JOC The Journal of Organic Chemistry

Article

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A Protocol for the *exo*-Mono and *exo,exo*-Bis Functionalization of the Diazocine Ring of Tröger's Base

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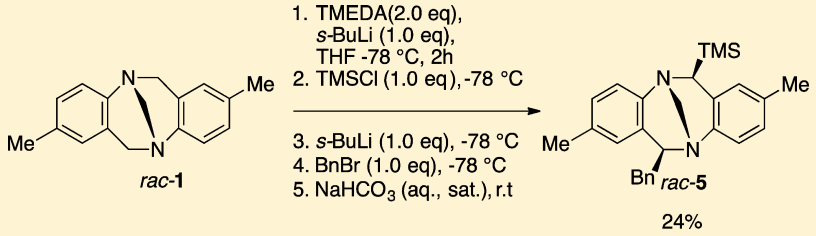
Supporting Information



ABSTRACT: An efficient protocol has been developed for the *exo*-mono and *exo,exo*-bis functionalization of Tröger's base in the benzylic 6 and 12 positions of the diazocine ring. The lithiation of Tröger's base using *s*-BuLi/TMEDA followed by electrophilic quench affords *exo*-mono- and *exo,exo*-bis-substituted derivatives of Tröger's base in good to excellent yields. The variation of the number of equivalents of *s*-BuLi/TMEDA and the order of addition of the electrophile strongly govern the outcome of the reaction for each electrophile.

INTRODUCTION

Tröger's base (TB, *rac*-**1**) was first synthesized in 1887 by the condensation of *p*-toluidine and methylal in hydrochloric acid.[1] TB exhibits interesting properties: it is a chiral C_2-symmetric rigid molecule with a diazocine core forming a hydrophobic cavity between its two aromatic rings that are situated at roughly 90° in relation to each other. It is chiral because of the presence of stereogenic nitrogen atoms.[2] The structural properties make TB and its analogues useful for applications as building blocks in the fields of molecular recognition, catalysis, and enzyme inhibition.[2]

The synthesis of TB analogues containing electron-poor substituents on their aromatic rings has been impractical because of the poor reactivity of starting anilines. This was overcome by the development of the synthesis of halogenated analogues of *rac*-**1** using paraformaldehyde and TFA,[3] which triggered the development of general methodologies for functionalizing the aryl rings of TB.[3,4] However, the same development has not been observed with the functionalization of its diazocine ring, for which new methodologies are still required. To date, the diazocine ring has been *N*-mono- or *N,N′*-dialkylated and modified on the methylene bridge either by cleavage and replacement or by direct exchange using various methods.[2c,5]

As part of ongoing work, we now report a new synthetic method for the functionalization of the 6-*exo* and 6,12-*exo,exo* positions of TB. Addressing the *exo* position of the TB framework is important because it may allow the development of new enantiomerically pure ligands for use in transition metal asymmetric catalysis as we have previously shown.[6b] The improved metalation conditions reported herein, compared to those previously reported,[6,7] allow not only the synthesis of the monosubstituted (*rac*-**2a**–**e**) and disubstituted (*rac*-**3a**–**e**) TB derivatives in good to excellent yield but also the synthesis of hetero-disubstituted derivatives, such as *rac*-**5**, in simple one-pot procedures (Figure 1).

In previous work by our groups toward the *exo* substitution of the diazocine ring of *rac*-**1**, it was shown that the treatment of *rac*-**1** with $BF_3{\cdot}OEt_2$ followed by *n*-BuLi and then quenching with an electrophile gave the *exo*-monosubstituted products in good yields,[6] whereas the preparation of the *exo,exo*-disubstituted derivatives required two sequential steps resulting in low overall yields.[6,7] In view of these limitations, the question of conducting the reaction with a different lithiating agent was raised. There are several reports of the use of alternative lithiating reagents on other molecules giving rise to differences in product distributions or yields.[9] In particular, it seemed likely that the reaction might proceed in a better manner under strong basic conditions in the absence of a Lewis acid, for example, with *s*-BuLi/TMEDA as a base

Received: August 20, 2015
Published: November 24, 2015

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DOI: 10.1021/acs.joc.5b01921
J. Org. Chem. 2015, 80, 12006–12014

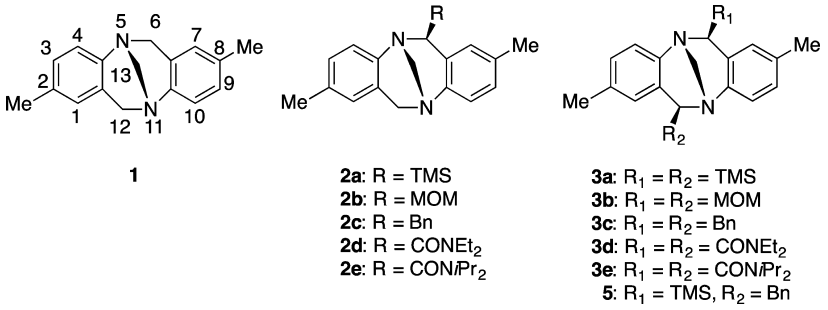


Figure 1. Tröger's base (*rac*-**1**) and synthesized derivatives described in this article.

Scheme 1. Product Distribution from the Reaction of *rac*-1 with TMEDA/*s*-BuLi Followed by Quenching with CH_3OH-d_4 or D_2O

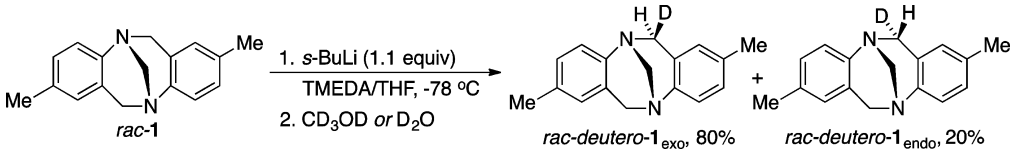
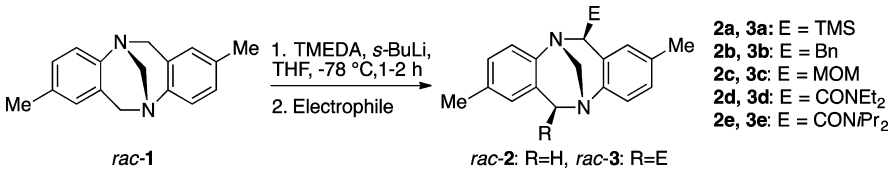


Table 1. Synthesis of 6-*exo*-Monosubstituted and 6,12-*exo*,*exo*-Substituted TB Derivatives *rac*-2a–e and *rac*-3a–e by the Direct-Addition Method



entry	*s*-BuLi/TMEDA (equiv)	electrophile	product	yield %[a]	yield using BF_3·Et_2O (%)[b]
1[c]	1.1	TMSCl (1.2)	*rac*-**2a**	76	66
2[c]	1.1	BnBr	*rac*-**2b**	51[e]	68
3[c]	1.1	MOMCl (1.2)	*rac*-**2c**	85	
4[c]	0.8	Et_2NCOCl (1.2)	*rac*-**2d**	42	
5[c]	1.0	iPr_2NCOCl (1.2)	*rac*-**2e**	32	
6[d]	2.2	TMSCl (2.5)	*rac*-**3a**	62	
7[d]	2.2	BnBr (2.5)	*rac*-**3b**	74	36
8[d]	2.2	MOMCl (2.5)	*rac*-**3c**	81	
9[d]	2.0	Et_2NCOCl (2.4)	*rac*-**3d**	42	
10[d]	2.0	iPr_2NCOCl (2.4)	*rac*-**3e**	44	

[a]Yield of the isolated analytically pure compound. [b]BF_3·OEt_2/*n*-BuLi method.[6b,7] [c]For entries 1–5, 1.2 equiv of electrophile was used. [d]In entries 6–10, 2.4 equiv of electrophile was used. [e]Approximately 20% of the disubstituted product and 20% of unreacted starting material were isolated. On the basis of 1.00 and 0.20 g of starting TB, optimal product yields of 51 and 58%, respectively, were obtained.

instead of *n*-BuLi, because of the former exhibiting a basicity 10^3 times stronger than that of the latter.[10]

RESULTS AND DISCUSSION

We first undertook *s*-BuLi/electrophile quench experiments to determine if a high *exo*/*endo* product ratio could be established. Thus, subjecting *rac*-**1** to 1.1 equiv of *s*-BuLi/TMEDA for 1–2 h at −78 °C in THF followed by quenching with 1.2 equiv of CD_3OD-d_4 or D_2O gave the *exo* monodeuterated TB derivative *rac-deutero*-$\mathbf{1}_{exo}$ in 80% yield and the *endo* monodeuterated TB derivative *rac-deutero*-$\mathbf{1}_{endo}$ in 20% yield, the same for both deuterium sources, as determined by ^{1}H NMR of the reaction mixture (Scheme 1). The *exo*-6-deuterio stereochemistry was established by the characteristic upfield shift of the remaining *endo*-6-H resonance.[11] The preference for *exo* selectivity is most likely the result of the approach of the electrophile to the incipient carbanion from the less sterically demanding convex surface of the bicyclic[3.3.1] framework.[6a]

On the basis of successful deuteration experiments, we investigated the scope and limitations of the reaction with respect to different electrophiles (Table 1). Hence, subjecting *rac*-**1** to 1.1 equiv of *s*-BuLi/TMEDA for 1 h at −78 °C followed by an electrophilic quench with 1.2 equiv of TMSCl (16 h) (see the reaction in Table 1) gave the *exo* monosilylated Tröger's base derivative *rac*-**2a** in a 76% yield of isolated and analytically pure product (Table 1, entry 1). This is an improvement on the 66% yield previously reported using the BF_3·OEt_2-mediated conditions[6a] and as such provides evidence of the superior performance of the new method.

However, repeating the metalation conditions, but now quenching the lithiated intermediate with BnBr (6 h), resulted in the formation of compound *rac*-**2b** in 51% yield, lower

DOI: 10.1021/acs.joc.5b01921
J. Org. Chem. 2015, 80, 12006–12014

compared to that obtained by the $BF_3{\cdot}OEt_2$ method.[6a] Roughly 20% of the recovered material was unreacted TB, and roughly 20% was the disubstituted derivative *rac*-**3b** as determined by ^{1}H NMR spectroscopy. The 6-*exo* stereochemistry of the *rac*-**2b** was supported by the characteristic upfield shift of remaining *endo*-6-proton resonance, by comparison to TB itself, for which the 6- and 12-*endo*-proton resonances are shifted upfield compared to the 6- and 12-*exo*-proton resonances.[11] The *exo* stereochemistry of *rac*-**2b** was firmly confirmed by an X-ray diffraction (XRD) analysis (Figure 2). This comparison between the 6-*exo* stereochemistry of *rac*-**2b** as determined by XRD analysis and the upfield shift of the 6-*exo*-proton resonance in the ^{1}H NMR spectrum supports the use of ^{1}H NMR spectroscopy for determining the 6-*exo*/*endo* stereochemistry of TB derivatives as previously done for TB itself.[11]

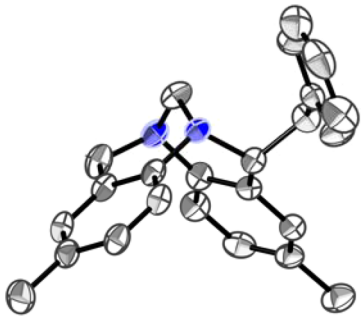


Figure 2. Molecular structure of compound *rac*-**2b** with thermal ellipsoids at the 30% probability level. Hydrogen atoms have been omitted for the sake of clarity.

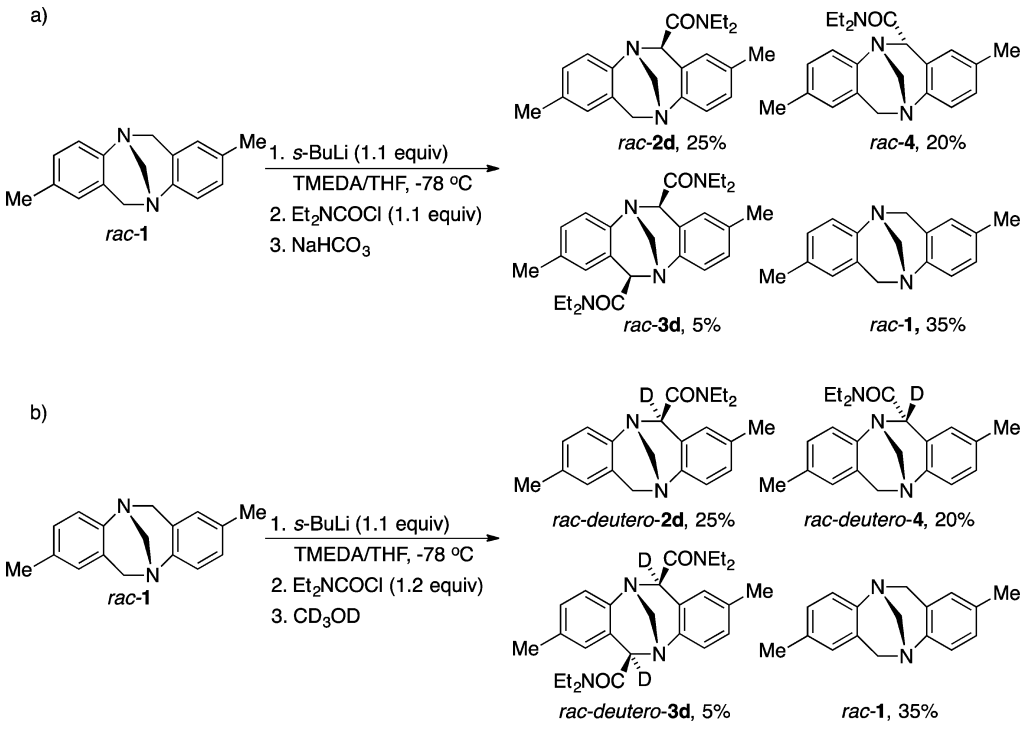
As the next experiment, subjecting *rac*-**1** to 1.1 equiv of *s*-BuLi/TMEDA for 1 h at −78 °C followed by quenching with 1.2 equiv of MOMCl (16 h) resulted in the formation of *rac*-**2c** in an excellent 85% yield (Table 1, entry 3).

It was noted that along with the desired TB derivative *rac*-**2a** (76%) and unreacted *rac*-**1** (11%), a small amount (9%) of *exo*,*exo*-6,12-disilylated TB derivative *rac*-**3a** was present in the lithiation/TMSCl quench reaction described above. The latter result suggested that the *s*-BuLi/TMEDA method would allow for the bis-functionalization of the diazocine ring of *rac*-**1**.

Hence, doubling the number of equivalents of *s*-BuLi/TMEDA to 2.0−2.2 equiv in the reactions with BnBr, TMSCl, and MOMCl, respectively, led to the synthesis of the *exo*,*exo*-disubstituted TB derivatives *rac*-**3a**−**c** in good to very good yields (Table 1, entries 6−8). The lithiation time of 1 h followed by electrophile quenching and allowing for the reaction mixture to slowly reach rt over 16−20 h were used as optimal conditions, although longer or shorter times were of little consequence for the observed yields. Particularly satisfying was the near doubling of the yield of the *exo*,*exo*-dibenzyl derivative (*rac*-**3b**) compared to that observed using the *n*-BuLi/$BF_3{\cdot}OEt_2$ method (Table 1, entry 7).[6a] The 6,12-*exo*,*exo* stereochemistry of *rac*-**3c** was confirmed by XRD analysis (Figure S-2 of the Supporting Information).

The yields obtained from the reactions using diethylcarbamoyl chloride (Et_2NCOCl) and *N*,*N*-diisopropylcarbamoyl chloride (iPr_2NCOCl) as electrophiles, on the other hand, were disappointing (Table 1, entries 4, 5, 9, and 10). Duplicate reactions using *s*-BuLi/TMEDA (1 h, 1.1 equiv) and *N*,*N*-Et_2NCOCl (15 h, 1.2 equiv) and working up the reaction mixture with a saturated aqueous $NaHCO_3$ solution revealed that, in addition to the expected *exo*-monosubstituted product *rac*-**2d** (∼25%), unreacted starting material (∼35%), traces of *rac*-**3d** (∼5%), and a compound that was identified as the *endo*-monosubstituted addition product *rac*-**4** (∼20%) were obtained (Scheme 2a) (see the Supporting Information).

Scheme 2. Product Distribution from the Reaction of TB (*rac*-1) with *s*-BuLi/TMEDA Followed by (a) Et_2NCOCl and (b) Successive Quenching with Et_2NCOCl and CD_3OD



DOI: 10.1021/acs.joc.5b01921
J. Org. Chem. 2015, 80, 12006−12014

Scheme 3. Mechanistic Rationalization of the Reaction of TB (*rac*-1) with *s*-BuLi/TMEDA Followed by Et_2NCOCl and CD_3OD

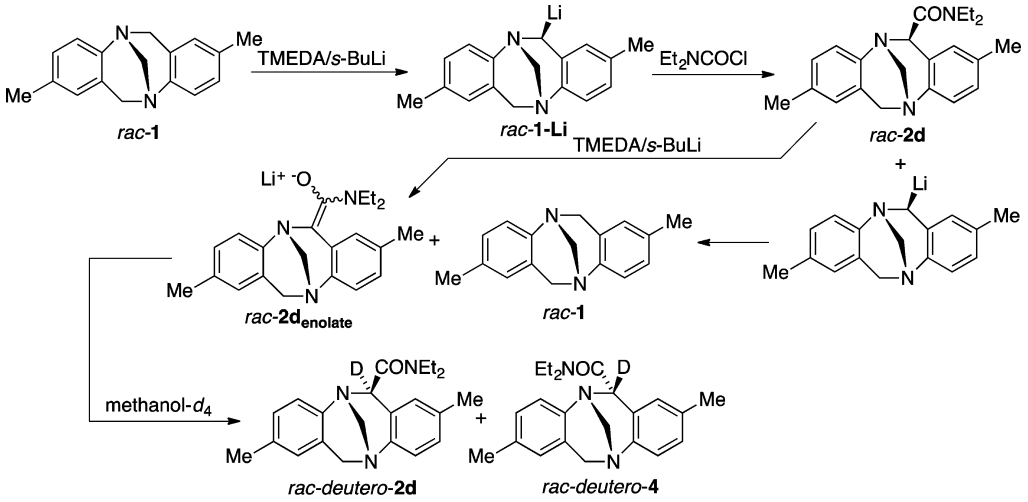
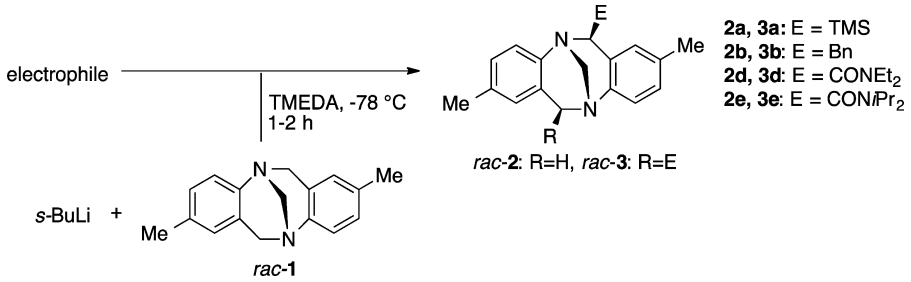


Table 2. Synthesis of 6-*exo* Mono and 6,12-*exo*,*exo*-Substituted TB Derivatives 2a−e and 3a−e by the Inverse-Addition Method



entry	*s*-BuLi/TMEDA (equiv)	electrophile (equiv)	product	yield (%)[a]	yield using $BF_3{\cdot}Et_2O$ (%)[b]
1	0.95	TMSCl (>10)	*rac*-**2a**	72	
2	0.95	BnBr (>10)	*rac*-**2b**	0[c]	68
3	0.95	Et_2NCOCl (>10)	*rac*-**2d**	70	
4	0.95	iPr_2NCOCl (7.5)	*rac*-**2e**	73	
5	3.0	TMSCl (>10)	*rac*-**3a**	89	
6	3.0	BnBr (>10)	*rac*-**3b**	96	34
7	3.0	Et_2NCOCl (>10)	*rac*-**3d**	97	
8	3.0	iPr_2NCOCl (7.5)	*rac*-**3e**	98	

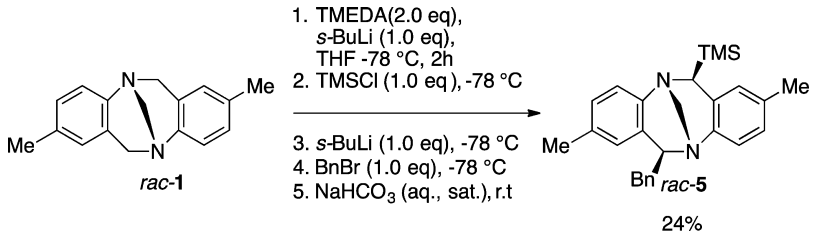
[a]Yields of isolated products after column chromatography and/or crystallization. [b]Yields using the *n*-BuLi/$BF_3{\cdot}OEt_2$ method, via direct addition.[7] [c]Traces of starting material (<5%) and polymeric material were obtained.

Using the same conditions but now quenching with CD_3OD resulted in part deuteration at the α-position of the amide group, yielding the TB amide derivatives *rac-deutero*-**2d**, *rac-deutero*-**3d**, and *rac-deutero*-**4** in the same ratios as described above as determined by ^1H NMR spectroscopy of the crude product (Scheme 2b) (see the Supporting Information). However, no deuterated TB (*rac*-**1**) was isolated from the same reaction quenched with CD_3OD, indicating that the enolization of *rac*-**2d** has at least partly proceeded via metalated *rac*-**1**, because the lithiation of *rac*-**1** using *s*-BuLi/TMEDA goes to completion (Scheme 1). Hence, from the product distribution and the deuteration experiments, it became apparent that either the lithiated TB or the excess *s*-BuLi/TMEDA species effects the deprotonation of the newly formed amide *rac*-**2d** in the reaction mixture, forming the corresponding enolate *rac*-$\mathbf{2d}_{\mathbf{enolate}}$ (Scheme 2). Hence, quenching with CD_3OD affords *endo* and *exo* isomers *rac*-**2d** and *rac*-**4**, respectively, in approximately equal amounts. Because the inverse-addition method *vide infra* (Scheme 3) solved this epimerization problem, this reaction was not further investigated.

To counter the setback described above, a method was developed on the basis of inverse addition that involved treating *rac*-**1** with *s*-BuLi/TMEDA in THF at −78 °C followed by the addition of the resulting lithiated TB species *rac*-**1-Li** to an excess of electrophile (>10 equiv) in THF at −78 °C (see Scheme 3 and the reaction in Table 2), then allowing the mixture to reach room temperature slowly (1−2 h), and finally quenching the reaction with a saturated aqueous solution of sodium bicarbonate. As established by the inverse-addition protocol, the presence of a large excess of an electrophile traps lithiated *rac*-**1** as it is formed, thus preventing its action as a base in deprotonating the newly formed product *rac*-**2d**. The results of the inverse-addition method are summarized in Table 2.

DOI: 10.1021/acs.joc.5b01921
J. Org. Chem. 2015, 80, 12006−12014

Scheme 4. Synthesis of the *exo,exo*-6,12-Heterosubstituted TB Derivative *rac*-5



In the process of the optimization of the inverse-addition method, it became apparent, as expected, that increasing the amount of *s*-BuLi/TMEDA for the lithiation step had an effect on the observed yields. Hence, treating *rac*-**1** with 1.1−2.2 equiv of *s*-BuLi/TMEDA resulted in reaction mixtures containing both mono- and disubstituted products *rac*-**2d** and *rac*-**3d**, respectively. Using 0.95 equiv of *s*-BuLi/TMEDA eliminated the formation of disubstituted product *rac*-**3d** with the drawback that some unreacted starting material (10−20%) was isolated. The starting material was, however, recovered by column chromatography and reused. Increasing the amount of *s*-BuLi/TMEDA to 3.0 equiv completely eliminated the formation of the monosubstituted product *rac*-**2d** and the starting material and also the necessity of column chromatography in the purification process.

Addition of the lithiated TB species *rac*-**1-Li** to an excess (>10 equiv) of the electrophile increased the overall yield of both mono- and difunctionalized TB derivatives *rac*-**2a**, *rac*-**2d**, *rac*-**2e**, *rac*-**3a**, *rac*-**3b**, *rac*-**3d**, and *rac*-**3e** (Table 2, entries 1 and 3−8, respectively), compared to adding a stoichiometric amount of the electrophile directly to the lithiated species (Table 1). Monosubstituted products *rac*-**2a**, *rac*-**2d**, and *rac*-**2e** (Table 2, entries 1, 3, and 4, respectively) were obtained in good to very good yields; however, some unreacted *rac*-**1** (20−30%) was always isolated from the crude reaction mixture, indicating incomplete metalation of *rac*-**1** under the <1.0 equiv of *s*-BuLi/TMEDA conditions. Notably, using the inverse-addition method, the yield of products *rac*-**2d** and *rac*-**2e** (Table 2, entries 3 and 4, respectively) was improved over the direct-addition method by as much as 35−40%. Oddly, this method proved to be ineffective in producing *rac*-**2b** (Table 2, entry 2); in addition to trace amounts of *rac*-**1**, only polymeric material was obtained. Because *rac*-**2b** was produced in an acceptable yield by the direct-addition method, this reaction was not further investigated. It can be suggested that during the conditions of the inverse-addition method, in which the lithiated TB encounters a large excess of benzyl bromide, the lithiated TB generates a benzyl radical by a single electron transfer to benzyl bromide, a reaction similar to what has been observed for the reaction of lithium reagents with alkyl halides.[8] It can, for example, be further suggested that the so-formed benzyl radical reacts quickly with benzyl bromide, leading to the depletion of the latter so that no benzyl benzylated TB can form. Notably, the yields of the disubstituted products *rac*-**3a**, *rac*-**3b**, *rac*-**3d**, and *rac*-**3e** ranged from very good to excellent, improving the yields compared to the direct-addition method by as much as 55 and 54% in the case of *rac*-**3d** and *rac*-**3e**, respectively. Rewardingly, the yield of the *exo,exo*-6,12-dibenzylated compound *rac*-**3b** was higher than that obtained by the $BF_3{\cdot}OEt_2$/*n*-BuLi method.[7]

To extend the use of our developed synthetic method to obtain *exo,exo*-6,12-heterodisubstituted TB derivatives, a one-pot direct-addition methodology was developed. Thus, a solution of *rac*-**1** containing 2.2 equiv of TMEDA was sequentially treated with 1.0 equiv of *s*-BuLi and TMSCl, respectively, followed, after 1 h, by 1.0 equiv of *s*-BuLi and BnBr, respectively, in succession to give the *exo*-6-benzyl-*exo*-12-trimethylsilyl TB derivative *rac*-**5** in 24% yield (Scheme 4). The low yield obtained is due to the formation of byproducts such as *rac*-**3a** that hampered the purification due to their R_f values being very close to that of *rac*-**5**.

In conclusion, two efficient methods for the synthesis of *exo*-6-monosubstituted and *exo,exo*-6,12-bis-substituted derivatives *rac*-**2a−e** and *rac*-**3a−e** of Tröger's base *rac*-**1** have been developed: a straightforward and simple one-pot, direct-addition method and a somewhat more cumbersome inverse-addition method. Both of these methods rely on using different amounts of *s*-BuLi/TMEDA as the metalating reagent and have distinct advantages. The direct-addition method does not require the use of excess electrophile, may be used to produce heterosubstituted TB derivatives *rac*-**5**, and is preferred for the synthesis of monosubstituted TB *rac*-**2a**, *rac*-**2b**, and *rac*-**2c**. The inverse-addition method shows yields vastly superior to those of the direct-addition method and other previously reported methods[6,7] for the preparation of the *exo,exo*-disubstituted TB derivatives. The inverse-addition method precludes the formation of enolate, thereby securing a high yield of the *exo* diastereomer of *rac*-**2d**, *rac*-**2e**, *rac*-**3d**, and *rac*-**3e**, compounds containing an acidic α-hydrogen atom. Another advantage of both the direct- and inverse-addition methods developed in the work is the use of the TMEDA additive that is less costly and more bench stable than $BF_3{\cdot}OEt_2$. Finally, our work has generated new TB derivatives or increased the availability of known TB derivatives with defined *exo* stereochemistry via a more efficient synthesis. These compounds constitute or may be modified into new building blocks that can be used in supramolecular chemistry and catalysis.

EXPERIMENTAL SECTION

General Methods. All chemicals were used as received from commercial sources without further purification unless stated otherwise. TMEDA was dried with KOH overnight and distilled under house vacuum prior to use. Benzyl bromide and *N,N*-diethylcarbamoyl chloride were distilled under house vacuum prior to use. *N,N*-Diisopropylcarbamoyl chloride was sublimed and kept under nitrogen prior to use. THF was dried with sodium and distilled under nitrogen. PE refers to petroleum ether (bp 40−60 °C). *s*-BuLi was titrated prior to use according to a literature method.[12] Precoated Merck silica gel 60 F_{254} plates were used for TLC analysis. Column chromatography was performed on silica gel (Davisil 35−70 μm). ^{1}H and ^{13}C NMR spectra were recorded on a 400 NMR spectrometer. Chemical shifts (δ) are reported relative to shift scale calibrated with residual NMR solvent peak $CDCl_3$ (δ 7.26

DOI: 10.1021/acs.joc.5b01921
J. Org. Chem. 2015, 80, 12006−12014

for ^{1}H NMR and δ 77.23 for ^{13}C NMR). Melting points were recorded on a Fischer-Jones apparatus, using plate technology. IR spectra were recorded on a FTIR spectrophotometer. HRMS data were obtained on a Q-TOF micro instrument.

Crystallography. Crystals of *rac*-**2b** were grown by dissolving 50 mg of *rac*-**2b** in ethyl acetate (1.0 mL), adding heptane (1.0 mL), and allowing the mixture to evaporate slowly at room temperature. Crystals of *rac*-**3c** were grown by dissolving 50 mg of *rac*-**3c** in diethyl ether (1.0 mL), adding heptane (1.0 mL), and allowing the mixture to evaporate slowly at room temperature. Intensity data were collected with an Oxford Diffraction Excalibur 3 system, using ω-scans and Mo Kα (λ = 0.71073 Å) radiation.[13] The data were extracted and integrated using Crysalis RED.[14] The structure was determined by direct methods and refined by full-matrix least-squares calculations on F^2 using SHELXL[15] and SIR-92.[16] Molecular graphics were generated using CrystalMaker version 8.3.5.[17] CCDC deposition numbers CCDC 1416673−1416674.

General Procedure for the Direct-Addition Method. The general procedure consists of 1.00 g of *rac*-**1** being dissolved in dry THF under N_2. TMEDA (amount indicated in entry) is added, and the solution is cooled to −78 °C. *s*-BuLi (amount indicated in entry) is added dropwise over 10−20 min at −78 °C. The solution is maintained at −78 °C for 1−2 h. The electrophile (amount specified in each entry) is then added dropwise at −78 °C, and the reaction mixture is allowed to reach room temperature. The reaction is then quenched by successively adding a saturated aqueous solution of $NaHCO_3$ (10 mL), CH_2Cl_2 (30 mL), and water (20 mL), and the phases are separated. The aqueous phase is extracted with additional CH_2Cl_2 (3 × 50 mL). The combined organic phase is washed with brine, dried with Na_2SO_4, and subjected to filtration and the solvent removed *in vacuo*. The crude material is purified as described in the each individual entry.

exo-2,8-Dimethyl-6-trimethylsilyl-6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine (**2a**). To a stirred solution of TB *rac*-**1** (0.998 g, 3.99 mmol) in anhydrous THF (30 mL) under an inert atmosphere was added TMEDA (0.66 mL, 4.4 mmol), and the resulting faint yellow solution was stirred at rt for 30 min before being cooled to −78 °C for 15 min. *s*-BuLi (1.31 M, 3.40 mL, 4.45 mmol) was then added dropwise over 30 min, and the resulting reaction mixture was stirred for an additional 1 h before the TMSCl (0.63 mL, 5.0 mmol) was slowly added over 30 min. The cooling bath was removed, and the reaction mixture was allowed to warm to rt (20 h) and the reaction quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by addition of CH_2Cl_2 (30 mL) and water (30 mL). The resulting layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, subjected to filtration, and evaporated *in vacuo* to dryness. The resulting residue was purified by column chromatography (3 cm × 10 cm, 9:1 PE/EtOAc) to give *rac*-**2a** as colorless crystals in 76% yield (0.98 g): R_f = 0.25 (9:1 PE/EtOAc); mp 128−130 °C (heptane/EtOAc); IR (CH_2Cl_2) 2953, 1488, 1322, 1244, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.1 Hz, 1H, H-10), 6.93 (dd, J = 8.4, 1.4 Hz, 1H, H-3), 6.91−6.87 (m, 2H, H-4 and H-9), 6.67 (s, 1H, H-1), 6.61 (s, 1H, H-7), 4.63 (d, J = 16.6 Hz, 1H, H-12x), 4.22 (dd, J = 12.7, 1.1 Hz, 1H, H-13), 4.16 (dd, J = 12.7, 1.0 Hz, 1H, H-13′), 4.07 (d, J = 16.5 Hz, 1H, H-12n), 3.84 (s, 1H, H-6), 2.20 (s, 6H, Ar-CH_3), 0.24 (s, 9H, -Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 144.9, 133.01, 132.97, 131.1, 128.1, 127.6, 127.3, 127.0, 126.9, 125.2, 124.9, 65.6, 63.7, 59.4, 21.2, 21.0, −1.2 (3C); HRMS-EI$^+$ m/z [M]$^+$ calcd for $C_{20}H_{26}N_2Si$ 322.1865, found 322.1867. Anal. Calcd for $C_{20}H_{26}N_2Si$: C, 74.48; H, 8.13; N, 8.69. Found: C, 74.44; H, 8.11; N, 8.65.

exo-2,8-Dimethyl-6-benzyl-6H,12H-5,11-methanodibenzo[b,f]-[1,5]diazocine (**2b**). TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (0.66 mL, 4.4 mmol), *s*-BuLi (1.30 M, 3.40 mL, 4.42 mmol), and benzyl bromide (0.570 mL, 4.79 mmol). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 6 h at rt. Purification by column chromatography (5 cm × 10 cm, 9:1 PE/EtOAc) gave *rac*-**2b** as an amorphous solid in 51% yield (0.70 g): R_f = 0.28 (9:1 PE/EtOAc); mp 134−136 °C (heptane/diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.43 (m, 4H, Ar-H), 7.35 (tt, J = 7.0, 1.9 Hz, 1H, Ar-H), 7.10 (d, J = 8.1 Hz, 1H, H-10), 7.03 (dd, J = 8.2, 1.8 Hz, 1H, H-9), 6.87 (s, 1H, H-1), 6.83 (dd, J = 8.1, 1.4 Hz, 1H, H-3), 6.68 (s, 1H, H-7), 6.46 (d, J = 8.1 Hz, 1H, H-4), 4.69 (d, J = 16.6 Hz, 1H, H-12x), 4.53 (dd, J = 12.9, 1.6 Hz, 1H, H-13), 4.26−4.21 (m, 2H, H-6 and H-13′), 4.14 (d, J = 16.6 Hz, 1H, H-12n), 3.22 (dd, J = 14.2, 4.4 Hz, 1H, -CH_2-Ph), 3.16 (dd, J = 14.1, 10.2 Hz, 1H, -CH_2-Ph), 2.28 (s, 3H, Ar-CH_3), 2.20 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.7, 140.2, 133.3, 133.2, 130.9, 129.7 (2C), 128.51, 128.47 (2C), 128.1, 127.5, 127.2, 126.4, 125.0, 124.6, 77.2, 69.3, 61.5, 58.6, 43.1, 21.1, 21.0; HRMS-ESI$^+$ m/z [M + H]$^+$ calcd for $C_{24}H_{25}N_2$ 341.2018, found 341.2031. Anal. Calcd for $C_{24}H_{24}N_2{\cdot}0.25H_2O$: C, 83.56; H, 7.16; N, 8.12. Found: C, 83.90; H, 7.39; N, 8.34.

exo-2,8-Dimethyl-6-methoxymethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2c**). TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (0.66 mL, 4.4 mmol), *s*-BuLi (0.530 M, 8.32 mL, 4.40 mmol), and MOMCl (0.360 mL, 4.74 mmol). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 16 h at rt. Purification by column chromatography (5 cm × 10 cm, 3:2 PE/EtOAc) gave *rac*-**2c** as an off-white highly viscous liquid in 85% yield (1.01 g): R_f = 0.30 (3:2 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.0 Hz, 1H, H-10), 7.02 (d, J = 7.9 Hz, 1H, H-4), 6.98 (dd, J = 8.2, 1.8 Hz, 1H, H-3), 6.95 (dd, J = 8.2, 1.4 Hz, 1H, H-9), 6.84 (s, 1H, H-1), 6.68 (s, 1H, H-7), 4.67 (d, J = 16.6 Hz, 1H, H-12x), 4.43 (dd, J = 12.9, 1.6 Hz, 1H, H-13), 4.25−4.18 (m, 2H, H-6 and H-13′), 4.09 (d, J = 16.5 Hz, 1H, H-12n), 3.83 (dd, J = 10.3, 9.1 Hz, 1H, -CH_2O-), 3.72 (dd, J = 10.4, 3.8 Hz, 1H, -CH_2O-), 3.54 (s, 6H, -OCH_3), 2.23 (s, 3H, Ar-CH_3) 2.23 (s, 6H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.34, 146.28, 133.50, 133.31, 128.8, 128.6, 128.3, 127.6, 127.5, 127.3, 125.2, 125.1, 76.2, 66.9, 62.1, 59.4, 58.5, 21.04, 21.00; HRMS-ESI$^+$ m/z [M + H]$^+$ calcd for $C_{19}H_{23}N_2O$ 295.1810, found 295.1785. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.48; H, 7.48; N, 9.46.

exo-2,8-Dimethyl-6-(N,N-diethylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2d**). TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (0.48 mL, 3.2 mmol), *s*-BuLi (1.29 M, 2.50 mL, 3.22 mmol), and *N,N*-diethylcarbamoyl chloride (0.610 mL, 4.80 mmol). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 15 min at rt. Purification by column chromatography (5 cm × 9 cm, 3:2 PE/EtOAc) gave *rac*-**2d** as colorless crystals in 42% yield (0.589 g): R_f = 0.21 (7:3 PE/EtOAc); mp 149−151 °C (heptane/EtOAc); IR (CH_2Cl_2) 3391, 3052, 2936, 1700, 1646, 1609, 1445, 1363, 1324, 1266, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.1 Hz, 1H, H-10), 7.02 (d, J = 8.1 Hz, 1H, H-4), 7.00−6.93 (m, 2H, H-3 and H-9), 6.72 (d, J = 0.8 Hz, H-1), 6.62 (d, J = 1.5 Hz, H-7), 4.91 (s, 1H, H-6), 4.83 (dd, J = 12.8, 1.8 Hz, 1H, H-13), 4.64 (d, J = 16.7 Hz, 1H, H-12x), 4.13−4.02 (m, 3H, H-13′, H-12n and N-CH_2-CH$_3$), 3.75 (dq, J = 14.7, 7.3 Hz, 1H, N-CH_2-CH$_3$), 3.54 (dq, J = 13.7, 6.9 Hz, 1H, N-CH_2-CH$_3$), 3.44 (dq, J = 13.7, 6.9 Hz, 1H, N-CH_2-CH$_3$), 2.22 (s, 3H, Ar-CH_3), 2.20 (s, 3H, Ar-CH_3), 1.46 (t, J = 7.1 Hz, 3H, -CH$_2$-CH_3), 1.21 (t, J = 7.1 Hz, 3H, -CH$_2$-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.8, 145.3, 133.8, 133.1, 128.9, 128.3, 128.2, 128.2, 127.9, 126.4, 124.8, 123.2, 66.5, 63.0, 58.6, 42.3, 41.1, 21.0, 20.8, 14.9, 13.0; HRMS-EI$^+$ m/z [M]$^+$ calcd for $C_{22}H_{27}N_3O$ 349.2154, found 349.2156. Anal. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.64; H, 7.74; N, 11.97.

exo-2,8-Dimethyl-6-(N,N-diisopropylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2e**). TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (0.60 mL, 4.0 mmol), *s*-BuLi (1.31 M, 3.00 mL, 3.93 mmol), and *N,N*-diisopropylcarbamoyl chloride (0.790 g, 4.83 mmol) dissolved in THF (5 mL). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 2 h at rt. Purification by column chromatography (5

DOI: 10.1021/acs.joc.5b01921
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cm × 10 cm, 3:2 PE/EtOAc) gave *rac*-**2e** as colorless crystals in 32% yield (0.49 g): R_f = 0.35 (7:3 PE/EtOAc); mp 201−203 °C (heptane/EtOAc); IR (neat) 1638, 1490, 1437, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.2 Hz, 1H, H-10), 6.99−6.94 (m, 3H, H-3, H-4 and H-9), 6.71 (s, 1H, H-1), 6.60 (s, 1H, H-7), 4.97 (septet, J = 6.7 Hz, 1H, -C*H*(CH_3)$_2$), 4.90 (s, 1H, H-6), 4.65−4.60 (m, 2H, H-12x and H-13), 4.12−4.08 (m, 2H, H-12n and H-13′), 3.47 (septet, J = 6.7 Hz, 1H, -C*H*(CH_3)$_2$), 2.21 (s, 3H, Ar-CH_3), 2.21 (s, 3H, Ar-CH_3), 1.47−1.40 (m, 12H, -CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.9, 145.3, 133.8, 132.9, 129.1, 129.0, 128.28, 128.25, 128.0, 126.7, 124.7, 122.8, 68.5, 63.3, 58.9, 49.2, 46.5, 21.4, 21.14, 20.96 (2C), 20.8, 20.4; HRMS-ESI$^+$ m/z [M + H]$^+$ calcd for $C_{24}H_{32}N_3O$ 378.2545, found 378.2547. Anal. Calcd for $C_{24}H_{31}N_3O$: C, 76.35; H, 8.28; N, 11.13; Found: C, 76.31; H, 8.26; N, 11.07.

*exo,exo-2,8-Dimethyl-6,12-bis(trimethylsilyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3a**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.31 mL, 8.79 mmol), *s*-BuLi (1.30 M, 6.66 mL, 8.79 mmol), and TMSCl (1.27 mL, 9.99 mmol). A 2.5 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 2 h at rt. Purification by column chromatography (5 cm × 20 cm, 20:1 PE/EtOAc) gave *rac*-**3a** as colorless crystals in 62% yield (0.980 g): R_f = 0.28 (40:1 PE/EtOAc); mp 139−141 °C (heptane/diethyl ether); IR (CH_2Cl_2) 2961, 1485, 1248, 1217, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 8.1 Hz, 2H, H-4 and H-10), 6.84 (dd, J = 8.1, 1.7 Hz, 2H, H-3 and H-9), 6.58 (s, 2H, H-1 and H-7), 4.07 (s, 2H, H-13), 3.80 (s, 2H, H-6 and H-12), 2.19 (s, 6H, Ar-CH_3), 0.23 (s, 18H, -Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 132.4, 131.1, 127.0, 126.7, 125.1, 64.2, 64.1 (1C), 21.2, −1.1 (6C); HRMS-EI$^+$ m/z [M]$^+$ calcd for $C_{23}H_{34}N_2Si_2$ 394.2261, found 394.2272. Anal. Calcd for $C_{23}H_{34}N_2Si_2$: C, 69.99; H, 8.68; N, 7.10. Found: C, 69.87; H, 8.58; N, 7.10.

*exo,exo-2,8-Dimethyl-6,12-bis(benzyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3b**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.34 mL, 9.00 mmol), *s*-BuLi (1.30 M, 6.90 mL, 8.97 mmol), and benzyl bromide (1.20 mL, 10.1 mmol). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 16 h at rt. Purification by column chromatography (5 cm × 10 cm, 4:1 PE/EtOAc) gave *rac*-**3b** as white crystals in 74% yield (1.28 g): R_f = 0.30 (4:1 PE/EtOAc); mp 220−222 °C (heptane/diethyl ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.39 (m, 8H, Ar-*H*), 7.31 (tt, J = 6.8, 2.1 Hz, 2H, Ar-*H*), 6.80 (dd, J = 8.1, 1.9 Hz, 2H, H-3 and H-9), 6.77 (s, 2H, H-4 and H-7), 6.40 (d, J = 8.1 Hz, 2H, H-3 and H-10), 4.37 (s, 2H, H-13), 4.16 (dd, J = 10.3, 4.2 Hz, 2H, H-6 and H-12), 3.16 (dd, J = 14.1, 4.2 Hz, 2H, -CH_2-Ph), 3.09 (dd, J = 14.1, 10.4 Hz, 2H, -CH_2-Ph), 2.17 (s, 6H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 140.3, 132.9, 130.8, 129.7, 128.5, 128.4, 128.3, 126.4, 124.6, 69.1, 56.1 (1C), 43.2, 21.1; HRMS-ESI$^+$ m/z [M + H]$^+$ calcd for $C_{31}H_{31}N_2$ 431.2487, found 431.2502. Anal. Calcd for $C_{31}H_{30}N_2$·0.25H_2O: C, 85.58; H, 7.07; N, 6.44. Found: C, 85.73; H, 7.05; N, 6.60.

*exo,exo-2,8-Dimethyl-6,12-bis(methoxymethyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3c**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.32 mL, 8.86 mmol), *s*-BuLi (0.530 M, 16.6 mL, 8.80 mmol), and MOMCl (0.730 mL, 9.61 mmol). A 1 h lithiation time was used before the addition of the electrophile. Purification by column chromatography (5 cm × 32 cm, 7:3 hexanes/EtOAc) gave *rac*-**3c** as a highly viscous liquid in 81% yield (1.10 g): R_f = 0.16 (7:3 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 2H, H-4 and H-10), 6.97 (dd, J = 8.2, 1.9 Hz, 2H, H-3 and H-9), 6.81 (d, J = 1.5 Hz, 2H, H-1 and H-7), 4.32 (s, 2H, H-13), 4.21 (dd, J = 9.0, 3.8 Hz, 2H, H-6 and H-12), 3.81 (dd, J = 10.4, 9.1 Hz, 2H, -CH_2O-), 3.72 (dd, J = 10.5, 3.8 Hz, 2H, -CH_2O-), 3.54 (s, 6H, -OCH_3), 2.21 (s, 6H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 133.3, 128.9, 128.4, 127.4, 125.3, 76.1, 66.6, 59.4, 57.2 (1C), 21.0; HRMS-ESI$^+$ m/z [M + H]$^+$ calcd for $C_{21}H_{27}N_2O_2$ 339.2073, found 339.2093. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.52; H, 7.77; N, 8.19.

*exo,exo-2,8-Dimethyl-6,12-bis(N,N-diethylcarbamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3d**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.20 mL, 8.05 mmol), *s*-BuLi (1.29 M, 6.20 mL, 8.00 mmol), and *N*,*N*-diethylcarbamoyl chloride (1.30 mL, 10.2 mmol). A 15 min lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 20 h at rt. Purification by column chromatography (5 cm × 10 cm, 3:2 PE/EtOAc) gave *rac*-**3d** as colorless crystals in 42% yield (0.766 g): R_f = 0.12 (7:3 PE/EtOAc); mp 224−226 °C recrystallized from heptane/diethyl ether; IR (NaCl) 2976, 1638, 1490, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.2 Hz, 2H, H-4 and H-10), 6.98 (dd, J = 8.2, 2.0 Hz, 2H, H-3 and H-9), 6.63 (d, J = 1.6 Hz, 2H, H-1 and H-7), 4.89 (s, 2H, H-6 and H-12), 4.49 (s, 2H, H-13), 4.11 (dq, J = 14.6, 7.3 Hz, 2H, N-CH_2-CH$_3$), 3.76 (dq, J = 14.6, 7.3 Hz, 2H, N-CH_2-CH$_3$), 3.55 (dq, J = 13.6, 6.9 Hz, 2H, N-CH_2-CH$_3$), 3.38 (dq, J = 13.6, 6.9 Hz, 2H, N-CH_2-CH$_3$), 2.20 (s, 6H, Ar-CH_3), 1.44 (t, J = 7.0 Hz, 6H, -CH$_2$-CH_3), 1.18 (t, J = 7.0 Hz, 6H, -CH$_2$-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.5, 133.3, 129.5, 129.1, 127.0, 122.8, 67.3, 59.1 (1C), 42.3, 41.3, 21.0, 14.9, 13.0; HRMS-EI$^+$ m/z [M]$^+$ calcd for $C_{27}H_{36}N_4O_2$ 448.2837, found 448.2838. Anal. Calcd for $C_{27}H_{36}N_4O_2$·0.33H_2O: C, 71.33; H, 8.13; N, 12.32. Found: C, 71.05; H, 8.30; N, 12.07.

*exo,exo-2,8-Dimethyl-6,12-bis(N,N-diisopropylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3e**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.20 mL, 8.05 mmol), *s*-BuLi (1.29 M, 6.20 mL, 8.00 mmol), and *N*,*N*-diisopropylcarbamoyl chloride (1.64 g, 10.0 mmol) dissolved in THF (5 mL). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched after the mixture had been stirred for 20 h at rt. Purification by column chromatography (5 cm × 10 cm, 4:1 PE/EtOAc) gave *rac*-**3e** as colorless crystals in 44% yield (0.902 g): R_f = 0.20 (4:1 PE/EtOAc); mp 261−262 °C (heptane/diethyl ether); IR (NaCl) 2970, 1638, 1492, 1443, 1334, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.3 Hz, 2H, H-4 and H-10), 6.95 (dd, J = 8.3, 1.8 Hz, 2H, H-3 and H-9), 6.61 (s, 2H, H-1 and H-7), 5.03 (septet, J = 6.6 Hz, 2H, -C*H*(CH_3)$_2$), 4.87 (s, 2H, H-6 and H-12), 4.37 (s, 2H, H-13), 3.46 (septet, J = 6.7 Hz, 2H, -C*H*(CH_3)$_2$), 2.20 (s, 6H, Ar-CH_3), 1.47−1.37 (m, 24H, -CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 145.3, 132.9, 130.0, 129.0, 127.0, 122.3, 69.2, 59.2 (1C), 49.1, 46.5, 21.4, 21.1, 21.0, 20.7, 20.3; HRMS-EI$^+$ m/z [M]$^+$ calcd for $C_{31}H_{44}N_4O_2$ 504.3464, found 504.3469. Anal. Calcd for $C_{31}H_{44}N_4O_2$·0.5H_2O: C, 72.48; H, 8.83; N, 10.91. Found: C, 72.68; H, 9.06; N, 10.56.

*endo-6-(N,N-Diethylcarbamoyl)-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**4**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was subjected to the general procedure using TMEDA (1.30 mL, 8.72 mmol), *sec*-BuLi (1.30 M, 6.80 mL, 8.84 mmol), and *N*,*N*-diethylcarbamoyl chloride (0.610 mL, 4.81 mmol). A 1 h lithiation time was used before the addition of the electrophile. The reaction was quenched with 10 mL of $NaHCO_3$ [aq, 10% (w/w)] after the mixture had been stirred for 4 h at rt. Purification by column chromatography (5 cm × 18 cm, 3:2 PE/EtOAc) gave *rac*-**4** as colorless crystals in 31% yield (0.439 g): R_f = 0.25 (3:2 PE/EtOAc); mp 155−157 °C (heptane/diethyl ether); IR (neat) 1641, 1489, 1428, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.1 Hz, 1H, H-10), 7.00 (dd, J = 8.2, 1.9 Hz, 1H, H-9), 6.81 (dd, J = 8.1, 1.4 Hz, 1H, H-3), 6.76 (brs, 1H, H-7), 6.72 (d, J = 8.2 Hz, 1H, H-4), 6.70 (brs, 1H, H-1), 5.40 (s, 1H, H-6), 4.64 (d, J = 16.8 Hz, 1H, H-12x), 4.41 (dd, J = 12.6, 1.5 Hz, 1H, H-13), 4.41−4.32 (m, 3H, N-CH_2-CH$_3$), 4.33 (d, J = 12.6 Hz, 1H, H-13′), 4.19 (d, J = 16.7 Hz, 1H, H-12n), 3.85−3.76 (m, 1H, N-CH_2-CH$_3$), 3.46 (dq, J = 14.9, 7.3 Hz, 1H, N-CH_2-CH$_3$), 3.26 (dq, J = 13.7, 6.9 Hz, 1H, N-CH_2-CH$_3$), 2.23 (s, 3H, Ar-CH_3), 2.18 (s, 3H, Ar-CH_3), 1.38 (t, J = 7.2 Hz, 3H, -CH$_2$-CH_3), 1.29 (t, J = 7.1 Hz, 3H, -CH$_2$-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 145.8, 141.4, 134.6, 133.4, 129.5,

DOI: 10.1021/acs.joc.5b01921
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128.8, 128.4, 127.2, 127.1, 126.94, 126.91, 125.0, 68.5, 65.9, 58.7, 41.7, 40.7, 21.2, 21.0, 15.2, 12.6; HRMS-ESI$^+$ m/z $[M + Na]^+$ calcd for $C_{22}H_{27}N_3ONa$ 372.2099, found 372.2052. Anal. Calcd for $C_{22}H_{27}N_3O{\cdot}0.14EtOAc$: C, 74.88; H, 7.83; N, 11.61. Found: C, 74.97; H, 7.44; N, 11.41.

*exo,exo-2,8-Dimethyl-12-benzyl-6-trimethylsilyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**5**).* To a solution of TB *rac*-**1** (1.00 g, 3.99 mmol) in anhydrous THF (30 mL) was added TMEDA (8.05 mmol, 1.20 mL), and the resulting faint yellow solution was stirred at rt for 30 min under an inert atmosphere before being cooled to −78 °C for 15 min. *s*-BuLi (1.30 M, 4.03 mmol, 3.10 mL) was then added dropwise over 15 min, and the resulting reaction mixture was additionally stirred for 1 h before TMSCl (4.02 mmol, 0.510 mL) was added dropwise over 15 min. The resulting reaction mixture was allowed to stir for 1 h. *s*-BuLi (4.03 mmol, 3.10 mL) was then added dropwise over 15 min, and the resulting reaction mixture was stirred for an additional 1 h before benzyl bromide (4.20 mmol, 0.500 mL) was added over 15 min. The reaction mixture was left in the cooling bath to slowly reach rt, and after the mixture had been stirred for 15 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by CH_2Cl_2 (30 mL) and water (30 mL). The resulting layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to dryness. The resulting residue was purified by column chromatography (5 cm × 20 cm, 20:1 PE/EtOAc) to give *rac*-**5** as colorless crystals in 24% yield (0.403 g): R_f = 0.28 (60:1 PE/EtOAc); mp 156−158 °C recrystallized from heptane/diethyl ether; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.37 (m, 4H, Ar-*H*), 7.32−7.27 (m, 1H, Ar-*H*), 6.96−6.91 (m, 2H, H-3 and H-4), 6.78 (s, 1H, H-1), 6.70 (dd, J = 8.1, 1.7 Hz, 1H, H-9), 6.54 (s, 1H, H-7), 6.39 (d, J = 8.1 Hz, 1H, H-10), 4.35 (dd, J = 12.9, 1.5 Hz, 1H, H-13), 4.16 (dd, J = 10.2, 4.2 Hz, 1H, H-12), 4.08 (d, J = 13.0 Hz, 1H, H-13′), 3.81 (s, 1H, H-6), 3.14 (dd, J = 14.1, 4.3 Hz, 1H, -C*H*$_2$-Ph), 3.08 (dd, J = 14.1, 10.2 Hz, 1H, -C*H*$_2$-Ph), 2.22 (s, 3H, Ar-C*H*$_3$), 2.13 (s, 3H, Ar-C*H*$_3$), 0.24 (s, 9H, -Si(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 146.0, 140.4, 132.7, 132.6, 131.0, 130.9, 129.7, 128.47, 128.42, 128.3, 126.8, 126.7, 126.4, 124.9, 124.8, 69.6, 63.4, 60.1, 43.4, 21.2, 21.1, −1.1; HRMS-ESI$^+$ m/z $[M + H]^+$ calcd for $C_{27}H_{33}N_2Si$ 413.2413, found 413.2413. Anal. Calcd for $C_{27}H_{32}N_2Si{\cdot}0.25H_2O$: C, 77.74; H, 7.88; N, 6.72. Found: C, 77.71; H, 7.82; N, 6.79.

General Procedure for the Inverse-Addition Method. *exo-2,8-Dimethyl-6-trimethylsilyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2a**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (0.57 mL, 3.8 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 2.70 mL, 3.78 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 1 h, after which it was added rapidly via a cannula to a flask of vigorously stirred TMSCl (10.0 mL, 79.0 mmol) cooled to −39 °C (1 °C above the freezing point). The reaction mixture was cooled to −78 °C and left to stir to slowly reach rt over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL), after which diethyl ether (50 mL) and water (30 mL) were added. The phases were separated. The aqueous phase was extracted with an additional 2 × 30 mL of diethyl ether. The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and evaporated *in vacuo* to dryness. The resulting residue was purified by column chromatography (3 cm × 10 cm, 9:1 PE/EtOAc) gave *rac*-**2a** as colorless crystals in 72% yield (0.93 g): R_f = 0.25 (9:1 PE/EtOAc); mp 128−130 °C (heptane/EtOAc). Spectral data were identical to those observed using the direct-addition method.

*exo-2,8-Dimethyl-6-(N,N-diethylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2d**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (0.57 mL, 3.8 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 2.70 mL, 3.78 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 1 h, after which it was added rapidly via a cannula to a flask of vigorously stirred Et_2NCOCl (109 mmol, 10 mL) in dry THF (10 mL) cooled to −78 °C. The reaction mixture was left to stir to reach rt over 15 h. The reaction mixture was quenched and worked up as in the general procedure for the inverse-addition method. The excess Et_2NCOCl was removed by vacuum distillation (bp 42−48 °C, 5 mbar). Purification by column chromatography (5 cm × 10 cm, 3:2 PE/EtOAc) gave *rac*-**2d** as colorless crystals in 70% yield (0.97 g): R_f = 0.12 (7:3 PE/EtOAc); mp 224−226 °C (heptane/diethyl ether). Spectral data were identical to those observed using the direct-addition method.

*exo-2,8-Dimethyl-6-(N,N-diisopropylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2e**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (0.57 mL, 3.8 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 2.71 mL, 3.79 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 1 h, after which it was added rapidly via cannula to a flask of vigorously stirred *i*Pr$_2$NCOCl (5.00 g, 30.6 mmol) in dry THF (10 mL) cooled to −78 °C. The cooling system (dry ice bath) was removed, and the reaction mixture was left to stir to reach rt over 2 h. The reaction mixture was quenched and worked up as in the general procedure for the inverse-addition method. Purification by column chromatography (5 cm × 10 cm, 3:2 PE/EtOAc) gave *rac*-**2e** as colorless crystals in 73% yield (1.07 g): R_f = 0.35 (7:3 PE/EtOAc); mp 201−203 °C (heptane/EtOAc). Spectral data were identical to those observed using the direct-addition method.

*exo,exo-2,8-Dimethyl-6,12-bis(trimethylsilyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3a**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (1.8 mL, 12.0 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 8.60 mL, 12.0 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 1 h, after which it was added rapidly via cannula to a flask of vigorously stirred TMSCl (79 mmol, 10 mL) cooled to −39 °C (1 °C above the freezing point). The reaction mixture was cooled to −78 °C and left to stir to slowly reach rt over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL), and diethyl ether (50 mL) and water (30 mL) were added. The phases were separated. The aqueous phase was extracted with an additional 2 × 30 mL of diethyl ether. The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and evaporated *in vacuo* to dryness. Purification by column chromatography (5 cm × 20 cm, 20:1 PE/EtOAc) gave *rac*-**3a** as colorless crystals in 89% yield (1.4025 g): R_f = 0.28 (40:1 PE/EtOAc); mp 139−141 °C (heptane/diethyl ether). Spectral data were identical to those observed using the direct-addition method.

*exo,exo-2,8-Dimethyl-6,12-bis(benzyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3b**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (1.8 mL, 12.0 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 8.60 mL, 12.0 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 2 h, after which the solution was added rapidly via cannula to a solution of BnBr (10.0 mL, 84.2 mmol) in dry THF (10 mL) cooled to −78 °C. The reaction mixture was left to stir to reach rt over 15 h. The solvent and excess BnBr were removed by vacuum distillation, and the residue was dissolved in 50 mL of dichloromethane and 50 mL of water. The phases were separated. The aqueous phase was extracted with an additional 2 × 50 mL of dichloromethane. The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and evaporated *in vacuo* to dryness. Purification by column chromatography (5 cm × 10 cm, 4:1 PE/EtOAc) gave *rac*-**3b** as white crystals in 96% yield (1.65 g): R_f = 0.30 (4:1 PE/EtOAc); mp 220−222 °C (heptane/diethyl ether). Spectral data were identical to those observed using the direct-addition method.

*exo,exo-2,8-Dimethyl-6,12-bis(N,N-diethylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3d**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (1.80 mL, 12.0

DOI: 10.1021/acs.joc.5b01921
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mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 8.6 mL, 12.0 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 2 h, after which the solution was added rapidly via cannula to a solution of Et_2NCOCl (10.0 mL, 109 mmol) in THF (10 mL) cooled to −78 °C. The reaction mixture was left to stir to reach rt over 15 h. The reaction mixture was quenched and worked up as in the general procedure for the inverse-addition method. The excess Et_2NCOCl was removed by vacuum distillation (bp 42−48 °C, 5 mbar). The crude could either be recrystallized from heptane and diethyl ether to yield 58% (1.05 g) pure *rac*-**3d** as colorless crystals: mp 224−226 °C. Alternatively, purification by column chromatography (5 cm × 10 cm, 3:2 PE/EtOAc) would yield *rac*-**3d** as colorless crystals in 97% yield (1.73 g): R_f = 0.12 (7:3 PE/EtOAc); mp 224−226 °C (heptane/diethyl ether). Spectral data were identical to those observed using the direct-addition method.

*exo,exo-2,8-Dimethyl-6,12-bis(N,N-diisopropylamide)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**3e**).* TB *rac*-**1** (1.00 g, 3.99 mmol) was dissolved in dry THF at rt, and TMEDA (1.80 mL, 12.0 mmol) was added to the stirred solution. The solution was cooled to −78 °C for 15 min, after which *s*-BuLi (1.40 M, 8.6 mL, 12.0 mmol) was added dropwise over 30 min at −78 °C. The solution was left at −78 °C for 2 h, after which the solution was added rapidly via cannula to a solution of iPr_2NCOCl (5.00 g, 30.6 mmol) in THF (10 mL) cooled to −78 °C. The reaction mixture was left to stir to reach rt over 15 h. The reaction mixture was quenched and worked up as in the general procedure for the inverse-addition method. Crystallization from heptane and diethyl ether yielded 1.41 g (70.0% yield) of *rac*-**3e** as colorless crystals. The mother liquor was evaporated, and the residue was purified by column chromatography (5 cm × 10 cm, 4:1 PE/EtOAc), giving an additional 0.44 g (0.87 mmol, 22.0% yield) of *rac*-**3e** as colorless crystals: R_f = 0.20 (4:1 PE/EtOAc); mp 261−262 °C recrystallized from heptane/diethyl ether. Spectral data were found to be identical to those observed using the direct-addition method.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01921.

X-ray crystallographic file for *rac*-**2b** (CIF)
X-ray crystallographic file for *rac*-**3c** (CIF)
Copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds and NOESY spectra for compounds **2d** and **4** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Swedish Research Council and the Royal Physiographic Society in Lund for funding.

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J. Org. Chem. 2015, 80, 12006−12014