Highly Efficient Asymmetric Michael Addition Reaction of Malonates to α,β-Unsaturated Ketones Promoted by a Chiral Thiourea/PPY Dual-Catalyst System

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Abstract: The enantioselective Michael addition reaction of malonates to α,β-unsaturated ketones is efficiently promoted by a combined dual-catalyst system composed of chiral thiourea and 4-pyrrolidinopyridine (PPY) in toluene. The expected Michael adducts with cyclic and acyclic enones are obtained in excellent yields and with excellent enantioselectivities.

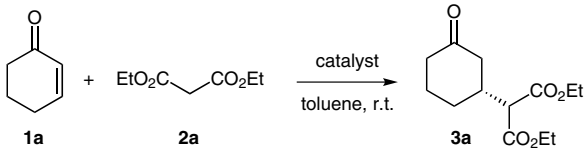
Key words: asymmetric Michael addition, malonates, α,β-unsaturated ketones, chiral thiourea, 4-pyrrolidinopyridine (PPY)

The Michael addition reaction is widely recognized as one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] In the case of malonates, due to the presence of two electron-withdrawing esters, the corresponding conjugate bases are readily accessible under relatively mild conditions and are frequently used as nucleophilic donors in the Michael addition reaction. In addition, the asymmetric Michael adducts of malonates to α,β-unsaturated ketones can serve as convenient chiral building blocks, particularly for the construction of biologically interesting natural products.[2] As a result, considerable attention has been given to the development of catalytic asymmetric transformations, and recent efforts in this area have been directed toward the development of asymmetric organocatalysis.[3]

In our laboratory, we have been working to develop a new method for Michael addition reactions using 4-dimethylaminopyridine (DMAP) and related organocatalysts.[4] As an extension of this work, we expected that the cooperative use of chiral thiourea and aminopyridine catalysts should be more effective for the asymmetric Michael addition reaction of malonates with α,β-unsaturated ketones. Although there have been reports of related work using cinchona alkaloid based bifunctional thiourea catalysts,[5] we have been interested in the use of a much simpler dual-catalyst system composed of chiral thioureas and 4-pyrrolidinopyridine (PPY) as a hydrogen-bonding activator[6] and a nucleophilic base.[7] We describe here the realization of this expectation.

First, we examined the reaction of 2-cyclohexen-1-one (**1a**) with diethyl malonate (**2a**) in the presence of several thiourea organocatalysts with or without PPY in toluene at room temperature as a model system.[8] The results are summarized in Table 1; catalysts **A**–**F** are shown in Figure 1.[9]

Table 1 The Asymmetric Michael Addition Reaction of 2-Cyclohexen-1-one (**1a**) with Diethyl Malonate (**2a**): Optimization[a]



1a **2a** **3a**

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	**A**	24	51	60
2[d]	**A** + PPY	24	52	54
3	**A** + **B**	10	94	13
4[d]	**A** + **B** + PPY	16	99	16
5	**C**	24	80	96
6	**C** + PPY	24	95	98
7	**D** + PPY	24	94	–98
8	**E**	24	trace	–
9	**E** + PPY	24	trace	–
10	**F**	24	0	–
11	**F** + PPY	24	trace	–

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 equiv), toluene (1.0 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC using Chiralcel OD-H (hexane–*i*-PrOH = 99:1).
[d] Conditions: 2 equiv of **1a** were used.

As expected, cyclohexanediamine catalyst **A** itself gave poor results even in the presence of PPY (Table 1, entries 1 and 2). Interestingly, the addition of thiourea **B** to these systems dramatically improved the chemical yields, albeit giving low enantioselectivities (Table 1, entries 3 and 4). Subsequently, we found that the *trans*-1,2-cyclohexanediamine-thiourea conjugate catalyst **C**[10] exhibited high catalytic activity, and product **3a** was formed with the best yield and enantioselectivity when the reaction was con-

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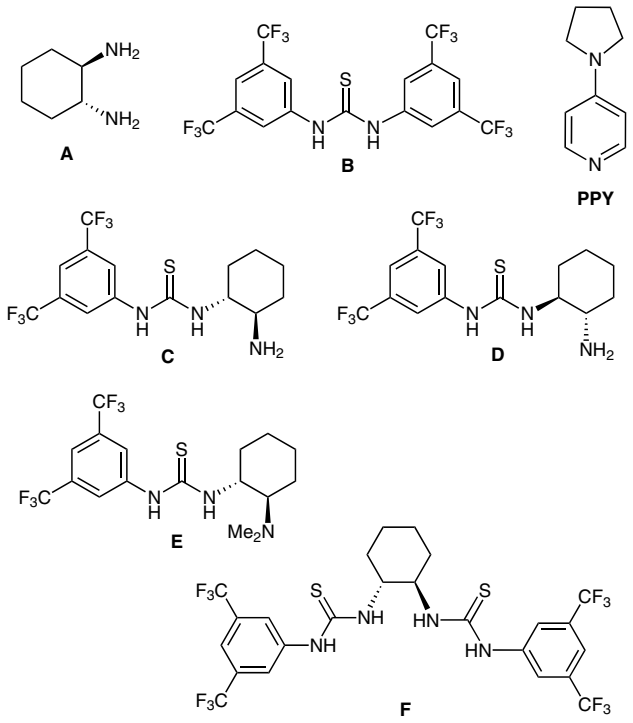
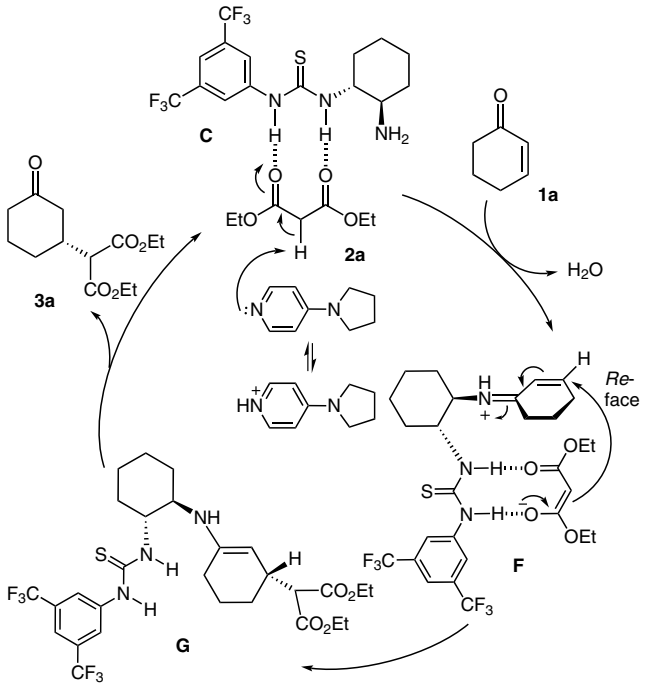


Figure 1



Scheme 1 A proposed catalytic cycle for the Michael addition reaction of **1a** with **2a** in the presence of catalyst **C** and PPY

ducted in the presence of PPY as a co-catalyst (Table 1, entries 5 and 6). The replacement of the chiral core (1*R*,2*R*)-cyclohexanediamine with its (1*S*,2*S*)-antipode (catalyst **D**) caused a complete reversal of the configuration of the product,[11] which indicates that the chiral motif of the 1,2-cyclohexanediamine skeleton plays a crucial role in determining the stereochemical outcome (Table 1, entry 7). In addition, we confirmed that the presence of a free primary amine moiety in catalyst **C** (or **D**) was essential, since the dimethylamine homologue **E**[12] and bisthiourea **F**[13] showed no catalytic activity (Table 1, entries 8–11).

Based on the absolute configuration of the Michael adduct **3a**[11] and the important role of the free primary amine functionality of catalyst **C**, we propose the following mechanism to account for the present asymmetric Michael addition reaction (Scheme 1).

Due to the high efficiency observed in this dual-catalyst system composed of chiral thiourea **C** and PPY, we believe that **2a** would be activated by a thiourea moiety through double hydrogen bonding, thus enhancing the acidity of **2a** (pK_a = 14.2 in DMSO)[14] and facilitating proton abstraction by PPY (pK_a = ca. 9.6 for the conjugate acid in H_2O, from the resemblance to DMAP).[15] Catalyst **C** would then interact with **1a** to form the activated ketiminium cation intermediate **F**, which could enable the nucleophilic attack of the malonate ion from the *Re* face with respect to the double bond as in an intramolecular approach. Next, the generated enamine intermediate **G** undergoes hydrolysis to release the product **3a** and catalyst **C**.

With the optimized reaction conditions in hand, we then investigated the general scope of this chemistry by using various α,β-unsaturated ketones as substrates. In all of these examples, the reactions without using PPY as a co-catalyst are shown for comparison (Table 2).[9,16,17]

First, we found that di-*tert*-butyl malonate (**2b**) reacted quite slowly with **1a** compared to the diethyl congener **2a** in the presence of catalyst **C** and PPY, and gave **3b** in 86% yield with 98% ee after 120 hours, while the same reaction using catalyst **C** alone resulted in only 19% yield of **3b** even after one week (Table 2, entries 1 and 2). A very similar behavior was observed for other Michael donors such as alkyl- or aryl-substituted malonates **2c**–**e**, and the desired adducts bearing a quaternary carbon center at the donor site were obtained in high yields with excellent enantioselectivities (Table 2, entries 3–8). For the sluggish reactions, all attempts to suppress the formation of the Rauhut–Currier-type adduct **4** (Figure 2)[18] failed (Table 2, entries 1, 3, 7, and 8).[19]

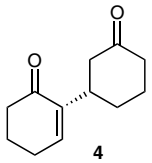
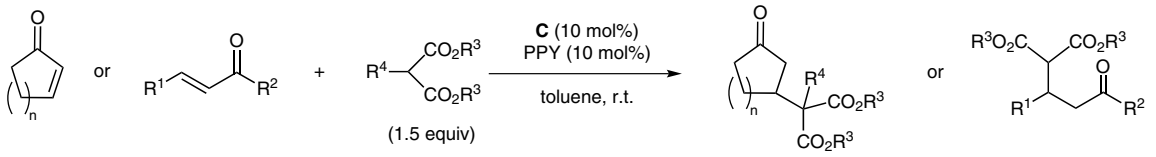


Figure 2

The reaction of 4,4-disubstituted cyclohexenone **1b** with **2a** proceeded without any difficulty under the catalysis of catalyst **C** and PPY to afford sterically congested **3f** (Table 2, entries 9 and 10). Cyclopentenone (**1c**) and cycloheptenone (**1d**) smoothly underwent the desired Michael

addition reaction to give the corresponding adducts **3g** and **3h** in high efficiency (Table 2, entries 11–14). Finally, we found that the reaction was also successful for acyclic enone substrates such as **1e** and **1f**, and the corresponding adducts **3i** and **3j** were obtained in high yields and with high enantioselectivities, whereas the sole use of catalyst **C** gave somewhat better results (Table 2, entries 15–18).

Table 2 The Asymmetric Michael Addition Reaction of α,β-Unsaturated Enones **1** with Malonates **2**[a]



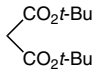
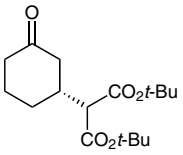
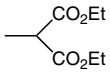
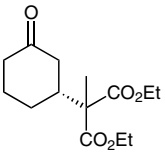
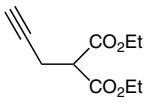
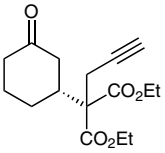
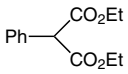
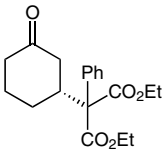
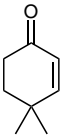
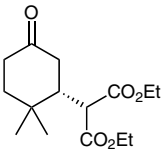
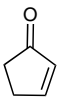
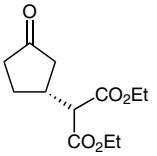
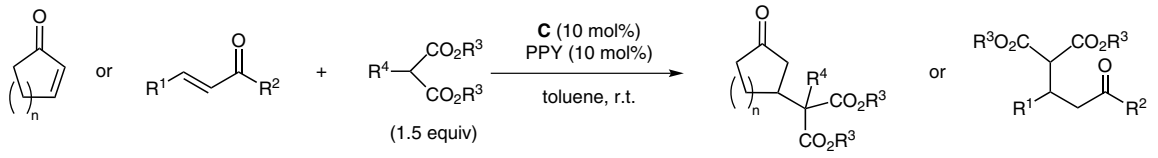
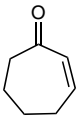
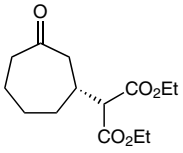
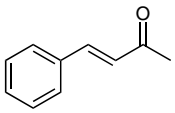
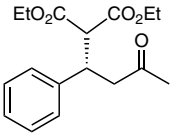
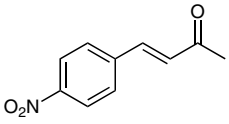
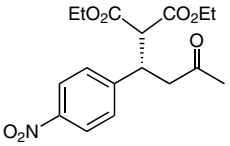
Entry	Acceptor **1**	Donor **2**	Product **3**[b]	Catalyst	Time (h)	Yield (%)[c]	ee (%)[d]
1 2	**1a**	 **2b**	 **3b**	**C** **C** + PPY	168 120	19[e,f] 86	93 98
3 4	**1a**	 **2c**	 **3c**	**C** **C** + PPY	168 52	16[f,g] 84	99 99
5 6	**1a**	 **2d**	 **3d**	**C** **C** + PPY	69 52	47[f] 99	99 99
7[h] 8[h]	**1a**	 **2e**	 **3e**	**C** **C** + PPY	168 53	15[f,i] 47[j]	99 98
9 10	 **1b**	**2a**	 **3f**	**C** **C** + PPY	93 48	64[f] 91	90 96
11[h] 12[h]	 **1c**	**2a**	 **3g**	**C** **C** + PPY	96 120	51[f] 64[f]	74 76

Table 2 The Asymmetric Michael Addition Reaction of α,β-Unsaturated Enones **1** with Malonates **2**[a] (continued)



Entry	Acceptor **1**	Donor **2**	Product **3**[b]	Catalyst	Time (h)	Yield (%)[c]	ee (%)[d]
13	 **1d**	**2a**	 **3h**	**C**	84	68[f]	99
14				**C** + PPY	72	95	98
15	 **1e**	**2a**	 **3i**	**C**	96	97	93
16				**C** + PPY	72	99	91
17	 **1f**	**2a**	 **3j**	**C**	138	94	93
18				**C** + PPY	120	90	88

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 equiv), catalyst **C** (10 mol%), PPY (10 mol%), toluene (1.0 mL), r.t.
[b] The absolute configuration of the products **3c**–**e** was surmised by analogy. See ref. 16 and 17.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis: Chiralpak AD for **3b**,**e**–**g**,**i**; Chiralpak AS-H for **3c**,**h**; Chiralcel OD-H for **3d**; Chiralpak AD-H for **3j**.
[e] Byproduct **4** was isolated in 39% yield (20% ee).
[f] Additional unidentified byproducts were formed.
[g] Byproduct **4** was isolated in 27% yield (21% ee).
[h] Conditions: 3 equiv of **2** were used.
[i] Byproduct **4** was isolated in 16% yield (29% ee).
[j] Byproduct **4** was isolated in 36% yield (38% ee).

In summary, we have developed a new combined dual-catalyst system composed of chiral thiourea catalyst **C** and PPY in toluene for the asymmetric Michael addition reaction of malonates with α,β-unsaturated ketones to obtain the desired products in high chemical yields with high enantioselectivities. This method is particularly useful for constructing complex molecules bearing sterically congested stereogenic centers. Further studies on the application of this method to natural product synthesis are now in progress in our laboratory.[20]

Acknowledgment

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(9) **General Procedure**
To a solution of PPY (14.8 mg, 0.1 mmol), α,β-unsaturated ketone (**1**, 1.0 mmol), and dialkyl malonate (**2**, 1.5 mmol) in toluene (1.0 mL) thiourea catalyst **C** (38.5 mg, 0.1 mmol) was added and the mixture was stirred until the reaction was complete. After concentration, the mixture was purified by silica gel column chromatography (elution with hexane–EtOAc = 4:1) to afford pure product **3**.

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(11) The absolute configuration of **3a** was determined to be *R* by comparison of its optical rotation with that in the literature [5]. (*R*)-**3a**: $[\alpha]_D^{22}$ +3.14 (*c* 1.00, $CHCl_3$; 98% ee); lit. [5] $[\alpha]_D^{22}$ +3.3 (*c* 1.00, $CHCl_3$; 93% ee). The ee was determined by chiral HPLC analysis [Chiralpak AS-H column, 0.46 × 25 cm, hexane–2-PrOH (70:30), 0.2 cm^3/min]: t_R (*R*) = 44.4 min; t_R (*S*) = 49.9 min.

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(16) (a) The absolute configuration of the products was determined by comparison with data in the literature. (*R*)-**3b**: $[\alpha]_D^{24}$ +5.32 (*c* 1.00, $CHCl_3$; 98% ee); lit.[16b] $[\alpha]_D^{20}$ +3.7 (*c* 1.00, $CHCl_3$; 86% ee).
(*S*)-**3f**: $[\alpha]_D^{24}$ +13.0 (*c* 1.00, $CHCl_3$; 96% ee); lit.[5] $[\alpha]_D^{28}$ +11.8 (*c* 1.03, $CHCl_3$; 91% ee).
(*R*)-**3g**: $[\alpha]_D^{25}$ +63.9 (*c* 1.00, $CHCl_3$; 76% ee); lit.[5] $[\alpha]_D^{27.5}$ +50.8 (*c* 1.07, $CHCl_3$; 63% ee).
(*R*)-**3h**: $[\alpha]_D^{24}$ +40.5 (*c* 1.00, $CHCl_3$; 99% ee); lit.[5] $[\alpha]_D^{27}$ +41.7 (*c* 1.02, $CHCl_3$; 93% ee).
(*S*)-**3i**: $[\alpha]_D^{25}$ +16.4 (*c* 1.00, $CHCl_3$; 91% ee); lit.[5] $[\alpha]_D^{28}$ +17.8 (*c* 1.02, $CHCl_3$; 96% ee).
(*S*)-**3j**: $[\alpha]_D^{25}$ +17.2 (*c* 1.00, $CHCl_3$; 88% ee); lit.[5] $[\alpha]_D^{29}$ +18.5 (*c* 1.02, $CHCl_3$; 93% ee). (b) Yoshida, M.; Narita, M.; Hara, S. *J. Org. Chem.* **2011**, *76*, 8513.

(17) The absolute configuration of the products **3c**–**e** was assigned by analogy.
Compound **3c**: $[\alpha]_D^{25}$ +17.9 (*c* 1.00, $CHCl_3$; 99% ee).
Compound **3d**: $[\alpha]_D^{24}$ +9.27 (*c* 1.00, $CHCl_3$; 99% ee).
Compound **3e**: $[\alpha]_D^{25}$ –3.04 (*c* 1.00, $CHCl_3$; 98% ee).

(18) (a) For a review on the Rauhut–Currier reaction, see: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069. (b) The absolute configuration of **4** was determined by comparison with data in the literature. (*S*)-**4**: $[\alpha]_D^{25}$ +3.52 (*c* 0.09, $CHCl_3$, 38% ee); lit.[18c] (*R*)-**4**: $[\alpha]_D^{r.t.}$ –3 (*c* 1.00, CH_2Cl_2; 47% ee) (c) Ceccarelli, R.; Insogna, S.; Bella, M. *Org. Biomol. Chem.* **2006**, *4*, 4281. (d) The ee was determined by chiral HPLC analysis [Chiralpak AD column, 0.46 × 25 cm, hexane–2-PrOH (95:5), 1.0 cm^3/min): t_R (*R*) = 25.1 min; t_R (*S*) = 35.7 min.

(19) Although we did not examine the role of PPY in detail, it can be supposed that PPY could suppress the formation of byproduct **4** by promoting the nucleophilic attack of **2** via deprotonation (Scheme 1).

(20) During the final preparation of a revised version of this paper, Kwiatkowski and co-workers reported a closely related work using catalyst **C** with benzoic acid in warmed toluene. See: Dudzinski, K.; Pakulska, A. M.; Kwiatkowski, P. *Org. Lett.* **2012**, *14*, 4222.

