Synthesis of Cyclic Sulfones by Ring-Closing Metathesis

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ABSTRACT



A general and highly efficient synthesis of cyclic sulfones based on ring-closing metathesis has been developed. The synthetic utility of the resulting cyclic sulfones was demonstrated by their participation in stereoselective Diels–Alder reactions and transformation to cyclic dienes by the Ramberg–Bäcklund reaction.

Sulfones are a major class of organosulfur compounds¹ that have been extensively used as versatile intermediates in organic synthesis.² The importance of the sulfone functional group in synthetic organic chemistry warrants significant interest in the development of new methodologies related to the introduction of the sulfone functionality into an organic molecule as well as the further synthetic transformation of the sulfone intermediate, and, when desirable and possible, its eventual elimination from the target. Cyclic sulfones, in particular, have unique synthetic utilities. For example, substituted 3-sulfolenes are an excellent source of conjugated dienes through SO₂ extrusion and have been employed as masked dienes for intramolecular Diels-Alder reactions in numerous complex syntheses.³ Medium ring cyclic sulfones can be used as precursors for the construction of cyclic olefins⁴ by the well-established Ramberg-Bäcklund reaction.^{5,6} Cyclic sulfones have also been investigated as the key subunit and scaffold for the construction of biologically

active molecules such as protease and β -lactamase inhibitors.^{7,8}

Although a plethora of methods for the synthesis of cyclic sulfones exists in the literature,^{1,2} a generally applicable and highly efficient approach to the synthesis of cyclic sulfones of various ring sizes and different substitution patterns is still highly desirable. The majority of existing methodologies for the synthesis of cyclic sulfones involve the construction of the corresponding cyclic sulfides from appropriately

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functionalized precursors that often require tedious multistep manipulations, followed by oxidation of the sulfides to sulfones. In this Letter, we describe a novel and versatile strategy for the synthesis of cyclic sulfones based on the ring-closing metathesis (RCM) of acyclic sulfones which can be readily prepared from alkenyl alcohols and alkenyl halides through standard functional group transformations (vide infra), as outlined in Scheme 1.



The rapidly emerging olefin metathesis reaction has found many spectacular applications in organic synthesis.⁹ In particular, the RCM of α, φ -dienes mediated by Grubbs' ruthenium-based catalysts 1^{10} and 2^{11} (Figure 1) has evolved



Figure 1. Grubbs Ru catalysts.

into a powerful tool for the construction of carbo- and heterocyclic compounds.^{9,12} The excellent functional group tolerance of **1** and **2** has allowed them to be widely applied to the synthesis of oxygen-, nitrogen-, and phosphoruscontaining cyclic molecules. However, the application of RCM to the synthesis of sulfur-containing heterocycles remains very limited. Thus, both (Cy₃P)₂(Cl)₂Ru(=CH- $CH=CPh_2)^{13}$ and 1 were shown to be either unreactive or of low reactivity toward the RCM of α, φ -dienes containing a sulfide moiety,14 possibly due to the poisoning of the ruthenium catalyst by the sulfide functionality. Although the

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RCM of substrates containing a sulfonamide group has been well documented¹⁵ and the cross metathesis of both allyl and vinyl sulfones has recently been described independently by the groups of Grubbs¹⁶ and Grela,¹⁷ the RCM of sulfone dienes remains rare and there is only one isolated example of the formation of a six-membered cyclic sulfone in the literature.¹⁸ The possibility of an internal Ru-sulfonyl oxygen ligation was recently proposed by Paquette et al. in their study on the macrocyclization of bicyclic sulfones.¹⁹ Additionally, the compatibility of sulfones with Ru carbene catalysts has previously been demonstrated by Fürstner.²⁰

We set out to examine the RCM of diallyl sulfone 3a as a test substrate (Scheme 2). Treatment of 3a with 2 mol %



of 1²¹ in CH₂Cl₂ (0.05 M) at reflux gave cleanly 3-sulfolene 4a, which was isolated in 95% yield after chromatography.

A number of structurally diverse sulforyl dienes (3b-3i)were then prepared and their RCM performed with the results listed in Table 1.²² The diene substrates²³ were conveniently prepared, as illustrated by the synthesis of **3b** in Scheme 3,



by a general and high-yielding protocol. This involved the Mitsunobu reaction of an alkenyl alcohol with thioacetic acid

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entry	Dienes	catalyst	conditions ^a	cyclic sulfone		yield ^b
1	0, ,0 S 3a	1 (2%)	CH ₂ Cl ₂ (0.05M) 1h	o, ,o ⟨⟩	4a	95%
2	O, O S B 3b	1 (2%)	CH ₂ Cl ₂ (0.05M) 1h	O, S PI	^າ 4b	99%
3	O, s, O Ph 3c	2 (5%)	CH ₂ Cl ₂ (0.05M) 18h	O.S.PH	^າ 4c	98%
4 ^c	JO, S, O 3d	2 (5%)	CH ₂ Cl ₂ (0.05M) 24h	°, s,́°	4d	99%
5	O, S,O Ph 3e	1 (2%)	CH ₂ Cl ₂ 0.05M) 2h	O、, O Ph	4e	100%
6	°, °, °, °, °, °, °, °, °, °, °, °, °, °	1 (2%)	CH ₂ Cl ₂ (0.05M) 2h	Ph S	4f	96%
7	O, S, O Ph 3g	1 (3%)	CH ₂ Cl ₂ (0.02M) 3.5h	O`S´Ph	4g	98%
8	0, ,0 S Bh Ph	1(6%)	CH ₂ Cl ₂ (0.005M) 24h	O.S.Ph	4h	85%
9 ^d		1 (6%)	CH ₂ Cl ₂ (0.003M) 18h		//S 4i	75%

Table 1. Formation of Cyclic Sulfones by Ring-Closing Metathesis Catalyzed by Grubbs Catalysts 1 and 2

^{*a*} All RCM reactions were carried out in CH_2Cl_2 at reflux with substrate concentration and reaction time as indicated. ^{*b*} Refers to isolated, pure products. ^{*c*} Diene **3d** was prepared according to the literature in footnote 24. ^{*d*} Diene **3i** was prepared from ring-opening of allyl glycidyl ether by allyl mercaptan, silylation of the resulting alcohol, and subsequent oxidation with mCPBA, see the Supporting Information.

(Ph₃P, DIAD in THF), subsequent one-step conversion of the thiolester to the sulfide²⁴ by in situ cleavage of the thiolester by KOH in MeOH, direct alkylation of the resulting thiolate with an alkenyl halide, and oxidation of the resulting sulfide with mCPBA to give the required sulfone.

As shown in Table 1, the new method can be applied to the synthesis of a variety of 3-sulfolenes. Formation of the 2-substituted 3-sulfolene **4b** proceeded smoothly with catalyst **1** (entry 2), but the cyclization of substrates containing a *gem*-disubstituted alkene (entries 3 and 4) required the more reactive catalyst **2**.^{11,21} Nevertheless, the tri- and tetrasubstituted cyclic olefins **4c** and **4d** were formed in essentially

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 $[\]left(22\right)A$ representative procedure for the RCM is provided in the Supporting Information.

⁽²³⁾ The known compound 3d was prepared according to ref 24.

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quantitative yield. It should be noted that the convenient synthesis of 4c points to a general and highly efficient approach to 2,4-dialkylated 3-sulfones which are known to be difficult to synthesize by existing methods.²⁵ Coupled with cheleotropic ring opening, this synthesis provides a rapid access to *trans*-1,3-disubstituted 1,3-dienes, as demonstrated by the reaction sequence shown in Scheme 4. The bicyclic





compound **8** was isolated as a single diastereomer in 93% yield from **4c** (directly used after the RCM of **3c** as shown) by a sequence of stereospecific SO₂ extrusion and an *endo*-selective Diels-Alder reaction.

We next examined the efficacy and generality of the protocol for the formation of six-membered and larger cyclic sulfones. As shown in Table 1, both the diene 3e (entry 5) and the enyne 3f (entry 6) were found to cyclize uneventfully

(25) It is well-known that alkylation of 3-substituted 3-sulfolene affords only the 2,3-disubstituted derivative. For example: Shing, Y. K. M.; Tang, Y. J. Chem. Soc., Perkin Trans. 1 **1994**, 1025. For a general discussion of this aspect of sulfolene chemistry, see ref 2.



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with catalyst **1**, whereas the formation of seven-, eight-, and nine-membered cyclic sulfones (entries 7-9) required a higher loading of the catalyst and the metathesis reaction to be performed under dilute conditions and for a longer reaction time. In all cases, however, the cyclized products were isolated in good to excellent yields.

Cyclic sulfones have previously been shown to be excellent precursors for the regiospecific construction of cyclic olefins.⁴ As shown in Scheme 5, both **4g** and **4h** underwent



clean and high-yielding Ramberg–Bäcklund rearrangement upon treatment with Br_2CF_2 in the presence of KOH supported on alumina.²⁶

In conclusion, a general and highly efficient synthesis of cyclic sulfones has been developed and their synthetic utility further demonstrated by SO₂ extrusion to afford a conjugated diene and by their transformation to cyclic dienes through the Ramberg–Bäcklund reaction.

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Supporting Information Available: Representative procedures for the synthesis of acyclic sulfone dienes and for the RCM reaction; NMR (¹H and ¹³C) and analytical data for compounds **3b–i**, **4b–i**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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