Pergamon

Tetrahedron Letters 40 (1999) 495–498

TETRAHEDRON LETTERS

Sulfoxides in Radical Chemistry. High 1,2-Asymmetric Induction in Radical Cyclizations

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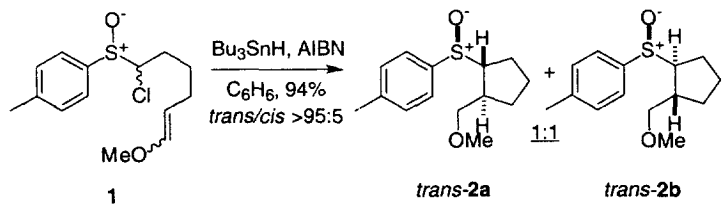
Received 23 October 1998; accepted 12 November 1998

Abstract: Very high levels of 1,2-asymmetric induction (>50:1) from the sulfur chiral center are reached for the cyclization of substituted 1-(*ortho*-chlorophenyl)sulfinyl-5-hexen-1-yl radicals. These reactions represent the first cases of high asymmetric 1,2-induction during cyclizations of non-stabilized sulfinylated alkyl radicals. They open promising perspectives for the synthesis of enantiomerically pure cyclic and polycyclic derivatives.

Radical reactions and in particular cyclizations and multiple cyclizations are becoming more and more popular in organic chemistry.[1] The diastereoselectivity of cyclization reactions is well understood and can be predicted with confidence by applying the Beckwith-Houk rules.[2] Enantiomerically pure compounds have been prepared by radical cyclizations under the control of different types of chiral auxiliaries.[3] The use of sulfoxides, easily available in enantiomerically pure form, as chiral template has been intensively investigated for carbanion alkylation, Michael addition and cycloadditions.[4] Radical reactions have also been investigated and excellent stereocontrol has been achieved with stabilized radicals derived from β-ketosulfoxides[5] and benzyl sulfoxides.[6] Simple sulfinylated alkyl radicals are of great synthetic interest, however, only low stereoselectivities have been obtained with these systems.[7-9] In an early work, we have reported, that the radical cyclization of the sulfoxide **1** produced a 1:1 mixture of the two possible *trans* isomers **2a** and **2b**. No control of the stereoselectivity from the sulfur chiral center was observed.[7a]

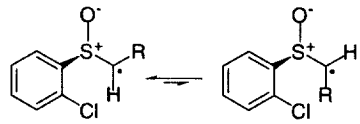


1 *trans*-**2a** *trans*-**2b**

A systematic investigation of the stereoselectivity of simple intermolecular reactions of sulfinylated alkyl radicals was undertaken.[7b-7e] The influence of the aryl moiety on the stereoselectivity of the process was studied. We found that good stereochemical control could be achieved with primary alkyl radicals when an

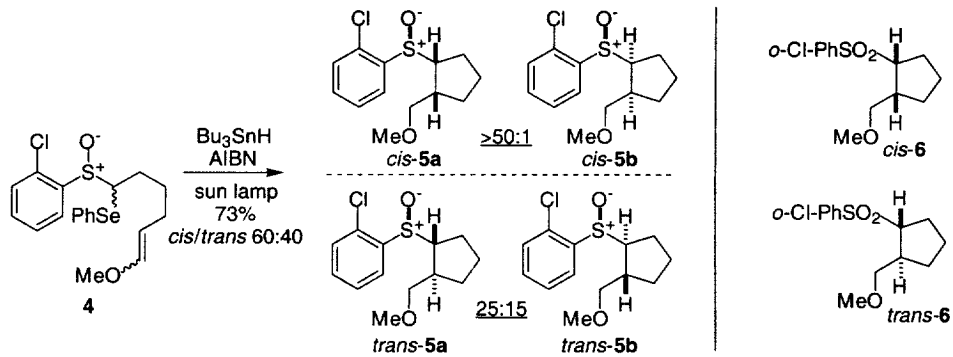
0040-4039/99/$ - see front matter
PII: S0040-4039(98)02420-4

ortho-chlorophenyl sulfoxide was used.[7e] The presence of an *ortho*-chlorine atom favors the *s-cis* conformation of the radical intermediate **3** relative to the *s-trans* conformer. We report here the extension of this strategy for the cyclization of sulfinylated alkyl radicals; the first examples of high stereoselectivities are reported .



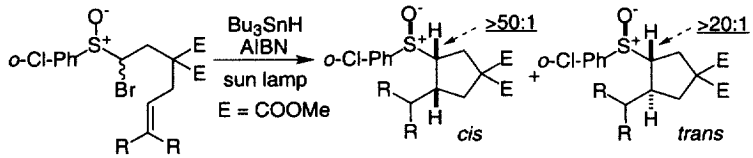
s-cis-**3** *s-trans*-**3**

The radical precursor **4**, an *ortho*-chlorinated analogue of **1**, was prepared in racemic form in order to test the effect of the aryl group modification on the stereochemisty of the cyclization process.[10] Irradiation of **4** in benzene at 10 °C in the presence of Bu_3SnH (1.0 equiv.) and AIBN (10 mol%) gave the cyclized product **5** as a 60:25:15 mixture of three diastereomers. These three diastereomers *cis*-**5a**, *trans*-**5a** and *trans*-**5b** were separated by semi-preparative HPLC. The fourth possible diastereomer *cis*-**5b** has not been detected. Oxidation of pure samples of *cis*-**5a**, *trans*-**5a** and *trans*-**5b** with *m*-CPBA afforded pure *cis* and *trans* sulfone **6**. Oxidation of the crude product gave the sulfone **6** as a *cis/trans* 60:40 mixture of isomers. The *cis* and *trans* configurations were assessed by ^{1}H-NMR using NOE difference spectra. The configurations relative to the sulfur center are not proved but are based on our model for the stereochemical outcome and also by analogy to the closely related examples described below. Interestingly, the *cis* isomer of **5** is formed with a complete 1,2-transfer of chirality from the sulfur atom (*cis*-**5a**/*cis*-**5b**, >50:1). The transfer of chirality is lower for the *trans* isomer (*trans*-**5a**/*trans*-**5b**, 25:15).



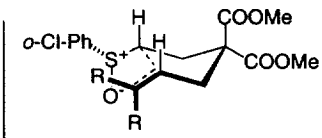
Systems which favor the formation of 1,5-*cis* disubstituted cyclopentanes were investigated next. Since the introduction of *gem*-disubstituents at position 3 is well known to favor the formation of 1,5-*cis* disubstituted cyclopentanes,[11] we decided to study the cyclization of the racemic precursors **7** and **8**, easily prepared from dimethyl malonate and 1-bromovinyl 2-chlorophenyl sulfoxide. Irradiation of **7** at 10 °C in benzene in the presence of AIBN and Bu_3SnH gave **9** in 73% yield as a mixture of two diastereomers in a 85:15 ratio. Oxidation of the crude **9** with *m*-CPBA gave the corresponding sulfone as a *cis/trans* 84:16 mixture. Cyclization of sulfoxide **8** under the same conditions gave **10** as a mixture of two diastereomers in a ratio 87:13. After separation of the two isomers of **10** by chromatography, crystals suitable for an X-ray analysis were obtained by recrystallization of the major isomer in hexane at -20°C. It has the relative

configuration shown in formula *cis*-**10a**.[12] Oxidation of crude **10** gave the sulfone as a *cis*/*trans* 87:13 mixture. This allows to conclude that with both radical precursors **7** and **8**, the 1,2-induction from the chiral sulfur center was excellent since no trace of the minor isomers **9b** and **10b** was detected. The relative configurations of the major isomers of **5** and **9** have not been proved but we assume that the topicity is similar for all reactions; therefore, by analogy to *cis*-**10a**, they should possess the configurations *cis*-**5a** and *cis*-**9a**.

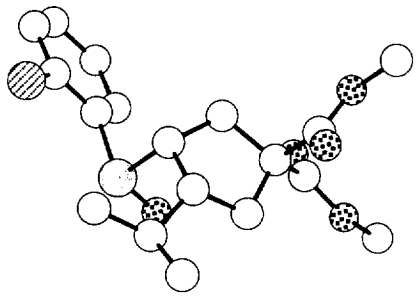


7 (R = H)
8 (R = Me)

9a (R = H, 73%, *cis*/*trans* 86:14)
10a (R = Me, 68%, *cis*/*trans* 83:17))



A chair-like transition state with *s-cis* conformation (→ *cis*-**a**)



X-Ray crystal-structure analysis of *cis*-**10a**

The preferential formation of *cis*-**9a** and *cis*-**10a** is explained by a preferential chair-like transition state **A** (Figure 2) according to the Beckwith-Houk model.[2] The very high 1,2-induction from the sulfur chiral center (>50:1 for the *cis* isomers) can be rationalized by the preferential *s-cis* conformation of the sulfinyl radical as predicted from our *ab initio* calculations (model **A**)[7e] and by preferential radical addition *anti* to the *o*-chlorophenyl moiety.

In summary, we have demonstrated that *ortho*-chlorophenyl sulfoxides can induce excellent 1,2-asymmetric induction in radical cyclizations. The second stereogenic center formed in the cyclization process can also be controlled according to Beckwith-Houk model. Application of such processes into multiple cyclization reactions (cascade processes) opens a very promising access to enantiomerically pure polycyclic carbocyclic and heterocyclic frameworks. Work in this direction is currently in progress in our laboratory and will be reported in due course.

Acknowledgments. This work was funded by the "Office Fédéral de l'Education et de la Science (OFES)" within a European cooperation program COST-D2 and by the "Fonds National Suisse de la Recherche Scientifique".

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