An Investigation of the Diastereoselectivity of Nucleophilic Additions to 6-Methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene-7-carbaldehyde. Hybridization of the Nucleophile Alters the Diastereoselectivity†

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6-Methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene-7-carbaldehyde was treated with a variety of nucleophiles under varying conditions. Whereas the 1,4-diastereoselectivity observed with sp^3 nucleophiles was more or less 1.0:1.1 in favor of attack anti to sulfur, sp^2 and sp nucleophiles exhibited relatively much improved but reversed π-selection under the same conditions. The highest selectivity observed was 3.5:1.0 in favor of attack syn to sulfur in reaction with PhMgBr in Et_2O at −80 °C. This selectivity was reduced to 1.6:1.0 when the reaction was conducted in a 9:1 mixture of Et_2O and HMPA but enhanced to 7.2:1.0 when the polarity of the reaction medium was reduced by conducting the reaction in a 1:1 mixture of Et_2O and *n*-hexane. Neither the anti to S nor the syn to S diastereoselectivity obeyed the dipole model reported by Wipf and Kim. The syn to S selectivity in reactions with sp^2 and sp nucleophiles may be a result of significant and yet specific electrostatic attraction of S for these nucleophilic species which have their negative charges concentrated largely on the carbon for their known significant polar characters.

Introduction

The study of diastereoface selection due to a strategically located heteroatom is of much current interest. It has been shown that with a heteroatom placed on a carbon adjacent to a center of nucleophilic attack, the nucleophile attacks preferentially syn to oxygen and anti to sulfur.[1] A vinylogous heteroatom will also be expected to relay its directing influence through the π bond. The diastereosense of attack, however, may now reverse due to the "vinylogous effect".[2] High diaseterofacial selectivity has been reported in the vinylogous cases as well. From a study of 4-alkoxy-4-alkylcyclohexadienones, Wipf and Kim[2a] have observed selection ranging from 4.8:1 to 32:1 in favor of attack anti to the C4-oxygen substituents.

Sato et al.[3] have studied the 1,4-diastereoselectivity of acyclic γ-sulfenyl and γ-alkoxy α-enones. While the γ-sulfenyl and the γ-silyloxy derivatives generated preferably the syn products, the γ-benzyloxy derivative furnished the anti product in reductions with selected hydride reagents. The variation in selectivity of the γ-oxygenated species was attributed to the differences in the preferred ground state conformations. While the γ-benzyloxy-α,β-unsaturated carbonyl compounds prefer the C_γ-H eclipse the olefin, the corresponding silyl ethers favor the C−O to eclipse.[4] The superior selectivity of the sulfenyl material was attributed to the effective $\sigma-\pi^*$ interaction which fixes the C−S bond orthogonal to one side of the enone. Obviously, the "vinylogous effect" did not apply; the stereochemical outcome would have otherwise been the opposite for the sulfenyl example. The lower diastereoselectivity observed with the γ-alkoxy enones was attributed to the rotation around the $C_\beta-C_\gamma$ bond which cannot be completely suppressed by the weak hyperconjugative effects of the C−O, C−C, or C−H bonds and leads, therefore, to stereochemical fluctuation.

Results and Discussion

Our study has focused on substrate **3** (R = H, Ph) (eq 1) wherein both the oxygen and sulfur atoms are placed at the γ-carbon with fixed stereodispositions. The C−S bond is pseudoaxial and the C−O pseudoequatorial. These orientations were deduced from the X-ray structures of the alcohols **4** (R = H, R′ = Me) (Figure 1) and **5** (R = H, R′ = Ph) (Figure 2).[5] These alcohols were synthesized as shown in eq 2. Whereas the more polar **4** of the pair **4**/**5** (R = H, R′ = Me) had the carbinol oxygen syn to the oxygen of the acetal across the cyclohexene mean plane, the less polar **5** of the pair **4**/**5** (R = H, R′ = Ph) had them anti. Since the oxygen atom binds better with silica gel than sulfur, both the oxygens placed syn are, therefore, likely to raise the polarity of the material in question. This notion finds further support from the X-ray structure of the more polar **6** (Figure 3) of the pair **6**/**7**. This diastereomeric pair of alcohols was prepared as shown in eq 3. This polarity-based stereochemical

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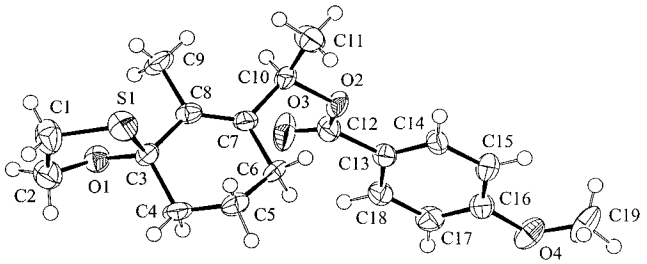


Figure 1. ORTEP plot of the *p*-methoxybenzoate derivative of compound **4** (R = H, R′ = Me). Selected torsion angles [deg]: S1−C3−C8−C 7102.7(9), O1−C3−C8−C7 142.3(9), C9−C8−C7−C10 2(1), C11−C10−C7−C8 95(1), O2−C10−C7−C8 148.7(9), S1−C3−C8−C9 76.7(8), O1−C3−C8−C9 38.3(10).

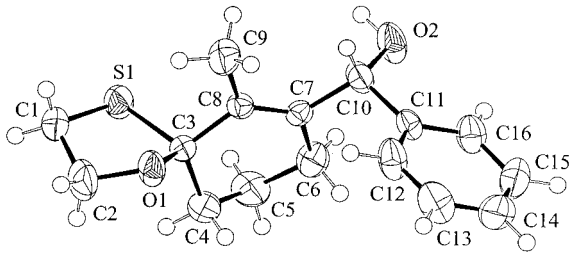


Figure 2. ORTEP plot of compound **5** (R = H, R′ = Ph). Selected torsion angles [deg]: S1−C3−C8−C7 111.5(3), O1−C3−C8−C7 134.2(3), C9−C8−C7−C10 6.5(6), C11−C10−C7−C8 113.7(4), O2−C10−C7−C8 125.7(4), S1−C3−C8−C9 69.7(4), O1−C3−C8−C9 44.6(4).

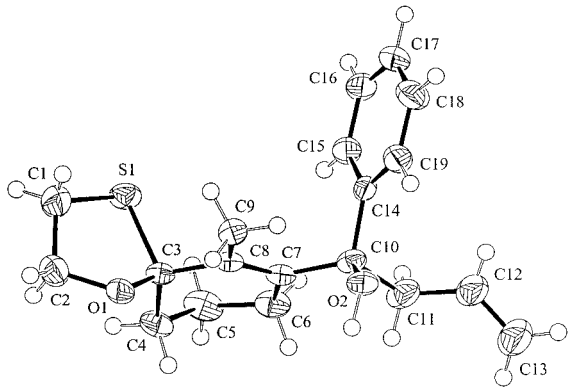
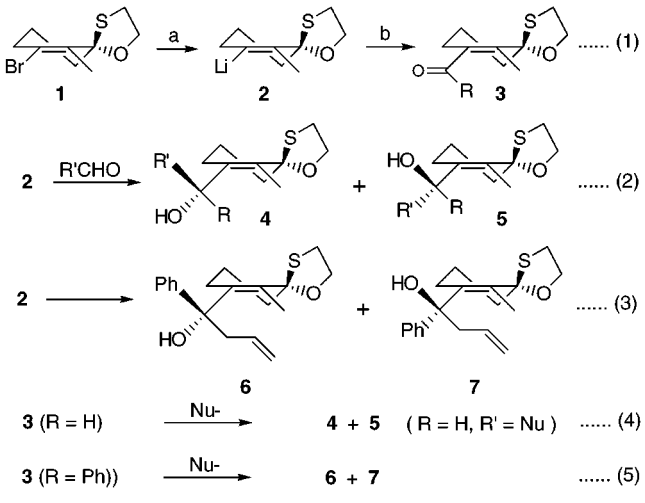


Figure 3. ORTEP plot of compound **6**. Selected torsion angles [deg]: S1−C3−C8−C7 99.2(2), O1−C3−C8−C7 147.2(2), C9−C8−C7−C10 1.2(3), C11−C10−C7−C8 167.1(2), O2−C10−C7−C8 46.6(3), S1−C3−C8−C9 78.1(2), O1−C3−C8−C9 35.5(2), C8−C7−C10−C14 71.5(3).

characterization can, therefore, be safely extended to other derivatives as well.

The C−S bond orbital will be expected to interact with $\pi_{C=C}$ by virtue of being axial in **3**. While the alkyl group at the γ-carbon is forced by the ring geometry to eclipse the olefin, the oxygen atom is in a configuration which resembles the configuration of the γ-benzyloxy-α-enones studied by Sato et al. The designated s-trans conformation of the enal **3** is in accord with the literature.[6,7] A 300 MHz ^{1}H spectrum showed only single singlets for the −C*H*=O (δ 10.14) and the *Me* (δ 2.20). The lower than the normal chemical shift of −C*H*=O will be attributed to the deshielding effect of the proximate π bond which



Reagents: (a) n-BuLi, THF, - 80°C (b) DMF or $PhCONMe_2$, 80% (c) allylphenyl ketone

could be experienced only in the s-trans arrangement.[7] The s-cis conformation will be disfavored for steric interactions between the carbonyl oxygen and the methyl substituent.[8] Following the observations of Sato et al., the nucleophile is predicted to attack anti to the more electron-donating sulfur group[9] and, hence, a preponderance of **5** over that of **4** (R = H, R′ = Nu) (eq 4) will be expected. Likewise, the ketone **3** (R = Ph) must exist in an s-cis conformation to avoid the severe steric interactions between the Ph and the Me groups in the alternate s-trans conformer and the product **7** will be predicted to predominate over **6**.

The results of our experiments with several representative nucleophiles are collected in Table 1. The diastereoselectivity with all the sp^3 nucleophiles (entries 1−6 and 16) was, at best, only marginally in favor of the less polar **5** (R = H, R′ = Nu). When compared to the high selectivity reported by Sato et al., this result is, indeed, very surprising. Further, there was a clean reversal in diastereoselectivity in reactions with sp^2/sp nucleophiles (entries 7−15). The highest selectivity (**4**:**5** = 3.5:1.0) was observed with PhMgBr in Et_2O at −80 °C (entry 9). The selectivity dropped to 2.5:1.0 in the reaction with 1-naphthyl-MgBr (entry 12). The selectivity with vinyl-MgBr (entry 14) under identical conditions was 1.8:1.0. It is interesting to note that the nucleophiles which may be considered intermediate to sp^3 and sp^2 (entries 17−21) showed no noticeable selectivity. The sp nucleophiles also exhibited reverse diastereoselection (entries 22−24). The diastereoselectivity was zero in reaction of allylmagnesium bromide with the single ketone example that we have examined (entry 18). All the diastereoselectivities were determined from the weights of the individual alcoholic products with the results being consistent over at least two independent experiments. Two significant points emerge: (i) the level of diastereoselection achieved from sp^3 nucleophiles is unexpectedly very low and (ii) the facial selectivity is reversed in reactions with sp^2 and sp nucleophiles.

It is important to note that all the products were found to be stable to silica gel chromatography. The conversion

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Table 1. Reaction of 3 with Various Representative Nucleophiles under Varying Conditions

entry	nucleophile	R	solvent and reactn condns	ratio of **4:5** or **6:7** [(more:less) polar][a]	yields,[b] %
1	MeMgI	H	Et_2O, −80 °C	1.0:1.14	95
2	EtMgI	H	Et_2O, −80 °C	1.0:1.14	95
3	$PhCH_2CH_2MgBr$	H	Et_2O, −80 °C	1.0:1.15	90
4	*s*-BuMgCl	H	Et_2O, −80 °C	1.0:1.14	90
5	*t*-BuMgCl	H	Et_2O, −80 °C	1.0:1.16	92
6	$Me_2CHMgBr$	H	Et_2O, −80 °C	1.0:1.16	80
7	PhMgBr	H	Et_2O, −80 °C	3.5:1.0	88
8	PhMgBr	H	THF, −80 °C	1.8:1.0	70
9	PhMgBr	H	Et_2O, 20 °C	1.2:1.0	96
10	PhMgBr	H	Et_2O:HMPA = 9:1, −80 °C	1.6:1.0	95
11	PhMgBr	H	Et_2O:hexane = 1:1, −80 °C	7.2:1.0	95
12	1-naphthyl-MgBr	H	Et_2O, −80 °C	2.5:1.0	94
13	vinyl-MgBr	H	THF, −80 °C	1.6:1.0	90
14	Vinyl-MgBr	H	Et_2O, −80 °C	1.8:1.0	95
15	PhLi	H	Et_2O, −80 °C	1.5:1.0	80
16	*n*-BuLi	H	THF, −80 °C	1.0:1.0	85
17	allyl-MgBr	H	Et_2O, −80 °C	1.0:1.0	95
18	allyl-MgBr	Ph	Et_2O, −80 °C	1.0:1.0	95
19	allyl-Br/Zn	H	DMF, 30 °C	1.0:1.1	92
20	$BrCH_2CO_2Et$/Zn	H	C_6H_6−THF, −80 to 20 °C	1.0:1.0	90
21	allyl-Br/In	H	THF, 20 °C	1.0:1.0	50[c]
22	$LiCCCH_2OTBDMS$	H	THF, −80 °C	1.7:1.0	70
23	$LiCCCH_2OTBDMS$	H	Et_2O, −80 °C	1.8:1.0	75
24	PhCCLi	H	Et_2O, −80 °C	1.4:1.0	80

[a] The ratios reported are the ratios of the actual quantities of the isolated pure isomers. These ratios are consistent over at least two independent experiments. [b] All the new products obtained in this study were fully characterized from a combination of routine spectroscopic data. [c] The reaction was very slow; only half of the aldehyde had reacted even after 36 h.

of one diastereomer into the other was not observed. The products of reaction with PhMgBr, in particular, may be expected to be vulnerable to silica gel for the benzylic as well as the allylic nature of the carbinols as these may be expected to undergo easy ionization under the influence of the acidic surface of silica gel and, thus, lead to transformation of one into the other. That this was not so was confirmed from definitive experiments in which both the diastereomers were separately stirred with column-grade silica gel in benzene for 12 h; in no instance was the other isomer detected by TLC.

The change in the selectivity pattern led us also to consider whether there was interconversion of the products formed under the conditions of the reaction. This interconversion could take place at the stage of either the metal alcoholate or the alcohol itself which is formed after quench with MeOH at −80 °C and then allowed to warm to room temperature. Two experiments were performed on **5** (R = H, R′ = Ph). In the first experiment, the lithium salt was generated on reaction with 1 equiv of *n*-BuLi at −80 °C. After 30 min, a TLC immediately on quench with MeOH at −80 °C and then again at room temperature did not show any of the isomer **4** (R = H, R′ = Ph). In the second experiment, Mg salt was prepared by reaction with *t*-BuMgCl at −80 °C and quenched 30 min later with MeOH. Again, **4** was not detected by TLC at either of the above two stages. Similar experiments on **5** (R = H, R′ = PhCC; Li salt) and **4** (R = H, R′ = Me; Mg salt) did not show any interconversion either. It is, therefore, reasonable to expect similar behaviors from the other alcohols too. The ratios of the isomers reported are, therefore, the true ratios of the isomers actually produced.

The change in diastereosense with the change in the hybridization character of the attacking nucleophile from sp^3 to sp^2 and sp is not totally unprecedented. From the studies on cis [9.3.1]bicyclic ketones, Paquette et al.[10] have observed the selectivity change from 21:79 in favor of attack syn to the larger ring in reaction with BuMgBr to 56:44 in the reaction with PhMgBr. Wipf and Kim[2a] have observed only reduction in the level of selectivity from 4.8:1 to 3.6:1 in favor of attack from anti to the OMe substituent when the nucleophile was changed from MeMgBr to PhMgBr in reactions of 4-methoxy-4-methyl-2,5-cyclohexadienone. These authors have recognized the sensitivity of stereoselection to the electronic structure and, hence, the state of aggregation of the nucleophile. Other variations in reaction parameters such as the solvent and the countercation were attempted but in no case were these authors able to observe the selectivity change in favor of syn to OMe. Clark and Warkentin[11] have studied 2-norbornen-7-one and reported the selectivity change from 77:23 in favor of syn to the π bond with MeLi to 30:70 and 28:72 in reactions with vinyllithium and PhLi, respectively.

Paquette has attributed the above change in selectivity to the larger steric requirement of PhMgBr than that of *n*-BuMgBr. However, since the syn face in 2-norbornen-7-one is somewhat less hindered than the other (anti) face, the reversal in selectivity in reactions with vinyllithium and PhLi appears surprising. The strong preference for anti attack by these lithium reagents was attributed to the fact that these compounds are more polar than their saturated analogs and that the negativeve charge approaching the carbonyl from the syn face encounters a repulsive interaction with the double bond. However, this contrasts the observation that both *n*-BuLi and PhLi gave the exact same stereochemistry in both polar (Et_2O) and nonpolar (*n*-hexane) solvents because the ionic character of the C−Li bond would otherwise be expected to be significantly different in the two solvents.

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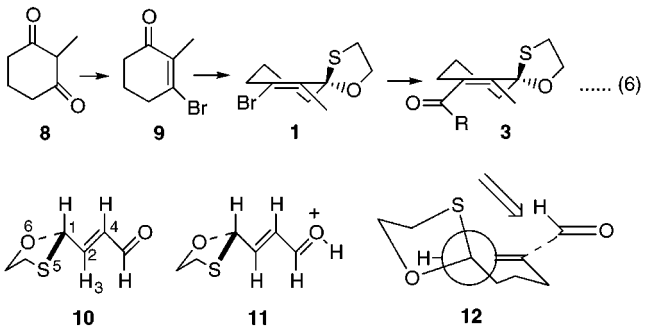
The present reversal in diastereoselectivity is definitely not steric in origin because, had it been so, a selectivity better than that achieved from PhMgBr must have been observed from 1-naphthyl-MgBr. Further, contrary to the observed results, a similar reversal in face selection must have also taken place when the nucleophile was changed from MeMgI to *t*-BuMgCl. Both, however, exhibited identical results. That the observed change in selectivity is indeed not steric in origin is further supported from the reported reactions of 4-*tert*-butylcyclohexanone in Et_2O with Grignard reagents such as *t*-BuMgBr, $PhCH_2MgCl$, EtMgBr, and PhMgBr which are respectively 100, 76, 71, and 49% equatorial selective.[12] Obviously, if only the sterics of the nucleophiles were involved, the selectivity with PhMgBr would be better than that with the Et- and $PhCH_2$-Grignards, and, almost certainly, comparable to that with *t*-BuMgBr.

Although the observed π-facial reversal can be easily explained by invoking an opportune conformational change in the enal subunit from s-trans to s-cis, such a prospect is hardly tenable. With everything but the actual nucleophile equal, it is highly unlikely that such a conformational change will occur only in those cases where sp^2 and sp nucleophiles are involved. In an elegant report, Wipf and Jung[2b] have recently correlated the diastereoselectivity of 4,4-disubstituted cyclohexadienones and naphthoquinones with the direction of the molecule's dipole along the *Z*-axis. The nucleophile approaches the carbonyl on the face which constitutes the positive end of the dipole. Given the fact that a S−C bond is electron releasing from S to C and that a C−O bond is electron attracting from C to O, a simple vector analysis of the dipoles in **3** would indicate a substantial component of this along the axis that is orthogonal to the molecular plane and points from the face containing S to the face possessing the acetal's O. This was confirmed from AM1 calculation[13] of dipoles; the component along the *Z* direction was 1.03 D. Nucleophiles will, therefore, be predicted to approach the carbonyl predominantly on the face that is syn to S. In sharp contradiction to this, the sp^3 nucleophiles exhibited attack anti to S. The level of the observed diastereoselectivity was, however, only marginal. The sp^2 and sp nucleophiles may appear to follow the dipole model since they exhibit preference for attack syn to S but then it is not so for the dipole reasons. A reaction that was carried out with PhMgBr (entry 10) in a 9:1 mixture of Et_2O and HMPA exhibited a drop in selectivity to 1.6:1 from the 3.5:1 exhibited in Et_2O. If the system must obey the dipole model, a rise in the dielectric constant of the reaction medium will be expected to raise the selectivity further due to a rise in the induced dipole moment of the substrate. On the contrary and even more interestingly, a reaction conducted in a 1:1 mixture of Et_2O and *n*-hexane exhibited a selectivity enhanced considerably to 7.2:1 (entry 11). The predominant attack anti to S in the acyclic examples studied by Sato et al. also contradicts the dipole model.

Sato et al. have claimed the diastereoselectivity of their acyclic systems to be a consequence of the electronic effects originating from the S on Cγ of the enone system. The fact that the C−S bond in **3** is (pseudo)axial despite the large bulk of S in comparison to that of the acetal's O is, in itself, indicative of some electronic effects. The enone unit, being electron deficient, must prefer the C−S bond parallel to its π-orbitals. This is achieved by having the C−S bond (pseudo)axial. This parallelism is strengthened on allowing the enone to become even more electron attracting by, say, cation complexation of the carbonyl oxygen.[14] That this is indeed so is demonstrated by ab initio MO calculations at the 6-31G* level on molecule **10** and its protonated derivative **11**. The torsion angle 5 1 2 3 (orbitrary numbering) changed from 70.32° in **10** to 82.79° in **11**. This conformational change is further supported by making the acetal's electron-attracting C−O bond more in the σ plane of the enone system. The torsion angle 6 1 2 4 changed from 137.97° in **10** to 149.78° in **11**. Since a similar conformational change must be expected of **3** in its reactions with nucleophiles, the utterly poor diastereoselectivity with all the sp^3 nucleophiles remains unexplained by the above electronic effects. The preferred syn to S attack in reactions with sp^2 and sp nucleophiles cannot be explained by these electronic effects either.



The above analysis led us to examine the materials studied by Sato et al. closely. In all but one S-containing substrate, the substituent on S is phenyl which is likely to orient over the enone function in an exercise to lower the energy through π-complexation.[15] This will restrict the rotation around the Cγ−S bond and, thus, block this face effectively to allow nucleophiles to enter predominantly from the anti face, as was observed. Since a substrate with Me as a substituent on S does not benefit from such a prospect and, also, since a Me group is smaller in size than a phenyl group, the diastereoselectivity observed is likely to be reduced. However, since large alkyl substituents such as *t*-Bu, *i*-Pr, *n*-C_6H_{13}, and *n*-C_7H_{15} (actually used in Sato's studies) on Cγ will also be expected to restrict the rotation around the Cγ−S bond to a large extent, the diastereoselectivity still may not

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decrease as much as expected above. This is also in good agreement with the reported experimental results. The diastereoselectivities observed by Sato et al. are, therefore, in line with Cram's steric approach model.[16] The electronic effects arising from S primarily influence the stable conformer determination. If there is any influence of these electronic effects on the observed diastereoselectivity, it is substantially small. A similar reasoning for the enone substrates bearing an oxygen on Cγ holds as well.

For the study of true electronic effects on diastereoselection, the substituents and the attacking reagent must be as small as possible. Moreover, the substituents must have no ability to complex with either the other reagent or a function within the same molecule. The substrate **3** which meets these criteria appears well suited to such an study. Whereas the very poor selectivity with the sp^3 nucleophiles is a consequence of only subtle electronic effects arising from the acetal function, the preferred attack syn to S by sp^2/sp nucleophiles is still not accounted for. In the transition structure **12**, the nucleophile is likely to suffer from some steric interaction with the axially substituted large S atom, and hence, more attack from the anti face is predicted. The observed syn attack may, therefore, be a consequence of some significant electrostatic attraction of S for sp^2 and sp nucleophiles which ensures the observed syn to S delivery of these nucleophile to the carbonyl carbon. Why is this electrostatic attraction of S only for the sp^2 and sp nucleophiles and not for the sp^3 counterparts? It is not clear to us due to the absence of significant physical data on such species. However, the known[12b] larger polar character of the sp^2 and sp nucleophiles and, hence, the larger concentration of the negative charge on the carbon in these species than those in the sp^3 nucleophiles may be held responsible for their special recognition by S.

In search for a vinologous Cram's rule, Fleming et al.[17] have observed no diastereoselection in the reductions of 4-methoxy-1,4-diphenyl-2-buten-1-one with $ZnBH_4$ and in the reaction of 4-methoxy-4-phenyl-2-butenal with PhMgBr. From the reaction of a γ-amino enal with various alkyllithiums, Grignard reagents, and $(i\text{-}PrO)_3$-TiMe, the observation of no diastereoselection has led Reetz et al.[18] to conclude that the possible electronic and steric effects are not transmitted through or across the alkene's π-system. The reduction of 1,1-*bis*-ethoxy-5-*tert*-butyldiphenylsilyloxy-3-hexen-2-one by a variety of reagents has been carried out by Dumartin et al.[19] to discover, once again, none or very little diastereoselection. Sato's report is the only report that has invoked the participation of a γC−S bond to have caused enough perturbation in the extended π-system of an acyclic enone that the anti to S face reacts in preference to the other. To the best of our knowledge, there is no other report on face selection of an enone system bearing a sulfur on the γ-carbon. It is, therefore, not surprising to seek an explanation for the high diastereoselection observed by Sato in Cram's steric approach model.

Recently, the indium-promoted allylation reaction has been shown to exhibit higher selectivity in the reactions of α-alkoxycyclohexanones than the related reactions involving other organometallic species.[10,20] The reaction is reported to be even more selective when conducted in water than when performed under strictly anhydrous conditions.[21] We, however, observed no selectivity in anhydrous THF (entry 21). The pH of the solution is reported to be lowered to 2.9 when the reaction is conducted in water.[22] For fear of destroying the acetal function at such a low pH, we did not use water as the reaction medium. Instead, we used phosphate buffer (pH = 6.8) and witnessed no reaction. A combination of buffer and THF was also unyielding.

Conclusion

A change in hybridization from sp^3 to sp^2 and sp of the nucleophile changed the diastereosense of the reaction of 6-methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene-7-carbaldehyde. Whereas the selectivity with sp^3 nucleophiles was surprisingly only in marginal favor of attack anti to S, the sp^2 and sp nucleophiles exhibited relatively much improved but reversed π-selection. The reason for this reversal is believed to be a meaningful electrostatic attraction of the electron-deficient S for the sp^2 and sp nucleophiles which, unlike the sp^3 nucleophiles, have the negative charge concentrated largely on the carbon for their significant polar characters. The observed diastereoselectivity is neither steric in nature nor does it obey the dipole model proposed by Wipf. The observation that the electronic effects are not manifest in the observed diastereoselection is in support of the observations of other researchers. The diastereoselectivity obsrved for the acyclic systems studied by Sato et al. can be explained very well by Cram's steric approach model as well.

Experimental Section

^1H NMR spectra were recorded on Bruker DRX-300, Bruker DPX-200, or Bruker WP-80 instruments in $CDCl_3$ and on a Varian EM-360L spectrometer in CCl_4. ^{13}C NMR spectra were measured on a Bruker DRX-300 at 75 MHz. Signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. All separations of the carbinol products obtained from nucleophilic reactions were performed on a Chromatotron using silica gel 60 PF_{254} (E. Merck) coated plates. All reactions were performed in an atmosphere of dry nitrogen. *t*-BuMgCl and *s*-BuMgCl (both in Et_2O) and vinylmagnesium bromide (THF solution) were purchased from Aldrich. The other Grignard reagents were prepared using standard methods in the requisite solvent. PhLi was prepared from PhBr on reaction with *n*-BuLi at − 80 °C for 5 min. The column grade silica gel (100−200 mesh) used for chromatography was purchased from Acme Synthetic Chemicals, India. The other general remarks are as reported elsewhere.[23]

3-Bromo-2-methyl-2-cyclohexenone (7). 3-Bromo-2-methyl-2-cyclohexenone was prepared from 2-methyl-1,3-cyclohexanedione (**6**) via its mesylate in an overall yield of 80% following modification of a literature procedure.[24] We have discovered that a simple replacement of K_2CO_3 by Et_3N was more convenient. The yield, however, remained unaltered. The

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^{1}H spectral characteristics corresponded well to those reported in the literature.[25]

7-Bromo-6-methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene (1). The procedure followed was that of Shih and Swenton[25] but under more dilute conditions. When 60 mL of C_6H_6 for every millimole of the bromoketone **7** was used, not only did the yield improve from 45% to 88% but also the formation of the *bis*-acetal of 2-methyl-1,3-cyclohexanedione was reduced from substantial to none. This acetal is highly unstable. When kept neat in a refrigerator at −10 °C, it decomposed within 3 days. This material, however, can be stored as a solution in hexane for weeks without significant decomposition. ^{1}H NMR (60 MHz): δ 4.55−3.80 (2H, m), 3.20−2.90 (2H, m), 2.70−2.30 (2H, m), 2.20−1.50 (4H, m), 1.85 (3H, t, J = 2 Hz). Anal. Calcd for $C_9H_{13}BrOS$: C, 43.55; H, 5.28. Found: C, 43.36; H, 5.40.

6-Methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene-7-carbaldehyde (3). A solution of **1** (249 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −80 °C and mixed with *n*-BuLi (625 μL of a 1.6 M solution in hexane). After the solution was stirred for 10 min, DMF (310 μL, 4.0 mmol) was added. The reaction mixture was stirred further for 30 min at −80 °C, quenched with MeOH (82 μL, 2.0 mmol), and allowed to warm to 20 °C. The reaction mixture was diluted with Et_2O (15 mL), mixed with saturated aqeous NH_4Cl (5 mL), and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined extracts were dried and concentrated to furnish a light yellow solid, 0.156 g. Purification yielded the pure aldehyde, 0.140 g, 70%, mp 48 °C.

^{1}H NMR (300 MHz): δ 10.14 (1H, s), 4.52−4.46 (1H, m), 4.18−4.10 (1H, m), 3.23−3.10 (2H, m), 2.21 (3H, t, J = 1.8 Hz), 2.30−1.50 (6H, m). IR (CCl_4): 1655, 1615, 750 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12. Found: C, 60.35; H, 7.16.

General Procedure for Reaction of 3 with Grignard Reagents. All the reactions were carried out on a 0.5 mmol of **3**. The solution/suspension of the Grignard reagent (0.6 mmol) in Et_2O/THF (3 mL) was cooled to −80 °C and mixed with a solution of **3** in the same solvent (2 mL). The reaction mixture was stirred for 1 h and then quenched by adding 4 equiv of MeOH at −80 °C. The reaction contents were diluted with Et_2O (5 mL) and saturated NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined extracts were dried and concentrated to furnish a residue which was chromatographed to isolate the two expected alcohols.

Reformatsky Reaction of $BrCH_2CO_2Et$ with 3. The procedure followed was that of Furstner.[26] Ethyl bromoacetate and grannular Zn were taken in a 3:1 benzene−THF solution and stirred at 20 °C until complete disappearance of Zn. The contents were cooled to −80 °C and mixed with a solution of the aldehyde in the same solvent mixture. The reaction was quenched at −80 °C and then brought to 20 °C before the aqueous workup.

The Reaction of Allylzinc Bromide with 3. A literature protocol[27] was used. The aldehyde and the allyl bromide were mixed in DMF and stirred with grannular Zn at 30 °C until complete disappearance of the aldehyde.

Except for the subtle differences in the multiplicity of the methylene protons, the ^{1}H spectra of the two isomeric alcohols were almost identical in each instance and, hence, the characteristic data for only one isomer for selected cases are given below.

4 (R = H, R′ = Me): ^{1}H NMR (300 MHz) δ 4.80−4.73 (1H, q, J = 6.5 Hz), 4.41−4.35 (1H, m), 4.09−4.00 (1H, m), 3.16−3.03 (2H, m), 1.74 (3H, t, J = 1.5 Hz), 2.05−1.55 (7H, m), 1.20 (3H, d, J = 6.5 Hz); IR ($CHCl_3$) 3420, 1625, 1435, 1040 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.65; H, 8.47. Found: C, 61.50; H, 8.62.

5 (R = H, R′ = Ph): ^{1}H NMR (300 MHz) δ 7.37−7.24 (5H, m), 5.7 (1H, d, J = 2.4 Hz), 4.46−4.40 (1H, m), 4.12−4.04 (1H, m), 3.18−3.10 (2H, m), 2.18−2.08 (2H, m), 1.93 (3H, s), 1.90−1.57 (5H, m); ^{13}C NMR (300 MHz) δ 142.0, 137.5, 132.0, 128.3, 127.0, 125.6, 95.8, 72.0, 71.1, 38.7, 34.9, 23.0, 20.4, 13.0; IR ($CHCl_3$) 3440, 1650, 1220, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.54; H, 7.30. Found: C, 69.46; H, 7.43.

4 (R = H, R′ = Ph): ^{13}C NMR (300 MHz) δ 142.1, 137.5, 132.0, 128.3, 127.1, 125.5, 96.4, 72.1, 71.2, 38.8, 34.9, 23.3, 20.7, 12.9.

4 (R = H, R′ = Et): ^{1}H NMR (60 MHz) δ 4.65−4.15 (2H, m), 4.15−3.77 (1H, m), 3.20−2.87 (2H, m), 1.70 (3H, bs), 0.90 (3H, t, J = 5 Hz), 2.50−1.20 (9H, m). Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.13; H, 8.84. Found: C, 62.97; H, 8.94.

4 (R = H, R′ = 2-phenethyl): ^{1}H NMR (60 MHz) δ 7.2 (5H, s), 4.65−3.65 (3H, m), 3.16−2.84 (2H, m), 2.83−2.43 (2H, m), 2.43−1.50 (9H, m), 1.60 (3H, bs); IR ($CHCl_3$) 3440, 1630, 1210, 750 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.02; H, 7.95. Found: C, 69.90; H, 8.10.

4 (R = H, R′ = *s*-Bu): ^{1}H NMR (60 MHz) δ 4.50−3.80 (3H, m), 3.17−2.87 (2H, m), 2.34−1.40 (10H, m), 1.70 (3H, bs), 1.0−0.6 (6H, m). Anal. Calcd for $C_{14}H_{24}O_2S$: C, 65.59; H, 9.44. Found: C, 65.45; H, 9.60.

4 (R = H, R′ = *t*-Bu): ^{1}H NMR (60 MHz) δ 4.50−3.80 (2H, m), 4.25 (1H, s), 3.17−2.87 (2H, m), 1.70 (3H, t, J = 1.2 Hz), 2.30−1.20 (7H, m), 0.90 (9H, s). Anal. Calcd for $C_{14}H_{24}O_2S$: C, 65.59; H, 9.44. Found: C, 65.42; H, 9.57.

4 (R = H, R′ = *i*-Pr): ^{1}H NMR (60 MHz) δ 4.6−3.8 (3H, m), 3.2−2.9 (2H, m), 1.75 (3H, t, J = 1.8 Hz), 1.05 (3H, d, J = 7 Hz), 0.75 (3H, d, J = 7 Hz); IR ($CHCl_3$) 3440, 1640, 1455, 1445, 1430, 1205, 1050, 1005, 750 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.43; H, 9.16. Found: C, 64.34; H, 9.30.

4 (R = H, R′ = vinyl): ^{1}H NMR (300 MHz) δ 5.90−5.79 (1H, m), 5.29−5.28 (1H, td, J = 17 and 1.5 Hz), 5.18−5.13 (1H, td, J = 10.5 and 1.5 Hz), 5.10 (1H, br s), 4.40−4.38 (1H, m), 4.12−4.04 (1H, m), 3.18−3.04 (2H, m), 2.24−2.05 (2H, m), 1.78 (3H, t, J = 1.8 Hz), 2.03−1.50 (5H, m); ^{13}C NMR (300 MHz) δ 137.7, 136.5, 130.8, 114.6, 96.4, 71.7, 71.1, 38.8, 34.7, 23.2, 20.7, 12.3; IR ($CHCl_3$) 3430, 1620, 1425, 1205 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.69; H, 8.02. Found: C, 63.74; H, 8.16.

5 (R = H, R′ = vinyl): ^{13}C NMR (300 MHz) δ 138.0, 136.6, 131.2, 114.7, 96.5, 71.9, 71.1, 38.9, 35.0, 23.1, 20.6, 12.7.

4 (R = H, R′ = 1-naphthyl): ^{1}H NMR (300 MHz) δ 7.87−7.84 (2H, m), 7.77 (1H, d, J = 8.1 Hz), 7.66 (1H, d, J = 7.2 Hz), 7.51−7.44 (3H, m), 6.25 (1H, s), 4.43−4.38 (1H, m), 4.07−3.99 (1H, m), 3.18−3.05 (2H, m), 2.01 (3H, s), 2.19−1.40 (7H, m); IR (film) 3410, 1670, 1585, 1495, 1050, 775 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_2S$: C, 73.59; H, 6.80. Found: C, 73.50; H, 6.90.

4 (R = H, R′ = *n*-Bu): ^{1}H NMR (80 MHz) δ 4.72−3.93 (3H, m), 3.25−3.00 (2H, m), 2.50−1.10 (13H, m), 1.78 (3H, bs), 0.90 (3H, t, J = 5 Hz); IR (film) 3400, 1640, 1450, 1440, 1430, 1260, 1165, 1040, 875, 750 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2S$: C, 65.59; H, 9.44. Found: C, 65.44; H, 9.60.

4 (R = H, R′ = allyl): ^{1}H NMR (200 MHz) δ 5.90−5.70 (1H, m), 5.18−5.09 (2H, m), 4.65−4.58 (1H, m), 4.42−4.35 (1H, m), 4.12−4.04 (1H, m), 3.14−3.05 (2H, m), 1.75 (3H, t, J = 1.8 Hz), 2.40−1.58 (9H, m); ^{13}C NMR (300 MHz) δ 137.6, 134.6, 130.3, 117.7, 96.3, 71.0, 70.3, 39.4, 38.8, 34.8, 23.1, 20.5, 12.4. IR (film) 3400, 1630, 1430, 1165, 905, 750 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2S$: C, 64.97; H, 8.39. Found: C, 64.82; H, 8.45.

5 (R = H, R′ = allyl): ^{13}C NMR (300 MHz) δ 137.3, 134.7, 133.6, 130.6, 117.7, 96.6, 71.0, 70.1, 39.4, 38.8, 34.8, 22.8, 20.5, 12.5.

4 (R = H, R′ = CH_2CO_2Et): ^{1}H NMR (60 MHz) δ 5.0−4.7 (1H, dd, J = 8.5 and 5 Hz), 4.4−4.1 (2H, m), 4.1 (2H, q, J = 7 Hz), 3.2−2.9 (2H, m), 1.7 (3H, t, J = 1.8 Hz), 1.2 (3H, t, J = 7 Hz). Anal. Calcd for $C_{14}H_{22}O_4S$: C, 58.72; H, 7.75. Found: C, 58.88; H, 7.92.

4 (R = H, R′ = PhCC): ^{1}H NMR (200 MHz) δ 7.47−7.42 (2H, m), 7.34−7.26 (3H, m), 5.51 (1H, d, J = 1.8 Hz), 4.46−4.36 (1H, m), 4.13−4.01 (1H, m), 3.20−3.04 (2H, m), 2.40−2.30 (2H, m), 1.87 (3H, t, J = 1.8 Hz), 2.20−1.62 (5H, m); ^{13}C NMR (300 MHz) δ 135.1, 132.4, 131.8, 128.4, 128.3, 122.6, 96.2, 88.3, 85.3, 71.1, 62.7, 38.7, 34.8, 24.1, 20.6, 12.6; IR (film) 3410, 1590, 1500, 1430, 1050, 775 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.97; H, 6.72. Found: C, 72.15; H, 6.85.

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5 (R = H, R′ = PhCC): ^{13}C NMR (300 MHz) 134.9, 132.6, 131.8, 128.4, 128.3, 122.6, 96.2, 88.3, 85.1, 71.2, 62.4, 38.5, 34.8, 23.8, 20.5, 12.6.

4 (R = H, R′ = TBDMSOCH$_2$CC): ^{1}H NMR (300 MHz) δ 5.32 (1H, s), 4.42−4.37 (1H, m), 4.35 (2H, d, J = 1.8 Hz), 4.11−4.03 (1H, m), 3.13−3.07 (2H, m), 2.28−2.24 (2H, m), 2.15−2.06 (1H, m), 2.02−1.93 (1H, dt, J = 11, 3 Hz), 1.89−1.80 (1H, m), 1.79 (3H, t, J = 1.8 Hz), 1.74−1.64 (1H, m), 0.91 (9H, s), 0.12 (6H, s). Anal. Calcd for $C_{19}H_{32}O_3SSi$: C, 61.93; H, 8.76. Found: C, 61.75; H, 8.90.

6 (R = allyl, R′ = Ph): ^{1}H NMR (300 MHz) δ 7.41−7.23 (5H, m), 5.87−5.73 (1H, m), 5.22−5.17 (2H, m), 4.40−4.33 (1H, m), 4.10−4.02 (1H, m), 3.08−3.03 (2H, m), 2.96−2.89 (1H, dd, J = 13.8, 7.2 Hz), 2.79−2.72 (1H, dd, J = 13.8, 7.5 Hz), 1.56 (3H, s), 2.40−1.57 (7H, m); IR ($CHCl_3$) 3440, 1650, 1210, 755 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.12; H, 7.65. Found: C, 71.94; H, 7.78.

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Supporting Information Available: ^{1}H NMR spectra of compounds **3**, **4** (R = H; R′ = Me, allyl, vinyl, 1-naphthyl, PhCC, $CCCH_2OSiMe_2Bu^t$), **5** (R = H; R′ = Me, allyl, vinyl, PhCC, Ph), and **6** (R = allyl, R′ = Ph), ^{13}C spectra of **4** and **5** (R = H, R′ = allyl, PhCC, vinyl, Ph), and selected X-ray data (bond lengths, bond angles, and torsion angles) on **4** (R = H, R′ = Me; the p-methoxybenzoate), **5** (R = H, R′ = Ph), and **6** (R = allyl, R′ = Ph) (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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