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\ Graphical Abstract

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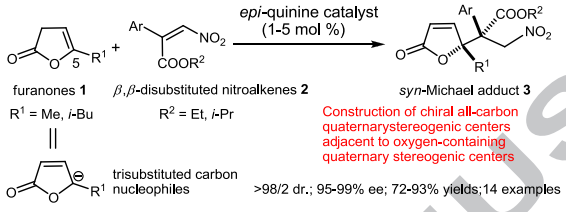

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ABSTRACT

Epi-quinine-catalyzed asymmetric nitro-Michael addition of furanones to *β,β*-disubstituted nitroalkenes is described. The reaction proceeded smoothly with 1-5 mol % loadings of *epi*-quinine catalysts at room temperature, giving the corresponding Michael adducts in high yields (72-93%) with extremely high diastereo- and enantioselectivities (>98/2 dr, *syn* major; 95-99% ee). This reaction provides an effective and straightforward method for constructing all-carbon quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic centers.

Quaternary carbon stereogenic centers exist widely in natural products and biologically active compounds.[1] Catalytic enantioselective construction of all-carbon quaternary stereogenic center is one of the most important subjects in organic synthesis.[2] Among various strategies for constructing enantiomerically enriched quaternary carbon centers, the catalytic asymmetric Michael addition of carbon nucleophiles to *β,β*-disubstituted nitroalkenes is one of the simple and straightforward method. However, only a handful studies are available dealing this reaction.[3] Significant steric repulsion between incoming carbon nucleophiles and sterically demanding *β,β*-disubstituted nitroalkenes seems to be the reason for the difficulty of the nitro-Michael reaction of *β,β*-disubstituted nitroalkenes.

We report herein the *epi*-quinine catalyzed asymmetric Michael addition of 5-substituted 2(3*H*)-furanones **1** to *β,β*-disubstituted nitroalkenes **2** as a highly effective method for constructing sterically congested all-carbon quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic center (Scheme 1).[4] To the best of our knowledge, catalytic asymmetric conjugate addition of trisubstituted carbon nucleophiles to *β,β*-disubstituted nitroalkenes is very rare.

With the purpose of evaluating the catalytic activity of a series of *epi*-quinine derivatives, the catalytic asymmetric

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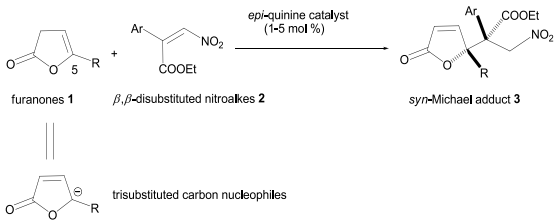
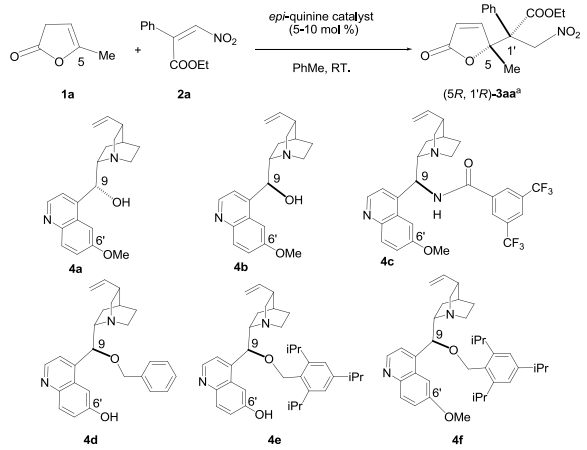


Scheme 1. Michael addition of furanones to *β,β*-disubstituted nitroalkenes.

Michael addition of angelica lactone **1a** to (*Z*)-1-phenyl-2-nitroacrylate **2a** was examined at 10 mol % loadings of *epi*-quinines at room temperature (Table 1). Solvent screening indicated toluene to be the solvent of choice. Quinine-derived catalysts **4** are capable of promoting the Michael addition of **1a** to **2a**, affording the corresponding Michael adduct **3aa** with *syn*-selectivity. For example, with a 10 mol % loading of quinine **4a**, the Michael adduct **3aa** was obtained in the moderate yield (67%), whereas diastereo- and enantioselectivity was very low (*syn*/*anti* = 76/24; 27% ee (*syn*)) (entry 1). Catalyst **4b**[5] showed no improvement of the catalytic activity (entry 2). To our surprise, amide catalyst **4c** exhibited very low diastereoselectivity (*syn*/*anti* = 53/47) (entry 3), although the nitro-Michael addition of furanones to *β*-nitrostyrene catalyzed by **4c** gave the Michael adducts with high *syn*-selectivity (>98/2 dr).[4a]

Table 1. Catalytic nitro-Michael addition of **1a** to **2a.**



Entry[b]	Catalyst	Reaction time (h)	Yield (%)[c]	*syn*/*anti*[d]	Ee [%] (*syn*)[e]
1	**4a**	17	67	76/24	27
2	**4b**	24	68	83/17	-11
3	**4c**	30	65	53/47	24
4	**4d**	17	65[g]	>98/2	90
5	**4e**	16	88	>98/2	91
6	**4f**	17	57	95/5	16
7[f]	**4e**	24	93	>98/2	98

[a] Absolute configuration was assigned by analogy with compound **3ad** (Table 2, entry 3). [b] Reaction of **1a** (0.5 mmol) with **2a** (0.25 mmol) was conducted with a 10 mol % loading of **4** at room temperature unless otherwise noted. [c]Isolated yield. [d]Diastereomer ration was determined by ^{1}H NMR analysis of the crude material. [e]Obtained by chiral HPLC analysis. [f] Reaction was conducted in the presence of MS 4 Å (50 mg) with a 5 mol % loading of **4e**. [g]Conjugate addition at the α carbon of **1a** took place as a side reaction, leading to moderate yield of **3aa**.

A significant improvement of the diastereo- and enantioselectivity has been attained upon the employment of *epi*-quinine derivatives **4d** and **4e** (entries 4 and 5). A 10 mol % loading of **4e** successfully catalyzed the Michael addition of **1a** to **2a**, affording the Michael adduct **3aa** in a 88% yield with high diastereo- and enantioselectivity (>98:2 dr, *syn* major; 91% ee) (entry 5). In contrast, the replacement of the 6'-OH of **4e** with 6'-OMe (**4f**) profoundly depresses the catalytic effectiveness (*syn*/*anti* = 95/5 ; 16% ee) (entry 6). These results conclusively revealed that the 6'-OH of *epi*-quinine derivatives **4d** and **4e** is essential for the high asymmetric induction. To our delight, the addition of MS 4Å to the reaction mixture considerably reduced the catalyst loading as low as 5 mol % without affecting high diastereo- and enantioselectivity (>98/2 dr, *syn* major; 98% ee) (entry 7).

We then turned out our attention to the substrate scope of the *syn*-selective nitro-Michael reaction catalyzed by **4e** (Table 2). A 5 mol % loading of catalyst **4e** allowed complete conversion of the *β,β*–disubstituted nitroalkenes **2** in toluene at room temperature, giving the corresponding Michael adducts **3** in good yields (72-93%) with extremely high diastereo- and enantioselectivities (>98/2 dr, *syn* major; 95-99% ee) (entries 1-14).

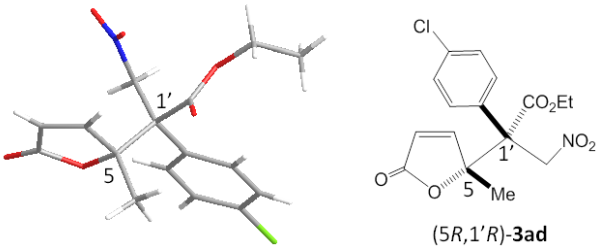
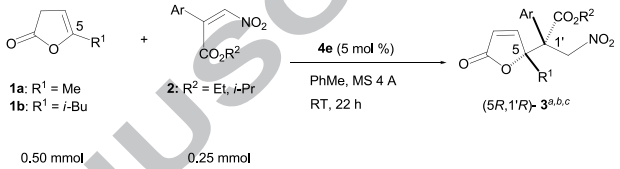


Figure 1. X-ray structure of compound **3ad.**

Table 2. Catalytic nitro-Michael addition of furanones **1** to *β,β*-disubstituted nitroalkenes **2.**



Entry	Furanone	Ar	R^2	Nitroalkene	Product	Yield [%][d]	Ee [%][e]
1	**1a**	4-MePh	Et	**2b**	**3ab**	91	95
2	**1a**	4-MeOPh	Et	**2c**	**3ac**	92	96
3	**1a**	4- ClPh	Et	**2d**	**3ad**[f]	89	97
4	**1a**	3-ClPh	Et	**2e**	**3ae**	87	97
5	**1a**	2-Thienyl	Et	**2f**	**3af**	89	98
6	**1b**	Ph	Et	**2a**	**3ba**	88	97
7	**1b**	4-MePh	Et	**2b**	**3bb**	82	99
8	**1b**	4-MeOPh	Et	**2c**	**3bc**	72	96
9	**1b**	4-ClPh	Et	**2d**	**3bd**	80	96
10	**1b**	3-ClPh	Et	**2e**	**3be**	79	97
11	**1b**	2-Thienyl	Et	**2f**	**3bf**	78	98
12	**1a**	Ph	*i*-Pr	**2g**	**3ag**	91	97
13	**1b**	Ph	*i*-Pr	**2g**	**3bg**	87	98
14[g]	**1a**	Ph	Et	**2a**	**3aa**	93	97

[a]^{1}NMR analysis of the crude material indicated that the diastereomer ration of all reactions is >2:98, *syn*-major. [b]Absolute configuration was assigned by analogy with compound **3ad** (entry 3). [c] Reaction of **1** (0.5 mmol) with **2** (0.25 mmol) was conducted with a 5 mol % loading of **4e** at room temperature for 22 h unless otherwise noted. [d] Isolated yield. [e]Obtained by chiral HPLC analysis. [f]Absolute configuration of **3ad** was determined by X-ray crystallographic analysis. [g] Large scale reaction of **1a** (20 mmol) with **2a** (10 mmol) was conducted with a 1 mol % loading of **4e** at room temperature for 91 h.

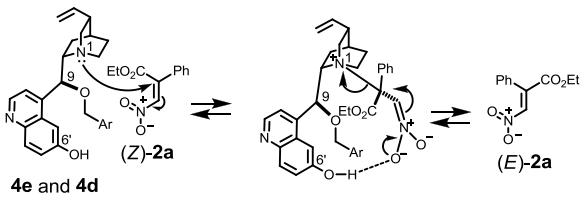
The absolute configurartion of the Michael adduct **3ad** (entry 3) was unambiguously determined by X-ray crystallographic analysis to be (5*R*, 1'*R*) (Figure 1).[6] The configurations of other Michael adducts **3** were assighned by analogy.

(*Z*)-1-Aryl-2-nitroacrylate **2** bearing electron-withdrawing and electron-releasing substituents on the aromatic ring reacted

smoothly with angelica lactone **1a**, affording **3ab** (91% yield, 95% ee), **3ac** (92% yield, 96% ee), **3ad** (89% yield, 97% ee), and **3ae** (87% yield, 97% ee) (entries 1-4). Thus, the electronic properties of substituents on the aromatic rings of Michael acceptors **2** have no effect on the reaction. Substitution pattern in the aromatic rings had no deleterious effect on the diastereo- and enantioselectivities (entries 3, 4, 9 and 10). Furthermore, the Michael additions of sterically demanding 5-(*iso*-butyl)furanone **1b** to *β*,*β*-disubstituted nitroalkenes **2a**, **2b**, **2c**, **2d**, and **2e** successfully took place, giving the *syn*-adducts **3ba** (97% ee), **3bb** (99% ee) , **3bc** (96% ee), **3bd** (96% ee) and **3be** (97% ee) in good yields (72-82%) (entries 6-10). The reaction of Michael acceptor **2f** bearing heteroaryl substituent with the Michael donor **1a** and **1b** also proceeded smoothly to furnish the corresponding adducts **3af** (98% ee) and **3bf** (98% ee) in good yields (entry 5 and 11). Furthermore, the nitroalkene **2g** bearing sterically demanding COO-*i*-Pr substituent also effectively underwent the **4e**-catalyzed Michael reaction with furanone **1a** and **1b**, furnishing the corresponding Michael adduct **3ag** and **3bg** in high yields (91% and 87%, respectively) with excellent diastereo- and enantioselectivities (97% ee and 98% ee, respectively) (entries 12 and 13). These results demonstrated that the steric bulkiness of the Michael donor **1** and Michael acceptor **2** had no effect on the yields as well as the diastereo- and enantioselectivities.

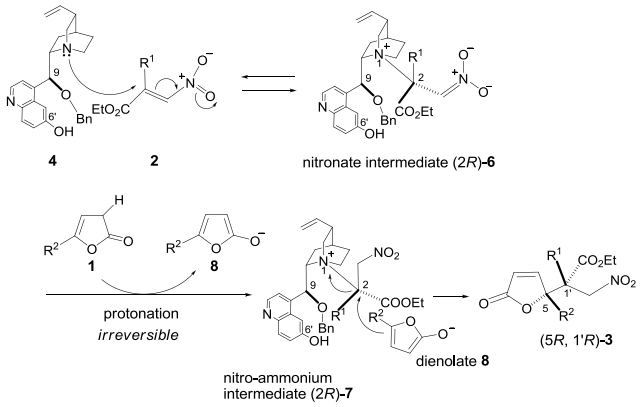
We examined the large scale reaction to establish practical reaction conditions. When the reaction of **1a** (20 mmol) and **2a** (10 mmol) was conducted at room temperature, it has been found that the catalyst loading could be reduced to only 1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yield of the Michael adduct **3aa** (>98/2 dr, 97% ee, 93% yield, TON = 93) (entry 14). Thus, the present method is demonstrated to be highly useful for the construction of sterically congested all-carbon quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic centers with extremely high diastereo- and enantioselectivities.

It is noteworthy that the isomerization of (*Z*)-1-phenyl-2-nitroacrylate (*Z*)-**2a** to (*E*)-**2a** took place in toluene at room temperature with 10 mol % loadings of **4d** and **4e**, afoording a mixture of geometrical isomers with a *Z*:*E* ratio of 74:16 after 4 h. In contrast, catalytic amounts of **4a**, **4b**, and **4c** did not promote the isomerization of (*Z*)-**2a**, suggesting that the 6'-OH of **4e** and **4d** plays a crucial role in the activation of the nitroalkenes (Scheme 2).



Scheme 2. Isomerization of (*Z*)-**2a** promoted by **4e** and **4d**.

Based on this result, we have made an assumption that the quinuclidine nitrogen (N1) of *epi*-quinine catalysts **4e** and **4d** would undergo the conjugate addition to the *re*-face of *β*,*β*-disubstituted nitroalkenes **2**, giving nitronate intermediate (2*R*)-**6** (Scheme 3). Protonation of **6** with furanone **1** affords nitro-ammonium intermediate (2*R*)-**7**. Subsequently, nucleophilic attack of dienolate **8** to the intermediate (2*R*)-**7** takes place from the *si*-face of **8** to give the Michael adduct (5*R*, 1'*R*)-**3**. Thus, the extremely high diastereo- and enantioselectivities of the nitro-Michael reaction catalyzed by **4e** would result from addition-elimination mechanism depicted in Scheme 3. However,



Scheme 3. Plausible reaction mechanism of the nitro-Michael reaction catalyzed by **4e**.

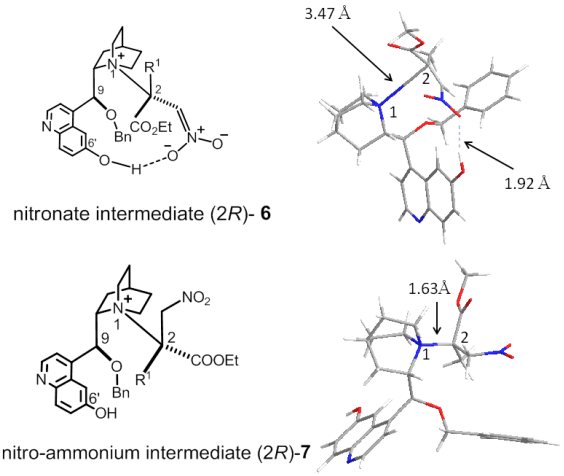


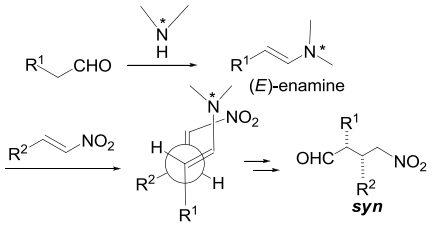
Figure 2. Simplified structure of nitronate intermediate (2***R***)-**6** and nitro-ammonium intermediate (2*R*)-**7** optimized at B3LYP/6-31G(d).

the ^{13}C NMR spectra of the mixture of **4e** and (*Z*)-1-phenyl-2-nitroacrylate **2a** (**4e** : **2a** = 1 : 2, C_6D_6) indicated that $\delta(^{13}C)$ of the C(1) atom of **2a** did not shift upon the addition of **4e**, indicating the very weak interaction between the quinuclidine N(1) of **4e** and nitrostyrene **2a**.

In order to reveal the role of the 6'-OH group of catalyst **4e**, we carried out theoretical calculations (Figure 2). The simplified structures of the nitronate intermediate (2*R*)-**6** and the nitro-ammonium intermediate (2*R*)-**7** were optimized at B3LYP/6-31G(d). The results of the calculations are wholly surprising. The optimized structure of the intermediate (2*R*)-**6** discloses the very weak interaction between the quinuclidine N(1) and nitroalkene as indicated by the very long N(1)-C(2) bond length (3.47 Å), which is roughly comparable to the sum of van der Waals radii of N and C (3.25 Å).[7] Thus, an intramolecular H-bonding between the 6'-OH and the nitronate oxygen seems to stabilize the intermediate (2*R*)-**6**. The theoretical calculation strongly supports a crucial role of the 6'-OH in promoting the conjugate addition of N(1) to the *re*-face of nitroalkene.

The long N(1)-C(2) bond length would be ascribed to the strong electrostatic repulsion between the nitrate moiety and N(1), which bears a considerable negative charge (-0.391: Mulliken). The formal positive charge on N(1) would be neutralized by electron releas from five neighboring hydrogen atoms in the geminal positions relative to N(1).[8] The electrostatic repulsion between N(1) and C(2) of the (2*R*)-**6** can be reduced when (2*R*)-**6** is protonated by furanones (Figure 2). The nitroammonium intermediate (2*R*)-**7** is considered thermodynamically stable, but the N(1)-C(2) bond length of 1.63 Å is considerably longer than a sum of covalent radii of N and C (1.46 Å).[9]

A large number of the nitro-Michael addition of aldehydes to *β*-monosubstituted nitroalkenes catalyzed by enamine catalysts and bifunctional hydrogen bonding catalysts have been reported.[10] The very high diastereo- and enantioselectivities of these reactions are explained by the transition state model proposed by Seebach, in which donor atoms and acceptor atoms are close to each other (Scheme 4).[11] It is interesting to note that although the nitro-Michael reaction catalyzed by **4e** proceeds through the totally different mechanism, the reaction shows an almost perfect diastereo- and enantioselectivity.



Scheme 4. Nitro-Michael reaction via Seebach's transition state model

More noteworthy is the extremely high catalytic activity of *epi*-quinine derived **4e**, which can promote the carbon-carbon bond formation between the sterically congested Michael donors such as compound **1b** and sterically demanding *β,β*-disubstituted nitroalkenes **2**, in spite of unfavorable steric repulsion.[12] The nitro-Michael reactions catalyzed by bifunctional hydrogen bonding catalysts such as thiourea derivatives and secondary amine catalysts proceed with a weak non-covalent H-bonding activation of nitroalkenes.[10d,h] In view of the weak activation of nitroalkenes in the reactions catalyzed by these catalysts, it is likely that the bifunctional hydrogen bonding catalysts as well as the secondary amine catalysts hardly promote the nitro-Michael addition of the sterically demanding Michael donors to *β,β*-disubstituted nitroalkenes **2.** As for the **4e**-catalyzed reaction, strong activation of nitroalkenes by a covalent bond eanbles the carbon-carbon bond formation containing highly sterically congested reaction centers.[12] Thus, the potential of the **4e** and similar catalysts for the other asymmetric Michael reactions containing sterically congested reaction centers seems to be very promising.

In summary, we have developed a highly diastereo- and enantioselective nitro-Michael addition of furanones to *β,β*-disubstituted nitroalkenes catalyzed by *epi*-quinine catalyst **4e**. The reaction offers an effective and reliable method for constructing chiral all-carbon quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic centers.

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Supplementary Material

Supplementary material associated with this article can be found, in online version, at http://

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12. Compounds **3** are highly sterically congested. The ^{1}H NMR spectra of compounds **3ba**, **3bb**, **3bc**, **3bd**, **3be**, **3bf**, and **3bg** displyed that two terminal methyl groups involved in *iso*-butyl groups are not chemical shift equivalent because of rotational hindrance of *iso*-butyl groups in sterically-congested environment. Two methyl groups of COO-*i*-Pr in compound **3ag** and **3bg** also are not chemical shift equivalent: see supporting material.

Highlights

- Michael Addition of Furanones to β,β-Disubstituted Nitroalkenes proceeded smoothly.
- Unusual high catalytic activity of *epi*-quinine derivatives was proved.
- Method for the construction of chiral all-carbon quaternary centers was developed.
- Diastereo- and enantioselectivities are almost perfect (>98:2 dr; 95-99% ee)