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DOUBLE DIASTEREODIFFERENTIATION IN THE HYDROXYLATIVE KNOVENAGEL CONDENSATION

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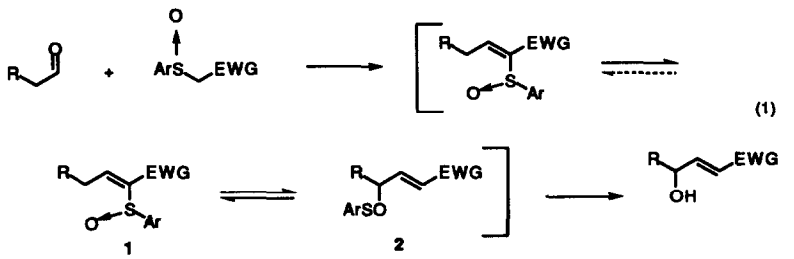
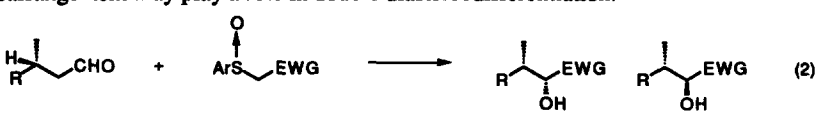
Summary: The stereoinduction in formation of γ-hydroxy-α,β-unsaturated enoates using chiral α-sulfinyl esters and chiral aldehydes is a function of the absolute stereochemistry of the sulfoxide, the substituent on the sulfoxide, and the amount of base.

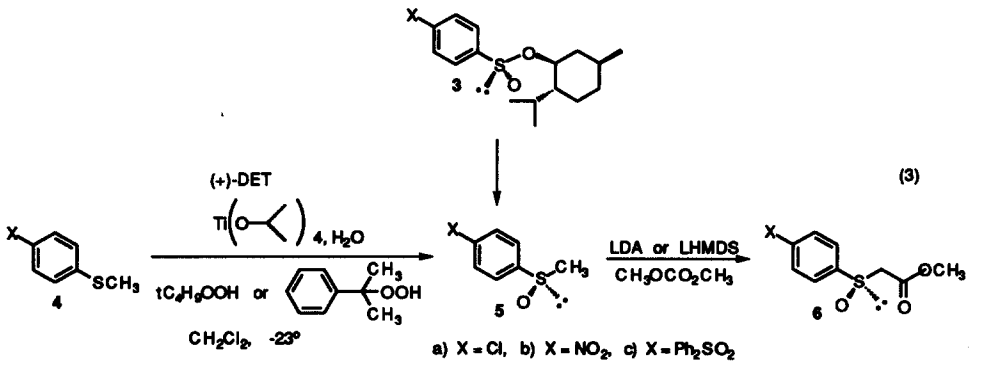
The hydroxylative Knovenagel condensation according to eq. 1[1] has proven to be a valuable chain extension method since it creates a useful juxtaposition of functionality for further structural elaboration. This



process becomes more valuable if it can simultaneously address the issue of stereochemistry. Using chiral sulfoxides, these reactions gave rise to asymmetric inductions ranging from 10-79% ee leading to the use of auxillary methods to boost the ee.[2,3] In such cases, it has been deduced that the asymmetric induction arises from asymmetric protonation to generate **1** rather than in the 2,3-sigmatropic rearrangement for which it is stated that "the sulfoxide chirality does not effect the stereochemical outcome because the sulfoxide rearranges on the face of the double bond which corresponds to minimum 1,3-allylic strain in the transition state."[3] In conjunction with a total synthesis of cembranes, we became interested in the question of double diastereodifferentiation (eq. 2).[4] These studies suggest that the stereochemistry of the sulfoxide in the [2.3] sigmatropic rearrangement may play a role in double diastereodifferentiation.



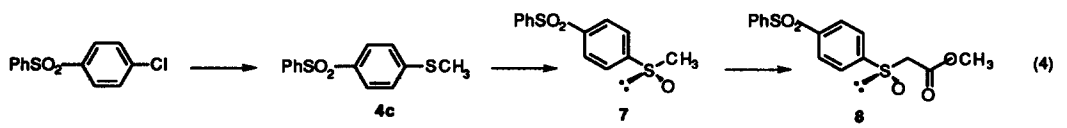
We prepared a series of methyl 2-arylsulfinylacetates bearing electron withdrawing groups as outline in eq. 3. Two methods were used for the construction of scalemic sulfoxides. In the first, the methyl sulfinate **3** (X = Cl) was obtained with >95% de by recrystallization and converted to its methyl sulfoxide **5a** of >95% ee.[5] Because this procedure relies on the ease of crystallization which is not predictable for other systems, we explored the protocol of Kagan who utilized a modification of the Sharpless epoxidation system for the asymmetric synthesis of sulfoxides.[6] Applying this method to 4- chlorophenyl methyl sulfide **4a** as in eq. 3 using t-butyl hydroperoxide gave the corresponding sulfoxide **5a** $[\alpha]_D^{20}$ +94.9° (c = 1.24, acetone) in 88% yield and 76% ee as established by comparison with the known compound and in agreement with the report of



Kagan. Methoxycarbonylation by adding dimethyl carbonate to a -78° THF solution of a 1:1 mixture of lithiated sulfoxide and LDA gave **6a**, $[\alpha]_D^{20}$ + 128.4° (c = 0.98, $CHCl_3$), 76% ee, which increased to 94% ee, $[\alpha]_D^{20}$ + 158.1° (c = 1.15, $CHCl_3$), upon one recrystallization from ether-hexane.

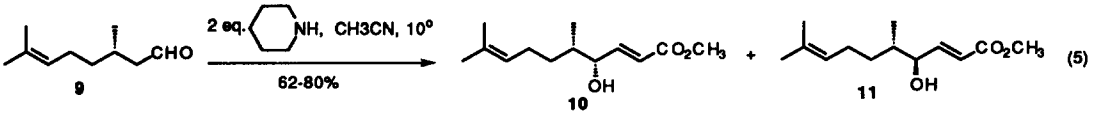
Since cumyl hydroperoxide is reported to give higher ee's in the asymmetric oxidation,[6b] the above protocol was utilized for the oxidation of the p-nitro analogue **4b** except for substituting cumyl hydroperoxide for t-butyl hydroperoxide. In this case, the sulfoxide **5b**, obtained in 67% yield, had $[\alpha]_D^{20}$ + 94.2° (c = 2.84, acetone) corresponding to an ee of 94%.[6] The resulting sulfinyl ester **6b**[3], $[\alpha]_D^{20}$ + 209.0° (c = 1.00, acetone), was obtained in 50% yield.

The chemical instabilities of nitroaromatics in basic media led us to examine the p-benzenesulfonyl



analogue **4c**, readily available by nucleophilic aromatic substitution of the commercially available 4-chlorophenyl phenyl sulfone.[7] Oxidation with (+)DET and cumyl hydroperoxide gave **5c**[8] in 72% yield and 88% ee, $[\alpha]_{20}^{20}$ + 61.5° (c = 1.0, acetone); whereas, use of (-)DET gave the S isomer **7**[8] in 78% yield and 88% ee, $[\alpha]_D^{20}$ - 61.5° (c = 1.0, acetone). Methoxycarbonylation as before gave the methyl esters **6c**[8], $[\alpha]_D^{20}$ + 147° (c = 1.13, acetone), 93% ee, and **8**[8], $[\alpha]_D^{20}$ - 153.5° (c = 1.29, acetone), 97% ee, after recrystallization from ethyl acetate-ether. Better yields (80%) were obtained in methoxycarbonylation by using lithium bis(trimethylsilyl)amide rather than LDA. The ee's were determined by nmr chiral shift studies using $Eu(hfc)_3$.

S-Citronellal (**9**) was examined as the substrate. Allowing a 0.4 M solution of the



6a (94% ee)	2.8 (3.1)	1
6b (94% ee)	4.7 (5.5)	1
6b* (94% ee)	5.9 (7.2)	1
6c (93% ee)	5.9 (7.3)	1
8 (97% ee)	1	4.3 (4.6)

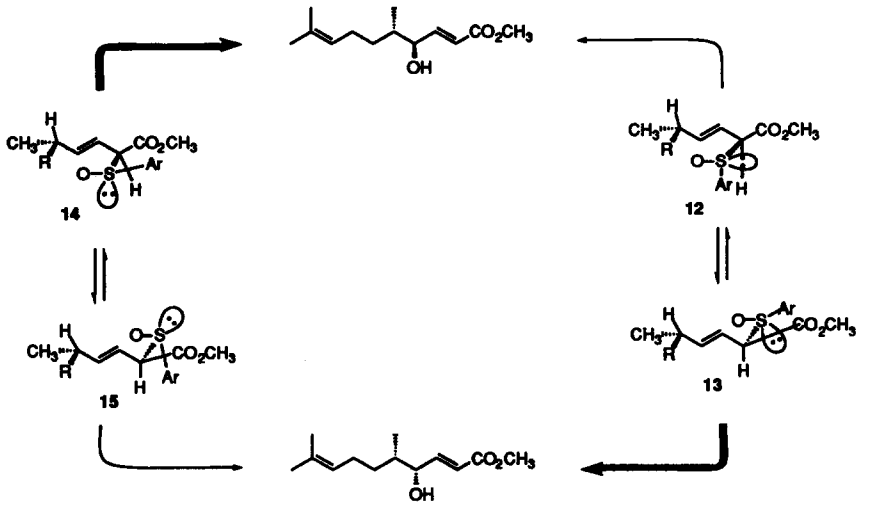
* In this case, 4 eq. of piperidine were employed.

sulfinylacetate and citronellal to stir at 10° in the presence of 2 eq. of piperidine gave complete reaction within 60 h (eq. 5). Using **6a** of 94% ee gave a 2.8:1 ratio favoring the 4R, 5S isomer **10**. Numbers in parentheses correct this ratio for the enantiomeric purity of the sulfoxide. The configuration of the carbon bearing the hydroxyl group was established by nmr spectroscopy of the O-methylmandelates.[9] Increasing the electron withdrawing nature of the aryl substituent by replacing chloro with nitro increases the diastereomeric ratio to 4.7:1. A further increase to 5.9:1 occurs with **6b** when the amount of piperidine increased to 4 eq.

The phenylsulfonyl substituted sulfoxide **6c** gave, within experimental error, identical results. On the other hand, the enantiomeric sulfoxide **8** gave the 4S, 5S diastereomer but with diminished selectivity (see eq. 5). Thus, there is clearly a matched (S citronellal with R ester) and a mismatched (S citronellal with S ester) pair.

Can these results arise by differential protonation of the diastereomeric sulfoxides to generate **1**? Considering that the stereogenic center from the aldehyde is so distal to that being created adjacent to the ester, this scenario appears unlikely. Furthermore, the dependence of the dr on the concentration of the piperidine also does not appear to be in accord with this explanation. An explanation that accommodates all of these facts is outline in the Scheme.

SCHEME. A Rationale for Double Differentiation



The reactive conformers are assumed to minimize allylic strain.[10] In doing so, the new C-O bond is being formed distal to the bulkier substituent in **13** and **15** which should be preferred. On the other hand, the aryl group of the sulfoxide is in an energetically more favorable exo orientation in **13** and **14**. Thus, of the four possible diastereomeric transition states, minimization of steric strain both with respect to the formation of the C-O bond and the aryl group occurs from diastereomer **13**. Indeed, the "matched" pair invokes this diastereomer as the reactive one. On the other hand, steric strain must be encountered in the transition states coming from either **14** or **15**. The facts that the difference in steric bulk between R and CH_3 is not so big in this case and that the sulfoxide oxygen is not a sterically very demanding attacking substructure impart greater importance to the steric strain with respect to the aryl group. As a result, the transition state for rearrangement

from **14** is preferred but to a diminished extent (i.e., is a "mistmatched" pair).

Excess piperidine assures that interconversion of the diastereomers is fast relative to their rearrangement. Furthermore, it may serve as a sulfenate ester trap to maximize kinetic capturing of the latter. The beneficial effect of electron withdrawing groups in the aryl substituent may derive from enhanced acidity to facilitate diastereomeric interconversion and more rapid cleavage of the sulfenate ester. Thus, good diastereoselectivity depends upon steric effects of substituents both at carbon and sulfur. The ease of availability, good stability, and good diastereoselectivity leads us to prefer the phenylsulfonyl derivatives **6c** and **8** for synthetic purposes.

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