β-Amino Acids

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Stereoselective Metal-Free Synthesis of β-Amino Thioesters with Tertiary and Quaternary Stereogenic Centers**

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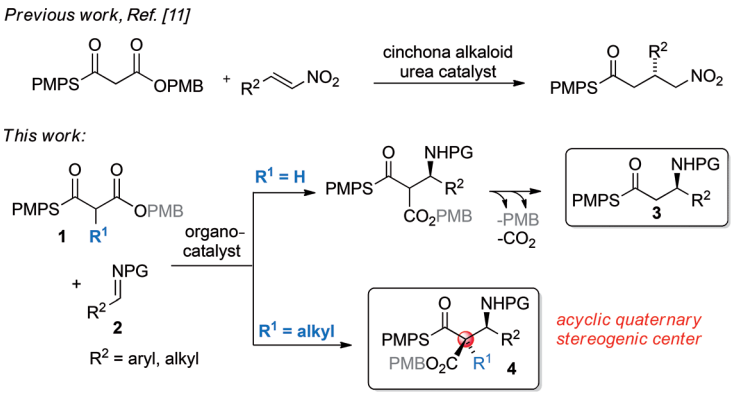
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *β-Amino thioesters are important natural building blocks for the synthesis of numerous bioactive molecules. An organocatalyzed Mannich reaction was developed which provides direct and highly stereoselective access to acyclic β^2- and $\beta^{2,3,3}$-amino thioesters with adjacent tertiary and quaternary stereocenters. Mechanistic studies showed that the stereochemical course of the reaction can be controlled by the choice of the substrates. The β-amino thioesters were further functionalized by, for example, stereoselective decarboxylation to access $\beta^{2,3}$-frameworks. In addition, the value of the β-amino thioesters was shown in coupling-reagent-free peptide synthesis.*



Scheme 1. Monothiomalonates (MTMs) as thioester enolate equivalents.

β-Amino thioesters are used by nature in the biosynthesis of a multitude of biologically active compounds.[1] As activated derivatives of β-amino acids, they are also attractive building blocks in organic synthesis and foldamer research.[2] Their use has, however, been limited since effective stereoselective syntheses are still rare.[3–6] Particularly interesting but, because of steric restraints, very challenging and not yet achieved, is the stereoselective synthesis of β-amino thioesters bearing an all-carbon quaternary stereogenic center.[7]

Catalytic asymmetric transformations of thioester enolate equivalents with imines are an attractive, direct way to generate β-amino thioesters.[3–6] However, the formation of thioester enolates under mild conditions is challenging because of the low acidity of the α-protons paired with the reactivity of thioesters towards nucleophiles.[8,9] Nature's thioester enolate equivalents, malonic acid half thioesters (MAHTs), have been used in organocatalytic decarboxylative Mannich reactions.[3,4] MAHTs are, however, prone to decarboxylate without a concomitant C–C bond formation.[3,4,10] Mild, non-decarboxylative organocatalytic approaches were introduced by the research groups of Barbas and Coltart, and utilize activated electron-poor thioesters or soft enolization, respectively.[4,5] All of these advances allow for the stereoselective synthesis of β-amino thioesters bearing tertiary stereogenic centers; however, high catalyst loadings of ≥ 10 mol% and long reaction times of days are common.[3–6] In addition, none of these methods enabled the synthesis of β-amino thioesters with quaternary stereogenic centers.

Recently, our research group introduced monothiomalonates (MTMs) as thioester enolate equivalents.[11] These MAHT analogues bear an easily removable protecting group on the ester moiety, which provides for controlled nucleophilic reactivity and with the decarboxylation occurring only upon removal of the protecting group. Previous studies showed that MTMs allow for highly stereoselective 1,4-addition reactions with nitroolefins in the presence of catalytic amounts of cinchona alkaloid urea derivatives (Scheme 1, top).[11,12] Encouraged by these findings, we became interested whether MTMs could also be used for the synthesis of β-amino thioesters, by using imines as electrophiles (Scheme 1, bottom).

Herein we present highly stereoselective syntheses of β-amino thioesters that proceed under mild organocatalytic conditions. Even acyclic $\beta^{2,2,3}$-amino thioesters, bearing an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter, formed in excellent yields and stereoselectivities. Furthermore, we show the synthetic value of the β-amino thioesters in coupling-reagent-free peptide synthesis.

We started with addition reactions of unsubstituted MTMs ($R^1 = H$, Scheme 1) to imines using conditions that had been found to be optimal for the previously examined

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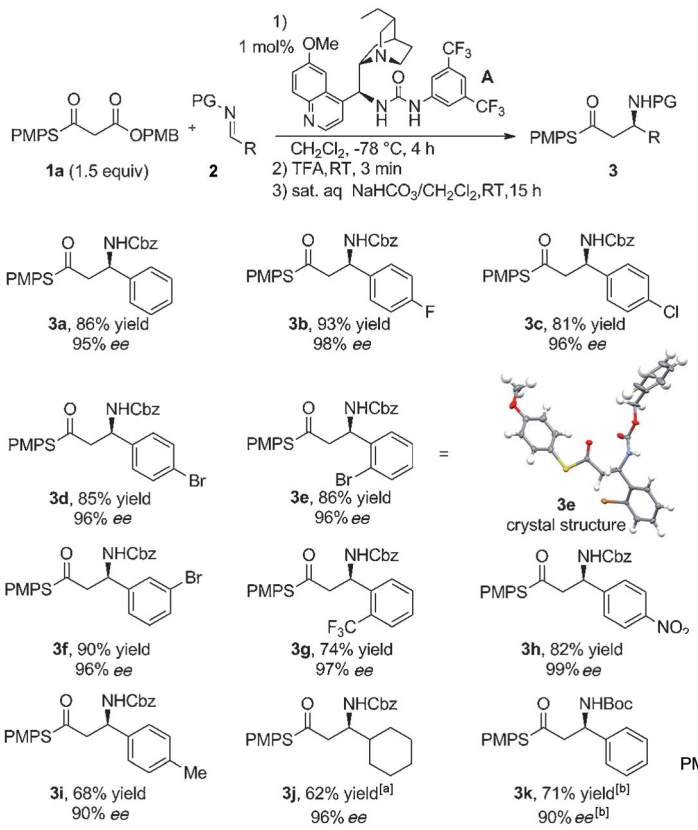
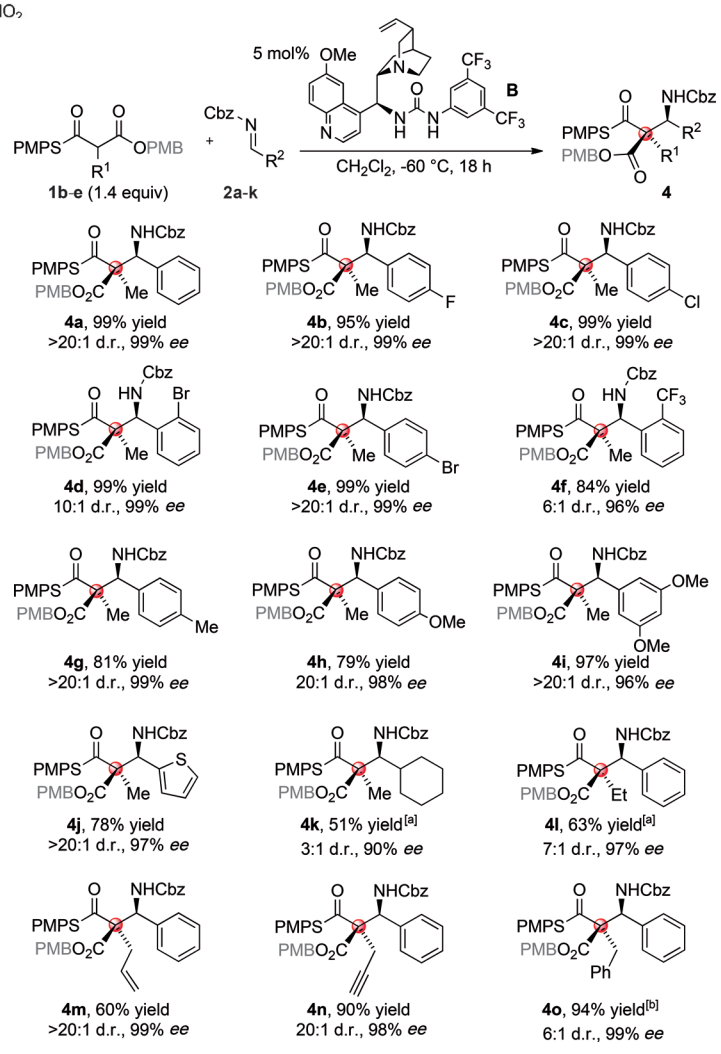


Scheme 2. Scope of Mannich reactions with unsubstituted MTM **1a**. Yields of isolated products; reactions were performed on a 0.2 mmol scale; *ee* values were determined by HPLC on a chiral stationary phase. [a] 5 mol% catalyst was used. [b] Determined after Boc (re)protection of the initially resulting free amine.

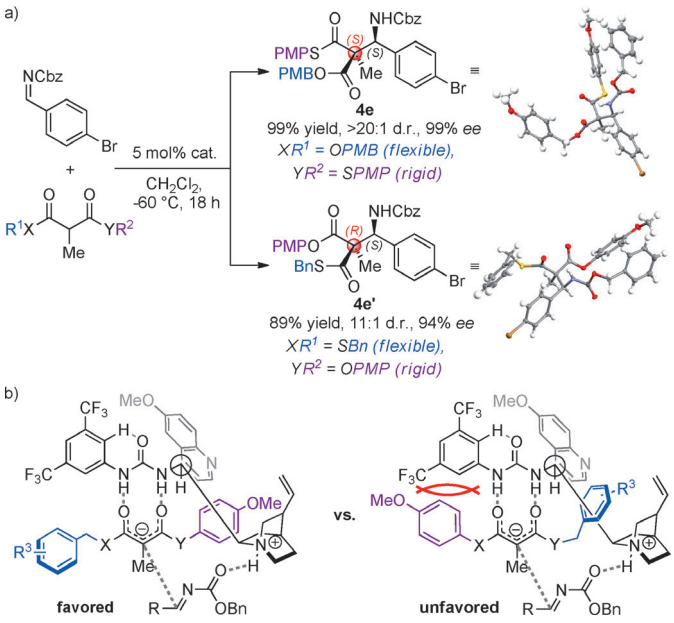
addition reactions with nitroolefins.[11] Cinchona alkaloid (thio)urea derivatives were, therefore, used as catalysts and MTM **1a** bearing a *p*-methoxyphenyl (PMP) thioester and a *p*-methoxybenzyl (PMB) oxoester group was used as the substrate. Variations in the catalyst, the nature of the protecting group (PG) of the imine, as well as other reaction parameters such as the solvent, stoichiometry, concentration, and catalyst loading showed that conditions similar to those used for reactions with nitroolefins are also ideal for reactions with Cbz- or Boc-protected imines (Cbz = carboxybenzyl, Boc = *tert*-butyloxycarbonyl) as electrophiles (see the Supporting Information for optimization and screening details). This versatility demonstrates that the reactivity of MTMs towards variations in the electrophile is general and robust. A large variety of different Cbz-protected imines **2** reacted readily with MTM **1a** in CH_2Cl_2 within 4 h at −78 °C in the presence of only 1 mol% of epidihydroquinine-urea **A** (Scheme 2). The desired β-amino thioesters **3a–j** were obtained in high yields and excellent enantioselectivities after removal of the PMB protecting group with trifluoroacetic acid (TFA) and base-induced decarboxylation. In comparison to previously reported methods for the synthesis of such β-amino thioesters,[3–6] the low catalyst loading of 1 mol%, the short reaction times, as well as the excellent enantioselectivities for a broad substrate range stand out.

Encouraged by these results, we next explored whether this method would also allow for the significantly more challenging reactions between α-substituted MTMs and imines to yield β-amino thioesters with a quaternary stereogenic center (Scheme 1, bottom). We therefore treated α-methyl-substituted MTM **1b** (R^1 = Me) with Cbz-protected imine **2a** (R^2 = Ph) under the developed conditions and were delighted to observe the formation of the desired Mannich product. Further optimization of the reaction parameters (see the Supporting Information) led to the formation of β-amino thioester **4a** in > 95% yield with excellent diastereoselectivity (> 20:1) and enantioselectivity (99% *ee*) in the presence of 5 mol% epiquinine-urea **B**.[13]

The substrate scope proved to be broad with respect to variations in both the imine **2** and the α-substituent of the MTM (Scheme 3). Mannich products **4a–o** were obtained in high yields, with excellent enantioselectivities of 90–99% *ee* and high diastereoselectivities of typically about 20:1 or greater. Even aromatic imines bearing substituents in the



Scheme 3. Scope of Mannich reactions with α-substituted MTMs **1b–e**. Yields of isolated products; reactions were performed on a 0.2 mmol scale; d.r. values were determined by ^{1}H NMR spectroscopy; *ee* values were determined by HPLC on a chiral stationary phase. [a] Reaction was performed at 0 °C. [b] 10 mol% catalyst, 0 °C, and 48 h were used.



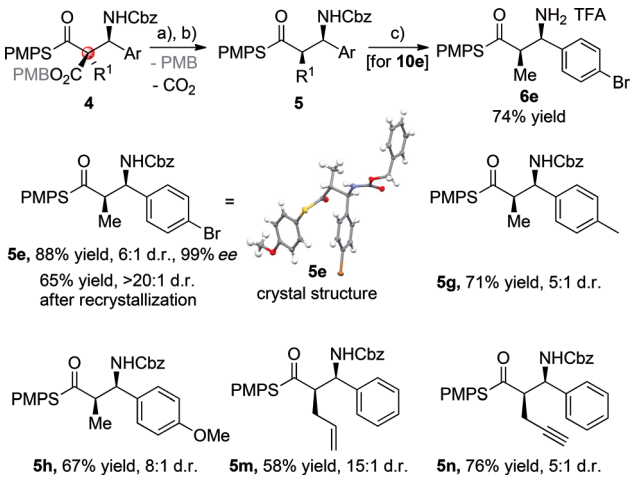
Scheme 4. a) Substrate-controlled diastereoselectivity and crystal structures of **4e** and **4e′**. b) Proposed transition state.

ortho position and aliphatic imines (**2d, 2f**, and **2k**), which are difficult substrates, gave diastereoselectivities of at least 3:1 and enantioselectivities of 99, 96, and 90% *ee*, respectively. MTMs bearing ethyl, benzyl, allyl, or propargyl substituents at the α-position were also tolerated well and the addition products **4l–4o** were obtained in high yields, with diastereoselectivities of 6:1–20:1 and enantioselectivities of 97–99% *ee*. Thus, in all of these addition reactions a remarkably high level of stereochemical differentiation between the two ester moieties of the MTM occurred. Current limitations are MTMs with larger α-substituents, such as Ph or *i*Pr as well as *N*-Boc-protected imines that did not react in the sterically challenging reaction with α-substituted MTMs or did so only sluggishly. The relative and absolute stereochemistry of the major Mannich products was unambiguously assigned by crystal structures of β-amino thioesters **3e** and **4e** (Schemes 2 and 4a).[14]

Next we investigated the reason for the high level of differentiation between the oxo- and thioester moieties in the stereochemical course of the reaction. Towards this goal we prepared a "reversed" MTM **1b′**, with a benzyl thioester (SBn) and a phenyl oxoester (OPMP), and allowed it to react under the same conditions as before with Cbz-protected imine **2e** (Scheme 4a). This reaction provided the diastereoisomeric addition product **4e′** with opposite stereochemistry to **4e** at the carbon atom bearing the ester moieties, as revealed by crystal-structure analysis (Scheme 4a). **4e′** was also obtained in high yield and stereoselectivity, thus demonstrating that diastereomeric products can be easily obtained with the same catalyst by changing the MTM substrate. The result also shows that it is not the oxo or thio moiety but the nature of the ester (flexible benzyl versus rigid phenyl)[15] that determines the stereochemical outcome of the reaction. A plausible transition state, therefore, involves coordination of the MTM to the urea moiety of the catalyst,[16] with the flexible benzyl ester on the same side as the 3,5-di(trifluoromethyl)phenyl group of the catalyst, and addition of the MTM enolate from the *Si* face in the case of **1b** (X = O, Y = S) to the *Re* face of the imine (Scheme 4b, left). This orientation is likely favored by stabilization through a hydrogen bond between the quinuclidine moiety and the carbamate protecting group. An alternative *Re-Re* face approach is less likely due to unfavorable steric interactions (Scheme 4b, right).

We then set out to evaluate the synthetic value of the β-amino thioesters and started by investigating the decarboxylation of representative examples of products **4**. Removal of the PMB protecting group using TFA followed by base-induced decarboxylation proceeded with good to excellent diastereoselectivities, thereby leading to *syn*-β[2,3]-amino thioesters **5e/g/h/m/n** (Scheme 5). It is noteworthy that this method provides products with higher selectivity than a direct decarboxylative approach using MAHTs and with opposite relative configuration (*syn* instead of *anti*).[3b,17] Furthermore, we found that Cbz cleavage is possible, despite the presence of a sulfur moiety, which sometimes impedes metal-catalyzed hydrogenations.[18] Acidolysis of **5e** with TFA, by using thioanisole as a nucleophilic promoter, led to the formation of **6e** in good yield and high purity (Scheme 5).

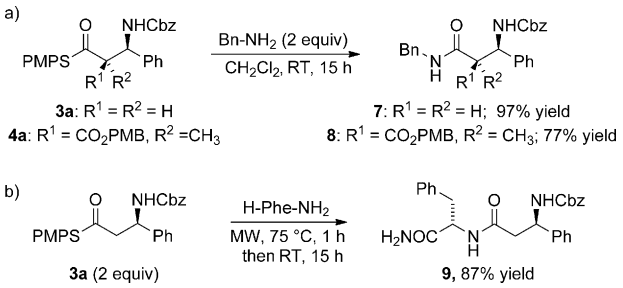
Finally, we explored the value of β-amino thioesters for peptide synthesis. Whereas thioesters are commonly used in nature and also for ligating two peptide or protein fragments by native chemical or Staudinger ligation, they are seldom used in peptide synthesis, since their formation is often difficult.[1,19,20] The incorporation of β-amino acids into a peptide by solution- or solid-phase peptide synthesis (SPPS) can be cumbersome and is generally achieved by the use of coupling reagents.[21] Despite their widespread use, coupling reagents are not atom-efficient and syntheses can be



Scheme 5. Decarboxylation of β-amino thioesters **4**. a) TFA/CH_2Cl_2 (1:1), 5 min; b) 10% Et_3N/CH_2Cl_2, 3 min; c) MeSPh in TFA, 3 h.

complicated when, for example, purification is difficult or side reactions occur. The presented β-amino thioesters are, therefore, attractive for enabling the incorporation of β-amino acids into peptides without coupling reagents.

To explore the value of the β-amino thioesters for coupling-reagent-free amidation reactions we initially treated **3a** with benzylamine (2 equiv) at room temperature and obtained the desired amide **7** in 97% yield (Scheme 6a). Even sterically hindered $\beta^{2,2,3}$-amino thioester **4a** was transformed to amide **8** under the same conditions in good yield (Scheme 6a). Transformations with less-reactive amines,

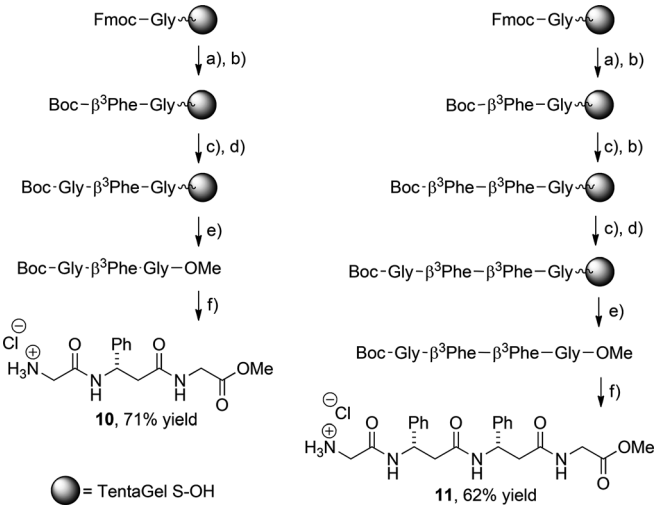


Scheme 6. Coupling-reagent-free amidation reactions. MW = microwaves.

such as the amino acid phenylalanine (Phe), were more difficult. Only traces of amide **9** were observed in the reaction of two equivalents of β^3-amino thioester **3a** in CH_2Cl_2 at room temperature. The use of pyridine as a solvent under microwave conditions significantly accelerated the reaction, and α,β-dipeptide **9** was isolated in 87% yield (Scheme 6b).

To our delight these coupling-reagent-free conditions were also applicable for SPPS with β^3-amino thioesters. *N*-Boc-protected β^3-amino thioester **3k** was readily incorporated into α,β-peptides **10** and **11**, which were isolated in 71% and 62% yields, respectively, by a simple precipitation without the need for purification by column chromatography (Scheme 7).

In summary we have developed a mild organocatalytic method for the synthesis of β-amino thioesters through Mannich reactions of MTMs. Not only β^3- but also $\beta^{2,2,3}$-amino thioesters, which contain an acyclic all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter, were for the first time obtained in excellent yields and remarkably high stereoselectivities. Mechanistic studies provided insight into the high stereochemical differentiation between the two ester moieties within the MTMs and showed that the stereochemistry can be controlled by the choice of the substrate. The functional groups within the β-amino thioesters were found to be orthogonal and can be selectively modified to provide, for example, access to *syn*-$\beta^{2,3}$-amino thioesters in high yields and stereoselectivities. Furthermore, we showed the synthetic value of β-amino thioesters as building blocks for coupling-reagent-free peptide synthesis. We are currently extending the scope of MTMs as thioester enolate equivalents and are performing further mechanistic studies.



Scheme 7. Solid-phase peptide synthesis (SPPS) with β-amino thioesters. a) 20% piperidine/DMF; b) Boc-β^3Phe-SPMP (**3k**), *i*Pr_2NEt, pyridine, 1 h MW at 75 °C, then 15 h at RT; c) 50% TFA/CH_2Cl_2; d) Boc-Gly-OH; HCTU, *i*Pr_2NEt, DMF; e) 10% Et_3N/MeOH; f) HCl in Et_2O (2 M). Fmoc = fluorenylmethoxycarbonyl, HCTU = N,N,N′,N′-tetramethyl-O-(6-chloro-1H-benzotriazol-1-yl)uronium hexafluorophosphate.

Experimental Section

Synthesis of Cbz-protected $\beta^{2,2,3}$-amino thioesters **4a–o**: The imines were prepared from the appropriate α-amido sulfone: An aqueous solution of Na_2CO_3 (10%, saturated with NaCl, 1 mL per mmol of α-amido sulfone) was added to a suspension of α-amido sulfone (1 equiv) in CH_2Cl_2 (0.1 M). The mixture was vigorously stirred for 15 h at room temperature. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 2.5 mL per mmol of sulfone). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting freshly prepared imine was then dissolved in dry CH_2Cl_2 (0.1 M), and MTM (1.4 equiv) was added. The reaction mixture was cooled to the temperature stated, and then the catalyst (5 mol%) added. The reaction mixture was stirred at the specified temperature for 18 h, followed by removal of all the volatiles at reduced pressure and purification by flash column chromatography on silica, using a mixture of CH_2Cl_2/methanol or EtOAc/*n*-pentane as eluents.

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[13] A catalyst loading of 1 mol% was sufficient to obtain the product in high yield and an enantioselectivity of 97% *ee*, although with lower diastereoselectivity (15:1) and reaction times of more than a day.

[14] The analytical data of the other addition products is in close analogy to those of **3e** and **4e**; see the Supporting Information.

[15] Experiments with MTMs without a combination of a benzyl and phenyl ester provided addition products with lower stereoselectivities.

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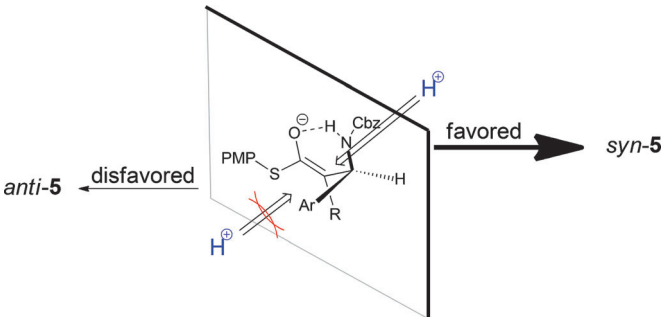
[17] The absolute configuration was unambiguously determined by a crystal structure of **5e**. A plausible rationale for the *syn* selectivity involves coordination of the NH-carbamate moiety to the thioester enolate, followed by protonation from the less-hindered side. In the case of **5e**, the *ee* value remained unchanged during decarboxylation to **4e**. HPLC chromatograms recorded on a chiral stationary phase under identical conditions as used for all other trans-configured compounds **5** show either single peaks or two peaks in a ratio of ≥93:7, thus suggesting that the enantiomeric integrity is either fully retained or only slightly eroded (see the Supporting Information)



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