Organic Process Research & Development **2006**, *10,* 457–463

Kinetic Studies of the Asymmetric Transfer Hydrogenation of Imines with Formic Acid Catalyzed by Rh−Diamine Catalysts

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Abstract:

Kinetic studies of the asymmetric transfer hydrogenation of imines with HCOOH using Rh−chiral diamine catalysts reveal anomalous concentration dependences attributed to the participation of both reactant and product in the formation of formate salts. The resting state of the catalyst is suggested to be the Rh hydride species 5. The role of bases such as Et_3N in metering HCOOH into the catalytic cycle is discussed. A practical reaction protocol for achieving high productivity based on slow addition of HCOOH is presented. These studies highlight the value of in situ reaction monitoring techniques in developing a detailed mechanistic picture of a complex reaction system.

Introduction

Asymmetric hydrogenation of C═O and C═N groups via transfer of hydrogen from an organic molecule has come under recent attention as an attractive alternative to reduction using gaseous hydrogen. Ru, Rh and Ir precursor complexes together with chiral diamine ligands have been shown to effect these reactions in high enantioselectivity and high efficiency.[1] Noyori and co-workers[2] have studied the mechanism of the reaction for ketones with both simple alcohols and formic acid as the source of hydrogen, and they were the first to propose that the reaction proceeds outside the coordination sphere of the metal. Such a concerted mechanism involving the transfer of both a metal hydride and a ligand proton has been supported by theoretical studies.[3] In addition, DFT (density functional theory) calculations[4] and deuterium-labeling studies[5] for ketone substrates suggested a similar mechanism for transfer hydrogenation and dehydrogenation reactions carried out using hydroxyclopentadienyl ligands.

However, the mechanism for the transfer hydrogenation of imines remains unexplored, although commercial processes using this technology have been developed successfully.[6] We report herein the first detailed kinetic studies of the asymmetric transfer hydrogenation of imines with formic acid using Rh−chiral diamine catalysts (Scheme 1). These studies suggest that under reaction conditions the resting state of the active catalyst is the metal hydride **5** (Scheme 2). Although mechanistic analogies may be drawn between C═O and C═N transfer hydrogenation systems, the increased basicity of the imine/amine system compared to ketone/alcohol systems can lead to intriguing behavior. Observed anomalies between initial rates and reaction progress kinetic behavior for reactions carried out in methanol is reconciled by taking into consideration the multiple acid−base equilibria that exist in this reaction environment. The deactivating effect of high concentrations of formic acid is documented, as well as the role of Et_3N in ameliorating this effect. We show that the rate behavior is a strong function of the reaction protocols, including the type of solvent and the method of addition of the transfer agent. A reaction protocol involving controlled dosing of formic acid is suggested for achieving high yields at high catalyst/substrate ratios.

Results and Discussion

Scheme 2 shows a proposed reaction mechanism for the transfer hydrogenation of imines based on analogy to the proposed concerted metal-hydride mechanism proposed for ketone substrates.[2] One of the special features of the imine-formic acid system is the acid−base equilibria that exist peripheral to the catalytic cycle. NMR studies show that under the reaction conditions of 1 M formic acid/0.4 M triethylamine in methanol, both the imine **1** and the amine **3** concentrations are strongly shifted to the protonated species **1′** and **3′** respectively. In addition, Et_3N is essentially fully protonated under these conditions. These equilibria help to dictate the instantaneous concentration of both formic acid and imine **1**.

In situ formation of the catalyst precursor **2** from the reaction of $(Rh(cp)Cl_2)_2$ and 1,2-diphenyl-1-tosyl-2-aminoethane is followed by reaction with base to remove HCl to afford the active catalyst species **4**. It is suggested that formic acid adds irreversibly to form the metal hydride **5**, which undergoes concerted transfer of the hydride and the N−H

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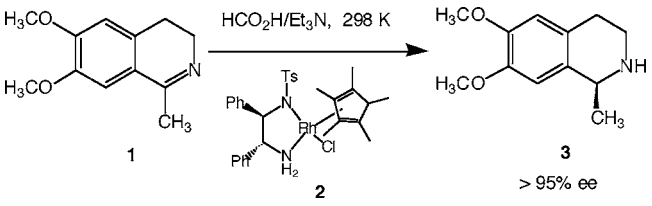
10.1021/op060033k CCC: $33.50
Published on Web 04/20/2006

Scheme 1. **Asymmetric transfer hydrogenation of 3,4-dihydro-6,7-dimethoxyisoquinoline (1) using formic acid as the hydrogen transfer agent and catalyst 2**



proton to afford the amine product. No erosion of ee with conversion was observed in our studies, supporting the suggestion of the irreversibility of the cycle. However, the potential for catalyst poisoning in side reactions that form CO has been noted.[7]

A series of reactions was carried out in methanol using a fixed initial concentration of formic acid of 1 M (HCOOH/Et_3N = 5:2) while varying other concentration variables. The reaction was found to exhibit first-order kinetics in [Rh]. Reactions were monitored by in situ FTIR spectroscopy for a range of initial concentrations of [**1**] as shown in Figure 1. Initial rates indicate that the reaction exhibits first-order kinetics in [imine] over the entire concentration range.

When reaction progress curves of these reactions are studied, however, a more complex scenario unfolds. Intriguingly, as the reaction progressed, those reactions carried out at the highest initial concentrations of imine did not continue to exhibit the first-order behavior shown in Figure 1. As shown in Figure 2, the reaction rate for $[\text{imine}]_0 = 0.25$ M proceeded with ca. *zero*-order kinetics in imine until over 90% conversion was attained.[8] Thus, as the reaction at high imine concentration progressed, the experimental rate at any given point was significantly *higher* than would have been predicted from the initial rates.

An explanation for the anomalous zero-order kinetic behavior at high $[\mathbf{1}]_0$ invokes the delicate balance in the various acid−base equilibria in the system that dictate the "true" concentration of imine available to undergo the reaction. At the outset of the reaction, the equilibria between formic acid and both Et_3N and the imine are shifted strongly toward the protonated species, decreasing the concentration of free formic acid accordingly. The system strives to maintain these equilibria as the reaction proceeds, during which time HCOOH is consumed as the amine product **3** is formed. This amine also begins to compete for HCOOH because the **3**−**3′** equilibrium is shifted strongly toward **3′**.[9] Thus, as conversion increases, an increasing fraction of the remaining free formic acid becomes occupied in formation of the aminium salt. This decrease in free [HCOOH] in turn shifts the imine/iminium salt equilibrium back toward the free imine. Thus, the imine salt **1′** serves as a "reservoir", slowly feeding the imine **1** into the catalytic cycle over the course of the reaction such that a constant concentration of **1** is maintained, with the result being that apparent zero-order kinetics in imine are observed.

This effect on "true" imine concentration was not observed for the reactions carried out at the lowest initial imine concentrations, which exhibited the expected first-order kinetics throughout the course of the reaction. This is because the perturbation caused in the overall HCOOH concentration over the course of the reaction, and therefore the extent of the effect on imine concentration, is minimal for reactions carried out at low initial imine concentration. We may quantify this by comparing how the concentration of free formic acid shifts over the course of the reaction for cases of low and high initial imine concentrations. Taking into account the HCOOH consumed in the reaction and in the formation of the salts **1′**, **3′**, and $Et_3NH^+COO^-$, we find, for example in the reaction shown in Figure 2a at $[\mathbf{1}]_0 = 0.25$ M, that the concentration of free formic acid shifts by nearly a factor of 4 over the course of the reaction. In contrast, for the reaction shown in Figure 2b at $[\mathbf{1}]_0 = 0.1$ M, [HCOOH] changes by only 20%, thus remaining in the formic acid buffer region throughout the reaction.

This role for the amine **3** in perturbing the **1**−**1′** equilibrium concentrations suggests that addition of **3** to the initial reaction mixture should increase the reaction rate by causing an increase in the effective imine concentration. Experiments were carried out by adding amine to the initial reaction mixture. As shown by comparing the slopes of the reaction progress curves in Figure 3, the presence of added amine clearly accelerates the reaction rate: a reaction carried out at 0.25 M initial imine concentration gives the same rate as a reaction carried out at 0.19 M $[\mathbf{1}]_0$ with [0.06 M [**3**] added. The rate for these reactions was 22% higher than that observed for a reaction carried out with $[\mathbf{1}]_0 = 0.19$ M with no added amine. This finding is consistent with the proposal that protonation of the more basic amine by HCOOH accelerates the rate by freeing imine to enter the catalytic cycle.

These results suggest that other basic species that can react with HCOOH may also shift the imine/iminium equilibrium toward imine and thus enhance the rate of reaction. This proposal was probed by studying the effect of Et_3N concentration on reaction rate, while holding initial [HCOOH] and [**1**] constant. Figure 4 shows that increased concentrations of Et_3N indeed resulted in faster rates of reaction. Strikingly, reactions carried out using Et_3N concentrations even *twice* that of the initial [HCOOH] continue to show enhanced rates, more than double that of the reaction carried out using standard azeotropic 5:2 ratio of [HCOOH]/[Et_3N]. Et_3N appears to be effective at tying up free HCOOH, thus suppressing iminium salt formation, but in a way that allows release of HCOOH as needed to react in the catalytic cycle.

These results indicate that higher productivity results from keeping the free formic acid concentration as low as possible.

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(8) For a reaction that is first order in substrate concentration, with rate constant k, the relationship between conversion, x, and time is given by: $x = 1 - e^{-kt}$ which shows that conversion is not a function of the initial substrate concentration. Therefore plots of x vs time should overlay for reactions carried out at different initial substrate concentrations. Figure 2 shows that these plots overlay up until ca. 20% conversion for reactions at high and low $[\mathbf{1}]_0$, after which point the curve in part (a) exhibits zero-order kinetics.

(9) Although amines are generally more basic than imines due to the increased p character of the sp^3 nitrogen, mesomeric effects render the imine **1** particularly strongly basic and thus potentially a better competitor for HCOOH than might be expected for most imine−amine combinations. As shown in the Experimental Section, however, NMR studies of a mixture of equal concentrations of the amine **3** and the formate salt of the imine **1′** showed a complete shift to the amine salt **3′**, showing conclusively that in methanol the amine **3** remains significantly more basic than the imine **1**.

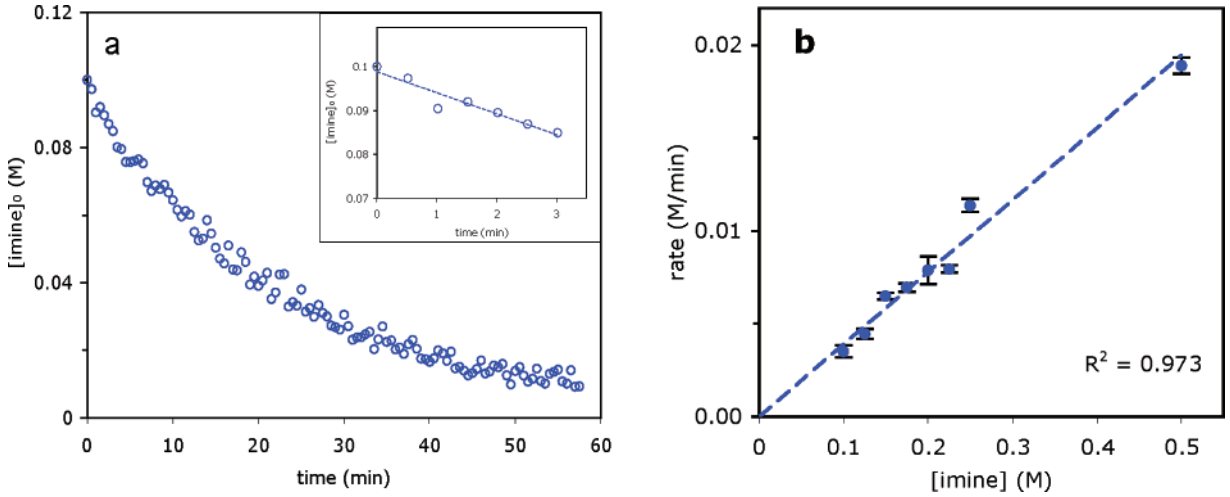
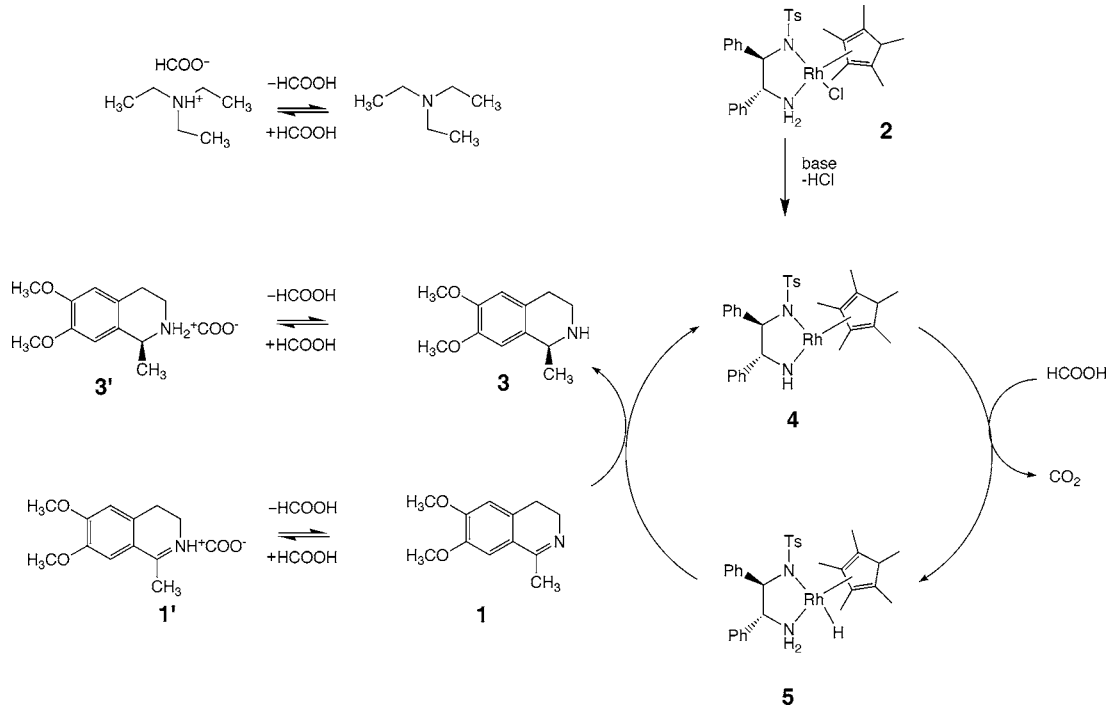


Figure 1. **(a) FTIR spectrum of the reaction progress of the reaction in Scheme 2 carried out at $[HCO_2H]_0 = 1$ M, $[1]_0 = 0.15$ M, $[2]_{total} = 0.002$ M. (Inset) Initial rate calculated from slope. (b) Initial rate vs $[1]_0$ for reactions carried out with varying initial imine concentrations. Standard deviations in the values for the individual points derived from initial rates are shown.**

Scheme 2



This suggests a reaction protocol in which formic acid is dosed into the system slowly over time rather than adding one large aliquot at the beginning of the reaction. The results of such dosing experiments are shown in Figure 5 for reactions carried out at 0.25 M $[\mathbf{1}]_0$ and two different concentrations of Et_3N. At the higher level of Et_3N (Figure 5a), the reaction begins slugglishly but then accelerates rapidly such that total conversion is achieved by the time the formic acid dosing is completed, suggesting that formic acid is being consumed as rapidly as it is introduced into the system. The reaction is initially faster with lower $[Et_3N]$ under dosing conditions (Figure 5b), and the reaction rate parallels the rate of dosing until higher conversions are reached, where the observed slowdown in reaction rate is likely due to the beginning of [HCOOH] buildup and the concomitant decrease in [**1**] as **1′** is formed.

In both cases shown in Figure 5, the reaction is more efficient with HCOOH dosing than it is under conditions where HCOOH is added in one aliquot at the beginning of the reaction. This increased productivity is especially clearly demonstrated in the case of low $[Et_3N]$ in Figure 5b. This result coupled with that of Figure 4 highlights the important role of Et_3N in these reactions. The $Et_3NH^+ \cdot HCOO^-$ salt serves as a reservoir for metering HCOOH into the catalytic cycle as required, helping to minimize the formation of the iminium salt that is deleterious to the reaction rate. These observations, which suggest that the reaction rate is sensitive to the concentration of **1** but is *not* sensitive to the concentration of HCOOH, allow us to add more detail to the mechanism proposed in Scheme 2. Lack of rate dependence on [HCOOH] suggests saturation kinetics in this substrate, implying that the hydride species **5** is the resting

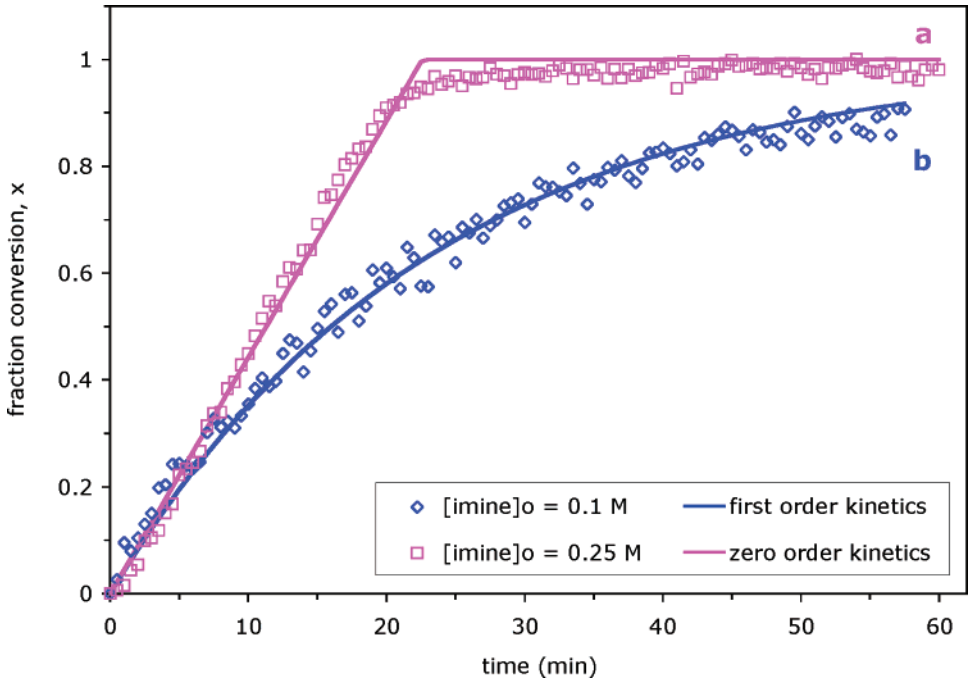


Figure 2. **Reaction progress curves showing fraction conversion of imine 1 vs time in the asymmetric transfer reaction in methanol solvent with $[HCO_2H]_0 = 1$ M, $Et_3N = 0.4$ M; $[2]_{total} = 0.002$ M (Scheme 6). (a) red □ = experimental data; red — = fit of $[1]_0 = 0.25$ M data to zero-order kinetics; (b) blue ◇ = experimental data, blue — = fit of $[1]_0 = 0.10$ M data to first-order kinetics.**

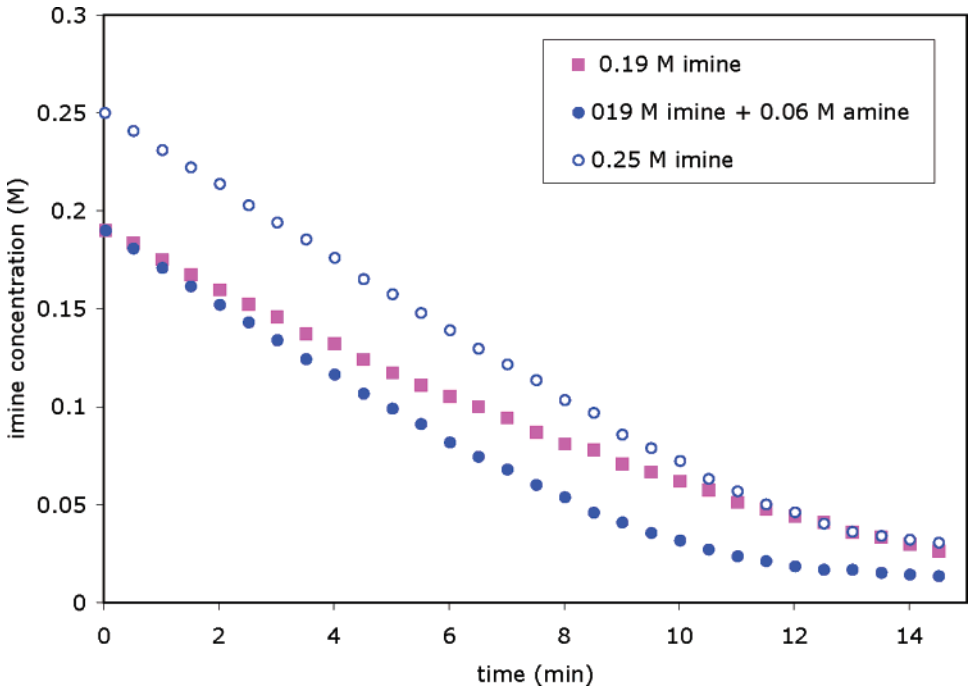


Figure 3. **Imine concentration vs time for reactions carried out at different initial imine concentrations with and without added amine product as indicated in the legend. Blue ● $[imine]_0 = 0.19$ M, no product added; Red ■ $[imine]_0 = 0.19$ M, 0.6 M product added; blue ○ $[imine]_0 = 0.25$ M, no product added.**

state in the catalytic cycle. Rate determining concerted hydride and proton transfer from **5** to the imine is consistent with positive order dependence on [**1**]. Thus the experimental data suggest that the rate law for the catalytic cycle in Scheme 2 may be written as:

$$\text{rate} = \frac{V_{max}[\mathbf{1}][HCOOH][\mathbf{2}]}{K + [HCOOH]} \approx V_{max}[\mathbf{1}][\mathbf{2}]$$

The parameter K is related to the inverse ratio of the formation of **5** to its consumption and is small compared to [HCOOH]. In addition, K will depend on the equilibrium relationships for the acid−base reactions of HCOOH, which must be determined if the "true" concentration of [**1**] is to be known. ^{1}H NMR spectra of the imine dosed with consecutive 0.5-equiv aliquots of formic acid showed no further shifts after 1 equiv of HCOOH. We can estimate the equilibrium constant for iminium ion formation to be at least 10 M^{-1}.

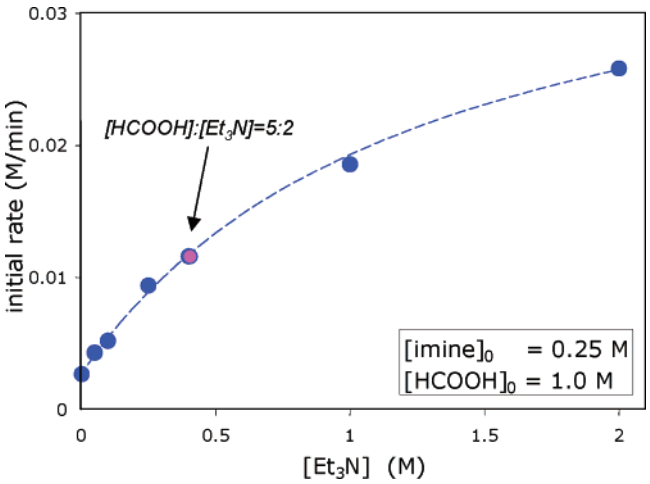


Figure 4. **Initial rate vs [Et_3N] for reactions carried out with $[1]_0 = 0.25$ M, $[HCOOH]_0 = 1.0$ M, and different [Et_3N].**

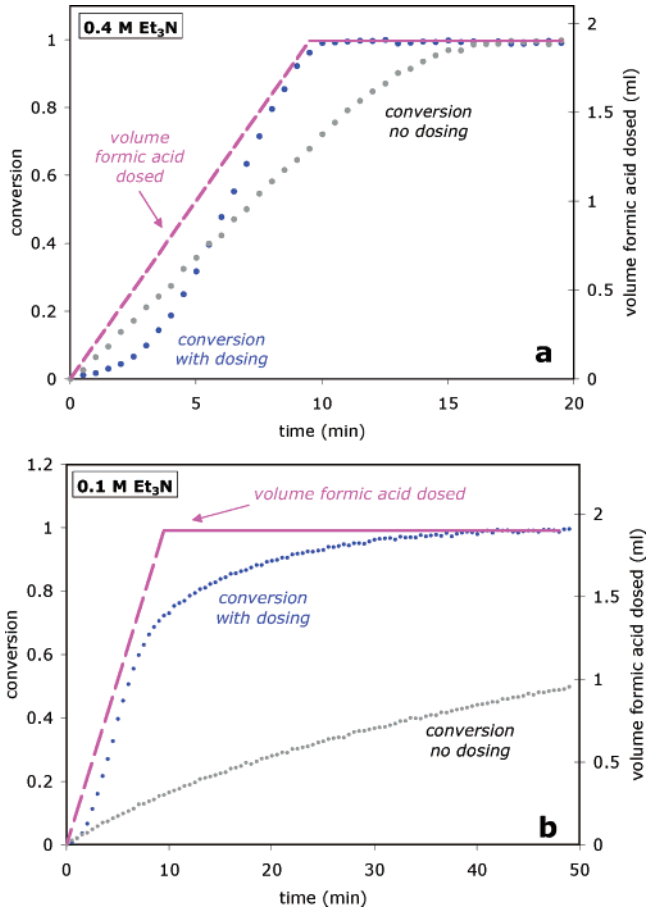


Figure 5. **Conversion vs time (left axis) for reactions in which formic acid is dosed slowly into the system over time (dashed pink line, right axis). $[1]_0 = 0.25$ M; total HCOOH added is equivalent 1 M; (a) 0.4 M Et_3N; (b) 0.1 M Et_3N. The grey symbols show the conversion vs time curves for the cases where HCOOH was added in a single aliquot at the beginning of the reaction.**

All of these reactions described thus far were carried out using methanol as solvent. Figure 6 shows the results of reactions carried out in other solvents, both polar and nonpolar, protic and nonprotic, under standard reaction conditions (1 M HCOOH (5:2 [HCOOH]:[Et_3N]), 0.25 M **1**, [substrate]/[catalyst] = 200). Other than water, where the reaction does not proceed at all, other solvents investigated exhibited faster initial rates than similar reactions carried out in methanol. In isopropyl alcohol, ether, and acetone, the reaction did not reach completion. Very rapid reaction rates were observed in acetonitrile and methylene chloride. However, when the reaction was attempted at higher substrate/catalyst ratios, only reactions in methanol exhibited high conversions. Irreversible catalyst deactivation is suggested as the cause of the stalled reactions in other solvents, as illustrated in Figure 7 for reaction in acetonitrile. At a substrate/catalyst ratio of 500, the reaction stalls after 100 turnovers. Additional aliquots of catalyst revive activity only to see the reaction stall again following a similar number of turnovers.

Conclusions

In situ reaction monitoring helped to reveal intriguing reaction behavior over the course of asymmetric transfer hydrogenation reactions using HCOOH as the transfer reagent. A detailed mechanistic picture emerges in which the acid−base equilibria peripheral to the catalytic cycle must be taken into consideration. A practical reaction protocol involving slow addition of HCOOH is proposed for achieving high productivity. A kinetic rate law is proposed based on the Rh hydride species **5** as the catalyst resting state. The role of bases such as Et_3N in mediating the concentration of free HCOOH is discussed.

Experimental Section

Methods. The reaction solvent methanol [HPLC grade, Fisher Chemicals] was prepared by purging with argon for 30 min. TEAF was prepared by the dropwise addition of distilled triethylamine [148 mL, 107.45 g, 1.06 mol] to formic acid [100 mL, 122.00 g, 2.65 mol] with rapid stirring. The precatalyst solution was prepared by adding methanol [2.5 mL: HPLC grade, Fisher Chemicals] and dichloromethane [0.5 mL: SLR grade, Fisher Chemicals] to the precatalyst components [0.0371 g, 0.0600 mmol, 0.0200 M, dichloro-(pentamethylcyclopentadienyl) rhodium(III) dimer; Strem Chemicals: 0.0439 g, 0.1198 mmol, 0.0399 M (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-diphenylethylenediamine; Aldrich]. This solution was purged with argon for 10 min prior to injection to the reaction mixture.

Instrumentation and Software. The IR reaction spectra were collected using the ASI Applied Systems ReactIR 1000 FTIR with a diamond sensor that collects spectra over the optical range 4400−2150 and 1950−650 cm^{-1}. The detector is a MCT (mercury cadmium telluride) that operates at liquid nitrogen temperature. Data acquisition parameters are 32 scans with a resolution of 8 cm^{-1}. A reaction profile was created to observe the imine concentration at wavenumber 1069 cm^{-1} (see Supporting Information). Reaction data were imported into Excel and normalized according to conversion values determined by GC.

GC data were collected using a J&W Scientific, DB-1 30 m × 0.32 mm × 0.25 μm, column fitted to a Varian

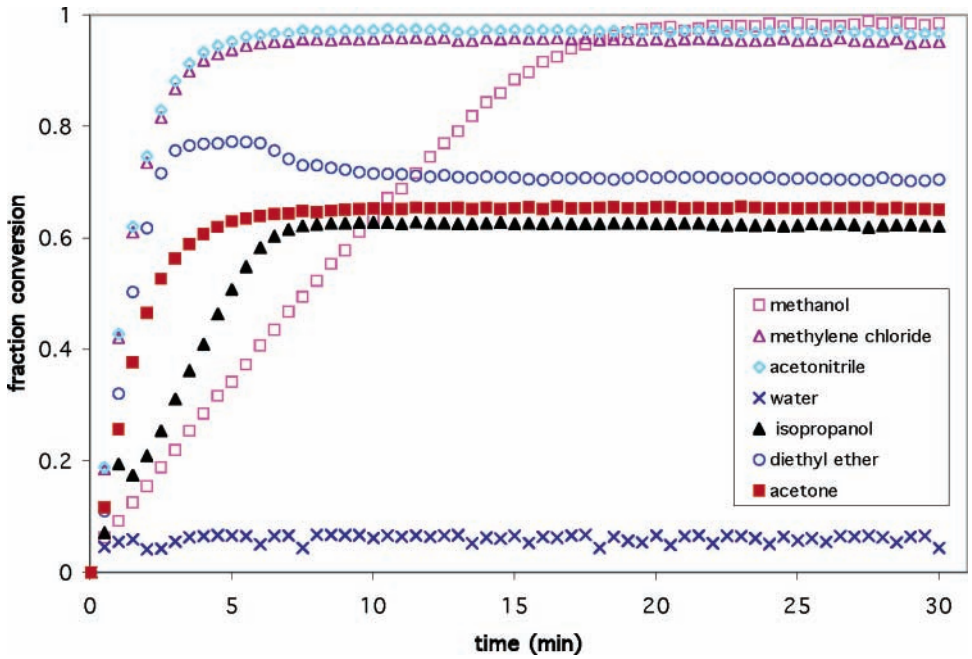


Figure 6. **Conversion vs time for reactions carried out in different solvents as indicated in the legend. $[1]_0 = 0.25$ M; $[HCOOH]_0 = 1$ M; $[Et_3N] = 0.4$ M; $[1]_0/[2] = 250$. Solvent symbols as designated in the legend.**

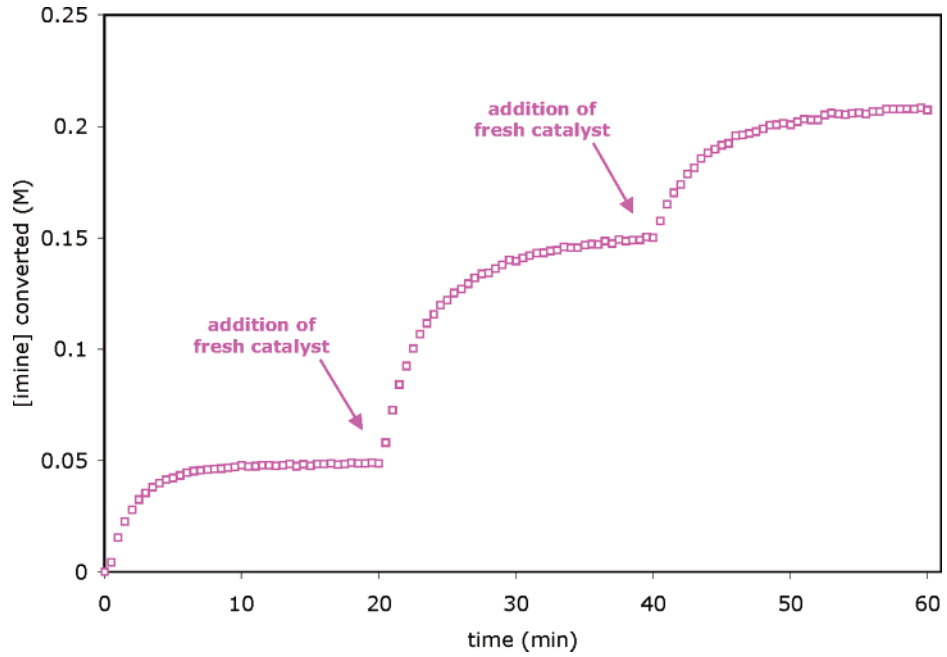


Figure 7. **Conversion vs time for reaction in CH_3CN with catalyst addition during reaction. $[1]_0 = 0.25$ M; $[HCOOH]_0 = 1$ M; $[Et_3N] = 0.4$ M; Initial catalyst/ substrate ratio $[1]_0/[2] = 500$; final catalyst/substrate ratio $[1]_0/[2] = 167$.**

CP-3800 gas chromatograph. The conditions were: injector 220 °C, column flow 3.2 mL/min, oven 120 °C for 25 min and detector FID at 300 °C. Retention times: phenanthrene 18.2 min, 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 19.3 min, and 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline 21.1 min.

General Information. The reaction solvent methanol [45.32 mL, 22.13 M (based on total volume after addition of precatalyst solution)], TEAF [4.68 mL, formic acid ~1.0 M: triethylamine ~0.4 M], and the internal standard phenanthrene [0.0891 g, 0.4999 mmol, 0.0100 M; Aldrich] were added to a specially adapted three-neck 100-mL round-bottomed flask. This was fitted onto the ReactIR probe. A background spectrum containing all of the above reagents was taken.

The 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline [2.5659 g, 12.50 mmol, 0.2500 M; Acros Organics] was added before placing the reaction vessel under vacuum and filling with argon three times. A sample spectrum was taken to confirm the imine concentration.

The collection of reaction spectra was initiated, and after the first spectrum was complete 2.5 mL of the precatalyst

solution was added via injection A sample spectrum was recorded every 30 s for 60 min.

Regular samples of 20 μL were taken and quenched using 2 M sodium hydroxide [BDH GPR] and dichloromethane. The organic was dried using magnesium sulphate (Fisher Scientific) before filtering and diluting to 2 mL using HPLC grade methanol. The samples were then analysed by GC.

Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review February 13, 2006.

OP060033K