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Asymmetric Conjugate Addition of Ketones to Maleimides Using Diaminomethyleneindenedione Organocatalyst

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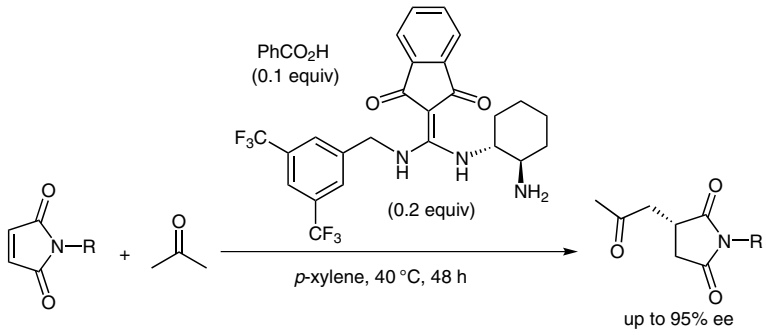

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Abstract A novel diaminomethyleneindenedione (DMI) organocatalyst efficiently promotes the asymmetric conjugate addition of a ketone to a maleimide to afford the corresponding addition product in a high yield with up to 99% enantiomeric excess.

Key words organocatalyst, maleimide, conjugate addition, asymmetric reaction, ketone

Asymmetric conjugate additions of nucleophiles to maleimides using organocatalysts have attracted a great deal attention,[1] because organocatalysis is an environmentally benign method, and the substituted succinimide derivative addition products are valuable intermediates for synthesizing natural products and some candidates for use as clinical drugs.[2] Melchiorre and coworkers described their pioneering work in this area using natural cinchona alkaloids to catalyze enantioselective conjugate additions of 1,3-dicarbonyl compounds to maleimides,[3] and Michael additions of various nucleophiles to maleimides have been developed.[1,4–6] There have been several reports of asymmetric conjugate additions of aldehydes to maleimides using organocatalysts,[4] but successful conjugate additions of simple ketones, such as acetone or cyclohexanone, to maleimides have rarely been reported.[5] Therefore, the development of a novel organocatalyst for Michael reactions between maleimides and simple ketones remains a challenging research theme in organic chemistry.

Conversely, thiourea and squaramide are excellent motifs for efficient organocatalysts, and they function as double-hydrogen-bonding donors that offer highly efficient catalytic activities in various asymmetric reactions, allowing the production of enantiomerically enriched molecules.[7] In recent years, we have developed the diaminomethylenemalononitrile (DMM) motif, which has an excellent double-hydrogen-donating functional group for use instead of the thiourea and squaramide motifs.[8–11] Organocatalyst **1**, which bears the DMM motif and a primary amine group, accelerates reactions between aldehydes and vinyl sulfone, giving the corresponding adducts with a high degree of stereoselectivity.[8] Furthermore, **1** promotes the conjugate addition of a malonate to an α,β-unsaturated ketone without requiring a reaction solvent, and Michael adducts with excellent enantioselectivities are produced.[9] We also reported that the pyrrolidine–DMM organocatalyst **2** is a good catalyst for asymmetric conjugate additions of ketones to nitroalkenes and stereoselective direct aldol reactions of ketones with aromatic aldehydes.[10] In addition, we have described a cinchona–DMM organocatalyst for the asymmetric conjugate addition of a 1,3-diketone to nitroalkenes.[11] To demonstrate further benefits of the DMM motif in organocatalysts, we attempted to use organocatalysts **1** and **2** (each have a DMM skeleton, Figure 1) to catalyze the asymmetric conjugate additions of simple ketones to maleimides.

We examined the abilities of the DMM organocatalysts **1** and **2** to catalyze the asymmetric conjugate addition of acetone to *N*-phenylmaleimide (**4a**), as shown in Table 1. Organocatalyst **1**, which has a primary amine group, provided the desired product **5a** in a low yield with moderate enantioselectivity (Table 1, entry 1). Organocatalyst **2**, which has a secondary amine group, promoted the conjugate addition reaction, and no **5a** was produced (Table 1, entry 2). Unfortunately, neither **1** nor **2** was a good catalyst for the Michael reaction of maleimides with acetone. However, a tendency was found for organocatalysts with primary amine groups, such as **1**, to be suitable for catalyzing conjugate addition. We presumed that introducing a more powerful electron-withdrawing group than the cyano

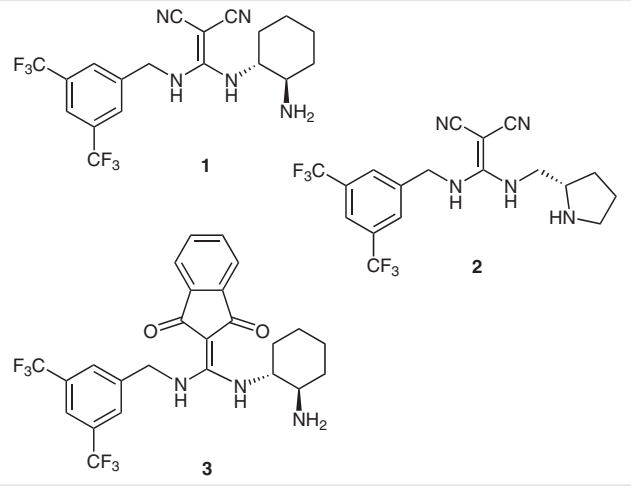
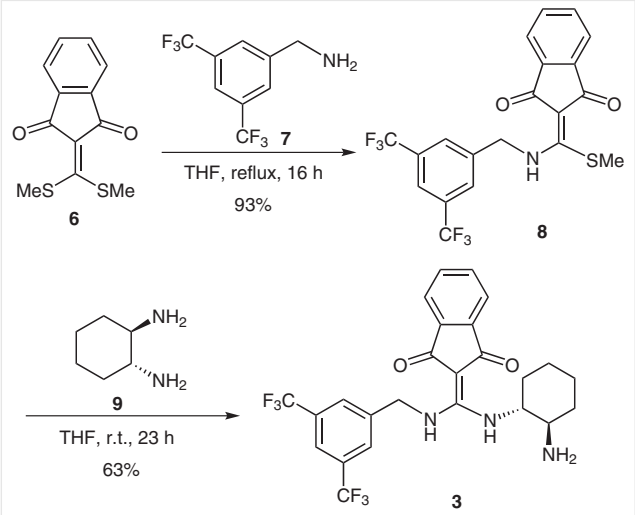


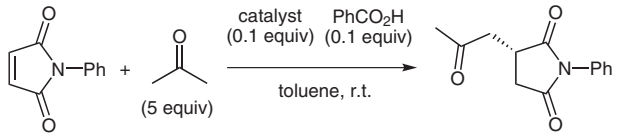
Figure 1 Structure of organocatalysts



Scheme 1 Preparation of organocatalyst **3**

group would be required to develop a more reactive organocatalyst. Organocatalyst **3**, which has a 2-(diaminomethylene)indene-1,3-dione (DMI) skeleton and contains carbonyl groups rather than the cyano groups that are present in **1**, was found to be a good catalyst, giving the desired adduct **5a** in moderate yield with a high degree of enantioselectivity (Table 1, entry 3). Here, we describe efficient conjugate additions of simple ketones to maleimides using the DMI organocatalyst **3** rather than the DMM motif.

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] Reactions 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 HPLC analysis.
[d] Not detected.

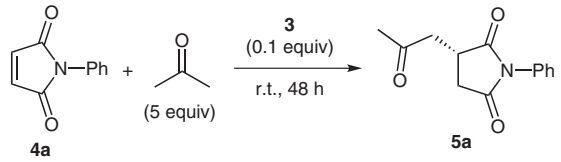
Organocatalyst **3** was easily prepared from the known compound **6**[12] in two steps, as shown in Scheme 1. The reaction of **6** with 3,5-bis(trifluoromethyl)benzylamine (**7**) under reflux conditions in THF provided intermediate **8** in 93% yield. Intermediate **8** was then reacted with (1*R*,2*R*)-cyclohexane-1,2-diamine (**9**) to afford the desired DMI organocatalyst **3**[13] in 63% yield.

We performed tests to determine the optimal conditions for the enantioselective conjugate addition using **3**, as shown in Table 2. The conjugate addition reactions were conducted using acetone and **4a** as test reactants in the presence of a catalytic amount of **3** and the chosen additive at room temperature. *p*-Xylene was found to be the most suitable of the reaction solvents that were tested (Table 2, entries 2–9). We examined the effects of the presence of different protic acids, and benzoic acid was found to be the most suitable additive (Table 2, entries 9–13). Adding 0.2 or 0.05 equivalents of benzoic acid resulted in a slight loss of enantioselectivity (Table 2, entries 14 and 15). Performing the reaction under dilute conditions tended to improve the enantioselectivity (Table 2, entry 16). Conducting the reaction at 40 °C in the presence of 0.2 equivalents of **3** gave both a high yield and a high degree of enantioselectivity (Table 2, entry 18).

Considering these optimal conditions, we examined the scope and limitations of the conjugate additions between ketones and maleimides **4** (Table 3).[14] The reaction between acetone and *N*-benzylmaleimide (**4b**) proceeded smoothly to afford the corresponding product **5b** in high yield with excellent enantioselectivity (Table 3, entry 2). We tested maleimides with electron-withdrawing groups, such as halogen atoms and trifluoromethyl groups, on the aromatic ring. The reactions between maleimides with electron-withdrawing groups and acetone proceeded smoothly giving the corresponding adducts **5c**–**e** in good to high yields and with a high degree of enantioselectivity (Table 3, entries 3–5).

Organocatalyst **3** promoted the reaction between acetone and maleimides bearing methyl or methoxy electron-donating groups to provide the corresponding adducts **5f**–**h** in good to high yields and with a high degree of enantiose-

Table 2 Optimization of Reaction Conditions[a]



4a **5a**

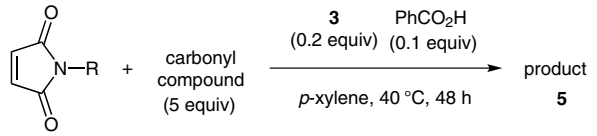
Entry	Solvent	Additive (equiv)	Yield (%)[b]	ee (%)[c]
1[d]	CH_2Cl_2	none	12	75
2	CH_2Cl_2	$PhCO_2H$ (0.1)	32	79
3	MeOH	$PhCO_2H$ (0.1)	37	37
4	MeCN	$PhCO_2H$ (0.1)	44	36
5	THF	$PhCO_2H$ (0.1)	61	85
6	toluene	$PhCO_2H$ (0.1)	58	89
7	*o*-xylene	$PhCO_2H$ (0.1)	63	88
8	*m*-xylene	$PhCO_2H$ (0.1)	60	88
9	*p*-xylene	$PhCO_2H$ (0.1)	50	91
10	*p*-xylene	$MeCO_2H$ (0.1)	70	89
11	*p*-xylene	4-$O_2NC_6H_4CO_2H$ (0.1)	51	88
12	*p*-xylene	TFA (0.1)	trace	–
13	*p*-xylene	4-$MeOC_6H_4CO_2H$ (0.1)	62	88
14	*p*-xylene	$PhCO_2H$ (0.2)	48	85
15	*p*-xylene	$PhCO_2H$ (0.05)	66	88
16[e]	*p*-xylene	$PhCO_2H$ (0.05)	57	93
17[e,f]	*p*-xylene	$PhCO_2H$ (0.1)	68	90
18[e,f,g]	*p*-xylene	$PhCO_2H$ (0.1)	81	92

[a] Reaction conditions (unless otherwise noted): **4a** (0.20 mmol), acetone (1.0 mmol), and catalyst **3** (0.020 mmol) in solvent (0.2 mL) were stirred at r.t. for 48 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The reaction was carried out for 65 h.
[e] *p*-Xylene (0.4 mL) was used.
[f] The reaction was carried out at 40 °C.
[g] Catalyst **3** (0.2 equiv) was used.

lectivity (Table 3, entries 6–8). Isobutyraldehyde reacted with *N*-phenylmaleimide (**4a**) to afford the corresponding adduct **5i** in 74% yield with 94% enantiomeric excess (Table 3, entry 9). Cyclohexanone, another type of ketone, reacted with **4a** to provide the corresponding product **5j** in 95% yield with poor diastereoselectivity, but the enantioselectivities for the *syn* and *anti* isomers were excellent (Table 3, entry 10). The stereochemistry of the addition products **5a–j** was determined by comparison with reported chiral-phase HPLC retention times and optical rotation data.[5]

After considering the stereochemistry of the addition products **5** we presumed that the conjugate addition of acetone to a maleimide involving the DMI organocatalyst **3** progressed via a plausible transition state (Figure 2). The primary amine group in **3** condenses with acetone to form enamine intermediates. The two amine protons of the DMI skeleton can then function as hydrogen-bonding donors, giving a rigid interaction with the maleimide oxygen. These interactions can control the direction (*Si*-face attack) from which the enamine intermediates approach the maleimide. This ultimately leads to the corresponding addition product being formed with excellent enantioselectivity.

Table 3 Conjugate Additions Using Organocatalyst **3**[a]



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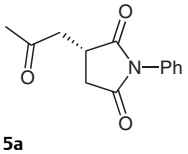
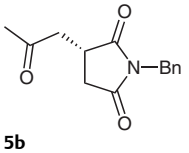
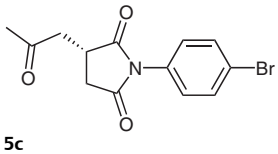
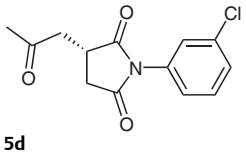
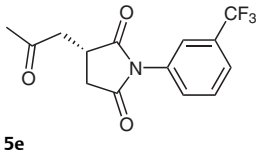
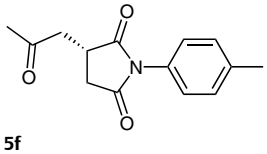
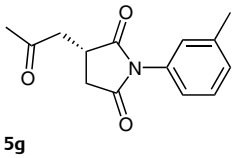
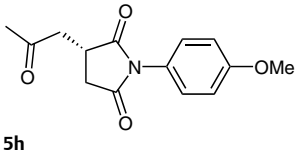
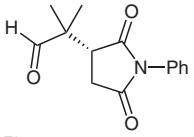
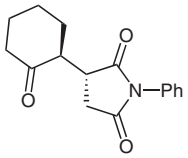
Entry	Product	Yield (%)[b]	ee (%)[c]
1	 **5a**	81	92
2	 **5b**	92	95
3	 **5c**	86	90
4	 **5d**	79	86
5[d]	 **5e**	65	92
6[e]	 **5f**	51	89
7	 **5g**	80	86

Table 3 (continued)

Entry	Product	Yield (%)[b]	ee (%)[c]
8	 **5h**	55	85
9	 **5i**	74	94
10	 **5j**	95[f]	99 (*syn*) 99 (*anti*)

[a] Reactions conditions (unless otherwise noted): **4** (0.20 mmol), carbonyl compounds (1.0 mmol), and catalyst **3** (0.040 mmol) in *p*-xylene (0.4 mL) were stirred at 40 °C for 48 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The reaction was carried out at r.t.
[e] The reaction mixture was stirred for 140 h.
[f] The ratio of *syn* and *anti* isomers was 51:49.

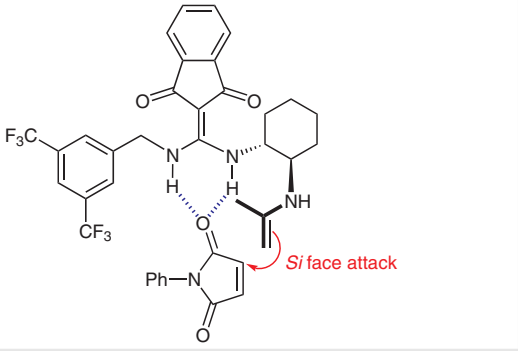


Figure 2 Plausible transition-state model

In conclusion, the DMI organocatalyst **3**, which can easily be prepared from **6** in two steps, is an excellent catalyst for the conjugate additions of ketones to maleimides, providing the corresponding addition products **5** in high yields and with a high degree of enantioselectivity (up to 99% ee). We have demonstrated that the DMI motif can function as a more efficient double-hydrogen-bond donor than can the DMM motif in conjugate additions to maleimides. In our laboratory, we are currently attempting to apply organocatalysts with DMI motifs to other types of stereoselective reaction and to develop additional novel DMI organocatalysts.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380382.

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(13) **Organocatalyst 3**
Yellow powder; mp 179–180 °C; $[\alpha]_D^{29}$ –10.9 (*c* 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.61 (br s, 1 H), 9.02 (d, *J* = 9.8 Hz, 1 H), 7.87 (s, 3 H), 7.61–7.57 (m, 2 H), 7.53–7.49 (m, 2 H), 5.13 (dd, *J* = 6.0, 16.3 Hz, 1 H) 4.88 (dd, *J* = 6.5, 16.3 Hz, 1 H), 3.15–3.06 (m, 1 H), 2.82–2.76 (m, 1 H), 1.89–0.87 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 161.5, 140.3, 138.6, 132.4 (q, $^2J_{C-F}$ = 33.7 Hz), 132.3, 127.1, 123.1 (q, $^1J_{C-F}$ = 273 Hz), 121.9, 120.5, 93.7, 61.3, 55.7, 47.7, 34.1, 33.2, 24.8, 24.2. Anal. Calcd for $C_{25}H_{23}F_6N_3O_2$: C, 58.71; H, 4.53; N, 8.22. Found: C, 58.62; H, 4.52; N, 8.22.

(14) **Typical Procedure of the Conjugate Additions to Maleimides Using 3**
To a mixture of *N*-phenylmaleimide (**4a**, 34.6 mg, 0.200 mmol) and acetone (73.4 µL, 1.00 mmol) in *p*-xylene (0.4 mL) was added organocatalyst **3** (20.5 mg, 0.040 mmol) and benzoic acid (2.5 mg, 0.020 mmol) at r.t. After stirring in closed tube at 40 °C for 48 h, the reaction mixture was directly purified by flash column chromatography on silica gel with a 3:2 to 1:1 mixture of hexane and EtOAc to afford **5a** (37.3 mg, 81%) as a white powder.