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Extending the Aminocatalytic HOMO-Raising Activation Strategy: Where Is the Limit?**

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Asymmetric aminocatalysis has greatly expanded chemists' ability to stereoselectively functionalize unmodified carbonyl compounds.[1] Crucial to the evolution of the field was the recognition that chiral amines can be used to activate carbonyl compounds through fundamental and general reactivity concepts (Figure 1).[2] The LUMO-lowering effect is the underlying activation principle of *iminium ion* catalysis.[1d] This activation mode is based on the ability of a chiral amine to reversibly condense with α,β-unsaturated carbonyls to form an iminium intermediate, rendering their β-carbon atoms susceptible to nucleophilic attack by lowering the lowest unoccupied molecular orbital (LUMO). Conversely, in the HOMO-raising activation approach,[1b,c] enolizable carbonyls are activated as a result of the formation of an *enamine* intermediate that increases the energy of the highest occupied molecular orbital (HOMO). The latter approach has demonstrated unique versatility, and has been successfully translated into other aminocatalytic activation modes.[2] SOMO (singly occupied molecular orbital) activation exploits the in situ one-electron oxidation of the enamine intermediate, which generates an electrophilic 3π-electron radical cation which may engage in α-stereoselective carbon–carbon bond formation with an electron-rich π-system.[3] Applying the HOMO-raising strategy to enolizable α,β-unsaturated carbonyls implies the formation of a *dienamine* intermediate, whose intrinsic vinylogous nucleophilicity can be used for the direct asymmetric functionalization of unmodified carbonyls at their γ position.[4] Recent findings have demonstrated that the HOMO-raising electronic effect can be further propagated within polyconjugated enals and enones of type **1**, thus leading to the in situ formation of *trienamine* intermediates (species **A** in Figure 1).[5,6] These species can readily participate in Diels–Alder processes as activated chiral dienes, thus intercepting a variety of electron-deficient dienophiles. The chemistry allows the rapid construction of cyclohexenyl rings **2** with a high density of stereocenters adorned with different substituents and with high stereocontrol. Remarkable features of the resulting methodologies are 1) perfect regioselectivity in the formation of two novel carbon–carbon bonds exclusively at the β and ε positions of the original carbonyl function in **1**; and 2) the impressive ability of the selected aminocatalysts **3** and **4** (vide infra) to communicate their inherent stereochemical information while the new stereocenter is forged at the ε position, six atoms away from the catalyst binding point within the trienamine intermediate.

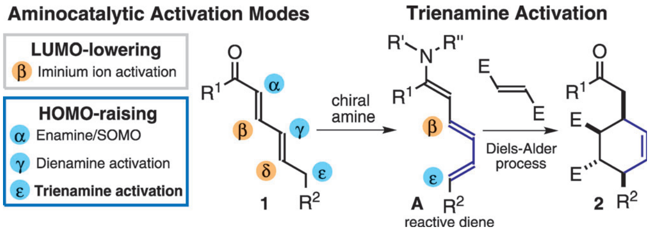

Figure 1. Established activation modes in aminocatalysis and the trienamine activation strategy; E: electron-withdrawing group; R^1: H or aryl.

The viability of trienamine activation was established in a collaborative project between the research groups of Chen and Jørgensen (Scheme 1).[5a] Condensation of diarylprolinol silyl ether aminocatalysts[7] of type **3** with 2,4-dienals **1a** leads to the transient formation of the extended conjugated trienamine intermediates **B**. Easy rotation to the more reactive triene **A** provides a diene moiety able to engage in a highly stereoselective pericyclic reaction with distinct classes of olefinic dienophiles, such as methyleneindolinones **5**,[5a] or olefinic cyanoacetates[5a] and azlactones.[5b] The resulting stereochemically complex cyclic adducts **6** are synthesized with impressive control over the regio-, diastereo-, and enantioselectivity. While the regioselectivity and *endo* selectivity is governed by orbital factors and secondary orbital interactions, the stereoselectivity is secured by the proven ability of chiral secondary amines **3** to ensure effective π-facial discrimination of the reactive covalent intermediate.[7] Trienamine activation was then successfully extended to include nitroalkenes **7** as the dienophile in the pericyclic reaction.[5c] Interestingly, while unsusbstituted 2,4-dienals **1a**

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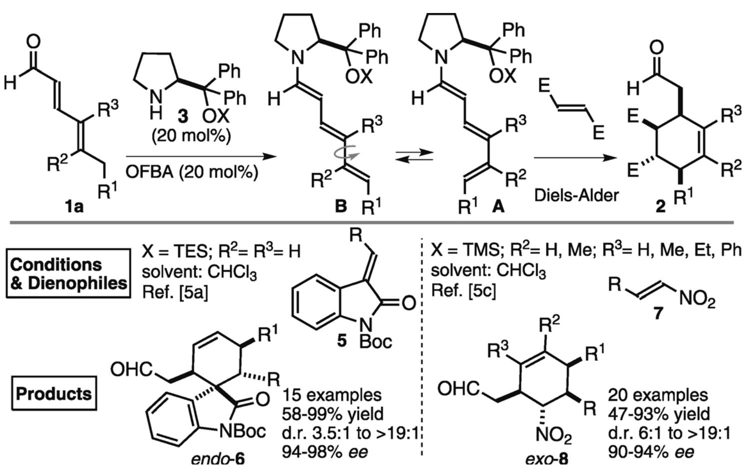
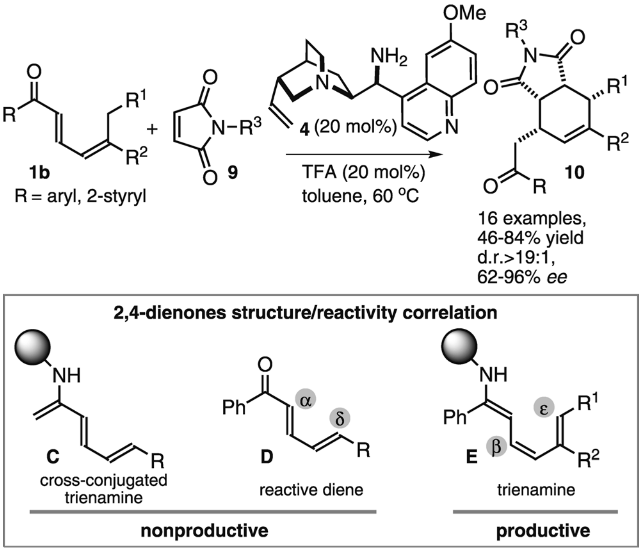


Scheme 1. Asymmetric Diels–Alder reaction of 2,4-dienals. OFBA: *o*-fluorobenzoic acid; TMS: trimethylsilyl, TES: triethylsilyl.

($R^2 = R^3 = H$) remained unreactive, the rational introduction of alkyl substituents to enals **1a**—aiming at raising the trienamine HOMO energy by electron-donating effects—accounted for a highly stereoselective Diels–Alder process. It is worth mentioning that the trienamine-driven transformation led to chiral adducts **8** through an unexpected *exo*-selective pericyclic reaction.

The general applicability of a chemical strategy is a crucial parameter for evaluating its potential to synthesize complex chiral molecules. Chen and colleagues have recently extended trienamine activation to another class of substrates: 2,4-dienones.[6] Key to their success was the established ability of the cinchona-based primary aminocatalyst **4** to effectively activate enone substrates through mechanistically different activation modes while reliably inducing a high level of stereocontrol.[8] Still, this was not a trivial achievement: building on experimental observations, a logical and careful design of the dienones was needed to effectively channel the reaction toward a productive pericyclic pathway induced by the trienamine intermediate **E** (Scheme 2). Indeed, the presence of an aryl group (R = Ph in **1b**) instead of an enolizable methyl substituent at the α position of the carbonyl was essential to suppress the detrimental formation of the cross-conjugated trienamine intermediate **C**, which completely inhibited the reactivity. Afterwards, a γ,γ-disubstituted pattern ($R^2 = Me$ in **1b**) was envisioned to prohibit the noncatalyzed Diels–Alder reaction of the dienone **D**, which is an intrinsically reactive diene conjugated between the α and δ carbons, assuring in this way an amine-catalyzed β,ε-regioselective cyclization.

The Diels–Alder reaction of maleimides **9** with a wide variety of structurally distinct dienones **1b** under the trienamine activation by the primary aminocatalyst **4** afforded the corresponding cyclic compounds **10** in high optical purity (Scheme 2). The chemistry was also extended to completely different classes of dienophiles, such as methyleneindolinones **5**, olefinic cyanoacetates, and nitroalkenes **7** preserving a very high degree of regio- and stereoselectivity, and *endo* selectivity.[6]



Scheme 2. Challenges arising from the trienamine activation of 2,4-dienones. TFA: trifluoroacetic acid; the black circle represents the catalyst scaffold.

Mechanistically, the described trienamine activation of enals and enones may be considered a logical extension of the general catalysis concept based on HOMO raising.[2] Still, it seems likely that the conceptualization and identification of trienamine reactivity, to date limited to the [4+2] cycloaddition, may drive further investigations aimed at its application to more general nucleophilic addition reactions and substitution manifolds. If successful, those efforts would provide an unprecedented way to directly and stereoselectively functionalize unmodified carbonyls at their ε-carbon atom. The results by Jørgensen and Chen illustrate how asymmetric aminocatalysis, despite the high levels of sophistication already reached, remains a highly active area of chemical research, able to provide innovative strategies to successfully address difficult challenges related to the synthesis of complex chiral molecules.

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