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Chiral Bicyclic Guanidine as a Versatile Brønsted Base Catalyst for the Enantioselective Michael Reactions of Dithiomalonates and β-Keto Thioesters

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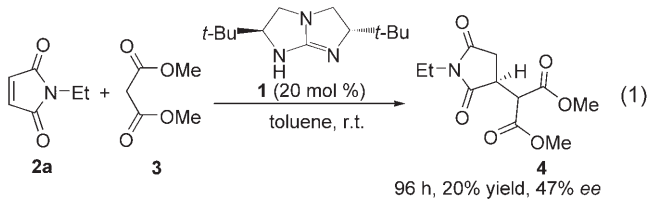
Abstract: A chiral bicyclic guanidine was developed as a versatile Brønsted base catalyst for the enantioselective Michael reactions of dithiomalonates and β-keto thioesters using a range of acceptors including maleimides, cyclic enones, furanone and acyclic 1,4-dicarbonylbutenes.

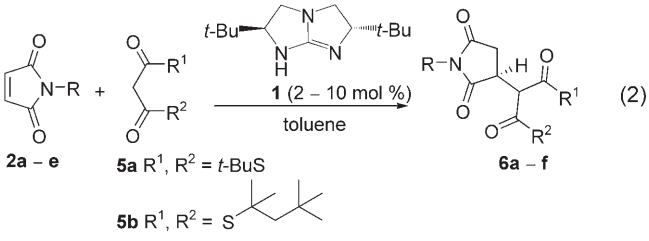
Keywords: asymmetric catalysis; dithiomalonates; guanidines; Michael addition; organic catalysis

Catalytic enantioselective Michael reactions are widely used for the construction of C–C bonds.[1] Tremendous advances have been achieved using Lewis acidic, metal-based catalysts for the Michael reaction of 1,3-dicarbonyl compounds.[2] Organocatalytic approaches have also gained wide popularity in recent years.[3] Successful organocatalysts include imidazolidines,[4] bifunctional thioureas,[5] *Cinchona* alkaloids and derivatives,[6] quaternary ammonium salts[7] and a proline-tetrazole.[8] These catalysts are typically reported as highly effective for a particular type of Michael acceptor. Catalysts that are applicable for a range of substrates are still of high interest.

Guanidines have been shown to catalyze the Strecker reaction with high enantioselectivity.[9] Chiral guanidines and guanidinium salts were also found to be useful for several other base-catalyzed reactions.[10] Recently, highly efficient axially chiral guanidine catalysts were reported.[1] We have also reported a chiral bicyclic guanidine-catalyzed anthrone Diels–Alder reaction.[12] Herein, we report the development of chiral bicyclic guanidine **1** as a versatile Brønsted base catalyst for the enantioselective Michael reactions of dithiomalonates and β-keto thioesters using a range of acceptors, including maleimides, cyclic enones, furanone and acyclic 1,4-dioxobutenes.

Our initial investigation revealed that with 20 mol% of guanidine **1**, dimethyl malonate **3** underwent a Michael addition to *N*-ethyl maleimide **2a** [Eq. (1)]. The reaction was relatively slow, giving the Michael adduct **4** in only 20% yield after 96 h and with 47% *ee*. The α-proton acidity of thioesters is usually higher than that of their corresponding esters due to the poor overlap of the C(2*p*) and S(3*p*) orbitals. This enhanced acidity makes thioesters useful enol equivalents in the laboratory as well as in nature (e.g., as acyl coenzyme A demonstrates). Seeking a more active donor, we prepared a series of *S*,*S*′-dialkyl dithiomalonates and they were tested in place of the dialkyl malonates. Significant improvements in both reaction rates and *ee* values were achieved [Eq. (2)].





With 10 mol% of catalyst **1**, the reaction between *S*,*S*′-di-*tert*-butyl dithiomalonate **5a** and maleimide **2a** was completed within 1 h at room temperature, giving

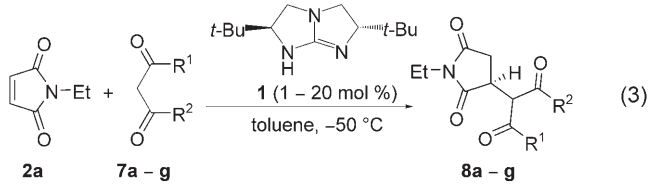
the Michael adduct **6a** in 97% yield and 78% *ee* (Table 1, entry 1). This dramatic rate improvement allowed us to conduct the reaction at lower temperatures. At −20 °C, the enantioselectivity improved to 90% *ee* (entry 2). By lowering the temperature further to −50 °C, the *ee* was improved to 95% and the Michael adduct was obtained with a yield of 98% (entry 3). Subsequently, we developed a more hindered dithiomalonate **5b**. Interestingly, the rate of reaction with this donor was not slower than with **5a**. The reactions of various alkyl maleimides **2a–d** and **5b** were conducted with 2 mol% of guanidine **1**. The corresponding adducts **6b–e** (entries 4–7) were obtained in excellent yields (87–99%) and high *ee*s (96–97%). The reaction of benzyl maleimide **2e** and **5b** required 5 mol% of guanidine **1**; a lower temperature of −70 °C was needed to achieve high *ee* for adduct **6f** (entry 8).

Table 1. Michael addition of *S,S′*-dialkyl dithiomaloates to alkyl maleimides catalyzed by bicyclic guanidine **1** [Eq. (2)].

Entry	**2** [R]	**5**	**6**	**1** [mol%]	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**2a** [Et]	**5a**	**6a**	10	25	1	97	78
2	**2a** [Et]	**5a**	**6a**	10	−20	4	99	90
3	**2a** [Et]	**5a**	**6a**	10	−50	6	98	95
4	**2a** [Et]	**5b**	**6b**	2	−50	20	99	96
5	**2b** [Me]	**5b**	**6c**	2	−50	20	99	97
6	**2c** [*n*-C_6H_{13}]	**5b**	**6d**	2	−50	24	87	97
7	**2d** [CH_2-*c*-hexyl]	**5b**	**6e**	2	−50	24	95	97
8	**2e** [Bn]	**5b**	**6f**	5	−70	14	94	97

[a] Isolated yield.
[b] Chiral HPLC.

Table 2. Chiral bicyclic guanidine **1**-catalyzed Michael reactions of ethyl maleimide and β-keto esters [Eq. (3)].



2a **7a – g** **8a – g**

Entry	**7** [R^1, R^2]	**8**	**1** [mol%]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**7a** [Ph, Ph]	**8a**	20	60	99	92
2[c]	**7b** [Ph, Me]	**8b**	20	120	99	95, 96
3[c,d]	**7c** [Ph, OEt]	**8c**	20	60	99	88
4[c]	**7d** [Ph, S-*t*-Bu]	**8d**	2	8	99	94, 95
5[c]	**7e** [Me, S-*t*-Bu]	**8e**	2	20	99	90, 90
6[c,e]	**7f** [4-MeOPh, S-*t*-Bu]	**8f**	2	17	99	94, 95
7[c,f]	**7g** [Ph, $SC(Me)_2CH_2C(Me)_3$]	**8g**	1	24	90	96, 96

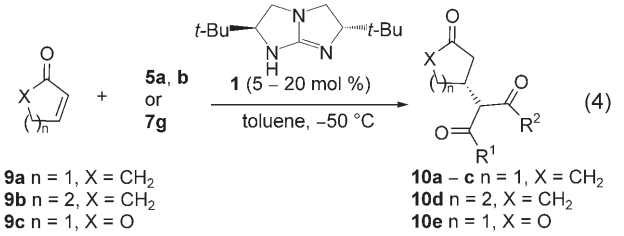
[a] Isolated yield.
[b] Chiral HPLC.
[c] *dr* 1:1.
[d] *ee* determined after decarboxylation.
[e] −60 °C.
[f] Methylmaleimide as acceptor.

Further studies revealed that 1,3-diketones **7a**, **b** and β-keto ester **7c** also add to maleimides with high enantioselectivity [Eq. (3)]. In these cases, the Michael adducts **8a–c** were all obtained in high yields and good *ee*s (Table 2, entries 1–3). However, these reactions were slower and required 20 mol% of catalyst. Upon using aryl and alkyl β-keto thioesters **7d–f**, the reaction rate was considerably enhanced. Using 2 mol% of guanidine **1**, adducts **8d–f** were obtained in high yields and high *ee*s with diastereomeric ratios of approximately 1:1 (entries 4–6). Once again, it was observed that the reaction rate of the more hindered donor **7g** was comparable to that of **7f** and it can operate under a low catalyst loading of 1 mol% (entry 7). At −50 °C, the reaction with **2a** gave adduct **8g** without compromising the yield and *ee*. We are currently exploring β-keto thioesters containing electron-withdrawing aryl groups and we expect these to be highly active donors.

Other cyclic substrates, such as cyclic enones and furanone were also explored as substrates for this reaction [Eq. (4)]. In general, these reactions were also slow. Using 5–10 mol% of guanidine **1** as catalyst, 2-cyclopenten-1-one **9a** underwent Michael addition with various thioesters (Table 3, entries 1–3), giving adducts **10a–c** in good enantioselectivities. With dithiomalonate **5b**, the catalyst loading can be decreased to 5 mol%. The reaction was completed in 30 h, giving **10b** in 91% yield and 97% *ee* (entry 2). The reactions with 2-cyclohexen-1-one **9b** and 2(5*H*)-furanone **9c** with dithiomalonate **5b** also worked well and gave adducts with good *ee*s (entries 4 and 5). To the best of our knowledge, there were no previous reports of the catalytic enantioselective Michael addition of 1,3-dicarbonyl donors to lactones.[13] The scarcity of such direct Michael reactions maybe due to the labile nature of lactones under strongly basic and Lewis acidic conditions.

To extend the scope of this reaction, we searched and found that methyl *trans*-4-oxo-4-phenylbut-2-

Table 3. Chiral bicyclic guanidine **1**-catalyzed Michael reactions of cyclic enones and furanone **9c** [Eq. (4)].



9a n = 1, X = CH_2
9b n = 2, X = CH_2
9c n = 1, X = O

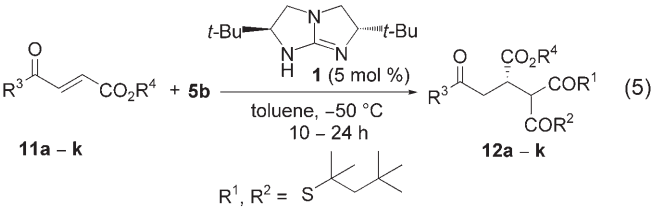
10a – c n = 1, X = CH_2
10d n = 2, X = CH_2
10e n = 1, X = O

Entry	9	Donor	10	1 [mol %]	T [°C]	t [h]	Yield [%][a]	ee [%][b]
1	**9a**	**5a**	**10a**	10	−50	48	96	95
2	**9a**	**5b**	**10b**	5	−50	30	91	97
3[c]	**9a**	**7g**	**10c**	10	−50	41	99	96, 98
4	**9b**	**5b**	**10d**	20	−20	60	86	90
5	**9c**	**5b**	**10e**	20	−50	56	85	96

[a] Isolated yield.
[b] Chiral HPLC.
[c] *dr* 1:1.

enoate **11a** (Table 4, entry 1) was a useful acyclic Michael acceptor [Eq. (5)]. With 5 mol % of guanidine **1**, dialkyl dithiomalonate **5b** reacted smoothly to give adduct **12a** in 96 % yield and 92 % *ee*. The reactions of the ethyl and benzyl analogues **11b**, **c** (entries 2 and 3) showed no significant change in *ee* and yield. A series of ethyl 4-oxo-4-arylbut-2-enoates **11d–k** (entries 4–11) with various aryl substitutents were prepared. These were found to be excellent acceptors and the substitution on the aromatic ring did not affect the reaction in terms of yield and *ee*. As expected, reaction rates were slightly faster for substrates with electron-poor aryl groups. This is a highly regioselective reaction; only the α-alkyl esters **12a–k** were detected. The other regioisomer in which the addition occurs at the β-position to the ester group was not observed at all. Absolute configurations and regiochemistry were determined through X-ray crystallography (see Supporting Information).

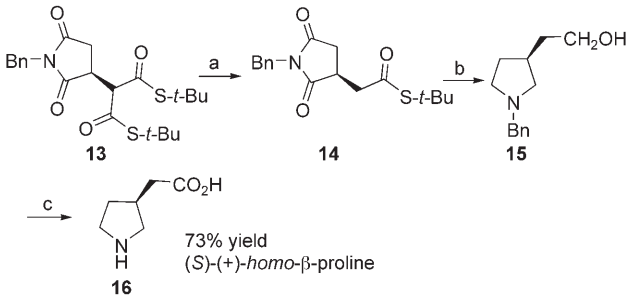
Table 4. Chiral bicyclic guanidine **1**-catalyzed Michael reactions of alkyl *trans*-4-oxo-4-arylbutenoates [Eq. (5)].



Entry	11 [R^3, R^4]	Product	Yield [%][a]	ee [%][b]
1	**11a** [Ph, Me]	**12a**	96	92
2	**11b** [Ph, Et]	**12b**	99	92
3	**11c** [Ph, Bn]	**12c**	85	92
4	**11d** [3-$MeOC_6H_4$, Et]	**12d**	99	94
5	**11e** [2-naphthyl, Et]	**12e**	99	92
6	**11f** [4-*t*-BuC_6H_4, Et]	**12f**	87	94
7	**11g** [4-PhC_6H_4, Et]	**12g**	90	91
8	**11h** [3,5-$Me_2C_6H_4$, Et]	**12h**	99	94
9	**11i** [2-furyl, Et]	**12i**	99	90
10	**11j** [4-ClC_6H_4, Et]	**12j**	99	92
11[c]	**11k** [4-CNC_6H_4, Et]	**12k**	94	90

[a] Isolated yield.
[b] Chiral HPLC.
[c] −70 °C.

In order to demonstrate the synthetic utility of this methodology and to determine the absolute configuration of the substituted succinimides **6a–f**, the first enantioselective synthesis of (*S*)-(+)-*homo*-β-proline **16** was carried out. (*S*)-(+)-*homo*-β-Proline is a potent γ-aminobutyric acid (GABA) agonist and uptake inhibitor.[14] GABA is a neurotransmitter present in 60–70 % of all synapses and has been implicated in several neurological disorders such as anxiety, pain, Parkinson's disease and epilepsy.[15] Current methods to prepare enantiopure **16** include the resolution of its racemate using pig liver esterase,[16] the use of (*S*)-(−)-1-phenylethylamine as a chiral auxiliary,[14d,17] and the chiral pool approach using aspartic acid.[18] We embarked on the synthesis from 300 mg of **13**, available in 92 % *ee* from the chiral guanidine **1**-catalyzed Michael reaction (see Supporting Information). Substituted succinimide **14** was obtained in 99 % yield through the decarboxylation of one of the thioesters (Scheme 1). No racemization was observed when **14** was analyzed using chiral HPLC. Reduction of **14** with $LiAlH_4$ went smoothly to generate the *N*-benzyl-*homo*-β-prolinol **15**. Jones' oxidation of **15** was



Scheme 1. Synthesis of (*S*)-(+)-*homo*-β-proline. *Reagents and conditions:* a) NaCl (3 equivs.), DMSO/H_2O (10:1), 110 °C, 9 h (99 %); b) $LiAlH_4$, THF, reflux, 22 h (92 %); c) (i) $HOOCNH_4$, Pd/C, MeOH, reflux, 0.5 h. (ii) CbzCl, K_2CO_3, THF/H_2O, −10 °C, 0.5 h. (iii) Jones' reagent, acetone, −10 °C, 0.5 h. (iv) H_2, Pd/C, MeOH, r.t., 2 h (80 % from **15**).

capricious and gave side products on some occasions. Exchanging the amino protecting group from a Bn to a Cbz group circumvented this problem. This is followed by Jones' oxidation and hydrogenolysis. These few steps were carried out efficiently, without the need of chromatographic purification and were achieved with a yield of 80% yield from **15**. This efficient enantioselective synthesis of (*S*)-(+)-*homo*-β-proline **16** (overall yield of 73% from **13**) allowed the unambiguous assignment of the absolute configuration of succinimides **6a–f**. The optical rotation of the synthetic (*S*)-(+)-*homo*-β-proline **16** matched well with values reported in the literature.

In summary, we have shown that chiral bicyclic guanidine **1** is a versatile Brønsted base catalyst for enantioselective Michael reactions. This is the first example of highly enantioselective Michael reactions of dithiomalonates and β-keto thioesters. These donors were previously avoided as they might poison organometallic catalysts. We have shown that they are excellent alternatives to conventional 1,3-dicarbonyl compounds. Both reaction rates and enantioselectivities can be dramatically improved. We postulate that many other organocatalytic reactions could benefit from this active donor, allowing a significant reduction in the catalyst loading. Thioesters are amenable to modification and mild conditions for decarboxylation were demonstrated in the synthesis of (*S*)-(+)-*homo*-β-proline **16**. Thioesters can be easily transformed into ketones, aldehydes or β-keto esters.[19] The dithiomalonate group can also be directly reduced to a saturated alcohol using Raney nickel.[20]

We have also shown that chiral bicyclic guanidine **1** is versatile and compatible for a range of Michael acceptors. Maleimides are extremely useful substrates in asymmetric catalytic Michael reactions.[21] A large number of biologically interesting α-substituted succinimides,[22] functionalized pyrrolidines[23] and other heterocycles can potentially be obtained *via* this approach. We demonstrated this through the first enantioselective synthesis of (*S*)-(+)-*homo*-β-proline **16**. Simple ring opening procedures would also mean rapid entry to functionalized open chain derivatives.[24] Michael addition of cyclic enones with 1,3-dicarbonyl compounds are well studied using organometallic catalysts. However, there are fewer organocatalytic examples.[8,25] Both 2(5*H*)-furanone **9c** and the alkyl 4-oxo-4-arylbut-2-enoates **11a–k** are substrates that are much less studied and there are only a few isolated examples of asymmetric Michael reactions using these substrates.[4b,13,25a,26] This methodology can thus provide a variety of new enantiopure compounds such as **10e** and **12a–k** which are inaccessible using other approaches.

Experimental Section

Typical Procedure for the Michael Reaction

N-Ethylmaleimide **2a** (0.1 mmol, 1.0 equiv., 12.5 mg) and dithiomalonate **5b** (0.3 mmol, 3.0 equivs., 108 mg) were dissolved in toluene (0.395 mL) and stirred at −50 °C for 30 min. A pre-cooled solution of catalyst **1** (0.002 mmol, 0.02 equivs., 0.447 mg in 5 μL toluene) was added and the reaction mixture was stirred at −50 °C. Upon completion of the reaction (20 h), the reaction mixture was loaded onto a short silica gel column and purified by gradient elution with hexane/ethyl acetate mixtures (0–10/1 ratio). After removing the solvent, product **6b** was obtained as colorless oil; yield: 43.6 mg (99%).

Supporting Information

Experimental procedures, characterization and spectroscopic data (PDF) are available as Supporting Information.

Acknowledgements

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