Studies on Organocatalytic Asymmetric Reactions Based on Recognition of Specific Conformations of Substrates

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2017

Contents

Abbreviation

α	observed optical rotation
Å	ångström
Ac	acetyl
Ar	aryl
aq	Aqueous
br	broad (spectral)
Bu	butyl
Bn	benzyl
Boc	tertiary butoxycarbonyl
Bz	benzoyl
c	concentration
°C	degrees Celsius
calcd	calculated
cat	catalyst
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
δ	chemical shift in perts per million
d	doublet (spectral)
d	day(s)
Δ	delta
DFT	density functional theory
dr	diastereomer ratio
E	electrophile
E	energy
E	*entgegen* (means “opposite”)
Ed(s)	editor(s)
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz (s^{-1})
i	iso
IR	infrared (spectral)
J	coupling constant (spectral)
J	Joule
k	kilo
m	multiplet (spectral)
m	meta
M	molar (1 M = 1 mol dm^{-3})
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mol	mole(s)
Mp.	melting point
MS	molecular sieves
nm	nanometer(s)
Ns	nitrobenzenesulfonyl
o	ortho
p	para
pp.	page(s)
Ph	phenyl
ppm	parts per million (spectral)
Pr	propyl
q	quartet (spectral)
R	rectus
rt	room temperature (*ca*. 25 °C)
s	singlet
S	sinister
sept	septet
sub	substrate
t	triplet
t (*tert*)	tertiary
TLC	thin-layer chromatography
UV	ultraviolet (spectral)
X	hetero atom
Z	*zusammen* (means “together”)

General Introduction

Chirality with high enantioselectivity in organic synthesis has attracted much attention, as chiral molecules are recognized as key features for the activity of pharmaceutical compounds and for properties of functional materials. In fact, various methods of asymmetric formations of chiral elements, such as kinetic resolution[1] and desymmetrization,[2] have been developed in addition to typical face-selective reactions of prochiral substrates.[3] Among them, organic transformations based on recognition of the molecular chirality of substrates have also contributed to the field of asymmetric syntheses. In this type of reaction, enzymes are known to be among the most powerful catalysts, producing excellent enantioselectivity in some molecular transformations. Recently, organocatalysts, some of which are regarded as biomimetic catalysts, have also enabled various asymmetric reactions, including those accomplished via molecular recognition. Bifunctional organocatalysts, bearing both a hydrogen bond donor and hydrogen bond acceptor, are especially useful for highly selective molecular recognition. In this thesis, the author will present asymmetric reactions via recognition of molecular chirality utilizing bifunctional organocatalysts. Specifically, reactions involving the formation of stereogenic elements via recognition of specific conformations of substrates by chiral catalysts will be discussed. Novel organocatalytic enantioselective reactions, such as syntheses of chiral heterocycles via asymmetric intramolecular hetero-Michael additions, and syntheses of axially chiral compounds via asymmetric aromatic electrophilic halogenations, were developed. In these reactions, the labile chirality present in the specific conformations recognized by chiral catalysts were translated into the chirality of the final products.

1. Asymmetric Reactions via Recognition of Specific Conformations of Achiral Substrates

In many asymmetric reactions, achiral substrates react with chiral catalysts and are transformed into chiral products (Figure 1).[3] In such reactions, chiral structures, such as chiral carbon centers, are newly constructed during the catalytic transformations.

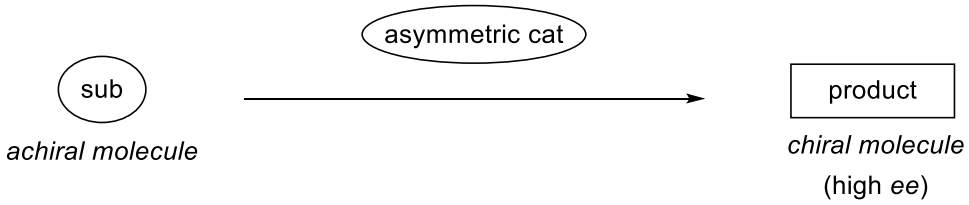


Figure 1. Typical asymmetric reactions from achiral substrates.

On the other hand, when a substrate already possesses chirality, there is sometimes a special matching between a chiral catalyst and only one of the enantiomers of the substrate. In this case, the chirality of the substrate can be recognized by the chiral catalyst, which can selectively accelerate reactions with the recognized enantiomer. Kinetic resolutions are regarded as a representative methodology based on such a recognition of chiral molecules by chiral catalysts, which is an effective method to obtain optically active products from racemic substrates, while retaining the unreacted enantiomer of the substrates in an optically active form (Figure 2, a).[1] In this type of reaction, the chiral structures, constructed prior to the catalytic transformations, are recognized by the chiral catalysts and discriminated by the catalytic reactions; furthermore, when there is equilibrium involving racemization, dynamic kinetic resolutions can be carried out to afford desired products in up to 100% conversion (Figure 2, b).[4] In this context, the author has noted that analogous racemization involving labile chirality can be found in the conformational changes of flexible molecules. Such compounds have various possible conformations, and each snapshot has chirality, although the averaged structures of the molecules are achiral. When chiral catalysts recognize specific "chiral" conformations of achiral substrates, the information of the recognized labile chirality present in specific conformations can be translated into the chirality of the final products (Figure 3). In this category of reactions, short-life chiral structures are generated before the catalytic transformations; one of them is grasped via recognition by the chiral catalysts and catalytically transformed to an isolatable optically active product.

In this type of reaction, the conformation recognized by the chiral catalyst should be similar to that of the transition state of the subsequent transformation. Thus, the activation energy of these kinds of reactions is relatively low, and the reaction proceeds quickly. To realize asymmetric induction in such systems, it is effective to employ simultaneous multiple mild activations by multifunctional organocatalysts via noncovalent interactions, such as hydrogen bonding.[5,6] This could be accomplished with enzyme-like systems, in which reactions cannot take place until the desired multiple activations of the substrates are satisfied, useful for recognizing specific conformations in a highly selective fashion.

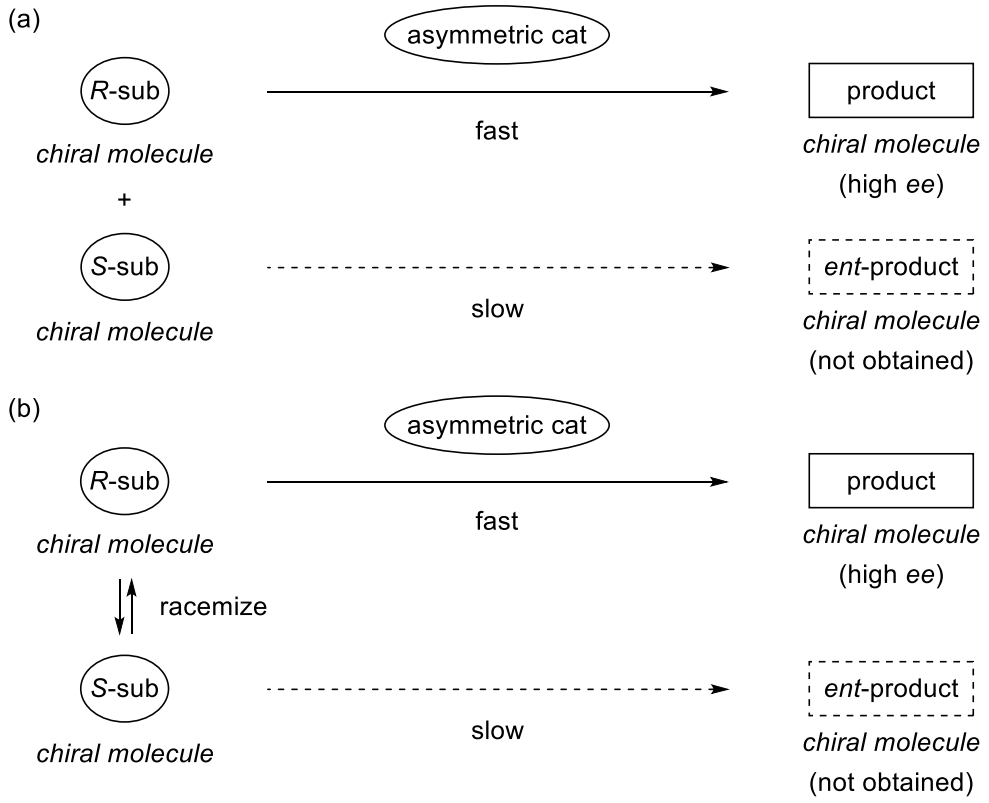


Figure 2. (a) Kinetic resolutions, and (b) dynamic kinetic resolutions.

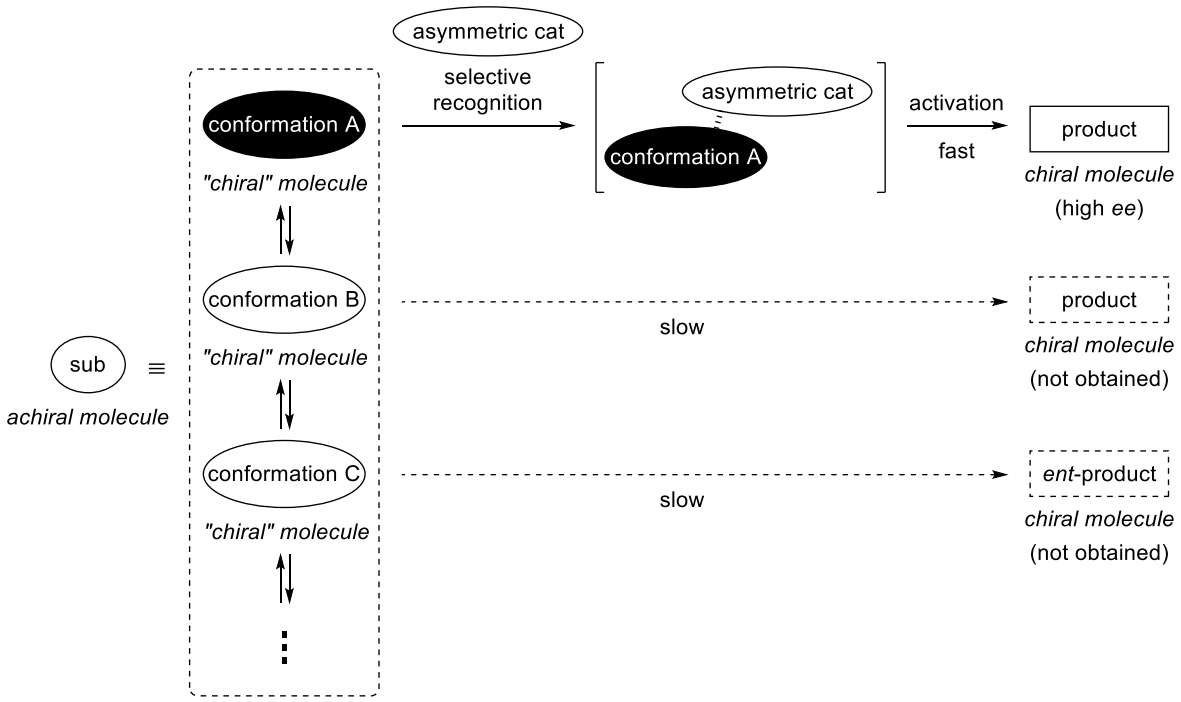


Figure 3. Asymmetric catalytic reactions based on recognition of specific conformations of substrates.

2. Asymmetric Cyclizations

Some asymmetric intramolecular cyclizations could be regarded as successful examples of the above-mentioned class of asymmetric reactions (Figure 4). Early on, cycloetherifications via intramolecular oxy-Michael additions suffered from the challenge of high nucleophilicity of the pendant OH groups, although these reactions were thought to provide straightforward access to various significant optically active heterocycles.[7] In 2007, Scheidt showed that asymmetric intramolecular conjugate additions from α-substituted chalcones could be accomplished with the use of chiral bifunctional organocatalysts[8] containing thiourea and tertiary amino groups (Scheme 1).[9] Later, You reported asymmetric desymmetrizations via intramolecular oxy-Michael reactions from cyclohexadienones bearing a pendant hydroxy group catalyzed by chiral phosphoric acids,[10] which can also recognize the substrates using dual hydrogen bonding (Scheme 2).[11]

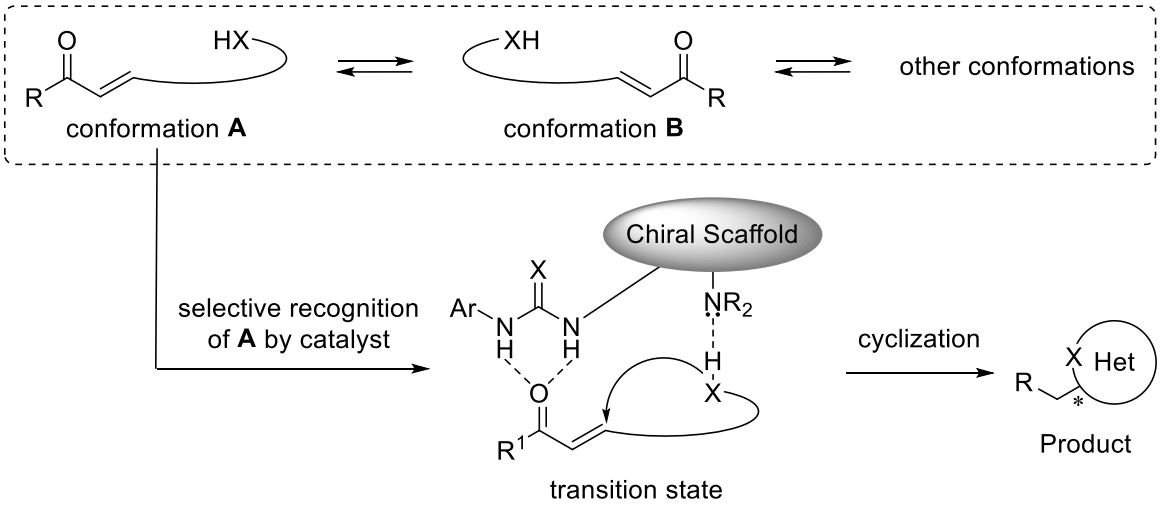
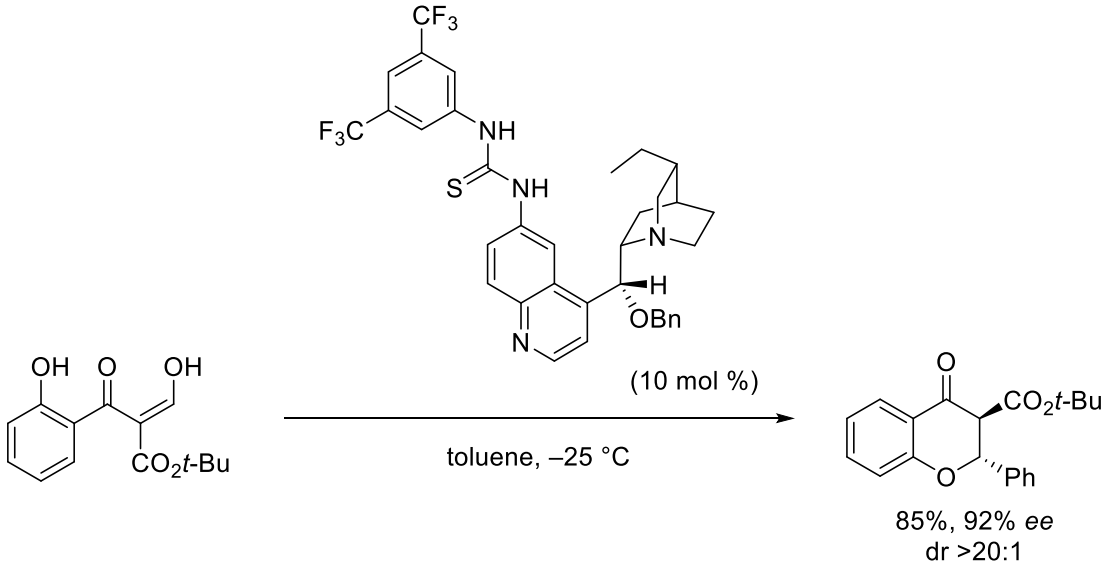
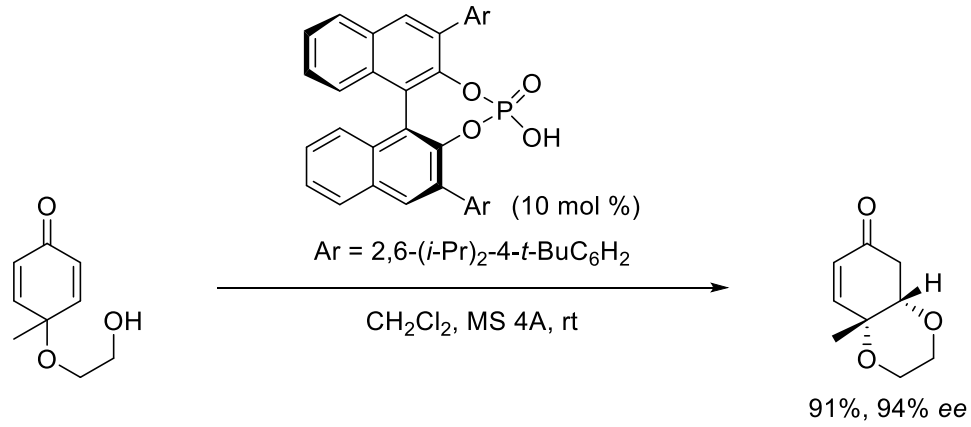


Figure 4. Asymmetric cyclizations via selective recognition of specific conformations utilizing bifunctional organocatalysts.

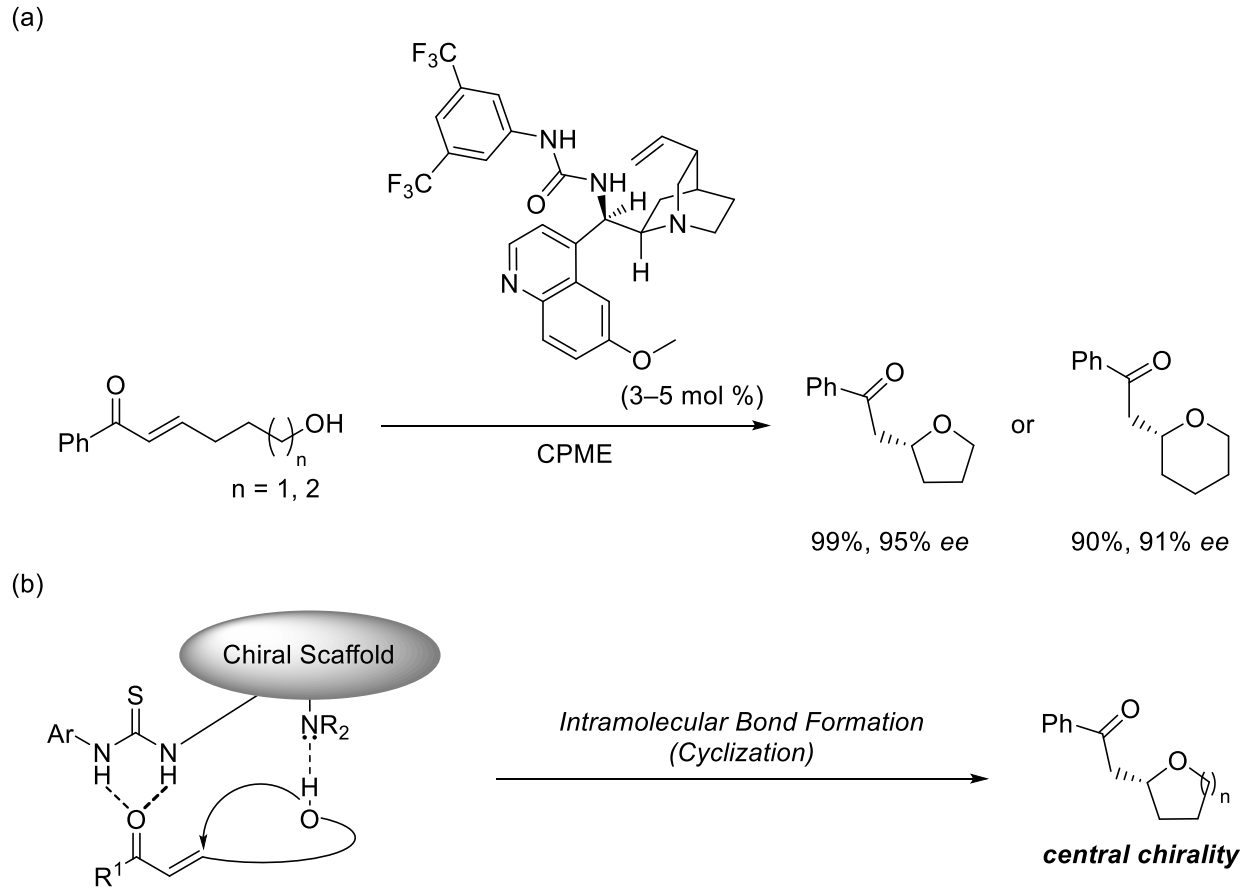


Scheme 1. Asymmetric intramolecular oxy-Michael addition from chalcone.

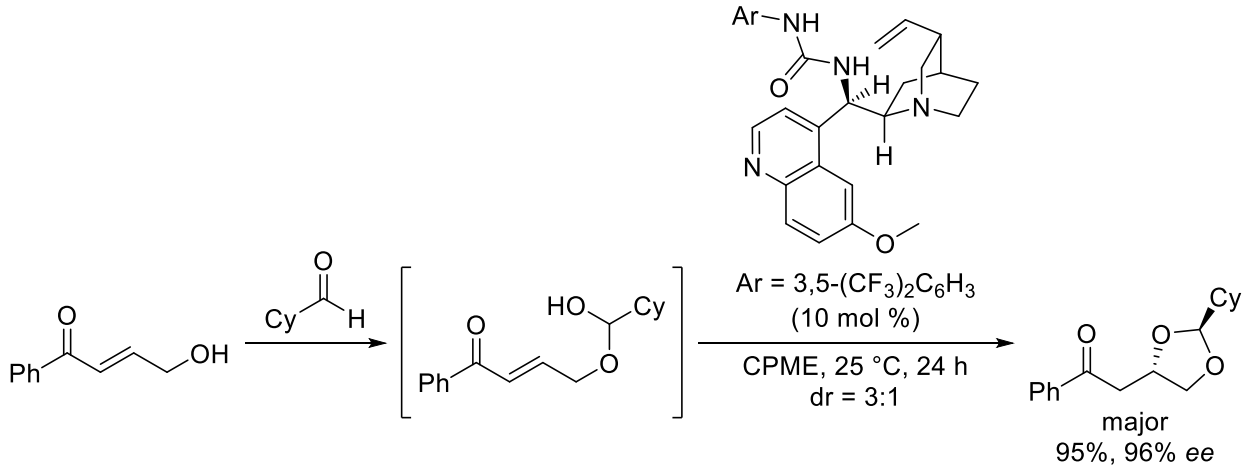


Scheme 2. Asymmetric desymmetrization by a chiral phosphoric acid catalyst via intramolecular oxy-Michael addition from cyclohexadienone.

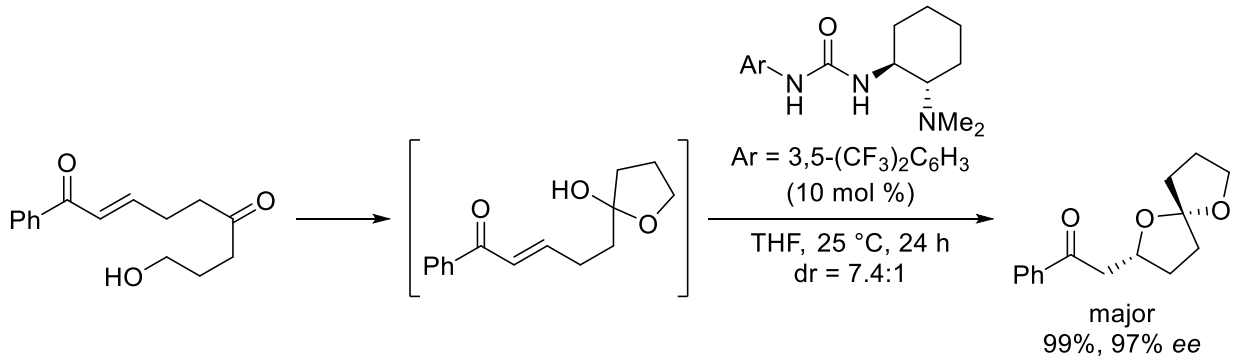
In 2012, Asano and Matsubara reported enantioselective intramolecular oxy-Michael addition reactions from *ε*- and *ζ*-hydroxy-*α*,*β*-unsaturated ketones with bifunctional aminothiourea catalysts[8] (Scheme 3, a).[12] They proposed that these processes involve multipoint interactions between the substrates and the catalysts via hydrogen bonding in the transition states (Scheme 3, b). In addition, they sought to utilize acetal intermediates generated *in situ* and applied their methodology to formal [3+2] cycloadditions from *γ*-hydroxy-*α*,*β*-unsaturated ketones and aldehydes (Scheme 4).[13] They also applied their methodology to asymmetric syntheses of spiroketals (Scheme 5).[14,15]



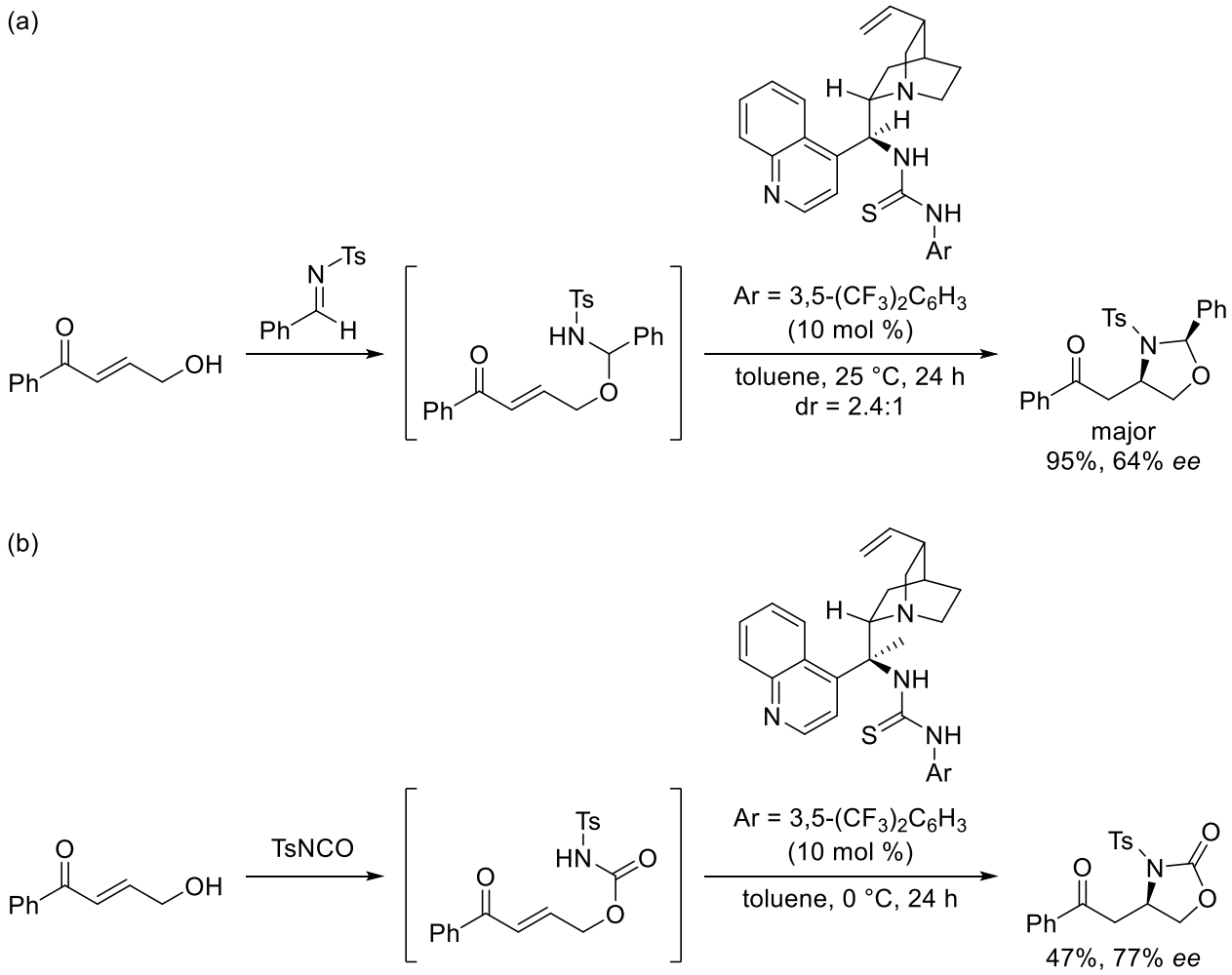
Scheme 3. (a) Enantioselective intramolecular oxy-Michael reactions from ω-hydroxy-α,β-unsaturated ketones, and (b) asymmetric induction via multipoint recognition and activation by bifunctional organocatalysts.



Scheme 4. Formal [3+2] cycloaddition via intramolecular oxy-Michael addition.



Scheme 5. Asymmetric synthesis of spiroketal via intramolecular oxycyclization.



Scheme 6. Intramolecular aza-Michael additions via recognition of specific conformations by a bifunctional organocatalyst (a) containing an imine, and (b) containing an isocyanate.

Asano and Matsubara also expanded their strategy to azacyclizations. They prepared *ε*-amino-*α*,*β*-unsaturated ketones *in situ* from *γ*-hydroxy-*α*,*β*-unsaturated ketones and imines[16] or

isocyanates,[17] and then controlled the subsequent intramolecular aza-Michael addition reactions with bifunctional aminothiourea organocatalysts (Scheme 6).

3. Enantioselective Synthesis of Axially Chiral Compounds

Asymmetric reactions that fix axial chirality from substrates bearing a rotational axis with a small rotational barrier could also be included in the present class of asymmetric reactions. Such substrate molecules can have various possible conformations corresponding to the dihedral angles. Some asymmetric catalysts recognize specific conformations of substrates and immediately activate them toward functionalization at the ortho positions, enhancing the rotational barrier to prohibit rotations, thereby leading to optically active products (Figure 5).[18]

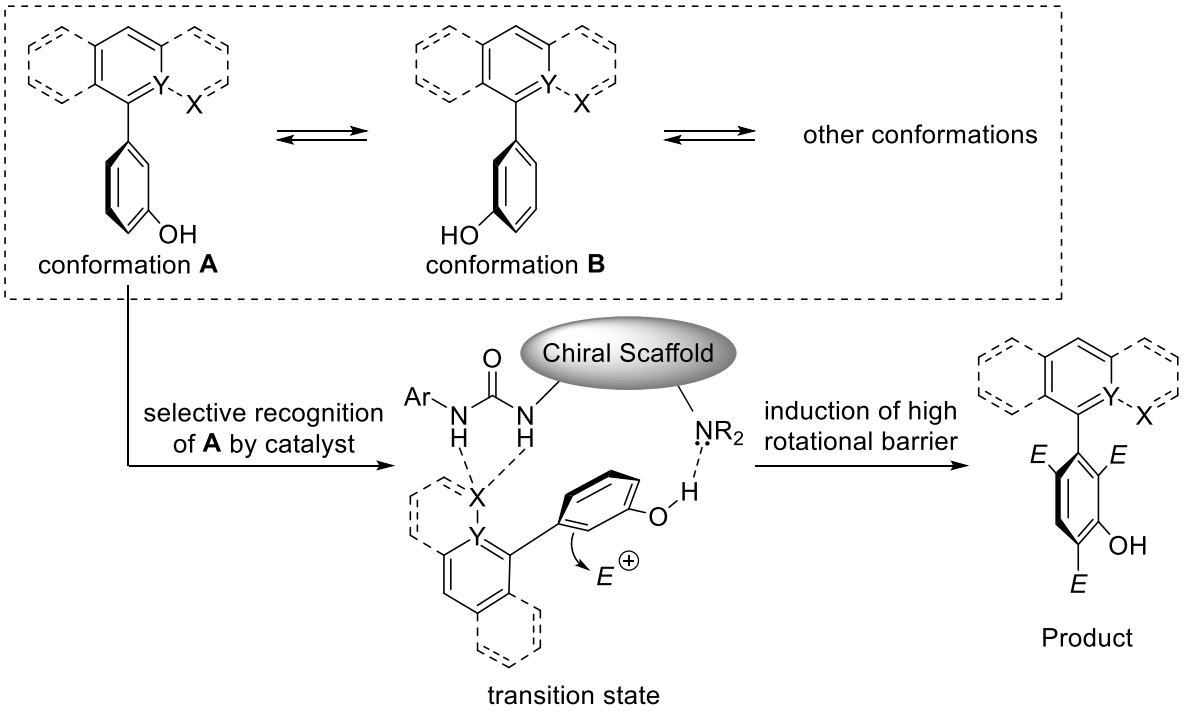
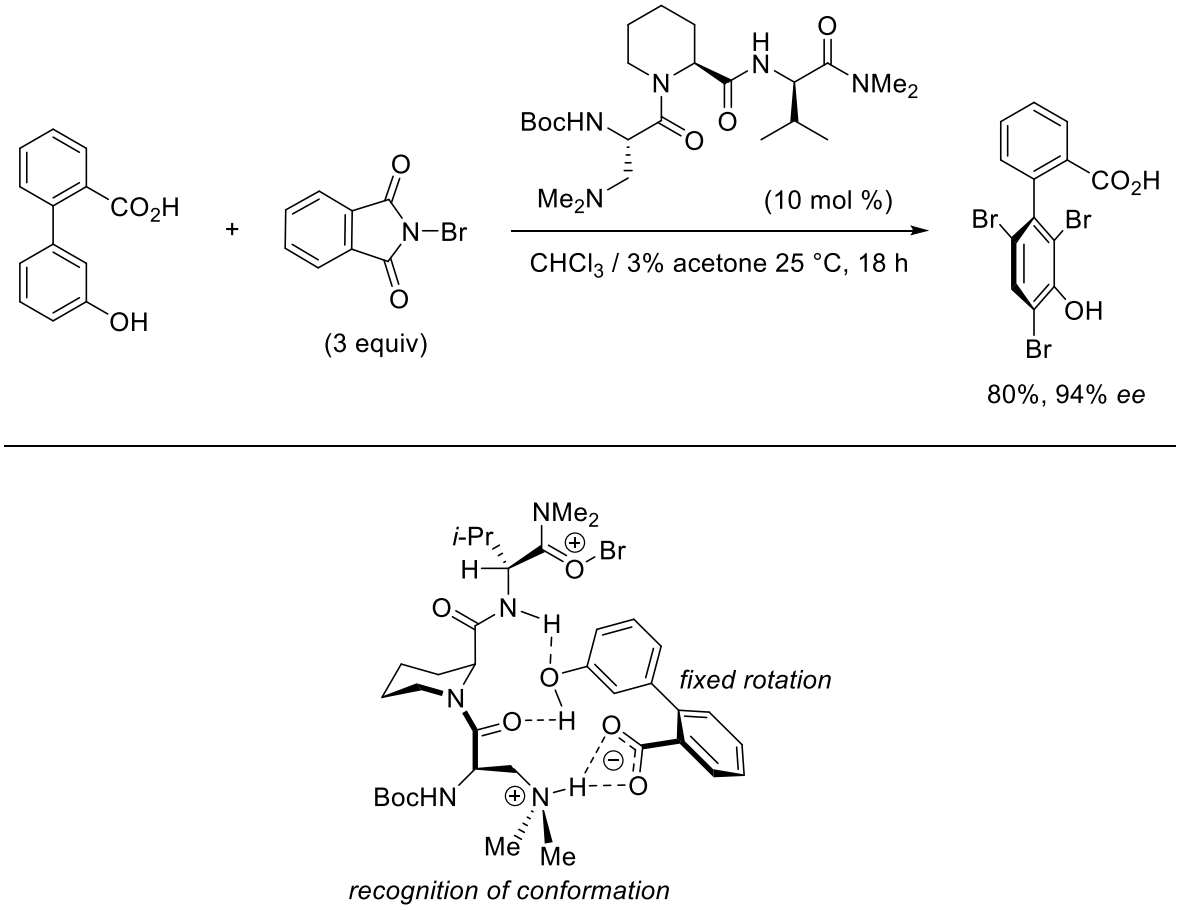


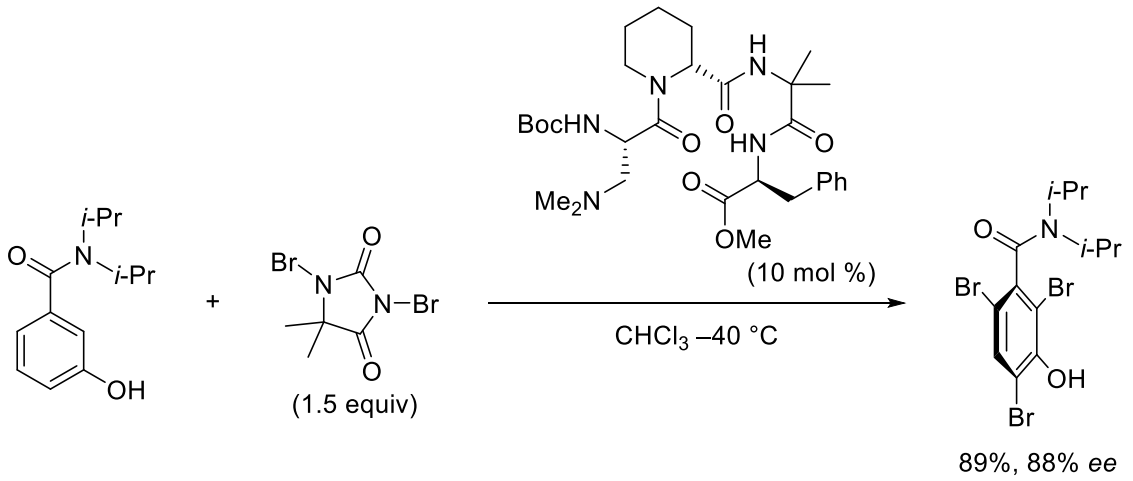
Figure 5. Asymmetric syntheses of axially chiral compounds via recognition of specific conformations utilizing bifunctional organocatalysts.

Recently, there have been some reports detailing such asymmetric syntheses. Miller reported asymmetric brominations of biphenyls bearing carboxylic acid and phenolic groups by multifunctional peptide catalysts in 2010 (Scheme 7).[19] In these reactions, the substrates could

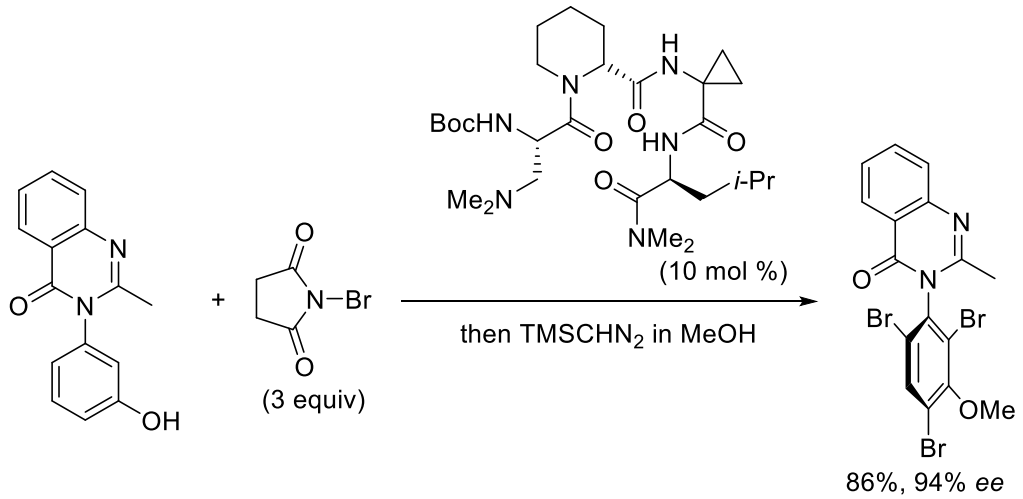
rotate around the bond connecting the two aromatic rings, and the peptide catalysts recognized specific conformations and activated subsequent brominations using a hydrogen bonding network. The conformations of the transition state were reflected onto the axial chirality of the final product. They also showed that this series of peptide catalysts was effective for the enantioselective syntheses of axially chiral benzamides (Scheme 8)[20] and quinazolines (Scheme 9),[21] both of which are found in biologically active compounds.[22] Shirakawa and Maruoka also demonstrated the enantioselective syntheses of anilides via asymmetric alkylations. In this transformation, the chiral quaternary ammonium catalysts affect the asymmetric alkylations, during which a high rotational barrier is installed (Scheme 10).[23]



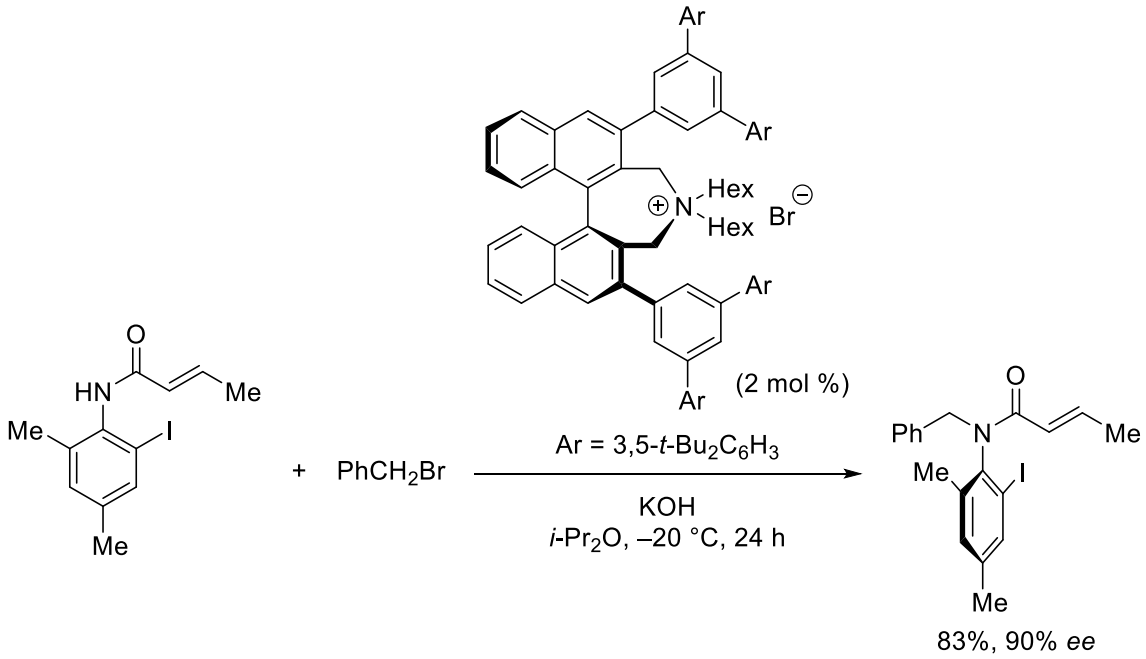
Scheme 7. Asymmetric synthesis of axially chiral biphenyl by a peptide catalyst.



Scheme 8. Asymmetric synthesis of axially chiral benzamide by a peptide catalyst.



Scheme 9. Asymmetric synthesis of axially chiral quinazoline by a peptide catalyst.



Scheme 10. Asymmetric alkylation of anilide by a chiral phase-transfer catalyst.

4. Overview of Thesis

In this thesis, special attention is given to bifunctional organocatalysts bearing both a hydrogen bond donor and acceptor. Such bifunctional catalysts have accomplished the simultaneous activation of a nucleophile and an electrophile in suitable spatial configurations and have been utilized in many asymmetric addition reactions. He sought to develop selective organic reactions utilizing a system in which bifunctional organocatalysts interact with substrates via hydrogen bonding at multiple points. He discovered that bifunctional organocatalysts that contain both urea and tertiary amino groups could recognize specific conformations of various substrates efficiently using multiple hydrogen bonds. When the catalysts recognize specific conformations of substrates, central chirality can be constructed via intramolecular cyclizations, while axial chirality can be established by installing a large rotational barrier through functionalizations around the rotational bonds.

4.1. Asymmetric Intramolecular Hetero-Michael Addition Reactions by Bifunctional Organocatalysts (Chapters 1 and 2)

The author first developed asymmetric hetero-Michael additions from *α*,*β*-unsaturated carbonyl compounds bearing a pendant OH or NH group using bifunctional organocatalysts to synthesize the significant chiral heterocycles chromans (Chapter 1) and indolines (Chapter 2). The hydrogen bond donor, a urea group, in these catalysts can interact with the carbonyl groups of the substrates; simultaneously, the hydrogen bond acceptor, an amino group, can recognize nucleophilic hetero atom groups (Figure 6). This multipoint hydrogen bonding can recognize particular conformations of the substrates, which can be reflected onto the absolute configurations of the final products in good enantioselectivities.

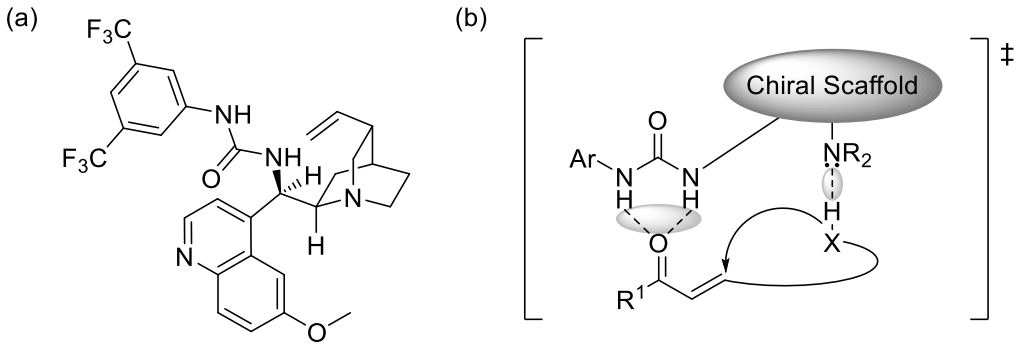
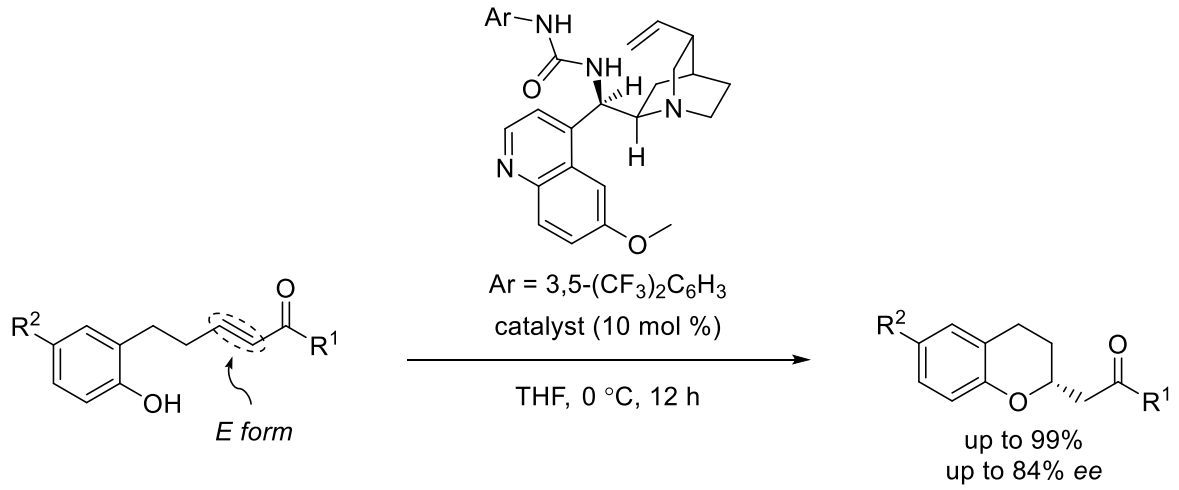


Figure 6. (a) Bifunctional organocatalyst bearing urea and tertiary amino groups and (b) multipoint recognition and activation of specific conformations of substrates for cyclizations.

4.1.1. Asymmetric Syntheses of Chromans via Intramolecular Oxy-Michael Addition Reactions (Chapter 1)

Chiral chromans are one of the most important classes of heterocycles, appearing in various natural products and biologically active compounds, such as Vitamin E.[24] Enantioselective intramolecular oxy-Michael additions are reliable, straightforward approaches to the synthesis of chiral chromans. However, with the exception of one example employing the *E* form of *α*,*β*-unsaturated amide substrates,[25] earlier methods[26] required substrates bearing the *Z* form of *α*,*β*-unsaturated ketones, which are difficult to prepare. Herein, the author describes the development of novel asymmetric syntheses of chromans via intramolecular oxy-Michael addition reactions, in which the bifunctional catalysts bearing urea and tertiary amino groups result in highly enantioselective intramolecular oxy-Michael reactions from the *E* enantiomer of *α*,*β*-unsaturated

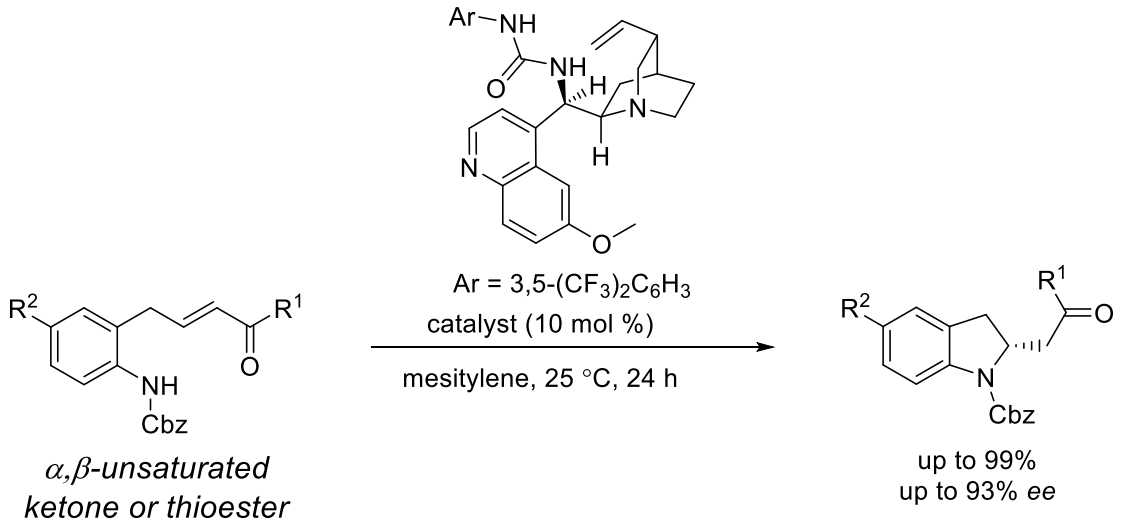
ketones and thioesters (Scheme 11).[27]



Scheme 11. Asymmetric chroman syntheses via intramolecular oxy-Michael additions by a bifunctional organocatalyst.

4.1.2. Asymmetric Syntheses of Indolines via Intramolecular Aza-Michael Addition Reactions (Chapter 2)

Encouraged by the achievement of asymmetric cyclizations from the phenol substrates, the author next examined asymmetric syntheses of chiral indolines[28] via intramolecular aza-Michael additions of anilines bearing *α*,*β*-unsaturated ketone moieties (Scheme 12).[29] This method utilized only noncovalent activations, thereby expanding the scope of useful Michael acceptors in the substrates. Previous methods involving chiral iminium intermediates could be applied for the reactions of *α*,*β*-unsaturated aldehydes[30] and ketones.[31] The developed activation methods also facilitated the use of *α*,*β*-unsaturated thioesters, which are useful for further transformations.[32]



Scheme 12. Asymmetric indoline syntheses via intramolecular aza-Michael addition reactions.

4.2. Asymmetric Syntheses of Axially Chiral Compounds by Bifunctional Organocatalysts (Chapters 3–5)

Bifunctional organocatalysts are also able to construct axial chirality;[33] catalysts can selectively recognize specific conformations of the substrates and catalyze subsequent aromatic electrophilic substitutions at the ortho positions of the rotational axes to inhibit rotation. This achieves excellent enantioselectivities from several types of substrates bearing two functional groups that interact with the bifunctional catalysts (Figure 7). The author obtained three kinds of axially chiral compounds –isoquinoline *N*-oxides (Chapter 3), benzamides (Chapter 4), and quinolines (Chapter 5) – in good-to-excellent enantioselectivities.

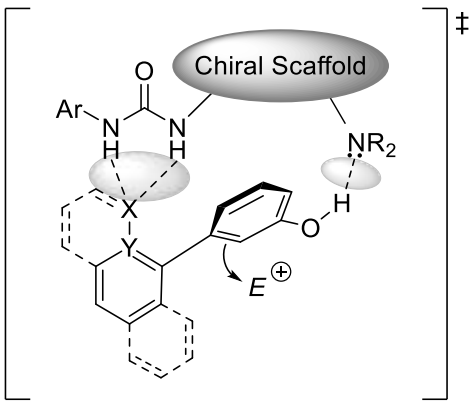
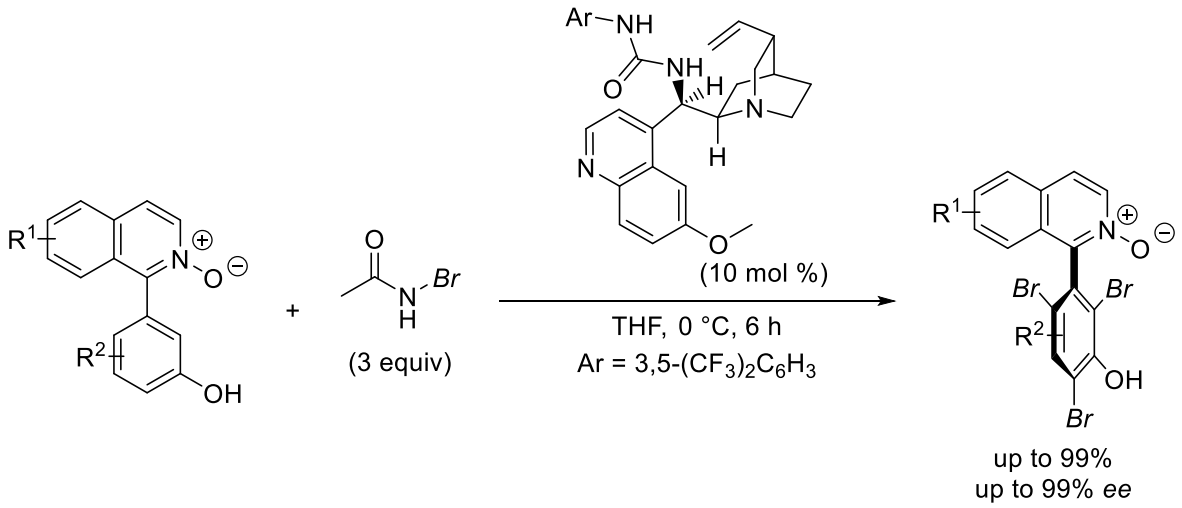


Figure 7. Multipoint recognition and activation of specific conformations of substrates bearing a rotational axis by bifunctional organocatalysts.

4.2.1. Enantioselective Syntheses of Axially Chiral Isoquinoline *N*-Oxides by Bifunctional Organocatalysts (Chapter 3)

Axially chiral *N*-oxides are known to be promising chiral catalysts,[34] but there are currently no catalytic enantioselective synthetic routes to prepare them. In this chapter, the author presents highly enantioselective brominations of 1-(3-hydroxyphenyl)isoquinoline 2-oxides with bifunctional organocatalysts (Scheme 13).[35] The negatively charged oxygen atom of the substrates behaves as a hydrogen bond acceptor to interact with the urea moiety in the catalysts, while the hydroxy group is recognized by the tertiary amino group. Excellent enantioselectivities could be achieved from substrates with various substituents at the isoquinoline or phenol ring.



Scheme 13. Asymmetric syntheses of axially chiral isoquinoline *N*-oxides by bifunctional organocatalysts.

Some experimental results that provide insight into the reaction pathways suggest that the first bromination occurs at the 2-position, and the enantioselectivity is determined at this stage because the monobrominated substrate already possesses a large rotational barrier due to the steric clash with the bromine atom (Figure 8). To our knowledge, these are the first reported asymmetric approaches to such axially chiral biaryls using bifunctional organocatalysts.[36]

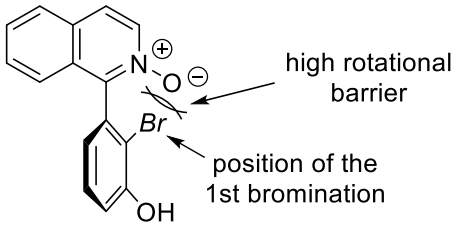
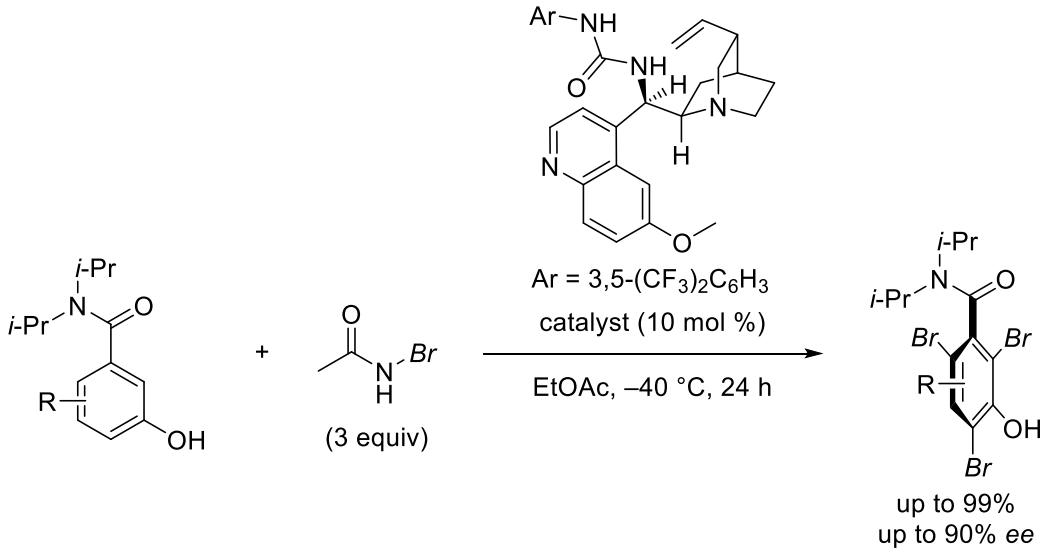


Figure 7. The intermediate after the first bromination in the synthesis of the isoquinoline *N*-oxide.

4.2.2. Enantioselective Syntheses of Axially Chiral Benzamides by Bifunctional Organocatalysts (Chapter 4)

Benzamides can also possess axial chirality around the bonds between the aromatic rings and the carbonyl groups when there are bulky substituents at the nitrogen atoms. There are many chiral benzamides known to exhibit strong biological activity that are of interest to many chemists.[37] Therefore, the author utilized the carbonyl groups of benzamides as hydrogen bond accepters to develop asymmetric syntheses of axially chiral benzamides with bifunctional organocatalysts (Scheme 14).[38]

Investigations into the reaction pathways suggest that the first brominations occur at the 2-position, similar to the isoquinoline *N*-oxides in Chapter 3. However, the rotational barriers of the benzamides were not high enough to stop the rotation of monobrominated compounds at ambient temperature. Hence, satisfying enantioselectivity could only be achieved at temperatures below –40 °C, assisted also by the bulky substituents on the nitrogen atoms (Figure 9). After the first brominations, rotation around the axes is almost completedly inhibited at low temperature, and the enantioselectivity is determined; subsequently, the second and third brominations could proceed without erosion of the optical purity.



Scheme 14. Asymmetric syntheses of axially chiral benzamides by a bifunctional organocatalyst.

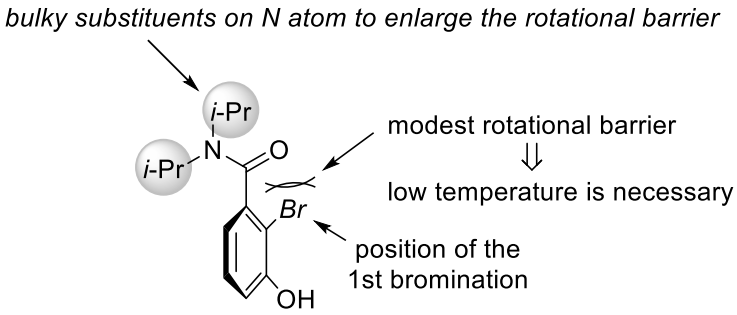
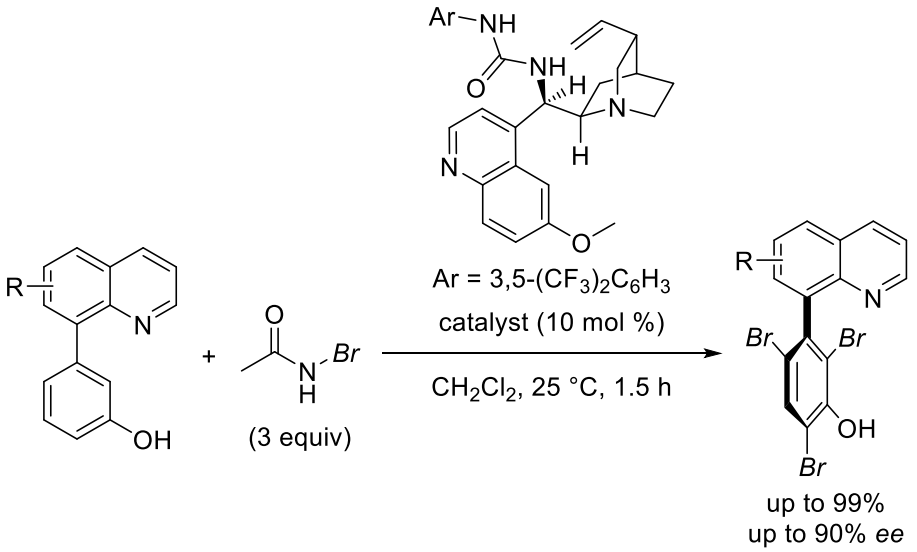


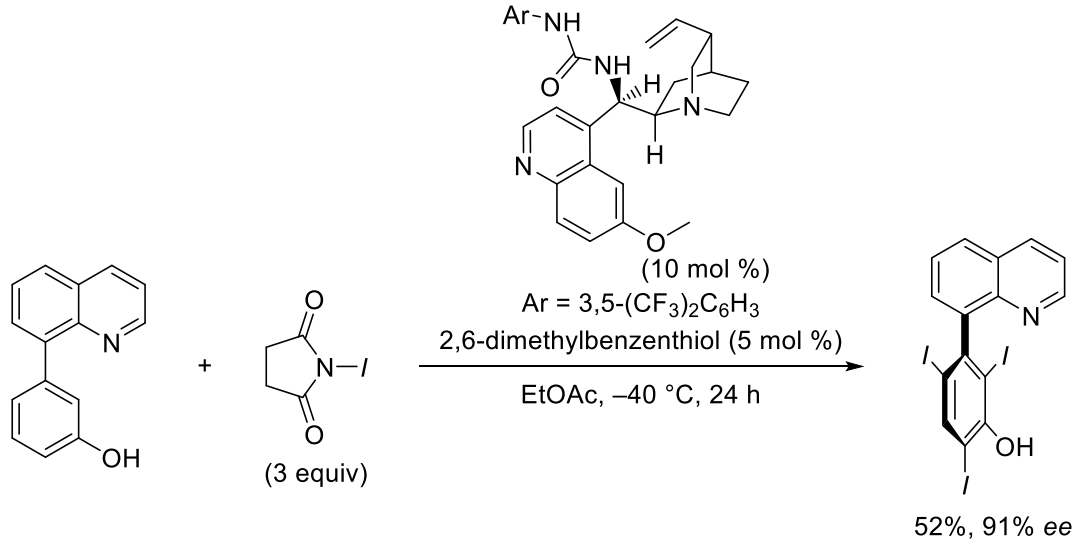
Figure 9. The intermediate after the first bromination in the synthesis of the benzamide.

4.2.3. Enantioselective Synthesis of Axially Chiral Quinolines by Bifunctional Organocatalysts (Chapter 5)

Quinolines have a lone pair of electrons on the nitrogen atom that can participate in hydrogen bonding; therefore, the author next sought to apply his synthetic strategy to the asymmetric syntheses of axially chiral quinolines (Scheme 15).[39,40] The bifunctional catalysts could affect the brominations of the 3-(quinolin-8-yl)phenols in high enantioselectivity. The author also found that asymmetric iodination could be achieved in good enantioselectivity with the bifunctional organocatalyst (Scheme 16).



Scheme 15. Asymmetric syntheses of axially chiral quinolines via brominations by a bifunctional organocatalyst.



Scheme 16. Asymmetric synthesis of an axially chiral quinoline via iodination by a bifunctional organocatalyst.

Different from the previous reactions, the enantioselectivity seemed to be determined at the bromination steps where both ortho positions of the rotational axes were substituted (Figure 10). Encouraged by this, the author next investigated the iodination of a substrate with a bromine substituent, which still had a low rotational barrier, giving the optically active product with two kinds of halogen atoms in 88 % *ee* (Scheme 17). The product could be used as a chiral building

block for expanded π-conjugated molecules or polysubstituted arenes possessing axial chirality.

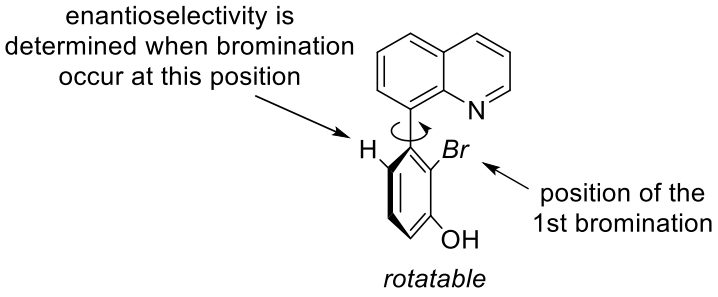
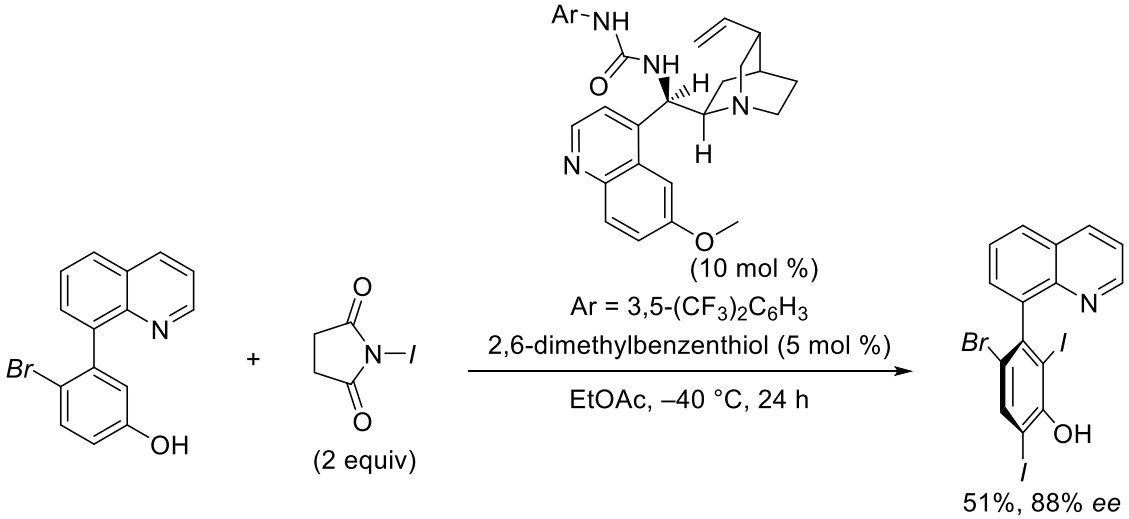


Figure 10. The intermediate after the first bromination in the synthesis of the quinoline.



Scheme 17. Asymmetric iodination of monobrominated substrate.

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Instrumental and Materials

^{1}H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using tetramethylsilane as an internal standard for 1H NMR (δ = 0 ppm) and $CDCl_3$ as an internal standard for ^{13}C NMR (δ = 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard (δ = 0 ppm). Mass spectra were recorded on a Thermo Scientific Exactive (ESI, APCI) spectrometers. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on Bruker Smart APEX X-Ray diffractometer and Rigaku XtalAB mini diffractometer and Rigaku R-AXIS RAPID diffractometer equipped with a CCD detector. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification. DFT calculations were performed with Gaussian 09 packages unless otherwise noted. The DFT method was employed using the B3LYP hybrid functional. Structures were optimized with the 6-31G(d) basis set.

Chapter 1

Asymmetric Syntheses of Chromans via Intramolecular Oxy-Michael Addition Reactions

Cinchona-alkaloid-urea-based bifunctional organocatalysts facilitate the catalytic asymmetric synthesis of chroman derivatives via an intramolecular oxy-Michael addition reaction. Phenol derivatives bearing an easily available (*E*)-α,β-unsaturated ketone or a thioester moiety are useful substrates for the title transformation. This method represents a facile synthesis of various optically active 2-substituted chromans in high yield.

Introduction

Chiral 2-substituted chromans are found in an extremely wide range of bioactive compounds, as typified by vitamin E, and their biological activities have attracted much attention (Fig. 1).[1] Thus, the enantioselective synthetic methods toward chroman derivatives are in high demand; indeed, a number of strategies have been reported, addressing this need.[2–5] Among them, the intramolecular oxy-Michael addition is a promising method for constructing the desired framework from easily available phenol derivatives bearing an *α*,*β*-unsaturated carbonyl; the remaining carbonyl group in the product allows for further structural modification, which may lead to the synthesis of various pharmacological compounds. However, only a few examples of such approaches have been reported to date.[4,5] In addition, most of these strategies display a significant limitation in that the substrate, typically an *α*,*β*-unsaturated ester moiety, must be in its (*Z*)-isomer form, and that the (*Z*)-forms of more electron-deficient olefins (*α*,*β*-unsaturated ketones and thioesters) are extremely difficult to prepare by means of simple methods such as Wittig reactions using stabilized ylides (Scheme 1). These problems must be solved to expand the scope of synthetically accessible chromans. The author has recently established a useful strategy for the asymmetric synthesis of five- or six-membered oxygen heterocycles via an intramolecular oxy-Michael addition starting from (*E*)-*α*,*β*-unsaturated carbonyl substrates (Scheme 2).[6,7] This method utilizes multipoint substrate recognition by bifunctional organocatalysts through hydrogen bonding;[8,9] the mild characteristics of activation through hydrogen bonding facilitate concerted catalysis efficient forobtaining high enantioselectivity even in rapid intramolecular processes for cycloetherifications.[6d] The efficiency of this protocol prompted him to explore the use of bifunctional organocatalysts for the intramolecular oxy-Michael addition from phenol derivatives bearing an (*E*)-*α*,*β*-unsaturated carbonyl moiety.[5,10] In this study, he presents a novel enantioselective synthesis of 2-substituted chromans via an intramolecular oxy-Michael addition using cinchona-alkaloid-urea-based bifunctional organocatalysts.

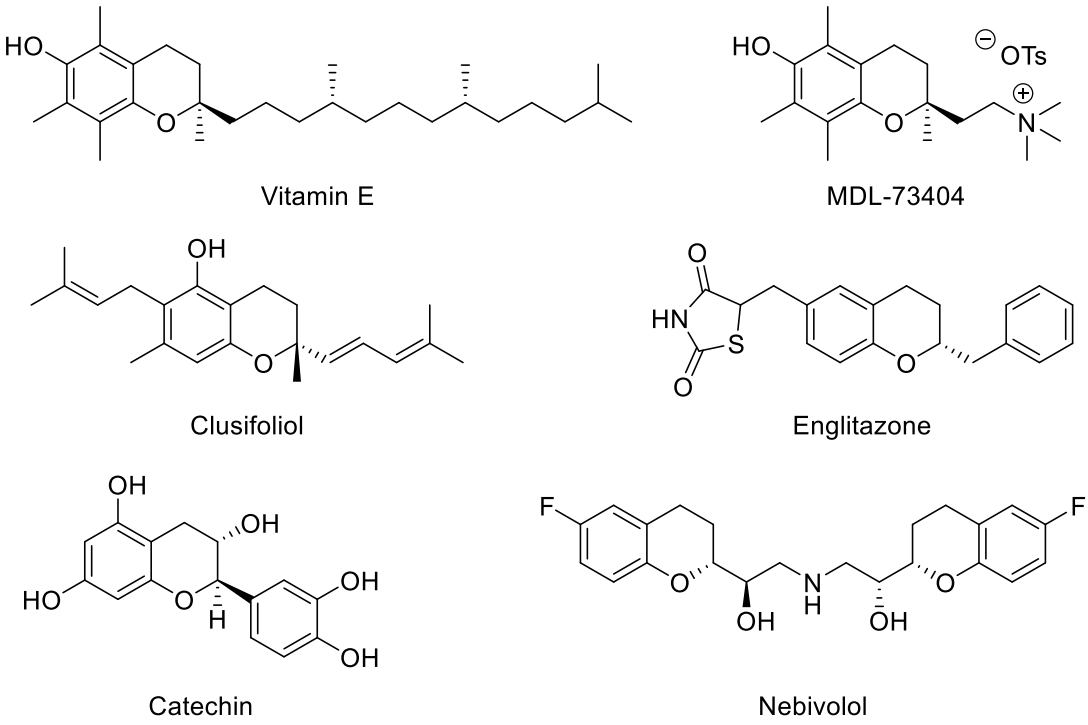
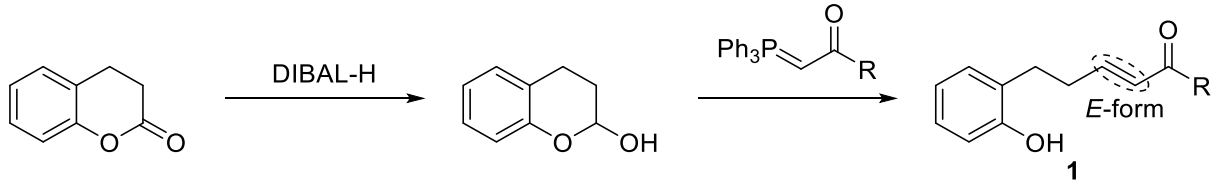
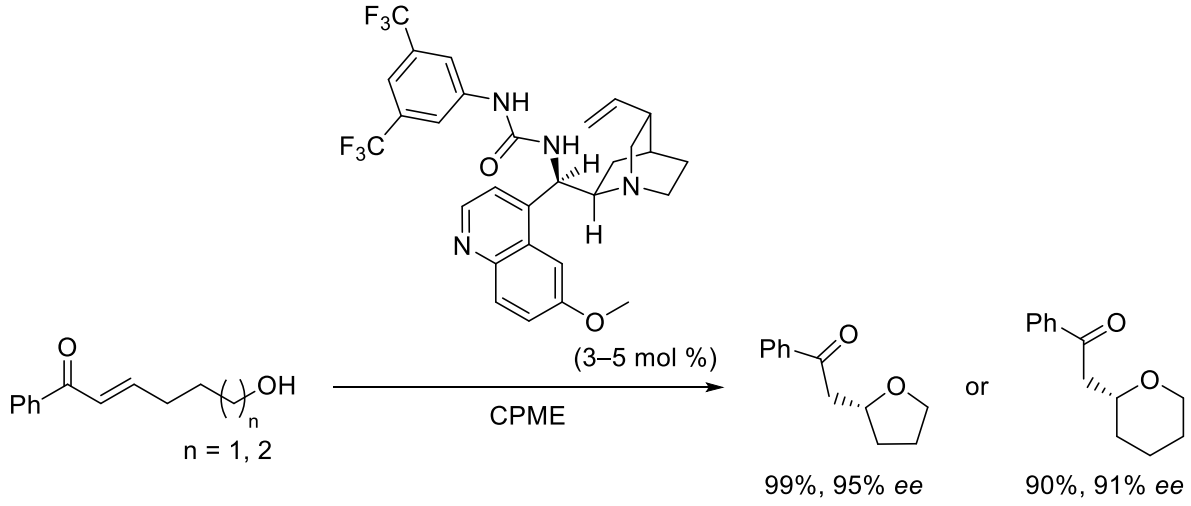


Figure 1. Representative 2-substituted chromans in bioactive compounds.



Scheme 1. Facile synthetic route to substrates **1**.



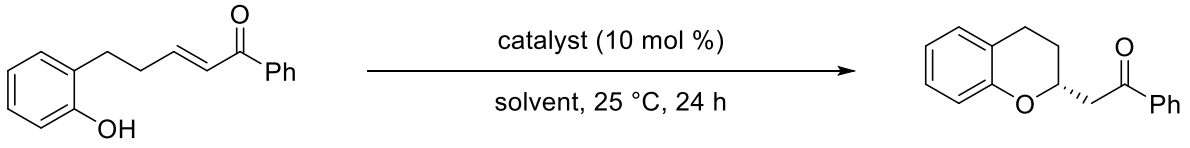
Scheme 2. Asymmetric synthesis of 2-substituted THF and THP by a bifunctional organocatalyst.

Results and Discussion

The author initiated his investigation using substrate **1a** with 10 mol % quinidine-derived bifunctional aminourea catalyst **3a** in CH_2Cl_2 at 25 °C over 24 h; chroman product **2a** was obtained with moderate enantioselectivity (Table 1, entry 1). Solvent screening revealed that THF was effective for both enantioselectivity and yield (Table 1, entry 9). A decrease in reaction temperature improved the enantioselectivity (Table 1, entry10). However, the use of a smaller amount of catalyst (5 mol %) led to lower enantioselectivity, which was likely due to the competing non-catalytic reaction (Table 1, entry 11). A time of 12 h was found to be sufficient for reaction completion, and higher enantioselectivity could be obtained (Table 1, entry 12). In this reaction, the urea catalyst **3a** was revealed to be more efficient than the corresponding thiourea catalyst **3b** (Table 1, entries 12 and 13).[7a] Further screening of urea catalysts showed that quinine-derived **3d** was an efficient catalyst for obtaining the opposite enantiomer of **2a** with good enantioselectivity (Table 1, entry 15).

The starting materials **1** were prepared through the synthetic route indicated in Scheme 1.[13] The investigation was initiated using substrate **1a** with 5 mol % quinidine derived bifunctional thiourea catalyst **3a** in cyclopentyl methyl ether (CPME) at 25 °C, and indoline product **2a** was obtained enantioselectively (Table 1, entry 1).

Table 1. Optimization of reaction conditions[a]



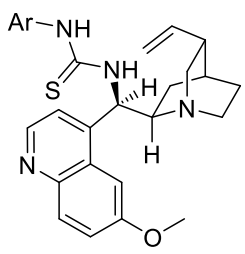
1a **2a**

entry	catalyst	solvent	yield[b] (%)	*ee* (%)
1	**3a**	CH_2Cl_2	99	63
2	**3a**	benzene	87	60
3	**3a**	pyridine	99	58
4	**3a**	DMSO	88	25
5	**3a**	Et_2O	91	69

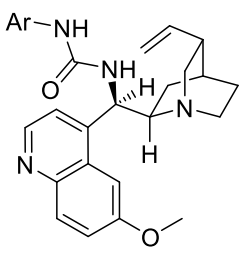
Table 1. (Continued)

6	**3a**	*t*-BuOMe	99	55
7	**3a**	CPME[c]	93	63
8	**3a**	1,4-dioxane	96	72
9	**3a**	THF	99	72
10[d]	**3a**	THF	99	81
11[d,e]	**3a**	THF	99	76
12[d,f]	**3a**	THF	95	84
13[d,f]	**3b**	THF	95	75
14[d,f]	**3c**	THF	86	82
15[d,f]	**3d**	THF	98	–80
16[d,f]	**3e**	THF	86	–78

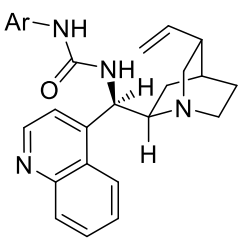
[a] Reactions were run using **1a** (0.1 mmol) and the catalyst (0.01 mmol) in the solvent (0.2 mL). [b] Isolated yields. [c] CPME = cyclopentyl methyl ether. [d] Reactions were run at 0 °C. [e] Reaction was run using 5 mol % of **3a** (0.005 mmol). [f] Reactions were run for 12 h.



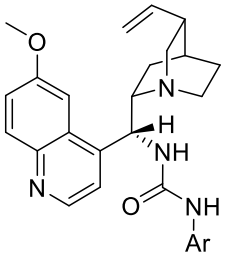
3a



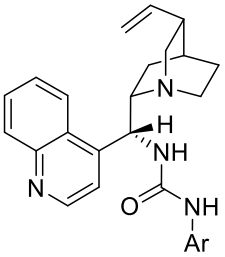
3b



3c



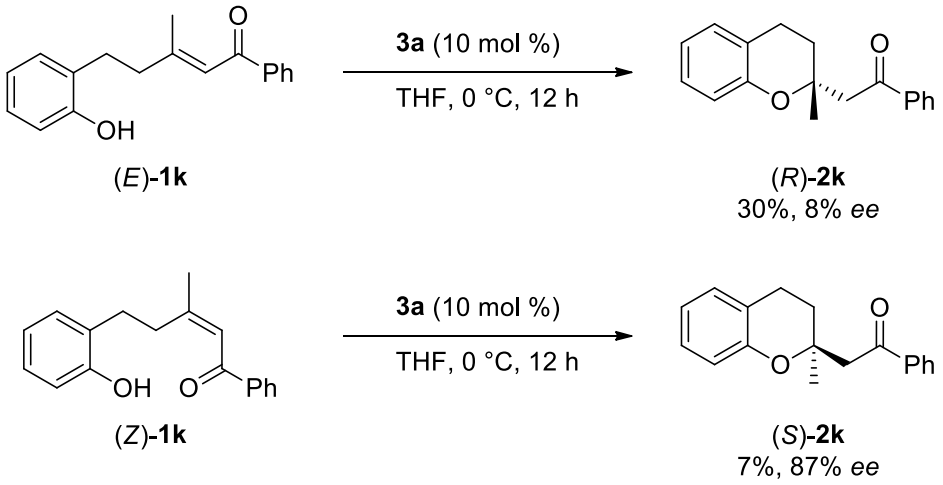
3d



3e

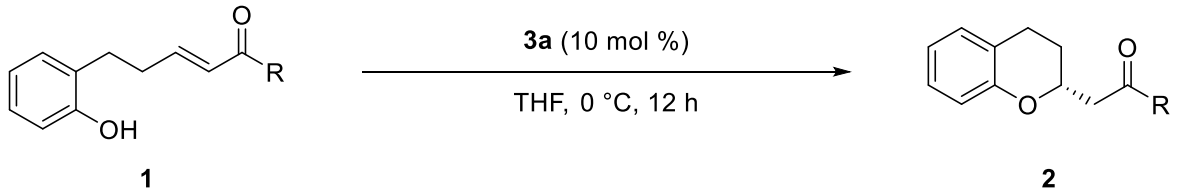
With catalyst **3a** and optimized reaction conditions identified, the author next investigated the reactions of substrates bearing other (*E*)-Michael-acceptor moieties.[11] Electron-rich substrates were also effective, providing the chroman products in high yield and comparable enantioselectivity (Table 2, entries 2 and 3). A starting material bearing an electron-withdrawing group afforded the corresponding product in high yield, although the enantiomeric excess was slightly lower (Table 2, entry 4). A substrate with a *p*-bromophenyl substituent yielded the corresponding product quantitatively in high enantioselectivity (Table 2, entry 5); however, a 2-naphthyl-substituted enone gave the resultant product in lower yield and stereoselectivity (Table 2, entry 6). Unfortunately, a methylketone proved to be an unsuccessful substrate (Table 2, entry 7). Substituents on the phenol moiety were also investigated, and a substrate with a methoxy group

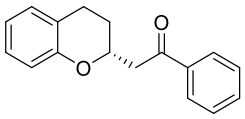
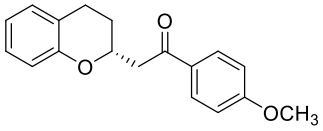
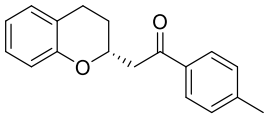
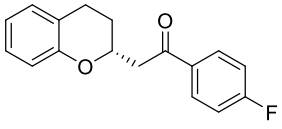
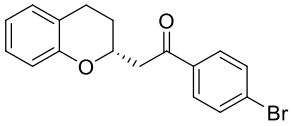
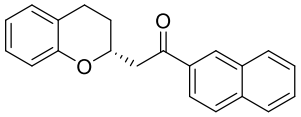
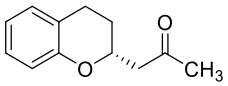
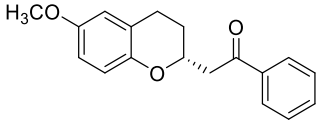
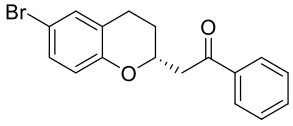
gave the corresponding product in good yield with moderate enantioselectivity (Table 2, entry 8), although a phenol derivative with a bromo group resulted in lower yield and stereoselectivity (Table 2, entry 9). Although reactions from *β*-disubstituted *α*,*β*-unsaturated ketones were also examined, they were less reactive in this catalytic process (Scheme 3). *β*-Disubstituted *α*,*β*-unsaturated ketones **1k** were less reactive through this catalytic process, and the enantiomeric excess of (*R*)-**2k** obtained from (*E*)-**1k** were only slight presumably because of the larger impact of noncatalytic racemic reaction under the current condition. On the other hand, the reaction starting from (*Z*)-**1k** afforded the opposite enantiomer (*S*)-**2k** with high enantioselectivity albeit in modest yield.



Scheme 3. Reactions from *β*-disubstituted *α*,*β*-unsaturated ketones.

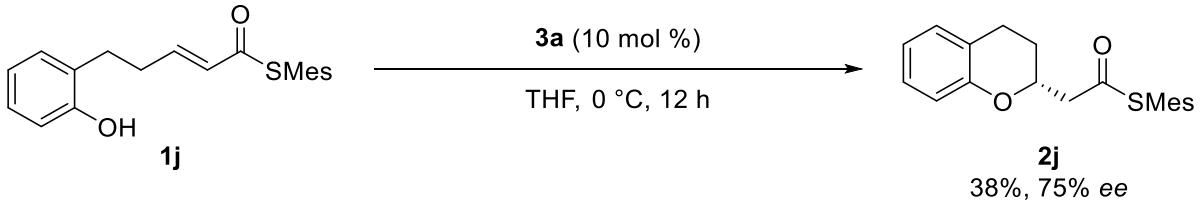
Table 2. Scope of substrates[a]



entry	product (**2**)	yield[b] (%)	*ee* (%)
1	 **2a**	95	84
2	 **2b**	81	84
3	 **2c**	95	84
4	 **2d**	95	70
5	 **2e**	99	83
6	 **2f**	66	72
7	 **2g**	64	36
8	 **2h**	86	74
9	 **2i**	68	65

[a] Reactions were run using **1** (0.1 mmol) and **3a** (0.01 mmol) in THF (0.2 mL). [b] Isolated yields.

To the author's delight, an *α*,*β*-unsaturated thioester participated in the cyclization reaction, yielding a chroman derivative suitable for various subsequent transformations, demonstrating the synthetic utility of his method (Scheme 4). The absolute configuration of **2e** was determined as (*R*) using X-ray analysis (see Experimental Section for details), and the configurations of all other examples were assigned accordingly.



Scheme 4. Reaction of *α*,*β*-unsaturated thioester.

Conclusion

In summary, the author has presented a novel asymmetric chroman synthesis via an intramolecular oxy-Michael addition employing bifunctional aminourea catalysts. In this method, substrates bearing an easily available (*E*)-Michael acceptor including *α*,*β*-unsaturated ketones and thioesters could be used, thereby leading to a facile and versatile approach to optically active chromans. Further studies on the expansion of the substrate scope and the application of this methodology toward other heterocyclic scaffolds are currently underway in his laboratory and will be reported in due course.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification. Substrate **1** were prepared from commercially available starting materials. Ylides used in Wittig reaction for substrate **1** were prepared according to the literature.[11] *β*-Disubstituted *α,β*-unsaturated ketones **1k** were prepared by modified procedures of the literature methods.[12,13]

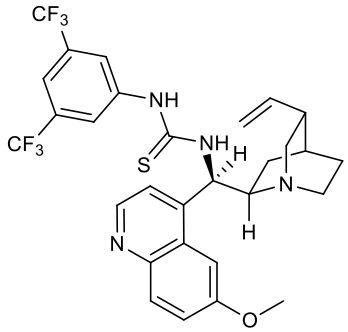
General procedure for asymmetric synthesis of 2-substituted chromans 2

In a 5-mL vial, the author sequentially added substrate **1** (0.10 mmol), THF (0.2 mL), and quinidine-derived bifunctional catalyst **3a** (0.010 mmol). The mixture was stirred in an oil bath maintained at 0 °C for 12 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding 2-substituted chroman **2**. Racemic compounds were prepared using *p*-toluenesulfonic acid as a catalyst.

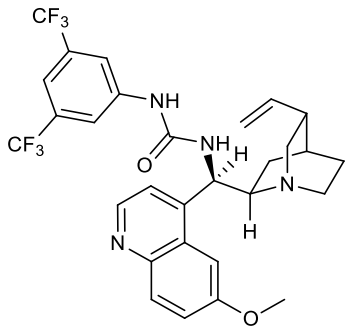
General procedure for preparation of bifunctional catalysts 3

Bifunctional organocatalysts **3** were prepared by the literature procedure.[14] A cinchona alkaloid (5 mmol) and triphenylphosphine (1.6 g, 6 mmol) were dissolved in THF (25 mL), and the solution was cooled to 0 °C. Diethyl azodicarboxylate (1.0 g, 6 mmol) was subsequently added. To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (1.3 mL, 6 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to ambient temperature. After being stirred for 24 h, it was heated to 50 °C and stirred for 10 h. Triphenylphosphine (1.7 g, 6.5 mmol) was added again, and the mixture was stirred at 50 °C for additional 15 h. After the solution was cooled to ambient temperature, H_2O (0.5 mL) was added, and the solution was stirred for 24 h. The solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2/10% aqueous HCl (25 mL/25 mL). The aqueous phase was separated and washed with CH_2Cl_2 (25 mL × 4). It was subsequently made alkaline with aqueous ammonia, and the aqueous phase was extracted with CH_2Cl_2 (25 mL × 4). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 9/1) then $CHCl_3$/CH_3OH (v/v = 8/2) as an eluent gave the corresponding 9-amino(9-deoxy)cinchona alkaloids. Next, to the solution of the obtained 9-amino(9-

deoxy)cinchona alkaloid in THF (6 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate or isothiocyanate (1 equiv) in THF (4 mL) at ambient temperature. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH_3OH (v/v = 95/5–97.5/2.5) or EtOAc as an eluent gave the corresponding bifunctional organocatalyst **3**. The characterization results are as below.

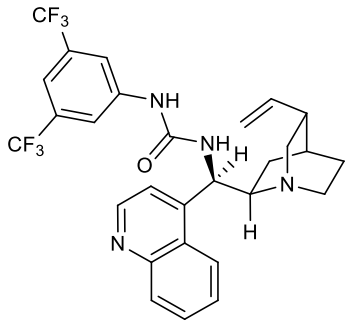


3a. White solid; 41% yield (for 2steps from quinidine). $[\alpha]_D^{23}$ +122.6 (*c* 1.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.65 (br s, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.86 (s, 2H), 7.67 (s, 1H), 7.59 (br s, 1H), 7.40 (d, *J* = 9.0 Hz, 1H), 7.23 (br s, 1H), 5.86 (br s, 2H), 5.19 (br s, 1H), 5.15 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 3.22 (br s, 1H), 3.10 (br s, 1H), 3.03 (m, 2H), 2.94 (m, 1H), 2.38 (m, 1H), 1.70 (s, 1H), 1.61 (m, 2H), 1.27 (br s, 1H), 1.02 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.0, 158.1, 147.3, 144.7, 144.5, 140.1, 139.6, 132.5 (q, *J* = 33.6 Hz), 131.6, 128.0, 123.5, 122.9 (q, *J* = 273.0 Hz), 122.3, 118.7, 115.3, 101.7, 61.4, 55.6, 48.5, 47.1, 38.7, 27.1, 26.1, 25.0. Mp. 125.0–125.2 °C. IR (KBr): 3221, 2944, 2361, 1735, 1623, 1511, 1475, 1384, 1278, 1177, 1134, 1034, 959, 916, 884, 850, 826, 682 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4OS$: $[M+H]^+$, 595.1966. Found: *m*/*z* 595.1961.

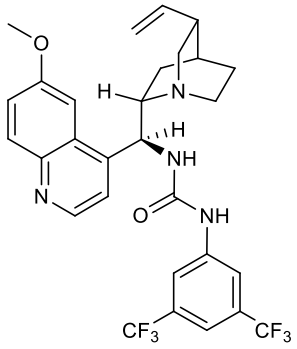


3b. White solid; 30% yield (for 2steps from quinidine). $[\alpha]_D^{18}$ +840.0 (*c* 2.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.76 (d, *J* = 4.5 Hz, 1H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.78 (s, 2H), 7.60 (s, 1H), 7.41

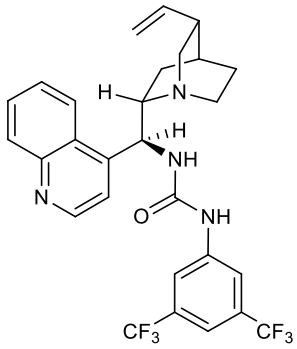
(m, 3H), 6.29 (br s, 1H), 5.88 (ddd, *J* = 15.0, 10.0, 4.0 Hz, 1H), 5.33 (br s, 1H), 5.13 (m, 2H), 3.99 (s, 3H), 2.97 (d, *J* = 10.0 Hz, 3H), 2.86 (t, *J* = 8.0 Hz, 2H), 2.23 (m, 1H), 1.82 (br s, 3H), 1.68 (br s, 1H), 1.51 (m, 1H), 1.03 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 158.4, 156.9, 156.2, 155.1, 147.7, 145.1, 140.9, 140.1, 132.3 (q, *J* = 33.2 Hz), 132.1, 128.3, 123.4 (q, *J* = 272.6 Hz), 118.5, 115.9, 115.4, 110.0, 101.7, 60.6, 55.8, 49.3, 47.2, 39.1, 32.2, 27.4, 26.6, 25.5. ^{19}F NMR ($CDCl_3$) δ 98.8. Mp. 133.0–133.5 °C. IR (KBr): 3321, 3080, 2941, 2875, 1705, 1676, 1624, 1570, 1511, 1475, 1434, 1389, 1279, 1245, 1229, 1179, 1132, 1096, 1036, 945, 917, 880, 852, 828, 703, 682 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4O_2$: $[M+H]^+$, 580.2223. Found: *m*/*z*580.2209.



3c. White solid; 40% yield (for 2steps from cinchonine). $[\alpha]_D^{23}$ +194.9 (*c* 0.59, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.91 (d, *J* = 4.5 Hz, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.18 (dd, *J* = 8.3, 0.75 Hz, 1H), 7.79 (s, 2H), 7.76 (dd, *J* = 8.3, 1.3, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 4.5 Hz, 1H), 7.43 (s, 1H), 6.35 (br s, 1H), 5,87 (ddd, *J* = 18.1, 15.0, 6.0 Hz, 1H), 5.30 (br s, 1H), 5.13 (dd, *J* = 24.0, 7.5 Hz, 2H), 2.94 (m, 5H), 2.31 (m, 1H), 1.84 (br s, 1H), 1.65 (br s, 1H), 1.57 (m, 1H), 1.49 (m, 1H), 1.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 154.9, 150.1, 148.7, 140.7, 139.6, 132.2 (q, *J* = 33.2 Hz), 130.6, 129.4, 127.0, 123.7 (q, *J* = 273.0 Hz), 123.1, 118.26, 118.23, 115.76, 115.73, 115.70, 115.3, 61.1, 49.0, 47.0, 39.0, 29.7, 27.3, 26.3, 25.0. ^{19}F NMR ($CDCl_3$) δ 98.8. Mp. 193.5–194.0 °C. IR (KBr): 3289, 3238, 3081, 2942, 2875, 2366, 1705, 1676, 1570, 1511, 1475, 1389, 1279, 1243, 1180, 1132, 945, 916, 881, 761, 683, 624 cm^{-1}. HRMS Calcd for $C_{28}H_{27}F_6N_4O$: $[M+H]^+$, 549.2084. Found: *m*/*z* 549.2077.



3d. White solid; 30% yield (for 2steps from quinine). $[\alpha]_D^{23}$ +20.4 (*c* 1.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.83 (d, *J* = 4.5 Hz, 1H), 8.06 (d, *J* = 9.5 Hz, 1H), 7.94 (br s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.42 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.34 (d, *J* = 4.5 Hz, 1H), 7.32 (s, 1H), 6.13 (br s, 1H), 5.64 (ddd, *J* = 17.0, 10.3, 6.8 Hz, 2H), 5.01 (d, *J* = 10.0 Hz, 1H), 4.84 (d, *J* = 17.0 Hz, 1H), 4.02 (s, 3H), 3.54 (br s, 1H), 3.18 (br s, 1H), 2.95 (m, 1H), 2.71 (m, 1H), 2.24 (br s, 2H), 2.11 (br s, 1H), 1.66 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 158.4, 154.6, 153.7, 147.3, 145.1, 140.5, 140.4, 131.932 (q, *J* = 33.2 Hz), 131.927, 130.2, 123.0 (q, *J* = 273.0 Hz), 118.4, 115.6, 115.1, 112.5, 109.7, 103.9, 60.1, 55.8, 55.4, 43.6, 41.4, 40.7, 38.6, 27.4, 26.9. ^{19}F NMR ($CDCl_3$) δ 98.6. Mp. 134.0–135.0 °C. IR (KBr): 3327, 3083, 2944, 2869, 2360, 1700, 1623, 1570, 1512, 1476, 1388, 1279, 1245, 1230, 1179, 1132, 1034, 881, 852, 682 cm^{-1}. HRMS Calcd for $C_{29}H_{29}F_6N_4O_2$: $[M+H]^+$, 580.2223. Found: *m*/*z* 580.2181.



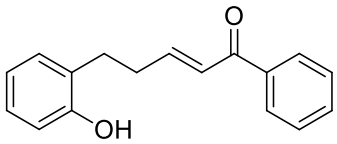
3e. White solid; 40% yield (for 2steps from cinchonidine). $[\alpha]_D^{23}$ –16.3 (*c* 3.67, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.93 (d, *J* = 3.0 Hz, 1H), 8.44 (d, *J* = 8.5 Hz, 1H), 8.17 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.76 (m, 3H), 7.66 (m, 1H), 7.48 (d, *J* = 5.0 Hz, 1H), 7.38 (s, 1H), 6.49 (br s, 1H), 5.61 (ddd, *J* = 17.3, 10.3, 7,5 Hz, 1H), 5.44 (br s, 1H), 4.90 (m, 2H), 3.17 (br s, 1H), 2.99 (dd, *J* = 13.5, 10.0 Hz, 2H), 2.61 (m, 1H), 2.41 (m, 2H), 2.23 (m, 1H), 1.63 (m, 2H), 1.56 (m, 1H), 1.36 (m, 1H), 0.93 (dd, *J* = 13.5, 6.0 Hz 1H). ^{13}C NMR ($CDCl_3$) δ 154.8, 149.9, 148.6, 148.5, 141.5, 140.8, 140.7, 132.0 (q, *J* = 33.2 Hz), 130.3, 129.6, 127.2, 123.28, 123.11 (q, *J* = 273.0 Hz), 118.2, 115.6, 114.8, 113.0,

61.9, 55.5, 40.9, 39.1, 35.0, 27.6, 27.0, 26.0. ^{19}F NMR ($CDCl_3$) δ 98.7. Mp. 140.0–141.0 °C. IR (KBr): 3309, 3081, 2947, 2869, 2360, 1700, 1623, 1570, 1511, 1473, 1389, 1346, 1279, 1243, 1180, 1132, 882, 760, 704, 683 cm^{-1}. HRMS Calcd for $C_{28}H_{27}F_6N_4O$: $[M+H]^+$, 549.2084. Found: *m*/*z* 549.2076.

General procedure for preparation of substrate 1

To a solution of a 3,4-dihydrocoumarin derivative (3.1 mL, 25 mmol) in toluene (25 mL) was added DIBAL-H (ca. 1.0 M hexane solution, 25 mL, 25 mmol) dropwise at –78 °C, and the mixture was stirred for 1 h. The reaction mixture was allowed to warm slowly to 0 °C. The reaction was quenched with 1 M aquous HCl (20 mL), and the mixture was subsequently extracted with toluene. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave chroman-2-ol as a colorless oil quantitatively. To the solution of chroman-2-ol (0.15 g, 1.0 mmol) in CH_2Cl_2 (10 mL), an ylide (5.0 mmol) was added. The reaction mixture was stirred for 2 days at 30 °C. After the solvent was evaporated, the residue was passed through a short silica gel pad to remove triphenylphosphine oxide, and the filtrate was concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/THF (v/v = 2/1) as an eluent gave (*E*)-5-(2-hydroxyphenyl)-pent-2-en-1-one (**1**) as a white solid in 30–50% yield. The characterization results of **1** are as below.

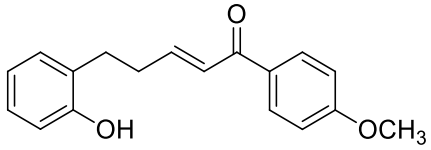
(*E*)-5-(2-Hydroxyphenyl)-1-phenylpent-2-en-1-one (1a).



White solid; 35% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.12 (m, 3H), 6.88 (m, 2H), 6.77 (dd, *J* = 6.5, 1.0 Hz, 1H), 5.23 (br s, 1H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.66 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 191.8, 153.9, 149.8, 137.8, 132.7, 132.2, 128.6, 128.5, 127.4, 127.2, 126.3, 120.6, 115.4, 33.0, 28.8. Mp. 103.0–103.5 °C. TLC: R_f 0.50 (hexane/THF = 2:1). IR (KBr): 3385, 3058, 2943, 1663, 1610, 1594, 1577, 1458, 1447, 1346, 1306, 1251, 1228, 1180, 1115, 974, 762, 753, 692, 658, 636, 490 cm^{-1}. HRMS Calcd for $C_{17}H_{17}O_2$: $[M+H]^+$, 253.1223. Found: *m*/*z* 253.1227.

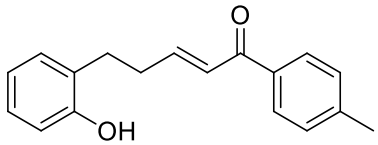
(*E*)-5-(2-Hydroxyphenyl)-1-(4-methoxyphenyl)pent-2-en-1-one (1b).



Yellow oil; 40% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.10 (dt, *J* = 15.5, 7.0 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.86 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.44 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.36 (d, *J* = 2.5 Hz, 1H), 5.08 (s, 1H), 3.76 (s, 3H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 191.2, 159.3, 154.3, 149.1, 138.0, 132.6, 130.8, 128.6, 128.5, 126.5, 119.5, 105.9, 102.0, 55.3, 33.3, 28.2. TLC: R_f 0.45 (hexane/THF = 2:1). IR (neat): 3421, 3065, 2931, 2848, 1685, 1620, 1582, 1506, 1449, 1282, 1201, 1157, 1128, 1114, 1036, 834, 756, 691, 474 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_3$: $[M+H]^+$, 283.1329. Found: *m*/*z* 283.1324.

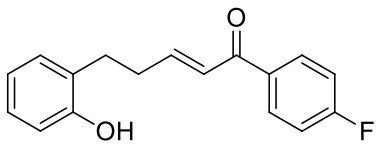
(*E*)-5-(2-Hydroxyphenyl)-1-(4-methylphenyl)pent-2-en-1-one (1c).



White solid; 30% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.81 (dt, *J* = 7.5, 1.5 Hz, 2H), 7.25 (m, 2H), 7.14 (dd, *J* = 6.0, 1.5 Hz, 1H), 7.09 (m, 2H), 6.89 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.86 (t, *J* =1.5 Hz, 1H), 6.77 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.13 (br s, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.65 (m, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 190.7, 153.6, 148.5, 143.4, 135.4, 130.3, 129.2, 128.7, 127.5, 127.2, 126.4, 120.9, 115.4, 32.9, 28.9, 21.6. Mp. 120.0–121.0 °C. TLC: R_f 0.48 (hexane/THF = 2:1). IR (KBr): 3262, 3024, 2954, 1956, 1654, 1612, 1591, 1564, 1457, 1349, 1254, 1230, 1179, 1110, 814, 760, 652, 461 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_2$: $[M+H]^+$, 267.1380. Found: *m*/*z* 267.1382.

(*E*)-1-(4-Fluorophenyl)-5-(2-hydroxyphenyl)pent-2-en-1-one (1d).

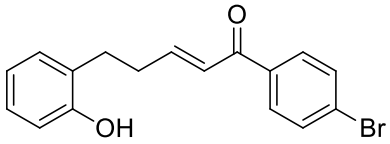


Yellow oil; 30% (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.17–7.08 (m, 5H), 6.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.84 (m, 1H), 6.78 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.37 (br s, 1H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.66 (m, 2H). ^{13}C NMR

($CDCl_3$) δ 189.7, 165.6 (d, *J* = 254.3 Hz), 153.7, 149.5, 134.2, 131.2 (d, *J* = 9.6 Hz) 130.3, 127.5, 127.2, 126.0, 120.8, 115.6 (d, *J* = 22.0 Hz), 115.4, 33.0, 28.8. ^{19}F NMR ($CDCl_3$) δ −56.0. TLC: R_f 0.50 (hexane/THF = 2:1). IR (KBr): 3266, 2940, 2371, 1662, 1618, 1597, 1507, 1457, 1335, 1231, 1157, 828, 755, 610 cm^{-1}. HRMS Calcd for $C_{17}H_{16}FO_2$: $[M+H]^+$, 271.1129. Found: *m*/*z* 271.1130.

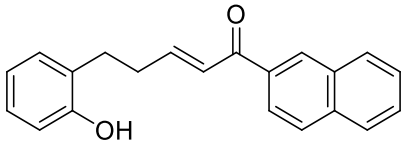
(*E*)-1-(4-Bromophenyl)-5-(2-hydroxyphenyl)pent-2-en-1-one (1e).



White soild; 40% (for the last step).

^1H NMR ($CDCl_3$) δ 7.74 (dt, *J* = 7.5, 2.0 Hz, 2H), 7.59 (dt, *J* = 7.5, 2.0 Hz, 2H), 7.10 (m, 3H), 6.88 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.81 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 4.89 (s, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.66 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 190.0, 153.5, 149.6, 136.7, 132.0, 131.8, 130.4, 130.1, 127.6, 127.1, 126.1, 121.0, 115.4, 32.9, 28.8. Mp. 93.0–94.0 °C. TLC: R_f 0.45 (hexane/THF = 2:1). IR (KBr): 3291, 3039, 2926, 2361, 1686, 1488, 1457, 1398, 1233, 1070, 1008, 758, 668, 374 cm^{-1}. HRMS Calcd for $C_{17}H_{16}BrO_2$: $[M+H]^+$, 331.0328. Found: *m*/*z* 331.0331.

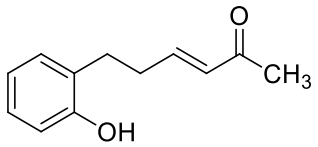
(*E*)-5-(2-Hydroxyphenyl)-1-(naphthalen-2-yl)pent-2-en-1-one (1f).



Yellow solid; 25% yield (for the last step).

^1H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.99 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 2H), 7.60 (m, 1H), 7.55 (m, 1H), 7.18 (m, 2H), 7.12 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.02 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.90 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.77 (dd, *J* =8.0, 1.0 Hz, 1H), 4.92 (s, 1H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 190.9, 153.5, 148.8, 135.4, 135.3, 132.6, 130.4, 130.0, 129.5, 128.4, 128.3, 127.8, 127.6, 127.2, 126.7, 126.5, 124.6, 121.0, 115.4, 33.0, 28.9. Mp. 139.0–140.0 °C. TLC: R_f 0.35 (hexane/THF = 2:1). IR (KBr): 3416, 3051, 2944, 2364, 1663, 1629, 1613, 1458, 1363, 1246, 1184, 1111, 824, 753, 616 cm^{-1}. HRMS Calcd for $C_{21}H_{19}O_2$: $[M+H]^+$, 303.1380. Found: *m*/*z* 303.1383.

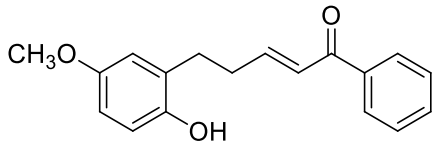
(*E*)-6-(2-Hydroxyphenyl)hex-3-en-2-one (1g).



White solid; 20% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.08 (m, 1H), 7.06 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.89 (dt, *J* = 16.0, 7.0 Hz, 1H), 6.84 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.21 (br s, 1H), 6.11 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.56 (m, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 199.3, 153.9, 148.4, 131.4, 130.1, 127.5, 127.1, 120.5, 115.3, 32.6, 28.8, 26.7. Mp. 63.5–64.5 °C. TLC: R_f 0.50 (hexane/THF = 2:1). IR (KBr): 3223, 3017, 2924, 2356, 1654, 1636, 1608, 1595, 1460, 1373, 1271, 1235, 1105, 973, 852, 753, 569 cm^{-1}. HRMS Calcd for $C_{12}H_{15}O_2$: $[M+H]^+$, 191.1067. Found: *m*/*z* 191.1070.

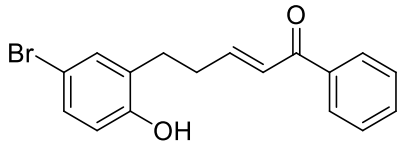
(*E*)-5-(2-Hydroxy-5-methoxyphenyl)-1-phenylpent-2-en-1-one (1h).



Pale yellow solid; 40% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.55 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.11 (dt, *J* = 16.5, 7.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.87 (dt, *J* = 15.0, 1.5 Hz, 1H), 6.43 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.37 (d, *J* = 2.0 Hz, 1H), 5.29 (s, 1H), 3.75 (s, 3H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.61 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 191.3, 159.2, 154.3, 149.4, 137.9, 132.7, 130.7, 128.6, 128.5, 126.3, 119.4, 105.7, 101.9, 72.4, 33.3, 28.2. Mp. 70.0–71.0 °C. TLC: R_f 0.36 (hexane/THF = 3:1). IR (KBr): 3084, 2929, 2837, 2349, 1731, 1681, 1659, 1563, 1462, 1189, 1120, 1028 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_3$: $[M+H]^+$, 283.1329. Found: *m*/*z* 283.1329.

(*E*)-5-(5-Bromo-2-hydroxyphenyl)-1-phenylpent-2-en-1-one (1i).

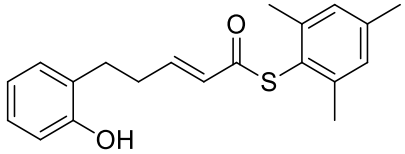


Colorless oil; 10% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.55 (tt, *J* = 7.0, 1.5 Hz, 1H), 7.49–7.45 (m, 3H), 7.19 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.07 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.87 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.66 (d, *J* = 8.5

Hz, 1H), 5.30 (s, 1H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 191.3, 152.71, 148.5, 137.8, 132.9, 132.7, 130.2, 129.6, 128.9, 128.5, 126.6, 117.0, 112.7, 32.8, 28.7. TLC: R_f 0.40 (hexane/THF = 3:1). IR (neat): 3019, 2872, 2788, 2349, 1769, 1737, 1681, 1650, 1567, 1511, 1453, 1426, 1334, 1243, 1173, 1121, 1025, 843 cm^{-1}. HRMS Calcd for $C_{17}H_{16}BrO_2$: $[M+H]^+$, 331.0328. Found: *m*/*z* 331.0327.

(*E*)-*S*-Mesityl 5-(2-hydroxyphenyl)pent-2-enethioate (1j).

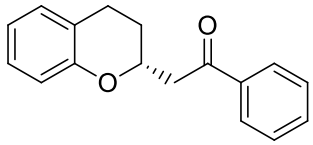


White solid; 32% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.12–7.02 (m, 3H), 6.98 (d, *J* = 0.50 Hz, 2H), 6.87 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.70 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.26 (dt, *J* = 15.5, 1.5 Hz, 1H), 5.03 (s, 1H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.56 (m, 2H), 2.32 (s, 6H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 188.1, 153.5, 145.6, 142.7, 139.8, 130.3, 129.2, 128.3, 127.5, 127.0, 123.5, 120.9, 115.3, 32.4, 28.7, 21.6, 21.1. Mp. 116.0–116.5 °C. TLC: R_f 0.41 (hexane/EtOAc = 3:1). IR (KBr): 3428, 3068, 2948, 1652, 1632, 1591, 1510, 1454, 1341, 1213, 1175, 1139, 1096, 963, 862, 750, 659 cm^{-1}. HRMS Calcd for $C_{20}H_{23}O_2S$: $[M+H]^+$, 327.1413. Found: *m*/*z* 327.1406.

Characterization Data of Products

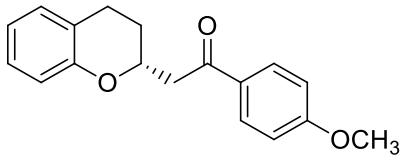
2-(Chroman-2-yl)-1-phenylethanone (2a).



Yield: 95%, 84% *ee*, white solid. $[\alpha]_D^{18}$ –39.5 (*c* 3.61, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (m, 2H), 7.59 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.49 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.09–7.05 (m, 2H), 6.84 (dt, *J* = 1.0, 7.0 Hz, 1H), 6.76 (dd, *J* = 8.5, 1.0 Hz, 1H), 4.69 (m, 1H), 3.57 (dd, *J* =16.0, 6.0 Hz, 1H), 3.18 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.94 (ddd, *J* = 16.5, 11.0, 6.0 Hz, 1H), 2.79 (ddd, *J* = 16.5, 5.5, 4.0 Hz, 1H), 2.20 (m, 1H), 1.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.6, 154.6, 137.2, 133.2, 129.5, 128.6, 128.2, 127.2, 121.8, 120.3, 116.8, 72.4, 44.2, 27.5, 24.5. Mp. 40.0–40.5 °C. TLC: R_f 0.60 (hexane/THF = 2:1). IR (KBr): 3076, 2916, 1685, 1582, 1487, 1451, 1218, 1116, 1051, 894, 756, 751, 692 cm^{-1}. HRMS Calcd for $C_{17}H_{17}O_2$: $[M+H]^+$, 253.1223. Found: *m*/*z* 253.1217. HPLC

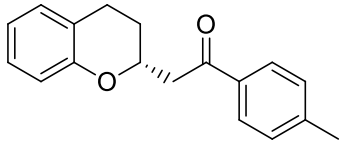
(Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 19.8 min, t_{major} = 22.1 min.

2-(Chroman-2-yl)-1-(4-methoxyphenyl)ethanone (2b).



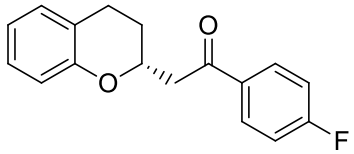
Yield: 81%, 84% *ee*, white solid. $[\alpha]_D^{18}$ –19.0 (*c* 5.20, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (dt, *J* = 9.5, 2.5 Hz, 2H), 7.07 (m, 2H), 6.96 (dt, *J* = 9.5, 2.5 Hz, 2H), 6.84 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.76 (dd, *J* = 7.5, 1.0 Hz, 1H), 4.67 (m, 1H), 3.88, (s, 3H), 3.52 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.13 (dd, *J* = 16.5, 7.5 Hz, 1H), 2.93 (m, 1H), 2.78 (ddd, *J* = 16.0, 5.0, 3.5 Hz, 1H), 2.20 (m, 1H), 1.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 196.1, 163.7, 154.6, 130.6, 130.3, 129.5, 127.2, 121.8, 120.2, 116.8, 113.8, 72.3, 55.5, 43.8, 27.5, 24.5. Mp.70.0–71.0 °C. TLC: R_f 0.57 (hexane/EtOAc = 3:1). IR (KBr): 3671, 3037, 2945, 2839, 1674, 1601, 1576, 1487, 1457, 1424, 1266, 1222, 1180, 1116, 895, 840, 769, 610 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_3$: $[M+H]^+$, 283.1329. Found: *m*/*z* 283.1322. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.0 min, t_{minor} = 12.1 min.

2-(Chroman-2-yl)-1-(4-methylphenyl)ethanone (2c).



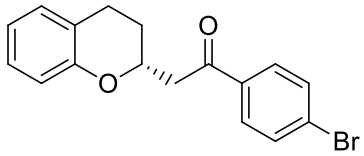
Yield: 95%, 84% *ee*, white solid. $[\alpha]_D^{18}$ –27.0 (*c* 3.95, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ7.89 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.27 (dd, *J* = 8.5, 0.50 Hz, 2H), 7.07–7.03 (m, 2H), 6.83 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.68 (m, 1H), 3.55 (dd, *J* = 16.5, 6.0 Hz, 1H), 3.16 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.93 (ddd, *J* = 16.5, 11.0, 6.0 Hz, 1H), 2.78 (ddd, *J* = 16.5, 5.0, 3.4 Hz, 1H), 2.43 (s, 3H), 2.20 (m, 1H), 1.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.3, 154.6, 144.1, 134.6, 129.5, 129.3, 128.4, 127.2, 121.8, 120.2, 116.8, 72.5, 44.0, 27.4, 24.5, 21.6. Mp. 78.0–79.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3038, 2962, 2358, 1674, 1607, 1570, 1487, 1457, 1361, 1301, 1244, 1180, 1053, 802, 746, 374 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_2$: $[M+H]^+$, 267.1380. Found: *m*/*z* 267.1373. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 4.8 min, t_{minor} = 5.6 min.

2-(Chroman-2-yl)-1-(4-fluorophenyl)ethanone (2d).



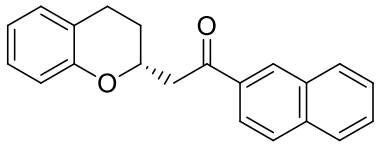
Yield: 95%, 70% *ee*, yellow oil. $[\alpha]_D^{18}$ –27.0 (*c* 3.95, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.15 (m, 2H), 7.07–7.06 (m, 2H), 6.85 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.75 (dd, *J* = 8.0 1.0 Hz, 1H), 4.67 (m, 1H), 3.54 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.14 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.94 (ddd, *J* = 16.5, 10.5, 6.0 Hz, 1H), 2.78 (ddd, *J* = 16.5, 6.0, 7.5 Hz, 1H), 2.20 (m, 1H), 1.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 196.0, 165.8 (d, *J* = 255.3 Hz), 154.5, 133.6, 130.9 (d, *J* = 9.2 Hz), 129.5, 127.2, 121.7, 120.3, 116.7, 115.7 (d, *J* = 22.0 Hz), 72.4, 44.1, 27.4, 24.4. ^{19}F NMR ($CDCl_3$) δ –57.0. Mp. 60.0–61.0 °C. TLC: R_f 0.48 (hexane/EtOAc = 3:1). IR (KBr): 3039, 2956, 2356, 1680, 1597, 1506, 1488, 1458, 1411, 1363, 1299, 1232, 1158, 1054, 989, 751, 605, 374, 341 cm^{-1}. HRMS Calcd for $C_{17}H_{16}FO_2$: $[M+H]^+$, 271.1129. Found: *m*/*z* 271.1121. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 5.3 min, t_{minor} = 6.8 min.

(*R*)-1-(4-Bromophenyl)-2-(chroman-2-yl)ethanone (2e).



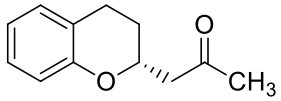
Yield: 99%, 83% *ee*, white solid. $[\alpha]_D^{18}$ –19.6 (*c* 2.80, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.87 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.62 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.08–7.04 (m, 2H), 6.84 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.66 (m, 1H), 3.52 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.12 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.93 (ddd, *J* = 16.5, 11.0, 6.0 Hz, 1H), 2.78 (ddd, *J* = 16.5, 5.0, 3.0 Hz, 1H), 2.18 (m, 1H), 1.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 196.7, 154.5, 136.0, 132.0, 129.8, 129.5, 128.5, 127.3, 121.7, 120.4, 116.8, 72.4, 44.2, 27.5, 24.5. Mp. 77.5–78.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3067, 2939, 2364, 1680, 1585, 1487, 1457, 1301, 1242, 1201, 1054, 988, 807, 746 cm^{-1}. HRMS Calcd for $C_{17}H_{16}BrO_2$: $[M+H]^+$, 331.0328. Found: *m*/*z* 331.0319. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.4 min, t_{major} = 5.7 min.

2-(Chroman-2-yl)-1-(naphthalen-2-yl)ethanone (2f).



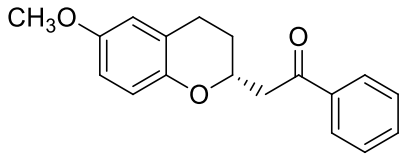
Yield: 66%, 72% *ee*, yellow solid. $[\alpha]_D^{18}$ –2.5 (*c* 2.03, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.52 (d, *J* = 1.5 Hz, 1H), 8.08 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.97 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.89 (dd, *J* = 8.0 , 0.5 Hz, 1H), 7.62 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.08 (m, 2H), 6.85 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.77 (dt, *J* = 6.5, 1.5 Hz, 1H), 4.75 (m, 1H), 3.72 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.30 (dd, *J* = 16.5, 1.5 Hz, 1H), 2.96 (ddd, *J* = 16.5, 11.0, 6.5 Hz, 1H), 2.81 (m, 1H), 2.25 (m, 1H), 1.87 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.6, 154.6, 135.7, 134.5, 132.5, 130.2, 129.6, 129.5, 128.6, 128.5, 127.8, 127.2, 126.8, 123.9, 121.8, 120.3, 116.8, 72.6, 44.2, 27.5, 24.5. Mp. 88.0–89.0 °C. TLC: R_f 0.55 (hexane/EtOAc = 3:1). IR (KBr): 3061, 2891, 2365, 1679, 1582, 1486, 1458, 1436, 1388, 1288, 1238, 1189, 1116, 838, 748 cm^{-1}. HRMS Calcd for $C_{21}H_{19}O_2$: $[M+H]^+$, 303.1380. Found: *m*/*z* 303.1372. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.3 min, t_{minor} = 35.2 min.

1-(Chroman-2-yl)propan-2-one (2g).



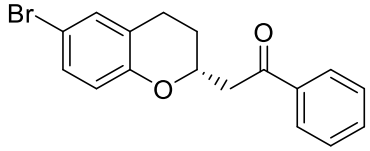
Yield: 64%, 36% *ee*, colorless oil. $[\alpha]_D^{18}$ +32.1 (*c* 0.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.07 (m, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.84 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.77 (dd, *J* = 8.5, 1.0 Hz, 1H), 4.48 (m, 1H), 2.92 (dd, *J* =16.0, 7.5 Hz, 1H), 2.88 (dd, *J* = 11.0, 6.0 Hz, 1H), 2.75 (m, 1H), 2.66 (dd, *J* = 16.0, 5.5 Hz, 1H), 2.25 (s, 3H), 2.07 (m, 1H), 1.74 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 206.4, 154.4, 129.5, 127.2, 121.6, 120.4, 116.8, 72.1, 49.1, 30.9, 27.4, 24.4. TLC: R_f 0.45 (hexane/EtOAc = 3:1). IR (neat): 3072, 2926, 2852, 1774, 1716, 1583, 1488, 1457, 1361, 1232, 1117, 977, 885, 756, 665, 462 cm^{-1}. HRMS Calcd for $C_{12}H_{15}O_2$: $[M+H]^+$, 191.1067. Found: *m*/*z* 191.1062. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.8 min, t_{minor} = 15.0 min.

2-(6-Methoxychroman-2-yl)-1-phenylethanone (2h).



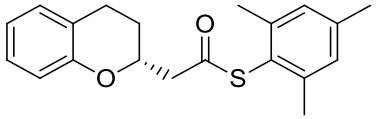
Yield: 86%, 74% *ee*, colorless oil. $[\alpha]_D^{18}$ –292.6 (*c* 0.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.01 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.59 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.45 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 4.68 (m, 1H), 3.73 (s, 3H), 3.55 (dd, *J* = 16.5, 6.0 Hz, 1H), 3.17 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.86 (ddd, *J* = 16.5, 11.0, 6.0 Hz, 1H), 2.72 (ddd, *J* = 16.5, 6.0, 3.5 Hz, 1H), 2.18 (m, 1H), 1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.6, 159.0, 155.2, 137.0, 133.3, 130.0, 128.6, 128.2, 113.9, 107.3, 101.5, 72.4, 55.3, 44.1, 27.6, 23.7. TLC: R_f 0.55 (hexane/EtOAc = 3:1). IR (neat): 3079, 2947, 2868, 2390, 1694, 1619, 1579, 1514, 1453, 1274, 1242, 1139, 1093, 1044, 995, 879, 773, 746 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_3$: $[M+H]^+$, 283.1329. Found: *m*/*z* 283.1328. HPLC (Daicel Chiralpak IA-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.7 min, t_{major} = 3.4 min.

2-(6-Bromochroman-2-yl)-1-phenylethanone (2i).



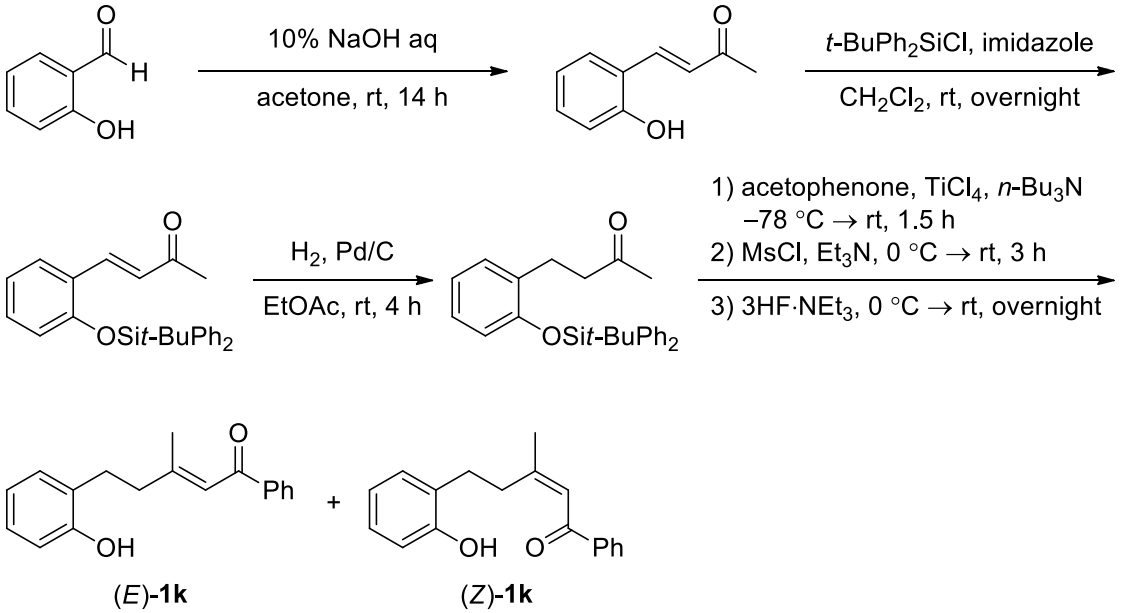
Yield: 68%, 65% *ee*, white solid. $[\alpha]_D^{18}$ –277.8 (*c* 0.18, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.99 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.59 (tt, *J* = 9.0, 1.5 Hz, 1H), 7.49 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.18 (m, 1H), 7.15 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 4.67 (m, 1H), 3.55 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.18 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.91 (ddd, *J* = 16.5, 11.0, 6.0, 1H), 2.75 (ddd, *J* = 16.5, 11.0, 8.5 Hz, 1H), 2.18 (m, 1H), 1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.4, 153.7, 136.9, 133.4, 132.0, 130.1, 128.7, 128.2, 123.9, 118.6, 112.3, 72.6, 43.9, 27.0, 24.4. Mp. 85.0–85.5 °C. TLC: R_f 0.60 (hexane/EtOAc = 3:1). IR (KBr): 3085, 2941, 2914, 2283, 1742, 1694, 1660, 1620, 1563, 1480, 1377, 1251, 1191, 1137, 1061, 998, 892, 804 cm^{-1}. HRMS Calcd for $C_{17}H_{16}BrO_2$: $[M+H]^+$, 331.0328. Found: *m*/*z* 331.0327. HPLC (Daicel Chiralpak IA-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.1 min, t_{major} = 3.4 min.

_S_-Mesityl 2-(Chroman-2-yl)ethanethioate (2j).



Yield: 38%, 75% *ee*, Colorless oil. $[\alpha]_D^{18}$ –128.8 (*c* 0.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.09 (m, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.99 (s, 2H), 6.85 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.55 (m, 1H), 3.13 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.93–2.86 (m, 2H), 2.79 (ddd, *J* = 16.5, 5.0, 3.5 Hz, 1H), 2.36 (s, 6H), 2.30 (s, 3H), 2.10 (m, 1H), 1.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 194.5, 154.6, 142.7, 140.2, 129.7, 129.4, 127.5, 123.9, 121.7, 120.6, 117.1, 73.0, 49.1, 27.4, 24.5, 21.8, 21.3. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (neat): 3023, 2924, 2852, 2364, 1696, 1583, 1488, 1457, 1235, 1116, 1059, 979, 894, 851, 753, 482 cm^{-1}. HRMS Calcd for $C_{20}H_{23}O_2S$: $[M+H]^+$, 327.1413. Found: *m*/*z*327.1404. HPLC (Daicel Chiralpak IB-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{minor} = 12.7 min, t_{major} = 16.2 min.

Procedure for preparation of 1k



To a solution of salicylaldehyde (10 g, 82 mmol) in acetone (20 mL) was added 10 wt% aquous NaOH (70 mL, 185 mmol) slowly at ambient temperature. The reaction mixture was stirred for 14 h. 1 M Aquous HCl (1 mL) was added, and the aqueous phase was washed with $CHCl_3$ (10 mL × 3). The aqueous phase was subsequently neutralized with 1 N aquous HCl until the pH value reached ca. 6, and an orange solid was precipitated. After the precipitate collected by

filtration was dried, recrystalization with EtOAc/benzene (v/v = 1/1) as a solvent gave (*E*)-4-(2-hydroxyphenyl)but-3-en-2-one as a yellow solid in 73% yield (9.8 g, 60 mmol). CAS RN [6051-53-2]. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, *J* = 16.5 Hz, 1H), 7.56 (s, 1H), 7.47 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.26 (dt, *J* = 2.5, 1.5 Hz, 1H), 7.04 (d, *J* = 16.5 Hz, 1H), 6.94–6.91 (m, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 201.0, 156.0, 140.6, 131.9, 129.6, 127.7, 121.6, 120.7, 116.6, 26.9.

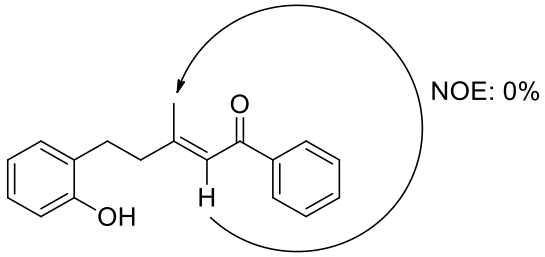
The solution of (*E*)-4-(2-Hydroxyphenyl)but-3-en-2-one (3.0 g, 19 mmol) and imidazole (1.7 g, 26 mmol) in CH_2Cl_2 (30 mL) was cooled to 0°C. To the mixuture was added TBDPSCl (5.7 mL, 22 mmol) dropwise slowly. The solution was warmed to ambient temperature and stirred overnight. The reaction mixture was quenched with H_2O (20 mL), and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with H_2O (30 mL×2) and brine,dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave (*E*)-4-(2-((tert-butyldiphenylsilyl)oxy)phenyl)but-3-en-2-one as a pale yellow oil quantitatively (7.0 g, 19 mmol). ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* = 16.5 Hz, 1H), 7.72 (dt, *J* = 6.0, 1.5 Hz, 4H), 7.58 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.45 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.40–7.37 (m, 4H), 6.96 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.89 (ddt, *J* = 1.5, 0.5, 7.0 Hz, 1H), 6.70 (d, *J* = 16.5 Hz, 1H), 6.50 (dd, *J* = 8.5, 1.0 Hz, 1H), 2.40 (s, 3H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 198.8, 154.4, 138.9, 135.4, 132.1, 131.3, 130.2, 128.0, 127.6, 127.1, 125.3, 121.5, 119.9, 31.6, 26.6, 19.6. TLC: R_f 0.46 (hexane/EtOAc = 3:1). IR (neat): 3090, 2959, 2860, 1669, 1599, 1483, 1250, 1114, 925, 822, 755, 701, 615, 572, 507. HRMS Calcd for $C_{26}H_{29}O_2Si$: $[M+H]^+$, 401.1931. Found: *m*/*z* 401.1926.

After Pd/C (10 wt%, 945 mg, 10 mol %) in a 100-mL flask was degassed under reduced pressure, H_2 gas (balloon) was introduced into the flask, and EtOAc (30 mL) was added. The solution of (*E*)-4-(2-((*tert*-butyldiphenylsilyl)oxy)phenyl)but-3-en-2-one (3.4 g, 8.5 mmol) in EtOAc (20 mL) was added, and the mixture was stirred at ambient temperature for 4 h. The reaction mixuture was diluted with EtOAc, passed through a short celite pad to remove Pd/C, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave 4-(2-((*tert*-butyldiphenylsilyl)oxy)phenyl)butan-2-one as a colorless oil quantitatively (3.4 g, 8.5 mmol). ^{1}H NMR ($CDCl_3$) δ 7.73–7.70 (m, 4H), 7.45–7.41 (m, 2H), 7.39–7.35 (m, 4H), 7.14 (m, 1H), 6.79 (m, 2H), 6.44 (m, 1H), 3.06 (t, *J* = 2.5 Hz, 2H), 2.84 (t, *J* = 2.5 Hz, 2H), 2.14 (s, 3H), 1.10 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 208.1, 153.4, 135.4, 132.8, 130.9, 130.1, 129.9, 127.8, 127.0, 121.1, 119.0, 43.9, 30.0, 26.6, 25.4, 19.5. TLC: R_f 0.35

(hexane/EtOAc = 3:1). IR (neat): 3072, 2959, 2859, 1719, 1583, 1492, 1428, 1252, 1112, 931, 823, 756, 701, 488. HRMS Calcd for $C_{26}H_{31}O_2Si$: $[M+H]^+$, 403.2088. Found: *m*/*z* 403.2083.

The solution of acetophenone (1.2 mL,10 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C. The solution of $TiCl_4$ (2.9 g, 15 mmol) in CH_2Cl_2 (15 mL) and Bu_3N (4.2 mL, 18 mmol) was added, and the mixture was stirred for 1.5 h. 4-(2-((*tert*-Butyldiphenylsilyl)oxy)phenyl)butan-2-one (4.0 g, 10 mmol) was then added slowly, and the solution was warmed to ambient temperature. The mixture was stirred for additional 1.5 h. After the reaction mixture was cooled to 0 °C, mesyl chloride(1.6 mL, 20 mmol) and Et_3N (1.7 mL, 12 mmol) was added. After being stirred for 3h, the reaction was quenched with saturated aquous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with saturated aquous $NaHCO_3$ (30 mL × 3) and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave each stereoisomer of 5-(2-((*tert*-butyldiphenylsilyl)oxy)phenyl)-3-methyl-1-phenylpent-2-en-1-one as a pale yellow oil in 10% yield for (*E*)-isomer (500 mg, 0.99 mmol) and in 3% yield for (*Z*)-isomer (145 mg, 0.29 mmol). The solution of each stereoisomer of 5-(2-((*tert*-butyldiphenylsilyl)oxy)phenyl)-3-methyl-1-phenylpent-2-en-1-one in CH_3CN (0.15 M) was cooled to 0 °C, and $3HF{\cdot}NEt_3$ (3 equiv) was added dropwise. The reaction mixture was subsequently warmed to ambient temperature and stirred overnight. The mixture was quenched by saturated aquous K_2CO_3. The aqueous phase was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with H_2O (30 mL × 2) and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave the corresponding stereoisomer of 5-(2-hydroxyphenyl)-3-methyl-1-phenylpent-2-en-1-one (**1k**).

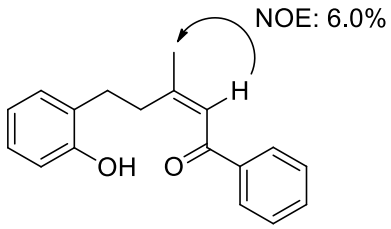
(*E*)-5-(2-Hydroxyphenyl)-3-methyl-1-phenylpent-2-en-1-one ((*E*)-1k).



Yield: 20%, Colorless oil. ^1H NMR ($CDCl_3$) δ 7.80–7.78 (m, 2H), 7.50 (t, *J* = 7.5, 1.0 Hz, 1H), 7.41 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.14–7.09 (m, 2H), 6.89 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.77 (dd, *J* = 8.0,

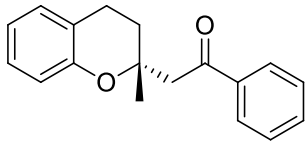
1.0 Hz, 1H), 6.63 (m, 1H), 5.06 (br s, 1H), 2.90 (t, J = 7.5 Hz, 2H), 2.57 (dt, J = 7.5, 0.50 Hz, 2H), 2.25 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 192.1, 158.8, 153.6, 139.2, 132.3, 130.4, 128.4, 128.3, 127.4, 121.4, 121.0, 115.3, 41.3, 28.4, 19.8. TLC: R_f 0.36 (hexane/EtOAc = 3:1). IR (neat): 2924, 2853, 1685, 1654, 1506, 1449, 1359, 1242, 1156, 1103, 1042, 856, 753, 689, 477 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_2$: $[M+H]^+$, 267.1380. Found: *m*/*z* 267.1375.

(*Z*)-5-(2-Hydroxyphenyl)-3-methyl-1-phenylpent-2-en-1-one ((*Z*)-1k).



Yield: 10%, pale yallow oil. ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 8.02 (t, J = 1.5 Hz, 2H), 7.57 (tt, J = 7.5, 1.5 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.17 (dt, J = 8.0, 2.0 Hz, 1H), 7.13 (dd, J = 7.5, 1.5 Hz, 1H), 7.00 (dd, J = 8.0, 1.5 Hz, 1H), 6.93 (d, J = 1.0 Hz, 1H), 6.85 (dt, J = 7.5, 1.5 Hz, 1H), 2.87–2.84 (m, 2H), 2.76–2,72 (m, 2H), 2.16 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 191.4, 162.7, 155.4, 138.7, 132.8, 129.8, 128.54, 128.50, 128.1, 126.1, 120.4, 119.9, 116.6, 36.4, 30.7, 26.8. TLC: R_f 0.36 (hexane/EtOAc = 3:1). IR (neat): 3026, 2978, 2933, 2366, 1676, 1654, 1603, 1503, 1465, 1244, 1221, 1102, 852, 754, 668, 466 cm^{-1}. HRMS Calcd for $C_{18}H_{19}O_2$: $[M+H]^+$, 267.1380. Found: *m*/*z* 267.1374.

2-(2-Methylchroman-2-yl)-1-phenyl-ethanone (2k)



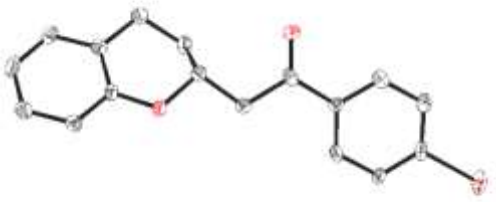
From (*E*)-**1i**: 30% yield, 8% *ee*.

From (*Z*)-**1i**: 7% yield, –87% *ee*; $[\alpha]_D^{18}$ –166.0 (*c* 0.053, CH_2Cl_2).

Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.96–7.94 (m, 2H), 7.55 (tt, J = 7.5, 1.5 Hz, 1H), 7.46–7.42 (m, 2H), 7.10–7.05 (m, 2H), 6.84 (dt, J = 8.0, 1.5 Hz, 1H), 6.71 (dd, J = 8.0, 1.0 Hz, 1H), 3.39 (d, J = 15.5 Hz, 1H), 3.23 (d, J = 15.5 Hz, 1H), 2.78 (m, 2H), 2.19–2.14 (m, 1H), 2.05–2.00 (m, 1H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.3, 153.3, 137.9, 133.1, 129.5, 128.5, 128.4, 127.4, 121.1, 120.1, 117.4, 75.8, 46.9, 31.0, 25.0, 22.1. TLC: R_f 0.51 (hexane/EtOAc = 3:1). IR (neat): 2966, 2928, 2856, 2366, 1654, 1636, 1592, 1507, 1457, 1420, 1261, 1105, 752, 665, 465 cm^{-1}. HRMS

Calcd for $C_{18}H_{19}O_2$: $[M+H]^+$, 267.1380. Found: *m*/*z* 267.1373. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): t_{major} = 12.4 min, t_{minor} = 13.0 min.

ORTEP Drawing of 2e



A. Crystal Data	
Identification code	**2e**
Empirical Formula	$C_{17}H_{15}BrO_2$
Formula Weight	331.21
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.200 X 0.200 X 0.200 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.365(2) Å
	b = 6.054(1) Å
	c = 12.676(2) Å
	β = 90.287(6)°
	V = 718.7(2) $Å^3$
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.530 g/cm^3
F_{000}	336.00
μ(MoKα)	28.663 cm^{-1}
B. Intensity Measurements	
Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	graphite monochromated
Voltage, Current	50 kV, 12 mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	540 exposures
ω oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
Detector Position	50.00 mm

Pixel Size	0.146 mm
$2\Theta_{max}$	55.0°
No. of Reflections Measured	Total: 7342
	Unique: 3259 (R_{int} = 0.0854)
	Friedel pairs: 1461
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.298–0.564)

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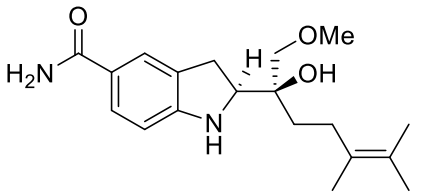
Chapter 2

Asymmetric Syntheses of Indolines via Intramolecular Aza-Michael Addition Reactions

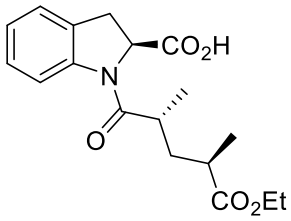
An enantioselective indoline synthesis via intramolecular aza-Michael addition reaction from aniline derivatives bearing α,β-unsaturated carbonyl moiety proceeded in the presence of cinchona-alkaloid-urea-based bifunctional organocatalysts. This protocol easily access to a wide range of chiral 2-substituted indolines.

Introduction

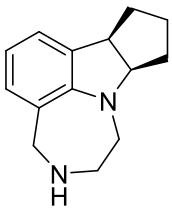
Optically active indoline frameworks are found in many natural products and biologically active agents (Figure1).[1] This has stimulated a great deal of research into the asymmetric synthesis of substituted indolines.[2–5] Among the approaches that have been studied, one of the most powerful candidates for the synthesis of 2-substituted indolines is intramolecular aza-Michael addition[6,7] from aniline derivatives that bear an *α*,*β*-unsaturated carbonyl moiety. This is a straightforward route to the desired structures and leaves a carbonyl group available for further structural modifications. Previous approaches utilizing chiral secondary[3a,3b] and primary[3c] amine catalysts have been shown to be useful for the reaction of *α*,*β*-unsaturated aldehydes and ketones, respectively. However, these methods are not applicable to substrates in a higher oxidation state because of the mechanistic necessity for iminium formation.[8] To expand the utility of this synthetic reaction, the development of a novel catalytic process is required. Asano and Matsubara have recently established a useful protocol for asymmetric heterocycle synthesis via an intramolecular hetero-Michael addition.[9] This methodology utilizes multipoint recognition by bifunctional aminothiourea catalysts through hydrogen bonding.[10,11] Thus, the author attempted to use this efficient cyclization approach in order to develop a novel asymmetric intramolecular aza-Michael addition reaction for generating a variety of 2-substituted indolines.[12] The potential versatility of this type of catalysis, utilizing noncovalent interactions, was demonstrated using a range of different substrates.



Benzastatin E



Pentopril



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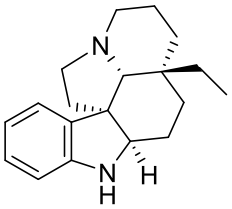
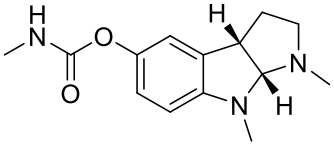


Aspidospermidine

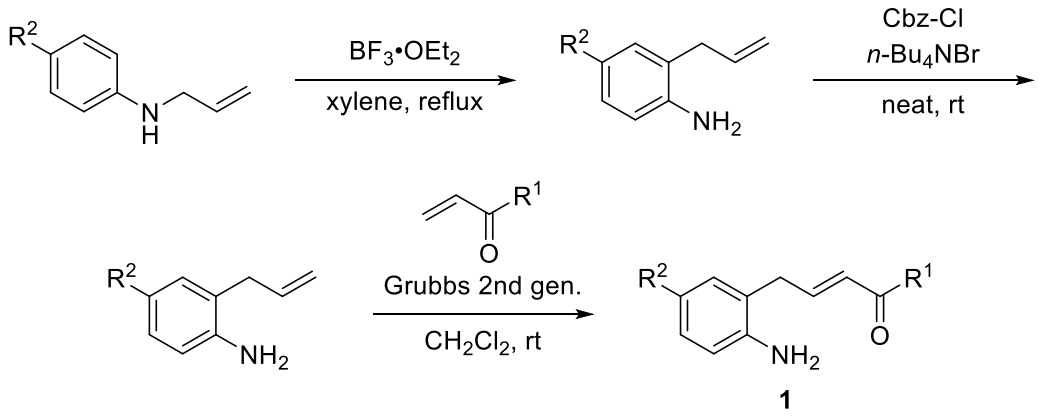


Physostigmine

Figure 1. Representative indoline derivatives in natural products.

Results and Discussion

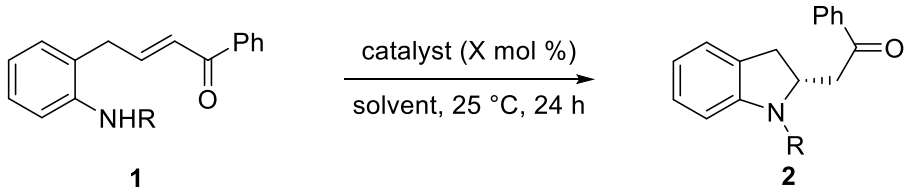
The starting materials **1** were prepared through the synthetic route indicated in Scheme 1.[13] The investigation was initiated using substrate **1a** with 5 mol % quinidine derived bifunctional thiourea catalyst **3a** in cyclopentyl methyl ether (CPME) at 25 °C, and indoline product **2a** was obtained enantioselectively (Table 1, entry 1).



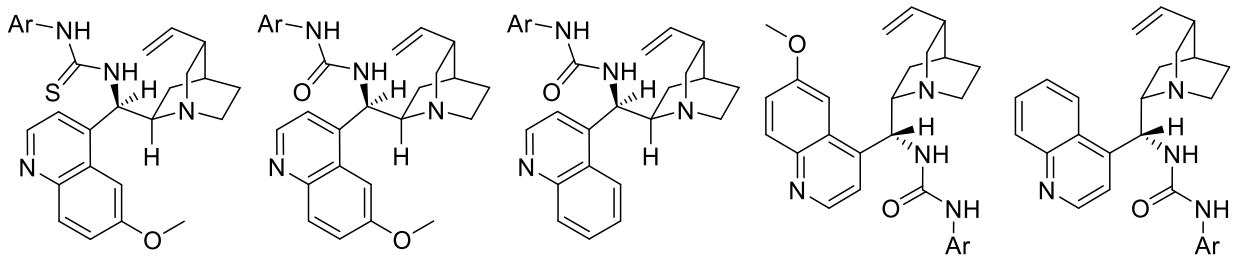
Scheme 1. Synthetic route to substrates **1**.

Screening of various solvents revealed that less polar aromatic solvents were the most effective for giving **2a** with high enantioselectivity and an acceptable yield (Table 1, entries 6–9). The fact that the reaction in a protic solvent resulted in poor yield and enantioselectivity implies the crucial role of hydrogen bonding in the catalysis mode of this reaction (Table 1, entry 5). As a longer reaction time led to lower enantioselectivity, which was likely due to the competing noncatalytic reaction (Table 1, entry 10), 10 mol % **3a** was employed to improve the yield (Table 1, entry 11). On decreasing the reaction temperature to 0 °C, the yield was considerably reduced, albeit with a slight increase in the enantioselectivity (Table 1, entry 12). The use of urea catalyst **3b** instead of thiourea catalyst **3a** largely improved both the yield and enantioselectivity (Table 1, entry 13). Substrates with other protecting groups (**1b**, **1c**) gave poorer results (Table 1, entries 14 and 15). Furthermore, the screening of urea catalysts showed that quinine-derived **3d** was an efficient catalyst for obtaining the opposite enantiomer of **2a** with good enantioselectivity (Table 1, entry 17).

Table 1. Optimization of reaction conditions[a]



1 **2**



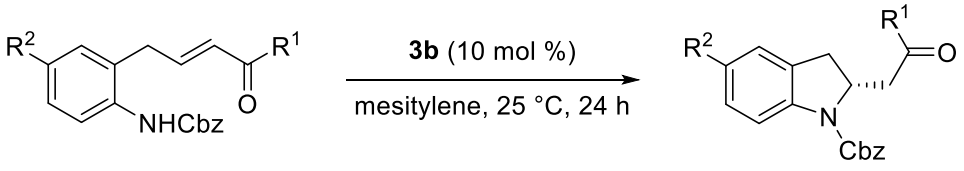
3a **3b** **3c** **3d** **3e**

entry	R	catalyst (mol %)	solvent	Yield (%)[b]	*ee* (%)
1	Cbz (**1a**)	**3a** (5)	CPME[c]	18	79
2	Cbz (**1a**)	**3a** (5)	Et_2O	10	76
3	Cbz (**1a**)	**3a** (5)	acetone	23	78
4	Cbz (**1a**)	**3a** (5)	CH_2Cl_2	80	67
5	Cbz (**1a**)	**3a** (5)	CH_3OH	10	11
6	Cbz (**1a**)	**3a** (5)	benzene	99	75
7	Cbz (**1a**)	**3a** (5)	toluene	73	79
8	Cbz (**1a**)	**3a** (5)	xylene	57	81
9	Cbz (**1a**)	**3a** (5)	mesitylene	57	83
10[d]	Cbz (**1a**)	**3a** (5)	mesitylene	70	79
11	Cbz (**1a**)	**3a** (10)	mesitylene	73	81
12[e]	Cbz (**1a**)	**3a** (10)	mesitylene	14	84
13	Cbz (**1a**)	**3b** (10)	mesitylene	99	87
14	Boc (**1b**)	**3b** (10)	mesitylene	46	75
15	Bz (**1c**)	**3b** (10)	mesitylene	48	1
16	Cbz (**1a**)	**3c** (10)	mesitylene	59	76
17	Cbz (**1a**)	**3d** (10)	mesitylene	66	–84
18	Cbz (**1a**)	**3e** (10)	mesitylene	53	–78

[a] Reactions were run using **1** (0.1 mmol) and the catalyst in the solvent (0.8 mL). [b] Isolated yields. [c] CPME = cyclopentyl methyl ether. [d] Reaction was run for 48 h. [e] Reaction was run at 0 °C

Subsequently, the scope of substrates that the reaction could be successfully applied to was explored using the optimized conditions (Table 2). Although urea catalyst **3b** exhibited low reactivity for an electron-rich enone, thiourea catalyst **3a** proved to be more suitable in this case for improving the yield while giving a similarly good enantiomeric excess (Table 2, entry 2). In contrast, an electron-poor enone afforded the corresponding product in good yield with high enantioselectivity using **3b** as a catalyst (Table 2, entry 3). In addition, a substrate bearing a naphthyl group also underwent this reaction in the presence of **3b**, yielding the indoline product (Table 2, entry 4). Notably, particularly high enantioselectivity was obtained using a substrate bearing a *p*-bromo group, which may then be easily transformed into other organic groups (Table 2, entry 5). Substituents on the aniline moiety were also investigated, and again in this case, thiourea catalyst **3a** was found to be better for a substrate with a methoxy group (Table 2, entry 6). Electron-poor anilines were tolerated by using **3b** as a catalyst and gave the corresponding products in moderate to good yield with high enantioselectivity (Table 2, entries 7 and 8). A bromo group in the enone moiety again provided good enantioselectivity in the reaction of an electron-rich aniline (Table 2, entry 9). An aliphatic ketone substrate was much less reactive, but moderate enantioselectivity was obtained (Table 2, entry 10).

Table 2. Scope of substrates[a]

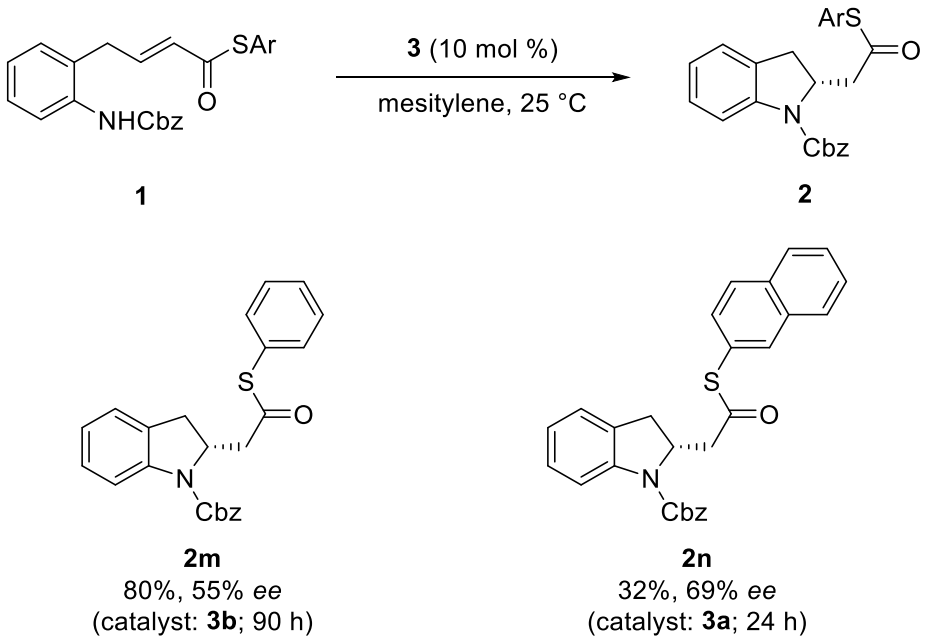


1 **2**

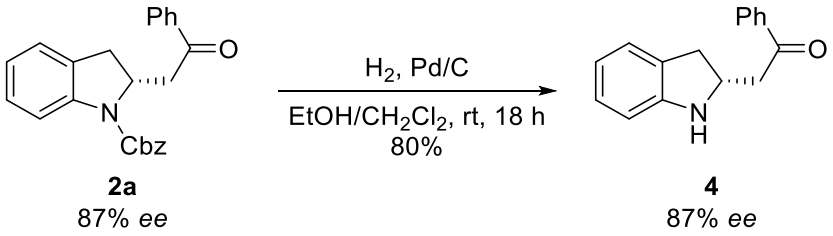
entry	R^1	R^2	**2**	yield (%)[b]	*ee* (%)
1	Ph	H	**2a**	99	87
2[c]	4-$CH_3OC_6H_4$	H	**2d**	73	84
				(26)[d]	(86)[d]
3	4-$CF_3C_6H_4$	H	**2e**	79	88
4	2-naphthyl	H	**2f**	83	88
5	4-BrC_6H_4	H	**2g**	75	91
6[c]	Ph	CH_3O	**2h**	82	83
				(33)[d]	(86)[d]
7	Ph	F	**2i**	69	82
8	Ph	Cl	**2j**	82	84
9	4-BrC_6H_4	CH_3O	**2k**	53	93
10[c]	CH_3	H	**2l**	18	74
				(24)[d]	(65)[d]

[a] Reactions were run using **1** (0.1 mmol) and **3b** (0.01 mmol) in mesitylene (0.8 mL). [b] Isolated yields. [c] Reactions were run using **3a** instead of **3b**. [d] Results of the reaction run using **3b**.

Moreover, higher oxidation state substrates, *α*,*β*-unsaturated thioesters **1m** and **1n**, were also applicable, although obtaining a further improvement in enantioselectivity requires additional investigation (Scheme 2). The thioester functionality allows for a variety of subsequent transformations, thereby offering an efficient pathway to a range of pharmacological compounds.[9d] This demonstrates the great potential of the reaction scheme described in this work for expanding the scope of compounds that can be successfully synthesized.



Scheme 2. Reaction from *α*,*β*-unsaturated thioesters.



Scheme 3. Deprotection of **2a**

In addition, deprotection of **2a** could be carried out under hydrogenation conditions to afford **4** in high yield without any erosion of optical purity (Scheme 3). The absolute configuration of **2g** was determined using X-ray analysis (see Experimental Section for details), and the configurations of all other examples were assigned accordingly.

Conclusion

In summary, the author has demonstrated a novel asymmetric synthesis of 2-substituted indolines via intramolecular aza-Michael addition by means of bifunctional organocatalysts. The reaction proceeded by activation via hydrogen bonding, enabling a flexible catalytic mechanism that was widely applicable to a range of substrates with *α*,*β*-unsaturated carboxylic acid derivatives. Further studies on the expansion of the substrate scope and the application of this methodology to other heterocycle syntheses are currently underway in his laboratory and will be reported in due course.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. The starting materials for the substrates **1a–1m** and for carbonyl ylides are commercially available. Bifunctional organocatalysts **3** were prepared according to the same procedure as that described in Chapter 1.

General procedure for asymmetric synthesis of 2-substituted indolines 2

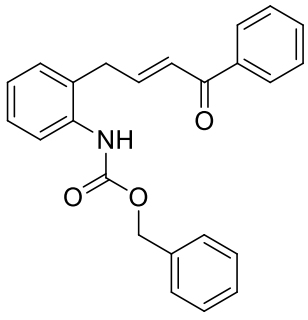
In a 5-mL vial, the author sequentially added substrate **1** (0.10 mmol), THF (0.8 mL), and quinidine-derived bifunctional catalyst **3b** (0.010 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded the corresponding 2-substituted indoline **2**. Racemic compounds were prepared using *p*-toluenesulfonic acid as a catalyst.

General procedure for preparation of substrate 1

The starting materials **1** were prepared by modified procedures of the literature methods.[15–17] The characterization data of the corresponding synthetic intermediates were identical to those reported in the literatures. To a solution of an *N*-allylaniline (3.4 mL, 20 mmol) in xylene (40 mL) was added $BF_3 \cdot OEt_2$ (3.8 mL, 20 mmol) at ambient temperature. The reaction mixture was

allowed to warm to 150 °C. After being stirred for 20 h, the reaction was quenched with 20% aquous NaOH (10 mL), and the mixture was subsequently extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave the corresponding *o*-allylaniline as a pale yellow oil in 40–60% yield. *N*-allylanilines commercially unavailable were prepared by the literature procedure.[18] To the *o*-allylaniline (10 mmol), tetrabutylammonium bromide (161 mg, 0.5 mmol) was added. Benzyl chloroformate was added dropwise into the mixture at 0 °C, and the mixture was stirred for 30 min. Then the reaction mixture was diluted by CH_2Cl_2, and stirred for 3 h. The reaction mixture was quenched with saturated aquous $NaHCO_3$ (10 mL), and the mixture was subsequently extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave *N*-benzyloxycarbonyl-*o*-allylaniline as a white solid in 80–100% yield. Next, to a solution of the *N*-benzyloxycarbonyl-*o*-allylaniline (1.0 mmol) and a vinylketone (5.0 mmol) in CH_2Cl_2 (10 mL), Grubbs-catalyst-2nd-generation (26 mg, 0.03 mmol) was added at ambient temperature. After the solution stirred for 20 h, solvents were removed in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave the corresponding *N*-benzyloxycarbonyl-(*E*)-4-(2-aminophenyl)-but-2-en-1-one (**1**). Vinyl ketones were prepared by the literature procedure.[18] The characterization results of **1** are as below.

_N_-Benzyloxycarbonyl-(_E_)-4-(2-aminophenyl)-1-phenylbut-2-en-1-one (1a).



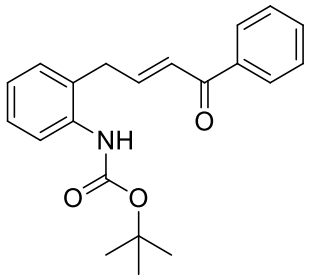
White solid; 40% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 7.77 (br s, 1H), 7.54 (m, 1H), 7.40 (m, 2H), 7.36 (m, 6H), 7.18 (m, 3H), 6.78 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.43 (br s, 1H), 5.17 (s, 2H), 3.62 (dd, *J* = 6.0, 2.0 Hz, 2H).

^{13}C NMR ($CDCl_3$) δ 190.1, 161.5, 147.3, 145.7, 139.1, 137.5, 135.9, 135.6, 132.9, 130.3, 128.60, 128.58, 128.52, 128.4, 128.1, 126.9, 125.4, 116.6, 67.2, 35.0. Mp. 105.0–105.5 °C. TLC: R_f 0.36

(hexane/EtOAc = 3:1). IR (KBr): 3285, 3032, 2961, 2903, 1696, 1668, 1624, 1591, 1530, 1453, 1352, 1248, 1058, 987, 914, 748, 691 cm^{-1}. HRMS Calcd for $C_{24}H_{22}NO_3$: $[M+H]^+$, 372.1594. Found: *m*/*z* 372.1587.

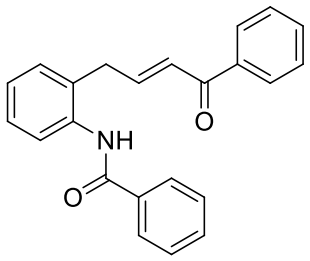
***N*-*tert*-Butoxycarbonyl-(*E*)-4-(2-aminophenyl)-1-phenylbut-2-en-1-one (1b)**.



White solid; 25% yield (for the last step).

^1H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.74 (m, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 7.29 (m, 1H), 7.19 (m, 2H), 7.12(dt, *J* = 7.5, 1.0 Hz, 1H), 6.81 (dt, 15.5, 1.5 Hz, 1H), 6.24 (br s, 1H), 3.63 (dd, *J* = 6.0, 1.5 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 190.3, 153.2, 145.9, 137.6, 136.1, 132.9, 130.2, 128.6, 128.5, 128.0, 126.9, 124.8, 123.2, 109.7, 80.7, 35.1, 28.3. Mp. 91.5–92.2 °C. TLC: R_f 0.35 (hexane/EtOAc = 3:1). IR (KBr): 3295, 2983, 2963, 2917, 1722, 1666, 1614, 1596, 1579, 1513, 1490, 1452, 1366, 1250, 1168, 1052, 1021, 986, 908, 781, 758, 691 cm^{-1}. HRMS Calcd for $C_{21}H_{24}NO_3$: $[M+H]^+$, 338.1758. Found: *m*/*z* 338.1761.

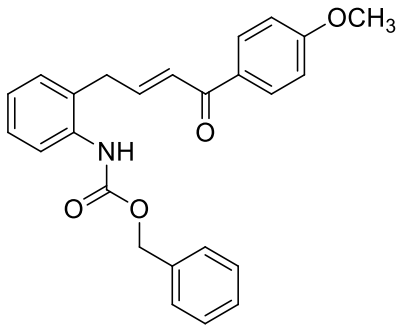
***N*-Benzoyl-(*E*)-4-(2-aminophenyl)-1-phenylbut-2-en-1-one (1c)**.



White solid; 20% (for the last step).

^1H NMR ($CDCl_3$) δ 7.84 (m, 1H), 7.82 (m, 3H), 7.55–7.29 (m, 10H), 7.20 (m, 2H), 6.88 (dt, *J* = 15.0, 1.5 Hz, 1H), 3.71 (dd, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189.1, 167.1, 146.5, 136.2, 136.0, 135.9, 135.6, 132.0, 131.9, 130.1, 128.6, 128.3, 128.0, 126.5, 126.4, 124.4, 115.7, 112.9, 55.5. TLC: R_f 0.37 (hexane/EtOAc = 3:1). Mp. 111.5–112.0 °C. IR (KBr): 3291, 3033, 2952, 2835, 1691, 1618, 1529, 1452, 1350, 1259, 749, 352 cm^{-1}. HRMS Calcd for $C_{23}H_{20}NO_2$: $[M+H]^+$, 342.1489. Found: *m*/*z* 342.1492.

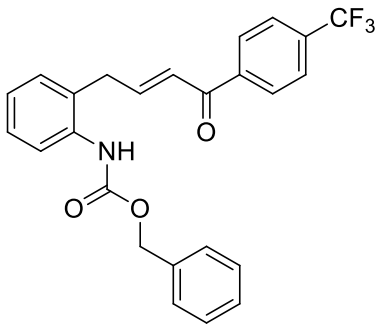
***N*-Benzyloxycarbonyl-(*E*)-4-(2-aminophenyl)-1-(4-methoxyphenyl)but-2-en-1-one (1d)**.



White solid; 25% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.86 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.77 (br s, 1H), 7.34 (m, 6H), 7.21 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.14 (m, 2H), 6.89 (dt, *J* = 7.0, 2.5 Hz, 2H), 6.79 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.45 (br s, 1H), 5.17 (s, 2H), 3.85 (s, 3H), 3.60 (dd, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 188.3, 179.7, 164.6 163.5, 162.5, 156.4, 144.5, 136.0, 130.9, 130.4, 128.6, 128.3, 128.1, 126.8, 125.3, 120.8, 113.8, 107.1, 67.2, 55.5, 35.0. Mp. 111.5–112.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3291, 3033, 2952, 2838, 1691, 1663, 1618, 1529, 1452, 1350, 1259, 749, 352 cm^{-1}. HRMS Calcd for $C_{25}H_{24}NO_4$: $[M+H]^+$, 403.1733. Found: *m*/*z* 403.1726.

***N*-Benzyloxycarbonyl-(*E*)-4-(2-aminophenyl)-1-(4-trifluoromethylphenyl)but-2-en-1-one (1e)**.

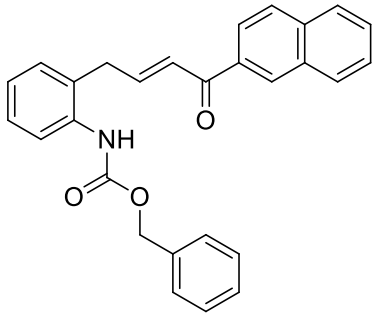


White soild; 30% (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 3.5 Hz, 2H), 7.73 (br s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7,34 (m, 6H), 7.19 (m, 3H), 6.74 (dt, *J* = 15.5, 1.8 Hz, 1H), 6.49 (br s, 1H), 5.17 (s, 2H), 3.63 (dd, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189.2, 162.4, 154.0, 147.2, 140.3, 135.9, 135.5, 134.0 (q, *J* = 32.6 Hz), 130.3, 128.8, 128.6, 128.4, 128.3, 126.6, 125.59, 125.57, 124.2, 123.6 (q, *J* = 272.6 Hz), 103.4, 67.3, 35.1. ^{19}F NMR ($CDCl_3$) δ 98.7. Mp. 136.0–137.0 °C. TLC: R_f 0.28 (hexane/EtOAc = 3:1). IR (KBr): 3474, 3290, 3078, 3036, 2963, 2375, 1690, 1624, 1528, 1326,

1257, 1172, 1126, 1067, 1017, 980, 750, 668 cm^{-1}. HRMS Calcd for $C_{25}H_{21}F_3NO_3$: $[M+H]^+$, 440.1468. Found: *m*/*z* 440.1463.

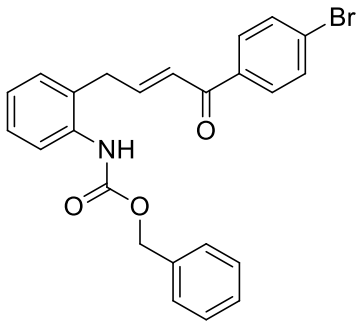
***N*-Benzyloxycarbonyl-(*E*)-4-(2-aminophenyl)-1-(naphthalen-2-yl)-2-en-1-one (1f)**.



White solid; 20% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.78 (br s, 1H), 7.60 (ddd, *J* = 8.0, 7.5, 1.0 Hz 1H), 7.54(ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 7.32 (m, 6H), 7.20 (m, 3H), 6.96 (dt, *J* = 15.0, 1.5 Hz, 1H), 6.48 (br s, 1H), 5.17 (s, 2H), 3.66 (dd, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189.9, 165.2, 151.7, 145.5, 140.7, 135.6, 135.5, 134.9, 134.1, 132.5, 130.4, 130.2, 129.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.1, 126.8, 124.3, 114.7, 109.7, 67.2, 35.1. Mp. 104.5–105.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3309, 3075, 3044, 2969, 2908, 2378, 1705, 1656, 1610, 1520, 1463, 1357, 1296, 1243, 1046, 983, 808, 748, 472 cm^{-1}. HRMS Calcd for $C_{28}H_{24}NO_3$: $[M+H]^+$, 422.1743. Found: *m*/*z* 422.1751.

***N*-Benzyloxycarbonyl-(*E*)-4-(2-aminophenyl)-1-(4-bromophenyl)but-2-en-1-one (1g)**.

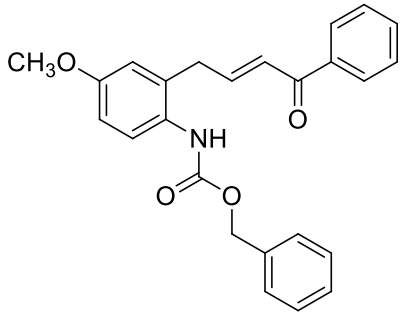


White solid; 32% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.70 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.54 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.32 (m, 7H), 7.17 (m, 3H), 6.72 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.40 (br s, 1H), 5.17 (s, 2H), 3.62 (dd, *J* = 6.5, 2.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189.0, 164.3, 146.2, 136.3, 135.9, 135.6, 131.9, 131.7, 131.5, 130.4, 130.0, 129.7, 128.6, 128.4, 128.3, 128.2, 128.0, 126.6, 67.3, 35.1. Mp. 94.0–95.0 °C. TLC: R_f 0.36

(hexane/EtOAc = 3:1). IR (KBr): 3289, 3066, 3033, 2950, 1684, 1667, 1586, 1528, 1452, 1397, 1240, 1071, 1011, 978, 836, 757, 665 cm^{-1}. HRMS Calcd for $C_{24}H_{21}BrNO_3$: $[M+H]^+$, 450.0699. Found: *m*/*z* 450.0689.

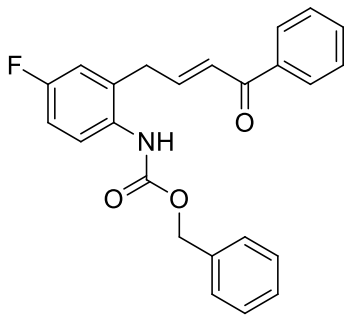
***N*-Benzyloxycarbonyl-(*E*)-4-(6-amino-3-methoxyphenyl)-1-phenylbut-2-en-1-one (1h)**.



White solid; 20% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.86 (dt, *J* = 7.5, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.43 (m, 2H), 7.35 (m, 5H), 7.15 (m, 1H), 6.84 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.78 (dt, *J* = 13.5, 1.5 Hz, 1H), 6.75 (d, *J* = 3.0 Hz, 1H), 6.25 (br s, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 3.58 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 190.1, 145.6, 137.5, 136.0, 135.6, 132.9, 130.3, 128.62, 128.58, 128.56, 128.51, 128.31, 128.30, 128.1, 127.0, 125.4, 115.9, 111.3, 67.2, 55.7, 35.0. Mp. 124.0–125.0 °C. TLC: R_f 0.40 (hexane/EtOAc = 3:1). IR (KBr): 3291, 3034, 2968, 2331, 1952, 1808, 1692, 1666, 1622, 1587, 1532, 1452, 1352, 1243, 1059, 988, 748, 692, 577 cm^{-1}. HRMS Calcd for $C_{25}H_{23}NO_4Na$: $[M+Na]^+$, 424.1519. Found: *m*/*z* 424.1523

***N*-Benzyloxycarbonyl-(*E*)-4-(2-amino-5-fluorophenyl)-1-phenylbut-2-en-1-one (1i)**.

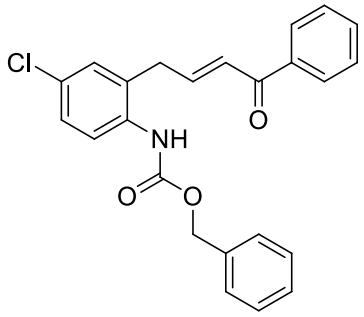


White solid; 20% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.86 (dt, *J* = 7.5, 1.5 Hz, 2H), 7.55 (tt, *J* = 4.5, 1.3 Hz, 1H), 7.44 (m, 2H), 7.34 (m, 6H), 7.12 (dt, *J* = 15.0, 6.0 Hz, 1H), 7.01 (dt, *J* = 3.0, 8.0 Hz, 1H), 6.94 (dd, *J* = 9.0, 8.0 Hz, 1H), 6.80 (dt, *J* = 15.0, 1.5 Hz, 1H), 6.33 (br s, 1H), 5.16 (s, 2H), 3.59 (dd, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189,8 153.7, 144.5, 141.1, 137.3, 135.7, 134.2, 133.0, 131.6, 129.1 (d, *J* =

246.7 Hz), 128.6, 128.53, 128.46, 128.4, 127.3, 124.3, 118.3, 105.4, 67.2, 35.0. ^{19}F NMR ($CDCl_3$) δ 77.1. Mp. 106.0–107.0 °C. TLC: R_f 0.23 (hexane/EtOAc = 3:1). IR (KBr): 3293, 3034, 2939, 2375, 1699, 1620, 1530, 1453, 1248, 1063, 986, 755, 694, 498 cm^{-1}. HRMS Calcd for $C_{24}H_{20}FNO_3Na$: $[M+Na]^+$, 412.1319. Found: *m*/*z* 412.1327.

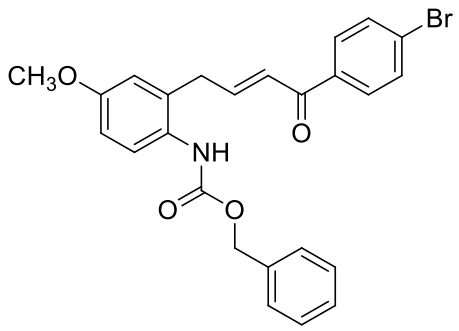
***N*-Benzyloxycarbonyl-(*E*)-4-(2-amino-5-chlorophenyl)-1-phenyl)but-2-en-1-one (1j)**.



White solid; 15% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.86(m, 2H), 7.73 (br s, 1H), 7.56 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.43 (tt, *J* = 7.5, 2.0Hz, 2H), 7.34 (m, 5H), 7.28 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H) 7.13 (dt, *J* = 15.0, 6.0 Hz, 1H), 6.79 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.41 (br s, 1H), 5.17 (s, 2H), 3.57 (d, *J* = 3.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 189.9, 157.6, 156.6, 145.1, 144.4, 137.4, 135.7, 134.3, 133.0, 130.1, 128.6, 128.5, 128.44, 128.37, 128.1, 127.4, 124.8, 122.3, 67.4, 34.7. Mp. 132.5–132.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (KBr): 3264, 3047, 2939, 2354, 1696, 1620, 1526, 1403, 1349, 1259, 1102, 1063, 990, 904, 697, 531 cm^{-1}. HRMS Calcd for $C_{24}H_{21}ClNO_3$: $[M+H]^+$, 406.1204. Found: *m*/*z* 406.1212.

***N*-Benzyloxycarbonyl-(*E*)-4-(6-amino-3-methoxyphenyl)-1-(4-bromophenyl)but-2-en-1-one (1k)**.

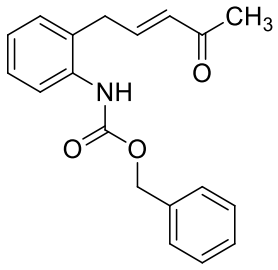


White solid; 20% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.71 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.54 (dt, *J* = 7.5, 2.0 Hz, 2H), 7.47 (br s, 1H),

7.34 (m, 5H), 7.15 (m, 1H), 6.84 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.74 (d, *J* = 3.0 Hz, 1H) 6.72 (dt, *J* = 15.5, 2.0 Hz, 1H), 6.23 (br s, 1H), 5.15 (s, 2H), 3.80 (s, 3H), 3.58 (dd, *J* = 6.0, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 188.8, 178.7, 164.2, 157.8, 151.7, 150.1, 143.4, 141.8, 138.2, 135.7, 131.9, 130.1, 127.7, 123.8, 118.1, 113.0, 111.7, 106.8, 67.2, 55.5, 35.3. Mp. 130.5–131.0 °C. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 3234, 3035, 2965, 2365, 1685, 1669, 1624, 1585, 1534, 1266, 1253, 1071, 1028, 861, 743, 697, 492 cm^{-1}. HRMS Calcd for $C_{25}H_{22}BrNO_4Na$: $[M+Na]^+$, 502.0624. Found: *m*/*z* 502.0634.

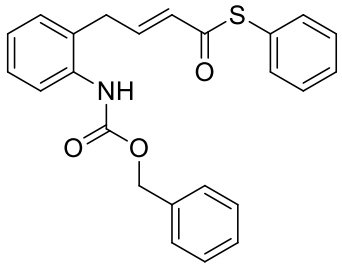
***N*-Benzyloxycarbonyl-(*E*)-5-(2-aminophenyl)-pent-3-en-2-one (1l)**.



Whitie solid; 50% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.57 (br s, 1H), 7.26–7.20 (m, 5H), 7.15 (m, 1H), 7.01 (m, 2H), 6.74 (dt, *J* = 16.0, 6.0 Hz, 1H), 6.35 (br s, 1H), 5.85 (dt, *J* = 6.0, 2.0 Hz, 1H), 5.05 (s, 2H), 3.38 (dd, *J* = 6.0, 2.0 Hz, 2H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.2, 154.0, 144.6, 135.9, 135.4, 132.0, 130.2, 129.9, 128.6, 128.3, 128.0, 127.5, 125.4, 123.5, 67.2, 34.5, 27.1. TLC: R_f 0.25 (hexane/EtOAc). The characterization data were identical to those reported in the literature.[19]

(*E*)-*S*-Phenyl 4-(2-(((benzyloxy)carbonyl)amino)phenyl)but-2-enethioate (1m).



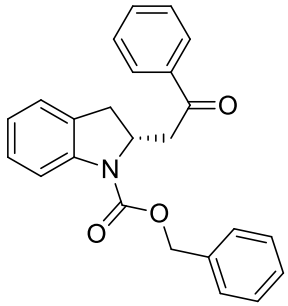
White solid; 34% (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.72 (br s, 1H), 7.41 (m, 7H), 7.37 (m, 3H), 7.31 (m, 1H), 7.16 (m, 2H), 7.09 (dt, *J* = 15.5, 1.0 Hz, 1H), 6.35 (br s, 1H), 6.05 (dt, *J* = 15.5, 2.0 Hz, 1H), 5.21 (s, 2H), 3.74 (dd, *J* = 6.0, 2.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 195.4, 183.3, 176.2, 175.3, 162.4, 153.9, 142.9, 136.0,

134.6, 130.3, 129.5, 129.2, 129.0, 128.6, 128.4, 128.2, 109.7, 102.5, 67.3, 34.4. Mp. 88.5–89.5 °C. TLC: R_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 3313, 3001, 2939, 2361, 1693, 1641, 1540, 1451, 1306, 1234, 1059, 1016, 918, 752, 694, 651 cm^{-1}. HRMS Calcd for $C_{24}H_{22}NO_3S$: $[M+H]^+$, 404.1315. Found: *m*/*z* 404.1320.

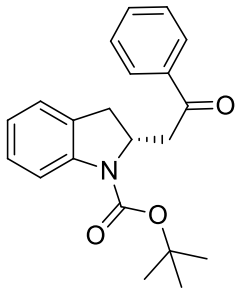
Characterization Data of Products

1-Phenyl-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2a).



Yield: 99%, 87% *ee*, white solid. $[\alpha]_D^{25}$ +74.7 (*c* 2.81, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.86 (br s, 1H), 7.47–7.31 (m, 10H), 7.21 (br s, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.32 (s, 2H), 4.93 (br s, 1H), 3.41 (dd, *J* = 16.5, 4.5 Hz, 1H), 3.27 (br s, 1H), 2.93 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 194.9, 141.9, 136.0, 134.4, 129.5, 129.2, 128.7, 128.5, 128.4, 128.3, 128.2, 127.7, 127.3, 125.1, 123.2, 115.5, 67.4, 56.5, 47.8, 33.8. Mp. 106.0–107.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3056, 2955, 2910, 2374, 1701, 1598, 1493, 1408, 1327, 1288, 1203, 1128, 1038, 994, 759, 697, 593 cm^{-1}. HRMS Calcd for $C_{24}H_{22}NO_3$: $[M+H]^+$, 372.1594. Found: *m*/*z* 372.1599. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98.0/2.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.1 min, t_{major} = 16.3 min.

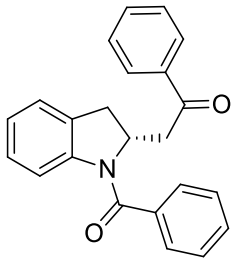
1-Phenyl-2-(*N*-*tert*-butoxycarbonylindolin-2-yl)ethanone (2b).



Yield: 46%, 75% *ee*, pale yellow oil. $[\alpha]_D^{25}$ +66.5 (*c* 2.03, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.80 (br s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* =

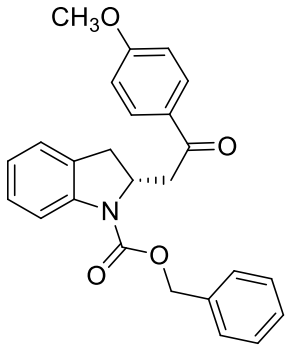
7.5 Hz, 1H), 7.14 (dd, *J* = 7.5, 0.50 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.00 (t, *J* = 4.5 Hz, 1H), 3.60 (br s, 1H), 3.46 (dd, *J* = 16.5, 9.0 Hz, 1H), 3.14, (br s, 1H), 2.77 (d, *J* = 16.5, 1H), 1.56 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 198,3, 152.1, 136.8, 133.3, 128.92, 128.86, 128.6, 128.1, 127.5, 125.1, 122.6, 115.4, 81.3, 56.3, 43.4, 34.2, 28.5. TLC: R_f 0.48 (hexane/EtOAc = 3:1). IR (neat): 3249, 3059, 1650, 1523, 1485, 1307, 997, 734, 717, 597, 470 cm^{-1}. HRMS Calcd for $C_{21}H_{24}NO_3$: $[M+H]^+$, 338.1751. Found: *m*/*z* 338.1747. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98.0/2.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.77 min, t_{major} = 4.40 min.

1-Phenyl-2-(*N*-benzoylindolin-2-yl)ethanone (2c).



Yield: 48%, 1% *ee*, white solid. $[\alpha]_D^{25}$ +1.2 (*c* 2.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.95 (br s, 2H), 7.57–7.44 (m, 9H), 7.20 (d, *J* = 12.5 Hz, 1H), 6.97 (m, 2H), 5.26 (br s, 1H), 3.82 (br s, 1H), 3.49 (dd, *J* = 16.0, 7.5 Hz, 1H), 3.10 (dd, *J* = 16.0, 12.5 Hz, 1H), 2.89 (d, *J* = 16.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 198.0, 168.7, 141.4, 136.5, 136.3, 133.4, 131.6, 130.6, 128.8, 128.7, 128.2, 127.4, 127.0, 125.8, 123.8, 116.3, 58.2, 42.4, 33.7. Mp. 106.0–107.0 °C. TLC: R_f 0.45 (hexane/EtOAc = 3:1). IR (KBr): 3056, 2955, 2910, 2374, 1701, 1598, 1493, 1408, 1327, 1288, 1203, 1128, 1038, 994, 759, 697, 593 cm^{-1}. HRMS Calcd for $C_{23}H_{19}NO_2Na$: $[M+Na]^+$, 364.1308. Found: *m*/*z* 364.1297. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90.0/10.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 9.16 min, t_{major} = 19.4 min.

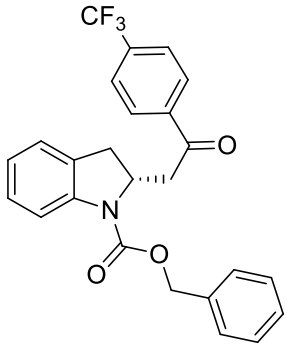
1-(4-Methoxyphenyl)-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2d).



Yield: 73%, 84% *ee*, white solid. $[\alpha]_D^{18}$ +31.0 (*c* 1.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.10–7.70

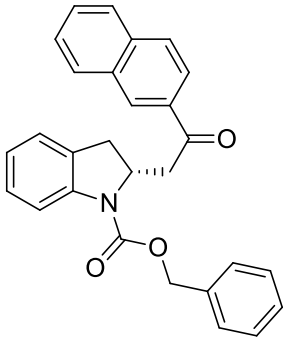
(m, 3H), 7.60–7.29 (m, 5H), 7.20 (br s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.90 (br s, 1H), 6.82 (br s, 1H), 5.28 (br s, 2H), 5.02 (t, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.49 (br s, 1H), 3.43 (dd, *J* = 16.0, 9.0 Hz, 1H), 3.02 (dd, *J* = 16.0, 10.5 Hz, 1H), 2.84 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 196.5, 163.7, 136.1, 130.5, 129.8, 128.7, 128.6, 128.34, 128.31, 128.3, 127.6, 125.2, 123.1, 115.4, 114.2, 113.8, 67.3, 56.5, 55.5, 43.3, 34.3. Mp. 94.2–94.5 °C. TLC: R_f 0.52 (hexane/EtOAc = 3:1). IR (KBr): 3073, 2965, 2840, 1711, 1664, 1512, 1489, 1399, 1365, 1281, 1262, 1172, 1138, 1022, 751, 697 cm^{-1}. HRMS Calcd for $C_{25}H_{24}NO_4$: $[M+H]^+$, 402.1700. Found: *m*/*z* 402.1692. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98.0/2.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 22.7 min, t_{major} = 24.5 min.

1-(4-Trifluoromethylphenyl)-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2e).



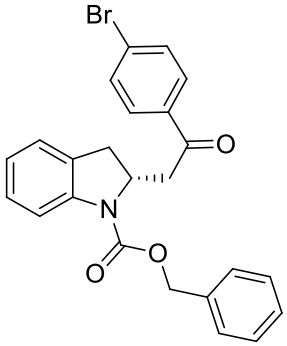
Yield: 79%, 88% *ee*, white solid. $[\alpha]_D^{18}$ +75.0 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.20–7.50 (m, 5H), 7.50–7.30 (m, 5H), 7.22 (br s, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.01 (m, 1H), 5.31 (m, 2H), 5.04 (m, 1H), 3.56 (br s, 1H), 3.49 (dd, *J* = 16.0, 9.5 Hz, 1H), 3.14 (dd, *J* = 16.0, 10.5 Hz, 1H), 2.85 (d, *J* = 17.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 197.1, 158.2, 139.1, 135.9, 135.0, 134.6 (q, *J* = 32.7 Hz), 128.7, 128.4, 127.71, 125.70, 125.68, 125.65, 125.2, 123.4 (q, *J* = 272.5 Hz), 123.2, 122.4, 115.4, 67.5, 56.1, 43.9, 34.3. ^{19}F NMR ($CDCl_3$) δ 98.7. Mp. 141.0–142.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3066, 3036, 2915, 2369, 1710, 1684, 1487, 1413, 1366, 1331, 1286, 1159, 1123, 1070, 911, 758, 600, 567 cm^{-1}. HRMS Calcd for $C_{25}H_{21}F_3NO_3$: $[M+H]^+$, 440.1468. Found: *m*/*z*440.1462. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.1 min, t_{major} = 9.5 min.

1-Naphthyl-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2f).



Yield: 83%, 88% *ee*, white solid. $[\alpha]_D^{18}$ +5.8 (*c* 0.43, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.35 (br s, 1H), 7.97–7.76 (m, 5H), 7.61 (dt, *J* = 1.5, 7.0 Hz, 1H), 7.53 (dt, *J* = 1.5, 7.0 Hz, 1H), 7.50–7.38 (m, 5H), 7.23 (br s, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.99 (m, 1H), 5.30 (m, 2H), 5.13 (t, *J* = 10.0 Hz, 1H), 3.65 (br s, 1H), 3.52 (dd, *J* = 16.0, 9.0 Hz, 1H), 3.28 (br s, 1H), 2.86 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 198.0, 159.3, 146.3, 136.1, 135.7, 134.0, 132.5, 130.1, 129.6, 128.7, 128.6, 128.5, 128.31, 128,25, 127.8, 127.6, 126.8, 125.2, 123.6, 123.1, 120.9, 115.5, 56.5, 43.7, 34.7, 30.9. Mp. 95.0–96.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3067, 3032, 2976, 2938, 2363, 2325, 1705, 1686, 1493, 1410, 1278, 1123, 1013, 824, 755, 699, 483 cm^{-1}. HRMS Calcd for $C_{28}H_{23}NO_3Na$: $[M+Na]^+$, 444.1570. Found: *m*/*z* 444.1567. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 16.8 min, t_{minor} = 20.3 min.

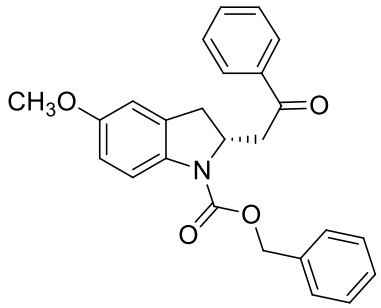
(*R*)-1-(4-Bromophenyl)-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2g).



Yield: 75%, 91% *ee*, white solid. $[\alpha]_D^{23}$ +63.9 (*c* 1.80, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.00–7.30 (m, 10H), 7.22 (br s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.99 (m, 1H), 5.28 (br s, 2H), 5.01 (m, 1H), 3.75 (br s, 1H), 3.46 (dd, *J* = 16.5, 9.5 Hz, 1H), 3.06 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.82 (d, *J* = 16.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 197.1, 176.4, 152.2, 144.6, 136.0, 135.2, 132.0, 129.6, 128.7, 128.6, 128.41, 128.35, 127.7, 125.2, 123.2, 115.5, 67.4, 56.3, 43.7, 34.2. Mp. 106.0–107.0 °C. TLC: R_f 0.49 (hexane/EtOAc = 3:1). IR (KBr): 3035, 2949, 2368, 1710, 1671, 1586, 1528, 1487, 1414,

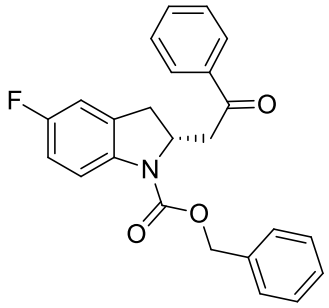
1369, 1286, 1210, 1147, 1047, 991, 816, 749, 694, 609, 576 cm^{-1}. HRMS Calcd for $C_{24}H_{21}BrNO_3$: $[M+H]^+$, 450.0699. Found: *m/z* 450.0713. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 24.1 min, t_{minor} = 49.2 min.

1-Phenyl-2-(*N*-benzyloxycarbony-5-methoxylindolin-2-yl)ethanone (2h).



Yield: 82%, 83% *ee*, white solid. $[\alpha]_D^{18}$ +65.4 (*c* 2.98, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47–7.34 (m, 8H), 6.75 (m, 2H), 5.26 (m, 2H), 5.03 (br s, 1H), 3.76 (s, 3H), 3.54 (m, 1H), 3.44 (dd, *J* = 12.5, 9.5 Hz, 1H), 3.10 (dd, *J* = 16.0, 11.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 198.2, 159.9, 156.1, 152.3, 136.6, 136.2, 133.4, 131.1, 128.7, 128.6, 128.3, 128.1, 120.1, 115.9, 112.4, 111.4, 67.1, 56.4, 55.7, 43.7, 34.7. Mp. 115.0–116.0 °C. TLC: R_f 0.45 (hexane/EtOAc = 3:1). IR (KBr): 3234, 3035, 2965, 2365, 1685, 1669, 1624, 1585, 1534, 1266, 1253, 1071, 1028, 861, 743, 697, 492 cm^{-1}. HRMS Calcd for $C_{25}H_{24}NO_4$: $[M+H]^+$, 402.1700. Found: *m/z* 402.1695. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.0 min, t_{major} = 24.0 min.

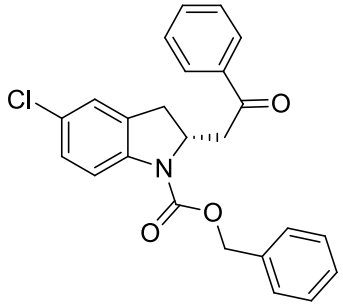
1-Phenyl-2-(*N*-benzyloxycarbony-5-fluorolindolin-2-yl)ethanone (2i).



Yield: 69%, 82% *ee*, white solid. $[\alpha]_D^{18}$ +23.3 (*c* 0.43, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.39 (m, 7H), 7.23 (br s, 1H), 7.16 (d, *J* = 7.0, 1H), 6.99 (t, *J* = 7.0 Hz, 1H), 5.29 (br s, 2H), 5.06 (t, *J* = 9.0 Hz, 1H), 3.53 (br s, 1H), 3.48 (dd, *J* = 16.5, 9.5 Hz, 1H), 3.12 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.84 (d, *J* = 16.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 198.1, 152.2,

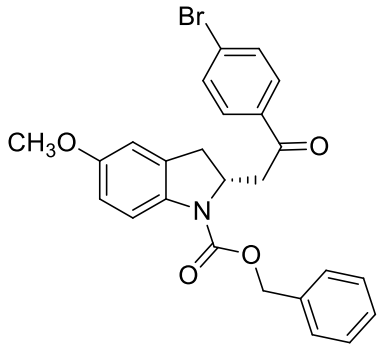
141.6, 136.6, 136.05, 135.99, 135.5, 133.3, 128.65, 128.62, 128.56 (d, J = 242.9 Hz), 128.28, 128.1, 125.2, 123.1, 115.4, 67.2, 56.3, 43.6, 31.7. ^{19}F NMR ($CDCl_3$) δ 77.1. Mp. 110.0–111.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr): 3054, 2932, 2857, 2354, 1905, 1712, 1672, 1600, 1486, 1450, 1406, 1368, 1283, 1213, 1145, 1047, 1020, 995, 867, 755, 730, 690, 605 cm^{-1}. HRMS Calcd for $C_{24}H_{19}FNO_4$: $[M+OH]^-$, 404.1304. Found: m/z 404.1286. HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.6 min, t_{major} = 6.4 min.

1-Phenyl-2-(*N*-benzyloxycarbony-5-chlorolindolin-2-yl)ethanone (2j).



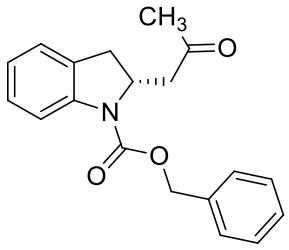
Yield: 82%, 84% *ee*, white solid. $[\alpha]_D^{18}$ +6.2 (*c* 0.65, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 3H), 7.56 (m, 1H), 7.36 (m, 7H), 7.17 (br s, 1H), 7.11 (m, 1H), 5.27 (br s, 2H), 5.05 (t, J = 9.5 Hz, 1H), 3.53 (br s, 1H), 3.45 (dd, J = 16.5, 9.5 Hz, 1H), 3.11 (dd, J = 16.5, 5.5 Hz, 1H), 2.81 (d, J = 16.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 197.8, 166.0, 136.5, 135.8, 134.4, 133.5, 131.5, 129.5, 128.71, 128.68, 128.45, 128.35, 128.1, 127.6, 125.3, 116.3, 67.8, 56.6, 43.5, 31.2. Mp. 122.0–123.0 °C. TLC: R_f 0.52 (hexane/EtOAc = 3:1). IR (KBr): 3066, 3032, 2928, 2354, 1700, 1666, 1595, 1486, 1399, 1359, 1293, 1227, 1144, 1025, 812, 766, 751, 694, 686, 615, 589 cm^{-1}. HRMS Calcd for $C_{24}H_{19}ClNO_4$: $[M+O-H]^-$, 420.1008. Found: m/z 420.1008. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.8 min, t_{major} = 9.9 min.

1-(4-Bromophenyl)-2-(*N*-benzyloxycarbony-5-methoxylindolin-2-yl)ethanone (2k).



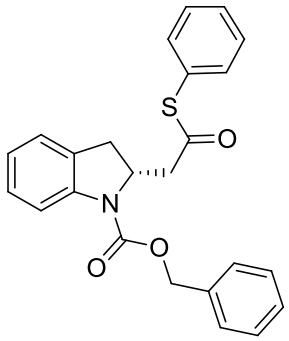
Yield: 53%, 93% *ee*, white solid. $[\alpha]_D^{18}$ +36.8 (*c* 3.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.90–7.50 (m, 3H), 7.48–7.26 (m, 7H), 6.74 (br s, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 5.25 (m, 2H), 4.99 (br s, 1H), 3.76 (s, 3H), 3.48 (br s, 1H), 3.43 (dd, *J* = 16.5, 9.0 Hz, 1H), 3.05 (dd, *J* = 16.5, 10.0, 1H), 2.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 197.1, 156.1, 142.6, 138.1, 136.1, 135.2, 131.94, 131.90, 129.6, 128.7, 128.6, 128.4, 115.9, 112.5, 111.4, 109.7, 67.2, 56.3, 55.7, 43.6, 34.6. Mp. 118.0–119.0 °C. TLC: R_f 0.51 (hexane/EtOAc = 3:1). IR (KBr): 3461, 3033, 2954, 2854, 1685, 1586, 1493, 1455, 1399, 1364, 1327, 1274, 1208, 1126, 1071, 1024, 990, 813, 742, 698, 572, 511 cm^{-1}. HRMS Calcd for $C_{25}H_{23}BrNO_4$: $[M+H]^+$, 480.0805. Found: *m*/*z* 480.0813. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.0 min, t_{major} = 14.3 min.

1-Methyl-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2l).



Yield: 18%, 74% *ee*, white solid. ^{1}H NMR ($CDCl_3$) δ (19H)7.84 (br s, 1H), 7.34 (m, 5H), 7.18 (br s, 1H), 7.14 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.28 (m, 2H), 4.86 (t, *J* = 10.0 Hz, 1H), 3.45 (dd, *J* = 16.5, 9.5 Hz, 1H), 2.97 (br s, 1H), 2.67 (m, 2H), 2.10 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 181.5, 165.1, 161.2, 146.1, 141.4, 130.5, 128.9, 128.6, 128.4, 127.9, 123.3, 115.7, 68.1, 58.0, 46.3, 36.4, 30.7. TLC: R_f 0.40 (hexane/EtOAc = 3:1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98.0/2.0, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.2 min, t_{minor} = 11.7 min. The characterization data were identical to those reported in the literature.[19]

1-Phenylthio-2-(*N*-benzyloxycarbonylindolin-2-yl)ethanone (2m).

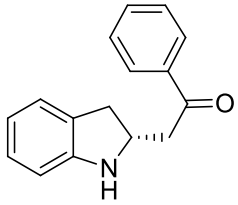


Yield: 55%, 52% *ee*, white solid. $[\alpha]_D^{18}$ +39.3 (*c* 1.78, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.86 (br s, 1H), 7.46–7.27 (m, 10H), 7.23 (br s, 1H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.00 (t, *J* = 7.0 Hz, 1H), 5.32 (br s, 2H), 4.92 (br s, 1H), 3.41 (dd, *J* = 16.5, 9.5 Hz, 1H), 3.15 (br s, 1H), 2.96 (dd, *J* = 16.5, 2.0 Hz, 1H), 2.91 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 194.9, 158.3, 143.5, 137.3, 136.0, 134.4, 129.5, 129.2, 128.7, 128.3, 128.2, 127.7, 127.3, 125.2, 123.2, 115.5, 67.4, 56.5 47.8, 33.9. Mp. 88.5–89.5 °C. TLC: R_f 0.45 (hexane/EtOAc = 3:1). IR (KBr): 3473, 3313, 3001, 2939, 2361, 1693, 1641, 1540, 1451, 1306, 1234, 1059, 1016, 918, 752, 694, 651 cm^{-1}. HRMS Calcd for $C_{24}H_{22}NO_3S$: $[M+H]^+$, 404.1315. Found: *m*/*z* 404.1308. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, flow rate = 2.0 ml/min, λ = 254 nm, 40 °C): t_{minor} = 8.7 min, t_{major} = 12.1 min.

Procedure for deprotection of 2b[20]

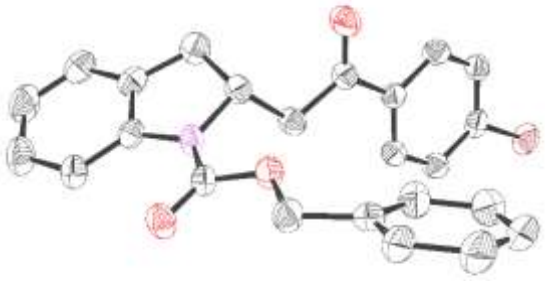
After Pd/C (0.010 g, 10%, 10 mol %) in a 20-mL flask was degassed under reduced pressure, H_2 gas (balloon) was introduced into the flask, and EtOH (0.15 mL) was added. To the mixture, a solution of **2a** (0.037 mg, 0.10 mmol) in CH_2Cl_2 (0.2 mL) and EtOH (0.45mL) was added. After being stirred for 6 h, the reaction mixuture was diluted with hexane/EtOAc (v/v = 1/1), passed through a short celite pad to remove Pd/C, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave (*R*)-1-phenyl 2-(idolin-2-yl)acetate (**4**).

(*R*)-1-Phenyl-2-(indolin-2-yl)ethanone (4).



Yield: 80%, 87% *ee*, colorless oil. $[\alpha]_D^{18}$ +24.4 (*c* 2.08, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.84 (br s, 1H), 7.47 (br s, 1H), 7.36 (m, 3H), 7.31 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.32 (m, 1H), 5.23 (m, 1H), 4.82 (m, 2H), 3.37 (dd, *J* = 16.5, 10.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 194.6, 144.3, 128.6, 128.5, 128.24, 128.20, 127.5, 125.5, 125.0, 123.0, 115.6, 67.1, 57.1, 33.9. TLC: R_f 0.48 (hexane/EtOAc = 2:1). IR (neat): 3442, 3064, 2923, 2362, 2331, 1688, 1603, 1486, 1465, 1419, 1368, 1126, 1042, 668, 461 cm^{-1}. HRMS Calcd for $C_{16}H_{16}NO$: $[M+H]^+$, 238.1226. Found: *m*/*z* 238.1225. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 7.7 min, t_{minor} = 20.3 min.

ORTEP Drawing of 2g



Identification code	**2g**	
Empirical formula	$C_{24}H_{20}BrNO_3$	
Formula weight	450.32	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 4.8951(6) Å	α= 90°
	b = 18.566(2) Å	β= 96.116(2)°
	c = 11.3888(14) Å	γ = 90°
Volume	1029.2(2) $Å^3$	
Z	2	
Density (calculated)	1.453 Mg/m^3	
Absorption coefficient	2.022 mm^{-1}	
F(000)	460	
Crystal size	0.50 x 0.30 x 0.30 mm^3	
Theta range for data collection	1.80 to 27.02°.	
Index ranges	–4<=h<=6, –23<=k<=23, –11<=l<=14	
Reflections collected	6282	
Independent reflections	4166 [R(int) = 0.0211]	
Completeness to theta = 27.02°	99.6 %	
Absorption correction	None	
Max. and min. transmission	0.5822 and 0.4313	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4166 / 1 / 214	
Goodness-of-fit on F^2	0.981	
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.0953	
R indices (all data)	R1 = 0.0579, wR2 = 0.1022	
Absolute structure parameter	0.014(10)	
Largest diff. peak and hole	0.523 and –0.166 e.$Å^{-3}$	

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Chapter 3

Enantioselective Syntheses of Axially Chiral Isoquinoline *N*-Oxides by Bifunctional Organocatalysts

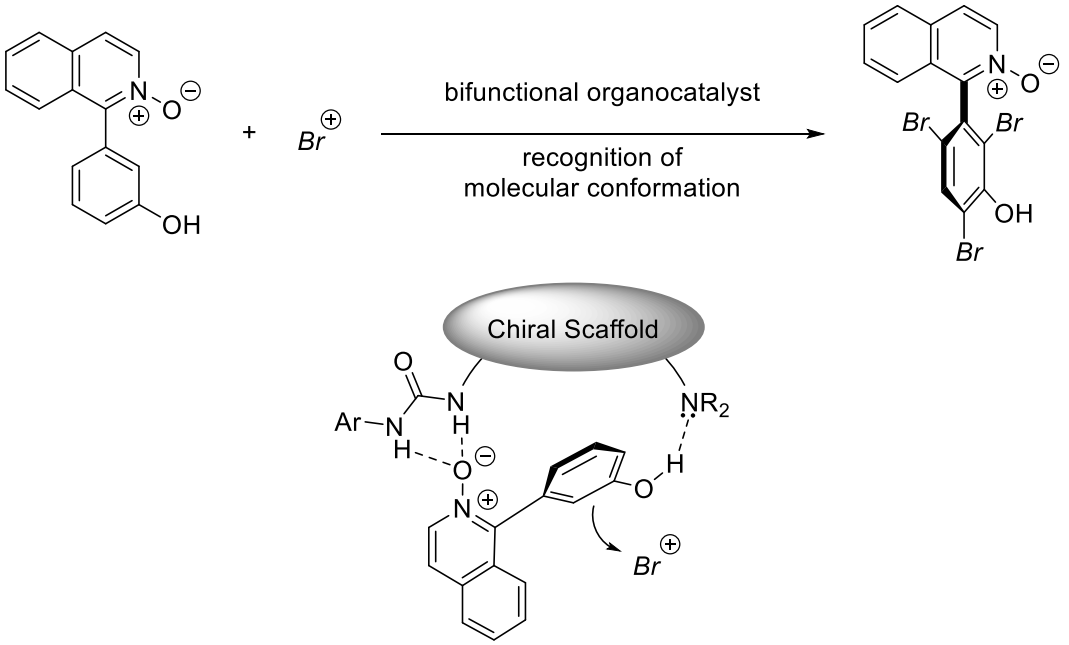
Bifunctional organocatalysts bearing amino and urea functional groups have been applied for a novel, highly enantioselective synthesis of axially chiral isoquinoline *N*-oxides, which are promising chiral ligands or organocatalysts in organic synthesis. This is the first example of highly enantioselective synthesis of axially chiral biaryls by bifunctional organocatalysts. Good- to excellent enantioselectivities were obtained with a range of substrates.

Introduction

Bifunctional organocatalysts have significantly contributed to the field of asymmetric synthesis.[1] In these catalysts, the (thio)urea and tertiary amino functional groups cooperatively realize the simultaneous activation of a nucleophile and an electrophile in a suitable spatial configuration. Previously, the author has used these organocatalysts for several asymmetric cyclization reactions via intramolecular hetero-Michael addition,[2] in which multipoint recognition by the catalysts stabilizes the specific conformations of the substrates in the transition state before the construction of a chiral center. Inspired by the success of these results, he envisaged that the utility of this class of small molecule catalysts could be expanded by translating the molecular torsion induced by bifunctional organocatalysts into axial chirality. Recently, although some organocatalysts have been reported to be useful for the enantioselective syntheses of axially chiral compounds,[3] thus far, methods employing this type of bifunctional organocatalysts have rarely been developed.[4] Here, he demonstrates the novel competence of bifunctional organocatalysts as an efficient avenue for the asymmetric construction of axially chiral compounds.

Results and Discussion

In this study, the author reports the highly enantioselective aromatic electrophilic bromination of 1-(3-hydroxyphenyl)isoquinoline 2-oxides (Scheme 1). The 1-(3-hydroxyphenyl)isoquinoline 2-oxide substrates have an isoquinoline *N*-oxide moiety, which can interact with a hydrogen-bond donor, and a phenol moiety, which can interact with a hydrogen-bond acceptor; such interactions are expected to twist the molecule in one direction. Meanwhile, the axially chiral *N*-oxides obtained are promising chiral ligands or organocatalysts in organic synthesis,[5] although thus far, their catalytic enantioselective synthesis has been underdeveloped, to the best of his knowledge.

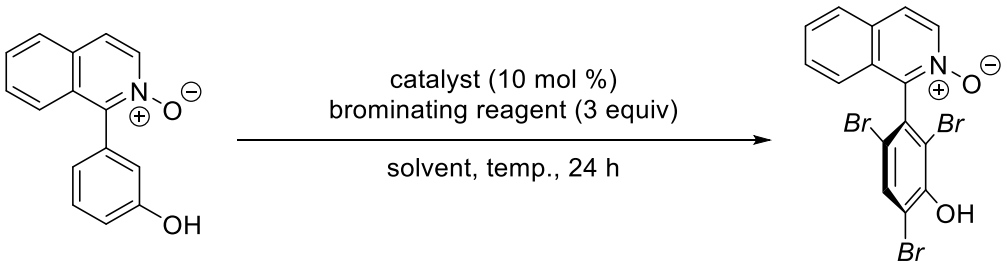


Scheme 1. Construction of axially chiral structure by bifunctional organocatalysts.

Table 1 shows the optimization of reaction conditions. First, the author investigated the reaction between 1-(3-hydroxyphenyl)isoquinoline 2-oxide (**1a**) and *N*-bromoacetamide (NBA, **4a**) as the brominating reagent with 10 mol % of quinidine-derived bifunctional catalyst **3a**[6] in CH_2Cl_2 at −40 °C. As expected, tribromide **2a** was obtained in good yield with moderate enantioselectivity (Table 1, entry 1). Second, the solvents were screened, and among those tested, THF was identified to be the most suitable solvent, demonstrating high enantioselectivity, albeit with an unsatisfactory product yield (Table 1, entry 5). Third, the effect of temperature on the reaction was studied: higher temperatures improved the product yield while maintaining excellent enantioselectivites (Table 1, entries 6 and 7); hence, the author selected 0 °C as the reaction temperature for further investigations. Meanwhile, the effect of various brominating reagents besides NBA (DBH (**4b**), NBS (**4c**), and NBP (**4d**)) was also studied. Figure 1 shows their chemical structures. As can be seen, no significant effects were observed with respect to the yields and enantioselectivities (Table 1, entries 8−10). Next, the effect of different catalysts was also investigated; other cinchona-alkaloid-derived catalysts also exhibited good stereoselectivities similar to that obtained with the use of **3a** (entry 6), and the use of **3c** and **3d** afforded the opposite enantiomer of the product with high enantioselectivities (Table 1, entries 11−13). Moreover, catalyst **3e**, with a cyclohexanediamine framework, also afforded a quantitative product yield with a slightly lower enantioselectivity (Table 1, entry 14). On the other hand, catalyst **3f**, which has

a significantly less basic nitrogen atom, failed to attain enantioselectivity (Table 1, entry 15). Moreover, quinidine (**3g**) also demonstrated enantioselectivity significantly lesser than those exhibited by catalysts **3a**−**3e** (Table 1, entry 16). These results demonstrate the significance of the bifunctionality of the catalyst containing amino and urea functional groups toward enantioselectivity.

Table 1. Optimization of conditions[a]



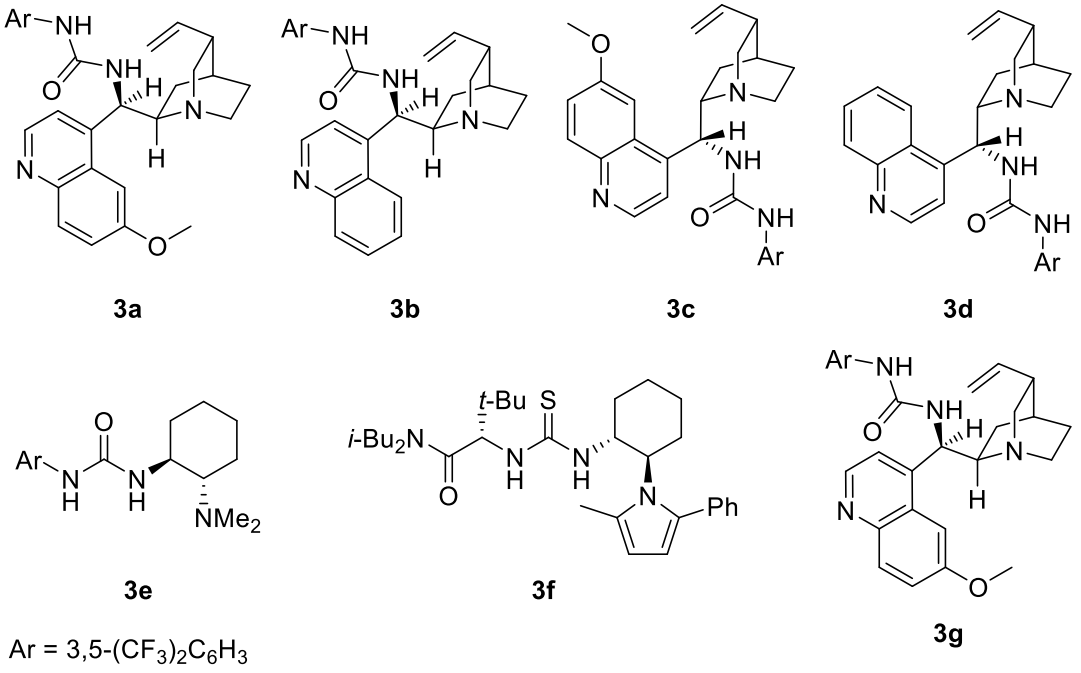
1a **2a**

entry	catalyst	brominating reagent	solvent	temp. (°C)	yield (%)[b]	*ee* (%)
1	**3a**	NBA (**4a**)	CH_2Cl_2	–40	95	54
2	**3a**	NBA (**4a**)	toluene	–40	7	74
3	**3a**	NBA (**4a**)	EtOAc	–40	50	93
4	**3a**	NBA (**4a**)	Et_2O	–40	<5	—
5	**3a**	NBA (**4a**)	THF	–40	32	99
6[c]	**3a**	NBA (**4a**)	THF	0	99	99
7[d]	**3a**	NBA (**4a**)	THF	25	99	97
8[c,d]	**3a**	DBH (**4b**)	THF	0	99	98
9[c]	**3a**	NBS (**4c**)	THF	0	99	98
10[c]	**3a**	NBP (**4d**)	THF	0	99	98

Table 1. (Continued)

11[c]	**3b**	NBA (**4a**)	THF	0	99	98
12[c]	**3c**	NBA (**4a**)	THF	0	85	96
13[c]	**3d**	NBA (**4a**)	THF	0	84	94
14[c]	**3e**	NBA (**4a**)	THF	0	99	91
15[c]	**3f**	NBA (**4a**)	THF	0	46	1
16[c]	**3g**	NBA (**4a**)	THF	0	91	42

[a] Reactions were run using **1a** (0.1 mmol), the brominating reagent (0.3 mmol), and the catalyst (0.01 mmol) in the solvent (10 mL). [b] Isolated yields. [c] Reactions were run for 6 h. [d] Reaction was run for 5 h. [e] 1.5 equiv of **4b** was used for the reaction.



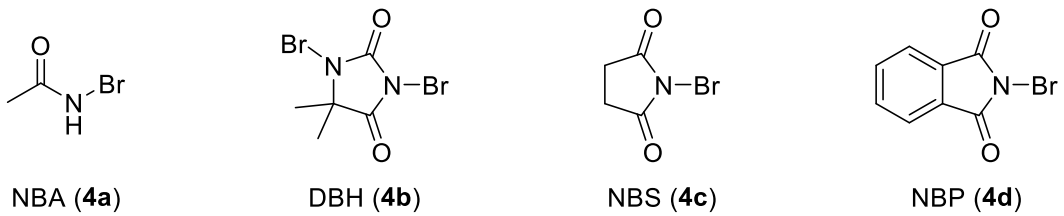
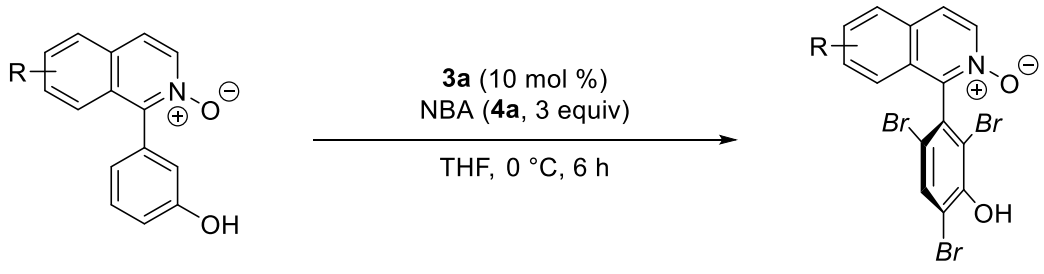


Figure 1. Brominating reagents.

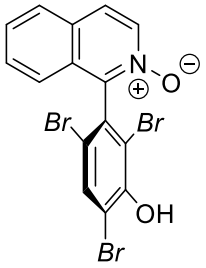
Next, the substrate scope was investigated, and the robustness of this synthetic method was confirmed. Table 2 shows the results. For substrates bearing fluoro and bromo functional groups on the isoquinoline ring, the desired products **2b** and **2c** were obtained with high enantioselectivities. Moreover, a nitro group was also tolerated, affording the corresponding product **2d** in high enantioselectivity. Furthermore, a substrate with a methyl group near the biaryl axis yielded the brominated product **2e** in excellent yield and enantioselectivity. In addition, a derivative bearing an expanded π-conjugate plane afforded the brominated product **2f** in good yield and stereoselectivity. Moreover, as shown in Scheme 2, substrates bearing substituted phenols were also investigated. A meta substituent on the phenol ring did not affect the reaction, affording **2g** in excellent yield and enantioselectivity. Moreover, when the reaction was carried out using **1h**, which has a substituent ortho to the hydroxy group, dibromination proceeded with quantitative yield with excellent enantioselectivity. Meanwhile, the absolute configuration of **2a** was determined by X-ray analysis (see the Experimental Section for details), and the configurations of all other examples were assigned analogously.

To gain insights on the reaction mechanism, reaction was run with only one equivalent of **4a**, and reaction mixture of crude products was analyzed by HPLC (Scheme 4). As a result, monobrominated products **1i** was observed as a major product, which already had great enantiopurity at this stage. And the other regioisomers of **1i** was seen in only trace amount although the remaining **1a** and product **2a** was also found. Next, the reactions of monobrominated racemic substrate **1i** was performed and almost no enantioselectivity was observed (Scheme 5). These results imply that the bromination at an ortho position of the axis is the enantiodetermining step in this reaction, and once one of the ortho positions is brominated, no racemization occurs by bond rotation during the course of further bromination (Scheme 6).[6]

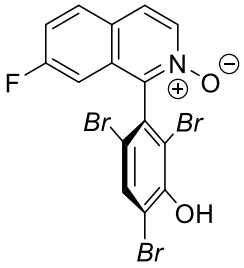
Table 2. Substrate Scope[a]



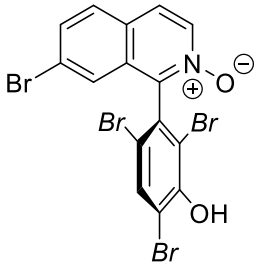
1 **2**



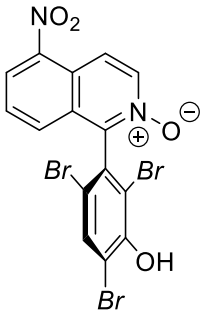
2a
99%, 99% *ee*



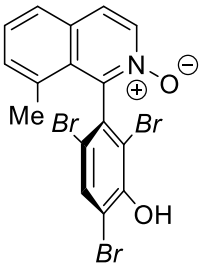
2b
99%, 93% *ee*



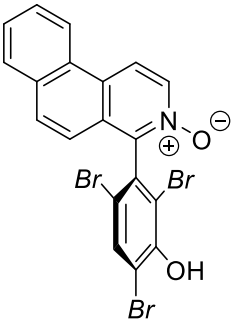
2c
97%, 93% *ee*



2d
99%, 94% *ee*

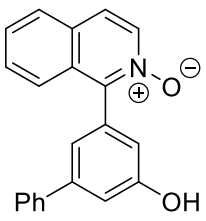


2e
99%, 98% *ee*

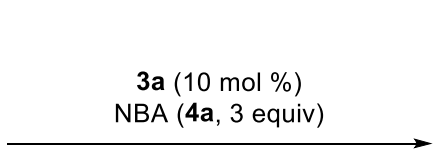


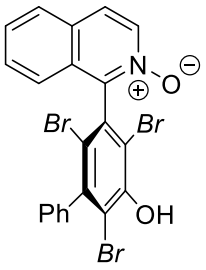
2f
92%, 96% *ee*

[a] Reactions were run using **1** (0.1 mmol), **4a** (0.3 mmol), and **3a** (0.01 mmol) in THF (10 mL). Yields represent material isolated after silica gel column chromatography.

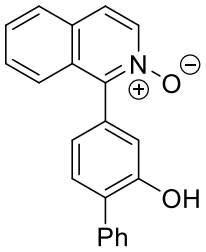


1g

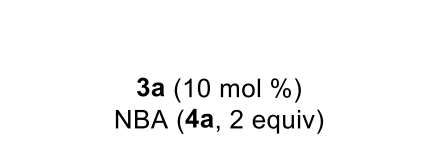


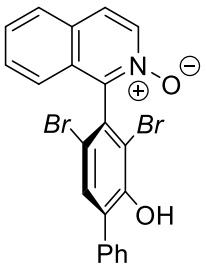


2g
99%, 98% *ee*



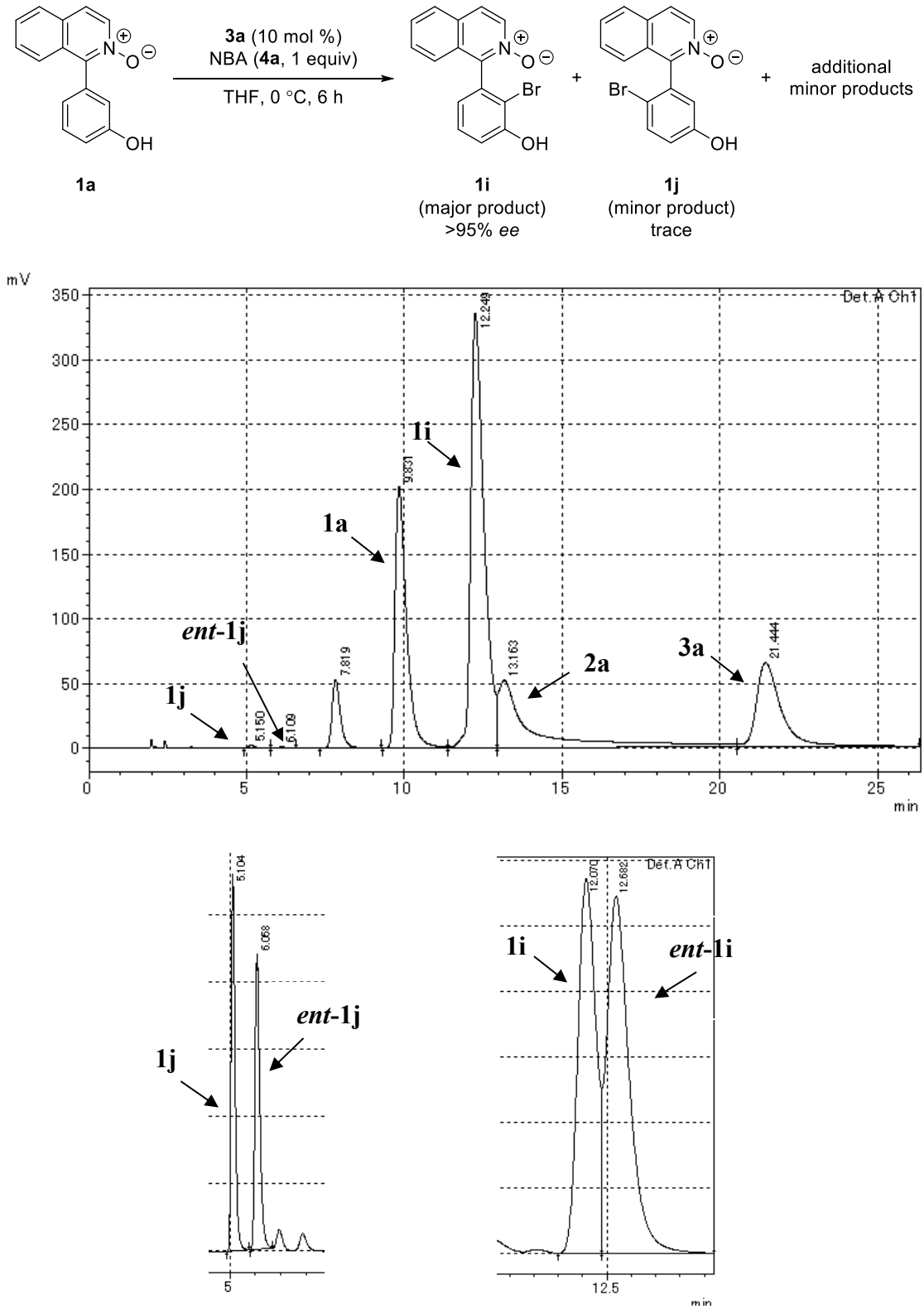
1h



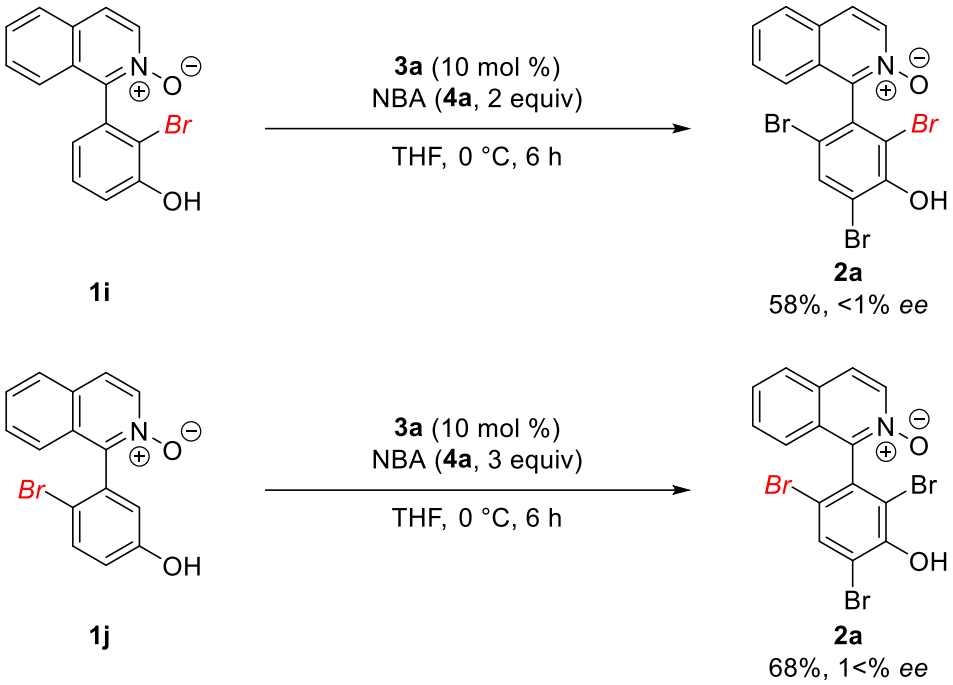


2h
99%, 99% *ee*

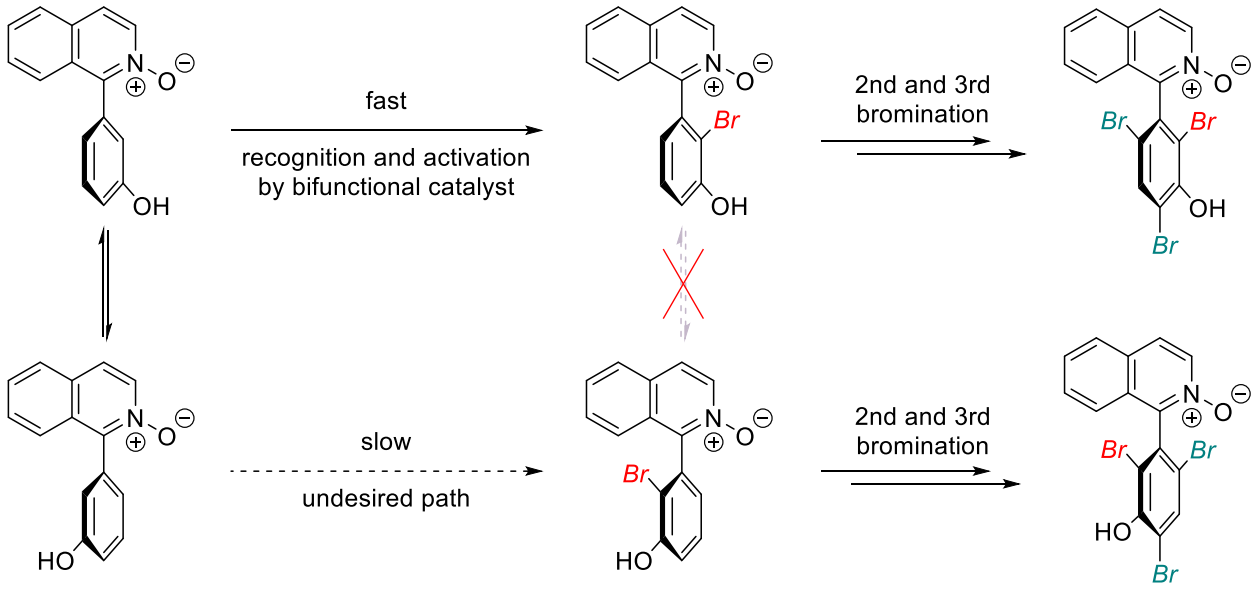
Scheme 3. Reactions of substrates with substituted phenols



Scheme 4. HPCL chromatogram profile of the mixture of crude products obtained after the reaction using 1 equiv of **4a**.



Scheme 5. Reactions of monobrominated substrate.



Scheme 6. Proposed reaction pathways.

Conclusion

In summary, the author presents a novel, highly enantioselective synthesis of axially chiral isoquinoline *N*-oxides using bifunctional organocatalysts. This method efficiently produces axially chiral *N*-oxides, which are promising chiral catalysts in organic synthesis. Notably, this is the first example of the use of simple bifunctional organocatalysts for the asymmetric synthesis of axially chiral biaryls. In addition, good-to-excellent enantioselectiveties were accomplished with a range of substrates. Thus, this methodology demonstrates utility for further application in the synthesis of various axially chiral compounds. Further studies regarding the detailed clarification of the reaction mechanism and application of this methodology to the construction of other axially chiral structures are currently underway and will be reported in due course.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. The 1-bromoisoquinoline for substrate **1a**, and strating anisidic acid derivatives for **1b**, **1c**, and **1e-1j**, and brominating reagent **4** are commercially available. Substrate **1a**, **1d**[7,8] and the other substrates[9] were synthesized by modified literature procedures. The bifunctional organocatalyst **3a–3e** was prepared by the same procedures as that in Chapter 1: and **3f** was purchased from Aldrich. Preparation of the catalyst **3e** was done according to the literature[1a].

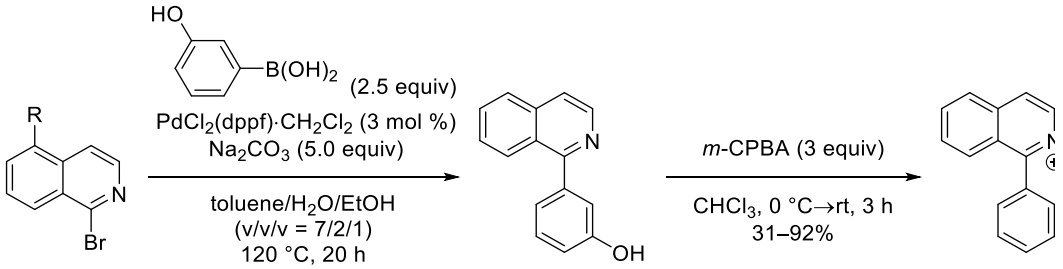
General procedure for asymmetric synthesis of 1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxides 2

In a 20-mL round-bottom flask, the author sequentially added substrate **1** (0.10 mmol), quinidine-derived bifunctional catalyst **3a** (5.8 mg, 0.010 mmol), and THF (10 mL). The mixture was stirred at 0 °C for 30 min. To the resulting solution was added *N*-bromoacetamide (**4a**, 41.4 mg, 0.3 mmol). The reaction mixture was then stirred for 6 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$, and then the aqueous phase was extracted with EtOAc (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using $CHCl_3$/MeOH (v/v = 12/1)

as an eluent afforded the corresponding 1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxides **2**.

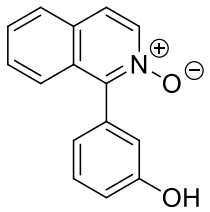
Racemic compounds were prepared using DABCO as a catalyst.

Procedure for preparation of substrates 1a and 1d



To a 50-mL round-bottom flask were added the palladium catalyst (25.8 mg, 3 mol %), Na_2CO_3, and H_2O (2 mL). Subsequently, the solution of a bromoisoquinoline (1 mmol) and 3-hydroxyphenylboronic acid (345 mg, 2.5 mmol) in toluene (7 mL)/EtOH (1 mL) was added. The reaction mixture was refluxed at 120 °C for 20 h. After cooling to ambient temperature, H_2O (15 mL) was poured into the flask. The aqueous phase was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 1/2) as an eluent gave the corresponding 1-(3-hydroxyphenyl)isoquinolines as white (R = H; 61% yield) or yellow (R = NO_2; 58% yield) solids. A solution of the 1-(3-hydroxyphenyl)isoquinoline (1 mmol) in $CHCl_3$ (4 mL) were put in 20-mL round-bottom flask and cooled to 0 °C. To the solution was slowly added *m*-CPBA (6 mL, c.a. 2 M $CHCl_3$ solution, 3 mmol). The reaction mixture was then warmed to ambient temperature and vigorously stirred for 3 h. Saturated aqueous $Na_2S_2O_3$ was poured into the mixture, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic layers were washed with brine and dried with Na_2SO_4. Purification by flush silica gel column chromatography using $CHCl_3$/MeOH (v/v = 10/1) as an eluent gave the corresponding 1-(3-hydroxyphenyl)isoquinoline *N*-oxides **1a** and **1d**.

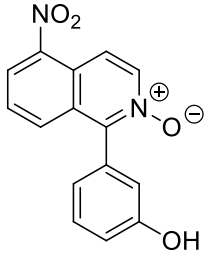
1-(3-Hydroxyphenyl)isoquinoline 2-oxide (1a).



White solid; 92% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.72 (br s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.72 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.69 (d, J = 5.5 Hz, 1H), 7.55 (ddd, J = 8.5, 7.0, 1.0 Hz, 1H), 7.30 (dd, J = 7.5, 7.5 Hz, 1H), 7.26 (s, 1H) 7.08 (d, J = 7.5 Hz, 1H), 6.88 (dd, J = 8.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 160.9, 157.0, 140.9, 139.3, 136.9, 130.6, 129.2, 128.1, 127.5, 126.9, 126.8, 121.4, 120.5, 117.5, 116.6. Mp. 165.0–166.0 °C. TLC: R_f 0.28 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3093, 2955, 2732, 2614, 1942, 1696, 1560, 1497, 1456, 1421, 1389, 1319, 1287, 1266, 1196, 1142, 967, 897, 867, 835, 777, 741 cm^{-1}. HRMS Calcd for $C_{15}H_{12}NO_2$: $[M+H]^+$, 238.0863. Found: *m*/*z* 238.0864.

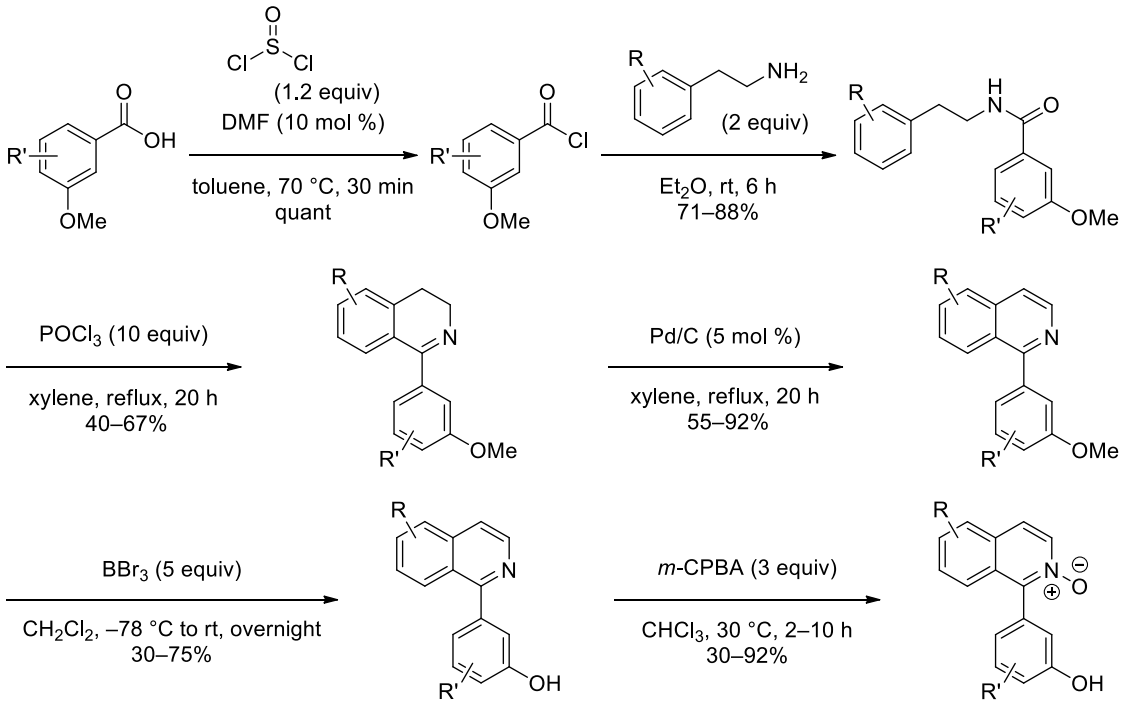
1-(3-Hydroxyphenyl)-5-nitroisoquinoline 2-oxide (1d).



Yellow solid; 31% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.67 (br s, 1H), 8.63 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.41 (dd, J = 7.5, 1.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.5, 8.0 Hz, 1H), 7.35 (dd, J = 7.5, 7.5 Hz, 1H), 6.93 (dd, J = 2.0, 1.5 Hz, 1H), 6.89 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 6.83 (ddd, J = 7.5, 1.5, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 157.8, 147.7, 145.1, 139.2, 133.1, 130.8, 130.3, 129.8, 128.1, 126.8, 122.2, 120.8, 119.3, 118.3, 117.5. Mp. 254.5–255.0 °C. TLC: R_f 0.31 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3802, 3095, 2667, 1700, 1597, 1529, 1447, 1395, 1343, 1319, 1243, 1218, 1196, 1146, 1088, 1033, 1010, 912, 815, 750, 723 cm^{-1}. HRMS Calcd for $C_{15}H_{11}N_2O_4$: $[M+H]^+$, 283.0713 Found: *m*/*z* 283.0710.

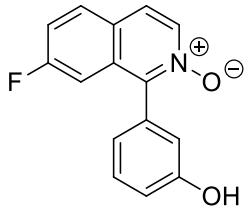
General procedure for preparation of substrates 1b, 1c and 1e–1h



To a solution of a 3-methoxybenzoic acid derivative (10 mmol) in toluene (15 mL) was added thionyl chloride (0.87 mL, 12 mmol) and a catalytic ammount of DMF (0.08 mL, 1.0 mol). After the resulting mixture was stirred for 30 min, the solvent was removed, and the crude product was dried in vacuo. The product was placed in a 50-mL reaction vessel at 0 °C. To the flask was added Et_2O (15 mL) and a 1-phenylethylamine derivative (2 equiv), and the solution was stirred for 6 h. The mixture was quenched with 1 M aqueous HCl (10 mL), and the organic layers were washed with 1 M aqueous HCl, brine and 1 M aqueous NaOH, and subsequently dried over Na_2SO_4. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the corresponding 3-methoxyamides as a white solid in 71–88% yield. To a solution of the 3-methoxybenzamide (7 mmol) in xylene (30 mL), $POCl_3$ (10 equiv) was added. The reaction mixture was then refluxed at 160 °C for 20 h. The resulting solution was evaporated, and then the mixture was carefully quenched with 10% aqueous NaOH (15mL), extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave the corresponding 1-(3-methoxyphenyl)-3,4-dihydroisoquinolines as a white solid in 40–67% yield. In a 50-mL round-bottom flask, Pd/C (10 mol %) was placed, and the solution of the 1-(3-methoxyphenyl)-3,4-dihydroisoquinoline in xylene (0.25 M) was added. The reaction mixture was refluxed overnight. The mixture was passed through a celite pad to remove black solid. The filtrate was

concentrated in vacuo. Purification by silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the corresponding 1-(3-methoxyphenyl)isoquinolines in 55–92% yield. To the solution of the 1-(3-methoxyphenyl)isoquinoline (2 mmol) in CH_2Cl_2 (10 mL) was added dropwise the solution of BBr_3 (10 mL, c.a. 1M in CH_2Cl_2, 10 mmol) at –78 °C. Then the reaction mixture was steadily warmed to ambient temperature. The resulting solution was carefully quenched with H_2O, extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush slica gel column chromatography using hexane/EtOAc (v/v = 1/2) gave the corresponding 1-(3-hydroxyphenyl)isoquinolines in 30–76% yield. A solution of the isoquinoline (1 mmol) in $CHCl_3$ (4 mL) was placed in 20 mL round-bottom flask and cooled to 0 °C. To the flask was added slowly the solution of *m*-CPBA (6 mL, c.a. 0.5 M in CH_2Cl_2 solution, 3 mmol). Subsequently, the reaction mixture was warmed to ambient temperature and vigorously stirred for 3 h. Saturated aqueous $Na_2S_2O_3$ was poured into reaction mixture, and the aqueous layers were extracted with CH_2Cl_2 (10 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel chromatography using $CHCl_3$/MeOH (v/v = 10/1) as an eluent gave the corresponding 1-(3-hydroxyphenyl)isoquinoline *N*-oxides **1b**, **1c**, and **1e**–1**h** in 30–92% yield.

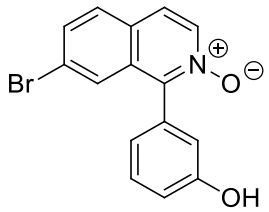
7-Fluoro-1-(3-hydroxyphenyl)isoquinoline 2-oxide (1b).



Orange solid; 26% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 9.49 (br s, 1H), 8.27 (d, *J* = 7.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 5.5 Hz, 1H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.38 (ddd, *J* = 9.0, 8.0, 2.5 Hz, 1H), 7.31 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.17 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.97 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.86 (ddd, *J* = 10.0, 2.0, 1.0 Hz, 1H), 6.82 (ddd, *J* = 7.5, 2.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 162.3 (d, *J* = 250.1 Hz), 157.9, 135.9, 130.9, 130.1, 130.0, 129.4, 129.3, 127.0, 123.3, 120.5, 119.7 (d, *J* = 25.9 Hz), 118.0, 117.5, 110.9 (d, *J* = 23.9 Hz). ^{19}F NMR ($CDCl_3$) δ 54.3. Mp. 208.0–208.5 °C. TLC: R_f 0.23 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3063, 2921, 2553, 1696, 1598, 1559, 1451, 1366, 1328, 1269, 1205, 1188, 1145, 1121, 1018, 973, 904, 867, 790, 699 cm^{-1}. HRMS Calcd for $C_{15}H_{11}FNO_2$: $[M+H]^+$, 256.0768. Found: *m*/*z* 256.0765.

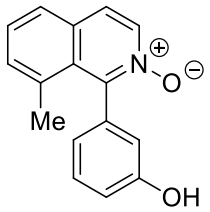
7-Bromo-1-(3-hydroxyphenyl)isoquinoline 2-oxide (1c).



White solid; 88% (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.33 (d, *J* = 7.0 Hz, 1H), 7.71–7.68 (m, 4H), 7.35 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.95 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 157.7, 136.8, 132.9, 130.5, 130.1, 129.9, 129.7, 128.7, 128.5, 128.2, 123.9, 123.4, 120.8, 118.1, 117.5. Mp. 242.0–243.0 °C. TLC: R_f 0.15 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3078, 2931, 1705, 1597, 1583, 1487, 1452, 1368, 1313, 1284, 1259, 1209, 1170, 1149, 1071, 898, 839, 764 cm^{-1}. HRMS Calcd for $C_{15}H_{11}BrNO_2$: $[M+H]^+$, 315.9968. Found: *m*/*z* 315.9967.

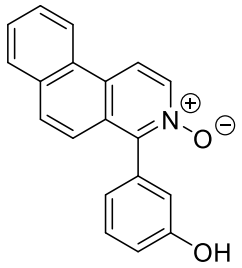
1-(3-Hydroxyphenyl)-8-methylisoquinoline 2-oxide (1e).



White solid; 84% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.60 (br s, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.28 (dd, *J* = 9.0, 8.5 Hz, 1H), 6.97 (dd, *J* = 7.5, 7.0 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.0 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 157.8, 148.0, 140.3, 136.2, 131.5, 130.7, 130.6, 129.6, 127.5, 126.9, 125.8, 122.9, 120.6, 117.8, 117.7, 21.7. Mp. 266.0–266.7. TLC: R_f 0.12 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3094, 2667, 1700, 1597, 1529, 1447, 1395, 1343, 1319, 1243, 1218, 1196, 1146, 1088, 1033, 1010, 912, 815, 750, 723 cm^{-1}. HRMS Calcd for $C_{16}H_{14}NO_2$: $[M+H]^+$, 252.1019. Found: *m*/*z* 252.1014.

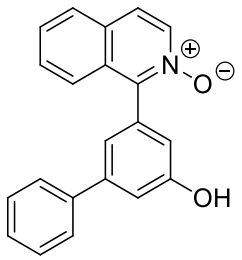
4-(3-Hydroxyphenyl)benzo[*f*]isoquinoline 3-oxide (1f).



White solid; 75% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.58 (d, *J* = 7.5 Hz, 1H), 8.57 (s, 1H), 8.51 (d, *J* = 7.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.78–7.71 (m, 3H), 7.41 (d, *J* = 9.5 Hz, 1H), 7.33 (dd, *J* = 7.5, 7.0 Hz, 1H), 7.00 (br s, 1H), 6.90–6.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 157.8, 148.3, 136.6, 133.2, 132.5, 131.0, 130.5, 130.1, 129.9, 129.7, 128.9, 128.5, 128.1, 123.4, 123.0, 120.9, 118.7, 117.8, 117.7. Mp. 244.0–244.5 °C. TLC: R_f 0.41 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3060, 2590, 1700, 1601, 1522, 1448, 1424, 1289, 1263, 1253, 1230, 1213, 1189, 1147, 996, 866, 835, 818, 777, 756, 699 cm^{-1}. HRMS Calcd for $C_{19}H_{14}NO_2$: $[M+H]^+$, 288.1019. Found: *m*/*z* 288.1014.

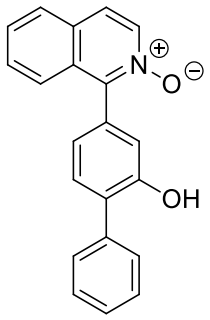
1-(5-Hydroxy-[1,1'-biphenyl]-3-yl)isoquinoline 2-oxide (1g).



White soild; 52% (for the last step).

^{1}H NMR ($CDCl_3$) δ 9.98 (br s, 1H), 8.36 (d, *J* = 7.0 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.47–7.44 (m, 2H), 7.30–7.26 (m, 2H), 7.23–7.20 (m, 1H), 7.10 (dd, *J* = 2.0, 1.5 Hz, 1H), 7.06 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.97 (dd, *J* = 2.0, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.8, 140.8, 136.8, 130.1, 129.3, 129.10, 129.06, 128.8, 128.63, 128.59, 128.47, 128.4, 128.23, 128.17, 127.3, 127.2, 124.5, 124.1, 116.8. Mp. 288.0–289.0 °C. TLC: R_f 0.48 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3070, 2931, 2800, 2674, 1718, 1595, 1559, 1500, 1454, 1403, 1363, 1315, 1277, 1205, 1196, 1143, 975, 861, 761, 703. HRMS Calcd for $C_{21}H_{16}NO_2$: $[M+H]^+$, 314.1176. Found: *m*/*z* 316.1167.

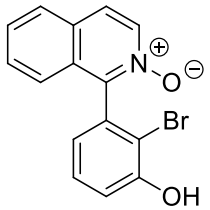
1-(2-Hydroxy-[1,1'-biphenyl]-4-yl)isoquinoline 2-oxide (1h).



White solid; 48% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.89 (br s, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.68–7.66 (m, 2H), 7.61 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.58–7.56 (m, 2H), 7.54 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.45–7.42 (m, 3H), 7.35 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 149.7, 144.9, 137.2, 135.6, 133.8, 132.5, 131.9, 129.9, 129.2, 128.73, 128.69, 128.51, 128.50, 127.1, 124.4, 124.0, 114.3, 113.4. Mp. 269.5–270.5 °C. TLC: R_f 0.10 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3081, 2886, 2541, 1943, 1610, 1582, 1559, 1491, 1456, 1410, 1362, 1318, 1289, 1216, 1192, 1139, 969, 906, 823, 767, 746, 694, 677 cm^{-1}. HRMS Calcd for $C_{21}H_{16}NO_2$: $[M+H]^+$, 314.1176. Found: *m*/*z* 314.1170.

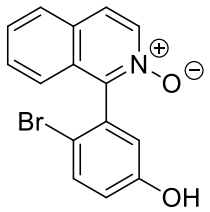
1-(2-Bromo-3-hydroxyphenyl)isoquinoline 2-oxide (1i).



White solid; 26% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 7.0 Hz, 1H), 8.06 (s, 1H), 7.96 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.0 Hz, 1H), 7.67 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.57 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.88 (dd, *J* = 7.5, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 154.5, 136.5, 133.3, 130.1, 129.8, 129.69, 129.68, 129.03, 128.98, 128.2, 126.9, 126.2, 124.2, 121.9, 118.3. Mp.232.0–233.0 °C. TLC: R_f 0.32 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3083, 2923, 2659, 2551, 1696, 1597, 1576, 1418, 1306, 1264, 1200, 1146, 1075, 899, 809, 749. HRMS Calcd for $C_{15}H_{11}BrNO_2$: $[M+H]^+$, 315.9968. Found: *m*/*z* 315.9964.

1-(2-Bromo-5-hydroxyphenyl)isoquinoline 2-oxide (1j).

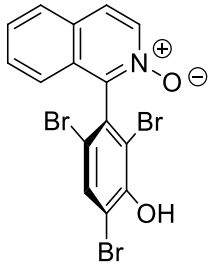


White solid; 69% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.65 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 7.56 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 7.41–7.36 (m, 2H), 6.73–6.72 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (15C) 157.1, 136.3, 133.6, 131.3, 130.0, 129.79, 129.75, 128.9, 126.7, 126.2, 125.5, 124.2, 119.75, 119.65, 111.9. Mp. 249.5–250.0 °C. TLC: R_f 0.40 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3121, 2924, 2562, 1734, 1719, 1589, 1560, 1451, 1400, 1324, 1299, 1203, 1148, 1144, 975, 883, 808, 752 cm^{-1}. HRMS Calcd for $C_{15}H_{11}BrNO_2$: $[M+H]^+$, 315.9968. Found: *m*/*z* 315.9961.

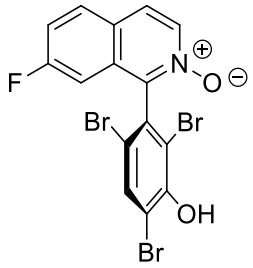
Characterization Data of Products

(*R*)-1-(2,4,6-Tribromo-3-hydroxyphenyl)isoquinoline 2-oxide (2a).



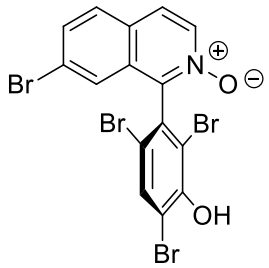
Yield: 99%, 99% *ee*, white solid. $[\alpha]_D^{18}$ –131.4 (*c* 1.61, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 9.16 (br s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83–7.81 (m, 2H), 7.65 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 7.59 (ddd, *J* = 8.5, 6.0, 1.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 151.3, 145.8, 136.5, 135.3, 132.5, 130.1, 129.6, 129.5, 128.1, 127.1, 124.6, 124.4, 114.6, 114.2, 113.7. Mp. 263.5–264.0 °C. TLC: R_f 0.35 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3149, 3068, 2807, 2575, 1773, 1701, 1570, 1501, 1420, 1381, 1328, 1278, 1190, 1133, 982, 875, 817 cm^{-1}. HRMS Calcd for $C_{15}H_9Br_3NO_2$: $[M+H]^+$, 473.8157. Found: *m*/*z* 473.8145. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 9.1 min, t_{major} = 12.4 min.

7-Fluoro-1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxide (2b).



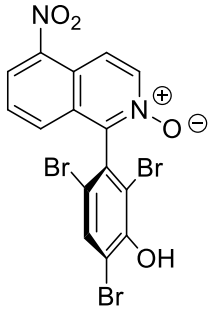
Yield: 99%, 93% *ee*, yellow solid. $[\alpha]_D^{18}$ +55.1 (*c* 0.50, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.28 (d, *J* = 7.0 Hz, 1H), 7.89 (dd, *J* = 9.5, 5.5 Hz, 1H), 7.87 (s, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.39 (ddd, *J* = 9.5, 9.5, 2.0 Hz, 1H), 6.85 (dd, *J* = 9.5, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 162.9 (d, *J* = 251.0 Hz), 150.9, 136.3, 135.4, 132.5, 129.94, 129.87, 129.77, 126.0, 124.3, 119.4 (d, *J* = 25.3 Hz), 114.3, 113.7, 113.2, 108.3 (d, *J* = 23.9 Hz). ^{19}F NMR ($CDCl_3$) δ 55.1. Mp. 266.5–267.2 °C. TLC: R_f 0.26 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3484, 3045, 2925, 2360, 1724, 1630, 1600, 1560, 1507, 1468, 1439, 1392, 1326, 1260, 1225, 1193, 1148, 1105, 846, 806, 753 cm^{-1}. HRMS Calcd for $C_{15}H_8Br_3FNO_2$: $[M+H]^+$, 491.8063. Found: *m*/*z* 491.8053. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 32 °C): t_{minor} = 7.2 min, t_{major} = 8.8 min.

7-Bromo-1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxide (2c).



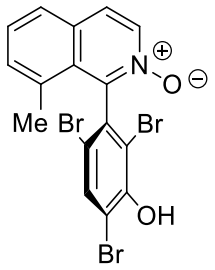
Yield: 97%, 93% *ee*, white solid. $[\alpha]_D^{18}$ +93.0 (*c* 1.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.90 (s, 1H), 7.77–7.73 (m, 2H), 7.69 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.34 (m, 1H), 7.05 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 150.5, 143.9, 137.4, 135.5, 132.6, 132.4, 129.5, 128.7, 127.3, 125.8, 124.7, 124.4, 114.4, 113.1, 112.8. Mp. 193.5–194.0 °C. TLC: R_f 0.25 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3445, 3076, 2969, 2359, 1620, 1592, 1533, 1491, 1437, 1388, 1320, 1231, 1163, 1136, 1072, 1002, 945, 837, 767 cm^{-1}. HRMS Calcd for $C_{15}H_8Br_4NO_2$: $[M+H]^+$, 553.7242. Found: *m*/*z* 553.7228. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 32 °C): t_{minor} = 7.0 min, t_{major} = 8.9 min.

5-Nitro-1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxide (2d).



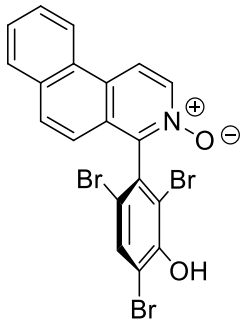
Yield: 99%, 94% *ee*, yellow solid. $[\alpha]_D^{18}$ –88.7 (*c* 0.52, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.71 (d, *J* = 7.5 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.42 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.89 (s, 1H), 7.70 (dd, *J* = 8.5, 8.0 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.8, 145.5, 139.6, 135.5, 135.2, 132.2, 130.3, 129.7, 129.1, 126.5, 121.4, 120.4, 114.3, 113.4, 113.3. Mp. 227.0–228.0 °C. TLC: R_f 0.57 ($CHCl_3$/MeOH = 12:1). IR (KBr): 3459, 3129, 2946, 2364, 1705, 1625, 1527, 1443, 1396, 1336, 1250, 1230, 1200, 1151, 1064, 1011, 865, 813, 741 cm^{-1}. HRMS Calcd for $C_{15}H_8Br_3N_2O_4$: $[M+H]^+$, 518.8008. Found: *m*/*z* 518.7999. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.6 min, t_{major} = 16.3 min.

8-Methyl-1-(2,4,6-tribromo-3-hydroxyphenyl)isoquinoline 2-oxide (2e).



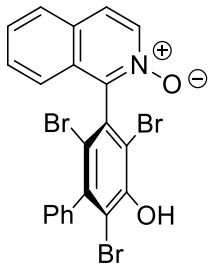
Yield: 99%, 98% *ee*, white solid. $[\alpha]_D^{18}$ +144.1 (*c* 1.62, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.77 (br s, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.83 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 1.0 Hz, 1H), 7.42 (dd, *J* = 9.0, 1.0 Hz, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 151.1, 145.4, 140.2, 136.5, 135.3, 132.8, 132.3, 129.8, 126.4, 126.3, 124.3, 124.0, 114.4, 114.3, 113.4, 21.8. Mp. 253.5–254.0 °C. TLC: R_f 0.26 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3137, 2923, 2363, 1723, 1611, 1560, 1534, 1447, 1424, 1357, 1332, 1274, 1185, 1173, 1132, 977, 882, 833, 753 cm^{-1}. HRMS Calcd for $C_{16}H_{11}Br_3NO_2$: $[M+H]^+$, 487.8314. Found: *m*/*z* 487.8303. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 10.6 min, t_{major} = 12.5 min.

4-(2,4,6-Tribromo-3-hydroxyphenyl)benzo[*f*]isoquinoline 3-oxide (2f).



Yield: 92%, 96% *ee*, white solid. $[\alpha]_D^{18}$ +85.0 (*c* 1.61, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.61–8.55 (m, 3H), 8.26 (br s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.79 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.73 (ddd, *J* = 8.0, 7.0 1.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.9, 145.8, 136.9, 135.4, 133.2, 132.5, 131.7, 129.1, 128.8, 128.32, 128.29, 127.8, 127.7, 122.9, 121,1, 119.8, 114.5, 114.1, 113.1. Mp. 237.0–238.0 °C. TLC: R_f 0.43 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3057, 2966, 2369, 1607, 1569, 1522, 1447, 1374, 1297, 1225, 1190, 1144, 1120, 1002, 870, 815, 754 cm^{-1}. HRMS Calcd for $C_{19}H_{11}Br_3NO_2$: $[M+H]^+$, 523.8314. Found: *m*/*z* 523.8308. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 32 °C): t_{major} = 12.7 min, t_{minor} = 14.5 min.

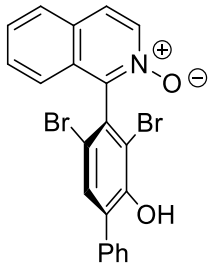
1-(2,4,6-Tribromo-5-hydroxy-[1,1'-biphenyl]-3-yl)isoquinoline 2-oxide (2g).



Yield: 99%, 98% *ee*, white solid. $[\alpha]_D^{18}$ –15.0 (*c* 0.18, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.29 (d, *J* = 7.5 Hz, 1H), 7.88 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.63–7.59 (m, 2H), 7.49–7.42 (m, 3H), 7.35–7.32 (m, 2H), 7.24 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 150.1, 145.2, 144.0, 140.6, 137.0, 133.7, 130.0, 129.3, 128.8, 128.7, 128.53, 128.50. 128.3, 127.2, 124.5, 123.8, 116.0, 114.0, 111.1. Mp. 197.0–198.0 °C. TLC: R_f 0.35 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3076, 2966, 2363, 1565, 1399, 1374, 1321, 1272, 1187, 1136, 1065, 984, 933, 816, 749, 700 cm^{-1}. HRMS Calcd for $C_{21}H_{13}Br_3NO_2$: $[M+H]^+$, 549.8470. Found: *m*/*z* 549.8456. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.5 min, t_{major} =

13.0 min.

1-(3,5-Dibromo-2-hydroxy-[1,1'-biphenyl]-4-yl)isoquinoline 2-oxide (2h).



Yield: 99%, 99% *ee*, white solid. $[\alpha]_D^{18}$ –513.5 (*c* 0.11, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.32 (d, *J* = 7.0 Hz, 1H), 7.88 (dd, *J* = 7.0 Hz, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.69 (s, 1H), 7.64–7.58 (m, 4H), 7.51 (dddd, *J* = 7.0, 7.0, 1.5, 1.0 Hz, 2H), 7.44 (dddd, *J* = 7.5, 7.5, 1.5, 1.5 Hz, 1H), 7.32 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 149.7, 144.9, 137.2, 135.6, 133.8, 132.5, 131.9, 129.9, 129.2, 128.74, 128.69, 128.52, 128.50, 127.1, 124.4, 124.0, 114.3, 113.4, 108.5. Mp. 245.5–246.5 °C. TLC: R_f 0.43 ($CHCl_3$/MeOH = 10:1). IR (KBr): 3035, 2971, 2370, 1696, 1560, 1453, 1403, 1374, 1328, 1270, 1223, 1167, 1133, 982, 828, 752 cm^{-1}. HRMS Calcd for $C_{21}H_{14}Br_2NO_2$: $[M+H]^+$, 471.9365. Found: *m*/*z* 471.9358. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 32 °C): t_{minor} = 14.1 min, t_{major} = 19.7 min.

ORTEP Drawings of 2a

Identification code	**2a**
Empirical Formula	$C_{15}H_8Br_3NO_2$
Formula Weight	473.95
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.490 × 0.290 × 0.270 mm
Crystal System	Orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 7.460(1) Å
	b = 9.018(2) Å
	c = 22.359(3) Å
	V = 1504.2(4) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	2.093 g/cm^3
F_{000}	904.00
μ(MoKα)	80.712 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	Graphite monochromated
Voltage, Current	50 kV, 12 mA

Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	540 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	16.0 sec./°
Detector Swing Angle	30.00°
Detector Position	50.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 16000
	Unique: 3448 (R_{int} = 0.0584)
	Friedel pairs: 1450
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.063–0.113)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(F_0^2–F_c^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(F_0^2) + (0.0339 \cdot P)^2$
	$+ 0.0000 \cdot P]$
	where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms

No. Observations (All reflections)	3448
No. Variables	190
Reflection/Parameter Ratio	18.15
Residuals: R1 (I>2.00σ (I))	0.0360
Residuals: R (All reflections)	0.0438
Residuals: wR2 (All reflections)	0.0802
Goodness of Fit Indicator	1.077
Flack Parameter (Friedel pairs = 1450)	0.004(14)
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map	0.42 $e^{-}/Å^3$
Minimum peak in Final Diff. Map	–0.62 $e^{-}/Å^3$

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6. The reaction conducted using 1 equiv of NBA (**4a**) afforded a mixture of multiple products including monobromide **1i**, while a small amount of **1j** was generated; the ee of **1i** was >95% ee as showed in Scheme 4. Thus, the author currently considers that the bromination at the ortho position of the hydroxy group occurs before the bromination at the para position of the hydroxy group.
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Chapter 4

Enantioselective Syntheses of Axially Chiral Benzamides by Bifunctional Organocatalysts

Bifunctional organocatalysts bearing amino and urea functional groups could be applied for an enantioselective synthesis of axially chiral benzamides via aromatic electrophilic bromination. These results demonstrate the versatility of bifunctional organocatalysts for the enantioselective construction of axially chiral compounds. Moderate-to-good enantioselectivities were obtained with a range of benzamide substrates, and the mechanistic investigations were also carried out.

Introduction

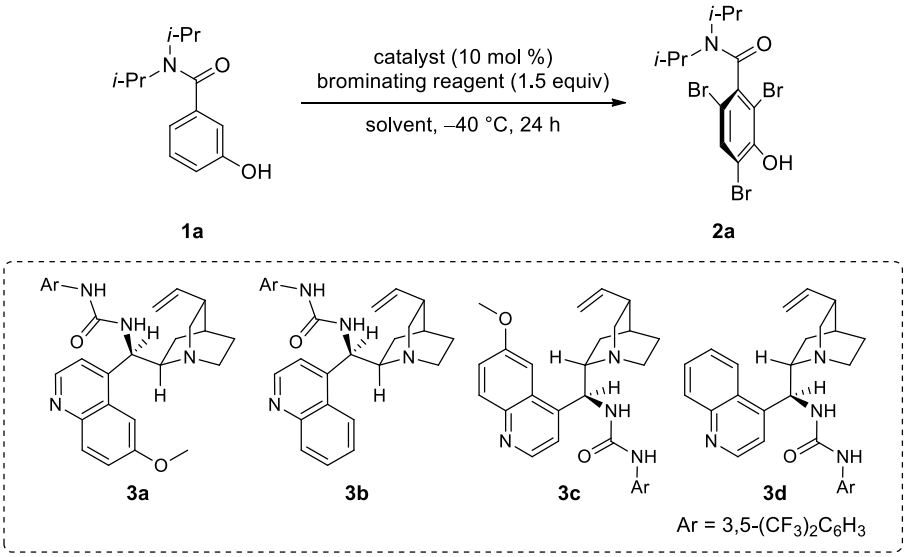
Bifunctional organocatalysts have significantly contributed to the field of asymmetric synthesis.[1] In these catalysts, the (thio)urea and tertiary amino functional groups cooperatively realize the simultaneous activation of a nucleophile and an electrophile in a suitable spatial configuration to enable various stereoselective addition reactions. The author has also used these organocatalysts for several asymmetric cyclizations via intramolecular hetero-Michael addition,[2] in which multipoint recognition by the catalysts stabilizes the specific conformations of the substrates in the transition state. In addition, those successful results and a recent trend of organocatalytic atroposelective reactions[3–9] stimulated him to expand the utility of this class of small-molecule catalysts; in Chapter 3, he demonstrated that bifunctional organocatalysts can also be applied to the asymmetric synthesis of axially chiral compounds, namely biaryls bearing isoquinoline *N*-oxides and phenolic moieties, by translating a specific conformation recognized by bifunctional organocatalysts into axial chirality.[6f] Thus, he supposed that the method developed by these structurally-simple organocatalysts can further be applied to the enantioselective synthesis of a range of axially chiral compounds. In this chapter, he presents the enantioselective synthesis of 3-hydroxybenzamides via aromatic electrophilic bromination (Scheme 1).[5] The 3-hydroxybenzamide substrates have an amide moiety, which can interact with a hydrogen-bond donor, and a phenolic moiety, which can interact with a hydrogen-bond acceptor; such interactions are expected to recognize a specific conformation of the substrate molecule to realize an enantioselective construction of axially chiral benzamides. Here, he presents the details of optimization, substrate scope, and investigations for mechanistic insights.

Results and Discussion

The author initiated his investigations using 3-hydroxy-*N*,*N*-diisopropylbenzamide (**1a**) and *N*-bromoacetamide (NBA, **4a**) as a brominating reagent with 10 mol % of quinidine-derived bifunctional catalyst **3a** in toluene at –40 °C. As expected, tribrominated product **2a** was obtained enantioselectively (Table 1, entry 1). Althogh a lower temperature did not improve the enantioselectivity (Table 1, entry 2), it was effective to lower the concentration of the reaction mixture (Table 1, entry 3). The screening of solvents identified ethyl acetate as the most suitable solvent for enantioselectivity (Table 1, entries 4–7). Other brominating reagents (Figure 1) were

also investigated; they resulted in less enantioselectivities than that obtained with **4a** (Table 1, entries 8–10). In addition, other bifunctional organocatalysts derived from easily available cinchona-alkaloids exhibited similarly good enantioselectivities; **3c** and **3d** afforded the opposite enantiomer of the product (Table 1, entries 11–13, results of further catalyst screening are described in the Experimental Section).

Table 1. Optimization of conditions.[a]



entry	catalyst	brominating reagent	solvent	yield (%)[b]	*ee* (%)
1[c]	**3a**	NBA (**4a**)	toluene	88	78
2[c,d]	**3a**	NBA (**4a**)	toluene	48	78
3	**3a**	NBA (**4a**)	toluene	58	84
4	**3a**	NBA (**4a**)	$CHCl_3$	73	84
5	**3a**	NBA (**4a**)	Et_2O	66	42
6	**3a**	NBA (**4a**)	THF	69	82
7	**3a**	NBA (**4a**)	EtOAc	84	87
8[e]	**3a**	DBH (**4b**)	EtOAc	99	77
9	**3a**	NBS (**4c**)	EtOAc	99	51
10	**3a**	NBP (**4d**)	EtOAc	99	72
11	**3b**	NBA (**4a**)	EtOAc	56	84
12	**3c**	NBA (**4a**)	EtOAc	89	–81
13	**3d**	NBA (**4a**)	EtOAc	76	–80

[a] Reactions were run using **1a** (0.1 mmol), the catalyst (0.01 mmol), and the brominating reagent (0.3 mmol) in the solvent (10 mL). [b] Isolated yields. [c] Reactions were run in 0.5 mL of toluene. [d] Reaction was run at –45 °C. [e] 1.5 equiv of **4b** was used for the reaction.

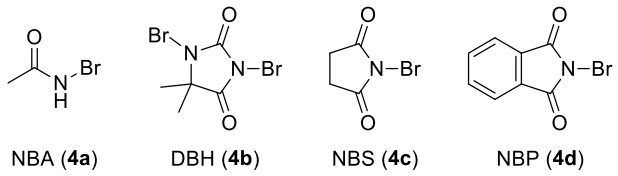
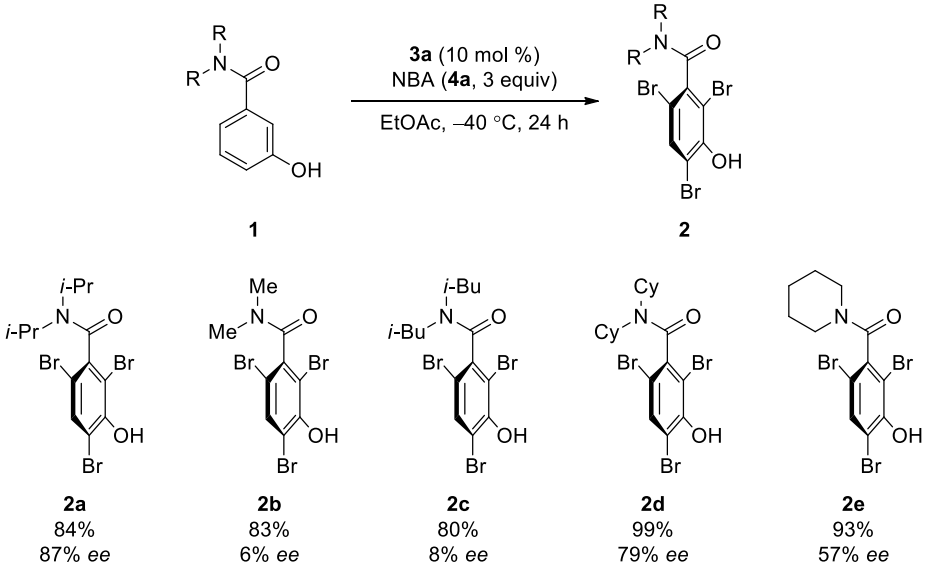


Figure 1. Brominating reagents.

The author then investigated substrates bearing other substituents in the amino group (Scheme 1). Dimethyl and diisobutyl amide groups resulted in much lower enantioselectivities (**2b** and **2c**). Substrates bearing cyclohexyl groups or a piperidinyl moiety provided the corresponding products in high yields, but the enantioselectivities were not as high as that of **2a**.

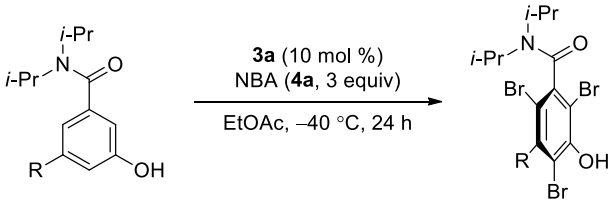


Scheme 1. Optimization of substituents of amide group. Reactions were run using **1** (0.1 mmol), **3a** (0.01 mmol), and **4a** (0.3 mmol) in EtOAc (10 mL). Yields represent material isolated after silica gel column chromatography.

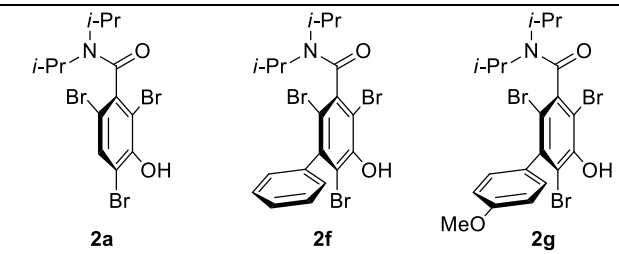
With the optimal conditions for the transformation established, the author then explored the substrate scope (Table 2). A substrate bearing a phenyl group yielded the product in high enantioselectivity (Table 2, **2f**), although the enantioselectivities became lower when the phenyl

group was replaced with substituted phenyl groups (Table 2, **2g** and **2h**). A substrate bearing a naphthyl group also afforded the corresponding product in moderate enantioselectivity (Table 2, **2i**). In addition, a benzamide with a cyclopropyl group also provided the product in good enantioselectivity (Table 2, **2j**).

Table 2. Substrate scope.[a]



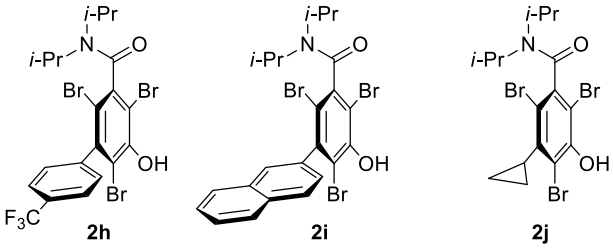
1 **2**



2a 84% 87% *ee*

2f 86% 90% *ee*

2g 88% 46% *ee*



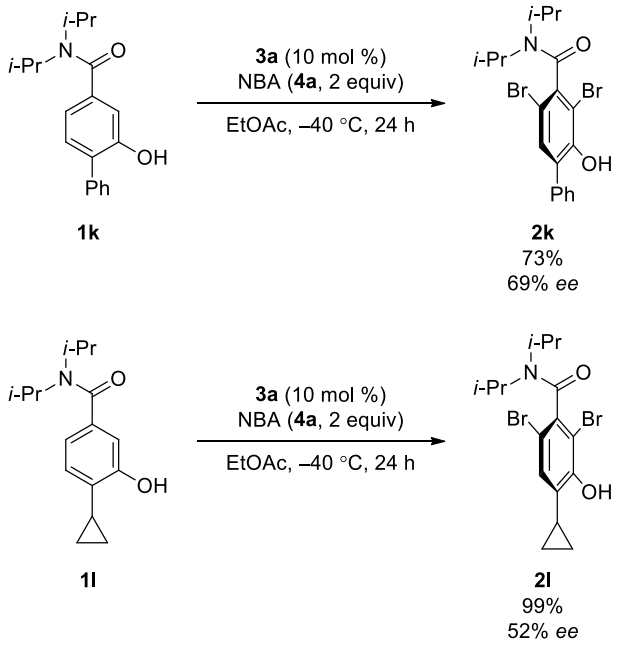
2h 99% 24% *ee*

2i 86% 68% *ee*

2j 69% 76% *ee*

[a] Reactions were run using **1** (0.1 mmol), **3a** (0.01 mmol), and **4a** (0.3 mmol) in EtOAc (10 mL). Yields represent material isolated after silica gel column chromatography.

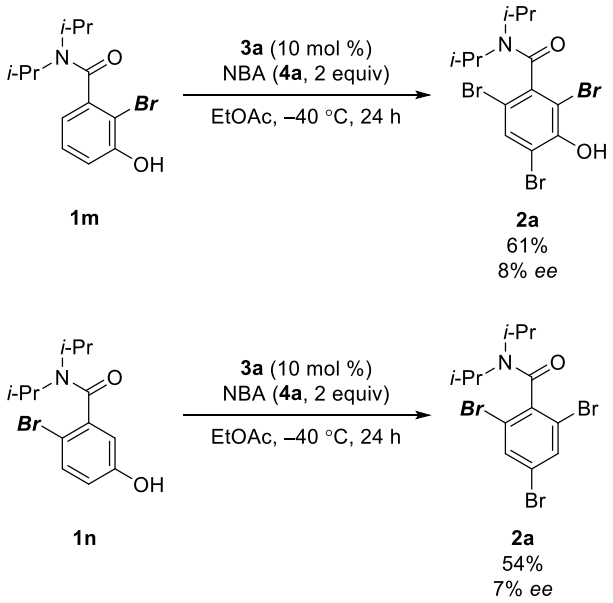
Furthermore, when the reaction was carried out using **1k** and **1l**, which have a substituent ortho to the hydroxy group, with 2 equiv of **4a**, dibromination proceeded in high yields with moderate enantioselectivities (Scheme 2). The absolute configuration of **2d** was determined by X-ray analysis (see the Experiment Section for details), and the configurations of all other examples were assigned analogously.



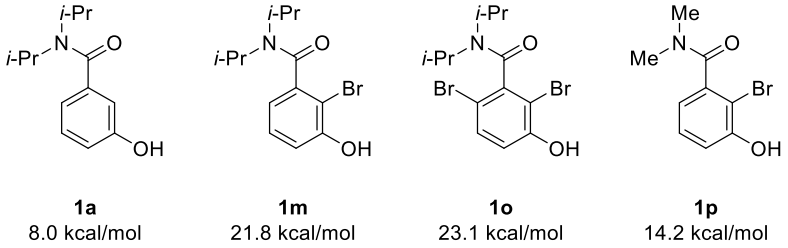
Scheme 2. Reactions of substrates with substituted phenols.

To gain insight into the reaction mechanism, the reactions were performed using substrates **1m** and **1n**, previously monobrominated at the ortho positions of the rotational axis; much lower enantioselectivities than the reaction from **1a** were observed in both reactions (Scheme 3). In addition, the reaction using 1 equiv of NBA (**4a**) was also carried out; the sole product was **1m** with most of the starting material recovered, and other products were not observed (see the Experimental Section for details). These results imply that the first bromination, which occurs at an ortho position of the axis (probably at 2-position), is the enantiodetermining step in this reaction, and once one of the ortho positions is brominated, racemization through bond rotation hardly occurs during the course of further bromination.[10] Actually, although the rotational barrier of substrate **1a**, calculated by B3YLP/6-31G(d), is only 8.0 kcal/mol, that of monobrominated intermediate **1m** is 21.8 kcal/mol (Scheme 4). However, it is not yet enough high to inhibit the bond rotation at room temperature, which is probably the reason why the reactions must be carried out at the low temperature, –40 °C, for obtaining high enantioselectivity; compound **1o**, further brominated at both ortho positions, has enough high rotational barrier to enable the isolation of optically active products even at room temperature. Furthermore, it is also important to employ the substrates bearing relatively bulky substituents on the nitrogen atom to inhibit the bond rotation of the monobrominated intermediate, realizing high enantioselectivity (Scheme 1): in fact, the rotational barrier of monobrominated compound **1p**, bearing methyl groups on the amide moiety, is much

lower than that of **1m**.



Scheme 3: Reactions of monobrominated substrates.



Scheme 4. Rotational barrier of substrates and intermediates calculated by B3YLP/6-31G(d).

Conclution

In summary, the author demonstrated a novel enantioselective synthesis of axially chiral benzamides using bifunctional organocatalysts via aromatic electrophilic halogenations. Moderate-to-good enantioselectiveties were accomplished with various benzamide substrates. These results along with his and others' previous report[6d–6f,9c,9d] verified the utility of bifunctional organocatalysts for application in the synthesis of various axially chiral compounds. Further studies regarding the detailed clarification of the reaction mechanism and application of this method to the construction of other axially chiral structures are currently underway and will be reported in due course.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. The starting materials such as carboxylic acids, arylethylamines, and brominating reagent **4** are commercially available. The bifunctional organocatalyst **3a–3d** was prepared with the same procedure in former chapters.

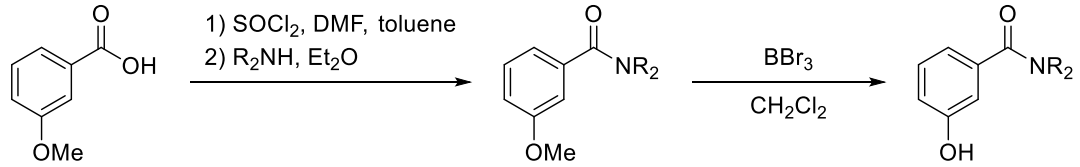
General procedure for asymmetric synthesis of 2,4,6-tribromo-3-hydroxybenzamides 2

In a 20-mL round-bottom flask, the autor sequentially added substrate **1** (0.10 mmol), quinidine-derived bifunctional catalyst **3a** (5.8 mg, 0.010 mmol), and EtOAc (10 mL). The mixture was stirred at –40 °C for 30 min. To the resulting solution was added *N*-bromoacetamide (**4a**, 41.4 mg, 0.30 mmol). The reaction mixture was then stirred for 12 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$, and then the aqueous phase was extracted with EtOAc (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent afforded the corresponding 2,4,6-tribromo-3-hydroxybenzamides **2**.

General procedure for reactions from substrates 1k and 1l

In a 20-mL round-bottom flask, the author sequentially added substrate **1** (0.10 mmol), **3a** (5.8 mg, 0.010 mmol), and EtOAc (10 mL). The mixture was stirred at –40 °C for 30 min. To the resulting solution was added **4a** (27.6 mg, 0.20 mmol). The reaction mixture was then stirred for 12 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$, and then the aqueous phase was extracted with EtOAc (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent afforded the corresponding product **2k** and **2l**.

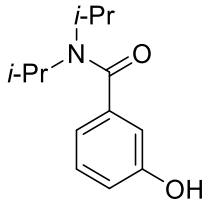
General procedure for preparation of substrates 1a–1e



Substrate **1a**–**1e** were prepared by the literature procedere.[11] To a solution of 3-methoxybenzoic acid (**5**, 1.5 g, 10 mmol) in toluene (15 mL) was added thionyl chloride (0.87 mL, 12 mmol) and a catalytic ammount of DMF (0.08 mL, 1.0 mmol). After the resulting mixture was stirred for 30 min, the solvents were removed, and the crude product was dried in vacuo. The product was placed in a 50-mL reaction vessel. To the flask was added CH_2Cl_2 (15 mL) and *N*,*N*-dialkyllamine (20 mmol), and the solution was stirred for 4 h. The mixture was quenched with 1 M aqueous HCl (10 mL), and the organic layers were washed with 1 M aqueous HCl, brine, and 1 M aqueous NaOH, subsequently dried over Na_2SO_4, concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave *N*,*N*-diisopropyl-3-methoxybenzamide **6** as a white solid in 41–99% yield.

To a solution of **6** (5.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise the solution of BBr_3 (20 mL, ca. 1 M in CH_2Cl_2 solution, 20 mmol) at –78 °C. Then, the reaction mixture was steadily warmed to ambient temperature. The resulting solution was carefully quenched with H_2O, extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Recrystallization from hot EtOH/hexane gave the corresponding 3-hydroxybenzamides **1a**–**1e** as a white solid in 58–98% yield.

3-Hydroxy-*N*,*N*-diisopropylbenzamide (1a).

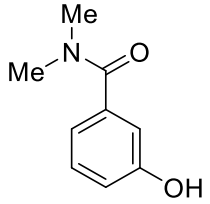


White solid; 95% yield, 76% yield (for each step).

^{1}H NMR ($CDCl_3$) δ 8.79 (s, 1H), 7.09 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.73 (br s, 1H), 6.69–6.66 (m, 2H), 3.91 (sept, *J* = 6.5 Hz, 1H), 3.51 (sept, *J* = 6.5 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 6H), 1.11 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 172.2, 157.0, 138.2, 129.4, 116.8, 116.0, 113.7, 51.2, 46.0, 20.6.

Mp. 124.0–125.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 1:1). IR (KBr): 3247, 3001, 2971, 2937, 1611, 1580, 1457, 1352, 1231, 1152, 1039, 877, 781, 710 cm^{-1}. HRMS Calcd for $C_{13}H_{20}NO_2$: $[M+H]^+$, 222.1489. Found: *m*/*z* 222.1485.

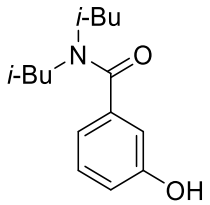
3-Hydroxy-*N*,*N*-dimethylbenzamide (1b).



White solid; 44% yield, 78% yield (for each step).

^1H NMR ($CDCl_3$) δ 8.21 (br s, 1H), 7.18 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.99 (dd, *J* = 1.5, 1.0 Hz, 1H), 6.83 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 6.82 (ddd, *J* = 7.5, 2.0, 1.5 Hz, 1H), 3.12 (s, 3H), 2.98 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.2, 156.9, 136.4, 129.4, 117.9, 117.3, 114.7, 39.7, 35.4. Mp. 125.0–126.0 °C. TLC: R_f 0.24 (hexane/EtOAc = 1:2). IR (KBr): 3105, 2944, 2363, 1619, 1591, 1521, 1448, 1464, 1352, 1286, 1233, 1197, 1076, 886, 754 cm^{-1}. HRMS Calcd for $C_9H_{12}NO_2$: $[M+H]^+$, 166.0863. Found: *m*/*z* 166.0861.

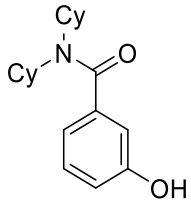
3-Hydroxy-*N*,*N*-diisobutylbenzamide (1c).



White solid; 66% yield, 58% yield (for each step).

^1H NMR ($CDCl_3$) δ 8.04 (br s, 1H), 7.14 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.88 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.36 (d, *J* = 7.0 Hz, 2H), 3.12 (d, *J* = 7.0 Hz, 2H), 2.12 (m, 1H), 1.84 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 6H), 0.73 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 173.2, 156.7, 137.3, 129.3, 117.9, 117.0, 115.0, 56.5, 51.2, 26.7, 26.1, 20.1, 19.7. Mp. 108.0–108.5 °C. TLC: R_f 0.32 (hexane/EtOAc = 1:2). IR (KBr): 3150, 2964, 2871, 1595, 1580, 1465, 1449, 1385, 1301, 1261, 1110, 889, 752 cm^{-1}. HRMS Calcd for $C_{15}H_{24}NO_2$: $[M+H]^+$, 250.1802. Found: *m*/*z* 250.1797.

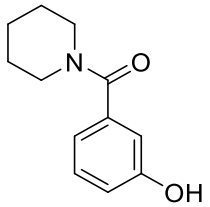
***N*,*N*-Dicyclohexyl-3-hydroxybenzamide (1d)**.



White solid; 75% yield, 85% yield (for each step).

^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1H), 7.08 (dd, *J* = 2.5, 2.5 Hz, 1H), 6.74 (m, 1H), 6.68–6.65 (m, 2H), 3.42 (br s, 1H), 3.03 (br s, 1H), 2.63 (br s, 2H), 1.83 (br s, 2H), 1.69–1.60 (m, 7H), 1.53–1.49 (m, 3H), 1.27 (br s, 3H), 1.02 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 156.9, 138.4, 129.3, 116.7, 116.1, 114.0, 60.0, 56.3, 31.1, 29.9, 26.6, 25.4. Mp. 232.0–232.9 °C. TLC: R_f 0.45 (hexane/EtOAc = 1:1). IR (KBr): 3069, 2938, 2861, 1577, 1469, 1452, 1377, 1321, 1233, 1179, 1125, 999, 781 cm^{-1}. HRMS Calcd for $C_{19}H_{28}NO_2$: $[M+H]^+$, 302.2115. Found: *m*/*z* 302.2107.

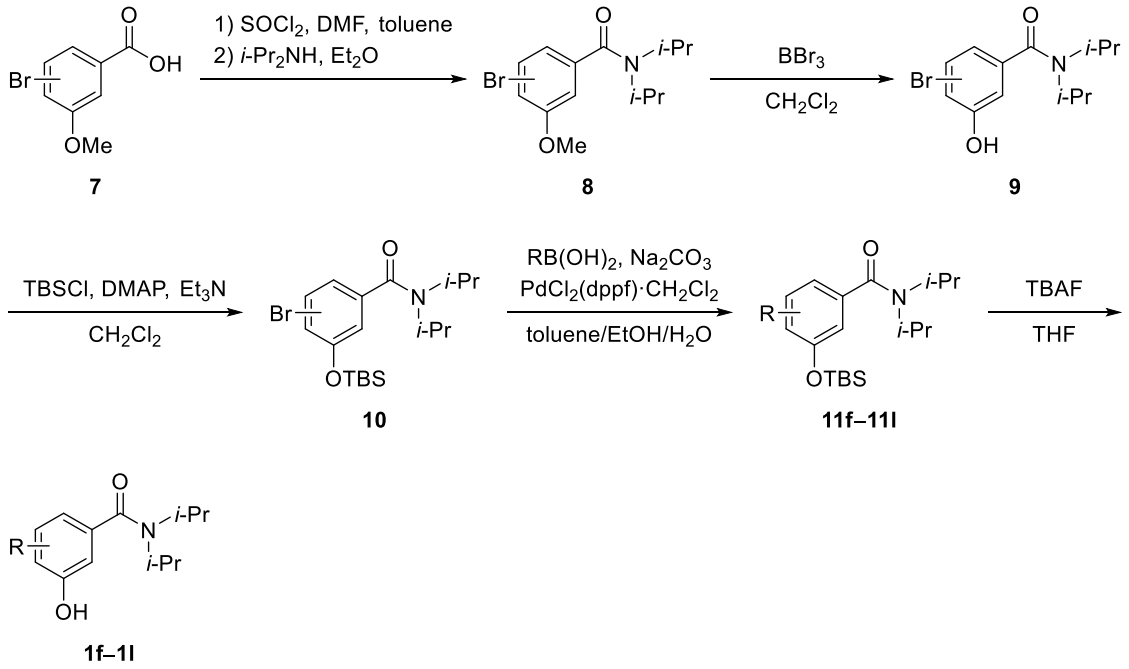
(3-Hydroxyphenyl)(piperidin-1-yl)methanone (1e).



White solid; 99% yield, 97% yield (for each step).

^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.18 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.98 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.81 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 6.80 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 3.71 (br s, 2H), 3.35 (m, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 170.0, 157.0, 136.7, 129.4, 117.5, 117.2, 114.6, 48.9, 43.3, 26.5, 25.6, 24.5. Mp. 174.0–175.0 °C. TLC: R_f 0.32 (hexane/EtOAc = 1:2). IR (KBr): 3139, 2964, 2928, 2865, 1603, 1507, 1460, 1348, 1294, 1224, 1156, 1123, 1030, 947, 880, 745, 691 cm^{-1}. HRMS Calcd for $C_{12}H_{16}NO_2$: $[M+H]^+$, 206.1176. Found: *m*/*z* 206.1173.

General procedure for preparation of substrates 1f–1l



General procedure for preparation of **10**

From 4/5-bromoanisidic acids **7**, 3-hydroxy-4/5-bromobenzamides **9** were prepared by the same procedure as that for the substrates **1a**–**1e**. Furthermore, substrates **1f**–**1l** were synthesized by the literature procedure.[12] To a 50-mL round-bottom flask, TBSCl (452 mg, 3.0 mmol) and DMAP (30 mg, 0.25 mmol) were placed, and they were cooled to 0 °C. Subsequently, the solution of the 3-hydroxy-4/5-bromobenzamide (2.5 mmol) in CH_2Cl_2 (20 mL) was added, and the reaction mixture was stirred at ambient temperature. After 20 h, the reaction was quenched with H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). Then the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave the corresponding products **10** quantitatively.

General procedure for preparation of **11**

In a 30-mL round-bottom flask, $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 mg, 0.061 mmol), Na_2CO_3 (750 mg, 7.1 mmol), and H_2O (4.0 mL) were mixed. Then the solution of **10** (1.5 mmol) and a boronic acid (2.0 mmol) in toluene/EtOH (21 mL, v/v = 7/1) was added. The mixture was stirred for 4 h at 120 °C, and then the reaction was quenched with H_2O (10 mL). The aqueous phase was extracted with EtOAc (7 mL × 3). The combined organic layers were washed with brine and dried over

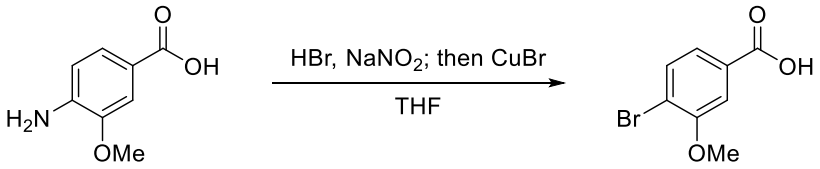
Na_2SO_4. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave the corresponding products **11** in 35–97% yield.

General procedure for preparation of **1f**–**1l**

In a 50-mL round-bottom flask, **11** (1.0 mmol) was placed and dissolved in THF (10 mL). To the solution was added dropwise the solution of TBAF (1.2 mL, c.a. 1 M in THF 1.2 mmol), and the mixture was stirred for 1 h. The reaction mixture was quenched with 1 M aqueous HCl, and the aqueous phase was extracted with EtOAc (7 mL × 3). Then the combined organic layers were washed with brine, and dried over Na_2SO_4. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the 4/5-substituted benzamides **1f**–**1l** in 51–99% yield.

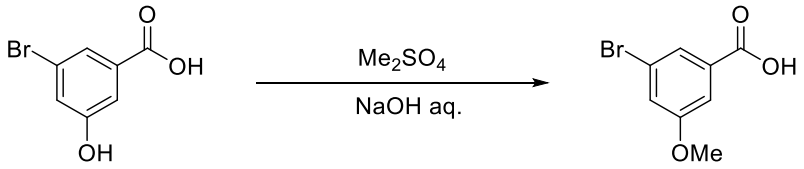
General procedure for preparation of **7**

The monobrominated anisidic acids **7** were prepared by the literature procedures.[12,13]



12 **7a**

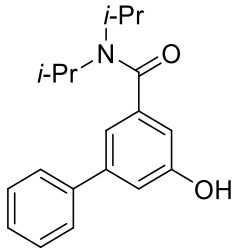
In a 50-mL round-bottom flask, 4-aminoanisidic acid (**12**, 836 mg, 5.0 mmol) was dissolved in MeCN (10 mL). To the solution was added slowly 47% aqueous HBr (10 mL) at 0 °C, and then $NaNO_2$ (380 mg, 5.5 mmol) was added to give a brown suspension. After the suspension was stirred for 30 min, CuBr (861 mg, 6.0 mmol) was added. Subsequently, the reaction mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then cooled to 0 °C, and cold H_2O (20 mL) was poured into the flask to form white precipitates. The solid was filtrated, washed with cold H_2O, and dried in vacuo. The reaction proceeded quantitatively to afford **7a**, and the crude product was used without further purification.



13 **7b**

3-Bromo-5-hydroxybenzoic acid (**13**, 2.2 g, 10 mmol) was placed in a 50-mL round-bottom flask, and dissolved in 10% aqueous NaOH (3.0 mL) to give a yellow solution. To the mixture was added dropwise Me_2SO_4 (1.7 mL, 18 mmol). Then the reaction mixture was warmed to 70 °C. After being stirred for 12 h, the reaction mixture was cooled to ambient temperature and quenched with 20% aqueous H_2SO_4 to give a white solid. The solid was filtrated and dried in vacuo to afford **7b** in 92%, and the crude product was used without further purification.

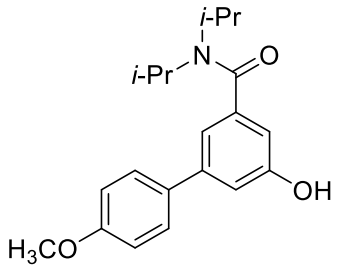
5-Hydroxy-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (1f).



White solid; 88% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.45 (br s, 1H), 7.45 (dd, J = 7.0, 1.5 Hz, 2H), 7.36 (m, 2H), 7.32 (m, 1H), 6.94 (dd, J = 1.5, 1.0 Hz, 1H), 6.90 (dd, J = 2.0, 1.5 Hz, 1H), 6.71 (dd, J = 2.0, 1.0 Hz, 1H), 3.80 (br s, 1H), 3.53 (br s, 1H), 1.57 (br s, 6H), 1.14 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 172.0, 157.2, 142.7, 140.4, 138.7, 128.6, 127.4, 127.1, 115.8, 115.3, 112.8, 51.3, 46.1, 20.6. Mp. 184.5–185.0 °C. TLC: R_f 0.38 (hexane/EtOAc = 1:1). IR (KBr): 3300, 2976, 2936, 1607, 1588, 1471, 1384, 1350, 1304, 1214, 1152, 1041, 865 cm^{-1}. HRMS Calcd for $C_{19}H_{24}NO_2$: $[M+H]^+$, 298.1802. Found: *m*/*z* 298.1796.

5-Hydroxy-*N*,*N*-diisopropyl-4'-methoxy-[1,1'-biphenyl]-3-carboxamide (1g).

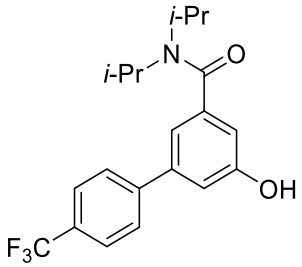


White solid; 91% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.03 (br s, 1H), 7.39 (ddd, J = 9.0, 2.5, 2.0 Hz, 2H), 6.91–6.86 (m, 4H), 6.67 (dd, J = 2.0, 1.5 Hz, 1H), 3.97 (br s, 1H), 3.82 (s, 3H), 3.53 (br s, 1H), 1.57 (br s, 6H), 1.13 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 171.9, 159.2, 157.0, 142.3, 138.9, 132.9, 128.1, 115.1, 115.0, 114.0,

112.1, 55.3, 51.2, 46.0, 20.6. Mp. 215.0–216.0 °C. TLC: R_f 0.35 (hexane/EtOAc = 1:1). IR (KBr): 3159, 2971, 1609, 1594, 1520, 1465, 1439, 1363, 1250, 1181, 1041, 829 cm^{-1}. HRMS Calcd for $C_{20}H_{26}NO_3$: $[M+H]^+$, 328.1907. Found: *m*/*z* 328.1899.

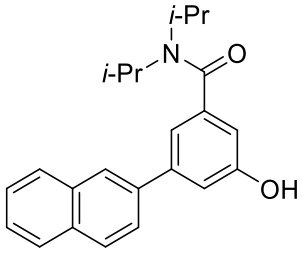
5-Hydroxy-*N*,*N*-diisopropyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxamide (1h).



White solid; 96% yield (for the last step).

^1H NMR ($CDCl_3$) δ 8.69 (br s, 1H), 7.56 (m, 2H), 7.49 (m, 2H), 6.91 (s, 1H), 6.84 (s, 1H), 6.73 (s, 1H), 3.94 (br s, 1H), 3.55 (br s, 1H), 1.57 (br s, 6H), 1.13 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 171.9, 143.8, 141.2, 138.9, 129.4 (q, *J* = 33.0 Hz), 127.2, 125.5 (d, *J* = 3.9 Hz), 124.1 (q, *J* = 270.6 Hz), 115.8 (d, *J* = 5.8 Hz), 115.1, 113.4 (d, *J* = 17.6 Hz), 51.4, 46.2, 20.6. ^{19}F NMR ($CDCl_3$) δ 99.2. Mp. 204.0–205.0 °C. TLC: R_f 0.41 (hexane/EtOAc = 1:1). IR (KBr): 3106, 2986, 1610, 1591, 1477, 1438, 1373, 1326, 1221, 1163, 1118, 1064, 836 cm^{-1}. HRMS Calcd for $C_{20}H_{23}F_3NO_2$: $[M+H]^+$, 366.1675. Found: *m*/*z* 366.1668.

3-Hydroxy-*N*,*N*-diisopropyl-5-(naphthalen-2-yl)benzamide (1i).

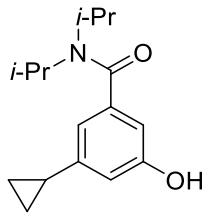


White solid; 84% yield (for the last step).

^1H NMR ($CDCl_3$) δ 8.27 (br s, 1H), 7.86 (s, 1H), 7.80 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 7.0 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.45 (ddd, *J* = 7.0, 7.0, 2.0 Hz, 1H), 7.42 (ddd, *J* = 7.0, 7.0, 1.5 Hz, 1H), 7.08 (dd, *J* = 1.5, 1.5 Hz, 1H), 7.01 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.74 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.01 (br s, 1H), 3.56 (br s, 1H), 1.59 (br s, 6H), 1.15 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 172.0, 157.1, 142.7, 138.9, 137.7, 133.5, 132.6, 128.3, 128.2, 127.5, 126.2, 125.9, 125.8, 125.3, 116.0, 115.7, 112.9, 51.3, 46.1, 20.6. Mp. 232.0–233.0 °C. TLC: R_f 0.41

(hexane/EtOAc = 1:1). IR (KBr): 3254, 2980, 1616, 1586, 1479, 1445, 1414, 1345, 1215, 1153, 1044, 858, 810 cm^{-1}. HRMS Calcd for $C_{23}H_{26}NO_2$: $[M+H]^+$, 348.1958. Found: *m*/*z* 348.1951.

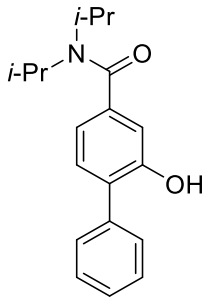
3-Cyclopropyl-5-hydroxy-*N*,*N*-diisopropylbenzamide (1j).



White solid; 61% yield (for the last step).

^1H NMR ($CDCl_3$) δ 7.94 (br s, 1H), 6.49 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.44 (dd, *J* = 1.5, 1.0 H, 1H), 6.40 (dd, *J* = 2.0, 1.0 Hz, 1H), 3.89 (br s, 1H), 3.49 (br s, 1H), 1.77 (m, 1H), 1.53 (br s, 6H), 1.11 (br s, 6H), 0.90 (m, 2H), 0.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 172.1, 156.8, 146.0, 138.4, 114.1, 113.7, 110.7, 51.1, 45.9, 20.6, 15.3, 9.3. Mp. 101.0–102.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 1:1). IR (KBr): 3242, 3002, 2971, 1610, 1592, 1458, 1372, 1347, 1280, 1208, 1158, 1041, 997, 866, 848, 766 cm^{-1}. HRMS Calcd for $C_{16}H_{24}NO_2$: $[M+H]^+$, 262.1802. Found: *m*/*z* 262.1800.

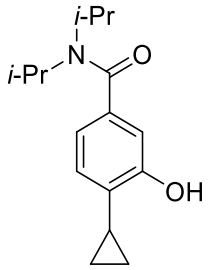
2-Hydroxy-*N*,*N*-diisopropyl-[1,1'-biphenyl]-4-carboxamide (1k).



White solid; 57% yield (for the last step).

^1H NMR ($CDCl_3$) δ 7.43–7.42 (m, 4H), 7.34 (m, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.15 (br s, 1H), 6.91 (d, *J* = 1.5 Hz, 1H), 6.83 (m, 1H), 4.01 (br s, 1H), 3.53 (br s, 1H), 1.55 (br s, 6H), 1.17 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 171.3, 153.3, 138.3, 137.3, 130.3, 129.1, 128.6, 127.4, 117.1, 114.1, 109.7, 51.1, 48.0, 20.6. Mp. 92.0–93.0 °C. TLC: R_f 0.42 (hexane/EtOAc = 1:1). IR (KBr): 3179, 2970, 1601, 1457, 1408, 1371, 1346, 1275, 1208, 1158, 1038, 877, 808, 759 cm^{-1}. HRMS Calcd for $C_{19}H_{24}NO_2$: $[M+H]^+$, 298.1802. Found: *m*/*z* 298.1795.

4-Cyclopropyl-3-hydroxy-*N*,*N*-diisopropylbenzamide (1l).



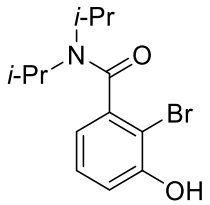
White solid; 78% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 7.09 (br s, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.69 (dd, J = 7.5, 1.5 Hz, 1H), 3.91 (br s, 1H), 3.50 (br s, 1H), 1.87 (m, 1H), 1.53 (br s, 6H), 1.24 (br s, 6H), 0.91 (m, 2H), 0.59 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.5, 155.5, 136.8, 129.5, 127.0, 116.8, 112.8, 51.0, 45.8, 20.6, 9.25, 6.24. Mp. 88.5–89.0 °C. TLC: R_f 0.48 (hexane/EtOAc = 1:1). IR (KBr): 3304, 3083, 2969, 1607, 1523, 1455, 1416, 1373, 1347, 1269, 1230, 1209, 1159, 1109, 1046, 1034, 957, 908, 891, 814 cm^{-1}. HRMS Calcd for $C_{16}H_{24}NO_2$: $[M+H]^+$, 262.1802. Found: *m*/*z* 262.1800.

Preparation of substrates 1m and 1n

Monobromoinated substrates **1m** and **1l** were prepared by the literature procedure.[11]

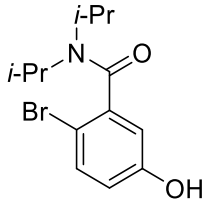
2-Bromo-3-hydroxy-*N*,*N*-diisopropylbenzamide (1m).



Whtie solid; 56% yield (overall).

^{1}H NMR ($CDCl_3$) δ 8.72 (br s, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 8.5, 3.0 Hz, 1H), 6.50 (d, J = 3.0 Hz, 1H), 3.69 (qq, J = 7.0, 7.0 Hz, 1H), 3.54 (qq, J = 7.0, 7.0 Hz, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.56 (d, J = 7.0 Hz, 3H), 1.24 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.6, 152.6, 138.5, 133.4, 118.4, 114.7, 107.4, 51.6, 46.2, 20.6, 20.4, 19.9. Mp. 236.0–237.0 °C. TLC: R_f 0.39 (hexane/EtOAc = 1:1). IR (KBr): 3160, 2971, 1616, 1569, 1466, 1444, 1374, 1350, 1289, 1235, 1208, 1164, 1044, 875, 823 cm^{-1}. HRMS Calcd for $C_{13}H_{19}BrNO_2$: $[M+H]^+$, 300.0594. Found: *m*/*z* 300.0583.

2-Bromo-5-hydroxy-*N*,*N*-diisopropylbenzamide (1n).

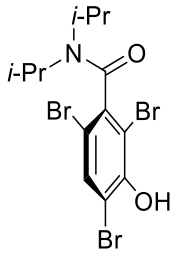


White solid; 48% yield (overall).

^{1}H NMR ($CDCl_3$) δ 8.72 (br s, 1H), 7.23 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.75 (dd, *J* = 2.5, 1.5 Hz, 1H), 3.63 (qq, *J* = 6.5, 6.5 Hz, 1H), 3.52 (qq, *J* = 6.5, 6.5 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 3H), 1.56 (d, *J* = 6.5 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167,6, 152.6, 140.6, 129.3, 118.2, 115.4, 107.2, 51.2, 46.0, 20.74, 20.66, 20.60, 20.1. Mp. 258.0–259.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:1). IR (KBr): 3225, 2971, 1608, 1567, 1447, 1372, 1351, 1292, 1199, 1121, 1042, 822, 797 cm^{-1}. HRMS Calcd for $C_{13}H_{19}BrNO_2$: $[M+H]^+$, 300.0594. Found: *m*/*z* 300.0588.

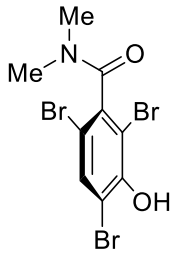
Characterization Data of Products

2,4,6-Tribromo-3-hydroxy-*N*,*N*-diisopropylbenzamide (2a).



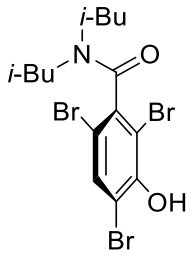
Yield: 84%, 87% *ee*, white solid. $[\alpha]_D^{18}$ –11.4 (*c* 1.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 6.28 (s, 1H), 3.53 (m, 2H), 1.59 (d, *J* = 3.0 Hz, 3H), 1.58 (d, *J* = 3.0 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.2, 149.6, 139.9, 135.2, 110.3, 109.8, 108.6, 51.9, 46.6, 21.0, 20.9, 19.99, 19.97. Mp. 258.0–258.5 °C. TLC: R_f 0.44 (hexane/EtOAc = 1:1). IR (KBr): 2982, 2598, 1605, 1539, 1474, 1448, 1370, 1329, 1208, 1159, 1132, 1045, 700 cm^{-1}. HRMS Calcd for $C_{13}H_{17}Br_3NO_2$: $[M+H]^+$, 457.8783. Found: *m*/*z* 457.8778. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.1 min, t_{major} = 9.2 min.

2,4,6-Tribromo-3-hydroxy-*N*,*N*-dimethylbenzamide (2b).



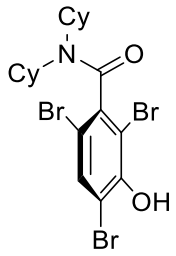
Yield: 83%, 6% *ee*, white solid. $[\alpha]_D^{18}$ –1.7 (*c* 0.98, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1H), 6.65 (br s, 1H), 3.16 (s, 3H), 2.86 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166.7, 149.8, 139.0, 135.0, 111.3, 109.7, 108.7, 37.4, 34.6. Mp. 145.5–146.0 °C. TLC: R_f 0.29 (hexane/EtOAc = 1:2). IR (KBr): 3031, 2980, 2487, 1605, 1541, 1470, 1434, 1368, 1200, 1158, 1124, 864, 700 cm^{-1}. HRMS Calcd for $C_9H_9Br_3NO_2$: $[M+H]^+$, 401.8157. Found: *m*/*z* 401.8145. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.3 min, t_{major} = 10.0 min.

2,4,6-Tribromo-3-hydroxy-*N*,*N*-diisobutylbenzamide (2c).



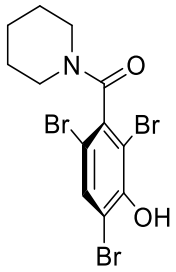
Yield: 80%, 8% *ee*, white solid. $[\alpha]_D^{18}$ –3.3 (*c* 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 6.70 (br s, 1H), 3.41 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.34 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.97 (br s, 1H), 2.96 (br s, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.03 (br s, 3H), 1.01 (br s, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.9, 149.6, 139.2, 135.3, 110.7, 110.4, 109.2, 56.6, 53.2, 26.9, 26.7, 20.99, 20.97, 20.60, 20.57. Mp. 114.0–114.5 °C. TLC: R_f 0.40 (hexane/EtOAc = 1:1). IR (KBr): 3362, 2989, 1611, 1466, 1431, 1389, 1362, 1271, 1258, 1205, 1174, 1131, 760 cm^{-1}. HRMS Calcd for $C_{15}H_{21}Br_3NO_2$: $[M+H]^+$, 485.9096. Found: *m*/*z* 485.9085. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.9 min, t_{major} = 6.3 min.

(*R*)- 2,4,6-Tribromo-*N*,*N*-dicyclohexyl-3-hydroxybenzamide (2d).



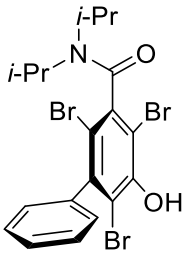
Yield: 99%, 79% *ee*, white solid. $[\alpha]_D^{18}$ –19.1 (*c* 2.99, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.93 (br s, 1H), 7.58 (s, 1H), 3.10 (m, 1H), 3.07 (m 1H), 2.72–2.67 (m, 2H), 2.02 (d, *J* = 12.0 Hz, 1H), 1.97 (d, *J* = 12.5 Hz, 1H), 1.85–1.83 (m, 2H), 1.73–1.67 (m, 4H), 1.62 (m, 1H), 1.56 (d, *J* = 9.0 Hz, 1H), 1.48–1.43 (m, 2H), 1.29–1.20 (m, 3H), 1.10–1.04 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 166.0, 150.0, 139.5, 135.3, 111.9, 109.9, 109.7, 61.1, 59.8, 31.11, 31.08, 29.2, 29.1, 26.4, 25.54, 25.46, 25.2, 25.1. Mp. 221.5–222.0 °C. TLC: R_f 0.52 (hexane/EtOAc = 2:1). IR (KBr): 3094, 2935, 2855, 1719, 1616, 1534, 1441, 1363, 1314, 1280, 1180, 999, 896, 759 cm^{-1}. HRMS Calcd for $C_{19}H_{25}Br_3NO_2$: $[M+H]^+$, 537.9409. Found: *m*/*z* 537.9400. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.9 min, t_{major} = 8.4 min.

Piperidin-1-yl(2,4,6-tribromo-3-hydroxyphenyl)methanone (2e).



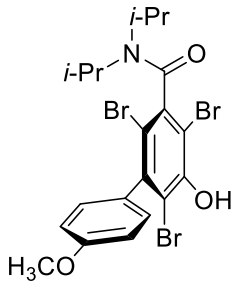
Yield: 93%, 57% *ee*, white solid. $[\alpha]_D^{18}$ –9.8 (*c* 1.42, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.14 (br s, 1H), 3.75 (d, *J* = 4.5 Hz, 2H), 3.17 (dd, *J* = 5.0, 4.5 Hz, 2H), 1.68 (br s, 4H), 1.60 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.0, 149.9, 138.7, 135.0, 111.7, 109.8, 109.2, 47.4, 42.5, 26.1, 25.2, 24.3. Mp. 169.5–170.0 °C. TLC: R_f 0.25 (hexane/EtOAc = 1:1). IR (KBr): 3078, 2945, 1615, 1533, 1477, 1451, 1402, 1296, 1221, 1134, 1022, 910, 861, 734 cm^{-1}. HRMS Calcd for $C_{12}H_{13}Br_3NO_2$: $[M+H]^+$, 439.8470. Found: *m*/*z* 439.8458. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.4 min, t_{major} = 10.9 min.

2,4,6-Tribromo-5-hydroxy-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (2f).



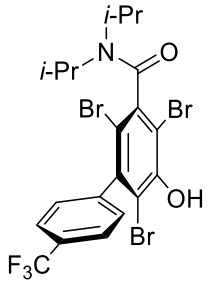
Yield: 86%, 90% *ee*, white solid. $[\alpha]_D^{18}$ –25.6 (*c* 1.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.47–7.42 (m, 3H), 7.18–7.17 (m, 2H), 6.37 (br s, 1H), 3.69 (qq, *J* = 6.5, 6.5 Hz, 1H), 3.55 (qq, *J* = 7.0, 7.0 Hz, 1H), 1.61 (d, *J* = 6.5 Hz, 3H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.3, 149.5, 143.8, 140.6, 140.4, 129.1, 128.7, 128.5, 128.4, 128.3, 111.8, 111.4, 106.6, 51.8, 46.5, 21.1, 20.8, 20.1, 19.9. Mp. 224.5–225.0 °C. TLC: R_f 0.45 (hexane/EtOAc = 1:1). IR (KBr): 3482, 3070, 2973, 1616, 1544, 1476, 1444, 1377, 1305, 1209, 1160, 1048, 789, 755, 701 cm^{-1}. HRMS Calcd for $C_{19}H_{21}Br_3NO_2$: $[M+H]^+$, 533.9096. Found: *m*/*z* 533.9080. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.7 min, t_{major} = 9.0 min.

2,4,6-Tribromo-5-hydroxy-*N*,*N*-diisopropyl-4'-methoxy-[1,1'-biphenyl]-3-carboxamide (2g).



Yield: 88%, 46% *ee*, white solid. $[\alpha]_D^{18}$ –10.1 (*c* 1.20, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.12–7.10 (m, 2H), 7.00–6.98 (m, 2H), 6.27 (br s, 1H), 3.86 (s, 3H), 3.68 (qq, *J* = 7.0, 6.5 Hz, 1H), 3.55 (qq, *J* = 7.0, 7.0 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.9, 159.4, 149.4, 143.6, 140.3, 133.4, 133.0, 130.0, 113.8, 113.6, 112.4, 112.0, 106.4, 55.2, 51.8, 46.5, 21.1, 20.8, 20.1, 19.9. Mp. 263.0–264.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:1). IR (KBr): 3072, 2972, 1623, 1609, 1511, 1474, 1370, 1249, 1180, 1046, 832 cm^{-1}. HRMS Calcd for $C_{20}H_{23}Br_3NO_3$: $[M+H]^+$, 563.9202. Found: *m*/*z* 563.9186. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 8.3 min, t_{major} = 12.3 min.

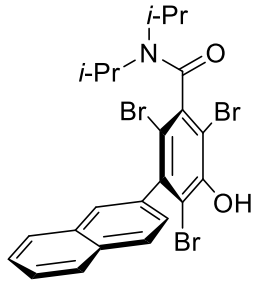
2,4,6-Tribromo-5-hydroxy-*N*,*N*-diisopropyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxamide (2h).



Yield: 99%, 24% *ee*, white solid. $[\alpha]_D^{18}$ –8.7 (*c* 0.89, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.34 (d, *J* = 9.0 Hz, 2H), 7.31 (m, 2H), 6.62 (br s, 1H), 3.67 (qq, *J* = 7.0, 7.0 Hz, 1H), 3.56 (qq, *J* = 6.5, 6.5 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.2, 149.9, 143.9, 142.4, 140.5, 136.6 (q, *J* = 32.5 Hz), 129.7, 129.4, 125.7 (d, *J* = 3.8 Hz), 125.4 (d, *J* = 3.9 Hz), 123.9 (q, *J* = 271.0 Hz), 111.7, 110.9, 107.8, 51.9, 46.6, 21.0, 20.8, 20.1, 19.9. ^{19}F NMR ($CDCl_3$) δ 99.1. Mp. 240.0–241.0 °C. TLC: R_f 0.45 (hexane/EtOAc = 1:1). IR (KBr): 3300, 2975, 1619, 1539, 1476, 1371, 1322, 1207, 1167, 1126, 1067, 1045, 1022, 953, 850, 689 cm^{-1}. HRMS Calcd for $C_{20}H_{20}Br_3F_3NO_2$: $[M+H]^+$,

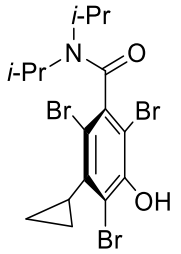
601.8970. Found: *m*/*z* 601.8952. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.7 min, t_{major} = 5.3 min.

2,4,6-Tribromo-3-hydroxy-*N*,*N*-diisopropyl-5-(naphthalen-2-yl)benzamide (2i).



Yield: 86%, 68% *ee*, white solid. $[\alpha]_D^{18}$ –20.1 (*c* 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.98 (br s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.88 (d, *J* = 3.0 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 3.5 Hz, 1H), 7.53 (d, *J* = 3.0 Hz, 1H), 3.72 (qq, *J* = 6.5, 2.0 Hz, 1H), 3.58 (qq, *J* = 7.0, 2.5 Hz, 1H), 1.63 (d, *J* = 2.0 Hz, 3H), 1.62 (d, *J* = 2.5 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.5, 149.3, 139.4, 133.8, 133.2, 133.0, 132.9, 130.1, 128.3, 128.2, 127.7, 126.7, 126.6, 126.5, 109.8, 109.1, 52.8, 46.5, 21.1, 20.9, 20.12, 20.07. Mp. 248.0–248.5 °C. TLC: R_f 0.46 (hexane/EtOAc = 1:1). IR (KBr): 3508, 3060, 2976, 1642, 1609, 1472, 1443, 1370, 1332, 1281, 1164, 1128, 1053, 858, 820, 750, 689 cm^{-1}. HRMS Calcd for $C_{23}H_{23}Br_3NO_2$: $[M+H]^+$, 583.9252. Found: *m*/*z* 583.9260. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 3.7 min, t_{major} = 5.3 min.

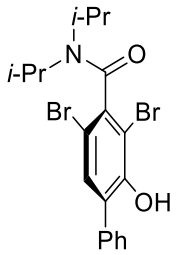
2,4,6-Tribromo-3-cyclopropyl-5-hydroxy-*N*,*N*-diisopropylbenzamide (2j).



Yield: 69%, 76% *ee*, white solid. $[\alpha]_D^{18}$ –23.1 (*c* 1.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.38 (br s, 1H), 3.55 (qq, *J* = 6.5, 1.0 Hz, 1H), 3.54 (qq, *J* = 6.5, 1.0 Hz, 1H), 1.74 (m, 1H), 1.60 (d, *J* = 1.0 Hz, 3H), 1.58 (d, *J* = 1.0 Hz, 3H), 1.29–1.26 (m, 2H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.80 (m, 1H), 0.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 165.6, 149.3, 141.4, 140.3, 115.4, 115.0, 105.5, 51.7, 56.5, 21.0, 20.8, 20.1, 19.9, 19.1, 11.8, 11.6. Mp. 138.0–139.0 °C. TLC: R_f 0.37

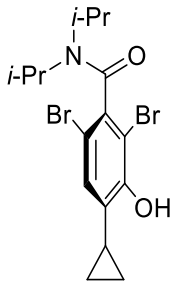
(hexane/EtOAc = 2:1). IR (KBr): 2978, 2936, 1609, 1534, 1475, 1446, 1381, 1370, 1338, 1208, 1156, 1134, 1045, 853, 821 cm^{-1}. HRMS Calcd for $C_{16}H_{21}Br_3NO_2$: $[M+H]^+$, 497.9096. Found: *m*/*z* 497.9090. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.8 min, t_{major} = 8.4 min.

3,5-Dibromo-2-hydroxy-*N*,*N*-diisopropyl-[1,1'-biphenyl]-4-carboxamide (2k).



Yield: 73%, 69% *ee*, white solid. $[\alpha]_D^{18}$ –18.5 (*c* 1.32, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.52–7.50 (m, 2H), 7.48–7.45 (m, 3H), 7.40 (m, 1H), 5.89 (br s, 1H), 3.70 (qq, *J* = 6.5, 2.5 Hz, 1H), 3.57 (qq, *J* = 6.5, 2.5 Hz, 1H), 1.62 (d, *J* = 2.5 Hz, 3H), 1.61 (d, *J* = 2.5 Hz, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.26 (d, *J* = 6.5 H, 3H). ^{13}C NMR ($CDCl_3$) δ 165.5, 149.1, 139.4, 135.6, 133.7, 130.1, 129.0, 128.7, 128.4, 109.7, 109.0, 51.8, 46.4, 21.1, 20.9, 20.13, 20.07. Mp. 176.0–177.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:1). IR (KBr): 3488, 3061, 2972, 1607, 1479, 1447, 1382, 1370, 1341, 1157, 1056, 1042, 882, 824, 766, 704 cm^{-1}. HRMS Calcd for $C_{19}H_{22}Br_2NO_2$: $[M+H]^+$, 455.9991. Found: *m*/*z* 455.9975. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 5.6 min, t_{major} = 9.1 min.

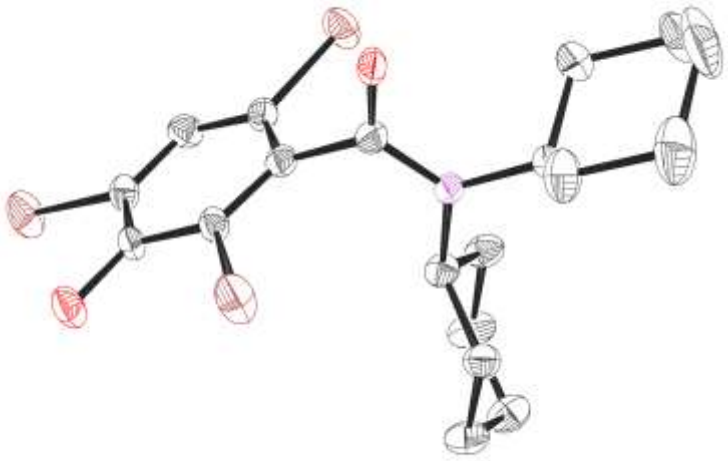
2,6-Dibromo-4-cyclopropyl-3-hydroxy-*N*,*N*-diisopropylbenzamide (2l).



Yield: 99%, 52% *ee*, white solid. $[\alpha]_D^{18}$ –16.6 (*c* 1.04, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 6.97 (s, 1H), 6.11 (br s, 1H), 3.59 (qq, *J* = 7.0, 3.5 Hz, 1H), 3.52 (qq, *J* = 6.5, 3.0 Hz, 1H), 2.08 (m, 1H), 1.59 (d, *J* = 3.5 Hz, 3H), 1.57 (d, *J* = 3.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.02–0.98 (m, 2H), 0.69–0.66 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.8, 151.0, 137.3, 132.2, 129.3, 109.4, 108.2, 51.7, 46.4, 21.0, 20.9, 20.1, 20.0, 10.2, 7.7, 7.6. Mp. 134.5–135.5 °C. TLC:

R_f 0.60 (hexane/EtOAc = 1:1). IR (KBr): 3000, 2972, 1603, 1483, 1446, 1370, 1341, 1276, 1204, 1164, 1137, 1045, 919, 821, 704 cm^{-1}. HRMS Calcd for $C_{16}H_{22}Br_2NO_2$: $[M+H]^+$, 419.9991. Found: *m*/*z* 419.9985. HPLC (Daicel Chiralpak ID-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 4.8 min, t_{major} = 8.3 min.

ORTEP Drawings of 2d



A. Crystal Data

Identification code	**2d**
Empirical Formula	$C_{19}H_{24}Br_3NO_2$
Formula Weight	538.12
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.760 × 0.560 × 0.550 mm
Crystal System	Orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 9.060(1) Å
	b = 14.023(2) Å
	c = 16.598(3) Å
	V = 2108.7(6) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.695 g/cm^3
F_{000}	1064.00
μ(MoKα)	57.681 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	Graphite monochromated
Voltage, Current	50 kV, 12 mA
Temperature	20.0 °C
Detector Aperture	75 mm (diameter)
Data Images	1080 exposures
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	30.00°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	29.81°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	29.81°
ω Oscillation Range	–60.0–120.0°
Exposure Rate	48.0 sec./°
Detector Swing Angle	29.81°
Detector Position	49.89 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.0°
No. of Reflections Measured	Total: 21842
	Unique: 4825 (R_{int} = 0.0993)
	Friedel pairs: 2089

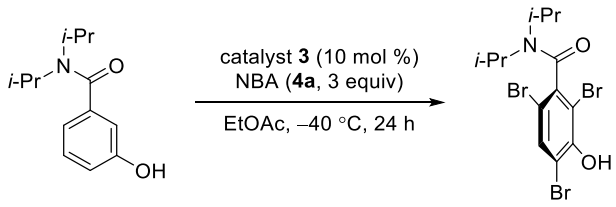
Corrections	Lorentz-polarization Absorption (trans. factors: 0.017–0.042)

C. Structure Solution and Refinement

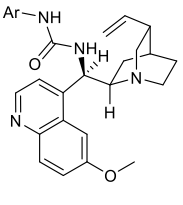
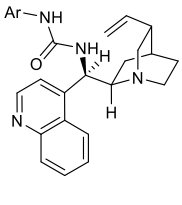
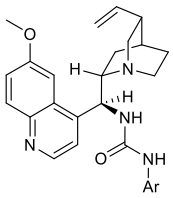
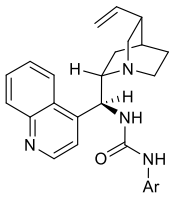
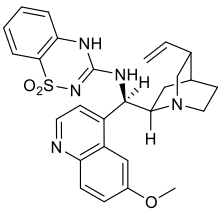
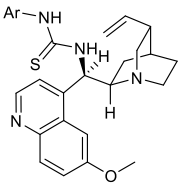
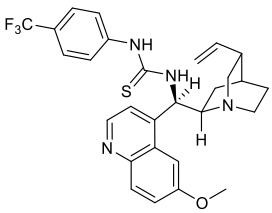
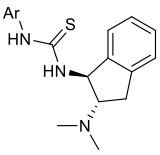
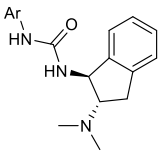
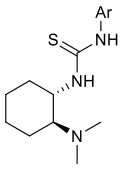
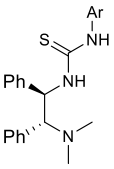
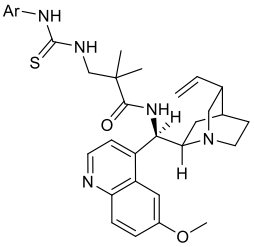
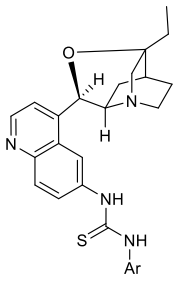
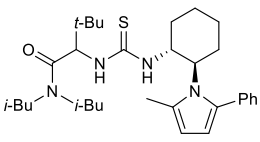
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_0^2) + (0.1000 \cdot P)^2 + 0.0000 \cdot P]$ where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4825
No. Variables	226
Reflection/Parameter Ratio	21.35
Residuals: R1 (I>2.00σ(I))	0.0415
Residuals: R (All reflections)	0.0487
Residuals: wR2 (All reflections)	0.1129
Goodness of Fit Indicator	0.649
Flack Parameter (Friedel pairs = 2089)	–0.007(15)
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map	1.19 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.83 $e^-/Å^3$

Screening of Catalysts

Table S1. Results for screening of catalysts.[a,b,c]

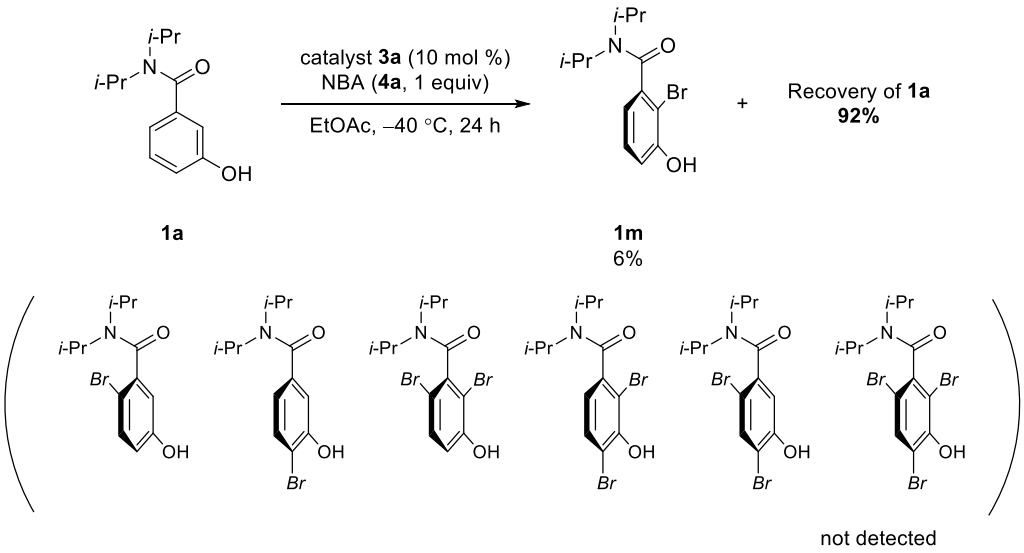


1a **2a**

 **3a** 84%, 87% *ee*	 **3b** 56%, 84% *ee*	 **3c** 89%, –81% *ee*	 **3d** 76%, –80% *ee*
 **3e** 37%, 41% *ee*	 **3f** 51%, 77% *ee*	 **3g** 74%, 60% *ee*	
 **3h** 64%, 83% *ee*	 **3i** 86%, 71% *ee*	 **3j** 70%, –30% *ee*	 **3k** 17%, 36% *ee*
 **3l** 82%, 16% *ee*	 **3m** 97%, 20% *ee*	 **3n** 43%, <1% *ee*	

[a] Reactions were run using **1a** (0.1 mmol), the catalyst (0.01 mmol), and the brominating reagent (0.3 mmol) in the solvent (10 mL). [b] Isolated yields. [c] Ar = 3,5-$(CF_3)_2C_6H_3$.

Reaction from 1a using 1 equivalent of NBA (4a).



Scheme S1. Reaction using 1 equivalent of **4a.** Reaction was run using **1** (0.1 mmol), **4a** (0.1 mmol), and **3a** (0.01 mmol) in EtOAc (10 mL). Yield represent material isolated after silica gel column chromatography.

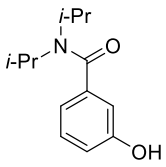
DFT calculations on rotational barrier of compound 1a, 1m, 1o, and 1p.

A. Reference.

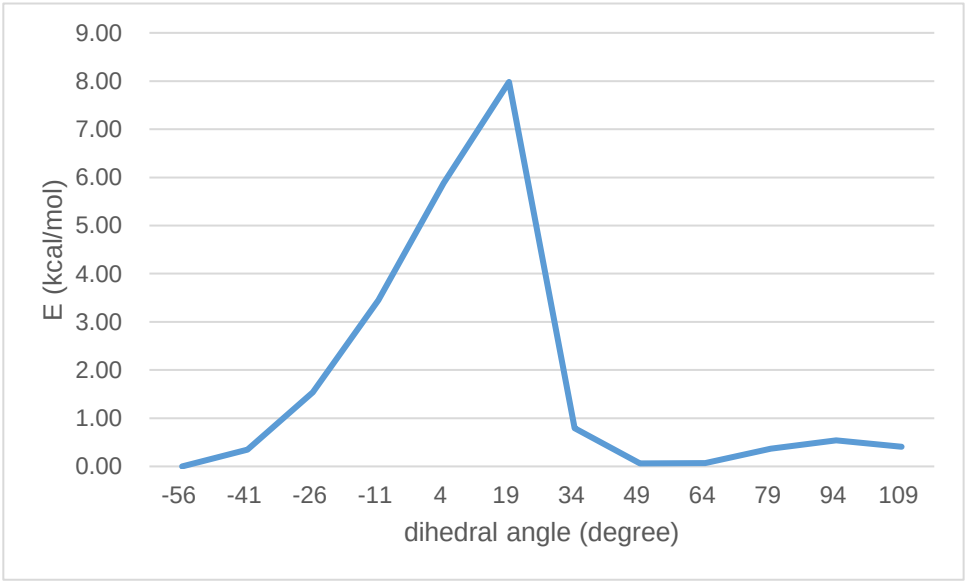
Gaussian 09, Revision B.01,

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F. ; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian, Inc., Wallingford CT, 2010.

B. Details of energy diagrams for rotation of **1a**, **1m**, **1o**, and **1p**, including information on their input files.



1a
8.0 kcal/mol



angle (degree)	energy(kcal/mol)	angle (degree)	energy(kcal/mol)
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–40.9542661191	–446809.2377977981	64.0457338809	–446809.5174072462
–25.9542661191	–446808.0475509562	79.0457338809	–446809.2147531392
–10.9542661191	–446806.1325350344	94.0457338809	–446809.0461858897
4.0457338809	–446803.7029876779	109.0457338809	–446809.1752620839
19.0457338809	–446801.6033264582	124.0457338809	–446809.4125353485
34.0457338809	–446808.7902881432	$\Delta G^{\ddagger}$ =	7.9809243550

%nprocshared=4
%mem=16GB
%chk=Amide2SCAN.chk
#p opt=modredundant b3lyp/6-31g(d) geom=connectivity

0 1

C	3.09796200	–1.43380300	0.99118200
C	3.78925800	–0.40712200	0.34474700

C	3.08952400	0.48747800	–0.47001900
C	1.70412500	0.36571900	–0.61903700
C	1.01618700	–0.65847600	0.03762000
C	1.72196800	–1.57350600	0.83213100
H	3.64590100	–2.13387700	1.61605400
H	4.86666000	–0.30715700	0.46502100
H	1.18809600	1.06756500	–1.26626900
H	1.18672500	–2.39095000	1.30327400
C	–0.45655900	–0.91942400	–0.19748200
O	–0.78446300	–2.04285400	–0.58244700
N	–1.36718300	0.09205700	–0.00586000
C	–2.78546200	–0.14230800	–0.39188300
H	–3.29334600	0.80005000	–0.16569600
C	–1.05523600	1.33501800	0.73578400
H	0.00831900	1.28486200	0.96900800
C	–1.80356200	1.41142000	2.07745200
H	–2.88837500	1.48904600	1.94491400
H	–1.59486700	0.52810000	2.68966400
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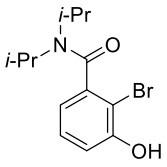
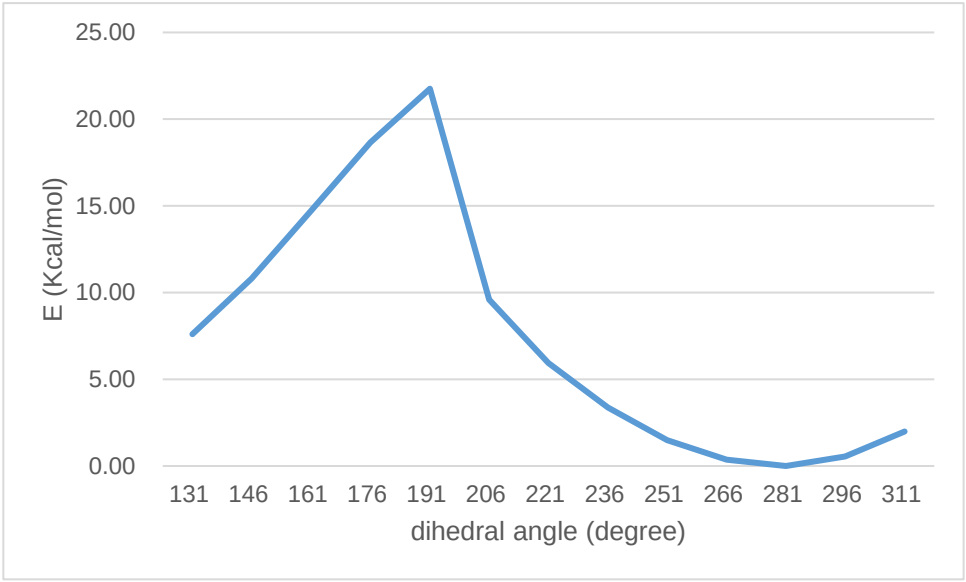
C	–1.28382400	2.59336600	–0.11588400
H	–2.34107700	2.73431900	–0.36759100
H	–0.95647300	3.48191300	0.43566600
H	–0.71712700	2.54541200	–1.05139700
C	–3.46935400	–1.24088700	0.43826300
H	–3.02686100	–2.21535200	0.22778700
H	–3.37821000	–1.03894100	1.51072300
H	–4.53725300	–1.27482100	0.19079700
C	–2.93002600	–0.38059000	–1.90215300
H	–3.99235500	–0.43748500	–2.16683600
H	–2.48165800	0.44216600	–2.46999800
H	–2.44687600	–1.31413000	–2.19645500
O	3.70175600	1.50675100	–1.14778500
H	4.65658800	1.46499900	–0.98340800



1m
21.8 kcal/mol



angle (degree)	energy(kcal/mol)	angle (degree)	energy(kcal/mol)
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146.1454719769	–2060190.0938935676	251.1454719769	–2060199.4067620572
161.1454719769	–2060186.1710493038	266.1454719769	–2060200.5351370897
176.1454719769	–2060182.2346006341	281.1454719769	–2060200.8997577599
191.1454719769	–2060179.1438465174	296.1454719769	–2060200.3428493536
206.1454719769	–2060191.3070200335	311.1454719769	–2060198.9080175064
221.1454719769	–2060194.9533271356	$\Delta G^{\ddagger}$ =	21.76

%nprocshared=4

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%chk= AMIDEBRSCAN.chk

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0 1

C	0.94537100	2.79860100	–0.78459000
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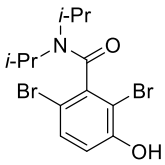

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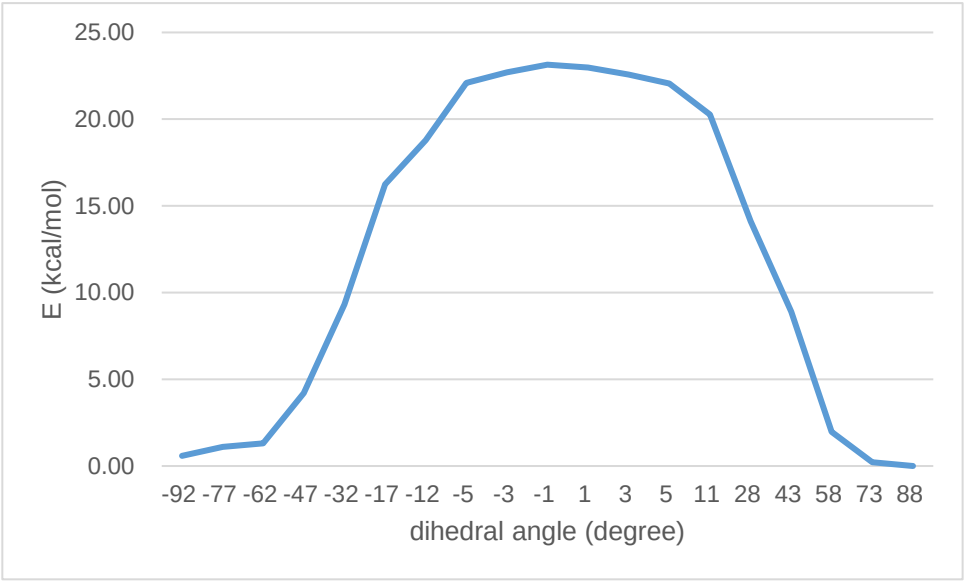
23.1 kcal/mol



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–47.3616241803	–3673583.2961728610	10.6381794589	–3673567.2281081281
–32.3616241803	–3673578.1727334959	27.6383758197	–3673573.3713508323
–17.3616241803	–3673571.2598754908	42.6383758197	–3673578.6075975792
–12.3618205411	–3673568.7057235730	57.6383758197	–3673585.5213089981
–5.3618205411	–3673565.4022437362	72.6383758197	–3673587.2796659176
–3.3618205411	–3673564.7996149878	87.6383758197	–3673587.4918645304
–1.3618205411	–3673564.3507072418	$\Delta G^{\ddagger}$ =	23.14

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H	1.64145200	1.91762400	–2.57611300
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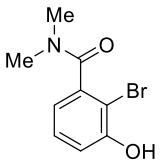
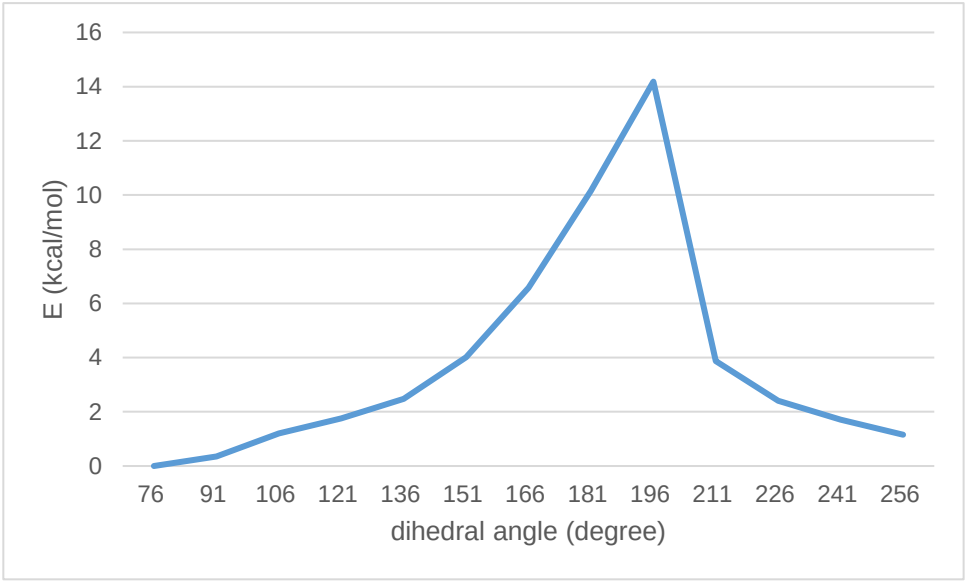


1p
14.2 kcal/mol



angle (degree)	energy(kcal/mol)	angle (degree)	energy(kcal/mol)
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105.5281991270	–1961519.2933751487	210.5281991270	–1961516.6220358317
120.5281991270	–1961518.7422335546	225.5281991270	–1961518.0860719709
135.5281991270	–1961518.0128604376	240.5281991270	–1961518.7804928087
150.5281991270	–1961516.4822831906	255.5281991270	–1961519.3402124573
165.5281991270	–1961513.9240901119	$\Delta G^{\ddagger}$ =	21.76

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C	0.46910200	2.34520100	–0.08080800
C	–0.02161500	1.03605600	–0.17678500
C	0.87048700	–0.03422200	–0.07685100

H	3.76776700	1.67372000	0.42313600
H	2.20085000	3.58667600	0.22510700
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C	–1.48613600	0.85412200	–0.52306800
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N	–2.32168000	0.37151500	0.44813600
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H	–3.94057200	–0.95419800	0.19496900
H	–4.37765100	0.66626000	0.79092400
H	–3.88660400	0.44616700	–0.91359300
C	–1.91556600	–0.00168900	1.79236400
H	–2.60301700	0.44732500	2.52023700
H	–1.93145800	–1.09133500	1.92364900
H	–0.90880900	0.35815900	2.00193200
O	3.06119900	–0.89575600	0.22868600
H	3.97229700	–0.58656300	0.35261400
Br	0.25284200	–1.83077800	–0.24737500

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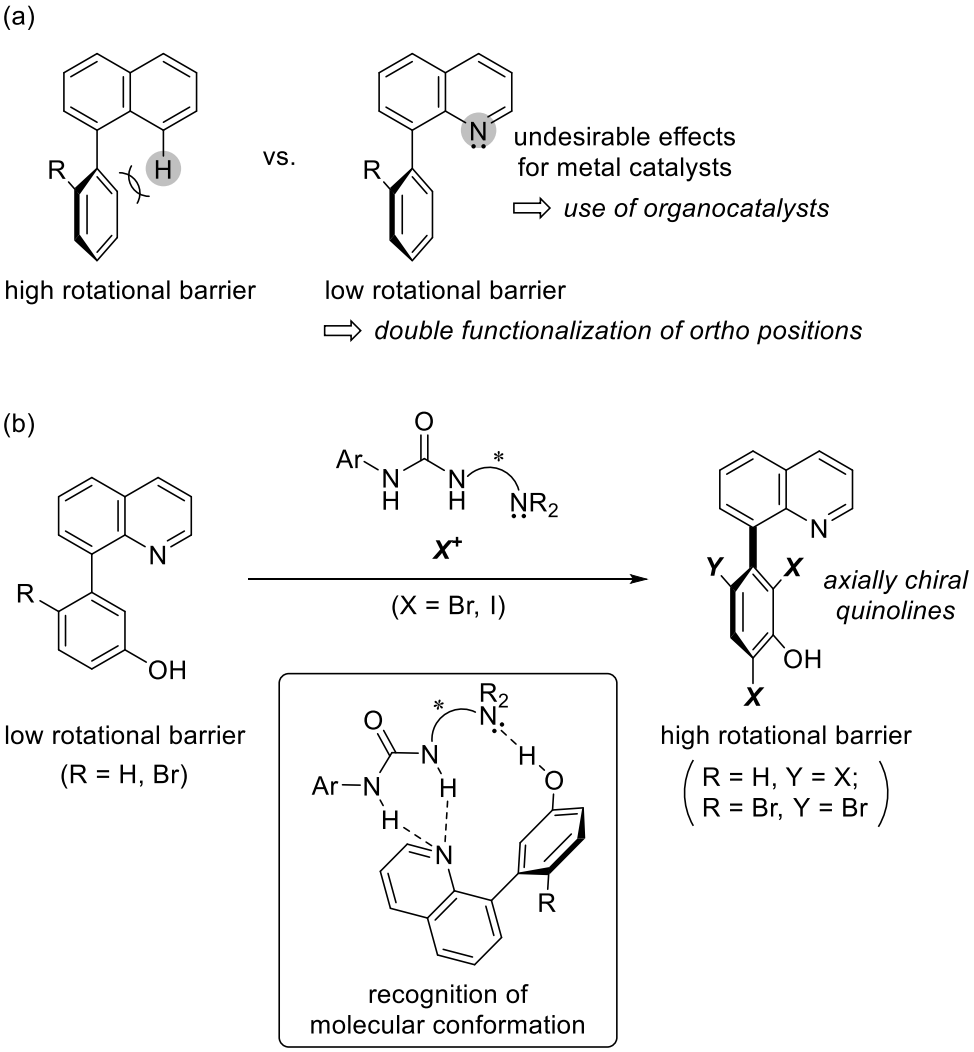
Chapter 5

Enantioselective Syntheses of Axially Chiral Quinolines by Bifunctional Organocatalysts

Enantioselective syntheses of axially chiral heterobiaryls were accomplished via aromatic electrophilic halogenations of 3-(quinolin-8-yl)phenols using bifunctional organocatalysts. Axially chiral quinoline derivatives, which have hardly been synthesized in a catalytic enantioselective manner, was afforded via bromination in moderate-to-good enantioselectivities, and an analogous protocol also enabled enantioselective iodination. In addition, the intrinsically modest steric barrier of quinolines led to the synthesis of their derivative bearing both bromo and iodine groups with high enantioselectivity.

Introduction

Axially chiral structures provide stereoisomers resulting from restricted rotaion about a single bond, and they are responsible for attractive properties of various functional molecules, such as chiral synthetic reagents,[1] bioactive compounds,[2] and organic materials.[3] Due to the importance of such frameworks, various methods have been developed for the enantioselective synthesis of axially chiral compounds.[4] However, despite such significant advances, general strategies have not been established thus far for atroposelective synthesis of heterobiaryls.[4f] Especially, the presence of a heteroatom adjacent to the biaryl linkage leads to lower rotational barrier, and its functionality can also be an obstacle in metal catalysis (Scheme 1a).[5] Recently, organocatalytic approaches also attract increasing attention,[4a–4g,6] in which protocols involving installation of high rotational barrier via aromatic electrophilic halogenations[7] are emerging strategies for the introduction of axial chirality in biaryl compounds.[8] The author also developed a method relying on bifunctional organocatalysts,[8f,9,10] which can recognize specific conformations of substrates via multiple hydrogen bonding interactions.[11] In this context, he envisaged that heterobiaryls can be involved in a desirable host-guest interaction with bifunctional organocatalysts for atroposelective reactions. Here, he presents a novel method for the enantioselective synthesis of axially chiral quinoline derivatives via aromatic electrophilic halogenations using bifunctional organocatalysts (Scheme 1b). Halogenations of both ortho positions of the biaryl axis could restrict its rotation; this method was useful not only for bromination but also for iodination. In addition, the intrinsically modest steric barrier of quinolines also enabled the synthesis of their optically active derivative bearing both bromo and iodine groups (Scheme 1b, X = I, R = Y = Br), useful for further site-selective transformations.[12,13] Thus, this catalytic protocol offer efficient routes to a range of axially chiral quinoline derivatives, while their catalytic enantioselective synthesis has been limited to only a recent example,[6ad] to the best of his knowledge, despite the potential as ligands for metal catalysts[14] and the promising biological activity.[15]

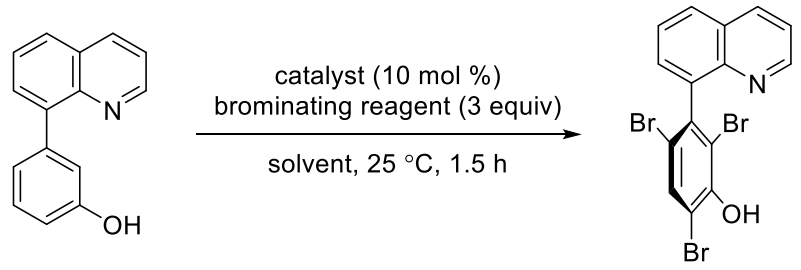


Scheme 1. Strategies for the synthesis of axially chiral quinolines.

Results and Discussion

The author initiated this study by investigating the interactions between 8-(quinoline-8-yl)phenol (**1a**) and quinidine-derived bifunctional catalyst **2a** (their chemical structures are shown in Table 1) using ^{1}H NMR analysis. The all signals associated with the protons of the phenolic hydroxy group in **1a** and the urea group in catalyst **2a** shifted (see the Experimental Section for details).[16] These results suggest the existence of multipoint interaction via hydrogen bonding between **1a** and **2a**. These observations stimulated him to apply **1a** as a substrate to the halogenations for the enantioselective synthesis of axially chiral quinoline derivatives.

Table 1. Optimization of conditions.[a]



1a **3a**

entry	catalyst	brominating reagent	solvent	yield (%)[b]	*ee* (%)
1	**2a**	NBA (**4a**)	THF	96	57
2	**2a**	NBA (**4a**)	toluene	99	14
3	**2a**	NBA (**4a**)	CH_3CN	99	68
4	**2a**	NBA (**4a**)	CH_2Cl_2	99	90
5[c]	**2a**	DBH (**4b**)	CH_2Cl_2	97	83
6	**2a**	NBS (**4c**)	CH_2Cl_2	99	78
7	**2a**	NBP (**4d**)	CH_2Cl_2	98	82
8	**2b**	NBA **(4a)**	CH_2Cl_2	99	78
9	**2c**	NBA **(4a)**	CH_2Cl_2	96	–82
10	**2d**	NBA **(4a)**	CH_2Cl_2	99	–86
11	**2e**	NBA **(4a)**	CH_2Cl_2	99	–86
12	**2f**	NBA **(4a)**	CH_2Cl_2	88	<1

[a] Reactions were run using **1a** (0.1 mmol), the catalyst (0.01 mol), and the brominating reagent (0.3 mmol) in the solvent (10 mL). [b] Isolated yields. [c] 1.5 equiv of **4b** was used for the reaction.

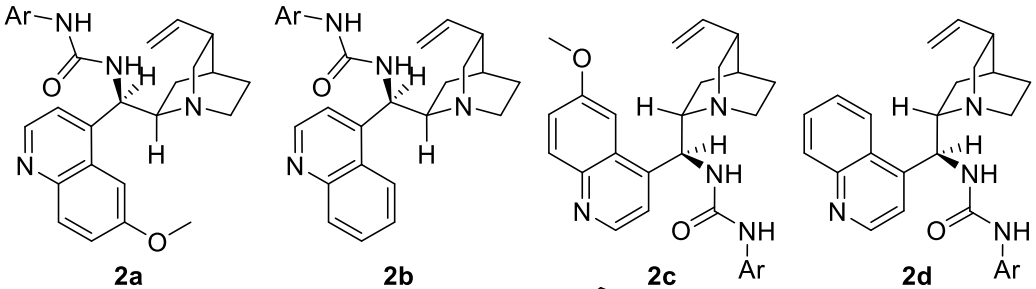


Table 1 shows the optimization of reaction conditions.[17] The bromination of **1a** using *N*-bromoacetamide (NBA, **4a**, Figure 1) as a brominating reagent with 10 mol % of **2a** in THF at 25 °C afforded tribrominated product **3a** in good yield with moderate enantioselectivity (Table 1, entry 1). Although the reactions in toluene and CH_3CN also resulted in low-to-moderate enantioselectivities (Table 1, entry 2 and 3), the use of CH_2Cl_2 largely improved the enantioselectivity to 90% *ee* while keeping the quantitative yield (Table 1, entry 4). The author next examined the effect of various brominating reagents besides **4a** (DBH (**4b**), NBS (**4c**), and NBP (**4d**)) (Figure 1; Table 1, entry 5–7); among them, **4a** achieved the highest enantioselectivity (Table 1, entry 4). He further investigated other cinchona-alkaloid derived catalysts (Table 1, entry 8–10); **2b** also gave moderate enantioselectivity, and the use of **2c** and **2d** afforded the opposite enantiomer of the product in slightly lower enantioselectivities. Moreover, catalyst **2e**, with a cyclohexanediamine framework, also afforded the product in quantitative yield with similar enantioselectivity (Table 1, entry 11). On the other hand, quinidine (**2f**) exhibited almost no enantioselectivity (Table 1, entry 12), suggesting the significance of the bifunctionality of the catalyst containing amino and urea functional groups toward enantioselectivity.

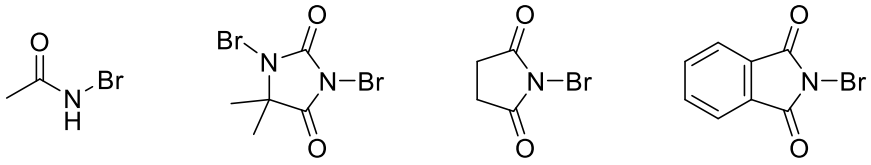
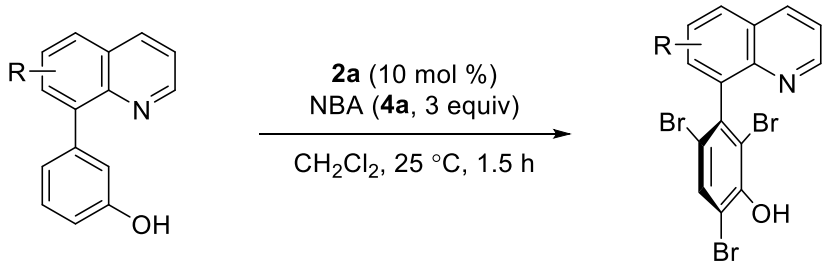


Figure 1. Brominating reagents.

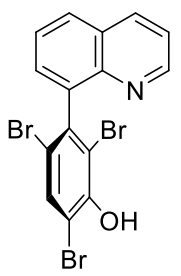
Next, the substrate scope was investigated with the optimal conditions, and moderate-to-good enantioselectivities were obtained from substrates bearing various substituents on the quinoline moiety (Table 2). A substrate with a methyl group at 6-position was tolerated to give the product **3b** in high enantioselectivity. Quinolines **1c** and **1d**, bearing bromo and fluoro groups at the same position, resulted in a slight decline of enantioselectivities. Substrates bearing electron-withdrawing groups, namely trifluoromethyl and nitro groups, at 5-position of the quinoline moiety also gave the desired products **3e** and **3f**, respectively, in high yields with moderate enantioselectivities, while a substrate with an electron-donating group gave **3g** in higher enantioselectivity. Furthermore, a substrate with a methyl group near the rotational axis also provided the product **3h** in moderate enantioselectivity albeit in lower yield. The optical purities of **3c** and **3e** were further increased after one-time recrystallization with the mixed solvents of 2-

propanol/ethyl acetate/THF; the absolute configuration of **3c** was determined by X-ray analysis (see the Experimental Section for details), and the configurations of all other examples were assigned analogously.

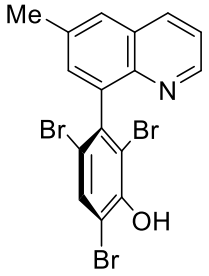
Table 2. Substrate scope.[a]



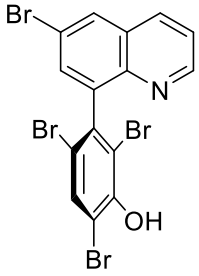
1 **3**



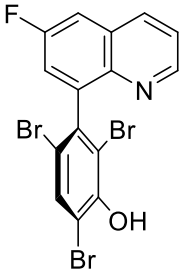
3a
99%, 90% *ee*



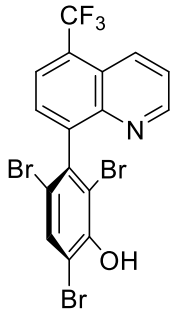
3b
99%, 88% *ee*



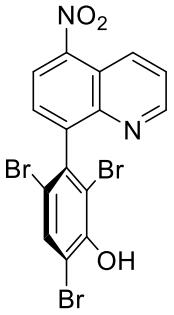
3c
99%, 76% *ee*
(54%, 88% *ee*)[b]



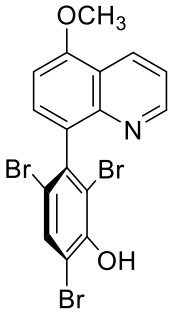
3d
99%, 76% *ee*



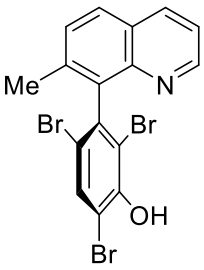
3e
98%, 65% *ee*
(57%, 98% *ee*)[b]



3f
99%, 61% *ee*



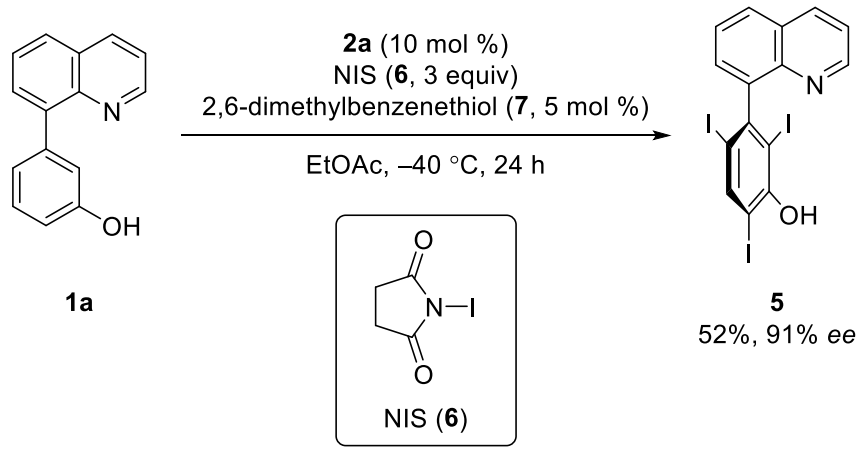
3g
97%, 81% *ee*



3h
57%, 70% *ee*

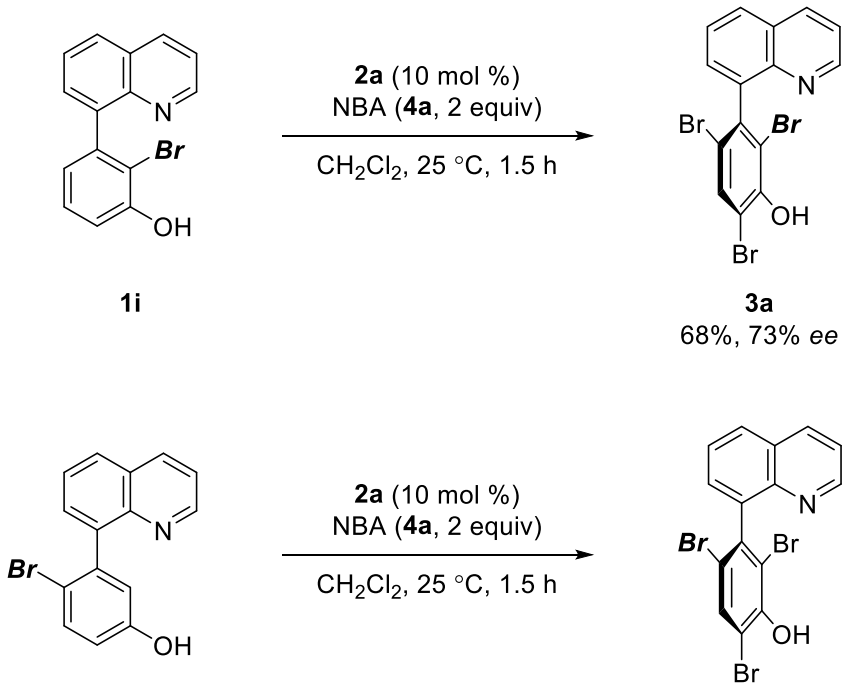
[a] Reactions were run using **1** (0.1 mmol), **2a** (0.01 mmol), and **4a** (0.3 mmol) in CH_2Cl_2 (10 mL). Yields represent material isolated after silica gel column chromatography. [b] After one-time recrystallization.

Moreover, this synthetic method could also be applied to the asymmetric iodination of **1a** with 3 equiv of *N*-iodosuccinimide (NIS, **6**) in the presence of bifunctional catalyst **2a** (Scheme 2). After the additional optimization of the reaction conditions,[18] the use of 5 mol % of 2,6-dimethylbenzenthiol (**7**) further improved the enantioselectivity.[19]



Scheme 2. Asymmetric iodination of **1a**.

To gain insight into the reaction mechanism of asymmetric bromination, the reactions were carried out from substrates **1i** and **1j**, previously monobrominated at ortho positions of the biaryl axis, with catalyst **2a** and 2 equiv of **4a** (Scheme 3). In both cases, optically active product **3a** could be obtained despite the slightly lower enantioselectivities than that of the reaction from **1a**, which suggests that the rotational barrier of the monobrominated substrates **1i** and **1j** is not enough high to completely inhibit the bond rotation about the biaryl axis. Thus, the enantioselectivity seems to be determined after both ortho positions of the rotational axis were brominated.[20] Actually, the rotational barrier of **1a**, calculated by B3YLP/6-31G(d), is slight, and that of the monobrominated coumpounds **1i** and **1j** is still modest; on the other hand, the dibrominated compound **1k** has a much larger value than them (Figure 2).



Scheme 3. Reactions of monobrominated substrates.

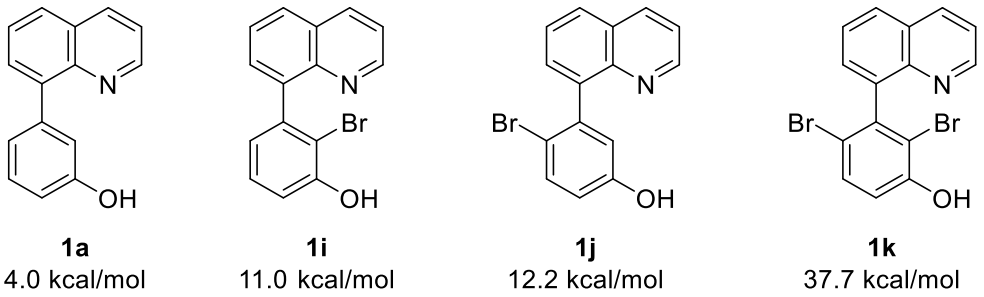
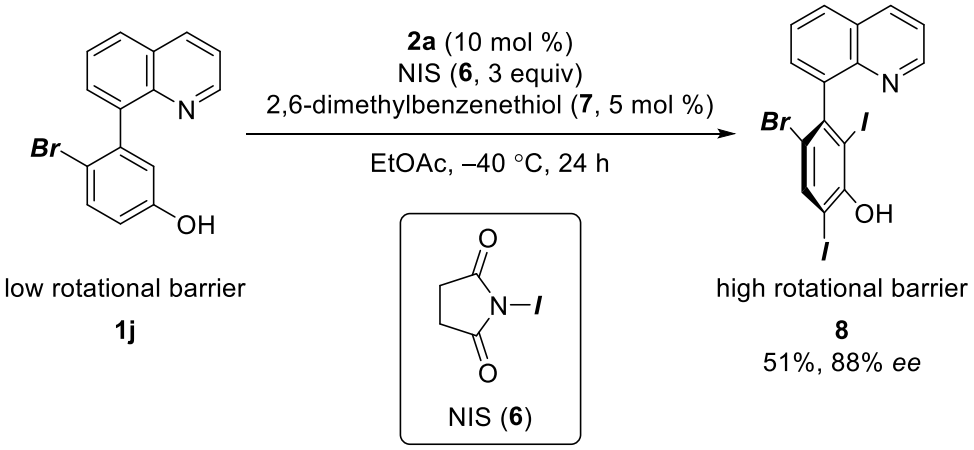


Figure 2. Rotational barrier of substrates and intermediates calculated by B3YLP/6-31G(d).

On the basis of the information regarding rotational barrier, indicating the monobrominated compounds is still able to racemize through bond rotation, substrate **1j** was subjected to the iodination on the conditions employed in Scheme 2; product **8**, bearing both bromo and iodine groups, was obtained in high enantioselectivity (Scheme 4), which demonstrates the utility of this synthetic protocol for offering complex organohalides bearing atropisomeric heteroaryl structures.



Scheme 4. Asymmetric iodination of **1j**.

Conclution

In summary, the author developed novel enantioselective synthesis of the heterobiaryls bearing quinoline moieties via aromatic electrophilic halogenations using the bifunctional organocatalysts. Axially chiral quinoline derivatives, which have been difficult to synthesize in a catalytic enantioselective manner, were obtained via bromination in moderate-to-good enantioselectivities, and this method could also be applied to the asymmetric iodination using the same organocatalyst with good enantioselectivity. Utilizing the moderate steric property of quinolines, the synthetic application was further demonstrated affording an optically active heterobiaryl bearing two different halogen groups. These products have a potential as synthetic precursors useful for the construction of important chiral sp^2 hybrid frameworks containing heteroaromatic rings. Further studies on the detailed clarification of the reaction mechanism and application of this method to the synthesis of various axially chiral heterobiaryls are currently underway in his laboratory and will be reported in due course.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. The starting materials such as 3-hydroxyphenylboronoic acid, anilines for quinoline syntheses, halogenating reagent **4**, and **6** are commercially available. The bifunctional organocatalyst **3a–3d** was prepared with the same procedure in former chapters.

Experimental Procedure

General procedure for asymmetric synthesis of 2,4,6-tribromo-3-(quinoline-8-yl)phenols 3

To a 20-mL round-bottom flask were added 3-(quinoline-8-yl)phenol **1** (0.10 mmol) and quinidine-derived bifunctional catalyst **2a** (5.8 mg, 0.010 mmol), and CH_2Cl_2 (10 mL). The solution was stirred at 25 °C for 30 min. Subsequently, *N*-bromoacetamide (**4a**, 41.4 mg, 0.30 mmol) was added to the solution, and the mixture was stirred for 1.5 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5.0 mL), and then the aqueous phase was extracted by EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent afforded the desired product **3** as a colorless solid.

General procedure for reactions from 1i and 1j

To a 20-mL round-bottom flask were added **1** (30 mg, 0.10 mmol) and **2a** (5.8 mg, 0.010 mmol), and CH_2Cl_2 (10 mL). The solution was stirred at 25 °C for 30 min. Subsequently, **4a** (27.6 mg, 0.20 mmol) was added to the solution, and the mixture was stirred for 1.5 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5.0 mL), and then the aqueous phase was extracted by EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent afforded the desired product **3a** as a colorless solid.

Iodination of substrate 1a

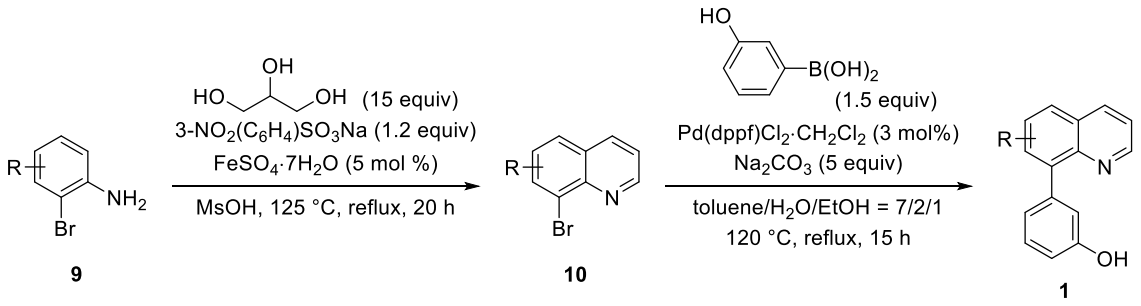
To a 10-mL round-bottom flask were added **1a** (22 mg, 0.10 mmol) and **2a** (5.8 mg, 0.010 mmol), 2,6-dimethylbenezenethiol (**7**, 0.60 μL, 0.0050 mmol), and EtOAc (5.0 mL). The solution was stirred at –40 °C for 30 min. Subsequently, *N*-iodosuccinimide (**6**, 67.5 mg, 0.30 mmol) was

added to the solution, and the mixture was stirred for 24 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5.0 mL), and then the aqueous phase was extracted by EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent afforded the desired product **5** as a colorless solid in 52%, 91% *ee*.

Iodination of 1j

To a 10-mL round-bottom flask were added **1j** (30 mg, 0.10 mmol) and **2a** (5.8 mg, 0.010 mmol), **7** (0.60 μL, 0.0050 mmol), and EtOAc (5.0 mL). The solution was stirred at –40 °C for 30 min. Subsequently, **6** (45.0 mg, 0.20 mmol) was added to the solution, and the mixture was stirred for 24 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5.0 mL), and then the aqueous phase was extracted by EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent afforded the desired product **5** as a colorless solid in 51%, 88% *ee*.

General procedure for preparation of substrates 1

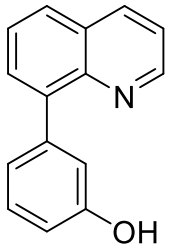


Substrate **1a**–**1h** were prepared by the literature procedere.[8f,21] In a 100-mL two-necked reaction flask, aniline (**9**, 7.5 mmol), sodium 3-nitrobenzenesurfonate (2.0 g, 9.0 mmol), and $FeSO_4·7H_2O$ (104 mg, 0.40 mmol) were placed. To the mixture were added MsOH (10 mL) and glycerol (10 mL), and they were stirred at 125 °C for 20 h. The solution was quenced with 10 % aqueous NaOH to basicify. Then, the organic phase was repeatedly washed with H_2O to remove the remaining glycerol, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave 8-bromoquinolines **10** in 17–95% yield.

In a 50-mL two-necked reaction flask was placed Pd catalyst (37 mg, 0.05 mmol) and Na_2CO_3 (795 mg, 7.5 mmol) under argon atmosphere. To the mixture, **10** (1.5 mmol), boronic acid (308 mg, 2.3 mmol), toluene (14 mL), water (4 mL), and EtOH (2 mL) were added, and the reaction mixture was stirred for 15 h at 120 °C. The solution was cooled to room temperature and quenched with H_2O. The aqueous phase was extracted with EtOAc (10 mL × 3). And the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification with flush silica gel column chromatography using hexane/EtOAc (v/v = 1.5/1) as an eluent and recrystallization from hot EtOH/hexane gave the corresponding **1a**–**1h** in 39–99% yield.

The characterization results are below.

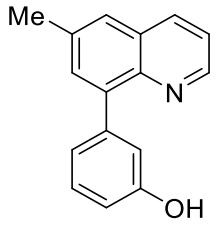
3-(Quinolin-8-yl)phenol (1a).



White solid; 92% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 9.15 (br s, 1H), 8.84 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.22 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.61 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.39 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.18 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.02 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H), 6.81 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 157.1, 149.7, 145.2, 141.0, 140.3, 137.4, 130.8, 129.7, 128.7, 127.4, 126.6, 121.2, 120.9, 117.7, 115.4. Mp. 173.5–174.0 °C. TLC: R_f 0.37 (hexane/EtOAc = 1.5:1). IR (KBr): 3050, 2728, 2598, 2473, 1951, 1597, 1492, 1450, 1390, 1313, 1299, 1235, 1178, 1161, 1072, 1001, 899, 841, 800, 766 cm^{-1}. HRMS Calcd for $C_{15}H_{12}NO$: $[M+H]^+$, 222.0913. Found: *m*/*z* 222.0912.

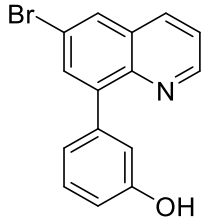
3-(6-Methylquinolin-8-yl)phenol (1b).



White solid; 85% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 9.25 (br s, 1H), 8.76 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.12 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.57–7.58 (m, 2H), 7.35 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.34 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.16 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.01 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 6.80 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 149.9, 149.6, 143.5, 141.2, 139.3, 136.25, 136.18, 134.7, 132.3, 128.6, 127.7, 121.4, 115.0, 114.1, 110.3, 21.6. Mp. 185.0–186.0 °C. TLC: R_f 0.39 (hexane/EtOAc = 1.5:1). IR (KBr): 3139, 2591, 1598, 1488, 1449, 1369, 1298, 1244, 1157, 1148, 997, 957, 890, 857, 813, 779 cm^{-1}. HRMS Calcd for $C_{16}H_{14}NO$: $[M+H]^+$, 236.1070. Found: *m*/*z* 236.1065.

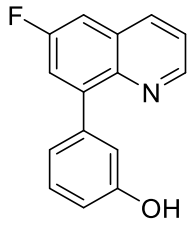
3-(6-Bromoquinolin-8-yl)phenol (1c).



White solid; 84% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.87 (br s, 1H), 8.84 (dd, *J* = 4.5, 2.0 Hz, 1H), 8.13 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.82 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.36 (dd, *J* = 7.5, 7.0 Hz, 1H), 7.09 (dd, *J* = 1.5, 1.5 Hz, 1H), 7.00 (ddd, *J* = 7.0, 2.5, 1.5 Hz, 1H), 6.81 (ddd, *J* = 7.5, 2.5, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 157.0, 150.0, 144.0, 142.8, 138.8, 136.4, 133.9, 129.91, 129.87, 129.2, 122.0, 120.9, 120.5, 117.4, 115.9. Mp. 195.0–195.5 °C. TLC: R_f 0.39 (hexane/EtOAc = 1:1). IR (KBr): 3163, 1600, 1586, 1450, 1448, 1374, 1292, 1235, 1232, 1158, 1002, 864, 802, 721, 695, 625, 581, 481 cm^{-1}. HRMS Calcd for $C_{15}H_{11}BrNO$: $[M+H]^+$, 300.0019. Found: *m*/*z* 300.0006.

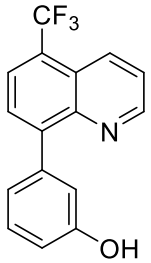
3-(6-Fluoroquinolin-8-yl)phenol (1d).



White solid; 78% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.84 (br s, 1H), 8.81 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.52 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.43 (ddd, *J* = 8.0, 5.0, 3.0 Hz, 1H), 7.42 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.13 (dd, *J* = 2.5, 2.0 Hz, 1H), 7.01 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H), 6.82 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 160.6, 158.6, 149.9 (d, *J* = 1.8 Hz), 149.5, 142.5, 142.0 (d, *J* = 9.6 Hz), 140.2, 136.0 (d, *J* = 5.8 Hz), 134.7, 129.2 (d, *J* = 10.0 Hz), 122.2, 120.9 (d, *J* = 26.3 Hz), 114.0 (d, *J* = 178.0 Hz), 111.8 (d, *J* = 21.0 Hz), 110.3. ^{19}F NMR ($CDCl_3$) δ 49.0. Mp. 187.0–187.5 °C. TLC: R_f 0.38 (hexane/EtOAc = 1:1). IR (KBr): 3062, 1597, 1488, 1449, 1387, 1369, 1298, 1243, 1157, 997, 957, 890, 857, 792, 751, 697 cm^{-1}. HRMS Calcd for $C_{15}H_{11}FNO$: $[M+H]^+$, 240.0819. Found: *m*/*z* 240.0815.

3-(5-trifluoromethylquinolin-8-yl)phenol (1e).

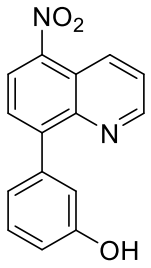


White solid; 61% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 8.95 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.58 (ddd, *J* = 9.0, 2.0, 1.5 Hz, 1H), 8.00 (br s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.38 (dd, *J* = 8.5, 8.0 Hz, 1H), 7.09 (dd, *J* = 2.0, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.86 (ddd, *J* = 8.5, 1.5, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 156.6, 150.3, 145.5 (d, *J* = 29.1 Hz), 139.5, 133.6, 129.5 (d, *J* = 102.1 Hz), 124.0 (q, *J* = 272.0 Hz), 125.5 (q, *J* = 31.2 Hz), 125.2, 125.1, 125.02, 124.96, 122.3, 121.4, 117.5, 116.9. ^{19}F NMR ($CDCl_3$) δ 59.3. Mp. 200.0–201.0 °C. TLC: R_f 0.21 (hexane/EtOAc = 1.5:1). IR (KBr): 3153, 1580, 1511, 1474, 1366, 1323, 1283, 1179, 1144, 1133, 1123, 1098, 947, 861, 797 cm^{-1}. HRMS Calcd for $C_{16}H_{11}F_3NO_2$: $[M+H]^+$, 290.0787. Found: *m*/*z*

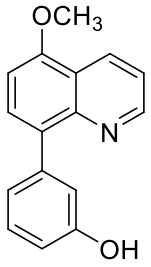
290.0781.

3-(5-Nitroquinolin-8-yl)phenol (1f).



Yellow solid; 87% yield (for the last step).
^{1}H NMR ($CDCl_3$) δ 9.08 (dd, *J* = 9.0, 1.5 Hz, 1H), 9.04 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.41 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.18 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 7.15 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.94 (ddd, *J* = 8.0, 3.0, 1.0 Hz, 1H), 5.74 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 155.5, 155.1, 147.5, 145.6, 144.7, 139.4, 132.3, 129.6, 128.4, 122.4, 123.7, 122.7, 121.8, 117.7, 115.8. Mp. 197.0–198.0 °C. TLC: R_f 0.24 (hexane/EtOAc = 1.5:1). IR (KBr): 3244, 1614, 1580, 1514, 1472, 1387, 1331, 1217, 1168, 1168, 1141, 1106, 1078, 1052, 997, 969, 879, 825, 804, 743, 699 cm^{-1}. HRMS Calcd for $C_{15}H_{11}N_2O_3$: $[M+H]^+$, 267.0764. Found: *m*/*z* 267.0758.

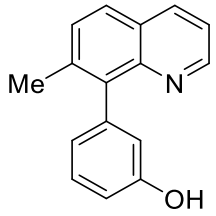
3-(5-Methoxyquinolin-8-yl)phenol (1g).



White solid; 37% yield (for the last step).
^{1}H NMR ($CDCl_3$) δ 9.06 (br s, 1H), 8.68 (d, *J* = 5.0 Hz, 1H), 8.21 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.70 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.15 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.00 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H), 6.79 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 6.72 (dd, *J* = 5.0, 1.0 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 162.9, 157.0, 150.7, 146.1, 140.8, 140.5, 131.1, 129.6, 125.5, 121.7, 121.2, 120.8, 117.7, 115.2, 100.0, 55.9. Mp. 207.5–208.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 1.5:1). IR (KBr): 3184, 1617, 1576, 1465, 1406, 1347, 1293, 1210,

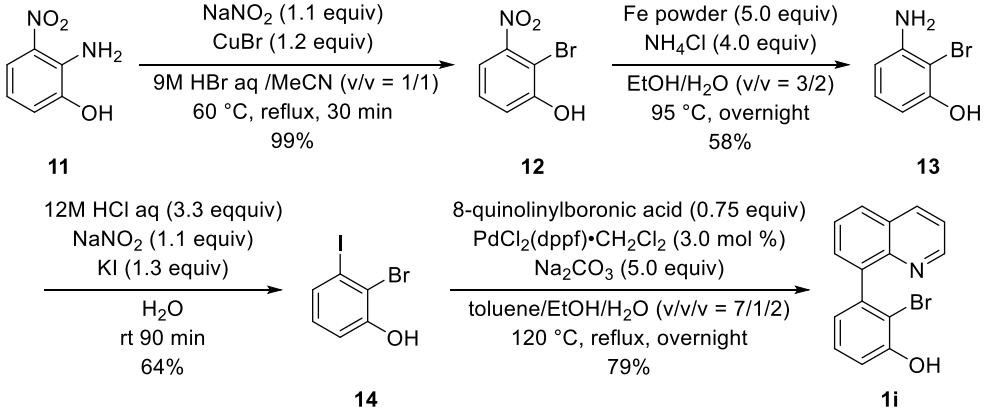
1198, 1167, 1144, 862, 710, 609 cm^{-1}. HRMS Calcd for $C_{16}H_{14}NO_2$: $[M+H]^+$, 252.1019. Found: *m*/*z* 252.1014.

3-(7-Methylquinolin-8-yl)phenol (1h).



White solid; 72% yield (for the last step).
^1H NMR ($CDCl_3$) δ 9.39 (br s, 1H), 8.82 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.75 (ddd, *J* = 7.5, 2.0, 1.0 Hz, 1H), 6.69 (ddd, *J* = 7.5, 2.0, 1.5 Hz, 1H), 6.55 (dd, *J* = 1.5, 1.0 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.1, 149.3, 146.2, 139.5, 139.3, 138.4, 136.9, 129.6, 129.5, 126.7, 126.6, 120.5, 120.2, 117.4, 115.3, 15.3. Mp. 207.5–208.5 °C. TLC: R_f 0.37 (hexane/EtOAc = 1.5:1). IR (KBr): 3051, 1613, 1582, 1506, 1454, 1366, 1297, 894, 833, 797, 780, 701, 700, 638 cm^{-1}. HRMS Calcd for $C_{16}H_{14}NO$: $[M+H]^+$, 236.1070. Found: *m*/*z* 236.1067.

Preparation of substrate 1i[22]



In a 50-mL round-bottom flask, 2-amino-3-nitrophenol (**11**, 3.1 g, 20 mmol) was suspended with MeCN (10 mL). To the mixture 9 M aqueous HBr was subsequently added dropwise. After stirring at ambient temperature for 30 min, 3 M aqueous $NaNO_2$ (3.0 mL, 9.0 mmol) was carefully added to the mixture, and warmed to 60 ºC. After being stirred for 1 h, the mixure was cooled to

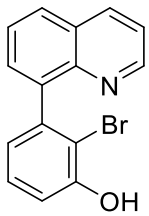
room temperature, and quenched with H_2O (20 mL). Then, precipitate was dissolved in CH_2Cl_2 (15 mL), and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers was washed by brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent afforded 2-bromo-3-nitrophenol **12** quantitively.

In a 100-mL round-bottom flask, **12** (4.3g, 20 mmol) was placed and dissolved in EtOH (30 mL). To the mixture, were added Fe powder (5.6 g, 100 mmol) and 4 M aqueous NH_4Cl (20 mL, 80 mmol). After stirring at 90 ºC for 15 h, the remaining Fe powder was removed by filtration over celite pad, washed with EtOAc (20 mL). Then the aqueous phase was extracted with EtOAc (10 mL × 3), and the organic layers were combined. The organic phase was washed by brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave 3-amino-2-bromophenol **13** in 58% yield.

In a 50-mL round-bottom flask, **13** (2.1 g, 11 mmol), H_2O (10 mL), and 12 M aqueous HCl (2.0 mL, 24 mmol) were placed. To the mixture, 6.0 M aqueous $NaNO_2$ (2.0 mL, 12 mmol) was added dropwise. After stirring for 10 min, 7.0 M aqueous KI (2.0 mL, 14 mmol) was poured then they were vigorously stirred for 30 min. They were quenched with saturated aqueous $Na_2S_2O_3$, and the aqueous phase was extracted with EtOAc (7 mL × 3). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. Purification by flush silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave 2-bromo-3-iodophenol **14** in 64% yield.

The coupling reaction of **12** (598 mg, 2.0 mmol) and 8-quinolinylboronic acid (259 mg 1.5 mmol) was run according to the same procedure as that for **1** from compound **10** and 3-hydroxyphenylboronic acid. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 1.5/1) as an eluent gave **1i** in 79% yield.

2-Bromo-3-(quinolin-8-yl)phenol (1i).

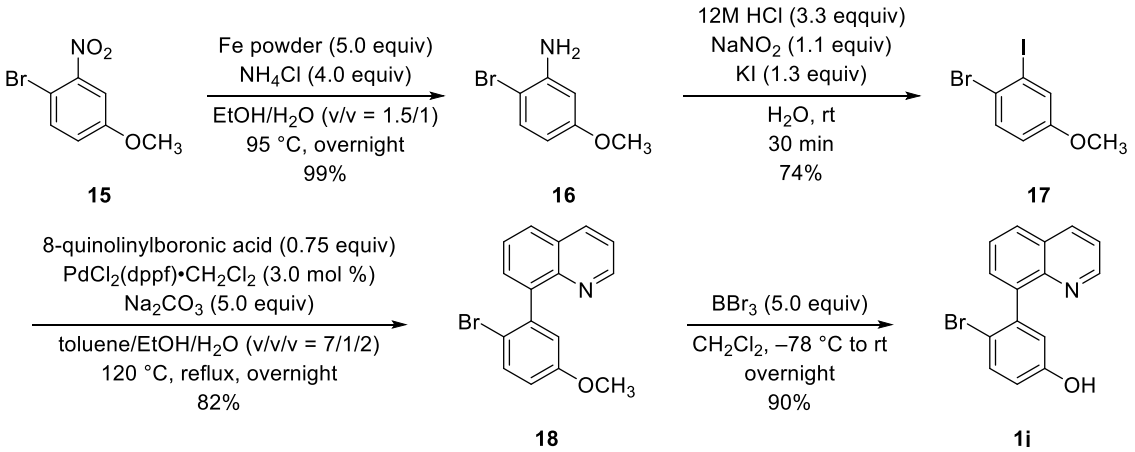


White solid; 79% yield (for the last step).

^{1}H NMR ($CDCl_3$) δ 9.51 (br s, 1H), 8.87 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.27 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.87 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.60 (dd, *J* = 7.5, 7.0 Hz, 1H), 7.57 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.48

(dd, J = 8.5, 4.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 6.63 (dd, J = 8.5, 3.0 Hz, 1H), 6.60 (3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 156.8, 149.7, 145.1, 140.1, 137.6, 133.2, 131.4, 128.6, 128.0, 126.4, 121.4, 119.3, 117.8, 113.0, 110.0. Mp. 246.0–247.0 °C. TLC: R_f 0.35 (hexane/EtOAc = 1.5:1). IR (KBr): 3037, 1603, 1566, 1505, 1454, 1381, 1343, 1279, 1246, 1136, 1038, 906, 832, 783, 722, 712 cm^{-1}. HRMS Calcd for $C_{15}H_{11}BrNO$: $[M+H]^+$, 300.0019. Found: *m/z* 300.0012.

Preparation of substrate 1j[23]



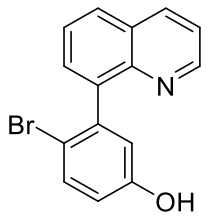
In a 50-mL round-bottom flask, 1-Bromo-4-methoxynitrobenzene (**15**, 1.6g, 7.0 mmol) was dissolved in EtOH (10 mL). To the mixture were added Fe powder (2.0 g, 35 mmol) and 3.5 M aqueous NH_4Cl (8 mL, 28 mmol) and stirred at 90 ºC for 12 h. The remaining Fe powder was removed by filtration over celite pad, washed with EtOAc (10 mL). Then, the aqueous phase was extracted by EtOAc (7 mL × 3). The combined organic layers were washed by brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the reaction mixture by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent afforded 2-bromo-5-methoxyaniline **16** in quantitative yield.

In a 50-mL round-bottom flask **16** (1.4 g, 7.0 mmol), H_2O (16 mL), and 12 M aqueous HCl (1.3 mL, 16mmol) was mixed. To the mixture, 7.7 M aqueous $NaNO_2$ (1.0 mL, 7.7 mmol) was added dropwise. After stirring for 10 min, 7.0 M aqueous KI (2.0 mL, 14 mmol) was poured, then they were vigorously stirred for 30 min. The solution was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), and the aqueous phase was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of them by flush silica gel column chromatography using hexane/EtOAc (v/v = 5/1) as an eluent afforded 1-bromo-2-iodo-4-methoxybenzene **17** in 74% yield.

Procedure of the coupling reaction of **17** (598 mg, 2.0 mmol) and 8-quinolinylboronic acid (259 mg 1.5 mmol) was same as above. Purification of the crude product by flush silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave 8-(2-bromo-5-methoxyphenyl)quinoline **18** in 82% yield.

To a solution of **18** (314 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise BBr_3 (5.0 mL, ca. 1 M in CH_2Cl_2 solution, 5.0 mmol) at –78 °C. Then the mixture was steadily warmed to room temperature. They were carefully quenched with H_2O and neutralized with 10% aqueous NaOH. The aqueous phase was extracted with Et_2O (8 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. Purification of them by flush silica gel column chromatography using hexane/EtOAc (v/v = 1.5/1) as an eluent gave substrate **1j** in 90% yield.

4-Bromo-3-(quinolin-8-yl)phenol (1j).



White solid; 90% yield (for the last step).
^{1}H NMR ($CDCl_3$) δ 8.95 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.29 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.93 (dd, *J* = 6.0, 4.0 Hz, 1H), 7.71 (br s, 1H), 7.66–7.63 (m, 2H), 7.49 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.92 (dd, *J* = 7.5, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 153.4, 150.1, 145.7, 141.2, 140.2, 137.0, 130.8, 128.5, 128.2, 126.2, 123.1, 121.2, 116.0, 113.0. Mp. 241.5–242.0 °C. TLC: R_f 0.34 (hexane/EtOAc = 1.5:1). IR (KBr): 3022, 1611, 1568, 1509, 1458, 1340, 1300, 1225, 1178, 877, 837, 799, 623 cm^{-1}. HRMS Calcd for $C_{15}H_{11}BrNO$: $[M+H]^+$, 300.0019. Found: *m*/*z* 300.0012.

^{1}H NMR study on multipoint interaction between deautirated substrate and catalyst

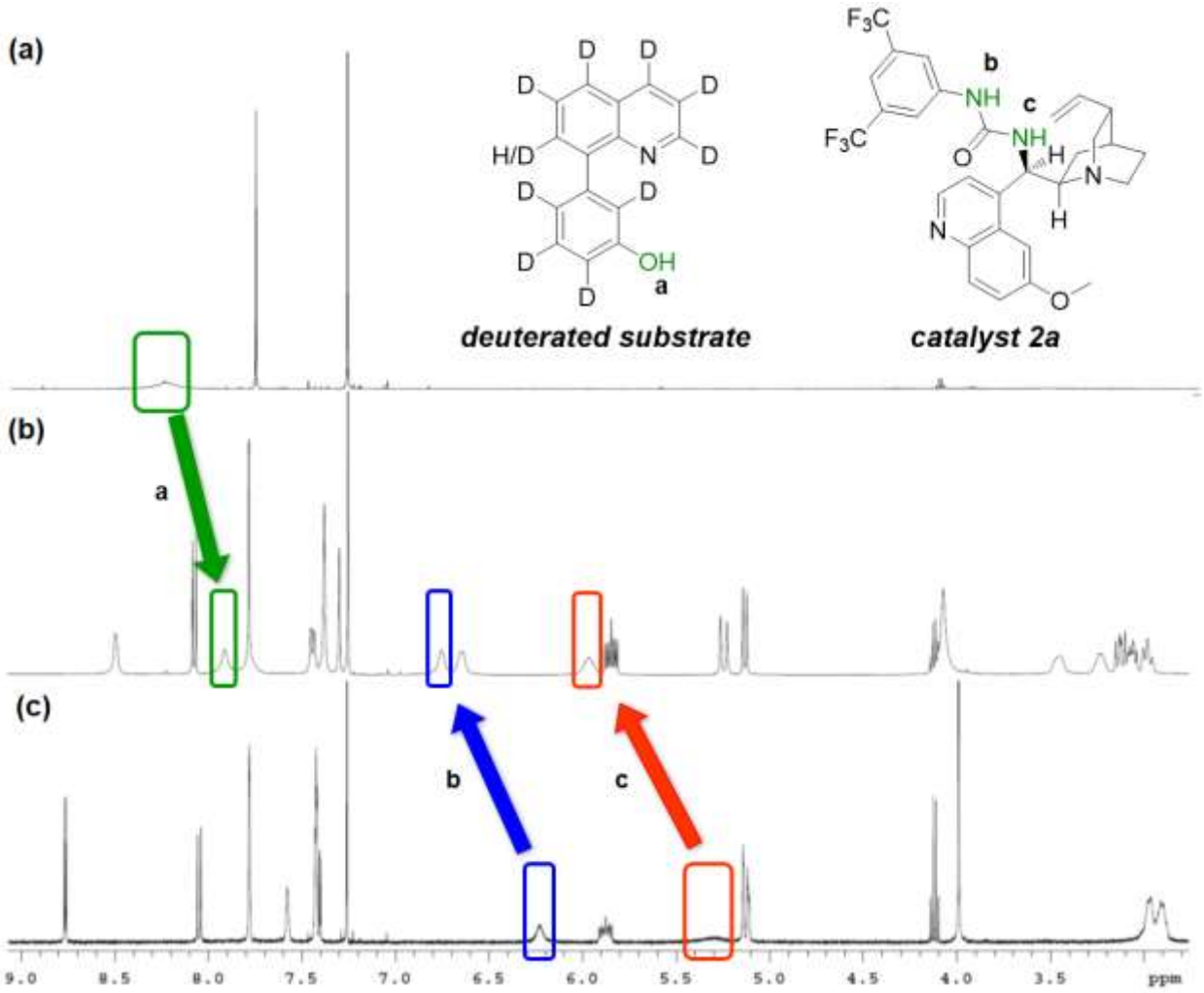
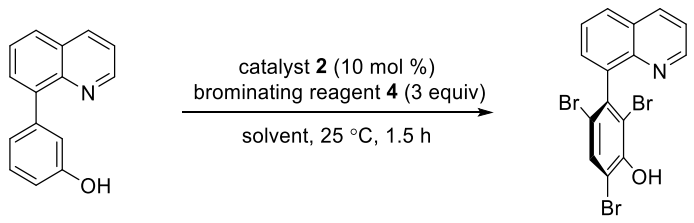


Figure 1. ^{1}H NMR spectra for (a) deuterated substrate, (b) mixture of deuterated substrate and **2a**, and (c) **2a** in $CDCl_3$.

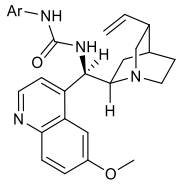
Table S1. Optimization of reaction conditions for enantioselective bromination.[a]



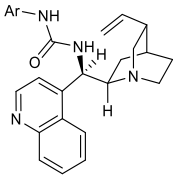
entry	catalyst	brominating reagent	solvent	yield (%)[b]	*ee* (%)
1	**2a**	NBA (**4a**)	THF	96	57
2	**2a**	NBA (**4a**)	toluene	99	14
3	**2a**	NBA (**4a**)	CH_3CN	99	68
4	**2a**	NBA (**4a**)	CHCl3	95	73
5	**2a**	NBA (**4a**)	1,2-dichloroethane	99	84
6	**2a**	NBA (**4a**)	CH_2Cl_2	99	90
7	**2a**	NBA (**4a**)	CH_2Cl_2	99	89
8[c]	**2a**	NBA (**4a**)	CH_2Cl_2	99	90
9[d]	**2a**	DBH (**4b**)	CH_2Cl_2	97	83
10	**2a**	NBS (**4c**)	CH_2Cl_2	99	78
11	**2a**	NBP (**4d**)	CH_2Cl_2	98	82
12	**2b**	NBA **(4a)**	CH_2Cl_2	99	78
13	**2c**	NBA **(4a)**	CH_2Cl_2	96	–82
14	**2d**	NBA **(4a)**	CH_2Cl_2	99	–86
15	**2e**	NBA **(4a)**	CH_2Cl_2	99	–86
16	**2f**	NBA **(4a)**	CH_2Cl_2	88	<1
17	**2g**	NBA **(4a)**	CH_2Cl_2	88	68
18	**2h**	NBA **(4a)**	CH_2Cl_2	82	5
19	**2i**	NBA **(4a)**	CH_2Cl_2	99	73
20	**2j**	NBA **(4a)**	CH_2Cl_2	93	2

[a] Reactions were run using **1a** (0.1 mmol), **2** (0.01 mmol), and **4** (0.3 mmol) in the solvent (10 mL). [b] Isolated yields. [c] 5 mL of solvent was used. [d] Ar = 3,5-$(CF_3)_2C_6H_3$.

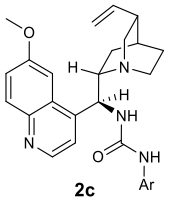
Table S1. (continued)



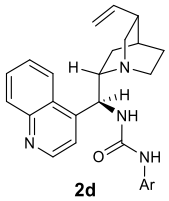
2a



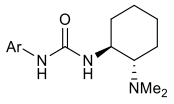
2b



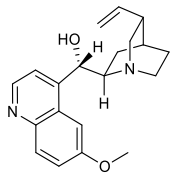
2c



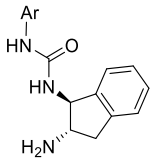
2d



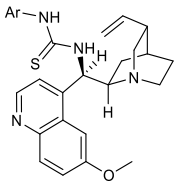
2e



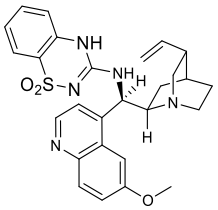
2f



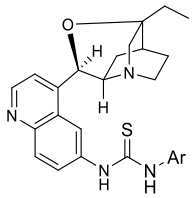
2g



2h

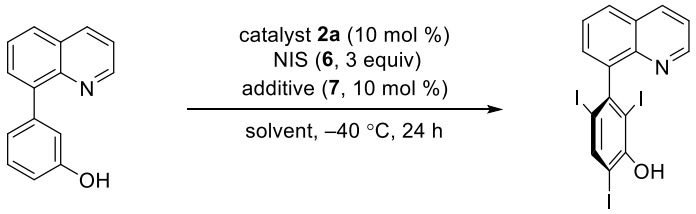


2i



2j

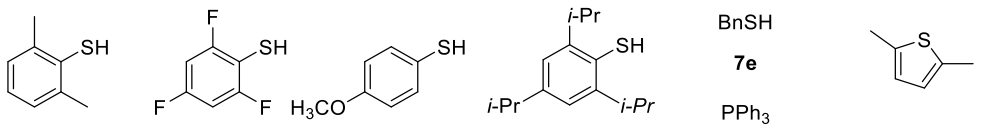
Table S2. Optimization of reaction conditions for enantioselective iodination.[a]



1a **5**

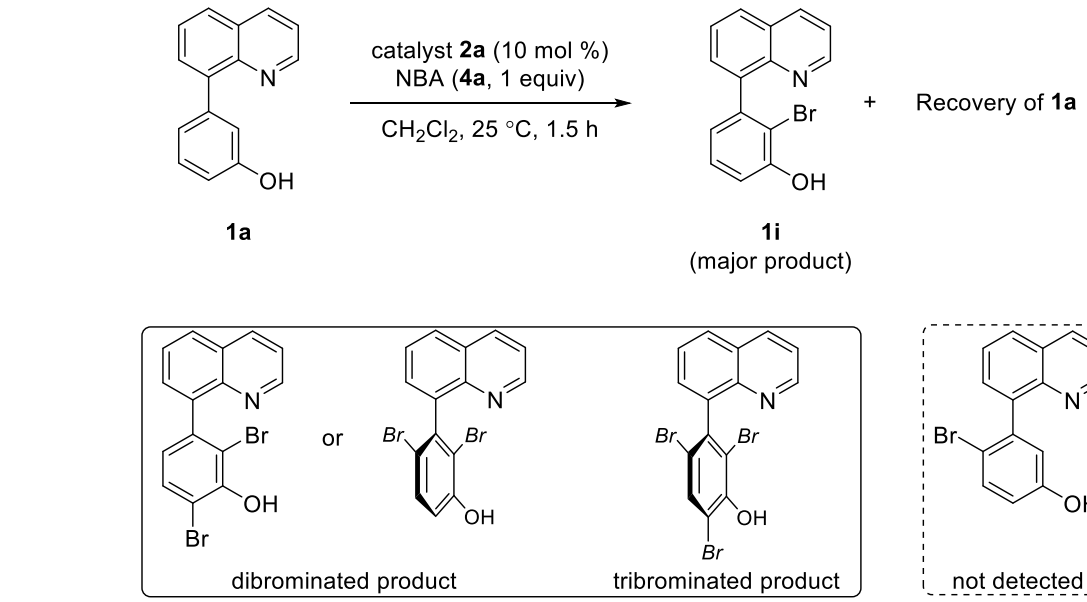
entry	solvent	additive (mol %)	yield (%)[b]	ee (%)
1	EtOAc	none	65	84
2	EtOAc	**7a** (10 mol %)	56	89
3	EtOAc	**7b** (10 mol %)	20	8
4	EtOAc	**7c** (10 mol %)	74	84
5	EtOAc	**7d** (10 mol %)	17	78
6	EtOAc	**7e** (10 mol %)	55	87
7	EtOAc	**7f** (10 mol %)	67	77
8	EtOAc	**7g** (10 mol %)	<1	—
9	THF	**7a** (10 mol %)	10	34
10	CH_2Cl_2	**7a** (10 mol %)	45	86
11	toluene	**7a** (10 mol %)	43	83
12	cyclohexane	**7a** (10 mol %)	63	80
13	EtOAc	**7a** (5 mol %)	51	90
14[c]	EtOAc	**7a** (5 mol %)	52	91
15[d]	EtOAc	**7a** (5 mol %)	52	84

[a]Reactions were run using **1a** (0.1 mmol), **2** (0.01 mmol), and **6** (0.3 mmol) in the solvent (10 mL). [b]Isolated yields. [c]5 mL of solvent was used. [d]3 mL of solvent was used.



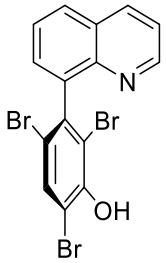
7a **7b** **7c** **7d** **7e** **7f** **7g**

Scheme S1. Reaction with 1 equiv of **4a**.



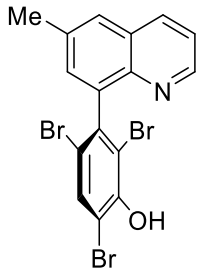
Characterization Data of Products

2,4,6-Tribromo-3-(quinolin-8-yl)phenol (3a).



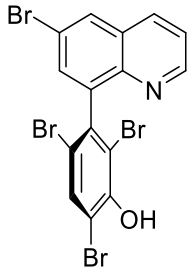
Yield: 99%, 90% *ee*, white solid. $[\alpha]_D^{18}$ –23.3 (*c* 0.22, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.95 (dd, *J* = 4.5, 2.0 Hz, 1H), 8.26 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.84 (s, 1H), 7.66 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.53 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.46 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 150.6, 149.7, 145.1, 141.3, 139.6, 136.7, 134.7, 130.8, 128.9, 128.5, 126.3, 121.5, 115.1, 113.9, 110.1. Mp. 219.0–220.0 °C. TLC: R_f 0.36 (hexane/EtOAc = 2:1). IR (KBr): 3066, 1596, 1510, 1439, 1381, 1315, 1287, 1263, 1207, 1137, 1065, 913, 859, 833, 792, 952 cm^{-1}. HRMS Calcd for $C_{15}H_8Br_3NO$: $[M+H]^+$, 457.8208. Found: *m*/*z* 457.8203. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 2.8 min, t_{minor} = 5.5 min.

2,4,6-Tribromo-3-(6-methylquinolin-8-yl)phenol (3b).



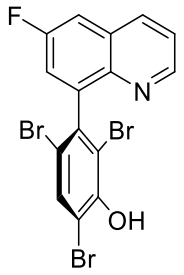
Yield: 99%, 88% *ee*, white solid. $[\alpha]_D^{18}$ –14.5 (*c* 2.89, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.89 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (s, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 149.9, 149.6, 143.5, 141.2, 139.3, 136.25, 136.18, 134.7, 133.0, 128.6, 127.7, 121.4, 115.0, 114.1, 110.3, 21.6. Mp. 235.0–236.0 °C. TLC: R_f 0.38 (hexane/EtOAc = 2:1). IR (KBr): 3045, 1730, 1583, 1555, 1502, 1450, 1393, 1355, 1323, 1195, 1162, 1127, 1039, 898, 867, 782 cm^{-1}. HRMS Calcd for $C_{16}H_{11}Br_3NO$: $[M+H]^+$, 471.8365. Found: *m*/*z* 471.8358. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.5 min, t_{minor} = 17.3 min.

(*R*)-2,4,6-Tribromo-3-(6-bromoquinolin-8-yl)phenol (3c).



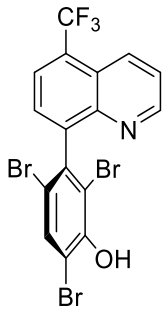
Yield: 99%, 76% *ee* (59%, 88% *ee* (after recrystallization with *i*-PrOH/hexane/EtOH)), white solid. $[\alpha]_D^{18}$ –33.9 (*c* 1.71, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.93 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 7.84 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.9, 143.9, 141.3, 139.9, 135.7, 135.4, 134.7, 133.8, 130.8, 129.6, 122.3, 119.8, 114.8, 113.5, 110.5. Mp. 234.0–234.5 °C. TLC: R_f 0.30 (hexane/EtOAc = 1.5:1). IR (KBr): 3030, 1582, 1499, 1443, 1389, 1355, 1316, 1288, 1133, 1088, 1033, 868, 787, 756, 668 cm^{-1}. HRMS Calcd for $C_{15}H_7Br_4NO$: $[M+H]^+$, 537.7293. Found: *m*/*z* 537.7276. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.2 min, t_{minor} = 14.6 min.

2,4,6-Tribromo-3-(6-fluoroquinolin-8-yl)phenol (3d).



Yield: 99%, 79% *ee*, white solid. $[\alpha]_D^{18}$ –26.9 (*c* 1.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.89 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.20 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.85 (s, 1H), 7.56 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.47 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.34 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.90 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 160.6, 158.6, 149.9 (d, *J* = 2.4 Hz, 1H), 149.5, 142.5, 142.0 (d, *J* = 9.6 Hz), 140.2, 136.0 (d, *J* = 5.8 Hz), 134.7, 129.2 (d, *J* = 10.0 Hz), 122.2, 120.9 (d, *J* = 26.5 Hz), 113.8 (d, *J* = 178.0 Hz), 111.8 (d, *J* = 21.0 Hz), 110.3. ^{19}F NMR ($CDCl_3$) δ –60.1. Mp. 237.5–238.5 °C. TLC: R_f 0.51 (hexane/EtOAc = 1:1). IR (KBr): 3062, 1735, 1619, 1586, 1502, 1451, 1417, 1394, 1358, 1332, 1251, 1200, 1126, 981, 909, 864 cm^{-1}. HRMS Calcd for $C_{15}H_7Br_3FNO$: $[M+H]^+$, 475.8114. Found: *m*/*z* 475.8105. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.0 min, t_{minor} = 11.1 min.

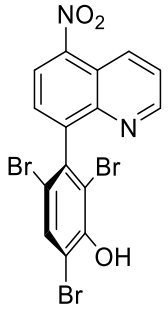
2,4,6-Tribromo-3-(5-trifluoromethylquinolin-8-yl)phenol (3e).



Yield: 98%, 65% *ee* (51% 98% *ee* (after recrystallization with *i*-PrOH/hexane/EtOH)), white solid. $[\alpha]_D^{18}$ –19.8 (*c* 1.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.98 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.58 (ddd, *J* = 9.0, 2.0, 1.5 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.85 (s, 1H), 7.59 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.58 (dd, *J* = 9.0, 4.5 Hz, 1H), 6.39 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 1551.2, 149.3, 145.6, 144.1, 140.7, 134.6, 132.8, 129.0, 127.2 (d, *J* = 6.6 Hz), 125.9 (q, *J* = 271.5 Hz), 124.95 (d, *J* = 6.3 Hz), 124.83

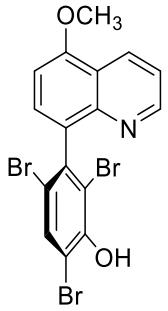
(d, J = 5.6 Hz), 124.7, 114.4, 112.8, 110.0. ^{19}F NMR ($CDCl_3$) δ –31.3. Mp. 227.0–228.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 2:1). IR (KBr): 3091, 1655, 1594, 1539, 1520, 1439, 1322, 1272, 1207, 1185, 1141, 1034, 958, 856, 793, 741, 693 cm^{-1}. HRMS Calcd for $C_{16}H_8Br_3F_3NO$: $[M+H]^-$, 523.7937. Found: m/z 523.7931. HPLC (Daicel Chiralpak IC-H, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 2.4 min, t_{minor} = 7.4 min.

2,4,6-Tribromo-3-(5-nitroquinolin-8-yl)phenol (3f).



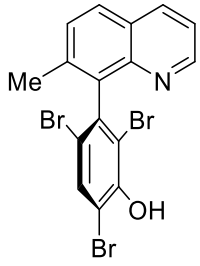
Yield: 99%, 61% *ee*, yellow solid. $[\alpha]_D^{18}$ –71.4 (*c* 0.42, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 9.07 (ddd, J = 8.5, 2.0, 1.5 Hz, 1H), 9.00 (dd, J = 4.0, 1.5 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.69 (ddd, J = 8.5, 4.0, 2.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 6.36 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 151.7, 149.4, 146.2, 145.7, 140.1, 134.7, 132.2, 128.90, 128.86, 124.3, 124.2, 121.5, 114.1, 112.4, 110.3. Mp. 246.0–247.0 °C. TLC: R_f 0.36 (hexane/EtOAc = 1.5:1). IR (KBr): 3082, 1596, 1506, 1438, 1342, 1305, 1278, 1204, 1185, 1053, 1034, 886, 796, 746, 692 cm^{-1}. HRMS Calcd for $C_{15}H_6Br_3N_2O_3$: $[M–H]^-$, 500.7914. Found: m/z 500.7913. HPLC (Daicel Chiralpak IC-H, hexane/i-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 4.5 min, t_{minor} = 11.5 min.

2,4,6-Tribromo-3-(5-methoxyquinolin-8-yl)phenol (3g).



Yield: 97%, 81% *ee*, white solid. $[\alpha]_D^{18}$ –16.7 (*c* 0.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.90 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.65 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.84 (s, 1H), 7.421 (d, *J* = 8.0 Hz, 1H), 7.417 (dd, *J* = 8.5, 4.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.55 (br s, 1H), 4.08 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 155.6, 150.8, 149.5, 145.8, 141.5, 134.6, 131.9, 131.3, 130.6, 120.8, 120.5, 115.8, 114.5, 109.7, 103.8, 55.8. Mp. 239.0–239.5 °C. TLC: R_f 0.40 (hexane/EtOAc = 1.5:1). IR (KBr): 3030, 1591, 1510, 1461, 1441, 1399, 1391, 1366, 1286, 1222, 1200, 1159, 1092, 824, 785, 754 cm^{-1}. HRMS Calcd for $C_{16}H_{11}Br_3NO_2$: $[M+H]^+$, 487.8314. Found: *m*/*z* 487.8299. HPLC (Daicel Chiralpak IE-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.7 min, t_{minor} =4.2 min.

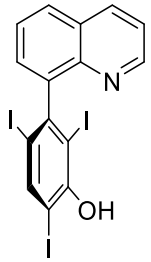
2,4,6-Tribromo-3-(7-methylquinolin-8-yl)phenol (3h).



Yield: 57%, 70% *ee*, white solid. $[\alpha]_D^{18}$ –60.8 (*c* 0.78, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.27 (s, 1H), 8.15 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.41 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 6.51 (br s, 1H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.1, 149.5, 146.2, 139.5, 139.3, 138.4, 136.9, 129.6, 129.5, 126.7, 126.6, 120.5, 120.2, 117.4, 115.3, 15.3. Mp. 231.0–232.0 °C. TLC: R_f 0.35 (hexane/EtOAc = 2:1). IR (KBr): 3030, 1617, 1598, 1499, 1437, 1388, 1347, 1314, 1236, 1193, 1170, 1134, 1034, 905, 865, 790, 718 cm^{-1}. HRMS Calcd for $C_{16}H_{11}Br_3NO$: $[M+H]^+$, 471.8365. Found: *m*/*z* 471.8350. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.2 min, t_{minor} = 6.1 min.

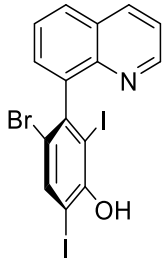
Characterization Data of Product 5 and 8

2,4,6-Triiodo-3-(quinolin-8-yl)phenol (5).



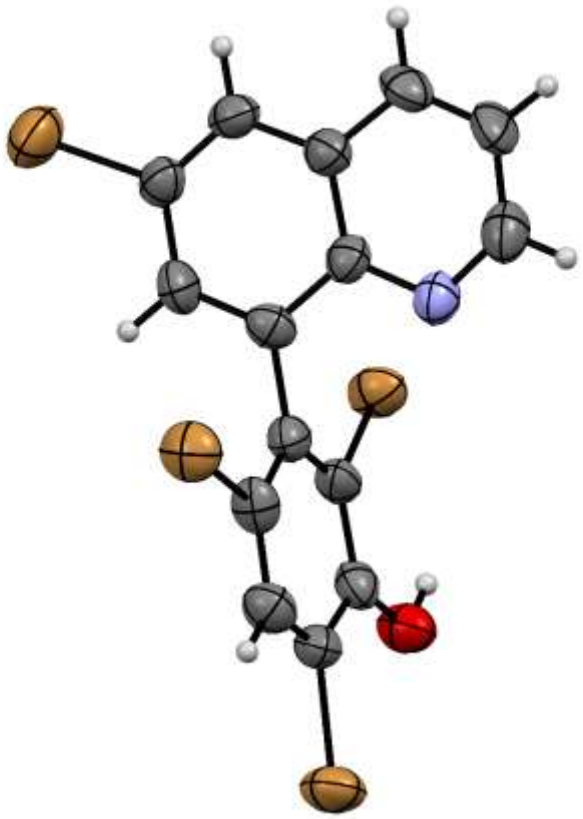
Yield: 52%, 91% *ee*, white solid. $[\alpha]_D^{18}$ –45.2 (*c* 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.95 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.28 (s, 1H), 8.25 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.46 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.38 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 154.5, 150.7, 147.0, 146.5, 144.7, 136.6, 130.5, 128.9, 128.5, 126.3, 121.5, 109.9, 89.6, 88.1, 82.2. Mp. 224.0–225.0 °C. TLC: R_f 0.40 (hexane/EtOAc = 2:1). IR (KBr): 3037, 1602, 1496, 1462, 1425, 1391, 1358, 1309, 1278, 1255, 1109, 1063, 863, 830, 791, 720, 628 cm^{-1}. HRMS Calcd for $C_{15}H_9I_3NO$: $[M+H]^+$, 599.7813. Found: *m*/*z* 599.7801. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.5 min, t_{minor} = 8.6 min.

4-Bromo-2,6-diiodo-3-(quinoline-8-yl)phenol (8).



Yield: 51%, 88% *ee*, white solid. $[\alpha]_D^{18}$ –34.7 (*c* 0.90, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.92 (dd, *J* = 4.5, 2.0 Hz, 1H), 8.24 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.06 (s, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.66 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.48 (dd, *J* = 7.0, 1.5 Hz ,1H), 7.45 (dd, *J* = 8.0, 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 153.4, 150.8, 146.4, 145.2, 143.3, 141.2, 136.3, 130.3, 128.9, 128.5, 126.2, 121.5, 114.1, 90.6, 81.1. Mp. 250.0–251.0 °C. TLC: R_f 0.38 (hexane/EtOAc = 2:1). IR (KBr): 3037, 1712, 1568, 1505, 1450, 1384, 1333, 1300, 1226, 1176, 1130, 1039, 905, 877, 837, 802, 766, 691, 623 cm^{-1}. HRMS Calcd for $C_{15}H_7BrI_2NO$: $[M–H]^-$, 549.7806. Found: *m*/*z* 549.7796. HPLC (Daicel Chiralpak IC-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 3.6 min, t_{minor} = 10.3 min.

ORTEP Drawings of 3c



A. Crystal Data

Identification code	**3c**
Empirical Formula	$C_{15}H_7Br_4NO$
Formula Weight	536.84
Crystal Color, Habit	Colorless, Prism
Crystal Dimensions	0.220 × 0.160 × 0.150 mm
Crystal System	Orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 10.077(2) Å
	b = 17.635(2) Å
	c = 8.813(2) Å
	V = 1566.1(4) $Å^3$
Space Group	$P2_12_12$ (#18)

Z value	4
D_{calc}	2.277 g/cm^3
F_{000}	1008.00
μ(MoKα)	103.059 cm^{-1}

B. Intensity Measurements

Diffractometer	XtaLAB mini
Radiation	MoKα (λ = 0.71075 Å)
	Graphite monochromated
Voltage, Current	50 kV, 12 mA
Temperature	20.0 ºC
Detector Aperture	75 mm (diameter)
Data Images	540 exposures
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º
ω Oscillation Range	–60.0–120.0^o
Exposure Rate	24.0 sec./º
Detector Swing Angle	30.00º

Detector Position	50.00 mm
Pixel Size	0.146 mm
$2\theta_{max}$	55.0º
No. of Reflections Measured	Total: 16169
	Unique: 3602 (R_{int} = 0.0978)
	Friedel pairs: 1530
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.087–0.213)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(F_0^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(F_0^2) + (0.0325 \cdot P)^2$
	$+ 0.0000 \cdot P]$
	where $P = (Max(F_0^2,0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	55.0º
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3602
No. Variables	190
Reflection/Parameter Ratio	18.96
Residuals: R1 (I>2.00σ(I))	0.0470
Residuals: R (All reflections)	0.0929
Residuals: wR2 (All reflections)	0.0926
Goodness of Fit Indicator	0.975
Flack Parameter (Friedel pairs = 1530)	0.04(2)
Max Shift/Error in Final Cycle	0.001
Maximum peak in Final Diff. Map	0.42 $e^-/Å^3$
Minimum peak in Final Diff. Map	–0.61 $e^-/Å^3$

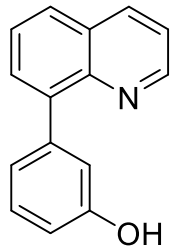
DFT calculations on rotational barrier of compound 1a, 1m, 1o, and 1p.

A. Reference.

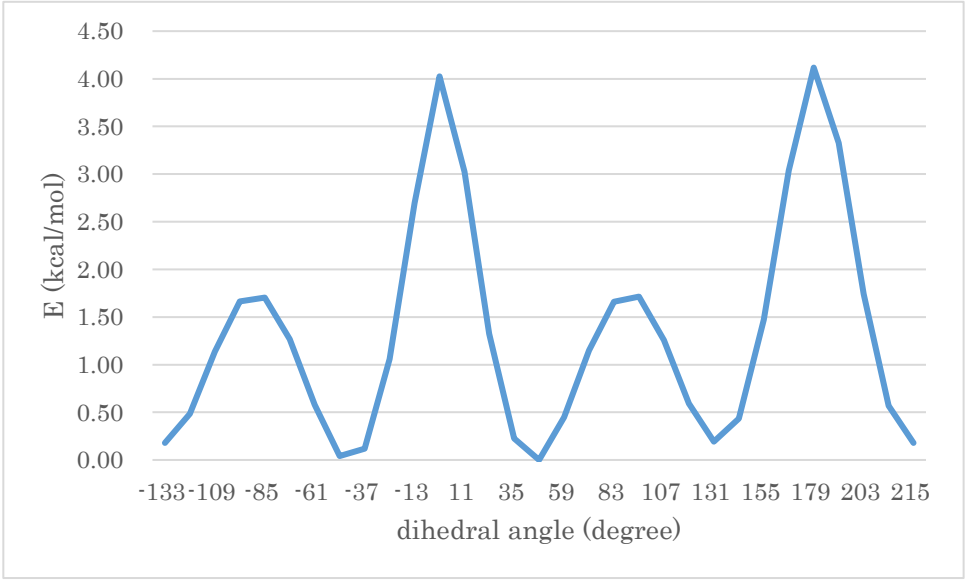
Gaussian 09, Revision B.01,

Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F. ; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian, Inc., Wallingford CT, 2010.

B. Details of imput files of calculations for rotation of **1a**, **1i**, **1j**, and **1k**, including information on their input files.



1a
4.1 kcal/mol



angle (degree)	energy (kcal/mol)	angle (degree)	energy (kcal/mol)
–133.1218735771	–444402.1063131318	58.8781264229	–444401.8367827413
–121.1218735771	–444401.8007787562	70.8781264229	–444401.1350758905
–109.1218735771	–444401.1479536404	82.8781264229	–444400.6253819267
–97.1218735771	–444400.6202708618	94.8781264229	–444400.5712498196
–85.1218735771	–444400.5820310603	106.8781264229	–444401.0265638102
–73.1218735771	–444401.0170708465	118.8781264229	–444401.6925013645
–61.1218735771	–444401.7065337319	130.8781264229	–444402.0936976807
–49.1218735771	–444402.2426414532	142.8781264229	–444401.8526926172
–37.1218735771	–444402.1670711116	154.8781264229	–444400.8138362071
–25.1218735771	–444401.2277659462	166.8781264229	–444399.2480506575
–13.1218735771	–444399.5896417288	178.8781264229	–444398.1678696093
–1.1218735771	–444398.2601530390	190.8781264229	–444398.9591490487
10.8781264229	–444399.2597486895	202.8781264229	–444400.5441928650
22.8781264229	–444400.9597578939	214.8781264229	–444401.7178414531
34.8781264229	–444402.0599031567	214.8781264229	–444402.1063150143
46.8781264229	–444402.2855580829	$\Delta G^{\ddagger}$ =	4.117688473

%nprocshared = 8

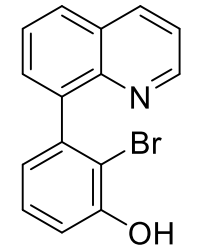
%mem = 30 GB

%chk = substrateSCAN2.chk

#p opt = modredundant b3lyp/6-31g(d) geom = connectivity

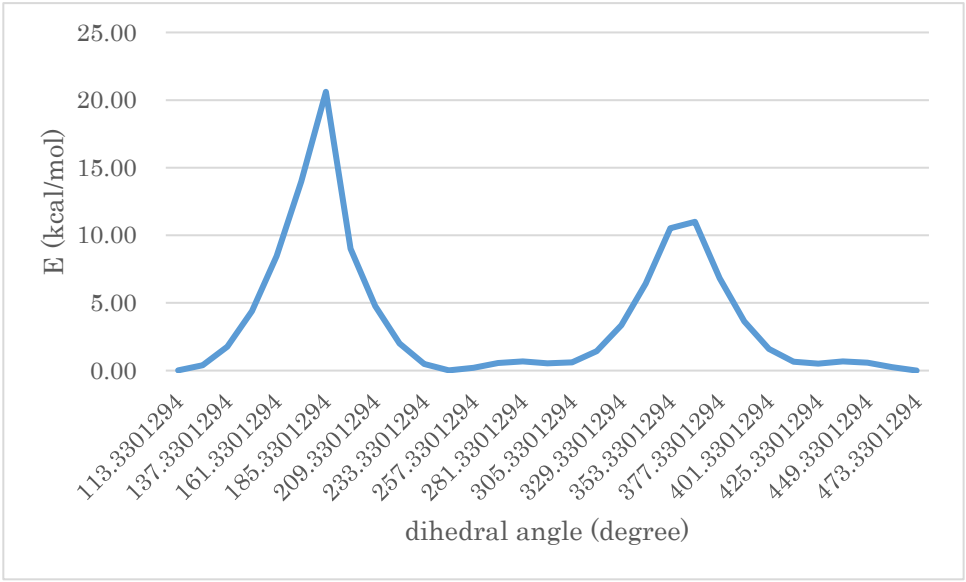
0 1

C	–1.95752300	–1.42760500	0.83929700
C	–3.32562500	–1.19869700	0.96233400
C	–3.92076900	–0.10126600	0.34041800
C	–3.12611900	0.77503500	–0.40526900
C	–1.75247200	0.55597400	–0.52821700
C	–1.15365100	–0.54868400	0.08969400
H	–1.50132400	–2.27295000	1.34524700
H	–3.93729100	–1.87665600	1.55173700
H	–4.99067100	0.07635800	0.43657300
H	–1.16339000	1.25656400	–1.10585500
C	0.29576400	–0.84484200	–0.07628500
C	1.31450700	0.15941500	0.07197500
C	0.69290400	–2.14007500	–0.37494100
C	2.69114900	–0.20650400	–0.10237200
C	2.04992600	–2.49504000	–0.54228000
H	–0.06935000	–2.90234000	–0.50753700
C	1.89238700	2.34377700	0.53215200
C	3.66795800	0.81036000	0.05391800
C	3.03632300	–1.54617500	–0.41287000
H	2.30528400	–3.52305800	–0.78439900
C	3.27575400	2.08860800	0.36856200
H	1.55666100	3.34764800	0.79224300
H	4.71845200	0.55955000	–0.07600400
H	4.08410100	–1.80501400	–0.54619600
H	3.99692500	2.89031900	0.49665200
N	0.95033300	1.43372100	0.39454400
O	–3.64224500	1.87003700	–1.04740100
H	–4.59684900	1.90756200	–0.88175600



1i

11.0 kcal/mol



angle (degree)	energy (kcal/mol)	angle (degree)	energy (kcal/mol)
113.3301	–2057796.23	305.3301	–2057795.63
125.3301	–2057795.85	317.3301	–2057794.80
137.3301	–2057794.47	329.3301	–2057792.88
149.3301	–2057791.83	341.3301	–2057789.80
161.3301	–2057787.77	353.3301	–2057785.72
173.3301	–2057782.27	365.3301	–2057785.23
185.3301	–2057775.63	377.3301	–2057789.41
197.3301	–2057787.23	389.3301	–2057792.60
209.3301	–2057791.47	401.3301	–2057794.64
221.3301	–2057794.24	413.3301	–2057795.58
233.3301	–2057795.75	425.3301	–2057795.72
245.3301	–2057796.23	437.3301	–2057795.57
257.3301	–2057796.04	449.3301	–2057795.66
269.3301	–2057795.67	461.3301	–2057795.99
281.3301	–2057795.56	473.3301	–2057796.24
293.3301	–2057795.71	$\Delta G^{\ddagger}$ =	11.00551889

%nprocshared = 8

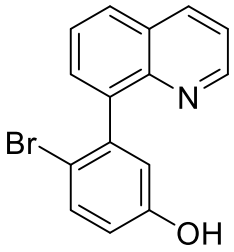
%mem = 30 GB

%chk = MONOBROMINATED_631GD_scan2.chk

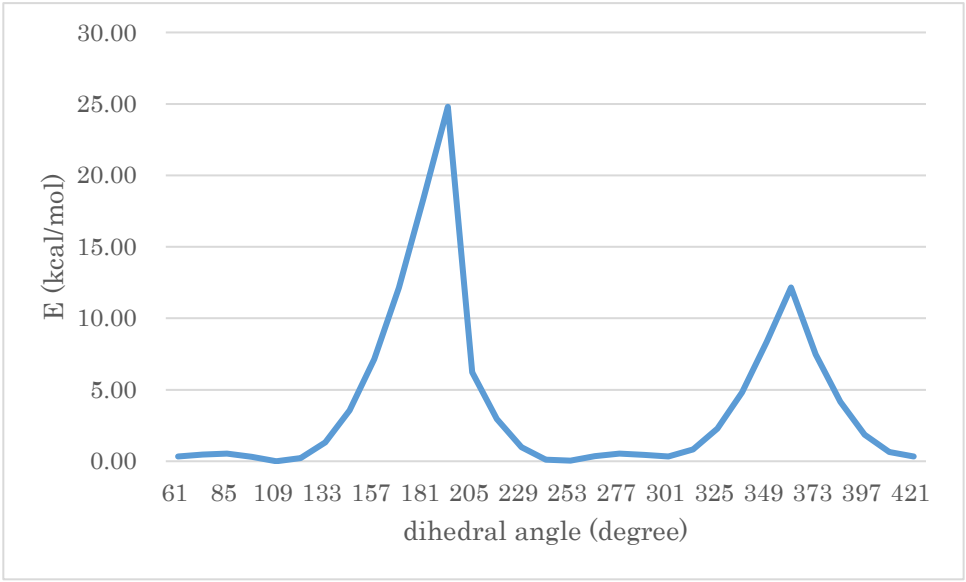
#p opt = modredundant b3lyp/6-31g(d) nosymm geom = connectivity

0 1

C	–2.17462900	–0.73251800	–0.66224900
C	–1.19256000	–1.43125800	0.01639500
C	–0.23196100	–0.70209600	0.79025300
C	–0.30054500	0.72833600	0.82042300
C	–1.31785100	1.40023500	0.09466800
C	–2.23917600	0.68051700	–0.62905300
H	–2.90670600	–1.28518200	–1.24438500
C	0.66714300	1.41390500	1.59907200
H	–1.35802600	2.48660800	0.12483800
H	–3.02108500	1.19141500	–1.18390300
C	1.61421200	0.69586200	2.28822800
C	1.58667400	–0.71828600	2.19787400
H	0.64331800	2.50058200	1.64040500
H	2.36912800	1.18695900	2.89490600
H	2.32560000	–1.30638300	2.74182500
N	0.71134100	–1.39806100	1.48666700
C	–1.18544800	–2.92205800	–0.01744700
C	–0.17935500	–3.66809400	–0.64450500
C	–2.25006500	–3.62342800	0.56599900
C	–0.20531200	–5.07034200	–0.68135700
C	–2.28999800	–5.01801000	0.53571000
H	–3.03676900	–3.06150100	1.05937500
C	–1.27582100	–5.74190800	–0.07921100
H	–3.11919600	–5.54451100	0.99980900
H	–1.28575400	–6.82657300	–0.11394300
Br	1.28209100	–2.80124200	–1.53493000
O	0.75297900	–5.81884200	–1.28273700
H	1.42689200	–5.21561600	–1.64826000



1j
12.2 kcal/mol



angle (degree)	energy (kcal/mol)	angle (degree)	energy (kcal/mol)
61.33846197	–2057792.776	253.338462	–2057793.055
73.33846197	–2057792.633	265.338462	–2057792.748
85.33846197	–2057792.576	277.338462	–2057792.567
97.33846197	–2057792.799	289.338462	–2057792.667
109.338462	–2057793.108	301.338462	–2057792.765
121.338462	–2057792.876	313.338462	–2057792.270
133.338462	–2057791.778	325.338462	–2057790.833
145.338462	–2057789.538	337.338462	–2057788.288
157.338462	–2057785.955	349.338462	–2057784.765
169.338462	–2057780.964	361.338462	–2057780.948
181.338462	–2057774.779	373.338462	–2057785.619
193.338462	–2057768.308	385.338462	–2057788.950
205.338462	–2057786.877	397.338462	–2057791.248
217.338462	–2057790.148	409.338462	–2057792.452
229.338462	–2057792.113	421.338462	–2057792.776
241.338462	–2057792.994	$\Delta G^{\ddagger}$ =	12.15925159

%nprocshared = 8

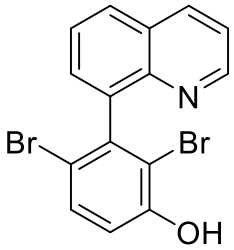
%mem = 30 GB

%chk = 6-monoBrSCAN2.chk

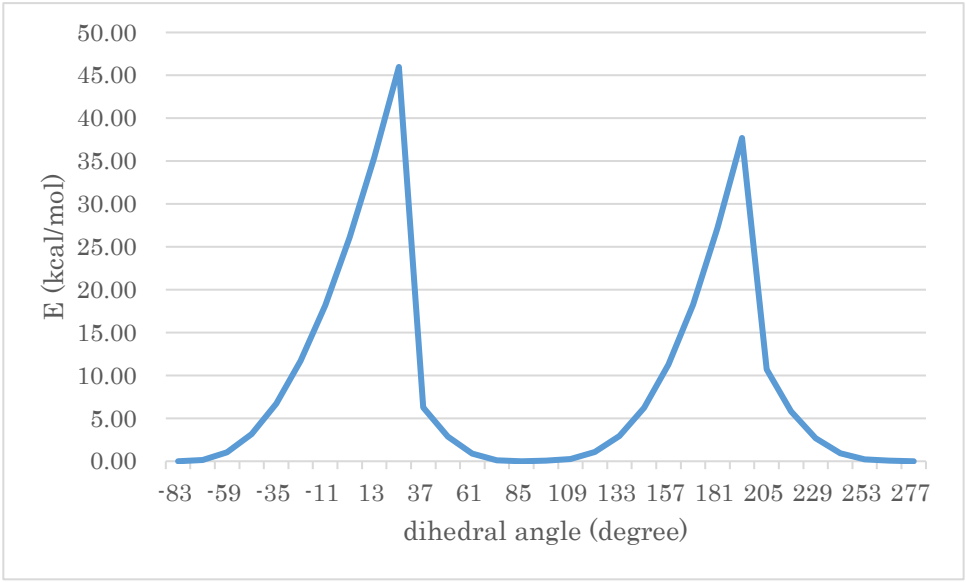
#p opt = modredundant b3lyp/6-31g(d) geom = connectivity

0 1

C	2.31222500	2.28404000	0.51899300
C	3.34862400	1.50530600	–0.00347700
C	3.10307900	0.17801300	–0.34534900
C	1.83591100	–0.37020600	–0.16088100
C	0.78029700	0.39214800	0.36848600
C	1.04574900	1.72693300	0.69850400
H	4.34069200	1.92857500	–0.14802600
H	3.89660300	–0.43316700	–0.76086800
H	0.25490900	2.35063300	1.09883100
C	–0.57741600	–0.16545300	0.63255900
C	–1.73612400	0.37920900	–0.01188000
C	–0.74086900	–1.20138000	1.53580500
C	–3.02707500	–0.16259900	0.29859600
C	–2.01568900	–1.72937400	1.84023500
H	0.13453200	–1.61747300	2.02483600
C	–2.64947800	1.87810400	–1.50205800
C	–4.15033300	0.39738500	–0.36267900
C	–3.14120500	–1.22091400	1.23487500
H	–2.09795900	–2.53910500	2.55979100
C	–3.96845400	1.41827000	–1.26359200
H	–2.48176500	2.68433400	–2.21614000
H	–5.14221800	0.00671600	–0.14647100
H	–4.12666100	–1.62037400	1.46298700
H	–4.80516100	1.86925300	–1.78864600
N	–1.57685100	1.39176900	–0.91275100
Br	1.58121200	–2.19531100	–0.69382900
O	2.47693700	3.59359500	0.87788800
H	3.39162100	3.85845400	0.69503800



1k
37.7 kcal/mol



angle (degree)	energy (kcal/mol)	angle (degree)	energy (kcal/mol)
–83.40421379	–3671187.022	108.5957862	–3671186.750
–71.40421379	–3671186.876	120.5957862	–3671185.957
–59.40421379	–3671185.972	132.5957862	–3671184.092
–47.40421379	–3671183.851	144.5957862	–3671180.784
–35.40421379	–3671180.320	156.5957862	–3671175.740
–23.40421379	–3671175.322	168.5957862	–3671168.771
–11.40421379	–3671168.849	180.5957862	–3671159.867
0.595786211	–3671160.929	192.5957862	–3671149.314
12.59578621	–3671151.610	204.5957862	–3671176.323
24.59578621	–3671141.044	216.5957862	–3671181.185
36.59578621	–3671180.737	228.5957862	–3671184.342
48.59578621	–3671184.139	240.5957862	–3671186.086
60.59578621	–3671186.133	252.5957862	–3671186.802
72.59578621	–3671186.908	264.5957862	–3671186.951
84.59578621	–3671187.017	276.5957862	–3671187.010
96.59578621	–3671186.941	$\Delta G^{\ddagger}$ =	37.70802477

%nprocshared = 8

%mem = 30 GB

%chk = DIBROMINATEDscan2.chk

#p opt = modredundant b3lyp/6-31g(d) nosymm geom = connectivity

0 1

C	–2.06725300	–0.71515900	–0.81446900
C	–1.19021400	–1.41879500	–0.01308100
C	–0.28223200	–0.70640900	0.82991800
C	–0.30352600	0.72500400	0.82183300
C	–1.21862300	1.40801300	–0.01989500
C	–2.08227500	0.69939600	–0.82238900
H	–2.76060100	–1.25940800	–1.44927700
C	0.60982400	1.39604700	1.67467600
H	–1.22601400	2.49547000	–0.01864600
H	–2.78429900	1.22052200	–1.46700200
C	1.46540500	0.66214200	2.46056500
C	1.40499000	–0.75221700	2.38854700
H	0.61924600	2.48349600	1.69442900
H	2.17710600	1.14165800	3.12583700
H	2.07729100	–1.35104400	3.00256000
N	0.57533000	–1.41960700	1.61310900
C	–1.19462300	–2.91059100	–0.01345000
C	–0.28629300	–3.64160700	–0.79041200
C	–2.11824200	–3.64923900	0.73737200
C	–0.27679600	–5.04310600	–0.83110900
C	–2.13475100	–5.04343600	0.71436000
C	–1.21991100	–5.73725000	–0.06616300
H	–2.86295400	–5.58157900	1.31056300
H	–1.21500700	–6.82182000	–0.09719700
Br	1.02055900	–2.72525900	–1.85141000
O	0.59503500	–5.76536100	–1.57588000
H	1.19268800	–5.14645200	–2.03553900
Br	–3.38977600	–2.74650100	1.84317200

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Publication List

1. Parts of present Thesis have been or are to be published in the following journals.

Chapter 1 Asymmetric Syntheses of Chromans via Intramolecular Oxy-Michael Addition Reactions

Ryota Miyaji, Keisuke Asano, and Seijiro Matsubara

Org. Biomol. Chem. **2014***, 12,* 119–122.

(Chapter 1 is the unedited Author's version of a Submitted Work that was subsequently accepted for publication in *Org. Biomol. Chem.*, copyright © the Royal Society of Chemistry after peer review. To access the final edited and published work see the following website:
http://pubs.rsc.org/en/Content/ArticleLanding/2014/OB/C3OB41938J)

Chapter 2 Asymmetric Syntheses of Indolines via Intramolecular Aza-Michael Addition Reactions

Ryota Miyaji, Keisuke Asano, and Seijiro Matsubara

Org. Lett. **2013**, *15*, 3658–3661.

(Chapter 2 is the unedited Author's version of a Submitted Work that was subsequently accepted for publication in *Org. Lett.*, copyright © American Chemical Society after peer review. To access the final edited and published work see the following website:
http://pubs.acs.org/doi/abs/10.1021/ol401538b)

Chapter 3 Enantioselective Syntheses of Axially Chiral Isoquinoline *N*-Oxides by Bifunctional Organocatalysts

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J. Am. Chem. Soc. **2015**, *137*, 6766–6769.

(Chapter 3 is the unedited Author's version of a Submitted Work that was subsequently accepted for publication in *J. Am. Chem. Soc.*, copyright © American Chemical Society after peer review. To access the final edited and published work see the following website:
http://pubs.acs.org/doi/abs/10.1021/ol401538b)

Chapter 4 Asymmetric Synthesis of Axially Chiral Benzamides by Bifunctional Organocatalysts
Ryota Miyaji, Keisuke Asano, and Seijiro Matsubara
To be submitted.

Chapter 5 Asymmetric Syntheses of Axially Chiral Quinolines by Bifunctional Organocatalysts
Ryota Miyaji, Keisuke Asano, and Seijiro Matsubara
To be submitted.

2. Following publication is not included in this Thesis.

Asymmetric Cycloetherifications by Bifunctional Aminothiourea Catalysts: The Importance of Hydrogen Bonding
Yukihiro Fukata, Ryota Miyaji, Takaaki Okamura, Keisuke Asano, and Seijiro Matsubara
Synthesis **2013**, *45*, 1627–1634.

Acknowledgement

The studies described in this thesis have been carried out under the direction of Professor Seijiro Matsubara at the Department of Material Chemistry, Graduate School of Engineering, Kyoto University, during April 2011 to March 2017. Professor Seijiro Matsubara always encouraged the author with a warm and gentle heart. He wishes to express his most grateful acknowledgement to Professor Matsubara for his kind guidance, constant support, and valuable discussions throughout the course of this work.

The author would like to express his gratitude to Professor Jun-ichi Yoshida and Professor Yoshiaki Nakao for their helpful discussions and suggestions. He is also deeply thankful to Professor Keisuke Asano for teaching him the fundamentals of organic chemistry and experimental techniques, and his courteous teaching, helpful discussions, and considerate suggestions. He is much grateful to Professor Takuya Kurahashi for his practical guidance and accurate advice. And he appreciates to Professor Timothy F. Jamison and Professor David Van Vranken for opportunity to study other areas of chemistry in their laboratory, their warm guidance and great discussion.

The author is thankful to Professor Masaki Shimizu, Professor Kazuhiko Semba, and Professor Teruhiko Saito for their generous help. He is grateful to Dr. Keiko Kuwata, and Dr. Karin Nishimura for mass spectrometry measurements.

It is great pleasure to express his appreciation to the members of Professor Matsubara's research group for their active and helpful discussions. He tenders his acknowledgment to Mr. Takaaki Okamura, Dr. Yukihiro Fukata, and Mr. Koichi Yao for their collaboration. He also wishes to express his appreciation to Dr. Hiroaki Horie, Dr. Masahiro Sai, Dr. Kenichiro Nakai, Dr. Tasuku Inami, Mr. Takuya Ozawa, Mr. Ryota Wakabayashi, Mr. Yoshiaki Takada, Mr. Yuji Yoshida, Dr. Ryosuke Haraguchi, Ms. Rihoko Tombe, Mr. Takahiro Shiba, Mr. Yuji Yoshida for their kind support and generous suggestions. He feels grateful to his compeers, Dr. Makoto Hasegawa, Mr. Haruo Katayama, Mr. Makoto Takeuchi, Mr. Takuma Terada, Mr. Satoru Teranishi, Mr. Masahiro Narita, Mr. Terumitsu Murakami, Mr. Satoshi Yamada, Mr. Ryuta Yoshii, Mr. Sei Manabe, Ms. Teodora Coroama, Ms. Kathalina Wenz, and Dr. Ashley Longstreet Ms. Jessica Weber, and Ms. Elizabeth Borah for their friendship.

Financial supports from JSPS, Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists, and from Naito foundation were indispensable, and the author would like to express his gratitude.

Moreover, the author would like to express his sincere appreciation to his parents, Masakazu

Miyaji, Yaeko Miyaji, Takashi Fujita, and Yuko Fujita for their support. Finally, he is always grateful especially to his family, Reo Miyaji and Keita Miyaji for their continuous encouragement.

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