Pergamon

Tetrahedron Letters, Vol. 35, No. 18, pp. 2891-2894, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0455-7

A First Approach to Asymmetric Protonation *Via* a Polymer Supported Chiral Proton Donor

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***Abstract** :Asymmetric protonation of achiral silyl enol ethers employing chiral proton donors is described for the first time. We have obtained modest enantiomeric excesses by carrying out these reactions in homogeneous solution. The subject of this paper is to report in a preliminary fashion the substantially improved asymmetric induction that can be achieved by supporting the proton donor on a polymeric resin (up to 94% ee). A temperature effect is observed and discussed.*

Enantioselective protonation first introduced by L. Duhamel[1] was applied to enolates in 1978[2]. Recently, we have been interested in the asymmetric protonation of achiral silyl enol ethers using chiral proton donors. Use of a chiral proton donor supported on a polymer appears to be a solution to some of the major problems of asymmetric synthesis, since it offers the following advantages : (i) the chiral inductor could be recovered by a simple filtration and recycled, thus minimising the cost of the synthesis, (ii) while very low temperatures are required using chiral proton donors in solution to obtain good enantiomeric excesses, the reactions could be carried out at more convenient temperatures employing a polymer support without causing a compromise in enantiomeric excess. This is due to decreased molecular mobility as a result of the rigidity of the polymeric chains[3].

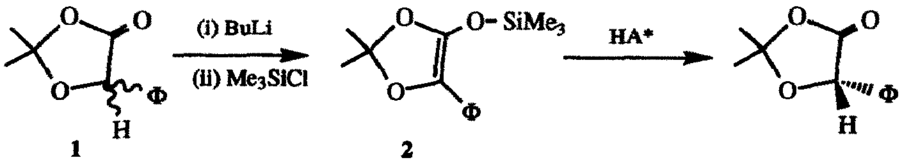
RESULTS AND DISCUSSION

Our preliminary study showed complete decomposition of a lithium enolate when the temperature was increased to -40°C. Due to this instability at higher temperature, a silyl enol ether, a less thermolabile species, was employed. Lithium enolates are prone to side-reactions like O-alkylations or bis-alkylations[4,5], however silyl enol ethers undergo exclusively C-alkylations[6].

In a previous investigation[7], we tested the enantioselective protonation and solvolysis in solution of the cyclic silyl enol ether **2**[8] prepared from the dioxolanone **1** which was in turn synthesized from mandelic acid (Figure 1).

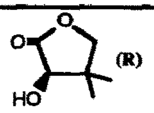
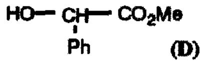
The results (Table 1) show that enantioselective protonation of silyl enol ethers by chiral alcohols like pantolactone or methyl mandelate is possible but only at very low temperatures (-78°C). On increasing the reaction temperature to -40°C, a complete loss of asymmetric induction was observed.

Figure 1



1 2

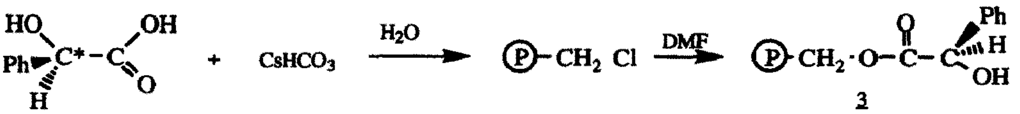
Table 1

HA*	Temp. °C	ee %	Major Enantiomer	Yield %	Reaction Time
 (R)	-78	50	L	88	<30min
	-40	0		95	<30min
 $HO-CH(Ph)-CO_2Me$ (D)	-78	21	L	87	4h
	-40	0		92	1h

Reaction conditions: Silyl enol ether 2, 1 eq. LiCl, 3 eq. HA* in THF. ee and yields are determined by HPLC[7,9]

In order to assess the effect of supporting the chiral proton donor on a polymer, firstly (D)-mandelic acid was bound on Merrifield resin, affording the polymer supported chiral proton donor 3 (Figure 2).

Figure 2

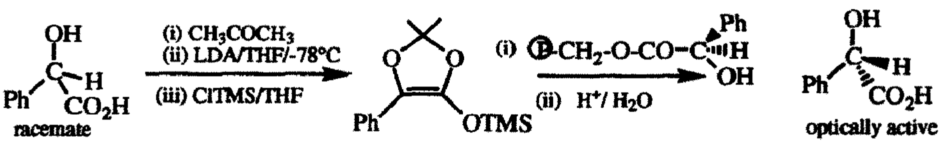


3

Ⓟ-CH$_2$ Cl = Merrifield resin (1meq./g)

The second step was asymmetric protonation of the silyl enol ether derived from racemic mandelic acid (Figure 3).

Figure 3



This reaction was carried out at a range of temperatures. The results (shown in Table II) show that the protonation reaction is virtually complete in all cases in less than 30 minutes. In contrast to observations of chiral protonation in solution, an optimal enantiomeric excess (94%) was found at -40°C.

A mechanism change (C-protonation versus O-protonation) when the temperature increases[10] does not explain our results. Only the "ISO inversion principle" proposed by Scharf and Coll.[11] is able to describe the presence of a maximum ee value. Contrary to the usual idea that ee increases when the temperature decreases, these authors describe some examples where the ee were brought to a maximum when the temperature increases, corresponding to the temperature-dependent dominance of activation entropy or enthalpy.

Table II

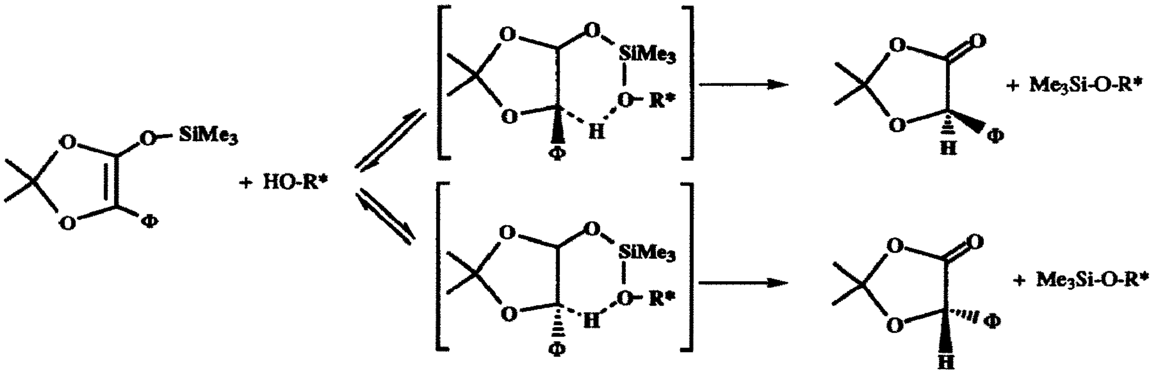
Temperature °C	ee % (a)	Major Enantiomer	Yield % (b)	Reaction Time
- 78	28	L	96	<30min
- 55	34	L	91	<30min
-40	94	L	95	<30min
- 25	26	L	92	<30min
+20	18	L	92	<30min

(a) Determined by HPLC after derivatization with ValOMe

(b) Determined by HPLC with an internal standard BnValGlyOMe

This interpretation assumes the reversibility of the protonation of the silyl enol ether (Figure 4).

Figure 4



In conclusion, several advantages of a polymer supported chiral proton donor over its homogeneous analogues have been demonstrated in this work :

1 - Chemical yields were higher at all temperatures.

2 - Reaction times were greatly reduced.

3 - The optimum ee on the reaction studied was considerably higher (94% compared to 21% ee).

4 - The chiral resin was recycled and used again with no observed decrease in the degree of asymmetric induction.

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(*Received in France* 21 *January* 1994; *accepted* 28 *February* 1994)