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Construction of Chiral Multi-Functionalized Polyheterocyclic Benzopyran Derivatives by Using an Asymmetric Organocatalytic Domino Reaction

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The asymmetric domino reaction of various α,α-dicyano olefins to 3-nitro-2*H*-chromenes was studied employing readily available cinchona-derived bifunctional thioureas as organocatalysts. These new transformations were highly regio-, chemo-, diastereo-, and enantioselective simultaneously giving chiral multi-functionalized polyheterocyclic benzopyran derivatives with multi-chiral carbon centers.

Introduction

Benzopyran is a well-known privileged structural motif, present in a number of physiologically active natural products as well as drugs, and it plays a key role in the regulation of various biopolymers.[1] Some representative active compounds that contain a benzopyran unit are shown in Figure 1. A number of studies show that delta-9-tetrahydrocannabinol (**A**, Δ^9-THC) provides medical benefits for cancer and AIDS patients by increasing appetite and decreasing nausea. It has also been shown to assist glaucoma patients by reducing pressure within the eye, and is used in the form of cannabis by a number of multiple sclerosis patients to alleviate neuropathic pain and spasticity.[2] Compound **C** has been shown to possess considerable hypertriglyceridemic activity.[3] Rhododauri-chromanic acid **D** (from *Rhododendron dauricum*) is of current interest, because it possesses potent anti-HIV and potent anti-inflammatory activities.[4] Owing to their pronounced biological activities, different approaches towards the synthesis of multi-functionalized polyheterocyclic benzopyran derivatives have been reported in the past ten years. The Nicolaou group has developed several reliable and versatile strategies for the construction of a 10000-membered benzopyran library by the directed split-and-pool chemistry with NanoKans and optical encoding.[5] The Park group has constructed a polyheterocyclic benzopyran library with diverse core skeletons by using diversity-oriented synthesis.[6] Polyheterocyclic benzopyran derivatives were also obtained by using [2+2] annulations by other research groups.[7] To the best of our knowledge, there are few reports of a direct catalytic asymmetric method for the synthesis of optically active multi-functionalized polyheterocyclic benzopyran derivatives.[8] It is worthwhile to construct a collection of drug-like small chiral molecules with diverse benzopyran-containing core skeletons. As such, the development of new and more general catalytic asymmetric methods for their preparation is of significant interest.

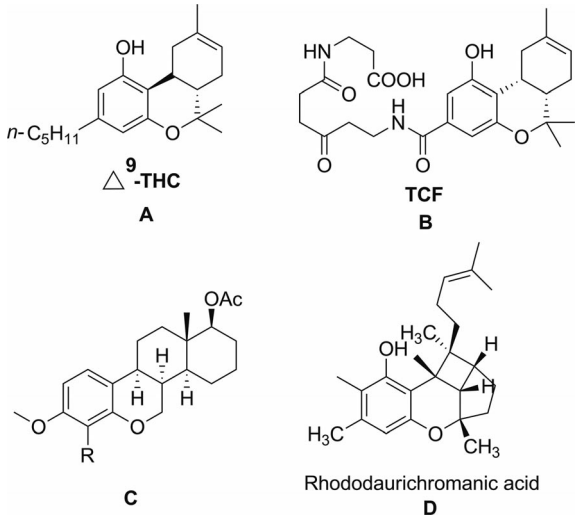

Figure 1. Some representative examples of benzopyran-containing natural products.

Results and Discussion

Organocatalytic asymmetric reactions have been used as efficient tools for the synthesis of enantiopure molecules under mild and environmentally benign conditions over the past decades.[9] In particular, asymmetric organocatalytic cascade processes have served as a powerful tool in organic synthesis because of their advantages, such as operational

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simplicity, environmental friendliness, and rapid one-pot entries to molecular complexity through atom-, step- and redox-economic or protecting-group-free protocols.[10] Herein we present an advance and its direct application in an atom-economical synthesis of chiral multi-functionalized polyheterocyclic benzopyran derivatives based on the development of an organocatalytic enantioselective domino Michael–cyclization–tautomerization reaction of α,α-dicyano olefins with 3-nitro-2*H*-chromenes. Notably, the reactions are highly regio-, chemo-, diastereo-, and enantioselective that simultaneously gives the desired multifunctional products with up to four vicinal chiral carbon centers.

Bifunctional thioureas **1a**–**d** are efficient organocatalysts for asymmetric additions of nucleophiles to nitro olefins (Figure 2),[11–14] and we have reported the highly regio-, chemo-, diastereo- and enantioselective asymmetric domino Michael-alkylation reaction of various 1,3-dicarbonyl compounds to α-bromonitroalkenes employing readily available cinchona-derived bifunctional thioureas as organocatalysts.[14] Recently, electron-deficient α,α-dicyano olefins, which act as versatile direct vinylogous donors in asymmetric Michael-addition reactions of electrophiles with excellent chemo- and stereoselectivity, have been reported.[15–16] We envisioned that bifunctional organocatalysts **1a**–**f** would be efficient catalysts for the domino Michael–cyclization–tautomerization reaction of α,α-dicyano olefins to 3-nitro-2*H*-chromenes.

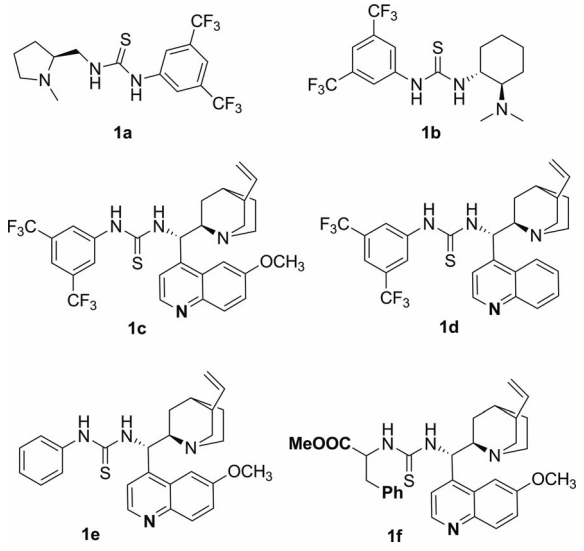
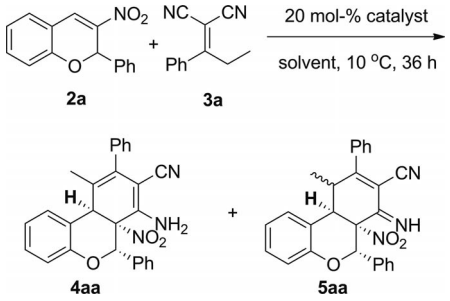


Figure 2. Structures of bifunctional organocatalysts **1a**–**1f**.

Table 1 shows some screening results for the reaction of **2a** with **3a**. Initially, bifunctional thiourea **1a** was investigated as the organocatalyst and very poor results were obtained (Table 1, Entry 1). To our delight, when the reaction was catalyzed by Takemoto's catalyst **1b**, chiral **4aa** and **5aa** were formed in moderate yields and good enantioselectivities (Table 1, Entry 2). Subsequently, we were pleased to find that bifunctional thioureas **1c**, **1d** and **1e** (20 mol-%), which are readily available from natural cinchona alkaloids, exhibited a much higher catalytic activity when the domino reaction was carried out at 10 °C after 36 h (Table 1, Entries 3–5). To our surprise, organocatalyst **1e**, derived from quinine, proved to be superior to **1c** in this domino reaction, and products were obtained with up to 89% *ee* (Table 1, Entry 5). Catalyst **1f** was inert in this reaction (Table 1, Entry 6). Various solvents were screened, and dichloromethane turned out to be optimal to give the product in higher enantioselectivities and yields (Table 1, Entry 5). Similar results were achieved in other solvents (Table 1, Entries 8–11). The *ee* was dramatically decreased by the combination of DABCO (20 mol-%) with bifunctional thiourea **1e**. By lowering the temperature to 0 °C, the enantioselectivity decreased in the presence of **1e** (Table 1, Entry 13). Moreover, kinetic resolution was involved in the domino Michael–cyclization–tautomerization reaction, and **2a** was obtained with 55% *ee* (Table 1, Entry 5).[17]

Table 1. Screening studies of the organocatalytic domino reaction of 3-nitro-2*H*-chromene **2a** and α,α-dicyano olefin **3a**.[a]



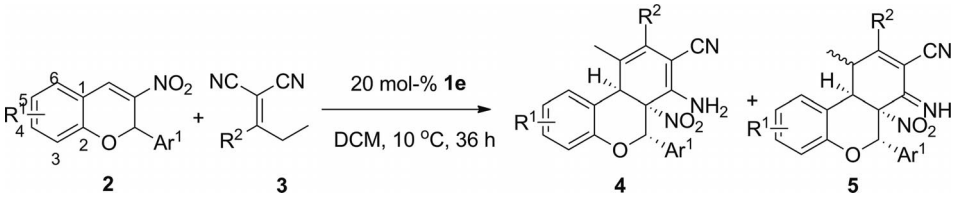
Entry	Catalyst	Solvent	Yield[b] [%]/*ee*[c] [%] **4aa**	Yield[b] [%]/*ee*[c] [%] **5aa**
1	**1a**	DCM	21/0	38/0
2	**1b**	DCM	40/79	35/79
3	**1c**	DCM	33/82	45/83
4	**1d**	DCM	28/83	38/86
5	**1e**	DCM	42/88	33/89
6	**1f**	DCM	–	–
8	**1e**	$CHCl_3$	48/75	25/80
9	**1e**	THF	44/76	36/81
10	**1e**	hexane	21/79	32/83
11	**1e**	toluene	30/79	37/81
12[d]	**1e**	DCM	68/0	17/0
13[e]	**1e**	DCM	23/71	40/72

[a] Reactions performed with **2a** (0.2 mmol), **3a** (0.1 mmol), **1** (20 mol-%) in solvent (1 mL) at 10 °C under N_2 for 36 h; DCM = dichloromethane. [b] Isolated yield and yield based on **3a**. [c] Determined by chiral HPLC analysis. [d] Adding DABCO (20 mol-%). [e] At 0 °C under N_2 for 36 h.

To test the substrate scope of the domino Michael–cyclization–tautomerization sequence, the reaction of various 3-nitro-2*H*-chromene derivatives **2** with α,α-dicyano olefins **3** was studied under the optimized conditions by using 20 mol-% of bifunctional thiourea **1e** as the catalyst. The results are summarized in Table 2.

As shown in Table 2, the domino Michael–cyclization–tautomerization reaction of various α,α-dicyano olefins **3** with 3-nitro-2*H*-chromene derivative **2** all gave good yields and high enantioselectivities of the desired products. High

Table 2. Evaluation of substrate scope: 3-nitro-2*H*-chromenes (**2**) and α,α-dicyano olefins (**3**).[a]



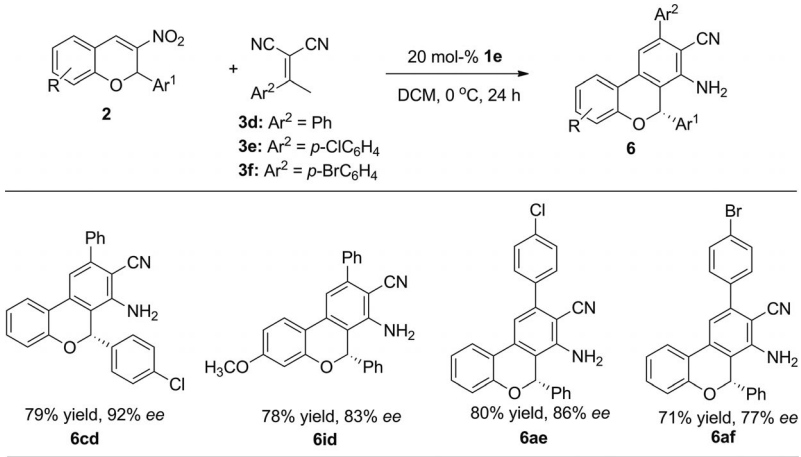
2 3 4 5

Entry	R^1	Ar^1	2	R^2	3	Yield[b] [%]/*ee*[c] [%]	4	Yield[b] [%]/*ee*[c] [%]	5
1	H	Ph	**2a**	Ph	**3a**	40/92	**4aa**	31/92	**5aa**
2	H	*p*-BrC_6H_4	**2b**	Ph	**3a**	38/86	**4ba**	35/86	**5ba**
3	H	*p*-MeC_6H_4	**2d**	Ph	**3a**	41/74	**4da**	29/78	**5da**
4	H	*p*-$MeOC_6H_4$	**2e**	Ph	**3a**	37/66	**4ea**	38/68	**5ea**
5	5-Cl	Ph	**2f**	Ph	**3a**	37/84	**4fa**	40/84	**5fa**
6	5-Br	Ph	**2h**	Ph	**3a**	44/82	**4ha**	23/80	**5ha**
7	4-MeO	Ph	**2i**	Ph	**3a**	43/91	**4ia**	30/91	**5ia**
8	H	Ph	**2a**	*p*-MeC_6H_4	**3b**	41/89	**4ab**	36/89	**5ab**
9	5-Cl	*p*-MeC_6H_4	**2g**	*p*-ClC_6H_4	**3c**	43/86	**4gc**	25/88	**5gc**
10	H	Ph	**2a**	*p*-ClC_6H_4	**3c**	46/90	**4ac**	30/90	**5ac**
11	H	*p*-ClC_6H_4	**2c**	*p*-ClC_6H_4	**3c**	44/85	**4cc**	32/85	**5cc**
12	H	Ph	**2a**	C_2H_5	**3h**	47/82	**4ah**	–	–

[a] Reactions performed with **2** (0.2 mmol), **3** (0.1 mmol), **1e** (20 mol-%) in DCM (1 mL) at 10 °C under N_2 for 36 h; DCM = dichloromethane. [b] Isolated yield and yield based on **3**. [c] Determined by chiral HPLC analysis.

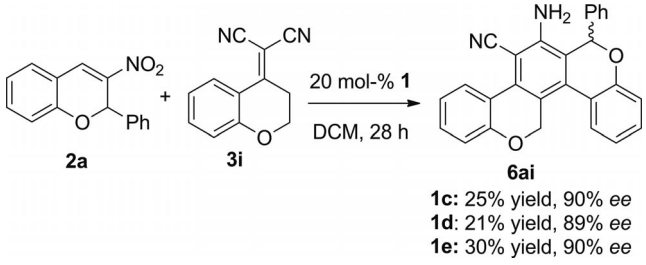
enantioselectivities were obtained in the domino reaction of α,α-dicyano olefins with an electron-withdrawing substituent on the Ar^1 ring of the 3-nitro-2*H*-chromene derivatives (Table 2, Entries 2, 11). On the contrary, an electron-donating substituent on the Ar^1 ring of 3-nitro-2*H*-chromene derivatives tended to decrease the reactivity and enantioselectivity (Table 2, Entries 3 and 4). Gratifyingly, the reaction of 3-nitro-2*H*-chromene derivatives **3** with an electron-withdrawing substituent or electron-donating group on the R^1 group afforded the desired products with a slight effect on the enantioselectivities (Table 2, Entries 5–7), and the enantioselectivities were up to 94%. In addition, the electronic nature of a substituent on the aromatic moiety of **3** has little effect on the domino Michael–cyclization–tautomerization reaction with our organocatalytic protocol (Table 2, Entries 8, 9). High *ee* values were also obtained in the reaction of linear alkyl α,α-dicyano olefin **3h** with 3-nitro-2*H*-chromene derivative **2a**, and product **4ah** was obtained with up to 82% *ee* in the domino reaction (Table 2, Entry 12). The relative configuration of compounds **4** was confirmed by the crystallographic study of racemic **4fa**.[18]

Interestingly, for acyclic β-phenyl α,α-dicyano olefins **3d**–**3g** that have small steric hindrance, only the benzannulation products were obtained with moderate to excellent enantioselectivities when the domino reaction was carried out at 0 °C for 24 h (Scheme 1). Apparently, the domino Michael–cyclization–tautomerization reaction proceeded smoothly, then the elimination of the nitro group took place under these conditions. Moreover, high *ee* was obtained when an electron-withdrawing substituent was introduced on the Ar^1 ring (Scheme 1, **6cd**). In addition, when R was an electron-donating substituent, the α,α-dicyano olefin substrate tended to decrease the reactivity without affecting the enantioselectivity (Scheme 1, **6id**).



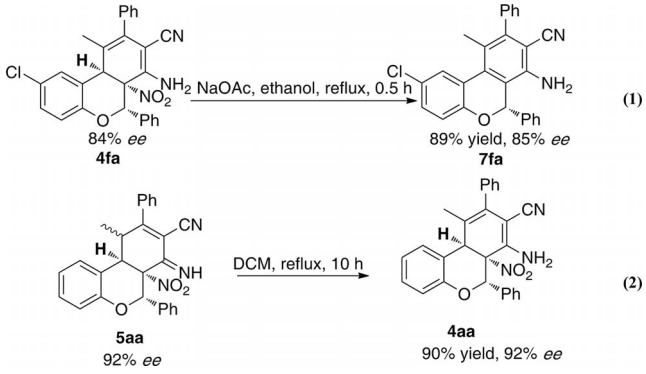
Scheme 1. Asymmetric domino reaction of 3-nitro-2*H*-chromenes **2** with α,α-dicyano olefins **3**.

Notably, high reactivity was observed for bulkier α,α-dicyano olefin **3i** (Scheme 2), the domino reaction proceeded smoothly and product **6ai** was isolated in 21–30% yields with good enantioselectivities (89–90% *ee*). Moreover, bifunctional thioureas **1c**–**1e** have little effects on the enantioselectivity and similar results were achieved.



Scheme 2. Asymmetric synthesis of pentacyclic dichromene **6ai**.

Scheme 3 illustrates the synthetic versatility of the multifunctional products in this methodology. Benzannulation product **7fa** was obtained when the domino reaction product **4fa** was heated to reflux in ethanol and catalyzed by NaOAc (100 mol-%; Scheme 3, Eq. 1). Product **5aa** could be cleanly converted into compound **4aa** without affecting the *ee* in CH_2Cl_2 under catalyst-free conditions (Scheme 3, Eq. 2).



Scheme 3. Selective transformations of the domino reaction product.

The absolute configuration of the multi-functionalized polyheterocyclic benzopyran was confirmed by single-crystal X-ray analysis of representative enantiopure **4ha** that bears a bromine atom. As shown in Figure 3, it has a (7*S*,8*R*,13*R*) configuration.

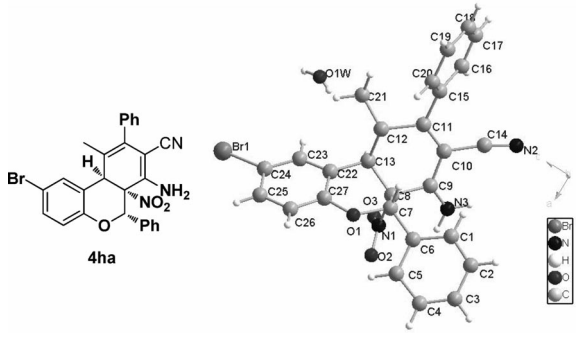


Figure 3. X-ray diffraction analysis of compound **4ha**.

The stereochemical outcome of the domino reaction can be rationalized by the following plausible mechanism. According to the literature,[11–14] α,α-dicyano olefins can be easily deprotonated by tertiary amines and 3-nitro-2*H*-chromenes **2** may be activated by the thiourea moiety through double H-bonding, furnishing the corresponding vinylogous carbanion. Subsequent domino Michael–cyclization–tautomerization reaction affords the desired products (Figure 4). The configuration is in accordance with the single-crystal X-ray analysis.

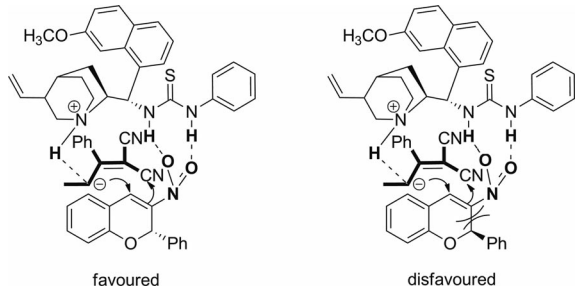


Figure 4. Proposed mechanism for the domino reaction.

Conclusions

In conclusion, we have successfully demonstrated the domino reaction of electron-deficient α,α-dicyano olefins to 3-nitro-2*H*-chromene derivatives with excellent diastereoselectivity and good-to-excellent enantioselectivity. Readily available bifunctional thiourea **1e** was employed as the organocatalyst, which is a more effective catalyst than the ditrifluoromethylated one. This methodology provides facile access to various enantio-enriched multifunctional compounds. Extension of this methodology to the synthesis of other natural products is under investigation.

Experimental Section

General: Column chromatography was performed with silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as solvent. Chemical shifts for protons are reported relative to residual $CHCl_3$ as internal reference (δ = 7.26 ppm). Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ = 77.0 ppm). IR spectra were recorded with a Perkin–Elmer 1600 Series FTIR. HRMS (ESI) spectra were measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer. Optical rotations were measured at 589 nm at 25 °C in a 1-dm cell and specific rotations are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excesses were determined by using HPLC analysis with a Daicel Chiralpak AS column (4.6 mm × 250 mm, 5 μm) and Daicel Chiralpak OD column (4.6 mm × 250 mm, 5 μm). Commercial grade solvents were dried and purified according to standard procedures as specified in ref.[19].

Typical Procedure for the Asymmetric Domino Reaction of 3-Nitro-2*H*-chromenes 2 with α,α-Dicyano Olefins 3a–3c, 3h: Compound **2a** (50.6 mg, 0.2 mmol), **3a** (18.2 mg, 0.1 mmol), and **1e** (9.1 mg,

0.02 mol) were stirred in CH_2Cl_2 (1 mL) at 10 °C under a nitrogen atmosphere for 36 h. Flash chromatography on silica gel (8% ethyl acetate/petroleum ether) gave **4aa** (17.4 mg, 40% yield) and **5aa** (13.5 mg, 31% yield) as pale yellow solids.

(6*S*,6a*R*,10a*R*)-7-Amino-10-methyl-6a-nitro-6,9-diphenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4aa): 17.4 mg, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 8 H), 7.16–7.14 (m, 3 H), 7.07–6.98 (m, 2 H), 5.94 (s, 1 H), 5.20 (s, 2 H), 4.14–4.08 (m, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 147.7, 136.8, 134.4, 129.7, 129.7, 129.3, 128.9, 128.5, 128.1, 126.8, 126.6, 122.3, 117.0, 116.1, 27.0 ppm. IR (KBr): 3350, 3251, 2957, 2202, 1718, 1663, 1565, 1477, 769 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{21}N_3O_3$ + Na 458.1475; found 458.1481. $[\alpha]_D^{25}$ = +11.1 (*c* = 0.30, CH_2Cl_2), 92% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.98 min, t_{minor} = 11.10 min.

(6*S*,6a*R*,10a*R*)-7-Imino-10-methyl-6a-nitro-6,9-diphenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5aa): 13.5 mg, 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.81 (s, 1 H), 7.54–7.52 (m, 2 H), 7.42–7.33 (m, 10 H), 7.10–7.05 (m, 2 H), 6.11 (s, 1 H), 4.24 (d, *J* = 5.9 Hz, 1 H), 3.55–3.51 (m, 1 H), 1.21 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 160.1, 153.1, 136.1, 131.0, 130.0, 129.3, 129.1, 128.3, 128.1, 128.0, 127.0, 122.0, 119.2, 117.9, 90.2, 41.6, 29.7, 18.7 ppm. IR (KBr): 3348, 3244, 2956, 2189, 1706, 1643, 1554, 1474 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{21}N_3O_3$ + Na 458.1475; found 458.1475. $[\alpha]_D^{25}$ = –36.3 (*c* = 0.27, CH_2Cl_2), 92% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 10.95 min, t_{major} = 14.03 min.

(6*S*,6a*R*,10a*R*)-7-Amino-6-(4-bromophenyl)-10-methyl-6a-nitro-9-phenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ba): 19.5 mg, 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 8 H), 7.18–7.16 (m, 4 H), 6.92–6.90 (m, 1 H), 5.95 (s, 1 H), 5.24 (s, 2 H), 4.17–4.11 (m, 1 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 136.8, 133.5, 132.0, 129.8, 129.2, 128.6, 128.2, 126.5, 124.0, 122.5, 117.0, 116.2, 27.0, 14.2 ppm. IR (KBr) : 3347, 3250, 2959, 2202, 1718, 1663, 1565, 1477, 769 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_3O_3$ + Na 536.0580; found 536.0581. $[\alpha]_D^{25}$ = +9.3 (*c* = 0.42, CH_2Cl_2), 86% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 8.43 min, t_{minor} = 9.60 min.

(6*S*,6a*R*,10a*R*)-6-(4-Bromophenyl)-7-imino-10-methyl-6a-nitro-9-phenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ba): 18.0 mg, 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 7.54–7.47 (m, 5 H), 7.41–7.33 (m, 4 H), 7.25–7.23 (m, 2 H), 7.09–7.07 (m, 2 H), 5.99 (s, 1 H), 4.20 (d, *J* = 5.9 Hz, 1 H), 3.51–3.48 (m, 1 H), 1.22 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 160.2, 152.9, 135.9, 133.5, 131.2, 131.1, 130.2, 129.7, 129.3, 128.5, 127.0, 123.2, 122.2, 117.9, 90.3, 41.6, 29.7, 18.6 ppm. IR (KBr): 3351, 3248, 2955, 2205, 1708, 1651, 1559, 1473, 771 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_3O_3$ + Na 536.0580; found 536.0586. $[\alpha]_D^{25}$ = +24.9 (*c* = 0.39, CH_2Cl_2), 86% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 9.41 min, t_{major} = 11.14 min.

(6*S*,6a*R*,10a*R*)-7-Amino-10-methyl-6a-nitro-9-phenyl-6-(*p*-tolyl)-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4da): 18.4 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 7.16–7.11 (m, 4 H), 7.06–6.98 (m, 4 H), 5.92 (s, 1 H), 5.19 (s, 2 H), 4.15–4.10 (m, 1 H), 2.34 (s, 3 H), 1.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 147.8, 139.8, 136.8, 131.3, 129.6, 129.6, 129.3, 128.5, 128.1, 126.8, 126.6, 122.3, 117.0, 116.1, 21.3 ppm. IR (KBr): 3357, 3252, 2961, 2214, 1720, 1669, 1553, 1482 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_3$ + Na 472.1632; found 472.1632. $[\alpha]_D^{25}$ = +24.0 (*c* = 0.32, CH_2Cl_2), 74% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.20 min, t_{minor} = 8.32 min.

(6*S*,6a*R*,10a*R*)-7-Imino-10-methyl-6a-nitro-9-phenyl-6-(*p*-tolyl)-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5da): 13.0 mg, 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 7.54–7.53 (m, 3 H), 7.41–7.40 (m, 2 H), 7.32–7.31 (m, 2 H), 7.25–7.23 (m, 2 H), 7.17–7.15 (m, 2 H), 7.09–7.05 (m, 2 H), 6.07 (s, 1 H), 4.23 (d, *J* = 5.9 Hz, 1 H), 3.54–3.50 (m, 1 H), 2.36 (s, 3 H), 1.20 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 160.2, 153.1, 139.0, 136.1, 131.4, 131.0, 130.0, 129.3, 128.8, 127.9, 127.0, 122.0, 119.1, 117.9, 90.1, 43.1, 41.7, 21.3, 18.7, 18.6 ppm. IR (KBr): 3340, 3247, 2941, 2198, 1705, 1651, 1571 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_3$ + Na 472.1632; found 472.1632. $[\alpha]_D^{25}$ = +13.3 (*c* = 0.24, CH_2Cl_2), 78% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 11.27 min, t_{major} = 15.12 min.

(6*S*,6a*R*,10a*R*)-7-Amino-6-(4-methoxyphenyl)-10-methyl-6a-nitro-9-phenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ea): 17.2 mg, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 5 H), 7.16–7.14 (m, 2 H), 7.06–7.03 (m, 3 H),6.99–6.97 (m, 1 H), 6.84–6.82 (m, 2 H), 5.91 (s, 1 H), 5.23 (s, 2 H), 4.14–4.09 (m, 1 H), 3.77 (s, 3 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 152.7, 147.8, 136.7, 129.5, 129.1, 128.4, 128.0, 128.0, 127.9, 126.4, 126.1, 122.1, 118.8, 116.9, 116.0, 114.1, 74.6, 55.2, 26.8 ppm. IR (KBr): 3349, 3246, 2946, 2200, 1711, 1659, 1545 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_4$ + Na 488.1581; found 488.1588. $[\alpha]_D^{25}$ = +7.6 (*c* = 0.18, CH_2Cl_2), 66% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 0.6 mL/min), t_{major} = 10.60 min, t_{minor} = 11.51 min.

(6*S*,6a*R*,10a*S*)-7-Imino-6-(4-methoxyphenyl)-10-methyl-6a-nitro-9-phenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ea): 17.7 mg, 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.82 (s, 1 H), 7.57–7.55 (m, 3 H), 7.44–7.43 (m, 2 H), 7.35–7.30 (m, 4 H), 7.11–7.10 (m, 2 H), 6.91–6.89 (m, 2 H), 6.09 (s, 1 H), 4.26 (d, *J* = 5.8 Hz, 1 H), 3.84 (s, 3 H), 3.57–3.53 (m, 1 H), 1.24 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 160.2, 160.0, 153.1, 136.1, 131.0, 130.0, 129.5, 129.3, 129.2, 127.0, 126.3, 121.9, 118.0, 113.5, 113.4, 90.0, 55.3, 55.3, 43.1, 41.7, 18.7 ppm. IR (KBr): 3345, 3241, 2887, 2185, 1700, 1651, 1548 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_4$ + Na 488.1581; found 488.1581. $[\alpha]_D^{25}$ = +32.2 (*c* = 0.48, CH_2Cl_2), 68% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 13.79 min, t_{major} = 19.12 min.

(6*S*,6a*R*,10a*R*)-7-Amino-2-chloro-10-methyl-6a-nitro-6,9-diphenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4fa): 17.4 mg, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 6 H), 7.31–7.25 (m, 2 H), 7.18–7.16 (m, 4 H), 6.97–6.95 (m, 1 H), 5.94 (s, 1 H), 5.21 (s, 2 H), 4.16–4.11 (m, 1 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 136.4, 133.9, 129.8, 129.7, 129.1, 128.9, 128.5, 128.1, 127.3, 126.6, 125.7, 117.3, 116.7, 60.4, 26.9, 14.1 ppm. IR (KBr): 3350, 3246, 2961, 2210, 1709, 1645, 1558 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}ClN_3O_3$ + Na 492.1085; found 492.1086. $[\alpha]_D^{25}$ = +9.3 (*c* = 0.30, CH_2Cl_2), 84% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 8.44 min, t_{minor} = 10.22 min.

(6*S*,6a*R*,10a*R*)-2-Chloro-7-imino-10-methyl-6a-nitro-6,9-diphenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5fa): 18.8 mg, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.85 (s, 1 H), 7.56–7.54 (m, 3 H), 7.40–7.36 (m, 5 H), 7.32–7.28 (m, 4 H), 7.05–7.02 (m, 1 H), 6.09 (s, 1 H), 4.20 (d, J = 5.7 Hz, 1 H), 3.50–3.46 (m, 1 H), 1.21 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 159.7, 151.7, 135.9, 131.1, 130.1, 129.3, 129.2, 128.1, 128.0, 127.8, 126.9, 119.3, 89.7, 41.4, 18.7 ppm. IR (KBr): 3338, 3241, 2937, 2197, 1713, 1658, 1560, 1472 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}ClN_3O_3$ + Na 492.1085; found 492.1084. $[\alpha]_D^{25}$ = +39.5 (c = 0.85, CH_2Cl_2), 84% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 9.035 min, t_{major} = 10.77 min.

(6*S*,6a*R*,10a*R*)-7-Amino-2-bromo-10-methyl-6a-nitro-6,9-diphenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ha): 22.6 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.47 (m, 2 H), 7.42–7.29 (m, 5 H), 7.19–7.00 (m, 6 H), 5.89 (s, 1 H), 5.15 (s, 2 H), 4.17–4.11 (m, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 136.4, 133.9, 132.6, 130.9, 129.8, 129.2, 129.1, 128.9, 128.5, 128.2, 128.0, 127.9, 126.9, 126.6, 125.8, 121.9, 117.9, 116.6, 114.6, 29.7, 18.6 ppm. IR (KBr): 3340, 3243, 2952, 2197, 1711, 1656, 1558, 1470, 762 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_3O_3$ + Na 536.0581; found 536.0580. $[\alpha]_D^{25}$ = +9.3 (c = 0.42, CH_2Cl_2), 82% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 8.79 min, t_{minor} = 10.61 min.

(6*S*,6a*R*,10a*R*)-2-Chloro-7-imino-10-methyl-6a-nitro-6,9-diphenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ha): 11.8 mg, 23% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.82 (s, 1 H), 7.53–7.52 (m, 2 H), 7.42–7.34 (m, 8 H), 7.31–7.30 (m, 2 H), 6.96 (d, J = 8.6 Hz, 1 H), 6.07 (s, 1 H), 4.18 (d, J = 5.9 Hz, 1 H), 3.49–3.42 (m, 1 H), 1.19 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 159.6, 152.1, 133.0, 131.0, 129.3, 129.2, 128.1, 128.0, 127.8, 126.9, 119.7, 114.1, 89.7, 42.9, 41.4, 18.6 ppm. IR (KBr): 3345, 3247, 2954, 2199, 1715, 1660, 1562, 1473, 765 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_3NaO_3$ 536.0581; found 536.0585. $[\alpha]_D^{25}$ = +24.9 (c = 0.39, CH_2Cl_2), 81% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 9.69 min, t_{major} = 11.75 min.

(6*S*,6a*R*,10a*R*)-7-Amino-3-methoxy-10-methyl-6a-nitro-6,9-diphenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ia): 20.0 mg, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 7 H), 7.19–7.14 (m, 4 H), 6.65–6.63 (m, 1 H), 6.54 (d, J = 2.5 Hz, 1 H), 5.91 (s, 1 H), 5.10 (s, 2 H), 4.15–4.10 (m, 1 H), 3.83 (s, 3 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 153.6, 134.3, 129.7, 129.2, 128.8, 128.5, 128.0, 127.1, 109.4, 55.4, 29.7 ppm. IR (KBr): 3349, 3253, 2962, 2205, 1713, 1656, 1567, 1479 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_4$ + Na 488.1579; found 488.1581. $[\alpha]_D^{25}$ = +7.1 (c = 0.17, CH_2Cl_2), 91% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 9.56 min, t_{minor} = 12.72 min.

(6*S*,6a*R*,10a*R*)-7-Imino-3-methoxy-10-methyl-6a-nitro-6,9-diphenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ia): 14.0 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.83 (s, 1 H), 7.52–7.51 (m, 3 H), 7.39–7.31 (m, 7 H), 7.21–7.19 (m, 1 H), 6.63–6.59 (m, 2 H), 6.11 (s, 1 H), 4.17 (d, J = 5.5 Hz, 1 H), 3.80 (s, 3 H), 3.54–3.47 (m, 1 H), 1.17 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 160.9, 159.9, 154.0, 130.9, 129.2, 129.1, 128.1, 128.0, 127.9, 127.0, 113.7, 110.9, 109.4, 102.1, 90.0, 55.5, 41.6, 29.7, 18.6 ppm. IR (KBr): 3348, 3248, 2956, 2198, 1717, 1658, 1564, 1476, 767 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_4$ + Na 488.1579; found 488.1588. $[\alpha]_D^{25}$ = –23.9 (c = 0.30, CH_2Cl_2), 91% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 11.87 min, t_{major} = 14.46 min.

(6*S*,6a*R*,10a*R*)-7-Amino-10-methyl-6a-nitro-6-phenyl-9-(*p*-tolyl)-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ab): 18.4 mg, 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 6 H), 7.20–7.18 (m, 3 H), 7.08–7.00 (m, 4 H), 5.96 (s, 1 H), 5.22 (s, 2 H), 4.16–4.11 (m, 1 H), 2.36 (s, 3 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 147.6, 137.6, 134.4, 133.7, 129.5, 129.5, 129.1, 129.0, 128.7, 128.3, 126.7, 126.2, 122.1, 117.0, 116.0, 29.6, 21.2, 14.1 ppm. IR (KBr): 3350, 3253, 2938, 2212, 1681, 1649, 1561, 1464 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_3$ + Na 472.1633; found 472.1641. $[\alpha]_D^{25}$ = +29.1 (c = 0.27, CH_2Cl_2), 90% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.50 min, t_{minor} = 9.20 min.

(6*S*,6a*R*,10a*R*)-7-Imino-10-methyl-6a-nitro-6-phenyl-9-(*p*-tolyl)-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ab): 16.2 mg, 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.76 (s, 1 H), 7.36–7.33 (m, 10 H), 7.10–7.05 (m, 3 H), 6.10 (s, 1 H), 4.23 (d, J = 5.8 Hz, 1 H), 3.55–3.51 (m, 1 H), 2.44 (s, 3 H), 1.21 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 160.3, 153.1, 141.6, 133.2, 130.0, 130.0, 129.2, 129.1, 128.3, 128.1, 128.0, 127.0, 122.0, 117.9, 90.3, 41.4, 29.7, 21.5, 21.3, 18.8 ppm. IR (KBr): 3351, 3255, 2963, 2206, 1715, 1664, 1545, 1471 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{23}N_3O_3$ + Na 472.1633; found 472.1632. $[\alpha]_D^{25}$ = +11.3 (c = 0.22, CH_2Cl_2), 89% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 11.49 min, t_{major} = 14.27 min.

(6*S*,6a*R*,10a*R*)-7-Amino-2-chloro-9-(4-chlorophenyl)-10-methyl-6a-nitro-6-(*p*-tolyl)-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4gc): 22.2 mg, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 2 H), 7.29–7.26 (m, 1 H), 7.19–6.92 (m, 8 H), 5.89 (s, 1 H), 5.26 (s, 2 H), 4.13–4.04 (m, 1 H), 2.34 (s, 3 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 131.8, 130.7, 130.6, 130.2, 130.1, 129.8, 129.6, 128.9, 128.8, 127.1, 127.1, 29.7, 21.2 ppm. IR (KBr): 3351, 3249, 2955, 2186, 1709, 1656, 1564, 1471 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{21}Cl_2N_3O_3$ + Na 540.0855; found 540.0853. $[\alpha]_D^{25}$ = +9.5 (c = 0.43, CH_2Cl_2), 86% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 6.99 min, t_{minor} = 8.09 min.

(6*S*,6a*R*,10a*R*)-2-Chloro-9-(4-chlorophenyl)-7-imino-10-methyl-6a-nitro-6-(p-tolyl)-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5gc): 12.9 mg, 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.69 (s, 1 H), 7.54–7.52 (m, 2 H), 7.44–7.39 (m, 2 H), 7.26–7.13 (m, 6 H), 7.02–6.99 (m, 1 H), 6.04 (s, 1 H), 4.14 (d, J = 6.7 Hz, 1 H), 3.52–3.49 (m, 1 H), 2.34 (s, 3 H), 1.20 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 160.0, 151.5, 138.9, 130.9, 129.2, 129.0, 128.6, 128.6, 127.9, 127.9, 127.0, 126.9, 119.1, 91.9, 89.9, 42.5, 41.8, 21.2, 18.4 ppm. IR (KBr): 3351, 3249, 2961, 2203, 1709, 1658, 1549, 1469, 771 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{21}Cl_2N_3O_3$ + Na 540.0852; found 540.0851. $[\alpha]_D^{25}$ = +32.2 (c = 0.18, CH_2Cl_2), 88% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 8.04 min, t_{major} = 9.00 min.

(6*S*,6a*R*,10a*R*)-7-Amino-9-(4-chlorophenyl)-10-methyl-6a-nitro-6-phenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ac): 21.6 mg, 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 7 H), 7.19–7.03 (m, 6 H), 6.00 (s, 1 H), 5.43 (s, 2 H), 4.17–4.13

(m, 1 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 148.3, 135.3, 134.4, 134.0, 130.8, 129.8, 129.0, 128.8, 127.6, 127.0, 127.0, 126.8, 122.4, 118.7, 117.0, 116.2, 74.9, 29.8, 21.8 ppm. IR (KBr): 3346, 3249, 2958, 2201, 1717, 1662, 1564, 1476, 768 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}ClN_3O_3$ + Na 492.1085; found 492.1093. $[\alpha]_D^{25}$ = +21.2 (c = 0.26, CH_2Cl_2), 90% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.57 min, t_{minor} = 10.13 min.

(6*S*,6a*R*,10a*R*)-9-(4-Chlorophenyl)-7-imino-10-methyl-6a-nitro-6-phenyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5ac): 14.1 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.87 (s, 1 H), 7.52–7.50 (m, 2 H), 7.36–7.27 (m, 9 H), 7.09–7.07 (m, 2 H), 6.11 (s, 1 H), 4.24 (d, J = 5.5 Hz, 1 H), 3.53–3.50 (m, 1 H), 1.20 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3, 130.0, 129.5, 129.0, 128.6, 128.3, 128.0, 127.8, 121.9, 117.8, 60.29, 18.5, 14.09 ppm. IR (KBr): 3350, 3245, 2961, 2191, 1702, 1658, 1557, 1466, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}ClN_3O_3$+ Na 492.1085; found 492.1086. HRMS (ESI): calcd. for $C_{26}H_{18}N_2NaO$ 397.13137, found 397.13113. $[\alpha]_D^{25}$ = +91.6 (c = 0.49, CH_2Cl_2), 90% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 9.48 min, t_{major} = 11.63 min.

(6*S*,6a*R*,10a*R*)-7-Amino-6,9-bis(4-chlorophenyl)-10-methyl-6a-nitro-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4cc): 22.1 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 6 H), 7.12–7.00 (m, 6 H), 5.93 (s, 1 H), 5.29 (s, 2 H), 4.17–4.11 (m, 1 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 147.6, 135.7, 135.0, 134.0, 132.7, 130.5, 129.8, 129.0, 128.7, 128.1, 126.9, 122.4, 118.2, 116.6, 116.1, 74.0, 14.1 ppm. IR (KBr): 3341, 3244, 2953, 2196, 1712, 1657, 1558, 1471, 762 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{19}Cl_2N_3O_3$ + Na 526.0693; found 526.0686. $[\alpha]_D^{25}$ = +11.4 (c = 0.41, CH_2Cl_2), 85% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.60 min, t_{minor} = 8.88 min.

(6*S*,6a*R*,10a*R*)-6,9-Bis(4-chlorophenyl)-7-imino-10-methyl-6a-nitro-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene-8-carbonitrile (5cc): 16.1 mg, 32% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.76 (s, 1 H), 7.52–7.48 (m, 2 H), 7.40–7.38 (m, 2 H), 7.33–7.27 (m, 6 H), 7.08–7.04 (m, 2 H), 6.01 (s, 1 H), 4.16 (d, J = 6.6 Hz, 1 H), 3.50–3.47 (m, 1 H), 1.20 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 159.9, 152.6, 137.1, 134.7, 134.1, 132.7, 130.0, 129.4, 129.4, 129.3, 128.4, 128.3, 128.0, 122.0, 118.7, 117.6, 113.3, 90.1, 75.7, 42.6, 41.3, 18.3 ppm. IR (KBr): 3343, 3245, 2952, 2210, 1711, 1659, 1559, 1466 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{19}Cl2N_3O_3$ + Na 526.0693: found 526.0695. $[\alpha]_D^{25}$ = +47.8 (c = 0.35, CH_2Cl_2), 85% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{minor} = 7.54 min, t_{major} = 8.74 min.

(6*S*,6a*R*,10a*R*)-7-Amino-9-ethyl-10-methyl-6a-nitro-6-phenyl-6a,10a-dihydro-6*H*-benzo[*c*]chromene-8-carbonitrile (4ah): 18.2 mg, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 1 H), 7.27–7.26 (m, 3 H), 7.21–7.14 (m, 3 H), 7.04–6.93 (m, 2 H), 5.67 (d, J = 7.0 Hz, 2 H), 4.93 (s, 2 H), 4.10 (d, J = 4.3 Hz, 1 H), 3.41–3.38 (m, 1 H), 1.73 (d, J = 7.1 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 144.9, 134.5, 130.9, 129.5, 128.8, 128.5, 127.6, 127.3, 122.3, 122.0, 121.8, 117.3, 116.5, 89.6, 78.5, 40.1, 33.2, 18.9, 13.2 ppm. IR (KBr): 3319, 3248, 3027, 2194, 1713, 1651, 1547, 1469, 753 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{21}N_3O_3$ + Na 410.148; found 410.1475. $[\alpha]_D^{25}$ = –31.0 (c = 0.42, CH_2Cl_2), 82% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 6.65 min, t_{minor} = 8.13 min.

Typical Procedure for Asymmetric Domino Reaction of 3-Nitro-2*H*-chromenes (2) and α,α-Dicyano olefins (3d–3f): Compound **2c** (57.4 mg, 0.2 mmol), **3d** (16.8 m, 0.1 mmol), **1e** (9.1 mg, 0.04 mmol) were stirred in CH_2Cl_2 (1 mL) at 0 °C under a nitrogen atmosphere for 24 h. Flash chromatography on silica gel (8% ethyl acetate/petroleum ether) gave **6cd** (32.2 mg, 79% yield) as a pale yellow solid.

(*S*)-7-Amino-6-(4-chlorophenyl)-9-phenyl-6*H*-benzo[*c*]chromene-8-carbonitrile (6cd): 32.2 mg, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.69 (m, 1 H), 7.65–7.63 (m, 2 H), 7.53–7.51 (m, 3 H), 7.30–7.26 (m, 6 H), 7.03–7.01 (m, 1 H), 6.91–6.89 (m, 1 H), 6.30 (s, 1 H), 4.36 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 146.0, 135.6, 131.2, 129.3, 129.2, 128.9, 128.8, 128.6, 124.1, 122.5, 118.5, 115.9, 113.8, 73.1 ppm. IR (KBr): 3397, 3106, 2184, 1701, 1632, 1581, 1438, 759 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{17}ClN_2O$ + Na 431.092; found 431.0921. $[\alpha]_D^{25}$ = –252.7 (c = 0.28, CH_2Cl_2), 92% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (20% 2-propanol/hexane, 1 mL/min), t_{major} = 7.64 min, t_{minor} = 8.54 min.

(*S*)-7-Amino-3-methoxy-6,9-diphenyl-6*H*-benzo[*c*]chromene-8-carbonitrile (6id): 31.5 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.62 (m, 2 H), 7.53–7.51 (m, 3 H), 7.34–7.23 (m, 7 H), 6.58–6.56 (m, 1 H), 6.44–6.44 (m, 1 H), 6.32 (s, 1 H), 4.30 (s, 2 H), 3.77 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.2, 129.0, 128.6, 128.5, 127.8, 113.0, 109.0, 103.0, 74.3, 55.3 ppm. IR (KBr): 3503, 3310, 3116, 2206, 1709, 1633, 1557, 1411, 743 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{20}N_2NaO_2$ 427.141; found 427.1417. $[\alpha]_D^{25}$ = –165.0 (c = 0.22, CH_2Cl_2), 83% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (20% 2-propanol/hexane, 1 mL/min), t_{major} = 7.85 min, t_{minor} = 9.28 min.

(*S*)-7-Amino-9-(4-chlorophenyl)-6-phenyl-6*H*-benzo[*c*]chromene-8-carbonitrile (6ae): 32.6 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.48 (m, 5 H), 7.31–7.22 (m, 7 H), 6.99–6.88 (m, 2 H), 6.31 (s, 1 H), 4.34 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 146.4, 136.9, 134.4, 131.2, 129.9, 129.2, 129.0, 128.9, 127.8, 123.9, 122.2, 118.5, 117.2, 113.5, 73.9, 29.7 ppm. IR (KBr): 3451, 3306, 3019, 2101, 1705, 1651, 1570, 1395, 718 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{17}ClN_2O$ + Na 431.092; found 431.0921. $[\alpha]_D^{25}$ = –451.0 (c = 0.24, CH_2Cl_2), 86% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (20% 2-propanol/hexane, 1 mL/min), t_{major} = 6.14 min, t_{minor} = 7.42 min.

(*S*)-7-Amino-9-(4-bromophenyl)-6-phenyl-6*H*-benzo[*c*]chromene-8-carbonitrile (6af): 32.1 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 3 H), 7.50–7.48 (m, 2 H), 7.30–7.18 (m, 7 H), 7.00–6.87 (m, 2 H), 6.30 (s, 1 H), 4.33 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 146.5, 134.5, 131.9, 131.3, 130.2, 129.3, 129.0, 127.9, 124.0, 122.3, 118.5, 113.4, 74.0 ppm. IR (KBr): 3391, 3217, 2209, 1684, 1627, 1527, 1461, 673 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{17}BrN_2O$ + Na 475.04; found 475.0417. $[\alpha]_D^{25}$ = –404.8 (c = 0.29, CH_2Cl_2), 77% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (20% 2-propanol/hexane, 1 mL/min), t_{major} = 6.35 min, t_{minor} = 7.65 min.

14-Amino-1-phenyl-1,7-dihydrobenzo[1,2-*c*:3,4-*c*′]dichromene-13-carbonitrile (6ai): 12.1 mg, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 7.9 Hz, 1 H), 7.39–7.35 (m, 1 H), 7.21–7.19 (m, 3 H), 7.10–6.96 (m, 5 H), 6.30 (s, 1 H), 5.46 (d, J = 13.0 Hz, 1 H), 5.09 (d, J = 13.0 Hz, 1 H), 4.35 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.9, 129.2, 128.9, 128.0, 125.9, 122.5, 119.3 ppm. IR (KBr): 3472, 3361, 3104, 2172, 1736, 1607, 1569, 1416, 739 cm^{-1}.

HRMS (ESI): calcd. for $C_{27}H_{18}N_2O_2$ + H 403.145; found 403.1441. $[a]_D^{25}$ = +21.8 (c = 0.43, CH_2Cl_2), 90% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (30% 2-propanol/hexane, 1 mL/min), t_{major} = 5.10 min, t_{minor} = 5.44 min.

(*S*)-7-Amino-2-chloro-10-methyl-6,9-diphenyl-6*H*-benzo[*c*]chromene-8-carbonitrile (7fa): Compound **4fa** (47.0 mg, 0.2 mmol) and NaOAc (1 mmol) were heated to reflux in ethanol (2 mL) for 0.5 h. Then the mixture was dried and concentrated. The residue was purified by using flash chromatography on silica gel (10% ethyl acetate/petroleum ether) to give **7fa** (39.0 mg, 93% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.65 (m, 1 H), 7.54–7.29 (m, 9 H), 7.12–7.09 (m, 1 H), 6.87–6.85 (m, 1 H), 6.29 (s, 1 H), 4.12 (s, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 143.0, 138.7, 135.6, 129.7, 129.3, 129.0, 128.9, 128.6, 128.5, 128.1, 128.0, 126.5, 125.3, 123.1, 121.1, 120.3, 116.9, 20.4 ppm. IR (KBr): 3517, 3361, 2192, 1751, 1639, 1601, 1555, 1394, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{19}ClN_2O$ + Na 445.107; found 445.1078. $[a]_D^{25}$ = –238.5 (c = 0.31, CH_2Cl_2), 85% *ee*; the enantiomeric ratio was determined by HPLC on Chiralpak IC column (20% 2-propanol/hexane, 1 mL/min), t_{minor} = 7.61 min, t_{major} = 10.43 min.

Procedure for Converting 5aa to 4aa: Compound **5aa** (13.1 mg) was heated to reflux in CH_2Cl_2 (1 mL) for 5 h. Flash chromatography on silica gel (20% ethyl acetate/petroleum ether) gave **4aa** (11.8 mg, 90% yield) as a pale yellow solid.

Crystal Data for 4ha: $C_{27}H_{20}BrN_3O_3{\cdot}H_2O$ (532.39), tetragonal, P4(3)2(1)2, a = 11.9954(8) Å, α = 90°, b = 11.9954(8) Å, β = 90°, c = 36.255(7) Å, γ = 90°, V = 5216.7(11) Å^3, Z = 8, specimen 0.34 × 0.18 × 0.14 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 1.612 mm^{-1}, reflections collected 22217, unique 3420 [R(int) = 0.4527], refinement by Full-matrix least-squares on F^2, data/ restraints/ parameters 3420/6/317, goodness-of-fit on F^2 = 0.916, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0903, $wR2$ = 0.2506, R indices (all data) $R1$ = 0.2889, $wR2$ = 0.3411, largest diff. peak and hole 1.162 and –0.507 e Å^{-3}.

Crystal Data for 4fa: $C_{27}H_{20}ClN_3O_3{\cdot}C_4H_8O_2$ (EtOAc) (558.01), monoclinic, space group $C2/c$, a = 32.3285(19) Å, b = 9.4572(5) Å, c = 20.5404(10) Å, V = 6260.5(6) Å^3, Z = 8, specimen 0.41 × 0.23 × 0.11 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.163 mm^{-1}, reflections collected 47924, independent reflections 7185 [R(int) = 0.0514], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 7185/0/362, goodness-of-fit on F^2 = 1.015, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0925, $wR2$ = 0.2549, R indices (all data) $R1$ = 0.1482, $wR2$ = 0.3076, largest diff. peak and hole 1.094 and –0.519 e Å^{-3}.

CCDC-900158 (for **4fa**) and -900159 (for **4ha**) contain the supplementary crystallographic data 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.

Supporting Information (see footnote on the first page of this article): NMR spectra and HPLC spectra are available in the Supporting Information.

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[1] a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) N. M. Kogan, R. Rabinowitz, P. Levi, D. Gibson, P. Sandor, M. Schlesinger, R. Mechoulam, *J. Med. Chem.* **2004**, *47*, 3800–3806.

[2] a) K. R. Müller-Vahl, U. Schneider, A. Koblenz, M. Jöbges, H. Kolbe, T. Daldrup, H. M. Emrich, *Pharmacopsychiatry* **2002**, *35*, 57–61; b) K. R. Müller-Vahl, H. Prevedel, K. Theloe, H. Kolbe, H. M. Emrich, U. Schneider, *Neuropsychopharmacology* **2003**, *28*, 384–388.

[3] a) A. G. Shavva, S. N. Morozkina, I. V. Ishchenko, I. I. Eliseev, G. L. Starova, S. I. Selivanov, Sh. N. Abusalimov, S. S. Selivanov, I. Y. Kameneva, N. D. Eshchenko, *Bioorg. Khim.* **2007**, *33*, 310–314; b) S. N. Morozkina, S. S. Selivanov, S. I. Selivanov, A. S. Drozdov, N. D. Eshchenko, A. G. Shavva, *Chem. Heterocycl. Compd.* **2009**, *45*, 1313–1318.

[4] a) Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke, S. L. M. Natschke, K. H. Lee, *Tetrahedron* **2001**, *57*, 1559–1563; b) A. V. Kurdyumov, R. P. Hsung, K. Ihlen, J. Wang, *Org. Lett.* **2003**, *5*, 3935–3938; c) Y. Kang, Y. Mei, Y. Du, Z. Jin, *Org. Lett.* **2003**, *5*, 4481–4484; d) Y. Hano, R. Inami, T. Nomura, *Heterocycles* **1993**, *35*, 1341–1350; e) M. P. Paduraru, P. D. Wilson, *Org. Lett.* **2003**, *5*, 4911–4913.

[5] a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; b) K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G. Q. Cao, R. L. Affleck, J. E. Lillig, *J. Am. Chem. Soc.* **2000**, *122*, 9954–9967; c) K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker, G. Q. Cao, *J. Am. Chem. Soc.* **2000**, *122*, 9968–9976.

[6] S. Oh, H. J. Jang, S. K. Ko, Y. Ko, S. B. Park, *J. Comb. Chem.* **2010**, *12*, 548–558.

[7] a) M. Mondal, V. G. Puranik, N. P. Argade, *J. Org. Chem.* **2007**, *72*, 2068–2076; b) A. V. Kurdyumov, R. P. Hsung, K. Ihlen, J. Wang, *Org. Lett.* **2003**, *5*, 3935–3938; c) Y. Kang, Y. Mei, Y. Du, Z. Jin, *Org. Lett.* **2003**, *5*, 4481–4484; d) M. P. Paduraru, P. D. Wilson, *Org. Lett.* **2003**, *5*, 4911–4913.

[8] a) Q. Ren, Y. Gao, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13594–13598; b) B. C. Hong, P. Kotame, C. W. Tsai, J. H. Liao, *Org. Lett.* **2010**, *12*, 776–779.

[9] For recent general reviews, see: a) Y. Sohtome, K. Nagasawa, *Synlett* **2010**, 1–22; b) L. W. Xu, J. Luo, Y. X. Lu, *Chem. Commun.* **2009**, 1807–1821; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; d) J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, *455*, 323–332; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; f) B. List, *Chem. Commun.* **2006**, 819–824.

[10] For selected reviews of organocatalytic cascade reactions, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020.

[11] For selected 1,2-diaminohexane-derived bifunctional thioureas, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; c) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964; d) A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799; e) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653.

[12] For selected cinchona-derived bifunctional thioureas, see: a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832; b) S. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621–631; c) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193; d) A. E. Mattson, A. M. Zuhl, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933; e) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*,

6367–6370; f) S. France, M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth, T. Lectka, *J. Am. Chem. Soc.* **2005**, *127*, 1206–1215; g) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.

[13] For pyrrolidine–thiourea, see: C. L. Cao, M. C. Ye, X. L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904.

[14] a) L. P. Fan, P. Li, X. S. Li, D. C. Xu, M. M. Ge, W. D. Zhu, J. W. Xie, *J. Org. Chem.* **2010**, *75*, 8716–8719; b) J. W. Xie, L. P. Fan, H. Su, X. S. Li, D. C. Xu, *Org. Biomol. Chem.* **2010**, *8*, 2117–2122.

[15] a) J. W. Xie, L. Yue, D. Xue, X. L. Ma, Y. C. Chen, Y. Wu, J. Zhu, J. G. Deng, *Chem. Commun.* **2006**, 1563–1565; b) J. W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. C. Chen, Y. Wu, J. Zhu, J. G. Deng, *Angew. Chem.* **2007**, *119*, 393–396; *Angew. Chem. Int. Ed.* **2007**, *46*, 389–392; c) P. Li, L. L. Luo, X. S. Li, J. W. Xie, *Tetrahedron* **2010**, *66*, 7590–7594.

[16] a) D. Xue, Y. C. Chen, L. F. Cun, Q. W. Wang, J. Zhu, J. G. Deng, *Org. Lett.* **2005**, *7*, 5293–5296; b) T. B. Poulsen, M. Bell, K. A. Jørgensen, *Org. Biomol. Chem.* **2006**, *4*, 63–70; c) T. Y. Liu, H. L. Cui, J. Long, B. J. Li, Y. Wu, L. S. Ding, Y. C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878–1879; d) H. L. Cui, Y. C. Chen, *Chem. Commun.* **2009**, 4479–4486, and references cited therein.

[17] Chiral **2a** was isolated in 56% yield (based on racemic **2a**). Recently we have reported that the kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives catalyzed by Takemoto's catalyst affords 3-nitro-2*H*-chromene derivatives **2** with good enantioselectivities, see ref.[14b].

[18] ORTEP diagram of **4fa**, see Supporting Information.

[19] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th ed., Butterworth Heinemann, **1997**.

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