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Organocatalytic Enantioselective Michael-Addition of Malonic Acid Half-Thioesters to β-Nitroolefins: From Mimicry of Polyketide Synthases to Scalable Synthesis of γ-Amino Acids

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Abstract: Highly enantioselective biomimetic Michael addition reactions of malonic acid half thioesters (MAHTs) to a variety of nitroolefins, affording the optically active γ-amino acid precursors, were developed by employing the *Cinchona*-based squaramides (up to >99% *ee*). Remarkably, this biomimetic process is enantioconvergent, a highly desirable feature of a catalytic asymmetric reaction, whereby *E*/*Z*-isomers of the nitroolefins afford the same product enantiomer. The synthetic utility of this organocatalytic protocol was also demonstrated in the formal synthesis of pharmaceutically important γ-amino acids such as baclofen. Moreover, a quantum chemical analysis of the catalyst-substrate complexes is shown to give a detailed and instrumental insight into the origin of the observed catalytic activity.

Keywords: γ-amino acids; biomimetic catalysis; *Cinchona*-based squaramide catalysts; malonic acid half thioesters (MAHTs); Michael addition; organocatalysis

Introduction

The direct generation of enolates or their equivalents for catalytic and stereoselective carbon-carbon bond formation reactions has been intensively investigated over the past decade. Both for metal-catalyzed and organocatalytic processes, however, the donor substrates are mostly limited to specific ketones or aldehydes. Use of donor substrates with the oxidation state of carboxylic acid derivatives remains a challenging task with very few successful reports[1] since the pK_a of the α-proton in carboxylic acid derivatives is much larger than that in ketones or aldehydes.[2] In contrast, in the biosynthesis of polyketides and fatty acids, nature freely uses the enzymatic activation of malonic acid half thioesters (MAHTs) to generate ester enolates or their equivalents that undergo the chain elongation step smoothly by the decarboxylative Claisen condensation.[3] Inspired by these biocatalytic processes, the groups of Shair[4] and Cozzi[5] reported independently on a Cu-catalyzed enantioselective thioester aldol reaction with MAHTs as direct thioester enolate donors. However, polyketide synthases do not possess metal ions, but only organic residues [cysteine, histidine and asparagines (or another histidine)] in their active sites. Shortly thereafter, Ricci[6] and Wennemers[7] independently demonstrated in their pioneering works that organocatalytic asymmetric transformations can also be accomplished with MAHTs *via* hydrogen bond catalysis using *Cinchona*-based organocatalysts such as β-isocupreidine and *Cinchona*-based (thio)ureas, respectively. Unfortunately, the catalytic activity and enantioselectivity achieved in their work were insufficient for synthetic use.

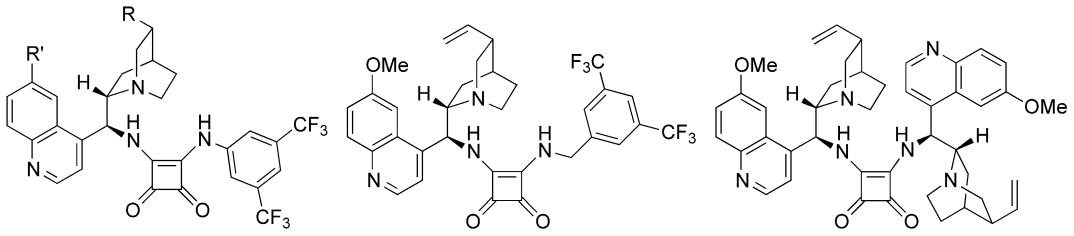


Figure 1. Squaramide-based bifunctional organocatalysts.

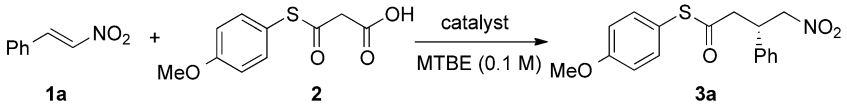
Quite recently, chiral squaramides[8] have been shown to serve as a more effective hydrogen bond donor than their thiourea analogues for a variety of enantioselective organocatalytic reactions, benefitting from the squaramide's characteristic dual hydrogen-bonding catalysis, due to the more accessible reaction site[8a,9] and fixed *anti/anti*-orientation[10–12] of the NH protons relative to the carbonyl groups. Moreover, the apparently higher Brønsted acidity of the NH protons of the squaramide with respect to those of thiourea allows the squaramide to activate the electrophile more efficiently.[13] Thus, we anticipated that squaramide-based bifunctional catalysts, such as **I–III** (Figure 1), would be more compatible for MAHT-associated asymmetric transformations.

We report herein the highly enantioselective and scalable organocatalytic Michael addition of MAHTs to nitroolefins using bifunctional squaramide-based organocatalysts, which allows a rapid access to optically pure γ-amino acids.[14] Remarkably, this biomimetic process was shown to be stereoconvergent, where *E*/*Z*-isomers of nitroolefins afford the same product enantiomer.

Results and Discussion

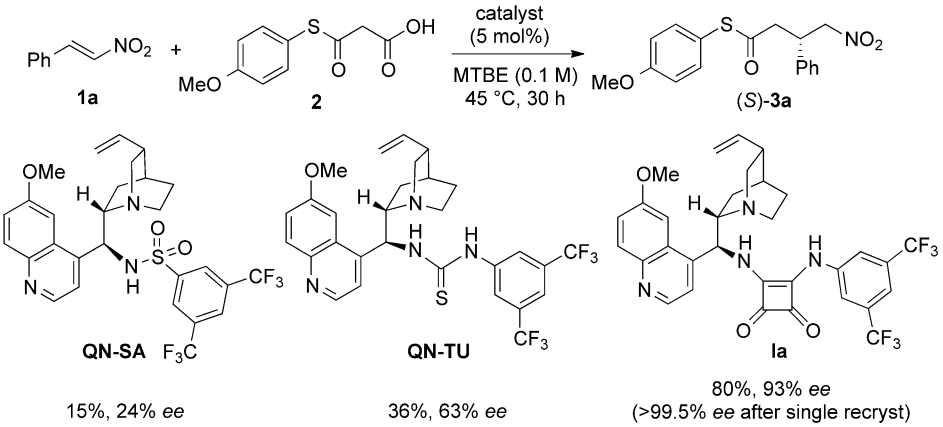
To assess the efficiency of different types of squaramide-based catalysts for the MAHT-associated asymmetric transformations, we initially examined the asymmetric Michael addition[15] of the MAHT **2** to *trans*-β-nitrostyrene (**1a**) as a model substrate in methyl *tert*-butyl ether (MTBE) at ambient temperature with the squaramide catalysts **I** (20 mol%).[16,17] Gratifyingly, as shown in Table 1, regardless of the substituent at the C-3 and C-6′ positions of alkaloids **Ia–c**, the Michael additions afforded the Michael adduct (*S*)-**3a**[18] in excellent yields with unprecedentedly high enantioselectivities (93% *ee*, entries 1–3).[19] However, a relatively long reaction time (72 h) was required for the completion of the reaction. A dramatic increase in the reactivity, without any erosion of the enantioselectivity, was achieved simply by increasing the reaction temperature. Thus, at 45 °C, the reaction was completed within 8 h to afford the product (*S*)-**3a** (93% *ee*, entry 4). At this temperature, a lower catalyst loading of up to 2 mol% still results in excellent catalytic activity and enantioselectivity

Table 1. Catalytic enantioselective Michael addition of MAHT **2** to *trans*-*β*-nitrostyrene (**1a**).[a]



Entry	Catalyst (mol%)	Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**Ia** (20)	20	72	96	93
2	**Ib** (20)	20	72	94	93
3	**Ic** (20)	20	72	89	93
4	**Ia** (20)	45	8	84	93
5	**Ia** (5)	45	30	80	93
6	**Ia** (2)	45	72	78	93
7	**II** (20)	20	72	48	77
8	**III** (20)	20	72	38	18

[a] Reactions were carried out with **1a** (0.2 mmol), 1.5 equiv. of MAHT **2** and catalysts (2–20 mol%) in MTBE (2 mL) at 20 °C or 45 °C.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC (see Supporting Information).



Scheme 1. Organocatalytic enantioselective Michael addition of MAHT **2** to *trans*-β-nitrostyrene.

(93% *ee*, entries 5 and 6). In contrast to these results, other types of squaramide catalysts **II** and **III** showed much inferior catalytic activity and enantioselectivity (entries 7 and 8), which might be due to the relatively lower acidity of the squaramide moiety than that of **I**.

The results described in Scheme 1 highlight the superior catalytic efficiency of the squaramide catalyst **Ia** relative to other H-bond donors, such as the thiourea analogue (**QN-TU**)[20] or the sulfonamide analogue (**QN-SA**).[21] Under the same reaction conditions [**1a** (1 mmol), **2** (1.5 equiv.), MTBE (10 mL), catalyst (5 mol%)], much better results were obtained with the squaramide catalyst **Ia** (93% *ee* and 80% yield) than with the thiourea catalyst **QN-TU** (63% *ee*, 36% yield) and the sulfonamide catalyst (24% *ee*, 15% yield).

The observed differences of catalytic activity of the sulfonamide **QN-SA**, the thiourea **QN-TU** and the squaramide **Ia** were in agreement with our quantum chemical analysis carried out by employing the density functional theory method (MPW1B95)[22] with the 6-311++G** basis set as implemented in the Gaussian 03 suite of programs.[23] Structures of the complexes **IV**, **V** and **VI** of *trans*-nitrostyrene **1a** with the sulfonamide, thiourea and squaramide catalysts, respectively, (modeled by substituting the NH-*epi*-alkaloid moiety by an NH–CH_3 to reduce computational efforts) were optimized using default criteria. The natural bond orbital (NBO) analyses[24] were then carried out to understand the nature of the activation of the β-carbon of **1a**. As shown in Figure 2, the hydrogen bonds in **VI** are shorter than those in **IV** and **V** (lengths: H-2–O-5 = 2.38 Å, H-2–O-3 = 2.32 Å for **IV**, H-4–O-7 = 2.20 Å, H-3–O-5 = 2.05 Å for **V**, H-4–O-7 = 2.26 Å, H-3–O-5 = 1.99 Å for **VI**). Moreover, the NBO charge at C-9 in **VI** (−0.086 e) was less negative than those of C-7 in **IV** (−0.105 e) and C-9 in **V** (−0.092 e), implying that the C-9 site in **VI** is more electrophilic than those of **IV** and **V**, which is consistent with the experimental observations in Scheme 1.

Having established that the squaramide catalyst **I** acts as a highly active and enantioselective catalyst, we undertook to explore the scope of the substrate under the optimized reaction conditions. All of the reactions were carried out in the presence of 5 mol% of the squaramide catalyst **Ia** at 45 °C in methyl *tert*-butyl ether (MTBE). As shown in Table 2, a variety of nitroolefins **1a**–**1j** bearing aryl, heteroaryl and alkyl groups at the β-position were smoothly converted into the desired Michael adducts **3a**–**3j** with excellent *ee* values (up to >99% *ee*).[25] To the best of our knowledge, this level of enantioselectivity is unprecedentedly high in biomimetic organocatalytic reactions in which MAHTs are utilized as the enolate precursors. Moreover, in most cases, a single recrystallization provides the enantiomerically pure form (> 99.5% *ee*) (from Et_2O). However, poor conversions were observed in the case of alkyl-substituted nitroolefins, perhaps due to their weak electrophilicity.

We also investigated the influence of the stereochemistry at the double bond of the nitroolefin. Remarkably, when we subjected both the isolated pure *E* or *Z*[26] isomers of β-nitrostyrene **1a** to our reaction conditions, the same (*S*)-enantiomer of the Michael adduct **3a** was obtained with the same *ee* value (entries 1 and 2 in Table 2, 93% *ee*). Similarly, *E*/*Z*-**1a** mixtures always gave the same result, and independent of their exact ratio, all of them furnished (*S*)-**3a** with 93% *ee* (Table 2, entry 3). Thus, this process is enantioconvergent, a highly desirable feature for a catalytic asymmetric reaction, where a mixture of stereoisomers affords only one product enantiomer.[27] Mechanistically, the *Z*-isomers of the β-nitroalkene are rapidly isomerized into the *E*-isomer in the presence of the squaramide catalysts **1**.[28]

The stereoconvergency of the reaction, the observed superior catalytic activity of the squaramide catalyst relative to that of the other H-donors examined in this study, and the retention of *ee* values at higher temperature strongly indicate that the strong

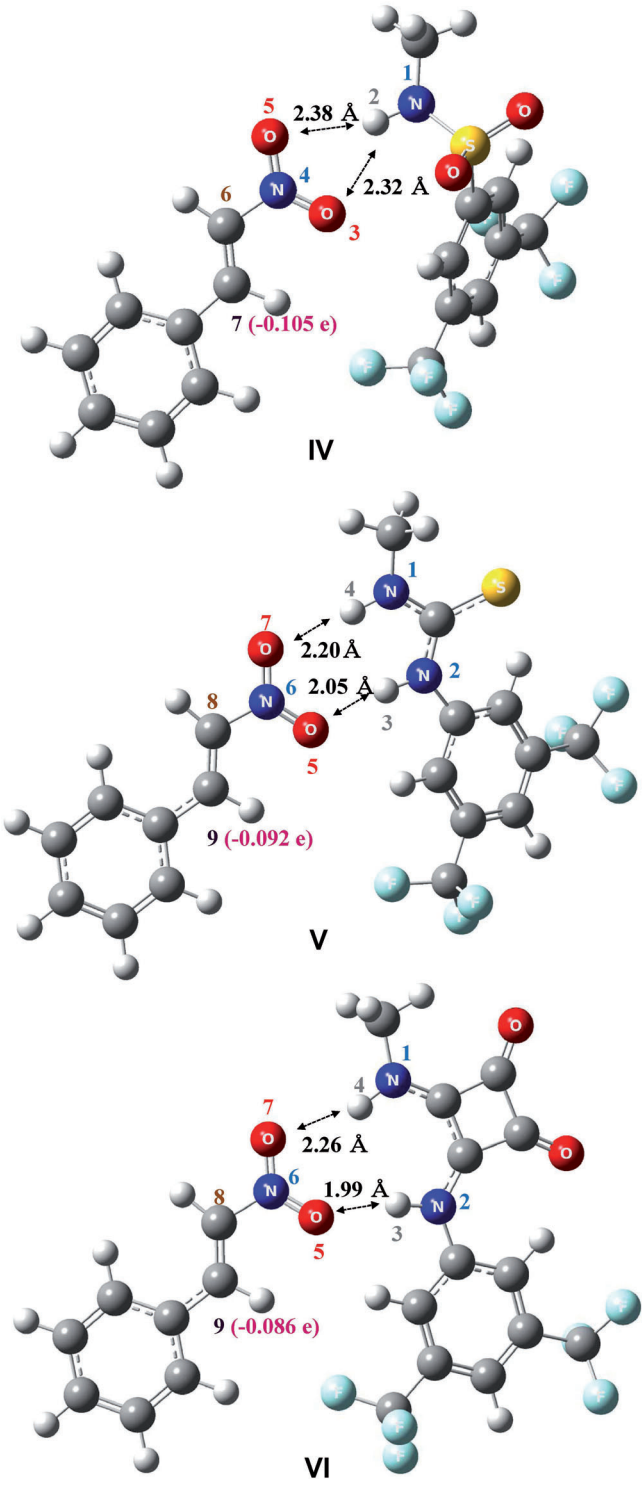


Figure 2. Calculated structures of **IV**, **V** and **VI**.

coordination of the nitroalkene to the squaramide moiety is crucial for catalysis.[29,30]

To illustrate the synthetic utility of our methodology, a short formal synthesis of pharmaceutically important γ-amino acids such as baclofen[31] was developed starting from *trans*-β-nitro-4-chlorostyrene (**1e**) (Scheme 2). The Michael addition of MAHT **2** to the nitroolefin **1e** proceeded smoothly on a 5-g scale of the substrate to afford the corresponding Michael adduct **3e** in high yield and excellent enantioselecitivity (82% yield and 91% *ee*). The reduction of the nitro group of **3e**, followed by intramolecular cyclization and recrystallization from Et_2O/hexane, affords enantiomerically pure γ-butyrolactam **4** (see the Supporting Information for details). Lactam **4** has already been transformed by hydrolysis[32] to (*S*)-(+)-baclofen·HCl salt[32,33]

Conclusions

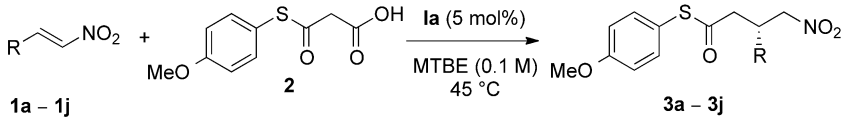
In summary, the *Cinchona*-based squaramides **I** were shown to act as remarkably effective catalysts for the biomimetic enantioselective Michael addition reactions of MAHTs to a variety of nitroolefins, affording optically active γ-amino acid precursors with up to >99% *ee*. Remarkably, this process was shown to proceed enantioconvergently. We also demonstrated the synthetic utility of our catalytic protocol in the formal synthesis of pharmaceutically important γ-amino acids, such as baclofen. Moreover, a quantum chemical analysis of the catalyst-substrate complexes is shown to give a detailed and instrumental insight into the origin of the observed catalytic activity. The more detailed mechanism of the reaction and the basis for enantioselectivity are currently under investigation and will be reported in due course.

Experimental Section

General Remarks

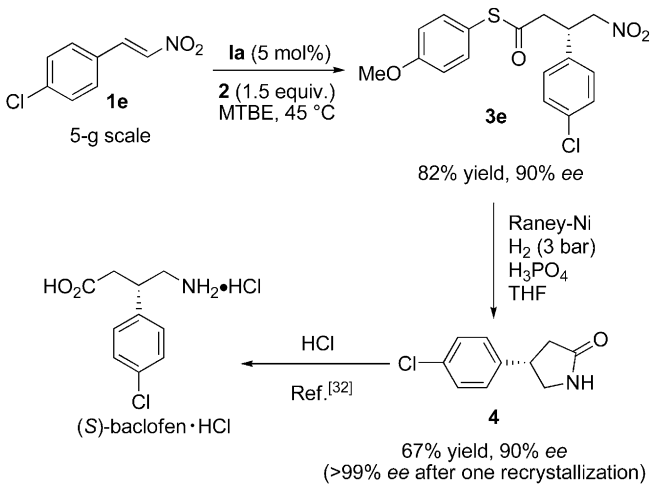
The organocatalysts examined in this study (**Ia**,[8g] **Ic**,[8g] **II**,[8a] **III**,[34] **QN-TU**[35] and **QN-SA**[21a]) were prepared starting from the corresponding 9-*epi*-amino-*Cinchona* alkaloids according to the literature procedures. MAHT was prepared according to the literature procedure reported by Shair et al.[36] (*Z*)-Nitrostyrene was prepared according to the literature procedure.[26] The chromatographic purification of the products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). Thin-layer chromatography was carried out on Merck silica gel 60F plates. HPLC analyses were performed on a Varian Pro Star Series instrument equipped with an isostatic pump using a CHIRALCEL OD-H Column (250×4.6 mm). The ^1H and ^{13}C NMR spectra were recorded on Varian 300 spectrometers. The IR spectra were obtained using a Bruker Vertex 70 spectrometer with MIRacle Micro ATR accessory. The HR-mass spectra were recorded on a Jeol JMS-700 M station. The melting points (mp) were determined on a Buchi B-540 melting point apparatus and are uncorrected. The optical rotation was measured on a Perkin–Elmer Polarimeter 343 plus. All chemicals used in this study were obtained from commercial sources and used without further purification.

Table 2. Enantioselective Michael addition of MAHT **2** to various nitrostyrenes **1a**-**1j**.[a]



Entry	R	Time [h]	Yield [%][b]	*ee* [%][c]
1	(*E*)-Ph (**1a**)	30	80 (96)[d]	93 (93)[d]
2[e]	(*Z*)-Ph (**1a**)	8	78	93
3[e]	(*E*)/(*Z*)-Ph (**1a**)	8	77	93
4	4-Me-C_6H_4 (**1b**)	34	81 (96)[d]	96 (96)[d]
5	4-MeO-C_6H_4 (**1c**)	34	80 (94)[d]	92 (92)[d]
6	4-F-C_6H_4 (**1d**)	25	82 (86)[d]	91 (91)[d]
7	4-Cl-C_6H_4 (**1e**)	22	80 (88)[d]	90 (90)[d]
8	4-Br-C_6H_4 (**1f**)	22	83 (86)[d]	91 (91)[d]
9	2-furyl (**1g**)	33	78 (88)[d]	88 (88)[d]
10	2-thienyl (**1h**)	24	79 (91)[d]	91 (91)[d]
11	*i*-Bu (**1i**)	60	22	92
12	cyclohexyl (**1j**)	60	15	>99

[a] Unless otherwise indicated, the reactions were carried out with **1** (0.2 mmol), 1.5 equiv. of MAHT **2** and catalyst **Ia** (5 mol%) in MTBE (2 mL) at 45 °C.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC (see Supporting Information).
[d] The values in parentheses were obtained from the reactions carried out using 20 mol% of **Ia** at room temperature for 3 days.
[e] For the *Z*- or *E*/*Z*- mixture, the reactions were performed at 45 °C using 20 mol% of **Ia**.



Scheme 2. Synthesis of (*S*)-baclofen.

Representative Procedure for Michael Addition Reactions

The nitrostyrene (**1a**, 30 mg, 0.2 mmol), MAHT **2** (68 mg, 0.3 mmol) and the catalyst (**Ia**, 6.3 mg, 0.01 mmol, 5 mol%) were dissolved in MTBE (2.0 mL) in a capped vial. After stirring at 45 °C for 30 h, the mixture was directly purified by column chromatography on silica gel (gradient of hexane/ethyl acetate, 8:1 to 4:1, in the case of the aliphatic compounds gradient of hexane/ethyl acetate, 20:1 to 8:1), affording the Michael adduct **3a**. The enantiomeric excesses were determined by chiral HPLC using a Daicel CHIRALCEL OD-H column.

Acknowledgements

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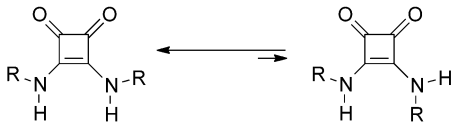

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[17] MAHTs with phenyl and benzyl substituents gave similar results (93% *ee* and 91% *ee*, respectively) to those obtained with MAHT **2**.

[18] Absolute configuration of **3a** was determined by comparison of the optical rotation value ($[\alpha]_D^{25}$: +30.0 (*c* 0.34, MeOH) of 4-phenyl-2-pyrrolidine (obtained by hydrogenation of **3a**) with the literature data. (lit. $[\alpha]_D^{25}$: +33.9 (*c* 0.89, MeOH) for *S*-enantiomer; A. I. Meyers, L. Snyder, *J. Org. Chem.* **1993**, *58*, 36–42; N. Langlois, N. Dahuron, H. Wang, *Tetrahedron* **1996**, *52*, 15117–15126; F. Felluga, V. Gombac, G. Pitacco, E. Valentin, *Tetrahedron: Asymmetry* **2005**, *16*, 1341–1345; J. Wang, W. Li, Y. Liu, Y. Chu, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, *12*, 1280–1283.

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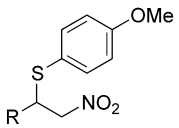
[25] Under the reaction conditions (5 mol% of catalyst loading and 45 °C), in the cases of R = aryl and heteroaryl, *ca.* 10–15% of the corresponding side product **5** was formed. However, in the case where R = alkyl, **5**



5

was obtained as the main product; see the Supporting Information.

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[28] We found that the *Z*-isomer of **1a** was rapidly isomerized to the thermodynamically more stable *E*-isomer in the presence of catalyst **I**.

[29] The retentionof the *ee* value at higher temperature was also observed in the enantioselective Michael addition of nitroalkanes to chalcones using squaramide-based organocatalysts; see: W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453.

[30] We envisioned that the chiral squaramide-based catalyst **VI** acts in a bifunctional fashion. The nitroalkene is fixed and activated by the squaramide moiety through double hydrogen bonding between the NH groups and the nitro group. Meanwhile, the MAHT is activated by the basic quinuclidine nitrogen atom. More detailed mechanistic insights, for example, determination of whether C–C bond formation is followed or preceded by decarboxylation, and the basis for enantioselectivity await further studies.

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