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## Oxidation of bis-sulfinyl carbanions as the pivot of ionic/radical tandem reactions



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### ABSTRACT

[1,4]-additions of various nucleophiles such as lithiated carbamates, alkoxides or ester enolates onto enantiopure alkylidene bis-sulfoxides proceed with high diastereoselectivity. The oxidation of the resulting carbanions with iron(III) salts induces the radical cyclizations onto alkenes with a high diastereoselectivity leading to enantiopure carbo- or heterocycles. Moreover, allylic radicals have been generated by deprotonation or [1,6]-conjugate addition from alkylidene bis-sulfoxides followed by oxidation.

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## 1. Introduction

There is no longer a need to prove the synthetic power of radical chemistry. The latter has indeed shown exceptional reliability in terms of efficiency and stereoselectivity to reach complex and polyfunctional molecular architectures [1]. Nevertheless, rendering the reaction conditions more sustainable, notably the elimination of heavily used tin-based mediators, remains a major challenge [2]. While searching a chemical agent acting as a surrogate to tributyltin hydride has been the object of intense investigations [2], the single electron transfer (SET) approach [3] has also emerged as an efficient solution toward greener radical chemistry, featuring also fascinating developments in photocatalysis [4]. Notably, the oxidation of electron rich centers has been widely accepted as a powerful method for the generation of

carbon-centered radicals. For example,  $\alpha$ -carbonyl radicals have been generated by employing metal salts at high oxidation states [5] or by organocatalysis with SOMO activation from neutral carbonyl substrates [6]. Alternatively, oxidation of enolates or related carbanions has been reported using a variety of reagents [7]. Such processes have been incorporated in ionic/radical domino reactions [8] to access carbo- and heterocycles. Notably, Dulcère and Rodriguez reported a pioneering ionic/radical tandem reaction involving conjugate addition onto nitroalkenes followed by cyclization of the radical formed by oxidation of the resulting carbanion onto an alkene [9]. In the same line, Jahn has widely developed the Michael additions of nucleophiles onto  $\alpha,\beta$ -unsaturated esters and the oxidation-cyclization of the resulting enolates [10]. Finally, quite recently, the photocatalytic oxidation of enolates has opened new perspectives for this type of transformation [11].

Our contribution to the field of ionic/radical tandem reactions consists of the conjugate additions of anionic reagents to alkylidene bis-sulfoxides followed by

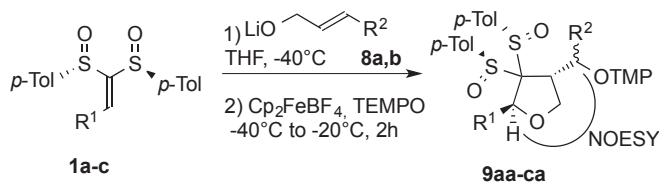
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**Table 1**  
Synthesis of bis-sulfinyl tetrahydrofurans **9**.



	Alkylidene <b>1</b>	Alkoxide <b>8</b>	Yield
1	<b>1a</b> , R <sup>1</sup> = Ph	<b>8a</b> , R <sup>2</sup> = H	<b>9aa</b> , 59%
2	<b>1a</b> , R <sup>1</sup> = Ph	<b>8b</b> , R <sup>2</sup> = Ph	<b>9ab</b> , 48% <sup>a</sup>
3	<b>1b</b> , R <sup>1</sup> = <i>i</i> -Pr	<b>8a</b> , R <sup>2</sup> = H	<b>9ba</b> , 41%
4	<b>1c</b> , R <sup>1</sup> = 2-(PhO)-C <sub>6</sub> H <sub>4</sub> -	<b>8a</b> , R <sup>2</sup> = H	<b>9ca</b> , 56%

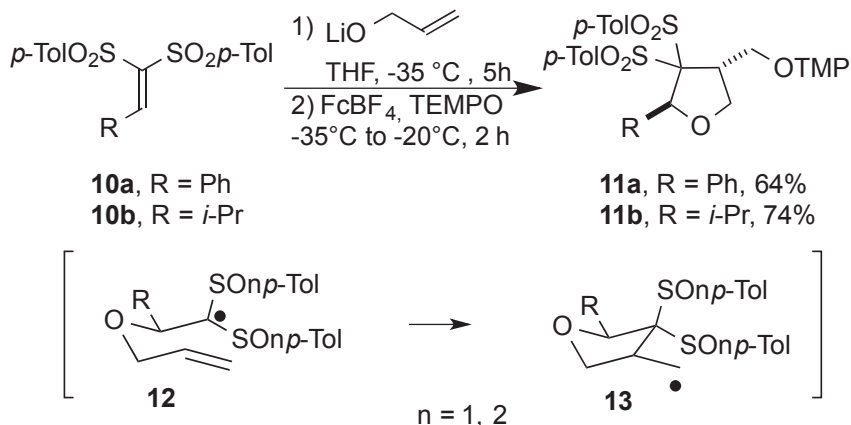
<sup>a</sup> 1.1:1 ratio of diastereoisomers was isolated.

derivatization of **11a** (see below). This observation suggests that the diastereoselective formation of the *trans* isomers **9** is independent of the stereogenicity of the sulfoxides. It is reasonable to hypothesize that bis-sulfoxides **9** and bis-sulfones **11** derivatives originate from pseudo-chair radical intermediates **12** in which the R substituent occupies a pseudo-equatorial position to minimize steric interactions (Scheme 3) giving radicals **13**. Overall the stereocenter between the oxygen and the bis-sulfoxide moiety methylene created in the Michael addition of the alkoxide is controlled by the bis-sulfinyl auxiliary while the second stereocenter created by the radical cyclization is controlled through a pseudo-chair transition state [14].

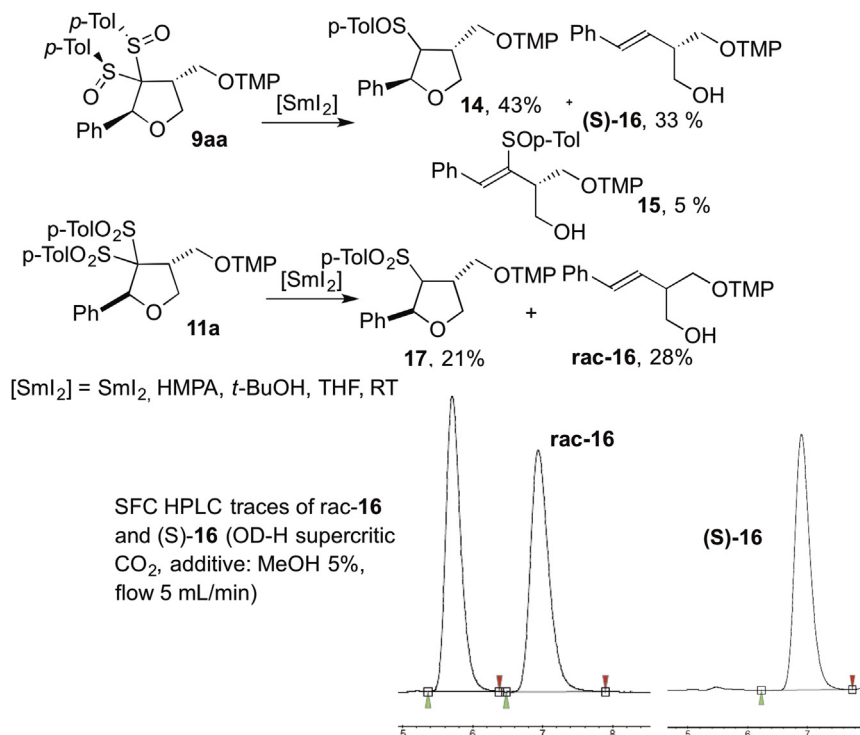
Adduct **9aa** was engaged in different oxidation reactions to transform the sulfoxide groups into sulfones and obtain enantioenriched **11a**. This could allow the comparison with the racemic sample **11a** obtained through the bis-sulfone route. However, all attempts failed to offer the desired compound, so we investigated other derivatizations. The carbon-sulfur bond is known to be reduced under electron transfer conditions by metallic complexes. Thus, both compounds **11a** and **9aa** were reacted with 7 equiv. of the SmI<sub>2</sub>/HMPA complex in the presence of *tert*-butanol (7 equiv.) (Scheme 4).

Under these conditions, bis-sulfoxide **9aa** provided sulfoxide **14** as the major product, resulting from a single reductive cleavage of one carbon-sulfur bond. Presumably, over-reduction of the radical intermediate provides a carbanionic entity which β-eliminates affording ring-opened vinylsulfoxide **15** in 5% yield. Alternatively, the carbon-sulfur bond of **14** was reduced by a second electron transfer process and a similar ring-opening occurred to generate the interesting styryl derivative **16** in 33% yield. It should be noted that we cannot exclude that **15** can also be reduced into **16**. A similar behavior was pointed out with the bis-sulfone analog **11a** and a mixture of **16** and **17** [15] was obtained in 28% and 21% yields, respectively. Compound **16** isolated from the two reactions was used to determine the enantiomeric excess of the stereogenic center formed by the 5-*exo*-trig radical cyclization. The tandem process from the alkylidene bis-sulfone **10a** gave **16** as a racemate whereas the enantioenriched (*S*)-**16** was obtained from the bis-sulfoxide analog **1a**. Chiral HPLC analyses showed that the enantiomeric excess of (*S*)-**16** is 98% which confirmed the high stereoselectivity of the sequence (Scheme 4).

We next investigated the potential of this process for the creation of nitrogen-containing heterocycles (Table 2). For this purpose, allylic alcohols were replaced by *N*-Boc



**Scheme 3.** Synthesis of bis-sulfonyl tetrahydrofurans.



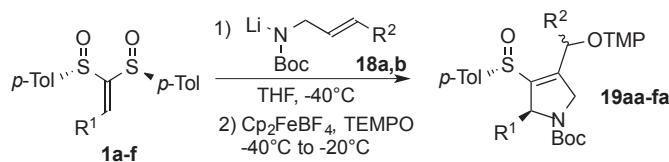
**Scheme 4.** Determination of the enantiopurity of bis-sulfinyl tetrahydrofuran **9ba**.

allylamines. Lithium salts **18a** and **18b** were generated by deprotonation of the corresponding allylcarbamate with *n*-BuLi at  $-40^{\circ}\text{C}$ . At that temperature, the alkylidene bis-sulfoxide was added to the reaction mixture and the conjugate addition progress was monitored by TLC. After a complete disappearance of the starting material, the ferrocenium salt was added and the temperature was increased slowly to  $-20^{\circ}\text{C}$ . After the work-up, the corresponding dihydropyrrole compounds **19a–f** were obtained in moderate to good yields. Presumably, as before, SET occurs followed by a 5-*exo*-trig cyclization and TEMPO trapping, leading to the formation of bis-sulfinyl pyrrolidine derivatives. The latter undergoes steric strain release by a regioselective sulfinic acid  $\beta$ -elimination [16].

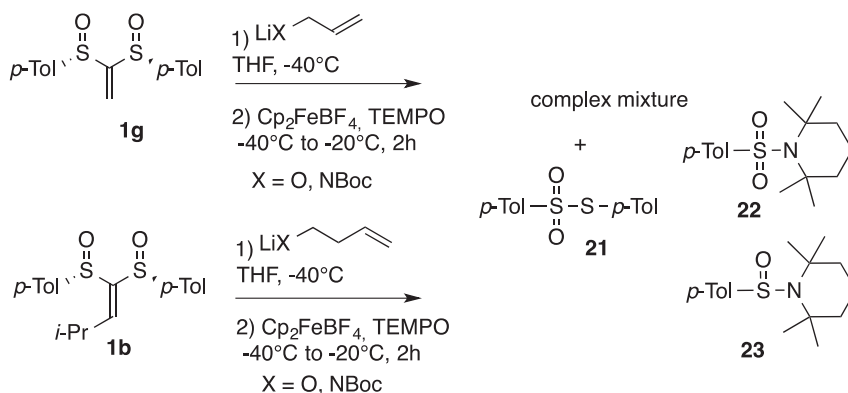
The *N*-deprotonated allylcarbamate **18a** gave similar results to benzylidene (**1a**, entry 1) and isopropylidene (**1b**, entry 3) acceptors, as a single diastereomer was isolated in 55% and 58% yields, respectively. When the *N*-deprotonated cinnamylcarbamate was used (entry 2), a comparable yield was obtained and a single diastereoisomer was isolated after purification. The latter readily epimerized at the benzylic center bearing the TEMPO residue so that equimolar mixtures of diastereoisomers were observed after 1 day standing in CDCl<sub>3</sub> [10f]. The sequence has been exemplified with different bis-sulfoxide derivatives and the lithiated carbamate **18a** and in each case, a single diastereoisomer was formed.

**Table 2**

Synthesis of sulfinyl dihydropyrroles **19**.



Entry	Alkylidenes <b>1</b>	Allylcarbamates <b>18</b>	Pyrrolidines <b>19</b>
1	<b>1a</b> , R <sup>1</sup> = Ph	<b>18a</b> , R <sup>2</sup> = H	<b>19aa</b> , 55%
2	<b>1a</b> , R <sup>1</sup> = Ph	<b>18b</b> , R <sup>2</sup> = Ph	<b>19ab</b> , 56%
3	<b>1b</b> , R <sup>1</sup> = <i>i</i> -Pr	<b>18a</b> , R <sup>2</sup> = H	<b>19ba</b> , 58%
4	<b>1e</b> , R <sup>1</sup> = <i>n</i> -Pr	<b>18a</b> , R <sup>2</sup> = H	<b>19ea</b> , 73%
5	<b>1f</b> , R <sup>1</sup> = <i>n</i> -C <sub>12</sub> H <sub>25</sub>	<b>18a</b> , R <sup>2</sup> = H	<b>19fa</b> , 71%

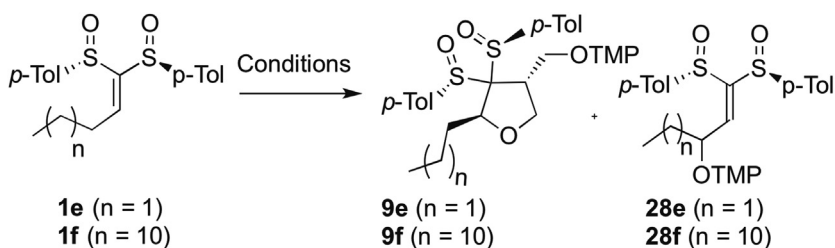


**Scheme 5.** Unsuccessful radical cyclizations.

The influence of the steric demand of the alkylidene substituent was confirmed with the use of two linear alkyl chains as substituents of the alkylidene. The propyl (**1e**) and the dodecyl (**1f**) alkylidene derivatives were engaged in the tandem sequence allowing the formation of the corresponding cyclic products in better yields (Table 2, entries 4 and 5) compared to the isopropyl group.

The following findings show some limitations of this ionic/radical tandem process when dealing with unsubstituted alkylidenes. Addition of the lithium salt of allyl alcohol or allyl carbamate followed by the introduction of the ferrocenium salt and TEMPO into the unsubstituted bis-sulfoxide alkylidene **1g** did not lead to the expected cyclized compounds but rather to a complex mixture of the Michael addition product and the sulfonyl and sulfinyl compounds **21–23** (Scheme 5).

The isolation of products **21–23** suggests that SET has taken place, following a favorable conjugate addition on these substrates. But the corresponding radical instead of undergoing cyclization would decompose via fragmentation, liberating a *p*-Tol-sulfinyl radical, as evidenced in a previous study [17]. It is indeed documented that compound **21** arises from the coupling of two sulfinyl radicals [18], and that sulfonyl piperidine **22** [19] is a rearranged coupling product of a sulfinyl radical with TEMPO and similarly **23** a rearranged coupling product between a thiyl radical and TEMPO [17]. The radical cyclization would presumably not occur because of the lack of substituent on the connecting chain between the radical center and the vinyl group [20], a phenomenon related to the Thorpe-Ingold effect [21]. We also targeted six membered rings of tetrahydropyrans and piperidines. However, the slower 6



Conditions A: **8a**, THF, **-40°C** then  $\text{Cp}_2\text{FeBF}_4$ , TEMPO, **-40°C to -20°C**

**9e**, 42% (1 dias)      **28e**, 10% (dr 1.5:1)  
**9f**, 43% (dr 5.6:1)      **28f**, 8% (dr 1.5:1)

Conditions B: **8a**, THF, **-40°C to -20°C** then  $\text{Cp}_2\text{FeBF}_4$ , TEMPO, **-20°C**

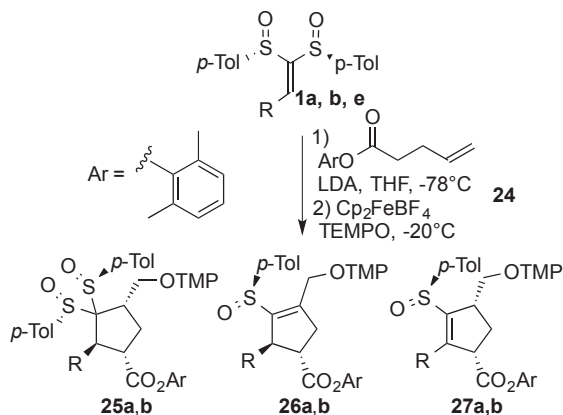
**9e**, 12% (1 dias)      **28e**, 46% (dr 1.5:1)  
**9f**, 6% (dr 5.6:1)      **28f**, 61% (dr 1.5:1)

Conditions C: *t*-BuOK, THF, **-40°C to -20°C** then  $\text{Cp}_2\text{FeBF}_4$ , TEMPO, **-20°C**

-      **28e**, 64% (dr 1.5:1)  
 -      **28f**, 68% (dr 1.5:1)

**Scheme 6.** Competition between the formation of tetrahydrofurans **9e,f** and allylic oxidation bis-sulfoxides **28e,f**.

**Table 3**  
Synthesis of sulfinyl cyclopentane derivatives **25–27**.



Alkylidene	Yield	<b>25:26:27</b>
<b>1a</b> , R = Ph	81%	1.8:1:1.6 <sup>a</sup>
<b>1b</b> , R = <i>i</i> -Pr	89%	0:1.5:1

<sup>a</sup> 0:1:1.7 after 3 days in CDCl<sub>3</sub>.

*exo*-trig cyclization was ineffective and again a complex mixture was obtained in which compounds **21–23** were detected (Scheme 6).

We have reported that ester enolates are efficient nucleophiles for the conjugate addition onto alkylidene bis-sulfoxides [13]. In this case, a C–C bond is formed instead of a carbon-heteroatom bond and could lead to the formation of carbocyclic derivatives after radical cyclization. The use of bulky *tert*-butyl or 2,6-dimethylphenyl substituents on the ester is important to avoid the Claisen condensation, transforming the substrate into the corresponding ketoester. Moreover, *E* enolates could be formed predominantly from these esters and high diastereoselectivities could be obtained from their addition onto alkylidene bis-sulfoxides. Usually higher diastereoisomeric excesses are obtained with the more hindered 2,6-

dimethylphenyl [22]. Therefore, the corresponding aryl pentenoate **24** was engaged in the tandem process (Table 3). The enolate was generated by deprotonation of **24** with LDA and a diastereoselective conjugate addition at  $-78^\circ\text{C}$  in THF led to the formation of the *anti* adduct due to the formation of the *E* enolate.

The subsequent addition of TEMPO and ferrocenium initiated the radical process of the tandem reaction to afford the bis-sulfinyl cyclopentane **25a** as a single diastereoisomer in the mixture with the two sulfinyl cyclopentenes **26a** and **27a** in 81% yield and a respective ratio of 1.8:1:1.6. Cyclopentenyl derivatives **26a** and **27a** originate from the bis-sulfinyl compound **25a** following two different modes of  $\beta$ -elimination of sulfinic acid [16]. The mixture ratio was modified after three days in CDCl<sub>3</sub>. A complete disappearance of **25a** was observed and the composition was stabilized as a 1:1.7 mixture of **26a** and **27a**. All our attempts to crystallize **25a** were unsuccessful due to the fast elimination processes.

We gained insight into the chemical structure and the relative stereochemistry of the reaction products by an X-ray crystal structure analysis of **27a** (Fig. 1) [23]. The ester and the CH<sub>2</sub>OTMP substituents show a *cis* relative relationship which is in agreement with the enolate addition model and the stereoselectivity of the 5-*exo* cyclization.

When the phenyl group of **1a** was replaced by an isopropyl, the eliminations occurred more rapidly to afford a mixture of **26b** and **27b** in 89% yield in a 1.5:1 ratio (inverse to the **26a:27b** ratio), while the bis-sulfinyl compound was not detected in the reaction mixture.

In studying the scope of the tetrahydrofuran synthesis (see above), a very interesting temperature effect was evidenced with primary substituted alkylidene bis-sulfoxide (e.g., **1e** and **1f**) and with lithium salt of allylic alcohol **8a** as a nucleophile. In a first series, lithium alkoxide **8a** was reacted with propylidene and dodecylidene bis-sulfoxides **1e** and **1f** at  $-40^\circ\text{C}$  and the conjugate addition was monitored by TLC (conditions A). After the disappearance of the starting material, the ferrocenium salt and TEMPO were added at  $-40^\circ\text{C}$  and the temperature was increased to  $-20^\circ\text{C}$ . These conditions allowed the formation of the cyclic derivatives **9e** and **9f** as the major products in 42% and 43% yields, respectively; **9e** was obtained as a single diastereoisomer whereas a 5.6:1 mixture was recorded for **9f**. Interestingly, allylic oxidation products **28e** and **28f** were isolated in 10% and 8% and as a 1.5:1 mixture of diastereoisomers. We then discovered that a slight modification of the temperature events led to a dramatic modification of the reaction outcome. When conditions B were applied, corresponding to the addition of the oxidant at  $-20^\circ\text{C}$  instead of  $-40^\circ\text{C}$ , the proportions of **9e/9f** and **28e/28f** were reversed affording mainly the oxidation compounds. Thus, **28e** was formed in 46% and a better yield of 61% was found for **28f**. The minor cyclic products **9e** and **9f** were not obtained at higher yields than 12%, with similar diastereoselectivity as recorded under conditions A (Scheme 6).

To rationalize the formation of **28e** and **28f**, we proposed the mechanism shown in Scheme 7. At low temperature, the conjugate addition of **8a** to **1** affords the carbanionic intermediate **29**. The subsequent oxidation of this anion into the corresponding radical **30** followed by a

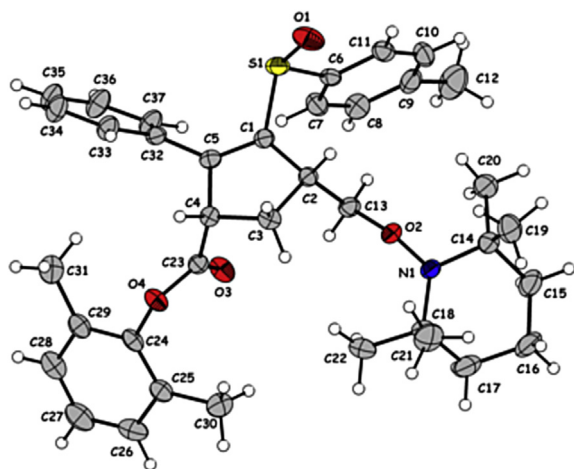
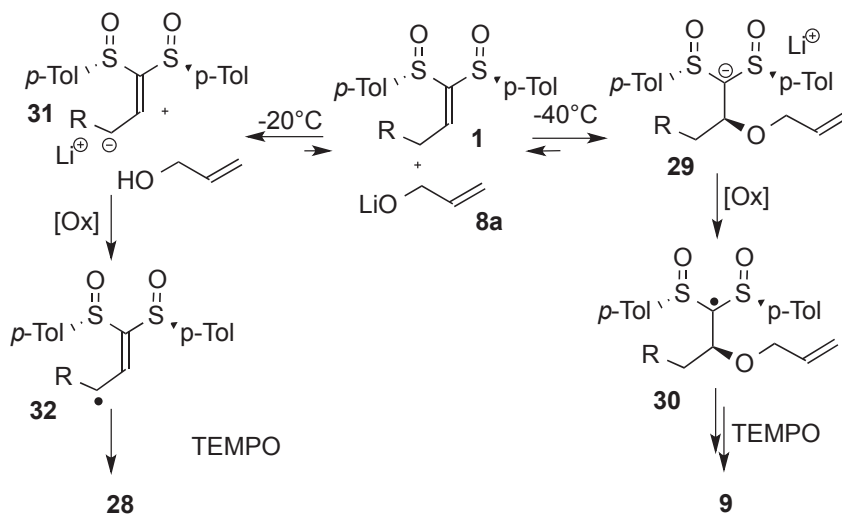


Fig. 1. X-ray crystal structure of **27a**.



**Scheme 7.** Divergent pathways for the synthesis of products **9** and **28**.

radical cyclization and a spin-trapping generate the cyclic compound **9**. If the temperature is increased, a retro-Michael addition would occur regenerating the allylic alkoxide that can react as a base to form allylic carbanion **31** and allylic alcohol in equilibrium with **1** and **8a**. This equilibrium can be shifted by a single electron oxidation converting **31** into **32**. Then, the so-formed allylic radical **32** reacts with TEMPO to give allylic oxidation compound **28**. To support this mechanism, the lithium salt of the allylic alcohol was replaced by potassium *tert*-butoxide, proving to be unreactive toward the conjugate addition onto alkylidene bis-sulfoxides (conditions C, **Scheme 7**). *tert*-Butoxide only acted as a base and under the same temperature conditions as conditions B, products **28e** and **28f** were isolated in 64% and 68% yields, respectively.

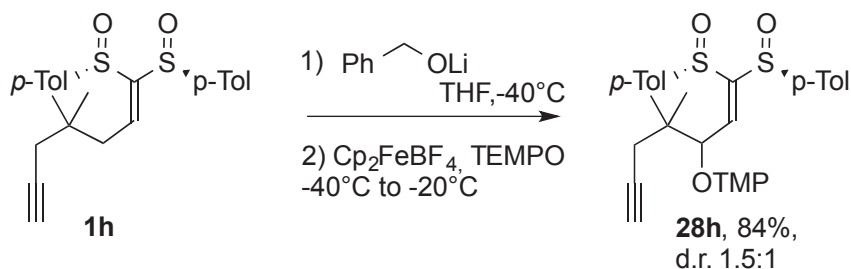
The retro-Michael addition was also illustrated by the reaction of **1h** with the benzylic lithium alkoxide, known as a very efficient nucleophile for the conjugate additions onto the alkylidene bis-sulfoxide [**13**] (**Scheme 8**). After the TLC monitoring of the reaction has shown a complete conversion of **1h**, the oxidant and the spin trap were added at  $-40\text{ }^{\circ}\text{C}$  and the temperature was increased to  $-20\text{ }^{\circ}\text{C}$ . Under these conditions, only **28h** was isolated in a high yield. The 6-*exo-dig* cyclization product was not observed and the retro-Michael process was almost exclusive.

Moreover, this oxidation showed a high selectivity in favor of the allylic position versus the propargylic one.

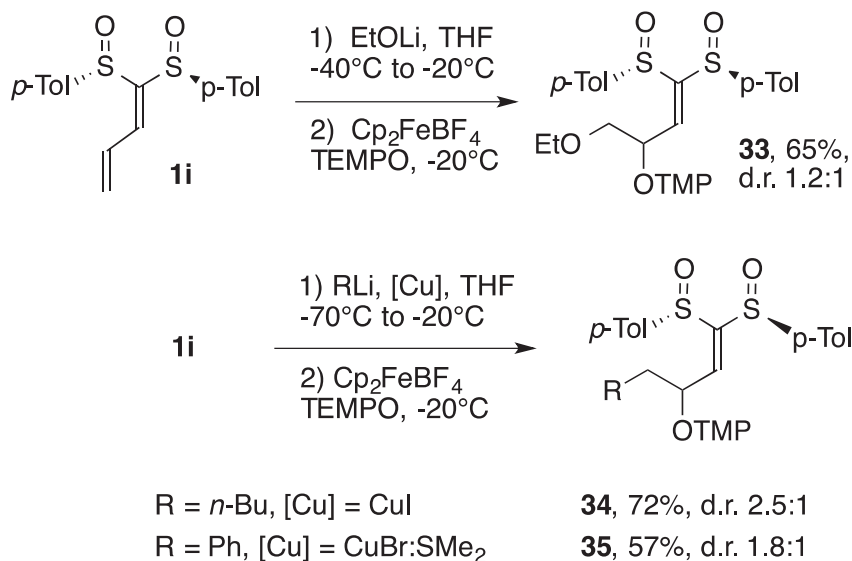
Finally, we focused on the use of dienyl-bissulfoxide **1i**. Our plan was to oxidize the carbanion resulting from the 1,6-addition of a nucleophile. We first tested this idea with lithium ethoxide. Gratifyingly, [1,6]-conjugate addition of lithium ethoxide onto dienylidene bis-sulfoxide followed by the addition of iron(III) and TEMPO allowed the formation of ethylether **33** in 65% yield with a 1,2 diastereoisomeric ratio (**Scheme 9**). One can imagine the synthetic potentiality of such transformation in the preparation of 1,2 diol or aminoalcohol. Cuprate reagents could also be engaged in this type of transformation [**24**], providing good yields of TEMPO adducts **34–35**. Further investigations are in progress in order to improve the diastereoselectivity and the versatility of such process.

### 3. Conclusion

In conclusion, we herein report the utilization of alkylidene bis-sulfoxide derivatives in ionic/radical tandem reactions. Alkoxides, carbamates and ester enolates could be introduced in a [1,4]-addition. Radical cyclization induced by single electron transfer from iron(III) salts could then respectively lead to enantiopure tetrahydrofurans,



**Scheme 8.** Synthesis of **28h**.



Scheme 9. 1,6-addition – oxidation tandem.

dihydropyrroles and cyclopentenes. Almost all of the cyclization compounds were isolated as single diastereomers thanks to highly stereoselective processes. An interesting allylic oxidation process resulting from allylic deprotonation and oxidation or from [1,6]-addition of alkoxides or organocopper reagents followed by oxidation was discovered.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.crci.2015.11.012>.

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