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Organocatalytic Enantioselective Decarboxylative Addition of Malonic Half Thioesters to Imines

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This article is dedicated to the memory of Professor Yoshihiko Ito of the Kyoto University.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

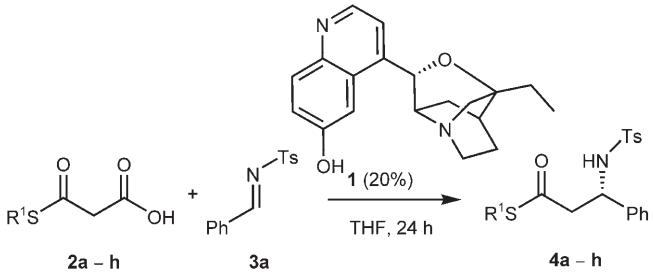
Abstract: We describe a biomimetic organocatalytic enantioselective decarboxylative addition of malonic acid half thioesters to imines. This simple protocol makes use of readily available *Cinchona*-derived organocatalysts and nucleophiles at the carboxylate oxidation state. The resulting β-amino thioesters, being attractive precursors for the preparation of optically active β-amino acids, are formed in good yields and in up to 79% *ee*. As suggested by several mechanistic insights the desired products are formed *via* initial formation of a thioester acetate enolate *via* decarboxylation of the malonic acid half thioester, followed by addition to the imine.

Keywords: β-amino acids; asymmetric catalysis; imines; Mannich reaction; organic catalysis

Recently, the metal-assisted direct aldol reaction, that is, the *in situ* formation of enolates and their involvement into a catalytic process, has gained sustained interest.[1a] The majority of this research focuses on the use of specific reactive ketone- or aldehyde-based nucleophiles. As a consequence, subsequent oxidation of the α-functionalized carbonyl compounds is required in order to obtain α-functionalized carboxylate compounds. Therefore it is desirable to develop processes using nucleophiles at the carboxylate oxidation state and as a result of this demand a few examples employing metal-based catalysts or promoters based on such system have been reported.[1b–g] However, the catalytic generation of an ester enolate is not a trivial task, due to the high pK_a value of the α-protons in the parent compound.[2] Inspired by naturally occurring enzymatic polyketide biosynthesis, proceeding through the decarboxylative generation of thioester enolates, Shair and co-workers used malonic acid half thioesters as thioester enolate intermediates in a copper-catalyzed decarboxylative aldol reaction.[3] Indeed, these thioesters are very attractive candidates for the generation of an ester enolate equivalent under very mild reaction conditions, due to the intrinsic driving force connected with the loss of CO_2, and the stabilizing effect of the sulfur moiety on the resulting enolate.[3] In order to avoid the use of metal salts as catalysts in this biomimetic process, an organocatalytic approach would be highly attractive. To the best of our knowledge there are no reports describing the use of chiral organocatalysts in such systems. Herein we would like to present a straightforward organocatalytic enantioselective decarboxylative addition of malonic acid half thioesters to imines (Mannich reaction) resulting in optically active β-amino thioesters which are obvious precursors of important β-amino acids.[4]

At the outset of this study initial attempts were performed using simple achiral organic bases as catalysts and we were pleased to find that the reaction could be catalyzed by simple organic bases such as DABCO, imidazole and DBU. For example, the reaction of malonic acid half thioester **2a** with *N*-Ts imine **3a** in toluene in the presence of 20 mol% DABCO led to good conversion (80%) of the imine after 24 h and the formation of the desired protected β-amino thioester **4a**. A screening (see Supporting information) of chiral catalysts derived from *Cinchona* alkaloids[5] and of the reaction conditions revealed that the use of 20 mol% **1**[6] as catalyst in THF in the reaction of malonic acid half thioester **2a** with imine **3a**[7] gave the best results, in terms of enantioselectivity[8] and yields.[9] We then proceeded to evaluate catalyst **1** in the decarboxylative addition to imine **3a** using a representative selection of malonic acid half thioesters **2a–h**. As shown in Table 1, the resulting products

Table 1. Asymmetric addition of malonic acid half thioesters **2a–h** to imine **3a** catalyzed by **1**.



Entry[a]	Thioester	R^1	Product	Yield [%]	*ee*[b] [%]
1	**2a**	C_6H_5	**4a**	83	48
2	**2b**	*o*-Me-C_6H_4	**4b**	75	24
3	**2c**	*p*-*t*Bu-C_6H_4	**4c**	40	21
4	**2d**	*p*-MeO-C_6H_4	**4d**	70	59
5[c]	**2e**	*p*-Cl-C_6H_4	**4e**	85	60 (67[d])
6	**2f**	$C_6H_5CH_2CH_2$	**4f**	72	15
7	**2g**	*n*-Bu	**4g**	69	31
8	**2h**	*i*-Pr	**4h**	75	4

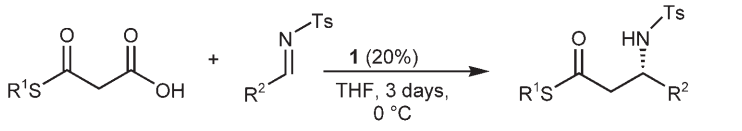
[a] The reactions were carried out at 20 °C using 0.2 mmol of **2**, 0.1 mmol of **3** and 0.02 mmol of catalyst **1** in THF (1 mL).
[b] The enantiomeric excess was determined by chiral HPLC.
[c] The reaction was carried out using ethyl acetate as solvent.
[d] After recrystallisation.

4a–h were obtained in moderate to good isolated yields within 24 h at room temperature using malonic acid half thioesters bearing both aromatic (entries 1–5) and aliphatic (entries 6–8) substituents at sulfur.

With the aim at accessing different β-amino thioesters using this transformation, malonic acid half thioesters **2d** and **2e** were evaluated as carboxylate enolate surrogates in the addition to several *N*-Ts imines **3a–f** (Table 2).

Moderate[10] to good yields were obtained running the reaction at 0 °C for 3 days using 20 mol% catalyst **1**. Under these conditions protected β-amino thioest-

Table 2. Asymmetric addition of malonic acid half thioesters **2d** and **e** to imines **3a–f**.[a]



2d R^1 = *p*-$OMeC_6H_4$
2e R^1 = *p*-ClC_6H_4

3a – f

4d, 5b – f R^1 = *p*-$OMeC_6H_4$
4e, 6b – e R^1 = *p*-ClC_6H_4

Entry	Thioester	Imine	R^2	Product	Yield [%]	ee[b] [%]
1	**2d**	**3a**	C_6H_5	**4d**	61	69
2	**2d**	**3b**	*p*-MeO-C_6H_4	**5b**	52	68
3	**2d**	**3c**	1-naphthyl	**5c**	76	64
4	**2d**	**3d**	$C_6H_5CH_2CH_2$	**5d**	42	79
5	**2d**	**3e**	*o*-Br-C_6H_4	**5e**	66	38
6[c]	**2d**	**3f**	*c*-C_6H_{11}	**5f**	41	60
7	**2e**	**3a**	C_6H_5	**4e**	83	63
8	**2e**	**3b**	*p*-MeO-C_6H_4	**6b**	55	65
9	**2e**	**3c**	1-naphthyl	**6c**	84	51
10	**2e**	**3d**	$C_6H_5CH_2CH_2$	**6d**	47	73
11	**2e**	**3e**	*o*-Br-C_6H_4	**6e**	68	21

[a] The reactions were carried out at 0 °C using 0.2 mmol of **2**, 0.1 mmol of **3** and 0.02 mmol of catalyst **1** in THF (0.5 mL).
[b] The enantiomeric excess was determined by chiral HPLC.
[c] Reaction performed at 20 °C.

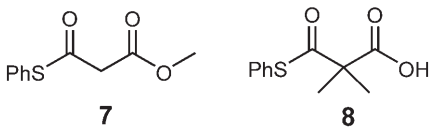


Figure 1. Structures of compounds **7** and **8**.

ers **5** and **6** were obtained with enantiomeric excesses up to 79% *ee*.

To shed light on the paths involved in this decarboxylative addition, some illustrative experiments were carried out.[11] The malonic acid half thioester **2a** was found to undergo decarboxylation in the presence of catalyst **1** forming *S*-phenyl thioacetate.[12] When methyl thioester malonate **7** was used as the substrate (Figure 1), starting materials and only slow and sluggish addition of **7** to imine **3a** in presence of **1** could be observed after 24 h reaction, supporting the crucial role of the decarboxylation for the occurrence of the reaction. Furthermore, using malonic acid half thioester **8** (Figure 1) in the reaction with imine **3a** in the presence of catalyst **1** resulted in decarboxylation of **8** but no addition product was observed. Probably, the high steric hindrance in malonic acid half thioester **8** prevents the formation of the adduct.

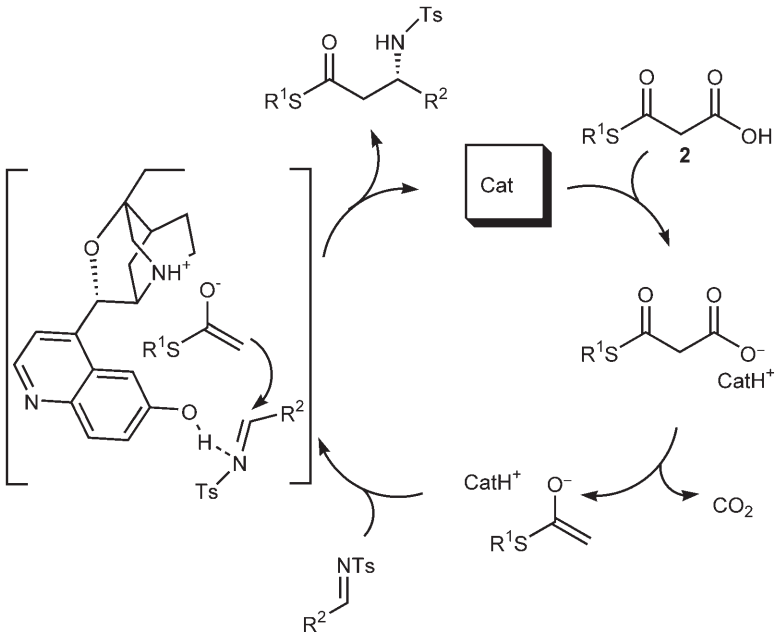
These experimental observations are compatible with the mechanistic proposal depicted in Scheme 1 in which the catalyst deprotonates the malonic acid half thioester **2** and the resulting carboxylate undergoes decarboxylation forming a thioacetate enolate. This, being in close proximity to the catalyst, as an ion-pair, reacts with the imine forming the product *N*-Ts β-amino thioester **3**.[13] As the initial screening of catalysts showed the importance of the acidic hydroxy group for the reaction efficiency we can speculate that the imines could be to some extent activated by a hydrogen bonding from the catalyst and thus both the electrophile and the nucleophile are influenced by the chiral environment generated by the catalyst.

In summary, we provide a biomimetic organocatalytic enantioselective decarboxylative addition of malonic acid half thioesters to imines. This simple protocol makes use of easily available *Cinchona*-derived organocatalysts and nucleophiles at the carboxylate oxidation state. The resulting optically active β-amino thioesters, attractive precursors for the preparation of optically active β-amino acids, are formed in good yields in up to 79% *ee*. A broader use of this novel organocatalytic protocol is a current topic in our laboratory.

Experimental Section

(*S*)-*S*-Phenyl 3-Phenyl-3-(tosylamino)propanethioate (4a)

To a solution of imine **3a**[14] (0.1 mmol, 26.0 mg) and catalyst **1**[6] (0.02 mmol, 6.2 mg) in THF (1.0 mL) was added malonic acid half thioester **2a**[15] (0.2 mmol, 39.2 mg). The reaction mixture was stirred at the temperature and the time stated, without any precaution of excluding moisture or air, after which **4a** was obtained through purification of the reaction mixture by chromatography on silica gel (EtOAc/*n*-hexane, 1:8) as a white solid; yield: 33.0 mg (83%); mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H); 2.98 (dd, 1H,



Scheme 1. Proposed mechanism for the asymmetric decarboxylative addition of malonic acid half thioester to imines.

$J=6.3$, 15.6 Hz), 3.10 (dd, 1H, $J=6.1$, 15.6 Hz), 4.70 (m, 1H), 5.56 (d, 1H, $J=7.6$ Hz), 6.96–7.20 (m, 9H), 7.24–7.38 (m, 3H), 7.47–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.7$, 49.7, 55.2, 126.7, 127.0, 127.3, 128.1, 128.8, 129.4, 129.7, 129.9, 134.5, 137.4, 139.1, 143.5, 195.7; Chiral HPLC analysis (Chiralpak OD, 90:10 *n*-hexane:*i*-PrOH, 0.75 mL min^{-1}, $\lambda=254$ nm) indicated 48% *ee*, t_R (minor) = 32.5 min, t_R (major) = 37.7 min; $[\alpha]_D^{20}$: 13.7 (*c* 1.1, EtOAc); HR-MS: $m/z=411.0960$, calcd. for $C_{22}H_{21}NO_3S_2$: 411.0963.

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[2] As a result most of the developed procedures providing α-functionalized carboxylates rely on the use of preformed silyl ketene acetals or acid chlorides. Alternatively, the ester enolate can benefit by a second anion-stabilising group (e.g., malonates) present in the product.

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[7] Use of imines with other protecting groups was found to give unsatisfactory results.

[8] The *ee* was found to be constant during the progress of the reaction.

[9] The desired *N*-Ts β-amino acids could be obtained by a facile hydrolysis, following a literature procedure: C. Fehr, N. Chaptal-Gradoz, J. Galindo, *Chem. Eur. J.* **2002**, *8*, 853–858. For example, treatment of **4a** with LiOH and H_2O_2 in H_2O/EtOH gave the corresponding *N*-Ts β-amino acid in 82% yield {$[\alpha]_D^{25}$: −17.0 (*c* 1.3, MeOH)}; [lit. 92% *ee* of the (*S*)-isomer; $[\alpha]_D^{25}$: −33.1 (*c* 1.0, $CHCl_3$), S. A. Sergeyev, M. Hesse, *Helv. Chim. Acta* **2002**, *85*, 161–167].

[10] The moderate yields observed in some cases can be ascribed to the low reaction rate observed for these reactions. It seems unlikely that competing formation of *ca.* 10–30% *S*-phenyl thioacetate (see note [13]) might influence the yields of the addition products since the malonic acid half thioesters are used in 200 mol%.

[11] No reaction could be observed between substrate **2a** and imine **3a** in the absence of catalyst.

[12] Using *S*-phenyl thioacetate as substrate resulted in no reaction with imine **2a** in the presence of **1**.

[13] The enolate can also be quenched by the protonated catalyst forming a thioacetate. In fact, this thioacetate is usually formed in 10–30% indicating a competitive reaction between the thioacetate enolate with the imine or the protonated catalyst. Increasing the amount of imine to 300 mol%, resulted in minor formation of thioacetate.

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