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Asymmetric synthesis of 1,2,3-trisubstituted indanes via an enantioselective copper(II)-catalyzed asymmetric nitroaldol reaction followed by an intramolecular Michael cyclization

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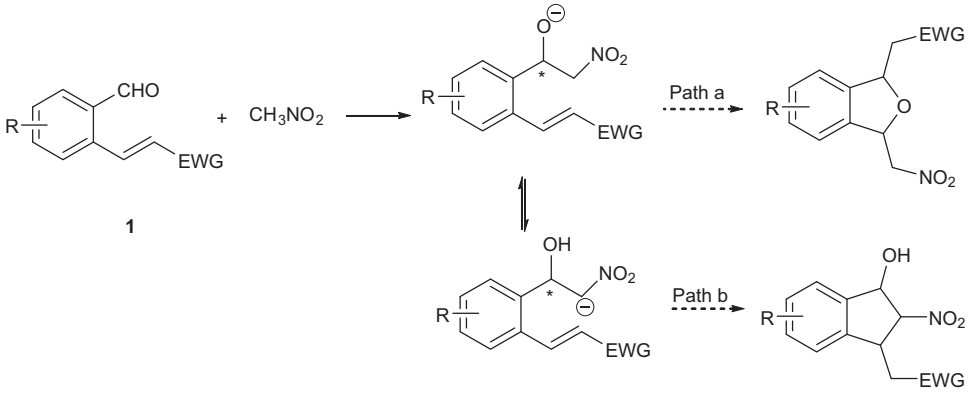
ABSTRACT

Herein we describe a novel approach for the synthesis of a chiral 1,2,3-trisubstituted indane, a privileged substructure in medicinal chemistry, via an enantioselective nitroaldol reaction and subsequent intramolecular Michael addition. The asymmetric copper(II)-catalyzed reactions of *ortho*-formyl cinnamates, *ortho*-formyl cinnamonitrile, or *ortho*-formyl α-benzalketones with nitromethane were carried out using the C1-symmetric chiral secondary diamine **L1** as a ligand, which afforded the nitroaldol products in high yields (up to 92%) and with good to excellent enantioselectivities (up to 97%) under mild conditions. The notable effect of the base and the dosage of nitromethane on the reaction are also discussed.

1. Introduction

Indanes have found widespread application as key structural units in medicinal chemistry;[1] many natural and synthetic compounds with this skeleton have shown significant biological activities.[2] For example, secaloside A, which is isolated mainly from rye, exhibits potent anti-tumor activity;[3] SB-209670 and SB-217242 are highly potent antagonists of endothelin receptors;[4] indatraline [(±)-trans-3-(3,4-dichlorophenyl)-*N*-methyl-1-indanamine] is an uptake inhibitor with high affinity for dopamine, serotonin, and norepinephrine transporters.[5] Due to the importance of these substance classes, a variety of synthetic strategies to obtain this type of compound have been developed. General synthetic methods include the reduction of indanoes,[6] [3+2]cycloaddition of a benzyl cation with styrenes[7] and palladium catalyzed intramolecular carboannulation reactions.[8] These approaches often facilitate the diasteroselective synthesis of indanes, but there are only a few reports on their enantioselective synthesis.[9] Therefore, the development of new strategies for the enantioselective synthesis of 1,2,3-trisubstituted indanes still remains an active field of research.

Recently, much effort has been devoted toward the development of catalytic asymmetric nitroaldol reactions by metal cataly-



Scheme 1. Possible reactions between **1** and nitromethane.

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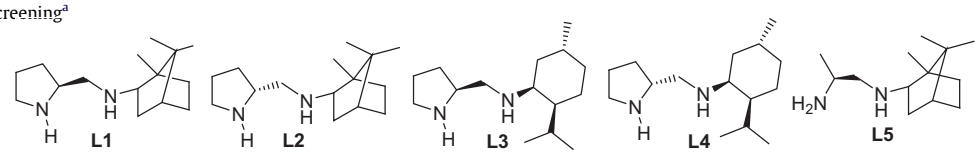
Table 1
Ligand and copper salt screening[a]



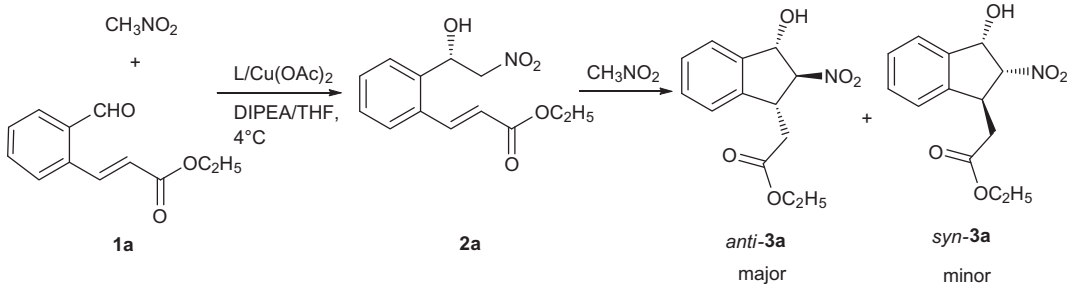
Entry	Catalyst	DIPEA (equiv)	Time[c] (h)	Yield[d] (%)	dr[e]	ee[f] (%)
1[b]	**L1**/Cu(OAc)$_2$·H$_2$O	0.1	24	82 **2a**	–	87
2[b]	**L1**/Cu(OAc)$_2$·H$_2$O	0.2	18	90 **3a**	79:21	82/71
3[b]	**L1**/Cu(OAc)$_2$·H$_2$O	1.0	12	90 **3a**	76:24	65/43
4	**L1**/Cu(OAc)$_2$·H$_2$O	0.1	24	82 **3a**	79:21	87/73
5	**L2**/Cu(OAc)$_2$·H$_2$O	0.1	24	79 **3a**	76:24	−45/nd[g]
6	**L3**/Cu(OAc)$_2$·H$_2$O	0.1	24	76 **3a**	73:27	81/nd[g]
7	**L4**/Cu(OAc)$_2$·H$_2$O	0.1	24	75 **3a**	74:26	−68/nd[g]
8	**L5**/Cu(OAc)$_2$·H$_2$O	0.1	24	77 **3a**	69:31	69/nd[g]
9	**L1**/CuCl$_2$·2H$_2$O	0.1	24	58 **3a**	75:25	81/nd[g]
10	**L1**/CuCl	0.1	30	70 **3a**	70:30	59/85
11	**L1**/CuBr$_2$	0.1	30	49 **3a**	73:27	80/53
12	**L1**/CuCN	0.1	30	66 **3a**	71:29	57/37
13	**L1**/CuSO$_4$·5H$_2$O	0.1	48	20 **3a**	72:28	86/11

[a] Unless otherwise stated, reactions were carried out with **1a** (0.2 mmol), nitromethane (2.0 mmol, 10 equiv), ligand–Cu(II) complex (5 mol %), and DIPEA (107 μL, 0.1 equiv) for the indicated time in THF (1.0 mL) at 4 °C, then 3.0 mL of nitromethane was added and the solution was stirred continuously for another 12 h.
[b] No additional 3.0 mL of nitromethane was added.
[c] Time of nitroaldol reaction, except for entry 2.
[d] Isolated yield.
[e] Determined by ^{1}H NMR spectroscopy of the crude products.
[f] Enantiomeric excess was determined by HPLC analysis.
[g] Not determined.

sis and organocatalysis.[10] Our group has also developed a series of novel chiral diamine ligands for copper-catalyzed asymmetric nitroaldol reactions.[10a] Motivated by this work, we anticipated that the two kinds of different anions generated during the asymmetric nitroaldol reaction would undergo intramolecular Michael addition with various intramolecular electron-deficient alkenes **1** competitively to yield either oxa-heterocyclic products (path a) or carbocyclic products (path b) under the basic conditions (Scheme 1). Luzzio et al. reported on a tandem nitroaldol/oxa-Michael route to the 1,3-disubstituted-1,3-dihydrobenzo[c] furan system utilizing 1,1,3,3-tetramethylguanidine as the catalyst.[11] However, to the best of our knowledge, the asymmetric nitroaldol reaction followed by a carbocyclic reaction has not been reported. Herein, we report a new synthetic approach to 1,2,3-trisubstituted indanes via a highly enantioselective copper(II)-catalyzed asymmetric nitroaldol reaction followed by an intramolecular Michael cyclization.

2. Results and discussion

Our initial studies began with the copper(II)-catalyzed reaction between (*E*)-ethyl 3-(2-formylphenyl)acrylate **1a** and nitromethane. The reaction was first performed using 5 mol % of **L1** and 5 mol % of Cu(OAc)$_2$·H$_2$O as the catalyst system in the presence of 0.1 equiv of diisopropylethylamine (DIPEA) in THF at 4 °C. The product analysis showed the common nitroaldol product **2a** was produced predominantly rather than the expected ring-closure products **3a**, and its ee value was determined by chiral HPLC (Table 1, entry 1). When an additional amount of DIPEA was added into the reaction system, the nitroaldol product **2a** disappeared readily and was converted into the carbocyclic compound **3a** with three adjacent stereogenic centers. Thus, the stereochemistry of the reaction was investigated by means of chiral HPLC and ^{1}H NMR. Two pairs of enantiomers were clearly detected, and the ee value for the major isomer was apparently higher than that for the minor isomer. In addition, the ee value of **3a** generated under the above conditions was lower than that of **2a**, which indicates that a racemization process happened through a competitive reversible nitroaldol reaction during the intramolecular Michael reaction (entries 2 and 3). At this juncture, we found a noteworthy phenomenon that the addition of a large excess of nitromethane to the reaction mixture, instead of additional DIPEA, also led to the complete conversion of **2a** into **3a**. Moreover, in this case there was no detectable loss in the enantiomeric purity for the major isomer (entry 4). The major isomer can be isolated from the minor isomer by silica gel column chromatography, and their structures were identified as *anti*-**3a** and *syn*-**3a** by their spin splitting constants and NOE analysis (Scheme 2).



Scheme 2. **L1**–Cu(OAc)$_2$ catalyzed nitroaldol reaction of **1a**.

Table 2
Optimization of the reaction parameters[a]

Entry	Solvent	Base	Time[b] (h)	Yield[c] (%)	dr[d]	ee[e] (%)
1	THF	DIPEA	24	82 **3a**	79:21	87/73
2	CH_3NO_2	DIPEA	6	82 **3a**	79:21	35/72
3	MeCN	DIPEA	24	51 **3a**	78:22	31/1
4	CH_2Cl_2	DIPEA	24	62 **3a**	74:26	39/53
5	Toluene	DIPEA	36	43 **3a**	81:19	59/26
6	CH_3OH	DIPEA	36	56 **3a**	75:25	13/10
7	Et_2O	DIPEA	24	82 **3a**	76:24	81/76
8	THF	Et_3N	24	81 **3a**	74:26	70/59
9	THF	Piperidine	30	51 **3a**	76:24	16/9
10	THF	NMM	36	80 **2a**	—	—
11	THF	Imidazole	48	nd	—	—
12	THF	DMAP	48	nd	—	—
13[f]	THF	DIPEA	36	91 **3a**	83:17	91/77

[a] Unless otherwise stated, reactions were carried out with **1a** (0.2 mmol), nitromethane (2 mmol, 10 equiv), **L1**–$Cu(OAc)_2{\cdot}H_2O$ complex (5 mol %), and base (0.1 equiv) in the indicated solvent (1.0 mL) at 4 °C, then 3.0 mL of nitromethane was added and the solution was stirred continuously for 6–12 h.
[b] Time for the nitroaldol reaction, except for entry 2.
[c] Isolated yield.
[d] Determined by ^{1}H NMR spectroscopy of the crude products.
[e] Enantiomeric excess was determined by HPLC analysis.
[f] Reaction was performed at −20 °C.

Based on the above observations, we realized that the combination of an enantioselective nitroaldol reaction and subsequent Michael addition promoted by an excess amount of nitromethane was an ideal choice for the synthesis of chiral 1,2,3-trisubstituted indanes.

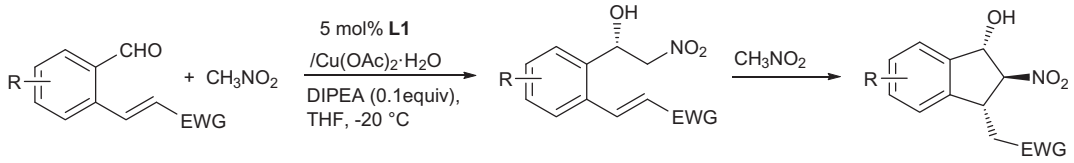
The catalytic activity of other chiral diamine ligands **L2–L5** was also estimated under the above reaction conditions. When ligand **L2** derived from D-proline was employed, the configuration-inversed enantiomer was formed with much lower enantioselectivity (entry 5). The ligands **L3** and **L4** derived from (+)-(1*S*,2*S*,5*R*)-menthylamine showed a similar change in stereoselectivity but failed to offer better results (entries 6 and 7). Ligand **L5** prepared from camphor amine with L-alanine also showed inferior enantioselectivities (entries 8). Among all of the ligands tested, **L1** was identified to be the best choice in terms of both the yield and enantioselectivity of the product **3a**. The effect of some representative copper salts on the reaction was also assessed in combination with **L1** in nitromethane at 4 °C (entries 9–13). Evidently, copper acetate provided the most satisfactory results among the copper salts tested, and was used in the following experiments.

The reaction conditions were then optimized utilizing this catalyst system. Further optimization was carried out by screening solvents, bases and reaction temperature. The observed data are given in Table 2. When the reaction was carried out in nitromethane, it proceeded smoothly and furnished indane **3a** in high yield, but with rather low enantioselectivity (Table 2, entry 2). Ether solvents provided better results than other types of solvents such as nitromethane, acetonitrile, dichloromethane, toluene, and methanol; among them THF proved to be the best solvent (Table 2, entries 1–7).

Next, various organic bases were assessed. Preliminary results showed that the use of DIPEA gave the highest yield and enantioselectivity of **3a** (Table 2, entries 1, 8, and 9). Meanwhile, *N*-methylmorpholine (NMM) favored the formation of nitroaldol product **2a** (entry 10), while imidazole and DMAP as the base showed worse catalytic activity, and almost no **2a** and **3a** could be isolated in each case (Table 2, entries 11 and 12). We also found that the reaction temperature had a certain influence on the reaction. At −20 °C, the reaction time was prolonged, but the ee value was elevated to 91% (entry 13). Thus, the optimal results (91% yield, 91% ee) were achieved when the reaction of **1a** with nitromethane (10 equiv) and DIPEA (0.1 equiv) was performed in THF at −20 °C in the presence of **L1**–$Cu(OAc)_2{\cdot}H_2O$ as the catalyst.

Under the optimized conditions, the substrate scope and limitations of this process were then investigated. For this purpose, various intramolecular Michael acceptors such as enones, cinnamates, cinnamonitrile, and a nitroolefin were prepared and utilized. The observed results are listed in Table 3, and the total reaction times varied from 42 to 80 h. Cinnamates **1a–f** were ideal substrates, and

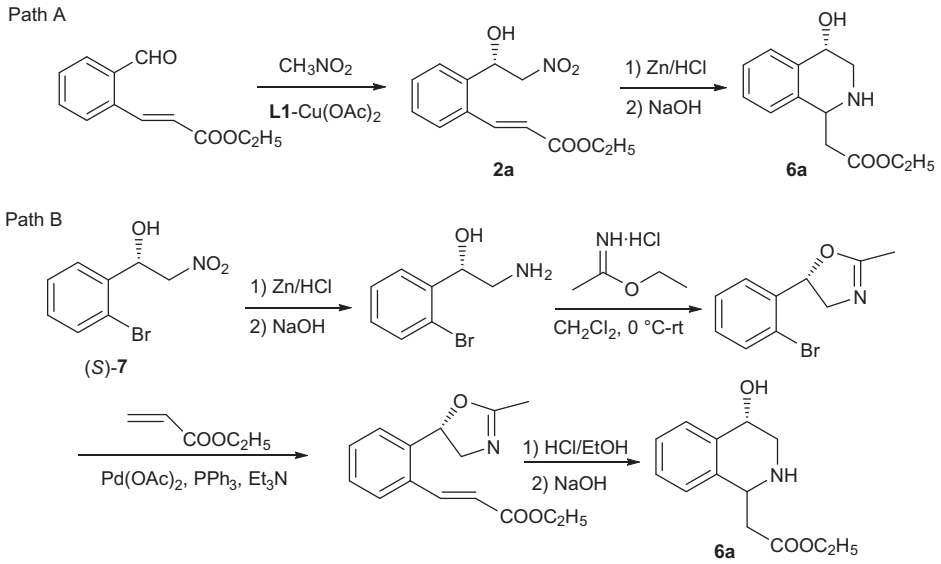
Table 3
Copper(II)-catalyzed asymmetric synthesis of 1,2,3-trisubstituted indanes[a]



1a: R=H, EWG=$COOC_2H_5$
1b: R=H, EWG=$COOCH_3$
1c: R=H, EWG=COOC4H9-*n*
1d: R=H, EWG=COOC4H9-*t*
1e: R=4-NO_2, EWG=$COOC_2H_5$
1f: R=3,4-OCH_2O, EWG=$COOC_2H_5$
1g: R=H, EWG=PhCO
1h: R=H, EWG=4-$CH_3OC_6H_4CO$
1i: R=H, EWG=4-ClC_6H_4CO
1j: R=H, EWG=CN

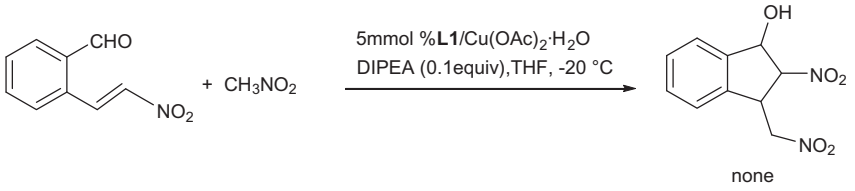
Entry	Substrate	Time[b] (h)	Yield **3**[c] (%)	dr[d]	ee[e] (%)
1	**1a**	36, 12	91	83:17	91/77
2	**1b**	33, 12	92	86:14	93/73
3	**1c**	40, 12	89	82:18	85/56
4	**1d**	40, 10	90	87:13	97/69
5	**1e**	35, 9	85	80:20	96/76
6	**1f**	40,12	89	86:14	97/71
7	**1g**	52, 8	50	78:22	58/nd[f]
8	**1h**	58, 8	56	76:24	81/nd
9	**1i**	70, 10	40	69:31	0/nd
10	**1j**	36, 12	82	86:14	92/nd

[a] Reactions were carried out with **1** (0.2 mmol), nitromethane (2 mmol, 10 equiv), **L1**–$Cu(OAc)_2{\cdot}H_2O$ complex (5 mol %), and DIPEA (107 μL, 0.1 equiv) in THF (1.0 mL) at −20 °C, and then 3.0 mL of nitromethane was added to the solution.
[b] Reaction time for each of the two steps.
[c] Isolated yield.
[d] Determined by ^{1}H NMR spectroscopy of the crude products.
[e] Enantiomeric excess of the diastereomers was determined by HPLC analysis.
[f] Not determined.



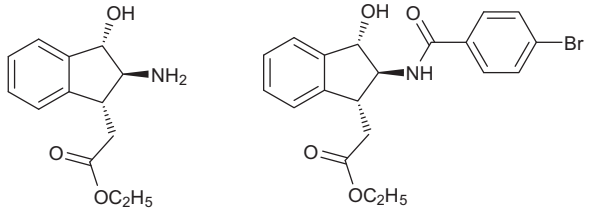
Scheme 3. Determination of the absolute configuration of **2a**.

their reactions proceeded readily under the optimal conditions to give the corresponding 1,2,3-trisubstituted indanes **3a–f** with high yields (up to 92%) and with good to excellent enantioselectivities (up to 97% ee), respectively (Table 3, entries 1–6). It was clear that the structure of the ester moiety had an effect on the reaction enantioselectivity (Table 3, entries 3 and 4) with cinnamate **1d**, with a bulky *t*-butyl group giving a higher ee value than substrate **1c** with an *n*-butyl group.



The electronic properties of the substituents on the aromatic ring were also found to have an effect on the reaction rate. The reaction of **1e** with an electron-withdrawing substituent, such as an $-NO_2$ group, was much faster than that of **1f** with an electron-donating substituent such as an $-OCH_2O-$ group (entries 5 and 6). Nonetheless, both of them gave excellent ee values despite a slight decrease in the product yield. We next turned our attention to another typical Michael acceptor enone. Relatively lower yields and ee values were observed in the case of the enones **1g–1i** (entries 7–9), which indicated that carbonyl group had a negative effect on the nitroaldol reaction, maybe due to its competitive coordinating role to the copper(II) ion. In addition, the electronic properties of the substituents on the aromatic ring of enones had an enormous influence on the reaction enantioselectivity. The reaction of enone **1h** with an electron-donating methoxy group on the benzene ring afforded good yield and ee values, whereas that of **1i** with an electron-withdrawing chloro group proceeded sluggishly, giving the desired product in only 40% yield with almost no enantioselectivity (entries 8 and 9). Next, cinnamonitrile was investigated as an intramolecular Michael acceptor. As expected, the behavior of cinnamonitrile was similar to the cinnamates, and product **3j** was obtained with high yield and excellent enantioselectivity (Table 3, entry10). It is noteworthy that the reaction of the enone **1g** with nitromethane did not take place in the absence of either DIPEA or **L1**–$Cu(OAc)_2{\cdot}H_2O$ complex. These results clearly indicate that the combination catalysis of a base and a diamine ligand–Cu salt complex is necessary for this transformation. In addition, the employment of nitroolefin **1k** as an intramolecular Michael acceptor did not give the desired product **3k** under the same conditions, possibly due to its ease for oligomerization under basic conditions.

We also decided to determine the absolute configuration of *anti*-**3a**. Some derivatives of *anti*-**3a** such as **4a** and **5a**, were thus prepared for single crystal X-ray diffraction. However, we were unable to obtain single crystals for each of the derivatives.



As a result, we tried to determine the absolute configuration of the intermediate **2a** through derivation from the known chiral source (*S*)-**7** along the routes shown in Scheme 3. As a consequence, **2a** was assigned to have an (*S*)-configuration. This result is consistent with our previous reports.[12]

3. Conclusion

In conclusion, we have developed a novel synthetic method for 1,2,3-trisubstituted indanes via the copper(II)-catalyzed asymmetric nitroaldol reaction of *ortho*-formyl cinnamates, *ortho*-formyl cinnamonitriles, and *ortho*-formyl α-benzalketones with subsequent intramolecular Michael addition under mild conditions. The reaction provided a wide variety of 1,2,3-trisubstituted indanes in good yields (up to 92%) with good to excellent enantioselectivities (up to 97%). Further applications of this methodology are currently underway in our laboratory.

4. Experimental

4.1. General

Solvents were purified according to standard procedures and distilled before use. Reagents and starting materials purchased from commercial suppliers were used without further purification unless otherwise stated. For thin-layer chromatography (TLC), silica gel plates GF 254 were used, and compounds were visualized by irradiation with UV light, I_2, or by treatment with basic $KMnO_4$. Optical rotations were measured in the solvent indicated. Flash chromatography was carried out on silica gel 200–300 mesh. NMR spectra were measured on a 400 MHz spectrometer. ^{1}H NMR chemical shifts are reported in ppm with tetramethylsilane (TMS, δ 0 ppm) as the internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Data for ^{13}C NMR are reported in ppm. High resolution mass spectroscopy analyses (HRMS) were measured using ESI ionization. High performance liquid chromatography (HPLC) analysis was performed on chiral columns.

4.2. General procedure for the enantioselective synthesis of 1,2,3-trisubstituted indanes

Ligand **L1** (0.01 mmol, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2 mg, 0.01 mmol, 5 mol %) were added to a test tube containing absolute THF (1.0 mL), and the mixture was stirred for 1 h at room temperature to afford a blue solution. To the mixture the corresponding aldehyde **1a** (41 mg, 0.2 mmol) was added, and the solution was then cooled to −20 °C with stirring, which was followed by the addition of nitromethane (107 μL, 5 mmol, 10 equiv) and DIPEA (3.3 μL, 0.1 equiv). Stirring was continued until all of the aldehyde was fully consumed as indicated by TLC, and then 3.0 mL of nitromethane was added to the solution. The mixture was continuously stirred at −20 °C and monitored by TLC until **2a** was completely converted, then 7 μL of 3 M aqueous HCl was added. The solvent was removed under reduced pressure, and the residue was directly purified by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate to afford the product **3a–j**.

4.3. Spectroscopic data for the products

4.3.1. (1*R*,2*S*,3*S*)-Ethyl (3-hydroxy-2-nitroindan-1-yl)acetate *anti*-3a

Colorless oil. $[\alpha]_D^{25} = -19.1$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (m, 1H), 7.42–7.37 (m, 2H), 7.24–7.18 (m, 1H), 5.70 (d, *J* = 5.5 Hz, 1H), 5.10 (dd, *J* = 7.1, 5.6 Hz, 1H), 4.19–4.09 (m, 3H), 3.32 (s, 1H), 3.03 (dd, *J* = 16.6, 5.3 Hz, 1H), 2.92 (dd, *J* = 16.6, 6.7 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.16, 139.63, 139.26, 129.77, 128.74, 124.52, 123.34, 97.70, 78.96, 61.21, 43.25, 37.42, 14.04. HRMS-ESI (*m*/*z*) calcd for $C_{13}H_{15}NO_5$ [M+Na$^+$]: 288.0848, found: 288.0851. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 38.8 min, t_{minor} = 44.7 min, 91% ee. *syn*-**3a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.42 (m, 1H), 7.42–7.34 (m, 2H), 7.27–7.17 (m, 1H), 5.58 (d, *J* = 6.3 Hz, 1H), 5.36 (t, *J* = 6.6 Hz, 1H), 4.19–4.08 (m, 3H), 3.34 (s, 1H), δ 2.95 (dd, *J* = 16.0, 5.3 Hz, 3H), 2.79 (dd, *J* = 16.0, 7.5 Hz, 1H),1.22 (t, 3H).

4.3.2. (1*R*,2*S*,3*S*)-Methyl (3-hydroxy-2-nitroindan-1-yl)acetate *anti*-3b

Pale yellow oil. $[\alpha]_D^{25} = -23.2$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.42 (m, 1H), 7.41–7.36 (m, 2H), 7.21–7.17 (m, 1H), 5.69 (d, *J* = 5.6 Hz, 1H), 5.07 (dd, *J* = 7.3, 5.6 Hz, 1H), 4.11 (dd, *J* = 12.8, 6.5 Hz, 1H), 3.70 (s, 3H), 3.42 (s, 1H), 3.04 (dd, *J* = 16.7, 5.4 Hz, 1H), 2.93 (dd, *J* = 16.7, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.66, 139.57, 139.14, 129.80, 128.77, 97.68, 78.88, 77.36, 52.09, 43.17, 37.10. HRMS-ESI (*m*/*z*) calcd for $C_{12}H_{13}NO_5$ [M+Na$^+$]: 274.0691, found: 274.0687. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 42.9 min, t_{minor} = 49.6 min, 93% ee. *syn*-**3b:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 1H), 7.54–7.49 (m, 1H), 7.27–7.21 (m, 2H), 5.87 (d, *J* = 5.9 Hz, 1H), 5.23 (dd, *J* = 7.9, 5.9 Hz, 1H), 4.30 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.71 (s, 2H), 3.51 (s, 1H), δ 3.46 (dd, *J* = 31.4, 6.5 Hz, 1H), 3.11 (dd, *J* = 33.0, 6.0 Hz, 1H).

4.3.3. (1*R*,2*S*,3*S*)-*n*-Butyl (3-hydroxy-2-nitroindan-1-yl)acetate *anti*-3c

Colorless oil. $[\alpha]_D^{25} = -23.4$ (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.43 (m, 1H), 7.41–7.36 (m, 2H), 7.23–7.17 (m, 1H), 5.70 (d, *J* = 5.5 Hz, 1H), 5.10 (dd, *J* = 7.1, 5.5 Hz, 1H), 4.14–4.06 (m, 3H), 3.27 (s, 1H), 3.03 (dd, *J* = 16.6, 5.4 Hz, 1H), 2.93 (dd, *J* = 16.6, 6.6 Hz, 1H), 1.59 (dt, *J* = 14.6, 6.8 Hz, 2H), 1.35 (dd, *J* = 15.1, 7.5 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.23, 139.68, 139.28, 129.74, 128.71, 124.52, 123.32, 97.63, 78.91, 65.07, 43.28, 37.34, 30.45, 19.04, 13.63. HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{19}NO_5$ [M+Na$^+$]: 316.1161, found: 316.1155. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 50.2 min, t_{minor} = 64.6 min, 85% ee. *syn*-**3c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 1H), 7.31–7.28 (m, 1H), 7.24–7.20 (m, 1H), 5.82 (dd, *J* = 9.7, 2.9 Hz), 4.68 (dd, *J* = 13.3, 9.7 Hz), 4.14–4.06 (m, 3H), 3.27 (s, 1H), 3.10 (dd, *J* = 14.7, 7.4 Hz), 3.03 (dd, *J* = 10.6, 5.3 Hz), 1.62–1.51 (m, 2H), 1.30 (ddd, *J* = 21.4, 14.6, 7.3 Hz, 2H), 0.96–0.86 (m, 3H).

4.3.4. (1*R*,2*S*,3*S*)-*t*-Butyl (3-hydroxy-2-nitroindan-1-yl)acetate *anti*-3d

Colorless oil. $[\alpha]_D^{25} = -7.4$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 1H), 7.41–7.35 (m, 2H), 7.24–7.18 (m, 1H), 5.69 (s, 1H), 5.11 (dd, *J* = 7.1, 5.6 Hz, 1H), 4.08 (dd, *J* = 12.4, 6.4 Hz, 1H), 3.42 (s, 1H), 2.94 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.84 (dd, *J* = 16.4, 6.6 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.41, 139.71, 139.41, 129.64, 128.61, 124.46, 123.46, 97.70, 82.00, 78.94, 43.47, 38.58, 27.89. HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{19}NO_5$ [M+Na$^+$]: 316.1155, found: 316.1162. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 18.0 min, t_{minor} = 20.0 min, 97% ee. *syn*-**3d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 1H), 7.59–7.55 (m, 2H), 7.56–7.51 (m, 1H), δ 5.87 (s, 1H), 5.21 (dd, *J* = 13.0, 7.2 Hz, 1H), 4.28 (dd, *J* = 14.9, 7.3 Hz, 1H) 3.41 (s, 1H), 3.10 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.04 (dd, *J* = 14.7, 6.2 Hz, 1H), 1.35 (s, 9H).

4.3.5. (1*R*,2*S*,3*S*)-Ethyl (3-hydroxy-2,5-dinitroindan-1-yl)acetate *anti*-3e

White solid. Mp 92.5–94.2 °C. $[\alpha]_D^{25} = -9.9$ (*c* 3.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.25 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 5.74 (d, *J* = 5.4 Hz, 1H), 5.20 (dd, *J* = 7.1, 5.5 Hz, 1H), 4.14 (dd, *J* = 7.1, 2.9 Hz, 3H), 3.59 (s, 1H), 3.04

(dd, J = 5.6, 3.7 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68, 148.71, 146.32, 141.70, 125.20, 124.27, 120.38, 96.90, 77.80, 61.55, 43.14, 36.63, 14.02. HRMS-ESI (m/z) calcd for $C_{13}H_{14}N_2O_7$ [M+Na$^+$]: 333.0699, found: 333.0690. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 80:20, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 19.5 min, t_{minor} = 21.0 min, 96% ee. *syn*-**3e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dt, J = 8.4, 1.7 Hz, 1H), 8.26 (s, 1H), 7.50 (dd, J = 18.1, 8.4 Hz, 1H), 5.88 (ddd, J = 8.9, 5.9, 3.0 Hz, 1H), 5.62–5.49 (m, 1H), 4.10–3.86 (m, 3H), 3.57 (s, 1H), 3.01–2.78 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H).

4.3.6. (1*R*,2*S*,3*S*)-Ethyl (7-hydroxy-6-nitro-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-yl) acetate *anti*-3f

Pale yellow solid. Mp 93.6–94.0 °C. $[\alpha]_D^{25} = -69.7$ (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.63 (s, 1H), 6.00 (d, J = 1.0 Hz, 2H), 5.55 (d, J = 4.2 Hz, 1H), 5.06 (dd, J = 6.4, 4.9 Hz, 1H), 4.18–4.11 (m, 2H), 3.99 (q, J = 6.1 Hz, 1H), 3.28 (s, 1H), 2.95 (dd, J = 16.6, 5.4 Hz, 1H), 2.86 (dd, J = 16.6, 6.6 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.13, 149.43, 148.49, 132.91, 132.79, 104.65, 103.54, 101.65, 97.72, 78.68, 61.19, 43.12, 37.70, 14.03. HRMS-ESI (m/z) calcd for $C_{14}H_{15}NO_7$ [M+Na$^+$]: 332.0746, found: 332.0749. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 62.9 min, t_{minor} = 72.7 min, 97% ee. *syn*-**3f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.04 (s, 1H), 6.05 (dd, J = 5.3, 1.3 Hz, 2H), 5.84 (dd, J = 9.5, 2.7 Hz, 1H), 4.51 (dd, J = 13.6, 9.6 Hz, 1H), 4.33–4.25 (m, 2H), δ 4.19–4.10 (m, 1H), 3.19 (s, 1H), δ 2.95 (dd, J = 16.7, 5.3 Hz, 1H), 2.86 (dd, J = 16.7, 6.6 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H).

4.3.7. (1*R*,2*S*,3*S*)-2-(3-Hydroxy-2-nitroindan-1-yl)-1-phenylethanone *anti*-3g

Pale yellow solid. Mp 98.6–99.1 °C. $[\alpha]_D^{25} = +8.4$ (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2H), 7.68–7.61 (m, 1H), 7.51 (dd, J = 15.5, 8.0 Hz, 3H), 7.37 (td, J = 13.1, 7.4 Hz, 2H), 7.16 (d, J = 7.3 Hz, 1H), 5.79 (d, J = 5.2 Hz, 1H), 5.06 (dd, J = 7.0, 5.3 Hz, 1H), 4.36 (dd, J = 12.5, 6.1 Hz, 1H), 3.70 (d, J = 5.8 Hz, 1H), 3.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.48, 140.32, 139.73, 136.27, 133.77, 129.80, 128.81, 128.56, 128.13, 124.51, 123.53, 97.94, 79.04, 42.81, 42.10. HRMS-ESI (m/z) calcd for $C_{17}H_{15}NO_4$ [M+Na$^+$]: 320.0899, found: 320.0897. HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 68.5 min, t_{minor} = 86.4 min, 58% ee.

4.3.8. (1*R*,2*S*,3*S*)-2-(3-Hydroxy-2-nitroindan-1-yl)-1-(4-methoxyphenyl)ethanone *anti*-3h

Pale yellow solid. Mp 99.5–101.0 °C. $[\alpha]_D^{25} = +5.5$ (c 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 7.0 Hz, 1H), 7.38–7.30 (m, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 5.75 (d, J = 4.3 Hz, 1H), 5.05 (dd, J = 6.8, 5.2 Hz, 1H), 4.31 (q, J = 6.1 Hz, 1H), 3.88 (s, 3H), 3.62 (d, J = 5.8 Hz, 2H), 3.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.91, 164.00, 140.55, 139.83, 130.46, 129.75, 129.39, 128.48, 124.51, 123.53, 113.94, 98.02, 79.16, 77.33, 77.22, 77.01, 55.56, 53.43, 43.05, 41.65. HRMS-ESI (m/z) calcd for $C_{18}H_{17}NO_5$ [M+Na$^+$]: 350.1004, found: 350.1010. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 20.4 min, t_{minor} = 24.5 min, 81% ee.

4.3.9. (1*R*,2*S*,3*S*)-1-(4-Chlorophenyl)-2-(3-hydroxy-2-nitroindan-1-yl)ethanone *anti*-3i

Pale yellow solid. Mp 105.2–106.2 °C. $[\alpha]_D^{25} = +0.40$ (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.92 (m, 2H), 7.51–7.47 (m, 3H), 7.37 (dd, J = 7.3, 5.6 Hz, 2H), 7.15 (d, J = 7.3 Hz, 1H), 5.78 (d, J = 5.3 Hz, 1H), 5.03 (dd, J = 7.1, 5.4 Hz, 1H), 4.35 (dd, J = 13.0, 6.4 Hz, 1H), 3.66 (d, J = 5.9 Hz, 2H), 3.25 (S, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.33, 140.36, 140.08, 139.65, 134.60, 129.85, 129.55, 129.18, 128.66, 124.55, 123.48, 97.88, 78.95, 42.67, 42.10. HRMS-ESI (m/z) calcd for $C_{17}H_{14}ClNO_4$ [M+Na$^+$]: 354.0509, found: 354.0498. HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 36.2 min, t_{minor} = 53.0 min, 0% ee.

4.3.10. (1*R*,2*S*,3*S*)-(3-Hydroxy-2-nitroindan-1-yl)acetonitrile *anti*-3j

Pale yellow solid. Mp 94.0–95.1 °C. $[\alpha]_D^{25} = +35.54$ (c 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.46 (m, 3H), 7.40 (dd, J = 8.0, 4.7 Hz, 1H), 5.77 (d, J = 6.3 Hz, 1H), 4.90 (dd, J = 8.2, 6.4 Hz, 1H), 4.08–3.95 (m, 1H), 3.23–3.00 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.22, 136.15, 130.22, 129.69, 124.68, 123.21, 116.66, 95.84, 77.38, 42.34, 20.88. HRMS-ESI (m/z) calcd for $C_{11}H_{10}N_2O_3$ [M+Na$^+$]: 241.0589, found: 241.0579. HPLC (Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 23.8 min, t_{minor} = 30.0 min, 92% ee.

4.3.11. Procedure for the synthesis of the compound 6a

4.3.11.1. Path A: preparation of (*E*)-ethyl 3-(2-(1-hydroxy-2-nitroethyl)phenyl)acrylate 2a. Ligand **L1** (4.8 mg, 0.02 mmol, 5 mol %) and Cu(OAc)2·H2O (4 mg, 0.02 mmol, 5 mol %) were added to a test tube containing absolute THF (2.0 mL), and the mixture was stirred for 1 h at room temperature to afford a blue solution. To the mixture the corresponding aldehyde **1a** (82 mg, 0.4 mmol) was added with stirring, then the solution was cooled to −20 °C, after which nitromethane (214 μL, 4 mmol, 10 equiv) and DIPEA (3.3 μL, 0.1 equiv) were added. The stirring was continued until the aldehyde was fully consumed as indicated by TLC, then 14 μL of 3 M HCl aqueous was added, and the mixture was concentrated and directly purified by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate to afford product **2a** (96 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 15.7 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.45 (td, J = 7.6, 1.1 Hz, 1H), 7.37 (dt, J = 7.5, 3.8 Hz, 1H), 6.35 (d, J = 15.7 Hz, 1H), 5.85 (dd, J = 9.6, 2.9 Hz, 1H), 4.56 (dd, J = 13.3, 9.6 Hz, 1H), 4.46 (dd, J = 13.3, 3.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.79, 140.36, 137.25, 132.24, 130.55, 128.99, 127.26, 126.64, 121.77, 80.59, 67.61, 61.02, 14.20.

Preparation of ethyl 2-((4*S*)-1,2,3,4-tetrahydro-4-hydroxyisoquinolin-1-yl)acetate **6a**. At first, Zn powder (390 mg, 6 mmol) was added to a solution of **2a** (0.3 mmol) in ethanol/H_2O (10:3, v/v) with rigorous stirring, and then concentrated HCl (2 mL) was added. The mixture was stirred at room temperature for 4 h. The solution was then neutralized by dilute aqueous NaOH until pH = 10, and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford the product **6a** as a pale yellow solid (46 mg, 65% yield). $[\alpha]_D^{25} = +73.3$ (c 2.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, J = 8.9, 6.5, 2.9 Hz, 1H), 7.34–7.27 (m, 2H), 7.18–7.06 (m, 1H), 4.56 (dt, J = 4.8, 2.9 Hz, 1H), 4.43 (ddd, J = 11.8, 9.7, 3.0 Hz, 1H), 4.26–4.14 (m, 2H), 3.28 (td, J = 12.5, 3.0 Hz, 1H), 3.12–2.99 (m, 2H), 2.84–2.55 (m, 3H), 1.29 (dt, J = 13.3, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.34, 172.11, 137.50, 137.21, 130.03, 129.40, 128.17, 127.95, 127.18, 127.00, 126.32, 125.14, 66.36, 66.02, 60.78, 60.71, 52.86, 52.12, 49.53, 46.11, 40.95, 39.91, 14.24, 14.18. HRMS-ESI (m/z) calcd for $C_{13}H_{17}NO_3$ [M+Na$^+$]: 258.1106, found: 258.1109.

4.3.11.2. Path B: (*S*)-1-(2-Bromophenyl)-2-nitroethanol 7. Ligand **L1** (12 mg, 0.05 mmol, 5 mol %) and $Cu(OAc)_2·H_2O$ (10 mg, 0.05 mmol, 5 mol %) were added to a test tube containing absolute THF (5 mL), and the mixture was stirred for 1 h at room

temperature to afford a blue solution. To the mixture the corresponding aldehyde **1** (185 mg, 1 mmol) was added with stirring, and the solution was then cooled to –20 °C, after which nitromethane (535 μL, 10 mmol, 10 equiv) and DIPEA (165 μL, 1.0 equiv) were added. After 350 μL of 3 M aqueous HCl was added, the mixture was concentrated and directly purified by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate to afford product **7** as a yellow oil (234 mg, 95% yield), $[\alpha]_D^{25} = -37.8$ (*c* 2.1, CH_2Cl_2). Lit.[10c] data: $[\alpha]_D^{25} = -27.3$ (CH_2Cl_2) 73% ee.

4.3.11.3. (*S*)-2-Amino-1-(2-bromophenyl)ethanol. At first, Zn powder (1.17 g, 18 mmol) was added to a solution of **7** (0.9 mmol) in ethanol/H_2O (12:3, v/v), followed by concentrated HCl (2.5 mL). The mixture was stirred at room temperature for 4 h. Then, the solution was neutralized by 5 M aqueous NaOH until the pH = 10, and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford the product as a pale yellow solid (185 mg, 95% yield).

4.3.11.4. (*S*)-5-(2-Bromophenyl)-4,5-dihydro-2-methyloxazole. To a stirred milky solution of ethyl acetimidate hydrochloride (113 mg, 0.9 mmol) in dry CCl_4 (2 mL) at 0 °C, a solution of (*S*)-2-amino-1-(2-bromophenyl)ethanol (94 mg, 0.7 mmol) in dry CCl_4 (3 ml) was added dropwise. The resulting mixture was stirred overnight at room temperature and poured into 5 mL of 2% aqueous $NaHCO_3$, and the organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography to give 151 mg (90% yield) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.50 (m, 1H), 7.35–7.30 (m, 2H), 7.15 (ddd, *J* = 8.4, 5.6, 3.6 Hz, 1H), 5.72 (dd, *J* = 10.2, 7.5 Hz, 1H), 4.39 (ddd, *J* = 14.3, 10.3, 1.5 Hz, 1H), 3.60 (ddd, *J* = 14.3, 7.5, 1.4 Hz, 1H), 2.11 (t, *J* = 1.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.55, 140.75, 132.76, 129.17, 127.66, 125.87, 120.69, 79.62, 62.33, 13.99.

4.3.11.5. (2*E*)-Ethyl-3-(2-((*S*)-4,5-dihydro-2-methyloxazol-5-yl)phenyl)acrylate. A mixture of (*S*)-5-(2-bromophenyl)-4,5-dihydro-2-methyloxazole (150 mg, 0.62 mmol), ethyl acrylate (530 μL), $Pd(OAc)_2$ (15 mg), PPh_3 (35 mg), and Et_3N (4 mL) was stirred at 80 °C for 16 h. The reaction was then cooled to room temperature, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated, and the crude material was purified by flash chromatography eluting with petroleum ether and ethyl acetate to afford the coupling product as a yellow oil (78 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.7 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45–7.37 (m, 2H), 7.37–7.31 (m, 1H), 6.36 (d, *J* = 15.7 Hz, 1H), 5.81 (dd, *J* = 10.3, 8.1 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.64 (ddd, *J* = 14.1, 8.1, 1.4 Hz, 1H), 2.12 (t, *J* = 1.3 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.42, 164.79, 140.55, 140.00, 131.91, 130.26, 128.23, 127.10, 125.24, 121.28, 77.96, 62.80, 60.67, 14.29, 13.94.

4.3.11.6. Ethyl 2-((4*S*)-1,2,3,4-tetrahydro-4-hydroxyisoquinolin-1-yl)acetate 6a. To a stirred solution of the above coupling product (60 mg, 0.25 mmol) in ethanol was added 3 M HCl (84 μL, 1.0 equiv). After stirring overnight, the solvent was neutralized with 1 M NaOH aqueous until pH = 10 and extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford product **6a** as a pale yellow solid (40 mg, 70%). $[\alpha]_D^{25} = +99.2$ (*c* 2.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, *J* = 8.9, 6.5, 2.9 Hz, 1H), 7.34–7.27 (m, 2H), 7.18–7.06 (m, 1H), 4.56 (dt, *J* = 4.8, 2.9 Hz, 1H), 4.43 (ddd, *J* = 11.8, 9.7, 3.0 Hz, 1H), 4.26–4.14 (m, 2H), 3.28 (td, *J* = 12.5, 3.0 Hz, 1H), 3.12–2.99 (m, 2H), 2.84–2.55 (m, 3H), 1.29 (dt, *J* = 13.3, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.34, 172.11, 137.50, 137.21, 130.03, 129.40, 128.17, 127.95, 127.18, 127.00, 126.32, 125.14, 66.36, 66.02, 60.78, 60.71, 52.86, 52.12, 49.53, 46.11, 40.95, 39.91, 14.24, 14.18. HRMS-ESI (*m*/*z*) calcd for $C_{13}H_{17}NO_3$ [M+Na$^+$]: 258.1106, found: 258.1110.

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