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Note

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Enantioselective Synthesis of 4-Methyl-3,4-dihydroisocoumarin via Asymmetric Hydroformylation of Styrene Derivatives

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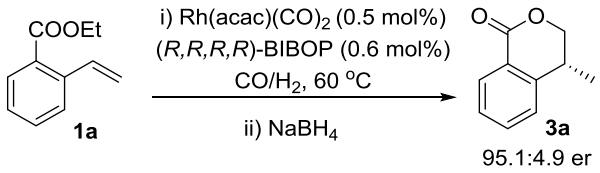
ABSTRACT



Enantioenriched aldehydes are produced through asymmetric hydroformylation of styrene derivatives using BIBOP type ligands. The featured example is enantioselective synthesis of 4-methyl-3,4-dihydroisocoumarin, which was prepared in a 95.1:4.9 enantiomeric ratio from asymmetric hydroformylation of ethyl 2-vinylbenzoate, then *in situ* lactonization during reduction process. The conditions are compatible with both electron-rich and electron-poor substituents.

3,4-Dihydroisocoumarins and their derivatives are widely present in nature as key intermediates for the synthesis of biologically active molecules.[1] They are regarded as highly attractive compounds and have many interesting activities. Naturally occurring 3,4-dihydroisocoumarins rarely have substitution at the 4-position.[2] They, nevertheless, have shown activities in many different disease areas such as antifungal,[3] antimicrobial,[4] antimalarial,[5] and insecticidal [6] (Figure 1).

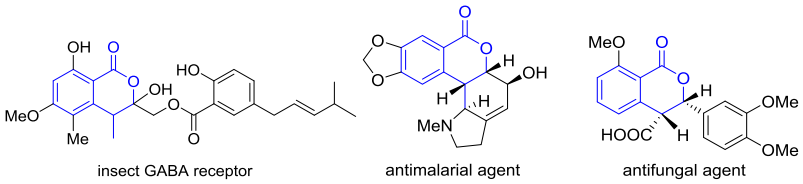
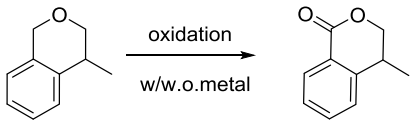


Figure 1. Representative 4-substituted 3,4-dihydroisocoumarins

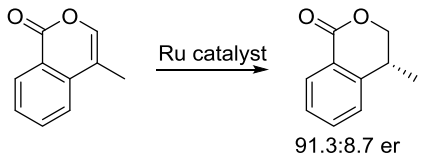
In view of the relevant importance of these molecules, facile and straightforward synthetic routes to 4-substituted 3,4-dihydroisocoumarins are highly desirable. Common methods involve oxidation of methylene groups adjacent to aromatic rings and/or ether oxygen atoms (Scheme 1a),[7] which require the use of often toxic oxidation reagents. Most recently, an elegant enantioselective synthesis of 4-methyl-3,4-dihydroisocoumarin was reported by asymmetric hydrogenation of 4-methyl isocoumarin (Scheme 1b).[8] Nevertheless, both approaches require pre-construction of the bicyclic ring structure.[7,8]

Scheme 1. Synthesis of 4-methyl-3,4-dihydroisocoumarin

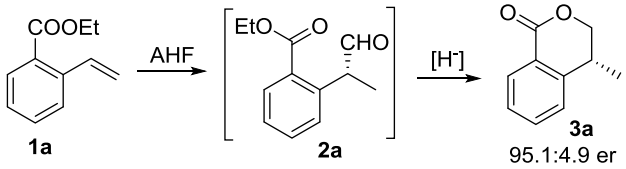
a: Selective Oxidation (ref 7)



b: Asymmetric hydrogenation (ref 8)



c. Enantioselective hydroformylation (This work):



Hydroformylation is an industrial process for the production of aldehydes from alkenes via the net addition of a formyl group and a hydrogen atom to a carbon-carbon double bond.[9] A number of synthetically useful intermediates can be derived from the resulting aldehydes.

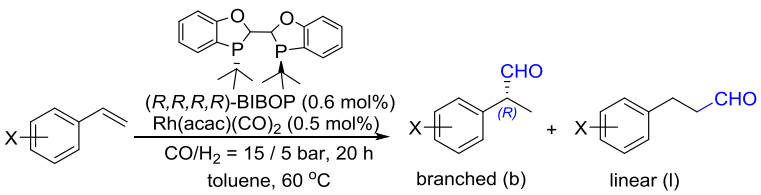
Applications to the synthesis of branched chiral aldehydes with a rhodium catalyst have also made much progress in recent years[10] with the discovery of effective chiral phosphine ligands including Ph-BPE, Binaphos, Chiraphite, Kelliphite, Yanphos, Duanphos and bis(diazaphospholane) (BDP) ligands.[11-16] The emergence of new ligand scaffolds that affect rapid, enantioselective, and regioselective hydroformylation provides new strategies for the efficient synthesis of chiral intermediates which otherwise cannot be accessed readily. Recently we reported that conformationally rigid bisdihydrobenzooxaphosphole ligands (BIBOPs) are highly effective and enantioselective for rhodium-catalyzed asymmetric hydroformylation (AHF) of various mono- and di-substituted alkenes.[17] Furthermore, these BIBOP ligands are stable in air and can be isolated as crystalline solid; which make them conveniently synthesized on kilogram scales.[18] To apply AHF toward the synthesis of highly functionalized intermediates, we hypothesized that asymmetric hydroformylation of an *ortho*-ester substituted styrene would produce an *in situ* cyclized six-membered chiral lactone during reduction of the aldehyde. Herein, we report the direct synthesis of highly enantioenriched α-methyl substituted 4-methyl-3,4-dihydroisocoumarin via asymmetric hydroformylation of ethyl 2-vinylbenzoate, followed by *in situ* lactonization during a subsequent reduction process.

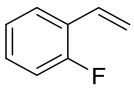
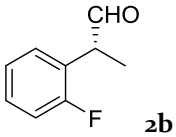
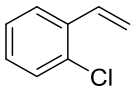
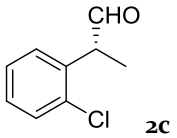
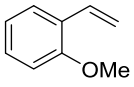
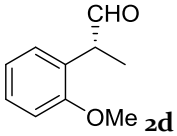
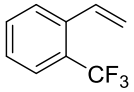
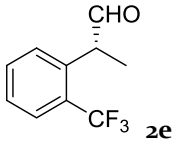
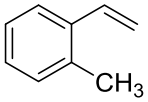
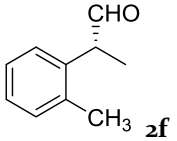
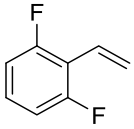
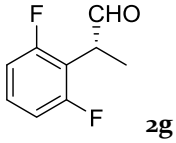
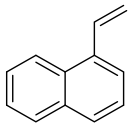
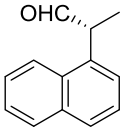
Commercially available ethyl 2-vinylbenzoate was selected for the study. It can also be accessed through vinylation of aryl bromide.[19] The reaction was tested in the presence of 0.5 mol% $Rh(acac)(CO)_2$ and 0.6 mol% of (*R*,*R*,*R*,*R*)-BIBOP ligand, and syn gas pressure of 15/5 bar of CO/H_2 at 60 °C. The starting material fully disappeared as judged by ^1H NMR analysis of the reaction mixture after 20 h. A major aldehyde compound was produced in a branched:linear (b/l) ratio of 12:1. The unpurified reaction mixture was then reduced with $NaBH_4$ at 0 °C. The isolated product was confirmed to be 4-methyl 3,4-dihydroisocoumarin **3a** with 90% yield and 95.1:4.9 er (Scheme 1c).

The AHF conditions were also applied to other *ortho*-substituted styrene derivatives (Table 1). Both electron rich and electron deficient styrene derivatives are compatible under the reaction conditions. 2-Fluoro styrene produced a high branched:linear ratio of 21.3:1 with 93.1:6.9 er for compound **2b**.[20] 2-Chloro and 2-methoxy styrenes gave similar selectivity at enantiomeric ratios of 93.9:6.1 and 94.2:5.8, respectively. For CH_3 or CF_3 substituted styrenes, same enantioselectivity of the aldehydes was obtained at 93:7 er, but with slightly decreased b/l

ratios at 4.7:1 and 2.2:1 respectively. The highest b/l ratio was obtained with bis-*ortho* fluoro-substituted styrene, where >100:1 of b/l ratio was obtained for **2g**. The reduced alcohol product **3g** was isolated in 94% yield and 94.5:5.5 er. 1-Vinylnaphthalene was hydroformylated in 5.1:1 of b/l ratio (**2h**) and an enantiomeric ratio of 89.5:10.5.

Table 1. AHF of the styrene derivatives

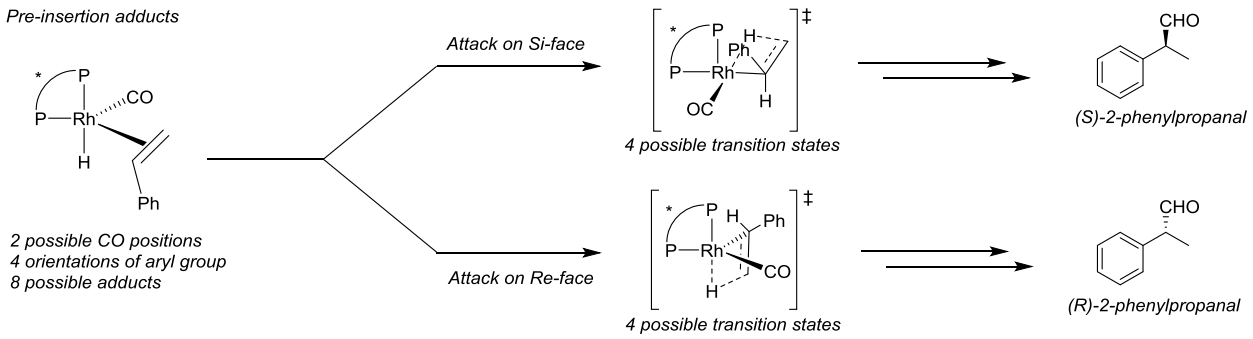


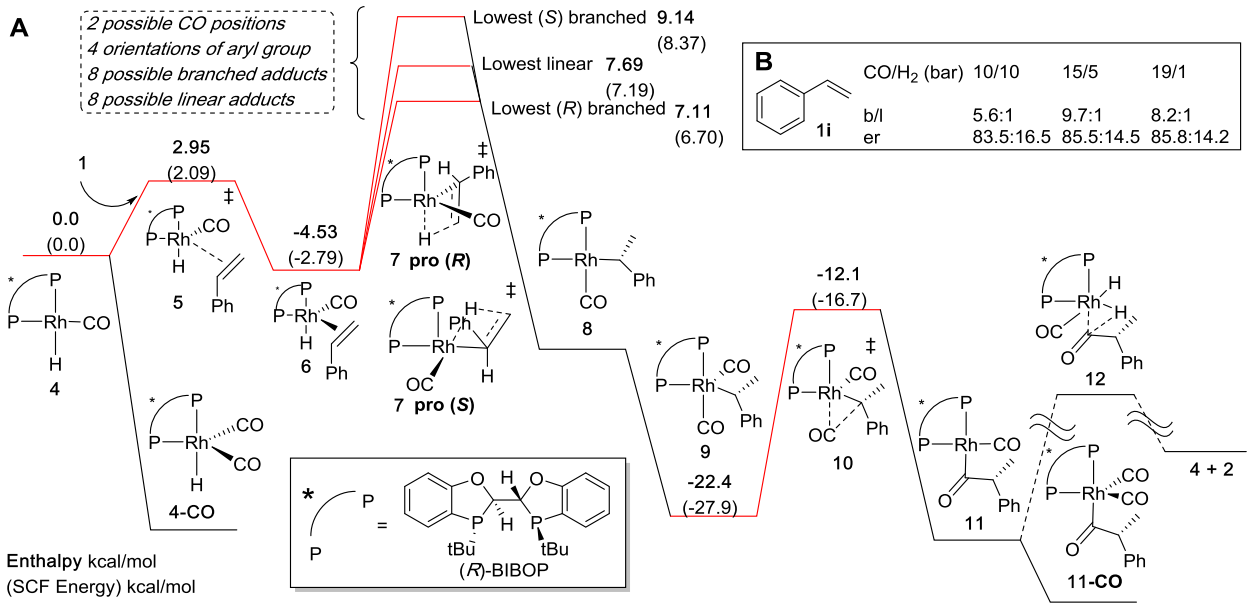
Entry	Substrate	Product	yield[a]	b:l[b]	er[c]
1		 **2b**	93%	21.3	93.1 : 6.9
2		 **2c**	86%	9.3	93.9 : 6.1
3		 **2d**	85%	8.5	94.2 : 5.8
4[d]		 **2e**	76%	4.7	93.2 : 6.8
5[e]		 **2f**	55%	2.2	93.0:7.0
6		 **2g**	94%	>100	94.5 : 5.5
7[e]		 **2h**	72%	5.1	89.5:10.5

[a] All the reactions proceeded at >99% conv. Isolated yields of the branched alcohol products (**3b-3h**) after $NaBH_4$ reduction; the corresponding linear products are the main side products. Absolute stereochemistry was assigned by comparing the sign of the optical rotation with those reported in the literature. [b] Determined by ^1H NMR spectroscopy on the aldehyde products (**2b-2h**). [c] Determined by Chiral GC and HPLC; same enantioselectivity was observed for the crude aldehyde products and the reduced products alcohols. [d] 1.0 mol% $Rh(acac)(CO)_2$, 1.2 mol% (*R,R,R,R*)-BIBOP. [e] 1.0 mol% $Rh(acac)(CO)_2$, 1.2 mol% (*R,R,R,R*)-MeO-BIBOP.

The mechanisms of rhodium catalyzed hydroformylation reactions are complex due to potentially reversible steps, steps disproportionately affected by CO or H_2 pressure, off-cycle intermediates, and the possibility of multiple selectivity and TOF determining steps.[21] A simplified version of the likely pathway is outlined in Scheme 2a. In related systems,[21,22] the most catalytically relevant steps are alkene coordination, alkene insertion, and CO insertion. Using a BP86 functional based on a published benchmarking study for related processes,[23] alkene insertion was found to be a high energy barrier, whereas the barriers for alkene coordination and CO insertion were considerably lower. Even so, the reaction of styrene with D_2/CO gave rise to products incorporating hydrogen instead of deuterium and recovered styrene containing deuterium (see SI), which is consistent with reversibility in the alkene insertion step. Varying the CO pressure (Scheme 2b) revealed a slight increase in enantioselectivity consistent with the barriers to alkene insertion becoming higher, and reducing the reversibility.[21d] In such a scenario, an energy span analysis is the most accurate protocol to estimate enantioselectivity or regioselectivity (b/l) by taking into account reversibility.[21a] However, a much simpler analysis using the relative transition state energies for the alkene insertion step has been found to provide a good approximation of these values.[21a,23,24]

Scheme 2. Mechanism of enantiodetermining olefin insertion in the asymmetric hydroformylation of styrene[a]

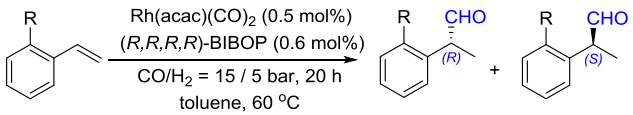




[a] Structures in red are calculated. Remaining structures are presented based on reported studies (see refs 21-24). For clarity, only one structure is shown per intermediate/transition state with the exception of the alkene insertion where the lowest energy transition states leading to the three possible isomers are shown.

Thus, the alkene adducts and the alkene insertion step were exhaustively explored with a total of 16 isomers of the latter being possible, eight that could lead to the chiral branched aldehyde and eight to linear the aldehyde. Ultimately, eight unique transition states were found that give the branched aldehyde (Scheme 2). Notably, the ligand was most stable in an axial/equatorial coordination mode and the lowest energy transition states positioned the hydride axial which, in turn, dictates approach of the styrene. The amount of (*R*)-2-phenylpropanal relative to that of (*S*)-2-phenylpropanal was calculated *via* a Boltzmann distribution analysis of these transition states. The results indicate that the model predicts the stereochemical outcome in good to excellent agreement with experiment for three substrates (Table 2). The lowest energy transition state leading to the linear isomer was also located for styrene and when the free energy was compared to that of the lowest energy branched isomer provided a fair estimate of the b/l ratios (expt = 10.2:1, computed = 4.3:1).

Table 2. Enantioselectivity predictions for the asymmetric hydroformylation of styrene derivatives



R	computed er[a] (*R*):(*S*)	experimental er (*R*):(*S*)
H[c]	84.9:15.1	83.5:16.5 85.3:14.7[b]
F	85.5:14.5	93.1:6.9
CF_3	83.2:16.8	93.4:6.6

[a] Calculated from Gibbs free energies obtained using BP86/(cc-pVTZ; Rh: SDD)-IEFPCM-Toluene // BP86/(6-31G*; Rh: LANL2DZ); [b] (*R*,*R*,*R*,*R*)-MeO-BIBOP was used. [c] Branched:linear ratios: expt = 10.2:1, computed = 4.3:1.

Our model and a distortion/interaction analysis[25] suggests that steric factors are the dominant control element in the hydroformylation. As shown in the lowest energy transition states leading to each enantiomer (Figure 2), the (*R*,*R*,*R*,*R*)-BIBOP ligand promotes asymmetric hydroformylation by sterically crowding the substrate in transition states leading to the (*S*)-enantiomer more significantly than in those leading to the (*R*)-enantiomer. In Panel **A**, the (*S*)-enantiomer approach places the phenyl group of styrene close to the large *tert*-butyl group on the ligand. Conversely, in Panel **B**, the (*S*)-enantiomer approach tilts the phenyl group of styrene away from the *tert*-butyl group on the ligand, and this structure is consequently more stable by 1.38 kcal/mol. This model also indicates that the position ortho to the phosphorous on the aromatic rings of the ligand comes in close proximity to the substrate and may be used to modulate the selectivity. With methoxy groups in these positions (Table 2, entry 1), slightly higher enantioselectivities were observed, illustrating the potential for exploration of further ligand variants along these lines.

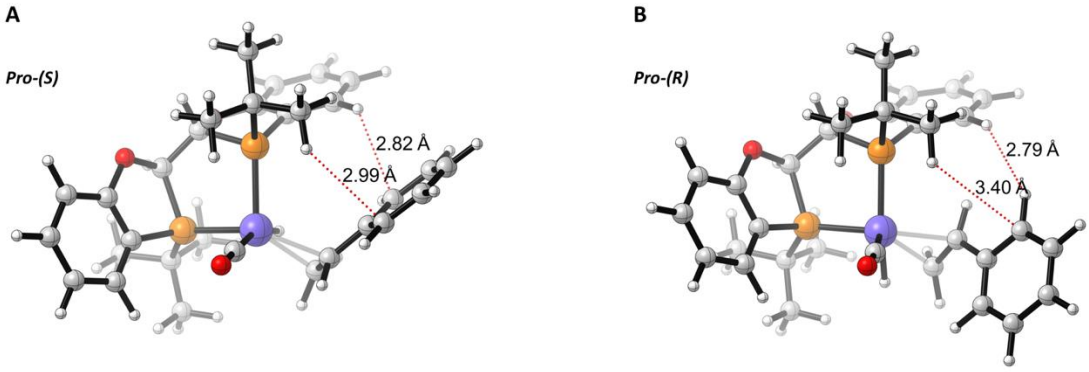


Figure 2. Three-dimensional representations of the computed lowest energy transition states leading to (*S*)-2-phenylpropanal (**A**) and (*R*)-2-phenylpropanal (**B**). The red double-headed arrows represent steric interactions. Both structures were calculated using BP86/(cc-pVTZ; Rh: SDD)-IEFPCM-Toluene // BP86/(6-31G*; Rh: LANL2DZ).

In summary, asymmetric hydroformylation is an atom-economical homogenous catalytic process that constructs optically active aldehydes in one step from alkenes in the presence of syn gas with minimal waste generation. BIBOP ligands have been found as effective in the enantioselective Rh-catalyzed asymmetric hydroformylation of styrene derivatives. Enantioenriched 4-methyl-3,4-dihydrocumarine was effectively synthesized from 2-vinylbenzoate using this method followed by reduction. Styrenes with different substituents underwent similar transformations. Calculations reveal a very rigid ligand architecture that reduces conformational freedom and positions the stereogenic *tert*-butyl groups directly into the reactive space. The stereochemistry was largely controlled by steric effects between the approaching styrene and these *tert*-butyl groups. Interaction with the arene backone of the ligand, indicate an opportunity for further catalyst engineering to improve outcomes.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an atmosphere of argon or nitrogen in dry glassware with magnetic stirring. All commercially available reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 MHz or DRX500 MHz spectrometer with TMS as internal reference. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet,

t = triplet, q = quartet, quint = quintet, hex = hexet, m = multiplet, br = broad), coupling constant, and integration. High resolution mass spectra (HRMS) were obtained on a Thermo LTQ FT Ultra Mass Spectrometer with heated electrospray ionization (positive), and using linear ion trap with a Fourier Transform ion cyclotron resonance (FTICR) MS detector. Chiral analyses were performed on an Agilent HP 1200 Series HPLC system or on SFC systems.

General Procedure for the Asymmetric Hydroformylation. In a glovebox filled with nitrogen, ligand (0.012 mmol) and [Rh(acac)$(CO)_2$] (0.01 mmol in 0.4 mL toluene) were added to a 2 mL vial. After stirring for 10 minutes, the substrate (1.0 mmol) and additional solvent were added to bring the total volume of the reaction mixture to 0.5 mL. The vial was transferred into an autoclave and taken out of the glovebox. Hydrogen and carbon monoxide were added sequentially. The reaction mixture was stirred at 60 ^{o}C for 20 hours under CO/H_2 pressure of 15/5 bar. The reaction was then cooled and the pressure was carefully released in a well-ventilated fume hood. The conversion and branched/linear ratio of this reaction were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The reaction vial was then placed into an ice-water bath, $NaBH_4$ and MeOH were added, after stirring for 30 min, water was added to quench the reaction. The mixture was extracted with EtOAc 3 times, organic phases were combined and dried with anhydrous Na_2SO_4 and concentrated under reduced pressure, the residue was chromatographed on silica gel to give the pure alcohol products **3a-h**. The enantiomeric excess was determined by HPLC or SFC analysis. For deuterioformylation of styrene, deuterium (5 bar) and carbon monoxide (15 bar) was added sequentially. The reaction mixture was stirred at 60 ^{o}C for 5 hours under CO/D_2 pressure of 15/5 bar.

Experimental Data of Products. *(R)-4-methylisochroman-1-one (**3a**).* The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 146.0 mg, 90% yield, 95.1:4.9 er; HPLC Chiralpak AD-3, isocratic: heptane/2-propanol = 85/15, flow rate = 0.5 mL/min; λ = 254 nm, retention time: 6.1 min (major), 7.0 min (minor). NMR data match those reported in the literature.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 4.51 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.24 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.21 – 3.12 (m, 1H), 1.37 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.1, 144.6, 133.9, 130.4, 127.5, 125.7, 124.4, 72.5, 31.7, 16.7. HRMS (ESI) $[M+H]^+$ *m/z* calcd for $[C_{10}H_{11}O_2]^+$ is 163.0754, found 163.0754.

*(R)-2-(2-fluorophenyl)propan-1-ol (**3b**)* The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 143.4 mg, 93% yield, 93.1:6.9 er; $[\alpha]_D^{22}$ = +13.97 (c = 1.335 in $CHCl_3$) ($[\alpha]_D^{25}$ = +13.5, c = 0.85 in DCM, 95% ee);[26]

SFC Chiralpak IC-3, 4.6 mm x 150 mm, temperature: 10 ºC, A: CO_2, B: isopropanol, isocratic: A/B: 98.5/1.5, v/v, flow rate = 2.5 mL/min; λ = 254 nm, retention time: 4.7 min (major), 5.0 min (minor). NMR data match those reported in the literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.13 (m, 2H), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H), 7.00 (ddd, *J* = 10.4, 8.1, 1.2 Hz, 1H), 3.69 (ddd, *J* = 17.1, 10.6, 6.9 Hz, 2H), 3.26 (hex, *J* = 6.9 Hz, 1H), 2.06 (br s, 1H), 1.27 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.1 (d, *J* = 245.0 Hz), 130.6 (d, *J* = 14.5 Hz), 128.5 (d, *J* = 5.1 Hz), 127.9 (d, *J* = 8.4 Hz), 124.2 (d, *J* = 3.4 Hz), 115.5 (d, *J* = 22.9 Hz), 67.2, 35.6, 16.6.

*(R)-2-(2-chlorophenyl)propan-1-ol (**3c**)*. The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 146.8 mg, 86% yield, 93.9:6.1 er; SFC Chiralpak IC-3, 4.6 mm x 150 mm, temperature: 10 ºC, A: CO_2, B: isopropanol, isocratic: A/B: 98.5/1.5, v/v, flow rate = 2.5 mL/min; λ = 220 nm, retention time: 7.2 min (major), 7.9 min (minor). NMR data match those reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.18 – 7.10 (m, 1H), 3.73 (dddd, *J* = 39.9, 10.8, 6.4, 1.5 Hz, 2H), 3.52 (hex, *J* = 6.7 Hz, 1H), 1.71 (br s, 1H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.9, 134.3, 129.7, 127.6, 127.6, 127.1, 67.1, 38.1, 16.8.

*(R)-2-(2-methoxyphenyl)propan-1-ol (**3d**)*. The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 141.3 mg, 85% yield, 94.2:5.8 er; SFC Chiralpak IC-3, 4.6 x 150 mm: 10 ºC, A: CO_2, B: isopropanol; isocratic: A/B: 99/1, v/v, flow rate 2.5 mL/min, λ = 220 nm, retention time: 13.0 min (major), 14.5 min (minor). NMR data match those reported in the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 6.98 – 6.90 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.77 – 3.61 (m, 2H), 3.47 – 3.36 (m, 1H), 1.74 (br s, 1H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 131.8, 127.4, 127.4, 120.8, 110.6, 67.8, 55.4, 35.2, 16.6.

*(R)-2-(2-(trifluoromethyl)phenyl)propan-1-ol (**3e**)*. The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 155.2 mg, 76% yield, 93.2:6.8 er; SFC Chiralpak IC-3, 4.6 x 150 mm: 10 ºC, A: CO_2, B: isopropanol; isocratic: A/B: 98.5/1.5, v/v, flow rate 2.5 mL/min, λ = 220 nm, retention time: 2.6 min (major), 2.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 3.84 – 3.65 (m, 2H), 3.41 (hex, *J* = 7.0 Hz, 1H), 1.59 (br s, 1H), 1.29 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.2, 132.0, 128.7 (d, *J* = 6.0 Hz), 127.7, 126.3, 125.9 (d, *J* = 6.0 Hz), 123.2 (q, *J* = 271.8 Hz), 67.9, 37.4 (d, *J* = 1.5 Hz), 18.5. HRMS (ESI) $[M+NH_4]^+$ *m*/*z* calcd for $[C_{10}H_{15}ONF_3]^+$ is 222.1100, found 222.1101.

*(R)-2-(o-tolyl)propan-1-ol (**3f**)*. The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as pale brown oil: 82.6

mg, 55% yield, 93.0:7.0 er; Aquity UPLC Lux 3μ Amylose-1, 3.0 x 150 mm, 10 ºC, A: CO_2, B: isopropanol; Isocratic: A/B: 99.7/0.3, v/v, flow rate 2.5 mL/min, λ = 220 nm, retention time: 3.7 min (minor), 4.1 min (major). NMR data match those reported in the literature.[26,28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.13 (m, 2H), 3.72 (m, 2H), 3.28 (m, 1H), 2.35 (s, 3H), 1.58 (br s, 1H), 1.24 (d, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.8, 136.4, 130.5, 126.4, 126.3, 125.5, 68.0, 37.2, 19.6, 17.6.

*(R)-2-(2,6-difluorophenyl)propan-1-ol (**3g**)*. The title compound was prepared according to the general procedure and purified by column chromatography (hexane/ethyl acetate = 4:1) to give the product as colorless oil: 161.8 mg, 94% yield, 94.5:5.5 er; SFC Chiralpak OD-3, 4.6 x 150 mm: 10 ºC, A: CO_2, B: isopropanol; isocratic: A/B: 99/1, v/v, flow rate 2.5 mL/min, λ = 220 nm, retention time: 4.0 min (major), 4.6 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.11 (m, 1H), 6.85 – 6.82 (m, 2H), 3.85 – 3.77 (m, 2H), 3.45 (hex, *J* = 7.2 Hz, 1H), 2.05 (br s, 1H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.8 (d, *J* = 9.4 Hz), 160.9 (d, *J* = 9.3 Hz), 127.9 (t, *J* = 10.6 Hz), 119.0 (t, *J* = 18.2 Hz), 111.6 (d, *J* = 5.8 Hz), 111.5 (d, *J* = 5.8 Hz), 66.0 (d, *J* = 2.5 Hz), 33.1, 15.7 (t, *J* = 2.5 Hz). HRMS (ESI) $[M+NH_4]^+$ *m/z* calcd for $[C_9H_{14}ONF_2]^+$ is 190.1038, found 190.1039.

*(R)-2-(naphthalen-1-yl)propan-1-ol (**3h**)*. The title compound was prepared according to the general procedure and purified by column chromatography with 100% dicholoromethane to give the product as colorless oil: 134 mg, 72% yield, 89.5:10.5 er; SFC Chiralpak IC-3, 4.6 x 150 mm: 10 ºC, A: CO_2, B: isopropanol; isocratic: A/B: 97/3, v/v, flow rate 2.5 mL/min, λ = 220 nm, retention time: 14.5 min (minor), 15.9 min (major). NMR data matches to those reported.[26,28] ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR: (500 MHz, $CDCl_3$): 8.16 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.50 (m, 4 H), 3.95 (m, 1H), 3.89 (m, 2 H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.37 (br s, 1H). ^{13}C{^{1}H} NMR: (126 MHz, $CDCl_3$): 139.5, 134.0, 131.9, 129.0, 127.1, 126.0, 125.5, 123.05, 123.04, 68.1, 36.4, 17.8.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website
HPLC, NMR spectra and calculation data (PDF)

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Notes
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