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Asymmetric Annulation of 3-Alkynylacrylaldehydes with Styrene-Type Olefins by Synergetic Relay Catalysis from AgOAc and Chiral Phosphoric Acid

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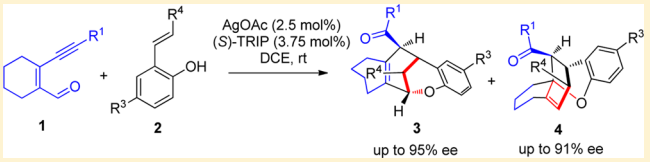
Supporting Information

ABSTRACT: Asymmetric annulation of 3-alkynylacrylaldehydes with 2-hydroxystyrenes has been studied and achieved by synergetic catalysis from AgOAc and chiral phosphoric acid, providing the corresponding multiring products with decent total yields and moderate to excellent enantioselectivities (up to 95% ee). The developed mild multibond-formation cascade reaction involves in situ generation of pyrylium intermediate by Ag(I)-catalyzed alkyne/carbonyl cycloisomerization, counteranion-directed asymmetric oxa [4 + 2]-cycloaddition, and intramolecular nucleophilic substitution.



INTRODUCTION

Pyrylliums, a unique type of reactive cyclic oxonium intermediate with erratic aromaticity, have been commonly applied as inseparable intermediates to the synthesis of various heterocycles.[1] For high reactivity, pure pyrylliums (without any stabilizing structural factors) have been rarely reported in complicated transformations,[2] and enantioselective reaction involving a pure pyrylium intermediate has remained as an unresolved challenge. To expand the application scope, several types of stabilized pyrylliums have been developed and applied to enantioselective transformations in recent years, including benzopyrylium,[3] isobenzopyrylium,[4] and oxidopyryliums[5,6] (Figure 1). Inspired by our recent achievement in the enantioselective transformations of isobenzopyryliums (also called isochromenyliums, a type of pyrylium stabilized with a fused benzene ring) with a supramolecular binary catalysis mode,[7] we tried to expand the developed binary catalytic methodology to the reactions involving a pure pyrylium intermediate. Two theoretical catalytic modes were accordingly proposed to achieve such an asymmetric transformation (Figure 1, types 1 and 2). Type 1 mechanism was deduced through the same supramolecular catalysis as our previous study on isochromenyliums,[7] while type 2, based on the asymmetric counterion-directed catalysis (ACDC) theory,[8,9] was considered as an alternative option to generate the required asymmetric environment. Herein, we report our results on the first catalytic enantioseletive reaction involving a pure unstabilized pyrylium via an asymmetric counterion-directed mechanism.

RESULTS AND DISCUSSION

As shown in the hypothesis in Figure 1, we first examined the reaction of 3-alkynylacrylaldehyde **1a** and 2-hydroxystyrene **2a** under our previous conditions[7] with a catalyst combination of 10 mol % $Pd(OAc)_2$ and 10 mol % (*S*)-TRIP at room temperature (**P-1**, Table 1, entry 1). Disappointedly, such a binary catalysis mode was proven to be less effecient for this reaction, affording two products **3aa** (the expected product, 12%, 65% ee) and **4aa** containing a quaternary carbon (an isomer of **3aa**, 6%, 59% ee) with low yields and moderate enantioselectivities after 26 h. The relative structures of these two products were determined by 2D NMR methods, and their absolute configurations were finally confirmed by the X-ray single crystal analysis of products **3cd** and **4ag** in a late stage of this study (see Supporting Information). Analysis of these results indicated that poor efficiency in generating the active pyrylium intermediate through $Pd(OAc)_2$ activation of the alkyne functionality might be a main reason. Once the pyrylium intermediate was produced, the subsequent [4 + 2]-cyclization of pyrylium with styrene **2a** proceeded as expected. To improve the results, several other bivalent metal catalysts were further screened together with (*S*)-TRIP (Table 1, entries 2−4). The reaction with $Cu(OAc)_2$ gave similar unsatisfactory results in a much longer reaction time (entry 2), and both $Fe(OAc)_2$ and $Zn(OAc)_2$ were found to be insufficiently active to trigger the reaction (entries 3 and 4).

The failure in achieving the type 1 mechanism turned our attention to the alternative ACDC mode[8,9] with a relay catalysis design (Figure 1, type 2).[10,11] A number of steps was expected to synergetically occur under such a mechanism, including converting substrate **1** into the corresponding metallopyrylium, protonolysis of the C−M bond with chiral phosphoric acid and forming a tight chiral ionic pair, assembling olefin **2** into the chiral environment through a hydrogen bond with the P═O bond, and triggering the key [4 + 2]-cycloaddition. To favor the production of pyrylium intermediate, new metal catalysts

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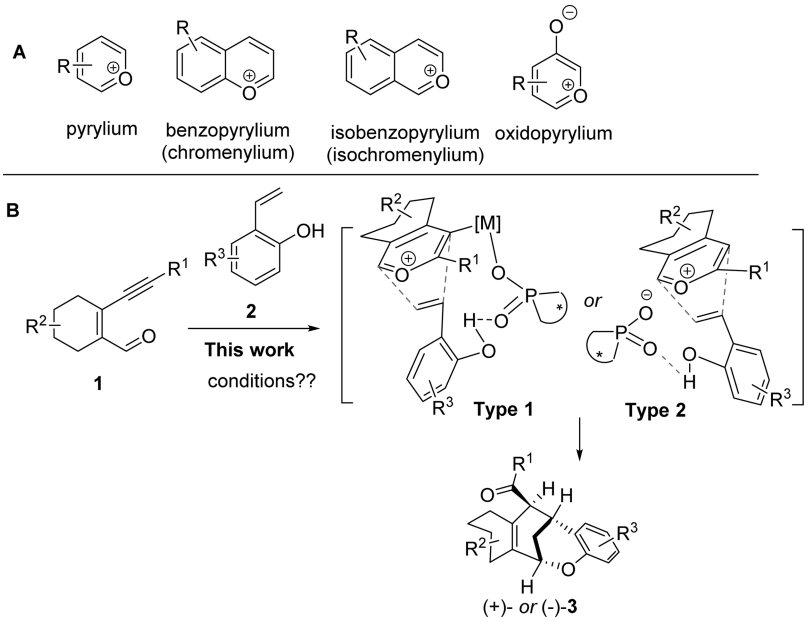
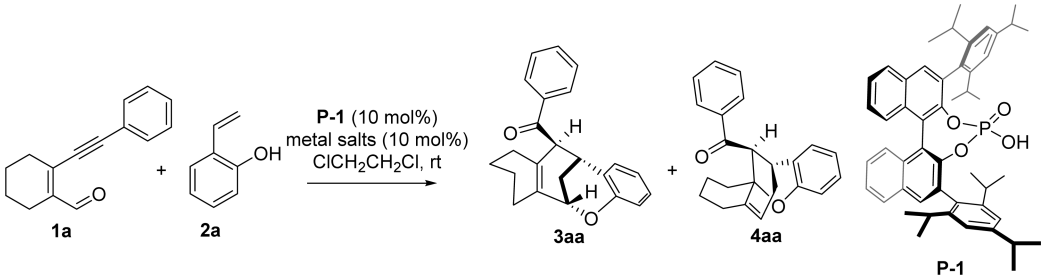


Figure 1. (A) Typical structures of pyrylium, benzopyrylium, isobenzopyrylium, and oxidopyrylium. (B) Initial design of asymmetric annulation of 3-alkynylacrylaldehydes **1** with 2-hydroxystyrenes **2**.

Table 1. Screening of Metal Catalysts[a]



entry	metal catal.	time	**3aa** (yield, ee)[b] (%)	**4aa** (yield, ee)[b] (%)
1	$Pd(OAc)_2$	26 h	12 (65)	6 (59)
2	$Cu(OAc)_2$	8 d	16 (60)	13 (50)
3[c]	$Zn(OAc)_2$	4 d	0	0
4[c]	$Fe(OAc)_2$	4 d	0	0
5	AuCl	60 h	0	0
6	AgOTf	1.5 h	42 (0)	36 (0)
7	AgOAc	6 h	28 (63)	32 (63)

[a]Unless otherwise noted, the reaction was conducted between **1a** (0.5 mmol) and **2a** (0.75 mmol), the metal catalyst (10 mol %), and **P-1** (10 mol %) in 1,2-dichloroethane (5 mL) at room temperature under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC. [c]No reaction occurred.

should have stronger ability to activate the alkyne functionality of substrate **1a** than $Pd(OAc)_2$. The monovalent gold(I) and silver(I) catalysts were therefore examined in the reaction together with chiral phosphoric acid **P-1** (Table 1, entries 5–7). To our delight, the two products could be obtained under cocatalysis from AgOAc and (*S*)-TRIP with moderate yields and enantioselectivities in a shorter reaction time (Table 1, entry 7). A parallel reaction catalyzed with AgOTf and (*S*)-TRIP gave the racemic products in similar yields (entry 6). It is suggested that exchange of the counterion of metal catalysts with chiral phosphoric acid was crucial in the reaction. Because the acidity of phosphoric acid **P-1** is stronger than that of acetic acid, the combination of AgOAc and (*S*)-TRIP would be favorable to produce Ag-(*S*)-TRIP in the reaction, and similar anionic exchange was forbidden for the catalyst combination of AgOTf and (*S*)-TRIP. Therefore, AgOAc was determined as the π-Lewis acid for our further optimization.

Because the enantioselectivity was controlled through the chiral phosphoric acid, we further screened a number of chiral phosphoric acids having various 3,3′-subsitituents (10 mol %) at room temperature (Table 2). The experiments showed that (*S*)-TRIP (**P-1**) was the best Brønsted acid catalyst for this asymmetric transformation (entry 1). The reactions with other binaphthol-based chiral phosphoric acids (**P-2** to **P-8**) and chiral spirophosphoric acids (**P-9** and **P-10**) could not afford better results.

With the catalyst combination of AgOAc and (*S*)-TRIP (**P-1**), other reaction parameters were then investigated (Table 3). The experiments indicated that DCE was the best solvent (entry 10), and the reaction cannot be completed in MeCN,

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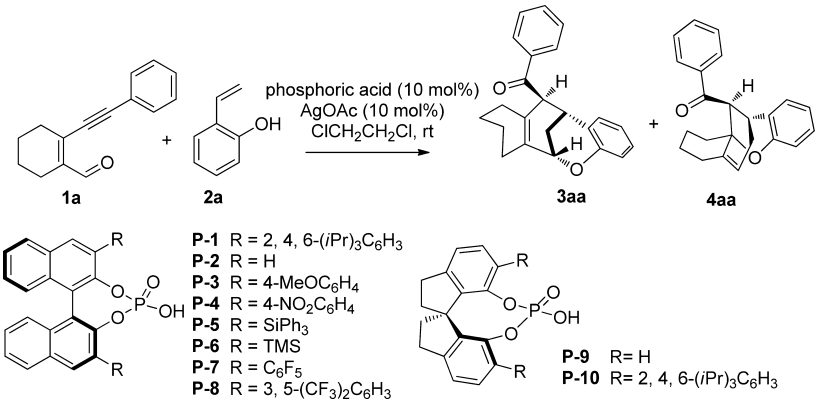
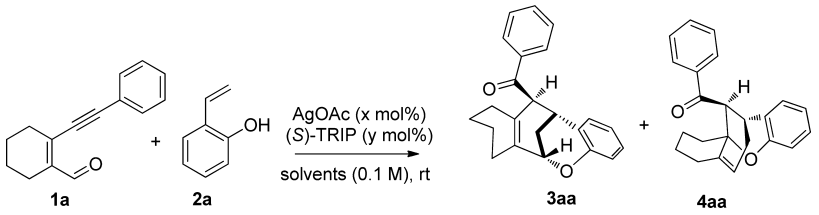
Table 2. Optimization of Chiral Phosphoric Acids[a]



entry	acid	time	conversion rate of **1a** (%)	**3aa** (yield, ee)[b] (%)	**4aa** (yield, ee)[b] (%)
1	**P-1**	6 h	100	28 (63)	32 (63)
2	**P-2**	4 d	50	12 (22)	20 (20)
3	**P-3**	4 d	60	27 (28)	28 (17)
4	**P-4**	4 d	60	26 (21)	27 (10)
5	**P-5**	4 d	20	7.2 (5)	trace
6	**P-6**	4 d	trace		
7	**P-7**	4 d	trace		
8	**P-8**	4 d	20	7.3 (17)	3.6 (11)
9	**P-9**	4 d	40	15 (−19)	11 (−11)
10	**P-10**	5 d	100	32 (−40)	29 (−27)

[a]Unless otherwise noted, the reaction was conducted between **1a** (0.5 mmol) and **2a** (0.75 mmol), AgOAc (10 mol %), and the phosphoric acid (10 mol %) in 1,2-dichloroethane (5 mL) at room temperature under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC.

Table 3. Optimization of Reaction Parameters[a]



entry	*x*	*y*	solvents	time	**3aa** (yield, ee)[b] (%)	**4aa** (yield, ee)[b] (%)
1	10	10	MeCN	4 d	0	0
2	10	10	1,4-dioxane	4 d	0	0
3	10	10	THF	4 d	0	0
4	10	10	DMF	4 d	0	0
5	10	10	toluene	33 h	7 (85)	8 (70)
6	10	10	DCM	12 h	19 (70)	19 (57)
7	10	10	DCE:toluene (5:1)	25 h	16 (71)	22 (63)
8	10	10	DCE:toluene (1:1)	43 h	10 (81)	14 (63)
9	10	10	DCE:toluene (1:5)	2.5 d	6.1 (85)	4.4 (65)
10	10	10	DCE	6 h	28 (63)	32 (63)
11[c]	10	10	DCE	6.5 d	15 (75)	12 (70)
12[d]	10	10	DCE	3 h	22 (63)	38 (62)
13	10	15	DCE	8 h	27 (68)	31 (61)
14	10	30	DCE	27 h	26 (66)	39 (62)
15	5	7.5	DCE	16 h	30 (72)	35 (69)
16	2.5	3.75	DCE	28 h	29 (73)	34 (71)
17[e]	2.5	3.75	DCE	20 h	19 (67)	18 (60)
18[f]	2.5	3.75	DCE	36 h	18 (67)	18 (59)

[a]Unless otherwise noted, the reaction was conducted between **1a** (0.5 mmol) and **2a** (0.75 mmol) with indicated catalysts in 5 mL of solvent at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC. [c]The reaction was performed at 0 °C. [d]The reaction was performed at 40 °C. [e]The reaction was performed without N_2 protection. [f]The reaction was conducted with the addition of water (1 equiv).

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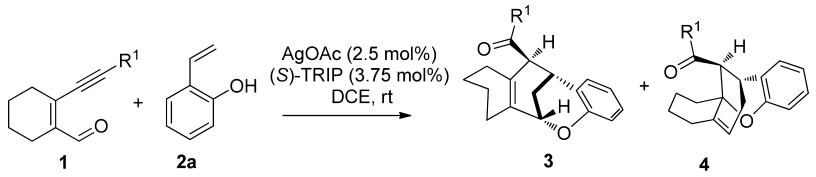
Table 4. Examination of the Reaction Scope of 3-Alkynylacrylaldehyde 1[a]



entry	1	time	3 (yield, ee) (%)[b]	4 (yield, ee) (%)[b]
1	**1b** (R^1 = 4-$NO_2C_6H_4$)	24 h	**3ab** (0)	**4ab** (0)
2	**1c** (R^1 = 4-CNC_6H_4)	72 h	**3ca** (32, 92)	**4ca** (34, 92)
3	**1d** (R^1 = 4-$CO_2MeC_6H_4$)	70 h	**3da** (28, 87)	**4da** (30, 84)
4	**1e** (R^1 = 4-FC_6H_4)	14 h	**3ea** (45, 83)	**4ea** (37, 83)
5	**1f** (R^1 = 4-BrC_6H_4)	42 h	**3fa** (34, 88)	**4fa** (30, 86)
6	**1g** (R^1 = 4-MeC_6H_4)	28 h	**3ga** (33, 82)	**4ga** (41, 82)
7	**1h** (R^1 = 4-$MeOC_6H_4$)	15 h	**3ha** (25, 78)	**4ha** (67, 78)
8	**1i** (R^1 = 3-$MeOC_6H_4$)	44 h	**3ia** (23, 15)	**4ia** (40, 9)
9	**1j** (R^1 = 2-$MeOC_6H_4$)	60 h	**3ja** (30, 58)	**4ja** (32, 57),
10	**1k** (R^1 = 3,4-$(MeO)_2C_6H_3$)	6.5 d	**3ka** (30, 65)	**4ka** (53, 65)
11	**1*l*** (R^1 = 3, 4,5-$(MeO)_3C_6H_2$)	44 h	**3*l*a** (29, 17)	**4*l*a** (42, 20)
12	**1m** (R^1 = *n*-C_5H_{11})	3d 10 h	**3ma** (27, 0)	**4ma** (37, 0)

[a]Unless otherwise noted, the reaction was conducted between **1** (0.5 mmol) and **2a** (0.75 mmol), AgOAc (2.5 mol %), and (*S*)-TRIP (3.75 mol %) in 5 mL of anhydrous DCE at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC.

1,4-dioxane, THF, and DMF (entries 1−4). Though the reaction afforded products with higher enantioselectivity in toluene (entry 5), severe side reactions were observed. We also tried to improve the enantioselectivity in the mixed solvents of toluene and DCE, but the results were unsatisfactory (entries 7−9). A slightly better enantioselectivity was observed when the reaction was performed at 0 °C but with much lower yields and in a much longer reaction time (entry 11). Higher reaction temperature could shorten the reaction time but could not improve the enantioselectivity (entry 12). Increasing the loading of (*S*)-TRIP over AgOAc showed a little improvement in the enantioselectivity, and 50% excess (0.5 equiv more than that of AgOAc) was found to be sufficient (entries 10, 13, and 14). To our surprise, lowering the catalyst loadings down to 2.5 mol % of AgOAc and 3.75 mol % of (*S*)-TRIP further improved the enantioselectivities of products up to 73% and 71% ee, respectively (entries 16). Water was found to be detrimental but not fatal to this reaction (entries 17 and 18), and anhydrous solvent is therefore preferred. Therefore, the optimal catalyst combination was finally determined as AgOAc (2.5 mol %) and (*S*)-TRIP (3.75 mol %).

The generality of reaction was explored under the above optimized conditions (Tables 4−6). Significant electronic effects of R^1 were observed (Table 4). When the electron density of the phenyl ring of R^1 decreased, the enantioselectivity of products turned out to be better (entries 2−5). In particular, the NO_2 group of substrate **1b** did not afford the desired products (entry 1). A significant effect of the R^1 substituent position(s) on the phenyl ring was also observed on the enantioselectivity. The meta-position substituent caused a dramatic decrease in the enantioselectivity (entries 8, 10, and 11). Unsatisfactory results also occurred for substrate **1** with an aliphatic substituent (entry 12). We guess that sufficient $\pi-\pi$ interactions[11c] between the R^1 functionality of substrate **1** and the chiral catalyst **P-1** might be helpful for enantioselective control of the reactions (for more discussion on the mechanism, see text below).

Unfortunately, the reactions of 3-alkynyl-2-enones **5** did not work at all with this catalytic system (Figure 2). No desired

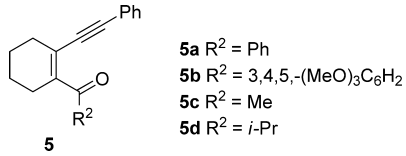


Figure 2. Examined 3-alkynyl-2-enone **5**.

products were obtained under standard conditions. Considering possible self-reaction of the pyrylium intermediate generated from ketones **5** with the aromatic ring of R^2 (**5a** and **5b**), we also tried to decrease the possible side reactions by introduction of alkyls into the substrate (**5c** and **5d**) or by running the reaction at lower temperatures. However, these attempts gave no desirable results.

The reactions of multisubstituted *o*-hydroxystyrene **2** were also examined (Table 5). A much slower reaction and a low conversion rate (ca. 30%) were observed when 3-alkynylacrylaldehyde **1a** reacted with olefin **2b** bearing a strong, electron-rich phenyl group (Table 5, entry 1, R^3 = *p*-OMe). The reactions with the styrenes **2** having a weak electronic-donating group or an electronic-withdrawing group afforded reasonable combined yields of products **3** and **4** with moderate ee values (entries 2−4, R^3 = *p*-Me, *p*-Br, or *p*-CO_2Me). Under standard conditions, the reactions of 1,2-disubstituted olefins were carried out for longer reaction times and gave compounds **4** as the major products (entries 5 and 6), while no reaction could be detected for the trisubstituted olefins after 4 days (entries 7 and 8).

On the basis of the above results (Tables 4 and 5), we reorganized a number of substrates for further examination (Table 6). The 3-alkynylacrylaldehyde **1** with an electron-rich phenyl group (**1g**, R^1 = 4-MeC_6H_4, entry 6; **1h**, R^1 = 4-$MeOC_6H_4$, entries 7−11) and an electron-poor phenyl group (**1c**, R^1 = 4-CNC_6H_4, entries 1−5) were applied to the reaction

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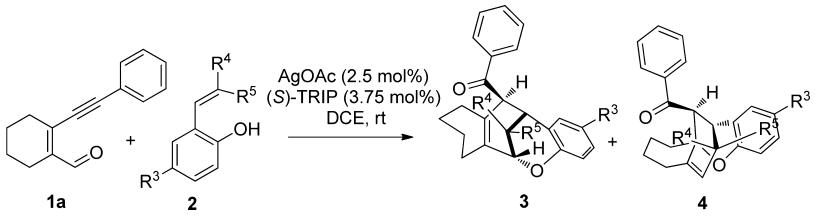
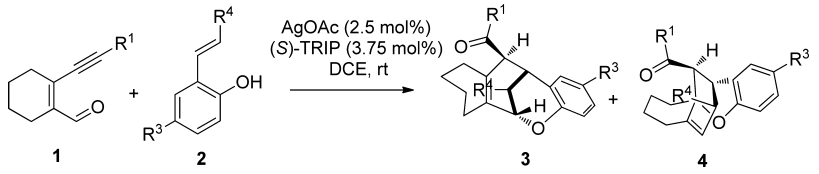
Table 5. Examination of the Scope of Olefin 2[a]



entry	2	time	3 (yield, ee) (%)[b]	4 (yield, ee) (%)[b]
1	**2b** (R^3 = 4-OMe, R^4 = H, R^5 = H)	8 d	**3ab** (9.6, 80)	**4ab** (15, 76)
2	**2c** (R^3 = 4-Me, R^4 = H, R^5 = H)	60 h	**3ac** (24, 72)	**4ac** (40, 66)
3	**2d** (R^3 = 4-Br, R^4 = H, R^5 = H)	19 h	**3ad** (44, 83)	**4ad** (38, 63)
4	**2e** (R^3 = 4-CO_2Me, R^4 = H, R^5 = H)	16 h	**3ae** (36, 80)	**4ae** (39, 60)
5	**2f** (R^3 = H, R^4 = CH_3, R^5 = H)	8 d	**3af** (12, 63)	**4af** (71, 60)
6	**2g** (R^3 = 4-Br, R^4 = CH_3, R^5 = H)	5 d	**3ag** (9.4, 75)	**4ag** (63, 53)[c]
7	**2h** (R^3 = H, R^4 = CH_3, R^5 = CH_3)	4 d	**3ah** (0)	**4ah** (0)
8	**2i** (R^3 = H, R^4/R^5 = *c*-C_5H_{10})	4 d	**3ai** (0)	**4ai** (0)

[a]Unless otherwise noted, the reaction was conducted between **1a** (0.5 mmol) and **2** (0.75 mmol), AgOAc (2.5 mol %), and (*S*)-TRIP (3.75 mol %) in 5 mL of anhydrous DCE at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC. [c]The absolute structure of **4ag** was determined by X-ray single crystal analysis (see Supporting Information).

Table 6. Further Examination of the Catalytic Asymmetric Reactions[a]



entry	1	2	time	3 (yield, ee) (%)[b]	4 (yield, ee) (%)[b]
1	**1c** (R^1 = 4-CNC_6H_4)	**2b** (R^3 = 4-OMe, R^4 = H)	48 h	**3cb** (0)	**4cb** (0)
2	**1c** (R^1 = 4-CNC_6H_4)	**2c** (R^3 = 4-Me, R^4 = H)	72 h	**3cc** (trace)	**4cc** (trace)
3	**1c** (R^1 = 4-CNC_6H_4)	**2d** (R^3 = 4-Br, R^4 = H,)	60 h	**3cd** (36, 95)[c]	**4cd** (33, 86)
4	**1c** (R^1 = 4-CNC_6H_4)	**2e** (R^3 = 4-CO_2Me, R^4 = H)	4 d	**3ce** (50, 94)	**4ce** (12, 91)
5	**1c** (R^1 = 4-CNC_6H_4)	**2f** (R^3 = H, R^4 = CH_3)	14 d	**3cf** (trace)	**4cf** (trace)
6	**1g** (R^1 = 4-Me C_6H_4)	**2d** (R^3 = 4-Br, R^4= H)	23 h	**3gd** (34, 91)	**4gd** (52, 82)
7	**1h** (R^1 = 4-$MeOC_6H_4$)	**2b** (R^3 = 4-OMe, R^4 = H)	9.5 d	**3hb** (29, 85)	**4hb** (38, 85)
8	**1h** (R^1 = 4-$MeOC_6H_4$)	**2c** (R^3 = 4-Me, R^4 = H)	8.5 d	**3hc** (24, 77)	**4hc** (58, 70),
9	**1h** (R^1 = 4-$MeOC_6H_4$)	**2d** (R^3 = 4-Br, R^4 = H)	53 h	**3hd** (40, 88)	**4hd** (45, 81)
10	**1h** (R^1 = 4-$MeOC_6H_4$)	**2e** (R^3 = 4-CO_2Me, R^4 = H)	4d 4h	**3he** (29, 88)	**4he** (30, 88)
11	**1h** (R^1 = 4-$MeOC_6H_4$)	**2f** (R^3 = H, R^4 = CH_3)	12 d	**3hf** (trace)	**4hf** (80, 71)

[a]Unless otherwise noted, the reaction was conducted between **1** (0.5 mmol) and **2** (0.75 mmol), AgOAc (2.5 mol %), and (*S*)-TRIP (3.75 mol %) in 5 mL of anhydrous DCE at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC. [c]The absolute structure of **3cd** was determined by X-ray single crystal analysis (see Supporting Information).

with the styrenes under standard reaction conditions, respectively. The results show that 3-alkynylacrylaldehyde **1c** only reacted with the styrenes having an electron-poor phenyl group (entries 3 and 4). The reaction of **1c** and **2d** afforded 36% yield of **3ce** (95% ee) and 33% yield of **4ce** (86% ee), and the reaction of **1c** and **2e** afforded 50% yield of **3ce** (94% ee) and 12% yield of **4ce** (91% ee) while 3-alkynylacrylaldehyde **1h** was found to react with all the styrenes and afforded the products with moderate to good enantioselectivity (entries 7–11). It is deduced that the relative stability of pyrylium intermediate and the acidity of the phenol group of **2**, as well as mutual reactivities of both substrates, might be all regulated by the electronic density of the involved phenyl rings.

To better understand the mechanism, several control experiments were conducted (Table 7). Failure of the cascade transformations at rt in the absence of either AgOAc or (*S*)-TRIP reveals that both the metal salt and the chiral phosphoric acid are essential for this reaction (entries 1 and 2). When Ag-(*S*)-TRIP alone was used as the only catalyst, the desired products could be obtained in lower yield and low enantioselectivity after a relatively longer reaction time (entry 3). This means that Ag-(*S*)-TRIP could not sufficiently achieve this transformation in a highly enantioselective fashion. Further addition of (*S*)-TRIP (1.25 mol %) and acetic acid (2.5 mol %) to the same reaction (entry 4) resulted in similar yields and enantiopurities of the products as those under standard conditions with AgOAc (2.5 mol %) and (*S*)-TRIP (3.75 mol %) (entry 5). In addition, treatment of the pure single products **3aa** and **4aa** was also examined, in parallel, under the standard catalytic reaction conditions, with AgOAc (2.5 mol %) and (*S*)-TRIP (3.75 mol %) in 1,2-dichloroethane at room temperature. Both substrates were unchanged after 3 days. Such results excluded the possibility of mutual transformation between these two products during the reaction process.

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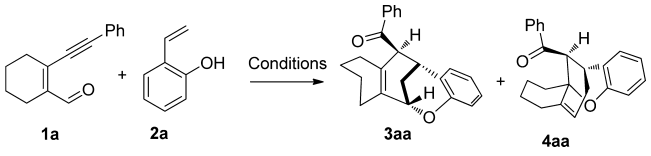
Table 7. Control Experiments for Mechanism Study[a]



entry	Ag(I) (2.5 mol %)	(*S*)-TRIP, mol %	time	**3aa** (yield, ee) (%)[b]	**4aa** (yield, ee) (%)[b]
1	AgOAc	–	7 d	0	0
2	–	3.75	7 d	0	0
3	Ag-(*S*)-TRIP	–	3 d	18, 62	17, 59
4[c]	Ag-(*S*)-TRIP	1.25	30 h	26, 70	28, 65
5	AgOAc	3.75	26 h	29, 73	34, 71

[a]Unless otherwise noted, the reactions were carried out between **1a** (0.5 mmol) and **2a** (0.75 mmol) with the indicated catalysts in 5 mL of anhydrous DCE at room temperature (23 °C) under nitrogen atmosphere. [b]Isolated yields and ee values were determined by chiral HPLC. [c]Acetic acid (2.5 mol %) was added.

A possible mechanism was proposed based on the above results and control experiments (Figure 3). First, the alkyne

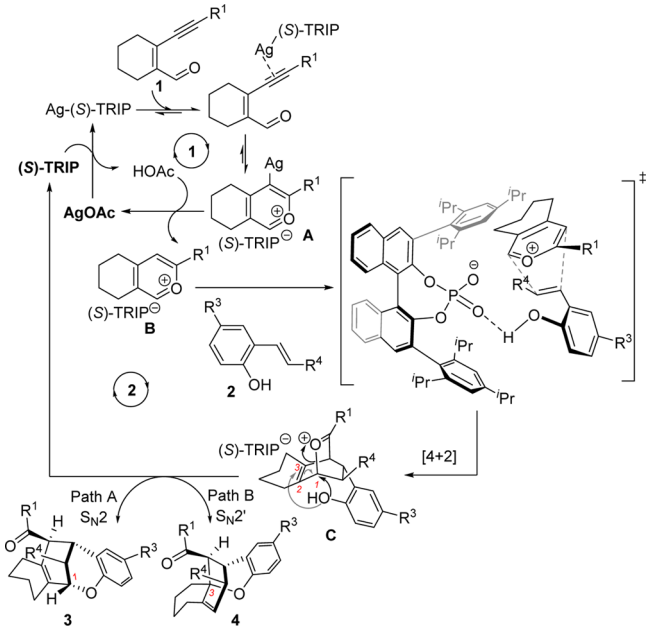


Figure 3. A proposed reaction mechanism.

bond of **1** is coordinated and activated by Ag(I), initiating the cycloisomerization with the internal carbonyl oxygen to afford a Ag(I)-pyrylium/chiral phosphate ionic pair **A**. Immediate protonolysis of the C–Ag bond with HOAc delivers AgOAc back to the first catalytic cycle and generates the key chiral pyrylium phosphate ionic pair **B**. Then the phosphate P=O bond of intermediate **B** grasps the 2-hydroxystyrene substrate **2** through a hydrogen bond with the phenolic hydroxyl group, and an asymmetric [4 + 2]-cycloaddition is immediately triggered.[12] We believe that certain $\pi-\pi$ interactions between the phenyl groups of the two substrates and chiral phosphate also contribute crucial driving forces in forming the transition state of asymmetric [4 + 2]-cycloaddition, though it cannot yet be precisely explained. Existence of such $\pi-\pi$ interactions also can explain our previous observation on significant electronic effects of the substrates in the reactions. Furthermore, the limited cavity of the ion pair results in the hindrance effects of the R^4 in the reactions. The larger the size of the R^4 group, the more difficult the delivery of styrene **2** to the cavity. That is why trisubstituted olefins cannot undergo this reaction. The resulting carbocation **C** is finally attacked by the internal phenolic hydroxyl group through a S_N2 (attack at C1 position) or a S_N2' (attack at C3 position) mechanism, providing the final products **3** and **4**, respectively. In the meanwhile, one molecule of chiral phosphoric acid is regenerated in the last step and returns to the synergetic catalytic cycle. In total, three new bonds and two rings are enantioselectively produced through this catalytic asymmetric cascade reaction starting from the two prochiral substrates **1** and **2**.

CONCLUSION

In summary, a catalytic asymmetric counterion-directed annulation of 3-alkynylacrylaldehydes and 2-hydroxystyrenes has been successfully developed through an in situ-generated unstabilized pyrylium with synergetic catalysis from AgOAc and chiral phosphoric acid (*S*)-TRIP under mild conditions, providing corresponding multiring products in moderate to excellent enantioselectivity (up to 95% ee). Three new bonds and two rings were totally generated through the developed cascade reaction, which is composed of an alkyne–carbonyl cycloisomerization, an oxa [4 + 2]-cycloaddition, and an intramolecular S_N2 or S_N2' substitution. Further study on the regioselective control of the reaction and application of the developed methodology to the synthesis of functional molecules will be studied in this laboratory.

EXPERIMENTAL SECTION

General. All the reactions were conducted using oven-dried glassware. DCE was distilled from CaH_2 prior to use. Hexane and ethyl acetate were obtained from commercial suppliers and used without further distillation. Chemical shifts for ^1H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard, and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a triplet at 77.16 ppm for deuteriochloroform. Enantiomeric ratios of products were determined by chiral HPLC with different chiral columns and hexane and *i*-PrOH as solvents. Melting points were uncorrected.

Representative Procedure. To a solution of AgOAc (2.8 mg, 2.5 mol %) and (*S*)-TRIP (14.1 mg, 3.75 mol %) in dry DCE (1 mL) in a dark reaction tube were added 3-alkynylacrylaldehyde **1a** (105 mg, 0.5 mmol) in dry DCE (2 mL) and 2-hydroxystyrene **2a** (90 mg, 0.75 mmol) in dry DCE (2 mL) under N_2 at rt. The resulting mixture was stirred at rt until starting material **1a** was consumed (monitored by TLC). The whole mixture was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 150:1 to 100:1) to give products **3aa** (47.8 mg, 29% yield, 73% ee) and **4aa** (56.1 mg, 34% yield, 71% ee) as white solids.

3aa. White solid; mp 146–148 °C; $[\alpha]_D^{25}$ −102.7 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.64 (tt, *J* = 7.6, 2.4 Hz, 1H), 7.56 (td, *J* = 6.0, 1.6 Hz, 2H), 7.24 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.16 (td, *J* = 7.6, 1.6 Hz, 1H), 6.91 (td, *J* = 7.2, 0.8 Hz, 1H), 6.82 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.50 (s, 1H), 4.10 (s, 1H), 3.17 (d, *J* = 1.6 Hz, 1H), 2.40–2.35 (m, 1H), 2.19–2.09 (m, 2H), 1.88–1.72 (m, 3H), 1.69–1.50 (m, 3H), 1.48–1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 153.3, 136.6, 133.4, 131.6, 130.2, 129.0, 128.7, 128.6, 128.3, 126.4, 120.1, 117.5, 71.4, 57.4, 33.2, 29.2, 28.4, 23.4, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2924, 2828, 2358, 1676, 1578, 1219, 1046, 1113, 1021, 967, 693, 581 cm^{-1}; HRMS (ESI, *m*/*z*)

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calcd for $C_{23}H_{22}O_2Na^+$ [M + Na]$^+$: 353.1517, found: 353.1514; HPLC analysis: 73% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm, t_1 = 10.3 min (minor), t_2 = 11.9 min (major)].

4aa. White solid; mp 125−128 °C; $[\alpha]_D^{25}$ 77.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.89−6.84 (m, 2H), 5.52 (d, *J* = 5.2 Hz, 1H), 3.88 (d, *J* = 3.2 Hz, 1H), 3.27 (brs, 1H), 2.35−2.31 (m, 1H), 2.21−2.12 (m, 3H), 2.05−1.95 (m, 2H), 1.83−1.76 (m, 2H), 1.69−1.66 (m, 1H), 1.60−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 153.0, 137.0, 135.2, 133.3, 128.9, 128.5, 128.29, 128.24, 127.4, 121.9, 120.2, 117.0, 74.3, 49.0, 35.0, 33.5, 31.9, 31.8, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2959, 1681, 1594, 1579, 1261, 1069, 1033, 958, 771, 700, 626, 590 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{22}O_2Na^+$ [M + Na]$^+$:353.1517, found: 353.1512; HPLC analysis: 71% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, t_1 = 10.4 min (major), t_2 = 11.7 min (minor)].

3ca. White solid, 56.8 mg, 32% yield; mp 137−141 °C; $[\alpha]_D^{25}$ −301.1 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 8.21 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.88 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.20−7.15 (m, 2H), 6.92 (dt, *J* = 7.2, 1.6 Hz, 1H), 6.83 (dd, *J* = 8.0, 0.4 Hz, 1H), 4.51 (s, 1H), 4.05 (s, 1H), 3.11 (d, *J* = 1.6 Hz, 1H), 2.41−2.36 (m, 1H), 2.19−2.11 (m, 1H), 2.05 (dt, *J* = 13.2, 2.4 Hz, 1H), 1.88 (dt, *J* = 13.2, 4.0 Hz, 1H), 1.79−1.72 (m, 2H), 1.68−1.62 (m, 1H), 1.59−1.52 (m, 2H), 1.47−1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 153.3, 139.6, 132.9, 132.3, 129.3, 128.9, 128.61, 128.60, 125.7, 120.2, 117.9, 117.6, 116.7, 71.1, 57.7, 33.0, 29.3, 28.4, 23.2, 22.6, 22.5 ppm; IR (KBr) ν_{max} 2923, 2853, 2231, 1685, 1579, 1483, 1216, 1139, 1043, 889, 754, 719, 642 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{20}NO_2^-$ [M − H]$^-$: 354.1500, found: 354.1499; HPLC analysis: 92% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm, t_1 = 15.0 min (minor), t_2 = 19.6 min (major)].

4ca. White solid, 60.3 mg, 34% yield; mp 123−126 °C; $[\alpha]_D^{25}$ 41.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.79 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.18 (td, *J* = 8.2, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.91−6.87 (m, 2H), 5.53 (d, *J* = 5.6 Hz, 1H), 3.85 (d, *J* = 3.2 Hz, 1H), 3.23 (brs, 1H), 2.30−2.20 (m, 3H), 2.13−2.05 (m, 2H), 1.97 (qt, *J* = 12.8, 3.2 Hz, 1H), 1.83−1.78 (m, 2H), 1.70 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.55−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 152.9, 139.9, 135.1, 132.8, 128.7, 128.55, 128.52, 126.8, 121.8, 120.4, 117.9, 117.2, 116.6, 74.0, 49.5, 34.8, 33.7, 31.88, 31.83, 25.7, 21.3 ppm; IR (KBr) ν_{max} 2936, 2227, 1687, 1594, 1486, 1238, 1122, 1090, 965, 770, 750, 648 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{20}NO_2^-$ [M − H]$^-$: 354.1500, found: 354.1500; HPLC analysis: 92% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 87:13, 0.5 mL/min, 254 nm, t_1 = 15.6 min (major), t_2 = 18.7 min (minor)].

3da. White solid, 54.3 mg, 28% yield; mp 154−158 °C; $[\alpha]_D^{25}$ −122.2 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.16 (m, 4H), 7.22−7.14 (m, 2H), 6.92 (dt, *J* = 7.6, 1.6 Hz, 1H), 6.82 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.51 (s, 1H), 4.09 (s, 1H), 3.98 (s, 3H), 3.14 (d, *J* = 1.6 Hz, 1H), 2.40−2.36 (m, 1H), 2.19−2.06 (m, 1H), 2.08 (dt, *J* = 13.2, 2.4 Hz, 1H), 1.87 (dt, *J* = 13.2, 3.6 Hz, 1H), 1.83−1.72 (m, 2H), 1.70−1.63 (m, 1H), 1.60−1.51 (m, 2H), 1.48−1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 166.2, 153.3, 139.9, 134.2, 132.0, 130.3, 129.8, 128.7, 128.5, 128.4, 126.1, 120.2, 117.5, 71.3, 57.8, 52.6, 33.0, 29.2, 28.4, 23.3, 22.68, 22.62 ppm; IR (KBr) ν_{max} 2932, 2860, 1723, 1680, 1608, 1580, 1277, 1216, 1114, 905, 754, 581 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{23}O_4^-$ [M − H]$^-$: 387.1602, found: 387.1605; HPLC analysis: 87% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm, t_1 = 12.5 min (minor), t_2 = 13.9 min (major)].

4da. White solid, 58.2 mg, 30% yield; mp 135−137 °C; $[\alpha]_D^{25}$ 60.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13−8.11 (m, 2H), 8.00−7.98 (m, 2H), 7.17 (td, *J* = 7.2, 2.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.90−6.88 (m, 2H), 5.52 (d, *J* = 5.2 Hz, 1H), 3.95 (s, 3H), 3.89 (d, *J* = 3.2 Hz, 1H), 3.25 (brs, 1H), 2.33−2.28 (m, 1H), 2.22−2.20 (m, 2H), 2.17 (td, *J* = 13.2, 4.0 Hz, 1H), 2.07−2.01 (m, 1H), 1.97 (qt, *J* = 13.2, 3.2 Hz, 1H), 1.85−1.78 (m, 2H), 1.70−1.67 (m, 1H), 1.55−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 166.2, 153.0, 140.2, 135.2, 134.1, 130.1, 128.5, 128.3, 128.2, 127.1, 121.9, 120.3, 117.1, 74.1, 52.6, 49.5, 34.9, 33.6, 31.9, 31.8, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2934, 2862, 1726, 1726, 1684, 1282, 1240, 1225, 1110, 955, 819, 750 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{23}O_4^-$ [M − H]$^-$: 387.1602, found: 387.1605; HPLC analysis: 84% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm, t_1 = 13.4 min (major), t_2 = 17.3 min (minor)].

3ea. White solid, 78.3 mg, 45% yield; mp 162−164 °C; $[\alpha]_D^{25}$ −156.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19−8.15 (m, 2H), 7.26−7.14 (m, 4H), 6.92 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.50 (s, 1H), 4.04 (s, 1H), 3.14 (d, *J* = 1.2 Hz, 1H), 2.36−2.35 (m, 1H), 2.17−2.08 (m, 2H), 1.86 (dt, *J* = 13.2, 3.6 Hz, 1H), 1.81−1.73 (m, 2H), 1.68−1.65 (m, 1H), 1.58−1.54 (m, 2H), 1.45−1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 167.2, 164.7, 153.4, 133.05, 133.02, 131.8, 131.3, 131.2, 130.0, 128.7, 128.4, 126.3, 120.1, 117.5, 116.3, 116.1, 71.4, 57.3, 33.3, 29.2, 28.4, 23.4, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2936, 2902, 2834, 1678, 1595, 1502, 1272, 1219, 1158, 1045, 874, 599 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}FO_2Na^+$ [M + Na]$^+$: 371.1423, found: 371.1421; HPLC analysis: 83% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, t_1 = 9.6 min (minor), t_2 = 11.1 min (major)].

4ea. White solid, 64.3 mg, 37% yield; mp 168−170 °C; $[\alpha]_D^{25}$ 78.3 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.96 (m, 2H), 7.19−7.11 (m, 3H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.89−6.85 (m, 2H), 5.52 (d, *J* = 4.8 Hz, 1H), 3.83 (d, *J* = 2.8 Hz, 1H), 3.25 (brs, 1H), 2.35−2.30 (m, 1H), 2.21−2.19 (m, 2H), 2.12 (qd, *J* = 13.2, 4.0 Hz, 1H), 2.06−2.00 (m, 1H), 1.96 (qt, *J* = 13.2, 3.2 Hz, 1H), 1.83−1.76 (m, 2H), 1.70−1.66 (m, 1H), 1.56−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 167.2, 164.6, 153.0, 135.2, 133.45, 133.42, 131.0, 130.9, 128.5, 128.3, 127.3, 121.9, 120.3, 117.1, 116.1, 115.9, 74.2, 49.0, 35.1, 33.6, 31.9, 31.8, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2923, 2862, 2836, 1679, 1595, 1503, 1227, 1205, 1160, 755, 580, 519 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{22}FO_2^+$ [M + H]$^+$: 349.1604, found: 349.1597; HPLC analysis: 83% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm, t_1 = 9.9 min (major), t_2 = 11.1 min (minor)].

3fa. White solid, 69.3 mg, 34% yield; mp 118−120 °C; $[\alpha]_D^{25}$ −151.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.19−7.14 (m, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.50 (s, 1H), 4.02 (s, 1H), 3.12 (d, *J* = 1.2 Hz, 1H), 2.40−2.35 (m, 1H), 2.16−2.07 (m, 2H), 1.88−1.71 (m, 3H), 1.66−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 153.4, 135.3, 132.4, 131.9, 130.1, 129.9, 128.7, 128.6, 128.4, 126.2, 120.1, 117.6, 71.4, 57.4, 33.2, 29.3, 28.4, 23.3, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2929, 2857, 2831, 1676, 1583, 1275, 1215, 1174, 1157, 905, 748 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}BrO_2Na^+$ [M + Na]$^+$: 431.0623, found: 431.0622; HPLC analysis: 88% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 11.9 min (minor), t_2 = 13.1 min (major)].

4fa. White solid, 61.2 mg, 30% yield; mp 146−148 °C; $[\alpha]_D^{25}$ 114.4 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.60 (dt, *J* = 8.4, 2.4 Hz, 2H), 7.17 (td, *J* = 7.6, 1.6 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.89−6.86 (m, 2H), 5.51 (d, *J* = 5.2 Hz, 1H), 3.81 (d, *J* = 3.2 Hz, 1H), 3.24 (brs, 1H), 2.32−2.28 (m, 1H), 2.21−2.19 (m, 2H), 2.11−1.91 (m, 3H), 1.82−1.76 (m, 2H), 1.70−1.66 (m, 1H), 1.53−1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 153.0, 135.7, 135.2, 132.2, 129.8, 128.6, 128.5, 128.3, 127.2, 121.9, 120.3, 117.1, 74.2, 49.1, 35.0, 33.6, 31.9, 31.8, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2931, 2860, 1678, 1580, 1261, 1242, 1151, 1126, 1096, 1070, 1021, 752 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{22}BrO_2^+$ [M + H]$^+$: 409.0803, found: 409.0794; HPLC analysis: 86% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 11.5 min (major), t_2 = 14.2 min (minor)].

3ga. White solid, 56.7 mg, 33% yield; mp 149−151 °C; $[\alpha]_D^{25}$ −216.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dt, *J* = 6.4, 1.6 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.16 (dt, *J* = 7.4, 2.0 Hz, 1H), 6.91 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.50 (s, 1H), 4.07 (s, 1H), 3.16 (d, *J* = 1.6

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Hz, 1H), 2.46 (s, 3H), 2.39−2.35 (m, 1H), 2.18−2.10 (m, 2H), 1.87−1.70 (m, 3H), 1.67−1.51 (m, 3H), 1.47−1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 153.4, 144.3, 134.1, 131.5, 130.4, 129.7, 128.7, 128.3, 126.5, 120.0, 117.5, 71.5, 57.2, 33.3, 29.2, 28.4, 23.4, 22.7, 22.6, 21.8 ppm; IR (KBr) ν_{max} 2942, 2901, 1672, 1604, 1578, 1220, 1199, 1183, 1113, 1046, 909, 756 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{24}O_2Na^+$ $[M + Na]^+$: 367.1674, found: 367.1675; HPLC analysis: 82% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 10.1 min (major), t_2 = 11.9 min (minor)].

4ga. White solid, 70.5 mg, 41% yield; mp 130−133 °C; $[\alpha]_D^{25}$ 76.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.16 (td, J = 7.6, 1.2 Hz, 1H), 7.03 (dd, J = 7.2, 0.8 Hz, 1H), 6.89−6.84 (m, 2H), 5.51 (d, J = 4.4 Hz, 1H), 3.86 (d, J = 2.8 Hz, 1H), 3.26 (brs, 1H), 2.41 (s, 3H), 2.35−2.31 (m, 1H), 2.21−2.11 (m, 3H), 2.04−1.90 (m, 2H), 1.82−1.75 (m, 2H), 1.69−1.66 (m, 1H), 1.55−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 153.1, 144.2, 135.2, 134.5, 129.6, 128.5, 128.4, 128.2, 127.6, 121.9, 120.2, 117.1, 74.3, 48.9, 35.2, 33.5, 31.96, 31.90, 25.8, 21.7, 21.4 ppm; IR (KBr) νmax 2920, 2887, 2862, 2835, 1681, 1604, 1582, 1240, 1202, 1190, 750, 580 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{25}O_2^+$ $[M + H]^+$: 345.1855, found: 345.1847; HPLC analysis: 82% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 96:4, 0.45 mL/min, 254 nm, t_1 = 13.2 min (major), t_2 = 14.0 min (minor)].

3ha. White solid, 45.0 mg, 25% yield; mp 150−154 °C; $[\alpha]_D^{25}$ −152.2 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dt, J = 9.2, 2.4 Hz, 2H), 7.24 (dd, J = 7.6, 1.6 Hz, 1H), 7.16 (td, J = 7.6, 2.4 Hz, 1H), 7.04 (dt, J = 9.2, 2.4 Hz, 2H), 6.91 (td, J = 7.6, 1.2 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 4.50 (s, 1H), 4.04 (s, 1H), 3.91 (s, 3H), 3.16 (d, J = 1.2 Hz, 1H), 2.39−2.35 (m, 1H), 2.17−2.12 (m, 2H), 1.88−1.70 (m, 3H), 1.68−1.58 (m, 2H), 1.55−1.50 (m, 1H), 1.48−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 163.8, 153.4, 131.5, 130.9, 130.5, 129.6, 128.8, 128.3, 126.7, 120.0, 117.5, 114.2, 71.6, 57.0, 55.7, 33.5, 29.2, 28.4, 23.5, 22.75, 22.71 ppm; IR (KBr) ν_{max} 2931, 2833, 1666, 1595, 1485, 1344, 1215, 1173, 1044, 998, 840, 759, 598 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{24}O_3Na^+$ $[M + Na]^+$: 383.1623, found: 383.1624; HPLC analysis: 78% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 80:20, 0.5 mL/min, 254 nm, t_1 = 10.8 min (major), t_2 = 14.6 min (minor)].

4ha. White solid, 120.6 mg, 67% yield; mp 180−181 °C; $[\alpha]_D^{25}$ 66.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dt, J = 8.8, 2.4 Hz, 2H), 7.17 (td, J = 8.0, 1.2 Hz, 1H), 7.04 (dd, J = 8.0, 1.2 Hz, 1H), 6.93 (dt, J = 9.2, 2.0 Hz, 2H), 6.89−6.85 (m, 2H), 5.52 (d, J = 4.8 Hz, 1H), 3.86 (s, 3H), 3.83 (d, J = 3.2 Hz, 1H), 3.26 (brs, 1H), 2.37−2.33 (m, 1H), 2.21−2.11 (m, 3H), 2.04−1.90 (m, 2H), 1.82−1.75 (m, 2H), 1.69−1.65 (m, 1H), 1.55−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 163.7, 153.1, 135.3, 130.6, 130.1, 128.5, 128.2, 127.7, 122.0, 120.1, 117.1, 114.0, 74.4, 55.6, 48.7, 35.3, 33.6, 31.98, 31.92, 25.8, 21.4 ppm; IR (KBr) ν_{max} 2935, 2836, 1670, 1599, 1482, 1243, 1182, 1018, 954, 867, 753, 619, 583 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{25}O_3^+$ $[M + H]^+$: 361.1804, found: 361.1799; HPLC analysis: 78% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm, t_1 = 11.5 min (major), t_2 = 15.8 min (minor)].

3ia. White solid, 41.4 mg, 23% yield; mp 154−156 °C; $[\alpha]_D^{25}$ −16.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (dt, J = 8.0, 1.6 Hz, 1H), 7.51 (td, J = 8.0, 2.0 Hz, 1H), 7.11 (td, J = 8.0, 1.6 Hz, 1H), 7.08−7.04 (m, 3H), 6.85 (td, J = 7.2, 1.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.46 (s, 1H), 4.18 (s, 1H), 4.01 (s, 3H), 3.14 (d, J = 1.2 Hz, 1H), 2.37−2.32 (m, 1H), 2.16−2.06 (m, 2H), 1.99−1.95 (m, 1H), 1.84 (dt, J = 13.2, 3.6 Hz, 1H), 1.76−1.63 (m, 2H), 1.59−1.53 (m, 2H), 1.47−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1, 157.9, 153.5, 133.5, 131.2, 130.7, 130.4, 129.0, 128.9, 128.0, 126.7, 121.2, 119.8, 117.2, 111.7, 71.7, 61.7, 55.7, 32.7, 29.4, 28.3, 23.7, 22.8, 22.7 ppm; IR (KBr) ν_{max} 2929, 2830, 1678, 1597, 1484, 1344, 1271, 1043, 890, 839, 752, 695, 575 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{24}NaO_3^+$ $[M + Na]^+$: 383.1623, found: 383.1621; HPLC analysis: 15% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 9.1 min (major), t_2 = 12.0 min (minor)].

4ia. White solid, 72.0 mg, 40% yield; mp 162−164 °C; $[\alpha]_D^{25}$ 10.0 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, J = 7.6, 2.0 Hz, 1H), 7.44 (td, J = 8.0, 2.0 Hz, 1H), 7.13 (td, J = 7.6, 1.6 Hz, 1H), 7.03−6.99 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.85−6.82 (m, 2H), 5.52 (d, J = 4.8 Hz, 1H), 3.96 (d, J = 2.8 Hz, 1H), 3.80 (s, 3H), 3.19 (brs, 1H), 2.42−2.37 (m, 1H), 2.24−2.18 (m, 3H), 2.04−1.87 (m, 3H), 1.79−1.57 (m, 2H), 1.54−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 157.7, 153.1, 135.3, 133.1, 129.9, 129.6, 128.5, 128.1, 127.9, 122.2, 120.9, 120.0, 116.9, 111.6, 74.4, 55.7, 53.2, 33.8, 33.5, 32.1, 31.9, 25.8, 21.4 ppm; IR (KBr) ν_{max} 2963, 2859, 1683, 1598, 1481, 1377, 1237, 1080, 965, 860, 782, 765, 681 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{25}O_3^+$ $[M + H^+]$: 361.1804, found: 361.1815; HPLC analysis: 9% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 65:35, 0.5 mL/min, 254 nm, t_1 = 9.1 min (major), t_2 = 11.3 min (minor)].

3ja. White solid, 54.0 mg, 30% yield; mp 92−95 °C; $[\alpha]_D^{25}$ −91.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 2.8, 2.4 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.23 (dd, J = 7.6, 1.6 Hz, 1H), 7.19−7.14 (m, 2H), 6.91 (td, J = 7.6, 0.8 Hz, 1H), 6.82 (dd, J = 8.0, 0.8 Hz, 1H), 4.50 (s, 1H), 4.07 (s, 1H), 3.91 (s, 3H), 3.18 (d, J = 1.6 Hz, 1H), 2.40−2.35 (m, 1H), 2.19−2.09 (m, 2H), 1.88−1.72 (m, 3H), 1.70−1.62 (m, 1H), 1.57−1.49 (m, 2H), 1.48−1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 160.2, 153.4, 138.0, 131.6, 130.2, 130.0, 128.7, 128.3, 126.4, 121.0, 120.1, 119.8, 117.5, 113.1, 71.5, 57.5, 55.6, 33.2, 29.2, 28.4, 23.4, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2930, 2832, 1660, 1595, 1458, 1343, 1244, 1142, 1043, 869, 775, 760, 666 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{24}O_3Na^+$ $[M + Na]^+$: 383.1623, found: 383.1623; HPLC analysis: 58% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm, t_1 = 12.3 min (minor), t_2 = 13.6 min (major)].

4ja. Pale yellow wax, 57.6 mg, 32% yield; $[\alpha]_D^{25}$ 50.5 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.49 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.17 (td, J = 7.8, 2.0 Hz, 1H), 7.12 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 7.03 (dd, J = 8.4, 1.6 Hz, 1H), 6.89−6.85 (m, 2H), 5.52 (d, J = 4.8 Hz, 1H), 3.86 (d, J = 3.2 Hz, 1H), 3.84 (s, 3H), 3.28 (brs, 1H), 2.35−2.30 (m, 1H), 2.22−2.10 (m, 3H), 2.05−1.89 (m, 2H), 1.84−1.77 (m, 2H), 1.71−1.66 (m, 1H), 1.55−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 160.2, 153.0, 138.4, 135.2, 129.9, 128.5, 128.2, 127.4, 121.9, 120.8, 120.2, 119.7, 117.0, 112.6, 74.3, 55.5, 49.2, 35.1, 33.6, 32.0, 31.9, 25.8, 21.4 ppm; IR (KBr) νmax 2963, 2859, 1683, 1598, 1481, 1377, 1237, 1080, 965, 860, 782, 765, 681 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{24}H_{25}O_3^+$ $[M + H]^+$: 361.1804, found: 361.1814; HPLC analysis: 57% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.5 mL/min, 254 nm, t_1 = 11.1 min (major), t_2 = 12.4 min (minor)].

3ka. White solid, 58.5 mg, 30% yield; mp 176−178 °C; $[\alpha]_D^{25}$ −110.0 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 7.6, 1.2 Hz, 1H),7.16 (dt, J = 7.4, 2.0 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.91 (dt, J = 7.2, 0.8 Hz, 1H), 6.83 (dd, J = 8.0, 0.4 Hz, 1H), 4.51 (s, 1H), 4.07 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.18 (brs, 1H), 2.40−2.35 (m, 1H), 2.18−2.14 (m, 2H), 1.86 (dt, J = 13.2, 3.2 Hz, 1H), 1.82−1.72 (m, 2H), 1.69−1.51 (m, 3H), 1.47−1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 153.6, 153.4, 149.4, 131.5, 130.4, 129.7, 128.6, 128.2, 126.6, 123.0, 120.0, 117.5, 110.8, 110.3, 71.5, 56.8, 56.2, 56.1, 33.6, 29.2, 28.4, 23.4, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2937, 2893, 1671, 1580, 1278, 1216, 1173, 1132, 1047, 1021, 852, 756 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{25}H_{26}O_4Na^+$ $[M + Na]^+$: 413.1729, found: 413.1724; HPLC analysis: 65% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm, t_1 = 13.0 min (minor), t_2 = 15.3 min (major)].

4ka. White solid, 103.3 mg, 53% yield; mp 75−77 °C; $[\alpha]_D^{25}$ 41.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.55 (m, 2H), 7.17 (td, J = 7.8, 1.6 Hz, 1H), 7.04 (dd, J = 8.4, 1.6 Hz, 1H), 6.90−6.85 (m, 3H), 5.52 (d, J = 4.8 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.85 (d, J = 2.8 Hz, 1H), 3.28 (brs, 1H), 2.39−2.34 (m, 1H), 2.22−2.09 (m, 3H), 2.06−1.90 (m, 2H), 1.83−1.76 (m, 2H), 1.70−1.66 (m, 1H), 1.59−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 153.5, 153.1, 149.4, 135.3, 130.1, 128.5, 128.2, 127.6, 122.9, 121.9, 120.2, 117.0, 110.3, 110.1, 74.4, 56.2, 56.0, 48.5, 35.5, 33.6, 32.0, 31.9, 25.8, 21.4 ppm; IR (KBr) ν_{max} 2931, 2833, 1678, 1581, 1454, 1413, 1324, 1240, 1127, 1003, 900, 812, 753 cm^{-1}; HRMS (ESI, m/z) calcd for

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$C_{25}H_{27}O_4^+$ [M + H]$^+$: 391.1909, found: 391.1905; HPLC analysis: 65% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm, t_1 = 12.2 min (major), t_2 = 17.7 min (minor)].

3la. White solid, 60.9 mg, 29% yield; mp 197−199 °C; $[\alpha]_D^{25}$ −25.5 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (s, 2H), 7.21 (td, *J* = 6.4, 2.8 Hz, 1H), 7.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.90 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.4, 0.8 Hz, 1H), 4.51 (s, 1H), 4.05 (s, 1H), 4.00 (s, 6H), 3.96 (s, 3H), 3.20 (d, *J* = 1.6 Hz, 1H), 2.40−2.36 (m, 1H), 2.19−2.10 (m, 2H), 1.87 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.83−1.73 (m, 2H), 1.70−1.67 (m, 1H), 1.63−1.49 (m, 2H), 1.48−1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 153.42, 153.40, 142.9, 131.6, 130.2, 128.3, 126.4, 120.0, 117.6, 106.1, 71.4, 61.1, 57.1, 56.4, 33.4, 29.2, 28.4, 23.3, 22.7, 22.6 ppm; IR (KBr) ν_{max} 2924, 2859, 2834, 1664, 1584, 1503, 1128, 1005, 979, 772, 704, 617 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{28}O_5Na^+$ [M + Na]$^+$: 443.1834, found: 443.1830; HPLC analysis: 17% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 75:25, 0.5 mL/min, 254 nm, t_1 = 10.5 min (minor), t_2 = 14.1 min (major)].

4la. White solid, 88.2 mg, 42% yield; mp 65−67 °C; $[\alpha]_D^{25}$ 13.8 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2H), 7.17 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.90−6.87 (m, 2H), 5.52 (d, *J* = 4.8 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 6H), 3.82 (d, *J* = 3.2 Hz, 1H), 3.30 (brs, 1H), 2.38−2.33 (m, 1H), 2.22−2.20 (m, 2H), 2.13 (td, *J* = 13.2, 4.4 Hz, 1H), 2.06−1.91 (m, 2H), 1.85−1.77 (m, 2H), 1.71−1.67 (m, 1H), 1.56−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 153.3, 153.1, 142.9, 135.2, 132.3, 128.5, 128.2, 127.5, 121.9, 120.3, 117.0, 105.8, 74.4, 61.0, 56.5, 48.7, 35.2, 33.6, 32.1, 31.9, 25.8, 21.4 ppm; IR (KBr) ν_{max} 2929, 2860, 2833, 1676, 1595, 1513, 1417, 1262, 1241, 1163, 1022, 955, 813, 755 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{29}O_5^+$ [M + H]$^+$: 421.2015, found: 421.2009; HPLC analysis: 20% ee [Daicel CHIRALPAK AS-H column, hexane/*i*-PrOH = 85:15, 0.65 mL/min, 254 nm, t_1 = 7.4 min (minor), t_2 = 10.1 min (major)].

3ma. White solid, 43.7 mg, 27% yield; mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.10 (m, 2H), 6.87 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.78 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.43 (s, 1H), 3.14 (s, 1H), 3.08 (d, *J* = 1.6 Hz, 1H), 2.75−2.67 (m, 1H), 2.60−2.52 (m, 1H), 2.34−2.30 (m, 1H), 2.12−2.01 (m, 2H), 1.89 (dt, *J* = 13.2, 3.6 Hz, 1H), 1.78−1.47 (m, 7H), 1.45−1.28 (m, 5H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.7, 153.3, 131.2, 130.0, 128.9, 128.2, 126.3, 120.0, 117.3, 71.4, 62.8, 42.9, 32.7, 31.6, 29.2, 28.3, 28.8, 23.7, 22.66, 22.64, 22.60, 14.0 ppm; IR (KBr) ν_{max} 2941, 2866, 2831, 1700, 1605, 1579, 1215, 1127, 1002, 891, 766, 591 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{27}O_2^-$ [M − H]$^-$: 323.2017, found: 323.2015; HPLC analysis: 0% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 98:2, 0.45 mL/min, 254 nm, t_1 = 10.2 min, t_2 = 11.0 min].

4ma. White solid, 59.9 mg, 37% yield; mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (td, *J* = 8.4, 1.6 Hz, 1H), 7.07 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.87 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.46 (d, *J* = 4.4 Hz, 1H), 3.24 (brs, 1H), 3.03 (d, *J* = 3.2 Hz, 1H), 2.58 (dt, *J* = 16.8, 7.6 Hz, 1H), 2.42 (dt, *J* = 16.8, 7.2 Hz, 1H), 2.36−2.30 (m, 1H), 2.15−2.13 (m, 2H), 2.07−2.01 (m, 1H), 1.98−1.85 (m, 2H), 1.77−1.72 (m, 2H), 1.66−1.56 (m, 3H), 1.49−1.41 (m, 1H), 1.35−1.24 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.9, 152.9, 134.9, 128.5, 128.1, 127.5, 122.0, 120.2, 117.0, 73.6, 53.7, 43.5, 34.1, 33.6, 32.1, 31.8, 31.5, 25.7, 23.5, 22.6, 21.3, 14.0 ppm; IR (KBr) ν_{max} 2927, 2852, 2359, 1704, 1581, 1484, 1431, 1240, 1131, 899, 772, 749 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{28}O_2Na^+$ [M + Na]$^+$: 347.1987, found: 347.1983; HPLC analysis: 0% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 98:2, 0.45 mL/min, 254 nm, t_1 = 12.6 min, t_2 = 13.5 min].

3ab. White solid, 17.2 mg, 9.6% yield; mp 145−147 °C; $[\alpha]_D^{25}$ −136.6 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13−8.11 (m, 2H), 7.63 (tt, *J* = 7.6, 1.6 Hz, 1H), 7.57−7.53 (m, 2H), 6.79 (t, *J* = 1.6 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 2H), 4.46 (s, 1H), 4.09 (s, 1H), 3.80 (s, 3H), 3.12 (d, *J* = 1.6 Hz, 1H), 2.37−2.34 (m, 1H), 2.17−2.07 (m, 2H), 1.87−1.69 (m, 3H), 1.66−1.52 (m, 3H), 1.62−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 153.1, 147.3, 136.6, 133.4, 131.6, 130.1, 129.1, 128.6, 127.0, 117.7, 114.5, 113.2, 71.3, 57.3, 55.9, 33.5, 29.3, 28.4, 23.3, 22.75, 22.70 ppm; IR (KBr) ν_{max} 2923, 2858, 2845, 1674, 1596, 1580, 1261, 1219, 1002, 906, 739, 690 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}O_3Na^+$ [M + Na]$^+$: 383.1623, found: 383.1620; HPLC analysis: 80% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 65:35, 0.5 mL/min, 254 nm, t_1 = 8.8 min (major), t_2 = 17.5 min (minor)].

4ab. White solid, 27.0 mg, 15% yield; mp 152−154 °C; $[\alpha]_D^{25}$ 45.5 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96−7.94 (m, 2H), 7.58 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.49−7.45 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.59 (d, *J* = 3.2 Hz, 1H), 5.53 (d, *J* = 4.4 Hz, 1H), 3.88 (d, *J* = 2.8 Hz, 1H), 3.74 (s, 3H), 3.23 (brs, 1H), 2.35−2.31 (m, 1H), 2.21−2.10 (m, 3H), 2.06−1.89 (m, 2H), 1.89−1.76 (m, 2H), 1.69−1.65 (m, 1H), 1.57−1.45 (m, 1H.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 153.2, 147.0, 137.0, 135.2, 133.3, 128.9, 128.3, 127.9, 121.7, 117.5, 114.1, 113.2, 74.1, 55.8, 49.0, 35.3, 33.5, 31.88, 31.87, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2926, 2866, 2833, 1680, 1593, 1233, 1219, 1144, 1036, 865, 693 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{25}O_3$ [M + H]$^+$: 361.1804, found: 361.1814; HPLC analysis: 76% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 50:50, 0.5 mL/min, 254 nm, t_1 = 8.5 min (major), t_2 = 10.0 min (minor)].

3ac. White solid, 41.2 mg, 24% yield; mp 156−159 °C; $[\alpha]_D^{25}$ −108.3 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15−8.13 (m, 2H), 7.65 (tt, *J* = 7.6, 1.6 Hz, 1H), 7.60−7.56 (m, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.47 (s, 1H), 4.09 (s, 1H), 3.12 (d, *J* = 1.6 Hz, 1H), 2.39−2.33 (m, 4H), 2.16−2.08 (m, 2H), 1.86−1.63 (m, 4H), 1.56−1.50 (m, 2H), 1.48−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 151.1, 136.7, 133.4, 131.6, 130.1, 129.19, 129.11, 129.0, 128.6, 126.0, 117.2, 71.3, 57.3, 33.2, 29.2, 28.4, 23.5, 22.7, 22.6, 20.8 ppm; IR (KBr) ν_{max} 2930, 2857, 1676, 1593, 1495, 1342, 1239, 1154, 1025, 908, 810, 726, 691 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}O_2Na^+$ [M + Na]$^+$: 367.1674, found: 367.1673; HPLC analysis: 72% ee [Daicel CHIRALPAK AS-H column, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, t_1 = 9.5 min (major), t_2 = 11.9 min (minor)].

4ac. White solid, 68.8 mg, 40% yield; mp 137−140 °C; $[\alpha]_D^{25}$ 80.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96−7.94 (m, 2H), 7.59−7.55 (m, 1H), 7.48−7.44 (m, 2H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.53 (d, *J* = 4.4 Hz, 1H), 3.87 (d, *J* = 3.2 Hz, 1H), 3.22 (brs, 1H), 2.34−2.30 (m, 1H), 2.26 (s, 3H), 2.21−2.18 (m, 2H), 2.13 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.04−1.90 (m, 2H), 1.82−1.76 (m, 2H), 1.70−1.57 (m, 1H), 1.55−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 150.8, 137.0, 135.2, 133.3, 129.4, 129.0, 128.95, 128.92, 128.3, 127.1, 121.9, 116.8, 74.2, 49.2, 35.0, 33.6, 31.9, 25.8, 21.3, 20.8 ppm; IR (KBr) ν_{max} 2925, 2853, 1686, 1595, 1494, 1362, 1262, 1198, 1143, 1093, 958, 860, 777 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}O_2Na^+$ [M + Na]$^+$: 367.1674, found: 367.1671; HPLC analysis: 66% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 8.7 min (major), t_2 = 9.9 min (minor)].

3ad. White solid, 89.7 mg, 44% yield; mp 185−187 °C; $[\alpha]_D^{25}$ −183.3 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (m, 2H), 7.65 (tt, *J* = 7.2, 2.2 Hz, 1H), 7.60−7.56 (m, 2H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 4.49 (s, 1H), 4.06 (s, 1H), 3.12 (d, *J* = 1.2 Hz, 1H), 2.36−2.32 (m, 1H), 2.15−2.10 (m, 2H), 1.83−1.68 (m, 4H), 1.60−1.53 (m, 2H), 1.44−1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 152.6, 136.5, 133.6, 131.4, 131.27, 131.21, 130.4, 129.2, 128.58, 128.50, 119.4, 111.8, 71.6, 57.1, 33.1, 29.3, 28.4, 23.1, 22.68, 22.64 ppm; IR (KBr) ν_{max} 2928, 2880, 1681, 1593, 1475, 1341, 1216, 1117, 1000, 908, 817, 770, 691 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{23}H_{21}BrO_2Na^+$ [M + Na]$^+$: 431.0623, found: 431.0618; HPLC analysis: 83% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.65 mL/min, 254 nm, t_1 = 7.4 min (minor), t_2 = 8.3 min (major)].

4ad. White solid, 77.5 mg, 38% yield; mp 158−160 °C; $[\alpha]_D^{25}$ 91.1 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.58 (dt, *J* = 7.0, 1.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.53 (d, *J* = 5.6 Hz, 1H), 3.84 (d, *J* = 3.2 Hz, 1H), 3.24 (brs, 1H), 2.35−2.30 (m, 1H), 2.20−2.10 (m, 3H), 2.03−1.90 (m, 2H), 1.82−1.76 (m, 2H), 1.70−1.66 (m, 1H), 1.54−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 152.3, 136.8, 135.1, 133.5, 131.13,

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131.11, 129.6, 129.0, 128.3, 121.9, 118.9, 112.1, 74.7, 48.6, 34.9, 33.4, 31.8, 25.7, 21.3 ppm; IR (KBr) ν_{max} 2928, 2859, 1684, 1595, 1485, 1350, 1288, 1149, 1034, 991, 812, 786, 691 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{23}H_{21}BrO_2Na^+$ $[M + Na]^+$: 431.0623, found: 431.0615; HPLC analysis: 63% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 96:4, 0.65 mL/min, 254 nm, t_1 = 7.5 min (major), t_2 = 8.6 min (minor)].

3ae. White solid, 69.8 mg, 36% yield; mp 106−108 °C; $[\alpha]_D^{25}$ −96.1 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.15−8.13 (m, 2H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.68−7.64 (m, 1H), 7.61−7.57 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.57 (s, 1H), 4.10 (s, 1H), 3.91 (s, 3H), 3.23 (d, *J* = 1.6 Hz, 1H), 2.37−2.33 (m, 1H), 2.20−2.13 (m, 2H), 1.87−1.72 (m, 3H), 1.68−1.62 (m, 1H), 1.58−1.50 (m, 2H), 1.47−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 167.2, 157.8, 136.5, 133.6, 131.5, 131.0, 130.7, 130.1, 129.2, 128.6, 126.3, 122.0, 117.5, 72.2, 57.1, 52.0, 33.1, 29.3, 28.4, 23.2, 22.65, 22.64 ppm; IR (KBr) ν_{max} 2926, 2857, 1680, 1604, 1475, 1261, 1223, 1117, 1004, 907, 818, 793, 593 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{25}H_{24}O_4Na^+$ $[M + Na]^+$: 411.1572, found: 411.1570; HPLC analysis: 80% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 80:20, 0.65 mL/min, 254 nm, t_1 = 7.3 min (major), t_2 = 12.5 min (minor)].

4ae. White solid, 75.9 mg, 39% yield; mp 173−177 °C; $[\alpha]_D^{25}$ 75.5 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.95−7.93 (m, 2H), 7.86 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.59 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.54 (d, *J* = 5.6 Hz, 1H), 3.87−3.86 (m, 4H), 3.34 (brs, 1H), 2.37−2.32 (m, 1H), 2.22−2.14 (m, 3H), 2.08−1.89 (m, 2H), 1.85−1.77 (m, 2H), 1.72−1.69 (m, 1H), 1.58−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 167.0, 157.3, 136.7, 135.2, 133.5, 130.8, 130.0, 129.0, 128.3, 127.4, 122.1, 117.1, 75.4, 51.9, 48.8, 35.0, 33.4, 31.8, 31.7, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2930, 2825, 1709, 1681, 1609, 1437, 1288, 1264, 11130, 954, 772, 688, 532 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{25}H_{24}O_4Na^+$ $[M + Na]^+$: 411.1572, found: 411.1567; HPLC analysis: 60% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 80:20, 0.65 mL/min, 254 nm, t_1 = 9.4 min (minor), t_2 = 11.3 min (major)].

3af. White solid, 20.6 mg, 12% yield; mp 158−159 °C; $[\alpha]_D^{25}$ −213.3 (*c* 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.04−8.02 (m, 2H), 7.65−7.55 (m, 3H), 7.24 (td, *J* = 7.6, 2.0 Hz, 1H), 7.15 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.91 (td, *J* = 7.2, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.17 (s, 1H), 3.85 (s, 1H), 3.25 (t, *J* = 1.6 Hz, 1H), 2.43−2.39 (m, 1H), 2.25−2.08 (m, 3H), 1.83−1.75 (m, 1H), 1.73−1.49 (m, 4H), 0.97 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 152.8, 137.7, 132.9, 129.5, 129.0, 128.8, 128.4, 128.3, 128.0, 120.0, 117.5, 76.6, 57.3, 38.9, 31.5, 29.3, 29.1, 22.9, 22.8, 15.0 ppm; IR (KBr) ν_{max} 2937, 2857, 1678, 1593, 1496, 1326, 1219, 1180, 991, 751, 690, 566 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{24}O_2Na^+$ $[M + Na]^+$: 367.1674, found: 367.1670; HPLC analysis: 63% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 8.6 min (minor), t_2 = 10.9 min (major)].

4af. White solid, 122.1 mg, 71% yield; mp 94−96 °C; $[\alpha]_D^{25}$ 107.2 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.92 (m, 2H), 7.55 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.48−7.45 (m, 2H), 7.15 (td, *J* = 7.6, 1.6 Hz, 1H), 7.02 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.87−6.83 (m, 2H), 5.47 (d, *J* = 4.4 Hz, 1H), 3.81 (d, *J* = 2.8 Hz, 1H), 3.26 (d, *J* = 2.8 Hz, 1H), 2.41−2.26 (m, 4H), 1.98 (qt, *J* = 12.8, 3.6 Hz, 1H), 1.81−1.58 (m, 4H), 0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 152.5, 137.1, 134.5, 133.2, 129.2, 128.9, 128.4, 128.1, 126.8, 120.0, 117.2, 73.9, 48.0, 42.3, 40.8, 33.8, 32.0, 25.6, 21.5, 18.9 ppm; IR (KBr) ν_{max} 2931, 2866, 1683, 1582, 1240, 1216, 1092, 1016, 963, 859, 753, 693 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{24}O_2Na^+$ $[M + Na]^+$: 367.1674, found: 367.1679; HPLC analysis: 60% ee [Daicel CHIRALPAK AS-H column, hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, t_1 = 8.1 min (minor), t_2 = 8.9 min (major)].

3ag. White solid, 19.8 mg, 9.4% yield; mp 61−65 °C; $[\alpha]_D^{25}$ −138.3 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.8 Hz, 2H), 7.66−7.57 (m, 3H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 4.16 (s, 1H), 3.80 (s, 1H), 3.21 (s, 1H), 2.39−2.35 (m, 1H), 2.25−2.07 (m, 3H), 1.81−1.77 (m, 1H), 1.71−1.52 (m, 4H), 0.95 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 152.0, 137.6, 133.0, 131.2, 130.8, 130.5, 129.7, 129.1, 128.9, 128.3, 119.4, 111.8, 76.7, 57.2, 38.8, 31.3, 29.27, 29.24, 22.9, 22.7, 14.8 ppm; IR (KBr) ν_{max} 2929, 2882, 1685, 1596, 1474, 1321, 1218, 1178, 1092, 987, 814, 750, 692 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{23}BrO_2Na^+$ $[M + Na]^+$: 445.0779, found: 445.0767; HPLC analysis: 75% ee [Daicel CHIRALPAK AS-H column, hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, t_1 = 8.5 min (major), t_2 = 9.6 min (minor)].

4ag. White solid, 133.2 mg, 63% yield; mp 192−194 °C; $[\alpha]_D^{25}$ 98.8 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.92−7.90 (m, 2H), 7.58 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.48 (d, *J* = 4.0 Hz, 1H), 3.75 (d, *J* = 3.2 Hz, 1H), 3.23 (d, *J* = 2.4 Hz, 1H), 2.40−2.20 (m, 4H), 1.95 (qt, *J* = 13.2, 3.2 Hz, 1H), 1.80−1.56 (m, 4H), 0.91(d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 151.7, 137.0, 134.4, 133.4, 131.3, 131.0, 130.9, 129.0, 128.4, 126.7, 119.1, 111.9, 74.4, 47.7, 42.2, 40.7, 33.7, 31.9, 25.5, 21.4, 18.9 ppm; IR (KBr) ν_{max} 2926, 2867, 2830, 1684, 1594, 1572, 1258, 1243, 1210, 657, 618, 528 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{24}BrO_2^+$ $[M + H]^+$: 423.0960, found: 423.0951; HPLC analysis: 53% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 9.3 min (major), t_2 = 10.1 min (minor)].

3cd. White solid, 78.1 mg, 36% yield; mp 221−224 °C; $[\alpha]_D^{25}$ −210.5 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.90 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.27−7.24 (m, 2H), 6.72−6.70 (m, 1H), 4.50 (s, 1H), 4.01 (s, 1H), 3.06 (d, *J* = 2.0 Hz, 1H), 2.37−2.33 (m, 1H), 2.17−2.05 (m, 2H), 1.86−1.69 (m, 4H), 1.64−1.47 (m, 2H), 1.45−1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 152.5, 139.6, 133.1, 132.1, 131.5, 131.0, 129.6, 128.9, 127.7, 119.5, 117.8, 116.9, 112.0, 71.3, 57.4, 32.9, 29.3, 28.2, 23.0, 22.6, 22.5 ppm; IR (KBr) ν_{max} 2943, 2859, 2228, 1679, 1447, 1284, 1216, 1126, 1018, 905, 849, 774, 584 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{20}BrNO_2^-$ $[M - H]^-$: 432.0605, found: 432.0601; HPLC analysis: 95% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm, t_1 = 14.2 min (minor), t_2 = 19.2 min (major)].

4cd. White solid, 71.6 mg, 33% yield; mp 216−219 °C; $[\alpha]_D^{25}$ 116.6 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.79 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.26 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 6.4 Hz, 1H), 5.53 (d, *J* = 6.4 Hz, 1H), 3.80 (d, *J* = 3.6 Hz, 1H), 3.20 (brs, 1H), 2.30−2.20 (m, 3H), 2.10−2.03 (m, 2H), 1.93 (qt, *J* = 13.2, 3.2 Hz, 1H), 1.82−1.77 (m, 2H), 1.70−1.68 (m, 1H), 1.54−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 152.1, 139.7, 135.0, 132.9, 131.3, 131.0, 128.9, 128.7, 121.8, 119.0, 117.6, 116.8, 112.3, 74.4, 49.1, 34.6, 33.5, 31.7, 25.6, 21.2 ppm; IR (KBr) ν_{max} 2929, 2860, 2231, 1689, 1474, 1243, 1209, 1172, 1093, 959, 805, 777, 538 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{24}H_{19}BrNO_2^-$ $[M - H]^-$: 432.0605, found: 432.0609; HPLC analysis: 86% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 80:20, 0.65 mL/min, 254 nm, t_1 = 9.6 min (major), t_2 = 11.4 min (minor)].

3ce. White solid, 103.2 mg, 50% yield; mp 195−197 °C; $[\alpha]_D^{25}$ −135.7 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.91−7.88 (m, 3H), 7.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.57 (brs, 1H), 4.05 (brs, 1H), 3.91 (s, 3H), 3.17 (d, *J* = 2.0 Hz, 1H), 2.39- 2.34 (m, 1H), 2.20−2.11 (m, 2H), 1.87 (dt, *J* = 13.6, 3.6 Hz, 1H), 1.79−1.71 (m, 2H), 1.68−1.66 (m, 1H), 1.62−1.53 (m, 2H), 1.47−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 167.0, 157.7, 139.5, 133.1, 132.1, 130.8, 130.3, 129.9, 129.0, 125.7, 122.2, 117.9, 117.6, 116.9, 71.9, 57.4, 52.1, 32.9, 29.4, 28.4, 23.1, 22.59, 22.53 ppm; IR (KBr) ν_{max} 2938, 2856, 2234, 1708, 1683, 1578, 1493, 1283, 1220, 1116, 844, 767, 543 cm^{-1}; HRMS (ESI, *m/z*) calcd for $C_{26}H_{22}NO_4^-$ $[M - H]^-$: 412.1554, found: 412.1557; HPLC analysis: 94% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 65:35, 0.5 mL/min, 254 nm, t_1 = 9.5 min (minor), t_2 = 11.4 min (major)].

4ce. White solid, 24.7 mg, 12% yield; mp 235−237 °C; $[\alpha]_D^{25}$ 97.8 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.80−7.78 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.54 (d, *J* = 4.8 Hz, 1H), 3.86 (s, 3H), 3.83 (d, *J* = 2.8 Hz,

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1H), 3.30 (brs, 1H), 2.31−2.19 (m, 3H), 2.13−1.91 (m, 3H), 1.85−1.69 (m, 3H), 1.56−1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 166.9, 157.1, 139.6, 135.1, 132.9, 130.7, 130.2, 128.7, 126.8, 122.4, 122.0, 117.8, 117.2, 116.8, 75.1, 52.0, 49.3, 34.7, 33.5, 31.74, 31.72, 25.6, 21.2 ppm; IR (KBr) ν_{max} 2930, 2860, 2231, 1716, 1691, 1581, 1435, 1262, 1226, 1150, 981, 804, 567 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{22}NO_4^-$ [M − H]$^-$: 412.1554, found: 412.1559; HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 15.1 min (major), t_2 = 18.4 min (minor)].

3gd. White solid, 71.9 mg, 34% yield; mp 211−215 °C; $[\alpha]_D^{25}$ −160.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.49 (s, 1H), 4.04 (s, 1H), 3.11 (d, *J* = 1.6 Hz, 1H), 2.47 (s, 3H), 2.35−2.31 (m, 1H), 2.14−2.11 (m, 2H), 1.82−1.63 (m, 4H), 1.58−1.50 (m, 2H), 1.49−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 152.6, 144.5, 134.0, 131.3, 131.23, 131.21, 130.6, 129.8, 128.7, 128.6, 119.4, 111.8, 71.6, 56.9, 33.3, 29.2, 28.3, 23.1, 22.68, 22.66, 21.8 ppm; IR (KBr) ν_{max} 2939, 2857, 1701, 1674, 1576, 1490, 1263, 1115, 1039, 999, 769, 688 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{23}BrO_2Na^+$ [M + Na]$^+$: 445.0779, found: 445.0771; HPLC analysis: 91% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 10.3 min (minor), t_2 = 11.8 min (major)].

4gd. White solid, 109.9 mg, 52% yield; mp 141−144 °C; $[\alpha]_D^{25}$ 77.7 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dt, *J* = 8.0, 1.8 Hz, 2H), 7.28−7.23 (m, 3H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 5.6 Hz, 1H), 3.81 (d, *J* = 3.2 Hz, 1H), 3.23 (brs, 1H), 2.42 (s, 3H), 2.35−2.30 (m, 1H), 2.20−2.09 (m, 3H), 2.02−1.86 (m, 2H), 1.80−1.75 (m, 2H), 1.69−1.66 (m, 1H), 1.56−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 152.3, 144.4, 135.1, 134.3, 131.1, 129.74, 129.71, 128.4, 121.9, 118.9, 112.1, 74.8, 48.4, 35.1, 33.4, 31.8, 25.7, 21.7, 21.3 ppm; IR (KBr) ν_{max} 2931, 2861, 1678, 1605, 1570, 1475, 1245, 1183, 1091, 951, 774, 656 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{23}BrO_2Na^+$ [M + Na]$^+$: 445.0779, found: 445.0777; HPLC analysis: 82% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 8.8 min (major), t_2 = 10.5 min (minor)].

3hb. White solid, 56.5 mg, 29% yield; mp 174−175 °C; $[\alpha]_D^{25}$ −165.5 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.03 (dt, *J* = 9.2, 2.0 Hz, 2H), 6.80 (t, *J* = 1.6 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 2H), 4.46 (s, 1H), 4.04 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.11 (d, *J* = 2.0 Hz, 1H), 2.37−2.33 (m, 1H), 2.16−2.10 (m, 2H), 1.86−1.65 (m, 4H), 1.59−1.47 (m, 2H), 1.45−1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 163.8, 153.0, 147.3, 131.4, 130.9, 130.3, 129.5, 127.3, 117.7, 114.5, 114.2, 113.1, 71.4, 56.9, 55.9, 55.7, 33.8, 29.2, 28.3, 23.5, 22.75, 22.71 ppm; IR (KBr) ν_{max} 2921, 2838, 1667, 1597, 1517, 1495, 1225, 1171, 1044, 838, 816, 595 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}O_4Na^+$ [M + Na]$^+$: 413.1729, found: 413.1723; HPLC analysis: 85% ee [Daicel CHIRALPAK OD-H column, hexane/*i*-PrOH = 75:25, 0.5 mL/min, 254 nm, t_1 = 11.0 min (minor), t_2 = 19.6 min (major)].

4hb. White solid, 74.1 mg, 38% yield; mp 135−137 °C; $[\alpha]_D^{25}$ 67.7 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dt, *J* = 8.8, 2.0 Hz, 2H), 6.93 (dt, *J* = 9.2, 2.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 5.52 (d, *J* = 4.4 Hz, 1H), 3.87 (s, 3H), 3.83 (d, *J* = 3.6 Hz, 1H), 3.73 (s, 3H), 3.21 (brs, 1H), 2.37−2.33 (m, 1H), 2.20−2.09 (m, 3H), 2.05−1.91 (m, 2H), 1.80−1.74 (m, 2H), 1.68−1.64 (m,1H), 1.56−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.7, 153.2, 147.0, 135.2, 130.6, 130.0, 128.1, 121.8, 117.5, 114.08, 114.06, 113.3, 74.2, 55.8, 55.6, 48.7, 35.6, 33.5, 31.9, 25.8, 21.3 ppm; IR (KBr) ν_{max} 2923, 2833, 1673, 1601, 1570, 1495, 1236, 1171, 1036, 954, 806, 582 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}O_4Na^+$ [M + Na]$^+$: 413.1729, found: 413.1727; HPLC analysis: 85% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 10.8 min (major), t_2 = 16.0 min (minor)].

3hc. White solid, 44.8 mg, 24% yield; mp 172−175 °C; $[\alpha]_D^{25}$ −163.3 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dt, *J* = 9.2, 2.0 Hz, 2H), 7.05 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.00 (d, *J* = 1.6 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.74 (s, 1H), 4.03 (s, 1H), 3.92 (s, 3H), 3.10 (d, *J* = 1.2 Hz, 1H), 2.38−2.33 (m, 4H), 2.17−2.10 (m, 2H), 1.86−1.61 (m, 4H), 1.58−1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 163.8, 151.1, 131.4, 130.9, 130.4, 129.6, 129.1, 129.09, 129.03, 126.2, 117.2, 114.2, 71.4, 57.0, 55.7, 33.5, 29.2, 28.4, 23.6, 22.75, 22.70, 20.8 ppm; IR (KBr) ν_{max} 2912, 2850, 1669, 1601, 1572, 1493, 1256, 1172, 1029, 818, 680, 609 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}O_3Na^+$ [M + Na]$^+$: 397.1780, found: 397.1771; HPLC analysis: 77% ee [Daicel CHIRALPAK AS-H column, hexane/*i*-PrOH = 85:15, 0.5 mL/min, 254 nm, t_1 = 9.3 min (major), t_2 = 11.1 min (minor)].

4hc. White solid, 108.4 mg, 58% yield; mp 164−165 °C; $[\alpha]_D^{25}$ 80.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dt, *J* = 9.2, 2.0 Hz, 2H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.93 (dt, *J* = 8.8, 2.0 Hz, 2H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 4.8 Hz, 1H), 3.86 (s, 3H), 3.82 (d, *J* = 3.2 Hz, 1H), 3.21 (brs, 1H), 2.36−2.31 (m, 1H), 2.26 (s, 3H), 2.20−2.18 (m, 2H), 2.12 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.04−1.88 (m, 2H), 1.80−1.75 (m, 2H), 1.69−1.64 (m,1H), 1.56−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.7, 150.8, 135.3, 130.6, 130.0, 129.3, 128.95, 128.92, 127.3, 121.9, 116.8, 114.0, 74.3, 55.6, 48.8, 35.3, 33.5, 31.9, 25.8, 21.4, 20.6 ppm; IR (KBr) ν_{max} 2933, 2837, 1668, 1599, 1574, 1494, 1243, 1177, 1018, 959, 804, 595 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{25}H_{26}O_3Na^+$ [M + Na]$^+$: 397.1780, found: 397.1775; HPLC analysis: 70% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 60:40, 0.5 mL/min, 254 nm, t_1 = 8.7 min (major), t_2 = 10.7 min (minor)].

3hd. White solid, 87.8 mg, 40% yield; mp 153−156 °C; $[\alpha]_D^{25}$ −199.4 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (dt, *J* = 8.8, 2.4 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 1H), 4.01 (s, 1H), 3.92 (s, 3H), 3.11 (d, *J* = 1.6 Hz, 1H), 2.35−2.31 (m, 1H), 2.17−2.10 (m, 2H), 1.82−1.62 (m, 4H), 1.59−1.49 (m, 2H), 1.46−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 163.9, 152.6, 131.28, 131.21, 131.1, 130.9, 130.7, 129.4, 128.7, 119.4, 114.3, 111.8, 71.7, 56.73, 55.74, 33.4, 29.2, 28.3, 23.1, 22.69, 22.66 ppm; IR (KBr) ν_{max} 2916, 2838, 1667, 1600, 1572, 1472, 1279, 1177, 1030, 998, 865, 578 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{23}BrO_3Na^+$ [M + Na]$^+$: 461.0728, found: 461.0725; HPLC analysis: 88% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 9.2 min (minor), t_2 = 10.0 min (major)].

4hd. White solid, 98.8 mg, 45% yield; mp 90−93 °C; $[\alpha]_D^{25}$ 78.8 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dt, *J* = 9.2, 2.0 Hz, 2H), 7.24 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.94 (dt, *J* = 9.2, 2.0 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.53 (d, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 3.78 (d, *J* = 3.2 Hz, 1H), 3.22 (brs, 1H), 2.36−2.32 (m, 1H), 2.19−2.11 (m, 3H), 2.03−1.86 (m, 2H), 1.80−1.76 (m, 2H), 1.69−1.65 (m,1H), 1.55−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 163.8, 152.3, 135.2, 131.1, 131.0, 130.6, 129.84, 129.82, 122.0, 118.9, 114.1, 112.1, 74.9, 55.6, 48.2, 35.2, 33.4, 31.8, 25.7, 21.3 ppm; IR (KBr) ν_{max} 2937, 2861, 1667, 1599, 1574, 1474, 1245, 1180, 1019, 954, 817, 590 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{24}BrO_3^+$ [M + H]$^+$: 439.0909, found: 439.0901; HPLC analysis: 81% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 75:25, 0.5 mL/min, 254 nm, t_1 = 9.5 min (major), t_2 = 11.6 min (minor)].

3he. White solid, 60.6 mg, 29% yield; mp 175−178 °C; $[\alpha]_D^{25}$ −220.5 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.06 (dt, *J* = 8.8, 2.0 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 4.56 (s, 1H), 4.05 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.22 (d, *J* = 1.2 Hz, 1H), 2.38−2.32 (m, 1H), 2.23−2.11 (m, 2H), 1.87−1.72 (m, 3H), 1.66−1.50 (m, 3H), 1.46−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 167.2, 163.9, 157.8, 131.3, 131.04, 131.01, 130.0, 129.4, 126.5, 121.9, 117.5, 114.3, 72.3, 56.7, 55.7, 52.0, 33.4, 29.3, 28.4, 23.3, 22.6 ppm; IR (KBr) ν_{max} 2940, 2836, 1717, 1664, 1603, 1573, 1421, 1262, 1177, 1039, 837, 604 cm^{-1}; HRMS (ESI, *m*/*z*) calcd for $C_{26}H_{26}O_5Na^+$ [M + Na]$^+$: 441.1678, found: 441.1677; HPLC analysis: 88% ee [Daicel CHIRALPAK AD-H column, hexane/*i*-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 9.5 min (minor), t_2 = 11.1 min (major)].

4he. White solid, 62.7 mg, 30% yield; mp 214−216 °C; $[\alpha]_D^{25}$ 158.3 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dt, *J* =

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8.8, 2.0 Hz, 2H), 7.85 (dd, J = 8.8, 2.4 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 6.94 (dt, J = 8.8, 2.0 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 5.53 (d, J = 5.6 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (d, J = 3.2 Hz, 1H), 3.33 (brs, 1H), 2.38−2.34 (m, 1H), 2.21−2.13 (m, 3H), 2.08−1.89 (m, 2H), 1.83−1.68 (m, 3H), 1.55−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 167.1, 163.8, 157.4, 135.3, 130.8, 130.6, 130.0, 129.7, 127.6, 122.2, 122.0, 117.1, 114.1, 75.5, 55.6, 52.0, 48.4, 35.3, 33.4, 31.82, 31.81, 25.6, 21.3 ppm; IR (KBr) ν_{max} 2909, 2833, 1708, 1674, 1599, 1575, 1436, 1259, 1174, 1036, 877, 675 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{26}H_{26}O_5Na^+$ $[M + Na]^+$: 441.1678, found: 441.1679; HPLC analysis: 88% ee [Daicel CHIRALPAK AD-H column, hexane/i-PrOH = 70:30, 0.5 mL/min, 254 nm, t_1 = 11.6 min (major), t_2 = 14.8 min (minor)].

4hf. White solid, 149.6 mg, 80% yield; mp 146−148 °C; $[\alpha]_D^{25}$ 116.6 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dt, J = 8.8, 2.0 Hz, 2H), 7.14 (td, J = 8.0, 2.4 Hz, 1H), 7.03 (dd, J = 8.4, 1.6 Hz, 1H), 6.93 (dt, J = 8.8, 2.0 Hz, 2H), 6.87−6.83 (m, 2H), 5.46 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.75 (d, J = 2.8 Hz, 1H), 3.25 (d, J = 2.8 Hz, 1H), 2.41−2.26 (m, 4H), 1.97 (qt, J = 13.2, 3.2 Hz, 1H), 1.86−1.76 (m, 2H), 1.73−1.59 (m, 2H), 0.92 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 163.5, 152.5, 134.6, 130.7, 130.3, 129.4, 128.4, 128.1, 126.7, 120.0, 117.2, 114.0, 74.0, 55.6, 47.7, 42.6, 40.8, 33.9, 32.0, 25.6, 21.5, 18.9 ppm; IR (KBr) ν_{max} 2927, 2858, 1680, 1597, 1509, 1455, 1266, 1174, 1021, 837, 757, 604 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{25}H_{26}O_3Na^+$ $[M + Na]^+$: 397.1780, found: 397.1797; HPLC analysis: 71% ee [Daicel CHIRALPAK AD-H column, hexane/i-PrOH = 97:3, 0.5 mL/min, 254 nm, t_1 = 10.8 min (major), t_2 = 12.3 min (minor)].

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, 2D NMR copies for compounds **3aa** and **4aa**, chiral HPLC analyses for all the products (PDF), and X-ray crystal data of compounds **3cd** and **4ag** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For a recent review of pyrylium and its benzo-derivatives, see: Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern heterocyclic chemistry*, 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Chapter 18, pp 1631−1682.

(2) For selected recent transformations involving a pyrylium intermediate, see: (a) Liang, S.; Zhu, L. Y.; Hurst, J. K. *Langmuir* **2012**, *28*, 12171−12181. (b) Velde, N. A.; Korbitz, H. T.; Garner, C. M. *Tetrahedron Lett.* **2012**, *53*, 5742−5744. (c) Velde, N. A.; Korbitz, H. T.; Bellert, D. J.; Garner, C. M. *J. Org. Chem.* **2013**, *78*, 11698−11706. (d) Carta, F.; Vullo, D.; Maresca, A.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem.* **2013**, *21*, 1564−1569. (e) Fărcaşiu, D.; Lezcano, M. *J. Labelled Compd. Radiopharm.* **2013**, *56*, 637−638. (f) Yang, L. J.; Ye, J. W.; Gao, Y.; Deng, D.; Lin, Y.; Ning, G. L. *Eur. J. Org. Chem.* **2014**, *3*, 515−522. (g) Sola, A.; Tárraga, A.; Molina, P. *Org. Biomol. Chem.* **2014**, *12*, 2547−2551.

(3) For representative enantioselective reactions of benzopyrylium intermediates, see: (a) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem.—Asian J.* **2010**, *5*, 2047−2052. (b) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096−7100. (c) Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 17142−17145. (d) Rueping, M.; Volla, M. R.; Atodiresei, C. I. *Org. Lett.* **2012**, *14*, 4642−4645. (e) Fañanás, F. J.; Mendoza, A.; Arto, T.; Temelli, B.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4930−4933. (f) Wang, H. H.; Kuang, Y. Y.; Wu, J. *Asian J. Org. Chem.* **2012**, *1*, 302−312. (g) Terada, M.; Yamanaka, T.; Toda, Y. *Chem.—Eur. J.* **2013**, *19*, 13658−13662. (h) Hsiao, C.-C.; Liao, H.-H.; Sugiono, E.; Atodiresei, I.; Rueping, M. *Chem.—Eur. J.* **2013**, *19*, 9775−9779.

(4) For a recent review on enantioselective reactions of benzopyrylium intermediates, see: Chen, J.-R.; Hu, X.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4038−4040.

(5) For representative enantioselective [3 + 2] reactions via oxidopyrylium intermediates, see: (a) Garnier, E.C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449−7458. (b) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578−14581.

(6) For a recent example on enantioselective [5 + 2] reactions via oxidopyrylium intermediates, see: Witten, M. R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2014**, *53*, 5912−5916.

(7) Yu, S.-Y.; Zhang, H.; Gao, Y.; Mo, L.; Wang, S. Z.; Yao, Z.-J. *J. Am. Chem. Soc.* **2013**, *135*, 11402−11407.

(8) For reviews on ACDC, see: (a) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603−614. (b) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518−533. (c) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534−561.

(9) For selected examples of chiral-anion catalysis by chiral phosphates, see: (a) Rueping, M.; Antonchick, A. P.; Dipl.-Chem, C. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903−6906. (b) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984−14986. (c) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096−4099. (d) Shi, S.-H.; Huang, F.-P.; Zhu, P.; Dong, Z.-W.; Hui, X.-P. *Org. Lett.* **2012**, *14*, 2010−2013.

(10) For reviews on relay catalysis system of transition metals and organocatalysts, see: (a) Wu, X.; Li, M. L.; Gong, L. Z. *Acta Chim. Sin.* **2013**, *8*, 1091−1100. (b) Lv, F. P.; Liu, S. Y.; Hu, W. H. *Asian J. Org. Chem.* **2013**, *2*, 824−836.

(11) For selected recent examples of enantioselective reaction in relay catalysis mode, see: (a) Chen, D.-F.; Wu, P.-Y.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 3958−3961. (b) Qian, D. Y.; Zhang, J. L. *Chem.—Eur. J.* **2013**, *19*, 6984−6988. (c) Calleja, J.; González-Pérez, A. B.; Lera, A. R.; Álvarez, R.; Fañanás, F. J.; Rodríguez, F. *Chem. Sci.* **2014**, *5*, 996−1007. (d) Wu, X.; Li, M.-L.; Wang, P.-S. *J. Org. Chem.* **2014**, *79*, 419−425. (e) Horino, Y.; Takahashi, Y.; Nakashima, Y.; Abe, H. *RSC Adv.* **2014**, *4*, 6215−6218.

(12) A mechanism of multistep cascade process could not be completely excluded for this oxa [4 + 2]-cyclization.