Tetrahedron Letters, Vol.30, No.7, pp 779-782, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

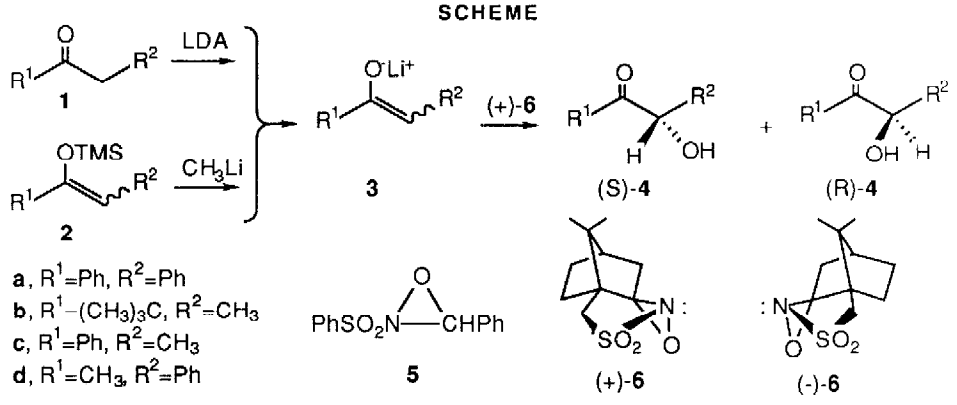
INFLUENCE OF ENOLATE GEOMETRY AND STRUCTURE ON THE STEREOCHEMISTRY OF THE ASYMMETRIC OXIDATION OF PROCHIRAL KETONE ENOLATES TO OPTICALLY ACTIVE α-HYDROXY KETONES

Franklin A. Davis,* Aurelia C. Sheppard and G. Sankar Lal
Department of Chemistry, Drexel University, Philadelphia, PA 19104

Summary: *The stereoselectivity for the asymmetric oxidation of enolates to optically active α-hydroxy ketones using (+)-(camphorylsulfonyl)oxaziridine is dependent on the enolate substitution pattern, the solution structure of the enolate and to a lesser extent the enolate geometry.*

Optically active α-hydroxy carbonyl compounds **4** are key intermediates in the enantioselective synthesis of natural products and a common feature of many biologically important molecules.[1] A convenient route to this important structural array is the direct oxidation of homochiral enolates with N-sulfonyloxaziridine **5**, an aprotic oxidizing reagent.[1b-d] Recently we introduced methodology for the asymmetric oxidation of prochiral enolates to optically active α-hydroxy carbonyl compounds using (+) and (-)-(camphorylsulfonyl)oxaziridines **6** (50-96% ee).[2] Since the configuration of the oxaziridine three-membered ring in **6** controls the product stereochemistry both optical isomers of **4** are easily accessible.[2d] To maximize the efficiency of this methodology an understanding of the factors controlling the stereochemical outcome of these oxidations is necessary (Scheme). In this context we report preliminary studies of the influence of enolate geometry and structure on the stereochemistry of the asymmetric oxidation of prochiral ketone enolates. These studies suggest that the stereoselectivity is highly dependent on both the enolate substitution pattern as well as its solution structure. Enolate geometry is of less importance.

SCHEME



The lithium enolates of deoxybenzoin (**1a**), 1-*tert*-butylpropanone (**1b**), 1-phenylpropanone (**1c**) and

phenylacetone (**1d**) were prepared by addition of the ketone (typically 0.5 mmol) in THF (3 mL) to 1.2 eq of LDA at -78 °C, as previously described.[2b] HMPA was added to the LDA solution prior to enolate formation. When unknown, the enolate geometry was determined by trapping with trimethylsilyl chloride (TMSCl),[3] and its stereostructure assigned by NMR as described in the literature.[3, 4] The enolates were oxidized at -78 °C by addition of 1.5 eq of (+)-**6** in THF (3 mL).[2] After 3 min the reaction mixture was warmed to 0 °C and quenched following 10 min by addition of sat. NH_4I solution. In separate experiments it was determined that oxidation is rapid and complete at -45 to -50 °C. Only the enolate of phenylacetone **3d**, in the presence of HMPA, oxidized at -78 °C (entry 8). The α-hydroxy ketones **4** were isolated by extraction into ethyl ether, washed with sat. $Na_2S_2O_3$, sat. brine, and purified by preparative silica gel TLC. The optical purities and absolute configurations of **4** were determined by comparison with optical rotations and by using the chiral shift reagent $Eu(hfc)_3$.

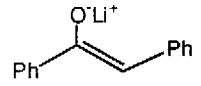
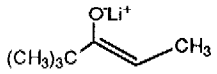
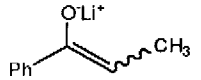
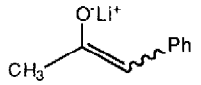
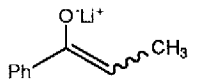
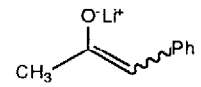
Studies of the aldol[5] and Michael[6] reactions reveal that there is often a strong correlation between the enolate geometry and stereostructure of the product. Generally Z-enolates exhibit higher selectivity than E-enolates.[5] For the asymmetric oxidation of the LDA derived enolates **3** the results in entries 1-8 suggest that the enolate geometry does have a role in determining the product stereochemistry, with Z-enolates exhibiting higher selectivity than E-enolates (compare entries 1, 3, 5 and 8 with 7). However, the dramatic effect that HMPA has on selectivity as well as the fact that Z-**3a**, Z-**3c** gave (S)-**4a**, (S)-**4c**, respectively, while Z-**3b** gave (R)-**4b** makes this assumption suspect. Note also that the lower selectivities observed for oxidation of enolates Z-**3a-c** in the presence of HMPA are not due to a change in enolate geometry, but rather to a change in the solution structure of the enolate.

To determine the influence of enolate geometry on the stereoselectivity for the asymmetric oxidation of enolates it is necessary to oxidize the pure E- and Z-**3** under identical conditions. This was accomplished by generating the E and Z-enolates from the corresponding E- and Z-silyl enol ethers **2** by treatment with MeLi (Scheme).[7] Studies by House[3a] have demonstrated the stereochemical integrity of enolates formed in this manner. Typically **2** (0.5 mmols) in THF (7 mL) was treated at 0 °C with 0.95 equivalents of a 1.4 M solution of methyllithium. After 1 hr the reaction mixture was cooled to -78 °C and oxidized with 1.2 eq of (+)-**6** as described above (Table; entries 9-20).

Several important trends are revealed by the results summarized in the Table (entries 9-20) for the asymmetric oxidation of enolates **3** under identical conditions. First, the stereoselectivity for oxidation of enolates Z-**3c** and Z-**3d** are identical whether or not the enolate is generated from the ketone using LDA or from the silyl enol ether using MeLi. This indicates that the presence or absence of the amine has little effect on the stereoselectivity.[10] Secondly, Z-**3c** exhibits higher selectivity than the E-**3c** affording (S)-α-hydroxy ketone **4c**. HMPA lowers the stereoselectivity. Quite different results are observed for the E- and Z-enolates of phenylacetone (**1d**). Surprisingly, *both* Z-**3d** and E-**3d** exhibit nearly identical stereoselectivities. In the absence of HMPA **4d** is obtained in only 9% ee, whereas in the presence of HMPA the optical purity of **4d** increases to 56-68 %ee. Both E-**3d** and Z-**3d**, in the presence of HMPA, afford **4d** having the R-configuration.

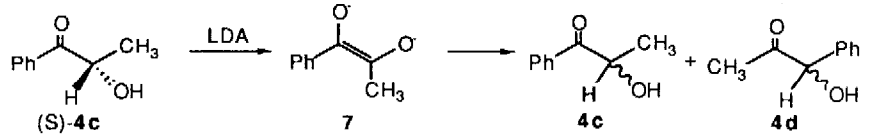
Complicating interpretation of the results summarized in the Table is possible racemization of the α-hydroxy ketones **4** under the reactions conditions. Indeed when >0.95 mmol of methyllithium is used to generate enolate **3c** from **2c** the isomerized α-hydroxy ketone **4d** was detected in addition to **4c** (entries 10,12,13, and 14). HMPA increased the percentage of **4d**. In separate experiments treatment of (-)-(S)-**4c** (63 % ee) with 1.5 eq of LDA (-78 to 0 °C; 15 min) afforded partially racemized **4c/4d**. Most likely enediolate **7** is involved in the isomerization/racemization of **4c** /**4d**.[11] Since **4c/4d** were not detected when <0.95 eq of MeLi was used to generate the enolates from **2** we believe that isomerization and/or loss of product optical purity is not important under these conditions. Furthermore, the results for the oxidation of the LDA derived enolates are valid because isomerization was not detected and (+)-**6** and its sulfonimine bi-

Table: **Oxidation of Lithium Ketone Enolates Using (+)-(Camphorylsulfonyl)oxaziridine (6)**

entry	Enolate (**3**)	Enolate Source/ Base (mol. equiv.)	Additive[a]	Geometry (Z/E)	% Yield[b] (**4c/4d**)[c]	% ee (config.)
1		**1a**/ LDA (1.2)	none	83/17	70	68 (S)[d]
2			HMPA	100/0	68	6 (S)
3		**1b**/ LDA (1.2)	none	100/0	55	32 (R)[e]
4			HMPA	100/0	50	12 (R)
5		**1c**/LDA (1.2)	none	98/2	45 (100/0)	39 (S)[d]
6			HMPA	100/0	42 (100/0)	11 (S)
7		**1d**/LDA (1.2)[f]	none	11/89	41 (0/100)[g]	3 (S)[h]
8			HMPA[i]	95/5	60 (0/100)	61 (R)
9		**2c**/MeLi (0.95)	none	97/3	45 (100/0)	35 (S)[d]
10		(1.1)	none		48 (95/5)	-
11		(0.95)	HMPA		40 (100/0)	11 (S)
12		(1.1)	HMPA		36 (75/25)	-
13		(1.25)	HMPA		50 (67/33)	-
14		(1.0)	none	7/93	45 (97/3)	4 (R)
15		(0.95)	HMPA		37 (100/0)	0
16		**2d**/MeLi (0.95)	none	95/5	51 (0/100)	6 (S)
17		(0.95)	none[j]		58 (0/100)	10 (R)
18		(0.95)	HMPA[i]		68 (0/100)	68 (R)
19		(0.95)	none	11/89	42 (0/100)[g]	9 (S)
20		(0.95)	HMPA[i]		31 (0/100)[g]	56 (R)

a) Ratio of THF to HMPA 20:1. b) Isolated yields. c) Ratio of **4c/4d** determined by NMR, see ref.16. d) Ref. 2b. e) Ref. 17. f) 50:50 mixture of **3d** and the non-conjugated enolate (see ref. 7). g) Yield based on total enolate content. h) Roger, A. *Biochem. Z.* **1931**, *230*, 320. i) Oxidation at -78 °C. j) Oxidation at -45 to -50 °C.

product are efficient quenches for excess base. Partial isomerization of E-**3d** to the more stable Z-**3d** under the conditions of oxidation cannot be entirely discounted. However, we believe this to be unlikely because oxidation is fast, similar results are observed for the LDA derived enolates and most importantly isomerization of **4c/4d** is not detected.



The preliminary results reported here indicate that the stereoselectivity for the asymmetric oxidation of prochiral ketone lithium enolates **3** to α-hydroxy ketones **4**, like the aldol and Michael reactions, are influenced by i) the enolate geometry, ii) the enolate substitution pattern, and iii) the enolate solution structure. What is surprising is the apparent minor role played by the enolate geometry. More important are the influences of R^1 (phenyl vs alkyl) and HMPA which alter the solution structure of the enolate. Although it is generally accepted that metal enolates exist and react as aggregates in solution[12,13] precise details of their solution structures are unknown. While HMPA is generally thought to alter the aggregation state of the enolates,[13b,14] making them more accessible to attack by the electrophile,[12a] their solution structures are also unknown. These results emphasize the difficulty in developing a transition state rationale based on small differences in energy from an inadequate knowledge of the structures of the reaction intermediates.[15]

Acknowledgements: We thank the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 34014 for generous support of this work.

REFERENCES AND NOTES

1. For leading references on optically active α-hydroxy carbonyl compound, see : (a) Brown, H. C.; Pal, G. G.; Jadhav, P. K. *J. Amer. Chem. Soc.* **1984** *106*, 1531. (b) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985** 3539. (c) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Amer.Chem. Soc.* **1985** *107*,4346. (d) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, 2437. (e) Gamboni, R.; Mohr, P.; Waesper-Sarcebvisc, N; Tamm, C. *Tetrahedron Lett.* **1985** 203 (f) Oppolzer, W.; Dudfield, P. *Helv. Chim. Acta* **1985** *68*,216. (g) Smith III, A. B.; Dorsey, B. D.; Obha, M.; Lupo Jr, A.T.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4341.
2. (a) Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987** *52*, 5288. (b) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986** *51* ,4083. (c) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986** *51*, 2402. (d) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.
3. (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969** *34*, 2324. (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90* , 4462, 4464.
4. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.
5. For an excellent review of the aldol reaction see: Heathcock, C. H., in *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press; 1984, Vol 3, Chapter 2; pp 111-206.
6. (a) Oare, D. A.; Heathcock, C. H. *Tetrahedron Lett.* **1986** 6169. (b) Heathcock, C. H.; Henderson, M. A.; Oare, D. A., Sanner, M. A., *J. Org. Chem.* **1985**, *50*, 3019. (c) Heathcock, C. H.; Oare, D.A. *J. Org. Chem.* **1985** *50*, 3024.
7. Silyl enol ether Z-**2c** was prepared from **1c** using Me_3SiI/Et_3N as described by Cazeau, et. al.[8a] E-**2c** was prepared by oxidizing the corresponding E-vinyllithium with bis(trimethylsilyl)peroxide as described by Davis, et. al.[8b] E- and Z-**2d** were prepared by trapping the enolate, formed by treatment of **1d** with LDA , with TMSCl as described by Corey and Gross.[9] In our hands a 50:50 mixture of conjugated **2d** and the non-conjugated silyl enol ethers of **1d** were obtained in the absence of HMPA.
8. a) Cazeaus, P.; Moulines, F.; Laporte, O.; Duboudin, F. *J. Organomet Chem.* **1980** *201*,C9-C13. (b) Davis, F. A.; Lal. G.S.; Wei, J. *Tetrahedron Lett.* **1988**, 4269.
9. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984** 495.
10. Quenching of LDA derived enolates as well as alterations in their reactivity have been attributed to coordination of amines to the enolate: see Strazewski, P.; Tamm, C., *Helv. Chim. Acta,* **1986**, *69,* 1041. Laube, T.; Dunitz, J. D.; Seebach, D., *Helv. Chim. Acta,* **1985**, *68,* 1373.
11. For leading references on the involvement of endiolates in the reactions of α-hydroxy carbonyl compounds see: Davis, F. A.; Haque, S.; Prezlewski, R., in press.
12. (a) Seebach, D.; Amstutz, R.; Dunitz, J. D., *Helv. Chim. Acta,* **1981**, *64,* 2622. (b) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D., *Helv. Chim. Acta,* **1981**, *64,* 2617. (c) Bauer, W.; Laube, T.; Seebach, D., *Chem. Ber.* **1985**, *118*, 764. Laube, T., Dunitz, J. D.; Seebach, D., *Helv. Chim. Acta,* **1985**, *68,* 1373. (d) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D., *J. Am. Chem. Soc.*, **1985**, *107,* 5403.
13. For leading references see: (a) Jackman, L. M.; Lange, B. C., *Tetrahedron*, **1977**, *33,* 2737. (b) Jackman, L. M.; Scarmooutzos, L. M.; Smith, B. D.; Williard, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 6058.
14. Jackman, K. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524.
15. The asymmetric oxidation of enolates using (camphorylsulfonyl)oxaziridines (**6**) has been interpreted in terms of a non-chelated or "open" transition state mechanism controlled by non-bonded steric interactions.[2]
16. Ratio determined by PMR ($CDCl_3$); Me **4c**: δ 1.46 (d) ppm; Me **4d** δ 2.09 (s) ppm.
17. Optically pure sample of (+)-(S)-**4b**; $[\alpha]_D$ +61.5° (c 2.0 $CHCl_3$) was prepared from t-BuLi and the 1,3-dioxolane of (+)(S)-lactic acid as previously described.[2b]

(Received in USA 1 November 1988)