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Synthesis of Novel Enantiopure Biphenyl *P*,*N*-Ligands and Application in Palladium-Catalyzed Asymmetric Addition of Arylboronic Acids to *N*-Benzylisatin

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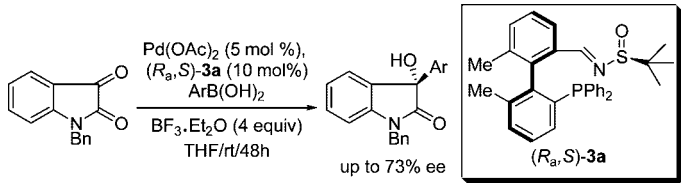

Enantiopure tetra-ortho-substituted biphenyl phosphinoimine ligands (R_a,*S*)-**3** and (S_a,*S*)-**3** were synthesized via multistep reactions. The first asymmetric addition reactions of arylboronic acids to *N*-benzylisatin catalyzed by $Pd(OAc)_2$ and (R_a,*S*)-**3** were studied to provide 3-aryl-3-hydroxyoxindoles in moderate yields and enantioselectivities.

Introduction

Chiral ligands have been considered one of the most interesting topics in organic synthesis over the last two decades owing to their fruitful applications to asymmetric synthesis.[1] Among the thousands of chiral ligands prepared, C_2-symmetric *P*,*P*- and *N*,*N*-ligands represented a major structural class and were well-documented in the literature,[2] while unsymmetric ligands with an axial chirality were paid less attention and remained underdeveloped.[3,4] Recent progress by Pfaltz demonstrated that the unsymmetric *P*,*N*-ligand, phosphinooxazoline **1**[5] (PHOX, Figure 1), showed very promising regio- and enantioselectivities in Pd-catalyzed allylic substitution compared to C_2-symmetric ligands.[6] In that reaction, the mixed *P*,*N*-ligand **1** provided an effective electronic and steric discrimination on the coordinated allylic substrate.

Besides chiral oxazoline and simple amine, chiral sulfinyl imine is also a potential transition-metal coordination unit. This concept has been well practiced by Ellman in the design of the sulfinyl imine *P*,*N*-ligand **2** (Figure 1).[7] Inspired by Ellman's successful ligand design and the fact that a variety of ligands with an axially chiral biaryl framework are widely observed to produce excellent performance in asymmetric catalysis,[8] we envisioned that novel biphenyl sulfinyl imine *P*,*N*-ligands with both sulfur chirality and axial chirality should provide a more rigid asymmetric environment for the enantioselective discrimination on a prochiral substrate. Furthermore, axially chiral resolution of such biphenyl sulfinyl imine *P*,*N*-ligands would be easily achieved by incorporation of an aldehyde precursor with chiral *tert*-butylsulfinamide (TBSA). In this paper, we

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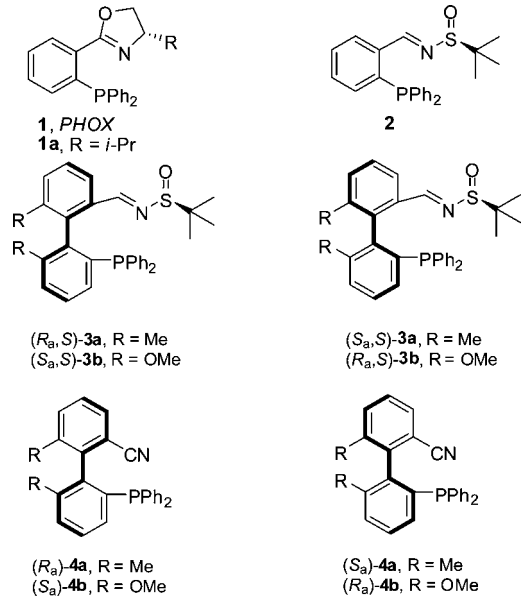


FIGURE 1. Unsymmetric *P*,*N*-ligands **1**−**4**.

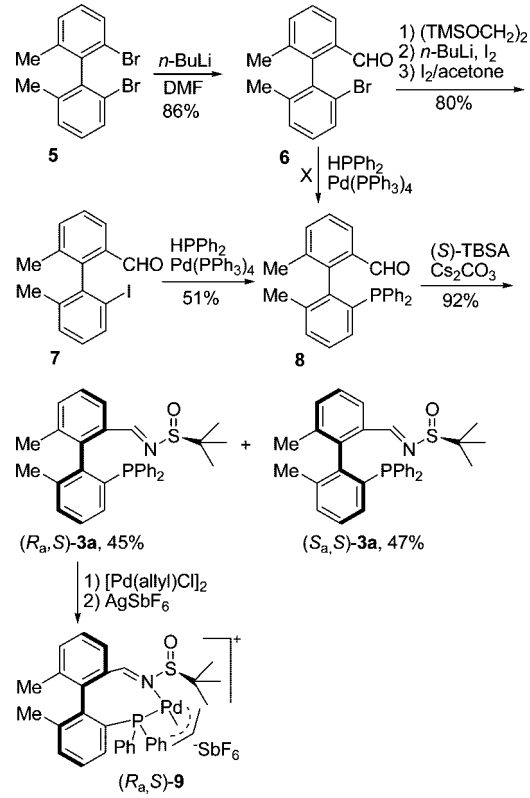
report the synthesis of enantiopure tetra-ortho-substituted biphenyl phosphinoimine ligands **3**, phosphinonitrile ligands **4**, and application in the palladium-catalyzed asymmetric addition of arylboronic acids to *N*-benzylisatin (Figure 1).

Results and Discussion

The synthesis of chiral ligand **3** was initiated from 6,6′-dimethylbiphenyl-2,2′-dibromine **5**[9] (Scheme 1). Bromine−lithium exchange by treatment of dibromine **5** with 1.1 equiv of *n*-BuLi at −78 °C and subsequent addition of dry DMF afforded formaldehyde **6** in an 86% yield. Unfortunately, initial attempts to direct conversion of **6** to diphenylphosphine **8** via cross-coupling reaction of **6** with diphenylphosphine by employing $Pd(PPh_3)_4$ as a catalyst were unsuccessful under various conditions.[10] After conversion of aryl bromide **6** to aryl iodide **7** in a three-step reaction of protection, halogen exchange, and deprotection, we were able to isolate diphenylphosphine **8** in a 51% yield via a cross-coupling reaction of **7** with diphenylphosphine under microwave-assisted conditions within 1 h in DMF. Microwave heating greatly promoted the reaction, while at least 4 days were needed to complete the cross-coupling reaction under classical conditions in DMF or toluene. As anticipated and pioneered by Lin and Xu,[11] axially chiral resolution of sulfinyl imine (R_a,*S*)-**3a** and (S_a,*S*)-**3a** was readily achieved in high yield by the condensation of aldehyde **8** with (*S*)-TBSA using Cs_2CO_3 as a condensation reagent.[12] Diastereomers (R_a,*S*)-**3a** and (S_a,*S*)-**3a** were easily separated by silical gel chromatography (R_f 0.40 for (R_a,*S*)-**3a**, R_f 0.36 for (S_a,*S*)-**3a**, eluted with ethyl acetate/petroleum (1:8)).

In order to elucidate the absolute configuration of axial chirality in (R_a,*S*)-**3a**, an eight-membered *P*,*N*-chelate palladium complex (R_a,*S*)-**9** was prepared by reaction of the less polar

SCHEME 1. Synthesis of Chiral Ligand 3a



diastereomer (R_a,*S*)-**3a** with $[Pd(allyl)Cl]_2$, followed by counterion exchange of Cl^- with SbF_6^- (Scheme 1). The X-ray crystallographic analysis of (R_a,*S*)-**9**[13] unambiguously confirms the absolute configuration of the less polar diastereomer (R_a,*S*)-**3a** with *R* axial chirality.

A methoxy group is the most frequently used electron-donating substituent in studies of the electronic effect of biaryl ligands on asymmetric catalysis.[14] Having accomplished the enantiopure **3a**, we then explored the synthesis of methoxy-substituted biphenyl phosphinoimine **3b** from the easily prepared 6,6′-dimethoxybiphenyl 2,2′-diiodide **10**[15] (Scheme 2). Direct introduction of a formaldehyde group on the phenyl ring of **10** to form aldehyde **13** by iodide−lithium exchange and DMF addition encountered with an extremely low yield (<8%) due to the unsuccessful first step of iodide−lithium exchange. A large amount of **10** remained unchanged after the reaction. Alternative transformation of iodide in **10** to cyanide or carbonamide by transition-metal-catalyzed cyanization[16] and aminocarbonylation[17] also failed. The reason for this unsuccessful reaction was probably ascribed to the electron-rich characteristics of the phenyl ring with stronger electron-donating methoxy groups. Theoretically, localized dispersion of the electronic density in the phenyl ring of **11** by forming lithium

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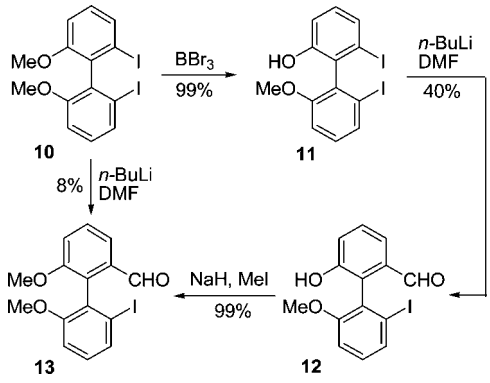
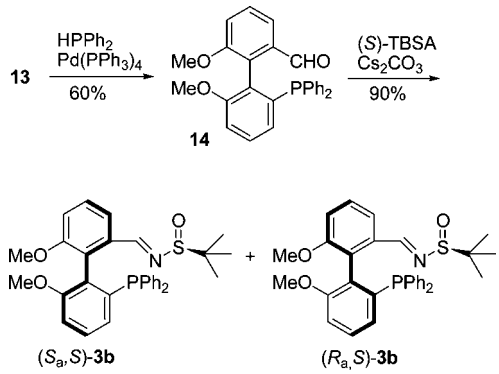
SCHEME 2. Synthesis of Formaldehyde 13



SCHEME 3. Synthesis of Chiral Ligand 3b



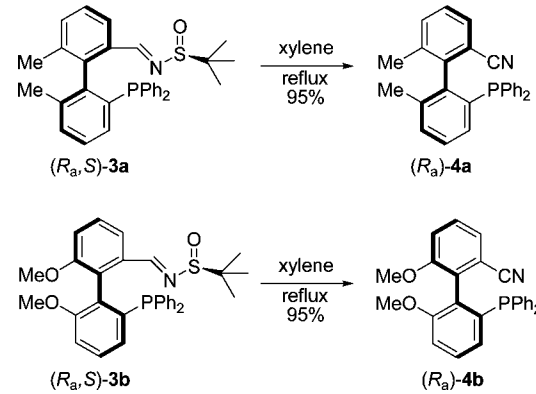
phenol salts should be beneficial to the subsequent iodide−lithium exchange. This consideration was proved to be reasonable by selective demethylation of **10**, followed by treatment of the resulting phenol **11** with 1.8 equiv of *n*-BuLi and DMF at −78 °C for 12 h to afford formaldehyde **12** in an acceptable yield (40%). Reprotection of the hydroxy group in **12** with a methyl group provided **13** in an excellent yield.

Conversion of **13** to **3b** is depicted in Scheme 3. Coupling of formaldehyde **13** with $HPPh_2$ in the presence of 5 mol % of $Pd(PPh_3)_4$ in toluene under N_2 for 16 h afforded phosphine **14**. Again, phosphine **14** was condensed with (*S*)-TBSA to give a mixture of two diastereomers (S_a,*S*)-**3b** and (R_a,*S*)-**3b** in a 90% isolated yield and a 1:1 ratio by flash chromatography under nitrogen atmosphere. It was noteworthy that (S_a,*S*)-**3b** and (R_a,*S*)-**3b** were less stable than the corresponding methyl ligands (R_a,*S*)-**3a** and (S_a,*S*)-**3a**. Separation of diastereomers (S_a,*S*)-**3b** and (R_a,*S*)-**3b** from each other by chromatography was more difficult than the separation of (R_a,*S*)-**3a** and (S_a,*S*)-**3a** (R_f 0.10 for (S_a,*S*)-**3b**, R_f 0.12 for (R_a,*S*)-**3b**, eluted with degassed ethyl acetate/petroleum (1:6)).

About 25% of **3b** was oxidized to the corresponding phosphine oxide when exposed to air during preparative TLC purification. Therefore, separation of (S_a,*S*)-**3b** and (R_a,*S*)-**3b** should be carried out with caution under nitrogen atmosphere. The absolute configuration of the axial chirality of (S_a,*S*)-**3b** and (R_a,*S*)-**3b** was determined by comparison of CD spectra of (R_a)-**4b** and (S_a)-**4b** with that of (R_a)-**4a** and (S_a)-**4a** after converting the sulfinyl imine group in **3** to a nitrile group in **4** (see Scheme 4 and the next paragraph).

Chiral biaryl phosphinonitriles are potential ligands for asymmetric catalysis and are useful precursors for preparation of biaryl phosphino-oxazoline ligands.[18] Conversion of the sulfinyl imine moiety in **3a** and **3b** to nitrile was easily realized

SCHEME 4. Synthesis of Chiral Phosphinonitrile 4



by refluxing in xylene under nitrogen atmosphere (Scheme 4).[19] Gratifyingly, as demonstrated by (R_a,*S*)-**3a** and (R_a,*S*)-**3b**, the reactions proceeded smoothly to give the desired (R_a)-**4a** and (R_a)-**4b**[20] at high yields without racemization (>98% ee).[21] Interestingly, unlike the sulfinyl imine (R_a,*S*)-**3b**, the phosphinonitrile (R_a)-**4b** was stable under chromatographic isolation.

3-Substituted 3-hydroxyoxindoles are widespread in natural products with important biological activities.[22] However, only two cases were reported to prepare this substructure in an asymmetric version by using chiral rhodium complex as a catalyst. Feringa described the first phosphoramidite−rhodium catalyzed addition of arylboronic acids to isatins with 55% ee.[23] Hayashi achieved a 93% ee in the asymmetric addition of arylboronic acids to isatins by using Rh/(*R*)-MeO-mop complex as a catalyst.[24] To the best of our knowledge, the palladium/ligand-catalyzed asymmetric addition of arylboronic acids to isatins has not been reported. To extend our studies on indole alkiloids,[25] the synthesized chiral ligands **3** and **4** were evaluated in the palladium-catalyzed asymmetric addition of arylboronic acids to *N*-benzyl isatin **15**.

As shown in Table 1, initial experiments gave very disappointing results in that a strong background addition of phenylboronic acid to **15** was observed when 5 mol % of either $Rh(CH_3CN)(cod)BF_4$ or $Rh_2(OAc)_4$ was used in the presence of 0.5 equiv of ^{t}BuOK in THF (Table 1, entries 1, 2, and 4). The rhodium-catalyzed addition reaction did not occur in the presence of 10 mol % of (R_a,*S*)-**3a** once the background reaction was completely suppressed by lowering the reaction temperature (Table 1, entries 3 and 5); these results indicated that $Rh(CH_3CN)(cod)BF_4$ and $Rh_2(OAc)_4$ might not efficiently

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(20) (R_a)-**4a** and (R_a)-**4b** gave a positive first Cotton effect at 280−330 nm in the CD spectra, while (S_a)-**4a** and (S_a)-**4b** were observed to give a negative first Cotton effect at 280−330 nm; see the Supporting Information.

(21) The enantiomeric excess of **4a** and **4b** was determined by HPLC analysis on a Chiralpak AD-H column (see the Supporting Information).

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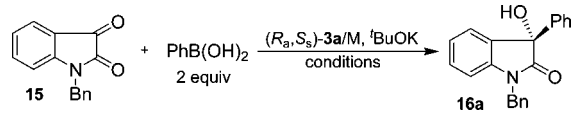
TABLE 1. Condition Screening for the Asymmetric Addition of Phenylboronic Acid to 15[a]



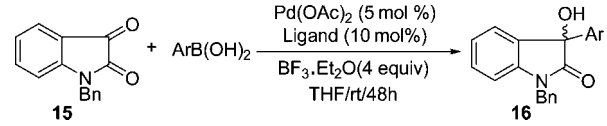
entry	M	solvent	T (°C)	additive (equiv)	yield[b] (%)	ee[c] (%) (config)[d]
1[e]	$Rh(CH_3CN)(cod)BF_4$	THF	25		80	0
2[e]	$Rh(CH_3CN)(cod)BF_4$	THF	−40		10	0
3	$Rh(CH_3CN)(cod)BF_4$	THF	−78		0	0
4[e]	$Rh_2(OAc)_4$	THF	50		75	0
5	$Rh_2(OAc)_4$	THF	25		0	
6	$[Pd(allyl)Cl]_2$	THF	50		0	
7	$Pd(PPh_3)_2(OAc)_2$	THF	50		0	
8	$Pd_2(dba)_3$	THF	50		6	13 (*S*)
9	$Pd(PPh_3)_4$	THF	50		5	17 (*S*)
10	$Pd(OAc)_2$	THF	50		4	90 (*S*)
11	$Pd(OAc)_2$	THF	50	$BF_3\cdot Et_2O$(1)	35	64 (*S*)
12	$Pd(OAc)_2$	THF	50	$BF_3\cdot Et_2O$(2)	60	62 (*S*)
13	$Pd(OAc)_2$	THF	50	$BF_3\cdot Et_2O$(4)	65	60 (*S*)
14	$Pd(OAc)_2$	THF	25	$BF_3\cdot Et_2O$(4)	63	67 (*S*)
15[f]	$Pd(OAc)_2$	THF	25	$BF_3\cdot Et_2O$(4)	10	-
16	$Pd(OAc)_2$	THF	0	$BF_3\cdot Et_2O$(4)	trace	-
17	$Pd(OAc)_2$	CH_2Cl_2	25	$BF_3\cdot Et_2O$(4)	20	40 (*S*)
18	$Pd(OAc)_2$	dioxane	25	$BF_3\cdot Et_2O$(4)	0	-
19	$Pd(OAc)_2$	DME	25	$BF_3\cdot Et_2O$(4)	trace	0
20	$Pd(OAc)_2$	MeCN	25	$BF_3\cdot Et_2O$(4)	0	0
21	$Pd(OAc)_2$	toluene	25	$BF_3\cdot Et_2O$(4)	12	5

[a] 5 mol % of M, 10 mol % of (R_a,*S*)-**3a**, 0.5 equiv of ^{t}BuOK. [b] Isolated yield. [c] ee values were determined by HPLC on a chiralcel OD-H column with hexane/2-propanol. [d] The absolute configuration of adduct was determined by comparing the optical rotation of its methyl-protected derivative with that of the known compound.[26] [e] Without addition of **3a**. [f] 5 mol % of $Pd(OAc)_2$ and 5 mol % of **3a** were used.

coordinate with (R_a,*S*)-**3a**. Encouraged by our previous experimental result that $[Pd(allyl)Cl]_2$ readily coordinated with (R_a,*S*)-**3a**, we then screened a variety of palladium salts (5 mol %) including $[Pd(allyl)Cl]_2$, $Pd(PPh_3)_2(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, and $Pd(OAc)_2$ in the addition reaction of phenylboronic acid to **15** in the presence of 10 mol % of (R_a,*S*)-**3a** and 0.5 equiv of ^{t}BuOK at 50 °C. Although the yield was very low (4%), $Pd(OAc)_2$ provided the adduct **16a** with a very promising ee value (90%) (Table 1, entries 6−10). A background reaction was not observed by using these palladium salts alone. In order to enhance the reactivity of the ketone group in **15**, a number of Lewis acids such as $Ti(O^iPr)_4$, $ZnCl_2$, $MgCl_2$, Et_3B, and $BF_3\cdot Et_2O$ were individually tested as an additive (1 equiv). To our delight, among the tested additives, $BF_3\cdot Et_2O$ was found to efficiently promote the addition reaction at 50 and 25 °C (Table 1, entries 11−14). Changing the ratio of (R_a,*S*)-**3a** to $Pd(OAc)_2$ from 2:1 to 1:1 and further lowering reaction temperature to 0 °C resulted in a dramatic loss of yield (Table 1, entries 15 and 16). Under the best conditions of 4 equiv of $BF_3\cdot Et_2O$, 5 mol % of $Pd(OAc)_2$, and 10 mol % of (R_a,*S*)-**3a**, the addition reaction of phenylboronic acid to **15** proceeded smoothly at room temperature for 48 h to afford (*S*)-**16a** in 63% yield and 67% ee. Variation of solvents did not improve the yield and ee value of the addition reaction at room temperature (Table 1, entries 17−21).

Under the best conditions, the performance of the known *P*,*N*-ligands (*S*)-**1a** and (*S*)-**2** as well as the synthesized ligands (R_a,*S*)-**3a**, (S_a,*S*)-**3a**, (R_a,*S*)-**3b**, (S_a,*S*)-**3b**, (R_a)-**4a**, and (R_a)-**4b** were comparatively tested in the addition reaction of phenylboronic acid to **15**. As shown in Table 2, ligands (*S*)-**1a**, (*S*)-**2**, (R_a)-**4a**, and (R_a)-**4b** did not catalyze the addition reaction at all (Table 2, entries 1−4). Ligands (S_a,*S*)-**3a**, (R_a,*S*)-**3b**, and (S_a,*S*)-**3b** were slightly less active compared with (R_a,*S*)-**3a** and provided similar enantioselectivities (Table 2, entries 5−8), which showed that the absolute configuration of adduct was controlled by the ligand's axial chirality rather than the sulfur chirality. The fact that (*S*)-**2** with the same coordinating units of imine and phosphine was incapable of catalyzing the addition reaction had demonstrated the importance of an axial chirality in **3a** and **3b**. Furthermore, the performance of ligand (R_a,*S*)-**3a** was further examined in the asymmetric additions of a variety of arylboronic acids to **15**. Under the best conditions, additions of 4-methoxy-

TABLE 2. Asymmetric Addition of Arylboronic Acids to 15 Catalyzed by Ligands 1−4[a]



entry	ligand	adduct **16** (Ar)	yield[b] (%)	ee[c] (%) (config)[d]
1	**1a**	**16a** (Ar = Ph)	0	
2	**2**	**16a** (Ar = Ph)	0	
3	(R_a)-**4a**	**16a** (Ar = Ph)	0	
4	(R_a)-**4b**	**16a** (Ar = Ph)	0	
5	(R_a,*S*)-**3a**	(−)-**16a** (Ar = Ph)	63	67 (*S*)
6	(S_a,*S*)-**3a**	(+)-**16a** (Ar = Ph)	48	62 (*R*)
7	(R_a,*S*)-**3b**	(−)-**16a** (Ar = Ph)	40	60 (*S*)
8	(S_a,*S*)-**3b**	(+)-**16a** (Ar = Ph)	30	57 (*R*)
9	(R_a,*S*)-**3a**	(+)-**16b** (Ar = 4-MeO-Ph)	78	38 (*S*)
10	(R_a,*S*)-**3a**	(−)-**16c** (Ar = 3-MeO-Ph)	51	73 (*S*)
11	(S_a,*S*)-**3a**	(+)-**16d** (Ar = 4-F-Ph)	36	65 (*S*)

[a] 5 mol % of M, 10 mol % of (R_a,*S*)-**3a**, 0.5 equiv of ^{t}BuOK. [b] Isolated yield. [c] ee values were determined by HPLC on a Chiralcel OD-H or AD-H column with hexane/2-propanol. [d] The absolute configuration of adduct was determined by comparing the optical rotation of it's methyl-protected derivative with that of the known compound.[26]

(26) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, 4040.

phenylboronic acid, 3-methoxyphenylboronic acid, and 4-fluorophenylboronic acid to **15** provided the corresponding tertiary alcohols (*S*)-**16b**, (*S*)-**16c**, and (*S*)-**16d** with acceptable enantioselectivities and yields (Table 2, entries 9−11).

Conclusion

In summary, we have developed a concise synthetic route to enantiopure tetra-ortho-substituted phosphinoimine ligand **3** with a biphenyl backbone. The first asymmetric additions of arylboronic acids to *N*-benzylisatin catalyzed by $Pd(OAc)_2$ and (R_a,*S*)-**3a** were realized to provide 3-aryl-3-hydroxyoxindoles **16** in moderate yields and enantioselectivities. Further application of these novel ligands in asymmetric catalysis is under investigation.

Experimental Section

General Procedure for the Synthesis of Ligands 3a and 3b. (R_a,*S*)-3a and (S_a,*S*)-3a. To a stirred solution of (*S*)-*tert*-butanesulfinamide (154 mg, 1.27 mmol) in dry toluene (10 mL) at 50 °C were added anhydrous Cs_2CO_3 (414 mg, 1.27 mmol) and **8** (500 mg, 1.27 mmol). After 18 h, the reaction mixture was filtered through a pad of Celite, concentrated, and purified by column chromatography (ethyl acetate/petroleum 1/8) under N_2 atmosphere to afford two diastereomers of ligand (R_a,*S*)-**3a** (284 mg, 45% yield) and (S_a,*S*)-**3a** (297 mg, 47% yield) as white powder. The absolute configuration of the first eluted diastereomer was confirmed with *R* axial chirality by X-ray crystallographic analysis of its palladium complex.[13] The diastereomeric purities of (R_a,*S*)-**3a** and (S_a,*S*)-**3a** were determined to be >99% de by chiral HPLC analysis [Daicel chiralcel OD-H column, 90:10 hexanes/IPA, 1.0 mL/min, 254 nm; (R_a,*S*)-**3a**, t_R = 8.0 min, (S_a,*S*)-**3a**, t_R = 3.9 min].

(R_a,*S*)-**3a**: R_f 0.40 eluted with EtOAc/petroleum 1:8; mp 60−62 °C; $[\alpha]^{20}_D$ +13.4 (c 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.58 (s, 3H), 1.87 (s, 3H), 7.05−7.08 (m, 1H), 7.10−7.14 (m, 2H), 7.15−7.17 (m, 2H), 7.18−7.31 (m, 9H), 7.37 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 20.3, 22.6 (3C), 57.4, 126.4, 127.8, 127.9, 128.1, 128.2, 128.3 (3C), 128.8, 130.9, 131.7, 132.2 (d, J_{cp} = 4 Hz), 133.1, 133.4, 133.6, 134.4, 134.6, 136.3 (d, J_{cp} = 12 Hz), 136.5 (d, J_{cp} = 6 Hz), 137.1 (dd, J_{cp} = 24, 11 Hz), 137.8, 141.6 (d, J_{cp} = 8 Hz), 143.2, 143.5, 162.2; ^{31}P NMR (161 MHz) δ −14.2; IR (KBr) 1083.6 cm^{-1}; HRMS-ESI calcd for $C_{31}H_{32}NNaOPS$ $(M + Na)^+$ 520.1834, found 520.1837.

(S_a,*S*)-**3a**: R_f 0.36 eluted with EtOAc/petroleum 1:8; mp 145−147 °C; $[\alpha]^{20}_D$ +389.6 (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.84 (s, 3H), 2.03 (s, 3H), 6.95−6.98 (m, 1H), 7.04−7.09 (m, 2H), 7.14−7.18 (m, 2H), 7.24−7.29 (m, 8H), 7.34 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 19.2, 21.4 (3C), 56.1, 123.4, 126.9, 127.2, 127.3 (4C), 127.4, 128.0, 129.9, 130.2, 131.4, 132.4, 132.6 (2C), 133.4, 133.5, 133.6, 135.1 (d, J_{cp} = 6 Hz), 135.9, 136.0, 136.4 (d, J_{cp} = 10 Hz), 141.0, 141.3 (d, J_{cp} = 5 Hz), 159.8; ^{31}P NMR (161 MHz) δ −12.6; IR (KBr) 1089.5 cm^{-1}; HRMS-ESI calcd for $C_{31}H_{32}NNaOPS$ $(M + Na)^+$ 520.1834, found 520.1830.

(R_a,*S*)-3b and (S_a,*S*)-3b. Under N_2, to a stirred solution of (S_s)-*tert*-butanesulfinamide (145 mg, 1.20 mmol) in dry toluene (10 mL) at 50 °C were added anhydrous Cs_2CO_3 (391 mg, 1.20 mmol) and **14** (512 mg, 1.20 mmol). After being stirred for 18 h, the reaction mixture was filtered, concentrated, and purified by column chromatography (EtOAc/petroleum 1:6) under N_2 atmosphere to afford a mixture of the two diastereomers (R_a,*S*)-**3b** and (S_a,*S*)-**3b** (572 mg, 90% overall yield) as a white powder. Separation of (R_a,*S*)-**3b** and (S_a,*S*)-**3b** from each other was realized by consecutive prepared TLC chromatography eluted with degassed EtOAc/petroleum (1:6) under nitrogen atmosphere to afford (R_a,*S*)-**3b** (224 mg, 39% yield) and (S_a,*S*)-**3b** (206 mg, 36% yield). The de values of (R_a,*S*)-**3b** and (S_a,*S*)-**3b** were determined to be >98% by chiral HPLC analysis [Daicel chiralcel OD-H column, 80:20 hexanes/IPA, 1.0 mL/min, 254 nm; (R_a,*S*)-**3b**, t_R = 9.4 min, (S_a,*S*)-**3b**, t_R = 4.4 min].

(R_a,*S*)-**3b**: R_f 0.12 eluted with EtOAc/petroleum 1:6; mp 78−80 °C; $[\alpha]^{20}_D$ +115.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H) 3.25 (s, 3H), 3.67 (s, 3H), 6.72 (dd, J = 7.6, 3.2 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.06−7.09 (m, 2H), 7.17−7.20 (m, 5H), 7.26−7.31 (m, 4H), 7.38 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 8.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6 (3C), 55.0, 55.7, 57.5, 111.4, 113.4, 119.8, 126.2, 128.0 (3C), 128.2, 128.3 (2C), 128.6, 128.7, 128.8, 129.2, 129.6, 133.2, 133.4, 134.0, 134.2, 136.6 (d, J_{cp} = 12 Hz), 137.6 (d, J_{cp} = 12 Hz), 139.5 (d, J_{cp} = 11 Hz), 157.2 (d, J_{cp} = 9 Hz), 157.5, 162.2; ^{31}P NMR (161 MHz) δ −13.1; IR (KBr) 1080.8 cm^{-1}; HRMS-ESI calcd for $C_{31}H_{32}NNaO_3PS$ $(M + Na)^+$ 552.1733, found 552.1735.

(S_a,*S*)-**3b**: R_f 0.10 eluted with EtOAc/petroleum 1:6; mp 150−152 °C; $[\alpha]^{20}_D$ +193.0 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H) 3.58 (s, 3H), 3.65 (s, 3H), 6.70 (dd, J = 7.6, 3.2 Hz, 1H), 6.96−7.05 (m, 4H), 7.17−7.23 (m, 5H), 7.26−7.35 (m, 4H), 7.39 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz,1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (3C), 55.6, 55.7, 57.2, 111.4, 113.7, 118.9, 125.7, 128.1, 128.2 (2C), 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.5, 133.6, 133.7, 133.8, 134.0, 134.2, 136.0 (d, J_{cp} = 11 Hz), 137.1 (d, J_{cp} = 13 Hz), 139.9 (d, J_{cp} = 10 Hz), 157.1 (d, J_{cp} = 9 Hz), 157.2, 161.7; ^{31}P NMR (161 MHz) δ −12.1; IR (KBr) 1082.4 cm^{-1}; HRMS-ESI calcd for $C_{31}H_{32}NNaO_3PS$ $(M + Na)^+$ 552.1733, found 552.1738.

Synthesis of Complex (R_a,*S*)-9. A solution of (R_a,*S*)-**3a** (61 mg, 0.12 mmol) and $[Pd(allyl)Cl]_2$ (20 mg, 0.06 mmol) in 3 mL of dry CH_2Cl_2 was prepared and degassed (three freeze−pump−thaw cycles). After this solution was stirred at room temperature for 2 h, the resulting mixture was added to the solution of $AgSbF_6$ (42 mg, 0.12 mmol) in 3.0 mL of THF by syringe. The resulting heterogeneous mixture was stirred for 15 min and then filtered through a pad of Celite. The filter cake was washed with CH_2Cl_2, and the filtrate was concentrated to give 106 mg of a yellow solid (99% crude yield). Single yellow crystals of (R_a,*S*)-**9** suitable for X-ray diffraction were obtained by vapor diffusion of Et_2O into a solution of (R_a,*S*)-**9** in $CHCl_3$: mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.07 (s, 9H), 1.18 (s, 3H), 1.24 (s, 3H), 1.87 (s, 3H), 1.88 (s, 3H), 2.32 (d, J = 12.8 Hz, 1H), 3.05 (d, J = 5.2 Hz, 1H), 3.09 (d, J = 12.0 Hz, 1H), 3.62 (d, J = 4.8 Hz, 1H), 3.90−3.99 (m, 2H), 4.95 (td, J = 6.4, 2.0 Hz, 1H), 5.08 (t, J = 6.0 Hz, 1H), 5.73−5.83 (m, 2H), 6.75 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 7.05−7.10 (m, 3H), 7.17−7.21 (m, 2H), 7.26−7.39 (m, 12H), 7.48−7.56 (m, 12H), 8.99 (s, 1H), 9.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (3C), 19.9, 22.0 (3C), 22.1 (3C), 59.3, 59.5, 60.2, 60.4, 82.2 (2C), 82.5 (2C), 120.8, 120.9, 121.0, 121.1, 124.8, 125.0, 126.2, 126.7, 127.2, 128.6, 128.9, 129.0, 129.1 (2C), 129.2 (2C), 129.3, 129.5, 129.6 (3C), 129.7 (2C), 129.9, 130.0 (2C), 131.5, 131.7, 132.0, 132.4, 132.5, 133.0, 133.1, 133.3 (2C), 133.4, 133.5, 135.0 (2C), 135.1, 135.2, 138.3, 138.4, 139.0 (2C), 141.3 (dd, J_{cp} = 15, 10 Hz), 174.1 (2C); ^{31}P NMR (161 MHz) δ 25.0, 25.4; IR (KBr) 658.8, 1102.0, 1605.3 cm^{-1}; MS-ESI 644.3 (M-SbF_6).

General Procedure for the Synthesis of 4a and 4b. (R_a)-4a. Under N_2, (R_a,*S*)-**3a** (50 mg, 0.10 mmol) was dissolved in dry xylene (2 mL), and the solution was heated to reflux for 2 h. The reaction solution was cooled to rt, and the most of the solvent was removed under vacuum to give a colorless residue. The residue was purified by flash column chromatography (hexane/ethyl acetate 50/1) under N_2 atmosphere to afford (R_a)-**4a** (37 mg, 95%) as a white solid. The ee value was determined to be >99% by chiral HPLC analysis [Daicel chiralcel AD column, 99:1 hexanes/IPA, 1.0 mL/min, 254 nm; (R_a)-**4a**, t_R = 12.1 min, (S_a)-**4a**, t_R = 7.5 min]: mp 139− 141 °C; $[\alpha]^{20}_D$ −29.9 (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 1.97 (s, 3H), 7.04 (dd, J = 6.8, 2.8 Hz, 1H), 7.18−7.34 (m, 13H), 7.40 (d, J = 7.6 Hz, 1H), 7.47

(d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 114.1, 118.1, 127.9, 128.2, 128.4 (2C), 128.5, 128.6, 128.7, 129.0, 130.3, 131.1, 131.9, 133.6, 133.8, 134.0, 134.1, 134.2, 136.2 (t, J_{cp} = 5 Hz), 136.3 (t, J_{cp} = 6 Hz), 137.3 (d, J_{cp} = 11 Hz), 138.3 (d, J_{cp} = 3 Hz), 142.7, 143.0, 143.7; ^{31}P NMR (161 MHz) δ −14.0; IR (KBr) 2224.7 cm^{-1}; HRMS-ESI calcd for $C_{27}H_{22}NNaP$ (M + Na)$^+$ 414.1382, found 414.1370.

Similar to the synthesis of (R_a)-**4a**, (S_a)-**4a** was prepared from (S_a,*S*)-**3a** as a white solid (95% yield): (S_a)-**4a**: mp 140−141 °C; $[\alpha]^{20}_D$ +29.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 1.98 (s, 3H), 7.04 (dd, J = 6.4, 3.6 Hz, 1H), 7.17−7.34 (m, 13H), 7.40 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 114.1, 118.1, 127.9, 128.2, 128.4 (2C), 128.5, 128.6, 128.7, 129.0, 130.3, 131.1, 131.9, 133.6, 133.8, 134.0, 134.1, 134.2, 136.2 (t, J_{cp} = 5 Hz), 136.3 (t, J_{cp} = 6 Hz), 137.3 (d, J_{cp} = 11 Hz), 138.3 (d, J_{cp} = 3 Hz), 142.7, 143.0, 143.7; ^{31}P NMR (161 MHz) δ −13.9; HRMS-ESI calcd for $C_{27}H_{22}NNaP$ (M + Na)$^+$ 414.1382, found 414.1375.

Similar to the synthesis of (R_a)-**4a**, (R_a)-**4b** and (S_a)-**4b** were prepared from (R_a,*S*)-**3b** and (S_a,*S*)-**3b** as a white solid (93−95% yield), respectively. The ee values of (R_a)-**4b** and (S_a)-**4b** were determined to be >98% by chiral HPLC analysis [Daicel chiralcel AD column, 95:5 hexanes/IPA, 1.0 mL/min, 254 nm; (R_a)-**4b**, t_R = 11.9 min, (S_a)-**4b**, t_R = 9.4 min].

(R_a)-**4b**: mp 158−160 °C; $[\alpha]^{20}_D$ +48.2 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.76 (s, 3H), 6.73 (dd, J = 7.6, 3.2 Hz, 1H), 7.01 (dd, J = 8.4, 4.8 Hz, 2H), 7.12−7.16 (m, 2H), 7.21−7.37 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 56.0, 111.9, 114.7, 115.5, 118.0, 124.2, 126.3, 128.1, 128.2, 128.3, 128.4 (3C), 129.3, 129.7, 129.8, 130.6 (d, J_{cp} = 8 Hz), 133.3, 133.5, 133.7, 133.9, 136.6 (d, J_{cp} = 12 Hz), 137.0 (d, J_{cp} = 11 Hz), 139.2 (d, J_{cp} = 12 Hz), 156.9 (d, J_{cp} = 9 Hz), 157.5; ^{31}P NMR (161 MHz) δ −13.1; IR (KBr) 2225.0 cm^{-1}; HRMS-ESI calcd for $C_{27}H_{22}NNaO_2P$ (M + Na)$^+$ 446.1280, found 446.1269.

(S_a)-**4b**: mp 159−161 °C; $[\alpha]^{20}_D$ −48.0 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.76 (s, 3H), 6.73 (dd, J = 7.6, 3.2 Hz, 1H), 7.01 (dd, J = 8.4, 4.8 Hz, 2H), 7.11−7.16 (m, 2H), 7.21−7.37 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 56.0, 111.9, 114.7, 115.5, 118.0, 124.2, 126.3, 128.1, 128.2, 128.3, 128.4 (3C), 129.3, 129.7, 129.8, 130.6 (d, J_{cp} = 8 Hz), 133.3, 133.5, 133.7, 133.9, 136.6 (d, *Jcp* = 12 Hz), 137.0 (d, J_{cp} = 11 Hz), 139.2 (d, J_{cp} = 12 Hz), 156.9 (d, J_{cp} = 9 Hz), 157.5; ^{31}P NMR (161 MHz) δ −13.0; HRMS-ESI calcd for $C_{27}H_{22}NNaO_2P$ (M + Na)$^+$ 446.1280, found 446.1274.

General Procedure for the Asymmetric Addition of Arylboronic Acids to *N*-Benzylisatin 15. Under nitrogen, a solution of $Pd(OAc)_2$ (0.5 mg, 0.0025 mmol) and (R_a,*S*)-**3a** (2.5 mg, 0.005 mmol) in THF (0.5 mL) was stirred for 30 min at room temperature. Meanwhile, another solution of $BF_3 \cdot Et_2O$ (0.2 mL, 0.2 mmol) and *N*-benzylisatin **15** (12.2 mg, 0.05 mmol) in THF (0.5 mL) was stirred for 30 min. The solution of Pd/(R_a,*S*)-**3a** was then transferred into the solution containing $PhB(OH)_2$ (12.2 mg, 0.1 mmol), followed by addition of the activated *N*-benzylisatin solution. After being stirred for 48 h at rt, the mixture was then directly passed through a pad of silica gel eluted with EtOAc. The solvent was removed under vacuum, and the residue was purified by preparative thin layer chromatography (EtOAc/$CHCl_3$ 1:20) to afford adduct (*S*)-**16a**.

(−)-(***S***)-**16a.** The ee value was determined to be 67% by chiral HPLC analysis [Daicel chiralcel OD column, 80:20 hexanes/IPA, 0.5 mL/min, 227 nm; (*S*)-**16a**, t_R = 14.2 min, (*R*)-**16a**, t_R = 15.5 min]: white solid; mp 141−142 °C; $[\alpha]^{20}_D$ −6.4 (c 0.46, acetone) with 67% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 1H), 4.97 (dd, J = 83.2, 16.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 7.05 (td, J = 8.0, 0.8 Hz, 1H), 7.22 (dd, J = 8.0, 1.6 Hz, 1H), 7.27−7.43 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.0, 77.9, 109.7, 123.5, 124.9, 125.3 (2C), 127.2 (2C), 127.7, 128.2 (2C), 128.5 (2C), 128.8, 129.8, 131.7, 135.4, 140.1, 142.5, 177.6. IR (KBr) 3370.9, 1705.5, 1613.9, 1493.2, 1468.2, 1377.5, 1172.9, 749.3 cm^{-1}; HRMS-ESI calcd for $C_{21}H_{18}NO_2$ (M + H)$^+$ 316.1338, found 316.1329.

(+)-(***S***)-**16b.** The ee value was determined to be 38% by chiral HPLC analysis [Daicel chiralcel AD column, 70:30 hexanes/IPA, 1.0 mL/min, 227 nm; (*S*)-**16b**, t_R = 19.3 min, (*R*)-**16b**, t_R = 13.8 min]: white solid; mp 152−153 °C; $[\alpha]^{20}_D$ +11.3 (*c* 0.80, acetone) with 38% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (s, 1H), 3.79 (s, 3H), 4.97 (dd, J = 67.2, 15.6 Hz, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.27−7.36 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.9, 55.2, 77.6, 109.4, 113.9, 123.4, 124.9, 126.6 (2C), 127.2 (2C), 127.6, 128.7 (2C), 129.5, 131.7, 132.2, 135.4, 142.5, 159.5, 177.6; IR (KBr) 3363.7, 1707.7, 1612.9, 1512.8, 1375.1, 1257.1, 748.7 cm^{-1}; HRMS-ESI calcd for $C_{22}H_{20}NO_3$ (M + H)$^+$ 346.1443, found 346.1445.

(−)-(***S***)-**16c.** The ee value was determined to be 73% by chiral HPLC analysis [Daicel chiralcel AD column, 70:30 hexanes/IPA, 1.0 mL/min, 227 nm; (*S*)-**16c**, t_R = 20.3 min, (*R*)-**16c**, t_R = 22.2 min]: white solid; mp 147−148 °C; $[\alpha]^{20}_D$ −16.0 (*c* 0.46, acetone) with 73% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 1H), 3.77 (s, 3H), 4.97 (dd, J = 90.8, 15.6 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.85 (dd, J = 8.4, 2.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.02−7.06 (m, 2H), 7.21−7.34 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.0, 55.1, 77.9, 109.6, 110.9, 113.9, 117.5, 123.5, 124.9, 127.2 (2C), 127.7, 128.8 (2C), 129.6, 129.7, 131.6, 135.4, 141.7, 142.5, 159.8, 177.5;IR (KBr) 3298.1, 1696.3, 1610.1, 1375.3, 1158.8, 749.2 cm^{-1}; HRMS-ESI calcd for $C_{22}H_{20}NO_3$ (M + H)$^+$ 346.1443, found 346.1456.

(+)-(***S***)-**16d.** The ee value was determined to be 65% by chiral HPLC analysis [Daicel chiralcel AD column, 80:20 hexanes/IPA, 1.0 mL/min, 227 nm; (*S*)-**16d**, t_R = 14.4 min, (*R*)-**16d**, t_R = 11.5 min]: white solid; mp 149−150 °C; $[\alpha]^{20}_D$ +15.0 (*c* 0.27, acetone) with 65% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 1H), 4.95 (dd, J = 76.0, 15.6 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 7.01−7.08 (m, 3H), 7.23−7.41 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.0, 77.6, 109.8, 115.2, 115.7, 123.6, 124.9, 127.2 (2C), 127.4, 127.8, 128.8 (2C), 129.9, 131.3, 135.2, 135.8, 142.5, 160.2, 165.1, 177.3; IR (KBr) 3369.5, 1703.7, 1614.7, 1508.9, 1383.2, 830.8 cm^{-1}; HRMS-ESI calcd for $C_{21}H_{17}FNO_2$ (M + H)$^+$ 334.1243, found 334.1236.

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Supporting Information Available: Experimental procedures, analytical data for compounds **6**−**8** and compounds **11**−**14**, X-ray crystallography of compound **9**, CD spectra of compound **4**, HPLC spectra of chiral compounds, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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