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Asymmetric Transfer Hydrogenation of Acetophenone with 1*R*,2*S*-Aminoindanol/Pentamethylcyclopentadienylrhodium Catalyst

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Abstract:

The chiral rhodium complex pentamethylcyclopentadienylrhodium chloride dimer combined with the ligand 1*R*,2*S*-aminoindanol provides a superior catalyst for the rapid, high-yielding asymmetric transfer hydrogenation of acetophenone with 2-propanol to produce (*R*)- and (*S*)-(1)-phenylethanol. The effects of various reaction parameters such as reaction temperature, catalyst and substrate concentration, gaseous environment, and acetone concentration on conversion and enantioselectivity were investigated. The results indicate that catalyst can be deactivated by high temperature and air atmosphere, acetone reduces the reaction rate, and enantioselectivity decreases with conversion.

1. Introduction

As a consequence of the importance of the synthesis of pharmacologically relevant substances, catalytic asymmetric hydrogenations are a field of considerable interest.[1,5,7,10,11,15,18,20,22−24] Asymmetric transfer hydrogenation with 2-propanol as hydrogen donor has been extensively investigated (refs 8, 9, 25, and 27). The use of hydrogen donor has some advantages over the use of molecular hydrogen, since it avoids the risks and the constraints associated with this reagent as well as the necessity for pressure vessels.

Various metals have been used in asymmetric catalysis. In 1968 Knowles[17] discovered that rhodium could be used in a chiral molecule to catalyse asymmetric hydrogenations. Crabtree et al.[6] showed that the cationic Ir catalyst $[Ir(cod)(Pcy_3)(Py)]^+$ (Cod = cyclooctadiene, Py = pyridine, cy_3 = tricyclohexylphosphine) was also active. Noyori[22] developed a Ru-BINAP catalyst, which is widely used for the synthesis of fine chemicals and pharmaceutical products. Based on experimental findings (refs 14, 16, 19, and 20) and theoretical calculations (refs 21 and 28), Noyori proposed the metal−ligand bifunctional mechanism for hydrogen transfer reactions.

In this work, the behaviour of the CATHy (catalytic asymmetric transfer hydrogenation) catalyst: 1*R*,2*S*-aminoindanol/pentamethylcyclopentadienylrhodium (refs 2 and 3) for acetophenone transfer hydrogenation is studied under various reaction conditions. Investigations of the CATHy catalyst with other ligands and substrates can be found elsewhere (ref 4). Since this catalyst's structure is similar to Noyori's catalyst, the metal−ligand bifunctional mechanism is considered to be valid as well (Scheme 1). In the presence of a base, the catalytic species **4** is formed from precursor **3** by HX removal. This active catalytic species **4** facilitates the H-transfer from the solvent 2-propanol (IPA) to the substrate ketone through the formation of intermediate **5** and acetone. The catalyst cycle is restored by the reduction of ketone.

2. Experimental Section

Pentamethylcyclopentadienylrhodium chloride dimer (11.2 mg, 18.1μmol) (Avecia), 1*R*,2*S*-aminoindanol (5.6 mg, 37.1μmol) (Avecia), and 2-propanol (100 mL, 1.3mol) (Aldrich 99.5%) were introduced into a flask reactor for catalyst preparation. N_2 (BOC CP grade) bubbling through the solution with a flow rate of 40 mL/min was used to keep an inert blanket. The mixture was stirred overnight at room temperature. A deep red catalyst solution was obtained.

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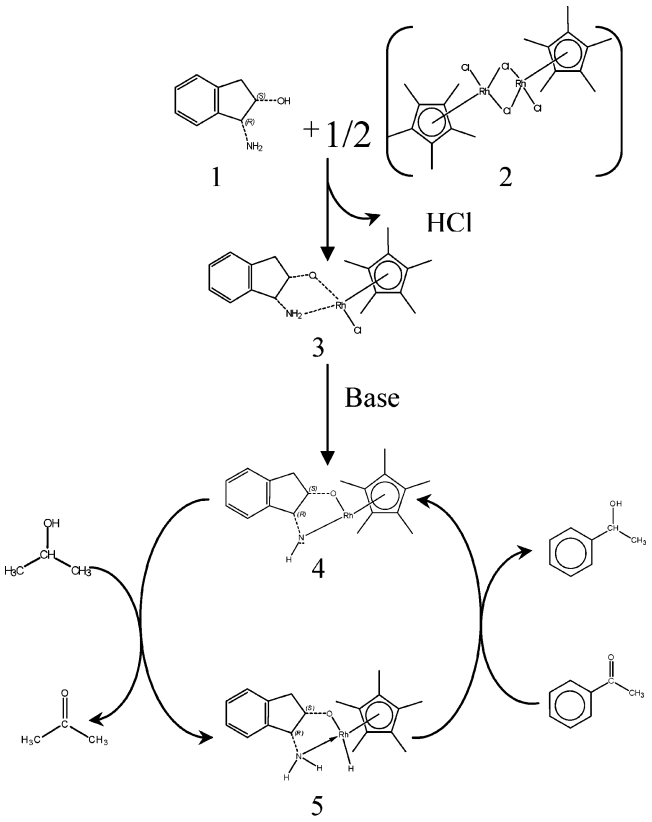
Scheme 1. **Metal−Ligand Bifunctional Catalysis Mechanism**



Acetophenone (4.5 g, 37.1 mmol) (Aldrich 99%) was introduced into the reactor containing the catalyst solution along with 2-propanol (150 mL, 1.95 mol) while stirring. The nitrogen flow rate was increased to 800 mL/min. Sodium isopropoxide (3 mL, 0.1 M) in 2-propanol solution was added by a syringe to the mixture, which was considered as reaction time zero. Temperature was kept constant at 30 °C by a water bath. The above conditions represent the base case experiment where the catalyst concentration is 0.000 144 M, substrate concentration/catalyst concentration is 1000:1, sodium isopropoxide concentration/catalyst concentration is 8:1, reaction system volume is 250 mL.

The reaction mixture was sampled at 2 min intervals in the first 10 min and subsequently every 10 min intervals in the first hour. A 0.4 mL sample was withdrawn by a syringe into a vial containing 10 μL of acetic acid (Aldrich 99.7%), which was used to stop further reaction, and then analysed by an Agilent 6890 GC system. The inlet temperature was 250 °C, the inlet pressure, 20 psi, and the split ratio, 200:1. An injection volume of 0.2 μL was used in the autoinjector. A CYCLODEX-B capillary column (30.0 m × 250 μm × 0.25 μm) was employed for the separation of the acetophenone, (*R*)-1-phenylethanol and (*S*)-1-phenylethanol, to estimate conversion and enantiomeric excess, along with a flame ionisation detector at 250 °C. The oven temperature was kept at 110 °C. The internal normalisation method (with acetophenone) (ref 26) was used for quantification. Acetone concentration was determined using a DB-624 capillary column (30.0 m × 530 μm × 3.00 μm) and a thermal conductivity detector at 250 °C, with an oven temperature program: 60 °C to 100 °C at 10 °C/min; 100 °C for 4 min; 100 °C to 200 °C at 40 °C/min; 200 °C for 2 min.

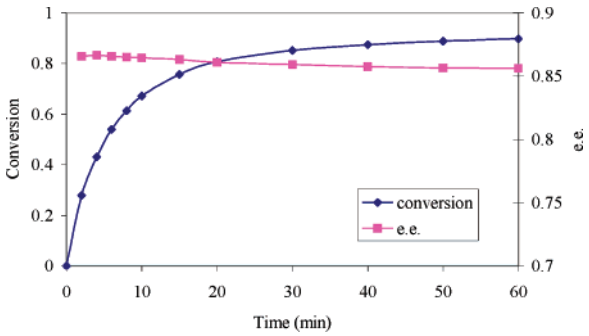


Figure 1. **Conversion and enantioselectivity vs reaction time for the base case experiment. Reaction conditions: temperature, 10 °C; [substrate] = 0.14 M; [substrate]/[catalyst] = 1000; nitrogen flow rate = 800 mL/min.**

The conversion of acetophenone was estimated as

$$\text{conversion} = \frac{[\text{Ap}]_0 - [\text{Ap}]}{[\text{Ap}]_0} = \frac{[R] + [S]}{[\text{Ap}] + [R] + [S]}$$

where, $[\text{Ap}]_0$ is initial acetophenone concentration, [Ap] is acetophenone concentration, [*S*] is (*S*)-1-phenylethanol concentration, and [*R*] is (*R*)-1-phenylethanol concentration.

The product enantioselectivity was characterised using enantiomeric excess (ee):

$$ee = \frac{[S] - [R]}{[S] + [R]}$$

Turnover frequency (TOF) was calculated from

$$\text{TOF} = \frac{n_{\text{product}}}{n_{\text{catalyst}} \cdot \text{time}}$$

where n_{product} is the number of moles of the product ((*S*)-1-phenylethanol and (*R*)-1-phenylethanol), n_{catalyst} is the number of moles of the catalyst, and time is the reaction time.

3. Results and Discussion

3.1. Base Case Experiment. Conversion and ee as a function of time for the base case experiment are shown in Figure 1. It can be seen that the initial reaction rate is very fast. Conversion reaches 80% in 20 min and 90% in 60 min. The average TOF is 2339 hr^{-1} and 905 hr^{-1}, respectively. The reaction continued after 60 min, and the conversion reached 97% in 240 min. The initial enantioselectivity obtained is 86.6%, and afterwards it decreased with time to 85.1% after 240 min. Carrying out the base case experiment 4 times, we established that ee was reproducible within ±0.1% and conversion was reproducible within ±1.3%. Four injections were made for one sample to check the analysis. The analysis error on ee was within ±0.1% and on conversion within ±0.07%. Other researchers have used different catalysts for the same reaction. Hashiguchi et al.[16] obtained (*S*)-1-phenylethanol with 97% ee and 95% yield using a 0.1 M solution of acetophenone in 2-propanol containing the in situ prepared Ru catalyst (*S*/*C* = 200) and

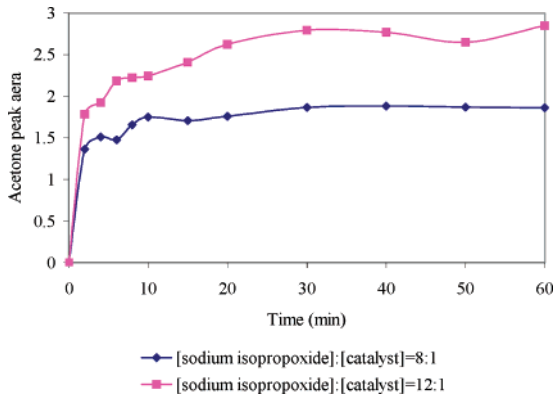


Figure 2. **Acetone concentration vs time in the absence of acetophenone at various sodium isopropoxide/catalyst precursor ratios.**

Scheme 2

1	+ *(1/2)* **2**	⇌	**3** + **HCl**	(step 1)
HCl	+ **sodium isopropoxide**	⇌	**NaCl** + **IPA**	(step 2)
3	+ **sodium isopropoxide**	⇌	**4** + **NaCl**	(step 3)

KOH (5 equiv to Ru atom) at room temperature in 15 h. Palmer et al. (ref 23) obtained (*S*)-1-phenylethanol in 70% isolated yield and 91% ee in 1.5 h with 1 mol % of (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol in conjunction with 0.25 mol % of the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and 2.5 mol % of KOH in 2-propanol ([ketone] = 0.1 M) at room temperature. The rhodium catalytic system in this work gives a faster reaction rate, although a slightly lower ee is obtained.

3.2. Blank Experiments in the Absence of Substrate. According to Noyori's mechanism (ref 21), acetone can be formed even without addition of substrate during formation of the metal hydride. In fact Haack et al.[14] isolated the hydride and confirmed its catalytic activity. Formation of acetone (and hence formation of the metal hydride) without closing the catalytic cycle was also confirmed in this work.

First, in preliminary experiments it was observed that mixing of precursor **3** and acetophenone does not initiate any chemical reactions. Only after the addition of sodium isopropoxide, the presence of acetone and phenylethanol was detected. Second, mixing of precursor **3** and sodium isopropoxide with IPA in the absence of acetophenone generated traces of acetone. Two experiments in the absence of substrate were conducted using two ratios of sodium isopropoxide: precursor **3**, namely 12:1 and 8:1. Peak areas of acetone measured with GC are given in Figure 2 as a function of time. Due to the low concentrations, accurate absolute quantification of acetone concentration was not possible. However, it is obvious that acetone concentration increased with increasing sodium isopropoxide amount. Theoretically, an amount of 2 equiv of sodium isopropoxide is enough to form an equivalent of active catalyst species **4** (Scheme 2). One equivalent is required to neutralise the HCl formed during the reaction forming precursor **3** and another equivalent is required to deprotonate the precursor **3** to form the active catalyst species **4**. However, the concentration of the catalytic species generated in situ remains unknown. It is reasonable to assume that the formation reactions of the active catalyst complex **4** are relatively fast, so an equilibrium

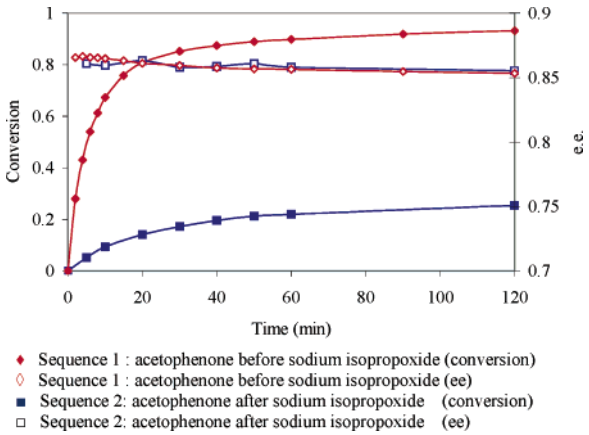


Figure 3. **Effect of addition sequence of catalyst/acetophenone/sodium isopropoxide solutions on conversion and enantioselectivity.**

is established quickly between catalyst precursor and active complex. Increasing sodium isopropoxide amount should first increase HCl consumption (Scheme 2, step 1) increasing the amount of precursor **3**, which in turn shifts the equilibrium of step 3 (Scheme 2) towards generating more active catalytic species **4**. Obviously, higher concentration of active catalytic species **4** increases the concentration of formed acetone as experimentally observed (see Scheme 1).

3.3. Influence of Addition Sequence of Reactants and Catalyst Solutions. The influence of an addition sequence was another factor investigated. Catalytic precursor **3** was made in both cases in situ. The procedure for sequence 1 consisted of mixing catalyst precursor **3** and acetophenone in IPA and, after 30 min of stirring, adding sodium isopropoxide solution. The sequence 2 procedure consisted of mixing catalyst precursor **3** and sodium isopropoxide in IPA and, after 30 min of stirring, adding acetophenone. Conversion and enantioselectivity obtained from each addition sequence are shown in Figure 3.

It can be seen that the effect of addition sequence is significant on the conversion of acetophenone. Conversion for sequence 2 increases much slower than conversion for sequence 1. In 60 min, conversion for sequence 1 reached almost 90%, while conversion for sequence 2 was just over 20%.

A possible reason of the effect of addition sequence on conversion is the following. In sequence 2, the active catalyst species **4** and catalyst intermediate **5** had been formed before addition of acetophenone, enhancing the extent of competitive reactions such as dimerisation which can form inactive compounds and limit the amount of rhodium available for transfer hydrogenation (ref 13). Another possible reason is that the central rhodium atom might combine with isopropoxide first, causing a loss of the catalyst ability to coordinate with acetophenone. Hence, the catalyst activity would decrease after staying with sodium isopropoxide for a long time. There was no obvious effect of addition sequence on enantioselectivity (Figure 3), consistent with the above hypothesis that sodium isopropoxide affects only the amount of active catalyst present.

Since the conversion of acetophenone was greatly affected by the addition sequence, with sequence 1 resulting in higher

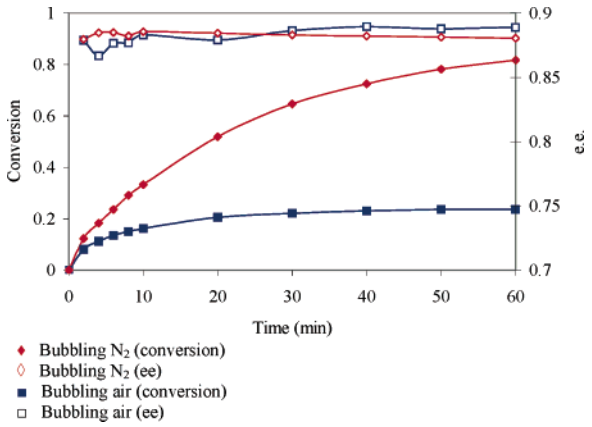


Figure 4. **Effect of presence of air on conversion and enantioselectivity. All experimental conditions were the same as the base case, except temperature was 15 °C and air was bubbled through the reaction mixture.**

conversion, the rest of experiments were carried out by mixing catalyst solution and acetophenone prior to adding sodium isopropoxide solution.

3.4. Effect of Presence of Air. The asymmetric transfer hydrogenation is operated under inert atmosphere, usually N_2. An experiment was conducted to investigate the influence of air presence on the activity of the catalytic system by bubbling air (800 mL/min) instead of N_2 into the reaction system. As can be seen from Figure 4, in the presence of air, 25% conversion was obtained compared to 95% with N_2 in 60 min. This suggests that catalyst might deactivate/decompose in the presence of air. However, there is still active catalyst available. The reaction sample was left for 1 week in the presence of air. The conversion went up to 58% and stabilised in another 2 weeks. The enantioselectivity of the catalyst was not affected by the presence of air. Although catalytic activity decreased, ee in both cases was 88% after 60 min.

3.5. Effect of Temperature. Experiments were conducted under different temperatures to study the effect of temperature on catalyst activity/selectivity. The results are shown in Figure 5 in terms of conversion (Figure 5a) and ee (Figure 5b). It can be seen that with increasing reaction temperature, the initial reaction rate increased as expected. However, ee decreased slightly. From 0 °C to 30 °C, the conversion increased with temperature. At 40 °C albeit the faster initial reaction rate, the conversion level dropped below that at 30 °C and leveled after 10 min, so that at 60 min it dropped below the value measured at 15 °C, indicating catalyst deactivation. It can be concluded that 30 °C represents an optimum temperature with high reaction rate and good catalyst stability. Consequently, 30 °C was selected for the experimental studies. While in this work ee changed from 89% to 85% (in 60 min) for a temperature range 0 to 40 °C, a much larger and qualitatively different influence of temperature on ee has been observed by other researchers. Wills et al.[29] observed a change of ee to S-product from 13.5% to 94.4% for the reduction of α-chloroacetophenone by phosphinamide for the temperature range 40 to 110 °C.

(29) Wills, M.; Gamble, M.; Palmer, M.; Smith, A.; Studley, J.; Kenny, J. *J. Mol. Catal. A: Chem.* **1999**, *146*, 139.

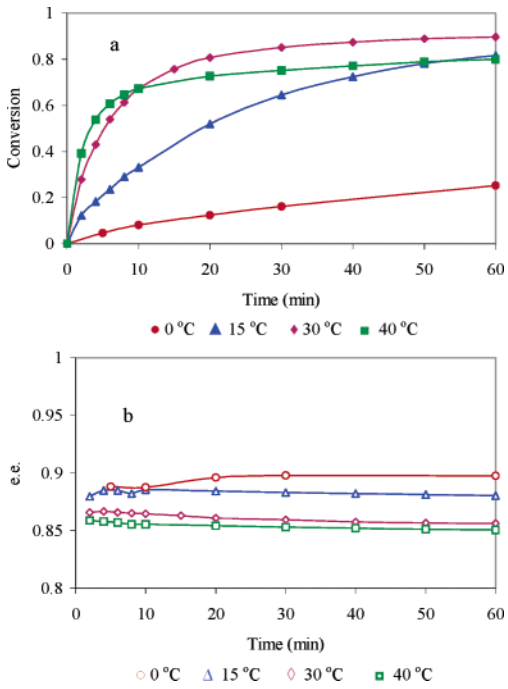


Figure 5. **Effect of temperature on conversion and enantioselectivity. (a) Conversion vs time for different temperatures. (b) Enantiomeric excess vs time for different temperatures.**

Zassinovich et al.[30] observed a change of ee from 2.2% to 24.9% for the range 65 to 83 °C for the reduction of acetophenone by $[Rh_2(ac)_4 \cdot 4H_2O]$ and (+)-(*S*)-3-*sec*-butyl-1,10-phenanthroline.

3.6. Effect of Acetone Concentration. If the reaction steps in Scheme 1 are reversible, removal of acetone is expected to affect reaction equilibrium. Consequently, we studied the effect of acetone concentration on reaction performance by adding acetone into the reaction mixture before starting the reaction. Experiments were run at different initial acetone concentrations in the range 0 to 0.5 M.

The results in terms of conversion vs initial acetone concentration are presented in Figure 6a for selected reaction times. Figure 6b represents ee as a function of conversion for different initial acetone concentrations used, while Figure 6c gives acetone concentration profiles. The results show that conversion decreased with increasing initial acetone concentration (Figure 6a). Although ee was not affected in the range 0 to 0.1 M throughout the whole conversion range, when initial acetone concentration was further increased to 0.5 M, ee decreased significantly at high conversions (Figure 6b). For 0.5 M initial acetone concentration, conversion increased from 52.8% to 60.0% from 180 min to 520 min, and ee dropped from 86.1% to 84.0%. Because of fast initial reaction rate, acetone concentration increased in the first 20 min for the range of initial acetone concentration 0M to 0.1M. Afterwards, it decreased slightly due to N_2 bubbling (Figure 6c).

Our results suggest that acetone presence inhibits the reaction and does not have a significant effect on enantioselectivity at least initially. The lower ee was obtained with 0.5 M acetone initial concentration. The possible reason

(30) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, 1051.

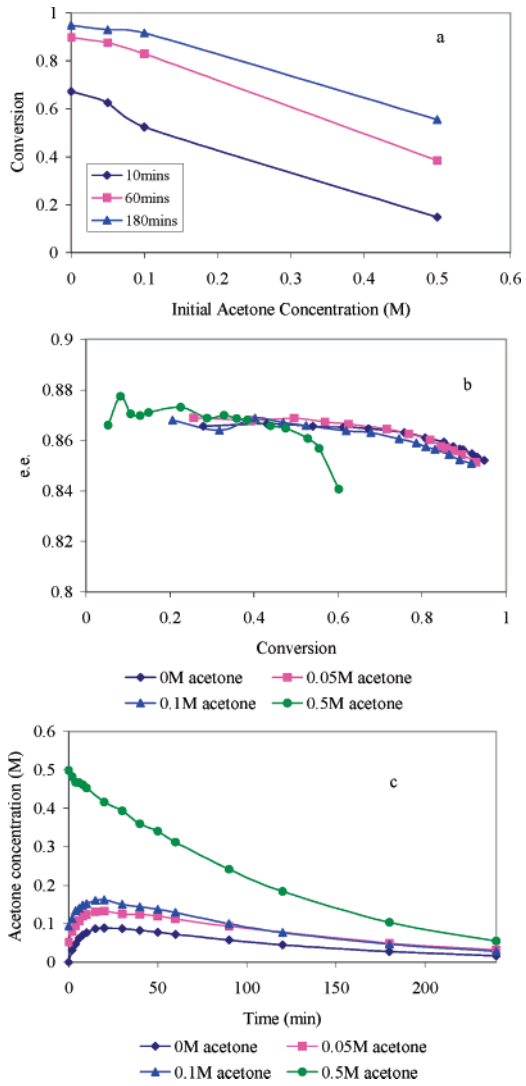


Figure 6. **Effect of initial acetone concentration on reaction performance. (a) Conversion at selected reaction times as a function of initial acetone concentration. (b) Enantiomeric excess vs conversion for different initial acetone concentrations. (c) Acetone concentration vs time for different initial acetone concentrations.**

might be that the reaction rate became slower with higher acetone initial concentration, and prolonged exposure of the product to the catalyst favored the reverse reactions (ref 20). de Bellefon and Tanchoux[8] observed that acetone inhibits the reaction as well that for the [Rh(1,5-cyclooctadiene)-Cl]$_2$/(1*S*,2*S*)-(−)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethanediamine catalyst system. However, increase of ee from 60% to 80% was observed when the initial acetone concentration increased from 0 to 0.9 kmol/m^3.

3.7. Effect of Catalyst Concentration. The effect of catalyst concentration on conversion and enantioselectivity was further investigated. The initial substrate concentration was kept constant (0.14 M), while the catalyst/substrate ratio was increased from 1:1000 to 2:1000. Conversion and ee obtained for the different catalyst/substrate ratios are plotted in Figure 7. It can be seen that conversion of 90% was obtained after 10 min using ratio of 2:1000 and after 30 min using a ratio of 1:1000. Enantiomeric excess decreased slightly from 86.5% using a ratio of 1:1000 to

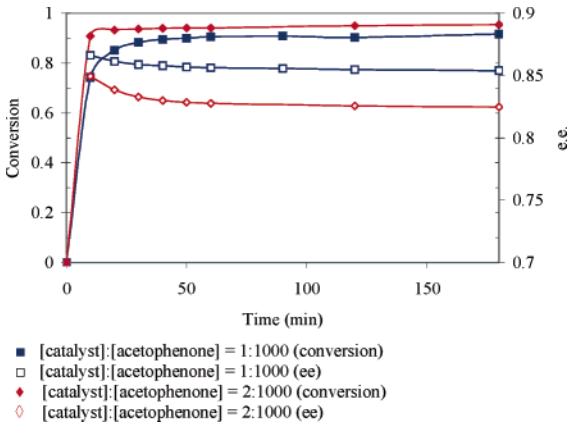


Figure 7. **Effect of catalyst concentration on conversion and enantioselectivity at constant substrate concentration.**

85.0% using a ratio of 2:1000 at 10 min and further decreased from 85.5% to 82.1% at 180 min, respectively.

The results show that conversion increased with catalyst concentrations as expected. The enantioselectivity slightly decreased with an increase of catalyst concentration. Gamez et al.[12] observed that conversion increased with an increase of catalyst concentration but enantioselectivity was not notably affected for the catalytic system [Rh(C_6H_{10})Cl]$_2$ (as catalytic precursor) and C_2 symmetric chiral diamines (as ligand) at 0.016 M substrate concentration and 82 °C temperature. On the other hand, Gladiali et al.[13] observed a decrease of ee as the amount of catalyst increased for the system [Rh(hd)Cl]$_2$ and chiral phenanthrolines with 0.16 M acetophenone in 2-propanol.

3.8. Effect of Initial Substrate Concentration at Constant Catalyst Concentration. In this series of experiments, the catalyst concentration was kept constant, while the substrate concentration varied over a range of 0.07 to 0.28 M. The results obtained in terms of conversion and enantioselectivity are given in Figure 8. At low substrate concentrations, much higher conversion was obtained (see Figure 8a) indicating that the reaction cannot described by a simple first-order kinetics. Figure 8b indicates that higher ee is obtained for smaller substrate concentrations at the same conversion. However, if one plots ee vs *S*-(1)-phenylethanol concentration (see Figure 8c), it is evident that when the same amount of product is required, it is better to operate at high substrate concentrations. In this way, if one operates far from equilibrium, forward reactions are enhanced and reverse reactions are minimised.

3.9. Effect of Initial Substrate Concentration at Constant Substrate/Catalyst Ratio. From a cost point of view, a high substrate concentration would be advantageous. Keeping the catalyst/acetophenone ratio constant, we conducted experiments with high acetophenone concentration. The results in terms of conversion vs time are given in Figure 9a, while Figure 9b shows ee as a function of conversion for different initial substrate concentrations.

There was no significant effect on the final conversion when the initial acetophenone concentration was increased from 0.14 M to 0.40 M (Figure 9a). Final ee dropped considerably from 85.2% at 0.14 M to 80.1% at 0.4 M initial acetophenone concentration. When acetophenone concentra-

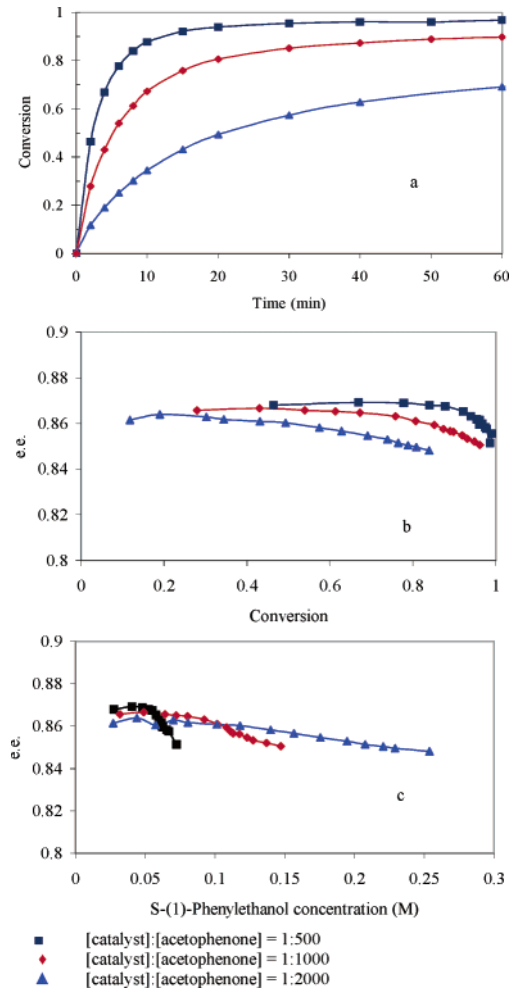


Figure 8. **Effect of substrate concentration on conversion and enantioselectivity at constant catalyst concentration. (a) Conversion vs time for different initial substrate concentrations. (b) Enantiomeric excess vs conversion for different initial substrate concentrations. (c) Enantiomeric excess vs *S*-(1)-phenylethanol concentration for different initial substrate concentrations.**

tion was further increased to 1 M, both conversion and enantioselectivity exhibited a significant drop. At 1 M initial acetophenone concentration, final ee dropped to 73.2% at 180 min.

The behaviour demonstrated in Figure 9 for increasing substrate concentration at constant catalyst/substrate concentration ratio is very similar to that in Figure 8 for increasing substrate concentration at constant catalyst amount. As observed in Figure 9c for certain *S*-(1)-phenylethanol concentration, the more concentrated (in substrate) solution provides higher ee. However, if high conversions are required, the more dilute (in substrate) solutions provide better final ee (Figure 9b). This is probably associated with higher equilibrium conversions for lower substrate concentrations (ref 20) as also indicated by Figure 9a.

4. Conclusions

The catalyst obtained when pentamethylcyclopentadienylrhodium chloride dimer is combined with 1*R*,2*S*-aminoindanol gives fast reaction rate of asymmetric transfer hydrogenation of acetophenone, with enantioselectivity decreasing with conversion at a level depending on catalyst

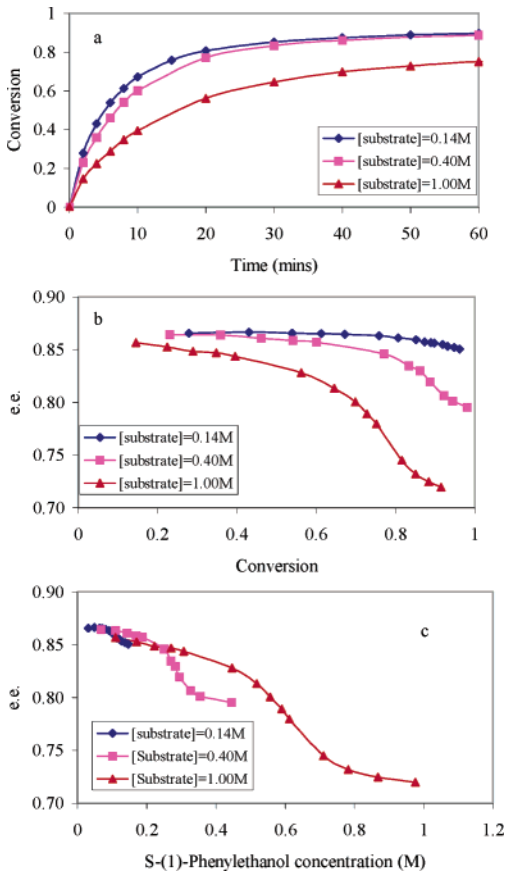


Figure 9. **Effect of substrate concentration on conversion and enantioselectivity at constant catalyst/substrate ratio. (a) Conversion vs time for different initial substrate concentrations. (b) Enantiomeric excess vs conversion for different initial substrate concentrations. (c) Enantiomeric excess vs *S*-(1)-phenylethanol concentration for different initial substrate concentrations.**

and substrate concentrations. The sequence of reactant addition was found to affect reactant conversion. When the experiment was carried out in air atmosphere, catalyst deactivation was observed. Increasing the amount of catalyst and temperature had detrimental effects on enantioselectivity. Temperature increase beyond 30 °C led to a decrease in conversion, possibly due to catalyst deactivation. Increasing reactant concentration led to a decrease in conversion and enantioselectivity. Adding acetone to the initial reaction mixture inhibited conversion but did not have a significant effect on initial enantioselectivity. The results indicate that a decrease of ee is primarily due to reverse reactions which are favoured at high product concentrations. Overall, this catalyst provides a more economic process than most others, is easily prepared, and gives a consistent high quality product. It is economic because of the cost of the catalyst (low usage, cheap ligand, and readily made) and the space/time yield in which the product can be made.

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