Published in final edited form as:

J Am Chem Soc. 2018 July 11; 140(27): 8434–8438. doi:10.1021/jacs.8b05421.

Highly Regio- and Stereoselective Catalytic Synthesis of Conjugated Dienes and Polyenes

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Abstract

Conjugated dienes and polyenes are typically synthesized by sequential introduction of C=C bonds. Here, we report a practical and scalable, catalytic dienylation that is highly regio- and stereoselective for both C=C bonds. The reaction is enabled by a stereoselective palladium-catalyzed cross-coupling that is preceded by a regioselective base-induced ring opening of readily available sulfolenes. The dienylation reaction is particularly useful for the synthesis of synthetically challenging dienes containing cis double bonds. We also show that the reaction can serve as a synthetic platform for the construction of conjugated polyenes.

Conjugated dienes and polyenes are key structural motifs of many natural products and pharmaceuticals.¹ They also play central roles in organic synthesis² and materials science.³ Construction of linear conjugated π -systems presents unique synthetic challenges, since every C=C bond has to be produced stereoselectively and with substituents introduced in a regioselective manner. In order to control the regio- and stereoselectivity, a number of catalytic cross-coupling methods have been developed that attach dienyl groups in a sequence of several steps, for example by a sequential appendage of two C=C units (Scheme 1, part A).^{4,5} A reaction that enables direct appendage of a C₄ unit will allow for a more convergent and efficient synthesis of conjugated dienes and polyenes. However, the development of this synthetic platform has been impeded by the lack of reactions that produce both C=C bonds in a regio- and stereoselective manner, and the lack of dienylation reagents that are stable and readily available in a variety of substitution patterns. Existing methods, for example, Pd-catalyzed arylation reactions of substituted conjugated dienes, produce mixtures of regio- and stereoisomers and suffer from low yields and narrow scope.⁶

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; characterization data (PDF)

Crystallographic data for **24** (CIF)

Crystallographic data for **64** (CIF)

Crystallographic data for **73** (CIF)

Although dienyloboronic acids have been explored for dienylation, they are unstable and difficult to prepare.⁷ Aromatic sulfinates have been recently introduced as a new class of stable nucleophiles for Pd-catalyzed biaryl couplings.⁸ However, stereoselective cross-coupling reactions of vinylic sulfinates have remained elusive.

We report herein a general and practical reaction that enables a regio- and stereoselective and scalable synthesis of substituted conjugated dienes and polyenes by dienylation with sulfolenes that form sulfinates under the reaction conditions (Scheme 1). Sulfolenes are air- and moisture-stable compounds that are readily accessible in a convergent manner and from simple precursors.^{9,10} Although sulfolenes can be α -alkylated and then converted to dienes by heating at elevated temperatures, typically 150–200 °C or by flash vacuum pyrolysis, this stepwise approach is unselective, inefficient, incompatible with many functional groups, and cannot be used to introduce aryl and vinyl substituents.¹⁰ We envisioned that a combination of a regio- and stereoselective baseinduced ring opening of sulfolenes (e.g., sulfolene **1** to sulfinate **2**, Scheme 1, part B) and a subsequent desulfitative Pd-catalyzed coupling (Scheme 1, part C) would result in a direct, regio- and stereoselective dienylation. Indeed, the sulfolene ring opening reaction proceeds regio- and stereoselectively and affords sulfinates **3** from 2-substituted sulfolenes **4**, and sulfinates **5** from 3-substituted sulfolenes **6**.¹¹ However, dienylnsulfinate salts may isomerize (e.g., as for sulfinates **7**) at higher temperatures or in the presence of catalytic amounts of base.^{11f} Thus, the catalyst will play the key role in determining the stereoselectivity of the C–C bond-forming step.

In initial experiments, a catalytic system consisting of Pd(OAc)₂ and a bisphosphine ligand in the presence of potassium methoxide showed promising activity in the model reaction of 4-bromobenzonitrile (**8**) and sulfolene **1** (Table 1, entries 1–3). 1,2-Bis(diphenylphosphino)benzene, dppbz, proved to be a particularly suitable ligand. The reaction favored *E*-diastereomer **9** with high *E*-diastereoselectivity (>30:1, entry 3). Although dioxane and tetrahydrofuran appeared to be equally suitable solvents (entries 3 and 4), a remarkable difference was observed when the reaction was carried out in the presence of potassium carbonate (entries 5 and 6). While only marginal improvement in the yield was observed in dioxane, a nearly quantitative conversion to *E*-diene **9** took place in tetrahydrofuran, and the product was isolated in 99% yield and with >30:1 *E/Z* ratio. The reaction was less efficient in other solvents, (e.g., toluene, entry 7). In addition, other combinations of basic additives (e.g., sodium and cesium carbonates) and alkoxide bases (e.g., sodium methoxide or potassium *tert*-butoxide) afforded product **9** in lower yields and with lower *E/Z* ratios (entries 8–11). No reaction occurred in the absence of an alkoxide base (entry 12), indicating that deprotonation of 3-sulfolene **1** is an important step in the catalytic process.

The generality of the coupling reaction with sulfolene **1** was examined with a number of bromo- and chloro(hetero)arenes (Table 2).

A variety of functional groups were tolerated in substituted bromobenzenes (**9–17**), including acetamide **10**. The *E*-1,3-butadienyl moiety was also successfully appended to naphthalenes (**18–20**) and phenanthrene (**21**). A primary amino group was tolerated (**19**), indicating that anilines can be good substrates for the coupling reaction. The conjugated

dienes were in all cases produced as single *E*-diastereomers or with high *E*-diastereoselectivity. Nitrogen-containing heterocyclic conjugated dienes (**22–34**) of the pyridine, quinoline, isoquinoline, and acridine series were also produced in high yields. 2- and 4-Chloropyridines and quinolines, as well as a substituted 4-chloroacridine were readily converted to dienes **22–27**. 2,4-Dichloropyridine afforded diene **22** with the dienyl group in the C2 position. Similarly, diene **28** was formed as the only product from 4-chloro-6-bromoquiniline. The reaction can also be used to install two dienyl moieties, e.g., as in product **29**. The reaction with 2- and 4-haloazines proceeded cleanly, and sulfones that could potentially be formed by the S_NAr reaction with the intermediate sulfinate **2** were not observed. Other heterocyclic conjugated dienes with benzothiophene, benzofuran, thiophene, and benzothiazole (**35–39**) were also successfully prepared. In addition, uracil-derived diene **40** was produced in 53% yield. The reaction was also tested with 1-bromocyclohexene, and triene **41** was isolated in 67% yield.

Similarly, two cholesterol- and stigmasterol-derived products **42** and **43** that contain a conjugated tetraene unit were produced, both in 54% yield from the corresponding dienyl bromides. These results demonstrate that the dienylation with sulfolenes can also be used for the synthesis of conjugated polyene systems.⁵

We next proceeded to explore the regio- and stereoselectivity of the dienylation with substituted sulfolenes **44–51** (Table 3). Good yields were observed for products **52–54** derived from 3,4-disubstituted sulfolene **44**. *E*-Diastereomers were produced in these cases. For conjugated dienes **52** and **53**, formation of small amounts of isomers **52a** and **53a** that are produced by the hydrogen migration from the proximal methyl group to the benzylic carbon was also observed. The ratio of conjugated dienes **52** and **53** to the isomers was 13 : 1 and 15 : 1, respectively. 2-Substituted sulfolenes **45–47** were examined next. Due to the regioselectivity of the basemediated sulfolene ring opening, 1,4-disubstituted conjugated dienes were expected to be formed in the ensuing Pd-catalyzed coupling reaction with haloarenes. Indeed, 1,4-disubstituted (1*E*,3*E*)-dienes **55–64** were produced in good yields in line with the mechanistic model. The reaction was *E*-diastereoselective with respect to the newly-formed styrene moiety. The cyclopropyl ring in products **59** and **60** remained unaffected.

3-Substituted sulfolenes **48** and **49** also reacted highly regioselectively and in line with the expected pattern of the ring opening. However, in this case the arylation proceeded with *Z*-diastereoselectivity. For example, (1*Z*)-conjugated dienes **65–69** were produced in good yields from isoprene- and myrcene-derived sulfolenes **48** and **49**. Similarly, 3,5-disubstituted sulfolene **50** produced (1*Z*)-conjugated dienes **70–75** in good yields and in line with the proposed model of regioselectivity. Cholesterol- and stigmasterol-derived products **74** and **75** that contain a disubstituted conjugated tetraene unit were produced in 92 and 72% yields, respectively. The reaction of 2-bromonaphthalene with sulfolene **50** was carried out with 2 mol% Pd, and diene **72** was produced in 80% yield, indicating that lower Pd catalyst loadings can also be used. The reaction with 1,1,3-trisubstituted sulfolene **51** was also *Z*-selective, in line with the reactivity of other 3-substituted sulfolenes (e.g., products **76–78**). While potassium methoxide was the base of choice for most of sulfolenes, potassium *tert*-

butoxide afforded conjugated dienes with higher yields and diastereoselectivity in reactions with 3-substituted sulfolenes **49** and **51**. Use of potassium *tert*-butoxide also led to higher yields of acetamide **10**, indicating that other alkoxide bases can be used for reaction optimization.

The dienylation reaction with 3-substituted sulfolenes **48–51** is particularly advantageous, because it introduces an aryl group at the more substituted double C–C bond, and it affords the synthetically challenging (1*Z*)-conjugated dienes. The syntheses of products **23**, **30**, **35**, **36**, and **72** were readily carried out on gram scales. The structures of products **24**, **64** and **73** were confirmed by X-ray crystallography.

Experimental evidence supports the mechanism that involves dienylsulfinate intermediates **7** (Scheme 1). No reaction was observed when sulfolenes **47** and **48** were replaced with the corresponding 1,3-dienes ((*E*)-1-cyclohexyl-1,3-butadiene and isoprene, respectively), indicating that cheletropic cycloelimination of sulfur dioxide from sulfolenes is not involved in the catalytic process. Similarly, no reaction was observed, when the sulfone that had been produced by the substitution of 4-chloro group in 4,7-dichloroquinoline with sulfinate **2** was used instead of the haloarene and sulfolene **1** (see Scheme S1 in the SI). This result suggests that the reaction does not proceed through formation of sulfones. However, diene **9** was formed in a nearly quantitative yield and with exclusive *E*-diastereoselectivity, when sulfolene **1** and potassium methoxide were replaced with potassium sulfinate ($K^+ \cdot Z\text{-2}$). Further, when sulfolene **1** was heated at 110°C with potassium methoxide in THF, rapid formation of potassium sulfinate ($K^+ \cdot Z\text{-2}$) was observed (95% conversion in 10 min). Taken together, these results indicate that the reaction proceeds through formation of dienylsulfates **7**. The isomerization of sulfinate $K^+ \cdot Z\text{-2}$ to the *E*-diastereomer $K^+ \cdot E\text{-2}$ was slower (7 : 1 *Z/E* ratio after 1 h at 110 °C in THF). This result may suggest that the *E*-selectivity of the reactions with sulfolenes **1** and **44–47**, and the *Z*-selectivity with sulfolenes **48–51** may reflect the kinetic preferences of the catalytic steps that involve intermediates **A–C** (Scheme 1).

In conclusion, this paper describes a simple and practical, regio- and stereoselective dienylation with readily available sulfolenes. The operationally simple reaction produces substituted conjugated dienes and polyenes on gram scales in a regio- and stereoselective manner. The regio- and stereoselectivity are determined by the substitution pattern in sulfolenes. While the *E*-selective dienylation is observed for sulfolenes **1**, and **44–47**, the reaction is *Z*-selective for sulfolenes **48–51**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

Financial support by the Welch Foundation (AX-1788), the NSF (CHE-1455061), NIGMS (SC3GM105579), and Max and Minnie Tomerlin Voelcker Fund is gratefully acknowledged.

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A. Synthetic approaches to conjugated dienes and polyenes

$[C_x + C_2 + C_2]$

$[C_x + C_4]$

More efficient and convergent approach

Problem: control of regio- and stereoselectivity for both C=C bonds in the C_4 unit

General synthesis of conjugated dienes and polyenes with high and predictable regio- and stereoselectivity

B. Site-selective deprotonation results in a regioselective ring opening

• Sulfones are air- and moisture-stable, easy to handle, feedstock-derived materials.

• Base-mediated ring opening of sulfones is regio- and stereoselective.

• Initially-formed (1Z)-dienylsulfonates may isomerize to the (1E)-diastereomers.

C. Pd catalyst determines the stereoselectivity of the C-C bond formation

• Synthesis of conjugated dienes on preparative scales with predictable regio- and stereoselectivity

Scheme 1.
Synthesis of conjugated dienes and polyenes

Table 1.

Optimization of Reaction Conditions ^a

entry	ligand	base/additive	solvent	yield, ^b %	E/Z ratio
1	dppe	CH ₃ OK	dioxane	12	1.5:1
2	dppf	CH ₃ OK	dioxane	24	1.3:1
3	dppbz	CH ₃ OK	dioxane	29	>30:1
4	dppbz	CH ₃ OK	THF	26	>30:1
5	dppbz	CH ₃ OK/K ₂ CO ₃	dioxane	32	>30:1
6	dppbz	CH ₃ OK/K ₂ CO ₃	THF	99 ^c	>30:1
7	dppbz	CH ₃ OK/K ₂ CO ₃	toluene	61	>30:1
8	dppbz	CH ₃ ONa/K ₂ CO ₃	THF	56	11:1
9	dppbz	CH ₃ OK/Na ₂ CO ₃	THF	59	1:2
10	dppbz	CH ₃ OK/Cs ₂ CO ₃	THF	18	8:1
11	dppbz	<i>t</i> -BuOK/K ₂ CO ₃	THF	62	1:1.5
12	dppbz	K ₂ CO ₃	THF	0	-

^aReaction conditions: 4-bromobenzonitrile (**8**) (1 mmol), sulfone **1** (2 mmol), Pd(OAc)₂ (5 mol %), ligand (8 mol %), base (1.6 mmol), additive (2 mmol), solvent (8 mL), 110 ° C, 14 h. dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,2-bis(di-phenylphosphino)ferrocene, dppbz = 1,2-bis(diphenylphosphino)-benzene.

^bDetermined by ¹H NMR spectroscopy with 1,4-dimethoxybenzene as an internal standard.

^cIsolated yield.

Table 2.

Scope of the Reaction with Sulfolene 1^a

^aReaction conditions for small scale reactions: haloarene (1 mmol), sulfolene 1 (2 mmol), Pd(OAc)₂ (5 mol %), dppbz (8 mol %), CH₃OK (1.6 mmol), K₂CO₃ (2 mmol), THF (8 mL), 110 °C, 14–36 h. Bromoarenes were used, and *E/Z* ratio >30:1, unless otherwise specified.

^bKOtBu (2.6 equiv.) was used as a base.

Table 3.

Scope of the Reaction with Substituted Sulfolenes ^a

^aFor reaction conditions see footnote to Table 2. X = Br, and *E/Z* or *Z/E* ratio >30:1, unless otherwise specified.

^bKOtBu as a base.