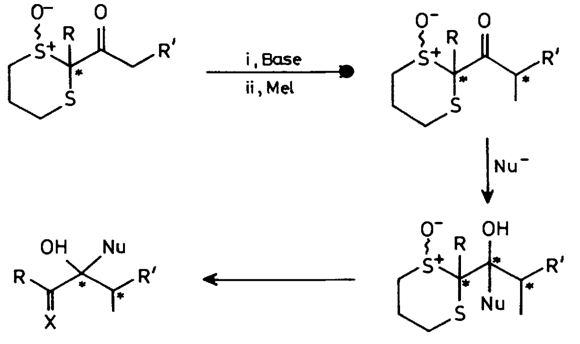
# Diastereoselective Control in the Addition of Grignard Reagents to Ketones using a 1,3-Dithiane 1-Oxide Auxiliary

**Philip C. Bulman Page* and Donald Westwood**
*Department of Chemistry, Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX*
**Alexandra M. Z. Slawin and David J. Williams**
*Department of Chemistry, The Imperial College of Science and Technology, South Kensington, London, SW7 2AY*

2-Acyl-1,3-dithiane 1-oxides undergo diastereoselective addition of Grignard reagents; very high selectivities have been observed under certain reaction conditions.

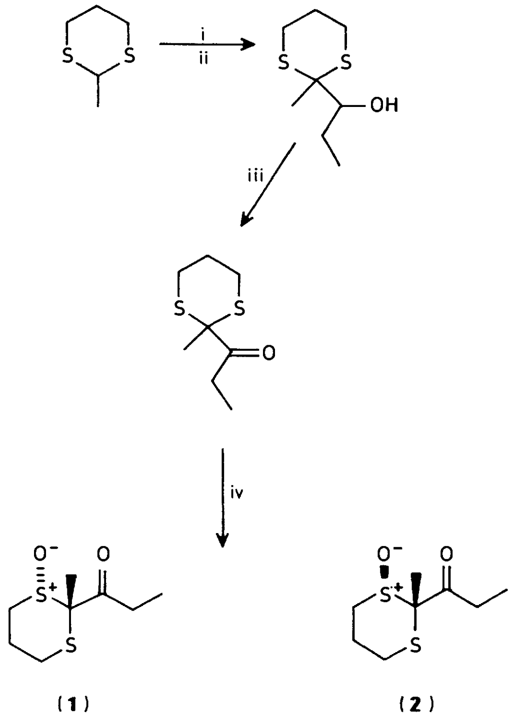
Recently in this laboratory we were able to demonstrate that enolates of 2-acyl-1,3-dithiane 1-oxides undergo diastereoselective alkylation in ratios up to *ca.* 25:1.[1] The 2-acyl-1,3-dithiane 1-oxide system is particularly interesting as a stereocontrol element because it allows stereocontrol of nucleophilic additions to the carbonyl group without loss of the auxiliary and because it may also be utilised as a synthetic building block (Scheme 1).



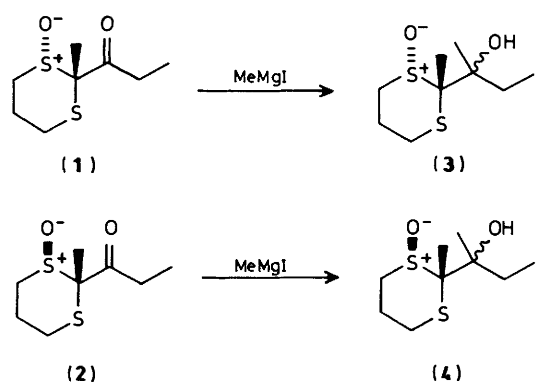
Scheme 1.

The addition of organometallic reagents to ketones containing a chiral grouping directly attached to the carbonyl group has been extensively studied.[2] The stereoselectivities of such reactions are generally not very high[3] unless one of the substituents adjacent to the ketone is capable of chelation with the organometallic reagent.[4] This is borne out by comprehensive studies of organometallic additions to enantiomerically pure 2-acyl-1,3-oxathiane[5] and chiral acyl diazabicyclopentane systems.[6] These studies also indicate that the selectivity of the addition shows a marked dependence upon the temperature of the reaction, the solvent used, and the nature of the organometallic reagent. We expected on the basis of our earlier work[1] that the sulphoxide unit of our auxiliary should influence the course of organometallic attack at the carbonyl group of an acyl dithiane oxide system by providing a highly dipolar unit to which the metal could chelate.

The preparation of 2-acyl-1,3-dithiane 1-oxide systems has been previously described.[1] Thus, high yields of the *syn* (**1**) and *anti* (**2**) 2-methyl-2-propionyl-1,3-dithiane 1-oxides were achieved *via* a three-step process (Scheme 2), followed by a chromatographic separation of diastereoisomers. We are currently investigating a simultaneous diastereoselective and enantioselective sulphoxidation process employing the modified Sharpless oxidation techniques of Kagan and Di Furia.[7]



**Scheme 2.** *Reagents*: i, BuLi; ii, propanal; iii, Swern; iv, $NaIO_4$, MeOH, $H_2O$



**Scheme 3.**

**Table.**

| Entry | Substrate | Solvent | Temp. (°C) | Product | Yield (%) | Ratio of isomers[a] |
|---|---|---|---|---|---|---|
| a | (1) | THF | 25 | (3) | 70 | 4:1 |
| b | (1) | THF | −20 | (3) | 95 | *ca.* 25:1[b] |
| c | (1) | THF | −78 | (3) | 95 | Exclusive[c] |
| d | (1) | $Et_2O$ | 25 | (3) | 93 | 1.1:1 |
| e | (1) | $Et_2O$ | −20 | (3) | 96 | 1:1.4 |
| f | (1) | $Et_2O$ | −78 | (3) | 33 | 1:1 |
| g | (2) | THF | 25 | (4) | 92 | 3:1 |
| h | (2) | THF | −20 | (4) | 96 | 7:1[b] |
| i | (2) | THF | −78 | (4) | 95 | 15:1[b] |
| j | (2) | $Et_2O$ | 25 | (4) | 100 | 2.3:1 |
| k | (2) | $Et_2O$ | −20 | (4) | 95 | 3:1[b] |
| l | (2) | $Et_2O$ | −78 | (4) | 96 | 3:1 |

[a] Determined by 250 MHz $^1$H n.m.r. [b] Determined by h.p.l.c. [c] Other isomer undetectable by h.p.l.c. or n.m.r.

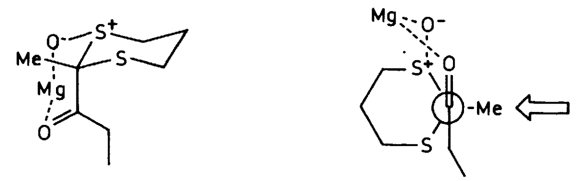


**Figure 1.**

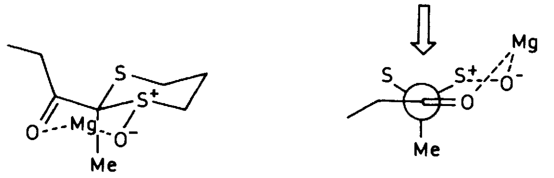


**Figure 2.**

We have chosen to investigate the reactions of the substrates (**1**) and (**2**) with methylmagnesium iodide (*ca.* 4 equiv.) in either tetrahydrofuran (THF) or diethyl ether solvents (Scheme 3) to give mixtures of the diastereoisomeric alcohols (**3**) and (**4**). The reactions have been carried out at a range of temperatures and were normally worked up by pouring onto saturated aqueous ammonium chloride followed by extraction with dichloromethane. The crude materials were generally chromatographed on silica gel and diastereoisomeric ratios analysed by 250 MHz $^1$H n.m.r. spectroscopy and by h.p.l.c. analysis. The isomeric ratios observed in these experiments are summarised in the Table.

As expected,[5,6] the diastereoselectivities observed show a dependence on temperature and solvent. Reactions carried out in tetrahydrofuran solution give results in accordance with chelated Cram type transition states containing equatorial sulphoxides. For the *syn* substrate (**1**), the approach of the nucleophile is controlled by the steric restriction imposed by the bulky dithiane 1-oxide ring *versus* that of the relatively small 2-methyl group (Figure 1), giving rise to excellent diastereoselectivities at low temperatures (entries b, c). For the *anti* substrate (**2**), the chelated transition state relies solely on the 2-methyl group to exert any steric hindrance towards the approach of the Grignard reagent, but even here very good diastereoselectivities (*ca.* 15:1, entry i) are achieved at low temperature (Figure 2).

Diastereoselectivities for the reactions carried out in tetrahydrofuran solution are much greater than those carried out in diethyl ether, providing further evidence that this is the solvent of choice for stereoselective additions of Grignard reagents.[8] Although reactions of the anti substrate (**2**) in ether still conform to the Cram chelate rule, we observed little or no temperature effect on the addition. Reactions of the *syn* substrate (**1**) in ether were anomalous and in one instance

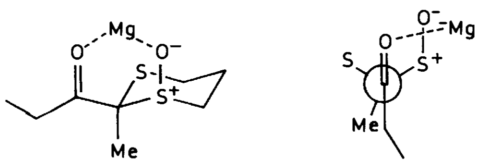


Figure 3.

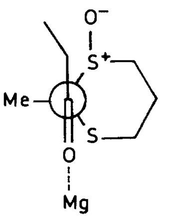
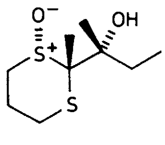


Figure 4.



(5)

violate the expected pattern (entry e). In this case an alternative chelated transition state containing an axial sulphoxide may apply (Figure 3), or possibly an open transition state[2] or dipolar system[9] (Figure 4).

Structural assignment of the products was carried out by comparison of their $^1$H n.m.r. spectra at 250 MHz with that of the major diastereoisomer (**5**) isolated from the addition of methylmagnesium iodide to the *syn* system (**1**) in THF solution (entries a, b, c), the structure of which was solved by *X*-ray analysis (Figure 5).* The structure is in accordance with the expected chelated transition state (Figure 1) and an approach of the nucleophile from the least hindered face of the carbonyl group.

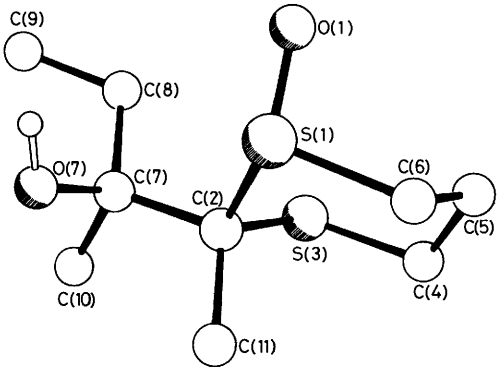


**Figure 5.** The molecular structure of one of the independent molecules of (**5**) in the crystal, showing the *trans* diaxial arrangement of the sulphoxide and methyl groups. Both independent molecules have identical conformations. There are intermolecular hydrogen bonds between the hydroxy oxygen atom O(7) and the sulphoxide oxygen atom O(1), 2.77 Å, and between O(7′) and O(1′), 2.79 Å (*i.e.* hydrogen bonds between 'like' molecules only)

This investigation has enjoyed the support of the S.E.R.C. and the Research Corporation Trust.

## References

1 P. C. B. Page, D. Westwood, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Perkin Commun.*, 1989, 185.
2 D. Y. Curtin, E. E. Harris, and E. K. Meislich, *J. Am. Chem. Soc.*, 1952, **74**, 2901; D. J. Cram and F. A. Abd Elhafez, *ibid.*, 5828.
3 For an example, see J. H. Morrison and H. S. Mosher in 'Asymmetric Organic Reactions,' Prentice Hall, New York, 1971.
4 D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, 1959, **81**, 2748; see also E. L. Eliel in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, London, 1986, vol. 2, ch. 5.
5 E. L. Eliel and S. V. Frye, *J. Am. Chem. Soc.*, 1988, **110**, 484; E. L. Eliel and S. Morris-Natschke, *ibid.*, 1984, **106**, 2937.
6 T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111; M. Asami and T. Mukaiyama, *Chem. Lett.*, 1983, 93.
7 S. H. Zhao, O. Samuel, and H. B. Kagan, *Tetrahedron*, 1987, **43**, 5135; O. Bortolini, F. Di Furia, G. Licini, G. Modena, and M. Rossie, *Tetrahedron Lett.*, 1986, **27**, 6257.
8 D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, 1963, **85**, 1249; W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, 1980, **21**, 1031.
9 J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.

*Received* 14*th December* 1989; *Paper* 8/04923H

---

* *Crystal Data.*—$C_9H_{13}O_2S_2$, $M = 222.4$, triclinic, $a = 9.024(5)$, $b = 10.644(5)$, $c = 11.607(5)$ Å, $\alpha = 94.08(4)$, $\beta = 89.94(4)$, $\gamma = 97.43(4)°$, $U = 1\,103$ Å$^3$, space group $P\bar{1}$, $Z = 4$ (2 crystallographically independent molecules), $D_c = 1.34$ g cm$^{-3}$, $\mu(\text{Cu-}K_\alpha) = 41$ cm$^{-1}$, $F(000) = 480$. 2 893 independent reflections ($\theta \leqslant 58°$) were measured on a Nicolet R3m diffractometer with Cu-$K_\alpha$ radiation (graphite monochromator) using ω-scans. Of these 2 502 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. Refinement converged to give $R = 0.096$, $R_w = 0.102$ [$w^{-1} = \sigma^2(F) + 0.006F^2$]. The high $R$ value is due to multiple twinning in the crystalline sample. The stereochemistry is however definitive. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1989)', *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.