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Organocatalytic asymmetric Michael-type reaction between β,γ-unsaturated α-keto ester and α-nitro ketone†

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A Michael-type reaction of β,γ-unsaturated α-keto ester and α-nitro ketone was established. With a thiourea catalyst derived from cinchona alkaloid, the reactions afford products in 47–94% yields with 68–96% ee.

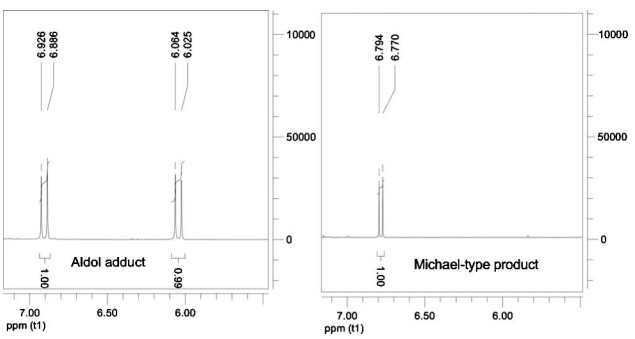
Organocatalysis has been an alternative and/or complementary approach to currently developed organometallic and enzymatic catalysis. Indeed, the emerging of an organocatalytic protocol has displayed great success in modular organic molecule assembly/transformations in the last decade.[1] In particular, organocatalytic asymmetric Michael addition reactions have received widespread attention for accessing a variety of optically active adducts which are synthetically useful building blocks in versatile organic synthesis.[2] Notably, the Michael-type domino reactions efficiently furnish complex chiral natural molecules and diverse intermediates in a one-pot process.[3]

β,γ-Unsaturated α-keto esters represent a resourceful moiety in synthetically useful components. For instance, the asymmetric aldol reactions of β,γ-unsaturated α-keto esters furnish β-hydroxy carbonyl compounds bearing a tertiary alcohol motif.[4] Enantioselective Diels–Alder reactions provide a beneficial route for assembling cyclic products.[5] Asymmetric Michael additions[6] and Michael-type tandem reactions[7] result in γ-functional carbonyl compounds, which can generally be further transformed to obtain the stereospecific molecules.

Recently, we successfully developed an organocatalytic asymmetric aldol reaction of a β,γ-unsaturated α-keto ester with a ketone.[8] We found that the aldol reaction, rather than Michael addition or Diels–Alder reaction, was occurred preferentially between the ketone and β,γ-unsaturated α-keto ester. Moreover, the size of the ketone substrate affected the product yield and stereo-induction greatly. These outcomes underlined the fact that a sterically more congested ketone could efficiently prevent the aldol reaction of β,γ-unsaturated α-ketoesters. Based on the aforementioned findings, we proposed a more active nucleophile with proper steric hindrance that might lead to a Michael-type reaction of β,γ-unsaturated α-keto esters. To examine this idea, a α-nitro ketone was chosen as the nucleophile and the model reactions of this ketone with a β,γ-unsaturated α-keto ester were then investigated.

Very recently, Wang[9a] and Yan[9b] reported the asymmetric organocatalytic Michael/hemiketalization/retro-Henry reaction between a β,γ-unsaturated α-keto ester and a α-nitro ketone, giving more than 90% ee and yield in the presence of the bifunctional Brønsted-base thiourea catalyst.[10] However, the reactions of aliphatic α-nitro ketones afforded relatively poor enantioselectivities (no more than 79% ee). Herein, we present this transformation in good yield with 68–96% ee using a thiourea catalyst derived from cinchona alkaloid. Notably up to 96% ee was obtained from the reaction of an aliphatic α-nitro ketone and a β,γ-unsaturated α-keto ester.

At the outset of our initial investigation, we focused on the reaction between methyl 2-oxo-4-phenylbut-3-enoate (**1a**) and 2-nitro-1-phenylethanone (**2a**). Interestingly, the ^{1}H NMR spectrum of the product showed that a Michael-type reaction occurred (Scheme 1). There were two groups of doublet peaks for two hydrogens of the C=C double bond conjugated with the aromatic ring at the range from 6.00 ppm to 7.00 ppm (J = 16.0 Hz) in the ^{1}H NMR spectrum of the aldol adduct. In contrast, only one group of doublet peaks near 6.8 ppm was found for the Michael-type product and the coupling constant had changed to 9.6 Hz. This information indicates that the conjugate system between the C=C double bond and the aromatic ring is broken.



Scheme 1 ^{1}H NMR spectra of products from 2-oxo-4-phenylbut-3-enoate.

Having confirmed the reaction type, we next carried out the screening of organocatalysts (Table 1). Catalyst **I** and **II** have

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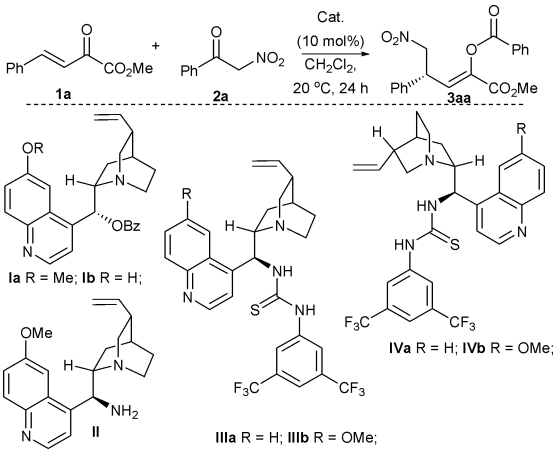
Table 1 Screening of organocatalysts[a]



Entry	Cat.	Yield (%)[b]	ee (%)[c]
1	**Ia**	53	41
2	**Ib**	60	4
3	**II**	30	11
4	**IIIa**	77	74
5	**IIIb**	69	77
6	**IVa**	73	–64
7	**IVb**	77	–72

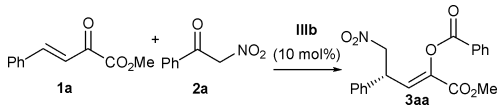
[a] Reaction conditions: **1a** (0.13 mmol), **2a** (0.1 mmol), catalyst (10 mol%) in CH_2Cl_2 (0.3 mL) at 20 °C for 24 h. [b] Isolated yield. [c] ee was determined by chiral HPLC.

been successfully employed in the asymmetric aldol reactions of β,γ-unsaturated α-keto esters with nitromethane[4b] and ketone,[8] respectively. However, unsatisfactory results were obtained from both **I**- and **II**-catalyzed reactions (Table 1, entries 1–3). When thiourea catalysts **III** and **IV** were used, remarkable enhancements of both yield and enantioselectivity were achieved. The best enantioselectivity was obtained with the aid of **IIIb** catalyst (77%, Table 1, entry 5). Particularly noteworthy was that this methodology could constitute an access to both enantiomers of **3aa**, taking advantage of the pseudoenantiomeric effect of thiourea catalyst derived from cinchona alkaloid.

Further optimization of reaction conditions was investigated and representative results are listed in Table 2. Commonly used organic solvents were examined and Et_2O was found to be more suitable for this transformation (Table 2, entries 1–7). Systematic screening studies including the effect of mixed solvents, reaction temperature, the molar ratio of reactants, various added additives and catalyst loading revealed that **IIIb** enabled the formation of **3aa** in 56% yield with 92% ee at 20 °C in 12 h (Table 2, entry 8, see ESI for more details†).

Under the optimized reaction conditions, **IIIb**-catalyzed Michael-type reactions between a series of β,γ-unsaturated α-keto esters **1** and **2a** were surveyed (Table 3). In the presence of **IIIb**, Michael-type products **3aa–ra** were isolated in 47–74% yield with 72–94% ee. The ester functionality of the β,γ-unsaturated α-keto ester had a large influence on the enantioselectivity: increasing the size of ester group resulted in lowering product ee (Table 3, entries 1–3). Various substituents, either electron-withdrawing (Table 3, entries 4–9, 12–15) or electron-donating groups (Table 3, entries 10–11, 16–17), could be introduced into the aromatic ring of β,γ-

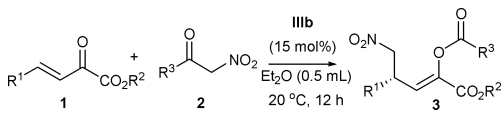
Table 2 Optimization of reaction conditions[a]



Entry	Solvent	T/°C	t/h	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	20	24	69	77
2	EtOAc	20	24	70	79
3	Toluene	20	24	62	85
4	THF	20	24	71	82
5	1,4-dioxane	20	24	79	80
6	*t*-BuOMe	20	24	44	93
7	Et_2O	20	24	48	93
8[d]	Et_2O	20	12	56	94

[a] Unless noted, the following reaction conditions were used: **1a** (0.13 mmol), **2a** (0.1 mmol), **IIIb** (10 mol%) in solvent (0.3 mL) at temperature indicated for the time given in Table 2. [b] Isolated yield. [c] ee was determined by chiral HPLC. [d] **IIIb** (15 mol %) and Et_2O (0.5 mL) were used.

Table 3 Substrate scope[a]



Entry	R^1	R^2	R^3	Product	Yield (%)[b]	ee (%)[c]
1	Ph	Me	Ph	**3aa**	56	94
2	Ph	Et	Ph	**3ba**	50	84
3	Ph	*i*-Pr	Ph	**3ca**	61	72
4	2-ClPh	Et	Ph	**3da**	50	82
5	2-BrPh	Et	Ph	**3ea**	71	86
6	3-ClPh	Et	Ph	**3fa**	62	84
7	3-BrPh	Et	Ph	**3ga**	58	91
8	3-NO_2Ph	Me	Ph	**3ha**	56	86
9	3-NO_2Ph	Et	Ph	**3ia**	49	90
10	3-MePh	Et	Ph	**3ja**	50	82
11	3-MeOPh	Et	Ph	**3ka**	47	86
12	4-FPh	Et	Ph	**3la**	56	88
13	4-ClPh	Et	Ph	**3ma**	47	88
14	4-BrPh	Et	Ph	**3na**	70	92
15	4-NO_2Ph	Et	Ph	**3oa**	58	84
16	4-MePh	Et	Ph	**3pa**	56	82
17	4-MeOPh	Et	Ph	**3qa**	63	73
18	5-Me-2-thienyl	Et	Ph	**3ra**	94	68
19	Ph	Me	*n*-Pr	**3ab**	51	96
20	Ph	Et	*n*-Pr	**3bb**	50	83
21	3-ClPh	Et	*n*-Pr	**3fb**	45	89
22	3-BrPh	Et	*n*-Pr	**3gb**	43	90
23	3-NO_2Ph	Et	*n*-Pr	**3ib**	61	82
24	3-MeOPh	Et	*n*-Pr	**3kb**	63	73
25	4-FPh	Et	*n*-Pr	**3lb**	69	84
26	4-ClPh	Et	*n*-Pr	**3mb**	55	88
27	4-BrPh	Et	*n*-Pr	**3nb**	50	94
28	4-MePh	Et	*n*-Pr	**3pb**	54	78

[a] Unless noted, the following reaction conditions were used: **1** (0.13 mmol), **2** (0.1 mmol), **IIIb** (15 mol%) in Et_2O (0.5 mL) at 20 °C for 12 h. [b] Isolated yield. [c] ee was determined by chiral HPLC.

unsaturated α-keto ester. No significant electronic effect on the aromatic moiety was observed. A heteroaromatic β,γ-unsaturated α-keto ester afforded **3ra** in up to 94% yield with 68% ee (Table 3, entry 18).

The reaction of challenging aliphatic α-nitro ketone with **1** was also probed. 1-Nitropentan-2-one (**2b**) reacted with **1a** to afford

3ab in moderate yield with up to 96% ee (Table 3, entry 19). Product **3bb** was formed in similar yield with 83% ee from ethyl 2-oxo-4-phenylbut-3-enoate (Table 3, entry 20). The substituted aromatic β,γ-unsaturated α-keto ester could also be employed to afford **3ab–3pb** in medium yields with good to excellent enantioselectivities (Table 3, entries 21–28). It should be noted that more than 90% ee were obtained not only from the aromatic α-nitro ketone but also from the aliphatic α-nitro ketone.

The absolute configuration of the products was *R*, which was determined by comparison of optical rotations with those in the literature.[9]

In conclusion, we have developed a new Michael-type reaction of β,γ-unsaturated α-keto ester with both aromatic and aliphatic α-nitro ketone to afford products in 47–94% yields with 68–96% ee. Compared with Wang's and Yan's reports,[9] higher ee values were obtained from aliphatic α-nitro ketone. It should be noted that this methodology offered an enantioselective pathway for the synthesis of chiral 5-nitro-pent-2-enoates, a precursor to chiral α-ketolactam. Development of new type organocatalysts and further applications of these reactions are currently under investigation.

Acknowledgements

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