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Organocatalytic Enantioselective Decarboxylative Michael Addition of β-Keto Acids to Dicyanoolefins and Disulfonylolefins

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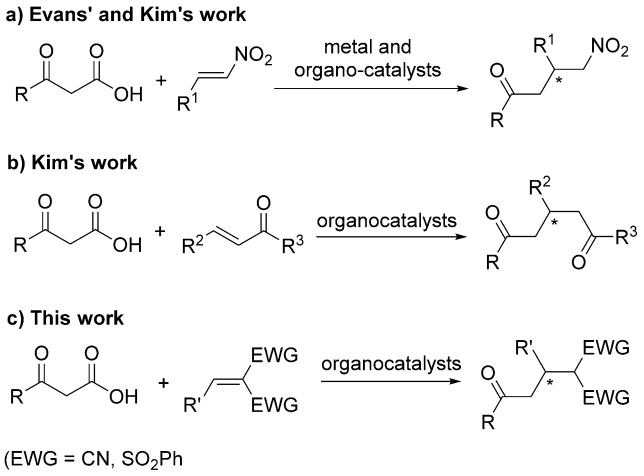
Abstract: A convenient organocatalytic enantioselective decarboxylative Michael addition of β-keto acids to dicyanoolefins and disulfonylolefins is realized. In the presence of saccharide-derived chiral amino thioureas, the reaction proceeded smoothly to afford a wide range of the Michael adducts in 62–99% yield with 70–94% *ee*. Moreover, one of the chiral adducts obtained could be readily converted into the monofluorinated product in a total 68% yield over four steps with 85% *ee*.

Keywords: amino thioureas; decarboxylative Michael addition; enantioselectivity; β-keto acids; organocatalysis

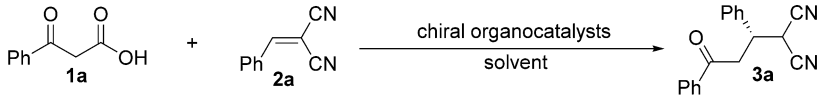
Since the Michael addition reaction[1] is arguably one of the most powerful organic transformations available for the construction of useful multifunctional molecules,[2] the development of efficient catalytic enantioselective approaches to this reaction has been an attractive subject in chemical research.[3] β-Keto acids are promising nucleophilic candidates for the generation of ketone enolate equivalents under very mild reaction conditions,[4] and recent studies have led to the rapid development of catalytic enantioselective decarboxylative reactions of β-keto acids with various electrophilic partners.[5,6] The asymmetric Michael addition reactions of β-keto acids to nitroolefins and α,β-unsaturated ketones have been approached using chiral metal complexes and small organic molecule catalysts by the groups of Evans[7a] and Kim[7b,c] (Scheme 1a and b). Encouraged by these results and the fact that dicyanoolefins[8] and disulfonylolefins[9] are highly reactive Michael acceptors, recently we have developed a new organocatalytic enantioselective decarboxylative Michael addition of β-keto acids to dicyanoolefins and disulfonylolefins that uses the readily accessible amino thioureas as bifunctional catalysts (Scheme 1c). Herein, we report the results of our exploration on this subject.

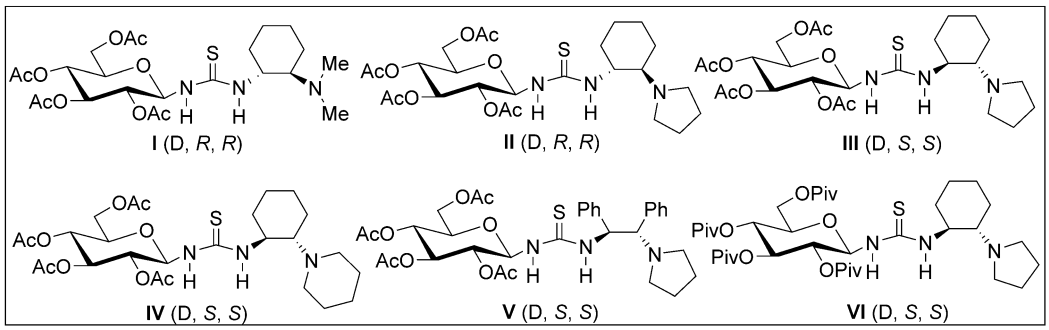
We initiated our studies by evaluating the enantioselective decarboxylative Michael addition of 3-oxo-3-phenylpropanoic acid **1a** to 2-benzylidenemalononitrile **2a** (Table 1) in tetrahydrofuran (THF) at 0 °C using the saccharide-derived amino thioureas **I–VI**, which were developed previously in our laboratory,[10] as chiral catalysts. Under these reaction conditions, the Michael addition product **3a** was obtained in excellent yield (Table 1, entries 1–6), with catalyst **III** giving the best enantioselectivity (51% *ee*). Subsequently, the solvent was found to have an important effect on the asymmetric induction (entries 7–10). Among the solvents tested, toluene was found to be the solvent of choice for this decarboxylative Michael addition with respect to both the yield and stereoselectivity (entry 9). When the reaction was performed at a lower temperature (entries 11 and 12), the enantioselectivity was improved from 73% *ee* at 0 °C to 88% *ee* at −20 °C. In addition, the stereoinduction



Scheme 1. Catalytic asymmetric Michael addition reactions of β-keto acids.

Table 1. Catalyst screening and optimization of the reaction conditions.[a]





Entry	Catalyst (mol%)	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**I** (10)	THF	0	48	95	0
2	**II** (10)	THF	0	48	93	8
3	**III** (10)	THF	0	48	98	51
4	**IV** (10)	THF	0	48	97	48
5	**V** (10)	THF	0	48	94	5
6	**VI** (10)	THF	0	48	97	24
7	**III** (10)	Et_2O	0	60	98	60
8	**III** (10)	DCM	0	60	96	58
9	**III** (10)	toluene	0	60	98	73
10	**III** (10)	CH_3CN	0	60	90	0
11	**III** (10)	toluene	−20	96	98	88
12	**III** (10)	toluene	−30	120	83	86
13	**III** (15)	toluene	−20	96	98	85
14	**III** (20)	toluene	−20	96	98	88

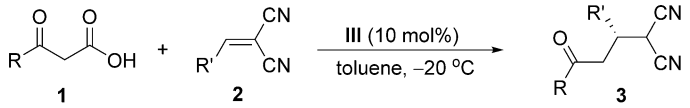
[a] *General reaction conditions:* **1a** (0.24 mmol), **2a** (0.2 mmol), and catalyst **I–VI** in solvent (2.0 mL) at the given temperature for the stated time.
[b] Yields of isolated product averaged over two runs.
[c] Determined by HPLC analysis on a chiral stationary phase. The absolute stereochemistry was assigned by comparison of the optical rotation with reported literature data (ref.[8e]).

was not improved when the catalyst loading was increased to 15 or 20 mol% (entries 13 and 14).

With the optimized conditions in hand, we turned our focus to the substrate scope and generality of this decarboxylative Michael addition reaction. The results are summarized in Table 2. First, a large variety of β-keto acids were examined for their reactions with 2-benzylidenemalononitrile **2a**. In the presence of 10 mol% catalyst **III**, the reaction of *ortho*-, *meta*-, and *para*-substituted phenyl β-keto acids with **2a** all proceeded smoothly, thus generating the Michael products **3a–3k** in high yields (88–98%) with good enantioselectivities (82–94% *ee*) (entries 1–11). Fused-ring aryl- or heteroaryl-substituted β-keto acids could also be used as the Michael donors, thus delivering the corresponding adducts **3l–3n** in 90–96% yield and 82–86% *ee* (entries 12–14). An alkyl-substituted β-keto acid is also a viable substrate, affording the desired product **3o** in 99% yield with 64% *ee* (entry 15). Further exploration of the substrate scope focused on the Michael acceptors. The introduction of electron-donating and electron-withdrawing groups on the phenyl ring of 2-benzylidenemalononitrile had little influence on the enantioselectivity. The desired products **3p–3w** were obtained in high yields with good enantioselectivities (entries 16–23). An acceptor substrate with a heteroaromatic group also reacted, affording the corresponding Michael adduct **3x** in 96% yield with 76% *ee* (entry 24). The use of alkyl-substituted dicyanoolefins furnished the expected products **3y** and **3z** in moderate yields and enantioselectivities (entries 25 and 26).

To further extend this asymmetric decarboxylative Michael addition protocol, we also used a series of disulfonylolefins as the Michael acceptors under the current reaction conditions. As shown in Table 3, all of the Michael adducts **5a–5o** were obtained with good to high enantioselectivities (80–93% *ee*) (en-

Table 2. The decarboxylative 1,4-addition of 2-benzylidenemalononitrile **2a** with various β-keto acids.[a]



Entry	R/R′ (**3**)	Time [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5/C_6H_5 (**3a**)	96	98	88
2	2-MeC_6H_4/C_6H_5 (**3b**)	96	93	86
3	3-MeC_6H_4/C_6H_5 (**3c**)	96	95	86
4	2,4-$Me_2C_6H_3/C_6H_5$ (**3d**)	144	97	87
5	4-$MeOC_6H_4/C_6H_5$ (**3e**)	96	98	85
6	3-$MeOC_6H_4/C_6H_5$ (**3f**)	144	93	84
7	4-FC_6H_4/C_6H_5 (**3g**)	144	88	94
8	2-FC_6H_4/C_6H_5 (**3h**)	144	96	84
9	4-ClC_6H_4/C_6H_5 (**3i**)	144	92	86
10	3-ClC_6H_4/C_6H_5 (**3j**)	96	91	84
11	4-BrC_6H_4/C_6H_5 (**3k**)	120	97	82
12	1-naphthyl/C_6H_5 (**3l**)	144	90	86
13	2-naphthyl/C_6H_5 (**3m**)	144	96	82
14	3-thiophenyl/C_6H_5 (**3n**)	144	90	85
15	cyclopropyl/C_6H_5 (**3o**)	20	99	64
16	C_6H_5/4-MeC_6H_4 (**3p**)	144	84	82
17	C_6H_5/4-$MeOC_6H_4$ (**3q**)	144	80	80
18	C_6H_5/3-$PhOC_6H_4$ (**3r**)	144	90	82
19	C_6H_5/4-FC_6H_4 (**3s**)	144	90	88
20	C_6H_5/4-ClC_6H_4 (**3t**)	144	92	86
21	C_6H_5/3,4-$Cl_2C_6H_3$ (**3u**)	48	98	82
22	C_6H_5/4-BrC_6H_4 (**3v**)	72	98	87
23	C_6H_5/3-$NO_2C_6H_4$ (**3w**)	72	98	87
24	C_6H_5/3-pyridyl (**3x**)	72	96	76
25	C_6H_5/*n*-propyl (**3y**)	72	60	70
26	C_6H_5/*i*-propyl (**3z**)	72	65	78

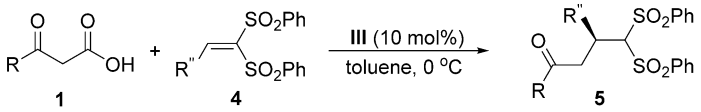
[a] *General reaction conditions:* **1** (0.24 mmol), **2** (0.2 mmol), and catalyst **III** (10 mol%) in toluene (2.0 mL) at –20 °C for the stated time.
[b] Yields of isolated product averaged over two runs.
[c] Determined by HPLC analysis on a chiral stationary phase.

tries 1–15), yet the chemical yields were dependent on the position and electronic properties of the substituents on the aromatic rings of the substrates. For example, β-keto acids that contain an electron-withdrawing group on the phenyl ring delivered the desired products **5f** and **5g** in relatively lower yields (entries 6 and 7), whereas disulfonylolefins that bear an electron-donating group on the phenyl ring reacted slowly with β-keto acids, furnishing the corresponding adducts **5k** and **5l** in 72% yield after prolonged reaction times (entries 11 and 12). However, alkyl-substituted β-keto acids and dicyanoolefins were found to be unsuitable for this asymmetric transformation and no expected product was observed.

Notably, the presence of the sulfonyl moiety within the Michael adducts allows facile access to optically enriched fluorine-containing building blocks.[11] For example, simple treatment of the decarboxylative Michael adduct **5a** with the Selectfluor under basic conditions led to the formation of the fluorinated ketone **6** in 92% yield with 87% *ee*. After the reduction of the carbonyl group of **6** with $NaBH_4$, the corresponding alcohol **7** was subjected to reductive desulfonylation and PCC oxidation to afford monofluorinated ketone **8** in 78% yield with 85% *ee* (Scheme 2). The absolute configuration of the major enantiomer was assigned by comparison of the optical rotation with the reported literature data.[12]

To explain the predominant production of adducts and to shed some light on the mechanism, the M06-2X DFT calculations[13,14] were performed with a view of delineating the interactions between organocatalyst and substrates (see the Supporting Information). The preliminary results show that the thiourea moiety of the organocatalyst favorably bonds to one *trans*-nitrogen atom of dicyanoolefins and one *cis*-oxygen atom of disulfonylolefins, respectively (Figure 1a). The multiple H–O bonding interactions between the saccharide unit of the organocatalyst and the olefin substrate may also play an important role in stabilizing

Table 3. The decarboxylative 1,4-dddition of β-keto acids **1** to vinyl sulfones **4**.[a]



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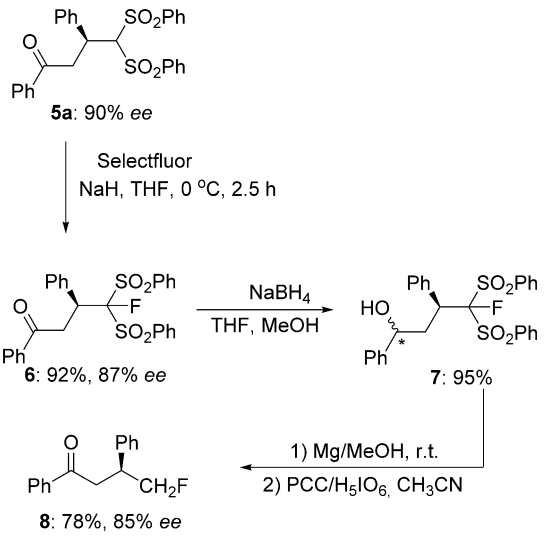
Entry	R/R″ (**5**)	Time [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5/C_6H_5 (**5a**)	48	98	90
2	4-MeC_6H_4/C_6H_5 (**5b**)	96	99	89
3	2,4-$Me_2C_6H_3/C_6H_5$ (**5c**)	96	94	92
4	4-$MeOC_6H_4/C_6H_5$ (**5d**)	96	92	80
5	3-$MeOC_6H_4/C_6H_5$ (**5e**)	96	93	93
6	4-FC_6H_4/C_6H_5 (**5f**)	48	62	88
7	4-ClC_6H_4/C_6H_5 (**5g**)	48	80	90
8	1-naphthyl/C_6H_5 (**5h**)	96	95	89
9	2-naphthyl/C_6H_5 (**5i**)	96	74	87
10	3-thiophenyl/C_6H_5 (**5j**)	96	90	87
11	C_6H_5/4-MeC_6H_4 (**5k**)	144	72	85
12	C_6H_5/4-$MeOC_6H_4$ (**5l**)	144	72	84
13	C_6H_5/4-FC_6H_4 (**5m**)	24	99	87
14	C_6H_5/4-ClC_6H_4 (**5n**)	48	75	86
15	C_6H_5/2-naphthyl (**5o**)	72	99	80

[a] *General reaction conditions:* **1** (0.24 mmol), **4** (0.2 mmol), and catalyst **III** (10 mol%) in toluene (2.0 mL) at 0 °C for the stated time.
[b] Yields of isolated product averaged over two runs.
[c] Determined by HPLC analysis on a chiral stationary phase.

the transition state. In addition, the β-keto acid is deprotonated by the tertiary amine moiety of the organocatalyst. After deprotonation, the enol species associates closely with the catalyst through ionic interactions. From the above analysis and the absolute configurations of the adducts, the transition states (**TS-A** and **TS-B**) for the Michael addition of β-keto acid **1** to olefins (**2** and **4**) in the presence of chiral organocatalyst **III** are proposed in Figure 1b. The *re*-face of the C=C group of dicyanoolefins is predominantly approached by the enol to give the observed major *S* enantiomer of **3**, whereas the attack of the enol to the *si*-face of the C=C group of disulfonylolefins leads to the formation of the *S*-configured adduct **5**. In addition, the catalytic cycle could involve a stepwise process, in which the Michael addition of β-keto acids to olefins gave the addition intermediates, followed by the decarboxylation to afford the desired adducts.



Scheme 2. Further synthetic transformations of the Michael adduct **5a**.

In summary, a new organocatalytic enantioselective decarboxylative Michael addition of β-keto acids to dicyanoolefins and disulfonylolefins has been presented. In the presence of the saccharide-derived chiral amino thioureas, the reaction proceeded smoothly to afford a wide range of the Michael adducts in 62–99% yield with 70–94% *ee*. Moreover, the products obtained can be converted into optically active monofluorinated molecules. Further mechanistic investigations and additional applications to the synthesis of biologically interesting targets are underway in our laboratory.

Experimental Section

General Procedure for Enantioselective Decarboxylative Michael Addition of β-Keto Acids to Dicyanoolefins

The 2-benzylidenemalononitrile **2** (0.2 mmol), catalyst **III** (0.02 mmol) and β-keto acid **1** (0.24 mmol) in toluene

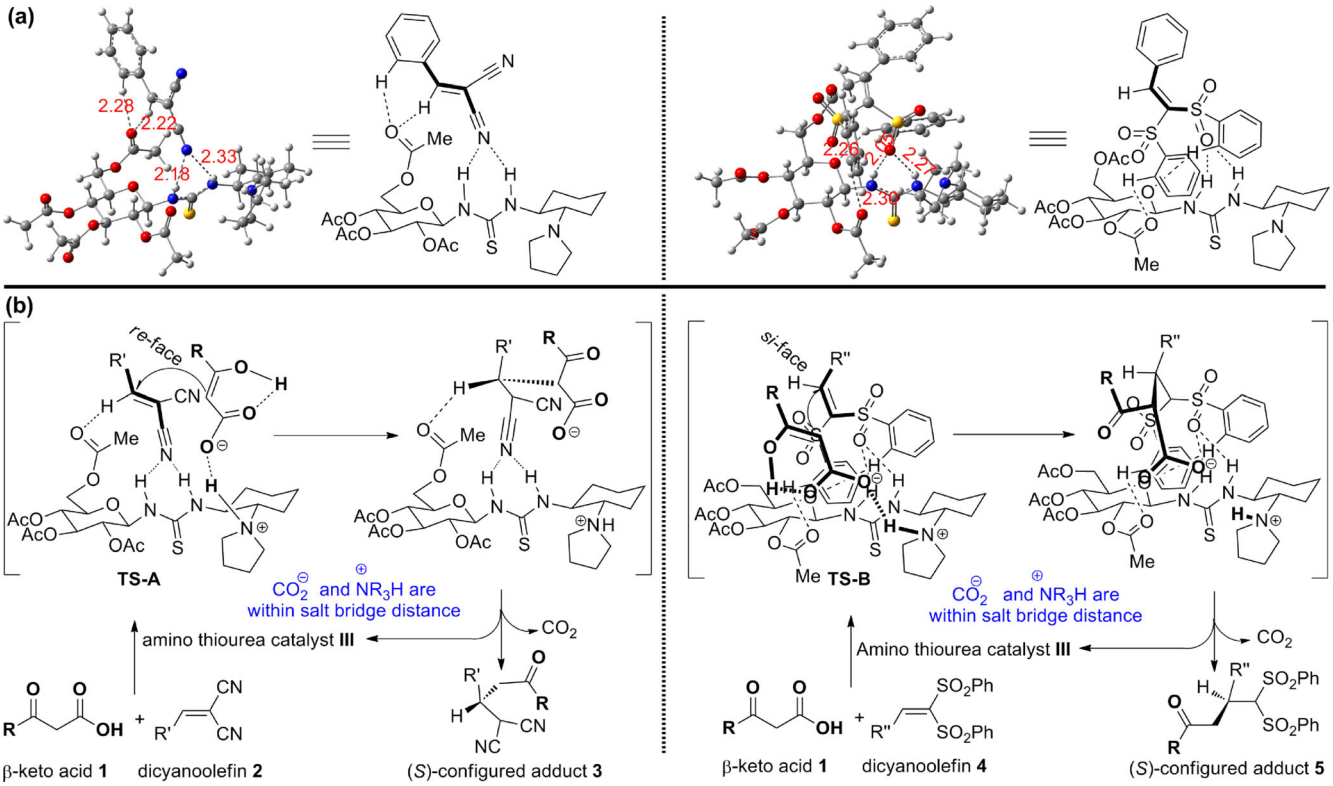


Figure 1. (a) Intermolecular complexes between organocatalyst and olefins (N blue, O red, S yellow). **(b)** Proposed reaction pathway.

(2.0 mL) were added into a 10-mL Schlenk flask equipped with a stirring bar. The reaction mixture was then stirred at −20 °C. After completion of the reaction (monitored by TLC), the residue was purified by column chromatography on silica gel (eluting with 5:1 petroleum ether/ethyl acetate) to give the addition product **3**.

General Procedure for the Decarboxylative Michael Addition of β-Keto Acids to Disulfonylolefins

The disulfonylolefin **4** (0.2 mmol), catalyst **III** (0.02 mmol) and β-keto acid **1** (0.24 mmol) in toluene (2.0 mL) were added into a 10-mL Schlenk flask equipped with a stirring bar. The reaction was then stirred at 0 °C. After completion of the reaction (monitored by TLC), the residue was purified by column chromatography on silica gel (eluting with 3:1 petroleum ether/ethyl acetate) to give the addition product **5**.

Acknowledgements

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