Tetrahedron Letters, Vol.31, No.32, pp 4569-4572, 1990
Printed in Great Britain

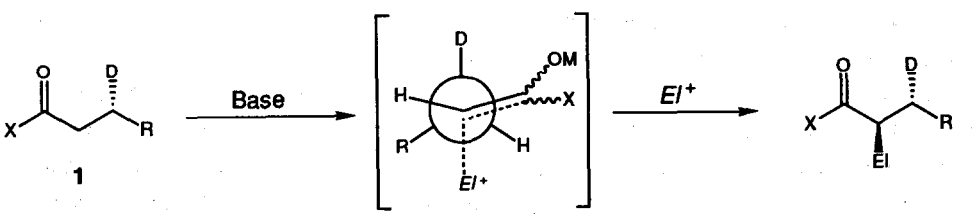
0040-4039/90 $3.00 + .00
Pergamon Press plc

# THE DIASTEREOSELECTIVE INFLUENCES OF REMOTE SUBSTITUENTS ON ENOLATE ALKYLATIONS

**Glenn J. McGarvey* and Marc W. Andersen**
*University of Virginia*
*Department of Chemistry*
*Charlottesville, Virginia 22901*

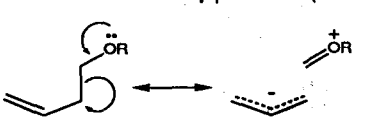
*SUMMARY:* The methylation of a series of γ-oxygenated ketones enolates (**3**) has been examined with the result that poor to outstanding levels of diastereoselectivity are observed that appear to be predictably consistent with a general model for asymmetric electrophilic addition reactions.

The effect of allylic substituents upon the facial selectivity in addition reactions of double bonds is well-documented and continues to be a topic of considerable interest.[1] In an effort to understand the stereodirecting effects of allylic centers in electrophilic addition reactions, we have examined the alkylation of enolates derived from precursors of the general type **1** (D = electron-donating substituent, R = alkyl substituent) under conditions unfavorable for chelation with the result that exceptional levels of stereoselection may be observed with strong σ-donating substituents (D).[2] This selectivity was rationalized by a staggered transition state geometry **2** which was derived through a consideration of stabilizing stereoelectronic effects and destabilizing steric effects.[2]




**1** **2**

Especially noteworthy in these studies was the remarkable diastereofacial preferences expressed by the alkylation reactions of enolates bearing oxygen substitution at a γ-position (D = $CH_2OR$). It was suggested that electronic donation in the transition state by this substituent resulted from a hyperconjugative interplay of the type shown in the Figure.[2] Previously, others have effectively argued for the participation of allylic σ-bonds in the stabilization of staggered transition states.[3]



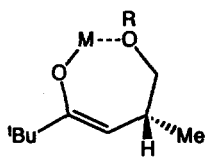

*Figure*

It is worth noting that the implied $n \rightarrow (\sigma^*)^{\ddagger}$ donation in this interaction bears resemblance to electronic explanations for the generalized *gauche* effect (including the anomeric effect).[4] In this

Communication, we examine the effect of varying the steric and electronic nature of γ-oxygen substituents on the selectivity of the methylation of a ketone enolate in an effort to shed light on the role of stereoelectronic influences on electrophilic addition reactions.

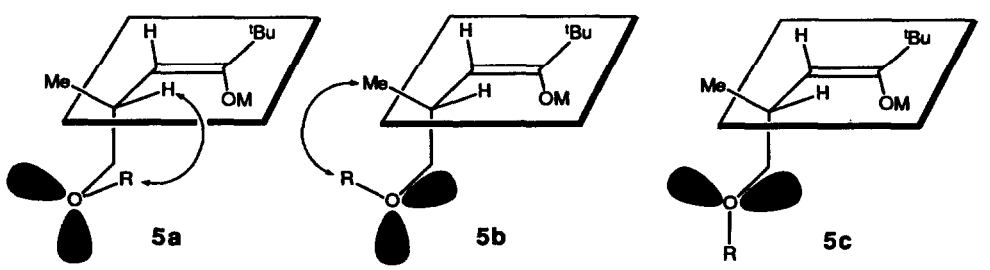
To minimize enolate geometry as a variable in this study, *t*-butyl ketones **3** were selected for investigation.[5] The Table gives the stereoselectivities resulting from methylation of the derived Z-enolates[6] bearing a variety of substituents on the terminal oxygen. Several features of these data deserve comment. As evidenced by entries 5, 6, and 10, bulky substituents on oxygen serve to diminish the levels of stereoselectivity. It is clear, however, that sterics alone do not control the outcome of these alkylations, a point illustrated by the higher *syn* selection observed with the $^{t}BuMe_2Si$ ether (entry 11) relative to the methyl ether (entry 3). Especially intriguing are the remarkably high levels of stereoselection observed in the methylation reactions of the aryl esters in entries 12, 13, and 14, where only the *syn* product was detected (NMR).

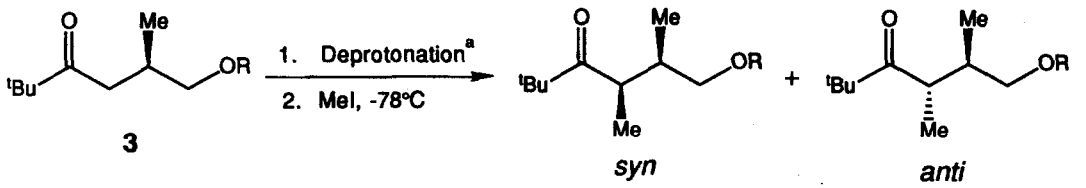
In the course of interpreting these results, the role of chelation (see **4**) in defining the transition state geometry was of particular concern since this would also predict the observed *syn* selectivity. While chelation cannot be discounted in the highly selective (but inefficient) reactions of the dianions of entries 1 and 2, it appears less plausible as an explanation for the *syn* selection displayed by entries 11-14. In addition, highly ionizing conditions (excess HMPA) were employed for all of the alkylations to discourage such an intramolecular association. This issue was specifically addressed by the experiments in entries 8 and 9, where it was observed that a change from a less ionic (lithium) to a more ionic enolate (potassium) in excess HMPA resulted in *increased* stereoselectivity.



**4**

Accepting minimal intervention by chelation, these findings appear consistent with the proposed transition state **2**. Staggered transition state models **5a-c** can be envisioned to accommodate the varying electronic and steric requirements of the substituents studied. In **5a** and **5b**, the desirable co-linearity of the oxygen lone pair and the allylic C-C σ-bond is maintained, correctly predicting *syn* selection. If the substituent is sterically demanding, however, destabilization by the indicated eclipsing interactions may suppress the lone pair interaction, leading to a diminished preference for the *syn* product (see entries 5, 6, and 10). A third possible model positions the substituent in the anti-periplanar orientation (**5c**). While this minimizes steric destabilization, it is electronically less attractive in all cases save that of the silyl ether where the substantial σ-donor properties of the Si-C bond may, in fact, favor this orientation.[7]

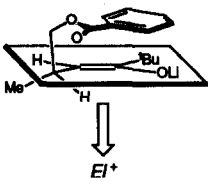




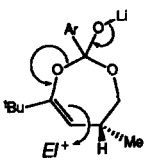

| Entry | R | Yield[b] | syn:anti[c] |
|---|---|---|---|
| 1[d] | Li | 34% | >95:5 |
| 2[e] | K | 17% | >95:5 |
| 3 | Me | 95% | 75:25 |
| 4 | $PhCH_2$ | 90% | 80:20 |
| 5 | $Me_3C$ | 60% | 60:40 |
| 6 | $Ph_3C$ | 92% | 60:40 |
| 7 | $MeOCH_2$ | 93% | 82:18 |
| 8 | $MeOCH_2CH_2OCH_2$ | 98% | 80:20 |
| 9[f] | $MeOCH_2CH_2OCH_2$ | 60% | 90:10 |
| 10 | $MeOC(Me)_2$ | 70% | 56:44 |
| 11 | $^tBuMe_2Si$ | 95% | 85:15 |
| 12 | PhCO | 79% | >95:5 |
| 13 | *p*-$NO_2$PhCO | 70% | >95:5 |
| 14 | *p*-MeOPhCO | 80% | >95:5 |

[a] except where noted, the standard deprotonation conditions are: 2.5 equiv. LDA, 10 equiv. HMPA, THF, 0°C
[b] yield of chromatographed material
[c] determined by integration of the $^1H$ NMR (360 MHz) of both the crude and purified products
[d] 5 equiv. LDA, 25 equiv. HMPA
[e] 5 equiv. $KN(TMS)_2$, 25 equiv. HMPA
[f] 2.5 equiv. $KN(TMS)_2$

Particularly interesting are the exceptional selectivities found for the aryl esters in entries 12-14. An intriguing explanation for these observations includes an attractive π-stacking interaction in the model to further enhance the favored bias (**6**).[8] Consistent with other reports, changes in the electronic density of the aromatic ring/carbonyl through ring substituents (entries 13 and 14) have little observable effect.[8] However, other possibilities, including the selective collapse of alkoxide **7**, cannot be excluded at this time.




**6**




**7**

These results demonstrate a means of efficiently forming a carbon-carbon bond with stereocontrol that may be predictably rationalized by transition state model **2**. While the data presented appear consistent with this model, further experimental and theoretical studies are necessary to complete an understanding of the subtle interplay of the steric and electronic effects influencing facial selectivity in these and related reactions. Studies are in progress to predictably apply stereoelectronic influences to asymmetric processes and to further test the validity of π-stacking in this context as a useful control element.

*Acknowledgements:* The financial support of the National Institutes of Health is gratefully acknowledged.

## References and Notes

1. For recent referenes that extensively cite related literature, see: (a) Seebach, D.; Zimmerman, J.; Gysel, U.; Ziegler, R.; Ha, T.-K.; *J. Am. Chem. Soc.* **1988**, *110*, 4763. (b) Johnson, C.R.; Tait, B.O.; Cieplak, A.S. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (c) Kahn, S.D.; Pau, C.F.; Chamberlin, A.R.; Hehre, W.J. *J. Am. Soc. Soc.* **1988**, *110*, 650.
2. McGarvey, G.J.; Williams, J.M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.
3. See reference 1. Also: Ahn, N.T.; Eisenstein, O. *Top. Curr. Chem.* **1980**, *88*, 145.
4. For general discussion, see: (a) Deslongchamps, P. *"Stereoelectronic Effects in Organic Chemistry"*, Pergamon Press: Oxford, 1983; Chapter 1. (b) Kirby, A. *"The Anomeric Effect and Related Stereoelectonic Effects at Oxygen"*, Springer-Verlag: New York, 1983. (c) *"Anomeric Effect, Origin and Consequences"*, Szarek, W.A.; Horton, D., Eds.; American Chemical Society: Washington, D.C., 1979.
5. Enolates of *t*-butyl ketones overwhelmingly favor the Z-geometry: Heathcock, C.H.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
6. Analysis of the corresponding silyl enol ethers by $^1$H NMR revealed a single stereoisomer.
7. The "β-silyl effect": Wiedner, U.; Schweig, A. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 146.
8. For a recent paper documenting the enhancement of stereoselectivity by suitably positioned aryl substituents, see: Evans, D.A.; Chapman, K.T.; Hung, D.T.; Kawaguchi, A.T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.

(Received in USA 12 September 1989)