Diastereoselective reduction of cyclohexanones with diisobutylaluminium phenoxides in terms of the isoinversion principle

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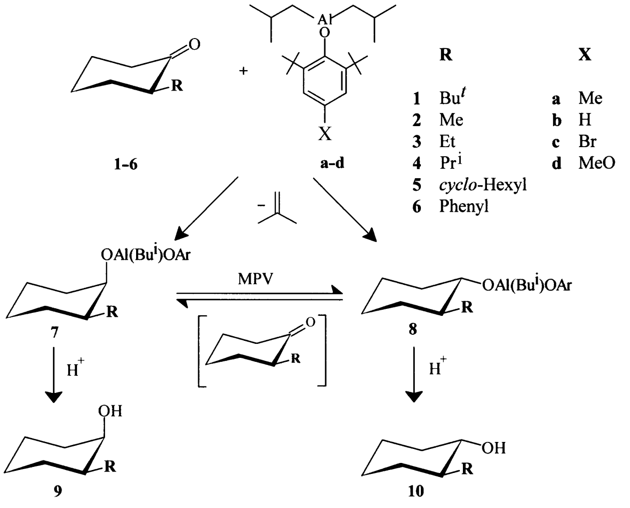
The diastereoselectivity of the reduction of 2-substituted cyclohexanones 1–6 with 4-substituted diisobutylaluminium phenoxides a–d has been investigated as a function of temperature. The high-temperature region is found to be dominated by hydride transfer, which is controlled by steric as well as electronic effects. However, at low temperatures the Meerwein–Ponndorf–Verley reaction gains in importance. This phenomenon is quantified by an isoinversion relationship.

Introduction

Diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide **a** is a useful reagent for the diastereoselective reduction of ketone intermediates in prostaglandin syntheses.[1–4] Haubenstock has studied the application of **a** in the reduction of cyclic ketones and deduced from his results that its mechanism is somewhat more complex than a single hydride transfer.[5]

Our investigations on the diastereoselective reduction of 2-*tert*-butylcyclohexanone **1** with **a** as a function of the temperature and the conversion gave us further insight into the selection mechanism. Obviously the ratio of **9** and **10** does not result exclusively from kinetically controlled formation of the alcoholates **7** and **8**. Equilibration phenomena of **7** and **8** also have a considerable influence on the diastereoselectivity. This equilibration phenomenon is ascribed to a Meerwein–Ponndorf–Verley (MPV) type mechanism and represents a relevant selection step in the overall reaction (Scheme 1). The diastereoselectivity is consequently the result of both selection steps.[6] However, further data on this type of reaction were required to verify the general validity of our conclusions on its mechanism. As steric and electronic effects are known to be relevant factors in controlling the stereochemical outcome of ketone reductions, we expected the systematic variation of the steric environment at the carbonyl function and the Lewis acidity of the aluminium phenoxide to be appropriate tools for characterizing the selection steps. For that purpose, we were prompted to study the influence of the temperature on the diastereoselectivity in the reduction of 2-substituted cyclohexanones **2**–**6** with **a**, and in the reduction of 2-methylcyclohexanone **2** with several diisobutylaluminium phenoxides **a**–**d**. We interpret the following results of the temperature-dependent measurements in terms of the isoinversion principle.[7]



Scheme 1

Table 1 Examples of the dependence of the diastereoselectivity as a function of reaction time for different temperatures on the diastereoselective reduction of cyclohexanones with **a** (1:10)

Ketone	T/°C	t/h	de (%)	Ketone (%)
5	+80	0.75	81.4	0
		18.0	81.5	0
		66.0	81.7	0
5	−45	20.0	94.9	38.2
		66.0	95.2	7.8
		114.0	95.3	2.8
		138.0	95.4	1.7
6	−75	43.0	91.1	23.8
		120.0	92.2	7.0
		144.0	92.2	4.6
		197.0	92.5	1.1

Results and discussion

All reductions were performed using a 10-fold excess of the aluminium reagent to ensure reasonable conversions even at very low temperatures. They were allowed to reach a point at which both conversion and selectivity remained constant with time. Usually at this point the whole ketone was consumed, apart from ketones **1**, **4** and **5**, where the conversion began to drop at temperatures below −30 °C. To exclude any exothermic effects the ketone was added to the reaction mixture over a period of 30 min. It is worth mentioning, however, that any further retardation of the rate of addition did not affect the final diastereoselectivity.

Ignoring reduction of 2-*tert*-butylcyclohexanone **1**,[6] we could detect no remarkable changes in diastereoselectivity as a function of time and conversion, respectively (Table 1).

Obviously, since time-dependent measurements provide only slight evidence for the complex kinetic behaviour of the reaction, investigations of temperature effects are more suitable for unravelling the details of the selection mechanism.

Evaluation of the results obtained on the conversion of **1**–**6** with **a**, and **2** with **a**–**d** according to eqn. (1) gives modified

$$\ln P = \ln \frac{k_1}{k_2} = -\frac{\Delta\Delta H^{\ddagger}}{R}\frac{1}{T} + \frac{\Delta\Delta S^{\ddagger}}{R} \qquad (1)$$

Eyring plots, which are presented in Figs. 1 and 2. In eqns. (1) and (2), k_1, and k_2 represent the overall rate constants for the

Table 2 Reduction of cyclohexanones **1–6** with diisobutylaluminium phenoxides **a–d**, inversion temperatures, T_{inv}, and activation parameters, $\Delta\Delta H_1^‡$, $\Delta\Delta S_1^‡$ ($T > T_{inv}$) and $\Delta\Delta H_2^‡$, $\Delta\Delta S_2^‡$ ($T < T_{inv}$).

System[a] (ketone/ phenoxide)	T_{inv}/ K (°C)	$\Delta\Delta H_1^‡$ $\Delta\Delta H_2^‡$/ kJ mol^{-1}	$\delta\Delta\Delta H^‡$/ kJ mol^{-1}	$\Delta\Delta S_1^‡$ $\Delta\Delta S_2^‡$/ J mol^{-1} K^{-1}	$\delta\Delta\Delta S^‡$/ J mol^{-1} K^{-1}	Ref.
1a	316 (43)	−2.63 18.79	21.42	29.87 104.08	74.21	6
2a	277 (4)	−17.91 −5.89	12.02	−53.54 −11.41	42.13	This work
3a	276 (3)	−16.70 −3.02	13.68	−47.71 2.09	49.80	This work
4a	262 (−11)	−7.67 −4.61	3.06	1.27 13.04	11.77	This work
5a	297 (24)	−8.10 −5.31	2.79	−2.61 7.93	10.54	This work
6a	272 (−1)	−13.70 −1.33	12.37	−32.00 13.82	45.82	This work
2b	299 (26)	−23.74 −5.38	18.36	−69.97 −8.68	61.29	This work
2c	277 (4)	−17.30 −3.83	13.47	−50.72 −2.02	48.70	This work
2d	298 (25)	−11.66 −2.30	9.36	−33.65 −2.24	31.42	This work

[a] System corresponds to the numbering in Figs. 1–3.

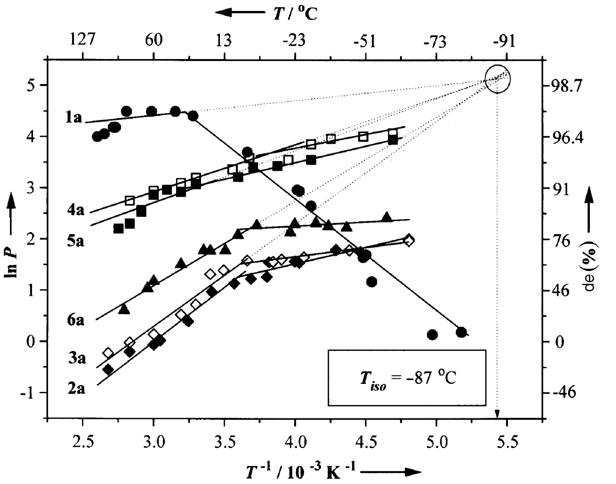


Fig. 1 Eyring plots and the isoselective temperature, T_{iso} (evaluated according to Giese[8]) for the diastereoselective reduction of 2-substituted cyclohexanones **1–6** with **a**. For the numbering of the plots see Table 2.

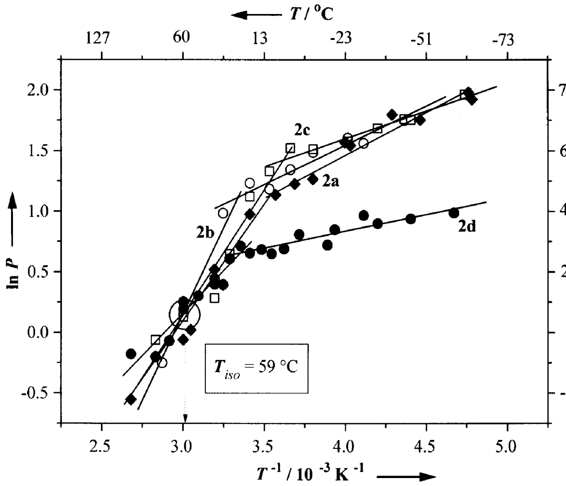


Fig. 2 Eyring plots and the isoselective temperatures, T_{iso} (evaluated according to Giese[8]) for the diastereoselective reduction of **2** with diisobutylaluminium phenoxides **a–d**. For the numbering of the plots see Table 2.

$$\frac{k_1}{k_2} = \frac{I_{ax}}{I_{eq}} \qquad (2)$$

formation of axial (1) and equatorial (2) alcohol, respectively, and I_{ax} and I_{eq} represent the intensity of the axial and equatorial alcohol (GC), respectively.

These plots demonstrate a considerable temperature-dependent influence of steric and electronic effects on the diastereoselectivity. Each of these series of measurements has two, nearly linear regions with corresponding inversion temperatures T_{inv}. In the high-temperature region ($T > T_{inv}$) the selectivity for the formation of the axial isomer increases with the reciprocal of temperature. In the low temperature ($T < T_{inv}$) area the formation of the equatorial isomer grows more favourable. According to the isoinversion principle the inversion temperature reveals two sets of activation parameters ($\Delta\Delta H_I^‡$, $\Delta\Delta S_I^‡$ for $T > T_{inv}$ and $\Delta\Delta H_2^‡$, $\Delta\Delta S_2^‡$ for $T < T_{inv}$) for each system (Table 2).[7]

In the appropriate temperature regions these parameters do not necessarily refer to one single relevant selection step but represent instead the complex composition of all relevant influences.[9]

The high-temperature range is characterized by the existence of isoselective relationships[8] for the steric variation of the cyclohexanone (Fig. 1) as well as for the electronic variation of the phenoxide (Fig. 2). According to Giese,[8] this observation indicates that the diastereodifferentiation in the high-temperature region is uniformly controlled by both steric and electronic factors. Furthermore, the rapid consumption of the ketone at elevated temperatures suppresses the possibility of isomerization of the aluminium alcoholates *via* the MPV reaction. With regard to these two features we conclude that the diastereoselectivity in the high-temperature region is dominated by the hydride transfer. The stereochemical course of this partial step is a direct consequence of the diastereodifferentiating approach of the aluminium reagent to the carbonyl function. On the one hand this initiating complexation is severely influenced by the steric demand of the substituents adjacent to the reaction centre and on the other hand it is controlled by the Lewis acidity of the aluminium reagent resulting from the electronic effects of the *para* substituents of the phenoxides.

A remarkable change in this rather simple situation at high temperatures occurs in the range between +40 °C and −10 °C, signalled by inversion points (T_{inv}) and followed by a linear dependence in the Eyring plot at further reduced temperatures. This phenomenon is accompanied by a dramatic increase in

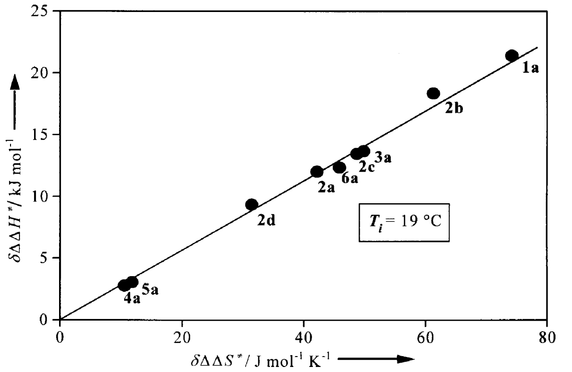


Fig. 3 $\delta\Delta\Delta H^{\ddagger}/\delta\Delta\Delta S^{\ddagger}$ diagram and the isoinversion temperature T_i for the diastereoselective reduction of 2-substituted cyclohexanones **1–6** with different diisobutylaluminium phenoxides **a–d**. For the values of $\delta\Delta\Delta H^{\ddagger}$, $\delta\Delta\Delta S^{\ddagger}$ and the numbering used, see Table 2.

the reaction time effecting a sufficiently high concentration to catalyse the MPV reaction. Consequently, the activation parameters determined for the low-temperature area represent a hybrid of the kinetic parameters for both the hydride transfer and the MPV reaction.† The absence of any isoselective relationships in this range is in accordance with that complex kinetic behaviour. Possibly this low-temperature region constitutes a part of the transitional region formerly postulated by Hale and Ridd.[10] Nevertheless, based on our measurements we find that it can be satisfactorily approximated by linear functions providing a second set of apparent activation parameters.

From the difference between the $\Delta\Delta H^{\ddagger}$ *vs.* $\Delta\Delta S^{\ddagger}$ values on either side of the maximum (T_{inv}) in the plots of ln *P* *vs.* T^{-1} we formulate an isoinversion relationship,[7] which is expressed as a strictly linear function in the $\delta\Delta\Delta H^{\ddagger}$ *vs.* $\delta\Delta\Delta S^{\ddagger}$ plot (Fig. 3). The slope determined in that manner is equivalent to the isoinversion temperature T_i.‡ This characteristic constant for the selection mechanism of the diastereoselective reduction of cyclohexanones with aluminium phenoxides makes it possible to predict that inversion temperatures (T_{inv}) of further systems concerning this type of reaction are in a similar area of T_i. This conclusion is of considerable practical importance. On applying the reduction method discussed here to a new system it is sufficient to perform the reaction at T_i and once on either side of T_i to roughly value the temperature dependence of the diastereoselectivity over the whole temperature range. Thus, it is possible to optimise any new system with only a few measurements.

Conclusions

In conclusion, we have validated the isoinversion principle as an appropriate instrument by which to elucidate the partial steps determining the diastereoselectivity of the aluminium phenoxide mediated reduction of cyclohexanones. These results emphasize the role of steric and electronic effects as factors directing the diastereodifferentiating hydride transfer at elevated temperatures as well as the complex composition of the selection mechanism caused by the MPV reaction at low temperatures. Moreover, the establishment of the corresponding isoinversion relationship permitted us to elaborate a generally applicable instruction for the optimization of systems related to those treated in this paper.

Experimental

Materials

Toluene was refluxed over sodium, distilled and stored over sodium. The DIBAH solution, 2,6-di-*tert*-butylphenol **11a** (99+%); 2,6-di-*tert*-butyl-4-methylphenol **11b** (99+%); 2,6-di-*tert*-butyl-4-bromophenol **11c** (99+%) and 3,5-di-*tert*-butyl-4-hydroxyanisole **11d** (99+% after recrystallization from hexane) were obtained from Aldrich. Compound **5** (99+%) was obtained from Fluka and **2–4** and **6** were prepared by oxidation of the corresponding alcohols. The GC analyses were performed on an HP 5890 series II gas chromatograph equipped with a flame ionization detector and an HP 3396 A integrator. A FFAP column was used (25 m × 0.32 mm) ($T = 70$ °C; *10 min;* $N_2 = 2$ atm). The apparatus was flame dried under argon. The retention times of the products were compared with samples of the authentic axial and equatorial alcohols.

General procedure for the reduction of cyclohexanones with diisobutylaluminium phenoxides

A toluene solution of DIBAH (20 cm^3 of 1 mol dm^{-3} DIBAH, 20 mmol) was transferred to a 100 cm^3 reaction flask which was equipped with a mechanical stirrer, a pressure equilibration addition funnel and a thermometer. A solution of 23.5 mmol of **11** in 10 cm^3 of toluene was added slowly at 0 °C and the mixture was stirred for 1.5 h. After temperature equilibration, a solution of **2–6** (2 mmol) in 10 cm^3 of toluene was added dropwise at a rate chosen to avoid remarkable exothermic effects. The diastereoselectivity and conversion of the reaction were monitored by GC. When the selectivity as well as the conversion were constant the mixture was hydrolysed with 10% HCl at the corresponding temperature, and diluted with diethyl ether and water. After extracting the aqueous layer twice more with diethyl ether the combined organic solutions were washed with saturated $NaHCO_3$, saturated NaCl and dried over anhydrous $MgSO_4$. The mixture was analysed by GC.

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† Due to this fact one might consider qualifying these parameters as 'apparent activation parameters'.

‡ T_i might also be obtained by calculating the average value of the inversion temperatures (T_{inv}). However, the merit of our graphical procedure lies in the weighting of the points furthest from the origin of the $\delta\Delta\Delta H^{\neq}$ *vs.* $\delta\Delta\Delta S^{\neq}$ plot, since these points resulting from two strikingly different slopes may be determined with more accuracy than such points localizing the inversion between two nearly equal slopes.