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Chiral diphenylperhydroindolinol silyl ether catalyzed domino oxa-Michael–aldol condensations for the asymmetric synthesis of benzopyrans

Ya-Hui Feng [a], Ren-Shi Luo [a], Lin Nie [a], Jiang Weng [a], Gui Lu [a,b,*]

[a] *Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, PR China*
[b] *Institute of Human Virology, Sun Yat-sen University, Guangzhou 510080, PR China*

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ABSTRACT

Asymmetric domino oxa-Michael–aldol reactions between *trans*-cinnamaldehydes and salicylic aldehyde derivatives have been developed. Using (2*S*,3a*S*,7a*S*)-diphenylperhydro indolinol silyl ether **4i** as the catalyst, most corresponding chiral benzopyrans can be obtained with excellent chemo- and enantioselectivities.

1. Introduction

The benzopyran, or the chromene skeleton, is a widespread element in natural products.[1] The synthesis of benzopyrans, especially chiral benzopyrans, has attracted the attention of many chemists because of their biological activities.[2] On the laboratory scale, practical synthetic routes to benzopyrans include enzyme-catalyzed kinetic resolutions,[3] metal-catalyzed reactions,[4,5] and organocatalytic reactions.[6,7] Organocatalytic enantioselective systems have rapidly grown to be a very exciting field in organic chemistry, and chiral secondary amines are probably the most commonly used organocatalysts, which activate substrates either by raising the highest occupied molecular orbital energy level or lowering the lowest unoccupied molecular orbital energy level.[8]

Domino reactions have been viewed as green processes because they remove the need for purification, minimize the generation of chemical waste, and save time. Brase, List, MacMillan, Jørgenson, Hayashi, and Enders et al. have developed many elegant domino reactions with various secondary amine catalysts.[9] Domino condensations between *trans*-cinnamaldehyde and salicylaldehyde, which function as Michael acceptors and Michael donors respectively, have proven to be a versatile route for the synthesis of benzopyrans. Brase et al. have prepared racemic benzopyrans using 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base.[10] Recently, highly enantioselective domino oxa-Michael–aldol reactions have been independently realized by several groups using chiral prolinol derivatives as catalysts, organic acids as additives.[11] For example, Aridsson et al. reported on an organocatalyzed asymmetric synthesis of chiral benzopyrans with (*S*)-diphenylpyrrolinol TMS ether in moderate yields and ees.[11a] Córdova[11b] and Wang[11c] further optimized this domino reaction independently; the addition of organic acid and molecular sieves was found to increase the ees and yields efficiently. Córdova has also extended the substrate scope from α,β-unsaturated aldehydes to ethyl *trans*-4-oxo-2-butenoate. Later, Xu et al. developed a chiral amine/chiral acid combinational system, which showed a synergistic effect for the improvement of the reaction performance.[11d] Xu et al. also demonstrated an improved protocol for this domino reaction with a recyclable tertiary amine-modified diarylprolinol silyl ether as the catalyst, with good ees (up to 90%) being obtained.[11e]

Compared with a proline catalyst, perhydroindole derivatives possess two more stereogenic centers in the backbone, and may exert stronger influences on both the orientation of the iminium intermediate and salicylaldehyde, hence improving the stereoselectivities for this domino oxa-Michael–aldol reaction. In previous work, we explored the application of perhydroindole derivatives in the asymmetric Michael reactions of aldehydes to nitroalkenes, and obtained high yields (up to 99%) together with excellent levels of enantioselectivities (up to 99%).[12] Herein we report the asymmetric synthesis of chiral benzopyrans via organocatalytic domino oxa-Michael–aldol reactions using a diphenylperhydroindolinol silyl ether as the catalyst.

2. Results and discussion

Preliminary studies were carried out on the model reaction of *trans*-cinnamaldehyde with salicylaldehyde. Perhydroindole

* Corresponding author. Tel./fax: +86 20 39943048.
E-mail address: lugui@mail.sysu.edu.cn (G. Lu).

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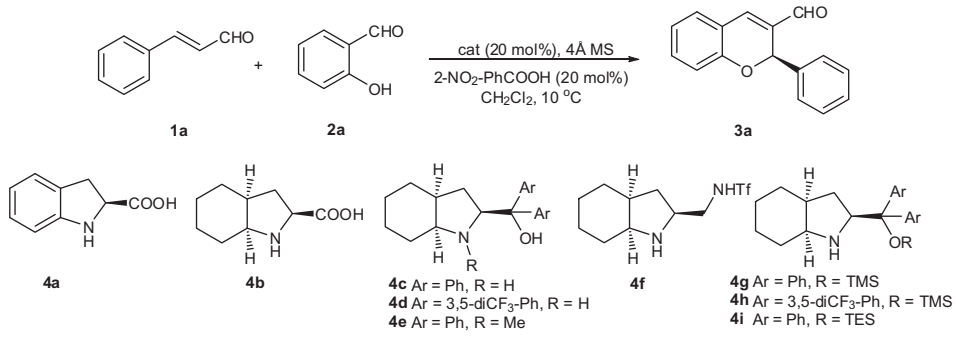
derivatives have proven to be efficient catalysts for Michael reactions in our previous work;[12] herein we mainly chose chiral indole and perhydroindole derivatives to catalyze the domino oxa-Michael–aldol reaction. (*S*)-Indoline-2-carboxylic acid **4a**, (2*S*,3*aS*,7*aS*)-perhydroindoline-2-carboxylic acid **4b**, (2*S*,3*aS*,7*aS*)-(octahydroindol-2-yl)-diphenylmethanol **4c** and **4e** were poor catalysts for this reaction, with less than 5% product being isolated even with 20 mol % catalyst loading for 84 h (Table 1, entries 1–3 and 5). When the hydroxy group of **4c** was protected by a siloxy group as **4g**, significant improvements in both the yield and ee were observed (Table 1, entry 3 vs 7), although this effect was not notable for a bulkier diarylperhydroindolinol silyl ether (Table 1, entry 4 vs 8).[11c] We also screened a chiral perhydroindolinol siloxyl ether with a different siloxy group. The best result was achieved for catalyst **4i** with a TES-protected group,[11a] which exhibited a comparable yield with the TMS-protected catalyst **4g**, but a significantly higher ee in the presence of 2-nitrobenzoic acid (86% ee, Table 1 entry 9). We also observed a slight decrease in enantioselectivity along with a perceptible drop in the yield when the reaction was performed at a lower temperature such as 0 °C.

After compound **4i** was selected as the catalyst, we screened the effects of different solvents on the domino oxa-Michael–aldol

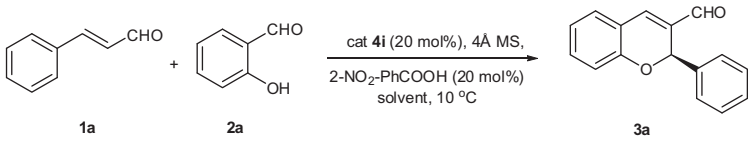
Table 1
Effects of catalysts on the domino oxa-Michael–aldol reaction[a]



Entry	Catalyst	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**4a**	84	<5	ND
2	**4b**	84	<5	ND
3	**4c**	84	<5	ND
4	**4d**	84	35	21
5	**4e**	84	<5	ND
6	**4f**	84	30	2
7	**4g**	84	81	75
8	**4h**	84	50	26
9	**4i**	84	82	86
10[d]	**4i**	84	70	83

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.25 mmol) and **2a** (0.5 mmol) in the presence of catalyst (0.05 mmol), 2-nitrobenzoic acid (0.05 mmol), 4 Å MS (0.1 g), and CH_2Cl_2 (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Preformed at 0 °C.

Table 2
Effects of solvents on the domino oxa-Michael–aldol reaction[a]



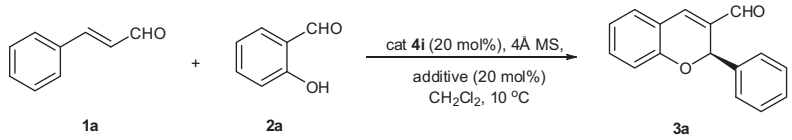
Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Hexane	68	60
2	Toluene	93	76
3	Xylene	71	67
4	THF	49	36
5	Et_2O	68	65
6	CH_3CN	NR	ND
7	DMF	34	16
8	$CHCl_3$	87	81
9	CH_2Cl_2	82	86
10	$ClCH_2CH_2Cl$	86	81

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.25 mmol) and **2a** (0.5 mmol) in the presence of catalyst **4i** (0.05 mmol), 2-nitrobenzoic acid (0.05 mmol), 4 Å MS (0.1 g), and solvent (1 mL) at 10 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

reaction. Highly polar solvents, such as DMF and CH_3CN, gave low yields and enantioselectivities (Table 2, entries 6 and 7), which was in agreement with the literature.[11a–e] Less polar halohydrocarbon solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, and $CHCl_3$ led to better yields and ees (Table 2, entries 8–10). Although toluene was reported to provide moderate yields in similar reactions,[11b] we did observe excellent yields with moderate ee in our system (Table 2, entry 2); we attributed this to the high solubility of catalyst **4i** in toluene. Finally CH_2Cl_2 was chosen as the optimal solvent (Table 2, entry 9).

The influence of various additives on the organocatalytic oxa-Michael–aldol reactions was investigated and the results are summarized in Table 3. In the absence of any additives, no product was observed (Table 3, entry 1); the organic acid additive may enhance the formation of active iminium-ion species. A series of benzoic acids and acetic acids were effective for this reaction (Table 3, entries 3–8). Stronger acids, such as CF_3COOH and D-(+)-10-camphorsulfonic acid, showed poor yields and ees (Table 3, entries 9 and 14). We also tried some chiral acids[11d] and found that in most cases the reaction rates were improved significantly, with good yields (80–85%) and enantioselectivities being obtained (Table 3, entries 10–13). Although Xu et al. reported that (*S*)-organic acids gave better results than their (*R*)-analogues,[11d] we only

Table 3
Effects of additives on the domino oxa-Michael–aldol reaction[a]

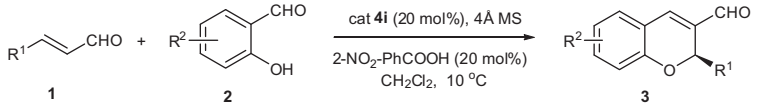


1a 2a 3a

Entry	Additive	*t* (h)	Yield[b] (%)	ee[c] (%)
1	No additive	72	<5	ND
2	PhCOOH	60	83	57
3	2-NO_2-PhCOOH	84	82	86
4	3-NO_2-PhCOOH	79	83	78
5	4-NO_2-PhCOOH	84	82	77
6	2-Br-PhCOOH	80	80	79
7	2-I-PhCOOH	87	90	80
8	$ClCH_2COOH$	84	75	74
9	CF_3COOH	88	31	38
10	(*S*)-*N*-Boc-indoline-2-carboxylic acid	80	85	81
11	(2*S*,3a*S*,7a*S*)-*N*-Boc-octahydro-indole-2-carboxylic acid	80	85	72
12	(*S*)-*N*-Boc-proline	80	80	74
13	(*R*)-*N*-Boc-proline	80	82	75
14	D-(+)-10-Camphorsulfonic acid	80	NR	ND

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.25 mmol) and **2a** (0.5 mmol) in the presence of catalyst **4i** (0.05 mmol), additive (0.05 mmol), 4 Å MS (0.1 g) and CH_2Cl_2 (1 mL) at 10 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

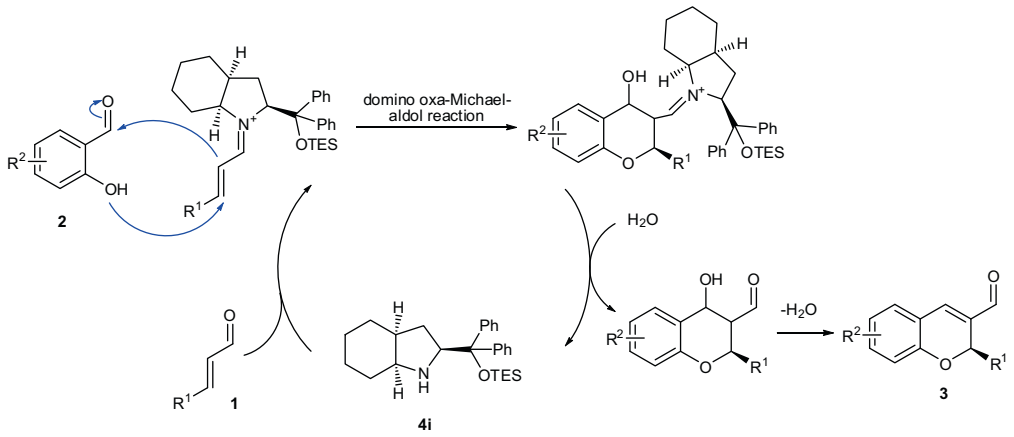
Table 4
Asymmetric domino oxa-Michael–aldol reaction of various α,β-unsaturated aldehydes and salicylaldehyde derivatives[a]



1 2 3

Entry	R^1	R^2	Product	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Ph	H	**3a**	84	82	86
2	Ph	4-OMe	**3b**	80	60	71
3	4-$NO_2C_6H_4$	H	**3c**	80	89	99
4	4-$NO_2C_6H_4$	5-Br	**3d**	60	95	83
5	4-$NO_2C_6H_4$	5-Cl	**3e**	84	90	86
6	2-$NO_2C_6H_4$	5-Br	**3f**	60	90	95
7	2-$NO_2C_6H_4$	5-Cl	**3g**	84	92	93
8	4-FC_6H_4	H	**3h**	84	81	93
9	4-FC_6H_4	5-Br	**3i**	60	86	83
10	4-FC_6H_4	5-Cl	**3j**	84	90	78
11	2,4,5-TrifluoroC_6H_2	H	**3k**	60	91	94
12	2,4,5-TrifluoroC_6H_2	4-OMe	**3l**	80	75	71
13[d]	4-$MeOC_6H_4$	5-Br	**3m**	84	80	78
14	4-MeC_6H_4	H	**3n**	84	70	78
15	Me	H	**3o**	84	51	75
16	Me	5-OMe	**3p**	84	63	67

[a] Unless otherwise specified, the reaction was carried out with α,β-unsaturated aldehyde **1** (0.25 mmol) and salicylaldehyde derivative **2** (0.5 mmol) in the presence of catalyst **4i** (0.05 mmol), 2-nitrobenzoic acid (0.05 mmol), 4 Å MS (0.1 g) in CH_2Cl_2 (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Performed at 20 °C.



Scheme 1. Possible mechanism for the organocatalytic oxa-Michael–aldol reaction.

observed comparable results when using (*S*)- and (*R*)-*N*-Boc-proline, respectively (Table 3, entries 12 and 13). Eventually, 2-nitrobenzoic acid was identified as the optimal additive because it gave the highest ee (86% ee, Table 3 entry 3).

Having established **4i** as a suitable catalyst, CH_2Cl_2 as the solvent, and 2-nitrobenzoic acid as an effective additive, we then investigated the substrate scope of this enantioselective domino oxa-Michael–aldol reaction. The system worked well for a variety of substituted cinnamaldehydes and salicylaldehyde derivatives, although the yields and enantioselectivities varied with the electronic and steric properties of the substrates. α,β-Unsaturated aldehydes bearing electron-withdrawing groups, such as a nitro or fluoro group, were good Michael acceptors, generally affording the desired products in high yields and with excellent enantioselectivities (Table 4, entries 3, 8, and 11). However, the results were not favorable for cinnamaldehydes with electron-donating substituents (Table 4, entry 14). No product was observed when the reaction was performed between 4-methoxycinnamaldehyde and 5-bromo-salicylaldehyde at 10 °C, and an elevated temperature (20 °C) was needed to ensure good conversion (Table 4, entry 13). This process also worked well for less reactive α,β-unsaturated aliphatic aldehydes, albeit with lower yields and enantioselectivities (Table 4, entries 15 and 16).

The enantioselectivity was also affected by the electronic properties of the substituents of salicylaldehydes. For example, 5-chloro and 5-bromo salicylaldehydes showed slightly lower ees than the unsubstituted salicylic aldehyde (Table 4, entries 3–5 and 8–10), while 4-methoxy salicylaldehyde underwent the asymmetric reaction with significantly lower yields and ee values (Table 4, entry 1 vs 2 and entry 11 vs 12). We assumed that the electron-donating properties of the 4-methoxy increased the charge density of the salicylic aldehydes, hence lowering both the reactivities and enantioselectivities. Furthermore, the results showed that proper steric hindrance at α,β-unsaturated aldehydes was beneficial for high ees (Table 4, entries 6, 7, and 11).

Based on the literature[11] and on our experimental results, we have proposed a possible mechanism for this reaction (Scheme 1). The domino oxa-Michael/aldol reaction started from the iminium activation of α,β-unsaturated aldehyde **1** by chiral indolinol derivative **4i**, whose bulky phenyl groups efficiently shielded the *Re*-face of the chiral iminium intermediate (R^1 = aryl; when R^1 = alkyl, *Si*-face was shielded) and resulted in a stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **1**. Then an intramolecular nucleophilic attack on the salicylaldehyde moiety took place, and was followed by hydrolysis of the resulting iminium intermediate and elimination of water. 2-Nitrobenzoic acid might act as a Brønsted acid to activate the salicylaldehyde moiety and to stabilize the iminium intermediate, while the 4 Å molecule sieves removed water from the reaction system to accelerate the aldol condensation.

3. Conclusion

We have described a new organocatalytic system, which readily facilitated the domino oxa-Michael–aldol reaction of a wide range of *trans*-cinnamaldehydes and salicylicaldehyde derivatives, affording the target products with good yields and excellent enantioselectivities. Further applications of this organocatalytic system to other enantioselective tandem reactions are currently underway in our laboratory.

4. Experimental section

4.1. General procedures

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. The solvents were distilled from standard drying agents. Unless otherwise stated, commercial reagents were purchased from Alfa Aesar, Acros and Aldrich chemical companies and used without further purification. Purification of the reaction products was carried out by flash chromatography with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Chemical shifts are reported as parts per million (ppm) in the δ scale downfield from tetramethylsilane (TMS). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were recorded on a Bruker spectrometer with complete proton decoupling, and chemical shifts are reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm). HPLC analyses were conducted on a Shimadzu 10 A instrument using Daicel Chiralcel OD-H, Chiralpak AD-H, Chiralpak AS-H columns (0.46 cm diameter × 25 cm length). Optical rotations were recorded on a Perkin–Elmer polarimeter (Model 341). HRMS spectra were recorded on an ESI-ion trap mass spectrometer (Shimadzu LCMS-IT-TOF) or an EI mass spectrometer (Thermo Trace DSQ). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV254 fluorescent sheets.

4.2. Typical procedure for the oxa-Michael–aldol reaction of α,β-unsaturated aldehydes with salicylic aldehyde derivatives

To a stirred solution of (2*S*,3a*S*,7a*S*)-diphenylperhydroindolinol silyl ether (0.05 mmol), α,β-unsaturated aldehyde (0.25 mmol)

and 4 Å MS (0.1 g) in CH_2Cl_2 (1 mL) were added and stirred at room temperature for ten minutes. Next, *o*-nitrobenzoic acid (0.05 mmol) and the salicylic aldehyde derivative (0.5 mmol) were added slowly over 10 min. The mixture was stirred for indicated time at 10 °C. The corresponding benzopyran was separated and purified by silica gel chromatography. The ee value of the product was determined by chiral HPLC analysis.

Compound **3a**:[11a] isolated yield 82%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 21.7 min (major), 24.6 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 7.24–7.36 (m, 7H), 7.41 (s, 1H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.3, 117.2, 120.0, 121.8, 126.8, 128.6, 128.7, 129.4, 133.7, 139.1, 140.8, 154.9, 190.0. MS (ESI): m/z 237.1 $[M+H]^+$.

Compound **3b**:[11c] isolated yield 60%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm): t_R = 20.3 min (major), 22.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.33 (s, 1H), 6.43 (d, J = 2.2 Hz, 1H), 6.49–6.56 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.28–7.32 (m, 3H), 7.35–7.39 (m, 3H), 9.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 74.5, 101.9, 108.9, 113.4, 126.7, 128.5, 130.6, 133.1, 139.3, 141.0, 156.7, 164.5, 189.7. MS (ESI): m/z 267.1 $[M+H]^+$.

Compound **3c**:[11a] isolated yield 89%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 30.1 min (minor), 32.4 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 4.0 Hz, 1H), 7.26–7.29 (m, 1H), 7.34–7.38 (m, 1H), 7.47 (s, 1H), 7.52–7.54 (m, 2H), 8.13 (d, J = 8.0 Hz, 2H), 9.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.0, 117.1, 119.6, 122.5, 123.8, 127.5, 129.7, 132.8, 134.3, 141.5, 146.2, 147.4, 154.4, 189.9. MS (ESI): m/z 282.0 $[M+H]^+$.

Compound **3d**: isolated yield 95%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 27.1 min (minor), 30.7 min (major). $[\alpha]_D^{20} = -41.4$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.38–7.44 (m, 3H), 7.47–7.52 (m, 2H), 8.14 (d, J = 6.0 Hz, 2H), 9.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.2, 114.4, 118.9, 121.3, 123.9, 127.6, 131.8, 133.5, 136.5, 139.7, 145.5, 148.0, 153.3, 189.6. HRMS (ESI): m/z calcd for $C_{16}H_9BrNO_4$ $[M-H]^-$: 357.9720, found: 357.9709.

Compound **3e**:[11c] isolated yield 90%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 25.3 min (minor), 28.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.27–7.31 (m, 2H), 7.40 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 8.12–8.18 (m, 2H), 9.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.2, 118.5, 120.7, 123.9, 127.3, 127.6, 128.8, 133.6, 133.7, 139.8, 145.5, 148.0, 152.8, 189.6. MS (ESI): m/z 314.0 $[M-H]^-$.

Compound **3f**: isolated yield 90%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm): t_R = 23.5 min (major), 26.5 min (minor). $[\alpha]_D^{20} = +273$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 7.21–7.24 (m, 1H), 7.33–7.36 (m, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.42–7.46 (m, 2H), 7.48 (s, 1H), 7.84–7.88 (m, 1H), 9.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.4, 100.0, 114.3, 119.2, 121.4, 125.0, 128.6, 130.0, 131.4, 132.6, 132.9, 136.4, 140.5, 153.1, 189.1. HRMS (ESI): m/z calcd for $C_{16}H_9BrNO_4$ $[M-H]^-$: 357.9720, found: 357.9700.

Compound **3g**:[11c] isolated yield 92%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm): t_R = 21.7 min (major), 25.9 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 7.18–7.25 (m, 3H), 7.44–7.47 (m, 2H), 7.49 (s, 1H), 7.84–7.89 (m, 1H), 9.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.5, 118.8, 120.8, 125.0, 127.2, 128.4, 128.6, 130.0, 131.4, 132.6, 132.9, 133.5, 140.6, 148.9, 152.6, 189.1. MS (ESI): m/z: 316.1 $[M+H]^+$.

Compound **3h**: isolated yield 81%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 24.1 min (major), 26.8 min (minor). $[\alpha]_D^{20} = -42.6$ (c 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1H), 6.86 (d, J = 12.0 Hz, 1H), 6.93–6.98 (m, 3H), 7.26–7.28 (m, 1H), 7.30–7.34 (m, 3H), 7.42 (s, 1H), 9.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.6, 115.6, 117.2, 119.9, 121.9, 128.6, 128.7, 129.4, 133.6, 133.8, 140.9, 154.6, 161.6, 164.1, 189.9. HRMS (ESI): m/z calcd for $C_{16}H_{11}FO_2Na$ $[M+Na]^+$: 277.0635, found: 277.0632.

Compound **3i**: isolated yield 86%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm): t_R = 13.3 min (major), 14.6 min (minor). $[\alpha]_D^{20} = +29.4$ (c 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (s, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 10.0 Hz, 2H), 7.27–7.31 (m, 2H), 7.35–7.39 (m, 3H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.8, 113.8, 115.5, 115.7, 119.0, 121.6, 128.7, 128.8, 131.4, 134.4, 136.1, 139.1, 153.5, 161.7, 164.2, 189.6. HRMS (ESI): m/z calcd for $C_{16}H_9BrFO_2$ $[M-H]^-$: 330.9775, found: 330.9777.

Compound **3j**: isolated yield 90%. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm): t_R = 12.8 min (major), 14.4 min (minor). $[\alpha]_D^{20} = +18.6$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 8.0 Hz, 2H), 7.23–7.25 (m, 2H), 7.28–7.31 (m, 2H), 7.36 (s, 1H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.8, 115.5, 115.7, 118.6, 121.0, 126.7, 128.5, 128.7, 128.8, 133.3, 134.4, 139.3, 153.0, 161.7, 164.2, 189.7. HRMS (ESI): m/z calcd for $C_{16}H_9ClFO_2$ $[M-H]^-$: 287.0281, found: 287.0275.

Compound **3k**: isolated yield 91%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95:5, 0.5 mL/min, 246 nm): t_R = 21.3 min (major), 24.4 min (minor). $[\alpha]_D^{20} = +42.0$ (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (s, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.95–7.01 (m, 3H), 7.29–7.33 (m, 2H), 7.55 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.8, 106.2, 116.8, 117.2, 119.3, 122.3, 129.5, 131.5, 134.1, 141.7, 145.5, 149.3, 151.8, 154.0, 156.9, 189.2. HRMS (ESI): m/z calcd for $C_{16}H_9F_3O_2Na$ $[M+Na]^+$: 313.0447, found: 313.0440.

Compound **3l**: isolated yield 75%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm): t_R = 26.6 min (major), 28.7 min (minor). $[\alpha]_D^{20} = -30.5$ (c 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 6.35 (d, J = 4.0 Hz, 1H), 6.54–6.57 (m, 2H), 6.93–7.00 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 9.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 67.9, 102.0, 109.5, 112.6, 128.7, 130.7, 141.9, 155.9, 164.8, 188.9. HRMS (ESI): m/z calcd for $C_{17}H_{11}F_3O_3Na$ $[M+Na]^+$: 343.0553, found: 343.0536.

Compound **3m**: isolated yield 80%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 70:30, 0.7 mL/min, 254 nm): t_R = 15.3 min (major), 20.9 min (minor). $[\alpha]_D^{20} = +36.1$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 6.26 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 7.23–7.25 (m, 2H), 7.34–7.36 (m, 2H), 7.38–7.39 (m, 1H), 9.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 74.3, 113.5, 114.0, 119.1, 121.8, 128.3, 130.5, 131.3, 134.7, 135.9, 138.8, 153.7, 160.1, 189.7. HRMS (ESI): m/z calcd for $C_{17}H_{13}BrO_3Na$ $[M+Na]^+$: 366.9940, found: 366.9957.

Compound **3n**:[11d] isolated yield 70%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm): t_R = 19.9 min (major), 23.7 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 6.29 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.22–7.25 (m, 4H), 7.39 (s, 1H), 9.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 74.2, 117.2, 120.0, 121.7, 126.8, 129.2, 133.6, 133.9, 136.1, 138.5, 140.7, 154.9, 190.0. MS (ESI): m/z 251.2 $[M+H]^+$.

Compound **3o**:[11c] isolated yield 30%. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 280 nm): t_R = 24.9 min (minor), 26.7 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.6 Hz, 3H), 5.42 (q, J = 6.6 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.98–6.91 (m, 1H), 7.23–7.18 (m, 2H), 7.35–7.27 (m, 1H), 9.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 69.8, 117.3, 119.9, 121.6, 129.2, 133.4, 136.2, 140.2, 154.4, 190.0.

Compound **3p**:[11d] isolated yield 50%. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm): t_R = 13.3 min (major), 15.3 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, J = 6.6 Hz, 3H). 3.79 (s, 3H), 5.40–5.34 (m, 1H), 6.74 (d, J = 2.9 Hz, 1H), 6.84–6.80 (m, 1H), 6.92–6.87 (m, 1H), 7.16 (s, 1H), 9.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 55.8, 69.6, 112.9, 118.1, 119.6, 120.3, 136.9, 140.2, 148.3, 154.2, 190.0.

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