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A Chiral Ruthenium-Monophosphine Catalyst for Asymmetric Addition of Arylboronic Acids to Aryl Aldehydes

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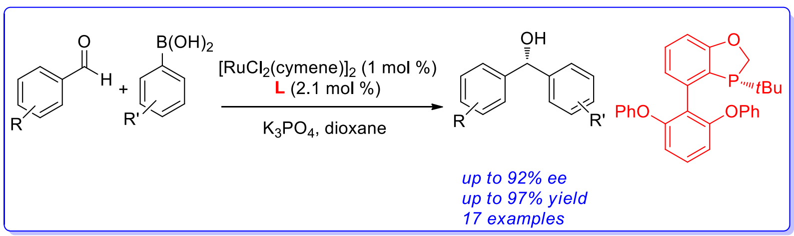


ABSTRACT: A novel ruthenium catalyst on the basis of a chiral monophosphorus ligand is efficient for the asymmetric addition of arylboronic acids to aryl aldehydes, providing a series of chiral diarylmethanols in excellent yields and enantioselectivities (up to 92% ee). Preliminary study has shown this process is catalyzed by a Ru complex with a single monophosphorus ligand.

Chiral diarylmethanols are important building blocks for many antihistamine compounds or therapeutic agents[1] such as (*R*)-orphenadrine, (*S*)-neobenodine,[2] (*S*)-carbinoxamine,[3] and bepotastine.[3] They also serve as pivotal structural units for chiral ligands in asymmetric catalysis.[4] Development of asymmetric catalytic methods for the syntheses of chiral diarylmethanols has thus gained significant interest.[5] Two recent advances include asymmetric hydrogenation of diarylketones[6] and asymmetric addition of aryl nucleophile to aryl aldehydes.[7] The asymmetric addition of arylboronic acids to aryl aldehydes to form chiral diarylmethanols remains one of most attractive methods owing to its mild reaction conditions, and the stable and nontoxic nature of arylboronic acids.[8-12]

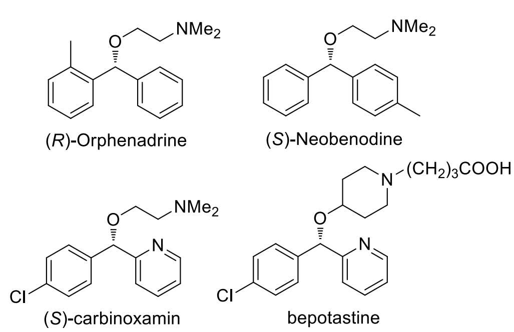


Figure1. Antihistimine compounds containing chiral diarylmethanol moiety

Although most progresses on asymmetric addition of arylboronic acids to aryl aldehydes have been achieved on chiral rhodium catalysts,[9] the development of novel and efficient catalysts with less expensive transition metals, broader substrate scope, and low catalyst loadings continue to be of great interest. The ruthenium–catalyzed asymmetric addition of arylboronic acids to aryl aldehydes offers great promise to provide a more economical and practical solution than the rhodium version. However, it remains an underdeveloped area. Only recently, Miyaura and coworkers have reported a chiral ruthenium catalyst with a bisphosphoramidite ligand can be highly efficient.[13] Nevertheless, the structure of its active ruthenium species remains to be elucidated. In addition, no efficient ruthenium catalyst in combination with a monophosphorus ligand has ever been reported. We herein describe a new and efficient ruthenium catalyst on the basis of a P-chiral monophosphorus ligand **L4** which has provided excellent yields and enantioselectivities for the syntheses of a wide array of chiral diarylmethanols.

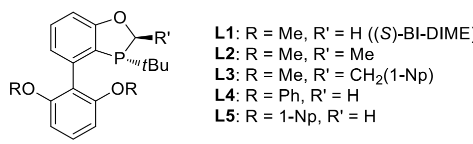
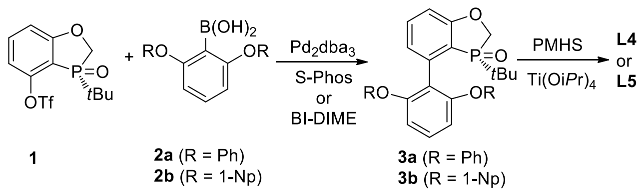


Figure 2. Chiral monophosphorus ligands

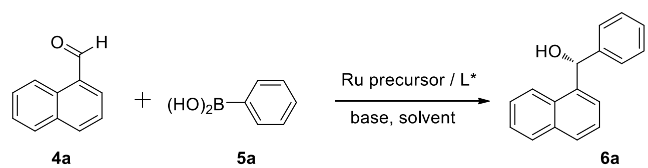
We have developed a series of chiral biaryl monophosphorus ligands for palladium-catalyzed asymmetric Suzuki-Miyaura coupling reactions (Figure 2).[14] The high tunability of these monophosphorus ligands and the facile syntheses from chiral triflate **1** (Scheme 1) allowed us to investigate their ruthenium complex as the catalyst for the addition of arylboronic acids to aryl aldehydes. The asymmetric addition of phenylboronic acid (5**a**) to 1-naphthaldehyde (**4a**) to form enantiomerically enriched naphthalen-1-yl(phenyl)methanol (**6a**) was studied. The reaction was performed under nitrogen in dioxane at 60 °C for 16 h with 1 mol % $[RuCl_2(cymene)]_2$ and 2 mol % ligand as the catalytic system. Initial screening of the chiral ligands (Table 1, entries 1-5) demonstrated that the ligand structure plays a significant role on both reactivity and selectivity. While BI-DIME (**L1**) provided a high yield and a good ee (82% ee, entry 1), the ligands with substituents at R' position provided diminished yields and enantioselectivities (entries 2-3). The substituents on the lower aryl ring of the ligands also provided profound influence on both reactivity and selectivity.



Scheme 1. Syntheses of Ligand L4 and L5

Ligand **L4** with two phenoxy groups on the low aryl ring further enhanced the enantioselectivity to 86% ee (entry 4). A slightly lower yield and ee were observed with **L5** containing two 1-naphthyloxy substituents (entry 5). The ruthenium precursors significantly affected the performance of the catalyst. While comparable results were observed with $[RuCl_2(C_6Me_6)]_2$ as the precursor (entry 6), use of $[RuCl_2(benzene)]_2$ as the precursor provided <5% conversion under similar reaction conditions. This could be largely attributed to the slow complex formation between $[RuCl_2(benzene)]_2$ and **L4** at 60 °C (entry 7). The reaction temperature also influenced both the reactivity and selectivity with $[RuCl_2(cymene)]_2$ as the catalyst precursor. Low reactivity and enantioselectivity was observed at 50 °C (entry 8), while a slightly diminished ee was also observed at 70 °C (entry 9). There were little differences on selectivity when various bases were employed (entries 10-14). Among them, potassium phosphate offered an excellent yield (96%) and good selectivity (87% ee) (entry 11).

Table 1. Asymmetric addition of phenylboronic acid to 1-naphthaldehyde

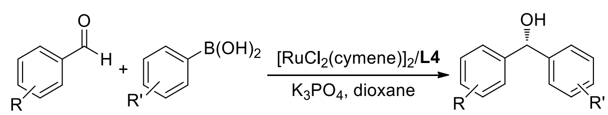


entry[a]	L*	Base	Ru Precursor	Yield (%)	ee (%)[b]
1	**L1**	K_2CO_3	$[RuCl_2(cymene)]_2$	87	69
2	**L2**	K_2CO_3	$[RuCl_2(cymene)]_2$	40	6
3	**L3**	K_2CO_3	$[RuCl_2(cymene)]_2$	45	8
4	**L4**	K_2CO_3	$[RuCl_2(cymene)]_2$	85	86
5	**L5**	K_2CO_3	$[RuCl_2(cymene)]_2$	68	78
6	**L4**	K_2CO_3	$[RuCl_2(C_6Me_6)]_2$	85	84
7	**L4**	K_2CO_3	$[RuCl_2(benzene)]_2$	<5	n.d
8[c]	**L4**	K_2CO_3	$[RuCl_2(cymene)]_2$	13	64
9[d]	**L4**	K_2CO_3	$[RuCl_2(cymene)]_2$	86	70
10	**L4**	KF	$[RuCl_2(cymene)]_2$	40	86
11	**L4**	K_3PO_4	$[RuCl_2(cymene)]_2$	96	87
12	**L4**	CsF	$[RuCl_2(cymene)]_2$	31	84
13	**L4**	KOH	$[RuCl_2(cymene)]_2$	45	84
14	**L4**	NaO*t*Bu	$[RuCl_2(cymene)]_2$	38	84

[a]The reactions were performed in dioxane at 60 °C under nitrogen for 16 h in the presence of 1 mol % Ru precursor and 2 mol % ligand, the absolute configuration was determined by comparing its optical rotation with reported data;[13a,b] [b]The ee was determined on a Chiralcel OD-H column; [c] T = 50 °C; [d] T = 70 °C.

We next investigated the substrate scope of this ruthenium catalyzed addition of arylboronic acids to aldehydes. It was found that excellent yields and enantioselectivities were achieved regardless of the electronic properties and substitution pattern of both aldehydes and arylboronic acids (Table 2). Both electronic-donating substituents such as methoxy group and electronic-withdrawing substituents such as fluoro and bromo groups provided comparably high yields and selectivities (entries 1-4, 8-10). Slightly lower ee's were observed when aryl aldehydes containing *ortho*-substituents were employed (entries 5-6). The Ru-**L4** system also provided excellent yields and enantioselectivies on substrates containing heteroaryls such as thiophene and furan (entries 13-15). By simply switching the substituents on arylboronic acids and arylaldehyde in Table 1, the same ruthenium catalyst can produce both enantiomers of the chiral biarylcarbinol in a comparably high ee and yield (entries 8 and 16), demonstrating the generality and efficiency of this methodology.

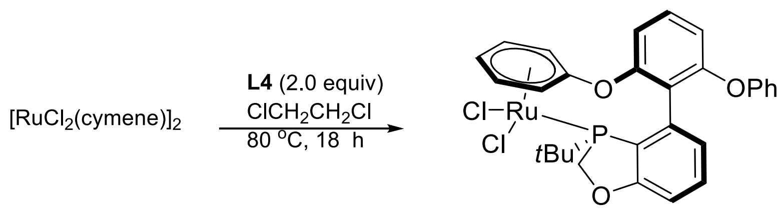
Table 2. Substrate scope of ruthenium-catalyzed addition of arylboronic acids to aryl aldehydes



entry[a]	Aldhehyde	Boronic acid	Yield (%)	ee(%)[b]
1	4-MeO-Ph (**4b**)	Ph (**5a**)	92 (**6b**)	89
2	4-F-Ph (**4c**)	Ph (**5a**)	95 (**6c**)	90
3	4-Br-Ph (**4d**)	Ph (**5a**)	85 (**6d**)	90
4	3-MeO-Ph (**4e**)	Ph (**5a**)	95 (**6e**)	87
5	2-Cl-Ph (**4f**)	Ph (**5a**)	90 (**6f**)	81
6	2-MeO-Ph (**4g**)	Ph (**5a**)	90 (**6g**)	84
7	4-NO_2-Ph (**4h**)	4-Cl-Ph(**5b**)	97 (**6h**)	82
8	2-naphthyl (**4i**)	Ph (**5a**)	93 (**6i**)	92
9	2-naphthyl (**4i**)	4-Ph-Ph(**5c**)	91 (**6j**)	86
10	2-naphthyl (**4i**)	4-MeO-Ph(**5d**)	93 (**6k**)	89
11	2-naphthyl (**4i**)	4-Cl-Ph(**5e**)	95 (**6l**)	89
12	*trans*-PhCH=CH (**4j**)	Ph (**5a**)	80(**6m**)	76
13	2-thienyl (**4k**)	Ph (**5a**)	95 (**6n**)	90
14	3-thienyl (**4l**)	Ph (**5a**)	93 (**6o**)	90
15	2-furyl (**4m**)	Ph (**5a**)	89 (**6p**)	87
16	Ph (**4n**)	2-naphthyl (**5f**)	93 (**6q**)	85

[a]The reactions were performed in dioxane at 60 °C under nitrogen for 16 h in the presence of 1 mol % Ru precursor and 2 mol % ligand; the absolute configuration was determined by comparing its optical rotation with reported data; [b]The ee's were determined on a Chiralcel OD-H column.

To better understand the structure of the active ruthenium catalyst for this transformation, we attempted to prepare a ruthenium complex of ligand **L4**. Thus, by stirring $[RuCl_2(cymene)]_2$ and **L4** at Ru:**L4** ratio of 1:1 in 1,2-dichloroethane as the solvent at 70 °C for 18 h, a new aryl-coordinated ruthenium complex **7** without a cymene moiety was isolated in 70% yield by column chromatography.[15] Interestingly, one phenoxy group of the ligand served as a coordinating aryl group within the complex, whose structure was confirmed by X-ray crystallography (Scheme 2).[16] Complex **7** could also be applied as a catalyst for the nucleophilic addition of **5a** to **4a** and the addition product **6a** was isolated in 84% ee and 80% yield. The high selectivity and reactivity observed with complex **7** highly suggests that the active ruthenium catalyst for this transformation is a ruthenium species coordinated with a single monophosphorus ligand. This is in contrast to Miyaura's ruthenium system where a bisphosphorus ligand was employed.[13a] Additional experiments with a scalemic catalyst composition of **L1** have shown a linear relationship of ees between the ligand and the product, further demonstrating the process catalyzed by a ruthenium catalyst coordinated with a single monophosphorus ligand (Figure 3). However, whether ligand **L1** or **L4** coordinates with the ruthenium metal through monodentate, bidentate, and/or aryl coordination during the catalyst cycle remain to be further elucidated.



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Scheme 2. Syntheses of chiral ruthenium complexes 7 and 8 and the X-ray crystal structure of 8 (H atoms and chloroform are omitted for clarity)

On the basis of these observations, we proposed a mechanistic cycle with a Ru(II)-monophosphine catalyst as depicted in Figure 4. Transmetallation of a **L4**-Ru(II) complex with $ArB(OH)_2$ in the presence of a base provided an aryl Ru(II) complex **I**. Coordination of an aryl aldehyde to complex **I** to form intermediate **II** followed by carbonyl insertion and transmetallation with $ArB(OH)_2$ provides chiral biarylmethanol **IV** and regenerate complex **I**. Further mechanistic study is ongoing to understand the stereoselection of this reaction and the detailed structure of each catalytic species.

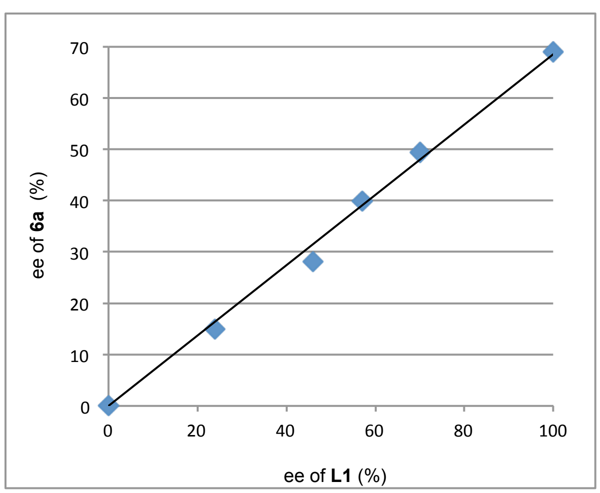


Figure 3. Linear relationship of ees between ligand L1 and product 6a

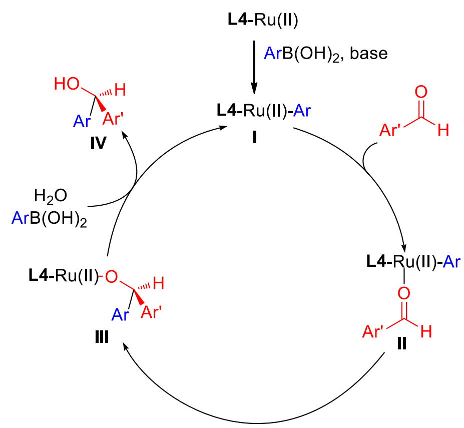
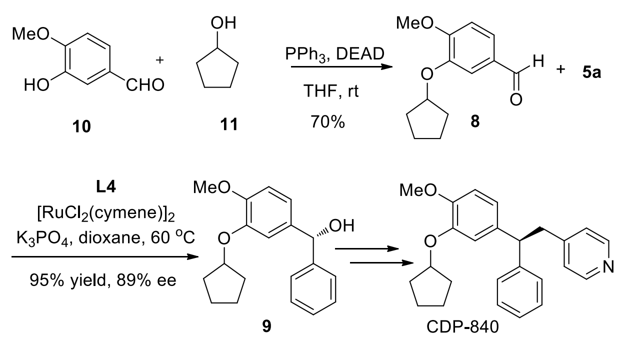


Figure 4. A postulated mechanistic cycle



Scheme 3. Synthetic utility of this methodology

To further demonstrate the synthetic utility of this methodology, the Ru-**L4** system was employed as a catalyst to synthesize chiral alcohol **9** (Scheme 3). Thus, Mitsunobu reaction between aldehyde **10** and cyclopentanol **11** provided **8** in 70% yield. The reaction of aldehyde **8** and phenylboronic acid (**5a**) was catalyzed by 1 mol % $[RuCl_2(cymene)]_2$ and 2 mol % **L4** to provide **9** in 95% yield and 89 % ee. Compound **9** can be further transformed according to a reported procedure[1a] to CDP-840,[17] a potent selective phosphodiesterase IV inhibitor.

In summary, we have developed a novel and efficient ruthenium catalyst based on a chiral monophosphorus ligand **L4** for asymmetric addition of arylboronic acids to aryl aldehydes, providing a series of chiral diarylcarbinols in excellent yields and ees. Studies have shown that this transformation is catalyzed by a Ru species coordinated with a single monophosphorus ligand.

EXPERIMENTAL SECTION

General information. All reactions were carried out under a nitrogen atomosphere unless otherwise specified. Dioxane (<0.02% water content), Et_2O, dioxane, MTBE, DCM, DCE, Xylene and toluene were used directly without further purifications. Commercialized reagents were used without further purifications. ^1H, ^{31}P and ^{13}C NMR data were recorded on 400 or 500 MHz at ambient temperature with $CDCl_3$ as the solvent. ^1H shifts were referenced to $CDCl_3$ at 7.26 ppm. ^{31}P shifts were referenced to 85% H_3PO_4 in D_2O at 0.0 ppm as external standard and obtained with ^1H decoupling. ^{13}C shifts were referenced to $CDCl_3$ at 77 ppm and obtained with ^1H decoupling. The mass analyzer type was Q-TOF used for the HRMS measurements. Chiral HPLC analyses were performed on a Chiralcel OD-H, Chiralpak AD-H or Lux Amylose-2 PA column. Racemic addition products were prepared by using $[RuCl_2(p\text{-cymene})]_2$ and S-phos as the catalytic system.

(*S*)-3-(*tert*-Butyl)-4-(2,6-diphenoxyphenyl)-2,3-dihydrobenzo[*d*][1,3]oxaphosphole 3-oxide (3a). To a mixture of triflate **1**[18] (2.0 g, 5.6 mmol) and arylboronic acid **2a** (2.57 g, 8.4 mmol, 1.5 equiv), Pd_2dba_3 (76.7 mg, 0.084 mmol, 0.03 equiv), S-Phos (0.23 g, 0.56 mmol, 0.2 equiv) and KF (1.3 g, 22.3 mmol, 4 equiv) was charged degassed dioxane (10 mL). The mixture was stirred at 100 °C under nitrogen for 24 h, concentrated, partitioned with water (30 mL) and DCM (30 mL). The DCM layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (eluent: hexane to EtOAc) to provide **3a** (1.9 g, 4.2 mmol, 75%) as white solid. **3a**: mp 97 -99 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31～7.39 (m, 7H), 7.10 (t, J = 7.1 Hz, 3H), 6.92～6.99 (m, 3H), 6.88 (dd, J = 8.2, 3.0 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 8.3 Hz, 1H), 4.54 (d, J = 14.3 Hz, 1H), 4.41 (dd, J = 13.6, 10.6 Hz, 1H), 1.09 (d, J = 16.0 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.17; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (d, J = 19.3 Hz), 158.5, 155.3, 137.0 (d, J = 5.6 Hz), 134.2, 13.5, 124.4 (dd, J = 75.7, 39.0 Hz), 122.0, 121.1, 119.4, 113.9 (dd, J = 166.3, 48.2 Hz), 110.1 (d, J = 73.0 Hz), 65.5 (d, J = 61.0 Hz), 33.8 (d, J = 71.6 Hz), 24.1 (d, J = 8.3 Hz); HRMS (ESI) calcd for $C_{29}H_{28}O_4P$ [M + H$^+$] 471.1725, found 471.1729.

(*R*)-3-(*tert*-Butyl)-4-(2,6-diphenoxyphenyl)-2,3-dihydrobenzo[*d*][1,3]oxaphosphole (L4). To a solution of **3a** (1.2 g, 2.5 mmol) in THF (12 mL) at rt was added PMHS (2.4 g) and $Ti(OiPr)_4$ (1.4 g, 5.0 mmol, 1.2 equiv). The mixture was stirred at reflux under nitrogen for 12 h, and then concentrated under vacuum to remove most THF. To the residue was treated carefully with 30% NaOH solution (15 mL). Gas was generated during addition. The resulting mixture was further stirred at 60 °C for 0.5 h. To the mixture at rt was added Et_2O (20 mL). The Et_2O layer was separated and the aqueous layer was washed with Et_2O under nitrogen. The Et_2O solution was dried, concentrated, and purified by passing through a neutral alumina plug (eluent: hexanes to hexanes/ether 5/1) to give the desired product **L4** as a white crystalline solid (1.0 g, 2.25 mmol, 90 %). **L4**: mp 76 -78 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 11.2, 4.4 Hz, 2H), 7.16 (dd, J = 11.0, 4.6 Hz, 2H), 7.02～7.10 (m, 3H), 6.95 (dd, J = 7.3, 4.2 Hz, 5H), 6.73～6.80 (m, 2H), 6.56 (d, J = 8.2 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 4.85 (t, J = 45.5 Hz, 1H), 4.46 (dd, J = 25.1, 12.6 Hz, 1H), 0.81 (d, J = 12.1 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.61; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 155.3 (dd, J = 46.0, 34.4 Hz), 135.7, 128.6 (dd, J = 106.1, 65.8 Hz), 122.7 (t, J = 46.7 Hz), 118.8 (d, J = 6.6 Hz), 110.5, 69.4 (d, J = 27.5 Hz), 30.0 (d, J = 18.7 Hz), 25.9 (d, J = 14.7 Hz); HRMS (ESI) calcd for $C_{29}H_{28}O_3P$ [M + H$^+$] 455.1776, found 455.1772.

(*S*)-4-(2,6-Bis(naphthalen-1-yloxy)phenyl)-3-(*tert*-butyl)-2,3-dihydrobenzo[*d*][1,3]oxaphosphole 3-oxide (3b). To a mixture of the chiral triflate (**1**, 307 mg, 0.86 mmol), 2,6-bis(naphthalen-1-yloxy)phenylboronic acid (**2b**, 420 mg, 1.03 mmol, 1.2 equiv), Pd_2dba_3 (23.5 mg, 0.0257 mmol, 0.03 equiv), BI-DIME[14c] (17.8 mg, 0.054 mmol, 0.061 equiv), and potassium fluoride (150 mg, 2.6 mmol, 3.0 equiv) was charged degassed dioxane (5 mL). The mixture was stirred at 100 °C under nitrogen for 24 h and then concentrated to remove most of dioxane. To the residue was added with dichloromethane (10 × 2 mL) and water (10 mL) and the mixture was filtered over a celite pad. The organic layer was separated, washed with brine, concentrated, and purified by silica gel column chromatography (eluent: hexane to EtOAc) to give **3b** as white crystalline solid (293 mg, 0.515 mmol, 60%). **3b**: mp 199 -200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.79 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.29～7.52 (m, 8H), 7.11 (t, J = 8.2 Hz, 3H), 6.79 (d, J = 8.0 Hz, 1H), 6.57 (dd, J = 20.4, 8.3 Hz, 2H), 4.60 (d, J = 13.6 Hz, 1H), 4.43～4.49 (m, 1H), 1.23 (d, J = 15.8 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.83; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 152.7 (d, J = 87.8 Hz), 135.3, 129.9, 127.8, 127.3 (d, J = 18.9 Hz), 126.6 (d, J = 9.0 Hz), 126.2, 125.96 (d, J = 15.3 Hz), 125.7 (d, J = 7.8 Hz), 124.5, 123.6 (d, J = 19.2 Hz), 122.7, 122.0, 121.7, 115.9, 113.2 (d, J = 20.8 Hz), 111.8 (d, J = 5.5 Hz), 65.3 (d, J = 60.0 Hz), 29.3 (d, J = 71.3 Hz), 24.1 (d, J = 1.3 Hz); HRMS (ESI) calcd for $C_{37}H_{32}O_4P$ [M + H$^+$] 571.2038, found 571.2030.

(*R*)-4-(2,6-Bis(naphthalen-1-yloxy)phenyl)-3-(*tert*-butyl)-2,3-dihydrobenzo[*d*][1,3]oxaphosphole (L5). Ligand **L5** was prepared according to a similar procedure described for **L4**. **L5:** white crystalline solid; 78% yield; mp 180 - 182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.41～7.53 (m, 6H), 7.31 (t, J = 7.9 Hz, 1H), 7.11～7.19 (m, 2H), 6.95～7.07 (m, 3H), 6.65～6.76 (m, 3H), 4.88 (dd, J = 12.5, 1.5 Hz, 1H), 4.55 (dd, J = 25.1, 12.6 Hz, 1H), 1.01 (d, J = 12.2 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ -8.38; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 156.4, 155.4, 153.2 (d, J = 4.3 Hz), 136.9 (d, J = 18.0 Hz), 135.0, 130.6, 129.1, 127.6 (d, J = 36.6 Hz), 126.9, 126.6, 125.8, 125.4, 124.9 (d, J = 14.8 Hz), 123.6, 122.76, 122.4 (d, J = 5.3 Hz), 122.0, 113.9, 113.4, 112.9, 109.9, 70.4 (d, J = 27.5 Hz), 31.2 (d, J = 18.6 Hz), 27.1 (d, J = 14.6 Hz); HRMS (ESI) calcd for $C_{37}H_{32}O_3P$ [M + H$^+$] 555.2089, found 555.2093.

Ruthenium complex 7. To a Schlenk flask was charged **L4** (100 mg, 0.22 mmol) and 1,2-dichloroethane (2 mL) followed by $[RuCl_2(p\text{-cymene})]_2$ (64 mg, 0.11 mmol) and the resulting dark red solution was stirred at reflux under nitrogen for 18 h. Solvent was removed under vacuum to yield a red solid. The crude product was purified by flash chromatography (eluent: ethyl acetate/hexanes 2:1) to yield **7** (79 mg 0.13 mmol, 60%) as a red solid. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, J = 18.3, 9.3 Hz, 4H), 7.21 (t, J = 7.1 Hz, 1H), 7.00 (dd, J = 22.2, 9.3 Hz, 5H), 6.81 (d, J = 8.3 Hz, 1H), 6.13 (s, 1H), 5.78 (s, 1H), 5.68 (d, J = 5.4 Hz, 2H), 5.23 (s, 1H), 5.16 (d, J = 12.9 Hz, 1H), 5.04 (dd, J = 12.6, 5.2 Hz, 1H), 1.11 (d, J = 15.3 Hz, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.99; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 157.9, 155.2, 150.4, 134.7, 132.7, 131.2, 129.9 (d, J = 57.6 Hz), 127.6, 125.0 (d, J = 17.1 Hz), 120.3, 116.7, 114.4, 112.7, 95.1 (d, J = 10.9 Hz), 92.9, 89.7, 74.8, 70.7, 66.6, 38.6 (d, J = 13.8 Hz), 27.44 (d, J = 3.1 Hz); HRMS (MALDI) calcd for $C_{29}H_{27}ClO_3PRu$ $C_{37}H_{32}O_3P$ 591.0430 found 591.0435 $[M - Cl]^+$.

General procedure for asymmetric addition of arylboronic acids to aldehydes. To a mixture of arylaldehyde (0.2 mmol, 1 equiv), arylboronic acid (0.4 mmol, 2 equiv), K_2CO_3 (43 mg, 0.2 mmol, 1 equiv), ligand **L1** or **L4** (0.0042 mmol, 2.1 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (1.2 mg, 0.002 mmol, 1.0 mol %) in a Schlenk tube was added dioxane (0.5 mL). The mixture was stirred at 60 ^{o}C for 16 h, then concentrated, and purified by silica gel column chromatography (eluents: hexanes/ethyl acetate 4/1) to afford the addition product. The enantioselectivity was determined by chiral HPLC on a chiralcel OD-H, chiralcel AD-H, or Lux Amylose-2 column.

(*R*)-Naphthalen-1-yl(phenyl)methanol (6a).[13] Liquid, 96% yield, 87% ee: $[\alpha]_D^{20}$ = +33.8 (c = 1.1, $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ = -46.3 (c = 0.3, $CHCl_3$) for 98% ee, (*S*)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.40～7.47 (m, 3H), 7.36 (t, J = 9.1 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.27～7.22 (m, 1H), 6.47 (s, 1H), 2.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.8, 133.9, 130.7, 128.8, 128.5, 128.5, 127.7, 127.1, 126.2, 125.6, 125.3, 124.6, 124.0, 73.6. Chiral HPLC conditions: Lux Amylose-2 PA, 25 ^{o}C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 254 nm, 8.6 min (*S*), 11.7 min (*R*).

(*R*)-(4-Methoxyphenyl)(phenyl)methanol (6b).[9f] Liquid (92% yield); 89% ee; $[\alpha]_D^{20}$ = 5.18 (c = 0.17, $CHCl_3$); (lit.[6] $[\alpha]_D^{20}$ = -14.8 (c = 0.81, $CHCl_3$) for 92% ee, (*S*)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23～7.29 (m, 4H), 7.20～7.17 (m, 3H), 6.78 (d, J = 8.7 Hz, 2H), 5.71 (s, 1H), 3.70 (s, 3H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 144.0, 136.2, 128.4, 127.9, 127.4, 126.4, 113.9, 75.8, 55.9. Chiral HPLC conditions: Lu-Amylose-2 PA, 25 ^{o}C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 254 nm, 10.98 min (*R*), 12.0 min (*S*).

(*R*)-(4-Fluorophenyl)(phenyl)methanol (6c).[12c] Solid (95% yield); 90% ee; $[\alpha]_D^{20}$ = -5.46. (c = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25～7.15 (m, 7H), 6.92 (t, J = 8.7 Hz, 2H), 5.70 (s, 1H), 2.32 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.46; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 160.9, 143.6, 139.5, 128.6, 128.43, 126.5, 115.3, 75.6. Chiral HPLC conditions: Chiralcel OD-H, 25 ^{o}C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 9.3 min (*R*), 9.8 min (*S*).

(*R*)-(4-Bromophenyl)(phenyl)methanol (6d).[13] Liquid (85% yield); 90% ee; $[\alpha]_D^{20}$ = -6.31 (c = 0.63, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H), 7.34 (d, *J* = 4.4 Hz, 4H), 7.24～7.30 (m, 3H), 5.79 (s, 1H), 2.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.7, 131.5, 128.6, 128.2, 127.9, 126.5, 121.4, 75.7. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 8.4 min (*R*), 9.4 min(*S*).

(*R*)-(3-Methoxyphenyl)(phenyl)methanol (6e).[13] Liquid (95% yield); 87% ee; $[\alpha]_D^{20}$ = -5.18 (c = 1.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31～7.38 (m, 4H), 7.24～7.27 (m, 2H), 6.94 (d, *J* = 7.4 Hz, 2H), 6.79～7.81 (m, 1H), 5.80 (d, *J* = 3.0 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 145.5, 143.7, 129.6, 128.5, 127.6, 126.6, 118.9, 113.0, 112.1, 76.2, 55.2. Chiral HPLC conditions: Lux Amylose-2 PC, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 75/25, 254 nm, 6.0 min (*R*), 6.9 min (*S*).

(*R*)-(2-Chlorophenyl)(phenyl)methanol (6f). Liquid (90% yield); 81% ee; $[\alpha]_D^{20}$ = 16.4 (c = 1.1, $CHCl_3$) (lit. [13] $[\alpha]_D^{20}$ = +16.2 (c = 1.05, $CHCl_3$) for 82% ee, (*R*)); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58～7.61 (m, 1H), 7.19～7.58 (m, 8H), 6.14 (s, 1H), 1.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.0, 132.5, 129.5, 128.8, 128.5, 128.0, 127.8, 127.1, 126.9, 72.7. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 8.4 min (*R*), 9.9 min (*S*).

(*R*)-(2-Methoxyphenyl)(phenyl)methanol (6g).[13] Liquid (90% yield); 84% ee; $[\alpha]_D^{20}$ = +16.3 (c = 0.62, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 6.77～6.86 (m, 3H), 6.84 (t, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 3.68 (s, 3H), 3.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 143.3, 132.0, 128.7, 128.2, 127.8, 127.1, 126.6, 120.8, 110.8, 72.2, 55.4. Chiral HPLC conditions: Lux Amylose-2 PA, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 75/25, 230 nm, 3.7 min (*R*), 4.2 min (*S*).

(*S*)-(4-Chlorophenyl)(4-nitrophenyl)methanol (6h).[13] Solid (96% yield); 82% ee; $[\alpha]_D^{20}$ = -11.58 (c = 1.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.3 Hz, 2H), 7.55 (d, 2H), 7.26～7.35 (m, 4H), 5.90 (s, 1H), 2.44 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.1, 134.4, 133.4, 133.2, 132.8, 128.6, 128.4, 128.1, 127.1, 126.7, 126.4, 125.8, 123.8, 38.8, 34.3. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 210 nm, 13.8 min (*S*), 16.6 min (*R*).

(*R*)-Naphthalen-2-yl(phenyl)methanol (6i).[13] Solid (93% yield); 92% ee; $[\alpha]_D^{20}$ = -5.99 (c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.75～7.82 (m, 3H), 7.47～7.43 (m, 2H), 7.39 (dd, *J* = 6.4, 4.4 Hz, 3H), 7.32 (dd, *J* = 10.1, 4.7 Hz, 2H), 7.23～7.27 (m, 1H), 5.94 (s, 1H), 2.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 141.1, 133.2, 132.9, 128.6, 128.3, 128.1, 127.7, 126.7, 126.5, 126.0, 125.0, 124.8, 76.3. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 254 nm, 15.68 min (*S*), 18.66 min (*R*).

(*R*)-Biphenyl-4-yl(naphthalen-2-yl)methanol (6j). Solid (91% yield); 86% ee; $[\alpha]_D^{20}$ = -15.8 (c = 0.62, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82～7.88 (m, 3H), 7.58 (d, *J* = 8.3Hz, 1H), 7.42～7,47 (m, 5H), 7.44 (t, *J* = 7.7Hz, 2H), 7.35 (t, *J* = 7.4Hz, 1H), 6.06 (s, 1H), 2.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.1, 134.4, 133.4, 133.2, 132.8, 128.6, 128.4, 128.1, 127.1, 126.7, 126.4, 125.8, 123.8, 38.8, 34.3. HRMS (ESI) calcd for $C_{23}H_{18}O$ $[M + H^+]$ 310.1358, found 310.1538. Chiral HPLC conditions: Chiralcel AD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 95/5, 254 nm, 14.4 min (*S*), 15.3 min (*R*).

(*R*)-(4-Methoxyphenyl)(naphthalen-2-yl)methanol (6k).[21] solid (93% yield); 89% ee; $[\alpha]_D^{20}$ = -7.92 (c = 1.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.77～7.84 (m, 3H), 7.43～7.49 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.95 (s, 1H), 3.78 (s, 3H), 2.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.3, 136.0, 133.2, 132.8, 128.2, 128.1, 127.6, 126.1, 125.9, 124.7, 113.9, 75.9, 55.37. Chiral HPLC conditions: Lux Amylose-2 PA, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 254 nm, 15.0 min (*S*), 17.0 min (*R*).

(*R*)-(4-Chlorophenyl)(naphthalen-2-yl)methanol (6l).[21] Liquid (95% yield); 89% ee; $[\alpha]_D^{20}$ = +5.04 (c = 2.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80～7.89 (m, 4H), 7.47～7.51 (m, 2H), 7.26～7.41 (m, 5H), 5.98 (s, 1H), 2.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.1, 134.4, 133.4, 133.2, 132.8, 128.6, 128.4, 128.1, 127.1, 126.7, 126.4, 125.8, 123.8, 38.8, 34.3. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 254 nm, 16.6 min (*S*), 18.4 min (*R*).

(*S*)-1,3-diphenylprop-2-en-1-ol (6m).[9f] Liquid (80% yield); 76% ee; $[\alpha]_D^{20}$ = +16.1 (c = 0.68, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35～7.42 (m, 2H), 7.34 (t, *J* = 7.8Hz, 4H), 7.22～7.30 (m, 3H), 7.20～7.24 (m, 1H), 6.66 (d, *J* = 15.9Hz, 1H), 6.36 (dd, *J* = 6.5Hz, *J* = 15.9Hz, 1H), 5.35 (d, *J* = 6.5Hz, 1H), 2.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.1, 134.4, 133.4, 133.2, 132.8, 128.6, 128.4, 128.1, 127.1, 126.7, 126.4, 125.8, 123.8, 38.8, 34.3. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 95/5, 230 nm, 7.8 min (*S*), 9.3 min (*R*).

(*R*)-Phenyl(thiophen-2-yl)methanol (6n). Liquid (95% yield); 90% ee; $[\alpha]_D^{20}$ = -7.6 (c = 0.59, $CHCl_3$) (lit.[13] $[\alpha]_D^{20}$ = +10.0 (c = 0.32., $CHCl_3$) for 92% ee, (*S*)); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.1Hz, 2H), 7.35 (t, *J* = 7.3Hz, 2H), 7.27～7.31 (m, 1H), 7.23 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.85 (d, *J* = 3.5 Hz, 1H), 6.00 (s, 1H), 2.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 143.1, 128.5, 128.0, 126.7, 126.3, 125.5, 124.9, 72.4. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 6.6 min (*S*), 7.0 min (*R*).

(*R*)-Phenyl(thiophen-3-yl)methanol (6o).[21] Solid (93% yield); 90% ee; $[\alpha]_D^{20}$ = -5.09 (c = 1.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32～7.39 (m, 4H), 7.24～7.30 (m, 2H), 7.16 (dd, *J* = 1.8, 1.0 Hz, 1H), 6.98 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.86 (s, 1H), 2.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 143.4, 128.6, 127.8, 126.5, 126.4, 126.2, 121.7, 72.9. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 10.4 min (*S*), 11.8 min (*R*).

(*R*)-furan-2-yl(phenyl)methanol (6p).[13] Liquid (89% yield); 87% ee; $[\alpha]_D^{20}$ = +5.03 (c = 1.65, $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ = -4.71 (c = 0.64, $CHCl_3$) for 82% ee, (*S*)); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44～7.39 (m, 2H), 7.29～7.35 (m, 4H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 5.78 (s, 1H), 2.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 142.6, 140.9, 128.5, 128.1, 126.7, 110.3, 107.5, 70.1 Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 90/10, 230 nm, 9.3 min (*S*), 11.2 min (*R*).

(*S*)-naphthalen-2-yl(phenyl)methanol (6q).[13] Liquid (93 % yield); ee 85%; $[\alpha]_D^{20}$ = 10.81 (c = 0.57, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.1 Hz, 1H), 7.40～7.47 (m, 3H), 7.36 (t, *J* = 9.1 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.27～7.22 (m, 1H), 6.47 (s, 1H), 2.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.8, 133.9, 130.7, 128.8, 128.5, 128.5, 127.7, 127.1, 126.2, 125.6, 125.3, 124.6, 124.0, 73.6. Chiral HPLC conditions: Chiralcel OD-H, 25 °C, flow rate: 1.0 mL/min, heptane/isopropanol: 80/20, 254 nm, 15.6 min (*S*), 18.4 min (*R*).

3-(Cyclopentyloxy)-4-methoxybenzaldehyde (8).[19] To a mixture of 3-hydroxy-4-methoxybenzaldehyde (**10**, 1.5 *g*, 10 mmol, 1 equiv), cyclopentanol (**11**, 1.7 g, 20 mmol, 2 equiv) and triphenylphosphine (1.7 g, 10 mmol, 1 equiv) in dry THF (10 mL) at 0 °C under nitrogen was added dropwise diethyl azodicarboxylate (1.7 g, 10 mmol, 1 equiv) over 10 min. The mixture was allowed to warm to rt and stir overnight and then quenched with 5% HCl (10 mL) and ether (10 mL). The organic phase was separated and the aqueous layer was further extracted with ether (2 × 10 mL). The combined ether solution was dried over sodium sulfate, concentrated, and purified by column chromatography (eluent: EA/Hexane 1:4) to yield **8** as yellow oil (1.5 g, 70% yield). **8:** ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.42 (dd, *J* = 11.9, 3.7 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.85 (dt, *J* = 9.4, 3.1 Hz, 1H), 3.93 (s, 3H), 1.96～2.04 (m, 2H), 1.81～1.91 (m, 4H), 1.61～1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 155.4, 148.3 130.1 126.3, 112.1, 110.8 80.5 56.2 32.7, 24.1.

(*R*)-(3-(Cyclopentyloxy)-4-methoxyphenyl)(phenyl) methanol (9).[20] Liquid (90% yield); 89% ee; $[\alpha]_D^{20}$ = +4.2 (c = 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30～7.38 (m, 4H), 7.23～7.27 (m, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.85 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.76 (s, 1H), 4.74 (s, 1H), 3.81 (s, 3H), 2.30 (s, 1H), 1.78～1.90 (m, 6H), 1.54～1.63 (m, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 147.7, 144.0, 136.5, 128.4, 127.5, 126.4, 118.9, 113.5, 111.8, 80.4 75.99, 56.11, 32.78, 24.09. Chiral HPLC conditions: Chiralcel AD-H, 25 ^{o}C, flow rate: 1.0 mL/min, heptane/isopropanol: 95/5, 230 nm, 12.9 min (*S*), 13.7 min (*R*).

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ASSOCIATED CONTENT

Supporting Information. NMR spectra of **L4** and **L5**, HPLC traces and NMR spectra of chiral diarylcarbinol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] CCDC 927144 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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