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Carbene-Catalyzed Atroposelective Construction of Chiral Diaryl Ethers

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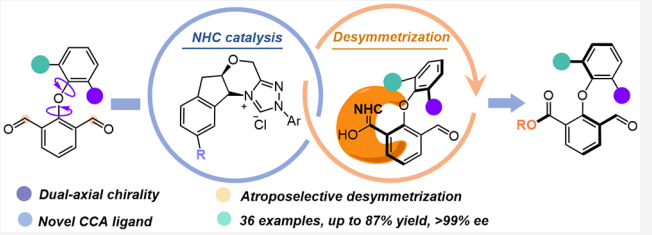
ABSTRACT: Atropoisomeric chemotypes of diaryl ethers-related scaffolds are prevalent in naturally active compounds. Nevertheless, there remains considerable research to be carried out on the catalytic asymmetric synthesis of these axially chiral molecules. In this instance, we disclose an N-heterocyclic carbene (NHC)-catalyzed synthesis of axially chiral diaryl ethers via atroposelective esterification of dialdehyde-containing diaryl ethers. NHC desymmetrization produces axially chiral diaryl ether atropisomers with high yields and enantioselectivities in moderate circumstances. Chiral diaryl ether compounds may be precursors for highly functionalized diaryl ethers with bioactivity and chiral ligands for asymmetric catalysis.



INTRODUCTION

Axially chiral biaryl compounds frequently exist as materials, as biologically active chemicals, and also as chiral ligands or organocatalysts.[1] Due to the importance of this structural motif, catalytic atroposelective biaryl scaffold synthesis has been extensively studied, with recent advances.[2] Although the majority of chemists have knowledge of the atropoisomeric axes about biaryls,[3] benzamides,[4] and anilides,[5] axial chirality in diaryl ethers with related scaffolds is frequently disregarded. Therefore, novel atropisomers have become an increasingly popular area of study. Diaryl ethers and related scaffolds are among the most common structural motifs found in many biologically active products and pharmaceuticals,[1i,6] such as the FDA-approved drugs Lenvatinib and Belzutifan and other Bruton's tyrosine kinase (BTK) inhibitors and protein receptor tyrosine kinase (RTK) inhibitors.[7] The two contiguous atropoisomeric C−O axes in diaryl ethers and related scaffolds are less stable and lack a sufficient rotational barrier to prevent racemization, making axial chirality difficult to develop.

In 1998, Fuji and co-workers reported that 8,8′-disubstituted 1,1′-binaphthyl ether showed atropisomerism.[8] The compound gave the half-life for racemization at 25 °C with up to 8 months ($t_{1/2}$ value) and the free energy of activation for the interconversion of stereoisomers with up to $\Delta G^{\ddagger}$ 126 kJ/mol. Clayden and co-workers have shown diphenyl ethers with both rings unsymmetrically substituted to demonstrate atropisomerism when one of the substituents is as large as a *tert*-butyl group (Scheme 1B).[9] They also found a biocatalytic atroposelective synthesis of axially chiral diaryl ethers from prochiral diols or dialdehydes using oxidase or ketoreductases.[10] However, the complex catalytic system and narrow range of substrates limit their application. More recently, our group reported an asymmetric organocatalytic dynamic kinetic resolution approach via a chiral phosphoric acid-catalyzed atroposelective transfer hydrogenation (ATH) reaction of dicarbaldehydes with anilines (Scheme 1C).[11] Later on, Yang's group developed a chiral phosphoric acid (CPA)-catalyzed electrophilic amination approach to access atropisomeric diaryl ethers, whose products could be facilely derivatized into a variety of structurally novel azaarene containing diaryl ethers atropisomers.[12] Very recently, Yao's group report an atroposelective copper-catalyzed cycloaddition between bisalkynes and azides. With a newly designed indane-fused BOX ligand, a series of C−O axially chiral diaryl ethers were obtained with good yields and excellent enantioselectivities.[13] Therefore, the development of convenient and direct construction of axially chiral diaryl ethers remains unexplored and highly attractive.

N-heterocyclic carbenes (NHCs) catalysis may build complex biological and therapeutic molecular structures.[14] Under oxidative conditions, NHCs can react with aldehydes to form acyl azolium intermediates in which alcohols or phenols could be further trapped to afford carboxylic esters.[15] In recent years, NHCs have been applied in preparing axially chiral compounds.[16] In the confined arena of axially chiral molecule synthesis, NHCs catalysis was previously used by Chi and others to mediate cycloaddition,[17] desymmetrization,[18] or kinetic resolution[19] to construct molecules bearing the chiral axis between two rigid rings. At this time, the groups of Mazzanti and

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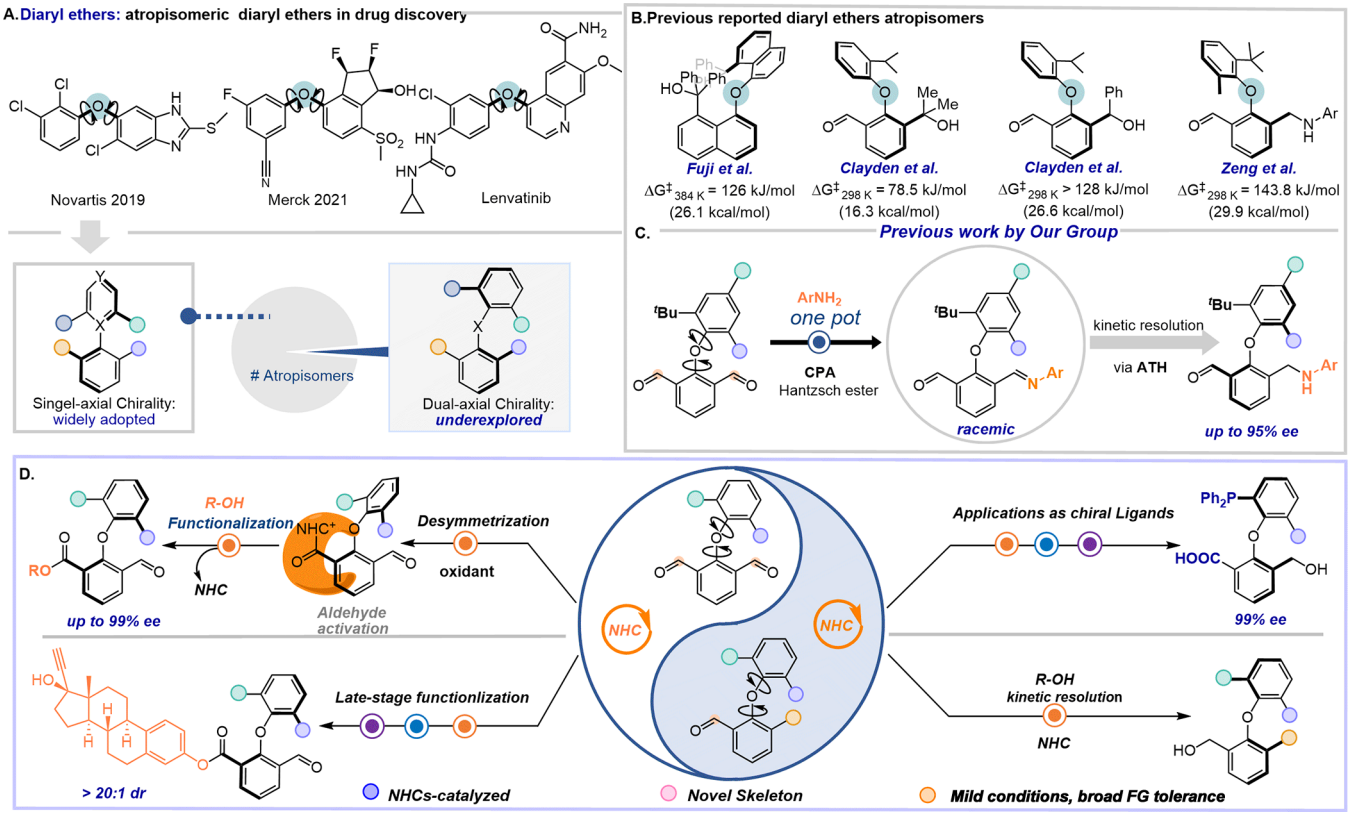
Scheme 1. NHCs-Catalyzed Atroposelective Construction of Axially Chiral Diaryl Ethers[a]



[a](A) Atropoisomeric was rapidly interconverting diaryl ethers in drug discovery. The relative number of atropisomers containing single-axial and dual-axial chirality. (B) Dual-axial chirality in diaryl ether derivatives. (C) One-pot dynamic kinetic resolution approach to axially chiral diaryl ethers by chiral phosphoric acid catalyzed ATH of imines formed in situ from dicarbaldehydes and amines. (D) NHCs are used as the sole organic catalyst for the enantioselective desymmetrization of prochiral diaryl ether dicarbalddehyde. These optical active axially chiral diaryl ethers can serve as chiral building blocks for rapid transformations to functionalized diaryl ethers with potential bioactivity and ligands for asymmetric catalytic reactions.

Mass,[20] Zhang,[16d] and Jin and Chi[21] have sequentially accomplished the formation of carbon-centered, axial, and planar chiralities by the enantioselective discrimination of prochiral dialdehydes using NHC as the catalyst. Mechanistically, the Breslow intermediate is oxidized by an internal or external oxidant to generate the acyl azolium, which then undergoes nucleophilic attack with stereodiscrimination in the oxidative activation of aldehydes mediated by chiral NHCs.

Desymmetrization[22] is an appealing and effective method for creating chiral biaryl scaffolds. It may be simple to obtain value-added, enantiomer-enriched biaryl aldehydes from readily accessible substrates by desymmetrizing axially biaryl dialdehydes. Zhang groups have discovered a straightforward enantioselective production of axially chiral aldehydes with an unprecedented NHCs-catalyzed desymmetrization of readily available dialdehydes in this domain.[16d] The strategy might provide an opportunity for desymmetrization of axially chiral diaryl ethers.

Unlike catalytic enantioselective synthesis of ordinary single-axis atropisomers, atroposelective synthesis of axially chiral ethers with flexible axes is difficult: (1) selecting a catalytic system to control the axial chirality of diaryl ethers since the rotation barrier is much lower than that of biaryl compounds; (2) Selection of acceptable NHCs for matched chiral acyl azole intermediates and steric hindrance to offer sufficient rotation energy to preserve the chiral dual axis; (3) the atroposelective construction of axially chiral diaryl ethers is still very limited. In the realm of enantioselective catalysis,[23] we report herein the NHC-catalyzed synthesis of axially chiral diaryl ethers through atroposelective esterification of prochiral dual-axis dialdehydes with alcohols and phenols via desymmetrization. At the time of submission of this article, four closely related studies by the Biju, Ye, Zhang, and Gao groups focused on NHC-catalyzed atroposelective desymmetrization of prochiral dialdehydes.[24] Although these studies successfully produced a range of axially chiral diaryl ethers with high enantioselectivities, further investigation into the practical applications of these products is warranted.

RESULTS AND DISCUSSION

Using these trends as guiding principles, we conducted an optimization study for esterification. The initial studies were conducted with temperature (Table 1, entries 1−3). Higher enantioselectivity was achieved at 30 °C, yielding 65% of product **3a** and a 13% diester byproduct **4aa** (Table 1, entry 3). The catalytic efficiency and enantioselectivity of the catalysts were reduced by changing the site resistance and scaffold of the NHCs (Table 1, entries 4−10). The electron effect is especially pronounced. After demonstrating the NHCs' effectiveness in our system, we examined the solvent effect. Although the use of polar solvents such as THF, CH_3CN, Et_2O, and DCM in this procedure, none of them gave a better result than toluene (Table

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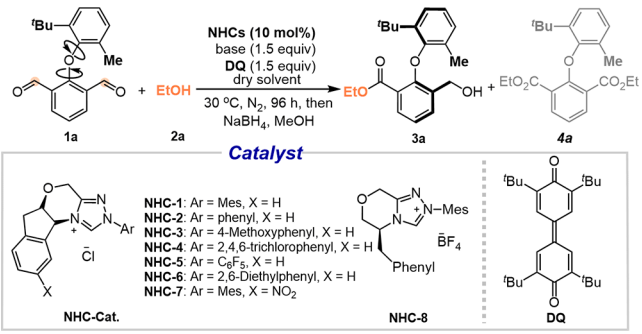
Table 1. Optimization of the Reaction Conditions[a]



entry	NHCs	solvent	base	3a yield[b] (%)	*ee*[c] (%)	4a yield[b] (%)
1[d]	NHCs-1	toluene	Cs_2CO_3	60	61	15
2[e]	**NHCs-1**	toluene	Cs_2CO_3	62	69	12
3	**NHCs-1**	toluene	Cs_2CO_3	65	98	13
4	**NHCs-2**	toluene	Cs_2CO_3	58	77	7
5	**NHCs-3**	toluene	Cs_2CO_3	51	89	6
6	**NHCs-4**	toluene	Cs_2CO_3	N.D.		
7	**NHCs-5**	toluene	Cs_2CO_3	trace		
8	**NHCs-6**	toluene	Cs_2CO_3	61	85	10
9	**NHCs-7**	toluene	Cs_2CO_3	N.D.		
10	**NHCs-8**	toluene	Cs_2CO_3	68	15	8
11	**NHCs-1**	THF	Cs_2CO_3	65	81	9
12	**NHCs-1**	DCM	Cs_2CO_3	52	82	5
13	**NHCs-1**	Et_2O	Cs_2CO_3	51	87	9
14	**NHCs-1**	MeCN	Cs_2CO_3	40	77	6
15	**NHCs-1**	toluene	DBU	trace	N.D.	
16	**NHCs-1**	toluene	TEA	trace	N.D.	
17[f]	**NHCs-1**	toluene	Cs_2CO_3	60	75	6
18[g]	**NHCs-1**	toluene	Cs_2CO_3	62	84	7

[a]Conditions: **1a** (0.2 mmol), **2a** (10.0 equiv), NHCs (10 mol %), base (1.5 equiv) and DQ (1.5 equiv), solvent (2.0 mL), 30 °C, N_2 atmosphere, 96 h. [b]Yields of an isolated product. [c]Determined by chiral HPLC using a Chiralpak AD-H column. [d]65 °C, 24 h. [e]55 °C, 36 h. [f]**2a** (5.0 equiv). [g]**2a** (10.0 equiv).

1, entries 10−13 and 16). Strong organic bases such as DBU and TEA were shown to be incompatible that, in these cases, thin layer chromatography (TLC) only detected a trace amount of **3a** (Table 1, entries 14−15). Lowering the amount of **2a** (Table 1, entries 17 and 18) further decreased *ee*. Consequently, this condition was determined as a standard condition for the esterification of axially diaryl ethers (Conditions a).

Next, we investigated the scope of the reaction (Scheme 2). Initially, the reaction's dicarbaldehydes were evaluated. Excellent enantioselectivities (**3aa**−**3ad**, 94−96% *ee*'s) might be obtained by dicarbaldehydes with electron-donating (Me, *t*-Bu) or electron-withdrawing (Cl, Br) groups on the aromatic ring. In addition, the aryl substitution at the 4-position of the aryl ring of diaryl ether was tolerated, and the target axially chiral products were formed with high yields and selectivities (**3ag**−**3ai**). The *ee* value dropped to 77% when the methyl group of dicarbaldehydes was replaced with chloro (**3ak**). More rigid axially prochiral substrates may produce esterification products with excellent enantioselective control (**3ae, 3af, 3al**). After substituting an ethyl group for the methyl group at the phenol moiety, the substituted product **3aj** was similarly produced with high enantioselectivity (86% *ee*).

The scope of the alcohol was further investigated by coupling with dicarbaldehyde **1a**. Comparably excellent efficiency and enantioselectivities were attained for several alcohols (**3ba**−**3bk**). Primary alcohols and alkyl alcohols substituted with functional (**3ba**−**3bg**) groups, small carbon rings (**3bh**), TMS (**3bk**), benzyl (**3bm**), alkynyl (**3bj**), and terminal (**3bp**) alkenyl groups showed complete compatibility, suggesting a wide range of functional group tolerance. Additionally, phenol (**3bl**) was shown to be appropriate for high chiral induction (92% *ee*). In addition, heteroaromatic benzyl alcohols (**3bn, 3bo**) showed good tolerance to the reaction conditions. With good yields (87, 82%) and excellent enantioselectivity (99% *ee*) to obtain the products. Prochiral acyclic 1,3-diols (**3bq, 3br, 3bs**) and glycerol (**3bt**) were also suitable substrates for the reaction to provide an enantioenriched product. This strategy achieves double desymmetrization of prechiral compounds while constructing quaternary carbon centers and axial chiral. Late-stage functionalization of natural products and biologically active compounds was feasible with this enantioselective esterification. Natural products include geraniol (**3bu**) and piperonyl alcohol (**3bw**); drugs such as paroxypropione (**3bx**) and ethynylestradiol (**3bv**) were able to produce the product in good yields with high to outstanding enantioselectivity (84−95% *ee*/*de*) and be well tolerated in this coupling.

A 3-mmol scaled asymmtric one-step condensation synthesis of **1a** and **2a** afforded **3a** in 67% yield and 95% *ee*, demonstrating the synthetic usefulness of axially chiral diaryl ethers. The product's configurational stability was investigated by heating a solution of **3a** in toluene at up to 150 °C for 24 h. Deteriorations of stereochemical integrity were negligible even under the conditions where the substrate began to decompose. To explore the utility of this catalytic strategy, we prepared a few racemic monoesters **4a** and subjected them to the kinetic resolution conditions, after optimizing the **4a** to **2a** equivalent ratio in the reaction, the type of NHCs catalyst, solvent, and solvent volume, and the equivalent of oxidant DQ (Scheme 3b, Table S2), product **5a** could be obtained with moderate enantioselectivity. Subsequently, we will continue to explore the application value of this new scaffold, including further derivatization of the dynamic splitting products. While synthesizing the axially chiral diaryl ether derivatives atroposelectively, we derivatized them to demonstrate their synthetic usefulness (Scheme 3). More significantly, **3a** may be hydrolyzed to produce axial chiral carboxylic acid, which has special qualities for enantioselective catalysis and almost no enantiopurity degradation. A single-step method for the conversion of esters **3a** to ketones **7** in 85% yield and 94% *ee*.[25]

To investigate the key steps controlling the stereoselectivity of the reaction, we conducted two control experiments (Scheme 4). First, when **1a** and **2o** reacted under the optimal reaction conditions with a reduced equivalent of **DQ** to 0.6 equiv, the desired product **3o** was obtained in 54% yield and with 94% *ee*, without observing the bis-esterification product **4o**. The excellent enantiomeric selectivity of **3o** indicates that desymmetrization (k_R:k_S = 32:1) plays a crucial role in controlling the stereoselectivity of the reaction. Furthermore, under the optimal conditions with an equivalent of **DQ** at 0.6, the racemic **3o** underwent a kinetic resolution to yield the chiral product **3o** in 35% yield and with 98% *ee*, along with the bis-esterification byproduct **4o** in 52% yield, with a splitting factor of s = 14 for this kinetic resolution. It can be reasonably assumed that **3o** is retained in the esterification reaction, while ent-**3o** is entirely converted into the bis-esterification byproduct **4o**. Control experiments indicate that the enantiomeric selectivity only arises from desymmetrization, ruling out the possibility of

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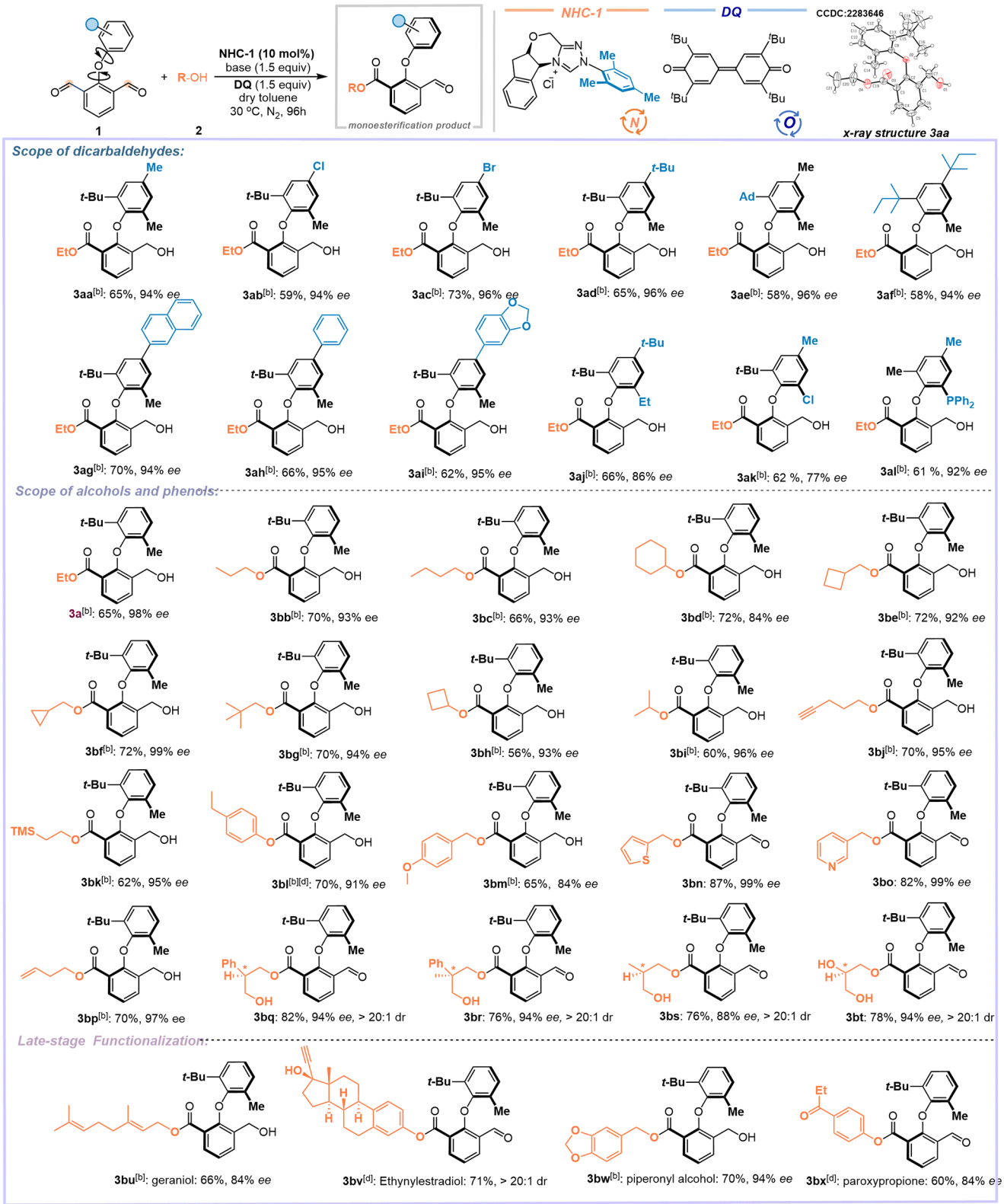
Scheme 2. Substrate Scope for Desymmetrization Esterification of Axially Prechiral Dialdehydes[a,c]



[a]Reaction conditions: **1** (0.1 mmol), **2** (2 mmol), NHC-1 (10 mol %), DQ (1.5 equiv), Cs_2CO_3 (1.5 equiv), and dry toluene (1.0 mL) at 30 °C under a N_2 atmosphere for 96 h. [b]Aldehyde is reduced to produce alcohol by $NaBH_4$. [c]Yield of an isolated product, *ee* was determined by a chiral stationary phase HPLC analysis. [d]Reactions were carried out with **2** (1.0 mmol) at 0 °C, 12h. [e]The dr was determined by ^1H NMR spectroscopic analysis.

synergistic desymmetrization and downstream kinetic resolution.

To create new axially chiral ligands/catalysts, alcohol **3al** was selectively derivatized and hydrolyzed to provide product **9**

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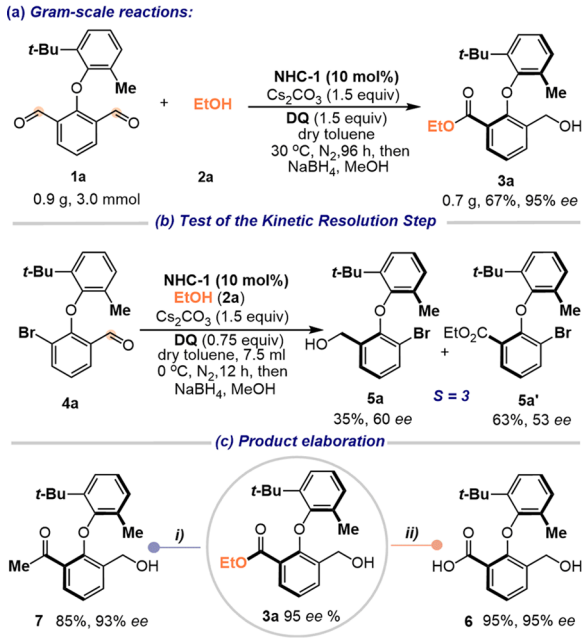
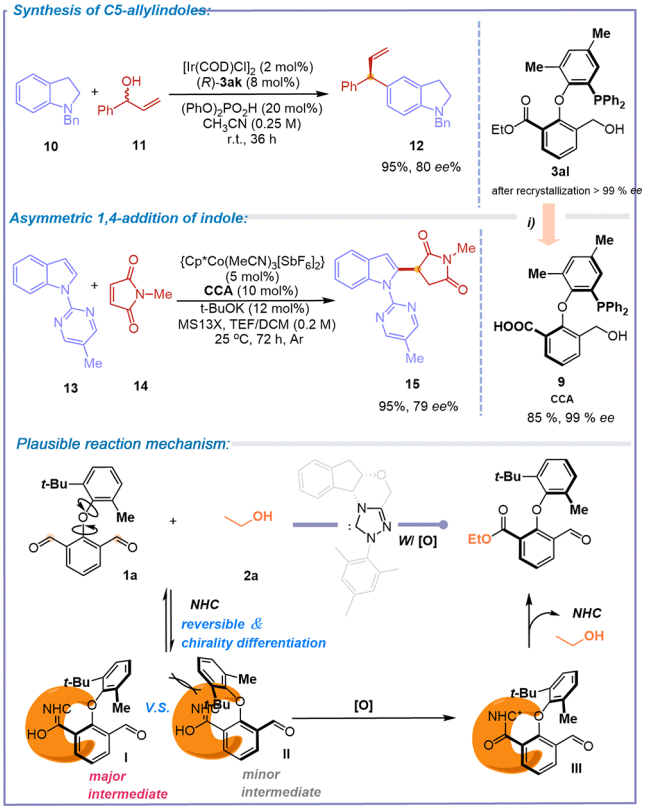
Scheme 3. Large-Scale Pattern and Synthetic Transformations of the Condensation Products[a]



[a](a) Gram-scale reactions. (b) Test of the kinetic resolution step. (c) Product elaboration: (i) $NaSO_2Me$ (1.2 equiv), LiHMDS (1.0 equiv), toluene, 80 °C, 4 h; (ii) NaOH (10.0 equiv), CH_3OH/H_2O = 4:1 (0.2 M), 70 °C, overnight. s = ln [(1 − Conv.) (1 − ee_s)]/ln [(1 − Conv.) (1 + ee_s)].

(Scheme 5a). Compound **3al** (99% *ee*, after recrystallization with Et_2O/hexane) was selected as the ligand for the Iridium/Brønsted acid cooperative catalyzed asymmetric allylic substitution reactions.[26] Gratifyingly, the reaction of racemic **11** and N-benzylindoline **10** proceeded effectively with 2 mol % of palladium catalyst and 8 mol % of **3al** to give the desired product **12** in 95% yield with 85% *ee* (Scheme 5a). The newly developed axially chiral carboxylic acids **9** were introduced as chiral ligands in asymmetric C−H functionalization.[27] Alkenyl C−H alkenylation-derived carboxylic acids **9** were preliminarily investigated in Co(III)-catalyzed asymmetric 1,4-addition of indole **13** with maleimide **14**, exhibiting **9** to be highly efficient

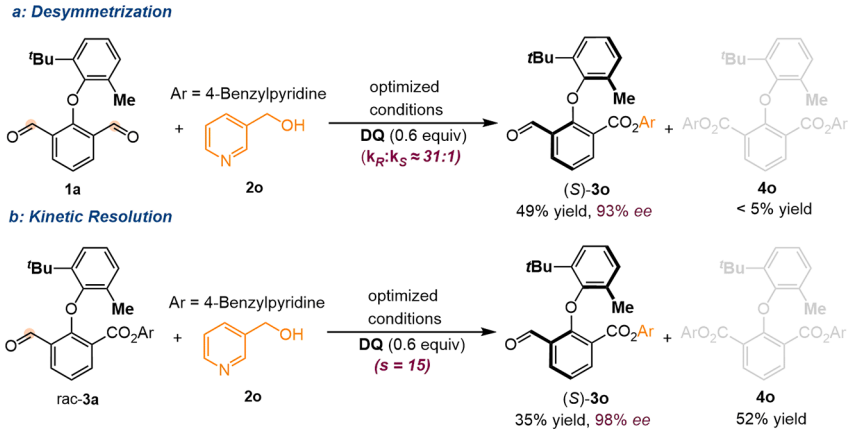
Scheme 5. Applications in Asymmetric Catalysis and Plausible Mechanism[a]



[a](a) Synthesis of C5-allylindoles: (i) NaOH (10.0 equiv), CH_3OH/H_2O = 4:1 (0.2 M), 70 °C, overnight. (b) Asymmetric 1,4-addtion of indole. (c) Plausible reaction mechanism.

with good enantioselectivity (79% *ee*) (Scheme 5b). Further research is being done on axially chiral diaryl ethers as catalysts or ligands for asymmetric processes. Based on experimental findings and Chi reports, Scheme 4 offers an enantioselective oxidative esterification method for this asymmetric reaction.[20] The enantioselective desymmetrization of prochiral dicarbaldehyde **1a** is catalyzed exclusively by N-heterocyclic carbene. Two diastereoisomeric Breslow intermediates **I** and **II** are reversible

Scheme 4. (a) Desymmetrization of Isophthalaldehyde 1a; (b) Kinetic Resolution of Racemic 3a Mechanistic Studies and Proposed Mechanism[a]



[a]s = ln[(1 − Conv.)(1 − ee_s)]/ln[(1 − Conv.)(1 + ee_s)].

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upon the addition of the chiral NHC catalyst. For steric reasons, the intermediate **II** forms more easily than the intermediate **I**, and under mild conditions, it can be oxidized to produce the chiral acylazolium intermediate **III**. The ultimate axially chiral ester product **3a** is produced via the esterification reaction between ethyl alcohol **2a** and intermediate **III**, which is catalyzed by the regeneration of the free NHC catalyst.

CONCLUSIONS

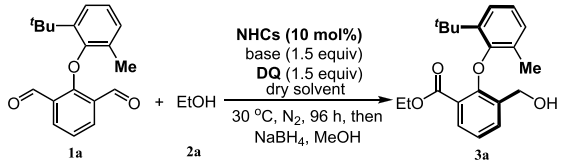
In summary, we presented the NHC organocatalytic atroposelective synthesis of axially chiral diaryl ether derivatives. NHC desymmetrized readily accessible dialdehydes to produce axially chiral diaryl ethers with good chemical yields and enantioselectivities. Additionally, highly enantiomeric diaryl ethers were effective chiral ligands in asymmetric catalysis and adaptable building blocks for other functional axially chiral compounds. NHC-catalyzed desymmetrization−functionalization may synthesize value-added axially chiral diaryl ethers and their derivatives on modularized platforms.

EXPERIMENTAL SECTION

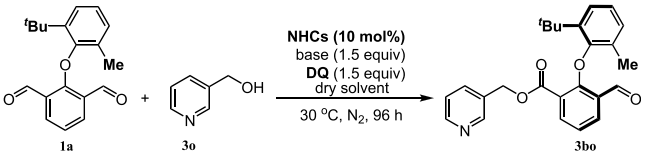
General Information. Analytical TLC was performed using a Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with a basic solution of potassium permanganate or an acidic solution of ceric molybdate. Flash column chromatography was performed using Merck aluminum oxide90 active neutral with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-d (7.26, singlet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (0.0) and relative to the signal of chloroform-d (77.0, triplet). Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) analysis on a chiral stationary phase, CHIRALCEL IA, CHIRALCEL OD, and CHIRALCEL AD. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensdchpolarimeter (Polartronic MH8) with a 10-cm cell (c given in g/100 mL). High-resolution mass spectra (HRMS) were performed on Waters Q-Tof Permies Mass Spectrometer, using Electro Spray Ionization (ESI) mode. A suitable crystal (mm × mm × mm) was selected and mounted on a Bruker D8 Venture diffractometer with Mo Ka radiation (l = 0.71073 Å) for cell determination and subsequent data collection at 170 K. $[\alpha]_D$ values are given in deg cm g^{-1} dm^{-1}. Under 589 nm, concentration c is listed in g (100 mL)$^{-1}$.

General synthesis procedures for phenols, **2a−2l** and substrates **3a−3l** are provided in the Supporting Information.

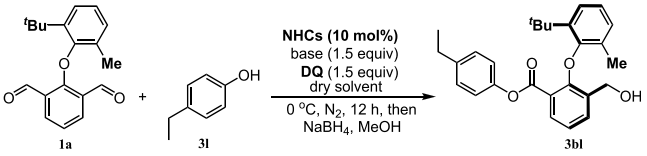
General Procedure for Synthesis of Compound 3. *General Procedure A.* In a nitrogen-filled glovebox, a flame-dried screw-cap reaction tube equipped with a Teflon-coated magnetic stir bar was charged with **NHC-1** (10 mol %, 8.36 mg), Cs_2CO_3 (98.0 mg, 1.5 equiv), and anhydrous toluene (2.0 mL). EtOH **2a** (0.2 mL, 20 equiv) was added. The mixture was stirred for 5 min followed by the addition of **1a** (0.2 mmol, 60.0 mg) and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (120 mg, 1.5 equiv). After stirring at the same temperature for 96 h, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:1) to afford the crude product. The crude product and excess sodium borohydride were added to a 100-mL vial containing a magnetic stir bar, and 30 mL MeOH was added to this bar. After stirring for 10 min, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:6) to afford the products **3a** as a yellow viscous liquid.



General Procedure B. In a nitrogen-filled glovebox, a flame-dried screw-cap reaction tube equipped with a Teflon-coated magnetic stir bar was charged with **NHC-1** (10 mol %, 8.36 mg), Cs_2CO_3 (98.0 mg, 1.5 equiv), and anhydrous toluene (2.0 mL). **3n** (0.2 mL, 20 equiv) was added. The mixture was stirred for 5 min followed by the addition of **1a** (0.2 mmol, 60.0 mg) and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (120 mg, 1.5 equiv). After stirring at the same temperature for 96 h, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:8) to afford the crude product.



General Procedure C. In a nitrogen-filled glovebox, a flame-dried screw-cap reaction tube equipped with a Teflon-coated magnetic stir bar was charged with **NHC-1** (10 mol %, 8.36 mg), Cs_2CO_3 (98.0 mg, 1.5 equiv), and anhydrous toluene (2.0 mL). **3n** (5 equiv) was added. The mixture was stirred for 5 min followed by the addition of **1a** (0.2 mmol, 60.0 mg) and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (120 mg, 1.5 equiv). After stirring at 0 °C for 12 h, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:8) to afford the crude product.



*(S)-Ethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3a**).* Prepared following ***general procedure A***. White oily liquid; yield: 13.3 mg (65%); $[\alpha]_D^{20}$ = −68.4 (c = 0.30, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 98% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.835 min, tr(major) = 8.621 min). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.58 (dd, J = 7.6, 1.8 Hz, 1H), 7.40 (dd, J = 7.7, 1.9 Hz, 1H), 7.28−7.23 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.95 (dd, J = 7.5, 1.8 Hz, 1H), 4.62 (s, 2H), 3.86 (m, 2H), 1.88 (s, 3H), 1.43 (s, 9H), 1.16

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(t, J = 7.1 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ 166.1, 152.3, 150.6, 140.0, 130.4, 129.7, 129.1, 128.8, 127.2, 124.3, 123.1, 121.7, 121.0, 60.2, 60.0, 34.3, 29.5, 16.7, 13.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{26}O_4+H^+$ 343.1845; found 343.1849.

*(S)-Ethyl-2-(2-(tert-butyl)-4,6-dimethylphenoxy)-3-(hydroxymethyl)benzoate (**3aa**).* Prepared following ***general procedure A***. Borwn oil; yield: 46.2 mg (65%); $[\alpha]_D^{20}$ = −41.5 (c = 0.054, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.75 min, tr(major) = 7.43 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.56 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (dd, J = 7.6, 1.8 Hz, 1H), 7.10−7.01 (m, 2H), 6.76 (d, J = 2.2 Hz, 1H), 4.60 (s, 2H), 3.96−3.79 (m, 2H), 2.28 (s, 3H), 1.84 (s, 3H), 1.41 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 167.3, 151.9, 151.1, 140.7, 133.3, 131.5, 130.6, 130.3, 129.8, 128.0, 126.1, 122.7, 121.8, 61.2, 61.1, 35.2, 30.6, 21.0, 17.6, 14.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}O_4+H^+$ 357.2062; found 357.2069.

*(S)-Ethyl-2-(2-(tert-butyl)-4-chloro-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3ab**).* Prepared following ***general procedure A***. White oil; yield: 40.8 mg (59%); $[\alpha]_D^{20}$ = −13.4 (c = 0.5, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.56 min, tr(major) = 8.50 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.61 (dd, J = 7.5, 1.8 Hz, 1H), 7.40 (dd, J = 7.7, 1.8 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 4.65 (t, J = 5.5 Hz, 2H), 3.97−3.85 (m, 2H), 1.84 (s, 3H), 1.41 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 165.9, 150.8, 150.2, 141.9, 130.2, 129.8, 128.8, 128.3, 127.8, 124.6, 121.5, 121.3, 60.3, 59.8, 34.6, 29.3, 16.7, 13.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{25}ClO_4+H^+$ 390.1433; found 390.1392.

*(S)-Ethyl-2-(4-bromo-2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3ac**).* Prepared following ***general procedure A***. White oil; yield: 56.9 mg (73%); $[\alpha]_D^{20}$ = −13.4 (c = 0.5, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.56 min, tr(major) = 8.50 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.61 (dd, J = 7.5, 1.8 Hz, 1H), 7.40 (dd, J = 7.7, 1.8 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 4.65 (t, J = 5.5 Hz, 2H), 3.97−3.85 (m, 2H), 1.84 (s, 3H), 1.41 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 165.9, 150.8, 150.2, 141.9, 130.2, 129.8, 128.8, 128.3, 127.8, 124.6, 121.5, 121.3, 60.3, 59.8, 34.6, 29.3, 16.7, 13.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{25}BrO_4+H^+$ 390.1433; found 390.1392.

*(S)-Ethyl-2-(2,4-ditert-butyl-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3ad**).* Prepared following **general procedure A**. Yellow oil; yield: 51.7 mg (65%); $[\alpha]_D^{20}$ = −54.4 (c = 0.56, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 96% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.53 min, tr(major) = 8.70 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.56 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (dd, J = 7.7, 1.8 Hz, 1H), 7.28−7.25 (m, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 4.70−4.63 (m, 2H), 3.76 (m, 2H), 1.87 (s, 3H), 1.43 (s, 9H), 1.30 (s, 9H), 1.13 (t, J = 7.1 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 167.3, 151.7, 150.8, 146.4, 140.2, 131.2, 130.8, 129.8, 127.4, 126.7, 122.5, 122.4, 121.7, 61.3, 61.2, 35.5, 34.5, 31.5, 30.7, 17.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}O_4+H^+$ 399.2459; found 398.2463.

*(S)-Ethyl-2-(2-((3r,5r,7r)-adamantan-1-yl)-4,6-dimethylphenoxy)-3-(hydroxymethyl)benzoate (**3ae**).* Prepared following ***general procedure A***. Yellow oil; yield: 50.3 mg (58%); $[\alpha]_D^{20}$ = −42.9 (c = 1, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak IF column, *ee* = 96% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 8.08 min, tr(major) = 8.69 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.56 (dd, J = 7.6, 1.8 Hz, 1H), 7.37 (dd, J = 7.7, 1.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 4.58 (d, J = 3.4 Hz, 2H), 3.97−3.81 (m, 2H), 2.28 (s, 3H), 2.17−2.09 (m, 6H), 2.05 (p, J = 3.0 Hz, 3H), 1.82 (s, 3H), 1.74 (t, J = 3.1 Hz, 6H), 1.18 (t, J = 7.1 Hz, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 166.3, 150.9, 150.4, 140.2, 132.4, 130.4, 129.5, 129.0, 128.7, 127.0, 124.9, 121.8, 120.7, 60.2, 60.2, 40.3, 36.4, 36.0, 28.0, 20.0, 16.5, 13.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{34}O_4+H^+$ 435.2612; found 435.2647.

*(S)-Ethyl-3-(hydroxymethyl)-2-(2-methyl-4,6-di-tert-pentylphenoxy)benzoate (**3af**).* Prepared following ***general procedure A***. White solid; yield: 49.1 mg (58%); mp 138.5−139.2 °C. $[\alpha]_D^{20}$ = −73.5 (c = 0.054, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 8.08 min, tr(major) = 8.69 min.) **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.55 (dd, J = 7.6, 1.8 Hz, 1H), 7.38 (dd, J = 7.7, 1.8 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.86 (dd, J = 2.5, 0.8 Hz, 1H), 4.58 (t, J = 4.1 Hz, 2H), 3.95−3.78 (m, 2H), 1.88−1.76 (m, 6H), 1.63−1.60 (m, 2H), 1.39 (d, J = 11.0 Hz, 6H), 1.25 (s, 6H), 1.16 (t, J = 7.2 Hz, 3H), 0.70 (td, J = 7.5, 2.9 Hz, 6H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 166.3, 150.8, 149.9, 143.4, 137.5, 130.5, 129.6, 128.7, 126.3, 126.1, 123.4, 121.8, 120.7, 60.1, 60.1, 37.9, 36.6, 35.9, 33.8, 27.6, 27.5, 27.1, 26.9, 17.1, 13.0, 8.3, 8.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{38}O_4+H^+$ 427.2814; found 427.2819.

*(R)-Ethyl-2-(2-(tert-butyl)-6-methyl-4-(naphthalen-2-yl)-phenoxy)-3-(hydroxymethyl)benzoate (**3ag**).* Prepared following ***general procedure A***. Yellow oil; yield: 65.5 mg (70%); $[\alpha]_D^{20}$ = −23.7 (c = 0.7, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 11.20 min, tr(major) = 12.738 min). **^1H NMR (500 MHz, Chloroform-*d*)** δ 7.99 (d, J = 1.9 Hz, 1H), 7.90 (dd, J = 8.3, 2.3 Hz, 2H), 7.86 (dd, J = 7.7, 1.6 Hz, 1H), 7.72 (dd, J = 8.5, 1.9 Hz, 1H), 7.64−7.59 (m, 2H), 7.53−7.42 (m, 3H), 7.31 (d, J = 2.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 4.71−4.69 (m, 2H), 3.98−3.80 (m, 2H), 1.98−1.96 (m, 3H), 1.53−1.50 (m, 9H), 1.16 (s, 3H). **$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)** δ = 167.2, 153.1, 151.6, 141.4, 138.4, 136.6, 133.7, 132.5, 131.4, 131.0, 129.9, 128.9, 128.5, 128.4, 128.1, 127.7, 126.3, 125.8, 125.5, 125.4, 124.6, 122.8, 122.2, 61.3, 61.1, 35.6, 30.6, 18.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{32}O_4+H^+$ 469.2354; found 469.2399.

*(S)-Ethyl-2-((3-(tert-butyl)-5-methyl-[1,1′-biphenyl]-4-yl)-oxy)-3-(hydroxymethyl)benzoate (**3ah**).* Prepared following ***general procedure A***. Brown oil; yield: 55.4 mg (66%); $[\alpha]_D^{20}$ = −56.8 (c = 0.5, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 95%

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(HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 11.20 min, tr(major) = 12.738 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.54 (dd, J = 7.5, 1.8 Hz, 1H), 7.50−7.44 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.38−7.30 (m, 3H), 7.28−7.24 (m, 1H), 7.14−7.10 (m, 1H), 7.04 (t, J = 7.6 Hz, 1H), 4.64−4.56 (m, 2H), 3.88−3.68 (m, 2H), 1.86 (s, 3H), 1.41 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 166.1, 151.9, 150.6, 140.2, 140.0, 135.7, 130.3, 129.9, 128.9, 127.7, 127.6, 127.4, 126.0, 125.9, 123.4, 121.7, 121.1, 60.3, 60.0, 34.5, 29.6, 16.9, 13.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{30}O_4$+H^+ 420.2233; found 420.2239.

*(S)-Ethyl-2-(4-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3ai**).* Prepared following ***general procedure A***. Yellow soild; yield: 57.2 mg (62%); mp 189.2−190.6 °C. $[\alpha]_D^{20}$ = −56.8 (c = 0.5, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 95% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 11.20 min, tr(major) = 12.738 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.60 (dd, J = 7.5, 1.8 Hz, 1H), 7.44−7.37 (m, 2H), 7.14−7.08 (m, 2H), 7.05−6.99 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 4.67 (s, 2H), 3.94−3.74 (m, 2H), 1.91 (s, 3H), 1.47 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 167.2, 152.6, 151.6, 148.1, 146.8, 141.2, 136.5, 135.5, 131.3, 130.9, 129.9, 128.4, 128.3, 124.1, 122.7, 122.1, 120.3, 108.6, 107.5, 101.1, 61.3, 61.0, 35.5, 30.6, 18.0. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{28}H_{30}O_6$+Na^+ 485.1934; found 485.1944.

*(S)-Ethyl-2-(2-(tert-butyl)-4,6-dimethylphenoxy)-3-(hydroxymethyl)benzoate (**3aj**).* Prepared following ***general procedure A***. White solid; yield: 61.9 mg (66%); mp 162.1−165.3 °C. $[\alpha]_D^{20}$ = −20.7 (c = 0.28, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 86% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 4.71 min, tr(major) = 5.37 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.56 (dd, J = 7.6, 1.8 Hz, 1H), 7.31 (dd, J = 7.8, 1.8 Hz, 1H), 7.29−7.25 (m, 1H), 7.07−7.01 (m, 2H), 4.67 (d, J = 4.5 Hz, 2H), 3.83−3.62 (m, 2H), 2.26 (qd, J = 7.6, 5.8 Hz, 2H), 1.42 (s, 9H), 1.32 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 166.3, 150.8, 149.0, 145.8, 139.7, 132.8, 130.1, 129.3, 128.8, 123.0, 121.4, 120.9, 120.4, 60.3, 60.2, 34.5, 33.6, 30.5, 29.7, 22.5, 12.9, 12.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{30}O_6$+H^+ 371.2212; found 371.2216.

*(S)-Ethyl-2-(2-(tert-butyl)-6-chloro-4-methylphenoxy)-3-(hydroxymethyl)benzoate (**3ak**).* Prepared following ***general procedure A***. Yellow oil; yield: 41.9 mg (62%); $[\alpha]_D^{20}$ = −33.5 (c = 1, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 77% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 5.66 min, tr(major) = 6.58 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.81−7.66 (m, 2H), 7.26 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.71−6.67 (m, 1H), 6.10 (d, J = 8.2 Hz, 1H), 4.60−4.46 (m, 2H), 4.10−3.97 (m, 2H), 2.19 (s, 3H), 1.43 (s, 9H), 0.92 (t, J = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 165.8, 155.5, 150.3, 136.3, 135.7, 132.7, 130.9, 130.5, 128.2, 127.1, 126.6, 125.2, 112.7, 61.1, 60.3, 34.9, 30.0, 29.8, 20.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}ClO_4$+H^+ 376.8770; found 376.8775.

*(S)-Ethyl-2-(2-(diphenylphosphaneyl)-4,6-dimethylphenoxy)-3-(hydroxymethyl)benzoate (**3al**).* Prepared following ***general procedure A***. White solid; yield: 55.90 mg (77%); mp 102.8−114.1 °C. $[\alpha]_D^{20}$ = −73.54 (c = 0.054, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 92% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.88 min, tr(major) = 11.94 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.72 (dd, J = 8.1, 1.2 Hz, 1H), 7.43−7.40 (m, 1H), 7.38−7.34 (m, 2H), 7.32−7.28 (m, 4H), 7.14−7.09 (m, 6H), 6.95 (dt, J = 2.2, 0.7 Hz, 1H), 4.72 (dd, J = 5.8, 0.8 Hz, 2H), 4.30 (q, J = 6.4 Hz, 2H), 2.72−2.69 (m, 1H), 2.24 (s, 3H), 2.06 (s, 3H), 1.37 (t, J = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ 188.8, 161.8, 157.3, 153.6, 149.6, 147.7, 139.3, 134.7, 129.7, 128.2, 127.9, 126.5, 126.3, 123.1, 122.4, 91.8, 90.1, 55.1, 43.7, 35.5, 34.6, 31.5, 30.5, 17.9. **^{31}P NMR (202 MHz, $CDCl_3$)** δ −14.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{29}O_4P$+H^+ 485.1876; found 485.1876.

*(S)-Propyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bb**).* Prepared following ***general procedure A***. Yellow oil; yield: 50.1 mg (70%); $[\alpha]_D^{20}$ = −31.78 (c = 0.6, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 93% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.31 min, tr(major) = 8.03 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.51 (ddd, J = 7.6, 1.8, 0.8 Hz, 1H), 7.34 (dd, J = 7.6, 1.8 Hz, 1H), 7.20−7.16 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.87 (ddd, J = 7.5, 1.8, 0.8 Hz, 1H), 4.53 (s, 2H), 3.76−3.63 (m, 2H), 1.80 (s, 3H), 1.36 (s, 9H), 0.80 (t, J = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 167.2, 153.4, 151.7, 141.0, 131.5, 130.8, 130.1, 129.8, 128.1, 125.4, 124.1, 122.7, 122.0, 66.8, 61.0, 35.4, 30.5, 21.8, 17.7, 10.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}O_4$+H^+ 358.2156; found 358.2159.

*(S)-Butyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bc**).* Prepared following ***general procedure A***. Colorless oil; yield: 48.8 mg (66%); $[\alpha]_D^{20}$ = −42.5 (c = 0.4, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 93% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 10.151 min, tr(major) = 10.818 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.51 (dd, J = 7.6, 1.8 Hz, 1H), 7.35−7.32 (m, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.87 (dd, J = 7.6, 1.8 Hz, 1H), 4.54 (s, 2H), 3.81−3.69 (m, 2H), 1.81 (s, 3H), 1.48−1.42 (m, 2H), 1.36 (s, 9H), 1.26−1.18 (m, 3H), 0.81 (t, J = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 166.1, 152.3, 150.7, 140.0, 130.4, 129.7, 129.1, 128.8, 127.1, 124.4, 123.1, 121.7, 121.0, 64.1, 60.0, 34.3, 29.5, 29.4, 18.1, 16.7, 12.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{30}O_4$+H^+ 370.2159; found 371.2163.

*(S)-Cyclohexyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bd**).* Prepared following ***general procedure A***. White oil; yield: 47.2 mg (72%); $[\alpha]_D^{20}$ = −17.3 (c = 0.8, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 84% (HPLC: IF, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 10.151 min, tr(major) = 10.818 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.50 (dd, J = 7.6, 1.8 Hz, 1H), 7.36 (dd, J = 7.7, 1.8 Hz, 1H), 7.19−7.16 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.86 (dd, J = 7.5, 1.7 Hz, 1H), 4.57−4.52 (m, 1H), 4.46−4.39 (m, 2H), 1.82 (s, 3H), 1.76−1.57 (m, 5H), 1.36 (s, 9H), 1.32−1.12 (m, 5H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 165.2, 152.7, 150.8, 139.8, 130.6, 129.6, 129.0, 128.8, 126.8, 124.5, 122.9, 122.5, 121.0, 72.5, 59.8, 34.3,

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30.4, 30.2, 29.5, 24.3, 22.6, 16.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{32}O_4$+H^+ 397.2987; found 396.2981.

*(S)-Cyclobutylmethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3be**).* Prepared following ***general procedure A***. Yellow oil; yield: 54.2 mg (72%); $[\alpha]_D^{20} = -52.8$ (c = 0.68, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 92% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.28 min, tr(major) = 7.17 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.60−7.57 (m, 1H), 7.41 (dd, J = 7.7, 1.8 Hz, 1H), 7.28−7.23 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.94 (ddd, J = 7.5, 1.8, 0.8 Hz, 1H), 4.58 (s, 2H), 3.82 (d, J = 6.9 Hz, 2H), 2.54 (p, J = 7.5 Hz, 1H), 2.02−1.95 (m, 2H), 1.88 (s, 3H), 1.86−1.77 (m, 2H), 1.74−1.66 (m, 2H), 1.43 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 167.2, 153.4, 151.7, 141.0, 131.5, 130.7, 130.1, 129.9, 128.0, 125.4, 124.1, 122.8, 122.0, 69.0, 61.0, 35.4, 33.9, 30.5, 24.8, 24.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}O_4$+H^+ 383.2264; found 383.2295.

*(S)-Cyclopropylmethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bf**).* Prepared following ***general procedure A***. Yellow oil; yield: 52.9 mg (72%); $[\alpha]_D^{20}$ = −47.8 (c = 0.58, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak IF column, *ee* = 99% (HPLC: IF, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 7.94 min, tr(major) = 8.33 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.38 (dd, J = 7.6, 1.8 Hz, 1H), 7.22 (dd, J = 7.7, 1.8 Hz, 1H), 7.04 (dd, J = 7.7, 1.8 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 4.44−4.40 (m, 1H), 4.37 (s, 2H), 2.06−2.00 (m, 2H), 1.80−1.72 (m, 2H), 1.67 (s, 3H), 1.56−1.47 (m, 2H), 1.22 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** 13C NMR (126 MHz, CDCl3) δ 166.2, 152.3, 150.7, 139.9, 130.5, 129.7, 129.1, 128.9, 127.1, 124.3, 123.0, 121.7, 121.0, 69.0, 60.0, 34.3, 29.5, 28.7, 16.7, 8.6, 2.4, 2.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}O_4$+H^+ 368.4399; found 368.4391.

*(S)-Neopentyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bg**).* Prepared following ***general procedure A***. Yellow oil; yield: 53.8 mg (70%); $[\alpha]_D^{20}$ = −57.9 (c = 0.58, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: IF, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.39 min, tr(major) = 6.71 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.52 (dd, J = 7.5, 1.8 Hz, 1H), 7.33 (dd, J = 7.7, 1.8 Hz, 1H), 7.20−7.17 (m, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 4.52 (s, 2H), 3.68−3.37 (m, 3H), 1.82 (s, 3H), 1.36 (s, 10H), 0.84 (s, 10H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 165.7, 152.4, 150.8, 140.0, 130.4, 129.7, 129.0, 128.6, 126.8, 124.5, 123.0, 121.7, 120.9, 73.4, 59.9, 34.3, 30.2, 29.5, 28.7, 25.4, 16.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}O_4$+H^+ 384.5160; found 384.5163.

*(S)-Cyclobutyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bh**).* Prepared following ***general procedure A***. Brown oil; yield: 41.2 mg (56%); $[\alpha]_D^{20}$ = −56.3 (c = 0.512, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 93% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.38 min, tr(major) = 7.10 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.53−7.49 (m, 1H), 7.34 (dd, J = 7.6, 1.8 Hz, 1H), 7.19−7.16 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.87 (m, 1H), 4.53 (s, 2H), 3.76−3.64 (m, 2H), 1.80 (s, 3H), 1.52−1.46 (m, 2H), 1.35 (s, 9H), 0.80 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 166.5, 153.4, 151.7, 140.9, 131.6, 130.7, 130.2, 130.0, 128.2, 125.4, 124.1, 122.8, 122.0, 69.7, 61.0, 30.5, 30.4, 30.1, 17.8, 13.6. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{28}O_4$+Na^+ 391.1879; found 391.1885.

*(S)-Isopropyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bi**).* Prepared following ***general procedure A***. Yellow oil; yield: 42.7 mg (60%); $[\alpha]_D^{20}$ = −58.7 (c = 0.506, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 96% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.83 min, tr(major) = 7.11 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.50 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (dd, J = 7.6, 1.8 Hz, 1H), 7.21−7.17 (m, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.87 (dd, J = 7.6, 1.8 Hz, 1H), 4.76 (p, J = 6.2 Hz, 1H), 4.45 (s, 2H), 1.82 (s, 3H), 1.36 (s, 9H), 1.11 (dd, J = 15.8, 6.2 Hz, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ 166.3, 156.3, 153.3, 138.2, 132.5, 129.2, 128.2, 128.2, 126.8, 124.8, 123.3, 122.7, 119.1, 69.9, 59.5, 35.1, 29.8, 21.8, 16.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}O_4$+H^+ 357.3454; found 357.3449.

*(S)-Pent-4-yn-1-yl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bj**).* Prepared following ***general procedure A***. White oil; yield: 53.2 mg (70%); $[\alpha]_D^{20}$ = −62.4 (c = 0.492, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 95% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 11.84 min, tr(major) = 12.74 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.60 (dd, J = 7.6, 1.8 Hz, 1H), 7.42 (dd, J = 7.7, 1.8 Hz, 1H), 7.28−7.24 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.96 (dd, J = 7.6, 1.8 Hz, 1H), 4.61 (d, J = 4.9 Hz, 2H), 3.98−3.87 (m, 2H), 2.25−2.15 (m, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.87 (s, 3H), 1.76 (d, J = 6.7 Hz, 2H), 1.43 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 165.9, 152.3, 150.8, 140.0, 130.6, 129.8, 129.1, 128.9, 126.9, 124.4, 123.1, 121.3, 121.0, 81.9, 68.0, 62.7, 60.0, 34.3, 29.5, 26.3, 16.7, 14.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{28}O_4$+H^+ 380.2011; found 380.2039.

*(S)-2-(Trimethylsilyl)ethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bk**).* Prepared following ***general procedure A***. Yellow oil; yield: 51.3 mg (62%); $[\alpha]_D^{20}$ = −33.1 (c = 0.46, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 95% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.34 min, tr(major) = 6.59 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.57 (dd, J = 7.6, 1.8 Hz, 1H), 7.37 (dd, J = 7.7, 1.8 Hz, 1H), 7.27−7.23 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.02−6.94 (m, 2H), 4.64 (d, J = 5.3 Hz, 2H), 3.93−3.75 (m, 2H), 1.88 (s, 3H), 1.43 (s, 9H), 0.94−0.85 (m, 2H), 0.01 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 168.9, 154.8, 153.1, 142.7, 132.8, 132.3, 131.6, 131.3, 129.9, 126.9, 125.7, 124.3, 123.5, 65.1, 62.7, 36.9, 32.1, 19.3, 18.7, 2.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{34}O_4Si$+H^+ 415.2316; found 415.2326.

*(S)-4-Ethylphenyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bl**).* Prepared following ***general procedure C***. Yellow oil; yield: 58.5 mg (70%); $[\alpha]_D^{20}$ = −38.0 (c = 0.43, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 91% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 16.75 min, tr(major) = 18.10 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.64−7.57 (m, 1H), 7.19−7.15 (m, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.96−6.90 (m, 2H), 6.69 (d, J = 8.5 Hz, 2H), 4.50 (tt, J = 13.6,

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7.0 Hz, 2H), 2.54 (q, J = 7.6 Hz, 2H), 1.85 (s, 3H), 1.35 (s, 9H), 1.13 (t, J = 7.6 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 164.3, 152.8, 151.4, 147.4, 140.6, 139.8, 131.5, 130.1, 129.5, 129.4, 127.5, 126.5, 124.8, 123.0, 121.2, 121.1, 120.2, 59.7, 34.4, 29.5, 27.2, 17.0, 14.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{27}H_{30}O_4$+H$^+$ 418.5330; found 418.5339.

*(S)-4-Methoxybenzyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bm**).* Prepared following ***general procedure A***. Brown oil; yield: 56.4 mg (65%); $[\alpha]_D^{20}$ = −56.3 (c = 0.512, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 84% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 14.06 min, tr(major) = 15.72 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.50 (dd, J = 7.6, 1.8 Hz, 1H), 7.32 (dd, J = 7.6, 1.8 Hz, 1H), 7.18 (dd, J = 7.9, 1.8 Hz, 1H), 7.08−7.02 (m, 4H), 6.99 (t, J = 7.6 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.86 (dd, J = 7.7, 1.7 Hz, 1H), 4.77−4.63 (m, 2H), 4.54 (s, 2H), 2.25 (s, 3H), 1.79 (s, 3H), 1.31 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 165.8, 152.3, 150.7, 140.0, 136.9, 131.6, 130.5, 129.8, 129.1, 128.9, 128.1, 127.2, 127.1, 124.4, 123.1, 121.2, 120.9, 65.8, 60.0, 34.3, 29.5, 20.2, 16.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{27}H_{30}O_5$+H$^+$ 435.2167; found 435.2199.

*(S)-Thiophen-2-ylmethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bn**).* Prepared following ***general procedure B***. Yellow oil; yield: 70.9 mg (87%); $[\alpha]_D^{20}$ = −28.7 (c = 0.60, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 99% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 14.73 min, tr(major) = 16.79 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.60−7.57 (m, 1H), 7.40 (dd, J = 7.7, 1.8 Hz, 1H), 7.29−7.25 (m, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.04−6.99 (m, 2H), 6.98−6.93 (m, 2H), 5.00−4.89 (m, 2H), 4.63 (d, J = 4.6 Hz, 2H), 1.87 (s, 3H), 1.40 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 165.5, 152.2, 150.8, 140.1, 136.5, 130.7, 129.8, 129.1, 129.0, 127.2, 127.1, 125.8, 125.7, 124.4, 123.2, 120.9, 120.7, 60.1, 60.0, 34.3, 29.5, 16.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{24}O_4S$+H$^+$ 408.5126; found 408.5124.

*(S)-Pyridin-3-ylmethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bo**).* Prepared following ***general procedure B***. Yellow oil; yield: 66.09 mg (82%); $[\alpha]_D^{20}$ = −36.3 (c = 0.244, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 99% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 16.94 min, tr(major) = 19.00 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.66 (d, J = 0.9 Hz, 1H), 8.57−8.47 (m, 2H), 7.88 (dd, J = 7.8, 2.0 Hz, 1H), 7.77 (dd, J = 7.6, 1.9 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.24−7.16 (m, 2H), 7.09 (d, J = 0.8 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 6.94−6.89 (m, 1H), 5.13−4.99 (m, 2H), 1.81 (s, 3H), 1.31 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 186.9, 164.7, 156.4, 153.8, 148.8, 139.9, 135.6, 135.1, 131.7, 130.1, 129.9, 126.6, 125.9, 125.0, 124.3, 122.4, 122.2, 121.0, 63.6, 34.2, 29.2, 16.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{25}H_{25}NO_4$+H$^+$ 404.1855; found 404.1823.

*(S)-But-3-en-1-yl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bp**).* Prepared following ***general procedure A***. Yellow oil; yield: 51.52 mg (70%); $[\alpha]_D^{20}$ = −4.9 (c = 0.51, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 97% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 5.15 min, tr(major) = 5.55 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.52 (dd, J = 7.6, 1.8 Hz, 1H), 7.33 (dd, J = 7.7, 1.8 Hz, 1H), 7.21−7.16 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.95−6.85 (m, 2H), 5.64 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.01−4.88 (m, 2H), 4.53 (s, 2H), 3.86−3.74 (m, 2H), 2.26−2.18 (m, 2H), 1.80 (s, 3H), 1.36 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 167.0, 153.3, 151.7, 141.0, 133.9, 131.6, 130.8, 130.1, 129.9, 128.1, 125.4, 124.1, 122.5, 122.0, 117.2, 64.2, 61.0, 35.4, 32.9, 30.5, 17.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{28}O_4$+H$^+$ 368.4739; found 368.4742.

*(S)-3-Hydroxy-2-phenylpropyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bq**).* Prepared following ***general procedure B***. Yellow oil; yield: 73.47 mg (82%); $[\alpha]_D^{20}$ = −28.7 (c = 0.60, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 9.44 min, tr(major) = 11.18 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.62 (dd, J = 7.3, 0.8 Hz, 1H), 7.85 (dd, J = 7.8, 2.0 Hz, 1H), 7.66 (ddd, J = 11.0, 7.6, 1.9 Hz, 1H), 7.25−7.10 (m, 7H), 7.05 (td, J = 7.7, 0.8 Hz, 1H), 6.99 (td, J = 7.7, 3.7 Hz, 1H), 6.88 (ddd, J = 7.7, 4.1, 1.6 Hz, 1H), 4.42−4.31 (m, 2H), 3.81−3.72 (m, 2H), 3.12 (td, J = 6.6, 4.7 Hz, 1H), 1.73 (d, J = 7.1 Hz, 3H), 1.35 (d, J = 6.9 Hz, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 167.3, 156.8, 153.2, 141.2, 138.2, 132.7, 129.2, 129.2, 128.2, 128.2, 127.5, 127.3, 126.8, 124.8, 123.3, 122.7, 119.1, 67.2, 63.3, 59.5, 46.9, 35.1, 29.8, 16.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{30}O_5$+H$^+$ 449.2695; found 449.2699.

*(S)-3-Hydroxy-2-methyl-2-phenylpropyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3br**).* Prepared following ***general procedure B***. Yellow oil; yield: 69.92 mg (76%); $[\alpha]_D^{20}$ = −36.3 (c = 0.244, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 9.44 min, tr(major) = 11.18 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** 1H NMR (500 MHz, CDCl3) δ 9.58 (dd, J = 12.4, 0.8 Hz, 1H), 7.84 (dt, J = 7.8, 1.8 Hz, 1H), 7.62 (dt, J = 7.6, 2.2 Hz, 1H), 7.28 (dd, J = 8.4, 1.3 Hz, 2H), 7.25−7.18 (m, 3H), 7.17−7.11 (m, 1H), 7.07−6.97 (m, 2H), 6.89 (dt, J = 7.4, 1.4 Hz, 1H), 4.46−4.25 (m, 2H), 3.67 (dd, J = 8.5, 3.7 Hz, 2H), 1.72 (d, J = 8.0 Hz, 3H), 1.35 (d, J = 6.2 Hz, 9H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ 186.9, 186.9, 165.2, 165.2, 156.4, 156.3, 154.0, 141.2, 141.2, 139.8, 139.8, 135.6, 135.4, 131.6, 131.5, 129.9, 129.9, 127.6, 126.5, 126.5, 125.9, 125.8, 125.4, 125.4, 125.0, 125.0, 124.2, 124.2, 122.6, 122.5, 121.0, 120.9, 68.6, 68.5, 67.1, 67.1, 42.9, 42.8, 34.3, 34.3, 29.3, 29.3, 19.7, 19.7, 16.5, 16.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{32}O_5$+H$^+$ 461.2375; found 461.2388.

*(S)-3-Hydroxy-2-methylpropyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bs**).* Prepared following ***general procedure B***. White oil; yield: 58.36 mg (76%); $[\alpha]_D^{20}$ = −26.7 (c = 0.388, CHCl$_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 88% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 9.44 min, tr(major) = 11.18 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.60 (dd, J = 3.8, 0.8 Hz, 1H), 7.87 (dd, J = 7.8, 2.0 Hz, 1H), 7.78 (ddd, J = 7.2, 5.0, 1.9 Hz, 1H), 7.22 (dd, J = 7.9, 1.7 Hz, 1H), 7.09 (td, J = 7.7, 0.8 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 0.8 Hz, 1H), 4.07 (ddd, J = 7.6, 5.8, 1.2 Hz, 2H), 3.49−3.40 (m, 2H), 1.98−1.93 (m, 1H), 1.84 (s, 3H), 1.36 (s, 9H), 0.88 (dd, J = 6.9, 2.0 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$)** δ = 187.0, 139.8, 135.6, 131.6, 131.5, 129.9, 125.9, 125.0, 124.2, 122.8, 122.7, 121.0,

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66.1, 63.4, 34.5, 34.5, 34.3, 29.3, 16.6, 12.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}O_5$+H^+ 385.3648; found 385.3651.

*(S)-3-Hydroxy-2-methylpropyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bt**).* Prepared following ***general procedure B***. White oil; yield: 60.21 mg (78%); $[\alpha]_D^{20} = -42.9$ (c = 0.384, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 13.67 min, tr(major) = 17.01 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.61 (dd, J = 4.1, 0.8 Hz, 1H), 7.87 (dd, J = 7.8, 1.9 Hz, 1H), 7.78 (ddd, J = 7.3, 5.0, 1.9 Hz, 1H), 7.24 (d, J = 1.7 Hz, 1H), 7.13−7.08 (m, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.94 (ddd, J = 7.6, 1.7, 0.8 Hz, 1H), 4.11−4.04 (m, 2H), 3.96−3.74 (m, 1H), 3.49−3.41 (m, 2H), 1.84 (s, 3H), 1.37 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ 186.9, 156.3, 154.0, 139.8, 135.6, 135.5, 131.6, 131.5, 129.9, 125.9, 125.0, 124.2, 121.0, 66.1, 63.4, 63.4, 34.5, 34.5, 34.3, 29.3, 16.6, 12.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}O_6$+H^+ 387.1802; found 387.1810.

*(S)-(E)-3,7-Dimethylocta-2,6-dien-1-yl-2-(2-(tert-butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoate (**3bu**).* Prepared following ***general procedure A***. Brown oil; yield: 59.4 mg (66%); $[\alpha]_D^{20} = -56.3$ (c = 0.512, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 84% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 8.40 min, tr(major) = 8.92 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.51 (dd, J = 7.6, 1.8 Hz, 1H), 7.33 (dd, J = 7.7, 1.9 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.96−6.86 (m, 2H), 5.24−5.09 (m, 1H), 5.06−4.86 (m, 1H), 4.57 (s, 2H), 4.30 (dd, J = 12.5, 6.9 Hz, 1H), 4.14 (dd, J = 12.4, 7.2 Hz, 1H), 1.81 (s, 3H), 1.60 (d, J = 1.5 Hz, 3H), 1.56 (d, J = 1.3 Hz, 3H), 1.52 (s, 3H), 1.36 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 166.2, 152.2, 150.6, 140.8, 140.0, 130.8, 130.4, 129.7, 129.1, 128.9, 127.2, 124.3, 123.1, 122.7, 121.5, 120.9, 117.1, 61.2, 60.1, 38.5, 34.3, 29.5, 28.7, 25.2, 24.7, 16.7, 16.7, 15.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{26}O_6$+H^+ 451.3854; found 451.3855.

*(S)-(8S,9R,13R,14R,17S)-17-Ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bv**).* Prepared following ***general procedure C***. White solid; yield: 86.05 mg (71%); mp 109.2−109.8 °C. $[\alpha]_D^{20}$ = −58.7 (c = 0.506, $CHCl_3$). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.61−9.55 (m, 1H), 8.00 (dt, J = 7.5, 1.6 Hz, 1H), 7.93 (dd, J = 7.8, 1.9 Hz, 1H), 7.25−7.15 (m, 5H), 7.01 (t, J = 7.6 Hz, 1H), 6.96 (dd, J = 7.7, 1.8 Hz, 1H), 6.79−6.74 (m, 1H), 6.69 (t, J = 2.4 Hz, 1H), 2.84−2.75 (m, 2H), 2.54 (s, 1H), 2.32−2.24 (m, 2H), 2.19 (t, J = 11.9 Hz, 1H), 1.98−1.93 (m, 1H), 1.90 (s, 3H), 1.88−1.78 (m, 3H), 1.75−1.62 (m, 3H), 1.51 (s, 7H), 1.38 (s, 9H), 0.81 (s, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 186.9, 147.3, 137.3, 137.1, 136.1, 132.1, 130.1, 126.4, 125.4, 125.1, 124.2, 122.5, 121.1, 120.4, 78.8, 73.1, 48.5, 46.0, 42.7, 38.0, 37.9, 34.3, 31.7, 29.3, 28.5, 26.0, 25.2, 21.8, 16.7, 11.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{39}H_{42}O_5$+H^+ 591.3105; found 391.3111.

*(S)-Benzo[d][1,3]dioxol-5-ylmethyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bw**).* Prepared following ***general procedure A***. White solid; yield: 62.72 mg (70%); mp 110.8−112.1 °C. $[\alpha]_D^{20}$ = −62.4 (c = 0.492, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak IF column, *ee* = 94% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 10.15 min, tr(major) = 10.18 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.69 (d, J = 0.8 Hz, 1H), 7.86 (dd, J = 7.8, 1.9 Hz, 1H), 7.74 (dd, J = 7.6, 2.0 Hz, 1H), 7.22 (dd, J = 7.8, 1.7 Hz, 1H), 7.07 (td, J = 7.6, 0.8 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 6.95−6.91 (m, 1H), 6.76−6.72 (m, 2H), 6.70−6.65 (m, 1H), 5.87 (s, 2H), 4.98−4.86 (m, 2H), 1.82 (s, 3H), 1.33 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 187.0, 164.8, 156.3, 153.8, 146.7, 146.7, 139.9, 135.6, 131.3, 129.9, 128.2, 126.7, 125.8, 124.9, 124.1, 122.7, 121.4, 120.9, 108.1, 107.2, 100.1, 66.2, 34.2, 29.3, 16.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{26}O_6$+H^+ 449.1789; found 449.1783.

*(S)-4-Propionylphenyl-2-(2-(tert-butyl)-6-methylphenoxy)-3-formylbenzoate (**3bx**).* Prepared following ***general procedure C***. Brown oil; yield: 53.28 mg (60%); $[\alpha]_D^{20} = -72.9$ (c = 0.130, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak IF column, *ee* = 84% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 16.75 min, tr(major) = 18.10 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 9.60 (d, J = 0.8 Hz, 1H), 8.02 (dd, J = 7.6, 1.9 Hz, 1H), 7.96 (dd, J = 7.8, 1.9 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.24−7.19 (m, 1H), 7.19−7.17 (m, 1H), 7.11−7.07 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.99−6.95 (m, 1H), 2.86 (t, J = 7.3 Hz, 2H), 1.89 (s, 3H), 1.70 (q, J = 7.3 Hz, 2H), 1.37 (s, 9H), 0.93 (t, J = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ = 199.1, 187.7, 163.8, 158.0, 155.3, 154.0, 140.9, 137.2, 134.9, 133.7, 131.2, 129.7, 127.3, 127.2, 126.3, 125.4, 122.6, 122.2, 121.7, 40.5, 35.4, 31.4, 30.3, 30.2, 17.7, 17.7, 13.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{28}O_5$+H^+ 444.5240; found 444.5245.

General Procedure for Synthesis of Compound 5a. In a nitrogen-filled glovebox, a flame-dried screw-cap reaction tube equipped with a Teflon-coated magnetic stir bar was charged with **NHC-1** (10 mol %), Cs_2CO_3 (1.5 equiv), and anhydrous toluene (7.5 mL). EtOH **2a** (15 equiv) was added. The mixture was stirred for 5 min followed by the addition of **1a** (0.2 mmol) and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (0.75 equiv). After stirring at 0 °C for 12 h, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:1) to afford the crude product. The crude product and excess sodium borohydride were added to a 100-mL vial containing a magnetic stir bar, and 30 mL MeOH was added to this bar. After stirring for 10 min, the reaction mixture was concentrated in vacuo to give a residue, which was purified by flash chromatography (PE:EA = 100:6) to afford the products **5a**.

*(S)-(3-Bromo-2-(2-(tert-butyl)-6-methylphenoxy)phenyl)-methanol (**5a**).* White oil; yield: 24.29 mg (35%); $[\alpha]_D^{20}$ = −12.7 (c = 0.43, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 60% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.24 min, tr(major) = 6.82 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.66 (dd, J = 7.9, 1.7 Hz, 1H), 7.43 (dd, J = 7.7, 1.7 Hz, 1H), 7.24 (dd, J = 7.9, 1.9 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.95−6.92 (m, 2H), 3.98−3.82 (m, 2H), 1.87 (s, 3H), 1.44 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*)** δ = 165.2, 151.4, 149.9, 139.9, 135.7, 128.7, 128.6, 127.1, 124.2, 123.7, 122.9, 121.7, 111.9, 60.5, 34.3, 29.5, 16.8, 12.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}O_4$+H^+ 314.1677; found 314.1689.

General Procedure for Synthesis of Compound 6. To a solution of **3a** (0.1 mmol) in MeOH/H_2O = 4:1 (0.2 M), NaOH was added (40 mg, 10.0 equiv). The mixture was heated to 70 °C (oil bath) overnight. Then, HCl (1.0 M) was added to adjust to

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pH = 2−3 and extracted with EA (3 × 5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (DCM:CH_3OH = 10:1) to give the desired product **6** as a white oil.

(S)-2-(2-(tert-Butyl)-6-methylphenoxy)-3-(hydroxymethyl)benzoic Acid (6). White oil; yield: 59.66 mg (95%); $[\alpha]_D^{20}$ = −38.0 (*c* = 0.43, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 95% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 6.83 min, tr(major) = 7.70 min). **^{1}H NMR (500 MHz, DMSO)** δ 7.75 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.45−7.42 (m, 1H), 7.39−7.34 (m, 2H), 7.33−7.28 (m, 4H), 7.11 (tt, *J* = 6.2, 1.6 Hz, 5H), 7.04 (t, *J* = 8.2 Hz, 1H), 6.96−6.94 (m, 1H), 4.72 (dd, *J* = 5.8, 0.8 Hz, 2H), 2.24 (s, 3H), 2.06 (s, 3H). **^{13}C{^{1}H} NMR (126 MHz, DMSO)** δ = 168.3, 157.5, 155.2, 137.0, 136.3, 134.0, 132.7, 132.1, 131.5, 129.9, 129.1, 128.9, 128.7, 128.3, 128.1, 122.5, 117.8, 59.4, 21.1, 15.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{22}O_4$+H^+ 314.1677; found 314.1689.

General Procedure for Synthesis of Compound 7. Reactions were performed on a 1.00 mmol scale unless otherwise noted. To a screw-cap vial with a magnetic stir bar were added sodium methanesulfinate (0.3 mmol, 3.00 equiv), lithium bis(trimethylsilyl)amide 1.0 M in toluene (3.00 equiv), and **3a** (0.1 mmol, 1.00 equiv). The final concentration of the limiting reagent is 0.33 M. Then, the vial was sealed and heated at 100 °C on a heating block for 8 h. The reaction mixture was cooled to ambient temperature and diluted with saturated aqueous ammonium chloride (4 mL per mmol of 3). The mixture was concentrated to dryness, and the product was purified on silica gel.

(S)-1-(2-(2-(tert-Butyl)-6-methylphenoxy)-3-(hydroxymethyl)phenyl)ethan-1-one (7). White oil; yield: 53.04 mg (85%); $[\alpha]_D^{20}$ = −10.6 (*c* = 0.65, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 93% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 98:2, flow rate: 1 mL/min, 25 °C, tr(minor) = 9.61 min, tr(major) = 10.27 min). **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.55−7.52 (m, 1H), 7.34 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.19 (q, *J* = 2.7 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.90−6.88 (m, 1H), 4.61 (s, 2H), 3.29 (s, 3H), 1.78 (s, 3H), 1.36 (s, 9H). **^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*)** δ = 166.6, 152.2, 150.8, 140.0, 130.5, 129.9, 129.2, 128.9, 127.0, 124.3, 123.1, 121.0, 121.0, 60.1, 50.9, 34.4, 29.5, 16.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{24}O_3$+H^+ 313.4090; found 313.4093.

General Procedure for Synthesis of Compound 9. To a solution of **3ak** (0.1 mmol) in MeOH/H_2O = 4:1 (0.2 M), NaOH (40 mg, 10.0 equiv) was added. The mixture was heated to 70 °C (oil bath) overnight. Then, HCl (1.0 M) was added to adjust to pH = 2−3 and extracted with EA (3 × 5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (DCM:CH_3OH = 10:1) to give the desired product **9** as a white solid.

(S)-2-(2-(Diphenylphosphaneyl)-4,6-dimethylphenoxy)-3-(hydroxymethyl)benzoic Acid (9). White solid; yield: 53.38 mg (85%); mp 189.2−190.6 °C. $[\alpha]_D^{20}$ = −38.0 (*c* = 0.43, $CHCl_3$). Enantiomeric excess was established by HPLC analysis using a Chiralpak ADH column, *ee* = 99% (HPLC: ADH, 254 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1 mL/min, 25 °C, tr(minor) = 12.77 min, tr(major) = 16.18 min). **^{1}H NMR (500 MHz, DMSO)** δ 7.75 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.44 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.40−7.26 (m, 4H), 7.14−7.01 (m, 5H), 6.97−6.93 (m, 1H), 4.72 (dd, *J* = 5.8, 0.8 Hz, 2H), 2.74−2.68 (m, 1H), 2.24 (s, 2H). **^{13}C{^{1}H} NMR (126 MHz, DMSO)** δ 168.33, 157.51, 155.19, 137.01, 136.26, 134.04, 132.72, 132.05, 131.50, 129.94, 129.10, 128.95, 128.68, 128.29, 128.12, 122.47, 117.80, 59.37, 21.13, 15.94. **^{31}P NMR (202 MHz, $CDCl_3$)** δ 42.7 HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{25}O_4P$+H^+ 457.1639; found 457.1689.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00330.

Experimental procedures, characterization of compounds, and NMR spectra of products (PDF)

Accession Codes

CCDC 2283646 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

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