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Synthesis of a class of chiral-bridged phosphoramidite ligands and their applications in the first iridium-catalyzed asymmetric addition of arylboronic acids to isatins

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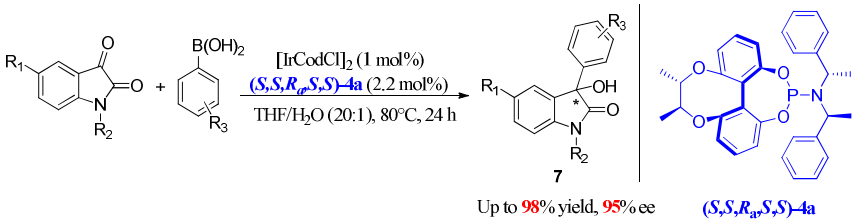


Abstract. A series of novel chiral phosphoramidite ligands based on chiral-bridged biphenyl backbones have been prepared conveniently and characterized. The ligands complexed with $[IrCodCl]_2$ provided the first iridium catalyst system for the asymmetric addition of arylboronic acids to N-protected isatins with high efficiency.

When performed in THF/H_2O at 80℃ with 2 equiv. of the arylboronic acids, the transformations acquired good to excellent results (up to 98% yield and 95% ee).

INTRODUCTION

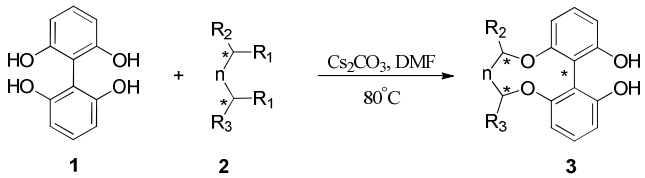
Transition metal-catalyzed asymmetric reactions lie at the core of organic synthesis, in which design and synthesis of efficient chiral ligands plays a key role. Since Monophos was synthesized in 1994[1] and employed in asymmetric addition reaction later,[2] a plenty of phosphoramidite ligands were developed for their easy synthesis, convenient modification and potential applications in many kinds of enantioselective catalytic reactions.[3] Nowadays chiral phosphoramidite compounds have become one of the most widely used ligands.

Chiral 3-substituted oxindoles are common structural motifs which constitute a useful class of compounds that can be found in various biologically active molecules and natural products.[4] A number of successful methods for 3-hydroxyoxindoles have been developed in recent years,[5] and the formation of quaternary carbon centers via addition of arylboronic acids to isatins seems to be one of the most useful methods for efficient construction of this structural scaffold. In 2006，Hayashi and coworkers first reported the asymmetric addition of arylboronic acids to N-protected isatins catalyzed with Rh/(R)-MeO-mop complex, achieving high enantioselectivities and excellent yields. In their paper, a chiral phosphoramidite ligand was also tested, however, the obtained enantioselectivity was only 39% ee.[6] Meanwhile, use of a rhodium/chiral H_8-BINOL-derived phosphoramidite as the catalyst afforded 55% ee in the similar reaction.[7] Recently, several ligands including Me-BIPAM,[8] H_8-BINOL-derived

phosphine-oxazoline ligands,[9] chiral NHC[10] and chiral sulfoxide phosphine[11] complexed with ruthenium, palladium, copper or rhodium were also employed for the catalysis. However, most of the obtained ee values via these cheaper central metal catalytic systems such as Ru or Pd are still lower than those with Rh complex. Relatively economical and efficient catalytic system is warmly expected. Herein, we disclose the development of a new type of chiral phosphoramidite ligands based on chiral-bridged biphenyl backbones[12] and their applications in the first iridium-catalyzed asymmetric addition of arylboronic acids to N-protected isatins. The addition reactions acquired high yields and good to excellent enantioselectivities.

RESULTS AND DISCUSSION

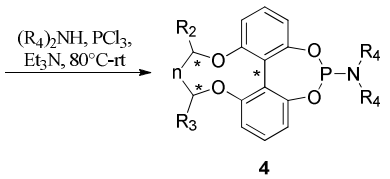
Scheme 1. Synthesis of ligands 4



1 2 3

(*R*)-**2a**: n = 0, R_1 = OMs, R_2 = Me, R_3 = H;
(*R*,*R*)-**2b**: n = 0, R_1 = OMs, R_2, R_3 = Me;
(*S*,*S*)-**2c**: n = 1, R_1 = OTs, R_2, R_3 = Me

(S,R_a)-**3a**: n = 0, R_2 = Me, R_3 = H
(S,S,R_a)-**3b**: n = 0, R_2, R_3 = Me
(R,R,S_a)-**3c**: n = 1, R_2, R_3 = Me



4

(S,S,R_a,S,S)-**4a**: n = 0, R_2, R_3 = Me, R_4 = (*S*)-1-phenylethyl
(S,S,R_a,R,R)-**4b**: n = 0,R_2, R_3 = Me, R_4 = (*R*)-1-phenylethyl
(S,S,R_a)-**4c**: n = 0, R_2, R_3 = Me, R_4 = benzyl
(S,S,R_a)-**4d**: n = 0, R_2, R_3 = Me, R_4 = ^{i}Pr
(S,S,R_a)-**4e**: n = 0, R_2, R_3 = Me, R_4 = Me
(S,R_a)-**4f**: n = 0, R_2 = Me, R_3 = H, R_4 = ^{i}Pr
(R,R,S_a,S,S)-**4g**: n= 1, R_2, R_3 = Me, R_4 = (*S*)-1-phenylethyl
(R,R,S_a,R,R)-**4h**: n= 1, R_2, R_3 = Me, R_4 = (*R*)-1-phenylethyl

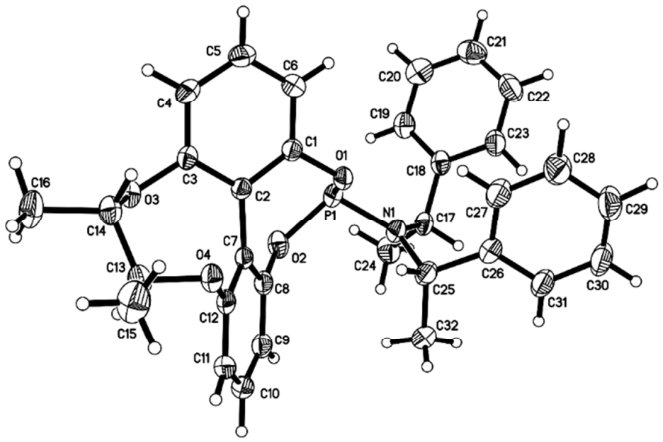
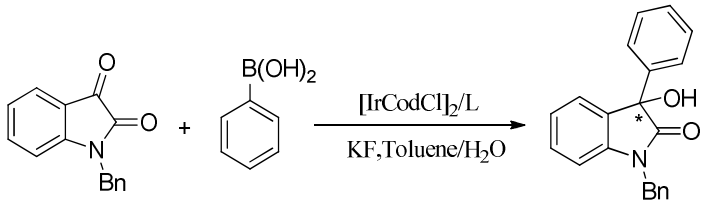


Fig.1. X-ray crystal structure of ligand (*S,S,R*$_a$,*S,S*)-4a (ORTEP drawing at 30% ellipsoid probability).

As shown in Scheme 1, synthesis of ligands **4** was quite simple and robust. The key desymmetrized annulation diphenol intermediates **3a-c** were readily prepared from prochiral 2,2,6,6-tetrahydroxy-biphenyl with different chiral bis(mesylate) or bis(tosylate) by a Williamson synthesis.[13] Following S_N2 substitution reaction mechanism, the central chirality configuration of the ether-linked backbone became reversed from **2**. Meanwhile, perfect chirality transfer from central to axial chirality was performed and products **3a-c** were given in 76%, 53% and 68% yields respectively.[14] Reaction of **3a-c** with phosphorus trichloride yielded corresponding intermediates phosphoryl chlorides first. Subsequent addition of the desired amine to the reaction system in the presence of a base finally acquired the phosphoramidite ligands **4a-d** and **4f-n**. Dimethylamine-derived phosphoramidite ligand (*S,S,R*$_a$)-**4e** was prepared via another reaction of (*S,S,R*$_a$)-**3b** with hexamethylphosphorus triamide (HMPT).[1] Through a single-crystal X-ray diffraction analysis of ligand (*S*,*S*,*R*$_a$,*S*,*S*)-**4a**, all its chiral configurations were confirmed (Fig. 1). It is worthy to note that these ligands are stable enough and can be purified by common silica gel column

chromatography without special precaution to water or air.

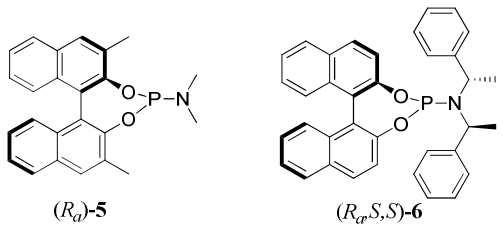
Table 1. Metal Sources and Ligands Screening[a]



7a

Entry	Metal	Ligand	Yield (%)[b]	Ee (%)[c]
1	$Rh(Cod)_2BF_4$	(*S,S,R$_a$,S,S*)-**4a**	86	8
2	$Rh(Cod)_2Cl_2$	(*S,S,R$_a$,S,S*)-**4a**	69	14
3	$[RhNBDCl]_2$	(*S,S,R$_a$,S,S*)-**4a**	86	2
4	$Pd(OAc)_2$	(*S,S,R$_a$,S,S*)-**4a**	81	8
5	$[IrCodCl]_2$	(*S,S,R$_a$,S,S*)-**4a**	88	84
6	$[IrCodCl]_2$	(*S,S,R$_a$,R,R*)-**4b**	87	15
7	$[IrCodCl]_2$	(*S,S,R$_a$*)-**4c**	53	17
8	$[IrCodCl]_2$	(*S,S,R$_a$*)-**4d**	61	21
9	$[IrCodCl]_2$	(*S,S,R$_a$*)-**4e**	75	10
10	$[IrCodCl]_2$	(*S,R$_a$*)-**4f**	84	13
11	$[IrCodCl]_2$	(*R,R,S$_a$,S,S*)-**4g**	48	55
12	$[IrCodCl]_2$	(*R,R,S$_a$,R,R*)-**4h**	43	76
13	$[IrCodCl]_2$	(*R$_a$*)-**5**	32	6
14	$[IrCodCl]_2$	(*R$_a$,S,S*)-**6**	83	81

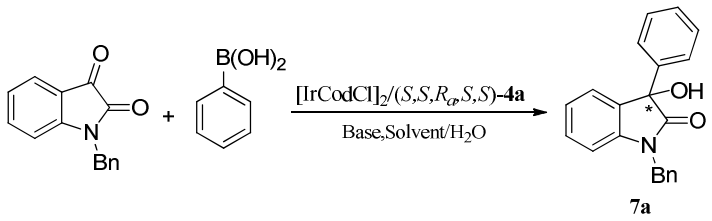
[a] Reaction conditions: 0.2 mmol of N-benzyl isatin, phenylboronic acid (2 equiv.), $[IrCodCl]_2$ (1 mol%), ligand (2.2 mol%), KF (2 equiv.), 50℃, 48 h, solvent: THF-H_2O (2 mL-0.1 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC.



(*R$_a$*)-**5** (*R$_a$,S,S*)-**6**

Fig. 2. Ligands (*R*)-**5** and (*R$_a$,S,S*)-**6**.

Table 2. Solvents, Bases, and Temperature Screening[a]



7a

Entry	Metal	Base	Solvent	Yield(%)[b]	Ee(%)[c]
1	$[IrCodCl]_2$	KF	$EtOH/H_2O$	76	90
2	$[IrCodCl]_2$	KF	$^{i}PrOH/H_2O$	66	90
3	$[IrCodCl]_2$	KF	$^{t}BuOH/H_2O$	93	88
4	$[IrCodCl]_2$	KF	THF/H_2O	95	91
5	$[IrCodCl]_2$	KF	$MTBE/H_2O$	97	88
6	$[IrCodCl]_2$	KF	DCM/H_2O	45	42.
7	$[IrCodCl]_2$	KF	$Dioxane/H_2O$	58	79
8	$[IrCodCl]_2$	KF	DME/H_2O	92	86
9	$[IrCodCl]_2$	KF	DMF/H_2O	28	71
10	$[IrCodCl]_2$	KF	$xylene/H_2O$	96	83
11	$[IrCodCl]_2$	KF	THF	37	90
12	$[IrCodCl]_2$	HKF	THF/H_2O	81	90
13	$[IrCodCl]_2$	K_2CO_3	THF/H_2O	88	91
14	$[IrCodCl]_2$	KOH	THF/H_2O	83	51
15	$[IrCodCl]_2$	K_3PO_4	THF/H_2O	64	72
16	$[IrCodCl]_2$	$KO^{t}Bu$	THF/H_2O	trace	ND[d]
17	$[IrCodCl]_2$	CsF	THF/H_2O	31	90
18	$[IrCodCl]_2$	Cs_2CO_3	THF/H_2O	54	79
19	$[IrCodCl]_2$	Et_3N	THF/H_2O	39	88
20	$[IrCodCl]_2$	$LiOH\ H_2O$	THF/H_2O	73	65
21	$[IrCodCl]_2$	DIPEA	THF/H_2O	<10	ND
22	$[IrCodCl]_2$	KF	THF/H_2O	27	93[e]
23	$[IrCodCl]_2$	KF	THF/H_2O	50	88[f]
24	$[IrCodCl]_2$	KF	THF/H_2O	64	90[g]
25	$[IrCodCl]_2$	KF	THF/H_2O	82	90[h]
26	$[IrCodCl]_2$	KF	THF/H_2O	98	93[i]
27	--	KF	THF/H_2O	--	--[j]
28	$[IrCodCl]_2$	KF	THF/H_2O	23	0[k]
29	$[IrCodCl]_2$	--	THF/H_2O	17	67[l]

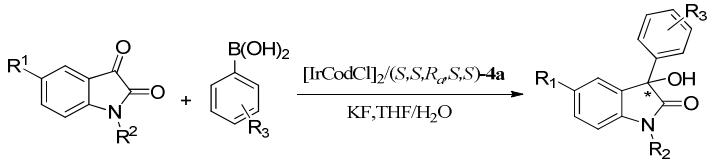
[a] Reaction conditions: 0.2 mmol of N-benzyl isatin, phenylboronic acid (2 equiv.), $[IrCodCl]_2$ (1 mol%), ligand (2.2 mol%), base (2 equiv.), 50℃, 48 h, solvent-H_2O (2 mL-0.1 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Not determined. [e] 50℃, 48 h, 1 equiv. base. [f] 50℃, 48 h, 3 equiv. base. [g] 60℃ 24 h, 1 equiv. base. [h] 70℃, 24 h, 1 equiv. base. [i] 80℃, 24 h, 1 equiv. base. [j] $[IrCodCl]_2$ was not used. [k] Ligand was not used. [l] Base was not used.

After acquiring the new type of ligands **4**, we turned into investigation on the asymmetric addition reaction of N-protected isatin and phenylboronic acid. At first,

complexes of ligand (*S,S,R*$_a$,*S,S*)-**4a** with different metal sources were examined for the reaction in the presence of 2.0 equiv. of KF as base at 50°C (Table 1, entries 1-5). $[IrCodCl]_2$ as the metal source afforded the best result with the yield up to 88% and 84% ee (Table 1, entry 5). In contrast, both palladium- and rhodium-catalyzed reaction with this ligand showed comparable activities but much lower enantioselectivities (Table 1, entries 1-4). To gain insight into this catalytic system, we then tested the rest of ligands (**4b-4h**) complexed with $[IrCodCl]_2$ in the reaction. In comparison with phosphoramidite (*S,S,R*$_a$,*S,S*)-**4a** bearing a highly bulky bis[(*S*)-1-phenylethyl]amine, ligand (*S,S,R*$_a$,*R,R*)-**4b** possessing a bis[(*R*)-1-phenylethyl]-amine counterpart provided a slight decrease in the yield and much poorer enantiomeric excess (Table 1, entry 5 vs 6). This may be due to the considerable effects of matching/mismatching between stereochemical elements of the chiral amine and axial chirality in the ligands.[15] Similar phenomenon also occurred in the reaction for ligands (*R,R,S*$_a$,*S,S*)-**4g** and (*R,R,S*$_a$,*R,R*)-**4h** (Table 1, entries 11 vs 12). Analysizing the catalytic results, we found that axial chirality contrary to the central chiralities of the amine was the matched configuration. Ligands (*S,S,R*$_a$)-**4c-4e** only provided moderate yields and very low ee's of the phenyl-adduct (Table 1, entries 7-9). The results indicated that both larger steric hindrance and proper central chirality in the amine unit of the phosphoramidite ligand led to higher enantioselection. Ligand (*S,R*$_a$)-**4f** derived from enantiomerically pure (*S*)-1,2-propanediol as the auxiliary shows two signals in ^{31}P NMR, because of the two possible diastereomers caused by the phosphorus centre and the C_1 symmetrical

propyldioxy backbone.[16] It also gave low enantioselectivity in spite of high yield (Table 1, entry 10). As a reference, we also used Feringa's (*R*)-BINOL-backbone ligands (R_a)-**5** and (R_a,*S*,*S*)-**6** (Fig. 2) to this model reaction. However, the former yielded a disappointing result (Table 1, entry 13). The latter provided a slight drop in the yield and enanoselectivity in comparison with ligand (*S*,*S*,R_a,*S*,*S*)-**4a** (Table 1, entries 14 vs 5), and ligand (*S*,*S*,R_a,*S*,*S*)-**4a** was shown to be the most effective for the arylation reaction. To improve the reaction, solvents, bases and temperature were further optimized, and the results are outlined in Table 2. Conditional experiments showed that THF, $[IrCodCl]_2$, and KF were the best combination for this reaction. It is noticed that, our system does require adding water as a protic source. Without water the yield of arylation product decreased dramatically from 95% to 37% (Table 2, entries 4 vs 11). While no ligand existed, $[IrCodCl]_2$ could just catalyze the reaction with low yield and racemic product (Table 2, entry 28). No base added in the reaction also acquired moderate enantioselectivity, however, the yield dropped sharply (Table 2, entry 29). Reaction temperature had little effect on enantiomeric excess of the product but it influenced the yield significantly. When the temperature was raised from 50 ℃ to 80 ℃, the yield increased from 64% to 98% (Table 2, entries 24-26).

Scheme 2. Catalytic asymmetric arylation of isatins with arylboronic acids[a,b,c,d]



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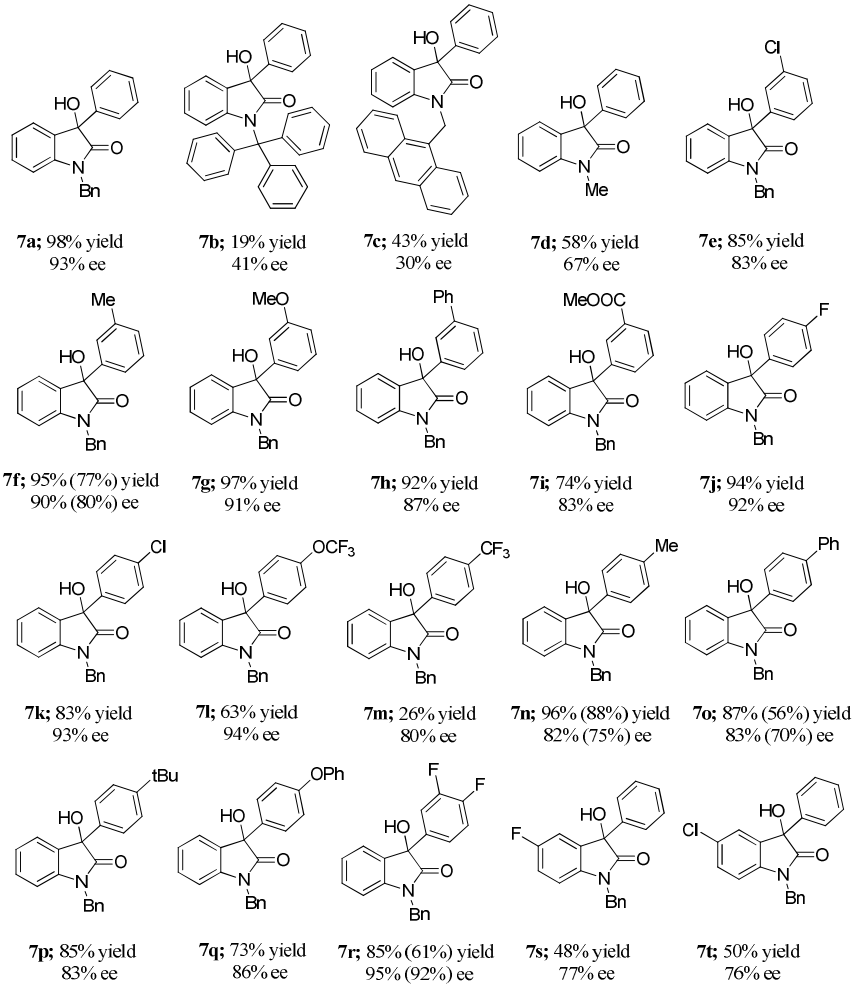

[a] Reaction conditions: 0.2 mmol of N-protected isatins, arylboronic acids (2 equiv.), $[IrCodCl]_2$ (1 mol%), (*S,S,R*$_a$,*S,S*)-**4a** (2.2 mol%), KF (1 equiv.), 80℃, 24 h, solvent: THF-H_2O (2 mL-0.1 mL). [b] Yield of isolated product. [c] The ee values were determined by chiral HPLC. [d] Data in the brackets represent the results with (*R*$_a$,*S,S*)-**6** as the ligand. Other reaction conditions were the same as listed above.

To evaluate the scope of the reaction, we examined different arylboronic acids and N-protected isatins under the optimal reaction conditions, and the results are summarized in Scheme 2. At first, various isatin substrates bearing methyl-, benzyl-, 1-trityl- or 1-anthracen-9-ylmethyl substituent on their nitrogen atoms were selected

for the reactions with phenylboronic acid. Benzyl-protected isatin got the best result, other N-protected isatins only acquired small amounts of the corresponding products with lower ee values (**7a-7d**). Further experiments showed that 5-substituent of the N-benzyl protected isatins on the aromatic rings had a significant influence on this reaction. The addition of phenylboronic acid to N-benzyl-5-chloro or N-benzyl-5-fluoro isatin all obtained lower enantioselectivities and yields in contrast with the reaction of non-substituted N-benzyl-isatin (**7s, 7t**). Moreover, N-benzyl-5-methoxy-isatin and free isatin as the substrates achieved hardly any of arylation products. This displayed the necessity of the N-benzyl protection in the catalytic system. Then, impact of boronic acids on the 1,2-addition reaction was explored. Arylboronic acids bearing weak electron-withdrawing substituents at para- or meta-position afforded corresponding 3-aryl-3-hydroxy-2-oxindole derivatives in high yields with excellent enantioselectivities in the range of 83–95% ees (**7e, 7j-7l** and **7r**), while introduction of strong electron-withdrawing group to the phenyl ring led to somewhat decrease of the yields and enantioselectivities (**7i**, **7m**). Interestingly, meta-electron-donating groups on the arylboronic acids resulted in high yields and enantioselectivities (**7f-7h**). However, para-substituted arylboronic acids possessing electron-donating substituents lowered both the yields and enantioselectivities (**7n-7q**). Besides, another phenomenon was also noted. Using ligand (R_a,*S*,*S*)-**6** instead of (*S*,*S*,R_a,*S*,*S*)-**4a**, the reactions afforded lower ee's and yields (7**f**, 7**n**, 7**o** and 7**r**). This demonstrates as well the effectiveness of our synthetic ligands. We infer that increase of the ligands' rigidity was favorable for the reaction's stereoselectivity and yield. We

have also examined other substrates such as benzaldehyde, 2,2,2-trifluoroacetophenone, 2-oxo-4-phenylbutyric acid ethyl ester, N,N-dimethylsulfamoyl-protected benzaldimine and chalcone. However, those substrates reacted with aryl boronic acid in trace or didn't react under the optimum conditions.

In conclusion, a class of novel chiral-bridged biphenyl phosphoramidite ligands has been synthesized on basis of inducing stereochemistry right in the beginning of the synthetic pathway. Iridium-catalyzed enantioselective addition of arylboronic acids to isatins was successfully realized unprecedentedly along with use of the ligands. A series of chiral 3-aryl-3-hydroxyl-2-oxindoles were afforded in high yields with up to 95% ee. The match of axial and central chiralities in the ligands showed significant influence on the reaction. Further applications of these newly developed phosphoramidite ligands in other asymmetric catalysis are on going in our laboratory.

EXPERIMENTAL SECTION

General Information. Anhydrous 1,4-Dioxane, THF and methyl tert-butyl ether (MTBE) were distilled from sodium and benzophenone before use. Anhydrous toluene, DMF, DME, Et_3N, DCM, pyridine, and xylene were refluxed and distilled from CaH_2. Ethanol, ^{t}BuOH and ^{i}PrOH were distilled over magnesium turnings. Reagents were obtained from commercial sources and used directly without further purification unless otherwise specified. NMR spectra were recorded on a 400 MHz or 300 MHz spectrometer. Optical rotations were measured on a polarimeter and calibrated with pure solvent as a blank. HRMS were recorded on a ESI-Q-TOF mass

spectrometer. Enantiomeric excesses (ee) were determined by HPLC using Daicel Chiralpak OD-H, IA-3 or IC-3 column

Preparation of (*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(2,2')-dihydroxy-(1,1')-biphenyl (*R,R,S*$_a$-3c). To a solution of 2,2',6,6'-tetrahydroxybiphenyl **1** (0.8 g, 3.67 mmol) and Cs_2CO_3 (3.56 g, 10.93 mmol) in 120 mL DMF was added a solution of compound (*S*,*S*)-**2c** (1.00 g, 2.43 mmol) in 100 mL DMF over a period of 4 h at 80 °C under N_2. The resulting suspension was stirred for 24 h at this temperature. The solvent was removed under reduced pressure and the obtained crude product was poured into water and extracted three times with ethyl acetate. The extract was washed successively with 1 N HCl solution, water and brine. The combined organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography to afford a white solid (*R,R,S*$_a$)-**3c**. White solid: 0.47 mg, 68% yield; mp 145-146 °C; $[\alpha]_D^{17}$ +140 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 6.65 – 6.58 (m, 2H), 4.69 – 4.57 (m, 2H), 1.36 (d, *J* = 6.5 Hz, 5H), 1.28 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 153.9, 129.4, 111.1, 110.1, 75.1, 40.8, 22.1. HRMS (ESI) $[M+H]^+$: calcd for $C_{17}H_{19}O_4^+$ 287.1283, found 287.1279.

General Procedure for the Synthesis of 4. Under N_2 atmosphere and at 80℃, a solution of PCl_3 (0.73 mmol), the corresponding amine (0.73 mmol) and triethylamine (3.65 mmol) in toluene (20 mL) was stirred for 6 h, then a solution of diol **3** (0.73 mmol) in THF (10 mL) was added into this solution. The resulting suspension was stirred further for 12 h at room temperature. The precipitated $Et_3N{\cdot}HCl$ salt was

filtered off, and the solvent of the filtrate was removed under vacuum. The residue was then purified by flash column chromatography on silica gel (PE/EA=10/1) to afford product ligand **4**.

(*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-bis((*S*)-1-phenylethyl)amine ((*S,S,R*$_a$,*S,S*)-4a). White solid: 341.1 mg, 89% yield; mp 92-93 °C; $[\alpha]_D^{27}$ +42 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H), 7.16 – 7.04 (m, 11H), 7.00 – 6.87 (m, 3H), 4.67 – 4.48 (m, 2H), 4.02 – 3.86 (m, 2H), 1.73 (d, J = 7.0 Hz, 6H), 1.42 (d, J = 5.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 152.5, 152.4, 151.4, 142.9, 129.7, 129.2, 128.0, 127.7, 126.6, 118.5, 118.2, 117.5, 116.9, 85.4, 85.2, 52.2, 52.0, 18.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.69. HRMS (ESI) $[M+H]^+$: calcd for $C_{32}H_{33}NO_4P^+$ 526.2147, found 526.2155.

(*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta[e, g][1,4])-bis((*R*)-1-phenylethyl)amine ((*S,S,R*$_a$,*R,R*)-4b). White solid: 325.7 mg, 85% yield; mp 83-84 °C; $[\alpha]_D^{27}$ +354 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 8.1 Hz, 1H), 7.22 – 7.10 (m, 12H), 7.01 (d, J = 8.1 Hz, 1H), 6.92 – 6.86 (m, 2H), 4.57 – 4.43 (m, 2H), 4.01 – 3.92 (m, 2H), 1.70 (d, 6H), 1.43 (dd, J = 5.6, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 159.1, 152.8, 152.7, 151.7, 143.2, 129.7, 129.3, 128.0, 128.0, 127.7, 126.6, 118.5, 118.1, 118.1, 117.7, 116.7, 85.4, 85.3, 54.3, 54.2, 22.9, 22.8, 18.8, 18.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ 149.67. HRMS (ESI) $[M+H]^+$: calcd for $C_{32}H_{33}NO_4P^+$ 526.2147, found 526.2162.

(*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-dibenzylamine ((*S,S,R*$_a$)-4c). White solid: 183.8 mg, 73% yield; mp

158-159 °C; $[\alpha]_D^{27}$ +176 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 5H), 7.34 – 7.28 (m, 6H), 7.22 – 7.17 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.33 (dd, J = 15.1, 7.9 Hz, 2H), 3.97 – 3.89 (m, 2H), 3.58 – 3.44 (m, 2H), 1.42 (dd, J = 13.5, 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 158.8, 152.2, 152.1, 151.2, 137.9, 129.7, 128.8, 128.3, 127.2, 118.6, 117.9, 117.9, 117.4, 117.0, 85.3, 85.2, 48.3, 48.1, 18.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 144.30. $[M+H]^+$: calcd for $C_{30}H_{29}NO_4P^+$ 498.1834, found 498.1851.

(*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-diisopropylamine ((*S,S,R*$_a$)-4d). White solid: 282.9 mg, 78 % yield; mp 130-131 °C; $[\alpha]_D^{27}$ +64 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.00 – 6.92 (m, 3H), 4.02 – 3.88 (m, 2H), 3.52 – 3.41 (m, 2H), 1.43 (dd, J = 6.0, 2.7 Hz, 6H), 1.21 (dd, J = 8.7, 6.9 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.9, 152.7, 152.6, 152.1, 129.6, 129.1, 118.2, 118.0, 118.0, 117.4, 116.9, 85.3, 85.2, 44.7, 44.6, 24.5, 24.4, 18.9, 18.9. ^{31}P NMR (162 MHz, $CDCl_3$) δ 142.20. $[M+H]^+$: calcd for $C_{22}H_{29}NO_4P^+$ 402.1834, found 402.1841.

(*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-dimethylamine ((*S,S,R*$_a$)-4e). White solid: 312 mg, 86% yield; mp 134-135 °C; $[\alpha]_D^{27}$ +19 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 8.1 Hz, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.02 – 3.84 (m, 2H), 2.63 (d, J = 9.1 Hz, 6H), 1.43 (dd, J = 5.9, 2.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2,

160.2, 153.7, 129.9, 115.5, 114.5, 114.3, 112.8, 86.1, 34.9, 34.5, 18.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ 147.97. HRMS (ESI) $[M+H]^+$: calcd for $C_{18}H_{21}NO_4P^+$ 346.1203, found 346.1208.

(*R*)-[6,6'-(2*S*-propyldioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-diisopropylamine ((*S,R*$_a$)-4f). White solid:189.2 mg, 67% yield; $[\alpha]_D^{27}$ +47 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 7.31 – 7.27 (m, 1H), 7.08 – 7.04 (m, 1H), 7.02 – 6.93 (m, 3H), 4.46 – 4.40 (m, 1H), 4.37 – 4.26 (m, 1H), 3.79 (dd, J = 22.4, 11.8 Hz, 1H), 3.52 – 3.40 (m, 2H), 1.38 (dd, J = 6.5, 3.4 Hz, 3H), 1.21 (td, J = 7.6, 2.9 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 159.2, 159.0, 158.8, 152.6, 152.5, 152.2, 129.8, 129.7, 129.3, 129.2, 118.6, 118.5, 118.3, 118.3, 118.2, 118.2, 117.6, 117.3, 117.3, 80.3, 78.3, 44.7, 44.6, 24.5, 24.5, 24.4, 17.2, 17.2. ^{31}P NMR (121 MHz, $CDCl_3$) δ 151.56, 151.24. $[M+H]^+$: calcd for $C_{21}H_{27}NO_4P^+$ 388.1672, found 388.1649.

(*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-bis((*S*)-1-phenylethyl)amine ((*R,R,S*$_a$,*S,S*)-4g). White solid: 338.3 mg, 86% yield; mp 102-103 °C; $[\alpha]_D^{27}$ -83 (c = 0.5 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 1H), 7.22 – 7.15 (m, 9H), 7.10 (t, 2H), 7.00 (t, J = 8.5 Hz, 2H), 6.83 (dd, J = 16.0, 8.1 Hz, 2H), 4.79 – 4.66 (m, 2H), 4.53 – 4.44 (m, 2H), 2.09 – 1.89 (m, 2H), 1.70 (d, J = 7.0 Hz, 6H), 1.44 (t, J = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 158.1, 153.0, 152.9, 152.1, 143.3, 129.1, 128.6, 128.0, 128.0, 127.7, 126.5, 116.1, 116.1, 115.9, 113.1, 111.6, 74.8, 74.4, 54.2, 54.1, 41.5, 22.9, 22.8, 22.6, 22.3. ^{31}P NMR (162 MHz, $CDCl_3$) δ 148.28. $[M+K]^+$: calcd for $C_{33}H_{34}NO_4PK^+$ 578.1862,

found 578.1834.

(*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(1,1')-biphenyl-(3,5-Dioxa-4-phosphacyclohepta [e,g][1,4])-bis((*R*)-1-phenylethyl)amine ((*R,R,S*$_a$,*R,R*)-4h). White solid: 330.5 mg, 84% yield; mp 109-110 °C; $[\alpha]_D^{27}$ +59 (c = 1.0 mg/mL,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.13 (bs, 2H), 6.98 (dd, J = 13.6, 8.2 Hz, 2H), 6.89 (t, J = 7.5 Hz, 2H), 4.77 – 4.68 (m, 2H), 4.63 – 4.52 (m, 2H), 2.08 – 1.89 (m, 2H), 1.44 (dd, J = 6.4, 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.9, 152.6, 152.5, 151.9, 143.0, 128.9, 128.5, 128.2, 128.0, 127.7, 127.7, 126.5, 120.8, 118.8, 116.2, 116.2, 115.6, 113.3, 111.8, 74.8, 74.5, 52.2, 52.0, 41.7, 22.6, 22.3. ^{31}P NMR (162 MHz, $CDCl_3$) δ 143.28. $[M+H]^+$: calcd for $C_{33}H_{35}NO_4P^+$ 540.2298, found 540.2299.

General Procedure for the Synthesis of 3-aryl-3-hydroxyoxindoles 7a-7t. Under an argon atmosphere, a solution of $[IrCodCl]_2$ (1.34 mg, 0.01 mmol) and (*S*,*S*,*R*$_a$,*S*,*S*)-**4a** (2.2 mg, 0.021 mmol) in THF (1.0 mL) was stirred for 30 min at room temperature. Isatins (0.20 mmol), arylboronic acids (0.4 mmol) and KF (11.6 mg, 0.1 mmol) were added. The resulting mixture was stirred for 24 h at 80℃. Then the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the desired product.

1-Benzyl-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7a) White solid: 61.7 mg, 98% yield; mp 132-133 °C; $[\alpha]_D^{18}$ +23 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.40 – 7.28 (m, 9H), 7.25 (td, J = 7.8, 1.3 Hz, 1H), 7.07 (td, J = 7.6, 0.9 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.08 (d, J = 15.7 Hz, 1H), 4.87 (d, J = 15.7

Hz, 1H), 3.41 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 140.2, 135.4, 129.7, 128.9, 128.7, 128.3, 127.8, 127.3, 125.4, 125.0, 123.6, 109.8, 44.1. HPLC Daicel Chiralpak OD-H column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 93% ee, 13.9 min (minor), 15.6 min (major).

1-Trityl-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7b) White solid: 17.7 mg, 19% yield; mp 165-166 °C; $[\alpha]_D^{18}$ -27 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.36 (m, 11H), 7.31 – 7.19 (m, 10H), 7.02 – 6.94 (m, 2H), 6.43 – 6.37 (m, 1H), 3.27 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 129.9, 129.1, 128.7, 128.6, 128.3, 128.3, 127.8, 127.0, 125.4, 125.3, 125.0, 124.4, 123.6, 123.0, 116.2, 108.7, 78.0. HPLC Daicel Chiralpak OD-H column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 30% ee, 10.1 min (major), 11.3 min (minor).

1-Anthracen-9-ylmethyl-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7c) White solid: 35.6 mg, 43% yield; mp 169-170 °C; $[\alpha]_D^{31}$ +11 (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.46 – 8.41 (m, 1H), 8.12 – 8.06 (m, 1H), 7.59 – 7.50 (m, 3H), 7.39 – 7.28 (m, 9H), 7.18 – 7.12 (m, 1H), 6.90 – 6.81 (m, 2H), 6.20 (d, *J* = 15.5 Hz, 1H), 5.82 (d, *J* = 15.5 Hz, 1H), 3.28 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 147.1, 138.3, 131.4, 130.8, 129.8, 129.6, 128.5, 127.4, 127.0, 125.3, 125.2, 124.5, 123.3, 119.1, 112.1, 37.9. HPLC Daicel Chiralpak IC-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 15/85, UV 227 nm): 30% ee, 21.7 min (major), 28.0 min (minor).

1-Methyl-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7d) White solid: 27.7 mg, 58% yield; mp 138-139 °C; $[\alpha]_D^{31}$ +52 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 7.35 – 7.28 (m, 3H), 7.15 – 7.09 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 3.36 (s, 1H), 3.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 143.5, 140.1, 131.6, 129.9, 128.6, 128.3, 125.4, 125.0, 123.6, 108.7, 26.5. HPLC Daicel Chiralpak OD-H column (flow rate 0.5 mL/min, *i*PrOH/Hex = 15/85, UV 227 nm): 91% ee, 25.0 min (minor), 31.8 min (major).

1-Benzyl-3-hydroxy-3-(3-chlorophenyl)-1,3-dihydro-indol-2-one (7e) White solid: 59.3 mg, 85% yield; mp 138-139 °C; $[\alpha]_D^{31}$ +24 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.37 – 7.17 (m, 10H), 7.04 (t, *J* = 10.8, 4.2 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.01 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.5 Hz, 1H), 4.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 142.6, 135.5, 134.8, 131.7, 131.2, 130.2, 129.8, 129.0, 128.6, 128.1, 127.5, 127.0, 126.5, 125.1, 124.9, 124.1, 122.9, 111.3, 109.1, 44.5. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 83% ee, 17.5 min (major), 19.5 min (minor).

1-Benzyl-3-hydroxy-3-m-tolyl-1,3-dihydro-indol-2-one (7f) White solid: 62.51 mg, 95% yield; mp 155-156 °C; $[\alpha]_D^{31}$ +54 (c = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.27 – 7.15 (m, 5H), 7.11 (d, *J* = 5.8 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 3.67 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 142.8, 140.4, 138.5, 135.7, 132.1, 129.8, 129.3, 129.1, 128.7, 128.0, 127.6, 126.1, 125.2, 123.8, 122.6, 109.9, 78.3, 44.4, 22.0. HPLC Daicel Chiralpak IA-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 15/85, UV 227 nm): 90% ee, 16.3 min (major), 18.4 min (minor).

1-Benzyl-3-hydroxy-3-(3-methoxyphenyl)-1,3-dihydro-indol-2-one (7g) White solid: 66.9 mg, 97% yield; mp 157-158 °C; $[\alpha]_D^{30}$ +69 (c = 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.27 – 7.18 (m, 4H), 7.06 – 6.99 (m, 2H), 6.91 (d, *J* = 7.7, 1.7 Hz, 1H), 6.84 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 158.5, 141.3, 140.5, 134.2, 130.4, 128.5, 128.4, 127.6, 126.5, 126.1, 123.7, 122.3, 116.3, 112.7, 109.8, 108.5, 76.8, 54.1, 43.0. HPLC Daicel Chiralpak IA-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 10/90, UV 227 nm): 91% ee, 30.5 min (major), 33.8 min (minor).

1-Benzyl-3-hydroxy-3-biphenyl-3-yl-1,3-dihydro-indol-2-one (7h) White solid: 71.9 mg, 92% yield; mp 164-165 °C; $[\alpha]_D^{30}$ +57 (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 5.5 Hz, 1H), 7.58 – 7.52 (m, 3H), 7.47 – 7.42 (m, 4H), 7.40 – 7.31 (m, 7H), 7.30 – 7.23 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.14 (d, *J* = 15.6 Hz, 1H), 4.82 (d, *J* = 15.6 Hz, 1H), 3.86 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 142.6, 141.6, 140.9, 140.8, 135.5, 131.8, 129.8, 129.1, 128.9, 128.7, 127.8, 127.4, 127.4, 127.3, 127.1, 125.0, 124.1, 124.1, 123.7, 109.8, 78.1, 44.1. HRMS (ESI) $[M+Na]^+$: calcd for $C_{27}H_{21}NO_2Na^+$ 414.1470, found 414.1482. HPLC Daicel Chiralpak IC-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 92% ee, 16.6 min (major), 18.9 min (minor).

1-Benzyl-3-hydroxy-3-(3-methoxycarbonylpheny)-1,3-dihydro-indol-2-one (7i) White solid: 55.2 mg, 74% yield; mp 148-149 °C; $[\alpha]_D^{30}$ +55 (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz,

1H), 7.58 – 7.52 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.39 – 7.25 (m, 6H), 7.11 – 7.04 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 3.93 (d, *J* = 3.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 166.7, 155.7, 142.6, 140.7, 135.3, 131.2, 131.2, 130.7, 130.1, 129.8, 129.7, 129.6, 129.0, 128.9, 127.9, 127.3, 126.5, 125.0, 123.8, 121.9, 120.1, 116.3, 110.0, 52.2, 44.2, 29.7. HRMS (ESI) $[M+Na]^+$: calcd for $C_{23}H_{19}NO_4Na^+$ 396.1206, found 396.1207. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 83% ee, 23.4 min (major), 25.7 min (minor).

1-Benzyl-3-hydroxy-3-(4-fluorophenyl)-1,3-dihydro-indol-2-one (7j) White solid: 62.6 mg, 94% yield; mp 145-146 °C; $[\alpha]_D^{30}$ +34 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.36 – 7.23 (m, 7H), 7.13 – 6.99 (m, 3H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 3.73 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 162.7 (d, *J* = 247.3 Hz), 142.6, 136.0, 135.9, 135.3, 131.4, 130.0, 128.9, 127.9, 127.4 (d, *J* = 8.3 Hz), 127.3, 125.0, 123.7, 115.6 (d, *J* = 21.7 Hz), 109.9, 44.1. ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.78. HRMS (ESI) $[M+Na]^+$: calcd for $C_{21}H_{16}FNO_2Na^+$ 356.1057, found 356.1067. HPLC Daicel Chiralpak IA-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 15/85, UV 227 nm): 92% ee, 16.5 min (major), 20.0 min (minor).

1-Benzyl-3-hydroxy-3-(4-chlorophenyl)-1,3-dihydro-indol-2-one (7k) White solid: 65.6 mg, 94% yield; mp 147-148 °C; $[\alpha]_D^{30}$ +25 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 10H), 7.23 – 7.19 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.81 – 6.76 (m, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.35 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 142.6, 139.0, 135.5, 134.4, 131.7, 130.1, 129.1, 128.9, 128.1, 127.5, 127.2, 125.1, 124.0, 110.1, 110.0, 44.4. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 93% ee, 21.6 min (major), 26.2 min (minor).

1-Benzyl-3-hydroxy-3-(4-trifluoromethoxyphenyl)-1,3-dihydro-indol-2-one (7l) White solid: 50.2 mg, 63% yield; mp 109-110 °C; $[\alpha]_D^{30}$ +33 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 5.7 Hz, 2H), 7.39 – 7.25 (m, 7H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 149.1, 142.5, 138.8, 135.2, 131.3, 130.1, 129.0, 127.9, 127.3, 127.1, 125.0, 123.8, 120.4 (q, *J* = 255.9 Hz), 121.0, 110.0, 77.6, 44.1. ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.79. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 94% ee, 17.2 min (major), 21.4 min (minor).

1-Benzyl-3-hydroxy-3-(4-trifluoromethylphenyl)-1,3-dihydro-indol-2-one (7m) White solid: 19.9 mg, 26% yield; mp 145-146 °C; $[\alpha]_D^{30}$ +48 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.31 (m, 5H), 7.31 – 7.23 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 4.30 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 144.2, 142.5, 135.2, 131.3, 130.2 (q, *J* = 32.2 Hz), 130.2, 129.0, 128.0, 127.3, 125.9, 125.6 (q, *J* = 3.8 Hz), 125.0, 124.0 (q, *J* = 270.4 Hz), 123.9, 110.0, 77.9, 44.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.66. HRMS (ESI) $[M+Na]^+$: calcd for $C_{22}H_{16}F_3NO_2Na^+$ 406.1025, found 406.1024. HPLC Daicel Chiralpak IA-3

column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 80% ee, 14.9 min (major), 16.9 min (minor).

1-Benzyl-3-hydroxy-3-p-tolyl-1,3-dihydro-indol-2-one (7n) White solid: 63.1 mg, 96% yield; mp 155-156 °C; $[\alpha]_D^{30}$ +28 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 7H), 7.26 – 7.18 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.94 (dd, *J* = 66.3, 15.6 Hz, 2H), 3.33 (s, 1H), 2.34 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 142.7, 138.2, 137.5, 135.7, 132.2, 129.8, 129.5, 129.1, 127.9, 127.5, 125.6, 125.2, 123.8, 109.9, 78.3, 44.4, 21.6. HPLC Daicel Chiralpak OD-H column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 82% ee, 14.8 min (minor), 16.1 min (major).

1-Benzyl-3-hydroxy-4-biphenyl-4-yl-1,3-dihydro-indol-2-one (7o) White solid: 68.0 mg, 87% yield; mp 169-170 °C; $[\alpha]_D^{30}$ +19 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 4H), 7.53 – 7.49 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.31 (m, 6H), 7.31 – 7.25 (m, 2H), 7.16 – 7.03 (m, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 3.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 142.7, 141.3, 140.6, 139.1, 135.4, 131.5, 129.9, 128.8, 127.9, 127.5, 127.3, 127.1, 125.8, 125.0, 123.7, 109.9, 100.0, 77.9, 44.1. HPLC Daicel Chiralpak IC-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 83% ee, 16.6 min (major), 22.8 min (minor).

1-Benzyl-3-hydroxy-3-(4-tertbutylphenyl)-1,3-dihydro-indol-2-one (7p) White solid: 63.0 mg, 85% yield; mp 135-136 °C; $[\alpha]_D^{30}$ +30 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 0.9 Hz, 3H), 7.34 – 7.28 (m, 6H), 7.26 – 7.23 (m, 1H),

7.22 – 7.18 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.7 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 151.5, 142.8, 137.3, 135.6, 131.8, 129.9, 129.1, 127.9, 127.5, 125.8, 125.3, 123.7, 110.0, 109.9, 78.1, 44.4, 34.9, 31.6. HPLC Daicel Chiralpak IC-3 column (flow rate 0.7 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 83% ee, 52.6 min (major), 55.6 min (minor).

1-Benzyl-3-hydroxy-3-(4-phenoxyphenyl)-1,3-dihydro-indol-2-one (7q) White solid: 59.4 mg, 73% yield; mp 138-139 °C; $[\alpha]_D^{30}$ +30 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 11H), 7.17 – 7.06 (m, 2H), 7.05 – 6.97 (m, 3H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.06 (d, *J* = 15.7 Hz, 1H), 4.86 (d, *J* = 15.7 Hz, 1H), 3.45 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 157.6, 156.7, 142.6, 135.4, 134.7, 131.5, 129.9, 129.8, 128.9, 127.8, 127.3, 127.0, 125.0, 123.6, 119.2, 118.7, 109.8, 44.1. HRMS (ESI) $[M+H]^+$: calcd for $C_{27}H_{22}NO_3^+$ 408.1594, found 408.1598. HPLC Daicel Chiralpak IC-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 86% ee, 20.4 min (major), 23.1 min (minor).

1-Benzyl-3-hydroxy-3-(3,4-fluorophenyl)-1,3-dihydro-indol-2-one (7r) White solid: 59.6 mg, 85% yield; mp 137-138 °C; $[\alpha]_D^{30}$ +39 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 8H), 7.18 – 6.99 (m, 3H), 6.84 (d, *J* = 7.7 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.82 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 151.5 (dd, *J* = 247.3, 12.7 Hz), 149.9 (dd, *J* = 247.6, 12.6 Hz), 142.4, 137.3 (d, *J* = 4.2 Hz), 135.2, 131.2, 130.2, 129.0, 128.0, 127.3, 124.9, 123.9, 121.6 (dd, *J* = 6.5, 3.7 Hz), 117.4 (d, *J* = 17.5 Hz), 115.1 (d, *J* = 18.8 Hz), 110.0, 44.1. ^{19}F NMR (377

MHz, $CDCl_3$) δ -136.44, -136.50, -138.07, -138.13. HRMS (ESI) $[M+Na]^+$: calcd for $C_{21}H_{15}F_2NO_2Na^+$ 374.0963, found 374.0970. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 10/90, UV 227 nm): 95% ee, 26.7 min (major), 32.3 min (minor).

1-Benzyl-5-fluoro-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7s) White solid: 31.9 mg, 48% yield; mp 151-152 °C; $[\alpha]_D^{30}$ +11 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.30 (m, 9H), 7.29 (s, 1H), 7.05 (dd, *J* = 7.6, 2.6 Hz, 1H), 6.94 (td, *J* = 8.8, 2.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.07 (d, *J* = 15.7 Hz, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 3.50 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 159.6 (d, *J* = 241.5 Hz), 139.7, 138.4, 135.1, 133.2 (d, *J* = 7.6 Hz), 129.0, 128.8, 128.6, 127.9, 127.3, 125.2, 116.1 (d, *J* = 23.7 Hz), 113.1 (d, *J* = 24.9 Hz), 110.51 (d, *J* = 7.9 Hz), 44.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.89. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 77% ee, 16.0 min (minor), 17.1 min (major).

1-Benzyl-5-chloro-3-hydroxy-3-phenyl-1,3-dihydro-indol-2-one (7t) White solid: 34.9 mg, 50% yield; mp 157-158 °C; $[\alpha]_D^{30}$ +98 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 9H), 7.30 – 7.28 (m, 2H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.06 (d, *J* = 15.7 Hz, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 3.48 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 141.1, 139.6, 134.9, 133.2, 129.7, 129.0, 129.0, 128.9, 128.7, 128.0, 127.3, 125.5, 125.2, 110.8, 44.2. HPLC Daicel Chiralpak IA-3 column (flow rate 0.5 mL/min, *i*PrOH/Hex = 20/80, UV 227 nm): 76% ee, 18.0 min (major), 21.7 min (minor).

Supporting Information

Crystallographic data (CIF file) of (*S,S,R*$_a$,*S,S*)-**4a**. ^{1}H, ^{13}C and ^{31}P NMR spectra and HPLC chromatograms for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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