

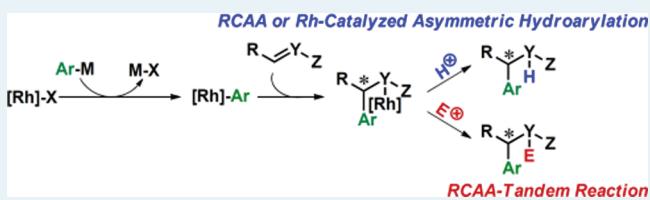
Rhodium-Catalyzed Asymmetric Arylation

Ping Tian, Han-Qing Dong,[†] and Guo-Qiang Lin^{*}

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ABSTRACT: Rhodium-catalyzed asymmetric arylation (RCAA) reactions provide one of the most straightforward and powerful ways to introduce aryl fragments in an enantioselective manner. The discovery of novel chiral ligands and catalytic systems is a major focus in generating optical chiralities for RCAA reactions. In the past decade, the chelating functionalities in ligands have been significantly expanded from traditional phosphorus to interesting diene, bisulfoxide, and their hybrids. Herein we highlight the research on these distinct families of chiral ligands and describe their applications in the RCAA of arylmetals to activated alkenes, aldehydes, ketones and imines, and RCAA-tandem reactions.

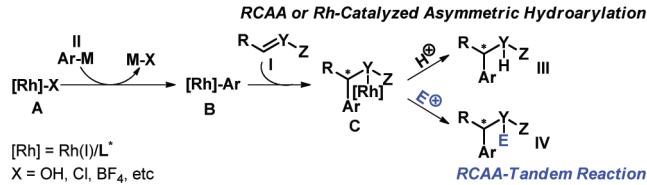
KEYWORDS: rhodium-catalyzed asymmetric arylation, conjugate addition, phosphorus ligands, diene ligands, bisulfoxide ligands, hybrid ligands, activated alkenes, imines, tandem reactions



1. INTRODUCTION

Over the past two decades, there has been dramatic growth in using transition-metal-catalyzed reactions for important organic transformations. Notably, significant attention has been paid to apply rhodium catalysts in the formation of C–C bonds, because of their special reactivity and selectivity compared to other catalytic systems, and their friendly reaction conditions allowing in many cases to have water as a cosolvent. In principle, any reaction that involves Rh-catalyzed asymmetric addition of an aryl group to a double or triple bond is called “Rh-catalyzed asymmetric arylation” (RCAA). A typical RCAA reaction of an aryl-metallic reagent Ar-M (**II**) to an electron-deficient acceptor (**I**) proceeds as follows: First, the transmetalation of an aryl group of Ar-M (**II**) with rhodium species A produces the reactive aryl-rhodium **B**. Then the double bond or triple bond in compound **I** coordinates with **B** and subsequently inserts into Rh–Ar bond to form the adduct **C**, which is readily protonated under aqueous conditions to generate the product **III**. This RCAA process is also named as “Rh-catalyzed asymmetric hydroarylation”. On the other hand, the adduct **C** can be trapped by other electrophiles to yield product **IV**. Such a transformation is often called RCAA-tandem reaction (Scheme 1).

Scheme 1. Concept of RCAA



Prior to our compilation, several authoritative reviews partially covered this subject, including contributions by

Hayashi^{1–8} and Fros⁹ devoted to rhodium-catalyzed asymmetric conjugate addition and its related synthetic applications, and collections by Rovis¹⁰ and Carreira¹¹ centered upon chiral olefins as steering ligands in asymmetric catalysis. Herein we summarize the recent development of RCAA and RCAA-tandem reactions during the period 1997–2011. The review commences with the general description of RCAA, followed by three separate sections focusing on RCAA to alkenes, aldehydes/ketones, and imines, respectively. The RCAA-tandem reaction is then discussed in terms of an intermolecular process with different electrophiles and various intramolecular cyclizations. For easy comparison, examples in each section are grouped by similarity, rather than by chronology.

2. GENERAL DESCRIPTION OF RCAA

RCAA of aryl-boronic reagents to α,β -unsaturated ketones has attracted the most attention in this research field, and is frequently chosen as a model reaction to investigate a variety of different ligand systems. More importantly, many of the characteristics discovered in the reaction with α,β -unsaturated ketones are applicable to other RCAA systems including the reactions from different alkene classes and nucleophilic aryl-metallic reagents.

2.1. History Remarks. The first Rh-catalyzed arylation of arylboronic acids to enones can be traced back to a publication in 1997 by Miyaura and co-workers.¹² In this report, the combination of $[\text{Rh}(\text{-acac})(\text{CO})_2]$ (acac = acetylacetato) and bisphosphine ligand dppb (dppb = 1,4-bis(diphenylphosphino)butane) could efficiently catalyze the conjugate addition of arylboronic acids to linear and cyclic α,β -unsaturated ketones in various aqueous cosolvent systems

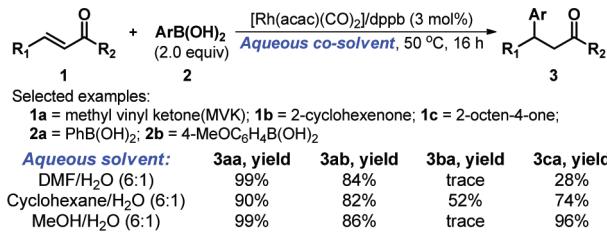
Received: October 31, 2011

Revised: December 5, 2011

Published: December 7, 2011

although in slightly lower yield for 2-cyclohexenone (**1b**) (Scheme 2).

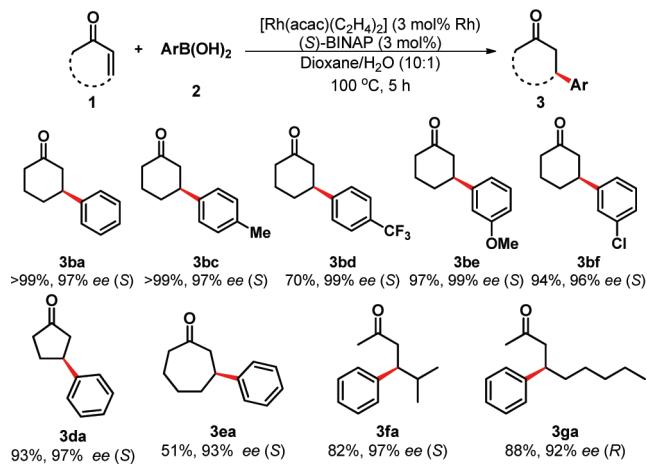
Scheme 2. Initial Report of Rh-Catalyzed Arylation to Enones



The merits of this reaction lie in the following: (i) neutral reaction conditions in the presence of water; (ii) no observation of either competitive uncatalyzed reaction of the arylboronic acids to the enones or the related 1,2-addition byproduct; and (iii) tolerance of a wide range of functional groups in organoboron reagents which are in contrast to organolithium and Grignard reagents.

A milestone of this asymmetric methodology appeared in 1998, when Hayashi and Miyaura described the RCAA of arylboronic acids to α,β -unsaturated ketones.¹³ For the first time, a broad range of aryl groups could be introduced into α,β -unsaturated ketones in high yields and excellent enantioselectivities using (S)-BINAP as the ligand (Scheme 3). There

Scheme 3. $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/(\text{S})\text{-BINAP}$ Catalyzed Asymmetric Arylation of Arylboronic Acids to Enones

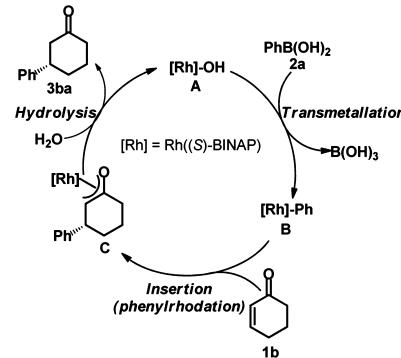


were multiple modifications from the original Miyaura's conditions: (i) different Rh-precursor, from $[\text{Rh}(\text{acac})(\text{CO})_2]$ to $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$; (ii) different solvent system, 1,4-dioxane/ H_2O (10:1); (iii) higher reaction temperature (100 °C) and shorter reaction time (5 h). Under the optimal reaction conditions, aryl groups with either electron-donating or electron-withdrawing substitutions were successfully added to both cyclic enones (2-cyclohexenone (**1b**)), 2-cyclopentenone (**1d**) and 2-cycloheptenone (**1e**)), and trans-linear enones with excellent enantioselectivities (Scheme 3).

These key groundbreaking findings paved the way for an intense and hot research activity in the area of RCAA and related processes. Nowadays, the reaction of RCAA of organoboronic acids to α,β -unsaturated ketones is usually called Hayashi–Miyaura reaction.

2.2. Mechanism and Stereoselectivity. In 2002, Hayashi and co-workers demonstrated the detailed mechanism in the RCAA to α,β -unsaturated ketones.¹⁴ An example of this catalytic cycle for the RCAA of phenylboronic acid to 2-cyclohexenone (**1b**) catalyzed by $\text{Rh}(\text{I})/(\text{S})\text{-BINAP}$ is illustrated in Scheme 4. The reaction is initiated through the

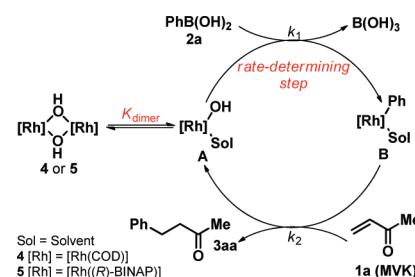
Scheme 4. Catalytic Cycle for the RCAA of Phenylboronic Acid to 2-Cyclohexenone by a $[\text{Rh}]\text{-OH}$ Complex



transmetalation of a phenyl group from boron to hydroxorhodium **A** to generate the phenylrhodium **B**. Subsequently, 2-cyclohexenone inserts into $\text{Rh}-\text{Ph}$ bond of **B** to form the oxa- π -allylrhodium **C**, which is unstable under protic condition and readily hydrolyzed to regenerate **A** and liberate the RCAA product **3ba**. It is noteworthy that rhodium remains at a constant oxidation state of +1 throughout the catalytic cycle.

Subsequently, Hayashi and co-workers accomplished a detailed kinetic study and revealed that the transmetalation from boron to rhodium was the rate-determining step in the catalytic cycle. It was also found that the equilibrium between the catalytically inactive dimeric hydroxorhodium complex **4** or **5** and the active monomeric species **A** significantly affected the reaction rate (Scheme 5).¹⁵ For example, the reaction rate

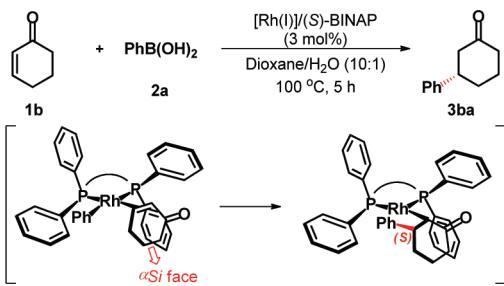
Scheme 5. Kinetic Study of Rh-Catalyzed Arylation to MVK



catalyzed by $[\text{Rh}(\text{OH})(\text{COD})]_2$ (**4**) was 20-fold faster than with $[\text{Rh}(\text{OH})((\text{R})\text{-BINAP})]_2$ (**5**) under the same conditions in Rh-catalyzed arylation of $\text{PhB}(\text{OH})_2$ to MVK.¹⁶ Such remarkably different catalytic activities between two Rh-complexes resulted from faster rates in both equilibrium and transmetalation steps by using Rh(I)/diene complex **4**.

In 1998, Hayashi and co-workers proposed the stereochemical pathway for the preferential formation of the *S* product in RCAA reaction catalyzed by $\text{Rh}(\text{I})/(\text{S})\text{-BINAP}$ complex with 2-cyclohexenone (**1b**) as an example (Scheme 6).¹³ Owing to the highly skewed structure known for transition metal complexes coordinated with a BINAP ligand,¹⁷ (*S*)-BINAP-Rh-Ph intermediate should have an open space at the lower part

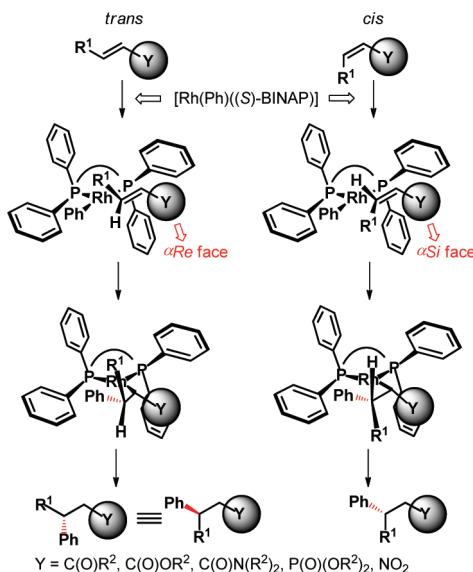
Scheme 6. Hayashi's Enantioselective Model for the RCAA to 2-Cyclohexenone Catalyzed by Rh(I)/(S)-BINAP Complex



of the vacant coordination site, with the upper being blocked by one of the phenyl rings of BINAP ligand. The alkenyl bond of 2-cyclohexenone can only coordinate rhodium with its αSi face and undergo migratory insertion to form a stereogenic carbon center with *S* configuration in product **3ba**.

In 2010, Hayashi and co-workers extended this stereochemical model to predict the absolute configurations of final products in Rh(I)/(S)-BINAP catalyzed asymmetric 1,4-addition reactions.⁸ As shown in Scheme 7, aryl-rhodium

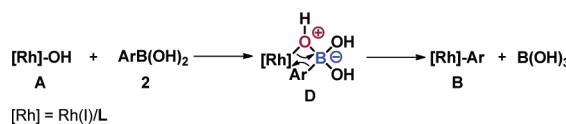
Scheme 7. Hayashi's Stereocontrol Model for the RCAA to *trans*- or *cis*-Olefins



species selectively coordinates with the αSi face of cyclic and *cis*-linear or αRe face of *trans*-linear alkenes, generating corresponding chiral stereocenters in the products. Notably, the *trans/cis* geometry of the double bond in linear alkenes plays a dominating role in the stereochemical outcome. The linear olefins in this model refer to α,β -unsaturated ketones, α,β -unsaturated esters and amides, alkenylphosphonates, and nitroalkenes.

2.3. Aryl-Metallic Reagents and Rh Precatalysts. **2.3.1. Arylboron Reagents.** The mechanism of transmetalation from boron to rhodium assumes that Rh-OH complex **A** can coordinate the highly oxophilic arylboronic acid **2** to give intermediate **D** as a quaternized boron anion, from which the aryl fragment is transferred to rhodium in an intramolecular fashion to generate the aryl-rhodium species **B** and boronic acid (Scheme 8).^{18,19} This transmetalation occurs

Scheme 8. Proposed Mechanism for the Transmetalation of Arylboronic Acids to Rhodium



under neutral conditions, but it can be greatly accelerated by the addition of a stoichiometric base. This is attributable to the quaternization of arylboronic acid, which facilitates the rupture of B-Ar bond.^{18,20}

Most arylboronic acids **2** are thermally stable and inert to water and oxygen, and they are widely used in RCAA reactions. It is found that trace amount of phenol existing in commercial phenylboronic acid can remarkably deactivate Rh(I)/chiral diene catalysts,²¹ especially in the case of low-catalyst loading. The phenol impurity can be easily removed by dehydration of boronic acid to form the cyclic trimeric anhydride (boroxine, **6**), followed by washing with hexane (Figure 1). The pure boroxine

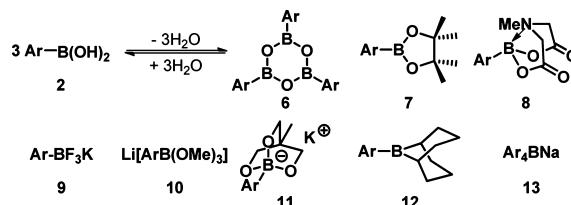
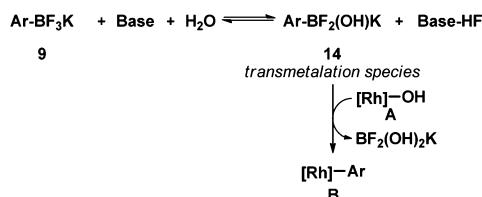


Figure 1. Arylboron Reagents for RCAA.

6 can be readily hydrolyzed back to the corresponding boronic acid **2** under basic aqueous conditions.²² Interestingly, boroxines **6** have become one of the preferential reagents for RCAA, because of the convenient addition in accurate stoichiometry and their better stability toward protodeboration than boronic acids, particularly at high temperature (ca. 100 °C).

Pinacol boronic esters **7** react slowly in RCAA because of their sluggish hydrolysis back to the corresponding boronic acids.²³ The additional coordination in *N*-methylimidodiacetic acid (MIDA) boronates **8** greatly improves their stability, resulting in slow release of boronic acids from MIDA boronates to keep minimal amount of free boronic acid throughout the RCAA reaction.²⁴ Potassium aryltrifluoroborate salts **9** have become a popular source of organoboron reagents,^{25–28} because they also exhibit better stability than the corresponding boronic acids while staying reactive in RCAA.²⁹ It is noteworthy that potassium organotrifluoroborates do not transmetallate directly to Rh(I), but rather through the monohydroxyborate **14** (Scheme 9).^{30–34}

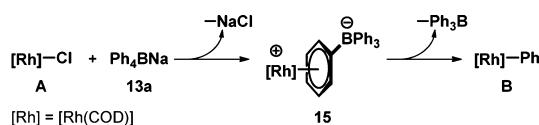
Scheme 9. Transmetalation of Potassium Aryltrifluoroborate



Lithium trimethylarylboration salts **10** are very reactive in RCAA, but unstable and require the preparation in situ.^{23,35,36}

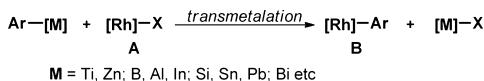
Similar to MIDA (8), cyclic aryltriolborates **11** are also very stable in air and water, and conveniently used in RCAA because of better solubility in organic solvents than related potassium organotrifluoroborates **9**.^{37,38} The reactive ArB(9-BBN) derivatives **12** are often applied in RCAA in aprotic solvents to afford a stable chiral boron enolate in the absence of base,³⁹ which can be further trapped by other electrophiles to undergo tandem reactions (cf. Section 6). Sodium tetraphenylborate salts **13** are also very reactive reagents for the RCAA. For example, sodium tetraphenylborate (**13a**) reacts with Rh-chloride complex **A** to afford Rh-tetraphenylborate complex **15** under neutral conditions, which subsequently releases the phenylrhodium species **B** (Scheme 10).⁴⁰

Scheme 10. Transmetalation of Sodium Tetraarylborate



2.3.2. Other Aryl-Metallic Reagents. Besides boron reagents, other organometallics can also be used in RCAA reactions (Scheme 11). Theoretically, all organometallics in

Scheme 11. Transmetalation of Aryl-Metallic Reagents with Rh



which the metal is less electronegative than rhodium and all organometallic species of similar electronegativity but with weaker carbon–rhodium bonds are potential candidates for transmetalation reactions with rhodium.⁴¹ For the sake of effective transmetalation, the arylmetallic reagents must be still stable under the hydrolysis conditions of the Rh-enolate, or they can directly transmetallate with the Rh-enolate.³⁹

Aryl-aluminum,⁴² -titanium,^{43–46} and -zinc^{47–50} reagents are much more nucleophilic than the corresponding arylboron species, enabling the transmetalation at room temperature under aprotic conditions.

Arylsilicon reagents are far less reactive than the corresponding boron, tin, titanium, and zinc derivatives. So far, arylsilanediols **16**,⁵¹ dichlorodiarylsilanes **17**,⁵² aryltriethoxysilanes **18**,⁵³ poly(phenylmethylsiloxane) **19**,⁵⁴ and [2-(hydroxymethyl)aryl]dimethylsilanes **20**⁵⁵ have been successively developed as the aryl-transfer reagents with rhodium (Figure 2).

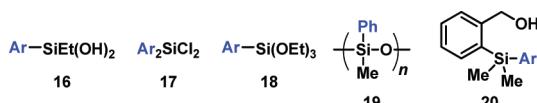
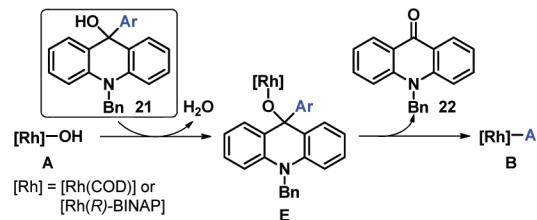


Figure 2. Arylsilicon reagents as aryl-transfer reagents.

Diarylindium hydroxides,⁵⁶ aryl-tin,^{57–59} aryl-lead,⁶⁰ and triarylbismuth^{61,62} reagents also prove to be competent aryl-transfer agents even in the presence of air and water. Interestingly, the reaction of [Rh]-OH with triarylmethanols **21**, which are derived from acridinone **22**, can produce different arylrhodiums **B** through β -aryl elimination of alkoxorhodium

intermediates **E**, providing a new effective aryl-transfer approach (Scheme 12).⁶³

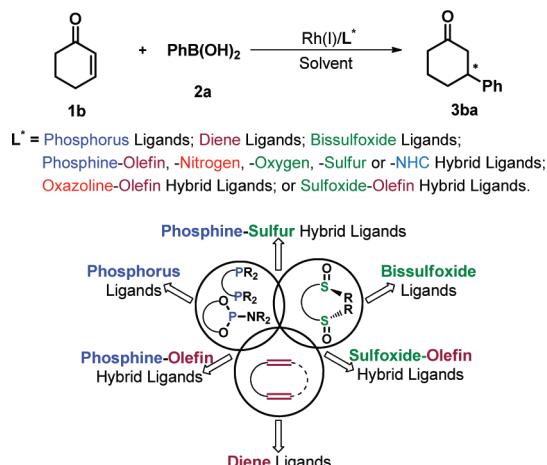
Scheme 12. Triarylmethanols as Aryl-Transfer Reagents



2.3.3. Rh-Precatalysts. $[\text{Rh}(\text{Cl})(\text{C}_2\text{H}_4)_2]$ is the favorable precatalyst because of its rapid and irreversible ligand exchange.¹³ However, COD-based Rh precursors, such as $[\text{Rh}(\text{Cl})(\text{COD})]$ ₂ and $[\text{Rh}(\text{OH})(\text{COD})]$ ₂, are usually avoided because they exhibit higher catalytic activity than chiral Rh-phosphine complex.^{20,64} Cationic rhodium precatalysts also demonstrate fast ligand exchange,⁶⁵ and are often applied in RCAA. For example, $[\text{Rh}(\text{COD})_2]\text{BF}_4^-$, $[\text{Rh}(\text{COD})(\text{MeCN})_2]\text{BF}_4^-$,^{58,59,66–71} and $[\text{Rh}(\text{nbd})_2]\text{BF}_4^-$,^{20,72} are excellent Rh-precatalysts,⁷³ which allow for the replacement of KOH with Et₃N in RCAA and thus make the reaction more functional group-tolerant.⁷⁴

2.4. Ligand Systems. Developing new ligands and new reactions has been always a major focus in the field of RCAA. In this section, an overview of the distinct ligands for RCAA of phenylboronic acid to 2-cyclohexenone (Hayashi–Miyaura reaction) will be presented. A variety of chiral ligands in RCAA reactions can be classified into the following families: phosphorus-, diene-, sulfoxide-, and their hybrid-structures. Comparison of different ligand motifs is usually performed by using Hayashi–Miyaura reaction as a model system (Scheme 13). It should be noted that this is just one

Scheme 13. RCAA of Phenylboronic Acid (2a) to 2-Cyclohexenone (1b) As a Model Reaction Using Different Ligands



comparison based on this model reaction, and some ligands might work better for other specific substrates.

2.4.1. Phosphorus Ligands. On the basis of the initial success of using chiral BINAP in RCAA, a large number of bidentate or monodentate phosphorus ligands have been applied in this area. These results are summarized in Figures 3, 5, 6, and 7.

The BINAP-based ligands L_2 ,⁷⁵ L_3 ,⁷⁵ and water-soluble L_4 ⁷⁶ provided similar outcomes with BINAP (Figure 3). Interestingly,

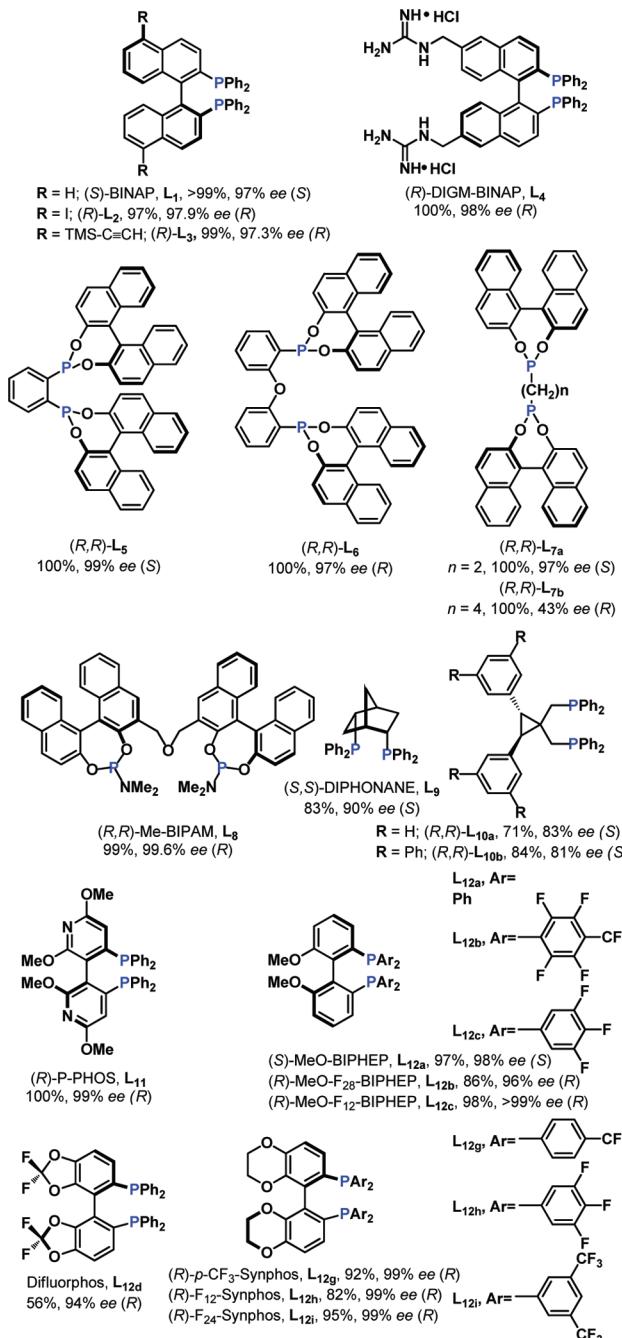


Figure 3. C_2 -Symmetric bidentate phosphorus ligands.

BINOL-based bisphosphonites⁷⁷ L_5 and L_6 or L_{7a} and L_{7b} gave excellent but sometimes reverse enantioselectivity depending on the linker between two separate phosphonites. Similarly, BINOL-based bisphosphoramide L_8 gave excellent results.^{74,78} The bisphosphine ligand L_9 ,⁷⁹ bearing a distinct norbornane backbone delivered high selectivities; however, the cyclopropane-based bisphosphines⁸⁰ L_{10a} and L_{10b} just achieved the moderate selectivities. The biphenyl-based bisphosphorus ligands L_{11} , L_{12a} , L_{12b} , L_{12c} , L_{12d} , L_{12g} , L_{12h} , and L_{12i} likewise acquired excellent enantioselectivities,^{81–88} in which (R)-F₁₂-BIPHEP L_{12c} and (R)-F₂₄-Synphos L_{12i} displayed a higher catalytic activity.

The catalytic activity of different bisphosphine ligands can be estimated by comparing their stretching frequencies (ν_{CO}) of carbonyl groups in the corresponding [RhCl(bisphosphine)-(CO)] complexes by IR (Figure 4). The ν_{CO} value of L_{12c} is

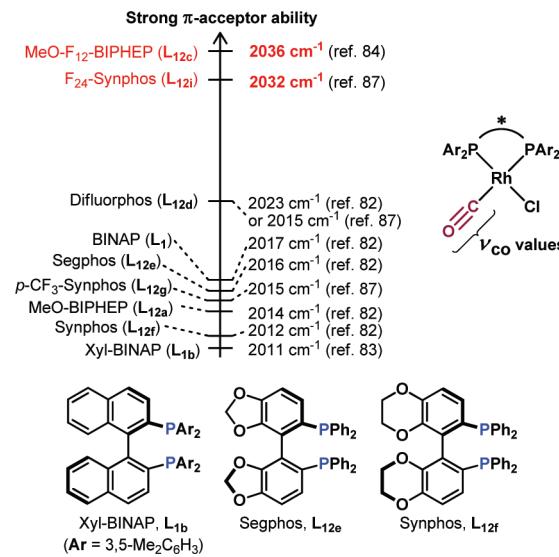


Figure 4. ν_{CO} values of the [RhCl(bisphosphine)(CO)] complexes.

shown to be higher than those of known bisphosphines,^{82,83,85} suggesting that L_{12c} has stronger π -acidic character.^{82,83,85} Such strong π -accepting ability can significantly accelerate the rate-determining transmetalation step in Hayashi–Miyaura reaction. As a result, L_{12c} showed the highest catalytic activity with turnover frequency (TOF) and turnover number (TON) up to 54,000 h⁻¹ and 320,000.⁸⁵

Axially chiral non- C_2 -symmetric bisphosphorus ligands L_{13a} ,⁸⁹ L_{13b} ,⁸⁹ and polystyrene-supported BINAP L_{14} ,⁹⁰ gave excellent enantioselectivities similar to BINAP (Figure 5). The

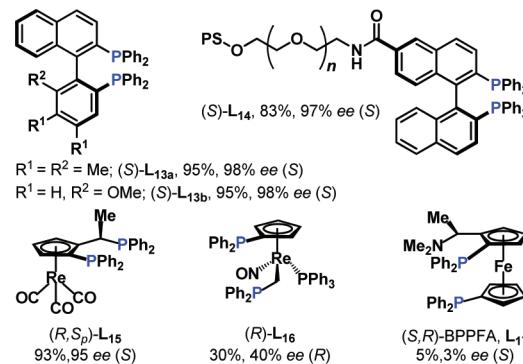


Figure 5. Non- C_2 -symmetric bidentate phosphorus ligands.

bisphosphine ligands L_{15} ,⁹¹ L_{16} ,⁹² and L_{17} ,⁹³ with planar chirality were also investigated in Hayashi–Miyaura reaction and only Re-based L_{15} gave significant selectivities.

The P-chiral bisphosphine ligands QuinoxP* (L_{18}),⁹⁴ tBu-BisP* (L_{19}),⁹⁵ L_{20} ,⁹⁵ and L_{21} ,⁹⁵ have been successfully developed and high enantioselectivity was achieved in Hayashi–Miyaura reaction (Figure 6). The experimental results obtained with alkyne-type ligands L_{20} and L_{21} are comparable or even superior to those obtained with BINAP (L_1), QuinoxP* (L_{18}), or tBu-BisP* (L_{19}).

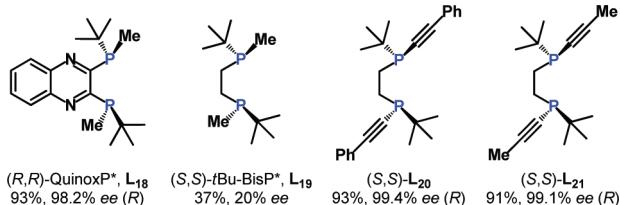


Figure 6. P-chiral bidentate phosphine ligands.

Phosphoramidite ligands were highly reactive and enantioselective in Rh-catalyzed asymmetric hydrogenation;⁹⁶ they also performed very well in Hayashi–Miyaura reaction because of their strong π -accepting properties.^{39,97–103} For the RCAA of phenylboronic acid to 2-cyclohexenone, H₈-BINOL-based phosphoramidite (*S*)-L₂₂ proved to be the most efficient.¹⁰⁰ Introducing the inexpensive methyl deoxycholic ester 23 as the source of chirality in phosphite L₂₃ validated the similar efficiency compared with L₂₄ (Figure 7).^{104,105}

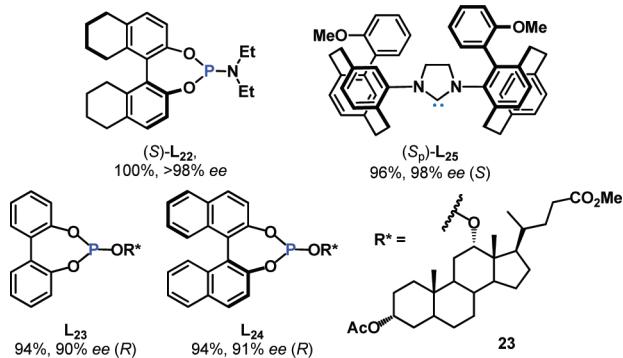


Figure 7. Monodentate phosphorus ligands.

The electron pair in *N*-heterocyclic carbenes (NHCs) makes them act as strong σ -donors. Despite their relatively weak π -acceptor property, NHC ligands still showed great catalytic activity in RCAA reaction. For example, the cyclophane-based NHC ligand L₂₅ was a quite unique monodentate ligand and proved to be powerful for Hayashi–Miyaura reaction.^{106,107} Remarkably, only 1 equiv of chiral NHC relative to rhodium was needed, as most monodentate ligands required 2 equiv to rhodium to achieve high selectivity (Figure 7).

2.4.2. Diene Ligands. As a result of two synergistic interactions of σ -donation from olefin to rhodium and π -back-donation from rhodium to olefin, structurally diverse chiral dienes should be excellent steering ligands. Indeed, the Rh(I)/chiral diene catalytic systems have proved to be one of the best catalytic methods for Rh-catalyzed asymmetric 1,4-addition because of the strong π -accepting ability of diene ligands. Since the first application of chiral diene L_{26b} in RCAA by Hayashi and co-workers,¹⁰⁸ a variety of bicyclic diene scaffolds have been successfully applied in this useful transformation (Figure 8).^{47,109–117} Almost at the same time, Carreira and co-workers reported that chiral diene is also effective for Ir-catalyzed allylic substitution.¹¹⁸ These independent discoveries have promoted intense research efforts in metal-catalyzed transformations, which were elegantly reviewed by Carreira in 2008.¹¹

As illustrated in Figure 8, all alkylated variations in chiral bicyclo[2.2.1]heptadiene scaffold, such as Me- (L_{26a}), Bn- (L_{26b}), Cy- (L_{26d}), *i*-Bu- (L_{26e}), and allyl- (L_{26f}) showed

excellent enantioselectivities (95–96% ee); and phenyl variation L_{26c} exhibited a higher enantiomeric excess (ee) value.^{119,120} Chiral-bridged dienes L₂₇, which were easily prepared through catalytic enantioselective Diels–Alder reaction using the CBS catalyst, also displayed excellent selectivities (96–98% ee).¹²¹ Other chiral bridged dienes, including bicyclo[2.2.2]octadiene variations (L₂₈, L₂₉, L₃₀, L₃₁, L₃₂, L₃₃, and L₃₄),^{110,118,121–129} bicyclo[3.3.1]nonadiene variations (L₃₅ and L₃₆),^{130,131} and bicyclo[3.3.2]decdiene variation L₃₇¹³¹ all gave excellent enantiomeric excesses for Hayashi–Miyaura reaction. Both optically pure enantiomers of bicyclo[3.3.0]octadiene-based chiral dienes L₃₈¹¹³ and L₃₉¹³² could be easily prepared through lipase-catalyzed kinetic resolution in >10 g scale. Hydrophilic diene ligand L₃₉ is quite soluble in water (solubility: 5 mg/mL) and for the first time successfully promoted the RCAA in aqueous media within diene series.¹³²

The Ph-dbcot L₄₀¹¹² and 1,5-Ph-cod L₄₁⁴⁷ are achiral, but the corresponding cationic rhodium complexes are chiral and both enantiomers can be resolved. The optically pure Rh-complexes with L₄₀ and L₄₁ gave the moderate enantioselectivity in RCAA. Utilizing the simple and flexible acyclic chiral 1,5-dienes L₄₂,¹³³ L₄₃,¹³³ L₄₄,¹³³ and L₄₅¹³⁴ as steering ligands for Hayashi–Miyaura reaction, good to excellent yields and ee were achieved (Figure 8).

2.4.3. Bisulfoxide Ligands. Bis-sulfoxides are a newly rising family of ligands in homogeneous catalysis by coordinating Rh with the sulfur atoms.^{135,136} Among them, chiral bis(*p*-tolyl-sulfoxide) ligands L₄₆¹³⁷ and L₄₇¹³⁸ were found to be outstanding ligands for Hayashi–Miyaura reaction, demonstrating near-perfect enantioselectivities over various cyclic α,β -unsaturated ketones (Figure 9). A comparison of the X-ray crystal structures of [RhCl((*R*)-BINAP)]₂, [RhCl(L_{28a})]₂,¹³⁹ and [RhCl(L₄₆)]₂ suggested that the ligating nature of bis-sulfoxides might stay somewhere between that of diene and bis-arylpophosphine ligands. Subsequently, a series of axially chiral bis(*tert*-butylsulfoxide) ligands L_{49a}-L_{51a} and bis(*p*-tolyl-sulfoxide) ligands L_{49b}-L_{51b} were synthesized, in which L_{49b}-L_{51b} bearing *p*-tolylsulfonyl group proved to be remarkably efficient ligands for Hayashi–Miyaura reaction with perfect enantioselectivity (>99% ee).¹⁴⁰ A simple and readily prepared chiral bis(*tert*-butylsulfoxide) ligand L₄₈ also afforded the corresponding RCAA products in excellent yields and enantioselectivities.¹⁴¹

An emerging class of chiral heterodisulfoxide ligands L₅₂-L₅₆ containing *tert*-butyl- and aryl-sulfoxides within a rigid benzene scaffold were developed and evaluated in the RCAA to chromenone (1h),^{142,143} which is one of the most challenging subjects in this field. The simple bis(*tert*-butylsulfoxide) ligand L₄₈ is still the most active and selective ligand in this subseries (Scheme 14).^{141–143} The highly electron-poor chiral diphosphine ligand L_{12c} was also applicable to this reaction, affording excellent yield and enantioselectivity.¹⁴⁴

2.4.4. Phosphine-Olefin, -Nitrogen, -Oxygen, -Sulfur, or -NHC Hybrid Ligands. Hybrid ligands contain two different coordinating centers, with a phosphorus center to tune the steric and electronic properties and another functionality (such as an olefin, nitrogen, oxygen, sulfur, and NHC) to stabilize the Rh-complex. Phosphines coordinate more strongly to late transition metals than alkenes do; thus, the latter in phosphine-olefin hybrid ligands are just to dilute the intense stickiness of the former to rhodium. Initially, the chiral phosphine-olefin ligand L₅₇ was applied in the RCAA to enones,¹⁴⁵ and exhibited

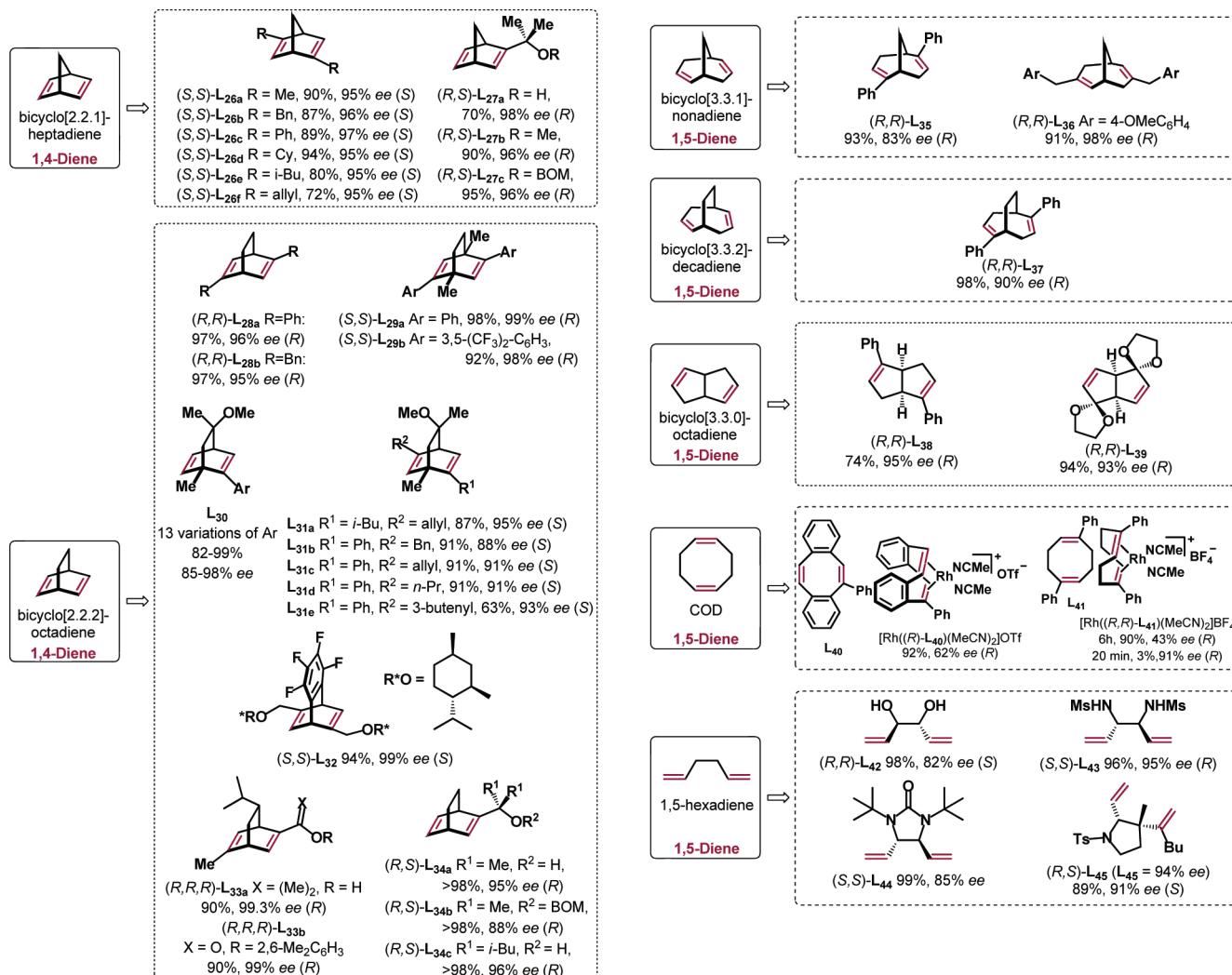


Figure 8. Chiral diene ligands.

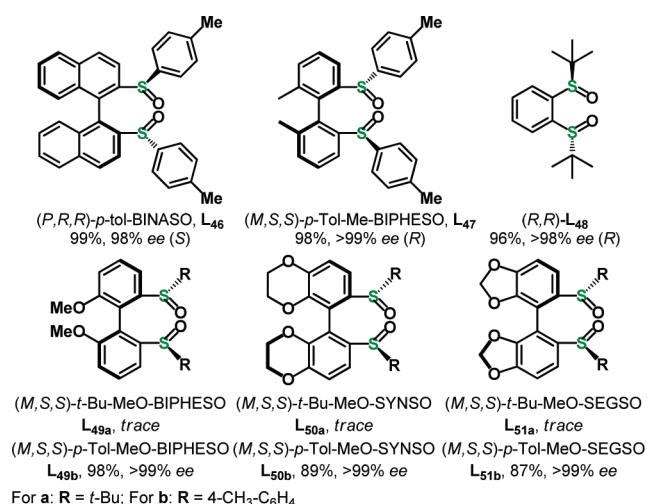
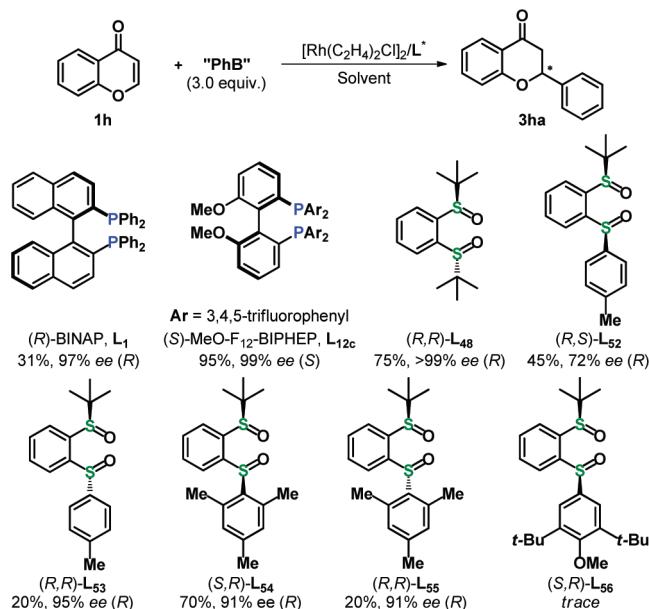


Figure 9. Chiral bis-sulfoxide ligands.

higher catalytic activity than a Rh/cod catalyst.¹⁴⁶ Subsequently, phosphine-olefin L₅₈¹⁴⁷ and L₅₉¹⁴⁸ amidophosphine-olefin L₆₀^{111,149,150} and carbohydrate phosphine-olefin L₆₁^{151,152} were developed and showed good activities and enantioselectivities in Hayashi–Miyaura reaction (Figure 10).

Scheme 14. Chiral bis-Heterosulfoxide Ligands



Phosphine-nitrogen hybrid ligand L₆₂⁹³ did not induce any enantioselectivity in RCAA, while the L-proline-derived

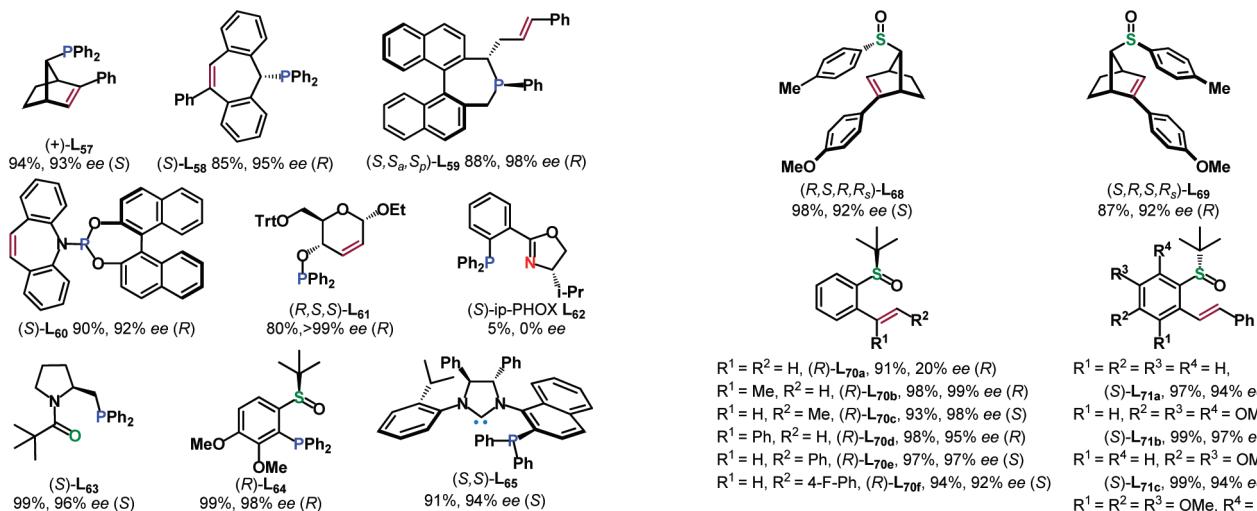


Figure 10. Phosphine-olefin, -nitrogen, -oxygen, -sulfur, or - NHC hybrid ligands.

phosphine-oxygen ligand L₆₃^{153–155} and phosphine-sulfoxide ligand L₆₄^{156,157} were found to be very effective. Phosphine-NHC hybrid ligand is a fairly new family and has been relatively little explored in RCAA. Helmchen and co-workers showed that phosphine-NHC hybrid ligand L₆₅¹⁵⁸ provided high yields and enantioselectivities in RCAA of arylboronic acids to enones and α,β -unsaturated esters (Figure 10).

2.4.5. Oxazoline-Olefin Hybrid Ligands. The oxazoline moiety is a ubiquitous, privileged structure in chiral ligands. With the idea that the combination of η^2 -binding olefins with oxazolines would produce new coordination geometries and possibilities, Glorius and co-workers first introduced a novel class of oxazoline-olefin ligand L₆₆ into RCAA reaction and demonstrated both modularity and versatility.¹⁵⁹ In contrast to many other classes of chiral ligands, this series are especially appealing because the steric and electronic properties of the olefin components can be easily tuned. Subsequently, Franzén reported the synthesis of a novel oxazoline-indoleolefin ligand L₆₇ and utilized it in Hayashi–Miyaura reaction (Figure 11).¹⁶⁰

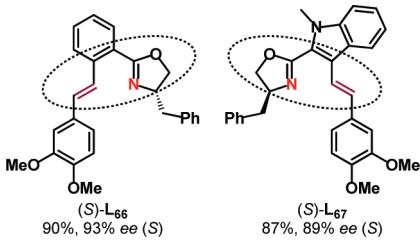


Figure 11. Oxazoline-olefin hybrid ligands.

2.4.6. Sulfoxide-Olefin Hybrid Ligands. Sulfoxide-olefin hybrids are also introduced as a new family of chiral heterobidentate ligands in RCAA. Knochel and co-workers first developed a concise synthesis of a couple of sulfoxide-olefin hybrid ligands L₆₈ and L₆₉, and applied them in Hayashi–Miyaura reaction to furnish the chiral products in excellent yields, with equally high enantioselectivities and opposite stereoconfigurations (Figure 12).¹⁶¹ Interestingly, a new class of chiral sulfoxide-olefin ligands L₇₀^{162,163} could induce reverse enantioselectivity by simply changing the substitutions at the olefin moiety (L_{70b} vs L_{70c} or L_{70d} vs L_{70e}).

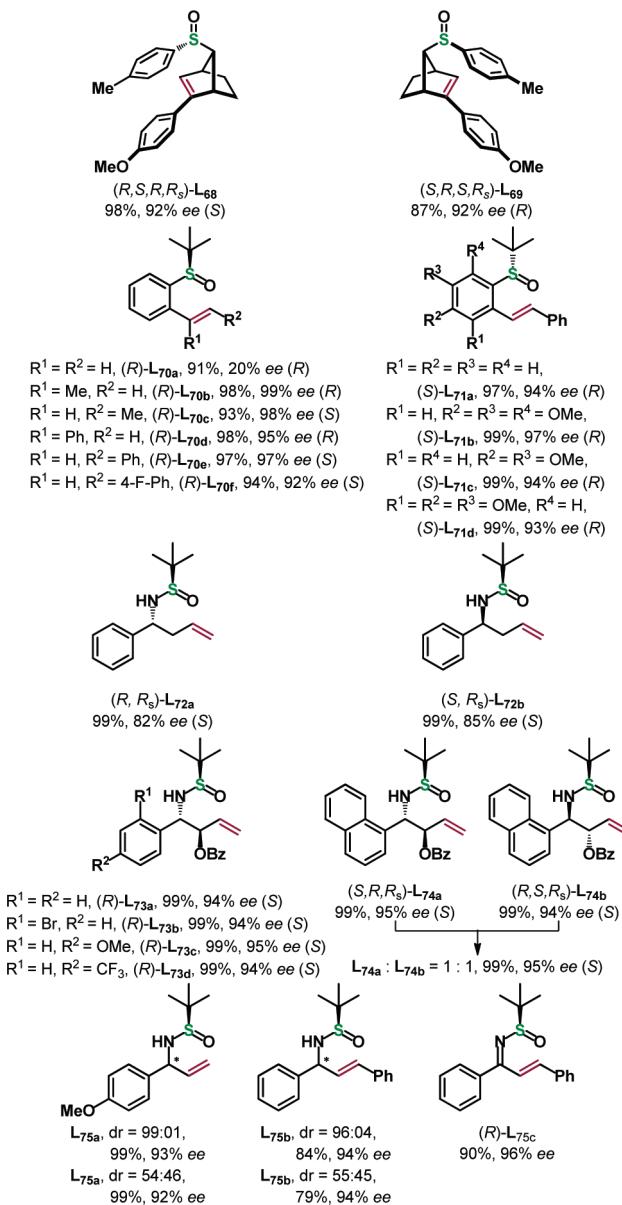


Figure 12. Sulfoxide-olefin hybrid ligands.

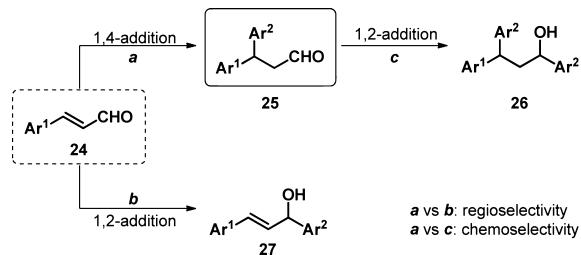
In other words, both enantiomers of the product can be synthesized by choosing different olefin-substituted (R)-L₇₀. Such a great advantage can potentially eliminate the process to prepare the ligands in both enantiomeric pure forms. At the same time, Xu and co-workers also reported this class of sulfoxide-olefin ligands L₇₁ for the same reaction.¹⁶⁴ Afterward, they demonstrated that the simple and readily available chiral sulfinamide-olefins L₇₂–L₇₄¹⁶⁵ also displayed great catalytic activities and enantioselectivities in Hayashi–Miyaura reaction. It is noteworthy that the sulfur-stereogenic center (L_{74a} vs L_{74b}) was the key chiral directing group and the two carbon chiralities seemed to be unnecessary in achieving excellent enantioselectivity. Facile preparation of these ligands is a remarkable advantage. The chiral sulfinamide-olefin ligands L₇₂–L₇₄ can be conveniently synthesized by using Zn-mediated allylation of chiral N-*tert*-butanesulfinylimines at room temperature, providing both enantiomers in high diastereo- and enantioselectivities.^{166–169} Du and co-workers independently described the development of similar N-sulfinyl-based chiral sulfur-olefin

ligands (\mathbf{L}_{75a} and \mathbf{L}_{75b})¹⁷⁰ and their successful application in the same reaction. The carbon chiral center was also observed to have no impact on the enantioselectivity in RCAA. The ease of synthesis and needless consideration of the carbon chirality make this type of ligand attractive and promising for asymmetric catalysis. More recently, chiral sulfinimide-olefin ligand \mathbf{L}_{75c} , with a single chiral sulfur atom, also exhibited promising activity and enantioselectivity in Hayashi–Miyaura reaction.¹⁷¹

3. RCAA TO ALKENES

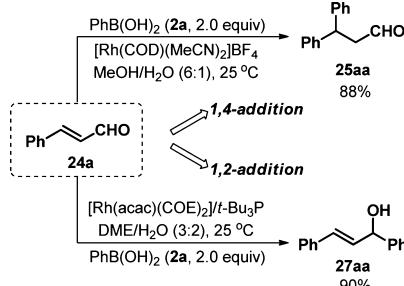
3.1. RCAA to α,β -Unsaturated Aldehydes. Rh-catalyzed conjugate addition to α,β -unsaturated aldehydes exhibited a special challenge because of the existence of a highly reactive aldehyde group, which can undergo 1,2-addition either in competition with 1,4-addition (path b vs path a) or further conversion of the RCAA product 25 to give alcohol 26 (Scheme 15). This competitive process is highly affected by the

Scheme 15. Competing Addition Reaction Pathways to Enals



properties of the ligands to afford different adducts.¹⁷² In the addition of phenylboronic acid ($2\mathbf{a}$) to cinnamaldehyde ($24\mathbf{a}$), the $t\text{-Bu}_3\text{P}$ complex yielded the 1,2-addition product $27\mathbf{aa}$ in 90% yield (Scheme 16), whereas the diene system afforded

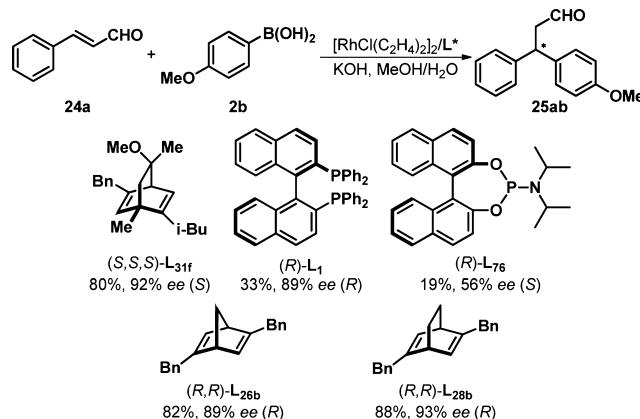
Scheme 16. Ligand Controlled 1,4- or 1,2-Addition Selectivity



1,4-addition product $25\mathbf{aa}$ in 88% yield without any 1,2-adduct even in the presence of excessive amount of phenylboronic acid (2 equiv). This interesting observation opens a door for the Rh(I)/chiral diene-catalyzed asymmetric conjugate addition to enals.

In 2005, Carreira and co-workers first presented a Rh(I)/chiral diene (\mathbf{L}_{31f})-catalyzed enantioselective 1,4-addition of arylboronic acids to enals.¹²⁵ The reaction was conducted in MeOH-water, giving the desired RCAA product $25\mathbf{ab}$ in 80% yield and 92% ee. Conventional ligands (R)-BINAP \mathbf{L}_1 and phosphoramidite (R)- \mathbf{L}_{76} gave poor results (only 33% and 19% yield, respectively) although the former provided the desired 1,2-adduct with 89% ee (Scheme 17). However, in the presence

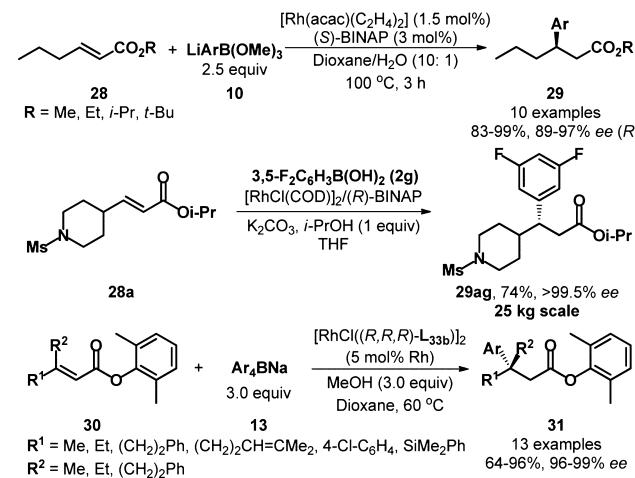
Scheme 17. RCAA to Cinnamaldehyde ($24\mathbf{a}$)



of chlorosilane, Rh(I)/(R)-BINAP proved to be a powerful catalytic system in the asymmetric 1,4-addition of arylzinc chlorides to enals, affording the corresponding 3,3-diarylpippanols with perfect enantioselectivities (98–99% ee).⁴⁸ Almost at the same time, the chiral dienes \mathbf{L}_{26b} and \mathbf{L}_{28b} were successfully applied in the same reaction by Hayashi and co-workers.¹²²

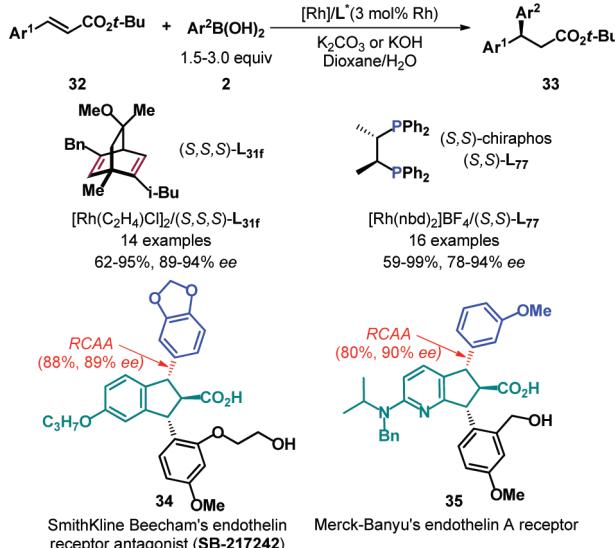
3.2. RCAA to α,β -Unsaturated Esters. α,β -Unsaturated esters are excellent substrates for RCAA, providing only the 1,4-addition products. For linear substrates 28 , the reactions proceeded smoothly when a more reactive arylboron reagent ($\text{LiArB}(\text{OMe})_3$, 10) was applied (Scheme 18).^{23,73} Interestingly,

Scheme 18. RCAA to Linear Enoates



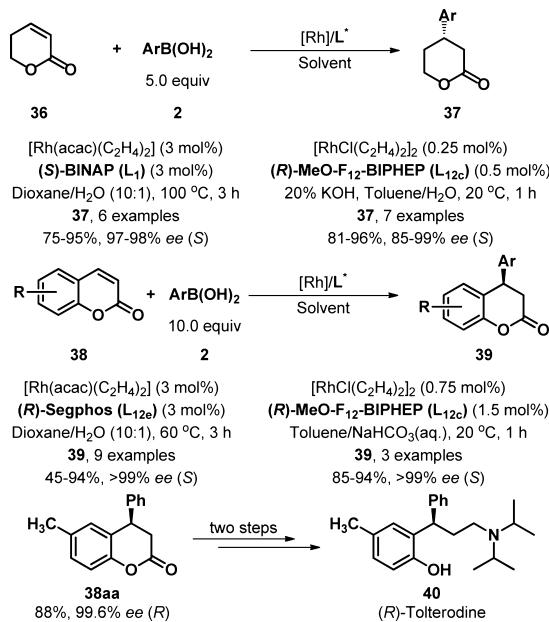
replacing water with 1 equiv of isopropanol could significantly reduce the protodeboration of arylboronic acids, and scale-up of $29\mathbf{ag}$ (25 kg) was successfully obtained by using this improved condition.¹⁷³ Highly efficient RCAA to β,β -disubstituted linear enoates 30 , providing quaternary stereocenters at the β -position of esters, was recently achieved by employing chiral diene \mathbf{L}_{33b} as the ligand.¹⁷⁴

RCAA to β -aryl substituted linear enoates 32 have been investigated with Rh(I)/chiral diene (\mathbf{L}_{31f}) complex¹⁷⁵ or a cationic Rh(I)/chiraphos (\mathbf{L}_{77}) system⁷² for the enantioselective preparation of β -diaryl esters 33 (Scheme 19). Both catalytic systems proved to be quite versatile and functional group-tolerant. This method was successfully applied as the key

Scheme 19. RCAA to Linear Enoates Bearing β -Aryl Group

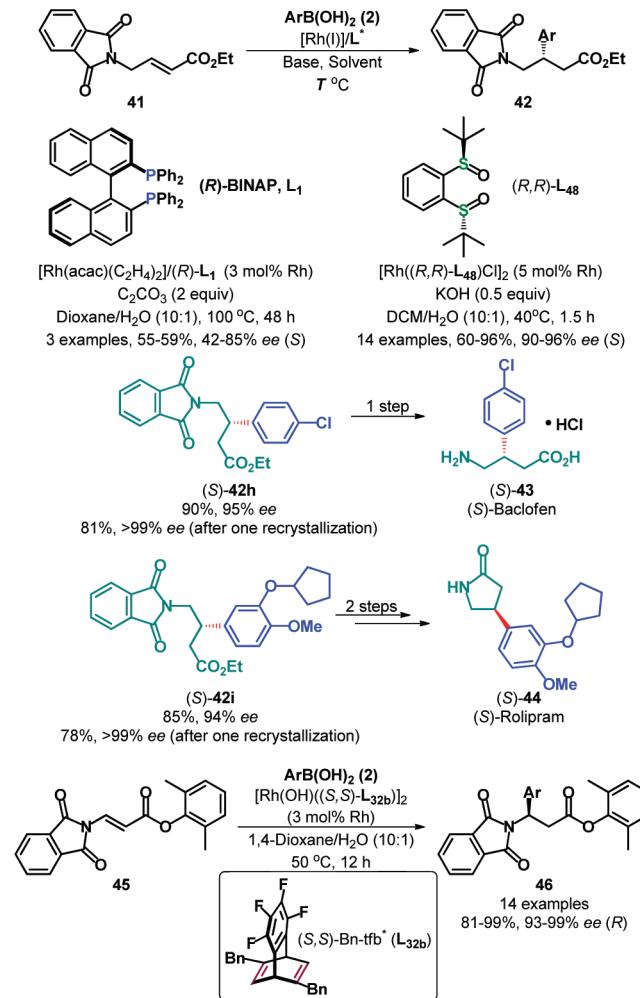
enantioselective step in the asymmetric synthesis of two endothelin receptor antagonists 34 and 35.

Rh(I)/(S)-BINAP system was highly efficient in the RCAA to cyclic enoates 36^{23,73} and Rh(I)/(R)-Segphos system presented excellent catalytic activity in the RCAA to coumarins 38.¹⁷⁶ This conversion was subsequently extended to the asymmetric synthesis of (*R*)-tolterodine (40). Because of its strong π -accepting ability, the electron-deficient ligand L_{12c}⁸⁶ exhibited a higher catalytic activity in the RCAA to the cyclic enoates although excessive arylboronic acids (10 equiv) were required (Scheme 20).

Scheme 20. RCAA to Cyclic Enoates

The RCAA to enoates bearing γ - or β -N-phthaloylamino acrylates provided a useful approach to synthesize chiral γ - or β -amino acids. Both bisphosphorus ligand (*R*)-BINAP (L₁)^{177,178} and bis-sulfoxide ligand L₄₈^{156,157} were effective for the γ -N-phthaloylamino acrylate 41, with the latter showing higher

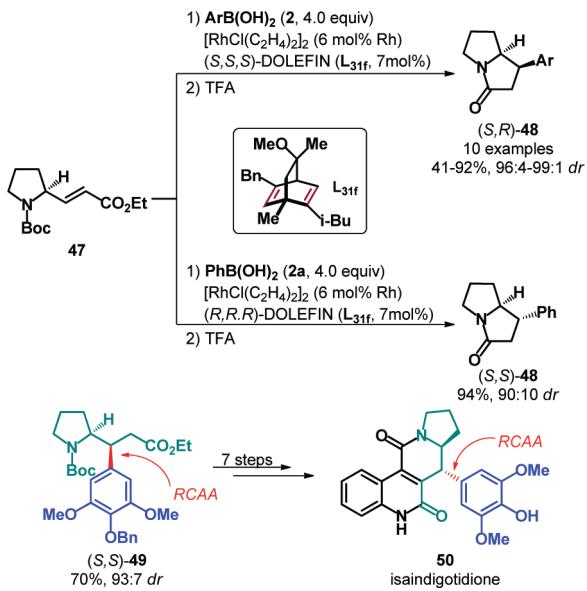
catalytic activity. These catalytic systems were applied to the asymmetric synthesis of (*S*)-Baclofen (43) and (*S*)-Rolipram (44). RCAA of arylboronic acids to β -N-phthaliminoacrylate ester 45 by using Rh(I)/chiral diene (L_{32b}) complex toward the synthesis of β -amino acids was realized, giving β -aryl- β -N-phthaloylamino acid esters in high yields and enantioselectivities (Scheme 21).¹⁷⁹

Scheme 21. RCAA to Enoates Bearing Phthalimidyl Amino Group

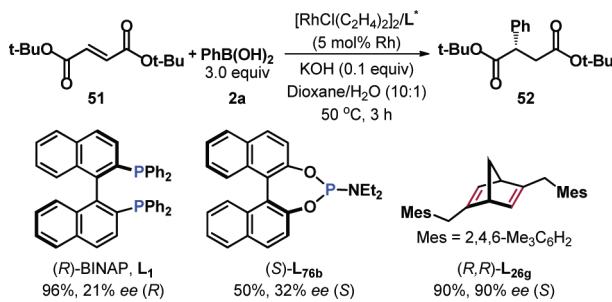
Diastereoselective RCAA was also explored with chiral enoate 47 as the substrate, providing a useful asymmetric synthesis of bicyclic pyrrolizidinones 48.¹⁸⁰ Chiral diene ligand (S,S,S)-L_{31f} enhanced the diastereoselectivity in the formation of (*S,R*)-48, while its enantiomeric ligand (*R,R,R*)-L_{31f} reversed the diastereoselectivity of the RCAA reaction to give (*S,S*)-48. This result suggests the RCAA process should be under ligand control. This diastereoselective RCAA methodology was applied in a concise asymmetric synthesis of isaindigotidine 50 (Scheme 22).¹⁸¹

Di-*tert*-butyl fumarate (51) is less reactive compared with general α,β -unsaturated esters in the RCAA with phenylboronic acid. Traditional bisphosphine ligand L₁ and phosphoramidite ligand L_{76b} gave poor yield and enantioselectivity for this transformation, while the bulky chiral diene ligand L_{26g} could improve the process, affording the desired product 52 in 90% yield and 90% ee (Scheme 23).¹⁸²

Scheme 22. Diastereoselective RCAA

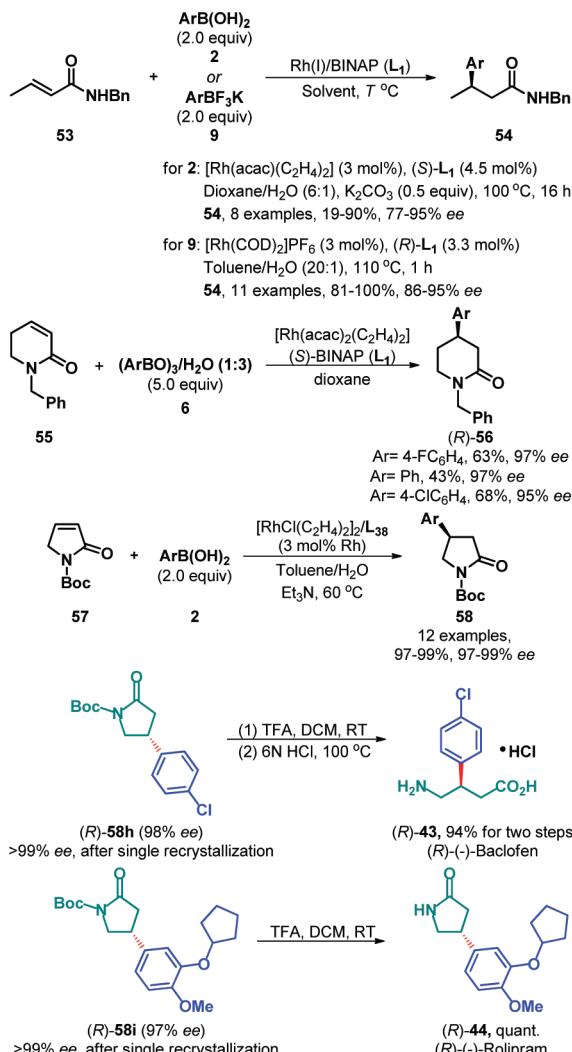
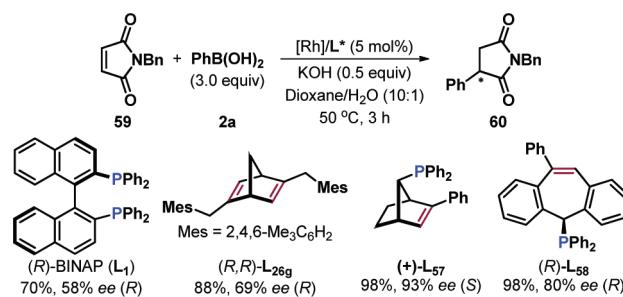


Scheme 23. RCAA of Phenylboronic Acid to Fumarate



3.3. RCAA to α,β -Unsaturated Amides. RCAA of linear α,β -unsaturated amide **53** with arylboronic acids performed similarly well despite its weaker reactivity than enones or enoates.⁶⁴ Replacing ArB(OH)_2 with ArBF_3K (**9**) as the arylboronic source could significantly increase the overall reaction yield (Scheme 24).¹⁸³ Moderate yields and high enantioselectivities were obtained in RCAA to cyclic α,β -unsaturated- δ -lactam **55**.²² Introducing N-Boc protecting group into the cyclic α,β -unsaturated amide **57** remarkably improved its reactivity,¹⁸⁴ affording β -substituted- γ -lactams with excellent yields and enantioselectivities. This highly efficient method was elegantly exemplified by the synthesis of two chiral drug molecules (*R*)-Baclofen (**43**) and (*R*)-Rolipram (**44**).

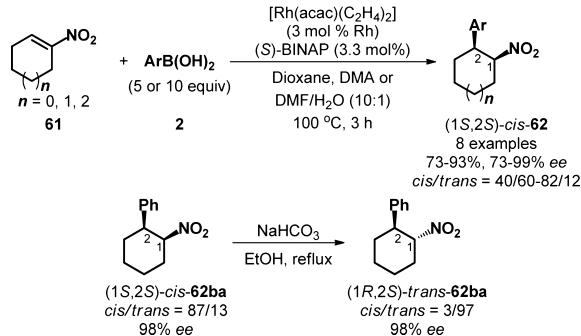
Because of its low reactivity, the RCAA of *N*-benzyl maleimide (**59**) with phenylboronic acid gave only moderate enantioselectivity using bisphosphine ligand (*R*)-BINAP (L_1).¹⁴⁵ Bulky chiral diene ligand L_{26g} ^{145,182} afforded α -phenylsuccinimide **60** in a higher yield, but still with low enantioselectivity. Further exploration revealed that phosphorus-olefin hybrid ligands L_{57} ,^{145,146} and L_{58} ,¹⁴⁷ produced the desired adduct in excellent yields and enantioselectivities (Scheme 25). RCAA to substituted maleimides was also examined, leading to high regioselectivity and enantioselectivity. Hayashi and co-workers also reported a highly diastereoselective synthesis of axially chiral *N*-arylsuccinimides by using RCAA.^{182,185,186}

Scheme 24. RCAA to Linear and Cyclic α,β -Unsaturated AmidesScheme 25. RCAA of PhB(OH)_2 to *N*-Benzyl Maleimide

In summary, the rate of 1,4-addition of arylboron reagents to α,β -unsaturated carbonyl compounds in the RCAA process relies on the reactivity of the acceptor and its steric bulk, with the trend in the following order: enals > enones > enoates > enamides > fumarates > maleimides.⁸ The steric bulk in proximity to the reactive unsaturated moiety will weaken the coordination of acceptor to rhodium and accordingly decrease the reactivity in RCAA. In addition, the catalytic activity of Rh(I)/ligand systems will increase for the ligands with stronger π -accepting abilities.

3.4. RCAA to Nitroalkenes. Hayashi and co-workers initially demonstrated that cyclic nitroalkenes **61** were good substrates for the RCAA reaction, affording thermodynamically less stable *cis*- β -aryl substituted cyclic nitroalkanes **62** with excellent enantioselectivities (Scheme 26).¹⁸⁷ It is noteworthy

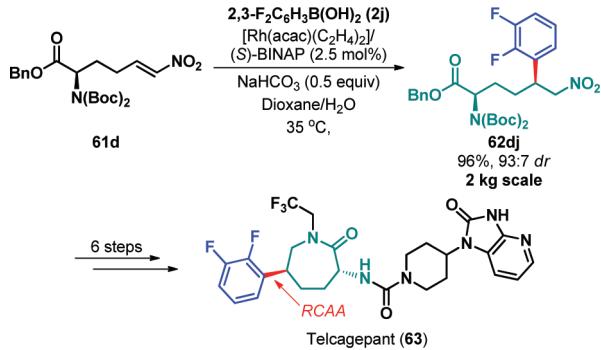
Scheme 26. RCAA to Cyclic Nitroalkenes



that, as an example of **62ba**, the stable *trans*-isomer could be easily obtained by treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol.

This efficient methodology was then elegantly applied by a research group at Merck in the synthesis of CGRP receptor antagonist telcagepant **63** (Scheme 27).¹⁸⁸ The RCAA of

Scheme 27. RCAA of a Nitroalkene on a Kilogram Scale

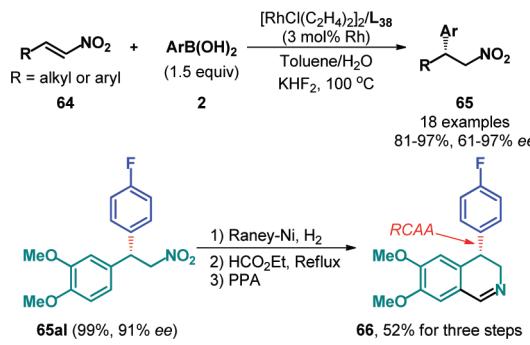


difluorophenylboronic acid (**2j**) to nitroalkene **61d** provided the key chiral intermediate nitroalkane **62dj**, which was further converted to telcagepant on a 2 kg scale. Bicarbonate was shown to be an effective activator in the RCAA reaction.

In 2010, Lin and co-workers reported the RCAA of aryl boronic acids to linear β -substituted 1-nitroalkenes and found the KHF_2 additive was crucial to promote this catalytic reaction.¹⁸⁹ With L_{38} as the ligand, excellent enantioselectivities (95–97% ee) were obtained when sterically more hindered arylboronic acids, such as 1-naphthylboronic acid and 2-tolylboronic acid, were used. To demonstrate the synthetic utility of this methodology, pharmaceutically interesting isoquinoline derivative **66** was easily prepared from the chiral β -arylnitroalkane product **65al** (Scheme 28).

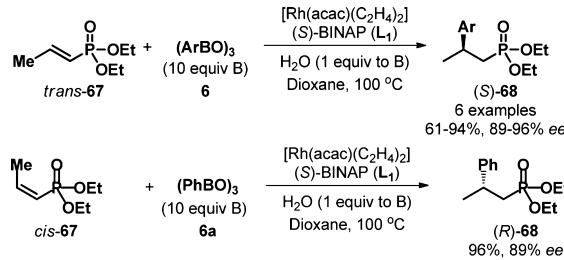
3.5. RCAA to α,β -Unsaturated Phosphonates. The RCAA to alkenylphosphonates was first reported by Hayashi and co-workers.¹⁹⁰ Although alkenylphosphonates are usually less reactive than α,β -unsaturated carbonyl compounds, the RCAA reaction proceeded smoothly by using Rh(I)/(S)-BINAP catalytic system with arylboroxines **6** as the boron source. Remarkably, the addition of 1 equiv of water (relative to boron

Scheme 28. RCAA to Linear Nitroalkenes



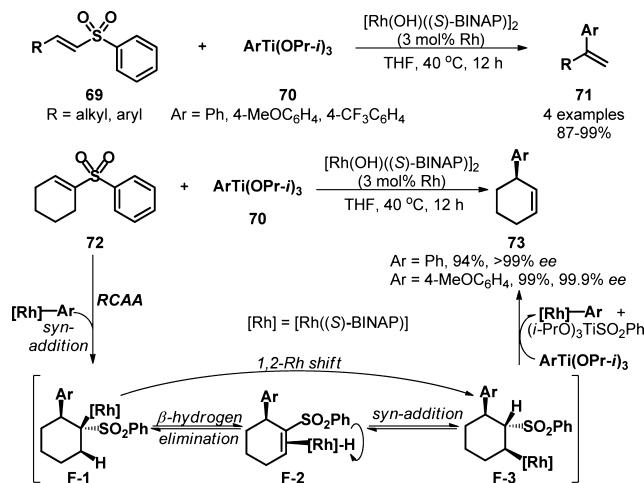
species) was required to achieve high yields. Consistent with the previous stereochemical model (cf. Scheme 7), the *trans* and *cis* geometries of alkenylphosphonate **67** afforded opposite enantiomers (*S*)-**68** and (*R*)-**68**, respectively (Scheme 29).

Scheme 29. RCAA to α,β -Unsaturated Linear Phosphonates



3.6. RCAA to α,β -Unsaturated Sulfones. The initial RCAA to α,β -unsaturated phenylsulfones **69** was investigated by Hayashi and co-workers, who discovered that the sulfonyl group was eliminated through 1,2-Rh shift after the conjugate addition of aryltitaniums **70** as nucleophilic reagents, affording the desulfonylated alkenes **71** or **73** (Scheme 30).⁴³ However,

Scheme 30. RCAA to Alkenyl Phenylsulfones

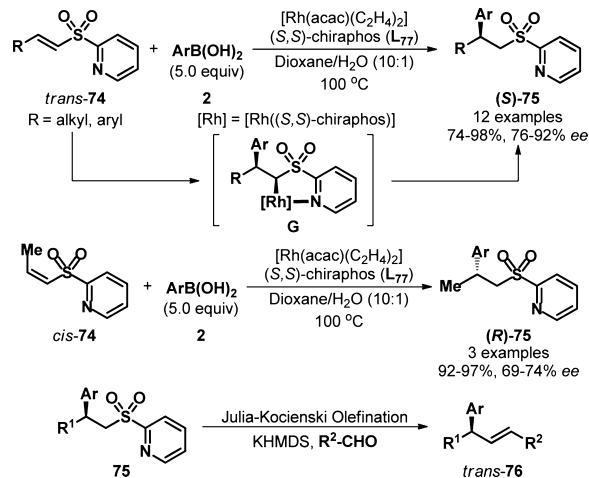


replacing the aryltitanium reagents with arylboron reagents such as phenyl-9-BBN (**12a**) or triphenylcyclotriphosphazane [$(\text{PhBO})_3$, **6a**] failed to promote RCAA. Neither this type of *cine* substitution nor the 1,4-addition products were generated.

With the pyridyl-N to stabilize the Rh-complex **G**, the RCAA of arylboronic acids to α,β -unsaturated 2-pyridyl sulfones **74**

was successfully achieved by using (*S,S*)-chiraphos (**L₇₇**) as the chiral ligand, providing β -substituted sulfones in high yields and enantioselectivities (Scheme 31).^{191–193} The *trans*- and

Scheme 31. RCAA to Alkenyl (2-Pyridyl)Sulfones



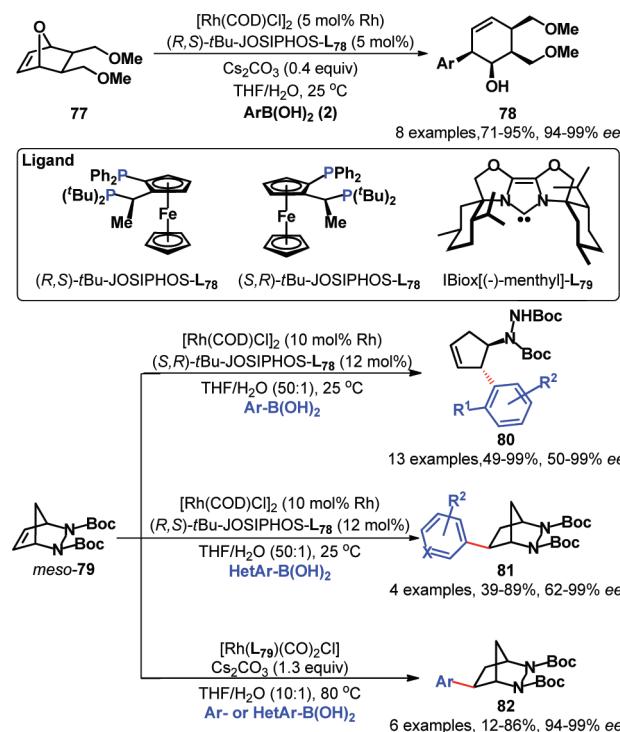
cis-alkenylsulfones produced the opposite enantiomers (*S*)-75 and (*R*)-75 in RCAA reaction. The elimination of the sulfonyl group via Julia-Kociensky olefination¹⁹⁴ provides a novel approach to the enantioselective synthesis of allylic substituted *trans*-alkenes 76.

3.7. RCAA to Strained or Weakly-Activated Alkenes.

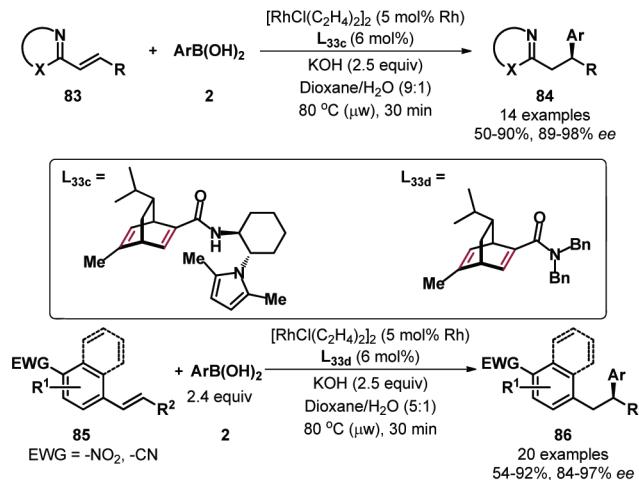
Rhodium-catalyzed arylation of aryl boronic acids to a variety of strained oxabenzonorbornadienes has been demonstrated by Murakami and co-workers,¹⁹⁵ with the insertion of a strained alkene into a rhodium-aryl bond as a key step.¹⁹⁶ The best results were obtained with a catalyst prepared by mixing $[\text{Rh}(\text{COD})\text{Cl}]_2$ with 2 equiv of $\text{P}(\text{OEt})_3$. Lautens and co-workers subsequently presented an asymmetric version of this RCAA reaction, which gave excellent enantio- and diastereoselectivities by using the $[\text{Rh}(\text{COD})\text{Cl}]_2/(R,S)$ -*t*Bu-JOSIPHOS-L₇₈ catalyst system (Scheme 32).¹⁹⁷ When *meso*-azabicycle 79 was used as the strained alkene, a chemodivergent desymmetrization occurred after the initial enantioselective carbometalation step. The reaction brings an interesting approach to open diazabicyclo[2.2.1]heptanes enantioselectively to obtain arylated cyclopentenamines 80. An alternative reaction pathway was discovered for heteroaryl boronic acids, in which C–H insertion/1,4-Rh migration occurred to give hydroarylation products 81. Recently, Lautens and co-workers demonstrated that Rh complex incorporating IBiox[(-)-menthyl] (**L₇₉**) as the ligand showed impressive selectivity, only allowing the hydroarylation of azabicyclic regardless of aryl or heteroaryl boronic acids.²⁰⁰

A highly enantioselective RCAA of arylboronic acids to β -monosubstituted alkenylheteroarenes 83 has been developed,²⁰¹ demonstrating the electron-deficient C=N-containing heteroarenes can activate the adjacent alkenes toward RCAA reactions (Scheme 33). Very recently, Lam and co-workers also described another highly enantioselective RCAA of arylboronic acids to alkenyl-*p*-nitroarenes and alkenyl-*p*-cyano-*m*-(trifluoromethyl)arenes 85.²⁰² These reactions represented the first examples of catalytic asymmetric additions of air- and moisture-stable organo-metallic reagents to alkenes activated by electron-deficient arenes.

Scheme 32. RCAA to Strained Alkenes

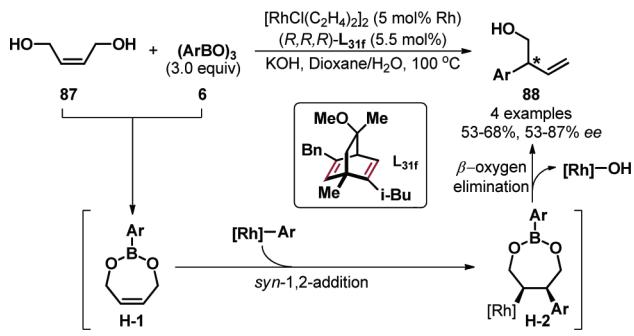


Scheme 33. RCAA to Alkenylheteroarenes and Alkenylarenes

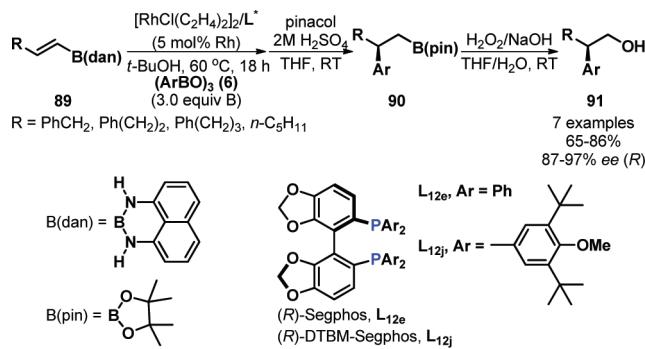


RCAA of arylboroxines 6 to *cis*-allylic diols 87 occurred using Rh(I)/chiral diene (**L_{31f}**) catalyst system. This reaction proceeded through the syn-1,2-addition of arylrhodium species across the double bond and subsequent β -oxygen elimination to form 2-aryl-3-en-1-ols 88 with good enantioselectivities (Scheme 34).²⁰³

Recently Hayashi and co-workers described the development of the RCAA of arylboroxines 6 to borylalkenes 89.²⁰⁴ The reaction afforded β -arylated alkylboron compounds 90 with high enantioselectivities by using Rh(I)/bisphosphine ligands such as (*R*)-Segphos(**L_{12e}**) and (*R*)-DTBM-Segphos(**L_{12j}**). In this case, the 1,8-naphthalenediaminatoboryl group, B(dan), served as a key masking group for alkenylboronic acids during the RCAA, and could be further converted to hydroxyl group (Scheme 35).

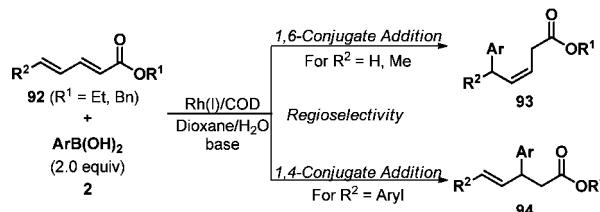
Scheme 34. RCAA to *cis*-2-Butene-1,4-diol (87)

Scheme 35. RCAA to Borylalkenes



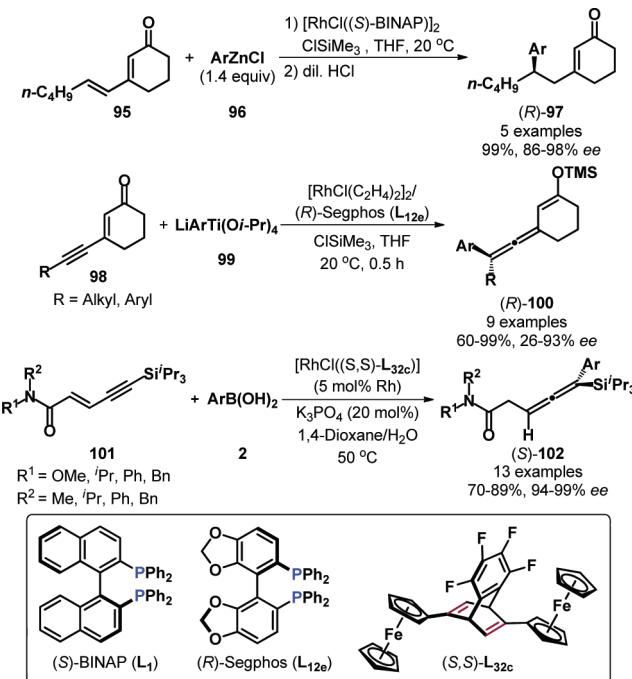
3.8. 1,6-Conjugate Addition. Because of the multiple possible reaction pathways controlled by the substitution pattern of the $\alpha,\beta,\gamma,\delta$ -diunsaturated carbonyl compounds, the selective 1,6-additions are especially challenging, as illustrated in Scheme 36.²⁰⁵ For unhindered dioenoates **92** ($\text{R}^2 = \text{H}$ or Me),

Scheme 36. Rh-Catalyzed 1,6-Addition or 1,4-Addition of Arylboronic Acids to 2,4-Dienoate Esters



the 1,6-addition product **93** was favored. However, when R^2 was an aryl group, the 1,4-addition product **94** became predominant.

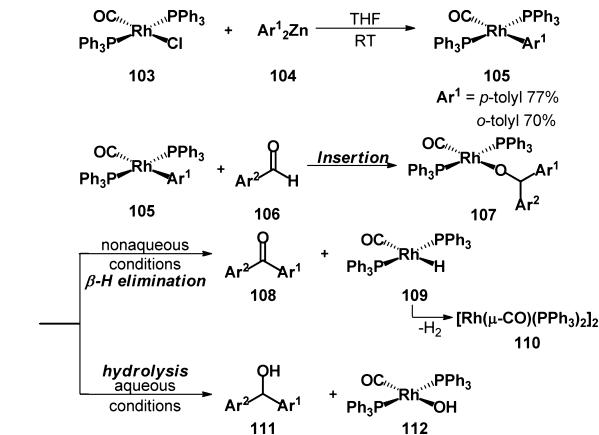
The regioselective 1,6-addition of β -substituted dioenoates were first realized by using reactive arylzinc reagents **96** in combination with ClSiMe_3 , providing (*R*)-**97** in almost quantitative yields and good to excellent enantioselectivities (Scheme 37).⁵⁰ The enantioselective 1,6-addition of aryltitanate to alkynenones **98** also proceeded by using $\text{Rh(I)/(R)-Segphos (L}_{12e}\text{)}$ catalytic system in the presence of ClSiMe_3 , affording enantiomerically enriched chiral allenes **100**.⁴⁶ In 2010, Hayashi and co-workers developed a Rh-catalyzed asymmetric 1,6-addition of arylboronic acids to linear enynamides **101** using a Rh(I) /chiral diene ((*S,S*)-**L**_{32c}) complex, producing axially chiral allenylsilanes **102** with high enantioselectivities.²⁰⁶

Scheme 37. Rh-Catalyzed Asymmetric 1,6-Addition onto $\alpha,\beta,\gamma,\delta$ -Diunsaturated Carbonyl Compounds

4. RCAA TO ALDEHYDES AND KETONES

4.1. RCAA to Aldehydes. As shown in Scheme 38, the rhodium-catalyzed arylation of aldehyde and diarylzinc could

Scheme 38. Reactions of Aldehydes with Aryl-Rhodium Complexes to Form Diarylketonates and Diarylmethanols

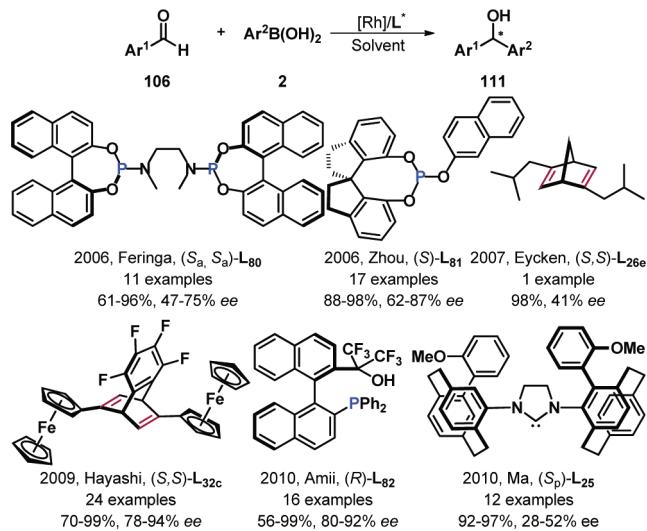


provide the desired product **111** under aqueous conditions. However, the ketone **108** was obtained under nonaqueous solvent system. Hartwig and co-workers looked into the mechanism of such a highly solvent-dependent process.²⁰⁷ Despite the difficulty in isolating the triphenylphosphine-ligated arylrhodium(I) complexes in a pure form,²⁰⁸ aryl-rhodium compounds with a mixed phosphine and CO ligation sphere are usually stable. They did indeed obtain the pure aryl-rhodium complex **105** by treatment of $(\text{PPh}_3)_3\text{Rh}(\text{CO})\text{Cl}$ with 1 equiv of diarylzinc in tetrahydrofuran (THF) at room temperature. The reaction of this stable complex **105** with aldehyde **106** led to the insertion of a carbonyl group into the aryl-rhodium

bond, generating rhodium-alkoxide **107**. Under nonaqueous (C_6D_6) condition, the reaction went through β -elimination to produce the diarylketone **108** and release a new rhodium-hydride complex **109**. This [Rh-H] complex was not very stable and subsequently decomposed under the reaction conditions to liberate hydrogen and form $[\text{Rh}(\mu\text{-CO})(\text{PPh}_3)_2]_2$ (**110**). Because of the high stability of aryl-rhodium complex **105**, the reaction could be conducted in aqueous media. By using a mixture of THF and water as solvent, the reaction exclusively generated the desired product, diarylmethanol **111** through hydrolysis (Scheme 38).

Phosphoramidite **L₈₀** is an effective chiral ligand in the RCAA of arylboronic acids to aldehydes, providing chiral diarylmethanols in high yields and up to 75% ee (Scheme 39).²⁰⁹

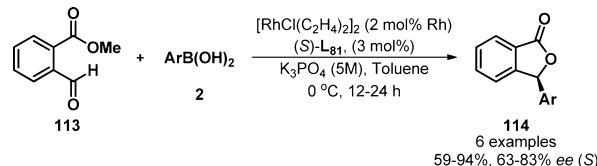
Scheme 39. RCAA to Aromatic Aldehydes



Chiral spiro-phosphite ligand **L₈₁** also proved to provide excellent yields and good enantiomeric excesses in RCAA of arylboronic acids to aldehydes.²¹⁰ Diene ligands were also applied in the RCAA reaction. Although the $[\text{RhCl}((S,S)\text{-L}_{26e})]_2$ -catalyzed 1,2-addition of phenylboronic acid to aryl aldehydes provided the desired alcohols in 98% yield, the enantioselectivity was quite poor (only 41% ee).¹²⁰ In 2009, Hayashi and co-workers developed a novel C_2 -symmetric tetrafluorobenzobarrelene ligand and applied it in the RCAA of arylboronic acids to aryl aldehydes, affording chiral diarylmethanols in high yields and high enantioselectivities.²¹¹ More recently, both chiral monophosphorus ligand (R) -**L₈₂** bearing a di(trifluoromethyl)alcohol moiety and chiral NHC-ligand (S_p) -**L₂₅**²¹³ demonstrated excellent catalytic activity for asymmetric 1,2-addition of arylboronic acids to aldehydes. Remarkably, the fluoroalcohol moiety in (R) -**L₈₂** played a pivotal role for the high enantioselectivity in Rh(I)-catalyzed transformation. However, only moderate enantioselectivity was observed in RCAA when using (S_p) -**L₂₅** (with 0.03–0.3 mol % loading) as the ligand.

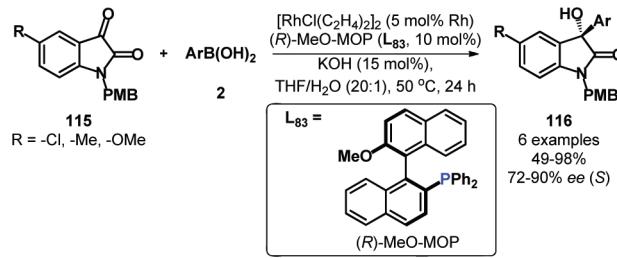
The chiral alcohol generated in RCAA can further react in situ with other functional groups in the molecule. As shown in Scheme 40, Hu and co-workers applied methyl 2-formylbenzoate (**113**) in the RCAA with various arylboronic acids; a series of chiral 3-substituted phthalides **114** (with up to 83% ee) were conveniently synthesized by using Rh(I)/SPINOL-based phosphite (**L₈₁**) catalytic system.²¹⁴

Scheme 40. RCAA to Methyl 2-Formylbenzoate (113)



4.2. RCAA to Ketones. Similar to aryl aldehydes, the carbonyl functionality activated by adjacent electron-withdrawing groups, like ester, amide, and trifluoromethyl, is also an excellent acceptor in RCAA. As shown in Scheme 41, the

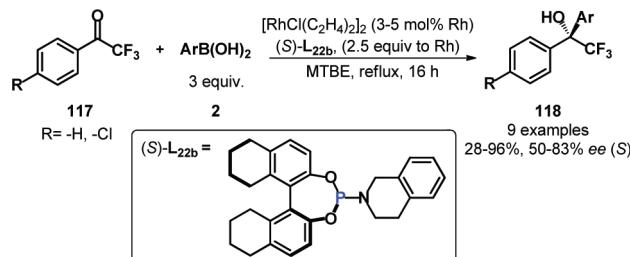
Scheme 41. RCAA to Isatins



carbonyl group in isatins **115** could react with arylboronic acids through RCAA to produce biologically relevant 3-aryl-3-hydroxy-2-oxindoles **116** in high yields and enantioselectivities by using (R) -MeO-MOP (**L₈₃**) as the ligand.²¹⁵

Feringa and co-workers reported the catalytic asymmetric 1,2-addition of a series of arylboronic acids to 2,2,2-trifluoroacetophenones **117**. The reaction afforded the tertiary alcohols **118** in high yields (up to 96%) and good enantioselectivities (up to 83% ee) by using a Rh(I)/phosphoramidite catalyst (Scheme 42).²¹⁶

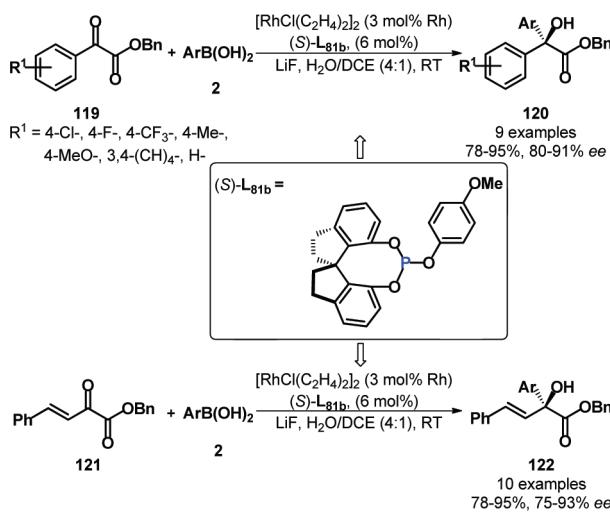
Scheme 42. RCAA to 2,2,2-Trifluoroacetophenones



Zhou and co-workers applied the chiral spirophosphite ligand (S) -**L_{81b}** in asymmetric addition of arylboronic acids to α -ketoesters **119**. Interestingly, the RCAA of **121** selectively took place on the activated carbonyl group rather than the alketyl via a 1,4-addition process. This protocol provided a new enantioselective approach to the synthesis of 2-hydroxydiarylacetates **120** and alkenylarylacetates **122**, which could be further derived to related α -hydroxy carboxylic acids and vicinal diols bearing a tertiary chiral center (Scheme 43).²¹⁷

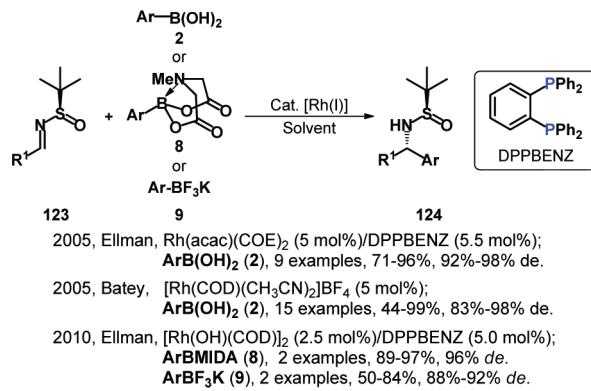
5. RCAA TO IMINES

Chiral diarylmethylamines and diarylmethanols are important structural motifs that are encountered in many pharmaceuticals and natural products.²¹⁸ Similar to the above RCAA of aldehydes/ketones to afford the diarylmethanols, imines are

Scheme 43. RCAA to α -Ketoesters

also suitable substrates for RCAA, representing one of the most straightforward ways to access chiral diarylmethylamines in high yields and stereoselectivities.

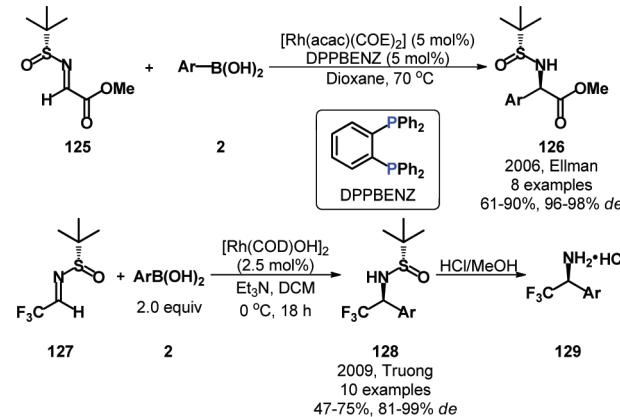
5.1. RCAA to Chiral Sulfinyl Imines. In 2005, Ellman and co-workers first reported the addition of arylboronic acids to both aromatic and aliphatic *N*-*tert*-butanesulfinyl imines **123**, providing the chiral sulfinamides **124** with high diastereoselectivities. More importantly, the *N*-*tert*-butanesulfinyl group can be conveniently cleaved under mild acidic conditions that tolerate much sensitive functionality.²¹⁹ As shown in Scheme 44, the RCAA of aryl trifluoroborates **9** or aryl MIDA

Scheme 44. Diastereoselective RCAA to *N*-*tert*-Butanesulfinyl Imines

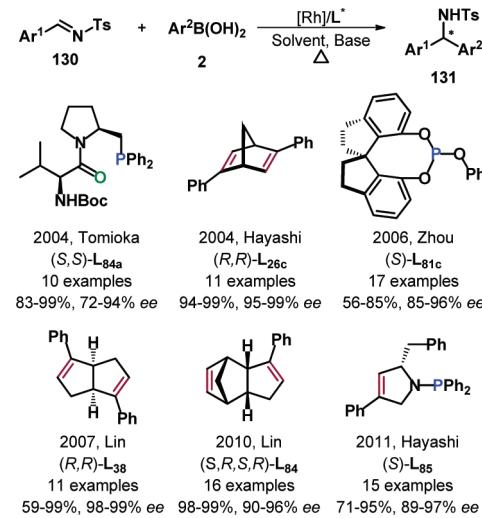
boronates **8** to *N*-*tert*-butanesulfinyl imines **123** also proceeded in excellent yields (up to 99%) and with very high diastereoselectivities (98:2 to >99:1).²²⁰ Almost at the same time, Batey and co-workers independently reported the RCAA of arylboronic acids to chiral sulfinylimines in the absence of external chiral phosphine ligands. This substrate-controlled asymmetric process also afforded the desired products with excellent diastereoselectivities.²²¹

N-Sulfinyl imino esters **125** stand out as stable, isolable compounds that can even be chromatographed on SiO_2 , and thus can serve as excellent starting materials for arylglycine synthesis.^{222–224} In 2006, Ellman and co-workers applied them in RCAA of arylboronic acids to give a variety of *N*-*tert*-butanesulfinamido arylglycine esters **126** with excellent

diastereoselectivities.²²⁵ In 2009, Truong and co-workers developed an efficient diastereoselective RCAA of arylboronic acids to *N*-*tert*-butanesulfinyl trifluoromethyl imine **127**, generating the corresponding sulfinamides **128** in good yields and excellent diastereoselectivities (up to 98% de).²²⁶ This protocol provides a convenient method to prepare a variety of chiral trifluoroethylamine analogues **129** (Scheme 45).

Scheme 45. Diastereoselective RCAA to *N*-*tert*-Butanesulfinyl Imino Esters

5.2. RCAA to Sulfonyl Imines. In 2004, Tomioka and co-workers reported the first RCAA of arylboronic acids and arylboroxines to *N*-tosylarylimines **130** using a chiral amidomonophosphane ligand (Scheme 46).²²⁷ Almost at the same time,

Scheme 46. RCAA to *N*-Tosyl Aldimines

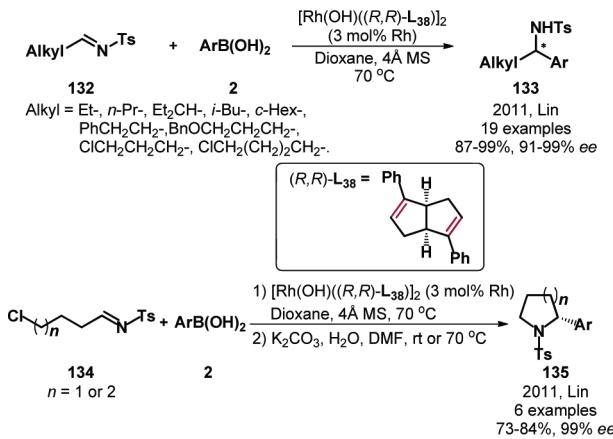
Hayashi and co-workers utilized bicyclo[2.2.2]octadiene ligands in the same transformation.^{119,131,139} In 2006, Zhou and co-workers applied the rhodium complex of monodentate spiro-phosphite (*S*-ShiP (**L**_{81c}) in RCAA. The reaction proceeded in aqueous toluene to give diarylmethylamines **131** in good yields and enantioselectivities (up to 96% ee).²²⁸

Bicyclo[3.3.0]diene (**L**₃₈) was found to be an excellent ligand for the arylation of sulfonyl imines. A wide variety of *N*-tosylarylimines with diverse steric and electronic properties successfully reacted with several arylboronic acids, providing the corresponding *N*- diarylmethyltosylamides with a very

narrow range of excellent enantioselectivities (98–99% ee). The electronic and steric nature of phenyl ring at either imines or arylboronic acids apparently had no influence on the enantioselectivity. Furthermore, tosylimines derived from heteroaryl aldehydes such as furanyl, thiophenyl, and indolyl aldehydes were also suitable substrates for this RCAA reaction.^{229,230} In 2010, a new class of monosubstituted C_1 -symmetric diene ligands with a DCP (dicyclopentadiene) backbone was developed by Lin and co-workers. The reaction proceeded smoothly to give the corresponding *N*-diarylalkyl tosylamides with excellent yields (98–99%) and high enantioselectivities (90–96% ee).²³¹ More recently, Hayashi designed and synthesized a novel chiral phosphine-olefin hybrid ligand L_{85} , an interesting bidentate binding to rhodium, which also resulted in high enantioselectivities in RCAA to imines **130** (Scheme 46).²³²

In spite of the considerable advancements, the imine substrates in RCAA reaction are usually limited to aromatic imines. The major challenge in this case is that aliphatic imines tend to undergo imine-enamine tautomerization, decomposition, and self-condensation under common RCAA reaction conditions. In 2011, Lin and co-workers successfully extended the RCAA reaction to aliphatic *N*-tosylimines **132** using chiral Rh(I)/diene complexes as catalyst under neutral reaction conditions.²³³ The bicyclo[3.3.0]octadiene L_{38} proved to be the superior ligand for this transformation, providing the desired products **133** in exceptionally high enantioselectivity (typically $\geq 99\%$ ee). With chloro-substituted imines **134** as substrates in RCAA, chiral 2-aryl pyrrolidines and piperidines were achieved in a one-pot procedure (Scheme 47). One drawback in this

Scheme 47. RCAA to *N*-Tosylalkylaldimines

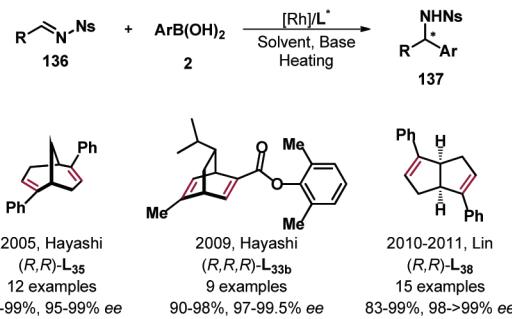


reaction is the difficulty in removing the tosyl group from nitrogen of the products **133** and **135**. It has been reported that the use of 4-nitrobenzenesulfonyl (Ns) group^{234–236} in place of tosyl group will facilitate the deprotection reaction.

Several groups explored the RCAA of *N*-4-nitrobenzenesulfonylimines. Unsurprisingly, high enantioselectivities and high catalytic activities were observed by using chiral diene ligands (L_{35} ,¹³⁰ L_{33b} ,¹²⁹ and L_{38}).²³³) The 4-nitrobenzene-sulfonyl (Ns) group could be readily removed from the products **137** without racemization or any side reactions (Scheme 48).

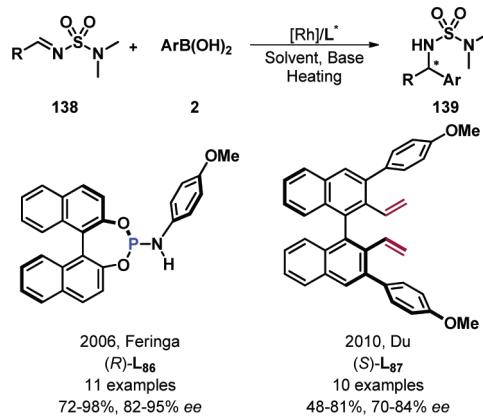
Feringa and co-workers introduced a small and cheap *N,N*-dimethylsulfamoyl protecting group into the catalytic asymmetric synthesis of diarylmethylamines by RCAA reaction. The addition of **138** with aryl boronic acids afforded high

Scheme 48. RCAA to *N*-(4-Nitrobenzene)sulfonyl Aldimines



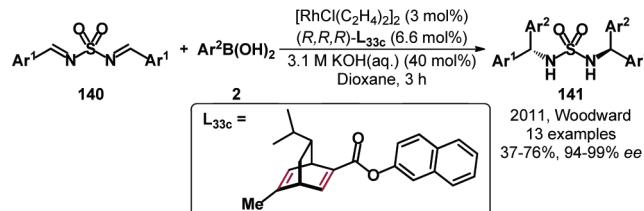
enantioselectivities (up to 95% ee) and high yields (up to 98%) by using a Rh(I)/phosphoramidite system.²³⁷ The protecting group could be easily removed by microwave-assisted transamination, representing a versatile and selective transformation to prepare chiral diarylmethylamines. Later on, Du and co-workers utilized bisnaphthyl-based chiral diene as the steering ligand for the enantioselective arylation of *N,N*-dimethylsulfamoyl-protected aldimines with arylboronic acids, providing the desired products **139** in moderate to good yields and up to 84% ee (Scheme 49).²³⁸

Scheme 49. RCAA to *N,N*-Dimethylsulfamoyl Aldimines



Bis-sulfamyl imines **140** are potentially ideal substrates for rhodium-catalyzed asymmetric additions of arylboron nucleophiles as they provided (i) near perfect enantioselectivities (11 examples, 98–99+% ee), (ii) good to excellent diastereoselectivities (10–32:1 rac/meso), and (iii) high functional group tolerance in the removal of protecting group via mild heating in aqueous pyridine (Scheme 50).²³⁹

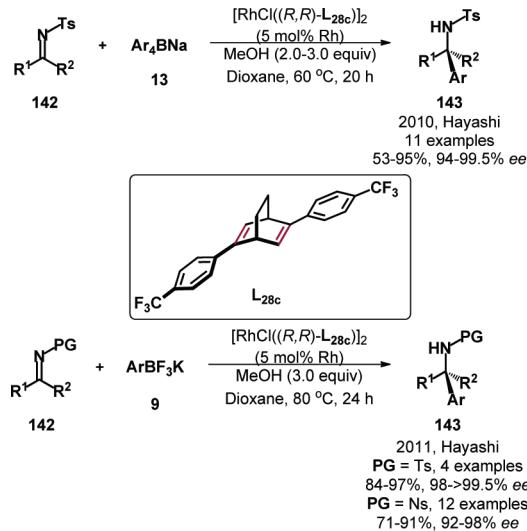
Scheme 50. RCAA to bis-Sulfamyl Aldimines



Recently, Hayashi and co-workers successfully extended the RCAA reaction to less reactive *N*-tosyl ketimines **142** using sodium tetraarylboration or aryl trifluoroborates as boron reagents. By employing chiral diene (*R,R*)- L_{28c} as the ligand,

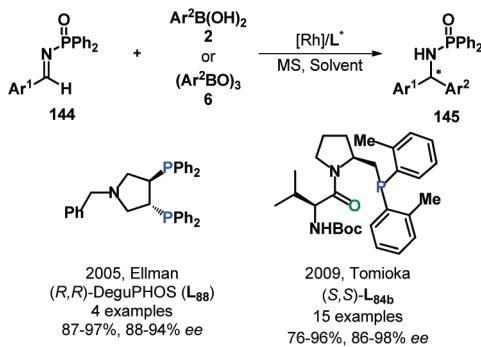
the reaction produced various chiral amine derivatives **143** possessing a tetrasubstituted carbon stereocenter in high yields and enantioselectivities (Scheme 51).^{240,241}

Scheme 51. RCAA to N-Tosyl Ketimines



5.3. RCAA to Phosphonyl Imines. In 2005, Ellman and co-workers reported the highly enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl benzaldimines **144** using chiral ligand **L₈₈**.²¹⁹ Later on, arylboroxines were also successfully applied in this RCAA reaction by sterically tuning the diphenylphosphorus moiety to a di(*o*-tolyl)phosphorus based ligand **L_{84b}**.^{242,243} Both chiral ligands provided high enantioselectivities in the preparation of diaryl derivatives **145**. It is noteworthy that *N*-diphenylphosphinoyl group can be readily cleaved under mild acidic conditions that tolerate much sensitive functionality (Scheme 52).

Scheme 52. RCAA to N-Diphenylphosphinoyl Aldimines

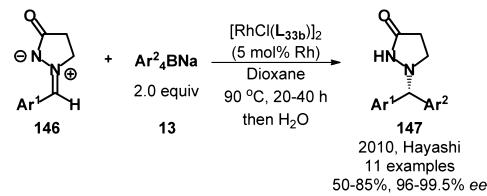


5.4. RCAA to Other Carbon–Nitrogen Double Bond.

Azomethine imines **146** are also suitable substrates for RCAA reaction. Hayashi and co-workers successfully developed a RCAA system by using sodium tetraarylborates as the nucleophile. With chiral diene (*R,R,R*)-**L_{33b}** as the ligand, the reaction generated a series of chiral 1-(diaryl methyl)-pyrazolidin-3-ones **147** in excellent yields and high enantioselectivities (Scheme 53).²⁴⁴

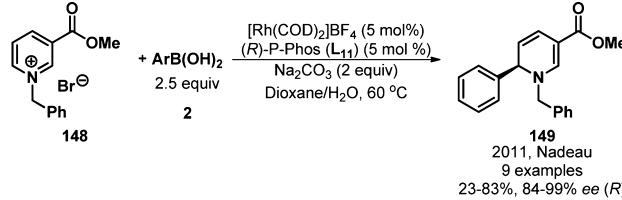
Very recently, Nadeau and co-workers developed the first RCAA of arylboronic acids to *N*-benzylnicotinate salts **148**.

Scheme 53. RCAA to Azomethine Imines



A variety of 6-substituted dihydropyridines **149** were isolated in good yields and excellent enantioselectivities (Scheme 54).²⁴⁵

Scheme 54. RCAA to N-Benzylnicotinate Salts



6. RCAA-TANDEM REACTION

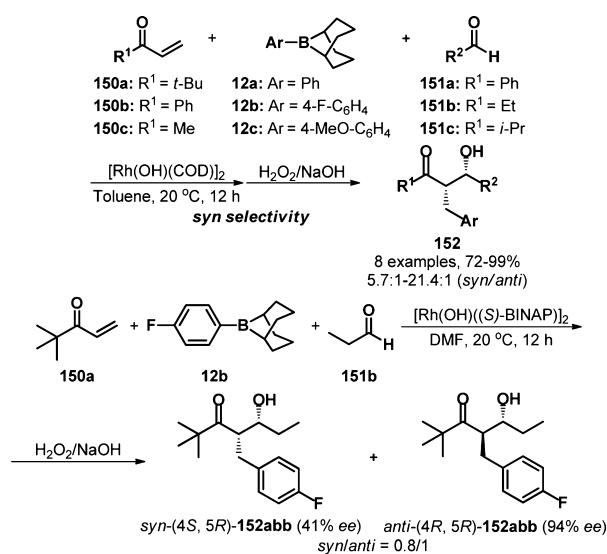
In the RCAA of organoboron reagents to electron-deficient alkenes described above, the insertion of unsaturated bonds to [Rh–Ar] intermediate always led to a chiral rhodium species, which could be further trapped by electrophiles other than a proton. In the case of using α,β -unsaturated ketone as the acceptor for RCAA, a chiral Rh-enolate is formed. This sequential “RCAA/enolate trapping” procedure represents one of the most effective strategies in asymmetric catalytic transformations, allowing for the formation of multiple C–C bonds in an atom-economic manner.²⁴⁶ On the other hand, arylrhodium(I) species can preferentially undergo facile 1,2-syn addition across C–C triple bond in the presence of alkene function within the molecule, the resulting alkenylrhodium(I) intermediate provides another entry for a tandem reaction to the neighboring C–C double bond. These tandem processes have been extensively discussed in the literature.^{247–249}

6.1. Tandem RCAA/Aldol Reaction. In 2002, Hayashi and co-workers developed an elegant three-component tandem RCAA/aldol reaction, which was realized with high syn selectivity (syn/anti up to 21.4:1) by using ArB(9-BBN) as arylboron reagents and [Rh(OMe)(COD)]₂ as a catalyst.²⁵⁰ Applying [Rh(OH)((S)-BINAP)]₂ as the chiral catalyst, the asymmetric version of the above reaction from *tert*-butyl vinyl ketone (**150a**), (4-F-C₆H₄)-B(9-BBN) (**12b**), and propanal (**151b**) gave optically active syn- and anti products. Despite the poor syn/anti selectivity (only 0.8:1), the *syn*-(4*S*,5*R*)-**152abb** and *anti*-(4*R*,5*R*)-**152abb** showed 41% ee and 94% ee, respectively (Scheme 55).

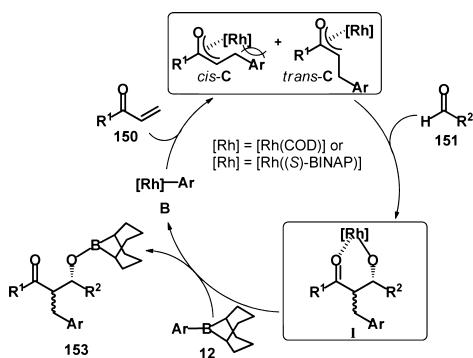
In the above case of using [Rh(OMe)(COD)]₂ as the catalyst, the high syn selectivity suggested the *cis*-Rh enolate (*cis*-C) should have served as the predominant intermediate in the sequential aldol reaction. When [Rh(OH)((S)-BINAP)]₂ was used as the catalyst, both *cis*- and *trans*-Rh enolates were formed because of the highly skewed structure and huge hindrance from (S)-BINAP ligand,¹⁷ generating a mixture of *syn*- and *anti*-aldol products (Scheme 56).

Hayashi and co-workers applied a new combination system of ArB(9-BBN) (**12**) and [Rh(OMe)((S)-BINAP)]₂ in tandem RCAA/aldol reaction. Cyclic α,β -unsaturated ketones could

Scheme 55. Three-Component Tandem RCAA/Aldol Reaction

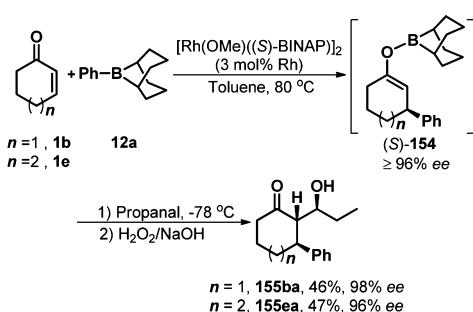


Scheme 56. Tandem RCAA/Aldol Reaction by $[\text{Rh}(\text{OMe})(\text{COD})]_2$ or $[\text{Rh}(\text{OH})((\text{S})\text{-BINAP})]_2$



generate chiral boron enolates (*S*)-154 in $\geq 96\%$ ee, which successfully underwent further aldol reaction to give 155ba and 155ea with perfect regio- and diastereoselectivities (Scheme 57).³⁹

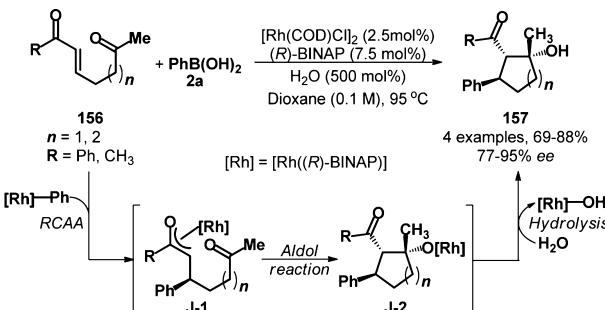
Scheme 57. Tandem RCAA/Aldol Reaction by $[\text{Rh}(\text{OMe})((\text{S})\text{-BINAP})]_2$



In 2003, Krische and co-workers reported an intramolecular tandem RCAA/aldol reaction with high diastereo- and enantioselectivities.²⁵¹ The RCAA of phenylboronic acid 2a to a monoketoenone 156 generated an (oxa- π -allyl)rhodium species J-1, which subsequently attacked the ketone acceptor and further liberated the cyclic aldol products 157 under protic

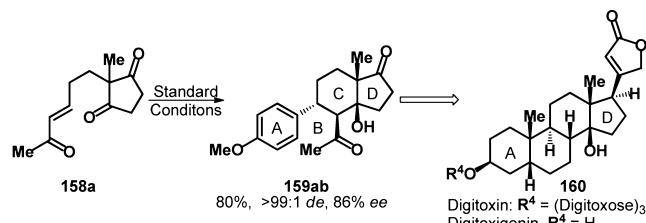
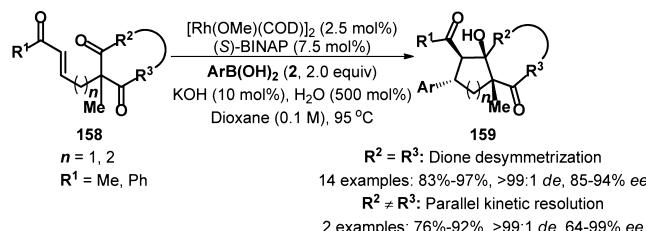
condition. Because of the high electrophilicity of the neighboring ketone, the subsequent aldol reaction was more kinetically favored than the hydrolysis of the (oxa- π -allyl) rhodium species J-1 (Scheme 58).

Scheme 58. Intramolecular Tandem RCAA/Aldol Reaction of Monoketoenones



In 2004, Krische and co-workers extended the above intramolecular tandem RCAA/aldol reaction to the desymmetrization and parallel kinetic resolution of diketoenones 158. This elegant tandem process provided interesting bicyclic products 159, which embody four contiguous stereocenters, including two adjacent quaternary centers, with quantitative diastereoselection and high levels of enantiomeric excess (Scheme 59).²⁵² This methodology enabled the rapid assembly

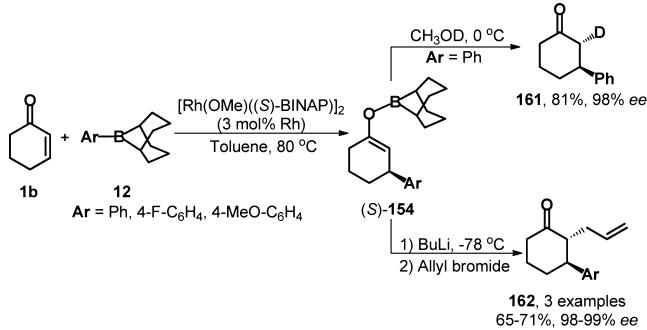
Scheme 59. Intramolecular Tandem RCAA/Aldol Reaction of Diketoenones



of complex polycyclic ring systems from simple precursors. For example, the RCAA/aldol tandem reaction of 158a allowed for a concise entry to optically pure seco-B ring steroid 159ab possessing a 14-hydroxy cis-fused C–D ring junction.

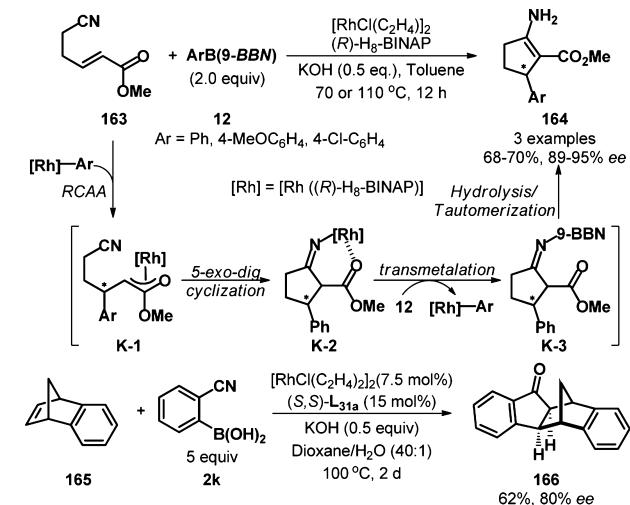
6.2. Tandem RCAA/Alkylation Reaction. The reaction of chiral boron- or rhodium-enolate with alkyl halides could give optically pure alkylated products. As shown in Scheme 60, the treatment of boron-enolate (*S*)-154 with *n*-butyllithium at $-78\text{ }^\circ\text{C}$, followed by reaction with allyl bromide, gave chiral 2-allylcyclohexanone 162 as a single diastereoisomer.³⁹ Similarly, treatment of chiral titanium-enolate or zinc-enolate in the same manner could also lead to the corresponding chiral RCAA/alkylation products.^{44,49}

Scheme 60. Tandem RCAA/Alkylation Reaction



6.3. Tandem RCAA/1, 2-Addition Reaction. Cyano group can also serve as an electrophilic acceptor to trap the rhodium-enolate. In 2007, Murakami and co-workers developed a new tandem reaction triggered by the RCAA of $\text{ArB}(9\text{-BBN})$ (**12**) to cyano-substituted α,β -unsaturated esters **163**, providing chiral five-membered α -enamino esters **164** with up to 95% ee (Scheme 61).²⁵³ Initially, RCAA of arylrhodium(I)

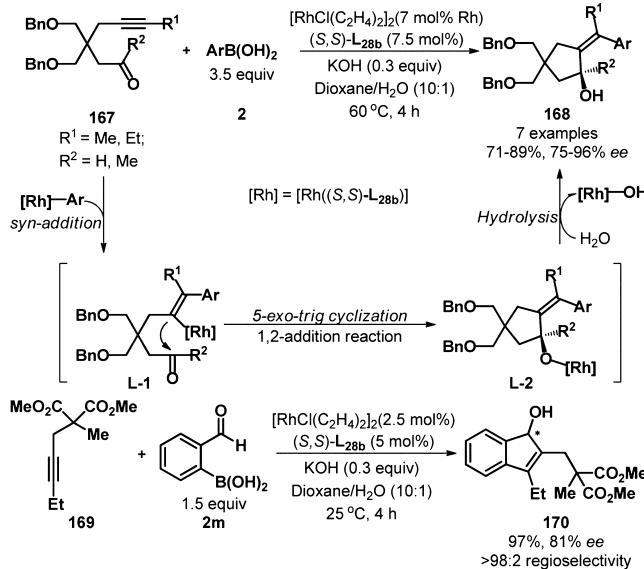
Scheme 61. Tandem RCAA/1,2 Addition onto a Cyano Group



species to **163** afforded the (oxa- π -allyl)rhodium(I) intermediate **K-1**, which underwent intramolecular 1,2-addition onto the cyano moiety to form the *N*-rhodium(I) imine **K-2**. Subsequent transmetalation of **K-2** with $\text{ArB}(9\text{-BBN})$ (**12**) produced the *N*-boryl imine species **K-3**, which led to the final product **164** through hydrolysis/tautomerization. A related example with strained bicyclic alkene **165** and bifunctional (2-cyanophenyl)boronic acid **2k** did demonstrate a [3 + 2] annulation reaction, through the tandem RCAA/1,2-addition process, to afford an optically active exo-adduct **166** by using a rhodium/ L_{31a} catalyst.²⁵⁴

Aryl-rhodium species can undergo syn-addition to dialkylacetylenes and subsequently cyclize through the intramolecular 1,2-addition to aldehydes or ketones. In 2005, Hayashi and co-workers described this tandem Rh-catalyzed arylation (RCA)/1,2-addition of arylboronic acids to alkynals and alkynones **167**. The reaction successfully afforded chiral cyclic allylic alcohols **168** in high yields and enantioselectivities by applying a Rh(I)/(*S,S*)- L_{28b} catalyst (Scheme 62).²⁵⁵ A related reaction between bifunctional (2-formylphenyl)boronic acid **2m** and alkyne **169**

Scheme 62. Tandem RCA/1,2-Addition to an Aldehyde Group

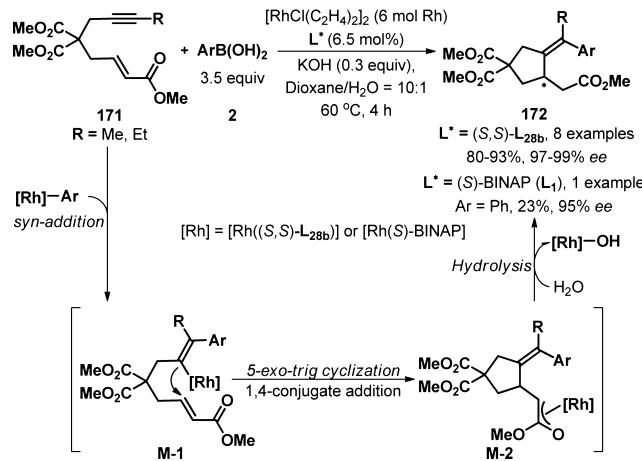


generated the optically active 2-indenol **170** through the tandem RCA/1,2-addition process.²⁵⁶

6.4. Tandem Carborhodation/Conjugate Addition.

Similar to the above process, aryl-rhodium species can undergo syn addition to a carbon–carbon triple bond, followed by cyclization through the intramolecular 1,4-conjugate addition to electron-deficient olefins. In 2005, Hayashi and co-workers developed a Rh-catalyzed arylative cyclization of alkyne-tethered α,β -unsaturated esters **171** with excellent chemo- and enantioselectivities by the use of a chiral diene ligand (*S,S*)- L_{28b} (Scheme 63).²⁵⁷ Interestingly, Rh(I)/bisphosphine system

Scheme 63. Rh-Catalyzed Arylative Cyclization of Alkyne-Tethered Electron-Deficient Olefins

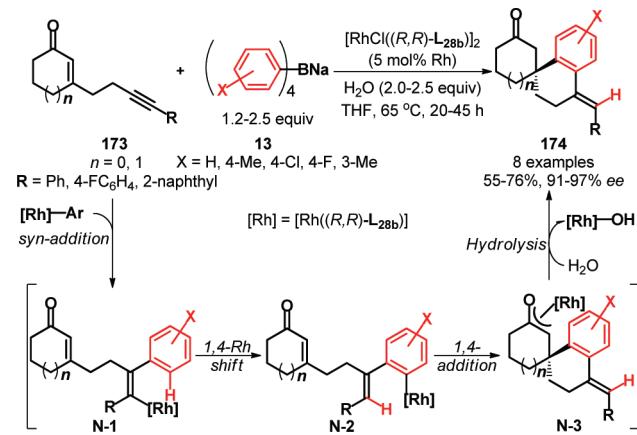


catalyzed the 1,4-addition of α,β -enoates more effectively than the arylation of alkynes, whereas a Rh(I)/diene catalyst exhibited high preference to the arylation of alkynes. This remarkably different behavior was probably due to the more electrophilic nature of a Rh(I)/diene complex than a Rh(I)/phosphine center.

Recently, this strategy was extended to alkyne-tethered 2-cycloalken-1-ones **173** and sodium tetraarylborates **13**,

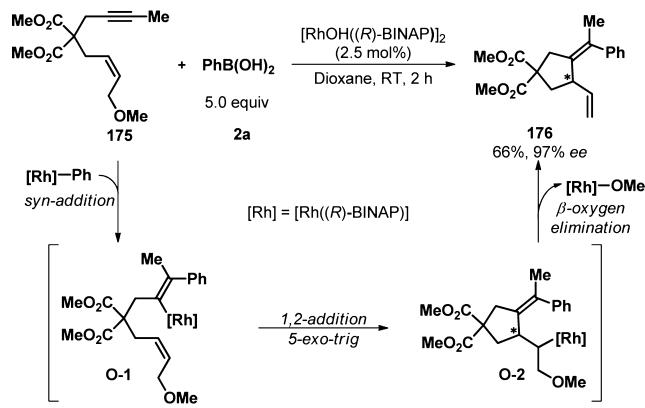
affording spirocarbocycles **174** with quaternary spirocarbon stereocenters in excellent enantiomeric purity.²⁵⁸ The aryl-rhodium species went through 1,2-syn insertion of the alkyne group in **173**, giving an alkenylrhodium intermediate **N-1**. An interesting 1,4-Rh migration occurred to generate a new arylrhodium species **N-2**, which further reacted with the intramolecular enone group to afford oxa- π -allylrhodium intermediate **N-3**. Protonation of **N-3** in an aqueous media provided the chiral spiro-cyclic product **174**. Overall, the aryl groups in tetraarylborates functioned as surrogates of 1,2-dimetalloarenes and sequentially formed two new carbon–carbon bonds (Scheme 64).

Scheme 64. Rh-Catalyzed Arylative Cyclization of Alkyne-Tethered 2-Cycloalken-1-ones



6.5. 1,6-Enyne Sequential Cyclization. Murakami and co-workers reported the Rh(I)/(*R*)-BINAP catalyzed cascade reaction of 1,6-enyne **175** with phenylboronic acid **2a** to produce optically active cyclopentane **176** with excellent enantioselectivity (Scheme 65).²⁵⁹ The whole sequence

Scheme 65. Rh-Catalyzed Arylative Cyclization of 1,6-Enyne-Tethered Allylic Ether

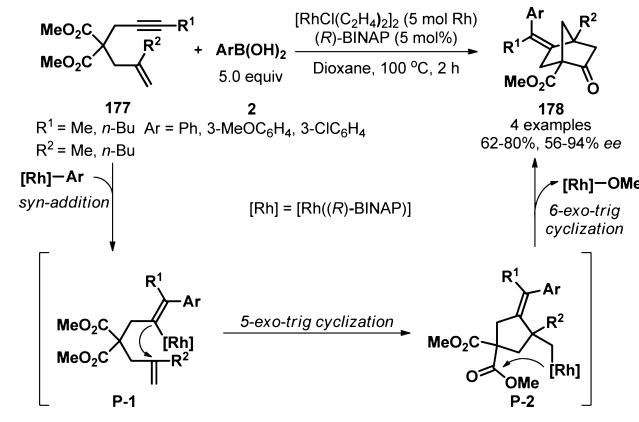


involved 1,2-syn addition to the triple bond, 5-exo-trig cyclization into the olefin, and β -oxygen elimination to give **176**. The methoxyl group played a dominating role in the catalytic cycle, terminating the alkyl-rhodium species **O-2** and regenerating the catalytically active methoxorhodium(I) species.

In the absence of a proper allylic leaving group as terminating function adjacent to the alkene moiety in 1,6-enyne, the

resulting alkyl-rhodium species **P-2** could not undergo either β -oxygen elimination or β -hydrogen elimination because of the existence of a substitution group R². Instead, the intermediate **P-2** further reacted with an electrophilic ester group in the molecule, through a 5-exo-trig cyclization, affording the optically active 2-norbornanone skeleton **178** with high enantioselectivities (Scheme 66).²⁶⁰

Scheme 66. Rh-Catalyzed Arylative Cyclization of 1,6-Enyne



7. OUTLOOK

Since the initial breakthrough in the field of RCAA in 1998, distinct families of chiral ligands and various highly efficient asymmetric catalytic systems have been developed and established for different reaction substrates. With a large number of chiral ligands and optimized conditions available in achieving high stereoselectivity, the RCAA reaction is becoming more and more important in organic synthesis. However, the generation of aryl-rhodium species from direct C–H activation instead of through transmetalation and further extension of RCAA reaction to the nonactivated alkenes are still quite challenging in the field. Additional approaches in this aspect are expected with much anticipation indeed.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +86-21-54925169. Fax: +86-21-64166263. E-mail: lingq@mail.sioc.ac.cn

Present Address

[†]OSI Pharmaceuticals, a Wholly Owned Subsidiary of Astellas Pharma, 1 Bioscience Park Drive, Farmingdale, NY 11735, U.S.A.

Funding

Financial support from the National Natural Science Foundation of China (21102161) and the State Key Laboratory of Bio-organic and Natural Products Chemistry (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences) is acknowledged.

■ REFERENCES

- (1) Hayashi, T. *Synlett* 2001, No. Special Issue, 879.
- (2) Hayashi, T. *Russ. Chem. Bull., Int. Ed.* 2003, 52, 2595.
- (3) Hayashi, T.; Yamasaki, K. *Chem. Rev.* 2003, 103, 2829.
- (4) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3, p 55.

- (5) Yoshida, K.; Hayashi, T. In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 4, p 171.
- (6) Shintani, R.; Hayashi, T. In *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley-Interscience: Hoboken N. J., 2007; Chapter 3, p 59.
- (7) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31.
- (8) Berthon, G.; Hayashi, T. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 1, p 1.
- (9) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093.
- (10) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.
- (11) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.
- (12) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.
- (13) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.
- (14) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
- (15) Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 3904.
- (16) Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, T. *Chem.—Asian J.* **2006**, *1*, 707.
- (17) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188.
- (18) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535.
- (19) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.
- (20) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.
- (21) Chen, F. -X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341.
- (22) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.
- (23) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.
- (24) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147.
- (25) Pucheault, M.; Darses, S.; Genêt, J. -P. *Eur. J. Org. Chem.* **2002**, *3552*.
- (26) Pucheault, M.; Darses, S.; Genêt, J. -P. *Tetrahedron Lett.* **2002**, *43*, 6155.
- (27) Darses, S.; Genêt, J. -P. *Eur. J. Org. Chem.* **2003**, *4313*.
- (28) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.
- (29) Navarre, L.; Martinez, R.; Genêt, J. -P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.
- (30) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099.
- (31) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
- (32) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
- (33) Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899.
- (34) Gendrineau, T.; Genêt, J. -P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.
- (35) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957.
- (36) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *Org. Synth.* **2002**, *79*, 84.
- (37) Yamamoto, Y.; Takizawa, M.; Yu, X.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928.
- (38) Yu, X.; Yamamoto, Y.; Miyaura, N. *Synlett* **2009**, 994.
- (39) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 1901.
- (40) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.
- (41) Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980.
- (42) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769.
- (43) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872.
- (44) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.
- (45) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.
- (46) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305.
- (47) Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889.
- (48) Tokunaga, N.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 607.
- (49) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.
- (50) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224.
- (51) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, S.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774.
- (52) Huang, T.; Li, C. *Chem. Commun.* **2001**, 2348.
- (53) Murata, M.; Shimazaki, R.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Synthesis* **2002**, 717.
- (54) Koike, T.; Du, X. L.; Mori, A.; Osakada, K. *Synlett* **2002**, 301.
- (55) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W. L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137.
- (56) Miura, T.; Murakami, M. *Chem. Commun.* **2005**, 5676.
- (57) Venkatraman, S.; Meng, Y.; Li, C. *J. Tetrahedron Lett.* **2001**, *42*, 4459.
- (58) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83.
- (59) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.
- (60) Ding, R.; Chen, Y. J.; Wang, D.; Li, C. *J. Synlett* **2001**, 1470.
- (61) Venkatraman, S.; Li, C. *J. Tetrahedron Lett.* **2001**, *42*, 781.
- (62) Huang, T. S.; Venkatraman, S.; Meng, Y.; Nguyen, T. V.; Kort, D.; Wang, D.; Ding, R.; Li, C. *J. Pure Appl. Chem.* **2001**, *73*, 1315.
- (63) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4937.
- (64) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944.
- (65) Lukin, K.; Zhang, Q. Y.; Leanna, M. R. *J. Org. Chem.* **2009**, *74*, 929.
- (66) Oi, S.; Moro, M.; Inoue, Y. *Chem. Commun.* **1997**, 1621.
- (67) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Organometallics* **2001**, *20*, 1036.
- (68) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667.
- (69) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97.
- (70) Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051.
- (71) Oi, S.; Taira, A.; Honma, Y.; Sato, T.; Inoue, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 598.
- (72) Itoh, T.; Mase, T.; Nishikata, T.; Iyama, T.; Tachikawa, H.; Kobayashi, Y.; Yamamoto, Y.; Miyaura, N. *Tetrahedron* **2006**, *62*, 9610.
- (73) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951.
- (74) Yamamoto, Y.; Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D. G.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 1224.
- (75) Shimada, T.; Suda, M.; Nagano, T.; Kakiuchi, K. *J. Org. Chem.* **2005**, *70*, 10178.
- (76) Amengual, R.; Michelet, V.; Genêt, J. -P. *Synlett* **2002**, 1791.
- (77) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083.
- (78) Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428.
- (79) Vandyck, K.; Matthys, B.; Willen, M.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, J. *Org. Lett.* **2006**, *8*, 363.
- (80) Gök, Y.; Noël, T.; Van der Eycken, J. *Tetrahedron: Asymmetry* **2010**, *21*, 2768.
- (81) Shi, Q.; Xu, L. J.; Li, X. S.; Jia, X.; Wang, R. H.; Au-Yeung, T. T. L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. C. *Tetrahedron Lett.* **2003**, *44*, 6505.
- (82) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J. -P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.
- (83) Mashima, K.; Kusano, K.; Saito, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.
- (84) Korenaga, T.; Osaki, K.; Maenishi, R.; Sakai, T. *Org. Lett.* **2009**, *11*, 2325.

- (85) Korenaga, T.; Maenishi, R.; Hayashi, K.; Sakai, T. *Adv. Synth. Catal.* **2010**, *352*, 3247.
- (86) Korenaga, K.; Maenishi, R.; Osaki, K.; Sakai, T. *Heterocycles* **2010**, *80*, 157.
- (87) Berhal, F.; Esseiva, O.; Martin, C. -H.; Tone, H.; Genêt, J. -P.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 2806.
- (88) Berhal, F.; Wu, Z.; Genêt, J. -P.; Ayad, T.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2011**, *76*, 6320.
- (89) Madec, J.; Michaud, G.; Genêt, J. P.; Marinetti, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2253.
- (90) Otomaru, Y.; Senda, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3357.
- (91) Stemmler, R. T.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 9925.
- (92) Kromm, K.; Eichenseher, S.; Prommesberger, M.; Hampel, F.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2005**, 2983.
- (93) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469.
- (94) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934.
- (95) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8636.
- (96) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.
- (97) Martina, S. L. X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L. *Tetrahedron Lett.* **2005**, *46*, 7159.
- (98) Duursma, A.; Boiteau, J. G.; Lefort, L.; Boogers, J. A.; de Vries, A. H.; De Vries, J.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045.
- (99) Boiteau, J. G.; Imbos, F.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681.
- (100) Boiteau, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481.
- (101) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111.
- (102) Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 2433.
- (103) Jagt, R. B. C.; Toullec, P. Y.; Schudde, E. P.; De Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *J. Comb. Chem.* **2007**, *9*, 407.
- (104) Iuliano, A.; Facchetti, S.; Funaioli, T. *Chem. Commun.* **2009**, 457.
- (105) Monti, C.; Gennari, C.; Piarulli, U. *Chem. Commun.* **2005**, 5281.
- (106) Ma, Y. D.; Song, C.; Ma, C. Q.; Sun, Z. J.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871.
- (107) Facchetti, S.; Cavallini, I.; Funaioli, T.; Marchetti, F.; Iuliano, A. *Organometallics* **2009**, *28*, 4150.
- (108) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, H. *J. Am. Chem. Soc.* **2003**, *125*, 11508.
- (109) Defieber, C.; Paquin, J.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.
- (110) Paquin, J.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.
- (111) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.
- (112) Lang, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997.
- (113) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331.
- (114) Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860.
- (115) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387.
- (116) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genêt, J. P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669.
- (117) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F. -X.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869.
- (118) Fischer, C.; Defieber, C.; Takeyuki, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.
- (119) Berthon-Gelloz, G.; Hayashi, T. *J. Org. Chem.* **2006**, *71*, 8957.
- (120) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961.
- (121) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172.
- (122) Hayashi, T.; Tokunaga, N.; Okamoto, K.; Shintani, R. *Chem. Lett.* **2005**, *34*, 1480.
- (123) Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 3213.
- (124) Shintani, R.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 4757.
- (125) Paquin, J. F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.
- (126) Chen, F.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341.
- (127) Tokunaga, N.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 513.
- (128) Soergel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589.
- (129) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815.
- (130) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.
- (131) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673.
- (132) Wang, Z. -Q.; Feng, C. -G.; Xu, M. -H.; Lin, G. -Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.
- (133) Wang, Y. -Z.; Hu, X. -C.; Du, H. -F. *Org. Lett.* **2010**, *12*, 5482.
- (134) Li, Q.; Dong, Z.; Yu, Z. -X. *Org. Lett.* **2011**, *13*, 1122.
- (135) Chen, M. S.; White, C. M. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
- (136) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, C. M. *J. Am. Chem. Soc.* **2005**, *127*, 6970.
- (137) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172.
- (138) Bürgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2768.
- (139) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.
- (140) Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org. Lett.* **2010**, *12*, 1928.
- (141) Chen, J.; Chen, J.-M.; Lang, F.; Zhang, X.-Y.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *J. Am. Chem. Soc.* **2010**, *132*, 4552.
- (142) Han, F.-Z.; Chen, G.-H.; Zhang, X.-Y.; Liao, J. *Eur. J. Org. Chem.* **2011**, 2928.
- (143) Zhang, X.-Y.; Chen, J.; Han, F.-Z.; Cun, L.-F.; Liao, J. *Eur. J. Org. Chem.* **2011**, 1443.
- (144) Korenaga, T.; Hayashi, K.; Akaki, Y.; Maenishi, R.; Sakai, T. *Org. Lett.* **2011**, *13*, 2022.
- (145) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611.
- (146) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130.
- (147) Piras, E.; Lang, F.; Ruegger, H.; Stein, D.; Worle, M.; Grützmacher, H. *Chem.—Eur. J.* **2006**, *12*, 5849.
- (148) Kasak, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084.
- (149) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.
- (150) Mariz, R.; Briceno, A.; Dorta, R. *Organometallics* **2008**, *27*, 6605.
- (151) Minuth, T.; Boysen, M. M. L. *Org. Lett.* **2009**, *11*, 4212.
- (152) Grugel, H.; Minuth, T.; Boyse, M. M. K. *Synthesis* **2010**, 3248.
- (153) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921.
- (154) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932.
- (155) Chen, Q.; Soeta, T.; Kuriyama, M.; Yamada, K. I.; Tomioka, K. *Adv. Synth. Catal.* **2006**, *348*, 2604.
- (156) Lang, F.; Li, D.; Chen, J.-M.; Chen, J.; Li, L.-C.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *Adv. Synth. Catal.* **2010**, *352*, 843.
- (157) Han, F.-Z.; Chen, J.; Zhang, X.-Y.; Liu, J.-B.; Cun, L.-F.; Zhu, J.; Deng, J.-G.; Liao, J. *Tetrahedron Lett.* **2011**, *52*, 830.
- (158) Becht, J.-M.; Bappert, E.; Helmchen, G. *Adv. Synth. Catal.* **2005**, *347*, 1495.

- (159) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.
- (160) Kuuloja, N.; Tois, J.; Franzén, R. *Tetrahedron: Asymmetry* **2011**, *22*, 468.
- (161) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182.
- (162) Chen, G.-H.; Gui, J.-Y.; Li, L.-C.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681.
- (163) Xue, F.; Li, X.-C.; Wan, B.-S. *J. Org. Chem.* **2011**, *76*, 7256.
- (164) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410.
- (165) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* **2011**, 7230.
- (166) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.
- (167) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.
- (168) Liu, M.; Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Chem.—Eur. J.* **2009**, *15*, 10217.
- (169) Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, 8460.
- (170) Feng, X.-Q.; Wang, Y.-Z.; Wei, B.-B.; Yang, J.; Du, H.-F. *Org. Lett.* **2011**, *13*, 3300.
- (171) Feng, X.-Q.; Wei, B.-B.; Yang, J.; Du, H.-F. *Org. Biomol. Chem.* **2011**, *9*, 5927.
- (172) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450.
- (173) Brock, S.; Hose, D. R. J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496.
- (174) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350.
- (175) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.
- (176) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.
- (177) Meyer, O.; Becht, J. M.; Helmchen, G. *Synlett* **2003**, 1539.
- (178) Becht, J.-M.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, 2805.
- (179) Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, Z.; Shintani, R.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464.
- (180) Zoute, L.; Kociok-Köhn, G.; Frost, C. G. *Org. Lett.* **2009**, *11*, 2491.
- (181) Hellal, M.; Cuny, G. D. *Org. Lett.* **2010**, *12*, 4628.
- (182) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425.
- (183) Pucheault, M.; Michaut, V.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4729.
- (184) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788.
- (185) Shintani, R.; Duan, W. L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628.
- (186) Duan, W. L.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529.
- (187) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.
- (188) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235.
- (189) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 5780.
- (190) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591.
- (191) Mauleon, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195.
- (192) Mauleon, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924.
- (193) Mauleón, P.; Carretero, J. *Chem. Commun.* **2005**, 4961.
- (194) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163.
- (195) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390.
- (196) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464.
- (197) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.
- (198) Menard, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085.
- (199) Panteleev, J.; Menard, F.; Lautens, M. *Adv. Synth. Catal.* **2008**, *350*, 2893.
- (200) Bexrud, J.; Lautens, M. *Org. Lett.* **2010**, *12*, 3160.
- (201) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373.
- (202) Saxena, A.; Lam, H. W. *Chem. Sci.* **2011**, *2*, 2326.
- (203) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595.
- (204) Sasaki, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 8145.
- (205) de la Herrán, G.; Murcia, C.; Csáký, A. G. *Org. Lett.* **2005**, *7*, 5629.
- (206) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12865.
- (207) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674.
- (208) Boyd, S. E.; Field, L. D.; Hambley, T. W.; Partridge, M. G. *Organometallics* **1993**, *12*, 1720.
- (209) Jagt, R. B. C.; Toullec, P. Y.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Biomol. Chem.* **2006**, *4*, 773.
- (210) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1479.
- (211) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, 5713.
- (212) Morikawa, S.; Michigami, K.; Amii, H. *Org. Lett.* **2010**, *12*, 2520.
- (213) Ma, Q.-S.; Ma, Y.-D.; Liu, X.; Duan, W.-Z.; Qu, B.; Song, C. *Tetrahedron: Asymmetry* **2010**, *21*, 292.
- (214) Xing, C.-H.; Liao, Y.-X.; He, P.; Hu, Q.-S. *Chem. Commun.* **2010**, 3010.
- (215) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353.
- (216) Martina, S. L. X.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2006**, 4093.
- (217) Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4351.
- (218) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454.
- (219) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092.
- (220) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147.
- (221) Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481.
- (222) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
- (223) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.
- (224) Jayathilaka, L. P.; Deb, M.; Standaert, R. F. *Org. Lett.* **2004**, *6*, 3659.
- (225) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304.
- (226) Truong, V. L.; Pfeiffer, J. Y. *Tetrahedron Lett.* **2009**, *50*, 1633.
- (227) Kuriyama, M.; Soeta, T.; Hao, X. Y.; Chen, O.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128.
- (228) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567.
- (229) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.
- (230) Yang, H.-Y.; Xu, M.-H. *Chem. Commun.* **2010**, 9223.
- (231) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 3820.
- (232) Shintani, R.; Narui, R.; Tsutsumi, Y.; Hayashi, S.; Hayashi, T. *Chem. Commun.* **2011**, 6123.
- (233) Cui, Z.; Yu, H.-J.; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 12394; see also ref 261.
- (234) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
- (235) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.
- (236) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 609.
- (237) 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.
- (238) Cao, Z.-P.; Du, H.-F. *Org. Lett.* **2010**, *12*, 2602.

- (239) Crampton, R.; Woodward, S.; Fox, M. *Adv. Synth. Catal.* **2011**, 353, 903.
- (240) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, 132, 13168.
- (241) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, 13, 2977.
- (242) Hao, X.-Y.; Kuriyama, M.; Chen, Q.; Yamamoto, Y.; Yamada, K.-I.; Tomioka, K. *Org. Lett.* **2009**, 11, 4470.
- (243) Hao, X.-Y.; Chen, Q.; Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Tetrahedron* **2011**, 67, 6469.
- (244) Shintani, R.; Soh, Y.-T.; Hayashi, T. *Org. Lett.* **2010**, 12, 4106.
- (245) Nadeau, C.; Aly, S.; Belyk, K. *J. Am. Chem. Soc.* **2011**, 133, 2878.
- (246) Trost, B. M. *Science* **1991**, 254, 1471.
- (247) Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, 45, 354.
- (248) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.
- (249) Youn, S. W. *Eur. J. Org. Chem.* **2009**, 2597.
- (250) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, 124, 10984.
- (251) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, 125, 1110.
- (252) Bocknack, B. M.; Wang, L. C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5421.
- (253) Miura, T.; Harumashi, T.; Murakami, M. *Org. Lett.* **2007**, 9, 741.
- (254) Miura, T.; Murakami, M. *Org. Lett.* **2005**, 7, 3339.
- (255) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, 127, 54.
- (256) Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, 34, 1294.
- (257) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, 44, 3909.
- (258) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, 49, 3795.
- (259) Miura, T.; Shimada, M.; Murakami, M. *Chem.—Asian J.* **2006**, 1, 868.
- (260) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, 127, 1390.
- (261) Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Synthesis* **2010**, 3263.