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# Hydroformylation of Alkynyl Sulfides: A Stereo- and Regioselective Route to $\alpha$ -Sulfenyl Acroleins

Patrick Wagner,<sup>a</sup> Mihaela Gulea,<sup>a,\*</sup> and Nicolas Girard<sup>a,\*</sup>

<sup>a</sup> Université de Strasbourg, CNRS, Laboratoire d'Innovation Thérapeutique, LIT UMR 7200, F-67000 Strasbourg, France  
phone: (+33)-(0)368854148  
E-mail: gulea@unistra.fr; nicolas.girard@unistra.fr

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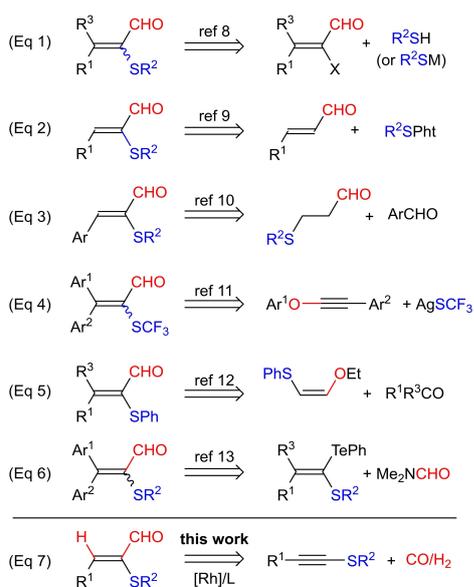
**Abstract:** The rhodium-catalyzed hydroformylation of alkynyl sulfides at 40 °C under 5 bars of *syngas* is described. The method gives access to  $\alpha$ -sulfenyl acroleins with  $\alpha/\beta$  regioselectivities up to 89/11 and is applicable to alkyl or aryl substituted substrates. It is effective even on more complex substrates, such as cysteine and cholesterol derivatives. To demonstrate the synthetic potential of the obtained products, (*Z*)-3-cyclohexyl-2-methylsulfenyl acrolein was selected as an example and its sulfur atom selectively oxidized to the corresponding sulfoxide or sulfone. Acid-promoted (*Z*) to (*E*) isomerization of the double bond occurred during oxidation. The three obtained sulfenyl-, sulfinyl-, and sulfonyl-functionalized acroleins have been then used as dienophiles to access cyclohexene carbaldehydes.

**Keywords:** Alkynyl sulfide; Rhodium-catalyzed hydroformylation;  $\alpha$ -Sulfenyl acroleins; Sulfur oxidation; Diels-Alder reaction

Heteroatom-substituted alkynes have emerged as valuable building blocks in organic chemistry due to their exceptional reactivity and versatility in a wide range of chemical transformations. Compared to *N*-substituted alkynes (i. e. ynamides),<sup>[1]</sup> which have been the most extensively studied, their *S*-substituted counterparts, namely the alkynyl sulfides (also called alkynyl thioethers or thioynol ethers) have received less attention. One explanation of this disparity can be the greater difficulty in accessing them. On the other hand, organosulfur compounds have long been considered a

poison for several transition metal catalysts, which may also have contributed to slowing the adoption of these compounds especially in the field of organometallic synthetic chemistry. However, in recent years, due to the growing interest in sulfur-containing molecules in the pharmaceutical or materials chemistry fields,<sup>[2]</sup> the chemistry of alkynyl sulfides has shown significant progress, whether for their synthesis<sup>[3]</sup> or for their applications.<sup>[4]</sup> They were used in particular as substrates of choice for various mono or difunctionalization reactions such as carbo- or hydrometallation,<sup>[5]</sup> or hydroelementation,<sup>[6]</sup> giving access stereo and regioselectively to functionalized tri- or tetrasubstituted alkenyl sulfides. Surprisingly, to date, the hydroformylation of alkynyl sulfides has not been addressed. However, this reaction would be a straightforward access to sulfenyl acroleins. Due to their versatile reactivity,  $\alpha$ -sulfenyl acroleins represent attractive building blocks in various synthetic applications.<sup>[7]</sup> Indeed, they possess on the same carbon of the double bond an electron-withdrawing formyl substituent and an electron-donating sulfenyl substituent, combining the rich reactivities of  $\alpha,\beta$ -unsaturated aldehydes and alkenyl sulfides. Additionally, one can take advantage of the possibility of the sulfur oxidation to obtain an alkenyl sulfoxide or sulfone, and so altering the electronic behavior of the carbon-carbon double bond.

So far, the synthesis of  $\alpha$ -sulfonyl acroleins (Scheme 1) is mainly based on general methods involving the incorporation of the sulfur function into an  $\alpha,\beta$ -unsaturated aldehyde as a nucleophile (Scheme 1, Eq 1),<sup>[8]</sup> or as an electrophile (Scheme 1, Eq 2).<sup>[9]</sup> Other strategies have also been reported, such as a cross-aldol condensation of an aromatic and a  $\beta$ -sulfenyl aldehyde (Scheme 1, Eq 3),<sup>[10]</sup> a 1,4-migration/trifluoromethylthiolation cascade (Scheme 1,



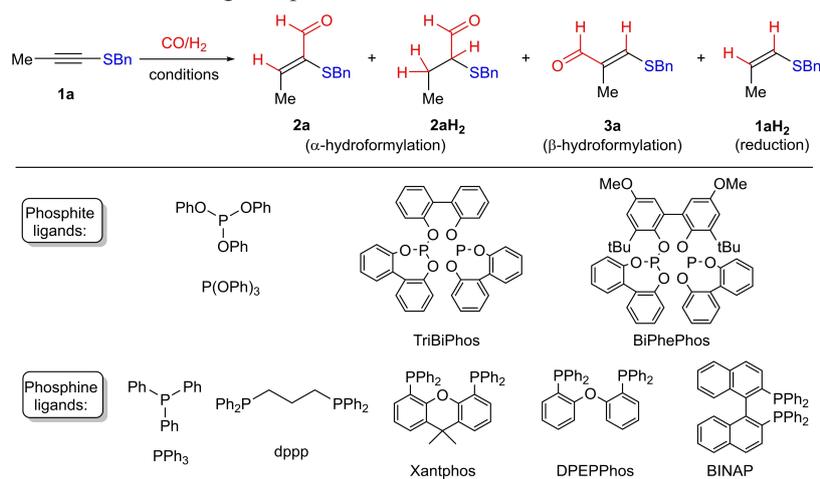
**Scheme 1.** Retrosynthetic scheme of reported syntheses of  $\alpha$ -sulfenyl acroleins and our proposed strategy for this study.

Eq 4),<sup>[11]</sup> or the synthesis of substituted 2-alkoxy vinyl sulfides followed by unmasking of the aldehyde through acid treatment (Scheme 1, Eq 5).<sup>[12]</sup> Only one general procedure has been proposed for the incorporation of the formyl group as the final step, which involves Te/Li exchange followed by a condensation of the lithium intermediate with dimethylformamide (Scheme 1, Eq 6).<sup>[13]</sup> Furthermore, it can be noted that no metal-catalyzed synthesis of  $\alpha$ -sulfenyl acroleins has been developed so far.

Prompted by our recent results in the regiodivergent rhodium-catalyzed hydroformylation of ynamides,<sup>[14]</sup> we envisaged to apply our method to alkynyl sulfides to access  $\alpha$ -sulfenyl acroleins (Scheme 1, Eq 7). The reaction poses some challenges like controlling regioselectivity and avoiding competitive hydrogenation. However, it secures the stereochemical control of the geometry of the resulting trisubstituted alkene, with H and CHO in *cis* configuration. Indeed, five products can potentially be formed in this transformation: the  $\alpha$ - and  $\beta$ -sulfenyl acrolein regioisomers, their corresponding saturated sulfenyl aldehydes, and the alkenyl sulfide resulting from competitive direct hydrogenation of the starting material. However, by tuning the different reactions parameters and the substrate structure, it would be possible to achieve our goal. It is also to notice that the hydroformylation of alkenyl sulfides has been already described and showed a beneficial effect of the presence of the sulfenyl group in terms of diminishing competing hydrogenation and in favoring the formation of the  $\alpha$ -formyl sulfide regioisomer.<sup>[15]</sup> Herein, we report the stereo- and regioselective synthesis of  $\alpha$ -sulfenyl acroleins by Rh-catalyzed hydro-

formylation and illustrate potential synthetic applications.

To start our study, we selected the *S*-benzylpropynyl thioether **1a**<sup>[16]</sup> having a small methyl substituent on the triple bond as the model substrate, so as to diminish the simple steric control for the benefit of the electronic effect and/or the metal-coordination of the sulfenyl function to evaluate its impact on the regioselectivity. First we tested the hydroformylation under reaction conditions commonly used in our laboratory: Rh(CO)<sub>2</sub>(acac) (2 mol%) as the rhodium source, a mono- or bidentate phosphorous ligand (8 mol%), toluene as the solvent (0.05 M), 70 °C, 16 hours, under a pressure of 5 bars of syngas (CO/H<sub>2</sub> 1:1), in a stainless steel autoclave. The influence of the ligand on the efficiency of the reaction, as well as on its chemo- and regioselectivity, was initially evaluated (Table 1). Using the simple triphenyl phosphite (entry 1) the conversion was incomplete (40%). However, we were able to identify by NMR analysis of the crude reaction mixture the formation of four compounds: the  $\alpha$ - and the  $\beta$ -sulfenyl acroleins **2a** and **3a**, the 2-(benzylsulfanyl)butanal **2aH<sub>2</sub>** (which is the hydrogenated **2a**), and the vinyl sulfide **1aH<sub>2</sub>** (resulting from the hydrogenation of the starting material **1a**). The chemoselectivity (hydroformylation vs hydrogenation) and the regioselectivity ( $\alpha$ - vs  $\beta$ -hydroformylation) of the reaction have been estimated by measuring by integration of the characteristic signals in <sup>1</sup>H NMR (see the Supplementary Material S15). In this case the results showed a poor chemoselectivity (ratio **Ald/1aH<sub>2</sub>**: 48/52) and an encouraging regioselectivity in the favor of the  $\alpha$ -isomer (ratio  $\alpha/\beta$ : 71/29). This agrees with results obtained by Takaya *et al.* for the hydroformylation of *S*-vinylsulfides.<sup>[15b]</sup> However an important amount of saturated aldehyde **2aH<sub>2</sub>** was formed (ratio **2a/2aH<sub>2</sub>**: 53/47). Interestingly, no saturated aldehyde resulting from the  $\beta$ -sulfenyl acrolein **3a** was detected. We suppose that this could be correlated with the lower ability of the sulfur atom to coordinate the rhodium complex, due to a push-pull effect in the case of **3a**. By using other simple monodentate or bidentate phosphine ligands, such as the triphenylphosphine or the 1,3-bis(diphenylphosphino)propane (dppp), the reaction failed, with conversion of less than 10% (entries 2 and 3). When Xantphos was used as a more electron-rich rigid diphosphine, the NMR analysis of the crude reaction mixture revealed a complete conversion of the starting material, a moderate chemoselectivity with a ratio **Ald/1aH<sub>2</sub>** of 72/28, and a poor regioselectivity with a ratio  $\alpha/\beta$  of 58/42 (entry 4). Moreover, in this case the  $\alpha$ -sulfenyl acrolein **2a** was completely hydrogenated into its saturated derivative **2aH<sub>2</sub>**. We then turned to the electron-poor and sterically hindered bidentate phosphite ligand, the BiPhePhos.<sup>[17]</sup> In this case, in addition to full conversion, a high chemoselectivity with a ratio **Ald/1aH<sub>2</sub>**

**Table 1.** Hydroformylation of substrate **1a**: ligand optimization.<sup>[a]</sup>

Entry	Ligand	Conv. (%) <sup>[b]</sup>	Ratio Ald/1aH <sub>2</sub> <sup>[b,c]</sup>	Ratio α/β <sup>[d]</sup>	Ratio 2a/2aH <sub>2</sub>
1	P(OPh) <sub>3</sub>	40	48/52	71/29	53/47
2	PPh <sub>3</sub>	< 10	–	–	–
3	dppp	< 10	–	–	–
4	Xantphos	100	72/28	58/42	0/100
5	BiPhePhos	100	95/5	84/16	4/96
6	DPEPPhos	93	81/19	47/53	32/68
7	BINAP	90	86/14	47/53	32/68
8	TriBiPhos	< 10	–	–	–

<sup>[a]</sup> Reaction conditions: Rh(CO)<sub>2</sub>(acac) (2 mol%), Ligand (8 mol%), Toluene (0.05 M), CO/H<sub>2</sub> (1:1, 5 bars), 70 °C, 16 h.

<sup>[b]</sup> Measured by <sup>1</sup>H NMR in the crude mixture.

<sup>[c]</sup> Ald: mixture of aldehydes (**2a** + **2aH<sub>2</sub>** + **3a**).

<sup>[d]</sup> Regioselectivity of the hydroformylation; α = (**2a** + **2aH<sub>2</sub>**), β = **3a**.

of 95/5 and a satisfactory regioselectivity with a ratio α/β of 84/16 have been reached (Table 1, entry 5). Only one fault still persisted, the almost complete hydrogenation of the α-isomer **2a** into the corresponding saturated aldehyde. When another diphosphite (i.e. TriBiPhos) or other diphosphines (i.e. DPEPPhos, BINAP) were tested, the reaction failed (entry 8) or

resulted in very poor regioselectivity (entries 6 and 7), but with a significant decrease of the amount of **1aH<sub>2</sub>** formed.

As BiPhePhos furnished finally the best result, it was selected as the rhodium ligand for further optimization study (Table 2). To limit the over-reduction of α-sulfenyl acrolein **2a**, we attempted to perform

**Table 2.** Hydroformylation of substrate **1a**: temperature, concentration, catalyst/ligand amount optimization.<sup>[a]</sup>

Entry	T (°C)	[c] (M)	[Rh]/L (mol%)	Conv. (%) <sup>[b]</sup>	Ratio Ald/1aH <sub>2</sub> <sup>[b,c]</sup>	Ratio α/β <sup>[d]</sup>	Ratio 2a/2aH <sub>2</sub>
1	55	0.05	2/8	100	91/9	78/22	51/49
2	40	0.05	2/8	13	94/6	80/20	91/9
3	20	0.05	2/8	< 10	–	–	–
4	40	0.10	2/8	50	94/6	78/22	85/15
5	40	0.15	2/8	60	94/6	77/23	82/18
6	40	0.20	2/8	70	95/5	77/23	77/23
7	40	0.15	4/8	100	96/4	76/24	42/58
8	40	0.15	2/4	90	94/6	77/23	81/19

<sup>[a]</sup> Reaction conditions: [Rh] = Rh(CO)<sub>2</sub>(acac), L = BiPhePhos, Toluene, CO/H<sub>2</sub> (1:1, 5 bars), 16 h.

<sup>[b]</sup> Measured by <sup>1</sup>H NMR in the crude mixture.

<sup>[c]</sup> Ald = mixture of aldehydes (**2a** + **2aH<sub>2</sub>** + **3a**).

<sup>[d]</sup> Regioselectivity of the hydroformylation; α = (**2a** + **2aH<sub>2</sub>**), β = **3a**.

the reaction at lower temperature. Thus, decreasing the temperature from 70 °C to 55 °C the conversion was still total and the ratio **2a/2aH<sub>2</sub>** increased significantly from 4/96 to 51/49 (entry 1). This improvement was even more pronounced when the reaction was performed at 40 °C (ratio **2a/2aH<sub>2</sub>**: 91/9), but the conversion dropped dramatically to 13% (entry 2). At room temperature (entry 3), the reaction did not proceed. In order to improve the conversion at 40 °C, we have increased the concentration of the reaction medium. Thus, by doubling the concentration (from 0.05 to 0.1 M), the conversion reached 50% (entry 4), and at 0.15 M it increased to 60% preserving a good  $\alpha$ -regioselectivity (entry 5). However, at 0.2 M (entry 6), despite a conversion of 70%, the proportion of the saturated aldehyde increased (ratio **2a/2aH<sub>2</sub>**: 77/23). To further improve the transformation keeping the concentration of 0.15 M and 40 °C, we finally varied the catalytic charge and/or the rhodium/ligand ratio (entries 7 and 8). The best combination was Rh(CO)<sub>2</sub>(acac) (2 mol%)/BiPhePhos (4 mol%), enabling a high conversion of 90%, while maintaining a good regioselectivity, and limiting the formation of hydrogenated side products (entry 8).

With these optimized reaction conditions in hand, we next investigated the scope and limitations of the reaction (Table 3). Starting from the model-substrate **1a**, the desired  $\alpha$ -benzylsulfanyl acrolein **2a** has been isolated in 40% yield (entry 1). The influence of the substituent attached to the sulfur atom has been first examined. By replacing the benzyl by a 2-chlorobenzyl (entry 2) or a 3-methyl pyridine substituent (entry 3), the conversions were total and similar regioselectivities in the favor of the  $\alpha$ -isomer were obtained. However, the formation of a significant amount of the saturated aldehydes **2(b,c)H<sub>2</sub>** was noted, which caused the isolated yields of the desired products **2b** and **2c** to drop (32 and 29%, respectively).

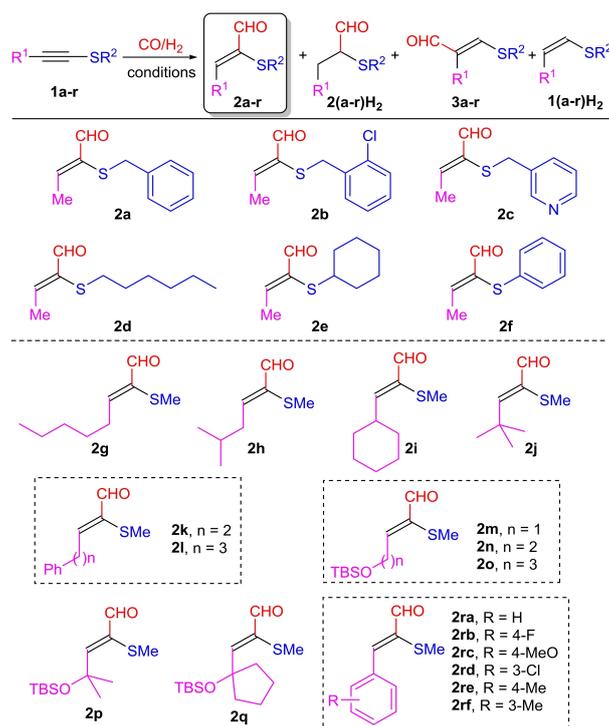
The *S*-hexyl and *S*-cyclohexyl derivatives **1d** and **1e** led to incomplete conversions of 67% and 47%, respectively (entries 4 and 5), with a higher  $\alpha$ -regioselectivity for the acyclic than for the cyclic substituent (84/16 vs 75/25) which is probably due to the steric hindrance of the latter. Interestingly, for the *S*-cyclohexyl product **2e**, the steric hindrance at the sulfur atom and a weaker coordination to rhodium slow down its reduction into **2eH<sub>2</sub>**. Lastly, the reaction on *S*-phenylpropynyl thioether (entry 6) gave a conversion of 71%, with low chemo and regio selectivities. Isolation of pure product **2f** from the mixture proved difficult, therefore only 10% yield could be obtained. In the next set of experiments, we used alkynes bearing a methylsulfanyl group and varied the substituents on the other side of the triple bond (entries 7 to 23).<sup>[18]</sup> In most cases, whatever the nature of the substituent, alkyl or aryl, the reaction took place with high or total conversion, with good chemo and

regioselectivities, and the  $\alpha$ -sulfenyl acroleins **2** were isolated with satisfactory yields. When using linear (entries 7, 11, and 12), branched (entry 8), or bulky (entry 9) alkyl substituents on the triple bond, the starting material was mainly converted into the hydroformylated product and the  $\alpha$ -regioisomer was the major one (ratio  $\alpha/\beta$  of about 80/20). The desired sulfenyl acroleins **2g–l**, have been obtained with isolated yields ranging from 44% to 69%. As expected, the best result was obtained with substrate **1j** bearing the bulky tert-butyl substituent, with a ratio  $\alpha/\beta$  of 89/11 and without any trace of the saturated aldehyde (entry 9). This allowed us to isolate product **2j** with a good yield of 60%, despite the fact that it was found to be very volatile. We then evaluated and compared the reactivities of five substrates with different steric hindrance, bearing a tert-butyldimethylsilyloxy (OTBS) group linked to the triple bond by one to three carbon atoms (entries 13 to 17). Regarding substrates **1n** and **1o** having respectively an ethylene or a propylene linker (entries 14 and 15), the presence of the OTBS group does not seem to have any influence, the results being comparable to those obtained in the case of *n*-pentyl substituted substrate **1g**. On the other hand, when the oxygen and triple bond are separated by only one carbon atom (entry 13), the proportion of the  $\beta$ -isomer **3m** increased, while the  $\alpha$ -isomer **2m** was almost completely hydrogenated into the saturated aldehyde **2mH<sub>2</sub>**, which was isolated in 55% yield. These results appear to be correlated with the participation of oxygen as an additional coordinating group.<sup>[18]</sup> This can be partially counteracted by increasing the steric hindrance on the carbon linking the OTBS and the triple bond. Indeed, using alkynes **1p** and **1q** as the substrates (entries 16 and 17), the saturated aldehydes were no longer detected, but at the expense of a decrease in conversion (68% and 30%, respectively). We have, however succeeded to isolate pure unsaturated aldehydes **2p** and **2q** in 36% and 16% yield, respectively.

Finally, the reaction was also performed on a range of six aryl substituted alkynes **1r** (entries 18 to 23). It was found to be effective in all cases, on aryl derivatives bearing electron-donating or electron-withdrawing groups at the meta or para positions, and the  $\alpha$ -sulfenyl cinnamaldehyde derivatives **2ra–2rf** have been isolated in good yields between 51% and 57%. Interestingly, although aryl acetylenes are known to be easily hydrogenated under hydroformylation conditions,<sup>[20]</sup> in our case, the presence of the sulfenyl function preserves a satisfactory chemoselectivity in favor of the hydroformylation. Moreover, the over-reduction of the unsaturated aldehyde has been minimized to less than 5%.

To evaluate the applicability of our methodology on more complex structures, we synthesized two new alkynyl sulfides **1s** and **1t**, bearing respectively on the

**Table 3.** Scope and limitations of the hydroformylation accessing  $\alpha$ -sulfenyl acroleins **2**: variation of  $\text{SR}^2$  (entries 1–6) and  $\text{R}^1$  (entries 7–23) groups.<sup>[a]</sup>



Entry	Conv. (%) <sup>[b]</sup>	Ratio Ald/ $1\text{H}_2$ <sup>[b,c]</sup>	Ratio $\alpha/\beta$ <sup>[d]</sup>	Ratio $2/2\text{H}_2$	Isolated product (yield %)
1	90	94/6	77/23	81/19	<b>2a</b> (40)
2	100	92/8	75/25	57/43	<b>2b</b> (32)
3	100	92/8	79/21	58/42	<b>2c</b> (29)
4	67	94/6	84/16	82/18	<b>2d</b> (39)
5	47	97/3	75/25	95/5	<b>2e</b> (36)
6	71	75/25	64/36	40/60	<b>2f</b> (10)
7	100	94/6	81/19	79/21	<b>2g</b> (44)
8	95	97/3	89/11	92/8	<b>2h</b> (57)
9	100	93/7	88/12	95/5	<b>2i</b> (69)
10	91	97/3	89/11	100/0	<b>2j</b> (60)
11	100	93/7	82/18	63/37	<b>2k</b> (50)
12	100	93/7	83/17	82/18	<b>2l</b> (50)
13	100	93/7	70/30	4/96 <sup>[e]</sup>	<b>2mH<sub>2</sub></b> (55)
14	100	91/9	80/20	78/22	<b>2n</b> (55)
15	100	93/7	84/16	82/18	<b>2o</b> (57)
16	68	91/9	80/20	100/0	<b>2p</b> (36)
17	30	88/12	78/22	100/0	<b>2q</b> (16)
18	100	75/25	77/23	97/3	<b>2ra</b> (57)
19	100	80/20	75/25	97/3	<b>2rb</b> (53)
20	100	80/20	80/20	96/4	<b>2rc</b> (56)
21	100	86/14	67/33	100/0	<b>2rd</b> (51)
22	100	63/37	87/13	91/9	<b>2re</b> (52)
23	100	73/27	73/27	94/6	<b>2rf</b> (57)

<sup>[a]</sup> Reaction conditions:  $\text{Rh}(\text{CO})_2(\text{acac})$  (2 mol%), BiPhePhos (4 mol%), Toluene (0.15 M),  $\text{CO}/\text{H}_2$  (1:1, 5 bars), 40 °C, 16 h.

<sup>[b]</sup> Measured by  $^1\text{H}$  NMR in the crude mixture.

<sup>[c]</sup> Ald: mixture of aldehydes (**2a** + **2aH<sub>2</sub>** + **3a**).

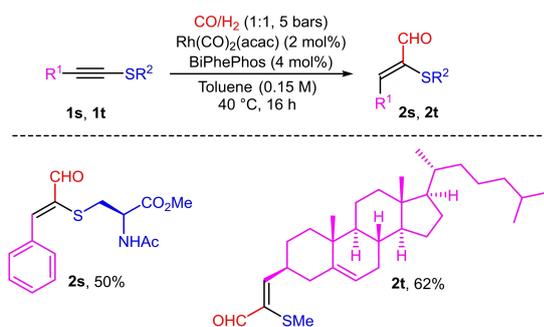
<sup>[d]</sup> Regioselectivity of the hydroformylation;  $\alpha = (2 + 2\text{H}_2)$ ,  $\beta = 3$ .

<sup>[e]</sup> Product **2mH<sub>2</sub>** could be isolated, but not **2m**.

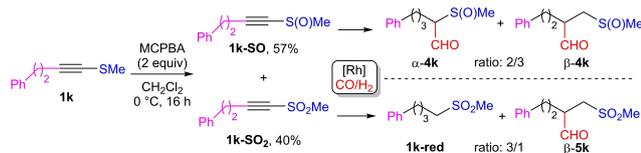
triple bond a sulfenyl moiety of the *N*-acetyl cysteine methyl ester,<sup>[21]</sup> or a cholesteryl group<sup>[22]</sup> (Scheme 2). We were pleased to conclude that the hydroformylation worked well, providing access to the desired unsaturated  $\alpha$ -sulfenylated unsaturated aldehydes **2s** and **2t** in good isolated yield, 50% and 62%, respectively.

We also examine the possibility of selectively mono or dioxidize the sulfur of the alkynes substrates and access via their hydroformylation to sulfinyl or sulfonyl acroleins, respectively. This has been attempted with substrate **1k**, which was oxidized by two equivalents of *meta*-chloroperbenzoic acid (MCPBA) into alkynyl sulfoxide **1k-SO** and alkynyl sulfone **1k-SO<sub>2</sub>** (Scheme 3). The hydroformylation of these derivatives to give the desired products was unsuccessful. <sup>1</sup>H NMR analysis of the crude reaction mixtures showed that the alkynyl sulfoxide led to a mixture of saturated  $\alpha$ - and  $\beta$ -sulfenyl aldehydes **4k** in a ratio of 2/3, while the alkynyl sulfone led to a mixture of fully hydrogenated substrate (product **1k-red**) and saturated  $\beta$ -sulfenyl aldehyde  **$\beta$ -5k** in a ratio of 3/1 (Scheme 3). These results show the influence of the electronic nature of the sulfur-substituent (i.e. electron-donating sulfenyl group vs electron-withdrawing sulfinyl or sulfonyl groups) on the reactivity of the triple bond toward the regioselectivity of the hydroformylation and the competitive hydrogenation. With the electron-poor alkynes the formation of the hydroformylated  $\beta$ -regioisomer and of the hydrogenated products is favored.

We then decided to perform the *S*-oxidation on an already prepared sulfenyl acrolein **2**. We used the 3-cyclohexyl-2-methylsulfenyl acrolein **2i** of which



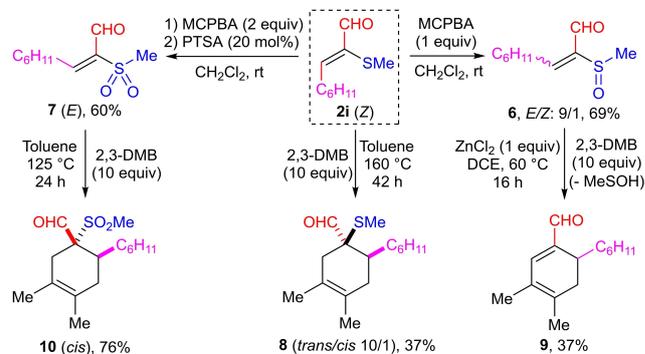
**Scheme 2.** Application of the hydroformylation to cysteine and cholesterol alkynyl sulfide derivatives.



**Scheme 3.** *S*-oxidation of **1k** and hydroformylation of the obtained sulfoxide and sulfone.

isolated yield was found to be the highest. By using one or two equivalents of MCPBA the oxidation led selectively to the formation of the desired sulfoxide **6** or sulfone **7**, respectively (Scheme 4). It should be noted that during this transformation, the *Z* into *E* isomerization occurred. A ratio *E/Z* of 90/10 was obtained for the vinyl sulfoxide, and of 85/15 for the vinyl sulfone. Treatment of the latter in the presence of a catalytic amount of Bronsted acid (*para*-toluenesulfonic acid: PTSA) allowed to complete the isomerization, while the same treatment of the vinyl sulfoxide led to its degradation. Finally, we engaged our three sulfur-containing acrolein derivatives in a Diels-Alder reaction with 2,3-dimethylbuta-1,3-diene (2,3-DMB) to evaluate their reactivity as dienophiles (Scheme 4). With 3-cyclohexyl-2-sulfenyl acrolein **2i**, the cycloaddition was carried out at 160 °C in toluene, and after 42 hours the conversion was found to be incomplete (72%). The expected *trans* cycloadduct **8** was obtained along with a small amount of its *cis* isomer (in a ratio of 10/1, 37% yield), which resulted probably from (*E*)-**2i** formed during the process. With sulfinylacrolein **6**, the previous conditions led to degradation of the starting material. However, when the reaction was performed at 60 °C in dichloromethane, in the presence of a Lewis acid (ZnCl<sub>2</sub>), the cycloaddition followed by a regioselective  $\beta$ -elimination of methanesulfenic acid, afforded the cyclohexa-1,4-dienal **9** in 37% isolated yield. Finally, for the sulfonylacrolein **7**, heating at 125 °C for 24 hours allowed the stereospecific obtention of cycloadduct **10** as a single *cis* isomer, with 76% yield.<sup>[23]</sup> Thus, depending on the degree of oxidation of the sulfur atom, it is possible to selectively obtain the functionalized cyclohexene carbaldehyde in *trans* or in *cis* relative configuration, or the cyclohexadiene carbaldehyde.

In summary, we have developed the rhodium catalyzed hydroformylation of alkynyl sulfides to access  $\alpha$ -sulfenyl acroleins with regioselectivities up to 89/11. This reaction takes place under mild conditions (at 40 °C under 5 bars of *syngas*) and is applicable to



**Scheme 4.** Synthetic applications of  $\alpha$ -sulfenyl acroleins: *S*-oxidation and/or Diels-Alder reaction of **2i**.

substrates bearing an alkyl substituent on the sulfur atom and an alkyl or aryl substituent on the carbon triple bond. In addition, we have demonstrated that the method also works on more complex substrates, such as cysteine and cholesterol derivatives. Finally, we were able to selectively oxidize the sulfur atom of the obtained (*Z*)  $\alpha$ -sulfenyl acroleins and access via an acid-promoted isomerization to their corresponding (*E*) sulfoxide or sulfone. These sulfur-substituted acrolein derivatives have been used as dienophiles in Diels-Alder reaction to give cyclohexene carbaldehydes with *trans* or *cis* relative configuration, or the cyclohexadiene carbaldehyde, depending on the degree of oxidation of the sulfur atom.

## Experimental Section

### General Procedure for the Hydroformylation of Alkynylthioether 1

In a dry Schlenk glassware under argon were introduced Rh(CO)<sub>2</sub>acac (2 mol%) and anhydrous degassed toluene (1 mL). BiPhePhos (4 mol%) was added and CO evolution was observed. Subsequent addition of alkynylthioether **1** was performed. The mixture was transferred via a syringe in a dry stainless autoclave under argon. The glassware was rinsed with anhydrous degassed toluene (3 times) to reach a final concentration of 0.15 M. The autoclave was purged with *syngas* (H<sub>2</sub>/CO 1:1) before setting the pressure at 5 bars of *syngas*. The autoclave was heated at 40 °C (internal temperature) during 16 h. The autoclave was then cooled to ambient temperature and vented to ambient pressure. The reaction medium was concentrated under vacuum and the crude product was purified by flash column chromatography, using a heptane/ethyl acetate or pentane/diethyl ether mixture as eluent, afforded pure  $\alpha$ -sulfenyl acrolein **2**.

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