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Synthesis of pyrrolidine-3-carboxylic acid derivatives via asymmetric Michael addition reactions of carboxylate-substituted enones

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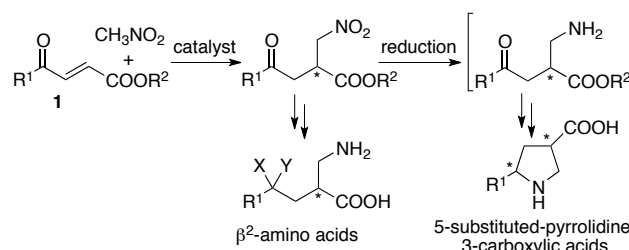
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To concisely synthesize highly enantiomerically enriched 5-alkylsubstituted pyrrolidine-3-carboxylic acids, organocatalytic enantioselective Michael addition reactions of 4-alkyl-substituted 4-oxo-2-enoates with nitroalkanes have been developed. Using the developed reaction method, 5-methylpyrrolidine-3-carboxylic acid with 97% ee was obtained in two steps.

Pyrrolidine-3-carboxylic acid (β -proline) derivatives and β^2 -amino acids are important molecules as bioactives, catalysts for chemical transformations, and their building blocks.^{1,2,3} For example, (*R*)-pyrrolidine-3-carboxylic acid derivatives have been reported as enzyme inhibitors and receptor agonists.^{1a,b} (3*R*,5*R*)-5-Methylpyrrolidine-3-carboxylic acid has been used as a catalyst for diastereo- and enantioselective organocatalytic reactions.^{2a,b} Homochiral pyrrolidine-3-carboxylic acid derivatives have often been synthesized from homochiral starting materials.^{2a,b,4} Enantioselective methods that provide β -proline and 2-, 3- and/or 4-substituted pyrrolidine-3-carboxylic acid derivatives with or without substitutions at the 5-position have also been reported;^{2c,5} however, the methods used for the synthesis of these compounds cannot be used for the synthesis of relatively simple 5-substituted pyrrolidine-3-carboxylic acid derivatives. The 3-carboxylic acid group on the pyrrolidine ring has also been introduced by late-stage transformations from olefin, furan, and isooxazole precursor groups at the 3-position on the pyrrolidine ring;⁶ but these methods are not atom-economical. Similarly, β^2 -amino acid derivatives are difficult to obtain.³ Here we report the development of concise, atom-economical methods for the synthesis of highly enantiomerically enriched 5-alkyl-substituted pyrrolidine-3-carboxylic acid derivatives and β^2 -amino acid derivatives via Michael addition of nitroalkanes to 4-alkyl-substituted 4-oxo-2-enoates (Scheme 1). To synthesize simple 5-substituted pyrrolidine-3-carboxylic acid derivatives, such as 5-methyl-substituted derivatives, we developed enantioselective Michael

addition reactions of 4-oxo-2-enoates bearing simple 4-alkyl substitutions.

Scheme 1. Synthesis of 5-substituted pyrrolidine-3-carboxylic acid derivatives and β^2 -amino acid derivatives.



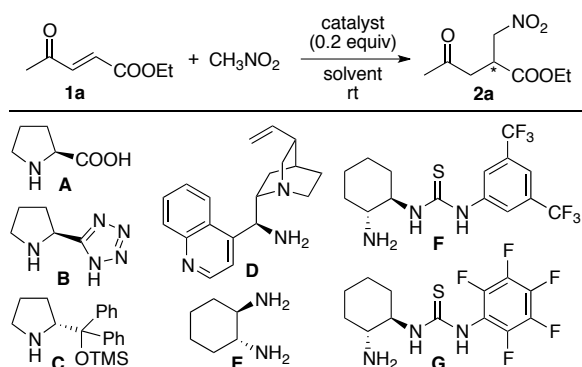
In previously reported enantioselective Michael addition reactions of nitroalkanes to acyclic enones, the enones were mostly non-enolizable with one or two aryl-substitutions.⁷ Although all alkyl-substituted enones have been used as reactants,^{7f,g,k} the use of 4-oxopent-2-enoates and their derivatives as Michael acceptors is rare.^{7d,m} In addition, for the reported reactions of 4-alkyl-substituted 4-oxo-2-enoates with nitroalkanes, only substituted nitroalkanes (such as 2-nitropropane) have been used;^{7d,m} this is probably to avoid potential polymerization and formation of byproducts via Henry reactions⁸ of the products. In our design (Scheme 1), carboxylic acid ester-substituted enones **1**, such as 4-oxopent-2-enoates (R^1 = methyl) and 4-oxohex-2-enoates (R^1 = ethyl), were used. We reasoned that it would be possible to identify catalyst systems and conditions that would accelerate enantioselective Michael addition reactions of simple nitromethane to the enones. These reactions would be used for concise formation of 5-alkyl-substituted pyrrolidine-3-carboxylic acids and functionalized β^2 -amino acids. With the use of substituted nitromethanes, $\beta^{2,3}$ -amino acids and pyrrolidine-3-carboxylic acids bearing substitutions at 2- and 5-positions would also be accessed.

First, catalysts and conditions for the Michael reaction step were screened in the reaction of enone **1a** with nitromethane to afford **2a**. We tested amine derivatives as the catalyst to accelerate the reaction through an iminium activation

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mechanism. Selected results are shown in Table 1. Of catalysts and conditions tested, the best results were obtained with the use of catalyst **F** or **G** in CH_2Cl_2 either with or without acetic acid additive.

Table 1. Catalyst and condition screening in the Michael reaction^a



entry	catalyst	additive	solvent	yield (%)	ee (%)
1	A	-	toluene	0	-
2	B	-	toluene	0	-
3	C	-	toluene	7	nd
4	D	-	toluene	14	21
5	E	-	toluene	10	-20
6	F	-	toluene	51	82
7	F	-	CH_2Cl_2	70	85
8 ^b	F	-	CH_2Cl_2	63	91
9 ^b	F	CH_3COOH^c	CH_2Cl_2	50	89
10 ^{b,d}	F	CH_3COOH^c	CH_2Cl_2	76	94
11 ^{b,e}	F	CH_3COOH^c	CH_2Cl_2	40	96
12 ^b	G	-	CH_2Cl_2	61	93
13 ^{b,d}	G	CH_3COOH^c	CH_2Cl_2	70	94

^a Conditions: Enone (0.2 mmol), nitromethane (1.0 mmol), and catalyst (0.04 mmol) in solvent (0.5 mL) at rt (24 °C) for 48 h. ^b Solvent (0.2 mL). ^c CH_3COOH (0.04 mmol). ^d 10 °C for 5 days. ^e 0 °C for 5 days.

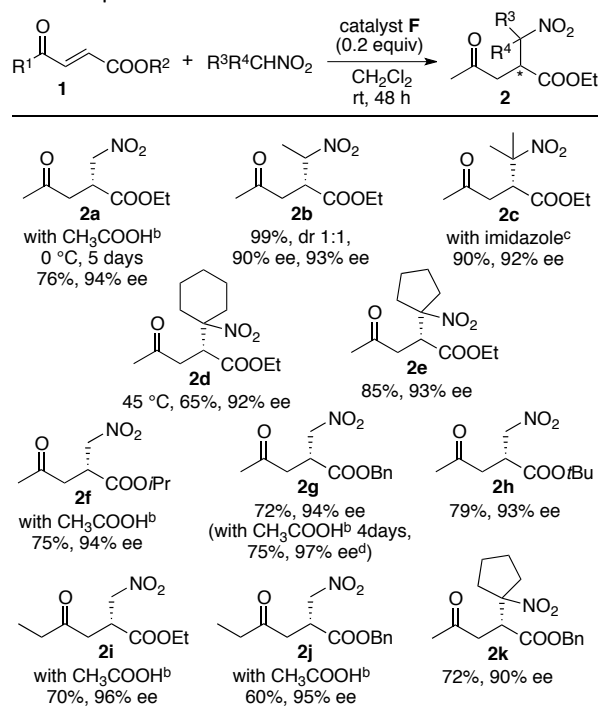
Next, the scope of the reaction catalyzed by catalyst **F** was analyzed (Table 2 and Scheme 2). Various products **2a-2m** were obtained. Although we designed the reactions to work with simple nitromethane, reactions with various nitroalkanes also afforded the Michael products. In addition to the 4-oxopent-2-enoates, 4-oxohex-2-enoates were effective substrates resulting in formation of **2i** and **2j**. The ester groups of the substrates worked in the reaction system included ethyl, isopropyl, benzyl, and *tert*-butyl esters (Table 2).⁹

When the (*Z*)-isomer of enone **1a** was used, product **2** was obtained with the same degrees of reactivity and enantioselectivity as in the reaction of the corresponding (*E*)-isomer substrate **1a** (Scheme 2). During the reaction, the (*Z*)-enone was isomerized to (*E*)-enone **1a**. The resulting (*E*)-enone may have reacted to give the product. Products **2l** and **2m** were also obtained, but as racemic forms (<5% ee).

Michael products **2** were transformed to pyrrolidine derivatives (Schemes 3 and 4). When **2g** was treated with Pd/C under hydrogen, (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid (**3**)^{2a} was directly obtained in 90% yield with 97% ee (Scheme 3). The absolute configuration of **2g** obtained by the Michael

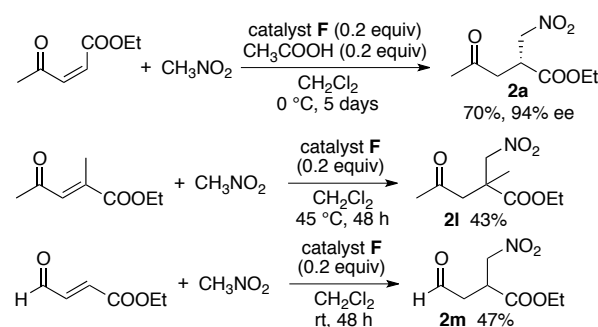
reaction was deduced from **3**. A plausible transition state of the Michael addition reaction to afford **2g** is also shown in Scheme 3. This route required only two steps to provide **3** from commonly accessible starting materials. Note that **3** was previously synthesized from 4-hydroxy-proline via more than 10 steps.^{2a} From **2h** and **2a**, pyrrolidine-3-carboxylic acid derivatives were also obtained (Scheme 4).

Table 2. Scope of the Michael reaction to afford **2**.



^a Conditions: Enone (0.2 mmol), nitroalkane (1.0 mmol), and catalyst **F** (0.04 mmol) in CH_2Cl_2 (0.2 mL) at 24 °C for 48 h. ^b CH_3COOH (0.04 mmol). ^c Imidazole (0.04 mmol). ^d Enone 6.4 mmol-scale reaction; ee was determined after transformation to **3**.

Scheme 2. Expanded scope of the Michael reaction to afford **2**.

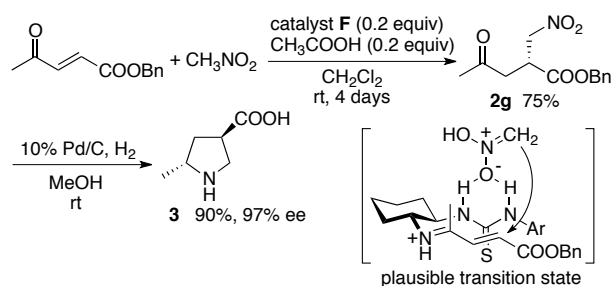


Acyclic β^2 -amino acid derivatives were also obtained from the Michael products (Scheme 5). Acetal protection of the ketone carbonyl group of **2a** afforded **6**. Using the reported reduction^{7h} of the nitro group of **6**, β^2 -amino acid derivative **7** can be obtained. Tosylhydrazone derivative **8** was also synthesized. This compound is a precursor of amino-functionalized β^2 -amino acid derivatives.

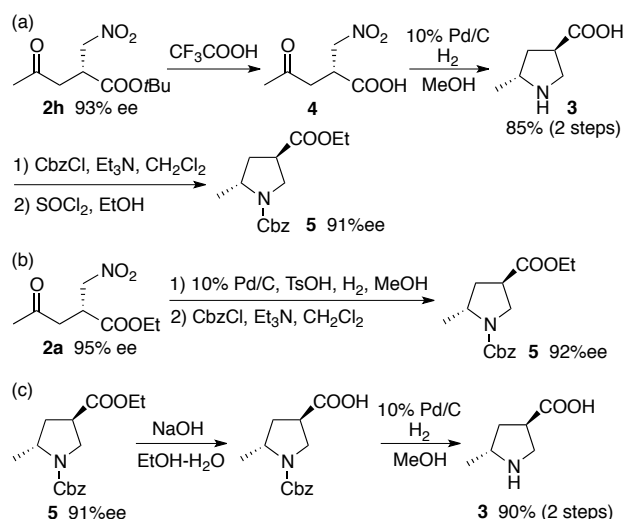
Further, the Michael products were transformed to lactam derivatives **9** (Scheme 6a). From the Michael product of the

reaction of a cyclic nitroalkane, spiropyrrolidine-3-carboxylic acid derivative **10** was obtained (Scheme 6b).

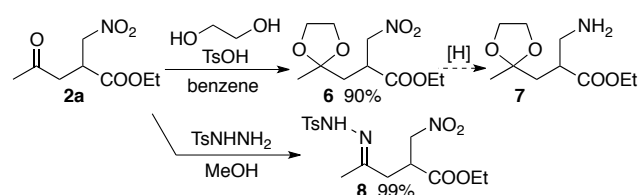
Scheme 3. Synthesis of (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid via the Michael reaction to afford **2g**.



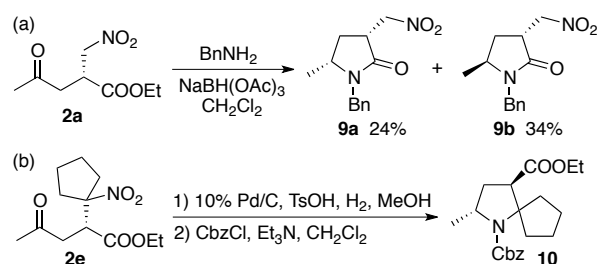
Scheme 4. Transformation of Michael products **2** to pyrrolidine-3-carboxylic acid derivatives.



Scheme 5. Transformation of **2** to acyclic β^2 -amino acid derivatives.



Scheme 6. Transformation of **2** to lactam and spiropyrrolidine derivatives.



In conclusion, we have developed organocatalytic enantioselective Michael reactions of 4-alkyl-substituted 4-oxo-2-enoates with nitroalkanes that are useful for the synthesis of pyrrolidine-3-carboxylic acid derivatives and β^2 -amino acid derivatives. Using the Michael reaction method, highly enantiomerically enriched 5-methylpyrrolidine-3-carboxylic acid was synthesized in two steps from easily accessible starting materials.

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There are no conflicts of interest to declare.

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- 9 The configuration of **2g** generated using catalyst **F** was determined to be (*R*) based on that *trans*-5-methylpyrrolidine-3-carboxylic acid (**3**) synthesized from **2g** had a (*3R,5R*) configuration (comparison of the $[\alpha]_D$ value with that of previously reported (*3R,5R*)-**3**^{2a}). Compounds **2a** and **2h** also had a (*R*) configuration; this was confirmed after transformation to **3** and **5**. For compounds **2b**, **2c**, **2d**, **2e**, **2i**, **2j**, and **2k** shown in Table 2, the stereochemistry was tentatively assigned by analogy.