Organocatalysis

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Asymmetric Synthesis of Cyclobutanes by a Formal [2+2] Cycloaddition Controlled by Dienamine Catalysis**

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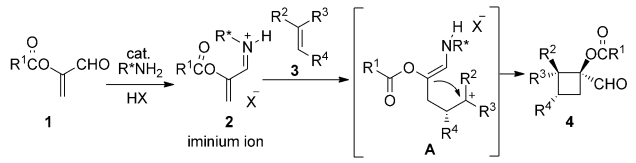
cooperative catalysis · cycloaddition · cyclobutanes · dienamine · organocatalysis

Cyclobutene derivatives have become increasingly important as molecular building blocks (a result of their ring strain, which allows their easy cleavage to other structures), resulting in the development of new methods for their synthesis.[1] However, most existing methods only give access to racemic cyclobutanes, and only a few examples of asymmetric metal-catalyzed reactions have been reported.[1b] In this context, asymmetric organocatalysis[2] has become extremely attractive over the last decade. In particular, aminocatalysis has proven to be a powerful synthetic tool and has found applications in a wide range of cycloadditions.[3] In this field, only one example has been reported (by Ishihara in 2007), in which an enantioselective [2+2] cycloaddition of unactivated alkenes (**3**) and α-acyloxyacroleins (**1**) was studied under iminium catalysis (Scheme 1).[4a] In addition, Miranda and Bach recently reported an intramolecular [2+2] photocycloaddition catalyzed by a chiral sensitizer, but it was restricted to a very specific transformation.[4b] Therefore, the problems associated with [2+2] asymmetric cycloadditions still present an important challenge for the development of new approaches, catalysts, and activation modes.



Scheme 1. Formal [2+2] reaction via iminium ion.

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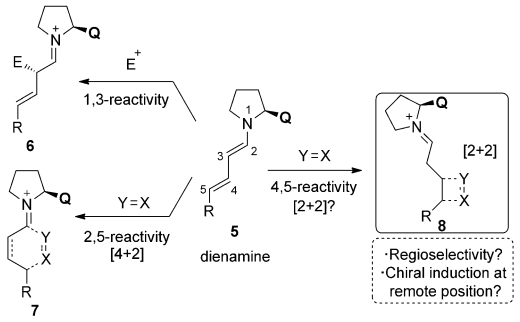
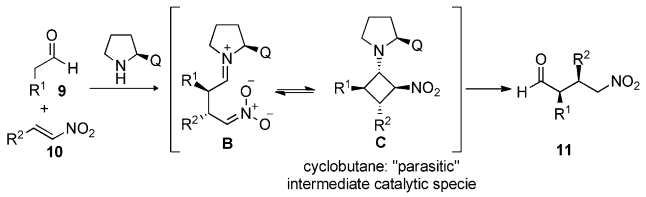
Regarding activation through aminocatalysis, HOMO-raising dienamines can lead to three different reactivities (Scheme 2):[5] 1) 1,3-reactivity with electrophiles (**6**); 2) 2,5-reactivity, which provides [4+2] cycloaddition products (**7**)



Scheme 2. Comparison of reactivities of dienamine systems.

and presents problems in recovering the catalyst, and 3) 4,5-reactivity, which would provide [2+2] cycloaddition products (**8**) by using an "inverse polarity" of the Ishihara iminium ion approach. This latter type of activation must overcome two problems: first, the catalyst must control the stereoselectivity at a remote position of the reactive double bond (positions 4,5), and second, it must achieve complete regioselectivity between the two double bonds of the dienamine intermediate.

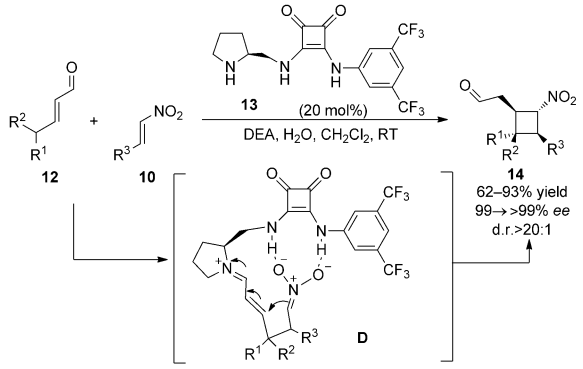
Interestingly, not until recently, when Blackmond and co-workers,[6a,b] and Seebach, Hayashi and their respective co-workers[6c] reported their ingenious works, did other groups find the inspiration to study new organocatalytic [2+2] cycloadditions. These authors thoroughly investigated the Michael addition of aldehydes (**9**) to nitroalkenes (**10**) catalyzed by diarylprolinol ethers (Scheme 3). Blackmond and co-workers[6a] used kinetic and structural studies to rationalize that the rate-determining step of this reaction was the formation of the iminium species as well as the important role played by the acid species used as co-catalysts. On the other hand, Seebach, Hayashi and co-workers[6c] complemented these results with an extensive study, in which the best co-catalyst for this asymmetric Michael addition was identified as 4-nitrophenol. One of the most important



Scheme 3. Identification of [2+2] reaction intermediates.

contributions of these studies was the identification by NMR studies of an unexpected cyclobutane intermediate (**C**) derived from a formal [2+2] cycloaddition. This cyclobutane **C** captures the catalyst from the catalytic cycle and is thus considered a "parasitic intermediate" in the addition of aldehydes to nitroalkenes, because it provokes a resting state of the catalyst and blocks on the catalytic cycle (Scheme 3). This interesting result implied the existence of a more complex reaction mechanism, and the possibility of developing new enantioselective organocatalyzed [2+2] cycloaddition reactions under the appropriate conditions.

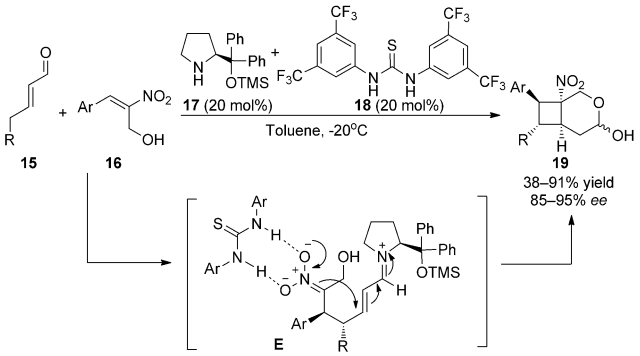
Inspired by these results, Jørgensen and co-workers[7] designed a novel catalyst (**13**) with the intention of effecting a double activation of α,β-unsaturated aldehydes and nitroalkenes through dienamine catalysis and use of bifunctional H-bonds, respectively (Scheme 4). In this case, the electrophile (nitroalkene, **10**) is well oriented by the squaramide



Scheme 4. Bifunctional H-bond-directed dienamine catalysis.

moiety[8] of the catalyst to regioselectively approach the dienamine and undergo an intramolecular reaction with the most remote double bond. The reaction becomes intramolecular because the hydrogen bonding to the catalyst, and therefore the 4,5 position of the dienamine, reacts with the nitroalkene to give intermediate **D**, which undergoes cyclization to cyclobutane **14**. The results were further supported by computational studies, and the authors concluded that a stepwise process would be the most plausible mechanism for this transformation (Scheme 4). Various cyclobutanes were efficiently synthesized by a formal [2+2] cycloaddition from aryl-, heteroaryl-, and alkyl-substituted nitroalkenes **10**, and 5-aryl- ($R^1 = H$, $R^2 = Ar$) and 5-alkyl-substituted ($R^1 = Me$, $R^2 = Me$) aldehydes **12** in high yields and excellent diastereo- and enantioselectivities.

Concurrently, Vicario and co-workers described another formal [2+2] reaction,[9] which involved cooperative catalysis, consisting of an arylprolinol ether (**17**) and a thiourea (**18**), which were used simultaneously to activate both reactants (Scheme 5). In this case, it was necessary to have a α-hydroxymethyl substituent on the nitroalkene (**16**) in order to



Scheme 5. Cooperative catalysis in the formal [2+2] cycloaddition.

push the reaction to the hemiacetal product (**19**) with full conversion. In the screening, the reaction between **15** (R = Ph) and **16** (Ar = Ph, Scheme 5) catalyzed by **17** and thiourea (**18**) as co-catalyst led to product **19** in 86% yield and 91% *ee*. This reaction povided a general protocol for a series of 5-aryl- (both electron-rich and electron-poor aryl substituents worked efficiently), 5-heteroaryl-, and 5-alkyl-substituted α,β-unsaturated aldehydes **15**. Regarding the substitution pattern at the nitroalkene **16**, both electron-donating and electron-withdrawing groups on the aromatic ring were tolerated. However, substitution of the alkyl chain was not described (Scheme 5).

Therefore, in Jørgensen's approach, the use of a new bifunctional catalyst brings the substrates into close proximity and increases the reactivity/stereoselectivity of the [2+2] cycloaddition (Scheme 4). On the other hand, Vicario and co-workers have described the use of two different catalysts in a cooperative manner, which required an additional driving force (hemiacetal formation) and resulted in the rational design of a specific electrophile (Scheme 5).

In conclusion, mechanistic studies on the addition of aldehydes to nitroalkenes have inspired the development of two new approaches for formal enantioselective organocatalyzed [2+2] cycloadditions. New [2+2] reactions with these two catalytic systems, expanding to electron-withdrawing groups other than nitro groups or a heterocyclic version, are expected. Therefore, we believe that these new reactions will open up new opportunities to find reactivities involving organocatalytic cycloadditions.

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