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Studies of π-Diastereofacial Selectivity: The Influence of α-Oxathiolane Ketals on Cyclic Ketones

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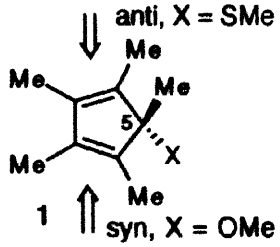
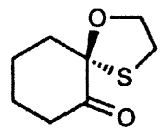
Abstract: The facial influence and synthetic utility of oxygen and sulfur heteroatoms adjacent to carbocyclic ketones upon nucleophilic addition has been investigated. Addition to the carbonyl group displayed a preference for attack *anti* to sulfur and *syn* to oxygen in synthetically useful ratios. Diisopropylaluminum hydride reduction in the cyclopentanone series reversed this facial preference.

Stereoselective additions to carbonyl groups have received considerable attention and have provided synthetic methods of broad utility. Consequently numerous investigations have examined the factors responsible for π-facial control, particularly the influence of an adjacent stereogenic centre.[1-8] Nevertheless the factors responsible are still imperfectly understood, and it is often difficult to ascertain the relative importance of steric versus electronic effects. We established that the π-facial diastereoselection in Diels-Alder reactions of cyclopentadienes can be reversed by altering the C_5 substituent. (*Cf.* **1**)[2,8] 1,3-Oxathiolanes have proved useful for radical cyclizations[9] and this ring system figures prominently in modified nucleosides for anti-HIV viral agents.[10] In addition, 1,3-oxathianes have been employed for diastereoselective alkylations and to control the reduction of acyl ketones.[11-12] α-Keto-1,3-oxathiolane ketals provide an opportunity to examine heteroatom directed control of π-diastereofacial nucleophilic additions in which the oxygen and sulfur atoms occupy stereochemically similar environments. We wish to report our initial results with the α-keto-oxathiolane ketals represented by cyclohexanone **2** and cyclopentanone **3**. Nucleophiles displayed a preference for addition *syn* to oxygen and *anti* to sulfur in synthetically useful ratios. The exception to this generalization occurred upon reduction of **3** with diisobutylaluminum hydride (DIBAL-H) where the opposite stereoselectivity was observed.





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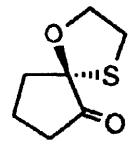

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The required ketones were synthesized from the corresponding α-diketones upon treatment with 2-mercaptoethanol in the presence of *para*-toluenesulfonic acid in refluxing benzene. The cyclohexanone **2**[13] was examined initially. As summarized in Table 1, the facial preference was constant for organolithium, organomagnesium and various hydride nucleophiles. The configurations of these cyclohexyl alcohols and the cyclopentane series below were established by X-ray analysis[14] of suitable urethane derivatives and related ^1H

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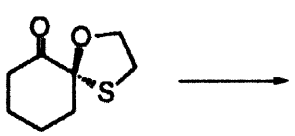
NMR studies. The reactions were performed in the common solvents employed for these synthetic transformations to facilitate the application of these results to other systems. In all cases 1.1 equivalents of the nucleophilic reagent were employed. The synthetic control exerted on the direction of attack is obvious but a comprehensive rationalization of these results is complicated by the facile conformational equilibrium between **2a** and **2b**. Additional uncertainty is associated with the nature of the transition state and establishing unambiguously the more reactive conformer. In spiro-tetrahydrofurans the axial isomer dominates.[15] However, the preference for the axial conformer of 2-methylthiocyclohexanone is larger than for 2-methoxycyclohexanone.[16] Small nucleophiles attack conformationally locked cyclohexanones such as 4-*t*-butylcyclohexanone with an ~80:20 axial preference.[17] Conjugate additions to 4-oxathianyl-2-cyclohexenones also display a *syn* to oxygen preference (~90:10)[18] although with a single oxygen substituent this selectivity is reversed.[19] The oxathiolane group may override the steric approach control believed to operate with cyclohexanones. Thus axial attack on conformer **2a** may be preferred as this avoids excess torsional strain[3] and is consistent with hyperconjugation stabilized attack *anti* to best sigma donor.[4] However, equatorial attack on **2b** (major conformer, ~4:1) gives the same result! Chelation may also be important, although as established by Fraser *et al.*[3f] both through-bond and through-space electrostatic interactions likely dominate in the transition state. To gain further insight into this behaviour the cyclopentanone **3** was examined.

Table 1 Additions to Cyclohexanone 2



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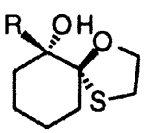

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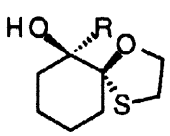
R = Me, H



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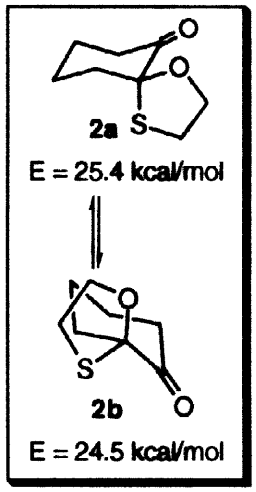
Entry	Reagent	Conditions	%Yield[a]	4 : 5 %Anti : %Syn[b]
a	MeLi	ether, 0 °C	76	91:9
b	MeMgBr	ether, 0 °C	79	85:15
c	MeMgCl	ether, 0 °C	78	89:11
d	$LiBH_4$	THF, 0 °C	91	83:17
e	$LiAlH_4$	ether, 0 °C	83	90:10
f	$LiAl(t\text{-}OBu)_3H$	ether, 0 °C	86	90:10
g	$LiB(CHMeEt)_3H$	THF, 0 °C	65	91:9
h	$Al(i\text{-}Bu)_2H$	THF, -78 °C	89	90:10



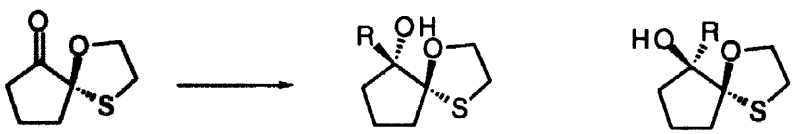
[a] Combined yield of isolated diastereomers. [b]Determined by GC-MS.

The results of the nucleophilic additions to cyclopentanone **3** are summarized in Table 2. In these cases also, a marked preference for attack on the face bearing the ether oxygen, (*i.e.*, *anti* to sulfur and *syn* to oxygen) was observed. A notable exception was the addition of the non-chelating nucleophile diisobutylaluminum hydride (Entries m-o) in which the facial preference was reversed. The DIBAL-H reductions with **3** indicate that solvent effects are not dominant as similar ratios were observed for THF, ether, and CH_2Cl_2. The reactions

with the ionic, alkaline chelators LiAl(*t*-OBu$_3$)H and Red-Al (Na(MeOCH$_2$CH$_2$O)$_2$AlH$_2$) (Entries j and l) indicate that high levels of diastereofacial control may be achieved depending upon the hydride source selected.

Several models have been advanced to rationalize the π-facial stereoselectivity of nucleophilic additions to carbonyl groups. Frye and Eliel[11a] examined the reactions of conformationally locked 1,3-oxathianyl ketones with various nucleophiles and found that complexation was necessary for high induction with chelating nucleophiles such as MeLi, MeMgBr, and L-selectride (LiB(CHMeEt)$_3$H). The authors suggested that these results were accommodated best by the Cram chelate model (**8**).[20] In the case of DIBAL-H the Cornforth dipolar model[21] or the Felkin-Anh type model (**9**)[22,23] in which the 'large' ligand adopts an antiperiplanar disposition relative to the new bond was preferred. Thus for α-heteroatom substituted ketones L (large) is defined as the group with the lowest σ^* orbital (sulfur).[24] According to the Cieplak hyperconjugation model, addition to **3** should occur opposite the antiperiplanar σ-bond that is the better donor (sulfur), as was observed.[4]

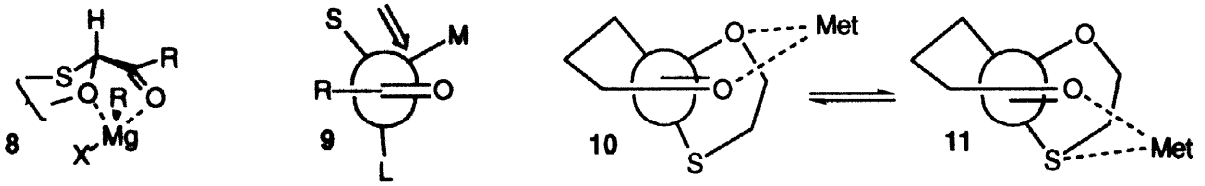
Table 2 Additions to Cyclopentanone 3



3 **6** R = Me, H **7**

Entry	Reagent	Conditions	%Yield[a]	6 : 7 %Anti : %Syn[b]
a	MeLi	ether, 0 °C	79	91:9
b	MeLi	THF, 0 °C	82	87:13
c	MeMgBr	ether, 0 °C	90	84:16
d	MeMgBr	THF, 0 °C	89	85:15
e	MeMgBr	THF, -78 °C	43	70:30
f	MeMgCl	ether, 0 °C	66	78:22
g	MeMgI	ether, 0 °C	88	86:14
h	$LiBH_4$	THF, 0 °C	89	83:17
i	$LiAlH_4$	ether, 0 °C	84	75:25
j	LiAl(*t*-OBu)$_3$H	ether, -78 °C	75	87:13
k	LiB(CHMeEt)$_3$H	THF, 0 °C	65	59:41
l	NaAl[MeO(CH$_2$)$_2$O]$_2$H	ether, 0 °C	77	96:4
m	Al(*i*-Bu)$_2$H	THF, -78 °C	74	16:84
n	Al(*i*-Bu)$_2$H	ether, -78 °C	69	9:91
o	Al(*i*-Bu)$_2$H	CH_2Cl_2, -78 °C	72	11:89

[a] Combined yield of isolated diastereomers. [b] Determined by GC-MS.



However, by analogy with our Diels-Alder studies,[8a,b] we have established that neither n-π orbital mixing nor σ-σ^* hyperconjugation provides the best explanation for the facial selectivity.[8c,d] a conclusion supported by recent studies with rigid ketones.[3f] In the carbonyl cases above the equilibria between the two complexed species **10** and **11** and the free ketone may be important. The lithium cation is a less effective oxygen chelator[25] than Mg^{2+} but the product ratios are very similar. Complexation as illustrated in **11** will free the upper face for rapid nucleophilic attack on the less encumbered side. In an attempt to resolve this issue, and determine the relative importance of the polar and steric effects, locked systems involving spiro 2-tetrahydrofuran and 2-tetrahydrothiophene cyclopentanones are described in the following paper.

In conclusion, by judicious choice of reagents, α-1,3-oxathiolane ketals may be used to control the π-facial selectivity of nucleophilic additions to adjacent ketones.

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