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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^[a], Nanna Ahlsten^[b], Alexander P. Pulis^[a], and David J. Procter^[a]*

Abstract: A transition metal-free, one-pot, stereoselective approach substituted (E,Z)-1,3-dienes utilizes an to 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 alkvl 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,¹ biologically active compounds,² and precursors to organic materials.³ They are also mandatory components in fundamental chemical transformations, such as the Diels-Alder cycloaddition.⁴ As different diene isomers can exhibit different physical properties and the stereochemistry of dienes can influence the outcome of further chemical transformations,⁵ 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.⁶

Substituted 1,3-dienes are typically prepared by transitionmetal-catalysed cross-coupling reactions between prefunctionalised olefinic cross-coupling partners of predefined stereochemistry.⁷ Alternatively, well-known olefination methods for the stereoselective synthesis of alkenes can be extended to the synthesis of dienes.⁸ Although useful for the synthesis of terminal dienes, application to the synthesis of substituted, conjugated dienes can be problematic. Additional approaches start from enynes,^{9a-b} alkynes,^{9c-f} or cyclobutenes,^{9g-i} 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,¹⁰ the elusive hypervalent intermediates have found little application in synthesis.¹¹ This is largely due to the challenge of controlling the selectivity of ligand coupling in sulfuranes.^{10,11} Inspired by the recent work of Stockman on the development of an approach to diarylmethanes that proceeds via ligand coupling in oxy-sulfurane intermediates,¹² we envisioned that selective $C(sp^2)-C(sp^2)$ coupling could be achieved by the coupling of two alkene ligands in all-carbon

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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 reactions¹³ of sulfoxides and alkene coupling partners¹⁴ followed by the addition of an organolithium or organomagnesium reagent to sulfur. In particular, the use of little explored yet readily accessible benzothiophene S-oxides¹⁵ 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_2O -activated 2-methylbenzothiophene **1a** and 2-fluorostyrene **2a**. After optimization (see Supporting Information for details), a one-pot procedure involving the addition of methyllithium 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).





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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 α,β -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)-lsomers are formed

exclusively. Isolated yields. ^a Yields determined by ¹H NMR analysis.^b 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 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 sp²-hybridised carbon ligands.





Employing dibenzothiophene *S*-oxides **5**, the reaction also proved amenable to the synthesis of 2,2'-disubstituted biaryls **6** (Scheme 5).¹⁶ 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**).

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Scheme 5. Application of the interrupted Pummerer/ligand coupling sequence to the synthesis of 2,2'-substituted biaryls. (*E*)-Isomers are obtained exlusively. Isolated yields. ^aYields determined by ¹H NMR analysis. ^b1:1 mixture of regioisomers. ^c10:1 mixture of regioisomers. ^dConditions as in Scheme 4.

In particular, sulfuranes 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**.



Scheme 6. A) Mechanism of the interrupted Pummerer reaction of benzothiophene S-oxides and styrenes. B) Proposed origin of selectivity in the ligand coupling of sulfuranes derived from benzothiophene. C) Proposed origin of regioselectivity in the ligand coupling of sulfuranes derived from dibenzothiophene.

Based previous reports describing on sulfurane intermediates¹⁰⁻¹² and our experimental observations, we propose the following mechanism for the interrupted Pummerer/ligand-coupling sequence (Scheme 6). Treatment of benzothiophene S-oxides $\mathbf{1}$ with Tf_2O 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 sp²-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 sulfuranes I, in which the nucleophile occupies an axial postion.11a,11c 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 2substituted benzothiophenium salts II ($R^1 \neq H$), attack opposite to the C2-S bond is favored (Scheme 6B, path a), resulting in sulfurane la which upon stereoretentive ligand-coupling delivers (E,Z)-dienes 3. With C2-unsubstituted benzothiophenium salts II $(R^1 = H)$, nucleophilic attack occurs opposite to the C_{7a}-S bond

(Scheme 5B, path b) and via sulfurane **Ib** 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,^{10g} 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**,¹⁷ sulfoxide **8**, and sulfone **9** can be readily carried out (Scheme 7). Employing **8** in subsequent sulfoxide-metal exchange processes¹⁸ 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*)-1,3diene products. ^{*a*} EtMgBr (1.5 eq.), THF, RT, 30 min, *then* NH₄Cl (aq.). ^{*b*} EtMgBr (1.5 eq.), THF, RT, 30 min, *then* I₂ (1.5 eq.). ^{*c*} EtMgBr (1.5 eq.), THF, RT, 30 min, *then* 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.

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

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