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# Bifunctional Activation and Racemization in the Catalytic Asymmetric Aza-Baylis−Hillman Reaction

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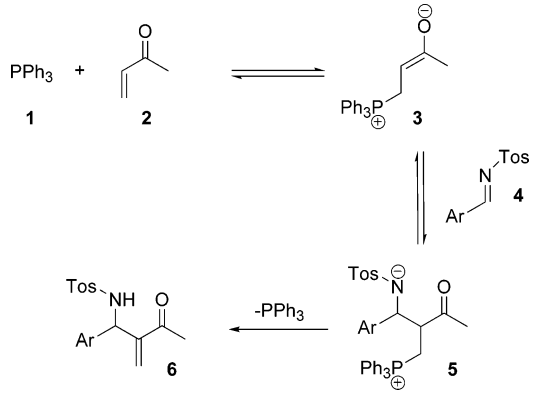
The aza-Baylis−Hillman (aza-BH) reaction is a versatile C−C bond forming reaction of activated alkenes with imines to form highly functionalized allylic amines.[1] It was not until most recently that chiral catalysts providing high levels of enantioselectivity in the asymmetric aza-BH reaction have been reported.[2] As a common theme, these organocatalysts are based on bifunctional chiral BINOL and phosphinyl BINOL compounds.[2c−e] So far, however, no detailed mechanistic information on the aza-BH reaction is available, and the factors responsible for enantiocontrol are not understood. In the present communication, we report conclusive evidence for the mechanism of bifunctional activation and demonstrate that racemization of the product under turnover conditions is a crucial aspect for future catalyst design.[8]

In accordance with the generally accepted mechanism of the Baylis−Hillman (BH) reaction, it is reasonable to assume a catalytic cycle for the aza-BH reaction where the initial step is the reversible conjugate addition of the phosphine catalyst **1** to the activated alkene **2** to generate the corresponding enolate **3**. Mannich-type addition of **3** to the imine **4** forms the zwitterion **5** followed by elimination to generate the product **6** liberating the catalyst (Scheme 1).[3]

***Scheme 1.*** Proposed Mechanism of the Aza-BH Reaction




For the BH reaction of acrylate esters with pyridinecarboxaldehydes, Kaye reported that the reaction is first order in aldehyde, amine, and acrylate.[3b] In a later investigation, McQuade observed that the reaction is second order in aldehyde and proposed the formation of a hemiacetal intermediate for the reaction in aprotic solvents.[4] Several groups noted large rate enhancements caused by water and other protic additives.[5] Aggarwal and Lloyd-Jones concluded that proton transfer is rate-limiting in the initial stage of the reaction, but becomes increasingly efficient at higher conversion causing the aldol-type coupling to become rate-limiting and making the reaction autocatalytic.[6]

In a first set of experiments, we performed kinetic studies on the aza-BH reaction of methyl vinyl ketone (**2**) with *N*-(3-fluorobenzylidene)-4-methylbenzenesulfonamide (**4**, Ar = *m*-F−$C_6H_4$) in the presence of $PPh_3$ (**1**) in THF at room temperature. The reactions were monitored by $^{19}F$ NMR spectroscopy. The rate

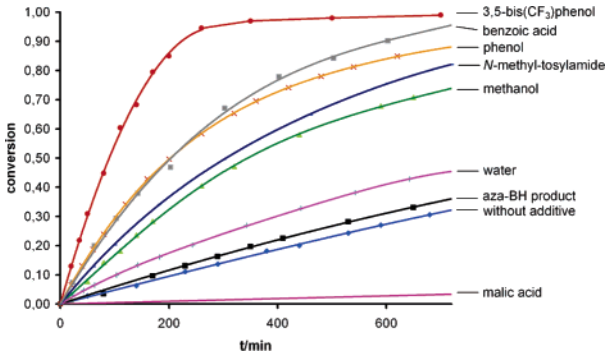



***Figure 1.*** Conversion time profiles for the aza-BH reaction of **2** (0.090 mmol) with imine **4** (0.075 mmol) using catalyst **1** (0.0075 mmol), and various additives (0.103 mmol) in THF-$d_8$ (0.6 mL).

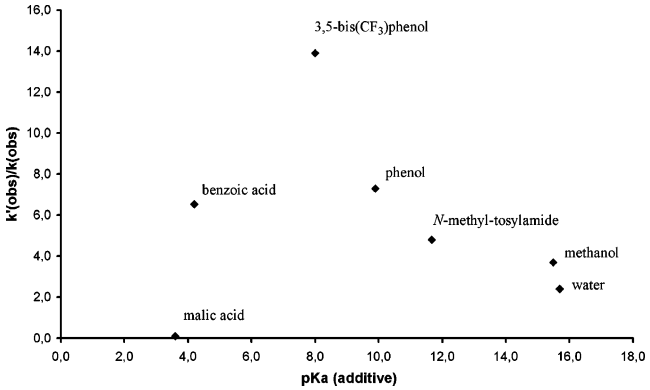



***Figure 2.*** Relative initial reaction rates ($k'_{obs}/k_{obs}$) for the aza-BH reaction as a function of the p$K_a$ of the additive.

law shown in eq 1 was derived by analyzing the initial rates as a function of concentration for the individual components. No evidence for autocatalysis was observed, and the broken order of 0.5 in imine **4** indicates that the rate-determining step (RDS) is partly influenced by proton transfer.

$$\text{rate} = k_{obs}\,[\mathbf{1}]^1[\mathbf{2}]^1[\mathbf{4}]^{0.5} \qquad (1)$$

We then conducted experiments to assess the influence of Brønsted acidic additives (1 equiv per **4**) with different p$K_a$ values (Figure 1). A maximum was observed with 3,5-bis($CF_3$)phenol at p$K_a \approx 8$ corresponding to a 14-fold rate enhancement as compared to the reaction without additive (Figure 2). Less acidic compounds show a smaller effect, but additives such as water still give a significant rate enhancement. If the additive is more acidic, the enhancement is also reduced owing to formation of the protonated form of enolate **3**, which could be detected and characterized by multinuclear NMR.

Examination of the kinetics in the presence of phenol as prototypical additive revealed that the rate law of the reaction



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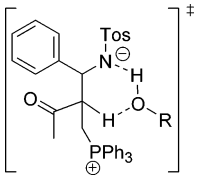
***Scheme 2.*** Transition State for the Brønsted Acid-Assisted Proton Transfer in the Aza-BH Reaction




changes in the presence of the Brønsted acid, showing first-order dependence in imine **4** (eq 2). This clearly demonstrates that the elimination step is not involved in the RDS anymore, and that the proton transfer must be accelerated by these additives. Scheme 2 shows the most likely transition state for the assisted proton transfer in this step.

$$\text{rate} = k'_{\text{obs}}\,[\mathbf{1}]^1[\mathbf{2}]^1[\mathbf{4}]^1 \qquad (2)$$

The results obtained so far substantiate that bifunctional activation using a basic and a protic center is a viable strategy for catalyst design in the asymmetric aza-BH reaction. However, as the individual steps of the catalytic cycle are potentially reversible, we investigated also the influence of the catalyst components on possible racemization pathways. Whereas Brønsted acids alone did not lead to racemization of **6**, complete and rapid racemization occurred by **1** either alone or in the presence of 3,5-bis($CF_3$)phenol (Figure 3).

Treating **6** (Ar = *p*-$BrC_6H_4$) with another imine of similar reactivity (Ar = *m*-$FC_6H_4$) did not result in the formation of the cross-coupled product under catalytic conditions, indicating that retro-Mannich reaction is not responsible for the racemization. However, rapid incorporation of deuterium from MeOD at the stereogenic center adjacent to the N−H group in the presence of **1** demonstrated that—despite the weak basicity of the aryl phosphine—racemization could occur via a deprotonation/protonation process.[7] In striking contrast, the chiral catalyst **7** developed by Shi et al. did not induce any racemization on a similar time scale, even though the basicity and the acidity of the two activation sites are similar to those of the combined **1**/3,5-bis($CF_3$)phenol system.

In summary, these studies show that the aza-BH reaction involves rate-limiting proton transfer in the absence of added protic species, but exhibits no autocatalysis. Brønsted acidic additives lead to substantial rate enhancements through acceleration of the elimination step. Furthermore, it was found that phosphine catalysts either alone or in combination with protic additives can cause racemization of the aza-BH product by proton exchange at the stereogenic center. This indicates that the spatial arrangement of a bifunctional chiral catalyst for the asymmetric aza-BH is crucial not only for the stereodifferentiation within the catalytic cycle but also for the prevention of subsequent racemization.

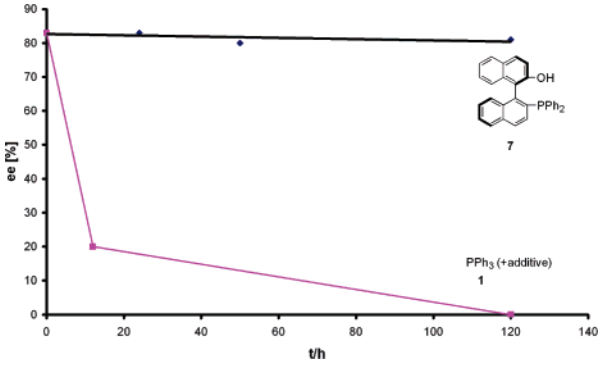



***Figure 3.*** Racemization of the aza-BH product **6** in the presence of various catalytic systems.

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**Supporting Information Available:** A complete description of experimental details, kinetics data, rate law derivation, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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