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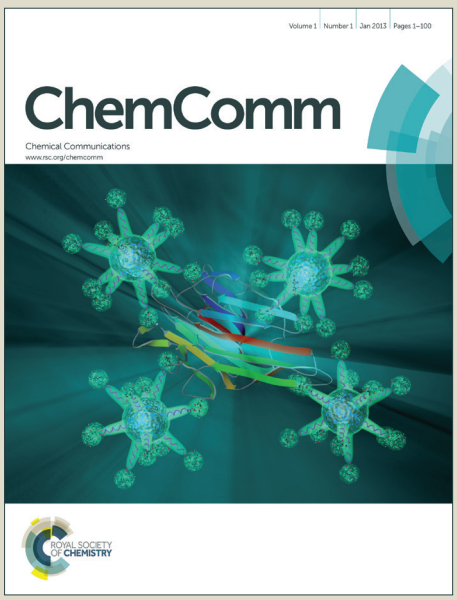

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ARTICLE TYPE

Organocatalytic cascade reaction of 2-nitrocyclohexanone and α,β-unsaturated aldehydes with unusual regioselectivity

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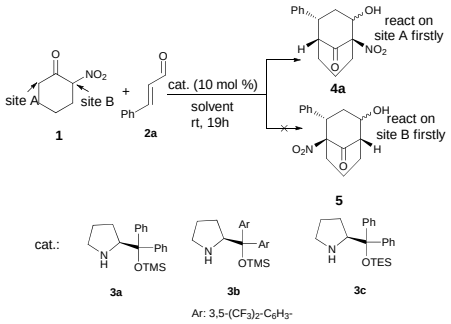
Organocatalytic cascade reaction of 2-nitrocyclohexanone and α, β-unsaturated aldehydes was developed. Bicyclo[3.3.1]nonanone products were obtained with good yields and excellent enantioselectivities. The reaction occurred with unusual regioselectivity. A dienolate-iminium activation mechanism was proposed. The products were transformed to eight-membered cyclic ketones with high enantioselectivity.

In the past decade, organocatalytic asymmetric conjugate additions have proved to be powerful tools for the synthesis of chiral compounds.[1] 1,3-dicarbonyl compounds, nitroalkanes and other carbon anion precursors have been applied as the nucleophilic reagents with great successes. α-Nitro ketones are useful nucleophilic reagents with attractive functional groups. The products are readily transformed to a number of useful compounds via different derivation pathways.[2,3] We and the others have developed an organocatalytic addition of acyclic α-nitroketones to β,γ-unsaturated α-keto esters.[4] The reaction provides 5-nitro-2-acyloxypent-2-enoates with excellent yields and enantioselectivities via cascade Michael addition/acyl transfer steps. Lately, Wang and co-workers reported the organocatalytic addition of 2-nitrocyclohexanone to β,γ-unsaturated α-keto esters. Bicyclic hemiketals were obtained with excellent yields and enantioselectivities.[5] As a continuous effort to explore the new applications of α-nitroketones in organocatalytic conjugate additions, herein, we report an unprecedented conjugate addition of 2-nitrocyclohexanone to α, β-unsaturated aldehydes with unusual regioselectivity. The reaction provided bicyclo[3.3.1]nonanone products in good yields and with excellent enantioselectivities.[6] The further elaboration led to the enantioenriched eight-membered cyclic ketones efficiently.

The reaction of cinnamaldehyde and 2-nitrocyclohexanone was first investigated using prolinol trimethylsilyl ether **3a** as the catalyst (Table 1). The reaction was expected to provide the product **5** via the conjugate addition on the site B and the consequent intramolecular aldol reaction. To our surprise, compound **5** was not observed**.** Instead, compound **4a** was obtained as the main product. The conjugate addition occurred regioselectively on the less acidic methylene group (site A) of 2-nitrocyclohexanone. Then a consequent intramolecular Henry reaction provided the product **4a**. To the best of our knowledge, such a reverse of the regioselectivity of α-nitroketones has never been reported before.[7] This reactivity appears to be quite similar with the dianions of acetoacetates generated under the strong basic conditions.[8]

Table 1 Screening of catalysts and solvents[a]



entry	cat.	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	CH_2Cl_2	33	79:21	92
2	**3b**	CH_2Cl_2	-	-	-
3	**3c**	CH_2Cl_2	35	79:21	94
4	**3c**	CH_3OH	7	80:20	-
5	**3c**	EtOAc	36	89:11	92
6	**3c**	toluene	45	85:15	93
7	**3c**	THF	36	86:14	96
8	**3c**	MeCN	46	80:20	90

[a] Unless otherwise stated, all reactions were performed at room temperature with **1** (0.24 mmol), **2a** (0.2 mmol), and catalyst (0.02 mmol) in 0.5 mL of solvent for 19 h. [b] Determined by HPLC analysis. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Values of the major diastereoisomer and were determined by chiral HPLC.

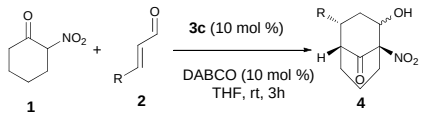
Furthermore the reaction was examined with other prolinol silyl ethers and solvents. The results are summarized in Table 1. Unexpectedly, trifluoromethyl substituted prolinol silyl ether **3b** is completely ineffective. Prolinol triethylsilyl ether **3c** provided better enantioselectivity (Table 1, entries 1–3). Protic solvents (such as methanol) were detrimental for the reaction and only trace amount of product was obtained (Table 1, entry 4). Other solvents such as toluene, ethyl acetate, tetrahydrofuran (THF) and acetonitrile provided the product with 36-46% yields (Table 2, entries 5-8). The best enantioselectivity was achieved in THF (Table 1, entry 7).

The effect of additives was also examined.[9] The addition of PhCOOH gave a lower yield. Inorganic base such as Na_2CO_3, K_2CO_3 and KOAc were also ineffective. In contrast, organic bases such as Et_3N, DMAP (4-Dimethylaminopyridine), *N*-methyl-pyrrolidine, DABCO (1, 4-Diazabicyclo[2.2.2]octane)

significantly improved the yields. DABCO was proved to be the best choice for the transformation. Full conversion was achieved in 3 h with excellent yield (96%) and enantioselectivity (99% ee). DIPEA (*N*,*N*-Diisopropylethylamine) and NMM (*N*-methyl-morpholine) were less efficient The addition of 2, 6-lutidine inhibited the reaction.

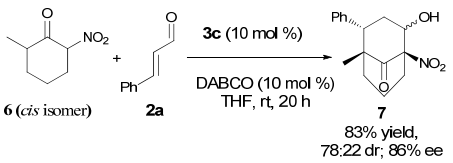
With the optimal reaction conditions in hand, the scope of α,β-unsaturated aldehydes was explored and the results are summarized in Table 2. Bicyclic products **4a-4l** containing four stereocenters were obtained in moderate to good yields and with excellent enantioselectivities (Table 2, entries 1-12). The *ortho*-, *meta*-, and *para*-substitutions on the phenyl ring of cinnamaldehydes were tolerated very well. The electronic property of the substituent has negligible effect on the yield and enantioselectivity (Table 2, entries 2~10). β-Heteroaryl α,β-unsaturated aldehydes also provided the expected products with high yields and excellent enantioselectivities (Table 2, entries 11 and 12). In general, the diastereoselectivity of the reaction was insensitive to electronic property of the substituent. Good diastereoisomeric ratios from 81/19 to 88/12 were obtained for all the products. β-Alkyl unsaturated aldehydes such as crotonaldehyde and *trans*-2-hexenal were examined, but no expected products could be separated (entries 13 and 14). 2-Nitrocyclopentanone and 2-nitrocycloheptanone were also tested, but the reactions did not give the expected products. The reaction of *cis*-2-methyl-6-nitrocyclohexanone occurred smoothly to provide the expected product with good yield and enantioselectivity (Scheme 1).

Table 2 Organocatalytic addition of 2-nitrocyclohexanone to α,β-unsaturated aldehydes[a]



entry	R	**4**, yield (%)[b]	dr[c]	ee (%)[d]
1	Ph, **2a**	**4a**, 94	88:12	99
2	4-Me-C_6H_4, **2b**	**4b**, 88	87:13	99
3	4-MeOC_6H_4, **2c**	**4c**, 89	84:16	99
4	2-Cl-C_6H_4, **2d**	**4d**, 86	88:12	99
5	3-Cl-C_6H_4, **2e**	**4e**, 88	85:15	99
6	4-Cl-C_6H_4, **2f**	**4f**, 70	85:15	99
7	4-Br-C_6H_4, **2g**	**4g**, 77	85:15	99
8	4-NO_2-C_6H_4, **2h**	**4h**, 88	82:18	99
9	4-CN- C_6H_4, **2i**	**4i**, 85	86:14	99
10	4-CF_3-C_6H_4, **2j**	**4j**, 74	81:19	95
11	2-furyl, **2k**	**4k**, 72	88:12	99
12	2-thienyl, **2l**	**4l**, 84	88:12	99
13	Me, **2m**	-	-	-
14	*n*-Pr, **2n**	-	-	-

[a] Unless otherwise stated, all reactions were performed with **1** (0.24 mmol), **2** (0.2 mmol), **3c** (0.02 mmol) and DABCO (0.02 mmol) in THF (0.5 mL) for 3 h. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Values of the major diastereoisomers and were determined by chiral HPLC.



Scheme 1 Organocatalytic addition of 2-methyl-6-nitrocyclohexanone to cinnamaldehyde

To explore the reaction mechanism, ^{1}H NMR spectrum of the mixture of 2-nitrocyclohexanone (**1**), DABCO and organocatalyst **3c** was investigated (Fig. 1b). In comparison with the spectrum of **1** (Fig. 1a), the ^{1}H signal of the site B (δ, 5.23 ppm, ddd, J = 11.7, 6.1, 1.0 Hz) declined, but the characteristic signal of the dienolate (δ, 4.39 ppm, t, J = 7.1 Hz) emerged. The mixture of **1** and DABCO showed the similar signal distribution (Fig. 1c). The spectrum of the mixture of **1** and catalyst **3c** also indicated the formation of the dienolate, but the signal intensity was rather weak (Fig. 1d). The results suggested that the dienolate intermediate was generated readily in the presence of DABCO.

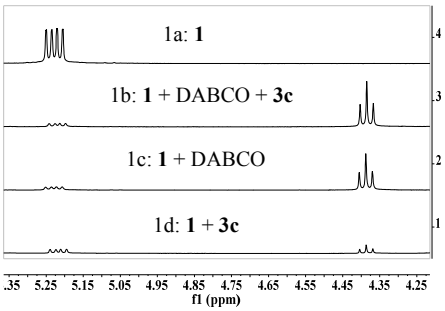
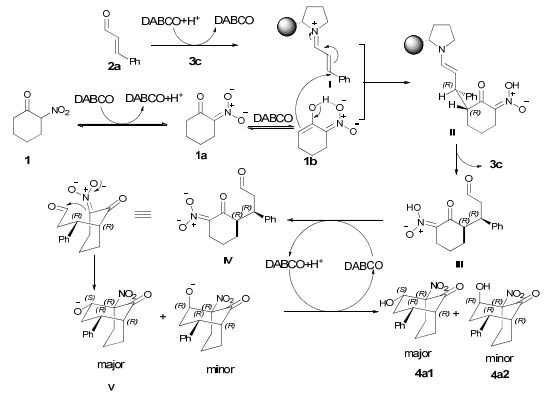


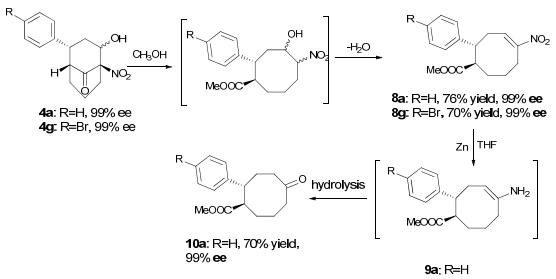
Fig. 1 ^{1}H NMR spectra of the mixtures of 2-nitrocyclohexanone (**1**), DABCO and organocatalyst **3c**

Based on the above experimental results and the relevant reports, a dual dienolate-iminium activation mechanism is proposed for the reaction of 2-nitrocyclohexanone and α,β-unsaturated aldehydes (Scheme 2). An iminium intermediate **I** is generated by the reaction of α, β-unsaturated aldehyde with catalyst **3c**. DABCO facilitates the deprotonation of 2-nitrocyclohexanone to provide nitro enolate **1a**. Further enolation of **1a** affords the dienolate **1b**. The site A of **1b** is more reactive than site B toward the conjugated addition. The attack of **1b** from the *si*-face of iminium intermediate **I** gives **II**. The consequent hydrolysis of **II** regenerates **3c** and provides intermediate **III**, which is deprotonated by DABCO to give the anion intermediate **IV**. The intramolecular Henry reaction of **IV** gives the products **4a1** and **4a2**. The transformation of **III** to **4a** was proposed to proceed very quickly, since no conjugate addition product **III** could be separated.

The treatment of **4a** and **4g** in methanol under reflux conditions led to ring opening and dehydration products **8a** and **8g** with good yields (Scheme 3). Further reduction of **8a** by Zinc dust afforded the unstable intermediate **9a.** The hydrolysis of **9a** provided eight-membered cyclic ketone **10a** with excellent enantioselectivity. Concerning the presence of the chiral eight-membered carbocycles in many natural products and the challenges for their synthesis,[10] the current method is attractive for the construction of some chiral eight-membered carbocycles.



Scheme 2 Proposed reaction mechanism



Scheme 3 Elaboration of products **4a** and **4g**

A single crystal of product **8g** was obtained and its absolute configuration was determined to be *1R,2R* via X-ray diffraction analysis.[9,11] Analogously, **8a** was assigned as the *1R,2R* configuration. The relative configuration of **4a1** was determined by NOE analysis. The hydroxyl group and nitro group are in *trans* arrangement (Scheme 2**, 4a1**).[9] The absolute configuration of major diastereoisomer **4a1** was assigned as *1R,2S,4R,5R*. Because both **4a1** and **4a2** could be transformed to **8a** (Scheme 3), the minor diastereoisomer **4a2** was assigned as *1R,2R,4R,5R*. The results are in good accordance with the proposed reaction mechanism (Scheme 2).

Conclusions

In summary, we have developed a cascade conjugate addition/Henry reaction of 2-nitrocyclohexanone and α, β-unsaturated aldehydes. Diarylprolinol triethylsilyl ether was identified as the efficient catalyst. 4-Aryl-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-ones with four stereocenters could be prepared in good yields and with excellent enantioselectivities. The reaction was initiated by an organocatalytic conjugate addition of 2-nitrocyclohexanone with reversed regioselectivity. The generation of the dienolate intermediate from 2-nitrocyclohexanone in the presence of organic base probably results in the unusual regioselectivity. The elaboration of the products provided eight-membered cyclic ketones with excellent enantioselectivity. Further investigation of the substrates scope and synthetic utility of the reaction is currently underway.

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Notes and references

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11 CCDC 999174 contains the supporting 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.