

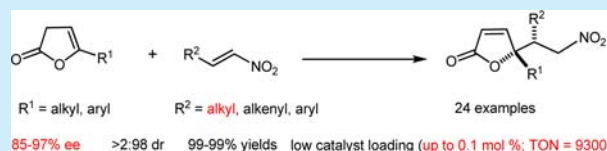
# Catalytic Activity of *epi*-Quinine-Derived 3,5-Bis(trifluoromethyl)benzamide in Asymmetric Nitro-Michael Reaction of Furanones

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**S** Supporting Information

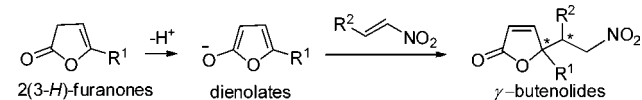
**ABSTRACT:** High catalytic activity of novel *epi*-quinine-derived 3,5-bis(CF<sub>3</sub>)benzamide in the asymmetric nitro-Michael reaction is described. With 0.1–5 mol % loadings of this catalyst, the addition of 5-substituted 2(3-*H*)-furanones to a wide range of nitroalkenes involving challenging substrates,  $\beta$ -alkylnitroalkenes, smoothly proceeded, giving the Michael adducts in high yields (>90%) with excellent diastereo- and enantioselectivity (>98:2 dr, *syn* major; 88–98% ee). DFT calculation was carried out to account for the high catalytic activity.



Among a large variety of the Michael reactions, nitroalkenes have been one of the most widely used Michael acceptors because of the versatility of nitro groups in numerous transformations.<sup>1</sup> Organocatalysts employed in the asymmetric nitro-Michael reaction have been mainly bifunctional enamine catalysts,<sup>1a,d,g</sup> although on use of the enamine catalysts the substrates are restricted to aldehydes and ketones.<sup>1f</sup> This limitation can be largely overcome by bifunctional hydrogen-bonding catalysts such as thiourea derivatives.<sup>2</sup> However, weak, noncovalent H-bonding activation of nitro groups often leads to moderate enantioselectivity (<90% ee), severely limited substrate scope, and the need for substoichiometric amounts of catalysts ( $\geq 10$  mol %).<sup>2b–j</sup>

Recently, organocatalytic diastereo- and enantioselective vinylogous Michael additions of furanone-derived dienolates to nitroalkenes have been reported as a straightforward route to highly functionalized chiral  $\beta$ -butenolides (Scheme 1).<sup>3</sup>  $\beta$ -

**Scheme 1. Michael Addition of Furanones to Nitroalkenes**



Butenolides are often subunits of natural products and biologically active compounds.<sup>4</sup> Given the great number of natural products containing chiral  $\beta$ -butenolides, the application of reactive 2(3-*H*)-furanones as a direct vinylogous nucleophile is highly promising.

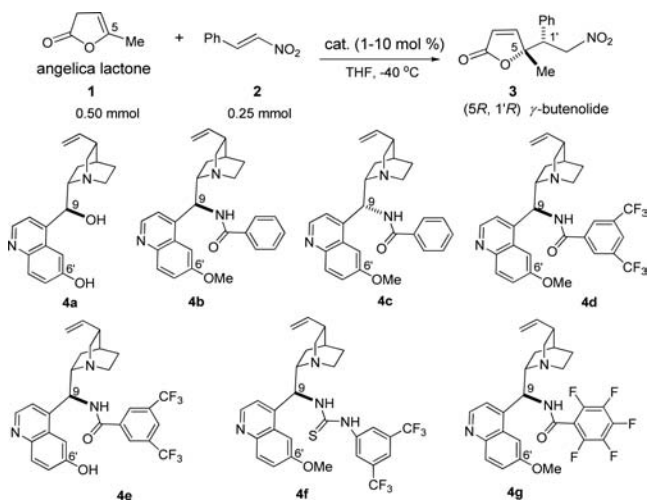
Herein, we report the remarkable activity of *epi*-quinine-derived 3,5-bis(CF<sub>3</sub>)benzamide catalyst in the asymmetric Michael addition of 2(3-*H*)-furanones to nitroalkenes. In particular, this catalyst has proved to be extremely effective in promoting the nitro-Michael reaction of low reactive  $\beta$ -

alkylnitroalkenes, which have been traditionally challenging substrates in the organocatalytic nitro-Michael reactions.<sup>2,3a</sup>

As shown in Table 1, we have found that bifunctional *epi*-quinine-derived catalysts are capable of promoting the Michael addition of angelica lactone **1** to (*E*)- $\beta$ -nitrostyrene **2** with 10 mol % of catalyst loading, affording the Michael adduct **3** (entries 1–6). Thus, with 10 mol % of **4a**, **3** was obtained in 56% yield with moderate diastereo- and enantioselectivity (70:30 = *syn:anti*; 71% ee (*syn*) (entry 4)). THF is the solvent of choice (entry 4). Next, we explored the effect of catalysts on the reaction. More effective catalyst (**4b**)<sup>5a</sup> was synthesized by replacing the 9-OH and 6'-OH of **4a** with 9-benzamide and 6'-OMe (entry 7). Although the enantioselectivity dropped considerably (58% ee), catalyst **4b** significantly improved the diastereoselectivity (*syn:anti* > 98:2) as well as the yield of **3** (80%). Interestingly, diastereomeric catalyst **4c**<sup>5b</sup> exhibited astonishingly reduced stereoselectivity (entry 8). A significant improvement of the catalytic performance has been attained upon the employment of *epi*-quinine-derived 3,5-bis(CF<sub>3</sub>)benzamide **4d**.<sup>5c</sup> A 5 mol % loading of **4d** successfully catalyzed the Michael addition of **1** to **2**, affording the Michael adduct **3** in 98% yield with high diastereo- and enantioselectivity ( $\geq 98:2$  dr, *syn* major; 90% ee) (entry 9). Furthermore, the practicability of the **4d** catalyzed nitro-Michael reaction was demonstrated by the large-scale reaction of **1** (7.5 mmol) and **2** (5 mmol) at only 1 mol % loading of **4d** to give **3** in 98% yield with high diastereo- and enantioselectivity (94% ee) (entry 10). Catalysts **4e** and **4f** showed no improvement of the catalytic effectiveness (entries 11 and 12). With the purpose of achieving further improvement of catalytic activity, we examined catalyst **4g**<sup>5d</sup> having pentafluorobenzamide, which is a stronger electron-withdrawing group than 3,5-bis(CF<sub>3</sub>)benzamide. To our surprise, with a 5 mol %

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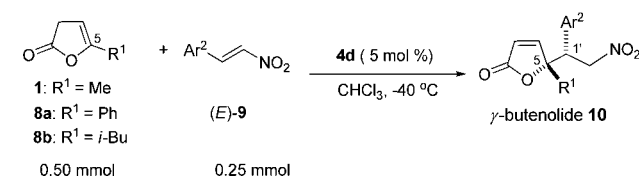
Table 1. Catalytic Nitro-Michael Addition of 1 to 2<sup>a</sup>

entry	catalyst <sup>b</sup>	solvent	t [h]	yield <sup>c</sup> (%)	syn/anti <sup>d</sup>	ee (%) (syn) <sup>e</sup>
1 <sup>f</sup>	4a	CH <sub>2</sub> Cl <sub>2</sub>	36	55	70/30	2 <sup>e</sup>
2 <sup>f</sup>	4a	PhMe	36	48	31/69	5 <sup>e</sup>
3 <sup>f</sup>	4a	Et <sub>2</sub> O	36	33	32/68	8 <sup>e</sup>
4	4a	THF	20	56	70/30	71
5	4a	MeCN	73	42	52/48	41
6	4a	dioxane	33	56	45/55	63
7	4b	THF	24	80	>98/2	58
8 <sup>f</sup>	4c	THF	96	50	87/13	4
9	4d	THF	24	98	>98/2	90
10 <sup>g</sup>	4d	CHCl <sub>3</sub>	48	98	>98/2	94
11	4e	THF	24	98	>98/2	88
12	4f	THF	24	82	>98/2	-50
13	4g	THF	24	78	>98/2	0

<sup>a</sup>Absolute configuration was assigned by analogy with compound **10ac** (Table 2, entry 3). <sup>b</sup>Reaction with 10 mol % loading of catalyst unless otherwise noted. <sup>c</sup>Isolated yield. <sup>d</sup>Diastereomer ratio was determined by <sup>1</sup>H NMR analysis. <sup>e</sup>Obtained by chiral HPLC analysis. <sup>f</sup>Reaction was conducted at room temperature. <sup>g</sup>The reaction was conducted with 1 mol % loading of **4d** on a large scale (1: 7.5 mmol; 2: 5 mmol) in CHCl<sub>3</sub>.

loading of **4g** the reaction afforded the racemic product **3** in 78% yield (entry 13).

We then turned our attention to the substrate scope of the nitro-Michael reaction in chloroform (Table 2). After solvent screening shown in Table 1, we have noticed chloroform bringing about higher diastereo- and enantioselectivity. Table 2 shows that 1–5 mol % loadings of catalyst **4d** allowed complete conversion of the  $\beta$ -arylnitroalkenes in chloroform, giving the corresponding Michael adducts in excellent yields (90–98%) with high levels of diastereo- and enantioselectivity (>98:2 dr; *syn*; 92–97% ee) (entries 1–12). A series of  $\beta$ -arylnitroalkenes bearing electron-withdrawing and electron-releasing substituents on the aromatic rings smoothly reacted with various 5-substituted furanones in high yields (>97%) with high diastereo- and enantioselectivity (>98:2 dr; 92–97% ee) (entries 4–7). Thus, electronic properties of substituents on the aromatic rings of  $\beta$ -arylnitroalkenes had no effect on the reaction. Furthermore, the substitution pattern on the aromatic rings (entries 8–10) and sterically demanding aromatic ring of  $\beta$ -arylnitroalkenes had no deleterious effect on the stereoselectivity as well as the yields (entries 1 and 2).

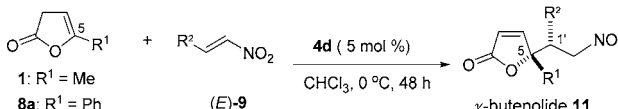
Table 2. Nitro-Michael Addition Catalyzed by **4d**<sup>a,b</sup>

entry	furanone	9: Ar <sup>2</sup>	time (h)	product	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	<b>1</b>	<b>9a</b> : 2-naphthyl	55	<b>10aa</b>	95	93
2	<b>1</b>	<b>9b</b> : 1-naphthyl	60	<b>10ab</b>	90	94
3	<b>1</b>	<b>9c</b> : 4-ClC <sub>6</sub> H <sub>4</sub>	55	<b>10ac</b> <sup>e</sup>	98	92
4	<b>8a</b>	<b>9d</b> : 4-MeOC <sub>6</sub> H <sub>4</sub>	18	<b>10ba</b>	97	96
5	<b>8a</b>	<b>9e</b> : 4-MeC <sub>6</sub> H <sub>4</sub>	37	<b>10bb</b>	97	97
6	<b>8a</b>	<b>9f</b> : 4-NCC <sub>6</sub> H <sub>4</sub>	48	<b>10bc</b>	98	94
7	<b>8a</b>	<b>9g</b> : 4-(F <sub>3</sub> C)C <sub>6</sub> H <sub>4</sub>	48	<b>10bd</b>	98	92
8	<b>8a</b>	<b>9h</b> : 4-ClC <sub>6</sub> H <sub>4</sub>	18	<b>10be</b>	97	96
9	<b>8a</b>	<b>9i</b> : 3-ClC <sub>6</sub> H <sub>4</sub>	33	<b>10bf</b>	96	94
10	<b>8a</b>	<b>9j</b> : 2-ClC <sub>6</sub> H <sub>4</sub>	33	<b>10bg</b>	92	96
11	<b>8a</b>	<b>9c</b> : 2-furyl	24	<b>10bh</b>	95	95
12	<b>8b</b>	<b>2</b> : C <sub>6</sub> H <sub>5</sub>	48	<b>10ca</b>	95	91

<sup>a</sup>All reactions exhibited >2:98 dr. <sup>b</sup>Absolute configuration was assigned by analogy with compound **10ac**. <sup>c</sup>Isolated yield. <sup>d</sup>Obtained by chiral HPLC analysis. <sup>e</sup>Absolute configuration of **10ac** was determined by X-ray crystallographic analysis.

There remains a severely critical problem with the organo-catalyst-promoted asymmetric nitro-Michael reaction, that is, very low reactivity of  $\beta$ -alkylnitroalkenes. Thus far, reports of the Michael reaction of  $\beta$ -alkylnitroalkenes catalyzed by H-bonding catalysts or enamine catalysts have been rare.<sup>1f,g,2</sup> While a few sporadic examples of this reaction have been reported,<sup>2b-j,3a</sup> most of them seem to be impractical in view of the requirement of the substoichiometric amount of the catalysts ( $\geq 10$  mol %) and the low to moderate stereoselectivity (<90% ee). Moreover, the structures of carbon nucleophiles, which can smoothly react with  $\beta$ -alkylnitroalkenes, are severely limited.<sup>6</sup> The low reactivity of  $\beta$ -alkylnitroalkenes is attributable to the high LUMO energy level induced by electron-donating alkyl groups, which leads to a large HOMO–LUMO gap.

We were pleased to find that 0.1–5 mol % loadings of catalyst **4d** are extremely effective in promoting the asymmetric nitro-Michael addition of various 5-substituted furanones to  $\beta$ -alkylnitroalkenes at 0 °C (Table 3). Generally, the **4d**-catalyzed reaction of  $\beta$ -alkylnitroalkenes exhibited high yields (>90%) with high diastereo- and enantioselectivity (>98:2 dr *syn*; 88–96% ee) (entries 1–10). For example, the Michael addition of furanone **1** to sterically demanding  $\beta$ -cyclohexylnitroalkene **9m**, which has been a challenging substrate,<sup>2a</sup> successfully took place, giving rise to the Michael adduct **11ac** with 91% ee (entry 3). Despite the low reactivities of **9m** and  $\beta$ -isobutylnitroalkene **9l**,<sup>3a</sup> the Michael addition of sterically demanding 5-phenylfuranone **8a** to **9l** and **9m** smoothly proceeded, affording the adducts **11ba** (96% ee) and **11bb** (94% ee) (entries 5 and 6). Thus, the present method is especially useful for constructing the sterically congested oxygen-containing quaternary stereogenic centers adjacent to ternary stereogenic centers.<sup>7</sup> To evaluate the potential of catalyst **4d**, the Michael additions of sterically demanding 5-isobutylfuranone **8b** to **9k**, **9l**, and  $\beta$ -alkylnitroalkenes **9n** were carried out, giving the corresponding Michael adducts **11ca** (94% ee), **11cb** (93% ee), and **11cc** (92% ee) in high yields (entries 8–10). The addition of **8b** to sterically hindered nitroalkenes **9m** needed

**Table 3.** Catalytic Nitro-Michael Addition of Furanones to (*E*)- $\beta$ -Alkyl- and  $\beta$ -Alkenylnitroalkenes<sup>a,b</sup>


1: R<sup>1</sup> = Me  
8a: R<sup>1</sup> = Ph  
8b: R<sup>1</sup> = *i*-Bu

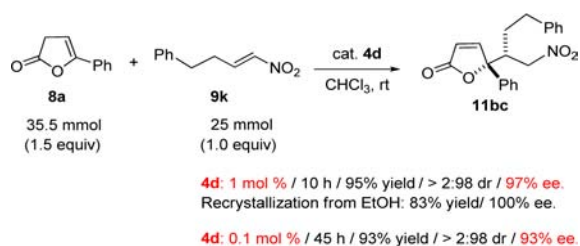
0.50 mmol      0.25 mmol

entry	furanone	9: R <sup>2</sup>	product	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	1	9k: CH <sub>2</sub> CH <sub>2</sub> Ph	11aa	99	88
2	1	9l: <i>i</i> -Bu	11ab	99	90
3	1	9m: Cy	11ac	98	91
4	1	9n: CH=CHPh	11ad	98	94
5	8a	9m: Cy	11ba	84	96
6	8a	9l: <i>i</i> -Bu	11bb	90	94
7	8a	9k: CH <sub>2</sub> CH <sub>2</sub> Ph	11bc	95	97
8 <sup>e</sup>	8b	9n: ( <i>E</i> )-CH=CHPh	11ca	98	94
9 <sup>e</sup>	8b	9l: CH <sub>2</sub> CH <sub>2</sub> Ph	11cb	98	93
10	8b	9k: <i>i</i> -Bu	11cc	94	92
11 <sup>f</sup>	8b	9m: Cy	11cd	99	91

<sup>a</sup>All reactions exhibited >2:98 dr. <sup>b</sup>Absolute configuration was assigned by analogy with compound 10ac. <sup>c</sup>Isolated yield. <sup>d</sup>Obtained by chiral HPLC analysis. <sup>e</sup>Reaction was conducted at -40 °C. <sup>f</sup>Reaction was conducted with 10 mol % loading of 4d.

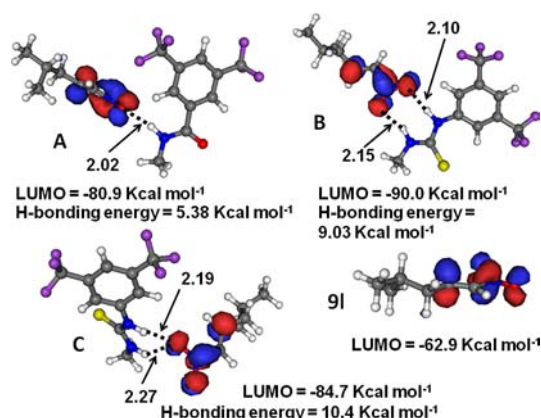
10 mol % catalyst loading for complete substrate conversion (entry 11). However, the corresponding adduct 11cd (91% ee) was obtained in 99% yield. We examined the large-scale reaction to establish the practical reaction conditions (Scheme 2). When

### Scheme 2. Practical Reaction Conditions



the reaction of 8a (35.5 mmol) and 9k (25.0 mmol) was conducted at room temperature, we found that catalyst loading could be reduced to only 0.1–1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yields of the Michael adduct 11bc (>2:98 dr, 93–97% ee, 93–95% yields). The reaction achieved a TON of 9300.<sup>8</sup> Single recrystallization of the crude product from ethanol gave enantiomerically pure 11bc in 83% yield.

To shed light on the mechanism accounting for the remarkable catalytic activity of 4d in the asymmetric nitro-Michael reaction, DFT calculations of the catalyst- $\beta$ -alkylnitroalkene adducts were carried out (Figure 1). The structure of 3,5-bis(CF<sub>3</sub>)benzamide- $\beta$ -isobutylnitroalkene 9I adduct A as a simplified model for 4d-9I adduct and the structure of thiourea-9I adduct B<sup>1d</sup> as a simplified model for thiourea catalyst-9I adduct were optimized at the B3LYP/6-311++G(d,p) level at theory. Thioureas are the most frequently used H-bonding catalysts in asymmetric nitro-Michael reactions.<sup>1a,d,f</sup> Thus, to explain the high catalytic activity of 4d, a comparison with thiourea-based catalysts should be helpful. The results of the calculations have revealed that (1) activation of 9I by the double H-bondings of thiourea provides a

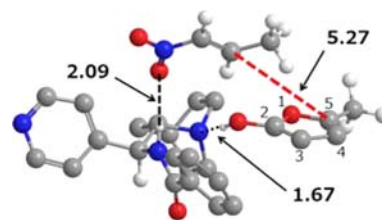


**Figure 1.** Optimized structures of benzamide- $\beta$ -isobutylnitroalkene 9I adduct (A) and thiourea-9I adduct (B). Hydrogen bond lengths in angstroms.

significant decrease in the LUMO energies of 9I (B, -27 kcal mol<sup>-1</sup>), while a decrease in the LUMO energy of 9I induced by benzamide is considerably smaller (A, -18 kcal mol<sup>-1</sup>), but it suffices for the smooth reaction of 9I with furanones (entries 2, 6, and 10 in Table 3); (2) despite the stronger H-bonding activation of 9I, most thiourea catalysts give unsatisfactory results of the Michael addition to  $\beta$ -alkylnitroalkenes;<sup>2b-n,3a</sup> (3) thiourea-9I adduct B has a conformationally rigid structure due to the strong double H-bondings (H-bonding energy: 9.03 kcal mol<sup>-1</sup>).<sup>1d,e</sup> In contrast, benzamide-9I adduct A, where 9I binds to the benzamide by single H-bonding, seems to be conformationally flexible (H-bonding energy: 5.38 kcal mol<sup>-1</sup>).

In general, the energy of transition state strongly depends on the angular geometry between HOMO and LUMO of reactants (i.e., angles between HOMO and LUMO).<sup>9</sup> The calculations strongly suggest that the thiourea-9I adduct B would hinder the maximum overlap of the HOMO and LUMO, since the conformationally rigid adduct B would distort the angular geometry of the HOMO and LUMO from the ideal angle in sterically congested chiral environment. In contrast, conformational flexibility of benzamide-9I adduct A would permit the nearly maximum HOMO-LUMO overlap in the transition state, allowing a smoother reaction via a transition state of lower energy. The DFT calculations sufficiently explain the higher catalytic activity of 4d compared to thiourea-based catalysts.

Figure 2 displays the simplified pre-transition-state assembly model optimized at the B3LYP/6-31G(d) level. The quinuclidine



**Figure 2.** Simplified pre-transition-state assembly model optimized at B3LYP/6-31G(d). Atomic distances in angstroms.

dine moiety shields the *si*-face of the nitroalkene bound to the amide hydrogen. To avoid the steric repulsion between the 5-substituent of the dienolate and the aromatic ring of the benzamide, the dienolate bound to the quinuclidinium hydrogen exposes the *si*-face to the nitroalkene. The addition of the



dienolate from the *si*-face to the exposed *re*-face of the nitroalkene predicts the sense of the asymmetric induction.

In summary, we have developed a highly enantioselective nitro-Michael reaction of furanones with very low reactive  $\beta$ -alkylnitroalkenes catalyzed by a novel *epi*-quinine-amide **4d**. The DFT calculations revealed that the conformational flexibility of the catalyst **4d**-nitroalkene adducts play a critical role in the high asymmetric induction. This result is entirely unexpected, since in general, asymmetric organocatalysts are designed to achieve the conformational rigidity (e.g., a series of iminium catalysts and thiourea-based catalysts).<sup>2</sup>

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedure and compound characterization data including CIF. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01224.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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  - (9) Houk, K. N.; Paddon-Row, M. N.; Rondon, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Richard, Y. L.; Loncharich, R. *J. Science* **1986**, *231*, 1108.