Asymmetric Catalysis

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# Systematically Probing the Effect of Catalyst Acidity in a Hydrogen-Bond-Catalyzed Enantioselective Reaction**

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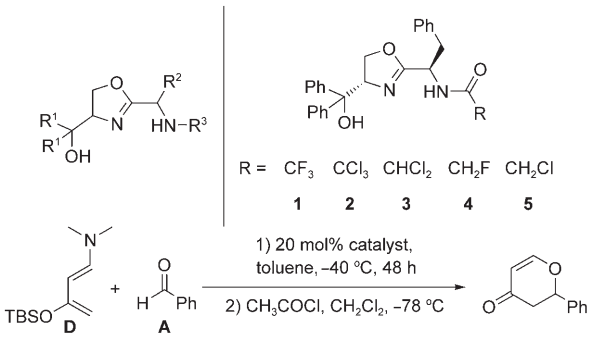
Hydrogen bonding is ubiquitous in nature and is a prevalent mode of substrate activation in enzymes. Recently, chemists have begun to exploit this mode of activation in asymmetric catalysis by designing synthetic catalysts that use hydrogen bonds.[1–3] These catalysts feature a variety of structural motifs and hydrogen-bond-donating functional groups. In light of the rapid development of new hydrogen-bond-catalyzed reactions, we felt that a greater understanding of the connection between catalyst activity and structure would aid the advancement of the field. While detailed mechanistic studies have been performed to clarify the role of hydrogen bonding in many enzymatic systems and on general acid catalysis,[4,5] few have been performed on synthetic asymmetric catalysts.[6] Herein, we present a systematic study on the effect of catalyst acidity in a hydrogen-bond-catalyzed reaction, wherein linear free energy relationships are observed between the catalyst acidity and both the reaction rate and enantioselectivity.

We have developed a hydrogen-bond catalyst which has a unique design featuring an oxazoline core with a pendant amine and alcohol group. This design provides two sites with hydrogen-bond donating groups which can be independently tuned (Scheme 1).[7] Catalysts of this type have been shown to be effective in the asymmetric hetero-Diels–Alder reaction between Rawal's diene (**D**) and benzaldehyde (**A**).[7–11] The modular nature of the catalyst makes it well suited for a mechanistic study, as catalyst derivatives can be rapidly synthesized and evaluated to probe the relationship between the catalyst structure and activity.

We hypothesized that a more acidic catalyst would be a better hydrogen-bond donor and thus would lead to enhanced substrate activation, as has been previously demonstrated.[12–14] To investigate this connection, systematic changes to the acidity of the N-H proton were made by synthesizing halogenated acetamide derivatives of the catalyst (Scheme 1). These variations were selected because of the substantial p$K_a$ range that may be studied while avoiding significant structural changes[15,16] and because the catalyst derivatives can be synthesized from a common precursor.[17] Compounds **1**–**5** were then evaluated as catalysts in the hetero-Diels–Alder reaction.[8–11] The yields of the isolated products after a 48 h reaction time suggest a relationship between acidity and catalyst activity (Scheme 1).[18] To our surprise, a trend in enantioselectivity was also observed, with the highest enantiomeric excess measured for the most acidic catalyst.




| Catalyst | R | p$K_a$ of $RCO_2H$ | Yield (%)[a] | *ee* (%)[b] | e.r. (*S*/*R*)[b] |
|---|---|---|---|---|---|
| **1** | $CF_3$ | –0.25 | 67 | 91 | 20 |
| **2** | $CCl_3$ | 0.65 | 61 | 81 | 9.6 |
| **3** | $CHCl_2$ | 1.29 | 53 | 75 | 7.0 |
| **4** | $CH_2F$ | 2.66 | 17 | 62 | 4.3 |
| **5** | $CH_2Cl$ | 2.86 | 32 | 52 | 3.1 |

[a] Yield of isolated product after column chromatography. [b] *ee* and e.r. values determined by HPLC on a chiral stationary phase.

***Scheme 1.*** Design of the oxazoline amine hydrogen-bond catalyst and evaluation of halogenated acetamide derivatives in a hetero-Diels–Alder reaction.

To better understand the observed trends corresponding to the electronic nature of the catalyst, kinetic measurements were performed to probe the general mechanistic features of the reaction. Using the optimal catalyst **1**, the following rate dependencies were observed: first-order dependence on [**1**], saturation in [aldehyde] (Figure 1), and first-order dependence on [diene] at high [aldehyde].[17] Based on these findings, a mechanism can be proposed in which the aldehyde (**A**) binds reversibly to **1** to form an activated complex (**C**:**A**), which reacts irreversibly with the diene (**D**) to form the product (**P**) and release the catalyst (Scheme 2). A rate law describing this process is depicted in Scheme 2.

Inspection of the rate law reveals that at high concentrations of the aldehyde, the initial rate becomes proportional to $k_2$, and thus the rate of the bond-forming step. Therefore, the effect of catalyst acidity on the bond-forming step can be probed by measuring the reaction rate of each catalyst at high aldehyde concentration, where saturation is assumed.[17] This was accomplished using in situ IR spectroscopy at −45 °C with

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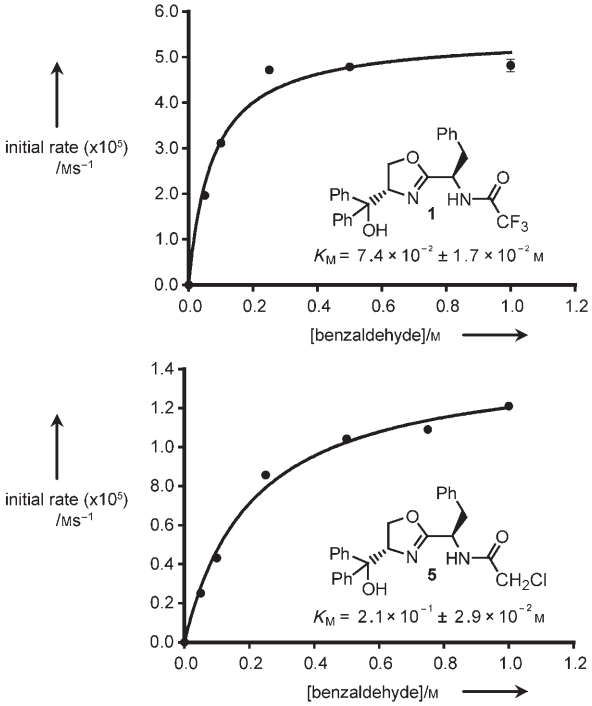
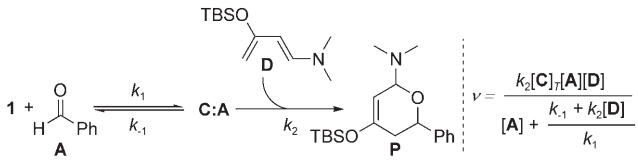



***Figure 1.*** Plot of the initial reaction rate versus [benzaldehyde] for catalysts **1** and **5**. The graphs are fit to the equation: rate = a[benzaldehyde]/(b+[benzaldehyde]), where a and b are constants with $a = k_2[\mathbf{C}]_T[\mathbf{D}]$ and $b = K_M = (k_{-1} + k_2[\mathbf{D}])/k_1$.



***Scheme 2.*** Proposed mechanism and derived rate law.

20 mol% catalyst to mimic the reaction conditions used to measure the enantiomeric ratio (Scheme 1). Greater catalyst acidity corresponds to faster reaction rates, which supports our initial hypothesis that increased hydrogen-bond donation could lead to enhanced substrate activation (Figure 2a). This observation is in agreement with recent computational studies which show an increase in hydrogen bonding in the transition state of the hetero-Diels–Alder reaction.[19] To correlate the observed trend in the rate to the electronic nature of the catalyst, a plot of the p$K_a$ value[20] of the corresponding acetic acid derivative (in water) versus the logarithm of the initial rate was constructed (Figure 2b). The assumption is that the electron-withdrawing ability of the R substituent affects the acidity of the catalyst in a similar manner as the acetic acid derivative. A linear free energy relationship (LFER; slope = $-0.46 \pm 0.03$) is observed, thereby providing an example of a direct relationship between the reaction rate and catalyst acidity which is consistent with previous studies on acid-catalyzed reactions.[12–14]

Catalyst acidity may not only affect the rate of the bond-forming step, as shown above, but substrate binding may also be influenced by catalyst acidity. To evaluate this possibility,

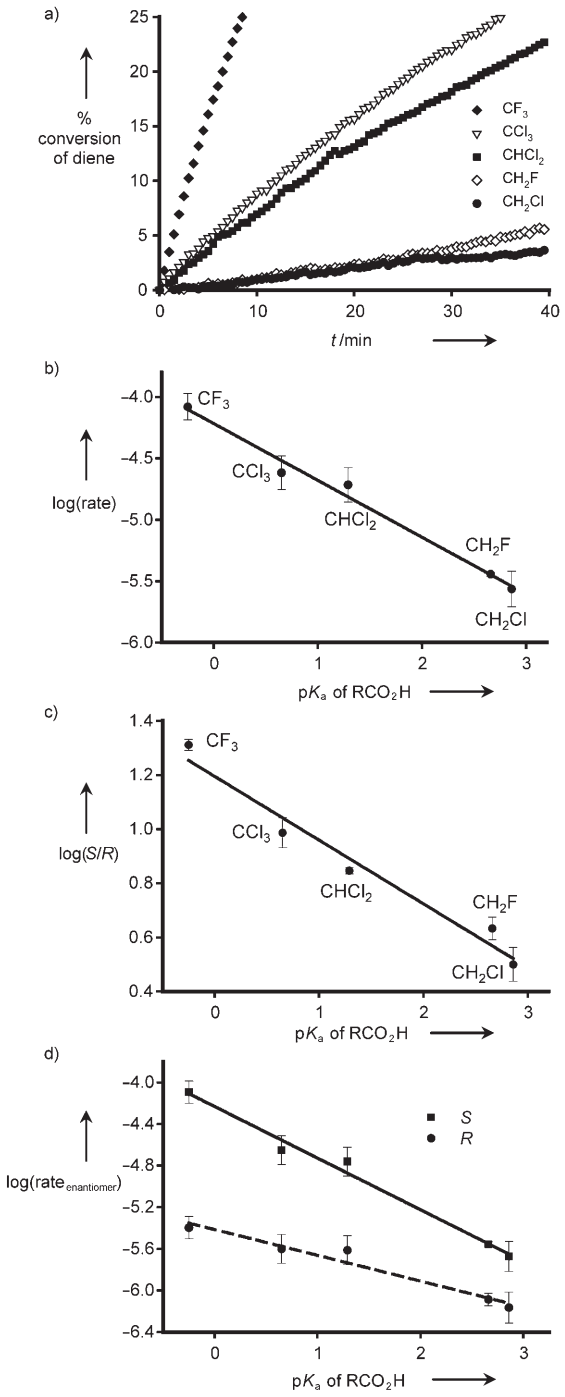



***Figure 2.*** a) Effect of catalyst acidity upon reaction rate as observed by monitoring diene conversion using in situ IR spectroscopy at −45 °C; ◆: catalyst **1**, ▽: catalyst **2**, ■: catalyst **3**, ◇: catalyst **4**, ●: catalyst **5**. b) LFER between catalyst acidity and initial reaction rate at −45 °C; slope = $-0.46 \pm 0.03$, $R^2 = 0.99$. c) LFER between catalyst acidity and enantiomeric ratio at −40 °C; slope = $-0.24 \pm 0.02$, $R^2 = 0.97$. d) LFER between the initial rate of formation of each enantiomer (■: *S* enantiomer, slope = $-0.50 \pm 0.03$, $R^2 = 0.99$; ●: *R* enantiomer, slope = $-0.25 \pm 0.03$, $R^2 = 0.96$) and catalyst acidity.

saturation data for the most (**1**) and least (**5**) acidic catalysts were compared (Figure 1). It should be pointed out that the initial rate of reaction is much slower for catalyst **5**. Addi-

tionally, a qualitative comparison of the curves reveals a considerable difference in the concentration at which saturation occurs. The calculated $K_M$ values support a higher affinity for the substrate by the more acidic catalyst **1**.

Encouraged by the observation of an LFER for the reaction rate, we examined whether the effect on enantioselectivity could also be directly correlated to the electronic nature of the catalyst. A plot of the p$K_a$ value of the corresponding carboxylic acid versus the logarithm of the enantiomeric ratio (a relative rate) reveals an LFER (slope = $-0.24 \pm 0.02$, Figure 2c). This relationship suggests that the relative rate of formation of each enantiomer is directly related to the electronic character of the catalyst, rather than any size change caused by substitution of a halogen for a hydrogen atom. While LFERs have been observed between enantiomeric ratio and catalyst electronic structure in other catalytic systems,[21–25] this is the first example of a direct electronic effect on enantioselectivity in a hydrogen-bond-catalyzed reaction. Of additional note, a plot correlating the initial rate of formation for each enantiomer was constructed. While the reaction rate was found to increase with the catalyst acidity for both enantiomers, the increase in the rate of formation of the major enantiomer is greater than that of the minor enantiomer (Figure 2d).

As is generally the case in asymmetric catalysis, understanding the origin of asymmetric induction is difficult because of the small energetic differences in the diastereomeric transition states (1–3 kcal mol$^{-1}$). In the current example, an increasing amide acidity leads to a higher enantiomeric ratio. This situation may arise from a more tightly bound substrate, which thereby increases the rigidity in the transition state. It has been reported that if the p$K_a$ value of the hydrogen-bond donor and that of the protonated hydrogen-bond acceptor are closely matched, a shorter and stronger hydrogen bond is formed.[26–28] One could assume that within this study the p$K_a$ values of the catalyst and protonated substrate are more closely matched as the amide acidity increases, even though the differences in the p$K_a$ values between the catalyst and protonated substrate are substantial. Other non-exclusive possibilities can be proposed to account for the observed relationship between catalyst acidity and enantioselectivity, including differences in binding geometry as a function of catalyst acidity.

In conclusion, by utilizing a modular catalyst design, the effect of catalyst acidity has been systematically probed in a hetero-Diels–Alder reaction catalyzed by hydrogen bonding. It was found that both the reaction rate and enantioselectivity can be directly correlated to catalyst acidity. The dependence of the enantioselectivity is especially exciting because it provides the basis for the design of new asymmetric catalysts. Current work is focused on probing the origin of the observed enhancement of the enantiomeric ratio as a function of the catalyst acidity.

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