mixture was concentrated in vacuo and the solid was dissolved in methanol and treated with a commercial solution of 4 M HCl in 1,4-dioxane (1 mL). Concentration in vacuo and crystallization from 2-propanol (9 mL) gave 233 mg (61%) of **6e** with decomposition above 200 °C (2-propanol): ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.43−4.55 (m, 2H), 4.81−5.05 (m, 4H), 7.34−7.51 (m, 4H), 7.78−7.79 (m, 1H), 7.90−7.95 (m, 1H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 58.0 (1C), 58.6 (1C), 67.9 (1C), 122.2 (1C), 125.6 (1C), 126.0 (1C), 127.3 (1C), 130.0 (1C), 130.4 (1C), 130.4 (1C), 131.0 (1C), 131.7 (1C), 132.9 (1C), 140.5 (1C), 148.4 (1C), 168.5 (1C, CO_2H); IR (KBr) 2829 (br, O−H), 1712, 1692, 1682 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{13}{}^{79}BrN_2O_2$ 344.0160, found 344.0164. Anal. Calcd for $C_{16}H_{14}BrClN_2O_2$: C, 50.35; H, 3.70; N, 7.34. Found: C, 50.28; H, 3.85; N, 7.45.

2-Bromo-8-(tributylstannyl)-6*H*,12*H*-5,11-meth-anodibenzo[*b*,*f*][1,5]diazocine (6f). 6f was prepared following general procedure II with the addition that the crude product was redissolved in Et_2O (10 mL) and stirred for 1 h with a 10% aqueous solution of KF. The white solid was filtered off and after separation of the two layers, the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo and the crude product was purified by CC, using **2** (192 mg, 0.51 mmol), 1.3 M *n*-BuLi (427 μL, 0.56 mmol), and tributylstannyl chloride (206 μL, 0.76 mmol) as the electrophile. CC (EtOAc (10−20%) in heptane) gave 210 mg (70%) of **6f**: mp 55.0−56.0 °C; R_f 0.26 (EtOAc (20%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85−0.90 (m, 9H, 3 × CH_3), 0.97−1.02 (m, 6H), 1.27−1.35 (m, 6H), 1.47−1.54 (m, 6H), 4.10−4.34 (m, 4H), 4.62−4.73 (m, 2H), 6.96 (s, 1H), 7.01−7.08 (m, 3H), 7.24−7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7 (3C), 13.8 (3C), 27.5 (3C), 29.2 (3C), 58.4 (1C), 58.8 (1C), 66.8 (1C), 116.6 (1C), 124.7 (1C), 127.0 (1C), 127.3 (1C), 129.9 (1C), 130.4 (1C), 130.5 (1C), 135.0 (1C), 135.6 (1C), 137.3(1C), 147.5 (1C), 147.8 (1C); HRMS (FAB+) calcd for $C_{27}H_{40}{}^{79}BrN_2{}^{120}Sn$ (M + H$^+$) 591.1397, found 591.1411. Anal. Calcd for $C_{27}H_{39}BrN_2Sn$: C, 54.94; H, 6.66; N, 4.75. Found: C, 54.88; H, 6.68; N, 4.73.

2-Bromo-8-cyano-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine (6g). 6g was prepared following general procedure II, using **2** (192 mg, 0.51 mmol), 1.3 M *n*-BuLi (427 μL, 0.56 mmol), and tosyl cyanide (137 mg, 0.76 mmol) in THF (1 mL) as the electrophile. CC (EtOAc (40%) in heptane) gave 99 mg (60%) of **6f**: mp 203.0−205.0 °C; R_f 0.18 (EtOAc (40%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10−4.19 (m, 2H), 4.26 (d, J = 1.2 Hz, 2H), 4.63−4.71 (m, 2H), 6.99−7.06 (m, 2H), 7.16−7.30 (m, 3H), 7.41−7.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.3 (1C), 58.5 (1C), 66.6 (1C), 107.5 (1C), 117.1 (1C), 118.8 (1C), 125.9 (1C), 126.9 (1C), 129.1 (1C), 129.5 (1C), 129.8 (1C), 131.0 (1C), 131.2 (1C), 131.5 (1C), 146.6 (1C), 152.7 (1C); IR (KBr) 2222 cm^{-1} (CN); HRMS (FAB+) calcd for $C_{16}H_{12}{}^{79}BrN_3$ 325.0215, found 325.0199. Anal. Calcd for $C_{16}H_{12}BrN_3$: C, 58.91; H, 3.71; N, 12.88. Found: C, 59.07; H, 3.69; N, 12.75.

Single Bromine−Lithium Exchange of 6b Followed by Reaction with an Electrophile: 2-Formyl-8-(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7a). 7a was prepared following general procedure I, using **6b** (187 mg, 0.50 mmol), 1.3 M *n*-BuLi (462 μL, 0.60 mmol), and DMF (58 μL, 0.75 mmol) as the electrophile. CC (EtOAc (30%) in heptane) gave 101 mg (63%) of **7a**: mp 214.0−215.0 °C; R_f 0.18 (EtOAc (40%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ

0.20 (s, 9H, 3 × CH_3), 4.24−4.37 (m, 4H), 4.72−4.80 (m, 2H), 7.05 (d, J = 0.5 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 7.25−7.34 (m, 2H), 7.45, (d, J = 1.6 Hz, 1H), 7.66−7.69 (dd, J = 8.3, 1.9 Hz, 1H), 9.83 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.0 (3C), 58.5 (1C), 58.9 (1C), 66.8 (1C), 124.6 (1C), 125.8 (1C), 126.9 (1C), 128.7 (1C), 128.7 (1C), 129.5 (1C), 132.2 (1C), 132.5 (1C), 132.7 (1C), 136.2 (1C), 148.4 (1C), 154.9 (1C), 191.2 (1C); IR (KBr) 1680 cm^{-1} (C═O); HRMS (FAB+) calcd for $C_{19}H_{22}N_2OSi$ 322.1501, found 322.1495. Anal. Calcd for $C_{19}H_{22}N_2OSi$: C, 70.77; H, 6.88; N, 8.69. Found: C, 70.64; H, 6.86; N, 8.54.

2-(Hydroxyphenylmethyl)-8-(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7b). 7b was prepared following general procedure I, using **6b** (184 mg, 0.49 mmol), 1.3 M *n*-BuLi (455 μL, 0.59 mmol), and benzaldehyde (75 μL, 0.74 mmol) as the electrophile. CC (EtOAc (60%) in heptane) gave 165 mg (84%) of **7b** as a mixture of diastereomers. An analytically pure sample was obtained by CC: mp 99.5−101.0 °C; R_f 0.25 (EtOAc (80%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23−0.24 (m, 9H, 3 × CH_3), 3.22 (br s, 1H, OH), 4.07−4.21 (m, 4H), 4.54−4.66 (m, 2H), 5.67 (br s, 1H, CH), 6.85−7.37 (m, 11H); HRMS (FAB+) calcd for $C_{25}H_{28}N_2OSi$ 400.1971, found 400.1977. Anal. Calcd for $C_{25}H_{28}N_2OSi$: C, 74.96; H, 7.05; N, 6.99. Found: C, 74.88; H, 7.11; N, 6.84.

2-(Tributylstannyl)-8-(trimethylsilyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (7c). 7c was prepared following general procedure I with the addition that the crude product was redissolved in Et_2O (10 mL) and stirred for 1 h with a 10% aqueous solution of KF. The white solid was filtered off and after separation of the two layers, the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo and the crude product was purified by CC, using **6b** (187 mg, 0.50 mmol), 1.3 M *n*-BuLi (424 μL, 0.55 mmol), and tributylstannyl chloride (204 μL, 0.75 mmol) as the electrophile. CC (EtOAc (15%) in heptane) gave 192 mg (66%) of **7c** as a colorless oil: R_f 0.24 (EtOAc (20%) in heptane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 9H, 3 × Si-CH_3), 0.87−0.91 (m, 9H, 3 × Sn-CH_3), 0.98−1.04 (m, 6H), 1.29−1.37 (m, 6H), 1.49−1.56 (m, 6H), 4.23 (dd, J = 16.7, 4.0 Hz, 2H), 4.33 (s, 2H), 4.74 (d, J = 16.6 Hz, 2H), 6.99 (d, J = 0.6 Hz, 1H), 7.06−7.17 (m, 3H), 7.25−7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.9 (3C), 9.7 (3C), 13.8 (3C), 27.5 (3C), 29.2 (3C), 58.6 (1C), 58.7 (1C), 66.8 (1C), 124.7 (1C), 124.9 (1C), 127.5 (1C), 127.8 (1C), 132.3 (1C), 132.3 (1C), 135.1 (1C), 135.4 (1C), 135.5 (1C), 136.8 (1C), 148.3 (1C), 149.2 (1C); HRMS (FAB+) calcd for $C_{30}H_{47}N_2Si$-^{120}Sn (M − H^+) 583.2531, found 583.2507. Anal. Calcd for $C_{30}H_{48}N_2SiSn$: C, 61.75; H, 8.29; N, 4.80. Found: C, 61.62; H, 8.21; N, 4.88.

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Note Added after ASAP. In the version posted on July 13, 2002, there were errors throughout the numbering of the references. The corrected version was posted on July 22, 2002.

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