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# Trienamines in Asymmetric Organocatalysis: Diels−Alder and Tandem Reactions

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Supporting Information

**ABSTRACT:** The discovery of a novel activation mode provided by organocatalysis is presented. It is demonstrated that the merger of optically active secondary amines and polyenals generates reactive trienamine intermediates, which readily participate in Diels−Alder reactions with different classes of dienophiles, hence, providing a facile entry to highly complex molecular frameworks with excellent stereocontrol. For the Diels−Alder reactions with 3-olefinic oxindoles, spirocyclic oxidoles are formed in high yields, and with enantioselectivities in the range of 94−98% ee. It is demonstrated, that some of these products can be transformed into the hexahydrofuro[2,3-b]indole fragment. The organocatalytic trienamine concept has been extended to also include Diels−Alder reactions of olefins substituted with cyanoacetates providing multifunctional cyclohexenes with three contiguous stereocenters in high yield and good stereocontrol. The novelty of this activation strategy lies within the perfect chirality relay over a distance of up to eight bonds. Moreover, we also present the first trienamine tandem reaction by combining trienamine catalysis with enamine activation. In addition to the experimental results, a detailed mechanistic survey is also provided including NMR spectroscopic studies and calculations of the reactive trienamine intermediates, rationalizing the origin of stereochemistry.


## INTRODUCTION

Nature, being the most profound pioneer of reaction mechanisms, is a source of inspiration for the discovery of new synthetic methods and activation modes in contemporary organic chemistry.[1] The ability of nature to employ enzyme-bound amines[2] as promoters for a range of transformations of carbonyl compounds has inspired the invention[3] and rapid exploration of the use of chiral amines as catalysts.[4] These transformations include a series of stereoselective reactions via HOMO (highest occupied molecular orbital),[5,6] LUMO (lowest unoccupied molecular orbital),[7] and SOMO (singly occupied molecular orbital)[8] activation.

The possibility to activate a carbonyl compound by HOMO-raising upon condensation with amines has led to the conceptualization of two unique catalytic strategies, mainly by enamine,[5] and more recently dienamine,[6] formation (Figure 1). The organocatalytic enantioselective α-functionalization of carbonyl compounds such as aldehydes, via enamine intermediates, is now an attractive and widely used procedure in organic synthesis.

In our attempts to try to discover and explore new reactivity pathways, we questioned whether the HOMO-activation could be projected to poly conjugated enals, such as 2,4-dienals, hence forming a reactive trienamine intermediate (Figure 1). A key challenge of the proposed trienamine activation mode is the simultaneous HOMO-raising of both the γ- and the ε-carbon atom, significantly lowering the predictability of the reaction course. Another major concern is the catalyst's ability to provide sufficient stereocontrol at the very remote ε-center—eight bonds from the stereocontrolling center.

Herein, as a proof of concept, we present the first amino-catalyzed Diels−Alder reaction[9] employing in situ formed trienamines with two different classes of olefinic dienophiles (Scheme 1, left), and the first amino-tandem reaction utilizing trienamine and enamine intermediates (Scheme 1, right). These reactions proceed with excellent regio-, diastereo-, and enantiocontrol by the application of a chiral secondary amine as the catalyst. It is also demonstrated that one class of olefins gives spirocyclic oxindoles which are converted into the hexa[2,3-b]indole fragment.[10] Furthermore, we present a series of experimental and computational studies that give information of the trienamine intermediate and provide a mechanistic rationalization for the origin of selectivity.

## RESULTS AND DISCUSSION

**NMR Spectroscopic Studies and Initial Mechanistic Survey.** Initial investigations were conducted to confirm the presence of the proposed trienamine intermediate, through which

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the reaction may occur. Samples were prepared with different ratios of 2,4-heptadienal **1a**, 2-(diphenyl((trimethylsilyl)oxy)-methyl)pyrrolidine **2a**[11] and *o*-fluorobenzoic acid (OFBA) in $CDCl_3$ (Table 1). The terminal methyl-group of aldehyde **1a** and the anticipated trienamine intermediate **3** can be easily differentiated and used for quantification by NMR spectroscopy, since it converts from pure aliphatic nature in **1a** to an allylic methyl group in **3** (see the Supporting Information). By mixing dienal **1a** and the diphenylprolinolsilyl ether **2a** in a 1:1 ratio (0.2 M) with no acid additive, less than 10% of **3** was observed after 1 h (Table 1, entry 1). After the same time but with 0.5 equiv of acid additive, the observed trienamine formation reached 50% (entry 2). Higher amounts of OFBA or longer reaction time did not significantly increase the amount of **3** relative to **1a** (entries 3, 5); however, prolonged equilibration time led to significant build-up of the amount of **3** in the sample without acid (entries 4, 6). Finally, a sample with substochiometric amounts of catalyst **2a** and acid was investigated (ratio **1**:**2**:OFBA identical to the reaction conditions later used in the Diels–Alder reactions). The catalyst incorporation reached 62% (entry 7), which is in accordance with the previous observation (entry 5). Moreover, the NMR spectroscopic studies showed that only one isomer of the trienamine intermediate **3** could be detected, which is assumed to be the lowest-energy all-trans conformation (close energy single-bond rotamers may not be differentiable). Iminium-ion formation was not observed,[12] suggesting that a fast isomerization to the corresponding trienamine intermediate takes place. This observation is in accordance with the fact that there is only scarce experimental precedence of an iminium-ion activated conjugate addition to 2,4-dienals.[7l] It is notable that the formed trienamine **3** is stable in the $CDCl_3$ solution (confirmed by added internal standard) and products resulting from dimerization reactions are minimal.

One issue of concern might be the simultaneous activation of both the $\gamma$- and the $\varepsilon$-center by raise of the HOMO of the trienamine intermediate. The preference for trienamine-catalysis in Diels–Alder-reactions ($\varepsilon$-center activation) is rationalized in Figure 2. Subsequent to the condensation of dienal **1** and diarylprolinolsilyl ether **2**, iminium-ion **A** rapidly isomerizes to the lowest energy all-trans conformation of trienamine intermediate **B**. Two single bond rotations, C2–C3 or C4–C5, will lead to the reactive conformations **D** or **C**, respectively. It is rationalized that the formation of **C** is favored due to minimal steric clash in the rotation, and thereby leading to the formation of product **E** by a Diels–Alder reaction. Noteworthily, catalyst inactivation would occur following the $\gamma$-activation pathway for

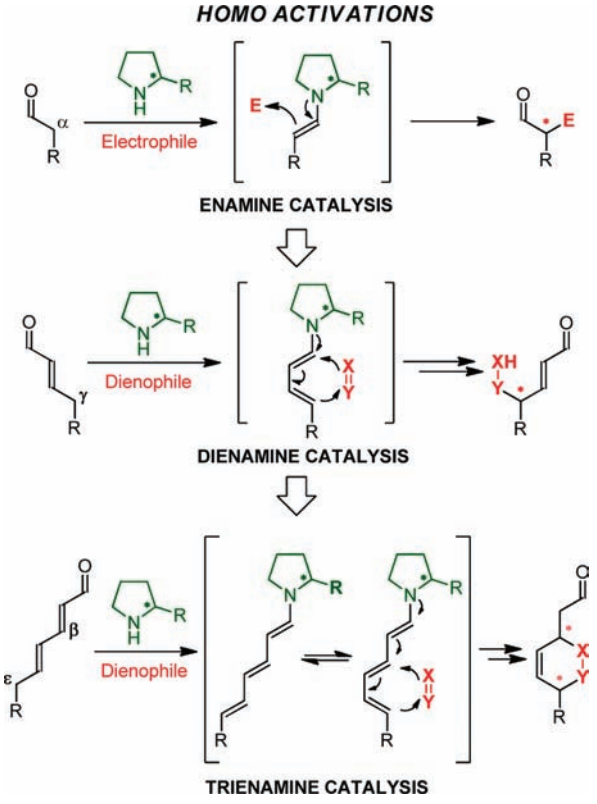
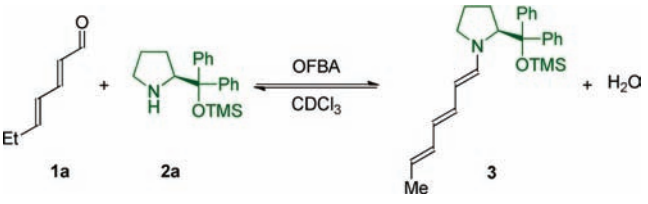



**Figure 1.** HOMO-activation modes of aldehydes provided by chiral secondary amines.

**Table 1. NMR Spectroscopic Study on Trienamine Intermediate Formation**




| entry | **1a**:**2a**:OFBA | [**1a**] [M] | *t* [h] | catalyst incorporation [%] |
|---|---|---|---|---|
| 1 | 1:1:0 | 0.2 | 1 | <10 |
| 2 | 1:1: 0.5 | 0.2 | 1 | 50 |
| 3 | 1:1:1 | 0.2 | 1 | 50 |
| 4 | 1:1:0 | 0.2 | 5 | 20 |
| 5 | 1:1:1 | 0.2 | 5 | 60 |
| 6 | 1:1:0 | 0.2 | 24 | 50 |
| 7[a] | 7.5:1:1 | 0.15 | 5 | 62 |

[a] Concentrations identical to the reaction conditions used in the Diels–Alder reactions.

**Scheme 1. Outline of the Developed Aminocatalyzed Reactions via the Trienamine Intermediate**



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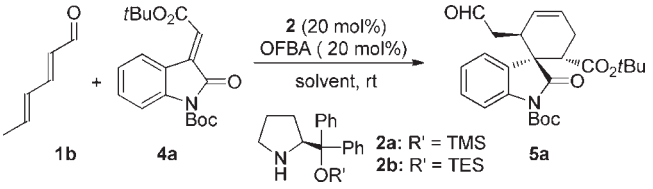
all-carbon based dienophiles (Y ≠ heteroatom). A parallel argument for the selection of the ε-activation as the favored pathway may be conducted on the basis of a FMO analysis. Therein, it is anticipated that the rotamer **C** possesses an energetically higher HOMO, which provides more favorable orbital overlap with the LUMO of the dienophile.

Computational studies were performed in order to support the rationale for a favored ε-activation pathway that sets the foundation of a successful catalytic cycle involving trienamines. A series of DFT-calculations at the B3LYP/6-31G(d) level of theory were performed using the Jaguar program[13] showing that the all-trans structure **B** is the lowest energy trienamine isomer (relative energy 0 kcal·mol$^{-1}$). Intermediates **C** and **D**, both obtained by a single-bond rotation from **B**, are similar in energy by only 3.6 and 3.8 kcal·mol$^{-1}$ above the minimum energy conformer **B**, respectively. However, a 360° conformational analysis of the single-bond rotations for the formation of **C** and **D** confirmed the initial hypothesis, that the bond rotation most distant to the steric bulk of the amino-catalyst results in the lowest rotational energy barrier, as the barrier to **C** is 1.8 kcal·mol$^{-1}$ lower in transition state energy than the formation of **D**. The HOMO and LUMO of both **C** and **D** are set up for a symmetry-allowed interaction with the LUMO and HOMO of an olefin. These orbital coefficients of importance have been calculated (HF/STO-3G). The coefficients at the carbon atoms of the reacting diene are −0.23 (C3, **C**), 0.34 (C6, **C**), −0.32 (C1, **D**), and 0.43 (C4, **D**). On the basis of these orbital coefficients, intermediate **D** should be expected to undergo the most favorable interaction with an olefin. However, the HOMO of **D** is located 2.17 eV lower in energy than the HOMO in **C** (located at −2.23 eV), and thus, the HOMO of **C** is more reactive than the HOMO of **D**. Furthermore, the LUMO in **C**, which is set up to interact with the HOMO of an olefin, is located 4.41 eV lower in energy than the corresponding LUMO in **D** (located at 2.04 eV). The location of the energetically important FMO points thus to **C** as the most reactive intermediate. In summary, the rotation barrier for the formation of **C** and the energy of the orbitals set up for interaction with the olefin both suggest that the ε-activation should be the predominant reaction pathway.

**Diels−Alder Reactions: Screenings and Scope.** Encouraged by the computational findings, we turned the attention toward finding an experimental proof of concept. The Diels−Alder reactions to be studied were of 3-olefinic oxindoles[14] and olefinic cyanoacetates.[15] Gratifyingly, the desired trienamine catalyzed Diels−Alder reaction could be achieved by reacting 2,4-hexadienal **1b** with 3-olefinic oxindole **4a** as dienophile in the presence of the diphenylprolinolsilyl ether **2a** and OFBA. Chlorinated solvents proved to be the most suitable for the reaction, and the

**Table 2. Optimization of the Diels−Alder Reaction of 2,4-Hexadienal 1b with 3-Olefinic Oxindole 4a**[a]




| entry | acid | solvent | $t$ [h] | yield [%][b] | ee [%][c] |
|---|---|---|---|---|---|
| 1 | OFBA | $CH_2Cl_2$ | 7 | 91 | 98 |
| 2 | BA | $CH_2Cl_2$ | 22 | 75 | 98 |
| 3 | BTFMBA[d] | $CH_2Cl_2$ | 7 | 86 | 97 |
| 4[e] | OFBA | $CH_2Cl_2$ | 7 | 95 | 98 |
| 5[e] | OFBA | $CHCl_3$ | 6 | 98 | 98 |

[a] Unless noted otherwise, reactions were performed with **1b** (0.15 mmol), **4a** (0.1 mmol), **2a** (0.02 mmol), and acid (0.02 mmol) in the solvent (1 mL) at rt. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase after derivatization by a Wittig reaction (see the Supporting Information); dr > 99:1. [d] BTFMBA = 3,5-bis(trifluoromethyl)benzoic acid. [e] **2b** as the catalyst.

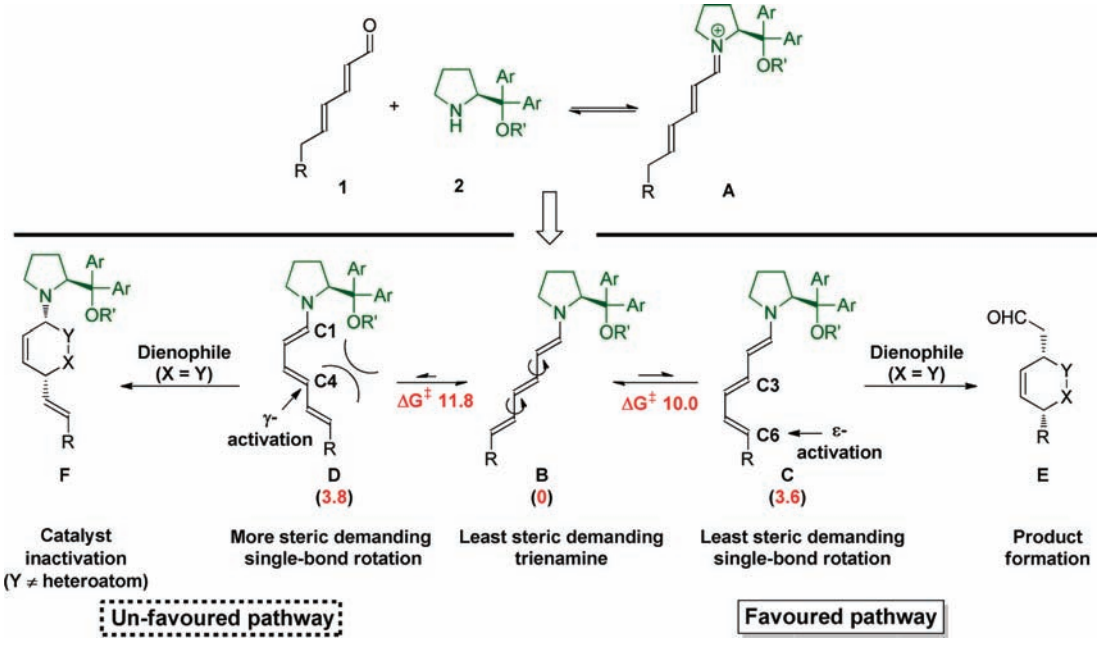



**Figure 2.** Possible reaction pathways of the trienamine intermediates and rationalization of the preference of ε-activation (red numbers are relative and in kilocalories per mole).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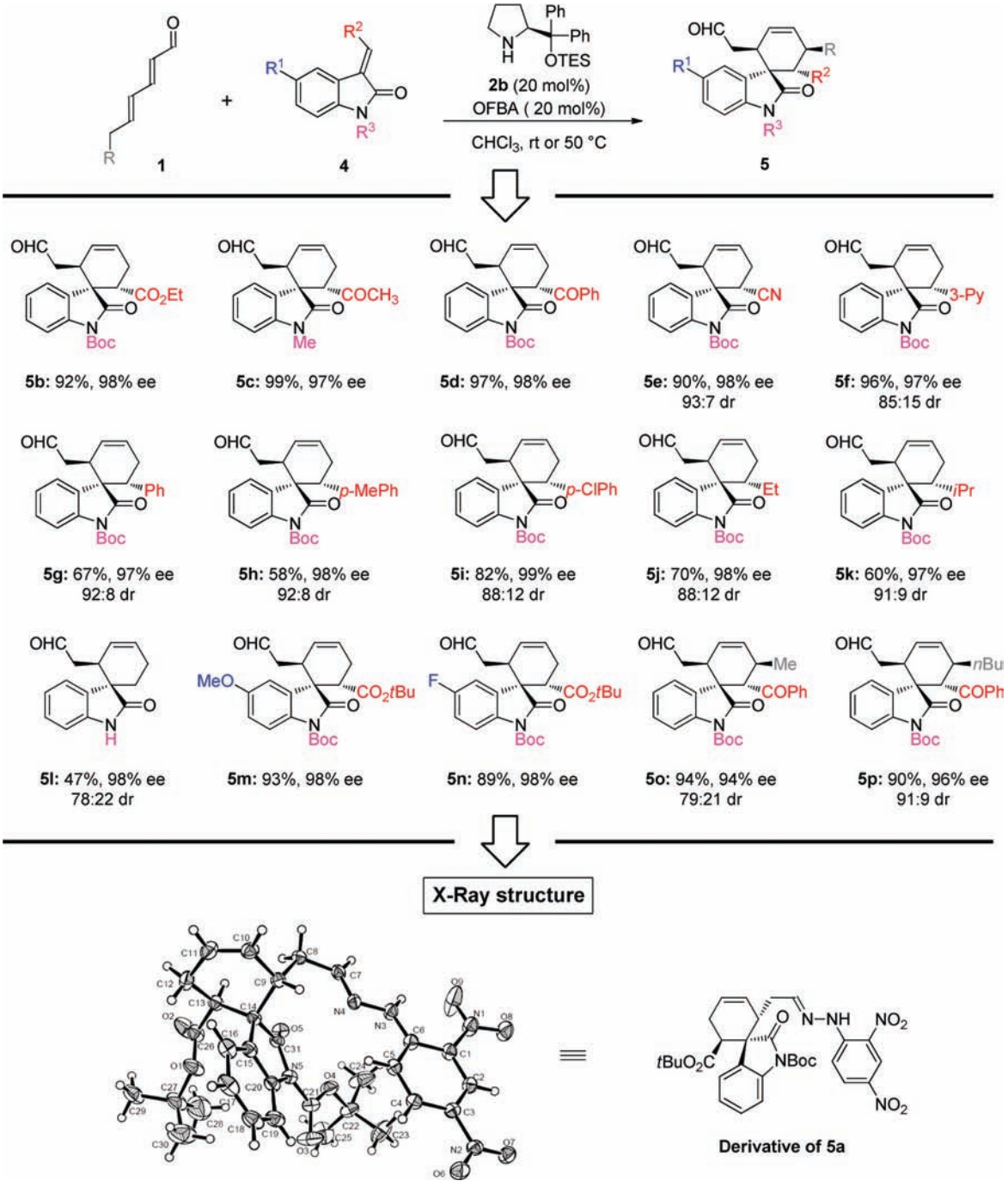


**Figure 3.** Scope of the organocatalyzed Diels–Alder reaction with 3-olefinic oxindoles involving a trienamine intermediate and X-ray structure for the determination of the absolute configuration.

desired cycloaddition proceeded smoothly in $CH_2Cl_2$ at room temperature furnishing the spirocyclic oxindole **5a** in 91% yield and 98% ee as a single diastereoisomer (Table 2, entry 1). Acid additives proved to have decisive effects on the reactivity. A weaker acid such as benzoic acid (BA) decreased the reaction rate significantly and resulted in lower isolated yield (entry 2), while a further increase in the acidity of the additive led to a slight drop in enantioselectivity (entry 3). Additional improvements could be achieved by employing the more sterically demanding *O*-TES ether analogue **2b** (entry 4) and $CHCl_3$ as catalyst and solvent, respectively (entry 5).

With the optimized reaction conditions in hand, the scope and limitations of the organocatalyzed Diels–Alder reactions involving trienamines were explored. The results are summarized in Figure 3. It is demonstrated that a variety of substitution patterns on the 3-olefinic oxindole dienophile can be tolerated. Excellent stereocontrol was observed for 3-olefinic oxindoles bearing electron-withdrawing groups furnishing products **5b–e** with high levels of stereocontrol (97–98% ee) and in excellent yields. Both electron-rich and -poor aromatic groups, as well as a heteroaromatic substituent on 3-olefinic oxindoles were compatible with the developed reaction, and products


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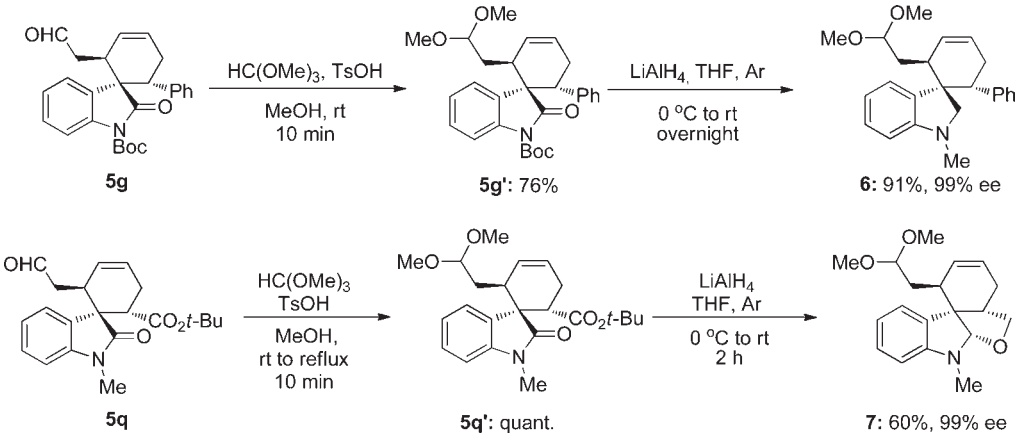
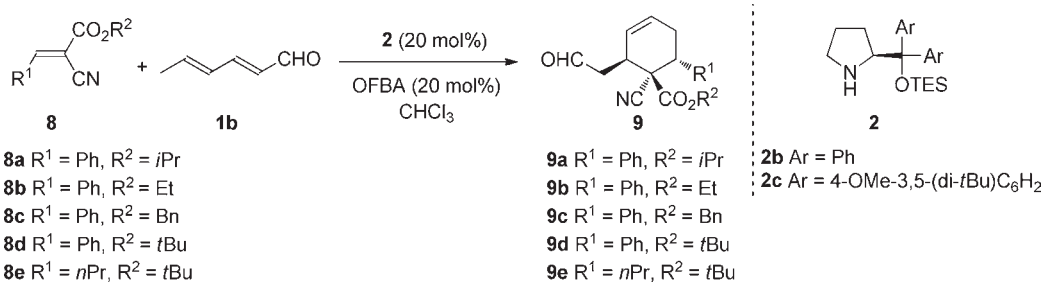



**Figure 4.** Synthetic transformations of spiro-oxindoles.

**Table 3. Optimization and Scope of the Diels–Alder Reaction Using Olefinic Cyanoacetates as Dienophiles**[a]




| entry | 8 | cat | $T$ [°C] | $t$ [h] | yield[b] [%] | ee[c] [%] | dr[d] |
|---|---|---|---|---|---|---|---|
| 1 | **8a** | **2b** | rt | 96 | trace | | |
| 2 | **8a** | **2b** | 40 | 96 | 71 (**9a**) | 85 | 86:14 |
| 3 | **8a** | **2c** | 50 | 60 | 81 (**9a**) | 89 | 86:14 |
| 4 | **8b** | **2c** | 50 | 48 | 87 (**9b**) | 86 | 80:20 |
| 5 | **8c** | **2c** | 50 | 29 | 97 (**9c**) | 88 | 78:22 |
| 6 | **8d** | **2c** | 50 | 60 | 71 (**9d**) | 89 | 90:10 |
| 7 | **8e** | **2c** | 50 | 48 | 72 (**9e**) | 86 | 82:18 |

[a] Unless noted otherwise, reactions were performed with **8** (0.1 mmol) and **1b** (0.2 mmol) in $CHCl_3$ (0.5 mL). [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by $^1H$ NMR analysis.

**5f–i** were also obtained with 97–99% ee even at 50 °C, albeit in slightly lower isolated yields due to decreased reactivity of the dienophiles. Moreover, 3-olefinic oxindoles carrying simple alkylic side-chains could also be successfully employed (**5j,k**), achieving results similar to those obtained for the aromatic counterparts. Noteworthily, the unsubstituted and unprotected 3-methyleneoxindole **4l** could also be used as reaction partner providing spiro compound **5l** having 98% ee; however, considerable side-reactions were observed resulting in lower yield. Tuning the electronic nature of the oxindole ring of the dienophile did not alter the reaction course, showing no preference for electron-donating or electron-withdrawing substituents (**5m,n**). Finally, other trienamine-precursors such as 2,4-heptadienal **1a** and 2,4-decadienal **1c** were evaluated for the Diels–Alder reaction. To our delight, the same high reactivity and remarkable stereocontrol were observed, affording products **5o,p** with four contiguous stereogenic centers in 90–94% yield, 79:21–91:9 dr, and 94–96% ee. The absolute configuration was unambiguously assigned by X-ray analysis on the 2,4-dinitrophenylhydrazone derivative of **5a** (see Figure 3, bottom).[16]

The organocatalytic Diels–Alder reaction of the trienamines can also be performed on a preparative scale (1.5 mmol) at lower catalyst loading (10 mol %) but with prolonged reaction time. This was shown for the formation of products **5a** (90% yield, dr > 99:1, 98% ee) and **5d** (97% yield, dr > 99:1, 98% ee).

The obtained spiro-oxindoles may be transformed into a variety of valuable synthetic building blocks such as indoline **6** and the fused hexahydrofuro[2,3-*b*]indole **7**.[10] As demonstrated in Figure 4, the transformation of the spiro-oxindoles into **6** and **7** proceeds in high yields maintaining the excellent enantiomeric excess obtained in the organocatalytic step.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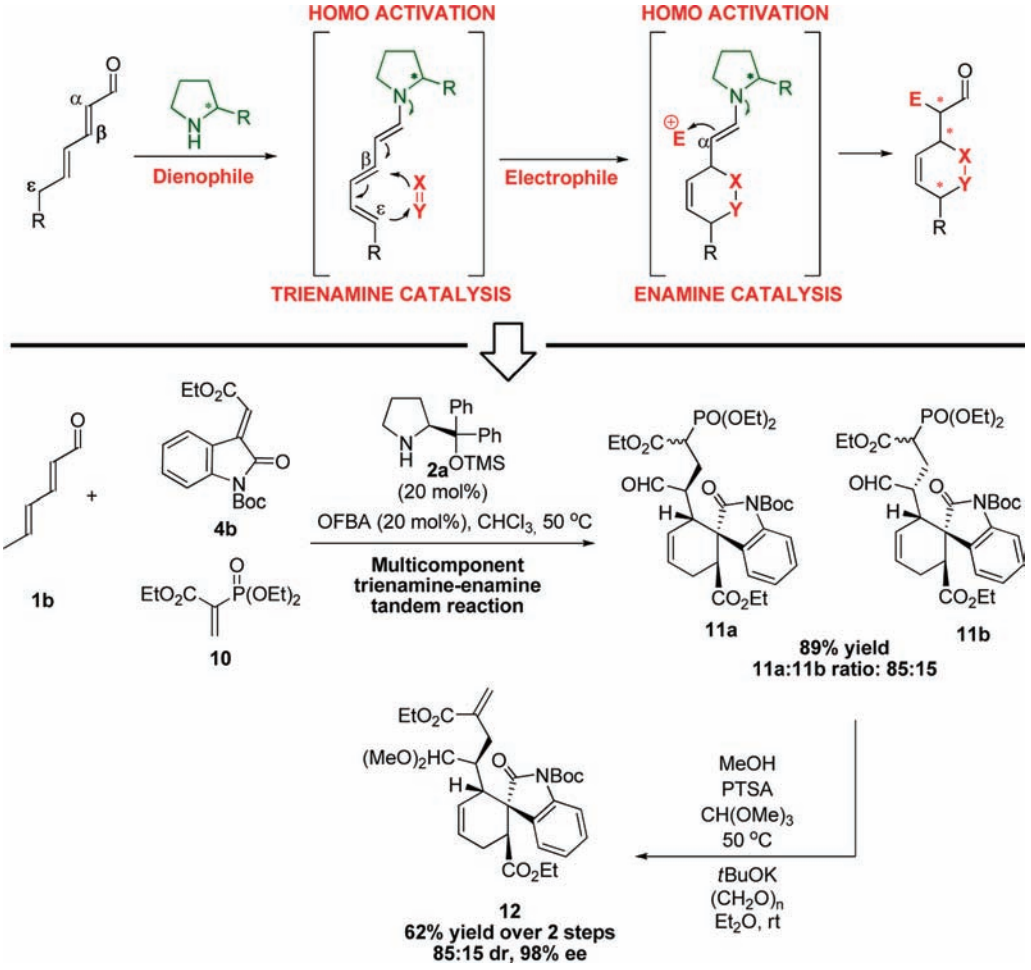


**Figure 5.** Design and realization of an organocatalytic trienamine−enamine multicomponent tandem reaction (ratio of **11a**/**b** and dr of **12** were determined by $^{31}P$ and $^{1}H$ NMR, respectively).

In order to further demonstrate the generality of the organocatalyzed Diels−Alder reaction via trienamines, it is shown that other types of activated olefins are equally capable to participate as dienophiles in the developed reaction (Table 3), as exemplified by the use of olefins **8**, formed by Knoevenagel condensation of benzaldehyde and different cyanoacetates.[15] A brief screening revealed that elevated temperatures were required to achieve proper reactivity and conversion of starting materials (compare entries 1 and 2). It was also discovered that the use of a bulky ester group in the dienophile, such as in *tert*-butyl cyanoacetate **8d**, in combination with the sterically more demanding catalyst **2c**[17] provided the best results in terms of diastereo- and enantioselectivity by which cyclohexene derivative **9d** was obtained in 71% yield, a diastereoisomeric ratio of 90:10 and 89% ee of the major diastereisomer (entry 6). The use of less sterically crowded cyanoacetates, such as **8a**−**c**, led to product formation with slightly lower diastero- or enantioselectivities (entries 3−5). Moreover, the alkyl-substituted substrate **8e** could also be applied, affording the cycloadduct **9e** in similar good results, showing that olefins having alkyl or aryl groups can participate in this organocatalytic trienamine Diels−Alder reaction. Other electron-deficient olefins commonly used in Diels−Alder reactions such as nitrostyrene, maleimide, and quinones did not provide the desired product under these conditions.

**Tandem Reactions Involving Trienamines.** Due to its high compatibility and reaction condition tolerance, organocatalysis has proven to be a highly powerful tool in promoting enantioselective tandem reactions,[7l,18] where multiple activation modes of the catalyst act tandemly for the construction of complex molecular frameworks in a single manual operation. It is believed that organocatalytic tandem reactions via trienamine intermediates may offer new perspectives in this respect and open up for novel transformations. A closer look at the reaction products of the organocatalyzed Diels−Alder reactions using the trienamine concept suggests that the α-position of the aldehyde is available to react following an enamine pathway. Hence, we proposed that an organocatalyst should be able to promote a double HOMO-activation of 2,4-dienals leading to a sequential and cycle specific trienamine and enamine tandem reaction (Figure 5).

Herein, we present the first example of an organocatalyzed trienamine−enamine tandem reaction. The double-activated ethyl 2-(diethoxyphosphoryl)acrylate **10** was selected as the electrophilic partner for the enamine-catalyzed reaction.[19] Remarkably, the performed reaction is completely cycle-specific. Despite the possibility of **10** to participate as a reactive dienophile, no crossover products were observed and compound **11** was formed in 89% yield. The organocatalytic trienamine cycle reached the same selectivity as earlier even at 50 °C, while the organocatalytic enamine addition led to a 85:15 dr at the


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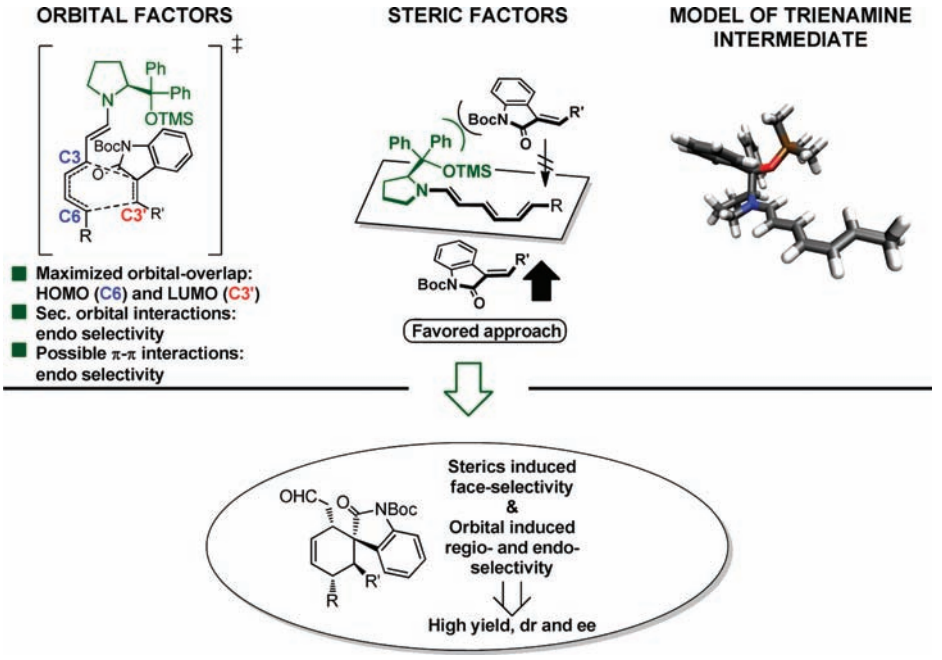


**Figure 6.** Rationalization of the regio-, diastereo-, and enantioselectivity.

α-center (to the aldehyde). In a parallel control-experiment where the electrophile was sequentially added, upon the completion of the initial Diels–Alder reaction, similar results were attained (94% yield, 85:15 dr). Noteworthily, there is a clear matched and mis-matched interaction between aminocatalyst and cycloadduct **5** (see Figure 3). By reacting preisolated **5b** with **10** in the presence of *ent*-**2a**, as catalyst, a 1:1 ratio of diastereoisomers **11a** and **11b** was observed. The other newly generated stereocenter, flanked by two electron-withdrawing groups, is labile due to the high acidity of the α-proton. However, this noncontrollable stereocenter is easily eliminated by an acetal protection/Horner–Wadsworth–Emmons reaction sequence forming compound **12** without epimerization of the remaining stereocenters.

**Origin of Selectivity.** The observed high regio-, diastereo-, and enantioselectivity can be explained by a combination of orbital and steric factors (Figure 6). Despite the possibility of numerous regio- and diastereoisomers, one predominant isomer is formed on the basis of several orbital factors:[20] (i) Since both the diene and dienophile are unsymmetric, maximizing the charge interaction and orbital-overlap between the reacting HOMO of the trienamine intermediate and the LUMO of the dienophile defines the regioselectivity. The HOMO of the diene moiety of the trienamine intermediate has the right symmetry and, furthermore, is enhanced at the C6 center by the aminocatalyst, while the largest coefficient of the LUMO of the dienophile is located at the C3′ center. These orbital data secure the perfect regioselectivity of the reaction. (ii) The high diastereoselectivity of the reaction is presumably a result of favorable secondary orbital interactions between the lactam-carbonyl and the forming double bond at the back of the diene-substrate (endo-selectivity).[21] Possible favorable $\pi-\pi$ interactions between catalyst (Ph groups) and oxindole might also partially account for the endo-selectivity. While orbital factors define the "alignment" of the trienamine and dienophile, steric reasons direct the approach of the dienophile from one preferred face. The face-selectivity, controlled by the aminocatalyst, is solely responsible for the excellent enantioselectivity in the Diels–Alder reaction. There may be doubts regarding the catalyst's ability to provide shielding at the remote ε-center; however, due to the concerted nature of the Diels–Alder reaction mechanism, steric shielding at the $\beta$-position (also forming a new bond) indirectly extends the chirality transfer from the aminocatalyst to the remote ε-center, and as result, highly enantioenriched products are obtained. The calculated model of the trienamine intermediate is also shown in Figure 6 showing the remote face shielding by the catalyst. To summarize, by combining steric-induced face-selectivity and orbital-induced regio- and endo-selectivity, the experimentally observed high regio-, diastereo-, and enantioselectivity can be rationalized.

Finally, it is noteworthy that a double conjugate addition sequence may also account for the formed products. However, by monitoring the reaction by NMR spectroscopy, no monoaddition intermediates could be observed, implying a concerted reaction mechanism (or a very fast second addition step). In fact, the high enantio- and diastereoselectivity also suggests a cycloaddition pathway. For a double-Michael mechanism, the reaction may occur from the all-trans trienamine, where steric face-shielding by the catalyst is minimal and a low enantiomeric excess should be expected. Good stereocontrol might occur by a resolution manner (dynamic kinetic asymmetric transformation);[22] however, due to the absence of observable and isolatable intermediates, this route seems to be unlikely.

## ■ CONCLUSION

We have demonstrated the discovery of a novel activation mode, provided by small molecule amines. The novelty of this activation strategy, named trienamine catalysis, lies within the perfect chirality relay over a distance of up to eight bonds. As a proof of concept, we have realized the first trienamine catalyzed Diels–Alder reaction of 2,4-dienals and two classes of olefins as trienamine precursors and dienophiles, respectively. A detailed


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mechanistic survey, including NMR and computational studies in concert with rationalization of the preferred reaction pathway and the origin of stereoselectivity, has been presented. Furthermore, we have illustrated that trienamine catalysis can be merged with other amino-catalyzed activation modes, as demonstrated by the first trienamine−enamine tandem reaction. We believe that this work may open up for new possibilities of trienamine catalyzed cycloadditions and tandem reactions, offering an interesting entry to complex molecule synthesis using asymmetric catalysis.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Complete experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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