Tetrahedron 68 (2012) 6123–6130

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of chiral tetronic acid derivatives via organocatalytic conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes

Yun-yun Yan [a], Rui-jiong Lu [a], Jin-jia Wang [a], Yi-ning Xuan [b], Ming Yan [a,*]

[a] Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[b] College of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, China

ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form 16 May 2012
Accepted 22 May 2012
Available online 28 May 2012

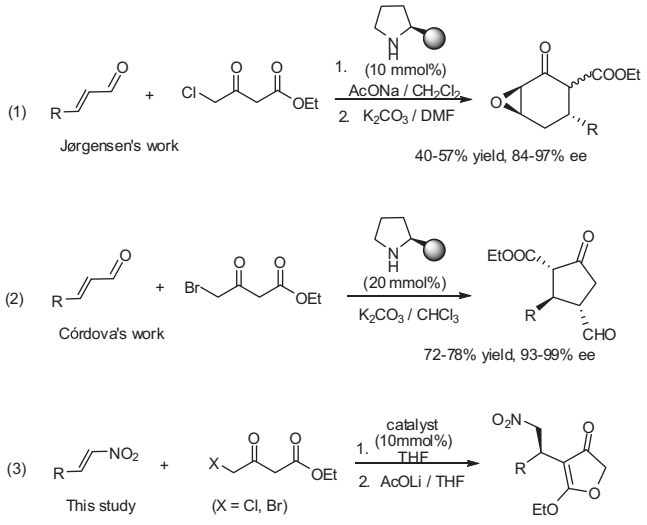
Keywords:
Organocatalysis
Asymmetric conjugate addition
Tetronic acid derivative
Ethyl 4-chloro-3-oxobutanoate
Nitroalkene

ABSTRACT

Asymmetric conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes and subsequent intramolecular cyclization had been developed. This one-pot reaction provided tetronic acid derivatives in good yields and with excellent enantioselectivities. 6′-Demethyl quinine was found to be the best catalyst for the conjugate addition and AcOLi was identified as the best base for the intramolecular cyclization. Various β-aryl, heteroaryl, and alkyl nitroalkenes are generally applicable in the reaction.

1. Introduction

During the past decade, asymmetric organocatalysis has made great progress.[1] A large number of organocatalytic reactions have been developed successfully. Organocatalytic asymmetric conjugate addition is one of the most powerful organocatalytic reactions in terms of its synthetic value and wide substrate scope.[2] The cascade reactions triggered by organocatalytic asymmetric conjugate addition are extremely efficient for the constitution of chiral cyclic compounds.[1a,3] Our strategy is to apply additional leaving groups with the nucleophiles. The reactive intermediates generated in the conjugate addition undergo subsequent intramolecular cyclization.[4,7] Recently we have studied organocatalytic asymmetric conjugate additions of bromonitroalkanes and bromomalonates. The reactions provided chiral cyclopropanes in excellent yields and with high enantioselectivities.[5] As a continuation of the studies, we envision that 4-chloro-3-oxobutanoates are valuable nucleophiles for the synthesis of chiral products with five member rings via the conjugate addition and cascade intramolecular cyclization. In 2006, Jørgensen and co-workers reported the organocatalytic domino reaction of 4-chloro-3-oxobutanoates with α,β-unsaturated aldehydes. Epoxycyclohexanone derivatives were prepared in excellent yields and enantioselectivities (Scheme 1, Eq. 1).[6] Lately Córdova and co-workers found that the similar reaction of 4-bromo-3-oxobutanoates led to chiral cyclopentanones (Scheme 1, Eq. 2).[7] These results demonstrate variable chemical reactivities of 4-halogen-3-oxobutanoates.



Scheme 1. Organocatalytic asymmetric conjugate addition of 4-halogen-3-oxobutanoates.

Tetronic acid derivatives are widespread in the nature.[8] Many of them possess potent biological activities. In addition, they are also valuable synthetic intermediates for many natural products and

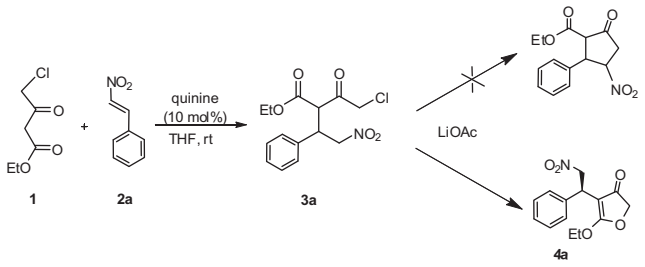
* Corresponding author. E-mail address: yanming@mail.sysu.edu.cn (M. Yan).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.05.082

drugs.[9] The synthesis of optically active tetronic acid derivatives is an important research area. So far, these compounds were prepared mostly starting from 'chiral pool' or other chiral reagents.[10,11] In 2010, Ramachary and Kishor reported the organocatalytic asymmetric synthesis of tetronic acid derivatives via cascade Michael addition/aldol reaction.[11] Very recently, Lu and co-workers developed an organocatalytic cascade reaction of 4-bromo-acetoacetates and nitroalkenes. A series of tetronic acid derivatives were prepared in good yields and enantioselectivities using a chiral amino-thiourea as the catalyst.[12] In this paper, we report the organocatalytic asymmetric conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes and subsequent intramolecular cyclization. The one-pot reaction provided chiral tetronic acid derivatives in good yields and with excellent enantioselectivities (Scheme 1, Eq. 3).

2. Results and discussion

Initially, the reaction of ethyl 4-chloro-3-oxobutanoate **1** with β-nitrostyrene **2a** was investigated in the presence of 10 mol % quinine (Scheme 2). The adduct **3a** was obtained as a mixture of two inseparable diastereoisomers. The treatment of **3a** with AcOLi or other bases did not provide the cyclopentanone, instead tetronic acid derivative **4a** was obtained in excellent yield. Recently we have developed an organocatalytic asymmetric Mannich reaction of **1** with *N*-Boc-imines. The Mannich products were found to undergo intramolecular alkylation reaction in the presence of triethylamine. Chiral tetronic acid derivatives were obtained in good yields and with moderate enantioselectivities.[13] These results implicate that the intramolecular cyclization of 2-substituted 4-chloro-3-oxobutanoates is an efficient method to prepare tetronic acid derivatives.



Scheme 2. Conjugate addition of **1** to **2a** and subsequent intramolecular cyclization.

The reaction was found to be more efficient in one pot without isolation of the intermediate **3a**. After **1** was consumed as indicated by TLC, AcOLi was added to promote the intramolecular cyclization. Although **4a** was obtained in good yield using quinine as the catalyst, no enantioselectivity was achieved (Table 1, entry 1). Cinchonidine also provided racemic **4a** (Table 1, entry 2). To improve the enantioselectivity of the reaction, several organocatalysts **5a**–**d** were examined and the results are summarized in Table 1. 6′-Demethyl quinine **5a** significantly improved the enantioselectivity (Table 1, entry 3). Free 6′-hydroxyl group seems to be crucial for achieving good enantioselectivity. Similar results were reported by Deng and co-workers in the conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes.[14] 9-Benzyl-6′-demethyl quinine **5b** gave inferior enantioselectivity and yield (Table 1, entry 4). Takemoto's amine-thiourea **5c** provided moderate enantioselectivity (Table 1, entry 5). More sterically demanding amine-thiourea **5d** gave better enantioselectivity (Table 1, entry 6).[15] Quinine derived amine-thiourea **5e** was also examined, however only moderate enantioselectivity was observed (Table 1, entry 7). Furthermore, the most promising catalyst **5a** was applied at lower reaction temperatures (Table 1, entries 8–10). Better yield and enantioselectivity (76% yield, 97% ee) were achieved at −20 °C. However, further decrease of the reaction temperature did not improve the enantioselectivity furthermore and led to a lower yield.

The effect of bases on the cyclization process was studied and the results are listed in Table 2. Triethylamine was identified as the best base in our previous study,[13] however it provided low yield in this reaction (Table 2, entry 1). Cs_2CO_3 and K_2CO_3 provided higher reaction rate, but with lower enantioselectivities (Table 2, entries 2 and 3). Weak bases, such as $NaHCO_3$, AcONa, and AcOLi worked better. Good yields and excellent enantioselectivities were achieved (Table 2, entries 4–6). Anhydrous AcOLi and $(NH_4)_2CO_3$ gave the similar yields and enantioselectivities (Table 2, entries 7 and 8). Finally, AcOLi was chosen concerning the reaction rate, yield, and enantioselectivity.

The reaction of ethyl 4-bromo-3-oxobutanoate with nitrostyrene **2a** was investigated (Scheme 3). Lower yield and enantioselectivity were obtained comparing with that of ethyl 4-chloro-3-oxobutanoate.

For a comparison, we also examined the intramolecular cyclization of ethyl 4-chloro-3-oxobutanoate in the presence of AcOLi (Scheme 4). The tetronic acid derivative could not be obtained even after extended reaction time. Other bases including AcONa, Et_3N, KOH, and K_2CO_3 also failed to promote this transformation. The result implicates that the 2-substitution is crucial for the intramolecular cyclization of 4-chloro-3-oxobutanoates.

A number of nitroalkenes were examined in this one-pot conjugate addition/cyclization reaction, and the results are summarized in Table 3. The substitutions at *ortho*-, *meta*-, and *para*-positions of the phenyl ring are tolerated very well. Good yields and excellent enantioselectivities were achieved generally (Table 3, entries 1–12). The effect of electronic property of the substituent is not obvious. In the case of 4-nitro substitution, lower yield was obtained (Table 3, entry 7). β-Naphthyl nitroethylene and β-heteroaryl nitroethylenes are suitable substrates (Table 3, entries 13–15). To our delight, β-alkyl nitroethylene also worked well. The corresponding tetronic acid derivatives **4p**,**q** were obtained in good yields and with excellent enantioselectivities (Table 3, entries 16 and 17). In the recent study of Lu and co-workers, a chiral amino-thiourea was selected as the catalyst and ethyl 4-bromo-acetoacetate was used as the substrate. Typically 90–94% ees were achieved in the presence of 20 mol % catalyst.[12] In comparison with Lu's work, our method possesses several distinct advantages: (1) the commercial availability of ethyl 4-chloro-acetoacetate; (2) easy access of the catalyst 6′-demethyl quinine; (3) lower catalyst loading; (4) better enantioselectivities. In addition, nitroalkenes with an electron-rich aryl group was also applicable (Table 3, entry 3).

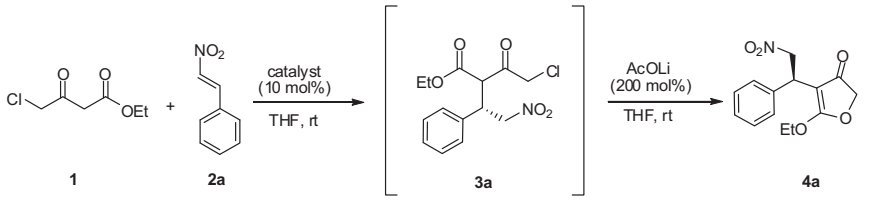
(*E*)-1-Nitroprop-1-ene is also an attractive substrate for the reaction, however it is not stable and enough pure material could not be obtained. Instead, the reaction of 2-acetyloxy-1-nitro-propane with ethyl 4-chloro-acetoacetate was examined. The expected tetronic acid derivative **4r** was obtained with good enantioselectivity, but in lower yield (Scheme 5). The in situ formation of (*E*)-1-nitroprop-1-ene is supposed by the elimination of the acetyloxy group.

The absolute configuration of product **4k** was assigned as *R* by X-ray diffraction analysis (Fig. 1).[16] Other products were suggested to have the same absolute configuration. The enantio-facial selectivity is in line with the reported reactions of acetoacetates with nitroalkenes catalyzed by 6′-demethyl quinine.[14]

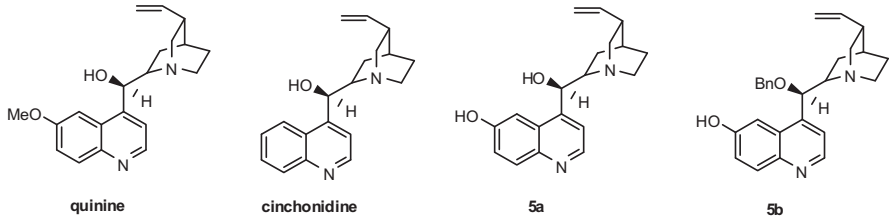
The reaction of tetronic acid **6** with nitroalkene **2c** was also examined using **5a** as the catalyst (Scheme 6). The adduct **7** was obtained in low yield. It was converted to *O*-methyl tetronic derivatives **8** with Me_3OBF_4.[17] Only 16% ee was observed via chiral HPLC analysis. The fact confirms that asymmetric conjugate addition of ethyl 4-chloro-3-oxobutanoate and subsequent cyclization is a superior method to prepare chiral tetronic acid derivatives.

Prostaglandin and their analogs possess a variety of important biological activities. Aza-mimics of prostaglandins were reported to have potent antiaggregatory effect.[18] The treatment of product **4c**

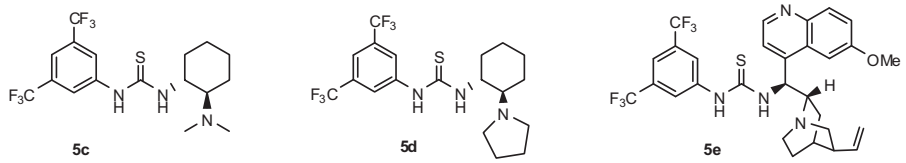
Table 1
Screening of catalysts[a]



1 2a 3a 4a



quinine cinchonidine 5a 5b



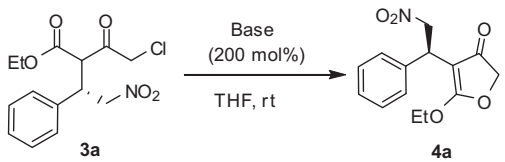
5c 5d 5e

Entry	Catalyst	Time/h	Yield[b]/%	ee[c]/%
1	Quinine	24	76	0
2	Cinchonidine	24	61	0
3	**5a**	6	65	91
4	**5b**	36	38	24
5	**5c**	24	64	68
6	**5d**	24	64	84
7	**5e**	72	60	76
8[d]	**5a**	10	61	95
9[e]	**5a**	12	76	97
10[f]	**5a**	48	70	97

[a] Reactions were carried out with **1** (0.2 mmol), **2a** (0.22 mmol), catalyst (10 mmol%) in THF (1.0 mL) at room temperature. After the complete consume of **1** as indicated by TLC, AcOLi·$2H_2O$ (0.4 mmol) and THF (1 mL) were added. The reaction mixture was stirred at room temperature for 36 h.
[b] Isolated yields of **4a**.
[c] ee values of **4a** were determined by chiral HPLC.
[d] Reaction was performed at 0 °C.
[e] Reaction was performed at −20 °C.
[f] Reaction was performed at −40 °C.

with *n*-$BuNH_2$ provided compound **9** in excellent yield (90%) with retained optical purity (95% ee). This result indicted the tetronic acid products could serve as useful intermediates for the synthesis of aza-mimics of prostaglandins (Scheme 7).

Table 2
Effect of bases on the cyclization[a]



3a 4a

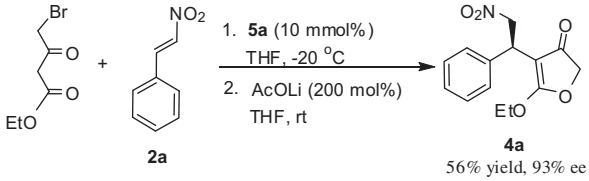
Entry	Base	Time/h	Yield/%	ee/%
1	Et_3N	36	50	96
2	Cs_2CO_3	0.5	93	87
3	K_2CO_3	0.5	95	91
4	$NaHCO_3$	72	95	97
5	AcONa	72	90	97
6	AcOLi	36	95	97
7	Anhydrous AcOLi	36	94	96
8	$(NH_4)_2CO_3$	36	95	96

[a] Reactions were carried out with **3a** (0.1 mmol) and base (0.2 mmol) in THF (1 mL) at room temperature.

The product **4a** was hydrolyzed with aqueous hydrogen chloride, and reduced with zinc powder according to the reported procedure.[12] Chiral γ-lactam **11** was obtained in good yield, which is a useful intermediate for the further synthesis of bioactive compounds (Scheme 8).

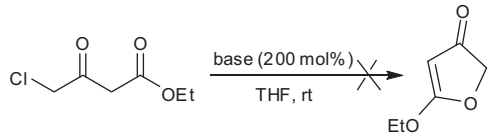
3. Conclusions

In conclusion, we have developed a one-pot organocatalytic asymmetric synthesis of tetronic acid derivatives. 6′-Demethyl quinine was found to be the efficient catalyst for the conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes. The intramolecular cyclization of the conjugate adducts was achieved using AcOLi as the base. β-Aryl, heteroaryl, and alkyl nitroalkenes



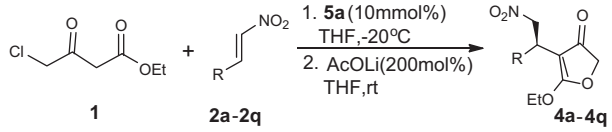
2a 4a
56% yield, 93% ee

Scheme 3. Reaction of ethyl 4-bromo-3-oxobutanoate with nitrostyrene **2a**.



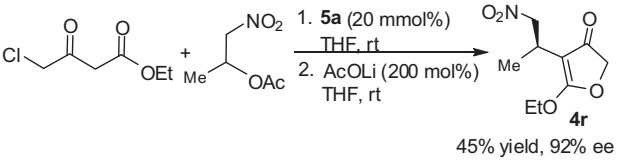
Scheme 4. Attempted intramolecular cyclization of ethyl 4-chloro-3-oxobutanoate in the presence of bases.

Table 3
Reactions of nitroalkenes with ethyl 4-chloro-3-oxobutanoate[a]



Entry	R	Yield[b]/%	ee[c]/%
1	Ph, **2a**	**4a**, 76	97
2	4-Me–C_6H_4, **2b**	**4b**, 76	98
3	4-MeO–C_6H_4, **2c**	**4c**, 65	94
4	4-F–C_6H_4, **2d**	**4d**, 76	98
5	4-Cl–C_6H_4, **2e**	**4e**, 74	98
6	4-Br–C_6H_4, **2f**	**4f**, 70	97
7	4-NO_2–C_6H_4, **2g**	**4g**, 54	97
8	2-Cl–C_6H_4, **2h**	**4h**, 76	97
9	2-Br–C_6H_4, **2i**	**4i**, 79	97
10	2-NO_2–C_6H_4, **2j**	**4j**, 76	96
11	3-Cl–C_6H_4, **2k**	**4k**, 75	97
12	2,4-DiCl–C_6H_3, **2l**	**4l**, 87	98
13	1-Naphthyl, **2m**	**4m**, 81	95
14	Thiophene-2-yl, **2n**	**4n**, 95	97
15	Furan-2-yl, **2o**	**4o**, 94	96
16	Isopropyl, **2p**	**4p**, 74	97
17	Cyclohexyl, **2q**	**4q**, 70	97

[a] Reactions were carried out with **1** (0.2 mmol), nitroalkene (0.22 mmol), **5a** (10 mmol%) in THF (1.0 mL) at −20 °C for 12 h. AcOLi·$2H_2O$ (0.4 mmol) and THF (1 mL) were added. The reaction mixture was stirred at room temperature for 36 h.
[b] Isolated yields.
[c] ee values of **4a**–**q** were determined by chiral HPLC.



Scheme 5. Synthesis of **4r** from 2-acetyloxy-1-nitro-propane.

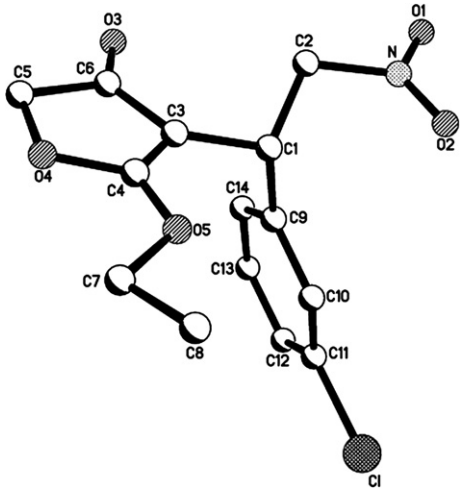
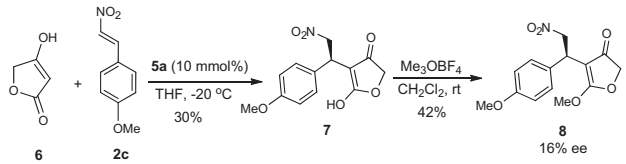
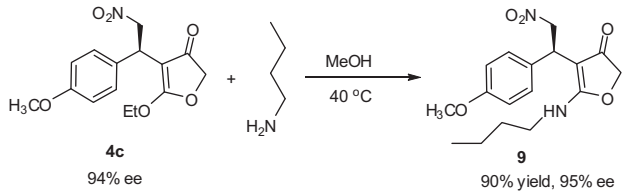


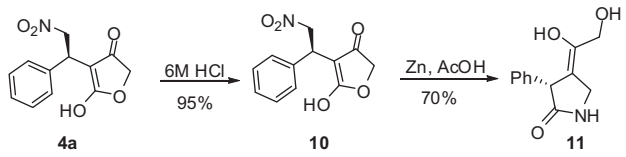
Fig. 1. X-ray structure of product **4k**.



Scheme 6. Reaction of tetronic acid **6** with nitroalkene **2c**.



Scheme 7. Synthesis of an aza-mimic of prostaglandin from product **4c**.



Scheme 8. Synthesis of γ-lactam **11** from product **4a**.

are generally applicable in this transformation. A number of tetronic acid derivatives were prepared in good yields and with excellent enantioselectivities. Furthermore, the products are synthetically useful for the preparation of chiral aza-mimics of prostaglandins and γ-lactams. In comparison with the study by Lu and co-workers, this method is more practical considering the commercial availability of ethyl 4-chloro-acetoacetate, easy access of the catalyst 6′-demethyl quinine, decreased catalyst loading, and improved enantioselectivities.

4. Experimental section

4.1. General information

^1H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer as solutions in $CDCl_3$ or CD_3OD. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ=0 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ=77.0 ppm). The following abbreviations are used to designate chemical shift multiplicities: s=singlet, d=doublet, m=multiplet. High-resolution mass spectra were obtained with Shimadazu LCMS-IT-TOF mass spectrometer. Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter and are reported as $[\alpha]_D^{20}$ (c in gram per 100 mL of solvent). The crystallographic data were obtained with Oxford Diffraction Xcalibur Nova diffractometer. The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co. Ltd. Melting points were recorded on an electrothermal digital melting point apparatus and were uncorrected. TLC analysis was performed on precoated silica gel GF254 slides, and visualized by either UV irradiation. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s=strong, m=medium, w=weak). Unless otherwise stated, all reagents were obtained from commercial sources and used as received. The solvents were used as commercial anhydrous grade without further purification.

Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AS-H column (4.6 mm×25 cm) and eluting with hexane/2-PrOH solution.

4.2. General procedure for the synthesis of racemic tetronic acid derivatives

To a solution of nitroalkene (0.22 mmol) in THF (1 mL) were added ethyl 4-chloro-3-oxobutanoate (27 μL, 0.2 mmol) and DABCO (0.04 mmol, 20 mol %). The mixture was stirred at room temperature until the complete consume of ethyl 4-chloro-3-oxobutanoate. $AcOLi\cdot 2H_2O$ (0.40 mmol) was added and the reaction mixture was stirred for 36 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:5 to 1:3).

4.3. General procedure for the asymmetric conjugate addition of ethyl 4-chloro-3-oxobutanoate to nitroalkenes and subsequent cyclization

To a solution of nitroalkene (0.22 mmol) in THF (1 mL) were added ethyl 4-chloro-3-oxobutanoate (27 μL, 0.2 mmol) and 6′-demethyl quinine **5a** (0.02 mmol, 10 mol %). The mixture was stirred at −20 °C for 12 h. $AcOLi\cdot 2H_2O$ (0.4 mmol) was added and the reaction mixture was stirred for 36 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:5 to 1:3).

4.4. Spectral data of products 4a–q

*4.4.1. (R)-5-Ethoxy-4-(2-nitro-1-phenylethyl)furan-3(2H)-one (**4a**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (42.1 mg, 76% yield); $[\alpha]_D^{20}$ −81.3 (*c* 0.76, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.33–7.23 (m, 3H), 5.24 (dd, *J*=12.7, 9.3 Hz, 1H), 4.87 (dd, *J*=12.7, 6.9 Hz, 1H), 4.55 (d, *J*=2.4 Hz, 2H), 4.52–4.39 (m, 3H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 181.2, 139.1, 128.9, 127.7, 127.6, 92.4, 76.5, 74.9, 66.7, 37.9, 14.7; IR (KBr) ν/cm^{-1}: 1692 (w), 1605 (s), 1552 (m), 1484 (m), 1454 (s), 1388 (m), 1354 (m), 1160 (s), 1066 (s); HRMS (ESI) calcd for $C_{14}H_{15}NNaO_5$ $(M+Na)^+$: 300.0848, found: 300.0843. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=15.0 min, t_{minor}=17.1 min, 97% ee.

*4.4.2. (R)-5-Ethoxy-4-(2-nitro-1-(p-tolyl)ethyl)furan-3(2H)-one (**4b**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (44.2 mg, 76% yield); $[\alpha]_D^{20}$ −70.0 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=8.1 Hz, 2H), 7.11 (d, *J*=7.9 Hz, 2H), 5.21 (dd, *J*=12.6, 9.3 Hz, 1H), 4.85 (dd, *J*=12.7, 7.0 Hz, 1H), 4.54 (d, *J*=2.8 Hz, 2H), 4.49–4.36 (m, 3H), 2.31 (s, 3H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 181.2, 137.3, 136.2, 129.6, 127.5, 92.5, 76.6, 74.9, 66.7, 37.6, 21.0, 14.7; IR (KBr) ν/cm^{-1}: 1695 (w), 1612 (s), 1552 (w), 1514 (w), 1443 (m), 1387 (m), 1354 (m), 1164 (s), 1074 (s); HRMS (ESI) calcd for $C_{15}H_{17}NNaO_5$ $(M+Na)^+$: 314.1004, found: 314.0998. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=13.0 min, t_{minor}=15.1 min, 98% ee.

*4.4.3. (R)-5-Ethoxy-4-(1-(4-methoxyphenyl)-2-nitroethyl)furan-3(2H)-one (**4c**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (39.9 mg, 65% yield); $[\alpha]_D^{20}$ −75.0 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 5.17 (dd, *J*=12.6, 9.2 Hz, 1H), 4.84 (dd, *J*=12.6, 7.1 Hz, 1H), 4.54 (d, *J*=2.0 Hz, 2H), 4.50–4.41 (m, 2H), 4.37 (dd, *J*=9.1, 7.1 Hz, 1H), 3.77 (s, 3H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 181.2, 159.0, 131.3, 128.8, 114.2, 92.7, 74.9, 66.7, 55.2, 37.2, 14.7; IR (KBr) ν/cm^{-1}: 1691 (w), 1593 (s), 1551 (w), 1481 (m), 1384 (m), 1356 (m), 1161 (s), 1077 (s); HRMS (ESI) calcd for $C_{15}H_{17}NNaO_6$ $(M+Na)^+$: 330.0954, found: 330.0947. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=16.5 min, t_{minor}=19.1 min, 94% ee.

*4.4.4. (R)-5-Ethoxy-4-(1-(4-fluorophenyl)-2-nitroethyl)furan-3(2H)-one (**4d**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (44.8 mg, 76% yield); $[\alpha]_D^{20}$ −80.6 (*c* 0.64, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 2H), 7.04–6.97 (m, 2H), 5.18 (dd, *J*=12.8, 8.9 Hz, 1H), 4.89 (dd, *J*=12.8, 7.3 Hz, 1H), 4.58 (d, *J*=2.4 Hz, 2H), 4.54–4.39 (m, 3H), 1.46 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 181.2, 163.4, 160.9, 135.0, 134.9, 129.4, 129.3, 115.8, 115.6, 92.3, 76.5, 74.9, 66.8, 37.2, 14.7; IR (KBr) ν/cm^{-1}: 2990 (w), 1694 (w),1612 (s), 1552 (m), 1510 (m), 1452 (s), 1389 (m), 1356 (m), 1224 (m), 1162 (s), 1041 (m); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5F$ $(M+Na)^+$: 318.0754, found: 318.0746. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=13.3 min, t_{minor}=15.7 min, 98% ee.

*4.4.5. (R)-5-Ethoxy-4-(1-(4-chlorophenyl)-2-nitroethyl)furan-3(2H)-one (**4e**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (46.0 mg, 74% yield); $[\alpha]_D^{20}$ −107.6 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J*=8.5 Hz, 2H), 7.31–7.25 (m, 2H), 5.16 (dd, *J*=12.8, 8.8 Hz, 1H), 4.89 (dd, *J*=12.8, 7.4 Hz, 1H), 4.56 (d, *J*=2.5 Hz, 2H), 4.52–4.37 (m, 3H), 1.44 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 181.2, 137.7, 133.5, 129.1, 129.0, 92.0, 76.3, 75.0, 66.9, 37.3, 14.7; IR (KBr) ν/cm^{-1}: 2922 (w), 1695 (w), 1605 (s), 1552 (m), 1492 (m), 1452 (s), 1388 (m), 1355 (m), 1162 (s), 1072 (s); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5Cl$ $(M+Na)^+$: 334.0458, found: 334.0457. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=12.3 min, t_{minor}=13.3 min, 98% ee.

*4.4.6. (R)-5-Ethoxy-4-(1-(4-bromophenyl)-2-nitroethyl)furan-3(2H)-one (**4f**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (50.0 mg, 70% yield); $[\alpha]_D^{20}$ −60.13 (*c* 0.78, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 5.16 (dd, *J*=12.8, 8.9 Hz, 1H), 4.88 (dd, *J*=12.8, 7.3 Hz, 1H), 4.56 (d, *J*=2.7 Hz, 2H), 4.51–4.43 (m, 2H), 4.41–4.35 (m, 1H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 181.2, 138.2, 132.0, 129.4, 121.6, 92.0, 76.2, 75.0, 66.9, 37.4, 14.7; IR (KBr) ν/cm^{-1}: 2921 (w), 1694 (w), 1610 (s), 1552 (m), 1488 (m), 1452 (s), 1388 (m), 1355 (m), 1159 (s), 1074 (s); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5Br$ $(M+Na)^+$: 377.9953, found: 377.9949. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=13.1min, t_{minor}=14.6 min, 97% ee.

*4.4.7. (R)-5-Ethoxy-4-(1-(4-nitrophenyl)-2-nitroethyl)furan-3(2H)-one (**4g**).* Prepared according to the general procedure in Section 4.3 as a yellow oil (34.8 mg, 54% yield); $[\alpha]_D^{20}$ −67.1 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.14 (m, 2H), 7.62–7.56 (m, 2H), 5.16 (dd, *J*=13.1, 8.3 Hz, 1H), 5.00 (dd, *J*=13.1, 7.8 Hz, 1H), 4.59 (d, *J*=3.8 Hz, 2H), 4.55–4.45 (m, 3H), 1.45 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 181.2, 147.4, 146.4, 128.7, 124.2, 91.3, 75.7, 75.1, 67.2, 37.6, 14.7; IR (KBr) ν/cm^{-1}: 2921 (w), 1695 (w), 1599 (s), 1553 (m), 1452 (m), 1387 (m), 1350 (m), 1162 (s), 1074 (s); HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_7$ $(M+Na)^+$: 345.0699, found: 345.0691. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=85:15, λ=254 nm, 0.8 mL/min); t_{major}=96.5 min, t_{minor}=105.0 min, 97% ee.

*4.4.8. (S)-5-Ethoxy-4-(1-(2-chlorophenyl)-2-nitroethyl)furan-3(2H)-one (**4h**).* Prepared according to the general procedure in Section

4.3 as a colorless oil (47.3 mg, 76% yield); $[\alpha]_D^{20}$ −131.8 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J*=7.5, 2.0 Hz, 1H), 7.37 (dd, *J*=7.6, 1.7 Hz, 1H), 7.25–7.18 (m, 2H), 5.27 (dd, *J*=12.9, 9.9 Hz, 1H), 4.99 (dd, *J*=9.9, 5.8 Hz, 1H), 4.77 (dd, *J*=12.9, 5.8 Hz, 1H), 4.58 (d, *J*=2.4 Hz, 2H), 4.50–4.41 (m, 2H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 181.6, 136.0, 133.2, 129.8, 129.5, 128.8, 127.4, 90.7, 75.0, 74.8, 66.8, 34.3, 14.6; IR (KBr) ν/cm^{-1}: 2360 (w), 1599 (m), 1453 (w), 1383 (w), 1351 (w), 1162 (s), 1075 (s); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5Cl$ $(M+Na)^+$: 334.0458, found: 334.0456. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=11.3 min, t_{minor}=13.5 min, 97% ee.

*4.4.9. (S)-5-Ethoxy-4-(1-(2-bromophenyl)-2-nitroethyl)furan-3(2H)-one (**4i**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (56.1 mg, 79% yield); $[\alpha]_D^{20}$ −156.3 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J*=7.8, 1.6 Hz, 1H), 7.56 (dd, *J*=8.0, 1.2 Hz, 1H), 7.31–7.26 (m, 1H), 7.12 (ddd, *J*=7.9, 7.5, 1.7 Hz, 1H), 5.28 (dd, *J*=12.9, 10.0 Hz, 1H), 4.98 (dd, *J*=10.0, 5.7 Hz, 1H), 4.75 (dd, *J*=12.9, 5.7 Hz, 1H), 4.59 (d, *J*=1.9 Hz, 2H), 4.52–4.40 (m, 2H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 181.7, 137.8, 133.2, 129.7, 129.1, 128.0, 123.7, 91.1, 75.0, 74.9, 66.8, 37.1, 14.6; IR (KBr) ν/cm^{-1}: 3000 (w), 2920 (w), 1689 (w), 1597 (s), 1550 (m), 1451 (m), 1420 (s), 1379 (m), 1349 (m), 1164 (s), 1071 (s); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5Br$ $(M+Na)^+$: 377.9953, found: 377.9950. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=11.4 min, t_{minor}=14.0 min, 97% ee.

*4.4.10. (R)-5-Ethoxy-4-(2-nitro-1-(2-nitrophenyl)ethyl)furan-3(2H)-one (**4j**).* Prepared according to the general procedure in Section 4.3 as a yellow oil (48.9 mg, 76% yield); $[\alpha]_D^{20}$ −215.3 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J*=7.9, 1.2 Hz, 1H), 7.82 (dd, *J*=8.1, 1.2 Hz, 1H), 7.58 (td, *J*=7.8, 1.3 Hz, 1H), 7.45–7.40 (m, 1H), 5.36 (dd, *J*=13.1, 9.3 Hz, 1H), 5.03 (dd, *J*=9.2, 5.9 Hz, 1H), 4.94 (dd, *J*=13.1, 5.9 Hz, 1H), 4.61 (d, *J*=5.1 Hz, 2H), 4.50–4.42 (m, 2H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 181.8, 149.9, 133.4, 133.2, 130.6, 128.6, 124.5, 91.3, 75.1, 74.9, 67.3, 32.6, 14.5. IR (KBr) ν/cm^{-1}: 2922 (w), 1605 (s), 1554 (m), 1453 (m), 1389 (m), 1357 (m), 1163 (s), 1077 (s); HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_7$ $(M+Na)^+$: 345.0699, found: 345.0695. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=17.1 min, t_{minor}=19.3 min, 96% ee.

*4.4.11. (R)-5-Ethoxy-4-(1-(3-chlorophenyl)-2-nitroethyl)furan-3(2H)-one (**4k**).* Prepared according to the general procedure in Section 4.3 as a milky-white solid (46.7 mg, 75% yield); mp 91–92 °C; $[\alpha]_D^{20}$ −76.5 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.33–7.29 (m, 1H), 7.26–7.21 (m, 2H), 5.17 (dd, *J*=12.9, 8.9 Hz, 1H), 4.89 (dd, *J*=12.9, 7.3 Hz, 1H), 4.58 (d, *J*=0.4 Hz, 2H), 4.54–4.44 (m, 2H), 4.40 (dd, *J*=8.8, 7.3 Hz, 1H), 1.45 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 181.2, 141.1, 134.6, 130.2, 127.8, 127.8, 125.9, 91.8, 76.1, 76.0, 66.9, 37.5, 14.7; IR (KBr) ν/cm^{-1}: 1691 (w), 1593 (s), 1551 (w), 1481 (m), 1384 (m), 1356 (m), 1161 (s), 1077 (s); HRMS (ESI) calcd for $C_{14}H_{14}NNaO_5Cl$ $(M+Na)^+$: 334.0458, found: 334.0452. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=14.1 min, t_{minor}=19.7 min, 97% ee.

*4.4.12. (S)-5-Ethoxy-4-(1-(2,4-dichlorophenyl)-2-nitroethyl)furan-3(2H)-one (**4l**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (60.0 mg, 87% yield); $[\alpha]_D^{20}$ −105.5 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.5 Hz, 1H), 7.39 (d, *J*=2.2 Hz, 1H), 7.22 (dd, *J*=8.4, 2.2 Hz, 1H), 5.22 (dd, *J*=12.9, 9.6 Hz, 1H), 4.94 (dd, *J*=9.6, 6.1 Hz, 1H), 4.78 (dd, *J*=12.9, 6.1 Hz, 1H), 4.59 (d, *J*=3.5 Hz, 2H), 4.51–4.43 (m, 2H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 181.5, 134.7, 134.0, 133.9, 130.4, 129.6, 127.7, 90.6, 75.0, 74.7, 67.0, 33.8, 14.6. IR (KBr) ν/cm^{-1}: 2921 (w), 1603 (s), 1552 (m), 1452 (m), 1387 (m), 1355 (m), 1162 (s), 1076 (s); HRMS (ESI) calcd for $C_{14}H_{13}NNaO_5Cl_2$ $(M+Na)^+$: 368.0068, found: 368.0065. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=9.8 min, t_{minor}=10.8 min, 98% ee.

*4.4.13. (R)-5-Ethoxy-4-(1-(naphthalen-1-yl)-2-nitroethyl)furan-3(2H)-one (**4m**).* Prepared according to the general procedure in Section 4.3 as a yellow solid (53.0 mg, 81% yield); mp 90–91 °C; $[\alpha]_D^{20}$ −116.0 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J*=8.5 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.76 (d, *J*=8.2 Hz, 1H), 7.64–7.59 (m, 1H), 7.60–7.55 (m, 1H), 7.53–7.47 (m, 1H), 7.44–7.39 (m, 1H), 5.41 (dd, *J*=12.0, 9.9 Hz, 1H), 5.34 (dd, *J*=9.9, 5.1 Hz, 1H), 4.90 (dd, *J*=12.1, 5.1 Hz, 1H), 4.56 (d, *J*=1.2 Hz, 2H), 4.46–4.37 (m, 2H), 1.38 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 181.4, 134.1, 134.0, 130.8, 129.1, 128.2, 126.7, 125.8, 125.4, 125.0, 122.8, 91.9, 75.7, 75.0, 66.8, 32.8, 14.6; IR (KBr) ν/cm^{-1}: 2929 (w), 1686 (w), 1586 (s), 1544 (m), 1453 (m), 1379 (m),1357 (m), 1167 (s), 1123 (m), 1079 (s); HRMS (ESI) calcd for $C_{18}H_{17}NNaO_5$ $(M+Na)^+$: 350.1004, found: 350.1001. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=14.0 min, t_{minor}=15.5 min, 95% ee.

*4.4.14. (R)-5-Ethoxy-4-(2-nitro-1-(thiophen-2-yl)ethyl)furan-3(2H)-one (**4n**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (53.8 mg, 95% yield); $[\alpha]_D^{20}$ −81.7 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=1.2 Hz, 1H), 6.29 (dd, *J*=3.2, 1.8 Hz, 1H), 6.17 (d, *J*=3.2 Hz, 1H), 5.04 (dd, *J*=12.8, 9.1 Hz, 1H), 4.90 (dd, *J*=12.8, 6.6 Hz, 1H), 4.63 (dd, *J*=9.0, 6.7 Hz, 1H), 4.59 (s, 2H), 4.48 (q, *J*=7.1 Hz, 2H), 1.43 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 181.0, 141.1, 127.1, 125.5, 124.7, 92.2, 75.0, 66.9, 32.6, 14.7; IR (KBr) ν/cm^{-1}: 1610 (s), 1552 (m), 1485 (m), 1452 (m), 1388 (m), 1355 (m), 1165 (s), 1076 (s); HRMS (ESI) calcd for $C_{12}H_{13}NNaO_5S$ $(M+Na)^+$: 306.0412, found: 306.0408. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=21.0 min, t_{minor}=23.3 min, 97% ee.

*4.4.15. (R)-5-Ethoxy-4-(1-(furan-2-yl)-2-nitroethyl)furan-3(2H)-one (**4o**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (50.2 mg, 94% yield); $[\alpha]_D^{20}$ −4.6 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J*=5.1 Hz, 1H), 7.02 (d, *J*=3.1 Hz, 1H), 6.92 (dd, *J*=5.0, 3.6 Hz, 1H), 5.15 (dd, *J*=12.6, 9.2 Hz, 1H), 4.87 (dd, *J*=12.6, 6.8 Hz, 1H), 4.77 (dd, *J*=8.8, 7.1 Hz, 1H), 4.57 (s, 2H), 4.49 (qd, *J*=7.1, 2.2 Hz, 2H), 1.45 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 181.6, 150.6, 142.1, 110.5, 107.0, 90.0, 75.1, 74.6, 67.1, 31.2, 14.6; IR (KBr) ν/cm^{-1}: 1695 (w), 1612 (s), 1546 (s), 1459 (m), 1424 (m), 1390 (m), 1357 (m), 1168 (s), 1123 (m), 1080 (s); HRMS (ESI) calcd for $C_{12}H_{13}NNaO_6$ $(M+Na)^+$: 290.0641, found: 290.0639. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=7.90 min, t_{minor}=7.42 min, 96% ee.

*4.4.16. (R)-5-Ethoxy-4-(3-methyl-1-nitrobutan-2-yl)furan-3(2H)-one (**4p**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (36.0 mg, 74% yield); $[\alpha]_D^{20}$ +36.1 (*c* 0.70, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, *J*=11.9, 10.4 Hz, 1H), 4.59 (dd, *J*=12.0, 5.2 Hz, 1H), 4.56 (s, 2H), 4.45 (qd, *J*=7.1, 1.5 Hz, 2H), 2.99 (ddd, *J*=10.3, 7.5, 5.2 Hz, 1H), 2.06–1.96 (m, 1H), 1.43 (t, *J*=7.1 Hz, 3H), 0.96 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 182.0, 90.8, 75.7, 74.7, 66.4, 38.9, 29.6, 20.7, 20.1, 14.7; IR (KBr) ν/cm^{-1}: 2964 (w), 1694 (w), 1611 (s), 1550 (m), 1443 (m), 1387 (m), 1354 (m), 1166 (s), 1077 (s); HRMS (ESI)

calcd for $C_{11}H_{17}NNaO_5$ $(M+Na)^+$: 266.1004, found: 266.0997. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=12.6 min, t_{minor}=9.8 min, 97% ee.

*4.4.17. (R)-5-Ethoxy-4-(1-cyclohexyl-2-nitroethyl)furan-3(2H)-one (**4q**).* Prepared according to the general procedure in Section 4.3 as a colorless oil (39.6 mg, 70% yield); $[\alpha]_D^{20}$ +29.8 (*c* 0.44, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, *J*=11.8, 10.5 Hz, 1H), 4.60 (dd, *J*=11.9, 5.1 Hz, 1H), 4.54 (s, 2H), 4.44 (qd, *J*=7.1, 0.8 Hz, 2H), 3.01 (ddd, *J*=10.4, 7.5, 5.1 Hz, 1H), 1.78–1.60 (m, 6H), 1.42 (t, *J*=7.1 Hz, 3H), 1.26–0.87 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 182.0, 90.7, 75.5, 74.7, 66.4, 38.8, 38.1, 31.1, 30.5, 26.1, 26.0, 25.9, 14.7; IR (KBr) ν/cm^{-1}: 2925 (w), 2853 (w), 1695 (m), 1614 (s), 1549 (m), 1485 (w), 1451 (m), 1387 (m), 1355 (m), 1162 (s), 1061 (s); HRMS (ESI) calcd for $C_{14}H_{21}NNaO_5$ $(M+Na)^+$: 306.1317, found: 306.1311. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=16.6 min, t_{minor}=15.4 min, 97% ee.

*4.4.18. (R)-5-Ethoxy-4-(1-nitropropan-2-yl)furan-3(2H)-one (**4r**).* To a solution of 2-acetyloxy-1-nitro-propane (0.22 mmol) in THF (1 mL) were added ethyl 4-chloro-3-oxobutanoate (27 μL, 0.2 mmol) and 6′-demethyl quinine **5a** (0.04 mmol). The mixture was stirred at room temperature for 96 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:3). The product **4r** was obtained as a colorless oil (19.4 mg, 45% yield). $[\alpha]_D^{20}$ +20.6 (*c* 0.56, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.80–4.61 (m, 1H), 4.54 (s, 2H), 4.52–4.42 (m, 3H), 3.34 (dd, *J*=14.3, 7.2 Hz, 1H), 1.44 (t, *J*=7.0 Hz, 3H), 1.25 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 181.2, 93.0, 78.1, 74.8, 66.5, 26.7, 16.1, 14.7; IR (KBr) ν/cm^{-1}: 2923 (w), 2852 (w), 1600 (s), 1550 (m), 1443 (m), 1386 (m), 1335 (w), 1094 (w), 1022 (w); HRMS (ESI) calcd for $C_9H_{13}NNaO_5$ $(M+Na)^+$: 238.0686, found: 238.0693. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=85:15, λ=220 nm, 0.8 mL/min); t_{major}=29.9 min, t_{minor}=31.3 min, 92% ee.

4.5. Synthesis of (*R*)-5-hydroxy-4-(1-(4-methoxyphenyl)-2-nitroethyl)furan-3(2*H*)-one (7)

To a solution of β-(4-methoxy-phenyl)-nitroethylene **2c** (0.22 mmol) in THF (1 mL) were added tetronic acid (20.0 mg, 0.20 mmol) and 6′-demethyl quinine **5a** (0.02 mmol, 10 mol %). The mixture was stirred at −20 °C for 48 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (CH_2Cl_2/MeOH=20:1) to give **7** as a white solid (16.7 mg, 30% yield). Mp 160 °C (decomposed); ^1H NMR (400 MHz, CD_3OD) δ 7.27 (d, *J*=8.8 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 5.18 (dd, *J*=13.1, 9.5 Hz, 1H), 4.81 (dd, *J*=13.1, 6.8 Hz, 1H), 4.61 (s, 2H), 4.54 (dd, *J*=9.4, 6.9 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.8, 176.5, 160.6, 131.9, 129.9, 115.2, 100.5, 77.7, 68.2, 55.7, 39.1, 34.0; IR (KBr) ν/cm^{-1}: 1599 (m), 1513 (m), 1385 (m), 1355 (m), 1162 (s), 1078 (s); HRMS (ESI) calcd for $C_{13}H_{13}BrNO_6$ $(M-H)^-$: 278.0665, found: 278.0670.

4.6. Synthesis of (*R*)-5-methoxy-4-(1-(4-methoxyphenyl)-2-nitroethyl)furan-3(2*H*)-one (8)

To a solution of **7** (27.8 mg, 0.10 mmol) in dry methylene dichloride (2 mL) was added trimethyloxonium fluoroborate (44.4 mg, 0.30 mmol). The resulting suspension was refluxed for 24 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:5 to 1:3) to give **8** as a yellow oil (12.3 mg, 42% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*=8.7 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 5.22 (dd, *J*=12.6, 9.3 Hz, 1H), 4.83 (dd, *J*=12.6, 6.9 Hz, 1H), 4.58 (d, *J*=2.6 Hz, 2H), 4.37 (dd, *J*=9.3, 6.9 Hz, 1H), 4.08 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 181.5, 158.0, 130.1, 127.8, 113.3, 91.6, 74.0, 55.7, 54.3, 36.3, 13.3; IR (KBr) ν/cm^{-1}: 2964 (w), 2922 (w), 1604 (m), 1387 (w), 1354 (w), 1261 (w), 1163 (s), 1076 (s); HRMS (ESI) calcd for $C_{14}H_{15}NNaO_6$ $(M+Na)^+$: 316.0797, found: 316.0796. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=18.6 min, t_{minor}=21.4 min, 16% ee.

4.7. Synthesis of (*R*)-5-(butylamino)-4-(1-(4-methoxyphenyl)-2-nitroethyl)furan-3(2*H*)-one (9)

A solution of **4c** (31 mg, 0.1 mmol) and butylamine (0.4 mmol) in methanol (3 mL) was stirred at 40 °C for 12 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:5 to 1:3) to give **9** as a yellow oil (30 mg, 90% yield). $[\alpha]_D^{20}$ −7.5 (*c* 1.08, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 5.44 (dd, *J*=13.2, 7.2 Hz, 1H), 5.22 (t, *J*=5.4 Hz, 1H), 4.88 (dd, *J*=13.2, 8.3 Hz, 1H), 4.47 (s, 2H), 4.29 (t, *J*=7.7 Hz, 1H), 3.78 (s, 3H), 3.27–3.19 (m, 2H), 1.45–1.37 (m, 2H), 1.21 (td, *J*=14.9, 7.5 Hz, 3H), 0.87 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 177.2, 159.2, 130.4, 128.9, 114.5, 89.5, 76.7, 73.9, 55.3, 41.2, 38.1, 31.8, 19.6, 13.5; IR (KBr) ν/cm^{-1}: 1673 (w), 1614 (w), 1545 (w), 1514 (w), 1439 (m), 1383 (m), 1254 (w), 1162 (s), 1066 (s); HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ $(M+Na)^+$: 357.1421, found: 357.1426. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH=60:40, λ=254 nm, 0.8 mL/min); t_{major}=15.4 min, t_{minor}=7.5 min, 97% ee.

4.8. Synthesis of (*E*)-3-(1,2-dihydroxyethylidene)-4-phenylpyrrolidin-2-one (11)[12]

To a solution of **4a** (0.2 mmol) in THF (2 mL) was added 6 M HCl (2 mL). The mixture was stirred at room temperature for 2 h and then concentrated under vacuum. The residue was extracted with ethyl acetate (5 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane=1:1 to 10:1) afforded tetronic acid **10** as a pale yellow solid (47.5 mg, 95% yield).

Compound **10** (0.18 mmol) was dissolved in a mixture of THF (1 mL) and AcOH (0.8 mL). Zn powder (1.8 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. The mixture was filtered through a layer of Celite, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH=5:1 to CH_2Cl_2/MeOH/TEA=5:1:1) to afford γ-lactam **11** as a pale yellow solid (27.6 mg, 70% yield). ^1H NMR (400 MHz, CD_3OH) δ 7.45–7.28 (m, 4H), 7.24 (dd, *J*=10.0, 4.1 Hz, 1H), 4.58–4.32 (m, 2H), 3.99 (dd, *J*=7.2, 3.9 Hz, 1H), 3.56 (dd, *J*=12.4, 7.4 Hz, 1H), 3.31–3.29 (m, 1H); ^{13}C NMR (100 MHz, CD_3OH) δ 191.0, 182.3, 141.9, 129.8, 129.0, 128.1, 92.5, 71.2, 45.3, 40.2; IR (KBr) ν/cm^{-1}: 2962 (w), 2923 (w), 1634 (s), 1559 (m), 1423 (m), 1384 (m), 1261 (m), 1097 (s), 1032 (s); HRMS (ESI) calcd for $C_{12}H_{14}NO_3$ $(M+H)^+$: 220.0967, found: 220.0968.

Acknowledgements

Financial supports from National Natural Science Foundation of China (Nos. 20972195, 21172270) and Guangdong Engineering Research Center of Chiral Drugs are gratefully acknowledged.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.082.

References and notes

1. For recent reviews of asymmetric organocatalysis, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660; (b) Yu, X.-H.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516–532; (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308; (d) Guillena, G.; Nájera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.
2. For the reviews of organocatalytic asymmetric conjugate addition, see: (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701–1716; (c) Chen, Y.-C. *Synlett* **2008**, 1919–1930; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.
3. For the reviews of organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; (c) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703–4832.
4. For the application of nucleophiles with leaving groups in organocatalytic asymmetric conjugate addition, see: (a) Lv, J.; Zhang, J.; Lin, Z.; Wang, Y. *Chem.—Eur. J.* **2009**, *15*, 972–979; (b) Rios, R.; Sundén, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028–1032; (c) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894; (d) Terrasson, V.; Van der Lee, A.; De Figueiredo, R. M.; Campagne, J. M. *Chem.—Eur. J.* **2010**, *16*, 7875–7880; (e) Ibrahem, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2008**, *14*, 7867–7879; (f) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539–7542; (g) Li, W.-J.; Li, X.; Ye, T.-T.; Wu, W.-B.; Liang, X.-M.; Ye, J.-X. *Tetrahedron Lett.* **2011**, *52*, 2715–2718; (h) El-Gokha, A.; Maas, G. *Tetrahedron* **2011**, *67*, 2849–2853.
5. (a) Dong, L.-T.; Du, Q.-S.; Lou, C.-L.; Zhang, J.-M.; Lu, R.-J.; Yan, M. *Synlett* **2010**, 266–270; (b) Du, Q.-S.; Dong, L.-T.; Wang, J.-J.; Lu, R.-J.; Yan, M. *ARKIVOC* **2009**, *XIV*, 191–199; (c) Zhang, J.-M.; Hu, Z.-P.; Dong, L.-T.; Xuan, Y.-N.; Yan, M. *Tetrahedron: Asymmetry* **2009**, *20*, 355–361; (d) Xuan, Y.-N.; Nie, S.-Z.; Dong, L.-T.; Zhang, J.-M.; Yan, M. *Org. Lett.* **2009**, *11*, 1583–1586.
6. Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479.
7. Rios, R.; Vesely, J.; Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5835–5839.
8. (a) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221; (b) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157–3188; (c) Athanasellis, G.; Markopoulou, O. I.; Markopoulos, J. *Bioinorg. Chem. Appl.* **2010**, *11*, 1–11.
9. (a) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413–2416; (b) Frackenpohl, J.; Adelt, I.; Antonicek, H.; Arnold, C.; Behrmann, P.; Blaha, N.; Böhmer, J.; Gutbrod, O.; Hanke, R.; Hohmann, S.; Houtdreve, M. V.; Lösel, P.; Malsam, O.; Melchers, M.; Neufert, V.; Peschel, E.; Reckmann, U.; Schenke, T.; Thiesen, H. P.; Velten, R.; Vogelsang, K.; Weiss, H. C. *Bioorg. Med. Chem.* **2009**, *17*, 4160–4184; (c) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425–7426; (d) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *J. Org. Chem.* **2006**, *71*, 8357–8364; (e) White, J. D.; Takabe, K.; Prisbylla, M. P. *J. Org. Chem.* **1985**, *50*, 5233–5244; (f) Shaabani, A.; Sarvary, A.; Keshipour, S.; Rezayan, A. H.; Ghadari, R. *Tetrahedron* **2010**, *66*, 1911–1914; (g) Yang, W.-Q.; Liu, J.-K.; Zhang, H.-B. *Tetrahedron Lett.* **2010**, *51*, 4874–4880.
10. For the synthesis of optically active tetronic acid derivatives from 'chiral pool' or other chiral reagents, see: (a) Donald, T.; Witiak, D. T.; Tehim, A. K. *J. Org. Chem.* **1990**, *55*, 1112–1114; (b) Mitsos, C. A.; Zografos, A. L.; Markopoulou, O. I. *J. Org. Chem.* **2000**, *65*, 5852–5853; (c) Schobert, R.; Jagusch, C. *J. Org. Chem.* **2005**, *70*, 6129–6132; (d) Rajaram, A. R.; Pu, L. *Org. Lett.* **2006**, *8*, 2019–2021; (e) Athanasellis, G.; Markopoulou, A. I.; Markopoulosb, J. *Synlett* **2002**, 1736–1739; (f) Effenberger, F.; Syed, J. *Tetrahedron: Asymmetry* **1998**, *9*, 817–825; (g) Duffield, J. J.; Regan, A. C. *Tetrahedron: Asymmetry* **1996**, *7*, 663–666; (h) Takabe, K.; Hashimoto, H.; Sugimoto, H.; Nomoto, M.; Yoda, H. *Tetrahedron: Asymmetry* **2004**, *15*, 909–912.
11. Ramachary, D. B.; Kishor, M. *Org. Biomol. Chem.* **2010**, *8*, 2859–2867.
12. During the preparation of this manuscript, Lu and co-workers reported a similar organocatalytic reaction of 4-bromo-acetoacetate and nitroalkenes, see: Dou, X. W.; Han, X. Y.; Lu, Y. X. *Chem.—Eur. J.* **2012**, *18*, 85–89.
13. Luo, N.-H.; Sun, X.; Yan, Y.-Y.; Nie, S.-Z.; Yan, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1536–1541.
14. Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907.
15. (a) Lu, R.-J.; Yan, Y.-Y.; Wang, J.-J.; Du, Q.-S.; Nie, S.-Z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230–6239; (b) Nie, S.-Z.; Hu, Z.-P.; Xuan, Y.-N.; Wang, J.-J.; Li, X.-M.; Yan, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2055–2059.
16. CCDC 846145 contains the supplementary crystallographic data of the compound **4k**. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
17. Paquette, L. A.; Kakihana, T.; Hansen, J. F.; Philips, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 152–159.
18. (a) Pashkovskii, F. S.; Shchukina, E. M.; Gribovskii, M. G.; Lakhvich, F. A. *Rus. J. Org. Chem.* **2008**, *44*, 657–670; (b) Pashkovskii, F. S.; Shchukina, E. M.; Gribovskii, M. G.; Lakhvich, F. A. *Russ. J. Org. Chem.* **2006**, *42*, 527–536.