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Diastereoselective Synthesis of Enantiopure Acyclic β,β′-Disubstituted Vinylsulfoxides

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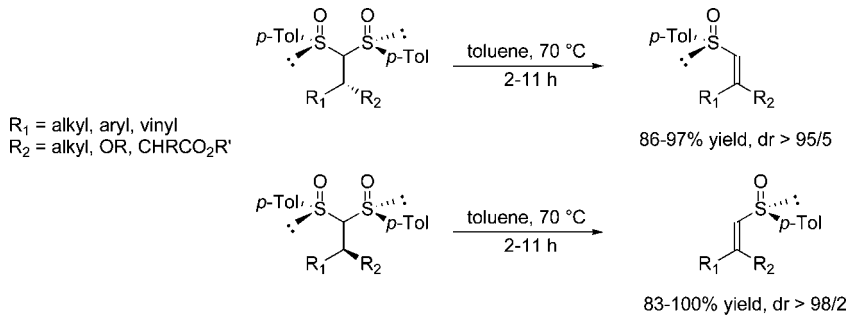
ABSTRACT



Thermal elimination of sulfenic acid from enantiopure β,β′-disubstituted bis-sulfoxides allows the stereoselective synthesis of enantiopure acyclic β,β′-disubstituted vinylsulfoxides. This mild and stereospecific synthesis provides either (*E*) or (*Z*) vinylsulfoxides in high yields and is compatible with acid or base sensitive functional groups.

Vinylsulfoxides are valuable intermediates in asymmetric synthesis as demonstrated by the many studies concerning their use as inductors of chirality.[1] For example, they are efficient partners in Diels−Alder reactions,[2] [2 + 2] and 1,3-dipolar cycloadditions,[3] Pauson−Khand reactions[4]and [3,3]-sigmatropic shift[5] and are powerful Michael acceptors in radical or anionic conditions.[2a,6] Vinylsulfoxides have also served as precursors of functionalized allenes whether by a radical or an organometallic route[7] and as monomers for anionic polymerization to give asymmetric star polymers.[8] Recently, also, an enantiopure vinylsulfoxide has been used as a key building block in the total synthesis of (+)-aspidospermidine.[9] Whereas numerous syntheses of enantiopure β-monosubstituted vinylsulfoxides have been developed,[10] only few methods allow the regio- and stereoselective preparation of their β,β′-disubstituted analogues and especially in acyclic series.[11] These methods are based mainly on the addition of an organometallic species (Cu,[11a,e] Zn,[11c]

(1) For recent reviews: (a) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559–5601.

(2) (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760, and references cited therein. (b) Carreño, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem.−Eur. J.* **2003**, *9*, 4118–4131, and references cited therein.

(3) [2 + 2]: (a) Bienaymé, H.; Guicher, N. *Tetrahedron Lett.* **1997**, *38*, 5511–5514. (b) Loughlin, W. A.; Rowen, C. C.; Healy, P. C. *J. Org. Chem.* **2004**, *69*, 5690–5698. (c) Loughlin, W. A.; Rowen, C. C.; Healy, P. C. *Synthesis* **2005**, 2220–2226, and references therein1,3-Dipolar: (d) Chaigne, F.; Gotteland, J.-P.; Malacria, M. *Tetrahedron Lett.* **1989**, *30*, 1803–1806. (e) Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M. *Tetrahedron* **1999**, *55*, 14791–14802. (f) Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–987. (g) Louis, C.; Hootele, C. *Tetrahedron: Asymmetry* **1997**, *8*, 109–131.

(4) Rivero, M. R.; Alonso, I.; Carretero, J. C. *Chem.−Eur. J.* **2004**, *10*, 5443–5459, and references cited thereins.

(5) (a) Marino, J. P. *Pure Appl. Chem.* **1993**, *65*, 667–674. (b) Alayrac, C.; Fromont, C.; Metzner, P.; Anh, N. T. *Angew. Chem., Int. Ed.* **1997**, *36*, 371–374.

(6) (a) Lacôte, E.; Delouvrié, B.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2116–2118. (b) Marino, J. P.; Viso, A.; Lee, J.-D.; Fernandez de la Pradilla, R.; Fernandez, P.; Rubio, M. B. *J. Org. Chem.* **1997**, *62*, 645–653. (c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377–10441, and references cited therein.

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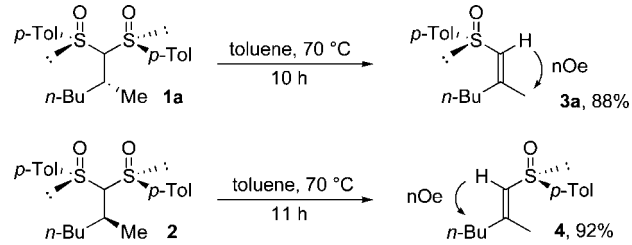
Te[11d]) to an acetylenic sulfoxide and proceed in good yield and stereoselectively. However, they are essentially limited to the formation of C−C bonds[12] and are not compatible with bases or reducing agent sensitive functional groups. Acyclic vinylsulfoxides substituted by a heteroatom (O, N, S) in the β position have also drawn a lot of attention, but only a few syntheses are stereoselective. In this context, there is still a need to develop a mild and neutral synthesis which enables us to prepare acyclic β,β'-disubstituted vinylsulfoxides bearing not only alkyl and aryl but also heteroatomic substituents in good yield and with high stereocontrol.

We recently reported the diastereoselective Michael addition of nucleophiles and radicals onto alkylidene bis-sulfoxides[13] affording enantiopure β,β'-disubstituted bis-sulfoxides.[14,15] In the course of these studies, we noticed some adducts were prone to spontaneously β-eliminate a molecule of sulfenic acid at room temperature to generate β,β'-disubstituted vinylsulfoxides (Scheme 1).[14,15] Although the β-elimination of sulfenic acid has been extensively studied[16] and has found applications for the synthesis of alkenes or α,β-unsaturated carbonyls,[17] only a limited number of examples involved bis-sulfoxides.[18] Interestingly, Trost described two examples of condensation of the lithium anion of bis(phenylsulfinyl)-methane with a primary alkyl halide followed by in situ elimination of sulfenic acid to afford only *E* vinylsulfoxides.[19] This encouraged us to investigate further this reaction as a potential new access to acyclic β,β'-disubstituted vinylsulfoxides.

In a first step, we tested the viability of our approach by studying the reactivity and the diastereoselectivity of the β-elimination. Our systems differ from others by the presence of a tertiary stereogenic carbon, and we designed different precursors to investigate its influence. The diastereoselectivity was examined from two diastereomeric bis-sulfoxides **1a**[15a] and **2**, prepared, respectively, by addition of MeCu·LiI and Me_3ZnLi on an alkylidene bis-sulfoxide. When heated at 70 °C in toluene, **1a** and **2** gave vinylsulfoxides **3a** and **4**, respectively, in high yield (Scheme 1). The double bond

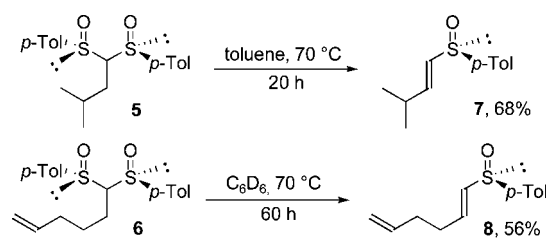
Scheme 1. Thermolysis of Diastereomeric β,β'-Disubstituted Bis-Sulfoxides: A Stereospecific Reaction



configurations were attributed by NOE and ^{13}C NMR γ-effect.[20] These reactions are completely stereospecific with regard to the carbon stereogenic center, and in both experiments, no trace of the other diastereomer was detected.

The β-elimination proceeded quite rapidly at moderate temperature,[21] and we examined if the steric strain in the starting material might play a significant role. Thus, we prepared bis-sulfoxide **5** by Meerwein−Ponndorf−Verley reduction of the adequate alkylidene bis-sulfoxide with lithium ethoxide, as well as **6** by condensation of the lithium anion of (S_S,S_S)-bis(*p*-tolylsulfinyl)methane onto 5-bromopentene. When heated at 70 °C, **5** and **6** afforded only the corresponding (*E*) vinylsulfoxides **7** and **8**, respectively, but with moderate yield and extended reaction time (Scheme 2). So the steric strain induced by both sulfoxide moieties and the substituents on the β-carbon would ease the elimination reaction, a finding which was already rationalized for simple sulfoxides by a steric destabilization of the starting material and release of the steric strain in the transition state.[16]

Scheme 2. Thermolysis of β-Monosubstituted Bis-Sulfoxides



(7) (a) Mouriès, V.; Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2002**, 1776–1787. (b) Varghese, J. P.; Knochel, P.; Marek, I. *Org. Lett.* **2000**, *2*, 2849–2852. See also: (c) Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776–11777.

(8) Zhao, Y.; Higashihara, T.; Sugiyama, K.; Hirao, A. *J. Am. Chem. Soc.* **2005**, *127*, 14158–14159.

(9) Marino, J. P.; Rubio, M. B.; Cao, G.; De Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399.

(10) Chernysheva, N. A.; Gusarova, N. K.; Trofimov, B. A. *Russ. J. Org. Chem.* **2000**, *36*, 1–23.

(11) (a) Truce, W. E.; Lusch, M. J. *J. Org. Chem.* **1978**, *43*, 2252–2258. (b) Alonso, I.; Carretero, J. C. *J. Org. Chem.* **2001**, *66*, 4453–4456. (c) Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345–1347. (d) Xu, Q.; Huang, X.; Ni, J. *Tetrahedron Lett.* **2004**, *45*, 2981–2984. (e) Xu, Q.; Huang, C.-Y. *Tetrahedron Lett.* **2004**, *45*, 5657–5660.

(12) Only rare examples of intermolecular addition of heteroatomic nucleophiles onto substituted acetylenic sulfoxides have been reported. See: (a) McMullen, C. H.; Stirling, C. J. M. *J. Chem. Soc. (B)* **1966**, *121*, 7–1220. (b) Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5550–5558.

(13) For the synthesis of alkylidene bis-sulfoxides see: Delouvrié, B.; Najera, F.; Fensterbank, L.; Malacria, M. *J. Organomet. Chem.* **2002**, *643−644*, 130–135.

(14) Brebion, F.; Vitale, M.; Fensterbank, L.; Malacria, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2889–2896.

(15) (a) Brebion, F.; Delouvrié, B.; Najera, F.; Fensterbank, L.; Malacria, M.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5342–5345. (b) Brebion, F.; Goddard, J.-P.; Louis Fensterbank, L.; Malacria, M. *Synthesis* **2005**, 2449–2452. (c) Brebion, F.; Goddard, J.-P.; Gomez, C.; Fensterbank, L.; Malacria, M. *Synlett* **2006**, 713–716. (d) For recent work on bis-sulfinyl derivatives: Goddard, J.-P.; Gomez, C.; Brebion, F.; Beauvière, S.; Fensterbank, L.; Malacria, M. *Chem. Commun.* **2007**, 2929–2931.

(16) (a) Cubbage, J. W.; Guo, Y.; McCulla, R. D.; Jenks, W. S. *J. Org. Chem.* **2001**, *66*, 8722–8736, and references cited therein. (b) McCulla, R. D.; Jenks, W. S. *J. Org. Chem.* **2003**, *68*, 7871–7879.

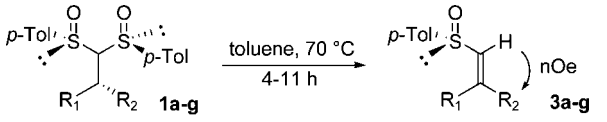
(17) (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363–382. (b) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453–461.

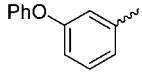
(18) (a) Carretero, J. C.; Garcia Ruano, J. L.; Martin Cabrejas, L. M. *Tetrahedron: Asymmetry* **1997**, *8*, 409–416. (b) Boivin, J.; Chauvet, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 4913–4916.

(19) Trost, B. M.; Bridges, A. J. *J. Org. Chem.* **1975**, *40*, 2014–16.

To determine the scope of this reaction, we performed the thermolysis of differently substituted bis-sulfoxides. First, we examined bis-sulfoxides **1a**−**g** prepared by conjugate addition of organocopper(I) reagents onto alkylidene bis-sulfoxides. The β-elimination proceeded with high yield and diastereoselectivity with alkyl, aryl, or functionalized substituents (Table 1). The reaction is finished after 4−11 h and

Table 1. Synthesis of β,β'-Disubstituted Vinylsulfoxides



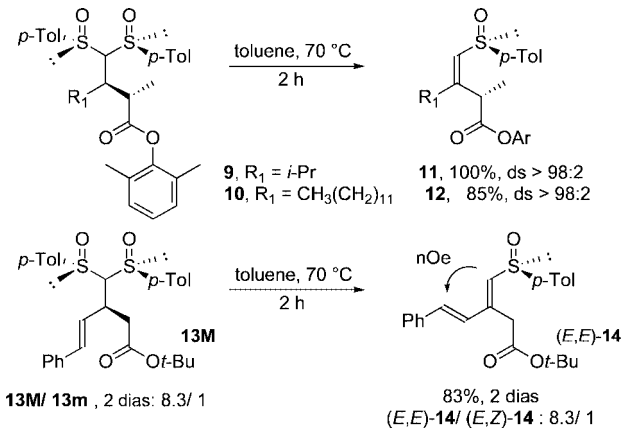
entry	R_1	R_2	product[a], yield (%)	dr[b]
1	*n*-Bu	Me	**3a**, 88	> 98:2
2	*i*-Pr	Me	**3b**, 86	95:5
3	*i*-Pr	*n*-Bu	**3c**, 86	96:4
4	CH_2OTBS	Me	**3d**, 54	> 98:2
5	Ph	Me	**3e**, 90[c]	> 98:2
6	Ph	*n*-Bu	**3f**, 89[c]	> 98:2
7		Me	**3g**, 97[c]	> 98:2

[a] Double bond configuration was determined by NOE. [b] Diastereoselectivity was determined by NMR. [c] Reaction is completed after 4−5 h.

is made easier by the formation of a π-conjugated system (Table , entries 5−7). The diastereoselectivity is complete except when R_1 is an isopropyl group (entries 2 and 3), but in these examples, the stereoselectivity remains superior to 95:5. Interestingly, the nature of R_1 and R_2 has no influence on the double bond configuration, and the sole stereochemistry of the stereogenic carbon seems to play a role which endows this reaction with a highly predictable outcome.

The reactivity of Michael adducts of ester enolates on alkylidene bis-sulfoxides was also investigated (Scheme 3).

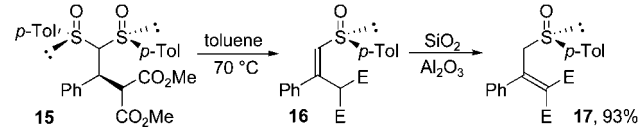
Scheme 3. Synthesis of Vinyl and Dienyl Sulfoxides Substituted by an Ester Group



When heated at 70 °C, **9**[15c] and **10**[15a] gave vinylsulfoxides **11** and **12**, respectively, with high yield and as unique products. The absence of double bond isomerization or epimerization demonstrates the compatibility of this reaction with base sensitive compounds. To the best of our knowledge, **11** and **12** are the first examples of vinylsulfoxides bearing a homochiral allylic stereogenic carbon in α position to an ester. We also applied this reaction to the synthesis of sulfinyl dienes. So an 8.3:1 mixture of two diastereomers **13M** and **13m** (epimers at the allylic position),[15c] differing only by the absolute configuration of the stereogenic carbon, gave the two dienes (*E*,*E*)-**15** and (*E*,*Z*)-**15** in a ratio of 8.3:1. Considering the previous results, it is reasonable to assume that each diastereomer gives only one diene, and the reaction is stereospecific.

In the same conditions, bis-sulfoxide **15** gave vinylsulfoxide **16** as the main product as indicated by the crude NMR (Scheme 4). Formally, **16** is equivalent to the addition

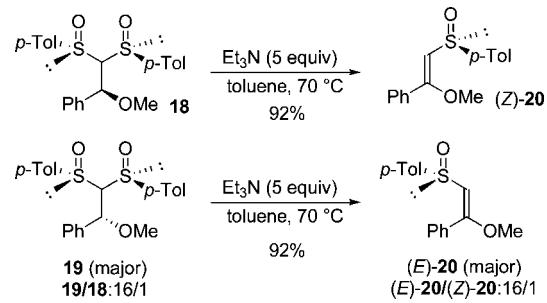
Scheme 4. Easy Isomerization into an Allylsulfoxide



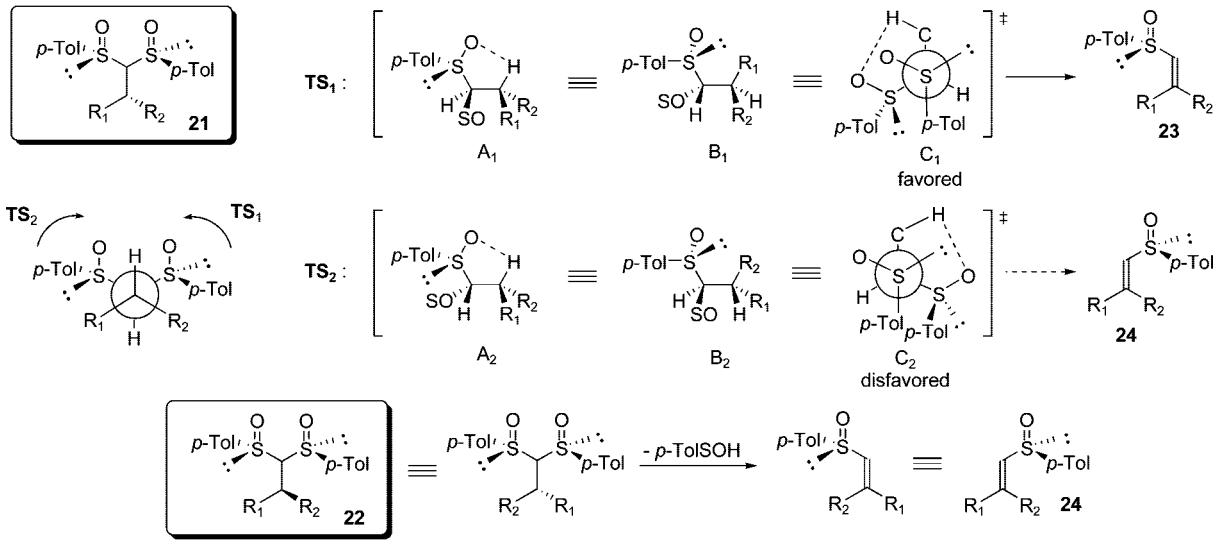
product of the malonate anion onto an acetylenic sulfoxide; such a reaction has never been reported so far. Our attempts to purify **16** by chromatography on silica or alumina were unsuccessful and led to the isomerization of the double bond to afford **17** in 93% yield. No analytical study was carried out to examine the possible racemization of the sulfur atom via a [2,3]-shift.[22]

The lack of efficient and stereoselective synthesis of acyclic β,β'-disubstituted vinylsulfoxides bearing an alkoxy substituent and the easy access to bis-sulfoxides of type **18** by conjugate addition of alkoxides onto alkylidene bis-sulfoxides[15a] prompted us to examine the thermolysis of diastereomers **18** and **19** as a straightforward synthesis of vinylsulfoxides **20**. The β elimination reactions took place but required triethylamine as an additive to scavenge the

Scheme 5. β,β'-Disubstituted Vinylsulfoxides Bearing an OR Moiety



Scheme 6. Proposition of a Diastereoselectivity Model



sulfenic acid formed during the reaction (Scheme 5). In the absence of Et_3N, only the keto sulfoxide resulting from acidic cleavage of **21** is isolated in low yield. The stereospecificity of this reaction is verified one more time, each bis-sulfoxide leading to a distinct vinylsulfoxide.

To rationalize our results, we propose the following model of diastereoselectivity (Scheme 6). Taking into consideration that both sulfoxides may participate to the *syn* concerted elimination, we envisaged for **21** the transition states TS_1 and TS_2. A*i*, B*i*, and C*i* are different views of TS*i* ($i = 1$ or 2). The geometric requirements for the planar five-centered transition state[16] are best depicted in A*i*. We propose that the sulfoxide which does not react adopts a conformation minimizing the steric interactions between its *p*-tolyl substituent and the eclipsed R group as represented in B*i*. Due to steric repulsion between the two *p*-tolyl groups, TS_2 is destabilized compared to TS_1 for which the interaction between a *p*-tolyl group and a lone pair is less (see C_1). A similar reasoning explains the formation of **24** starting from **22** (Scheme 6). This model based on steric hindrance explains the formation of vinylsulfoxides **23** or **24** and why the stereoselectivity is weakly influenced by the nature of R_1 or R_2. Thus, only the configurations of the stereogenic carbon and sulfur atoms play a part in the diastereoselectivity.

In summary, enantiopure acyclic β,β'-disubstituted vinyl sulfoxides are easily prepared from β,β'-disubstituted bis-sulfoxides. This mild, efficient, and stereospecific synthesis allows the formation of enantiopure disubstituted vinylsulfoxides bearing alkyl, aryl, base, or acid sensitive functional groups. The ease of synthesis of various bis-sulfoxides confers to this synthesis a broad scope. We envisage preparing vinylsulfoxides that would be substituted by various heteroatomic substituents (ether, thioether, amines) and should be interesting ligands in asymmetric catalysis and promising partners in cycloaddition reactions. Results of these investigations will be communicated in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Crews, P.; Rodriguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: New York, Oxford, 1998.

(21) Unless the elimination of sulfenic acid leads to a π-conjugate system, a temperature superior to 100 °C and extended reaction times are often required for simple vinylsulfoxides. For a discussion about factors influencing the thermal sulfoxide elimination, see ref 16.

(22) Allyl sulfoxides are known to racemize at room temperature via a [2,3]-sigmatropic shift, known as Evans−Mislow rearrangement. For a review, see: Braverman, S. In *The Chemistry of Sulfones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley: London, 1988; Chapter 14.