JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 317–324
Published online 26 January 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.730

Kinetic analysis of the asymmetric amplification exhibited by *B*-chlorodiisopinocampheylborane

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Received 5 August 2003; revised 22 October 2003; accepted 24 October 2003

ABSTRACT: A quantitative investigation was undertaken to determine experimentally the relative reaction rates of the heterochiral and homochiral species of *B*-chlorodiisopinocampheylborane (Dip-Cl), a reagent that exhibits asymmetric amplification. Using the method of flooding to reduce the apparent second-order reaction to pseudo-first-order conditions, rate constants of $3.8\ (\pm 1.0) \times 10^{-4}$ and $1.7\ (\pm 0.8) \times 10^{-5}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ (at $-15\ ^{\circ}\mathrm{C}$) were found for the homochiral and heterochiral species, respectively. The resulting relative reaction rate, the value of g in Kagan and co-workers' model, was 0.04 ± 0.03. Additional experiments were conducted to confirm this value. The deterioration of the chiral purity of the final product was simulated throughout reaction conversion and compared with actual values. Through minimization, a relative reaction rate (g) of 0.08 ± 0.04 was determined. Finally, using 8-hydroxyquinoline complexation, the change in isomeric ratio of the Dip-Cl remaining in the reaction solution was measured. The relative reaction rate (g) required to consume the isomers at the observed rate was determined as 0.08 ± 0.01. Thus, three independent methods have been used to determine the relative reaction rate (g) of the heterochiral to homochiral species with good agreement to give an average value of 0.07 ± 0.03. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: *B*-chlorodiisopinocampheylborane; asymmetric amplification; relative reaction rate; pseudo-first-order kinetics

INTRODUCTION

Asymmetric amplification is a fascinating phenomenon in asymmetric syntheses that allows the preparation of chiral products having enantiomeric purity greater than that of the starting materials. An excellent example is the reduction of ketones with *B*-chlorodiisopinocampheylborane[1] (Dip-Cl, **1**). When Dip-Cl is prepared from α-pinene of only 70% enantiomeric excess (*ee*), the corresponding chiral alcohols are obtained in >90% *ee* (Scheme 1). This is extremely advantageous as less expensive, enantiomerically impure α-pinene can be used to prepare the Dip-Cl but the corresponding reduction products are still obtained in very high enantiomeric excess. Merck has synthesized many intermediates in their LTD_4 antagonist program via chiral alcohols prepared using the Dip-Cl reduction.[2]

Asymmetric amplification is part of a broader class of phenomena called non-linear effects (NLEs), which have been the subject of recent reviews.[3] Asymmetric amplification occurs when there is a positive deviation of the nonlinear effect, (+)-NLE, and results from the formation of a less reactive or non-reactive heterochiral species that limits the formation of any undesired enantiomers. Kagan and co-workers have developed the prevailing theory of NLEs and proposed a set of mathematical equations that model this phenomenon.[3] Blackmond has provided an important extension of Kagan and co-workers' theory that allows the prediction of experimental values of the system.[4] The model most applicable to Dip-Cl is the ML_2 model (Scheme 2), which considers a reactive center (M) and two chiral ligands [$L_{(+)}$, $L_{(-)}$] that combine to form two homochiral [$ML_{(+)}L_{(+)}$, $ML_{(-)}L_{(-)}$] and one heterochiral [($ML_{(+)}L_{(-)}$] species. Thus, one begins with a mixture of enantiomers but, upon complexation, diastereomeric ML_2 species are formed which react at different rates to form chiral products.

Of the equations that model this system, the most important is

$$EE_{\mathrm{prod}} = EE_{\mathrm{o}} \times ee_{\mathrm{hux}} \frac{1+\beta}{1+g\beta} \qquad (1)$$

where EE_{prod} (*ee* of chiral alcohol product) depends on EE_{o} (the highest possible product purity that can be obtained using optically pure ligand) and ee_{aux} (the chiral purity of L). The terms β [Eqn. (2)] and K [Eqn. (3)] provide the relative amounts of the heterochiral (z) and homochiral (x, y) stereoisomers. Important for this paper

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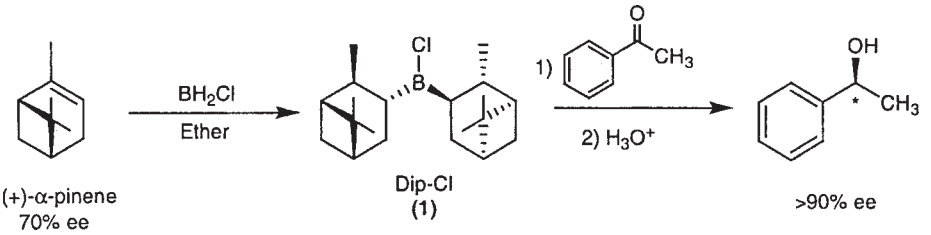
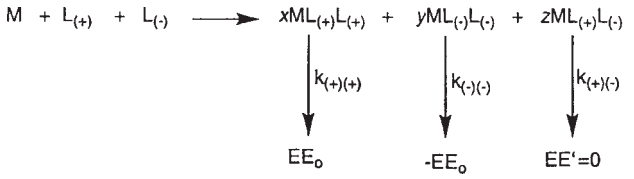


Scheme 1. Preparation of Dip-Cl and reduction of acetophenone



Scheme 2. ML_2 model

is the term g [Eqn. (4)], which represents the relative reaction rate of the heterochiral and homochiral species.

$$\beta = z/(x+y) \tag{2}$$

$$K = z^2/xy \tag{3}$$

$$g = k_{\text{heterochiral}}/k_{\text{homochiral}} \tag{4}$$

We have developed a research program to determine experimentally the parameters of Eqn. (1) for the Dip-Cl reagent. In a previous study, we determined β and K by complexation of Dip-Cl with 8-hydroxyquinoline followed by chiral HPLC analysis.[5] We showed how the reaction conditions for the preparation of Dip-Cl affect the distribution of stereoisomers and, thus, the terms β, K and EE_{prod}. Since this was the first quantitative, stereochemical analysis of a reagent that exhibits the NLE phenomenon, it provided the first experimental verification of the part of Kagan and co-workers' theoretical model dealing with the distribution of stereoisomers (i.e. β). Furthermore, the experimental values are in excellent agreement with those presented in the literature.[4] In this paper, we present an analysis of the kinetic portion of Kagan and co-workers' model by determining g for the Dip-Cl reagent.

RESULTS AND DISCUSSION

For this entire study, the process that we chose to investigate is described in Scheme 1. In a previous study,[5] we showed that the distribution of the steroisomers of the Dip-Cl reagent varies with the temperature (0–20 °C) of preparation of this reagent. Therefore, in this study, we prepared all Dip-Cl reagents at a single temperature of 10 °C. In addition, qualitative observations indicate that the enantiomeric excess of the *sec*-phenethanol reduction product is also affected by temperature, hence all reduction reactions we performed at −15 °C.

Derivation of kinetic equations

In studying the kinetics of this reaction, it will be initially assumed that the reduction of a ketone (acetophenone) with Dip-Cl is a second-order reaction. Hence the reaction rate will be proportional to the product of the concentrations of the two reagents as shown by

$$\frac{-\text{d[acetophenone]}}{\text{d}t} = \frac{-\text{d[Dip-Cl]}}{\text{d}t} = \frac{\text{d[ROH]}}{\text{d}t} = k[\text{Dip-Cl}][\text{acetophenone}] \tag{5}$$

By performing the reaction with a large excess of one reagent, such that its concentration is essentially unchanged over the course of the reaction, the reaction order is effectively reduced to pseudo-first-order conditions (for additional information on second-order kinetics and the method of flooding, see Ref. 6). Hence the reaction is performed with a large excess of acetophenone to give the following simplified rate law:

$$\frac{-\text{d[Dip-Cl]}}{\text{d}t} = k_\psi[\text{Dip-Cl}] \tag{6}$$

where k_ψ is the apparent rate constant (to obtain the second-order rate constant, one divides the apparent rate constant, k_ψ, by the mean concentration of acetophenone, $[\text{acetophenone}]_{\text{average}}$, in the interval of the reaction used for the rate determination[6]):

$$k_\psi = k[\text{acetophenone}]_{\text{average}} \tag{7}$$

Knowing that 1 equiv. of Dip-Cl gives 1 equiv. of *sec*-phenethyl alcohol (ROH) and the identities shown in Eqns (8) and (9), the integrated rate equation, Eqn. (10), can be derived.

$$[\text{Dip-Cl}]_t + [\text{ROH}]_t = [\text{Dip-Cl}]_{\text{initial}} = [\text{ROH}]_\infty \tag{8}$$

$$[\text{ROH}]_{\text{initial}} = 0 \tag{9}$$

$$\text{In}\left(1 - \frac{[\text{ROH}]_t}{[\text{Dip-Cl}]_{\text{initial}}}\right) = -k_\psi t \tag{10}$$

Thus, a plot of $1 - ([\text{ROH}]_t/[\text{Dip-Cl}]_{\text{initial}})$ against time should reveal a linear relationship with a slope equal to apparent rate constant (k_ψ) and an intercept of zero.

The fact that Dip-Cl forms as a mixture of isomers adds additional complication to this system; there are as many as three reacting species in the system. However, we know from our previous study[5] that 70% *ee* α-pinene only forms two isomers, the (+)(+)−**1** and (+)(−)−**1** species; this is a useful simplification [the isomeric ratio found when 70% *ee* α-pinene is used to prepare Dip-Cl is 78.9% (+)(+), 21.2% (+)(−) and 0.0% (−)(−) isomer]. Given pseudo-first-order conditions of excess acetophenone and Dip-Cl as a mixture of isomers, one would expect the reaction to proceed according to two different apparent reaction rates depending on the percentage conversion of the reaction. The apparent rate constant in the 'early' regime would be a combination of the homochiral and heterochiral rate constants:

$$k_\psi = (k_{\text{homochiral}} + k_{\text{heterochiral}})[\text{acetophenone}]_{\text{average}} \quad (11)$$

The apparent rate constant in the 'late' regime, when all of the homochiral species have been completely consumed, is given by

$$k_\psi = k_{\text{heterochiral}}[\text{acetophenone}]_{\text{average}} \quad (12)$$

First, the heterochiral reaction rate, $k_{\text{heterochiral}}$', can be determined by measuring the apparent rate constant after all of the homochiral species have been consumed and using Eqn. (12). Next, the homochiral reaction rate, $k_{\text{homochiral}}$', can be determined by measuring the apparent rate constant when both the heterochiral and homochiral species are reacting and rearranging Eqn. (11). The value of g can be calculated from these two values. The results of these experiments are described below.

Kinetic determinations

Solutions of Dip-Cl were prepared from 70% *ee* α-pinene and used to reduce excess acetophenone. The plot of $\{1 - ([\text{ROH}]_t/[\text{Dip-Cl}]_{\text{initial}})\}$ vs time shows two distinct regions, each with a linear relationship, as shown in Fig. 1 (lower curve). As predicted, a break in the curve occurs after ca 79% of the Dip-Cl has been consumed (the homochiral species are completely consumed when the reaction is 78.9% complete and k_ψ would change after this point). Both regions of the reaction were subjected to least-squares regression and a linear relationship was observed. (Each reduction was performed in duplicate. The residual sum of squares was divided into two parts, one from the experimental error and the other from the lack of fit of the linear model. The F-ratio was calculated and compared with that obtained from the statistical table representing 95% confidence and the appropriate degrees of freedom. In every case, the assumed linear model adequately described the data.) The resulting slopes were recorded and 95% confidence intervals were calculated; a correlation coefficient (r^2) of 0.88 was found for the 'early' regime and 0.72 for the 'late' regime. The heterochiral rate constant, $k_{\text{heterochiral}}$, calculated from the 'late' regime, was found to be 1.6 ($\pm$0.7) $\times 10^{-5}$ M^{-1} s^{-1}. The linear plots confirm our initial assumption that the reaction is second order; first order in Dip-Cl and first order in acetophenone (Fig. 1).

An additional determination of the heterochiral rate constant was performed. Solutions of Dip-Cl were prepared from nearly racemic (−1.2% *ee*) α-pinene and used to reduce excess acetophenone (the racemic α-pinene obtained from Aldrich registered an *ee* value of −1.2% using the method described by Moeder *et al.*;[7] additional confirmation was found when product chiral purity values measured at low reaction conversion consistently recorded slightly negative *ee* values). In this case, the homochiral isomer concentration and reaction rate were such that practical sampling of the early regime was not possible. [Dip-Cl prepared from −1.2% *ee* α-pinene results in an isomeric ratio of 16.9% (+)(+)-Dip-Cl, 16.2% (−)(−)-Dip-Cl and 66.9 (+)(−)-Dip-Cl. The homochiral species are consumed after the reaction is 33.1% complete, after ca 20 min. Thus, accurate sampling was deemed impractical and was not attempted.] However, for the later regime, a plot of $\ln\{1 - ([\text{ROH}]_t/[\text{Dip-Cl}]_{\text{initial}})\}$ vs time reveals a linear relationship as shown in Fig. 1 (top curve). (As expected, the lines are parallel; the slopes are of equal value. This reflects the independence of reagent concentration on reaction rate that is indicative of a pseudo-first-order reaction.) The resulting data were treated using least-squares regression, the slope was recorded and the 95% confidence interval calculated; a correlation coefficient of 0.91 was found. The heterochiral rate constant, $k_{\text{heterochiral}}$, was found to be 1.9 ($\pm$0.4) $\times 10^{-5}$ M^{-1} s^{-1}. Using the

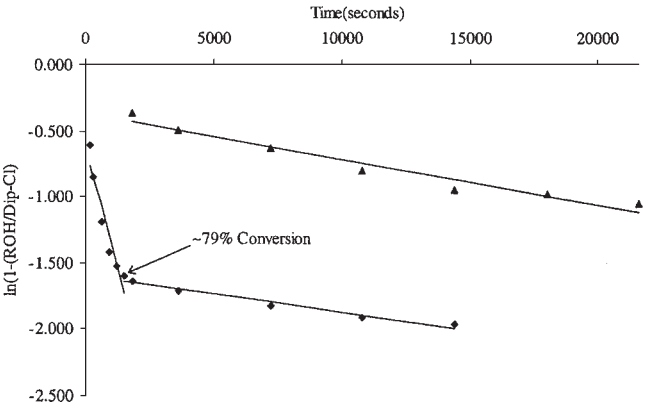


Figure 1. Pseudo-first-order kinetic plots for the reduction of acetophenone with Dip-Cl at −15 °C using Dip-Cl prepared from 70% *ee* and racemic α-pinene. ◆, ln[acetophenone] using Dip-Cl prepared from 70% *ee* α-pinene; •, ln[acetophenone] using Dip-Cl prepared from racemic α-pinene

Table 1. Summary of rate constants

ee of α-pinene (%)	Species	k ($M^{-1}\,s^{-1}$)	Correlation coefficient (r^2)
70	Heterochiral	$1.6\ (\pm 0.7) \times 10^{-5}$	0.67
0	Heterochiral	$1.9\ (\pm 0.4) \times 10^{-5}$	0.91
		Av.: $1.7\ (\pm 0.8) \times 10^{-5}$	
70	Homochiral	$3.8\ (\pm 1.0) \times 10^{-4}$	0.88

average heterochiral rate constant and the average acetophenone concentration, the homochiral rate constant, $k_{\text{homochiral}}$, was calculated from the apparent rate constant, k_{ψ}, of the 'early' regime and Eqn. (11). The value was $3.8\ (\pm 1.0) \times 10^{-4}\,M^{-1}\,s^{-1}$. [An attempt to determine $k_{\text{homochiral}}$ using pseudo-first-order conditions using an excess of Dip-Cl (97% *ee*) was made. However, this gave a larger value of $1.4\ (\pm 0.3) \times 10^{-3}\ M^{-1}\,s^{-1}$. It is thought that this method gives rates that are too fast for our sampling technique and thus the rate is overestimated.] A summary of these results is given in Table 1.

From the rate constants in Table 1, a value of 0.04 ± 0.03 is obtained for the relative reaction rate of the heterochiral to homochiral species (g). This value indicates that the heterochiral species is 22 times less reactive than the homochiral species. Our value shows reasonable agreement with the previously reported value ($g = 0.1$)[4] using an iterative curve-fitting method. Moreover, the agreement also seems reasonable considering that the data were obtained from a reduction reaction performed at a different temperature (−25 °C) than ours (−15 °C) using a different ketone substrate. The iterative curve-fitting method was used to investigate our system and the resulting value of g was found to be 0.06 ± 0.01. However, there are several additional methods that can be used to determine g. Since most of these were available using the data at hand, these methods were utilized to provide additional insight into the value of g.

Modeling chiral purity over time

The second method of determination of the relative reaction rate (g) involved modeling the product chiral purity, EE_{prod}, values over time. EE_{prod} will erode at a rate that is driven by the relative reaction rate of the heterochiral and homochiral species (g). This study was conducted in conjunction with the kinetic studies discussed above.

When Dip-Cl is prepared from 70% *ee* α-pinene, utilized in a reaction with excess acetophenone, and Dip-Cl is the limiting reagent, the overall chiral purity of the product cannot exceed 75.7% (Table 2). Hence it is estimated that a 20.3% ($EE_{\text{initial}} - EE_{\text{final}}$) change in chiral purity of the product can occur over the course of the reaction.

It is known that product concentration under pseudo-first-order conditions changes according to

$$[\text{ROH}] = [\text{Dip-Cl}]_{\text{initial}}\,(1 - e^{-kt}) \tag{13}$$

This equation can be modified to accommodate the multiple isomers of Dip-Cl and their respective rate constants:

$$[\text{ROH}] = [\text{Dip-Cl}]_{\text{homo}}(1 - e^{-k_{\text{homo}}t}) + [\text{Dip-Cl}]_{\text{hetero}}(1 - e^{-k_{\text{hetero}}t}) \tag{14}$$

The generation of ROH can be further divided into contributions from both the heterochiral and homochiral species and their respective chiral purities as shown in Table 3.

Thus, the chiral purity of the product, EE_{prod}, can be estimated at any time, t, knowing EE_{o} and the rate constant of each species:[4]

$$EE_{\text{prod}} = \frac{\sum[(R) - \text{ROH}] - \sum[(S) - \text{ROH}]}{\sum[(R) - \text{ROH}] + \sum[(S) - \text{ROH}]} \times 100 \tag{15}$$

Given the isomeric ratio and concentration of Dip-Cl used, a mathematical model was built based on the series of equations shown in Table 3. The differences between the predicted and actual values of chiral purity were minimized at each time point and the relative reaction rate of the heterochiral to homochiral species (g) was

Table 2. Calculation of EE_{prod} during reaction conversion

ee_{aux}	x	y	z	EE_{initial} (predicted)[a]	EE_{initial} (observed)	EE_{final} (predicted)[b]
−1.2	0.169	0.162	0.669	2.0	0.08	0.7
10.6	0.179	0.063	0.758	46.0	38.2	11.1
22.2	0.272	0.032	0.696	75.8	64.4	23.0
34.4	0.427	0.015	0.558	89.5	78.8	39.6
46.6	0.569	0.001	0.430	95.7	85.6	54.5
58.6	0.674	0.000	0.326	96.0	88.9	64.7
71.2	0.789	0.000	0.211	96.0	91.0	75.7
97.0	0.989	0.000	0.012	96.0	95.9	94.9

[a] $EE_{\text{initial}} = (x - y/x + y) \times ee_{\text{o}} \times 100$, where ee_{o} is 0.960.
[b] $EE_{\text{final}} = (x - y/x + y + z) \times ee_{\text{o}} \times 100$ where ee_{o} is 0.960.

Table 3. Generation of (*R*)- and (*S*)-ROH at time *t*

Species	(*R*)-ROH formed at time *t*	(*S*)-ROH formed at time *t*
(+)(+)−1	$\left(\frac{1+ee_o}{2}\right)[(+)(+)-1]_i(1-e^{-k_{homo}t})$	$\left(\frac{1-ee_o}{2}\right)[(+)(+)-1]_i(1-e^{-k_{homo}t})$
(−)(−)−1	$\left(\frac{1-ee_o}{2}\right)[(-)(-)-1]_i(1-e^{-k_{homo}t})$	$\left(\frac{1+ee_o}{2}\right)[(-)(-)-1]_i(1-e^{-k_{homo}t})$
(+)(−)−1	$\frac{1}{2}[(+)(-)-1]_i(1-e^{-k_{hetero}t})$	$\frac{1}{2}[(+)(-)-1]_i(1-e^{-k_{hetero}t})$

estimated. These calculations were performed on the reduction of excess acetophenone using Dip-Cl prepared from 70% *ee* α-pinene and averaged over two runs. The calculated relative reaction rate (g) was 0.08 ± 0.04. A plot of the actual vs predicted values of EE_{prod} is shown in Fig. 2.

The analysis of EE_{prod} as a function of time (shown in Fig. 2) when Dip-Cl is the limiting (or stoichiometric) reagent reveals some unexpected results: the EE_{prod} values at the beginning of the reaction are lower than expected from the ee_o value, and the EE_{prod} values at the end of the reaction are higher than expected from the ee_{aux} value. The trend that the EE_{prod} values were lower than expected at low conversion as predicted by ee_o was systematically observed throughout the study. When Dip-Cl was prepared from 97% *ee* pinene, the resulting EE_{prod} recorded at low conversion was ca 96% *ee*, in agreement with the ee_o value. However, as the chiral purity of the pinene was decreased, the EE_{prod} values recorded at low conversion varied from the predicted value by as much as 17% (the maximum deviation was observed at the lowest pinene purity). It appears that some non-specific reduction is taking place upon reagent addition; perhaps the heat of reaction is not efficiently dissipated and results in an area of increased heterochiral reaction rate.

This phenomenon complicates the calculations. By definition, the mathematical model provides initial EE_{prod} values that are a function of EE_o. During the minimization procedure, each rate constant, especially the heterochiral rate constant, is adjusted to an artificially high level to approach better the lower observed EE_{prod} values. If the EE_o value of the model is changed to the highest value observed during reaction conversion, a significantly improved fit can be achieved. A correlation coefficient of 0.99 was observed. Unfortunately, this switch greatly affects the value of the relative reaction rate (g). The calculated value, 0.009 ± 0.001, is thought to be unreasonable given the other independent determinations already made. Hence it seems that the analysis using the known value of EE_o gives a more reliable estimate (0.08 ± 0.04) of the relative reaction rate (g).

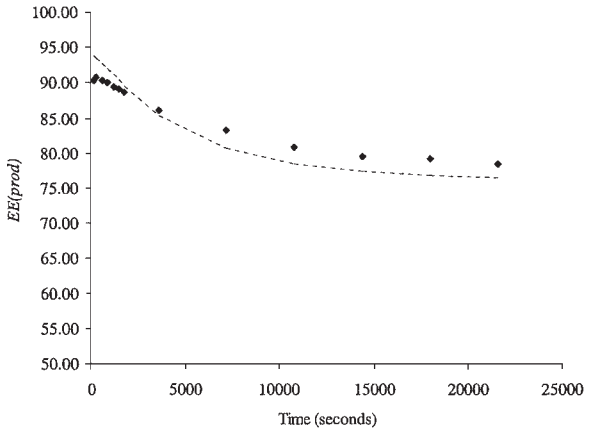


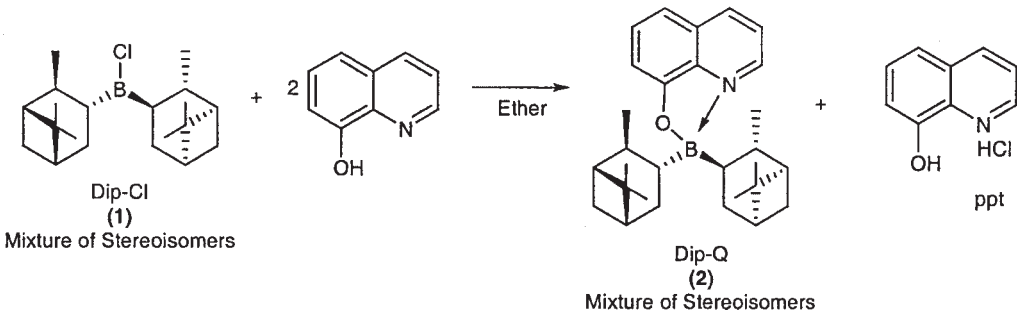
Figure 2. Plot of EE_{prod} (best fit) vs time. ◆, EE_{prod} (observed); dashed line, EE_{prod} (predicted)

The EE_{prod} value that is greater than the ee_o value at reaction completion is significant and was not recognized at the time of our original investigation. It is well documented that when Dip-Cl is used in stoichiometric amounts, the chiral purity of the product, EE_{prod}, cannot exceed ee_{aux}.[3,4] This argument is founded on the assumption that all of the α-pinene is consumed during hydroboration and that the minor enantiomer of α-pinene can only result in (+)(−)-**1** or (−)(−)-**1**. Each erodes EE_{prod} such that it cannot possibly exceed ee_{aux}. However, the isomeric ratios presented in Table 2 clearly show that the EE_{prod} values observed at reaction completion can exceed those predicted by ee_{aux}. This unexpected result arises from a Dip-Cl preparation that utilizes excess α-pinene. We have previously shown that variation in preparation temperature can influence the isomeric ratio of the resulting Dip-Cl and that a higher preparation temperature generates higher levels of the homochiral species.[5] This manipulation is only possible when excess α-pinene is used. Indeed, when Dip-Cl prepared from excess α-pinene is used to reduce excess ketone (as described in the Experimental section), the resulting EE_{prod} value is greater that the ee_{aux} value (see Table 2). Hence the method of Dip-Cl preparation can improve the amplification that is exhibited by the reagent.

Modeling ratio of Dip-Q isomers

Another method of determining the relative reaction rate of the heterochiral to homochiral species (g) utilizes 8-hydroxyquinoline to complex the Dip-Cl stereoisomers. In this method, 8-hydroxyquinoline is added to aliquots of the reaction mixture to complex the remaining heterochiral and homochiral species as shown in Scheme 3.

A solution of Dip-Cl was prepared with 70% *ee* α-pinene and used to reduce excess acetophenone. As the reaction conversion was monitored, the Dip-Cl remaining in solution was complexed with the 8-hydroxyquinoline



Scheme 3. Complexation of Dip-Cl with 8-hydroxyquinoline

reagent (Scheme 3). If the isomeric ratio and concentration of the Dip-Cl are known before the initiation of reduction, the concentrations of the homochiral and heterochiral species (and their isomeric ratio) can be predicted from the reaction conversion and the relative reaction rate (g). Conversely, if one minimizes the difference between the actual and predicted isomeric ratios at each point in the reaction, a 'best fit' value of the relative reaction rate (g) may be obtained. A graphical representation of the isomeric ratio remaining in solution is shown in Fig. 3. In this case, the value of the relative reaction rate (g) is 0.08 ± 0.01. The ramifications of this experiment are important to the mathematical model used to understand asymmetric amplification. The excellent fit lends additional validity to the model, especially Eqn (1), and is an important confirmation of our estimation of the relative reaction rate (g). More importantly, it proves that the stereoisomers isomers of Dip-Cl do *not* reequilibrate as described by Curtin–Hammett conditions and, thus, as previously discussed for Dip-Cl, K cannot be used as an equilibrium constant.[5]

CONCLUSION

Three independent methods have been used to determine the relative reaction rate of the heterochiral to homochiral species (g). A summary of the results is shown in Table 4. The average value of g of 0.07 ± 0.03 indicates that the homochiral species reacts 17 times faster than the heterochiral species. Furthermore, our value is consistent with that determined by the iterative curve fitting model (0.06 ± 0.01). Thus, the relative reaction rate of the heterochiral to homochiral species (g) has been rigorously determined and the multiple methods of determination lend credibility to this value and the versatility of Kagan and co-workers' theory. Experimental determination of g completes the experimental determination of all of the parameters of Kagan and co-workers' equation and shows that the relative reaction rate is critical to the asymmetric amplification observed with Dip-Cl.

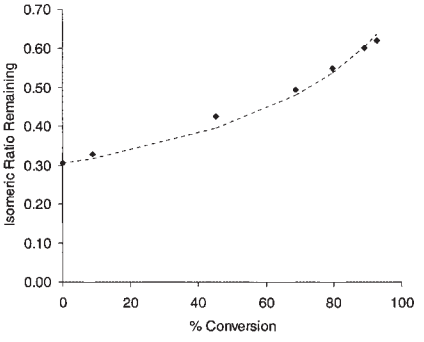


Figure 3. Change in ratio of Dip-Cl stereoisomers determined by complexation with 8-hydroxyquinoline. ◆, Observed; dashed line predicted ($g = 0.08$)

Table 4. Summary of relative reaction rates

Method	g
Kinetic studies	0.04 ± 0.03
Modeling of chiral purity over time	0.08 ± 0.04
Modeling ratio of Dip-Q isomers	0.08 ± 0.01
	Av.: 0.07 ± 0.03

EXPERIMENTAL

General. The following reagents were purchased from Aldrich Chemical. (Milwaukee, WI, USA) and used without further purification: acetophenone, α-pinene, anisole, monochloroborane–methyl sulfide complex, 8-hydroxyquinoline and (+)- and (*S*)-(−)-1-phenylethanol. Cyclodextrin (DM-β-CD) was obtained from Cerestar (Hammond, IN, USA). Solvents for reactions and HPLC were obtained from Fisher Scientific (Pittsburgh, PA, USA). Glassware was dried at 105 °C for at least 3 h and allowed to cool to ambient temperature in a desiccator with $CaSO_4$ desiccant.

Instrumentation. High-performance liquid chromatographic (HPLC) analyses (reversed phase and normal phase) were performed on two Spectra-Physics (Fremont, CA, USA) instruments. The first was equipped with a Model 8700 pump, Model 8780 autosampler with a 10 µl injection loop and a Model 753A UV detector (Applied Biosystems, Foster City, CA, USA). The second was

equipped with a Model P4000 pump, a Model AS3000 autosampler with a 10 µl loop and a Model UV1000 UV detector. Gas chromatographic (GC) analyses were performed on an HP 5890 gas chromatograph with flame ionization detection. GC response factors for α-pinene and isopinocampheol relative to the internal standard anisole were determined.

Software. P-E Nelson (Cupertino, CA, USA) Access* Chrom software was used for the analysis of HPLC data. Non-linear regression analyses for the 'Iterative curve fitting method' (for K and g), 'Modeling chiral purity over time' and 'Modeling ratio of Dip-Q isomers' sections were determined with the Solver tool of the Microsoft Excel software package.

Preparation of B-chlorodiisopinocampheylborane (Dip-Cl) solutions. A 100 ml, three-necked, jacketed flask was connected to a nitrogen/vacuum manifold and equipped with a magenetic stir bar. The flask was evacuated and refilled with nitrogen three times. Using a plastic syringe, anhydrous diethyl ether (5.5 ml) was added and, with stirring, the vessel was cooled to $-10\,^{\circ}$C. A 3.2 ml (20.1 mmol) aliquot of α-pinene was added. Monochloroborane–methyl sulfide complex (1.0 ml, 9.6 mmol) was added in a single addition using a plastic syringe. The vessel was warmed to the desired temperature of 10 °C and allowed to stir for ca 15 h at constant temperature. A fine white slurry was observed after several hours. Analysis (see below) indicated a concentration of 1.0 M in Dip-Cl.

Quantitation of Dip-Cl. The quantitation of Dip-Cl is performed by oxidation of the isopinocampheyl ligands to isopinocampheol and analysis by GC using anisole as an internal standard. To a 100 ml volumetric flask was added tetrahydrofuran (4 ml), aqueous sodium hydroxide [2 ml, 25% (w/v)] and a stir bar. A precisely measured aliquot (1.0 ml) of the mixture was removed from the Dip-Cl reaction vessel. This aliquot was added to the basic solution at the bottom of the 100 ml volumetric flask. The solution was stirred for 30 min, then hydrogen peroxide (2 ml, 30%) was added and the solution was stirred for another 30 min. A solution of anisole in methanol [3.0% (v/v), 0.28 M] was prepared for use as an internal standard, and a 10.0 ml aliquot was added to the volumetric flask. Water (10 ml) was added and the solution was diluted to volume with methanol. The resulting solution was analyzed by GC using a Stabilwax column (30 m o.d. × 0.53 mm i.d., 1.0 µm film thickness) with the following temperature program: 50 °C for 2 min, 10 °C min^{-1} to 200 °C, 200 °C for 2 mins. The injector temperature was 170 °C and the detector temperature was 230 °C. A 1.0 µl injection was used and the column flow-rate was 8 ml min^{-1} with a split flow of 100:1. The following retention times were typical: α-pinene 3.8 min, anisole 9.2 min and isopinocampheol 14.4 min. Peak areas were corrected for the response factors of α-pinene (0.66) and isopinocampheol (0.63) to anisole.

General procedure for the preparation of bis(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)borinic acid-8-quinolyl (Dip-Q) solutions. A 10 ml stock solution of 8-hydroxyquinoline (1.0 M) was prepared in anhydrous diethyl ether; sonication was required to complete dissolution. The stock solution (1.0 ml) was added to a clean, dry test-tube. A 0.5 ml aliquot of Dip-Cl reaction mixture was slowly added to the solution and a white precipitate immediately formed and the solution turned fluorescent green–yellow. The solution was vortex mixed to complete mixing. The solution was filtered through a 0.2 µm filter to give a clear fluorescent green–yellow solution which was used for analysis by HPLC (see below).

Stereochemical analysis of Dip-Q complexes. From the above Dip-Cl solutions, 100 µl were diluted to 100 ml with methanol to a final concentration of ca 0.15 mg ml^{-1}. Analysis was performed using an HPLC system equipped with a YMC J-sphere M-80 ODS column (25.0 × 0.46 cm i.d.) and a UV ($\lambda = 265$ nm). The mobile phase consisted of 85:15 methanol–water and dimethyl-β-cyclodextrin (DM-β-CD) (10 mM l^{-1}) as a chiral mobile phase additive. HPLC was performed at ambient temperature with a flow-rate of 0.5 ml min^{-1}. The column was allowed to equilibrate for ~90 min (approximately three column volumes). The total run time was 100 min; typical retention times were (+)(−)-isomer 61.8 min ($k' = 11.1$), (+)(+)-isomer 67.2 min ($k' = 12.1$) and (−)(−) isomer 70.3 min ($k' = 12.7$).

Stereochemical analysis of Dip-Cl via Dip-Q complexation during conversion. Approximately 1 ml of the reduction reaction mixture was quenched into a test-tube containing 2 ml of 1.0 M 8-hydroxyquinoline in diethyl ether. The resulting slurry was filtered through a 0.45 µm syringe filter. A 1.0 ml aliquot of the filtrate was diluted to 100 ml with methanol to a final concentration of ca 0.8 mg ml^{-1}. The resulting solution was analyzed using the conditions described in 'Stereochemical analysis of Dip-Q complexes' above.

Analysis of reaction conversion (all studies). To monitor the reaction, ~200 µl of the reaction mixture were removed and diluted to 100 ml with 10% water in methanol, resulting in a concentration of ca 0.05 mg ml^{-1} in (*S*)-(−)-1-phenylethanol. The solution was analyzed by gradient HPLC with the mobile phases of 0.1% phosphoric acid in water (mobile phase A) and acetonitrile (mobile phase B). The gradient delivery system was programmed to deliver a 25–75% gradient sweep of mobile phase B over 15 min followed by a 5 min hold at 75% B. A Zorbax Rx C_8 column (15.0 × 0.46 cm i.d.) (MAC MOD Analytical, Chadds Ford, PA, USA) was used at ambient

temperature with a flow-rate of 1.0 ml min^{-1}. The UV detector was set at 210 nm. The following retention times were typical: methyl sulfide 3.0 min, 1-phenylethanol 3.6 min, acetophenone 5.4 min and α-pinene 15.6 min. When molar conversion was required, response factors of 0.79 for *sec*-phenethyl alcohol and 0.66 for acetophenone were used.

Analysis of enantiomeric excess of reduction product (all studies). The enantiomeric excess of the reduction product, 1-phenylethanol, was monitored by normal-phase HPLC using a Chiralcel OD column (25.0 × 0.46 cm i.d.) (Exton, PA, USA) with hexane–2-propanol (99:1) as mobile phase. The flow-rate was 1.0 ml min^{-1}, the column temperature was ambient and UV detection at 210 nm was used. An 8 ml sample of the solution used to monitor the reaction conversion was evaporated to dryness under a steady stream of nitrogen and reconstituted with 2 ml of the 99:1 hexane–2-propanol mobile phase. The run time was 50 min. The (+)-enantiomer eluted at 26.9 min ($k' = 7.4$) and the (−)-enantiomer at 35.1 min ($k' = 9.9$).

Reduction of acetophenone: excess acetophenone (pseudo-first-order conditions). A stock solution of acetophenone [30% (v/v), 2.6 M] and anisole [2% (v/v), 0.18 M] was prepared in 100 ml of anhydrous tetrahydrofuran. A solution of Dip-Cl (9.7 ml, 1.0 M), prepared as described above, was cooled to −15 °C. Separately, a 100 ml, three-necked, jacketed flask was connected to a nitrogen/vacuum manifold and equipped with a magnetic stir bar. The flask was evacuated and filled with nitrogen three times. Using a plastic syringe, the stock solution of acetophenone and anisole (10.0 ml) was added, and with stirring, the vessel was cooled to −15 °C. An aliquot (3.0 ml, 3.0 mmol) of the Dip-Cl solution was added dropwise over ca 30 s to the solution of acetophenone and anisole. The reaction mixture was stirred at −15 °C and the reaction was monitored by HPLC until it was >85% complete. Reaction work-up and analysis for conversion and enantiomeric excess of the reduction product are described above.

Reduction of acetophenone: excess Dip-Cl. A stock solution of acetophenone [8% (v/v), 0.69 M] and anisole [8% (v/v), 0.74 M] was prepared in 25 ml of anhydrous tetrahydrofuran. A solution of Dip-Cl (9.7 ml, 1.0 M), prepared using an ee_{aux} of 0.97, was cooled to −15 °C. An aliquot (1.0 ml, 1.0 mmol) of the acetophenone solution was added dropwise over ca 30 s to the flask. The reaction mixture was stirred at −15 °C and the reaction was analyzed at ca 10 min intervals for ca 2 h. Reaction work-up and analysis for conversion and enantiomeric excess of the reduction product are described above.

Acknowledgement

The authors are grateful to Merck for support of this work through a doctoral educational fellowship for C.W.M.

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