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A New Class of Versatile Chiral-Bridged Atropisomeric Diphosphine Ligands: Remarkably Efficient Ligand Syntheses and Their Applications in Highly Enantioselective Hydrogenation Reactions

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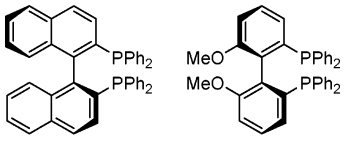
Abstract: A series of chiral diphosphine ligands denoted as PQ-Phos was prepared by atropdiastereoselective Ullmann coupling and ring-closure reactions. The Ullmann coupling reaction of the biaryl diphosphine dioxides is featured by highly efficient central-to-axial chirality transfer with diastereomeric excess >99%. This substrate-directed diastereomeric biaryl coupling reaction is unprecedented for the preparation of chiral diphosphine dioxides, and our method precludes the tedious resolution procedures usually required for preparing enantiomerically pure diphosphine ligands. The effect of chiral recognition was also revealed in a relevant asymmetric ring-closure reaction. The chiral tether bridging the two aryl units creates a conformationally rigid scaffold essential for enantiofacial differentiation; fine-tuning of the ligand scaffold (e.g., dihedral angles) can be achieved by varying the chain length of the chiral tether. The enantiomerically pure Ru- and Ir-PQ-Phos complexes have been prepared and applied to the catalytic enantioselective hydrogenations of α- and β-ketoesters (C=O bond reduction), 2-(6′-methoxy-2′-naphthyl)-propenoic acid, alkyl-substituted β-dehydroamino acids (C=C bond reduction), and *N*-heteroaromatic compounds (C=N bond reduction). An excellent level of enantioselection (up to 99.9% ee) has been attained for the catalytic reactions. In addition, the significant ligand dihedral angle effects on the Ir-catalyzed asymmetric hydrogenation of *N*-heteroaromatic compounds were also revealed.

Introduction

The design and development of new chiral ligands for efficient chirality transfer has a pivotal role in transition metal-catalyzed asymmetric reactions.[1] In this regard, chelating diphosphine ligands with an atropisomeric biaryl scaffold proved to be highly efficient chiral inducers in many enantioselective transformations.[2−7]

Among many successful ligand systems, axially chiral BINAP, MeO-Biphep, and P-Phos, etc. are the prototypical supporting ligands that have found widespread uses in many metal-catalyzed asymmetric reactions. Notable examples include enantioselective hydrogenations and hydrosilylations with remarkable degree of enantioselectivities.[2a−c,8−9] Notwithstanding,



BINAP BIPHEP

asymmetric hydrogenation of certain substrates (e.g., α- and β-ketoesters[3e,f,5b]) using these diphosphine ligands remains problematic due to the lack of ligand rigidity. Moreover, several

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studies revealed the influence of the bite angles in the chiral diphosphines on the reactivity and selectivity of some catalytic reactions, and optimal dihedral angles are essential for attaining high enantioselectivities in asymmetric catalysis.[3c−e,5b,10] For example, a family of Tunaphos ligands with adjustable dihedral angles was shown to effect highly enantioselective Ru-catalyzed hydrogenation of β-ketoesters and enol acetates.[11]

Chirality transfer from central to planar/axial asymmetry for the syntheses of optically active biaryl-derived diols has been successfully demonstrated.[12] Compared to the classical coupling−resolution approaches, realization of highly diastereomeric aryl−aryl coupling reactions through central-to-axial chirality transfer is conceptually appealing since it avoids the tedious resolution procedures for acquiring enantiomerically pure diphosphine ligands (Figure 1). To our knowledge, the concept of central-to-axial chirality transfer remains unexplored for the development of atropisomeric biarylphosphines.

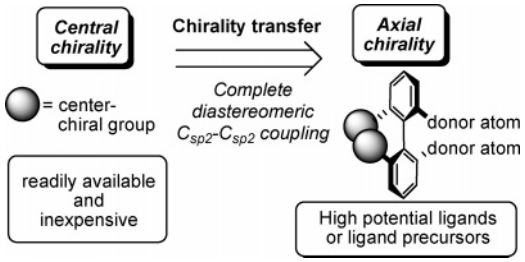

Figure 1. Central-to-axial chirality transfer for chiral ligand synthesis.

Pertinent to this concept, we previously pursued the intermolecular Ullmann coupling of two chiral dioxolane-modified phosphine oxides with 40% de, and the two diastereomeric diphosphine dioxides were separated chromatographically to afford optically pure diphosphine ligands.[13] The presence of additional chiral centers on the ligand backbones was found to exert significant influences on the enantioselectivity and activity of the catalysts in asymmetric hydrogenations.[13] Recently, we succeeded in achieving a highly atropdiastereoselective Ullmann coupling for preparing a novel bridged C_2-symmetric biphenyl-based diphosphine ligand (*R*)-[6,6′-(2*S*,3*S*-butadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl [(R_{ax},2*S*,3*S*)-**7a**],[14] abbreviated as *RSS*-**7a**. The atropdiastereoselective Ullmann coupling reaction produced a diastereomerically pure biaryl diphosphine dioxide, and thus no subsequent resolution was required for the preparation of the enantiomerically pure chiral ligand. The ligand *RSS*-**7a** showed excellent enantioselectivities in asymmetric hydrogenations. As part of our continuing effort in designing new ligand scaffolds for asymmetric catalysis, we herein present a full account of the atropdiastereomeric Ullmann coupling reactions for the synthesis of a series of atropisomeric PQ-Phos such as (*R*,2*S*,3*S*)-Bu-PQ-Phos, **7a**, (*S*,2*R*,4*R*)-Pent-PQ-Phos, **7b**, and (*S*,2*R*,5*R*)-Hex-PQ-Phos, **7c**. Moreover, we also present a ring-closure synthetic route (Scheme 2) as an alternative pathway for preparing the opposite isomers of the PQ-Phos ligands, which are unobtainable via the intramolecular Ullmann coupling reaction. It is also noted that introduction of a chiral bridge provides additional handles for fine-tuning the ligand rigidity and the dihedral angle (and bite angle). The catalytic activities of the Ru(II)- or Ir(I)-PQ-Phos complexes in asymmetric hydrogenation reactions of α- and β-ketoesters, 2-(6′-methoxy-2′-naphthyl)propenoic acid, β-dehydroamino acids, and nitrogen-containing heteroaromatic compounds are presented.

Results and Discussion

Diastereoselective Ullmann Coupling Reactions. Scheme 1 depicts the diastereoselective Ullmann coupling reactions (*reaction e*) for the synthesis of the chiral diphosphines **7**.[14]

Treatment of diol tosylates/mesylates [$n = 0$ (**2a**); $n = 1$ (**2b**); $n = 2$, (**2c**)] with 3-bromoanisole afforded chiral bis(bromoether) **3a**−**c** in 53%, 57%, and 74% yield, respectively. Lithium/bromine exchange of **3** with *n*-BuLi followed by the addition

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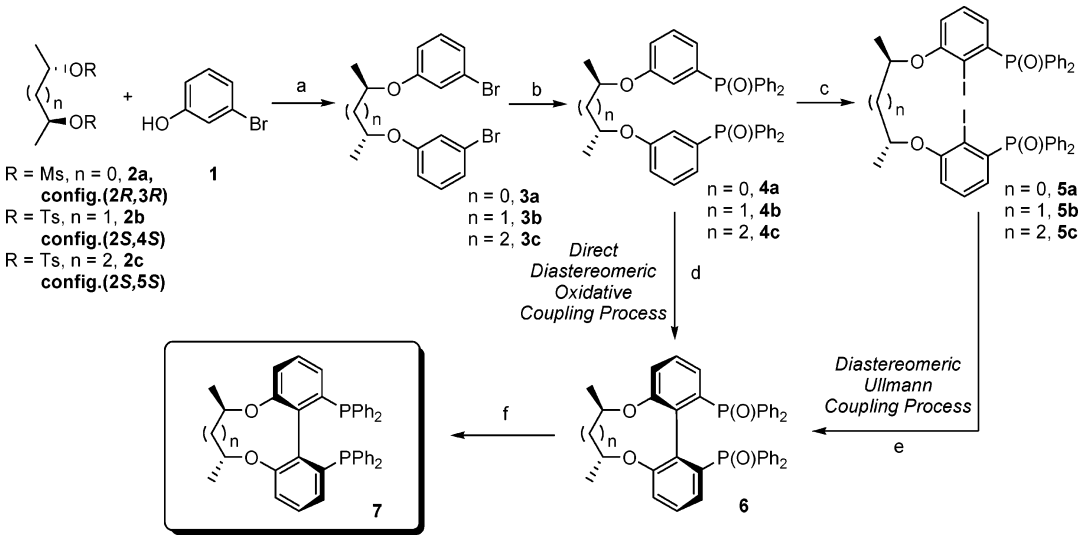
Scheme 1. Intramolecular Diastereoselective Coupling Pathways[a]



[a] Reaction conditions: (a) K_2CO_3 or Cs_2CO_3, DMSO, rt; (b) i. *n*-BuLi, THF, −78 °C; ii. Ph_2PCl, −78 °C − rt; iii. H_2O_2, acetone, 0 °C; (c) i. LDA, THF, −78 °C; ii. I_2, −78 °C − rt; (d) i. LDA, −15 °C; ii. $FeCl_3$, rt. (e) Cu, DMF, 140 °C; (f) $HSiCl_3$, Bu_3N, toluene, reflux.

of chlorodiphenylphosphine furnished the corresponding chiral bridged arylphosphines, which were subsequently converted to diphosphine oxides using 30% H_2O_2: 85% (**4a**), 86% (**4b**), and 91% (**4c**) yield. Ortho-lithiation with lithium diisopropylamide at −78 °C followed by I_2 quenching gave diiodides in good yields: (89%) **5a**, (82%) **5b**, and 84% (**5c**).[9b] During an optimization study, we found that when an iodine solution in THF was added to the lithiated **4** at −78 °C, the product diiodide was formed in only 30−40% yield along with a complicated mixture of products. However, reversing the order of addition, i.e., adding the lithiated **4** in THF to the iodine solution at −78 °C, afforded the diiodide products in up to 89% yield.

By employing the copper-mediated Ullmann coupling protocol, the chiral bridged phosphine oxides **5a**−**c** underwent homocoupling with excellent central-to-axial chirality transfer, and the corresponding diphosphine dioxides [(*RSS*)-**6a**, de > 99%; (*SRR*)-**6b**, de > 99%; (*SRR*)-**6c,** de = 98%] were obtained in 91%, 71%, and 61% yields, respectively (Scheme 1). Reduction of **6** with $HSiCl_3/Bu_3N$ afforded the desired optically pure PQ-Phos ligand **7a**−**c** in 96%, 93%, and 97% yields, respectively.

Previously, we showed that direct oxidative coupling of **4a** ($n = 0$) was also a viable route to (*RSS*)-**6a**, which was formed in 61% yield with > 99% de.[14] In this study, we also attempted to synthesize the chiral bridged diphosphine dioxides (*SRR*)-**6b**,**c** directly from **4b**,**c** ($n = 1$ and 2) by the oxidative coupling reaction. Using a lithium diisopropylamide/anhydrous $FeCl_3$ procedure,[14,15] the reactions of **4b** and **4c** produced (*SRR*)-**6b** and (*SRR*)-**6c** in only 10−20% yields.

As noted earlier, the intramolecular Ullmann coupling reaction of **5a** produced (*RSS*)-**6a** with >99% diastereoselectivity. In this work, the intramolecular Ullmann coupling of diiodides **5b**,**c** containing C_3 ($n = 1$)- and C_4 ($n = 2$)-bridges were examined. For example, intramolecular coupling of **5b** was found to produce (*SRR*)-**6b** with >99% de based on ^{1}H NMR and HPLC analyses of the crude reaction mixture and optical rotation measure of its crystal. Similarly, the analogous reaction of **5c** afforded (*SRR*)-**6c** in 98% de according to HPLC analysis of the crude product. However, the intramolecular Ullmann coupling reactions of **5b** and **5c** containing C_3- and C_4-bridges gave the corresponding diphosphine dioxides in lower yields [71% for (*SRR*)-**6b** and 61% for (*SRR*)-**6c**]. Nevertheless, optically pure diphosphine dioxides **6b**,**c** were obtained (71% and 61% yields, respectively) after simple column chromatography without chiral resolution.

Diastereomeric Ring-Closure Reaction. As noted above, the chiral tether-directed intramolecular Ullmann coupling reactions proved to be highly successful. However, attainment of such a high diastereoselectivity limited the access to the other diastereomers (e.g., (*SSS*)-**6a**, (*RRR*)-**6b**, and **6c**) of the PQ-Phos family of ligands. Considering the importance of structural diversity in designing new chiral ligands for asymmetric catalysis, we developed a diastereomeric ring-closure route for preparing the other diastereomeric forms of the diphosphine dioxides using C_2-symmetric chiral diols as reagents (Scheme 2).

At the outset, demethylation of (*S*)- or (*R*)-MeO-BiphepO **8** with BBr_3 followed by hydrolysis furnished (*S*)- or (*R*)-HO-BiphepO **9** in 75% and 78% yields, respectively.[16] Subsequently, (*S*)- or (*R*)-**9** reacted with (2*R*,3*R*)-butanediol dimesylate **(2a)** in the presence of Cs_2CO_3 afforded (*SSS*)-**6a** or its diastereomer (*RSS*)-**6a** in 58% and 64% yields, respectively. Likewise, treatment of (*S*)- or (*R*)-**9** with (2*S*,5*S*)-hexanediol tosylate **(2c)** and K_2CO_3 as base produced (*SRR*)-**6c** in 68% yield. (*RRR*)-**6c** was also isolated in 55% yield after chromatographic purification.

The reaction of (*S*)-**9** with (2*S*,4*S*)-pentanediol di-*p*-tosylate **(2b)** produced (*SRR*)-**6b** in 72% yield via the ring-closure reaction. However, if (*R*)-**9** was employed as the starting material, the (R_{ax})-form diastereomer was not obtained from the analogous reaction with (2*S*,4*S*)-pentanediol di-*p*-tosylate. ^{1}H NMR analysis of the reaction mixture containing (*R*)-**9** and (2*S*,4*S*)-pentanediol di-*p*-tosylate revealed a mixture of oligomers. With racemate **9** as the starting material, the reaction with

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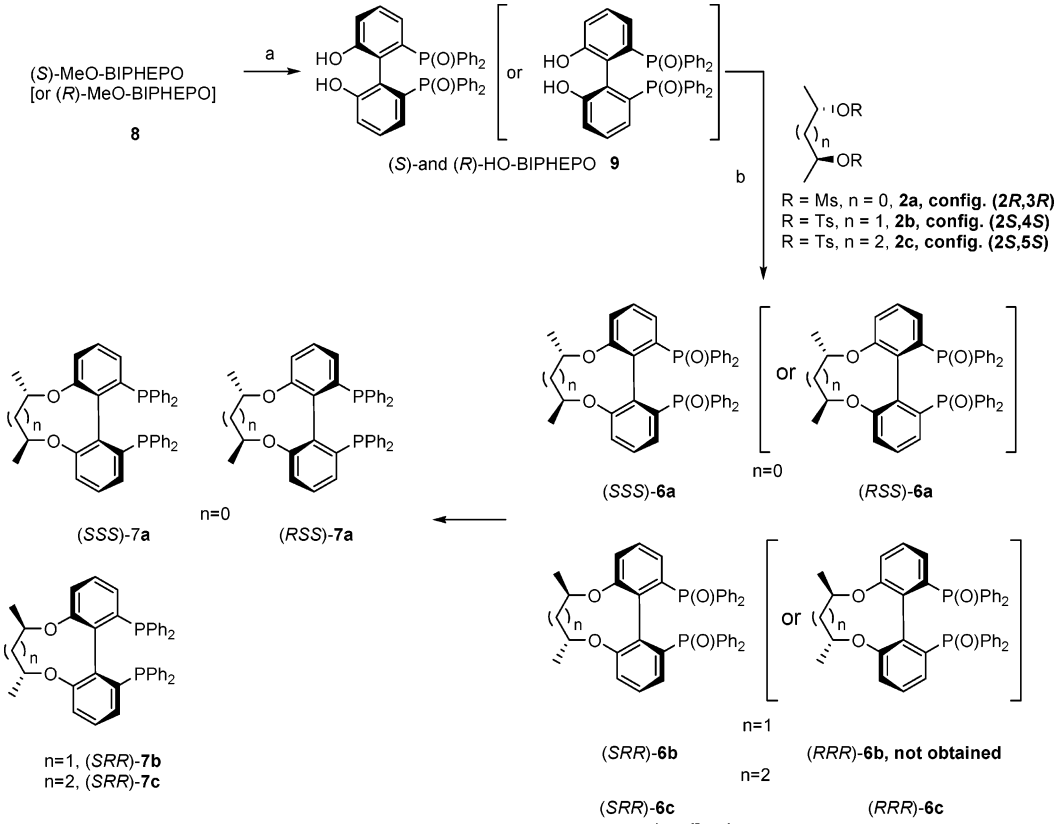
Scheme 2. Ring Closure Pathways[a]



[a] Reaction conditions: (a) BBr_3, CH_2Cl_2, −78 °C− rt; (b) DMF, 55−60 °C, Cs_2CO_3 for **6a**, K_2CO_3 for **6b**, **6c**.

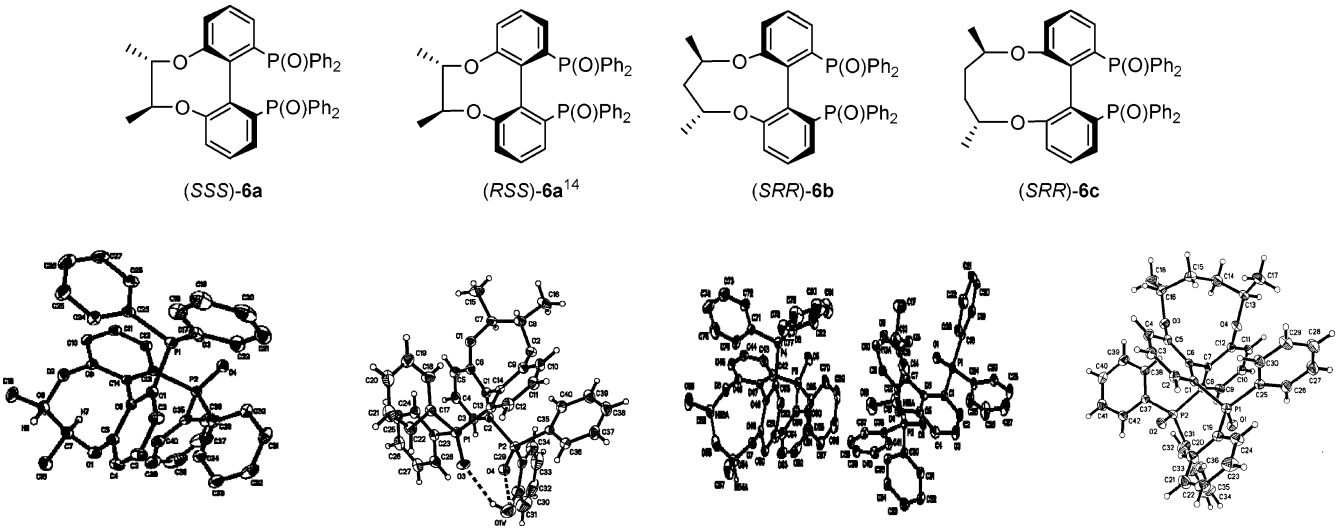


Figure 2. ORTEP structures of diphosphine dioxides **6**.

(2*S*,4*S*)-pentanediol di-*p*-tosylate gave (*SRR*)-**6b** exclusively as a single diastereomer. These results clearly revealed the precise chiral recognition directed by the linking unit in this ring-closure reaction. To our best knowledge, this is the first successful example to obtain single diastereomeric diphosphine oxides by substrate-directed asymmetric ring-closure reaction. The molecular structures of **6a**, **6b**, **6c** prepared via the two synthetic routes were all determined by single-crystal X-ray diffraction (Figure 2).

MM2 Calculations of the Dihedral Angle of the New Diphosphine Ligands. Bite angles (P−M−P) of chelating diphosphine ligands are known to exert influence on the reactivity and selectivity of some asymmetric reactions.[5b,11] It is conceivable that the bite angle should increase with an increase in the dihedral angles of the chelating atropisomeric diphosphines. In this work, we have estimated the dihedral angles of the PQ-Phos ligands **7a**−**7c** using Chem 3D MM2 modeling, and the values are given in Table 1.[17] To validate this method, we also computed the dihedral angle of BINAP by the Chem 3D MM2 method, and comparable values (86° and 87°) to the literature values were obtained.[3f,11a] As shown in Table 1, the dihedral angles show significant dependence on

(17) *Chem 3D Ultra*, 7.0.0 Version; Cambridge Scientific Computing, Inc., 2001.

Table 1. Dihedral Angles of Ligands **7a-d**

ligand	(*SSS*)-**7a**	(*RSS*)-**7a**	(*SRR*)-**7b**	(*SRR*)-**7c**	MeO−Biphep	BINAP
dihedral angle	64.8°	−66.5°	80.0°	88.8°	83.2°	86.6°

the length of the chiral tethers: 64.8° [(*SSS*)-**7a**], −66.5° [(*RSS*)-**7a**], 80.0° [(*SRR*)-**7b**] and 88.8° [(*SRR*)-**7c**].

Asymmetric Hydrogenation of α-Ketoesters. The enantioselective hydrogenation of α-ketoesters provides a direct approach to optically pure α-hydroxyesters, which are important blocks for organic syntheses. In contrast to the great success achieved in the asymmetric hydrogenation of β-ketoesters, the success in the homogeneous asymmetric hydrogenation of α-ketoesters has been quite limited.[3c−d,4e,5b,18] α-Ketoesters are known to be sensitive substrates for asymmetric hydrogenation and often require delicate optimization of reaction conditions. Occasionally, acid additives may be necessary to increase both the activity and selectivity of the ruthenium catalysts for the hydrogenation of ketones.[18b] Recently, we reported some preliminary results of the ruthenium-catalyzed enantioselective hydrogenation of methyl benzoylformate.[14] The reaction employing (*RSS*)-**7a** as ligand afforded much better enantioselectivity (97% ee) than that when using BINAP (79% ee) as ligand. Here we describe a comprehensive study on the scope and limitations on the Ru-PQ-Phos-catalyzed asymmetric hydrogenation of α-ketoesters.

Treatment of ethyl pyruvate (R^1 = Me, R^2 = Et) with [Ru(*RSS*-**7a**)(C_6H_5)Cl]Cl (0.167 mol %) in MeOH (1 mL) under 500 psig H_2 at room temperature for 44 h furnished ethyl (*R*)-lactate in 93% yield and 93% ee (Table 2, entry 1). The formation of methyl (*R*)-lactate (7%) due to transesterification was also detected by chiral GC analysis. The ruthenium catalyst was prepared by heating [Ru(benzene)Cl_2]$_2$ and **7** in a solution of EtOH and CH_2Cl_2, following a literature procedure. For the asymmetric hydrogenation of pyruvate, the current Ru-catalyzed system based on *RSS*-**7a** can be used with high efficiency under relatively mild hydrogen pressure and room temperature without the need of additives.

As shown in Table 2, methanol was the solvent of choice for the Ru-PQ-Phos-mediated asymmetric hydrogenation. Poor conversion and enantioselectivities were obtained in THF and dichloromethane as solvent (entries 2 and 3). To avoid transesterification of the ethyl esters, ethanol had been used as solvent for the catalytic hydrogenation. The Ru-catalyzed hydrogenation of ethyl pyruvate in ethanol showed 87% conversion after 48 h with 84% ee (entry 4). Although higher reaction temperature (50−90 °C) accelerated the reaction to complete substrate consumption in 24 h, the enantioselectivities decreased to the level of 76−79% ee (entries 5 and 6).

The asymmetric hydrogenation of ethyl pyruvate using other ligands *SSS*-**7a**, *SRR*-**7b**, and *SRR*-**7c** also gave excellent enantioselectivity (89−90% ee) under similar reaction conditions. As expected, comparable results (91−92% ee) were obtained for the asymmetric hydrogenation of methyl pyruvate (entries 10−13). The PQ-Phos ligands are also effective for the asymmetric hydrogenation of ethyl α-ketoesters bearing bulky R^1 groups such as *i*-Pr, Ph, Ph$(CH_2)_2$; enantioselectivities of 96−98% ee have been attained (entries 14−31). To our knowledge, these results are among the best thus far reported for the homogeneous asymmetric hydrogenation of α-ketoesters. A notable example in the literature is the asymmetric hydrogenation of methyl benzoylformate using [RuI(*p*-cymene)-BICHEP]I as a catalyst, and the product lactate was formed in 99% ee.[18a]

Asymmetric Hydrogenation of β-Ketoesters. The PQ-Phos ligands have been applied for the catalytic hydrogenation of β-ketoesters, and the results are summarized in Table 3.[11a,19] Excellent ee's of β-hydroxyesters were obtained with ligands **7a**−**c**. In most cases, the ee's compared favorably with the results obtained using the MeO-Biphep or BINAP ligands. For the hydrogenation of ethyl 2-chlorobenzoyl acetate, the Ru-(BINAP) system was found to achieve only 16 and 10% ee for the anti and syn products (entry 6). However, when the PQ-Phos ligands (*RSS*)-**7a** and (*SRR*)-**7b** were employed for the Ru-catalyzed ethyl 2-chlorobenzoyl acetate hydrogenation, the *anti*-β-hydroxyester was obtained in 93% ee and 95% ee, respectively. For the *syn*-β-hydroxyester, enantioselectivities of 26% (for *RSS*-**7a**) and 37% (for *SRR*-**7b**) were observed.

In this study, we did not observe significant variation of enantioselectivities with the dihedral angles (64°−89°) of the PQ-Phos ligands in the asymmetric hydrogenation of substrates having small R^1 and R^2 groups (entries 1−4). This finding was rather distinct from the earlier findings by Zhang and co-workers involving TunaPhos as ligand.[11a] However, for β-ketoesters having bulkier R^1 or R^2 groups such as ethyl benzoyl acetate and ethyl 2-chlorobenzoyl acetate (R^1 = Ph, R^2 = Cl) (entries 5 and 6), the influence of the dihedral angles on the enantioselectivities became more apparent. The best results (97% ee) for ethyl benzoyl acetate were obtained using ligand (*SRR*)-**7b** with a dihedral angle = 80° (entry 5). This observation may be attributed to the steric interaction between the substrates and the PQ-Phos ligand.

Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid. Asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid is an economical method for the preparation of naproxen, a nonsteroidal antiinflammatory drug.[2b,13,14,20] The PQ-Phos ligands have been tested in this reaction. As shown in Table 4, the reactivities and enantioselectivities of the Ru catalysts with **7a**−**c** as ligands compared favorably with the Ru(BINAP) and Ru(MeO-Biphep) systems. Methanol was found to be the best solvent; better ee's were obatined at 0 °C and under 1000 psi H_2 pressure. Little dependence of the ee values upon the ligand dihedral angles was observed.

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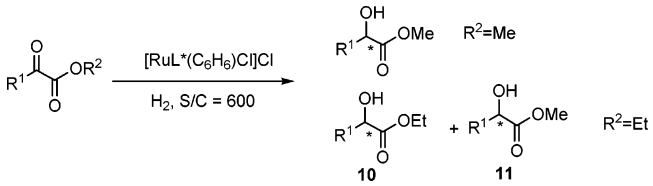
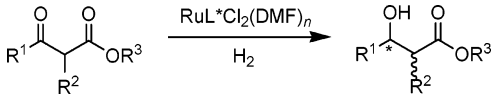
Table 2. Asymmetric Hydrogenation of α-Ketoesters Catalyzed by [RuL(η^6-C_6H_6)Cl]Cl[a]



entry	R^1	R^2	ligand	solvent	*T* (°C)	time (h)	conv (%)	**10**/(**10**+**11**) %	ee of **10**,[b] config
1	Me	Et	(*RSS*)-**7a**	MeOH	rt	44	>99	93	93 (*R*)
2	Me	Et	(*RSS*)-**7a**	THF	rt	48	16	–	–
3	Me	Et	(*RSS*)-**7a**	DCM	rt	48	0	–	–
4	Me	Et	(*RSS*)-**7a**	EtOH	rt	48	87	100	84 (*R*)
5	Me	Et	(*RSS*)-**7a**	EtOH	50	24	>99	100	79 (*R*)
6	Me	Et	(*RSS*)-**7a**	EtOH	90	20	>99	100	76 (*R*)
7	Me	Et	(*SSS*)-**7a**	MeOH	rt	48	>99	92	90 (*S*)
8	Me	Et	(*SRR*)-**7b**	MeOH	rt	48	>99	96	90 (*S*)
9	Me	Et	(*SRR*)-**7c**	MeOH	rt	48	>99	97	89 (*S*)
10	Me	Me	(*SSS*)-**7a**	MeOH	rt	48	>99	–	91 (*S*)
11	Me	Me	(*RSS*)-**7a**	MeOH	rt	48	>99	–	92 (*R*)
12	Me	Me	(*SRR*)-**7b**	MeOH	rt	48	>99	–	91 (*S*)
13	Me	Me	(*SRR*)-**7c**	MeOH	rt	48	>99	–	91 (*S*)
14	*i*-Pr	Et	(*SSS*)-**7a**	MeOH	rt	100	>99	97	96 (S)
15	*i*-Pr	Et	(*RSS*)-**7a**	MeOH	rt	44	>99	99	98 (*R*)
16	*i*-Pr	Et	(*SRR*)-**7b**	MeOH	rt	100	>99	97	97 (*S*)
17	*i*-Pr	Et	(*SRR*)-**7c**	MeOH	rt	100	>99	96	96 (*S*)
18	Ph	Me	(*SSS*)-**7a**	MeOH	rt	20	>99	–	97 (*S*)
19	Ph	Me	(*RSS*)-**7a**	MeOH	rt	20	>99	–	98 (*R*)
20	Ph	Me	(*SRR*)-**7b**	MeOH	rt	20	>99	–	98 (*S*)
21	Ph	Me	(*SRR*)-**7c**	MeOH	rt	20	>99	–	97 (*S*)
22	Ph	Et	(*SSS*)-**7a**	MeOH	rt	62	>99	88	96 (*S*)
23	Ph	Et	(*RSS*)-**7a**	MeOH	rt	40	96	93	97 (*R*)
24	Ph	Et	(*RSS*)-**7a**	MeOH	rt	55	>99	89	98 (*R*)
25	Ph	Et	(*SRR*)-**7b**	MeOH	rt	60	>99	88	96 (*S*)
26	Ph	Et	(*SRR*)-**7c**	MeOH	rt	60	99	89	95 (*S*)
27	$Ph(CH_2)_2$	Et	(*SSS*)-**7a**	MeOH	rt	72	99	92	97 (*S*)
28	$Ph(CH_2)_2$	Et	(*RSS*)-**7a**	MeOH	rt	48	>99	94	98 (*R*)
29	$Ph(CH_2)_2$	Et	(*SRR*)-**7b**	MeOH	rt	72	>99	84	96 (*S*)
30	$Ph(CH_2)_2$	Et	(*SRR*)-**7c**	MeOH	rt	60	98	89	97 (*S*)
31	$Ph(CH_2)_2$	Et	(*SRR*)-**7c**	MeOH	rt	74	>99	79	97 (*S*)

[a] Reaction conditions: substrate/catalyst = 600:1 (mol/mol); substrate concentration = 0.5 mmol/mL, *P* = 500 psi H_2. [b] The ee values were determined by chiral GC with a J&W Scientific Cyclosil-B column.

Table 3. Asymmetric Hydrogenation of β-Ketoesters Catalyzed by $RuLCl_2(DMF)_n$[a]

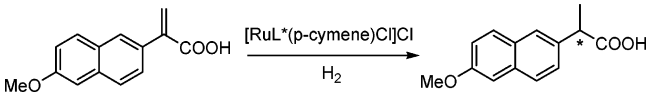


				ee, config					
entry	R^1	R^2	R^3	(*SSS*)-**7a**	(*RSS*)-**7a**	(*SRR*)-**7b**	(*SRR*)-**7c**	(*S*)-MeO–Biphep	(*S*)-BINAP
1[b]	Me	H	Me	99.8 (*S*)	>99 (*R*)	98 (*S*)	99 (*S*)	98 (*S*)	98 (*S*)
2[b]	Me	H	Et	99.8 (*S*)	>99 (*R*)	99 (*S*)	99 (*S*)	98 (*S*)	98 (*S*)
3[b]	Me	H	CH_2Ph	>99 (*S*)	>99 (*R*)	99 (*S*)	>99 (*S*)	98 (*S*)	96 (*S*)
4[b]	$ClCH_2$	H	Et	97 (*R*)	97 (*S*)	96 (*R*)	96 (*R*)	96 (*R*)	94 (*R*)
5[c]	Ph	H	Et	89 (*R*)	96 (*S*)	97 (*R*)	95 (*R*)	93 (*R*)	89 (*R*)
6[c]	Ph	Cl	Et	71	93	95	73	71	16
				(13% anti)	(22% *anti*)	(2*S*,3*S*)	(14% *anti*)	(16% *anti*)	(10% anti)
				(2*S*,3*S*)	(2*R*,3*R*)	(28% a*nti*)	(2*S*,3*S*)	(2*S*,3*S*)	(2*S*,3*S*)
				9	26	37	7	5	10
				(87% syn)	(78% *syn*)	(72% *syn*)	(86% *syn*)	(84% *syn*)	(90% syn)
				(2*R*,3*S*)	(2*S*,3*R*)	(2*R*,3*S*)	(2*R*,3*S*)	(2*R*,3*S*)	(2*R*,3*S*)

[a] Reaction conditions: solvents = 12.5 μL CH_2Cl_2 + 987.5 μL MeOH or EtOH; reaction time = 24 h, except for entry 6 (100 h); substrate/[Ru]= 667:1 (mol/mol), except for entry 6 (substrate/[Ru] = 100/1); substrate concentration = 0.5 mmol/mL; *T* = 70 °C, except for entry 6 (room temperature) and entry 4 (optimum temperature, 70−100 °C); *P* = 50 psi H_2, except for entry 6 (1000 psi H_2); complete conversions were obtained in all cases. [b] The ee values were determined by chiral GC with a Varian CP Chirasil-DEX CB column (25 m × 0.25 mm) after converting the products to the corresponding acetyl derivatives. [c] The ee values were determined by chiral HPLC with a Daicel Chiralcel OD column; the ratios of anti to syn products were determined by ^1H NMR.

Asymmetric Hydrogenation of (β-Acylamino)acrylates. Enantiomerically pure β-amino acids and their derivatives are important ingredients or intermediates for pharmaceutical products.[21] The asymmetric hydrogenation of dehydroamino

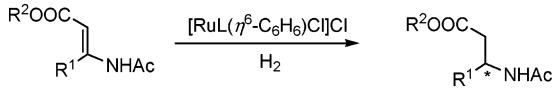
Table 4. Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid with [RuL(*p*-cymene)Cl]Cl[a,b]



				ee,conversion[b]					
entry	P_{H2} (psi)	T (°C)	reaction time (h)	(*SSS*)-**7a**	(*RSS*)-**7a**	(*SRR*)-**7b**	(*SRR*)-**7c**	(*S*)-MeO–Biphep	(*S*)-BINAP
1	1000	rt	4	91 (*S*)	90 (*R*)	89 (*S*)	88 (*S*)	89 (*S*)	89 (*S*)
2	1500	rt	4	93 (*S*)	91 (*R*)	90 (*S*)	90 (*S*)	90 (*S*)	90[c] (*S*)
3	1000	rt	0.5	91 (81%) (*S*)	89 (98%) (*R*)	89 (100%) (*S*)	88 (100%) (*S*)	89 (100%) (*S*)	89 (90%) (*S*)
4	1000	0	24	96 (*S*)	95 (*R*)	95 (*S*)	95 (*S*)	94 (*S*)	94 (*S*)
5	1500	0	24	97 (*S*)	96 (*R*)	95 (*S*)	95 (*S*)	94 (*S*)	–

[a] Reaction conditions: solvent = MeOH (2.5 mL), substrate/catalyst = 100:1 (mol/mol), substrate concentration = 2.0 mg/mL. [b] The ee values were determined by chiral HPLC with a Sumichiral OA-2500 column; complete conversions were obtained in all cases, except for entry 3. [c] P = 1600 psi H_2.

Table 5. Asymmetric Hydrogenation of β-(Acylamino)Acrylates with [RuL(η^6-C_6H_6)Cl]Cl[a]



				time	ee,[b] config.			
entry	R^1	R^2	T (°C)	(h)	(*SSS*)-**7a**	(*RSS*)-**7a**	(*SRR*)-**7b**	(*SRR*)-**7c**
1	Me	Me	rt	6	97 (*R*)	96 (*S*)	96 (*R*)	97 (*R*)
2	Me	Me	0	48	97 (*R*)	98 (*S*)	97 (*R*)	98 (*R*)
3	Me	Et	rt	6	97 (*R*)	96 (*S*)	96 (*R*)	97 (*R*)
4	Me	Et	0	48	97 (*R*)	98 (*S*)	97 (*R*)	99 (*R*)
5	Et	Me	rt	6	95 (*R*)	95 (*S*)	94 (*R*)	95 (*R*)
6	Et	Me	0	48	95 (*R*)	97 (*S*)	96 (*R*)	97 (*R*)
7	*i*-Pr	Me	rt	6	95 (*R*)	94 (*S*)	95 (*R*)	96 (*R*)
8	*i*-Pr	Me	0	48	97 (*R*)	99 (*S*)	96 (*R*)	97 (*R*)
9	*n*-Pr	Et	rt	6	93 (*R*)	94 (*S*)	92 (*R*)	94 (*R*)
10	*n*-Pr	Et	0	48	94 (*R*)	96 (*S*)	92 (*R*)	95 (*R*)
11	*t*-Bu	Me	rt	6	99.8 (*R*)	99.8 (*S*)	99.6 (*R*)	>99.9 (*R*)

[a] Reaction conditions: 1.7 mg substrate; substrate/catalyst = 100 (mol/mol); substrate concentration = 0.05−0.09 M in MeOH, P = 250 ps i H_2; the conversions were determined by NMR and GC analysis and were found to be higher than 99.9% in all cases. [b] The ee values were determined by chiral GC with a 25 m × 0.25 mm Chirasil-DEX CB column or 30 m × 0.25 mm γ-DEX-225 column.

acids is one of the most efficient routes to the corresponding optically active β-amino acids. Rh-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates has recently been developed successfully.[22] However, satisfactory examples with ruthenium-catalyzed systems are limited.[23]

In this work, we found that the cationic Ru(II) complexes of PQ-Phos showed a high level of asymmetric induction in the asymmetric hydrogenation of β-alkyl-substituted β-(acylamino)-acrylates (Table 5). Methanol was the best solvent for the catalytic reaction. Generally, low reaction temperature (0 °C) was essential to high enantioselectivity (>97% ee). No characteristic dependence of the enantioselectivity upon the dihedral angles of the ligands was apparent. Substrates with a bulky alkyl substituent gave the best ee (up to 99.9%, entry 11).

Asymmetric Hydrogenation of *N*-Heteroaromatic Compounds. The asymmetric hydrogenation of C=N bonds is an appealing protocol for the synthesis of chiral amines. The enantioselective hydrogenation of quinolines and other *N*-heteroaromatic compounds, which are easily available, provides enantiomerically pure tetrahydroquinoxalines and heterocycloalkanes of great biological interest.[24] Thus far, there are limited successful literature examples concerning highly enantioselective hydrogenation of C=N bond to chiral amines.[25,26] Recently, the asymmetric hydrogenation of quinolines using [Ir(COD)Cl]$_2$/MeO-Biphep/I_2 catalyst was established and 83−95% yield and >90% ee were reported.[26a]

In this regard, we undertook a study on the asymmetric hydrogenation of *N*-heteroaromatic compounds using the PQ-Phos ligands **7a**−**7c** instead of MeO-Biphep. As shown in Table 6, this reaction was strongly solvent dependent. Toluene was found to be the solvent of choice for the reaction of quinoline **12**. For example, the best enantioselectivity (92% ee) was obtained for the hydrogenation of 2,6-dimethylquinoline in toluene (entry 3). Nevertheless, for the hydrogenation of 2-methylquinoxaline **13** and 2,3,3-trimethylindolenine **14**, THF and CH_2Cl_2 appeared to be the best solvents (entries 8 and 10). Further studies are listed in Table 7.

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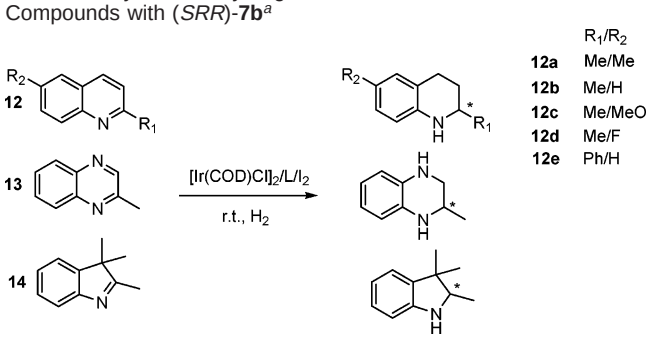
Table 6. Asymmetric Hydrogenation of *N*-Heteroaromatic Compounds with (*SRR*)-**7b**[a]



entry	substrate	solvent	ee[b] (%)	config
1	**12a**	*i*-PrOH	58	*S*
2	**12a**	CH_2Cl_2	80	*S*
3	**12a**	toluene	92	*S*
4	**12a**	THF	84	*S*
5	**13**	*i*-PrOH	−	
6	**13**	CH_2Cl_2	64	*R*
7	**13**	toluene	61	*R*
8	**13**	THF	80	*R*
9	**14**	*i*-PrOH	15	*R*
10	**14**	CH_2Cl_2	72	*R*
11	**14**	toluene	50	*R*
12	**14**	THF	42	*R*

[a] Reaction conditions: 0.2 mmol substrate, substrate/catalyst = 100 (mol/mol), substrate concentration = 0.2 mmol/mL, P = 700 psi H_2, reaction time = 20 h, the conversions were higher than 99% in all cases. [b] The ee values were determined by chiral HPLC.

Table 7. Asymmetric Hydrogenation of *N*-Heteroaromatic Compounds[a]

			ee,[b] config				
entry	substrate	solvent	(*RSS*)-**7a**	(*SSS*)-**7a**	(*SRR*)-**7b**	(*SRR*)-**7c**	(*S*)-MeO−Biphep
1	**12a**	toluene	85 (*R*)	88 (*S*)	92 (*S*)	91 (*S*)	90 (*S*)
2	**12b**	toluene	82 (*R*)	88 (*S*)	89 (*S*)	79 (*S*)	83 (*S*)
3	**12c**	toluene	77 (*R*)	81 (*S*)	89 (*S*)	84 (*S*)	88 (*S*)
4	**12d**	toluene	89 (*R*)	92 (*S*)	93 (*S*)	92 (*S*)	94 (*S*)
5	**12e**	toluene	53 (*S*)	61 (*R*)	70 (*R*)	64 (*R*)	72 (*R*)
6	**13**	toluene	39 (*S*)	39 (*R*)	61 (*R*)	21 (*R*)	28 (*R*)
7	**13**	THF	−	−	80 (*R*)	−	65 (*R*)
8	**14**	toluene	27 (*S*)	32 (*R*)	50 (*R*)	27 (*R*)	50 (*R*)
9	**14**	CH_2Cl_2	−	−	72 (*R*)	−	55 (*R*)

[a] Reaction conditions: 0.2 mmol substrate, substrate/catalyst = 100 (mol/mol), substrate concentration = 0.2 mmol/mL, P = 700 psi H_2, reaction time = 20 h, the conversions were higher than 99.9% in all cases. [b] The ee values were determined by chiral HPLC.

Treatment of **12a** with [Ir(COD)Cl]$_2$/ *SRR*-**7b** (1 mol %) in the presence of I_2 (10 mol %) in toluene at room temperature and 700 psi H_2 afforded 2,6-dimethyl-1,2,3,4-tetrahydroquinoline in 90% yield and 92% ee (entry 1). Full substrate conversion was achieved in 20 h based on crude ^{1}H NMR analysis. Similarly, **7b** was also found to produce comparable results for other substrates under identical reaction conditions (entries 2−9).

Interestingly, the enantioselectivities were highly sensitive to the dihedral angles of the ligands in the hydrogenation of all studied *N*-heteroaromatic substrates. With (*RSS*)-**7a** as ligand (dihedral angle = −66.5°), the catalytic hydrogenation of **12c** gave 6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline in 93% yield and 77% ee (Table 7, entry 3). Likewise, 91% yield and 84% ee were obtained for the analogous reaction with (*SRR*)-**7c** as ligand (dihedral angle = 88.8°). The best results (89% ee) were attained with ligand (*SRR*)-**7b** with dihedral angle = 80.0°, which was close to that of MeO-Biphep (83.2°). A more pronounced dihedral angle effect was observed for the hydrogenation of substrates **13** and **14** (Table 7, entries 6 and 8). Hence, (*SRR*)-**7b** is probably a more general ligand in asymmetric hydrogenation of substituted quinoline compounds.

Conclusions

A practical protocol for the synthesis of enantiopure, axially chiral diphosphine ligands has been developed. The chiral-bridged diphosphine ligands were successfully prepared via two synthetic routes: highly diastereoselective Ullmann coupling and ring-closure processes. The introduction of a chiral bridge with variable chain length offered a great potential in ligand dihedral angle fine-tuning. Moreover, the chiral bridge provided extra ligand rigidity and chiral control, which led to high enantioslectivity in asymmetric hydrogenation. In particular, highly efficient central-to-axial chirality transfer was realized in the Ullmann coupling for atropdiastereoselective synthesis of biaryl diphosphine dioxides. Thus, no resolution step was required for the preparation of the enantiomerically pure chiral ligands. In addition, it was not even necessary to separate the diastereomers since essentially perfect diastereoselectivity has been achieved. This pathway is also of high atom economy. Besides, the effect of chiral recognition was also revealed in a relevant asymmetric ring-closure reaction. These methodologies are obviously useful for the development of new enantiomerically pure phosphine ligands. The Ru or Ir complexes with PQ-Phos ligands exhibited versatile use in the hydrogenation of C=O, C=C, and C=N bonds and showed excellent asymmetric induction abilities. The dihedral angle effect of the ligands in the Ir-catalyzed asymmetric hydrogenation of *N*-heteroaromatic compounds was also revealed. Further modifications and explorations of these ligands to other asymmetric catalytic reactions are in progress.

Experimental Section

General Procedures. All reactions were carried out under an inert atmosphere of dry nitrogen and were followed by TLC. Glassware was flame dried before use. Standard syringe techniques were applied to transfer dry solvents and reagents. The preparation of samples and the setup of the high-pressure reactor were carried out either in a nitrogen-filled continuously purged MBRAUN model lab master 230 glovebox or by using standard Schlenk-type techniques. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Varian 500 spectrometer (500, 202, and 125 MHz, respectively) or on a Bruker DPX-400 spectrometer (400, 162, and 100 MHz respectively). Chemical shifts (δ) were given in ppm and were referenced to residual solvent peaks (^{1}H NMR, ^{13}C NMR) or to an external standard (85% H_3PO_4, ^{31}P NMR). Mass spectra and accurate mass measurements were carried out with a VG MICROMASS, Fison VG platform, or a Finnigan model Mat 95 ST instrument. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter in a 10-cm cell. HPLC analyses were performed using a Waters model 600 with a Waters 486 UV detector. Gas chromatography was performed on an HP 4890A GC with an FID detector. THF and toluene were freshly distilled from sodium/benzophenone ketyl, while DMSO, DMF, CH_2Cl_2, and Bu_3N were distilled from CaH_2 under nitrogen atmosphere. MeOH and EtOH were distilled from magnesium under nitrogen atmosphere. All other chemicals were used as received from Aldrich, Acros, or Strem without further purification. All substrates used in moisture-sensitive reactions were predried twice with toluene azeotrope prior to use.

Synthesis of (2*R*,4*R*)-2,4-Bis(3-bromophenoxy)pentane (3b). A mixture of 3-bromophenol (0.746 g, 4.3 mmol) and K_2CO_3 (1.192 g, 8.6 mmol) in DMSO (5 mL) was stirred at room temperature for 1 h, and then a solution of (2*S*,4*S*)-pentanediol di-*p*-tosylate (0.889 g, 2.2

mmol) in DMSO (10 mL) was added dropwise into this mixture over a period of 4 h. The mixture was continuously stirred at room temperature for 48 h before pouring into water (100 mL). The organic phase was extracted with CH_2Cl_2. The extract was treated with 2 N HCl solution (10 mL) and washed with water and brine again. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified through a silica gel column (eluent: EtOAc/hexane = 5/100) to give a colorless oil, **3** (0.505 g, 1.2 mmol, 56.5% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.30 (d, J = 6.0 Hz, 6H), 1.95 (dd, J = 5.5 Hz, 7.0 Hz, 2H), 4.55−4.61 (m, 2H), 6.72−6.75 (m, 2H), 6.96−7.06 (m, 6H); ^{13}C NMR ($CDCl_3$) 125 MHz: δ 20.06, 44.76, 71.07, 114.74, 119.44, 122.82, 123.92, 130.51, 158.83; MS (EI + VE + LMR): calcd for $C_{17}H_{18}Br_2O_2$ $[M]^+$ 414.1, found 414.0; HRMS (EI + VE + LMR): calcd for $C_{17}H_{18}Br_2O_2$ $[M]^+$ 411.9674, found 411.9726; $[\alpha]^{20}_D = -77.2$ (c = 1, hexane).

Synthesis of (2*R*,5*R*)-2,5-Bis(3-bromophenoxy)hexane (3c). 3c was prepared from **1** and (2*S*,5*S*)-hexanediol-ditosylate (**2c**) by following the same procedure described above for **3b** as a colorless oil (74.4% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.34 (d, J = 6.5 Hz, 6H), 1.71−1.77 (m, 2H), 1.88−1.92 (m, 2H), 4.37−4.41 (m, 2H), 6.83−6.86 (m, 2H), 7.09−7.17 (m, 6H); ^{13}C NMR ($CDCl_3$) 125 MHz: δ 19.43, 31.79, 73.59, 114.38, 118.88, 122.71, 123.47, 130.48, 158.69; HRMS (EI + VE + LMR): calcd for $C_{18}H_{20}Br_2O_2$ $[M]^+$ 425.9830, found 425.9896; $[\alpha]^{20}_D = -26.0$ (c = 1, $CHCl_3$).

Synthesis of (2*R*,4*R*)-2,4-Bis[3-(diphenylphosphoryl)phenoxy]-pentane (4b). Compound **3b** (2.64 g, 6.4 mmol) was azeotropically dried with dry toluene (15 mL × 2) and dissolved in dry THF (80 mL). *n*-BuLi (13.5 mmol, 1.6 M solution in hexane) was added dropwise into the solution at −78 °C within 30 min under N_2. After stirring for an additional 1 h at this temperature, chlorodiphenylphosphine (2.5 mL, 13.5 mmol) in THF (5 mL) was added dropwise to the resulting mixture. The reaction was continued at −78 °C for 1 h and then at room temperature overnight. The resulting light-yellow solution was extracted with CH_2Cl_2/water. The organic phase was separated, washed with water and brine, and dried over Na_2SO_4. After evaporation of the solvent, a light-yellow solid was obtained. The residue was purified by silica gel column chromatography (eluent: EtOAc/hexane = 5/100) to give a colorless oily solid. An aqueous H_2O_2 solution (30%, 8.5 mL) was added to a solution of this oily solid in acetone (30 mL) at 0 °C. The reaction was monitored by thin-layer chromatography. The product was extracted with dichloromethane twice. The combined extract was washed successively with $Na_2S_2O_3$ solution, water, and brine, was dried over anhydrous Na_2SO_4, and was concentrated in vacuo to give a crude product. Purification by silica gel column chromatography (eluent: EtOAc/$CHCl_3$/MeOH = 200/200/20) afforded a pure colorless solid **4b** (3.62 g, 5.5 mmol, 86.2% yield based on **3b**). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.22 (d, J = 6.0 Hz, 6H), 1.90 (t, J = 6.3 Hz, 2H), 4.53−4.59 (m, 2H), 6.89−6.92 (m, 2H), 7.04 (dd, J = 12.0 Hz, 7.5 Hz, 2H), 7.14−7.21 (m, 4H), 7.38−7.64 (m, 20H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ 32.13; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 19.90, 44.36, 70.93, 119.22, 119.31, 119.59, 119.61, 124.23, 124.32, 128.39, 128.49, 129.62, 129.74, 131.92, 131.98, 132.06, 132.72, 133.23, 134.05, 157.87, 157.99; MS (ESI) calcd for $C_{41}H_{38}P_2O_4$ $[M]^+$ 656.7, found 657; HRMS (CI): calcd for $C_{41}H_{39}P_2O_4$ $[M + H]^+$ 657.2324, found 657.1990; $[\alpha]^{20}_D = -61.0$ (c = 1, $CHCl_3$).

Synthesis of (2*R*,5*R*)-2,5-Bis[3-(diphenylphosphoryl)phenoxy]-hexane (4c). 4c was prepared from **3c** by following the same procedure described above for **4b** as a pure, colorless solid (91.2% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.16 (d, J = 6.0 Hz, 6H), 1.52−1.58 (m, 2H), 1.71−1.79 (m, 2H), 4.26−4.32 (m, 2H), 6.93−6.96 (m, 2H), 7.05 (dd, J = 11.5 Hz, 6.5 Hz, 2H), 7.16−7.20 (m, 2H), 7.22−7.27 (m, 2H), 7.35−7.39 (m, 8H), 7.43−7.47 (m, 4H), 7.58−7.63 (m, 8H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ 30.34; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 19.23, 31.68, 73.40, 118.45, 118.53, 119.40, 119.42, 123.84, 123.92, 128.19, 128.29, 129.48, 129.59, 131.70, 131.73, 131.81, 132.58, 133.13, 133.95, 157.69, 157.81; MS (ESI) calcd for $C_{42}H_{40}P_2O_4$ $[M]^+$ 670.7, found 671; HRMS (ESI): calcd for $C_{42}H_{41}P_2O_4$ $[M + H]^+$ 671.2481, found 671.2407; $[\alpha]^{20}_D = -13.2$ (c = 1, $CHCl_3$).

Synthesis of (2*R*,4*R*)-2,4-Bis[2-iodo-3-(diphenylphosphoryl)phenoxy]pentane (5b). To a solution of compound **4b** (1.00 g, 1.5 mmol) in THF (40 mL) was added dropwise lithium diisopropylamide (1.7 mL, 2.0 M) at −78 °C over a period of half an hour. After stirring for an additional 3 h, the reaction mixture was cannulated into a flask containing I_2 (1.523 g, 6.0 mmol) and 40 mL of THF at −78 °C over 30 min. The mixture was warmed to ambient temperature over 2 h, and the reaction was continued overnight. After the evaporation of the solvent with a rotary evaporator, the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed successively with saturated aqueous ammonium chloride solution, water, and saturated sodium thiosulfate solution, followed by drying over anhydrous Na_2SO_4. Concentration in vacuo gave a crude product. Purification by silica gel column chromatography afforded pure compound **5b** (1.117 g, 1.23 mmol, 82.0% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.34 (d, J = 6.0 Hz, 6H), 2.07 (dd, J = 5.5 Hz, 7 Hz, 2H), 4.77−4.83 (m, 2H), 6.55−6.60 (m, 2H), 6.80 (d, J = 8.0 Hz, 2H), 7.08 (dt, J = 3.2 Hz, 7.5 Hz, 2H), 7.40−7.46 (m, 8H), 7.51−7.55 (m, 4H), 7.61−7.68 (m, 8H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ 34.66; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 20.03, 44.76, 72.82, 93.85, 93.91, 116.55, 116.57, 128.10, 128.19, 128.37, 128.41, 128.46, 128.51, 128.85, 128.96, 131.38, 131.68, 131.70, 131.72, 132.03, 132.11, 132.18, 132.23, 137.00, 137.84, 157.16, 157.26. MS (ESI) calcd for $C_{41}H_{36}I_2P_2O_4$ $[M]^+$ 908.5, found 909; HRMS (ESI): calcd for $C_{41}H_{37}I_2P_2O_4$ $[M + H]^+$ 909.0257, found 909.0283; $[\alpha]^{20}_D = -126.8$ (c = 1, $CHCl_3$).

Synthesis of (2*R*,5*R*)-2,5-Bis[2-iodo-3-(diphenylphosphoryl)phenoxy]hexane (5c). 5c was prepared from **4c** by following the same procedure described above for **5b** (84.0% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.34 (d, J = 6.5 Hz, 6H), 1.82−1.86 (m, 2H), 1.94−1.98 (m, 2H), 4.35−4.50 (m, 2H), 6.63−6.69 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.17 (dt, J = 7.6 Hz, 3.0 Hz, 2H), 7.42−7.48 (m, 8H), 7.51−7.56 (m, 4H), 7.66−7.71 (m, 8H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ 34.86; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 19.26, 31.42, 75.38, 93.98, 94.03, 116.18, 127.87, 127.97, 128.19, 128.28, 128.29, 128.50, 128.61, 131.10, 131.50, 131.52, 131.82, 131.85, 131.89, 131.93, 137.01, 137.85, 157.01, 157.11; HRMS (ESI): calcd for $C_{42}H_{39}I_2P_2O_4$ $[M + H]^+$ 923.0414, found 923.0385; $[\alpha]^{20}_D = -62.0$ (c = 1, $CHCl_3$).

Synthesis of (*S*)-[6,6′-(2*S*,3*S*-Butadioxy)]-(2,2′)-bis(diphenylphosphoryl)-(1,1′)-biphenyl [(*SSS*)-6a]. Synthetic Route II: Ring-Closure Pathway. (*S*)-(6,6′-Dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) **9** (0.550 g, 0.938 mmol) was stirred at ambient temperature in DMF (50 mL) in the presence of Cs_2CO_3 (2.445 g, 7.508 mmol) for an hour. Into this mixture was added dropwise a DMF (25 mL) solution of (2*R*,3*R*)-butanediol-dimesylate **2a** (0.925 g, 3.755 mmol) for 3 h at room temperature. The reaction continued at 60 °C for 48 h. The DMF was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water and brine successively. The organic solution was dried over anhydrous Na_2SO_4 and was concentrated in vacuo to give a crude product which could be purified by silica gel column chromatography to obtain a pure white solid (*SSS*)-**6a** (0.346 g, 0.540 mmol, 57.6% yield based on (*S*)-**9**). ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 5.0 Hz, 6H), 3.95−4.03 (m, 2H), 6.72 (d, J = 8.0 Hz, 2H), 6.94 (dd, J = 13.5 Hz, 7.0 Hz, 2H), 7.06 (dt, J = 7.8 Hz, 3.3 Hz, 2H), 7.19−7.22 (m, 4H), 7.29−7.44 (m, 12H), 7.70−7.75 (m, 4H); ^{31}P NMR: δ 28.69; ^{13}C NMR: δ 19.43, 78.30, 125.37, 127.44, 127.53, 127.86, 127.89, 127.95, 127.98, 128.52, 128.64, 130.58, 130.60, 130.98, 131.00, 131.86, 131.93, 132.41, 132.49, 133.31, 134.15, 135.27, 136.10, 154.98, 155.08; HRMS (ESI): calcd for $C_{40}H_{35}P_2O_4$ $[M + H]^+$ 641.2011, found 641.1973. $[\alpha]^{20}_D = +134.5$ (c = 1, $CHCl_3$).

Synthesis of (*R*)-[6,6′-(2*S*,3*S*-Butadioxy)]-(2,2′)-bis(diphenylphosphoryl)-(1,1′)-biphenyl [(*RSS*)-6a]. Synthetic Route II. (*RSS*)-**6a** was prepared from (*R*)-**9** and **2a** by following the same procedure described above for (*SSS*)-**6a** as a pure white solid (63.7% yield).

Synthesis of (*S*)-[6,6′-(2*R*,4*R*-Pentadioxy)]-(2,2′)-bis(diphenylphosphoryl)-(1,1′)-biphenyl [(*SRR*)-6b]. Synthetic Route I. Asymmetric Ullmann Coupling. DMF (5 mL) was added into a flask containing Cu powder (0.215 g, 3.36 mmol) and **5b** (0.382 g, 0.42 mmol). The resulting mixture was stirred at 140 °C for 12 h under a nitrogen atmosphere. After the removal of the DMF solvent under reduced pressure, the residue was boiled for 5 min with hot $CHCl_3$ (10 mL × 3). The insoluble solid was removed by filtration and was washed with hot $CHCl_3$ (5 mL × 3). The combined filtrate was washed successively with saturated aqueous ammonium chloride and brine and was dried over anhydrous Na_2SO_4. After the solvent was removed, the residue was purified by silica gel column chromatography to give (*SRR*)-**6b** as a white solid (194 mg, 0.296 mmol, 70.5% yield) and a recovered compound **4c** (50 mg, 0.076 mmol, 18.1% yield).^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.19−1.21 (d, J = 6 Hz, 6H), 1.64 (t, J = 4.0 Hz, 2H), 4.31−4.36 (m, 2H), 6.82 (d, J = 7.5 Hz, 2H), 6.86−6.90 (dd, J = 13.3 Hz, 7.8 Hz, 2H), 7.04−7.14 (m, 6H), 7.24 (t, J = 7.3 Hz, 2H), 7.31−7.35 (m, 8H), 7.41 (t, J = 7.5 Hz, 2H), 7.65−7.69 (dd, J = 11.5 Hz, 7.0 Hz, 4H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ 29.29; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 21.84, 40.57, 75.52, 120.52, 120.54, 126.77, 126.86, 127.19, 127.29, 127.80, 127.89, 128.44, 128.55, 130.43, 130.45, 131.00, 132.36, 132.44, 132.54, 133.01, 133.25, 133.69, 134.11, 134.51, 134.94, 156.99, 157.10; MS (ESI): calcd for $C_{41}H_{36}P_2O_4$ $[M]^+$ 654.7, found 655; HRMS (ESI): calcd for $C_{41}H_{37}P_2O_4$ $[M + H]^+$ 655.2168, found 655.2181; $[\alpha]^{20}_D = +170.0$ (c = 1, $CHCl_3$).

Synthetic Route II. (*S*)-(6,6′-Dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) **9** (0.403 g, 0.68 mmol), was stirred at ambient temperature in DMF (50 mL) in the presence of K_2CO_3 (0.51 g, 3.70 mmol) for an hour. To this mixture was added dropwise a solution of (2*S*,4*S*)-pentanediol-di-*p*-tosylate (1.135 g, 2.75 mmol) in DMF (30 mL) over a period of 3 h at room temperature. The reaction continued at room temperature for 12 h and then at 55 °C for 72 h. After the removal of the DMF solvent under reduced pressure, the residue was dissolved in CH_2Cl_2. The resulting solution was washed successively with water and brine, followed by drying over anhydrous Na_2SO_4 and concentration in vacuo to give a crude product. Purification was performed by silica gel column chromatography as synthetic route I to afford (*SRR*)-**6b** as a white solid (323 mg, 0.49 mmol, 71.7% yield based on substrate **9**). The acquired spectra and the optical rotation are the same as those acquired via synthetic route I.

Synthesis of (*S*)-[6,6′-(2*R*,5*R*-Hexadioxy)]-(2,2′)-bis(diphenylphosphoryl)-(1,1′)-biphenyl [(*SRR*)-6c]. Synthetic Route I. (*SRR*)-**6c** was prepared from **5c** by following the same procedure described above for (*SRR*)-**6b** as a white solid (61.0% yield). At the same time, **(***R*)-[6,6′-(2*R*,5*R*-hexadioxy)]-(2,2′)-bis(diphenylphosphoryl)-(1,1′)-biphenyl ((*RRR*)-**6c**) was produced as a trace part. The ratio of (*SRR*)-**6c** to (*RRR*)-**6c** was 99:1 by HPLC analysis (HPLC conditions: AD-H column, eluent: hexane/*i*-PrOH = 85/15, λ = 254 nm, flow rate = 0.5 mL/min); t_1 = 19.8 min for (*SRR*)-**6c**. t_2 = 41.2 min for (*RRR*)-**6c**). A recovered compound **4c** was also acquired in 20.5% yield.

Synthetic Route II. (*SRR*)-**6c** was prepared from (*S*)-**9** and **2c** by following the same procedure described above for (*SSS*)-**6a** (68.4% yield)**.** ^{1}H NMR ($CDCl_3$): δ 0.97 (d, J = 6 Hz, 6H), 1.16 (d, 10.0 Hz, 2H), 1.72 (d, J = 9.0 Hz, 2H), 4.42−4.49 (m, 2H), 6.82 (dd, J = 13.5 Hz, 7.5 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 7.11−7.15 (m, 2H), 7.20−7.23 (m, 4H), 7.32−7.38 (m, 6H), 7.41−7.45 (m, 6H), 7.74 (dd, J = 11.8 Hz, 7.2 Hz, 4H); ^{31}P NMR: δ 30.03; ^{13}C NMR: δ 18.65, 25.63, 75.61, 118.90, 125.88, 125.98, 127.31, 127.40, 127.80, 127.89, 128.05, 130.49, 130.51, 130.94, 132.27, 132.35, 132.55, 132.63, 132.78, 133.36, 133.65, 133.88, 134.19, 134.71, 155.82, 155.93; HRMS (ESI): calcd for $C_{42}H_{39}P_2O_4$ $[M + H]^+$ 669.2324, found 669.2251; $[\alpha]^{20}_D = +76.0$ (c = 1, $CHCl_3$).

Synthesis of (*S*)-[6,6′-(2*S*,3*S*-Butadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl [(*SSS*)-7a]. A 100-mL, two-necked flask flitted with a magnetic stirring bar and a reflux condenser was charged with (*SSS*)-**6a** (515 mg, 0.804 mmol, 100% de) and the system was flushed with nitrogen gas and azeotropically dried with dry toluene (10 mL × 2). Under nitrogen atmosphere dry and degassed toluene (10 mL), tributylamine (3.8 mL, 16.1 mmol), and trichlorosilane (1.7 mL, 16.1 mmol) were added to the flask by means of syringe. The mixture was stirred at reflux overnight. After the solution was cooled to 0 °C, a 30% aqueous sodium hydroxide solution (24 mL) was carefully added. The mixture was then stirred at 60 °C until the organic and aqueous layers become clear. The organic product was extracted with toluene (10 mL × 3, under nitrogen atmosphere), and the extract was washed successively with water (10 mL × 2) and brine (10 mL × 2) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give a crude product containing tributylamine. It was washed with hexane (3 × 2 mL) to give a pure white, powdery product (*SSS*)-**7a** (489 mg, 95.0% yield). ^{1}H NMR ($CDCl_3$): δ 0.95 (d, J = 6.5 Hz, 6H), 3.92−3.99 (m, 2H), 6.28 (d, J = 8.5 Hz, 2H), 6.73−6.76 (m, 2H) 7.05−7.09 (m, 6H), 7.16−7.26 (m, 6H), 7.32−7.37 (m, 6H), 7.49−7.53 (m, 4H); ^{31}P NMR: δ −6.58; ^{13}C NMR: δ 18.75, 76.93, 122.68, 127.74, 127.77, 127.80, 127.84, 128.10, 128.26, 128.29, 128.31, 128.36, 128.59, 133.07, 133.19, 133.31, 133.55, 133.63, 133.72, 134.17, 134.26, 134.35, 136.51, 136.54, 136.58, 138.17, 138.23, 138.30, 140.80, 140.82, 140.84, 154.80, 154.83, 154.86; MS (ESI): calcd for $C_{40}H_{34}P_2O_2$ 608.6, found 609; HRMS (ESI): calcd for $C_{40}H_{35}P_2O_2$ $[M + H]^+$ 609.2113, found 609.2087. $[\alpha]^{20}_D = +351.5$ (c = 1, toluene).

Synthesis of (*S*)-[6,6′-(2*R*,4*R*-Pentadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl [(*SRR*)-7b]. (*SRR*)-**7b** was prepared from (*SRR*)-**6b** by following the same procedure described above for (*SSS*)-**7a** as a white powder (93.1% yield). ^{1}H NMR ($CDCl_3$) 500 MHz: δ 1.23 (d, J = 6.5 Hz, 6H), 1.72 (t, J = 4.0 Hz, 2H), 4.36−4.42 (m, 2H), 6.68 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 7.5 Hz, 2H), 7.05−7.20 (m, 12H), 7.30−7.40 (m, 6H), 7.56−7.60 (m, 4H); ^{31}P NMR ($CDCl_3$) 202 MHz: δ −9.88; ^{13}C NMR ($CDCl_3$) 125 MHz: δ 22.03, 40.72, 74.97, 118.03, 127.40, 127.56, 127.58, 128.16, 128.19, 128.22, 128.25, 128.63, 133.47, 133.55, 133.62, 133.81, 133.90, 133.98, 135.43, 135.56, 135.69, 137.38, 137.42, 137.45, 138.51, 138.57, 138.63, 138.70, 157.61, 157.65, 157.70; MS (ESI): calcd for $C_{41}H_{36}P_2O_2$ $[M]^+$ 622.7, found 623; HRMS (ESI): calcd for $C_{41}H_{37}P_2O_2$ $[M + H]^+$ 623.2269, found 623.2250; $[\alpha]^{20}_D = +313.8$ (c = 1, toluene).

Synthesis of (*S*)-[6,6′-(2*R*,5*R*-Hexadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl [(*SRR*)-7c). (*SRR*)-**7c** was prepared from (*SRR*)-**6c** by following the same procedure described above for (*SSS*)-**7a** as a light-yellow needle crystal (97% yield). ^{1}H NMR ($CDCl_3$): δ 1.00 (d, J = 6.5 Hz, 6H), 1.17−1.20 (m, 2H), 1.71−1.78 (m, 2H), 4.36−4.44 (m, 2H), 6.62 (d, J = 7.5 Hz, 2H), 6.75 (d, 8.5 Hz, 2H), 7.08−7.17 (m, 12H), 7.24−7.26 (m, 6H), 7.38−7.41 (m, 4H); ^{31}P NMR: δ −10.75; ^{13}C NMR: δ 19.28, 27.17, 75.82, 115.75, 126.42, 127.50, 127.52, 127.55, 127.60, 127.92, 128.10, 128.12, 128.14, 128.45, 133.60, 133.69, 133.77, 133.82, 133.91, 133.99, 134.88, 135.02, 135.16, 137.46, 137.50, 137.55, 138.62, 138.67,138.74, 139.23, 139.25, 139.27, 156.41, 156.46, 156.50; HRMS (ESI): calcd for $C_{42}H_{39}P_2O_2$ $[M + H]^+$ 637.2425, found 637.2402; $[\alpha]^{20}_D = +243.5$ (c = 1, Toluene).

Synthesis of (*S*)-(6,6′-Dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) ((*S*)-9). (*S*)-**9** was prepared from (*S*)-**8** by following the same procedure reported in the literature as a white powder (83.0% conversion, 90.9% selectivity).[16] ^{1}H NMR (*d*-DMSO) 500 MHz: δ 6.53 (dd, J = 13.8 Hz, 7.3 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 6.97−7.00 (m, 2H), 7.28−7.55 (m, 20H), 9.00 (s, 1H); ^{31}P NMR (*d*-DMSO) 202 MHz: δ 29.2; ^{13}C NMR ($CD_3OD + CD_2Cl_2$) 100 MHz: δ 123.83, 129.71, 129.84, 132.50, 132.62, 132.69, 132.85, 135.15, 136.04, 136.19, 136.57, 136.67, 136.78, 136.88, 137.03, 137.13, 138.07, 138.17, 160.08, 160.22; HRMS (EI): calcd for $C_{36}H_{28}P_2O_4$ $[M]^+$ 586.1463, found. 586.1439; $[\alpha]^{20}_D = -80.6$ (c = 1, 1:1 CH_2Cl_2 + MeOH).

Synthesis of (*R*)-(6,6′-Dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) ((*R*)-9). (*R*)-**9** was prepared from (*R*)-**8** by following the same procedure reported in the literature as a white powder (85.0% conversion, 91.6% selectivity).[16] ^{1}H NMR (*d*-DMSO) 500 MHz: δ 6.54 (dd, $J = 13.3$ Hz, 8.3 Hz, 2H), 6.73 (d, $J = 8.0$ Hz, 2H), 6.97−7.01 (m, 2H), 7.28−7.56 (m, 20H), 9.01 (s, 1H); ^{31}P NMR (*d*-DMSO) 202 MHz: δ 29.2; ^{13}C NMR ($CD_3OD + CD_2Cl_2$) 100 MHz: δ 123.99, 129.80, 129.92, 132.50, 132.53, 132.62, 132.66, 132.83, 135.07, 136.04, 136.55, 136.65, 136.78, 136.88, 137.00, 137.23, 138.04, 138.27, 160.12, 160.26; HRMS (ESI): calcd for $C_{36}H_{29}P_2O_4$ $[M + H]^+$ 587.1541, found 587.1530; $[\alpha]^{20}_D = +80.2$ ($c = 1$, 1:1 CH_2Cl_2 + MeOH).

Preparation of Catalysts $RuLCl_2(DMF)_n$, $[RuL(\eta^6\text{-}C_6H_6)Cl]Cl$ and $[RuL(\eta^6\text{-}C_6H_6)Cl]Cl$. Catalysts $RuLCl_2(DMF)_n$, $[RuL(\eta^6\text{-}C_6H_6)Cl]Cl$ and $[RuL(\eta^6\text{-}C_6H_6)Cl]Cl$ were prepared by following the same procedures reported in the literature.[14]

^{31}P NMR (202 MHz, CD_2Cl_2) for $[RuL(\eta^6\text{-}C_6H_6)Cl]Cl$:
[Ru(*SSS*-**7a**)(η^6-C_6H_6)Cl]Cl: δ 31.53 (d, $J = 65.1$ Hz), 38.37 (d, $J = 65.1$ Hz);
[Ru(*SRR*-**7b**)(η^6-C_6H_6)Cl]Cl: δ 31.87 (d, $J = 65.4$ Hz), 39.22 (d, $J = 65.4$ Hz);
[Ru(*SRR*-**7c**)(η^6-C_6H_6)Cl]Cl: δ 31.60 (d, $J = 64.8$ Hz), 38.62 (d, $J = 64.8$ Hz).

^{31}P NMR (202 MHz, $CDCl_3$) for [RuL(*p*-cymene)Cl]Cl:
[Ru(*SSS*-**7a**)(*p*-cymene)Cl]Cl: δ 29.40 (d, $J = 64.1$ Hz), 43.10 (d, $J = 64.1$ Hz);
[Ru(*SRR*-**7b**)(*p*-cymene)Cl]Cl: δ 28.90 (d, $J = 64.4$ Hz), 43.00 (d, $J = 64.4$ Hz);
[Ru(*SRR*-**7c**)(*p*-cymene)Cl]Cl: δ 28.74 (d, $J = 63.8$ Hz), 42.63 (d, $J = 63.8$ Hz);
[Ru(*S*)-MeO-Biphep(*p*-cymene)Cl]Cl: δ 27.04 (d, $J = 63.0$ Hz), 41.49 (d, $J = 63.0$ Hz).

General Procedures for the Asymmetric Hydrogenation of α-Ketoesters, β-Ketoesters, 2-(6′-Methoxy-2′-naphthyl)propenoic Acid and β-Dehydroamino Acids. Asymmetric hydrogenation of α-ketoesters, β-ketoesters, 2-(6′-methoxy-2′-naphthyl)propenoic acid, and β-dehydroamino acids were carried out by following the same procedures described in the literature.[14]

General Procedures for the Asymmetric Hydrogenation of *N*-Heteroaromatic Compounds. A mixture of $[Ir(COD)Cl]_2$ (1×10^{-3} mmol) and ligand (2.2×10^{-3} mmol) in toluene (1 mL) was stirred at room temperature for 30 min in a drybox, and the solution was transferred to an autoclave into which I_2 (1×10^{-2} mmol) and substrate (0.2 mmol) had been placed beforehand. The hydrogenation reaction was performed at room temperature under H_2 (700 psi) for 20 h. After releasing the hydrogenation, the reaction mixture was diluted with dichloromethane (4 mL), and to this was added saturated Na_2CO_3 solution (1 mL), after which the mixture was then stirred for 15 min. The aqueous layer was extracted with dichloromethane (5 mL × 3), and the combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude product. Purification was performed by a silica gel column eluted with hexane/EtOAc to give pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OJ-H for **12a**−**12c** and **13**, **14**, OD-H for **12d**, AS-H for **12e**).

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Supporting Information Available: Spectroscopic characterization for all new compounds; crystallographic data for compounds (*SSS*)-**6a**, (*SRR*)-**6b**, and (*SRR*)-**6c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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