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Kinetic Studies on the Asymmetric Transfer Hydrogenation of Acetophenone Using a Homogeneous Ruthenium Catalyst with a Chiral Amino-Alcohol Ligand

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Abstract:

The overall kinetics of the asymmetric transfer hydrogenation of acetophenone to 1-phenyl-ethanol using a Noyori-type homogeneous Ru-catalyst with a chiral amino-alcohol ligand ((1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol) were determined in a batch reactor with on-line FT-IR spectroscopy. Data analysis showed that the transfer hydrogenation is an equilibrium reaction with additional inhibition terms of both reactants and products. The rate equation is best expressed as: $R_A = -(k_1C_AC_B - k_{-1}C_CC_D)/(k_1C_A + k_2C_B + k_{-1}C_C + k_{-2}C_D)$ where C_A, C_B, C_C, and C_D are the concentration levels of acetophenone (A), 2-propanol (B), phenyl ethanol (C), and aceton (D), repectively. The overall kinetics are in agreement with the proposed mechanism of transfer hydrogenation of ketones by Noyori. The equilibrium constant for the transfer hydrogenation was about 0.19 at T = 33 °C. The enantiomeric excess of the asymmetric conversion was high (ee = 0.92) and almost no reduction was observed in the course of the reaction. The kinetic data have been applied to optimise the production of enantiomerically pure 1-phenyl-ethanol in a batch reactor setup.

Introduction

The interest for enantiomerically pure compounds, including alcohols, has increased significantly over the last several years.[1] It has been reported that chiral secondary alcohols, in most cases obtained by reduction of the corresponding ketone, are key intermediates in the preparation of many commercially attractive pharmaceuticals, agrochemicals, fragrances, flavors, and specialty materials.[2] The procedures most often utilized for preparation of optically active alcohols are chiral chromatography, utilization of the chiral pool, kinetic resolution, and enantioselective synthesis. In many ways, asymmetric synthesis is considered to be the most attractive procedure, as it provides large amounts of chiral products at relatively low cost. Well-known methods for the asymmetric conversion of ketones towards chiral alcohols are hydrosilylations,[3] hydroborations,[4] bio-reductions,[5] and catalytic (transfer) hydrogenations.[6] The success of the last approach can be attributed to outstanding work of Nobel Laureate R. Noyori.[7]

From an industrial point of view, asymmetric catalytic transfer hydrogenation is an attractive alternative for high-pressure catalytic hydrogenations with molecular hydrogen.[8] Here, hydrogen donors such as secondary alcohols (e.g., 2-propanol) or formates are applied to convert carbonyl compounds to alcohols. The risk associated with the use of molecular hydrogen at high pressures is thereby eliminated. Homogeneous ruthenium complexes are considered to be the most attractive catalysts for transfer hydrogenation reactions, though other metal complexes have also been used successfully.[9] Varying levels of efficiency were observed for ruthenium complexes with ligands such as diamines,[10] amino alcohols,[11] phosphanes,[12] peptide analogues,[13] ferronecyl derivatives,[14] aminophosphines,[15] and oxazoline-2-yl pyridines.[16]

Thus far, one of the most successful approaches for asymmetric transfer hydrogenation is based on $[RuCl_2(arene)]_2$ in combination with enantiomerically pure 1,2-amino alcohols or mono-*N*-sulfonated 1,2-diamines.[17] To the best of our knowledge, overall kinetic expressions for transfer hydrogenation reactions of ketones using these types of Ru catalysts have not been reported in the literature. In addition,

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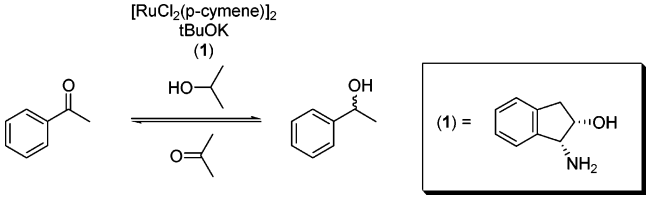
Scheme 1. **Transfer hydrogenation of acetophenone**



equilibrium data for the reaction are scarce and have not been determined experimentally. We here report a combined experimental and modelling study to obtain an overall kinetic expression for a model transfer hydrogenation reaction of acetophenone using 2-propanol as the hydrogen donor and an in situ formed homogeneous ruthenium catalysts. The catalyst was prepared by reacting $[RuCl_2(p\text{-cymene})]_2$ with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol in the presence of a base (tBuOK) (Scheme 1).

The values of the equilibrium constant of the transfer hydrogenation reaction and the enantiomeric excess of the chiral alcohol formed were investigated during reaction. The consequences of these findings for the optimal mode of operation of a batch reactor setup will be discussed.

Results and Discussion

Effects of the Concentration of Acetophenone (A), 1-Phenyl-ethanol (C) and Acetone (D) on the Initial Reaction Rate of the Transfer Hydrogenation. Design of experiments (DOE) techniques were applied to study the effect of the concentration of substrate and products on the initial reaction rate.[18] According to a Box−Behnken design[19] a total of 16 experiments was conducted with the initial concentrations of acetophenone (A), 1-phenyl-ethanol (C) and acetone (D) as the independent variables, see Table 1 for details. The initial reaction rate of acetophenone ($R'_{A,0}$) was selected as a response and was determined from the experimentally obtained concentration−time profiles using FT-IR spectroscopy. The initial reaction rates were normalised on catalyst concentration to compensate for small variations in the ruthenium intake. The reaction temperature (33 ± 0.5 °C), catalyst concentration (1.24 ± 0.02 mM), and concentration of 2-propanol were kept at a constant value. Runs 2, 7, 11, and 14 were replicates, and statistical analysis revealed that the reproducibility of the experiments was very good ($R'_{A,0} = 1.14 \times 10^{-2} \pm 3.7 \times 10^{-4}$ mol L^{-1} min^{-1} [mM $catalyst^{-1}$]). Runs 4 and 6 were not performed as the concentrations of two of the independent variables for these experiments were set at zero by the design, excluding the occurrence of a chemical reaction.

Table 1. **Initial Reaction Rates of the Transfer Hydrogenation of Acetophenone in 2-propanol using (eq 1)**

run	acetophenone (M) A	1-phenyl-ethanol (M) C	acetone (M) D	$-R'_{A0}$ (mol L^{-1} min^{-1} (mM $catalyst)^{-1}$)
1	0	0.252	0.479	-0.30×10^{-2}
2	0.255	0.249	0.246	1.13×10^{-2}
3	0.494	0.000	0.246	1.73×10^{-2}
5	0.257	0.000	0.000	2.51×10^{-2}
7	0.255	0.249	0.246	1.10×10^{-2}
8	0.466	0.470	0.232	0.93×10^{-2}
9	0	0.479	0.246	-0.40×10^{-2}
10	0.253	0.000	0.487	1.08×10^{-2}
11	0.255	0.249	0.246	1.14×10^{-2}
12	0.49	0.247	0.488	1.14×10^{-2}
13	0.253	0.493	0.487	0.57×10^{-2}
14	0.255	0.249	0.246	1.19×10^{-2}
15	0.252	0.491	0.000	1.28×10^{-2}
16	0.488	0.246	0.000	2.27×10^{-2}

The reactions were monitored on-line with an FT-IR probe. A typical reaction profile for the asymmetric transfer hydrogenation is given in Figure 1. The areas of the absorbances of acetophenone (1679 cm^{-1}) and acetone (1710 cm^{-1}) were applied for determination of the concentration of the various components during reaction.

The highest initial reaction rate was observed in run 5. Here, only reactants and no products were present at the start of the reaction. After 20 min reaction time, the conversion of acetophenone reached 80%, corresponding to a catalyst turnover frequency (TOF) of 540 (mol [mol $catalyst^{-1}$] $hour^{-1}$). A considerable reduction in initial reaction rate was observed in case the products phenyl ethanol (C) and acetone (D) were present at the start of the reaction (compare, for example, runs 5 and 7). This observation was expected as the reaction is known to be an equilibrium reaction. It was confirmed by carrying out reactions in the presence of both products and the absence of acetophenone (runs 1 and 9). Here, the backward reaction occurred, and acetophenone was formed in substantial amounts. Surprisingly, a significant reduction of the initial reaction rate was observed when the reaction was carried out in the presence of only one of the products of the reaction, e.g., 1-phenyl-ethanol (C) or acetone (D) (runs 3, 10, 15, and 16). This effect is likely not only due to the occurrence of the backward reaction but suggests that each of the products inhibits the reaction rate as well (vide infra). It also suggests that the overall kinetic expression for the reaction is not that of a simple elementary equilibrium reaction but is a more complex equation with at least product concentrations in the denominator term.

The effect of the individual components on the initial reaction rates was assessed by statistical data analyses. The initial rates could be modelled very satisfactorily with three

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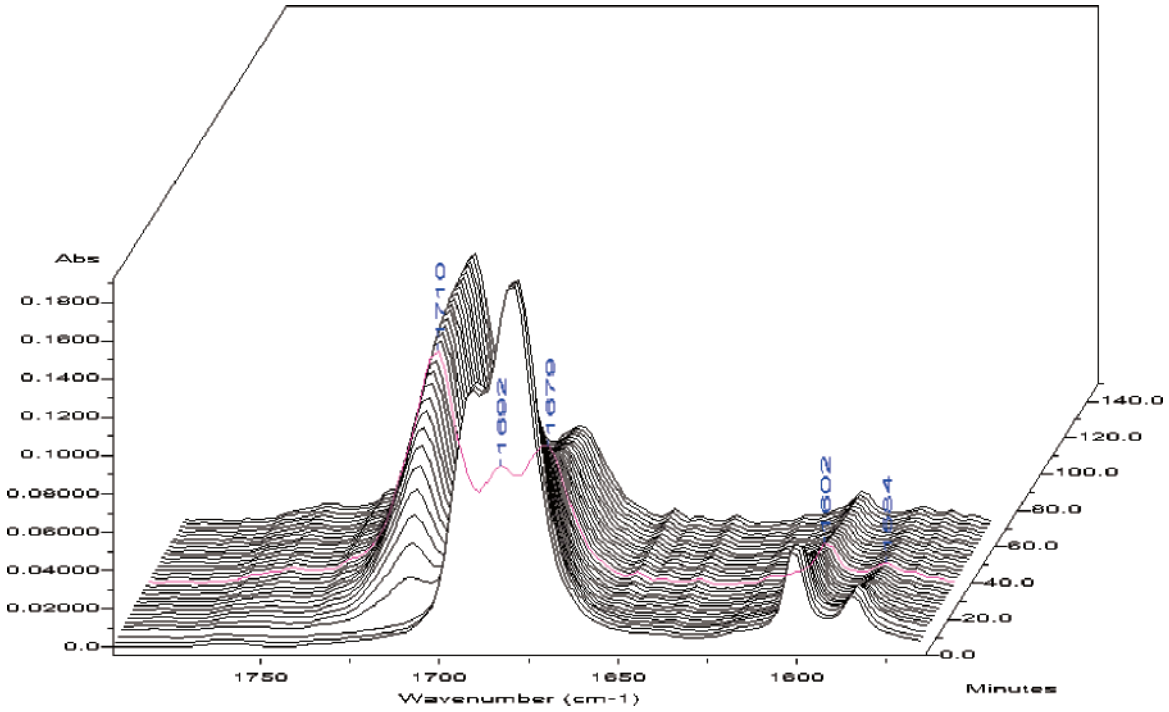

Figure 1. **FT-IR spectrum of a typical reaction profile (run 16) for the asymmetric transfer hydrogenation of acetophenone.**

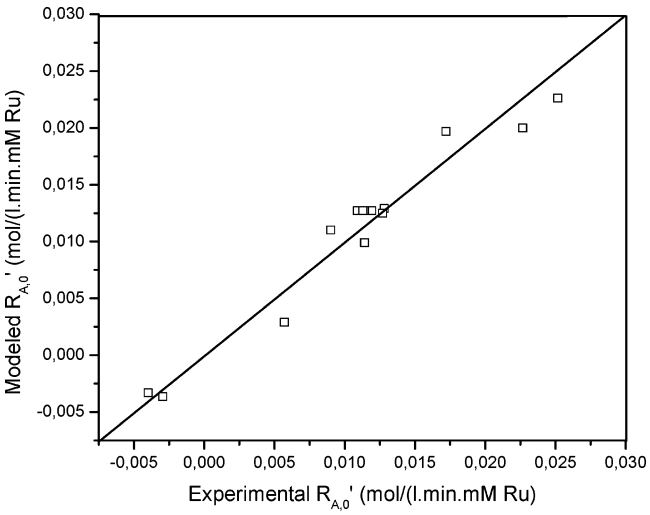

Figure 2. **Parity plot of the experimental - versus the modelled initial reaction rate.**

linear terms, one for each component, and a quadratic term for acetophenone (A), see eq 1.

$$-R'_{A0} = 0.011 + 0.057C_A - 0.019C_C - 0.020C_D - 0.061C_A^2 \quad (1)$$

Here, R'_{A0} is the initial rate of acetophenone consumption (mol/[L min mM catalyst]) and C_A, C_C, and C_D the concentrations of acetophenone (A), 1-phenyl-ethanol (C), and acetone (D) respectively (mol/L). A parity plot with the experimental and modelled initial reaction rate for acetophenone is given in Figure 2.

Reaction Modelling of the Asymmetric Transfer Hydrogenation of Acetophenone Using Empirical Rate Laws. The modelling activities described in the previous paragraph were concerned only with initial reaction rates.

Table 2. **Correlation coefficients for the various empirical reaction rate models**

model	n	m	p	correlation coefficient (R^2)	model	n	m	p	correlation coefficient (R^2)
S1	0	0	0	0.9880	S5	2	2	0	0.9955
S2	1	0	0	0.9900	S6	2	2	1	0.9971
S3	2	0	0	0.9895	S7	2	2	2	0.9971
S4	2	1	0	0.9959	S8	1	1	1	0.9971

However, there is more information available from online FT-IR measurements in the form of concentration−time profiles. These data may be applied to determine the overall rate expression of the reaction. Data analysis on the initial reaction rates implied that the reaction is an equilibrium reaction with additional inhibition terms. A number of empirical rate laws of the type given in eq 2 were tested using various integer values for n, m, and p ($0 \le n, m, p \le 2$). The concentration of acetophenone was not included in the denominator term as its concentration remains about constant during the reaction (12 mol/L).

$$-R_A = \frac{k_1 C_A C_B - k_{-1} C_C C_D}{1 + k_2 {C_A}^n + k_3 {C_D}^m + k_4 {C_C}^p} \quad (2)$$

The values of n, m, and p describe the extent of reactant/product inhibition on the reaction rate. The concentration profile of acetophenone (A) in the batch setup may be calculated using the following batch design equation:

$$-\frac{dC_A}{dt} = -R_A = \frac{k_1 C_A C_B - k_{-1} C_C C_D}{1 + k_2 {C_A}^n + k_3 {C_D}^m + k_4 {C_C}^p} \quad (3)$$

The experimental data were modeled with eq 3 using the Scientist software platform. A total of eight runs, consisting of 270 data points, were fitted simultaneously to determine

Table 3. **Kinetic coefficients and standard deviations for eq 4 ($m = n = p = 1$)**

$k_1 \pm \sigma_{k1}$ (L mol^{-1} s^{-1})	$k_{-1} \pm \sigma_{k-1}$ (L mol^{-1} s^{-1})	$k_2 \pm \sigma_{k2}$ (L mol^{-1})	$k_3 \pm \sigma_{k3}$ (L mol^{-1})	$k_4 \pm \sigma_{k4}$ (L mol^{-1})
0.047 ± 0.019	0.203 ± 0.083	16.7 ± 7.9	17.6 ± 7.5	5.69 ± 2.71

the values of the kinetic constants (k_1, k_{-1}, k_2, k_3, and k_4) at preselected values of n, m, and p. The modelling results for the various runs are depicted in Table 2.

Inspection of the correlation coefficient for the various kinetic expressions (see Table 2) revealed that the quality of the fits improved significantly when all denominator terms are taken into account ($m, n, p > 0$). The values of the kinetic constants for ($m = n = p = 1$) are represented in Table 3. It is evident from these empirical modelling activities that the reaction may not be modelled solely as an equilibrium reaction ($m = n = p = 0$) but denominator terms are required to improve the model fits. These findings are in line with the results obtained from the initial rate analysis (vide supra).

Reaction Modelling Using a Mechanistic Model. Recently, a variety of mechanistic studies on the metal-catalyzed hydrogen transfer reaction of alcohols to ketones were reported in the literature by various research groups.[20] Noyori proposed a novel mechanism for catalysts consisting of $[RuCl_2(benzene)]_2$, a base, and a β-amino-alcohol such as ephedrine or the amino-indanol used in our experiments. The NH_2 or NH group of the amino-alcohol appeared to be crucial for catalytic activity, and for instance, dimethylamino analogues are not active. On the basis of these findings, supported by extensive theoretical calculations (ab initio MO calculations at MP4/MP2 level), a novel nonclassical metal−ligand bifunctional mechanism is proposed, which is schematically represented in Figure 3.

The mechanism involves only two ground-state components, an 18-electron metal hydride (M1) with a coordinated amine and a 16-electron amido species (M2). It is assumed that catalyst formation from the ruthenium chloride precursor by reaction with a base (See Scheme 2) is fast compared to subsequent steps in the catalytic cycle.

Assuming elementary kinetics for the reactions depicted in Figure 3, the following relations hold:

$$R_A = k_{-1}C_C C_{M2} - k_1 C_A C_{M1} \quad (4)$$

$$R_B = k_{-2}C_D C_{M1} - k_2 C_B C_{M2} \quad (5)$$

$$R_{M1} = -k_1 C_A C_{M1} + k_{-1}C_C C_{M2} + k_2 C_B C_{M2} - k_{-2}C_D C_{M1} \quad (6)$$

The catalyst intake (C_{M0} in mol/L) is divided between catalyst states M_1 and M_2 according to:

$$C_{M1} + C_{M2} = C_{M0} \quad (7)$$

Using the pseudo-steady-state assumption for the intermediates M_1 and M_2 and combining this with eq 7, C_{M1} and C_{M2} can be expressed as:

$$C_{M1} = C_{M0}\frac{k_{-1}C_C + k_2 C_B}{k_1 C_A + k_2 C_B + k_{-1}C_C + k_{-2}C_D} \quad (8)$$

$$C_{M2} = C_{M0}\frac{k_1 C_A + k_{-2}C_D}{k_1 C_A + k_2 C_B + k_{-1}C_C + k_{-2}C_D} \quad (9)$$

The reaction rate of acetophenone ($-R_{A,SS}$) can subsequently be obtained by combining eqs 4, 8, and 9:

$$-R_{A,SS} = k_1 C_A C_{M1} - k_{-1}C_C C_{M2} = C_{M0}\left[\frac{k_1 k_2 C_A C_B - k_{-1}k_{-2}C_C C_D}{k_1 C_A + k_2 C_B + k_{-1}C_C + k_{-2}C_D}\right] \quad (10)$$

The expression contains a nominator term typical for an equilibrium reaction and a denominator term including concentration levels of all four components taking place in the reaction. The denominator terms can be viewed as inhibition terms. The experimental data were modelled using the Scientist software platform. A total of eight runs (270 data points) were fitted simultaneously to determine the values of the kinetic constants (k_1, k_{-1}, k_2, k_{-2}) in eq 10. Agreement between experimental and fitted data was good ($R^2 = 0.9971$) and similar to the best empirical models (Table 2). However, the empirical models contain five parameters whereas the Noyori-based overall kinetic model only contains four parameters, which makes the latter preferred and statistically more relevant. The values of the kinetic constants and their standard deviations are shown in Table 4. Typical experimental and modeled concentration profile for a number of datasets are given in Figure 4.

It follows that both the values for k_1 and k_{-2} are significantly higher than the other two kinetic constants. Considering the overall kinetic expression (eq 10) and realizing that the concentration level of 2-propanol is about 20−100 times higher than the others, the denominator terms with the concentrations of acetophenone ($k_1 \cdot C_A$), acetone ($k_{-2} \cdot C_D$), and 2-propanol ($k_2 \cdot C_B$) are significantly higher than the phenyl ethanol ($k_{-1} \cdot C_C$) term. This suggests that inhibition by phenyl ethanol is of less importance than of the other components.

Although we are aware of the fact that overall kinetics do not provide sufficient information to discriminate between the various mechanistic catalytic cycles proposed in the literature, it is evident that the experimentally determined overall kinetics are in agreement with the proposed mechanism of Noyori.

Equilibrium Constant Calculations. Transfer hydrogenations of carbonyl compounds with 2-propanol are known to be equilibrium reactions. To the best of our knowledge, the equilibrium constant for the reaction between 2-propanol and acetophenone has not been quantified fully to date. Our experimental data allow calculation of the equilibrium constant for the transfer hydrogenation reaction at $T = 33$ °C. For some of the runs, the reaction reaches equilibrium within 1 h reaction time, allowing determination

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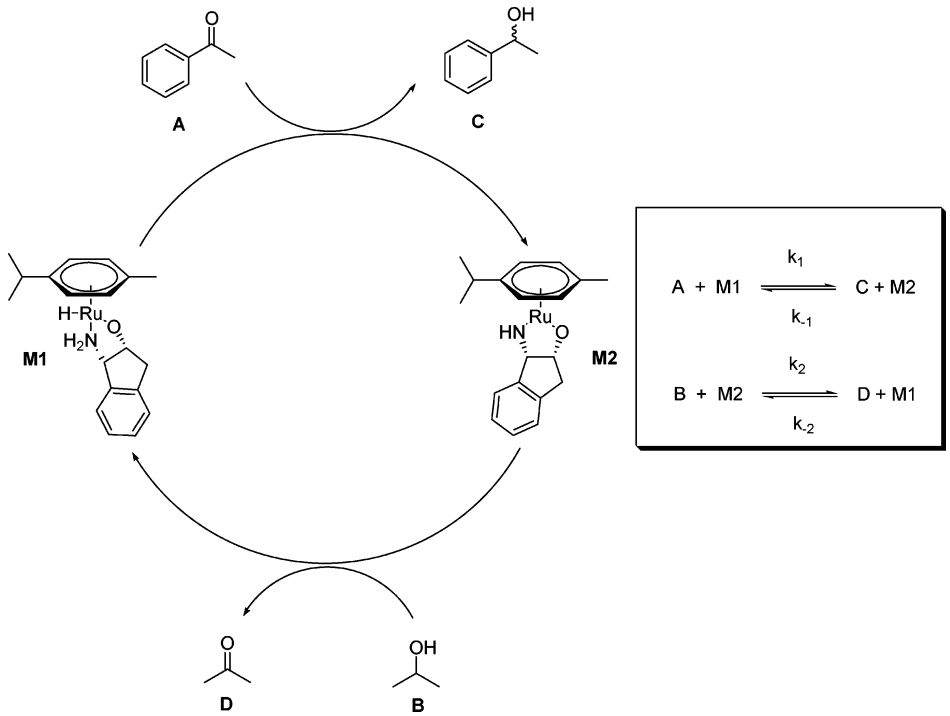

Figure 3. **Metal−ligand bifunctional mechanism for transfer hydrogenation (reversibility of the reactions not included for reasons of clarity).**

Scheme 2

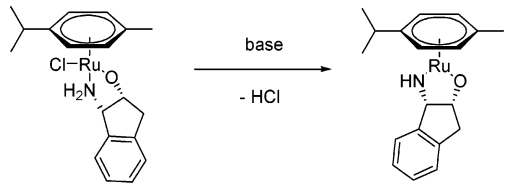

Table 4. **Kinetic constants for the kinetic model provided in eq 10**

$k_1 \pm \sigma_{k1}$ (L mol^{-1} s^{-1})	$k_{-1} \pm \sigma_{k-1}$ (L mol^{-1} s^{-1})	$k_2 \pm \sigma_{k2}$ (L mol^{-1} s^{-1})	$k_{-2} \pm \sigma_{k-2}$ (L mol^{-1} s^{-1})
231 ± 37	11.5 ± 0.8	1.8 ± 0.1	167 ± 21

of the equilibrium concentrations of the reactants and products using eq 11:

$$K = \left[\frac{C_C \cdot C_D}{C_A \cdot C_B}\right]_{\text{at equilibrium}} \tag{11}$$

Here, C_A, C_B, C_C, and C_D are the equilibrium concentrations of acetophenone (A), 2-propanol (B), phenyl-ethanol (C), and aceton (D). For the four replicate runs (2, 7, 11, and 14), the average equilibrium using this method was 0.186 (±0.005). The modelling results using the overall kinetic expression (eq 10) also allows for the determination of the equilibrium constant. At equilibrium, the net rate of reaction is zero and eq 10 reduces to:

$$K = \frac{k_1 \cdot k_2}{k_{-1} \cdot k_{-2}} \tag{12}$$

Using this relation in combination with the kinetic constants provided in Table 4, the equilibrium constant for the reaction

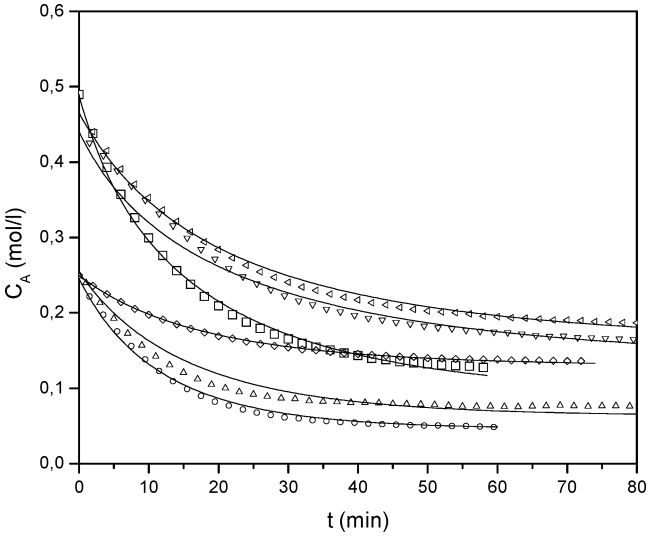

Figure 4. **Experimental data and modeled profiles using the Noyori model (eq 10).**

is 0.22 ± 0.02 at $T = 33$ °C. This value is close to the value obtained using the experimentally obtained equilibrium concentrations.

The equilibrium constant is less than 1, and therefore high acetophenone conversions can only be achieved if one of the reagents in excess (i.e. by using 2-propanol both as the reactant and solvent) or one of the products formed during the reaction is removed from the reaction mixture (i.e. by evaporation of acetone).

Batch Process Optimisation. With an overall kinetic expression available, it is possible to model the conversion of acetophenone as a function of the time in a batch setup with the initial concentration of acetophenone as the variable ($T = 33$ °C, catalyst concentration 1.24×10^{-3} M). The

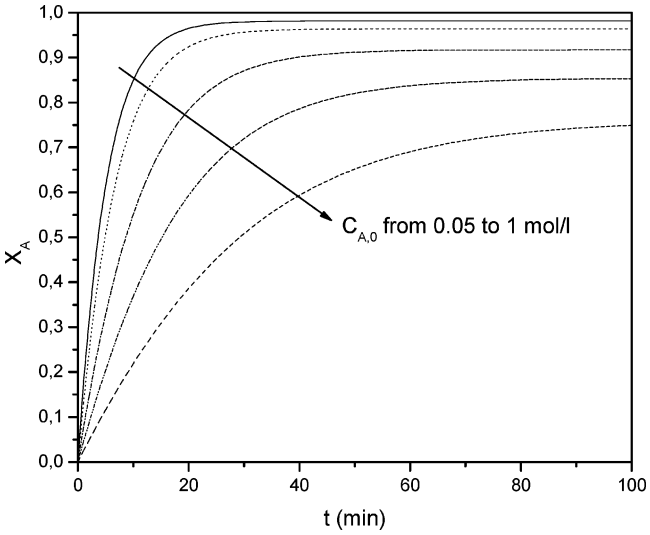

Figure 5. **Modelled conversion of acetophenone as a function of time and initial acetophenone concentration (0.05, 0.1, 0.25, 0.5 and 1 mol/L, $T = 33$ °C, $C_{catalyst} = 1.24 \times 10^{-3}$ mol/L) in a batch setup.**

results obtained are graphically represented in Figure 5. As anticipated, the equilibrium conversion is a function of the initial acetophenone concentration. Lowering the initial concentration of acetophenone leads to a substantial increase in the equilibrium conversion. The equilibrium conversion of the reaction may be expressed by the following implicit relation:

$$K = \frac{(X_{A,eq})^2}{(1 - X_{A,eq})(\theta - X_A)} \qquad (13)$$

Here θ equals the ratio of the initial concentrations of 2-propanol and acetophenone, respectively. When increasing the ratio of θ, i.e lowering the initial concentration of acetophenone, the equilibrium conversion increases significantly ($X_{A,eq} = 0.98$ for $\theta = 240$ ($C_{A,0} = 0.05$ mol/L) and $X_{A,eq} = 0.77$ for $\theta = 12$ ($C_{A,0} = 1$ mol/L)).

The reaction time required to achieve equilibrium also depends on the initial acetophenone concentration (Figure 5), with lower concentrations leading to a reduction in time required to reach equilibrium. Typically, for initial concentrations less than 0.5 mol/L, equilibrium is reached within 100 min.

Selection of the optimum initial acetophenone concentration for a batch process is a delicate balance between kinetic considerations as reported previously and the ease of separation of reactants and products in the workup section. It is clear that higher initial acetophenone concentrations lead to longer reaction times and lower equilibrium conversions. Without additional research on the workup section, it is not possible at this stage to optimise the total process and to select the optimum reaction time and initial acetophenone concentration.

The ee (enantiomeric excess) of the chiral alcohol formed during the asymmetric transfer hydrogenation reaction is expected to be a function of the batch time, owing to the reversibility of the reaction. Erosion of the ee has been reported in the literature to be substantial and thereby puts constraints on the maximum allowable batch time. However, over the reaction time studied, it was found that the ee was close to about 0.915 at the start of the reaction and only gradually decreased to 0.902 after 90 min reaction time.[21] By taking into account that for most of the runs performed in this study the equilibrium of the transfer hydrogenation was reached within 90 min, the erosion in ee is not significant.

Conclusions

The overall kinetics of the asymmetric transfer hydrogenation of acetophenone to 1-phenyl-ethanol using a Noyori-type homogeneous Ru-catalyst with a chiral amino-alcohol ligand ((1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol) were determined in a batch reactor with on-line FT-IR spectroscopy. Analysis of the initial reaction rates using a design of experiments (DOE) strategy indicated that the reaction is an equilibrium reaction. In addition, the initial rate was also affected by the individual reaction products, an indication for product inhibition other than equilibrium effects. The concentration−time curves were modeled using various emperical rate laws as well as a rate law based on a postulated mechanism by Noyori. The experimental data were successfully modeled using the latter, thereby supporting its validity. The equilibrium constant of the reaction was found to be about 0.19 at 33 °C. The rate law and equilibrium data were applied to model a typical batch reactor setup. The equilibrium conversion of acetophenone is a strong function of the initial acetophenone concentration, with low concentrations leading to high equilibrium conversions.

Experimental Section

General Procedures. All reactions were performed under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further treatment or purification. Solvents were degassed prior to use and stored under a protective nitrogen atmosphere.

Description of a Typical Run (Run 16, Table 1). The catalyst precursor was prepared in situ by dissolving (*p*-cymene)ruthenium(II) chloride dimer (19.0 mg, 0.031 mmol) and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (19.0 mg, 0.127 mmol) in degassed 2-propanol (20 mL) under a nitrogen atmosphere. The solution was subsequently warmed-up to $T = 80$ °C and stirred for 30 min at this temperature. After cooling to room temperature, acetophenone (2.9 mL, 24.6 mmol) and racemic 1-phenylethanol (1.5 mL, 12.4 mmol) were added to the light-brown solution. The total reaction volume was adjusted to 50 mL by adding 2-propanol. The reaction temperature was set at 33 ± 0.5 °C, and the FT-IR probe was inserted in the solution. The reaction was initiated by adding *t*-BuOK (35 mg, 0.31 mmol) to the reaction mixture.

FT-IR spectra were measured on a Mettler Toledo "ReactIR 1000" Fourier spectrometer with a silicon probe. The absorbances were measured with intervals of 2 min, and the specific frequencies of acetophenone (1679 cm^{-1}) and

(21) In agreement with values reported by: Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

acetone (1710 cm^{-1}) were used for the analyses. A typical IR spectrum is depicted in Figure 1. Calibrations with stock solutions of acetophenone and acetone were performed to convert measured absorbances to concentrations.

Experimental Design Analyses. The software package *Design Expert*, version 5.0.4, producer Stat-Ease Corporation was used to set up the design and to analyse the data. A Box−Behnken response surface design was applied with the concentrations of acetophenone (A), 1-phenyl-ethanol (C), and acetone (D) as the independent variables. The initial reaction rate was taken as the response. The response was modelled using a standard expression:

$$y = b_0 + \sum_i b_i x_i + \sum_i b_{ii} x_i^2 + \sum_j \sum_k b_{jk} x_j x_k \qquad (14)$$

b_i, b_{ii}, and b_{jk} are the regression coefficients obtained by statistical analysis of the data. Significant factors were selected on the basis of their *p*-value in the ANOVA analyses. Factors with a $p < 0.05$ were regarded as significant and included in the response model. Backward elimination was applied to eliminate all statistically insignificant terms. After each elimination step, a new ANOVA table was generated to select the subsequent nonsignificant factor.

The kinetic modelling has been performed with the statistical software package *Scientist*, version 2.01, from Micro Math using a stiff Episode integrator and a standard Levenberg−Marquardt optimiser.

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