Organic LETTERS

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

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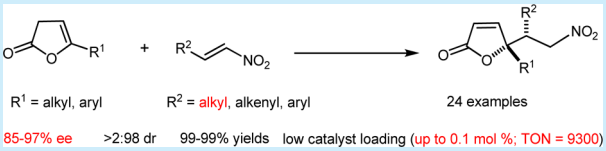
Supporting Information

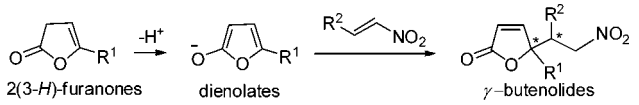
ABSTRACT: High catalytic activity of novel *epi*-quinine-derived 3,5-bis(CF_3)benzamide in the asymmetric nitro-Michael reaction is described. With 0.1−5 mol % loadings of this catalyst, the addition of 5-substituted 2(3-*H*)-furanones to a wide range of nitroalkenes involving challenging substrates, *β*-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, nitroalkens have been one of the most widely used Michael acceptors because of the versatility of nitro groups in numerous transformations.[1] Organocatalysts employed in the asymmetric nitro-Michael reaction have been mainly bifunctional enamine catalysts,[1a,d,g] although on use of the enamine catalysts the substrates are restricted to aldehydes and ketones.[1f] This limitation can be largely overcome by bifunctional hydrogen-bonding catalysts such as thiourea derivatives.[2] 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 (≥10 mol %).[2b−j]

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 *β*-butenolides (Scheme 1).[3] *β*-

Scheme 1. Michael Addition of Furanones to Nitroalkenes



Butenolides are often subunits of natural products and biologically active compounds.[4] Given the great number of natural products containing chiral *β*-butenolides, the application of reactive 2(3*H*)-furanones as a direct vinylogous nucleophile is highly promising.

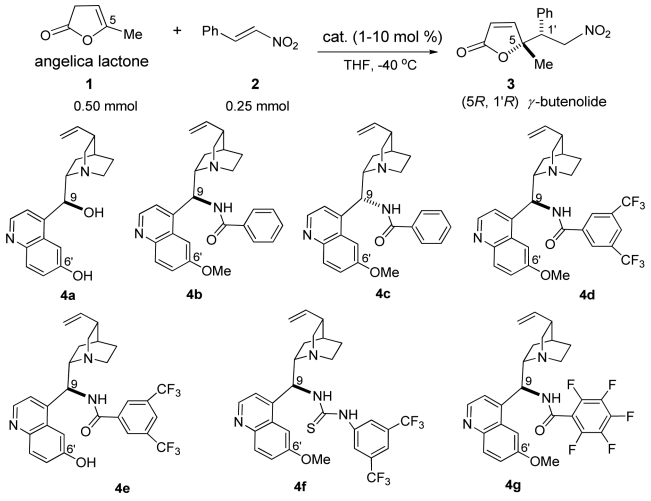
Herein, we report the remarkable activity of *epi*-quinine-derived 3,5-bis(CF_3)benzamide catalyst in the asymmetric Michael addition of 2(3-*H*)-furanones to nitroalkenes. In particular, this catalyst has proved to be extremely effective in promoting the nitro-Michael reaction of low reactive *β*-alkylnitroalkenes, which have been traditionally challenging substrates in the organocatalytic nitro-Michael reactions.[2,3a]

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*)-*β*-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**)[5a] 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**[5b] 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_3)-benzamide **4d**.[5c] 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 (≥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**[5d] having pentafluorobenzamide, which is a stronger electron-withdrawing group than 3,5-bis(CF_3)benzamide. To our surprise, with a 5 mol %

Received: May 4, 2015

DOI: 10.1021/acs.orglett.5b01224
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Catalytic Nitro-Michael Addition of 1 to 2[a]



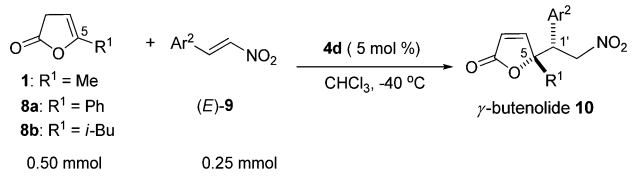
entry	catalyst[b]	solvent	t [h]	yield[c] (%)	*syn*/*anti*[d]	ee (%) (*syn*)[e]
1[f]	**4a**	CH_2Cl_2	36	55	70/30	2[e]
2[f]	**4a**	PhMe	36	48	31/69	5[e]
3[f]	**4a**	Et_2O	36	33	32/68	8[e]
4	**4a**	THF	20	56	70/30	71
5	**4a**	MeCN	73	42	52/48	41
6	**4a**	dioxane	33	56	45/55	63
7	**4b**	THF	24	80	>98/2	58
8[f]	**4c**	THF	96	50	87/13	4
9	**4d**	THF	24	98	>98/2	90
10[g]	**4d**	$CHCl_3$	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

[a]Absolute configuration was assigned by analogy with compound **10ac** (Table 2, entry 3). [b]Reaction with 10 mol % loading of catalyst unless otherwise noted. [c]Isolated yield. [d]Diastereomer ratio was determined by ^{1}H NMR analysis. [e]Obtained by chiral HPLC analysis. [f]Reaction was conducted at room temperature. [g]The reaction was conducted with 1 mol % loading of **4d** on a large scale (**1**: 7.5 mmol; **2**: 5 mmol) in $CHCl_3$.

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 β-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 β-arylnitroalkenes bearing electron-withdrawing and electron-releasing substituents on the aromatic rings smoothyl reacted with various 5-substituted furanones in high yields (>97%) with high diastereo- and enantioslectivity (>98:2 dr; 92−97% ee) (entries 4−7). Thus, electronic properties of substituents on the aromatic rings of β-arylnitroalkenes had no effect on the reaction. Furthermore, the substitution pattern on the aromatic rings (entries 8−10) and sterically demanding aromatic ring of β-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[a,b]



entry	furanone	9: Ar^2	time (h)	product	yield[c] (%)	ee[d] (%)
1	**1**	**9a**: 2-naphthyl	55	**10aa**	95	93
2	**1**	**9b**: 1-naphthyl	60	**10ab**	90	94
3	**1**	**9c**: 4-ClC_6H_4	55	**10ac**[e]	98	92
4	**8a**	**9d**: 4-$MeOC_6H_4$	18	**10ba**	97	96
5	**8a**	**9e**: 4-MeC_6H_4	37	**10bb**	97	97
6	**8a**	**9f**: 4-NCC_6H_4	48	**10bc**	98	94
7	**8a**	**9g**:4-$(F_3C)C_6H_4$	48	**10bd**	98	92
8	**8a**	**9h**: 4-ClC_6H_4	18	**10be**	97	96
9	**8a**	**9i**: 3-ClC_6H_4	33	**10bf**	96	94
10	**8a**	**9j**: 2-ClC_6H_4	33	**10bg**	92	96
11	**8a**	**9c**: 2-furyl	24	**10bh**	95	95
12	**8b**	**2**: C_6H_5	48	**10ca**	95	91

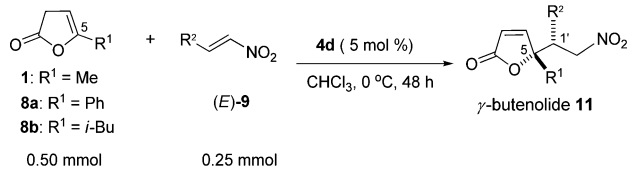
[a]All reactions exhibited >2:98 dr. [b]Absolute configuration was assigned by analogy with compound **10ac**. [c]Isolated yield. [d]Obtained by chiral HPLC analysis. [e]Absolute configuration of **10ac** was determined by X-ray crystallographic analysis.

There remains a severely critical problem with the organocatalyst-promoted asymmetric nitro-Michael reaction, that is, very low reactivity of β-alkylnitroalkenes. Thus far, reports of the Michael reaction of β-alkylnitroalkenes catalyzed by H-bonding catalysts or enamine catalysts have been rare.[1f,g,2] While a few sporadic examples of this reaction have been reported,[2b−j,3a] most of them seem to be impractical in view of the requirement of the substoichiometric amount of the catalysts (≥10 mol %) and the low to moderate stereoselectivity (<90% ee). Moreover, the structures of carbon nucleophiles, which can smoothly react with β-alkylnitroalkenes, are severely limited.[6] The low reactivity of β-alkylnitroalkenes is attributable to the high LUMO energy level induced by electoron-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 β-alkylnitroalkenes at 0 °C (Table 3). Generally, the **4d**-catalyzed reaction of β-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 β-cyclohexylnitroalkene **9m**, which has been a challenging substrate,[2a] successfully took place, giving rise to the Michael adduct **11ac** with 91% ee (entry 3). Despite the low reactivities of **9m** and β-isobutylnitroalkene **9l**,[3a] the Michael addition of sterically demanding 5-phenylfuranone **8a** to **9l** and **9m** smoothyl 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.[7] To evaluate the potential of catalyst **4d**, the Michael additions of sterically demanding 5-isobutylfuranone **8b** to **9k**, **9l**, and β-alkenylnitroalkenes **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

DOI: 10.1021/acs.orglett.5b01224
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Catalytic Nitro-Michael Addition of Furanones to (*E*)-*β*-Alkyl- and *β*-Alkenylnitroalkenes[a,b]

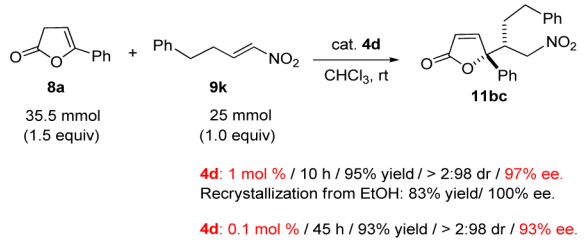


entry	furanone	9: R^2	product	yield[c] (%)	ee[d] (%)
1	**1**	**9k**: CH_2CH_2Ph	**11aa**	99	88
2	**1**	**9l**: *i*-Bu	**11ab**	99	90
3	**1**	**9m**: Cy	**11ac**	98	91
4	**1**	**9n**: CH═CHPh	**11ad**	98	94
5	**8a**	**9m**: Cy	**11ba**	84	96
6	**8a**	**9l**: *i*-Bu	**11bb**	90	94
7	**8a**	**9k**: CH_2CH_2Ph	**11bc**	95	97
8[e]	**8b**	**9n**: (*E*)-CH═CHPh	**11ca**	98	94
9[e]	**8b**	**9k**: CH_2CH_2Ph	**11cb**	98	93
10	**8b**	**9l**: *i*-Bu	**11cc**	94	92
11[f]	**8b**	**9m**: Cy	**11cd**	99	91

[a]All reactions exhibited >2:98 dr. [b]Absolute configuration was assigned by analogy with compound **10ac**. [c]Isolated yield. [d]Obtained by chiral HPLC analysis. [e]Reaction was conducted at −40 °C. [f]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.[8] 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 nitiro-Michael reaction, DFT calculations of the catalyst-*β*-alkylnitroalkene adducts were carried out (Figure 1). The structure of 3,5-bis(CF_3)benzamide-*β*-isobutylnitroalkene **9l** adduct **A** as a simplified model for **4d**−**9l** adduct and the structure of thiourea−**9l** adduct **B**[1d] as a simplified model for thiourea catalyst−**9l** 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-Michel reactions.[1a,d,f] 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 **9l** by the double H-bondings of thioerea provides a

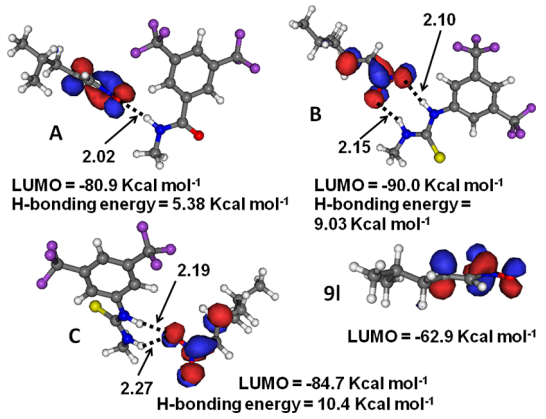


Figure 1. Optimized structures of benzamide-*β*-isobutylnitroalkene **9l** adduct (A) and thiourea-**9l** adduct (B). Hydrogen bond lengths in angstroms.

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

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).[9] The calculations strongly suggest that the thiourea−**9l** adduct **B** would hinder the muximum 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−**9l** 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 quinucli-

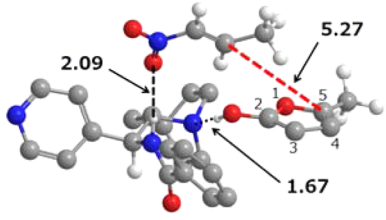


Figure 2. Simplified pre-transition-state assembly model optimized at B3LYP/6-31(G). Atomic distances in angstroms.

dine moiety shields the *si*-face of the nitroalkene bound to the amide hygrogen. 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

DOI: 10.1021/acs.orglett.5b01224
Org. Lett. XXXX, XXX, XXX−XXX

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 β-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).[2]

■ 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

This work has been supported by a Grant-in-Aid for Scientific Research (C) (20550101) from JSPS.

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DOI: 10.1021/acs.orglett.5b01224
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