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Direct asymmetric Michael reaction of α,β-unsaturated aldehydes and ketones catalyzed by two secondary amine catalysts

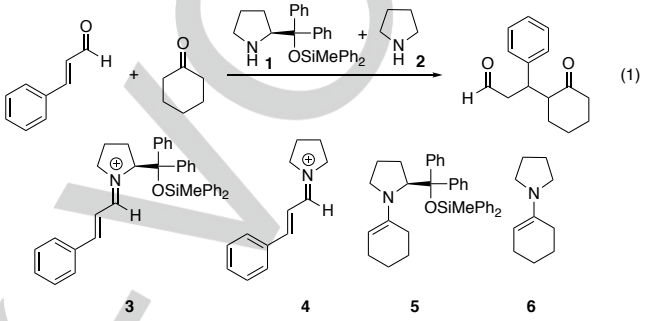
Yujiro Hayashi,*[a] Nariyoshi Umekubo[a]

Dedicated to Professor E. J. Corey on the occasion of his 90th birthday

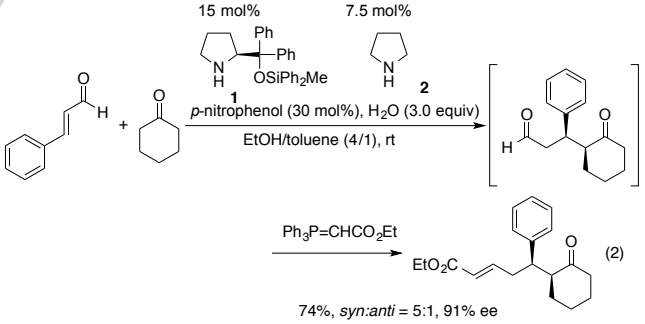
Abstract: *Direct asymmetric Michael reaction of α,β-unsaturated aldehydes and ketones proceeds in the presence of two pyrrolidine-type catalysts, such as diphenylprolinol silyl ether and hydroxyproline, to afford synthetically useful δ-keto aldehydes with excellent diastereo- and enantioselectivities. Although there are several iminium ions and enamines in the reaction mixture, an iminium ion generated from the former catalyst reacts preferentially with an enamine generated from the latter catalyst.*

The conjugate addition of a carbon nucleophile to electron-deficient alkenes is one of the most important carbon–carbon bond-forming reactions in synthetic organic chemistry.[1] Although the asymmetric Michael reaction of an α,β-unsaturated aldehyde and ketone is a useful reaction for the synthesis of chiral δ-keto aldehydes, its asymmetric direct reaction has been difficult. There is an issue in the control of 1,4- and 1,2-addition reactions; as α,β-unsaturated aldehydes are reactive electrophiles, possessing two electrophilic sites, 1,4-addition is a major reaction path in organocatalyst-mediated reactions involving an iminium ion as an intermediate.[2] As diphenylprolinol silyl ether[3] is known as a catalyst for the generation of an effective chiral iminium ion from α,β-unsaturated aldehydes,[4] there are several asymmetric Michael reactions involving this iminium ion as an intermediate.[5] As for the activated ketone possessing an acidic proton as a Michael donor, there are few reports as far as we are aware, using acetophenone[6] and a vinylogous phenyl ketone[7] as a Michael donor involving enol as an intermediate. Because of the difficulty in using a nonactivated ketone as a Michael donor, its silyl enol ether was employed as an indirect method.[8] In spite of the successful examples of Michael reaction using diphenylprolinol silyl ether, there is no report using nonactivated ketones such as cyclohexanone as a Michael donor via iminium ion catalysis. In this communication, we will describe the first Michael reaction of nonactivated ketones and α,β-unsaturated aldehydes catalyzed by organocatalysts.

As secondary amines are known to generate enamines from nonactivated ketones, it was expected that a combination of diphenylprolinol silyl ether **1** and pyrrolidine **2**, for example, would afford a chiral Michael product. However, there is a fundamental difficulty in this synthetic design, which will be explained using the Michael reaction of cinnamaldehyde and cyclohexanone as an example (Eq. 1): As pyrrolidine **2** is more nucleophilic than diphenylprolinol silyl ether **1**, **2** would generate not only enamine **6** but also nonchiral iminium ion **4** more readily than the generation of **3**. The reaction of **4** and **6** would afford a racemic product. Despite this seeming difficulty, we tried the reaction.



When a mixture of cinnamaldehyde and cyclohexanone was treated with 15 mol% of diphenylprolinol silyl ether **1**[9] and 7.5 mol% of pyrrolidine **2** in the presence of *p*-nitrophenol and water, the reaction proceeded successfully to afford the Michael product. To determine the enantiomeric excess (ee), the Michael product was treated with Wittig reagent *in situ* to afford the α,β-unsaturated ester, which was obtained in good yield (74%) with good *syn*-selectivity (5:1) and excellent enantioselectivity (91% ee) (Eq. 2). Intrigued with this enantioselectivity, the generation of chiral iminium ion **3** and nonchiral iminium ion **4** and that of chiral enamine **5** and nonchiral enamine **6** were investigated.



First, the speed of the generation of iminium ions was examined using $H_2{}^{18}O$ (Eq. 3, Figure 1). To monitor the reaction by mass spectrometry, 3-(3,4-dimethoxyphenyl)propenal **7**[10] was employed instead of cinnamaldehyde, and **7** was treated with amine catalyst **1** or **2** in the presence of 4 equiv of $H_2{}^{18}O$ and 10 mol% of *p*-nitrophenol.[11] As the iminium ion reacts with $H_2{}^{18}O$ to afford ^{18}O-aldehyde **7**, the generation of ^{18}O-aldehyde reflects the generation of iminium ion. According to Figure 1, pyrrolidine **2** is slightly more reactive than diphenylprolinol silyl ether **1** in the generation of ^{18}O-aldehyde, which indicates that both chiral and nonchiral iminium ions **3** and **4** are generated.

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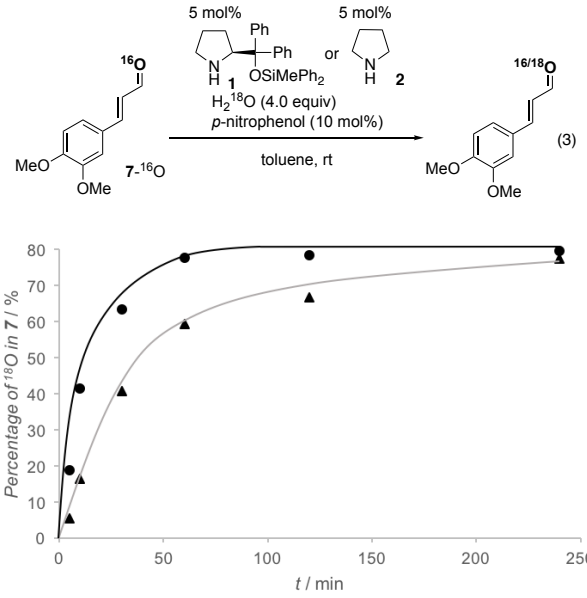


Figure 1. The effect of the catalyst in $^{16}O/^{18}O$ exchange of α,β-unsaturated aldehyde **7**. Triangle point: using catalyst **1**, Round point: using catalyst **2**

The speed of the generation of an enamine was also examined using $H_2{}^{18}O$ (Eq. 4, Figure 2). The reaction of cyclohexanone derivative **8** was investigated in the presence of 4 equiv of $H_2{}^{18}O$ and 10 mol% of *p*-nitrophenol. The generation of ^{18}O-ketone was fast in the case of pyrrolidine **2**, while ^{18}O-ketone was not observed in the case of diphenylprolinol silyl ether **1**. These results would be predicted from the fact that diphenylprolinol silyl ether **1** is less nucleophilic than pyrrolidine **2** because of its steric and electronic effects.

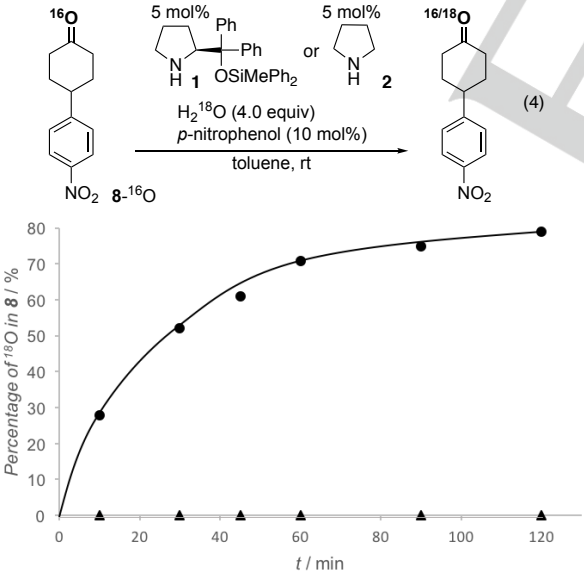
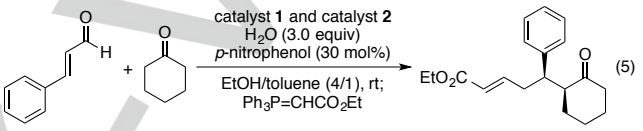
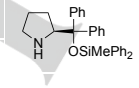
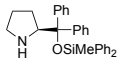
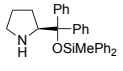
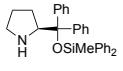
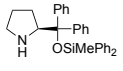
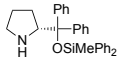


Figure 2. The effect of the catalyst in $^{16}O/^{18}O$ exchange of ketone **8**. Triangle point: using catalyst **1**, Round point: using catalyst **2**

These results clearly indicate that the concentrations of chiral and nonchiral iminium ions **3** and **4** are similar while only nonchiral enamine **6** is observed without detection of chiral enamine **5**. When these nonchiral iminium ion **4** and nonchiral enamine **6** react, a racemic product is formed. However, excellent enantioselectivity is obtained (Eq. 2), which indicates that the reaction of chiral iminium ion **3** must proceed preferentially. This phenomenon would be explained based on Mayr's investigation[12] on the reactivity of iminium ions **3** and **4**. Mayr investigated the electrophilic reactivity of several iminium ions, and the electrophilicity *E* was defined. *E* of the iminium ion of cinnamaldehyde of diphenylprolinol trimethylsilyl ether is –8.2, while that of **4** is –9.8, which indicates that the iminium ion of diphenylprolinol silyl ether **3** is more electrophilic than that of pyrrolidine **2**. Thus, even though the nonchiral iminium ion **4** is formed as well, the iminium ion **3** of diphenylprolinol silyl ether **1** would react preferentially with the enamine **6** of pyrrolidine because of its higher reactivity.

Table 1. The effect of the second amine in the asymmetric Michael reaction of diphenylprolinol silyl ether[a]



Entry	Catalyst **1**	Catalyst **2**	Time [h]	*syn:anti* [b]	Yield [%][c]	Ee [%][d]
1			24	5:1	74	91
2			30	5:1	67	98
3			32	5:1	78	97
4			36	11:1	71	82
5			40	15:1	74	96
6			40	10:1	70	–95

[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde (0.5 mmol), cyclohexanone (1.5 mmol), catalyst **1** (0.075 mmol), catalyst **2** (0.0375 mmol), *p*-nitrophenol (0.15 mmol), water (1.5 mmol), in EtOH (0.4 mL) and toluene (0.1 mL) at room temperature. After the reaction, Wittig reagent (0.75 mmol) was added. See supporting information for details. [b] Determined by ^{1}H-NMR. [c] Yield of a diastereomer mixture. [d] Determined by HPLC analysis on a chiral column material.

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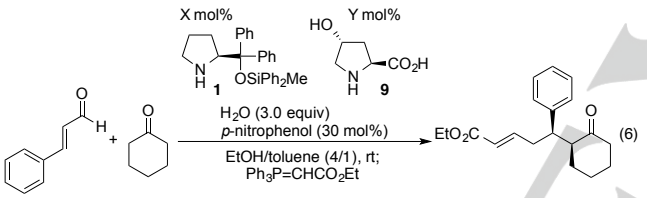
Next, a secondary amine was examined for higher diastereo- and enantioselectivities (Table 1). When piperidine and morpholine were used, excellent enantioselectivity was obtained, but the diastereoselectivity did not improve (entries 2, 3). When proline[13] was employed with **1**, diastereoselectivity increased to 11:1, while enantioselectivity decreased (82% ee) (entry 4). After the intensive screening of amine catalysts, it was finally found that both excellent diastereoselectivity (15:1) and enantioselectivity (96% ee) were realized when L-*trans*-4-hydroxyproline **9**[14] was employed (entry 5). To investigate which chirality of these two amine catalysts, such as L-diphenylprolinol silyl ether **1** and L-*trans*-4-hydroxyproline **9**, determined the enantioselection of the product, D-diphenylprolinol silyl ether was used in the combination of L-4-*trans*-hydroxyproline (entry 6). The same enantioselectivity with an opposite absolute configuration to that of entry 5 was obtained; therefore, the chirality of diphenylprolinol silyl ether predominantly controls the absolute configuration of the product. Instead of diphenylprolinol silyl ether **1**, MacMillan's catalyst was employed with hydroxyproline **9** under the same reaction conditions, but the reaction did not proceed at all after 72 h.

The effect of solvent on the diastereo- and enantioselectivities was examined, and a mixture of toluene and EtOH was found to be a suitable solvent (see SI). The ratio of the two amines was investigated (Table 2). With neither L-*trans*-4-hydroxyproline **9** nor diphenylprolinol silyl ether **1**, the reaction did not proceed (entries 1, 7). Thus, both catalysts are necessary for the progress of the reaction. The reaction proceeded faster with a decrease in the enantioselectivity as the amount of 4-hydroxyproline increased. In terms of the reaction time and enantioselectivity, we selected the ratio of 2:1 between diphenylprolinol silyl ether **1** and 4-hydroxyproline **9** (entry 3). It should be noted that a small amount of water is also crucial for the reaction. Without water, the reaction is slow and low diastereoselectivity is obtained, while enantioselectivity decreased in the presence of an excess amount of water (10 equiv, see SI). *p*-Nitrophenol is also essential; without *p*-nitrophenol, the reaction is slow with a decrease in yield and selectivity (see SI).

When the best reaction conditions were determined, the generality of the reaction using 15 mol% of diphenylprolinol silyl ether **1** and 7.5 mol% of 4-hydroxyproline **9** was investigated. First, the generality of the α,β-unsaturated aldehyde was examined (Table 3). As for the substituent at the 3-position of propenal, not only phenyl and naphthyl but also phenyl groups with electron-donating substituents such as *p*-methyl, *p*-

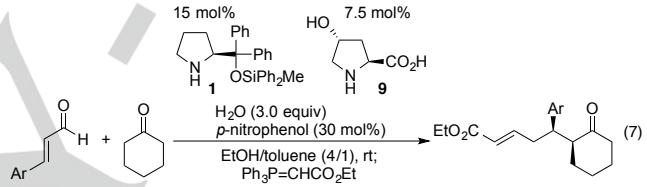
Table 2. The effect of the ratio of the two amine catalysts in the asymmetric Michael reaction[a]



Entry	X [mol%][b]	Y [mol%][c]	Time [h]	*syn:anti*[d]	Yield [%][e]	Ee [%][f]
1	20	0	72	n.d.[g]	<5	n.d.[g]
2	15	5	73	24:1	68	96
3	15	7.5	40	15:1	74	96
4	10	10	24	12:1	74	93
5	7.5	15	16	11:1	73	91
6	5	15	12	11:1	70	88
7	0	20	148	n.d.[g]	<5	n.d.[g]

[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde (0.5 mmol), cyclohexanone (1.5 mmol), **1** (0.075 mmol), **9** (0.0375 mmol), *p*-nitrophenol (0.15 mmol), water (1.5 mmol), in EtOH (0.4 mL) and toluene (0.1 mL) at room temperature. After the reaction, Wittig reagent (0.75 mmol) was added. See supporting information for details. [b] Amount of **1**. [c] Amount of **9**. [d] Determined by ^{1}H-NMR. [e] Yield of a diastereomer mixture. [f] Determined by HPLC analysis on a chiral column material. [g] n.d. = not determined.

Table 3. Generality of the asymmetric Michael reaction of various α,β-unsaturated aldehyde and cyclohexanone[a]



Entry	Ar	Time [h]	*syn:anti*[b]	Yield [%][c]	Ee [%][d]
1	Phenyl	40	15:1	74	97
2	2-Naphtyl	16	13:1	88	96
3	*p*-MeC_6H_4	45	10:1	71	94
4	*p*-$MeOC_6H_4$	48	14:1	78	96
5	3,4-$(CH_3O)_2C_6H_3$	24	9:1	81	96
6	*o*-FC_6H_4	19	7:1	67	82
7	*o*-ClC_6H_4	36	5:1	71	89
8	*o*-BrC_6H_4	48	5:1	72	92
9	*p*-ClC_6H_4	36	9:1	77	98
10	*p*-BrC_6H_4	40	8:1	71	>99
11	2-Furyl	72	6:1	61	89

[a] Unless otherwise shown, the reaction was performed by employing α,β-enal (0.5 mmol), cyclohexanone (1.5 mmol), **1** (0.075 mmol), **9** (0.0375 mmol), *p*-nitrophenol (0.15 mmol), water (1.5 mmol), in EtOH (0.4 mL) and toluene (0.1 mL) at room temperature. After the reaction, Wittig reagent (0.75 mmol) was added. See supporting information for details. [b] Determined by ^{1}H-NMR. [c] Yield of a diastereomer mixture. [d] Determined by HPLC analysis on a chiral column material.

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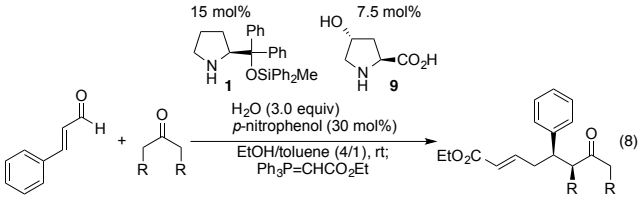
methoxy, and 3,4-dimethoxy groups, and phenyl groups with electron-withdrawing groups such as *o*-fluoro, *o*-chloro, *o*-bromo, *p*-chloro, and *p*-bromo substituents are suitable to afford the corresponding products with good *syn*-selectivity and excellent enantioselectivity. Heteroaromatic groups like furan are also suitable substituents. The α,β-unsaturated aldehydes with β-alkyl groups like 2-butenal are not suitable Michael acceptors.

Next the generality of the Michael donor was investigated (Table 4). Not only cyclohexanone but also cycloheptanone is a suitable donor to provide the product with excellent enantioselectivity (entry 3), although cyclopentanone affords moderate enantioselectivity (77% ee, entry 2). 1-Benzyl-4-piperidone, tetrahydro-4*H*-pyran-4-one, and 4,4-dimethylcyclohexanone are also suitable substrates to afford the products with excellent enantioselectivity (entries 4, 5, and 6).

Table 4. Generality of the asymmetric Michael reaction of cinnamaldehyde and various ketones[a]

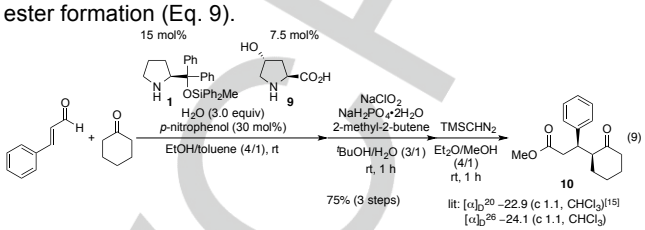


Entry	Ketone	Time [h]	*syn:anti*[b]	Yield [%][c]	Ee [%][d]
1		40	15:1	74	96
2		30	3:1	48	77
3		406	4:1	63	97
4		19	5:1	64	97
5		16	>20:1	54	94
6		50	3:1	74	95

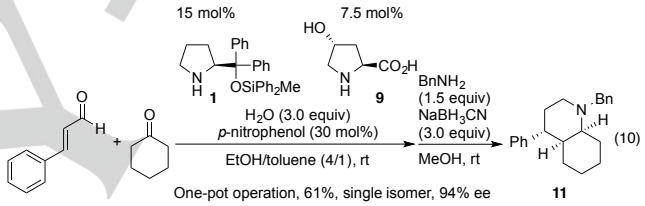
[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde (0.5 mmol), ketone (1.5 mmol), **1** (0.075 mmol), **9** (0.0375 mmol), *p*-nitrophenol (0.15 mmol), water (1.5 mmol), in EtOH (0.4 mL) and toluene (0.1 mL) at room temperature. After the reaction, Wittig reagent (0.75 mmol) was added. See supporting information for details. [b] Determined by ^{1}H-NMR. [c] Yield of a diastereomer mixture. [d] Determined by HPLC analysis on a chiral column material.

The reaction proceeded in a larger scale as well: The reaction of cinnamaldehyde (1 g) with cyclohexanone afforded the product in 76% yield with excellent diastereoselectivity *syn:anti* = 15:1) and enantioselectivity (93% ee) (see SI).

Relative and absolute configurations were determined by a comparison of the physical data with the known methyl ester **10**[15] including the optical rotation, which was synthesized from the Michael product via Kraus–Pinnick oxidation[16] and methyl ester formation (Eq. 9).



As an application of the Michael reaction, the Michael adduct was converted into a *cis*-decahydroquinoline derivative (Eq. 10). That is, after the Michael reaction, benzylamine, $NaBH_3CN$, and MeOH were added to the same vessel. *cis*-Decahydroquinoline **11** was obtained as a single isomer in 61% yield over two steps in a single pot[17] without decreasing the enantioselectivity.



In summary, we found that the asymmetric direct Michael reaction of α,β-unsaturated aldehydes and ketones can proceed in the presence of two catalysts, such as diphenylprolinol silyl ether **1** and L-*trans*-4-hydroxyproline **9**, in which diphenylprolinol silyl ether reacts with the α,β-unsaturated aldehyde to give a reactive chiral iminium ion and 4-hydroxyproline reacts with the ketone to give an enamine. Although 4-hydroxyproline reacts readily with α,β-unsaturated aldehydes to generate the corresponding iminium ion, preferential reaction of the iminium ion of diphenylprolinol silyl ether compared with the iminium ion of 4-hydroxyproline was realized owing to the higher electrophilicity of the former iminium ion. This is a first example to indicate that diphenylprolinol silyl ether can be employed together with secondary amine catalyst, which will broaden the synthetic utility of diphenylprolinol silyl ether catalyst. Synthetically useful δ-keto aldehydes were prepared with excellent diastereo- and enantioselectivities.

Acknowledgements

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Keywords: organocatalyst • Michael reaction • enamine • asymmetric synthesis

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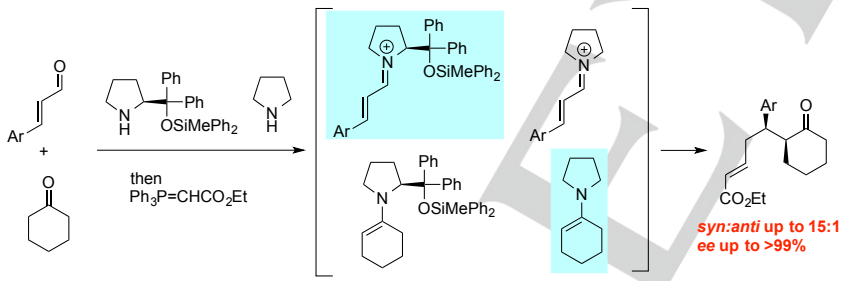

Although there are several species in the reaction mixture, iminium ion of diphenylprolinol silyl ether and enamine of pyrrolidine selectively react to provide the synthetically useful δ-keto aldehydes with excellent enantioselectivity.

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Title

Direct asymmetric Michael reaction of α,β-unsaturated aldehydes and ketones catalyzed by two secondary amine catalysts