Organocatalysis

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Cooperative Dienamine/Hydrogen-Bonding Catalysis: Enantioselective Formal [2+2] Cycloaddition of Enals with Nitroalkenes**

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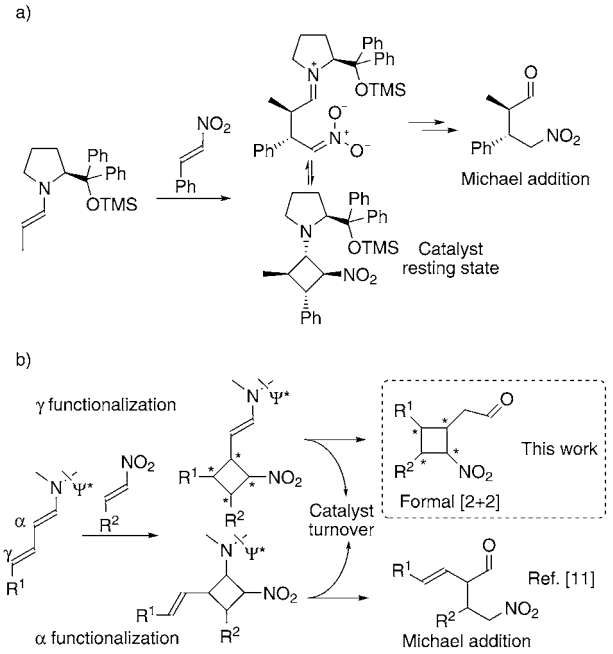
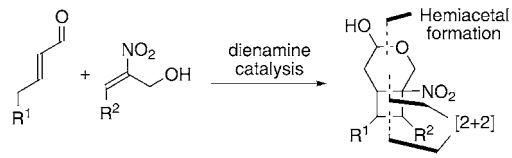
The cyclobutane scaffold is a structural motif incorporated into a wide range of naturally occurring products, as well as into transiently generated intermediates in primary and secondary metabolism.[1] Moreover, the reactivity pattern shown by cyclobutanes when exploiting ring strain as a driving force to facilitate novel reactivity has also opened the way for their use as intermediates in the synthesis of complex molecules.[2] However, despite their interest, the development of methodologies for the stereocontrolled synthesis of cyclobutanes has received little attention over the years.[3] In this context, the [2+2] cycloaddition represents one of the most straightforward approaches for the stereoselective construction of this structure with several reported and efficient examples, which rely on the use of chiral ligands,[4] auxiliaries,[5] or Lewis acid catalysts.[6]

Within this context, we wondered if aminocatalysis could contribute to this field by facing the challenge of setting up an enantioselective version of a [2+2] cycloaddition reaction between α,β-unsaturated aldehydes and nitroalkenes. We were inspired by recent work by Seebach, Hayashi, and co-workers,[7] and Blackmond and co-workers[8] (Scheme 1) in which kinetic and structural studies of *O*-trimethylsilyldiphenylprolinol-catalyzed Michael addition of aldehydes to nitroolefins led to the detection of an aminonitrocyclobutane intermediate, which was identified as a resting state for the catalyst. Taking this discovery into account, we hypothesized that enolizable enals could undergo a similar reaction based on the dienamine activation mode[9] where the catalyst would be able to undergo turnover, thus furnishing a final nitrocyclobutane product. In fact, literature precedent exists for the related [2+2] cycloaddition of enamines with electron-poor alkenes, thus showing that this process can occur spontaneously without the need of photochemical activation.[10] In contrast, there is also literature precedent which shows that the reaction of nitroalkenes with enolizable α,β-unsaturated aldehydes under dienamine catalysis leads to the exclusive formation of Michael-type adducts through the selective α-functionalization of the dienamine intermediate and therefore no opportunity arises for cyclobutane formation.[11]



Scheme 1. a) Previous work: addition to nitroolefins throuh enamine catalysis. b) Working hypothesis: formal [2 + 2] cycloaddition through dienamine catalysis. TMS = trimethylsilyl.

Herein, we wish to present our initial results on a novel chiral secondary amine catalyzed enantioselective formal [2+2] cycloaddition of enolizable α,β-unsaturated aldehydes with α-hydroxymethyl-substituted nitroalkenes which leads to the formation of cyclobutanes in a single step (Scheme 2). This reaction is in sharp contrast with previously published work which, as already mentioned, shows the preference for dienamine intermediates generated from enals to undergo



Scheme 2. One-step synthesis of cyclobutanes by [2+2] cycloaddition/hemiacetalization under dienamine catalysis.

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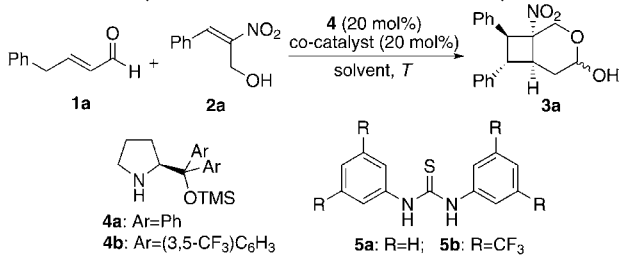
α functionalization with nitroalkenes.[11] It should also be pointed out that there is only one literature precedent dealing with an enantioselective intermolecular [2+2] cycloaddition between enals and electron-rich alkenes which proceeds under iminium catalysis,[12] and the dienamine route presented herein is still an unexplored approach[13] which is also a complementary methodology to reported example, as it allows the [2+2] cyclocondensation of enals with an electron-poor alkene. In addition, this new process leads to the formation of cyclobutanes that are not obviously accessible using other methods.

We started our study by surveying the best reaction conditions for the transformation using the reaction of the enal **1a** with nitroalkene **2a** as a model system (Table 1). We initially tested the performance of catalyst **4a** under standard reaction conditions, which involve the use of benzoic acid as Brønsted acid co-catalyst in $CHCl_3$ at 4 °C (entry 1). Under these reaction conditions, the adduct **3a** was isolated in moderate yield with a promising 74% *ee*. Importantly, NMR analysis of the crude reaction mixture indicated that **3a** had been formed as a 1:1 mixture of α and β anomers. No other diastereoisomers could be detected, which indicated that the formal [2+2] cycloaddition process also had taken place with complete diastereocontrol. Increasing the steric bulk at the aryl moieties of the diarylprolinol catalyst (entry 2) did not result in any significant improvement. We next evaluated the influence of the solvent by adopting **4a** as the most efficient catalyst, and observed that running the reaction in toluene led to a slight increase in the enantioselectivity (entry 3), whereas other more polar solvents were incompatible with this transformation (entries 4 and 5). We also found that working at a lower temperature led to **3a** with an excellent *ee* value, but in much lower yield (entry 6). With the aim of improving this latter parameter, we next considered the possibility of a dual activation approach for both the aldehyde and the nitroalkene by using the combination of the amine catalyst **4a** and the achiral thiourea **5a**, which was expected to engage in selective hydrogen bonding with the nitroalkene.[14] When we used this catalyst combination, the yield increased to 70% without affecting the enantioselectivity (entry 7), and an even better result was obtained when thiourea **5b** was employed (entry 13).

Having established the best protocol for the reaction, we next surveyed the scope of this transformation with respect to the α,β-unsaturated aldehydes and nitroolefins. As summarized in Table 2, the reaction behaved well in all cases tested when γ-aryl-substituted α,β-unsaturated aldehydes were employed, regardless of the electronic nature of the γ substituent. In this sense, both the electron-rich (**1b**) and electron-poor (**1c**) aryl-substituted enals reacted efficiently with α-hydroxymethylnitrostyrene (**2a**) to furnish the corresponding bicyclic adducts **3b** and **3c**, respectively, in good yields and excellent enantioselectivities (entries 2 and 3). The γ-heteroaryl-substituted enal **1d** also performed well in the reaction with **2a**, thus delivering **3d** in good yield and enantioselectivity (entry 4). Regarding the nitrostyrene reagent we evaluated the use of the **2a** and other derivatives incorporating electron-donating or electron-withdrawing substituents at the aryl moiety, and, in all cases the reaction also proceeded with similar levels of chemical efficiency and stereocontrol (entries 5–11). We also evaluated the use of a β-alkyl-substituted α,β-unsaturated aldehyde such as 2-hexenal (**1f**), which led to the formation of the desired cyclobutane adduct with a somewhat lower yield, but still with good levels of stereocontrol (entry 12). This final experiment also points toward the ability of the γ-aryl substituent on the enal

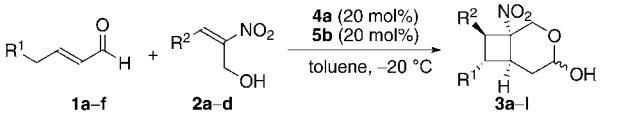
Table 1: Screening for the best experimental conditions using the reaction of aldehyde **1a** and nitroalkene **2a** as a model system.[a]



Entry	4	Co-catalyst	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**4a**	$PhCO_2H$	$CHCl_3$	4	59	74
2	**4b**	$PhCO_2H$	$CHCl_3$	4	0	–
3	**4a**	$PhCO_2H$	toluene	4	56	86
4	**4a**	$PhCO_2H$	THF	4	<5	n.d.
5	**4a**	$PhCO_2H$	EtOH	4	<5	n.d.
6	**4a**	$PhCO_2H$	toluene	−20	47	90
7	**4a**	**5a**	toluene	−20	70	91
8	**4a**	**5b**	toluene	−20	86	91

[a] Reaction conditions: **1a** (0.35 mmol), **2a** (0.52 mmol), catalyst **4** (20%), and co-catalyst (20%) were stirred in the specified solvent and temperature for 72 h. [b] Yield of pure product as a 1:1 mixture of α and β anomers after column chromatography. [c] Determined by HPLC analysis of the corresponding lactone. n.d. = not determined, THF = tetrahydrofuran.

Table 2: Scope of the reaction.[a]

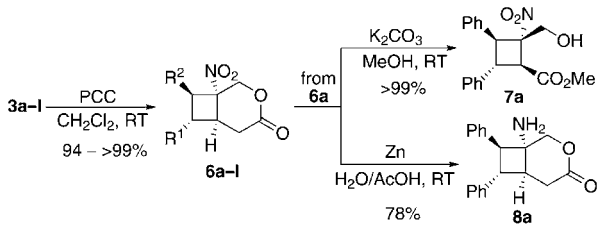


Entry	3	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	**3a**	Ph	Ph	86	91
2	**3b**	4-MeC_6H_4	Ph	88	92
3	**3c**	4-FC_6H_4	Ph	77	92
4	**3d**	2-thienyl	Ph	73	89
5	**3e**	Ph	4-$MeOC_6H_4$	72	95
6	**3f**	4-MeC_6H_4	4-$MeOC_6H_4$	91	94
7	**3g**	4-FC_6H_4	4-$MeOC_6H_4$	91	94
8	**3h**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	90	94
9	**3i**	Ph	4-ClC_6H_4	67	92
10	**3j**	4-MeC_6H_4	4-ClC_6H_4	69	94
11	**3k**	Ph	2-thienyl	52	94
12	**3l**	Et	Ph	38	85

[a] All reactions carried out on 0.35 mmol scale of **1a**. [b] Yield of pure product as a 1:1 mixture of α and β anomers (NMR analysis) after column chromatography. [c] Determined by HPLC analysis of the corresponding lactone.

reagents **1a–e** to stabilize the dienamine intermediate by extending the conjugated system, which facilitates the reaction. Finally, it should noted that, as it happened in the model reaction, the formation of the cyclobutane scaffold took place in all cases with complete diastereoselection, and only the expected α and β anomers, resulting from the formation of the hemiacetal moiety, were observed; no other diastereoisomer was detected in the NMR spectra of the crude reaction mixtures.

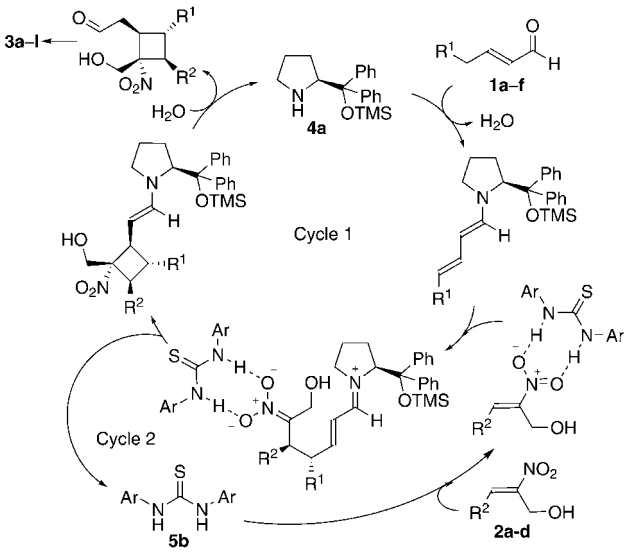
Considering that the cyclobutane adducts **3a–l** had been obtained as mixtures of anomers, we decided to carry out their oxidation to the corresponding lactones for the purpose of better characterization, thus obtaining bicyclic adducts **6a–l** in excellent yields and as single diastereoisomers (Scheme 3).



Scheme 3. Oxidation of compounds **3a–l** and survey of transformations carried out on compound **6a**. PCC = pyridium chlorochromate.

We could also grow a crystal of compound **6a** suitable for X-ray analysis,[15] and established unambiguously the absolute configuration of the products **3** and **6**. In addition, we also decided to explore some possible transformations of the obtained bicyclic adducts to illustrate their potential application as chiral building blocks in organic synthesis (Scheme 3). For example, using lactone **6a** as a model substrate, we quantitatively obtained the tetrasubstituted cyclobutane **7a** by base-promoted methanolysis. We have also carried out the reduction of the nitro group under standard reaction conditions to give the corresponding amine **8a** in good yield.

We propose a catalytic cycle (Scheme 4) which starts with the activation of the enal by the amine catalyst **4a** through dienamine formation, and then generation of the cyclobutane ring is proposed to most likely occur by means of a stepwise Michael/Michael process, in which the dienamine undergoes a conjugate addition at its γ-carbon atom with the nitroalkene **2** and a subsequent intramolecular reaction of the generated nitronate intermediate with the remaining α,β-unsaturated iminium ion moiety. Once this cascade takes place, an enamine intermediate is formed which undergoes hydrolysis, thus releasing the catalyst and delivering the final adduct **3** after an hemiacetalization process. The thiourea co-catalyst is proposed to be involved in the activation of the nitroalkene in the initial Michael reaction, although it can also participate in the stabilization of the nitronate intermediate during the subsequent intramolecular Michael reaction. Similarly, the formation of the final adducts as stable hemiacetal derivatives is also believed to play a crucial role,[16] thereby providing a thermodynamic driving force for the reaction to proceed to completion.



Scheme 4. Proposed reaction mechanism.

In summary, we have presented an efficient methodology for the enantio- and diastereoselective synthesis of substituted cyclobutanes by direct reaction of enolizable α,β-unsaturated aldehydes and α-hydroxymethylnitrostyrenes using a chiral secondary amine and an achiral thiourea as a catalytic couple. The success of the reaction relies on the dual activation of both the enal and the nitroalkene reagents by the two catalysts, the former being engaged in a cascade Michael/Michael reaction through activation by the amine catalyst and the latter being activated by the thiourea through hydrogen bonding. This is the first example of a cascade reaction involving the dienamine/iminium manifold and also a good example of the great potential offered by the combination of the different organocatalytic activation mechanisms, which can lead to the discovery of new transformations and novel reactivity patterns.

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[13] After our manuscript had been submitted the elegant work by Jørgensen and co-workers appeared describing a similar formal [2+2] cycloaddition reaction between enals and nitroalkenes under dienamine catalysis: L. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodriguez-Escrich, R. L. Davis, K. A. Jørgensen *J. Am. Chem. Soc.* **2012**, *134*, 2543.

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[15] CCDC 861549 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] The reaction of **1a** with nitrostyrene under the reaction conditions reported herein afforded the corresponding cyclobutane product in < 10% yield, which is also consistent with the results reported by Jørgensen and co-workers (see Ref. [13]). We have also tested the reaction of **1a** with α-methylnitrostyrene under our reaction conditions and in this case the cyclobutane adduct was isolated in 15% yield. All these experiments points towards the key role played by the hemiacetal formation step as driving force for bringing the reaction to completion.

