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Enantioselective organocatalytic conjugate addition of α-nitroacetate to α,β-unsaturated ketones in water

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ABSTRACT

The catalytic enantioselective conjugate addition reaction of α-nitroacetate to α,β-unsaturated ketones promoted by chiral bifunctional organocatalysts is described. The treatment of α-nitroacetate to α,β-unsaturated ketones under aqueous-phase reaction conditions afforded the corresponding Michael adducts with high enantioselectivity. The conjugate addition adducts are easily converted to chiral δ-keto nitroalkanes and δ-keto esters.

Enantioselective construction of stereogenic carbon center is a formidable challenge in organic synthesis. The Michael addition reaction is widely recognized as one of the most general methods for the formation of C–C bonds in organic synthesis,[1] and the development of enantioselective catalytic conjugate addition reaction has been the subject of intensive research.[2] In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric conjugate addition reaction has been explored intensively in recent years.[3,4] Enantioselective organocatalytic conjugate addition reaction of nitroalkanes to α,β-unsaturated carbonyl compounds represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, etc.[5] Although a number of catalytic enantioselective conjugate addition reaction of nitroalkanes to α,β-unsaturated ketones have been reported,[6] up to now there are few examples of these reactions with α-nitroacetate using chiral organocatalysts.[7] However, an enantioselective conjugate addition of α-nitroacetate to α,β-unsaturated ketones catalyzed by chiral primary amine organocatalysts remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under mild conditions, it could provide a highly attractive, convergent approach toward optically active δ-keto nitroalkanes and δ-keto esters. Recently, chiral primary amines have emerged as new and powerful catalysts for enantioselective organocatalytic reactions.[8] The development of enantioselective organocatalytic methodology in an aqueous medium has become the most desirable area of organic chemistry, due to the favorable features of water as an inexpensive, safe, and environmentally benign medium.[9]

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[10] we recently reported asymmetric conjugate addition reaction of active methylenes and methines.[11] Herein, we wish to describe the enantioselective asymmetric conjugate addition of α-nitroacetate to α,β-unsaturated ketones promoted by bifunctional organocatalysts containing chiral primary amines in water. The products resulted from a conjugate addition reaction will generate chiral δ-keto nitroalkanes and δ-keto esters, which can be conveniently elaborated in organic synthesis.

Validation of the feasibility of the proposed Michael addition process started by evaluating a model reaction between α-nitroacetate (**2**) and (*E*)-4-phenylbut-3-en-2-one (**1a**) in the presence of 20 mol % bifunctional catalysts (Fig. 1) and 40 mol % of benzoic acid as additive in water at room temperature. As shown in Table 1, 9-amino-9-deoxyepicinchona alkaloids (**I–VI**) effectively promoted the addition in high yield and high enantioselectivity (entries 1–6). While chiral primary amine organocatalysts (**VII–X**) bearing both central and axial chiral elements gave low ee values (entries 7–10). The best result has been obtained with 9-amino-9-deoxyepicinchonine (**IV**). Based on the exploratory studies, we decided to select catalyst **IV** for further optimization of reaction conditions. We examined our investigations by examining the reactivity and selectivity with organocatalyst **IV** in the presence of different acids, such as benzoic acid, substituted benzoic acids,

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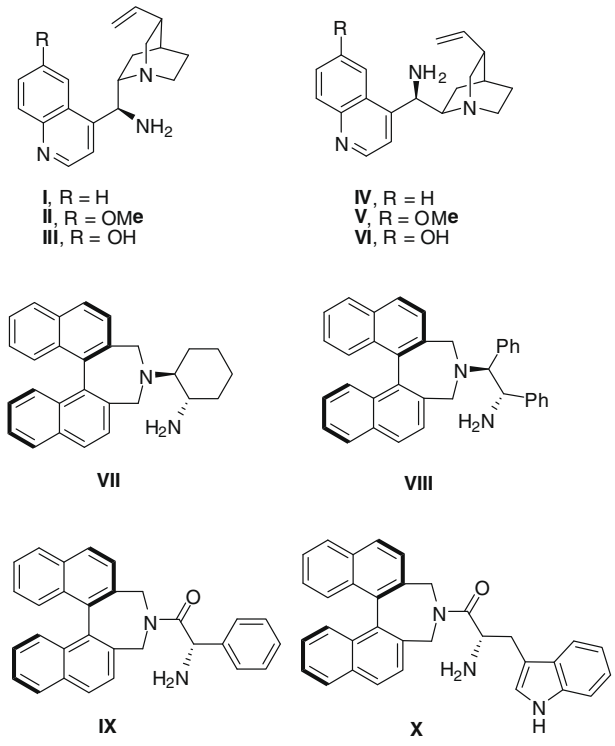
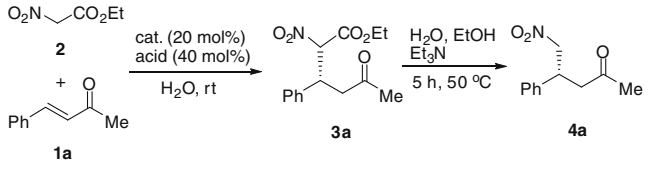


Figure 1. Structure of chiral primary amine catalysts.

picolinic acid, and aliphatic carboxylic acids as additives (entries 4 and 11–17). Among the additives probed, the best results (98% yield and 93% ee) were achieved when the reaction was conducted in benzoic acid (entry 4).

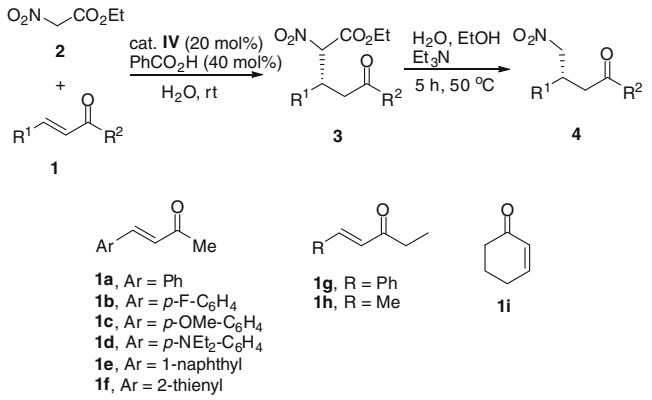
Table 1
Optimization of the reaction conditions



Entry	Cat.	Acid	Time (h)	Yield[a] (%)	ee[b] (%)
1	**I**	$PhCO_2H$	3	95	77
2	**II**	$PhCO_2H$	4	93	90
3	**III**	$PhCO_2H$	2	92	83
4	**IV**	$PhCO_2H$	2	98	93
5	**V**	$PhCO_2H$	3	97	77
6	**VI**	$PhCO_2H$	2	92	92
7	**VII**	$PhCO_2H$	10	90	37
8	**VIII**	$PhCO_2H$	13	71	59
9	**IX**	$PhCO_2H$	3	90	15
10	**X**	$PhCO_2H$	3	98	39
11	**IV**	*m*-CN-$C_6H_4CO_2H$	5	93	93
12	**IV**	2-Cl-4,5-F_2-$C_6H_2CO_2H$	4	94	75
13	**IV**	*p*-NO_2–$C_6H_4CO_2H$	5	93	65
14	**IV**	*o*-SH-$C_6H_4CO_2H$	7	90	87
15	**IV**	Picolinic acid	7	87	89
16	**IV**	$BrCH_2(CH_2)_4CO_2H$	12	89	61
17	**IV**	CH_3COCO_2H	2 d	28	65

[a] Isolated yield of **4a**.
[b] Enantiomeric excess was determined by HPLC analysis using a Chiralpak AS column.

Table 2
Enantioselective conjugate addition of α-nitroacetate to α,β-unsaturated ketones

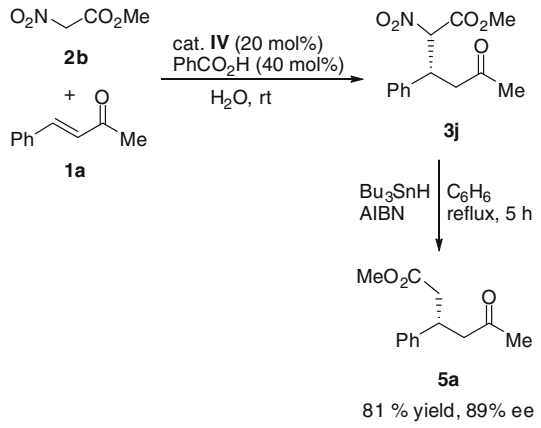


Entry	1	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	2	**4a**, 98	93
2[c]	**1b**	2.5	**4b**, 96	83
3[c]	**1c**	2	**4c**, 95	81
4	**1d**	2	**4d**, 97	65
5[c]	**1e**	2	**4e**, 95	77
6	**1f**	2.5	**4f**, 96	73
7	**1g**	2.2	**4g**, 97	89
8	**1h**	2.3	**4h**, 94	83
9	**1i**	2	**4i**, 93	85

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis using chiral columns (Chiralpak AS for **4a**, AS–H for **4g**, IC for **4h**, AD–H for **4b–d**, **4f**, **4i**, and Chiralcel OD–H for **4e**).
[c] *m*-CN–$C_6H_4CO_2H$ was used as acid additive.

With optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of α,β-unsaturated ketones for the conjugate addition reaction are summarized in Table 2. As demonstrated, organocatalyst **IV**-catalyzed Michael addition of α-nitroacetate (**2**) to α,β-unsaturated ketones **1** proved to be a general approach for the synthesis of versatile chiral δ-keto-α-nitroacetates **3** with diastereomeric ratios of 1:1–1:1.2. The conjugate addition adducts **3** can be readily converted into the corresponding δ-keto nitroalkanes **4** by decarboxylation.[7,14] Notably, good to high enantiomeric excess was obtained (up to 93% ee). The α,β-unsaturated ketones bearing substituted aryl, naphthyl, heteroaromatic, and methyl groups in β-position could effectively participate in the process (entries 1–8). Furthermore, cyclic system was also effective substrate for the process (entry 9). Absolute configuration was determined by comparison of the optical rotation and chiral HPLC data of the corresponding δ-keto nitroalkanes **4**.[6,12] The conjugate addition adduct **3j** can be readily converted into the corresponding δ-keto ester **5a** by denitration without racemization (Scheme 1).[5a,13]

In conclusion, we have developed organocatalytic enantioselective conjugate addition reaction of α-nitroacetate (**2**) to α,β-unsaturated ketones **1** to afford synthetically useful chiral γ-nitro ketones in water. The process is efficiently catalyzed by a simple cinchona alkaloid derivative containing chiral primary amine. The significance of the approach is highlighted by its capability to introduce δ-keto nitroalkanes and δ-keto ester with high enantioselectivity and yields under aqueous reaction conditions. Further details and application of this asymmetric Michael addition of nitroalkane nucleophiles will be presented in due course.



Scheme 1. Denitration of 1,4-addition adduct **3j** into δ-keto ester **5a**.

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14. *General procedure for asymmetric conjugate addition of α-nitroacetate (**2**) to α,β-unsaturated ketones* **1**: α,β-Unsaturated ketones **1** (0.3 mmol), 9-amino-9-deoxyepiquinine (**IV**, 17.6 mg, 0.06 mmol), and benzoic acid (14.6 mg, 0.12 mmol) in 0.9 mL of H_2O were stirred at room temperature for 5 min. Ethyl 2-nitroacetate (**2**, 79.8 mg, 0.6 mmol) was added and the reaction mixture was stirred at room temperature for a specified reaction time period. EtOH (1.2 mL), H_2O (1.2 mL), and triethylamine (0.4 mL) were added into the reaction mixture and the resulting mixture was stirred at 50 °C. After being stirred for 5 h, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 5:1 to give the desired product **4**.