Diastereoselective Conjugate Additions Reactions of a Lithiated Allylic Sulfoximine to Acyclic Enones

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The conjugate addition reactions of lithiated *N*-*p*-tosyl *S*-phenyl *S*-prop-2-enyl sulfoximine **4** with cyclic and acyclic enones gives exclusively $1,4-\alpha$ adducts, the reactions with acyclic enones are highly diastereoselective.

In contrast to the chemistry of allylic sulfoxides¹⁻⁴ and sulfones,^{5,6} relatively little is known about the chemistry of allylic sulfoximines.⁷ In 1979, Johnson⁸ disclosed the synthesis of the first reported allylic sulfoximine. The synthesis of enantiomerically pure allylic sulfoximines has been recently reported,^{9,10} and Gais has demonstrated they undergo S_N2 or S_N2' like displacement reactions with homocuprates.⁹ Harmata¹¹ reported that the reaction of lithiated **1** with either 2-cyclopentenone or 2-cyclohexenone gave mixtures in which the 1,4- α adducts were slightly favoured over the 1,4- γ adducts. More recently we have reported that the conjugate



 Table 1 Conjugate addition reactions of lithiated 4 with enones

Enone			
R ¹	R ²	Diastereoisomeric ratio	Yield (%)
-(CH ₂) ₂ -		49:33:10:8	87
-(CH ₂) ₃ -		47:25:14:14	92
Ph	Ph	93:7	90
Me	Ph	90:10	45
Ph	Me	94:6	61

addition reactions of lithiated **3** with cyclic and acyclic Michael acceptors give mainly 1,4- γ and 1,4- α adducts respectively in THF and 1,4- α and 1,4- γ adducts respectively in HMPA-THF.¹² Although the 1,4- γ adducts from cyclic enones could be isolated in high diastereomeric purity, these reactions proceeded with modest regioselectivity with respect to α verses γ attack on the lithiated sulfoximine. Furthermore acyclic enones gave products from 1,2 and 1,4 addition of lithiated **3**. Here we report the conjugate addition reactions of lithiated *N-p*-tolyl *S*-phenyl *S*-prop-2-enyl sulfoximine **4** with cyclic and acyclic enones. In contrast to lithiated **1** and **3**, the conjugate addition reactions of lithiated **4** are highly regioselective with respect to α attack on the allylic anion and are highly diastereoselective for acyclic enones. Furthermore, we report the first stereochemical study of this type of reaction



Fig. 1 Molecular projections of (a) 5 and (b) 6; 20% thermal ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å

from single crystal X-ray structural analyses of two of the reaction products.

Racemic allyl sulfoximine 4 (mp 82-83 °C) was prepared in 81% yield from sulfoximine 2^{12} by treatment with p-toluenesulfonyl chloride (1.2 equiv.) and pyridine (1.2 equiv.) in dichloromethane at 22 °C for 1 h. Addition of n-butyllithium (BunLi, 1.1 equiv.) to a solution of 4 in THF at -78 °C gave an immediate yellow-orange solution of lithiated 4. After 15 min, the solution was treated with the enone (1.2 equiv.). After 3 min at -78 °C the almost colourless reaction mixture was quenched with acetic acid (1 equiv.) and then an aqueous solution of saturated ammonium chloride. The diastereoselectivities of these reactions were determined by ¹H NMR analysis of the crude reaction mixtures. The reaction products were purified by column chromatography on silica gel with ethyl acetate-hexanes as eluent and the chemical yields were determined on purified samples. The results of these investigations are summarized in Table 1.

In contrast to the chemistry reported for lithiated 1 and 3, lithiated 4 gave exclusively $1, 4-\alpha$ adducts with both cyclic and acyclic enones. Interestingly the regiochemistry of the reaction of lithiated 4 with enones is also different to that of lithiated allyl phenyl sulfone which gives exclusive $1,4-\gamma$ adducts with cyclic enones and $1,4-\alpha$ adducts with acyclic enones.5

When 2-cyclopentenone and 2-cyclohexenone were treated with lithiated 4, the 1,4- α adducts were obtained but as a mixture of the four possible diastereoisomers (Table 1). The relative $(3S^*, 1'R^*, SS^*)$ stereochemistry of the major diastereomeric adduct 5 from the former reaction was secured by a single crystal X-ray structural analysis as shown in Fig. 1a. The relative stereochemistry of the major adduct from the reaction of lithiated 4 and 2-cyclohexanone is assumed to be the same as that in 5 on the basis of its similar ¹H NMR spectrum.

In contrast, the reaction of lithiated 4 and the acyclic enones, benzylideneacetophenone, benzalacetone and (E)-1phenylbut-2-en-1-one were highly diastereoselective (Table 1). The relative $(3R^*, 4R^*, SS^*)$ stereochemistry of the major diastereomeric adduct 6 from the reaction of lithiated 4 and benzylideneacetophenone was determined by a single crystal X-ray structural analysis (Fig. 1b). The relative stereochemistry of the major adducts from the reaction of lithiated 4 and benzalacetone and (E)-1-phenylbut-2-en-1-one is assumed to be the same as that in 6 on the basis of their similar ¹H NMR spectra.

The stereochemical outcome of these reactions with respect to the stereogenic centre α to the sulfoximine group can be rationalised as arising from attack on the carbanion whose structure is as shown in 7 (only the monomeric species is considered) that may be similar to that of an α -lithiated benzyl sulfone or sulfoximine.^{13,14} The α -substituent (CH...CH₂) of the sulfoximine would be expected to be anti to the bulky N-p-tosyl group. Electrophilic attack on 7 should occur anti to the S-phenyl group and syn to lithium. The overall stereochemical outcome of these reactions can be rationalised as arising from the chelated transition states 8 and 9 in which the two bulky groups of each reaction partner, the sulfoximidoyl group and the β -enone substituent, are *anti* to minimise steric interactions.

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Footnote

† Crystal data for 5: C₂₁H₂₃NO₄S₂, a = 21.534(5), b = 5.867(3), c = 18.288(5) Å, $\beta = 116.17(2)^\circ$, V = 2074 Å³. 2θ_{max} = 47.5°; N = 2671, $N_{\rm o} = 1177; R = 0.055, R_{\rm w} = 0.050. (x, y, z, U_{\rm iso})_{\rm H}$ included constrained at estimated values.

6: $C_{31}H_{29}NS_2O_4$, a = 12.205(4), b = 12.566(6), c = 19.669(6) Å, $\beta = 112.71(2)^\circ$, V = 2783 Å³. $2\theta_{max} = 60^\circ$; N = 4804, $N_o = 2825$; R = 0.669(6) Å 0.052, $R_w = 0.053$. $(x, y, z, U_{iso})_H$ all refined.

Unique, room temp. diffractometer data sets (T ca. 295 K, 20/0 scan mode, monochromatic Mo-K α radiation, $\lambda = 0.71073$ Å) yielding N independent, gaussian-absorption-corrected data, No with $I > 3\sigma(I)$ used in the full-matrix least-squares refinement (anisotropic non-hydrogen thermal parameter form, statistical reflection weights). Both structures monoclinic, $P2_1/c$.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1, 1994.

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