1
Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions

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1.1
Introduction

Since the seminal report by Uemura [1] in 1995 for palladium, and by Miyaura in 1997 for rhodium [2], the late transition metal-catalyzed conjugate addition of organoboron reagents to activated alkenes has emerged as one of the most functional group-tolerant and reliable carbon–carbon bond-forming processes. The maturity of this methodology is such that it has become an ideal testing ground for new ligand concepts and design, as will be illustrated throughout this chapter. A true statement to the robustness of this process is the application of Rh-catalyzed enantioselective conjugate addition (ECA) on a kilogram-scale for the manufacture of advanced pharmaceutical ingredients, and its use as a key step in the synthesis of complex natural products [3–5].

In this chapter, an overview will be provided – spanning from 2003 to mid-2009 – of the developments in the field of rhodium- and palladium-catalyzed ECA of organometallic reagents (B, Si, Zn, and Ti) to activated alkenes. The chapter is not intended to be comprehensive, and will include only selected examples of this powerful methodology. For more in-depth and comprehensive accounts, the reader should consult a number of excellent reviews that are available on this subject [6–16].

1.2
Rh-Catalyzed ECA of Organoboron Reagents

This section will include details of the state of the art for the rhodium-catalyzed ECA of organoboron reagents to activated olefins. Special emphasis will be placed on α,β-unsaturated ketones, as this substrate class has attracted the most attention and undergone thorough investigation with a plethora of different ligand systems. Many of the findings described for α,β-unsaturated ketones are also applicable to other olefin classes and other nucleophilic organometallic reagents, unless otherwise specified.

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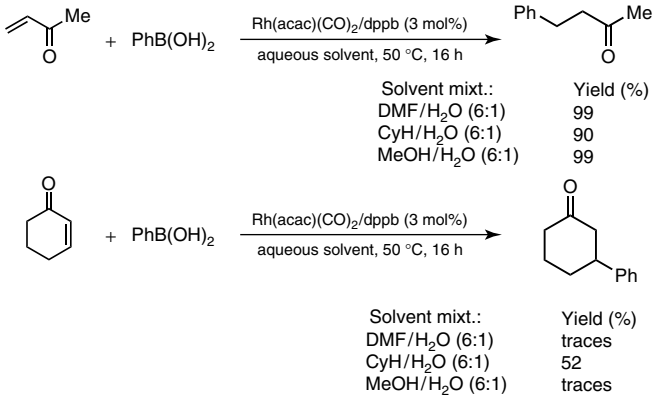


Scheme 1.1 Seminal report of Rh-catalyzed conjugate addition of organoboronic acids.

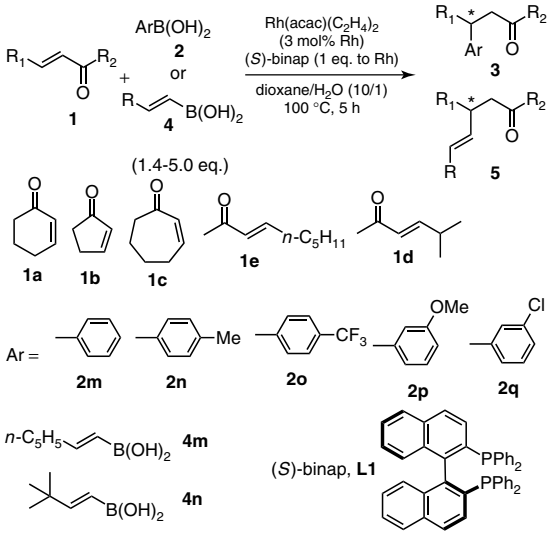
1.2.1
α,β-Unsaturated Ketones

1.2.1.1 A Short History

The first example of conjugate addition of an arylboronic acid to an enone catalyzed by transition metal complexes can be traced back to a report from 1995 by Uemura and coworkers [1]. This reaction was carried out ligand-less and with a high catalyst loading (10 mol%). The interest in this reaction remained limited until 1997, when Miyaura reported that the [Rh(acac)$(CO)_2$]/dppb (acac = acetylacetonato; dppb = 1,4-bis(diphenylphosphino)butane) system would efficiently catalyze the conjugate addition of a wide range of aryl- and alkenylboronic acids to methyl vinyl ketone (MVK) in high yields, and also to β-substituted enones including 2-cyclohexenone, albeit in lower yields (Scheme 1.1) [2].

The hallmarks of this reaction are: (i) no competitive uncatalyzed reaction of the organoboronic acids onto the enone; (ii) no 1,2-addition of the organoboron reagent; and (iii) a large functional group tolerance which is in contrast to organolithium and Grignard reagents.

A real breakthrough in this methodology came in 1998, when Hayashi and Miyaura described the first example of a rhodium-catalyzed ECA [17]. For the first time, a wide range of aryl and alkenyl fragments could be added in high yields and with exquisite enantioselectivity to an α,β-unsaturated ketone using (*S*)-binap ((*S*)-**L1**) as the chiral diphosphine ligand (Scheme 1.2) [17]. Since this initial report, great progress has also been made in the copper-catalyzed ECA using Grignard and organozinc reagents (this subject is treated in detail in Chapter 3) [18–21]. In order to achieve such high enantioselectivities in the Rh-catalyzed ECA, several factors had to be modified from the original conditions: namely, the rhodium precursor was changed from [Rh(acac)$(CO)_2$] to [Rh(acac)$(C_2H_4)_2$]; the solvent system was changed to 1,4-dioxane/H_2O (10 : 1); the temperature was increased to 100 °C; and the reaction time was shortened to 5 h. The scope of the reaction was very broad, and a wide range of arylboronic acids (**2**)



Entry	Enone 1	Boronic acid 2 or 4 (eq to 1)	Yield (%)	Ketone 3 or 5	ee (%)
1	1a	2m (5.0)	3am	>99	97 (*S*)
2	1a	2n (5.0)	3an	>99	97
3[a]	1a	2o (2.5)	3ao	70	99
4	1a	2p (5.0)	3ap	97	96
5	1a	2q (5.0)	3aq	94	96
6	1b	2m (1.4)	3bm	93	97 (*S*)
7	1c	2m (1.4)	3cm	51	93
8	1d	2m (5.0)	3dm	82	97
9	1e	2m (2.5)	3em	88	92
10	1a	4m (5.0)	5am	88	94
11	1a	4n (5.0)	5an	76	91
12	1b	4m (2.5)	5bm	64	96

[a] In 1-propanol / H_2O (10:1).

Scheme 1.2 ECA of organoboronic acids to α,β-unsaturated ketones catalyzed by [Rh(acac)(C_2H_4)]/(*S*)-binap.

substituted with electron-donating or -withdrawing groups could be added to 2-cyclohexenone (**1a**) with high enantioselectivities (Scheme 1.2, entries 2–5). The ECA of alkenylboronic acids **4m** and **4n** to 2-cyclohexenone and 2-cyclopentenone was also very selective (Scheme 1.2, entries 11 and 12). Linear enones having a *trans* geometry also gave high enantioselectivities (Scheme 1.2, entries 8 and 9).

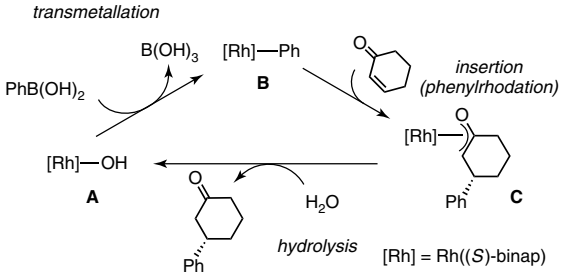
These key seminal findings set the stage for an intense research activity in the area of rhodium-catalyzed ECAs, and related processes, which goes unabated in

2009. In the following sections, the mechanism will be discuss and a working model postulated for the observed enantioselectivity. Using the insights brought by the mechanistic studies, the importance of the Rh precatalyst, as well of the organoboron derivatives that can be used, will also be discussed. An overview will then be presented, by ligand class, of all ligands systems reported until mid-2009, after which the different substrate classes and other competent organometallic reagents in Rh-catalyzed ECA will be reviewed. Following a section devoted to tandem processes involving a conjugate addition step, the chapter will conclude with details of the palladium catalysts for ECAs.

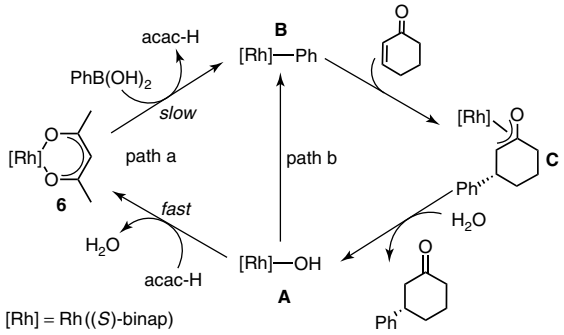
1.2.1.2 **Catalytic Cycle**

In 2002, Hayashi and coworkers established the detailed mechanistic cycle for the rhodium-catalyzed ECA. An example of this catalytic cycle for the ECA of phenylboronic acid onto 2-cyclohexenone (**1a**) is given in Scheme 1.3 [22]. The cycle goes through three identifiable intermediates: the hydroxyrhodium **A;** the phenylrhodium **B;** and the oxa-π-allylrhodium (rhodium-enolate) **C** complexes. These intermediates are related to the cycle as follows. The reaction is initiated through the transmetallation of a phenyl group from boron to hydroxyrhodium **A** to generate the phenylrhodium **B**. The 2-cyclohexenone will subsequently insert into Rh–Ph bond of **B** to form the oxa-π-allylrhodium **C**. The rhodium enolate **C** is unstable under protic condition, and will be readily hydrolyzed to regenerate **A** and liberate the ECA product. It is important to note that, throughout the catalytic cycle, rhodium remains at a constant oxidation state of +I.

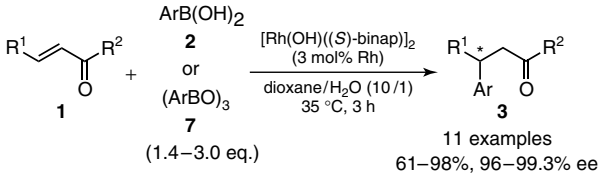
This cycle was validated through the observation of **A**, **B**, **C** in stoichiometric nuclear magnetic resonance (NMR) experiments [22] in which the $[Rh(OH)((S)\text{-binap}))]_2$ dimer was used as the precursor to monomeric species **A**, and extraneous triphenylphosphine was added to stabilize coordinatively unsaturated complex **B**. Remarkably, in these NMR experiments all of the elementary steps readily occurred at 25 °C. This was in contrast to the reaction catalyzed by [Rh(acac)(binap)] (**6**), which required a temperature of 100 °C in order for it to occur. This apparent discrepancy in activity was pinpointed to the presence of acac-H in the reaction mixture when [Rh(acac)(binap)] was used. Acac-H readily reacts with [Rh(OH)((*S*)-binap)] at 25 °C to regenerate [Rh(acac)((*S*)-binap)], which



Scheme 1.3 Catalytic cycle for an ECA catalyzed by a hydroxyrhodium complex.



Scheme 1.4 Catalytic cycle for an ECA catalyzed by a rhodium acac complex.



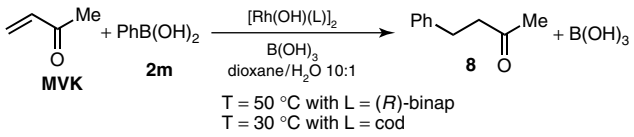
Scheme 1.5 ECA with $[Rh(OH)(binap)]_2$.

in turn transmetallates very slowly with $PhB(OH)_2$ at the same temperature (Scheme 1.4). Therefore, the acetylacetonato ligand inhibits the reaction, and should be avoided if a high catalytic activity is required.

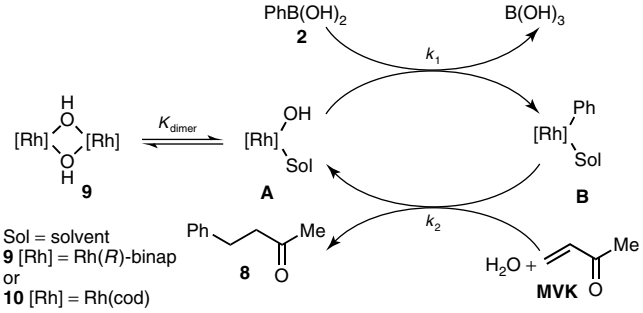
Based on the information gleaned from the mechanistic studies, the $[Rh(OH)((S)\text{-binap}))]_2$ dimer (an acac-free rhodium source) was evaluated as a catalyst (Scheme 1.5). This increased the reaction rate drastically and enabled the reaction to be completed in 3 h at 35 °C. In turn, lowering the temperature increased the enantioselectivity, the yield, and also limited the protodeboration of the arylboronic acid. Thus, only 1.4 equiv. of $ArB(OH)_2$ were necessary relative to the acceptor. In this improved protocol, arylboroxines (**7**) were found to be good precursors to boronic acids (cf. Section 1.4).

Following this initial mechanistic study, Hayashi and coworkers performed a detailed kinetic study of the catalytic cycle of Rh-catalyzed ECA using the reaction calorimetry methodology and analysis developed by Blackmond [23, 24]. For this study, the reaction between phenylboronic acid and MVK in the presence of boric acid ($B(OH)_3$) was used (Schemes 1.6 and 1.7). These conditions were chosen to achieve a high reproducibility and sufficiently exothermic reactions for an accurate calorimetric analysis. The reaction network was modeled as follows: The catalytically inactive $[Rh(OH)((R)\text{-binap})]_2$ dimer (**9**) is in equilibrium with the weakly solvated hydroxyrhodium monomer **A** that transmetallates with phenylboronic acid at a rate k_1. The subsequent steps – the insertion of MVK and hydrolysis to yield **8**, (which are kinetically indistinguishable) – are combined in one rate constant, k_2. The analysis, under catalytically relevant conditions, revealed that $K_{dimer} = 8 \times 10^2\ M^{-1}$ and $k_1 = 0.5\ M^{-1}\ s^{-1}$; however k_2 was too large to be obtained with

Model reaction:



Reaction network:



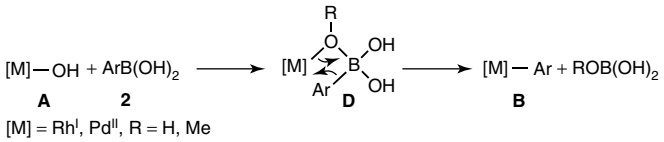
Scheme 1.6 Model reaction and reaction network used for conjugate addition of $PhB(OH)_2$ to MVK in the presence of Rh/binap and Rh/cod catalysts.

a statistically meaningful value. Thus, the rate-determining step of the catalytic cycle was the transmetallation from boron to rhodium. Furthermore, the large value for K_{dimer} indicated that most of the rhodium lay in the catalytically dormant [Rh(OH)((*R*)-binap)]$_2$ (**9**) dimer.

Using the same methodology, Hayashi and coworkers performed the kinetic analysis of the reaction catalyzed by [Rh(OH)(cod)]$_2$ (**10**) (cf. Section 1.5) [25]. Under identical conditions, the rate of the reaction with [Rh(OH)(cod)]$_2$ (**10**) was 20-fold faster than with [Rh(OH)((*R*)-binap)]$_2$ (**9**). For the quantitative analysis, the reaction temperature was set to 30 °C, which led to $K_{dimer} = 3.2 \times 10^2$ M^{-1} and $k_1 = 1.3$ M^{-1} s^{-1}, and k_2 was estimated to be 16 M^{-1} s^{-1}. On the assumption that K_{dimer} did not vary much between 30 and 50 °C, k_1 was calculated as 6.7 M^{-1} s^{-1}. Thus, the remarkably large catalytic activity of rhodium–diene complexes can be attributed to both a lower K_{dimer} and the higher rate of transmetallation of [Rh(OH)(cod)] (**10**) versus [Rh(OH)(binap)] (**9**). There is, to date, no rational why π-accepting diene ligands accelerate the rate-determining transmetallation by an order of magnitude relative to diphosphine ligands. Other π-accepting ligands, such as phosphoramidites, also have a beneficial effect on the reaction rate [26].

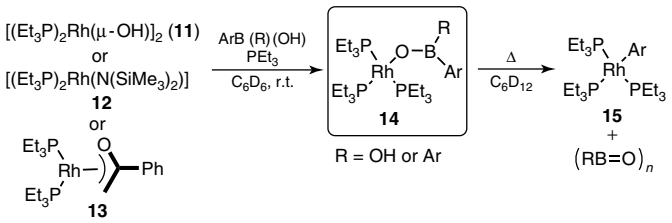
The transmetallation step is arguably one of the least understood process in homogeneous catalysis. In the case transmetallation from boron to rhodium or palladium under the conditions of conjugate addition, the mechanism is thought to occur through a metal hydroxy complex **A** which can coordinate to highly oxophilic arylboronic acid to give intermediate **D**; the latter can then deliver the aryl fragment

to rhodium in an intramolecular fashion to furnish the aryl-rhodium species **B** (Scheme 1.7) [16, 27].



Scheme 1.7 Proposed mechanism for the transmetallation of organoboronic acids.

Direct evidence for this mechanism was provided by Hartwig and coworkers, who showed that a boronic acid would react cleanly with the hydroxy dimer **11**, **12**, or the Rh-enolate **13** to give complex **14** which could be isolated [28]. Upon heating, **14** would rearrange to form a Rh-aryl bond and extrude an insoluble boroxine oligomer (Scheme 1.8).



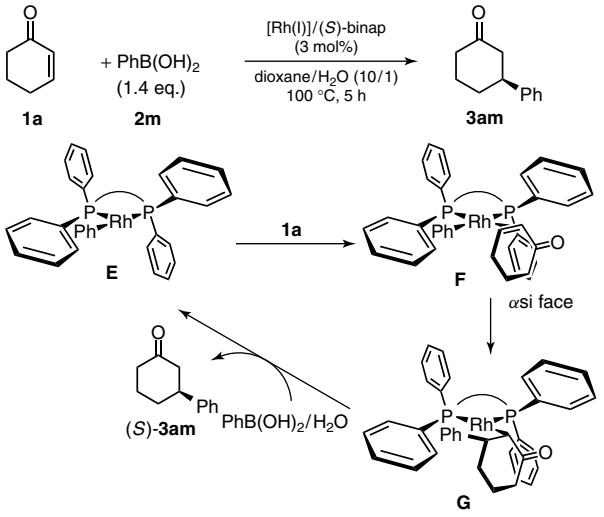
Scheme 1.8 Direct observation of the transmetallation from boron to rhodium.

Although this process occurs under neutral conditions, it is greatly accelerated by the presence of stoichiometric amounts of base. This is rationalized by the quaternization of the arylboronic acid, which facilitates rupture of the $B-C_{sp2}$ bond [16, 29].

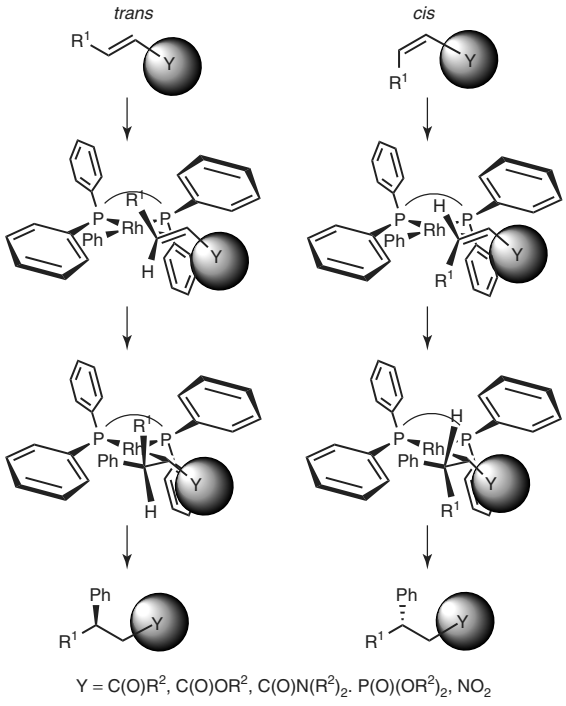
1.2.1.3 Model for Enantioselection

Scheme 1.10 shows the proposed stereochemical pathway in the reaction catalyzed by rhodium complex coordinated with (*S*)-binap (**L1**) [17]. According to the highly skewed structure known for transition metal complexes coordinated with a binap ligand [30], the (*S*)-binap rhodium intermediate **E** should have an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the binap ligand. The olefinic double bond of 2-cyclohexenone (**1a**) coordinates to rhodium, with its α*Si* face forming **F** rather than with its α*Re* face, which undergoes migratory insertion to form a stereogenic carbon center in **G**, the absolute configuration of which is *S*.

This stereocontrol model can be applied to predict the absolute configurations of all 1,4-addition products with the (*S*)-binap–rhodium intermediate. This intermediate attacks the α*si* face of α,β-unsaturated ketones, both cyclic and linear forms, as well as other electron-deficient olefins such as α,β-unsaturated esters and amides, nitroalkenes, and alkenylphosphonates. For the ECA of linear alkenes, the geometry of the double bond plays a determining role in the stereochemical outcome (Schemes 1.9 and 1.10). This is again explained



Scheme 1.9 Proposed model for the enantioselection with [Rh((S)-binap)] complex.



Scheme 1.10 Stereocontrol model for the ECA of *trans* and *cis* olefins.

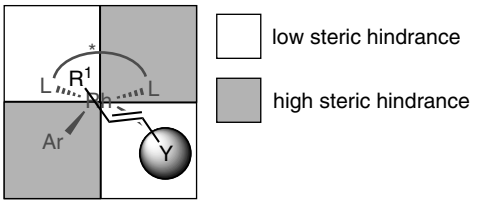


Figure 1.1 Generalized model for the stereochemical outcome of an enantioselective conjugate addition (ECA).

by which enantiotopic face the electron-deficient olefins can coordinate to the [Rh(Ph)((*S*)-binap)] intermediate.

This stereochemical model can be extended to a wide range of C_2 symmetric bidentate ligands by considering how the ligand, when it is coordinated to rhodium, is capable of bisecting the space around the rhodium into a quadrant, and which enantiotopic face of the alkene will minimize steric interaction upon coordination to Rh (Figure 1.1) [22].

1.2.1.4 **Organoboron Sources Other than Boronic Acids**

Although organoboronic acids (**2**) are the most practical and widespread source of organoboron reagents, other sources have proven to be equally effective (Figure 1.2). Boronate esters from catechol (**16**), ethylene glycol (**17**), and pinacol (**18**) can be used in Rh-catalyzed ECAs [31, 32]. The rate of the ECA reaction of these boronate esters is directly related to the ease of their hydrolysis back to the corresponding boronic acid. While catechol boronates will react quickly, pinacol boronic esters react slowly in Rh-catalyzed ECAs [31]. This feature can be used advantageously in the one-pot alkyne hydroboration with catecholborane, followed by Rh-catalyzed ECA [32].

Boronic acids are in equilibrium with oligomeric species of various degrees of hydration. The complete dehydration of organoboronic acid leads to the well-defined cyclic organoboroxine (**7**). Boroxines are readily hydrolyzed back to the corresponding boronic acid with 1 equiv. of water relative to boron under basic aqueous conditions [33]. Organoboroxines have become the preferred reagents for Rh-ECAs,

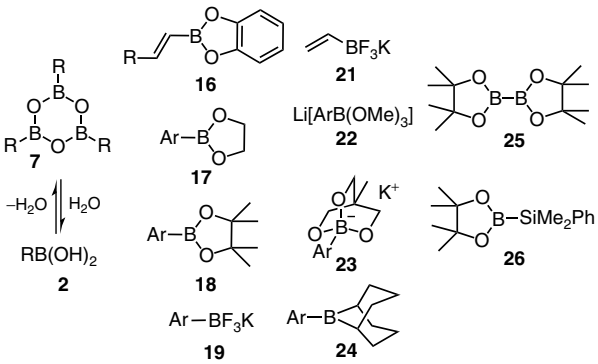
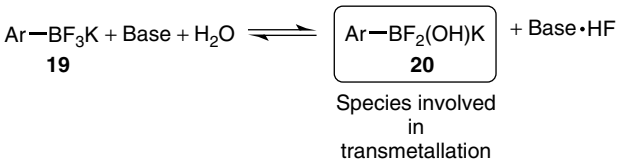


Figure 1.2 Organoboron reagent competent for Rh-catalyzed ECAs.

because they enable addition of the organoboron reagent with a precise stoichiometry, and are also more stable towards protodeboration than boronic acids, especially at an elevated temperature (ca. 100 °C).

Potassium aryltrifluoroborate salts (**19**) have become a very popular source of organoboron reagents [34–36], because they are more stable than the corresponding boronic acids while still being reactive in Rh-cat. ECAs [37]. One particularly useful reagent is potassium vinyltrifluoroborate (**21**), which enables the introduction of a vinyl group in excellent yields with high enantioselectivities [38]. The corresponding vinylboronic acid cannot be used because it is unstable and readily undergoes protodeboration and polymerization [39]. It is important to note, that potassium organotrifluoroborates do not transmetallate directly to rhodium(I), but rather that a monohydroxyborate (**20**) is probably the boron species that effects the transmetallation step, with a mechanism akin to that depicted in Scheme 1.8. This monohydroxyborate (**20**) has been observed to be in equilibrium with the corresponding potassium organotrifluoroborates (**19**) under basic aqueous conditions for Rh-catalyzed ECAs (Eq. (1.1)) [40–44].



(1.1)

Lithium trimethylarylborate (**22**) is also a very active reagent for the ECA, but is relatively unstable and is best formed *in situ* by lithium/halogen exchange on an aryl bromide, followed by addition of trimethoxyborane [31, 45]. Cyclic aryl triolborates (**23**) are also convenient and reactive reagents for Rh-catalyzed ECAs [46, 47]; these reagents have the advantage of being very stable in air and water, and more soluble in organic solvents than related potassium organotrifluoroborates. The reactive ArB(9-*BBN*) (**24**) derivatives can be used in ECA reactions in aprotic solvents, and also in the absence of base to yield a stable boron enolate [48]. The chiral boron enolate can be further reacted with an electrophile to yield a ketone with a high diastereoselectivity (see Scheme 1.18). Reagents such as bis(pinacolato)diboron (**25**) [49] and dimethylphenylsilylpinacolatoboron (**26**) [50, 51] have been used to introduce a boron and silyl moiety in Rh-catalyzed addition reactions (cf. Section 1.6; see Scheme 1.59).

1.2.1.5 **Rh Precatalysts**

As noted above, the nature of the Rh precatalyst used in the ECA reaction is of crucial importance. In the first step, the Rh precursor must enable a rapid exchange of ligands in order to form quantitatively the enantioselective catalytic species. Thus, when $[Rh(acac)(C_2H_4)_2]$ is used in conjunction with a chiral bidentate ligand, high enantioselectivities are observed, whereas when $[Rh(acac)(CO)_2]$ is used lower selectivities are obtained because of the strong binding of CO [17]. As discussed the acac ligand has an inhibiting effect on the reaction; therefore, acac-free $[Rh(Cl)(C_2H_4)_2]_2$ is the precatalyst of choice because it enables rapid

and irreversible ligand exchange. Other cod-containing rhodium precursors, such a $[Rh(Cl)(cod)]_2$ and $[Rh(\mu\text{-}OH)(cod)]_2$, should be avoided because of their higher catalytic activity than the Rh–phosphine complex [29, 52]. Thus, only trace amounts of these complexes (due to incomplete ligand exchange) will suffice to significantly lower the observed enantioselectivity of an ECA.

Chiral cationic rhodium complexes, formed *in situ* by the reaction of $[Rh(cod)_2]^+BF_4^-$, $[Rh(cod)(MeCN)_2]^+BF_4^-$ [53–60], or $[Rh(nbd)_2]^+BF_4^-$ [29, 61] with a chiral ligand, are also active rhodium precatalysts [62]. Under the basic aqueous conditions used for Rh-catalyzed ECAs, the cationic precursors are presumably converted *in situ* into the neutral Rh–OH species bearing the chiral ligands. Thus, the $[Rh(nbd)_2]^+BF_4^-$ complex should be preferred because the corresponding $[Rh(\mu\text{-}OH)(nbd)]_2$ complex is a poor catalyst for the reaction. One practical advantage of using cationic rhodium precursors is that they enable more robust reaction conditions, and lead more consistently to higher enantioselectivities when the catalyst is generated *in situ* with a chiral ligand than with the corresponding neutral Rh precursor [63]. This is presumably due to the faster exchange of the diene for the chiral ligands on the cationic rhodium relative to the neutral precursors [63]. Furthermore, with cationic rhodium precursors, Et_3N can be used instead of KOH as the activator, thus making the ECA protocol more functional group-tolerant [64].

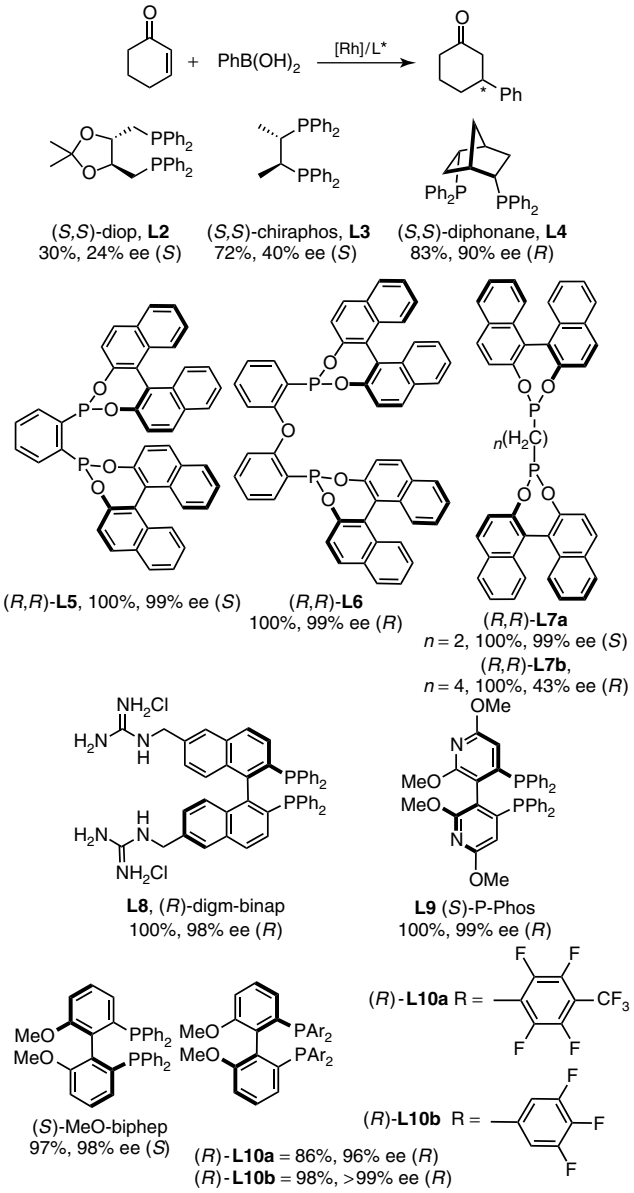
Hayashi and coworkers found that traces of phenol (0.05 ± 0.02 mol%) present in commercial phenylboronic acid can significantly deactivate chiral diene rhodium catalysts [65]. This deactivation pathway becomes prevalent under low-catalyst loading conditions (below 0.05 mol%). The phenol impurity can be removed by dehydration of the boronic acid to the boroxine (**7**), followed by washing with hexanes. These findings are probably more applicable to other Rh systems for ECAs, which are used at low catalyst loadings.

1.2.1.6 **Ligand Systems**

In this section, an overview will be presented of the different ligand designs and concepts that have been applied to the rhodium-catalyzed ECAs of organoboronic acids to α,β-unsaturated ketones. Very early on, the ECA of phenylboronic acid onto 2-cyclohexenone was chosen as a model reaction for Rh-catalyzed ECAs. The wealth of reports using this model reaction enables the direct comparison of a wide gamut of ligand structures. To facilitate the comparison, the ligands have been grouped by families (i.e., phosphorus-based bidentate, monodentate, mixed ligands, and others). When a family of ligands was prepared, only the best-performing ligand will be discussed. It should be borne in mind that this is only a comparison on a fixed model reaction, and some ligands might be better suited for specific substrates; when possible, this will be highlighted.

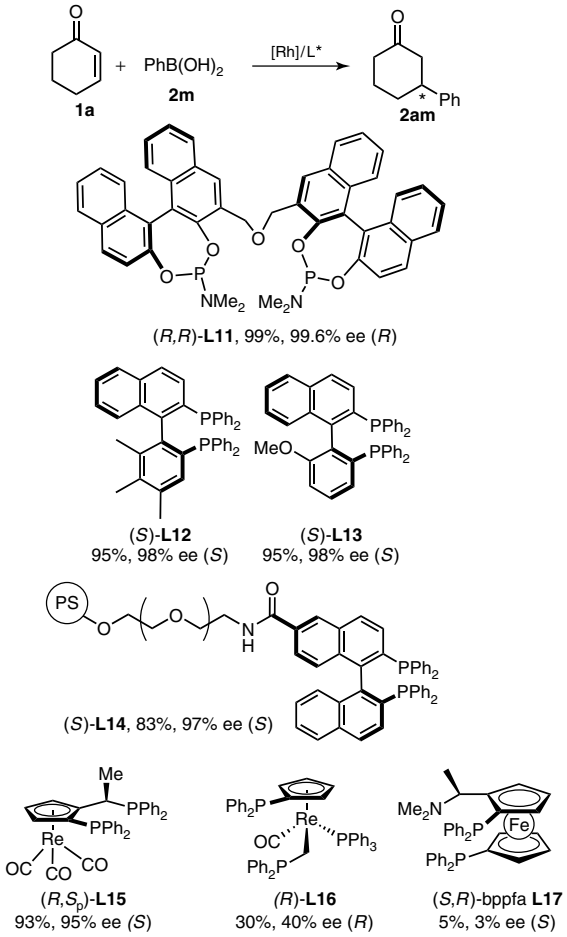
1.2.1.7 **Bidentate Phosphorus Ligand**

Following the initial breakthrough for Rh-catalyzed ECA, using binap as a ligand, a flurry of reports has emerged employing bidentate phosphorus ligands. These results are summarized in Schemes 1.11 and 1.12. Diop (**L2**) [66], and chiraphos



Scheme 1.11 ECA catalyzed by C_2-symmetric bidentate ligand rhodium complexes.

(**L3**) [66] gave low enantioselectivities. The diphonane ligand **L4** bears an interesting backbone and gives good selectivities [67]. Binol-based bisphosphonites **L5** and **L6** performed well in Rh-catalyzed ECA and interestingly, depending on the carbon chain length separating the phosphonites in **L7a** and **L7b**, the enantioselectivity is reversed [68]. Similarly, binol-based bisphosphoramidite **L11** linked together in the

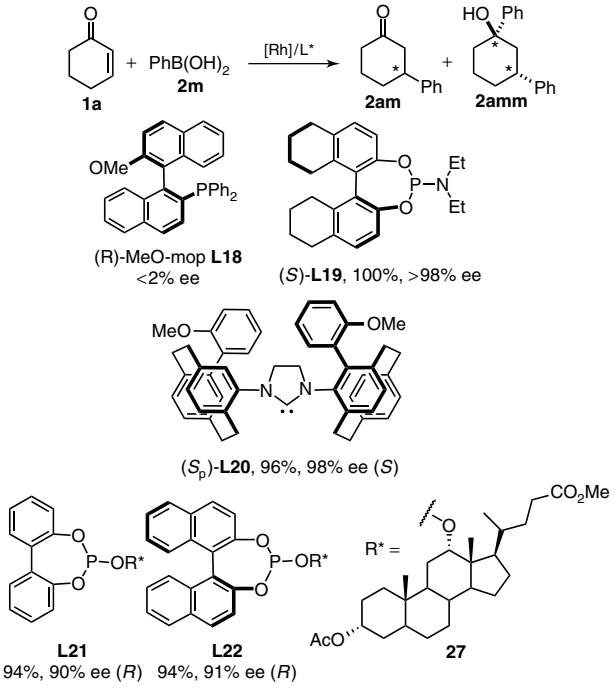


Scheme 1.12 ECA catalyzed by bidentate ligand rhodium complexes.

3-position gave excellent results [64, 69]. The water-soluble binap-based ligand **L8** catalyzed the ECA in aqueous media with a turnover number (TON) of 13 200 [70]. The observation that π-accepting ligands accelerate the rate-determining transmetallation in Rh-catalyzed ECAs was confirmed by the use of π-accepting ligands **L10a** and **L10b**, which displayed a higher catalytic activity than the corresponding MeO-biphep [71]. In general, axially chiral ligands such as **L9** [72], (*S*)-MeO-biphep [71] **L10** [71], **L12** [73], **L13** [73], and polystyrene-supported binap **L14** [74] all produce excellent enantioselectivities on par with binap. Substitution in remote positions (not 3 and 3′) of the binaphthyl backbone of the binap ligands has little influence on the stereochemical outcome [75, 76]. The diphosphine ligand **L15** [77], **L16** [78], and **L17** [66] bearing planar chirality were investigated, although only Re-based **L15** gave high enantiomeric excess (ee) values.

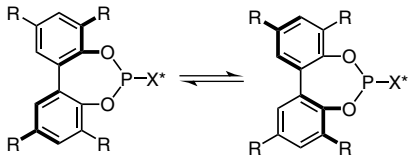
1.2.1.8 **Monodentate Ligand**

Although monodentate chiral ligands (P-stereogenic) were the first class of ligands to be used in Rh-catalyzed asymmetric homogeneous catalysis, they have since been replaced by rigid bidentate ligands [79]. Early attempts to use the monodentate (*R*)-MeO-mop (**L18**) as a ligand for Rh-catalyzed ECA proved to be disappointing, with low conversion and enantioselectivities [66]. The discovery by de Vries and Feringa that binol-based phosphoramidites where highly active and enantioselective in Rh-catalyzed hydrogenation [80] has spurred a renewed interest in monodentate ligands in asymmetric catalysis. A great impetus for this growing trend in homogeneous catalysis is the cheap and rapid synthesis of monodentate ligands over bidentate ones. As for asymmetric hydrogenation, phosphoramidite ligands performed very well in Rh-catalyzed ECAs due to their strong π-accepting properties, which renders them more reactive than phosphines (cf. Section 1.2) [26, 38, 81–86]. For the addition phenylboronic acid onto 2-cyclohexenone, H_8-binol-based phosphoramidite (*S*)-**L19** proved to be the most efficient [82]. Phosphoramidite ligands have also been used for the addition of potassium organotrifluoroborates [38]. In an early and elegant report of a chiral monodentate *N*-heterocyclic carbene (NHC), Andrus and coworkers showed that the cyclophane-based NHC (**L20**) was very effective for Rh-catalyzed ECA [87, 88]. Importantly, only 1 equiv. of chiral NHC relative to rhodium was necessary to obtain high selectivity, this being in stark contrast to other monodentate ligands, which require 2 equiv. per rhodium (Scheme 1.13).



Scheme 1.13 ECA catalyzed by monodentate ligand rhodium complexes.

The use of inexpensive methyl deoxycholic ester **27** as the source of chirality in phosphite **L21** proved efficient [88, 89]. The deoxycholic moiety induces only one conformation in the *tropos* biphenyl backbone (Eq. (1.2)).



R = H, *t*-Bu, Me (1.2)

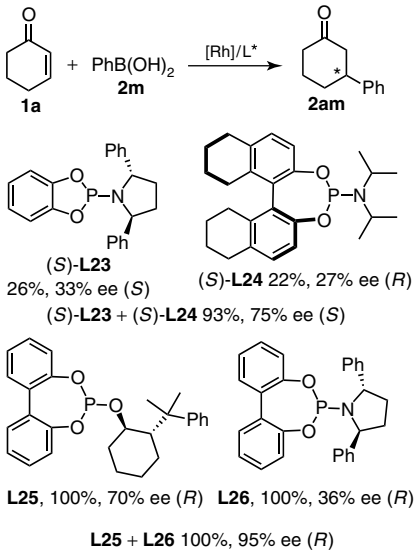
This approach alleviates the need to use binol as the source of chirality. When the deoxycholic moiety is paired with each enantiomer of binol, only one the diastereoisomers (**L22**) was catalytically active, demonstrating the value of having a flexible *tropos* backbone. In addition, depending on the molar ratio of phosphite **L21** relative to Rh, the reactivity and selectivity of the addition could be modulated. With only 1 equiv. of phosphite per Rh, the major product was **2am**, while with 2 equiv. of phosphite **L21**, **2am** underwent a diastereoselective 1,2-addition to furnish the bisphenylated **2amm** product as a single diastereoisomer [89].

The use of a monodentate ligand offered the tantalizing possibility to mix different monodentates together to quickly generate combinatorial libraries of complexes. This fascinating approach goes beyond the traditional parallel preparation of modular ligands. Thus, mixtures of monodentate ligands $\mathbf{L^a}$ and $\mathbf{L^b}$ can, upon exposure to a transition metal [M], form not only the two homocombinations [M($\mathbf{L^a}$)$_2$] and [M($\mathbf{L^a}$)$_2$] but also the heterocombination [M($\mathbf{L^a}$)($\mathbf{L^b}$)]. For example, a 1 : 1 : 1 mixture of $\mathbf{L^a}$, $\mathbf{L^b}$, and metal precursor is used (and no other interaction exists) a statistical mixture of [M($\mathbf{L^a}$)$_2$], [M($\mathbf{L^a}$)$_2$] and [M($\mathbf{L^a}$)($\mathbf{L^b}$)] in a 1 : 1 : 2 ratio will be obtained (Eq. (1.3)). If the heterocombination is more reactive and selective than the homocombinations, an improved catalyst system is formed without the need to synthesize new ligands. This approach – dubbed *combinatorial transition-metal catalysis* – has been reviewed in an excellent article by Reetz [90].

$$\underset{(1:1:1)}{\mathbf{L^a} + \mathbf{L^b} + [M]} \longrightarrow \underset{\text{Homo-L}^a}{[M(\mathbf{L^a})_2]} + \underset{\text{Homo-L}^b}{[M(\mathbf{L^b})_2]} + \underset{\text{Hetero}}{[M(\mathbf{L^a})(\mathbf{L^b})]}$$

Statistical distribution: 1 : 1 : 2 (1.3)

The first example of this approach applied to Rh-catalyzed ECA was described by Feringa with mixtures of phosphoramidites [84]. Each homo combination of **L23** and **L24** performed significantly less well than the hetero combination generated *in situ* (Scheme 1.14) [84]. An interesting extension of this approach is to use mixtures of *tropos* monodentate phosphoramidites ligand. In this example, the combinatorial mixing of ligand led also to the identification of hetero combination **L25** and **L26** that performed significantly better than both homocombinations of ligands (Scheme 1.14) [91].



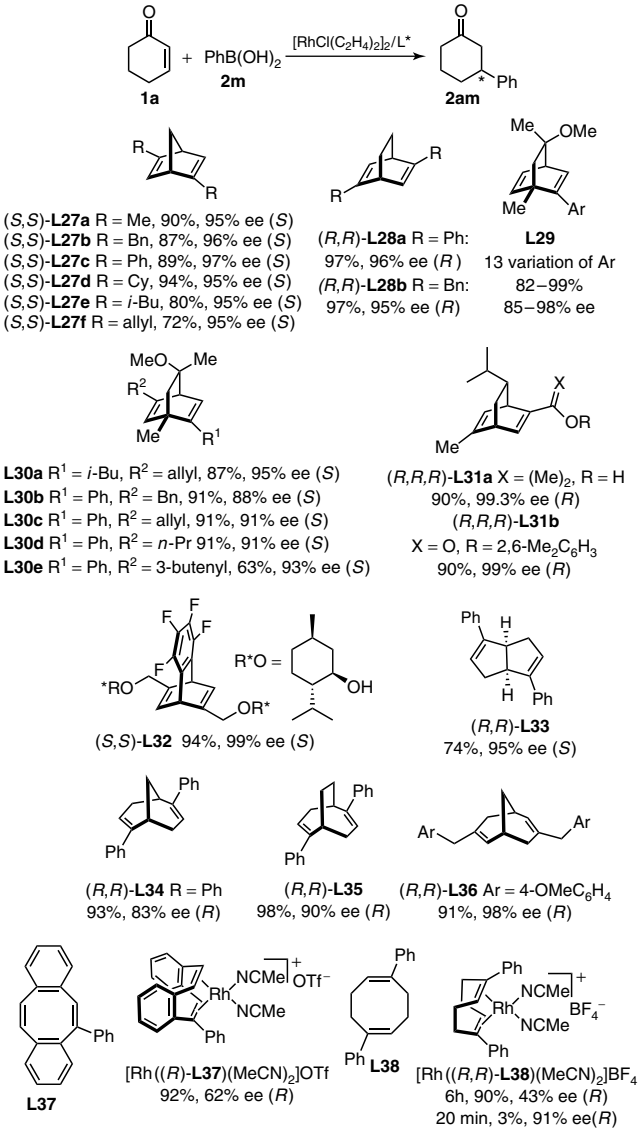
Scheme 1.14 Rh-catalyzed ECA using mixtures of chiral monodentate ligands.

1.2.1.9 **Diene Ligands**

The seminal observation by Miyaura and coworkers that $[Rh(\mu\text{-}OH)(cod)_2]$ is the most active catalyst (with a TON of up to 375 000) for rhodium-catalyzed conjugate addition [29, 92] prompted the investigation of optically active diene as ligand for this transformation. Since the first application of chiral (*S*,*S*)-2,5-dibenzylbicyclo[2.2.1]heptadiene ((*S*,*S*)-**L27b**) in the addition of phenylboronic acid to cyclohex-2-enone by Hayashi and coworkers [93], a variety of bicyclic diene scaffolds [94–104] has been successfully applied (Scheme 1.15). Independently, Carriera and coworkers reported the application of a chiral diene for Ir-catalyzed allylic substitution [105]. These independent discoveries have spurred intense research efforts in homogeneous catalysis which were compiled in 2008 in an excellent review by Carreira and Grützmacher [106].

An examination of the substituent-effect in chiral bicyclo[2 : 2 : 1]heptadiene scaffold revealed that just two methyl groups in ligand **L27a** are sufficient to impart a high enantioselectivity (95% ee) in the ECA reaction [99]. Moreover, variation of the alkyl group to Bn (**L27b**), Cy (**L27d**), allyl (**L27f**), and *i*-Bu (**L27e**) does not significantly influence the selectivity when compared to **L27a** [107]; only when moving to a phenyl substituent is a higher ee-value obtained. A systematic exploration of different bicyclic scaffolds for chiral diene, revealed that the 2,5-disubstituted bicyclo[2.2.1]heptadiene (**L27**) [93, 108], bicyclo[2.2.2]octadiene (**L28**, **L29**, **L30**, **L31**, **L32**) [95, 105, 109–115], and bicyclo[3.3.0]octadiene (**L33**) [100, 116] gave high enantiomeric excesses over a wide range of substrates.

On the other hand, the first-generation 2,6-disubstitued bicyclo[3.3.1]nonadiene (**L34**) [117, 118] and bicyclo[3.3.1]decadiene (**L35**) [118] gave inferior results. A re-examination of the substitution pattern on these dienes revealed that 3,7-disubstituted bicyclo[3.3.1]nonadienes (**L36**) gave excellent results and greatly surpassed previous chiral dienes as ligands for the ECA of alkenyl boronic acid



Scheme 1.15 Chiral diene ligands in the Rh-catalyzed addition of phenylboronic acid to 2-cyclohexenone.

onto β-silyl α,β-unsaturated ketones [104]. Using the scaffold developed by Carreria (**L30**), it was found that just the mono-substitution of the bicyclo[2.2.2]octadiene framework with an aryl moiety (**L29**) was necessary to achieve high enantioselectivities [44, 103]. In this first systematic investigation of the steric effects of *mono*-substituted chiral dienes, the *ortho* positions on the aromatic moiety (i.e., 2,6-Me_2 C_6 H_3) were found to be important to achieve highest selectivities.

The lengthy synthesis of **L27** and the need to resolve **L28**, **L34**, **L35**, and **L36** by preparative high-performance liquid chromatography (HPLC) has impeded the widespread investigation of chiral dienes. To overcome this limitation, several readily accessible scaffolds have been synthesized. Ligand **L30** is conveniently synthesized in seven steps from readily available (−)-carvone [105]. Interestingly, the allyl-functionalized **L30c** gave significantly higher ee-values than the *n*-propyl-substituted **L30d**. A reinvestigation of the synthesis of the 2,5-disubstituted bicyclo[2.2.1]heptadiene family (**L27**) led to a much shorter and efficient five-step synthesis from inexpensive bicyclo[2 : 2 : 1]heptadiene, using an iron-catalyzed cross-coupling as the key step [99]. A very concise two-step entry into the chiral bicyclo[2.2.2]octadiene framework (**L31**) was reported by Hayashi and Rawal, using as the key step a Diels–Alder reaction between (*R*)-α-phelandrene and propiolate esters, followed by the addition of MeLi for **L31a** or a simple transesterification for **L31b** [102, 119]. Dienes **L31a** proved to be highly effective ligands for the Rh-catalyzed ECA on a range of cyclic and linear α,β-unsaturated ketones, giving near-perfect enantioselectivity. Strikingly, the α,β-unsaturated ester moiety in diene **L31b** does not insert in the Rh-aryl bond during the catalytic cycle, most likely because the alkene in the rigid bicyclic framework cannot be co-planar to the coordination plane of Rh, which is necessary for insertion into the Rh-aryl bond. Furthermore, the use of strongly π-accepting α,β-unsaturated ester significantly accelerates the reaction rate, presumably by facilitating the transmetallation process to form the Rh-aryl bond *trans* to the enoate moiety of **L31b**. This *trans* influence on the transmetallation process is highly beneficial because it forces the substrate to coordinate *cis* to the bulky ester moiety, leading to a more effective enantioselection. This *trans* effect could also explain the high enantioselectivities obtained with mono-substituted chiral diene **L29**.

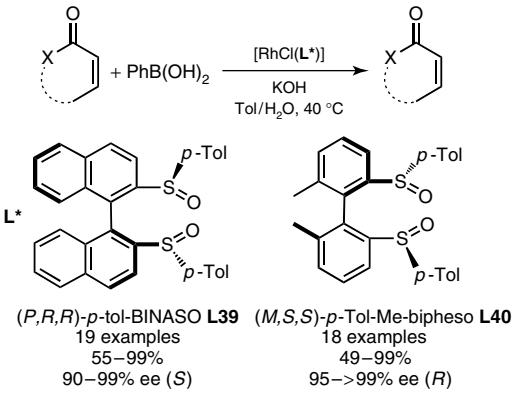
Chiral tetrafluorobenzobarralene **L32** was obtained directly from the [4+2] cycloaddition of 1,4-bis((−)-menthoxymethyl)benzene with *in situ*-generated tetrafluorobenzyne, albeit with a low (8%) yield. The resulting diastereoisomers were separated by column chromatography to afford the desired chiral diene [101].

The Ph-dbcot (**L37**) [98] and 1,5-Ph-cod (**L38**) [97] are achiral dienes, but when coordinated to Rh they become conformationally locked, which leads to a pair of enantiomers that can be subsequently resolved such that, ultimately, enantiomerically pure cationic rhodium complexes [Rh((*R*)-**L37**)$(MeCN)_2$] (OTf) and [Rh((*R*,*R*)-**L38**)$(MeCN)_2$](BF_4) can be obtained. Complex [Rh((*R*)-**L37**)$(MeCN)_2$](OTf) leads to a moderate 62% ee [97], while complexes [Rh((*R*,*R*)-**L38**)$(MeCN)_2$](BF_4) gave high ee-values at low conversion. However, the enantioselectivity was eroded at higher conversions due to the conformational instability of ligand **L38** of the complex [98].

1.2.1.10 **Bis-Sulfoxide**

Bis-sulfoxides are an emerging class of ligands in homogeneous catalysis [120, 121]. Dorta and coworkers reported the first chiral bis-sulfoxides ligand **L39** [122] and **L40** [123], and found them to be exceptional ligands for the Rh-catalyzed ECA of arylboronic acids, giving near-perfect enantioselectivities over a wide

range of cyclic α,β-unsaturated ketones (Scheme 1.16). The biphenyl bis-sulfoxide **L40** was found to be more active and selective than binaphthyl derivative **L39** [123]. A comparison of the X-ray crystal structures of [RhCl((*R*)-binap)]$_2$, [RhCl((S,S)-**L28a**)]$_2$ [124], and [RhCl((R,*R*)-**L39**)]$_2$ [123] indicated that the ligating properties of *bis*-sulfoxides might lie somewhere between that of diene and *bis*-arylphosphine ligand.



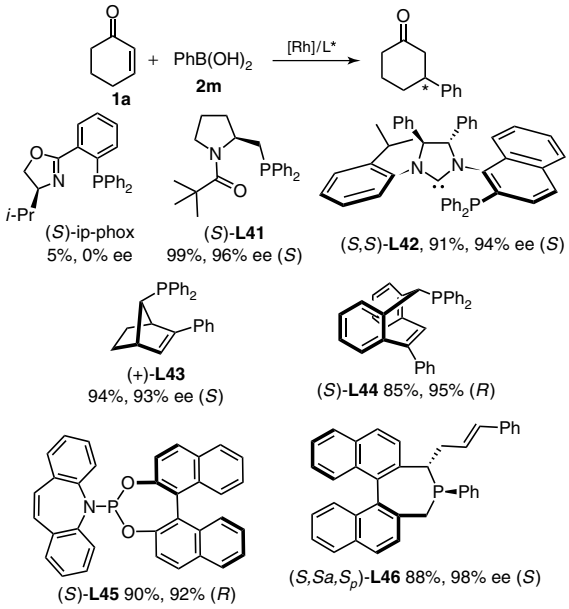
Scheme 1.16 Chiral *bis*-sulfoxide ligands for Rh-cat ECA.

1.2.1.11 **Mixed Donor Ligands**

A range of chiral ligands bearing a phosphorus center and another coordinating functionality have been investigated in the Rh-catalyzed ECA of boronic acid onto α,β-unsaturated carbonyls (Scheme 1.17). Interestingly, the ligand (*S*)-ip-phox family performed poorly in this transformation [66], while the L-proline-derived amido phosphines (*S*)-**L42** was found to be very active and selective [125, 126], and has been applied in diastereoselective ECA processes [127]. The combination of NHC and a phosphine moiety **L42** was successful [128]. Based on the observation that phosphines coordinate more strongly to late transition metals than do alkenes, but that the latter provide an effective chiral environment, Shintani and Hayashi synthesized the chiral phosphines-alkene ligand **L43**, and this proved to be highly effective for both the ECA onto enones and maleimides [129]. The kinetic study of the Rh/**L43** system in ECA, revealed that the catalytic activity with **L43** to be intermediate to that of diphosphines and dienes [130]. Good activities and enantioselectivities were obtained with ligands **L44** [131], amidophosphine-alkene **L45** [132] (first synthesized by Carreira [133]) and with the chiral phosphine-olefin **L46** [134].

1.2.1.12 **Trapping of Boron Enolates**

In the rhodium-catalyzed ECA of organoboron reagents to electron-deficient alkenes, the protic solvent is essential for hydrolyzing oxo-π-allylrhodium to regenerate the active hydroxorhodium species and liberate the 1,4-addition product (cf. Scheme 1.3). However, this process does not take full advantage of the chiral rhodium-enolate that is transiently formed, and which could further react either

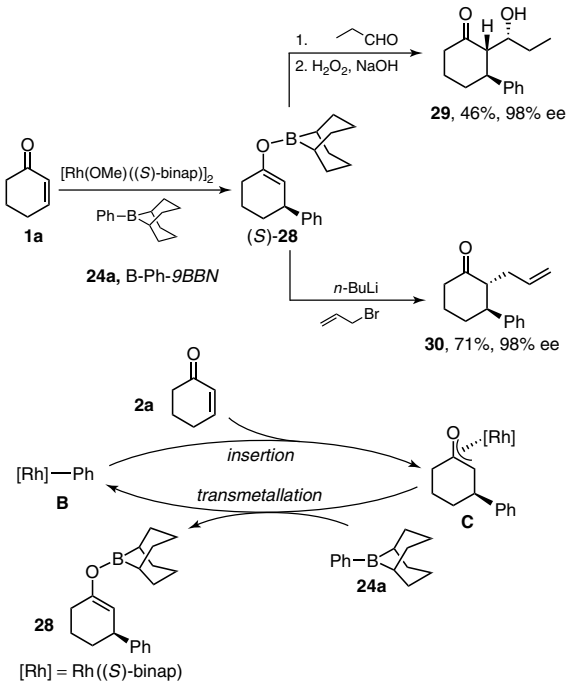


Scheme 1.17 ECA catalyzed by bidentate ligand rhodium complexes.

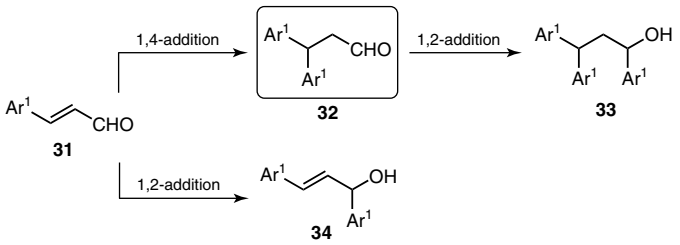
inter- or intramolecularly with an electrophile. To tap into this reactivity, Hayashi and coworkers found that, under aprotic conditions, the use of ArB(9-*BBN*) (**24**) was sufficiently reactive to form quantitatively – and with exquisite selectivity – the chiral boron enolates (see Scheme 1.18) [48, 135]. As a typical example, the reaction of 2-cyclohexenone (**1a**) with 1.1 equiv. of PhB(9-*BBN*) (**24a**) in the presence of a rhodium catalyst generated from [Rh(OMe)((*S*)-binap)]$_2$ and in toluene gave a high yield of the boron enolate (*S*)-**28** with 98% ee. The boron enolate formation was not observed in the reaction with phenylboronate esters, phenylboroxine, or tetraphenylborate. Unfortunately, the scope of this reaction is limited and a chiral boron-enolate was isolated only for 2-cyclohexenone (**1a**) and 2-cycloheptenone (**1c**). One of the most useful reactions of the resulting boronates is the aldol reaction with aldehydes (such as propanal), which is known to proceed through a well-organized transition state to give the *anti*-aldol product as a single diastereoisomer (**29**). Treatment of the boron enolate with *n*-butyllithium at −78 °C, followed by reaction with allyl bromide, gave 2-allylcyclohexanone **30** as a single diastereoisomer.

1.2.1.13 α,β-Unsaturated Aldehydes

Aldehydes are among the most versatile functional groups in organic chemistry, thus an ECA protocol to generate chiral 3,3-diarylpropanals (Scheme 1.19; **32**) is highly desirable and can be used in the synthesis of biologically active substances. However, enals represent an especially challenging class of substrates in Rh-catalyzed ECAs [112, 109, 136]. This can be attributed to the high reactivity of



Scheme 1.18 Tandem Rh-catalyzed ECA with PhB(9-*BBN*) onto 2-cyclohexenone.

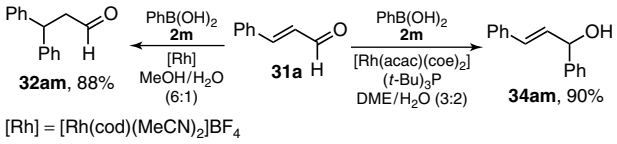


Scheme 1.19 Reaction pathways in the Rh-catalyzed conjugate addition of arylboronic acids to enals.

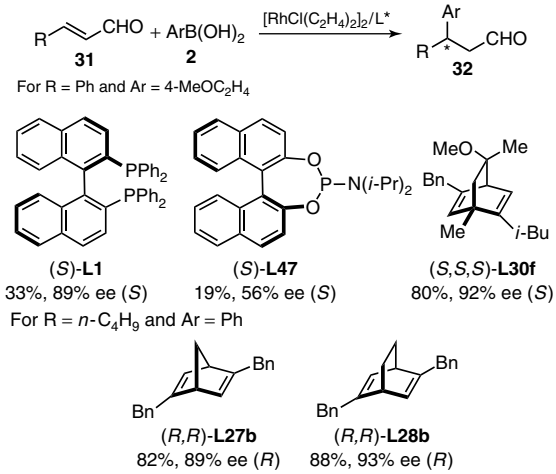
aldehydes, which can undergo competitive 1,2-addition either in competition with (**34**) or after the 1,4-addition (**33**) (Scheme 1.19).

The influence of the ligand on the selectivity of the transformation is shown in Scheme 1.20 [137]. Whereas, the use of phosphines ligands in the addition of phenylboronic acid to cinnamaldehyde **31a** led selectively to the allyl alcohol **34am**, the Rh/diene-catalyzed process resulted in the formation of the desired 1,4-adduct **32am**.

The use of chiral dienes (**L30f**, **L27b**, and **L28b**) was optimal for the formation of a wide range of enantiomerically enriched 3,3-diarylpropanals and 3-arylalkanals.



Scheme 1.20 Ligand control of the selectivity for 1,2- or 1,4-additon to enal **31a**.



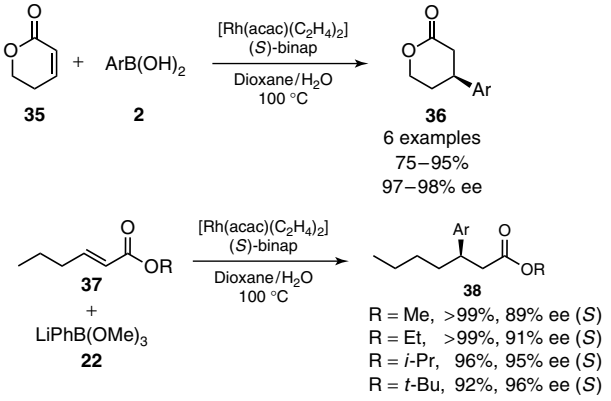
Scheme 1.21 Rh-catalyzed ECA of arylboronic acids to enals.

However, poorer results were obtained with conventional ligands such as (*R*)-binap (**L1**) or phosphoramidite **L47** (Scheme 1.21).

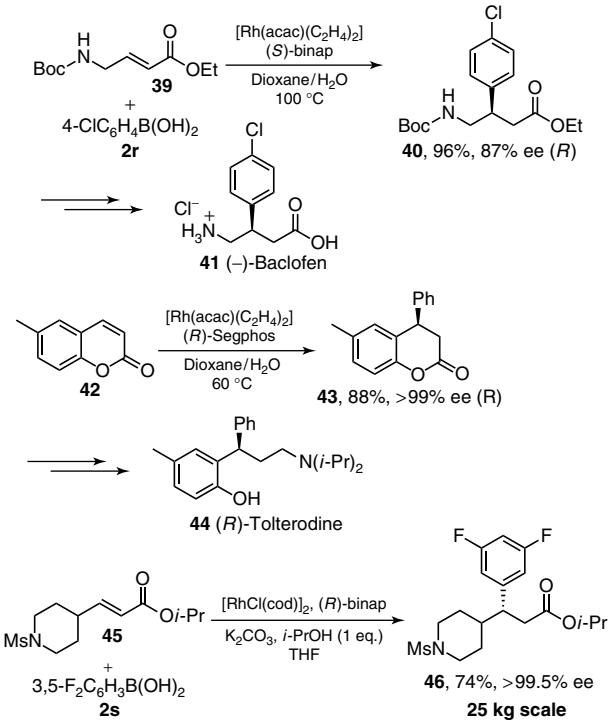
1.2.2
α,β-Unsaturated Esters and Amides

Following the initial discovery of rhodium-catalyzed ECA organoboron reagents onto α,β-unsaturated ketones, the methodology was rapidly expanded to other classes of α,β-unsaturated carbonyl compounds. Cyclic α,β-unsaturated esters (**35**) react well with arylboronic acids in the ECA, catalyzed by the Rh/(*S*)-binap system [31, 62]. However, for linear enoates (**37**) the more reactive $LiArB(OMe)_3$ (**22**, generated *in situ*) organoboron reagent is necessary to obtain acceptable yields (Scheme 1.22). In addition, the bulkier ester function (R = *t* − Bu) has a positive effect on the enantioselectivity on the process, but lowers the yield of the ECA.

The Rh-catalyzed ECA on α,β-unsaturated esters has been applied as the key step in the synthesis of a series of biologically active compounds such as baclofen (**41**) and tolterodine (**44**) (Scheme 1.23) [4, 138, 139]. Especially noteworthy, is the first reported application of a Rh-catalyzed ECA on a multi-kilogram scale on **45** (25 kg) [4]. A key result of the multi-kilogram scale-up of this reaction is the unexpected discovery that the use of a minimal quantity of 2-propanol (1 equiv.), rather than water as the co-solvent, reduces the extent of rhodium-mediated protodeboration



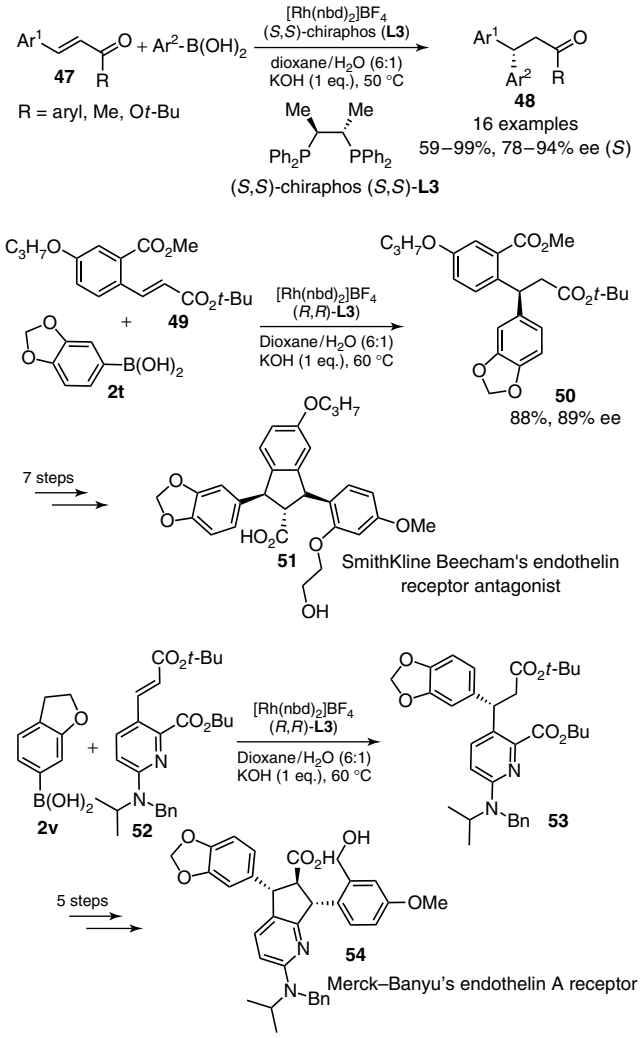
Scheme 1.22 [Rh]/(*S*)-binap-catalyzed ECA of organoboron reagent to cyclic and linear α,β-unsaturated esters.



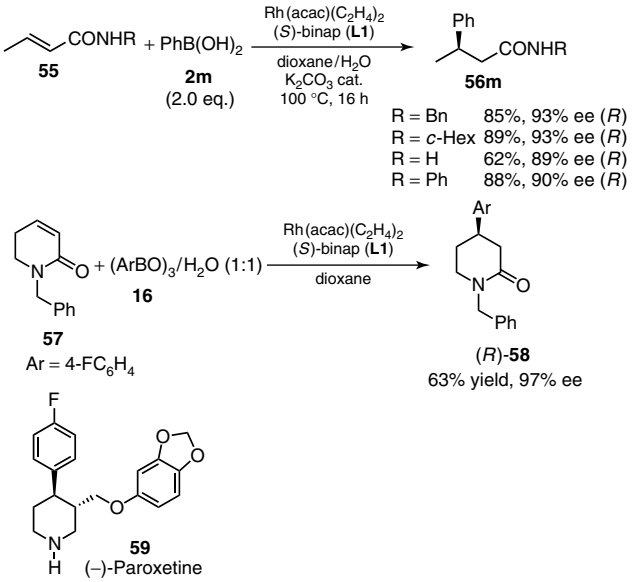
Scheme 1.23 Applications of the Rh-catalyzed ECA of ester in the synthesis of active pharmaceutical ingredients.

of the boron species. In addition, potassium carbonate (K_2CO_3) was found to be a useful additive.

A cationic rhodium(I)–chiraphos (**L3**) system was developed by Miyaura for the enantioselective preparation of β-diaryl carbonyl compounds (**48**) via the ECA of arylboronic acids (**2**) to β-aryl-α,β-unsaturated ketones or esters (**47**) (Scheme 1.24) [61]. As with other systems, the increase in the size of the ester group to CO_2t-Bu, led to a slight increase in enantioselectivity. The chiraphos ligand (**L3**) was quite effective for these substrates, but was a poor ligand for the Rh-catalyzed



Scheme 1.24 Rh-catalyzed ECA of arylboronic acid on β-aryl α,β-unsaturated esters and applications to the synthesis of active pharmaceutical ingredients.

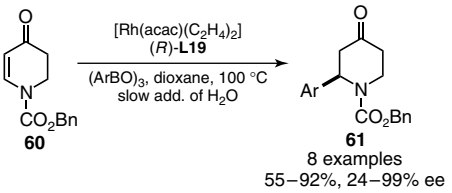


Scheme 1.25 [Rh]/(*S*)-binap catalyzed ECA of organoboron reagent to linear and cyclic α,β-unsaturated amides.

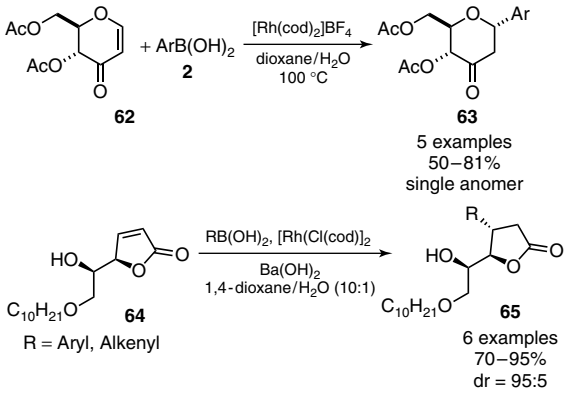
ECA of cyclic enones (cf. Scheme 1.11). This system proved quite versatile and functional group-tolerant, and was successfully applied as the key enantioselective step in the synthesis of two endothelin receptor antagonists **51** [140] and **54** [141].

Although less reactive than enones and enoates, linear α,β-unsaturated amides **55** perform similarly well under standard Rh-catalyzed ECA conditions [62]. The use of K_2CO_3 as an activator significantly increased the overall reaction yield. Comparable results were obtained for the addition of 4-fluorophenylboronic acid to 5,6-dihydro-2(1*H*)-pyridinones **57** to yield **58**, a key intermediate in the synthesis of paroxetine [33]. The asymmetric addition onto α,β-unsaturated amides has also been applied in total synthesis [142] (Scheme 1.25).

The use of boroxines with the Rh/phosphoramidite (**L19**) catalytic system enabled the synthesis of 2-aryl-4-piperidones **60**, which serve as a useful framework and are found in a number of active pharmaceutical ingredients (APIs) (Scheme 1.26) [85]. The use of aryl boroxines (**7**) and the slow addition of water were necessary to



Scheme 1.26 Rh-catalyzed ECA on 2,3-dihydro-4-pyridones.



Scheme 1.27 Examples of a diastereoselective Rh-catalyzed conjugate addition.

minimize protodeboration. For a variant of this transformation with organozinc, see Scheme 1.48 [143].

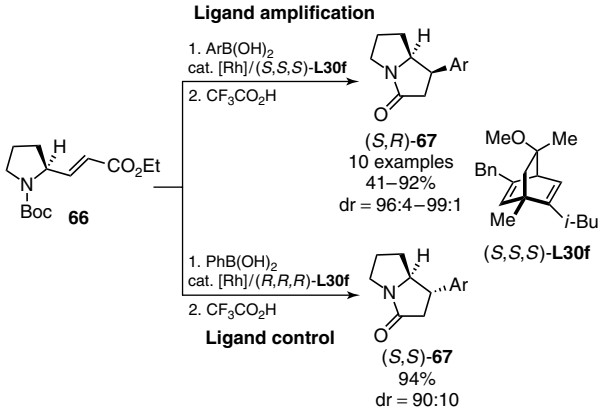
1.2.2.1 Diastereoselective Conjugate Addition

The presence of a chiral center in close proximity to the β position of an α,β-unsaturated carbonyl compound can be used to control the diastereoselectivity of a Rh-catalyzed conjugate addition, without the need for extraneous chiral ligand on Rh. The first example of such a diastereoselective reaction was reported for the synthesis *C*-glycosides **63** from the enantiomerically pure cyclic esters **62** [144]. The reaction was efficiently catalyzed by a cationic Rh source to give the *C*-glycosides **63** as single anomers. Another example is the Rh-catalyzed addition of aryl- and alkenylboronic acids onto butenolide **64**, leading to the products **65** with high diastereoselectivities (Scheme 1.27) [145]. In this regard, the presence of an unprotected hydroxyl group may also provide an enhancement of the diastereocontrol at the addition.

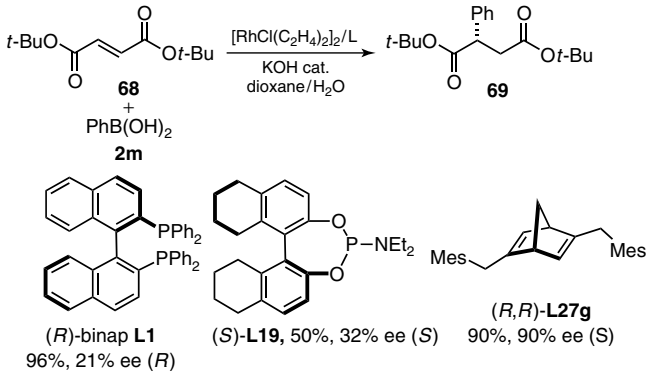
A similar approach was used for the asymmetric synthesis of functionalized pyrrolizidinones **67** (Scheme 1.28) [146]. In this case, chiral diene (*S,S,S*)-**L30f** was used to enhance the diastereoselectivity of the process leading to (*S,R*)-**67**. On the other hand. the use of the other enantiomer of the ligand (*R,R,R*)-**L30f**, reversed the diastereoselectivity of the ECA to afford (*S,S*)-**67** (Scheme 1.28). Therefore, the process is under ligand control.

1.2.2.2 Fumarate and Maleimides

Although the ECA products of fumarates and maleimides are synthetically useful 2-substituted 1,4-dicarbonyl compounds, they represent a difficult class of substrates because they are relative unreactive. In the ECA of phenylboronic acid onto di-*tert*-butyl fumarates (**68**), traditional diphosphine ligands (**L1**) and phosphoramidite ligands (**L19**) gave poor yields and enantioselectivities, while the bulky chiral diene **L27g** gave higher yields and synthetically useful enantiomeric excesses (Scheme 1.29) [108].



Scheme 1.28 Asymmetric synthesis of functionalized pyrrolizidinones using [Rh]/diene catalytic system.

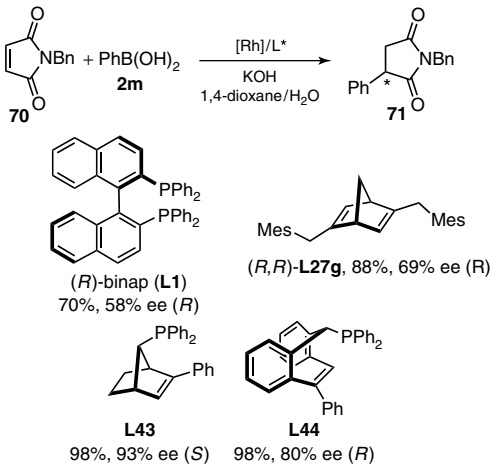


Scheme 1.29 Rh-catalyzed ECA of phenylboronic acid onto di-*tert*-butyl fumarate.

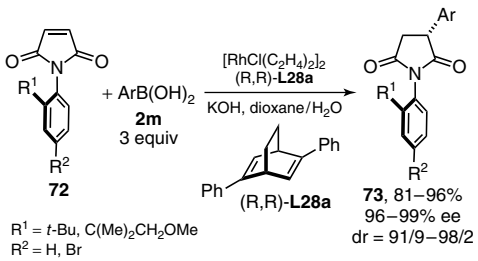
Similarly, phosphine-based ligands such as (*R*)-binap (**L1**) lead only to moderate enantioselectivity for the ECA of phenylboronic acid (**2m**) onto benzyl maleimide [129]. First-generation chiral dienes such as **L27g** showed increased reactivity [129], but the enantioselectivity remained low. A breakthrough was achieved with the use of phosphorus–olefin hybrid ligands **L43** [129, 130], and **L44** [131] that gave excellent yields and enantioselectivities.

The efficient diastereoselective synthesis of axially chiral *N*-arylsuccinimides **73** has been achieved by using chiral diene **L28a** (Scheme 1.30) [108, 147]. Diphosphine ligands gave lower diastereoselectivities and enantioselectivities (Scheme 1.31).

An elegant application of maleimide **73** is the use of the axial chirality as a stereochemical relay for subsequent transformations, such as an alkylation of **73m** to generate a quaternary chiral center with diastereoselectivity and near-perfect



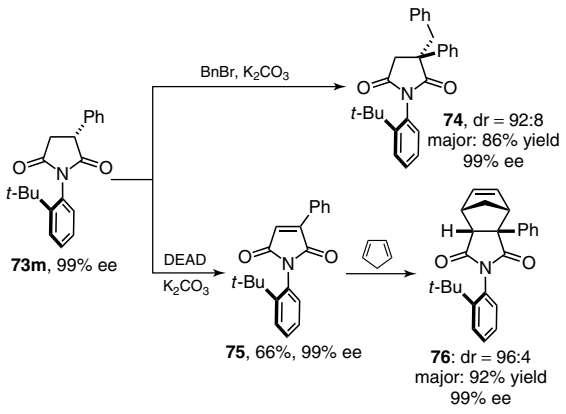
Scheme 1.30 Activity and selectivity of different ligand in the Rh-catalyzed ECA of $PhB(OH)_2$ onto maleimide **70**.



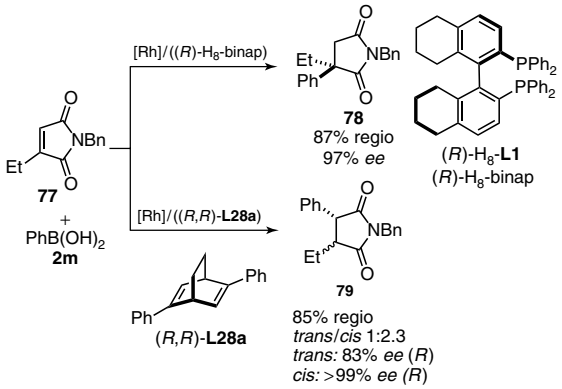
Scheme 1.31 Diastereoselective synthesis of axially chiral arylsuccinimides.

enantioselectivity. The maleimide **73m** can also be oxidized to dienophile **75** which undergoes a smooth stereoselective Diels–Alder to yield bicycle **76** (Scheme 1.32) [147].

The effective construction of chiral quaternary carbons is arguably one of the biggest challenges in asymmetric catalysis [148–150]. There are very few examples



Scheme 1.32 Transfer of the axial chirality of **73m**.



Scheme 1.33 Influence of the ligand on the regioselectivity of Rh-catalyzed ECA onto maleimides.

of ECA to β,β-disubstituted α,β-unsaturated carbonyl compounds [149]. During an examination of the use of substituted maleimides, Hayashi and coworkers discovered that the regioselectivity of the addition is a function of the ligand employed (Scheme 1.33) [151]. Whereas, Rh/(H_8-binap)-catalyzed processes give rise preferably to 1,4-adducts **78** with a quaternary stereogenic center, the Rh/((*R*,*R*)-**L28a**) catalyst leads to *cis*/*trans* mixtures of **79**.

1.2.2.3 Synthetically Useful Acceptors for Rh-Catalyzed ECAs

Today, a range of synthetically useful acceptors is available that can be used in the Rh-catalyzed ECA (see Figure 1.3). For example, the use of β-silyl-substituted α,β-unsaturated carbonyl compounds **80** as acceptors is of special interest as these compounds can be transformed to β-hydroxyketones by Tamao–Fleming oxidation [111]. In addition, the introduction of an alkenyl group onto the β-silyl enone **80** leads to a chiral allylsilane that can further react with the ketone moiety in an intramolecular Sakurai [152] reaction [153]. The 3,7-disubstituted bicyclo[3.3.1]octadiene **L36** performs particularly well with these substrates [104]. Another family of acceptors that enable the straightforward modification of the resulting adducts are α,β-unsaturated esters **47** [95], and α,β-unsaturated Weinreb

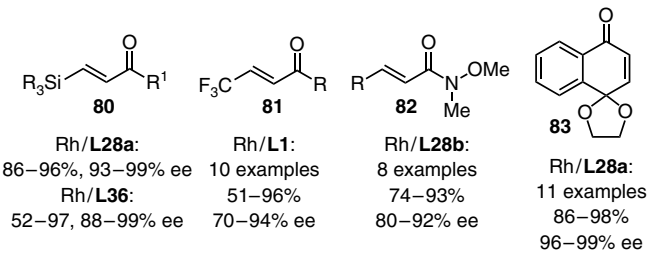
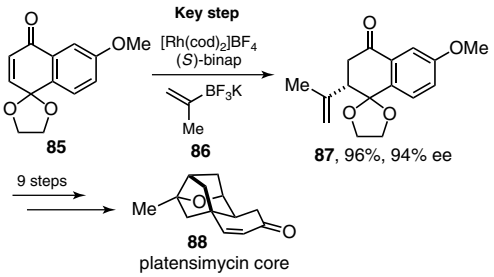


Figure 1.3 Synthetically useful acceptors in Rh-catalyzed ECAs.

amides **82** [154]. The ECA product using β-trifluoromethyl-α,β-unsaturated ketones **81** are of particular interest in the medicinal, pharmaceutical, and agricultural fields [155]. Lastly, α-arylated tetralones can be accessed in high yields and stereoselectivity by Rh/diene-catalyzed ECA of organoboron reagents to quinone monoketal **83** [114].

The Rh-catalyzed ECA of alkenyltrifluoroborate (**86**) onto quinone monoketals **85** was used by Corey and coworkers as a key step in the synthesis of platensimycin, a potent anti-cancer agent [3, 156] (Scheme 1.34).

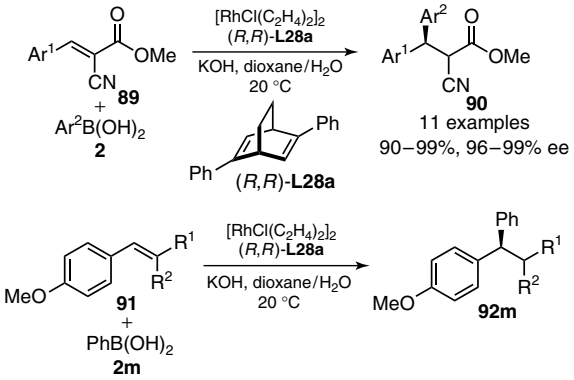


Scheme 1.34 Application of Rh-catalyzed ECA as a key step in the total synthesis of platensimycin.

To summarize the general trends in Rh-catalyzed ECAs of organoboron reagents onto α,β-unsaturated carbonyl compounds, the rate of the conjugate addition decreases with the reactivity of the acceptor and its steric bulk. Thus, acceptors can be classified into the following order of decreasing reactivities: enals > enone > enoate > enamides > fumarates > maleimides. Because effective coordination of the acceptor to rhodium is crucial for the reaction, acceptors that bear steric bulk in proximity to the unsaturation will be less reactive than unhindered ones. In addition, the activity of Rh/ligand catalytic systems increases with increasing π-accepting properties of the ligand.

1.2.3 Other Alkenes

The enantioselective construction of stereogenic carbon centers substituted with two aryl groups and one alkyl group is a subject of importance, because this structural motif is often found in pharmaceuticals and natural products. As discussed previously in Scheme 1.21 and Figure 1.3, their asymmetric synthesis has been reported by the chiral diene/rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated aldehydes (**31**) and esters (**47**). An alternative approach to such chiral building blocks has been demonstrated by Hayashi and coworkers with the use of arylmethylene cyanoacetates **89** as substrates (Scheme 1.35) [115]. The ECA product **90** can be easily decarboxylated to give the corresponding enantiopure β, β′-diaryl nitrile. The best results were obtained with the chiral diene (*R*,*R*)-**L28a** which enabled consistently high enantioselectivities to be achieved. As shown in the table in Scheme 1.35, the presence of both



Entry	Substrate	R^1	R^2	Product	Yield (%)	ee (%)
1	91a	CO_2Me	CN	92am	99	99 (*R*)
2	91b	CN	CN	92bm	9	n.d.
3	91c	CO_2Me	CO_2Me	92cm	11	n.d.
4	91d	CN	H	92dm	74	52 (*R*)
5	91e	CO_2Me	H	92em	99	57 (*R*)

Scheme 1.35 Rh-catalyzed ECA of arylboronic acids to arylmethylene cyanoacetates.

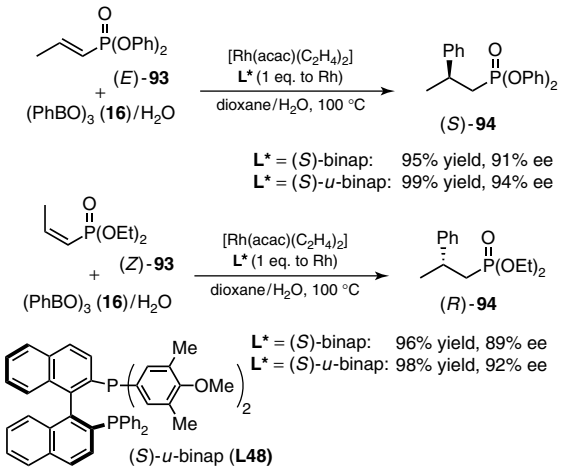
cyano and ester groups at the α-position of the substrates is essential for the high reactivity and enantioselectivity in the present reaction. Other combinations gave poor results.

1.2.3.1 Alkenylphosphonates

The Rh-catalyzed ECA onto alkenylphosphonates was first reported by Hayashi and coworkers. This class of substrate is less reactive than α,β-unsaturated carbonyl compounds, and the use of arylboroxine (**7**) instead of arylboronic acids (**2**), in the presence of 1 equiv. of water, was necessary to obtain high yields (Scheme 1.36) [157]. The enantioselectivities and chemical yields were slightly higher in the reaction catalyzed by the rhodium complex coordinated with unsymmetrically substituted binap ligand, (*S*)-u-binap, which has diphenylphosphino and *bis*(3,5-dimethyl-4-methoxyphenyl)- phosphino groups at the 2 and 2′ positions on the 1,1′-binaphtyl skeleton (Scheme 1.36). In agreement with the stereochemical model depicted in Scheme 1.10, the *trans* and *cis* geometries of alkenylphosphonate **93** give rises to opposite enantiomers.

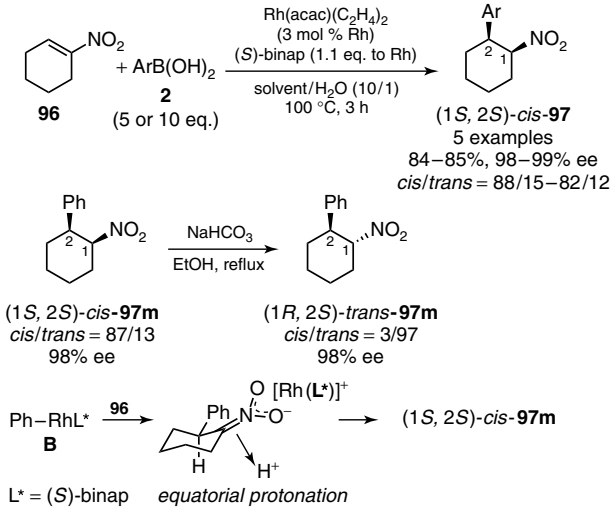
1.2.3.2 Nitroalkenes

Nitroalkenes are good substrates for the rhodium-catalyzed ECA of organoboronic acids [158]. Hayashi reported that the reaction of 1-nitrocyclohexene (**96**) with phenylboronic acid (**2m**) in the presence of the rhodium/(*S*)-binap catalyst gave an 89% yield of the 2-phenyl-1-nitrocyclohexane (**97m**) (Scheme 1.37). The main phenylation product **97m** is a *cis* isomer (*cis*/*trans* = 87/13), and both the *cis*



Scheme 1.36 Rh-catalyzed ECA of arylboronic onto alkenylphosphonates.

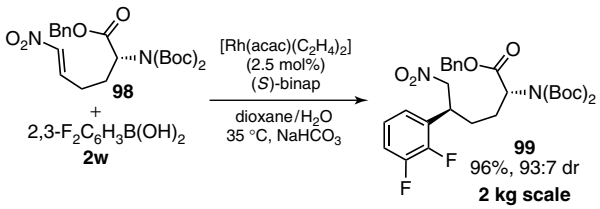
and *trans* isomers were 98% enantiomerically pure. Treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol caused *cis*–*trans* equilibration, giving thermodynamically more stable *trans* isomer (*trans*/*cis* = 97/3). It should be noted, that this rhodium-catalyzed asymmetric phenylation produced thermodynamically less stable *cis* isomer of high enantiomeric purity, and it can be isomerized, if so desired, into the *trans* isomer without any loss of its enantiomeric purity. The preferential formation of *cis*-**97** in the catalytic arylation may



Scheme 1.37 Rh-catalyzed ECA of arylboronic onto nitroalkenes.

indicate the protonation of a rhodium nitronate intermediate in the catalytic cycle (Scheme 1.38).

The optically active nitroalkanes obtained by the present method are useful chiral building blocks, which can be readily converted into a wide variety of optically active compounds by taking advantage of the versatile reactivity of nitro compounds. An example of the usefulness of this transformation was reported by the research group at Merck, who performed a Rh-catalyzed ECA of difluorophenylboronic acid onto nitroalkene **98** as the key step in the synthesis of nitroalkane **99** on a 2 kg scale, this being a precursor to a migraine headache treatment [5]. Bicarbonate was found to be a useful activator in this reaction.

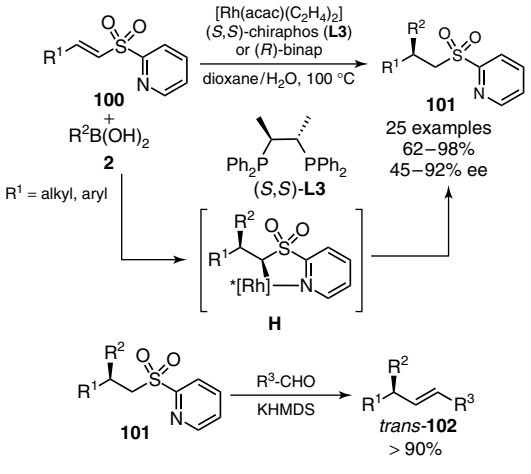


Scheme 1.38 Application of Rh-catalyzed ECA of a nitroalkene on a kilogram-scale.

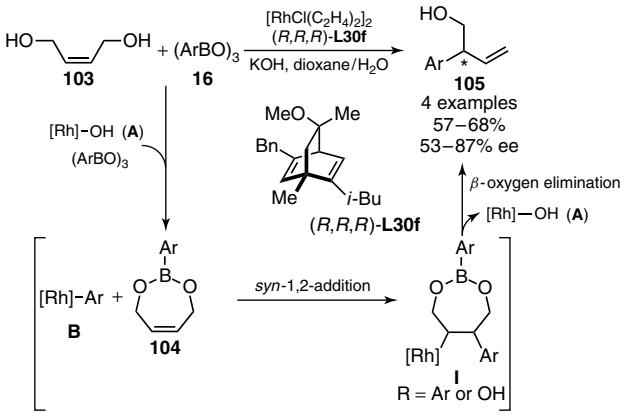
1.2.3.3 **Sulfones**

Hayashi disclosed that α,β-unsaturated phenyl sulfones do not react with organoboron reagents under the usual rhodium-catalyzed conditions. When nucleophilic aryltitanium reagents were employed, an elimination of the sulfonyl group occurred after the conjugate addition, leading to desulfonylated alkenes as final products (cf. Scheme 1.48) [159]. The key to this synthetic challenge was found through the use of a rhodium-coordinating α,β-unsaturated 2-pyridylsulfone (**100**). With these pyridyl sulfones, it was possible to obtain a general methodology for providing β-substituted sulfones in high yields and enantioselectivities ranging from 76 to 92% ee with (*S*,*S*)-chiraphos (**L3**) as the chiral ligand (Scheme 1.39) [160, 161]. The corresponding 4-pyridyl sulfone analogs displayed no reactivity, demonstrating the necessity of the 2-pyridyl sulfone moiety to stabilize **H**. The *cis*-alkenylsulfone (*cis*-**100**) gave the opposite enantiomer to *trans*-alkenylsulfone (*trans*-**100**), and this can be rationalized by the general stereochemical model depicted in Scheme 1.12 [160, 161]. The chiral β-substituted sulfones **101** readily participates in a Julia–Kocienski olefination [162] to provide a novel approach to the enantioselective synthesis of allylic substituted alkenes *trans*-**102**. In addition, the chiral sulfones **101** can be alkylated and the sulfonyl removed by Zn reduction [161]. This approach was extended to the addition of alkenylboronic acids to β-aryl-β-methyl-α,β-unsaturated pyridylsulfones, which enabled the efficient stereoselective formation of quaternary centers with up to 99% ee [163].

A novel and original approach for the synthesis of enantiomerically enriched 2-arylbut-3-enols **105** makes use of *cis*-allyldiol **103** and arylboroxines (**7**)



Scheme 1.39 Rh-catalyzed ECA of organoboronic acid with alkenyl sulfones.



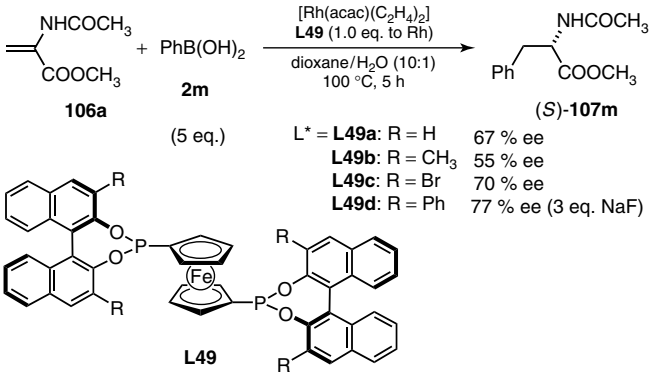
Scheme 1.40 Rh-catalyzed substitutive arylation of a *cis*-allylic diol with arylboroxines.

(Scheme 1.40) [164]. Under the reaction conditions, *cis*-diol **103** readily forms the cyclic arylboronic ester **104** which serves as an acceptor for a *syn*-1,2-carborhodation by [Rh(μ-OH)(**L30f**)] to give intermediate **I**. A subsequent β-oxygen elimination regenerates the active rhodium-hydroxide species **A** and releases the optically active alcohols **105**.

1.2.3.4 1,4-Addition/Enantioselective Protonation

So far, the Rh-catalyzed ECA process with β-substituted α,β-unsaturated carbonyl compounds has been reviewed. With this family of substrates, the enantio-determining step is the 1,2-insertion of the acceptor into the Rh–C_{sp2} bond. However, when α-substituted α,β-unsaturated carbonyl compounds are employed, the enantio-determining step is the protonation of the oxo-π-allylrhodium species (see Scheme 1.10). The asymmetric variant of this mechanistic manifold was first exploited by Reetz and coworkers, in the ECA of α-acetamidoacrylic ester

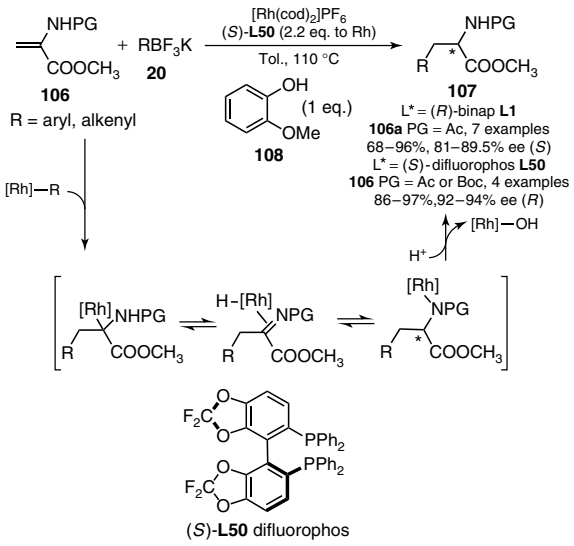
106 by phenylboronic acid (**2m**), giving the phenylalanine derivative **(107m)** in up to 77% ee (Scheme 1.41) [68]. A similar asymmetric transformation has also been reported by Frost and coworkers [165]. This reaction represents a convenient alternative to the synthesis of unnatural phenylalanine derivates (**107**), which are commonly accessed through Rh-catalyzed asymmetric hydrogenation of β-aryl-α-acetamidoacrylic esters [166].



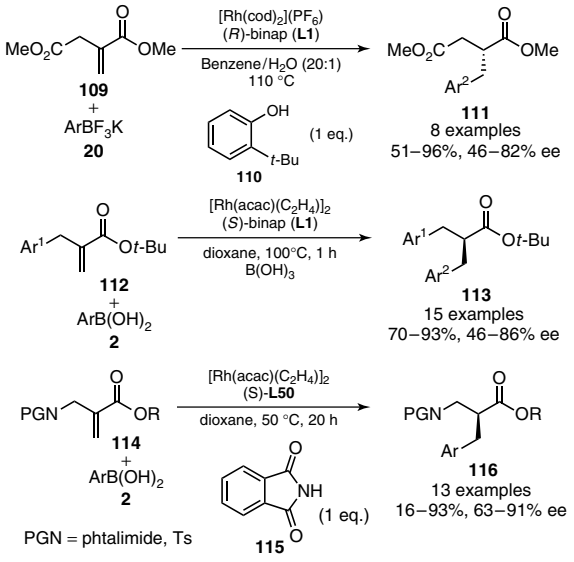
Scheme 1.41 Rh-catalyzed conjugate addition/enantioselective protonation.

In recognizing the importance of the proton source in this process, Genêt and Darses investigated a wide range of phenols instead of water as the proton donor [37, 167]. Guaiacol (**108**) proved to be the best proton donor and enabled a satisfactory enantioselectivity with a range of potassium organotrifluoroborates (Scheme 1.42). The ratio of metal to ligand had a notable effect on the enantioselectivity of the reaction, with 2.2 equiv. of chiral ligand relative to metal being optimal. Higher temperatures and the use of toluene or dioxane increased both conversion and enantioselectivity. Importantly, the presence of water accelerated the reaction 10-fold relative to guaiacol, but drastically decreased the enantioselectivity to 16% ee. The use of organoboronic acids also leads to lower yields and enantioselectivities, presumably due to residual traces of water. As with the ECA of enoate (see Scheme 1.22), increasing the size of the ester substituent in **106** leads to a slight increase in enantiomeric excesses. The use of more π-acidic (*S*)-difluorophos (**L50**) yields faster and more selective transformation relative to binap (**L1**). In-depth mechanistic studies and density functional theory (DFT) calculations into this process suggested that the actual mechanism goes through a sequential conjugate addition and β-hydride elimination to form an imine and a Rh-hydride species. The Rh-hydride subsequently reinserts into the imine enantioselectively, and the Rh-amino bond is then hydrolyzed to generate the reaction product [37].

The scope of substrates amenable to the enantioselective protonation was expanded to include dimethyl itaconate (**109**) [168], α-benzyl acrylates (**112**) [169], and α-aminomethyl acrylates (**114**) [170] (Scheme 1.43) [165]. In all of



Scheme 1.42 Rh-catalyzed conjugate addition/enantioselective protonation using guaiacol of the sole proton source.

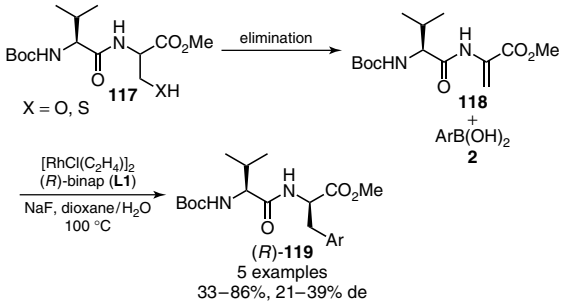


Scheme 1.43 Applications of Rh-catalyzed addition/enantioselective protonation.

these examples the choice of the additional proton source (phenol **110**, boric acid ($B(OH)_3$), or phthalimide **115**) was critical to obtain high yields and good selectivities.

An interesting application of the Rh-catalyzed enantioselective protonation is the peptide modification via site-selective residue interconversion, through an elimination and conjugate addition sequence (Scheme 1.44). Thus, a serine or

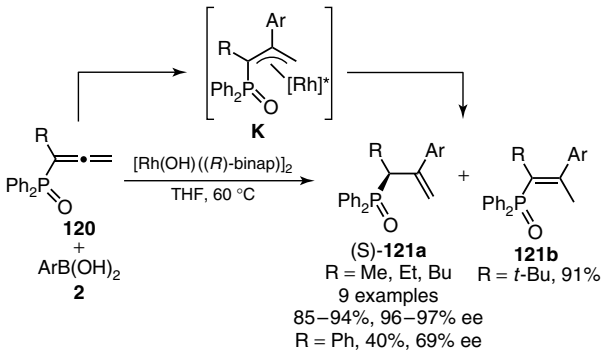
cysteine (**117**) can be selectively eliminated from a peptide chain to form a dehydroalanine fragment (**118**) that can subsequently undergo a Rh-catalyzed ECA to yield peptide with modified Ph-alanine fragment (**119**). Although the diastereoisomeric excesses are modest, this transformation can be applied on a range of di- and tripeptides [171].



Scheme 1.44 Application of the addition/enantioselective protonation to the synthesis unnatural peptides through site interconversion.

The enantioselective protonation was also applied to the hydroarylation of diphenylphosphinylallenes [172]. Unlike the oxo-π-allylrhodium species in previous examples, the π-allylrhodium intermediate **K** can be protonated α or γ to the phosphorus center to give intermediates **121a** and **121b**, respectively. Tetrahydrofuran (THF) was found to minimize the amount of **121b** formed. Furthermore, bulkier R groups (*t*-Bu) in allene **120** led to **121b** because protonation at the least-hindered position was favored. Under these conditions, the boronic acid would act as the proton source (Scheme 1.45).

An excellent overview of enantioselective protonation has been recently published [173].

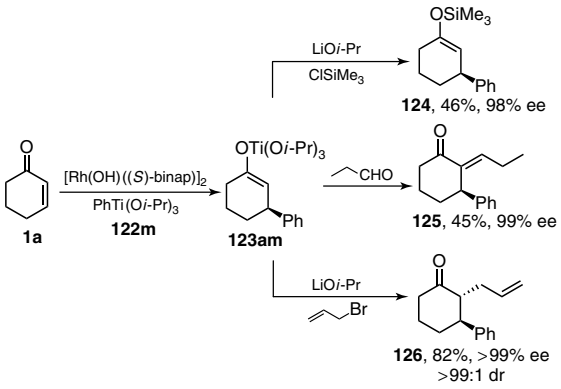


Scheme 1.45 Rh-catalyzed enantioselective addition to diphenylphosphinylallenes.

1.3
Rh-Catalyzed ECA Organotitanium and Organozinc Reagents

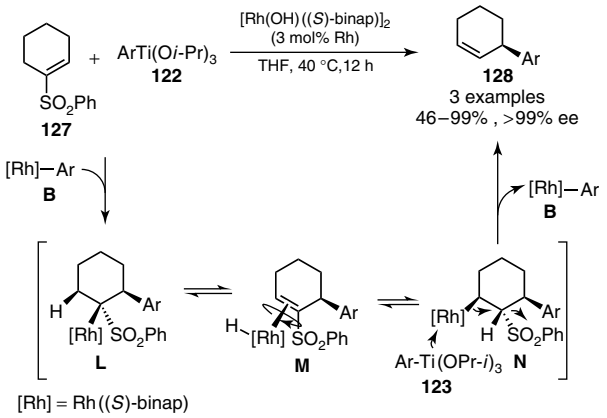
Hayashi and coworkers expanded the scope of nucleophilic reagents amenable to Rh-catalyzed ECA transformation to organotitanium [159, 174, 175] and organozinc [97, 136, 143, 176] reagents. These reagents are far more nucleophilic than the corresponding organoboron derivatives, and can be added to α,β-unsaturated compounds at room temperature. Furthermore, the reactions are run under aprotic conditions which enables trapping of the stable titanium and zinc enolates formed *in situ* with a range of electrophiles. The aryltitanium and arylzinc reagents are conveniently generated *in situ* through the addition of the corresponding aryllithium to $ClTi(Oi\text{-}Pr)_3$ [174] and $ZnCl_2$, respectively [143].

The titanium-enolate (**123am**) obtained from 2-cyclohexenone (**1a**) was treated with lithium isopropoxide, to generate a more reactive titanate, and with $ClSiMe_3$ to yield a silyl enol ether (**124**). Treatment of the titanium enolate with propanal resulted in formation of the *exo*-*E*-enone (**125**) by aldol addition and elimination (Scheme 1.46), but no elimination occurred with boron enolate (cf. Scheme 1.20). Allyl bromide could also be added to **123am** to give (2*R*,3*S*)-*trans*-3-phenyl-2-allylcyclohexanone (**126**) in 82% yield as a single diastereomer, the enantiomeric purity of which was more than 99% (Scheme 1.46).



Scheme 1.46 Rh-catalyzed ECA of phenyltitanium reagent onto 2-cyclohexenone.

α,β-Unsaturated sulfones, bearing no coordinating function, are resilient to Rh-catalyzed ECA with organoboron reagents. However, the Rh-catalyzed addition of aryl titanium reagents (**122**) on α,β-unsaturated sulfones revealed an interesting mechanistic pathway, in which the *cine*-substitution product **128** was formed (Scheme 1.47) [159]. This reaction was successfully exploited to form enantiopure allylic arenes (**128**). The reaction is thought to proceed through the stereoselective aryl-rhodium into the alkenyl sulfone (**L**), followed by β-hydrogen elimination

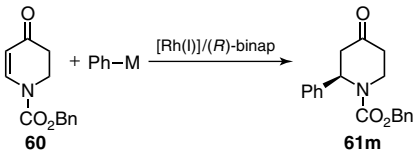


Scheme 1.47 Rh-catalyzed asymmetric cine-substitution of alkenyl sulfones.

(**M**)/hydride insertion sequence to form the alkyl-rhodium intermediate **N**. Subsequent *anti*-elimination of a sulfinyl produces the allylic arenes **128** and regenerates the aryl-rhodium species (Scheme 1.47).

It was found that a combination of lithium aryltitanates ($LiArTi(Oi\text{-}Pr)_4$) and chlorotrimethylsilane constitutes an effective arylating reagent, producing high yields of silyl enol ethers as 1,4-addition products [177]. Such titanates are generated *in situ* from the addition of an aryllithium onto $Ti(Oi\text{-}Pr)_4$. A mechanistic study of this system revealed that the reaction passed through similar intermediates as with organoboron reagents. The $ClSiMe_3$ was necessary to promote the addition of organotitanium reagents.

The stereoselective synthesis of chiral β-substituted piperidones through a Rh-catalyzed ECA is challenging because of the low reactivity of vinologous amides **60**. To overcome this, the more reactive arylzinc reagents (**129**), in conjunction with a Rh/binap catalyst, were employed (Scheme 1.48) [143]. Importantly, only a small excess of arylzinc relative to the enone was necessary to obtain a full conversion, while at least 3 equiv. of phenylboronic acid were required (Scheme 1.48).

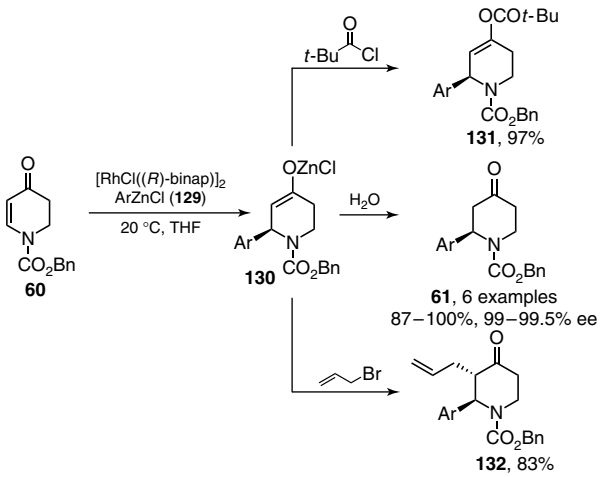


Entry	Ph-M (eq.)	Yield (%)	ee (%)
1	$PhB(OH)_2$ (3)	78	98
2	PhB(9-*BBN*) (3)	33	97
3	$PhTi(Oi\text{-}Pr)_3$ (1.5)	70	>99.5
4	PhZnCl (**129m**) (1.5)	95	>99.5

Scheme 1.48 Rh/(*R*)-binap-catalyzed ECA of organometallic reagents.

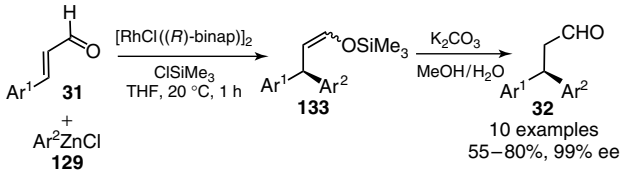
These conditions enabled the synthesis of a range of β-arylpiperidones **61** with near-perfect enantioselectivities.

In addition, the stable zinc-enolate formed during the reaction could be subsequently trapped with electrophiles such as pivaloyl chloride and allyl bromide to yield **131** and **132** (single diastereoisomer), respectively [143] (Scheme 1.49).



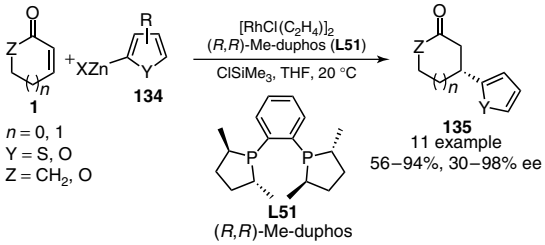
Scheme 1.49 Rh-catalyzed ECA with arylzinc onto piperidones.

The combination of arylzinc reagent (**129**) and $ClSiMe_3$ was found to be well suited to the Rh-catalyzed ECA onto enals, a challenging class of substrates (cf. Section 1.8) (Scheme 1.50). Only a limited amount of 1,2-addition product was observed (ca. <20%). Similar to the addition of organotitanates, $ClSiMe_3$ is necessary to activate the arylzinc reagents, the product being obtained as the corresponding silyl enol ether (**133**). For this transformation, arylzinc reagents were superior to organoboron and organotitanium reagents.



Scheme 1.50 Rh-catalyzed ECA of arylzinc/$ClSiMe_3$ onto enals.

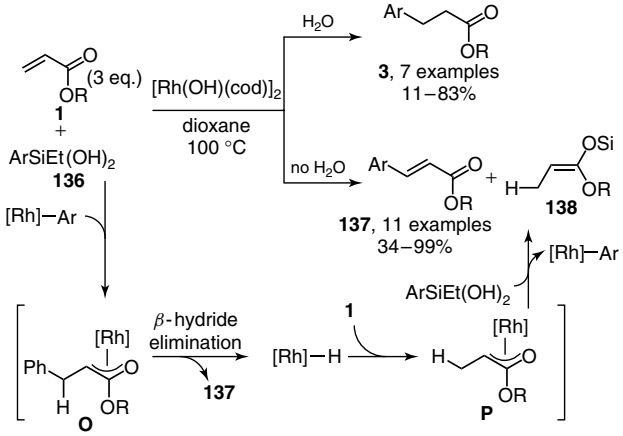
The combination of heteroarylzinc reagent (**134**) and $ClSiMe_3$ chloride has also been applied to the ECA of heteroaromatic compounds to α,β-unsaturated ketones and esters (Scheme 1.51) [178]. Interestingly, (*R,R*)-Me-duphos (**L51**) proved to be the best chiral ligand for this transformation, but it performed poorly for the ECA of organoboron reagents (cf. Scheme 1.11).



Scheme 1.51 Rh-catalyzed ECA of heteroaromatic zinc reagents to α,β-unsaturated ketones and esters.

1.4
Rh-Catalyzed ECA of Organosilicon Reagents

Today, organosilicon reagents play a growing role in organic synthesis due to their low cost, low toxicity, ease of handling, tolerance to a variety of functional groups, and simplicity of byproduct removal [179–181]. Unfortunately, organosilicon reagents are far less reactive than their boron, tin, titanium, and zinc counterparts, and this has led to a relatively slow development as nucleophiles in Rh-catalyzed ECA reaction. The first Rh-catalyzed addition of organosilicon reagent to α,β-unsaturated carbonyls was independently reported in 2001 by Mori and Li [182, 183]. By analogy with organoboronic acids, Mori made use of silanediols **136** as the nucleophiles and $[Rh(OH)(cod)]_2$ as the catalyst (Scheme 1.52). Depending on whether the reaction conditions where anhydrous or not, either the Mizoroki–Heck-type product **137** or the addition product **3** were observed. The Mizoroki–Heck-type product is due to the β-hydride elimination from the rhodium-enolate **O**, followed by conjugate reduction of an acrylate and subsequent transmetallation of the resulting Rh-enolate **P** (Scheme 1.52). Thus, as had been

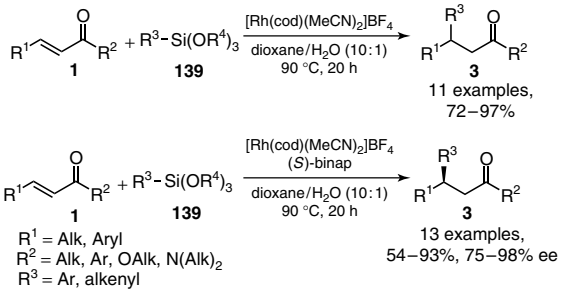


Scheme 1.52 Rh-catalyzed addition of arylsilanol to acrylates.

observed for organoboron reagent, water proved to be essential in these reactions to hydrolyze the Rh-enolate and regenerate the active hydroxyrhodium species. Using similar conditions, poly(phenylmethylsiloxane) (arylated silicone oil) proved to be a competent organosilicon derivative in Rh-catalyzed conjugate addition [184].

Li and coworkers found that a combination of dichlorodiarylsilanes and NaF, using water as the solvent and a cationic rhodium source ($[Rh(cod)_2]BF_4$), was optimal for the addition onto a wide range of acceptors, including challenging maleates and β-aminoacrylate [183]. It is likely that, under these conditions, silanols are formed.

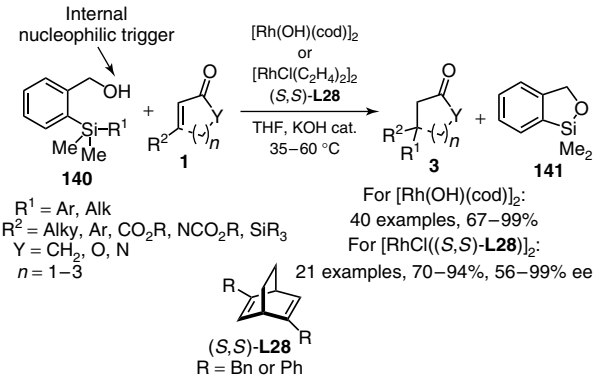
Interestingly, Oi and coworkers found that organosiloxanes generated from alkoxysilanes ($RSi(OR')_3$) **139** were a good alternative to hydrolytically unstable chloro- and fluoro-organosilicon derivatives, and $[Rh(cod)(MeCN)_2]BF_4$ proved to be the best catalyst for this transformation (Scheme 1.53) [56, 185]. With cationic rhodium complexes, organosiloxanes do not require external activator to transmetallate to rhodium. These conditions were applied successfully to the asymmetric variant of this reaction, using (*S*)-binap as the chiral ligand (Scheme 1.53) [58]. The enantioselectivities observed were very close to those obtained with organoboronic acid, indicating a similar reaction pathway [17, 60]. In a one-pot procedure, using the same cationic $[Rh((S)\text{-binap})(MeCN)_2]BF_4$ complex, alkenylsilanes can be generated *in situ* by hydrosilylation of the corresponding alkyne, and then subjected to ECA [186, 187]. Organosiloxanes were also used in the Rh-catalyzed asymmetric addition to α-substituted acrylic esters (for the reaction with organoboronic acids; cf. Scheme 1.43) [188].



Scheme 1.53 Rh-catalyzed ECA of organosiloxanes onto α,β-unsaturated carbonyls.

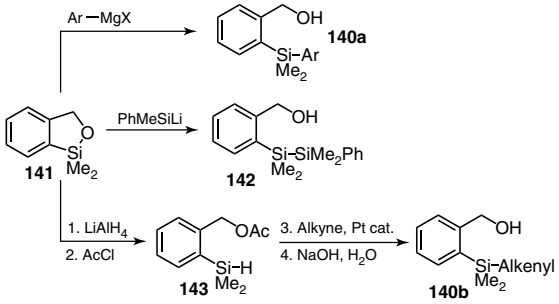
Based on the seminal studies of Hudrilk [189, 190], Hiyama and Nakao introduced the stable and reusable tetraorganosilicon reagents, alkenyl-, aryl-, and silyl[2-(hydroxymethyl)phenyl]dimethylsilanes **140**, which undergo 1,4-addition reactions to α,β-unsaturated carbonyl acceptors under mild rhodium catalysis (Scheme 1.54) [153, 191–193]. The only byproduct in this case was the volatile cyclic siloxane **141**. These reagents were the first examples of stable tetraorganosilicon compounds that could efficiently transmetallate from Si to Pd and Rh under mild, fluoride-free conditions. The key to the success of the tetraorganosilicon **140** is the internal hydroxy nucleophilic trigger, which increases the polarization of the

Ar–Si bond upon deprotonation. This reagent enables the introduction of a large gamut of aryl and alkenyl groups onto all α,β-unsaturated ketones, ester, amides, nitriles, vinylogous amides, fumarates, and maleimides (Scheme 1.54) [192]. Chiral diene ligands **L28** are extremely effective for this transformation, using the tetraorganosilicon reagents **140**.



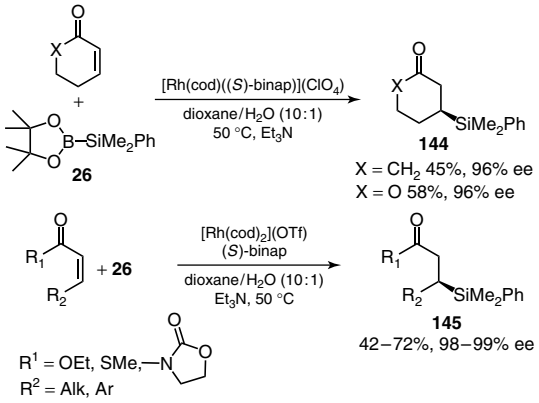
Scheme 1.54 Rh-catalyzed ECA of tetraorganosilicon reagent **141** to α,β-unsaturated carbonyls.

The aryl derivative of reagent **140a** can be easily regenerated by addition of the corresponding Grignard reagent onto **141**, whereas the alkenyl functionalized **140b** is obtained by reduction of **141** by $LiAlH_4$ followed by protection and subsequent regioselective alkyne hydrosilylation and deprotection (Scheme 1.55) [193]. The silyl variant (**142**) of reagent **140** can also function as a silyl transfer, albeit with only moderate yield due to competitive loss of silane [192].



Scheme 1.55 Regeneration of the tetraorganosilicon reagents **141**.

In addition to aryl and alkenyl groups, bis(pinacolato)diboron (**25**) and silyl boronic ester **26** can be used in Rh-cat conjugate additions to transfer boron [49] and silyl groups respectively. Thus, the $SiMe_2Ph$ group can be introduced onto linear and cyclic α,β-unsaturated carbonyl compounds in moderate yields and with high enantioselectivity (Scheme 1.56) [50, 51].



Scheme 1.56 Rh-catalyzed ECA with (pin)B-$SiMe_2Ph$.

1.5
Rh-Catalyzed ECA with Other Organometallic Reagents

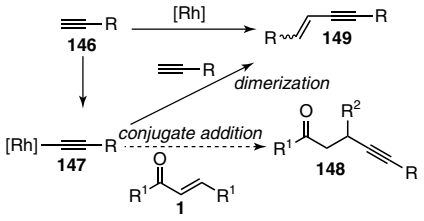
Apart from B, Si, Ti, and Zn, several other organometallic reagents have been used successfully in Rh-catalyzed ECA. Alkenyl zirconium species, derived from the hydrozirconation [194] of primary alkynes by Schwartz reagent ($[Cp_2Zr(H)(Cl)]$), are useful reagents in Rh-catalyzed ECAs [59, 195, 196]. Aryl-lead [197], -tin [54, 57, 198], and triarylbismuth [199] compounds are also competent aryl-transfer agents in Rh-catalyzed conjugate additions, even in the presence of air and water [200]. Diaryl indium hydroxides represent an interesting class of organometallic reagents in rhodium-catalyzed ECAs. These are readily obtained from the reaction of the corresponding aryl lithium or aryl Grignard onto indium trichloride followed by hydrolysis; more importantly, they are nontoxic and stable under aqueous conditions [201]. As with organoboronic acids, the presence of an hydroxide on indium is necessary for smooth transmetallation, and a similar transmetallation step can be surmised (cf. Scheme 1.8) [201].

It thus appears, that the main criteria for effectiveness of an organometallic reagent are that: (i) it can smoothly and efficiently transmetallate to the rhodium center; and (ii) it is stable under the conditions necessary to hydrolyze the rhodium-enolate, or that the reagent can transmetallate directly with the Rh-enolate.

1.6
Rh-Catalyzed ECA of Alkynes

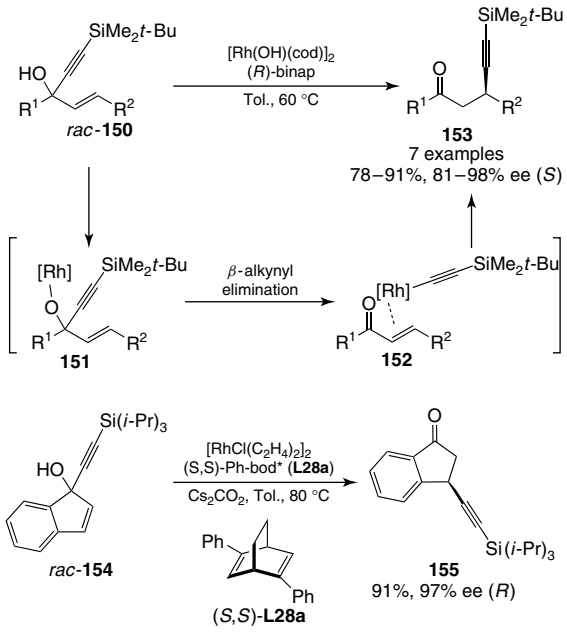
Alkyne as a nucleophile for Rh-catalyzed conjugate addition has been studied minimally, with the earliest reports employing only MVK as the acceptor and having long reaction times [202, 203]. The major hurdle with Rh-catalyzed alkynylation is that an primary alkyne (**146**) is generally more reactive than an enone towards Rh-alkynylides (**147**), and this results in the preferential formation of alkyne dimer

(**149**) rather than the conjugate addition product **148** (Scheme 1.57). The state of the art for asymmetric alkylation methodologies was reviewed in 2009 [204].



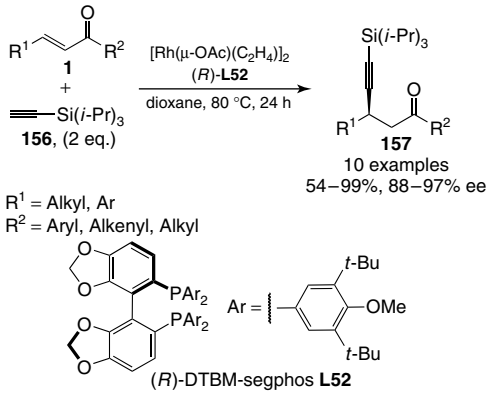
Scheme 1.57 Competitive reaction pathways for ECA of alkynes onto α,β-unsaturated compounds.

Hayashi and coworkers developed three methods to overcome competitive alkyne dimerization in rhodium-catalyzed ECAs of alkynes to enones [205, 206]. The first method consisted of the rearrangement of racemic alkynyl-alkenyl alcohols of type **150** (obtained from the 1,2-addition of a silylated alkynyl lithium onto an enone) to the conjugate addition product **153** (Scheme 1.58). This rearrangement was proposed to occur by the formation of rhodium-alkoxide **151**, followed by a β-alkyne elimination to form a chiral alkynyl-rhodium complex **152**, from which the ECA occurred. The key to this reaction is that the enone is in the coordination sphere of the rhodium center as the Rh-alkynyl is generated, and that no free alkyne is present during the reaction, thus shutting down the alkyne dimerization pathway. Interestingly, for indenone derivative **154**, the diene ligand (*S*,*S*)-**L28a** gave higher yields and enantioselectivity than (*R*)-binap (Scheme 1.58).



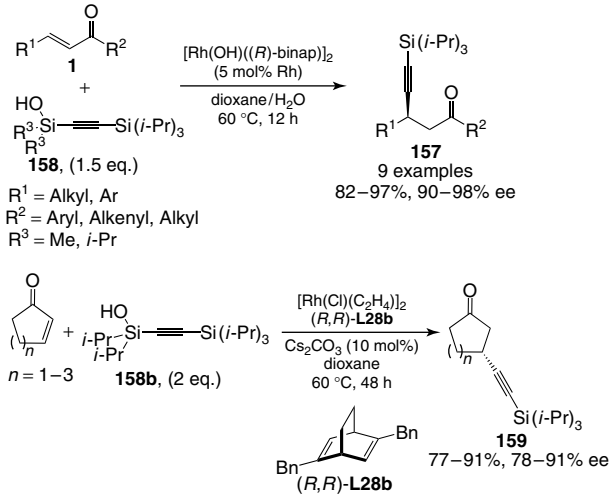
Scheme 1.58 Rh-catalyzed rearrangement of *rac*-**150** into chiral β-alkynyl ketones.

The second method for Rh-catalyzed conjugate alkynylation is the bimolecular addition of an alkyne onto an enone. The success of this method relies on the careful tuning of the catalyst and substrates (Scheme 1.59). Hence, to prevent competitive alkyne dimerization, the size of the alkyne was increased by using (triisopropylsilyl)acetylene (**156**). The use of the bulky (*R*)-DTBM-Segphos (**L52**) was also instrumental in accessing high enantioselectivities. Interestingly, cyclic enones were also alkynylated with excellent enantioselectivities, albeit in lower yields (55% for indenone). Although this method is high yielding and enantioselective, the scope of ketone amenable to this transformations is rather limited.



Scheme 1.59 Direct Rh-catalyzed ECA of alkyne onto α,β-unsaturated ketones.

The final method improved on these results by using bulky internal bis-silylated alkyne **158** [207]. The silanol in alkyne **158** enables a smooth transmetallation of the alkyne from Si to Rh while maintaining **158** bulky enough to prevent undesired alkyne dimerization. By using the alkynylsilanols **158**, the reaction time



Scheme 1.60 Rh-catalyzed ECA of alkynylsilanols onto α,β-unsaturated ketones.

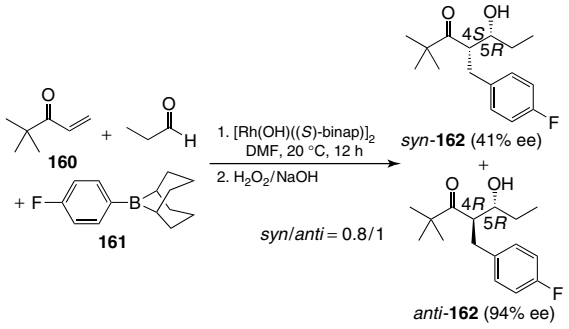
could be reduced to 12 h and the temperature lowered to 60 °C. Importantly, this methodology enabled the ECA of alkynes onto cyclic ketones, which were previously too unreactive to compete against alkyne dimerization, to form **159** (Scheme 1.60). In this case a catalytic amount of base (Cs_2CO_3) was necessary to accelerate the rate of the reaction.

1.7
Rh-Catalyzed Tandem Processes

In the previous sections, the rhodium-catalyzed ECAs of organometallic reagents on a wide range of acceptors has been described. In this case, the more electron-deficient the unsaturated substrate is, the more readily it will react with the organorhodium species generated by transmetallation from boron to rhodium. Thus, it is possible to program carborhodation cascades by assembling inter- or intramolecularly acceptors of differing reactivity. The cascade is initiated by carborhodation onto the most reactive acceptors, which subsequently react with the second most reactive acceptors, and so forth, until the sequence is terminated by protonolysis of the organorhodium intermediate. Such cascade sequences, which consist of multiple carbometallation steps, provide powerful methods for the construction of structurally complex molecules in an efficient and atom-economic manner [208]. These transformations have been the object of several reviews [209–211].

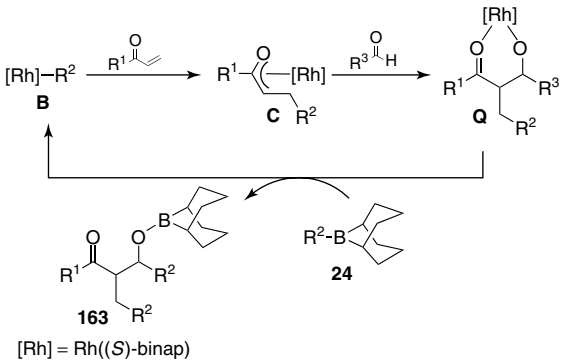
1.7.1
Tandem ECA/Aldol Reaction

An elegant three-component Rh-catalyzed tandem ECA/aldol reaction was developed by Hayashi and coworkers [135]. The reaction of ArB(9-*BBN*) (**24**), vinyl ketone **160**, and propanal catalyzed by $[Rh(OH)((S)\text{-binap})]_2$ as a catalyst gave optically active products, *syn*-(4*S*,5*R*)-**162** in 41% ee and *anti*-(4*R*,5*R*)-**162** in 94% ee, though the *syn*/*anti* selectivity was only 0.8/1 (Scheme 1.61). Formation of the enantiomerically enriched products demonstrated that the reaction proceeded



Scheme 1.61 Three-component Rh-catalyzed tandem ECA/aldol reaction.

through the (oxa-π-allyl)rhodium complex **C** coordinated with (*S*)-binap ligand, and underwent an aldol-type reaction, with aldehyde forming rhodium aldolate **Q** (Scheme 1.62). The aldolate further reacted with **24** to form **163** and regenerate **B**. The boron enolate as an intermediate was ruled out, which would lead to a racemic aldol product. An analogous zirconium-based three-component coupling reaction was reported by Nicolaou and coworkers [196].

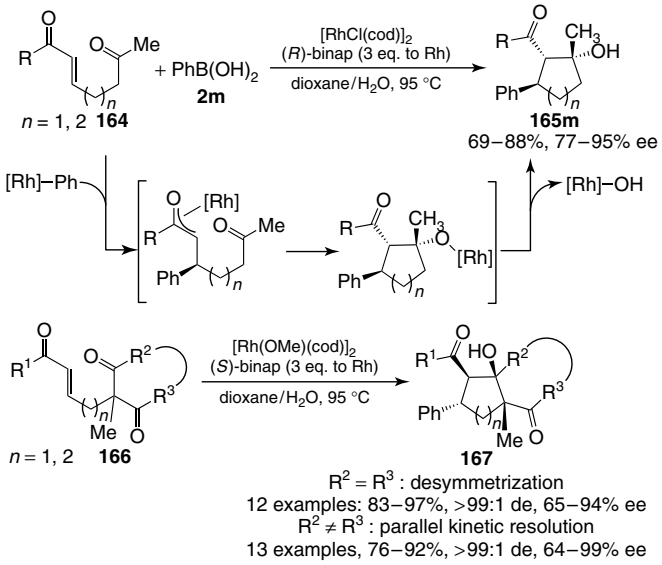


Scheme 1.62 Rh-catalyzed tandem ECA/aldol reaction.

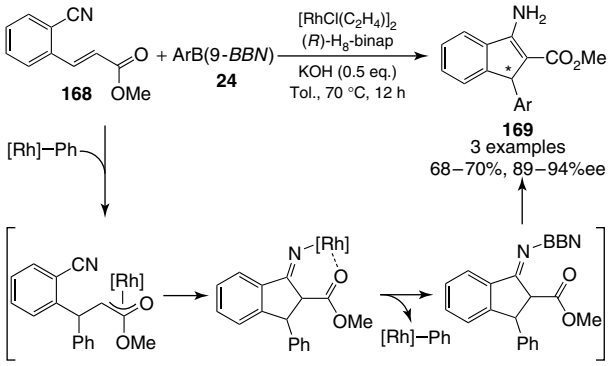
Krische and coworkers reported the intramolecular trapping of a chiral Rh-enolate by an electrophile [212]. The ECA of phenylboronic acid onto an α,β-unsaturated ketone having a pendant ketone (**164**) results in the formation of an (oxa-π-allyl)rhodium species, which subsequently undergoes an intramolecular aldol addition onto the ketone fragment. Because of the close proximity of the electrophile, the reaction is kinetically favored and protic conditions can be used. This sequence produces cyclic aldol adduct **165** with a near-perfect control of relative and absolute stereochemistries (Scheme 1.63) [212]. For example, the reaction of keto-enone **164a** (n = 1) with phenylboronic acid in the presence of a rhodium/(R)-binap catalyst gave the five-membered ring aldol product **165am** exclusively, in 88% chemical yield and 94% ee. This method was elegantly applied to the desymmetrization of diketoenones **166**, which resulted in the stereoselective formation of bicycle **167** with four contiguous stereogenic centers, including a quaternary center (Scheme 1.63) [213].

1.7.2
Tandem Conjugate Addition/1,2-Addition

Cyano groups can also serve as electrophiles for Rh-catalyzed tandem cyclization triggered by the conjugate addition of arylboron reagents to form five- and six-membered β-enamino esters **169** from the cyano enoate **168** (Scheme 1.64) [214]. An (oxa-π-allyl)rhodium intermediate, generated by the initial conjugate addition of an arylrhodium species, undergoes a facile intramolecular addition to the cyano group followed by sequential transmetallation with Ar-B(9-*BBN*) (**24**).



Scheme 1.63 Rh-catalyzed intramolecular tandem ECA/aldol reaction.

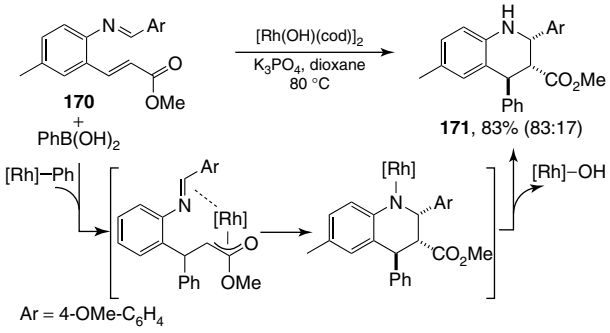


Scheme 1.64 Tandem Rh-catalyzed ECA/1,2-addition onto a cyano group.

The use of (*R*)-H_8-binap for the reaction of **168** gave the ECA/1,2-addition product **169** with up to 95% ee.

1.7.3
Tandem ECA/Mannich Reaction

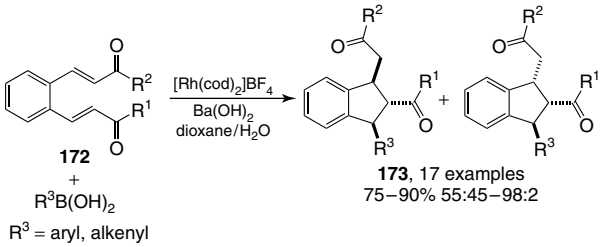
A Rh-catalyzed tandem conjugate addition/Mannich cyclization reaction of imine-substituted electron-deficient alkenes **170** with arylboronic acids has been achieved (Scheme 1.65) [215]. This sequence provides a versatile entry into highly functionalized tetrahydroquinolines **171** with acceptable diastereoselectivities.



Scheme 1.65 Tandem Rh-catalyzed conjugate addition/1,2 addition onto an imine function.

1.7.4
Tandem Conjugate Addition/Michael Cyclization

A stereoselective Rh-catalyzed tandem annulation reaction triggered by the conjugate addition of arylboronic acids to enones **172**, followed by an intramolecular Michael reaction leading to **173**, has been reported (Scheme 1.66) [216]. This sequence afforded 1,2,3-trisubstituted indanes **173** in a highly regio- and diastereoselective fashion. On the other hand, the corresponding reactions with α,β-unsaturated esters gave rise to a complex mixture of reaction products.

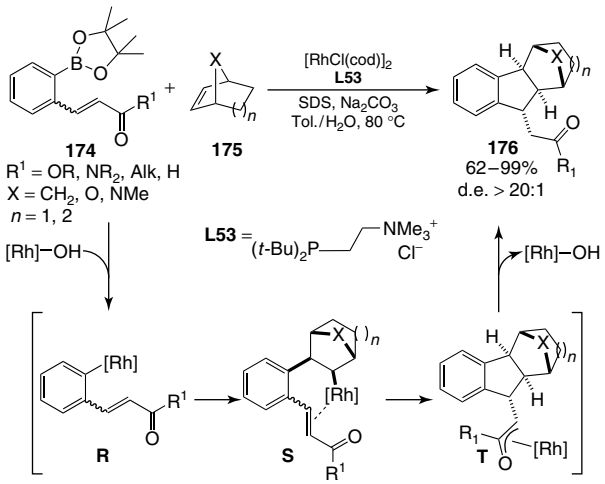


Scheme 1.66 Tandem Rh-catalyzed conjugate addition/Michael cyclization.

1.7.5
Tandem Carborhodation/Conjugate Addition

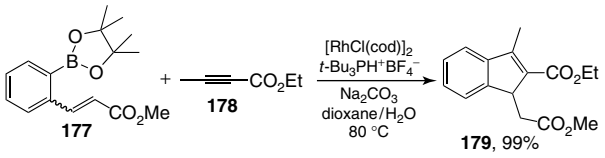
In 2000, Miura disclosed that strained alkenes, such as 2-norbornene, could efficiently undergo sequential carborhodation processes [217]. Lautens and coworkers exploited this observation for the rapid assembly of highly functionalized polycyclic systems **176** in a diastereoselective fashion (Scheme 1.67) [218, 219]. This sequence relies on the subtle coexistence, within **174**, of an arylboronate esters and an α,β-unsaturated carbonyl function which cannot react intramolecularly or dimerize under Rh-catalyzed reaction conditions, but which can undergo a carborhodation with **175** followed by an intramolecular conjugate addition. The reaction

is performed in aqueous media with water-soluble electron-rich phosphines as ligands. Under these conditions, the boron pinacol ester is slowly hydrolyzed to generate a boronic acid, which will subsequently transmetallate with rhodium to generate intermediate **R** (Scheme 1.67). The arylrhodium species generated adds onto the strained alkene through the *exo* face (Scheme 1.67, **S**). In the resulting alkylrhodium species, rhodium is presumably coordinated to the internal pendant olefin. Subsequent conjugate addition occurs by a 5-*exo-trig* process to generate a rhodium-enolate **T**. Rapid hydrolysis of the Rh-enolate **T**, releases the fused indane product and regenerates the hydroxorhodium catalyst. The scope of this sequence has been expanded to bifunctional boronates esters/Michael acceptor building blocks bearing heteroaromatic rings (i.e., indole, benzofuran, benzothiophene, and thiophene) [220].



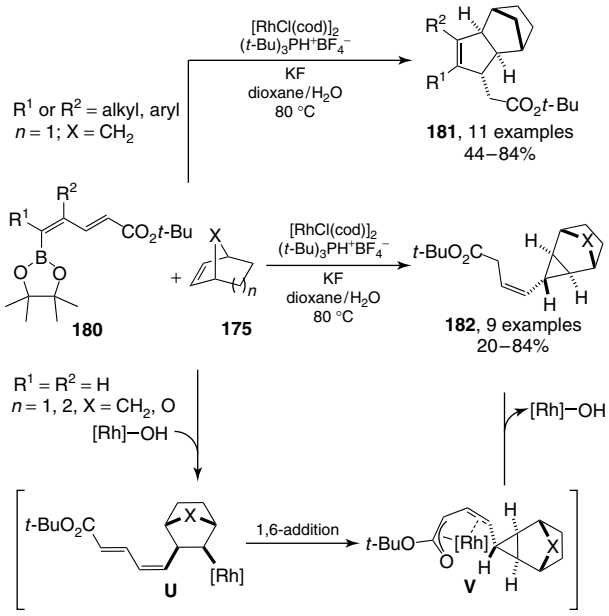
Scheme 1.67 Tandem Rh-catalyzed carborhodation/conjugate addition.

Activated alkynes such a **178** can react with **177** under similar conditions, to afford 1*H*-indenes **179** (Scheme 1.68) [221].



Scheme 1.68 Tandem Rh-catalyzed carborhodation/conjugate addition.

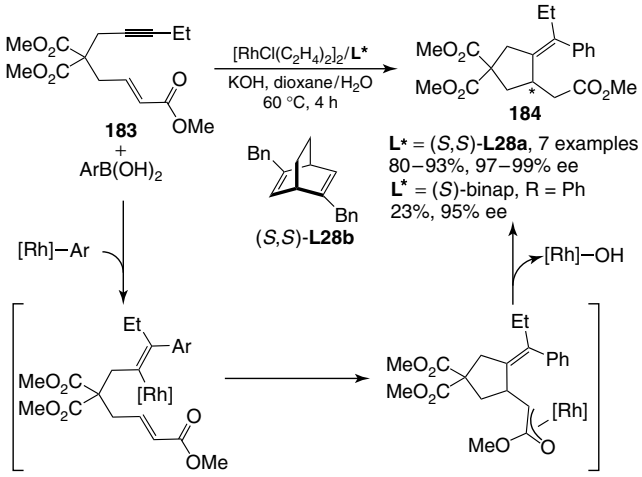
A closely related Rh-catalyzed tandem cyclization reaction has been achieved by using a boronate ester **180** in which the aryl function has been replaced by a *cis*-alkene (Scheme 1.69) [222, 223]. With this substrate class, after the initial carborhodation with **175** (intermediate **U**), a vinylcyclopropanation reaction occurs through a rare selective 1,6-addition of an alkylrhodium species in preference to



Scheme 1.69 Tandem Rh-catalyzed carborhodation/conjugate addition.

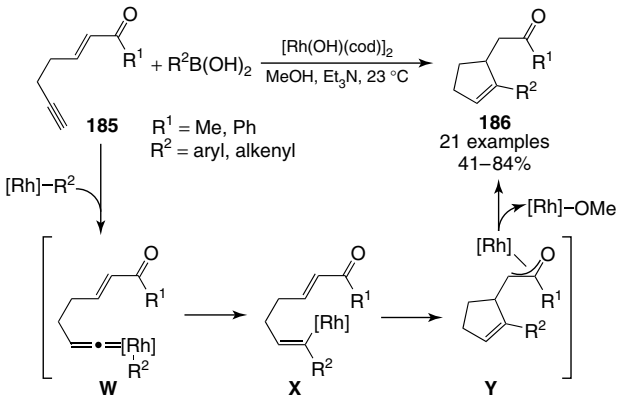
1,4-addition to form exclusively cyclopropane **182**. The exclusive formation of a *cis*-alkene was thought to be favored due to internal coordination of the carbonyl group, which locks the (oxa-π-allyl)rhodium **V** into one conformation. Depending on the substitution pattern of the dienylboronate esters, the reaction pathway can switch from an intramolecular 1,6-addition leading to **182**, to a 1,4-addition mechanism affording carbocycles **181** containing cyclopentene moiety instead of a vinylcyclopropane. Moreover, low yields are observed if the dienylboronate esters **180** are substituted α or γ to the ester function [223].

Interestingly, a Rh/diene (**L28b**) catalyst is far more chemo- and enantioselective at promoting arylative cyclization of alkyne-tethered electron-deficient olefin **183** to cyclopentene **184** than a Rh/diphosphine catalyst (Scheme 1.70) [224]. The observed chemoselectivity, which involves an initial carborhodation of the triple bond of **183** instead of the conjugated double bond, is in accord with the observation that the Rh/diene catalyst displays a higher activity in the arylation of alkynes than in the 1,4-addition to α,β-unsaturated esters, whereas a Rh/diphosphine catalyst behaves in the opposite manner. This behavior could be due to the more electrophilic nature of a Rh/diene complex relative to a Rh/phosphine center. A related addition/cyclization, involving the initial carborhodation of an alkyne followed by an enantioselective 1,2-addition onto a tethered aldehyde, was reported by Hayashi and coworkers [225]. For this reaction, chiral dienes **L27b** and **L28b** also proved instrumental in accessing high activity and enantioselectivity.



Scheme 1.70 Rh/diene-catalyzed arylative cyclization of alkyne-tethered electron-deficient olefins.

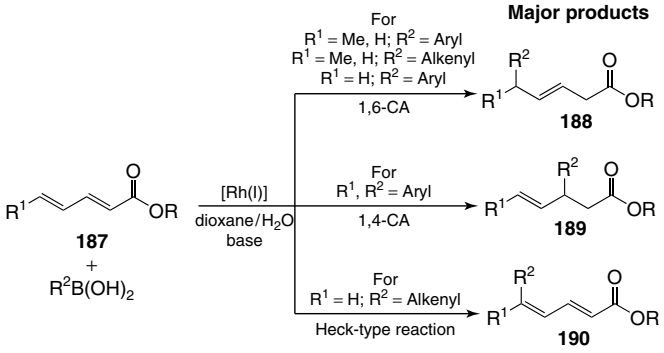
Syn-1,2-addition is the most common pathway for the insertion of an alkyne onto a Rh–carbon bond. However, 1,1-carborhodation pathway was recently observed with **185**, in which an *endo*-olefin cyclic product **186** is formed (Scheme 1.71) [226]. This novel addition/cyclization reaction occurred through an alkylidenerhodium-mediated 1,1-carborhodation process. Following the formation of vinylidenerhodium **W**, α-migration of the R^2 group from the Rh center to the vinylidene ligand provides alkenylrhodium intermediate **X**, which then undergoes addition to the pendant enone to give rhodium enolate **Y**. Finally, protonation of **Y** produces cyclopentene derivatives and regenerates the methoxyrhodium species.



Scheme 1.71 Tandem 1,1-carborhodation/conjugate addition.

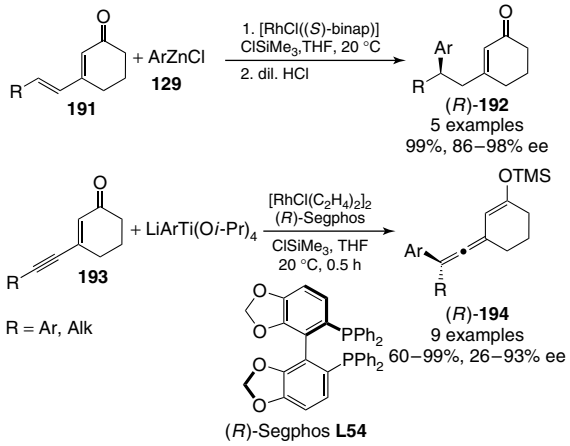
1.8
1,6-Conjugate Additions

From this review, it is apparent that Rh-catalyzed ECA additions are now a well-understood process. Arguably, the new frontier in Rh-catalyzed ECA methodology is now the control of the regio- and enantioselectivity in 1,6-additions processes. The 1,6-additions onto α,β, γ, δ-di-unsaturated carbonyls are particularly challenging because of the multitude of possible reaction pathways which are under substrate control. This is clearly illustrated in Scheme 1.72 [227] where, depending on the substitution pattern of the α,β, γ, δ-di-unsaturated esters **187** and the nature of the organoboron reagent, three competitive reaction pathways coexist. For unhindered dienoates **187** (R^1 = H or Me) the 1,6-addition product **189** is favored. However, when R^1 and R^2 are aromatic the 1,4-addition (**188**) becomes predominant, and when R^2 is an alkenyl group the fully conjugated Heck-type product **190** is observed.



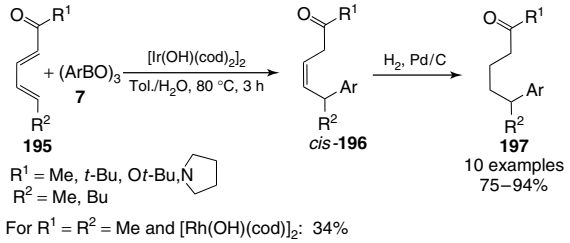
Scheme 1.72 Rh-catalyzed 1,6-addition of organoboronic acid onto α,β, γ, δ-diunsaturated esters.

Hayashi and coworkers were able to control the regioselectivity of the 1,6-addition β-substituted dienoates by using reactive arylzinc reagent (**129**) in conjunction with $ClSiMe_3$ (Scheme 1.73) [176]. Lower yields were observed with anionic aryltitanium reagents, and no reaction occurred with arylboronic acids. The β-disubstitution in **191** is essential to prevent competitive 1,4-ECA. The 1,6-addition products were obtained as the corresponding silyl-enol ether as a mixture of geometrical isomers which, after hydrolysis, gave (*R*)-**192** in near-quantitative yields and good to excellent enantioselectivities [176]. A related transformation, involving the enantioselective 1,6-addition of aryltitanate to 3-alkynyl-2-en-1-ones (**193**) in the presence of chlorotrimethylsilane enabled the formation of enantiomerically enriched allenes **194** (Scheme 1.73) when (*R*)-Segphos was used as a chiral ligand.



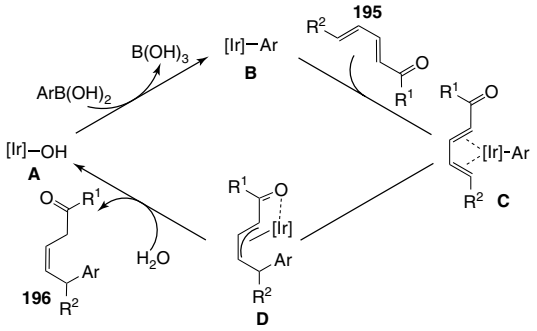
Scheme 1.73 Rh-catalyzed asymmetric 1,6-addition of arylzinc reagents onto α,β, γ, δ-diunsaturated ketones.

In 2006, Hayashi and coworkers reported a breakthrough in transition metal-catalyzed 1,6-addition methodology with organoboronic acids, through the use of $[Ir(\mu\text{-}OH)(cod)]_2$ the catalyst (Scheme 1.74) [228]. Importantly, this was the first report of an iridium-catalyzed addition of organoboronic acid onto an electron-deficient alkene or diene. The 1,6-addition products **191** were obtained preferentially as the *cis* isomer, and compound **196** was hydrogenated to **197** to facilitate analysis. The high 1,6-selectivity obtained with the iridium catalyst was in stark contrast to that observed with the parent $[Rh(\mu\text{-}OH)(cod)]_2$ complex as catalyst, under the same reaction conditions (Scheme 1.74). Thus, the rhodium-catalyzed reaction gave the 1,4-adduct as the main isomer (55% yield) and a minor amount (34% yield) of 1,6-adducts **196** (as a mixture of geometric isomers).



Scheme 1.74 Ir-catalyzed 1,6-conjugate addition with arylboroxines.

Competition experiments revealed that the iridium catalyst had a much stronger reactivity toward the dienone than the enone, while the opposite reactivity was observed for $[Rh(\mu\text{-}OH)(cod)]_2$. On the basis of the high reactivity towards the diene moiety and the high *cis* selectivity in the 1,6-addition product, the catalytic cycle that was surmised is depicted in Scheme 1.75. Here, transmetallation of an aryl group



Scheme 1.75 Proposed catalytic cycle to the Ir-catalyzed 1,6-addition with arylboronic acids.

from the boron to iridium-hydroxide **A** forms an aryl–iridium species **B** [229]; the coordination of the dienone to the phenyl–iridium complex with a cisoid diene moiety results in the formation of a (η^4-diene)–iridium complex **C**. Insertion of the diene into the phenyl–iridium bond then occurs, forming the π-allyl–iridium moiety **D**, and this is followed by a selective hydrolysis of **D** at the α position to the carbonyl function with the assistance of phenylboronic acid or boric acid to give the 1,6-addition product *cis*-**196** and regenerate the hydroxo–iridium species **A**.

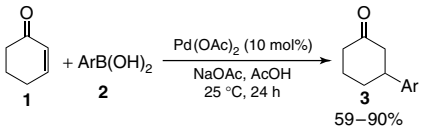
1.9 Pd-Catalyzed ECA

As described above, the rhodium-catalyzed ECA is now a relatively mature and well-understood technology, providing a very robust and flexible approach to the introduction of aryl and alkenyl groups in high yields, with excellent enantioselectivities and chemoselectivities. However, from an economic point of view, rhodium remains the most onerous metal, its price having been the subject of intense speculation over the past decade.[1)] Such high, and fluctuating, prices hampers the use of Rh-catalyzed ECA on a large industrial scale, and creates a need for alternative methodologies based on cheaper transition metals, such as palladium. Several reviews have been produced on the subject of Pd-catalyzed ECAs [15, 230–234].

The first use of palladium as a catalyst for conjugate addition onto α,β-unsaturated ketones can be traced back to the studies of Cacchi and coworkers, who employed organotin [235] and organomercury [236] reagents in an acidic two-phase system. In 1995, Uemura and coworkers reported [1] that organoboronic could be used in the Pd-catalyzed addition onto enones. This reaction was performed under acidic

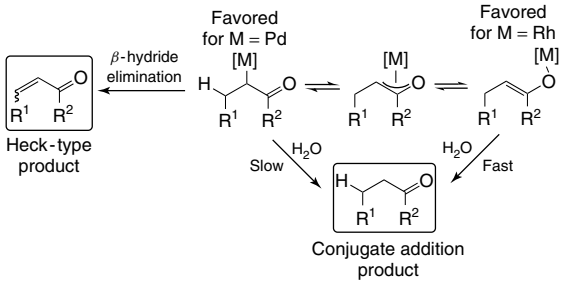
1) At its peak in 2008, the price of Rh (US$ 10 000 per ounce; US$ 300 per gram) was 23-fold higher than that of Pd (US$471 per ounce; US$15 per gram).

conditions and with a high catalyst loading (Scheme 1.76). Additionally, $NaBPh_4$ in conjunction with $SbCl_3$ could be used to deliver the phenyl fragment to the enone.



Scheme 1.76 First report of a Pd-catalyzed conjugate addition of organoboronic acids.

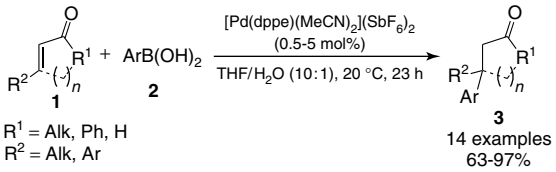
Although these early reports showed the potential of the palladium-catalyzed conjugate addition, the methodology lagged behind the rhodium-catalyzed reaction. The most likely reason for the underdevelopment of Pd-catalyzed conjugate addition is the propensity of neutral Pd-enolates, which are carbon-centered rather than oxygen-centered (i.e., Rh-enolates), to undergo competitive β-hydride elimination rather than hydrolysis (Scheme 1.77). This generates Heck-type coupling with concomitant Pd-black formation.



Scheme 1.77 Difference in reactivity between neutral Pd- and Rh-enolates.

Based on the findings that cationic palladium-enolates are much more susceptible to hydrolytic Pd–carbon bond cleavage than are neutral species [237], and that cationic-palladium species are much more reactive towards the addition to alkenes, Miyaura and coworkers developed a highly efficient Pd-catalyzed conjugate addition using dicationic $[Pd(dppe)(MeCN)_2](SbF_6)_2$ complex as the catalyst (Scheme 1.78) [238, 239]. The use of a cationic palladium source in the presence of water causes the β-hydride elimination from the Pd-enolate to be completely shut down by increasing the hydrolysis rate. The cationic Pd source is very active, promoting conjugate addition at room temperature. The use of a bidentate phosphine ligands with a two-carbon spacer, such as 1,2-*bis*(diphenylphosphino)ethane (dppe), proved essential to obtain reactivity. Diphosphine ligands with larger bite-angles [240] were ineffective [diphenylphosphinopropane (dppp), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), and Ph_3P gave no catalytic activity). Although the presence of a base such as K_2CO_3 accelerates the reaction rate, it also promotes β-hydride elimination. Variation of the non-coordinating anion (SbF_6^-, BF_4^-, PF_6^-) had no significant influence on the reactivity. Under these conditions, addition to β-arylenals **31**

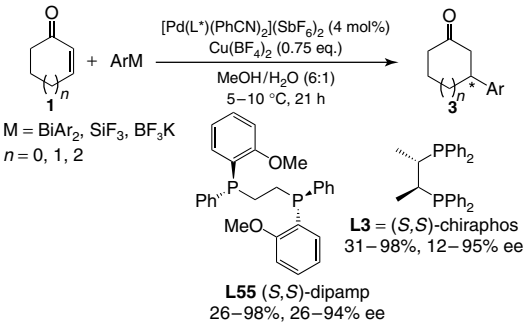
proved completely chemoselective, with only the 1,4-addition product being observed. Enoates were sluggish substrates, while the α,β-unsaturated amides were unreactive.



Scheme 1.78 Conjugate addition of organoboronic acid catalyzed by cationic Pd/dppe complex.

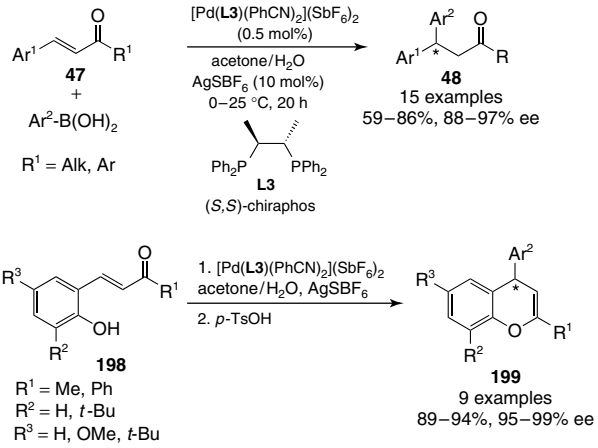
Initially, it was considered that the nitrile ligands (acetonitrile or benzonitrile) on the palladium were necessary to stabilize the catalyst and to obtain catalytic activity. However, later studies revealed that nitrile-free complexes generated by the *in situ* oxidation of $Pd(dba)_2$ with $Cu(BF_4)_2$ in the presence of phosphorus ligands were much more active catalysts. This enabled an expansion of the scope to use arylsiloxanes [239, 241] as the nucleophilic component.

In 2004, Miyaura and coworkers reported the first Pd-catalyzed ECA onto α,β-unsaturated ketones using triarylbismuth reagents [242]. In this seminal study, the combination of $[Pd(MeCN)_2](SbF_6)_2$ with (*S,S*)-dipamp (**L55**) or (*S,S*)-chiraphos (**L3**), as the chiral ligands, with $Cu(BF_4)_2$ as a substoichiometric additive in a MeO/H_2O (6 : 1) mixture, proved to be the most reactive and enantioselective system (Scheme 1.79). The organobismuth reagents were especially reactive and gave full conversion at just −5 °C. Using the same conditions, the scope of the reaction could be expanded to potassium aryltrifluoroborates and aryltrifluorosilanes [243]. The yields were high with both the triarylbismuth and $ArBF_3K$ reagents, but slightly lower with $ArSiF_3$. Most importantly, the enantioselectivities observed did not vary with the nature of the nucleophilic reagent ($BiAr_3$, $ArSiF_3$, or $ArBF_3K$).



Scheme 1.79 Rh-catalyzed ECA of organometallic reagents onto α,β-unsaturated ketones.

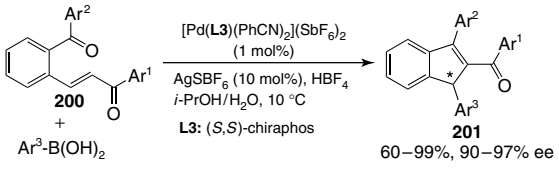
Miyaura and coworkers further developed the methodology to realize the use of more readily available arylboronic acids. Under optimized conditions, acetone was found to be a more suitable solvent than MeOH, while the addition of 5–10 mol% $AgBF_4$ or $AgSbF_6$ was found to improve the catalytic activity and stability of the dicationic Pd(II) catalyst, presumably by oxidizing the inactive Pd(0) complexes back to the dicationic active species [239]. With these additives, the catalyst loading could be lowered to 0.01 mol% [244], under which conditions the β-arylenones underwent ECA smoothly with organoboronic acid at 0 or 25 °C, and with a low catalyst loading (Scheme 1.80). One interesting application of this methodology was the efficient synthesis of optically active chromenes **199** through a ECA/dehydration sequence of β-arylenones **198** (Scheme 1.80) [244].



Scheme 1.80 Pd-catalyzed ECA of arylboronic acids to β-arylenones.

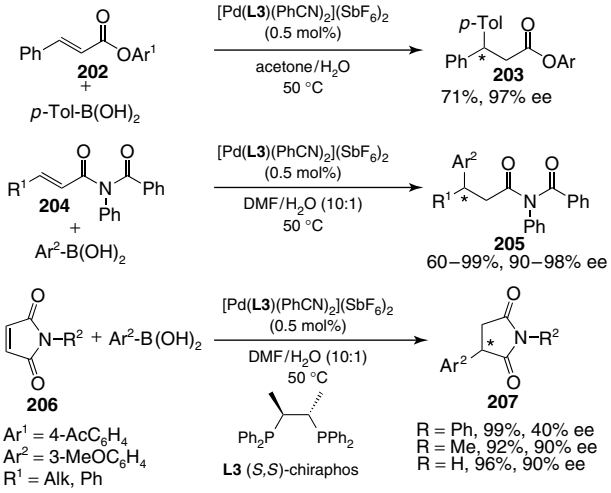
This process was ingeniously used for the synthesis of enantiopure 1-aryl-1 *H*-indenes **201** via a tandem Pd-catalyzed ECA/aldol condensation of substrate **200**, as shown in Scheme 1.81 (for the related Rh-catalyzed transformation, see Scheme 1.63.) [245].

The Pd-catalyzed ECA with linear α,β-unsaturated esters and amides has proved problematic due to the competing formation of Heck-type products. An alternative entry into this substrate class is to use the α,β-unsaturated aryl ester **202** [246] and α,β-unsaturated *N*-benzoylamides **204** [247], which afford the ECA product



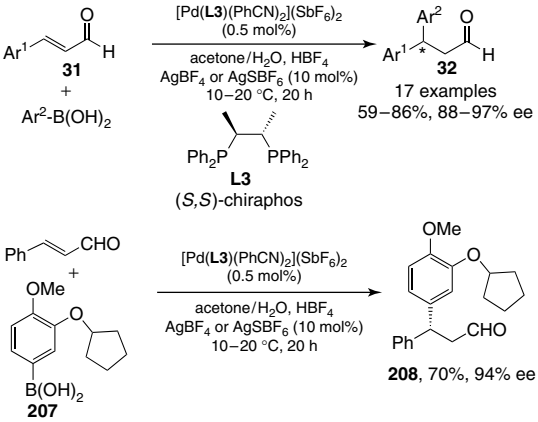
Scheme 1.81 Tandem Pd-catalyzed ECA/aldol condensation.

203 and **205** in high yields and enantioselectivities, without the concomitant formation of Heck-type products (Scheme 1.82). The effectiveness of amide **204** for these substrates resides in the coordinating of the two carbonyls, which shifts the C-centered Pd-enolate to an O-centered one. Similarly, maleimides **206** [247] proved to be competent substrates in Pd-catalyzed ECA, although the enantioselectivity was seen to depend heavily on the *N*-substituent (Scheme 1.82).



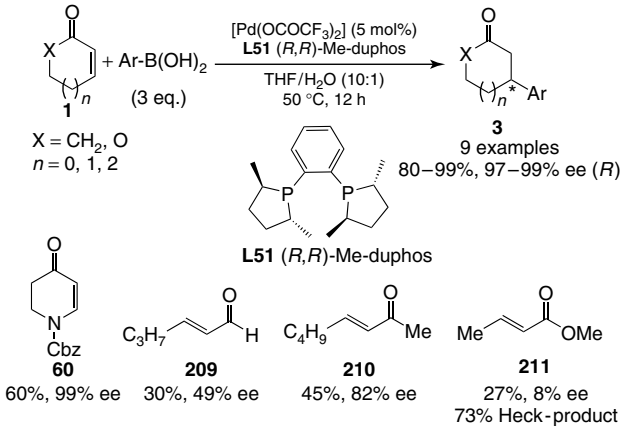
Scheme 1.82 Pd-catalyzed ECA of organoboronic acids to α,β-unsaturated esters and amides.

When the methodology was extended to β-aryl enals (**31**), it was again found that the addition of HBF_4 and $AgBF_4$ caused a dramatic increase in the reaction rate. It was proposed that an additional role of HBF_4 was to accelerate the rate of exchange between aldehyde and their corresponding hydrates, which is their favored form in aqueous solvents (Scheme 1.83) [248].



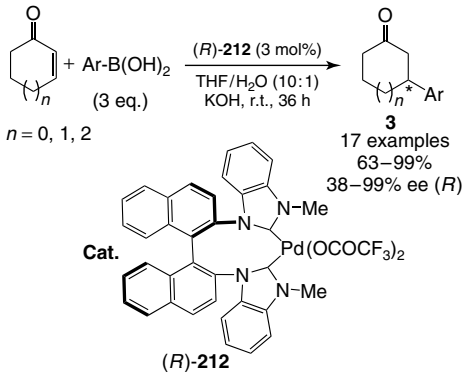
Scheme 1.83 Pd-catalyzed ECA of organoboronic acids onto β-aryl enals.

Minnaard and coworkers reported that the Pd-catalyzed ECA is efficiently catalyzed by $Pd(OCOCF_3)_2$ as a catalyst precursor [249]. In this case, an active cationic Pd species generated from $Pd(OCOCF_3)_2$ and (*R,R*)-Me-duphos (**L51**) proved to be the most effective ligand. The reaction did not take place if $Pd(OAc)_2$ was used as the precatalyst, as it required additional activation with triflic acid (CF_3SO_3H), though the yields were variable. The yields and enantioselectivities were high for cyclic α,β-unsaturated ketone and esters, but the ee-value was much lower for linear enals (**209**) and enones (**210**), For linear enoate **211**, formation of the Heck-type product became predominant (Scheme 1.84). A variation of this system could be used for the ECA of organosiloxanes, although ZnF_2 was required as an activator.



Scheme 1.84 Pd-catalyzed ECA of arylboronic acids onto α,β-unsaturated carbonyls.

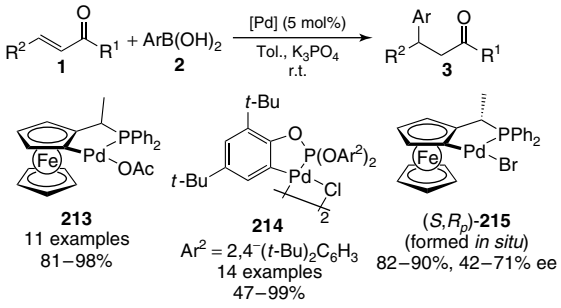
Cationic palladium(II) complexes (*R*)-**212** bearing a chelating chiral bidentate NHC was reported to be active in the asymmetric conjugate addition of arylboronic acids to cyclic enones (Scheme 1.85) [250].



Scheme 1.85 Pd-catalyzed ECA of arylboronic acids onto α,β-unsaturated carbonyls.

It was also reported that a $Pd(OAc)_2$/2,2′-bipyridine catalytic system is highly effective for the addition of arylboronic acids to enones, enals, nitroalkenes and, very interestingly, also to cinnamates and acrylates (although the latter substrates have posed longstanding problems) [251]. The reaction can also be run in water in the presence of anionic surfactants [252].

In 2007, Hu and coworkers showed that palladacycle **213** is a highly efficient catalyst for the addition of organoboronic acids to enones (Scheme 1.86) [253]. The reaction is performed in toluene at room temperature, using K_3PO_4 as the base to activate the boronic acid. In contrast to dicationic Pd catalysts, a Lewis acidic activator such $AgSbF_6$ or HBF_4 is not necessary. Notably, palladacycle **213** can also promote the 1,2-addition to α-ketoesters [253], while palladacycle **214** derived from the inexpensive and π-acidic *tris*(2,4-di-*tert*-butylphenyl)phosphite (a plasticizer) was also found to promote the conjugate addition (Scheme 1.86) [254]. The enantiopure palladacycle **215**, generated *in situ* from optically active ferrocenyl phosphine ligand and $Pd(dba)_2$, was applied to the conjugate addition of arylboronic acids to cyclohexenone; the reaction afforded good yields and a promising 71% ee (Scheme 1.86) [255]. Considering that palladacycles are extremely stable and robust species, and that no onerous activator is needed, these type of catalyst will surely be developed further.

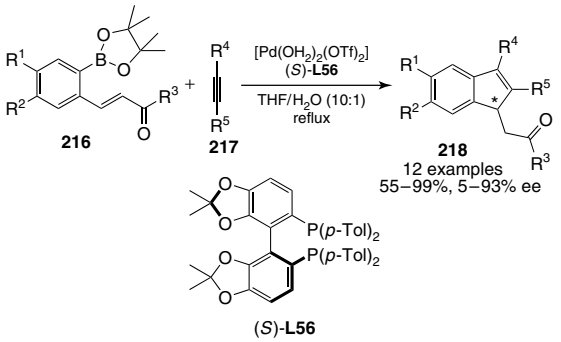


Scheme 1.86 Palladacycles as catalysts for with the conjugate addition of organoboronic acids.

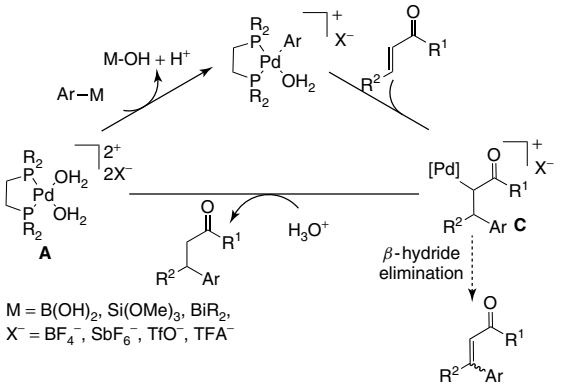
In analogy to the tandem carborhodation/ECA processes developed for rhodium (cf. Section 1.5), Lu and coworkers developed a Pd-catalyzed variation of this transformation using **216** and internal alkynes (**217**) (Scheme 1.87) [256]. Interestingly, ligand (*S*)-**L55** proved to be the best chiral ligand – a striking outcome considering that these types of ligand performed poorly in Pd-catalyzed ECA.

1.9.1 Catalytic Cycle

The proposed mechanism for the Pd-catalyzed conjugate addition is depicted in Scheme 1.88, and is closely related to that shown in Scheme 1.3 for rhodium. The main difference is that cationic palladium intermediates are involved instead



Scheme 1.87 Pd-catalyzed carborhodation/ECA.



Scheme 1.88 Proposed catalytic cycle for Pd-catalyzed conjugate addition.

of neutral rhodium species. The easy transmetallation of the ArM reagent occurs from the dicationic precursor **A** to generate the cationic Pd–Ar species **B**; this subsequently adds to the α,β-unsaturated carbonyl to produce the C-centered Pd-enolate **C**, the hydrolysis of which yields the addition product and **A**. The slow hydrolysis of **C** results in a competitive β-hydride elimination.

The mode of enantioselection in the Pd-catalyzed ECA is thought to occur in a similar fashion as for Rh-catalyzed ECA (cf. Scheme 1.6).

1.10 Conclusions

Major progress has been achieved in the field of Rh-catalyzed ECAs since the initial reports during the late 1990s. Today, synthetic organic chemists have at their disposal a large toolbox of conditions and ligands from which to select, such that they can confidently tackle ECA in a complex setting, and on a large scale. Nonetheless, there remain some unsolved issues with rhodium-catalyzed ECA,

such as the addition of an sp^3 carbon onto an activated alkene. In this respect, the Rh- and Pd-based methodologies are complementary to the copper-catalyzed processes that are well suited for the ECA of an alkyl Grignard, zinc, or aluminum reagent to an α,β-unsaturated carbonyl.

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