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Highly Stereoselective Synthesis of Tertiary Propargylic Centers and Their Isomerization to Enantiomerically Enriched Allenes

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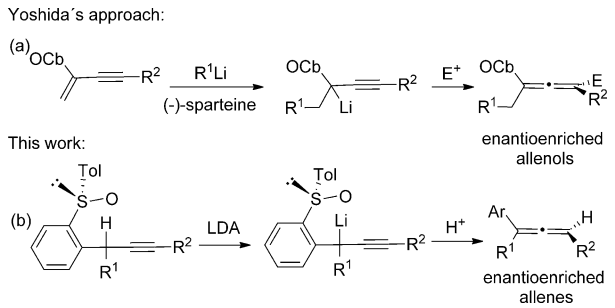
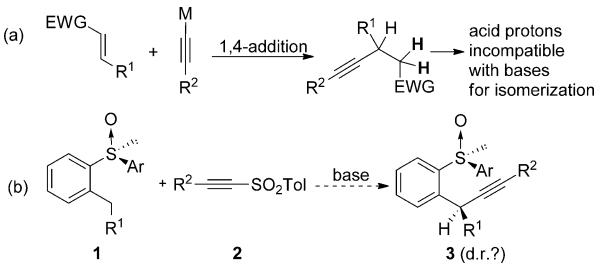
Allenes are important compounds that exhibit axial chirality[1] and are present in a large number of medicinal and natural products.[2] One of the most frequently used methods for obtaining racemic allenes involves the isomerization of propargylic centers.[3] However, it is surprising that this method has rarely been used for preparing enantiomerically pure compounds, probably due to the rather poor results obtained in its application. Thus, the few examples reported for the synthesis of allenols using chiral auxiliaries are minimally successful,[4] and only moderate enantiomeric excess (*ee*) has been achieved with organocatalytic methods.[5] Very recently Yoshida et al. reported one of the best procedures for the synthesis of allenols (74 to 92% *ee*), which is based on the method previously published by Hoppe and co-workers.[6] It consists of the carbolithiation of 2-OCb (OCON*i*Pr$_2$) conjugated enynes in the presence of stoichiometric (−)-sparteine, followed by addition of the resulting propargylic anions to electrophiles to give the corresponding allene derivatives (Scheme 1a). The key to the success of this nice transformation seems to be related to the chemical and configurational stability of the propargylic lithium carbanion by association with the OCb group and the (−)-sparteine, which is used in stoichiometric amounts. These results suggest that the main difficulty for obtaining enantiomerically enriched allenes by isomerization of compounds with chiral propargylic centers of a defined configuration is due to the configurational stabilization of the propargylic carbanion intermediates.



Scheme 1. Approaches used in the synthesis of enantioenriched allenes.

In recent years, we have reported that an *ortho*-sulfinyl group is able to provide a high configurational stabilization to differently substituted benzylic anions, allowing them to react with various electrophiles in an almost completely stereoselective manner.[7] From these results we hypothesized that *ortho*-sulfinyl benzylcarbanions containing acetylenic moieties joined to the benzyl carbon would be able to evolve in a highly stereoselective manner into enantiomerically enriched allenes due to the configurational stabilization provided by the sulfinyl group (Scheme 1b). To confirm this hypothesis, it was necessary to prepare the propargylic precursors shown in Scheme 1. The results obtained in these two fields, synthesis of alkynes and their isomerization into trisubstituted allenes,[8] are presented herein.

The preparation of enantiomerically pure tertiary propargylic centers can be achieved by the nucleophilic addition of acetylenic residues to proper electrophiles such as enones,[9] enals,[10] nitroalkenes,[11] Meldrum's acid derivatives,[12] and thioamides.[13] In all these cases, the acetylenic moiety is supported by the reagent acting as nucleophile, and the electrophile contains an electron-withdrawing group (EWG) to allow the conjugate addition (Scheme 2a). As the acidity of the α protons to these groups could interfere with the abstraction of the propargylic protons required for the isomerization to the allene, the resulting compounds from these routes are not appropriated for our study.



Scheme 2. Asymmetric synthesis of propargylic centers.

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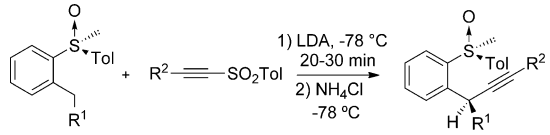
Our group has recently published that arylsulfonylacetylenes, such as **2**, can act as alkynylating reagents of Csp^2–H and Csp^3–H bonds due to their unexpected electrophilic behavior when they react with aryllithiums at the α carbon, resulting in the formation of alkynes by elimination of $ArSO_2^-$.[14] As this reaction seemed to be efficient for creating $C(sp^3)$–C(sp) bonds, we wondered if it would be also successful in enantioselective generation of propargylic centers starting from configurationally stabilized carbanions, such as the 2-*p*-tolylsulfinyl benzylalkyl carbanions derived from **1**. These reactions would provide enantiomerically enriched alkynyl derivatives **3**, lacking of the EWG groups, and therefore suitable for the isomerization studies (Scheme 2b).

Reaction of enantiomerically pure **1A** (0.4 mmol, 98% *ee*) with sulfone **2a** in the presence of LDA at −78 °C (see the Supporting Information for screening details, Table S-1) and final protonation with NH_4Cl at −78 °C, yielded the alkynyl derivative **3Aa** in 64% yield as a single diastereomer (diastereomeric ratio (d.r.) >98:2 by NMR spectroscopy and 98% *ee* by HPLC). When the reaction was carried out on larger scales (2.0 mmol), **3Aa** was obtained with similar yield and complete diastereoselectivity (compare entries 1 and 2, Table 1). Next, we investigated the scope of this reaction with different arylsulfonylalkynes (**2a–i**) and different sulfoxides (**1A–E**; Table 1). The reaction was successful for electrophiles containing electron-donating (*p*-MeO, *p*-Me, Table 1, entries 3 and 4) and electron-withdrawing (*p*-F, entry 5) groups on the aryl aromatic ring of the alkyne, including those with *ortho* substitution (*o*-Cl, entry 6). Reactions of acetylenes containing an alkyl chain were unsuccessful, affording only the starting material (Table 1, entry 7), likely due to competitive deprotonation of the propargylic position. This explanation is further supported by the fact that *tert*-butyl derivative **2h**, lacking acidic protons, gave the addition product **3Ah** in 60% yield (Table 1, entry 8), despite the large size of the *t*Bu group. The reaction with **2i** was analogously successful (entry 9), with an 84% yield for **3Ai** under the standard conditions. Finally, we studied the influence of R^1 on the reaction, obtaining similar yields with different alkyl groups (**1B–E**) and with complete diastereoselectivity (only one diastereoisomer was detected by NMR spectroscopy). The structure and absolute configuration (S*S*, 3*R*) of **3Aa** were unequivocally established by using X-ray analysis (Figure 1).[15] This assignment was then extended to all the alkynyl derivatives **3**.

Table 1. Reactions of the sulfoxides **1A–E** with alkynes **2a–i**.[a]



Entry	R^1	R^2	Yield [%] (product)	d.r.[b]
1	Me-**1A**	C_6H_5-**2a**	64 (**3Aa**)	>98:2
2	Me-**1A**	C_6H_5-**2a**	60 (**3Aa**)[c]	>98:2
3	Me-**1A**	*p*-$MeOC_6H_4$-**2b**	57 (**3Ab**)	95:5
4	Me-**1A**	*p*-MeC_6H_4-**2c**	63 (**3Ac**)	>98:2
5	Me-**1A**	*p*-FC_6H_4-**2d**	49 (**3Ad**)	>98:2
6	Me-**1A**	*o*-ClC_6H_4-**2e**	72 (**3Ae**)	>98:2
7	Me-**1A**	Et-**2f**	–[d]	–
8	Me-**1A**	*t*Bu-**2h**	60 (**3Ah**)	92:8
9	Me-**1A**	TIPS-**2i**	84(**3Ai**)	92:8
10	Et-**1B**	C_6H_5-**2a**	52 (**3Ba**)	>98:2
11	*n*Bu-**1C**	C_6H_5-**2a**	65(**3Ca**)	>98:2
12	allyl-**1D**	C_6H_5-**2a**	58 (**3Da**)	>98:2
13	benzyl-**1E**	C_6H_5-**2a**	68 (**3Ea**)	>98:2

[a] All reactions were performed on a 0.4 mmol scale. [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] Reaction carried out at 2.0 mmol scale. [d] Recovered starting material.

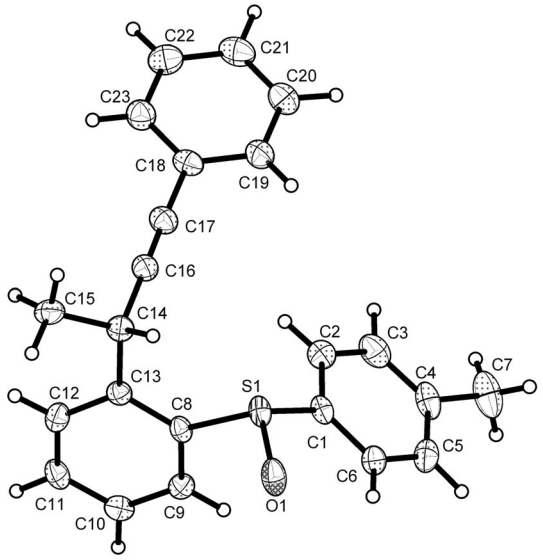
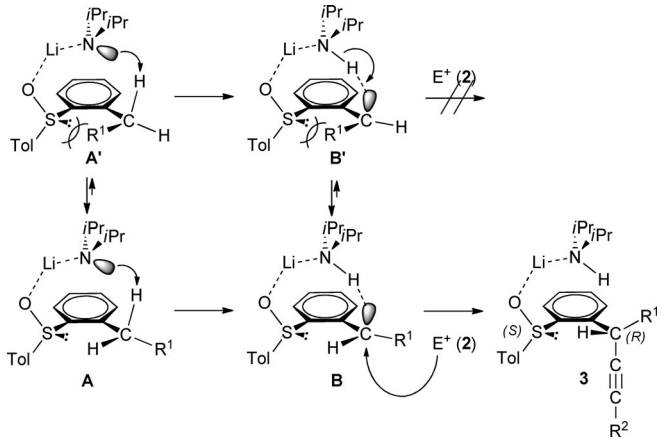


Figure 1. X-ray ORTEP of compound **3Aa**.

The main conclusion deduced from these results is that the alkynylation reaction of β-substituted electrophilic sulfone (**2**) with 2-*p*-tolylsulfinyl benzylcarbanions derived from **1** proceeds with complete stereochemical control, thus providing a new entry for the synthesis of compounds with enantiomerically pure benzyl propargylic centers.[16] It is worth noting that the alkyne moiety shows umpolung reactivity; it is usually employed as nucleophile,[9–13] however in this case it acts as an electrophile.

The stereochemical results obtained in these reactions can be explained as follows. According to theoretical calculations,[17] the sulfinylated benzylcarbanion should adopt the structure **B** (Scheme 3), stabilized by a hydrogen bond formed with the aminic nitrogen of the iPr_2NH, whose nitrogen acts as ligand of the lithium cation. This would result in the stereoselective deprotonation of compounds **1** (they mainly adopt the **A** conformation, because the **A′** conformation is relatively destabilized by steric reasons) with the LDA used as base, which is previously associated to the sulfinyl oxygen (Scheme 3). The approach of the electrophile to the lower face of **B** (the upper face would be hindered by the amine) would result in the formation of the diastereoiso-

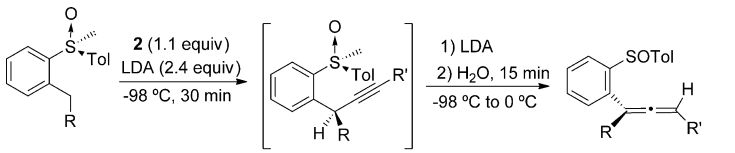


Scheme 3. Stereochemical proposal for explaining alkynylation reactions.

mers **3**, with *R* configuration at the benzylic carbon. In case that deprotonation was not highly stereoselective, thus yielding **B** and **B′**, their equilibration (with **B** favored by steric reasons) could also explain the stereochemical results.[18]

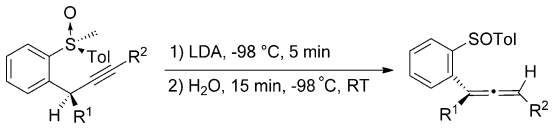
Having obtained compounds **3**, we studied their isomerization to chiral allenes **4** by deprotonation with lithium bases at the benzyllic position (Table 2). We studied the influence of the base (NaHDMS, LiHDMS, LDA), temperature (RT to −98 °C), and solvent (THF, Et_2O, CH_2Cl_2, toluene). The best stereochemical results for **3Aa** were obtained by using LDA as the base in THF at −98 °C, and H_2O as the proton source (see the Supporting Information for screening details, Table S-2). Under these conditions, optically enriched allene **4Aa** was obtained in good yield (71 %) and d.r. = 95:5 (entry 1, Table 2). Almost identical results were achieved when the reaction was performed on higher scales (starting from 1.15 mmol of **3Aa**, Table 2, entry 2). Other alkynyl derivatives **3** exhibit a similar behavior under these conditions, to afford **4** in good yields and stereoselectivities (Table 2). In most cases, the diastereomeric ratio was higher than 90:10, even in cases with alkyl groups different to Me at the benzylic position (entries 9–12). It is worth noting that the negative influence exerted by steric effects, which decreases the reactivity of the substrates with bulkiest groups (a lower conversion was shown for **3Ah** (Table 2, entry 7) and no reaction for **3Ai** (entry 8)) and the stereoselectivity (entry 7). Strong EDG, such as OMe (Table 2, entry 3), also decrease the stereoselectivity.

Finally, we carried out a one-pot procedure for the direct preparation of allenes **4** from 2-*p*-tolylsulfinyl benzylcarbanions derived from **1** (Scheme 4), avoiding isolation of the alkyne intermediates. Treatment of **1A** and **1D** with LDA (2.4 equiv) at −98 °C in the presence of **2a**, followed by addition of H_2O at the same temperature afforded the allenes **4Aa** and **4Da**, respectively, in good yields and diastereomeric ratios. Similar results were obtained by reaction of **1A** with **2c**, yielding **4Ac**. In all these cases, the stereoselectivity was identical to that obtained in Table 2 and the yields clearly higher than those obtained in two steps from **1** (Tables 1 and 2).



Scheme 4. One-pot synthesis of allenes **4**.

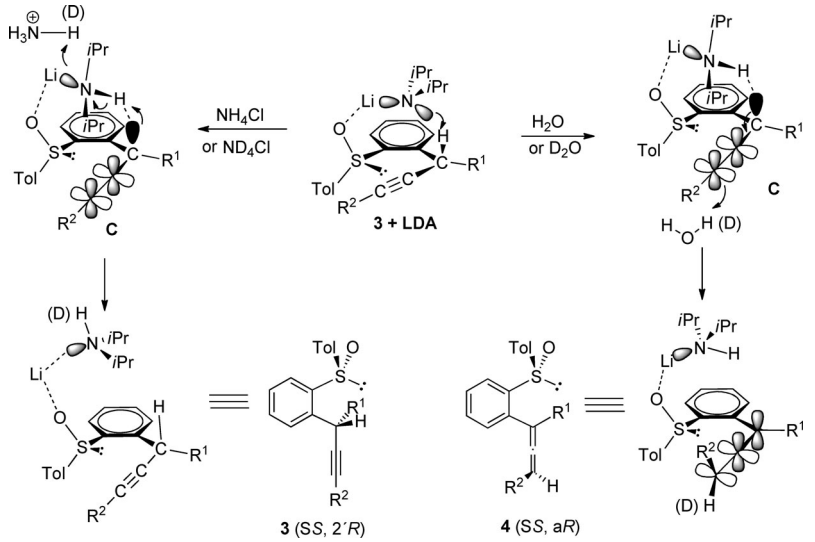
Table 2. Isomerization of alkynes **3** into allenes **4**.[a]



Ent	R^1/R^2-Starting Material	Yield [%] (product)	d.r.[b]
1	Me/C_6H_5-**3Aa**	71 (**4Aa**)	95:5
2	Me/C_6H_5-**3Aa**	67 (**4Aa**)[c]	95:5
3	Me/*p*-$MeOC_6H_5$-**3Ab**	70 (**4Ab**)	81:19
4	Me/*p*-MeC_6H_5-**3Ac**	75 (**4Ac**)	90:10
5	Me/*p*-FC_6H_5-**3Ad**	83 (**4Ad**)	93:7
6	Me/*o*-ClC_6H_5-**3Ae**	72 (**4Ae**)	>98:2
7	Me/*t*Bu-**3Ah**	45 (**4Ah**)[d]	75:25
8	Me/TIPS-**3Ai**	–	n.r.[e]
9	Et/C_6H_5-**3Ba**	48 (**4Ba**)	94:6
10	*n*Bu/C_6H_5-**3Ca**	58 (**4Ca**)	95:5
11	allyl/C_6H_5-**3Da**	69 (**4Da**)	90:10
12	benzyl/C_6H_5-**3Ea**	77 (**4Ea**)	95:5

[a] All reactions were performed on a 0.12 mmol scale starting from sulfoxides with the indicated diastereoselectivity in Table 1. [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] Reaction carried out at 1.15 mmol scale. [d] Conversion measured by ^1H NMR spectroscopy because this compound was unstable under flash chromatography. [e] n.r. = No reaction.

These results indicate that the regioselectivity of the protonation seems to be completely dependent on the reaction conditions. According to our previous DFT calculations,[17] *ortho*-sulfinylated benzyl carbanions are strongly stabilized by forming a hydrogen bond with iPr_2NH after the abstraction of the proton (Scheme 4). Starting from compounds **3**, and taking into account the lower size of the alkynyl group with respect to R^1, the presumably most stable structure of the benzylic carbanion is **C** (Scheme 5). Due to conjugation, propargylic carbanions are species with two basic centers, the propargylic C(sp^3) and the alkynylic C_β(sp), which are both susceptible to protonation. To explain the formation of the alkynyl derivatives with NH_4Cl (indicating protonation is taking place on the propargylic C(sp^3)), we postulate that this acid protonates the nitrogen of the amine, which indirectly produces the protonation at propargylic carbon with complete retention of the configuration of the carbanion[19] (Scheme 5). This is supported by the results obtained with ND_4Cl, which did not produce deuterated alkynes. The lower acidity of the water makes difficult the protonation at

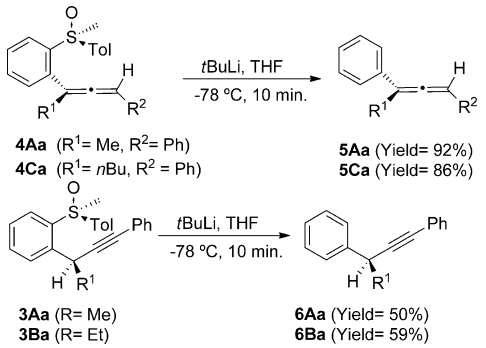


Scheme 5. Tentative mechanism for the formation of allenes **4**.

In conclusion, we have presented a new conceptually different approach for the synthesis of enantiomerically enriched propargylic centers, involving the incorporation of alkynyl moieties into electrophilic reagents. Our method involves the reaction of *ortho*-sulfinylated benzyllithiums with β-substituted sulfonylacetylenes. In addition, the obtained propargylic substrates can be stereospecifically isomerized into allenes, due to the chemical and configurational stabilization exerted by the sulfinyl group on the propargylic benzylcarbanion.

the nitrogen,[20] and the reaction course is different. In this case, the incorporation of the proton must take place at the favored C_β, thus affording allenes. The high stereoselectivity observed in this reaction must be explained taking into account the desymmetrization of the two π bonds forming the triple bond produced by the conjugation with the carbanion. Only the π bond adopting a parallel orientation with respect to the orbital containing the lone electron pair (which has a defined orientation) will be electron-rich and therefore susceptible to protonation. The favored approach of the H_2O will take place to the lower face, thus avoiding steric interactions with the amine blocking the upper face, resulting in the stereoselective formation of allenes **4** with the configuration (a*R*). This explanation is also supported by the incorporation of deuterium to C3 observed when D_2O is used as reagent. This fact, as well as the high stereoselectivity observed, would be difficult to explain by assuming the formation of a free carbanion. The different protonation site for H_2O (C_β at triple bond) and NH_4Cl (propargylic carbon) would also explain that the large size of the substituents at triple bond, like *t*Bu and TIPS, only affects negatively the reactivity of the process yielding allenes (entries 7 and 8, Table 2).[21]

Removal of the sulfinyl group of compounds **3** and **4** can be easily performed by reaction of these substrates with *t*BuLi (Scheme 6) without erosion in the optical purity of the resulting alkynes and allenes. Allenes **5Aa** and **5Ca** were obtained in almost quantitative yields from **4Aa** and **4Ca**, respectively, whereas alkynes **6Aa** and **6Ba** resulted in reactions from **3Aa** and **3Ba**, respectively (Scheme 6). The absolute configuration (S*S*, a*R*) of **4Ca** was established by chemical correlation and comparison of optical rotation of **5Ca**, which is a compound of known configuration[22] (see the Supporting Information for more details). This assignment was then extended to all the allene derivatives **4**.



Scheme 6. Desulfinylation reactions of allenes (**4**) and alkynes (**3**).

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Keywords: allenes · anti-michael addition · propargylic centers · sulfonylacetylenes · sulfoxides

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[15] CCDC-790355(**3Aa**) contains the supplementary crystallographic data for this paper (also see the Supporting Information for details). 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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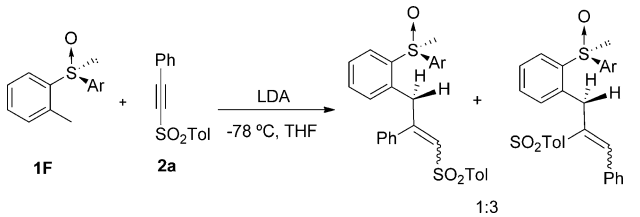
[18] Results obtained in the reaction of the 2-*p*-tolylsulfinyltoluene **2F** with sulfinylacetylene **2A**, in the presence of LDA, were surprising. We did not observe the formation of the expected alkyne, but a mixture (1:3) of the olefins resulting in the Michael and anti-Michael additions of the carbanion to the triple bond were observed. On the other hand, the fact that the "anti-Michael product" did not evolve into the alkynyl derivative would be explaining by assuming the quick transformation of the primary olefinic anion into the allenyl carbanion, stabilized by the sulfinyl group.



[19] This proposal is also in agreement with the fact that all the trials to epimerize the benzylic center of enantiomerically pure **3Aa** have been unsuccessful because the processes of deprotonation and protonation are both stereoselective, obtaining, in all cases, the original configuration.

[20] Additionally, the retention of configuration at the benzylic center observed in the transformation (see Scheme 5) supports that protonation takes place on the nitrogen atom.

[21] The lower stereoselectivity observed in the reaction of the *t*Bu alkyne (entry 7, Table 2) could be attributed to steric effects, which could difficult the stabilization of the anion by association. This effect, but to a lesser extent, is also observed in the alkyne formation (entries 8 and 9, Table 1) in which the stereoselectivity control is not complete for substrates **2h** and **2i** (d.r. 92:8).

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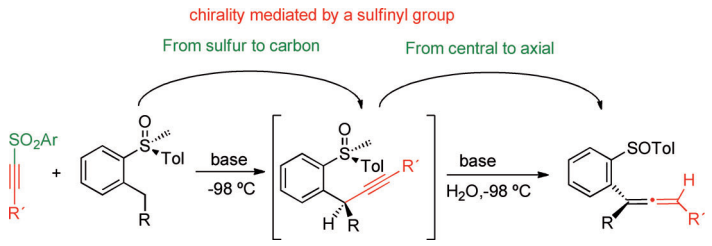
Synthetic Methods

J. L. García Ruano, L. Marzo, V. Marcos, C. Alvarado, J. Alemán** ..... ▮▮▮▮–▮▮▮▮

Highly Stereoselective Synthesis of Tertiary Propargylic Centers and Their Isomerization to Enantiomerically Enriched Allenes



Center of attention: A new approach for the synthesis of enantiomerically enriched allenes by isomerization of 2-*p*-tolylsulfinylphenyl propargylic derivatives is presented, which in turn are prepared by reaction of sulfinylated lithium benzylcarbanions with arylsulfonylacetylenes (see scheme). The high control of stereoselectivity in both steps is exerted by the sulfinyl group.

