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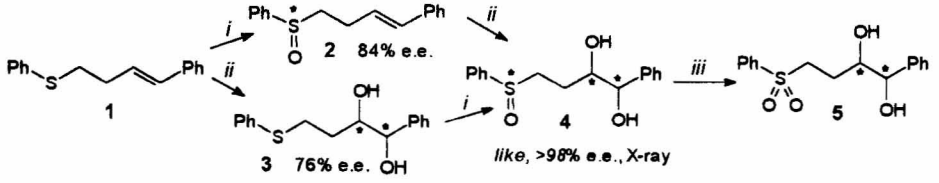
SEQUENTIAL STEREOSELECTIVE OXIDATIONS: SIMPLE ROUTES TO ENANTIOMERIC γ-HYDROXYSULFOXIDES

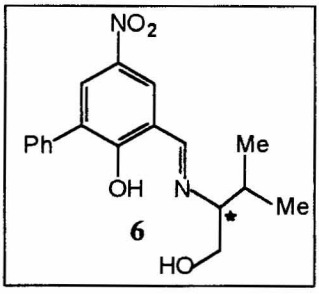
Abstract: New synthetic approaches to the enantiomeric hydroxysulfoxides are presented. The first one is based on the sequential asymmetric dihydroxylation and sulfoxidation of homoallylic sulfides. The second approach takes advantage of the highly enantioselective addition of thiophenol to enones. Subsequent reduction and stereoselective sulfoxidation allow the practical preparation of all corresponding chiral hydroxysulfoxides. Thus obtained products, derivatives with three stereogenic centers can be further transformed documenting their synthetic utility.

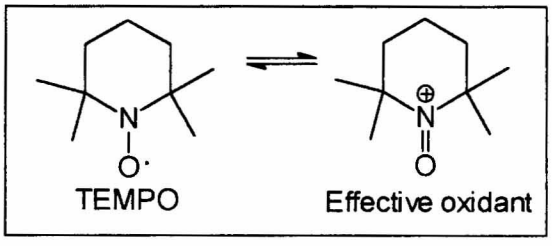
General selectivity in the preparation of enantiomerically pure C_n-symmetric compounds can be enhanced by carrying out the same stereoselective reaction on two or more prochiral centers of the symmetric precursor. This effect comes from statistics[1]. We exploited this approach using the catalytic sulfoxidation as a means for the easy transformation of bis(arylthio)alkanes into C_2-symmetric chiral sulfoxides.[2] The other way of selectivity improvement can arise from subsequential two or more stereoselective transformations run at different prochiral or stereogenic centers. In that case, double stereoselection can result in the gain of overall enantioselectivity.[3] Here we exemplify the use of this kind of strategy for the synthesis of enantiomeric hydroxysulfoxides. These compounds belong to an important class of chiral building blocks. Their preparations are usually based on the diastereoselective reduction of the corresponding enantiomeric ketosulfoxides, but this simple synthetic scheme is less suitable for the preparation of γ-hydroxysulfoxides.

The first synthetic route is based on the sequential asymmetric dihydroxylation and sulfoxidation of homoallylic sulfides. The osmium-catalyzed asymmetric dihydroxylation (AD)[4] and the vanadyl-based catalytic asymmetric sulfoxidation[2, 5] were used, and we studied the mutual interplay of both transformations. It is important that in both cases the stereochemical outcome can be predicted. We oxidized homoallylic sulfides **1** to the enantioenriched sulfoxides **2** with the absolute configuration at sulfur corresponding to that of the ligand **6**.



i, $VO(acac)_2$, H_2O_2, ligand **6** or TEMPO, NaOCl; *ii*, AD-mix α or AD-mix β or K_2OsO_4/quinuclidine, $K_3[Fe(CN)_6]$; *iii*, Oxone®





We also examined asymmetric dihydroxylation using AD-mix α and β.[4] These reagents, when applied to **1** gave **3** in 71% ee (*S*, *S*) and 76% ee. (*R*, *R*), respectively. Both products were oxidized with Oxone® to the corresponding sulfones **5** and their recrystallization gave these compounds in over 95% ee. This reaction sequence is more selective than the direct AD of the corresponding homoallylic sulfone (40% ee). When enantioenriched sulfoxides **2** were dihydroxylated with both AD-mixes, AD-mix α led to (S_C, S_C)-isomer and AD-mix β to (R_C, R_C)-isomer, regardless the configuration at sulfur. We observed better match (higher diastereoselectivity) for the formation of an *unlike* diastereomer (*u*). However, in the mismatch cases (lower de), (*l*)-isomers formed as the main products could be recrystallized to give pure (S_S, *S*, *S*)-

and (R_S, *R*, *R*)-**4**. These assignments were confirmed by a single crystal X-ray analysis for (S_S, *S*, *S*)-**4**.

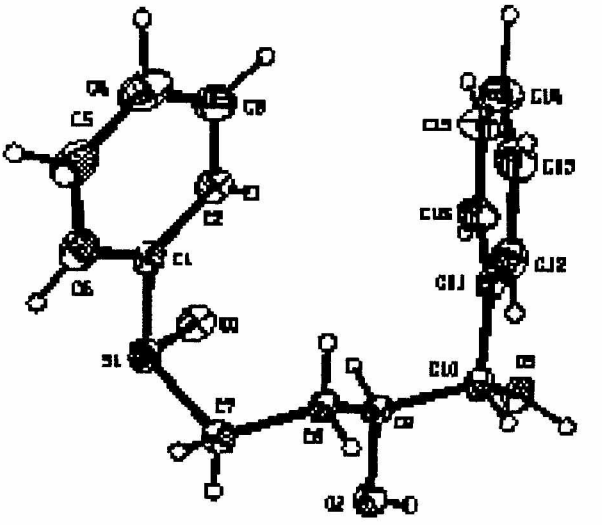
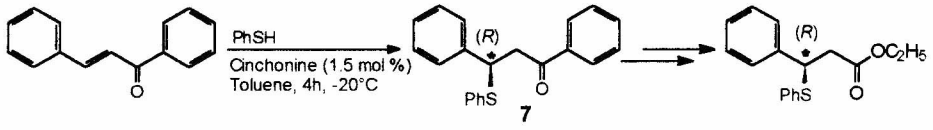


Fig.1. An ORTEP view of the molecule **4**.[7]

Their further oxidation with Oxone® led again to enantiomeric sulfones **5**. Finally, we examined the sulfoxidation of chiral diols **3** using $VO(acac)_2$-chiral ligand 6/30 % H_2O_2 and TEMPO/NaOCl systems. The last oxidant has already been used in sulfoxidation with high chemo- and diastereoselectivity.[6] The obtained results suggest that the stereoselectivity of the first reaction is steered by the configuration of diol substrate, leading to (*u*)-**4** in ca. 20 % de. Thus, in spite of the fact that usually the R_S configuration in sulfoxide is induced by (*R*)-**6**, in the case of (*R*, *R*)-**3** the formation of (S_S, *R*, *R*)-**4** was favored. We reasoned that the chiral diol moiety builds into the coordination sphere of the vanadyl oxidant, thus changing its regular stereochemical preferences. However, it was interesting to note that at the same time, kinetic resolution of the enantioenriched substrate/product took place, so the sulfone **5** obtained after second oxidation step was of higher ee than the starting dihydroxysulfide **3**. The TEMPO-catalyzed sulfoxidation led to higher yields of *l* diastereomers, but the products obtained at ca. 50 % conversion were less enantioenriched than the starting diols.

Thus, three new stereogenic centres were generated *via* sequential asymmetric dihydroxylation and sulfoxidation of homoallylic sulfides. As expected, one route (order of oxidations) leads to the higher stereoselectivity of overall transformation. However, in the cases studied the key factor is not match/mismatch substrate-catalyst selection, but efficient diastereo- and enantioenrichment of the final product due to its simple recrystallization.[7]

Our second synthetic approach to the enantiomeric hydroxysulfoxides is also based on the stereoselective oxidations.[8,9] During our recent work on the catalytic application of metal complexes,[5b] we tested the asymmetric conjugate addition of thiophenol to enones. For comparison, we also examined this reaction catalyzed by *Cinchona* alkaloids. We found that the Michael addition of thiophenols to chalcones in the presence of 1.5 mol% (+)-cinchonine followed by crystallization led to the corresponding adducts **7** in up to over 95 % ee.[8] The stereoselective Beckmann rearrangement of oxime of (+)-1,3-diphenyl-3-phenylsulfanyl-propan-1-one gave anilide of (+)-(*R*)-3-phenyl-3-phenylsulfanylpropanoic acid (X-ray structure) and its alcoholysis led to the known optically pure ethyl ester.[8] Thus, the absolute configuration of the created stereogenic center was proved undoubtedly.



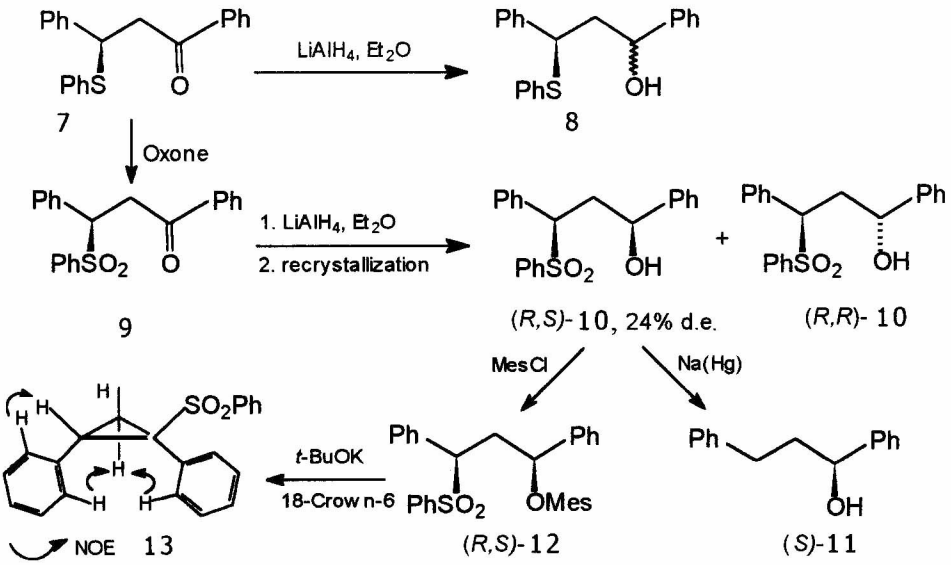
7

70 % yield, up to >95% e.e.
after recrystallization

The obtained optically active γ-ketosulfide **7** with two prochiral centers was a suitable precursor for subsequent stereoselective transformations into hydroxy-, sulfinyl- or sulfonyl functionalities. Because of our interest in the preparation of stereodifferentiating ligands, we undertook the elaboration of both prochiral groups into new chiral derivatives of this type, possibly with the divergent stereochemistry.

Unfortunately, reduction of (+)-(*R*)-1,3-diphenyl-3-phenylsulfanyl-propan-1-one (**7**) by various hydrides led to the inseparable diastereomeric mixture of alcohols **8** in excellent yield but in ca. 1:1 dr. However, when (*R*)-**7** was oxidized with Oxone® to the corresponding sulfone (*R*)-**9**, its subsequent reduction gave the mixture of diastereomers (24% de) and the obtained products (*R,R*)- and (*R,S*)-**10** were separated by crystallization. In order to prove its configurations pure (*R,S*)-**10** was desulfonylated to the known (*S*)-1,3-diphenylpropanol-1 (**11**). The alcohol (*R,S*)-**10** was mesylated to (*R,S*)-**12**, and this derivative in the presence of potassium *tert*-butoxide and catalytic amount

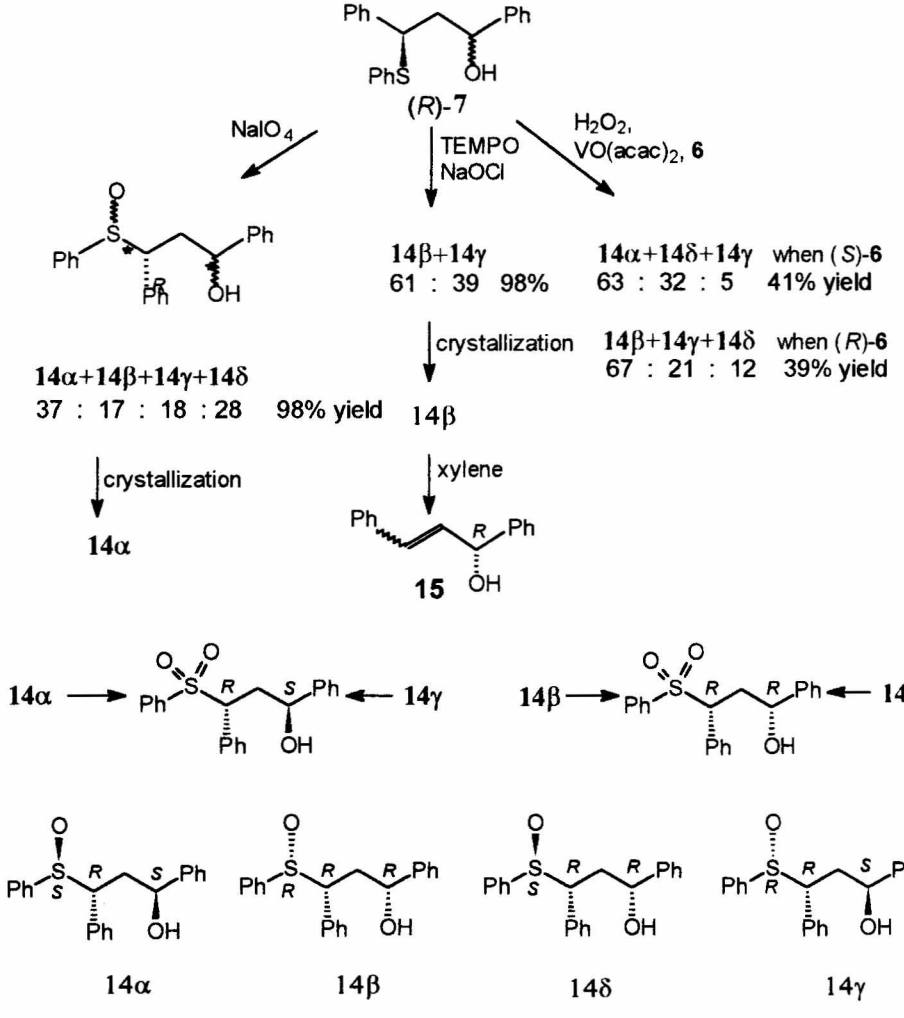
of 18-crown-6 reacted *via* intramolecular S_N2 reaction resulting in homochiral E-1,2-diphenyl-1-phenylsulfonylcyclopropane (**13**). The stereochemical outcome of this reaction was based on the fact that a single, optically active diastereomer with *cis*-located phenyl groups (NOE) was obtained as the only product, so these experiments also confirmed the ascribed configuration.[9]



In order to exploit well known stereodirecting properties of the phenylsulfinyl group, we turned to the sulfoxidation of the diastereomeric mixture of **8**. When mild chemoselective oxidant ($NaIO_4$) was used, all four possible diastereomeric γ-hydroxysulfoxides **14** (**α, β, γ, δ**) were formed in comparable yields. The ^1H NMR spectrum for each diastereomer exhibited different from the other resonance pattern for the methine hydrogens. Recrystallization of the mixture gave one pure isomer **14α** in 21% yield. Further oxidation of this product with Oxone® produced sulfone identical with (*R, S*)-**10**. Then, the diastereoselective catalytic system relaying on TEMPO oxidized by sodium hypochlorite[6], was applied. Only two diastereomeric **14** (**β** and **γ**) were produced, both different from the previously isolated one. The main diastereomer **14β** (22% de) easily crystallized in pure form, while the second one (**14γ**) was isolated after chromatography and recrystallization. Both, major **14β** and minor **14γ** were oxidized separately with Oxone® to (*R,R*)-**10** and (*R,S*)-**10**, respectively. Moreover, **14β** in boiling xylene underwent thermal elimination furnishing the *cis/trans* mixture of known (+)-(*R*)-allylic alcohol **15**. At that point, the absolute configuration at the sulfur atom in all obtained γ-hydroxysulfoxides remained obscure.

In order to solve this problem we used our optimized version (30% H_2O_2/$VO(acac)_2$ - chiral ligand **6**) of the Bolm catalytic sulfoxidizing system.[5]

The system, when containing (*S*)-ligand **6**, is known for the preference of formation of sulfoxides with S_S configuration and with (*R*)-**6**, R_S configuration. Thus, when the oxidant with (*S*)-**6** was applied, two diastereomers were dominating (**14α** and **14δ**). Fortunately, they were separable, and one of them was identical with that previously isolated after oxidation with $NaIO_4$, *i.e.* **14α** (26 % yield). Based on this, we assigned it tentatively being (*R*,*S*,S_S)-**14**. In the next experiment we used (*R*)-**6** and the main formed product (**14β**, 26 % yield) was identical with the major product obtained after oxidation with TEMPO/NaOCl. On this ground we assigned it being (*R*,*R*,R_S)-**14**. Analogously, we provisionally assigned the absolute configuration of both remaining sulfoxides as **14δ** being (*R*,*R*,S_S)-**14** and **14γ** being (*R*,*S*,R_S)-**14**.



It has been known that the absolute configuration of sulfoxides correlates with their chiroptical properties. Thus, we measured CD spectra of the obtained diastereomeric sulfoxides and the absolute configurations at the created stereogenic sulfur were clearly confirmed. Thus, the sequential reduction and oxidation run on two prochiral groups of the enantiomeric precursor led to the simple preparation of all possible products with three stereogenic centers.

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Sekwencja stereoselektywnych reakcji utleniania: łatwa droga syntezy enancjomerycznych γ-hydroksysulfotlenków

Streszczenie: Przedstawiono nowe metody syntezy enancjomerycznych hydroksysulfotlenków. Pierwsza polega na asymetrycznej dihydroksylacji i S-utlenianiu sulfidów homoallilowych. Druga metoda wykorzystuje wysoce enancjoselektywną addycję tiofenolu do enonów. Dalsza redukcja i stereoselektywne utlenianie pozwalają na otrzymanie odpowiednio wszystkich chiralnych hydroksysulfotlenków. Tak syntezowane produkty o trzech centrach stereogennych mogą ulegać dalszym reakcjom, co świadczy o ich użyteczności w syntezie.