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Asymmetric [2,3]-Wittig Rearrangement: Synthesis of Homoallylic, Allenylic, and Enynyl α-Benzyl Alcohols

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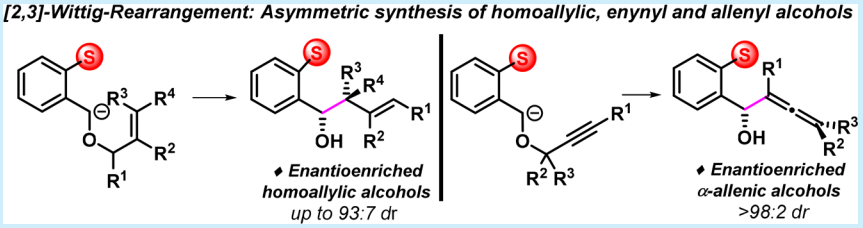
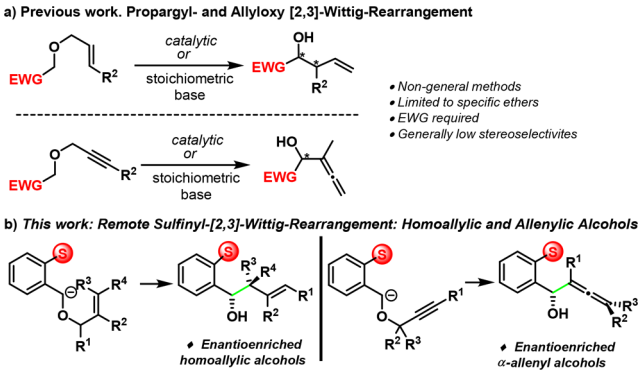
Supporting Information



ABSTRACT: A highly stereoselective [2,3]-Wittig rearrangement of allylic and propargylic ethers controlled by a chiral sulfoxide moiety is presented. The activation provided by the sulfoxide at the remote *ortho* position allows the rearrangement of less-activated and unexplored benzylic carbanions. Thus, this general methodology gives access to the asymmetric synthesis of homoallylic, enynyl, and allenylic α-benzyl alcohol derivatives.

[2,3]-Sigmatropic rearrangements hold a preferred position in the synthetic chemist's arsenal, as they represent a powerful tool for the rapid installation of molecular complexity in organic chemistry.[1] Recently, the enantioselective version has experienced an important development,[2] mainly via onium ylides[3] generated from diazo compounds.[2b,4] More specifically, advances in the development of the asymmetric anionic Wittig reaction, which involves the formation of α-oxycarbanion, are less prevalent, because of the need for strong bases. Nevertheless, methods based on the use of (i) strong Brønsted bases, such as *n*-BuLi or *t*-BuLi, in the presence of a stoichiometric ligand,[5] and (ii) stoichiometric amounts of a chiral boron reagent have been reported.[6] Moreover, stereoselective [2,3]-rearrangements with substrates bearing either existing stereocenters[5b,7] or chiral auxiliaries[5b,8] (Scheme 1a) to control the configuration of the newly formed σ-bond have been studied. Although rare, more recently, different groups[9−12] have described interesting organocatalyzed asymmetric [2,3]-rearrangement methodologies of allyloxy derivatives for the asymmetric synthesis of allylic alcohols. The asymmetric [2,3]-Wittig rearrangement of propargylic ethers, which lead to enantio-enriched functionalized allenes, has also been explored. Regardless of the great interest in developing such methods for the enantioselective preparation of synthetically valuable allenes,[13] very few examples have been reported for that purpose, following the deprotonation strategy.[14] The low reactivity shown by propargylic ethers is the main shortcoming that these methodologies need to overcome. Despite the great advances made in this field, prerequisite high catalyst loadings, low diastereoselectivities and enantioselectivities, and the restricted array of suitable substrates—in which the presence of an electron-withdrawing group (EWG) is required in order to promote the deprotonation step—still remain as the primary drawbacks and limitations of pre-existing methods (Scheme 1a).

Scheme 1. Previous Related Approaches and the Present Work



Chiral sulfoxides have been widely used to induce stereocontrol in a variety of organic transformations.[15] Despite the well-known ability of sulfoxides to direct reactions in

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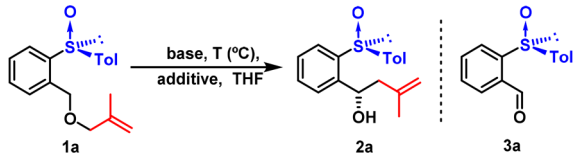
Table 1. Remote [2,3]-Wittig Rearrangement of 1a[a]



	base (equiv)	additive	temperature, T (°C)	yield[c] (%)	diastereomeric ratio, dr[b]
1	KHMDS (1.5)	–	−78	n.r.	–
2	KHMDS (1.5)	–	0	n.r.	–
3	*s*-BuLi (1.5)	TMEDA	−78	–[d]	–
4	LDA (1.5)	–	−78	–[d]	–
5	LDA (1.5)		0	35	85:15
6	LDA (4)		0	35	85:15
7	LDA (1.5)	TMEDA	0	54	85:15
8	LDA (1.5)	HMPA (1:6)	−78	–[e]	–
9	**LDA (1.5)**	**TMEDA**	**-78**	**56**	**90:10**

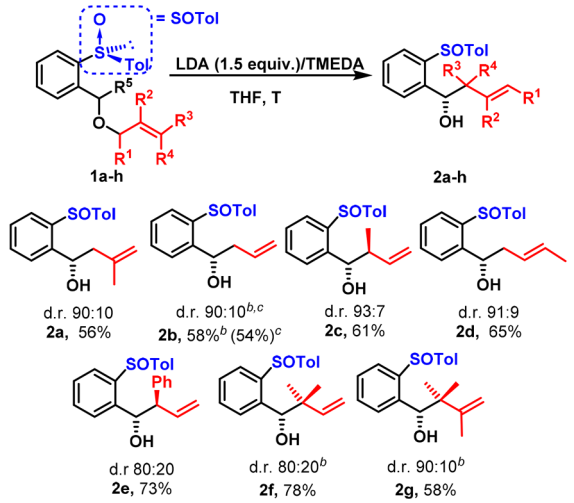
[a]All the reactions were performed on 0.273 mmol scale of **1a** in 4 mL of THF and the corresponding additive. [b]Determined by ^{1}H NMR. [c]Isolated yield of compound **2a** after flash chromatography. [d]Aldehyde **3a** was obtained as major product. [e]Complex mixture. Legend: KHMDS = potassium hexamethyldisilazane, *s*-BuLi = *sec*-butyllithium, TMEDA= tetramethylethylenediamine, LDA = lithium diisopropylamide, and HMPA = hexamethylphosphoramide.

strong basic media,[16] to the best of our knowledge, chiral sulfoxides have never been employed to induct a [2,3]-Wittig rearrangement. The presence of a chiral sulfoxide in the ortho position of an aromatic ring promotes the formation of stable chiral lithium carbanions. Therefore, laterally lithiated sulfoxides have been reported to react with a variety of electrophiles.[16] Thus, we envisioned that this strategy could lead to a [2,3]-sigmatropic rearrangement upon deprotonation of the benzylic position (Scheme 1b) without the need of EWGs to enhance the acidity, as in all previous works. The easy installation and removal (without racemization of the synthesized stereogenic center) of the sulfoxide moiety in the *ortho* position of the aromatic ring and the limitations of previously reported methods would make this approach a highly attractive and efficient alternative for the preparation of synthetically useful and enantio-enriched homoallylic alcohols. Moreover, by subjecting the corresponding propargylic ether derivatives to the [2,3]-Wittig rearrangement, enantiopure allenyl alcohol derivatives, which are otherwise difficult to access, could be efficiently obtained. In this work, we report the development of a general [2,3]-sigmatropic rearrangement method that hinges on the presence of the *ortho* sulfoxide, giving access to a variety of enantio-enriched homoallyl and allenyl α-benzyl secondary and tertiary alcohols.

We began our studies by investigating the [2,3]-Wittig rearrangement of sulfoxide **1a**, which was easily prepared in two steps (see the Supporting Information (SI)) from commercially available starting materials (see Table 1). The reaction did not proceed when a bulky base, such as potassium hexamethyldisilazane, was used (Table 1, entries 1 and 2), recovering the unaffected starting material. Other bases, such as *s*-BuLi or LDA at −78 °C did not conduct to the desired homoallylic alcohol, while aldehyde **3a**, which is formed via elimination of the stabilized allyl anion, followed by the oxidation of the benzylic position, was observed as the major product (Table 1, entries 3 and 4). Interestingly, LDA (1.5 or 4 equiv) at higher temperature (0 °C) led to the desired alcohol (**2a**) in moderate yield and good diastereomeric ratio (85:15), detecting aldehyde **3a** again as side product (Table 1, entries 5 and 6). The presence of TMEDA as an additive at the same temperature (0 °C) clearly improved the reaction and **2a** was isolated in diastereomerically pure fashion in 54% yield (see Table 1, entry 7). When other additives were employed, such as HMPA (Table 1, entry 8), a complex mixture was obtained, whereas TMEDA at −78 °C allowed us to isolate alcohol **2a** in 56% yield and with very good diastereoselectivity (Table 1, entry 9).

After optimizing the reaction conditions, we studied the scope of the reaction using differently substituted allylic ethers **1** as starting materials (see Table 2). Terminal allylic ether derivatives were well-tolerated and gave the rearranged products with high diastereoselectivities (**2a** and **2b**). In addition, the reaction was scaled up to 1.1 mmol with similar results. The [2,3]-Wittig rearrangement efficiently proceeded with α-branched terminal allylic ether (**2d**), leading to similar levels of diastereoselectivity. Substrates bearing β-substituted double bonds were then tested in the reaction. While aliphatic

Table 2. Remote Asymmetric [2,3]-Wittig Rearrangement of Sulfoxides 1[a]



[a]All the reactions were performed on 0.273 mmol scale of **1a** in 4 mL of THF at −78 °C. [b]Reactions performed at 0 °C. [c]1.1 mmol scale reaction. Diastereomeric ratios were determined using ^{1}H NMR.

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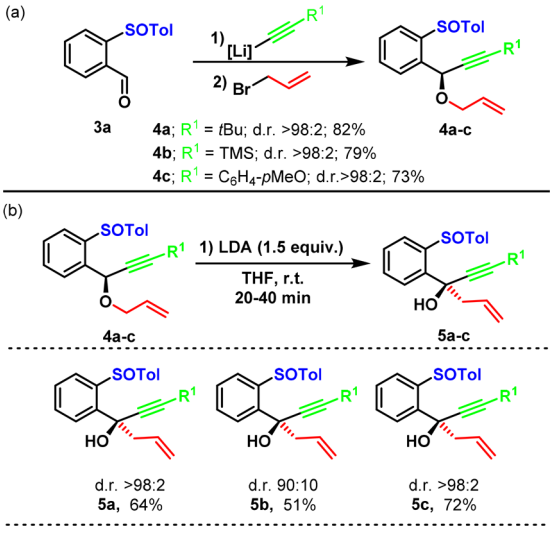
substitution on the double bond (**2c**) led to very good diastereoselectivity, the aryl-substituted double bond (**2e**) proceeded with lower stereoinduction. With a β-disubstituted double bond derivative, a slight erosion in the stereoselectivity was observed (**2f**). To our delight, the very challenging allylic substrate bearing a tetrasubstituted double bond rearranged to the homoallylic product with high diastereoselectivity and 58% isolated yield (**2g**).

Encouraged by the good results obtained in the [2,3]-Wittig rearrangement for the synthesis of secondary homoallylic alcohols and with the aim of synthesizing enantio-enriched tertiary alcohols, we studied the behavior of the corresponding reaction with secondary ether derivatives **4** (Scheme 2). For

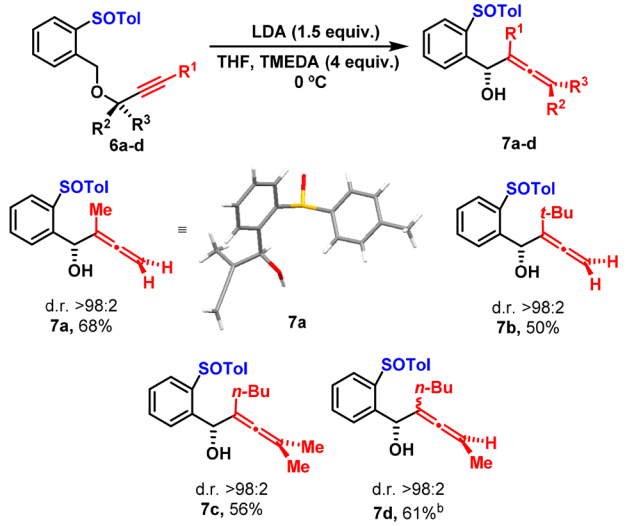
Scheme 2. Sulfinyl Double Induction: Synthesis and [2,3]-Wittig Rearrangement of Tertiary Allylic Alcohols



the construction of the chiral scaffold required for the rearrangement, we have taken advantage of the presence of the *ortho*-sulfinyl group. The addition of lithium acetylides to the aldehyde **3a** gives rise to the propargylic alcohols with excellent diastereoselectivities in all cases.[17] Simple allylation leads to the aforementioned chiral platforms (**4a**–**4c**) (eq a in Scheme 2). TMS, as well as alkyl- and aryl-substituted alkyne derivatives, were very well-tolerated in the [2,3]-sigmatropic rearrangement, leading to the desired tertiary alcohols with excellent diastereoselectivities (eq b in Scheme 2). Consequently, the presence of the chiral *ortho*-sulfinyl inductor is able to orchestrate the entire synthetic process.

Considering the limitations reported in the literature, where only few reports have described [2,3]-Wittig rearrangements for the asymmetric synthesis of allenyl alcohols,[14a,b] and to further extend the applicability of the sulfinyl-promoted asymmetric [2,3]-Wittig rearrangement, the reaction of propargylic alcohol derivatives was then considered. With that purpose, differently substituted propargylic ethers **6** were tested under the optimized reaction conditions (Table 3). Both methyl and bulky *tert*-butyl substituted alkynes efficiently led to the allenyl alcohols with complete diastereoselectivity (**7a** and **7b**). In the presence of a tertiary propargylic ether (**6c**), the reaction occurred in a highly stereoselective manner, observing only one diastereomer (**7c**). When an enantiopure (*S*)-oct-3-yn-2-ol derivative (**6d**) was used, the sulfoxide was able to control the stereoselectivity, including the axial chirality

Table 3. Remote [2,3]-Wittig Rearrangement of Propargylic Ethers for the Synthesis of α-Allenyl Alcohols[a]

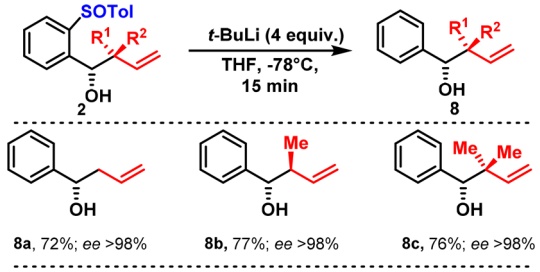


[a]All the reactions were performed on 0.273 mmol scale of **6** in 4 mL of THF. The diastereomeric ratio (dr) has been determined using ^{1}H NMR.

of the formed allene (**7d**), and only one diastereomer was obtained.[18] The absolute configuration of the asymmetric centers of **7a** were unequivocally assigned as (*S*, *R*) by X-ray crystallographic analysis (see the SI). The same stereochemical outcome was assumed for all of the compounds of the series.

Apart from the high stereoinduction provided, the *ortho*-sulfinyl group is an easily removable chiral auxiliary (Scheme 3). Direct treatment of allylic alcohols **2a**, **2b**, and **2c** with *t*-BuLi conducted to the desulfinylated products in good yields without erosion in the enantiomeric purity.

Scheme 3. Desulfinylation of the Allylic Alcohols 2



The absolute configuration of the asymmetric centers of minor diastereomer **2e′** was unequivocally assigned as (*S*, 1*R*, 2*R*) by X-ray crystallographic analysis (see the SI), whereas the major diastereomers were correlated with known compounds in the literature (**8a**, **8b**, and **8c**; see Scheme 3 and the SI). The same stereochemical outcome was assumed for all of the compounds of the series (**2a**–**2g**, **5a**–**5c**). With all this information in hand, it is clear that the rearranged products featuring two new stereocenters (**2c** and **2e**) are epimers in the carbon that bears the hydroxyl group. A plausible explanation for the exclusive formation of two diastereomers in the reactions presented in Table 2 is depicted in Scheme 4. We propose, based on previous DFT calculations,[16e,f] the formation of two plausible carbanions, that are capable of reacting in a completely stereoselective way, which would

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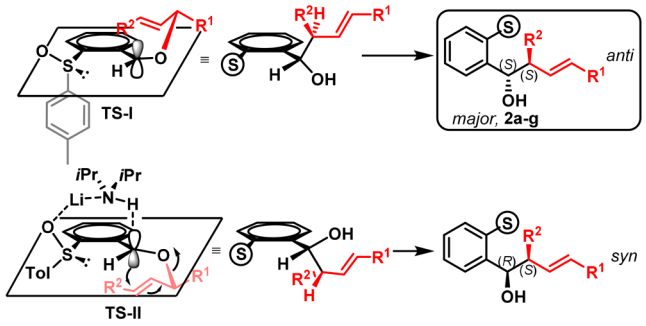
Scheme 4. Proposed Mechanism



establish the opposite configuration at the benzylic center. The results obtained can be rationalized with the formation of a free carbanion, which adopts a planar C(sp^2) structure (**TS-I**). This is in accordance with the observed better outcome at higher temperatures (0 °C) and in the presence of TMEDA, which would preferably avoid interactions between Li^+ and the carbanionic center. Therefore, the sulfinyl group assumes an *anti*-arrangement (S−O bond versus the carbanionic C−O bond), with respect to the benzyl carbanion center, in order to avoid unfavorable electrostatic interactions. The reaction is then controlled by sterics, the upper face being clearly favored for the approach of the alkene as the *p*-tolyl group is blocking the opposite face (**TS-I**). A five-membered envelope-type transition state[2b] and the defined *E* configuration of the double bond leads to the formation of the *anti*-isomer. A similar approach would explain the configuration obtained in the synthesis of enantio-enriched allenyl alcohols. In order to explain the observed minor diastereomers, we propose the formation of a "chelated" carbanion (**TS-II**), where the anion is formed and the top face is blocked. Therefore, the alkene reacts from the bottom face, establishing the opposite confirmation at the benzylic center (*R*).

In conclusion, the involvement of the key chiral auxiliary *ortho*-sulfinyl group has led to an asymmetric [2,3]-Wittig rearrangement in a nonactivated benzylic position. A wide range of ethers have been studied, wherein allylic and propargylic ethers efficiently rearranged to the corresponding homoallylic and allenyl alcohols with very high diastereoselectivities. Finally, the auxiliary can be easily removed, leading to the desired enantiomerically pure homoallylic alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03659.

^{1}H and ^{13}C spectra for all new compounds and X-ray data for **2e′** and **7a** (PDF)

Accession Codes

CCDC 1875997 and 1875998 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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