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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Asymmetric Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis

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Supporting Information

ABSTRACT: A new concept in organocatalysis allowing for the construction of cyclobutanes with four contiguous stereocenters with complete diastereo- and enantiomeric control by a formal [2 + 2]-cycloaddition is presented. The concept is based on simultaneous dual activation of α,β-unsaturated aldehydes and nitroolefins by amino- and hydrogen-bonding catalysis, respectively. A new bifunctional squaramide-based aminocatalyst has been designed and synthesized in order to enable such an activation strategy. The potential and scope of the reaction are demonstrated, and computational studies which account for the stereochemical outcome are presented.

The development of new reactions is a fundamental goal and challenge in synthetic organic chemistry. With stoichiometric approaches being replaced by catalytic ones, this task is associated with the design of new catalysts and discovery of new activation modes. These two issues are dominating the field of asymmetric aminocatalysis,[1] where methodologies based on HOMO- (enamine,[2] dienamine,[3] trienamine[4]), LUMO-[5] (iminium ion) and SOMO-activations[6] have emerged as powerful tools. In particular, the activation of α,β-unsaturated aldehydes via formation of dienamine species is an important strategy for the enantioselective functionalization of aldehydes.[3] Reactions involving dienamine intermediates can proceed through different pathways (Figure 1). Classical enamine 1,2-reactivity, which results

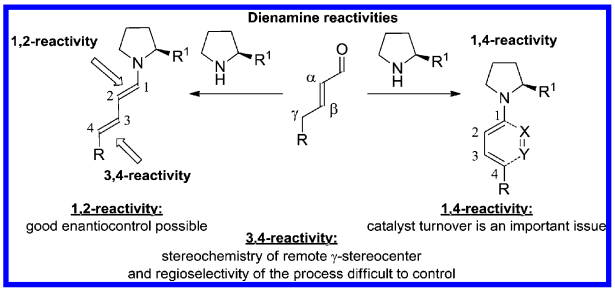


Figure 1. Dienamine chemistry: reactivity patterns.

in selective α-functionalization of α,β-unsaturated aldehydes, is well-recognized and usually proceeds with good levels of stereocontrol.[7] Another possibility involves a [4 + 2]-cycloaddition pathway (1,4-reactivity).[8] The main difficulty of the latter approach is associated with the catalyst turnover since the catalyst is trapped, via a C−N single bond, in the 6-membered intermediate formed during the cycloaddition. This problem is not encountered in the case of 3,4-reactivity enabling remote γ-functionalizations.[9] However, challenges related to stereocontrol of the γ-carbon[7c] (5 bonds away from the stereocenter of the catalyst) and regioselectivity (1,2- vs 3,4-reactivity)[9d] are often encountered.

In order to address this remote reactivity, a novel approach based on bifunctional H-bond directing dienamine catalysis has been devised. It was envisioned that the application of an aminocatalyst, containing a functional group capable of H-bonding interactions, would allow for control of both regio- and stereoselectivity of the process by interactions between the H-bond donor and incoming electrophile (Figure 2, right).

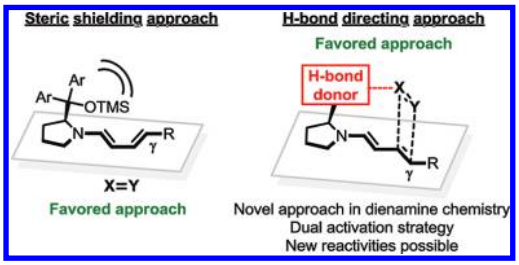


Figure 2. Steric shielding vs H-bond directing dienamine catalysis.

In such a setup, the electrophile would be positioned away from the α-carbon of the dienamine, favoring regioselective functionalization of the remote double bond. In terms of stereochemical induction, the facial selectivity should be opposite to that of classical steric shielding dienamine catalysis (Figure 2, left). Finally, the dual activation mode offered by this H-bond directing strategy, which results in simultaneous activation of the α,β-unsaturated aldehyde (via dienamine formation) and electrophile (via H-bonding), could also be essential for improving the reactivity of less electrophilic substrates. Therefore, such an approach could lead to the development of new regioselective reaction pathways enabling good control of the stereochemistry at remote stereocenters.

Catalyst Design. There were two factors that seemed of particular importance in developing a suitable bifunctional catalyst. First, the H-bond directing group must be an appropriate distance from the secondary amine moiety to allow for a proper positioning of the approaching electrophile

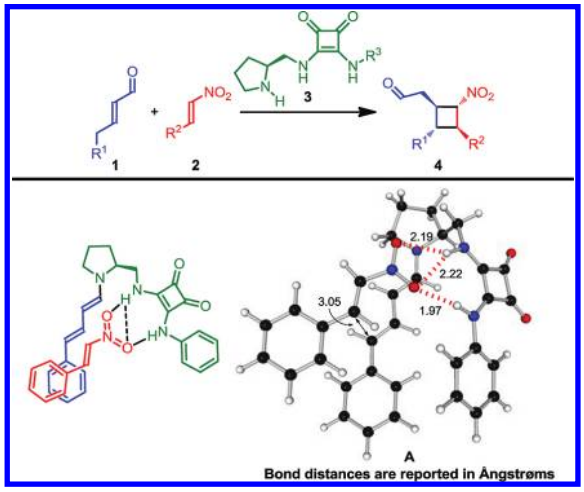
Received: December 20, 2011
Published: January 23, 2012

   dx.doi.org/10.1021/ja211878x | J. Am. Chem.Soc. 2012, 134, 2543−2546

in relation to the dienamine intermediate. Second, the H-bond donor needed to be capable of efficient activation of different electrophiles. A squaramide-based aminocatalyst, derived from optically active 2-aminomethylpyrrolidine, seemed well-suited for this task.

To provide a proof of concept for the activation strategy, nitroolefins were chosen as electrophilic counterparts[10] (Scheme 1, top). It was anticipated that a reaction between

Scheme 1. Organocatalytic [2 + 2]-Cycloaddition: Reaction Design and Intermediate Considerations

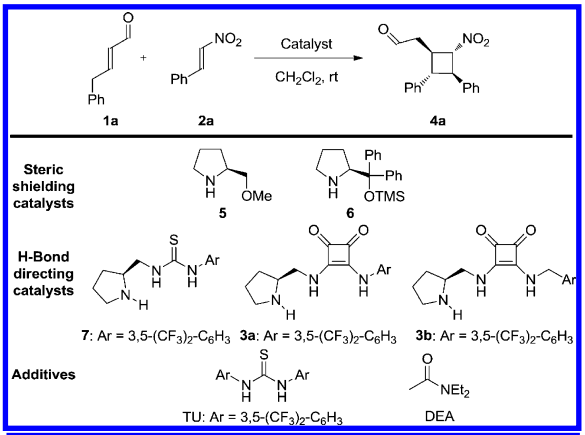


the dienamine derived from **1** and nitroolefin **2** could proceed via a formal [2 + 2]-cycloaddition resulting in a facile, stereoselective synthesis of fully substituted cyclobutanes.[11] These structural motifs are present in a large number of different natural products and biologically relevant molecules.[12]

To provide insight as to how the squaramide in the dienamine intermediate interacts with the nitroolefin, computational studies were undertaken. A conformational analysis of the dienamine intermediate, formed by condensation of **1** (R^1 = Ph) and **3** (R^3 = Ph), was performed using the M06-2X/6-31G(d) method (Scheme 1, top).[13] When the nitroolefin **2** (R^2 = Ph) was introduced, the lowest energy structure (**A**) was calculated to have the squaramide arranged with a *syn*/*syn* configuration of the amine protons.[14] This conformation of the squaramide allows for three H-bonding interactions with the nitro group and a staggered π-stacking interaction between the phenyl rings of the nitroolefin and the dienamine (Scheme 1, bottom).[10a,15] No other conformation of the dienamine intermediate was able to take advantage of all of these interactions. Further examination of **A** showed that the β-carbon of the nitroolefin is positioned 3.05 Å above the γ-carbon of the dienamine. This led us to believe that the squaramide catalyst would provide the proper positioning of the electrophile and therefore allow for regio- and stereocontrolled functionalization at the γ-carbon.

Reaction Development. With the design of a novel catalytic system completed, a screening of a model reaction between (*E*)-3-phenylbut-2-enal **1a** and β-nitrostyrene **2a** was initiated (Table 1).[16] Catalyst screening revealed that steric shielding catalysts **5** and **6** were unable to promote the reaction (entries 1−3), even when an achiral thiourea (TU) cocatalyst was applied (entry 3). To our delight, smooth conversion into cyclobutane **4a** was observed when H-bond directing catalysts

Table 1. Screening of Catalysts and Reaction Conditions[a]



ent	cat	additive	conc [M]	conv (yield)[b] [%]	dr[c]	ee[d] [%]
1	**5**	-	0.5	<5	-	-
2	**6**	-	0.5	<5	-	-
3	**6**	TU[e]	0.5	<5	-	-
4	**7**	-	0.5	48	>20:1	-
5	**3a**	DEA[f]	0.5	84	>20:1	-
6	**3b**	DEA[f]	0.5	83	>20:1	-
7[g]	**3a**	DEA[f]	0.5	>95(84)[h]	>20:1	>99
8[g]	**3a**	DEA[f]	0.25	>95(84)[h]	>20:1	>99
9[g]	**3a**	DEA[f]	0.1	38	>20:1	-
10[g]	**3a**	DEA[f]/H_2O[i]	0.25	>95(86)[j]	>20:1	>99

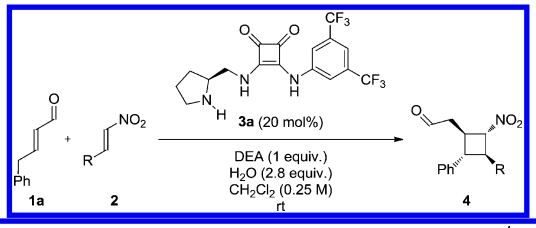
[a]All reactions performed using **1a** (0.15 mmol), **2a** (0.1 mmol), and catalyst (0.02 mmol) (see Supporting Information). [b]Conversion of **2a** as determined by ^{1}H NMR spectroscopy after 18 h, isolated yield in parentheses. [c]Determined by ^{1}H NMR of the crude reaction mixture. [d]Determined by CSP-HPLC after reduction to the corresponding alcohol. [e]20 mol % used. [f]1 equiv applied. [g]2 equiv of **1a** applied. [h]Conversion after 48 h. [i]5 μL (2.8 equiv) applied. [j]Conversion after 24 h.

3a,**b** and **7** were used (entries 4−6), with **3a** proving the most efficient (entry 5). In the case of squaramide-based aminocatalysts **3a**,**b**, the addition of *N*,*N*-diethylacetamide (DEA) was necessary due to low catalyst solubility. The reactivity and complete diastereoselectivity observed in the reaction catalyzed by bifunctional systems **3a**,**b** support the importance of the dual activation strategy to enable unprecedented reactivity. A solvent screening[16] revealed CH_2Cl_2 to be the best solvent, allowing for full conversion of **2a** in 48 h (entry 7). Importantly, under these conditions the resulting cyclobutane contained four contiguous stereocenters and was formed in 84% yield as a single diastereoisomer with exceptionally high enantioselectivity (>99% ee) confirming the potential of the concept. Further screening (entries 7−9) provided the optimal concentration (entry 8). Finally, it was found that the presence of water resulted in a significant increase of the reaction rate allowing for the reaction to be terminated within 24 h (entry 10).

With the optimized reaction conditions in hand, we turned our attention to the nitroolefin scope (Table 2). In this context, it is worth mentioning that the catalyst loading could be decreased to 10 or even 5 mol % affording **4a** in good yield and excellent stereoselectivity, albeit longer reaction times were required (entries 2,3). For this reason, 20 mol % of catalyst **3a** was routinely used. A selection of β-nitrostyrenes **2b**−**i** reacted smoothly with **1a** demonstrating that the reaction is unbiased toward both electronic properties of the aromatic moiety and the substitution pattern (entries 4−11). Furthermore, a

dx.doi.org/10.1021/ja211878x | *J. Am. Chem.Soc.* 2012, 134, 2543−2546

Table 2. Organocatalytic Formal [2 + 2]-Cycloadditions: Nitroolefin Scope[a]



ent	R	time [h]	yield [%][b]	dr[c]	ee[d] [%]
1	Ph	24	**4a** - 86	>20:1	>99[e]
2[f]	Ph	72	**4a** - 84	>20:1	>99[e]
3[g]	Ph	288	**4a** - 81	>20:1	>99[e]
4	4-F-C_6H_4	48	**4b** - 90	>20:1	>99[e]
5	4-Br-C_6H_4	24	**4c** - 84	>20:1	>99[e]
6	2-Cl-C_6H_4	48	**4d** - 80	>20:1	>99
7	3-NO_2-C_6H_4	32	**4e** - 82	>20:1	>99
8	4-Me-C_6H_4	48	**4f** - 84	>20:1	>99
9	4-MeO-C_6H_4	72	**4g** - 80	>20:1	>99[e]
10	2,6-Cl_2-C_6H_3	48	**4h** - 87	>20:1	>99[e]
11	2,5-$(MeO)_2$-C_6H_3	40	**4i** - 83	>20:1	>99
12	2-Furyl	48	**4j** - 74	>20:1	>99[e]
13	*n*-Bu	24	**4k** - 62	>20:1	>99

[a]All reactions performed on a 0.2 mmol scale (see Supporting Information for details). [b]Yield after isolation by FC. [c]Determined by ^{1}H NMR of the crude reaction mixture. [d]Determined by CSP-HPLC. [e]Determined after reduction to the corresponding alcohol. [f]Reaction performed using 10 mol % of **3a**. [g]Reaction performed using 5 mol % of **3a** on a 0.1 mmol scale.

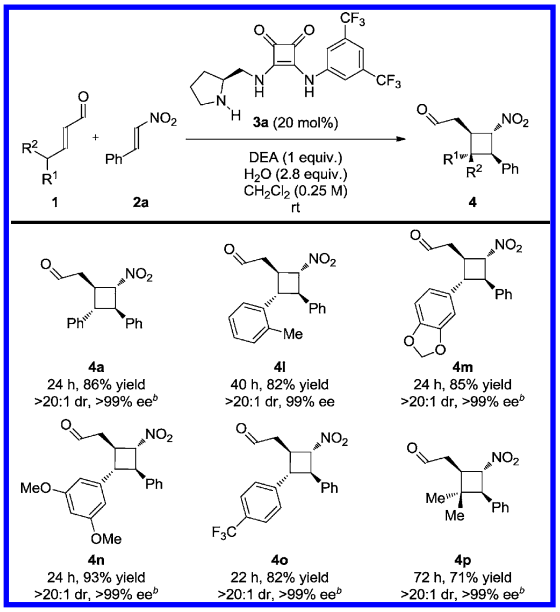
heteroaromatic framework could be incorporated into the cyclobutanes, as shown for the furyl-substituted product **4j** (entry 12). Gratifyingly, the formal [2 + 2]-cycloaddition proved not to be restricted to aromatic nitroolefins. When aliphatic nitroolefin **2k** was reacted, cyclobutane **4k** was efficiently accessed (entry 13). Remarkably, good yields and excellent diastereo- and enantioselectivities were obtained for all substrates evaluated, demonstrating the generality and robustness of the present dual activation system.

In the course of the further studies, the α,β-unsaturated aldehyde scope was evaluated (Scheme 2). The electronic nature and substitution pattern of the aromatic moiety of the starting aldehydes **1b−e** had no significant influence on the reaction since both electron-poor and -rich dienamines were successfully employed in the reaction sequence. In all cases, the cyclobutanes **4l−o** were formed with comparably good yields and excellent stereoselectivities. Aliphatic enals could also be applied in the developed reaction sequence, as demonstrated for (*E*)-4-methylpent-2-enal **1g** affording cyclobutane **4p** with a quaternary carbon atom incorporated.

Finally, the potential of this methodology was further demonstrated in the synthesis of cyclobutane **4q** which contains a quaternary stereocenter (Scheme 3). To our delight, α-branched nitroolefin **2l** underwent the formal [2 + 2]-cycloaddition affording **4q** with high yield and complete stereoselectivity.

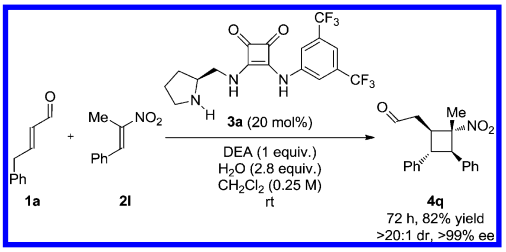
Mechanism. The calculated reaction pathway from **A** (Scheme 1) to the catalyst-bound cyclobutane intermediate **C** reveals that the reaction occurs in a stepwise manner (Figure 3).[13] The first step in the formal [2 + 2]-cycloaddition involves the formation of the bond between the γ-carbon of the dienamine and the β-carbon of the nitroolefin. This step occurs with a

Scheme 2. Organocatalytic Formal [2 + 2]-Cycloadditions: α,β-Unsaturated Aldehyde Scope[a]



[a]All reactions performed on a 0.2 mmol scale (see Supporting Information). Yield after isolation by FC is given. dr determined by ^{1}H NMR of the crude reaction mixture. ee determined by CSP-HPLC. [b]Determined after reduction to the corresponding alcohol.

Scheme 3. Enantioselective Synthesis of Cyclobutane Containing a Quaternary Stereocenter



barrier of 9.8 kcal/mol (**A-TS**) and leads to intermediate **B**. In the second step, the bond between the β-carbon of the iminium ion and the carbon adjacent to the nitro group is formed leading to **C**. This step has a higher energy barrier, 17.6 kcal/mol (**B-TS**), that likely results from the weakening of the H-bonding interactions present in intermediate **B**. This mechanism is consistent with the experimentally observed reactivity and selectivity. Furthermore, this reaction pathway explains the absolute stereochemistry of the fully substituted cyclobutane which was assigned by single crystal X-ray analysis.[16]

In conclusion, a new dual activation mode in organocatalysis has been demonstrated. Rational catalyst design supported by computational studies enabled development of a novel reaction pathway affording fully substituted cyclobutanes by an organocatalytic formal [2 + 2]-cycloaddition. Simultaneous activation of α,β-unsaturated aldehydes, via dienamine formation, and nitroolefins, via H-bonding, proved beneficial enabling the reaction to proceed in high yields and excellent diastereo- and enantioselectivities. A stepwise mechanism has been elucidated by computational studies.

dx.doi.org/10.1021/ja211878x | *J. Am. Chem.Soc.* 2012, 134, 2543−2546

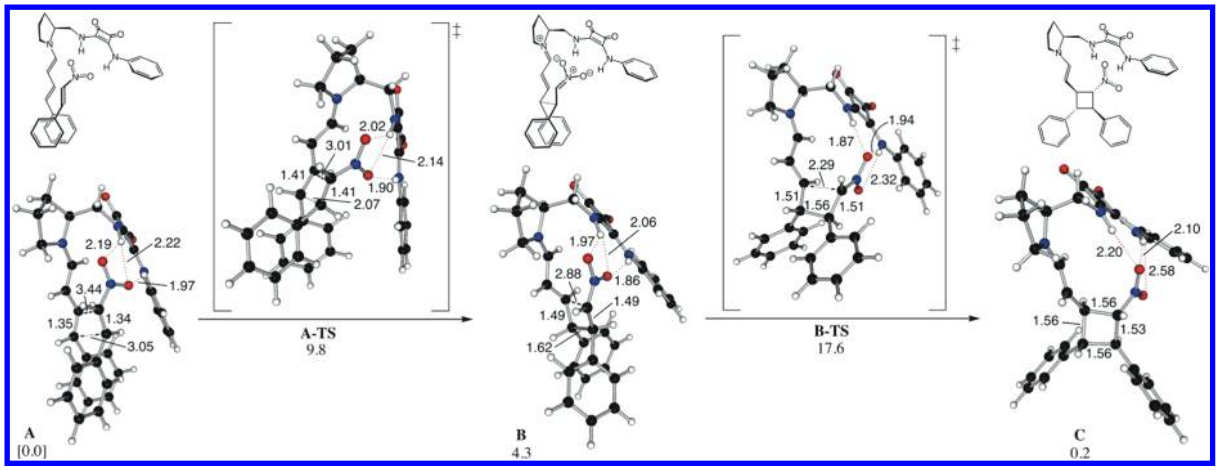


Figure 3. Calculated reaction pathway of the H-bond directed organocatalytic formal [2 + 2]-cycloaddition. Energies are reported in kcal/mol and are relative to the energy of the reactant complex, **A**. Bond distances are reported in Å.

■ ASSOCIATED CONTENT

Supporting Information

Screening results, experimental procedures, analytical data, computational details, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Aarhus University, FNU and the Carlsberg Foundation. C.R.-E. thanks the Generalitat de Catalunya for a Beatriu de Pinós postdoctoral fellowship. F.C.A. thanks CSIC for a predoctoral JAE grant. Dr. Jacob Overgaard is acknowledged for performing X-ray analysis.

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