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Squaramide-Catalyzed Asymmetric Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Carbonyls Containing Benzyl Alcohol: Construction of Chiral 1-Substituted Phthalans

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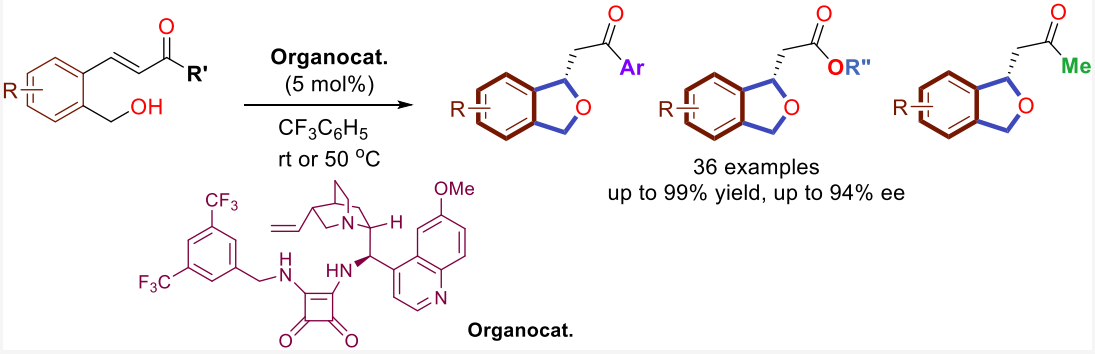

ABSTRACT: Organocatalytic enantioselective intramolecular oxa-Michael reactions of benzyl alcohol bearing α,β-unsaturated carbonyls as Michael acceptors are presented herein. Using cinchona squaramide-based organocatalyst, enones as well as α,β-unsaturated esters containing benzyl alcohol provided their corresponding 1,3-dihydroisobenzofuranyl-1-methylene ketones and 1,3-dihydroisobenzofuranyl-1-methylene esters in excellent yields with high enantioselectivities. In addition, enantioenriched 1,3-dihydroisobenzofuranyl-1-methylene ketone could be obtained from the Wittig/oxa-Michael reaction cascade of 1,3-dihydro-2-benzofuran-1-ol.

INTRODUCTION

Oxygen-containing heterocycles are privileged motifs and have attracted immense attention in recent times due to their widespread presence in natural products and biologically active compounds, as well as their increasing importance in the fields of pharmaceuticals and fine chemicals. Therefore, the development of new synthetic methodologies for these oxacyclic frameworks, especially in their chiral forms, is of great interest in organic synthesis.[1] In particular, chiral 1,3-dihydroisobenzofuran, commonly referred to as phthalan, is abundant in bioactive natural products, which display pharmacological properties such as antibacterial, anti-inflammatory, antidepressive, antioxidant, and anti-influenza (Figure 1).[2] Several synthetic methods have been developed for phthalans based on cyclization strategies.[3] However, most reactions are limited to the synthesis of nonchiral phthalans. Catalytic asymmetric synthesis of chiral phthalans is still a particularly challenging task, and only a few catalytic methods are known.[4]

The oxa-Michael reaction, conjugate addition of oxygen-centered nucleophiles to α,β-unsaturated compounds, is one of the simplest and most direct strategies to develop carbon−oxygen bonds.[5] In the last decade, the asymmetric catalytic oxa-Micheal reaction has been used as a powerful tool in the synthesis of chiral oxygen-containing heterocycles through the combination of cascade reactions and utilization of organocatalysts.[6] The catalytic asymmetric intramolecular oxa-Michael reaction (AIOM) strategy has been used to directly and effectively access chiral tetrahydrofuran (THF), tetrahydropyran (THP), 2,3-dihydrobenzofuran, and chromane rings.[1,7] In 2012, Matsubara and co-worker succeeded in the enantioselective intramolecular oxa-Micheal reaction of ε-hydroxy-α,β-unsaturated ketone substrates catalyzed by a cinchona thiourea-based bifunctional organocatalyst for the construction of chiral THF and THP.[7a] Subsequently, Zhao and co-workers reported the chiral primary−secondary diamine-catalyzed AIOM of α,β-unsaturated ketone substrates bearing a pendant hydroxyl group yielding enantioenriched THF and THP.[7b] In 2018, Song and co-workers developed a highly efficient chiral cooperative cation-binding catalyst system for AIOM.[7c]

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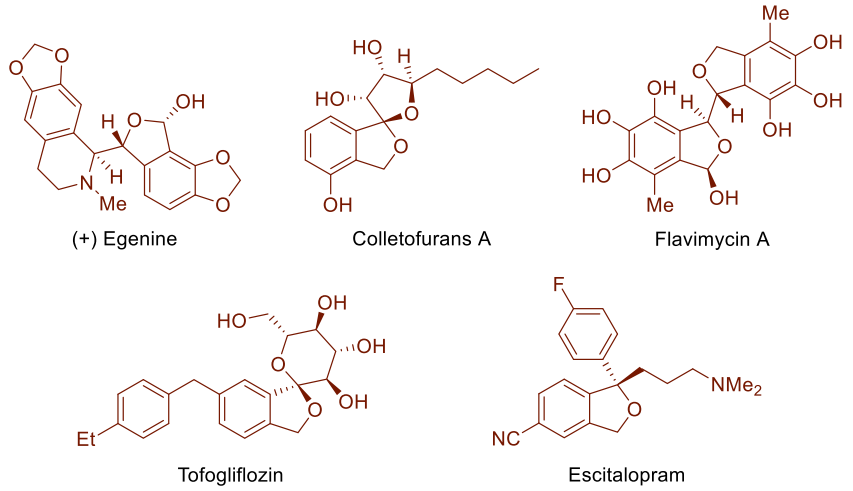
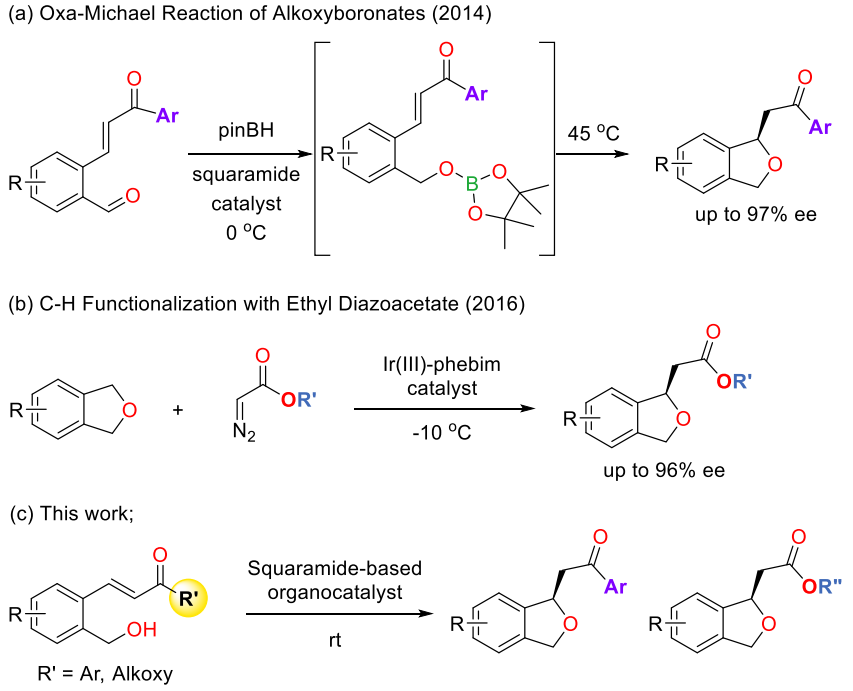


Figure 1. Biologically active chiral compounds containing the 1,3-dihydroisobenzofuran scaffold.

Scheme 1. Approaches for the Synthesis of Enantioenriched 1-Substituted 1,3-Dihydroisobenzofurans



The enantioselective synthesis of chromane using AIOM was achieved well ahead of that of THF and THP.[8] In 2004, Merschaert and co-workers established the cinchona alkaloid-catalyzed AIOM of α,β-unsaturated esters bearing phenol to afford 2-substituted chiral chromanes.[8a] In 2013, similar results for the synthesis of enantioenriched dihydrobenzofuranyl acetates were presented by Hintermann and co-workers.[8b] Soon after, the AIOM of α,β-unsaturated ketones bearing phenol, catalyzed by a bifunctional cinchona thiourea catalyst, generating optically active chromanes was reported by Matsubara and co-workers.[8d] Takemoto and co-workers developed methods for the AIOM of α,β-unsaturated amides bearing phenol and α,β-unsaturated carboxylic acids bearing phenol catalyzed by chiral aminobenzothiadiazine and chiral aminothiourea, respectively.[8c,e]

Despite the aforementioned achievements, the AIOM of α,β-unsaturated carbonyl substrates bearing a benzyl alcohol group,[9] affording chiral 1,3-dihydroisobenzofuran, has received considerably less attention and not been described thus far. There are still challenging issues associated with this AIOM that would need to be addressed, including its rapid cyclization and reversibility. In addition, the difficulty in the synthesis of α,β-unsaturated ketones bearing benzyl alcohol prevented this type of AIOM.[9d,e] To overcome such challenges and synthesize chiral 1,3-dihydroisobenzofuran, Ghorai and co-workers established the AIOM of α,β-unsaturated ketones bearing benzyloxyboronate, generated in situ from *o*-formyl chalcones catalyzed by a squaramide organocatalyst affording enantioenriched 1,3-dihydroisobenzofuranyl-1-methylene aromatic ketones (Scheme 1a).[4c] The synthetic approach for enantioenriched 1,3-dihydroisobenzofuranyl-1-methylene esters was also reported by Blakey and co-workers, in which enantioselective C−H insertion of ethyl diazoacetates into phthalan was achieved using an Ir(III)-phebim catalyst (Scheme 1b).[4d] Nevertheless, we still questioned the feasibility of the direct AIOM of α,β-unsaturated carbonyl substrates bearing benzyl

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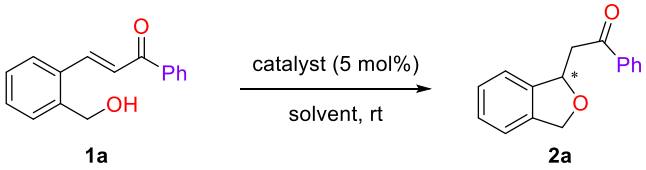
alcohol. If α,β-unsaturated carbonyl substrates bearing benzyl alcohol are synthesized more easily and subsequent AIOM is possible, chiral 1-substituted phthalan could be easily accessed (Scheme 1c). For this reason, we have revisited this direct AIOM through careful investigation. Herein, we report the direct AIOM of β-unsaturated carbonyl substrates (ketones and esters) bearing benzyl alcohol using a cinchona squaramide-based organocatalyst.

RESULTS AND DISCUSSION

First, a variety of β-(2-hydroxymethyl)phenyl α,β-unsaturated carbonyl compounds **1** and **3** were successfully synthesized in three steps from *o*-methylbenzoic acids via modified previously reported procedures.[10] Our asymmetric catalytic studies were initiated with the intramolecular oxa-Michael reaction of (*E*)-3-(2-(hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one **1a** using 5 mol % of the Takemoto bifunctional thiourea catalyst **Ia**[11] (Table 1). When the reaction was conducted for 30 h in toluene at room temperature, phthalan **2a** was obtained in 97% yield with moderate enantioselectivity (56% enantiomeric excess (ee), Table 1, entry 1). Having identified the chiral discrimination by the hydrogen-bonding interactions as the activation mode for this AIOM reaction, we turned our attention to determine the optimal catalyst for high enantioselectivity.

Table 1. Optimization of the Reaction Conditions[a]

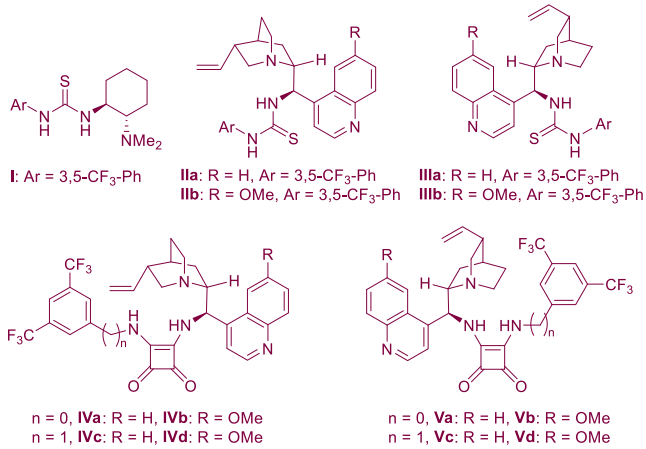


1a **2a**

entry	catalyst	solvent	time (h)	yield (%)[b]	ee[c]
1	**I**	toluene	30	97	56
2	**IIa**	toluene	8	96	66
3	**IIb**	toluene	6	97	75
4	**IIIa**	toluene	6	96	73
5	**IIIb**	toluene	6	95	70
6	**IVa**	toluene	2	92	86
7	**IVb**	toluene	2	99	88
8	**IVc**	toluene	24	90	85
9	**IVd**	toluene	2	96	91
10	**Va**	toluene	2	93	89
11	**Vb**	toluene	2	96	90
12	**Vc**	toluene	28	90	83
13	**Vd**	toluene	2	95	90
14	**IVd**	*o*-xylene	3	97	89
15	**IVd**	*m*-xylene	6	95	89
16	**IVd**	*p*-xylene	3	95	90
17	**IVd**	$CF_3C_6H_5$	3	90	94
18	**IVd**	CH_2Cl_2	2	93	91
19	**IVd**	CH_3CN	24	91	88
20	**IVd**	THF	120	91	80
21	**IVd**	MeOH	120	66	71
22[d]	**IVd**	$CF_3C_6H_5$	48	87	92
23[e]	**IVd**	$CF_3C_6H_5$	3	82	89

[a]The reactions were carried out in solvent (0.5 M) with 1a (0.1 mmol) and catalyst (5 mol %). [b]After chromatographic purification. [c]Determined by chiral-phase high-performance liquid chromatography (HPLC) analysis. [d]Reaction carried out at 0 °C. [e]2 mol % catalyst used.

With the optimized conditions in hand, we next examined the generality of the quinidine-derived squaramide-catalyzed AIOM (Scheme 2). β-(2-Hydroxymethyl)phenyl α,β-unsaturated aromatic ketones **1a−g** bearing different aromatics such as para- or meta-substituted phenyl groups smoothly participated in the intramolecular oxa-Michael reaction to furnish enantioenriched phthalan products **2a−g** in good to excellent yields with high enantioselectivities. Moreover, heteroaryls such as 2-furyl (**2h**) and 2-thiophenyl (**2i**) on the enone successfully underwent AIOM in excellent yields with 86 and 89% ee, respectively. Additionally, substitution on the central aryl moiety was tested under the optimized reaction conditions. Regardless of the electron nature and position of the R group in the aromatic ring, substituents such as Me (**2j** and **2k**), MeO (**2l**), Br (**2m** and **2n**), Cl (**2o**), F (**2p**), F_3C (**2q**), and NO_2 (**2r**) were well tolerated and provided outstanding enantioselectivities (83−94% ee). The absolute configurations of phthalans **2** were confirmed by comparison with Ghorai's work.[4c]



A variety of chiral bifunctional alkaloid organocatalysts were screened in this AIOM (Table 1). Cinchona-derived thiourea-based catalysts[12] provided excellent yields with 66−75% ee (Table 1, entries 2−5). On the other hand, cinchona-derived squaramide-based catalysts[13] also showed excellent yields with high enantioselectivites (83−90% ee, Table 1, entries 6−13). Squaramide catalysts featuring a methoxy group on the quinolone moiety exhibited higher enantioselectivities (Table 1, entries 6 and 8 vs entries 7 and 9, entries 10 and 12 vs entries 11 and 13). Among the bifunctional squaramides tested (see Table S1 in the Supporting Information), 3,5-bis-(trifluoromethyl)benzylamine-containing quinidine-derived squaramide **IVd** was found to be the optimal catalyst in terms of reactivity and enantioselectivity (96% yield, 91% ee, Table 1, entry 9). To further optimize the reaction conditions, screening of various organic solvents such as toluene, *o*-xylene, *m*-xylene, *p*-xylene, $CF_3C_6H_5$, CH_2Cl_2, CH_3CN, and THF was performed using **IVd** (Table 1, entries 14−20). In $CF_3C_6H_5$, an increase in enantioselectivity to 94% ee was observed while maintaining the yield (Table 1, entry 17). Interestingly, the AIOM using **IVd** exhibited enantio-induction resulting in 71% ee even in protic solvents such as MeOH (Table 1, entry 21). Lowering the reaction temperature and catalyst loading did not increase reactivity or enantioselectivity (Table 1, entries 22 and 23).

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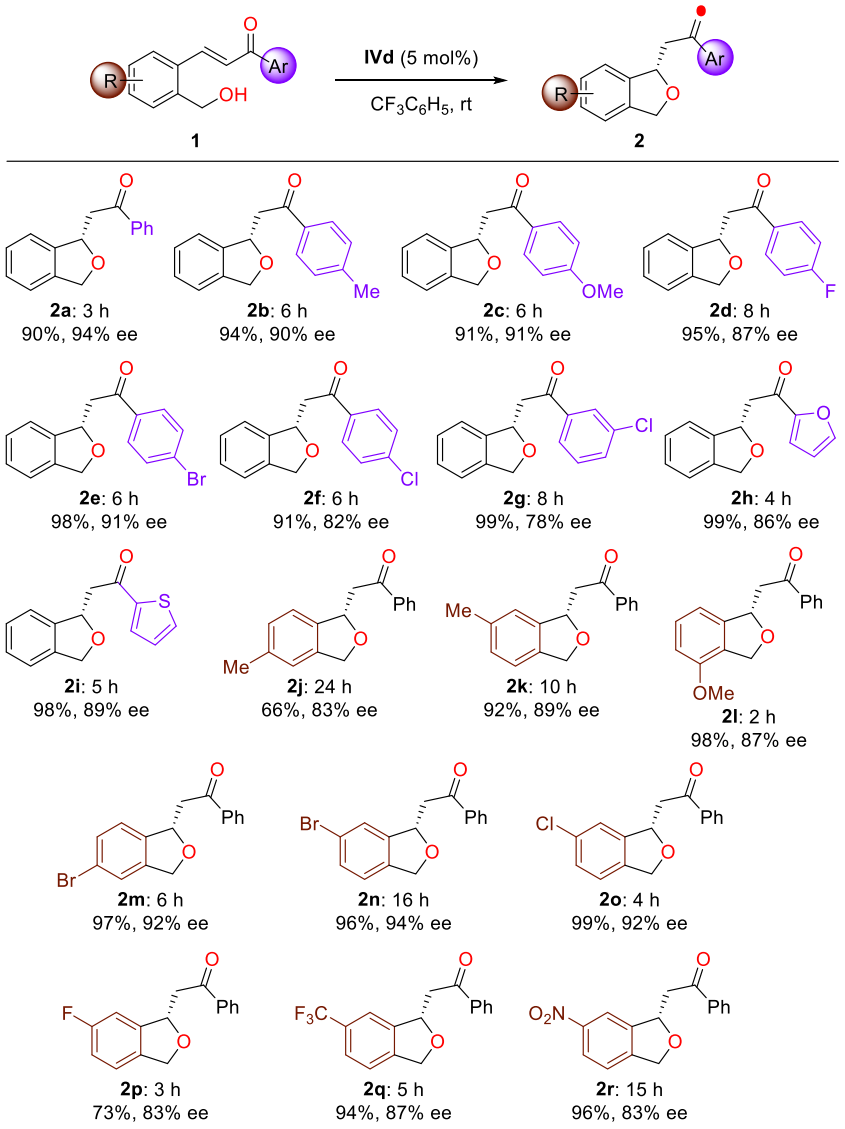
Scheme 2. Substrate Scope of *β*-(2-(Hydroxymethyl)phenyl) *α,β*-Unsaturated Aromatic Ketones[a,b,c]



[a]The reactions were carried out in $CF_3C_6H_5$ (0.5 M) with **1** (0.2 mmol) and **IVd** (5 mol %). [b]Yield after chromatographic purification. [c]Determined by chiral-phase HPLC analysis.

After accomplishing the AIOM of *β*-(2-hydroxymethyl)-phenyl *α,β*-unsaturated aromatic ketones **1**, we attempted to broaden the scope of enones to deliver 1-substituted 1,3-dihydroisobenzofurans. The *β*-(2-hydroxymethyl)phenyl *α,β*-unsaturated esters **3** were applied in this AIOM (Scheme 3). *α,β*-Unsaturated esters **3** were less reactive than *α,β*-unsaturated aromatic ketones **1**; therefore, the reaction proceeded at 50 °C and provided slightly reduced but still high enantioselectivities (80−87% ee). Irrespective of the ester type, the reactions proceeded smoothly to give the corresponding phthalans **4a−c** in good yields and with high enantioselectivities. Among the esters, benzyl ester **3c** efficiently furnished the corresponding product **4c** with the best results (81% yield, 85% ee). A series of *β*-(2-hydroxymethyl)phenyl *α,β*-unsaturated benzyl esters **3d−m** bearing various R groups on the central aryl moiety, regardless of the electron nature and position of the R group, were suitable substrates for this reaction and afforded phthalans **4d−m** in good to excellent yields with high enantioselectivities. Ethyl ester substrates **3o−q** bearing Br or Cl groups on the aryl ring were less reactive than the benzyl ester substrates, and the reactions were conducted at 80 °C, delivering products **4o−q** in high yields with 79−80% ee. The absolute configurations of 1,3-dihydroisobenzofuranyl-1-methylene esters **4** were confirmed by comparison with Blakey's work.[4d]

This strategy was also applied to substrates containing aliphatic ketones. *β*-(2-Hydroxymethyl)phenyl *α,β*-unsaturated methyl ketone **5** efficiently furnished phthalan **6** in 95% yield and 78% ee (Scheme 4A). More importantly, we further examined the possibility of a Wittig/AIOM cascade reaction of 1,3-dihydro-2-benzofuran-1-ol. Interestingly, though the reaction was not optimized, the one-pot reaction of 1,3-dihydro-2-benzofuran-1-ol **7** with triphenyl phosphonium ylide **8** using the quinidine-derived squaramide **IVd** catalyst in $CF_3C_6H_5$ at room temperature provided the corresponding phthalan **2a** in moderate yield (58%) and with a good enantioselectivity of 84% ee (Scheme 4B).[14]

Next, to demonstrate the utility of this AIOM, we performed a one-mmol-scale reaction and synthetic transformation (Scheme 5). The one-mmol-scale reaction of *β*-(2-

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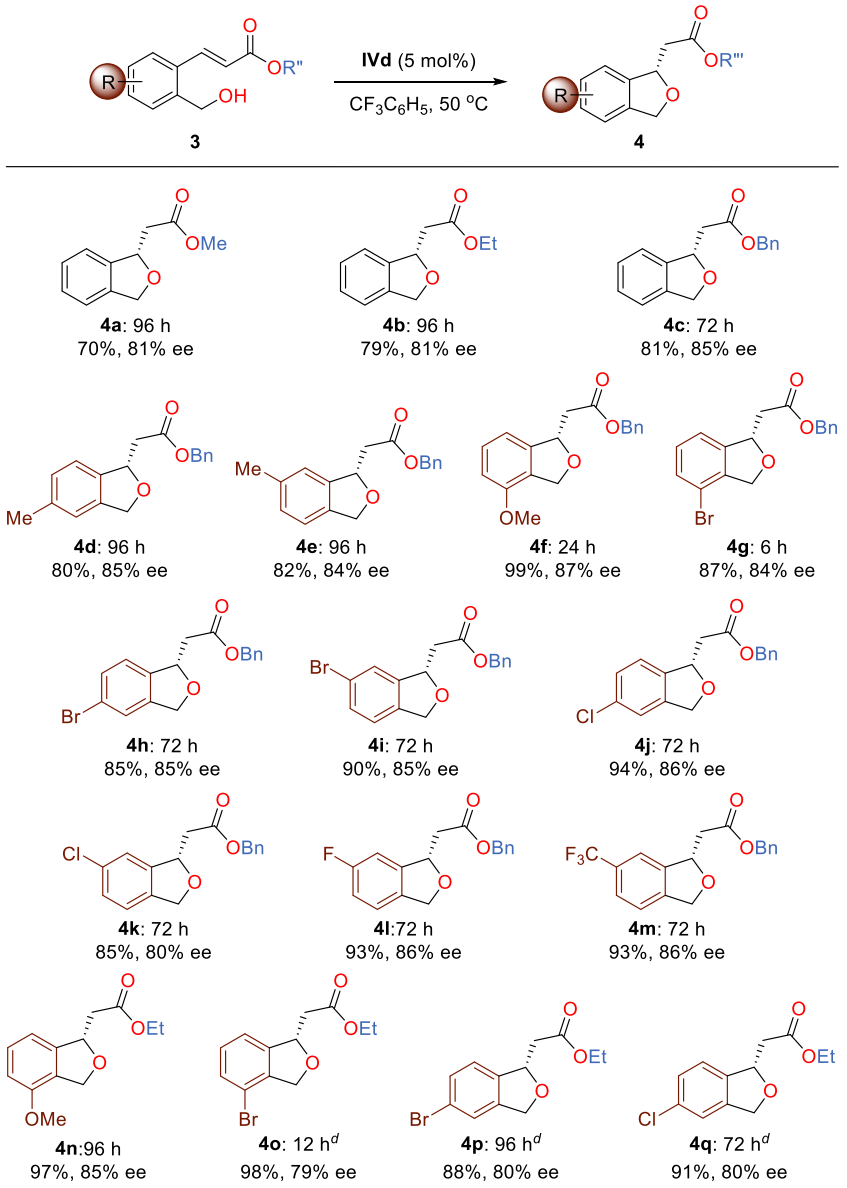
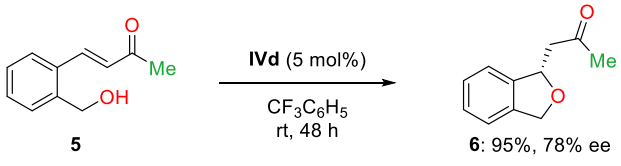
Scheme 3. Substrate Scope of β-(2-(Hydroxymethyl)phenyl) α,β-Unsaturated Esters[c,c,c]



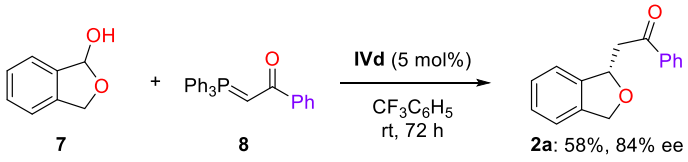
[d]Stirred at 80 °C. [a]The reactions were carried out in $CF_3C_6H_5$ (0.5 M) with **1a** (0.2 mmol) and **IVd** (5 mol %). [b]Yield after chromatographic purification. [c]Determined by chiral-phase HPLC analysis.

Scheme 4. Further Extension of Substrate Scope and Reaction Conditions

A: Asymmeric Reaction of β-(2-(Hydroxymethyl)phenyl) α,β-Unsaturated Methyl Ketone



B: Enantioselective Synthesis of 2a via Wittig/oxa-Michael Reaction



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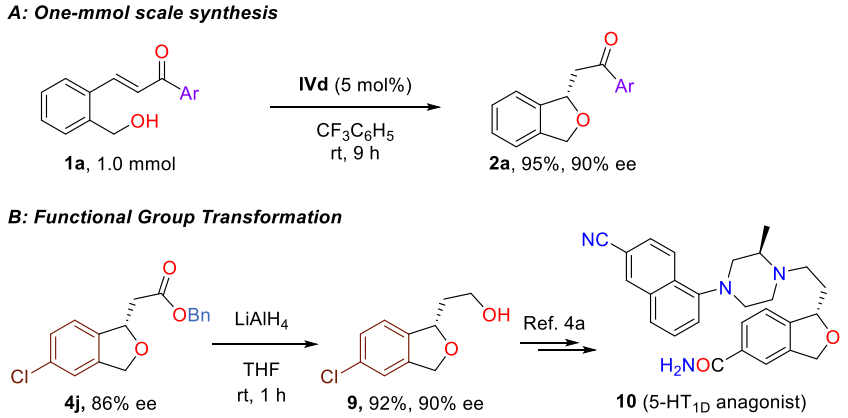
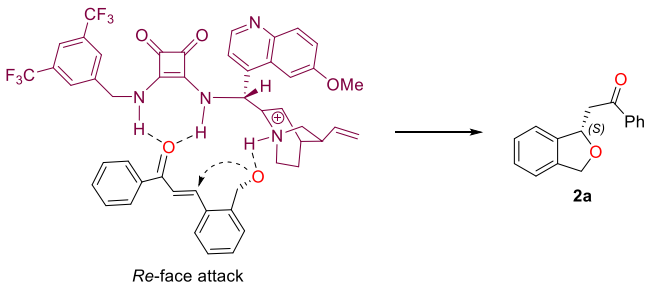
Scheme 5. Reaction Utility



hydroxymethyl)phenyl α,β-unsaturated phenyl ketone **1a** successfully produced to give product **2a**, retaining a high yield of 95% with a similar enantioselectivity of 90% ee (Scheme 5A). In addition, Cl group-containing phthalan **4j** was reduced by the treatment of $LiAlH_4$ at room temperature, thereby producing the corresponding phthalanyl alcohol **9** in 92% yield with 90% ee, which could be further transformed to compound **10**, which acts as a 5-HT_{1D} antagonist. The increase in ee value is thought to be caused by crystallization during purification (Scheme 5B).

On the basis of our experimental results and previous literature,[13] a plausible transition state for this AIOM was proposed to reveal the influence of the chiral bifunctional squaramide catalyst on the enantioselectivity in Scheme 6. β-

Scheme 6. Plausible Transition State



(2-Hydroxymethyl)phenyl α,β-unsaturated phenyl ketone **1a** is assumed to interact with the squaramide of catalyst **IVd** by double hydrogen bonding, which fixes and activates the substrate in a bidentate interaction. Meanwhile, the hydroxymethyl moiety is deprotonated by the basic nitrogen atom of the tertiary amine moiety in the catalyst; the deprotonated oxygen atom is assumed to interact with the protonated amine by hydrogen bonding. Thereafter, the sterically crowded organocatalyst dominates so that the oxygen atom of hydroxymethyl moiety attacks at the *Re* face of the enone, leading to the intramolecular attack affording the desired *S*-configurational product **2a**.

CONCLUSIONS

In summary, an AIOM of benzyl alcohol bearing α,β-unsaturated carbonyls as Michael acceptors, using a chiral cinchona squaramide-based organocatalyst, has been developed. 1,3-Dihydroisobenzofuranyl-1-methylene ketones and 1,3-dihydroisobenzofuranyl-1-methylene esters are obtained with excellent yields, high enantioselectivities, and with a broad substrate scope. In addition, enantioenriched 1,3-dihydroisobenzofuranyl-1-methylene ketone was obtained from the Wittig/oxa-Michael reaction cascade of 1,3-dihydro-2-benzofuran-1-ol. The AIOM can be scaled up, and the synthetic utility of the obtained 1,3-dihydroisobenzofuran was demonstrated by further transformation.

EXPERIMENTAL SECTION

General Information. Organic solvents were distilled prior to use. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32−64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms were visualized by fluorescence quenching and with anisaldehyde stain. ^1H and ^{13}C NMR spectra were recorded (400 MHz for ^1H and 100 MHz for ^{13}C) and were internally referenced to residual protic solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on an Fourier transform infrared (FTIR) spectrometer and are reported in wave numbers. Optical rotations were taken on a digital polarimeter. High-resolution mass spectroscopy (HRMS) was performed by an electron impact ionization (EI-magnetic sector) mass spectrometer. Enantiomeric excesses were determined using an HPLC instrument with Chiralpak columns as noted.

Typical Procedure for β-(2-(Hydroxymethyl)phenyl) α,β-Unsaturated Carbonyl Compounds.[10] To a solution of alkylbenzoic acid (3.0 mmol) and $Na_2S_2O_8$ (2.1 g, 9.0 mmol) in CH_3CN (15 mL) was added tetrabutylammonium bromide (TBAB, 1.9 g, 6.0 mmol) at room temperature. The reaction mixture was stirred at 80 °C in an oil bath until alkylbenzoic acid was almost consumed, as determined by TLC. Then, the resulting mixture was diluted with water and extracted with EtOAc. The organic layer was washed with aqueous (aq) $NaHCO_3$ and brine gradually and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography with EtOAc/hexane as an eluent to afford the desired phthalide. Next, to a stirred solution of phthalide (1.0 mmol) in CH_2Cl_2 (5 mL) was added diisobutylaluminum hydride (DIBAL-H) (1.1 mmol, 1.2 M in toluene) at −78 °C. After stirring for 10 min, the reaction was quenched with sat. Na_2SO_4 (0.5 mL) and allowed to warm to room temperature. After adding additional dry Na_2SO_4, the resulting mixture was stirred for 1 h and filtered through a plug of celite. The organic residue was concentrated in vacuo to give desired 1,3-dihydro-2-benzofuran-1-ol (including 2-(hydroxymethyl)benzaldehyde tautomer), which was used in the Wittig reaction without further

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purification. To a solution of 1,3-dihydro-2-benzofuran-1-ol (1.0 mmol) in CH_2Cl_2 (5 mL) was added triphenyl phosphonium ylide (1.5 mmol) at 0 °C. The reaction mixture was stirred overnight at the same temperature, allowed to warm to room temperature, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography with EtOAc/hexane as an eluent to afford the desired α,β-unsaturated carbonyl containing benzyl alcohol **1** or **3**.

*(E)-3-(2-(Hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one (**1a**).*[9e,f] 188 mg, yield 79%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 15.6 Hz, 1H), 8.12−7.98 (m, 2H), 7.83−7.72 (m, 1H), 7.64−7.57 (m, 1H), 7.57−7.31 (m, 6H), 4.89 (d, J = 5.3 Hz, 2H), 1.84 (t, J = 5.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.6, 141.6, 140.1, 138.2, 133.8, 133.0, 130.5, 129.0, 128.8, 128.7, 128.5, 127.2, 124.4, 63.2.

*(E)-3-(2-(Hydroxymethyl)phenyl)-1-(p-tolyl)prop-2-en-1-one (**1b**).* 200 mg, yield 79%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 15.6 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.81−7.69 (m, 1H), 7.54−7.33 (m, 4H), 7.30 (d, J = 7.9 Hz, 2H), 4.88 (d, J = 5.4 Hz, 2H), 2.44 (s, 3H), 2.03 (t, J = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.1, 143.9, 141.2, 140.1, 135.6, 133.9, 130.4, 129.5, 129.0, 128.9, 128.4, 127.1, 124.4, 63.1, 21.8; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_2$: 252.1150, found: 252.1174.

*(E)-3-(2-(Hydroxymethyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**1c**).*[9e,f] 109 mg, yield, 41%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 15.5 Hz, 1H), 8.08−7.98 (m, 2H), 7.73 (dd, J = 7.5, 1.4 Hz, 1H), 7.58−7.31 (m, 4H), 7.04−6.92 (m, 2H), 4.89 (brs, 2H), 3.89 (s, 3H), 2.00 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.8, 163.6, 140.8, 140.1, 134.0 (two peaks overlapped), 131.1, 130.3, 129.0, 128.4, 127.1, 124.3, 114.0, 63.1, 55.6.

*(E)-1-(4-Fluorophenyl)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-one (**1d**).* 166 mg, yield 65%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 15.5 Hz, 1H), 8.11−7.99 (m, 2H), 7.80−7.67 (m, 1H), 7.53−7.34 (m, 4H), 7.23−7.11 (m, 2H), 4.88 (d, J = 4.7 Hz, 2H), 1.91 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.9, 165.8 (d, J^1 = 254.7 Hz), 141.9, 140.1, 134.5 (d, J^4 = 2.9 Hz), 133.8, 131.3 (d, J^3 = 9.3 Hz), 130.6, 129.1, 128.5, 127.2, 123.9, 115.9 (d, J^2 = 21.8 Hz), 63.2; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}FO_2$: 256.0900, found: 256.0927.

*(E)-1-(4-Bromophenyl)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-one (**1e**).* 82 mg, yield, 26%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 15.6 Hz, 1H), 7.94−7.87 (m, 2H), 7.79−7.71 (m, 1H), 7.70−7.60 (m, 2H), 7.52−7.35 (m, 4H), 4.88 (d, J = 5.5 Hz, 2H), 1.76 (t, J = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.5, 142.2, 140.2, 136.9, 133.7, 132.1, 130.7, 130.3, 129.1, 128.5, 128.9, 127.2, 123.8, 63.3; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0099.

*(E)-1-(4-Chlorophenyl)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-one (**1f**).* 95 mg, yield, 35%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 15.6 Hz, 1H), 8.04−7.92 (m, 2H), 7.79−7.69 (m, 1H), 7.54−7.34 (m, 6H), 4.88 (d, J = 5.4 Hz, 2H), 1.89 (t, J = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.3, 142.2, 140.2, 139.5, 136.5, 133.7, 130.7, 130.1, 129.1, 129.1, 128.5, 127.2, 123.8, 63.2; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0601.

*(E)-1-(3-Chlorophenyl)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-one (**1g**).* 87 mg, yield, 32%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 15.6 Hz, 1H), 8.00 (t, J = 1.8 Hz, 1H), 7.96−7.85 (m, 1H), 7.80−7.69 (m, 1H), 7.56 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.53−7.35 (m, 5H), 4.89 (d, J = 5.4 Hz, 2H), 1.84 (t, J = 5.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.3, 142.5, 140.2, 139.8, 135.1, 133.6, 132.9, 130.8, 130.1, 129.1, 128.8, 128.5, 127.2, 126.8, 123.7; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0619.

*(E)-1-(Furan-2-yl)-3-(2-(hydroxymethyl)phenyl)prop-2-en-1-one (**1h**).* 125 mg, yield, 55%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 15.7 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 1.0 Hz, 1H), 7.53−7.31 (m, 5H), 6.60 (dd, J = 3.6, 1.7 Hz, 1H), 4.90 (d, J = 4.7 Hz, 2H), 1.89 (t, J = 5.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.1, 153.8, 146.8, 140.7, 140.2, 133.6, 130.6, 129.0, 128.4, 127.2, 123.5, 117.9, 112.7, 63.1; HRMS (EI) m/z calcd for $[M]^+$ $C_{14}H_{12}O_3$: 228.0786, found: 228.0786.

*(E)-3-(2-(Hydroxymethyl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**1i**).*[9a] 81 mg, yield, 33%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 15.5 Hz, 1H), 7.88 (dd, J = 3.8, 1.0 Hz, 1H), 7.80−7.65 (m, 2H), 7.52−7.34 (m, 4H), 7.19 (dd, J = 4.9, 3.8 Hz, 1H), 4.89 (d, J = 3.4 Hz, 2H), 1.98 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.2, 145.5, 140.9, 140.2, 134.2, 133.6, 132.2, 130.6, 129.0, 128.4, 128.4, 127.2, 124.0, 63.1.

*(E)-3-(2-(Hydroxymethyl)-4-methylphenyl)-1-phenylprop-2-en-1-one (**1j**).* 121 mg, yield, 48%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 15.6 Hz, 1H), 8.05−8.01 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.60−7.46 (m, 4H), 7.30 (s, 1H), 7.19 (d, J = 7.9 Hz, 1H), 4.86 (d, J = 5.0 Hz, 2H), 2.40 (s, 3H), 1.87 (t, J = 5.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.68, 141.57, 141.09, 140.13, 138.34, 132.94, 130.88, 129.84, 129.17, 128.76, 128.70, 127.18, 123.27, 63.15, 21.61; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_2$: 252.1150, found: 252.1170.

*(E)-3-(2-(Hydroxymethyl)-5-methylphenyl)-1-phenylprop-2-en-1-one (**1k**).*[9e] 179 mg, yield, 71%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 15.6 Hz, 1H), 8.03 (dd, J = 5.2, 3.3 Hz, 2H), 7.61−7.47 (m, 5H), 7.35 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 4.84 (d, J = 5.1 Hz, 2H), 2.40 (s, 3H), 1.91 (t, J = 5.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.6, 141.8, 138.2, 138.2, 137.4, 133.7, 133.0, 131.3, 129.3, 128.8, 128.7, 127.7, 124.0, 63.0, 21.3.

*(E)-3-(2-(Hydroxymethyl)-3-methoxyphenyl)-1-phenylprop-2-en-1-one (**1l**).* 67 mg, yield, 25%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 15.6 Hz, 1H), 8.07−7.97 (m, 2H), 7.62−7.56 (m, 1H), 7.54−7.43 (m, 3H), 7.37−7.30 (m, 2H), 6.97 (dd, J = 7.5, 1.6 Hz, 1H), 4.89 (brs, 2H), 3.91 (s, 3H), 2.21 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.6, 158.5, 142.1, 138.2, 135.9, 133.0, 129.3, 128.8, 128.8, 128.5, 125.8, 119.8, 112.1, 56.7, 55.9; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_3$: 268.1099, found: 268.1087.

*(E)-3-(4-Bromo-2-(hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one (**1m**).* 149 mg, yield, 47%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 78.07−7.96 (m, 3H), 7.69 (d, J = 2.0 Hz, 1H), 7.64−7.57 (m, 2H), 7.56−7.45 (m, 4H), 4.87 (d, J = 5.4 Hz, 2H), 1.89 (t, J = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.2, 142.0, 140.2, 138.0, 133.2, 132.4, 131.6, 131.4, 128.9, 128.7, 128.5, 124.8, 124.6, 62.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0115.

*(E)-3-(5-Bromo-2-(hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one (**1n**).* 222 mg, yield, 70%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−7.99 (m, 3H), 7.85 (d, J = 2.0 Hz, 1H), 7.61 (ddd, J = 6.6, 3.9, 1.3 Hz, 1H), 7.55−7.47 (m, 4H), 7.38 (d, J = 8.2 Hz, 1H), 4.84 (d, J = 5.1 Hz, 2H), 1.91 (t, J = 5.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.0, 139.9, 139.0, 137.9, 135.7, 133.3, 133.2, 130.5, 129.8, 128.9, 128.8, 125.2, 122.3, 62.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0104.

*(E)-3-(5-Chloro-2-(hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one (**1o**).* 131 mg, yield, 48%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.01 (m, 3H), 7.70 (d, J = 2.1 Hz, 1H), 7.64−7.58 (m, 1H), 7.55−7.42 (m, 4H), 7.38 (dd, J = 8.2, 2.1 Hz, 1H), 4.85 (brs, 2H), 1.94 (brs, 1H); ^{13}C{^{1}H} MR (100 MHz, $CDCl_3$) δ 190.1, 140.0, 138.5, 137.9, 135.4, 134.2, 133.3, 130.3, 130.2, 128.9, 128.8, 126.9, 125.1, 62.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0619.

*(E)-3-(5-Fluoro-2-(hydroxymethyl)phenyl)-1-phenylprop-2-en-1-one (**1p**).*[9f] 164 mg, yield, 64%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 15.6, 1.3 Hz, 1H), 8.03 (dd, J = 5.2, 3.3 Hz, 2H), 7.65−7.58 (m, 1H), 7.56−7.40 (m, 5H), 7.11 (td, J = 8.3, 2.6 Hz, 1H), 4.85 (d, J = 5.1 Hz, 2H), 1.89 (t, J = 5.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.2, 162.6 (d, J^1 = 246.9 Hz), 140.3 (d, J^4 = 2.4 Hz), 137.9, 136.0 (d, J^4 = 3.1 Hz), 135.9 (d, J^3 = 7.7 Hz), 133.3, 131.1 (d, J^3 = 8.3 Hz), 128.9, 128.7, 125.1, 117.2 (d, J^2 = 21.3 Hz), 113.6 (d, J = 22.3 Hz), 62.54.

*(E)-3-(2-(Hydroxymethyl)-5-(trifluoromethyl)phenyl)-1-phenylprop-2-en-1-one (**1q**).* 202 mg, yield, 66%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 15.7 Hz, 1H), 8.05 (d, J = 7.4 Hz, 2H), 7.94 (s, 1H), 7.67 (s, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.54 (dd, J = 15.1, 7.0 Hz, 3H), 4.95 (d, J = 4.9 Hz, 2H), 2.11 (t, J = 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.0, 143.6, 139.8, 137.8, 134.2, 133.4, 130.6 (q, J^2 = 32.7, 32.7 Hz), 128.9, 128.84, 128.79, 126.8 (q, J^3 = 3.7 Hz), 125.5, 124.0 (q, J^1 = 272.3 Hz), 123.7 (q, J^3 = 3.8 Hz), 62.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{13}F_3O_2$: 306.0868, found: 306.0867.

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*(E)-3-(2-Hydroxymethyl)-5-(nitrophenyl)-1-phenylprop-2-en-1-one (**1r**).* 116 mg, yield, 41%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.3 Hz, 1H), 8.27 (dd, J = 8.5, 2.3 Hz, 1H), 8.09−8.01 (m, 3H), 7.77 (d, J = 8.5 Hz, 1H), 7.67−7.61 (m, 2H), 7.58−7.52 (m, 2H), 5.01 (d, J = 5.3 Hz, 2H), 2.09 (t, J = 5.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.5, 147.8, 146. 7, 138.5, 133.6, 129.0, 128.9, 128.9, 128.8, 128.4, 126.3, 124.6, 121.6, 62.2; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}NO_4$: 283.0845, found: 283.0854.

*Methyl (E)-3-(2-(Hydroxymethyl)phenyl)acrylate (**3a**).*[9b,c] 157 mg, yield 82%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 15.9 Hz, 1H), 7.67−7.59 (m, 1H), 7.51−7.30 (m, 3H), 6.41 (d, J = 15.9 Hz, 1H), 4.84 (brs, 2H), 3.81 (s, 3H), 1.75 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.4, 141.7, 139.5, 133.3, 130.3, 128.9, 128.5, 127.0, 120.1, 63.2, 51.9.

*Ethyl (E)-3-(2-(Hydroxymethyl)phenyl)acrylate (**3b**).*[9d] 128 mg, yield 62%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 15.9 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.50−7.28 (m, 3H), 6.41 (d, J = 15.9 Hz, 1H), 4.85 (d, J = 5.4 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.72 (t, J = 5.5 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 141.4, 139.6, 133.3, 130.3, 128.8, 128.4, 127.0, 120.5, 63.1, 60.8, 14.5.

*Benzyl (E)-3-(2-(Hydroxymethyl)phenyl)acrylate (**3c**).* 169 mg, yield 63%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 15.9 Hz, 1H), 7.65−7.58 (m, 1H), 7.48−7.32 (m, 8H), 6.46 (d, J = 15.9 Hz, 1H), 5.26 (s, 2H), 4.84 (d, J = 5.1 Hz, 2H), 1.79 (t, J = 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 142.0, 139.6, 136.1, 133.2, 130.4, 128.9, 128.7, 128.5, 128.4, 128.4, 127.1, 120.1, 66.6, 63.1; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_3$: 268.1099, found: 268.1083.

*Benzyl (E)-3-(2-(Hydroxymethyl)-4-methylphenyl)acrylate (**3d**).* 203 mg, yield 72%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 15.8 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.47−7.29 (m, 6H), 7.14 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 5.25 (s, 2H), 4.81 (brs, 2H), 2.37 (s, 3H), 1.68 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 142.0, 141.0, 139.6, 136.34, 130.4, 129.8, 129.3, 128.8, 128.5, 128.5, 127.2, 119.1, 66.6, 63.2, 21.6; HRMS (EI) m/z calcd for $[M]^+$ $C_{18}H_{18}O_3$: 282.1256, found: 282.1268.

*Benzyl (E)-3-(2-(Hydroxymethyl)-5-methylphenyl)acrylate (**3e**).* 200 mg, yield 71%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 15.9 Hz, 1H), 7.45−7.30 (m, 7H), 7.20 (d, J = 7.6 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 5.26 (s, 2H), 4.79 (s, br, 2H), 2.36 (s, 3H), 1.64 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 142.2, 138.3, 136.8, 136.2, 133.1, 131.2, 129.1, 128.7, 128.4, 128.4, 127.7, 119.9, 66.5, 63.0, 21.3; HRMS (EI) m/z calcd for $[M]^+$ $C_{18}H_{18}O_3$: 282.1256, found: 282.1248.

*Benzyl (E)-3-(2-(Hydroxymethyl)-3-methoxyphenyl)acrylate (**3f**).* 244 mg, yield 82%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 15.8 Hz, 1H), 7.47−7.26 (m, 6H), 7.18 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 5.26 (s, 2H), 4.84 (brs, 2H), 3.89 (s, 3H), 2.19 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 158.3, 142.4, 136.1, 135.1, 129.3, 128.7, 128.5, 128.4, 128.1, 121.3, 119.6, 111.9, 66. 6, 56.6, 55.9; HRMS (EI) m/z calcd for $[M]^+$ $C_{18}H_{18}O_4$: 298.1205, found: 298.1176.

*Benzyl (E)-3-(3-Bromo-2-(hydroxymethyl)phenyl)acrylate (**3g**).* 291 mg, yield 84%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 15.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.46−7.33 (m, 5H), 7.19 (t, J = 7.9 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 5.26 (s, 2H), 4.94 (brs, 2H), 1.99 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 142.2, 138.0, 137.0, 136.0, 134.4, 130.0, 128.8, 128.5, 128.5, 126.9, 126.2, 122.3, 66.7, 61.8; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0214.

*Benzyl (E)-3-(4-Bromo-2-(hydroxymethyl)phenyl)acrylate (**3h**).* 187 mg, yield 54%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 15.8 Hz, 1H), 7.64 (s, 1H), 7.54−7.29 (m, 7H), 6.43 (d, J = 15.8 Hz, 1H), 5.25 (s, 2H), 4.81 (brs, 2H), 1.79 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 141.45, 140.7, 136.0, 131.8, 131.5, 131.4, 128.8 (two peaks overlapped), 128.5 (two peaks overlapped), 124.7, 120.6, 66.7, 62.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0201.

*Benzyl (E)-3-(5-Bromo-2-(hydroxymethyl)phenyl)acrylate (**3i**).* 260 mg, yield 75%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 15.9 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.2, 1.9 Hz, 1H), 7.46−7.29 (m, 6H), 6.44 (d, J = 15.8 Hz, 1H), 5.26 (s, 2H), 4.78 (brs, 2H), 1.75 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 140.5, 138.4, 136.0, 135.1, 133.1, 130.3, 129.8, 128.8, 128.5, 128.4, 122.3, 121.4, 66.7, 62.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0225.

*Benzyl (E)-3-(4-Chloro-2-(hydroxymethyl)phenyl)acrylate (**3j**).* 105 mg, yield 52%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 77.95 (d, J = 15.9 Hz, 1H), 7.50 (dd, J = 12.4, 5.2 Hz, 2H), 7.44−7.27 (m, 6H), 6.42 (d, J = 15.8 Hz, 1H), 5.25 (s, 2H), 4.82 (brs, 2H), 1.81 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 141.311, 140.631, 136.4, 136.0, 131.3, 128.8, 128.48 (two peaks overlapped), 128.46, 128.4, 128.3, 120.5, 66.7, 62.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}ClO_3$: 302.0710, found: 302.0721.

*Benzyl (E)-3-(5-Chloro-2-(hydroxymethyl)phenyl)acrylate (**3k**).* 200 mg, yield 66%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.47−7.31 (m, 7H), 6.45 (d, J = 15.8 Hz, 1H), 5.26 (s, 2H), 4.79 (s, 2H), 1.83 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 140.6, 137.9, 136.0, 134.8, 134.3, 130.2, 130.1, 128.8, 128.5, 128.4, 126.9, 121.3, 66.7, 62.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}ClO_3$: 302.0710, found: 302.0704.

*Benzyl (E)-3-(5-Fluoro-2-(hydroxymethyl)phenyl)acrylate (**3l**).* 160 mg, yield 56%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 15.9, 1.4 Hz, 1H), 7.45−7.33 (m, 6H), 7.28 (dd, J = 9.7, 2.7 Hz, 1H), 7.07 (td, J = 8.3, 2.6 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 5.26 (s, 2H), 4.79 (d, J = 4.6 Hz, 2H), 1.76 (t, J = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 162.6 (d, J = 247.0 Hz), 140.9 (d, J = 3.1 Hz), 136.0, 135.5 (d, J = 3.1 Hz), 135.3 (d, J = 7.8 Hz), 130.9 (d, J = 8.3 Hz), 128.8, 128.48, 128.46, 121.2, 117.1 (d, J = 21.3 Hz), 113.6 (d, J = 22.4 Hz), 66.7, 62.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{15}FO_3$: 286.1005, found: 286.0976.

*Benzyl (E)-3-(2-(Hydroxymethyl)-5-(trifluoromethyl)phenyl)-acrylate (**3m**).* 174 mg, yield 52%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 16.0 Hz, 1H), 7.81 (s, 1H), 7.69−7.59 (m, 2H), 7.46−7.33 (m, 5H), 6.51 (d, J = 15.9 Hz, 1H), 5.27 (s, 2H), 4.89 (brs, 2H), 1.85 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 143.1, 140.5, 135.8, 133.5, 130.59 (q, J^2 = 32.7 Hz),128.8, 128.7, 128.53, 128.47, 126.7 (q, J^3 = 3.6 Hz), 123.90 (q, J^1 = 272.4 Hz), 123.74 (q, J^3 = 3.8 Hz), 121.8, 66.8, 62.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{18}H_{15}F_3O_3$: 336.0973, found: 336.0965.

*Ethyl (E)-3-(2-(Hydroxymethyl)-3-methoxyphenyl)acrylate (**3n**).* 158 mg, yield 67%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 15.8 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.37 (d, J = 15.8 Hz, 1H), 4.85 (brs, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 2.16 (brs, 1H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 158.3, 141.8, 135.3, 129.3, 128.0, 121.8, 119.5, 111.8, 60.7, 56.6, 55.9, 14.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{13}H_{16}O_4$: 236.1049, found: 236.1054.

*Ethyl (E)-3-(3-Bromo-2-(hydroxymethyl)phenyl)acrylate (**3o**).* 231 mg, yield 81%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 15.8 Hz, 1H), 7.61 (dd, J = 8.0, 1.1 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 6.38 (d, J = 15.8 Hz, 1H), 4.94 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 141.4, 140.1, 131.9, 131.4, 131.4, 128.4, 124.5, 121.1, 62.4, 60.9, 14.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{12}H_{13}BrO_3$: 284.0048, found: 284.0074.

*Ethyl (E)-3-(4-Bromo-2-(hydroxymethyl)phenyl)acrylate (**3p**).* 165 mg, yield 58%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 15.8 Hz, 1H), 7.64 (s, 1H), 7.45 (s, 2H), 6.38 (d, J = 15.8 Hz, 1H), 4.82 (brs, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.81 (brs, 1H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 141.6, 137.9, 137.1, 134.3, 130.0, 126.9, 126.2, 122.8, 61.8, 60.9, 14.5; HRMS (EI) m/z calcd for $[M]^+$ $C_{12}H_{13}BrO_3$: 284.0048, found: 284.0025.

*Ethyl (E)-3-(4-Chloro-2-(hydroxymethyl)phenyl)acrylate (**3q**).* 142 mg, yield 59%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 15.9 Hz, 1H), 7.51 (dd, J = 14.0, 5.2 Hz, 2H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 6.37 (d, J = 15.8 Hz, 1H), 4.83 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.82 (s, 1H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz,

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$CDCl_3$) δ 166.8, 141.2, 140.0, 136.2, 131.4, 128.5, 128.4, 128.3, 121.0, 62.5, 60.9, 14.4; HRMS (EI) m/z calcd for $[M]^+$ $C_{12}H_{13}ClO_3$: 240.0553, found: 240.0565.

*(E)-4-(2-(Hydroxymethyl)phenyl)but-3-en-2-one (**5**).*[9a,f] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 16.2 Hz, 1H), 7.69−7.59 (m, 1H), 7.49−7.32 (m, 3H), 6.68 (d, J = 16.1 Hz, 1H), 4.85 (d, J = 4.3 Hz, 2H), 2.40 (s, 3H), 1.76 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.7, 140.3, 139.7, 133.5, 130.5, 129.1, 128.7, 127.0, 63.4, 27.8.

General Procedure I for Asymmetric Intramolecular Oxa-Michael Reaction of β-(2-(Hydroxymethyl)phenyl) α,β-Unsaturated Ketones. To a solution of β-(2-(hydroxymethyl)phenyl) α,β-unsaturated ketone **1** (0.20 mmol, 1.0 equiv) in trifluorotoluene (0.4 mL) was added catalyst **IVd** (0.010 mmol, 0.05 equiv) at room temperature. The reaction mixture was stirred at the same temperature until β-(2-(hydroxymethyl)phenyl) α,β-unsaturated ketone **1** was completely consumed, as determined by TLC. Then, the resulting mixture was diluted with EtOAc/hexane (1:1), filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by flash column chromatography with EtOAc/hexane as an eluent to afford the desired product **2**.

*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2a**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 43 mg, yield 90%), white solid; m.p. 83−85 °C; $[\alpha]_D^{28}$ = −16.2 (c = 0.40, $CHCl_3$); 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.91 (m, 2H), 7.65−7.54 (m, 1H), 7.50−7.40 (m, 2H), 7.34−7.22 (m, 4H), 5.91 (ddd, J = 7.1, 4.8, 2.2 Hz, 1H), 5.22−4.99 (m, 2H), 3.55 (dd, J = 16.7, 7.3 Hz, 1H), 3.35 (dd, J = 16.7, 5.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 141.6, 139.4, 137.2, 133.4, 128.7, 128.4, 127.9, 127.6, 121.6, 121.2, 80.3, 72.8, 45.8 cm^{-1}; IR (neat) 2910.2860, 1678, 1595, 1576, 1476, 1448, 1402, 1357, 1299, 1286, 1207, 1177, 1103, 1018 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{14}O_2$: 238.0994, found: 238.1006; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 24.7 min and minor-isomer t_r = 34.6 min.

*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-(p-tolyl)ethan-1-one (**2b**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 47 mg, yield 94%), white solid; m.p. 76−78 °C; $[\alpha]_D^{28}$ = −24.7 (c = 0.40, $CHCl_3$); 90% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 2H), 7.32−7.22 (m, 6H), 5.90 (td, J = 5.2, 2.6 Hz, 1H), 5.13 (dt, J = 26.2, 7.3 Hz, 2H), 3.52 (dd, J = 16.6, 7.3 Hz, 1H), 3.32 (dd, J = 16.6, 5.2 Hz, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 144.2, 141. 7, 139.4, 134.8, 129.4, 128.6, 127.9, 127.6, 121. 7, 121.1, 80.3, 72.8, 45.6, 21.8; IR (neat) 2949, 2891, 2869, 1675, 1606, 1574, 1494, 1477, 1434, 1403, 1369, 1333, 1285, 1220, 1180, 1066, 1041 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_2$: 252.1150, found: 252.1144; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 17.8 min and minor-isomer t_r = 27.9 min.

*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-methoxyphenyl)-ethan-1-one (**2c**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 49 mg, yield 91%), white solid; m.p. 109−111 °C; $[\alpha]_D^{27}$ = −34.2 (c = 0.41, $CHCl_3$); 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−7.93 (m, 2H), 7.31−7.22 (m, 4H), 6.99−6.87 (m, 2H), 5.89 (td, J = 5.2, 2.6 Hz, 1H), 5.20−5.02 (m, 2H), 3.87 (s, 3H), 3.50 (dd, J = 16.4, 7.3 Hz, 1H), 3.29 (dd, J = 16.4, 5.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.5, 163.7, 141.7, 139.4, 130.8, 130.4, 127.9, 127.6, 121.7, 121.1, 113.9, 80.5, 72.7, 55.6, 45.4; IR (neat) 2942, 2902, 2860, 1739, 1670, 1621, 1575, 1555, 1510, 1468, 1445, 1416, 1383, 1331, 1288. 1167, 1114, 1065 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_3$: 268.1099, found: 268.1117; Chiralpak OJ-H column and OJ-H guard column, 10% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 29.7 min and minor-isomer t_r = 44.5 min.

*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-fluorophenyl)ethan-1-one (**2d**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 49 mg, yield 95%), white solid; m.p. 69−71 °C; $[\alpha]_D^{27}$ = +27.8 (c = 0.40, $CHCl_3$); 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.98 (m, 2H), 7.32−7.23 (m, 4H), 7.18−7.09 (m, 2H), 5.88 (ddd, J = 7.3, 4.8, 2.1 Hz, 1H), 5.12 (qd, J = 12.2, 1.6 Hz, 2H), 3.51 (dd, J = 16.5, 7.4 Hz, 1H), 3.31 (dd, J = 16.5, 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.4, 166.00 (d, J^1 = 255.0 Hz), 141.4, 139.3, 133.70 (d, J^4 = 3.0 Hz), 131.12 (d, J^3 = 9.4 Hz), 128.0, 127.6, 121.6, 121.2, 115.86 (d, J^2 = 21.9 Hz), 80.3, 72.8, 45.7; IR (neat) 3074, 2916, 2852, 1681, 1594, 1505, 1479, 1462, 1410, 1352, 1319, 1300, 1224, 1207, 1155, 1100, 1035 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}FO_2$: 256.0900, found: 256.0886; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 21.8 min and minor-isomer t_r = 28.4 min.

*(S)-1-(4-Bromophenyl)-2-(1,3-dihydroisobenzofuran-1-yl)ethan-1-one (**2e**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 62 mg, yield 98%), white solid; m.p. 101−103 °C; $[\alpha]_D^{28}$ = −6.03 (c = 0.40, $CHCl_3$); 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.80 (m, 2H), 7.65−7.55 (m, 2H), 7.32−7.21 (m, 4H), 5.87 (td, J = 5.1, 2.4 Hz, 1H), 5.20−5.03 (m, 2H), 3.49 (dd, J = 16.5, 7.4 Hz, 1H), 3.31 (dd, J = 16.5, 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 141.3, 139.3, 136.0, 132.1, 130.0, 128.6, 128.0, 127.6, 121.6, 121.2, 80.3, 72.8, 45.7; IR (neat) 2924, 2855, 1727, 1680, 1651, 1580, 1566, 1514, 1503, 1481, 1461, 1392, 1305, 1253, 1194, 1141, 1102, 1032 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0114; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 26.2 min and minor-isomer t_r = 31.9 min.

*(S)-1-(4-Chlorophenyl)-2-(1,3-dihydroisobenzofuran-1-yl)ethan-1-one (**2f**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 50 mg, yield 91%), white solid; m.p. 95−96 °C; $[\alpha]_D^{28}$ = −6.26 (c = 0.40, $CHCl_3$); 82% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.87 (m, 2H), 7.49−7.39 (m, 2H), 7.33−7.21 (m, 4H), 5.88 (td, J = 5.1, 2.4 Hz, 1H), 5.23−5.03 (m, 2H), 3.50 (dd, J = 16.5, 7.5 Hz, 1H), 3.31 (dd, J = 16.5, 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.8, 141.3, 139.9, 139.3, 135.5, 129.9, 129.1, 128.0, 127.6, 121.6, 121.2, 80.3, 72.8, 45.7; IR (neat) 2957, 2926, 2855, 1754, 1729, 1680, 1612, 1582, 1503, 1485, 1434, 1427, 1321, 1281, 1212, 1179, 1121, 1084, 1032 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0579; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 23.0 min and minor-isomer t_r = 29.4 min.

*(S)-1-(3-Chlorophenyl)-2-(1,3-dihydroisobenzofuran-1-yl)ethan-1-one (**2g**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 54 mg, yield 99%), colorless gum; $[\alpha]_D^{24}$ = −3.12 (c = 0.40, $CHCl_3$); 78% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, J = 1.8 Hz, 1H), 7.90−7.82 (m, 1H), 7.54 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.32−7.23 (m, 4H), 5.88 (td, J = 5.1, 2.4 Hz, 1H), 5.12 (qd, J = 12.1, 1.8 Hz, 2H), 3.51 (dd, J = 16.6, 7.5 Hz, 1H), 3.32 (dd, J = 16.6, 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.8, 141.3, 139.3, 138.7, 135.1, 133.3, 130.1, 128.6, 128.0, 127.7, 126.5, 121.5, 121.2, 80.2, 72.8, 45.8; IR (neat) 2954, 2903, 2855, 1723, 1683, 1591, 1571, 1471, 1462, 1423, 1362, 1318, 1286, 1259, 1199, 1106, 1070, 1037 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0613; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 23.5 min and minor-isomer t_r = 27.1 min.

*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-(furan-2-yl)ethan-1-one (**2h**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 45 mg, yield 99%), colorless gum; $[\alpha]_D^{27}$ = −25.4 (c = 0.41, $CHCl_3$); 86% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.7, 0.7 Hz, 1H), 7.33−7.19 (m, 5H), 6.54 (dd, J = 3.6, 1.7 Hz, 1H), 5.93−5.77 (m, 1H), 3.38 (dd, J = 15.8, 7.8 Hz, 1H), 3.20 (dd, J = 15.8, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 153.0, 146.8, 141.3, 139.3, 128.0, 127.6, 121.5, 121.2, 117.9, 112.5, 80.2, 72.8, 45.7; IR (neat) 3131, 2904, 2855, 1667, 1567, 1464, 1393, 1364, 1318, 1304, 1235, 1194, 1158, 1107, 1085, 1040 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{14}H_{12}O_3$: 228.0786, found: 228.0764; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 33.9 min and minor-isomer t_r = 50.9 min.

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*(S)-2-(1,3-Dihydroisobenzofuran-1-yl)-1-(thiophen-2-yl)ethan-1-one (**2i**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 48 mg, yield 98%), white solid; m.p. 80−81 °C; $[\alpha]_D^{27} = -16.9$ (c = 0.2140, $CHCl_3$); 89% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 3.8, 1.1 Hz, 1H), 7.66 (dd, J = 4.9, 1.1 Hz, 1H), 7.31−7.22 (m, 4H), 7.13 (dd, J = 4.9, 3.8 Hz, 1H), 5.87 (td, J = 5.3, 2.5 Hz, 1H), 5.14 (dt, J = 30.6, 7.2 Hz, 2H), 3.46 (dd, J = 15.8, 7.6 Hz, 1H), 3.27 (dd, J = 15.8, 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.7, 144.7, 141.3, 139.3, 134.2, 132.7, 128.3, 128.0, 127.6, 121.6, 121.2, 80.4, 72.8, 46.5; IR (neat) 3090, 2901, 2853, 1651, 1611, 1518, 1478, 1413, 1355, 1317, 1299, 1286, 1234, 1215, 1168, 1106, 1030 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{14}H_{12}O_2S$: 244.0558, found: 244.0532; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 32.3 min and minor-isomer t_r = 38.4 min.

*(S)-2-(5-Methyl-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2j**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 33 mg, yield 66%), white solid; m.p. 77−79 °C; $[\alpha]_D^{21} = -5.11$ (c = 0.40, $CHCl_3$); 83% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dt, J = 8.5, 1.6 Hz, 2H), 7.62−7.53 (m, 1H), 7.53−7.40 (m, 2H), 7.19−7.01 (m, 3H), 5.86 (d, J = 5.4 Hz, 1H), 5.09 (dt, J = 24.9, 7.3 Hz, 2H), 3.52 (dd, J = 16.6, 7.3 Hz, 1H), 3.33 (dd, J = 16.6, 5.1 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 139.7, 138.8, 137.8, 137.2, 133.4, 128.7, 128.4 (two peaks overlapped), 121.7, 121.4, 80.2, 72.7, 45.9, 21.4; IR (neat) 2950, 2901, 2870, 1681, 1643, 1595, 1581, 1489, 1463, 1595, 1536, 1502, 1468, 1450, 1402, 1381, 1298, 1264, 1181, 1063 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_2$: 252.1150, found: 252.1144; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 19.6 min and minor-isomer t_r = 30.2 min.

*(S)-2-(6-Methyl-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2k**).*[4c] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 46 mg, yield 92%), white solid; m.p. 114−116 °C; $[\alpha]_D^{25} = -47.1$ (c = 0.40, $CHCl_3$); 89% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dt, J = 8.5, 1.6 Hz, 2H), 7.63−7.53 (m, 1H), 7.53−7.41 (m, 2H), 7.16−7.01 (m, 3H), 5.86 (td, J = 5.2, 2.6 Hz, 1H), 5.10 (dt, J = 25.3, 7.0 Hz, 2H), 3.53 (dd, J = 16.7, 7.3 Hz, 1H), 3.34 (dd, J = 16.7, 5.0 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 141.9, 137.4, 137.2, 136.5, 133.4, 128.8, 128.7, 128.4, 122.2, 120.9, 80.1, 72.7, 45.8, 21.5; IR (neat) 3056, 2902, 2870, 1682, 1596, 1576, 1492, 1447, 1405, 1356, 1291, 1259, 1202, 1179, 1109, 1046 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_2$: 252.1150, found: 252.1142; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 18.0 min and minor-isomer t_r = 22.4 min.

*(S)-2-(4-Methoxy-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2l**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 53 mg, yield 98%), white solid; m.p. 79−81 °C; $[\alpha]_D^{21} = -2.22$ (c = 0.40, $CHCl_3$); 87% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dt, J = 8.5, 1.6 Hz, 2H), 7.62−7.54 (m, 1H), 7.50−7.42 (m, 2H), 7.25 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 5.91 (td, J = 4.9, 2.2 Hz, 1H), 5.11 (ddd, J = 13.9, 12.5, 2.2 Hz, 2H), 3.84 (s, 3H), 3.53 (dd, J = 16.6, 7.4 Hz, 1H), 3.33 (dd, J = 16.6, 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 154.2, 143.6, 137.2, 133.4, 129.5, 128.7, 128.4, 127.2, 113.7, 109.4, 80.8, 71.3, 55.4, 45.8; IR (neat) 2938, 2901, 2839, 1680, 1613, 1597, 1581, 1485, 1471, 1448, 1362, 1313, 1287, 1264, 1208, 1181, 1099, 1035 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{16}O_3$: 268.1099, found: 268.1107; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 29.8 min and minor-isomer t_r = 34.8 min.

*(S)-2-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2m**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 61 mg, yield 97%), white solid; m.p. 109−111 °C; $[\alpha]_D^{25} = -5.47$ (c = 0.40, $CHCl_3$); 92% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.94 (m, 2H), 7.63−7.54 (m, 1H), 7.52−7.43 (m, 2H), 7.42−7.35 (m, 2H), 7.14 (d, J = 7.8 Hz, 1H), 5.84 (t, J = 6.2 Hz, 1H), 5.16−5.01 (m, 2H), 3.54 (dd, J = 16.8, 6.8 Hz, 1H), 3.33 (dd, J = 16.8, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 141.9, 140.8, 137.0, 133.5, 130.7, 128.8, 128.4, 124.5, 123.4, 121.8, 80.1, 72.2, 45.5; IR (neat) 3085, 2897, 2870, 1683, 1597, 1578, 1470, 1448, 1420, 1401, 1353, 1325, 1299, 1272, 1178, 1117, 1046 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0085; Chiralpak OJ-H column and OJ-H guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 30.1 min and minor-isomer t_r = 49.9 min.

*(S)-2-(6-Bromo-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2n**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 61 mg, yield 96%), white solid; m.p. 150−151 °C; $[\alpha]_D^{21} = -13.4$ (c = 0.41, $CHCl_3$); 94% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 5.2, 3.3 Hz, 2H), 7.64−7.54 (m, 1H), 7.52−7.44 (m, 2H), 7.42 (d, J = 6.1 Hz, 2H), 7.15−7.06 (m, 1H), 5.87 (t, J = 6.0 Hz, 1H), 5.07 (dt, J = 25.3, 7.3 Hz, 2H), 3.56 (dd, J = 17.0, 6.9 Hz, 1H), 3.34 (dd, J = 17.0, 5.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.5, 144.1, 138.5, 137.0, 133.5, 131.0, 128.8, 128.4, 125.1, 122.7, 121.4, 79.9, 72.5, 45.5; IR (neat) 3055, 2901, 2871, 1681, 1645, 1595, 1577, 1467, 1447, 1404, 1354, 1322, 1300, 1284, 1200, 1179, 1068, 1042 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}BrO_2$: 316.0099, found: 316.0105; Chiralpak OJ-H column and OJ-H guard column, 3% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, minor-isomer t_r = 39.9 min and major-isomer t_r = 42.6 min.

*(S)-2-(6-Chloro-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2o**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 54 mg, yield 99%), white solid; m.p. 123−125 °C; $[\alpha]_D^{25} = -39.2$ (c = 0.41, $CHCl_3$); 92% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.95 (m, 2H), 7.63−7.56 (m, 1H), 7.52−7.44 (m, 2H), 7.26 (s, 2H), 7.20−7.12 (m, 1H), 5.87 (t, J = 6.1 Hz, 1H), 5.09 (dt, J = 24.9, 7.4 Hz, 2H), 3.56 (dd, J = 17.0, 6.9 Hz, 1H), 3.34 (dd, J = 17.0, 5.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 143.8, 137.9, 137.0, 133.5, 133.5, 128.8, 128.4, 128.2, 122.3, 122.2, 79.9, 72.4, 45.5; IR (neat) 3046, 2902, 2873, 1681, 1644, 1579, 1553, 1470, 1447, 1403, 1383, 1323, 1314, 1285, 1203, 1177, 1076, 1044 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}ClO_2$: 272.0604, found: 272.0607; Chiralpak IC column and IC guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 19.8 min and major-isomer t_r = 37.7 min.

*(S)-2-(6-Fluoro-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2p**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 37 mg, yield 73%), white solid; m.p. 109−111 °C; $[\alpha]_D^{27} = -81.9$ (c = 0.40, $CHCl_3$); 83% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−7.93 (m, 2H), 7.64−7.54 (m, 1H), 7.53−7.43 (m, 2H), 7.21−7.11 (m, 1H), 6.99 (dd, J = 12.7, 5.6 Hz, 2H), 5.87 (t, J = 6.2 Hz, 1H), 5.16−4.97 (m, 2H), 3.57 (dd, J = 16.9, 6.8 Hz, 1H), 3.34 (dd, J = 16.9, 5.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 162.8 (d, J = 244.7 Hz), 143.9 (d, J = 8.2 Hz), 137.0, 134.72 (d, J = 2.3 Hz), 133.5, 128.8, 128.4, 122.29 (d, J = 8.9 Hz), 115.09 (d, J = 23.1 Hz), 109.2 (d, J = 23.9 Hz), 80.1 (d, J = 2.7 Hz), 72.3, 45.5; IR (neat) 2903, 2875, 1674, 1613, 1597, 1580, 1502, 1483, 1448, 1402, 1326, 1285, 1208, 1160, 1135, 1077, 1046 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{13}FO_2$: 256.0900, found: 256.0912; Chiralpak OD-H column and OD-H guard column, 1% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, minor-isomer t_r = 28.7 min and major-isomer t_r = 31.4 min.

*(S)-1-Phenyl-2-(6-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)ethan-1-one (**2q**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 58 mg, yield 94%), white solid; m.p. 109−110 °C; $[\alpha]_D^{24} = -1.37$ (c = 0.41, $CHCl_3$); 87% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dt, J = 8.5, 1.6 Hz, 2H), 7.64−7.53 (m, 3H), 7.51−7.46 (m, 2H), 7.35 (d, J = 7.9 Hz, 1H), 5.94 (t, J = 6.1 Hz, 1H), 5.16 (q, J = 12.9 Hz, 2H), 3.59 (dd, J = 17.0, 6.9 Hz, 1H), 3.39 (dd, J = 17.0, 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.4, 143.5, 142.6, 136.9, 133.6, 130.4 (q, J^2 = 32.2 Hz), 128.8, 128.4, 125.3 (q, J^3 = 3.7 Hz), 124.3 (d, J^1 = 272.3 Hz), 121.6, 119.0 (q, J^3 = 3.8 Hz), 80.0, 72.5, 45.4; IR (neat) 3068. 2909, 2868, 1695, 1624, 1596, 1489, 1462, 1448, 1408, 1371, 1357, 1285, 1257, 1206, 1180, 1126, 1065, 1043 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{17}H_{13}F_3O_2$: 306.0868, found: 306.0878; Chiralpak IC column and IC guard column, 5% i-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 14.1 min and minor-isomer t_r = 30.1 min.

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*(S)-2-(6-Nitro-1,3-dihydroisobenzofuran-1-yl)-1-phenylethan-1-one (**2r**).* Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:10, 54 mg, yield 96%), white solid; m.p. 197−199 °C; $[\alpha]_D^{25}$ = −6.99 (*c* = 0.40, $CHCl_3$); 83% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.16 (s, 1H), 8.06−7.93 (m, 2H), 7.68−7.58 (m, 1H), 7.48 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 5.95 (d, *J* = 5.8 Hz, 1H), 5.26−5.12 (m, 2H), 3.62 (dd, *J* = 17.2, 6.6 Hz, 1H), 3.44 (dd, *J* = 17.2, 5.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.1, 148.3, 146.8, 143.7, 136.8, 133.7, 128.9, 128.4, 123.9, 121.9, 117.6, 79.9, 72.4, 45.1; IR (neat) 2956, 2921, 2853, 1730, 1672, 1593, 1575,, 1516, 1445, 1407, 1342, 1323, 1285, 1250, 1206, 1174, 1125, 1081, 1046 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{16}H_{13}NO_4$: 283.0845, found: 283.0863; Chiralpak OJ-H column and OJ-H guard column, 10% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 120 min and minor-isomer t_r = 139 min.

General Procedure II for Asymmetric Intramolecular Oxa-Michael Reaction of *β*-(2-(Hydroxymethyl)phenyl) *α,β*-Unsaturated Esters. To a solution of *β*-(2-(hydroxymethyl)phenyl) *α,β*-unsaturated ester **3** (0.20 mmol, 1.0 equiv) in trifluorotoluene (0.4 mL) was added catalyst **IVd** (0.010 mmol, 0.05 equiv) at room temperature. The reaction mixture was allowed to stir at 50 °C in an oil bath until *β*-(2-(hydroxymethyl)phenyl) *α,β*-unsaturated ketone **3** was completely consumed, as determined by TLC. Then, the reaction was cooled to room temperature and diluted with EtOAc/hexane (1:1). The resulting mixture was filtered through a plug of celite and concentrated in vacuo. The crude residue was purified by flash column chromatography with EtOAc/hexane as an eluent to afford the desired product **4**.

*Methyl (S)-2-(1,3-Dihydroisobenzofuran-1-yl)acetate (**4a**).*[4d] Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 27 mg, yield 70%), colorless gum; $[\alpha]_D^{24}$ = −2.81 (*c* = 0.40, $CHCl_3$); 81% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.17 (m, 4H), 5.71−5.62 (m, 1H), 5.14 (ddd, *J* = 31.4, 16.8, 7.2 Hz, 2H), 3.75 (s, 3H), 2.78 (qd, *J* = 15.6, 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.4, 140.7, 139.3, 128.0, 127.6, 121.3, 121.2, 80.4, 72.9, 52.0, 41.6; IR (neat) 2952, 2909, 2851, 1732, 1650, 1493, 1479, 1461, 1435, 1414, 1366, 1319, 1299, 1285, 1259, 1219, 1191, 1160, 1108, 1036 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{11}H_{12}O_3$: 192.0786, found: 192.0801; Chiralpak OJ-H column and OJ-H guard column, 2% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 21.0 min and minor-isomer t_r = 23.7 min.

*Ethyl (S)-2-(1,3-Dihydroisobenzofuran-1-yl)acetate (**4b**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 33 mg, yield 79%), colorless gum; $[\alpha]_D^{26}$ = −35.8(*c* = 0.40, $CHCl_3$); 81% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.17 (m, 4H), 5.74−5.61 (m, 1H), 5.13 (dt, *J* = 31.6, 7.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.77 (qd, *J* = 15.6, 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.0, 140.8, 139.3, 128.0, 127.6, 121.3, 121.2, 80.5, 72.9, 60.9, 41.8, 14.3; IR (neat) 2980, 2924, 2855, 1730, 1633, 1612, 1462, 1393, 1372, 1318, 1299, 1287, 1258, 1217, 1159, 1109, 1035 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{12}H_{14}O_3$: 206.0943, found: 206.0943; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 12.4 min and minor-isomer t_r = 15.9 min.

*Benzyl (S)-2-(1,3-Dihydroisobenzofuran-1-yl)acetate (**4c**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 55 mg, yield 81%), colorless gum; $[\alpha]_D^{27}$ = −30.5 (*c* = 0.40, $CHCl_3$); 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.09 (m, 9H), 5.77−5.63 (m, 1H), 5.25−5.03 (m, 4H), 2.83 (qd, *J* = 15.6, 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 140.7, 139.3, 135.9, 128.7, 128.5, 128.4, 128.0, 127.6, 121.3, 121.2, 80.4, 72.9, 66.6, 41.7; IR (neat) 3329, 2922, 2851, 1677, 1495, 1454, 1380, 1359, 1291, 1273, 1260, 1190, 1113, 1030 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{16}O_3$: 269.1099, found: 268.1085; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 24.2 min and minor-isomer t_r = 31.4 min.

*Benzyl (S)-2-(5-Methyl-1,3-dihydroisobenzofuran-1-yl)acetate (**4d**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 45 mg, yield 80%), colorless gum; $[\alpha]_D^{20}$ = −3.54 (*c* = 0.41, $CHCl_3$); 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.30 (m, 5H), 7.08−6.99 (m, 3H), 5.65 (t, *J* = 6.0 Hz, 1H), 5.24−5.14 (m, 2H), 5.08 (dt, *J* = 26.0, 7.4 Hz, 2H), 2.81 (qd, *J* = 15.6, 6.3 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 139.6, 137.9 (two peaks overlapped), 135.9, 128.7, 128.4, 128.41, 128.37, 121.7, 121.0, 80.3, 72.7, 66.6, 41.8, 21.4; IR (neat) 3033, 2952, 2917, 2860, 1731, 1620, 1494, 1455, 1382, 1356, 1296, 1282, 1214, 1154, 1037 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{18}H_{18}O_3$: 282.1256, found: 282.1266; Chiralpak OJ-H column and OJ-H guard column, 3% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 39.1 min and minor-isomer t_r = 66.4 min.

*Benzyl (S)-2-(6-Methyl-1,3-dihydroisobenzofuran-1-yl)acetate (**4e**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 46 mg, yield 82%), colorless gum; $[\alpha]_D^{20}$ = −7.16 (*c* = 0.40, $CHCl_3$); 84% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.30 (m, 5H), 7.10 (s, 2H), 6.95 (s, 1H), 5.65 (td, *J* = 5.2, 2.6 Hz, 1H), 5.23−5.14 (m, 2H), 5.08 (dt, *J* = 26.4, 7.2 Hz, 2H), 2.89−2.74 (m, 2H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 141.0, 137.4, 136.4, 135.9, 128.9, 128.7, 128.4, 128.4, 121.8, 120.9, 80.3, 72.7, 66.6, 41.8, 21.4; IR (neat) 3033, 2953, 2918, 2859, 1731, 1620, 1495, 1455, 1382, 1360, 1290, 1259, 1216, 1153, 1037 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{18}H_{18}O_3$: 282.1256, found: 282.1248; Chiralpak OJ-H column and OJ-H guard column, 3% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 35.4 min and minor-isomer t_r = 58.0 min.

*Benzyl (S)-2-(4-methoxy-1,3-dihydroisobenzofuran-1-yl)acetate (**4f**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 59 mg, yield 99%), colorless gum; $[\alpha]_D^{26}$ = −3.13 (*c* = 0.40, $CHCl_3$); 87% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.29 (m, 5H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 8.2 Hz, 2H), 5.69 (td, *J* = 5.1, 2.3 Hz, 1H), 5.24−5.02 (m, 4H), 3.83 (s, 3H), 2.90−2.74 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 154.2, 142.7, 135.9, 129.5, 128.7, 128.4, 128.4, 127.1, 113.4, 109.5, 80.9, 71.5, 66.6, 55.4, 41.8; IR (neat) 3033, 2939, 2904, 2840, 1731, 1614, 1598, 1486, 1440, 1410, 1383, 1360, 1315, 1288, 1263, 1152, 1100, 1034 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{18}H_{18}O_4$: 298.1205, found: 298.1212; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 44.2 min and minor-isomer t_r = 51.6 min.

*Benzyl (S)-2-(4-Bromo-1,3-dihydroisobenzofuran-1-yl)acetate (**4g**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 60 mg, yield 87%), colorless gum; $[\alpha]_D^{20}$ = +1.16 (*c* = 0.41, $CHCl_3$); 84% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.29 (m, 6H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.76 (t, *J* = 5.9 Hz, 1H), 5.19 (d, *J* = 12.6 Hz, 2H), 5.07 (dt, *J* = 22.3, 7.8 Hz, 2H), 2.83 (d, *J* = 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 142.7, 140.0, 135.8, 131.0, 129.6, 128.7, 128.5 (two peak overlapped), 120.2, 116.0, 81.6, 74.0, 66.7, 41.6; IR (neat) 3033, 2952, 2917, 2853, 1730, 1608, 1498, 1453, 1383, 1360, 1309, 1295, 1281, 1257, 1228, 1155, 1132, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0202; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 27.6 min and minor-isomer t_r = 36.3 min.

*Benzyl (S)-2-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)acetate (**4h**).* Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 59 mg, yield 85%), colorless gum; $[\alpha]_D^{20}$ = −3.15 (*c* = 0.41, $CHCl_3$); 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.29 (m, 7H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.61 (t, *J* = 5.5 Hz, 1H), 5.17 (s, 2H), 5.05 (q, *J* = 12.6 Hz, 2H), 2.81 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 141.8, 139.8, 135.7, 130.7, 128.7, 128.50, 128.47, 124.6, 122.9, 121.9, 80.1, 72.3, 66.7, 41.4; IR (neat) 3033, 2953, 2917, 2858, 1730, 1603, 1583, 1498, 1471, 1455, 1412, 1383, 1354, 1312, 1294, 1254, 1212, 1153, 1062, 1037 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0208; Chiralpak IA column and IA guard column, 2% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, minor-isomer t_r = 16.8 min and minor-isomer t_r = 19.2 min.

*Benzyl (S)-2-(6-bromo-1,3-dihydroisobenzofuran-1-yl)acetate (**4i**).* Synthesized by the general procedure II; flash chromatography

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(EtOAc/hexane = 1:5, 62 mg, yield 90%), colorless gum; $[\alpha]_D^{20}$ = −7.72 (*c* = 0.40, $CHCl_3$); 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.29 (m, 7H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.64 (t, *J* = 6.1 Hz, 1H), 5.18 (s, 2H), 5.05 (dt, *J* = 25.4, 7.4 Hz, 2H), 2.82 (dd, *J* = 6.3, 1.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 143.2, 138.4, 135.7, 131.1, 128.7, 128.5 (two peak overlapped), 124.7, 122.8, 121.3, 80.0, 72.6, 66.8, 41.4; IR (neat) 3033, 2954, 2917, 2855, 1730, 1604, 1584, 1498, 1470, 1455, 1410, 1384, 1359, 1309, 1277, 1253, 1215, 1154, 1064 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}BrO_3$: 346.0205, found: 346.0197; Chiralpak OJ-H column and OJ-H guard column, 20% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 27.5 min and minor-isomer t_r = 30.5 min.

Benzyl (S)-2-(5-Chloro-1,3-dihydroisobenzofuran-1-yl)acetate ***(4j)***. Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 57 mg, yield 94%), colorless gum; $[\alpha]_D^{20}$ = −1.06 (*c* = 0.37, $CHCl_3$); 86% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.29 (m, 5H), 7.25−7.15 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 5.63 (t, *J* = 6.2 Hz, 1H), 5.17 (s, 2H), 5.12−4.98 (m, 2H), 2.82 (dd, *J* = 6.3, 1.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 141.4, 139.3, 135.8, 133.97, 128.7, 128.50, 128.47, 127.9, 122.5, 121.6, 80.1, 72.4, 66.7, 41.5; IR (neat) 3032, 2952, 2918, 2858, 1730, 1607, 1586, 1498, 1475, 1455, 1416, 1383, 1355, 1312, 1295, 1254, 1154, 1073, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}ClO_3$: 302.0710, found: 302.0705; Chiralpak IA column and IA guard column, 3% EtOH/hexanes, 0.5 mL/min flow, λ = 254 nm, minor-isomer t_r = 14.1 min and major-isomer t_r = 16.0 min.

Benzyl (S)-2-(6-Chloro-1,3-dihydroisobenzofuran-1-yl)acetate ***(4k)***. Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 52 mg, yield 85%), colorless gum; $[\alpha]_D^{20}$ = −7.50 (*c* = 0.41, $CHCl_3$); 80% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.32 (m, 5H), 7.27−7.24 (m, 1H), 7.18−7.11 (m, 2H), 5.64 (t, *J* = 6.1 Hz, 1H), 5.18 (s, 2H), 5.06 (dt, *J* = 24.9, 7.4 Hz, 2H), 2.87−2.79 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 142.8, 137.9, 135.8, 133.5, 128.7, 128.5 (two peak overlapped), 128.3, 122.4, 121.8, 80.1, 72.5, 66.8, 41.4; IR (neat) 3034, 2954, 2921, 2855, 1731, 1607, 1586, 1497, 1474, 1455, 1415, 1383, 1359, 1310, 1278, 1253, 1216, 1154, 1078, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}ClO_3$: 302.0710, found: 302.0708; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 39.6 min and minor-isomer t_r = 44.9 min.

Benzyl (S)-2-(6-Fluoro-1,3-dihydroisobenzofuran-1-yl)acetate ***(4l)***. Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 53 mg, yield 93%), colorless gum; $[\alpha]_D^{20}$ = −1.81 (*c* = 0.40, $CHCl_3$); 86% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.29 (m, 5H), 7.15 (dd, *J* = 8.3, 4.8 Hz, 1H), 6.98 (td, *J* = 8.5, 2.2 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.65 (t, *J* = 6.3 Hz, 1H), 5.18 (s, 2H), 5.05 (q, *J* = 12.3 Hz, 2H), 2.82 (d, *J* = 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 135.77, 162.7 (d, J^1 = 244.9 Hz), 143.0 (d, J^3 = 8.1 Hz), 134.7 (d, J^4 = 2.3 Hz), 128.73, 128.5 (two peaks overlapped), 122.4 (d, J^3 = 8.9 Hz), 115.2 (d, J^2 = 23.1 Hz), 108.8 (d, J^2 = 23.8 Hz), 80.2 (d, J^4 = 2.7 Hz), 72.5, 66.7, 41.4; IR (neat) 3034, 1730, 1615, 1603, 1488, 1455, 1436, 1384, 1364, 1311, 1283, 1254, 1245, 1216, 1155, 1104, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{17}H_{15}FO_3$: 286.1005, found: 286.1013; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 39.0 min and minor-isomer t_r = 47.5 min.

Benzyl (S)-2-(6-(Trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)acetate ***(4m)***. Synthesized by the general procedure II; flash chromatography (EtOAc/hexane = 1:5, 62 mg, yield 93%), colorless gum; $[\alpha]_D^{20}$ = −2.49 (*c* = 0.41, $CHCl_3$); 86% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1H), 7.45 (s, 1H), 7.41−7.30 (m, 6H), 5.71 (t, *J* = 6.1 Hz, 1H), 5.24−5.06 (m, 4H), 2.97−2.79 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.3, 143.4, 141.7, 135.7, 130.4 (q, J^2 = 32.4 Hz), 128.74, 128.49, 128.5, 125.4 (q, J^3 = 3.7 Hz), 124.2 (q, J^1 = 272.3 Hz), 121.7 (two peaks overlapped), 118.6 (q, J^3 = 3.8 Hz), 80.1, 72.6, 66.8, 41.3; IR (neat) 3035, 2953, 2862, 1732, 1598, 1499, 1455, 1438, 1385, 1327, 1277, 1260, 1219, 1156, 1116, 1062, 1039 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{18}H_{15}F_3O_3$: 336.0973, found: 336.0970; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, minor-isomer t_r = 50.2 min and major-isomer t_r = 71.3 min.

Ethyl (S)-2-(4-Methoxy-1,3-dihydroisobenzofuran-1-yl)acetate ***(4n)***. Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:5, 46 mg, yield 97%), colorless gum; $[\alpha]_D^{20}$ = −5.30 (*c* = 0.40, $CHCl_3$); 85% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 3.9 Hz, 1H), 6.78 (d, *J* = 4.6 Hz, 1H), 6.76 (d, *J* = 5.2 Hz, 1H), 5.74−5.59 (m, 1H), 5.12 (dt, *J* = 32.0, 7.6 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.75 (qd, *J* = 15.6, 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.0, 154.2, 142.8, 129.5, 127.1, 113.4, 109.4, 81.0, 71.4, 60.8, 55.4, 41.8, 14.3; IR (neat) 2979, 2939, 2840, 1730, 1614, 1599, 1486, 1472, 1441, 1410, 1314, 1289, 1263, 1231, 1158, 1097, 1035 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{13}H_{16}O_4$: 236.1049, found: 236.1054; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 16.1 min and minor-isomer t_r = 18.7 min.

Ethyl (S)-2-(4-Bromo-1,3-dihydroisobenzofuran-1-yl)acetate ***(4o)***.[40] Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:5, 56 mg, yield 98%), colorless gum; $[\alpha]_D^{20}$ = +9.73 (*c* = 0.41, $CHCl_3$); 79% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7 7.41 (d, *J* = 7.2 Hz, 1H), 7.20−7.10 (m, 2H), 5.81−5.71 (m, 1H), 5.08 (ddd, *J* = 14.2, 13.0, 2.0 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.84−2.72 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 142.8, 140.0, 131.02, 129.6, 120.2, 116.0, 81.6, 74.0, 60.9, 41.7, 14.3; IR (neat) 2980, 2906, 2854, 1730, 1608, 1577, 1451, 1373, 1309, 1281, 1254, 1228, 1162, 1133, 1096, 1049 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{12}H_{13}BrO_3$: 284.0048, found: 284.0031; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 10.5 min and minor-isomer t_r = 13.5 min.

Ethyl (S)-2-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)acetate ***(4p)***. Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:5, 50 mg, yield 88%), colorless gum; $[\alpha]_D^{20}$ = −2.05 (*c* = 0.41, $CHCl_3$); 80% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.34 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 5.60 (dd, *J* = 6.8, 5.7 Hz, 1H), 5.09 (dt, *J* = 30.3, 7.5 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.75 (dd, *J* = 6.3, 2.6 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 141.8, 140.0, 130.7, 124.5, 122.9, 121.9, 80.2, 72.3, 60.9, 41.5, 14.3; IR (neat) 2980, 2906, 2858, 1728, 1603, 1581, 1471, 1446, 1412, 1373, 1352, 1296, 1268, 1252, 1211, 1159, 1062, 1036 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{12}H_{13}BrO_3$: 284.0048, found: 284.0031; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 16.9 min and minor-isomer t_r = 33.0 min.

Ethyl (S)-2-(5-Chloro-1,3-dihydroisobenzofuran-1-yl)acetate ***(4q)***. Synthesized by the general procedure I; flash chromatography (EtOAc/hexane = 1:5, 44 mg, yield 91%), colorless gum; $[\alpha]_D^{20}$ = −2.78 (*c* = 0.41, $CHCl_3$); 80% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.19 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 5.67−5.58 (m, 1H), 5.09 (dt, *J* = 30.7, 7.5 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.75 (dd, *J* = 6.3, 2.9 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 141.4, 139.4, 134.0, 127.87, 122.5, 121.6, 80.1, 72.4, 60.9, 41.6, 14.3; IR (neat) 2981, 2907, 2859, 1729, 1607, 1586, 1475, 1446, 1416, 1374, 1353, 1311, 1297, 1269, 1251, 1214, 1160, 1073, 1039 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{12}H_{13}ClO_3$: 240.0553, found: 240.0532; Chiralpak OJ-H column and OJ-H guard column, 5% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 15.1 min and minor-isomer t_r = 27.8 min.

Asymmetric Intramolecular Oxa-Michael Reaction of *β*-(2-(Hydroxymethyl)phenyl) *α*,*β*-Unsaturated Methyl Ketone. To a solution of *β*-(2-(hydroxymethyl)phenyl) *α*,*β*-unsaturated methyl ketone **5** (35 mg, 0.20 mmol) in trifluorotoluene (0.4 mL) was added catalyst **IVd** (6.4 mg, 0.010 mmol) at room temperature. The reaction mixture was allowed to stir at room temperature until *β*-(2-(hydroxymethyl)phenyl) *α*,*β*-unsaturated methyl ketone **5** was completely consumed, as determined by TLC. Then, the reaction was cooled to room temperature and diluted with EtOAc/hexane (1:1). The resulting mixture was filtered through a plug of celite and concentrated in vacuo. The crude residue was purified by flash column

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chromatography with (EtOAc/hexane = 1:10) as an eluent to afford the desired product **6** (33 mg, yield 95%).

(S)-1-(1,3-Dihydroisobenzofuran-1-yl)propan-2-one. Colorless gum; $[\alpha]_D^{27}$ = −30.5 (*c* = 0.40, $CHCl_3$); 78% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.16 (m, 4H), 5.76−5.59 (m, 1H), 5.20−5.00 (m, 2H), 3.01−2.80 (m, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.8, 141.2, 139.3, 127.9, 127.6, 121.3, 121.2, 80.0, 72.8, 50.5, 31.1; IR (neat) 3030, 2955, 2917, 2853, 1712, 1479, 1462, 1415, 1359, 1317, 1257, 1181, 1160, 1107, 1047 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{11}H_{12}O_2$: 176.0837, found: 176.0847; Chiralpak OJ-H column and OJ-H guard column, 2% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, major-isomer t_r = 10.8 min and minor-isomer t_r = 89.2 min.

Enantioselective Synthesis of 1,3-Dihydroisobenxofuran 2a via Wittig/Oxa-Michael Reaction. To a solution of 1,3-dihydro-2-benzofuran-1-ol **7** (27 mg, 0.20 mmol) and catalyst **IVd** (6.4 mg, 0.010 mmol) in CH_2Cl_2 (2 mL) was added triphenyl phosphonium ylide **8** (114 mg, 0.30 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 72 h. Then, the resulting mixture was filtered through a plug of celite and concentrated in vacuo. The crude residue was purified by flash column chromatography with (EtOAc/hexane = 1:10) as an eluent to afford the desired product **2a** (28 mg, 58%, 84% ee) as a white solid.

Procedure for a 1 mmol Scale Synthesis of 2a. To a solution of *β*-(2-(hydroxymethyl)phenyl) *α*,*β*-unsaturated ketone **1a** (238 mg, 1.0 mmol) in trifluorotoluene (2 mL) was added catalyst **IVd** (32 mg, 0.050 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 12 h. Then, the resulting mixture was diluted with EtOAc/hexane (1:1), filtered through a plug of celite, and concentrated in vacuo. The crude residue was purified by flash column chromatography with (EtOAc/hexane = 1:10) as an eluent to afford the desired product **2a** (226 mg, 95% yield, 90% ee) as a white solid.

Procedure for the Functional Group Transformation. To a solution of compound **4j** (30 mg, 0.10 mmol) in THF (1 mL) was added dropwise $LiAlH_4$ (0.3 mL, 1 M in THF) at 0 °C. The reaction mixture was allowed to stir at room temperature until compound **4j** was completely consumed (1 h), as determined by TLC. Then, the reaction mixture was poured into a vigorously stirring solution of Et_2O and a saturated aqueous Rochelle's salt solution. Et_2O was added, and the resulting biphasic mixture was stirred vigorously for 1 h. The organic layer was extracted, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography with (EtOAc/hexane = 1:3) as an eluent to afford the desired product **9** (18 mg, 92% yield).

(S)-2-(5-Chloro-1,3-dihydroisobenzofuran-1-yl)ethan-1-ol.[4a,c] White solid; m.p. 53−55 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (ddd, *J* = 16.0, 6.5, 5.7 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.47−5.34 (m, 1H), 5.08 (dt, *J* = 32.1, 7.4 Hz, 2H), 3.95−3.76 (m, 2H), 2.50 (s, 1H), 2.13 (dddd, *J* = 14.3, 6.7, 4.3, 3.3 Hz, 1H), 1.92 (dddd, *J* = 14.5, 8.7, 7.2, 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.2, 140.2, 133.7, 127.9, 122.3, 121.6, 83.4, 72.2, 60.9, 37.9; IR (neat) 3276, 2923, 2895, 2863, 1738, 1607, 1585, 1476, 1462, 1440, 1419, 1373, 1351, 1326, 1246, 1218, 1162, 1073, 1038 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{10}H_{11}ClO_2$: 198.0448, found: 198.0432; Chiralpak IA column and IA guard column, 3% *i*-PrOH/hexanes, 1.0 mL/min flow, λ = 254 nm, minor-isomer t_r = 29.5 min and major-isomer t_r = 44.9 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00715.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra and HPLC analysis (PDF)

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Notes

The authors declare no competing financial interest.

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