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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 desilyation/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*-butyldimethylsilyl 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,

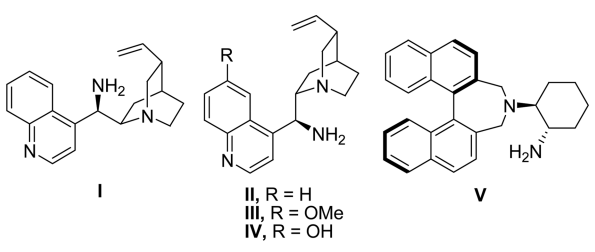
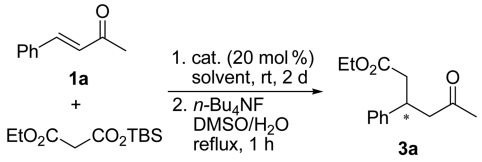


Figure 1. Structure of chiral primary amine catalysts.

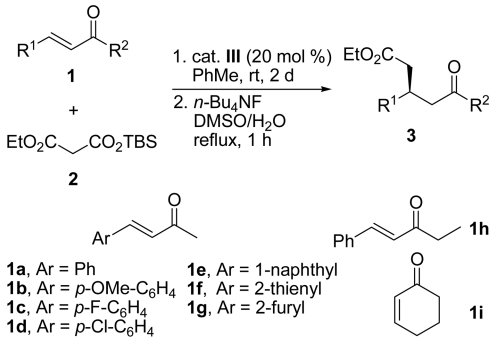
Table 1. Optimization of the reaction conditions



Entry	Cat.	Solvent	Yield (%)[a]	ee (%)[b]
1	**I**	PhMe	67	91 (*S*)
2	**II**	PhMe	66	63 (*R*)
3	**III**	PhMe	60	97 (*R*)
4	**IV**	PhMe	64	83 (*R*)
5	**V**	PhMe	63	91 (*R*)
6	**III**	CH_2Cl_2	63	93 (*R*)
7	**III**	$CHCl_3$	66	95 (*R*)
8	**III**	$ClCH_2CH_2Cl$	67	89 (*R*)
9	**III**	THF	54	55 (*R*)
10	**III**	H_2O	64	81 (*R*)

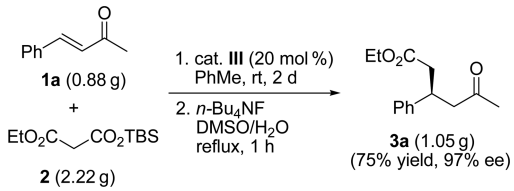
[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using a Chiralpak IC column.

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



Entry	1	Yield (%)[a]	ee (%)[b]
1	**1a**	**3a**, 60	97
2	**1b**	**3b**, 87	75
3	**1c**	**3c**, 77	95
4	**1d**	**3d**, 83	75
5	**1e**	**3e**, 80	97
6	**1f**	**3f**, 83	95
7	**1g**	**3g**, 80	93
8	**1h**	**3h**, 76	97
9	**1i**	**3i**, 84	91

[a]Isolated yield. [b]Enantiopurity 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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