

Organocatalytic Enantioselective Michael Addition of Silyl Malonate to α,β -Unsaturated Enones: One-pot Synthesis of Chiral δ -Keto Esters

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The Michael addition reaction is widely recognized as one of the most efficient carbon-carbon bond-forming reactions in organic synthesis,¹ and the development of enantioselective catalytic Michael reaction has been the subject of intensive research.² In addition to the great success catalyzed by metal complexes, the environmentally friendly organocatalyst-mediated asymmetric Michael reaction has been explored intensively in recent years.^{3,4} Although a number of catalytic enantioselective Michael reaction of dialkyl malonates to α,β -unsaturated enones have been reported,⁵ up to now there is no report for the enantioselective Michael reaction of silylmalonate to α,β -unsaturated enones. The δ -keto esters are valuable intermediates in organic synthesis.⁶ A few synthetic methods for the catalytic asymmetric synthesis of δ -keto esters are now known. Some representatives examples include tandem Michael addition/decarboxylation of dialkyl malonates to α,β -unsaturated enones,^{5d} chiral Lewis acid-catalyzed Mukaiyama-Michael reaction,⁷ tandem Michael addition/denitration of nitroacetate to α,β -unsaturated enones,⁸ and Michael addition of chiral carbene complexes.⁹ Although several efficient methods have been achieved by these systems, an effective method for the synthesis of δ -keto esters is still a challenge.

As part of our research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,¹⁰ we recently reported the asymmetric Michael addition of active methylenes and methines using chiral catalysts.¹¹ Herein, we wish to describe the one-pot enantioselective formation of δ -keto esters *via* an organocatalytic domino sequence of Michael reaction and desilylation/decarboxylation.

To validate the feasibility of the proposed the domino reaction sequence, the one-pot reaction was achieved *via* the addition of DMSO/water in the reaction mixtures after the completion of Michael reaction of ethyl *tert*-butyldimethyl-

silyl malonate (**2**) with (*E*)-4-phenylbut-3-en-2-one (**1a**) in the presence of 20 mol % bifunctional catalysts (Figure 1) in toluene, followed by treatment with *n*-tetrabutylammonium fluoride, to provide ethyl 5-oxo-3-phenylhexanoate (**3a**). As shown in Table 1, 9-amino-9-deoxyepicinchona alkaloids (**I–IV**) and primary amine organocatalyst (**V**) bearing both central and axial chiral elements effectively promoted the addition in high yields and high enantioselectivities (entries 1–5). The best result has been obtained with 9-amino-9-deoxyepiquinine (**III**). In order to further improve the selectivity, different solvents were then tested in catalyst **III**. Among the solvents probed, the best result was achieved when the reaction was conducted in toluene (97% ee, entry 3).

With optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of enones for the conjugate addition reaction are summarized in Table 2. As demonstrated, organocatalyst **III**-catalyzed Michael addition of silyl malonate **2** to enones **1** afforded the conjugate addition adducts, subsequently gave the corresponding δ -keto esters **3** after treatment of *n*-tetrabutylammonium fluoride in DMSO/water. The α,β -unsaturated ketones bearing substituted aryl, naphthyl,

Table 1. Optimization of the reaction conditions

Entry	Cat.	Solvent	Yield (%) ^a	ee (%) ^b
1	I	PhMe	67	91 (<i>S</i>)
2	II	PhMe	66	63 (<i>R</i>)
3	III	PhMe	60	97 (<i>R</i>)
4	IV	PhMe	64	83 (<i>R</i>)
5	V	PhMe	63	91 (<i>R</i>)
6	III	CH ₂ Cl ₂	63	93 (<i>R</i>)
7	III	CHCl ₃	66	95 (<i>R</i>)
8	III	ClCH ₂ CH ₂ Cl	67	89 (<i>R</i>)
9	III	THF	54	55 (<i>R</i>)
10	III	H ₂ O	64	81 (<i>R</i>)

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using a Chiralpak IC column.

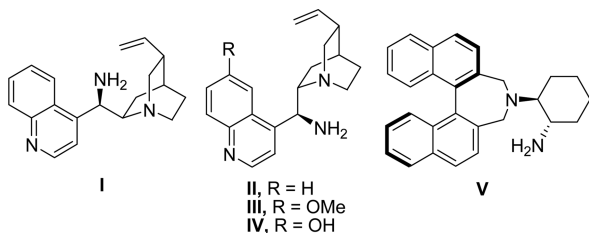
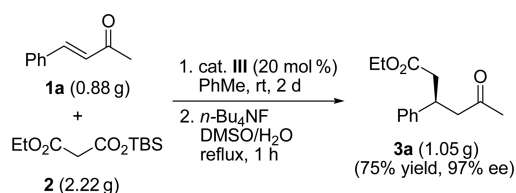


Figure 1. Structure of chiral primary amine catalysts.

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

Entry	1	Yield (%) ^a	ee (%) ^b
1	1a , Ar = Ph	3a , 60	97
2	1b , Ar = <i>p</i> -OMe-C ₆ H ₄	3b , 87	75
3	1c , Ar = <i>p</i> -F-C ₆ H ₄	3c , 77	95
4	1d , Ar = <i>p</i> -Cl-C ₆ H ₄	3d , 83	75
5	1e , Ar = 1-naphthyl	3e , 80	97
6	1f , Ar = 2-thienyl	3f , 83	95
7	1g , Ar = 2-furyl	3g , 80	93
8	1h , Ar = Ph	3h , 76	97
9	1i , Ar = cyclohexyl	3i , 84	91

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using Chiralpak IC (for **3a–3d**, **3f–3h**) OB-H (for **3i**) and Whelk-O1 (for **3e**) columns.

**Scheme 1.** Large-scale reaction of *tert*-butyldimethylsilyl ethyl malonate (**2**) with (*E*)-4-phenylbut-3-en-2-one (**1a**).

and heteroaromatic groups in β -position could effectively participate in the process (entries 1–8). Furthermore, cyclic system was also effective substrate for the process (entries 9). Absolute configurations of δ -keto esters **3** were determined by comparison of the optical rotation and chiral HPLC data with those of the reported ones.^{5d,7–9}

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 1, when silyl malonate **2** was treated with (*E*)-4-phenylbut-3-en-2-one (**1a**) under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired product **3a** at the gram scale with 75% yield and 97% ee (Scheme 1).

In summary, we have developed organocatalytic enantioselective domino sequence of conjugate addition reaction/desilylation/decarboxylation of silyl malonate **2** to enones **1** to afford synthetically useful chiral δ -keto esters **3**. The significance of the approach is highlighted by its capability to introduce δ -keto esters **3** with high enantioselectivity in one-pot.

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