Pot-Economy Autooxidative Condensation of 2-Aryl-2-lithio-1,3-dithianes

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Supporting Information

ABSTRACT: The autoxidative condensation of 2-aryl-2-lithio-1,3-dithianes is here reported. Treatment of 2-aryl-1,3-dithianes with n-BuLi in the absence of any electrophile leads to condensation of three molecules of 1,3-dithianes and formation of highly functionalized α-thioether ketones ortho-thioesters in 51–89% yields upon air exposure. The method was further expanded to benzaldehyde dithioacetals, affording corresponding ortho-thioesters and α-thioether ketones in 48–97% yields. The experimental results combined with density functional theory studies support a mechanism triggered by the autoxidation of 2-aryl-2-lithio-1,3-dithianes to yield a highly reactive thioester that undergoes condensation with two other molecules of 2-aryl-2-lithio-1,3-dithiane.

INTRODUCTION

Organolithium compounds can undergo autoxidation toward formation of highly unstable organolithium peroxides, which upon fast interaction with another organolithium leads to the ultimate formation of lithium alkoxides.1 Oxidation of RLi with ROOLi was proven by Müller and Töpel2 in 1939 and used in several oxidative processes,3 and the autoxidation of organolithiums further explored in preparation of alcohols.4

The first reports of Corey and Seebach5 on the use of lithiated 1,3-dithianes as synthetic equivalents to acyl anions have rapidly gathered the attention of the synthetic community. The umpolung strategy rendered by transformation of aldehydes to 2-substituted 1,3-dithianes and subsequent formation of the lithiated acyl anion equivalent have been explored for preparation of a wide array of products,6,7 namely in natural product synthesis.8 Other thioacetals can lead to the formation of similar acyclic lithiated anions,9 but it was soon realized that cyclic 2-lithio-1,3-dithianes were advantageous due to their ease of preparation and general suitability.10 Despite the undisputable importance of 2-lithio-1,3-dithianes in synthetic chemistry, inconsistent yields and formation of side products have been reported.10 Problems derived from its high reactivity and strong basicity have been overcome either by transmetalation,11−13 or using less reactive silyl,14−16 or tin10a,17 analogues. The autoxidation of 2-lithio-1,3-dithiane (Scheme 1) upon air exposure has been reported by Wade and co-workers,18 after observing formation of 1 and 2 in absence of an electrophile. The formation of 1 was also later reported by Argade and co-workers when preparing 2-lithio-1,3-dithiane.19

Scheme 1

Argade and co-workers when preparing 2-lithio-1,3-dithiane.19

The presence of an oxidizing impurity in older bottles of n-BuLi was advanced as the cause for the formation of the oxidized products. The same compound was reported to be formed in 25% yield when preparing 2-lithio-1,3-dithiane in THF, proposed by the authors to arise from the unlikely reaction of the desired intermediate with solvent.20 Presence of dimers
derived from single electron transfer processes have been observed in several other works, especially in the presence of nitro substituted compounds. The nucleophilic addition of 2-lithio-1,3-dithianes to acyl chlorides and esters reported by Kutateladze and co-workers is one example from the vast array of dithiane umpolung reactivity of carbonyl compounds (Scheme 1). Interestingly, when an aldehyde other than acetaldehyde is used, the reaction proceeds through addition of a second dithiane molecule through ring-opening of the first installed dithiane unit.

Considering the previous reports on the autoxidation of 2-lithio-1,3-dithianes, we envisioned that 2-aryl-2-lithio-1,3-dithianes could be oxidized in situ to yield a thioester capable of undergoing a similar attack by the excess organolithium eventually forming compounds similar to those described by Kutateladze in a pot economy. Previously reported transformations of the envisioned products include desulfurizing difluorination of the α-thioether ketone and dithioketal moieties or trifluoromethylation of benzylic orthoesters. Orthoesters can be converted to esters, thioesters and α-thioether ketones have also been used in the oxidative coupling of benzyl ketones.

RESULTS AND DISCUSSION

Gratifyingly, when reacting 2-phenyl-2-lithium-1,3-dithiane with S-benzyl benzothioate, product 5a was obtained in 89% yield (Table 1, entry 1). The ability of the thioester group to undergo the same transformation as benzoyl chloride (entry 2) prompted us to assess the possibility for in situ formation of the thioester by oxidation of the lithium dithiane. Hence, the argon atmosphere of a solution of 2-phenyl-2-lithium-1,3-dithiane from 4a was replaced by oxygen and kept for 5 min to afford the thioorthoester in 69% yield (entry 3). The simple exposure of the reaction mixture to air for 30 min allowed formation of thioorthoester 5a in 41% yield (entry 4), which was increased to 68% by decreasing exposure to air to less than a minute (entry 5), and to 71% by forming the lithiated dithiane at 0 °C (entry 6). Modification of the stoichiometric amounts of n-BuLi or other solvents (entries 7–10) did not improve the reaction success. Although a fast process at 0 °C, air exposure of the organolithium at −78 °C led to only traces of product and unreacted dithiane (entry 11).

Finally, the optimized protocol retrieved formation of orthothioester 5a in 76% and the scope of the method was evaluated (Scheme 2). Formation of ortholithiation derived products was not observed even in the presence of directing metalating groups. The correspondent orthothioesters derived from electron rich or electron poor aryl dithianes could be obtained in reasonable yields. Phenyl-1,3-dithianes decorated with halogens at the para-position were successfully transformed into the corresponding orthothioesters 5d and 5e, although LDA had to be used for the bromide derivative to avoid transmetalation with n-BuLi. TBDMS and TBDPS silyl protective groups were stable to the reaction conditions, and silyl ethers 5j and 5k could be obtained in up to 89% yield. A dithiane derived from 2-formylpyridine resulted in formation of 5i in 57% yield. Despite several attempts on the autoxidative addition of nitrophenyl-1,3-dithianes, only alkyldened ketones or starting materials were obtained. Other electron deficient dithianes such as pentfluorophenyl or para-trifluoromethyl phenyl derivatives were unstable toward the lithiation conditions tested.

Acyclic benzaldehyde dithioacetals derived from primary and secondary thiols undergo the same process to yield α-thioether ketones 7 and orthothioesters 8 (Table 2). Dithioester 6e derived from tert-butyl mercaptan failed to provide the corresponding ketone or orthothioesters likely due to steric hindrance as only thioester 9 could be obtained. The use of O₂ instead of air was observed to be detrimental for the reaction yield, as complex mixtures of products were obtained in such cases.

In order to evaluate the scope of the transformation concerning the nature of the 2-substituent of 1,3-dithianes,

![Scheme 2](image)

**Table 1. Optimization of Reaction Conditions**

| entry | deviation from reaction conditions | yield (%) | 
|-------|-----------------------------------|-----------|
| 1     | PhC(O)Sn (0.65 equiv), no air     | 89        |
| 2     | PhC(O)Cl (0.65 equiv), no air     | 71        |
| 3     | O₂ balloon for 5 min              | 69        |
| 4     | 30 min air exposure               | 41        |
| 5     | rt, 20 min                        | 68        |
| 6     | 0 °C to rt, 20 min                | 71        |
| 7     | 1.0 equiv n-BuLi, 0 °C to rt, 20 min | 66         |
| 8     | 1.6 equiv n-BuLi, 0 °C to rt, 20 min | 60         |
| 9     | Et₃O, 0 °C to rt, 20 min          | 46        |
| 10    | toluene                           | 39        |
| 11    | air exposure at −78 °C             | traces    |

<n-BuLi (2.5 M in hexanes, 1.3 mmol) was added dropwise to a solution of dithiane 4a (1 mmol) in THF (5 mL) under argon atmosphere at −78 °C. The mixture was left to reach rt after 20 min, and opened to air 1 min before addition of NH₄Cl saturated aqueous solution. Isolated yield.>

For reaction conditions see footnote a, Table 1. LDA as base.
several 2-alkyl-1,3-dithianes were submitted to our autoxidative conditions (Scheme 3). The autoxidation of 2-lithio-1,3-dithiane under the reaction conditions resulted in the unsurprising formation of alcohol 1a as previously reported by Wade and co-workers (Scheme 3, eq 1).18 2-Alkyl substituted 1,3-dithianes undergo autoxidation to some extent, however the reaction is halted before orthothioester formation and 10 are obtained in up to 27% yields (Scheme 3, eq 2) probably due to the competitive formation of the lithium enolate of product. Similar yields of the products were observed when increasing the amount of n-BuLi. The presence of a bulky t-butyl substituent alters the outcome of the reaction. Dithioester 11, resulting from condensation of two oxidized species was the only product identified (Scheme 3, eq 3).

Scheme 3

![Scheme 3](image)

“For reaction conditions see footnote a, Table 1. Isolated yield.

aUnreacted dithiane 4 was isolated as the major species. b2-(n-Hexyl)-1,3-dithiane was also isolated in 23%.

The autoxidative addition of 1,3-dithiane derived from silyl protected glycoaldehyde yields 10p together with hexyl substituted 1,3-dithiane. The formation of the later is likely to occur by trapping of the ketene dithiane with n-butyl lithium.30 Several attempts to apply this procedure to 2-silyl substituted 1,3-dithianes, such as 2-TMS-1,3-dithiane 2-TBDPS-1,3-dithiane, resulted in the formation of complex mixtures of unidentified products.

The role of atmospheric oxygen as the oxidant species in the process was confirmed by running the autoxidative condensation reaction under $^{18}$O$_2$, affording the $^{18}$O isotopically labeled 5a in 72% yield (Scheme 4, eq 1). Impelled by the previous suggestions that a SET mechanism could be involved, the exposure to air in the presence of TEMPO was performed (Scheme 4, eq 2). Trapped intermediates were not identified and only compound 2 was isolated, already known to derive from SET.12a,14c,21 Notably, formation of compound 5a was not observed, which might indicate the SET process to be a pitfall prior to the organolithium autoxidation. The presence of 12 as intermediate in the reaction was supported by its reaction with lithium dithiane derived from 4a (Scheme 4, eq 3).

In order to get some insight on the reaction mechanism, the several putative processes involved in the transformation were studied by DFT calculations.31 The spontaneous autoxidation of the organolithium compound was verified through optimization of relevant intervenient species (Scheme 5). The process seems highly favorable, as the lithium alkoxide formation is balanced by the release of 25.4 kcal/mol upon reaction of lithium dithiane with triplet oxygen30 followed by release of 88.9 kcal/mol upon reaction of the lithium peroxide with lithium dithiane to form the corresponding lithium alkoxide.

According to our calculations, formation of thioester B from lithium alkoxide A requires only 2.7 kcal/mol (Figure 1). The thiolate charge in thioester B is highly stabilized by lithium and becomes more stabilized upon interaction with a lithium

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Table 2. Autooxidative Condensation of Benzaldehyde-Derived Dithioacetals

| Entry | R       | 7 Yield (%) | 8 Yield (%) |
|-------|---------|-------------|-------------|
| 1     | Ph      | 7a, 48      | 8a, 8c      |
| 2     | n-Bu    | 7b, 97      | 8b, 72      |
| 3     | (CH$_3$)$_2$Me | 7c, 73 | 8c, 56 |
| 4     | sec-Bu  | 7d, 67      | 8d, 7c      |
| 5     | t-Bu    |             | 9, 62       |

"For reaction conditions see footnote a, Table 1. Isolated yield. bObserved in $^1$H NMR of the crude mixture but not isolated.

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Scheme 4

![Scheme 4](image)

Scheme 5

![Scheme 5](image)
The presence of lithium increases the $\text{C=O}$ polarization of the thioester assisting the nucleophilic attack of a lithium dithiane molecule, and requires 11.2 kcal/mol. The transition state $\text{TS}_{\text{CD}}$ resembles an early one, as suggested by the rather long forming $\text{C-C}$ bond and small Wiberg index (32 ($d = 2.84$ Å and WI = 0.13), which becomes considerably shorter in the tetrahedral intermediate $\text{D}$ ($d = 1.61$ Å and WI = 0.90). The collapse of intermediate $\text{D}$ to the more stable pair of ketone and lithium thiolate ($\text{E}$) requires only 5.0 kcal/mol to overcome the transition state $\text{TS}_{\text{DE}}$ energy barrier. Interaction of the lithium cations with sulfur atoms is visible in calculated $\text{TS}_{\text{DE}}$, although such stabilization is likely to take place by the solvent molecules. The pair of products represented in $\text{E}$ is highly stabilized by interaction of lithium cations with both sulfur atoms of the thiolate and the carbonyl oxygen.

Condensation of the ketone 12 in $\text{E}$ with another lithium dithiane molecule was considered, as observed experimentally (Scheme 4, eq 3), by taking the nucleophilic attack of the organolithium to a sulfur atom of the $\alpha$-disubstituted ketone (Figure 2). The calculated transition state for this reaction $\text{TS}_{\text{FG}}$ is characterized by distension of the $\text{C-S}$ bond of the ketone (2.11 Å in $\text{TS}_{\text{FG}}$ and 1.85 Å in $\text{F}$) and formation of a new $\text{C-S}$ bond (2.49 Å and WI = 0.29) with the lithium dithiane molecule, demanding for 11.2 kcal/mol. Weakening of the carbon–oxygen bond from $\text{F}$ to $\text{G}$ is visible by its length (1.23 Å in $\text{F}$ and 1.29 Å in $\text{G}$) and weaker Wiberg index in the lithium enolate product $\text{G}$ (WI = 1.65 in $\text{F}$ and 1.31 in $\text{G}$), accompanied by strengthening of the $\text{C-C}$ bond (1.55 Å; WI = 0.95 in $\text{F}$ and 1.40 Å; WI = 1.47 in $\text{G}$). Although we cannot rule out a radical mechanism based on our calculations (as suggested by Kutateladze25 and considered in Supporting Information), the low energy barrier determined for the ionic

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Figure 1. Free energy profile (PBE0) for deterioration of lithium alkoxide and reaction with 2-phenyl-2-lithio-1,3-dithiane, and mechanistic representation. Optimized structures of minima and transition states are presented with bond distances and Wiberg indexes (in italics) for the more relevant bonds. Free energies values are presented in kcal/mol, referring to the initial intermediate A.

Figure 2. Free energy profile (PBE0) for nucleophilic condensation of $\alpha$-disubstituted ketone with 2-phenyl-2-lithio-1,3-dithiane and mechanistic representation. Optimized structures of minima and transition states are presented with bond distances and Wiberg indexes (in italics) for the more relevant bonds. Free energies values are presented in kcal/mol, referring to the initial intermediate A from Figure 1.
nucleophilic attack might indicate this as the main route for formation of the orthoester product.

**CONCLUSION**

In summary, we have shown that 2-aryl-2-lithium-1,3-dithianes undergo autodissociative condensation forming α-thioether ketones orthoesters in reasonable to good yields upon aerobic oxidation. The procedure can be expanded to other benzaldehyde derived dithioacetals, affording orthoesters and α-thioether ketones in good to excellent yields. 2-Alkyl substituted 1,3-dithianes also undergo a similar autodissociative process upon treatment with n-BuLi and air exposure; however, condensation of a third dithiane unit is hampered by presence of enolizable positions on the condensation intermediate. DFT calculations support a reaction mechanism that starts with the highly thermodynamic favorable autodissociation of the organolithium dithiane, leading to formation of the thioester that is further trapped by another 2-lithium-1,3-dithiane. The herein described process might be on the basis of the known limitations on the use of 2-thioether ketones in synthetic chemistry, and it is also a way to achieve highly functionalized and stable orthoesters.

**EXPERIMENTAL SECTION**

**General Remarks.** Reactions were monitored through thin-layer chromatography (TLC) with commercial silica gel plates (Merck silica gel, 60 F254). Visualization of the developed plates was performed under UV lights at 254 nm and by staining with cerium ammonium molybdate, 2,4-dinitrophenylhydrazine and vanillin stains. Flash chromatography (TLC) with commercial silica gel plates (Merck silica) was dried by distillation under argon with sodium metal and dried by distillation under argon with calcium hydride. Isotope labeled oxygen-18 (99% isotopic purity) was purchased from Sigma-Aldrich (CAS Number 32767-18-3). A small balloon was filled with oxygen-18 and used directly in the oxidation reaction.

**General Procedure for Preparation of 2-Substituted 1,3-Dithianes (Method A).** On the basis of a modified previously reported method,3 aldehyde (15 mmol, 1 equiv) and 1,3-propanediol (3 mL, 16.5 mmol, 1.1 equiv) were dissolved in dichloromethane (50 mL) in a round-bottom flask. Iodine (381 mg, 1.5 mmol, 0.1 equiv) was slowly added do the stirring solution as to prevent vigorous boiling of the solvent. The reaction was quenched with 2% Na2S2O3 aqueous solution (10 mL) 30 min after complete iodine addition. Upon separation, the organic layer was washed successively with a 10% aqueous NaOH solution (10 mL), water (10 mL) and brine (10 mL). The organic solvent was dried over MgSO4 and filtered. After evaporating the solvent, the product was recrystallized from isopropanol. 4a Prepared according to a modified previously reported method.35 4-(Dimethylamino)benzaldehyde (1 g, 6.7 mmol, 1 equiv) and 1,3-propanediol (0.74 mL, 7.4 mmol, 1.1 equiv) were dissolved in 10 mL of dry DCM in an argon purged round-bottom flask. The solution was cooled to 0°C and BF3·OEt2 (1.16 mL, 9.4 mmol, 1.4 equiv) was added dropwise. The solution was then left warming to room temperature for 1 h. The reaction was quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated and the organic phase collected and washed with water (10 mL) and Brine (10 mL). The organic solvent was dried over MgSO4 and filtered. After evaporation of the solvent, the product was recrystallized from isopropanol to give 4b as yellow crystals in 93% yield (1.498 g, 6.26 mmol). Obtained with same spectral characterization as previously described.36 4H NMR (300 MHz, CDCl3) δ ppm 7.33 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 5.12 (s, 1H), 3.17–2.86 (m, 4H), 2.94 (s, 6H), 2.20–2.10 (m, 1H), 1.97–1.82 (m, 1H).

4c. Prepared according to method A. 89% yield (2.997 g, 13.54 mmol), white crystals. Obtained with same spectral characterization as previously described.38 4H NMR (300 MHz, CDCl3) δ ppm 7.80–7.57 (m, 4H), 5.17 (s, 1H), 3.11–3.01 (m, 2H), 2.96–2.90 (m, 2H), 2.23–2.15 (m, 1H), 2.01–1.86 (m, 1H).

4d. Prepared according to method A. 81% yield (3.628 g, 13.18 mmol), white crystals. Obtained with same spectral characterization as previously described.37 4H NMR (300 MHz, CDCl3) δ ppm 7.49–7.44 (m, 2H), 7.05–7.32 (m, 2H), 5.11 (s, 1H), 3.10–3.00 (m, 2H), 2.94–2.86 (m, 2H), 2.22–2.12 (m, 1H), 1.99–1.84 ppm (m, 1H).

4e. Prepared according to method A. 76% yield (1.515 g, 7.07 mmol), white crystals. Obtained with same spectral characterization as previously described.39 4H NMR (300 MHz, CDCl3) δ ppm 7.47–7.42 (m, 2H), 7.05–6.99 (m, 2H), 5.14 (s, 1H), 3.10–3.01 (m, 2H), 2.94–2.87 (m, 2H), 2.22–2.13 (m, 1H), 1.99–1.84 (m, 1H).

4f. Prepared according to method A. 69% yield (1.253 g, 5.96 mmol), white crystals. Obtained with same spectral characterization as previously described.34 4H NMR (300 MHz, CDCl3) δ ppm 7.61–7.57 (m, 1H), 7.24–7.13 (m, 3H), 5.33 (s, 1H), 3.14–3.04 (m, 2H), 2.95–2.88 (m, 2H), 2.45 (s, 3H), 2.23–2.14 (m, 2H), 2.02–1.87 (m, 1H).

4g. Prepared according to method A. 88% yield (1.681 g, 5.56 mmol), pale yellow solid. Product was isolated by flash chromatography (Hex:AcOEt, 95:5).1H NMR (300 MHz, CDCl3) δ ppm 7.60 (dd, J = 7.3, 1.8 Hz, 1H), 7.47–7.30 (m, 3H), 7.21 (td, J = 7.8, 1.5 Hz, 1H), 7.00–6.95 (m, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.76 (s, 1H), 5.13 (s, 2H), 3.13–2.85 (m, 2H), 2.92–2.85 (m, 2H), 2.20–2.11 (m, 1H), 2.00–1.85 (m, 1H). 13C NMR (75 MHz, CDCl3) δ ppm 154.8, 137.2, 129.4, 129.3, 128.7, 128.1, 128.0, 127.3, 121.5, 112.7, 70.6, 44.2, 44.1, 32.5, 25.5. HR-MS (ESI) m/z calculated for C17H19OS2· [M + H]+: 303.0872, found 303.0884.

4h. Prepared according to method A. 76% yield (1.172 g, 4.57 mmol), white crystals. Obtained with same spectral characterization as previously described.33 4H NMR (300 MHz, CDCl3) δ ppm 7.15 (dd, J = 2.3, 1.2 Hz, 1H), 6.83–6.76 (m, 2H), 5.67 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.16–3.06 (m, 2H), 2.93–2.86 (m, 2H), 2.20–2.12 (m, 1H), 2.01–1.86 (m, 1H).

4i. Prepared according to a modified previously reported method.36 Freshly distilled picolinaldehyde (1 mL, 10.51 mmol, 1 equiv) and 1,3-propanedithiol (1.16 mL, 11.56 mmol, 1.1 equiv) were dissolved in DCE (20 mL). p-Toluenesulfonyl acid (200 mg, 1.05 mmol, 0.1 equiv) was added to the mixture and the solution refluxed for 24 h. The reaction was cooled to room temperature and quenched with a 10% aqueous NaOH solution (10 mL). The layers were separated and the organic phase collected and washed with water (10 mL) and brine (10 mL). The organic solvent was dried over MgSO4 and filtered. The solvent was evaporated and the product isolated by flash chromatography (Hex:AcOEt, 70:30) to give 4i as a yellow solid in 54% yield (1.111 g, 5.63 mmol), with same spectral characterization as previously described.36 4H NMR (300 MHz, CDCl3) δ ppm 8.57 (dd, J = 4.4, 1.5 Hz, 1H), 7.67 (td, J = 7.6, 1.8 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.22–7.18 (m, 1H), 5.35 (s, 1H), 3.11–2.92 (m, 2H), 2.23–2.13 (m, 1H), 2.05–1.90 (m, 1H).

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4-(1,3-Dithian-2-yl)-2-methoxyphenol. Prepared according to method A and used in preparation of 4j and 4k. 84% yield (6.723 g, 27.73 mmol), white crystals. Obtained with same spectral characterization as previously described.13 1H NMR (300 MHz, CDCl3) δ ppm 7.00−6.84 (m, 2H), 6.87−6.84 (m, 1H), 5.64 (s, 1H), 5.11 (s, 1H), 3.90 (s, 3H), 3.10−2.87 (m, 2H), 2.93−2.86 (m, 2H), 2.21−2.12 (m, 1H), 1.99−1.84 (m, 1H).

4j. 4-(1,3-Dithian-2-yl)-2-methoxyphenol (0.5 g, 2.06 mmol, 1 equiv), imidazole (155 mg, 2.27 mmol, 1.1 equiv) and 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.1 equiv) were dissolved in dry DCM (10 mL) in an argon purged round-bottom flask. Then, tert-butyl(chloro)diphenylsilane was added dropwise to the stirring solution. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with H2O (10 mL) and the layers were separated. The organic layer was collected and washed with water (10 mL) and Brine (10 mL), dried over MgSO4, filtered and evaporated. The product was purified by flash chromatography (Hex:AcOEt, 97:3) to yield 4j as a colorless oil (918 mg, 1.91 mmol) with same spectral characterization as previously described.4j 1H NMR (300 MHz, CDCl3) δ ppm 7.34 (d, J = 7.3 Hz, 2H), 7.29−7.27 (m, 4H), 2.85−2.80 (m, 4H), 2.15−2.05 (m, 1H), 1.92−1.79 (m, 2H).

4k. Prepared according to a modified previously reported method.33 Butyraldehyde (0.2 mL, 1.3 mmol, 1 equiv) and 1,3-propanedithiol (0.6 mL, 6.1 mmol, 1.2 equiv) were dissolved in 20 mL of dry DCM under argon. The solution was stirred at room temperature and BF3·OEt2 (0.43 mL, 0.7 mmol, 0.1 equiv) was added dropwise. After 90 min, the reaction was quenched by washing the reaction mixture twice with 20 mL of 10% aqueous NaOH. The combined aqueous layers were then extracted twice with 20 mL of DCM. The organic layers were combined, washed with 25 mL of brine and dried over MgSO4. The organic solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography (hexane/EtOAc 98:2) to afford 4k as a colorless solid (0.6 mL, 4.08 mmol). Obtained with same spectral characterization as previously described.4j 1H NMR (300 MHz, CDCl3) δ ppm 4.05 (t, J = 6.7 Hz, 1H), 2.92−2.76 (m, 4H), 2.14−2.06 (m, 1H), 1.90−1.77 (m, 1H), 1.75−1.67 (m, 2H), 1.59−1.45 (m, 2H), 0.85−0.97 (m, 3H).

4l. Prepared according to a modified previously reported method. Pivaldehyde (5 mmol, 1 equiv) and N-bromosuccinimide (178 mg, 1 mmol, 0.2 equiv) were dissolved in CH2Cl2 (25 mL). The solution was then stirred under argon at rt and 1,3-propanedithiol (1.2 equiv) was added dropwise. The reaction was monitored by TLC and quenched with 10% aqueous NaOH (25 mL) when the aldehyde was consumed (30−80 min). Aqueous and organic layers were separated and the aqueous layer was washed with CH2Cl2 (2 × 25 mL). The combined organic layers were washed with 25 mL of brine, dried over MgSO4, filtered and concentrated under reduced pressure. 62% yield (544 mg, 3.08 mmol), white solid was obtained with same spectral characterization as previously described.4l 1H NMR (300 MHz, CDCl3) δ ppm 3.99 (s, 1H), 2.90−2.86 (m, 4H), 2.11−2.02 (m, 1H), 1.86−1.74 (m, 1H), 1.10 (s, 9H).

4m. Prepared according to method A. Flash chromatography gradient eluent: Hex:AcOEt (85:15 to 60:40). 33% yield (433 mg, 1.64 mmol), colorless oil. 1H NMR (300 MHz, CDCl3) δ ppm 4.17−4.17 (m, 1H), 3.85 (d, J = 6.4 Hz, 2H), 2.90−2.75 (m, 4H), 2.15−2.06 (m, 1H), 1.96−1.85 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H).13C NMR (75 MHz, CDCl3) δ ppm 66.1, 48.6, 29.1, 26.2, 26.0, 18.5−18.6. HRMS (ESI) m/z calculated for C15H23O2S2Si+ [M + HI]+ 481.1866, found 481.1867.

4n. Prepared according to method B. Flash chromatography eluent: Hex:AcOEt (97:3). 91% yield (1.218 g, 4.54 mmol), colorless oil. 1H NMR (300 MHz, CDCl3) δ ppm 7.39−7.20 (m, 15H), 5.42 (s, 1H).

6a. Prepared according to a modified previously reported method.33 Benzaldehyde (0.51 mL, 5 mmol, 1 equiv) and benzenethiol (1.08 mL, 10.5 mmol, 2.1 equiv) were dissolved in CHCl3 (25 mL). The solution was then stirred at rt and I2 (0.13 g, 0.5 mmol, 0.1 equiv) was added. The reaction was monitored by TLC. When the aldehyde was consumed (30 min) the reaction mixture was quenched with H2O (20 mL) and then washed twice with 10% aqueous NaOH (25 mL). Aqueous and organic layers were separated and the aqueous layer was washed with CH2Cl2 (2 × 25 mL). The combined organic layers were washed with 25 mL of brine, dried over MgSO4, filtered and concentrated under reduced pressure to yield the crude product. The crude product was then purified by recrystallization from hexane to afford 6a as white crystals in 66% yield (1.01 g, 3.28 mmol) with the same spectral characterization as previously described.4m 1H NMR (300 MHz, CDCl3) δ ppm 7.39−7.20 (m, 15H), 5.42 (s, 1H).
4H), 1.59 equiv) solution in hexanes was added dropwise to the reaction mixture was quenched with 10 mL of a saturated aqueous NH₄Cl solution. Ten balloon was replaced with an atmospheric air balloon and an additional cooled to 78 °C. The solution was left stirring at 78 °C for 2 h of complete addition, the reaction was quenched with a 2% Na₂S₂O₃ aqueous solution (10 mL). The layers of the solvent. After 2 h of complete addition, the reaction was washed with cold isopropanol to yield 4a 127.5, 63.5, 29.3, 24.1. HR-MS (ESI) m/z calculated for C₇H₇O₄S₂ [M − H]⁺ 491.3740, found 491.3757.

6d. Prepared according to method B. 86% yield (1.150 g, 4.29 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (97:5:2.5). H NMR (300 MHz, CDCl₃) δ ppm 7.47 (d, J = 7.6 Hz, 2H), 7.34–7.22 (m, 3H), 4.94 (s, 1H), 2.88–2.63 (m, 2H), 1.66–1.42 (m, 4H), 1.24–1.20 (m, 6H), 0.97–0.88 (m, 6H). 13C NMR (75 MHz, CDCl₃) δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. HR-MS (ESI) m/z calculated for C₇H₇O₄S₂ [M − H]⁺ 267.1236, found 267.1243.

6e. Prepared according to a modified previously reported method. Benzil (1g, 4.76 mmol, 1.2 equiv) was dissolved in dry DCM (5 mL) in an argon purged round-bottom flask. The solution was cooled to 0 °C in an ice bath bath. A solution of 1.3-propanedithiol (398 µL, 3.96 mmol, 1 equiv) and BF₃·Et₂O (489 µL, 3.96 mmol, 1 equiv) in dry DCM (1.5 mL) was added dropwise at 0 °C. The reaction was warmed to room temperature for 3 h and quenched with 10 mL of a saturated aqueous NaHCO₃ solution. The layers were separated and the organic phase collected. The aqueous phase was extracted two times over MgSO₄. The solvent wasow through the chromatography eluent: Hex:AcOEt (97:5:2.5). H NMR (300 MHz, CDCl₃) δ ppm 7.48–7.44 (m, 2H), 7.32–7.26 (m, 2H), 7.23–7.18 (m, J = 1.3 Hz, 1H), 5.02 (s, 1H), 1.29 (s, 1H). 13C NMR (75 MHz, CDCl₃) δ ppm 144.1, 128.7, 127.7, 127.4, 48.8, 45.8, 31.3. HR-MS (ESI) m/z calculated for C₇H₇O₄S₂ [M − H]⁺ 267.1236, found 267.1243.

12. Prepared according to method B. 87% yield (1.171 g, 4.37 mmol, 1.2 equiv) was dissolved in dry DCM (5 mL) in an argon purged round-bottom flask. The solution was cooled to 0 °C in an ice bath bath. A solution of 1.3-propanedithiol (398 µL, 3.96 mmol, 1 equiv) and BF₃·Et₂O (489 µL, 3.96 mmol, 1 equiv) in dry DCM (1.5 mL) was added dropwise at 0 °C. The solution was warmed to room temperature for 3 h and quenched with 10 mL of a saturated aqueous NaHCO₃ solution. The layers were separated and the organic phase collected. The aqueous phase was extracted with DCM (3 × 10 mL) and the organic phases combined, dried over MgSO₄ filtered and the solvent evaporated. The dry crude was dissolved in hot isopropanol and left cooling at room temperature. After 3 h, the product precipitated as a white solid and was filtered and washed with cold isopropanol to yield 12 as a white solid in 54% yield (853 mg, 2.13 mmol). 1H NMR (300 MHz, CDCl₃) δ ppm 7.68–7.66 (m, 2H), 7.57 (dd, J = 7.9, 1.5 Hz, 2H), 7.38–7.28 (m, 4H), 7.23–7.17 (m, 2H), 3.62 (ddd, J = 14.4, 12.0, 2.9 Hz, 2H), 2.80–2.73 (m, 4H, 1.82–1.80 (m, 1H), 2.17–2.08 (m, 1H, 1.82–1.80 (m, 1H), 1.21–1.08 (m, 1H). 13C NMR (300 MHz, CDCl₃) δ ppm 192.8, 139.0, 134.5, 132.2, 130.8, 129.8, 128.8, 127.7, 127.5, 63.5, 29.3, 24.1. HR-MS (ESI) m/z calculated for C₇H₇O₄S₂ [M + H]⁺ 530.0715, found 530.0734.

General Procedure for Autoxidative Addition of Dithiane 4a–c and 4e–k. Dithiane (1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetone/liquid nitrogen bath. n-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. As oxidation took place the solution warmed up and color change was usually observed. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH₄Cl solution. Ten mL of EtO₂ were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with EtO₂ (2 × 10 mL). The organic phases were combined and dried over MgSO₄. The solvent was filtered and evaporated. The product was purified by flash chromatography.
2H). 13C NMR (75 MHz, CDCl₃) δ ppm 194.7, 153.7, 153.4, 152.6, 152.2, 151.1, 130.7, 128.2, 126.7, 119.5, 116.0, 115.6, 115.6, 114.8, 114.2, 113.8, 113.0, 111.8, 62.5, 56.7, 56.2, 55.9, 55.8, 55.8, 52.1, 52.9, 30.9, 29.0, 28.6, 24.4. HR-MS (ESI) m/z calculated for C₂₀H₁₇OS⁺ [M + H]⁺ 307.1095, found 307.1092.

3f. 89% yield (239 mg, 0.19 mmol), amorphous white solid. Flash chromatography eluent: Hex:AcOEt (50:50:2) because the compound was unstable on silica without treatment with triethylamine. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.94–7.90 (m, 2H), 7.38–7.17 (m, 12H), 5.85 (s, 1H). ¹C NMR (75 MHz, CDCl₃) δ ppm 194.8, 136.6, 135.6, 134.1, 133.4, 133.1, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 60.4. HR-MS (ESI) m/z calculated for C₁₈H₂₁OS⁺ [M + H]⁺ 305.0995, found 305.1013. The corresponding orthoester product 8a could not be isolated due to low polarity and structural similarity to 6a. However, the following characteristic peaks for the 8a can be observed from the NMR spectrum of a mixture with the dithiocal. 8a. ¹H NMR (300 MHz, CDCl₃): 7.69–7.64 (m, 2H). ¹C NMR (75 MHz, CDCl₃) δ ppm 139.4, 132.9, 128.8, 128.3, 128.0, 127.9, 7.05.

7a. 97% yield (92 mg, 0.32 mmol), white solid. Flash chromatography eluent: Hex:AcOEt (95:5.5). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.99–7.96 (m, 2H), 7.53–7.23 (m, 8H), 5.55 (s, 1H), 2.56–2.42 (m, 2H), 1.58–1.48 (m, 2H), 1.41–1.29 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ¹C NMR (75 MHz, CDCl₃) δ ppm 195.3, 136.9, 135.9, 133.3, 129.0, 128.9, 128.7, 128.0, 55.5, 31.3, 31.2, 22.1, 13.7. HR-MS (ESI) m/z calculated for C₁₈H₂₂OS⁺ [M + H]⁺ 285.1380, found 285.1328.

8b. 72% yield (86 mg, 0.24 mmol), colorless oil. Flash chromatography eluent: Hex:AcOEt (95:5). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.99–7.96 (m, 2H), 7.53–7.23 (m, 8H), 5.55 (s, 1H), 3.16, 29.7, 29.7, 29.7, 29.6, 29.3, 29.2, 29.2, 29.0, 22.8, 14.3. HR-MS (ESI) m/z calculated for C₁₈H₂₂OS⁺ [M + H]⁺ 305.0998, found 305.1013. The corresponding orthoester product 8a could not be isolated due to low polarity and structural similarity to 6a. However, the following characteristic peaks for the 8a can be observed from the NMR spectrum of a mixture with the dithiocal. 8a. ¹H NMR (300 MHz, CDCl₃): 7.69–7.64 (m, 2H). ¹C NMR (75 MHz, CDCl₃) δ ppm 139.4, 132.9, 128.8, 128.3, 128.0, 127.9, 7.05.

7c. 73% yield (99 mg, 0.25 mmol), pale yellow solid. Flash chromatography gradient eluent: Hex:Toluene (80:20 to 50:50). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.99–7.96 (m, 2H), 7.54–7.23 (m, 8H), 5.55 (s, 1H), 2.55–2.41 (m, 2H), 1.59–1.49 (m, 2H), 1.30–1.22 (m, 18H), 0.90–0.86 (m, 3H). ¹C NMR (75 MHz, CDCl₃) δ ppm 195.3, 136.9, 136.0, 133.3, 129.1, 129.0, 128.9, 128.8, 128.0, 55.6, 31.6, 31.6, 29.7, 29.7, 29.6, 29.5, 29.3, 29.2, 29.2, 29.0, 22.8, 14.3. HR-MS (ESI) m/z calculated for C₁₈H₂₂OS⁺ [M + H]⁺ 307.1156, found 307.1155.

6c. 56% yield (131 mg, 0.19 mmol), white solid. Flash chromatography eluent: Hex:Hexane (100%). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.97–7.88 (m, 2H), 7.35–7.21 (m, 3H), 2.57 (s, J = 7.3 Hz, 6H), 1.54–1.44 (m, 6H), 1.31–1.24 (m, 54H), 0.90–0.86 (m, 9H). ¹C NMR (75 MHz, CDCl₃) δ ppm 142.1, 128.1, 127.8, 73.7, 32.1, 32.0, 29.8, 29.8, 29.6, 29.4, 29.3, 28.6, 22.9, 14.3. HR-MS (ESI) m/z calculated for C₁₈H₂₂S⁺ [M − S(CH₃)₂]+ 283.1308, found 283.1303.

7d. 67% yield (63 mg, 0.22 mmol), pale yellow solid. 1:1 mixture of diasteromers. Flash chromatography eluent: Hex:AcOEt (95:5). ¹H NMR (300 MHz, CDCl₃) δ ppm 8.01–7.97 (m, 4H), 7.54–7.23 (m, 16H), 5.61 (s, 2H), 2.75–2.61 (m, 2H), 1.72–1.42 (m, 4H), 1.30 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 0.98–0.86 (m, 6H). ¹C NMR (75 MHz, CDCl₃) δ ppm 195.5, 195.4, 137.2, 135.9, 133.3, 129.0, 128.9, 128.9, 128.7, 127.9, 54.7, 54.6, 42.1, 41.9, 29.7, 29.7, 21.0, 20.6, 11.3, 11.2. HR-MS (ESI) m/z calculated for C₁₈H₂₂SO⁺ [M + H]⁺ 285.1308, found 285.1303. The corresponding orthoester product 8d could not be isolated due to low polarity and structural similarity to 6d. However, the following characteristic peaks for 6d can be observed
in NMR spectrum of the crude reaction mixture: 8d 13C NMR (75 MHz, CDCl3) δ ppm 69.3, 29.0, 20.1, 11.5.

9. Dithiocacetal 6e (0.5 mmol, 1 equiv) was dissolved in dry THF (2.5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetonitrile/nitrogen bath. n-BuLi (1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. The argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 min the solution was quenched with 5 mL of a saturated aqueous NH4Cl solution. Ten mL of Et2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et2O (2 × 5 mL). The organic phases were combined and dried over MgSO4. The solvent was evaporated and the product was purified by preparative TLC (eluent: pentane) to yield 9 as a colorless oil (62%, 60 mg, 0.31 mmol) with the same spectral characterization as previously described.47 1H NMR (300 MHz, CDCl3) δ ppm 7.85–7.90 (m, 1H), 7.65–7.51 (m, 4H), 2.91–2.76 (m, 4H), 2.14–2.06 (m, 2H), 1.91–1.79 (m, 2H), 1.76–1.68 (m, 2H), 1.54–1.44 (m, 2H), 1.32–1.24 (m, 4H), 0.89–0.85 (m, 3H). HR-MS (ESI) m/z calculated for C19H15N (M + H) + 289.1216, found 289.1217.

**Reaction of 4a with Benzyl Chloride.** Dithiane 4a (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetonitrile/nitrogen bath. n-BuLi (0.53 mL of a 2.5 M solution, 1.32 mmol, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Benzyl chloride (77 μL, 0.66 mmol, 0.65 equiv) was added dropwise to the solution and after 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH4Cl solution. Ten mL of Et2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et2O (2 × 10 mL). The organic phases were combined and dried over MgSO4. The solvent was filtered and evaporated. The product was purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford 5a in 71% yield (180 mg, 0.36 mmol) as a pale yellow oil.

**Reaction of 4a with 5-Benzyl Benzothioate.** Dithiane 4a (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetonitrile/nitrogen bath. n-BuLi (0.53 mL of a 2.5 M solution, 1.32 mmol, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Then, 5-benzyl benzothioate (151 mg, 0.66 mmol, 0.65 equiv) in dry THF (1 mL) was added dropwise to the solution. After 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH4Cl solution. Ten mL of Et2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et2O (2 × 10 mL). The organic phases were combined and dried over MgSO4. The solvent was filtered and evaporated. The product was purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford 5b in 89% yield (226 mg, 0.45 mmol) as a pale yellow oil.

**Reaction of 4a in the Presence of 18O2.** General procedure for autoxidative addition of dithianes was used, although a small balloon filled with 18O2 was used directly in the oxidation reaction. HR-MS (ESI) m/z calculated for C27H28O2SNa (M + Na) + 521.0958, found 521.0955.

**Reaction of 4a in the Presence of TEMPO.** Dithiane 4a (200 mg, 1.02 mmol, 1 equiv) was dissolved in dry THF (5 mL) in an argon purged round-bottom flask. The solution was cooled to −78 °C in an acetonitrile/nitrogen bath. n-BuLi (0.53 mL of a 2.5 M solution, 1.3 equiv) solution in hexanes was added dropwise to the reaction mixture at −78 °C. The solution was left stirring at −78 °C for 20 min and then left to warm up to room temperature for 40 min. Then, TEMPO (206 mg in 1.5 mL of dry THF, 1.12 mmol, 1.3 equiv) was added dropwise to the solution. After 2 min, the argon balloon was replaced with an atmospheric air balloon and an additional needle was inserted in the septum as to allow air flow through the surface of the solution. After 1 min the solution was quenched with 10 mL of a saturated aqueous NH4Cl solution. Ten mL of Et2O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted two times with Et2O (2 × 10 mL). The organic phases were combined and dried over MgSO4. The solvent was filtered and evaporated. The product was purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford 5c in 89% yield (226 mg, 0.45 mmol) as a pale yellow oil.
acetone/liquid nitrogen bath. n-BuLi (0.45 mL of a 2.5 M solution, 1.12 mmol, 1.1 equiv) solution in hexanes was added dropwise to the reaction mixture at ~78 °C. The solution was left stirring at ~78 °C for 20 min and then left to warm up to room temperature for 40 min. Phenyl(2-phenyl-1,3-dithian-2-yl)methanone 12 (337 mg, 1.12 mmol, 1.1 equiv) in THF (5 mL) was added dropwise to the solution. After 2 min, while under argon, the reaction was quenched with 10 mL of a saturated aqueous NH₄Cl solution. Ten mL of Et₂O were added and the layers were separated. The organic phase was collected and the aqueous phase was extracted twice with Et₂O (2 × 10 mL). The organic phases were combined and dried over MgSO₄. The solvent was filtered, evaporated, and the product purified by flash chromatography (eluent Hex:AcOEt, 90:10) to afford 5a in 75% yield (381 mg, 0.77 mmol) as a pale yellow oil.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02896.

Full accounts on computational calculations and copies of spectra for all reported compounds (PDF)

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**Notes**
The authors declare no competing financial interest.

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