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Cyclic sulfones from double conjugate addition of Rongalite

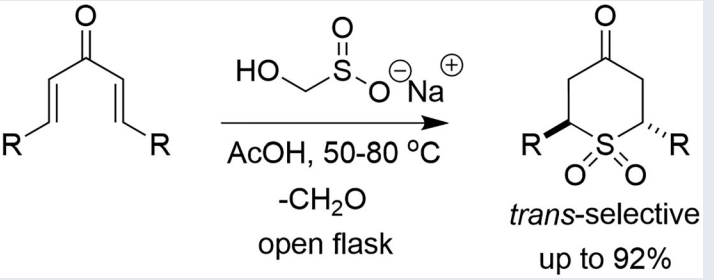
Melina Goga, Hao Zong, Jazmine Prana, Rudolph Michel, Antonia Muro, Elana Rubin, Janet Brenya, and Magnus W. P. Bebbington

Department of Chemistry and Biochemistry, College of Science and Mathematics, Montclair State University, Montclair, NJ, USA

ABSTRACT

Cyclic sulfones are obtained in up to 92% yield by double conjugate addition of Rongalite (sodium hydroxymethyl sulfinate) to dienones. The major product in each case is the kinetic *trans*-isomer of the 3,5-disubstituted ketosulfone. Eleven examples, including aryl and alkyl substituted substrates, are reported. The advantages of the method are its experimental simplicity, tolerance for both protic and oxidation-sensitive functional groups, and sterically challenging substrates. The work also significantly expands the scope of Rongalite as a conjugate nucleophile.

GRAPHICAL ABSTRACT



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KEYWORDS
Conjugate addition; dienones; Rongalite; sulfones

Introduction

The sulfonyl group is among the most common in licensed drugs.[1] Consequently, there is ongoing interest in practical and sustainable methods for the preparation of these important compounds, including reagents that behave as SO_2 equivalents and green free-radical-based methods.[2,3] However, still the most common approach to sulfones is to use a low-valent sulfur nucleophile and oxidize the resulting sulfide to the corresponding sulfone.[4]

Rongalite™ is a low-cost commodity chemical used as a bleaching agent in the dyeing industry.[5,6] It has seen increasing use in the synthetic laboratory as a reducing agent or radical initiator,[7–11] as a C1 synthon,[12–14] and also as a doubly nucleophilic

CONTACT Magnus W. P. Bebbington bebbingtonm@montclair.edu Department of Chemistry and Biochemistry, College of Science and Mathematics, Montclair State University, Montclair, NJ 07043, USA.

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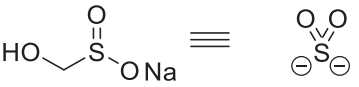
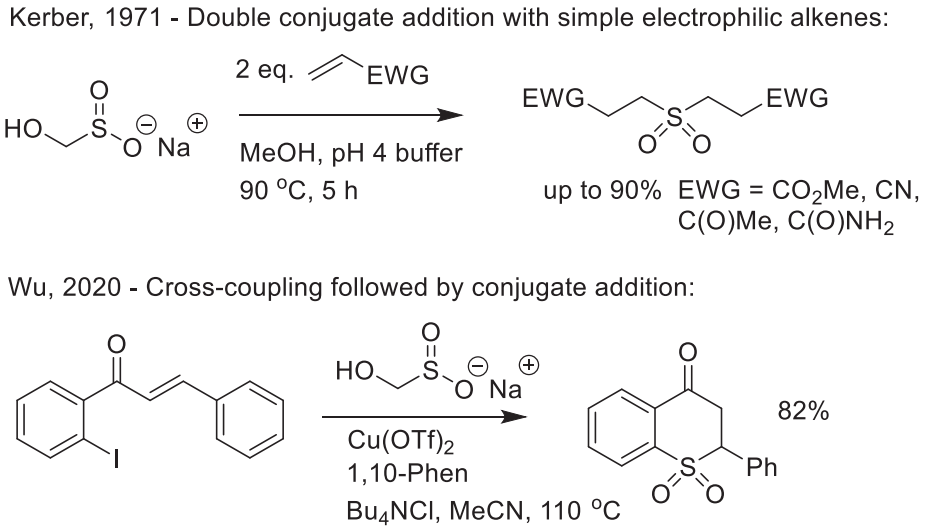


Figure 1. Rongalite as an equivalent of the unstable hyposulfite ion.



Scheme 1. Progression of Rongalite conjugate additions.

sulfur source, specifically as an equivalent of the unstable hyposulfite (SO_2^{2-}) ion (Fig. 1).[15,16]

Although the first reports of its use in the preparation of sulfones were now more than 50 years ago,[17] the reagent was left largely unexplored until the early years of this century.[5,6] It is now known to react with a wide variety of electrophiles. Derivatization of the Rongalite hydroxyl group has led to useful reagents for the installation of various sulfonyl functional groups.[18,19]

Despite the widespread use of sulfur nucleophiles for conjugate additions, there is a paucity of reported conjugate additions with Rongalite (Scheme 1), and the process is not general.[17,20]

This may be due to its effectiveness as a conjugate-reducing agent under certain circumstances.[20] In our laboratories, the focus has been on the use of unmodified Rongalite for unexplored transformations. We reasoned that a suitable double

electrophile would produce cyclic sulfones directly upon reaction with Rongalite and so we chose to study the reaction of Rongalite with dibenzalacetone.

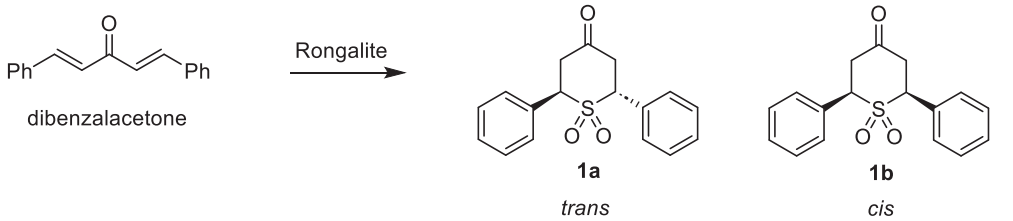
Results and discussion

The earliest report by Kerber and Starnick[17] of two-directional conjugate addition (Scheme 1) used an excess of monosubstituted electron-deficient alkenes and a pH 4 acetate buffer as the solvent. This was our starting point for the model reaction, and we were pleased to note that some of the expected diastereomeric sulfones were formed under these conditions (Table 1, entry 3). Further experimentation showed that the buffer was less effective for this reaction than simply an acetic acid/water mixture (entries 1 and 2). A solvent screen or the use of TBAB as a phase transfer catalyst did not result in any further improvement in yield (entries 4–7).

The sulfones were readily separated by chromatography and the major isomer **1a** had characterization data that were identical to those presented by Detty,[21] when the *trans* and *cis*-sulfone **1a** and **1b** were separated for the first time (see electronic Supporting Information). The yield here compares favorably to that reported by the two-step procedure (75% overall) and in practical terms the reaction is much more straightforward. The diastereoselectivity is similar to that in the earlier work.

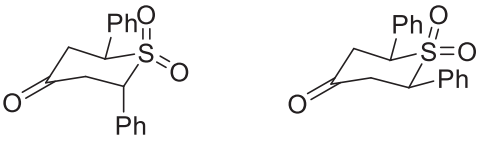
Having verified the structure of the major diastereomer, we searched the literature in search of an explanation for the diastereoselectivity. We suspected that the major product would be formed under kinetic control because the minor *cis*-product was thought likely to be more stable (both phenyl groups can be equatorial simultaneously in the chair conformation). By subjecting the major product **1a** to our original reaction conditions, we established that any isomerization from *trans* to *cis* was very slow (<2% isomerization by ^{1}H NMR after 24 h at 80 °C). Both phenyl groups can be in equatorial positions in a chair conformation in **1b** (Scheme 2), but not in the major product **1a**, where one must always be axial. Despite this, there is precedent for a related

Table 1. Optimization of Rongalite addition to dibenzalacetone.



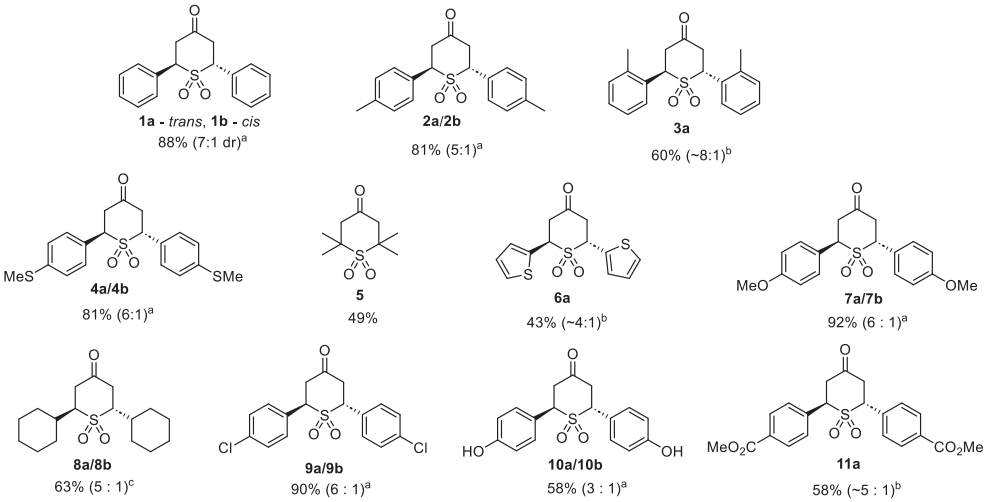
Entry	Solvent	Time/h	Temp/°C	Equiv. Rongalite	Yield/%	dr
1	aq. AcOH	3	80	1.5	75	6:1
2	aq. AcOH	18	50	1.5	88	7:1
3	pH 4 acetate buffer	3	80	1.5	30	6:1
4	aq. DMSO, K_2CO_3	18	50	1.5	9	7:1
5	aq. DMSO	18	50	1.5	28	7:1
6	aq. DMSO/AcOH	1	50	1.5	28	7:1
7	aq. EtOH	2	50	1.5	23	7:1

Other aprotic solvents, e.g., ethyl acetate, DMF, THF, dioxane, diethyl ether gave negligible yields (<3%) by ^{1}H NMR of the crude reaction mixture. Addition of tetra *n*-butylammonium bromide had no obvious effect in this case.



1a (major) **1b** (minor)

Scheme 2. Chair conformers of diastereomeric products **1a** and **1b**.

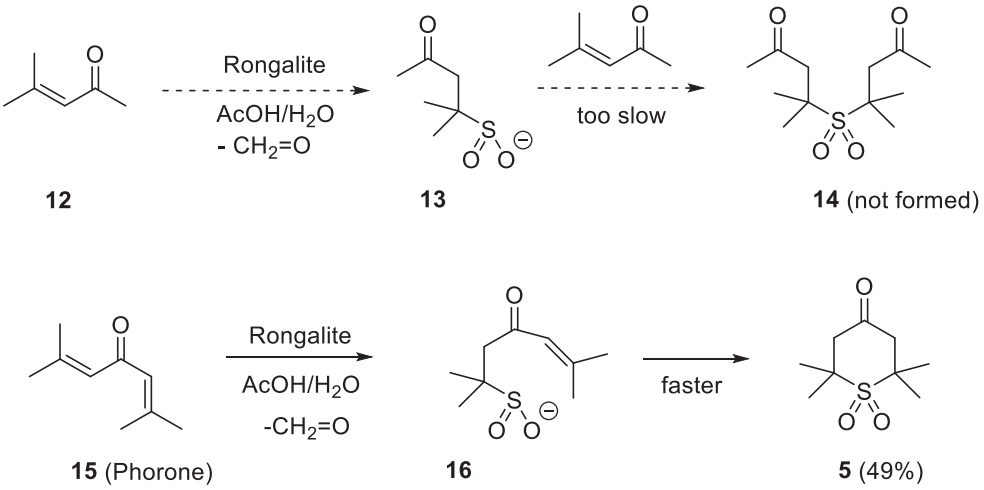


Scheme 3. Substrate scope for double conjugate addition (50 °C, 16 h or 80 °C, 3 h). [a]Combined yield of both diastereomers. [b]Yield of major isomer only—minor isomer impure. [c]Isomers were not separated as they co-eluted in chromatography.

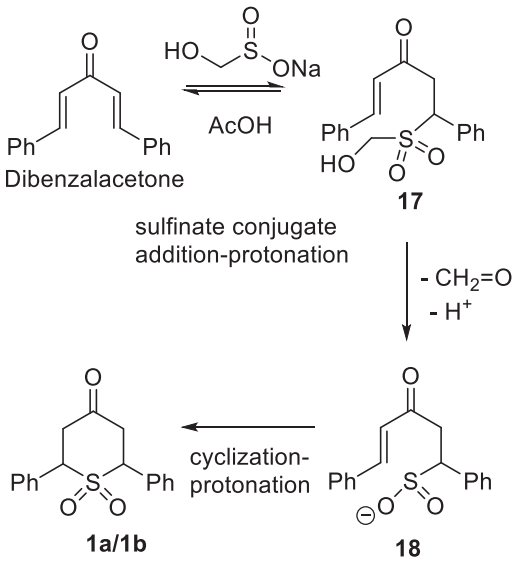
stereochemical outcome in related cyclizations involving sulfur.[22,23] A boat-like transition state has been proposed by these workers, but a full rationalization of the diastereoselectivity is yet to be established.

We next explored the substrate scope (Scheme 3). The reaction was compatible with various substituents on the aromatic ring and with both electron-donating and electron-withdrawing groups. The number of equivalents of Rongalite were adjusted according to the reactivity observed by some substrates, and some substrates reacted better at 80 °C (see electronic Supporting Information). In particular, substituents containing acidic protons (**10a/b**), alkyl substituents (sulfones **8a**/**8b**), and oxidation-sensitive groups (**4a/4b**, **6a**) are also tolerated. The reaction is also particularly tolerant of steric bulk at the β-position, as shown by the success in preparing sulfone **5** from phorone, which has two fully substituted carbons on either side of the sulfone. This represents a very significant increase in scope for Rongalite conjugate addition.

To determine whether there was an observable benefit from the use of the dienone substrates, instead of other standard enones, we tested the reaction of Rongalite with mesityl oxide **12** and found no trace of product formation. This indicates that the second *intermolecular* conjugate addition of the hindered sulfinate **13** is too slow to be useful, in contrast to the *intramolecular* reaction of presumed intermediate **16** to give **5**[24] (Scheme 4). Work-up of this reaction at partial conversion led only to the



Scheme 4. Contrasting reactions of mesityl oxide **12** and phorone **15**.



Scheme 5. Sequence of possible reaction intermediates.

observation of starting materials and final products, which may indicate that the first conjugate addition is subject to an unfavorable equilibrium and that the overall process is driven to completion by the irreversible elimination of formaldehyde, perhaps driven by acetate ion formed following the formation of **17** and subsequent cyclization of **18** to give sulfone products (**1a/1b** illustrated here) (Scheme 5).

Summary

We have developed a one-pot synthesis of cyclic sulfones from Rongalite and readily available dienones. This circumvents the need for oxidation of a sulfide intermediate, such that protic groups and oxidation-sensitive functionality are readily tolerated. The

reaction is practically straightforward to carry out, with no need for inert atmosphere techniques. This represents a significant expansion in scope for the reactivity of Rongalite, allowing the preparation of sterically congested sulfones. Further studies of this reaction, as well as other reaction development using Rongalite are underway in our laboratory.

Experimental

General information

Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Spectrospin 400 spectrometer at 400 MHz and referenced to residual solvent. ^{13}C NMR spectrum were recorded using the same spectrometer at 100 MHz, respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δH 7.26). *J* values are given in Hz and s, d, dd, ddd, t, dt, q, m, br, and app. abbreviations correspond to singlet, doublet, doublet of doublet, doublet of doublet of doublet, triplet, triplet of doublet, quartet, multiplet, broad, and apparent, respectively. High resolution mass spectra were obtained using a Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer (Montclair State) or an LTQ Orbitrap (Purdue Univ.). Infrared spectra were obtained on Perkin-Elmer Spectrum Two FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 precoated sheets and visualized by UV (254 nm) and stained by the use of aqueous acidic $KMnO_4$. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon.

General procedure A for double conjugate addition

Glacial acetic acid (4.7 ml/mmol substrate) was added to dienone substrate (1–2 mmol) in an open round bottom flask, followed by water (0.8 mL/mmol Rongalite) and Rongalite (1.5–3 equiv.) The mixture was stirred (350 rpm) at 50 °C for 18 h. Equal volumes of ethyl acetate (25 mL/mmol substrate) and water (25 ml/mmol substrate) were added and the mixture was extracted twice more with ethyl acetate (25 mL/mmol). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (25 mL/mmol substrate) and water (25 mL/mmol substrate). The organic layer was separated and dried (Na_2SO_4) and the solvent was removed at reduced pressure. The product diastereomers were separated by column chromatography on silica gel (EtOAc/hexanes). The major *trans*-isomer invariably eluted with a higher R_f.

General procedure B for double conjugate addition

Glacial acetic acid (4.7 ml/mmol substrate) was added to dienone substrate (1–2 mmol) in an open round bottom flask, followed by water (0.8 mL/mmol Rongalite) and Rongalite (1.5–3 equiv.) The mixture was stirred (350 rpm) at 80 °C for 3 h. Equal volumes of ethyl acetate (25 mL/mmol substrate) and water (25 ml/mmol substrate) were

added and the mixture was extracted twice more with ethyl acetate (25 mL/mmol). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (25 mL/mmol substrate) and water (25 mL/mmol substrate). The organic layer was separated and dried (Na_2SO_4) and the solvent was removed at reduced pressure. The product diastereomers were separated by column chromatography on silica gel (EtOAc/hexanes). The major *trans*-isomer invariably eluted with a higher R_f.

Sulfones 1a/1b[21]. Procedure A with 500 mg (2.1 mmol) 1,5-Diphenylpenta-1,4-dien-3-one (dibenzalacetone), 493 mg, Rongalite (1.5 equiv., 3.2 mmol), 1.3 ml H_2O and 10 mL of acetic acid gave 494 mg of **1a** and 71 mg of **1b** (88% total).

Trans-*2,6-Diphenyltetrahydro-4*H*-thiopyran-4-one-1,1-dioxide 1a.* **^{1}H-NMR (400 MHz, DMSO-*d6*):** R_f (50% EtOAc/hexanes) 0.45. Off-white solid, m.p. 175–176 °C (EtOAc/Hexanes) [lit. 179–180 °C (Et_2O)] ^{1}H NMR (400 MHz, DMSO) δ 7.48–7.39 (m, 10H), 5.16 (dd, $J = 11.7$, 3.8 Hz, 2H), 3.71 (dd, $J = 16.6$, 11.7 Hz, 2H), 3.05 (dd, $J = 16.6$, 3.8 Hz, 2H).

^{13}C-NMR ^{13}C NMR (101 MHz, DMSO) δ 204.7, 131.2, 130.3, 129.4, 129.0, 62.2, 43.5. **HRMS** ($M + H^+$), calcd for $C_{17}H_{17}SO_3 = 301.089842$, Found 301.09048 ($\delta = 2.1$ ppm).

Cis-*2,6-Diphenyltetrahydro-4*H*-thiopyran-4-one-1,1-dioxide 1b.* **^{1}H-NMR (400 MHz, $CDCl_3$):** R_f (50% EtOAc/hexanes) 0.23 Off-white solid, m.p. 234–235 °C (EtOAc/hexanes) [lit. 237–238 °C (Et_2O)] $\delta = {}^1$H NMR (400 MHz, $CDCl_3$), δ 7.55-7.40 (m, 10H), 4.63 (dd, $J = 14.3$, 3.3 Hz, 2H), 3.82 (t, $J = 14.3$ Hz, 2H), 3.05 (d, $J = 14.3$ Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 202.1$, 129.8, 129.6, 129.0, 128.5, 64.4, 45.8. **HRMS** ($M + H^+$), calcd for $C_{17}H_{17}SO_3 = 301.089842$, Found 301.09039 ($\delta = 1.9$ ppm).

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References

[1] Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832–2842. DOI: 10.1021/jm401375q.

[2] Emmett, E. J.; Willis, M. C. The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry. *Asian J. Org. Chem.* **2015**, *4*, 602–611. DOI: 10.1002/ajoc.201500103.

[3] For a recent review and other references to sulfonyl radical conjugate addition, see Qian, B.; Zhu, C.; Shen, G. The Application of Sulfonyl Hydrazides in Electrosynthesis: A Review of Recent Studies. *ACS Omega* **2022**, *7*, 39531–39561. DOI: 10.1021/acsomega.2c04205.

[4] Matavos-Aramyan, S.; Soukhakian, S.; Jazebizadeh, M. H. Selected Methods for the Synthesis of Sulfoxides and Sulfones with Emphasis on Oxidative Protocols. *Phosphorus Sulfur Silicon Relat. Elem.* **2020**, *195*, 181–193. DOI: 10.1080/10426507.2019.1672691.

[5] Kotha, S.; Khedkar, P. Rongalite: A Useful Green Reagent in Organic Synthesis. *Chem. Rev.* **2012**, *112*, 1650–1680. DOI: 10.1021/cr100175t.

[6] Kotha, S.; Khedkar, P.; Dommaraju, Y. Synthetic Applications of Rongalite: A Green Tool in the Service of Diels–Alder Chemistry and beyond. *Tetrahedron Lett.* **2019**, *60*, 631–648. DOI: 10.1016/j.tetlet.2019.01.031.

[7] Yu, F.; Mao, R.; Yu, M.; Gu, X.; Wang, Y. Generation of Aryl Radicals from Aryl Halides: Rongalite-Promoted Transition-Metal-Free Arylation. *J. Org. Chem.* **2019**, *84*, 9946–9956. DOI: 10.1021/acs.joc.9b01113.

[8] Golla, S.; Kokatla, H. P. Rongalite-Mediated Transition Metal- and Hydride-Free Chemoselective Reduction of α-Keto Esters and α-Keto Amides. *J. Org. Chem.* **2022**, *87*, 9915–9925. DOI: 10.1021/acs.joc.2c00936.

[9] Laha, J. K.; Gupta, P. Sulfoxylate Anion Radical-Induced Aryl Radical Generation and Intramolecular Arylation for the Synthesis of Biarylsultams. *J. Org. Chem.* **2022**, *87*, 4204–4214. DOI: 10.1021/acs.joc.1c03031.

[10] Zhang, G.; Sang, Z.; Wu, W.; Fan, Q.; Ding, C. Rongalite Promoted Reductive Esterification of Sulfonyl Chlorides: An Efficient Preparation of Sulfinic Esters. *ChemistrySelect* **2022**, *7*, e202202833. DOI: 10.1002/slct.202202833.

[11] Wang, M.; Tang, B.; Xiang, J.; Chen, X.; Ma, J.; Wu, Y.; Wu, A. Aryldiazonium Salts Serve as a Dual Synthon: Construction of Fully Substituted Pyrazoles via Rongalite-Mediated Three-Component Radical Annulation Reaction. *Org. Lett.* **2019**, *21*, 8934–8937. DOI: 10.1021/acs.orglett.9b03212.

[12] Chen, X.; Wang, H.; Wu, C.; Tang, B.; Hu, Y.; Ma, J.; Zhuang, S.; Yu, Z.; Wu, Y.; Wu, A. Synthesis of Tetrahydro-2*H*-Thiopyran 1,1-Dioxides via [1 + 1+1 + 1+1 + 1] Annulation: An Unconventional Usage of a Tethered C-S Synthon. *Org. Lett.* **2022**, *24*, 7659–7664. DOI: 10.1021/acs.orglett.2c03194.

[13] Golla, S.; Jalagam, S.; Poshala, S.; Kokatla, H. P. Transition Metal-Free Functionalization of 2-Oxindoles via Sequential Aldol and Reductive Aldol Reactions Using Rongalite as a C1 Reagent. *Org. Biomol. Chem.* **2022**, *20*, 4926–4932. DOI: 10.1039/d2ob00665k.

[14] Chen, X.; Wu, C.; Ma, J.; Zhuang, S.; Yu, Z.; Wu, Y.; Wu, A. Rongalite as C1 Synthon and Sulfone Source: A Practical Sulfonylmethylation Based on the Separate-Embedding Strategy. *Org. Lett.* **2022**, *24*, 223–227. DOI: 10.1021/acs.orglett.1c03877.

[15] Shavnya, A.; Coffey, S. B.; Hesp, K. D.; Ross, S. C.; Tsai, A. S. Reaction of Alkyl Halides with Rongalite: One-Pot and Telescoped Syntheses of Aliphatic Sulfonamides, Sulfonyl Fluorides, and Unsymmetrical Sulfones. *Org. Lett.* **2016**, *18*, 5848–5851. DOI: 10.1021/acs.orglett.6b02894.

[16] Alvarez, E. M.; Plutschack, M. B.; Berger, F.; Ritter, T. Site-Selective C–H Functionalization-Sulfination Sequence to Access Aryl Sulfonamides. *Org. Lett.* **2020**, *22*, 4593–4596. DOI: 10.1021/acs.orglett.0c00982.

[17] Kerber, R.; Starnick, J. Anlagerungs- und Eliminierungsreaktionen mit Schwefelsauerstoff-Verbindungen, I. Darstellung von symmetrischen Sulfonen durch Anlagerung von Sulfoxylsäurederivaten an aktivierte Doppelbindungen. *Chem. Ber.* **1971**, *104*, 2035–2043. DOI: 10.1002/cber.19711040703.

[18] Kim, D.; Um, H.; Park, H.; Kim, S.; Choi, J.; Lee, C. Silyloxymethanesulfinate as a Sulfoxylate Equivalent for the Modular Synthesis of Sulfones and Sulfonyl Derivatives. *Chem. Sci.* **2020**, *11*, 13071–13078. DOI: 10.1039/d0sc02947e.

[19] Shavnya, A.; Hesp, K. D.; Tsai, A. S. A Versatile Reagent and Method for Direct Aliphatic Sulfonylation. *Adv. Synth. Catal.* **2018**, *360*, 1768–1774. DOI: 10.1002/adsc.201800071.

[20] Chen, X.; Tang, B.; He, C.; Ma, J.; Zhuang, S.; Wu, Y.; Wu, A. Rongalite as a Sulfone Source: A Novel Copper-Catalyzed Sulfur Dioxide Anion Incorporation Process. *Chem. Commun.* **2020**, *56*, 13653–13656. DOI: 10.1039/d0cc05800a.

[21] Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. Syntheses of 4*H*-Thiopyran-4-One 1,1-Dioxides as Precursors to Sulfone-Containing Analogs of Tetracyanoquinodimethane. *J. Org. Chem.* **1995**, *60*, 1665–1673. DOI: 10.1021/jo00111a027.

[22] Baxter, C. A. R.; Whiting, D. A. Stereochemistry and Structure in the Tetrahydro-1-Thio-4-Pyrone and Tetrahydro-4-Pyrone Series. *J. Chem. Soc. C* **1968**, 1174–1178. DOI: 10.1039/j39680001174.

[23] Gendron, T.; Kessedjian, H.; Davioud-Charvet, E.; Lanfranchi, D. A. Diastereoselective Synthesis of 2,6-Diaryltetrahydrothiopyran-4-Ones by Phase-Transfer Catalysis. *Eur. J. Org. Chem.* **2015**, *2015*, 1790–1796. DOI: 10.1002/ejoc.201403516.

[24] Borsdorf, R.; Remane, H. Arbeitsvorschriften und Meßergebnisse. Frequenz und Intensität der Carbonylbande von Thiacycloalkanonen und Thiacycloalkanon-1,1-dioxiden im mittleren IR. *J. Prakt. Chem.* **1980**, *322*, 152–154. DOI: 10.1002/prac.19803220119.