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Rhodium-Catalyzed Asymmetric Arylation

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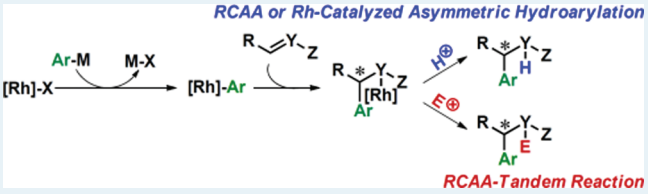
ABSTRACT: Rhodium-catalyzed asymmetric arylation (RCAA) reactions provide one of the most straightforward and powerful ways to introduce aryl fragments in an enantioselective manner. The discovery of novel chiral ligands and catalytic systems is a major focus in generating optical chiralities for RCAA reactions. In the past decade, the chelating functionalities in ligands have been significantly expanded from traditional phosphorus to interesting diene, bissulfoxide, 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.

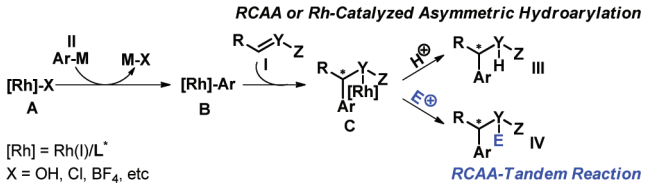


KEYWORDS: *rhodium-catalyzed asymmetric arylation, conjugate addition, phosphorus ligands, diene ligands, bissulfoxide ligands, hybrid ligands, activated alkenes, imines, tandem reactions*

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 Fros[9] devoted to rhodium-catalyzed asymmetric conjugate addition and its related synthetic applications, and collections by Rovis[10] and Carreira[11] 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 [Rh-(acac)$(CO)_2$] (acac = acetylacetonato) 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

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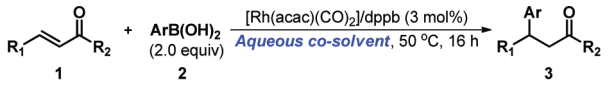
although in slightly lower yield for 2-cyclohexenone (**1b**) (Scheme 2).

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



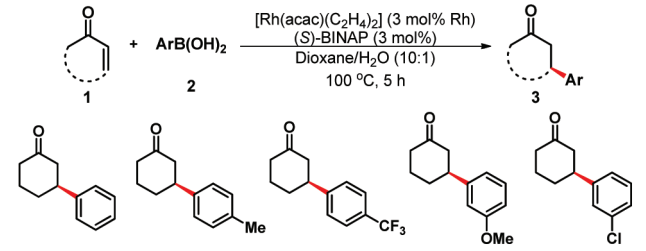
Selected examples:
1a = methyl vinyl ketone(MVK); **1b** = 2-cyclohexenone; **1c** = 2-octen-4-one;
2a = $PhB(OH)_2$; **2b** = 4-$MeOC_6H_4B(OH)_2$

Aqueous solvent:	3aa, yield	3ab, yield	3ba, yield	3ca, yield
DMF/H_2O (6:1)	99%	84%	trace	28%
Cyclohexane/H_2O (6:1)	90%	82%	52%	74%
MeOH/H_2O (6:1)	99%	86%	trace	96%

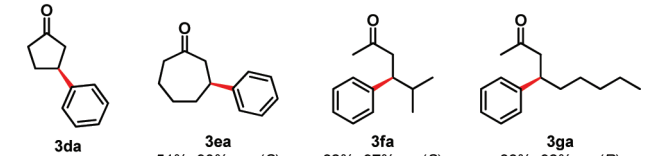
The merits of this reaction lie in the following: (i) neutral reaction conditions in the presence of water; (ii) no observation of either competitive uncatalyzed reaction of the arylboronic acids to the enones or the related 1,2-addition byproduct; and (iii) tolerance of a wide range of functional groups 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. $[Rh(acac)(C_2H_4)_2]$/(*S*)-BINAP Catalyzed Asymmetric Arylation of Arylboronic Acids to Enones



3ba >99%, 97% *ee* (*S*) **3bc** >99%, 97% *ee* (*S*) **3bd** 70%, 99% *ee* (*S*) **3be** 97%, 99% *ee* (*S*) **3bf** 94%, 96% *ee* (*S*)



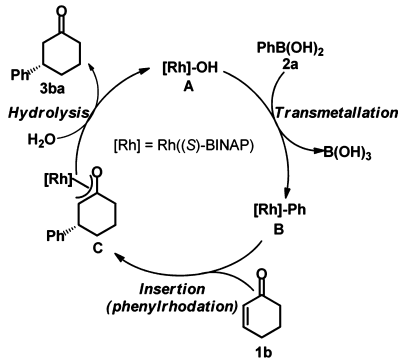
3da 93%, 97% *ee* (*S*) **3ea** 51%, 93% *ee* (*S*) **3fa** 82%, 97% *ee* (*S*) **3ga** 88%, 92% *ee* (*R*)

were multiple modifications from the original Miyaura's conditions: (i) different Rh-precursor, from $[Rh(acac)(CO)_2]$ to $[Rh(acac)(C_2H_4)_2]$; (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 Rh(I)/(*S*)-BINAP is illustrated in Scheme 4. The reaction is initiated through the

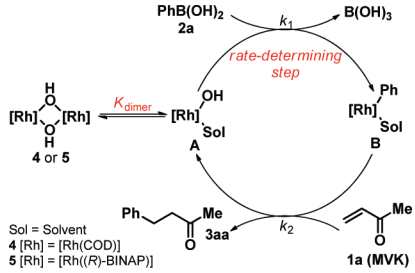
Scheme 4. Catalytic Cycle for the RCAA of Phenylboronic Acid to 2-Cyclohexenone by a [Rh]–OH Complex



transmetalation of a phenyl group from boron to hydroxorhodium **A** to generate the phenylrhodium **B**. Subsequently, 2-cyclohexenone inserts into Rh–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 $[Rh(OH)(COD)]_2$ (**4**) was 20-fold faster than with $[Rh(OH)((R)\text{-BINAP})]_2$ (**5**) under the same conditions in Rh-catalyzed arylation of $PhB(OH)_2$ 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 Rh(I)/(*S*)-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

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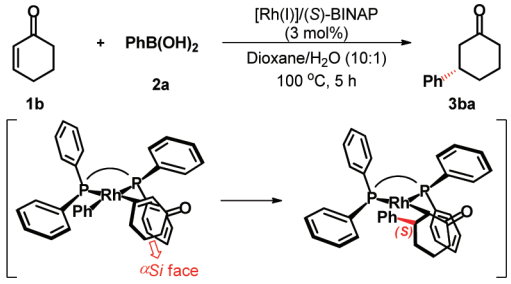
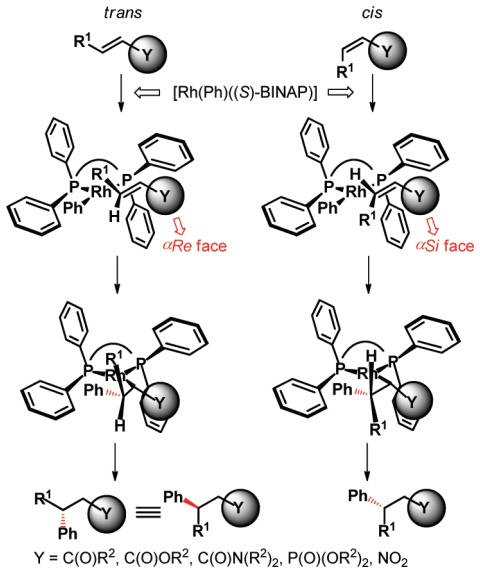
Scheme 6. Hayashi's Enantioselective Model for the RCAA to 2-Cyclohexenone Catalyzed by Rh(I)/(*S*)-BINAP Complex



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

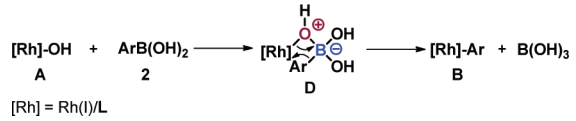
Scheme 7. Hayashi's Stereocontrol Model for the RCAA to *trans*- or *cis*-Olefins



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 Transmetallation 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

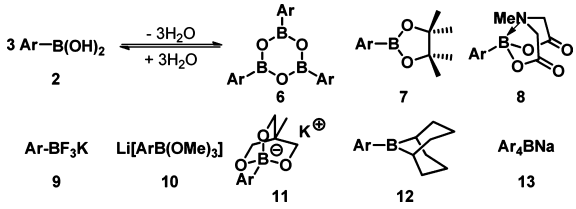
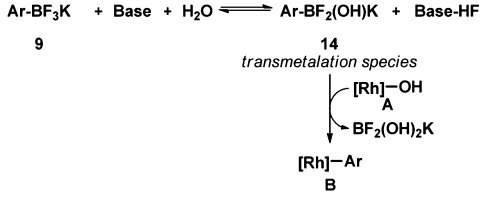


Figure 1. Arylboron Reagents for RCAA.

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*-methyliminodiacetic 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. Transmetallation of Potassium Aryltrifluoroborate



Lithium trimethylarylborate salts **10** are very reactive in RCAA, but unstable and require the preparation in situ.[23,35,36]

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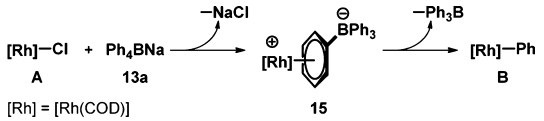
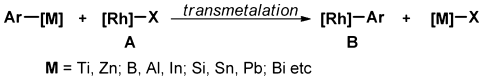
Similar to MIDA (**8**), cyclic aryltriolborates **11** are also very stable in air and water, and conveniently used in RCAA because of better solubility in organic solvents than related potassium organotrifluoroborates **9**.[37,38] The reactive ArB(9-BBN) derivatives **12** are often applied in RCAA 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 tetraarylborate 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 phenyl-rhodium species **B** (Scheme 10).[40]

Scheme 10. Transmetallation 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. Transmetallation 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-(hydroxylmethyl)aryl]dimethylsilanes **20**[55] have been successively developed as the aryl-transfer reagents with rhodium (Figure 2).

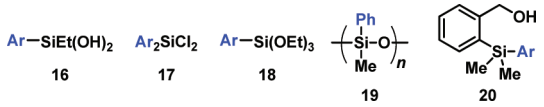
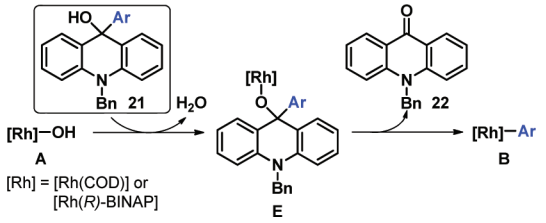


Figure 2. Arylsilicon reagents as aryl-transfer reagents.

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]

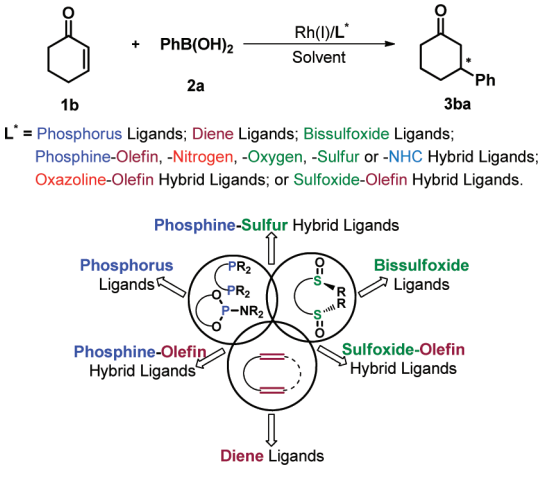
Scheme 12. Triarylmethanols as Aryl-Transfer Reagents



2.3.3. Rh-Precatalysts. $[Rh(Cl)(C_2H_4)_2]_2$ is the favorable precatalyst because of its rapid and irreversible ligand exchange.[13] However, COD-based Rh precursors, such as $[Rh(Cl)(COD)]_2$ and $[Rh(OH)(COD)]_2$, 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, $[Rh(COD)_2]BF_4$, $[Rh(COD)(MeCN)_2]BF_4$,[58,59,66−71] and $[Rh(nbd)_2]BF_4$,[20,72] are excellent Rh-precatalysts,[73] which allow for the replacement of KOH with Et_3N 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.

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The BINAP-based ligands $\mathbf{L_2}$,[75] $\mathbf{L_3}$,[75] and water-soluble $\mathbf{L_4}$[76] provided similar outcomes with BINAP (Figure 3). Interestingly,

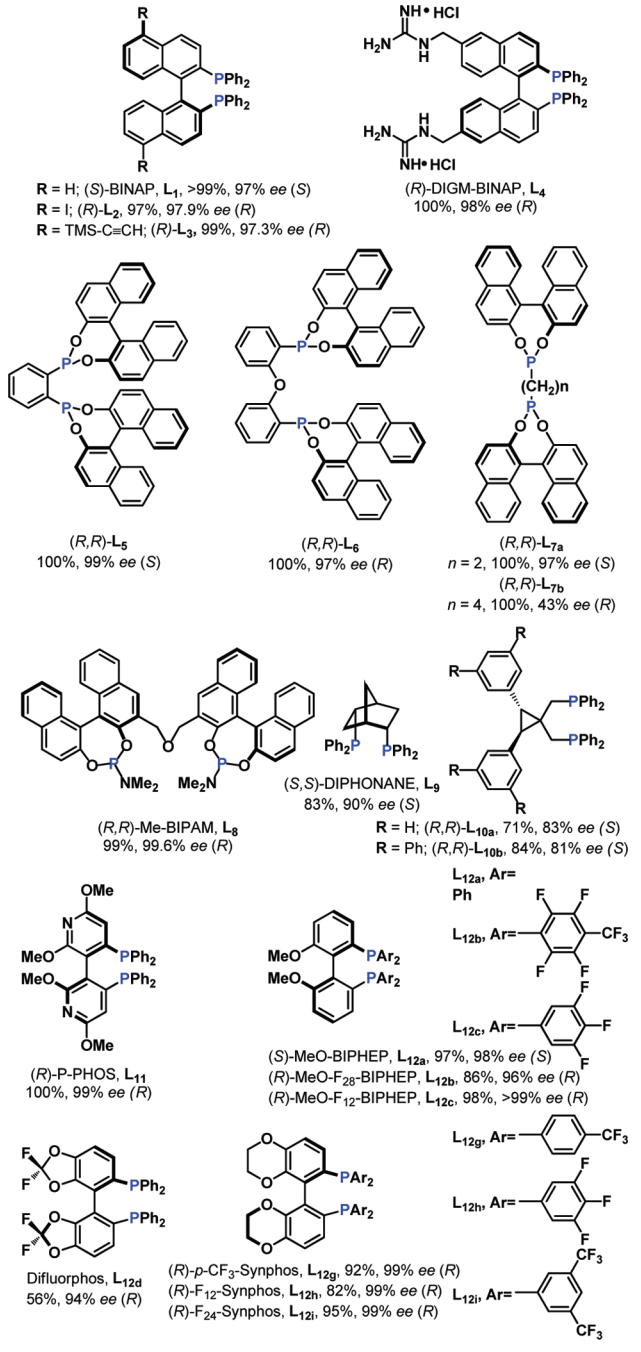

Figure 3. C_2-Symmetric bidentate phosphorus ligands.

BINOL-based bisphosphonites[77] $\mathbf{L_5}$ and $\mathbf{L_6}$ or $\mathbf{L_{7a}}$ and $\mathbf{L_{7b}}$ gave excellent but sometimes reverse enantioselectivity depending on the linker between two separate phosphonites. Similarly, BINOL-based bisphosphoramidite $\mathbf{L_8}$ gave excellent results.[74,78] The bisphosphine ligand $\mathbf{L_9}$[79] bearing a distinct norbornane backbone delivered high selectivities; however, the cyclopropane-based bisphosphines[80] $\mathbf{L_{10a}}$ and $\mathbf{L_{10b}}$ just achieved the moderate selectivities. The biphenyl-based bisphosphorus ligands $\mathbf{L_{11}}$, $\mathbf{L_{12a}}$, $\mathbf{L_{12b}}$, $\mathbf{L_{12c}}$, $\mathbf{L_{12d}}$, $\mathbf{L_{12g}}$, $\mathbf{L_{12h}}$, and $\mathbf{L_{12i}}$ likewise acquired excellent enantioselectivities,[81−88] in which (*R*)-F_{12}−BIPHEP $\mathbf{L_{12c}}$ and (*R*)-F_{24}−Synphos $\mathbf{L_{12i}}$ 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(bisphos-phine)(CO)] complexes by IR (Figure 4). The ν_{CO} value of $\mathbf{L_{12c}}$ is

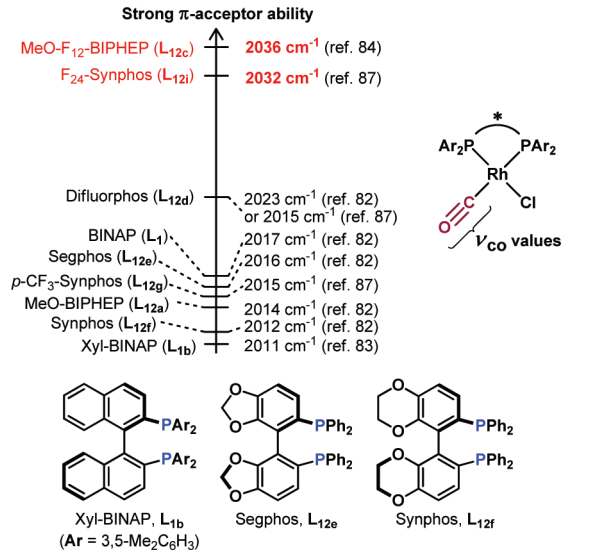

Figure 4. ν_{CO} values of the [RhCl(bisphosphine)(CO)] complexes.

shown to be higher than those of known bisphosphines, suggesting that $\mathbf{L_{12c}}$ 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, $\mathbf{L_{12c}}$ 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 $\mathbf{L_{13a}}$,[89] $\mathbf{L_{13b}}$,[89] and polystyrene-supported BINAP $\mathbf{L_{14}}$[90] gave excellent enantioselectivities similar to BINAP (Figure 5). The

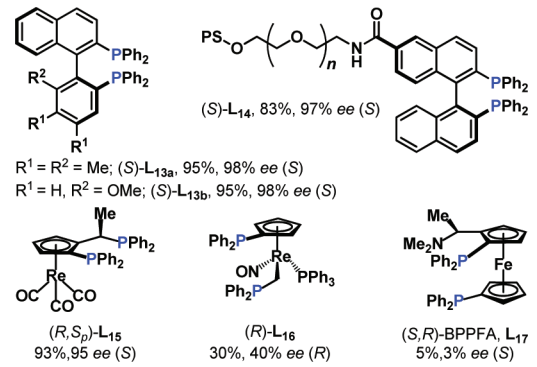

Figure 5. Non-C_2-symmetric bidentate phosphorus ligands.

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

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

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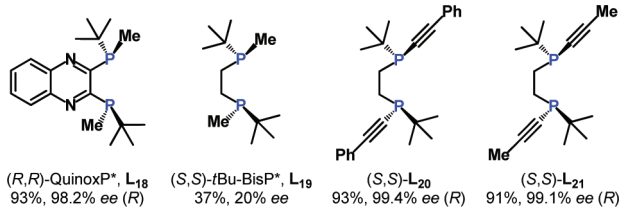

Figure 6. P-chiral bidentate phosphine ligands.

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, H_8–BINOL-based phosphoramidite (*S*)-$\mathbf{L_{22}}$ proved to be the most efficient.[100] Introducing the inexpensive methyl deoxycholic ester **23** as the source of chirality in phosphite $\mathbf{L_{23}}$ validated the similar efficiency compared with $\mathbf{L_{24}}$ (Figure 7).[104,105]

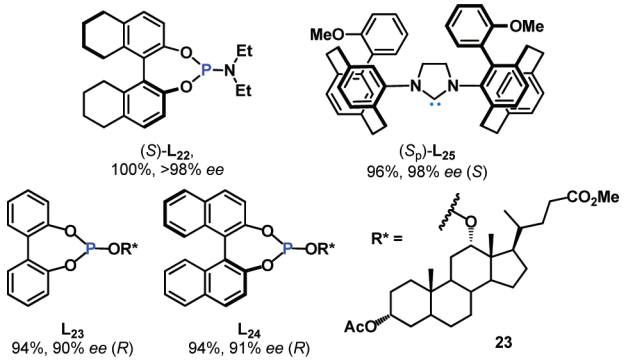

Figure 7. Monodentate phosphorus ligands.

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 $\mathbf{L_{25}}$ 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 $\mathbf{L_{26b}}$ 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- ($\mathbf{L_{26a}}$), Bn- ($\mathbf{L_{26b}}$), Cy- ($\mathbf{L_{26d}}$), *i*-Bu- ($\mathbf{L_{26e}}$), and allyl- ($\mathbf{L_{26f}}$) showed excellent enantioselectivities (95–96% ee); and phenyl variation $\mathbf{L_{26c}}$ exhibited a higher enantiomeric excess (ee) value.[119,120] Chiral-bridged dienes $\mathbf{L_{27}}$, 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 ($\mathbf{L_{28}}$, $\mathbf{L_{29}}$, $\mathbf{L_{30}}$, $\mathbf{L_{31}}$, $\mathbf{L_{32}}$, $\mathbf{L_{33}}$, and $\mathbf{L_{34}}$),[110,118,121−129] bicyclo[3.3.1]nonadiene variations ($\mathbf{L_{35}}$ and $\mathbf{L_{36}}$),[130,131] and bicyclo[3.3.2]decadiene variation $\mathbf{L_{37}}$[131] all gave excellent enantiomeric excesses for Hayashi–Miyaura reaction. Both optically pure enantiomers of bicyclo[3.3.0]octadiene-based chiral dienes $\mathbf{L_{38}}$[113] and $\mathbf{L_{39}}$[132] could be easily prepared through lipase-catalyzed kinetic resolution in >10 g scale. Hydrophilic diene ligand $\mathbf{L_{39}}$ 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 $\mathbf{L_{40}}$[112] and 1,5-Ph-cod $\mathbf{L_{41}}$[47] are achiral, but the corresponding cationic rhodium complexes are chiral and both enantiomers can be resolved. The optically pure Rh-complexes with $\mathbf{L_{40}}$ and $\mathbf{L_{41}}$ gave the moderate enantioselectivity in RCAA. Utilizing the simple and flexible acyclic chiral 1,5-dienes $\mathbf{L_{42}}$,[133] $\mathbf{L_{43}}$,[133] $\mathbf{L_{44}}$,[133] and $\mathbf{L_{45}}$[134] as steering ligands for Hayashi–Miyaura reaction, good to excellent yields and ee were achieved (Figure 8).

2.4.3. Bissulfoxide 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*-tolylsulfoxide) ligands $\mathbf{L_{46}}$[137] and $\mathbf{L_{47}}$[138] 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 $[RhCl((R)\text{-BINAP})]_2$, $[RhCl(\mathbf{L_{28a}})]_2$,[139] and $[RhCl(\mathbf{L_{46}})]_2$ suggested that the ligating nature of *bis*-sulfoxides might stay somewhere between that of diene and *bis*-arylphosphine ligands. Subsequently, a series of axially chiral bis(*tert*-butylsulfoxide) ligands $\mathbf{L_{49a}}$-$\mathbf{L_{51a}}$ and bis(*p*-tolyl-sulfoxide) ligands $\mathbf{L_{49b}}$-$\mathbf{L_{51b}}$ were synthesized, in which $\mathbf{L_{49b}}$-$\mathbf{L_{51b}}$ bearing *p*-tolylsulfinyl 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 $\mathbf{L_{48}}$ also afforded the corresponding RCAA products in excellent yields and enantioselectivities.[141]

An emerging class of chiral heterodisulfoxide ligands $\mathbf{L_{52}}$-$\mathbf{L_{56}}$ 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 $\mathbf{L_{48}}$ is still the most active and selective ligand in this subseries (Scheme 14).[141−143] The highly electron-poor chiral diphosphine ligand $\mathbf{L_{12c}}$ 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 $\mathbf{L_{57}}$ was applied in the RCAA to enones,[145] and exhibited

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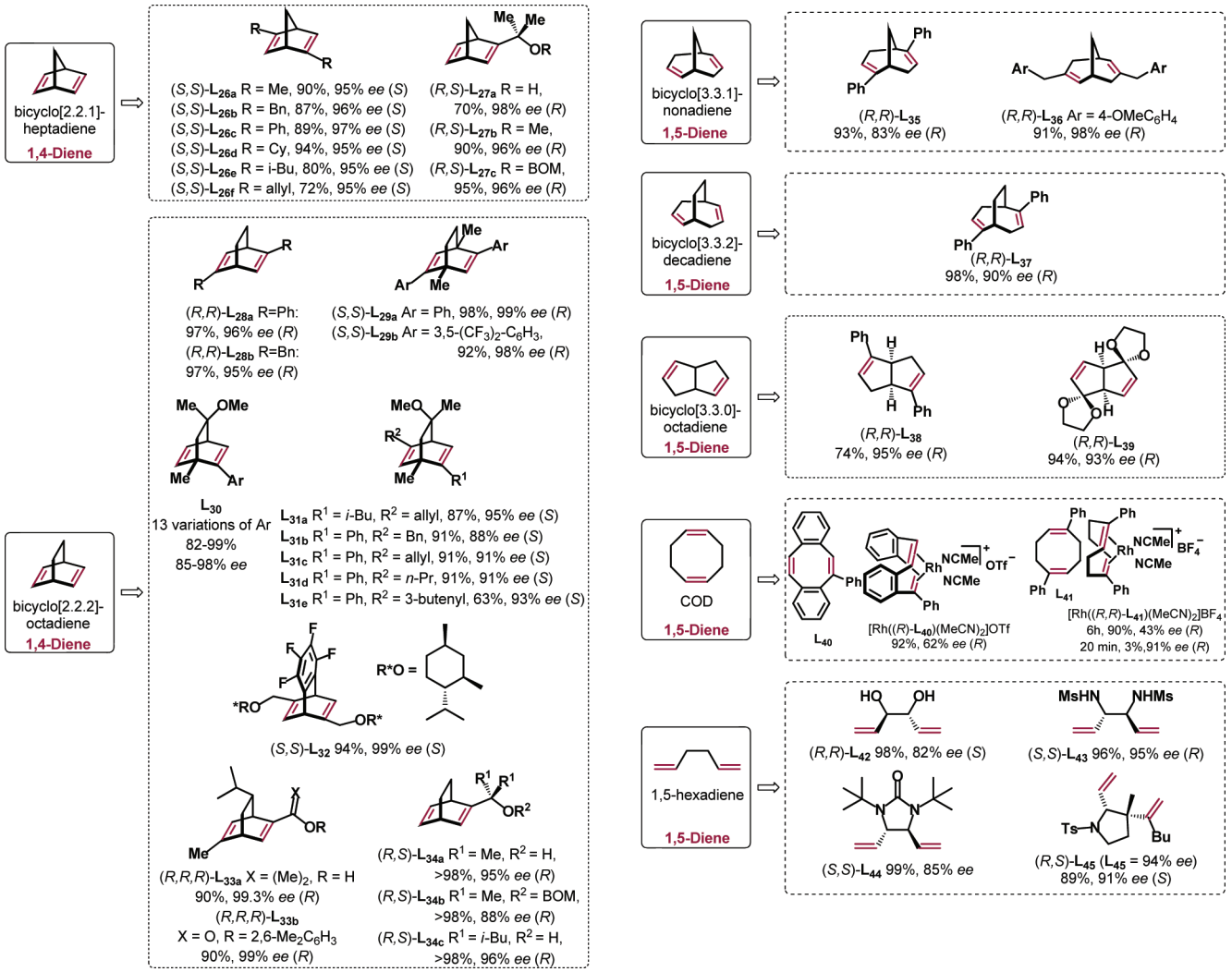


Figure 8. Chiral diene ligands.

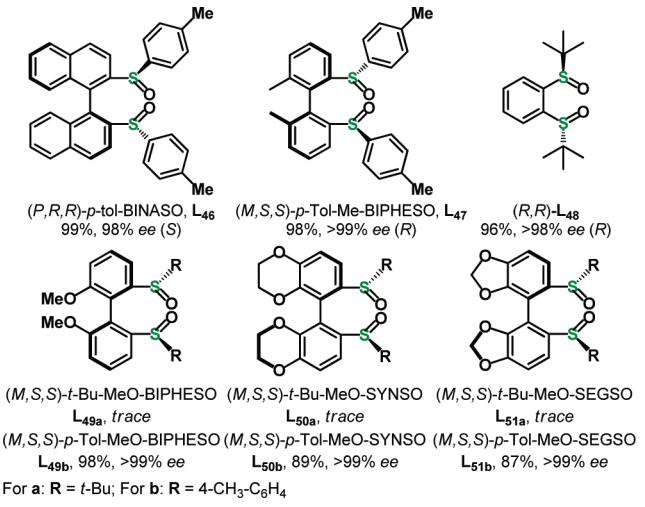
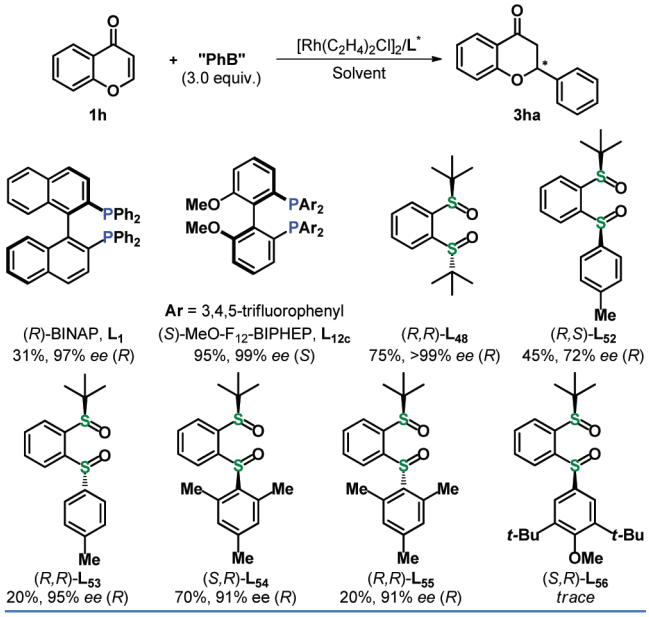


Figure 9. Chiral bis-sulfoxide ligands.

higher catalytic activity than a Rh/cod catalyst.[146] Subsequently, phosphine-olefin $\mathbf{L_{58}}$[147] and $\mathbf{L_{59}}$,[148] amidophosphine-olefin $\mathbf{L_{60}}$[111,149,150] and carbohydrate phosphine-olefin $\mathbf{L_{61}}$[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 $\mathbf{L_{62}}$[93] did not induce any enantioselectivity in RCAA, while the L-proline-derived

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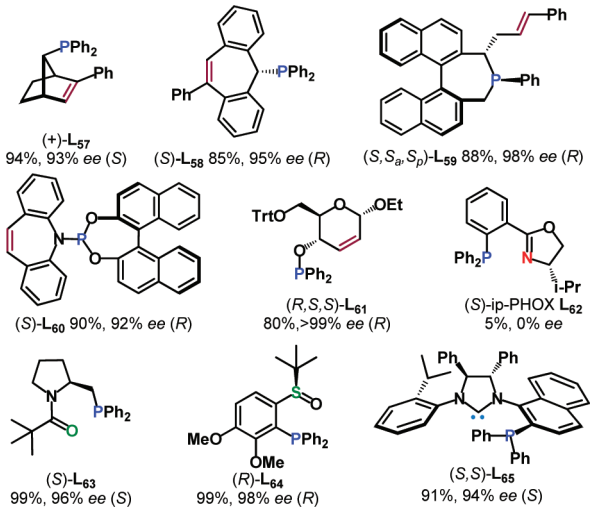

Figure 10. Phosphine-olefin, -nitrogen, -oxygen, -sulfur, or - NHC hybrid ligands.

phosphine-oxygen ligand $\mathbf{L}_{63}$[153−155] and phosphine-sulfoxide ligand $\mathbf{L}_{64}$[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 $\mathbf{L}_{65}$[158] 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 $\mathbf{L}_{66}$ 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 $\mathbf{L}_{67}$ and utilized it in Hayashi−Miyaura reaction (Figure 11).[160]

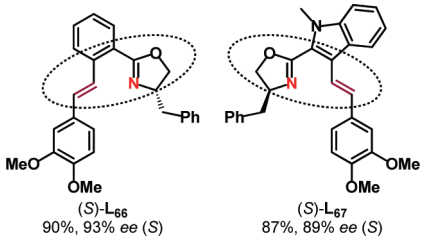

Figure 11. Oxazoline-olefin hybrid ligands.

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 $\mathbf{L}_{68}$ and $\mathbf{L}_{69}$, 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 $\mathbf{L}_{70}$[162,163] could induce reverse enantioselectivity by simply changing the substitutions at the olefin moiety ($\mathbf{L}_{70b}$ vs $\mathbf{L}_{70c}$ or $\mathbf{L}_{70d}$ vs $\mathbf{L}_{70e}$).

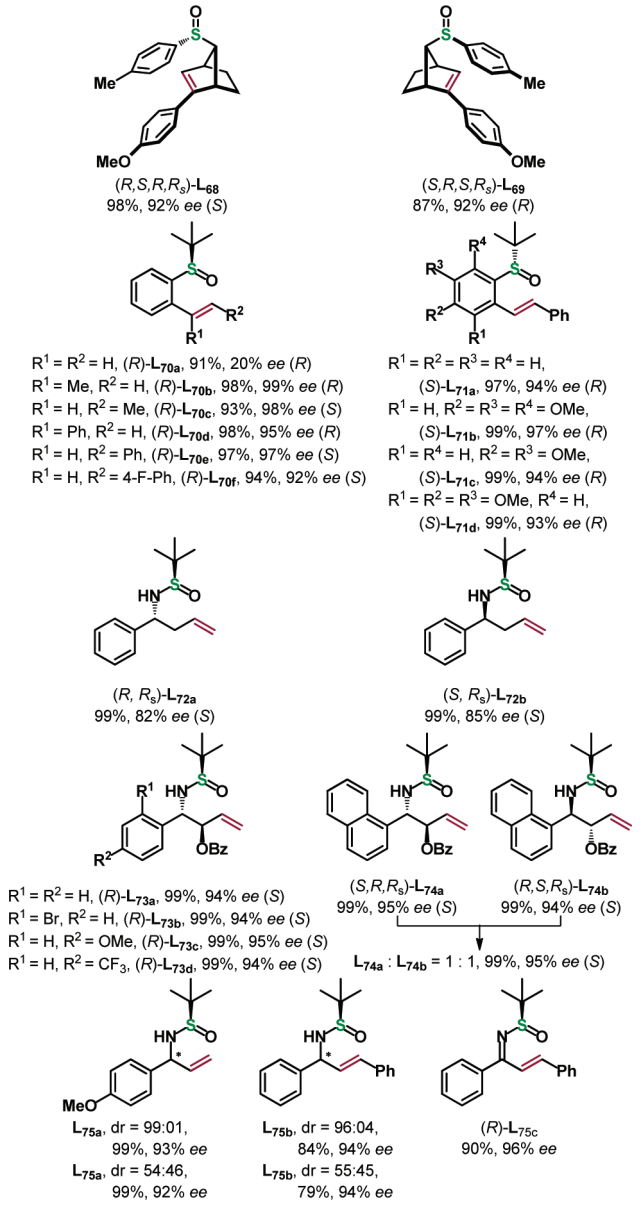

Figure 12. Sulfoxide-olefin hybrid ligands.

In other words, both enantiomers of the product can be synthesized by choosing different olefin-substituted (*R*)-$\mathbf{L}_{70}$. 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 $\mathbf{L}_{71}$ for the same reaction.[164] Afterward, they demonstrated that the simple and readily available chiral sulfinamide-olefins $\mathbf{L}_{72}$-$\mathbf{L}_{74}$[165] also displayed great catalytic activities and enantioselectivities in Hayashi−Miyaura reaction. It is noteworthy that the sulfur-stereogenic center ($\mathbf{L}_{74a}$ vs $\mathbf{L}_{74b}$) 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 $\mathbf{L}_{72}$-$\mathbf{L}_{74}$ 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

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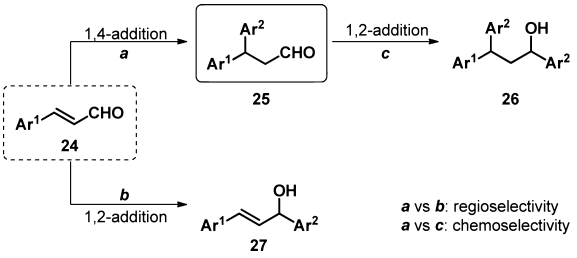
ligands ($\mathbf{L}_{75a}$ and $\mathbf{L}_{75b}$)[170] and their successful application in the same reaction. The carbon chiral center was also observed to have no impact on the enantioselectivity in RCAA. The ease of synthesis and needless consideration of the carbon chirality make this type of ligand 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

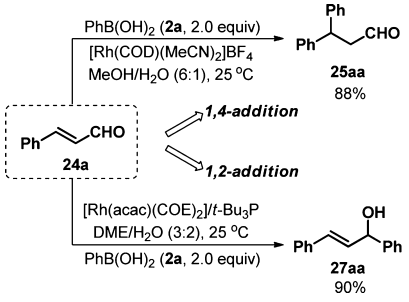
3.1. RCAA to α,β-Unsaturated Aldehydes. Rh-catalyzed conjugate addition to α,β-unsaturated aldehydes exhibited a special challenge because of the existence of a highly reactive aldehyde group, which can undergo 1,2-addition either in competition with 1,4-addition (path b vs path a) or further conversion 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 (**2a**) to cinnamaldehyde (**24a**), the t-Bu$_3$P complex yielded the 1,2-addition product **27aa** in 90% yield (Scheme 16), whereas the diene system afforded

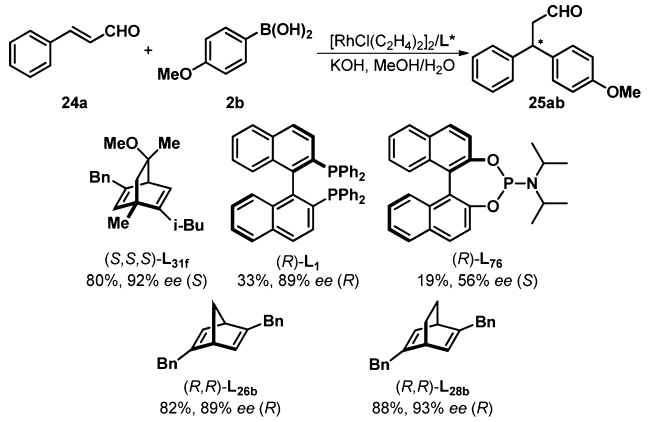
Scheme 16. Ligand Controlled 1,4- or 1,2-Addition Selectivity



1,4-addition product **25aa** 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 **25ab** 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

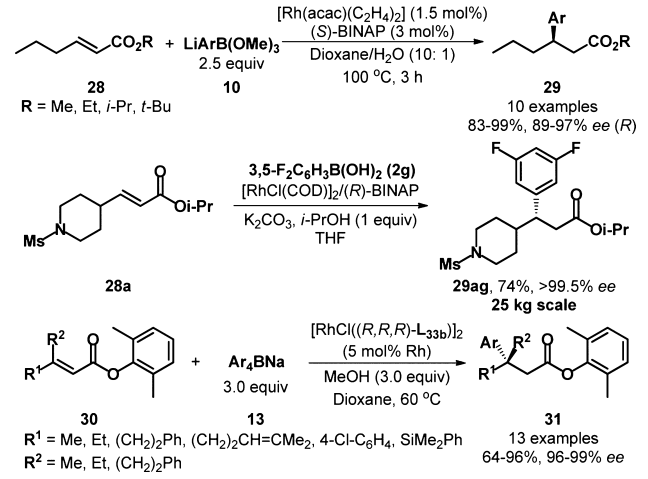
Scheme 17. RCAA to Cinnamaldehyde (24a)



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-diarylpropanals 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 (LiArB(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 **29ag** (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 ($\mathbf{L}_{31f}$) complex[175] or a cationic Rh(I)/chiraphos ($\mathbf{L}_{77}$) system[72] 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

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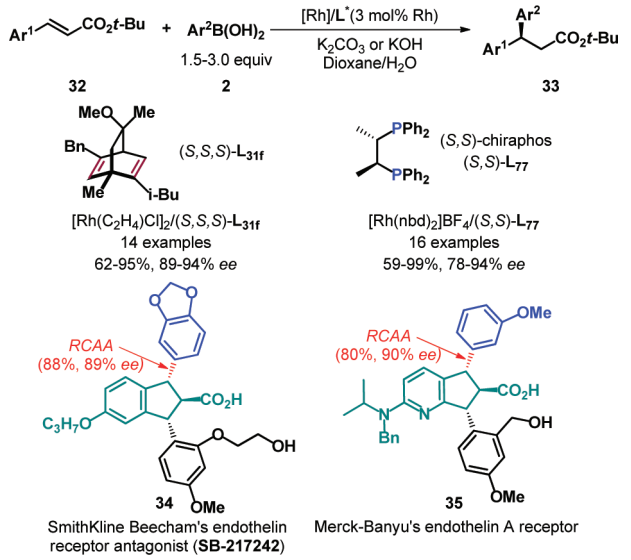
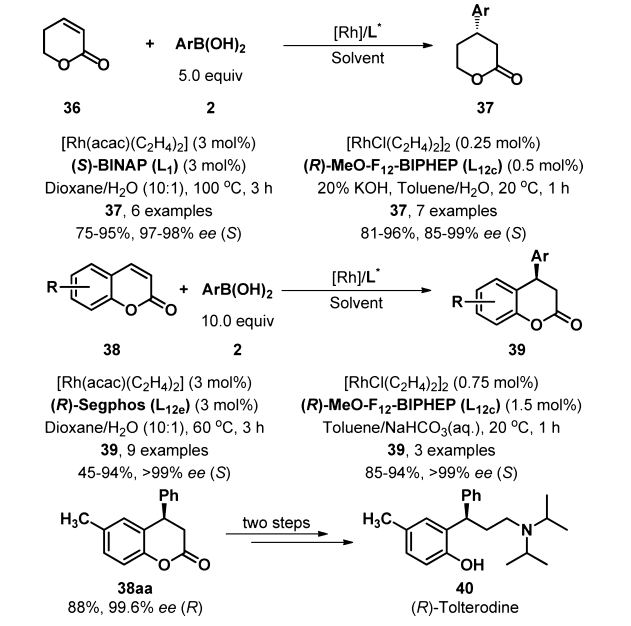
Scheme 19. RCAA to Linear Enoates Bearing β-Aryl Group



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

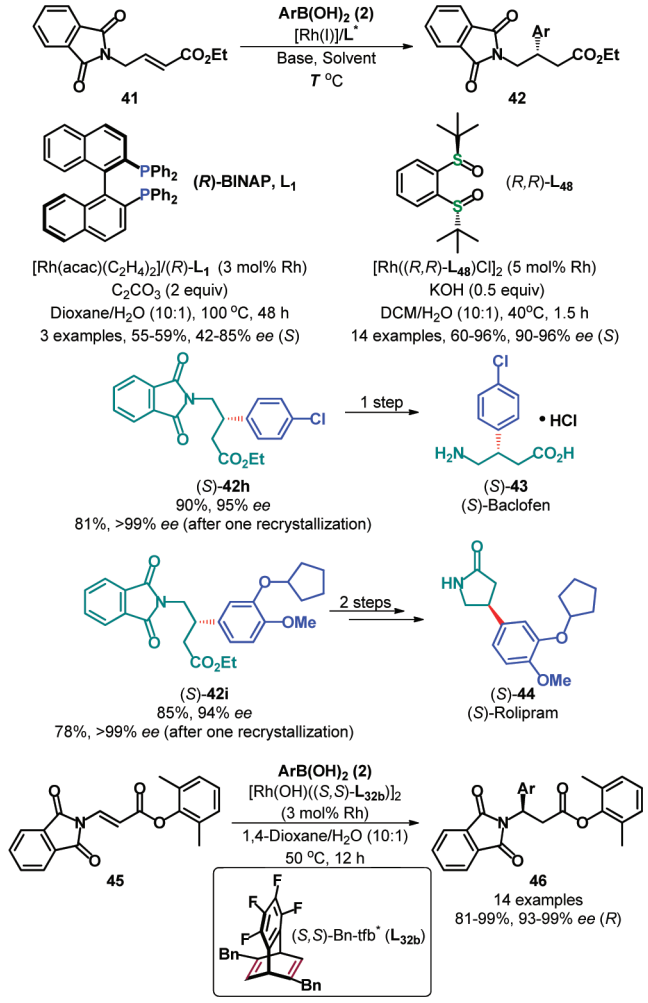
Rh(I)/(*S*)-BINAP system was highly efficient in the RCAA to cyclic enoates **36**[23,73] and Rh(I)/(*R*)-Segphos system presented excellent catalytic activity in the RCAA to coumarins **38**.[176] This conversion was subsequently extended to the asymmetric synthesis of (*R*)-tolterodine (**40**). Because of its strong π-accepting ability, the electron-deficient ligand $\mathbf{L_{12c}}$[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 ($\mathbf{L_1}$)[177,178] and bis-sulfoxide ligand $\mathbf{L_{48}}$[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 ($\mathbf{L_{32b}}$) 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 bicyclopyrrolizidinones **48**.[180] Chiral diene ligand (*S,S,S*)-$\mathbf{L_{31f}}$ enhanced the diastereoselectivity in the formation of (*S,R*)-**48**, while its enantiomeric ligand (*R,R,R*)-$\mathbf{L_{31f}}$ 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 isaindigotidione **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 $\mathbf{L_1}$ and phosphoramidite ligand $\mathbf{L_{76b}}$ gave poor yield and enantioselectivity for this transformation, while the bulky chiral diene ligand $\mathbf{L_{26g}}$ could improve the process, affording the desired product **52** in 90% yield and 90% ee (Scheme 23).[182]

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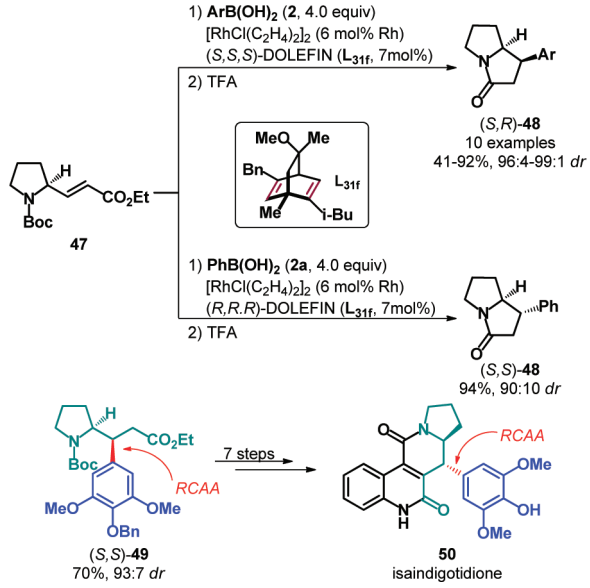
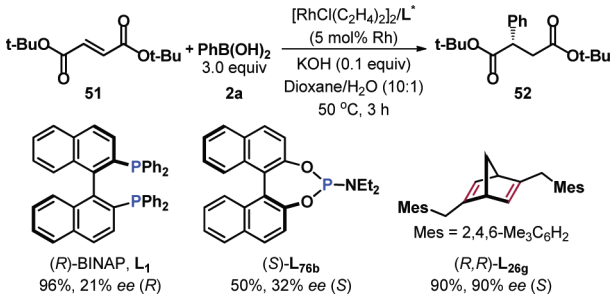
Scheme 22. Diastereoselective RCAA



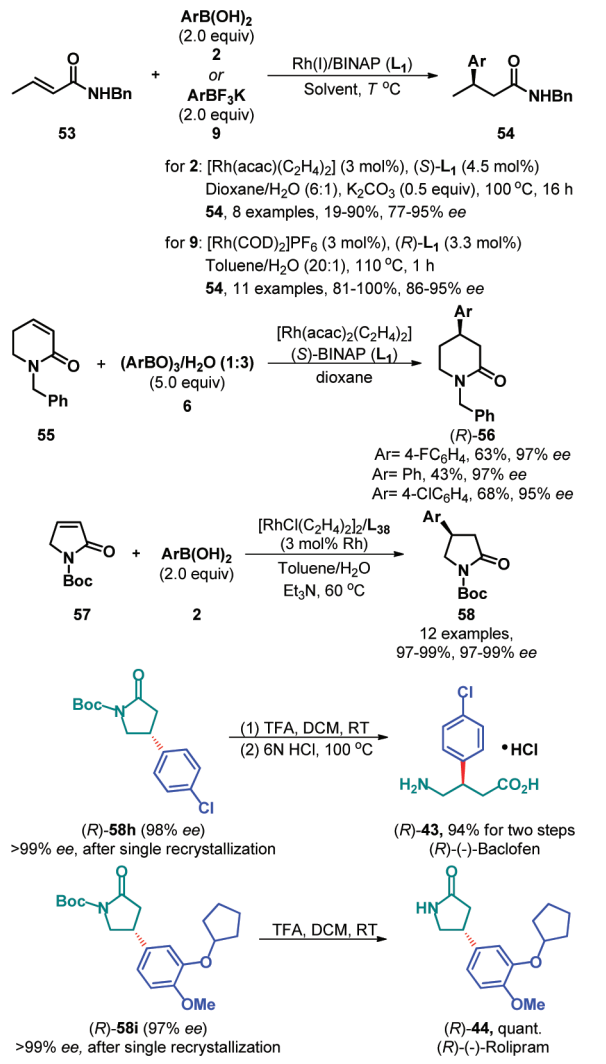
Scheme 23. RCAA of Phenylboronic Acid to Fumarate



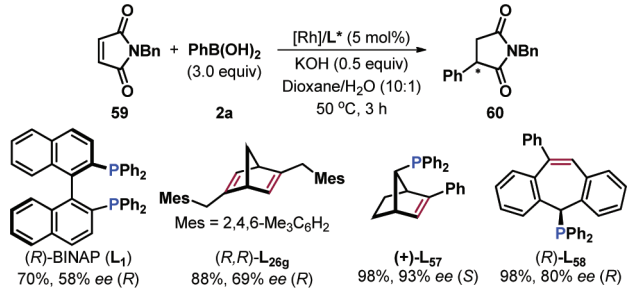
3.3. RCAA to α,β-Unsaturated Amides. RCAA of linear α,β-unsaturated amide **53** with arylboronic acids performed similarly well despite its weaker reactivity than enones or enoates.[64] Replacing $ArB(OH)_2$ with $ArBF_3K$ (**9**) as the arylboronic source could significantly increase the overall reaction 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 Amides



Scheme 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.

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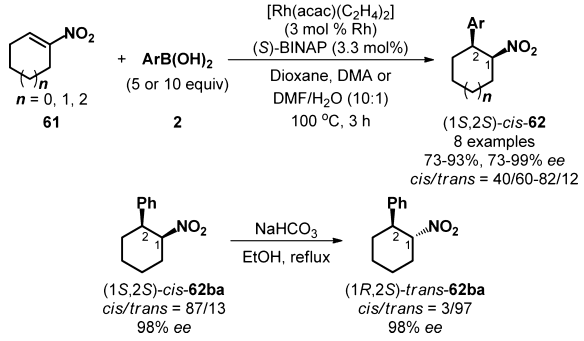
3.4. RCAA to Nitroalkenes. Hayashi and co-workers initially demonstrated that cyclic nitroalkenes **61** were good substrates for the RCAA reaction, affording thermodynamically less stable *cis*-*β*-aryl substituted cyclic nitroalkanes **62** with excellent enantioselectivities (Scheme 26).[187] It is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

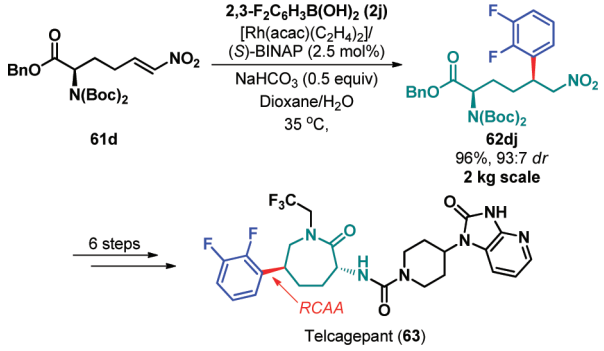
Scheme 26. RCAA to Cyclic Nitroalkenes



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

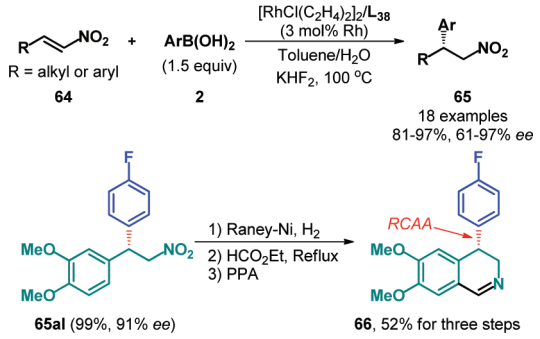


difluorophenylboronic acid (**2j**) to nitroalkene **61d** provided the key chiral intermediate nitroalkane **62dj**, which was further converted to telcagepant on a 2 kg scale. Bicarbonate was shown to be an effective activator in the RCAA reaction.

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).

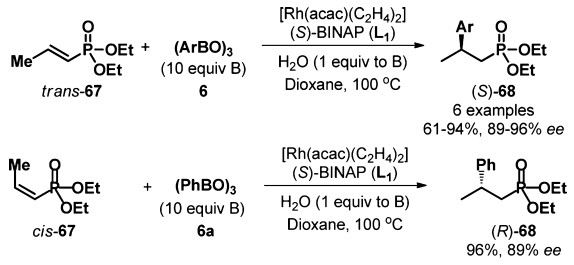
3.5. RCAA to *α,β*-Unsaturated Phosphonates. The RCAA to alkenylphosphonates was first reported by Hayashi and co-workers.[190] Although alkenylphosphonates are usually less reactive than *α,β*-unsaturated carbonyl compounds, the RCAA reaction proceeded smoothly by using Rh(I)/(*S*)-BINAP catalytic system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

Scheme 28. RCAA to Linear Nitroalkenes



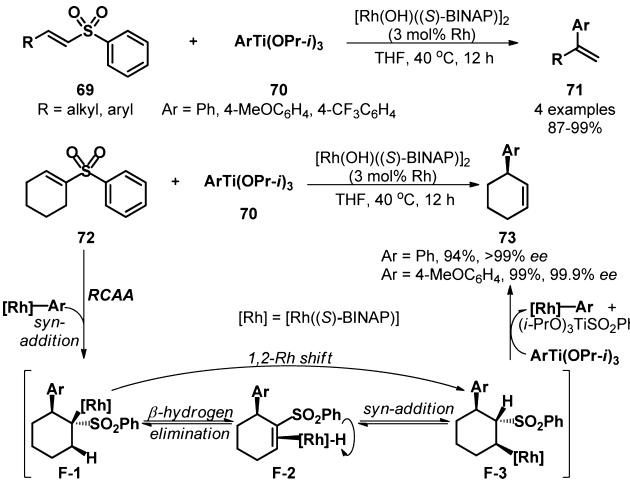
species) was required to achieve high yields. Consistent with the previous stereochemical model (cf. Scheme 7), the trans and cis geometries of alkenylphosphonate **67** afforded opposite enantiomers (*S*)-**68** and (*R*)-**68**, respectively (Scheme 29).

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 triphenylcyclotriboroxane [$(PhBO)_3$, **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**

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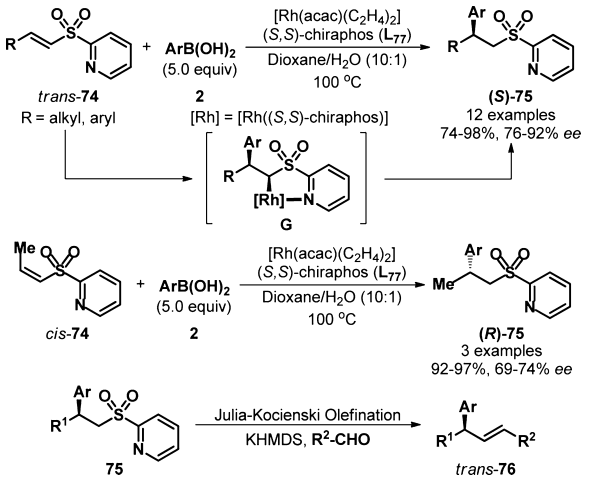
was successfully achieved by using (*S*,*S*)-chiraphos ($\mathbf{L_{77}}$) as the chiral ligand, providing β-substituted sulfones in high yields and enantioselectivities (Scheme 31).[191−193] The *trans*- and

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



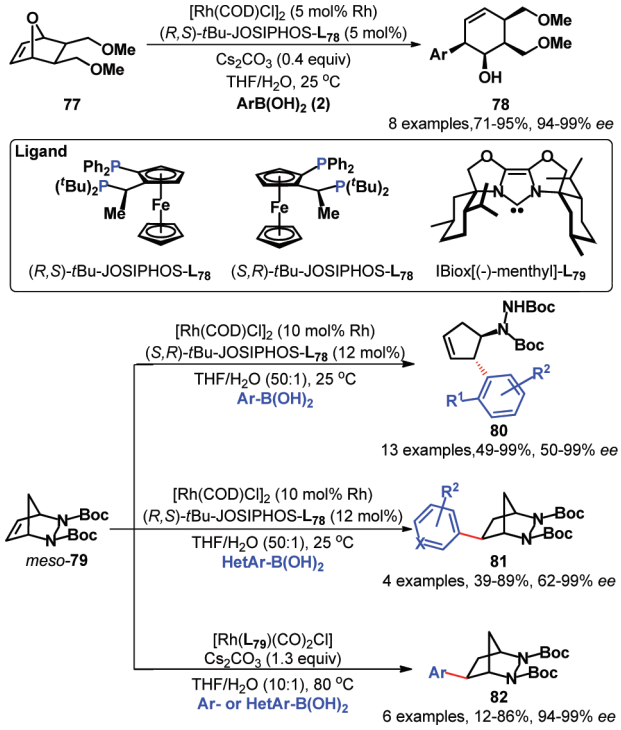
cis-alkenylsulfones produced the opposite enantiomers (*S*)-**75** and (*R*)-**75** in RCAA reaction. The elimination of the sulfonyl group via Julia-Kociensky olefination[194] provides a novel approach to the enantioselective synthesis of allylic substituted *trans*-alkenes **76**.

3.7. RCAA to Strained or Weakly-Activated Alkenes.

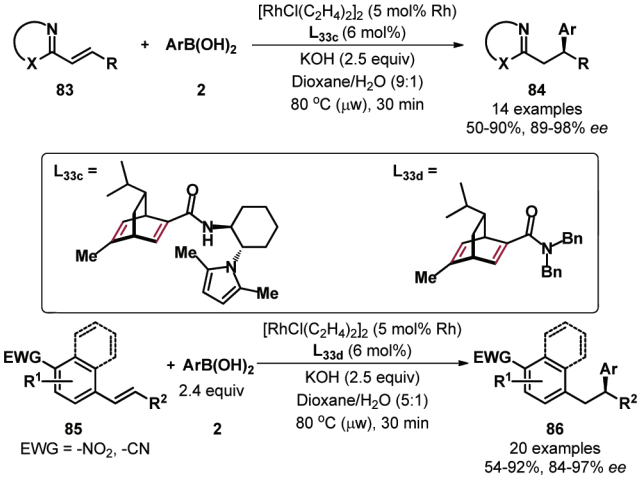
Rhodium-catalyzed arylation of aryl boronic acids to a variety of strained oxabenzonorbornadienes has been demonstrated by Murakami and co-workers,[195] with the insertion of a strained alkene into a rhodium-aryl bond as a key step.[196] The best results were obtained with a catalyst prepared by mixing $[Rh(COD)Cl]_2$ with 2 equiv of $P(OEt)_3$. Lautens and co-workers subsequently presented an asymmetric version of this RCAA reaction, which gave excellent enantio- and diastereoselectivities by using the $[Rh(COD)Cl]_2$/(*R*,*S*)-*t*Bu-JOSIPHOS-$\mathbf{L_{78}}$ 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**.[198,199] Recently, Lautens and co-workers demonstrated that Rh complex incorporating IBiox[(−)-menthyl] ($\mathbf{L_{79}}$) as the ligand showed impressive selectivity, only allowing the hydroarylation of azabicycle 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 ($\mathbf{L_{31f}}$) 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($\mathbf{L_{12e}}$) and (*R*)-DTBM-Segphos($\mathbf{L_{12j}}$). 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).

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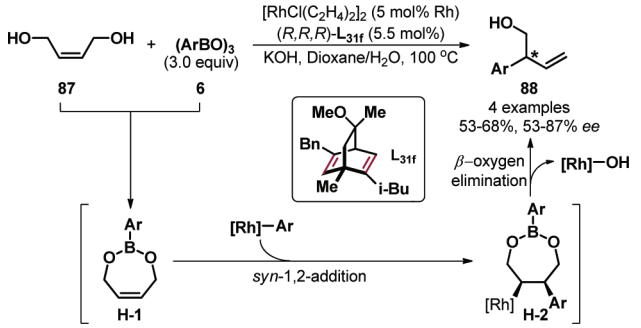
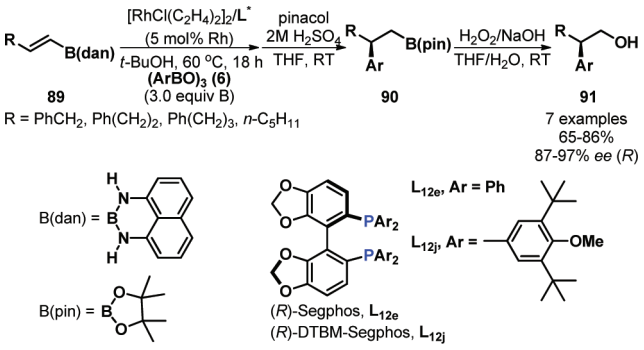
Scheme 34. RCAA to *cis*-2-Butene-1,4-diol (87)

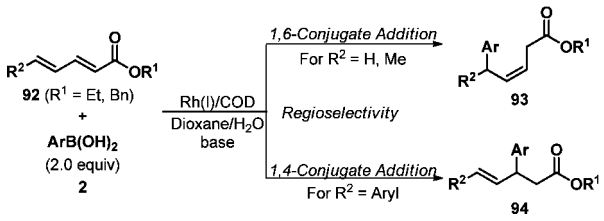


Scheme 35. RCAA to Borylalkenes



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 dienoates **92** (R^2 = H or Me),

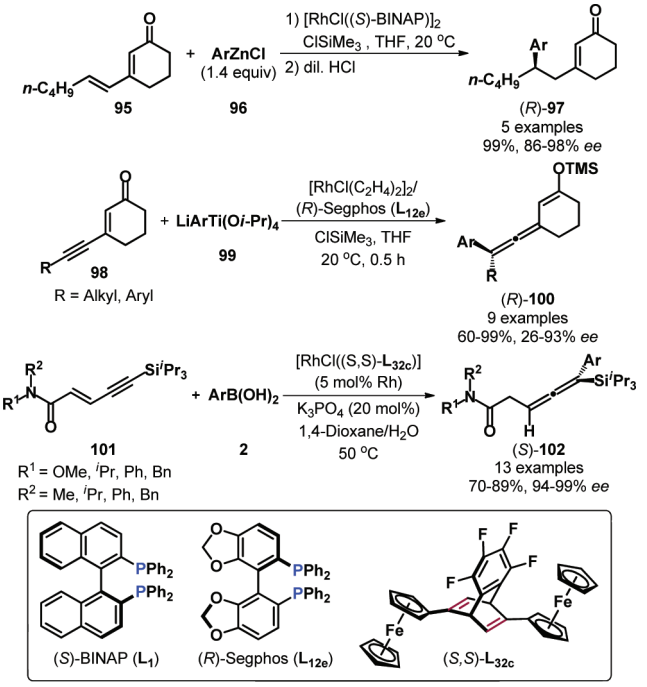
Scheme 36. Rh-Catalyzed 1,6-Addition or 1,4-Addition of Arylboronic Acids to 2,4-Dienoate Esters



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 dienoates 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 alkynylenones **98** also proceeded by using Rh(I)/(*R*)-Segphos ($\mathbf{L_{12e}}$) 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)-$\mathbf{L_{32c}}$) complex, producing axially chiral allenylsilanes **102** with high enantioselectivities.[206]

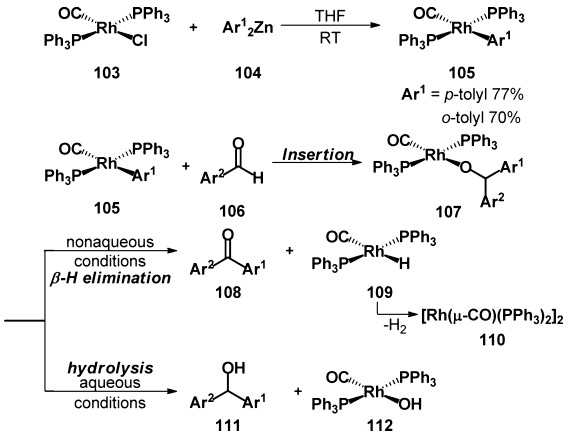
Scheme 37. Rh-Catalyzed Asymmetric 1,6-Addition onto $\alpha,\beta-\gamma,\delta$-Diunsaturated Carbonyl Compounds



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 Diarylketones 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 $(PPh_3)_2Rh(CO)Cl$ 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

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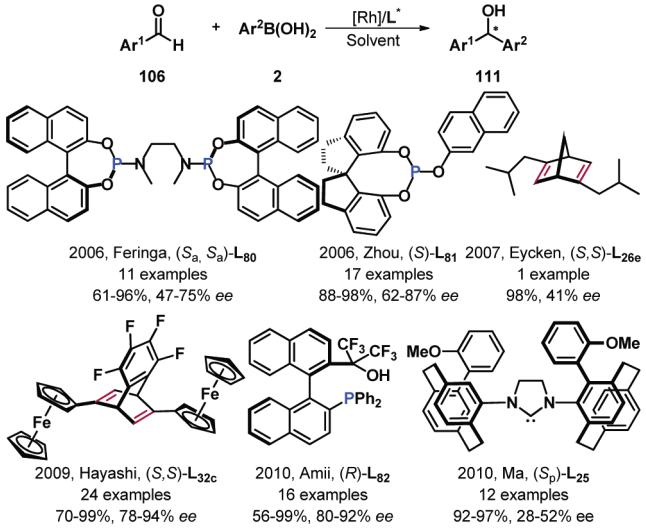
bond, generating rhodium-alkoxide **107**. Under nonaqueous (C_6D_6) condition, the reaction went through β-elimination to produce the diarylketone **108** and release a new rhodium-hydride complex **109**. This [Rh−H] complex was not very stable and subsequently decomposed under the reaction conditions to liberate hydrogen and form $[Rh(\mu\text{-}CO)(PPh_3)_2]_2$ (**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 $\mathbf{L_{80}}$ 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]

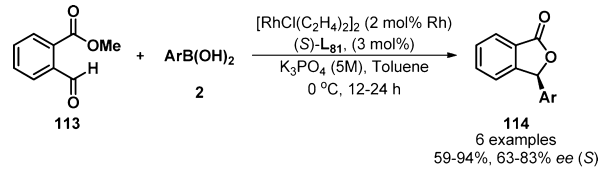
Scheme 39. RCAA to Aromatic Aldehydes



Chiral spiro-phosphite ligand $\mathbf{L_{81}}$ 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 $[RhCl((S,S)\text{-}\mathbf{L_{26e}})]_2$-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 $(R)\text{-}\mathbf{L_{82}}$[212] bearing a di(trifluoromethyl)alcohol moiety and chiral NHC-ligand $(S_p)\text{-}\mathbf{L_{25}}$[213] demonstrated excellent catalytic activity for asymmetric 1,2-addition of arylboronic acids to aldehydes. Remarkably, the fluoroalcohol moiety in $(R)\text{-}\mathbf{L_{82}}$ played a pivotal role for the high enantioselectivity in Rh(I)-catalyzed transformation. However, only moderate enantioselectivity was observed in RCAA when using $(S_p)\text{-}\mathbf{L_{25}}$ (with 0.03−0.3 mol % loading) as the ligand.

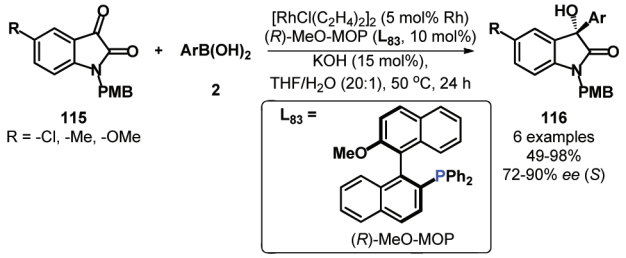
The chiral alcohol generated in RCAA can further react in situ with other functional groups in the molecule. As shown in Scheme 40, Hu and co-workers applied methyl 2-formylbenzoate (**113**) in the RCAA with various arylboronic acids; a series of chiral 3-substituted phthalides **114** (with up to 83% ee) were conveniently synthesized by using Rh(I)/SPINOL-based phosphite ($\mathbf{L_{81}}$) 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

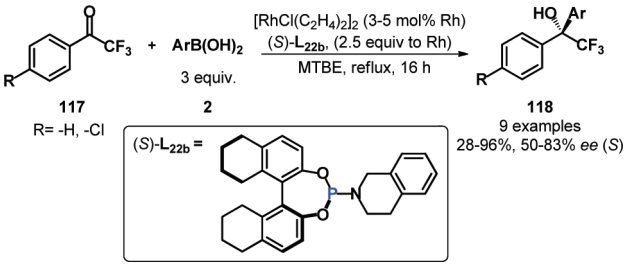
Scheme 41. RCAA to Isatins



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 ($\mathbf{L_{83}}$) 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 $(S)\text{-}\mathbf{L_{81b}}$ 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 alkenyl 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

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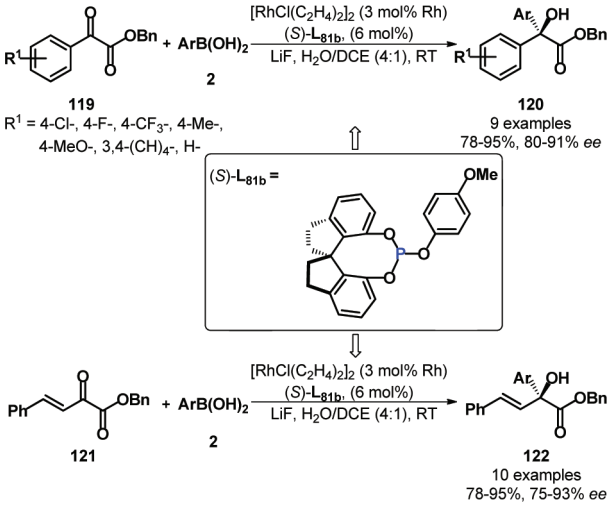
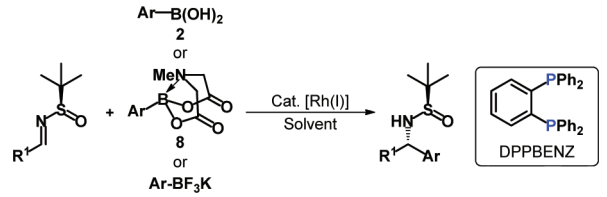
Scheme 43. RCAA to α-Ketoesters



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



2005, Ellman, Rh(acac)(COE)$_2$ (5 mol%)/DPPBENZ (5.5 mol%); **ArB(OH)$_2$ (2)**, 9 examples, 71-96%, 92%-98% de.

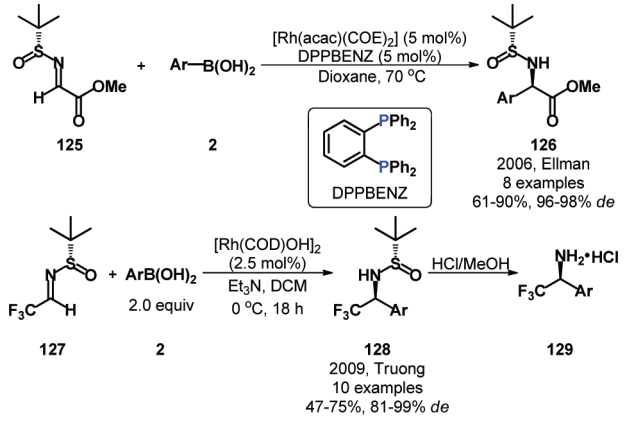
2005, Batey, [Rh(COD)(CH$_3$CN)$_2$]BF$_4$ (5 mol%); **ArB(OH)$_2$ (2)**, 15 examples, 44-99%, 83%-98% de.

2010, Ellman, [Rh(OH)(COD)]$_2$ (2.5 mol%)/DPPBENZ (5.0 mol%); **ArBMIDA (8)**, 2 examples, 89-97%, 96% *de*. **ArBF$_3$K (9)**, 2 examples, 50-84%, 88%-92% *de*.

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]

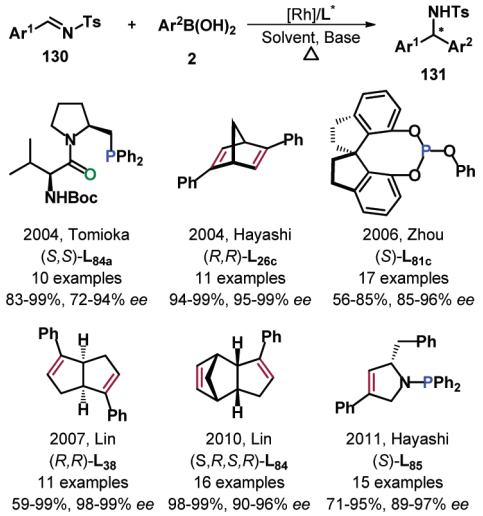
N-Sulfinyl imino esters **125** stand out as stable, isolable compounds that can even be chromatographed on SiO$_2$, and thus can serve as excellent starting materials for arylglycine synthesis.[222−224] In 2006, Ellman and co-workers applied them in RCAA of arylboronic acids to give a variety of *N*-*tert*-butanesulfinamido 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 spirophosphite (*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

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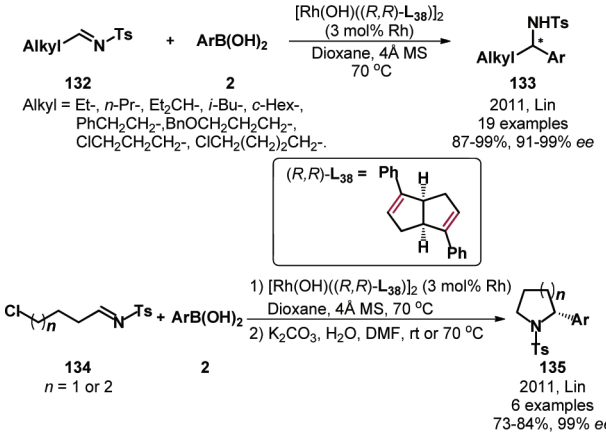
narrow range of excellent enantioselectivities (98−99% ee). The electronic and steric nature of phenyl ring at either imines or arylboronic acids apparently had no influence on the enantioselectivity. Furthermore, tosylimines derived from heteroaryl aldehydes such as furanyl, thiophenyl, and indolyl 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*-diarylmethyl 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 $\mathbf{L_{85}}$, 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 $\mathbf{L_{38}}$ proved to be the superior ligand for this transformation, providing the desired products **133** in exceptionally high enantioselectivity (typically ≥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

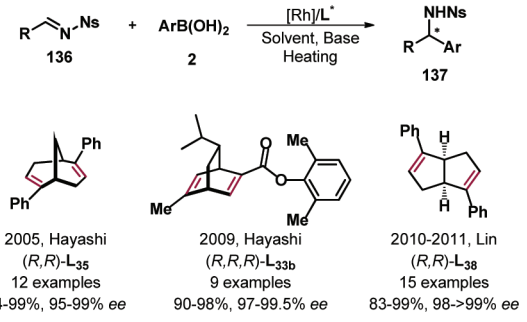


reaction is the difficulty in removing the tosyl group from nitrogen of the products **133** and **135**. It has been reported that the use of 4-nitrobenzenesulfonyl (Ns) group[234−236] in place of tosyl group will facilitate the deprotection reaction.

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

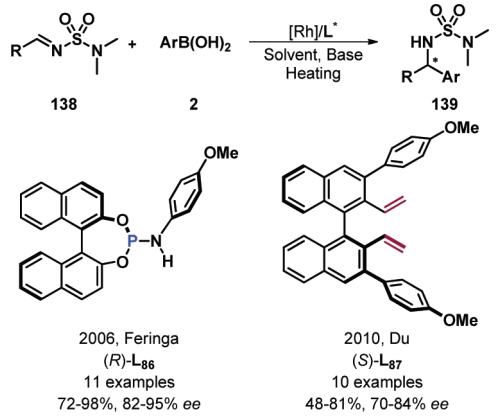
Feringa and co-workers introduced a small and cheap *N*,*N*-dimethylsulfamoyl protecting group into the catalytic asymmetric synthesis of diarylmethylamines by RCAA reaction. The addition of **138** with aryl boronic acids afforded high

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



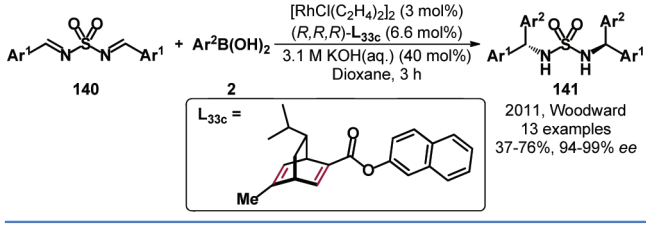
enantioselectivities (up to 95% ee) and high yields (up to 98%) by using a Rh(I)/phosphoramidite system.[237] The protecting group could be easily removed by microwave-assisted transamination, representing a versatile and selective transformation to prepare chiral diarylmethylamines. Later on, Du and 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 tetraarylborates or aryl trifluoroborates as boron reagents. By employing chiral diene (*R*,*R*)-$\mathbf{L_{28c}}$ as the ligand,

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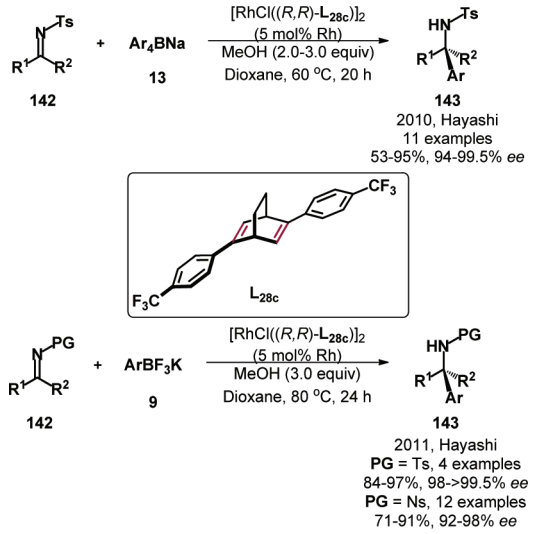
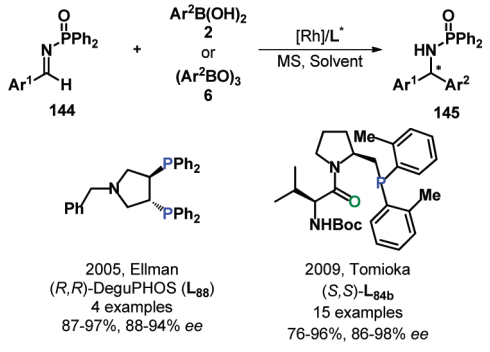
the reaction produced various chiral amine derivatives **143** possessing a tetrasubstituted carbon stereocenter in high yields and enantioselectivities (Scheme 51).[240,241]

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 $\mathbf{L}_{88}$.[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 $\mathbf{L}_{84b}$.[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).

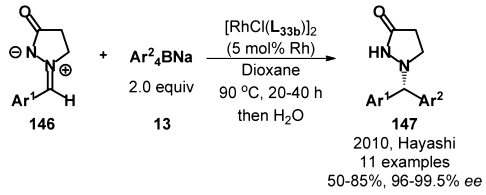
Scheme 52. RCAA to *N*-Diphenylphosphinoyl Aldimines



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*)-$\mathbf{L}_{33b}$ as the ligand, the reaction generated a series of chiral 1-(diarylmethyl)-pyrazolidin-3-ones **147** in excellent yields and high enantioselectivities (Scheme 53).[244]

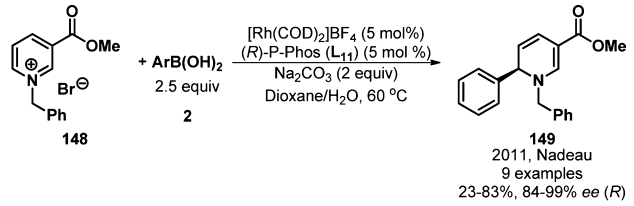
Very recently, Nadeau and co-workers developed the first RCAA of arylboronic acids to *N*-benzylnicotinate salts **148**.

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 $[Rh(OH)((S)\text{-BINAP})]_2$ as the chiral catalyst, the asymmetric version of the above reaction from *tert*-butyl vinyl ketone (**150a**), (4−F-C_6H_4)-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 $[Rh(OH)((S)\text{-BINAP})]_2$ 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 $[Rh(OMe)((S)\text{-BINAP})]_2$ in tandem RCAA/aldol reaction. Cyclic α,β-unsaturated ketones could

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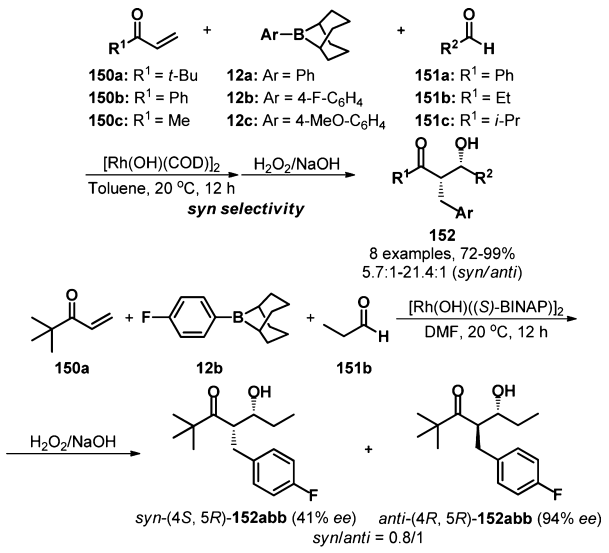
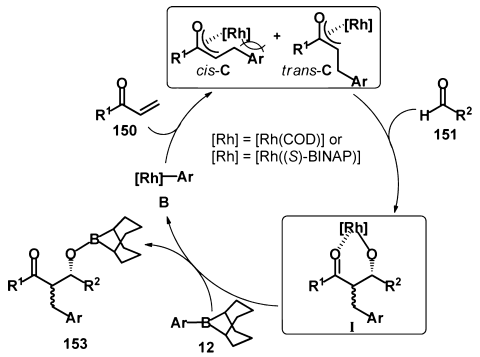
Scheme 55. Three-Component Tandem RCAA/Aldol Reaction

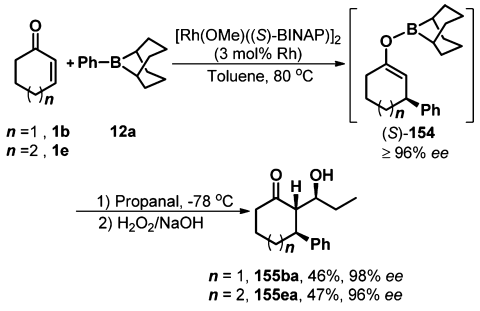


Scheme 56. Tandem RCAA/Aldol Reaction by $[Rh(OMe)(COD)]_2$ or $[Rh(OH)((S)\text{-BINAP})]_2$



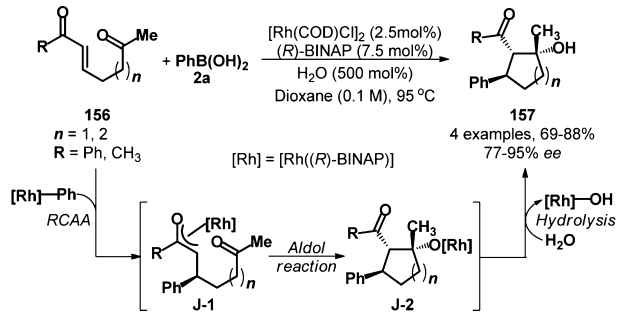
generate chiral boron enolates (*S*)-**154** in ≥96% ee, which successfully underwent further aldol reaction to give **155ba** and **155ea** with perfect regio- and diastereoselectivities (Scheme 57).[39]

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



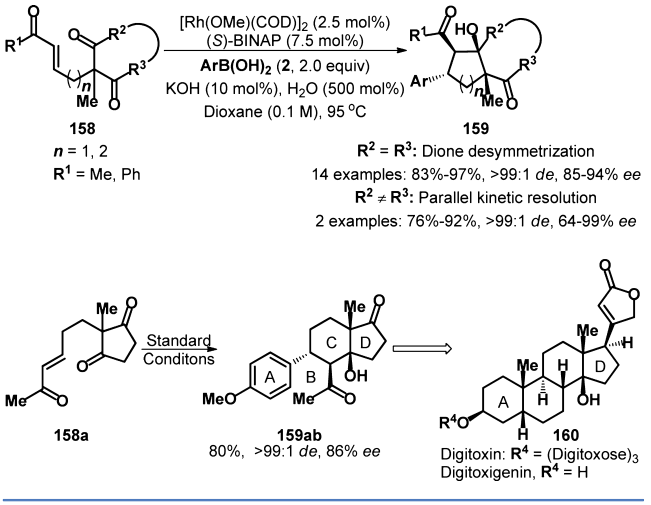
In 2003, Krische and co-workers reported an intramolecular tandem RCAA/aldol reaction with high diastereo- and enantioselectivities.[251] The RCAA of phenylboronic acid **2a** to a monoketoenone **156** generated an (oxa-π-allyl)rhodium species **J-1**, which subsequently attacked the ketone acceptor 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 bicycle 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 °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]

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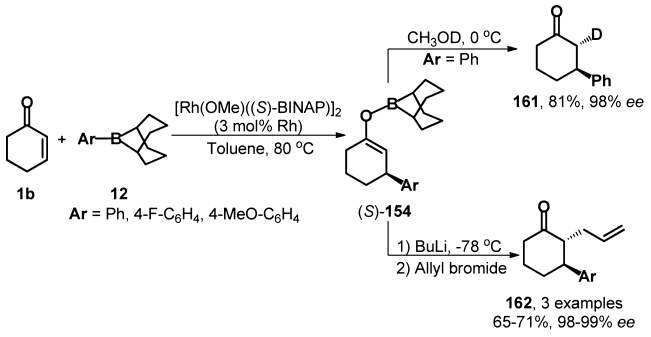
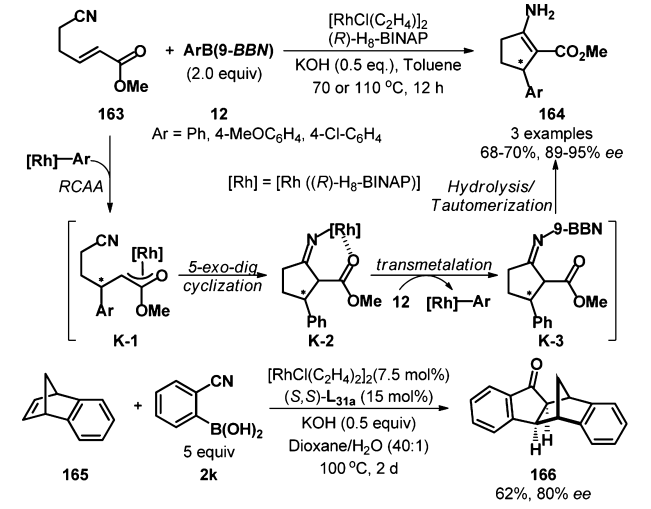
Scheme 60. Tandem RCAA/Alkylation Reaction



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 ArB(9-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)

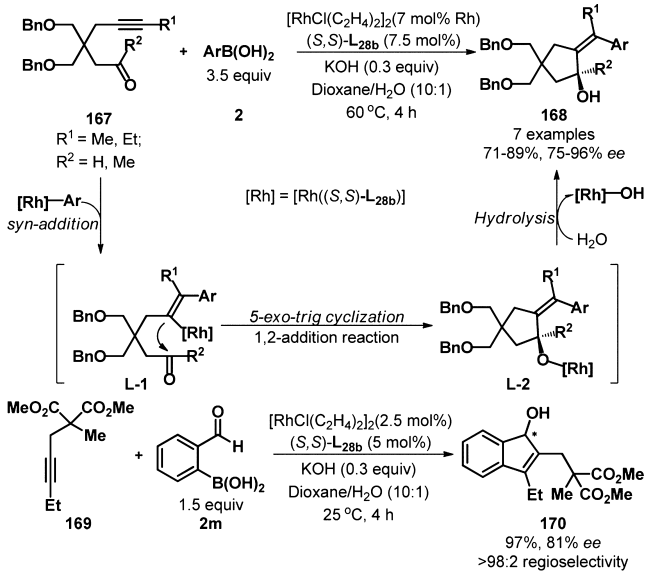
Scheme 61. Tandem RCAA/1,2 Addition onto a Cyano Group



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 ArB(9-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/$\mathbf{L_{31a}}$ 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*)-$\mathbf{L_{28b}}$ catalyst (Scheme 62).[255] A related reaction between bifunctional (2-formylphenyl)boronic acid **2m** and alkyne **169**

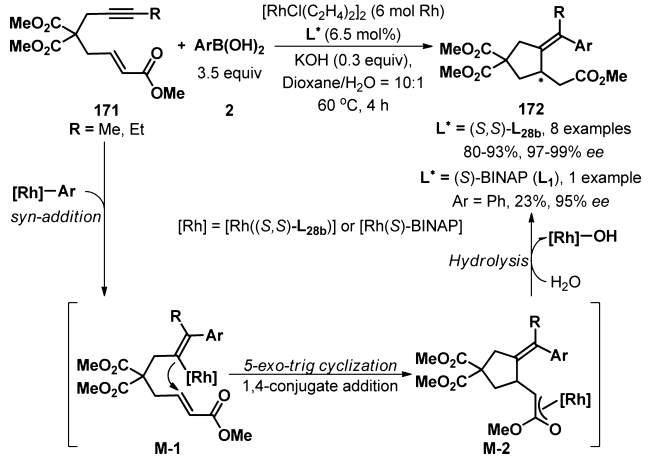
Scheme 62. Tandem RCA/1,2-Addition to an Aldehyde Group



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*)-$\mathbf{L_{28b}}$ (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**,

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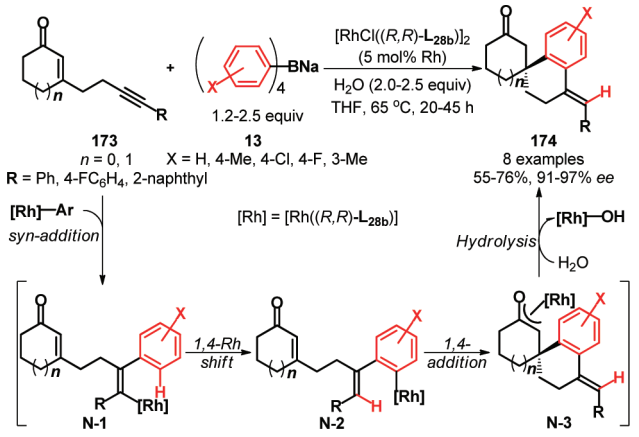
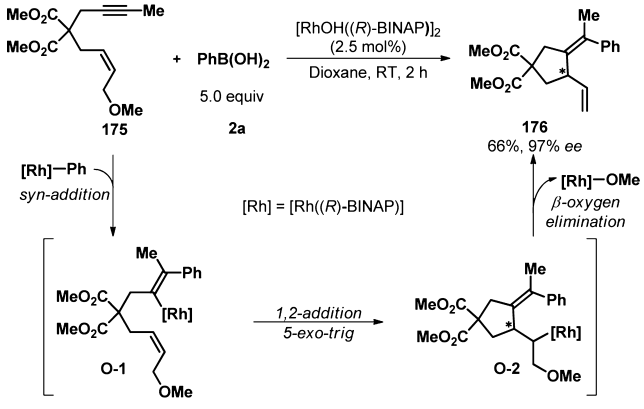
affording spirocarbocycles **174** with quaternary spirocarbon stereocenters in excellent enantiomeric purity.[258] The aryl-rhodium species went through 1,2-syn insertion of the alkyne group in **173**, giving an alkenylrhodium intermediate **N-1**. An interesting 1,4-Rh migration occurred to generate 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

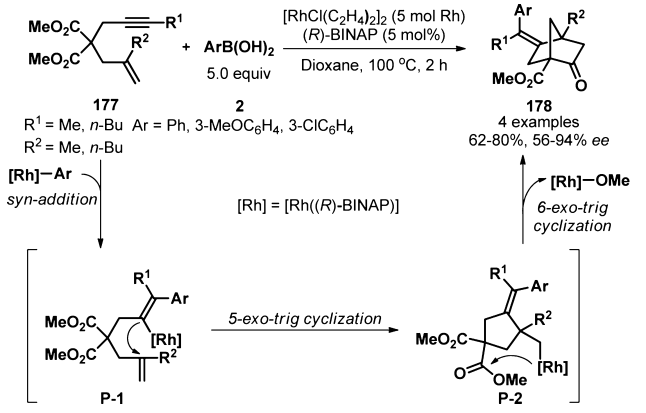
Scheme 65. Rh-Catalyzed Arylative Cyclization of 1,6-Enyne-Tethered Allylic Ether



involved 1,2-syn addition to the triple bond, 5-exotrig 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 R^2. Instead, the intermediate **P-2** further reacted with an electrophilic ester group in the molecule, through a 5-exotrig 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.

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