Tetrahedron: Asymmetry Vol. 4, No. 12, pp. 2501-2505, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Deracemization of silyl enol ethers

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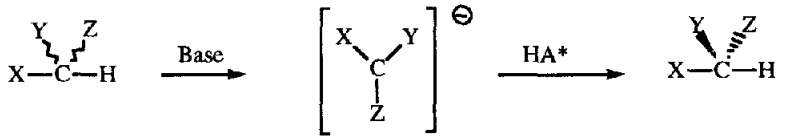
(*Received in UK 7 October* 1993)

Abstract: The deracemization by enantioselective protonation of silyl enol ethers was tested using 2,2-dimethyl 5-phenyl 1,3-dioxolan 4-one **1**. The results obtained, especially with pantolactone as a chiral proton donor, are better than when the deracemization is carried out with the lithium enolate of **1**.

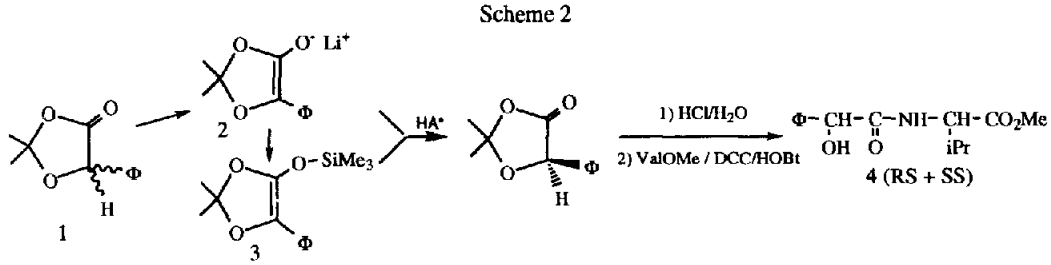
Among methods of obtaining optically pure compounds, the deracemization method first developed by Matsushita et al.[1] and Duhamel et al.[2] is the most recent but has not yet received much attention. This method is in principle applicable to any compound in which a stereogenic center is bound to an acidic hydrogen. It allows the quantitative transformation of a mixture of enantiomers into only one[2]. Deracemization proceeds through two steps: deprotonation of an enantiomeric mixture leading to a prochiral anion followed by asymmetric protonation by a chiral proton donor HA* (Scheme 1).

Scheme 1



For this enantioselective protonation, Duhamel et al.[2] proposed kinetic control at low temperature whereas Matsushita et al.[1] suggested two mechanisms: kinetic control at low temperatures and thermodynamic control at higher temperatures. The deracemization method has been applied to carbonyl compounds[1-3], amino acids[2] and α-hydroxy acids[4,5]. Recent work has been directed to the search for efficient chiral proton sources[3,5]. To obtain a high ee, the system must allow good transition state discrimination which is only obtained with a sufficiently rigid transition state. This rigidity is favoured by: (i) multiple chelations either with heteroatoms present in the molecule or with secondary amines (such as diisopropyl amine when LDA is used for the deprotonation), (ii) choice of a suitable solvent avoiding charge separation, (iii) use of a weakly acidic proton donor, (iv) very low reaction temperature (-50 to -100°C). Use of low temperature is also necessitated by the frequent instability of enolates. The aim of this work was to carry out the enantioselective protonation of silyl enol ethers which are more stable than enolates, with a view to studying the effect of temperature on the ee of the reaction. We chose as a model the cyclic ester of mandelic acid **1** described by Hünig[4] and we measured ee and yields by our accurate method[6] based on derivatization with valine methyl followed by HPLC analysis of the diastereoisomeric mixture **4** (Scheme 2).

Scheme 2



Of the two possible pathways,C *vs* O-protonation, only C-protonation can afford an enantioselective reaction. In the case of alkylation reactions, several studies[7-9] have established that C-alkylation of silyl enol ethers is the normal route. No systematic study of the enantioselective protonation of silyl enol ethers has been described. To our knowledge, only Takano et al.[10] have used protonation of silyl enol ethers in order to favour C-protonation. A study of protonolysis of silyl enol ethers carried out by Novice et al.[11] indicated C-protonation in the case of t-butyl dimethyl silyl enol ethers whilst no conclusion was arrived at for trimethyl silyl enol ethers.

Materials and methods

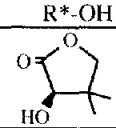
Homochiral or racemic dioxolanone **1** was prepared by acetalation of mandelic acid (homochiral or racemic) with acetone according to Soulier's method[12]. The trimethylsilyl enol ether **3** was prepared as described by Hünig[4]. This compound was obtained pure after evaporation of solvent and volatile reagents followed by precipitation of LiCl by addition of hexane.

During the protonation and solvolysis of **3**, the extent of reaction was followed by hydrolysis of aliquots of the mixture with D_2O and comparison of the integration of the NMR signal for the remaining CH_α with that for the phenyl group. After completion of the reaction, the dioxolanone was hydrolyzed with aqueous hydrochloric acid, and the isolated mandelic acid was coupled with valine methyl ester. The ee was determined by HPLC analysis. The chemical yield of the reaction was also measured by HPLC using the protected dipeptide Bn-Val-Gly-OMe as standard.

Results and discussion

In order to apply our method, we first reproduced one of Hünig's experiments[4]: deprotonation of dioxolanone **1** by LiHMDS in THF at -78°C followed by protonation with (R) pantolactone gave 36% ee whereas Hünig obtained 53%. This difference could be explained by the imprecision of the polarimetric method used in the previous work. Employing BuLi in the deprotonation step led to 40% ee. In both experiments yields were 50-52% (not given by Hünig). We then protonated the corresponding trimethylsilyl enol ether **3** with pantolactone and we monitored the progress of the reaction by hydrolysis of aliquots with D_2O. The reaction was complete after 2h at -78°C and return to room temperature over 6h. Under these conditions we obtained 13% ee and 87% yield (Table 1). In spite of the low ee, this experiment shows that enantioselective protonation of a silyl enol ether is possible. However, the rate of protonation with alcohols is relatively slow. We tried using Z-phenylalanine (Table 1), a more acidic chiral proton donor. By deuteration it was found that the reaction is terminated in less than 30 minutes. The yield is very high but the ee is only 7%.

Table 1

R*-OH	ee %	Major enantiomer	Yield %
 (R)	13[a]	(S)	87
Z-NH-CH(CH$_2\Phi$)-CO$_2$H (S)	7[b]	(S)	92

Reaction conditions: [a]) 2h at -78°C then return at room temperature in 6h; [b]) 30 min. at -78°C then return to room temperature over 1h.

Since reactions of silyl enol ethers are in general catalyzed by Lewis acids[13-14], we studied the effect of some additives in our reaction (Table 2).

Table 2

Additive*	ee %	Major enantiomer	yield %
$ZnCl_2$	38	(S)	90
LiCl	50	(S)	88
$Ti(OiPr)_4$	11	(S)	87
BF_3 Et_2O	-	-	-

*) Protonation of **3** at -78°C by (R) pantolactone in presence of one equivalent of additive

With the exception of $BF_3{\cdot}Et_2O$ which brings about decomposition of the silyl enol ether, the protonation reaction is complete in less than 30 min. as shown by deuteration. Since the best enantioselectivity was obtained with LiCl, we used this salt in the following experiments by omitting its elimination in the preparation of the silyl enol ether. We then studied the protonation reaction with various chiral proton donors. The results (Table 3) show that hard acidic proton donors such as tartaric acid, give rise to high yields but with no enantioselectivity. Among the other proton donors, pantolactone is the best, leading to 50% ee and 88% yield whilst Hünig's method in our hands led to only 36% ee and 52% yield.

Table 3

R*-OH	ee %	Major enant.	Yield %	React. time
Tartaric acid (D)	0	-	98	<30 min.
Hydroxypinanone(-)*	24	R	78	4h
Prolinol (L)	18	R	82	3h
Methyl mandelate (R)	20	S	87	3h
HYTRA**	20	S	95	2h
Pantolactone (R)	50	S	88	<30 min.

Reaction conditions: Silyl enol ether **3** , 1 eq. LiCl, 3 eq. R*-OH, THF -78°C.
*) 1S,2S,5S 2-hydroxy 3-pinanone[15]; **) (S) 1,1,2-triphenyl ethanol 2-acetate

To determine the influence of temperature, we repeated the last experiment, protonation of **3** by pantolactone, but at -40°C instead of -78°C. Under these conditions a zero ee was observed. This shows the great importance of the use of very low temperatures to promote enantioselective protonations.

Conclusion

This work shows that enantioselective protonation of silyl enol ethers is possible, probably by a C-protonation mechanism. In the case studied, the yields and enantiomeric excesses are better than those observed in the case of enantioselective protonation of lithium enolates. However, the greater stability of silyl enol ethers does not allow the avoidance of low temperature reactions since increase in temperature greatly decreases the ee.

Experimental

Melting points were measured with a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Brüker WP 80/CW spectrometer. Chemical shifts are quoted in ppm relative to tetramethylsilane as internal standard. HPLC measurements were carried out with a Waters Associates system (two 510 pumps, U6K injector, variable UV 484, Maxima control system), using a Spherisorb C_{18} column in an oven stabilized at 35°C.

2,2-Dimethyl 5-phenyl 1,3-dioxolan 4-one **1**

Boron trifluoride etherate (10.4g, 70mmol) was added to a solution containing 6.2g (40mmol) of mandelic acid (optically pure or racemic) and 3ml (40mmol) of acetone in 20ml of ether. Stirring was continued for 12h at room temperature. The mixture was washed with saturated $NaHCO_3$, and then water to neutral pH. The solution was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting white solid was recrystallized in hexane : 7.2g (95%) yield ; m.p.47°C (Litt.[12] 47-48°C); Rf 0.7 (AcOEt) ; ^1H NMR ($CDCl_3$) : 1.6 and 1.7 (2s, 6H, $(CH_3)_2$) ; 5.3 (s, 1H, CH) ; 7.4 (m, 5H, C_6H_5).

2,2-Dimethyl 4-trimethylsilyloxy 5-phenyl dioxola 4-ene **3**

BuLi (3.6ml, 5.7mmol of 1.6M solution in hexane) was slowly added under nitrogen to a solution of 0.9ml (6.3mmol) of diisopropylamine in 20ml of anhydrous THF cooled to -78°C. The solution was allowed to reach room temperature and then re-cooled to -78°C. Dioxolanone **1** (1g, 5mmol) in 3ml of THF was added and the mixture was stirred for 5min. Chlorotrimethylsilane (3.2ml, 25mmol) was added and the mixture stirred at -78°C for 10 min and was then allowed to warm to room temperature. THF, diisopropylamine and excess of chlorosilane were evaporated under reduced pressure. If desired, LiCl was eliminated by precipitation with hexane followed by filtration. The pure silylenol ether **3** was obtained in quantitative yield after evaporation of the solvent. ^1H NMR ($CDCl_3$: 0.3 (s, 9H, $SiMe_3$); 1.6 (s, 6H, $(CH_3)_2$); 7.3 (m, 5H, C_6H_5).

Deracemization of dioxolanone **1**

A solution of 3g (15mmol) of dioxolanone **1** in 50ml of anhydrous THF in a Schlenk tube under nitrogen was cooled to -40°C, and 15ml (15mmol) of 1M solution of LiHMDS in hexane was slowly added by syringe. After stirring for 30min at -40°C the solution turned yellow. Chiral proton donor (45meq. in 15ml of THF) was then slowly added and the temperature kept at -78°C. In order to follow the course of the reaction, aliquots of 1ml were taken every 30min, hydrolyzed with a few drops of D_2O, dried under reduced pressure, and analyzed by NMR. The reaction was complete when the integration for the proton in position 5 corresponded to 1H by comparison with the phenyl group integration. The solvent was then evaporated and the residue chromatographed on a short silicagel column to eliminate the proton donor (eluent ether/hexane, 50/50). The isolated dioxolanone was dissolved in 50ml of THF and hydrolyzed by addition of 20ml of 6N HCl. After stirring for 1h at room temperature, the solvents were removed under reduced pressure and the residue was dissolved in benzene and evaporated to dryness. A known quantity of dipeptide Bz-Val-Gly-OMe was added to the residue as internal standard, and the mixture was analyzed by HPLC : eluent MeOH/H_2O, 40/60, flow 1ml/min, λ=214nm, retention times t_R(min) : standard : 18,8 ; Φ-CH(OH)-CO-NH-CH(iPr)-CO_2Me diastereoisomers D,L, t_R=22.5 and L,L, t_R=33.6. The ee and yields were determined from the area of each peak.

Deracemization of silyl enol ether **3**

The same procedure was followed but starting from silyl enol ether **3** both in the presence or absence of one equivalent of additive. The results are given in Tables 1-3.

References

1. a) Matsushita, H.; Noguchi, M.; Saburi, M. and Yoshikawa, S.; *Bull. Chem. Soc. Jap., 48*, **1975**, 3715. b) Matsushita, H.; Noguchi, M. and Yoshikawa, S.; *Chem. Lett.*, **1975**, 1313. c) Matsushita, H.; Tsujino, Y.; Noguchi, M. and Yoshikawa, S.; *Bull. Chem. Soc. Jap., 49*, **1976**, 3629. d) Matsushita, H.; Tsujino, Y.; Noguchi, M.; Saburi, M. and Yoshikawa, S.; *Bull. Chem. Soc. Jap., 51*, **1978**, 862.
2. a) Duhamel, L. and Plaquevent, J-C; *Tetrahedron Lett.*, **1977**, 2285. b) Duhamel, L. and Plaquevent, J-C; *J. Am. Chem. Soc., 100*, **1978**, 7415. c) Duhamel, L. and Plaquevent, J-C; *Tetrahedron Lett., 21*, **1978**, 2521. d) Duhamel, L. and Plaquevent, J-C; *Bull. Soc. Chim. II*, **1982**, 69. e) Duhamel, L. and Plaquevent, J-C; *Bull. Soc. Chim. II*, **1982**, 75. f) Duhamel, L. and Plaquevent, J-C; *Bull. Soc. Chim. II*, **1984**, 421. g) Duhamel, L.; Duhamel, P.; Fouquay, S.; Eddine, J.J; Peschard, O.; Plaquevent, J-C; Ravard, A.; Solliard, R.; Valnot, J-Y and Vincens, H.; *Tetrahedron, 44*, **1988**, 5495.
3. Fehr, C. and Galindo, J.; *J. Am. Chem. Soc., 110*, **1988**, 6909.
4. Gerlach, U. and Hünig, S.; *Angew. Chem. Int. Ed., 26*, **1987**, 1283.
5. Potin, D.; Williams, K. and Rebek, J.; *Angew. Chem. Int. Ed., 29*, **1990**, 1420.
6. Cavelier, F.; Gomez, S.; Jacquier, R.; Llinares, M.; Mercadier, J-L; Petrus, C. and Verducci, J.; preceeding paper.
7. Jefford, C.W.; Sledeshi, A.W.; Lelandais, P. and Boukouvalas, J.; *Tetrahedron Lett., 33*, **1992**, 1855.
8. D'Angelo, J.; *Tetrahedron, 32*, **1976**, 2979.
9. Reetz, M.T.; *Angew. Chem. Int. Ed., 21*, **1982**, 96.
10. Takano, S.; Kudo, J.; Takahashi, M. and Ogasawara, K.; *Tetrahedron Lett., 27*, **1986**, 2405.
11. Novice, M.H.; Seikaly, H.R.; Seiz, A,D. and Tidwell, T.T.; *J. Am. Chem. Soc., 102*, **1980**, 5835.
12. Farines, M. and Soulier, J.; *Bull. Soc. Chim. France*, **1970**, 332.
13. Toshimitsu, A.; Hirosawa C. and Tanimoto, S.; *Chem Lett.*, **1992**, 239.
14. Gennari, C.; Molinari, F.; Cozzi, P.G. and Oliva, A.; *Tetrahedron Lett., 30*, **1989**, 5163.
15. Carlson, R.G. and Pierce, J.K; *J. Org. Chem., 36*, **1971**, 2319.