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Synthesis of Unfunctionalized Carbonated Fragments Containing Two Vicinal Chiral Centers: Stereocontrolled Benzylation of Vinylsulfones Mediated by a Remote Sulfinyl Group

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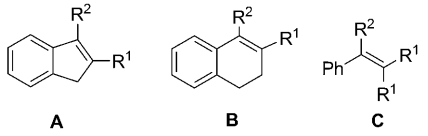
The synthesis of carbon skeletons containing two adjacent stereogenic centers in a single step is a difficult task, especially when no functional groups are joined to any of these centers. The most direct approaches for the synthesis of these carbonated fragments is the asymmetric hydrogenation of unfunctionalized tetrasubstituted olefins,[1] but only two main papers have been reported in this field from the groups of Buchwald[1b] and Pfaltz.[1c] In these papers, only hydrogenation of endocyclic alkenes (types **A** and **B** in Scheme 1) was reported with good enantiomeric excess (*ee*)



Scheme 1. Unfunctionalized tetrasubstituted olefins, the catalytic asymmetric hydrogenation of which has been successfully studied.

values (better for cyclopentenes). Despite the limitations in the scope, these methods have become highly important because they are the only ones able to afford unfunctionalized carbon skeletons with two connected chiral centers in a short synthetic sequence. Moreover, the obtained compounds have benzylic carbon stereocenters, which are found in over 5000 isolated natural products and have gained a privileged status as a stereochemical motif in medicinal chemistry because of their presence in many therapeutic agents as well as in important nonsteroidal estrogen compounds. However, to the best of our knowledge, no reports concerning the asymmetric hydrogenation of tetrasubstituted acyclic alkenes leading to compounds with two chiral centers have appeared in the literature. Only catalytic hydrogenation of compounds **C** (Scheme 1), yielding compounds with only one chiral center, has been described.[1a–b]

We have recently described the successful asymmetric benzylation of some electrophiles with substituted benzylcarbanions containing a remote *ortho*-sulfinyl group as a chiral inducer.[2] This method allowed us to provide almost complete control of the stereoselectivity at the benzylic center and, starting from prochiral electrophiles, also at the chiral carbon joined to the benzylic one. Electrophiles studied so far involved compounds with C=O[2a] or C=N[2b–c] bonds and, therefore, at least one of the obtained chiral centers was functionalized. On these precedents, we reasoned that conjugated additions of the *ortho*-sulfinyl benzylcarbanions derived from **1** to activated olefins would provide an indirect method for the synthesis of nonfunctionalized alkyl chains with two adjacent stereogenic centers, whenever the activating group could be easily removed. Vinylsulfones were chosen for this study because the sulfonyl group can be easily removed or, which could be even more interesting, transformed into a diversity of functional groups without affecting the chirality introduced in the first step (Scheme 2).[3] Herein, we present our results concerning the reactions indicated in Scheme 2 that allow the synthesis of alkyl chains with two adjacent stereogenic centers (one of them benzylic) by the reaction of alkyl-substituted 2-*p*-tolylsulfinylcarbanions derivatives with (*E*)-alkyl or aryl vinylsulfones and further removal of the sulfur functions.

Conjugated addition (CA) of organometallic reagents to vinylsulfones has been one of the synthetic procedures most widely used in asymmetric synthesis for the carbon–carbon

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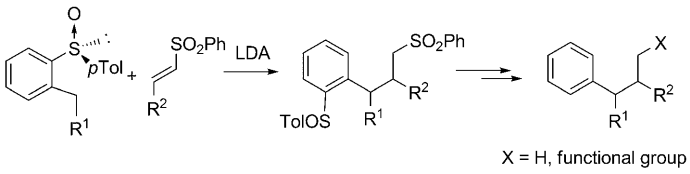


Scheme 2. Synthesis of alkyl chains with two adjacent stereogenic centers. LDA = lithium diisopropylamide.

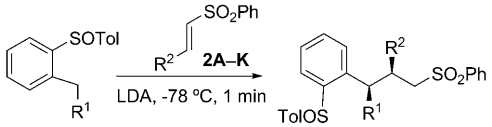
bond formation.[3] In this field, many catalytic methods have been reported in recent years, mainly from the groups of Carretero,[4] Feringa,[5] and Charette,[6] allowing hydride reduction as well as the arylation and alkylation of the double bond with enantioselectivity ranging from moderate to very good. However, as far as we know, the catalytic benzylation of vinylsulfones has never been reported and the use of prochiral nucleophiles in catalytic conjugated additions, providing two connected chiral centers in the same step, remains an unsolved problem. Both facts increased the interest in investigating the reactions shown in Scheme 2.

Compounds **1** were easily available from 2-bromotoluene in a two-step sequence (sulfinylation and alkylation) with very high yields.[7] Vinylsulfones **2** were commercially available or very easily prepared.[4a] Reaction of equimolecular amounts of the simplest sulfinyl carbanion derived from (*S*)-**1a** (R^1 = H; Table 1, entry 1) with styrylphenylsulfone **2A**, resulted in the formation of a complex mixture, in which products of double addition could be present.[8] However, the reaction of **2A** with the methylbenzyl carbanion derived from (*S*)-**1b** (R^1 = Me; Table 1, entry 2) as a prochiral nucleophile, was very fast (less than 1 min) and provided **3bA** as only diastereoisomer (diastereomeric excess (*de*) > 98%) in 70% yield (Table 1, entry 2). Reactions with other 2-arylvinylsulfones (**2B–G**) were also studied. Results were similar when an electron-donating group or a naphthyl group were incorporated (**2B**, **2C**; Table 1, entries 3 and 4, respectively), whereas the presence of electron-withdrawing groups at the 2-aryl ring decreased the stereoselectivity. Thus, compound **2D** (R^2 = *p*-ClC_6H_4) yielded an 84:16 diastereoisomeric mixture of **3bD** and **3′bD** (Table 1, entry 5), and **2E** (R^2 = *p*-CNC_6H_4) evolved in an even lower stereoselective manner, affording a 72:28 mixture of **3bE** and **3′bE** (Table 1, entry 6). These results suggested a significant role of the electronic factors in the stereochemical course of the reactions. Compounds with substituents at the *ortho* position provided better stereoselectivity than those observed with the same substituent at the *para* position. Thus, **2F** (R^2 = *o*-ClC_6H_4) afforded a 92:8 mixture of **3bF** and **3′bF** (Table 1, entry 7). Differences between entries 5 and 7 can be explained by assuming that steric effects, which would increase as a consequence of the loss of planarity, also have an important role on the stereoselectivity. In this sense, compound **2G** (*o*-BrC_6H_4) evolved in a completely stereoselective manner, only yielding **3bG** (Table 1, entry 8), which could be attributed to the larger size of the bromine.

To broaden the scope of these reactions, we studied the behavior of **1b** with (*E*)-2-alkyl vinylsulfones (**2H–2J**). Reactions were completely stereoselective with primary (**2H**) and secondary (**2I**) alkyl residues (Table 1, entries 9 and 10), however, no conversion was observed with the *tert*-butyl derivative **2J** (Table 1, entry 11).[9] Finally, we also studied the reaction of **1b** with the 2-alkenyl derivative **2K** (Table 1, entry 12) for expanding the scope of the reaction and evaluating the 1,4 versus 1,6 addition. The reaction was completely regio- and stereoselective, only affording the 1,4 addition product **3bK** as a single diastereoisomer in good yield.

To check the influence of the steric effects on the stereoselectivity and extend the scope of the reaction, we investigated the behavior of compounds (*S*)-**1c–f** acting as precursors of different alkyl benzyl carbanions (Table 2). Their reactions with styrylphenylsulfone **2A** evolved in moderate

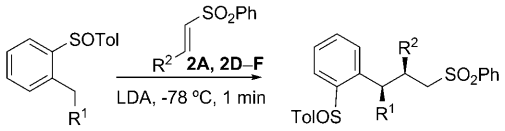
Table 1. Reactions of (*S*)-**1a** and (*S*)-**1b** with vinylsulfones **2A–K**.[a]



	Sulfoxide	R^1	R^2	Sulfone	Product (yield [%])	d.r. (**3**/**3′**)[b]
1	**1a**	H	Ph	**2A**	c.m.[c]	
2	**1b**	Me	Ph	**2A**	**3bA** (70)	> 98:2
3	**1b**	Me	*p*-$MeOC_6H_4$	**2B**	**3bB** (71)	> 98:2
4	**1b**	Me	2-naphthyl	**2C**	**3bC** (83)	> 98:2
5	**1b**	Me	*p*-ClC_6H_4	**2D**	**3bD** (71)	84:16
6	**1b**	Me	*p*-CNC_6H_4	**2E**	**3bE** (83)	72:28
7	**1b**	Me	*o*-ClC_6H_4	**2F**	**3bF** (68)	92:8
8	**1b**	Me	*o*-BrC_6H_4	**2G**	**3bG** (73	> 98:2
9	**1b**	Me	*s*Bu	**2H**	**3bH** (54)	> 98:2
10	**1b**	Me	*i*Pr	**2I**	**3bI** (59)	> 98:2
11	**1b**	Me	*t*Bu	**2J**	n.r.[d]	–
12	**1b**	Me	(*E*)-PhCH=CH	**2K**	**3bK** (62)	> 98:2

[a] All reactions were performed on a 0.4 mmol scale in 0.4 mL of THF and stopped after 1 min. [b] Diastereomeric ratio determined by NMR spectroscopy. [c] Complex mixture. [d] No reaction.

Table 2. Reactions of (*S*)-**1b–f** with vinylsulfones.[a]



	Sulfoxide	R^1	R^2	Sulfone	Yield [%]	Product [%]
1	**1c**	CH_2CH_3	Ph	**2A**	61	**3cA**
2	**1d**	benzyl	Ph	**2A**	59	**3dA**
3	**1e**	allyl	Ph	**2A**	54	**3eA**
4	**1f**	$CH_2CH_2C{\equiv}CH$	Ph	**2A**	47	**3fA**
5	**1d**	benzyl	*o*-ClC_6H_4	**2F**	58	**3dF**
6	**1d**	benzyl	*p*-ClC_6H_4	**2D**	61	**3dD**
7	**1d**	benzyl	*p*-CNC_6H_4	**2E**	77	**3dE**

[a] All reactions were performed on a 0.4 mmol scale in 0.4 mL of THF and stopped after 1 min.

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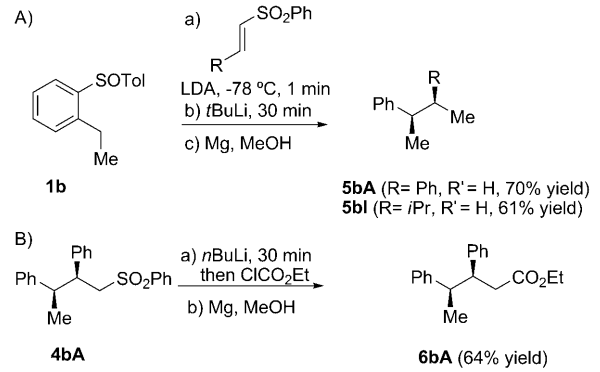
or good yields with complete stereoselectivity, regardless of the saturated (Table 2, entry 1), or unsaturated (Table 2, entries 2–4) character of the alkyl-chain at benzylic position. This reaction was compatible with the presence of acetylenic protons (Table 2, entry 4) by increasing the amount of LDA used (to 2.4 equiv). But the most interesting feature of these reactions was the substantial increase in the stereoselectivity observed when the size of the chain at the benzylic position (R^1 in Table 2) was larger than Me. Thus, reactions of **1d** (R^1 = Bn) with **2D**–**2F** afforded only one diastereoisomer, which is in contrast with the incomplete stereoselective evolution of these three vinylsulfones in their reactions with **1b** (Table 1, entries 5–7). This significant improvement could be a consequence of the increase in size of R^1.

Configurational assignment for compounds **3** was tentatively made from their NMR spectroscopy data (significant differences between the diastereoisomers of **3** and **3′**) and later unequivocally confirmed by X-ray analysis of compounds **3bB** and **3dA**[10] (see the Supporting Information).

The obtained compounds **3** could be easily transformed into desulfinylated product **4** by treatment with *t*BuLi.[11] After several trials, we checked that conditions of these reactions were also efficient when they were applied to the crude mixture of the reaction of **1** with **2**, which allowed the direct synthesis of **4** without isolating the sulfinyl derivatives **3**. Under the conditions of the "one-pot process", the obtained yields of **4** were much better than those obtained in the two-step sequence by isolation of compounds **3**.[12] We have checked the efficiency of these transformations in different cases and the results are shown in Table 3. Benzylation and desulfinylation took place in high yields in 30 min and very smooth conditions without epimerization of the chiral centers (Table 3, entries 1–3). One relevant point of this sequence was that a multigram scale can be applied to these processes. Thus, reaction of **1b** (1 g, 4.1 mmol) with **2A** (0.98 g, 4.0 mmol) and further treatment with *t*BuLi afforded **4bA** in 81% yield (Table 3, entry 4), after column chromatography to remove some impurities.

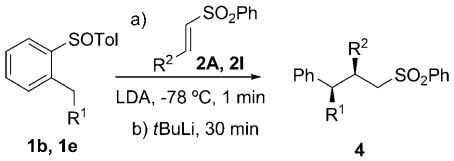
We have studied two applications of compounds **4** that illustrate their large synthetic possibilities. The first one, connected with the original goal of this paper, was the synthesis of hydrocarbons by removal of the sulfone group, and the second one was the preparation of esters, by taking advantage of the easy introduction of the functional groups on C-α of the sulfones. Removal of the sulfonyl groups at **4** can be made with Mg in MeOH,[13] without affecting the optical purity of the substrates (Scheme 3A). These reaction conditions could be applied to the crude reaction mixtures, yielding **4**, once liberated from the salts, thus affording hydrocarbons **5** in good yields and with complete stereoselectivity control. These reactions, involving subsequent benzylation, desulfinylation, and desulfonylation steps, have been studied in two cases. The first one provided the optically inactive *meso*-**5bA** from **1b** and **2A** in 70% yield. Compound **5bI**, obtained from **1b** and **2I** (61% yield), had an identical *ee* value to that of the starting sulfoxide **1b**.[14] We have also introduced the ester group at **4bA** before removal of the sulfonyl group by using a two-step procedure, yielding **6bA** in 64% yield (Scheme 3B).



Scheme 3. Synthesis of acyclic enantiomerically pure compounds with two connected stereogenic centers from **1b** and **4bA**.

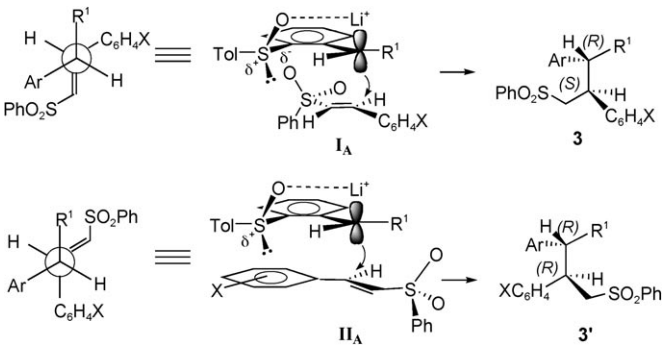
Stereochemical results can be explained by assuming that the chelated structure shown in Scheme 4, with the metal joined to the benzyllic carbon and the sulfinyl oxygen, is the most stable one for benzyllic carbanions derived from **1** (supported by theoretical calculations in the case of **1b**[15]).

Table 3. One-pot conversion of (*S*)-**1b** and **1e** with the vinylsulfone **2A** into desulfinylated compounds **4**.[a]



	Sulfoxide	R^1	R^2	Sulfone	Yield [%]	Product [%]
1	**1b**	Me	Ph	**2A**	75	**4bA**
2	**1e**	allyl	Ph	**2A**	91	**4eA**
3	**1b**	Me	*i*Pr	**2I**	71	**4bI**
4	**1b**	Me	Ph	**2A**	81[b]	**4bA**

[a] All reactions were performed on a 0.4 mmol scale in 0.2 mL of THF and finally stopped after 1 min. [b] This reaction was carried out in a 4.0 mmol scale in 1 mL of THF.



Scheme 4. Diastereoselectivity control in the formation of sulfones **3** and **3′**.

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Since Li is blocking the upper face of the carbanion, the electrophilic attack can only take place from the bottom face, thus yielding compounds with *R* configuration at the benzyllic carbon. Intermediates $\mathbf{I_A}$ and $\mathbf{II_A}$ (Scheme 4) are presumably the most stable approaches because they only exhibit two significant *gauche* interactions (Newman projections show the hydrogen atoms in antiperiplanar arrangement). Intermediate $\mathbf{I_A}$ must be favored by steric grounds (the two aryl groups adopt an antiperiplanar arrangement) and the repulsion between SO and SO_2 functions can be attenuated by the attractive interaction between positively charged sulfinyl sulfur and the negatively charged sulfonyl oxygen. Intermediate $\mathbf{II_A}$ would be only considered in those cases in which a stabilizing π–π stacking interaction between the two aromatic rings could be postulated (X = electron-withdrawing groups). In the rest of the cases (X = electron-donating groups and 2-alkyl sulfones) the repulsive steric interactions (Ar/Ar or R/Ar) are predominant and decrease the stability of the approach $\mathbf{II_A}$. The presence of *ortho* substituents at the aromatic ring distorts its planarity, thus decreasing the π–π stacking interaction and unstabilizing $\mathbf{II_A}$. On the other hand, the increase in the size of R^1 mainly reduces the stability of $\mathbf{II_A}$ because the interaction R^1/SO_2Ph (Scheme 4) is larger.

In summary, optically pure hydrocarbons with two connected stereogenic centers can be directly obtained from easily available 2-*p*-tolylsulfinylarenes and (*E*)-2-substituted vinylsulfones in a sequence involving benzylation–desulfinylation with *t*BuLi (one-pot process), followed by desulfonylation with Mg/MeOH.

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Keywords: asymmetric hydrogenation · asymmetric synthesis · carbanions · remote stereocontrol · vinylsulfones

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[8] According to the mass spectra, a signal at 719 was detected between others, indicating the double addition of these carbanions.

[9] To obtain quaternary centers, reactions of the sulfinylcarbanion derived from **1b** with β,β-disubstituted-vinylsulfones were also investigated. However, only starting materials could be identified in the crude mixtures obtained under similar conditions to those used in the reactions given in Tables 1 and 2.

[10] CCDC-765581 (**3bB**) and 765582 (**3dA**) 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.

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[12] Difficulties associated with the isolation of the highly polar compounds **3** are circumvented in the one-pot reactions by obtaining the less-polar compounds **4**, thus explaining the observed improvements in the yields.

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