Tetrahedron 67 (2011) 10186–10194

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Biscinchona alkaloids as highly efficient bifunctional organocatalysts for the asymmetric conjugate addition of malonates to nitroalkenes at ambient temperature

Fei Li [a], Ying-Zi Li [a], Zhen-Shan Jia [a], Ming-Hua Xu [b], Ping Tian [a,*], Guo-Qiang Lin [a,*]

[a] CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 25 May 2011
Received in revised form 23 August 2011
Accepted 23 August 2011
Available online 27 August 2011

Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday on December 31, 2011

Keywords:
Bifinctional
Biscinchona alkaloids
Nitroalkenes
Conjugate addition
Baclofen

ABSTRACT

The novel bifunctional bisalkaloids have been developed as highly efficient catalysts for the asymmetric conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes with low catalyst loading (1 mol %) at ambient temperature, providing the products with excellent enantioselectivities (up to 97% ee).

1. Introduction

Readily available and inexpensive cinchona alkaloids with their pseudoenantiomeric forms, such as quinine and quinidine or cinchonine and cinchonidine, are among the most privileged chiral catalysts or ligands in the area of asymmetric catalysis.[1,2] For instance, the demethylated C6′–OH cinchona alkaloids along with their C9-O substituted derivatives (**Q1a**–**c** and **QD1a**–**c**), in which C6′–OH group serves as an effective H-bond donor, while the tertiary quinuclidine nitrogen acts as a powerful Lewis base, were first successfully used as catalysts for the enantioselective conjugate addition of malonates to nitroalkenes (Fig. 1).[5c] Indeed, to date these cinchona alkaloids derivatives including β-isocupreidine (β-ICD, **Q2**), have been developed and already shown outstanding bifunctionally catalytic abilities in numerous reactions, such as Morita–Baylis–Hillman reaction,[3,4] conjugate addition to nitroalkenes,[5] α,β-unsaturated aldehydes,[6a] ketones,[6b] cyanides,[6c] and sulfones,[6d] Henry reaction,[7] Mannich reaction,[8] allylic nucleophilic substitution,[9] Diels–Alder reaction,[10] formal [3+2]cycloaddition reaction,[11] Kornblum DeLaMare rearrangement reaction,[12] and α-amination reaction.[13]

Among these reactions, modification of cinchona alkaloids' C_9–OH appears to hinder free rotation of C_8–C_9 and C_4'–C_9 σ-bonds and favor only a narrow range of the conformational space of the molecules, which could be more adaptable toward structural variation for optimization of catalyst activity and selectivity.

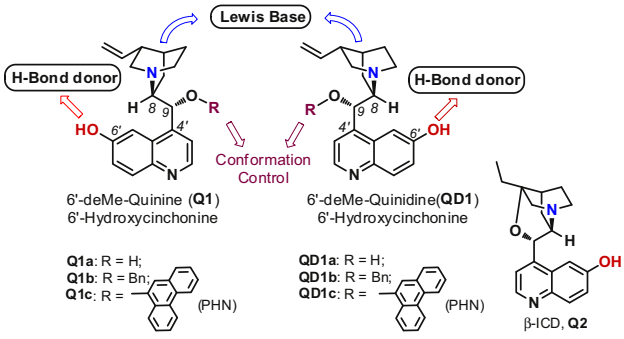
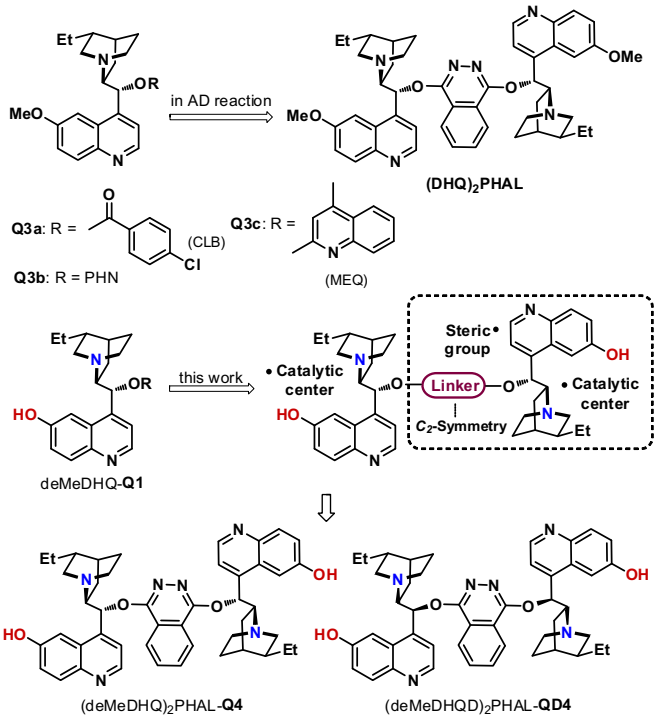


Fig. 1. Active sites in bifunctional cinchona alkaloid catalysts.

* Corresponding authors. Tel.: +86 21 54925169; fax: +86 21 64166263; e-mail addresses: tianping@sioc.ac.cn (P. Tian), lingq@mail.sioc.ac.cn (G.-Q. Lin).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.08.070

Furthermore, extensive studies focused on skeleton modification of cinchona alkaloids in Sharpless AD reaction had demonstrated that second generation dimeric ligands, such as $(DHQ)_2PHAL$, which possessed an enzyme-like binding pocket[14] showed superior activity and selectivity than those monomers bearing C9–O substituents **Q3** in most cases. Inspired by the successful achievement of dimeric cinchona alkaloids in Sharpless AD reaction, we hope to design a new type of biscinchona alkaloid, which could be utilized as an efficient catalyst in other asymmetric field. Herein, we disclose the first synthesis of bis(demethylated-alkaloids) organocatalysts **Q4** and **QD4**, as well as the application in the addition of malonates to nitroalkenes (Scheme 1).



Scheme 1. Concept and design of bisalkaloid catalysts **Q4** and **QD4**.

2. Results and discussion

2.1. Preparation of bisalkaloid catalysts Q4 and QD4

Our investigations began with the preparation of biscinchona alkaloid catalyst $(deMeDHQ)_2PHAL$–**Q4**. Direct demethylation of $(DHQ)_2PHAL$ with strong acid[15] or NaSEt[5c] afforded complicated products and no bisphenolic product **Q4** was obtained. Due to the high sensitivity of phthalazinyl ether to strong acid or nucleophilic reagent, demethylation had to be performed on a synthetic precursor. Treated with HBr (aq, 40%) dihydroquinine was successfully converted to the demethylated product **Q5a**, and phenolic hydroxy group was selectively protected by triphenylmethyl group to give **Q6** by using phase transfer reaction. Through nucleophilic substitution, two **Q6** molecules coupled with dichlorophthalazine **1** (PHAL), and the product **Q7** was deprotected under acidic condition giving the biscinchona alkaloid catalyst $(deMeDHQ)_2PHAL$–**Q4** in an overall 54% yield[16] (Scheme 2). Bisalkaloid catalyst **QD4** was obtained from dihydroquinidine (DHQD) via the same procedures.

To gain insight into the steric nature of these novel catalysts, single-crystal X-ray diffraction of crystals of **Q4** obtained in methanol was conducted. X-ray diffraction analysis indicated that *transoid* conformation of di[demethyl(dihydroquinine)] moieties (both quinuclidine rings are opposite to each other with respect to the PHAL ring) is adopted in the crystal lattice. The structure showed that both quinuclidine rings of **Q4** are hydrogen bonded to methanol molecules but substructures exposed that N2 hydrogen bonded to methanol O10 toward its intramolecular bystander quinolyl ring at 2.056 Å and N6 hydrogen bonded to methanol O11 toward intermolecular bystander quinolyl ring of another **Q4** at 1.984 Å. The packing forces are mainly due to the intermolecular H-bond between quinolyl ring and phenolic hydroxy group at the length of 1.893 Å (Fig. 2). In conclusion, the crystallographic data not only proves that each independent demethylated dihydroquinine part can be used as a chiral catalytic center, but also reveals its bystander quinolyl ring and the phthalazine plane ring could provide steric blocking for other operative alkaloid moiety and vice versa (identify with the binding pocket).

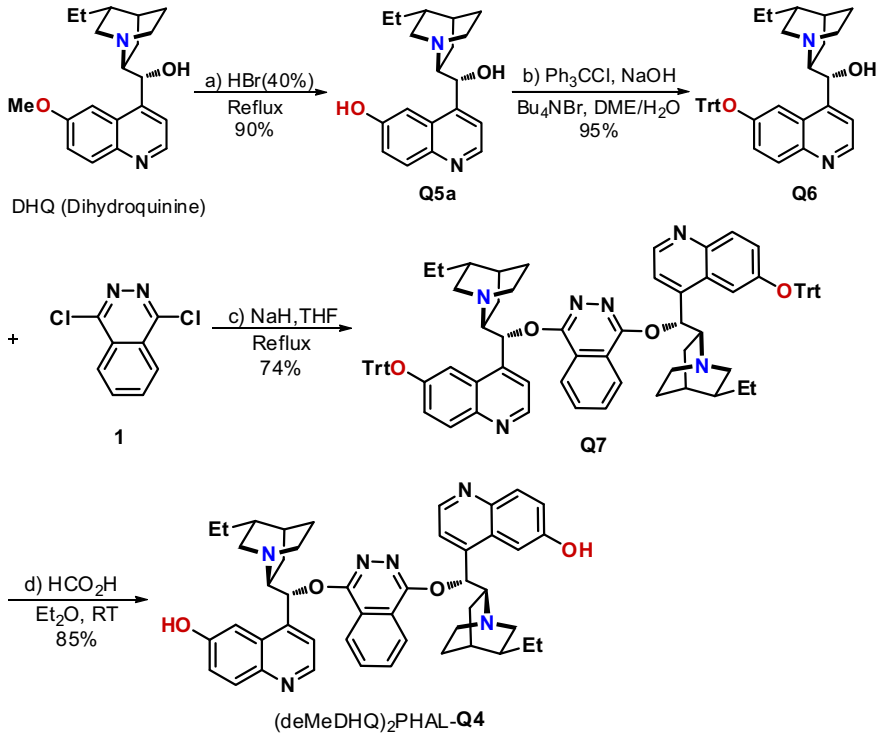
2.2. Asymmetric conjugate addition to nitroalkenes

The Michael addition of malonates to nitroalkenes was selected as a model reaction. In this system, high enantioselectivity has been achieved catalyzed by cinchona alkaloids **Q1a** at low temperature by Deng et al.[5] Good results have also been achieved with chiral transition metal complexes[17] or bifunctional organic catalysts derived from chiral thioureas,[18] guanidines,[19] and aminobenzimidazoles.[20] However, there is still room for improvement in terms of both reaction mildness and lower catalyst loading.

Initially, addition of dimethyl malonate **3a** to nitroalkene **2a** catalyzed by 5 mol % of **Q4** at ambient temperature (ca. 20 °C) was investigated in THF. Gratifyingly, the adduct **4a** was obtained with almost quantitative yield and excellent enantioselectivity (94% ee) (entry 1, Table 1). Decrease of the reaction temperature resulted in little enantioselectivity improvement but much longer reaction time (entries 2 and 3 vs 1). It indicates that the selectivity of the catalyst **Q4** was less sensitive to the temperature than that of **Q1a** described in the literature (entries 4 and 5). Better results were achieved with dimethyl rather than diethyl malonate **3b** or diisopropyl malonate **3c** (entries 6 and 7 vs 1). Then, the loading of catalyst could be reduced to 1 mol % without compromising the enatioselectivity (entries 8 and 9). The studies using **Q1a** and **Q5a** that afforded the same results demonstrated that C10–C11 double or single bond is less effective of the enantioselectivity in this reaction (entries 10 and 11). Screening with 1 mol % amount catalysts uncovered that among the catalysts of O9 substituents, **Q4** gave the best catalyst performance in terms of the reactivity and selectivity (entries 9–13), reaching up to 99% yield and 94% ee at room temperature. Finally THF was the best choice of solvent. (Entries 14–17 vs 9.) Thus the best reaction conditions were acquired using dimethyl malonate **3a** as substrate catalyzed by 1 mol % of catalyst **Q4** in THF at room temperature.

Having established the optimized reaction conditions, we then turned our attention to substrate generality. A variety of aromatic and aliphatic *trans*-nitroalkenes were evaluated under the conditions. All aromatic nitroalkenes with either electron-donating or electron-withdrawing groups on aromatic rings can proceed smoothly to give the corresponding adducts **4** or **5** with excellent yields and enantioselectivities (Table 2, entries 1–10). High enantioselectivities and yields were also observed with aliphatic nitroalkenes (entries 11–14). All of the results prove that the biscinchona alkaloid organocatalysts **Q4** or **QD4** exhibit good to excellent compatibility with the various nitroalkene substrates.

In the course of substrate investigation, we found that catalyst **Q4** had not so much apparent advantage over **Q1a**, especially when a hydrogen-affinity group was in the *para* position of the aryl ring (entry 2 and 3 Table 3). It was supposed that two H-bonds formed between catalyst and the nitroalkene substrate (two phenolic hydroxides and the NO_2 and H-affinity group, such as MeO, F, NO_2 in



Scheme 2. Preparation of bisalkaloid catalyst **Q4**.

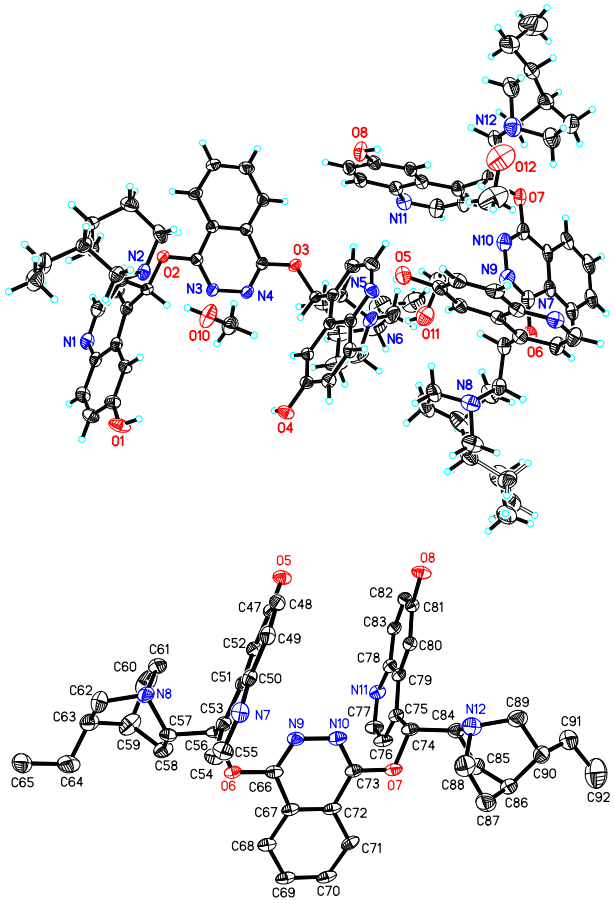


Fig. 2. X-ray crystal structure of (deMeDHQ)$_2$PHAL–**Q4**.

entries 2–4) resulted in the reduced catalyzing effect. Therefore, a mono-protected catalyst **Q8**, which will never form a second H-bond with substrate was synthesized[21] and evaluated in the reaction. The higher selectivity catalyzed by **Q8** testified the supposition to some extent obviously when substrates **2h** and **2o** were used (entry 3 and 4 Table 3). On the other hand, the distances between the two phenolic O atoms of **Q4** are 6.040 Å (O1–O4) and 5.570 Å (O5–O8) in the lattice,[22] which also suggested the possible existence of double H-bond interaction to the substrates (Fig. 2).

2.3. Asymmetric synthesis of optical (*R*)-(−)-baclofen

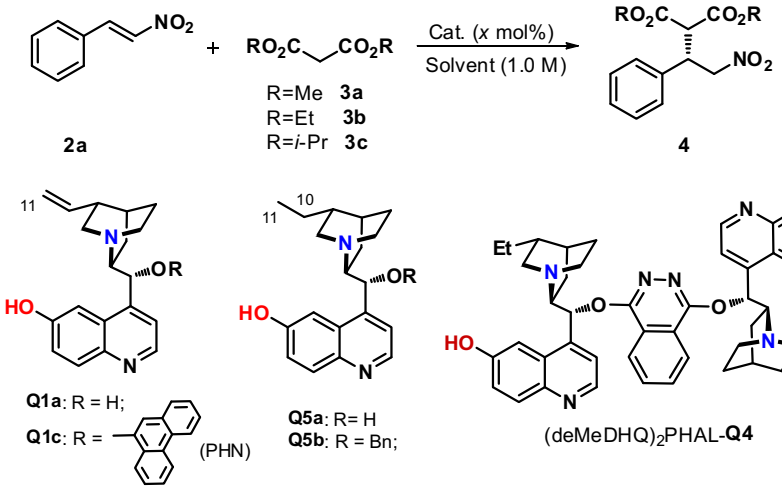
The chiral adducts **4** and **5** can be easily transformed to the chiral β-substituted γ-lactams, which are very useful building blocks for assembling some bioactive compounds.[5,18–21] Herein, the synthetic application of this methodology is demonstrated by a four-step synthesis of a selective GABA$_B$ receptor agonist, (*R*)-baclofen hydrochloride.[23]

After a single recrystallization, the optically pure adduct **5b** was obtained with >99% ee and further converted to (*R*)-4-(4-chlorophenyl)-2-pyrrolidinone **7** in four steps with overall 72% yield, which was easily hydrolyzed to afford optical pure (*R*)-baclofen hydrochloride **8** (Scheme 3).

3. Summary

In summary, the novel powerful chiral bifunctional bisalkaloid organocatalysts **Q4** and **QD4** have been developed and applied to the conjugate addition of dimethyl malonate to nitroalkenes. These addition reactions proceed with low catalyst loading (1 mol%) at ambient temperature with excellent enantioselectivities. These addition products are important intermediates for the syntheses of chiral 4-substituted pyrrolidinones and optically pure (*R*)-baclofen was prepared as a demonstration. Further studies and extension of these two catalysts are currently underway.

Table 1
Asymmetric conjugate addition of malonates to nitroalkene **2a**[a,b]



Entry	T (°C)	**11** (mol %)	Cat	**3**	Sol	Time (h)	Yield[c] (%)	ee[d] (%)
1	20	5	**Q4**	**3a**	THF	6	99	94
2	10	5	**Q4**	**3a**	THF	12	99	95
3	0	5	**Q4**	**3a**	THF	36	99	96
4	20	10	**Q1a**	**3a**	THF	2	99	89
5	−20	10	**Q1a**	**3a**	THF	36	97	96
6	20	5	**Q4**	**3b**	THF	18	99	63
7	20	5	**Q4**	**3c**	THF	72	90	57
8	20	3	**Q4**	**3a**	THF	10	99	94
9	20	1	**Q4**	**3a**	THF	20	99	94
10	20	2	**Q1a**	**3a**	THF	6	98	89
11	20	2	**Q5a**	**3a**	THF	6	99	89
12	20	2	**Q5b**	**3a**	THF	12	98	90
13	20	2	**Q1c**	**3a**	THF	60	97	92
14	20	1	**Q4**	**3a**	DCM	26	96	94
15	20	1	**Q4**	**3a**	DMF	72	73	57
16	20	1	**Q4**	**3a**	Dioxane	30	98	94
17	20	1	**Q4**	**3a**	DCE	72	75	91

[a] Reactions were carried out at different temperature with 0.2 mL of solvent using 0.2 mmol of **2a** (1.0 equiv), 0.6 mmol of **3** (3.0 equiv), and catalyst, unless otherwise stated.
[b] The absolute configuration of **4a** was determined by comparison of the specific rotation of the corresponding literature.[17a]
[c] Isolated yield.
[d] Determined by HPLC analysis using a chiral column.

4. Experimental

4.1. General methods

All solvents were dried before use following the standard procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on 300 or 400 MHz spectrometers in the indicated solvents. Chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (δ=77.05 ppm) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1030 polarimeter.

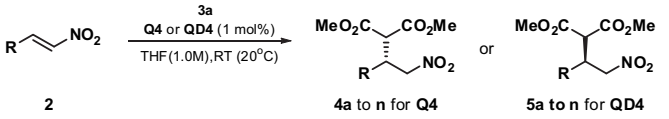
4.2. Preparation of catalysts

4.2.1. 6′-Hydroxy dihydroquinine ***Q5a***. The solution of dihyroquinine (40 g, 12.3 mmol) in 500 mL of HBr (aq, 40%) was stirred and refluxed until a TLC analysis showed the starting material was completely consumed (12–24 h). The solution was removed about 1/3 volume under reduced pressure when the reaction mixture was cooled down to room temperature, and then mixed with satd NH_3 (aq, 25–27%). The pH value of the solution was adjusted to be around 7. The resulting mixture was extracted with solution of CH_2Cl_2 and MeOH (10/1, 3×100 mL). The organic phase was washed with water (50 mL), dried over Na_2SO_4, and concentrated in vacuo to give a brown solid (34.7 g, 90% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.70 (d, J=4.6 Hz, 1H), 7.98 (d, J=9.1 Hz, 1H), 7.78 (d, J=4.5 Hz, 1H), 7.52–7.30 (m, 2H), 6.02 (s, 1H), 4.40–4.15 (m, 1H), 3.76–3.51 (m, 2H), 3.36–3.17 (m, 1H), 3.08–3.01 (m, 1H), 2.41–1.79 (m, 5H), 1.65–1.49 (m, 1H), 1.47–1.23 (m, 2H), 0.89 (t, J=7.4 Hz, 3H); ESI-MS (m/z): 313.2 ($M+H^+$); $[\alpha]_D^{27}$ −149.4 (c 1.23, EtOH).

6′-Hydroxy dihydroqunidine **QD5a**[3e] was obtained as a brown solid (32.5 g, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J=4.4 Hz, 1H), 7.92 (d, J=9.7 Hz, 1H), 7.57 (d, J=4.4 Hz, 1H), 7.45–7.27 (m, 2H), 6.41 (d, J=3.5 Hz, 1H), 5.86 (br s, 1H), 3.76–3.60 (m, 1H), 3.53–3.12 (m, 4H), 2.32–2.14 (m, 1H), 1.94–1.65 (m, 4H), 1.62–1.40 (m, 2H), 1.25–1.06 (m, 1H), 0.89 (t, J=7.3 Hz, 3H). $[\alpha]_D^{27}$ +168.9 (c 1.05, EtOH); ESI-MS (m/z): 313.5 ($M+H^+$).

4.2.2. 6′-TrtO-dihydroquinine ***Q6***. To the solution of NaOH (3.84 g, 96 mmol) in water (50 mL) were added **Q5** (10 g, 32 mmol) and Bu_4NBr (103 mg, 0.32 mmol). The resulting mixture was stirred at room temperature for 15 min. Then solution of Ph_3CCl (9.35 g, 33.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise in 30 min. The reaction mixture was stirred for 2 h and the organic phase was separated. Another solution of Ph_3CCl (0.94 g, 3.4 mmol) in CH_2Cl_2 (20 mL) was added to the aqueous phase. The reaction mixture was stirred for 2 h and the organic phase was separated. The combined organic phase was washed with solution of NaOH (aq, 10%) and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue

Table 2
Asymmetric conjugate addition of **3a** to nitroalkenes[a]

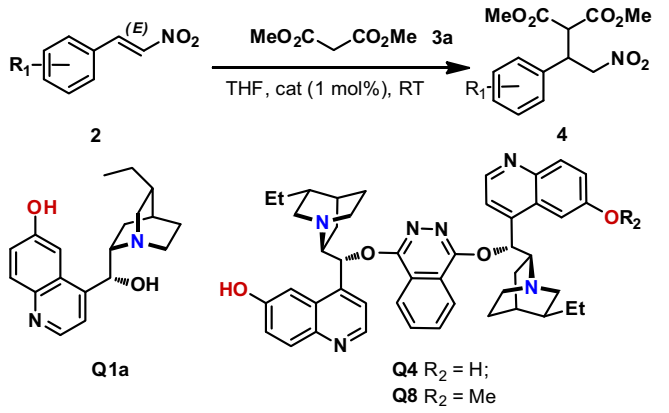


2 4a to n for Q4 5a to n for QD4

Entry	Nitroalkenes	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	Ph–	24 (24)	97 (98)[d]	94 (−92)[d]
2	**2b**	4-Cl–Ph–	18 (24)	97 (98)[d]	95 (−92)[d]
3	**2c**	2-Cl–Ph–	18 (24)	>99 (98)[d]	96 (−93)[d]
4	**2d**	4-Br–Ph–	18 (24)	97 (99)[d]	94 (−92)[d]
5	**2e**	2-Br–Ph–	18 (24)	97 (97)[d]	95 (−92)[d]
6	**2f**	4-Me–Ph–	36 (36)	97 (97)[d]	93 (−93)[d]
7	**2g**	4-MeO–Ph–	48 (48)	99 (98)[d]	94 (−91)[d]
8	**2h**	4-F–Ph–	18 (24)	>99 (99)[d]	90 (−90)[d]
9	**2i**	1-Naphthyl–	18 (24)	98(>99)[d]	96 (−93)[d]
10	**2j**	2-Furyl–	36 (36)	98 (96)[d]	97 (−95)[d]
11[f]	**2k**	PhCH=CH–[e]	60 (72)	90 (91)[d]	90 (−84)[d]
12[g]	**2l**	Cyclohexyl-	60	92	89
13[f]	**2m**	*iso*-Butyl	72	79	89
14	**2n**	$PhCH_2CH_2$–	60	83	86

[a] Unless noted, reactions were carried out at room temperature with 0.2 mL of THF using 0.2 mmol of **2** (1.0 equiv), 0.6 mmol of **3a** (3.0 equiv), and catalyst **Q4** or **QD4** (1 mol %).
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column.
[d] Results in parentheses were obtained with $(deMeDHQD)_2PHAL$–**QD4**.
[e] *trans*-Double bond.
[f] The catalyst **Q4** or **QD4** was used with 3 mol %.
[g] The catalyst **Q4** was used with 5 mol %.

Table 3
Asymmetric conjugate addition of **3a** to nitroalkenes[a]



Q1a Q4 R_2 = H; Q8 R_2 = Me

Entry	Nitroalkenes	R_1	ee[b] (%) (**Q1a**)	ee[b] (%) (**Q4**)	ee[b] (%) (**Q8**)
1	**2a**	H	89	94	93
2	**2g**	4-MeO	93	94	94
3	**2h**	4-F	91	90	93
4	**2o**	4-NO_2	76	81	89

[a] Unless noted, reactions were carried out at room temperature with 0.2 mL of THF using 0.2 mmol of **2** (1.0 equiv), 0.6 mmol of **3a** (3.0 equiv), and catalyst **Q1a**, **Q4** or **Q8** (1 mol %).
[b] Determined by HPLC analysis using a chiral column.

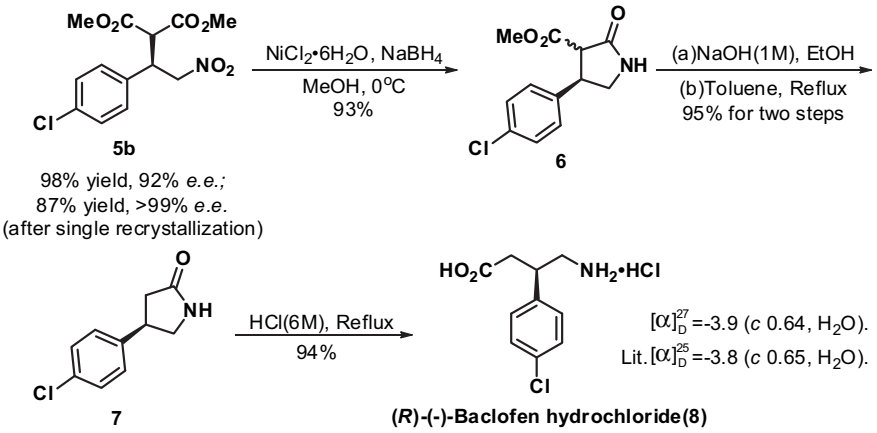
was purified by flash chromatography (MeOH/EtOAc=1/10) to give a yellowish foam (5.06 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J=4.5 Hz, 1H), 7.76 (d, J=9.2 Hz, 1H), 7.51 (d, J=7.5 Hz, 6H), 7.33–7.11 (m, 12H), 4.90 (d, J=6.2 Hz, 1H), 3.01–2.79 (m, 3H), 2.47–2.33 (m, 1H), 2.20–2.09 (m, 1H), 1.76–1.62 (m, 1H), 1.54–1.15 (m, 7H), 0.85 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.0, 147.5, 144.3, 143.8, 130.6, 128.9, 127.9, 127.4, 126.3, 125.0, 118.7, 111.4, 90.9, 72.0, 59.7, 58.3, 42.8, 37.6, 28.4, 27.7, 25.5, 23.4, 12.2; FT-IR (KBr, cm^{-1}) ν 2930, 2867, 1617, 1505, 1448, 1234, 1001, 702; $[\alpha]_D^{20}$ −197.9 (c 1.23, $CHCl_3$); ESI-MS (m/z): 555.4 ($M+H^+$); HRMS (ESI-MS) for $C_{38}H_{39}N_2O_2(M+H^+)$: calcd 555.3005, found 555.3006.

6′-*TrtO-dihydroquinidine* **QD6** was obtained as a yellowish foam (91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J=4.5 Hz, 1H), 7.77 (d, J=9.2 Hz, 1H), 7.50 (d, J=7.6 Hz, 6H), 7.34–7.05 (m, 12H), 4.94 (d, J=6.5 Hz, 1H), 2.85–2.39 (m, 5H), 1.68–1.14 (m, 7H), 1.10–0.93 (m, 1H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 147.9, 147.4, 144.3, 143.8, 130.6, 128.9, 127.9, 127.4, 126.2, 125.0, 119.0, 111.6, 90.8, 71.8, 59.6, 50.9, 49.8, 37.4, 27.0, 26.1, 25.1, 22.7, 12.0; FT-IR (KBr, cm^{-1}) ν 2930, 2869, 1616, 1505, 1448, 1217, 1186, 703; $[\alpha]_D^{27}$ +171.7 (c 1.06, $CHCl_3$); ESI-MS (m/z): 555.3 ($M+H^+$); HRMS (ESI-MS) for $C_{38}H_{39}N_2O_2(M+H^+)$: calcd 555.3004, found 555.3006.

4.2.3. (6′-TrtO-dihydroquinine)$_2$PHAL **Q7**. Under N_2 atmosphere, to a solution of dried compound **Q6** (16.6 g, 30 mmol) in THF (60 mL, freshly distilled in the presence of Na) was added NaH (1.44 g, 60% oil dispersion, 1.2 equiv) in small portions. The resulting mixture was stirred at room temperature for 2 h. Then 1,4-dichlorophthalazine (2.98 g, 15 mmol) was added in three portions under N_2 atmosphere at 0 °C. The reaction mixture was then warmed and refluxed. When the reaction was completed, water (5 mL) was added to quench. The mixture was extracted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography ($MeOH/CH_2Cl_2$=1/50 to 1/25 to 1/15) to give a yellowish foam (13.7 g, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J=4.5 Hz, 2H), 8.25 (dd, J=6.0, 3.3 Hz, 2H), 7.86 (dd, J=5.9, 3.3 Hz, 2H), 7.73 (d, J=9.2 Hz, 2H), 7.56–7.39 (m, 14H), 7.31 (d, J=4.4 Hz, 2H), 7.20–7.06 (m, 14H), 6.98 (t, J=7.1 Hz, 6H), 6.45 (d, J=5.2 Hz, 2H), 3.17–2.68 (m, 6H), 2.50–2.34 (m, 2H), 2.11–1.87 (m, 2H), 1.79–1.53 (m, 8H), 1.47–1.11(m, 8H), 0.84 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 154.6, 148.0, 145.2, 144.9, 143.9, 132.2, 130.7, 129.1, 129.1, 128.0, 127.5, 126.4, 125.5, 123.0, 122.6, 113.0, 91.4, 59.9, 58.8, 42.9, 37.7, 29.0, 27.9, 25.9, 23.5, 12.4; FT-IR (KBr, cm^{-1}) ν 2927, 2861, 1616, 1504, 1448, 1354, 1186, 701; ESI-MS (m/z): 1274.7 ($M+K^+$), 1257.8 ($M+Na^+$), 1235.8 ($M+H^+$), 618.7 ($M+2H^+$); $[\alpha]_D^{27}$ +108.1 (c 1.02, $CHCl_3$); ESI-MS (m/z): 1235.7 ($M+H^+$), 619.3 ($M+2H^+$); HRMS (ESI-MS) for $C_{84}H_{79}N_6O_4(M+H^+)$:calcd 1235.6157, found 1235.6150.

(6′-*TrtO-dihydroquinidine*)$_2$*PHAL* **QD7** was obtained as a yellowish foam (63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J=4.4 Hz, 2 H), 8.24 (dd, J=5.1, 2.9 Hz, 2H), 7.83 (dd, J=6.0, 3.2 Hz, 2H), 7.72 (d, J=9.2 Hz, 2H), 7.58–7.31 (m, 16H), 7.22–6.98 (m, 20H), 6.46 (d, J=6.3 Hz, 2H), 3.13–2.92 (m, 2H), 2.76–2.31 (m, 8H), 1.85–1.70 (m, 2H), 1.38 (m, 14H), 0.80 (t, J=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 154.3, 147.9, 144.9, 143.8, 132.0, 130.5, 129.0, 127.9, 127.4, 126.2, 125.3, 122.9, 122.4, 113.3, 91.2, 59.6, 50.6, 49.9, 45.9, 37.5, 27.2, 26.4, 25.3, 23.5, 11.9; FT-IR (KBr, cm^{-1}) ν 3445, 2931, 2870, 1616, 1504, 1387, 1355, 702; $[\alpha]_D^{27}$ −24.4 (c 1.06, $CHCl_3$); ESI-MS (m/z): 1235.8 ($M+H^+$), 618.7 ($M+2H^+$); HRMS (ESI-MS) for $C_{84}H_{79}N_6O_4(M+H^+)$: calcd 1235.6157, found 1235.6136.

4.2.4. (deMeDHQ)$_2$PHAL **Q4**. A mixture of compound **Q7** (3.7 g, 3 mmol), Et_2O (15 mL) and HCO_2H (15 mL) was stirred at room temperature until a TLC analysis showed that the starting material was completely consumed (15 min). The resulting mixture was poured into ice water (50 mL). The water phase was separated and washed with Et_2O (2×20 mL). Then the combined organic phase was extracted with water (2×20 mL). The combined aqueous phase was mixed with satd NH_3 (aq, 25%) until the pH value of the solution was adjusted to be around 8 and then extracted with solution of CH_2Cl_2 and MeOH (10/1, 3×100 mL). The organic phase was combined, dried over Na_2SO_4 and concentrated in vacuo to afford white powder after crystallization in $CHCl_3$ (34.7 g, 85% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.55–8.44 (m, 4H), 8.14 (dd, J=6.0,



Scheme 3. Asymmetric synthesis of (*R*)-baclofen hydrochloride **8**.

3.3 Hz, 2H), 7.93 (d, *J*=9.1 Hz, 2H), 7.59–7.48 (m, 4H), 7.38 (dd, *J*=9.1, 2.4 Hz, 2H), 7.03 (d, *J*=2.9 Hz, 2H), 3.52–3.38 (m, 2H), 3.31–3.16 (m, 2H), 3.05 (dd, *J*=13.4, 10.1 Hz, 2H), 2.69–2.52 (m, 2H), 2.43–2.31 (m, 2H), 2.10–1.70 (m, 8H), 1.61–1.43 (m, 4H), 1.42–1.22 (m, 4H), 0.85 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.5, 145.9, 144.2, 143.0, 133.1, 130.2, 127.2, 122.7, 122.2, 122.2, 118.3, 104.3, 76.1, 59.2, 58.0, 42.6, 37.0, 27.7, 27.1, 25.3, 22.0, 10.9; FT-IR (KBr, cm^{-1}) ν 3072, 2930, 2869, 1620, 1471, 1393, 1092, 851; $[\alpha]_D^{29}$ +291.7 (*c* 1.06, EtOH); ESI-MS (*m*/*z*): 751.3 ($M+H^+$), 457.0 ($M+2H^+$); HRMS (ESI-MS) for $C_{46}H_{51}N_6O_4(M+H^+)$: calcd 751.3976, found 751.3966; Crystallographic data for **Q4** ($C_{48}H_{58}N_6O_6$): *T*=133 (2) K; Wavelength: 0.71073 Å; crystal system: tetragonal, space group: *P*4 (3); unit cell dimensions: *a*=18.8464 (13) Å, *b*=18.8464 (13) Å, *c*=24.2401 (16) Å, α=90°, β=90°, γ=90°; *V*=8609.8 (10) Å^3; *Z*=8; ρ_{calcd}=1.257 Mg m^{-3}; *F*(000)=3488; final *R* indices [$I>2\sigma(I)$]: R_1=0.0570, ωR_2=0.1557; *R* indices (all data), R_1=0.0754, ωR_2=0.1717; 48,364 reflections measured, 16,274 were unique ($R_{(int)}$=0.0614). CCDC-826830 (**Q4**) contains the supplementary crystallographic data (and details of the data handling and structure refinement) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*deMeDHQD*)$_2$*PHAL* **QD4** was obtained as a white powder after crystallization in $CHCl_3$ (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) δ 8.51–8.38 (m, 4H), 8.07 (dd, *J*=6.0, 3.3 Hz, 2H), 7.93 (d, *J*=9.1 Hz, 2H), 7.46–7.30 (m, 6H), 7.14 (s, 2H), 3.30–3.21 (m, 2H), 2.97–2.78 (m, 6H), 2.77–2.62 (m, 2H), 2.30–2.21 (m, 2H), 1.80 (s, 2H), 1.65–1.31 (m, 12H), 0.86 (t, *J*=7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD) δ 156.3, 156.1, 145.7, 143.8, 142.9, 132.7, 130.4, 126.9, 122.6, 122.3, 122.3, 117.6, 104.0, 75.7, 58.7, 50.6, 49.5, 36.8, 26.3, 26.0, 25.0, 21.2, 11.2; FT-IR (KBr, cm^{-1}) ν 3419, 2931, 2867, 1618, 1516, 1387, 1230, 843; $[\alpha]_D^{26}$ −217.8 (*c* 0.96, $CHCl_3$/MeOH=1/1); ESI-MS (*m*/*z*): 751.2 ($M+H^+$), 773.4 ($M+Na^+$); HRMS (ESI-MS) for $C_{46}H_{51}N_6O_4(M+H^+)$: calcd 751.3976, found 751.3966.

4.2.5. [(deMeDHQ)(DHQ)]PHAL ***Q8***. Under N_2 atmosphere, to a solution of dried compound **Q6** (10.6 g, 18 mmol) in THF (40 mL, freshly distilled in the presence of Na) was added NaH (866 mg, 60% oil dispersion, 1.2 equiv) in small portions. The resulting mixture was stirred at room temperature for 2 h. Then 1,4-dichlorophthalazine (3.66 g, 18.4 mmol) was added in one portion under N_2 atmosphere at 0 °C. The reaction mixture was then warmed and kept at room temperature. When the reaction was completed, brine (5 mL) was added to quench. The mixture was added to water (100 mL) and extracted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography ($MeOH/CH_2Cl_2$: 1/50 to 1/25 to 1/15) to give a yellowish foam (5*R*)-2-((*R*)-((4-chlorophthalazin-1-yl)oxy)(6-(trityloxy)quinolin-4-yl)methyl)-5-ethylquinuclidine (13.2 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J*=4.4 Hz, 1H), 8.33–8.26 (m, 1H), 8.23–8.09 (m, 1H), 8.02–7.83 (m, 2H), 7.77–7.61 (m, 2H), 7.59–7.44 (m, 6H), 7.36 (d, *J*=4.4 Hz, 1H), 7.32–7.15 (m, 9H), 7.10 (dd, *J*=9.2, 1.8 Hz, 1H), 6.79 (d, *J*=6.5 Hz, 1H), 3.37–3.20 (m, 1H), 3.13–2.85 (m, 2H), 2.60–2.39 (m, 1H), 2.25–2.05 (m, 1H), 1.86–1.20 (m, 8H), 0.88 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.9, 150.4, 148.1, 145.1, 144.2, 144.2, 133.4, 133.2, 130.7, 129.3, 128.1, 128.0, 127.6, 126.6, 125.8, 125.6, 123.3, 121.8, 119.2, 113.3, 91.6, 78.3, 59.9, 58.7, 42.8, 37.7, 29.0, 28.0, 25.8, 24.3, 12.4; FT-IR (KBr, cm^{-1}) ν 2925, 2860, 1616, 1504, 1394, 1292, 1225, 703; $[\alpha]_D^{27}$ +124.8 (*c* 1.06, $CHCl_3$); ESI-MS (*m*/*z*): 739.2 ($M+Na^+$), 718.2 ($M+H^+$); HRMS (ESI) for $C_{46}H_{42}N_4O_2Cl$ ($M+H^+$): calcd 717.2987, found 717.2991.

Under N_2 atmosphere, to a solution of dried compound dihydroquinine (745 mg, 2.3 mmol) in THF (20 mL, freshly distilled in the presence of Na) was added NaH (183 mg, 60% oil dispersion, 1.2 equiv) in small portions. The resulting mixture was stirred at room temperature for 2 h. Then the previously obtained intermediate (1.80 g, 2.5 mmol) was added in one portion under N_2 atmosphere at room temperature. When the reaction was completed, brine (5 mL) was added to quench. The mixture was added to water (100 mL) and extracted with EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography ($MeOH/CH_2Cl_2$: 1/15) to afford a yellowish foam (5*R*)-2-((*R*)-((4-chlorophthalazin-1-yl)oxy)(6-(trityloxy)quinolin-4-yl)methyl)-5-ethylquinuclidine (1.15 g, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J*=4.5 Hz, 1H), 8.57 (d, *J*=4.5 Hz, 1H), 8.34 (d, *J*=7.8 Hz, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 8.00 (d, *J*=9.2 Hz, 1H), 7.94–7.85 (m, 2H), 7.70 (d, *J*=9.2 Hz, 1H), 7.61–7.40 (m, 9H), 7.36–7.31 (m, 2H), 7.17–7.04 (m, 11H), 6.49 (d, *J*=6.1 Hz, 1H), 3.85 (s, 3H), 3.47 (dd, *J*=13.2, 8.1 Hz, 1H), 3.27–2.74 (m, 5H), 2.68–2.29 (m, 4H), 2.07–1.15 (m, 16H), 0.87–0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.5, 156.3, 154.6, 148.1, 147.5, 145.2, 145.1, 145.0, 144.0, 132.4, 131.8, 130.5, 129.2, 128.0, 127.4, 127.3, 126.5, 125.8, 123.1, 122.8, 122.7, 122.6, 122.2, 118.8, 118.4, 113.4, 102.3, 91.5, 76.5, 60.2, 58.7, 55.9, 43.1, 42.8, 37.7, 37.6, 28.8, 27.9, 25.7, 25.7, 24.0, 23.1, 12.3, 12.3; $[\alpha]_D^{27}$ +151.6 (*c* 1.04, $CHCl_3$); FT-IR (KBr, cm^{-1}) ν 2925, 2862, 1619, 1552, 1353, 1227, 983, 702; ESI-MS (*m*/*z*): 1029.5 ($M+Na^+$), 1007.5 ($M+H^+$); HRMS (ESI) for $C_{66}H_{67}N_6O_4(M+H^+)$: calcd 1007.5218, found 1007.5207.

A mixture of the previously obtained intermediate (1.15 g, 1.14 mmol), Et_2O (15 mL) and HCO_2H (15 mL) was stirred at room temperature until a TLC analysis showed that the starting material

was completely consumed (15 min). The resulting mixture was poured into ice water (60 mL). The water phase was separated and washed with Et_2O (3×30 mL). Then the combined organic phase was extracted with water (2×20 mL). The combined aqueous phase was mixed with satd NH_3 (aq, 25%) until the pH value of the solution was adjusted to be around 8 and then extracted with solution of CH_2Cl_2 (3×100 mL). The organic phase was combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (MeOH/CH_2Cl_2: 1/15) to afford a yellowish powder **Q8** (785 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J=4.6 Hz, 1H), 8.55 (d, J=4.5 Hz, 1H), 8.42–8.35 (m, 1H), 8.30 (d, J=7.7 Hz, 1H), 8.00–7.82 (m, 4H), 7.54 (d, J=2.5 Hz, 1H), 7.51–7.42 (m, 2H), 7.33–7.21 (m, 4H), 7.16 (d, J=5.0 Hz, 1H), 6.97 (s, 1H), 3.87 (s, 3H), 3.54–3.39 (m, 1H), 3.38–2.99 (m, 3H), 2.89–2.81 (m, 1H), 2.75–2.51 (m, 2H), 2.35 (d, J=14.4 Hz, 1H), 2.18 (d, J=12.9 Hz, 1H), 2.01–1.08 (m, 17H), 0.82 (t, J=7.3 Hz, 3H), 0.75 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.5, 156.2, 156.1, 146.8, 146.2, 145.1, 144.1, 143.7, 143.6, 132.5, 132.4, 131.3, 130.8, 127.2, 122.8, 122.6, 122.5, 122.4, 122.3, 119.6, 118.1, 118.1, 118.0, 104.9, 101.9, 75.7, 60.1, 59.1, 58.3, 58.2, 55.7, 42.8, 42.7, 42.6, 37.3, 37.1, 28.4, 28.3, 27.6, 27.3, 25.4, 25.4, 23.0, 21.9, 12.0, 12.0; FT-IR (KBr, cm^{-1}) ν 3583, 3015, 2350, 1620, 1351, 1229, 930, 776; $[\alpha]_D^{27}$ +306.2 (c 0.86, $CHCl_3$); ESI-MS (m/z): 765.4 ($M+H^+$); HRMS (ESI) for $C_{47}H_{53}N_6O_4$($M+H^+$): calcd 765.4132, found 765.4123.

4.3. General procedure for enantioselective 1,4-addition of Dimethyl malonate to nitroalkenes

At room temperature, to a solution of nitroalkenes **2** (0.2 mmol) and chiral catalyst **Q4** or **QD4** in THF was added dimethyl malonate **3** (68 μL, 0.3 mmol). The resulting mixture was purified by flash chromatography when **2** was consumed through a TLC analysis to afford the product **4** or **5**.

4.3.1. (S)-Dimethyl 2-(2-nitro-1-phenylethyl)malonate ***4a***[5c,17d,e]. White solid: $[\alpha]_D^{25}$ +6.1 (c 1.1, $CHCl_3$, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.13 (m, 5H), 4.97–4.82 (m, 2H), 4.24 (td, J=8.9, 5.3 Hz, 1H), 3.87 (d, J=9.1 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H); ESI-MS (m/z): 281.9 ($M+H^+$), 304.0 ($M+Na^+$); HPLC: Chiralcel OD-H Column (250 mm); detected at 220 nm, hexane/*i*-propanol=70/30, flow=0.7 mL/min, t (major)=18.1min, t (minor)=20.7 min. The absolute configuration of (+)-**4a** was determined as *S* by comparison of the specific rotation of the corresponding literature.[17a]

4.3.2. (S)-Dimethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate ***4b***[5c,17c]. White solid: $[\alpha]_D^{25}$ +7.6 (c 1.42, $CHCl_3$, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J=8.5 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H), 4.94–4.81 (m, 2H), 4.23 (td, J=9.1, 5.0 Hz, 1H), 3.83 (d, J=9.0 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm); detected at 220 nm, hexane/*i*-propanol=70/30, flow=0.7 mL/min, t (major)=11.9 min, t (minor)=16.4 min.

4.3.3. (S)-Dimethyl 2-(1-(2-chlorophenyl)-2-nitroethyl)malonate ***4c***[18e]. White solid: $[\alpha]_D^{29}$ +3.2 (c 1.0, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.35 (m, 1H), 7.30–7.18 (m, 3H), 5.12 (dd, J=13.7, 8.6 Hz, 1H), 4.96 (dd, J=13.7, 4.5 Hz, 1H), 4.76 (td, J=8.5, 4.5 Hz, 1H), 4.12 (d, J=8.4 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm, hexane/*i*-propanol=70/30, flow=0.7 mL/min, t (major)=9.1 min, t (minor)=19.5 min.

4.3.4. (S)-Dimethyl 2-(1-(4-bromophenyl)-2-nitroethyl)malonate ***4d***[5c]. White solid: $[\alpha]_D^{24}$ +6.7 (c 1.2, $CHCl_3$, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 4.99–4.76 (m, 2H), 4.21 (td, J=9.0, 5.0 Hz, 1H), 3.83 (d, J=9.0 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H); ESI-MS (m/z): 360.0 ($M+H^+$), 382.1 ($M+Na^+$); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm; hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=14.2 min, t (minor)=18.4 min.

4.3.5. (S)-Dimethyl 2-(1-(2-bromophenyl)-2-nitroethyl)malonate ***4e***[19]. White solid: $[\alpha]_D^{24}$ +2.7 (c 1.43, $CHCl_3$, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J=7.9, 0.8 Hz, 1H), 7.29–7.20 (m, 2H), 7.13–7.02 (m, 1H), 5.05 (dd, J=13.7, 8.6 Hz, 1H), 4.89 (dd, J=13.7, 4.5 Hz, 1H), 4.70 (td, J=8.2, 4.5 Hz, 1H), 4.04 (d, J=7.9 Hz, 1H), 3.65 (s, 3H), 3.58 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm, hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=9.7 min, t (minor)=20.6 min.

4.3.6. (S)-Dimethyl 2-(1-(4-methylphenyl)-2-nitroethyl)malonate ***4f***[5c,17c]. White solid: $[\alpha]_D^{24}$ +2.9 (c 1.17, $CHCl_3$, 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.09 (m, 4H), 4.93–4.82 (m, 2H), 4.20 (td, J=8.9, 5.3 Hz, 1H), 3.84 (d, J=9.0 Hz, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 2.30 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm, hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (minor)=10.0 min, t (major)=14.7 min.

4.3.7. (S)-Dimethyl 2-(1-(4-methoxylphenyl)-2-nitroethyl)-malonate ***4g***[5c]. White solid: $[\alpha]_D^{24}$ +4.82 (c 1.42, $CHCl_3$, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 4.94–4.76 (m, 2H), 4.19 (td, J=9.0, 5.1 Hz, 1H), 3.83 (d, J=9.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.57 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm; hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=13.6 min, t (minor)=15.6 min.

4.3.8. (S)-Dimethyl 2-(1-(4-flurophenyl)-2-nitroethyl)malonate ***4h***[5c]. Colorless oil: $[\alpha]_D^{24}$ +5.82 (c 1.18, $CHCl_3$, 90% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J=8.7, 5.2 Hz, 2H), 7.02 (t, J=8.6 Hz, 2H), 4.97–4.76 (m, 2H), 4.24 (td, J=9.2, 5.0 Hz, 1H), 3.83 (d, J=9.1 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 3H); HPLC: Chiralcel AD-H Column (250 mm), detected at 220 nm, hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=8.6 min, t (minor)=17.1 min.

4.3.9. (S)-Dimethyl 2-(1-(1-naphthyl)-2-nitroethyl)malonate ***4i***[5c]. Colorless oil: $[\alpha]_D^{24}$ −3.74 (c 0.88, $CHCl_3$, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=8.4 Hz, 1H), 7.88 (d, J=8.1 Hz, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.66–7.58 (m, 1H), 7.53 (t, J=7.1 Hz, 1H), 7.40 (dt, J=7.2, 6.7 Hz, 2H), 5.28–5.01 (m, 3H), 4.11 (d, J=7.5 Hz, 1H), 3.72 (s, 3H), 3.54 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm; hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=17.8 min, t (minor)=27.7 min.

4.3.10. (S)-Dimethyl 2-(1-(2-furyl)-2-nitroethyl)malonate ***4j***[19]. Yellowish oil: $[\alpha]_D^{25}$ −4.59 (c 0.86, $CHCl_3$, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J=0.6 Hz, 1H), 6.29 (s, 1H), 6.22 (d, J=3.2 Hz, 1H), 4.98–4.82 (m, 2H), 4.39 (dt, J=13.1, 6.7 Hz, 1H), 3.95 (d, J=7.8 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm; hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=7.7 min, t (minor)=18.8 min.

4.3.11. (R)-(E)-Dimethyl 2-(1-nitro-4-phenylbut-3-en-2-yl)malonate ***4k***[5d]. White solid: $[\alpha]_D^{24}$ +21.8 (c 1.02, $CHCl_3$, 90% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 5H), 6.58 (d, J=15.8 Hz, 1H), 6.19–6.01 (m, 1H), 4.81–4.62 (m, 2H), 3.84–3.62 (m, 8H); HPLC: Chiralcel AD-H Column (250 mm), detected at 220 nm; hexane/*i*-propanol=70/30, flow=1.0 mL/min, t (major)=8.8 min, t (minor)=10.2 min.

4.3.12. (R)-Dimethyl 2-(1-cyclohexyl-2-nitroethyl)malonate ***4l***[5c]. Colorless oil: $[\alpha]_D^{23}$ +17.7 (c 3.53, $CHCl_3$, 89% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, J=14.6, 4.3 Hz, 1H), 4.62 (dd, J=14.6, 6.5 Hz, 1H), 3.79–3.70 (m, 7H), 2.99–2.78 (m, 1H), 1.86–1.61 (m, 5H), 1.54–1.36

(m, 1H), 1.30–0.86 (m, 5H); ESI-MS (m/z): 288.1 ($M+H^+$), 310.0 ($M+Na^+$), 326.1 ($M+K^+$); HPLC: Chiralcel OD-H Column (250 mm), detected at 215 nm; hexane/*i*-propanol=90/10, flow=1.0 mL/min, *t* (major)=6.6 min, *t* (minor)=16.7 min.

4.3.13. (R)-Dimethyl 2-(1-iso-butyl-2-nitroethyl)malonate ***4m***[19]. Colorless oil: $[\alpha]_D^{23}$ +9.4 (*c* 0.13, $CHCl_3$, 89% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (dd, *J*=13.4, 5.3 Hz, 1H), 4.52 (dd, *J*=13.4, 6.4 Hz, 1H), 3.80–3.73 (m, 6H), 3.66 (d, *J*=5.5 Hz, 1H), 3.08–2.86 (m, 1H), 1.74–1.56 (m, 1H), 1.39–1.23 (m, 2H), 0.99–0.84 (m, 6H); ESI-MS (m/z): 299.1 ($M+K^+$); HPLC: Chiralcel OD-H Column (250 mm), detected at 215 nm, hexane/*i*-propanol=90/10; flow=1.0 mL/min, *t* (major)=8.8 min, *t* (minor)=20.1 min.

4.3.14. (R)-Dimethyl 2-(1-nitro-4-phenylbutan-2-yl)malonate ***4n***. Colorless oil: $[\alpha]_D^{23}$ +3.0 (*c* 0.58, $CHCl_3$, 86% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 2H), 7.24–7.10 (m, 3H), 4.74 (dd, *J*=13.5, 5.2 Hz, 1H), 4.56 (dd, *J*=13.5, 6.6 Hz, 1H), 3.75 (s, 6H), 3.71 (d, *J*=5.9 Hz, 1H), 2.94 (dd, *J*=12.2, 5.8 Hz, 1H), 2.69 (td, *J*=7.1, 1.5 Hz, 2H), 1.80 (dd, *J*=15.9, 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 140.2, 128.6, 128.2, 126.4, 52.9, 52.8, 52.3, 36.5, 32.9, 31.7; ESI-MS (m/z): 310.0 ($M+H^+$), 332.1($M+Na^+$); HRMS (ESI) for $C_{15}H_{19}NNaO_6$ ($M+Na^+$): calcd 332.1105, found 332.1117. HPLC: Chiralcel OD-H Column (250 mm), detected at 215 nm, hexane/*i*-propanol=90/10, flow=1.0 mL/min, *t* (major)=15.1 min, *t* (minor)=19.5 min.

4.3.15. (+)-Dimethyl 2-(2-nitro-1-(4-nitrophenyl)ethyl)malonate ***4o***[5d]. White solid: $[\alpha]_D^{27}$ +7.1 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=8.7 Hz, 2H), 5.02–4.84 (m, 2H), 4.37 (td, *J*=8.7, 5.5 Hz, 1H), 3.88 (d, *J*=8.8 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H); ESI-MS (m/z): 349.1 ($M+Na^+$); HPLC: Chiralcel OD-H Column (250 mm), detected at 220 nm, n-hexane/*i*-propanol=80/20, flow=1.0 mL/min, *t* (major)=19.4 min, *t* (minor)=30.6 min.

4.4. Preparation of (*R*)-(−)-baclofen hydrochloride 8

4.4.1. (4R)-Methyl 4-(4-chlorophenyl)-2-oxopyrrolidine-3-carboxylate ***6***. Under Ar atmosphere, to a solution of **5b** (316 mg, 1 mmol, >99% ee) and $NiCl_2\cdot 6H_2O$ (238 mg, 1 mmol) in methanol (5 mL) was added $NaBH_4$ (454 mg, 12 mmol) at 0 °C. The resulting mixture was kept at room temperature until the **5b** was consumed. The reaction was quenched with NH_4Cl (aq) and diluted with $CHCl_3$. The organic phase was separated and extracted with $CHCl_3$. The combined organic phase dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH=15/1) to give product **6** (235 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=8.4 Hz, 2H), 4.09 (dd, *J*=17.8, 8.6 Hz, 1H), 3.85–3.74 (m, 4H), 3.54 (d, *J*=9.7 Hz, 1H), 3.40 (t, *J*=8 Hz, 1H); $[\alpha]_D^{29}$ −126.8 (*c* 1.15, $CHCl_3$); ESI-MS (m/z): 276.0 ($M+Na^+$).

4.4.2. (R)-4-(4-Chlorophenyl)pyrrolidin-2-one ***7***[18b]. To a solution of **6** (200 mg, 0.78 mmol) and EtOH (2.8 mL) was added 1 N NaOH (0.9 mL) at room temperature. The resulting mixture was concentrated in vacuo when **6** was consumed. To the residue was added water (5 mL) and 5 N HCl. The pH value of the solution was determined to be around 3. The aqueous phase was extracted with $CHCl_3$ and dried over Na_2SO_4 and concentrated in vacuo. To the solution of resultant in toluene (10 mL) was refluxed. After 8 h, the mixture was concentrated in vacuo and the residue was purified by chromatography on silica gel ($CHCl_3$/MeOH=7/1) to give the white solid **7** (147 mg, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*=8.4 Hz, 2H), 6.44 (br s, 1H), 3.79 (t, *J*=8.8 Hz, 1H), 3.73–3.62 (m, 1H), 3.38 (dd, *J*=9.3, 7.2 Hz, 1H), 2.74 (dd, *J*=16.9, 8.9 Hz, 1H), 2.45 (dd, *J*=16.9, 8.6 Hz, 1H); $[\alpha]_D^{26}$ −35.7 (*c* 0.92, EtOH); EI-MS (m/z): 195 (M^+, 33.82), 138 (100), 140 (30.94), 103 (20.85), 197 (15.07), 77 (11.69), 139 (11.18), 91 (9.09).

4.4.3. (R)-(−)-Baclofen hydrochloride ***8***[24]. To a solution of **7** (100 mg, 0.51 mmol) and 6 N HCl (2.8 mL) was refluxed for 24 h. The resulting mixture was concentrated in vacuo to afford (*R*)-(−)-Baclofen hydrochloride **8** (120 mg, 94%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.24 (br s, 1H), 8.11 (s, 3H), 7.57–7.13 (m, 4H), 3.15–3.07 (m, 1H), 3.04–2.92 (m, 1H), 2.86 (dd, *J*=16.3 Hz, 5.4 Hz, 1H), 2.57 (dd, *J*=16.3, 9.4 Hz, 1H); $[\alpha]_D^{26}$ −3.9 (*c* 0.64, H_2O); ESI-MS (m/z): 214.1 ($M+H^+$).

Acknowledgements

Financial support from the Major State Basic Research Development Program 2010CB833302, and the Shanghai Municipal Committee of Science and Technology 09JC1417300 is greatly acknowledged.

References and notes

1. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693.
2. For the recent reviews see: (a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279; (b) Lee, J. W.; Song, C. E. *Cinchona Alkaloids in Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2009; (c) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496–7504; (d) Tian, S. K. i; Chen, Y. G.; Hang, J. F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631.
3. For asymmetric Morita–Baylis–Hillman reaction see: (a) Zhong, F. R.; Chen, G. Y.; Lu, Y. X. *Org. Lett.* **2011**, *13*, 82–85; (b) Guan, X. Y.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2010**, *16*, 13617–13621; (c) Liu, Y. L.; Wang, B. L.; Cao, J. J.; Chen, L.; Zhang, Y. X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178; (d) Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2006**, *8*, 5357–5360; (e) Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 381–389; (f) Shi, M.; Jiang, J. K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941–1947; (g) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.
4. For asymmetric Aza-Morita–Baylis–Hillman reaction see: (a) Guan, X. Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2010**, 4098–4105; (b) Shi, M.; Qi, M. J.; Liu, X. G. *Chem. Commun.* **2008**, 6025–6027; (c) Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem.—Eur. J.* **2005**, *11*, 1794–1802; (d) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103–3105; (e) Shi, M.; Xu, Y. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510.
5. For asymmetric conjugate addition to nitroalkenes see: (a) Shi, M.; Lei, Z. Y.; Zhao, M. X.; Shi, J. W. *Tetrahedron Lett.* **2007**, *48*, 5743–5746; (b) Li, H. M.; Wang, Y.; Tang, L.; Wu, F. H.; Liu, X. F.; Guo, C. Y.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105–108; (c) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; (d) Li, X.-J.; Liu, K.; Ma, H.; Nie, J.; Ma, J.-A. *Synlett* **2008**, 3242–3246.
6. For asymmetric conjugate addition to α,β-unsaturated aldehydes, ketones, cyanides and sulfones see: (a) Wu, F. H.; Hong, R.; Khan, J. H.; Liu, X. F.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301–4305; (b) Wu, F. H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947–950; (c) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; (d) Li, H. M.; Song, J.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949.
7. For asymmetric Henry reaction see: (a) Li, H. M.; Wang, B. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733; (b) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun.* **2008**, 4360–4362; (c) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Synlett* **2005**, 2817–2819.
8. For asymmetric Mannich reaction see: (a) Cheng, L.; Kiu, L.; Jia, H.; Wang, D.; Chen, Y. J. *J. Org. Chem.* **2009**, *74*, 4650–4653; (b) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040.
9. For asymmetric allylic nucleophilic substitution see: (a) Peng, J.; Huang, X.; Cui, H. L.; Chen, Y. C. *Org. Lett.* **2010**, *12*, 4260–4263; (b) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281–286; (c) Du, Y. S.; Han, X. L.; Lu, X. Y. *Tetrahedron Lett.* **2004**, *45*, 4967–4971.
10. For asymmetric Diels–Alder reaction see: Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365.
11. For asymmetric formal [3+2] cycloaddition reaction see: Guo, C.; Xue, M. X.; Zhu, M. K.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414–3417.
12. For asymmetric Kornblum DeLaMare rearrangement reaction see: Staben, S. T.; Xin, L. H.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658–12659.
13. For asymmetric α-amination reaction see: Saaby, S.; Bella, M.; Jérgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.
14. Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291.

15. (a) Lohray, B. B.; Singh, S. K.; Bhushan, V. *Indian J. Chem., Sect. B* **2002**, *41B*, 1226–1233; (b) Diaz-Arauzo, H.; Cook, J. M.; Christie, D. J. *J. Nat. Prod.* **1990**, *53*, 112–124.
16. Lin, G. Q.; Li, F.; Tian, P.; Xu, M. H.; Jia, Z. S. Chinese Patent CN101869846A, Oct. 27, 2010.
17. (a) Ji, J. G.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216; (b) Barnes, D. M.; Ji, J. G.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; (c) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; (d) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959; (e) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592; (f) Tsubogo, T.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9117–9120; (g) Nichols, P. J.; DeMattei, J. A.; Barnett, B. R.; LeFur, N. A.; Chuang, T.-H.; Piscopio, A. D.; Koch, K. *Org. Lett.* **2006**, *8*, 1495–1498.
18. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125; (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370; (d) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389–1391; (e) Jiang, X. X.; Zhang, Y. F.; Liu, X.; Zhang, G.; Lai, L. H.; Wu, L. P.; Zhang, J. N.; Wang, R. *J. Org. Chem.* **2009**, *74*, 5562–5567; (f) Peng, F.-Z.; Shao, Z.-H.; Fan, B.-M.; Song, H.; Li, G.-P.; Zhang, H.-B. *J. Org. Chem.* **2008**, *71*, 5202–5205; (g) Andres, J. M.; Manzano, R.; Pedrosa, R. *Chem.—Eur. J.* **2008**, *14*, 5116–5119.
19. Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455.
20. (a) Zhang, L.; Lee, M.-M.; Lee, S.-M.; Lee, J.; Cheng, M. S.; Jeong, B.-S.; Park, H.-G.; Jew, S.-S. *Adv. Synth. Catal.* **2009**, *351*, 3063–3066; (b) Almasi, D.; Alonso, D. A.; Gomez-Bengoa, E.; Najera, C. *J. Org. Chem.* **2009**, *74*, 6163–6168.
21. **Q8** was synthesized by separate steps of coupling **Q5a** and then DHQ with PHAL and subsequent deprotection of Trt-group of the product.
22. The distances between the two phenolic O atoms in two **Q4** molecules are different, because two conformations exist in the lattice. One **Q4** (O5 and O8) is in the center and the other one (O1 and O4) is at the corner.
23. (a) Olpe, H. R.; Demieville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133–136; (b) Berthelot, P.; Vaccher, C.; Flouquet, N.; Debaert, M.; Luyckx, M.; Brunet, C. *J. Med. Chem.* **1991**, *34*, 2557–2560; (c) Kerr, D. I. B.; Ong, J. *Med. Res. Rev.* **1992**, *12*, 593–636.
24. Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788–791.