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# Transition metal-free cross-coupling of benzothiophenes and styrenes in a stereoselective synthesis of substituted (*E,Z*)-1,3-dienes

Mindaugas Šiaučiulis<sup>[a]</sup>, Nanna Ahlsten<sup>[b]</sup>, Alexander P. Pulis<sup>[a]</sup>, and David J. Procter<sup>[a]\*</sup>

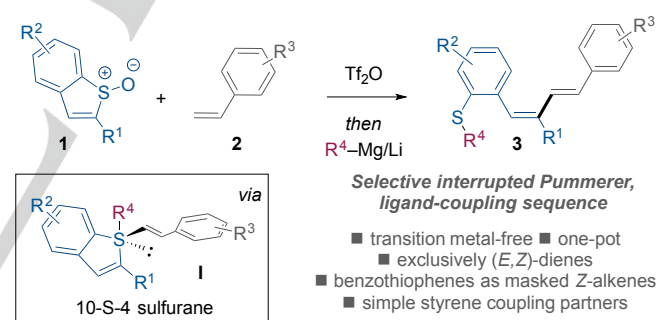
**Abstract:** A transition metal-free, one-pot, stereoselective approach to substituted (*E,Z*)-1,3-dienes utilizes an interrupted Pummerer/ligand-coupling strategy. Readily available benzothiophene *S*-oxides, conveniently prepared by oxidation of the parent benzothiophenes, undergo Pummerer coupling with styrenes. Reaction of the resultant sulfonium salts with alkyl lithium/magnesium reagents generates underexploited hypervalent sulfurane intermediates that undergo selective ligand coupling, resulting in the dismantling of the benzothiophene motif and the formation of decorated (*E,Z*)-1,3-dienes.

Conjugated dienes constitute an important molecular motif found in natural products,<sup>1</sup> biologically active compounds,<sup>2</sup> and precursors to organic materials.<sup>3</sup> They are also mandatory components in fundamental chemical transformations, such as the Diels-Alder cycloaddition.<sup>4</sup> As different diene isomers can exhibit different physical properties and the stereochemistry of dienes can influence the outcome of further chemical transformations,<sup>5</sup> it is highly desirable that any synthesis of substituted dienes be stereoselective. Unfortunately, this remains a challenge and fully stereoselective methods for the construction of substituted dienes are scarce.<sup>6</sup>

Substituted 1,3-dienes are typically prepared by transition-metal-catalysed cross-coupling reactions between prefunctionalised olefinic cross-coupling partners of predefined stereochemistry.<sup>7</sup> Alternatively, well-known olefination methods for the stereoselective synthesis of alkenes can be extended to the synthesis of dienes.<sup>8</sup> Although useful for the synthesis of terminal dienes, application to the synthesis of substituted, conjugated dienes can be problematic. Additional approaches start from enynes,<sup>9a-b</sup> alkynes,<sup>9c-f</sup> or cyclobutenes,<sup>9g-i</sup> for example. New methods for the stereoselective synthesis of substituted 1,3-dienes are needed that complement the above approaches.

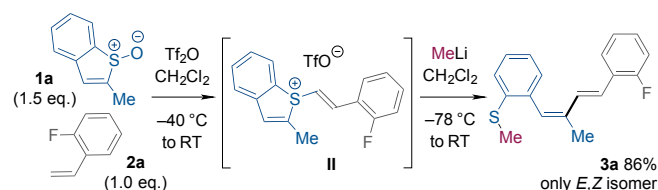
Since the seminal work of Trost and Oae on all-carbon sulfurane formation,<sup>10</sup> the elusive hypervalent intermediates have found little application in synthesis.<sup>11</sup> This is largely due to the challenge of controlling the selectivity of ligand coupling in sulfuranes.<sup>10,11</sup> Inspired by the recent work of Stockman on the development of an approach to diarylmethanes that proceeds via ligand coupling in oxy-sulfurane intermediates,<sup>12</sup> we envisioned that selective C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling could be achieved by the coupling of two alkene ligands in all-carbon

sulfuranes. Such a process would mimic reductive elimination from a transition metal, with sulfur taking the place of palladium, for example, and deliver 1,3-dienes. We postulated that the key all-carbon sulfuranes could be conveniently formed in one-pot by the facile interrupted Pummerer reactions<sup>13</sup> of sulfoxides and alkene coupling partners<sup>14</sup> followed by the addition of an organolithium or organomagnesium reagent to sulfur. In particular, the use of little explored yet readily accessible benzothiophene *S*-oxides<sup>15</sup> as the sulfoxide partner was particularly attractive as the benzothiophene unit in the sulfoxide would serve as a masked *Z*-alkene and thus allow stereocontrolled access to 1,3-dienes. Herein, we report an efficient, transition metal-free, one pot procedure for the stereocontrolled synthesis of substituted (*E,Z*)-1,3-dienes. Benzothiophene *S*-oxides **1** are used to engage styrene partners **2** by efficient interrupted Pummerer reaction. Subsequent addition of an organolithium/magnesium triggers the formation of hypervalent sulfurane intermediates **I** and selective dismantling of the benzothiophene motif through selective ligand-coupling to give substituted (*E,Z*)-1,3-dienes **3** (Scheme 1).



**Scheme 1.** An interrupted Pummerer/ligand-coupling strategy for the construction of (*E,Z*)-1,3-dienes.

We began by investigating the interrupted Pummerer reaction between Tf<sub>2</sub>O-activated 2-methylbenzothiophene **1a** and 2-fluorostyrene **2a**. After optimization (see Supporting Information for details), a one-pot procedure involving the addition of methyl lithium to the intermediate *E*-alkenyl sulfonium salt **II** gave the desired tri-substituted (*E,Z*)-1,3-diene **3a** in 86% isolated yield. No other stereoisomers of **3a** were detected (Scheme 2).

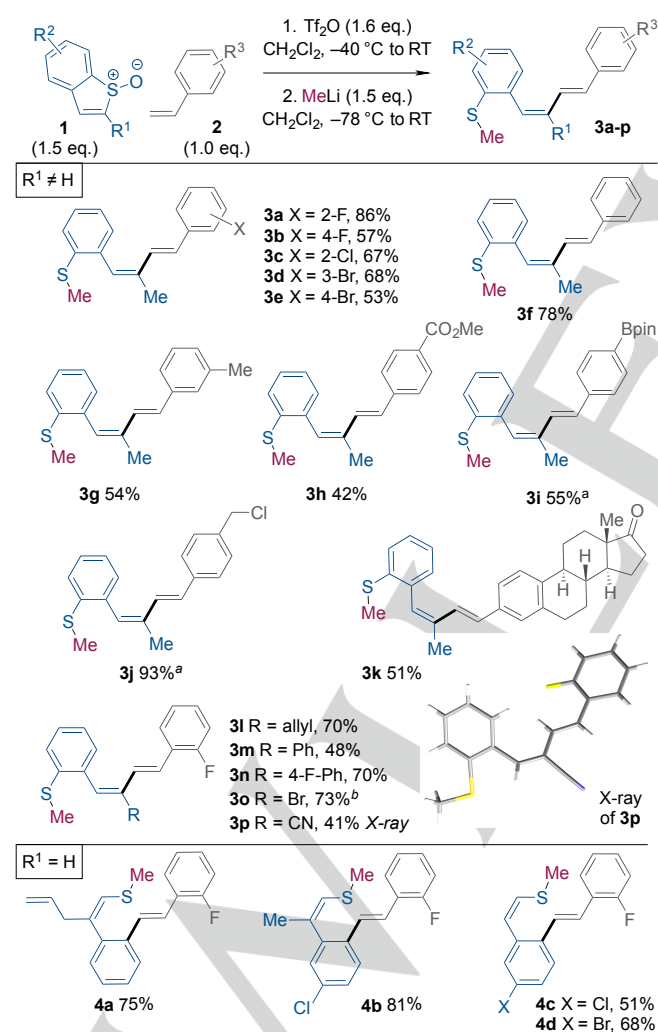


**Scheme 2.** One-pot, interrupted Pummerer/ligand-coupling sequence for the construction of (*E,Z*)-diene **3a** from benzothiophene *S*-oxide **1a** and styrene **2a**.

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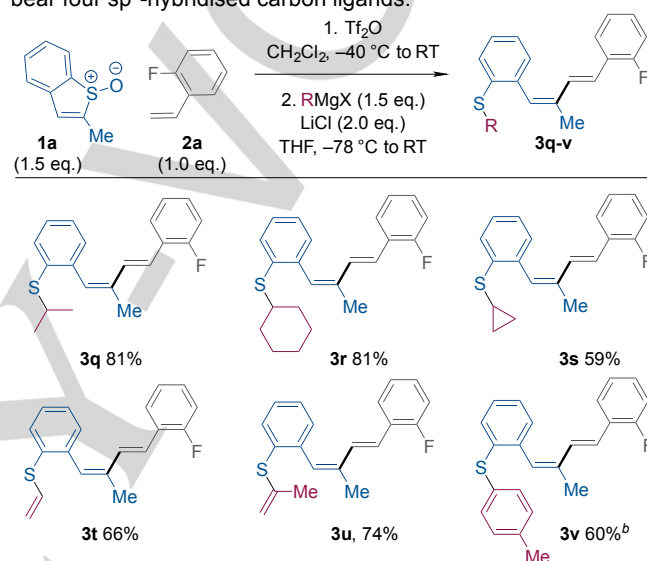
Exploring the scope of the reaction with respect to the styrene partner, we found that various substitution patterns and functional groups were tolerated in the process and diene products (**3a-3p**) were formed as single stereoisomers in all cases (Scheme 3). Remarkably, functional groups that are typically incompatible with organometallic reagents, such as aryl bromide (**3d**, **3e**), ester (**3h**), boronate ester (**3i**) and benzylic chloride (**3j**) emerged from the sequence unscathed. The process was successfully applied to the coupling of complex ketone, vinyl estrone, to give **3k** in moderate yield. Convenient variation of the 2-substituent on the benzothiophene-*S*-oxide **1** allowed (*E,Z*)-1,3-dienes bearing a range of substituents on the internal carbons (**3a**, **3i-3p**) to be assembled, including dienyl bromide (**3o**) and sensitive  $\alpha,\beta$ -unsaturated nitrile (**3p**). The structure of **3p** was confirmed by X-ray crystallographic analysis. In contrast, the use of benzothiophene *S*-oxides lacking substituents at the 2-position (*i.e.*  $R^1 = H$ ) resulted in a clean switch to an alternative ligand coupling in the sulfurane intermediates (*vide infra*) and the formation of 2-alkenyl sulfide stilbene products (**4a-d**) (Scheme 3).



**Scheme 3.** Scope with regard to the styrene and benzothiophene partners in the stereoselective synthesis of (*E,Z*)-1,3-dienes. (*E,Z*)-Isomers are formed

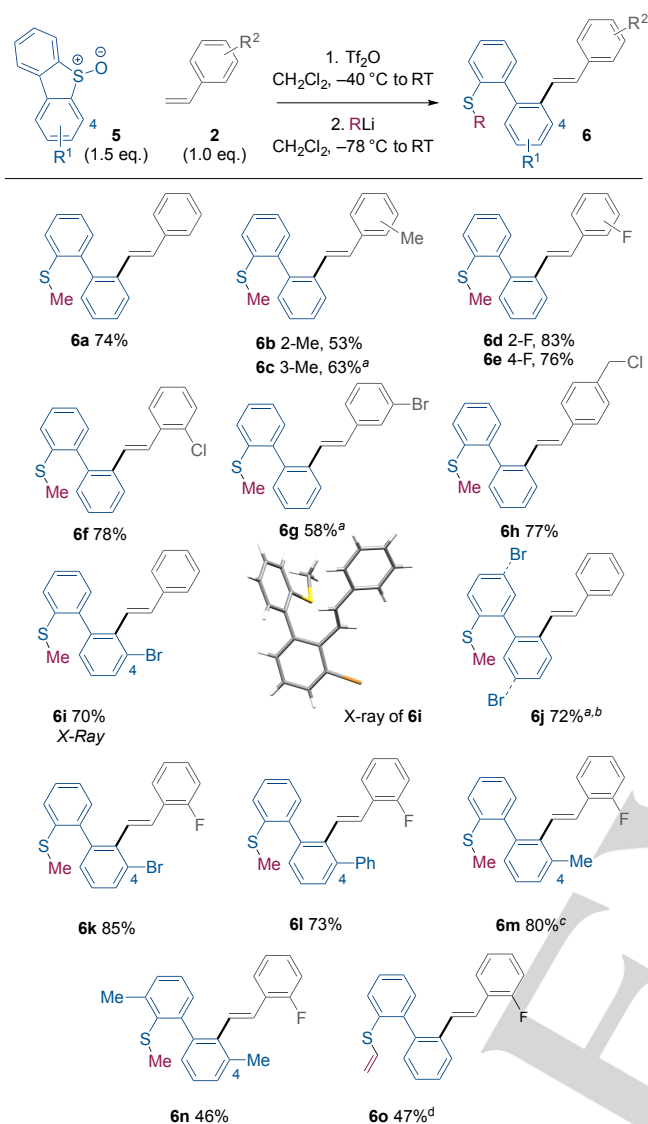
exclusively. Isolated yields. <sup>a</sup> Yields determined by  $^1\text{H}$  NMR analysis. <sup>b</sup>  $\text{MeMgBr}$  (1.5 eq.) used.

The use of alternative organometallic reagents to trigger ligand coupling in the one-pot process was investigated using the pairing of methylbenzothiophene *S*-oxide **1a** and 2-fluorostyrene **2a** (Scheme 4). The addition of  $\text{LiCl}$  proved to be beneficial for efficient conversion of sulfonium salts to the dienes **3** when organomagnesium reagents were used. A range of Grignard reagents were successfully employed, including cycloalkyl (**3q**, **3r**), benzyl (**3s**), alkenyl (**3t**, **3u**), and aryl (**3v**). Interestingly, when alkenyl and aryl organomagnesium reagents were used, selective ligand coupling to give the diene products (**3t-u**) was observed even though the sulfurane intermediates bear four  $\text{sp}^2$ -hybridised carbon ligands.

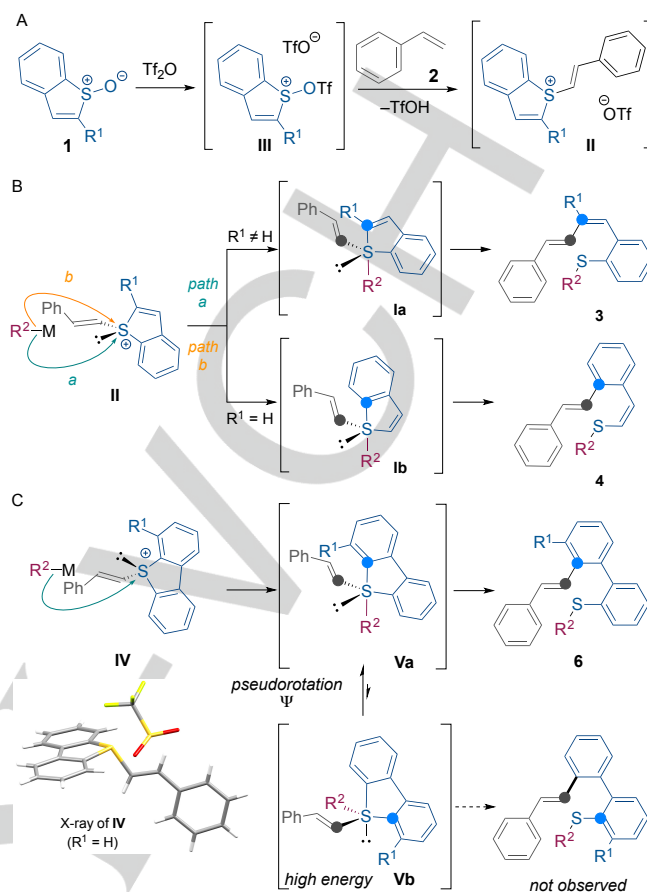


**Scheme 4.** Scope with regard to the organometallic partner in the stereoselective synthesis of (*E,Z*)-1,3-dienes. (*E,Z*)-Isomers are formed exclusively. Isolated yields. <sup>a</sup> Yields determined by  $^1\text{H}$  NMR analysis.

Employing dibenzothiophene *S*-oxides **5**, the reaction also proved amenable to the synthesis of 2,2'-disubstituted biaryls **6** (Scheme 5).<sup>16</sup> A variety of substituted styrenes were tolerated in the process (**6a-h**), including those containing sensitive aryl bromide (**6g**) and benzylic chloride (**6h**) functionalities. Substituted dibenzothiophene *S*-oxides could also be employed leading to decorated biaryls (**6i-n**).



In particular, sulfuranones generated from 4-substituted dibenzothiophene *S*-oxides underwent selective ligand coupling at the more hindered position, leading to more sterically congested products (**6i,k-m**). Alternative organometallic reagents successfully triggered ligand coupling in these reactions; for example, vinylmagnesium bromide was used in the preparation of **6o**.



Based on previous reports describing sulfuranone intermediates<sup>10-12</sup> and our experimental observations, we propose the following mechanism for the interrupted Pummerer/ligand-coupling sequence (Scheme 6). Treatment of benzothiophene *S*-oxides **1** with  $\text{TiF}_2\text{O}$  generates sulfoxonium salts **III** that are capable of engaging styrenes **2** in an interrupted Pummerer process (Scheme 6A). The resultant (*E*)-alkenyl sulfonium salts **II** can then be activated towards ligand-coupling by addition of an organometallic reagent and generation of hypervalent (10-*S*-4) sulfur intermediates **I** (Scheme 6B). Favourable orbital overlap between  $\text{sp}^2$ -hybridised axial and equatorial ligands then leads to ligand-coupling and formation of the desired diene products. It is considered that nucleophilic additions to sulfonium salts **II** occur opposite to an existing ligand to give sulfuranones **I**, in which the nucleophile occupies an axial position.<sup>11a,11c</sup> The most accessible lines of attack are opposite to the C–S bonds of the heterocycle and the least sterically hindered approach is preferred. In the case of 2-substituted benzothiophenium salts **II** ( $\text{R}^1 \neq \text{H}$ ), attack opposite to the C<sub>2</sub>–S bond is favored (Scheme 6B, path a), resulting in sulfuranone **Ia** which upon stereoretentive ligand-coupling delivers (*E,Z*)-dienes **3**. With C<sub>2</sub>-unsubstituted benzothiophenium salts **II** ( $\text{R}^1 = \text{H}$ ), nucleophilic attack occurs opposite to the C<sub>7a</sub>–S bond

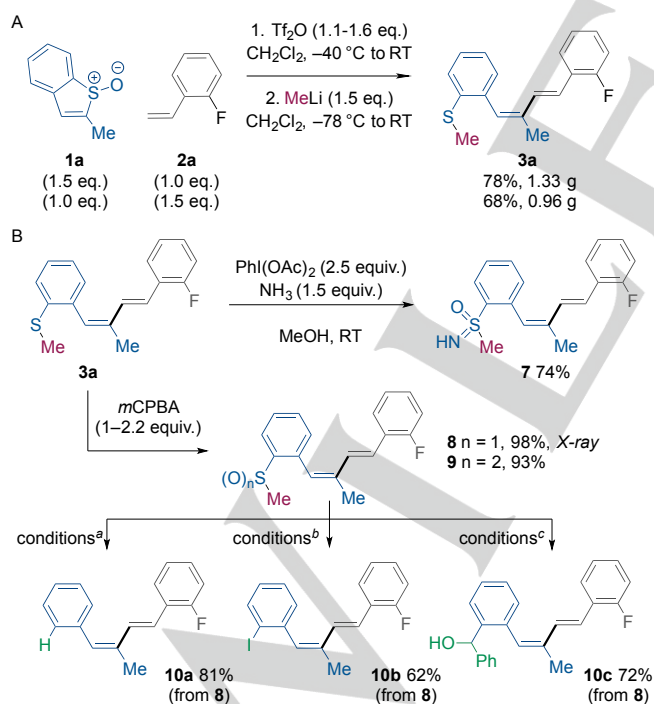
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(Scheme 5B, path b) and via sulfurane **1b** to stilbenes **4**. The impact of sterics can also be seen in the reactions of unsymmetrical 4-substituted dibenzothiophenium salts **IV** (Scheme 5C). Nucleophilic attack along the least sterically hindered line of attack delivers intermediate sulfurane **Va** – with the substituted aryl unit in the axial position. Subsequent ligand coupling with the equatorial styryl group then delivers biaryls **6**. While pseudorotation of intermediate sulfuranes **Va** is possible,<sup>10g</sup> formation of the isomeric product requires access to a high energy sulfurane **Vb** in which a lone pair unfavourably occupies an axial position.

To demonstrate the synthetic utility of the interrupted Pummerer/ligand-coupling reaction sequence, we successfully accomplished gram scale synthesis of (*E,Z*)-1,3-diene **3a**. Crucially, the stoichiometry of starting materials can be reversed without significantly affecting the efficiency of the reaction.

Finally, the organosulfanyl unit in the (*E,Z*)-1,3-diene products of the transition-metal-free cross-coupling render them useful building blocks for further manipulation. For example, selective oxidation of diene **3a** to the corresponding sulfoximine **7**,<sup>17</sup> sulfoxide **8**, and sulfone **9** can be readily carried out (Scheme 7). Employing **8** in subsequent sulfoxide-metal exchange processes<sup>18</sup> and quenching with various electrophiles allows access to a range of 1,3-dienes. For example, quenching of the intermediate arylmetal with water, iodine, and benzaldehyde delivers 1,3-dienes **10a**, **10b** and **10c**, respectively. Crucially, products **10** contain no trace of the sulfur atom of the benzothiophene ring system used to selectively construct the (*E,Z*)-1,3-diene systems.



**Scheme 7.** A) Larger scale Interrupted Pummerer/ligand-coupling sequence. B) Representative manipulations of the organosulfanyl unit in the (*E,Z*)-1,3-diene products. <sup>a</sup>  $\text{EtMgBr}$  (1.5 eq.), THF, RT, 30 min, then  $\text{NH}_4\text{Cl}$  (aq.). <sup>b</sup>  $\text{EtMgBr}$  (1.5 eq.), THF, RT, 30 min, then  $\text{I}_2$  (1.5 eq.). <sup>c</sup>  $\text{EtMgBr}$  (1.5 eq.), THF, RT, 30 min, then  $\text{PhCHO}$  (1.5 eq.).

In summary, we have developed a transition-metal-free stereoselective, one pot synthesis of (*E,Z*)-1,3-dienes that exploits a new interrupted Pummerer/ligand-coupling sequence. Readily accessible yet underexplored benzothiophene *S*-oxides couple with styrene partners and addition of an organometallic reagent triggers controlled dismantling of the benzothiophene scaffold by selective ligand-coupling in rarely-exploited sulfurane intermediates.

## Acknowledgements

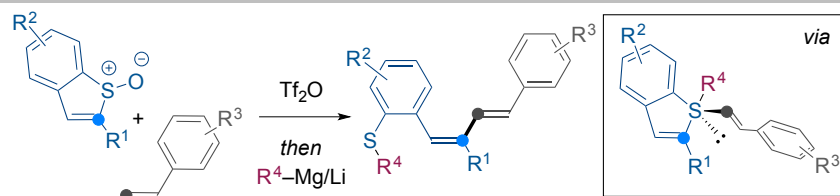
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**Keywords:** sulfoxides • sulfur • Pummerer • sulfurane • ligand coupling

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## Entry for the Table of Contents



**Transition metal-free cross-coupling of benzothiophenes and styrenes in a stereoselective synthesis of substituted (E,Z)-1,3-dienes**

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A transition metal-free stereoselective, one pot synthesis of (E,Z)-1,3-dienes exploits an interrupted Pummerer/ligand-coupling sequence. Readily accessible yet underexplored benzothiophene S-oxides couple with styrene partners and addition of an organometallic reagent triggers controlled dismantling of the benzothiophene scaffold by selective ligand-coupling in rarely-exploited sulfurane intermediates.