Organocatalysis

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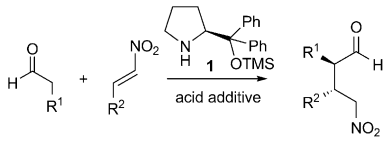
Mechanism of Diphenylprolinol Silyl Ether Catalyzed Michael Addition Revisited—but Still Controversial**

*Christina Moberg**

enantioselectivity · Michael reaction · organocatalysis · reaction mechanisms · reactive intermediates

The stereoselective conjugate addition of chiral enamines to prochiral nitro alkenes to provide γ-nitro carbonyl derivatives is widely recognized as a powerful carbon–carbon bond-forming process. The discovery that the enamine can be produced in situ from the carbonyl compound and a catalytic amount of a chiral amine[1] led several research groups to search for efficient amine catalysts. Among the different catalysts applied to the reaction, the silylated prolinol **1**, introduced by Hayashi and co-workers, proved to be particularly efficient (Scheme 1).[2] The reaction shown in Scheme 1 exhibits high facial selectivity with respect to both reaction

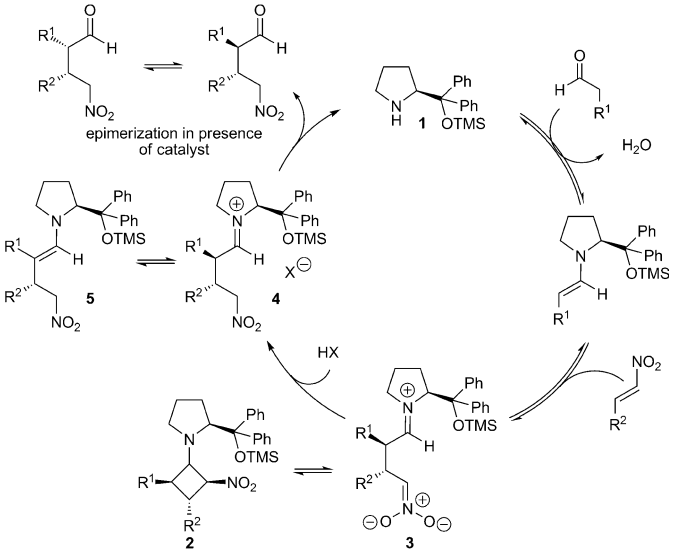


Scheme 1. Organocatalyzed conjugate addition of aldehyde to nitro olefin. TMS = trimethylsilyl.

partners, thus allowing two adjacent stereogenic centers to be installed with high enantio- and diastereoselectivity using a wide range of substrates. Its synthetic versatility has been demonstrated by cascade reaction sequences leading to complex biologically active compounds.[3] This Michael addition also serves as a benchmark for assessing new catalysts.

Although this catalytic process has attracted high interest and stimulated extensive experimental activities, limited attention has, until very recently, been devoted to detailed mechanistic studies. This may seem surprising in view of the early seminal studies of the corresponding stoichiometric diastereo-[4] and enantioselective[5] Michael additions by Seebach and co-workers, in which the basic features of the process were established. Recent studies by Seebach, Hayashi and co-workers[6] as well as by Blackmond and co-workers[7] have shed light on the mechanism of the catalytic process, but also led to controversy regarding the role of observed intermediates.

Kinetic studies and characterization of reaction intermediates revealed that the reaction is more complex than previously anticipated. Species which had been found to be intermediates in the stoichiometric reaction have now also been detected in the catalytic process. In the initial part of the reaction, the cyclobutane derivative **2** (Scheme 2) is rapidly



Scheme 2. Suggested mechanism for addition of aldehyde to nitro olefin catalyzed by diphenylprolinol trimethylsilyl ether.

formed, as evidenced by reaction calorimetry reported by Blackmond and co-workers,[7] as well as by in situ NMR spectroscopy by Seebach, Hayashi and co-workers,[6] and later also by X-ray crystallographic studies.[8] The cyclobutane is obtained as a single isomer by reversible formal [2+2] cycloaddition of the enamine and the nitro olefin, most likely occurring via the zwitterionic intermediate **3**,[9] which results from reversible addition of the enamine to the nitro olefin. The cyclobutane was found to serve as the off-cycle resting state of the catalyst. The initial studies[6,7] led both groups to conclude that the reaction follows the mechanism outlined in Scheme 2, where the rate-determining step is the protonation of the zwitterionic intermediate **3**.

Acid additives are known to play a vital role in the reaction; the reaction rate is proportional to the concentration of acid up to one equivalent. A systematic study by Seebach, Hayashi, and co-workers on the influence of acid

[*] Prof. C. Moberg
Department of Chemistry, Organic Chemistry
Royal Institute of Technology, 10044 Stockholm (Sweden)
E-mail: kimo@kth.se

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additives on each step revealed that although several steps are accelerated by the acid, its decisive role is in the protonation of the zwitterionic intermediate **3** to yield the iminium compound **4**. The pK_a value of the acid is crucial for the efficiency of the catalytic cycle, with optimum values (in water) being 6–8.[6] The acid was also found to have a beneficial role for diastereoselectivity by suppressing the deprotonation of **4** to give the product enamine **5**.

According to the generally accepted model, the enantioselectivity is determined in the initial addition of the enamine to the nitro alkene, according to Seebach's topological rule (Figure 1).[4] This conclusion has now been challenged by Blackmond and co-workers,[10] who, supported by extensive experimental data, suggest that the product enamine **5** as well as the cyclobutane are not off-cycle species, but occur within the catalytic cycle.[11] In a catalytic cycle passing through **5**, the stereocenter α to the imine is destroyed and, consequently, the diastereoselectivity determined in the final product-forming step and dictated by the relative stability and reactivity of downstream intermediates. According to this model, enamine protonation is a highly selective process. This scenario provides a rationale for the reluctance of 2-methylpropanal, which is devoid of an α proton and thus unable to form product enamine **5**, to serve as a competent reaction partner. It also explains the strong kinetic isotope effect observed when α-deuterated aldehyde was used in combination with fully deuterated acetic acid. Blackmond and co-workers also argue that the facial selectivity with respect to the nitro olefin is better explained by this reaction scheme rather than by the generally accepted model (Figure 1).

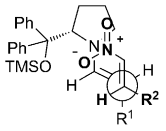
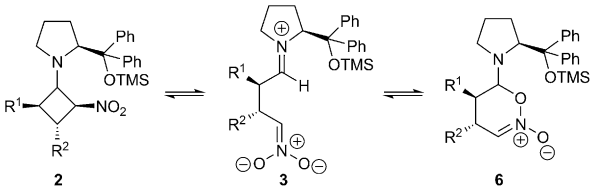


Figure 1. Trajectory for approach of enamine and nitro olefin.[4]

Seebach's more recent studies led to a different explanation of the observed experimental results. In addition to the cyclobutane **2** a minor product, which equilibrates with **2** and which proved to be the 1,2-oxazine *N*-oxide **6** resulting from a formal [2+4] addition of the enamine and nitro olefin, was identified (Scheme 3).[8] This compound has previously also been shown to be an intermediate in stoichiometric processes.[5] The zwitterionic intermediate **3**, which is excluded from Blackmond's modified catalytic cycle, plays according to Seebach a crucial role in the reaction as it may lead to dissociation to enamine and nitro olefin, to cyclobutane **2** and oxazine **6**, as well as to product. Sequestering of the catalyst in **2** and **6** also favors the diastereoselectivity of the reaction by preventing accumulation of the iminium intermediate, and thereby product enamine, during reaction turnover.



Scheme 3. Equilibration of cyclobutane **2** and 1,2-oxazine *N*-oxide **6** via zwitterion **3**.

Seebach and co-workers also found that the more heavily substituted cyclobutane and oxazine derivatives are exceedingly stable and serve as irreversible traps for the catalyst. They argue that the unreactivity of substituted aldehydes originates from the reluctance of **2** and **6** to ring-open to the zwitterion **3**, thereby preventing product formation, a conclusion which is in sharp contrast to that of Blackmond and co-workers (Figure 2).

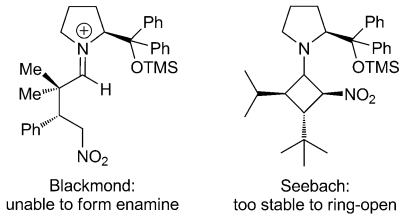


Figure 2. Possible reasons for low reactivity.

Although major controversy regarding the reaction route of this versatile process still remains, the recent detailed mechanistic investigations demonstrate that the tool box of organic chemistry is highly relevant for multistep organocatalytic processes and may lead to more detailed insight into the mechanisms of synthetically important reactions. This recent work not only provides information on the important process commented on herein, but hopefully also stimulates additional fundamental mechanistic studies.[12]

Please note: Minor changes pertaining to the text as well as Figure 2 and the reference section have been made to this manuscript since its publication in *Angewandte Chemie* EarlyView. The Editor.

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