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An Enantioselective Approach toward 3,4-Dihydroisocoumarin through the Bromocyclization of Styrene-type Carboxylic Acids

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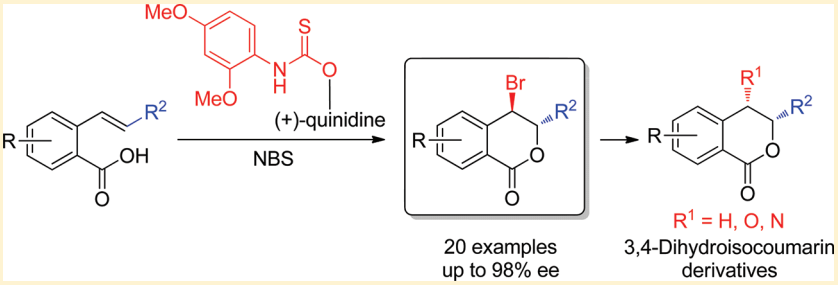
Supporting Information

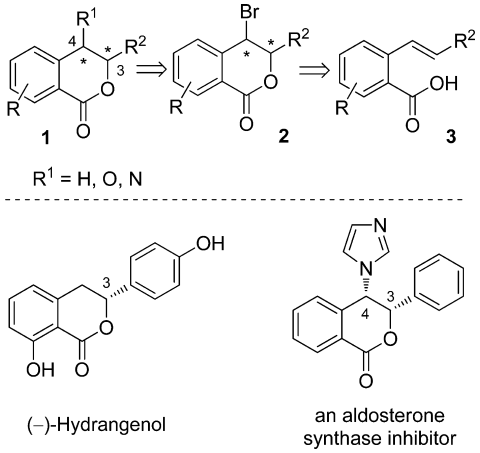


ABSTRACT: A facile and enantioselective approach toward 3,4-dihydroisocoumarin was developed. The method involved an amino-thiocarbamate catalyzed enantioselective bromocyclization of styrene-type carboxylic acids, yielding 3-bromo-3,4-dihydroisocoumarins with good yields and ee's. 3-Bromo-3,4-dihydroisocoumarins are versatile building blocks for various dihydroisocoumarin derivatives in which the Br group can readily be modified to achieve biologically important 4-O-type and 4-N-type 3,4-dihydroisocoumarin systems. In addition, studies indicated that, by refining some parameters, the synthetically useful 5-exo phthalide products could be achieved with good yields and ee's.

INTRODUCTION

3,4-Dihydroisocoumarin is the fundamental unit of many compounds that possess a wide spectrum of biological activity. Of particular interest, 3-substituted 3,4-dihydroisocoumarin (e.g., 3-aryl) core **1** (R^1 = H) has attracted much attention since this structural motif is present in many natural products and bioactive molecules.[1] The related frameworks of **1**, which include the 4-O-type (R^1 = O) and the 4-N-type (R^1 = N) 3,4-dihydroisocoumarins, are also attractive targets for synthetic chemists as they constitute a number of important pharmaceuticals (Scheme 1).[2]

Scheme 1. Biologically Important 3,4-Dihydroisocoumarins



Over the past decades, significant efforts have been devoted to the construction of isocoumarin systems.[3] Their asymmetric variants, however, are scattered. A well-known approach is the asymmetric lithiation process, which involved the use of stoichiometric amounts of chiral amine.[4] Other methods, including Sharpless asymmetric dihydroxylation,[5] rhodium-catalyzed intermolecular [4 + 2] annulation,[6] and enzymatic catalysis,[7] were also applied to construct the 3,4-dihydroisocoumarin skeletons. Despite the attractive biological properties of 3,4-dihydroisocoumarins, a general and versatile approach toward the enantioselective synthesis of this class of compounds, however, is still in its infancy. Herein, we report a diversified approach toward the enantioselective synthesis of 3,4-dihydroisocoumarin **1** and its related skeletons.

We rationalized that 3,4-dihydroisocoumarin **1** could be originated from 4-bromo-3,4-dihydroisocoumarin **2**, which could be furnished by the catalytic asymmetric bromocyclization of styrene-type carboxylic acid **3**. Although bromocyclization of **3** seems routine based on the history of bromolactonization over the past decades, the breakthrough of the asymmetric variants only appeared recently. The scopes were rather limited, and to date, the enantioselective halocyclization of **3** remains unknown.[8]

In addition, there are two other challenges that exist in the halocyclization of the styrene-type carboxylic acid **3**: (1) The rigidity of the skeleton due to the aryl ring significantly reduced

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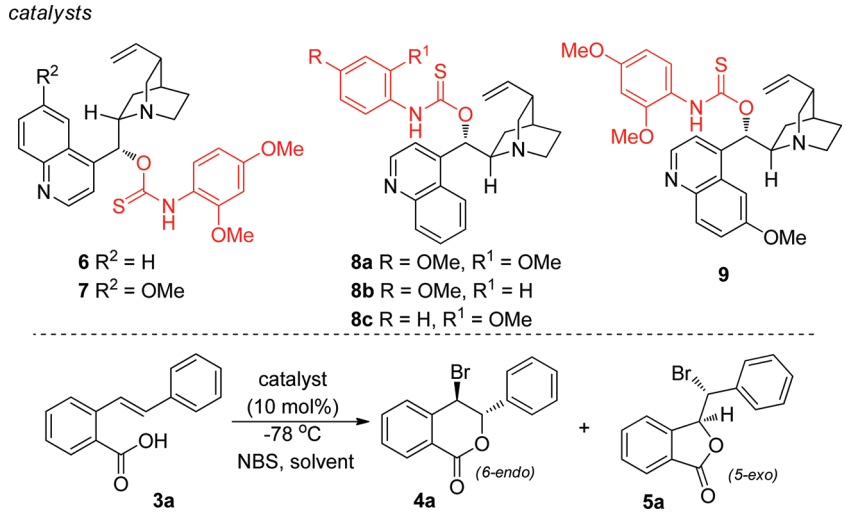
Table 1. Optimization of the Bromocyclization of 3a[a]

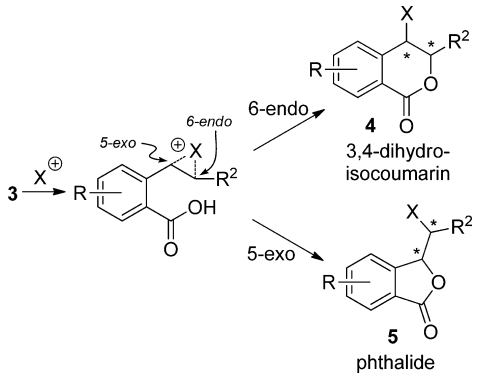


entry	catalyst	solvent	time (d)	% yield[b] (4a:5a)[c]	% ee 4a
1	6	CH_2Cl_2	5	trace (ND)	ND
2	7	CH_2Cl_2	5	trace (ND)	ND
3	8a	CH_2Cl_2	5	75 (5:1)	86
4	9	CH_2Cl_2	5	96 (5.5:1)	92
5[d]	9	CH_2Cl_2	6	96 (5.5:1)	92
6	8b	CH_2Cl_2	6	30 (5:1)	60
7	8c	CH_2Cl_2	6	29 (5:1)	63
8	9	hexane/$CHCl_3$ (1:1)	6	73 (3:1)	73
9	9	PhMe/$CHCl_3$ (2:1)	6	65 (3:1)	84

[a]Reactions were carried out with olefinic acid **3a** (0.1 mmol), catalyst (0.01 mmol), and NBS (0.12 mmol) in solvent (3.5 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Reaction was conducted on a 4.0 mmol scale.

the cyclization efficiency. In fact, at room temperature, the bromocyclization of **3a** (Table 1) using NBS was sluggish even in the presence of a Lewis base catalyst.[9] (2) Both 6-endo (product **4**) and 5-exo (product **5**) cyclization pathways (Scheme 2) may happen depending on various factors (vide infra).[10]

Scheme 2. 6-endo and 5-exo Cyclization



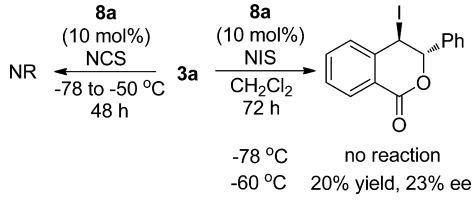
RESULTS AND DISCUSSION

6-endo Cyclization of Styrene-type Carboxylic Acids 3.

Previously, we have reported the use of amino-thiocarbamate as the catalyst in the enantioselective bromocyclization.[8d,j−m] In this context, we attempted to apply this catalytic protocol to the cyclization of styrene-type carboxylic acid. Thus, the bromocyclization of **3a** was selected as a model reaction and NBS was used as the stoichiometric brominating agent. The amino-thiocarbamate catalysts that contain 2,4-dimethoxyphenyl units were investigated initially. After a round of catalyst screening, it was surprising to find that cinchonidine- and quinine-derived amino-thiocarbamates **6** and **7** were unable to promote the reaction (Table 1, entries 1 and 2). In sharp contrast, cinchonine- and quinidine-derived amino-thiocarbamates **8a** and **9** were able to promote the desired reaction and furnished isocoumarin **4a** with appreciable ee's and yields (Table 1, entries 3 and 4). This is quite unusual since cinchonidine and quinine are commonly regarded as the pseudoenantiomeric catalyst skeletons of cinchonine and quinidine, respectively.[11] This drastic difference implies that the vinyl substituent may play a crucial role in this type of reaction.

Next, examinations on the methoxylated phenyl unit of the thiocarbamate showed that the 2,4-dimethoxyphenyl unit appeared to be critical for the reaction (Table 1, entries 6 and 7). Other halogen sources, including *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), were examined, and the reactions were sluggish with low enantioselectivities (Scheme 3).[12]

Scheme 3. Halocyclization of 3a Using NCS and NIS



A survey on the solvent effect was also performed. Interestingly, solvent blends, including hexane/chloroform and

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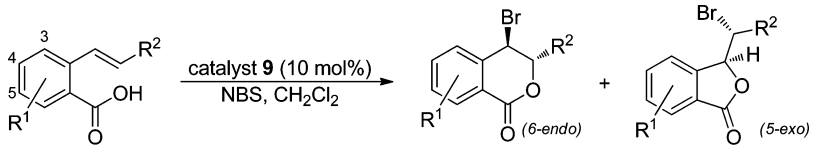
Table 2. Asymmetric Bromocyclization of 3[a]



3 4 5

entry	substrate, R^1, R^2	T (°C), time (d)	% yield[b] (4:5)[c]	% ee 4
1	**3b**, H, 4-FC_6H_4	−50, 4	98 (9:1)	91
2	**3c**, H, 4-ClC_6H_4	−60, 4	95 (3.2:1)	95
3	**3d**, H, 4-BrC_6H_4	−60, 4	94 (2.5:1)	95
4	**3e**, H, 4-$CH_3C_6H_4$	−78, 3	95 (15:1)	83
5	**3f**, H, 2-naphthyl	−60, 5	95 (10:1)	88
6	**3g**, H, 4-$AcOC_6H_4$	−60, 5	87 (2.5:1)	80
7	**3h**, H, 4-$CH_3OC_6H_4$	−78, 3	99 (40:1)	24
8	**3i**, H, 3-$CH_3C_6H_4$	−65, 4	97 (7.4:1)	90
9	**3j**, 3-CH_3, C_6H_5	−78, 5	97 (50:1)	84
10	**3k**, 4-F, C_6H_5	−60, 4	98 (8.5:1)	90
11	**3l**, 4-Cl, C_6H_5	−60, 7	91 (8.4:1)	89
12	**3m**, 5-F, C_6H_5	−60, 4	97 (12:1)	93

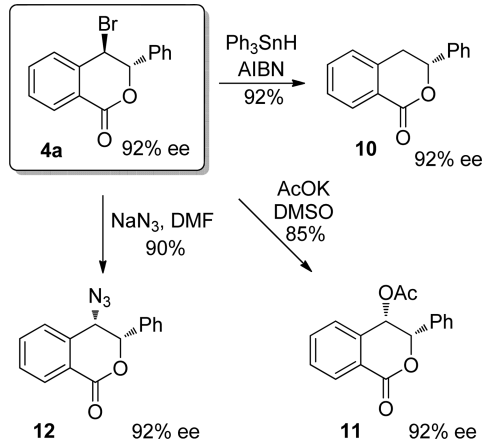
[a]Reactions were carried out with olefinic acid **3** (0.1 mmol), catalyst **9** (0.01 mmol), and NBS (0.12 mmol) in solvent (3.5 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR.

toluene/chloroform, which were proven to be useful in a number of organocatalytic enantioselective halogenation systems,[8] had a deteriorated effect on the reaction rate, ee, and the 6-endo/5-exo selectivity (Table 1, entries 8 and 9).

With the optimized conditions in hand (Table 1, entry 4), a variety of styrene-type carboxylic acids were subjected to investigation. In general, excellent reaction yields were achieved (Table 2). For the substrates with electron-deficient R^2 aryl substituents, good to excellent ee's were obtained (Table 2, entries 1−3). Other R^2 substituents, including 4-methylphenyl, 2-naphthyl, 4-acetoxyphenyl, and 3-methylphenyl groups, were also examined, which returned with high ee's and high endo/exo ratios (Table 2, entries 4−6, 8). For the substrates with R^2 as a 4-methoxyphenyl group, although an excellent endo/exo ratio was observed, a relatively low ee was obtained (Table 2, entry 7).[13] Other than the R^2 group, some substrates with different substituents in the benzoic acid moiety were also investigated, and good yields, ee's, and high endo/exo ratios were observed (Table 2, entries 9−12). The absolute configuration of isocoumarins **4** were assigned based on the X-ray crystallographic structure of **4f**.

Conversion of 3-Bromo-3,4-dihydroisocoumarin 4a into Other Useful Building Blocks. To demonstrate the practicality of this approach toward the enantioenriched 3,4-dihydroisocoumarin system, we attempted to scale up the reaction to 4.0 mmol, in which the efficiency and the enantioselectivity were maintained (Table 1, entry 5). The derivatization of bromoisocoumarin **4** was then performed. It was found that the Br atom in **4a** could be removed by the Ph_3SnH/AIBN reduction, yielding 3-phenyl-3,4-dihydroisocoumarin (**10**), which is a very important core of many drug molecules (Scheme 4).[1] The Br unit in **4a** could readily be converted to other functional groups. For instance, a nucleophilic acetate displacement of **4a** allowed us to obtain the 4-oxygenated 3,4-dihydroisocoumarin core **11**, which is the fundamental unit of a proinflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and an enzyme cyclooxygenase-2 (COX-2) inhibitor.[2f] In addition, an azide

Scheme 4. Conversion of 4a into Derivatives 10−12



substitution of **4a** using sodium azide gave the nitrogen-substituted core **12**, which resembles the structures of an aldosterone synthase inhibitor that is used for the treatment of disease mediated by an aldosterone synthase (CYP11B2).[2a]

On the other hand, **4a** is manipulated with a two-step sequence: (1) reduction of the lactone in **4a** to form the epoxy alcohol **13** and (2) an acid-promoted epoxide opening, followed by an intramolecular etherification, yielding enantioenriched alcohol **14**, which is a useful skeleton for natural product synthesis (Scheme 5).[14] The structure of **14** was confirmed by an X-ray study.

Investigation of the Factors That Favor the Formation of 5-exo Cyclized Product 5. In the studies of dihydrocoumarin **4** synthesis, it was found that many substrates have a bias in favor of the formation of 6-endo product **4**,[15] which could be attributed to the following reason(s): (1) the skeleton rigidity restricted the formation of 5-exo product **5** and/or (2) the electron-withdrawing property of the carboxylic acid group destabilized the 5-exo cyclization pathway. Despite our success in the catalytic approach toward the enantioenriched 6-endo product **4**, understanding the factors that can

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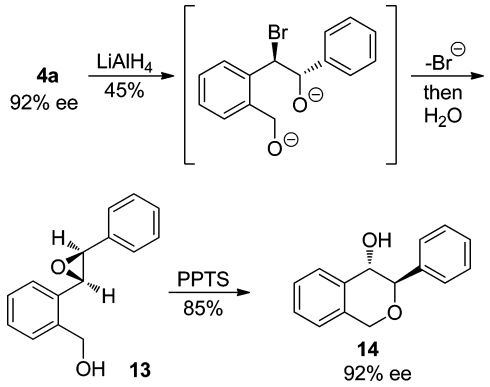
Scheme 5. Conversion of 4a into 14



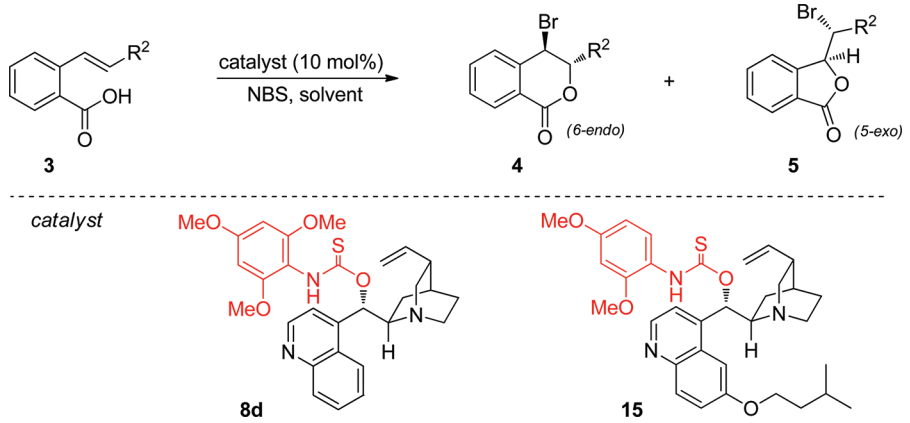
favor the formation of 5-exo product **5** is equally important since the phthalide **5** is also a useful building block.[16]

During the substrate investigation, it appears that the 5-exo/6-endo ratio is partly dependent on the nature of the substrates in which typically a more electron-rich R^2 group favored the 6-endo product. For instance, the electron-deficient R^2, in particular, the 3-substituted aryl system, gave higher 5-exo selectivity (Table 3, entries 1−4). A 1:4.5 ratio of 6-endo/5-exo product was obtained when using the 3,5-bis(trifluoromethyl)-phenyl substrate **3p** (Table 3, entry 3); the substrates with a relatively more electron-deficient R^2 group returned with more 5-exo product **5**, preferentially due to the destabilization of the 6-endo cyclization pathway (Scheme 2). For the R^2 as a 2-substituted aryl group, the product returned with high 5-exo selectivity; the 6-endo/5-exo ratio was 1:15.4 when R^2 was a 2-chlorophenyl group (Table 3, entry 5). Other than some specific aryl systems, R^2 as a hydrogen or other alkyl substituents also returned with good 5-exo selectivity (Table 3, entries 6−8).

Although we have identified some features of the substrates that might be responsible for the higher 5-exo selectivity, the enantioselectivities of phthalide **5** in these reaction were generally not very satisfactory. Thus, we further investigated other parameters that could favor the phthalide product **5** formation with a higher enantioselectivity.

Studies showed that reaction in chloroform favored a better 5-exo product yield (Table 3, entry 10 vs 11).[17] Moreover, a better ee of the 5-exo product was obtained when changing the quinidine-derived catalyst **9** to cinchonine-derived catalyst **8a** (Table 3, entry 11 vs 13). Additionally, the ee of phthalide **5** could further be improved by using the 2,4,6-trimethoxyphenyl thiocarbamate catalyst **8d** (Table 3, entry 13 vs 15). Attempts to apply these modifications to some electron-deficient substrates,

Table 3. Studies on Optimizing the Formation of 5[a]



entry	substrate, R^2	cat.	solvent	temp (°C), time (d)	% yield[b] (4:5)[c]	% ee (4, 5)
1	**3n**, 3-ClC_6H_4	**9**	CH_2Cl_2	−60, 6	89 (1.5:1)	96, −41
2	**3o**, 3-$NO_2C_6H_4$	**9**	CH_2Cl_2	−30, 4	96 (1:3.8)	98, −47
3	**3p**, 3,5-$(CF_3)_2C_6H_3$	**9**	CH_2Cl_2	−30, 6	84 (1:4.5)	93, −17
4	**3q**, 4-$CF_3C_6H_4$	**9**	CH_2Cl_2	−45, 5	90 (1:2)	88, −44
5	**3r**, 2-ClC_6H_4	**9**	CH_2Cl_2	−45, 5	92 (1:15.4)	33, −32
6	**3s**, H	**9**	CH_2Cl_2	−60, 4	90 (only exo)	NA, −34
7	**3t**, *n*Pr	**9**	CH_2Cl_2	−78, 4	95 (1:7)	53, −12
8	**3u**, cyclohexyl	**9**	CH_2Cl_2	−78, 4	96 (1:8)	58, −28
9	**3a**, C_6H_5	**9**	CH_2Cl_2	−78, 5	96 (5.5:1)	92, −16
10	**3a**, C_6H_5	**9**	CH_2Cl_2	−60, 5	93 (4.5:1)	88, −13
11	**3a**, C_6H_5	**9**	$CHCl_3$	−60, 5	97 (2.1:1)	77, 18
12	**3a**, C_6H_5	**8a**	CH_2Cl_2	−78, 5	75 (5:1)	86, 24
13	**3a**, C_6H_5	**8a**	$CHCl_3$	−60, 5	90 (2.7:1)	82, 51
14	**3a**, C_6H_5	**8d**	CH_2Cl_2	−78, 5	92 (3.1:1)	77, 70
15	**3a**, C_6H_5	**8d**	$CHCl_3$	−60, 5	91 (2:1)	73, 79
16	**3n**, 3-ClC_6H_4	**8d**	$CHCl_3$	−50, 4	89 (1:2.3)	73, 66
17	**3q**, 4-$CF_3C_6H_4$	**8d**	$CHCl_3$	−45, 5	90 (1:4)	58, 53
18	**3a**, C_6H_5	**15**	CH_2Cl_2	−78, 5	93 (5.3:1)	91, −25

[a]Reactions were carried out with acid **3** (0.1 mmol), catalyst (0.01 mmol), and NBS (0.12 mmol) in the absence of light. [b]Isolated yield. [c]Determined by ^1H NMR.

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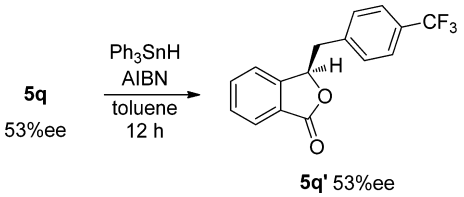
such as **3n** and **3q**, allowed us to obtain better yields and enantioselectivities of the phthalides **5n** and **5q** (Table 3, entries 1 vs 16, 4 vs 17). The absolute configuration of 5-exo products **5** was assigned by converting **5q** to the corresponding debrominated phthalide **5q′**, which was compared with the literature known compound (Scheme 6).[18,19]

Scheme 6. Debromination of 5q

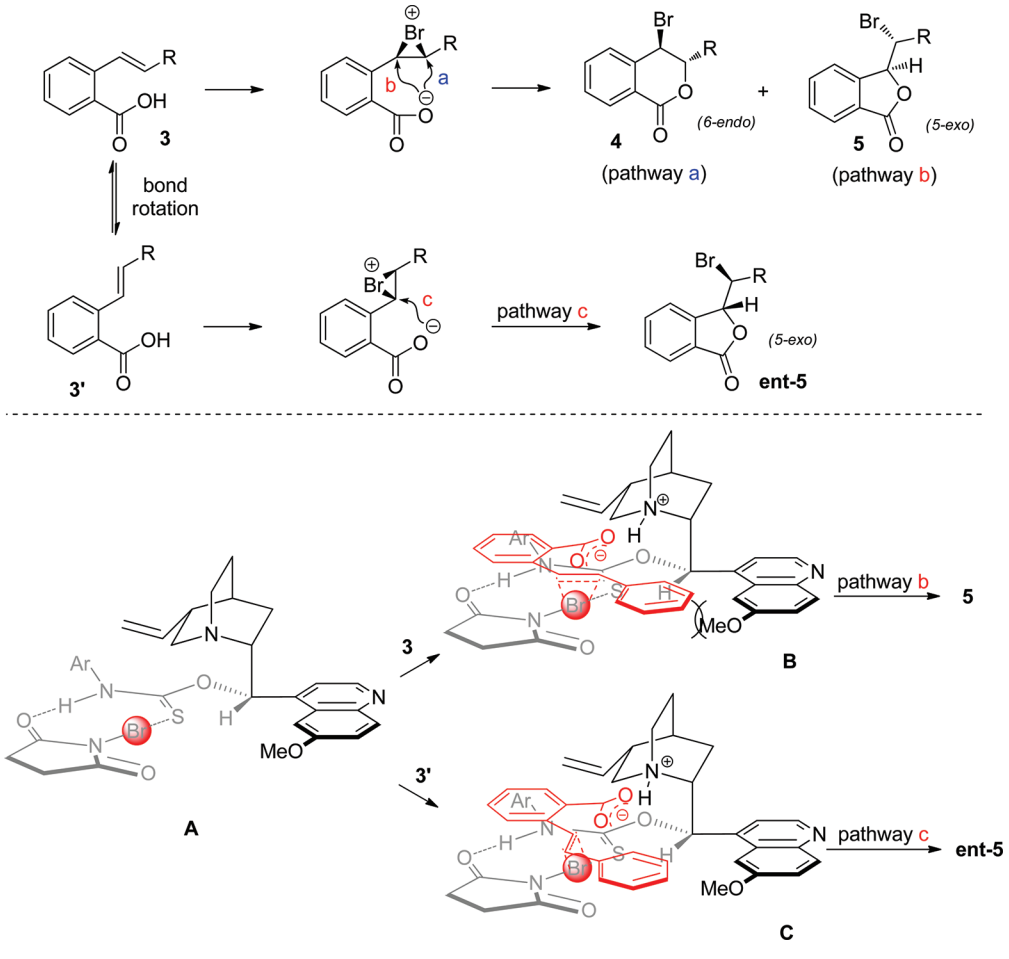


It is important to note that, apart from the solvent effect, it seems that the catalyst structure is also responsible to the 5-exo product selectivity. For this type of cyclization, potentially there are three different pathways (Scheme 7): (1) 6-endo cyclization of conformer **3** (pathway a), (2) 5-exo cyclization of conformer **3** (pathway b), and (3) 5-exo cyclization of conformer **3′** (pathway c). The formation of more 5-exo product **5** could be attributed to the more favorable cyclization (pathway b) when using the cinchonine-derived catalyst; an increase in ee's of **5** was observed when changing the catalyst from **9** to **8** (Table 3, entries 10 vs 13, 12 vs 14). In fact, increasing the bulkiness of the 6-alkoxy substituent of quinoline in catalyst **9** (i.e., catalyst **15**) gave more **ent-5** product, as reflected by the higher, but negative, ee value (Table 3, entry 9 vs 18). On the basis of our previous mechanistic picture (Scheme 7, complex **A**),[8j] a possible explanation is that the 6-methoxy group of quinoline in the quinidine-derived catalyst **9** may serve as a steric-screening group, which suppresses the formation of 5-exo product **5** (Scheme 7, **B** → **5**, pathway b) and favors the formation of more **ent-5** (Scheme 7, **C** → **ent-5**, pathway c), that is, reduce the ee of **5**. Although the roles of the solvent and thiocarbamate's aryl group on the 5-exo/6-endo selectivity remain unclear and are subjected to further investigation, the above-mentioned results suggest that, in addition to the selection of a suitable substrate, further refinement of other parameters might open an avenue toward the nonclassical, but synthetically useful, 5-exo cyclized phthalide product **5**.

CONCLUSION

In summary, we have developed a facile, efficient, and enantioselective approach toward 4-bromo-3-aryl-3,4-dihydroisocoumarins **4** through an amino-thiocarbamate-catalyzed bromocyclization process. **4** is a versatile building block for the synthesis of biologically important 3-substituted 3,4-dihydroisocoumarins and its related cores. Studies indicate that, other than the substrate selection, adjusting some parameters, such as solvent and catalyst structure, may allow us to obtain the synthetically useful 5-exo phthalide product **5** with good yield and ee. Further investigation on other applications and studies of the mechanism are underway.

Scheme 7. Plausible Pathways toward 5 and ent-5



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EXPERIMENTAL SECTION

General. All reactions that required anhydrous conditions were carried by standard procedures under a nitrogen atmosphere. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. Infrared spectra were recorded on an FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). Melting points were determined on a melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz and a 500 MHz spectrometer. Chemical shifts (δ) are reported in parts per million relative to TMS (δ 0.00) for the ^1H NMR and to chloroform (δ 77.0) for the ^{13}C NMR measurements. Low-resolution mass spectra were obtained on a mass spectrometer in ESI mode. High-resolution mass spectra were obtained from EI or ESI mass spectrometers. Enantiomeric excesses were determined by HPLC analysis using analytical chiral columns. Optical rotations were recorded on a polarimeter equipped with a sodium lamp source (589 nm). Analytical thin-layer chromatography (TLC) was performed with precoated TLC plates (silica gel 60 F254 on aluminum sheets). Flash chromatography separations were performed on 60 (0.040−0.063 mm) mesh silica gel. Amino-thiocarbamate catalysts **6**−**9**[8d] and carboxylic acid **3**[20] were prepared according to the literature proceudures.

General Procedure for the Preparation of Racemic 4 and 5. To a mixture of **3** (0.1 mmol, 1.0 equiv) and Ph_3PS (5.9 mg, 0.02 mmol, 0.2 equiv) in CH_2Cl_2 (3.5 mL) at low temperature in the dark under N_2 was added *N*-bromosuccinimide (26.7 mg, 0.15 mmol, 1.5 equiv). After the reaction mixture was continued for 24 h, the reaction was quenched with saturated Na_2SO_3 (4.0 mL) at the reaction temperature and then was warmed to 25 °C. The solution was diluted with water (4.0 mL) and extracted with CH_2Cl_2 (3 × 6 mL). The combined extracts were washed with brine (10.0 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to yield (50−70%) of the corresponding racemic isocoumarins **4** and **5**.

Representative Procedure for the Enantioselective Bromocyclization of 3. To a solution of acid **3a** (0.1 mmol, 1.0 equiv), catalyst **9** (6.0 mg, 0.01 mmol, 0.1 equiv) in CH_2Cl_2 (3.5 mL) at low temperature in the dark under N_2 was added *N*-bromosuccinimide (21.2 mg, 0.12 mmol, 1.2 equiv). The resulting mixture was stirred at −78 °C for 5 days. The reaction was quenched with saturated Na_2SO_3 (2.0 mL) at the reaction temperature and then was warmed to 25 °C. The solution was diluted with water (3.0 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5.0 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to yield the corresponding isocoumarin **4a**. White solid, mp 130.7−132.5 °C: $[\alpha]_D^{26}$ −70.2 (*c* 1.0, $CHCl_3$, 92% ee); IR (KBr): 3013, 2361, 1712, 1385, 1242, 1119, 962, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50−7.45 (m, 2H), 7.33−7.25 (m, 5H), 5.91 (d, *J* = 4.4 Hz, 1H), 5.57 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 137.7, 136.3, 134.6, 130.4, 129.8, 128.9, 128.8, 128.3, 126.4, 124.1, 84.1, 46.1; HRMS (EI) Calcd for $C_{15}H_{11}O_2$ *m*/*z* [M − Br]$^+$: 223.0754; found, 223.0765; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 18.4 min (minor), t_2 = 19.8 min (major).

(*E*)-2-Styryl Benzoic Acid (3a). White solid: ^1H NMR (300 MHz, $CDCl_3$): δ 11.43 (brs, 1H), 8.13−8.08 (m, 2H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.59−7.57 (m, 3H), 7.41−7.27 (m, 4H), 7.05 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 140.1, 137.3, 133.1, 131.8, 131.6, 128.7, 127.9, 127.5, 127.3, 127.2, 126.9; MS (ESI) *m*/*z* [M − H]$^-$: 223.2.

(*E*)-2-(4-Fluorostyryl)benzoic Acid (3b). White solid, mp 149.0−150.3 °C: IR (KBr): 3069, 2972, 2863, 2632, 1683, 1507, 1402, 1229, 829, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.54 (brs, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 16.1 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.61−7.51 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.10−6.07 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 162.5 (d, *J* = 246.3 Hz), 140.1, 133.3 (d, *J* = 19.4 Hz), 133.2, 131.7, 130.6, 128.5 (d, *J* = 7.5 Hz), 127.3, 127.1, 115.6 (d, *J* = 21.5 Hz); HRMS (ESI) Calcd for $C_{15}H_{10}FO_2$ *m*/*z* [M − H]$^-$: 241.0670; found, 241.0671.

(*E*)-2-(4-Chlorostyryl)benzoic Acid (3c). White solid: ^1H NMR (300 MHz, $CDCl_3$): δ 11.0 (brs, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 16.4 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.41−7.32 (m, 3H), 6.97 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 139.9, 135.8, 133.6, 133.2, 131.7, 130.4, 128.9, 128.15, 128.06, 127.5, 127.3, 127.2; MS (ESI) *m*/*z* [M − H]$^-$: 257.2.

(*E*)-2-(4-Bromostyryl)benzoic Acid (3d). White solid, mp 179.8−181.3 °C: ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 16.3 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.58 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.51−7.36 (m, 5H), 6.95 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 139.9, 136.3, 133.2, 131.8, 131.7, 130.5, 128.4, 128.3, 127.5, 127.3, 127.2, 121.8; MS (ESI) *m*/*z* [M − H]$^-$: 301.1.

(*E*)-2-(4-Methylstyryl)benzoic Acid (3e). White solid: ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 16.1 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 16.1 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 140.4, 137.9, 134.6, 133.1, 131.8, 131.6, 129.4, 127.2, 127.1, 127.0, 126.9, 126.5, 21.3; MS (ESI) *m*/*z* [M − H]$^-$: 237.1.

2-[(*E*)-2-(2-Naphthyl)ethenyl]carboxylic Acid (3f). White solid: ^1H NMR (300 MHz, DMSO-d_6): δ 8.08 (d, *J* = 16.4 Hz, 1H), 8.00−7.88 (m, 6H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55−7.47 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 137.8, 134.7, 133.2, 132.7, 131.9, 130.7, 130.3, 129.8, 128.3, 127.9, 127.6, 127.5, 126.7, 126.5, 126.1, 123.6; MS (ESI) *m*/*z* [M − H]$^-$: 273.2.

(*E*)-2-(4-Acetoxystyryl)benzoic Acid (3g). White solid, mp 179.8−181.7 °C: IR (KBr): 2991, 2870, 2670, 2548, 1758, 1671, 1504, 1300, 1194, 971, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 16.1 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.60−7.55 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 16.1 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.5, 150.3, 140.0, 135.1, 133.1, 131.7, 130.7, 127.9, 127.8, 127.3, 127.2, 121.8, 21.1; HRMS (ESI) Calcd for $C_{17}H_{13}O_4$ *m*/*z* [M − H]$^-$: 281.0819; found, 281.0815.

(*E*)-2-(4-Methoxystyryl)benzoic Acid (3h). White solid: ^1H NMR (300 MHz, MeOD): δ 7.89−7.84 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.54−7.45 (m, 3H), 7.30 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.04 (d, *J* = 16.3 Hz, 1H), 6.91 (dd, *J* = 6.9 Hz, 2.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, MeOD): δ 171.2, 161.1, 140.5, 133.1, 131.8, 131.7, 130.4, 129.1, 127.8, 127.5, 126.1, 115.1, 55.7; MS (ESI) *m*/*z* [M − H]$^-$: 253.1.

(*E*)-2-(3-Methylstyryl)benzoic Acid (3i). White solid: ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 16.4 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.40−7.35 (m, 3H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 16.1 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 140.3, 138.2, 137.3, 133.1, 132.0, 131.6, 128.8, 128.6, 127.7, 127.34, 127.30, 127.2, 124.1, 21.4; MS (ESI) *m*/*z* [M − H]$^-$: 237.1.

(*E*)-3-Methyl-2-styryl Benzoic Acid (3j). White solid: ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.55−7.45 (m, 4H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.33−7.29 (m, 2H), 6.57 (d, *J* = 16.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 139.2, 137.4, 137.3, 134.6, 133.7, 129.5, 128.6, 128.5, 127.7, 126.9, 126.6, 126.5, 21.1; MS (ESI) *m*/*z* [M − H]$^-$: 237.0.

(*E*)-4-Fluoro-2-styryl Benzoic Acid (3k). White solid, mp 182.2−182.6 °C: IR (KBr): 3082, 2820, 1682, 1489, 1238, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 7.3, 2.5 Hz, 1H), 8.09 (d, *J* = 16.5 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.44−7.29 (m, 4H), 7.08−7.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 165.65 (d, *J* = 252.7 Hz), 143.6 (d, *J* = 8.6 Hz), 136.9, 134.6 (d, *J* = 9.7 Hz), 133.0, 128.8, 128.3, 127.1, 126.5, 123.2, 114.4 (d, *J* = 22.1 Hz), 113.9 (d, *J* = 22.6 Hz); HRMS (ESI) Calcd for $C_{15}H_{10}FO_2$ *m*/*z* [M − H]$^-$: 241.0670; found, 241.0671.

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(*E*)-4-Chloro-2-styryl Benzoic Acid (3l). White solid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93−7.86 (m, 3H), 7.57 (d, J = 7.3 Hz, 2H), 7.45−7.41 (m, 3H), 7.38−7.27 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.7, 140.0, 136.8, 132.3, 132.1, 128.7, 128.2, 128.1, 127.1, 126.7, 126.1, 125.5; MS (ESI) m/z [M − H]$^-$: 257.0.

(*E*)-5-Fluoro-2-styryl Benzoic Acid (3m). White solid, mp 182.8−184.7 °C: IR (KBr): 2972, 2812, 1680, 1573, 1412, 1254, 1134, 984 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 16.1 Hz, 1H), 7.80 (dd, J = 9.4, 2.9 Hz, 1H), 7.73 (dd, J = 8.8, 5.6 Hz, 1H), 7.55 (d, J = 7.3 Hz, 2H), 7.41−7.26 (m, 4H), 6.98 (d, J = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 161.5 (d, J = 246.8 Hz), 137.2, 136.6, 132.0, 129.3 (d, J = 7.5 Hz), 128.7, 128.5, 128.1, 126.9, 126.4, 120.5 (d, J = 21.5 Hz), 118.2 (d, J = 23.7 Hz); HRMS (ESI) Calcd for $C_{15}H_{10}FO_2$ m/z [M − H]$^-$: 241.0670; found, 241.0680.

(*E*)-2-(3-Chlorostyryl)benzoic Acid (3n). White solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 16.1 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.52 (s, 1H), 7.45−7.24 (m, 4H), 6.95 (d, J = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 139.8, 139.2, 134.6, 133.3, 131.8, 130.4, 129.9, 129.1, 127.8, 127.6, 127.5, 127.3, 126.9, 125.0; MS (ESI) m/z [M − H]$^-$: 257.0.

(*E*)-2-(3-Nitrostyryl)benzoic Acid (3o). Light yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.15−8.00 (m, 3H), 7.90−7.84 (m, 2H), 7.69 (t, J = 7.9 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 148.3, 139.1, 137.3, 132.6, 132.0, 130.4, 130.3, 130.1, 129.9, 128.4, 128.0, 127.0, 122.2, 120.9; MS (ESI) m/z [M − H]$^-$: 268.1.

(*E*)-2-[3,5-Bis(trifluoromethyl)styryl]benzoic Acid (3p). White solid, mp 197.1−198.5 °C: IR (KBr): 3089, 2887, 2656, 1687, 1573, 1142, 1254, 984 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.34 (d, J = 16.4 Hz, 1H), 8.21 (s, 2H), 8.05 (d, J = 7.6 Hz, 1H), 7.93−7.87 (m, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ 168.5, 141.5, 139.1, 133.2, 132.6 (q, J = 32.8 Hz), 131.8, 130.4, 129.1, 128.6, 128.2, 127.7, 124.5 (q, J = 270.5 Hz), 121.5; HRMS (ESI) Calcd for $C_{17}H_9F_6O_2$ m/z [M − H]$^-$: 359.0512; found, 359.0509.

(*E*)-2-(4-Trifluoromethylstyryl)benzoic Acid (3q). White solid, mp 148.6−149.6 °C: IR (neat): 3068, 2986, 2876, 2650, 1686, 1415, 1332, 1111, 1069, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20−8.14 (m, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.66−7.58 (m, 5H), 7.42 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 140.8, 139.6, 133.4, 131.8, 130.2, 129.6 (q, J = 32.3 Hz), 127.9, 127.5, 127.3, 127.0, 125.65, 125.60, 124.2 (q, J = 269.9 Hz); HRMS (ESI) Calcd for $C_{16}H_{10}F_3O_2$ m/z [M − H]$^-$: 291.0638; found, 291.0641.

(*E*)-2-(2-Chlorostyryl)benzoic Acid (3r). White solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 16.4 Hz, 1H), 7.79 (t, J = 8.5 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.45−7.39 (m, 3H), 7.31−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 140.0, 135.4, 133.6, 133.3, 131.7, 130.1, 129.7, 128.8, 127.81, 127.77, 127.7, 127.3, 127.1, 127.0; MS (ESI) m/z [M − H]$^-$: 257.1.

2-Vinylbenzoic Acid (3s). White solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 7.6 Hz, 1H), 7.65−7.53 (m, 3H), 7.38 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 16.8 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 140.7, 136.1, 133.1, 131.3, 127.7, 127.5, 127.1, 116.8; MS (ESI) m/z [M − H]$^-$: 147.0.

2-[(*E*)-pent-1-enyl] Benzoic Acid (3t). Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.19 (brs, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.33−7.26 (m, 2H), 6.13 (dt, J = 15.9 Hz, 6.8 Hz, 1H), 2.27 (dt, J = 7.1 Hz, 2H), 1.55 (tq, J = 7.4 Hz, 7.1 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 140.7, 134.2, 132.9, 131.2, 128.7, 127.5, 126.8, 126.5, 35.2, 22.4, 13.7; MS (ESI) m/z [M − H]$^-$: 189.1.

2-[(*E*)-2-Cyclohexylvinyl] Benzoic Acid (3u). Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.10 (brs, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.33−7.24 (m, 2H), 6.13 (dd, J = 15.8 Hz, 6.7 Hz, 1H), 2.24−2.17 (m, 1H), 1.89−1.69 (m, 4H), 1.42−1.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 140.9, 140.0, 132.8, 131.2, 127.4, 126.9, 126.5, 126.2, 41.2, 32.8, 26.2, 26.0; MS (ESI) m/z [M − H]$^-$: 229.1.

(3*S*,4*R*)-4-Bromo-3,4-dihydro-3-phenylisochromen-1-one (4a).[21] White solid, mp 130.7−132.5 °C: $[\alpha]_D^{26}$ −70.2 (c 1.0, $CHCl_3$, 92% ee); IR (KBr): 3013, 2361, 1712, 1385, 1242, 1119, 962, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.3 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.50−7.45 (m, 2H), 7.33−7.25 (m, 5H), 5.91 (d, J = 4.4 Hz, 1H), 5.57 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 137.7, 136.3, 134.6, 130.4, 129.8, 128.9, 128.8, 128.3, 126.4, 124.1, 84.1, 46.1; HRMS (EI) Calcd for $C_{15}H_{11}O_2$ m/z [M − Br]$^+$: 223.0754; found, 223.0765; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 18.4 min (minor), t_2 = 19.8 min (major).

(*R*)-3-[(*S*)-Bromo(phenyl)methyl]isobenzofuran-1(3*H*)-one (5a). White solid: 79% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.5 Hz, 1H), 7.65 (dt, J = 7.8, 1.1 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.53 (dt, J = 7.4, 0.5 Hz, 1H), 7.41 (dd, J = 8.0, 1.4 Hz, 2H), 7.34−7.28 (m, 3H), 5.94 (d, J = 6.0 Hz, 1H), 5.23 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2; 146.2, 135.9, 133.8, 129.9, 129.0, 128.61, 128.57, 126.7, 125.7, 123.8, 82.5, 53.4; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 26.9 min (minor), t_2 = 33.4 min (major).

(3*S*,4*R*)-4-Bromo-3-(4-fluorophenyl)-3,4-dihydroisochromen-1-one (4b). White solid, mp 113.2−115.0 °C: $[\alpha]_D^{28}$ −34.6 (c 1.0, $CHCl_3$, 91% ee); IR (KBr): 3425, 2958, 1727, 1514, 1266, 1118, 1085 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.9 Hz, 1H), 7.65−7.60 (m, 1H), 7.53−7.47 (m, 2H), 7.31−7.26 (m, 2H), 7.05−7.00 (m, 2H), 5.84 (d, J = 5.6 Hz, 1H), 5.51 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 162.8 (d, J = 247.4 Hz), 137.7, 134.7, 132.2, 130.5, 129.9, 128.6 (d, J = 7.0 Hz), 128.5, 123.9, 115.8 (d, J = 22.1 Hz), 83.5, 46.2; HRMS (EI) Calcd for $C_{15}H_{10}O_2F$ m/z [M − Br]$^+$: 241.0659; found, 241.0655; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 47.7 min (minor), t_2 = 49.5 min (major).

(3*S*,4*R*)-4-Bromo-3-(4-chlorophenyl)-3,4-dihydroisochromen-1-one (4c). White solid, mp 112.5−114.3 °C: $[\alpha]_D^{28}$ −51.0 (c 1.0, $CHCl_3$, 95% ee); IR (KBr): 3437, 3082, 2910, 2362, 1732, 1255, 1081, 998 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 8.12 (d, J = 7.7 Hz, 1H), 7.59 (dt, J = 7.6, 1.3 Hz, 1H), 7.49−7.44 (m, 2H), 7.30−7.19 (m, 4H), 5.81 (d, J = 5.3 Hz, 1H), 5.47 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 137.6, 135.0, 134.81, 134.76, 130.5, 129.9, 129.0, 128.5, 127.9, 123.9, 83.4, 46.0; HRMS (EI) Calcd for $C_{15}H_{10}O_2BrCl$ m/z [M]$^+$: 335.9547; found, 335.9568; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 33.1 min (minor), t_2 = 36.4 min (major).

(3*S*,4*R*)-4-Bromo-3-(4-chlorophenyl)-3,4-dihydroisochromen-1-one (4d). White solid, mp 130.3−132.3 °C: $[\alpha]_D^{28}$ −64.5 (c 1.0, $CHCl_3$, 95% ee); IR (KBr): 3428, 2910, 2363, 1730, 1257, 1079, 997, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.52−7.45 (m, 4H), 7.18 (d, J = 8.5 Hz, 2H), 5.83 (d, J = 5.3 Hz, 1H), 5.50 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 137.6, 135.3, 134.8, 132.0, 130.5, 129.9, 128.4, 128.2, 123.9, 123.2, 83.4, 45.9; HRMS (ESI) Calcd for $C_{15}H_{10}O_2Br_2$ m/z [M]$^+$: 379.9042; found, 379.9046; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 35.5 min (minor), t_2 = 40.4 min (major).

(3*S*,4*R*)-4-Bromo-3,4-dihydro-3-*p*-tolylisochromen-1-one (4e). White solid, mp 104.6−106.2 °C: $[\alpha]_D^{28}$ −73.4 (c 1.0, $CHCl_3$, 83% ee); IR (KBr): 3033, 1717, 1599, 1264, 1119, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.7 Hz, 1H), 7.59 (dt, J = 7.6, 1.5 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 7.17−7.10 (m, 4H), 5.88 (d, J = 4.4 Hz, 1H), 5.54 (d, J = 4.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 138.9, 137.8, 134.5, 133.4, 130.4, 129.8, 129.5, 128.3, 126.3, 124.2, 84.1, 46.2, 21.1; HRMS (ESI) Calcd for $C_{16}H_{13}BrO_2$ m/z [M − Br]$^+$: 237.0910; found, 237.0912; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 26.7 min (minor), t_2 = 29.4 min (major).

(3*S*,4*R*)-4-Bromo-3,4-dihydro-3-(naphthalen-2-yl)isochromen-1-one (4f). White solid, mp 145.0−146.5 °C: $[\alpha]_D^{28}$ −95.3 (c 1.0, $CHCl_3$, 88% ee); IR (KBr): 3439, 2910, 1732, 1459, 1255, 1113, 1003 cm^{-1};

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^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, J = 7.3 Hz, 1H), 7.83−7.73 (m, 4H), 7.60−7.45 (m, 5H), 7.39 (dd, J = 8.5, 1.7 Hz, 1H), 6.08 (d, J = 4.4 Hz, 1H), 5.69 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 137.7, 134.6, 133.6, 133.1, 132.8, 130.4, 129.9, 128.8, 128.3, 128.2, 127.6, 126.8, 126.7, 126.1, 124.1, 123.3, 84.2, 46.0; HRMS (EI) Calcd for $C_{19}H_{13}O_2Br$ m/z $[M]^+$: 352.0093; found, 352.0104; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 37.3 min (minor), t_2 = 40.3 min (major).

(3*S*,4*R*)-4-Bromo-3-(4-acetoxyphenyl)-3,4-dihydroisochromen-1-one (4g). White solid, mp 136.6−138.5 °C: $[\alpha]_D^{25}$ −58.6 (c 1.0, $CHCl_3$, 80% ee); IR (KBr): 3445, 2951, 1755, 1705, 1511, 1212, 1118, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 5.90 (d, J = 4.4 Hz, 1H), 5.53 (d, J = 4.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 162.9, 150.9, 137.6, 134.7, 133.8, 130.5, 129.9, 128.5, 127.7, 124.0, 122.0, 83.6, 45.9, 21.1; HRMS (EI) Calcd for $C_{17}H_{13}O_4Br$ m/z $[M]^+$: 359.9992; found, 359.9986; HPLC (Daicel Chiralpak IB, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 19.7 min (minor), t_2 = 22.1 min (major).

(3*S*,4*R*)-4-Bromo-3-(4-methoxyphenyl)-3,4-dihydroisochromen-1-one (4h). White solid, mp 108.0−109.8 °C: 24% ee; IR (KBr): 3402, 2962, 1704, 1607, 1518, 1256, 1121, 1022, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 8.5 Hz, 1H), 7.61 (dt, J = 7.4, 1.3 Hz, 1H), 7.48 (dt, J = 7.4, 1.2 Hz, 2H), 7.18 (dt, J = 8.5, 2.8 Hz, 2H), 6.83 (dt, J = 8.9, 2.8 Hz, 2H), 5.84 (d, J = 5.0 Hz, 1H), 5.53 (d, J = 4.8 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 159.9, 137.9, 134.6, 130.4, 129.8, 128.43, 128.36, 127.9, 124.1, 114.1, 83.9, 55.2, 46.4; HRMS (EI) Calcd for $C_{16}H_{13}O_3Br$ m/z $[M]^+$: 332.0043; found, 332.0045; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 26.5 min (major), t_2 = 29.4 min (minor).

(3*S*,4*R*)-4-Bromo-3-(3-methylphenyl)-3,4-dihydroisochromen-1-one (4i). White solid, mp 124.6−126.3 °C: $[\alpha]_D^{27}$ −71.2 (c 1.0, $CHCl_3$, 90% ee); IR (KBr): 3421, 3014, 2919, 1722, 1376, 1242, 1114, 1050, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.3 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.19 (t, J = 7.9 Hz, 1H), 7.12−7.10 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 5.88 (d, J = 4.4 Hz, 1H), 5.57 (d, J = 4.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 138.6, 137.8, 136.2, 134.5, 130.4, 129.8, 129.7, 128.6, 128.3, 127.0, 124.1, 123.4, 84.1, 46.1, 21.4; HRMS (EI) Calcd for $C_{16}H_{13}O_2$ m/z $[M - Br]^+$: 237.0910; found, 237.0906; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm): t_1 = 29.8 min (major), t_2 = 31.6 min (minor).

(3*S*,4*R*)-4-Bromo-3,4-dihydro-5-methyl-3-phenylisochromen-1-one (4j). White solid, mp 133.4−135.1 °C: $[\alpha]_D^{26}$ −111.8 (c 1.0, $CHCl_3$, 84% ee); IR (KBr): 3409, 3024, 1712, 1447, 1377, 1263, 1126, 1077 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.6 Hz, 1H), 7.40−7.24 (m, 5H), 7.16 (d, J = 7.6 Hz, 2H), 6.10 (s, 1H), 5.63 (d, J = 0.6 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 136.8, 136.2, 135.7, 135.4, 129.6, 128.9, 128.6, 128.3, 125.6, 124.6, 83.7, 42.7, 17.9; HRMS (EI) Calcd for $C_{16}H_{13}O_2$ m/z $[M - Br]^+$: 237.0910; found, 237.0909; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 16.7 min (major), t_2 = 20.8 min (minor).

(3*S*,4*R*)-4-Bromo-6-fluoro-3,4-dihydro-3-phenylisochromen-1-one (4k). White solid, mp 122.0−124.0 °C: $[\alpha]_D^{25}$ −18.6 (c 1.0, $CHCl_3$, 90% ee); IR (KBr): 3415, 2921, 1713, 1612, 1260, 1107, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (dd, J = 8.8, 5.6 Hz, 1H), 7.36−7.27 (m, 5H), 7.20 (dd, J = 8.8, 2.3 Hz, 1H), 7.14 (dd, J = 8.5, 2.3 Hz, 1H), 5.86 (d, J = 5.3 Hz, 1H), 5.50 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1 (d, J = 256.5 Hz), 162.2, 140.9 (d, J = 9.1 Hz), 136.0, 133.6 (d, J = 9.7 Hz), 129.2, 128.9, 126.5, 120.5, 117.4 (d, J = 22.1 Hz), 115.6 (d, J = 23.7 Hz), 84.0, 45.4; HRMS (EI) Calcd for $C_{15}H_{10}O_2F$ m/z $[M - Br]^+$: 241.0659; found, 241.0657; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 16.0 min (minor), t_2 = 17.4 min (major).

(3*S*,4*R*)-4-Bromo-6-chloro-3,4-dihydro-3-phenylisochromen-1-one (4l). White solid, mp 121.1−123.0 °C: $[\alpha]_D^{26}$ −27.2 (c 1.0, $CHCl_3$, 89% ee); IR (KBr): 3412, 3027, 1712, 1596, 1376, 1259, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 8.2 Hz, 1H), 7.48−7.28 (m, 7H), 5.88 (d, J = 5.0 Hz, 1H), 5.49 (d, J = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 141.0, 139.4, 136.0, 132.0, 130.3, 129.2, 128.9, 128.5, 126.4, 122.5, 84.0, 45.1; HRMS (EI) Calcd for $C_{15}H_{10}O_2Cl$ m/z $[M - Br]^+$: 257.0364; found, 257.0358; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 15.9 min (minor), t_2 = 17.2 min (major).

(3*S*,4*R*)-4-Bromo-7-fluoro-3,4-dihydro-3-phenylisochromen-1-one (4m). White solid, mp 120.0−121.3 °C: $[\alpha]_D^{27}$ −75.9 (c 1.0, $CHCl_3$, 93% ee); IR (KBr): 3422, 3082, 2958, 1716, 1486, 1274, 1064, 982 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (dd, J = 8.2, 2.3 Hz, 1H), 7.47 (dd, J = 8.5, 5.0 Hz, 1H), 7.34−7.25 (m, 6H), 5.93 (d, J = 4.4 Hz, 1H), 5.55 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (d, J = 250.1 Hz), 162.1, 136.1, 133.8, 130.7 (d, J = 7.5 Hz), 129.1, 128.9, 126.3, 122.0 (d, J = 22.0 Hz), 117.0 (d, J = 23.7 Hz), 84.4, 45.1; HRMS (EI) Calcd for $C_{15}H_{10}O_2F$ m/z $[M - Br]^+$: 241.0659; found, 241.0659; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 13.5 min (minor), t_2 = 14.6 min (major).

(3*S*,4*R*)-4-Bromo-3-(3-chlorophenyl)-3,4-dihydroisochromen-1-one (4n). White solid, mp 119.0−121.0 °C: $[\alpha]_D^{26}$ −25.4 (c 1.0, $CHCl_3$, 96% ee); IR (KBr): 3420, 2923, 1719, 1599, 1373, 1239, 1118, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.3 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.32−7.24 (m, 3H), 7.18 (d, J = 7.0 Hz, 1H), 5.83 (d, J = 5.3 Hz, 1H), 5.52 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 138.3, 137.5, 134.8, 130.5, 130.1, 129.9, 129.3, 128.5, 126.8, 124.8, 123.9, 83.3, 45.8; HRMS (EI) Calcd for $C_{15}H_{10}O_2Cl$ m/z $[M - Br]^+$: 257.0364; found, 257.0360; HPLC (Daicel Chiralpak IB, i-PrOH/hexane = 25/75, 0.6 mL/min, 230 nm): t_1 = 14.4 min (minor), t_2 = 16.2 min (major).

(*S*)-3-[(*R*)-Bromo(3-chlorophenyl)methyl]isobenzofuran-1(3*H*)-one (5n). White solid, mp 101.1−103.1 °C: $[\alpha]_D^{25}$−24.3 (c 1.0, $CHCl_3$, 66% ee); IR (KBr): 3486, 1759, 1472, 1286, 1078, 982 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.71−7.67 (m, 2H), 7.60−7.53 (m, 1H), 7.40 (s, 1H), 7.33−7.27 (m, 3H), 5.91 (d, J = 6.4 Hz, 1H), 5.09 (d, J = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 146.1, 138.2, 134.5, 134.0, 130.2, 129.9, 129.3, 128.7, 126.8, 126.6, 125.9, 123.8, 82.1, 52.1; HRMS (EI) Calcd for $C_{15}H_{10}O_2Cl$ m/z $[M - Br]^+$: 257.0364; found, 257.0369; HPLC (Daicel Chiralpak IC, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 22.2 min (minor), t_2 = 23.4 min (major).

(3*S*,4*R*)-4-Bromo-3-(3-nitrophenyl)-3,4-dihydroisochromen-1-one (4o). White solid, mp 125.0−127.0 °C: $[\alpha]_D^{25}$ +23.4 (c 0.5, $CHCl_3$, 98% ee); IR (KBr): 3421, 3074, 2950, 1714, 1525, 1350, 1263, 1114, 1082, 996, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26−8.16 (m, 3H), 7.74−7.51 (m, 5H), 5.89 (d, J = 6.4 Hz, 1H), 5.56 (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 148.3, 138.4, 137.4, 135.0, 132.9, 130.7, 130.1, 130.0, 128.7, 124.2, 122.0, 82.9, 45.9; HRMS (EI) Calcd for $C_{15}H_{10}NO_4$ m/z $[M - Br]^+$: 268.0604; found, 268.0600; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 30/70, 0.6 mL/min, 230 nm): t_1 = 18.3 min (major), t_2 = 21.0 min (minor).

3-[Bromo(3-nitrophenyl)methyl]isobenzofuran-1(3*H*)-one (5o). White solid, mp 142.4−144.1 °C: $[\alpha]_D^{25}$ +12.8 (c 1.0, $CHCl_3$, −47% ee); IR (KBr): 3500, 3079, 1760, 1529, 1349, 1073, 980, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.86−7.80 (m, 3H), 7.72 (t, J = 7.2 Hz, 1H), 7.61−7.52 (m, 2H), 6.00 (d, J = 7.0 Hz, 1H), 5.14 (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 148.1, 145.9, 138.5, 134.7, 134.3, 130.4, 129.8, 126.3, 126.1, 123.9, 123.8, 123.4 81.8, 50.9; HRMS (EI) Calcd for $C_{15}H_{10}NO_4$ m/z $[M - Br]^+$: 268.0604; found, 268.0610; HPLC (Daicel Chiralpak IA, i-PrOH/hexane = 50/50, 0.6 mL/min, 230 nm): t_1 = 26.6 min (minor), t_2 = 32.4 min (major).

3-{[3,5-Bis(trifluoromethyl)phenyl]bromomethyl}-isobenzofuran-1(3*H*)-one (5p). White solid, mp 98.7−100.7 °C: $[\alpha]_D^{27}$ −3.7 (c 1.0, $CHCl_3$, −34% ee); IR (KBr): 3492, 1758, 1283, 1189, 1126, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85−7.80 (m, 5H), 7.73 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.3 Hz, 1H), 5.99 (d, J = 7.0 Hz, 1H), 5.14 (d, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 145.7, 139.2, 134.3, 132.2 (q, J = 33.9), 130.5, 128.8, 126.3, 126.2, 123.8, 123.0, 122.8 (q, J = 271.0), 81.5, 50.5; HRMS (EI) Calcd

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for $C_{17}H_9O_2F_6$ m/z $[M]^+$: 359.0501; found, 359.0496; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 22.5 min (minor), t_2 = 27.6 min (major).

(3*S*,4*R*)-4-Bromo-3-[4-(trifluoromethyl)phenyl]-3,4-dihydroisochromen-1-one (4q). White solid, mp 101.7−103.2 °C: $[\alpha]_D^{28}$ −84.2 (*c* 0.5, $CHCl_3$, 88% ee); IR (KBr): 3424, 2957, 2361, 1727, 1327, 1166, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 1H), 7.66−7.60 (m, 3H), 7.53−7.44 (m, 4H), 5.92 (d, J = 5.3 Hz, 1H), 5.54 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 140.1, 137.4, 134.9, 131.2 (q, J = 32.8 Hz), 130.6, 130.0, 128.5, 127.0, 125.8 (q, J = 3.8 Hz), 123.8, 123.6 (J = 271.0 Hz), 83.3, 45.7; HRMS (EI) Calcd for $C_{16}H_{10}O_2BrF_3$ m/z $[M]^+$: 369.9811; found, 369.9815; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 31.8 min (minor), t_2 = 33.3 min (major).

(*S*)-3-{(*R*)-Bromo[4-(trifluoromethyl)phenyl]methyl}-isobenzofuran-1(3*H*)-one (5q) (From Table 3, Entry 17). Colorless oil: $[\alpha]_D^{28}$ −11.1 (*c* 0.9, $CHCl_3$, 53% ee); IR (KBr): 3474, 3037, 1756, 1450, 1280, 1180, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 7.6 Hz, 1H), 7.72−7.52 (m, 7H), 5.96 (d, J = 6.4 Hz, 1H), 5.17 (d, J = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 146.0, 140.1, 134.1, 130.9 (q, J = 32.3 Hz), 130.2, 129.1, 126.5, 126.0, 125.7 (q, J = 3.9 Hz), 123.69, 123.65 (q, J = 271.0 Hz), 82.1, 51.8; HRMS (EI) Calcd for $C_{16}H_{10}O_2BrF_3$ m/z $[M]^+$: 369.9811; found, 369.9819; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 61.1 min (minor), t_2 = 69.0 min (major).

(*R*)-3-[4-(Trifluoromethyl)benzyl]isobenzofuran-1(3*H*)-one (5q′).[18] To a solution of **5q** (from Table 3, entry 17) (37 mg, 0.1 mmol, 1.0 equiv) in toluene (1.5 mL) was added AIBN (1.6 mg, 0.01 mmol, 0.1 equiv) and Ph_3SnH (77 μL, 0.3 mmol, 3.0 equiv). The mixture was refluxed for 2 h, then cooled to 25 °C, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give phthalide **10r′** (27 mg, 92%) as a white solid: $[\alpha]_D^{26}$ +44.0 (*c* 0.89, $CHCl_3$, 53% ee); ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.6 Hz, 1H), 7.68−7.64 (m, 1H), 7.55−7.51 (m, 3H), 7.35−7.30 (m, 3H), 5.71 (t, J = 6.1 Hz, 1H), 3.33 (dd, J = 14.3, 5.4 Hz, 1H), 3.24 (dd, J = 14.3, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 148.6, 139.1, 134.0, 130.0, 129.7, 129.5, 129.3, 126.2, 125.9, 125.41 (q, J = 3.6 Hz), 124.1 (q, J = 269.8 Hz), 80.5, 40.6. (The data are in full accordance with the literature in all respects.)[18]

(3*S*,4*R*)-4-Bromo-3-(2-chlorophenyl)-3,4-dihydroisochromen-1-one (5r). White solid, mp 114.2−116.2 °C: −32% ee; IR (KBr): 3445, 1762, 1468, 1285, 1057, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.68−7.40 (m, 3H), 7.35−7.25 (m, 3H), 6.00 (d, J = 6.1 Hz, 1H), 5.80 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 146.0, 133.8, 132.9, 131.1, 130.2, 130.1, 129.7, 127.4, 126.7, 125.8, 124.0, 81.3, 48.4; HRMS (EI) Calcd for $C_{15}H_{10}O_2Cl$ m/z $[M - Br]^+$: 257.0364; found, 257.0364; HPLC (Daicel Chiralpak IB, *i*-PrOH/hexane = 5/95, 0.6 mL/min, 230 nm): t_1 = 22.3 min (major), t_2 = 26.2 min (minor).

3-(Bromomethyl)isobenzofuran-1(3*H*)-one (5s). White solid, mp 60.2−62.2 °C: $[\alpha]_D^{27}$ −27.2 (*c* 1.0, $CHCl_3$, −34% ee); IR (KBr): 3492, 3056, 1753, 1466, 1287, 1210, 1061, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.64−7.57 (m, 2H), 5.70 (t, J = 5.0 Hz, 1H), 3.77 (d, J = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 147.1, 134.3, 130.0, 126.5, 125.9, 122.4, 78.6, 32.1; HRMS (EI) Calcd for $C_9H_7O_2Br$ m/z $[M]^+$: 225.9624; found, 225.9628; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm): t_1 = 15.6 min (minor), t_2 = 21.8 min (major).

3-(1-Bromobutyl)isobenzofuran-1(3*H*)-one (5t). Colorless oil: −12% ee; IR (KBr): 3453, 2922, 2847, 1774, 1475, 1289, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 5.60 (d, J = 5.9 Hz, 1H), 4.21 (dd, J = 13.4 Hz, 6.2 Hz, 1H), 1.79−1.67 (m, 1H), 1.67−1.45 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 146.9, 134.0, 129.9, 126.8, 125.8, 123.6, 82.3, 54.8, 36.0, 20.3, 13.2; HRMS (EI) Calcd for $C_{12}H_{13}O_2$ m/z $[M - Br]^+$: 189.0910; found, 189.0917; HPLC (Daicel Chiralpak IB, *i*-PrOH/hexane = 25/75, 0.6 mL/min, 254 nm): t_1 = 20.1 min (minor), t_2 = 24.1 min (major).

3-[Bromo(cyclohexyl)methyl]isobenzofuran-1(3*H*)-one (5u). White solid, mp 137.0−139.0 °C: −28% ee; IR (KBr): 3444, 2926, 2852, 1764, 1471, 1295, 1078, 977 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (t, J = 8.2 Hz, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 5.70 (d, J = 8.8 Hz, 1H), 3.95 (dd, J = 8.5 Hz, 3.8 Hz, 1H), 2.07−2.00 (m, 2H), 1.83−1.54 (m, 4H), 1.50−1.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 147.8, 133.9, 129.8, 126.3, 125.7, 124.4, 79.5, 62.5, 40.2, 31.5, 28.1, 26.1, 25.9, 25.5; HRMS (EI) Calcd for $C_{15}H_{17}O_2$ m/z $[M - Br]^+$: 229.1223; found, 229.1225; HPLC (Daicel Chiralpak IB, *i*-PrOH/hexane = 25/75, 0.6 mL/min, 230 nm): t_1 = 17.5 min (major), t_2 = 26.3 min (minor).

Amino-Thiocabamate 8b. 71%, light yellow solid, mp 82.6−84.6 °C: $[\alpha]_D^{28}$ −112.2 (*c* 1.2, $CHCl_3$); IR (KBr): 2942, 1622, 1510, 1359, 1231, 991 cm^{-1}; ^1H NMR (the compound existed as a mixture of rotamers, and the major rotamer was assigned) (300 MHz, $CDCl_3$): δ 8.88 (d, J = 4.6 Hz, 1H), 8.69 (s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.60−7.57 (m, 2H), 7.43−7.40 (m, 2H), 7.16−7.00 (m, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.13−5.90 (m, 1H), 5.09 (d, J = 16.8 Hz, 2H), 3.82 (s, 3H), 3.52−3.32 (m, 1H), 2.93−2.69 (m, 4H), 2.27−2.24 (m, 1H), 1.99−1.74 (m, 2H), 1.56−1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 149.3, 148.5, 145.4, 140.4, 130.3, 129.1, 126.6, 126.4, 125.7, 124.0, 120.6, 119.2, 114.9, 110.6, 60.6, 55.7, 49.7, 49.2, 40.0, 37.5, 27.9, 26.4, 12.0; HRMS (ESI) Calcd for $C_{27}H_{30}N_3O_2S$ m/z $[M + H]^+$: 460.2053; found, 460.2059.

Amino-Thiocabamate 8d. 82%, white solid, mp 191.0−192.6 °C: $[\alpha]_D^{28}$ +6.0 (*c* 1.0, $CHCl_3$); IR (KBr): 2931, 1623, 1511, 1247, 1166, 1033 cm^{-1}; ^1H NMR (the compound existed as a mixture of rotamers, and the major rotamer was assigned) (300 MHz, $CDCl_3$): δ 8.83 (d, J = 4.4 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.68−7.62 (m, 2H), 7.47−7.42 (m, 1H), 7.32 (d, J = 4.4 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.09 (s, 2H), 5.82−5.70 (m, 1H), 5.05−4.97 (m, 2H), 3.86 (s, 3H), 3.57 (s, 6H), 3.24−3.15 (m, 1H), 2.86−2.82 (m, 2H), 2.64−2.59 (m, 2H), 2.17−2.14 (m, 2H), 1.88−1.80 (m, 1H), 1.66 (br, 1H), 1.53−1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 160.7, 156.5, 149.7, 148.6, 145.2, 140.5, 130.1, 128.7, 126.3, 126.1, 124.3, 119.8, 114.7, 90.4, 81.4, 60.0, 55.4, 49.5, 49.1, 40.7, 28.3, 26.3, 23.3; HRMS (ESI) Calcd for $C_{29}H_{34}N_3O_4S$ m/z $[M + H]^+$: 520.2265; found, 520.2274.

Amino-Thiocabamate 15. 76%, light yellow solid: ^1H NMR (the compound existed as a mixture of rotamers, and the major rotamer was assigned) (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.5 Hz, 1H), 8.38 (s, 1H), 7.98 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 7.44−7.33 (m, 3H), 6.48 (d, J = 2.4 Hz, 1H), 6.46 (s, 1H), 6.09−5.92 (m, 1H), 5.29−5.05 (m, 2H), 4.15−4.05 (m, 2H), 3.82 (s, 6H), 3.44−3.41 (m, 1H), 2.90−2.71 (m, 4H), 2.25−2.10 (m, 3H), 2.02−1.74 (m, 4H), 1.56−1.49 (m, 3H), 0.99 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 157.3, 151.4, 147.2, 144.7, 143.4, 140.3, 131.4, 127.6, 124.1, 122.4, 119.5, 114.8, 104.0, 102.7, 98.8, 80.6, 66.9, 60.0, 55.5, 49.2, 40.3, 37.8, 27.9, 26.4, 25.1, 24.4, 22.6.

(*R*)-3,4-Dihydro-3-phenylisochromen-1-one (10). To a solution of **4a** (61 mg, 0.2 mmol, 1.0 equiv) in toluene (2 mL) was added AIBN (1.6 mg, 0.01 mmol, 0.05 equiv) and Ph_3SnH (153 μL, 0.6 mmol, 3.0 equiv). The mixture was refluxed for 2 h, then cooled to 25 °C, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give lactone **10** (42 mg, 93%) as a white solid, mp 81.5−83.4 °C: $[\alpha]_D^{25}$ +168.5 (*c* 1.0, $CHCl_3$, 93% ee); IR (neat): 3434, 2363, 1717, 1275, 1119, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J = 7.9 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.49−7.34 (m, 6H), 7.29 (d, J = 7.6 Hz, 1H), 5.56 (dd, J = 12.0, 2.9 Hz, 1H), 3.34 (dd, J = 16.4, 12.0 Hz, 1H), 3.13 (dd, J = 16.7, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 138.9, 138.6, 133.9, 130.4, 128.6, 127.8, 127.3, 126.1, 125.1, 79.9, 35.5; HRMS (EI) Calcd for $C_{15}H_{12}O_2$ m/z $[M]^+$: 224.0832; found, 224.0838; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 230 nm): t_1 = 21.0 min (major), t_2 = 24.6 min (minor).

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(3*S*,4*S*)-3,4-Dihydro-1-oxo-3-phenyl-1*H*-isochromen-4-yl Acetate (11). To a stirred solution of **4a** (61 mg, 0.2 mmol) in DMSO (4 mL) was added CH_3CO_2K (59 mg, 0.6 mmol) at rt. The reaction mixture was then stirred for 3 days and diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (20 mL) and then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to give acetate **11** (48 mg, 85%) as a white solid: $[\alpha]_D^{28}$ +265.3 (*c* 2.0, $CHCl_3$, 93% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.70−7.57 (m, 3H), 7.51 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.44−7.36 (m, 3H), 6.12 (d, *J* = 2.0 Hz, 1H), 5.73 (d, *J* = 1.5 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 164.2, 136.3, 134.8, 134.3, 130.4, 129.0, 128.7, 128.4, 126.5, 125.1, 80.7, 67.9, 20.5; HRMS (ESI) Calcd for $C_{17}H_{14}O_4Na$ *m*/*z* [M + Na]$^+$: 305.0784; found, 305.0789; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 230 nm): t_1 = 19.8 min (major), t_2 = 22.2 min (minor).

(3*S*,4*S*)-4-Azido-3,4-dihydro-3-phenylisochromen-1-one (12). To a solution of **4a** (61 mg, 0.2 mmol, 1.0 equiv) in DMF (2 mL) was added NaN_3 (39 mg, 0.6 mmol, 3.0 equiv) at 25 °C. The mixture was refluxed at 65 °C for 24 h; then water (7 mL) was added. The mixture was extracted with EtOAc (3 × 6 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to give azide **12** (48 mg, 90%) as a white solid, mp 92.4−96.3 °C: $[\alpha]_D^{25}$ +287.1 (*c* 2.0, $CHCl_3$, 93% ee); IR (neat): 3425, 3066, 2106, 1723, 1268, 1116, 1091 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 7.6 Hz, 1H), 7.75 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.65 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.50−7.39 (m, 4H), 5.71 (d, *J* = 1.8 Hz, 1H), 4.69 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 135.9, 135.0, 134.5, 131.2, 130.6, 129.0, 128.6, 127.8, 126.4, 124.5, 80.5 60.8; HRMS (EI) Calcd for $C_{15}H_{11}NO_2$ [M − N_2]$^+$: 237.0784; found, 237.0789; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 254 nm): t_1 = 21.8 min (major), t_2 = 32.6 min (minor).

(3*R*,4*S*)-3,4-Dihydro-3-phenyl-1*H*-isochromen-4-ol (14). To a solution of lactone **4a** (121 mg, 0.4 mmol, 1.0 equiv) in anhydrous Et_2O (6 mL) was added $LiAlH_4$ (38 mg, 1.0 mmol, 2.5 equiv) at −40 °C under N_2. After stirring for 3 h at the same temperature, the reaction was quenched with water (0.1 mL). The resulting mixture was warmed to 25 °C and filtered through a thin pad of silica gel eluted with EtOAc (10 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give epoxide **13** (41 mg, 45%). A solution of epoxide (34 mg, 0.15 mmol, 1.0 equiv) and PPTS (7.5 mg, 0.03 mmol, 0.2 equiv) in CH_2Cl_2 (2 mL) was stirred at 25 °C overnight. The reaction was quenched with saturated $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give alcohol **14** (29 mg, 85%) as a white solid, mp 100.6−102.6 °C: $[\alpha]_D^{25}$ −116.1 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 6.8 Hz, 1H), 7.50−7.28 (m, 7H), 7.06 (d, *J* = 6.9 Hz, 1H), 5.01 (d, *J* = 15.1 Hz, 1H), 4.93 (d, *J* = 15.1 Hz, 1H), 4.81 (d, *J* = 8.4 Hz, 1H), 4.44 (d, *J* = 8.6 Hz, 1H), 1.85 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 136.4, 134.6, 128.6, 128.5, 127.4, 127.2, 127.1, 126.5, 123.5, 82.0, 70.4, 68.3; HRMS (EI) Calcd for $C_{15}H_{14}O_2$ *m*/*z* [M]$^+$: 226.0988; found, 226.0989; HPLC (Daicel Chiralpak IA, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 230 nm): t_1 = 21.6 min (minor), t_2 = 26.9 min (major).

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data for compounds **4f** and **14** (CIF) and copies of ^{1}H ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Compund 8 in Table 3 was corrected and this paper reposted on January 4, 2012.