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Stereoselective conjugate addition of carbonyl compounds to maleimides using a diaminomethyleneindenedione organocatalyst

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ABSTRACT

A diaminomethyleneindenedione motif can serve as an excellent double hydrogen bonding donor. Bifunctional chiral primary amine **3** bearing a diaminomethyleneindenedione motif is an excellent organocatalyst to promote the asymmetric conjugate additions of various carbonyl compounds to maleimides in high yields with up to 99% ee.

1. Introduction

Substituted succinimide derivatives obtained via the stereoselective conjugate addition of various nucleophiles to maleimides are valuable intermediates in the synthesis of natural products and some clinical drug candidates.[1] Organocatalysis, an environmentally benign chemistry, is one of the most effective synthetic strategies to obtain chiral succinimide derivatives.[2] The asymmetric conjugate additions of 1,3-dicarbonyl compounds to maleimides using natural cinchona alkaloid organocatalysts were reported in pioneering work by Melchiorre et al.[3] Since then, several research groups have reported on the organocatalytic conjugate additions of various nucleophilic carbonyl compounds to maleimides.[2,4–6] Thus, the asymmetric conjugate addition of nucleophilic aldehydes to maleimides using organocatalysts represents an important synthetic method, and a large number of articles have been reported on this regard.[4] We have also reported on the asymmetric conjugate additions of aldehydes to maleimides using thiourea organocatalysts.[4e,g] To the best of our knowledge, although conjugate additions of simple linear and cyclic ketones such as acetone and cyclohexanone to maleimides are particularly important, they have been successfully achieved by only three groups.[5] Therefore, the development of an effective and easily prepared organocatalyst for the conjugate addition of simple ketones to maleimides remains as an essential research theme in organic chemistry. Organocatalysts bearing a motif that functions as a double hydrogen bonding donor, such as thiourea and squaramide, have been intensively investigated as they exhibit highly efficient catalytic activity in various asymmetric reactions to enantiomerically enriched molecules.[7] In addition, modified Takemoto catalysts, which have shown enhanced acidity due to the introduction of an electron-withdrawing group, have been developed.[8]

We have recently developed a diaminomethylenemalononitrile motif serving as an excellent double hydrogen donating functional group in the substitution of thiourea and squaramide.[9–14] Thus, organocatalyst **1** bearing both a chiral primary amine group and a diaminomethylenemalononitrile motif was found to accelerate the asymmetric conjugate additions of aldehydes to vinyl sulfone[9] and the conjugate additions of malonates to α,β-unsaturated ketones under neat conditions.[10] We also reported that a diaminomethylenemalononitrile organocatalyst **2** bearing a chiral secondary amine is a good catalyst for the asymmetric conjugate additions of ketones to nitroalkenes[11] and stereoselective direct aldol reactions of ketones with aromatic aldehydes.[12] In addition, we found that a diaminomethylenemalononitrile organocatalyst bearing a cinchona alkaloid as a chiral tertiary amine catalyzed the asymmetric conjugate additions of 1,3-diketones to nitroalkenes[13] and the asymmetric hydrophosphonylation of aldehydes with diaryl phosphonates.[14] Very recently, we reported in a preliminary communication that organocatalyst **3** bearing a 2-(diaminomethylene)-1*H*-indene-1,3(2*H*)-dione skeleton promotes the conjugate additions of acetone or cyclohexanone to maleimides yielding the corresponding adducts with excellent stereoselectivities.[15] Herein, we describe the full details of the asymmetric conjugate additions of various carbonyl compounds to maleimides using **3** (Fig. 1).

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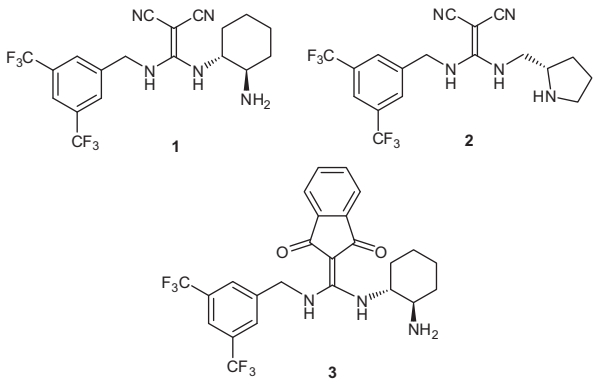
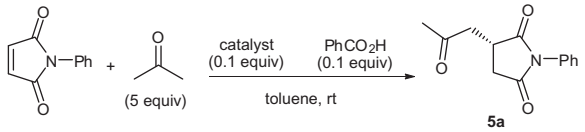


Figure 1. Structure of organocatalysts.

2. Results and discussion

We first examined diaminomethylenemalononitrile organocatalysts **1** and **2** for the asymmetric conjugate addition of acetone to *N*-phenylmaleimide **4a** as shown in Table 1. Organocatalyst **1** bearing a primary amine group provided the desired product **5a** in low yields and with moderate enantioselectivity (Table 1, entry 1). Organocatalyst **2** bearing a secondary amine group showed no reactivity (Table 1, entry 2). Although both **1** and **2** were poor catalysts for the Michael reactions of maleimides with acetone, organocatalysts bearing a primary amine group, such as **1**, tend to be suitable for the conjugate addition. We presumed that the introduction of a more powerful electron-withdrawing functionality (as compared to the cyano group) is required for the development of a more reactive organocatalyst. We selected a carbonyl group (i.e., acetophenone) with a lower pK_a value as compared to that of acetonitrile (24.7 vs 31.3, DMSO).[16] Thus, organocatalyst **3** bearing a diaminomethyleneindenedione skeleton containing carbonyl functionalities instead of the cyano groups of **1** was found to be a good catalyst, which afforded the desired adduct **5a** in moderate yields and with high enantioselectivity (Table 1, entry 3).

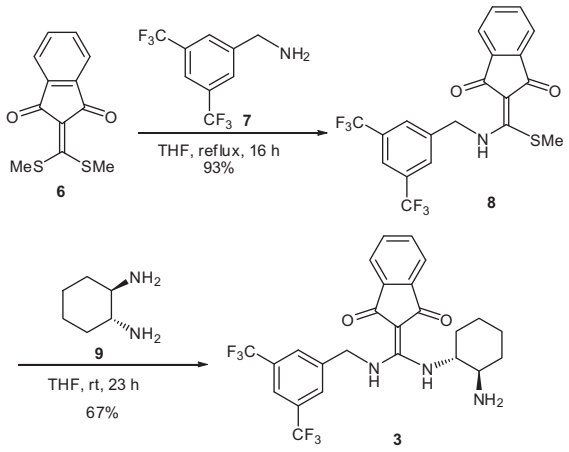
Table 1
Selection of organocatalysts[a]



Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	170	16	57
2	**2**	170	N.D.[d]	—
3	**3**	95	59	89

[a] Reaction conditions: **4a** (0.20 mmol), acetone (1.0 mmol), and catalyst (0.020 mmol) in toluene (0.2 mL) were stirred at rt.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Not detected.

As shown in Scheme 1, organocatalyst **3** can be easily prepared (i.e., two steps) from indenedione derivative **6**.[17] The substitution reaction of **6** with 3,5-bis(trifluoromethyl)benzylamine **7** proceeded smoothly under THF reflux conditions to provide intermediate **8** in 93% yield. In a subsequent step, the substitution reaction of **8** with (1*R*,2*R*)-cyclohexane-1,2-diamine **9** in THF afforded the desired diaminomethyleneindenedione organocatalyst **3** in 63% yield.



Scheme 1. Preparation of organocatalyts **3.**

The studies carried out to find the optimal conditions for the enantioselective conjugate addition using **3** are summarized in Table 2. The conjugate addition reactions were conducted with acetone and **4a** as test reactants in the presence of catalytic amounts of **3** and an additive at room temperature. The reaction in CH_2Cl_2 without an additive was very slow (Table 2, entry 1). The addition of catalytic amounts of benzoic acid enhanced the reaction rate while improving the enantioselectivity (Table 2, entry 2). Therefore, we studied the reaction in a typical reaction solvent and in the presence of benzoic acid. The reaction in less polar solvents such as 1,2-dichloroethane, hexane, and ethyl acetate afforded moderate enantioselectivities (entries 3–5). The stereoselectivity was improved using ethereal solvents (entries 6–8). Polar solvents, such as MeCN, DMF, and MeOH were poor reaction solvents to give low enantioselectivities (entries 9–11). Aromatic solvents were good reaction solvents to provide higher stereoselectivities. Among the aromatic solvents examined, *p*-xylene was found to be the most suitable showing high enantioselectivities (Table 2, entries 13–16). Furthermore, effects associated with the presence of other protic acids in addition to benzoic acid were tested; however the latter was found to be the most suitable additive (Table 2, entries 16–27). Changes in the amount of benzoic acid added (0.2 or 0.05 equiv) resulted in a slight reduction in the enantioselectivity (Table 2, entries 28 and 29). The enantioselectivity was improved by the reaction under dilute conditions (Table 2, entry 30). Finally, both high yield and stereoselectivity were observed when the reaction was conducted at 40 °C and in the presence of 0.2 equiv of **3** (Table 2, entry 32).

Once the optimal conditions were identified, we investigated the scope and limitations of the conjugate additions between various carbonyl compounds and maleimides **4** (Table 3). The reaction of acetone with *N*-benzylmaleimide **4b** proceeded smoothly to give the corresponding addition product **5b** in high yield and with excellent enantioselectivity (Table 3, entry 2). Subsequently, we investigated the substituent effects of the benzene ring during the conjugate additions of maleimides. Bromo-, chloro-, and trifluoromethyl-substituents were chosen as representative electron-withdrawing groups. *N*-(4-Bromophenyl)maleimide **4c** and *N*-(4-chlorophenyl)maleimide **4d** coupled with acetone to give the corresponding adducts in high yield and with high enantioselectivity (Table 3, entries 3 and 4, respectively). *N*-Phenylmaleimide **4e** bearing a trifluoromethyl group reacted with moderate yield and high enantioselectivity (Table 3, entry 5). We selected methyl- and methoxy-substituents as representative electron-donating groups. The maleimides bearing a methyl substituent at the *para* **4f** and *meta* **4g** positions were converted into