Tetrahedron Letters 51 (2010) 5134–5136

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic asymmetric thio-Michael addition of arylmethyl mercaptans to cyclic enones by a primary amino acid

Masanori Yoshida *, Yasunobu Ohno, Shoji Hara

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, 8, Kita 13-jo Nishi, Kita-ku, Sapporo, Hokkaido 060-8628, Japan

ARTICLE INFO

Article history:
Received 24 June 2010
Revised 13 July 2010
Accepted 16 July 2010
Available online 25 July 2010

ABSTRACT

A simple primary amino acid was found to be an efficient catalyst for thio-Michael addition of benzyl mercaptan to cyclic enones.

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Thio-Michael addition of mercaptans to α,β-unsaturated carbonyl compounds is a useful methodology to introduce a sulfur functionality into the β-position of the carbonyl group and many asymmetric processes have been developed.[1,2] From a synthetic point of view, benzyl mercaptan is an attractive Michael donor because the benzyl group can be removed easily to give a thiol.[3] Catalytic asymmetric thio-Michael addition of benzyl mercaptan to enones or enals has been achieved by both organometallic and organic catalyses; however, there are only a few reports regarding the thio-Michael addition of benzyl mercaptan to cyclic enones by organocatalysis and it is very difficult to carry out the reaction with high enantioselectivity.[4–6] Indeed, to the best of our knowledge, the highest enantioselectivity which has been obtained from the reaction of benzyl mercaptan with 2-cyclohexen-1-one by organocatalysis is 21% ee as reported by Deng's group in 2002,[6a] while 90% ee was achieved by organometallic catalysis as reported by Shibasaki's group in 1998.[4e] Therefore, it is still a challenging subject to investigate an organocatalytic asymmetric thio-Michael addition of benzyl mercaptan to cyclic enones.

Recently, we reported that *O*-TBDPS L-serine lithium salt (**1a**) progressed the Michael addition of malonates to cyclic enones effectively to give 3-substituted cyclic ketones in good yields with high enantioselectivity (Fig. 1).[7,8] In this context, we attempted the thio-Michael addition of benzyl mercaptan with 2-cyclohexen-1-one (**2a**) in the presence of the catalyst **1a** (Scheme 1). The reaction slowly proceeded to give the desired Michael adduct, 3-(phenylmethylthio)cyclohexanone (**3a**); however, the enantioselectivity was quite low (7% ee). Encouragingly, it was found that the use of amino acid **1b** as a catalyst raised the enantioselectivity dramatically to 38% ee. To find a more selective catalyst, we carried out a catalyst screen for the thio-Michael addition of benzyl mercaptan with **2a** as shown in Table 1.[9] It was found that the use of *O*-TIPS L-serine (**1c**) or *O*-TBDPS L-tyrosine (**1e**) as a catalyst resulted in a lower enantioselectivity than that of **1b** (Table 1, entries 1 and 3). While *O*-triphenylmethyl L-serine (**1d**) gave the Michael adduct **3a** with only 3% ee, *S*-triphenylmethyl L-cysteine (**1f**) improved the selectivity to 45% ee (Table 1, entries 2 and 4). A secondary amino acid **1g** was also examined as a catalyst; however, poor enantioselectivity was observed (Table 1, entry 5). Thus, we chose **1f** as a catalyst for further investigations.

We then carried out a solvent screen for the thio-Michael addition using **1f** (Table 2). It was found that the reaction smoothly proceeded in a high-polarity solvent, DMSO or MeOH; however, the product **3a** was obtained as a racemate (Table 2, entries 1 and 2). After further solvent screening, dichloromethane was found

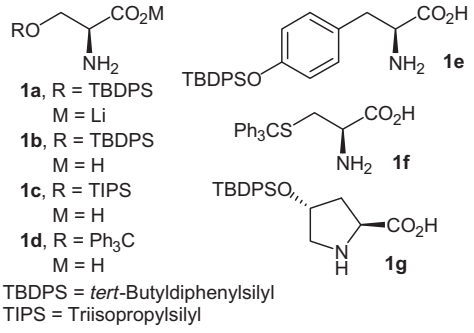
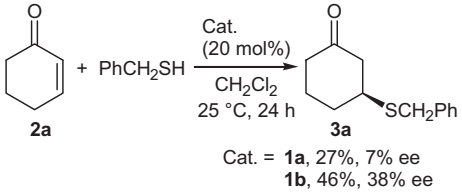


Figure 1. Catalysts used in the thio-Michael addition of mercaptans to enones.



Scheme 1. Thio-Michael addition of benzyl mercaptan with **2a** using **1a** or **1b**.

* Corresponding author. Tel./fax: +81 11 706 6557.
E-mail address: myoshida@eng.hokudai.ac.jp (M. Yoshida).

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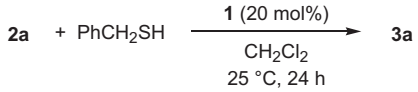
doi:10.1016/j.tetlet.2010.07.089

Table 1
Catalyst screen for thio-Michael addition of benzyl mercaptan with **2a**[a]



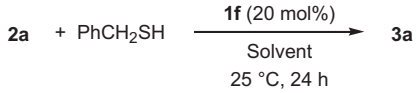
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1c**	11	23
2	**1d**	50	3
3	**1e**	10	30
4	**1f**	17	45
5	**1g**	53	6

[a] The reaction was carried out with **2a** (0.5 mmol), benzyl mercaptan (0.55 mmol), and **1** (0.1 mmol) in dichloromethane (1 mL) at 25 °C for 24 h.
[b] Isolated yield based on **2a**.
[c] Determined by chiral HPLC analysis.

to be a suitable solvent to obtain the best enantioselectivity (45% ee), although the reaction was very slow (Table 2, entry 10). The reaction rate could be improved by adding a small amount of DMSO to dichloromethane without any loss of enantioselectivity (Table 2, entries 11–14).[10]

Encouraged by these results, we carried out a detailed screening of additives for the thio-Michael addition of benzyl mercaptan to **2a** using catalyst **1f** in dichloromethane (Table 3). Interestingly, when the amount of DMSO was reduced to 1 equivalent to **2a**, the enantioselectivity was improved to 56% ee (Table 3, entry1). The addition of diphenylsulfoxide gave a result similar to that of DMSO, while a lower enantioselectivity was obtained by the addition of dimethylsulfone (Table 3, entries 2 and 3). MeOH and H_2O did not greatly affect the yield and enantioselectivity, though triethylamine reduced the selectivity (Table 3, entries 4–6). We then performed optimization of the reaction conditions using DMSO as an additive. The most effective amount of DMSO added was determined to be 50 mol % (Table 3, entry 7). Although the thio-Michael addition was very slow at 25 °C, the reaction was completed within 72 h by carrying out the reaction at 37 °C (Table 3, entries 9 and 10). The amount of catalyst **1f** could be reduced to 10 mol % without considerable loss of yield and selectivity (Table 3, entry 11). Under the reaction conditions, the Michael adduct **3a** was obtained in 85% yield with 55% ee.

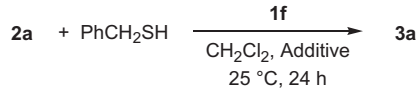
Table 2
Solvent screen for thio-Michael addition of benzyl mercaptan with **2a**[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	DMSO	85	0
2	MeOH	75	0
3	AcOEt	37	14
4	MeCN	37	35
5	THF	53	33
6	1,4-Dioxane	44	34
7	Et_2O	11	3
8	Toluene	Trace	-
9	H_2O	71	7
10	CH_2Cl_2	17	45
11	CH_2Cl_2/DMSO (1:1)	83	11
12	CH_2Cl_2/DMSO (2:1)	82	17
13	CH_2Cl_2/DMSO (4:1)	69	35
14	CH_2Cl_2/DMSO (9:1)	59	47

[a] The reaction was carried out with **2a** (0.5 mmol), benzyl mercaptan (0.55 mmol), and **1f** (0.1 mmol) in a solvent (1 mL) at 25 °C for 24 h.
[b] Isolated yield based on **2a**.
[c] Determined by chiral HPLC analysis.

Table 3
Optimization of the reaction conditions using **1f**[a]

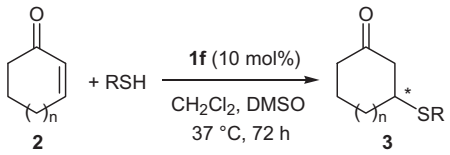


Entry	**1f** (mol %)	Additive (mol %)	Yield[b] (%)	ee[c] (%)
1	20	DMSO (100)	28	56
2	20	Diphenylsulfoxide (100)	24	55
3	20	Dimethylsulfone (100)	25	38
4	20	MeOH (100)	27	47
5	20	H_2O (100)	15	51
6	20	Triethylamine (100)	90	4
7	20	DMSO (50)	23	59
8	20	DMSO (20)	20	60
9[d]	20	DMSO (50)	53	60
10[d,e]	20	DMSO (50)	83	55
11[d,e]	10	DMSO (50)	85	55
12[d,e]	3	DMSO (50)	61	55

[a] Unless otherwise mentioned, the reaction was carried out with **2a** (0.5 mmol), benzyl mercaptan (0.55 mmol), **1f**, and an additive in dichloromethane (1 mL) at 25 °C for 24 h.
[b] Isolated yield based **2a**.
[c] Determined by chiral HPLC analysis.
[d] The reaction was carried out for 72 h.
[e] The reaction was carried out at 37 °C.

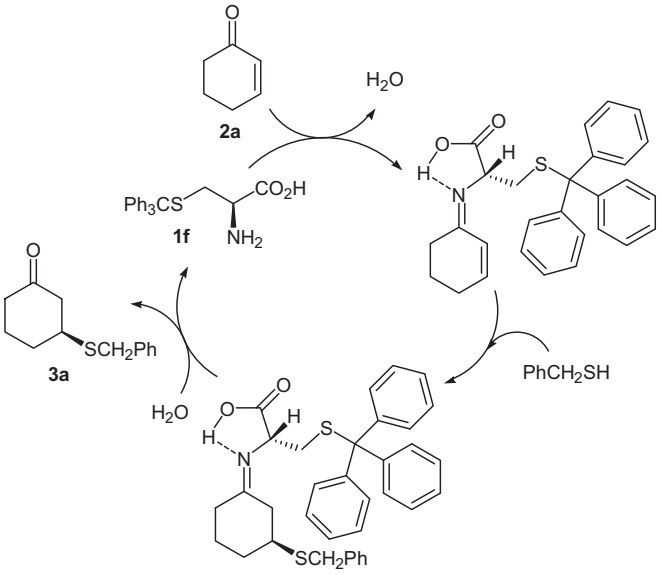
Then the thio-Michael addition of various arylmethyl mercaptans to cyclic enones was carried out in the presence of catalyst **1f** (Table 4). By carrying out the reaction of **2a** with benzyl mercaptan at 25 °C for seven days, the Michael adduct **3a** was obtained in 75% yield with a slightly better selectivity (58% ee) (Table 4, entry 2). 2-Cyclohepten-1-one (**2b**) provided a Michael adduct **3b** in good yields (81–82%), although a relatively lower enantioselectivity was observed (23–30% ee) (Table 4, entries 3 and 4). Unfortunately, the reaction of 2-cyclopenten-1-one (**2c**) was very slow even at 37 °C (Table 4, entry 5).[7,9] As for a Michael donor, it was found that an electron-deficient mercaptan gave lower enantioselectivity. For example, the reaction of **2a** with 4-chlorophenylmethyl mercaptan afforded a Michael adduct **3d** with 27% ee, while 4-methoxyphenylmethyl mercaptan afforded **3e** with 50% ee (Table 4, entries 6 and 7). Likewise, diphenylmethyl mercaptan showed lower enantioselectivity than that of benzyl mercaptan

Table 4
Substrate scope[a]



Entry	Substrate	R	Yield[b] (%)	ee[c,d] (%)
1	**2a**, $n = 1$	$PhCH_2$	**3a**, 85	55, (*S*)
2[e]	**2a**	$PhCH_2$	**3a**, 75	58, (*S*)
3	**2b**, $n = 2$	$PhCH_2$	**3b**, 81	23, (*S*)
4[e]	**2b**	$PhCH_2$	**3b**, 82	30, (*S*)
5	**2c**, $n = 0$	$PhCH_2$	**3c**, 44	24, (*S*)
6	**2a**	4-$ClC_6H_4CH_2$	**3d**, 81	27
7	**2a**	4-$MeOC_6H_4CH_2$	**3e**, 81	50
8	**2a**	Ph_2CH	**3f**, 86	39
9	**2a**	Ph_3C	**3g**, 69	8

[a] Unless otherwise mentioned, the reaction was carried out with **2** (0.5 mmol), mercaptan (0.55 mmol), DMSO (0.25 mmol), and **1f** (0.05 mmol) in dichloromethane (1 mL) at 37 °C for 72 h.
[b] Isolated yield based on **2**.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of **3a–c** was determined by comparison of the optical rotation with that of the literature.[4d,4e]
[e] The reaction was carried out at 25 °C for 7 days.



Scheme 2. Plausible reaction mechanism.

and better selectivity than that of triphenylmethyl mercaptan (Table 4, entries 8 and 9).

A plausible reaction mechanism for the thio-Michael addition of benzyl mercaptan with **2a** using the catalyst **1f** is depicted in Scheme 2.[7,11] The primary amino acid catalyst **1f** reacted with **2a** to give an α,β-unsaturated imine. Although (*E*)- and (*Z*)-stereoisomers can be formed, a relatively bulky methylene group comes to the less-hindered side rather than the vinyl group. The carboxyl group coordinates with the nitrogen atom of imine by hydrogen bonding to reduce the electron density of the β-carbon and to hold the side chain of the amino acid on the *Re*-face of the imine. Therefore, benzyl mercaptan attacks from the *Si*-face of the imine to give (*S*)-Michael adduct **3a** predominantly.

In summary, we found that a simple and commercially available primary amino acid, *S*-triphenylmethyl L-cysteine (**1f**), promoted the thio-Michael addition of arylmethyl mercaptans to cyclic enones with fair to high enantioselectivity. To the best of our knowledge, this is the most successful report among the reported organocatalytic asymmetric thio-Michael additions of benzyl mercaptan to cyclic enones.

Acknowledgment

This work was partly supported by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) from the Ministry of Education, Culture, Sports, Science and technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.089.

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