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An Efficient Organocatalytic Method for Highly Enantioselective Michael Addition of Malonates to Enones Catalyzed by Readily Accessible Primary Amine-Thiourea

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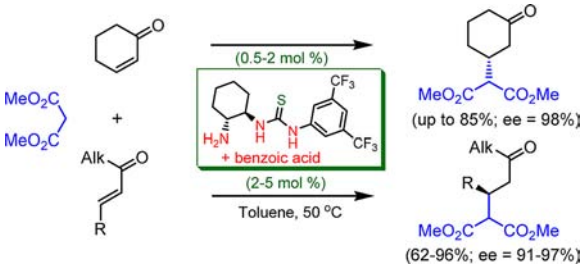
ABSTRACT



A practical and highly enantioselective Michael addition of malonates to enones catalyzed by simple and readily available bifunctional primary amine-thiourea derived from 1,2-diaminocyclohexane is reported. The addition of weak acids and elevated temperature (*ca.* 50 °C) improved the efficiency of the Michael reaction. This approach enables the efficient synthesis of 1,5-ketoesters with good yields, excellent enantioselectivities (up to 99% ee), and low loading (0.5−5 mol %) of simple chiral primary amine-thiourea catalysts, and is applicable in multigram scale synthesis.

Asymmetric organocatalysis promoted by secondary and primary amines (aminocatalysis) has been recognized in the past decade as a very powerful tool in organic synthesis.[1] This approach has been successfully applied, among others, to various asymmetric conjugate addition reactions proceeding via an iminium activation mode.[2] However, in contrast to catalysis with metal complexes, application of aminocatalysis in the fine chemical industry is still limited.[3] The major drawback of many organocatalytic reactions is the requirement of a relatively high catalyst loading (≥10%) and long reaction times.

Currently, of particular interest are organocatalytic reactions operating with low loadings (≤5 mol %)[4] of easily accessible organic molecules, as well as the development of more efficient organic catalysts. In some cases simple modification of a chiral amine structure by the introduction of, e.g., a thiourea moiety can significantly improve the catalytic properties.[5] In this communication special attention is focused on catalysis with chiral bifunctional primary amine-thioureas. This group of molecules (e.g., **1a**−**e**, Figure 1) was successfully introduced to organocatalysis by Jacobsen[6] and Tsogoeva[7] and found applications mostly in reactions operating via an enamine intermediate.[8] In recent years this type of catalyst was

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also utilized in selected reactions of α,β-unsaturated carbonyl compounds based on iminium activation.[9,10] Ye and Liang[10] intensively explored additions of various nucleophiles to enones catalyzed by primary-tertiary amine-thiourea catalysts of type **1j** derived from 1,2-diaminocyclohexane and 9-amino-*epi*-cinchona alkaloids. This catalytic system was also successfully applied in Michael additions of malonates to enones.[10b] However, results obtained by Duan and Wang[9a] indicated that the presence of an additional tertiary amine is not essential for the catalytic activity of primary amine-thiourea in the Michael addition of nitromethane to enones.[11]

During our studies on Michael reactions catalyzed by primary amines,[12] we observed that simple and easily available primary amine-thioureas derived from 1,2-diaminocyclohexane, e.g. **1a**, were efficient catalysts for the addition of malonates to various enones. Moreover, we found that the addition of weak acids as cocatalysts and elevated temperature (*ca.* 50 °C) significantly improved the efficiency of the reaction.

An enantioselective organocatalytic Michael addition of malonates to enones can be realized using catalysts containing secondary[13] and tertiary[14] amines as well as chiral ammonium salts (phase-transfer catalysis).[15] In recent years, more attention has been paid to catalysis with primary amines.[16] Also this group of compounds was successfully applied for the addition of malonates to enones.[10b,17]

In our studies we focused on the 1,4-conjugate addition of malonates to enones in the presence of easily available primary amine-thioureas derived from 1,2-diaminocyclohexane of type **1a**–**c** (Figure 1).

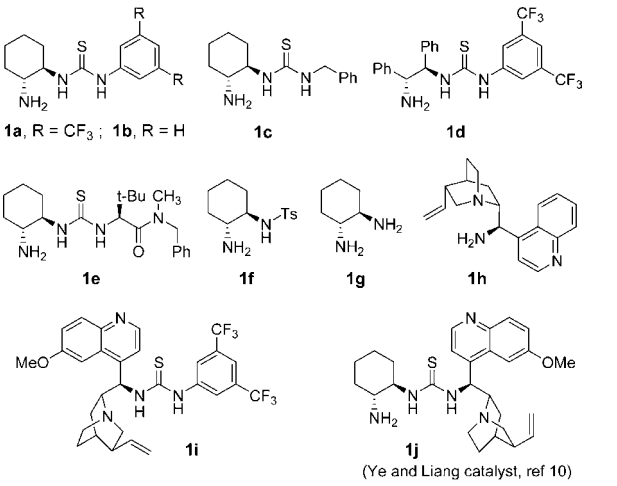

Figure 1. Organocatalysts examined in the Michael reaction.

As a model reaction we chose the addition of dimethyl malonate to cyclohexenone (**2a**, Table 1).[18] The product of this reaction (**3a**) is a very interesting building block and was utilized in the synthesis of several natural products,[19] e.g., (−)-strychnine,[19a,b] tubifolidine,[19c] and (−)-gilbertine.[19d] Typically Shibasaki's BINOL/La catalyst[20] was applied for preparation of an optically pure product **3a**.

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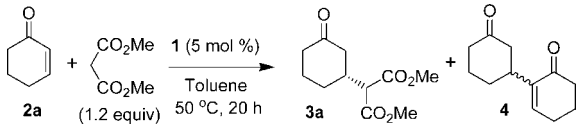
During our preliminary investigations we observed that readily available amino-thiourea **1a** (5 mol %) can be a very promising catalyst in the reaction of cyclohexenone with dimethyl malonate (Table 1, entries 1−4). An addition of 5 mol % of benzoic acid as a cocatalyst and an increase of temperature to 50 °C improved the reaction rate (conv > 99%, entry 4). In the presence of stronger acids (e.g., TFA) the yield was very low (entry 5). Among various primary amines **1a**−**h** (Figure 1) tested in the presence of benzoic acid, the best results were observed with thiourea derivatives **1a**−**e**. Although conversions were high (> 88%), yields of expected product were lower (51−77%) due to the formation of byproducts; among them dimer **4** dominated.[21] The highest enantioselectivity (97−98% ee) was obtained with catalysts **1a** and **1d** (entries 3, 4, and 8). Finally a more readily available catalyst **1a** was used for further investigations.

Table 1. Catalyst Screening in the Model Reaction[a]



entry	amine (5 mol %)	acid (5 mol %)	temp (°C)	yield (conv) (%)[b]	ee (%)[c]
1	**1a**	none	20	42 (46)	96 (*R*)
2	**1a**	none	50	66 (78)	95 (*R*)
3	**1a**	BzOH	20	71 (91)	97 (*R*)
4	**1a**	BzOH	50	68 (>99)	97 (*R*)
5	**1a**	TFA	50	8 (25)	>95
6	**1b**	BzOH	50	54 (98)	90 (*R*)
7	**1c**	BzOH	50	51 (>99)	90 (*R*)
8	**1d**	BzOH	50	77 (88)	98 (*R*)
9	**1e**	BzOH	50	61 (99)	65 (*R*)
10	**1f**	BzOH	50	18 (72)	40 (*R*)
11	**1g**	BzOH	50	40 (64)	56 (*R*)
12	**1h**	BzOH	50	40 (43)	96 (*R*)
13	**1i**	none	50	<2	>90

[a] Reaction conditions: **2a** (1 mmol, c = 1.0 mol/L), dimethyl malonate (1.1−1.2 mmol), amine **1** (0.05 mmol), acid (0.05 mmol) in toluene (*ca.* 0.75 mL), 20 or 50 °C, 20 h. [b] Determined by GC analysis with internal standard. [c] Determined by GC analysis using CP-Chirasil-Dex CB column.

We studied the influence of benzoic acid as an additive in more detail in the reaction of dimethyl malonate with cyclohexenone (**2a**) and benzylideneacetone (**2e**), with 2 mol % of amine **1a** at 50 °C (Figure 2). The best results in terms of yield and enantioselectivity for Michael addition to cyclohexenone were observed in the presence of 2 equiv of benzoic acid vs **1a**.[22] Using these optimized conditions with only 1−2 mol % of **1a** we improved the yield of **3a** (> 80%, Table 2, entries 2 and 7) and reduced the amount of byproducts. The reaction can be effectively performed in different solvents as well as neat without loss of enantioselectivity (entries 4−6). A higher temperature (75 °C) lowered yields presumably due to catalyst decomposition (entry 3). Moreover, we demonstrated that the reaction is efficient and highly enantioselective (98% ee) with the use of only 0.5 mol % of catalyst **1a**·2BzOH and is applicable in multigram scale synthesis (30 mmol, entry 8). In our opinion this is a very attractive and practical method for the large-scale preparation of an optically pure compound **3a**. The advantages of this method are the need for small amounts of catalyst (0.5−1 mol %), almost equimolar amounts of reagents (1.05−1.2 equiv of dimethyl malonate), a high concentration of the reaction mixture (c = 2.5−3 mol/L), and a simple procedure.

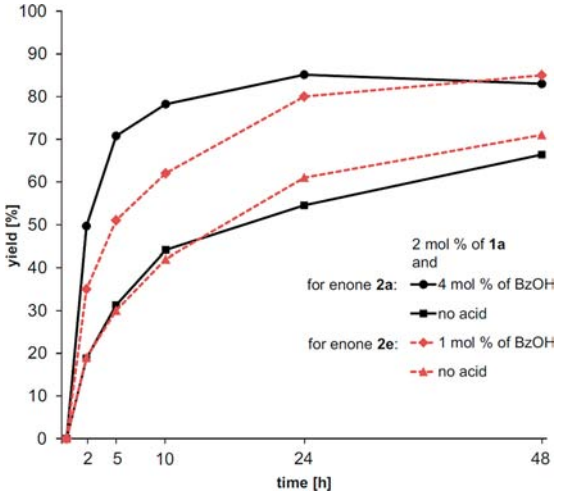


Figure 2. Effect of BzOH additive on the reaction of enone **2a** and **2e** with dimethyl malonate.

Having established the optimal conditions for the reaction of cyclohexenone (**2a**) with dimethyl malonate, we extended investigations to other nucleophiles (Figure 3, products **5**, **6**, and **7**) and other cyclic enones (see products **3b**, **3c**, and **3d**). In the case of cyclopentenone, an acceptable yield was obtained when the reaction was carried out in THF in the presence of 1 equiv of water (product **3d**). In all of the cases, good to very high enantioselectivity was observed.

The reaction of benzylideneacetone (**2e**) and dimethyl malonate is efficient with 2 mol % of **1a** and a lower concentration of benzoic acid (1 mol %) (Figure 2)[22] and is applicable in 10 mmol scale. This catalytic system (2−5 mol %) is quite efficient for reactions of malonates with a broad range of acyclic enones (Scheme 1). In most cases, high enantioselectivity and good yields were achieved after 20 h (products **3e**−**3i**). For acyclic enones containing more sterically demanding substituents, e.g. isopropyl or isobutyl groups neighboring the carbonyl, the reaction time was prolonged up to 5 days and products **3l** and **3m** were isolated with good yields and high enantioselectivities.

(21) When the reaction was carried out without dimethyl malonate with 5 mol % of **1a**·BzOH at 50 °C, the conversion of **2a** was *ca.* 60% after 20 h.

(22) For more details, see Supporting Information.

Table 2. Model Reaction Optimization Studies[a]

entry	**1a**·2BzOH (mol %)	solvent	temp (°C)	conv (%)[b]	yield (%)[b,c]	ee (%)[d]
1	2	toluene	20	57	53	98
2	2	toluene	50	95	85 (82)	98
3	2	toluene	75	84	73	98
4	2	THF	50	85	73	99
5	2	AcOEt	50	86	66	99
6	1	no solvent	50	93	87	98
7[e]	1	toluene	50	96	88 (84)	98.5
8[f]	0.5	toluene	50	80	75 (72)	98
9[g]	0.2	toluene	50	48	46	99

[a] Reaction conditions: **2a** (1 mmol, c = 1.0 mol/L), dimethyl malonate (1.1−1.2 mmol), catalyst **1a**·2BzOH in toluene (*ca.* 0.75 mL), 20−75 °C, 20 h. [b] Determined by GC analysis with internal standard. [c] Numbers in parentheses refer to isolated yields. [d] Determined by GC analysis using CP-Chirasil-Dex CB column. [e] **2a** (20 mmol scale, c = 2.5 mol/L). [f] **2a** (30 mmol scale, c = 2.9 mol/L), 72 h. [g] 48 h.

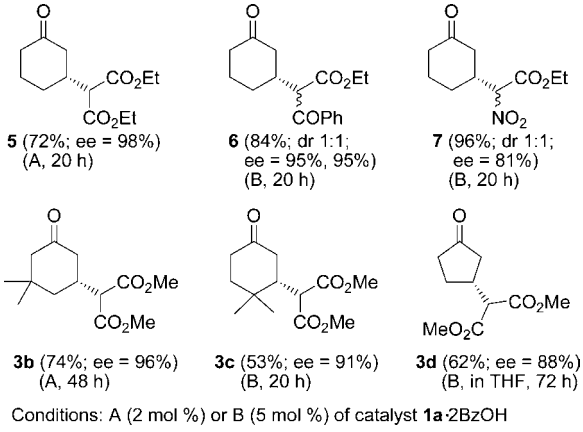
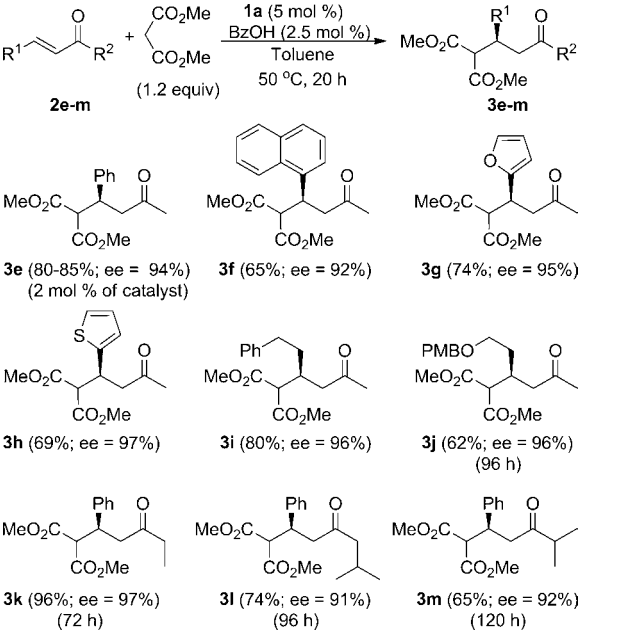


Figure 3. Products of Michael reaction with cyclic enones catalyzed by 2−5 mol % of **1a**·2BzOH (isolated yield given).

The application of the catalyst (1*R*,2*R*)-**1a** resulted in formations of, e.g., (*R*)-(+)-**3a**, (*R*)-(+)-**3d**, and (*S*)-(+)-**3e** products. Such a direction in asymmetric induction can be explained by a simplified stereochemical model presented in Figure 4, where cyclohexenone forms an iminium ion with primary amine and malonate is stabilized via hydrogen bonds with a thiourea moiety.

In conclusion, we demonstrate practical and highly enantioselective Michael additions of malonates to cyclic and acyclic enones catalyzed by simple and readily available bifunctional primary amine-thiourea derived from 1,2-diaminocyclohexane. We observed that the addition of weak acids (e.g., benzoic acid) and increasing the temperature to 50 °C can significantly improve the efficiency of the Michael reaction. This approach works well with a low loading (0.5−5 mol %) of simple chiral

Scheme 1. Addition of Dimethyl Malonate to Acyclic Enones



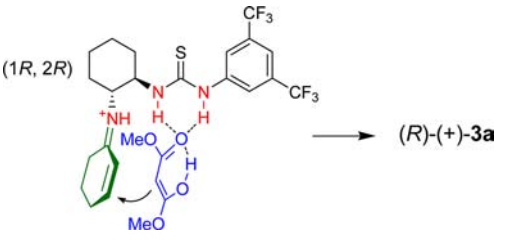


Figure 4. Proposed stereochemical model.

primary amine-thiourea catalysts and with a small excess of dimethyl malonate (1.05−1.2 equiv) in a concentrated solution. This method allows an efficient synthesis of 1,5-ketoesters with good yields (53−96%) and excellent enantioselectivities up to 99% ee and is applicable for multigram scale synthesis.

Moreover, our results confirmed that the presence of an additional basic site (e.g., tertiary amine) in the primary amine-thiourea catalyst structure is not essential for the efficiency of this reaction.

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Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.