Tetrahedron Letters, Vol.31, No.38, pp 5409-5412, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

EVALUATION OF A CHIRAL ARYL AUXILIARY DESIGN FOR SULFUR: REGIO- AND DIASTEREOSELECTIVE CONJUGATE ADDITIONS OF AUXILIARY-MODIFIED ALLYLIC SULFOXIDE REAGENTS

Charles S. Swindell* and Frances Rose Blase

Department of Chemistry, Bryn Mawr College
Bryn Mawr, Pennsylvania 19010-2899

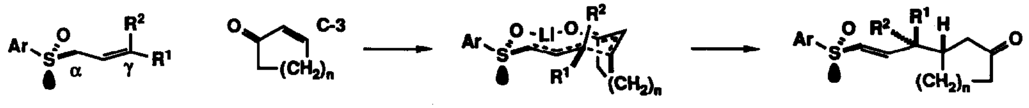
Drake S. Eggleston[1] and Jeanette Krause

Smith Kline & French Laboratories, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

***Summary:** Auxiliary-modified allylic sulfoxides 2 - 5 exhibit greatly biased ambient temperature sulfinyl epimeric equilibria brought about by the reversible sulfoxide-sulfenate rearrangement, and provide lithio anions that undergo highly regio- and diastereoselective conjugate addition reactions with cyclopentenone, and in the case of reagent 5, to cyclohexenone.*

Allylic sulfoxides are potentially powerful reagents for enantioselective synthesis. Through their derived lithio anions, they undergo, with certain cyclic enones, highly regio- and diastereoselective conjugate addition reactions (Scheme I) that Haynes has suggested pass through ten-membered ring transition structure 1.[2] When conducted with optically active sulfoxides configurationally defined at sulfur, these carbon-carbon bond constructions proceed with sulfinyl control over adduct absolute configuration at C-3 and C-γ.[3] Furthermore, it is clear that the nickel-catalyzed substitution of sp^2 carbon-bound sulfur by Grignard reagents[4] offers a means of replacing adduct vinylic sulfoxide functionality with carbon and hydrogen substituents, thus allowing a limited number of allylic sulfoxide reagents to provide structurally diverse β-substituted ketones. In this regard, allylic sulfoxides are of particular interest as enantioselective conjugate addition vehicles.[5]

Scheme I

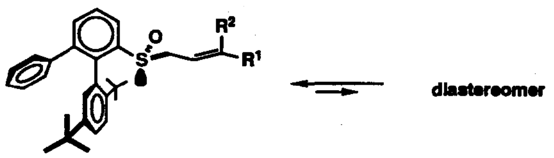


1

These attractive features aside, the usefulness of this methodology is compromised by the lack of general ways to introduce and preserve the absolute configuration of allylic sulfoxide sulfur. The conventional Andersen route to optically active sulfoxides is limited in its application to allylic sulfoxides.[6] In addition, substances that possess the sulfinyl center as the only stereogenic element racemize readily at ambient temperatures through the reversible sulfoxide-sulfenate rearrangement.[7]

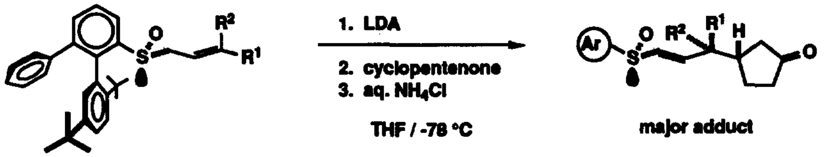
In the previous Letter,[8] we reported the syntheses of racemic sulfoxides 2 - 5 (Scheme II) in which auxiliary configuration is relayed to the sulfinyl centers through sulfoxide-sulfenate sigmatropy, thereby turning into an advantage the ambient temperature fluxional stereochemistry characteristic of these substances. Since a previous attempt to involve auxiliary-bearing allylic sulfoxide reagents in the above conjugate addition chemistry failed,[9] we considered it prudent to assess 2 - 5 in this regard prior to optimizing

Scheme II



		Diastereomer Ratio
2	$R^1, R^2 = H$	92 : 8
3	$R^1 = Me, R^2 = H$	87 (E) : 3 (E) : 10 (Z)
4	$R^1 = Ph, R^2 = H$	92 : 8
5	$R^1, R^2 = Me$	93 : 7

Scheme III



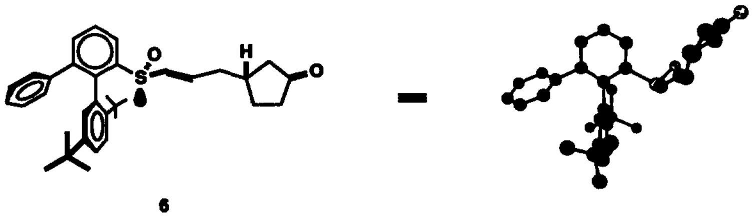
	Reagent	Adduct	Diastereomer Ratio*	Yield
$R^1, R^2 = H$	2	6	92 : 8	80%
$R^1 = Me, R^2 = H$	3	7	85 : 15	54%
$R^1 = Ph, R^2 = H$	4	8	90 : 10	60%
$R^1, R^2 = Me$	5	9	93 : 7	86%

*Two significant products formed in each case within the limits of conventional NMR procedures.

the auxiliary design and developing optically active reagents. It being unnecessary to repeat the survey of reactivity toward enone structural types carried out by Haynes[2] and Hua,[3] we screened 2 - 5 against cyclopentenone and cyclohexenone as these enones are among the least forgiving with respect to sulfoxide-induced diastereoselectivity.[2] Herein we report that 2 - 5 undergo conjugate additions to these electrophiles with equal or greater regio- and diastereoselectivity than those exhibited by simpler reagents. These are the first examples of such reactions that proceed both efficiently and with a well defined relationship between auxiliary configuration and C-3 and C-γ configurations.

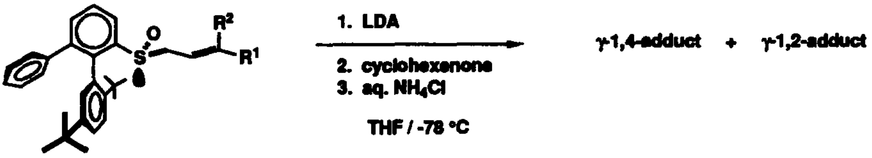
Reagents 2 - 5 were employed in the reactions described below with the equilibrium diastereomer distributions indicated in Scheme II; neither recrystallization nor chromatography delivered pure diastereomers. Of course, pure sulfoxide diastereomers of this type would be expected to revert to the equilibrium mixtures more or less rapidly at ambient temperatures, and it has been our aim to develop reagents whose ambient temperature diastereomeric *equilibria* are usefully biased. Lithiation of 2 - 5 with LDA in THF at -78 °C followed by addition of enone and, immediately thereafter, saturated aqueous ammonium chloride provided, after conventional extractive workup, the conjugate addition products and varying amounts of starting allylic sulfoxides. The yields reported have not been corrected for recovered starting material. The product distributions were determined by NMR prior to purification.

The conjugate additions of 2 - 5 to cyclopentenone (Scheme III) were uniformly regioselective and essentially diastereospecific – that is, the diastereomer distributions of the adducts were commensurate with those of the respective reagents. An X-ray crystallographic analysis of the major allyl sulfoxide-cyclopentenone adduct 6[10,11] established its relative stereochemistry and confirmed that the Haynes stereochemical model 1 had been adhered to; the relative stereochemistries for the remaining major adducts in Scheme III were assigned by analogy to this product. When the reactions involving the crotyl (3) and cinnamyl (4) reagents were not



6

Scheme IV



	Reagent	γ-1,4 Diastereomer Ratio*	γ-1,4 Yield	γ-1,2 Diastereomer Ratio*	γ-1,2 Yield
$R^1, R^2 = H$	2	70 : 30	67%	70 : 30	30%
$R^1 = Me, R^2 = H$	3	55 : 45	60%	55 : 45	16%
$R^1 = Ph, R^2 = H$	4	55 : 45	86%	-	0%
$R^1, R^2 = Me$	5	93 : 7	85%	-	0%

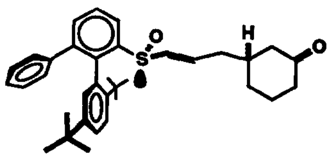
*Two significant products formed in each case within the limits of conventional NMR procedures.

quenched promptly, diastereoselectivity was significantly poorer suggesting that post-addition proton transfer between C-γ of the vinylic sulfoxide side chains and product enolates obtained. Attention to the geometrical purity of crotyl reagent 3[8] would lead to a significant improvement in the diastereomeric purity of its adduct with cyclopentenone.

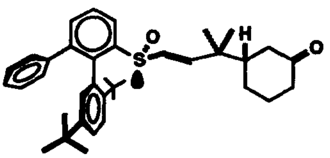
The efficacy in these reactions of the allyl (2) and prenyl (3) reagents is worth noting since Haynes has shown them to be often stereochemically indiscriminate, especially when not paired with favorably substituted cyclopentenones. For example, phenyl prenyl sulfoxide adds to cyclopentenone with only 80% diastereoselectivity.[2] The excellent selectivity attainable with unsubstituted cyclopentenone and 5 might result from a pronounced preference for the sterically demanding auxiliary to be disposed equatorially in transition structure 1; it is unlikely to be traceable to direct stereochemical induction from the auxiliary.

The additions to cyclohexenone (Scheme IV) paralleled prior experience[2,3] in that poorly stereoselective 1,2- and/or 1,4-addition occurred in most instances. However in comparison to the behavior of simpler analogues, reagents 2 - 5 exhibited improved regioselectivity toward cyclohexenone. For example, α-1,2-addition was not observed with any of the reagents described herein and the degree of γ-1,2-addition diminished with increasing steric hindrance at the γ carbon, cinnamyl reagent 4 and prenyl reagent 5 adding completely regioselectively γ-1,4 to cyclohexenone. Both phenyl allyl sulfoxide and phenyl prenyl sulfoxide give substantial amounts of α-1,2-addition with cyclohexenone.[2]

With the exception of the process involving 5, stereoselectivity in the conjugate addition reactions with cyclohexenone was generally unimpressive. In this series, differentially γ-substituted reagents 3 and 4 were the least effective while reagents 2 and 5, which possess equivalent γ-substituents, behaved diastereoselectively. This is a reversal of the trend observed with simple allylic sulfoxide reagents and cyclopentenones.[2] Most noteworthy, of course, is the diastereospecific γ-conjugate addition of 5, a result that suggests that a broader group of enones might be amenable to this chemistry. According to the Haynes model, major allyl and prenyl



10



11

γ-1,4-adducts would have structures **10** and **11**, respectively; we know of no published verification that cyclohexenones adhere to this model.[12]

From this study, it is clear that auxiliary-modified reagents **2** - **5** undergo conjugate additions to enones as effectively or more so than previously known allylic sulfoxide reagents. Their diastereomeric excesses are transferred faithfully into their adducts with cyclopentenone and, in the case of prenyl reagent **5**, with cyclohexenone. Furthermore, the sterically demanding auxiliary endows **2** - **5** with better regio- and diastereoselectivity than characteristic of simpler aryl allylic sulfoxide analogues. Thus the extension to other enone structural types of the conjugate addition chemistry that usefully involves auxiliary-modified reagents of this kind might be possible, especially with a better understanding of the important mechanistic features of these processes. The optimization of the auxiliary design and the development of optically active reagents, perhaps available through kinetic oxidation-resolution at the sulfide stage,[13] would appear to be worthwhile goals.

Acknowledgment. Acknowledgement is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for the partial support (to CSS) of this research. The acquisition of a GC/MS system was made possible by grants from the Camille and Henry Dreyfus Foundation and the PQ Corporation, and of a high field NMR spectrometer by grants from the W. M. Keck Foundation and Merck & Co., Inc.

References and Notes:

1. To whom inquiries regarding the X-ray crystal structure determination of **6** should be addressed.
2. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411. Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423.
3. Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719.
4. Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. Wenkert, E.; Ferreira, T. W.; Michelotti, E. L.; *J. Chem. Soc., Chem. Commun.* **1979**, 637.
5. For stereoselective conjugate additions of anions derived from optically active P-allyl oxazaphospholidin-2-oxides to cyclopentenone, cyclohexenone, and cycloheptenone, see: Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026.
6. Andersen, K. K. *Tetrahedron Lett.* **1962**, 93. For example, optically active crotyl sulfoxides cannot be prepared in this way.[7]
7. Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100. Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
8. Swindell, C. S.; Blase, F. R.; Carroll, P. J., preceding Letter.
9. For optically active allylic sulfoxide reagents configurationally defined at sulfur by appended camphor-derived auxiliaries, see: Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D. *J. Org. Chem.* **1988**, *53*, 2881. The effective use of these reagents in conjugate additions has proven to be problematic, however; see: Binns, M. R.; Goodridge, R. J.; Haynes, R. K.; Ridley, D. D. *Tetrahedron Lett.* **1985**, *26*, 6381.
10. A crystal of dimensions 0.15 x 0.20 x 0.60 mm, grown from 95% ethanol solution, was used for X-ray diffraction measurements. Crystal data: $C_{34}H_{40}O_2S$, FW = 512.76, monoclinic, $P2_1/n$, $a = 23.132(6)$, $b = 8.234(2)$, $c = 31.411(9)$ Å, $\beta = 95.02(2)°$, $V = 5959.4(11)$ Å^3, $Z = 8$, $d_{calcd} = 1.143$ g/cm^3, $\mu = 1.290$ cm^{-1}. Intensity measurements in the range $2° \leq 2\theta \leq 44°$ were collected using variable speed ω–2θ scans at room temperature with graphite monochromated molybdenum radiation on an Enraf-Nonius CAD4 diffractometer. A total of 7289 unique reflections were measured. After corrections for background, Lorentz, polarization, decay (max. loss 8.4%) and absorption effects were applied, 2823 data were considered observed ($I \geq 2\sigma(I)$). The structure was solved using the MULTAN program package as incorporated in the Enraf-Nonius SDP, a locally modified version of which was the source of all programs. All non-hydrogen atoms were refined with anisotropic thermal parameters by full matrix least-squares which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. Hydrogen atoms were added to the model at fixed calculated positions and were assigned thermal factors equivalent to 1.3 x B_{iso} of the atom to which they were attached. Refinement with 668 parameters converged at $R = 0.077$, $R_w = 0.087$ with goodness of fit = 1.62. The remaining details will be revealed in the full account.
11. All new compounds reported herein were characterized by conventional spectroscopic means as well as by combustion or high resolution mass spectral analysis.
12. Prenyl sulfoxide-cyclohexenone adduct **11** is an oil and attempts to prepare a crystalline derivative of it for X-ray crystallographic analysis failed.
13. Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. Davis, F. A.; ThimmaReddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964.

(Received in USA 23 May 1990)