Quantitative Stereochemical Analysis of a Reagent That Exhibits Asymmetric Amplification, *B*-Chlorodiisopinocampheylborane (Dip-Cl)

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Abstract: We show that complexation of *B*-chlorodiisopinocampheylborane (Dip-Cl) with 8-hydroxyquinoline results in an air- and moisture-stable complex. Using enantiomerically pure (+)-α-pinene, the (+,+)-Dip-quinoline complex, $[(+)\text{-}C_{10}H_{17}]_2B(\eta^2\text{-}N,O\text{-}C_{10}H_6NO)$, was isolated and characterized by spectroscopic and crystallographic methods. When Dip-Cl is prepared from enantiomerically impure (+)-α-pinene a mixture of heterochiral, (+,−)-Dip-Cl, and homochiral, (+,+)-Dip-Cl and (−,−)-Dip-Cl, stereoisomers are formed. We have developed the 8-hydroxyquinoline complexation method for quantification of these stereoisomers by chiral HPLC. Since this is the first quantitative analysis of a reagent that exhibits asymmetric amplification, it enables us to verify part of Kagan's model for this phenomenon and evaluate the terms β and K which are measures of the relative amounts of stereoisomers. Our analysis shows that there is a preference for the formation of the heterochiral (+,−)-Dip-Cl isomer; therefore, the stereoisomers are not statistically distributed. This is beneficial for the asymmetric amplification process because it causes the heterochiral diastereomer to absorb the minor (−)-α-pinene enantiomer, thereby increasing the effective concentration of (+,+)-Dip-Cl that is formed from (+)-α-pinene. We also studied the distribution of stereoisomers as a function of the preparation temperature of the Dip-Cl reagent (0, 10, 20 °C). Increasing the preparation temperature increases the relative amounts of the homochiral stereoisomers, suggesting that the activation energy for the formation of the homochiral isomers is greater than for the heterochiral isomer. Thus, at higher preparation temperatures greater amounts of (−,−)-Dip-Cl are formed from (−)-α-pinene. However, there is a surprising benefit as higher levels of asymmetric induction are observed, especially when low enantiomeric purity α-pinene is used. In addition, the reduction reactions proceed slightly faster when Dip-Cl is prepared at higher temperature. In sum, the complexation of Dip-Cl with 8-hydroxyquinoline and subsequent analysis by chiral HPLC provides considerable insight into the asymmetric amplification process observed with this reagent. Moreover, we have shown how the conditions used for the preparation of the reagent affect the asymmetric amplification process.

Introduction

In most asymmetric reactions, there is a linear relationship between the enantiomeric purity of the reagents used to induce chirality and the enantiomeric purity of the products. Recently the phenomenon of nonlinear effects has appeared in the literature.[1] In this phenomenon, a nonlinear relationship exists between enantiomeric purity of the reagents that induce chirality and the products. Depending on the direction of the deviation from linearity this effect may be observed as a positive nonlinear effect, (+)-NLE which is often termed "asymmetric amplification", or a negative nonlinear effect, (−)-NLE. An example of a reaction that exhibits a strong (+)-NLE is the reduction of acetophenone to *sec*-phenethyl alcohol by *B*-chlorodiisopinocampheylborane (**1**, Dip-Cl).[2] When prepared from (+)-α-pinene that is only 70% enantiomerically pure, Dip-Cl reduces acetophenone to the chiral alcohol in >90% enantiomeric excess (EE[3]) (Scheme 1).[4]

Since α-pinene is difficult to obtain in its enantiomerically pure form, the practical implications are apparent. A cheaper, enantioenriched form of α-pinene can be used to prepare the Dip-Cl reagent and at the same time provide a reduction product of very high chiral purity. Merck has exploited this phenomenon on a production scale. In a critical step of the synthesis of an LTD_4 antagonist, Dip-Cl prepared from 70% EE α-pinene is used to produce intermediate **I** in 95% EE.[5] In addition, the

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(1) (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am Chem. Soc*. **1986**, *108*, 2353−2357. (b) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc*. **1994**, *116*, 9430−9439.

(2) Girard, C.; Kagan, H. B. *Tetrahedron Asymmetry* **1995**, *6*, 1881−1884.

(3) To be consistent with terminology in this area, uppercase (EE) terms are expressed as percentages, lowercase (ee) terms as their absolute values.

(4) Zhao, M.; King, A. O.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 2641−2644.

(5) (a) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; Labelle, M.; Prasit, P.; Zamboni, R. J. *J. Org. Chem*. **1993**, *58*, 3731−3735. (b) Shinkai, I.; King, A. O.; Larsen, R. D. *Pure Appl. Chem*. **1994**, *66*, 1551−1556.

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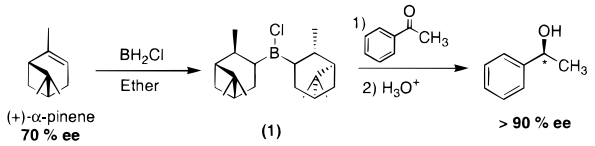
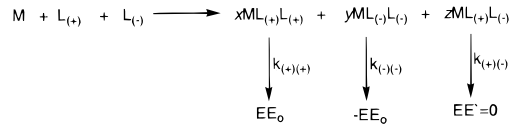
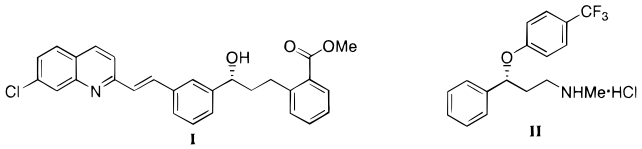
Scheme 1



Scheme 2



use of Dip-Cl to prepare the antidepressant (−)-Fluoxetine (**II**, Prozac, Eli Lilly and Co.) has also been reported.[6]



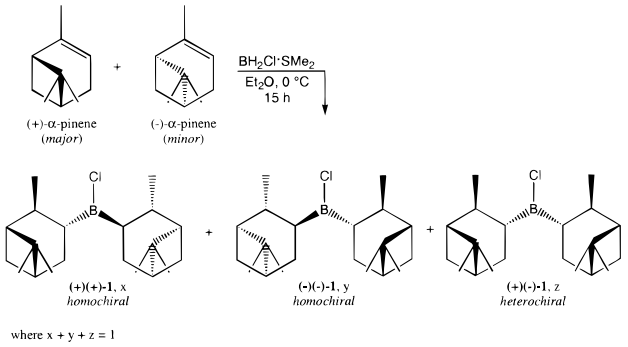
Theoretical models and practical applications of this phenomenon have been the subject of recent publications and reviews.[7] Asymmetric amplification has also been observed in catalytic asymmetric reactions including aldolizations,[8] organozinc alkylations,[9] Sharpless epoxidations,[10] sulfoxidations,[11] and Diels−Alder reactions.[12] Furthermore, this phenomenon has recently been implicated in theories of the origin of life. What were the chemical events that caused life to evolve with the predominance of enantiomerically pure amino acids in the levorotatory form? Theories suggest that asymmetric amplification may have been involved.[13]

Kagan has developed a model describing nonlinear effects in asymmetric synthesis.[1b] The ML_2 model is the simplest and considers a reactive center (M) and two chiral ligands ($L_{(+)}$, $L_{(-)}$) that combine to form $ML_{(+)}L_{(+)}$, $ML_{(-)}L_{(-)}$, and $ML_{(+)}L_{(-)}$ species in amounts of *x*, *y*, and *z*, respectively (Scheme 2).

The formation of the ML_2 species may be reversible (e.g., catalytic systems) or, as in the case of Dip-Cl, irreversible. Once the ML_2 species are formed, they react at specific rates to form the chiral products. The basis of asymmetric amplification is the formation of a less reactive, heterochiral *meso*-compound, $ML_{(+)}L_{(-)}$, which traps the undesired minor enantiomer of the chiral auxiliary.

Kagan developed a series of equations to mathematically model this ML_2 system. The cornerstone of the model is eq 1, which predicts the product enantiomeric excess (EE_{prod}) from

Scheme 3



the enantiomeric excess of the chiral auxiliary (ee_{aux}) and two other factors, *g* and β. In this equation, EE_{prod} is a function of

$$EE_{prod} = (EE_o)(ee_{aux})\frac{1+\beta}{1+g\beta} \quad (1)$$

the following: EE_o, the maximum enantiomeric excess for the reaction product obtained when $ee_{aux} = 1.00$; ee_{aux}, the chiral purity of the ligand used to prepare the reagent; β, the relative distribution of the stereoisomers (eq 2); and *g*, the relative reactivity (expressed in terms of rate constants) of the ML_2 stereoisomers toward the substrate (eq 3).

$$\beta = z/(x+y) \quad (2)$$

$$g = k_{heterochiral}/k_{homochiral} \quad (3)$$

In the case of Dip-Cl, ee_{aux} is the enantiomeric purity of the α-pinene. In the preparation of this reagent (Scheme 3), two homochiral and one heterochiral species are formed. The *x*, *y*, *z* terms correspond to the relative amounts of homochiral, (+,+)-**1** and (−,−)-**1**, and heterochiral, (+,−)-**1**, species, respectively.

Because up to now there has not been a way to measure β directly, eq 1 is often rearranged to express β in terms of ee_{aux} and *K* as shown in eq 4.

$$\beta = \frac{-Kee_{aux}^{\ 2} + \sqrt{-4Kee_{aux}^2 + K(4 + Kee_{aux}^2)}}{4 + Kee_{aux}^2} \quad (4)$$

$$K = z^2/xy \quad (5)$$

The term *K*, expressed in eq 5, has traditionally been viewed as the equilibrium constant between the M and L species under Curtin−Hammett conditions.[14] Since the formation of Dip-Cl is an irreversible reaction, the value of *K* has little experimental applicability to this situation. However, *K* does have some theoretical utility as eqs 1 and 4 can be used to analyze plots of EE_{prod} vs ee_{aux}. Thus, for a plot of EE_{prod} vs ee_{aux}, minimization of the least-squares function will yield best-fit values of *K* and *g*.[15a] For example, Blackmond[15a] performed an analysis of plots of EE_{prod} vs ee_{aux} for the reduction of acetophenone with Dip-Cl which was prepared from borohydride, boron trichloride, and α-pinene in diglyme.[4] Using data for EE_{prod} taken at low conversion, Blackmond found that $K = 49$ and $g = 0.1$ best represented the system. Moreover, Blackmond extended the interpretation of Kagan's model and predicted values for *x*, *y*,

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(7) (a) Kagan, H. B.; Girard, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345−352.

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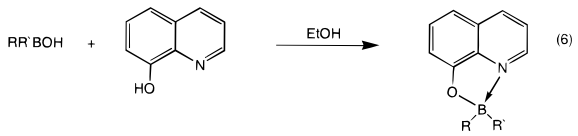
(14) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 647.

(15) (a) Blackmond, D. *J. Am. Chem. Soc.* **1998**, *120*, 13349−13353. (b) Blackmond, D. *J. Am. Chem. Soc.* **1997**, *119*, 12934−12939.

and *z*. The calculations showed that the homo- and heterochiral species were formed in nonstatistical ratios.[15a]

Kagan's model assumes that there is a distribution of homochiral and heterochiral species that react at different rates. However, the exact ratio of stereoisomers formed during the preparation of Dip-Cl has never been directly determined. As indicated above, values of *x*, *y*, and *z* for the homo- and heterochiral species have only been predicted on the basis of the chirality of the auxiliary and estimated values of *g* and *K*.[15a] The difficulty in determining the relative amounts of the stereoisomers of Dip-Cl is the compound's reactivity. In addition, its lack of a chromophore makes detection by conventional chromatographic and spectroscopic techniques difficult. Complexation to a less reactive compound appears to be a viable opportunity for separation and quantitation of isomers.

Letsinger and Skoog first reported the complexation of diarylborinic acids with ethanolamine to form β-aminoethyl diarylborinate complexes.[16] Douglass noted that 8-hydroxyquinoline (oxine, 8-quinolinol) possessed the same critical reactive grouping as ethanolamine and used it to prepare derivatives of diaryl-, arylalkyl-, and dialkylborinic acids (eq 6).[17] In addition, 8-hydroxyquinoline has been extensively used



as a post- and precolumn complexation agent for the detection and analysis of metals by high-pressure liquid chromatography (HPLC).[18] The use of 8-hydroxyquinoline to complex boron before analysis by inductively coupled plasma atomic emission spectroscopy (ICP-AES) has also been reported.[19]

The above studies indicate that 8-hydroxyquinoline could be an excellent complexation reagent for the analysis of Dip-Cl. Herein, we report the complexation of Dip-Cl isomers with 8-hydroxyquinoline and their subsequent separation by chiral HPLC. For the first time, the amounts of stereoisomers (*x*, *y*, *z*) formed during an asymmetric amplification reaction are directly measured. The results confirm the predictions of Kagan and Blackmond and prove the validity of the ML_2 model for asymmetric amplification.

Results

Preparation of the Dip-Quinoline Complex, (+,+)-2. Using 97% EE (+)-α-pinene, a solution of (+,+)-Dip-Cl, (+,+)-**1**, was prepared by reaction with the dimethyl sulfide complex of chloroborane (Scheme 1).[20] The reaction progress was monitored by measuring the amount of isopinocampheol formed upon oxidation of the Dip-Cl solution (see Experimental Section in the Supporting Information). Once the reaction was completed (ca. 15 h), an aliquot of the reaction mixture was removed and added to a 2-fold molar excess of 8-hydroxyquinoline in ether

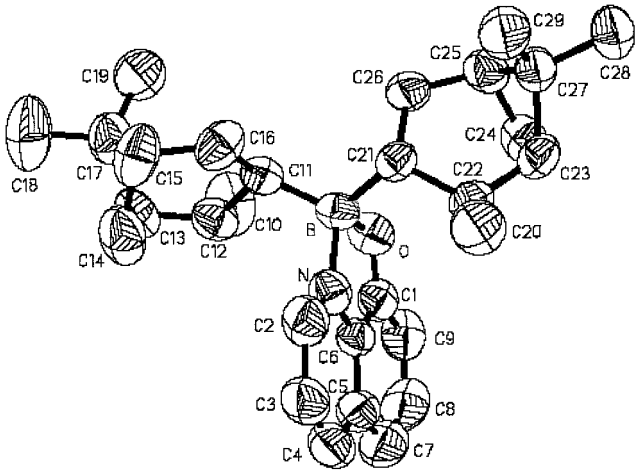
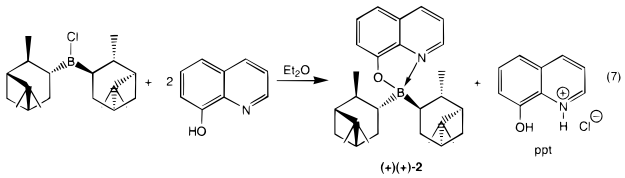


Figure 1. ORTEP diagram of (+,+)-Dip-Cl ((+,+)-**2**).

(eq 7). Immediately, a fluorescent green-yellow solution of



(+,+)-**2** formed with a white precipitate of the 8-hydroxyquinoline-HCl salt. The precipitate was removed via filtration, and the filtrate containing the Dip-quinoline complex ((+,+)-**2**) was evaporated to dryness under a steady stream of nitrogen to give a fluorescent orange oil in quantitative yield.

For characterization purposes, an effort was made to obtain a crystalline solid. The oil was reconstituted in absolute ethanol, and a small amount (35% yield) of (+,+)-**2** crystallized as brilliant yellow crystals as the ethanol evaporated under a steady stream of nitrogen. Although the compound as a solid is sensitive to light over long periods of time, it is stable in air at room temperature.

The Dip-quinoline (+,+)-**2** complex was characterized by elemental analysis, ^{1}H and ^{13}C NMR, UV−vis, and fluorescence spectroscopic methods (see Experimental Section in the Supporting Information). An X-ray diffraction study of crystals of (+,+)-**2** confirms the assigned structure, see Figure 1. This crystal structure complements the previously reported crystal structure of Dip-Cl by Brown and co-workers.[23a]

Preparation of Dip-Cl Stock Solutions. To understand how the distribution of the three possible stereoisomers of Dip-Cl varies as a function of the EE of (+)-α-pinene (ee_{aux}), a series of Dip-Cl solutions were prepared. Solutions were prepared at 0, 10, and 20 °C reaction temperatures at nine different values of ee_{aux} ranging from racemic (~0% EE) to nearly enantiomerically pure (97% EE). The EE of the initial charge of (+)-α-pinene was determined by chiral HPLC using α-cyclodextrin (α-CD) as a chiral mobile phase additive (CMPA). These values are reported in Table 1 as ee_{aux}. An aliquot of each solution was oxidized with basic peroxide solution to form 2 equiv of isopinocampheol per equivalent of Dip-Cl. Quantitative analysis of the oxidation products by gas chromatography using anisole as an internal standard (see Experimental Section in the Supporting Information) indicated greater than 96% conversion of the α-pinene to Dip-Cl in almost every case. We find that this is an excellent way to standardize Dip-Cl solutions.

Stereochemical Analysis of Dip-Cl Stock Solutions. Once the structure of the (+,+)-**2** was confirmed, 8-hydroxyquinoline

(16) Letsinger, R. L.; Skoog, I. *J. Am. Chem. Soc.* **1954**, *77*, 2491−2494.
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(20) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417−2422.

Table 1. For Dip-Cl Prepared at (a) 0, (b) 10, and (c) 20 °C, Data for the Distribution of Stereoisomers of Dip-Cl As Determined by Complexation with 8-Hydroxyquinoline and EE_{prod} Data for Reduction of Acetophenone at −20 °C as a Function of ee_{aux}

(a) 0 °C

				β				
ee_{aux}	*x* (+,+)-**1**	*y* (−,−)-**1**	*z* (+,−)-**1**	actual	pred[a]	*K*[b]	EE_{prod}[c]	% conv (time, h)
-0.012	0.093	0.101	0.806	4.15	4.64	69	-0.1	94.5 (24)
0.106	0.147	0.056	0.797	3.93	3.96	77	25.6	96.2 (24)
0.222	0.257	0.018	0.725	2.64	2.68	114	49.0	97.2 (24)
0.344	0.381	<0.001	0.619	1.62	1.70	∝	66.0	99.9 (24)
0.466	0.488	<0.001	0.512	1.05	1.09	∝	85.4	99.3 (8)
0.586	0.618	<0.001	0.382	0.62	0.69	∝	79.6	99.5 (8)
0.712	0.742	<0.001	0.258	0.35	0.40	∝	89.0	99.7 (5)
0.838	0.863	<0.001	0.137	0.16	0.19	∝	92.4	99.8 (5)
0.970	0.971	<0.001	0.029	0.03	0.03	∝	89.2	99.8 (5)

(b) 10 °C

				β				
ee_{aux}	*x* (+,+)-**1**	*y* (−,−)-**1**	*z* (+,−)-**1**	actual	pred[d]	*K*[e]	EE_{prod}[f]	% conv (time, h)
-0.012	0.169	0.162	0.669	2.02	3.59	16	-0.1	99.5 (24)
0.106	0.179	0.063	0.758	3.13	3.22	51	29.4	93.4 (24)
0.222	0.272	0.032	0.696	2.29	2.38	56	53.2	96.8 (24)
0.344	0.427	0.015	0.558	1.26	1.60	49	78.8	99.9 (24)
0.466	0.569	0.001	0.430	0.75	1.05	∝	88.6	98.9 (8)
0.586	0.674	<0.001	0.326	0.48	0.68	∝	87.4	99.8 (8)
0.712	0.789	<0.001	0.211	0.27	0.40	∝	92.0	99.7 (5)
0.838	0.880	<0.001	0.120	0.14	0.19	∝	92.4	99.8 (5)
0.970	0.989	<0.001	0.012	0.01	0.03	∝	94.4	99.0 (2)

(c) 20 °C

				β				
ee_{aux}	x (+,+)-**1**	*y* (−,−)-**1**	*z* (+,−)-**1**	actual)	pred[g]	*K*[h]	EE_{prod}[i]	% conv (time, h)
-0.012	0.267	0.250	0.483	0.093	3.20	3.5	-1.8	98.9 (24)
0.106	0.227	0.072	0.701	2.34	2.91	30	35.8	97.6 (24)
0.222	0.309	0.032	0.659	1.93	2.23	44	61.2	98.6 (24)
0.344	0.469	0.015	0.515	1.06	1.55	38	79.0	99.9 (24)
0.466	0.546	0.007	0.447	0.81	1.03	52	83.8	99.5 (8)
0.586	0.674	0.001	0.325	0.48	0.67	∝	91.8	99.7 (5)
0.712	0.809	<0.001	0.191	0.24	0.39	∝	90.6	99.8 (5)
0.838	0.887	<0.001	0.113	0.13	0.19	∝	92.6	98.9 (2)
0.970	0.979	<0.001	0.021	0.02	0.03	∝	91.7	99.5 (2)

[a] Predicted from eq 4 with average $K = 87 \pm 26$. [b] Average value, $K = 87 \pm 26$. [c] Determined at >94% conversion. [d] Predicted from eq 4 with average $K = 52 \pm 4$. [e] Average value, $K = 52 \pm 4$. See ref 26. [f] Determined at >93% conversion. [g] Predicted from eq 4 with average $K = 41 \pm 11$. [h] Average value, $K = 41 \pm 11$. See ref 26. [i] Determined at >97% conversion.

was developed as a complexation agent for the analysis of the stereoisomers of Dip-Cl. The reaction of 8-hydroxyquinoline with these mixtures was rapid and quantitative. An HPLC method was developed to separate the stereoisomers of **2**.[21] The method used an octadecylsilane (ODS) column with methanol/water mobile phase and dimethyl-*β*-cyclodextrin (DM-*β*-CD) as a CMPA. A chromatogram of the quinoline complex of Dip-Cl (**2**) prepared from racemic α-pinene (Figure 2) shows near baseline separation of the stereoisomers.

For racemic α-pinene, if there were to be a statistical distribution of isomers, one would expect a 2:1:1 ratio of (+,−)-**1**, (+,+)-**1**, and (−,−)-**1**. However, the distribution of isomers in Figure 2 is 8:1:1, indicating that the isomers are not statistically distributed. The 8:1:1 ratio is unchanged on reanalysis of the Dip-Cl solution after 24 h storage at 0 °C.[22]

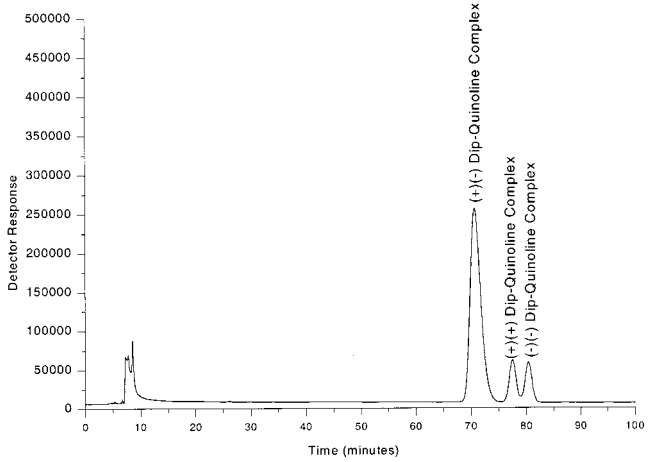

Figure 2. Chromatogram illustrating the separation of the (+,−), (+,+), and (−,−) stereoisomers of the Dip-quinoline complexes (**2**) by HPLC. The Dip-Cl was prepared from racemic α-pinene at 0 °C.

As additional confirmation, the formation of Dip-Cl was monitored with the 8-hydroxyquinoline complexation at various intervals during the reagent preparation. Again, the isomeric ratio remained essentially unchanged throughout the reaction

(21) The complexation of the (+,−)-Dip-Cl potentially results in two isomers with the boron as a pseudoasymmetric atom (*r*-(+,−)-**2**), *s*-(+,−)-**2**)). However, if formed they do not separate under our chromatographic conditions. No attempt has been made to further characterize these species. For a discussion of compounds containing pseudoasymmetric centers, see ref 14, p 123.

(22) Preliminary studies indicate there is some redistribution of the isomers of Dip-Cl when solutions are stored at temperatures higher than those at which they are made. This suggests that the formation of Dip-Cl may be reversible, but the rate of reequilibration is slow.

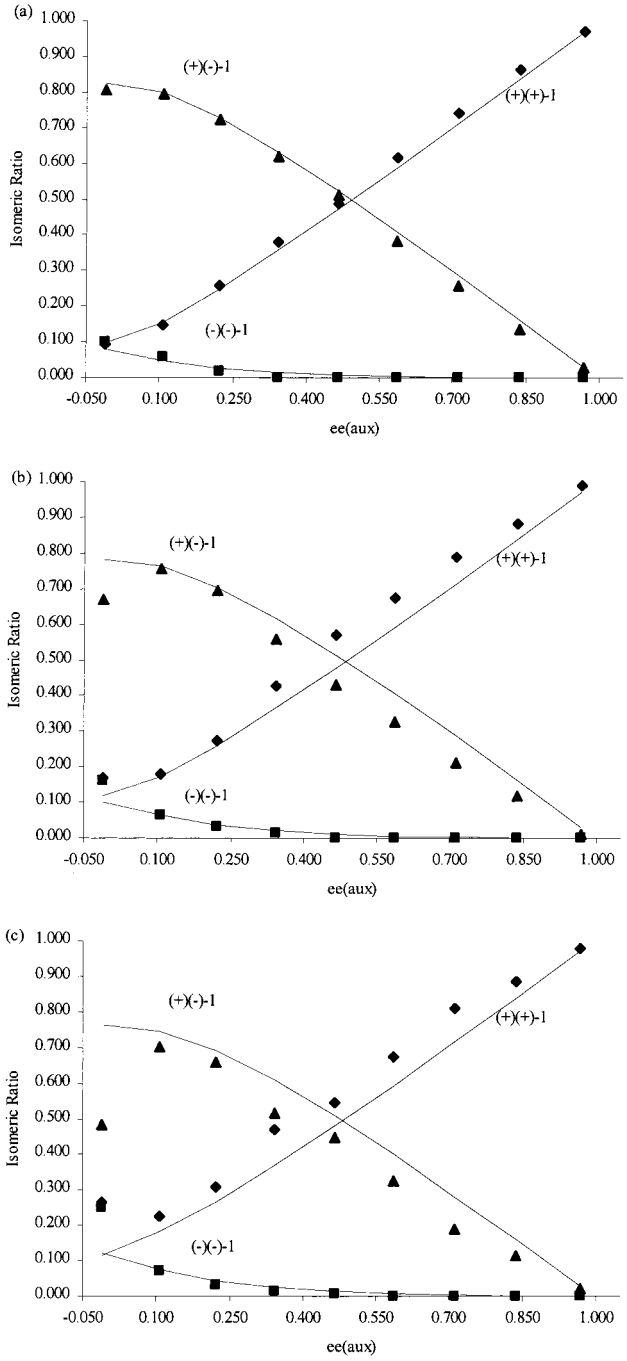

Figure 3. Distribution of (+,−)-, (+,+)-, and (−,−)-Dip-Cl (**1**) species for Dip-Cl prepared at (a) 0, (b) 10, and (c) 20 °C as determined by complexation with 8-hydroxyquinoline. Predicted curves are obtained from eqs 2 and 4, and $x + y + z = 1$ with $K =$ (a) 87, (b) 52, and (c) 41 as shown in ref 15a.

time. These studies indicate that the distribution of stereoisomers of Dip-Cl is stable over time and can be quantitatively determined by complexation with 8-hydroxyquinoline.

From the stock solutions of Dip-Cl prepared at 0, 10, and 20 °C, aliquots were removed and complexed with 8-hydroxyquinoline. The relative amounts of the stereoisomers at each ee_{aux} were determined by chiral HPLC and are listed in Table 1 and shown in Figure 3. As ee_{aux} increases, the concentration of the (−,−)-**1** decreases below the limit of detection. This occurs at increasingly higher values of ee_{aux} (0.344, 0.586, and 0.712) for the Dip-Cl solutions prepared at increasingly higher temperatures (0, 10, and 20 °C, respectively). In addition, at ee_{aux} values of 0.466 (10 °C Dip-Cl preparation) and 0.586 (20 °C preparation temperature), the *y* values were both 0.1%, which is at the limit of detection of the method and below the limit of quantitation (∼1.0%). Thus, there is a significant error associated with these values. From the *x*, *y*, and *z* data, the terms β and *K* were calculated using eqs 2 and 5, respectively. The value of β was easily calculated for each data point. However, there was some difficulty in the calculation of *K*. As the value of *y* approached the limit of detection of the method (<1.0% in peak area), significant error was observed in *K*. Furthermore, as *y* approached zero, the value of *K* approached infinity. The results of these calculations are shown in Table 1.

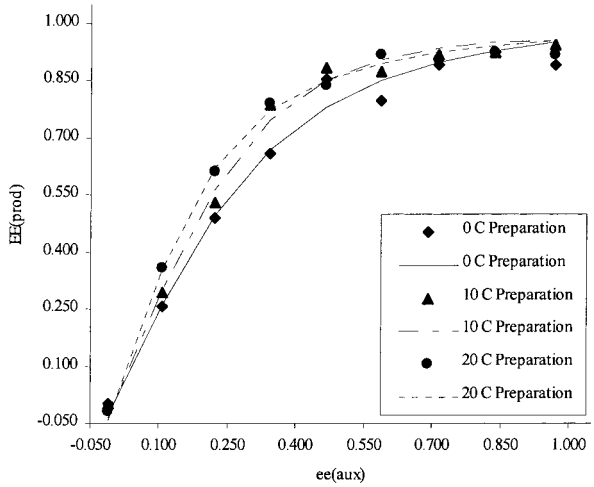

Figure 4. Experimental plots of the enantiomeric excess of *sec*-phenylethyl alcohol (EE_{prod}) for the reduction of acetophenone (>94% conversion) using Dip-Cl prepared from (+)-α-pinene of various enantiomeric purity (ee_{aux}) using Dip-Cl prepared at 0, 10, and 20 °C. Each set of data is fit to a modified form of eq 1 using β as defined in eq 4.

Reduction of Acetophenone. The level of asymmetric amplification by each solution of Dip-Cl was obtained by reduction of acetophenone using an excess of Dip-Cl (ca. 5 equiv) as recommended by Girard and Kagan.[2] To determine the chiral purity of the reduction product (EE_{prod}) at maximum conversion, the reaction conversion was measured at 2.5, 5, 8, and 24 h intervals. The estimate of EE_o (95.7%) was obtained from EE_{prod} for the reduction of acetophenone with Dip-Cl solutions prepared from 97% EE_{aux} (+)-α-pinene and agrees with the value reported by Brown and co-workers.[23] This value was obtained at a reaction time of 2.5 h in order to minimize contribution of the trace amounts of (+,−)-**1** in the reduction. Generally, stock solutions prepared from (+)-α-pinene at EE_{aux} < 34% took longer to achieve maximum conversion (24 h), whereas stock solutions prepared from (+)-α-pinene at EE_{aux} > 70% were complete in less than 5 h. This is consistent with Blackmond's prediction that reactions with a higher percentage of the less reactive heterochiral isomer will be slower.[15b] The EE_{prod} values at maximum conversion are listed in Table 1.

Graphical analysis of EE_{prod} vs ee_{aux} (Figure 4) indicates that the three Dip-Cl systems behave as expected; strong (+)-NLEs are observed. As shown, the data points in each graph can be fit to Kagan's eq 1 using eq 4 to express β by varying the parameters *K* and *g* to obtain the best fit. This gives the following *K* and *g* values: 28 and 0.14 (0 °C); 19 and 0.016 (10 °C); and 58 and 0.074 (20 °C). However, these values must

(23) A value of 97% for EE_o was obtained for the reduction of acetophenone using Dip-Cl which was prepared from α-pinene of 98% ee_{aux}. See: (a) Brown, H. C.; Chandrasekharan, J.; Ramachadran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539−1546. (b) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141−2144.

be interpreted with caution since they are based on EE_{prod} values taken at 99% of reaction conversion. Blackmond has shown that the *K* and *g* values obtained by this minimization procedure must be obtained using EE_{prod} data taken at low conversion (10−20%) in order to minimize the contribution of (+,−)-Dip-Cl. Unfortunately, even our earliest set of EE_{prod} data (2.5 h) showed a minimum conversion of 55%. Below we discuss how *K* is obtained directly by complexation with 8-hydroxyquinoline. In addition, since this paper focuses on the quantitative analysis of the stereoisomers of Dip-Cl, we will defer discussion of *g* to a future report.[24]

Discussion

Reaction of Dip-Cl with 8-hydroxyquinoline forms a stable tetrahedral boron complex that is useful for the study of the phenomenon of asymmetric amplification. The highly colored complex is stable in protic solvents and, thus, can be analyzed by reversed-phase HPLC using conventional UV detection. Since the rate of complexation is fast and the formation of Dip-Cl is static at any given temperature,[22] 8-hydroxyquinoline is an effective kinetic quenching agent that traps the stereoisomers of Dip-Cl in their original distribution. The relative amounts of stereoisomers are integral to the phenomenon of asymmetric amplification, and our analysis provides a unique opportunity to examine Kagan's mathematical model. Noyori has characterized reactive and unreactive stereoisomers of an organozinc reagent that exhibits asymmetric amplification.[9a] However, this is the first quantitative, experimental determination of the exact amounts of all stereoisomers present in a system that exhibits asymmetric amplification.[25] Our analysis also gives the first understanding of how reaction conditions for the preparation of the Dip-Cl reagent affect its performance in asymmetric reductions.

The plots in Figure 3 show that we are able to map out the distribution of the (+,−), (+,+) and (−,−) stereoisomers of Dip-Cl as a function of ee_{aux}. Indeed, that a distribution of these stereoisomers is obtained is one confirmation of Kagan's model. However, we also show (excepting the points at racemic ee_{aux} for the 20 °C preparation of Dip-Cl, Figure 3c, Table 1c) that the isomeric distribution is nonstatistical. This is significant because it shows that the formation of (+,−)-Dip-Cl is favored at the expense of the formation of (−,−)-Dip-Cl. As illustrated in all three plots, significant amounts of (+,−)-Dip-Cl (*z*) are formed, and the amount of (−,−)-Dip-Cl (*y*) drops to zero, even when substantial amounts of (−)-α-pinene are initially present. This demonstrates how (+,−)-DipCl acts to trap the minor (−)-α-pinene enantiomer, which is beneficial for the asymmetric amplification process as it increases the effective concentration of the (+)-α-pinene isomer for formation of (+,+)-DipCl reagent. The plots also illustrate that there are significant differences in the isomeric distributions as the temperature of the preparation of the Dip-Cl reagent is changed from 0 to 20 °C. Below we show how these isomeric distributions are applied to eqs 1−5 of Kagan's mathematical model[1] and how they correlate with recent predictions by Blackmond.[15a]

When the Dip-Cl is formed from racemic α-pinene at 0 °C, a nonstatistical distribution (8:1:1, *z*:*x*:*y*) of isomers is observed (Table 1a). This distribution precisely agrees with Blackmond's prediction of the distribution of isomers.[15a] However, the preparation of Dip-Cl at 10 °C results in an isomeric ratio of 4:1:1, and preparation at 20 °C results in a ratio of 2:1:1 (Table 1b,c). The stereoisomers approach a statistical distribution as the preparation temperature increases. This indicates that the selective formation of (+,−)-Dip-Cl, (+,−)-**1**, is favored at low temperature, but selectivity is reduced as the preparation temperature increases. This implies that the energy of activation for the formation of the homochiral complexes is higher than that of the heterochiral complex.

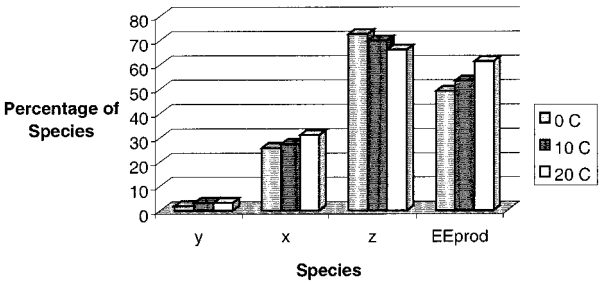

Figure 5. Affect of reagent preparation temperature on EE_{prod} using $EE_{aux} = 22.2\%$.

The tendency toward a nonstatistical distribution increases as ee_{aux} increases, and nonstatistical distributions are always observed beyond racemic ee_{aux}. For example, at 22.2% EE_{aux} we expect a statistical ratio of ca. 3:2:1 (*z*:*x*:*y*) but observe ratios of 40:14:1 at 0 °C, 22:8.5:1 at 10 °C, and 20:9.6:1 at 20 °C. Indeed, selectivity is reduced at higher preparation temperatures; however, the effect is not as dramatic as it is with racemic α-pinene. This trend is dramatically illustrated in Figure 3, where the points *x*, *y*, and *z* at racemic ee_{aux} come closer together as the preparation temperature of the Dip-Cl reagent increases.

The trend in selectivity is also observed in the amount of (−,−)-**1** (*y*), which becomes negligible at increasingly higher values of ee_{aux} as the temperature of reagent preparation increases. This compound becomes immeasurable at the following values of EE_{aux}: 34.4% (0 °C preparation temperature), 58.6% (10 °C), and 71.2% (20 °C). Since more (−,−)-**1** is formed at higher preparation temperatures, this supports our previous statement that the energy of activation for the formation of the homochiral complexes is higher than the heterochiral complex.

It is interesting to consider how the preparation temperature of the Dip-Cl reagent affects EE_{prod}. Since the amount of (−,−)-**1** increases at higher preparation temperatures, one might expect this to have a deleterious affect on EE_{prod}. As shown in Figure 4, this is not the case: the reagents prepared at higher temperatures give higher EE_{prod} values especially *at lower values of* ee_{aux}. Even though the concentration of (−,−)-**1** increases at higher preparation temperatures, the relative amount of (−,−)-**1** remains small. This point is illustrated in Figure 5, where at $EE_{aux} = 22.2\%$, the amount of (−,−)-**1** is small and only changes from 1.8 (at 0 °C) to 3.4% (at 20 °C), whereas EE_{prod} increases from 49.0 to 61.2%, respectively. However, the two parameters that significantly change in accord with EE_{prod} are the amounts of (+,+)-**1** and (+,−)-**1** (see Figure 5). Thus, at $EE_{aux} = 22.2\%$, (+,+)-**1** increases from 25.7 (0 °C) to 30.9% (20 °C), a 5.2% change which directly correlates with an increase in EE_{prod}. Furthermore, since (+,−)-**1** produces racemic product, the decrease in (+,−)-**1** from 72.5 (0 °C) to 65.9% (20 °C) correlates with an increase in EE_{prod}.

The effect of preparation temperature is also seen in β, a parameter from Kagan's model (eq 2) which gives the relative amount of heterochiral with respect to the homochiral isomers. The term β is calculated for each ee_{aux} (Table 1) and is shown

(24) Moeder, C. W.; Sowa, J. R., Jr. Manuscript in preparation.

(25) An NMR method for analysis of the diastereomers of Dip-Cl has been presented. See: Medina, J. R.; Soderquist, J. A. *Abstracts of Papers*, 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21−25, 1999; American Chemical Society: Washington, DC, 1999; ORGN 132.

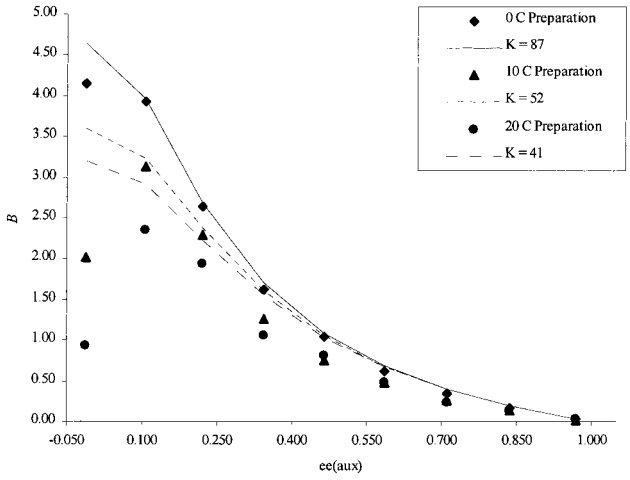

Figure 6. Experimental and predicted plots of β as a function of ee_{aux} for Dip-Cl solution prepared at 0, 10, and 20 °C.

graphically in Figure 6. At a given ee_{aux}, the data show that β decreases as the preparation temperature increases; however, as β decreases EE_{prod} increases. For example, at $EE_{aux} = 22.2\%$, β values decrease from 2.64 (0 °C) to 2.29 (10 °C) to 1.93 (20 °C), and EE_{prod} increases from 49.0 to 53.2 to 61.2%, respectively. This is true because β is a measure of the relative amount of heterochiral to homochiral species, and since the heterochiral isomer reacts to give racemic products, lower amounts of this isomer are beneficial toward increasing EE_{prod}. This trend seems to contradict eq 1, which predicts an increase in EE_{prod} as β increases. The reason is unclear; however, eq 1 assumes Curtin−Hammett conditions where β remains constant throughout the reaction as in the catalytic reactions.[1] Perhaps the contradiction between the trend in the experimental results and eq 1 is because Dip-Cl does not follow Curtin−Hammett conditions.

The benefit of increasing EE_{prod} with decreasing β is clearly good to $EE_{aux} = 58.6\%$ (see β and EE_{prod} data in Table 1). Although the effect is discernible at $EE_{aux} = 71.2\%$, at higher EE_{aux} differences in β and EE_{prod} are negligible. Consider that the Dip-Cl reagent is typically prepared from α-pinene of 70% EE_{aux}; our analysis suggests that using a higher temperature range could be enough to increase EE_{prod} a few percentage points.

It is interesting that as β decreases, representing less heterochiral compound, Blackmond[15b] predicted that reduction reactions should be faster. Indeed, this trend is observed as reaction completion is achieved in a shorter time as the Dip-Cl preparation temperature increases. For example, at the 0 °C preparation temperature when $\beta = 0.62$ (Table 1a), the reduction reaction was 99.5% complete in 8 h. But at the 20 °C preparation temperature when $\beta = 0.48$ (Table 1c), the reduction reaction was 99.7% complete in 5 h. *Therefore, our study suggests two benefits for preparation of the Dip-Cl reagent at higher temperatures. First, EE_{prod} values are for the most part higher, especially at lower values of ee_{aux}. Second, the reduction reactions are slightly faster.*

As discussed in the Introduction, *K* was originally defined as the equilibrium constant for the formation of ML_2 stereoisomers under Curtin−Hammett conditions. However, this condition does not to apply to Dip-Cl. Nevertheless, Blackmond showed how *K* could be determined from plots of EE_{prod} vs ee_{aux} by a nonlinear regression analysis of eqs 1 and 4.[15a] For Dip-Cl, this analysis requires that EE_{prod} be measured early in the course of the reduction reaction (10−20% conversion) since the stereoisomers react at different rates and *K* at the beginning of the reaction will be different from that at the end. We find that complexation with 8-hydroxyquinoline is an alternate way to measure *K* because this analysis is independent of the reduction reaction and only requires a few values of ee_{aux}.

We have obtained values for the term *K* (eq 5) at each ee_{aux} (Table 1) where the value of *y* may be precisely measured (>1.0% by area). Our data show that there is considerable variability in *K*; for example, *K* depends on the reagent preparation temperature and on ee_{aux}. This is especially apparent when *K* is calculated at racemic ee_{aux}; the value decreases from 69 (0 °C preparation temperature) to 16 (10 °C) to 3.5 at 20 °C. The last of the three values is, within experimental error, equivalent to the statistical value of 4. At higher ee_{aux}, the *K* values seem to become more consistent at each preparation temperature; nevertheless, the average *K* values still decrease as the preparation temperature of the Dip-Cl reagent increases from 0° (87 ± 26) to 10° (52 ± 4) to 20 °C (41 ± 11).[26] Blackmond's value of *K* (49), which was calculated from plots of EE_{prod} vs ee_{aux}, falls within the range of our experimental values. In terms of Kagan's theory, values of *K* may be used to predict β and, thus, EE_{prod} using eqs 4 and 1, respectively. Fortunately, this analysis is rather forgiving of a lack in precision of the value of *K*. Thus, at 70% EE α-pinene, for $K = 114$ (our highest value), β is 0.42, and for $K = 30$ (our lowest nonracemic value), β is 0.41. Despite the large difference in *K*, the β values are the same within experimental error, and, therefore, the effect on calculation of EE_{prod} is negligible. Thus, it appears that our method of measurement of *K* is completely satisfactory, given the precision necessary for calculation of β and EE_{prod}.

The validity of eq 4 may also be evaluated using the experimentally determined values of β and *K*. Predicted values of β at each ee_{aux} are calculated using eq 4 and *K* for each Dip-Cl preparation (Table 1). Comparison of predicted and experimental β values in Figure 6 indicates excellent agreement except for the points at racemic ee_{aux}. However, it is not surprising that points at racemic ee_{aux} are off since these points are so strongly affected by conditions of reagent preparation.

We hoped to obtain a value for *g* (eq 3) by rearranging eq 1 and using the calculated values of β and ee_{aux}. Unfortunately, these values varied such that *g* obtained by this method was considered to be unreliable. Instead, we have embarked on a kinetic study that will provide an accurate determination of *g*. These results will be reported subsequently.[24]

Conclusion

Dip-Cl, a valuable reagent for the asymmetric reduction of ketones, exhibits the phenomenon of asymmetric amplification. To understand how the amplification occurs, we have employed 8-hydroxyquinoline as a complexation agent for analysis of Dip-Cl by chiral HPLC. When Dip-Cl is prepared from enantiomerically impure α-pinene, our analysis shows that a distribution of heterochiral ((+,−)-Dip-Cl) and homochiral ((+,+)-Dip-Cl and (−,−)-Dip-Cl) stereoisomers are formed. Our study shows there is also a kinetic preference for the formation of the heterochiral stereoisomer; therefore, the distribution of stereoisomers is nonstatistical. This is beneficial toward asymmetric amplification because the heterochiral diastereomer removes the minor enantiomer of α-pinene and increases the effective concentration of Dip-Cl that is formed from the major enantiomer of α-pinene.

Our method provides the first quantitative stereochemical analysis of a reagent that exhibits asymmetric amplification and

(26) When calculating average *K* values, we choose not to include the values at racemic ee_{aux} at the 10 and 20 °C preparation temperatures.

allows us to evaluate Kagan's general theory of nonlinear effects (NLE) in asymmetric synthesis.[1] Indeed, that a distribution of heterochiral and homochiral stereoisomers is observed is one confirmation of Kagan's theory. Furthermore, since we have a direct measurement of the parameters *x*, *y*, and *z*, we can evaluate the β and *K* terms of Kagan's mathematical model and show how the preparation conditions of the reagent affect β and *K* as well as the enantiomeric excess of the product (EE_{prod}). A significant finding is that at a given enantiomeric excess of α-pinene, the amount of Dip-Cl formed from the minor isomer (in this case (−,−)-Dip-Cl) is always very small and the amount increases only very slightly as the preparation temperature increases. In contrast, there is both a stronger relative increase in the amount of (+,+)-Dip-Cl and a decrease in the amount of heterochiral isomer (+,−)-Dip-Cl. This results in an overall increase in EE_{prod} and reduction rate. This trend is most dramatically observed at low enantiomeric purities of α-pinene and suggests a benefit for preparing Dip-Cl at higher temperatures.

In sum, the complexation of Dip-Cl with 8-hydroxyquinoline gives the first quantitative analysis of a reagent that exhibits asymmetric amplification. Our study verifies a major aspect of Kagan's general theory of nonlinear effects in asymmetric synthesis: that a distribution of heterochiral and homochiral isomers is formed when certain chiral reagents are prepared from nonracemic starting materials. In addition, we have obtained considerable insight into how the reaction conditions for the preparation of the Dip-Cl reagent affect the distribution of stereoisomers and the β, *K*, and EE_{prod} terms of Kagan's mathematical model.

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Supporting Information Available: The entire Experimental Section, including X-ray crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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