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Organocatalytic Michael Addition of Nitro Esters to α,β-Unsaturated Aldehydes: Towards the Enantioselective Synthesis of *trans*-3-Substituted Proline Derivatives

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Abstract: A facile five-step strategy has been developed for the enantioselective synthesis of *trans*-3-substituted proline derivatives with high diastereoselectivity ($dr > 20:1$) and enantioselectivity (up to 97% *ee*). The key step is the asymmetric organocatalytic Michael addition of nitro esters to α,β-unsaturated aldehydes, which affords the chiral Michael adducts in high yields (up to 96%) and excellent enantioselectivity (up to 99% *ee*) by using diarylprolinol silyl ether as the organocatalyst.

Keywords: asymmetric organocatalysis; Michael addition; *trans*-3-substituted proline derivatives

Due to their structural uniqueness, *trans*-3-substituted proline derivatives[1] are widely used as building blocks for the synthesis of conformationally-constrained peptides[2] with high biological activities. Moreover, *trans*-3-substituted proline scaffolds are important structural motifs existing in many natural products and pharmaceuticals[3] (Figure 1). Over the past decades, progress has been made in synthesizing chiral 3-substituted proline derivatives[4] by using an organometallic reagent or a chiral precursor/auxiliary. For example, Schmalz and co-workers[4a] recently developed a Cu-catalyzed 1,4-addition strategy to synthesize the racemic *trans*-3-substituted proline derivatives in four steps. The chiral *trans*-3-vinylproline could, accordingly, be obtained with 74% *ee* in six steps *via* the Evans auxiliary approach. Another strategy to synthesize the chiral 3-substituted prolines is the optical resolution[4k] of the reduction/decarboxylation products after the Michael addition of aminomalonates to α,β-unsaturated aldehydes.

On the other hand, asymmetric organocatalysis[5] has emerged as an attractive tool for the synthesis of optically active compounds. In this regard, Hayashi[6] as well as Rios and Córdova[7] have applied organocatalytic Michael reactions for the enantioselective synthesis of 3-aryl-substituted prolines. Hayashi and co-workers[6] synthesized substituted tetrahydropyrans *via* a Michael/isomerization reaction of nitroethanol and α,β-unsaturated aldehydes. The phenyl-substituted tetrahydropyran intermediate could be further transformed to the *trans*-3-phenylproline derivative.[6] Rios, Córdova and co-workers[7] realized the organocatalytic tandem reaction of 2-acylaminomalonates and α,β-unsaturated aldehydes to synthesize a series of 5-hydroxypyrrolidines. The reductive deoxygena-

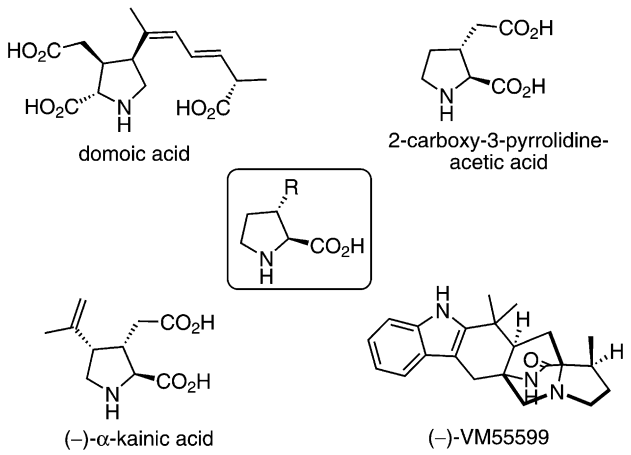
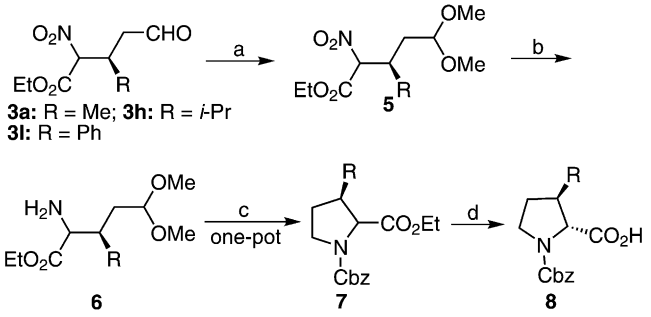


Figure 1. Representative natural products and pharmaceuticals containing *trans*-3-substituted proline moieties.

tion of phenyl-substituted 5-hydroxypyrrolidine and the sequential processes of decarboxylation/epimerization/ester hydrolysis afforded the *trans*-3-phenylproline derivative.[7]

The organocatalytic synthesis of *trans*-3-alkyl-substituted proline derivatives was first attempted by Belokon and co-workers[8] in 1993. However, the reaction products were obtained as mixtures with poor diastereoselectivity (1:1.1) and low enantioselectivity (42% *ee*). In 2007, Hamada and co-workers[9] succeeded in synthesizing 3-hydroxy-3-substituted proline derivatives with low to moderate enantioselectivity (30–88% *ee*) by intramolecular asymmetric aldol reaction. Due to the use of ketoaldehyde substrates, however, the synthesis of 3-alkyl-substituted prolines (without 3-hydroxy substitution) could not be realized *via* this strategy.

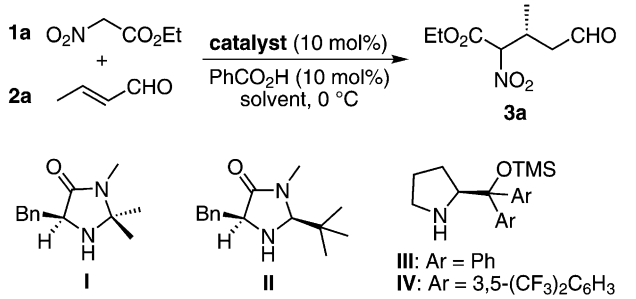
Accordingly, there is still in urgent need to develop a facile and general method for the enantioselective synthesis of *trans*-3-substituted, especially *trana*-3-alkyl-substituted prolines. Herein, we report an organocatalytic asymmetric Michael reaction of nitro esters to α,β-unsaturated aldehydes (Table 2 and Table 3) with high yields (up to 96%) and excellent enantioselectivities (up to 99% *ee*) *via* iminium catalysis.[10] It is worthy of mention that although the enantioselective Michael addition of nitro esters to α,β-unsaturated ketones has recently been developed,[11] that of nitro esters to α,β-unsaturated aldehydes has not been investigated. The only relevant work is that of Jørgensen and co-workers[12] who reported one example of the double addition of a nitro ester to an α,β-unsaturated aldehyde *via* organocatalysis. Furthermore, we demonstrate a facile approach (Scheme 1) to provide optically pure *trans*-3-substituted proline derivatives from the Michael adducts in four steps. *Via* this approach, *trans*-3-substituted proline derivatives could be successfully obtained with excellent diastereoselectivity (up to $dr > 30{:}1$) and enantioselectivity (up to 97% *ee*).



Scheme 1. Synthesis of chiral *trans*-3-substituted proline derivatives. *Experimental conditions:* (a) MeOH, PTSA·H_2O, $CH(OMe)_3$, 81% yield for **5a**; 84% yield for **5h**; 69% yield for **5l**. (b) Raney Ni, H_2, 70 °C; 74% yield for **6a**; $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, 47% yield for **6h**; 50% yield for **6lL**. (c) One-pot operation: HCl, MeOH, 70 °C; Pd/C, H_2, MeOH; Et_3N, CbzCl, THF, 21% yield for **7a**; 28% yield for **7h**; 24% yield and 80%/86% *ee* for **7l**. (d) LiOH, H_2O/MeOH/THF (1:1:3), 0–10 °C, 65% yield and 88% *ee* for **8a**; 55% yield and 97% *ee* for **8h**; 69% yield and 66% *ee* for **8l**.

Aiming at the enantioselective synthesis of *trans*-3-substituted proline derivatives, we first studied the organocatalytic asymmetric Michael addition reaction of nitro esters to α, β-unsaturated aldehydes. We chose initially the conjugate addition of ethyl nitroacetate **1a** to crotonaldehyde **2a** as the model reaction to examine the yield and the stereoselectivity of the products **3a**. As shown in Table 1, the screening (Table 1, entries 1–4) of chiral secondary amine catalysts[13] **I–IV** in toluene revealed that, in the presence of benzoic acid (10 mol%), catalysts **II** and **IV** are both effective in the enantioselectivity control at room temperature. With **II** (entry 2) or **IV** (entry 4)

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1[e]	**I**	toluene	30	1:1.1	27/32
2[e]	**II**	toluene	66	1:1.2	77/78
3[e]	**III**	toluene	78	1:1.0	59/62
4[e]	**IV**	toluene	87	1:1.0	79/76
5	**II**	toluene	61	1:1.3	81/83
6	**IV**	toluene	95	1:1.0	90/89
7	**IV**	DCM	94	1:1.3	89/89
8	**IV**	*p*-xylene	91	1:1.2	88/89
9	**IV**	*n*-hexane	76	1:1.0	88/88
10	**IV**	Et_2O	78	1:1.0	86/86
11	**IV**	THF	84	1:1.3	81/84
12[f]	**IV**	toluene	85	1:1.0	86/87
13[g]	**IV**	toluene	84	1:1.0	89/89

[a] Unless otherwise noted, the experimental conditions are: a mixture of **1a** (0.158 mmol), crotonaldehyde **2a** (0.158 mmol), catalyst (10 mol%), and $PhCO_2H$ (10 mol%) in 0.32 mL of solvent was stirred at 0 °C for 4 h.

[b] Isolated yield after purification by flash chromatography.

[c] Determined by ^1H NMR analysis of the crude mixture.

[d] Determined by chiral HPLC analysis after the aldehydes were converted into the corresponding α,β-unsaturated esters.

[e] Reaction was performed at room temperature.

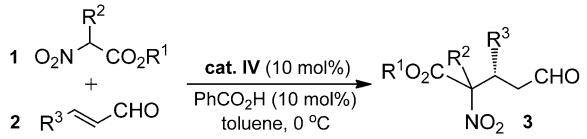
[f] Reaction was performed at a 0.25 M concentration.

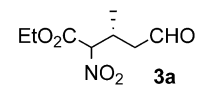
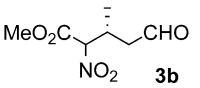
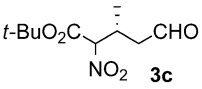
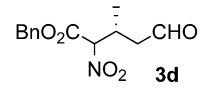
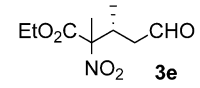
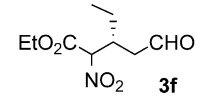
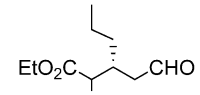
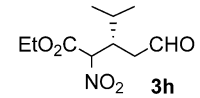
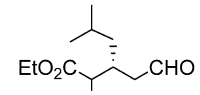
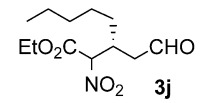
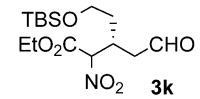
[g] 5 mol% of **IV** was used.

as the catalyst, the obtained enantioselectivities of the products **3a** are 77%/78% and 79%/76% *ee*, respectively; while the reaction yields are 66% and 87%, respectively. When the reaction temperature was lowered to 0 °C, catalyst **IV** (entry 6) proved to be superior to catalyst **II** (entry 5), which was evidenced by the increased yield of 95% and the increased enantioselectivity of 90%/89% *ee*. We also tested the catalytic activity of catalyst **IV** in other solvents, such as DCM, *p*-xylene, *n*-hexane, Et_2O, and THF, but no improvement in the yield or enantioselectivity could be observed (entries 7–11). Addition of other acidic additives, such as (+)-CSA, *p*-nitrobenzoic acid, 3,5-dinitrobenzoic acid, or PTSA, could not further improve the results either (see the Supporting Information for details). When the substrates **1a** and **2a** were diluted in toluene at a 0.25 M concentration (entry 12) or 5 mol% of catalyst **IV** was used (entry 13), the products **3a** were obtained in slightly lowered yields and enantioselectivities. It should be noted that, in all cases, the low diastereoselectivity (*dr* from 1:1.0 to 1:1.3) was attributable to the high CH acidity[8] of the α-proton in **3a**. Fortunately, the diastereoselectivity of the synthesized 3-substituted proline derivatives could be significantly improved to *dr* > 20:1 by efficient kinetic discrimination. Accordingly, the optimal conditions for the organocatalytic asymmetric Michael addition of nitro esters to α, β-unsaturated aldehydes were selected as: 10 mol% of catalyst **IV**, 10 mol% of benzoic acid, toluene as the solvent, and reaction at 0 °C.

With the optimal reaction conditions in hand, we next investigated the substrate scope for the asymmetric Michael reaction. The addition reaction of crotonaldehyde **2a** with different nitro esters was firstly examined. As summarized in Table 2, excellent yields (93–96%) and high enantioselectivities (79%/88% to 90%/89% *ee*) were successfully obtained by using an array of nitro esters with different ester moieties (Table 2, entries 1–4). Remarkably, the trisubstituted substrate, ethyl 2-nitropropanoate, also gave the desired product **3e** in good *ee* value (82%/88% *ee*), but the diastereoslectivity did not show an appreciable improvement (*dr* of 1:1.3) and the yield dropped to 44% (entry 5). To further expand the scope of this reaction, a number of aliphatic α,β-unsaturated aldehydes was employed as the Michael acceptor with structural diversity. To our delight, aliphatic α,β-unsaturated aldehydes were identified as suitable substrates (Table 2, entries 6–10), affording the desired adducts in high yields (78–94%) and excellent enantioselectivities (94%/92% to 97%/98% *ee*). Notably, when the oxygen heteroatom was introduced to the substrate, the reaction also gave the desired product in good yield (89%) and high enantioselectivity (91%/92% *ee*, entry 11).

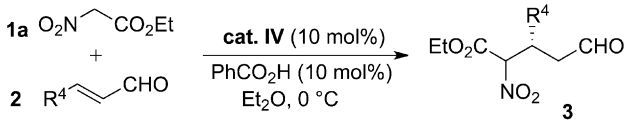
Table 2. Substrate scope of the asymmetric Michael addition with aliphatic α,β-unsaturated aldehydes as the Michael acceptor.[a]

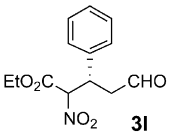
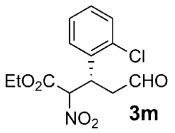
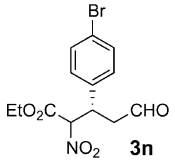
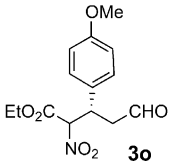


Entry	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	 **3a**	4	95	1:1.0	90/89
2	 **3b**	4	96	1:1.1	86/87
3	 **3c**	7	93	1:1.2	86/86
4	 **3d**	6	94	1:1.0	79/88
5	 **3e**	22	44	1:1.3	82/88
6	 **3f**	5	90	1:1.0	95/96
7	 **3g**	6	94	1:1.0	94/92
8	 **3h**	44	78	1:1.7	97/98
9	 **3i**	15	93	1:1.0	95/99
10	 **3j**	24	94	1:1.0	94/94
11	 **3k**	6	89	1:1.1	91/92

[a] *Experimental conditions:* a mixture of **1** (0.158 mmol), **2** (0.158 mmol), catalyst **IV** (10 mol%), and $PhCO_2H$ (10 mol%) in 0.32 mL of toluene was stirred at 0 °C.
[b] Isolated yield after purification by flash chromatography.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Determined by chiral HPLC analysis after the aldehydes were converted into the corresponding α,β-unsaturated esters.

Table 3. Substrate scope of the asymmetric Michael addition with α,β-unsaturated aromatic aldehydes as the Michael acceptor.[a]



Entry	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	 **3l**	17[e] 17	60[e] 80	1:1.0[e] 1:1.2	76/78[e] 81/88
2	 **3m**	48	72	1:1.2	81/83
3	 **3n**	52	64	1:1.0	75/77
4	 **3o**	24	52	1:1.0	43/45

[a] *Experimental conditions:* a mixture of **1a** (0.158 mmol), **2** (0.158 mmol), catalyst **IV** (10 mol%), and $PhCO_2H$ (10 mol%) in 0.32 mL of Et_2O was stirred at 0 °C.
[b] Isolated yield after purification by flash chromatography.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Determined by chiral HPLC analysis after the aldehydes were converted into the corresponding α,β-unsaturated esters.
[e] Toluene as the solvent.

We also tested the possibility of applying α,β-unsaturated aromatic aldehydes as the Michael acceptor in this reaction (Table 3). Considering the different reactivity between aromatic and aliphatic α,β-unsaturated aldehydes, we first examined the solvent effect with cinnamaldehyde as the Michael acceptor. Compared with toluene as the solvent (60% yield, 76%/78% *ee*), Et_2O proved more suitable for this reaction, giving the desired product with higher yield (80%) and higher enantioselectivity (81%/88% *ee*) (Table 3, entry 1, see the Supporting Information for details). With Et_2O as the sovlent, the halogen-substituted (2-Cl or 4-Br) aromatic aldehydes gave the desired products in moderate yields and enantioselectivities as well (Table 3, entries 2 and 3). However, when an electron-donating group (4-OMe) was employed on the aromatic moiety, the reaction product **3o** was obtained with low yield (52%) and low enantioselectivity (43%/45% *ee*) (Table 3, entry 4).

Having developed the asymmetric organocatalytic methodology to obtain the key intermediates **3**, we next embarked on the enantioselective synthesis of *trans*-3-substituted proline derivatives. Initially, we conducted the direct intramolecular reductive alkylation of **3a** to construct the *trans*-3-methyl-substituted pyrrolidine **7a**. Unfortunately, all attempts to use the literature protocols, such as metal/acid[14] or H_2/Raney Ni,[15] were in vain. The direct reductive alkylation conditions[15] led to complicated side reactions, which suggests the necessity to protect the aldehyde group of **3a**. Accordingly, the synthetic strategy *via* the protection of the aldehyde group was chosen (Scheme 1).

Firstly, we were able to obtain directly the key intermediate acetal **5a**[16] by using the one-pot operation without separating the Michael adduct **3a** (see the Supporting Information for details). This method was also scalable to at least 4.5 mmol without any loss of the *ee* value. Subsequently, the reduction of nitro group of **5a** with Raney Ni afforded the product **6a** in the yield of 74%. Remarkably, we succeeded next in constructing the *N*-Cbz-protected pyrrolidine **7a** through the one-pot operation, including intramolecular cyclization,[17] hydrogenation,[18] and *N*-Cbz protection.[19] Finally, in order to further improve the low diastereoselectivity,[4a] the product **7a** was treated with 0.98 equiv. of LiOH in H_2O/MeOH/THF. The efficient kinetic discrimination and hydrolysis resulted in the *trans*-diastereomer **8a** with high enantioselectivity (88% *ee*) and excellent diastereoselectivity ($dr >$ 30:1). The product **8a** was easily converted into the corresponding 3-methylproline, the absolute configuration of which was determined by comparing the optical rotation value with that reported in the literature[4l] (see the Supporting Information for details).

To further demonstrate the utility of this methodology, another two typical *trans*-3-substituted proline derivatives, *trans*-3-isopropyl- and *trans*-3-phenylproline derivatives were synthesized from the corresponding Michael products *via* the same synthetic strategy, respectively. As shown in Scheme 1, *trans*-3-isopropyl proline derivative **8h** could be obtained with excellent enantioselectivity (97% *ee*) and diastereoselectivity ($dr > 20$:1). *trans*-3-Phenylproline derivative **8l** could also be obtained with high diastereoselectivity ($dr > 20$:1) by isomerization of mixture of **7l** with 0.98 equiv. of LiOH. However, a decrease in enantioselectivity (66% *ee*) from that of **7l** (80/86% *ee*) was observed, probably due to the partial racemization of the benzyl carbon at the 3-position in the presence of basic LiOH.

In summary, we have developed a simple and general procedure for the enantioselective synthesis of *trans*-3-substituted proline derivatives, the key step of which is the organocatalytic asymmetric Michael addi-

tion reaction of nitro esters and α,β-unsaturated aldehydes. The Michael addition reaction is applicable to a variety of aliphatic and aromatic α,β-unsaturated aldehydes, affording the desired Michael adducts in high yields (up to 96%) and excellent enantioselectivities (up to 99% *ee*). The Michael adducts with low diastereoselectivity (*dr* from 1:1.0 to 1:1.3) could be transformed to the corresponding *trans*-3-substituted prolines with excellent diastereoselectivity ($dr > 20:1$) *via* the efficient kinetic discrimination. The enantioselective route we developed for the facile synthesis of *trans*-3-substituted, especially *trans*-3-alkyl-substituted, proline derivatives may, therefore, find further applications towards the construction of conformationally constrained peptides and structurally complicated natural products.

Experimental Section

Representative Procedure for Asymmetric Michael Addition of Nitro Esters to α,β-Unsaturated Aldehydes

To a solution of crotonaldehyde **2a** (11.1 mg, 0.158 mmol), catalyst **IV** (9.4 mg, 0.0158 mmol) and benzoic acid (1.9 mg, 0.0158 mmol) in toluene (0.32 mL), was added ethyl nitroacetate **1a** (21.0 mg, 0.158 mmol) at 0 °C. After stirring for 4 h at this temperature, the reaction mixture was directly subjected to flash column chromatography (petroleum ether/EtOAc = 4/1 as eluent) to afford the desired product **3a** as a light yellow liquid; yield: 30.5 mg (95%).

The product **3a** was converted to the corresponding α,β-unsaturated ester, which was subjected to chiral HPLC analysis to determine the enantiomeric excess.

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