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Enantioselective Organocatalytic Conjugate Addition of Aldehydes to α,β-Unsaturated Thiol Esters

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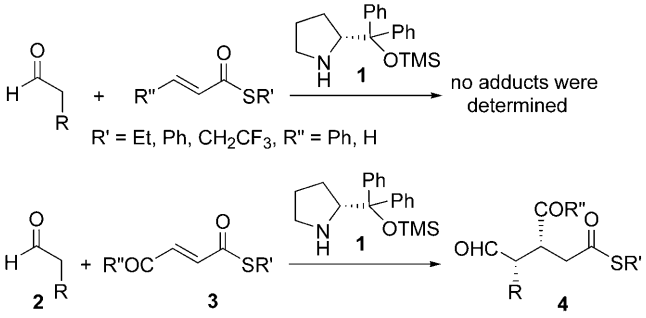
Abstract: The first example of an organocatalytic asymmetric Michael addition of aldehydes to α,β-unsaturated thiol esters promoted by chiral diphenylprolinol silyl ether is presented. The reaction occurs with good yields, diastereoselectivity and excellent enantioselectivity.

Keywords: asymmetric catalysis; enamine activation; Michael addition; organocatalysis; α,β-unsaturated thiol esters

In recent years, the Michael addition of aldehydes to electron-deficient olefins using chiral amines as the organocatalysts has received much attention.[1] This transformation normally provides highly functionalized adducts with excellent enantioselectivity, thereby offering a powerful method for the assembly of bioactive molecules. Although some highly reactive electron-deficient olefins, which include nitroalkenes,[2a,3] vinyl ketones,[4] maleimides,[5] benzoquinones,[6a] vinyl sulfones,[6b–e] vinyl phosphonates,[6f,g] alkylidenemalonates,[6h] α-keto-α,β-unsaturated esters,[2c] and γ-keto-α,β-unsaturated esters,[2d] have been revealed as suitable Michael acceptors for this reaction, more efforts for the discovery of new Michael acceptors are still required. This campaign would fully demonstrate the synthetic usage of this reaction.

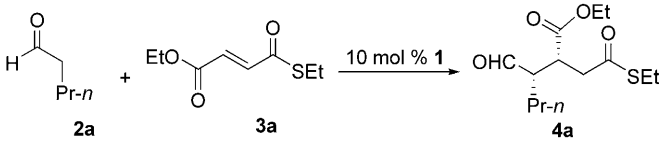
Thiol esters are useful synthetic intermediates that can be converted into aldehydes, ketones and lactones conveniently.[7] Compared with α,β-unsaturated esters, α,β-unsaturated thiol esters are more electron-deficient olefins. Thus, we decided to explore the possibility of whether the α,β-unsaturated thiol esters could reacted with the aldehydes under the catalysis of chiral amines. Initially, we tried to use some acrylic thio esters and β-phenyl-substituted α,β-unsaturated thiol esters as reactants, and found that they failed to give any adducts under various reaction conditions (Scheme 1). Inspired by the success in employing α-keto-α,β-unsaturated esters as the Michael acceptors,[2c] we moved our attention to olefins **3**, α,β-unsaturated thiol esters with a γ-ester or amide moiety. We were pleased to discover that the chiral amine-catalyzed reaction of these special α,β-unsaturated thiol esters with aldehydes proceeded smoothly to give Michael adducts **4** in good yield and diastereoselectivity with excellent regioselectivity and enantioselectivity. Herein we wish to detail our results.

The required (*E*)-α,β-unsaturated thiol esters were prepared by a Wittig reaction of glyoxylate esters (or amides) with thiol ester-derived ylides. We chose the reaction of *n*-pentanal **2a** with thio ester **3a** as the model to explore the optimized reaction conditions. As indicated in Table 1, this reaction worked in water to afford **4a** in 58% yield under the catalysis of 10 mol% of diphenylprolinol silyl ether **1** and 50 mol% of HOAc (entry 1). Changing the reaction media to organic solvents such as chloroform, toluene and dichloromethane failed to give improved results. In these cases moderate yields were observed mainly because of poor conversion (entries 2–4). However,



Scheme 1. Organocatalytic Michael addition of aldehydes to α,β-unsaturated thiol esters.

Table 1. Optimization of reaction conditions.[a]



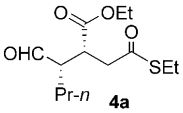
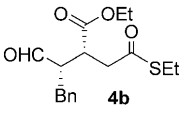
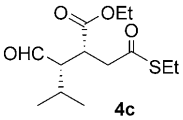
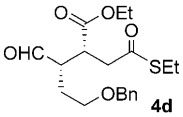
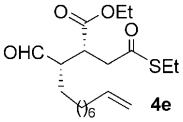
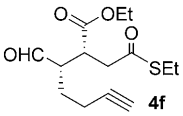
Entry	Solvent	Additive	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	H_2O	HOAc	24	58	6:1	>99
2	$CHCl_3$	HOAc	24	42	12:1	>99
3	$PhCH_3$	HOAc	24	47	3:1	95
4	CH_2Cl_2	HOAc	24	58	6:1	>99
5	CH_3CN	HOAc	24	85	6:1	>99
6	MeOH	HOAc	22	100	7:1	>99
7	MeOH	$PhCO_2H$	24	96	2:1	>99
8	MeOH	HOAc[e]	24	85	11:1	>99

[a] *Reaction conditions:* **2a** (0.4 mmol), **3a** (0.2 mmol), 10 mol% **1**, 50 mol% HOAc, 0.4 mL of solvent, 0 °C for 1 h, then room temperature for the indicated time.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral phase HPLC analysis for the *syn*-product.
[e] 10 mol% HOAc was used.

the reaction in acetonitrile produced **4a** in 85% yield with 6:1 diastereoselectivity and greater than 99% *ee* (entry 5), while a better yield was obtained when methanol was chosen as a solvent (entry 6). To increase the diastereoselectivity by slowing down the reaction, we tried to switch the additive to benzoic acid, but disappointingly found that the diastereoselectivity dropped dramatically (entry 7). However, reducing the ratio of the catalyst **1** and HOAc gave improved diastereoselectivity, but the reaction yield decreased slightly (entry 8). Based on these studies, we decided to use methanol as a solvent, and a ratio of 1:5 for catalyst and additive in later investigations. Under these conditions, fumaric diesters did not give the desired adducts, indicating that a thioester group is important in this case. Noteworthy is that in all cases **4a** was isolated as a single regioisomer, indicating that this addition occurred exclusively at the β-position of the thio ester. This is understandable because the thio ester group and the ester group have an over 1000-fold difference in electron-withdrawing ability (pK_a is 21.0 for CH_3COSEt, and 25.6 for CH_3COOEt).[8]

With the optimized reaction conditions in hand, we explored the scope and limitations of the reaction by varying the aldehydes. The results are summarized in Table 2. In general, the Michael adducts were obtained in good yield and diastereoselectivity with excellent enantioselectivity (entries 1–6). Not only *n*-pentanal, but also other linear aldehydes such as 3-phenylpropanal (entry 2, Table 2), could be employed

Table 2. Enantioselective Michael addition of aldehydes to 3-ethylsulfanylcarbonyl-acrylic acid ethyl ester **3a**.[a]

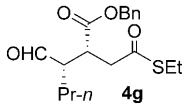
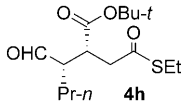
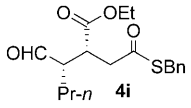
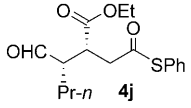
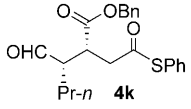
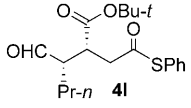
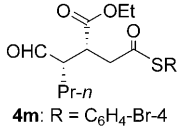
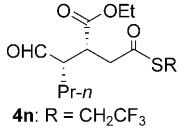
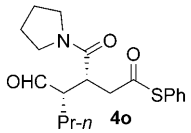
Entry	Product	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	 **4a**	22	100	7:1	>99
2	 **4b**	48	94	7:1	>99
3	 **4c**	38	69[e]	9:1	>99
4	 **4d**	27	90	6:1	>99
5	 **4e**	36	100	8:1	>99
6	 **4f**	26	95	8:1	>99

[a] *Reaction conditions:* thio ester (0.2 mmol), aldehyde (0.4 mmol), 10 mol% **1**, 50 mol% HOAc, 0.4 mL of methanol, 0 °C for 1 h, then room temperature for the indicated time.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral phase HPLC analysis for the *syn*-product.
[e] 20 mol% **1** and 100 mol% HOAc were used.

successfully as the Michael donors. However, the reaction became slower when branched aldehydes such as isovaleraldehyde were used (entry 3, Table 2). In this case only a moderate yield (69%) was obtained even when the catalyst loading was increased. Besides these simple alkyl substituents, benzoxy-, olefin- and alkyne-embodied substrates were compatible with these conditions, giving the corresponding adducts in excellent yields (entries 4–6). The additional functional groups in these products can be further modified to afford molecules with higher complexity.

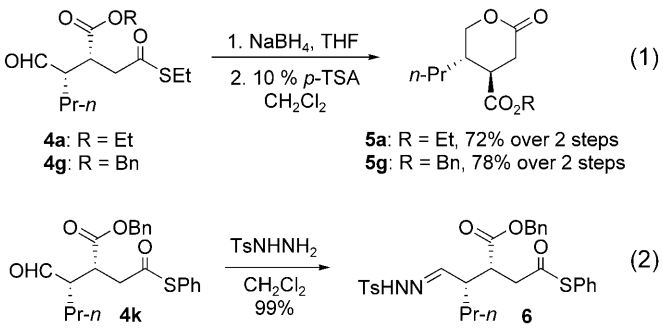
We next checked the scope of the reaction by using different thio esters. As shown in Table 3, the ethyl, benzyl and *tert*-butyl ester moieties have limited influence on the yield of this reaction, while high diastereoselectivity and enantioselectivity were also obtained (entries 1, 2 and entries 4–6). Meanwhile, the substituents at the sulfur atom play an important role

Table 3. Enantioselective Michael addition of *n*-pentanal to 3-sulfanylcarbonyl-acrylic acid ester.[a]

Entry	Product	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	 **4g**	19	99	12:1	>99
2	 **4h**	21	100	9:1	>99
3	 **4i**	23	100	12:1	>99
4	 **4j**	4[e]	99	12:1	>99
5	 **4k**	3.5[e]	94	9:1	>99
6	 **4l**	5[e]	90	9:1	>99
7	 **4m**: R = C_6H_4-Br-4	2[e]	93	12:1	>99
8		7[f]	91	8:1	92
9	 **4n**: R = CH_2CF_3	7[f]	92	8:1	>99
10	 **4o**	5[e]	92	8:1	82

[a] *Reaction conditions:* thio ester (0.2 mmol), aldehyde (0.4 mmol), 10 mol% **1**, 50 mol% HOAc, 0.4 mL of solvent, 0 °C for 1 h, then room temperature for the indicated time.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral phase HPLC analysis for the *syn*-product.
[e] 5 mol% **1** was used
[f] 2 mol% **1** was used.

for reaction rate. For examples, when phenyl thio esters were employed, excellent results were obtained by using 5 mol% catalyst in less than 5 h (entries 4–6). The 4-bromophenyl thio ester reacted faster than corresponding phenyl thio ester (compare entries 4 and 7). For 4-bromophenyl- and trifluoroethyl-substituted thio esters, using 2 mol% catalyst could give satisfactory results (entries 8 and 9). These results indicated that the ability for promoting the reaction is Et ~ Bn < Ph < *p*-BrPh ~ CH_2CF_3, which is consistent with the order of their electron-withdrawing ability. Additionally, it was found that the ester group can be changed to an amide without any significant effect on the reaction rate, but provided the adduct **4o** with moderate enantioselectivity (entry 10).



Scheme 2. Synthesis of δ-lactones **5** and hydrazone **6**.

Reduction of compounds **4a** and **4g** with $NaBH_4$ followed by treatment with TsOH afforded δ-lactones **5a** and **5g** in good yields [Eq. (1), Scheme 2], indicating that the present products could be converted into some useful chiral building blocks.

Based on previous studies, the present Michael adducts should have *syn* selectivity.[9] This hypothesis was further confirmed by an X-ray analysis of hydrazone **6** (Figure 1) that was generated from the reaction of **4k** with *p*-toluenesulfonylhydrazide [Eq. (2), Scheme 2].[10]

In conclusion, we have revealed that γ-ester substituted α,β-unsaturated thiol esters could react with aldehydes to deliver the corresponding Michael adducts, which provides another successful example for chiral amine-catalyzed Michael additions. Considering

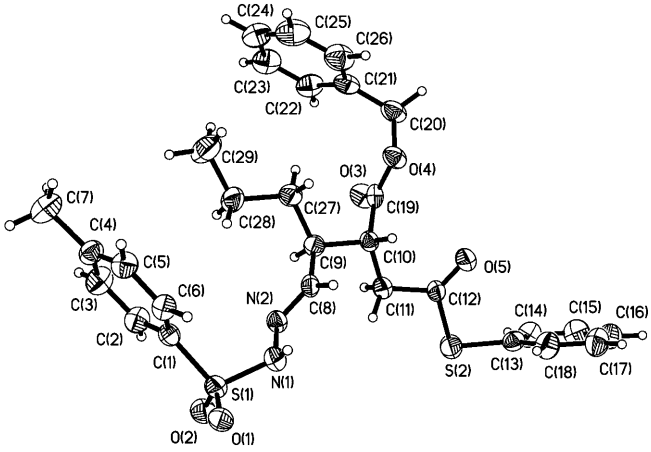


Figure 1. X-ray crystal structure of the hydrazone **6**.

that the diverse functional groups in these adducts are ready for further conversions, the present method may find wide applications in organic synthesis.

Experimental Section

General Procedure for Organocatalytic Michael Addition of Aldehydes to α,β-Unsaturated Thiol Esters

To a suspension of catalyst **1** (1–10 mol%), HOAc (5–50 mol%) and α,β-unsaturated thiol esters (0.20 mmol) in methanol was added aldehyde (0.4 mmol) at 0 °C. After the reaction mixture had been stirred for 1 h at the same temperature, it was allowed to warm to room temperature. The stirring was continued until the α,β-unsaturated thiol ester was consumed (monitored by TLC). The reaction mixture was directly loaded on a silica gel column, and eluted with 30:1 to 15:1 *n*-pentane and ethyl acetate to afford the Michael adduct.

Acknowledgements

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[10] CCDC 734452 contains the supplementary crystallographic data for the hydrazone **6** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

