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"On Water" Organocatalyzed [4 + 2] Cycloaddition of Enones and Nitro Dienes for the Enantioselective Synthesis of Densely Substituted Cyclohexanones

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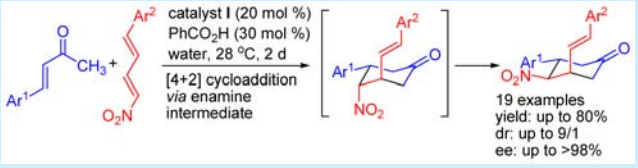
Supporting Information

ABSTRACT: An "on water" hydroquinine-based primary amine–benzoic acid organocatalyst system was found to be best suited to produce 3,4,5-trisubstituted cyclohexanones with a nitro group in the 4-position from enones and nitro dienes under ambient conditions in good yield, with good diastereoselectivity, and with excellent enantioselectivity. An appreciable rate enhancement by water was observed compared to organic solvents. Mechanistic analysis of the reaction suggests that it followed an *endo* [4 + 2] cycloaddition with enamine of enone as diene and nitro diene as dienophile.



Use of water as a reaction medium in organic synthesis[1] is gaining popularity because it is cheap, nontoxic, and nonflammable. However, most of the organic compounds are poorly soluble in water, which restricts its use in organic synthesis. The studies of Breslow[2] for water as a reaction medium provided a major impetus in this direction. The concept of "on water" for the use of water as a reaction medium was introduced by Sharpless and co-workers,[3] and it has become one of the most intriguing areas of research in Green Chemistry. Organocatalysis[4] has now become an established and leading synthetic tool for stereoselective organic reactions in addition to metal catalysis and biocatalysis. The organocatalyzed reactions are commonly performed in organic solvents because of the solubility of the reactants and catalyst in the medium. Recently, the use of water as a medium in organocatalysis has gained popularity because its of changing reactivity and selectivity patterns compared to organic media.[5,6]

Nitro-substituted cyclohexanones are valuable building blocks for the synthesis of natural products and biologically active compounds.[7] Therefore, there has been a surge in interest for the synthesis of 4-nitro-substituted cyclohexanones.[8] Chiral pyrrolidine derivatives[9] have been shown to catalyze the [4 + 2] cycloaddition between nitro olefins and acyclic enones, providing 4-nitrosubstituted cyclohexanones with variable yields and poor enantioselectivity. Subsequently, cinchona-derived primary amines have been introduced as organocatalysts in the double-Michael addition of nitro olefins and acyclic enones for direct synthesis of nitro-substituted cyclohexanones.[9,10] These reactions were mostly performed in organic solvents, and the deactivation of the catalyst system has been reported when attempted in water as reaction medium.[10] Thiourea-based dual-activation organocatalysts have been shown to catalyze the Michael addition of curcumin to nitro olefins in organic solvents. Potassium carbonate promoted intramolecular Michael addition then provided densely functionalized 4-nitrocyclohexanones.[11] Compared to the abundant use of nitroalkenes, nitro dienes are sparsely used in this type of reaction, and cyclohexenones have been shown to react with nitro dienes to give bridged bicyclic systems.[12] However, we are not aware of any report pursuing an enantioselective synthesis of densely substituted cyclohexanones from acyclic enones and nitro dienes in aqueous or organic medium. In many organocatalyzed Michael additions, it has been observed that increasing conjugation to the Michael acceptor often altered reactivity and selectivities.[12−14] So, the reactivity, selectivity and reaction modes of nitro dienes with acyclic enones are yet to be established. Owing to the importance of the densely and diversely functionalized 4-nitrocyclohexanones and our continued interest in organocatalyzed reactions,[15] we herein disclose a highly diastereo- and enantioselective [4 + 2] cycloaddition of enones and nitro dienes leading to such cyclohexanones "on water" using a cinchona alkaloid derived organocatalyst.

Chiral pyrrolidine derivatives can activate α,β-unsaturated ketones via enamine formation.[16,17] However, it has been established that cinchona alkaloid-derived primary amine with a combination of chiral or achiral protic acid can generate enamine and iminium ion from both hindered and unhindered α,β-unsaturated ketones with ease.[18,19] The enamine **B** (Scheme 1) in principle can react with nitro diene to provide the 3,4,5-trisubstituted cyclohexanone by two different reaction modes, double Michael addition[20] or a [4 + 2] cycloaddition.[21] Based on this hypothesis, we selected few cinchona alkaloid

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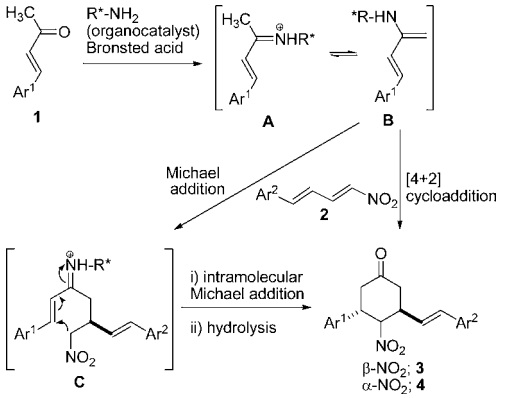
Scheme 1. Possible Pathways for 4-Nitrocyclohexanones



based primary amines[19,22] **I**–**IV** (Figure 1) for the present study.

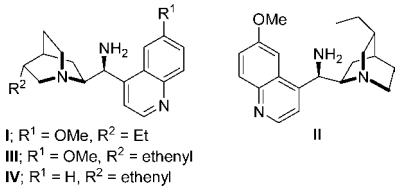
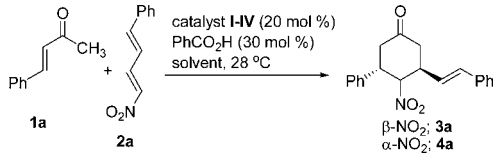


Figure 1. Structure of organocatalysts **I**–**IV**.

For the model reaction, benzylidene acetone **1a** was chosen as the enone, and 4-phenyl-1-nitrobutadiene **2a** was chosen as the nitro diene component. Initially, we screened the catalysts **I**–**IV** (20 mol %) in combination with benzoic acid (30 mol %) as an additive in toluene (0.4 M) at rt (28 °C). All of the catalysts showed positive results (Table 1, entries 1–4) with the formation of the desired nitro-substituted cyclohexanones **3a** and **4a**, but catalyst **I** provided the best result. We chose catalyst **I** for further optimization with different Brønsted acid additives (see the Supporting Information) using toluene as the solvent. Benzoic acid still remained the additive of choice because of its superior yield and selectivities. Variation in the polarity of the organic solvents did not improve the yield or selectivities in a meaningful way compared to toluene (Table 1, entries 5–9), but an exciting result was obtained when water was used as a medium, although none of the reactants or the catalyst was soluble in water (Table 1, entry 10). The reaction was greatly accelerated (completed in 2 d), resulting in good yield. The diastereoselectivity was improved now to an acceptable level, and enantioselectivity was excellent for both diastereoisomers. Thus, the optimized conditions were to use enone (2 equiv) (see the SI for optimization) with respect to nitro diene (1 equiv) in the presence of catalyst **I** (20 mol %), benzoic acid (30 mol %), and water at rt for 2 d. The antipode of **I** is difficult to obtain because of its unnatural configuration. However, catalyst **II**, the pseudoenantiomer of catalyst **I**, gave **3a** with a similar level but opposite enantioselectivity (Table 1, entry 2). Therefore, with catalysts **I** and **II** both enantiomers of **3a** can be prepared.

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	time (d)	3a/4a[b]	yield[c] (%)	ee[d] (%)
1	**I**	toluene	4	65:35	52	99
2	**II**	toluene	4	64:36	46	96[e]
3	**III**	toluene	4	44:56	35	98
4	**IV**	toluene	4	40:60	22[f]	96
5	**I**	xylene	5	50:50	38	95
6	**I**	$CHCl_3$	5	67:33	42	96
7	**I**	MTBE	5	83:17	39	>99
8	**I**	THF	5	50:50	41	92
9	**I**	MeOH	5	50:50	32	94
10	**I**	H_2O	2	80:20	75	>98

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (0.04 mmol), and benzoic acid (0.06 mmol) in solvent (0.5 mL). [b]Determined by ^{1}H NMR. [c]Isolated yield of diastereoisomer **3a**. [d]ee of **3a** as determined by HPLC. [e]Product with opposite enantioselectivity. [f]Incomplete reaction.

After the optimal reaction conditions were established, the substrate scope was explored using variety of enones and nitro dienes having electron-donating and electron-withdrawing functionalities at the aromatic rings of both components. The products **3a**–**t**, formed by reaction of various enones and 4-aryl-1-nitrobutadienes, is presented in Scheme 2.

The reaction worked well for nitro dienes **2** where the aryl ring was functionalized with electron-donating or -withdrawing groups at various positions. Similarly, the outcome of the reaction did not depend much on the nature and positioning of the aryl substituents of arylidene acetones **2**. All of the products were solid, and many of them could be made enantiopure just by single recrystallization. It is worth mentioning that the reaction worked well with (*E*)-1-phenylpent-1-en-3-one as enone, providing product **3t** with an additional chiral center. The relative and absolute configuration of the cyclohexanones[23] **3g**, **3l**, **3m**, and **3s** were confirmed unambiguously as depicted by single-crystal X-ray crystallography. The stereochemistry of the other products in this series was also assigned by analogy.

To gain further insight into the mechanism of this cyclohexanone formation, a series of control experiments were performed (Scheme 3). As shown in Scheme 1, the unsaturated methyl ketone would react with primary amine organocatalyst in the presence of Brønsted acid to give the iminium **A**, which remains in equilibrium with the enamine **B**. The enamine, in principle, can react with nitro diene **2** to provide the 3,4,5-trisubstituted cyclohexanone **3**/**4** either by a double Michael addition or [4 + 2] cycloaddition. The Diels–Alder pathway was initially ignored from the stereochemical outcome of the reaction because the *cis*-relationship between nitro and styryl substituents in the major diastereoisomer **3** does not conserve the *E*-stereochemistry of the dienophile fragment, i.e., nitro diene. We found that the major and the minor diastereoisomers **3a** and **4a**, respectively, have the same enantioselectivity. The major diastereoisomer **3a** was stable toward isomerization on separate treatment with the catalytic system while the nitro-bearing center of the minor diastereoisomer **4a** slowly epimerized to the major diastereoisomer **3a** under the same conditions (Scheme 3).

To elucidate if the diastereoisomer **3a** formed directly in the reaction or it is a secondary product derived from the isomerization of **4a**, the progress of cyclohexanone formation from nitro diene **2a** and enone **1a** was monitored by ^{1}H NMR spectroscopy. An interesting change in the ratio of **3a**/**4a** was

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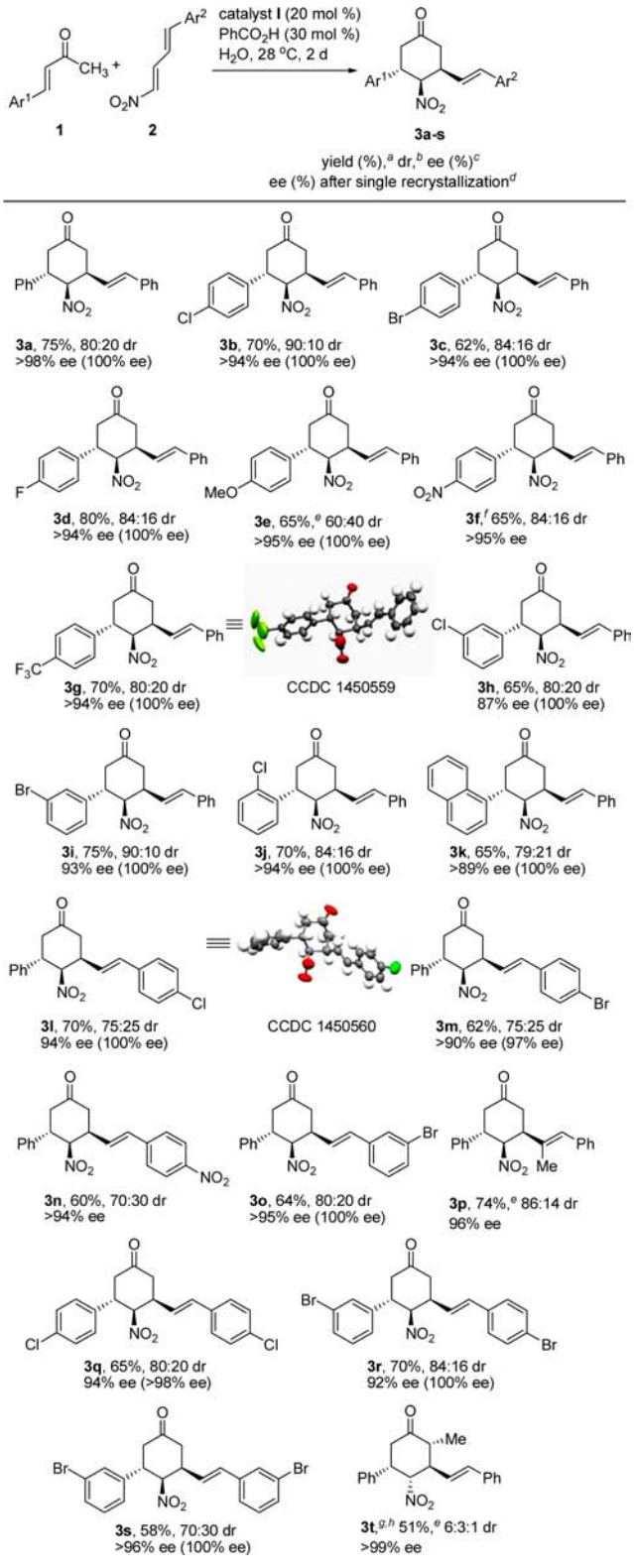
Scheme 2. Synthesis of Cyclohexanones 3a−s



[a]Isolated yield of the major diastereoisomer (shown). [b]Determined by ^{1}H NMR. [c]Determined for major diastereoisomer by HPLC. [d]% ee after single recrystallization. [e]Combined isolated yield of both diastereoisomers. [f]Reaction performed at 40 °C. [g](*E*)-1-Phenylpent-1-en-3-one was used instead of **1**. [h]See the SI for details.

observed as the time progressed (Table 2). After 2 h, the diastereoisomer **4a** was almost the sole product in the

Scheme 3. Mechanistic Studies

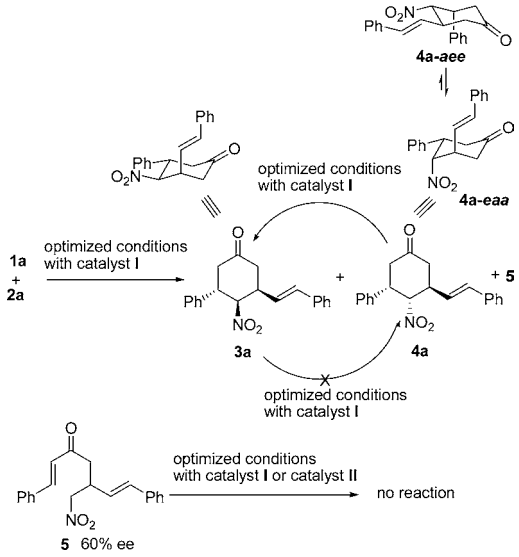
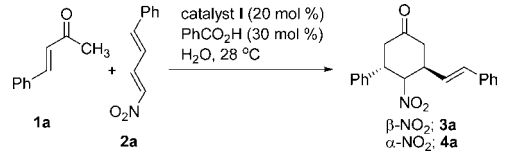


Table 2. Time-Dependent NMR Study



entry	time (h)	3a/4a[a]	yield[b] (%)	ee[c] (%)
1	2	4:96	*d*	
2	6	15:85	*d*	
3	24	62:38	*d*	
4	48	80:20	75	>98
5	168	90:10	82	>98
6	120[e]	90:10	80	94

[a]Determined by ^{1}H NMR. [b]Isolated yield of **3a**. [c]ee of **3a** as determined by HPLC. [d]Incomplete reaction; yield not determined. [e]Reaction performed for 48 h at rt and then 72 h at 40 °C.

incomplete reaction. But as the time advanced, the conversion also progressively increased, and the diastereoisomer ratio **3a**/**4a** was also changed from 4/96 to 8/2 after 2 d. The ratio of **3a**/**4a** could further be improved to 9/1 if the reaction was left for 6 d at rt without any loss of enantioselectivity or yield. These experiments confirm that the diastereoisomer **4a** was initially formed as a kinetic *endo* [4 + 2] cycloaddition product which over the time isomerizes under the reaction conditions to thermodynamically more stable diastereoisomer **3a**.

The ease of epimerization of **4a** to **3a** can be explained by analyzing the conformational preferences for **3a** and **4a** (Scheme 3). After the cycloaddition and catalyst partition, the product **4a** principally can adopt two conformations, **4a**-*eaa* and **4a**-*aee*. Considering the substituent steric factors (cyclohexane *A* values), conformer **4a**-*eaa* would be preferred over **4a**-*aee*. The NO_2 group in **4a**-*eaa* is axially disposed would thus prefer to become equatorial by epimerization leading to diastereoisomer **3a** with a conformation where the Ph and NO_2 groups are equatorial as supported by X-ray structures. The evidence in favor of a [4 + 2] cycloaddition pathway was further augmented by appreciable rate acceleration of the reactions in water[24] compared to organic solvents (Table 1, entry 10). We have also isolated a very small amount of Michael

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addition product **5** from the reaction between nitro diene **2a** and enone **1a** under the optimized conditions in <4% yield and with poor enantioselectivity (60% ee). This adduct did not undergo intramolecular Michael-type cyclization to give the 4-nitrocyclohexanone(s) **3a**/**4a** under the optimized conditions using catalyst **I** or **II**. This observation also suggests that a double-Michael addition may not be the preferred process in the current synthesis of densely substituted 4-nitrocyclohexanones.

In conclusion, an eco-friendly "on water" organocatalytic method for densely substituted cyclohexanones has been established. Water accelerated the reactions and also improved selectivities. The salient feature of this reaction is the complete diastereocontrol of the aryl- and arylalkenyl-bearing centers in the cyclohexanones. The observed diastereoisomers are due to the epimerizable nitro-bearing center. The diastereoisomer ratio (**3**/**4**) in favor of the thermodynamic product **3** could be improved by heating (40 °C) the reaction mixture before workup with a small drop in ee. Mechanistic analysis of the reaction goes in favor of an *endo* [4 + 2] cycloaddition, which is different from nitro olefin acyclic enone reactions reported so far using primary amine catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00460.

Experimental procedure, characterization data, and HPLC traces for **3a**−**t**, **4a**, **5**, and **6**; X-ray crystallographic information (PDF)

^{1}H and ^{13}C spectra for **3a**−**t**, **4a**, **5**, and **6** (PDF)

X-ray crystallographic data for **3g**,**l**,**o**,**s** (CIF)

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Notes

The authors declare no competing financial interest.

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