Organocatalysis

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Mimicry of Polyketide Synthases—Enantioselective 1,4-Addition Reactions of Malonic Acid Half-Thioesters to Nitroolefins**

*Jana Lubkoll and Helma Wennemers**

Thioesters are versatile building blocks that allow for a wide range of subsequent transformations into, for example, amides, aldehydes, α-ketoalkynes, and ketones.[1] A straightforward method for the introduction of thioesters is the addition of thioester enolates to electrophiles. In organic synthesis, thioester enolates are typically generated by reaction of the thioester with a metal-based Lewis acid.[2] In contrast, nature does not rely on metal ions for the generation of thioester enolates. Instead, malonic acid half-thioesters (MAHTs) serve as thioester enolate equivalents and are used in the biosynthesis of fatty acids and polyketides in all kingdoms of life.[3] The activation and reaction of MAHTs is achieved by polyketide synthases (PKSs), which lack metal ions and have in common the amino acids cysteine (Cys), histidine (His), and asparagine (Asn; or another histidine) in their active sites.[3,4] Within the catalytic triad, the His-Asn motive is responsible for activating the CoA-bound deprotonated MAHT that reacts upon decarboxylation with a second Cys-bound thioester (Figure 1). This inspired us to

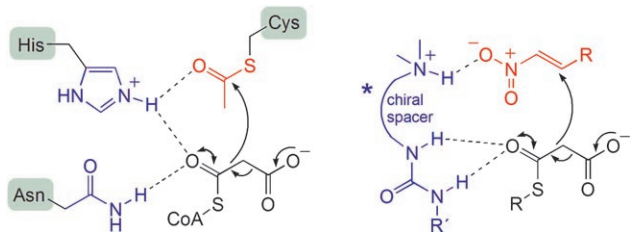

Figure 1. Left: Activation of MAHT in the active site of polyketide synthases (adapted from reference [4b]); right: schematic representation of the catalyst design.

address the question of whether metal-free organocatalysts can catalyze addition reactions of MAHTs to electrophiles.[5–7]

Herein we report details of our discovery of the first enantioselective MAHT addition reactions catalyzed in the absence of metal ions.[8] We show that urea derivatives of cinchona alkaloids catalyze the conjugate addition of MAHTs to nitroolefins under mild reaction conditions. Furthermore, we demonstrate that the resulting γ-nitrothioesters can be readily converted into chiral γ-butyrolactams such as the antidepressant rolipram.

We started our investigations by examining the reactivity of MAHTs with nitrostyrene in the presence of different bases. Substoichiometric amounts (20 mol%) of tertiary amines (for example, NEt_3, Hünig's base, quinuclidine) or imidazole in THF led to the formation of the desired conjugate addition product, but in yields lower than 15%; the main product was decarboxylated MAHT. These initial experiments also showed that the stability of MAHTs depends largely on the solvent.[9,10] Decarboxylation occurs in polar protic solvents within hours, while the stability is significantly higher in, for example, CH_2Cl_2, THF, and other ethers. Thus, these initial trials revealed that there is a subtle balance between product formation and nonproductive decarboxylation, thus demonstrating that controling the reactivity of the MAHTs is a challenging task.

Since PKSs accomplish the activation of MAHTs by coordination through Asn and protonated His residues,[3,4] we speculated that bifunctionality within the catalyst structure would be the key to efficient catalysis. A basic site was envisioned to allow for deprotonation of the MAHT and, together with a second coordination site, for orienting the MAHT and the nitroolefin in a chiral environment (Figure 1). Since urea and thiourea functionalities are known to be excellent coordination sites for carbonyl moieties[11] we chose to use urea-functionalized cinchona alkaloids to evaluate our catalyst design. Cinchona alkaloid derivatives **1**–**8** (Scheme 1), which have previously been used as catalysts for a range of different reactions,[11,12] were prepared and their catalytic activity tested in the reaction of MAHT **9** with nitrostyrene as a first test substrate.

We were pleased to observe both catalyst turnover and enantioselectivity when compounds **1**–**8** were added to the reaction of MAHT **9** and nitrostyrene (Table 1). Epiquinine-urea **2** proved to be the most active and selective catalyst: Mixing a 2:1 mixture of MAHT **9** and nitrostyrene in THF with 20 mol% of **2** afforded the 1,4-addition product in 94% yield and 63% *ee* within 24 h (Table 1, entry 2).

Experiments with the other catalysts (Table 1, entries 1–8) demonstrated the importance of the relative configuration at C(8) and C(9) (**1**, Table 1, entry 1), the methoxyquinoline moiety (**4**, Table 1, entry 4), and an electron-poor urea substituent (**6** and **7**, Table 1, entries 6 and 7) for good selectivity. Replacement of the vinyl group of **2** with an ethyl group (**5**, Table 1, entry 5) had no effect on the enantioselectivity, but reduced the activity of the catalyst. The presence

[*] Dipl.-Chem. J. Lubkoll, Prof. Dr. H. Wennemers
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-0976
E-mail: helma.wennemers@unibas.ch

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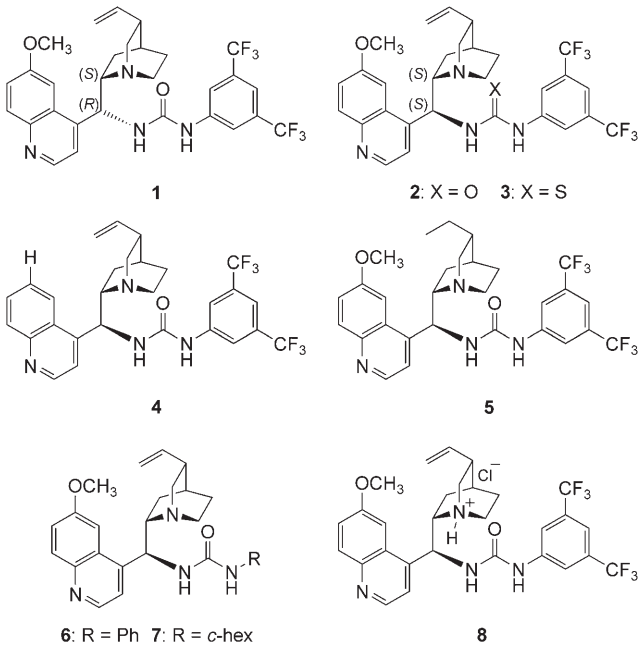
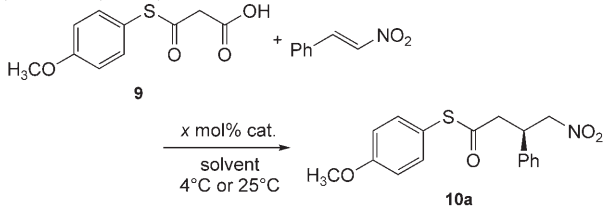
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Cinchona alkaloid derivatives **1**–**8**.

Table 1: Decarboxylative 1,4-addition reactions of MAHT **9** to nitrostyrene catalyzed by cinchona alkaloid derivatives **1**–**8**.[a]



Entry	Cat.	Mol %	*T* (°C)	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1**	20	25	THF	72	65	24
2	**2**	20	25	THF	24	94	63
3	**3**	20	25	THF	120	69	54
4	**4**	20	25	THF	24	52	47
5	**5**	20	25	THF	96	64	63
6	**6**	20	25	THF	24	47	58
7	**7**	20	25	THF	24	78	51
8	**8**	20	25	THF	120	no reaction[d]	
9	**2**	20	4	THF	120	87	66
10	**2**	10	25	THF	120	82	64
11	**2**	20	25	CH_2Cl_2	120	13	56
12	**2**	20	25	DME[e]	72	60	55
13	**2**	20	25	EtOAc	72	40	52
14	**2**	20	25	EVE	72	57	88

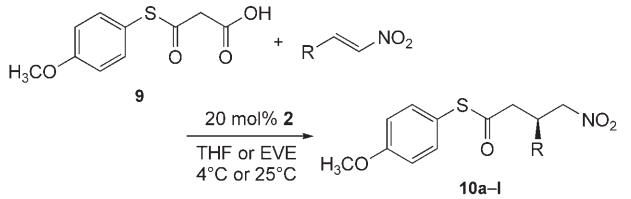
[a] Reactions were performed with 2 equiv of **9** except for the reaction in ethyl vinyl ether (EVE) where 1.2 equiv of **9** were used. [b] Yields of isolated products. [c] Determined by chiral-phase HPLC analysis. [d] Starting materials were recovered. [e] DME = 1,2-dimethoxyethane.

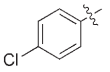
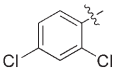
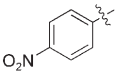
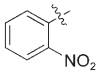
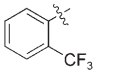
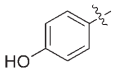
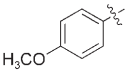
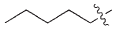
of a basic site proved crucial since protonation of the quinuclidine moiety resulted in complete loss of catalytic activity (**8**, Table 1, entry 8). In contrast to other reactions catalyzed by urea-based catalysts,[11,12] the urea moiety (**2**) proved superior to a thiourea (**3**), both in terms of activity and selectivity, thereby demonstrating that the degree of coordination is crucial for efficient catalysis.

In the case of epiquinine-urea **2**, lowering the catalyst loading to 10 mol % or performing the reaction at a lower reaction temperature (4 °C) necessitated longer reaction times but yielded the 1,4-addition product with comparable or slightly higher enantioselectivity (Table 1, entries 9 and 10). Of the solvents tested (Table 1, entries 11–14 and see the Supporting Information), THF proved best with respect to catalytic activity and selectivity. Higher selectivities were observed in ethyl vinyl ether (EVE).[13] Although the reaction is slower in EVE, the 1,4-addition product formed with 88 % *ee* (Table 1, entry 14).[14]

With these reaction parameters defined, the reaction of MAHT **9** with a variety of aromatic and aliphatic nitroolefins was explored. As shown in Table 2, the reaction catalyzed by **2** in THF generally gave high yields and enantioselectivities of

Table 2: Scope of the decarboxylative 1,4-addition reaction of MAHT **9** to nitroolefins.



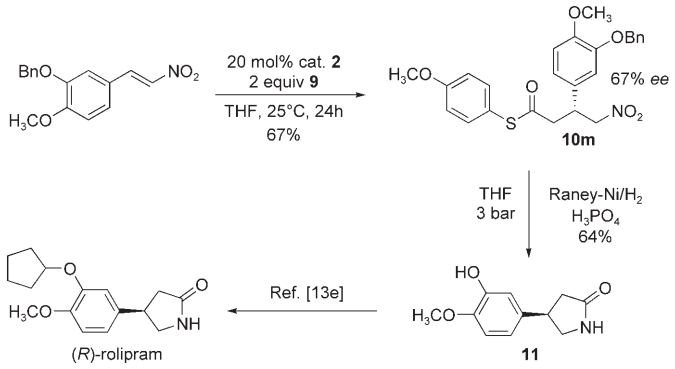
		THF[a]		EVE[b]	
Entry	R	Yield[c] [%]	*ee*[d] [%]	Yield[c] [%]	*ee*[d] [%]
1		94	63 (90)[e]	57	88 (99)[e]
2		96	61	41	79
3		92	56	63[f]	84[f]
4		94	55	61[f]	82[f]
5		99[f]	67[f]	51[f]	90[f]
6		89[f]	65[f]	36	86
7		93[f]	61[f]	13	73
8		78[f]	62[f] (97)[e]	nd[g]	nd[g]
9		78[f]	66[f]	97[f]	75[f]
10		71[f]	57[f]	43	79
11		16	63	23	78

[a] Reactions were performed at 25 °C for 24 h using 2 equiv of **9**. [b] Reactions were performed at 25 °C for 72 h using 1.2 equiv of **9**. [c] Yields of isolated products. [d] Determined by chiral-phase HPLC analysis. [e] Values in parentheses are after recrystallisation. [f] Reaction was performed at 4 °C. [g] Not determined because of reaction of the phenolic nitroolefin with EVE.

55–67% *ee*. Electron-deficient aromatic nitroolefins afforded products in yields of greater than 89% (Table 2, entries 2–6), while electron-rich aromatic nitroolefins gave products in slightly lower yields (Table 2, entries 8 and 9). Poor conversion was only observed in the case of the cyclohexylnitroolefin (Table 2, entry 11). It is noteworthy that no protection of the phenolic hydroxy group was necessary (Table 2, entry 8). In EVE, the products were obtained in lower yields but higher enantioselectivities of 73–90% *ee*. Enantiomeric enrichment of up to 99% *ee* was achieved by a single recrystallization of the solid 1,4-addition products (Table 2, entries 1 and 8).

Preliminary experiments have been performed to elucidate the mechanism of the reaction. The rate of the reaction decreases with increasing equivalents of MAHT **9**, which suggests that the coordination of MAHT to the urea is crucial for catalysis. Simple urea compounds did not mediate the reaction (starting materials could be recovered), further demonstrating the importance of bifunctionality for catalysis. More detailed mechanistic insights, for example, determination of whether C–C bond formation is followed or preceded by decarboxylation, and elucidation of the effect of EVE on the enantioselectivity await further studies.

γ-Nitrothioesters are versatile building blocks for further modifications. One example is the formation of γ-butyrolactams by reduction of the nitro group, followed by intramolecular cyclization. As an illustration, we have used the decarboxylative 1,4-addition reaction for the synthesis of the key intermediate **11** en route to the antidepressant rolipram (Scheme 2).[15]



Scheme 2. Synthesis of the antidepressant rolipram. Bn = benzyl.

In conclusion, our results demonstrate that organocatalysts enable the use of MAHTs as ester enolate equivalents in organic synthesis. Guided by natural PKSs, we have provided the first examples[8] of enantioselective MAHT addition reactions to nitroolefins, catalyzed by a synthetic metal-free organocatalyst. The 1,4-addition reactions occur under mild conditions, and tolerate both moisture and air. Combined with the versatility of thioesters, which hence allows for a range of subsequent transformations,[1] the results raise intriguing prospects for future applications of MAHTs in organic synthesis.

Experimental Section

General procedure for 1,4-addition reactions of MAHT **9** to nitroolefins: The nitroolefin (0.67 mmol, 1.0 equiv), **9** (303 mg, 1.34 mmol), and the catalyst (0.134 mmol, 20 mol%) were dissolved in THF (2.5 mL) in a capped vial. After stirring the reactions for 24 h, the mixture was purified by column chromatography on silica gel (gradient of pentane/ethyl acetate 5:1 to 3:1; in the case of the aliphatic compounds the gradient was pentane/ethyl acetate 10:1 to 5:1).

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