Asymmetric Synthesis

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Complete Regio- and Stereoselectivity Control in the Halohydroxylation of Non-activated Allenes Mediated by a Remote Sulfinyl Group**

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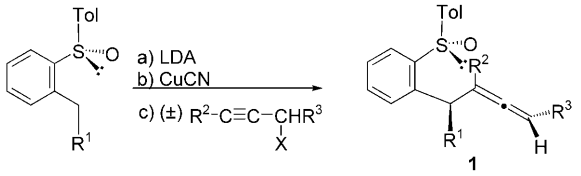
Dedicated to Professor Josep Font Cierco on the occasion of his 70th birthday

Allenes have recently gained much attention as versatile building blocks. The allene motif is present in a large number of medicinal and natural products.[1] One of the most used methods for the synthesis of optically pure allenes involves the highly stereoselective addition of organocopper reagents to optically pure propargylic derivatives.[1] The main limitation of this procedure centers around the availability of the alcohols used as starting materials. We have recently reported that reactions of copper/*ortho*-sulfinyl benzyl carbanions with racemic propargyl derivatives allow the synthesis of optically pure γ-sulfinyl allenes with central and/or axial chirality.[2] The influence of the remote sulfinyl group on the stereochemical outcome of these reactions is reflected in the complete kinetic resolution that it is observed (Scheme 1).



Scheme 1. Synthesis of optically pure sulfinylated allenes. Tol = *p*-tolyl, LDA = lithium diisopropylamide, X = halogen or methanesulfonate group.

The lack of regioselectivity control is one of the main problems encountered when trying to functionalize allenes. Normally, mixtures of regioisomers are obtained unless the C=C=C system is polarized by strongly electron-donating[3] or electron-withdrawing groups.[4] Moreover, control of the stereoselectivity in allenic system is not an easy task, unless, a chiral center is directly connected to the reactive double bond.[5] On the basis of this prior knowledge, we envisioned that allenes **1** (Scheme 1) could be appropriate substrates for the remote control of both regio- and stereoselectivity of reactions taking place on the nonpolarized allenic systems—the ability of the sulfinyl group to participate in anchimeric assistant is the controlling factor.[6] The anchimeric assistance that is provided by a sulfinyl group has been successfully exploited by Ma et al. in the conversion of allenyl sulfoxides into allylic alcohols by halohydroxylation.[7] However, the complete regioselectivity observed in these reactions occurred as a consequence of the well-known influence of the electron-withdrawing group, like sulfinyl, which was directly bonded to the allene moiety. It is also known that control of stereoselectivity, which is also complete when starting from allenes with axial chirality, is exclusively dependent on the configuration of the chiral axis, regardless of the configuration at the sulfinyl group. Thus, the synthesis of optically pure secondary allylic alcohols is only possible when starting from enantiopure sulfinyl allenes. In turn, these allenes are obtained from enantiopure propargyllic alcohols; this approach is not synthetically useful because of the limited availability of the starting substrates. Herein, we report the ability of a remote sulfinyl groups to control both the regio- and stereoselectivity in the halohydroxylation of scarcely polarized allenes **1**. We also highlight several synthetic uses for the resulting halohydrines, which are used as chiral synthons.

We first studied the reaction of allene **1a** with different halogen sources (Table 1). The use of bromine as a reagent afforded a complex mixture of diastereoisomers, regioisomers, and other by-products (Table 1, entries 1 and 2). These results were improved with NBS, which only gave **2a** as a 86:14 mixture of stereoisomers in 84% yield with complete control of the regioselectivity (Table 1, entry 3).[8] The addition of LiOAc had a negative influence on the reaction and gave **2a**/**3a** as a 60:40 mixture of regioisomers (Table 1, entry 4). The use of either NIS/H_2O or NIS in the presence of LiOAc provided similar results to when NBS was employed (70–74% *de*; Table 1, entries 5 and 6). Whereas, the use of I_2/H_2O resulted in a completely diastereoselective reaction, and exclusively afforded one diastereoisomer of **4a** in moderate yield (Table 1, entry 7), which was substantially improved by addition of LiOAc (Table 1, entry 8). Thus, the treatment of **1a** with I_2/LiOAc/H_2O occurs in a completely regioselective

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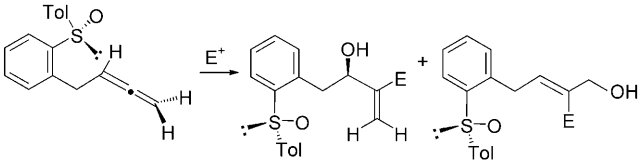
Table 1: Screening of reaction conditions for the addition of halogens to γ-sulfinylallenes.[a]



1a **2a** (E=Br) **4a** (E=I) **3a** (E=Br) **5a** (E=I)

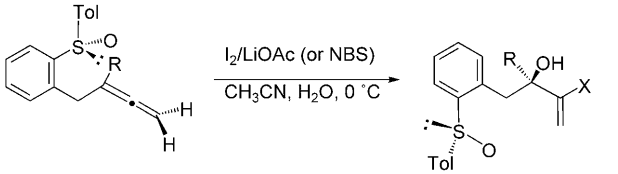
Entry	Electrophile (E^+)	**2a**/**3a**	**4a**/**5a**	Yield [%][b]	d.r.[c]
1	Br_2/H_2O	–[d]	–	–	–
2	Br_2/LiOAc/H_2O	–[d]	–	–	–
3	NBS/H_2O	>98:2	–	84[e]	86:14
4	NBS/LiOAc/H_2O	40:60	–	71[e]	n.d.
5	NIS/H_2O	–	>98:2	n.d.	85:15
6	NIS/LiOAc/H_2O	–	>98:2	70[e]	87:13
7	I_2/H_2O	–	>98:2	40	>98:2
8	I_2/LiOAc/H_2O	–	>98:2	83	>98:2

[a] Reaction conditions: **1a** (0.2 mmol), the corresponding electrophile (0.5 mmol), CH_3CN (4.0 mL) and H_2O (0.2 mL) at 0°C. [b] Yield of isolated product. [c] Diastereomeric ratio of epimers at the hydroxylated carbon atom in **2a** or **4a.** [d] A complex reaction mixture. [e] Combined yield. NBS = *N*-bromosuccinimide, n.d. = not determined, NIS = *N*-iodosuccinimide.

and stereoselective manner, only yielding **4a** in 83% yield (Table 1, entry 8). In summary, the reaction conditions outlined in entries 3 and 8 of Table 1 are the most convenient for achieving bromohydroxylation and iodohydroxylation of **1a**, respectively.

To investigate the scope of these reactions, we studied the behavior of 1,1-disubstituted allenes (only having the sulfinyl group as the chiral element) under the best reaction conditions (Table 1, entries 3 and 8). The results are shown in Table 2. Iodohydroxylation of **1b–e** gave **4b–e** as the only products, thus indicating that both the stereoselectivity and regioselectivity are completely controlled by the sulfinyl group[9] regardless of the nature of the R group (Table 2, entries 2–5). Bromohydroxylation of allenes **1b**,**d** was also completely regioselective and highly stereoselectivity, and with slightly better results than those observed for **1a** (compare Table 2, entries 7–8 with entry 6), and provided compounds **2** with up to 95:5 d.r. This selectivity indicates that substituents at C1 have a positive influence on the stereoselectivity of the reaction. The yield obtained under the various reaction conditions shown in Table 2 ranged between 62% and 95%.

Table 2: Scope of the halohydroxylation of γ-sulfinylallenes.[a]



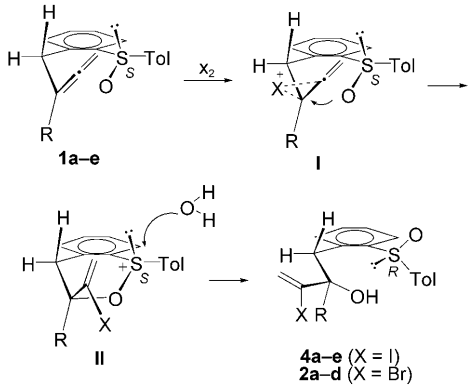
1a–f **2a–c** (X=Br) **4a–f** (X=I)

Entry	Allene	R	X	Product	Yield [%][a]	d.r. [%][b]
1	**1a**	H	I	**4a**	83	>98:2
2	**1b**	Me	I	**4b**	80	>98:2
3	**1c**	Et	I	**4c**	84	>98:2
4	**1d**	*n*Pent	I	**4d**	62	>98:2
5	**1e**	Ph	I	**4e**	75	>98:2
6	**1a**	H	Br	**2a**	84[c]	88:12
7	**1b**	Me	Br	**2b**	99	93:7
8	**1d**	*n*Pent	Br	**2d**	95	95:5

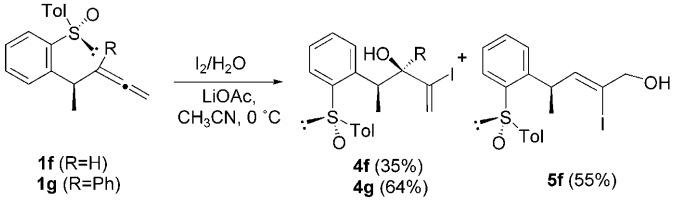
[a] Combined yield after chromatographic purification. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction performed at −10°C.

The absolute configuration of the halohydrin derivatives obtained in these reactions as major or exclusive products, was unequivocally established by X-ray diffraction studies **4e**[10] (see the ORTEP plot in the Supporting Information). This study also revealed that the configuration at the sulfinyl group of **4e** is *R*, which is opposite to the configuration of **1e**, thus indicating that halohydroxylation takes place with inversion of configuration at the sulfur atom. A plausible mechanism explaining the stereochemical outcome is indicated in Scheme 2. The halonium intermediate **I**, which is generated in the first step of these reactions, is attacked by the oxygen atom of the sulfinyl group, thus providing the cyclic alkoxysulfonium species **II**. Intermediate **II** is then opened by attack of water on the sulfur atom, thereby inverting its configuration. To provide additional proof to support the mechanism proposed in Scheme 2, the reaction of **1a** with I_2/MeOH (instead water) also afford iodohydrin **4a** as the exclusive product. This result confirms that it is not the solvent but is instead the sulfinyl oxygen atom which opens the iodosulfonium intermediate.[9] According to Ma et al.,[3f] the ability of the LiOAc to neutralize strong acids could be responsible for the improved yield and d.r. value when the reactions are carried out in the presence of I_2/H_2O (see Table 1).[11]

Finally, we have also studied the reaction of allenes **1f** and **1g**, which have two chiral centers, with I_2/H_2O. Allene **1f** gave a 40:60 mixture of regioisomers **4f** (*de* > 98%) and **5f**, whereas **1g** exhibited similar behavior to that of the compounds described in Table 1 and only yielded optically pure **4g** (Scheme 3). These results suggest that regiochemistry—but not stereochemistry—could be altered by the presence of substituents at the benzylic position, however, further studies will be necessary to confirm this assumption.

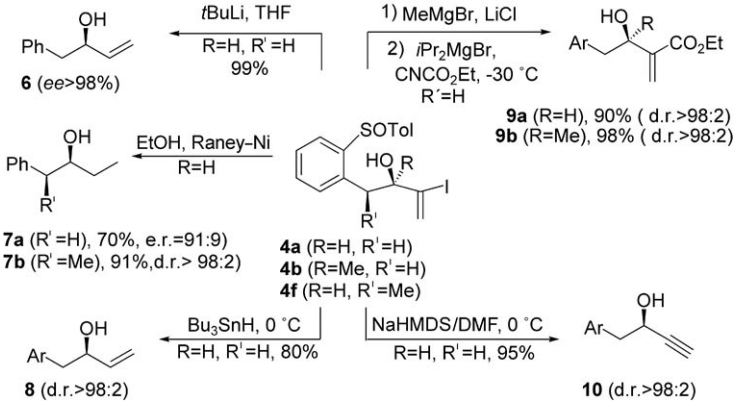


Scheme 2. Stereochemical course for the halohydroxylation of **1a**–**1e**.



Scheme 3. Reaction of **1f** and **1g**.

The halohydrin derivatives obtained were easily desulfinylated and could be targets of high synthetic potential.[12] This potential has been illustrated for some compounds (**4**) in reactions that yielded allylic and propargylic alcohols, or Baylis–Hillman products (Scheme 4). Desulfinylation of **4a** using *t*BuLi took place with concomitant deiodination and afforded alcohol **6**. Meanwhile, Raney nickel (Raney-Ni) was also used to reduce the double bond and gave **7a** and **7b** with good yields. Deiodination of **4a** was carried out with Bu_3SnH and the allylic alcohol **8** was obtained. The iodine/magnesium exchange and subsequent treatment with ethyl cyanoacetate yielded the Baylis–Hillman-type product **9a**. This reaction also efficiently gave the tertiary alcohol **9b**, which is not easily accessible by other methods.[13] In both cases, almost quantitative yields and d.r. values higher than 98:2 were obtained. Finally, iodohydrins **4** can also be used to access propargylic alcohols. Thus, dehydrohalogenation of **4a** with NaHMDS in DMF,[14] led to optically pure propargylic alcohol **10**[15] in high yield (95%) and with a diastereomeric ratio up to 98:2.



Scheme 4. The use of the iodohydrins as precursors for various synthetic targets. Ar = 2-(*p*-tolylsulfinyl), DMF = *N*,*N*-dimethylformamide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, THF = tetrahydrofuran.

In conclusion, we have demonstrated that both regioselectivity and stereoselectivity of the halohydroxylation of non-activated allenes **1a**–**1g** are completely controlled by a remote sulfinyl group, and thereby takes advantage of its ability to participate in anchimeric assistance. The resulting secondary or tertiary allylic alcohols are excellent chiral targets used for the preparation of optically pure propargylic alcohols and Baylis–Hillman-type products.

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[8] This result was slightly improved when the reaction was performed at −10 °C (12 h; d.r. 88:12) instead of 0 °C (2 h; d.r. 86:14).

[9] Iodohydroxylation of the sulfone obtained by oxidation of **1a** with iodine in water gave the opposite regioselectivity to **1a**. This outcome can be attributed to inductive effects, which decrease the electronic density of the double bond next to the sulfonylated ring. This behavior suggests a significant role played by the sulfinyl group of **1a** in controlling the regioselectivity.

[10] CCDC 705625 (**4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] The lower yield obtained in reactions with NBS/H_2O/LiOAc (see Table 1) could be attributed to the decomposition of NBS in the presence of LiOAc. However, we do not have an explanation for the negative influence of LiOAc on the regioselectivity of this reaction.

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