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# On the Mechanism of the Organocatalytic Asymmetric Epoxidation of α,β-Unsaturated Aldehydes

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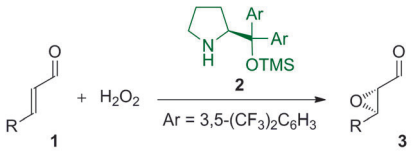
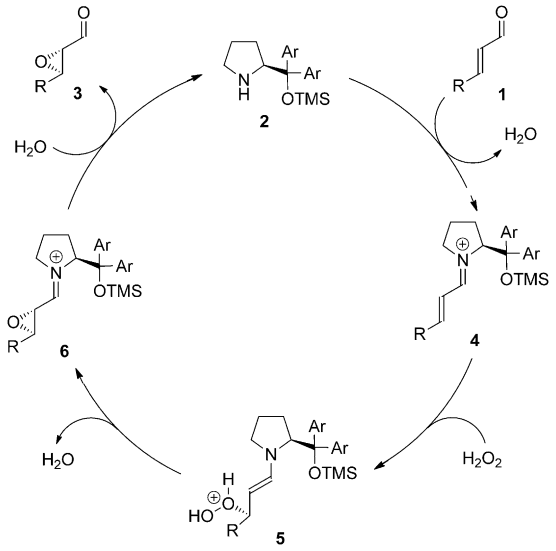
**Abstract:** Mechanistic studies on the organocatalytic epoxidation of α,β-unsaturated aldehydes explore the autoinductive behavior of the reaction and establish that the hydrate/peroxyhydrate of the product is acting as a phase-transfer catalyst. Based on these studies, an improved methodology that provides high selectivities and decreased catalyst loading, through the addition of chloral hydrate, is developed.

Catalytic asymmetric epoxidations are powerful transformations in contemporary organic synthesis as they allow for the formation of enantioenriched epoxides. Epoxides have been shown to be highly useful intermediates in the synthesis of, for example, natural products and pharmaceuticals.[1] The Sharpless and Jacobsen–Katsuki transition-metal-catalyzed, asymmetric epoxidations are two fundamental reactions in this area.[2] Furthermore, the role of the catalysts and the mechanisms of these reactions are well-established.[3] More recently, organocatalytic asymmetric epoxidation methods have been developed, vastly increasing the range of synthetically accessible epoxides.[4] However, unlike their transition-metal-catalyzed counterparts, the mechanisms of organocatalytic asymmetric epoxidations are much less understood.[5]

One highly useful and widely employed organocatalytic asymmetric epoxidation method involves the use of a secondary amine catalyst in combination with an α,β-unsaturated aldehyde and hydrogen peroxide (Scheme 1).[4c,6,7] This method has been shown to provide good yields and high enantiomeric excess for a wide range of α,β-unsaturated aldehydes. The proposed, and generally accepted, mechanism for the organocatalytic epoxidation of α,β-unsaturated aldehydes is outlined in Scheme 2. The first step in this catalytic cycle involves condensation of the trimethylsilyl (TMS)-prolinol catalyst **2** with **1** to form the iminium-ion intermediate **4**. This is followed by the nucleophilic addition of the peroxide to the β-carbon atom of the iminium-ion species. In the next step, the epoxide is formed via attack of the α-carbon atom on the electrophilic oxygen atom of **5**. Hydrolysis of the iminium-ion intermediate **6** produces the epoxyaldehyde and regenerates the catalyst.




**Scheme 1.** Organocatalytic epoxidation of α,β-unsaturated aldehydes.




**Scheme 2.** Generally accepted mechanism of the organocatalytic epoxidation of α,β-unsaturated aldehydes.

Herein, we present a mechanistic study on the organocatalytic epoxidation reaction of α,β-unsaturated aldehydes (Scheme 1).[4c] During the development and application of this reaction, it was surprisingly found that the reaction rate increased as the conversion increased. This unusual rate behavior inspired us to explore the effects of solvent, products and additives on the performance of the reaction. The complex nature of this reaction was uncovered when the data showed that the product formed is involved in the rate-limiting step of the reaction. Based on our mechanistic findings, we have also developed an improved protocol for this epoxidation reaction. By the application of an achiral additive, our new procedure allows for decreased catalyst loading and shorter reaction times while maintaining high selectivity. The epoxidation reac-

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tion in Scheme 1 has been studied for *trans*-2-nonenal (**1a**) (R = *n*-hexyl) using the TMS-prolinol catalyst **2** in both $CH_2Cl_2$ and EtOH—two solvents that have previously been shown to promote high yields and selectivities.[4c,6a] Due to the heterogeneous nature of the reaction in $CH_2Cl_2$, all reactions were monitored by using GC.[8] A plot of conversion versus time provides a sigmoidal curve for the reaction in $CH_2Cl_2$, showing that the rate increases over time (Figure 1). This is in contrast to the

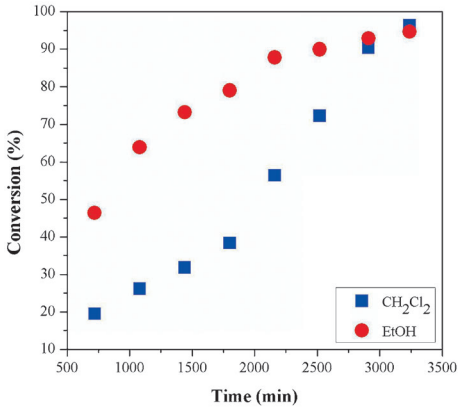
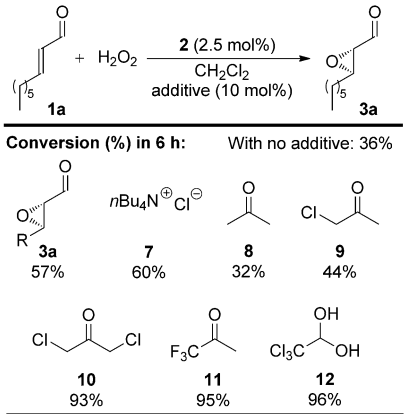



**Figure 1.** Conversion versus time (min) for the organocatalytic epoxidation of *trans*-2-nonenal (**1a**).[a] [a] Reactions were carried out on a 0.5 mmol scale with 1.0 mmol $H_2O_2$ (35% aqueous) and 1 mol% of **2** in 1 mL of solvent (see Supporting Information for details).

epoxidation in EtOH, which shows no rate increase. Monitoring of the enantiomeric excess of the epoxy aldehyde **3a** over the course of the reactions in Figure 1 revealed that, in both cases, the enantiomeric excess remains constant throughout the reaction (97% *ee* for the reaction in $CH_2Cl_2$ and 86% *ee* in EtOH).

The rate acceleration observed in $CH_2Cl_2$ (Figure 1) suggests that epoxyaldehyde **3** plays a role in the rate-limiting step of the epoxidation reaction. To provide insight as to the role of the product **3** in the heterogeneous reaction, its ability to promote the reaction was examined. We began by identifying whether the epoxyaldehyde could independently catalyze the reaction.[9] The addition of 10 mol% of epoxyaldehyde **3a** to a mixture of *trans*-2-heptenal (**1b**) and $H_2O_2$ in $CH_2Cl_2$ (without the TMS-prolinol catalyst **2**) generated no reaction. This shows that **3** does not independently catalyze the reaction.

As the epoxyaldehyde **3** is shown to play no role in the rate-limiting step of the homogeneous (EtOH as solvent) reaction, it appears that **3** might be involved in the phase-transfer step of the heterogeneous reaction.[10] The role of the epoxyaldehyde **3** in the rate-limiting step of the epoxidation of *trans*-2-nonenal (**1a**) was further investigated by performing the reaction with 2.5 mol% of the TMS-prolinol catalyst **2** and 10 mol% of epoxyaldehyde **3a** (Scheme 3). Examination of the reaction mixture after 6 h showed an increase in conversion from 36% (with no additives) to 57% (with 10 mol% of **3a**). As the epoxyaldehyde **3** is considered to be acting as a phase-transfer catalyst, we were also interested in how a well-known phase-transfer catalyst, tetrabutylammonium chloride (**7**), might affect the reaction. The use of 10 mol% of **7** in the reaction



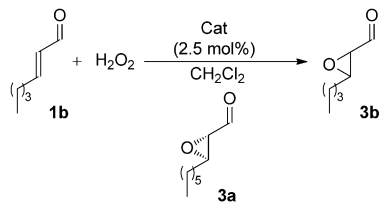

**Scheme 3.** Effects of additives on the rate of epoxidation.[a] [a] Reaction time: 6 h. Reactions were performed at room temperature with 0.5 mmol **1a** and 1.0 mmol $H_2O_2$ (35% aqueous) in 1.0 mL solvent. Values below additives are % conversions as determined by CSP-GC. See Supporting Information for details.

gave 60% conversion in 6 h, only 3% more than the reaction with 10 mol% of **3a**.

The results of these initial additive studies led us to consider how epoxyaldehyde **3** was acting as a phase-transfer catalyst. While using the epoxidation chemistry for other applications, it was observed that it was problematic to determine the exact conversion numbers by comparing the aldehyde CHO signals in the NMR-spectrum. The product signal was usually smaller than the other signals. The "hiding" of this proton led us to the hypothesis that it is not **3**, but its hydrate, that is accelerating the reaction. To test this hypothesis, a series of ketones with different affinities for forming their corresponding hydrates were examined as additives in the epoxidation of *trans*-2-nonenal (**1a**) (Scheme 3).[11] The two ketones with low affinities for forming hydrates, acetone **8** and chloroacetone **9**, had little influence on the conversion, with **8** slightly slowing down the reaction and **9** slightly increasing the rate. Ketones **10** and **11**, which both have a high affinity for forming their hydrates, were shown to dramatically increase the reaction rate, providing almost full conversion in 6 h. Finally, we examined the effect of chloral hydrate **12** on the epoxidation. The addition of 10 mol% of **12** resulted in 96% conversion in 6 h.[12,13] The trend established by the ketone additives and the effectiveness of the chloral hydrate in increasing the rate of reaction suggests that it is not the epoxyaldehyde **3**, but its hydrate **13** that is acting as a phase-transfer catalyst and promoting the epoxidation in $CH_2Cl_2$ (Scheme 3). However, it should be noted that these trends do not rule out the formation of the peroxyhydrate of **3** being involved in the reaction as $H_2O_2$ is more nucleophilic than water.

In addition to examining the role of epoxyaldehyde **3a** as a phase-transfer catalyst, we also explored the influence of this chiral additive on the enantioselectivity of the reaction. To assess the effects of a match-mismatch pairing of catalyst and product on the enantioselectivity of the reaction, the epoxidation of *trans*-2-heptenal (**1b**) was performed with ***ent*-2** as the catalyst and 10 mol% of **3a** (97% *ee*) (Table 1). In the mis-

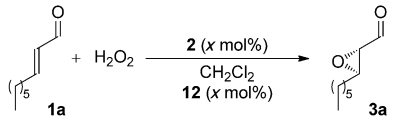
**Table 1.** Effects of match-mismatch pairing.[a]




| Entry | **3a** [mol%] | Cat. | *t* [h] | Conv. [%][b] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | 0 | **2** | 4 | 53 | 96 |
| 2 | 10 | **2** | 4 | 72 | 97 |
| 3 | 10 | *ent*-**2** | 4 | 74 | −97 |

[a] Reactions were performed at room temperature with 0.5 mmol **1b** and 1.0 mmol $H_2O_2$ (35% aqueous) in 1.0 mL solvent. [b] Determined by CSP-GC of the crude reaction mixture.

**Table 2.** Optimization of the organocatalytic epoxidation of α,β-unsaturated aldehydes with chloral hydrate **12**.[a]




| Entry | **3** [mol%] | **12** [mol%] | *t* [h] | Conv. [%][b] |
|---|---|---|---|---|
| 1 | 2.5 | 0 | 18 | 90 |
| 2 | 2.5 | 2.5 | 5 | 72 |
| 3 | 2.5 | 5 | 5 | 98 |
| 4 | 2.5 | 10 | 5 | 93 |
| 5 | 1 | 0 | 60 | 84 |
| 6 | 1 | 5 | 24 | 96 |
| 7 | 1 | 10 | 24 | 95 |

[a] Reactions were performed at room temperature with 0.5 mmol **1a** and 1.0 mmol $H_2O_2$ (35% aqueous) in 1.0 mL solvent. [b] Determined by CSP-GC of the crude reaction mixture. In all entries the enantiomeric excess remained between 96–98% *ee*.

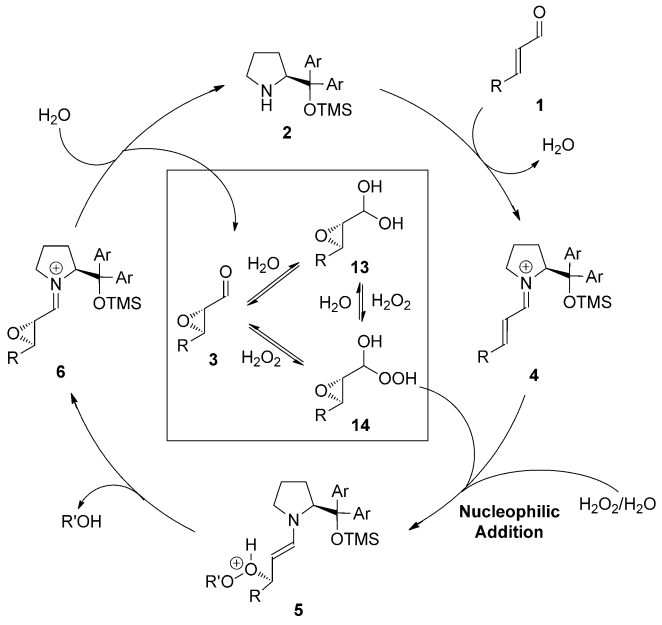
matched case, the addition of **3a** increases the rate of the reaction, just as in the matched case. In both the matched and mismatched cases the enantioselectivity remained at 96–97% *ee*.[14]

As shown in the additive studies, compounds that readily form hydrates greatly influence the rate of the reaction; however, as mentioned previously this does not rule out the possibility of other species, such as a peroxyhydrate, being the species responsible for the rate increase.[15] In an attempt to determine if such peroxyhydrates are formed in significant amount, a series of NMR studies were performed (see Supporting Information for details). Monitoring the reaction of **12** with aqueous $H_2O_2$ by $^{13}C$ NMR spectroscopy showed a down field shift in the hydrate carbon atom from 95.7 ppm to 103.6 ppm. It should be noted that this shift was not observed when **12** was combined with $H_2O$ alone. This suggests the formation of the peroxyhydrate of **12**. Based on the results of our experiments, we propose a new mechanism for the catalytic cycle of this reaction (Scheme 4). In this mechanism, the reaction still occurs through formation of the iminium-ion intermediate **4** and a subsequent addition of the peroxide followed by cyclization to form the epoxide **6**. Unlike the previously proposed catalytic cycle shown in Figure 1,[4c] in this mechanism the epoxyaldehyde **3** plays an important role in the phase-transfer step of the catalytic cycle.

Intrigued by how well chloral hydrate **12** was able to accelerate the epoxidation of α,β-unsaturated aldehydes (Scheme 3), we next decided to investigate how much of this additive was necessary to achieve the fastest reaction times with both 2.5 and 1.0 mol% catalyst loading (Table 2). Varying the concentration of **12** from 0–10 mol% reveals that the reaction is most efficient with 5 mol% of **12**. The addition of only 2.5 mol% additive was found to be less effective, whereas the addition of more than 5 mol% of **12** resulted in a slight decrease in the rate of reaction. This is likely due to condensation of the catalyst with the chloral hydrate, which is observed by $^{19}F$ NMR spectroscopy.

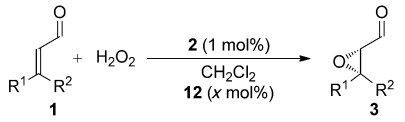
The new methodology was also tested on two other aldehydes to demonstrate its generality (Table 3). The reactions were performed without **12** and with 5 mol% of **12**. In the epoxidation of both **1c** and **1d**, the addition of chloral hydrate showed a marked increase on the rate of the reaction and had no effect of the enantioselectivity.

In summary, mechanistic studies on the organocatalytic epoxidation of α,β-unsaturated aldehydes in $CH_2Cl_2$ reveal that the reaction exhibits an increase in rate as it proceeds. This autoinductive behavior is dependent on the solvent employed and is thought to result from the products ability to act as




**Scheme 4.** Proposed catalytic cycle for reaction in $CH_2Cl_2$.

**Table 3.** Scope of the organocatalytic epoxidation of α,β-unsaturated aldehydes with chloral hydrate **12**.[a]




| Entry | 1 | 12 [mol%] | t [h] | Conv. [%][b] | ee [%][b] |
|---|---|---|---|---|---|
| 1 | **1c**: $R^1 = i$Pr, $R^2$ = H | 0 | 6 | 42 | ND[c] |
| 2 | **1c**: $R^1 = i$Pr, $R^2$ = H | 5 | 6 | 74 | 97 |
| 3 | **1d**: $R^1 = CO_2Et$, $R^2$ = H | 0 | 3 | 77 | 86 |
| 4 | **1d**: $R^1 = CO_2Et$, $R^2$ = H | 5 | 3 | 89 | 86 |

[a] Reactions were performed at room temperature with 0.5 mmol **1a** and 1.0 mmol $H_2O_2$ (35% aqueous) in 1.0 mL solvent. [b] Determined by CSP-GC of the crude reaction mixture. [c] ND = not determined.

a phase-transfer catalyst. Further studies revealed that it is likely the peroxyhydrate of the epoxyaldehyde that is responsible for the observed rate acceleration. Based on these studies, it has been determined that the addition of chloral hydrate to the reaction significantly increases the rate of reaction. This improved methodology for the organocatalytic epoxidation of α,β-unsaturated aldehydes provides high selectivities and low catalyst loading, making it as efficient a method as those employing transition-metal catalysts and increasing its applicability in an industrial setting.

## *Acknowledgements*

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**Keywords:** asymmetric epoxidation · organocatalysis · reaction mechanisms

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[12] Additional studies on the chloral hydrate **9** revealed that the additive was unable to catalyze the epoxidation reaction in the absence of the TMS-prolinol catalyst **2**. These studies also reveal that this additive has no effect on the rate of the reaction in EtOH.

[13] The role of acid in affecting the rate of the reaction was also tested by adding 10 mol% benzoic acid. After 6 h, the reaction gave 66% conversion, providing a similar rate increase as 10 mol% of epoxyaldehyde **3a**. It seems likely that the acid could be involved in the formation of the hydrate of epoxyaldehyde **3a**.

[14] The lack of a mismatch effect was confirmed by experiments using another chiral aldehyde (L-glyceraldehyde acetonide). The addition of 10 mol% of this aldehyde with both enantiomers of the catalyst resulted in 95–96% *ee*. See Supporting Information for details.

[15] In addition to the possibility of forming a peroxyhydrate, the formation of a peroxy hemiaminal was also considered. $^{19}F$ NMR studies on the catalyst **2** with **12** and $H_2O_2$ showed the formation of a new peak upfield (−62.6 ppm) suggesting the formation of a small amount of such a species. See Supporting Information for details.

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