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Dienamine Catalysis: Organocatalytic Asymmetric γ-Amination of α,β-Unsaturated Aldehydes

Søren Bertelsen, Mauro Marigo, Sebastian Brandes, Peter Dinér, and Karl Anker Jørgensen*

Contribution from The Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Received June 30, 2006; E-mail: kaj@chem.au.dk

Abstract: A new concept in organocatalysis is presented, the direct asymmetric γ-functionalization of α,β-unsaturated aldehydes. We disclose that secondary amines can invert the usual reactivity of α,β-unsaturated aldehydes, enabling a direct γ-amination of the carbonyl compound using azodicarboxylates as the electrophilic nitrogen-source. The scope of the reaction is demonstrated for the enantioselective γ-amination of different α,β-unsaturated aldehydes, giving the products in moderate to good yields and with high enantioselectivities up to 93% ee. Experimental investigations and DFT calculations indicate that the reaction might proceed as a hetero-Diels-Alder cycloaddition reaction. Such a mechanism can explain the "unexpected" stereochemical outcome of the reaction.

Introduction

The continuous discovery of new and more efficient catalytic reactions is one of the key steps in the development of simpler, cheaper, and more environmentally friendly syntheses of complex molecules. In particular, catalytic asymmetric reactions are important, because they lead to the creation of new chemical bonds along with the stereoselective formation of new chiral centers.

In this broad research field, it is possible to identify a large number of reactions that are catalyzed by metal-free organic compounds, and these different organocatalysts[1] are often classified on the basis of their activation mechanism. It is well documented that, for example, Brønsted acids can be used to catalyze the nucleophilic addition to imines and carbonyl compounds.[2] On the other hand, tertiary amines derived from cinchona alkaloids[3] or chiral guanidine derivatives[4] are often found to be very effective in the activation of weakly acidic nucleophiles such as 1,3-dicarbonyl compounds, cyanoacetates, or allylic systems. To promote the reaction of less electrophilic species, or of less acidic nucleophiles, a well-established strategy consists of the use of phase-transfer catalysts in combination with inorganic bases.[5] Chiral phosphines (or tertiary amines) are also applied in a variety of different asymmetric transformations, and their catalytic properties are connected with their nucleophilic nature.[6] Inspired by nature, organic chemists have also applied chiral carbenes as organocatalysts for a series of new stereoselective bond-forming reactions.[7] Furthermore, many catalysts are now designed to combine some of the previously introduced concepts and to activate both partners of the reaction, as in the case of the catalyst developed by Takemoto et al.[8]

Chiral secondary amines and chiral imidazolidinones are a class of organocatalysts that play a fundamental role in a large variety of important transformations. In the early 1970s, Eder, Sauer and Wiechert, and Hajos and Parrish reported a new approach to the intramolecular aldol reaction using L-proline as the chiral catalyst.[9]

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Almost 30 years later, List and Barbas rediscovered and expanded the catalytic properties of proline by presenting the first enantioselective, intermolecular aldol reaction of acetone with aromatic aldehydes.[10] The same year, MacMillan's group reported the application of chiral imidazolidinones derived from phenylalanine in the organocatalytic, enantioselective Diels−Alder reaction of α,β-unsaturated aldehydes with dienes.[11]

Despite the fundamental analogies in the structure of these catalysts and substrates, the mechanisms of these reactions are very different. In the case of the α-functionalization of aldehydes and ketones, an enamine is formed by the optically active catalyst and the carbonyl compound giving a chiral nucleophile, which will attack the electrophile (Scheme 1, eq 1). In the case of the α,β-unsaturated systems, the catalyst activates the substrate by decreasing the energy of the LUMO in the intermediate iminium-ion, thereby facilitating the transfer of the chirality by addition of the nucleophile to the β-position (Scheme 1, eq 2).

Following these two inspiring articles, numerous innovative and increasingly sophisticated examples of the use of aminocatalysis have emerged in what can be called an explosive expansion of the field of organocatalysis, thereby producing a "nearly endless" number of optically active building blocks by applying these ideas.[12] Furthermore, the combination of organocatalytic asymmetric β- and α-functionalization of α,β-unsaturated carbonyl compounds has also been pursued in the development of domino reactions,[13] leading to the formation of molecules of even higher complexity, having several chiral centers. List recently described the potential and generality of these complementary approaches, the enamine and iminium-ion catalysis, as the Ying and Yang of aminocatalysis.[12a]

In this paper, we introduce a new concept in chiral amine-catalyzed reactions, opening a new dimension in the field of organocatalysis. Here, we wish to present the first direct γ-functionalization of α,β-unsaturated carbonyl compounds catalyzed by proline derivatives (Scheme 2), by describing the reaction between α,β-unsaturated aldehydes and azodicarboxylates. Furthermore, to disclose the potential and possible limitations of this new enantioselective γ-functionalization, a series of experimental and computational studies on the mechanism and on the properties of the reactive dienamine intermediate(s) will be presented.

Results and Discussion

^{1}H NMR Investigations. We have recently reported a number of enantioselective conjugated additions to α,β-unsaturated aldehydes using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine **2a** as the organocatalyst.[13d,14] This organocatalyst, derived from proline, is proposed to activate the Michael acceptor through the formation of a reactive iminium-ion **3a** as outlined in Scheme 3. During these studies, we have often been surprised by the short reaction times observed, even when the absence of a background reaction indicated an intrinsic low reactivity of the chosen reagents.

To further extend the scope of our catalytic system, we decided to investigate the reasons for this remarkable activity. We therefore undertook ^{1}H NMR spectroscopic investigations in the attempt to characterize the expected iminium-ion intermediate **3a** formed by reaction of 2-pentenal **1a** and the chiral catalyst **2a**. In contrast to our expectations, approximately 30

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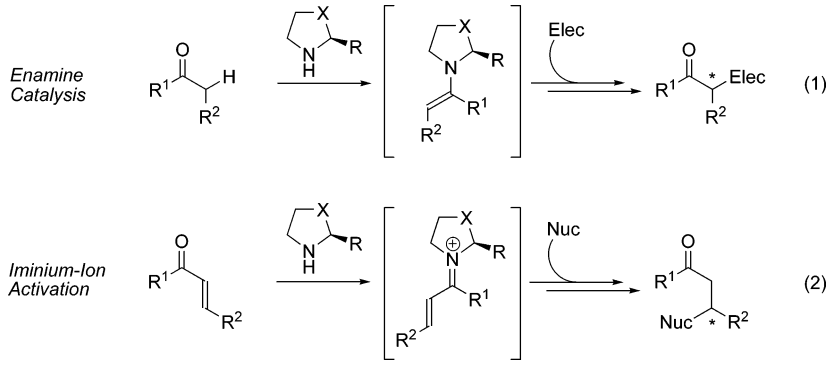
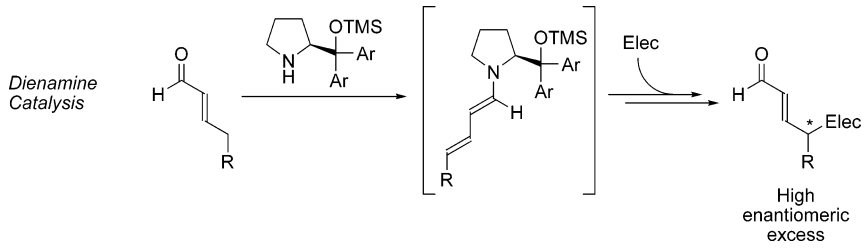
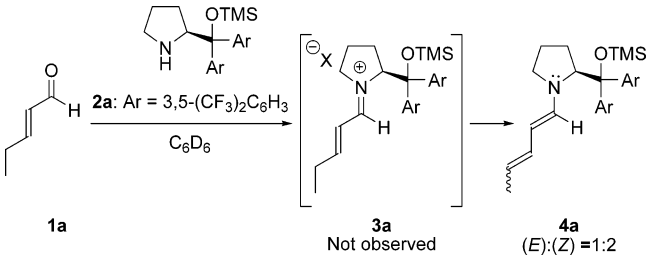
Scheme 1. Enamine Catalysis (Equation 1), Activation of Aldehydes and Ketones in the Direct Asymmetric α-Functionalization of Carbonyl Compounds; Imminium-Ion Catalysis (Equation 2), Activation of α,β-Unsaturated Carbonyl Compounds in the Direct Asymmetric β-Functionalization of Enals and Enones



Scheme 2. Dienamine Catalysis: Direct Asymmetric γ-Functionalization of α,β-Unsaturated Aldehydes



Scheme 3. Formation of the Dienamine Intermediate **4a** in the Reaction between 2-Pentenal **1a** and the Chiral Catalyst **2a** as Observed by ^{1}H NMR Spectroscopy (See Supporting Information)



min after the addition of **2a** (10 mol %) to a 0.5 M solution of **1a** in C_6D_6, we observed that more than 50% of the catalyst was present in the form of the dienamine **4a** and we could not detect the "expected" iminium-ion **3a** (Scheme 3). Dienamines are well-known organic compounds, but it was surprising to discover that, under the conditions that usually favor the conjugated addition to **1a**, the most abundant compound in solution, formed by the catalyst **2a** with **1a**, was instead the electron-rich species **4a**.[15]

The experimental detection of the dienamine **4a** led us to think that an inversion of the normally electrophilic nature of α,β-unsaturated aldehydes might be an option. Could it be possible to exploit the nucleophilicity in the γ-position, instead of the traditional electrophilicity of the β-position?

Catalyst Screening and Optimization of the Reaction Conditions. To investigate the potential of our discovery of the dienamine intermediate, we decided to perform a series of experiments to establish the postulated ability to γ-functionalize aldehydes. As a model system, the reaction between 2-pentenal **1a** and diethyl azodicarboxylate (DEAD) **5** was chosen. The high reactivity of DEAD **5** has previously been shown to enable successful organocatalytic α-aminations of a variety of different carbonyl compounds.[16] The reaction was tested in the presence of a number of chiral amines **2a**−**g** as catalysts and in the presence of different additives in various solvents. Selected results are presented in Table 1.

A wide range of catalysts, additives, and solvents was screened in an attempt to optimize the reaction. The limiting reagent DEAD **5** was found to be consumed within 3−5 h as observed by ^{1}H NMR spectroscopy. The γ-functionalization proceeds with an excellent enantioselectivity of 97% ee in CH_2Cl_2; however, the yield of **6a** was only 21% (Table 1, entry 1). The addition of benzoic acid improves the yield to 46% and maintains the high enantiomeric excess (entry 2). Changing the solvent to toluene in the presence of benzoic acid leads to an increase of the yield of **6a** to 56% at the expense of a minor reduction in enantiomeric excess (entries 3, 4). It was found that the use of other solvents diminished the yield considerably (entries 5−7), which is believed to be due to an extensive polymerization of the starting aldehyde and of the product.[17] The catalyst of choice for the organocatalytic direct γ-amination

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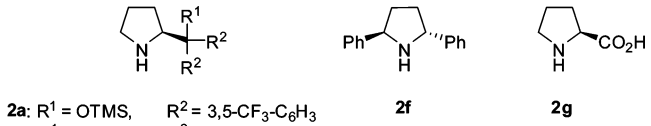
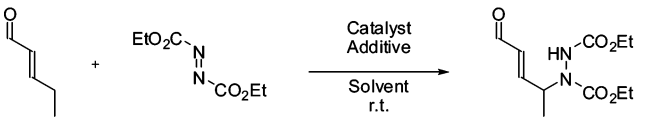
(17) The isolated product proved to be unstable upon standing in toluene at room temperature in the presence of **2a**, but was stable under the same reaction conditions in the absence of catalyst **2a**.

Table 1. Screening of Various Reaction Conditions for the γ-Amination of α,β-Unsaturated Aldehydes[a]





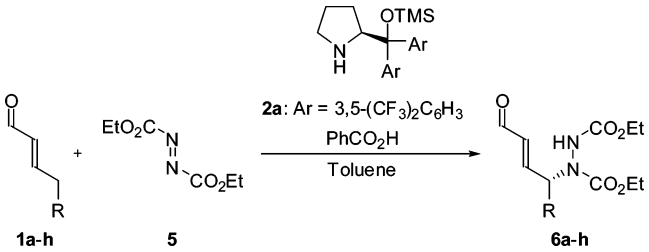
entry	solvent [concentration of DEAD]	catalyst	additive	yield[b] (%)	ee (%)
1	CH_2Cl_2 [0.5 M]	**2a**		21	97
2	CH_2Cl_2 [2 M]	**2a**	$PhCO_2H$	46[c]	97
3	toluene [0.5 M]	**2a**	$PhCO_2H$	33	n.d.
4	toluene [2 M]	**2a**	$PhCO_2H$	56[c]	89
5	MeCN [2 M]	**2a**	$PhCO_2H$	34	n.d.
6	THF [2 M]	**2a**	$PhCO_2H$	35	n.d.
7	DMSO [2 M]	**2a**	$PhCO_2H$	0	n.d.
8	toluene [2 M]	**2b**	$PhCO_2H$	0	n.d.
9	toluene [2 M]	**2c**	$PhCO_2H$	30	n.d.
10	toluene [2 M]	**2d**	$PhCO_2H$	0[d]	n.d.
11	toluene [2 M]	**2e**	$PhCO_2H$	0	n.d.
12	toluene [2 M]	**2f**	$PhCO_2H$	17	n.d.
13	toluene [2 M]	**2g**	$PhCO_2H$	10	n.d.
14	toluene [2 M]	**2a**	$PhCO_2H$ (100%)	0	n.d.
15	toluene [2 M]	**2a**	*p*-NO_2–$PhCO_2H$	0	n.d.

[a] Conditions: 0.375 mmol of **1a**, catalyst **2** (10 mol %), and the indicated additive (10 mol %) were stirred in the specified solvent for 15 min before the addition of 0.25 mmol of DEAD **5**. [b] Based on formation of **6a** with **5** as the limiting reagent measured by ^{1}H NMR after 3−5 h, corresponding to a full conversion of **5**. [c] Isolated yield. [d] Low conversion of **5**.

of α,β-unsaturated aldehydes was 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine **2a**, and product **6a** was obtained in considerable higher yields than with the other organocatalysts tested. It is notable that an exchange of the trifluoromethyl groups in catalyst **2a**, with methyl (**2b**) or hydrogen (**2d**), led to no formation of the product (entries 8, 10).[12d] In the case of **2b**, only polymeric products were observed. In contrast, catalyst **2d** led to poor overall conversion of DEAD as a consequence of the poor solubility of the catalyst. We also studied the TBDMS-protected analogue (**2c**) to evaluate the influence of a more bulky substituent on the catalyst; however, the increased steric hindrance did not suppress the polymerization of the aldehydes (entry 9). Proline **2g** afforded a mere 10% conversion within 3 h, and extensive polymerization was observed as in the case of **2e** and **2f** (entries 11−13).

The effect of acid additives was also studied. The presence of 10 mol % benzoic acid enhanced the rate and yield of the reaction markedly, but the use of a stronger acid (*p*-nitro-benzoic acid) or of a stoichiometric amount of benzoic acid led to extensive polymerization, and no product could be isolated (entries 14, 15). The reaction gave the best results using a slight excess of aldehyde (1.5 equiv), and it was found that these reaction conditions provided product **6a** in a constant yield and enantioselectivity over a range of temperatures (from 4 to 40 °C).

Table 2. Scope of the Organocatalytic γ-Amination of α,β-Unsaturated Aldehydes[a]



entry	R	reaction time (h)	yield[b] (%)	ee[c] (%)
1	**1a** − Me	3	**6a** − 56	89
2	**1b** − Et	6	**6b** − 58	89
3	**1c** − Pr	5	**6c** − 56	88
4	**1d** − hexyl	8	**6d** − 49	88
5	**1e** − pent-2-ene-yl	4.5	**6e** − 54	89
6	**1f** − CH_2Ph	4	**6f** − 52	93
7	**1g** − $CH(CH_3)_2$	56	**6g** − 40	89
8	**1h** − CH_2SCH_3	1.5	**6h** − 43	88

[a] Conditions: 0.375 mmol of **1**, catalyst **2a** (10 mol %), and benzoic acid (10 mol %) were stirred in 0.125 mL of toluene for 10 min before the addition of 0.25 mmol of DEAD **5**. [b] Isolated yield after flash chromatography. [c] Enantiomeric excess determined after reduction ($NaBH_4$, MeOH) and protection (*p*-chlorobenzoyl chloride, Et_3N) by chiral HPLC.

Scope of the γ-Amination of α,β-Unsaturated Aldehydes. A range of substrates was shown to be compatible with the presented protocol for the γ-amination of α,β-unsaturated aldehydes using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine **2a** as the catalyst (Table 2).

The reaction is general for α,β-unsaturated aldehydes with a β-monosubstituted double bond. Linear aliphatic chains gave 49−58% yield and more than 88% ee (Table 2, entries 1−4). Olefinic and aromatic substituents in the side chain gave similar results, albeit the aromatic substituents (**1f**) led to a slight increase in enantioselectivity to 93% ee (entry 6). An increase in the steric bulk of the side chain, as in **1g**, led to significantly higher reaction times, but with comparable enantioselectivity and slightly lower yield (entry 7). The presence of heteroatoms, such as the sulfur atom in the side chain of compound **1h**, is also tolerated, and the enantiomeric excess was retained (entry 8). We believe that the main reason for the moderate yields of the γ-aminated products **6a**−**h** is polymerization of the starting material and of the product under the given reaction conditions. Furthermore, we have also observed the reaction between catalyst **2a** and DEAD **5**.

Previous reactions using 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine **2a** as the organocatalyst for the α- or β-functionalization of saturated aldehydes and α,β-unsaturated aldehydes, respectively, have all been very consistent with regard to the absolute configuration of the optically active products formed.[14] In all of these reactions, the catalyst shields the same face in the enamine or iminium-ion intermediate. However, the γ-amination reaction of the α,β-unsaturated aldehydes proceeds with a stereoselectivity that is apparently opposite to this trend, leading to the formation of the (*R*)-enantiomer of the γ-aminated product **6** (Figure 1).[18] This stereochemical outcome of the reaction and the surprisingly

(18) The absolute configuration was determined on the basis of optical rotation comparison. See the Supporting Information for further details.

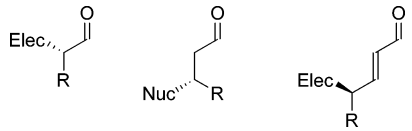


Figure 1. Stereochemistry of the formed products from α-, β-, and γ-functionalization of aldehydes and α,β-unsaturated aldehydes using **2a** as the catalyst.

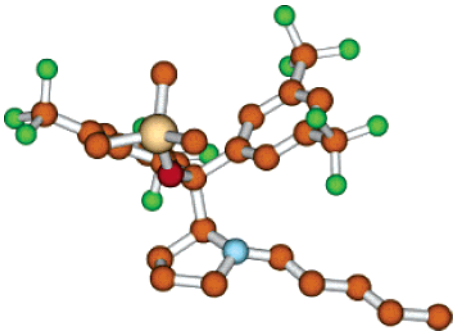


Figure 2. Optimized structure of the dienamine intermediate (*E*,*s-trans*,*E*)-**4a** (Ar = 3,5-$(CF_3)_2C_6H_3$).

high selectivity, considering the 2:1 *Z*:*E*-ratio of the dienamine in solution (Scheme 3), encouraged us to start a more detailed study of the mechanism of the reaction.

Mechanistic Investigations of the γ-Amination of α,β-Unsaturated Aldehydes. The mechanism of this γ-functionalization of α,β-unsaturated aldehydes was investigated using experimental and computational approaches. The first issue to address was to understand why the functionalization preferably takes place at the γ-carbon atom instead of the α-carbon atom.

The reaction starts with the addition of catalyst **2a** to aldehyde **1** forming the iminium-ion intermediate **3**, with hydroxide or benzoate ion as the counterion (Scheme 3). The iminium-ion is then presumed to be deprotonated, forming the dienamine intermediate **4** (Scheme 4), which will react with the electrophile.

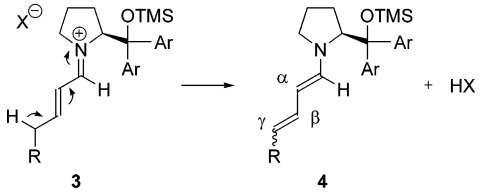
To understand the difference in reactivity at the α- and γ-carbon atoms of the intermediate, the structure of the dienamine **4a**, formed from reaction of 2-pentenal **1a** with 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]-pyrrolidine catalyst **2a**, was optimized using density functional theory (DFT) calculations (Figure 2).[19]

Using a simple frontier molecular orbital model, the calculated coefficients at the α- and γ-carbon atoms of the HOMO of the dienamine intermediate did not differ significantly and thus could not account for the difference in reactivity at the α- and γ-positions at the B3LYP/6-31G(d) level of theory.[20] Therefore, to explain the observed reactivity, we performed calculations of the transition states for the addition of the electrophile to the dienamine intermediate. In the initial investigations, a model system was used, in which dimethyl azodicarboxylate (DMAD) was added to the α- and γ-positions in the dienamine intermediate of pyrrolidine and 2-pentenal. The results showed that there was only a small difference in energy (0.8 kcal mol^{-1}) in favor of the transition state leading to the γ-addition reaction path.

(19) Frisch, M. J.; et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(20) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (d) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (e) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

Scheme 4. Formation of the Dienamine Intermediate **4**



Because this small energy difference could not explain the difference in the observed reactivity at the different positions, we also considered the possibility of a Diels−Alder [4+2]-cycloaddition reaction path, rather than the expected direct addition of the azodicarboxylate to the α- or γ-carbon atoms of intermediate **4**. This possibility is also supported by the known reactivity of dienamine species.[15]

We have calculated the energy of activation for a [4+2]-cycloaddition between the *s-cis*-dienamine (formed from pyrrolidine and **1a**) and DMAD and found the Diels−Alder transition state to be 1.5 kcal mol^{-1} lower in energy than the transition state energy for the direct addition to the γ-position. This indicated that a Diels−Alder reaction might be a plausible pathway for this γ-functionalization. These results led us to investigate both the α- and the γ-addition, as well as the Diels−Alder reaction path of DEAD to different conformations of a number of dienamine intermediates formed by reaction of catalyst **2a** with 2-pentenal **1a** according to the reaction paths outlined in Figure 3.

We have optimized the structure of the four different intermediates (*E*,*s-trans*,*E*)-**4a**, (*E*,*s-trans*,*Z*)-**4a**, (*E*,*s-cis*,*E*)-**4a**, and (*E*,*s-cis*,*Z*)-**4a** shown in Figure 3 at the B3LYP/6-31G(d) level of theory. Furthermore, we have located the transition states for the three different types of reaction paths outlined for the amination of the four dienamine intermediates, leading to a total of six transition states, two each for the α- and γ-amination reaction pathways and two for the Diels−Alder [4+2]-cycloaddition reaction path.

We have calculated a difference in energy of only 1.2 kcal mol^{-1} between the dienamines (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a**, which shows that the two *trans*-dienamines are close in energy, as is observed experimentally by ^{1}H NMR spectroscopy. The barrier for rotation (**TS2$_{ROT}$**) around the β,γ-double bond in the dienamines (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a** was calculated to be 46.2 kcal mol^{-1}, which suggests that these two dienamines do not interconvert through a rotation, but rather through a protonation/deprotonation step via the iminium ion **3** (Figure 3 and Table 3).

The barriers for the rotation around the C−C single bond of dienamine intermediates (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a**, forming dienamines (*E*,*s-cis*,*E*)-**4a** and (*E*,*s-cis*,*Z*)-**4a**, respectively, were calculated to be 7.7 and 6.8 kcal mol^{-1}. This shows that (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a** can interconvert rapidly with their respective *s-cis*-conformers, (*E*,*s-cis*,*E*)-**4a** and (*E*,*s-cis*,*Z*)-**4a**, and the low activation barriers indicate that the formation of the two latter intermediates is a feasible process, thus making the Diels−Alder pathway possible. The energies of (*E*,*s-cis*,*E*)-**4a** and (*E*,*s-cis*,*Z*)-**4a** are elevated by 4.2 and 4.8 kcal mol^{-1}, relative to (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a**, respectively, which is in agreement with the ^{1}H NMR experiments, in which only the two latter dienamines are observed.

The transition states were located for the addition of DEAD to the α- or γ-position in (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-

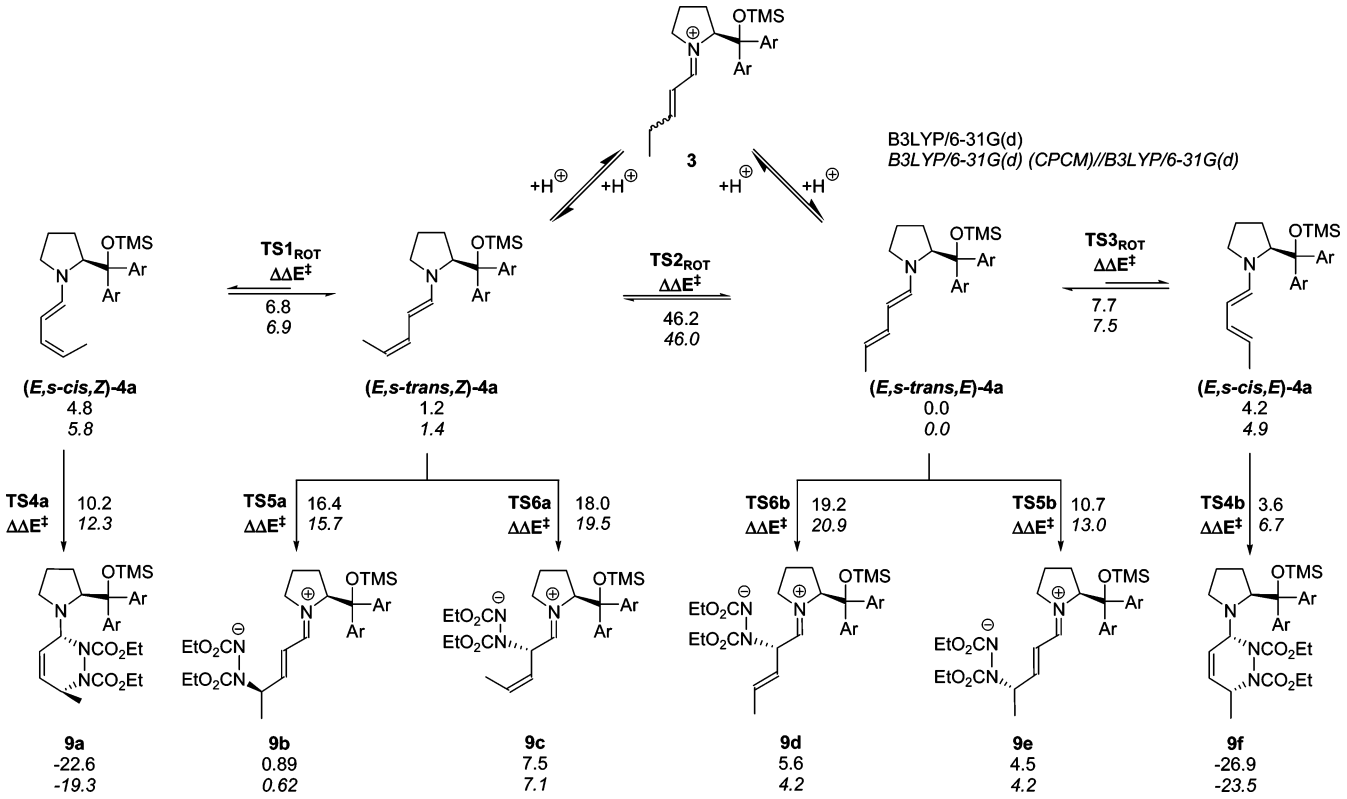


Figure 3. Intermediates and reaction paths calculated for the asymmetric electrophilic γ-amination of α,β-unsaturated aldehydes. Electronic and solvation energies at the B3LYP/6-31G(d) level of theory for the potential energy surface of the addition of DEAD to different dienamine intermediates. The numbers below the intermediates are the energies relative to (*E*,*s-trans*,*E*)-**4a** calculated by B3LYP/6-31G(d) and for the numbers in italics by B3LYP/6-31G(d)-(CPCM)/B3LYP/6-31G(d).

Table 3. Electronic and Solvation Energies of the Reactants, Transition States, and Products for the Addition of DEAD to Different Dienamines at the B3LYP/6-31G(d) Level of Theory

	E_{elec} [hartree][a]	ΔE_{elec} [kcal mol^{-1}][b]	E_{solv} [hartree][a]	ΔE_{solv} [kcal mol^{-1}][b]
(*E*,*s-trans*,*E*)-**4a**	−2740.18369	0.0	−2740.15142	0.0
(*E*,*s-cis*,*Z*)-**4a**	−2740.17603	4.8	−2740.14219	5.8
(*E*,*s-trans*,*Z*)-**4a**	−2740.18184	1.2	−2740.14922	1.3
(*E*,*s-cis*,*E*)-**4a**	−2740.17707	4.2	−2740.14366	4.9
TS1$_{ROT}$	−2740.17103	7.9	−2740.13824	8.3
TS2$_{ROT}$	−2740.11000	46.2	−2740.07817	46.0
TS3$_{ROT}$	−2740.17144	7.7	−2740.13949	7.5
TS4a	−3385.17255	16.4	−3385.13226	18.1
TS4b	−3385.18623	7.8	−3385.14250	11.6
TS5a	−3385.17056	17.6	−3385.13380	17.1
TS5b	−3385.181540	10.7	−3385.14025	13.0
TS6a	−3385.16616	19.2	−3385.12776	20.9
TS6b	−3385.168048	20.4	−3385.12799	20.7
9a	−3385.23456	−22.6	−3385.19179	−19.3
9b	−3385.19720	0.89	−3385.16006	0.62
9c	−3385.18669	7.5	−3385.14974	7.1
9d	−3385.16805	5.6	−3385.15439	4.2
9e	−3385.19145	4.5	−3385.15442	4.2
9f	−3385.24150	−26.9	−3385.19843	−23.5

[a] Absolute energies for calculated compounds. [b] Energies are given relative to (*E*,*s-trans*,*E*)-**4a** and DEAD on the potential energy surface.

4a. The calculated energies of the transition states (**TS6a** and **TS6b**) showed that the activation barriers for the addition of DEAD to the α-position of (*E*,*s-trans*,*Z*)-**4a** and (*E*,*s-trans*,*E*)-**4a** are considerably higher (18.0 and 19.2 kcal mol^{-1}, respectively), as compared to both the transition state energies (**TS5b** and **TS5a**) for direct addition to the γ-position of (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a** (10.7 and 16.4 kcal mol^{-1}, respectively) and the transition state energies for the Diels−Alder reaction pathway (vide infra). Below, in Figure 4, the calculated lowest energy transition state structures for the addition of DEAD to the α- and γ-positions in the dienamine intermediate (*E*,*s-trans*,*E*)-**4a** are shown.

The bond lengths of the forming C−N bonds in the α- or direct γ-addition are calculated to be 1.875 and 1.940 Å, respectively, and these are comparable to the C−N bond distance (1.8 Å) previously calculated for the transition state of the α-hydroxyamination of aldehydes.[21a]

The higher energy for the transition state (**TS6b**) of the α-addition of DEAD to the dienamine intermediate (*E*,*s-trans*,*E*)-**4a** might be accounted for by the fact that addition of DEAD in the α-position leads to a product where the conjugation between the two dienamine double bonds is broken, while addition in the γ-position yields a product with the double bond in conjugation with the iminium double bond. It also appears from the transition state structures in Figure 4 that there is a steric interaction between the CF_3-group and the diene-part in the dienamine for the α-addition transition state; this is less pronounced in the γ-addition transition state.

The direct addition of DEAD **5** to the γ-carbon atom from the unshielded lower face of the different dienamine intermediates (*E*,*s-trans*,*E*)-**4a** and (*E*,*s-trans*,*Z*)-**4a** leads to different

(21) For other mechanistic and computational investigations on organocatalytic aminations, see: (a) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912. (b) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770. (c) Iwamura, H.; Wells, D. H., Jr.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312. For other computational studies, see, for example: (d) Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543. (e) Clemente, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 11294. (f) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.

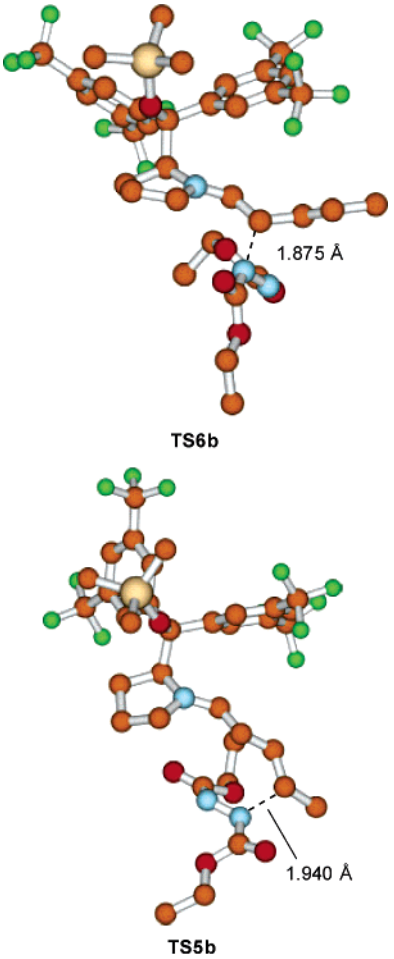


Figure 4. Optimized transition state structures for the α- and γ-addition (**TS6b** and **TS5b**, respectively) of DEAD **5** to the dienamine intermediate (*E*,*s-trans*,*E*)-**4a** at the B3LYP/6-31G(d) level of theory.

configurations in the final products. The addition of DEAD to (*E*,*s-trans*,*E*)-**4a** would lead to an (*S*)-configuration (**9e**) at the γ-carbon atom, while reaction of the (*E*,*s-trans*,*Z*)-**4a** leads to the (*R*)-product (**9b**) with a preference for the former product, due to the lower transition state energy from the direct γ-addition reaction path. However, the formation of the (*S*)-configuration is not in accordance with the experimental results.

The transition state **TS4b** for the reaction between DEAD **5** and dienamine (*E*,*s-cis*,*E*)-**4a** in a concerted, Diels−Alder reaction pathway leading to (*R*)-product was calculated to have the lowest transition state energy on the potential energy surface. The transition state structure indicates a synchronous reaction path; that is, the forming C−N bonds are quite similar (2.137 and 2.211 Å), suggesting a concerted [4+2]-cycloaddition transition state (Figure 5). It should be noted that previously calculated transition states of Diels−Alder reactions in organocatalysis have been asynchronous.[21d] The energy difference between the transition state for direct γ-addition **TS5b** (leading to the wrong configuration of the product) and the Diels−Alder transition state **TS4b** (providing the observed absolute configuration of the product) is 3.0 kcal mol^{-1} based on the energy of (*E*,*s-trans*,*E*)-**4a**, showing a preference for the Diels−Alder reaction path. Because of the fact that the direct γ-addition leads to a zwitterionic product, solvent effects could have a large influence on the transition state energies. Therefore, the solvation energies of the transition states were estimated with a single-point calculation of the optimized gas-phase geometries using the CPCM model.[22] The solvent calculation decreases the energy difference between transition states **TS5b** and **TS4b** to 1.41 kcal mol^{-1}.

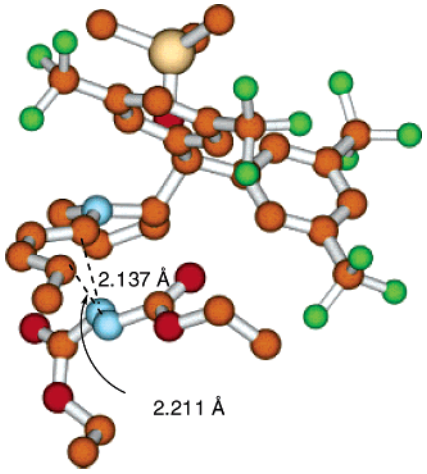


Figure 5. DFT-optimized transition state for the Diels−Alder reaction between DEAD and the dienamine (*E*,*s-cis*,*E*)-**4a**.

Calculated total and relative energies for the intermediates and transition states in Figure 3 are given in Table 3. As seen from Table 3, the aminal intermediates **9a** and **9f**, formed by the Diels−Alder reaction pathways, are more stable than the zwitterionic intermediates **9b** and **9e**.

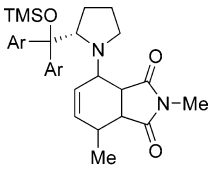
The two reaction paths leading to the intermediates **9b** and **9f** having the observed stereochemistry at the γ-carbon atom have different transition state energies. The Diels−Alder reaction path is nearly 10 kcal mol^{-1} lower in energy as compared to the direct γ-addition reaction path. This indicated to us that the Diels−Alder reaction might account for the reaction course. Furthermore, it is also worth noting that, according to the calculations, the formation of **9c**−**e** is thermodynamically as well as kinetically unfavorable, and that the formation of **9b** is essentially thermoneutral, while both [4+2]-cycloadditions are significantly exothermic.

The aminal intermediates **9a** and **9f** can easily be hydrolyzed to give the γ-aminated product **6** and to release the catalyst **2a**. The configuration of the double bond in the products **6** has been determined by ^{1}H NMR spectroscopy to be *E*. This seems to be in contrast to the proposed [4+2]-cycloaddition reaction path, which leads to the intermediates **9a** and **9f**, both having a *Z*-double bond. The change from the *Z*-isomer to the thermodynamically more stable *E*-isomer is believed to happen through a reversible addition of a nucleophile (e.g., catalyst or water) to the β-position of the intermediate iminium-ion **3**.

To further support the hypothesis of a Diels−Alder reaction path for the γ-functionalization, we performed an experiment using 2-pentenal **1a** in combination with *N*-methylmaleimide rather than azodicarboxylate **5**. *N*-Methylmaleimide was chosen because it is a dienophile that commonly reacts in concerted [4+2]-cycloaddition reactions. Product **8** was formed under the slightly modified reaction conditions (1 equiv of catalyst **2a**) in a diastereomeric ratio of 2:1, which might be due to the exo and endo attack of the dienophile. Compound **8** could be easily

(22) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. (c) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799.

isolated by flash chromatography (see Supporting Information). This new optically active product indicates that dienamine catalysis might be applied in other reactions and not just in the γ-amination of α,β-unsaturated aldehydes.



8
Ar = 3,5-$(CF_3)_2C_6H_3$

Conclusion

In summary, we have reported the first organocatalytic enantioselective γ-functionalization of α,β-unsaturated aldehydes. We disclosed that secondary amines, and in particular 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]-pyrrolidine, can invert the common reactivity of α,β-unsaturated aldehydes, thereby transforming an electron-poor alkene into an electron-rich diene. As an example of this inverted reactivity, we have presented the electrophilic γ-amination of α,β-unsaturated aldehydes with high enantioselectivity. Computational and experimental investigations indicate that the γ-amination of α,β-unsaturated aldehydes might be the result of a [4+2]-cycloaddition reaction between the diethyl azodicarboxylate and the chiral dienamine formed in situ with the catalyst. Furthermore, the results and the information presented seem to open the possibility for a new series of enantioselective transformations.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation. P.D. thanks the Wenner-Gren Foundation for financial support.

Supporting Information Available: Complete experimental procedures and characterization; complete ref 19. This material is available free of charge via the Internet at http://pubs.acs.org.

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