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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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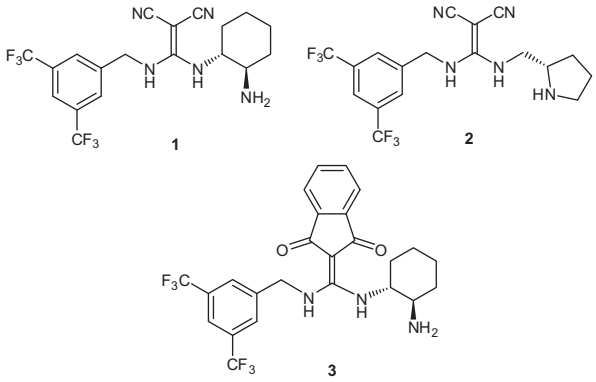
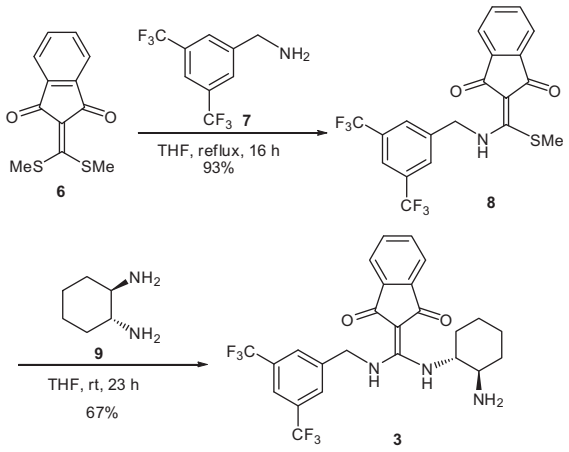


Figure 1. Structure of organocatalysts.

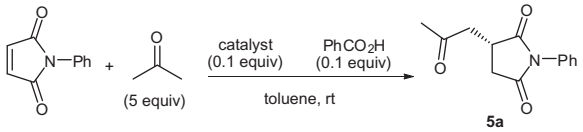


Scheme 1. Preparation of organocatalyts **3.**

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

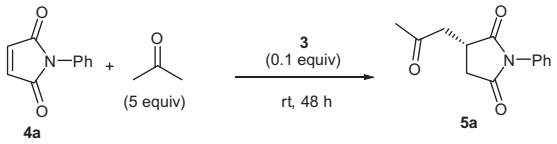
[a] Reaction conditions: **4a** (0.20 mmol), acetone (1.0 mmol), and catalyst (0.020 mmol) in toluene (0.2 mL) were stirred at rt.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Not detected.

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.

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

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	$ClCH_2CH_2Cl$	$PhCO_2H$ (0.1)	34	79
4	Hexane	$PhCO_2H$ (0.1)	63	64
5	AcOEt	$PhCO_2H$ (0.1)	59	80
6	Et_2O	$PhCO_2H$ (0.1)	60	83
7	THF	$PhCO_2H$ (0.1)	61	85
8	1,4-Dioxane	$PhCO_2H$ (0.1)	66	88
9	MeCN	$PhCO_2H$ (0.1)	44	36
10	DMF	$PhCO_2H$ (0.1)	32	0
11	MeOH	$PhCO_2H$ (0.1)	37	37
12	Neat	$PhCO_2H$ (0.1)	72	49
13	Toluene	$PhCO_2H$ (0.1)	58	89
14	*o*-Xylene	$PhCO_2H$ (0.1)	63	88
15	*m*-Xylene	$PhCO_2H$ (0.1)	60	88
16	*p*-Xylene	$PhCO_2H$ (0.1)	50	91
17	*p*-Xylene	HCO_2H (0.1)	59	87
18	*P*-Xylene	$MeCO_2H$ (0.1)	70	89
19	*p*-Xylene	$EtCO_2H$ (0.1)	62	88
20	*p*-Xylene	*n*-$PrCO_2H$ (0.1)	65	89
21	*p*-Xylene	4-$MeOC_6H_4CO_2H$ (0.1)	62	88
22	*p*-Xylene	4-$MeC_6H_4CO_2H$ (0.1)	60	88
23	*p*-Xylene	4-$ClC_6H_4CO_2H$ (0.1)	42	89
24	*p*-Xylene	4-$O_2NC_6H_4CO_2H$ (0.1)	51	88
25	*p*-Xylene	2-$O_2NC_6H_4CO_2H$ (0.1)	28	87
26	*p*-Xylene	2,4-$(O_2N)_2C_6H_3CO_2H$ (0.1)	9	87
27	*p*-Xylene	CF_3CO_2H (0.1)	Trace	—
28	*p*-Xylene	$PhCO_2H$ (0.2)	48	85
29	*p*-Xylene	$PhCO_2H$ (0.05)	66	88
30[e]	*p*-Xylene	$PhCO_2H$ (0.05)	57	93
31[e,f]	*p*-Xylene	$PhCO_2H$ (0.1)	68	90
32[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 rt for 48 h.
[b] Isolated yields.
[c] Determined by chiral 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.

the corresponding addition products **5f** and **5g** with high enantioselectivities (Table 3, entries 6 and 7, respectively). The maleimide bearing a methoxy group at the *para*-position **4h** afforded **5h** in lower yields but with high enantioselectivity (Table 3, entry 8). Next, we examined the reactivity of maleimides with various ketones. Maleimide **4a** readily reacted with a cyclic ketone, such as cyclohexanone, to provide the corresponding adduct **5i** in excellent yield without diastereoselectivity and with the highest enantioselectivities (each >99% ee) (Table 3, entry 9). Cyclohexanone bearing a protective acetal group added to **4a** afforded adduct **5j** in high yield, excellent enantioselectivities, and no diastereoselectivity (Table 3, entry 10). Cyclopentanone was added to **4a** to give adduct **5k** with moderate diastereoselectivity (Table 3, entry 11). Long-chain aliphatic ketones, such as pentan-3-one and heptan-4-one, were found to be poor substrates because of their steric hindrance. Thus, low to moderate yields and no diastereoselectivities were obtained in spite of longer reaction times. However, products **5l** and **5m** were obtained with high enantioselectivities (Table 3, entries 12 and 13). The reaction of pentane-2,4-dione with **4a** afforded adduct **5n** in good yield and with moderate enantioselectivity (Table 3, entry 14). The conjugate addition of 1-methoxypropan-2-one to **4a** provided **5o** in high yield with low diastereoselectivity. Unlike the minor diastereomer, the enantioselectivity of the major diastereomer was low (Table 3, entry 15). Furthermore, we investigated the reactivity of maleimide **4a** with various aldehydes using organocatalyst **3**. Isobutyraldehyde reacted with **4a** to provide the corresponding adduct **5p** in good yield and with excellent stereoselectivity (Table 3, entry 16). 2-Ethylbutanal afforded **5q** with low rates and moderate yield and enantioselectivity in spite of the long reaction time (Table 3, entry 17). Aldehydes bearing a cycloalkane moiety such as cyclopentanecarboxaldehyde and cyclohexanecarboxaldehyde were converted into their corresponding adducts **5r** and **5s** in high yield and with high enantioselectivities (Table 3, entries 18 and 19, respectively). The asymmetric addition of a simple linear aldehyde, such as propanal, proceeded to the diastereo-mixture **5t** with excellent enantioselectivities (Table 3, entry 20). Dimethyl malonate afforded the adduct **5u** in low yield due to the difficult formation of the enamine by reaction between **3** and dimethyl malonate (Table 3, entry 21).

We speculate that the conjugate addition of acetone to maleimides promoted by diaminomethyleneindenedione-organocatalyst **3** follows the reaction mechanism as shown in Scheme 2 that considers the stereochemistry of addition products **5a**. The primary amine group of **3** condenses with acetone to the enamine intermediate **10**. The enediamine protons of the diaminomethyleneindenedione skeleton acting as hydrogen bonding donors then capture one of the carbonyl oxygens of the maleimide. Furthermore, the carbonyl group is activated by the hydrogen bonding to enhance the reactivity of the β-position. These interactions can control the approach direction (*Si* face attack) of the enamine intermediates to the maleimides as shown in transition state **A**. This ultimately affords the corresponding addition products with excellent enantioselectivities. After the addition of the enamine to the maleimide, iminium intermediate **11** is obtained. Finally, iminium **11** is hydrolyzed to afford adduct **5a** and organocatalyst **3**. Information supporting the presence of the enamine intermediate and the transition state could not be obtained by NMR measurement. However, the enamine intermediate **10** was detected by mass spectrometry.

3. Conclusion

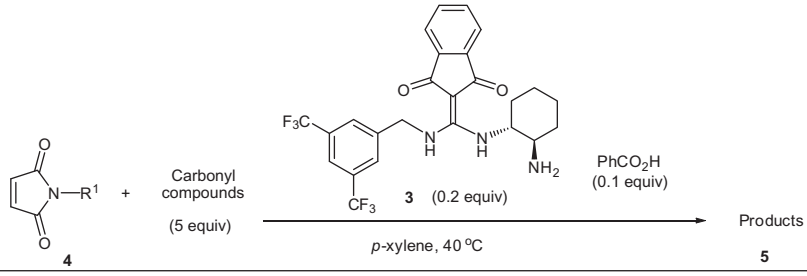
In conclusion, the diaminomethyleneindenedione-organocatalyst **3** can be readily synthesized from **6** in only two steps. Catalyst **3** efficiently promoted the conjugate additions of various carbonyl compounds to maleimides **4** to afford the corresponding addition products **5** in good to high yields with high stereoselectivities (up to 99% ee). We have demonstrated that a diaminomethyleneindenedione skeleton is a more efficient double hydrogen bond donor than diaminomethylenemalononitrile for the conjugate additions to maleimides. The application of organocatalysts with diaminomethyleneindenedione motifs to other types of asymmetric reactions as well as the development of novel diaminomethyleneindenedione-organocatalysts are currently underway in our laboratory.

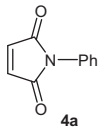
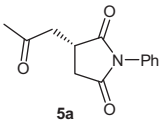
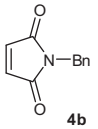
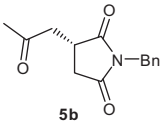
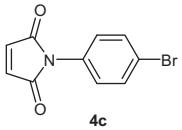
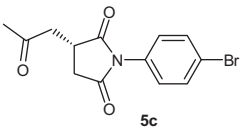
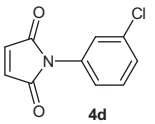
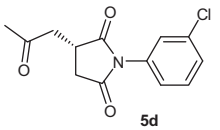
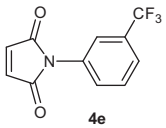
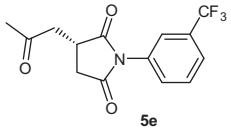
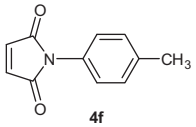
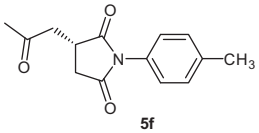
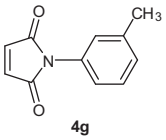
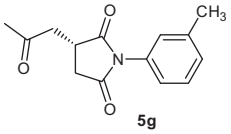
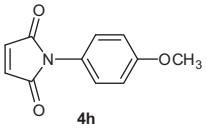
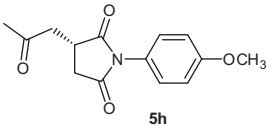
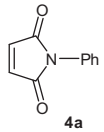
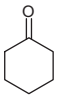
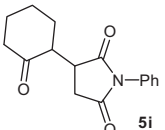
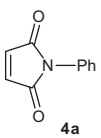
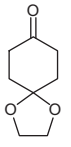
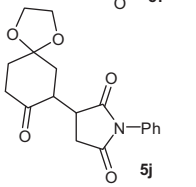
4. Experimental

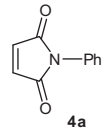
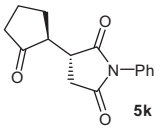
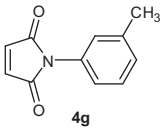
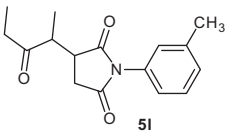
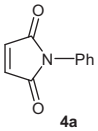
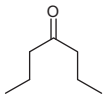
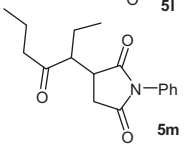
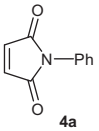
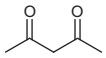
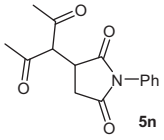
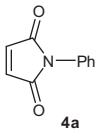
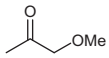
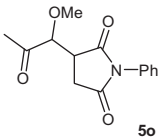
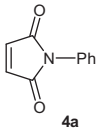
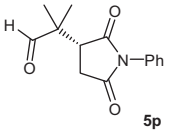
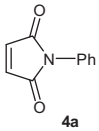
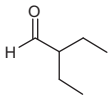
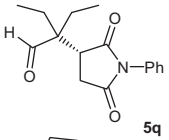
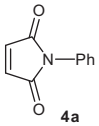
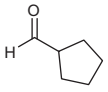
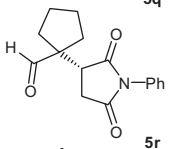
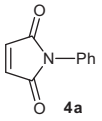
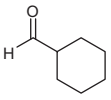
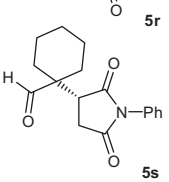
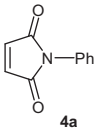
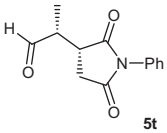
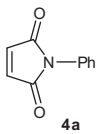
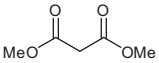
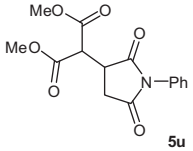
4.1. General

^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker DPX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts are expressed in ppm downfield from tetramethylsilane ($\delta = 0.00$) as an internal standard. Mass

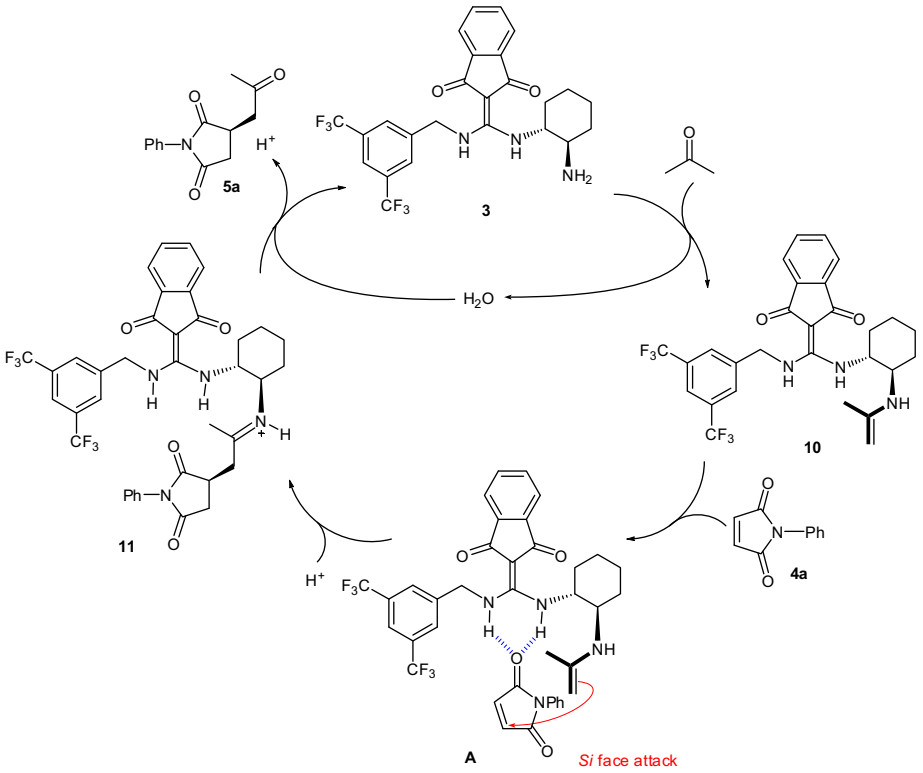
Table 3
Michael reactions of various maleimides with carbonyl compounds in the presence of organocatalyts **3**



Entry	Maleimide **4**	Carbonyl compound	Product **5**	Time (h)	Yield[a] (%)	Diastereo ratio[b]	ee[c] (%)
1	 **4a**		 **5a**	48	81	—	92
2	 **4b**		 **5b**	48	92	—	95
3	 **4c**		 **5c**	48	86	—	90
4	 **4d**		 **5d**	48	79	—	86
5[d]	 **4e**		 **5e**	48	65	—	92
6	 **4f**		 **5f**	140	51	—	89
7	 **4g**		 **5g**	48	80	—	86
8	 **4h**		 **5h**	48	55	—	85
9	 **4a**		 **5i**	48	95	51:49	99 (99)[e]
10	 **4a**		 **5j**	24	88	55:45	96 (99)[e]

Entry	Maleimide **4**	Carbonyl compound	Product **5**	Time (h)	Yield[a] (%)	Diastereo ratio[b]	ee[c] (%)
11	 **4a**		 **5k**	24	67	73:27	87(62)[e]
12	 **4g**		 **5l**	160	65	51:49	96 (88)[e]
13	 **4a**		 **5m**	140	14	53:47	90 (82)[e]
14	 **4a**		 **5n**	168	75	—	40
15	 **4a**		 **5o**	24	87	57:43	29 (73)[e]
16	 **4a**		 **5p**	48	74	—	94
17	 **4a**		 **5q**	168	62	—	76
18	 **4a**		 **5r**	48	95	—	91
19	 **4a**		 **5s**	48	84	—	94
20	 **4a**		 **5t**	24	83	57:43	95 (92)[e]
21	 **4a**		 **5u**	96	18	—	3

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis.
[d] The reaction was carried out at rt.
[e] Enantiomeric excess of the major isomer. Enantiomeric excess of the minor isomer in parentheses.



Scheme 2. Proposed reaction mechanism for asymmetric conjugate addition.

spectra were recorded by an electrospray ionization-time of flight (ESI-TOF) mass spectrometer (Micromass LCT). For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Flash column chromatography was performed on neutral silica gel (40–50 μm).

4.2. Preparation of the organocatalyst

4.2.1. 2-({[3,5-Bis(trifluoromethyl)benzyl]amino}(methylsulfanyl)methylidene)-2,3-dihydro-1*H*-indene-1,3-dione 8

To a stirred solution of compound **6**[17] (1.6 g, 6.5 mmol) in THF (22 mL) was added 3,5-bis(trifluoromethyl)benzylamine **7** (1.6 g, 6.5 mmol). The mixture was stirred at reflux for 16 h. TLC indicated the reaction was completed, the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was crystallized from $CHCl_3$ and hexane to afford compound **8** (2.7 g, 93%). Yellow powder; mp 183–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.12 (br s, 1H), 7.86 (s, 1H), 7.77 (s, 2H), 7.74–7.72 (m, 2H), 7.62–7.60 (m, 2H), 5.01 (d, J = 6.3 Hz, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 139.3, 133.3, 132.5 (q, $^2J_{C-F}$ = 33.7 Hz), 127.5, 123.0 (q, $^1J_{C-F}$ = 273 Hz), 122.1 (q, $^3J_{C-F}$ = 3.7 Hz), 121.6, 104.8, 47.9, 19.1; HRMS (ESI-TOF): calcd for $C_{20}H_{14}F_6NO_2S$ $(M+H)^+$: 446.0644, found: 446.0647.

4.2.2. 2-({[(1*R*,2*R*)-2-Aminocyclohexyl]amino}{[3,5-bis(trifluoromethyl)benzyl]amino}methylidene)-2,3-dihydro-1*H*-indene-1,3-dione 3

To a stirred solution of compound **8** (2.0 g, 4.5 mmol) in THF (15 mL) was added (1*R*,2*R*)-cyclohexane-1,2-diamine **9** (512.7 mg, 4.5 mmol). The mixture was stirred at room temperature for 23 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH. Afforded compound **3** was recrystallized two times from $CHCl_3$ and hexane to afford pure **3** (1.49 g, 67%). Yellow powder; mp 179–180 °C; $[\alpha]_D^{29}$ = −10.9 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (br s, 1H), 9.02 (d, J = 9.8 Hz, 1H), 7.87 (s, 3H), 7.61–7.57 (m, 2H), 7.53–7.49 (m, 2H), 5.13 (dd, J = 6.0, 16.3 Hz, 1H) 4.88 (dd, J = 6.5, 16.3 Hz, 1H), 3.15–3.06 (m, 1H), 2.82–2.76 (m, 1H), 1.89–0.87 (m, 10H); ^{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.

4.3. Typical procedure for a conjugate addition using organocatalyst 3 (Table 2)

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

4.3.1. (*S*)-3-(2-Oxopropyl)-1-phenylpyrrolidine-2,5-dione 5a[5c]

$[\alpha]_D^{27}$ = +10.0 (c 1.0, CH_2Cl_2). 92% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 75:25), flow rate = 0.5 mL/min; λ = 220 nm; t_{major} = 57.8 min, t_{minor} = 72.3 min.

4.3.2. (*S*)-1-Benzyl-3-(2-oxopropyl)pyrrolidine-2,5-dione 5b[5c]

$[\alpha]_D^{27}$ = −2.0 (c 1.0, CH_2Cl_2). 95% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 18.6 min, t_{minor} = 28.5 min.

4.3.3. (*S*)-1-(4-Bromophenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione 5c[5c]

$[\alpha]_D^{27}$ = +5.5 (*c* 1.0, CH_2Cl_2). 90% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 26.2 -min, t_{minor} = 45.3 min.

4.3.4. (*S*)-1-(3-Chlorophenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione 5d[5a]

$[\alpha]_D^{27}$ = +9.2 (*c* 1.0, CH_2Cl_2). 86% ee; Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 18.8 -min, t_{minor} = 17.4 min.

4.3.5. (*S*)-3-(2-Oxopropyl)-1-[3-(trifluoromethyl)phenyl]pyrrolidine-2,5-dione 5e[5a]

$[\alpha]_D^{25}$ = +7.3 (*c* 1.0, CH_2Cl_2). 92% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 15.4 -min, t_{minor} = 20.7 min.

4.3.6. (*S*)-1-(4-Methylphenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione 5f[5a]

$[\alpha]_D^{25}$ = +11.7 (*c* 1.0, CH_2Cl_2). 89% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 23.1 -min, t_{minor} = 31.8 min.

4.3.7. (*S*)-1-(3-Methylphenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione 5g[5a]

$[\alpha]_D^{27}$ = +13.1 (*c* 1.75, CH_2Cl_2). 86% ee; Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 20.5 -min, t_{minor} = 16.8 min.

4.3.8. (*S*)-1-(4-Methoxyphenyl)-3-(2-oxopropyl)pyrrolidine-2,5-dione 5h[5a]

$[\alpha]_D^{25}$ = +11.9 (*c* 1.0, CH_2Cl_2). 85% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 220 nm; t_{major} = 38.0 -min, t_{minor} = 68.4 min.

4.3.9. 3-(2-Oxocyclohexyl)-1-phenylpyrrolidine-2,5-dione 5i[5b,c]

Compound **5i** was obtained as an inseparable mixture. The signal of ^{1}H NMR for *anti*-isomer is 3.23–3.35 ppm and the signal for *syn*-isomer is 3.18–3.22 ppm.[5b] The ratio of diastereomers was determined *syn*:*anti* = 51:49 by the integral of their signals. Enantiomeric excess of each diastereomers was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 70:30), flow rate = 0.5 mL/min; λ = 220 nm; $t_{major\ (anti)}$ = 28.3 min, $t_{minor\ (anti)}$ = n.d. $t_{major\ (syn)}$ = 34.4 min, $t_{minor\ (syn)}$ = n.d. (>99% ee for *syn* diastereomer, >99% ee for *anti* diastereomer).

4.3.10. 3-(8-Oxo-1,4-dioxaspiro[4.5]decan-7-yl)-1-phenylpyrrolidine-2,5-dione 5j[5b]

Compound **5j** was obtained as an inseparable mixture. The ratio of diastereomers is determined 55:45 by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (hexane/2-propanol = 60:40), flow rate = 0.5 mL/min; λ = 254 nm; major diastereomer: t_{major} = 76.5 min, t_{minor} = 144.0 -min. minor diastereomer: t_{major} = 86.6 min, t_{minor} = 119.4 min. (96% ee for major diastereomer, 99% ee for minor diastereomer).

4.3.11. (*R*)-3-[(*S*)-2-Oxocyclopentyl]-1-phenylpyrrolidine-2,5-dione 5k[5c]

$[\alpha]_D^{20}$ = +97.9 (*c* 0.5, CH_2Cl_2). 87% ee for major diastereomer (*anti*-isomer); $[\alpha]_D^{20}$ = −22.9 (*c* 0.5, CH_2Cl_2). 62% ee for minor diastereomer (*syn*-isomer); The ratio of diastereomers was determined 73:27 (*anti*:*syn*) by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralPak IB column (hexane/2-propanol = 80:20), flow rate = 0.5 mL/min; λ = 210 nm; major diastereomer (*anti*-isomer): t_{major} = 51.2 min, t_{minor} = 48.7 min. minor diastereomer (*syn*-isomer): t_{major} = 66.7 -min, t_{minor} = 58.8 min.

4.3.12. 3-(3-Oxopentan-2-yl)-1-(m-tolyl)pyrrolidine-2,5-dione 5l[5a]

$[\alpha]_D^{20}$ = −27.0 (*c* 1.0, CH_2Cl_2). 96% ee for major diastereomer; $[\alpha]_D^{20}$ = +32.5 (*c* 1.0, CH_2Cl_2). 88% ee for minor diastereomer; The ratio of diastereomers was determined 51:49 by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralPak AS-H column (hexane/2-propanol = 70:30), flow rate = 0.6 mL/min; λ = 240 nm; major diastereomer: t_{major} = 21.5 -min, t_{minor} = 24.3 min. minor diastereomer: t_{major} = 19.3 min, t_{minor} = 18.3 min.

4.3.13. 3-(4-Oxoheptan-3-yl)-1-phenylpyrrolidine-2,5-dione 5m[5a]

Compound **5m** was obtained as an inseparable mixture. The ratio of diastereomers is determined 53:47 by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2- propanol = 75:25), flow rate = 0.5 mL/min; λ = 240 nm; major diastereomer: t_{major} = 25.7 -min, t_{minor} = 22.3 min. minor diastereomer: t_{major} = 25.7 min, t_{minor} = 22.3 min.

4.3.14. 3-(2,4-Dioxopentan-3-yl)-1-phenylpyrrolidine-2,5-dione 5n[6o]

$[\alpha]_D^{20}$ = −46.8 (*c* 1.0, $CHCl_3$). 47% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 85:15), flow rate = 1.0 mL/min; λ = 210 nm; t_{major} = 66.2 -min, t_{minor} = 52.7 min

4.3.15. 3-(1-Methoxy-2-oxopropyl)-1-phenylpyrrolidine-2,5-dione 5o[5c]

$[\alpha]_D^{20}$ = −0.1 (*c* 1.0, CH_2Cl_2). 29% ee for *anti*-isomer; $[\alpha]_D^{20}$ = +59.1 (*c* 1.0, CH_2Cl_2). 73% ee for *syn*-isomer; The ratio of diastereomers was determined *syn*:*anti* = 43:57 by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralPak IC column (hexane/2-propanol = 85:15), flow rate = 1.0 mL/min; λ = 220 nm; major diastereomer (*anti*-isomer): t_{major} = 46.7 min, t_{minor} = 29.0 min. minor diastereomer (*syn*-isomer): t_{major} = 53.0 -min, t_{minor} = 40.9 min.

4.3.16. (*R*)-2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal 5p[4c,5c]

$[\alpha]_D^{27}$ = +1.8 (*c* 1.0, CH_2Cl_2). 94% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 75:25), flow rate = 0.9 mL/min; λ = 220 nm; t_{major} = 22.2 -min, t_{minor} = 17.9 min.

4.3.17. (*R*)-2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-ethylbutanal 5q[4c]

$[\alpha]_D^{19}$ = +2.9 (*c* 1.0, $CHCl_3$); 76% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 80:20), flow rate = 1.0 mL/min; λ = 240 nm; t_{major} = 31.7 -min, t_{minor} = 18.5 min.

4.3.18. (*R*)-1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclopentane-1-carbaldehyde 5r[4b]

$[\alpha]_D^{19}$ = −12.7 (*c* 1.0, $CHCl_3$). 91% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 75:25), flow rate = 0.5 mL/min; λ = 210 nm; t_{major} = 50.6 -min, t_{minor} = 35.9 min.

4.3.19. (*R*)-1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclohexane-1-carbaldehyde 5s[4b,c]

$[\alpha]_D^{20}$ = +1.8 (*c* 1.0, $CHCl_3$). 94% ee; Enantiomeric excess was determined by HPLC with ChiralCel OD-H column (hexane/2-propanol = 75:25), flow rate = 0.5 mL/min; λ = 210 nm; t_{major} = 46.6 -min, t_{minor} = 36.4 min.

4.3.20. (*R*)-2-[(*R*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl]propanal 5t[4b]

Compound **5t** was obtained as an inseparable diastereo mixture. The ratio of diastereomers is determined 57:43 by the integral of their signals. Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 80:20), flow rate = 0.5 mL/min; λ = 210 nm; major diastereomer: t_{major} = 46.7 -min, t_{minor} = 40.9 min. minor diastereomer: t_{major} = 61.8 min, t_{minor} = 36.2 min. (95% ee for major diastereomer, 92% ee for minor diastereomer).

4.3.21. Dimethyl 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)propanedioate 5u[6o]

$[\alpha]_D^{19}$ = +0.1 (*c* 0.3, $CHCl_3$). 3% ee; Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane/2-propanol = 92:8), flow rate = 1.0 mL/min; λ = 230 nm; t_{major} = 102.1 -min, t_{minor} = 53.9 min.

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