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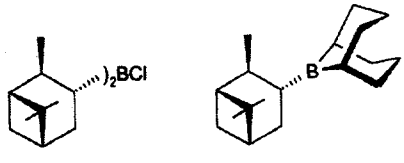
The Influence of Electronic Effects and Temperature on the Enantioselective Reductions of Acetophenone Derivatives with (-)-Diisopinocampheylchloroborane - A Dynamic Model of Enantioselection

Andreas Wiegers, Hans-Dieter Scharf *

Institut für Organische Chemie der RWTH Aachen, Prof. Pirlet-Str. 1, D-52056 Aachen

Abstract: The asymmetric reduction of acetophenone derivatives with (-)-diisopinocampheylchloroborane, with respect to temperature and different electronic situations present in the carbonyl group, has been investigated. The temperature dependence of enantioselectivity reveals that enantioselection is not the result of a one-step-process. Together with the subtle electronic effects observed a dynamic selection model takes shape. Copyright © 1996 Elsevier Science Ltd

(-)-Diisopinocampheylchloroborane, (-)-Ipc_2BCl **1** (fig. 1), reduces numerous prochiral ketones preferentially to the corresponding *secondary* (*S*)-alcohols[1,2]. Brown et al.[1] proposed for this reaction a one-step transition state model to explain the observed stereoselection which is in line with the one Midland and co-workers applied to the asymmetric reduction of ketones with *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane **2**, (Alpine-Borane™)[3]. This model (see figure 2) considers the unfavourable steric interaction between the larger group R_L of the ketone and the methyl group of the pinanyl moiety only, implying that stereoselection is achieved in just a simple step[4].



(-)-Ipc_2BCl, 1 *R*-Alpine-Borane, 2

Figure 1.

Though this model explains the results successfully in a fair number of cases, some results cannot easily be understood on the basis of steric interactions exclusively (cf. table 1)[5,6]. For example 2,6-dimethoxyacetophenone **3** yields the corresponding *R*-alcohol with 20 %ee (which is the wrong enantiomer according to the model) while **4** is reduced to the *S*-alcohol with again 20 %ee. Although the substituents in the 2- and 6-positions should enhance stereochemical differentiation, enantioselectivity is much lower than with acetophenone itself (98 %ee *S*-configuration[1]).

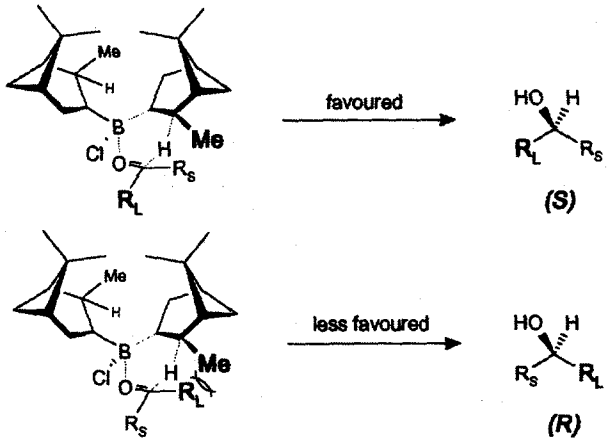
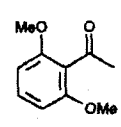
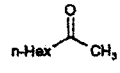
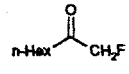
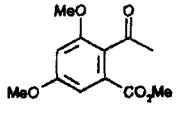
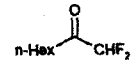
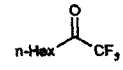


Figure 2: One-step transition state model for the asymmetric reduction of ketones with (-)-Ipc_2BCl proposed by Brown et al.[1]

In the series of fluorinated ketones **6-8** (table 1), enantioselectivity is again difficult to understand on the basis of simple steric influences[5]. Gradually changing the degree of fluorination results in dramatic changes in extent and direction of enantioselectivity. These results suggest that electronic effects should be involved in stereoselection as well, indicating that in addition to steric interactions another partial step might be relevant. Thus, systematically changing the electronic situation on the carbonyl group should give further insight into these steps determining enantioselectivity.

The temperature and/or pressure dependence of (stereo) selectivity, with respect to the isoinversion principle[7], is a sensitive tool for the investigation of such selectivity phenomena. If the mechanism of a reaction is

Table 1: Some unusual reductions of ketones with **1**.

compd.	ketone	ee[a,c]	compd.	ketone	ee[b]
3		20% *R*	5		7% *R*
			6		40% *R* [d]
4		20% *S*	7		32% *S* [d]
			8		91% *S* [d]

[a] Ref.13. [b] Ref.12. [c] typical: acetophenone 98 %ee *S* (Ref.8) [d] Note that the configuration of the fluorinated compounds corresponds to the opposite configuration in the non fluorinated compounds.

known, it can reveal information about the partial steps of a particular reaction responsible for the production of selectivity. The appearance of specific inversion temperatures T_{inv} in the modified Eyring plots, clearly indicates the presence of more than one partial step or reaction pathway being relevant for stereoselection[7,8,9]. Relying on these considerations, the presented results on the enantiodifferentiating reduction of ketones with the boron reagent **1** unveil whether its stereochemical outcome is determined by one or more partial steps.

In recent years, the observation of temperature effects in connection with the Eyring theory, has been frequently used to get a better understanding of the factors, influencing the stereochemical outcome of various reactions. Examples are the Paternò-Büchi-reaction[7], the Sharpless asymmetric dihydroxylation of olefins[10], the titanocene/alumoxan-catalysed polymerisation of propene[11], the photodimerisation of some stilbenes[12], the catalytic, asymmetric styrene hydroformylation[13], the asymmetric tautomerisation of photodienols[14] and the diastereoselective reduction of cyclic ketones with diisobutyl-aluminium-2,6-di-*t*-butyl-4-methylphenoxide[8].

To get further insight into those steps generating stereoselectivity, we started a more detailed investigation of both, the influence of temperature *and* electronic effects on the enantiomeric ratios of the reductions of ketones with (-)-Ipc_2BCl **1**.

RESULTS AND DISCUSSION

To obtain reliable data concerning the electronic effects, the steric surroundings of the carbonyl groups of the substrates has to be kept as constant as possible. Acetophenones can be electronically modified simply by variation of the substituent attached to the phenyl moiety. If these substituents are placed in the *meta*- or *para*-position only, changes in the steric situation at the carbonyl group are negligible. Thus, for our purposes, those substituted acetophenones were the substrates of choice. We choose the following X-acetophenones, in which X is: 4-F, 4-Cl, 4-Br, 4-H, 4-Me, 4-MeO, 3-MeO, 4-PhO and 4-MeS, respectively. In order to minimise erratic results, all reactions were run under standardised conditions using stock solutions of both the ketones and the reagent **1**. Moreover, each experiment was repeated up to three times under exactly the same conditions and in all systems two different workup techniques were randomly used. These were the oxidative workup using $H_2O_2/NaHCO_3$[15] and the diethanolamine method[1]. The enantiomeric ratios were determined by chiral capillary GC on a permethylated β-cyclodextrin stationary phase. In order to guarantee a quantitative baseline separation of the enantiomeric alcohols, all crude alcohols were transferred into their corresponding acetates or propionates (see fig. 3)[16]. All reactions were run until no further conversion was detectable by GC[17].

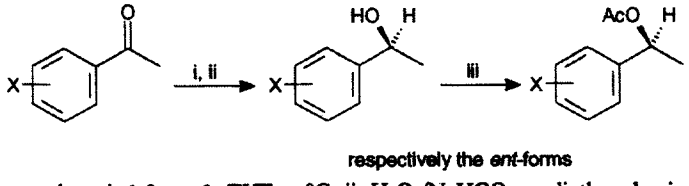


Figure 3. Standard procedure: i. 1.3 eq. **1**, THF, *x* °C; ii. $H_2O_2/NaHCO_3$ or diethanolamine; iii. pyridine, acetylchloride, Et_2O, room temperature (except in the case of X = 4-MeS, where propionylchloride was used).

The Eyring diagrams for the reduction of halogenated acetophenones (X = 4-F, 4-Cl and the 4-Br; see figure 4) show a strictly linear dependence between ln P (with P = [S]/[R], enantiomeric ratio) and the reciprocal temperature $1/T$ in the whole temperature range (+64 to -55 °C). All plots have the same slope and show a small, but significant order in the extent of enantioselectivity ($ee_F > ee_{Cl} > ee_{Br}$), detectable via linear regression.

In contrast to the halogenated acetophenones, both Eyring plots of the reductions of acetophenone and 4-Me-acetophenone exhibit an inversion point T_{inv} at approximately +10 °C (X = H) and 0 °C (X = 4-Me) (see figure 5). In the high temperature region ($T > T_{inv}$), the enantioselectivities and the slopes of the plots are quite similar to those obtained from the reductions of the halogen compounds. In the low temperature region ($T < T_{inv}$), however, their behaviour is clearly different. Although stereoselection is enhanced with decreasing temperature, too, the achievable enantiomeric excesses are significantly diminished.

In the group of ether- and thioether-derivatives of acetophenone (X = 3-MeO, 4-MeO, 4-PhO, 4-MeS), 3-MeO-acetophenone is the only one, whose Eyring diagram shows no inversion point (figure 5). The temperature dependence of its enantioselectivity is very similar to those observed for the 4-halogen-acetophenones, having almost the same slope of the plot. The obtainable stereoselectivities rank between those corresponding to 4-Cl- and 4-Br-acetophenone. The Eyring plots of 4-PhO- as well as of 4-MeS-acetophenone both exhibit an inversion point (T_{inv} (4-PhO) = +11 °C; T_{inv} (4-MeS) = +33 °C). Both Eyring plots are almost identical with respect to slope and selectivity (cf. fig. 6) and show small deviations from linearity only. Again, in the high temperature region the enantiomeric ratios are very similar to those observable in all the other systems. In the low temperature region, however, they show slightly lower selectivities than in the cases of 4-Me- and 4-H-acetophenone.

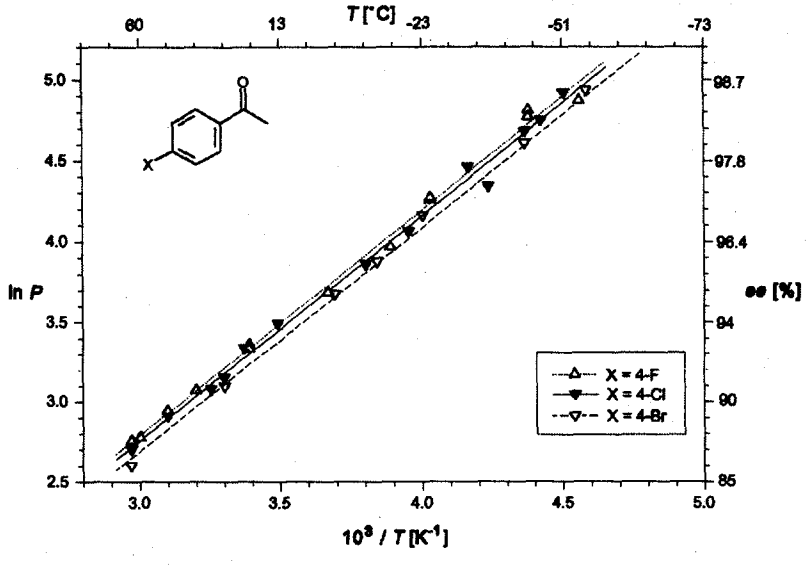


Figure 4. Eyring diagram for the reduction of the 4-halogen-acetophenones with **1**.

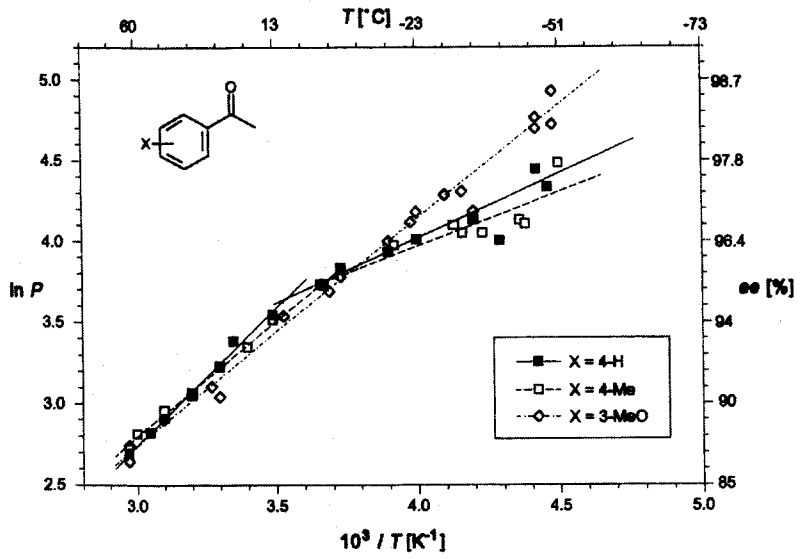


Figure 5. Eyring diagram for the reduction of the 4-X-acetophenones (X = H, Me) and of 3-MeO-acetophenone with **1**.

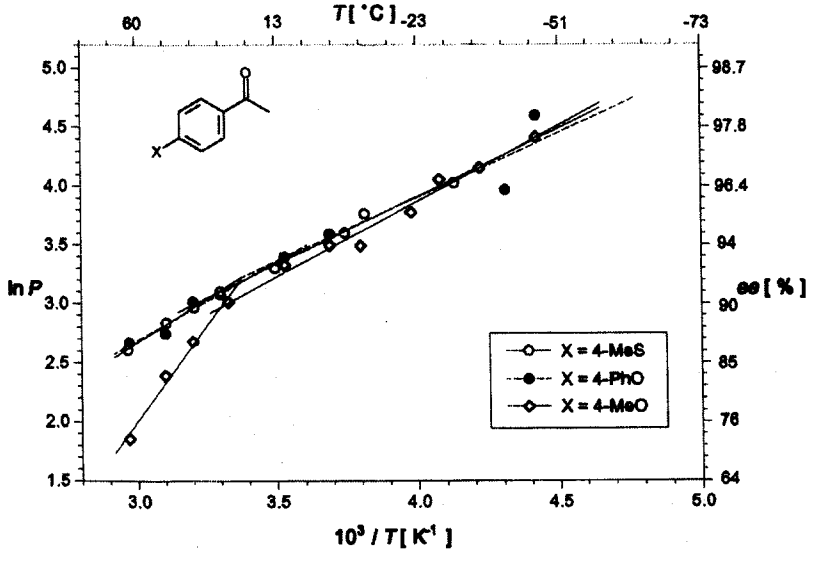


Figure 6. Eyring diagram for the reduction of ether- and thioether-acetophenones (X = 4-MeO, 4-PhO, 4-MeS) with **1**.

4-MeO-acetophenone, finally, behaves completely different in comparison with all previous systems. A distinct inversion point (T_{inv} = +30 °C) together with a dramatically decreased selectivity in the high temperature range is observed. As all other systems exhibit similar selectivities in the high temperature region, approximately

86-88 %ee (at +64 °C), only 74 %ee (at +64 °C) is attained in this case. In the low temperature range, the enantioselectivity is slightly lower than those obtained from the 4-PhO- and the 4-MeS-derivatives. Thus, over the whole temperature range 4-MeO-acetophenone is reduced with the lowest selectivity of all the substrates examined in this investigation.

In figure 7 the observed selectivities are plotted against the appropriate Hammett constants σ, of the substituents X[18]. Although the correlation is moderate, a clear trend is perceptible. Comparing all results, the highest degrees of stereoselection are obtainable with those acetophenones, which are substituted by electron withdrawing substituents, possessing positive Hammett constants σ (X = 4-F, 4-Cl, 4-Br, 3-MeO)[18]. With those substituents the corresponding Eyring plots exhibit no inversion points. It has to be noted, that there is a maximum value where no further increase in selectivity is possible. This seems to be around a value of σ = +0.1.

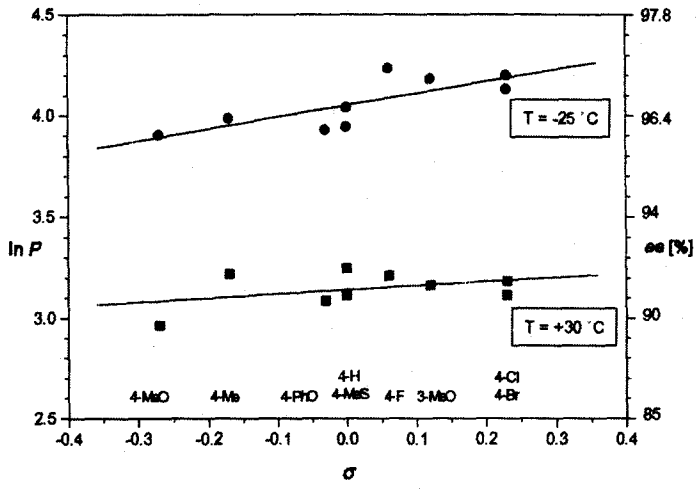


Figure 7. Plot of the ln *P*-values (at T = -25 °C and +30 °C) achievable with each substituent X *vs.* the corresponding Hammett constants σ.

Electron donating substituents (X = 4-H, 4-Me, 4-PhO, 4-MeS) with Hammett constants σ between 0.0 and -0.2 lead to decreased selectivities in the low temperature range. Together with slight to medium deviations from linearity in the Eyring diagrams, this indicates the beginning influence of a second partial selection step. If, in addition, strong mesomeric effects are involved, enantioselectivities are reduced even in the high temperature region, too. Actually in the case of 4-MeO-acetophenone (σ = -0.27) the selection level takes effect in decreasing the observed stereoselectivity at any temperature. Furthermore, we observe that electronic effects loose their influence with rising temperature. At +30 °C enantioselectivity is almost independent of the kind of substituent attached to the phenyl moiety.

It is well known, that substituents with negative Hammett constants σ lead to an increase in Lewis basicity of the carbonyl oxygenatom of acetophenones, while such substituents with positive σ-values diminish it[19]. Obviously, those acetophenones are reduced most selectively, which exhibit a Lewis acidic carbonyl oxygenatom.

As 1 is a Lewis acid, too, it seems, that weak acid-base interactions cause an increased selectivity of the reaction, while more basic acetophenones are reduced less selectively.

A tentative model of this reaction derived from the above observations is depicted in fig.8. The educts are in equilibrium with the corresponding *E*- and *Z*-adducts, respectively, before the reaction is irreversibly shifted to the side of the diastereomeric alkoxyboranes, by transfer of an hydrogen atom from the pinanyl moiety to the carbonyl group, accompanied by simultaneous elimination of α-pinene. Due to less steric interaction between the methyl group of the pinanyl rest and the *anti*-oriented rest R_L (here: substituted phenyl moiety), **path A** is the favoured sequence. The *Z*-adducts, formed in **path B**, preferently decompose to the educts again as a result of their lower stability ($k_3 < k_{-3}$). In the course of the reaction, the equilibrium is more and more shifted to the side of alkoxyboranes generated from the *E*-adducts ($k_1 > k_{-1}$). This is especially true, when the inherently weak *Z*-adducts are further destabilised by lowered acid-base-interactions, effecting an enhanced tendency to decomposition ($k_3 << k_{-3}$), as it is the case with acidic, electronwithdrawing substituted acetophenones. Here the sterically favoured path is even more preferred. As **path B** has almost no influence, and therefore **path A** exclusively dominates the selectivity, a linear relationship in the Eyring diagram is the result. No deterioration of enantioselectivity through **path B** occurs.

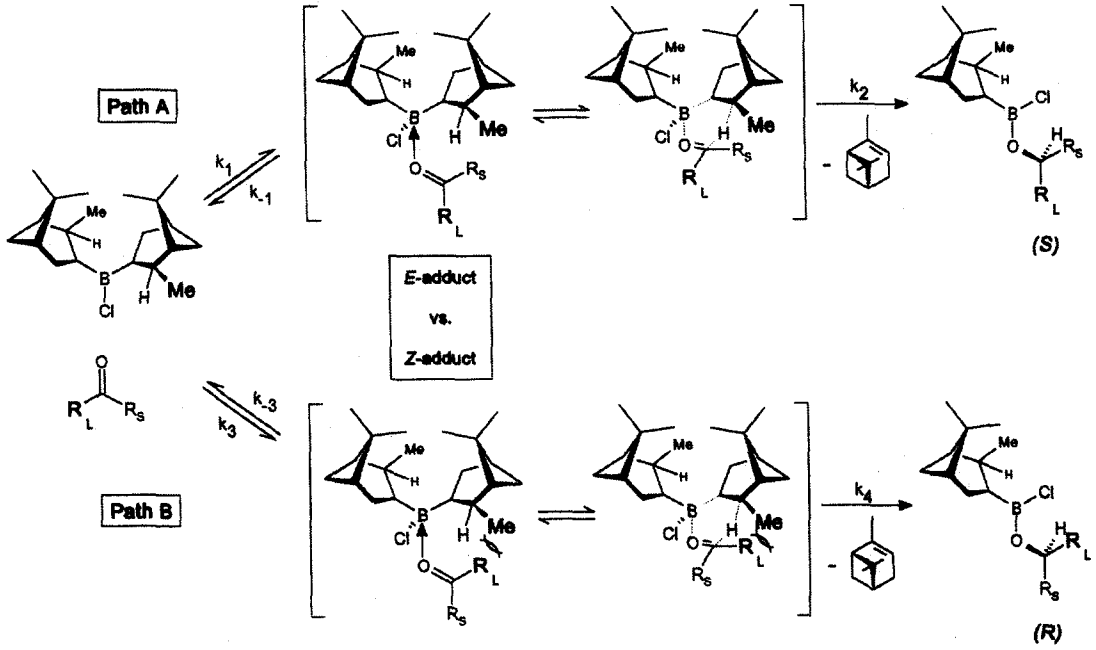


Figure 8. Tentative model of the partial steps in asymmetric reductions of ketones with (-)-Ipc_2BCl being relevant for stereoselection (here: R_L = Ph, R_S = Me).

If Lewis basicity on the carbonyl oxygen is enhanced (electron donating substituents), however, the decomposition rate of the intermediate boron adducts is remarkably lowered ($k_1 > k_{-1}$; $k_3 > k_{-3}$). The respective

preequilibria between educts and adducts are shifted to the side of the adducts. As, hereby, the lifetime of the less stable *Z*-adducts is increased, their irreversible reduction by the transfer of a hydrogen atom (**path B**) distinctly grows in favour. On the other hand, with increasing temperature the adducts are destabilised for entropic reasons, thus diminishing the influence of **path B** leading to enantioselectivities almost independent of the acidity of the carbonyl oxygenatom. Consequently, the enantiomeric ratio decreases whenever with **path B** a contraselectively operating, second reaction channel becomes effective. This necessarily results in the fact that ln *P*-1/T-relationships are no longer linear and inversion points T_{inv} are observed.

CONCLUSIONS

For the first time, the influences of electronic effects *and* of temperature on the enantioselectivity of the asymmetric reduction of acetophenone derivatives with (-)-Ipc_2BCl **1** have been investigated systematically. Utilising the isoinversion methodology, subtle electronic, stereochemically operative effects could be detected. We found, that acetophenones whose substituents increase Lewis acidity of the carbonyl oxygenatom are reduced most selectively, whereas with more Lewis basic acetophenones enantiomeric ratios are diminished. In addition to this, the Eyring plots of the "acidic" acetophenones show little or no deviation from linearity; "basic" acetophenones, however, show distinct inversion points. This indicates, that stereoselectivity, in general, is the result of a two-step process rather than of a concerted way. With weak acid-base interactions only the sterically favoured **path A** is relevant. The contraselective reaction channel (**path B**), however, is opened by an increased acid-base interaction between **1** and the acetophenone. With this model, it is now possible to access a better understanding of the influences of electronic effects on the stereochemistry of this reaction, thus making more precisely predictions available, than with the simple one-step transition state model.

EXPERIMENTAL SECTION

General. Conversions were determined on a Hewlett-Packard HP 5890 series II gas chromatograph, using a HP FFAP capillary column (25 m x 0.25 mm; carrier gas N_2). Analysis of the enantiomeric ratios were performed on a Hewlett-Packard HP 5890 series II plus gas chromatograph, using a permethylated cyclodextrin capillary column (FS-CYCLODEX-β-I/P 25 m x 0.25 mm; carrier gas H_2). Both GCs were equipped with flame ionisation detectors and connected to Hewlett-Packard HP 3396 series II integrators. All chromatograms obtained were compared with those from authentic references of educts and products at appropriate temperatures. All reaction temperatures were kept constant by means of cryostats (below room temperature) or electronically controlled heating baths. The actual temperature was determined within the reaction flask.

Materials. THF was distilled from benzophenone/sodium and stored under argon. All other solvents were dried and distilled prior to use. (-)-Ipc_2BCl was purchased from Aldrich and used as received. 4-MeS-acetophenone

was synthesised from thioanisole and $AlCl_3$/acetylchloride according to the literature[20]. All other ketones and reagents were commercially available. All ketones used were of ≥ 99 % purity (GC). References of the phenylethanols were obtained by reduction of the corresponding acetophenones with $NaBH_4$ in EtOH. Esterification of the racemic alcohols was done in analogy to the procedure described below. All racemic alcohols and esters, as well as the ketones, gave correct ^1H- and ^{13}C-NMR spectra.

Reduction of acetophenone derivatives with (-)-Ipc$_2$BCl.

General procedure. All reactions with (-)-Ipc_2BCl were carried out in flame dried flasks under an atmosphere of argon. (-)-Ipc_2BCl **1** (4 mmol, 8.0 mL of a 0.5 *M* solution in THF) was brought to the desired reaction temperature (0.5 to 1 h of equilibration) and the respective acetophenone (3 mmol, 2.0 mL of a 1.5 *M* solution in THF containing an equimolar amount of cis/trans-decahydronaphthalene as an internal standard) was added without noticeable exothermic reaction. At periodic intervals aliquots (1.0 mL) were taken from the reaction mixture and either worked up using H_2O_2/$NaHCO_3$ or diethanolamine. The conversion was determined via GC.

H_2O_2/$NaHCO_3$ workup: 1.0 mL of the reaction mixture was quenched with 2 mL of saturated $NaHCO_3$, 2 mL of H_2O_2 (30 %) was added and, after thorough mixing, set aside for 1 h at room temperature. Saturated $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na_2SO_4 and analysed for conversion by GC.

Diethanolamine workup: 1.0 mL of the reaction mixture was added to diethanolamine (100-120 mg) in a centrifuge vial, 3 mL of Et_2O was added and the mixture was stirred over night at room temperature. Then the mixture was centrifuged and the supernatant solution was removed via pipette. The solid residue was washed with hexane (2 x 2 mL) and again centrifuged. The combined organic phases were finally filtered and the conversion was analysed. Before esterification the solvents were removed and the residue was dissolved in 10 mL of Et_2O.

When no further conversion was detectable, the crude alcohols were esterified. The ethereal solutions were cooled to 0 °C and 1.2 mL of pyridine was added. After addition of 1.0 mL of acetylchloride (1.1 mL of propionylchloride in the case of 4-MeS-acetophenone) stirring at room temperature was continued over night. The mixture was washed with HCl (2 *M*, 2 x 10 mL), neutralised with saturated $NaHCO_3$ (2 x 10 mL) and washed with brine. After removal of the solvent, the residue was distilled with a Kugelrohr apparatus at reduced pressure (0.01 mm Hg) and appropriate temperatures. Enantiomeric ratios were finally determined by GC.

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9. If no inversion temperatures T_{inv} are detected there may be two main explanations: either T_{inv} corresponds to a temperature not tolerated by the reaction (temperature window) or the reaction proceeds via a mechanism, which furnishes selectivity in only one step (e.g. in concerted reactions).
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16. This is advisable, as with the used permethylated cyclodextrin phase, the underivatised phenylethanols show significant tailings. This often makes baseline separations impossible, thus diminishing the accuracy of enantiomer analysis.This drawback is avoided by derivatising the alcohol.
17. In a preliminary experiment we examined the influence of ether cleavage, occurring as a side reaction at elevated temperatures, on enantioselectivity: we kept 8.0 mL of **1** (0.5 *M* in THF) at +64 °C for 72 h, added acetophenone (2.0 mL of 1.5 *M*) and continued heating for another 24 h. After workup no formation of 1-phenylethanol was detectable at all (GC). In all reductions of acetophenones with **1**, however, conversions were quantitative at temperatures above +40 °C. Furthermore complete consumption of **1** in ether cleavage of the THF takes about two weeks at 30 °C (0.5 *M* **1** in THF), whereas the reductions are completed after 36 h at +30 °C. This indicates, that reduction is by far faster than ether cleavage, showing that $Ipc_2BO(CH_2)_4Cl$, formed at elevated temperatures, has no influence on stereoselectivity. Furthermore, there are no effects of stoichiometry on enantioselectivity, at least in the range from 10:1 to 1: 3 (**1** : acetophenone). Although Brown et al.[1] have shown, that no such reaction occurs even at 25 °C, a second equivalent of α-pinene could theoretically be eliminated at elevated temperatures. We checked this in an experiment, where 2 eq. of acetophenone reacted with 1 eq. of **1** at +64 °C under standard conditions. We found that only 1 eq. acetophenone was consumed in this reaction.
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