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Diastereo- and Enantioselective Construction of 3,3′-Pyrrolidinyldispirooxindole Framework via Catalytic Asymmetric 1,3-Dipolar Cycloadditions

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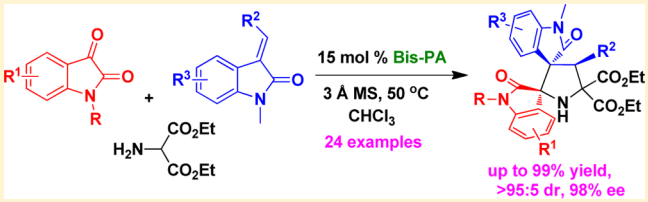
Supporting Information

ABSTRACT: The first catalytic enantioselective construction of a 3,3′-pyrrolidinyldispirooxindole scaffold has been established via organocatalytic asymmetric 1,3-dipolar cycloadditions of isatin-derived azomethine ylides with methyleneindolinones, which afforded structurally complex bis-spirooxindoles containing three contiguous and two quaternary stereogenic centers in generally high yields (up to 99%) and excellent diastereo- and enantioselectivities (up to >95:5 dr, 98% ee). This reaction also provides a good example for the application of catalytic asymmetric 1,3-dipolar cycloadditions in constructing enantioenriched bis-spirooxindole frameworks with structural complexity and rigidity.



INTRODUCTION

Spirooxindoles are fascinating frameworks which constitute the core structures of many natural alkaloids and bioactive molecules.[1,2] Among them, 3,3′-pyrrolidinylspirooxindole skeletons are frequently found in natural products as exemplified by (−)-horsfiline[1c] and (−)-spirotryprostatin A[1d] (Figure 1). More importantly, 3,3′-pyrrolidinyldispirooxindoles (compounds **I**–**III**) exhibit prominent bioactivities such as anticancer,[2a] antifungal,[2b] and antimicrobial[2c] activities. As a result, it is highly valuable to construct this class of bis-spirooxindole scaffolds, especially in an enantioselective manner, because the bioactivity of the two enantiomers may differ from each other or from the racemic compounds.[3]

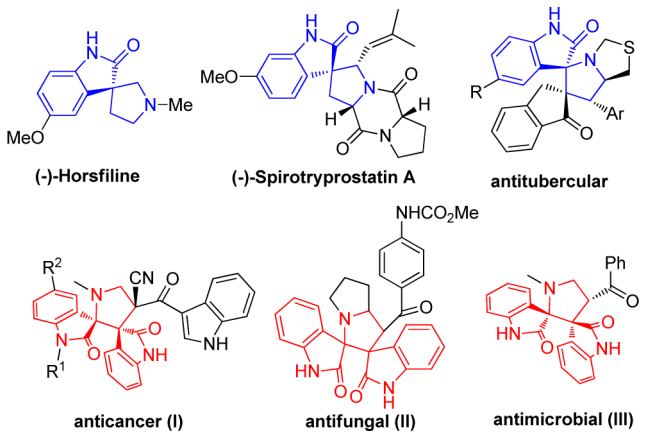
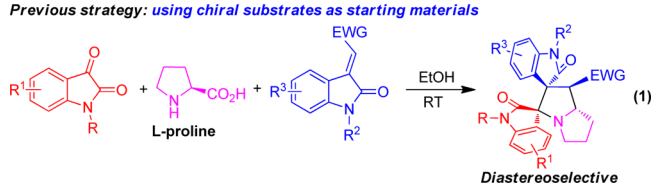


Figure 1. Some 3,3′-pyrrolidinyl spirooxindoles and bis-spirooxindoles.

However, a survey of the literature disclosed that most of the approaches were concentrated on the synthesis of racemic bis-spiro products,[4] and no enantioselective methods have been reported to access this type of chiral bis-spirooxindoles.[5] This is mainly ascribed to the difficulty in constructing such structurally rigid bis-spirooxindole frameworks with at least two quaternary stereogenic centers. Recently, Chen, Yang, and co-workers[5a] and the Shi group[5b] developed a diastereoselective strategy to achieve the construction of a chiral 3,3′-pyrrolidinyldispirooxindole skeleton by using chiral L-proline as a starting material (eq 1). In spite of these creative works,[5]



the catalytic enantioselective construction of this class of bis-spirooxindole scaffolds by utilizing achiral starting materials has not yet been achieved. Thus, there is a great demand to develop catalytic asymmetric strategies for the construction of such bis-spirooxindole frameworks in an enantioselective way.

One of the most efficient ways to enantioselectively construct pyrrolidine skeleton is Lewis acid catalyzed[6] or organocatalytic[7]

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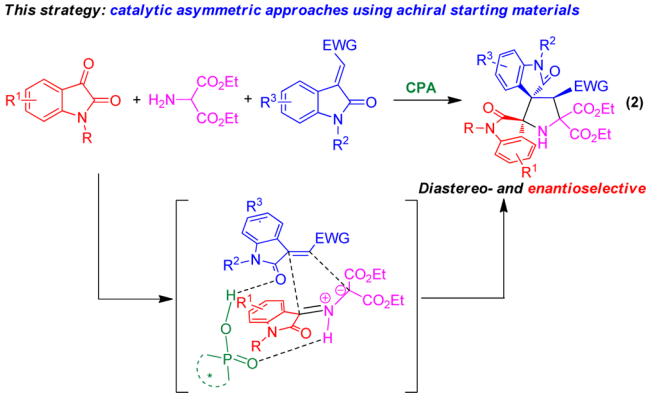
asymmetric 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylide.[8] In particular, chiral phosphoric acid[9] (CPA) catalyzed asymmetric 1,3-DC of isatin-derived azomethine ylide with electron-deficient alkenes or alkynes has proven to be a robust method to build up the 3,3′-pyrrolidinylspirooxindole scaffold in a highly enantioselective fashion.[10] However, this strategy has not been employed for the enantioselective construction of the structurally more complex and rigid bis-spirooxindole motif, which remains a great challenge in catalytic asymmetric 1,3-DCs. In order to confront this challenge, we designed a CPA-catalyzed asymmetric 1,3-DC of isatin-derived azomethine ylide with methyleneindolinone (Scheme 1, eq 2). On the basis of

Scheme 1. Design of Catalytic Asymmetric 1,3-DC to Enantioselectively Construct the 3,3′-Pyrrolidinyldispirooxindole Framework



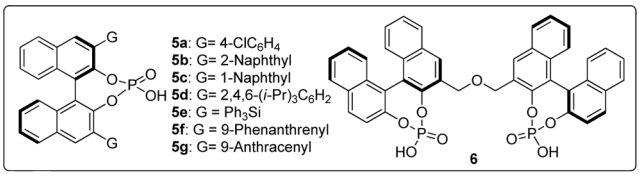
our previous experience in CPA-catalyzed reactions,[11] we envisioned that the two reactants would be simultaneously activated by CPA via a dual hydrogen-bonding activation mode, thus leading to the diastereo- and enantioselective construction of the 3,3′-pyrrolidinyldispirooxindole framework (Scheme 1).

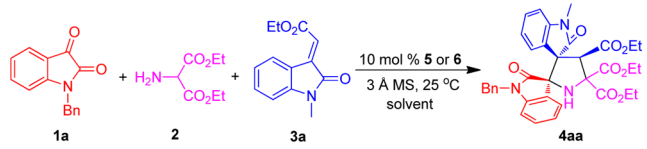
Herein, we report the first diastereo- and enantioselective construction of the 3,3′-pyrrolidinyldispirooxindole scaffold via a catalytic asymmetric 1,3-DC of isatin-derived azomethine ylide with methyleneindolinone, which efficiently afforded structurally complex bis-spirooxindoles bearing two quaternary and three contiguous stereogenic centers in high yields (up to 99% yield) and excellent diastereo- and enantioselectivities (up to >95:5 dr, 98% ee).

RESULTS AND DISCUSSION

At the beginning, the reaction of *N*-benzylisatin **1a**, diethyl 2-aminomalonate **2**, and methyleneindolinone **3a** was employed as a model reaction to evaluate BINOL-derived CPAs **5a**–**g** (Table 1, entries 1–7). Although these reactions afforded the desired bis-spirooxindole product **4aa** in high yields (79%–86%) and excellent diastereoselectivities (all >95:5 dr), the enantioselective control of these catalysts on the reaction was very frustrating. In detail, CPAs **5a**–**f** bearing either small or bulky 3,3′-substituents nearly had no enantioselective induction on the reaction, and the generated bis-spirooxindole products were almost racemates (entries 1–6). Only CPA (**5g**) with a very bulky 9-anthracenyl group at the 3,3′-positions of the BINOL-backbone could control the enantioselectivity to some extent, but the ee value was still very low (entry 7). These results indicated that the capability of BINOL-derived CPAs in controlling the enantioselectivity of this reaction was not promising. In recent years, chiral bis-phosphoric acid (Bis-PA,

Table 1. Screening of Catalysts and Solvents[a]





entry	solvent	Cat.	yield[b] (%)	dr[c]	ee[d] (%)
1	toluene	**5a**	83	>95:5	0
2	toluene	**5b**	85	>95:5	4
3	toluene	**5c**	80	>95:5	5
4	toluene	**5d**	86	>95:5	6
5	toluene	**5e**	79	>95:5	3
6	toluene	**5f**	83	>95:5	3
7	toluene	**5g**	81	>95:5	31
8	toluene	**6**	61	>95:5	68
9	CH_2Cl_2	**6**	39	>95:5	57
10	$CHCl_3$	**6**	56	>95:5	82

[a]Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in a solvent (1 mL) with 3 Å MS (100 mg) at 25 °C for 15 h, and the mole ratio of **1a**/**2**/**3a** was 1.2:1:1.5. [b]Isolated yield. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR and HPLC. [d]The enantiomeric excess (ee) was determined by HPLC.

6) has exhibited its great potential in catalytic asymmetric 1,3-DCs,[7c,10b,d] which is far superior to mono-CPAs in terms of enantioselective control. Therefore, we tentatively utilized Bis-PA (**6**) as a catalyst to the model reaction. Indeed, this reaction under the catalysis of Bis-PA (**6**) delivered the product **4aa** in a much higher enantioselectivity of 68% ee albeit with a moderate yield of 61% (entry 8). Then, in the presence of Bis-PA (**6**) as the most suitable catalyst, the model reaction was subjected to a variety of solvents mainly including arenes and chloro-substituted alkanes (see the Supporting Inforamtion for details) with the aim of further improving the enantioselectivity. It was found that chloroform could offer the reaction in the highest enantioselectivity of 82% ee, although the yield was decreased to some extent (entry 10). Thus, chloroform was selected as an optimal reaction medium for subsequent condition optimization.

As shown in Table 2, further optimization of reaction conditions was focused on screening additives, temperature, reaction time, and catalyst loading. The evaluation of molecular sieves (MS) and anhydrous sulfates as water absorbers disclosed that anhydrous sulfates were inferior to MS with regard to the enantioselectivity (entries 4–5 vs 1–3). Among different types of MS, 4 Å MS afforded the best enantioselectivity of 87% ee, but the yield was very low (entry 2). Considering the balance of the yield and the enantioselectivity, 3 Å MS was finally chosen as a more suitable reaction additive (entry 1). Then, by elongating the reaction time from 15 to 36 h, the yield was improved from 56% to 74% with almost retained enantioselectivity (entry 1 vs 6). Furthermore, elevating the reaction temperature from 25 to 50 °C resulted in a significantly increased yield of 94% and a slightly ameliorated enantioselectivity of 83% ee (entry 7 vs 6). Finally, properly increasing the catalyst loading to 15 mol % led

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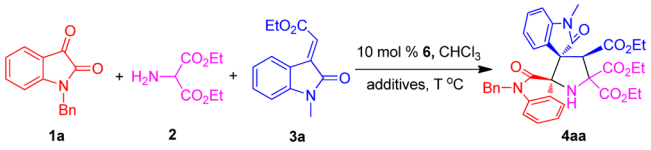
Table 2. Further Optimization of Conditions[a]



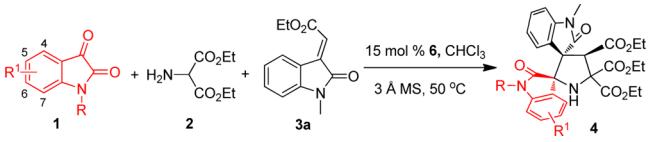
entry	additives	T (°C)	yield[b] (%)	dr[c]	ee[d] (%)
1	3 Å MS	25	56	>95:5	82
2	4 Å MS	25	33	>95:5	87
3	5 Å MS	25	44	>95:5	82
4	$MgSO_4$	25	61	>95:5	55
5	Na_2SO_4	25	59	>95:5	57
6[e]	3 Å MS	25	74	>95:5	80
7[e]	3 Å MS	50	94	>95:5	83
8[e,f]	3 Å MS	50	99	>95:5	86

[a]Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in chloroform (1 mL) with additives (100 mg) at the indicated temperature for 15 h, and the mole ratio was **1a**/**2**/**3a** was 1.2:1:1.5. [b]Isolated yield. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR and HPLC. [d]The enantiomeric excess (ee) was determined by HPLC. [e]The reaction time was 36 h. [f]In the presence of 15 mol % of **6**.

to a quantitative yield of 99% and a high enantioselectivity of 86% ee (entry 8).

After establishing the optimal reaction conditions, we carried out the investigation on the substrate scope of isatins **1** via the reactions with diethyl 2-aminomalonate (**2**) and methyleneindolinone **3a**. As shown in Table 3, a wide scope of isatins bearing different R/R^1 groups could be successfully utilized to the catalytic asymmetric 1,3-DCs, which offered the desired bis-spirooxindoles **4** with two quaternary stereogenic centers in high yields (75−99%) and excellent stereoselectivities (all >95:5 dr, 82−92% ee). In detail, this protocol is applicable to a series of *N*-benzyl-, phenyl-, or alkyl-substituted isatins (entries 1−7), and there is no significant difference among *N*-benzyl-substituted substrates **1a−e** in terms of enantioselectivity (entries 1−5). Notably, *N*-phenylisatin **1f** displayed higher capability in enantioselective control than its *N*-benzyl- or *N*-alkyl-substituted counterparts (entry 6 vs 1−5 and 7). In addition, a variety of isatins with different substituents at the C5−C7 positions of the phenyl ring could smoothly participate in the reaction in generally high yields and good enantioselectivities (entries 8−13). It seemed that the position of the substituent had some effect on the enantioselectivity since C7-fluoro-substituted isatin delivered a higher ee value than the C5-fluoro-substituted isatin (entry 13 vs 8). The electronic nature of the substituents might also influence the enantioselectivity to some extent because substrates **1j,k** offered the products with higher ee value than substrate **1i** did (entries 10 and 11 vs 9).

Table 3. Substrate Scope of Isatins 1[a]

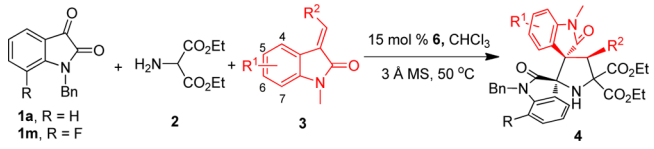


entry	4	R/R^1 (**1**)	yield[b] (%)	dr[c]	ee[d] (%)
1	**4aa**	Bn/H (**1a**)	99	>95:5	86
2	**4ba**	*p*-*t*BuC$_6$H$_4$CH$_2$/H (**1b**)	95	>95:5	88
3	**4ca**	*p*-BrC$_6$H$_4$CH$_2$/H (**1c**)	89	>95:5	84
4	**4da**	*m*-ClC$_6$H$_4$CH$_2$/H (**1d**)	85	>95:5	88
5	**4ea**	*o*-ClC$_6$H$_4$CH$_2$/H (**1e**)	86	>95:5	86
6	**4fa**	Ph/H (**1f**)	88	>95:5	90
7	**4ga**	Me/H (**1g**)	83	>95:5	80
8	**4ha**	Bn/5-F (**1h**)	93	>95:5	86
9	**4ia**	Bn/6-MeO (**1i**)	75	>95:5	82
10	**4ja**	Bn/6-Cl (**1j**)	90	>95:5	90
11	**4ka**	Bn/6-Br (**1k**)	90	>95:5	88
12	**4la**	Bn/7-CF$_3$ (**1l**)	82	>95:5	88
13	**4ma**	Bn/7-F (**1m**)	87	>95:5	92

[a]Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in chloroform (1 mL) with 3 Å MS (100 mg) at 50 °C for 36 h, and the mole ratio of **1**:**2**:**3a** was 1.2:1:1.5. [b]Isolated yield. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR. [d]The enantiomeric excess (ee) was determined by HPLC.

Next, the substrate scope with respect to methyleneindolinones **3** was studied by the reactions with isatin **1a** or **1m** and amino ester **2** under the standard conditions. As illustrated in Table 4, this approach was amenable to a wide range of methyleneindolinones bearing distinct R^1/R^2 groups, leading to structurally complex bis-spirooxindoles in overall high yields (62%−92%) and excellent diastereo- and enantioselectivities (all >95:5 dr, 86%−98% ee). For the R^1 group, there was no obvious electronic effect on the enantioselectivity because either electron-donating or electron-withdrawing groups at the same position could give the similar ee value (entry 1 vs 2, entry 3 vs 4−5, entry 6 vs 7), but the position of the R^1 group seemed to impose some effect on the enantioselectivity due to the fact that C6-substituted substrates provided higher ee value than their C5- or C7-substituted analogues (entries 3−5 vs 1, 2 and 6, 7). As for the R^2 group, it could be successfully changed from an ester group to a benzoyl group or a cyano group, which gave the corresponding bis-spirooxindoles with perfected enantioselectivities (96%−98% ee, entries 8 and 9). These results demonstrated that this reaction had a wide substrate scope, which could be readily utilized for the enantioselective synthesis of such bis-spirooxindoles with structural diversity.

Table 4. Substrate Scope of Methyleneindolinones 3[a]



entry	4	R (**1**)	R^1/R^2 (**3**)	yield[b] (%)	dr[c]	ee[d] (%)
1	**4ab**	H (**1a**)	5-Me/CO$_2$Et (**3b**)	90	>95:5	88
2	**4mc**	F (**1m**)	5-Cl/CO$_2$Et (**3c**)	64	>95:5	86
3	**4md**	F (**1m**)	6-MeO/CO$_2$Et (**3d**)	90	>95:5	92
4	**4mae**	F (**1m**)	6-Br/CO$_2$Et (**3e**)	87	>95:5	94
5	**4mf**	F (**1m**)	6-Cl/CO$_2$Et (**3f**)	85	>95:5	92
6	**4ag**	H (**1a**)	7-Me/CO$_2$Et (**3g**)	82	>95:5	88
7	**4mh**	F (**1m**)	7-F/CO$_2$Et (**3h**)	62	>95:5	86
8	**4 mi**	F (**1m**)	H/COPh (**3i**)	80	>95:5	98
9	**4mj**	F (**1m**)	H/CN (**3j**)	92	>95:5	96

[a]Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in chloroform (1 mL) with 3 Å MS (100 mg) at 50 °C for 36 h, and the mole ratio of **1**/**2**/**3** was 1.2:1:1.5. [b]Isolated yield. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR. [d]The enantiomeric excess (ee) was determined by HPLC.

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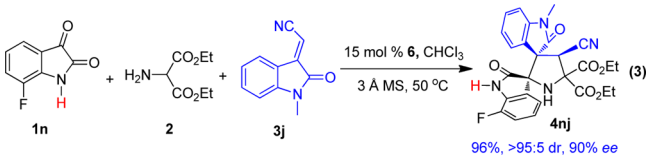
Finally, in order to examine the applicability of *N*-unprotected isatin in the reaction, we employed *N*-H isatin **1n** as a substrate to the reactions with amino ester **2** and methyleneindolinone **3j** (eq 3). Gratifyingly, this *N*-unprotected isatin successfully participated in the desired reaction to afford the corresponding bis-spirooxindole **4nj** in a high yield of 96% and an excellent stereoselectivity of >95:5 dr and 90% ee, which indicated that the *N*-H group of isatins had no remarkable effect on the reactivity and the stereoselectivity. In addition, we also investigated the effect of nitro functionality as a strong electron-withdrawing group on the reaction by using C5-nitro-substituted isatin **1o** as a reactant (eq 4). Indeed, the nitro group imposed an obviously negative effect on the stereoselectivity because the product **4oj** was generated in a low diastereo- and enantioselectivity albeit with a high yield.



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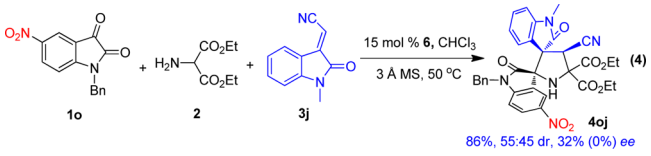

(4)

The absolute configuration of bis-spirooxindole **4aa** was unambiguously determined to be (3*R*,4*S*,5*R*) by X-ray single-crystal analysis (>99% ee after recrystallization).[12] The relative and absolute configurations of other bis-spirooxindole products **4** were assigned by analogy. Based on the experimental results and previous report[10b] on the activation mode of bis-PA to dipoles as well as dipolarophiles in catalytic asymmetric 1,3-DCs, we suggested a possible reaction pathway and activation mode. As illustrated in Scheme 1, bis-PA simultaneously generated two hydrogen bonds with the amide C═O group of methyleneindolinones and the N−H group of azomethine ylides, which were produced in situ by the condensation of isatins and amino ester in the presence of bis-PA. Thus, bis-PA acted as a bifunctional catalyst, and this dual-activation mode of the catalyst to the two reactants facilitated the subsequent enantioselective [3 + 2] cycloaddition. The reaction may largely undergo a concerted pathway because no intermediate Michael addition product was observed at all. Obviously, the regioselectivity of the 1,3-DC was controlled by the amide C═O group rather than the ester group of methyleneindolinones, which may also be ascribed to the hydrogen-bonding interaction between the catalyst and the amide C═O group. Bis-PA was supposed to form an intramolecular hydrogen-bond between the two acidic functionalities, thus making it easy for this catalyst to hold bulky isatin-derived substrates and impose the effect of enantioselective induction.[10b] Therefore, the unique structure of bis-PA and its powerful dual hydrogen-bonding activation mode contributed greatly to the observed excellent stereoselectivity of the reaction.

CONCLUSIONS

In summary, we have achieved the first catalytic enantioselective construction of the 3,3′-pyrrolidinyldispirooxindole scaffold, which takes use of organocatalytic asymmetric 1,3-DCs of isatin-derived azomethine ylides with methyleneindolinones. By using this strategy, a variety of structurally complex bis-spirooxindoles containing three adjacent and two quaternary stereogenic centers have been efficiently synthesized in generally high yields (up to 99%) and excellent diastereo- and enantioselectivities (up to >95:5 dr, 98% ee). The experimentally observed excellent stereoselectivity may largely be attributed to the unique structure of bis-PA catalyst and its powerful dual hydrogen-bonding activation mode to the reactants. This reaction not only provides a robust method for diastereo- and enantioselective construction of the chiral bis-spirooxindole scaffold but also greatly expands the application of catalytic asymmetric 1,3-DCs of azomethine ylides in synthesizing biologically important spirooxindoles with optical purity.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (ESI) was determined using an HRMS/MS instrument. Enantiomeric excesses (ee) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric excesses by chiral HPLC was Chiralpak AD-H and IA. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single-crystal X-ray diffraction analysis of compound **4aa** was Cu Kα (λ = 1.54178), and the thermal ellipsoid was drawn at the 30% probability level. Analytical-grade solvents for column chromatography and commercially available reagents were used as received. All commercially available starting materials were used directly. Substrates **1** and **3** were synthesized according to the literature methods.[10b,13] Catalyst **6** was prepared according to the procedures reported in the literature.[7c]

Typical Procedure for the Catalytic Enantioselective Synthesis of 3,3′-Pyrrolidinyldispirooxindoles 4. After a solution of isatins **1** (0.12 mmol), amino ester **2** (0.1 mmol), the catalyst **6** (0.015 mmol), and 3 Å molecular sieves (100 mg) in chloroform (0.5 mL) was stirred at room temperature for 30 min, the solution of methyleneindolinones **3** (0.15 mol) in chloroform (0.5 mL) was added. After being stirred at 50 °C for 36 h, the reaction mixture was filtered to remove the molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford bis-spirooxindole products **4**.

*Compound **4aa**:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield 99% (61.9 mg); >95:5 dr; white solid; mp 148−149 °C; $[\alpha]_D^{20}$ = +63.5 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.21−7.15 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.88−6.80 (m, 2H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 1H), 5.21 (s, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 4.55−4.39 (m, 2H), 4.38−4.29 (m, 2H), 4.14 (d, *J* = 15.6 Hz, 1H), 3.81−3.66 (m, 2H), 2.88 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.1, 171.7, 169.2, 167.3, 142.7, 141.4, 137.8, 134.5, 129.8, 129.5, 129.2, 128.7, 127.9, 127.8, 127.4, 126.9, 125.5, 124.4, 122.1, 121.9, 108.7, 107.6, 74.9, 74.2, 64.8, 63.1, 63.0, 60.9, 58.9, 43.5, 26.7, 14.0, 13.8, 13.4; IR (KBr) 3450, 3270, 3003, 2977, 1731, 1647, 1557, 1541, 1473, 757 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{35}N_3O_8 + Na)^+$ requires *m*/*z* 648.2316, found *m*/*z* 648.2301; ee 86%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 9.58 min (minor), t_R = 18.05 min (major).

*Compound **4ba**:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield 95% (64.7 mg);

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>95:5 dr; white solid; mp 99−101 °C; $[\alpha]_D^{20}$ = +114.3 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ7.89 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.30−7.26 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.17−7.11 (m, 1H), 7.10−7.04 (m, 1H), 7.03−6.96 (m, 1H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 5.22 (s, 1H), 4.94 (d, *J* = 15.4 Hz, 1H), 4.62 (s, 1H), 4.54−4.41 (m, 2H), 4.37−4.27 (m, 2H), 4.11 (d, *J* = 15.4 Hz, 1H), 3.79−3.65 (m, 2H), 2.87 (s, 3H), 1.36−1.30 (m, 6H), 1.27 (s, 9H), 0.69 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.7, 171.7, 169.2, 167.3, 150.2, 142.7, 141.6, 132.7, 129.4, 129.0, 128.9, 127.9, 127.2, 127.0, 125.4, 124.6, 121.9, 121.8, 108.9, 107.3, 74.8, 74.2, 64.9, 63.1, 63.0, 60.9, 58.9, 43.5, 34.4, 31.3, 26.5, 14.0, 13.8, 13.4; IR (KBr) 3429, 3277, 3060, 2971, 1732, 1612, 1569, 1493, 758 cm^{-1}; ESI FTMS exact mass calcd for $(C_{39}H_{43}N_3O_8 + Na)^+$ requires *m*/*z* 704.2942, found *m*/*z* 704.2947; enantiomeric excess 88%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 7.22 min (minor), t_R = 9.68 min (major).

Compound ***4ca****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 89% (62.6 mg); >95:5 dr; white solid; mp 128−129 °C; $[\alpha]_D^{20}$ = +83.2 (*c* 1.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.30−7.26 (m, 3H), 7.16−7.09 (m, 1H), 7.08−6.97 (m, 2H), 6.69 (t, *J* = 8.3 Hz, 3H), 6.48 (d, *J* = 7.7 Hz, 1H), 5.15 (s, 1H), 4.89 (d, *J* = 15.8 Hz, 1H), 4.59−4.38 (m, 3H), 4.38−4.28 (m, 2H), 4.11 (d, *J* = 15.8 Hz, 1H), 3.78−3.70 (m, 2H), 2.88 (s, 3H), 1.35−1.29 (m, 6H), 0.72 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 173.2, 171.5, 169.1, 167.2, 142.8, 141.3, 134.7, 131.6, 129.5, 129.1, 128. 9, 128.8, 127.7, 127.3, 124.4, 122.1, 122.0, 121.3, 108.6, 107.3, 75.0, 74.3, 64.7, 63.0, 60.9, 58.7, 43.2, 26.5, 14.0, 13.8, 13.4; IR (KBr) 3446, 3281, 3053, 2978, 1727, 1610, 1578, 1488, 765 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}BrN_3O_8 + Na)^+$ requires *m*/*z* 726.1421, found *m*/*z* 726.1419; enantiomeric excess: 84%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 10.71 min (minor), t_R = 14.20 min (major).

Compound ***4da****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 85% (56.0 mg); >95:5 dr; white solid; mp 119−121 °C; $[\alpha]_D^{20}$ = +112.4 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.29−7.26 (m, 1H), 7.19−7.10 (m, 3H), 7.08−6.98 (m, 2H), 6.80 (d, *J* = 11.4 Hz, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.21 (s, 1H), 4.98 (d, *J* = 15.8 Hz, 1H), 4.59 (s, 1H), 4.52−4.41 (m, 2H), 4.36−4.28 (m, 2H), 4.08 (d, *J* = 15.8 Hz, 1H), 3.78−3.68 (m, 2H), 2.93 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H), 0.69 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.1, 171.7, 169.1, 167.2, 142.7, 141.3, 137.8, 134.4, 129.8, 129.5, 129.2, 128.7, 127.8, 127.8, 127.3, 126.9, 125.4, 124.4, 122.1, 121.9, 108.7, 107.6, 74.9, 74.2, 64.8, 63.1, 63.0, 60.9, 58.8, 43.5, 26.7, 14.0, 13.8, 13.4; IR (KBr) 3445, 3273, 2979, 2925, 1716, 1608, 1576, 1489, 754 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}ClN_3O_8 + Na)^+$ requires *m*/*z* 682.1926, found *m*/*z* 682.1917; enantiomeric excess 88%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 9.98 min (minor), t_R = 17.02 min (major).

Compound ***4ea****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 86% (56.7 mg); >95:5 dr; white solid; mp 97−98 °C; $[\alpha]_D^{20}$ = +81.0 (*c* 0.92, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.32−7.27 (m, 1H), 7.25−7.20 (m, 1H), 7.17−7.10 (m, 2H), 7.06−6.95 (m, 3H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 1H), 4.98 (d, *J* = 16.5 Hz, 1H), 4.60 (s, 1H), 4.53−4.28 (m, 5H), 3.81−3.69 (m, 2H), 2.97 (s, 3H), 1.37−1.29 (m, 6H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 173.3, 171.6, 169.1, 167.2, 142.7, 141.4, 132.8, 132.7, 129.6, 129.5, 129.1, 128.9, 128.6, 127.8, 127.7, 127.3, 126.8, 124.4, 122.1, 122.0, 108.9, 107.3, 74.9, 74.3, 64.7, 63.1, 63.0, 60.9, 59.0, 41.6, 26.6, 14.0, 13.8, 13.4; IR (KBr) 3477, 3298, 2976, 2923, 1728, 1612, 1491, 755 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}ClN_3O_8 + Na)^+$ requires *m*/*z* 682.1926, found *m*/*z* 682.1926; enantiomeric excess 86%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 8.43 min (minor), t_R = 12.28 min (major).

Compound ***4fa****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 88% (53.8 mg); >95:5 dr; white solid; mp 173−175 °C; $[\alpha]_D^{20}$ = −12.8 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.65 (m, 1H), 7.53−7.47 (m, 1H), 7.38−7.31 (m, 2H), 7.30−7.27 (m, 1H), 7.25−7.19 (m, 1H), 7.15−7.09 (m, 1H), 7.07−7.01 (m, 1H), 7.01−6.96 (m, 1H), 6.95−6.91 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 1H), 4.55 (s, 1H), 4.51−4.40 (m, 2H), 4.40−4.29 (m, 2H), 3.82−3.74 (m, 2H), 2.96 (s, 3H), 1.38−1.29 (m, 6H), 0.77 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 172.8, 171.3, 169.0, 167.3, 143.0, 142.6, 133.9, 129.4, 129.4, 129.1, 128.6, 127.9, 127.1, 127.1, 126.4, 124.2, 122.3, 122.0, 109.0, 107.4, 75.6, 74.9, 64.9, 63.0, 62.9, 60.9, 58.2, 26.5, 14.0, 13.9, 13.5; IR (KBr) 3461, 3276, 3056, 2980, 1718, 1610, 1594, 1498, 751 cm^{-1}; ESI FTMS exact mass calcd for $(C_{34}H_{33}N_3O_8 + Na)^+$ requires *m*/*z* 634.2160, found *m*/*z* 634.2159; enantiomeric excess 90%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 15.19 min (minor), t_R = 17.14 min (major).

Compound ***4ga****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 83% (45.6 mg); >95:5 dr; white solid; mp 184−186 °C; $[\alpha]_D^{20}$ = +103.1 (*c* 0.91, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.25−7.19 (m, 2H), 7.09−6.98 (m, 2H), 6.70−6.59 (m, 2H), 5.19 (s, 1H), 4.52 (s, 1H), 4.49−4.36 (m, 2H), 4.35−4.22 (m, 2H), 3.76−3.65 (m, 2H), 2.95 (s, 3H), 2.88 (s, 3H), 1.33−1.27 (m, 6H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.7, 171.6, 169.0, 167.2, 142.7, 142.5, 129.5, 129.0, 128.7, 127.3, 127.2, 124.2, 121.7, 121.6, 108.1, 107.4, 74.7, 73.9, 64.3, 63.0, 62.9, 60.9, 59.4, 26.6, 26.5, 13.9, 13.8, 13.4; IR (KBr) 3425, 3279, 2958, 2924, 2359, 1721, 1611, 1539, 1495, 766 cm^{-1}; ESI FTMS exact mass calcd for $(C_{29}H_{31}N_3O_8 + Na)^+$ requires *m*/*z* 572.2003, found *m*/*z* 572.2031; enantiomeric excess 80%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 8.27 min (minor), t_R = 10.86 min (major).

Compound ***4ha****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 93% (59.8 mg); >95:5 dr; white solid; mp 163−164 °C; $[\alpha]_D^{20}$ = +88.0 (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.25−7.23 (m, 1H), 7.21−7.16 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.86−6.78 (m, 3H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.47−6.41 (m, 1H), 5.17 (s, 1H), 4.98 (d, *J* = 15.7 Hz, 1H), 4.62 (s, 1H), 4.53−4.40 (m, 2H), 4.39−4.28 (m, 2H), 4.11 (d, *J* = 15.7 Hz, 1H), 3.77−3.67 (m, 2H), 2.91 (s, 3H), 1.37−1.30 (m, 6H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.7, 171.62, 169.1, 167.1, 158.5 (*J* = 239.2 Hz), 142.7, 137.5, 137.4, 135.3, 129.8, 129.7, 129.3, 128.9, 128.6, 127.6, 127.0, 124.3, 122.0, 115.8 (*J* = 8.3 Hz), 115.5 (*J* = 10.8 Hz), 109.3 (*J* = 8.0 Hz), 107.4, 74.8, 74.5, 64.8, 63.2, 63.1, 61.0, 58.8, 44.0, 26.6, 14.0, 13.9, 13.4; IR (KBr) 3429, 3278, 3084, 2924, 1718, 1636, 1559, 1507, 787 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}FN_3O_8 + Na)^+$ requires *m*/*z* 666.2222, found *m*/*z* 666.2258; enantiomeric excess 86%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm) t_R = 8.28 min (minor), t_R = 13.84 min (major).

Compound ***4ia****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 75% (49.1 mg); >95:5 dr; white solid; mp 150−151 °C; $[\alpha]_D^{20}$ = +69.9 (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.1 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.25−7.23 (m, 1H), 7.22−7.12 (m, 3H), 7.10−7.00 (m, 1H), 6.85−6.79 (m, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.50−6.45 (m, 1H), 6.09 (d, *J* = 2.3 Hz, 1H), 5.16 (s, 1H), 5.06−4.86 (m, 1H), 4.55−4.39 (m, 3H), 4.37−4.27 (m, 2H), 4.11 (d, *J* = 15.7 Hz, 1H), 3.79−3.70 (m, 2H), 3.69 (s, 3H), 2.90 (s, 3H), 1.35−1.30 (m, 6H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.3, 171.7, 169.1, 167.4, 160.6, 143.0, 142.8, 135.6, 129.0, 128.8, 128.5, 128.1, 127.4, 127.0, 124.6, 121.9, 119.6, 107.3, 105.3, 96.9, 74.8, 74.0, 64.8, 62.7, 60.9, 58.7, 55.2, 43.8, 26.5, 14.0, 13.9, 13.4; IR (KBr) 3476, 3352, 3065, 2957, 1732, 1622, 1578, 1504, 797 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{37}N_3O_9 + Na)^+$ requires *m*/*z* 678.2422, found *m*/

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z 678.2458; enantiomeric excess 82%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 12.69 min (minor), t_R = 25.04 min (major).

Compound ***4ja:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 90% (59.3 mg); >95:5 dr; white solid; mp 159−160 °C; $[\alpha]_D^{20}$ = +88.3 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.1 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.30−7.26 (m, 1H), 7.22−7.16 (m, 3H), 7.09−7.02 (m, 1H), 7.00−6.94 (m, 1H), 6.84−6.78 (m, 2H), 6.70 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 1.8 Hz, 1H), 5.16 (s, 1H), 4.96 (d, J = 15.7 Hz, 1H), 4.55 (d, J = 15.5 Hz, 1H), 4.52−4.39 (m, 2H), 4.37−4.26 (m, 2H), 4.11 (d, J = 15.7 Hz, 1H), 3.80−3.67 (m, 2H), 2.90 (s, 3H), 1.37−1.26 (m, 6H), 0.70 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 173.0, 171.6, 169.1, 167.2, 142.8, 142.7, 135.2, 135.0, 129.3, 128.8, 128.7, 128.3, 127.6, 127.0, 126.3, 124.3, 122.1, 122.0, 109.5, 107.5, 74.8, 74.0, 64.8, 63.1, 63.1, 61.0, 58.7, 43.9, 26.6, 14.0, 13.9, 13.4; IR (KBr) 3441, 3282, 2974, 2936, 2362, 1727, 1610, 1560, 1492, 753 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}ClN_3O_8 + Na)^+$ requires m/z 682.1926, found m/z 682.1912; enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 9.56 min (minor), t_R = 17.25 min (major).

Compound ***4ka:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 90% (63.3 mg); >95:5 dr; white solid; mp 148−149 °C; $[\alpha]_D^{20}$ = +102.6 (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.77 (m, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.29−7.26 (m, 1H), 7.23−7.17 (m, 3H), 7.15−7.10 (m, 1H), 7.09−7.03 (m, 1H), 6.85−6.77 (m, 2H), 6.70 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 1.7 Hz, 1H), 5.16 (s, 1H), 4.96 (d, J = 15.7 Hz, 1H), 4.51−4.40 (m, 2H), 4.37−4.25 (m, 2H), 4.11 (d, J = 15.7 Hz, 1H), 3.83−3.68 (m, 2H), 2.91 (s, 3H), 1.32 (t, J = 7.1 Hz, 6H), 0.70 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.8, 171.6, 169.0, 167.1, 142.9, 142.7, 135.0, 129.2, 128.8, 128.6, 128.6, 127.6, 126.9, 126.8, 124.9, 124.2, 123.2, 122.1, 112.2, 107.4, 74.8, 74.0, 64.7, 63.1, 63.1, 60.9, 58.7, 43.8, 26.6, 14.0, 13.8, 13.4; IR (KBr) 3417, 3339, 3021, 2938, 1728, 1607, 1587, 1489, 754 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}BrN_3O_8 + Na)^+$ requires m/z 726.1421, found m/z 726.1427; enantiomeric excess 88%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 9.56 min (minor), t_R = 18.01 min (major).

Compound ***4la:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 82% (56.8 mg); >95:5 dr; white solid; mp 141−143 °C; $[\alpha]_D^{20}$ = +104.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.76 (m, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.25−7.19 (m, 1H), 7.17−7.12 (m, 1H), 7.13−7.08 (m, 3H), 7.07−7.00 (m, 1H), 6.68 (d, J = 7.7 Hz, 1H), 6.66−6.61 (m, 2H), 5.26 (s, 1H), 5.03 (t, J = 21.7 Hz, 1H), 4.69 (t, J = 13.5 Hz, 2H), 4.55−4.40 (m, 2H), 4.39−4.25 (m, 2H), 3.79−3.64 (m, 2H), 2.96 (s, 3H), 1.37−1.29 (m, 6H), 0.70 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.7, 171.8, 169.2, 166.9, 142.6, 139.8, 135.9, 131.3, 131.1, 129.2, 129.0, 128.0, 127.6 (J = 6.1 Hz), 126.6, 125.6, 124.6, 124.0, 122.1, 121.9, 121.3, 112.6 (J = 32.7 Hz), 107.5, 74.6, 72.6, 64.9, 63.2, 63.1, 61.0, 59.2, 45.9, 45.9, 26.6, 14.0, 13.8, 13.4; IR (KBr) 3487, 3279, 3061, 2983, 1732, 1612, 1597, 1498, 1096, 751 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{34}F_3N_3O_8 + Na)^+$ requires m/z 716.2190, found m/z 716.2191; enantiomeric excess: 88%, determined by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.15 min (minor), t_R = 10.10 min (major).

Compound ***4ma:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 87% (55.9 mg); >95:5 dr; white solid; mp 115−116 °C; $[\alpha]_D^{20}$ = +110.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.84 (m, 1H), 7.30−7.26 (m, 1H), 7.26−7.23 (m, 1H), 7.20−7.14 (m, 3H), 7.10−7.05 (m, 1H), 6.99−6.91 (m, 2H), 6.90−6.86 (m, 2H), 6.67 (d, J = 7.6 Hz, 1H), 5.20 (s, 1H), 4.95 (d, J = 15.2 Hz, 1H), 4.56−4.39 (m, 3H), 4.37−4.25 (m, 2H), 3.76−3.63 (m, 2H), 2.84 (s, 3H), 1.36−1.29 (m, 6H), 0.67 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (J = 38.6 Hz), 171.8, 169.1, 167.1, 148.6, 146.2, 142.6, 136.8, 131.0, 129.1 (J = 15.9 Hz), 128.3, 128.2, 127.5, 127.3, 124.2, 123.4 (J = 3.2 Hz), 122.4 (J = 6.3 Hz), 121.9, 117.6 (J = 19.2 Hz), 107.4, 74.7, 74.3, 74.2, 65.0, 63.2, 63.1, 60.9, 58.9, 45.3, 45.2, 26.5, 13.9, 13.8, 13.4; IR (KBr) 3457, 3387, 3079, 2976, 1718, 1629, 1608, 1489, 771 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{34}FN_3O_8 + Na)^+$ requires m/z 666.2222, found m/z 666.2217; enantiomeric excess 92%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.82 min (minor), t_R = 15.82 min (major).

Compound ***4ab:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 90% (57.5 mg); >95:5 dr; white solid; mp 81−82 °C; $[\alpha]_D^{20}$ = +88.4 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.50−7.46 (m, 1H), 7.21−7.16 (m,, 3H), 7.14−7.09 (m, 1H), 7.08−7.04 (m, 1H), 7.03−6.97 (m, 1H), 6.86−6.79 (m, 2H), 6.59 (d, J = 7.9 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 5.13 (s, 1H), 5.06 (d, J = 15.8 Hz, 1H), 4.59−4.42 (m, 3H), 4.41−4.30 (m, 2H), 4.15 (d, J = 15.8 Hz, 1H), 3.87−3.75 (m, 2H), 2.90 (s, 3H), 2.32 (s, 3H), 1.39−1.32 (m, 6H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.4, 171.5, 169.0, 167.4, 141.9, 140.6, 135.6, 131.4, 129.5, 129.4, 129.3, 128.5, 127.6, 127.3, 127.0, 126.8, 124.2, 121.9, 108.8, 107.0, 75.3, 74.4, 64.6, 62.3, 62.9, 60.8, 58.4, 43.7, 26.4, 21.3, 14.0, 13.9, 13.4; IR (KBr) 3432, 3278, 2981, 2937, 1730, 1613, 1500, 1470, 1357, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{37}N_3O_8 + Na)^+$ requires m/z 662.2473, found m/z 662.2471; enantiomeric excess 88%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.97 min (minor), t_R = 13.22 min (major).

Compound ***4mc:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 64% (43.3 mg); >95:5 dr; white solid; mp 163−165 °C; $[\alpha]_D^{20}$ = +59.5 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.9 Hz, 1H), 7.31−7.27 (m, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.21−7.15 (m, 3H), 7.01−6.86 (m, 4H), 6.58 (d, J = 8.3 Hz, 1H), 5.14 (s, 1H), 4.96 (d, J = 15.2 Hz, 1H), 4.57−4.26 (m, 6H), 3.88−3.71 (m, 2H), 2.81 (s, 3H), 1.34 (q, J = 7.2 Hz, 6H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (J = 5.1 Hz), 171.4, 169.0, 166.8, 147.4 (J = 242.2 Hz), 141.2, 136.7, 130.7, 129.4, 128.9, 128.3, 128.2 (J = 8.7 Hz), 127.5, 127.4, 127.4, 127.3, 125.8, 123.3 (J = 3.2 Hz), 122.5 (J = 6.3 Hz), 117.7 (J = 9.6 Hz), 108.2, 74.5, 74.1, 74.0, 64.5, 63.3, 63.2, 61.1, 58.5, 45.3, 45.2, 26.6, 13.9, 13.8, 13.5; IR (KBr) 3442, 3288, 3061, 2935, 1731, 1612, 1567, 1489, 1473, 737 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{33}ClFN_3O_8 + Na)^+$ requires m/z 700.1832, found m/z 700.1877; enantiomeric excess 86%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.57 min (minor), t_R = 9.39 min (major).

Compound ***4md:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 90% (60.6 mg); >95:5 dr; white solid; mp 151−153 °C; $[\alpha]_D^{20}$ = +128.9 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.5 Hz, 1H), 7.25−7.21 (m, 1H), 7.21−7.14 (m, 3H), 7.04−6.85 (m, 4H), 6.61−6.51 (m, 1H), 6.24 (d, J = 2.3 Hz, 1H), 5.13 (s, 1H), 4.98 (d, J = 15.2 Hz, 1H), 4.60 (s, 1H), 4.54−4.38 (m, 3H), 4.37−4.25 (m, 2H), 3.80 (s, 3H), 3.80−3.59 (m, 2H), 2.81 (s, 3H), 1.40−1.25 (m,6H), 0.74 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (J = 6.7 Hz), 171.7, 169.2, 167.2, 160.7, 147.3 (J = 241.9 Hz), 144.0, 136.8, 131.1 (J = 2.1 Hz), 129.9, 128.3, 128.2, 127.4, 127.4, 127.3, 123.2 (J = 3.1 Hz), 122.4 (J = 6.3 Hz), 117.5 (J = 19.3 Hz), 115.9, 104.9, 95.8, 74.6, 74.3, 74.2, 64.7, 63.1, 63.0, 60.9, 58.8, 55.3, 45.3, 45.2, 26.5, 13.9, 13.8, 13.5; IR (KBr) 3419, 3292, 2961, 2851, 1732, 1651, 1597, 1471, 1280, 702 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{36}FN_3O_9 + Na)^+$ requires m/z 696.2328, found m/z 696.2350; enantiomeric excess: 92%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 10.09 min (minor), t_R = 18.46 min (major).

Compound ***4me:*** flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 87% (62.7 mg); >95:5 dr; white solid; mp 138−140 °C; $[\alpha]_D^{20}$ = +135.5 (*c* 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 1H), 7.25−7.19 (m, 4H), 7.19−7.15 (m, 1H), 7.00−6.89 (m, 4H), 6.74 (d, J = 1.7 Hz, 1H), 5.14 (s, 1H), 4.93 (d, J = 15.1 Hz, 1H), 4.57−4.51 (m, 2H), 4.50−4.38 (m, 2H), 4.37−4.26 (m, 2H), 3.80−3.69 (m, 2H),

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2.75 (s, 3H), 1.31 (t, J = 7.1 Hz, 6H), 0.75 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (J = 15.4 Hz), 171.5, 169.2, 166.9, 148.4 (J = 242.1 Hz), 143.8, 136.7, 130.8 (J = 2.0 Hz)„ 130.4, 128.4, 128.1 (J = 8.5 Hz)„ 127.7, 127.6, 127.5, 124.7, 123.3 (J = 3.2 Hz), 123.1, 122.9, 122.5 (J = 6.3 Hz), 117.7 (J = 19.3 Hz), 111.1, 74.5, 74.2, 74.1, 64.7, 63.3, 63.2, 61.1, 58.6, 45.4, 45.3, 26.6, 14.0, 13.8, 13.5; IR (KBr) 3417, 3279, 3067, 2974, 1733, 1606, 1541, 1490, 737 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{33}BrFN_3O_8 + Na)^+$ requires m/z 744.1327, found m/z 744.1314; enantiomeric excess 94%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.66 min (minor), t_R = 12.55 min (major).

Compound ***4mf****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 85% (57.6 mg); >95:5 dr; white solid; mp 144−145 °C; $[\alpha]_D^{20}$ = +133.7 (c 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1H), 7.25−7.17 (m, 4H), 7.05−7.00 (m, 1H), 6.99−6.88 (m, 4H), 6.60 (d, J = 1.9 Hz, 1H), 5.15 (s, 1H), 4.94 (d, J = 15.1 Hz, 1H), 4.54 (d, J = 14.8 Hz, 2H), 4.51−4.38 (m, 2H), 4.37−4.25 (m, 2H), 3.81−3.68 (m, 2H), 2.77 (s, 3H), 1.37−1.27 (m, 6H), 0.75 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (J = 29.4 Hz), 171.5, 169.2, 166.9, 147.4 (J = 242.1 Hz), 143.7, 136.7, 135.0, 130.8 (J = 2.0 Hz), 130.1, 128.4, 128.1 (J = 8.5 Hz), 127.7, 127.6, 127.5, 123.3 (J = 3.2 Hz), 122.6 (J = 6.2 Hz), 122.5, 121.8, 117.7 (J = 19.4 Hz), 108.3, 74.5, 74.3, 74.2, 64.6, 63.3, 63.1, 61.1, 58.6, 45.4, 45.3, 26.6, 13.9, 13.8, 13.5; IR (KBr) 3437, 3279, 2975, 2926, 1732, 1610, 1557, 1495, 737 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{33}ClFN_3O_8 + Na)^+$ requires m/z 700.1832, found m/z 700.1826; enantiomeric excess 92%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 6.58 min (minor), t_R = 12.47 min (major).

Compound ***4ag****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 82% (52.4 mg); >95:5 dr; white solid; mp 143−145 °C; $[\alpha]_D^{20}$ = +118.7 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.66 (m, 1H), 7.43 (d, J = 7.1 Hz, 1H), 7.24−7.16 (m, 3H), 7.15−7.07 (m, 1H), 7.02−6.92 (m, 3H), 6.92−6.86 (m, 2H), 6.52 (d, J = 7.7 Hz, 1H), 5.23 (s, 1H), 5.01 (d, J = 15.8 Hz, 1H), 4.55−4.40 (m, 2H), 4.38−4.26 (m, 2H), 4.14 (d, J = 15.8 Hz, 1H), 3.84−3.68 (m, 2H), 3.19 (s, 3H), 2.44 (s, 3H), 1.36−1.29 (m, 6H), 0.72 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.9, 171.8, 169.1, 167.4, 141.6, 140.5, 135.7, 132.9, 129.4, 128.5, 127.9, 127.4, 127.2, 126.9, 126.6, 125.2, 121.8, 121.7, 118.5, 108.9, 75.0, 74.5, 64.5, 63.1, 63.0, 60.8, 59.1, 43.8, 30.2, 19.3, 14.00, 13.9, 13.4; IR (KBr) 3477, 3289, 3029, 2973, 1732, 1609, 1488, 1468, 746 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{37}N_3O_8 + Na)^+$ requires m/z 662.2473, found m/z 662.2482; enantiomeric excess 88%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 10.54 min (minor), t_R = 18.50 min (major).

Compound ***4mh****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 62% (41.0 mg); >95:5 dr; pale yellow solid; mp 134−136 °C; $[\alpha]_D^{20}$ = +79.3 (c 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.67 (m, 1H), 7.24−7.20 (m, 4H), 7.04−6.98 (m, 2H), 6.98−6.91 (m, 4H), 5.26 (d, J = 30.1 Hz, 1H), 5.00 (t, J = 17.5 Hz, 1H), 4.65−4.39 (m, 4H), 4.36−4.26 (m, 2H), 3.84−3.64 (m, 2H), 3.26−2.87 (m, 3H), 1.35−1.29 (m, 6H), 0.73 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (J = 29.0 Hz), 171.7, 168.0 (J = 215.9 Hz), 148.5, 146.2 (J = 10.6 Hz), 136.7, 130.7, 130.7, 129.4 (J = 8.3 Hz), 128.5, 128.1 (J = 8.6 Hz), 127.6, 127.4 (J = 1.5 Hz), 127.0 (J = 2.6 Hz), 125.0 (J = 3.2 Hz), 123.4 (J = 3.2 Hz), 122.5 (J = 6.3 Hz), 122.2 (J = 6.2 Hz), 117.7 (J = 19.3 Hz), 117.0 (J = 18.7 Hz), 74.5, 74.3, 74.2, 65.2 (J = 2.1 Hz), 63.3, 63.1, 61.0, 59.0, 45.3, 45.3, 29.1, 29.0, 14.0, 13.8, 13.4; IR (KBr) 3487, 3281, 3068, 2982, 2361, 1732, 1629, 1598, 1488, 734 cm^{-1}; ESI FTMS exact mass calcd for $(C_{35}H_{33}F_2N_3O_8 + Na)^+$ requires m/z 684.2128, found m/z 684.2150; enantiomeric excess 86%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 7.37 min (minor), t_R = 15.00 min (major).

Compound ***4mi****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 80% (54.1 mg); >95:5 dr; yellow solid; mp 155−157 °C; $[\alpha]_D^{20}$ = +168.4 (c 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.1 Hz, 1H), 7.49−7.43 (m, 2H), 7.42−7.34 (m, 2H), 7.25−7.17 (m, 3H), 7.16−7.09 (m, 4H), 7.07−7.00 (m, 1H), 6.99−6.92 (m, 1H), 6.89−6.80 (m, 2H), 6.40 (d, J = 7.6 Hz, 1H), 6.31 (s, 1H), 4.93 (d, J = 12.8 Hz, 2H), 4.57−4.41 (m, 3H), 4.40−4.23 (m, 2H), 2.37 (s, 3H), 1.32−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 172.4, 172.1 (J = 10.8 Hz), 169.5, 147.5 (J = 242.0 Hz), 141.7, 136.9, 136.8, 133.0, 131.7 (J = 2.1 Hz), 130.6, 129.1, 128.6, 128.3, 128.2, 128.1, 127.5, 127.4, 127.3, 123.4 (J = 3.1 Hz), 123.3, 122.4 (J = 6.3 Hz), 121.9, 117.4 (J = 19.3 Hz), 107.3, 75.4, 75.1, 75.0, 66.4, 63.2, 63.1, 61.2, 45.3, 45.2, 26.0, 13.9, 13.8; IR (KBr) 3453, 3276, 3062, 2927, 1732, 1611, 1597, 1492, 752 cm^{-1}; ESI FTMS exact mass calcd for $(C_{39}H_{34}FN_3O_7 + Na)^+$ requires m/z 698.2273, found m/z 698.2272; enantiomeric excess 98%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.07 min (minor), t_R = 12.42 min (major).

Compound ***4mj****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 92% (54.8 mg); >95:5 dr; white solid; mp 93−95 °C; $[\alpha]_D^{20}$ = −224.8 (c 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 1H), 7.25−7.18 (m, 4H), 7.17−7.08 (m, 3H), 6.91−6.78 (m, 3H), 6.63 (d, J = 7.8 Hz, 1H), 4.96−4.79 (m, 2H), 4.71 (s, 1H), 4.50−4.37 (m, 4H), 4.10 (s, 1H), 3.05 (s, 3H), 1.42−1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7 (J = 5.5 Hz), 167.9, 166.7, 148.1, 145.7, 143.7, 136.1, 130.6 (J = 4.4 Hz), 130.1, 128.5, 127.5, 127.4, 125.8 (J = 3.1 Hz), 123.5, 123.4 (J = 6.5 Hz), 120.6 (J = 1.6 Hz), 120.1, 119.0 (J = 19.4 Hz), 116.1, 108.2, 75.0, 73.9, 73.8, 63.6, 63.2, 59.8, 45.3, 45.2, 42.3, 26.2, 14.1, 14.0; IR (KBr) 3467, 3255, 3021, 2928, 2246, 1732, 1612, 1531, 1472, 757 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{29}FN_4O_6 + Na)^+$ requires m/z 619.1963, found m/z 619.1954; enantiomeric excess 96%, determined by HPLC (Daicel Chiralpak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 9.14 min (minor), t_R = 7.48 min (major).

Compound ***4nj****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 96% (48.6 mg); >95:5 dr; white solid; mp 222−223 °C; $[\alpha]_D^{20}$ = −129.1 (c 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.30−7.26 (m, 1H), 7.11−7.04 (m, 2H), 6.89−6.78 (m, 2H), 6.64 (d, J = 7.8 Hz, 1H), 4.70 (s, 1H), 4.50−4.33 (m, 4H), 4.07 (s, 1H), 3.05 (s, 3H), 1.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 174.6, 167.8, 166.7, 146.5 (J = 243.5 Hz), 143.8, 130.3, 129.2 (J = 12.8 Hz), 127.3, 125.9 (J = 3.3 Hz), 123.6, 123.2 (J = 5.8 Hz), 120.5 (J = 3.4 Hz), 120.1, 117.8 (J = 16.8 Hz), 115.9, 108.2, 74.4, 74.3, 63.6, 63.5, 59.7, 42.0, 26.1, 14.0, 13.9; IR (KBr) 3450, 3310, 3066, 2914, 1731, 1647, 1557, 1530, 1489, 757 cm^{-1}; ESI FTMS exact mass calcd for $(C_{26}H_{23}FN_4O_6 + Na)^+$ requires m/z 529.1499, found m/z 529.1487; enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak OD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 8.46 min (minor), t_R = 13.23 min (major).

Compound ***4oj****:* flash column chromatography eluent, petroleum ether/ethyl acetate = 5/1; reaction time = 36 h; yield: 86% (54 mg); 55:45 dr (inseparable diastereomers); white solid; mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 2.2 Hz, 1.2H), 8.22−8.17 (m, 1H), 8.04−8.00 (m, 1.2H), 7.96−7.92 (m, 1H), 7.68 (d, J = 7.6 Hz, 1.2H), 7.47 (d, J = 2.3 Hz, 1H), 7.40−7.27 (m, 8H), 7.25−7.18 (m, 4H), 6.99−6.87 (m, 4H), 6.73−6.64 (m, 2.4H), 6.58−6.43 (m, 2.4H), 5.49 (s, 1H), 5.16 (d, J = 15.6 Hz, 1H), 5.00 (d, J = 15.9 Hz, 1.2H), 4.81 (s, 1.2H), 4.60 (d, J = 15.9 Hz, 1.2H), 4.51−4.41 (m, 9.8H), 4.12 (s, 1.2H), 3.85 (s, 1H), 3.08 (s, 3.6H), 3.02 (s, 3H), 1.43−1.35 (m, 13.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 175.2, 174.1, 170.2, 168.6, 167.5, 167.2, 166.6, 149.3, 149.1, 143.8, 143.5, 143.1, 142.7, 134.1, 133.6, 130.9, 130.4, 129.0, 128.9, 128.2, 128.0, 127.7, 127.5, 127.3, 127.2, 127.1, 124.2, 124.2, 123.6, 123.5, 123.2, 122.0, 121.0, 119.8, 115.9, 114.9, 109.2, 109.0, 108.8, 108.6, 73.3, 72.6, 71.7, 63.9, 63.8, 63.7, 63.5, 62.7, 59.5, 44.6, 44.1, 41.9, 41.4, 26.7, 26.3, 14.1, 14.0, 13.9, 13.9; IR (KBr) 3415, 3336, 3088, 2982, 1739, 1614, 1522, 1482, 1472, 758 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{29}N_5O_8 +$

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$Na)^+$ requires m/z 646.1913, found m/z 646.1919; enantiomeric excess of major diastereomer 32%, determined by HPLC (Daicel Chiralpak OD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R = 27.28 min (minor), t_R = 34.46 min (major).

■ ASSOCIATED CONTENT

Supporting Information

Details on screening of catalysts and solvents, characterization data (including ^1H and ^{13}C NMR and HPLC spectra) for all products, and single-crystal data of product **4aa**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00708.

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Notes

The authors declare no competing financial interest.

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