

Polymer supported enantioselective reactions. III. Protonation of lithioenamine derivatives of racemic 2-methylcyclohexanone

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Asymmetric protonations, with enantioselectivities ranging to 90%, were observed in reactions of lithioenamines derived from imines of racemic 2-methylcyclohexanone and insoluble cross-linked copolymers of polystyrene and divinylbenzene substituted with (S)-2-aminoalkoxymethyl groups.

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On a observé des protonations asymétriques, avec des sélectivités énantiométriques allant jusqu'à 90%, lors de réactions de lithioenamines provenant des imines de la méthyl-2 cyclohexanone racémique avec un copolymère réticulé et insoluble de polystyrène et de divinylbenzène portant des groupes aminoalkoxyméthyle-2(S).

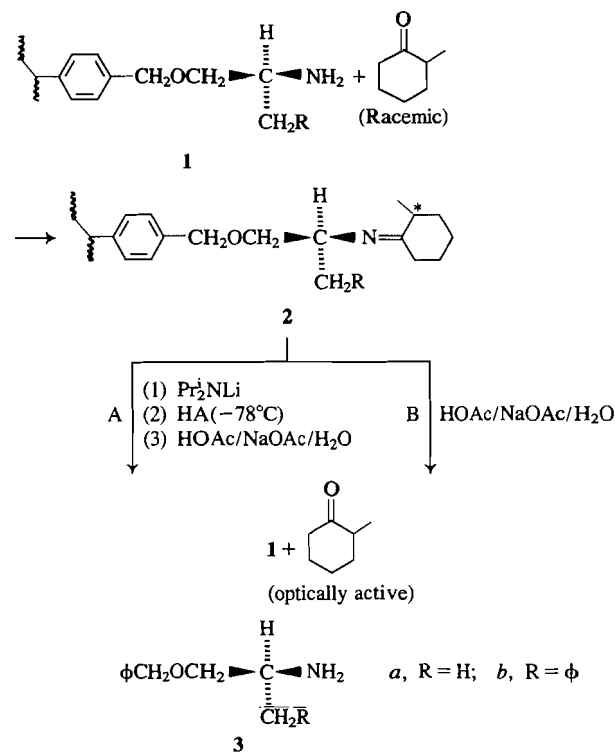
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Recently we reported the use of insoluble cross-linked copolymers of styrene and divinylbenzene with covalently bonded (S)-2-aminoalkoxy groups (1) in the asymmetric methylation of the lithioenamines derived from cyclohexanone and 1. The polymeric system afforded higher enantioselectivities than were observed through the use of analogous systems, under comparable conditions, in solution (1).

We now report preliminary results in our study of asymmetric *protonations* of the lithioenamines derived from the polymer-bound ketimines 2 formed from reaction of 1 with racemic 2-methylcyclohexanone (pathway A).

Two examples of nonbiological systems involving asymmetric protonations, conducted in the solution phase, have been reported recently. Thus, amino-acids may be "deracemized" to 70% e.e. (2), and a bicyclobutane bridged enolate anion has been enantioselectively protonated to 48% e.e. (3).

In our studies, to distinguish between asymmetric protonation of the lithioenamines from 2 and a bias in the reaction of enantiomers during imine formation from racemic 2-methylcyclohexanone, imines 2 were subjected to direct hydrolysis (pathway B). The degree of resolution depends on the structure of 1. Thus, 2-aminopropoxymethylated polystyrene (1a) led to no apparent resolution, while the 3-phenyl derivative (1b) afforded the 2-methylcyclohexanones with 50% excess of the (S)-enantiomer (Table 1). While 2b, then, must have (S)-2-methylcyclohexylidene moieties in 50%



e.e., this chiral centre would be expected to be lost on deprotonation at the 2-position if a planar lithioenamine is assumed (see below).

The enantioselectivity of pathway A was found to be highly dependent on both the structure of the asymmetric inducing moiety on the polymer, and on the structure of the protonating species (Table 1). Bias is moderately towards formation of excess

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TABLE 1. Enantiomeric excesses of product 2-methylcyclohexanone^a

		Enantiomeric excess (<i>R</i>) or (<i>S</i>) (%) ^b	
		R = H	R = ϕ
HA in Pathway A	HOAc	20 (<i>R</i>)	22 (<i>S</i>)
	Et ₃ NHCl in THF	36 (<i>R</i>)	—
	2,6-Di- <i>t</i> -butyl <i>p</i> -cresol in THF	8 (<i>R</i>)	—
	<i>t</i> -BuOH	—	0
	EtOH + Et ₃ NHCl in THF	—	82 (<i>S</i>)
	EtOH	22 (<i>R</i>)	90 (<i>S</i>)
Pathway B		0	50 (<i>S</i>)

^aIsolated as previously described (1); > 98% pure as determined by gc; yields 0.1–0.2 mmol per g of polymer.^bBased on optical rotation of pure (*R*)-2-methylcyclohexanone at –16.4°C (8).

(*R*)-2-methylcyclohexanone using **1a**, but more strongly towards (*S*)-2-methylcyclohexanone using **1b** (of the same chirality). It is noteworthy that, in the case of **1b**, bond formation to the proton must have occurred on the side of the 2-position opposite to that in bond formation to carbon in the methylation reactions described earlier (1) in order for both to lead to (*S*)-2-methylcyclohexanone.

Most significant are two extremum results. (*S*)-2-Methylcyclohexanone was obtained in 90% e.e. when the lithioenamine from **2b** was protonated using ethanol, but only racemic product was obtained using *tert*-butyl alcohol, after the resulting polymers were hydrolyzed under the same conditions. These observations are consistent with regioselective deprotonation of **2b** at the 2-position to form a planar lithioenamine followed by highly diastereoselective *C*-protonation when ethanol is used, or nondiastereoselective selective protonation with *tert*-butyl alcohol. Predominant deprotonation at the more highly alkylated α -position has been observed in other ketimines (4, 5) including those of cyclohexanone imines (4) using alkyl lithium reagents. In view of the studies of Knorr and Löw (6) the *C*-protonation may be a result of a tautomerization² following an initial kinetically controlled *N*-protonation to form an enamine.

Another possibility may be deprotonation at the 6-position of the 2-methylcyclohexanone imine system, as observed by Meyers *et al.* (7) in reactions of lithium diisopropylamide on imines in solution, followed by a complex equilibration prior to hydrolysis.²

In any event, diastereoselective *C*-protonation at the 2-position ultimately must have occurred prior to hydrolysis by a mechanism that is highly influenced by the structure of the protonating species.

An analogous system in solution was investigated. The imine from racemic 2-methylcyclohexanone and (*S*)-2-aminopropyl benzyl ether (**3a**)

(**1**) was treated under the same conditions as those in pathway A for the polymeric system. The product exhibited no optical activity. We plan to examine the analogous system derived from (*S*)-2-amino-3-phenylpropyl benzyl ether (**3b**).

Our result of 90% e.e. would appear to be unprecedented in enantioselective protonation reactions in nonbiological systems. These results are consistent with earlier observations (1) of enhancement of enantioselectivities through the use of polymer supported asymmetric inducing agents relative to analogous systems in solution. While mechanisms have been proposed to explain the predominant enantioselectivities in related reactions (9, 10) additional studies are required to rationalize the results that we report here. Studies in this area are continuing.

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²We appreciate these alternative explanations suggested by one referee.