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# 2,6,7-Trithiabicyclo[2.2.2]octanes as Promising Photolabile Tags for Combinatorial Encoding

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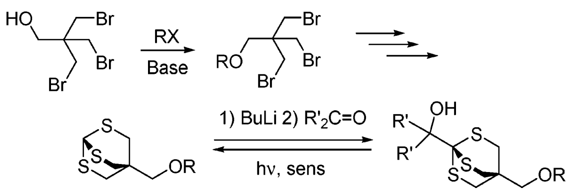
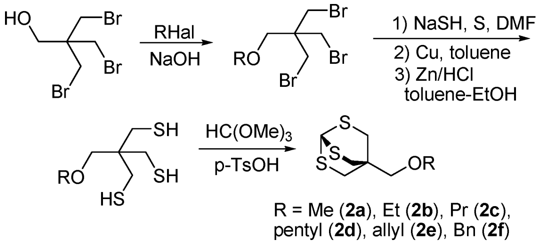


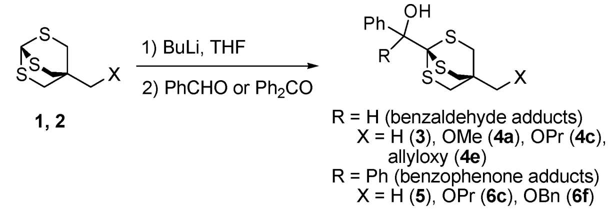
The adducts of trithiabicyclo[2.2.2]octane (TTBO) and carbonyl compounds undergo efficient photoinduced fragmentation with quantum yields comparable to that of dithiane adducts. The effect of the third sulfur on the stability of the respective radical cations and radicals is examined computationally and experimentally in a laser flash photolysis study. A straightforward synthetic approach to a variety of 4-substituted trithiabicyclo[2.2.2]octanes from 3-bromo-2,2-bis(bromomethyl)propanol is developed, making a diverse set of mass-differentiated photolabile tags readily available for combinatorial encoding.

We have been developing photolabile systems capable of detecting molecular recognition events. The methodology is based on sensitized photofragmentations in α-hydroxyalkyldithianes,[1] which can be made contingent on an external molecular recognition event and therefore can be used to detect and report such events at a molecular level. Most recently, we have adopted this methodology to the encoding and screening of solution-phase combinatorial libraries, either unsupported or immobilized on nanosized carriers too small for mechanical manipulations.[2] The encoding dithiane-based tags are released into solution only when a binding event occurs between the ligand and the receptor, outfitted with an electron-transfer sensitizer. The released tags are detected by ubiquitous analytical techniques, such as GCMS, and used as binary digits revealing the identity of the lead ligand or narrowing the range of potential leads. The following considerations were taken into account in designing the tags: the tags should (i) be amendable for detection at very low concentrations by ubiquitous analytical techniques; (ii) not possess any functional groups implicated in biological interactions; (iii) not interfere with synthetic steps; (iv) be easy to separate from the aqueous screening environment, for example, due to significant hydrophobicity; and (v) be accessible via a simple and straightforward synthetic approach. We have demonstrated that 2-alkyl-1,3-dithianes satisfy these requirements and can be used for encoding as binary digits. Low oxidation potential of dithianes, the very property which aids the photoinduced electron-transfer fragmentation, makes them also amenable for high-sensitivity MS detection with electron impact ionization. Individual dithianes can be detected with a greater than 10:1 signal-to-noise ratio at a subpicomolar level using a standard mass-produced HP GCMS.

**SCHEME 1**



**SCHEME 2**



As a large set of tags may be needed for the encoding of high-dimensional combinatorial libraries, we systematically sought other di- or trisulfides that can be utilized as photoactive molecular encoding tags. In this note, we report that a diverse auxiliary set of mass-differentiated 2,6,7-trithiabicyclo[2.2.2]octanes (TTBO) can be readily synthesized and used for combinatorial encoding. The photophysical properties of the synthesized TTBO adducts with carbonyl compounds were investigated experimentally and computationally.

4-Methyl-TTBO (**1**) was first described in 1955 by Doering.[3] A decade later, as a part of the umpolung strategy development, reaction of lithiated TTBO with electrophiles was described by Seebach.[4] 4-Methyl-TTBO ($\mathrm{p}K_a^{\mathrm{DMSO}}$ 30.5) is over 8 orders of magnitude more acidic than 1,3-dithiane ($\mathrm{p}K_a^{\mathrm{DMSO}}$ ∼39),[5] which makes it easier to deprotonate for subsequent reactions with electrophiles.

We found that a diverse set of 4-alkoxymethyl TTBOs can be synthesized starting from inexpensive commercially available pentaerythritol tribromide as shown in Scheme 1. TTBOs were then lithiated and reacted with benzaldehyde or benzophenone to give photoactive adducts **3**−**6** (Scheme 2).

The most likely mechanism of photoinduced fragmentation in adducts **3**−**6** in the presence of benzophenone as an electron-

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(1) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924−9931.

(2) Kottani, R.; Valiulin, R. A.; Kutateladze, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 13917−13921.

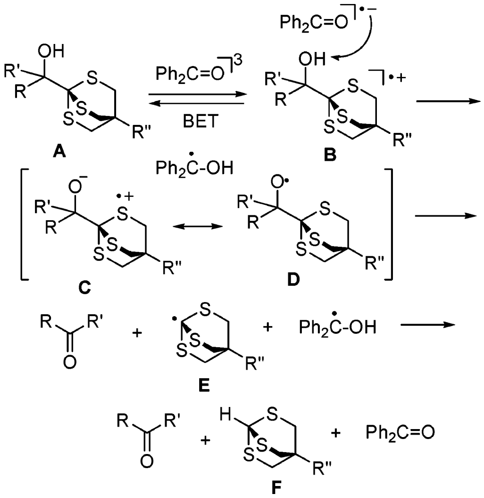
(3) Doering, W. v. E.; Levy, L. K. *J. Am. Chem. Soc.* **1955**, *77*, 509−513.

(4) Seebach, D.; Geiss, K. H.; Beck, A. K.; Graf, B.; Daum, H. *Chem. Ber.* **1972**, *105*, 3280−3300.

(5) (a) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van, der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326−332. (b) Bordwell, F. G.; Drucker, G. E.; Andersen, N. H.; Denniston, A. D. *J. Am. Chem. Soc.* **1986**, *108*, 7310−7313.

10.1021/jo702091e CCC: $40.75

SCHEME 3



transfer sensitizer is shown in Scheme 3. It involves photoinduced electron transfer from the trithiabicyclo[2.2.2]octane moiety to excited triplet benzophenone, followed by mesolytic fragmentation in the generated radical cation. The fragmentation is assisted by the benzophenone radical anion deprotonating the hydroxy group in radical cation **B**. In the fragmentation mechanism for the similar dithiane-based adducts, we found evidence[6] that such deprotonation is coupled with intramolecular electron transfer, furnishing the oxygen centered radical of type **D**, which fragments spontaneously, although the fragmentation concerted with deprotonation or the involvement of the charge separated species **C** was not completely ruled out.

**TABLE 1. Relative Quantum Yields of Fragmentation**

| | $CD_3CN$ | $CD_2Cl_2$ |
|---|---|---|
| Benzophenone adducts | | |
| **5** | 1.69 | 1.83 |
| **6c** | 1.01 | − |
| **6f** | 1.53 | − |
| benzophenone-methyldithiane | (1.0) | (1.0) |
| Benzaldehyde adducts | | |
| **3** | 0.64 | − |
| **4a** | 0.69 | 0.61 |
| **4c** | 0.49 | − |
| **4e** | 0.39 | − |
| benzaldehyde-methyldithiane | (1.0) | (1.0) |

As the primary focus of this study was to develop an auxiliary set of encoding tags other than dithiane adducts, we compared the photophysical properties of adducts **3**−**6** with those of dithiane adducts. As follows from Table 1, the overall quantum yields of fragmentation for TTBO-benzophenone adducts are improved over dithianes, whereas their benzaldehyde adducts fragmented with somewhat lesser relative efficiency.

Our nanosecond laser flash photolysis (LFP) experiments showed that the rate of initial electron-transfer quenching of the sensitizer's triplet state was also faster for the TTBO adducts (Table 2). In the sterically hindered benzophenone adduct, the partitioning of the ion radical pair **B** between the productive fragmentation channel and the wasteful back electron transfer (BET) primarily controls the quantum yield of fragmentation. The TTBO moiety, which contains three sulfur atoms, is more accessible and also is expected to produce a more stable radical cation, improving the driving force for the forward electron transfer and rendering the BET less likely. Both the improved quantum yields for the benzophenone adducts and the faster rate of initial electron-transfer quenching seem to corroborate this conclusion. In the benzaldehyde adducts, the fragmentation channel appears to be more sensitive to the lower stability of the TTBO radical.

**TABLE 2. Electron-Transfer Rate Constants for TTBO or Methyldithiane Adducts of Benzophenone and Benzaldehyde in MeCN**

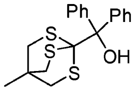
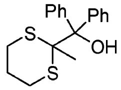
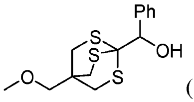
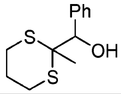
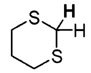
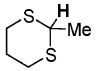
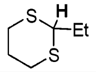
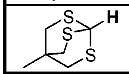
| TTBO or Dithiane Compounds | $k_{ET}$, $M^{-1}$ $s^{-1}$ |
|---|---|
| Benzophenone adducts | |
|  (**5**) | $13.7 \pm 1.3 \times 10^8$ |
|  | $5.7 \pm 0.45 \times 10^8$ |
| Benzaldehyde adducts | |
|  (**4a**) | $16.7 \pm 4.2 \times 10^8$ |
|  | $8.44 \pm 0.99 \times 10^8$ |

**TABLE 3.**[a]

| R-H | $R\text{-}H^{+\bullet}$ | | R• |
|---|---|---|---|
| | Vertical IP, eV | Non-vertical IP, eV | RSE[b] kcal/mol |
|  | 8.18[c] | 7.84 | 17.0 |
|  | 8.05 | 7.66 | 18.2 |
|  | 7.98 | 7.58 | 18.4 |
|  | 7.70 | 7.50 | 7.9 |

[a] Zpe (zero point energy)-corrected b3lyp/6-311+g(2d,p)//b3lyp/6-311+g(2d,p) energies (except for the vertical IP, which is not corrected). [b] Radical resonance stabilization energy. [c] Calcd IP is 0.36 eV lower than the reported experimental value (ref[12]); the relative values are more significant.

DFT computations at the B3LYP/6-311+G(2d,p) level show that the gas-phase vertical ionization potential of the parent 4-methyl-TTBO is almost 0.5 eV lower than dithiane's (Table 3). A simple MO picture helps understand this in semiqualitative terms. The radical cation in dithianes is stabilized due to the formation of 3-electron-2-center bond between two sulfurs.[7] The $C_3$ symmetric TTBO framework offers additional stabilization in a form of cyclic array of atomic orbitals which

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(6) Li, Z.; Kutateladze, A. G. *J. Org. Chem.* **2003**, *68*, 8236−8239.

(7) For a review on the 2-center-3-electron sulfur-sulfur bonds, see: Asmus, K.-D. *Acc. Chem. Res.* **1979**, *12*, 436−442.

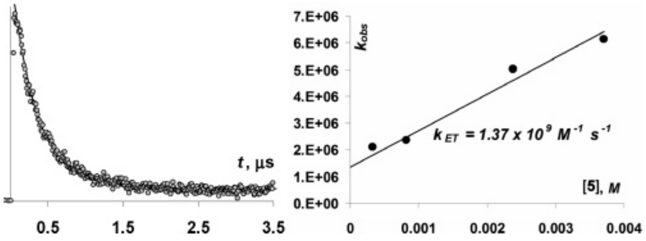

**FIGURE 1.** Typical LFP waveform at 520 nm (left) and a typical concentration series for determination of the second-order electron-transfer rate constant, $k_{\mathrm{ET}}$ (right), for the benzophenone adduct **5**.

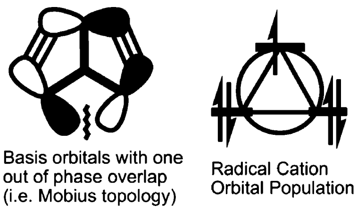

**FIGURE 2.** Möbius cyclopropenyl topology.

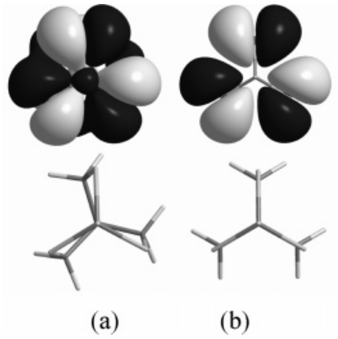

**FIGURE 3.** TTBO: (a) $C_3$-symmetric (twisted) ground state and its HOMO (b) $C_{3v}$-symmetric radical cation and its SOMO.

can be loosely referred to as a 3-center-5-electron bond. In the neutral precursor, the three p lone pairs are considerably destabilized by repulsion. A more helpful way of thinking about this is to apply Zimmerman's circular mnemonic[8] to the 6-electron Möbius antiaromatic arrangement of sulfurs' p lone pairs in TTBO (i.e., Möbius cyclopropenyl topology), Figure 2. Removal of an electron from this system relieves the unfavorable orbital interaction, leading to lower ionization potential.

This rationale finds support in DFT computations with an extended triple-ζ basis set, 6-311+G(2d,p). The neutral ground state TTBO has a twisted $C_3$ symmetry, where the lone pairs repulsion is somewhat minimized by a screw-type distortion from the $C_{3V}$ structure. On the contrary, the radical cation of TTBO has a perfect $C_{3V}$ geometry, which is a true minimum as shown by vibrational analysis. Its antisymmetric singly occupied HOMO (i.e., SOMO) is shown in Figure 3b.

Although the quantum yields of fragmentation generally correlate with the stability of radical cations, there is no correlation with the stability of the resulting radical (of type **E**, Scheme 3). We calculated the radical resonance stabilization energies (RSE) for unsubstituted and substituted dithian-2-yl radicals and radical **E** at the B3LYP/6-311+G(2d,p) level of theory based on Pasto's[9] isodesmic reaction R-H + $CH_3\bullet \rightarrow R\bullet + CH_4$ (Table 3). The RSE for **E** (7.9 kcal/mol) is a factor of 2 smaller, which can be rationalized in terms of unfavorable overlap between sulfurs' p lone pairs and the singly occupied orbital on the pyramidalized carbon radical center.

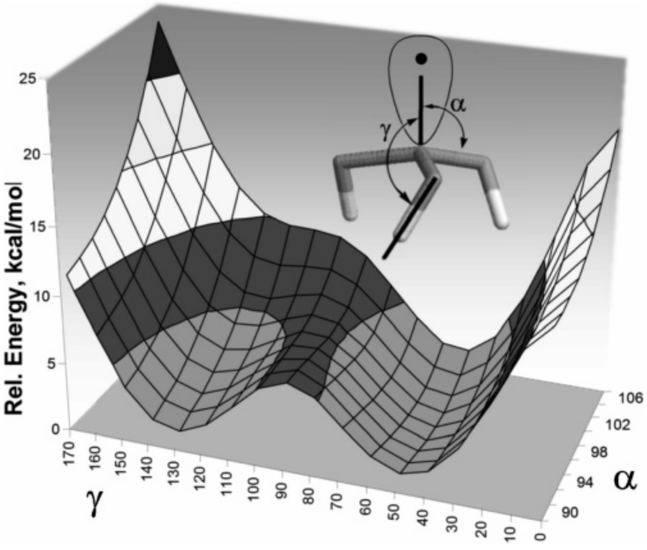

**FIGURE 4.** DFT, B3LYP/6-311+G(2d,p), potential energy surface of $C_3$-symmetric $(HS)_3C\bullet$ radical with a global minimum at $\alpha = 98.1°$ and $\gamma = 51.3°$.

Zpe-corrected DFT activation energy for the fragmentation of the oxy-radical **D** (benzophenone adduct) is 4.8 kcal/mol. Such DFT barrier for fragmentation in benzophenone-ethyldithiane is much smaller, 1.7 kcal/mol for the most favorable conformation (experimental $\Delta H^{\ddagger} = 1.5$ kcal/mol).[10] Due to decreased resonance stabilization of radical **E**, fragmentation of the oxygen centered radical **D** has a late transition state, with the stretched CC bond length of 1.927 Å, compared to only 1.745 Å for the corresponding methyl-dithiane adduct and 1.735 Å for the ethyldithiane adduct.

To better understand the effect of geometry on stabilization of the radical center in tris-alkylthiomethyl radicals we have scanned the potential energy surface for the parent tris-mercaptomethyl radical, $(HS)_3C\bullet$, as a function of two variables: (i) the pyramidalization angle α, defined as the angle between the singly occupied orbital on carbon and the C−S bond, that is, S−C-⟨•⟩ and (ii) the torsional dihedral γ, defined as H−S−C-⟨•⟩. The rest of internal variables were optimized without constraints at the B3LYP/6-311+G(2d,p) level of theory (Figure 4).

The radical's relaxed geometry is more planar with only a slight pyramidalization ($\alpha = 98.1°$). The SH bonds, however, deviate from the SSS plane, with torsional dihedral $\gamma = 51.3°$. In the TTBO radical α and γ are constrained by the bicyclic framework to 103.9 and 166.5°, respectively. Although this pyramidalization of 103.9° is less pronounced than in the parent hydrocarbon for which $\alpha = 107.1°$, the geometry constraints decrease the radical resonance stabilization energy for TTBO radical by 10 kcal/mol compared with dithianyl radicals (Table 3).

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[8] (8) Zimmerman, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 1564−1565. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272−280.

[9] (9) (a) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062−3072. (b) Pasto, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 8164−8175.

[10] (10) Gustafson, T. P.; Kurchan, A. N.; Kutateladze, A. G. *Tetrahedron* **2006**, *62*, 6574−6580.

However, it is not surprising that the relatively low stability of TTBO radical (**E**) does not have as large a detrimental effect on the efficiency of fragmentation as does the back electron transfer. Enhanced stability of the TTBO radical cations seems to play a critical role in the fragmentation mechanism. Additionally, the overall effect on the quantum efficiency of fragmentation is mitigated by yet another factor: the accessibility of sulfurs for the sensitizer approach, which enhances the rates of the initial electron-transfer quenching, $k_{ET}$, of triplet benzophenone. The LFP experiments consistently show that $k_{ET}$ for the TTBO adducts are greater than for dithiane adducts. These rates also correlate (i.e., are attenuated) with the steric crowding introduced by the carbonyl component: the adducts with benzaldehyde quench the triplet sensitizer with a 40−50% higher rate than the more crowded adducts of benzophenone (Table 2).

The features discussed above account for the superior quantum yields of sensitized fragmentation in benzophenone adducts of TTBOs compared with benzophenone adduct of methyldithiane. Although the benzaldehyde adducts of TTBOs showed somewhat lesser quantum efficiencies, when compared with benzaldehyde adduct of methyldithiane (Table 1), adducts **4** with alkoxy substituents were found to be adequate for tagging as they cleanly produce TTBO tags upon sensitized irradiation. Only allylic compound **4e** produced traces of side product, which is conceivably the result of Paternò-Büchi cycloaddition of the sensitizer to the double bond.

Similar to dithianes, TTBOs **1** and **2** can be detected with excellent sensitivity using mass-produced analytical instruments, for example, GCMS. The enhanced stability of their radical cations accounts for their low detection limit.

In conclusion, 4-substituted trithiabicyclo[2.2.2]octanes are versatile and readily accessible mass-differentiated tags for the encoding of combinatorial libraries, which can be photoreleased with high quantum efficiencies and detected in minute amounts by ubiquitous analytical techniques.

## Experimental Section

**General Procedure for Preparation of TTBOs. (A) 1-Bromo-2,2-bis(bromomethyl)-3-alkoxypropanes.** Fine-powdered KOH was added to a vigorously stirred solution of 3-bromo-2,2-bis(bromomethyl)propanol and an alkyl halide in 35 mL of DMSO. The temperature was kept below 60 °C using an ice bath. After the initial exothermic step, the stirred solution was heated at 60 °C for 2 h and cooled to 20 °C; 100 mL of water was added, and the aqueous phase was extracted with 3 × 50 mL of $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ followed by the removal of the solvent.

**(B) 2,2-Bis(mercaptomethyl)-3-alkoxypropanethiol.** $NaHS·9H_2O$ and elementary sulfur powder were dissolved in DMF upon warming, heated at 80 °C for 1 h, and cooled to ~ 40 °C, and then the 1-bromo-2,2-bis(bromomethyl)-3-alkoxypropane (from step A) was added. The temperature was raised to 80−90 °C and kept there for 7−8 h. DMF was removed under reduced pressure, and copper powder and toluene (30 mL) were added to the resulting crude product and refluxed overnight. Black copper sulfide was filtered off, then zinc dust and 20−30 mL of ethanol were added to the yellow filtrate. Concentrated HCl was added dropwise under stirring. The resulting solution was stirred for 24 h under nitrogen; the toluene layer was separated from the ethanol−water mixture, washed with water (20 mL), and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to furnish oil with a characteristic smell, which was used without further purification.

**(C)** 4-Alkoxymethyl-2,6,7-trithiabicyclo[2.2.2]octane. The solution of 2,2-bis(mercaptomethyl)-3-alkoxypropanethiol (from step B) and methyl orthoformate in toluene with several crystals of $TsOH•H_2O$ was refluxed for 24 h, washed with saturated $NaHCO_3$ and water, and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the resulting yellow solid was purified by column chromatography (silica gel, hexane/EtOAc, 20:1).

**1-Bromo-2,2-bis(bromomethyl)-3-methoxypropane:** Prepared from 5.13 g (91.5 mmol) of KOH, 7.00 g (20.8 mmol) of 3-bromo-2,2-bis(bromomethyl)propanol and 13.00 g (91.5 mmol) of iodomethane in 35 mL of DMSO: 5.49 g, 78%.

**2,2-Bis(mercaptomethyl)-3-methoxypropanethiol:** Prepared from 3.23 g (57.7 mmol) of $NaSH·9H_2O$, 2.6 g (81.3 mmol) of S powder, 4.88 g (14.4 mmol) of 1-bromo-2,2-bis(bromo-methyl)-3-methoxypropane, 2.5 g (39.3 mmol) of Cu powder, 13.7 g of Zn dust (216 mmol) and 70 mL of conc. HCl. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.33 (s, 3H), 3.29 (s, 2H), 2.62 (d, 6H, $J = 8.9$ Hz), 1.22 (t, 3H, $J = 8.9$ Hz).

**4-Methoxymethyl-2,6,7-trithiabicyclo[2.2.2]octane (2a):** Prepared from 2.86 g (14.5 mmol) of 2,2-bismercaptomethyl-3-methoxypropane-1-thiol, 2.3 g (21.7 mmol) of methyl orthoformate: 2.77 g (92%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.60 (s, 1H), 3.37 (s, 3H), 3.19 (s, 2H), 3.05 (s, 6H). $^{13}C$ NMR (500 MHz, $CDCl_3$) $\delta$ 80.55, 59.43, 39.04, 33.29,30.68.

**General Procedure for Preparation of Adducts 3−6.** *n*-BuLi (1.6 M in hexane) was added to TTBO in 5−10 mL of THF under nitrogen and stirred for 10−15 min at 25 °C, at which point a 2 mL solution of benzaldehyde or benzo-phenone in THF was added and stirred for 3 h, quenched with aqueous ammonium chloride, extracted with $CH_2Cl_2$ (2 × 20 mL), and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the crude material was purified by column chromatography on silica gel (hexane/EtOAc).

**Adduct 4a:** Prepared from 100 mg (0.48 mmol) of 4-methoxymethyl-2,6,7-trithiabicyclo[2.2.2]octane (**2a**), 0.66 mL (1.06 mmol) of *n*-BuLi (1.6 M in hexane), and 76 mg (0.72 mmol) of benzaldehyde: 47 mg (31%) after purification on silica gel, hexane/EtOAc = 10:1, then 3:1. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.57 (m, 2H), 7.38 (m, 3H), 5.00 (d, 1H, $J = 3.1$ Hz), 3.34 (s, 3H), 3.18 (dd, 2H, $J = 14.9.$ Hz, $J = 9.01$ Hz), 3.05 (dd, 3H, $J = 11.7$ Hz, $J = 2.0$ Hz), 2.95 (d, 1H, $J = 3.3$ Hz), 2.93 (dd, 3H, $J = 11.7$ Hz, $J = 2.0$ Hz). $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 136.87, 129.00, 128.32, 127.81, 79.83, 78.27, 65.90, 59.39, 34.76, 32.52.

**Computational Methods.** The structures and the energies were computed with Gaussian 03, Rev. C02, computational package.[11] The values in Table 3 and elsewhere in the text represent zpe-corrected B3LYP/6-311+G(2d,p) energies, obtained for geometries optimized at the same theory level.

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**Supporting Information Available:** Additional experimental information, spectra, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Frisch, M. J.; et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2003.

[12] Sweigart, D. A.; Turner, D. W. *J. Am. Chem. Soc.*, **1972**, *94*, 5599−5603.