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The Temperature Dependence of the Diastereoselective Reduction of 2-*t*-Butylcyclohexanone with Diisobutylaluminium-2,6-di-*t*-butyl-4-methylphenoxide

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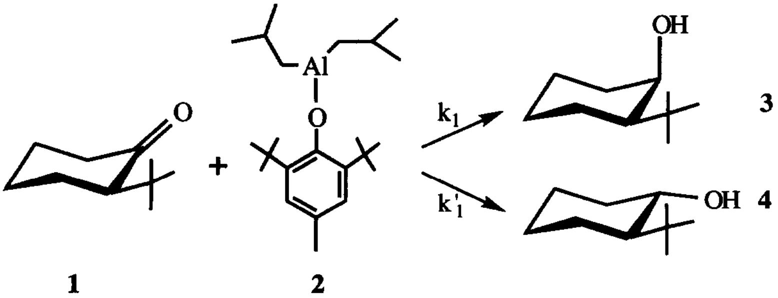
Abstract: The diastereoselectivity of the reduction of 2-*t*-butylcyclohexanone (**1**) with diisobutylaluminium-2,6-di-*t*-butyl-4-methylphenoxide (**2**) is investigated as a function of the temperature and the conversion. The relevant selection steps are characterized on the basis of the isoinversion principle. The kinetically controlled formation of the alcoholate intermediates as well as the thermodynamically controlled Meerwein-Ponndorf-Verley type equilibration are recognized as the two selection steps of the reduction.

It has been demonstrated that the stereochemistry in the reduction of cyclic and acyclic ketones with complex metal-hydrides is not uniformily influenced by the temperature.[1-4] Hitherto, there exists no easy understanding of this phenomenon.

In the present paper we describe the influence of the temperature on the diastereoselectivity in the reduction of 2-*t*-butylcyclohexanone (**1**) with diisobutylaluminium-2,6-di-*t*-butyl-4-methylphenoxide (DDMPO) (**2**) and we give an explanation for the temperature dependence of this diastereoselective reduction.



Scheme 1

DDMPO is a useful and highly selective reducing reagent in prostaglandin synthesis.[5-8] Haubenstock has studied the application of DDMPO in the reduction of cyclic ketones.[9]

In accordance with the results of Haubenstock[9] we observed in our system a remarkable dependence of the diastereoselectivity on conversion (reaction time) (Fig. 1). Consequently, the selectivity of (**3**) and (**4**) results not only from a single kinetically controlled reaction as it often was assumed in other systems.[6,9] We interpret the following results of the temperature dependent measurements in terms of the isoinversion principle.[10] It turns out that equilibration phenomena have a considerable influence on the diastereoselectivity. They represent a relevant selection step in the over all reaction. This equilibration phenomenon is a Meerwein-Ponndorf-Verley (MPV) type mechanism. It also has been described by Haubenstock.[9]

Figure 2 shows the modified Eyring plots of the results according to equation 1 for two different substrate concentrations (ketone/DDMPO: 1/2 and 1/10). Each of these two series of measurements has two linear regions with a corresponding inversion temperature T_{inv}. According to the isoinversion principle consequently two sets of activation parameters ($\Delta\Delta H_1^{\neq}$; $\Delta\Delta S_1^{\neq}$ for $T>T_{inv}$ and $\Delta\Delta H_2^{\neq}$; $\Delta\Delta S_2^{\neq}$ for $T<T_{inv}$) are obtained.[10]

$$\ln P = \ln \frac{k_1}{k'_1} = -\frac{\Delta\Delta H^{\neq}}{R}\frac{1}{T} + \frac{\Delta\Delta S^{\neq}}{R} \qquad \text{(eq 1)}$$

$$\frac{k_1}{k'_1} = \frac{I_{cis}}{I_{trans}}$$

k_1 = overall rate constant of the formation of the cis alcohol
k'_1 = overall rate constant of the formation of the trans alcohol
I_{cis} = intensity of the cis alcohol (GC)
I_{trans} = intensity of the trans alcohol (GC)

The occurrence of two selection steps of the reaction mechanism represents the condition for the existence of an inversion temperature in the Eyring plot. From the obtained results the selection mechanism in scheme 2 is derived. The general kinetic scheme of the isoinversion principle[10] also implies this individual selection mechanism. In this model the first relevant selection step of the reaction is the kinetically controlled formation of the alcoholates (**5**,**6**) which is also described by Yamamoto[6] and Haubenstock.[9] The following thermodynamically controlled Meerwein-Ponndorf-Verley type equilibration represents the second relevant selection step. The ketone from the alcoholate is regenerated (retro cleavage) and recycled into the reaction process. The high diastereoselectivity obtained by the first selection step is therefore partially destroyed. The conversion dependency of the diastereoselectivity (Fig. 1) clearly shows that the second selection step favours the formation of the *trans*-product.

The diastereoselectivity is consequently the result of both partial selection steps. Both selection steps are different with regard to its enthalpic ($\Delta\Delta H^{\neq}$) resp. entropic ($\Delta\Delta S^{\neq}$) contributions to $\Delta\Delta G^{\neq}$. Depending on the temperature, one of both steps controls the selectivity. In the high temperature region ($T > T_{inv}$) the first selection step dominates as a consequence of the fast diminution of the ketone and complete conversion. The Meerwein-Ponndorf-Verley equilibration is supressed. In contrast the second selection step is dominant in the low temperature region ($T < T_{inv}$), where the reaction is slow and the conversion is uncomplete. The concentration of the ketone is high enough to catalyze efficiently the *cis-trans* isomerisation.

This fact can also be derived from the time dependence depicted in figure 1. At the temperature of 25°C the influence of the equilibration (2nd selection step) is lower compared with 0°C, as a result of the faster consumption of the ketone. Consequently, the diastereoselectivity is mainly controlled kinetically in the high temperature region whereas in the low temperature region it is mainly controlled thermodynamically.

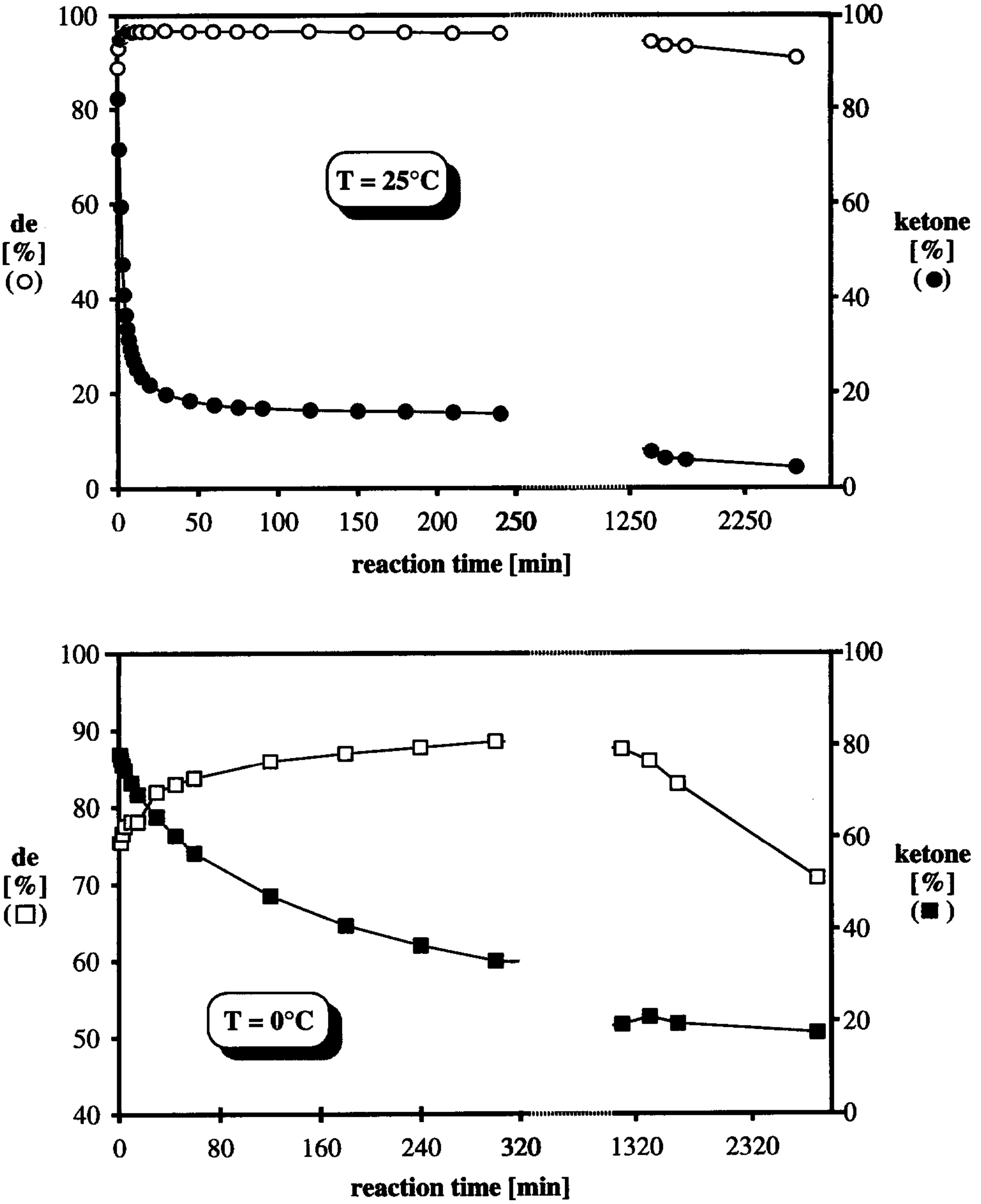


Figure 1: Dependency of the diastereoselectivity of the reduction of 2-*t*-butylcyclohexanone with DDMPO (1:1) on conversion (reaction time) for two different temperatures (0°C; 25°C): ○ diastereoselectivity at 25°C, ● ketone concentration at 25°C; □ diastereoselectivity at 0°C, ■ ketone concentration at 0°C.

The concentration effects which are observed by Haubenstock[9] can also be easily explained with these considerations. According to our experience the second selection step is very sensitive to reaction conditions (especially the rate of

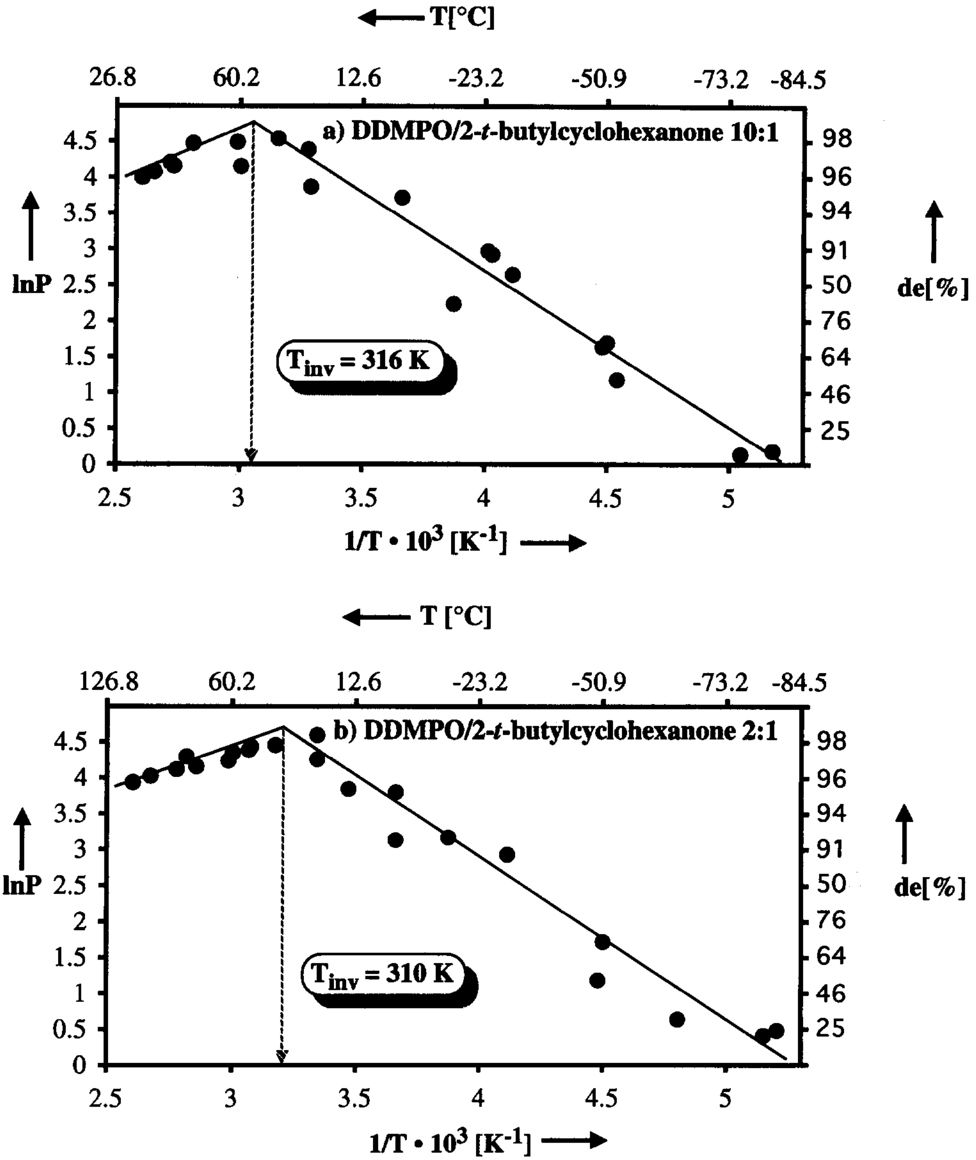
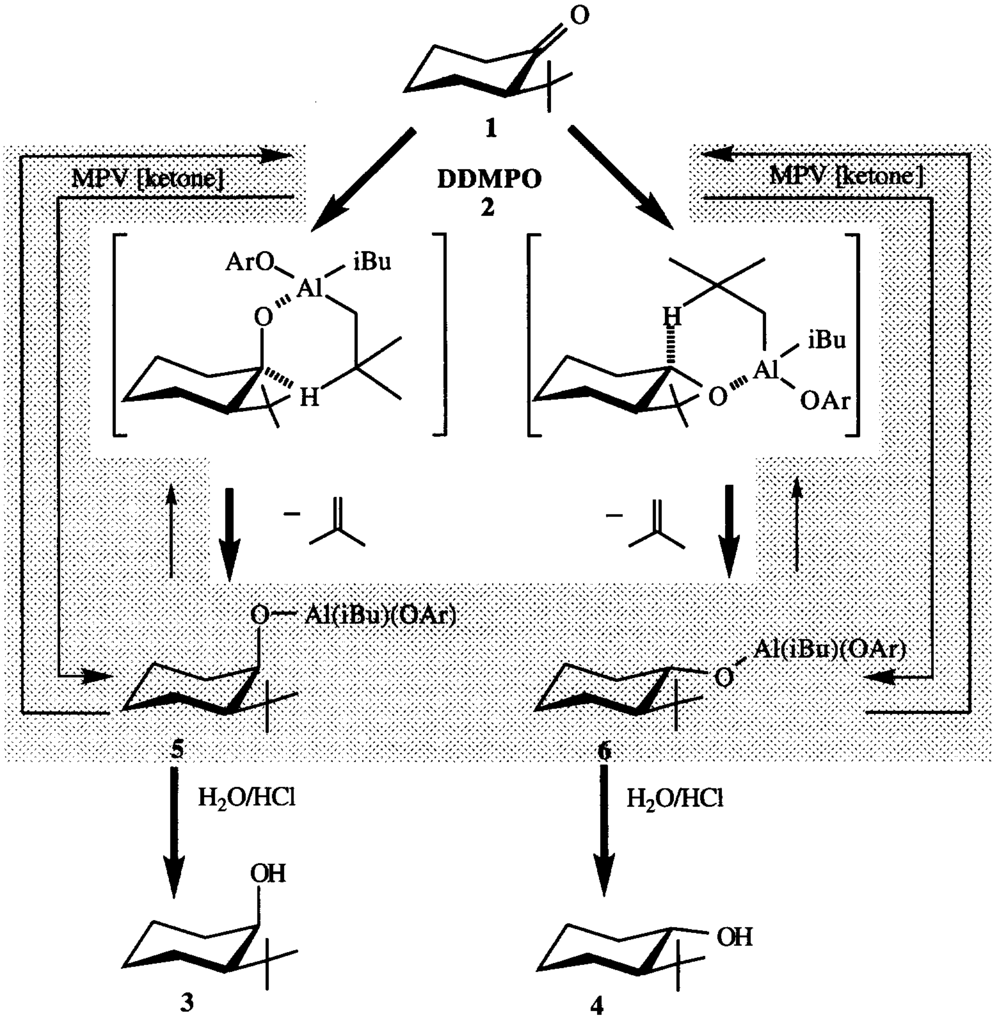


Figure 2: Eyring plots for the diastereoselective reduction of 2-*t*-butylcyclohexanone with DDMPO for two different concentrations: a) DDMPO/ketone 10:1; $T_{inv} = 316$ K; $T > T_{inv}$: $\Delta\Delta H_1^{\neq} = -6.125$ kJmol^{-1}; $\Delta\Delta S_1^{\neq} = 18.047$ Jmol^{-1}K^{-1}; $T < T_{inv}$: $\Delta\Delta H_2^{\neq} = 18.309$ kJmol^{-1}; $\Delta\Delta S_2^{\neq} = 95.405$ Jmol^{-1}K^{-1}. b) DDMPO/ketone 2:1; $T_{inv} = 310$ K; $T > T_{inv}$: $\Delta\Delta H_1^{\neq} = -7.638$ kJmol^{-1}; $\Delta\Delta S_1^{\neq} = 13.069$ Jmol^{-1}K^{-1}; $T < T_{inv}$: $\Delta\Delta H_2^{\neq} = 18.461$ kJmol^{-1}; $\Delta\Delta S_2^{\neq} = 97.170$ Jmol^{-1}K^{-1}.

ketone addition[11], and perhaps the nitrogen-pressure and the isobutene concentration in the solution). The mean error of the measuring points in the corresponding low temperature region (Figure 2) can be explained by slight variation of the reaction conditions. Furthermore this is an indication that the second selection step is a complex composition of se-



Scheme 2: Simplyfied selection mechanism of the diastereoselective reaction of 2-*t*-butylcyclohexanone with DDMPO: ☐ first relevant selection step; ▨ second relevant selection step.

veral elementary steps. As a result the generation of the diastereoselectivity of the reduction of ketones is a dynamic phenomenon of two relevant selection steps. It has been demonstrated that the investigation of the temperature dependence on the basis of the isoinversion principle is obviously a suitable tool to study complex systems of selection procedures.

Further systems of this reaction concerning the interpretation of the selection mechanism and the formulation of the isoinversion relationship[10] are investigated and will reported later.

Experimental

Toluene was refluxed over sodium, distilled and stored over sodium. 2,6-Di-*t*-butyl-4-methylphenol (99+%) and the DIBAH solution in toluene were obtained from Aldrich. 2-*t*-Butylcyclohexanone was prepared by oxidation of the corresponding alcohol. The GC analyses were performed on a HP 5890 series II gas chromatograph equipped with a flame ionization detector and a HP 3396 A integrator. A FFAP column was used (25 m x 0.32 mm) (T = 100°C - 10 min; N_2 = 2 atm). The apparates were flame-dried under dry nitrogen. The retention times of the products were compared with samples of the authentic *cis* and *trans* alcohols.

General procedure for the reduction of 2-*t*-butylcyclohexanone (1) with diisobutylaluminium-2,6-di-*t*-butyl-4-methyl-phenoxide (2).

A toluene solution of DIBAH (20 ml of 1M DIBAH, 20 mmol) is transferred to a 100 ml reaction flask which is equipped with a mechanical stirrer, pressure equilibration addition funnel and thermometer. At the temperature of 0°C a solution of 5.2 g (23.5 mmol) 2,6-di-*t*-butyl-4-methylphenole in 10 ml toluene is added slowly. The mixture is stirred for 1.5 h. The ratio of ketone and reduction reagent is prepared by the variation of the ketone concentration . After the temperature equilibration, the solution of the ketone in 10 ml toluene is added dropwise without considerable exothermic effect. The diastereoselectivity and the conversion of the reaction are controlled by GC. When the selectivity as well as the conversion are constant the mixture is hydrolyzed with 10% HCl at the corresponding temperature and dilute with ether and water. The separated aqueous layer is extracted with ether until extraction is complete concerning the alcohols and the ketone. The combined organic solution is washed with saturated $NaHCO_3$, saturated NaCl and dried over $MgSO_4$. This mixture is analyzed by GC.

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11. This is also an indication of the thermodynamically controlled selection step.

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