JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

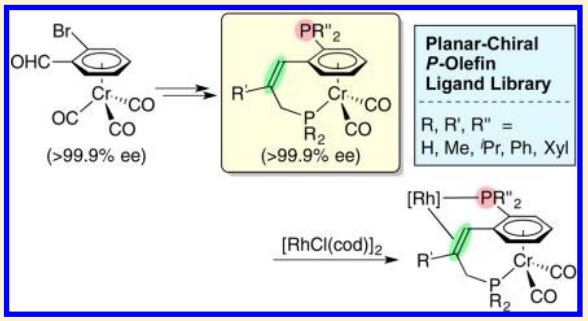
Phosphine−Olefin Ligands Based on a Planar-Chiral (π-Arene)chromium Scaffold: Design, Synthesis, and Application in Asymmetric Catalysis

Masamichi Ogasawara,*[,†] Ya-Yi Tseng,[‡] Sachie Arae,[†] Tomotaka Morita,[‡] Takeshi Nakaya,[†] Wei-Yi Wu,[†,‡] Tamotsu Takahashi,*[,†] and Ken Kamikawa*[,‡]

[†]Catalysis Research Center and Graduate School of Life Science, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan
[‡]Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Supporting Information

ABSTRACT: The NMR and X-ray crystallographic studies clarified that planar-chiral alkenylene-bridged (phosphino-π-arene)-(phosphine)chromium complexes **3** were capable of coordinating to a rhodium(I) cation in a bidentate fashion at the (π-arene)-bound phosphorus atom and at the olefin moiety. The *P*-olefin chelate coordination of **3** constructs the effective chiral environment at the metal center, and thus, these rhodium complexes display high performances in various rhodium-catalyzed asymmetric 1,4- and 1,2-addition reactions with arylboron nucleophiles. The control experiments demonstrated that the (η^2-olefin)−Rh interaction as well as the bridging structure in **3** played the pivotal roles in the high enantioselectivity of the Rh-catalyzed asymmetric reactions. To enhance the synthetic utilities of these phosphine−olefin ligands, an enantiospecific and scalable synthetic method was developed. The novel synthetic method is flexible in terms of the substituent variation, and a library of the planar-chiral (arene)chromium-based phosphine−olefin ligands was established by the combinatorial approach. Among the newly prepared ligand library, compound **3g**, which is with a bis(3,5-dimethylphenyl)-phosphino group on the η^6-arene ring, was found to be a far better chiral ligand in the rhodium-catalyzed asymmetric reactions showing excellent enantioselectivity and high yields.



INTRODUCTION

Unsymmetrically substituted ferrocenes[1] and (π-arene)-chromium complexes[2] are two notable families of planar-chiral transition-metal species, and they have found widespread application in asymmetric synthesis as useful chiral scaffolds. Although planar-chiral (π-arene)$Cr(CO)_3$ species have been utilized as chiral building blocks in asymmetric total synthesis of various natural product,[3] (π-arene)chromium-based chiral ligands have drawn less attention and their successful applications have been limited.[4−6] This is a striking contrast to planar-chiral ferrocenylphosphines, which are one of the most successful classes of chiral phosphine ligands so far.[7] Selected representative examples of (arene)chromium-based chiral ligands are shown in Figure 1. To our best knowledge, the first planar-chiral (arene)chromium-phosphine ligand is compound **A** reported by Uemura and Hayashi in 1992 (Figure 1, top-left).[5] The compound has a substructure analogous to that in ferrocenylphosphine ligand PPFA,[8] and was applied to the asymmetric cross-coupling reactions showing modest enantioselectivity. A majority of the other (arene)chromium-based chiral phosphines are also mimicking the structures and/or the synthetic methods of the forerunning ferrocenylphosphine families.[6] However, such (arene)chromium-phosphine ligands have failed to surpass the ferrocene-based analogues in most cases, which hampers the synthetic attractiveness of the (arene)chromium-based ligands. Whereas the steric environments and the electronic properties provided by the (η^6-arene)Cr motifs are significantly different from those in ferrocenes, distinctive ligand designs utilizing the (arene)chromium skeletons have been clearly awaited to develop truly innovative (arene)chromium-based chiral ligands.

Recently, we developed highly enantioselective kinetic resolution of various racemic planar-chiral (π-arene)chromium species by the Mo-catalyzed asymmetric ring-closing metathesis (ARCM) (Scheme 1, top).[9] During the course of the studies, phosphine derivative **3a**, which was obtained in an essentially enantiomerically pure form via recrystallization/derivatization of preformed ARCM product **2a**, was found to be an exceptionally effective chiral ligand in the rhodium-catalyzed asymmetric 1,4-addition reaction (the Hayashi−Miyaura conjugate addition reaction)[10] of phenylboronic acid to 2-cyclohexenone. The rhodium catalyst coordinated with (*R*)-**3a** afforded (*R*)-3-phenylcyclohexanone in nearly quantitative yield (98%) with excellent enantioselectivity of 99.5% ee (Scheme 1, bottom).

Received: March 26, 2014
Published: June 16, 2014

dx.doi.org/10.1021/ja503060e | J. Am. Chem. Soc. 2014, 136, 9377−9384

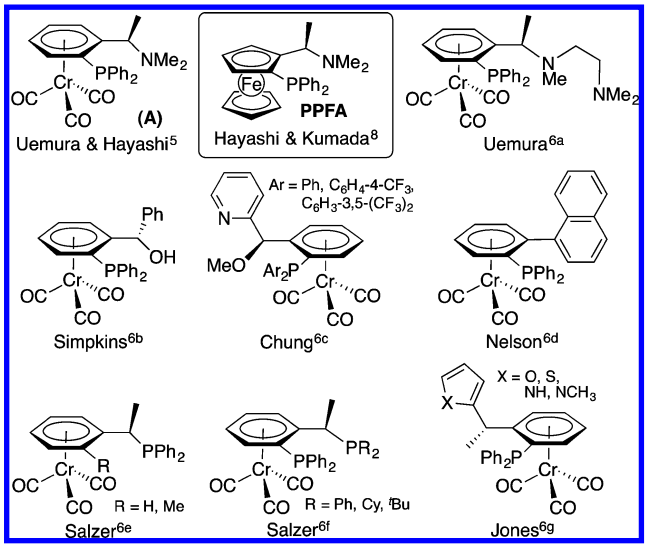
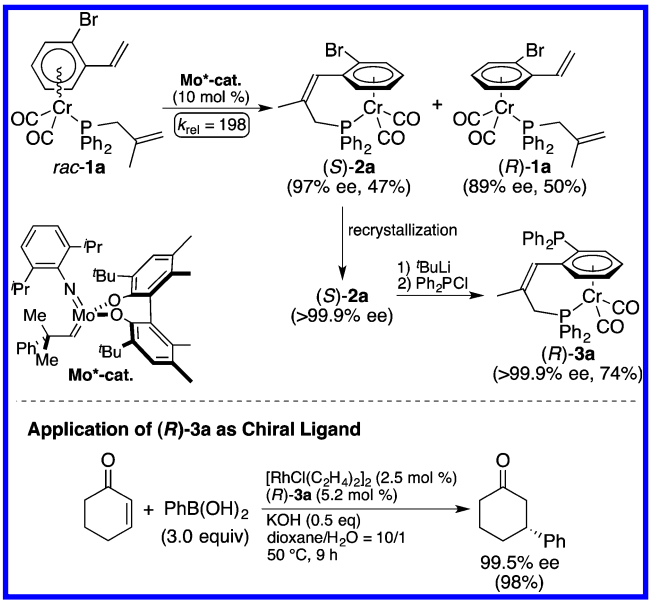


Figure 1. Structures of representative (η^6-arene)chromium-based planar-chiral phosphines and PPFA.

Scheme 1. Mo-Catalyzed Kinetic Resolution of Racemic Planar-Chiral (Arene)chromium Complex and Application to Rh-Catalyzed Asymmetric 1,4-Addition Reaction[9]



With the serendipitous discovery of extremely efficient chiral ligand **3a**, we decided to investigate the nature of this novel chiral ligand in detail. The X-ray crystallography and the NMR spectroscopy of a rhodium complex coordinated with **3a** revealed that the olefin moiety in **3a** served as a two-electron donor, which makes **3a** as a bidentate phosphine−olefin ligand. The chelate coordination as well as the rigid framework of **3a** play the pivotal roles in the high enantioselectivity of the Rh-catalyzed asymmetric reactions. It should be pointed out that chiral phosphine−olefin species have emerged as new entries for chiral ligands in various transition metal-catalyzed asymmetric reactions (such as Rh-catalyzed conjugate addition of arylboronic acids to enones, Rh-catalyzed addition of arylboronic acids to imines, and Ir-catalyzed hydrogenation of imines) and have been developed by several research groups in recent years.[11] The phosphine−olefin hybrid ligands may possess the benefits from chiral diene ligands, of which synthetic utilities have been demonstrated during the past decade,[12,13] as well as from traditional chiral bisphosphine ligands.

To enhance the synthetic usefulness of the (π-arene)-chromium-based phosphine−olefin chiral ligand, we have developed a more efficient and more practical synthetic route to **3a**, which enables a multigram-scale preparation of the ligand. The newly developed synthetic method has also allowed us to establish a series of the (arene)Cr-based phosphine−olefin ligand library by a combinatorial approach, that eventually led to the discovery of the more enantioselective variant of the phosphine−olefin ligand. Herein, we would like to report the results of our studies on the planar-chiral (arene)chromium-based phosphine−olefin ligands.

RESULTS AND DISCUSSION

Structure of Rhodium Complex Coordinated with 3a.

At the outset, the coordination mode of **3a** to a Rh(I) cation was investigated by various NMR measurements. A reaction of (*R*)-**3a** (^{31}P NMR: δ $-10.0_{\text{free-P}}$ and $96.5_{\text{P-Cr}}$) and 0.5 equiv of $[RhCl(cod)]_2$ in C_6D_6 at room temperature afforded a new dinuclear rhodium species (*R*,*R*)-**4**, in which the two Rh(I) cations were bridged by the two μ-chloro ligands (vide infra), quantitatively in the time of mixing (Figure 2, top). Upon the coordination to the Rh(I) cation, the ^{31}P NMR resonance for the free phosphine in (*R*)-**3a** was shifted downfield to δ 67.5 in (*R*,*R*)-**4** with the large P−Rh coupling ($J_{\text{P-Rh}}$ = 198 Hz), which indicated the direct ligation at the Ph_2P-(η^6-arene) to the rhodium atom. The phosphorus atom bound to the chromium atom in (*R*,*R*)-**4** was detected at δ 99.8 in the ^{31}P NMR

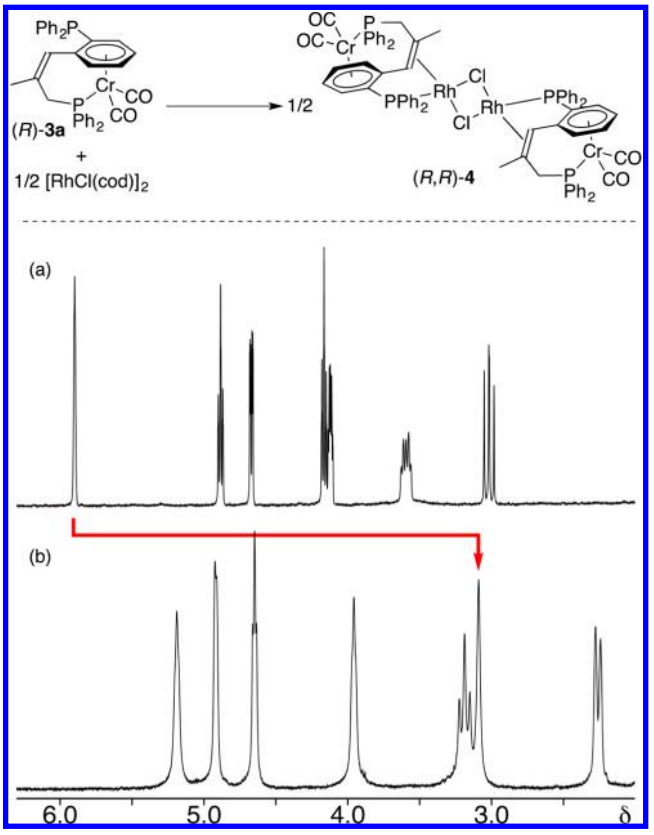


Figure 2. ^{1}H NMR spectra in the olefinic/π-arene/allylic region at 400 MHz in C_6D_6: (a) free (*R*)-**3a**; (b) (*R*,*R*)-**4**. The signals for the olefinic hydrogens are marked with a red arrow.

dx.doi.org/10.1021/ja503060e | J. Am. Chem. Soc. 2014, 136, 9377−9384

spectrum, which also showed a small coupling with Rh(I) (J_{P-Rh} = 7.8 Hz). In the ^{1}H NMR spectra, the olefinic H atom in (*R*)-**3a** was detected at δ 5.91, which was shifted upfield to δ 3.10 upon the coordination to Rh(I) in (*R*,*R*)-**4** (Figure 2, bottom). All these NMR observations clearly indicate that the chromium complex (*R*)-**3a** behaves as a *P*-olefin chelating ligand in (*R*,*R*)-**4**.

The coordination of the olefin donor to the rhodium(I) cation in (*R*,*R*)-**4** is fairly robust due probably to the strong chelate effect of bidentate ligand (*R*)-**3a**. Even in the presence of extra (*R*)-**3a**, the coordinating olefin moiety was not replaced by the Ph_2P-(η^6-arene) moiety in the unligated extra (*R*)-**3a** molecules.

Single crystals of *rac*-**4** suitable for X-ray crystallographic analysis were obtained as orange blocks by recrystallization from hot benzene. The dinuclear complex cocrystallized with two molecule of benzene per dimeric unit, and the ball and stick drawing of (*R**,*R**)-**4** is shown in Figure 3 (see

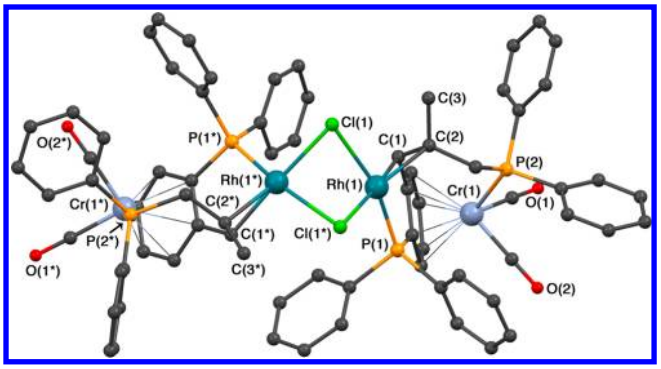


Figure 3. Ball and stick drawing of [RhCl/(*R**)-**3**]$_2$ ((*R**,*R**)-**4**) with selected atom numbering. Hydrogen atoms and cocrystallized benzene molecules are omitted for clarity.

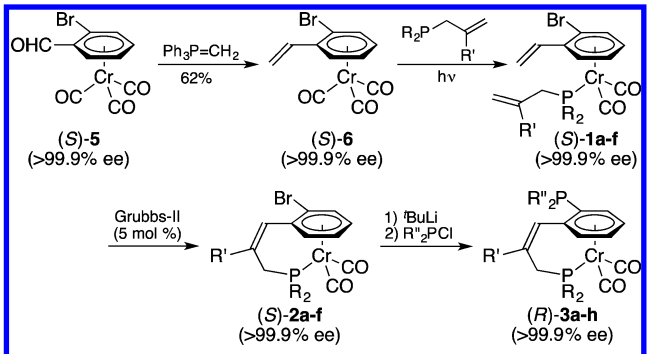
Supporting Information for details).[14] The sample for the X-ray analysis was prepared from [RhCl(cod)]$_2$ and *rac*-**3a**, and thus, the crystals contain both (*R*,*R*)- and (*S*,*S*)-**4** enantiomers in the 1:1 ratio. The rhodium complex coordinated with **3a** showed the strong preference for the formation of the homoenantiomeric dimer, and the corresponding mesomeric dimer, (*R*,*S*)-**4**, was detected neither by the crystallography nor by the NMR measurements.

The dinuclear complex (*R**,*R**)-**4** is C_2-symmetric, in which the axis of symmetry is at the center of the Rh(1)−Cl(1)−Rh(1*)−Cl(1*) square and is perpendicular to both Rh(1)−Rh(1*) and Cl(1)−Cl(1*) axes. The bond lengths of Rh(1)−Cl(1)/Rh(1*)−Cl(1*) (2.464(2) Å) that are trans to phosphorus are significantly longer than Rh(1)−Cl(1*)/Rh(1*)−Cl(1) distances (2.383(2) Å) due to the stronger trans influence of phosphorus. The chelate coordination of **3a** at the -PPh_2 and the olefin moieties, which was detected by the NMR measurements, was retained in the crystals of **4**. The bond length of the coordinating olefin moiety (C(1)−C(2)) in **4** is 1.374(8) Å, which is ca. 5% longer than that in unligated (*R*)-**3a** (1.32(1) Å).[9] The distance between Rh(1) and the C(1)−C(2) centroid is 2.012 Å, and the angle for P(1)−Rh(1)−[C(1)−C(2) centroid] is 90.72°.

Enantiospecific Synthesis of Planar-Chiral 3a and Related Compounds. The original synthesis of (*R*)-**3a** is briefly depicted in Scheme 1.[9] Although the ARCM protocol is a very unique method to prepare (*R*)-**3a** in the single enantiomeric form, the method has several drawbacks for applying to the macroscale synthesis: (i) the first step is the molybdenum-catalyzed kinetic resolution of racemic (η^6-bromoarene)chromium substrate **1a**. Thus, the theoretical maximum yield of the each enantiomer of **1a**/**2a** is 50% at most, (ii) after the kinetic resolution reaction, chromatographic separation of the RCM product, (*S*)-**2a**, from unreacted substrate (*R*)-**1a** is indispensable, (iii) the chiral molybdenum-alkylidene precatalyst used for the ARCM kinetic resolution is fairly air- and moisture-sensitive,[15] and its handling in large scale is problematic, especially with 10 mol % catalyst-loading, (iv) initially obtained ARCM product (*S*)-**2a** is not enantiomerically pure (97% ee), and the recrystallization is necessary prior to the derivatization to (*R*)-**3a**.

To avoid the above-mentioned drawbacks and to realize the macroscale preparation of single-enantiomeric **3a** (and related compounds **3b**−**h**), a more practical and enantiospecific synthetic route was developed as shown in Scheme 2. The

Scheme 2. Enantiospecific Preparation of Planar-Chiral (Arene)chromium-Based phosphine−olefin Ligands



	R	R'	R"	yield of **1**	yield of **2**	yield of **3**
a	Ph	Me	Ph	63%	91%	74%
b	^{i}Pr	Me	Ph	64%	89%	65%
c	3,5-Xyl	Me	Ph	68%	93%	55%
d	Ph	Ph	Ph	62%	80%	44%
e	Ph	H	Ph	66%	55%	77%
f	Ph	CH_2Ph	Ph	65%	65%	59%
g	Ph	Me	3,5-Xyl	(**1a**)	(**2a**)	71%
h	Ph	Me	^{i}Pr	(**1a**)	(**2a**)	64%

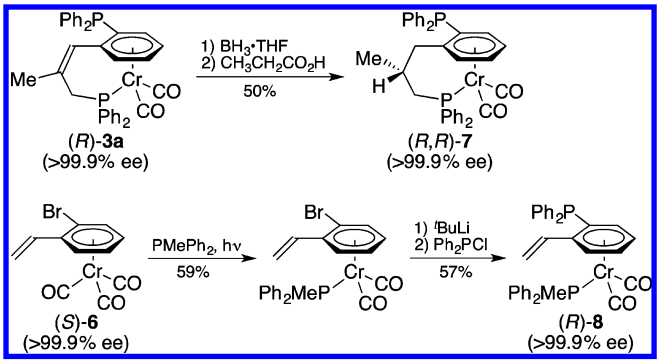
key compound in the alternative route to **3** is (η^6-*o*-bromobenzaldehyde)chromium complex **5**, which is easily obtained in a multiglam scale in a single-enantiomeric form by the reported methods.[16] The Wittig reaction of (*S*)-**5** afforded the corresponding *o*-bromostyrene complex (*S*)-**6** in 62% yield, and the subsequent photoinduced ligand exchange with an allylic phosphine to give a series of chromium complexes (*S*)-**1a**−**f** in reasonable yields. Compounds **1** thus obtained were also enantiomerically pure, since no racemization was associated with the transformation from **5** to **1**. Consequently, the following RCM reaction of (*S*)-**1** could be conducted with an achiral metathesis catalyst, and the use of the fragile chiral molybdenum-alkylidene catalyst was eliminated. And indeed, the commercially available Grubbs-II catalyst, which is much easier to handle than the Mo-catalyst, was found to be effective for the RCM transformation of (*S*)-**1** to afford the corresponding bridged (η^6-bromoarene)chromium complexes (*S*)-**2** in high yields.[17] Bromoarene complexes (*S*)-**2** were converted to various phosphine derivatives (*R*)-**3** in good yields by the standard lithiation/phosphanylation sequence.

dx.doi.org/10.1021/ja503060e | *J. Am. Chem. Soc.* 2014, 136, 9377−9384

An extra benefit of this enantiospecific synthesis of (*R*)-**3** is high tunability with respect to the substituents introduced. A wide range of hydrocarbyl groups can be introduced at the R, R′, and R″ positions in (*R*)-**3**, and thus, a highly diverse library of the (arene)Cr-based planar-chiral *P*-olefin ligands could be easily established (Scheme 2).

The X-ray structure of (*R**,*R**)-**4** (Figure 3) postulated that the two factors, the *P*-olefin bidentate coordination of **3a** as well as the rigid (η^6-arene)(phosphine)chromium framework based on the bridging structure, might play important roles in the excellent enantioselectivity of the Rh/(*R*)-**3a** catalyst in the asymmetric 1,4-addition reaction (Scheme 1, bottom). For the control experiments proving these hypotheses, ligands (*R*,*R*)-**7** and (*R*)-**8** were prepared as shown in Scheme 3. The double

Scheme 3. Preparation of (Arene)chromium-Based Phosphines with Saturated Bridging Tether (7) and with Nonbridged Tether (8)

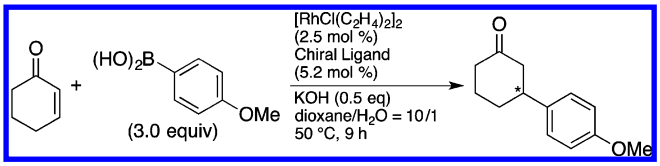


bond in (*R*)-**3a** was reduced by hydroboration and subsequent protonolysis[18] to give (*R*,*R*)-**7** as a single diastereomer in 50% yield. Ligand (*R*)-**8**, which is with the nonbridged structure, was synthesized from (*S*)-**6** and methyl(diphenyl)phosphine.

Application of Planar-Chiral (Arene)chromium Phosphines to Rh- and Pd-Catalyzed Asymmetric Reactions. With the newly developed ligand library in our hands, their applications in the two prototypical rhodium-catalyzed asymmetric reactions were examined.

The first one is asymmetric 1,4-addition reaction of 4-methoxyphenylbronic acid to 2-cyclohexenone (Table 1).[10] Ligand **3a**, which showed the excellent enantioselectivity (99.5% ee) in the analogous reaction with phenylboronic acid (Scheme 1, bottom), gave the desired product in 99% yield with 98% ee (entry 1). When R substituents on the phosphorus atom coordinating to the chromium center were replaced from the phenyl groups to isopropyl or 3,5-xylyl groups, both yield and ee decreased (entries 2 and 3). Since these R substituents were remote from the coordination sphere of the rhodium atom (see, Figure 3), the effects of the R substituents on the enantioselectivity were minimal. The R′ groups are directly bound to the olefinic donor moieties, and thus more crucial effects on the enantioselectivity are expected. Indeed, the effects from the R′ substituents are fairly visible in the rhodium-catalyzed reaction. However, changing the R′ substituent in **3** from the methyl group in **3a** to any of phenyl (**3d**), hydrogen (**3e**), or benzyl (**3f**) groups lowered the enantioselectivity and the chemical yields of the rhodium-catalyzed reaction significantly (entries 4−6). The R″ groups, which are substituents at the phosphorus donor atoms in **3**, are also pivotal. And, to our delight, when the R″ substituents were

Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of 4-Methoxyphenylboronic Acid to 2-Cyclohexenone[a]



entry	chiral ligand	yield (%)[b]	% ee[c]
1	(*R*)-**3a**	99	98 (*R*)
2	(*R*)-**3b**	32	95 (*R*)
3	(*R*)-**3c**	68	94 (*R*)
4	(*S*)-**3d**	57	96 (*S*)
5	(*R*)-**3e**	43	61 (*R*)
6	(*S*)-**3f**	56	80 (*S*)
7	(*S*)-**3g**	98	99.6 (*S*)
8	(*S*)-**3h**	34	4 (*S*)
9	(*R*,*R*)-**7**	27	<1 (−)
10	(*R*)-**8**	47	59 (*S*)

[a]The reaction was carried out in dioxane/H_2O (10/1) in the presence of the rhodium catalyst (5 mol %) generated in situ from $[RhCl(C_2H_4)_2]_2$ and the chiral ligand. [b]Isolated yield by silica gel chromatography. [c]Determined by chiral HPLC analysis.

replaced with 3,5-xylyl groups, the enantioselectivity of the reaction was greatly improved to 99.6% ee with 98% yield (entry 7). On the other hand, when the R″ groups were changed to *iso*-propyl groups, both enantioselectivity and chemical yield of the 1,4-addition product dropped significantly (entry 8).

Comparison between **3a**, **7**, and **8** clarified some important structural characteristics in the chiral phosphine/olefin hybrid ligand **3**. Ligand (*R*,*R*)-**7** possesses the saturated bridging tether but is otherwise isostructural to (*R*)-**3a**. Due to the absence of an olefinic donor moiety, **7** is unable to coordinate to a Rh(I) atom in the bidentate fashion as with the case of **3**. The outcome of this structural change is drastic and the rhodium species coordinated with (*R*,*R*)-**7** gave nearly racemic 3-(4-methoxyphenyl)cyclohexane (<1% ee) in 34% yield (entry 9). Meanwhile, the high-performance of **3** in the Rh-catalyzed asymmetric reaction can partly be attributed to the (π-arene)-phosphine bridging structure. The bridging structure in (*R*)-**3a** locates the olefin donor on the side of the *re*-face of the π-arene plane, on which the chromium atom is coordinated. And thus, upon the complexation with **3a**, the rhodium atom is placed in closer proximity to the $Cr(CO)_2$ fragment, of which the η^6-coordination defines the planar chirality in **3a** (Figure 4, left). On the other hand, the vinyl pendant in nonbridged analogue (*R*)-**8** is able to rotate around the (π-arene)-vinyl single bond.

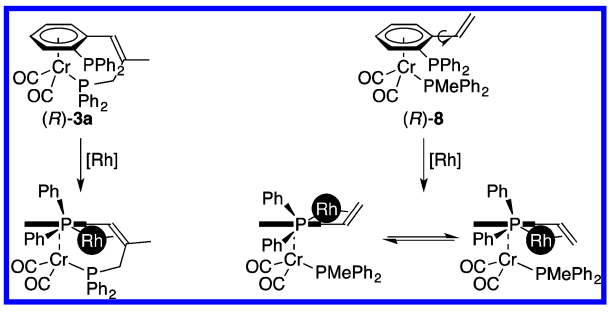


Figure 4. Difference of conformational flexibility between bridged (*R*)-**3a** and nonbridged (*R*)-**8**.

dx.doi.org/10.1021/ja503060e | J. Am. Chem. Soc. 2014, 136, 9377−9384

For this reason, the position of the coordinated Rh atom might be hardly fixed in the complex, that will lower the enantioselectivity (Figure 4, right). Indeed, (*R*)-**8** showed much inferior enantioselectivity in the Rh-catalyzed asymmetric 1,4-addition reaction (entry 10).

Metallocene/half-metallocene-based planar-chiral phosphine−olefin hybrid ligands **9**,[11g] **10**,[11g,p] and **11**[11p] were reported recently, and all of them were applied in the asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexenone. As expected from the analysis shown above and in Figure 5, bridged ligand **11** displayed better enantioselectivity

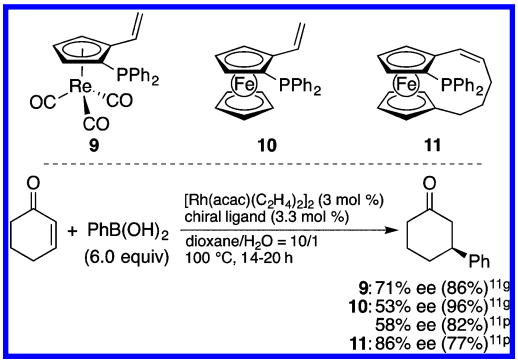
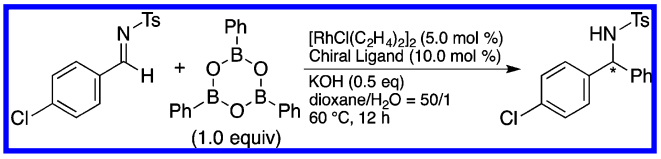


Figure 5. Metallocene/half-metallocene-based planar-chiral phosphine−olefin ligands and their application in the rhodium-catalyzed 1,4-addition of $PhB(OH)_2$ to cyclohexenone.[11g,p]

(86% ee) than nonbridged ligands **9** (71% ee) and **10** (53−58% ee). It should be mentioned that (*π*-arene)chromium-based planar-chiral phosphine−olefin ligand (*R*)-**3a** showed an enantioselectivity much higher than that of **11** in the same reaction and afforded the 1,4-addition product in 99.5% ee (Scheme 1).[9]

The chiral ligand library **3a−h**, **7**, and **8** showed similar trends in the rhodium-catalyzed asymmetric 1,2-addition of phenylboroxine to *p*-chlorobenzaldehyde *N*-tosylimine (Table 2).[19] Among these ligands, **3g**, which is with the di(3,5-xylyl)phosphino substituent on the (η^6-arene) ring, displayed the best performance to give the phenylation product in 93% ee with 98% yield (entry 7). Once again, the ligand with the hydrogenated bridging tether, (*R*,*R*)-**7**, afforded the nearly racemic product of 5% ee (entry 9), and unbridged phosphine−olefin ligand (*R*)-**8** was unsatisfactory by far to give the addition product in as low as 47% ee (entry 10).

Table 2. Rhodium-Catalyzed Asymmetric 1,2-Addition of Phenylboroxine to *p*-Chlorobenzaldehyde *N*-Tosylimine[a]



entry	chiral ligand	yield (%)[b]	% ee[c]
1	(*R*)-**3a**	94	88 (*S*)
2	(*R*)-**3b**	68	84 (*S*)
3	(*R*)-**3c**	99	81 (*S*)
4	(*S*)-**3d**	25	30 (*R*)
5	(*R*)-**3e**	63	14 (*S*)
6	(*S*)-**3f**	72	22 (*R*)
7	(*S*)-**3g**	98	93 (*R*)
8	(*S*)-**3h**	68	84 (*R*)
9	(*R*,*R*)-**7**	61	5 (*R*)
10	(*R*)-**8**	47	47 (*R*)

[a]The reaction was carried out in dioxane/H_2O (50/1) in the presence of the rhodium catalyst (10 mol %) generated in situ from $[RhCl(C_2H_4)_2]_2$ and the chiral ligand. [b]Isolated yield by silica gel chromatography. [c]Determined by chiral HPLC analysis.

With more enantioselective chiral ligand **3g** in hand, its additional application was examined and the results are shown in Table 3. The Michael addition reaction to 2-cyclohexenone works well with the other arylboron nucleophiles, such as *p*-tolyl- and *p*-(trifluoromethyl)phenylboronic acids, in the presence of Rh/(*S*)-**3g** catalyst, and the corresponding (*S*)-3-arylcyclohexanones were obtained in >97% ee (entries 1 and 2).

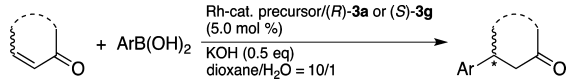
The 1,4-addition reaction of phenylboronic acid to the other Michael acceptors were also studied. The representative reactions were conducted with both (*R*)-**3a** and (*S*)-**3g** for comparison. The phenylation of 2-cyclopentenone proceeded in excellent enentioselectivity and the reaction with Rh/(*R*)-**3a** catalyst afforded (*R*)-3-phenylcyclopentanone in 99.5% ee and 95% yield (entry 3). As expected, the use of (*S*)-**3g** ligand in place of (*R*)-**3a** further improved the enantioselectivity to the astonishing level giving the (*S*)-product in 99.9% ee (entry 4). The same trend could be seen in the reaction of 5,6-dihydro-2*H*-pyran-2-one with phenylboronic acid, and the rhodium catalyst coordinated with (*R*)-**3a** or (*S*)-**3g** afforded the 1,4-addition product, phenylvalerolactone, in 89% yield with 99.4% ee or in 95% yield with 99.5% ee, respectively (entries 5 and 6). The advantage of (*S*)-**3g** over (*R*)-**3a** is more visible in the reaction with *N*-benzylmaleimide. While the rhodium complex coordinated with (*R*)-**3a** gave the addition product in 81% ee (entry 7), Rh/(*S*)-**3g** catalyst gave the phenylsuccinimide in 94% ee (entry 8).

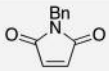
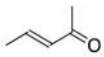
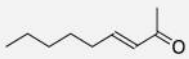
On the other hand, the reactions with acyclic enones were problematic. Due to the absence of bulky substituents and conformational flexibility, 3-penten-2-one is a challenging substrate for the 1,4-addition reaction. Indeed, the phenylation reaction catalyzed by Rh/(*R*)-**3a** species proceeded in only 57% ee, but the enantioselectivity could be improved to 88% ee by the use of (*S*)-**3g**. In both cases, the yields of the addition product were a little over 30% (entries 9 and 10). The phenylation of 3-nonen-2-one was much more sluggish, and the reaction in the presence of Rh/(*R*)-**3g** (5 mol %) at 50 °C afforded the addition product, 4-phenylnonan-2-one, in only 4% yield (entry 11). The yields could be increased to over 40% by the reactions at higher temperature (75 °C), and the rhodium catalyst coordinated with (*R*)-**3a** or (*S*)-**3g** provided the 1,4-addition product in 58% ee or in 88% ee, respectively (entries 12 and 13).

Potential usefulness of the (arene)chromium-based phosphine−olefin ligands was explored for the palladium-catalyzed asymmetric allylic alkylation reaction.[20,21] The palladium complexes generated in situ from $[PdCl(\pi\text{-allyl})]_2$ and (*R*)-**3a** or (*S*)-**3g** catalyzed the reaction of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of BSA to give the alkylation product in 74% ee or 94% ee, respectively (Scheme 4). Once again, (*S*)-**3g** showed superior selectivity over (*R*)-**3a** as in the case of the Rh-catalyzed reactions. These results clearly indicate that the applications of the phosphine−olefin ligands **3** are not limited to the Rh(I)-catalyzed arylation reactions, and the ligands might be

dx.doi.org/10.1021/ja503060e | J. Am. Chem. Soc. 2014, 136, 9377−9384

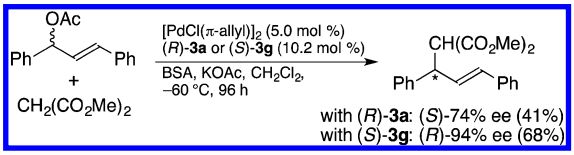
Table 3. Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds[a]



entry	substrate	Ar (equiv.)[b]	chiral ligand	Rh-cat. precursor	time (h)	temp. (°C)	yield (%)[c]	% ee[d]
1		*p*-tol (3.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	9	50	>99	98.4 (*S*)
2		*p*-$C_6H_4CF_3$ (3.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	9	50	95	97 (*S*)
3		Ph (3.0)	(*R*)-**3a**	$[RhCl(C_2H_4)_2]_2$	24	50	95	99.5 (*R*)
4		Ph (3.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	24	50	92	99.9 (*S*)
5		Ph (3.0)	(*R*)-**3a**	$[RhCl(C_2H_4)_2]_2$	24	50	89	99.4 (*R*)
6		Ph (3.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	24	50	95	99.5 (*S*)
7[e]		Ph (3.0)	(*R*)-**3a**	$[Rh(OH)(cod)]_2$	15	−20 to 0	85	81 (*R*)
8[e]		Ph (3.0)	(*S*)-**3g**	$[Rh(OH)(cod)]_2$	15	−20 to 0	83	94 (*S*)
9		Ph (3.0)	(*R*)-**3a**	$[RhCl(C_2H_4)_2]_2$	24	50	31	57 (*S*)
10		Ph (3.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	24	50	34	88 (*R*)
11		Ph (5.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	12	50	4	---
12		Ph (5.0)	(*R*)-**3a**	$[RhCl(C_2H_4)_2]_2$	12	75	13	58 (*S*)
13		Ph (5.0)	(*S*)-**3g**	$[RhCl(C_2H_4)_2]_2$	12	75	43	88 (*R*)

[a]The reaction was carried out in dioxane/H_2O (10/1) in the presence of a rhodium catalyst (5.0 mol %) generated in situ from an appropriate Rh-cat. precursor and a chiral ligand. [b]Numbers in parentheses are the amounts of the boronic acids relative to substrates. [c]Isolated yield by silica gel chromatography. [d]Determined by chiral HPLC analysis. [e]In Et_2O/H_2O = 7/1 without KOH.

Scheme 4. Pd-Catalyzed Asymmetric Allylic Alkylation of *rac*-1,3-Diphenyl-2-propenyl Acetate



applicable to various transition-metal-catalyzed asymmetric reactions.

Consideration of Stereochemical Pathways in Rhodium-Catalyzed 1,4-Addition Reaction. Figure 6 shows the monomeric substructure of (*R**,*R**)-**4** for analyzing the mode of coordination of the *P*-olefin ligand. While the Ph_2P−Rh−(η^2−CH═CMe) moiety is drawn in a space-filling model, the rest of the ligand skeleton was in a capped-stick model for clarity. The two phenyl groups on the phosphorus atom take the face and the edge orientation, respectively. Similar conformation of the Ph_2P- moieties has been well-recognized in transition-metal complexes coordinated with a binap (or a related) ligand. The phenyl group in the face orientation shields the top-left quadrant, while the bottom left section is left unblocked. On the other hand, the top- and the bottom-right quadrants are effectively discriminated by the steric difference between the vinylic hydrogen atom (labeled in Figure 4) and the methyl group on the olefin. These analyses postulate that the R′ and the R″ substituents in **3** (see Scheme 2) are highly contributory to formation of the effective chiral environment around the rhodium atom. Indeed, this explanation is consistent with the results of the asymmetric reactions in Tables 1 and 2, in which the R′ and the R″ substituents showed huge influences in the enantioselectivity.

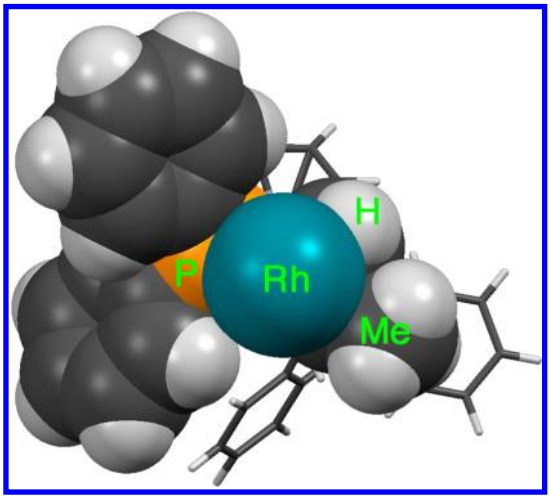


Figure 6. Space-filling/capped-stick drawing of the monomeric substructure in (*R**,*R**)-**4** with selected labels.

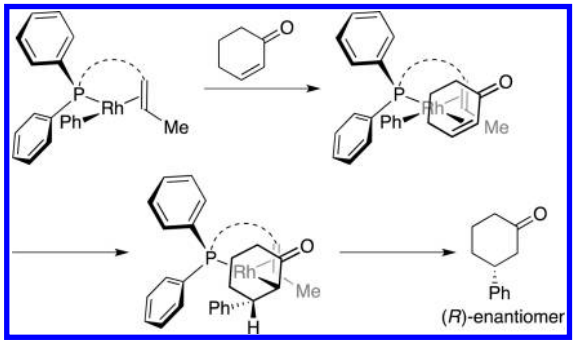
On the basis of the results in Table 1 and the structural analyses above, the stereochemical pathway of the 1,4-addition reaction catalyzed by Rh/(*R*)-**3a** can be rationalized as shown in Scheme 5. The phenylrhodium species has trans-relationship between the Rh-bound phenyl group and the olefin ligand,[11f] and 2-cyclohexenone binds to the rhodium center with its *re* face at the *cis*-position of the olefin ligand to minimize the steric interaction with the chiral ligand. Insertion of cyclohexenone to the Rh−Ph bond and subsequent hydrolysis to give 1,4-adduct with (*R*)-configuration. On the contrary, coordination of cyclohexenone to rhodium with the *si* face was disfavored by the steric repulsion between the cyclohexene ring and the methyl group on the olefin tether.

■ CONCLUSIONS

It has been clarified that planar-chiral alkenylene-bridged (phosphino-π-arene)(phosphine)chromium species **3** are capable of coordinating to a rhodium(I) cation in the bidentate fashion at the phosphorus atom as well as at the olefin moiety.

dx.doi.org/10.1021/ja503060e | J. Am. Chem. Soc. 2014, 136, 9377−9384

Scheme 5. Proposed Stereochemical Pathway for the Rh/(*R*)-3a-Catalyzed Enantioselective 1,4-Addition of Phenylboronic Acid to 2-Cyclohexan-1-one



The *P*-olefin chelate coordination of **3** constructs the effective chiral environment at the rhodium(I) center, and thus, some of their rhodium complexes display high enantioselectivity in the asymmetric 1,4- and 1,2-addition reactions of the arylboron nucleophiles. We have also succeeded in developing the general and more effective enantiospecific synthetic method of these phosphine−olefin ligands. The new synthetic method is quite flexible in terms of the substituent variation, and a library of the planar-chiral (arene)chromium-based phosphine−olefin ligands can be established by the combinatorial approach. Among the newly prepared ligand library, **3g**, which is with the bis(3,5-dimethylphenyl)phosphino group on the η^6-arene ring, was found to be the excellent chiral ligand in the rhodium-catalyzed asymmetric reactions showing excellent enantioselectivity of up to 99.9% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, and crystallographic data of $[RhCl/(R^*)\text{-}\mathbf{3}]_2$ ((R^*,R^*)-**4**) (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

ogasawar@cat.hokudai.ac.jp
tamotsu@cat.hokudai.ac.jp
kamikawa@c.s.osakafu-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Cooperative Research Program from Catalysis Research Center, Hokkaido University (Grant #11A0003 and #12A0001) and a Grant-in-Aid for Scientific Research from MEXT, Japan (to M.O. and K.K.).

■ REFERENCES

(1) (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (b) Wagner, G.; Herrmann, R. In *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995; Chapter 4, p 173. (c) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475. (d) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (e) Štěpnička, P.; Lamač, M. In *Ferrocenes*; Štěpnička, P., Ed.; Wiley: Chichester, 2008; Chapter 7, p 237. (f) Arae, S.; Ogasawara, M. *J. Synth. Org. Chem., Jpn.* **2012**, *70*, 593.

(2) (a) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (b) Rose-Munch, F.; Rose, E. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 11, p 368. (c) Gibson, S. E.; Ibrahim, H. *Chem. Commun.* **2002**, 2465. (d) Kündig, E. P.; Pache, S. H. *Sci. Synth.* **2003**, *2*, 155. (e) Salzer, A. *Coord. Chem. Rev.* **2003**, *242*, 59. (f) Schmalz, H.-G.; Dehmel, F. In *Transition Metals for Organic Synthesis. Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004, Vol. *1*, Chapter 3.12, p 601. (g) *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis*; Kündig, E. P., Ed.; Springer, Berlin, 2004, Topics in Organometallic Chemistry Vol. *7*. (h) Uemura, M. *Org. React.* **2006**, *67*, 217. (i) Rosillo, M.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2007**, *36*, 1589.

(3) (a) Majdalani, A.; Schmalz, H.-G. *Tetrahedron Lett.* **1997**, *38*, 4545. (b) Schellhaas, K.; Schmalz, H.-G.; Bats, J. W. *Chem.—Eur. J.* **1998**, *4*, 57. (c) Ratini, H.; Kündig, E. P. *Org. Lett.* **1999**, *1*, 1997. (d) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938. (e) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52.

(4) Bolm, C.; Muñiz, K. *Chem. Soc. Rev.* **1999**, *28*, 51.

(5) (a) Uemura, M.; Miyake, R.; Nishimura, H.; Matsumoto, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 213. (b) The racemate of compound A was reported in 1988 prior to the Uemura and Hayashi's enantiospecific synthesis. See Heppert, J. A.; Thomas-Miller, M. E.; Milligan, M. L.; Velde, D. V.; Aubé, J. *Organometallics* **1988**, *7*, 2581.

(6) For selected examples, see: (a) Hayashi, Y.; Sakai, H.; Kaneta, N.; Uemura, M. *J. Organomet. Chem.* **1995**, *503*, 143. (b) Ariffin, A.; Blake, A. J.; Li, W.-S.; Simpkins, N. S. *Synlett* **1997**, 1453. (c) Han, J. W.; Jang, H.-Y.; Chung, Y. K. *Tetrahedron: Asymmetry* **1999**, *10*, 2853. (d) Nelson, S. G.; Hilfiker, M. A. *Org. Lett.* **1999**, *1*, 1379. (e) Englert, U.; Haerter, R.; Vasen, D.; Salzer, A. *Organometallics* **1999**, *18*, 4390. (f) Vasen, D.; Salzer, A.; Gerhards, F.; Gals, H.-J.; Stürmer, R.; Bieler, N. H.; Togni, A. *Organometallics* **2000**, *19*, 539. (g) Weber, I.; Jones, G. B. *Tetrahedron Lett.* **2001**, *42*, 6983.

(7) (a) Hayashi, T. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995; Chapter 2, p 105. (b) Togni, A. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim, 1998; Vol. *2*, Chapter 11, p 685. (c) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101. (d) Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L. *Coord. Chem. Rev.* **2004**, *248*, 2131. (e) Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674. (f) Fu, G. C. *Acc. Chem. Res.* **2006**, *39*, 853. (g) Ganter, C. In *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 4.3, p 393.

(8) (a) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 4405. (b) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718. (c) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138. (d) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.

(9) Ogasawara, M.; Wu, W.-Y.; Arae, S.; Morita, T.; Watanabe, S.; Takahashi, T.; Kamikawa, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2951.

(10) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. For review, see: (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (f) Hayashi, T. In *Modern Rhodium-Catalyzed Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 55.

(11) For selected examples, see: (a) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C. Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (c) Shintani, R.; Duan, W.-L.; Okamoto, K.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 3400. (d) Piras, E.; Läng, F.; Rüegger, H.; Stein, D.; Wörle, M.; Grützmacher, H. *Chem.—Eur. J.* **2006**, *12*, 5849. (e) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry*

2006, *17*, 3084. (f) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (g) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, 1365. (h) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (i) Štěpnička, P.; Lamač, M.; Císarová, I. *J. Organomet. Chem.* **2008**, *693*, 446. (j) Pregosin, P. S. *Chem. Commun.* **2008**, 4875. (k) Mariz, R.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2008**, *27*, 6605. (l) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212. (m) Drinkel, E.; Briceño, A.; Dorta, R.; Dorta, R. *Organometallics* **2010**, *29*, 2503. (n) Grugel, H.; Minuth, T.; Boysen, M. M. K. *Synthesis* **2010**, 3248. (o) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. (p) Csizmadiová, J.; Mečiarová, M.; Rakovský, E.; Horváth, B.; Šebesta, R. *Eur. J. Org. Chem.* **2011**, 6110. (q) Wang, H.-L.; Hu, R.-B.; Zhang, H.; Zhou, A.-X.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5302. (r) Liu, Y.; Du, H. *Org. Lett.* **2013**, *15*, 740.

(12) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(13) (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (c) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (d) Feng, C. G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, 1345. (e) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95.

(14) CCDC 983250 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CambridgeCrystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) (a) Hoveyda, A. H.; Schrock, R. R. *Chem.—Eur. J.* **2001**, *7*, 945. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (c) Hoveyda, A. H.; Schrock, R. R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 2004; Supplement 1, Chapter *44*, p 207. (d) Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2085.

(16) (a) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 47. (b) Taniguchi, N.; Uemura, M. *Tetrahedron* **1998**, *54*, 12775.

(17) Ogasawara, M.; Wu, W.-Y.; Arae, S.; Morita, T.; Watanabe, S.; Takahashi, T.; Kamikawa, K. *J. Organomet. Chem.* **2011**, *696*, 3987.

(18) Brown, H. C.; Murray, K. *J. Am. Chem. Soc.* **1959**, *81*, 4108.

(19) For selected examples, see: (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307. (d) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815. (e) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567. (f) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (g) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (h) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623. (i) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2009**, *351*, 260. (j) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602. (k) Shintani, R.; Narui, R.; Tsutsumi, Y.; Hayashi, S.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 6123. (l) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5059.

(20) (a) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. *II*, p 833. (e) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 593.

(21) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568.