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Organocatalytic and Enantioselective Direct Vinylogous Michael Addition to Maleimides

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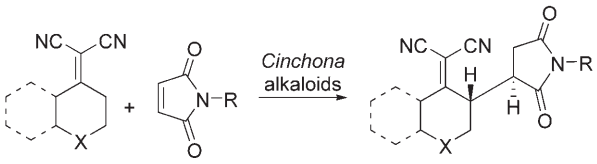
Abstract: An organocatalytic enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins to maleimide has been developed; the products could be obtained in good yields and high enantioselectivities.

Keywords: *Cinchona* alkaloids; dicyanoolefins; enantioselective Michael addition; maleimides; organocatalysis

In recent years, organocatalysis has become a powerful tool in the field of organic chemistry.[1] Organocatalysts that possess both an acidic and a basic/nucleophilic structural moiety constitute an increasingly powerful platform for the development of asymmetric catalysis.[2] Among them, the catalytic enantioselective conjugate addition of compounds using organocatalysts with a prochiral nucleophilic carbon atom to α,β-substituted Michael acceptors provides one of the most versatile and attractive approaches for the generation of optically active compounds. To date, the acceptors employed in the enantioselective Michael reactions have been nitroalkenes,[3] enones,[4] and unsaturated imides.[5] Our interest in the use of conjugate addition for the synthesis of complex molecules has encouraged us to investigate the asymmetric conjugate addition of carbon-centered nucleophiles to maleimides. Succinimides are such moieties, found in numerous biologically interesting molecules and pharmaceuticals; therefore, they are often used as pharmacophores in drug discovery.[6] However, the enantioselective Michael reaction using maleimides as the acceptors has been relatively unexplored.[7] In this paper, we report the development of the first enantioselective direct conjugate addition of α,α-dicyanoolefins to maleimides promoted by *Cinchona* alkaloids as chiral catalysts [Eq. (1)].[8] The reactions afforded highly functionalized products with two adjacent stereogenic carbon atoms in high levels of enantio- and diastereoselectivities.



(1)

The feasibility of our organocatalytic asymmetric approach was first tested by mixing α,α-dicyanoolefin (**1a**) and maleimide (**2a**) in dichloromethane (0.1 M) in the presence of a catalytic amount of a *Cinchona* alkaloid derivative (10 mol%). Representative results of the extensive screening of reaction conditions using the alkaloids shown in Figure 1 are listed in Table 1. The results of the investigation revealed that the reaction could proceed smoothly to yield the desired products. However, the enantioselectivities varied greatly depending on the *Cinchona* alkaloid derivative used. Organocatalyst **4i** exhibited the most promising results in terms of *ee* (74%), *dr* (9/1), and conversion (90%). The studies showed that the free hydroxy group R^2 in catalyst **4i** plays a key role in substrate activation, since the corresponding catalyst **4j** showed significantly lower efficiency (*ee* 17%, Table 1, entry 10). As shown from the results (Table 1, entry 7 *vs.* 8), it was also necessary that the C-9 alcohol group be protected in the form of ether.

Therefore, catalyst **4i** was selected for the subsequent studies. We next investigated the effect of the reaction medium, reaction temperature and catalyst loading in the presence of a catalytic amount of **4i**. It was found that the reaction proceeded smoothly in non-polar solvents (Table 2, entries 1–7), but poor result was obtained with polar protic solvent (Table 2, entry 8). This is expected since non-polar solvents can minimize the disruption of the hydrogen-bonding interactions between catalyst and substrates; and thus

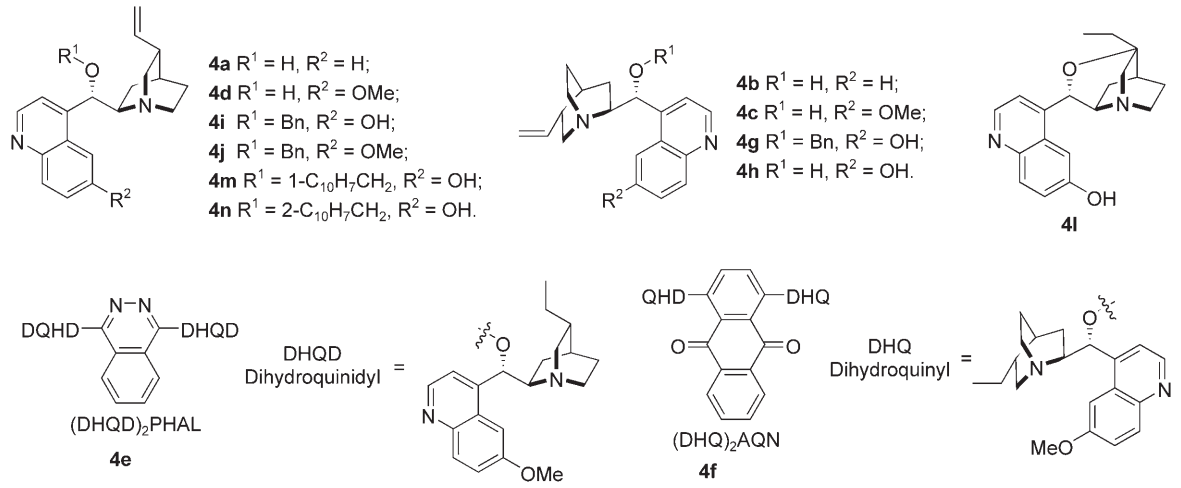
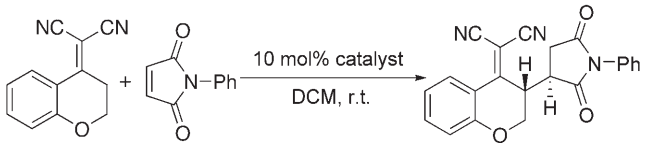


Figure 1. Structures of the *Cinchona* alkaloid catalysts.

Table 1. Organocatalytic asymmetric conjugate addition of **1a** to **2a**.[a]



Entry	Catalyst	Conv. [%][b]	*dr*[b]	*ee* [%][c]
1	**4a**	93	90/10	5
2	**4b**	97	80/20	11
3	**4c**	93	70/30	5
4	**4d**	89	70/30	11
5	**4e**	86	78/22	44
6	**4f**	85	85/15	36
7	**4g**	92	88/12	66
8	**4h**	10	70/30	30
9	**4i**	90	90/10	74
10	**4j**	88	90/10	17

[a] The reactions were performed on a 0.1 mmol scale (0.1 M).
[b] Conversion and *dr* were determined by ^{1}H NMR spectroscopic analysis of the crude product mixture.
[c] *ee* of the major diastereoisomer.

high catalytic activity and stereoselectivity toward the reaction are generally observed. The most encouraging result was obtained when the reaction was carried out in toluene (Table 2, entry 9). By lowering the temperature to −20 °C, the desired product could be furnished in good yield and high enantioselectivity. Furthermore, only the *anti*-Michael addition product was obtained (Table 2, entry 9, Figure 3). No further improvement could be found when the process was carried out under other reaction conditions (Table 2, entries 10–13). Prompted by these results, more catalysts were synthesized, and their catalytic activities were also investigated (Table 2, entries 14–18). From the

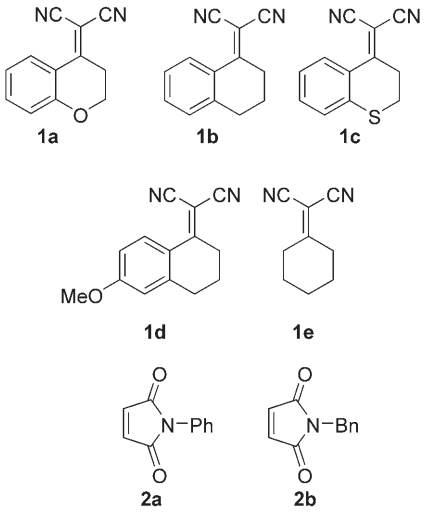
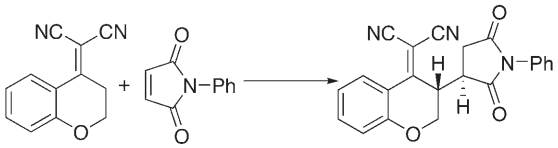


Figure 2. Structures of the α,α-dicyanoolefins and maleimides used in this study.

results, it was found that catalyst **4n** also showed good reactivity and selectivity for the asymmetric Michael addition of α,α-dicyanoolefins to maleimides.

Having optimized the reaction conditions for the asymmetric Michael addition of α,α-dicyanoolefins to maleimides in toluene, it was extended to other substrates using both the catalysts, **4i** and **4n**. A variety of α,α-vinylmalononitriles and -maleimides (Figure 2) were evaluated under the optimized reaction conditions, and the results are summarized in Table 3. In most of the cases, the reactions proceeded smoothly to furnish the desired products in good yields and high enantioselectivities, and only the *anti*-products were observed in the reactions. However, when the cyclic aliphatic substrate **1e** was tested, the major product could be obtained in excellent enantioselectivity and moderate yield while the minor diastereomer could also be isolated with moderate enantiose-

Table 2. Optimization of reaction conditions of asymmetric conjugate addition of **1a** to **2a**.[a]



Entry	Catalyst (mol%)	Solvent	Temp. [°C]	Time [h]	Conv. [%][b]	*dr*[b]	*ee* [%][c]
1	**4i** (10)	DCM	r.t.	8	90	90/10	74
2	**4i** (10)	THF	r.t.	8	44	82/18	81
3	**4i** (10)	toluene	r.t.	8	94	89/11	85
4	**4i** (10)	*t*-BuOMe	r.t.	8	93	95/5	45
5	**4i** (10)	$ClCH_2CH_2Cl$	r.t.	8	88	50/50	75
6	**4i** (10)	xylene	r.t.	8	90	91/9	78
7	**4i** (10)	4-$CF_3C_6H_5$	r.t.	8	65	83/17	70
8	**4i** (10)	*i*-PrOH	r.t.	8	85	50/50	5
9	**4i** (10)	toluene	−20	48	80	100	88 (95)[d]
10	**4i** (20)	toluene	r.t.	8	96	90/10	84
11	**4i** (15)	toluene	0	24	94	89/11	80
12	**4i** (10)	toluene	−40	80	62	100	83
13	**4i** (5)	toluene	−20	48	48	100	88
14	**4k** (10)	toluene	r.t.	8	90	91/9	40
15	**4l** (10)	toluene	r.t.	8	92	86/14	12
16	**4m** (10)	toluene	r.t.	8	86	89/11	50
17	**4n** (10)	toluene	r.t.	8	92	90/10	86
18	**4n** (10)	toluene	−20	48	82	>98/2	89

[a] The reactions were performed on a 0.1 mmol scale (0.1 M).
[b] Conversion and *dr* were determined by ^{1}H NMR spectroscopic analysis of the crude product mixture.
[c] *ee* of the major diastereoisomer.
[d] After a single crystallization.

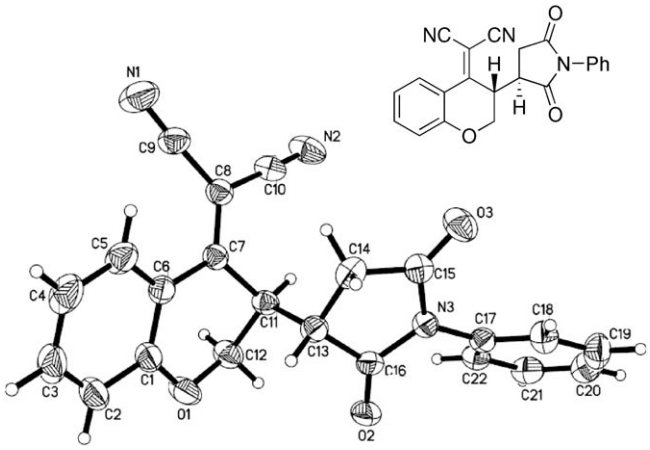


Figure 3. X-ray crystallographic structure of *rac*-**3aa**.

lectivity (Table 3, entries 13 and 16). Surprisingly, when the reaction of **1a** and **2b** was carried out under the present reaction conditions, the enantioselectivity was improved to >99% *ee* (Table 3, entries 11 and 14). In addition, an electron-donating substituent on the aryl ring of the α,α-dicyanoolefin substrate tended to decrease their reactivity without affecting the good enantioselectivity (Table 3, entries 4 and 9).

To determine the absolute configuration of the vinylogous Michael addition products, enantiopure **3ca** (>99% *ee*), which contains a sulfur atom, was crystallized slowly from 2-propanol. The crystals obtained were suitable for X-ray structural analysis. The relative and absolute configurations of the two contiguous stereogenic carbons in **3ca** could easily be determined by X-ray crystallographic analysis. As shown in Figure 4, the two newly created stereocenters of **3ca**

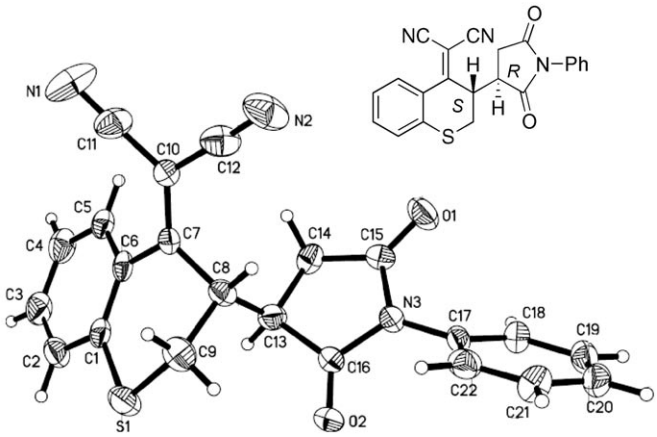
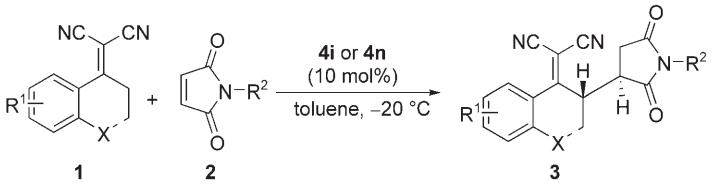


Figure 4. X-ray crystallographic structure of **3ca.**

Table 3. Asymmetric conjugate addition of α,α-dicyanoolefins to maleimides.[a]



Entry	Catalyst	1	2	Product	Yield [%][b]	*ee* [%][c]
1	**4i**	**1a**	**2a**	**3aa**	80	88 (95)[d]
2	**4i**	**1b**	**2a**	**3ba**	81	85
3	**4i**	**1c**	**2a**	**3ca**[e]	90	85 (99)[d]
4	**4i**	**1d**	**2a**	**3da**	35	81
5	**4i**	**1e**	**2a**	**3ea**	78	80
6	**4n**	**1a**	**2a**	**3aa**	86	92
7	**4n**	**1b**	**2a**	**3ba**	82	96
8	**4n**	**1c**	**2a**	**3ca**	88	82
9	**4n**	**1d**	**2a**	**3da**	36	82
10	**4n**	**1e**	**2a**	**3ea**	74	82
11	**4i**	**1a**	**2b**	**3ab**	81	>99
12	**4i**	**1c**	**2b**	**3cb**	89	92
13	**4i**	**1e**	**2b**	**3eb**	41 (16)	94 (70)[f]
14	**4n**	**1a**	**2b**	**3ab**	85	>99
15	**4n**	**1c**	**2b**	**3cb**	88	95
16	**4n**	**1e**	**2b**	**3eb**	42 (14)	95 (74)[f]

[a] The reaction was carried out on a 0.1 mmol scale (0.1 M).
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral phase.
[d] After a single recrystallization.
[e] The absolute configuration was determined to be C-8: *S*, C-13: *R* by X-ray crystallographic analysis.
[f] Data in brackets are for the separable minor diastereomer.

were revealed to possess (8*S*,13*R*)-configuration with an *anti*-structure.

In summary, to the best of our knowledge, this paper represents the first organocatalytic and asymmetric direct vinylogous Michael addition of α,α-dicyanoolefins to maleimides, generating the products in good yields with excellent diastereo- and enantioselectivities. Further studies are well under way to expand the synthetic utility of this new reaction, as well as the application of this catalytic system in other asymmetric transformations.

Experimental Section

Typical Procedure (Table 3, entry 1)

A mixture of **1a** (19.6 mg, 0.1 mmol), **2a** (17.3 mg, 0.1 mmol), and catalyst **4i** (0.01 mmol) in toluene (1.0 mL) was stirred for 48 h at −20 °C. Then the reaction was quenched by adding 0.5 mL 1 M HCl. The mixture was extracted with EtOAc and the extract dried with anhydrous sodium sulfate. The crude product was purified by column chromatography on silica gel to give the desired product **3aa** in 80% yield with 88% *ee*, determined by HPLC (Chiralpak AS, 30% 2-propanol/hexane, 1.5 mL min^{-1}): t_{minor} = 26.126 min, t_{major} = 43.415 min.

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