Rh-Catalyzed asymmetric 1,4-addition reactions to α,β -Unsaturated Carbonyl and related Compounds: An update

Majid. M. Heravi,* Mahzad Dehghani, Vahideh Zadsirjan

Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran

**Corresponding author: Fax: + 98 21 88041344; e-mail: mmh1331@yahoo.com (M. M. Heravi)*

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Abstract:

The Rh-catalyzed asymmetric 1,4-addition of organometallic reagents to an appropriate receptor has been a growing area of research over the last decade. The receptors for such a 1,4-addition reaction are chiefly α,β -unsaturated ketones, esters, amides, enones, nitroalkenes, and occasionally phosphonates etc. This reaction in the presence of chiral rhodium complexes introduce the aryl and alkenyl groups at the β -position of the above electron poor olefins, enantioselectively. Chiral Rh complexes similar to other transition metals can be added to some

electron poor olefins, in turn making them viable to attack by various organometallic reagents for highly enantioselective C-C bond formation. The Rh-catalyzed asymmetric 1,4-addition of organometallic reagents to electron poor olefins has been reviewed in 2003. Due to the importance of the asymmetric C-C bond formation via 1,4-conjugate addition reactions and the number of such reactions catalyzed by Rh-complexes, in this review we highlight the recent advances in Rh-complex asymmetric catalyzed 1,4-addition reactions since 2003.

1. Introduction

Asymmetric synthesis is the selective synthesis of one enantiomeric form of a desired optically active molecule: in recent decades, it has attracted much attention and stirred up the interest of synthetic organic chemists. Asymmetric synthesis is a key process in modern organic chemistry and is particularly important in the field of the total synthesis of natural products, since the different enantiomers or diastereomers of a molecule often show different biological activities. In this way, several scaffolds of biological systems, such as sugars and amino acids are produced entirely as one enantiomer. Therefore, these living systems possess a high level of chemical chirality and frequently react inversely with the various enantiomers of certain compounds. As a result, asymmetric synthesis is of great significance, but it is not readily accomplished. Enantiomers possess identical enthalpies and entropies, and should be produced in equal amounts and result in a racemic mixture. The solution to this is, is to induce a chiral entity, which will promote the generation of one enantiomer over another via an effective interaction in the transition state. This is recognized as asymmetric induction, which involves chiral features in the substrate, reagent, or even environment. Perhaps, the most remarkable and practical approach, is making the activation energy required to form one enantiomer lower than that of the

opposing enantiomer. This can be achieved by using different chiral catalysts, via asymmetric catalyzed reactions.¹

The development of asymmetric synthesis is very important in those parts of industry, which are engaged with the mass production of some useful natural products such as amino acids.² Asymmetric synthesis is a key step in modern organic chemistry and is vital in the field of pharmaceuticals, as the different enantiomers or diastereomers of a molecule often have different biological activities and in some cases while one of them is remedial, the opposite stereoisomer is devastating.^{2,3}

A catastrophic example is the prescribed drug thalidomide, which was produced and sold as a racemic mixture. In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities such as phocomelia, due to thalidomide's use as racemic mixture taken by mothers while pregnant.⁴

In general, four different strategies are known and practiced, for the synthesis of optically active organic compounds in relatively pure form. The first protocol involves a resolution step at an appropriate stage of a racemic.⁵

The second protocol involves starting with an enantiomerically pure starting material. These starting materials are often obtained from enantiomerically pure naturally occurring compounds, their derivatives, or their structurally modified forms. These enantiomerically pure natural products are frequently obtained from the so-called "chiral pool." Among them, amino acids, saccharine, and simple terpenes are the more commonly used for this purpose.⁶

Another strategy involves the covalent installation of an enantiomerically pure fragment with a well-defined absolute configuration, known as a chiral auxiliary onto a molecule. This resultant molecule, with the attached chiral auxiliary can then be used as an enantioenriched substrate, which can subsequent transformation directly with high selectivity and more importantly with a highly predictable relative stereochemistry, in this case with diastereoselectivity. Noticeably, at this stage any undesired diastereomer can be separated efficiently, then in a separate step, the temporary chiral auxiliary fragment is cleaved to afford the desired pure enantiomer along with removal of the chiral auxiliary, which is frequently recycled directly or after some modification. Both strategies have their own merits and drawbacks.^{7, 8} Undoubtedly, when there is no serious limitation observed, asymmetric catalysis is method of choice for the synthesis of either enantiomerically or diastereomerically pure products. An asymmetric catalyzed synthesis

involves the use of a catalytic amount of an enantiomerically pure (enriched) agent. Practically, an enantiomerically pure catalyst brings about an asymmetric environment in the transition state of the reaction, inducing a certain chirality, which then results in the selective generation of one enantiomer over the opposite one in the desired product. Thus a catalytic asymmetric induction provides an overall amplification of asymmetry in the reacting system.^{9, 10}

Despite the superiority of asymmetric catalysis over other approaches, examples of high efficiency regarding the catalytic activity and enantioselectivity remain rare in the C-C bond formation via catalyzed asymmetric synthesis.¹¹⁻¹⁵

Carbon-carbon bond forming reactions are the most important reactions in organic chemistry. Some examples are aldol reactions, Diels-Alder reactions, the addition of a Grignard reagent to a carbonyl group, Heck reactions, Michael reactions, Wittig reactions and 1,4-additions.

Among them 1,4-addition reaction are one of the largest and most diverse. Conjugation of a double bond to a carbonyl group transmits the electrophilic character of the carbonyl carbon to the β -carbon of the double bond. These conjugated carbonyls are called enones or α,β -unsaturated carbonyls.¹⁶⁻¹⁸ Thus, the asymmetric version of this reaction is frequently used for stereoselective C-C bond formation.^{6,7,11,19}

The conjugate addition of organometallic reagents to electron-deficient olefins has been recognized for a long time and known as one of the most useful processes in organic synthesis.^{5, 6}

The organometallic reagents most frequently employed for these reactions are organolithiums, -magnesiums, and zincs mediated by copper or nickel, which often afford the desired adducts in high yields. However these reactions can be problematic mainly due to the incompatibility of organometallic reagent used with some functional groups, as well as the competitive non-catalyzed 1,2-addition reaction. Some of these problems have been circumvented by using more active catalysts combined with the use of a less reactive organometallic reagent.

One of the best examples of catalytic asymmetric synthesis leading to enantioselectivity is catalytic asymmetric carbon-carbon bond formation.^{11a, b}

In asymmetric carbon-carbon bond formations, chiral transition metal complexes are frequently used as catalysts. One of the most important and promising reactions frequently employed for C-C bond formation in synthetic organic chemistry is the 1,4-addition reaction of various nucleophiles to appropriate α,β -unsaturated carbonyl compounds.¹⁶⁻¹⁸

This well-established reaction has also been performed for catalytic asymmetric synthesis and has become a field of high importance in its practical synthetic usefulness as well as its scientific interest. Due to this importance during the 1980s, and thereafter, much attention has been paid and remarkable efforts have been focused on organocatalyzed asymmetric 1,4-conjugate additions to various α,β -unsaturated carbonyl compounds.¹¹

Probably, the most fruitful example is the 1,4-addition of organozincs under catalysis of copper (I) complexes bearing chiral phosphorus ligands.²⁰⁻²⁶ In these copper-catalyzed 1,4-additions, high enantioselectivity has been observed ($> 90\%$ *ee*) for several types of α,β -unsaturated ketones. Unfortunately, the organic groups introduced were limited to primary alkyl groups and no additions of sp^2 carbons with high enantioselectivity were achieved.

During 1991-1992, the innovation and developments of Rh-catalyzed 1,4-conjugate additions have been comprehensively reviewed.^{16, 17, 27} In recent years, Rh-catalyzed reactions have also been the center of attention.²⁸

In 1997, Miyaura *et al.* achieved and reported the first non-asymmetric 1,4-addition of aryl- and alkenyl-boronic acids to α,β -unsaturated ketones employing a phosphine-Rh complex as a catalyst system.²⁹ This new successful report of Rh-catalyzed 1,4-conjugate additions stimulated the interest of synthetic organic chemists worldwide to focus on the asymmetric catalysis of 1,4-additions using asymmetric Rh-catalyzed 1,4-addition reaction with the hope of achieving high enantioselectivity. Naturally, the best possible way to achieve such an invaluable strategy was using Rh-complexes bearing a chiral ligand as catalyst.

In recent years a plethora of high to excellent enantioselective Rh-catalyzed asymmetric 1,4-conjugate additions have been achieved and reported. This catalyzed asymmetric 1,4-addition reaction showed the advantage of allowing the introduction of sp^2 carbons to a wide variety of electron-poor olefins under mild reaction conditions.³⁰⁻³²

Recent developments of Rh-catalyzed carbon-carbon bond formations using organometallic reagents, including the 1,4-addition of both non-asymmetric and asymmetric versions have been reviewed by Lautens *et al.*³¹ As a typical example, the reaction of cyclohex-2-enone with phenylboronic acid catalyzed by a Rh-complex bearing a chiral ligand gave (*S*)-3-phenylcyclohexanone in satisfactory yield and with 97% *ee*.³¹

After publication of this important achievement, several reports appeared in the chemical literature regarding successful utilization of some other chiral phosphorus ligands for these

classes of Rh-catalyzed 1,4-addition of organoboronic acids to α,β -unsaturated ketones under similar conditions.^{33, 34}

Later on, the Rh-catalyzed stereoselective reaction was applied to diverse organometallic reagents and electron-deficient olefins. In 2003, a comprehensive and invaluable review entitled “Rhodium-catalyzed asymmetric 1,4-addition and its related asymmetric reactions” by Hayashi *et al.* appeared.³²

We are interested in the asymmetric synthesis,³⁵⁻⁴³ and applications of named reactions in the total synthesis of natural products which usually use asymmetric synthesis in one or more steps in their multi-step synthesis.⁴⁴⁻⁴⁸

Due to the increasing number of articles published concerning asymmetric 1,4-addition reactions, catalyzed by Rh-complexes, we were prompted to update the invaluable review by Hayashi *et al.* in 2003.³² Herein we highlight the recent advances in Rh-complex asymmetric catalyzed 1,4- addition reactions from 2003 to date.

2.1. Organoborates

In 2003, Chan *et al.* successfully accomplished and reported the reactions of α,β -unsaturated ketones **1a-e** with arylboronic acids **2** catalyzed by a rhodium species created in situ from Rh(acac)(C₂H₄) and (*S*)-P-Phos in dioxane/water.⁴⁹ They obtained the desired corresponding products **3a-p** in high chemical yields and with excellent enantiomeric excess (up to 99% *ee*). In this way, P-Phos was proven to act as an efficient ligand in the Rh-catalyzed 1,4-additions of various arylboronic acids. The potency and stereorecognition aptitude of Rh(I)/P-Phos acting as a catalyst in the aforementioned addition reaction is comparable or even better than those that employed Binap, Binol-based diphosphonites and hemilabile bidentate amido monophosphine as the catalyst (Scheme 1, Table 1).⁴⁹

Scheme 1.

Table 1. Stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated ketones catalyzed by $\text{Rh}(\text{I})/(\text{S})\text{-P-Phos}$.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1b	Ph	3a : 89	97
2	1c	Ph	3b : 88	98
3	1d	Ph	3c : 90	90
4	1e	Ph	3d : 86	96
5	1a	4-MeOC ₆ H ₄	3e : 82	99
6 ^a	1a	4-MeOC ₆ H ₄	3e : 90	99
7	1b	4-MeOC ₆ H ₄	3f : 77	99
8 ^a	1b	4-MeOC ₆ H ₄	3f : 90	99
9	1c	4-MeOC ₆ H ₄	3g : 62	99
10 ^a	1c	4-MeOC ₆ H ₄	3g : 86	99
11	1a	4-MeC ₆ H ₄	3h : >99	99
12	1a	4-CF ₃ C ₆ H ₄	3i : 97	99
13	1a	4-FC ₆ H ₄	3j : 97	96
14	1a	3-MeOC ₆ H ₄	3k : 95	99

15	1a	3-ClC ₆ H ₄	3l : 97	99
16	1a	3,5-Me ₂ -4-MeOC ₆ H ₂	3m : 94	99
17	1a	2-naphthyl	3n : 98	97
18	1a	2-MeC ₆ H ₄	3o : 74	99
19 ^a	1a	2-MeC ₆ H ₄	3o : 90	99
20	1a	2-MeOC ₆ H ₄	3p : 15	99
21 ^a	1a	2-MeOC ₆ H ₄	3p : 44	99

^a Dioxane (1 ml) / H₂O (0.05 ml).

Monodentate phosphoramidites as chiral ligands were used in rhodium-catalyzed enantioselective conjugate additions of variously substituted arylboronic acids to enones, unsaturated esters, lactones, and nitroalkenes. These reactions proceed smoothly and rapidly to give the products in high chemical yields and with *ee*'s up to 89%. Successful rhodium-catalyzed conjugate additions of phenylboronic acids **2** to enones **1a-d**, unsaturated esters **1i**, lactones **1f-g** and nitroalkenes **1h** were performed to give the desired products. The used phosphoramidite ligands were stable under the reaction conditions resulting in moderate to high *ee* and high chemical yields. H8-MonoPhos **L3** was found to be the ligand of choice in terms of selectivity compared to the other related ligands. The best results were obtained when cyclohexenone **1a** was used as the 1,4-adduct and an *ee* of 89% was achieved. When H8-MonoPhos **L3** was used at 100 °C, full conversion was reached after only 15 min. A comparative study between the ligands was developed. It showed that the bidentate ligand-based catalytic systems were actually superior in scope. The preliminary results from this reaction, which employed simple and commercially available monodentate phosphoramidites, stimulated the development of a wide range of applicable monodentate ligands for Rh-catalyzed conjugate additions.⁵⁰ Conjugate additions of phenylboronic acid to several alkenones using a catalyst prepared from **L2** or **L3** are shown in Table 2.⁵⁰

Scheme 2.

Table 2. Conjugate addition of phenylboronic acid to several alkenones using catalysts prepared from **L2** or **L3**.

Entry	1	Ln	Yield (%)	<i>ee</i> (%)
1	1a	L2	4a: 100	84
2	1a	L3	4a: 100	89
3	1b	L2	5a: 100	15
4	1b	L3	5a: 100	50
5	1c	L2	6a: 64	71
6	1c	L3	6a: 80	78
7	1f	L2	7a: 50	38
8	1f	L3	7a: 45	14
9	1g	L2	8a: 100	29
10	1g	L3	8a: 100	62
11	1h	L2	9a: 100	44
12	1d	L2	10a: 100	16

13	1i	L2	11a: 87	23
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The influence of ligands and bases in the Rh(I)-catalyzed 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds were reexamined to develop the reaction under mild conditions. The stereoselective additions of arylboronic acids **2** to α,β -unsaturated ketones, aldehydes, esters, and amides **1** as examples, under catalysis of [Rh(*R*-binap)(nbd)]BF₄/ Et₃N are outlined in Table 3. Differently substituted arylboronic acids can be added to 2-cyclohexenone giving excellent yields and high enantioselectivities of up to 99% *ee* for α,β -unsaturated ketones, 92% for aldehydes, 94% for esters and 92% for amides, respectively.⁵¹

Scheme 3.

Table 3. Stereoselective addition to α,β -unsaturated carbonyl compounds

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	12a : 99	99
2	1a	3-MeOC ₆ H ₄	12b : 98	99
3	1a	3-ClC ₆ H ₄	12c : 97	99
4	1a	4-MeOC ₆ H ₄	12d : 87	n.d.
5	1b	3-ClC ₆ H ₄	12e : 99	97
6	1j	Ph	12f : 98	83
7	1j	3-MeOC ₆ H ₄	12g : 91	88

8	1k	Ph	12h : 75	97
9	1k	3-MeOC ₆ H ₄	12i : 82	98
10	1l	3-MeOC ₆ H ₄	12j : 59	86
11	1m	Ph	12k : 56	92
12	1n	4-MeOC ₆ H ₄	12l : 93	94
13	1o	Ph	12m : 97	92

The preparation of a C₂-symmetric chiral diene ligand and its positive utilization for the Rh-catalyzed stereoselective 1,4-additions of various organometallic reagents has been accomplished.⁵² The diene ligand exhibited a high and unique capability in the Rh-catalyzed stereoselective 1,4-addition of organoboron and tin reagents. The in situ prepared Rh-complex was employed as a catalyst for the stereoselective 1,4-addition of organoboron reagents to α,β -unsaturated ketones and esters.⁵³⁻⁶⁸ The results illustrated in Scheme 4 disclose the following issues: (a) the catalytic effectiveness is at its highest for the chiral Rh catalysts employed for the stereoselective 1,4-addition. The addition of phenylboronic acid **3m-u** to enone **2a-e** affords of 1,4-addition adducts **5a-p** in high yields; (b) the enantioselectivities obtained from this reaction actually are among the highest for Rh-catalyzed stereoselective 1,4-additions so far observed. The observed selectivity was over 90% *ee* in the majority of the reactions tested for many cyclic and linear enones and for most aryl- and alkenylboron reagents.⁵²

Scheme 4.

Table4. Stereoselective 1,4-addition of organoboron reagents ArB(OH)₂ **3** to α,β -unsaturated ketones and esters catalyzed by [RhCl(C₂H₄)₂]₂/(*R,R*)-**L5**

Entry	1	Ar 2 or 13	Yield (%)	<i>ee</i> (%)	Config.
1	1a	2 : Ph	14a : 94	96	(<i>R</i>)
2	1a	2 : Ph	14b : 85	96	(<i>R</i>)
3	1a	2 : Ph	14c : 94	95	(<i>R</i>)
4	1a	13 : 3-MeOC ₆ H ₄	14d : 92	97	(<i>R</i>)
5	1a	13 : 4-MeOC ₆ H ₄	14e : 89	95	(<i>R</i>)
6	1a	13 : 4-MeC ₆ H ₄	14f : 88	96	(<i>R</i>)
7	1a	13 : 3-ClC ₆ H ₄	14g : 92	93	(<i>R</i>)
8	1a	2 : 4-CF ₃ C ₆ H ₄	14h : 90	99	(<i>R</i>)
9	1a	13 : 4-FC ₆ H ₄	14i : 91	97	(<i>R</i>)
10	1a	13 : 2-naphthyl	14j : 96	96	(<i>R</i>)
11	1a	2 : (<i>E</i>)- <i>n</i> -C ₅ H ₁₁ CH=CH	14k : 73	88	(<i>R</i>)
12	1b	13 : Ph	14l : 88	88	(<i>R</i>)
13	1b	2 : (<i>E</i>)- <i>n</i> -C ₅ H ₁₁ CH=CH	14m : 78	96	(<i>R</i>)
14	1c	2 : Ph	14n : 81	90	(<i>R</i>)
15	1d	2 : Ph	14o : 81	97	(<i>R</i>)
16	1p	13 : Ph	14p : 73	92	(<i>R</i>)

The addition of phenylboronic acid **2** to 2-cyclohexenone **1a** was performed at either 20 or 30 °C in dioxane/H₂O mediated by KOH to afford the 1,4-addition product **14m** in high yield. (c) The enantioselectivities observed in this reaction actually were among the highest for the Rh-catalyzed stereoselective 1,4-addition. The observed selectivity was over 90% *ee* for the majority of reactions tested for cyclic and linear enones and also for aryl- and alkenylboron reagents, (d) The absolute configuration of all the products obtained were determined as as (*R*) for (*R,R*)-**L5**. The (*R,R*)-**L5**-Rhodium complex discriminates the enantiofaces of the enones via the steric repulsions between the benzyl group on the diene and the carbonyl moiety causing the coordination with the *re*-face being favorable for both cyclic and linear enones, resulting in the formation of products with an (*R*)-configuration (Scheme 4).

Scheme 5.

Bisphosphine ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl(binap) supported on a polystyrene-poly(ethylene glycol) copolymer PS-PEG resin **L6** exhibited high catalytic potency and high enantioselectivity was provided and employed in a Rh-catalyzed stereoselective 1,4-additions of phenylboronic acid **2** to various α,β -unsaturated ketones **1** in water as a green and abundant solvent to afford products **22a-e**. As depicted in Table 5, the 1,4-addition progressed in water with high enantioselectivity using both cyclic enones **1a-c** and acyclic enones **1d, e**.⁶⁹

Scheme 6.

Table 5. Stereoselective 1,4-addition of phenylboronic acid to α,β -unsaturated ketones **7** catalyzed by PS-PEG-(*S*)-Binap **L6**/Rh in water

Entry	1	Yield (%)	<i>ee</i> (%)	Config.
1	1a	22a : 95	94	(<i>S</i>)
2	1b	22b : 83	97	(<i>S</i>)
3	1c	22c : 86	95	(<i>S</i>)
4	1d	22d : 71	96	(<i>S</i>)
5	1e	22e : 80	91	(<i>S</i>)

A general strategy for the enantioselective catalytic 1,4-conjugate addition to acyclic α,β -unsaturated sulfones **23a-h** was established and reported in 2004. Employing metal-chelating α,β -unsaturated pyridyl sulfones as substrates, the Rh-catalyzed chiral phos-mediated addition of organoboric acids **2** occurs to give the corresponding products in excellent yield and with high enantioselectivities. A catalytic approach to enantioselective 1,4-conjugate addition of carbon nucleophiles to α,β -unsaturated sulfones has also been developed. The attainment of this rhodium-catalyzed 1,4-addition of boronic acids is heavily based on the use of α,β -unsaturated 2-pyridyl sulfones **23a-h** as key Rh-coordinating substrates and chiral phos as an ideal chiral

ligand. This strategy shows the broad scope concerning both the arylboronic acid and the sulfone substrate, providing the 1,4-conjugate addition products in excellent yields (up to >90%) and high enantioselectivities (76-92% *ee*). The facile elimination of the pyridylsulfonyl group via Julia-Kocienski olefination is a novel protocol for the enantioselective synthesis of allylic substituted alkenes.

As a model reaction, the behaviour of diverse propenyl sulfones **23a-h**, bearing various aromatic substitution at sulfur, under conventional experimental conditions was observed for the Rh-catalyzed 1,4-conjugate additions of organoboronic acids to sulfone Rh(acac)(C₂H₄)₂, PhB(OH)₂ (excess) **2**, dioxane/H₂O (10:1), at 100 °C (Scheme 7).⁷⁰

Scheme 7. Rhodium-catalyzed reaction of differently substituted propenyl sulfones with phenyl boronic acid.

From the model reaction, it was found that (*S,S*)-chiraphos **L7** exhibited the best reactivity/enantioselectivity profile when the structural scope of this enantioselective reaction was investigated (Table 6). Both the substitution at the aryl boronic acid **2** (three electronically various reagents) and the bulkiness at the α -position on the α,β -unsaturated pyridyl sulfone **1** (substrates **25a-d**) were at work, resulting in the formation of **26a-l**.⁷⁰

Scheme 8.

Table 6. Enantioselective Rhodium-catalyzed addition of boronic acids to α,β -unsaturated 2-pyridyl sulfones

Entry	R ¹ 25	Ar 2	Yield (%)	<i>ee</i> (%)
1	25a :Me	Ph	26a : 97	81
2	25a :Me	4-FC ₆ H ₄	26b : 98	84
3	25a :Me	4-MeOC ₆ H ₄	26c : 89	77
4	25b : <i>n</i> -Pent	Ph	26d : 98	84
5	25b : <i>n</i> -Pent	4-FC ₆ H ₄	26e : 94	87
6	25b : <i>n</i> -Pent	4-MeOC ₆ H ₄	26f : 92	81
7	25c : <i>i</i> -Pent	Ph	26g : 93	78
8	25c : <i>i</i> -Pent	4-FC ₆ H ₄	26h : 93	85
9	25c : <i>i</i> -Pent	4-MeOC ₆ H ₄	26i : 74 (94) ^a	76
10	25d : β -naphthyl	Ph	26j : 96	87
11	25d : β -naphthyl	4-FC ₆ H ₄	26k : 97	92
12	25d : β -naphthyl	4-MeOC ₆ H ₄	26l : 84 (94) ^a	85

^a Converted product.

It has been demonstrated that the Rh-catalyzed cascade carbometallation/enantioselective protonation is a highly effective process for the introduction of a substituent at the β -position of an electron-poor alkene with simultaneous control of the chirality at the stereogenic center. In this cascade process, the utilization of phenol derivatives, especially using the nontoxic and inexpensive commercially available guaiacol as the proton source, was essential for

accomplishing acceptable levels of enantioselectivities and for the recyclability of the reaction. This proton source can be easily recovered and completely suppresses the competitive reduction of the organometallic reagent, which is frequently observed in these Rh-catalyzed reactions. The use of dehydroamino esters in this reaction causing the transfer of substituted α -aminoesters in high yields and with high enantioselectivity (up to 90%) when binap is used as the chiral ligand. The generality of the reaction under these optimal conditions ($[\text{Rh}(\text{cod})_2][\text{PF}_6]$ and (*R*)-binap **L4** as the catalyst precursor in the presence of guaiacol **29** was established by treatment of substrate **27** with different potassium trifluoro(organo) borates **28a-g** (Scheme 9).⁷¹

- 30a:** R = Ph, yield = 89%, *ee* = 89.5%
30b: R = 3-MeOC₆H₄, yield = 89%, *ee* = 89.5%
30c: R = naphthalene, yield = 88%, *ee* = 86.5%
30d: R = 4-FC₆H₄, yield = 82%, *ee* = 83%
30e: R = 4-BrC₆H₄, yield = 75%, *ee* = 81%
30f: R = thiophene, yield = 68%, *ee* = 81%
30g: R = CH=CH-(4-MeC₆H₄), yield = 96%, *ee* = 88%

Scheme 9. Tandem 1,4-addition/enantioselective protonation of RBF_3K to dehydroamino esters.

The scope of the present tandem 1,4-addition/enantioselective protonation was further extended by studying the organometallic partner **2h-n** that could carbometallate the dehydroamino ester **27**. In fact, some other organometallic reagents, such as tin, silicon and other boron derivatives were also, examined under the previously optimized reported conditions, employing guaiacol **29** as the proton source (Scheme 10).⁷¹

Scheme 10. Other organometallic reagents used in the tandem 1,4-addition/ enantioselective protonation

A general mechanism of this conversion can be postulated (Scheme 11). The first step involves the transmetallation of the organoboron reagent. However, there is no evidence that potassium trifluoro(organo)borates are directly transmetallating the RhI species. Superior coordination of one face of the amidoacrylate (involving a second coordination of the NHAc group) with subsequent insertion of the R substituent gives an oxa- π -allylrhodium intermediate (steps 2 and 3). The last step (step 4) involves the protonation of the rhodium enolate. As a matter of fact, the proton transfer takes place either by H-transfer from the Rh center or by external protonation of the enolate. In either case, it is clear that the bulkiness and/or coordination of the *ortho*-substituent on the phenol actually plays an important role.

Scheme 11. Proposed reaction mechanism, PG = protecting group.

A Rh-catalyzed stereoselective 1,4-addition of diverse arylboronic acids **2** to maleimides **38a-c** has been developed. While phosphorus based chiral ligands failed to induce high stereoselectivity, chiral norbornadiene ligands proved to be effective in achieving high enantioselectivity in these 1,4-addition reactions. The origin of the stereocontrol in these reactions can be rationalized and understood by analysis of the crystal structure of the Rh/chiral norbornadiene complex. High enantioselectivity with the chiral norbornadiene ligand was also realized in the stereoselective 1,4-additions to maleimides **38a-c**, which are substrates that are particularly interesting due to the importance of the 1,4-adducts that are well known for the R-substituted succinimides.⁷³⁻⁷⁵ The reaction of *N*-methylmaleimide with $\text{ArB}(\text{OH})_2$ mediated by bisphosphine ligands furnished the 1,4-adducts **39a-m** with acceptable *ee* (Scheme 12).⁷²

Scheme 12.

Table 7. Rhodium-catalyzed 1,4-addition of arylboronic acids to maleimides.

Entry	Ln	R 38	Ar 2	Yield (%)	<i>ee</i> (%)
1	(<i>R</i>)- L4	38a :Me	Ph	39a : 100	51
2	(<i>R</i>)- L8	38a :Me	Ph	39b : 100	47
3	(<i>S</i>)- L1	38a :Me	Ph	39c : 98	28
4	(<i>S</i>)- L9	38a :Me	Ph	39d : 100	45
5	(<i>R,R</i>)- L5a	38a :Me	Ph	39e : 89	70
6	(<i>R,R</i>)- L5b	38a :Me	Ph	39f : 88	85
7	(<i>R,R</i>)- L5b	38b :Cy	Ph	39g : 85	87
8	(<i>R,R</i>)- L5b	38c :Bn	Ph	39h : 88	69 (<i>R</i>)
9	(<i>R,R</i>)- L5b	38b :Cy	4-MeOC ₆ H ₄	39i : 77	84
10	(<i>R,R</i>)- L5b	38b :Cy	4-FC ₆ H ₄	39j : 88	85
11	(<i>R,R</i>)- L5b	38b :Cy	3-ClC ₆ H ₄	39k : 92	82
12	(<i>R,R</i>)- L5b	38b :Cy	2-naphthyl	39l : 93	84
13	(<i>R,R</i>)- L5b	38b :Cy	2-MeC ₆ H ₄	39m : 95	92

A Rh-catalyzed stereoselective 1,4-addition of various organoboronic acids to different α,β -unsaturated ketones in the presence of (*S*)-binap was reported in 1998, after which several chiral ligands were employed as catalysts, in this reaction; bisphosphine ligands were found to be

especially efficient. Based on these successful achievements, chiral bisphosphine ligands were employed in the reaction of di-*tert*-butyl fumarate with PhB(OH)₂ in combination with rhodium (Table 8). Thus, an Rh-catalyzed stereoselective 1,4-addition of differently substituted arylboronic acids **2** to fumaric and diesters compounds **40** was developed. While phosphorus based chiral ligands could not induce high stereoselectivity, chiral norbornadiene ligands were found to be exceptionally effective in inducing high enantioselectivity in these 1,4-addition reactions. The stereocontrol in these reactions can be rationalized from the X-ray crystal structure analysis of the Rh/ chiral norbornadiene complex.⁷²

Table 8. Rhodium-catalyzed stereoselective 1,4-addition of arylboronic acids to *di-tert*-butyl fumarate.

Entry	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	(<i>R</i>)- L4	Ph	41a : 96	21	(<i>R</i>)
2	(<i>R</i>)- L8	Ph	41b : 99	3	(<i>R</i>)
3	(<i>S</i>)- L1	Ph	41c : 94	13	(<i>S</i>)
4	(<i>S</i>)- L9	Ph	41d : 50	32	(<i>S</i>)
5	(<i>R,R</i>)- L5a	Ph	41e : 78	90	(<i>S</i>)
6	(<i>R,R</i>)- L5b	Ph	41f : 90	90	(<i>S</i>)
7	(<i>R,R</i>)- L5b	4-MeOC ₆ H ₄	41g : 78	86	(<i>S</i>)
8	(<i>R,R</i>)- L5b	4-FC ₆ H ₄	41h : 85	90	(<i>S</i>)
9	(<i>R,R</i>)- L5b	2-naphthyl	41i : 91	87	(<i>S</i>)
10	(<i>R,R</i>)- L5b	2-MeC ₆ H ₄	41j : 80	91	(<i>S</i>)

This steric discrepancy is much more profound in the present stereoselective reactions than other systems such as Rh/(*R*)-binap, where the origin of their stereocontrol is the result of the face-and-edge difference of the phenyl groups on the phosphorus atoms of (*R*)-binap.⁷⁶ Based on the X-ray

crystal structural analysis of Rh/(*R,R*)-**L5a**, the stereochemical outcome of the 1,4-addition to maleic derivatives is illustrated in Figure 1.

Figure 1. Proposed stereochemical pathways for the asymmetric 1,4-addition to fumaric acid diester **42** and maleimide **43** catalyzed by rhodium/chiral norbornadiene.

An appropriate Rh complex can catalyze the reaction of unactivated Baylis–Hillman adducts **1a-g** with various arylboronic acids **2a-g** to provide tri-substituted alkenes **3a-m** in satisfactory yields. This highly efficient reaction under aerobic conditions at low temperature is believed to proceed via an unexpected mechanism involving 1,4-addition/ β -hydroxy elimination steps and π -allyl type Rh intermediates are not generated (Scheme 14).⁷⁷

Scheme 14.

Table 9. Aerobic rhodium-catalyzed addition of **2** to BH adduct **44**.

Entry	R ¹ 44	Ar 2	Yield (%)	<i>E/Z</i>
1	44a : Me	Ph	45a : 90	99/1
2	44a : Me	4-CF ₃ C ₆ H ₄	45b : 86	99/1
3	44a : Me	4-MeOC ₆ H ₄	45c : 97	99/1
4	44a : Me	1-naphthyl	45d : 92	99/1
5	44a : Me	3-CF ₃ C ₆ H ₄	45e : 77	96/4
6	44b : <i>n</i> -C ₉ H ₁₉	2-naphthyl	45f : 92	97/3
7	44b : <i>n</i> -C ₉ H ₁₉	2-MeC ₆ H ₄	45g : 89	96/4

8	44c: (Me) ₂ CHCH ₂	4-MeC ₆ H ₄	45h: 66	96/4
9	44c: (Me) ₂ CHCH ₂	Ph	45i: 87	97/3
10	44d: cyclohexyl	Ph	45j: 32	90/10
11	44e: 1-naphthyl	Ph	45k: 80	98/2
12	44f: 4-NO ₂ C ₆ H ₄	Ph	45l: 86	96/4
13	44g: 4-ClC ₆ H ₄	Ph	45m: 71	99/1

The high regioselectivity and the higher reactivity observed for unactivated BH adducts can be rationalized by postulating a 1,4-addition type mechanism involving an elimination step of the β -hydroxy group.⁷⁸⁻⁸⁴ The expected initial step of the catalytic cycle must consist of the transmetalation of the organoboron reagent ArB(OH)₂ to the [Rh(I)] species followed by coordination of the BH adduct (Scheme 15). Next, the 1,4-insertion of the substituent Ar generates the Rh intermediate with a hydroxyl group in the β -position. The final step of the mechanism involves a *syn*- β -hydroxy elimination⁷⁸⁻⁸⁴ of [Rh]-OH to give the alkene **45**. The origin of the high stereoselectivity has not been logically described so far. However, it can be attributed to steric interactions during the β -hydroxy elimination stage.

Scheme 15. Proposed mechanism.

Miyaura *et al.* reported the successful use of phosphoramidites in a 1,4-addition reaction.⁸⁵ In continuation of their work, an efficient catalyst system was developed. Due to this development, rhodium phosphoramidite-catalyzed conjugate additions of arylboronic acid **2** to enones **1a-c, g** can be performed at ambient temperature. This development involved combining an inexpensive commercially available or readily accessible monodentate phosphoramidite ligand and $[\text{Rh}(\text{OH})(\text{cod})]_2$ or $[\text{RhCl}(\text{cod})]_2/\text{KOH}$ as a stable and applicable catalyst system. Furthermore, the loading of the catalyst was decreased with no appreciable decrease in the enantioselectivity. These results of **50a-e** being obtained in high yields and with excellent enantioselectivities opened up a gateway for the use of rhodium-phosphoramidite as an efficient catalyst in stereoselective conjugate additions of a wide variety of arylboronic acid derivatives to enones at ambient temperature. Furthermore, it was observed that under milder reaction conditions, smaller amounts of arylboronic acid reagents are required with no decrease in the yields of products (Scheme 16).⁸⁶

Scheme 16.

Table 10. Stereoselective conjugate addition of arylboronic acid to cyclic enones **1**.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	H	50a :86	99
2	1a	4-FC ₆ H ₄	50b : 84	98
3	1b	H	50c : 90	87
4	1c	H	50d : 78	95

The catalytic cycle has been suggested for the rhodium–binap catalyzed reaction of phenylboronic acid with 2-cyclohexenone **1a** as illustrated in Scheme 17. Studying this reaction, three key intermediates were detected by ^{31}P NMR spectroscopy. (a) Phenyl–rhodium **51**, which can be formed by transmetalation of a phenyl group from phenylboronic acid to hydroxo-rhodium **53**, (b) oxa-*p*-allylrhodium **52**, which can be generated by insertion of the C–C bond of the enone into the phenyl–rhodium bond with subsequent isomerization into a complex which is thermodynamically stable, and (c) hydroxo-rhodium complex **53**, which can be formed upon hydrolysis of oxa- π -allylrhodium **52** with water.

Scheme 17. Suggested mechanism for the rhodium–Binap-catalyzed conjugate addition of phenylboronic acid to cyclohexenone **1a**

In 2005, Hayashi *et al.* reported the synthesis of enantiomerically pure *C*₂-symmetric bicyclo[2.2.2]octa-2,5-dienes **L11** and their use as chiral diene ligands. Excellent enantioselectivity (up to 99% *ee*) along with high catalytic potency were obtained in the addition to both cyclic and linear compounds in Rh-catalyzed stereoselective 1,4-additions of differently arylboronic acids **2** to various α,β -unsaturated ketones **54a–f** (Scheme 18).⁸⁷

Scheme 18.

Table 11. Stereoselective 1,4-addition of phenylboronic acid **2** to enones **1a** and **1d** catalyzed by $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/\text{dienes } \textbf{L11}$.

Entry	Ln	[Yield (%)] <i>ee</i> (%) (Config.)	
		54a	54d
1	L11a	[97] 95 (<i>R</i>)	[97] 94 (<i>R</i>)
2	L11b	[97] 96 (<i>R</i>)	[95] 85 (<i>R</i>)
3	L11c	[97] 83 (<i>R</i>)	[89] 78 (<i>R</i>)
4	L11d	[99] 81 (<i>R</i>)	[88] 87 (<i>R</i>)
5	L11e	[99] 95 (<i>R</i>)	[91] 78 (<i>R</i>)
6	L11f	[96] 94 (<i>R</i>)	[90] 92 (<i>R</i>)

Table 12. Stereoselective 1,4-addition of phenylboronic acid **2** to enones **1** catalyzed by $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/$ (*R,R*)-dienes **L11a**, **L11b** and **L12**.

Entry	Product	[Yield (%)] <i>ee</i> (%) (Config.)		
		Bn-bod* L11a	Ph-bod* L11b	Bn-nod* L12
1	54a	[97] 95 (<i>R</i>)	[97] 96 (<i>R</i>)	[94] 96 (<i>R</i>)
2	54b	[94] 86 (<i>R</i>)	[97] 99 (<i>R</i>)	[88] 88 (<i>R</i>)
3	54c	[91] 91 (<i>R</i>)	[95] 92 (<i>R</i>)	[81] 90 (<i>R</i>)
4	54d	[97] 94 (<i>R</i>)	[95] 85 (<i>R</i>)	[81] 97 (<i>R</i>)
5	54e	[94] 98 (<i>S</i>)	[90] 83 (<i>S</i>)	[84] 95 (<i>S</i>)
6	54f	[79] 65 (<i>R</i>)	[75] 95 (<i>R</i>)	[44] 89 (<i>R</i>)

The enantioselectivity was high for a series of differently substituted arylboronic acids in 1,4-additions to cyclopentenone **1b** and 3-nonen-2-one **1e** with Rh-complexes coordinated with Ph-bod* **L11b** and Bn-bod* **L11a**, catalysis respectively (Schemes 19, 20). Furthermore, the addition of methoxyarylboronic acids or trifluoromethyl group at the *p*-position as well as methyl group at the *ortho*-position all afforded the respective 1,4-addition products with up to 95% *ee* for both **1b** and **1e**.

Scheme 19.

Scheme 20.

The Rh complex coordinated with the chiral bicyclo[2.2.2]octa-2,5-dienes **L11a,b** with (*R,R*) absolute configuration creates efficient *C*₂-symmetric surroundings with the benzyl or aryl substituents placed at the upper left and lower right locations (Scheme 21). Upon the addition of a phenylrhodium species, enones enter the catalytic cycle. The double bond of the enones can coordinate to the Rh in a fashion that prevents the steric repulsions between the substituent on the diene ligand and the carbonyl group of the enones. The alkyl substituent at the α -position is not an important factor with regards to adjusting the enantioface of the olefin coordination. Thus, both linear enones and cyclic enones can be subjected to phenylrhodation from their *re*-face to afford the 1,4-arylation products with the expected absolute configuration.

for cyclic enones:

for acyclic enones:

Scheme 21.

Novel chiral phosphine–olefin ligands (+)-**L13** have been efficiently synthesized with high enantioselectivities. These ligands behave as bidentate with some transition metals and are highly effective in the Rh-catalyzed stereoselective 1,4-addition of aryl boronic acids **2** to *N*-substituted maleimides **38a-f** to provide the corresponding 1,4-adducts **61a-j** in consistently high yield and enantioselectivity with respect to the nucleophilic nature of component. In this way, a wide range of aryl boronic acids were successfully coupled with *N*-benzylmaleimide with high stereoselectivity (Table **13**).⁸⁸

Scheme 22.

Table 13. Rh-(+)-**L13**-catalyzed stereoselective 1,4-addition of aryl boronic acids to maleimides.

Entry	R 38	Ar 2	Yield (%)	<i>ee</i> (%)
1	38a : Me	Ph	61a : 91	88
2	38b : Cy	Ph	61b : 96	94
3	38f : CHPh ₂	Ph	61c : 95	94
4	38d : CPh ₃	Ph	61d : 95	94
5	38e : Ph	Ph	61e : 88	90
6	38c : Bn	Ph	61f : 98	93
7	38c : Bn	4-MeOC ₆ H ₄	61g : 98	93
8	38c : Bn	4-FC ₆ H ₄	61h : 90	89
9	38c : Bn	3,5-MeO ₂ C ₆ H ₃	61i : 90	92
10	38c : Bn	2-MeC ₆ H ₄	61j : 98	95

This catalytic enantioselective reaction can be extended to the asymmetric synthesis of several other biologically active compounds. For instance, the addition of 2-MeOC₆H₄B(OH)₂ to maleimide **62** under Rh-(+)-**L13** catalysis resulted in 1,4-adduct **63** in 83% yield and with 92% *ee* (Scheme 23).⁸⁸

Scheme 23.

The stereochemical logic and outcome of these Rh-(+)-**L13**-catalyzed 1,4-additions can be understood as illustrated in Scheme 24. It is rational to assume that the maleimide approaches the aryl rhodium species bearing ligand (+)-**L13** *cis* to the olefin portion of the ligand. In order to avoid the steric repulsion between the imide motif of the maleimide and the phenyl group on the olefin, the obtained product is expected to be (*S*)-isomer, which is in agreement with the defined stereochemistry (Scheme 24).⁸⁸

Scheme 24. Proposed stereochemical pathway for the stereoselective 1,4-addition to a maleimide catalyzed by Rh-(+)-**L13**.

The Rh-(+)-**L13** catalyst was found highly effective for stereoselective 1,4-additions to other α,β -unsaturated carbonyl compounds. For instance, both cyclic enones and enoates provide the respective 1,4-adducts with high chemical yield and enantioselectivity (Scheme 25).

Scheme 25.

Bolm et al. in 2005 reported the synthesis of novel cyrhetrenes **L14a**, **L14b**. These planar-chiral, mono- and di-phosphines have been employed as ligands in Rh-catalyzed 1,4-addition reactions to activated olefins, to afford the corresponding products **66a-j** with up to 97 and 93% *ee*, respectively.⁸⁹

This is the first example of the application of a planar chiral nonmetallocene ligand in the Rh-catalyzed 1,4-addition of arylboronic acids **66a-j** to enones and enoates **1a** resulting in high *ee*(>90%). It was found that cyrhetrene **L14a**, which is the easiest to purify and handle, is the most active in both catalytic reactions, furnishing the products with up to 97 and 93% *ee*. For evaluating the scope of the catalyst system, different arylboronic acids **2** bearing electron-withdrawing as well as electron-donating groups using cyrhetrene **L14a**, **L14b** as the ligand were examined (Table 14).⁸⁹

Scheme 26.

Table 14. Various arylboronicacids **2** in the Rh-catalyzed 1,4-addition to cyclohexenone **1a**.

Entry	Ar 2	Ln	Yield (%)	<i>ee</i> (%)
1	Ph	L14a	66a : 93	95
2	4-MeC ₆ H ₄	L14a	66b : 67	92
3	4-CF ₃ C ₆ H ₄	L14a	66c : 99	92
4	4-ClC ₆ H ₄	L14a	66d : 99	97
5	2-MeC ₆ H ₄	L14a	66e : 99	90

6	2-MeC ₆ H ₄	L14b	66f : 99	83
7	3-MeOC ₆ H ₄	L14a	66g : 71	93
8	4-MeOC ₆ H ₄	L14a	66h : 47	82
9	1-naphthyl	L14a	66i : 51	85
10	2-naphthyl	L14a	66j : 64	35

The reactions of other acyclic and cyclic enones **1a-c, 1e, 1g** with phenylboronic acid **2** were also examined (Table 15).

Scheme 27.

Table 15. Rh-catalyzed stereoselective 1,4-addition of PhB(OH)₂ **2** to α,β -unsaturated compounds **1**.

Entry	1	Ln	Yield (%)	<i>ee</i> (%)
1	1b	L15	66a : 52	73
2	1b	L14a	66b : 47	73
3	1c	L14a	66c : 92	35
4	1c	L14b	66d : 99	76
5	1e	L15	66e : 76	62
6	1e	L14a	66f : 97	69
7	1g	L14a	66g : 95	88
8	1g	L14b	66h : 98	88

An effective and enantioselective conjugate addition of highly stable potassium trifluoro(organo) borates to α,β -unsaturated esters has been achieved and reported. The reaction is catalyzed by chiral Rh(I) complexes, giving Michael adducts in high yields and with *ee* up to 96%. From the preliminary observations, it could be seen that potassium trifluoro(organo) borates **28** were very effective and enantioselective partners in Rh-catalyzed enantioselective 1,4-additions to α,β -unsaturated esters **67a-i**. It is also noteworthy that the reaction proceeds smoothly giving high yields and good to excellent *ee*. This reaction was catalyzed by chiral Rh(I) complexes to give Michael adducts **68a-n**.⁹⁰

As an alternative, it was confirmed that potassium trifluoro(organo) borates⁹¹ were also highly appropriate either in Pd-catalyzed cross-coupling reactions⁹² or in Rh-catalyzed reactions. Several efficient protocols for stereoselective 1,4-additions to enones and enamides were developed⁹³ in which only low amounts of organoboron derivatives in comparison with trivalent organoboron species were used.⁹⁴⁻⁹⁸ As a result of this, potassium trifluoro(organo) borates were used in Rh-catalyzed stereoselective 1,4-additions to α,β -unsaturated esters, thus expanding upon the scope of previously reported approaches (Scheme 28). In fact, in the presence of cationic $[\text{Rh}(\text{cod})_2]\text{PF}_6$ in along with (*R*) or (*S*)-Binap, 1,4-addition of potassium aryltrifluoroborates to α,β -unsaturated esters proceeded smoothly in a biphasic solvent such as toluene/water at 110 °C (Table 19).⁹⁰

Scheme 28.

Table 19. Stereoselective 1,4-addition of RBF_3K to α,β -unsaturated esters.

Entry	67	R 28	Yield (%)	<i>ee</i> (%)	Config.
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1	67a	Ph	68a : 95	90	(<i>S</i>)
2	67b	Ph	68b : 96	84	(<i>R</i>)
3	67c	Ph	68c : 98	86	(<i>R</i>)
4	67d	Ph	68d : 91	85	(<i>S</i>)
5	67e	Ph	68e : 93	93	(<i>S</i>)
6	67f	Ph	68f : 96	86	(<i>S</i>)
7	67g	4-MeOC ₆ H ₄	68g : 88	87	(<i>S</i>)
8	67g	Ph	68h : 95	86	(<i>S</i>)
9	67h	3-BrC ₆ H ₄	68i : 50	91	(<i>S</i>)
10	67h	naphthalene	68j : 75	90	(<i>S</i>)
11	67h	Ph	68k : 87	96	(<i>S</i>)
12	67h	3-ClC ₆ H ₄	68l : 66	90	(<i>S</i>)
13	67h	4-CF ₃ C ₆ H ₄	68m : 54	89	(<i>S</i>)
14	67i	Ph	68n : 55	93	(<i>R</i>)

The wide range of these kinetic data revealed the large difference in reactivity between these organoboron derivatives. It was observed that the reaction with phenylboronic acid occurs almost instantaneously while an induction period is seen when potassium trifluoro(phenyl)borate was used.⁹³ These results show that transmetalation of boronic acids to the Rh/Binap precursor is rapid, while it did not take place or was slow with trifluoroborate derivatives. This rapid transmetalation of boronic acids led to an accumulation of phenyl-Rh species, which are very susceptible to hydrolysis, which is usually a competitive process with the insertion of the carbon-carbon double bond (Scheme 29).^{97, 98}

Scheme 29. Proposed simplified mechanism.

The Rh-catalyzed diastereoselective additions of different arylborons to *N*-sulfinylimines have been successfully achieved and reported. The sulfinamide adducts were obtained with high diastereoselectivities and provided an easy access to enantiomerically pure diarylmethylamines. The reactions took place under milder conditions than those recently reported by Ellman *et al.*, which took place at ambient temperature, while the addition of either an external phosphine ligand or syringe pump addition of the arylboronic acids was non-required. This scope is an advantage, in comparison with analogous methods. The reaction only proceeds smoothly and cleanly, when water was used as a co-solvent. In this case, the sulfinamide adducts were obtained with high diastereoselectivities, thus offering a convenient pathway to the synthesis of enantiomerically pure chiral benzylic amines.⁹⁹

Thus a range of substituted aryl-, heteroaryl-, and alkyl-based *N*-*tert*-butanesulfinimines **71a-i** were treated with *p*-tolylboronic acid under a conventional set of conditions (Scheme 30), employing Rh(I) catalyst and Et₃N in dioxane/water (1:2) at ambient temperature. The diastereoselectivities of the adducts **72a-i** were frequently high (83- 98% *de*).⁹⁹

- 72a:** R = Ph, yield = 78%, *de* = 85%
72b: R = 4-MeOC₆H₄, yield = 59%, *de* = ≥98%
72c: R = 4-ClC₆H₄, yield = 92%, *de* = 83%
72d: R = 4-CF₃C₆H₄, yield = quant, *de* = 91%
72e: R = 2-CF₃C₆H₄, yield = 73%, *de* = 97%
72f: R = naphthalene, yield = 80%, *de* = 84%
72g: R = furan, yield = 60%, *de* = 89%
72h: R = CH₂CH₂Me, yield = 59%, *de* = 97%
72i: R = cyclohexane, yield = 44%, *de* = 92%

Scheme30. Reaction of sulfinimines **71** with *p*-tolylboronic acid

The influence of the arylboronic acid was evaluated by employing the *p*-trifluoromethylphenyl substrate **71d** under a conventional set of conditions (Scheme 31). Good stereoselectivities were observed for a range of arylboronic acids **2**, involving both electron-rich and electron-poor

species. Nevertheless, the yields of the reaction were subject to steric as well as electronic effects on the boronic acid (**73d** and **73e**, Scheme 31).⁹⁹

Scheme 31. Reactions of **71d** with different arylboronic acids.

In addition to boronic acids themselves, their derivatives were also subjected to this reaction (Scheme 32). Under the standard conditions, phenylpinacolboronate ester, phenylisopropyl boronate ester and trifluoro(phenyl)borate potassium salt all efficiently reacted with **71d** under standard conditions to afford **28** with high diastereoselectivities comparable to those of phenylboronic acid.⁹⁹

73g: $\text{X} = \text{B}(\text{OH})_2$, yield = 94%, $de = 93\%$

73h: $\text{X} = \text{—B—}$ (cyclobutane ring with two methyl groups on each carbon), yield = 79%, $de = 95\%$

73i: $\text{X} = \text{B}(\text{O}^i\text{-Pr})_2$, yield = 65%, $de = 88\%$

73j: $\text{X} = \text{BF}_3\text{K}$, yield = 61%, $de = 92\%$

Scheme 32. Reactions of **71d** with different phenylboron derivatives to form **73g-j**.

The highly enantioselective synthesis of 2-aryl-4-piperidones **75a-h** by Rh/phosphoramidite-catalyzed conjugate additions of different arylboroxines **13** to 2,3-dihydro-4-pyridones **74** has been developed. As a result, both enantiomers of a wide variety of products with sterically and electronically different R substituents were provided in high isolated yields (82-92%) and with excellent enantioselectivities (up to 99% ee). To prove the applicability of this reaction on a laboratory scale, it was conducted on a bench scale. The product was isolated in 86% yield and with 99% ee after flash chromatography. Under these obtained optimized conditions, the scope of the stereoselective conjugate addition of arylboroxines to **74** was studied. High ee values were obtained with a wide range of sterically and electronically diverse arylboroxines, *meta* and *para*-tolyl groups. A drastic decrease in the enantioselectivity was seen for the more sterically demanding *ortho*-tolyl group, thus showing a possible limitation of the catalytic method. Products with one or two electron-donating groups on the aryl were obtained in high yields and with high enantioselectivities. On the other hand, electron-withdrawing groups such as chloride or fluoride make the reaction sluggish, resulting in incomplete transformations. In spite this observation, the enantioselectivity is mainly independent on the electronic properties of the

substituents, since all *para*- or *meta*-substituted products were obtained with excellent *ee* values (94-98% *ee*) (Scheme 33).¹⁰⁰

Scheme 33. Scope of arylboroxines in the Rhodium-catalyzed stereoselective 1,4-addition to **74**.

Hayashi *et al.* reported a novel synthetic approach for the synthesis of chiral organosilicon compounds via a Rh-catalyzed stereoselective 1,4-addition of diverse arylboronic acids **2** to β -silyl α,β -unsaturated carbonyl compounds **76a-c**. They utilized (*R,R*)-Bn-bod* as a ligand to obtain a Rh-complex for use in the 1,4-addition of arylboronic acids to obtain the corresponding adducts with very high *ee*. These obtained β -silyl 1,4-adducts **77a-h** can be transformed into the corresponding β -hydroxy carbonyl compounds or allylsilanes with complete retention of their stereochemical configuration (Scheme 34).¹⁰¹

Scheme 34.

Table 17. Rh/(*R,R*)-Bn-bod*-catalyzed stereoselective 1,4-addition of arylboronic acids to β -phenyldimethylsilyl enones **76**.

Entry	R 76	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
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1	76a : Me	Ph	77a : 94	99	(<i>S</i>)
2	76b : Et	Ph	77b : 89	98	(<i>S</i>)
3	76c : Ph	Ph	77c : 94	97	(<i>S</i>)
4	76a : Me	4-MeOC ₆ H ₄	77d : 95	96	(<i>S</i>)
5	76a : Me	4-CF ₃ C ₆ H ₄	77e : 94	95	(<i>S</i>)
6	76a : Me	3-ClC ₆ H ₄	77f : 92	95	(<i>S</i>)
7	76a : Me	naphthalene	77g : 96	93	(<i>S</i>)
8	76a : Me	2-MeC ₆ H ₄	77h : 90	93	(<i>S</i>)

In addition, appropriate substrates for this reaction are not restricted to β -phenyldimethylsilyl enones. Therefore, as illustrated in Table 18, other β -silyl enones (e.g., β -(*tert*-butyl) dimethylsilyl and β -triphenylsilyl enones) **76a-c** also can be subjected to this 1,4-addition reaction with high enantioselectivity (91-95% yield, 97->99% *ee*). Furthermore, β -silyl enoates can also be used as substrates, to furnish the 1,4-adducts **77i-l** in high chemical yield and with high to excellent *ee* (86-88% yield, 93-95% *ee*).¹⁰¹

Scheme 35.

Table 18. Rh/(*R, R*)-Bn-bod*-catalyzed stereoselective 1,4-addition to other β -Silyl α,β -unsaturated carbonyl compounds.

Entry	76	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	76a	Ph	77i : 95	>99	(<i>S</i>)
2	76b	Ph	77j : 91	97	(<i>S</i>)
3	76c	Ph	77k : 88	95	(<i>S</i>)
4	76c	4-MeOC ₆ H ₄	77l : 86	93	(<i>S</i>)

The Rh-catalyzed stereoselective 1,4-addition of divers arylboronic acids **2** to coumarin derivatives **79a-d** proceeded to completion in high chemical yields and with excellent enantioselectivity (>99% *ee*). In the presence of a Rh- catalyst prepared from Rh(acac)(C₂H₄)₂, (*R*)-Segphos **L8** afforded the corresponding (*R*)-4-arylchroman-2-ones **80a-j** with over 99% *ee*. This stereoselective reaction offers an efficient pathway to enantiomerically pure compounds where the stereogenic center is bonded to two different aryl groups, and is considered as the stereoselective synthesis of (*R*)-tolterodine **78** (Figure 2).¹⁰²

Figure 2.

The scope and restriction of the present stereoselective addition to coumarin derivatives **79a-d** is outlined in Table 19. Under the optimized conditions, 6-methylcoumarin **79a** was subjected to stereoselective addition of methyl-substituted phenylboronicacids **2** to afford the corresponding products **80b** and **80c** in high chemical yields (over 90%) and with virtually perfect enantioselectivity (>99% *ee*). The enantioselectivity also was high for the addition of *p*-chlorophenylboronic acid and *p*-methoxyphenylboronic acid, although the chemical yields were unsatisfactory. Unsubstituted coumarin **79b** is a good substrate, affording high yields of the stereoselective arylation products upon reaction with phenyl- and tolylboronic acids. The addition of phenylboronic acid **2** to 6-methoxycarbonylcoumarin **79c** afforded the adduct **80i** in high yield. Alternatively, the addition to 7-methoxycoumarin **79d** proceeded sluggishly, thus confirming that electron-donating groups, such as methoxy groups, decrease the reactivity of the coumarin moiety (Scheme 36).¹⁰²

Scheme 36.

Table 19. Stereoselective addition of arylboronic acids **2** to coumarins **79** catalyzed by Rh/(*R*)-Segphos.

Entry	R 79	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	79a : 6-Me	Ph	80a : 88	99.6	(<i>R</i>)
2	79a : 6-Me	4-MeC ₆ H ₄	80b : 91	99.8	(<i>R</i>)
3	79a : 6-Me	3-MeC ₆ H ₄	80c : 93	99.7	(<i>R</i>)
4	79a : 6-Me	4-ClC ₆ H ₄	80d : 45	99.1	(<i>R</i>)
5	79a : 6-Me	4-MeOC ₆ H ₄	80e : 75	99.5	(<i>R</i>)
6	79b : 6-H	Ph	80f : 86	99.4	(<i>R</i>)
7	79b : 6-H	4-MeC ₆ H ₄	80g : 89	99.7	(<i>R</i>)
8	79b : 6-H	3-MeC ₆ H ₄	80h : 90	99.7	(<i>R</i>)
9	79c : 6-CO ₂ Me	Ph	80i : 94	99.3	(<i>R</i>)
10	79d : 7-OMe	Ph	80j : 28	n.d.	-

A linear α,β -unsaturated ester **81** bearing a 2-methoxy-5-methylphenyl group at the β -position was also tested for Rh-catalyzed stereoselective additions of phenylboronic acid. This reaction is important since the adduct (*S*)-**82** would be another suitable precursor to tolterodine if the enantioselectivity was high (Scheme 37). The stereoselective phenylation led to low enantioselectivity with either a Segphos or Binap ligand to afford (*S*)-**82** with approximately 50% *ee*.

Scheme 37. Rhodium-catalyzed stereoselective addition of phenylboronic acid **2** to cinnamate ester **81**.

The Rh-catalyzed enantioselective 1,4-addition of arylboronic acid **2** to the bifunctional Michael acceptors **83a-c** mediated by phosphoramidites **L2**, **L9**, **L10**, **L17**, which takes place regioselectively at the endocyclic C-C double bond, has been reported by Krause et al.. In this approach, the 1,4-addition products were obtained with high chemical yields and excellent enantioselectivities (up to 95% *ee*.) Notably, this addition to chiral enone **2** occurs with

epimerization resulting in the thermodynamically more stable *trans*-isomer with excellent enantioselectivities (up to 98% *ee*). Thus, Rh-catalyzed enantioselective 1,4-additions can be fruitfully applied to differently substituted cycloenones.¹⁰³

The bifunctional Michael acceptors **83a-c**¹⁰⁴ can also be subjected to consecutive 1,4-additions of two nucleophiles to the endocyclic and exocyclic acceptor system. Interestingly it was observed that in all cases, the addition occurs exclusively at the endocyclic double bond. 6-Methyl-substituted cyclohex-2-enone **2** is a chiral compound. In this case, 1,4-additions to Michael acceptors of this type can occur enantioselectively either under reagent control with or without product epimerization to the thermodynamically more stable product, or via a kinetic resolution on the racemic mixture of the enone.¹⁰⁵

Scheme 38.

Table 20. Rhodium-catalyzed 1,4-addition of arylboronic acids to dienones **83a-c**.

Entry	83	Ln	Ar 2 (equiv)	Yield(%)	<i>ee</i> (%)
1	83a	L17	Ph (5.0)	84a : 6	n.d.
2 ^a	83a	L17	Ph (5.0)	84b : 87	89
3	83a	L2	Ph (3.0)	84c : 90	75
4	83a	L9	Ph (3.0)	84d : 95	86
5	83a	L9	Ph (3.0)	84e : 98	88
6	83a	L9	Ph (1.5)	84f : 98	93

7	83a	L10	Ph (1.5)	84g : 93	95
8	83a	L9	4-CF ₃ OC ₆ H ₄ (1.5)	84h : 67	90
9	83b	L9	Ph (1.5)	84i : 93	92
10	83b	L9	4-CF ₃ OC ₆ H ₄ (1.5)	84j : 53	90
11	83c	L9	Ph (1.5)	84k : 98	94

^a 1 equiv KOH was added

Known unactivated Baylis-Hillman adducts have been successfully and regioselectively used in the presence of potassium trifluoro(organo)borates to give stereodefined trisubstituted alkenes in good chemical yields. This highly efficient reaction under phosphane ligand free and mild reaction conditions is assumed to proceed smoothly *via* a 1,4-addition followed by hydroxy elimination. Continuation of these highly efficient reactions has been performed to afford stereocontrolled trisubstituted alkenes starting from readily available BH adducts and potassium trifluoro(organo)borates **28** to give stereo-defined trisubstituted alkenes **44** in good chemical yields.¹⁰⁶ This reaction is believed to proceed *via* 1,4-addition/ β -hydroxy elimination mechanism. It takes place under mild, aerobic and phosphane ligand free conditions at low temperatures. The generality of this reaction was examined under these optimal conditions using [Rh(cod)Cl]₂ as the catalyst in a toluene/methanol system as the solvent at 70 °C. These conditions are general and more importantly independent of the nature of the BH adduct or the potassium trifluoro(aryl)borate used in the reaction (Table 21). Very high yields were obtained independent of the electronic nature of the trifluoro(aryl)borate and for a given BH adduct, the isomeric ratios were constant. Regarding the BH adduct partner, either aliphatic or aromatic substrates can contribute equally well, contrary to the Pd-catalyzed reaction of the BH adduct.¹⁰⁷

Scheme 39.

Table 21. Aerobic rhodium-catalyzed addition of potassium aryltrifluoroborates to BH adducts.

Entry	R ¹ 44	R ² 28	Yield (%)	E/Z (%)
1	44a : Me	Ph	85a : 86	99/1

2	44a: Me	4-CF ₃ C ₆ H ₄	85b: 63	99/1
3	44a: Me	3-ClC ₆ H ₄	85c: 58	99/1
4	44a: Me	3-MeOC ₆ H ₄	85d: 85	99/1
5	44a: Me	naphthalene	85e: 98	99/1
6	44c: <i>i</i> -Bu	4-MeOC ₆ H ₄	85f: 70	96/4
7	44c: <i>i</i> -Bu	Ph	85g: 91	96/4
8	44b: <i>n</i> -C ₉ H ₁₉	2-MeC ₆ H ₄	85h: 90	96/4
9	44b: <i>n</i> -C ₉ H ₁₉	Ph	85i: 96	96/4
10	44h: Ph	Ph	85j: 98	97/3
11	44h: Ph	4-FC ₆ H ₄	85k: 98	98/2
12	44i: 1-naphthalene	Ph	85l: 98	98/2
13	44i: 1-naphthalene	4-BrC ₆ H ₄	85m: 98	97/3

With regards to their readily availability and higher stability in comparison with trivalent organoboron derivatives, the reactivities of potassium alken-1-yltrifluoroborates were examined for this reaction (Table 22).¹⁰⁶

Scheme 40.

Table 22. Aerobic rhodium-catalyzed addition of potassium trifluoro(alkenyl)borates to BH adducts

Entry	R ¹ 44	R ² 28	Yield (%)	E/Z (%)
1	44a: Me	4-MeC ₆ H ₄	86a: 91	99/1
2	44a: Me	Ph	86b: 84	98/2
3	44c: <i>i</i> -Bu	Ph	86c: 94	96/4
4	44i: 1-naphthalene	H	86d: 44	99/1

This high regioselectivity is induced by a π -allyl-type interaction that is not shown in the proposed mechanism, where deuterium incorporation should have been observed in both positions. Therefore, the reaction should include the regioselective 1,4-addition of the

organometallic reagent with subsequent β -hydroxy elimination, to create the expected alkene and an appropriate hydroxo rhodium complex for transmetalation with an organoboron species (Scheme 41).¹⁰⁶

Scheme 41. Proposed mechanism.

A highly stereoselective Rh-catalyzed 1,4-addition of diverse arylboronic acids **2** to 3-substituted maleimides **89a-c** providing 3,3-disubstituted succinimides **90** has been reported. It has been found that the regioselectivity is mainly controlled by the choice of ligand (dienes or bisphosphines). Thus the desired 1,4-adduct bearing a quaternary stereogenic center can be obtained in both high regio- and enantioselectivity by the utilization of (*R*)-H₈-binap. Both substrates **89a** and **89b** react smoothly with differently substituted arylboronic acids with high regioselectivity (81/19- 92/8), to give the desired 1,4-adducts **90** with high to excellent enantioselectivity (90-97% *ee*). It is noteworthy that an *o*-tolyl group can be assembled in **89a** with virtually perfect regioselectivity (>98/2, 90% *ee*). Furthermore, substrate **89c** (R = *i*-Pr) can be subjected to the 1,4-addition with very high regio- and excellent enantioselectivity (97/3, 98% *ee*).¹⁰⁸

Scheme 42.

Table 23. Rhodium-catalyzed stereoselective 1,4-addition of arylboronic acids to substituted maleimides.

89					
Entry	R 89	Ar 2	Yield (%) ^a	90/91 ratio	<i>ee</i> (%) of 90
1	89a : Et	Ph	98	87/13	97
2	89a : Et	3-ClC ₆ H ₄	95	92/8	97
3	89a : Et	2-naphthyl	90	86/14	96
4	89a : Et	4-MeC ₆ H ₄	82	>98/2	90
5	89b : Me	Ph	98	81/19	96
6	89b : Me	4-MeOC ₆ H ₄	95	84/16	90
7	89b : Me	4-FC ₆ H ₄	95	86/14	96
8	89c : <i>i</i> -Pr	Ph	90	97/3	98
9	89c : <i>i</i> -Pr	4-MeC ₆ H ₄	85	97/3	98

^aCombined yield of **90** and **91**

The observed regioselectivity in these 1,4-additions to 3-substituted maleimides can be explained as follows. In the presence of a Rh-catalyst bearing (*R*)-H₈-binap **L17** (Figure 3), due to the pronounced steric repulsion between the R substituent on the maleimide and the phenyl moiety from the phosphorus atom of the ligand, maleimide favorably coordinates to rhodium, maintaining its R group away from the ligand phenyl group, resulting in the selective formation of **90**.

Figure 3. Proposed stereochemical pathway for the stereoselective 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(*R*)-H₈-binap.

Conversely, in the presence of (*R,R*)-Ph-bod* **L11a** (Figure 4), the upward direction of the phenyl substituent on the diene ligand reduces the steric repulsion with the R group on maleimide. For this reason, the steric hindrance between the aryl group on the rhodium and the R group on maleimide becomes the determining factor, resulting in selective insertion of maleimide towards the generation of **91**.

Figure 4. Proposed stereochemical pathway for the stereoselective 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(*R,R*)-Ph-bod*

Reactions with quinone-based substrates have also been examined in 1,4-conjugate additions. For instance, 2-methyl-1,4-naphthoquinone **96** was subjected to the 1,4-addition of PhB(OH)₂ in the presence of Rh/(*R*)-binap to give product **97** in 70% yield and with excellent enantioselectivity (>99% *ee*) (Scheme 43).

Scheme 43.

Johan Van der Eycken et al. reported several new C_2 -symmetric bicyclo[2.2.1]hepta-2,5-dienes ligands with different substituents ($R = \text{Bn}$, $i\text{-Bu}$, $c\text{-Hex}$, allyl) that were synthesized starting from the respective enantiomerically pure bis-triflate ($R = \text{OTf}$). These chiral ligands were examined in the $[\text{RhCl}(\text{S,S})\text{-allyl-nbd}^*]_2$ -catalyzed 1,4-addition of phenylboronic acids **1a,b** to cyclic enones **2** to obtain **98a-g**; in all cases high enantioselectivities were obtained.¹⁰⁹ It was found that the reactivity and selectivity could be increased by the introduction of sterically demanding or olefin substituents on the above ligands. This is significant, since NMR experiments show that complexation of (*S,S*)-allyl-nbd* with rhodium takes place exclusively *via* the norbornadiene endocyclic double bonds, contrary to the previously reported similar ligands.¹¹⁰

Scheme 44.

Table 24. Rhodium(I)-catalyzed stereoselective 1,4-addition of PhB(OH)_2 **2** to cyclic enone **1**.

Entry	1	Ln	Yield (%)	ee (%)
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1	1a	L5a	98a: 95	96
2	1a	L5b	98b: 80	95
3	1a	L5c	98c: 94	95
4	1a	L5d	98d: 72	95
5	1b	L5b	98e: 73	85
6	1b	L5c	98f: 54	82
7	1b	L5d	98g: 44	90

A chiral bidentate phosphoramidite **L19a** was prepared using Shibasaki's linked-(*R*)-BINOL and P(NMe₂)₃ as the ligand for Rh(I)-catalyzed stereoselective 1,4-addition of a wide range of arylboronic acids to various α,β -unsaturated carbonyl compounds **1a-c**, **99a-g**. The influence of the catalysts, phosphoramidites **L18**, **L19** and bases on the enantioselectivities and on reaction rates in this Rh-catalyzed reaction were studied comprehensively. Conventional monodentate phosphoramidite ligands **L18** afforded satisfactory *ee* for only cyclic enones; bidentate phosphoramidite **L19a** acted is an excellent ligand for both cyclic and acyclic enones. In addition, the reaction was completed in a short time at ambient temperature.¹¹¹

The performance of monodentate and bidentate phosphoramidite ligands for the stereoselective addition of arylboronic **2** acids to α,β -unsaturated carbonyl compounds **1a-c**, **99a-g** to provide products **100** was also reported (Scheme 45).¹¹² Noticeably, the reaction was accelerated in the presence of commercially available bases such as KOH and Et₃N, resulting in completion of the reaction at the lower temperatures (even lower 50 °C). The addition to cyclic enones, for example 2-cyclopentenone, 2-cyclohexenone and 2-cycloheptenone at 50 °C in the presence of an [Rh(coe)₂Cl]₂-**L18** (R¹, R² = Et) complex led to the desired products with up to 98%*ee* although it was less efficient for acyclic enones (0-70% *ee*).

Scheme 45. Stereoselective 1,4-addition of arylboronic acids to enones catalyzed by Rh(I)-phosphoramidite complexes.

The effects of monodentate phosphoramidite ligands **L18** above reaction are enlisted in Table 25.

Table 25. 1,4-Addition of arylboronic acid to α,β -unsaturated carbonyl compounds catalyzed by Rh(I)-**L18** complexes.

Entry	1/99	Ligand L18		Ar 2	Yield (%)	<i>ee</i> (%)	Config.
		R ⁴	R ⁵				
1	1a	Me	Me	Ph	100a : 85	85	(<i>R</i>)
2	1a	Et	Et	Ph	100a : 89	91	(<i>R</i>)
3	1a	Et	Et	3-MeOC ₆ H ₄	100b : 85	98	-

4	1a	Et	Et	4-MeC ₆ H ₄	100c : 95	96	-
5	1a	CH ₂ Ph	CH ₂ Ph	Ph	100a : 45	57	(<i>R</i>)
6	1a	<i>i</i> -Pr	<i>i</i> -Pr	Ph	100a : 11	4	(<i>S</i>)
7	1a	–CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ –		Ph	100a : 83	68	(<i>R</i>)
8	1a	–CH ₂ CH ₂ NCH ₂ CH ₂ –		Ph	100a : 89	91	(<i>R</i>)
9	1b	Et	Et	Ph	100d : 95	75	-
10	1b	Et	Et	3-ClC ₆ H ₄	100e : 98	81	-
11	1b	Et	Et	3-MeOC ₆ H ₄	100f : 97	95	-
12	1c	Et	Et	Ph	100g : 90	94	-
13	99a	Et	Et	Ph	100h : 96	0	-
14	99a	Me	Et	Ph	100h : 99	16	(<i>S</i>)
15	99a	Me	<i>n</i> -Pr	Ph	100h : 95	24	(<i>S</i>)
16	99a	Me	CH ₂ Ph	Ph	100h : 94	10	(<i>S</i>)
17	99a	Me	Ph	Ph	100h : 28	29	(<i>R</i>)
18	99a	Me	<i>i</i> -Pr	Ph	100h : 94	35	(<i>R</i>)
19	99a	Me	1-adamantyl	Ph	100h : 55	47	(<i>R</i>)
20	99a	Me	<i>t</i> -Bu	Ph	100h : 41	70	(<i>R</i>)

Using the optimal conditions, the generality of reaction was established by using differently substituted arylboronic acids **2** added to various α,β -unsaturated carbonyl compounds **1a-c**, **99a-g** in the presence of Rh(nbd)₂]BF₄ and **L19a** as the catalyst system at ambient temperature mediated by Et₃N in dioxane and water. This catalyst was also found to be efficient for acyclic enones. The results are summarized in Table 26.¹¹¹

Table 26. 1,4-Addition of arylboronic acid to α,β -unsaturated carbonyl compounds catalyzed by a Rh(+)-**L19a** complex.

Entry	1/99	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	100a : 99	99.6 (<i>R</i>)
2	1a	3-MeOC ₆ H ₄	100b : 90	99.5 (<i>R</i>)
3	1a	4-MeOC ₆ H ₄	100i : 99	99.8
4	1a	3-ClC ₆ H ₄	100j : 86	99.8
5	1b	3-ClC ₆ H ₄	100e : 99	96
6	1b	4-MeOC ₆ H ₄	100k : 99	96

7	1c	H	100g : 90	98
8	99a	H	100h : 87	74
9	99a	H	100h : 42	84
10	99a	3-MeO	100i : 98	80
11	99a	3-MeO	100i : 65	83
12	99a	3-F	100m : 97	81
13	99b	3-MeO	100n : 91	85
14	99c	H	100o : 80	92 (<i>R</i>)
15	99c	3-MeO	100p : 78	94
16	99c	3-F	100q : 71	90
17	99d	3-MeO	100r : 62	81
18	99e	3-MeO	100s : 98	85
19	99f	3-MeO	100t : 99	78
20	99g	3-MeO	100u : 98	66

The 1,4-additions of arylboronic acids to unsaturated lactones and acyclic esters with Rh(I)-phosphoramidites complexes were studied from different points of view. Stereoselective 1,4-additions to acyclic and cyclic α,β -unsaturated esters are illustrated in Scheme 46. The reaction was found to be slower than that for enones, however high enantioselectivities comparable to those of the respective enones were clearly observed. Methyl crotonate, 5H-furan-2-one, and 5,6-dihydro-2*H*-pyran-2-one gave **102** (75% *ee*), **103** (77% *ee*), **104a** (89% *ee*) and **104b** (91% *ee*), respectively, catalyzed by [Rh(nbd)₂]BF₃-**L19a** and Et₃N at ambient temperature. Alternatively, the use of monodentate phosphoramidites such as **L18** (R⁴, R⁵ = Et) failed for 5*H*-furan-2-one and for 5,6-dihydro-2*H*-pyran-2-one at 50°C catalyzed by Rh(acac)(coe)₂ in the presence of Et₃N in dioxane-H₂O (6/1) the corresponding product was obtained in 35% yield and 72% *ee* (Scheme 46).¹¹¹

Scheme 46. Stereoselective 1,4-addition to unsaturated esters.

It has been reported that chiral bicyclo[3.3.0]octadiene ligands **L20a** and **L20b** are readily available. As depicted in Scheme 47, diphenyl- and dibenzylsubstituted ligands **L20a** and **L20b** demonstrate very different activities. The effectiveness of ligands **L20** in the Rh-catalyzed 1,4-addition of arylboronic acids **2** to cyclic and acyclic enones **1a-c** and **1p, q** can be easily achieved. More remarkably, the substitution pattern of the diene results in extra activity and substrate specificity of the catalyst. When cyclic enones **1a-c** were used, the enantiomeric diphenyldienes (3a*R*,6a*R*)- and (3a*S*,6a*S*)-**L20a** were found to be more selective than the respective dibenzyl diene ligands **L20b**. However, when acyclic enones **1p, q** were employed, this result, completely reversed. Ligands **L20a** were practically inactive while di-benzyl dienes **L20b** gave adducts **107** with enantioselectivities of up to 91%. Therefore, it should be established whether this would also be observed for other catalytic reactions.¹¹³

Scheme 47.

Table 27. Rhodium-catalyzed addition of arylboronic acids **2** to cyclic enones **1a-c** using ligands **(3aR, 6aR)-L20a, b** and **(3aS, 6aS)-L20a**.

Entry	1	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	1b	(3aS, 6aS)-L20a	Ph	105a : 74	95	(<i>R</i>)
2	1b	(3aR, 6aR)-L20a	Ph	105a : 80	93	(<i>S</i>)
3	1b	(3aR, 6aR)-L20b	Ph	105a : 73	75	(<i>S</i>)
4	1a	(3aS, 6aS)-L20a	Ph	105b : 95	88	(<i>R</i>)
5	1a	(3aR, 6aR)-L20a	Ph	105b : 93	84	(<i>S</i>)
6	1a	(3aR, 6aR)-L20b	Ph	105b : 78	73	(<i>S</i>)
7	1c	(3aS, 6aS)-L20a	Ph	105c : 47	83	(<i>R</i>)
8	1c	(3aR, 6aR)-L20a	Ph	105c : 51	76	(<i>S</i>)
9	1b	(3aR, 6aR)-L20a	4-MeC ₆ H ₄	106a : 85	93	(<i>S</i>)
10	1a	(3aR, 6aR)-L20a	4-MeC ₆ H ₄	106b : 81	84	(<i>S</i>)
11	11c	(3aR, 6aR)-10a	4-MeC ₆ H ₄	106c : 71	76	(<i>S</i>)

Scheme 48.

Table 28. Rhodium-catalyzed addition of arylboronic acids **2** to acyclic enones **1p, q** using ligands (3a*R*, 6a*R*)- and (3a*S*,6a*S*)-**L20a,b**.

Entry	1	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	1p	(3a <i>S</i> ,6a <i>S</i>)- L20a	Ph	107a : <1	1	-
2	1p	(3a <i>R</i> ,6a <i>R</i>)- L20a	Ph	107a : <1	0	-
3	1p	(3a <i>S</i> ,6a <i>S</i>)- L20b	Ph	107a : 71	91	(<i>S</i>)
4	1p	(3a <i>R</i> ,6a <i>R</i>)- L20b	Ph	107a : 59	89	(<i>R</i>)
5	1q	(3a <i>S</i> ,6a <i>S</i>)- L20a	Ph	107b : <1	16	+
6	1q	(3a <i>R</i> ,6a <i>R</i>)- L20a	Ph	107b : 1	10	-
7	1q	(3a <i>S</i> ,6a <i>S</i>)- L20b	Ph	107b : 73	89	+
8	1q	(3a <i>R</i> ,6a <i>R</i>)- L20b	Ph	107b : 45	88	-
9	1p	(3a <i>R</i> ,6a <i>R</i>)- L20b	4-MeC ₆ H ₄	108a : 68	89	(<i>R</i>)
10	1q	(3a <i>R</i> ,6a <i>R</i>)- L20b	4-MeC ₆ H ₄	108b : 58	86	-

Chiral phosphine-olefin ligands attached to rhodium as the Rh-catalyst **1** can catalyze the stereoselective 1,4-addition of arylboronic acids **2** to α,β -unsaturated carbonyl compounds

1a,b,g,e,r. Catalyst Rh/(7*S*)-**L21a** afforded 1,4-adducts **109** in consistently high yields (89- 99% yield). Kinetic studies using a reaction calorimeter revealed that the Rh/**L21** catalyst showed very high catalytic activity in these reactions. It was also found that its activity is even higher than a Rh/cod catalyst which is regarded as one of the most effective catalysts in Rh-catalyzed 1,4-addition reactions. It has also been shown that the enantioselectivity obtained by using Rh/**L21a** is as high as Rh/Ph-bod*. In this case, transmetallation takes place at the *trans*-position to the olefin ligand of Rh/**L21** while the stereochemical consequence is controlled at the *cis*-position to the olefin. Using ³¹P NMR spectroscopy, it was established that the catalytic cycle with Rh/**L21** was basically the same as that obtained from Rh/binap. However, it involved a trimer monomer equilibrium of the catalyst, rather than a dimer monomer equilibrium, as shown by the kinetic investigations with a reaction calorimeter.¹¹⁴

Scheme 49.

Table 29. Rh/(7S)-L21-catalyzed stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds.

Entry	1	Ar 2	Ln	Yield (%)	<i>ee</i> (%)	Config.
1	1b	Ph	L21a	109a : 91	98 (99)	(<i>R</i>)
2	1b	4-MeOC ₆ H ₄	L21a	109b : 94	98 (98)	(<i>R</i>)
3	1b	4-CF ₃ OC ₆ H ₄	L21a	109c : 92	95 (96)	(<i>R</i>)
4	1b	2-MeC ₆ H ₄	L21a	109d : 99	98 (96)	(<i>R</i>)
5	1a	Ph	L21a	109e : 94	93 (96)	(<i>R</i>)

6	1e	Ph	L21a	109f : 91	72 (83)	(<i>S</i>)
7	1g	Ph	L21a	109g : 89	97 (95)	(<i>R</i>)
8	1r	Ph	L21a	109h : 98	93 (91)	(<i>R</i>)
9	1r	Ph	L21b	109i : 90	94	(<i>R</i>)
10	1r	Ph	L21c	109j : 97	95	(<i>R</i>)
11	1r	Ph	L21d	109k : 96	93	(<i>R</i>)
12	1r	Ph	L21e	109l : 99	84	(<i>R</i>)
13	1r	Ph	L21f	109m : 96	91	(<i>R</i>)

By analyzing the results of these 1,4-additions and by analogy with the stereochemical control of a Rh/(*R, R*)-Ph-bod* catalyst, the stereochemical induction with Rh/(7*S*)-**L21a** was reorganized as illustrated in Figure 5. The phenyl rhodium species has a *trans*-relationship between the phenyl group and the olefin ligand, while the substrate, i.e., 2-cyclohexen-1-one, binds to Rh with its R-group *re* face at the *cis*-position of the olefin ligand, resulting in the 1,4-adduct with an (*R*)-configuration.

Figure 5. Proposed stereochemical pathway for the Rh/(7*S*)-**L21a**-catalyzed stereoselective 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one.

The regioselectivity realized in the Rh-catalyzed stereoselective 1,4-addition of phenylboronic acid to 1-benzyl-3-methylmaleimide **89b** also indicates the origin of the stereochemical control

of Rh/(7*S*)-**L21a**. Thus, phenylation of maleimide **89a** preferentially affords compound **113** in the presence of chiral bisphosphine ligand (Table 30, entry 1), whereas the use of diene ligand (*R,R*)-Ph-bod* gives compounds **114** as the major products (entry 2). The observed regioselectivity can be understood and rationalized by the steric interaction between substrate **7** and the ligand substituent, which is *cis* to **89b**.¹¹⁴

Scheme 49.

Table 30. Rhodium-catalyzed stereoselective 1,4-addition of phenylboronic acid to maleimide **89b**:
ligand effect on the regioselectivity.

Entry	Ln	Yield (%)	113/114 (<i>trans/cis</i>)	<i>ee</i> (%) of 113	<i>ee</i> (%) of 114 (<i>trans, cis</i>)
1	L4	99	75/25 (2.1/1)	95	0, 96
2	L11	94	11/89 (1/1.4)	93	79, 99
3	L21a	99	17/83 (1/1.2)	77	95, >99

A variety of *N,N*-disubstituted 4-oxobutenamides were found suitable to be coupling partners with arylboronic acids under catalysis of a chiral Rh complex **L22**, which induces high regio- and enantioselectivity (97:3 to >99:1, >96% *ee*) and gave moderate to excellent yields (54-99%). This high selectivity can be attributed to the use of sterically demanding *P*-chiral diphosphines, for example Tangphos or Duanphos. The oxobutanamide products **116a-n** were converted into other targets by selective derivatization of either the amide or ketone functional groups. A stereochemical model was in agreement with the absolute sense of induction based on single-crystal X-ray structures of product and precatalyst. The reaction is tolerant of various substitution on the boronic acid and the corresponding 2-aryl-4-oxobutanamides were obtained with high regioselectivity and excellent *ee*. The structural analysis of absolute configuration of products and pre-catalyst provides a simple and predictive stereochemical model for a typical 1,4-conjugate addition of these substrates.

Using the optimized reaction conditions, the generality of this regioselective 1,4-conjugate addition considering the nucleophilic coupling partner was studied (Scheme 51). Several commercially available or readily accessible *meta*- and *para*-substituted boronic acids **2** were used and found to be suitable coupling partners with **115a** (Scheme 51). Both electron rich and electron poor boronic acids were obtained with high enantio- and regioselectivity induced by complex **L22** as the chiral catalyst.

The 1,4-conjugate addition reaction to **115a** catalyzed by complex **L22** was also found to be tolerant of *ortho*-substitution on the boronic acid nucleophile **2**, providing excellent regioselectivities and enantioselectivities in most cases (Scheme 51). With *o*-halo-substituted boronic acids, increasing the halogen size led to a decrease in yield of the products (Cl 68% yield; Br <10% conversion).¹¹⁵

- 116a:** Ar = 4-OMeC₆H₄, yield = 93%, ee = 98%
116b: Ar = 4-MeC₆H₄, yield = 98%, ee = 98%
116c: Ar = 4-CF₃C₆H₄, yield = 97%, ee = >99%
116d: Ar = 4-SO₂MeC₆H₄, yield = 98%, ee = 98%
116e: Ar = 4-BrC₆H₄, yield = 73%, ee = 99%
116f: Ar = 3-BrC₆H₄, yield = 99%, ee = 93%
116g: Ar = 1-methyl-1H-indole, yield = 71%, ee = 97%
116h: Ar = naphthalene, yield = 60%, ee = 98%
116i: Ar = CH=CHC₆H₅, yield = 92%, ee = 99%
116j: Ar = 2-MeC₆H₄, yield = 99%, ee = >99%
116k: Ar = 3-CF₃-6-FC₆H₃, yield = 80%, ee = 98%
116l: Ar = 2-ClC₆H₄, yield = 68%, ee = 97%
116m: Ar = 2-BrC₆H₄, yield = <10%, ee = n.d.
116n: Ar = 2,6-(Me)₂C₆H₃, yield = 94%, ee = 14%

Scheme 51. Effect of the boronic acid structure on the yield, product distribution, and enantioselectivity in the reaction of **115a**.

The reaction scope considering the electrophile structure was then studied. Oxobutenamides **115b-k** were synthesized *via* the enol-cyclopropanation/ring-expansion protocol innovated by

Zercher¹¹⁶ and reacted under optimized reaction conditions with boronic acid **2** catalyzed by complex **L22** (Table 31). Aliphatic oxobutenamides consistently gave high regio- and enantioselectivities similar to their aryl counterparts (**115c,d** vs. **115a,b**). The more bulky isopropyl and *tert*-butyl acrylamides **115e**, **115f** showed lower reactivity in comparison with other substrates. Increased catalyst loadings and/or selecting a stronger base, such as potassium hydroxide, gave better yields.

Variation of the amide structure disclosed the more insightful differences in reaction selectivity. Following the previous trend, *N,N*-di-alkylamides uniformly gave high enantio- and regioselectivities (Table 31). While the 1,4-conjugate addition to Weinreb amide **115i** gave products with high enantioselectivity (97% *ee*), the regioselectivity was low (2:1) although the desired regiochemistry was still favored. Submitting mono substituted amide **115j** to the optimized reaction conditions resulted in a moderate reversal of selectivity, favoring the formation of the undesired conjugate addition product **118j** (Table 31). Interestingly in this case the enantioselectivity of the desired regioisomer **117j** was still high (97% *ee*). Primary amide **115k** was found to be unstable under even the optimized reaction conditions and the expected desired product was obtained.

Scheme 52.

Table 31. Effect of ketone and amide substituent on conjugate addition reaction of **115b-k** with **2**.

Entry	115	117:118	Yield (%)	<i>ee</i> (%) of 117
1	115b	>99:1	117b : 97	98

2	115c	97:3	117c : 90	97
3	115d	>95:5	117d : 91	99
4	115e	>95:5	117e : 82	99
5	115f	>95:5	117f : 78	99
6	115g	>99:1	117g : 89	97
7	115h	>99:1	117h : 90	99
8	115i	2:1	117i : 91	97
9	115j	1:1.3	117j : 60	97
10	115k	n.d.	117k : n.d.	n.d.

Analysis of the sense of the stereochemistry of the product combined with the solid-state structure of precatalyst **L22** were used for a simple steric model to predict the stereochemical outcome. Based on the generally established mechanism for the Rh-catalyzed 1,4-conjugate addition (Scheme 53), an aryl rhodium(I) species, created from the transmetallation of the boronic acid, coordinated the substrate enone **115** to generate complex **121**. In this reaction, the stereochemical determination step is the coordination of the substrate, which is followed by irreversible migratory insertion to form a rhodium enolate species **122**, which upon hydrolysis gave the product along with regeneration of the active catalytic species.

Scheme 53. Proposed catalytic cycle for rhodium-catalyzed conjugate addition of aryl boronic acids.

The catalytic stereoselective formation of chiral C-N axes was developed *via* a Rh-catalyzed stereoselective 1,4-addition reaction. Interestingly, both central chirality and axial chirality could be controlled at the same time when Rh/(*R,R*)-Ph-bod* **L11** catalyst was used with high enantio- and diastereoselectivity. This methodology was also employed for the synthesis of a planar-chiral ferrocene derivative. The resulting chiral C-N axis can be used as an appropriate template to control the stereochemistry in the other desired subsequent transformations such as alkylation and Diels-Alder reactions. For a brief introduction to the scope of this reaction, is see Table 32 under the optimal conditions with Rh/(*R,R*)-Ph-bod*. A wide variety of arylboronic acids **2** can be coupled with **123a-c** to furnish the respective axially chiral succinimides **124a-i** with high *de* and excellent *ee*. Other maleimides, such as **123b** and **123c**, are also suitable for use for this system to afford the products with the same efficiency.¹¹⁷

Scheme 54.

Table 32. Rhodium-catalyzed stereoselective construction of C-N axes.

Entry	123	Ar 2	<i>dr</i>	Yield (%)	<i>ee</i> (%)
1	123a	Ph	96/4	124a : 96	99
2	123a	4-MeOC ₆ H ₄	98/2	124b : 95	97
3	123a	2-FC ₆ H ₄	96/4	124c : 92	99
4	123a	2-BrC ₆ H ₄	97/3	124d : 88	98
5	123a	3-ClC ₆ H ₄	97/3	124e : 88	96
6	123a	2-naphthyl	96/4	124f : 93	97
7	123a	2-MeC ₆ H ₄	98/2	124g : 97	98
8	123b	Ph	91/9	124h : 81	99
9	123c	Ph	97/3	124i : 96	99

The stereochemical result observed in the reaction with Rh/(*R,R*)-Ph-bod* catalyst can be described as follows (Figure 6). To avoid the disfavored steric interaction between the imide moiety of maleimide and the phenyl group on the olefin of (*R,R*)-Ph-bod*, the generation of intermediate **125** is disfavored for the creation of **126**, furnishing product **124a** with a well-determined (*R*)-configuration at the 3-position. For the control of the axial chirality, due to the bulkiness of the *tert*-butyl group on maleimide, the coordination of **123a** is much more favored in **125** than in **127**, resulting in the generation of a C-N axis with an (*S*)-configuration.

Figure 6. Proposed stereochemical pathway for the reaction of **123a** with phenylboronic acid catalyzed by Rh/(*R,R*)-Ph-bod*.

This type of facial discrimination by a Rh/chiral diene catalyst can also be employed in the addition of phenylboronic acid **2** to ferrocenobenzoquinone **128** to afford adduct **129** with excellent enantioselectivity (Scheme 55).¹¹⁷

Scheme 55.

A novel synthetic strategy to 2-aryltetralones **131a-k** with high *ee* has been achieved via stereoselective 1,4-addition of arylboronic acids **2** to naphthoquinone monoketals **130a,b** under catalysis by a Rh-complex with the (*R,R*)-Ph-bod* ligand. This stereoselective addition led to high yields with excellent enantioselectivity. This reaction presents a new efficient synthetic pathway to enantiomerically enriched α -arylated tetralones, which are invaluable chiral frameworks for the synthesis of some biologically active compounds. Thus under similar reaction conditions using (*R,R*)-Ph-bod* as a ligand, differently substituted aryl groups were introduced onto naphthoquinone monoketals **130a,b** in high yields with excellent enantioselectivity (96-99% *ee*) (Table 33).¹¹⁸

Scheme 56.

Table 33. Stereoselective 1,4-addition of arylboronic acids **2** to naphthoquinone monoketals **130** catalyzed by Rh/(*R,R*)-Ph-bod*

Entry	R 130	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	130a : H	Ph	131a : 98	98	(<i>R</i>)
2	130a : H	4-MeOC ₆ H ₄	131b : 94	99	(<i>R</i>)
3	130a : H	4-FC ₆ H ₄	131c : 93	98	(<i>R</i>)
4	130a : H	3-ClC ₆ H ₄	131d : 95	99	(<i>R</i>)
5	130a : H	3,4-(MeO) ₂ C ₆ H ₃	131e : 94	98	(<i>R</i>)
6	130a : H	3,5-(MeO) ₂ C ₆ H ₃	131f : 86	97	(<i>R</i>)
7	130a : H	benzo[<i>d</i>][1,3]dioxol-5-yl	131g : 95	96	(<i>R</i>)
8	130a : H	2-MeC ₆ H ₄	131h : 96	99	(<i>R</i>)
9	130a : H	naphthalen-2-yl	131i : 97	98	(<i>R</i>)
10	130a : H	thiophene	131j : 87	98	(<i>R</i>)
11	130b : -OCH ₂ O-	3,4-(MeO) ₂ C ₆ H ₃	131k : 95	98	(<i>R</i>)

Stereoselective alkenylation of the mono-ketal **130a** also progressed to completion with high enantioselectivity using alkenylboron reagents **132a,b** and Rh/(*R,R*)-Ph-bod* as a catalyst to afford the respective 1,4-adducts **133a,b** with high to excellent enantioselectivity (96–99% *ee*) (Scheme 57). For the introduction of the unsubstituted vinyl group, potassium trifluoro(vinyl)borate¹¹⁹ **132b** is required.

Scheme 57. Stereoselective 1,4-addition of alkenylborons **132** to monoketal **130a** catalyzed by Rh/(*R,R*)-Ph-bod*

Dihydroquinone monoketal **130c**¹²⁰ is another good substrate, which undergoes asymmetric 1,4-addition of arylboronic acids **2** with high enantioselectivity (96–98% *ee*), although the chemical yields are slightly lower (Scheme 58).

Scheme 58. Asymmetric 1,4-addition of arylboronic acids **2** to dihydrobenzoquinone monoketal **130c**.

The (*R*)-configuration was defined for the 1,4-addition products **131**, **134** obtained using (*R,R*)-Ph-bod*. This (*R*)-configuration is consistent with the steric aspects of the Rh/(*R,R*)-Ph-bod*

complex (Figure 7). The coordination of the carbon-carbon double bond on monoketal **130** with its α -*si* face is much more favored than that with its α -*re* face because of the steric repulsions of the phenyl rings of the chiral diene ligand.

Figure 7. Enantioselection in the rhodium-catalyzed stereoselective 1,4-addition.

Novel C_2 -symmetric chiral diene ligands involving a tetrafluorobenzobarrelene scaffold were synthesized in two steps starting from commercial reagents. The diene ligands were subjected to Rh-catalyzed stereoselective additions of arylboronic acids **2** to various α,β -unsaturated carbonyl compounds **1a-c,e,t,u,v** affording β -arylcarbonyl compounds in high yields and with high enantioselectivity.

The scope of this enantioselective arylation catalyzed by Rh/(*R,R*)-**L23** was investigated. It was found that the 1,4-addition of differently substituted arylboronic acids **2** to 2-cyclohexen-1-one **1a** in the presence of $[\text{Rh}(\text{OH})((R,R)\text{-1})_2]$ afforded the respective 3-arylcyclohexanones **137a-o** in satisfactory chemical yields and with excellent enantioselectivity (98-99% *ee*). For example, the addition of (*E*)-3,3-dimethyl-1-butenylboronic acid afforded the respective 3-alkenylcyclohexanone in high yield and with high *ee* (Scheme 59).¹²¹

Scheme 59.

Table 34. Stereoselective 1,4-addition catalyzed by [Rh(OH)-((*R,R*)-L23)]₂.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	1a	Ph	137a : 98	99	(<i>R</i>)
2	1a	4-MeC ₆ H ₄	137b : 94	99	(<i>R</i>)
3	1a	4-MeOC ₆ H ₄	137c : 97	99	(<i>R</i>)
4	1a	4-ClC ₆ H ₄	137d : 95	99	(<i>R</i>)
5	1a	3-ClC ₆ H ₄	137e : 91	99	(<i>R</i>)
6	1a	4-CF ₃ C ₆ H ₄	137f : 95	99	(<i>R</i>)
7	1a	4-FC ₆ H ₄	137g : 92	99	(<i>R</i>)
8	1a	2-naphthyl	137h : 89	98	(<i>R</i>)
9	1a	<i>E</i> - <i>t</i> -BuCH=CH	137i : 86	84	(<i>R</i>)
10	1b	Ph	137j : 99	94	(<i>R</i>)
11	1c	Ph	137k : 88	96	(<i>R</i>)
12	1t	Ph	137l : 85	99	(<i>S</i>)

13	1t	Ph	137m : 99	99	(<i>R</i>)
14	1u	Ph	137n : 97	98	(<i>R</i>)
15	1v	Ph	137o : 80	99	(<i>R</i>)

The bicyclo[3.3.0]diene ligands **L20a** were employed as novel effective chiral ligands in the Rh-catalyzed enantioselective arylations of *N*-tosylarylimines as well as for the Rh-catalyzed stereoselective 1,4-additions of arylboronic acids **2** to α,β -unsaturated cyclic carbonyl compounds **1a,b,g,f**, such as 2-cyclohexenone **1a** and 2-cyclopentenone **1b**. Under the optimal conditions, the reactions proceeded smoothly at ambient temperature with high to excellent enantioselectivities (up to 98% *ee*) and satisfactory chemical yields. Noticeably, the electron-donating or -withdrawing moieties on the phenyl ring of boronic acids did not show any appreciable effect in terms of the yields of the products or the enantioselectivity of the reaction (Scheme 60).¹²²

Scheme 60.

Table 35. Stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated cyclic carbonyl compounds catalyzed by $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/(\text{S,S})\text{-L20a}$.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1b	Ph	138a : 96	96
2	1b	4-FC ₆ H ₄	138b : 96	96
3	1b	4-ClC ₆ H ₄	138c : 97	97
4	1b	4-BrC ₆ H ₄	138d : 96	97
5	1b	4-MeC ₆ H ₄	138e : 94	96
6	1b	4-MeOC ₆ H ₄	138f : 98	96
7	1b	3-ClC ₆ H ₄	138g : 81	94
8	1b	2-MeOC ₆ H ₄	138h : 93	97

9	1b	2-MeC ₆ H ₄	138i : 98	98
10	1b	1-naphthyl	138j : 97	98
11	1a	Ph	138k : 96	91
12	1a	4-FC ₆ H ₄	138l : 91	86
13	1a	4-CF ₃ C ₆ H ₄	138m : 73	86
14	1a	3-ClC ₆ H ₄	138n : 79	91
15	1a	2-MeOC ₆ H ₄	138o : 89	90
16	1a	2-MeC ₆ H ₄	138p : 91	93
17	1a	1-naphthyl	138q : 87	96
18	1g	Ph	138r : 87	93
19	1g	2-MeC ₆ H ₄	138s : 91	97
20	1g	4-MeC ₆ H ₄	138t : 93	89
21	1g	2-naphthyl	138u : 94	94
22	1f	2-MeC ₆ H ₄	138v : 55	95

A series of modified chiral diene ligands were designed and prepared by Hayashi *et al.*, for the synthesis of Rh and Ir organometallic catalysts for stereoselective synthesis.¹²³⁻¹²⁷ The applications of Rh-bis-sulfoxide compounds as effective catalysts are well established.^{128,129} However, the applications of bis-sulfoxide ligands in stereoselective synthesis have been largely overlooked.¹³⁰⁻¹³⁷

In 2008, Dorta *et al.* have disclosed that chiral bis-sulfoxides can be employed as ligands in stereoselective late-transition metal catalysis. Pre-catalyst [{(*P,R,R*)-*p*-tol-BINASO}RhCl]₂ **L24** acts as a reactive showing excellent stereoselectivities in the 1,4-addition of different arylboronic acids **2** to cyclic, electron-poor compounds **1a-c,g,w**. The scope of the aforementioned catalyst system has recently been expanded to other substrates. Scheme 61 illustrates that the catalytic effectiveness of **L24** frequently resulted in complete conversion. The observed enantioselectivities are among the highest for Rh-catalyzed stereoselective 1,4-additions, giving more than 90% *ee* and is higher in all cases except for one of the reactions tested (Table 36).¹³⁸

Scheme 61. Catalytic results with [$\{(P,R,R)\text{-}p\text{-tol-BINASO}\}\text{RhCl}$] $_2$ **L24**.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	139a : 99	98 (<i>S</i>)
2 ^a	1a	Ph	139b : 99	98 (<i>R</i>)
3	1a	4-MeC ₆ H ₄	139c : 97	96
4	1a	4-ClC ₆ H ₄	139d : 86	98
5	1a	4-FC ₆ H ₄	139e : 90	98
6	1a	4-MeOC ₆ H ₄	139f : 92	99
7	1a	3-MeC ₆ H ₄	139g : 93	99
8	1a	4-CF ₃ C ₆ H ₄	139h : 94	97
9	1a	3-ClC ₆ H ₄	139i : 93	99
10	1a	3-FC ₆ H ₄	139j : 91	97
11	1a	3-MeOC ₆ H ₄	139k : 55	97
12	1a	2-MeC ₆ H ₄	139l : 98	90
13	1a	2-FC ₆ H ₄	139m : 60	99
14	1a	1-naphthyl	139n : 99	90
15	1a	2-naphthyl	139o : 89	96
16	1a	1-pyrene	139p : 90	95
17	1b	Ph	139q : 99	96

18	1c	Ph	139r : 98	66
19	1g	Ph	139s : 98	91
20	1w	2-naphthyl	139t : 49 (<i>cis</i>)	94
			139t : 49 (<i>trans</i>)	94

^aUsing [$\{(M,S,S)\text{-}p\text{-tol-BINASO}\}\text{RhCl}_2$] **L24** as catalyst

A general strategy has been accomplished and reported for highly effective Rh-catalyzed 1,4-additions of potassium trifluorovinylborate salts **140a-c** to cyclic enones **1a-c,e,x** mediated by Et₃N at ambient temperature in excellent chemical yields and enantioselectivities to provide **141a-g**. By using this strategy, the enantioselective addition of an isopropenyl group to cyclic enones was accelerated. Notably, this reaction could not be accomplished using previously reported strategies. The collected evidence showed a significant acceleration of the transmetallation step by triethylamine of the 1,4-conjugate addition (Scheme 62).¹³⁹

Scheme 62.

Table 37.

Entry	1	140	Yield (%)	<i>ee</i> (%)
1	1b	140a	141a : 80	93
2	1a	140a	141b : 87	>98
3	1c	140a	141c : 89	>98
4	1x	140a	141d : 81	-
5	1e	140a	141e : 89	-
6	1b	140b	141f : 89	70
7	1b	140c	141g : 83	70

Darses et al. in 2008 revealed that monosubstituted chiral dienes are appropriate ligands for Rh-catalyzed stereoselective 1,4-additions of boronic acids **2** to α,β -unsaturated substrates **1a-c,f,g,y** as Michael acceptors and enantioenriched products **142a-p** were provided with 92% *ee*. These ligands are readily accessible *via* a four step reaction starting from commercially available, natural product carvones, and obtained with high enantioselectivities in the formation of a new carbon-carbon bond at the β -position of Michael acceptors. The synthesis of this monosubstituted ligand is straight forward, giving high yields, and giving access to a large library of chiral ligands derived from either enantiomer of inexpensive carvones, which is a useful, readily available catalyst in asymmetric synthesis (Scheme 62).¹⁴⁰

Scheme 63.

Table 38. Monosubstituted chiral diene (-)-(SRR)-L25 in rhodium-catalyzed 1,4-addition of boronic acids to α,β -unsaturated substrates.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1b	Ph	142a : 95	96 (<i>S</i>)
2	1b	3-OMeC ₆ H ₄	142b : 85	96
3	1a	Ph	142c : >99	98 (<i>S</i>)
4	1a	Ph	142d : 89	97 (<i>R</i>)
5	1a	4-OMeC ₆ H ₄	142e : 83	98
6	1a	3-OMeC ₆ H ₄	142f : 93	95
7	1a	4-FC ₆ H ₄	142g : 84	98

8	1a	4-ClC ₆ H ₄	142h : 77	93
9	1a	4-CF ₃ C ₆ H ₄	142i : 66	98
10	1a	1-naphthyl	142j : 45	75 (<i>S</i>)
11	1c	Ph	142k : 53	93
12	1f	Ph	142l : 56	90
13	1g	1-naphthyl	142m : 95	86
14	1g	4-OMeC ₆ H ₄	142n : 95	97
15	1g	Ph	142o : 95	97
16	1y	Ph	142p : 40	90

The stereoselective 1,4-addition reaction has been extended to a wide range of arylboronic acids **2** to arylmethylene cyanoacetates **143a-g** proceeding smoothly and cleanly in the presence of a Rh- catalyst coordinated with a chiral diene ligand, (*R,R*)-Ph-bod*, to give high yields of the respective methyl 3,3-diaryl-2-cyanopropanoates **144m-w** with excellent enantioselectivity (up to 99% *ee*) in high chemical yields (>90%) using a chiral diene-Rh catalyst. Arylmethylene cyanoacetates substituted with a methoxy group at the 4-, 3-, and 2-positions on the phenyl were all found to be suitable substrates, affording the respective adducts with up to 96% *ee* in the reaction with phenyl-, 4- or 3-methylphenyl-, and 4-bromophenyl boronic acids. Notably, the enantioselectivities were also very high for arylmethylene cyanoacetates where the aryl groups were 2-methylphenyl, 2-naphthyl, and 4-chlorophenyl (Table 39).¹⁴¹

Scheme 64.

Table 39. Stereoselective 1,4-addition of arylboronic acids **2** to arylmethylene cyanoacetates **143** catalyzed by Rh/(*R,R*)-Ph-bod*

Entry	Ar ^I 143	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	143a : 4-MeOC ₆ H ₄	Ph	144a : 99	99	(<i>R</i>)
2	143b : 3-MeOC ₆ H ₄	Ph	144b : 99	98	(<i>R</i>)

3	143c : 2-MeOC ₆ H ₄	Ph	144c : 94	99	(<i>R</i>)
4	143d : 2-MeC ₆ H ₄	Ph	144d : 92	96	(<i>R</i>)
5	143e : 2-naphthyl	Ph	144e : 91	98	(<i>R</i>)
6	143a : 4-MeOC ₆ H ₄	4-MeC ₆ H ₄	144f : 96	97	(<i>R</i>)
7 ^a	143a : 4-MeOC ₆ H ₄	3-MeC ₆ H ₄	144g : 95	96	(<i>S</i>)
8	143a : 4-MeOC ₆ H ₄	4-BrC ₆ H ₄	144h : 92	98	(<i>S</i>)
9	143f : Ph	4-MeC ₆ H ₄	144i : 95	97	(<i>S</i>)
10	143f : Ph	4-BrC ₆ H ₄	144j : 96	98	(<i>S</i>)
11	143g : 4-ClC ₆ H ₄	4-BrC ₆ H ₄	144k : 90	96	(<i>S</i>)

^aThe reaction was carried out at 30 °C.

A highly stereoselective synthesis has been reported by the chiral diene/ rhodium-catalyzed stereoselective 1,4-addition of arylboronic acids **2** to β -aryl-substituted α,β -unsaturated aldehydes and esters **1u,v**, which gave the corresponding β,β -diaryl substituted products **145a, b** with 90-93% *ee*¹⁴²⁻¹⁴⁴ (Scheme 56).

Scheme 65.

1,4-Conjugate additions of potassium trifluoro(organo)borates **28** to dehydroalanine derivatives **146a-e** catalyzed by a chiral Rh-catalyst and in situ asymmetric protonation, gave direct access to a wide range of protected R-amino esters **147a-r** in high chemical yields and with excellent enantioselectivity (up to 95% *ee*). Among the examined optically active ligands and proton sources, binap incorporated with guaiacol (2-methoxyphenol), as an inexpensive commercially available and nontoxic phenol, provided the highest stereoselective inductions. Organostannanes have also proved to be able to participate in this reaction. By fine-tuning of the ester group, and

utilization of difluorophos as a chiral ligand, enantioselectivities appreciably increased, generally reaching up to 95%. Deuterium labelling experiments supported by DFT calculations, suggested an infrequent mechanism involving a hydride transfer from the amido moiety to the R carbon justifying the observed high levels of enantioselectivity resulting from controlling this (*R*)-stereogenic center.¹⁴⁵

The scope of the reaction, by reacting various dehydroalanines with potassium aryl- and even alken-1-yl-trifluoroborates was investigated (Scheme 66) under conventional conditions. By analyzing the results, it was concluded that a wide variety of arylalanine derivatives could be easily obtained by employing this cascade carbometallation followed by enantioselective protonation. Interestingly, moderate to excellent degrees of enantioselectivity ranging from 75 to 95% were generally attained. As realized previously, the *ee* increased with the bulkiness of the ester moiety. For instance, the addition of potassium trifluoro(4-fluorophenyl)borate on acetyl and Boc dehydroalanines **146a** and **146c** gave **147d** and **147a** with 83 and 81% *ee*, respectively, while by using isopropyl esters **147f** and **147g**, the enantioselectivity increased to 90 and 94%, respectively. In the case of using **147h** bearing a *tert*-butyl ester group *ee* up to 95% was achieved. Employing potassium trifluoro(alkenyl)borates **28**, efficiently gave alkenyl substituted alanine derivative **147q** with good enantioselectivity and chemical yield. Noticeably in this reaction some isomerization of the double bond was observed, probably via Rh-catalyzed double-bond migration (Scheme 66).¹⁴⁵

Scheme 66. Scope of the 1,4-addition/enantioselective protonation.

Table 40.

Entry	146	Ar 28	Yield (%)	<i>ee</i> (%)
1	146a	4-FC ₆ H ₄	147a : 84	81
2	146b	4-FC ₆ H ₄	147b : 67	95
3	146c	4-FC ₆ H ₄	147c : 52	95
4	146d	4-FC ₆ H ₄	147d : 82	83
5	146e	4-FC ₆ H ₄	147e : 64	90
6	146a	3-MeOC ₆ H ₄	147f : 72	85
7	146b	3-MeOC ₆ H ₄	147g : 72	92
8	146d	3-MeOC ₆ H ₄	147h : 89	89.5
9	146e	3-MeOC ₆ H ₄	147i : 73	91
10	146a	naphthalene	147j : 79	86
11	146b	naphthalene	147k : 83	90
12	146d	naphthalene	147l : 88	87
13	146d	4-BrC ₆ H ₄	147m : 75	81
14	146e	4-BrC ₆ H ₄	147n : 20	88
15	146d	4-MeOC ₆ H ₄	147o : 55	85
16	146b	4-MeOC ₆ H ₄	147p : 72	91
17	146d	4-MeC ₆ H ₄	147q : 96	88
18	146d	thiophene	147r : 68	81

Korenaga et al. succeeded in developing novel and highly electron-poor chiral diphosphine ligands; the MeO-F₁₂-BIPHEP **L27**-ligated Rh catalyst showed excellent catalytic activity with high % *ee* for asymmetric 1,4-additions of arylboronic acids **2** to α,β -unsaturated carbonyls (cyclic and acyclic) **1a-d, g** to give good yields and enantioselectivities. The strong π -acceptor ability of **L27** was found to greatly improve upon the catalytic activity for Rh-catalyzed 1,4-additions at room temperature. The utility of **L27** is especially promising for other asymmetric catalytic reactions that can be accelerated by π -acceptor ligands. Arylboronic acids **2** and cyclic and acyclic enones **1** gave good yields and enantioselectivities (Scheme 67).¹⁴⁶

Scheme 67.

Table 41. Rh-catalyzed stereoselective 1,4-addition.

Entry	1	Ar 2	Yield (%)	ee (%)
1	1b	3-MeC ₆ H ₄	148b : 92	>99
2	1b	4-MeC ₆ H ₄	148c : 92	99
3	1b	3-MeOC ₆ H ₄	148d : 94	99
4	1b	3-FC ₆ H ₄	148e : 85	>99
5 ^a	1b	3-FC ₆ H ₄	148e : 97	>99
6	1b	4-FC ₆ H ₄	148f : 89	>99
7	1b	3-CF ₃ C ₆ H ₄	148g : 86	>99
8	1a	Ph	148a : 96	90
9 ^b	1c	Ph	148a : 96	98
10	1g	3-CF ₃ C ₆ H ₄	148g : 90	>99

^a 40% of KOH

^b At 30 °C

In 2009, Iuliano *et al.* reported on various tropos deoxycholic acid derived biphenylphosphites, which were used as appropriate Rh(I) chiral ligands, at P/Rh 1:1 and 2:1 molar ratios to provide mono- or disubstituted Rh(I) complexes, which behave as catalytic precursors in the stereoselective conjugate addition of differently substituted arylboronic acids **2** to cyclohexenone **1a** to affording adducts **149a-m** in high to virtually quantitative yields and with high *ee*'s of up

to 92%. Furthermore upon employing an excess of arylboronic acid, only the disubstituted complexes afforded diastereomerically pure 1,3-diarylcyclohexanols with *ee*'s up to 94% (Scheme 68).¹⁴⁷

Scheme 68.

Table 42. Stereoselective conjugate addition of arylboronic acids to cyclohexenone promoted by phosphites **L28a-e**, **L29 a, b**.

Entry	Ln	Ar (2)	Yield (%)	<i>ee</i> (%)	Config.
1	L28a	Ph	149a : 99	88	(<i>R</i>)
2	L28b	Ph	149b : 50	62	(<i>R</i>)
3	L28c	Ph	149c : 96	78	(<i>R</i>)
4	L28d	Ph	149d : 90	69	(<i>R</i>)
5	L28e	Ph	149e : 67	33	(<i>S</i>)
6	L29b	Ph	149f : 94	91	(<i>R</i>)
7	L29a	Ph	149g : -	-	-
8	L28a	4-MeC ₆ H ₄	149h : 99	92	(<i>R</i>)
9	L28a	4-MeOC ₆ H ₄	149i : 99	86	(<i>R</i>)
10 ^a	L28a	4-MeOC ₆ H ₄	149j : 99	92	(<i>R</i>)
10	L28a	3-MeOC ₆ H ₄	149k : 99	87	(<i>R</i>)

12	L28a	3-CF ₃ C ₆ H ₄	149l : 40	82	(<i>R</i>)
13 ^a	L28a	3-CF ₃ C ₆ H ₄	149m : 50	88	(<i>R</i>)

^a(Rh : L* 1:2)

The results obtained from evaluating ligands **L28a-e** in the conjugate addition of different arylboronic acids **2** to cyclopentenone **1b** are illustrated in Table 43. It was found that the cyclopentenone reacted more rapidly than cyclohexenone with phenylboronic acid using both monosubstituted and disubstituted rhodium (I) complexes of **L28a-e**, to afford satisfactory yields of (*R*)-3-phenylcyclopentanone (Scheme 69).¹⁴⁷

Scheme 69.

Table 43. Stereoselective conjugate addition of arylboronic acids to cyclopentenone promoted by phosphites **L28a-e**.

Entry	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	L28a	Ph	150a : 100	56	(<i>R</i>)
2	L28b	Ph	150b : 70	45	(<i>R</i>)
3	L28c	Ph	150c : 100	72	(<i>R</i>)
4	L28d	Ph	150d : 92	59	(<i>R</i>)
5	L28e	Ph	150e : 92	35	(<i>R</i>)
6	L28c	4-MeC ₆ H ₄	150f : 98	68	(<i>R</i>)
7	L28c	4-MeOC ₆ H ₄	150g : 98	40	(<i>R</i>)
8	L28c	3-MeOC ₆ H ₄	150h : 70	90	-
9	L28c	3-CF ₃ C ₆ H ₄	150i : 50	77	(<i>R</i>)
10	L28d	3-MeOC ₆ H ₄	150j : 80	83	-
11	L28d	4-MeC ₆ H ₄	150k : 100	67	(<i>R</i>)

The Rh-catalyzed 1,4-addition of tetraarylborates to a β,β-disubstituted α,β-unsaturated ketones **151a-e** has recently been developed. Highly efficient stereoselective catalysis to generate

quaternary carbon stereogenic centers by using an easily accessible chiral diene ligand (*R*)-**L30** has been also reported. Rh/(*R*)-**L30** has catalyzed the reaction of a series of cyclic enone substrates efficiently. They have been subjected to β -phenylation to afford the respective ketones bearing a quaternary carbon stereogenic center in good to high yield and with high to excellent enantioselectivity (75-83% yield, 89-98% *ee*).

(*R,R*)-Bn-bod* induces better enantioselectivity (92-94% yield, 78-91% *ee*) to acyclic enones. Noticeably the *E*- and *Z*-substrates afforded the opposite enantiomers. Regarding the nucleophilic species, in addition to phenyl, some other aryl groups can also be added to enone **151a** with high levels of enantioselectivity (62-84% yield, 91-97% *ee*) (Scheme 70).¹⁴⁸

Scheme 70.

Table 44. Rhodium-catalyzed stereoselective 1,4-addition of sodium tetraarylborates to **151**.

Entry	151	Ar 152	Yield (%)	<i>ee</i> (%)	Config.
1	151a	152a: Ph	153a: 83	98	(<i>R</i>)
2	151b	152a: Ph	153b: 79	98	(<i>R</i>)

3	151c	152a: Ph	153c: 80	98	(<i>S</i>)
4	151d	152a: Ph	153d: 75	89	(<i>R</i>)
5	(<i>E</i>)- 151e	152a: Ph	153e: 92	78	(<i>S</i>)
6	(<i>Z</i>)- 151e	152a: Ph	153f: 94	91	(<i>R</i>)
7	151a	152b: 4-MeC ₆ H ₄	153g: 73	91	(<i>R</i>)
8	151a	152c: 4-FC ₆ H ₄	153h: 62	91	(<i>R</i>)
9	151a	152d: 3-MeC ₆ H ₄	153i: 84	95	(<i>R</i>)
10	151a	152e: 3-ClC ₆ H ₄	153j: 65	97	(<i>R</i>)

Based on the above considerations, a suggested catalytic cycle for this catalysis is depicted in Scheme 71. Initially, complex **155**, generated by the reaction of [RhCl(cod)]₂ with sodium tetraphenylborate, was subjected to transmetalation to afford a phenylrhodium species and triphenylborane followed by insertion of enone **151a** into the phenyl-rhodium bond mediated by triphenylborane as the Lewis acid. Subsequently, protonolysis gave 1,4-adduct **153** together with the generation of an alkoxorhodium intermediate. The ligand of this intermediate was then exchanged with sodium tetraphenylborate to recreate complex **155**. In this way, the cycle was terminated.

Scheme 71. Proposed catalytic cycle for the rhodium-catalyzed 1,4-addition of sodium tetraphenyl borate to **151a** { [Rh] = Rh(cod) }.

The Rh-catalyzed 1,4-addition of various arylboronic acids **2** to an enantioenriched heterocyclic acceptor **156** prepared from commercial amino acids proceeded under adaptable ligand control to affect a stereoselective synthesis of functionalized pyrrolizidinones **157a-i**. This strategy allows facile access to all four stereoisomers of pyrrolizidinone **157a** (Ar = Ph) by selection of substrate and catalyst. Although all possible stereoisomers are accessible, rational matching of the substrate and catalyst leads to high diastereoselectivity. This was vividly observed in the case of (*S,S,S*)-dolefin ligand **L31** under the practical optimized reaction conditions; the scope of the reaction with respect to the boronic acid was also investigated. In all cases, the enantiopure acceptor **156** was utilized as the substrate. The diastereoselectivity was steadily high for a wide range of boronic acids (Scheme 72).¹⁴⁹

Scheme 72. Stereoselective synthesis of pyrrolizidinones

A series of acyclic chiral dienes **L32** were synthesized via a one-step Pd(0)-catalyzed stereoselective deamination. They were used in the Rh(I)-catalyzed stereoselective conjugated 1,4-additions, and promising results (up to 99% yield and 85% *ee*) were obtained. The chiral diene **L32**-modified Rh catalysts successfully catalyzed these reactions to give the corresponding products in moderate to excellent chemical yields (51-99% yields) and with modest to good enantioselectivities (55-85% *ee*'s). When *meta*- or *para*-substituted arylboronic acids **2** was added to 2-cyclohexenone **1a,b,g** in the presence of Rh(I)/**L32**, the corresponding adduct **158a-k**

was obtained in excellent yields and with good *ee*'s. Remarkably, when the boronic acids with electron-donating groups were employed, the corresponding **158a-k** was obtained in higher yields (Scheme 73).¹⁵⁰

Scheme 73.

Table 45. Rh(I)/**L32**-catalyzed stereoselective 1,4-additions.

Entry	1	2	Yield (%)	<i>ee</i> (%)
1	1a	PhB(OH) ₂	158a : 99	85
2	1a	(PhBO) ₃	158b : 93	75
3	1a	PhBF ₃ K	158c : 51	80
4	1a	4-MeC ₆ H ₄ B(OH) ₂	158d : 96	80
5	1a	Me-C ₆ H ₄ -B(O-C(CH ₃) ₂ -CH ₂) ₂	158e : 87	76
6	1a	4-MeOC ₆ H ₄ B(OH) ₂	158f : 98	85
7	1a	4-FC ₆ H ₄ B(OH) ₂	158g : 56	84
8	1a	3-MeC ₆ H ₄ B(OH) ₂	158h : 96	78
9	1a	naphthalen-1-yl B(OH) ₂	158i : 88	55
10	1b	PhB(OH) ₂	158j : 81	43
11	1g	PhB(OH) ₂	158k : 77	61

An active Rh- complex catalyst system was developed, employing a series *tert*-butanesulfinyl phosphines as bidentate ligands, which exclusively bear sulfur chirality and enjoy the merits of both sulfoxide and phosphine ligands. Excellent yields (up to 99% yield) and enantioselectivities (up to 98% *ee*) were observed in Rh-catalyzed stereoselective 1,4-additions of differently

substituted arylboronic acids **2** to electron-deficient olefins, such as α,β -unsaturated carbonyl compounds **1a-c,g,z** under mild reaction conditions to provide **159a-q** (Table 46).¹⁵¹

Scheme 74.

Table 46. Catalytic stereoselective 1,4-addition of arylboronic acids **1** to electron-deficient olefins **2**.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1b	Ph	159a : 99	98
2	1b	4-FC ₆ H ₄	159b : 98	96
3	1b	4-ClC ₆ H ₄	159c : 99	96
4	1b	4-MeC ₆ H ₄	159d : 89	95
5	1b	4-MeOC ₆ H ₄	159e : 93	94
6	1b	4- ^t BuC ₆ H ₄	159f : 99	96
7	1b	3-ClC ₆ H ₄	159g : 67	96
8	1b	3-MeC ₆ H ₄	159h : 97	96
9	1b	2-MeC ₆ H ₄	159i : 92	95
10	1b	2-MeOC ₆ H ₄	159j : 79	86
11	1b	3,5-(Me) ₂ C ₆ H ₃	159k : 99	96
12	1b	naphthalen-1-yl	159l : 93	98
13	1b	naphthalen-2-yl	159m : 83	96
14	1a	Ph	159n : 99	74
15	1c	Ph	159o : 98	80
16	1g	Ph	159p : 94	88
17	1z	Ph	159q : 92	28

The stereochemical result of these Rh-complex catalyzed 1,4-additions can be explained as illustrated in Figure 8. The Rh-complex distinguishes the cyclohexenone by steric repulsion between the bulky *tert*-butyl moiety and the carbonyl group. Thus, it can be concluded that the coordination with the *re*-face is favored for the cyclic enones in this reaction, which results in the formation of the (*R*)-isomer, which is in agreement with the observed stereochemical outcome.

Figure 8. Stereochemical pathway for the stereoselective 1,4-addition.

Korenaga *et al.*¹⁵² reported on a highly efficient and enantioselective stereoselective 1,4-addition of phenylboronic acid **2** to cyclohexenone **1a,d** catalyzed by an Rh complex ligated to the electron-poor MeO-F₁₂-BIPHEP. This Rh/(*R*)-**L27** showed excellent catalytic activity for stereoselective 1,4-additions. It can effectively catalyze the reaction of less reactive coumarin as the substrate.¹⁵³ The catalytic activity of the electron-poor diphosphane-ligated Rh complex was also studied by the same group. The authors claimed that chiral electron-poor diphosphane behaves efficiently even at elevated temperatures. The enantioselectivities of the products obtained from the same reaction, using this catalyst were sustained at a high level of 98% *ee* (Scheme 75).¹⁵²

Scheme 75.

Table 47. Low catalyst loading and high TOF of Rh/(*R*)-**L27** catalyst for the stereoselective 1,4-addition of **2** to **1**.

Entry	1	Ar 2	Temperature (°C)	Yield (%)	<i>ee</i> (%)
1	1a	Ph	30	162a : 41	>99
2 ^a	1a	Ph	30	162a : 0	-
5	1a	Ph	50	162a : 92	99
6	1a	Ph	80	162a : 90	99
7	1a	Ph	100	162a : 96	98
9	1a	4-MeC ₆ H ₄	100	162b : 79	97
10	1a	3-MeOC ₆ H ₄	100	162c : 55	98
11	1a	4-FC ₆ H ₄	100	162d : 54	96
12	1d	Ph	100	162e : 52	95

^a Without TOF [h⁻¹]

A series of chiral C2-symmetric disulfoxide ligands bearing biaryl atropisomeric scaffolds was synthesized, and their catalytic activities in classical Rh-catalyzed 1,4-additions of an appropriate phenylboronic acid to 2-cyclohexen-1-one were examined. The investigation revealed that even a slightly more acidic character for sulfoxide substituents and more electron rich scaffolds deliver catalytic systems towards superiority in terms of reactivity and selectivity in the 1,4-addition of phenylboronic acid **2** to 2-cyclohexen-1-one **1a**. Furthermore, smaller R groups at the *para* position of the aromatic rings of the sulfoxide substituents and bulkier atropisomeric frameworks are also enhance the catalytic induction.¹⁵⁴ In contrast to more conventional chiral ligand scaffolds, electronic factors arising from the sulfoxide motif seem to be partially responsible for the high enantioselectivities observed in the catalysis. The modification of the *p*-tolyl motif of the parent *p*-tol-Binaso ligand also resulted in remarkable differences in term of reactivity.

Comparable influences have been observed with diphosphine ligands when changing from aromatic to aliphatic substituents on the phosphorus.¹⁵⁵

Scheme 76.

Table 48. Catalytic results with complexes **L34–L41** in the coupling of **1a** with arylboronic acid **2**.

Entry	Ln	Yield (%) of 163	<i>ee</i> (%)	Config.
1	L34	99	98	(<i>R</i>)
2	L34	86	98	(<i>R</i>)
3	L34	55	97	(<i>R</i>)
4	L35	98	>99	(<i>R</i>)
5	L35	99	>99	(<i>R</i>)
6	L35	98	>99	(<i>R</i>)
7	L36	99	>99	(<i>R</i>)
8	L36	99	98	(<i>R</i>)
9	L36	99	98	(<i>R</i>)
10	L37	98	89	(<i>R</i>)

11	L37	96	79	(<i>R</i>)
12	L37	70	76	(<i>R</i>)
13	L38	97	>99	(<i>R</i>)
14	L38	99	92	(<i>R</i>)
15	L38	84	90	(<i>R</i>)
16	L39	0	0	-
17	L40	99	79	(<i>R</i>)
18	L40	99	76	(<i>R</i>)
19	L40	72	75	(<i>R</i>)
20	L41	45	32	(<i>S</i>)
21	L41	42	32	(<i>S</i>)
22	L41	29	29	(<i>S</i>)

A stereoselective 1,4-addition reaction using Binap-Rh was established for the catalytic cycle illustrated in Scheme 77, following the publication of the detailed research by Hayashi et al..¹⁵⁶ The activities disulfoxide and diphosphine Rh-dimers with chloro and hydroxo bridges were studied for reaction route **A**.¹⁵⁷ This investigation indicated that diphosphine compounds are actually less active than the disulfoxides under the same reaction conditions. It was also realized that for diphosphine ligands, the conversion from the chloro-bridged dimer to the active species was undoubtedly more challenging than the generation of monomeric [Rh]-OH species *via* dimer separation. The opposite was observed with disulfoxide ligands, for which the catalytic run conducted by utilization of the chloro-bridged dimers occurred rapidly and more effective than with the respective [Rh]-OH dimer. Furthermore, for access to the [Rh]-OH active species, the contribution of the polarized oxygen atom of the sulfoxide in the transmetallation step may make the transfer easier for the aryl group to the Rh-**B**.^{158,159} In addition to the higher reactivity of these disulfoxide ligands, their mode of action during enantio discriminating step **C** is important. The stereochemical route in the Miyaura-Hayashi reaction mediated by Binap, as well as in the prodigious majority of metal-catalyzed stereoselective reactions, relies on the postulation that the substrates approach the metal so as to minimize the steric interactions with the expanded R groups of the chiral ligand structure.¹⁶⁰ Nevertheless, the half view of the Rh-disulfoxide complexes described above indicates that the system is barren of any remarkable steric hindrance around the metal center. In fact, the aryl groups on the sulfoxide moities are directed away from

the metal center and parallel to the atropisomeric scaffold, parting the oxygen atoms of the sulfoxide moieties as the only segments upcoming the metal center. In-depth DFT computational works were completed to gain insight into step **C** of the catalytic cycle for this reaction. Although the Miyaura-Hayashi reaction introduces one of the most direct entries into beneficial chiral organic frameworks, and it has been developed as an important strategy in organic synthesis, there have been very few semi-empirical investigations for elucidation of the reaction route.¹⁶¹ The enantioselective step (step **C**) starts with coordination of both enantiofaces of substrate **1a** to the [Rh]-Ph complex, which makes progress without any appreciable energy barrier.

Scheme 77. Catalytic cycle for the rhodium catalyzed 1,4-addition of PhB(OH)_2 to 2-cyclohexen-1-one.

Stereoselective catalysis resulted in effective and expedient strategies for the synthesis of enantiopure compounds.¹⁶² Currently a new group of chiral hybrid bidentate ligands (P-SO ligands) employing a *tert*-butylsulfinyl moiety,¹⁶³ unite and cause chirality in Cu-, Pd-, and Rh-catalyzed transformations.¹⁶⁴⁻¹⁶⁶ A new and easily synthesized *C*₂-symmetric chiral bis-sulfoxide ligand was designed for the Rh-catalyzed stereoselective 1,4-addition of different arylboronic acids **2** to α,β -unsaturated compounds **1a-c,g,z** and gave the respective products in good chemical yields and with high to excellent enantioselectivities. In accordance with this strategy,

enantiomerically pure flavanones via the 1,4-addition of arylboronic reagents to chromenones **164** were obtained. As a model reaction, the rhodium-catalyzed 1,4-addition of different arylboronic acids to electron-deficient olefins was performed to evaluate (*R,R*)-**L42** in stereoselective catalysis. This work actually was pioneered by Hayashi and Miyaura and nowadays regarded as a useful tool for stereoselective carbon-carbon bond formation.¹⁶⁷ The products were obtained in good to excellent chemical yields (87-99%) and with high to excellent enantioselectivities (92-98%) catalyzed by an appropriate Rh complex. Excellent results were accomplished when differently substituted arylboronic acids **2** were employed with different electron-deficient olefins **1a-c,g, z** and **164**, comprising of cyclic enones, a cyclic ester, and a cyclic ether (Scheme 78).¹⁶²

Scheme 78.

Table 49. Rh-catalyzed stereoselective 1,4-addition of arylboronic acid to olefins **1** and **164**.

Entry	1/164	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	165a : 96	98 (<i>R</i>)
2	1a	4-FC ₆ H ₄	165b : 97	97
3	1a	4-ClC ₆ H ₄	165c : 99	97
4	1a	4-MeC ₆ H ₄	165d : 95	95
5	1a	4- <i>t</i> -BuC ₆ H ₄	165e : 87	97
6	1a	3-ClC ₆ H ₄	165f : 99	98

7	1a	3-MeC ₆ H ₄	165g : 97	96
8	1a	2-MeC ₆ H ₄	165h : 90	96
9	1a	3,5-Me ₂ C ₆ H ₃	165i : 95	97
10	1a	1-naphthyl	165g : 93	92
11	1a	2-naphthyl	165k : 98	93
12	1b	Ph	165l : 98	94
13	1c	Ph	165m : 95	93
14	1g	Ph	165n : 87	94
15	1z	Ph	165o : 97	98
16	164	Ph	165q : 32	99

It is noteworthy that such a transformation could be highly promoted by using of sodium *tetra*-arylborates **167a-d**^{168, 169} instead of PhB(OH)₂. Under the optimized conditions, the desired products **168a-l** can be obtained in satisfactory yields (58-75%; Table 50, **167a-l**) and with excellent enantioselectivity, up to >99% *ee*.

Scheme 79.

Table 50. Rh-catalyzed stereoselective 1,4-addition of sodium tetraarylborates to chromenones **166**.

Entry	R 166	Ar 167	Yield (%)	<i>ee</i> (%)
1	166a : H	167a : Ph	168a : 75	>99 (<i>R</i>)
2	166b : 6-Cl	167a : Ph	168b : 71	>99
3	166c : 6-Me	167a : Ph	168c : 62	99
4	166d : 6-OMe	167a : Ph	168d : 68	>99
5	166e : 6-F	167a : Ph	168e : 58	99
6	166f : 6-Br	167a : Ph	168f : 63	>99
7	166g : 7-Br	167a : Ph	168g : 67	99
8	166h : 7-Me	167a : Ph	168h : 57	99
9	166i : 4 <i>H</i> -benzo[h]	167a : Ph	168i : 59	>99

10	166a : H	167b : 4-MeC ₆ H ₄	168j : 70	>99
11	166a : H	167c : 3-MeC ₆ H ₄	168k : 64	98
12	166a : H	167d : 3-ClC ₆ H ₄	168l : 25	97

In 2010 Hayashi *et al.* reported on the utilization of simple β , β -disubstituted α,β -unsaturated ketones in stereoselective 1,4-additions of organoboron nucleophiles that are stable under an ambient atmosphere.¹⁷⁰ Recently a Rh-catalyzed stereoselective 1,4-addition of sodium *tetra*-arylborates in the presence of chiral diene ligand (*R*)-**L30**,^{171,172} was achieved as depicted in Scheme 80. Highly effective stereoselective catalysis has also been accomplished to generate a quaternary carbon stereogenic center with a chiral tetrafluorobenzobarrelene as the ligand. The reaction conditions for the phenylation of 3-methyl-2-cyclohexen-1-one **151a** to afford 1,4-adduct **169a** were restudied (Scheme 80).¹⁷⁰

Scheme 80.

A wide range of cyclic enones **151a,b**, **151f-h** were reacted with phenylboroxine **13** employing [Rh(OH)((*R,R*)-Ph-tfb*)]₂ as the catalyst, to afford the respective β -phenylketones **169a-l** in satisfactory yields (70-99%) and with excellent enantioselectivities (98-99% *ee*).

Table 51. Rhodium-catalyzed stereoselective 1,4-addition of arylboroxines to β , β -disubstituted α,β -unsaturated ketones **151**.

Entry	151	Ar 13	Yield (%)	<i>ee</i> (%)	Config.
1	151a	Ph	169a : 99	99	(<i>R</i>)
2	151b	Ph	169b : 88	99	(<i>R</i>)
3	151f	Ph	169c : 70	98	(<i>R</i>)
4	(<i>E</i>)- 151e	Ph	169d : 82	86	(<i>S</i>)
5	(<i>E</i>)- 151g	Ph	169e : 80	81	(<i>S</i>)
6	(<i>Z</i>)- 151e	Ph	169f : 78	99	(<i>R</i>)
7	151a	4-MeOC ₆ H ₄	169g : 81	99	(<i>R</i>)
8	151a	4-FC ₆ H ₄	169h : 94	99	(<i>R</i>)
9	151a	4-ClC ₆ H ₄	169i : 97	99	(<i>R</i>)
10	151a	3-ClC ₆ H ₄	169j : 85	99	(<i>R</i>)
11	151a	2-ClC ₆ H ₄	169k : 87	99	(<i>R</i>)
12	151a	2-naphthyl	169l : 95	99	(<i>R</i>)

Based on these results, the catalytic cycle of the reaction of **151a** with phenylboroxine was suggested (Scheme 82). Phenylrhodium species **170**, initially created by the transmetallation between phenylboroxine and a hydroxorhodium complex, is subjected to insertion of **151a** to

afford oxa- π -allylrhodium intermediate **171**. Transmetalation of this intermediate with phenylboroxine recreates phenylrhodium **170** along with the generation of boron enolate **172**,¹⁷³ which forms **169** upon the addition of water at the final stage of the reaction.

Scheme 82. Proposed catalytic cycle for the rhodium-catalyzed 1,4-addition of phenylboroxine to **151a**.

Several novel vicinal-diamine-based chiral chain diene ligands have been readily synthesized in satisfactory yields via a direct synthetic pathway. Ligand **L44** is a very efficient steering ligand for Rh-catalyzed stereoselective conjugated additions of various organoboronic acids **2** to different α,β -unsaturated carbonyl compounds **1a-c, g** to give the desired products **173a-k** in satisfactory chemical yields and enantioselectivities *ee*'s (Scheme **83**).¹⁷⁵

Scheme 83.

Table 2. Enantioselective conjugated additions catalyzed by the Rh(I)/**L44** complex.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	173a : 96	95
2	1a	4-MeOC ₆ H ₄	173b : 97	94
3	1a	4-FC ₆ H ₄	173c : 90	92
4	1a	3-MeC ₆ H ₄	173d : 99	94
5	1a	3-ClC ₆ H ₄	173e : 84	93
6	1a	2-MeOC ₆ H ₄	173f : 97	82
7	1a	2-ClC ₆ H ₄	173g : 96	84
8	1a	3,5-Me ₂ C ₆ H ₄	173h : 99	94
9	1a	naphthalen-2-yl	173i : 94	95
10	1a	naphthalen-1-yl	173j : 98	82
11	1a	PhCH=CH	173k : 54	90
12	1g	Ph	173a : 95	90
13	1c	Ph	173a : 93	84
14	1b	Ph	173a : 81	76

Carnell *et al.* in 2010 successfully achieved an efficient synthesis of the chiral C2-symmetric bicyclic[2.2.2]diene ligand system that can be subjected to versatile substitution at the 1- and 4-positions.¹⁷⁶ Their synthetic approach is short, giving high yields and involves an easy operational lipase resolution as a key step that can be scaled-up; this is an alternative to resolution by using chiral preparative HPLC. Thus a new series of 1,4-dimethyl 2,5-diaryl bicyclo[2.2.2]octadiene ligands for Rh-catalyzed stereoselective conjugate addition to a wide variety of cyclic and acyclic enones were obtained. The addition of 1,4-methyl substituent groups in the ligands enabled the research group to observe a remarkable electronic effect, which influenced the catalytic properties. The catalysts containing electron rich ligands provided excellent activity for all substrates and particularly excellent enantioselectivity for cyclic enones with high atom efficiency (only 1.1–1.2 equiv arylboronic acid is required), even for problematic substrates such as 6-methylcoumarin. Nevertheless, this merit was not extended to or shared by linear enones in term of enantioselectivity. This problem could be resolved by introducing electron withdrawing groups on the ligand to obtain high *ee* for all types of substrates. However,

2-3 equivalents of arylboronic acid are required to compensate for protecting boronation and to obtain high yields.

The 1,4-diester ligands (*S,S*)-**L45a-g** (Scheme 84), were screened for the stereoselective conjugate addition of phenylboronic acid **2** to 3-nonen-2-one **1e** employing previously known optimized conditions (Scheme 84, Table 53).

Scheme 84. Stereoselective conjugate addition to substrates **1**.

Table 53. Ligand screen for the stereoselective conjugate addition to **1e**.

Entry	Ln	Yield (%) of 174a	<i>ee</i> (%) of 174a
1	L45a	95	75
2	L45b	93	83
3	L45c	98	73
4	L45d	95	82
5	L45e	99	74

6	L45f	43	89
7	L45g	96	70

The methyl ester groups were converted into methyl groups, and ligands **L5a** and **L5f** were evaluated for a range of acyclic and cyclic enones **6a–e** (Scheme 2, Table 2).

Table 54. Comparison between **L46** and **L47** with various substrates.

Entry	1	Product 174	Yield (%) [<i>ee</i> (%)]		Config.
			L46	L47	
1	1e	174a	99 [52]	99 [97]	(<i>S</i>)
2	1e'	174b	99 [67]	99 [95]	(<i>S</i>)
3	1a	174c	98 [99]	92 [98]	(<i>R</i>)
4	1b	174d	100 [99]	80 [96]	(<i>R</i>)
5	1f	174e	95 [98]	76 [92]	(<i>R</i>)

The product obtained from the 1,4-conjugate addition of phenyl boronic acid to 6-methylcoumarin **175** was used in the synthesis of a prescribed urological drug, known as tolterodine.¹⁷⁷ Hayashi et al. showed that phosphine ligands can induce excellent enantioselectivity (>99% *ee*), although phenylboronic acid was essential to attain a high chemical yield.¹⁷⁷ Notably, only one example employing a chiral diene for this reaction has been reported by Carreira *et al.*, where 43% chemical yield and 98% *ee* were achieved in the addition of phenylboronic acid **2** to coumarin **175** at 50 °C using **L48** derived ligand to afford **176** (Scheme 85).¹⁷⁶

Scheme 85. Ligand **L48** for stereoselective conjugate addition to **175**.

The stereoselective conjugate addition of differently substituted aryl boronic acids to *N*-benzyl maleimide **38c** in spite of giving biologically useful products is known to be problematic. For example, the chiral phosphine ligand binap affords the desired compounds in only 70% yield and with 58% *ee*, whereas a chiral norbornadiene ligand afforded the desired product in 88% yield and with 69% *ee*. On the other hand, the phosphine-alkene hybrid ligands developed by Grutzmacher and Hayashi *et al.* both provide the desired product in high yield and with Hayashi's hybrid ligand afforded 89-95% *ee*.¹⁷⁸ Nevertheless, in most cases, large excesses of arylboronic acids were required to ensure the desired products in high yields. It was also found that by using ligand **L46** both high activity and enantioselectivity could be achieved for the formation of **(R)-177a-d** utilizing only ArB(OH)₂ **2** at ambient temperature (Scheme 86).

177a: Ar = Ph, yield = 95%, *ee* = 95%

177b: Ar = 4-MeOC₆H₄, yield = 98%, *ee* = 99%

177c: Ar = 2-CF₃C₆H₄, yield = 92%, *ee* = 99%

177d: Ar = 2-MeO-1-naphthyl, yield = 98%, *ee* = 99%

Scheme 86. Stereoselective conjugate addition to *N*-benzyl maleimide **38c**.

An effective Rh-catalyzed stereoselective addition of arylboronic acids **2** to β -phthaliminoacrylate esters **177**, which used an hydroxorhodium/chiral diene complex, has been achieved and reported. The products were β -aryl- β -*N*-phthaloylamino acid esters **179a-m**, which were obtained in high yields and with high enantioselectivity.

R = 2,6-(Me)₂C₆H₃

- 179a:** Ar = Ph, yield = 94%, *ee* = 98%
179b: Ar = 4-MeC₆H₄, yield = 99%, *ee* = 97%
179c: Ar = 2-MeC₆H₄, yield = 90%, *ee* = 99%
179d: Ar = 3,4-Me₂C₆H₃, yield = 99%, *ee* = 99%
179e: Ar = 3,5-Me₂C₆H₃, yield = 98%, *ee* = 98%
179f: Ar = 3,4-(OCH₂O)C₆H₃, yield = 95%, *ee* = 98%
179g: Ar = 3,4-(^{*t*}BuMe₂SiO)₂C₆H₃, yield = 96%, *ee* = 98%
179h: Ar = 4-OHC₆H₄, yield = 92%, *ee* = 97%
179i: Ar = 4-FC₆H₄, yield = 93%, *ee* = 97%
179j: Ar = 4-BrC₆H₄, yield = 90%, *ee* = 97%
179k: Ar = 4-CF₃C₆H₄, yield = 81%, *ee* = 96%
179l: Ar = 2-naphthyl, yield = 97%, *ee* = 97%
179m: Ar = 1-cyclohexenyl, yield = 87%, *ee* = 93%

Scheme 87. Rhodium-catalyzed stereoselective 1,4-addition of arylboronic acids to **178**

A highly efficient Rh-diene catalyzed stereoselective conjugate addition of various organoboronic acids with diverse steric and electronic properties **2** to problematic α -unsubstituted nitroalkene substrates **180a-f** has been reported. In this protocol, chiral bicyclo[3.3.0]dienes were identified as superior ligands. Under the optimized conditions, the reaction proceeds smoothly and cleanly with high enantioselectivity to furnish a wide range of synthetically useful intermediates, such as chiral β,β -disubstituted nitroalkanes **181a-o**. The use of boronic acids in along with potassium acid fluoride as reactive organoboron reagents was found to be a promising alternative to organotrifluoroborates in transition-metal-catalyzed reactions (Table 55).¹⁸⁰

Under the optimal reaction conditions, the addition reactions unanimously furnished the expected products in excellent chemical yields but with moderate to good *ee* values. However, excellent enantioselectivities (95–97%) were detected when more bulky groups, such as 1-naphthylboronic acid and 2-tolylboronic, and were introduced. The electron-withdrawing group on the phenyl moiety of the boronic acids was helpful for obtaining high enantioselectivity (Table 55). Conversely, the electronic properties of the substituent on the phenyl moiety of the substrates did not show any appreciable effect with regards to the reaction stereoselectivity (Table 55). More significantly, when aliphatic 2-nitrovinylcyclohexane underwent the conjugate addition with 4-anisylboronic acid, the same degree of enantioselectivity was observed. The utilization of the linear nitro olefin, 1-nitrohexene, as the substrate led to significantly lower enantioselectivity in comparison to 2-nitrovinylcyclohexane. Nevertheless, the selectivity was dramatically increased when sterically hindered 2- tolylboronic acid was used as substrate (Table 55).¹⁸⁰

Scheme 88.

Table 55. Stereoselective conjugate addition to nitroalkenes catalyzed by [Rh]/**L20c**.

Entry	R 180	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	180a : Ph	4-MeOC ₆ H ₄	181a : 96	78	(<i>R</i>)
2	180a : Ph	4-FC ₆ H ₄	181b : 96	89	(<i>R</i>)
3	180a : Ph	4-ClC ₆ H ₄	181c : 92	92	(<i>R</i>)
4	180a : Ph	4-BrC ₆ H ₄	181d : 91	92	(<i>R</i>)
5	180a : Ph	4-MeC ₆ H ₄	181e : 95	81	(<i>R</i>)
6	180a : Ph	4- ^t BuC ₆ H ₄	181f : 92	81	(<i>R</i>)

7	180a: Ph	3-ClC ₆ H ₄	181g: 99	92	(<i>R</i>)
8	180a: Ph	2-MeC ₆ H ₄	181h: 85	97	(<i>R</i>)
9	180a: Ph	2-naphthyl	181i: 99	84	(<i>R</i>)
10	180a: Ph	1-naphthyl	181j: 92	95	(<i>R</i>)
11	180b: 4-MeOC ₆ H ₄	Ph	181k: 99	89	(<i>S</i>)
12	180b: 4-MeOC ₆ H ₄	2-MeC ₆ H ₄	181l: 85	97	(<i>R</i>)
13	180c: 4-ClC ₆ H ₄	Ph	181m: 95	82	(<i>S</i>)
14	180c: 4-ClC ₆ H ₄	2-MeC ₆ H ₄	181n: 97	97	(<i>R</i>)
15	180d: 1-naphthyl	Ph	181o: 99	85	(<i>S</i>)
16	180e: C ₆ H ₁₁	4-MeOC ₆ H ₄	181p: 90	84	(<i>R</i>)
17	180f: <i>n</i> -Bu	4-MeOC ₆ H ₄	181q: 81	61	(<i>R</i>)
18	180f: <i>n</i> -Bu	2-MeC ₆ H ₄	181r: 95	86	(<i>R</i>)

Although the exact mechanism remains ambiguous, and the probability of an equilibrium between the fluoroborate and the boronic acid cannot definitely be ruled out, these results suggest a fast transmetallation between the rhodium nitronate **182/182'** and the relevant organoborate intermediate **183/184** promoted by hydrolysis of potassium organotrifluoroborate (Scheme 89). It is worthwhile to mention that the fluoride ions may also play a key role in the stabilization of the various catalytic intermediates.¹⁸⁰

Scheme 89. Proposed reaction mechanism.

Several chiral diene-metal catalysts, in particular, Rh-complexes have since been examined in catalytic stereoselective C-C bond formation reactions.¹⁸¹ It was found that they show more effective catalytic behaviours and enantioselectivities compared with those bearing phosphine ligands.¹⁸²⁻¹⁸⁴ Thus, the design and synthesis of chiral dienes for their use as ligands to prepare chiral organometallic catalysts in various stereoselective syntheses has gained the interest of synthetic organic chemists worldwide.¹⁸⁵⁻¹⁹³ A series of chiral 2,5-disubstituted bicyclo[2.2.1]heptadiene ligands **L50** were synthesized and fully characterized. These stable diene ligands were found to be highly active and efficient in stereoselective conjugate addition reactions of various arylboronic acids **2** to a wide variety of acceptors. The addition of arylboronic acids, bearing both electron-donating and electron withdrawing groups, to enone **185a-g** afforded the respective adducts **186a-s** with high to excellent enantioselectivities (90 to >99.5% *ee*) and satisfactory chemical yields (68 to 99%). This strategy provides an effective synthetic approach to obtain enantioenriched 1,4-addition adducts using commercially available or readily accessible arylboronic acids.

Scheme 90.

Table 56. The stereoselective 1,4-addition reaction of various acceptors.

Entry	185	Ar (2)	Yield (%)	<i>ee</i> (%)	Config.
1	185a	Ph	186a: 73	96	(<i>R</i>)
2	185a	2-MeC ₆ H ₄	186b: 68	98	(<i>R</i>)
3	185a	4-PhC ₆ H ₄	186c: 72	97	(<i>R</i>)
4	185a	4-MeOC ₆ H ₄	186d: 77	93	(<i>R</i>)
5	185a	1-naphthyl	186e: 77	95	(<i>R</i>)
6	185a	4-CF ₃ C ₆ H ₄	186: 74	96	(<i>R</i>)
7	185a	3-MeOC ₆ H ₄	186g: 86	94	(<i>R</i>)
8	185b	Ph	186h: 94	90	(<i>S</i>)
9	185b	2-MeC ₆ H ₄	186i: 80	95	(<i>S</i>)
10	185b	4-CF ₃ C ₆ H ₄	186j: 99	>99.5	(<i>S</i>)
11	185b	4-ClC ₆ H ₄	186k: 98	93	(<i>S</i>)
12	185b	4-MeC ₆ H ₄	186l: 98	>99.5	(<i>S</i>)
13	185b	3-ClC ₆ H ₄	186m: 99	96	(<i>S</i>)
14	185c	Ph	186n: 98	96	(<i>S</i>)
15	185d	Ph	186o: 95	94	(<i>S</i>)
16	185e	Ph	186p: 81	98	(<i>S</i>)
17	185f	4-MeOC ₆ H ₄	186q: 92	99	(<i>R</i>)
18	185g	Ph	186r: 88	96	(<i>S</i>)

In the case of cyclic α,β -unsaturated carbonyl compounds, such as 2-cyclohexene-1-one **1a**, when RhI-**L50** was used as the catalyst in dioxane as the solvent, the respective adduct **187** was generated in 94% chemical yield and with 91% *ee* (Scheme 91).

Scheme 91. The stereoselective 1,4-addition reaction to 2-cyclohexene-1-one.

Structurally simple and easily accessible chiral sulfinamide-olefins have been proven to show high catalytic activities and enantioselectivities in Rh-catalyzed 1,4-addition stereoselective reactions, as reported by Xu *et al.* The chiral sulfur-olefin ligand class was used for transition metal-catalyzed stereoselective synthesis. By selecting the well known sulfonamide-olefin novel ligand **L51**, its Rh-complex **L51** was prepared and employed in catalytic stereoselective reactions such as 1,4-additions of differently substituted aryl bronics **2** to enones **1a,b,g,g'**. In all cases, the reaction proceeded smoothly, and gave the respective the products **188a-u** in high chemical yields and with good to excellent enantioselectivities (Scheme 92).¹⁹⁴

Scheme 92.

Table 57. Stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated cyclic carbonyl compounds catalyzed by $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2/\text{L51}$.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	188a : 99	95
2	1a	4-MeC ₆ H ₄	188b : 98	96
3	1a	4-FC ₆ H ₄	188c : 99	97
4	1a	4-ClC ₆ H ₄	188d : 99	95
5	1a	4-MeOC ₆ H ₄	188e : 98	95
6	1a	3-MeC ₆ H ₄	188f : 98	98
7	1a	2-MeC ₆ H ₄	188g : 53	98
8	1a	2-MeOC ₆ H ₄	188h : 92	97
9	1a	1-naphthyl	188i : 99	98
10	1a	2-naphthyl	188j : 98	97
11	1b	Ph	188k : 99	92
12	1b	4-MeC ₆ H ₄	188l : 96	88
13	1b	4-ClC ₆ H ₄	188m : 96	92
14	1b	4-MeOC ₆ H ₄	188n : 98	87
15	1b	1-naphthyl	188o : 99	93
16	1b	3-MeC ₆ H ₄	188p : 93	98
17	1g	Ph	188q : 91	78
18	1g	4-ClC ₆ H ₄	188r : 85	89
19	1g	2-MeOC ₆ H ₄	188s : 74	94
20	1g	3-MeC ₆ H ₄	188t : 86	84
21	1g'	Ph	188u : 88	85

In 2011, Yamamoto *et al.* reported on the Rh-catalyzed 1,4-addition of lithium 5-methyl-2-furyltriolborate ($[\text{ArB}(\text{OCH}_2)_3\text{CCH}_3]\text{Li}$, Ar = 5-methyl-2-furyl) to various unsaturated ketones **1a-c**, **189a-e** to afford β -furyl ketones **191a-j**, which upon subsequent ozonolysis of the furyl ring, an enantioselective synthesis of γ -oxo-carboxylic acids was accomplished. By using $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (nbd=2,5-norbornadiene) chelated with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap) or 2,3-bis(diphenylphosphino)butane(chiraphos) high yields and high enantioselectivities (91–99% *ee*) were obtained for the respective reactions with unsaturated esters, i.e, methyl crotonate. However, the 1,4-adduct was successfully achieved in good

chemical yield and with 94% *ee* when more electron-deficient phenylcrotonate was employed as the substrate (Scheme 93).¹⁹⁵

Scheme 93. Stereoselective synthesis of γ -oxo-carboxylic acids by the 1,4-addition of lithium 2-furanyltriolborate to α,β -unsaturated carbonyl compounds.

Table 58.

Entry	1/189	Ln	Yield (%)	<i>ee</i> (%)
1	1b	L4	191a: 92	91
2	1b	L52	191b: 71	95
3	1a	L4	191c: 82	95
4	1c	L4	191d: 65	95
5	189a	L4	191e: 90	99
6	189b	L4	191f: 79	99
7	189c	L4	191g: 35	96

8	189c	L7	191h : 83	91
9	189d	L4	191i : 86	92
10	189e	L4	191j : 70	94

The stereoselective addition of arylboroxines **13** to β -alkoxyacrylate **192a-f** esters was conducted in the presence of a Rh complex, which was coordinated with a chiral diene ligand to provide high chemical yields of β -alkoxy- β -arylcarboxylic acid esters **193a-m** as well as very high enantioselectivity, which can be attributed to the Rh/chiral diene catalyst. This catalytic system can be used for the stereoselective addition of several arylboroxines to β -alkoxyacrylates to give the desired products with excellent enantioselectivity (Table 59). Aryl groups **13** bearing various substituents were introduced at the β -position of the β -isopropoxyacrylate **192a** to afford the respective adducts **193a-h** in high chemical yields and with up to 99.5% *ee*. The addition of phenylboroxine **13** to β -alkoxyacrylates **192b-f** gave the respective **193i-m** with 99.5% *ee* (Scheme 94).¹⁹⁶

Scheme 94.

Table 59. Stereoselective addition of arylboroxine **13** to **192**.

Entry	R' 192	Ar 13	Yield (%)	<i>ee</i> (%)
1	192a : <i>i</i> -Pr	Ph	193a : 95	> 99.5
2	192a : <i>i</i> -Pr	2-MeC ₆ H ₄	193b : 91	>99.5
3	192a : <i>i</i> -Pr	3-MeC ₆ H ₄	193c : 96	>99.5

4	192a : <i>i</i> -Pr	4-MeC ₆ H ₄	193d : 94	>99.5
5	192a : <i>i</i> -Pr	4-MeOC ₆ H ₄	193e : 91	>99.5
6	192a : <i>i</i> -Pr	4-ClC ₆ H ₄	193f : 90	>99.5
7	192a : <i>i</i> -Pr	4-CF ₃ C ₆ H ₄	193g : 68	>99.5
8	192a : <i>i</i> -Pr	2-naphthyl	193h : 90	>99.5
9	192b : cyclohexyl	Ph	193i : 92	>99.5
10	192c : Et	Ph	193j : 87	>99.5
11	192d : Me	Ph	193k : 75	>99.5
12	192e : benzyl	Ph	193l : 88	>99.5
13	192f : <i>p</i> -methoxybenzyl	Ph	193m : 88	>99.5

Several *N*-sulfinyl-based chiral sulfur-olefin ligands have been successfully synthesized via the combination of *tert*-butanesulfinamide and olefin moieties and were applied to efficient Rh-catalyzed and highly enantioselective 1,4-additions. Remarkably, the easy synthesis and no essential carbon chirality makes this type of ligand in demand for asymmetric catalysis. Ligands **L54a** and **L54b** were chosen and examined for the substrate scope for this type of ligand in Rh(I)-catalyzed 1,4-additions. Differently substituted arylboronic acids **2** and enones **1a-c, g** underwent this reaction under the optimized reaction conditions, and the results are shown in Table 60.¹⁹⁷

Scheme 95.

Table 60. Rhodium-catalyzed stereoselective 1,4-additions.

Entry	1	Ln	Ar 2	Yield (%)	ee (%)
1	1a	L54a	Ph	194a: 90	94
2	1a	L54b	Ph	194a: 79	95
3	1a	L54a	4-MeOC ₆ H ₄	194b: 99	93
4	1a	L54a	4-FC ₆ H ₄	194c: 90	93
5	1a	L54a	4- ^t BuC ₆ H ₄	194d: 80	94
6	1a	L54a	3-ClC ₆ H ₄	194e: 81	89
7	1a	L54a	3-MeC ₆ H ₄	194f: 86	95
8	1a	L54a	3,5-Me ₂ C ₆ H ₄	194g: 57	92
9	1a	L54a	2-ClC ₆ H ₄	194h: 81	40
10	1a	L54a	2-MeOC ₆ H ₄	194i: 92	37
11	1a	L54b	2-ClC ₆ H ₄	194h: 98	97
12	1a	L54b	2-MeOC ₆ H ₄	194i: 90	95
13	1b	L54b	4-MeC ₆ H ₄	194j: 55	39
14	1b	L54b	4-MeC ₆ H ₄	194j: 62	99
15	1b	L54b	3-ClC ₆ H ₄	194e: 62	93
16	1b	L54b	2-FC ₆ H ₄	194k: 68	97
17	1c	L54a	Ph	194a: 98	82
18	1c	L54b	Ph	194a: 71	92
19	1g	L54a	Ph	194a: 83	89
20	1g	L54b	Ph	194a: 87	90

The use of ligand **L54b** can be also expanded to the Rh(I)-catalyzed stereoselective addition of differently substituted arylboronic acids to *tert*-butyl cinnamate **195** under similar conditions to afford the desired products **196a, b** in satisfactory chemical yields and with good *ee*'s which required no further optimization (Scheme 96).¹⁹⁷

196a: Ar = 4-MeOC₆H₄, yield = 71%, *ee* = 88%

196b: Ar = 4-AcC₆H₄, yield = 67%, *ee* = 89%

Scheme 96. Rh(I)-catalyzed stereoselective addition of arylboronic acids to *tert*-butyl cinnamate.

The Rh/diene-catalyzed 1,4-additions of sodium tetraarylborates **167a-c**, **e-g** to β,β -disubstituted α,β -unsaturated esters **197d-h** afforded **198a-j** in satisfactory yields. An efficient and highly asymmetric catalysis has also been achieved to generate quaternary carbon stereogenic centers at the β -position of esters by tuning the ester group of the substrates and using chiral diene (*R*)-**L55** as the ligand. Furthermore, a new strategy for the synthesis of 3,3-disubstituted 1-indanones has been accomplished via arylation in a mixture of methanol and dioxane as the solvent (Scheme 97).¹⁹⁸

Scheme 97.

Table 61. Rhodium-catalyzed stereoselective 1,4-addition of sodium tetraarylborates to β,β -disubstituted α,β -unsaturated esters **197**

Entry	197	Ar 167	Yield (%)	<i>ee</i> (%)	Config.
1	<i>(E)</i> - 197a	167a : Ph	198a : 93	99	(<i>S</i>)
2	<i>(E)</i> - 197a	167a : Ph	198a : 79	99	(<i>S</i>)
3	<i>(Z)</i> - 197a	167a : Ph	198a : 95	99	(<i>R</i>)
4	<i>(E)</i> - 197b	167a : Ph	198b : 90	99	(<i>S</i>)
5	<i>(Z)</i> - 197b	167a : Ph	198b : 89	99	(<i>R</i>)
6	<i>(E)</i> - 197c	167a : Ph	198c : 92	97	(<i>S</i>)
7	<i>(E)</i> - 197d	167a : Ph	198d : 93	99	(<i>S</i>)
8	<i>(E)</i> - 197e	167a : Ph	198e : 84	96	(<i>S</i>)
9	<i>(E)</i> - 197b	167e : 4-MeOC ₆ H ₄	198f : 90	98	(<i>S</i>)
10	<i>(E)</i> - 197b	167b : 4-MeC ₆ H ₄	198g : 89	98	(<i>S</i>)

11	(<i>E</i>)- 197b	167f : 4-ClC ₆ H ₄	198h : 85	98	(<i>S</i>)
12	(<i>E</i>)- 197b	167g : 3-MeOC ₆ H ₄	198i : 64	96	(<i>S</i>)
13	(<i>E</i>)- 197b	167c : 3-MeC ₆ H ₄	198j : 96	98	(<i>S</i>)

Phenylation of α,β -unsaturated lactone **199** was achieved under similar conditions to afford compound **200** in excellent yield and enantioselectivity (99% *ee*) (Scheme 98).¹⁹⁸

Scheme 98.

The stereochemical logic in the reaction of (*E*)-**197a** with sodium *tetra*-phenylborate catalyzed by Rh/(*R*)-**L55** can be understood as illustrated in Figure 9.

Figure 9. Proposed stereochemical pathway for the Rh/(*R*)-**L55**-catalyzed 1,4-addition of sodium tetraphenylborate to (*E*)-**197a**.

Liao *et al.* accomplished a single step synthesis of a new class of benzene-based chiral heterodisulfoxide ligand **L56**. The disulfoxide ligands obtained were employed in the Rh-catalyzed stereoselective 1,4-addition of various arylboronic acids **2** to a wide variety of chromenones **203a-h**. The addition of differently substituted arylboronic acids to various chromenones proceeded smoothly to give flavanones **204a-m** with excellent enantioselectivities (92–95% *ee*) and up to 70% chemical yield under mild reaction conditions. This reaction

represents an operational protocol for the synthesis of a series of chiral flavanones via Rh-catalyzed 1,4-addition (Scheme 99).¹⁹⁹

Scheme 99.

Table 62. Rh-catalyzed enantioselective 1,4-addition of arylboronic acids to chromenones **203**.

Entry	3	Ar 2	Yield (%)	<i>ee</i> (%)
1	203a	Ph	204a : 67	94
2	203b	Ph	204b : 53	94
3	203c	Ph	204c : 60	92
4	203d	Ph	204d : 70	92
5	203e	Ph	204e : 65	93
6	203f	Ph	204f : 60	93
7	203g	Ph	204g : 53	95
8	203h	Ph	204h : 56	93
9	203a	4-MeC ₆ H ₄	204i : 64	95
10	203a	3-MeC ₆ H ₄	204j : 60	92
11	203a	2-MeC ₆ H ₄	204k : 35	95
12	203a	3-MeOC ₆ H ₄	204l : 63	95
13	203a	2-naphthyl	204m : 67	95

An efficient and highly enantioselective synthesis of bioactive chiral flavanones (*S*)-**L27** was achieved via the Rh-catalyzed stereoselective 1,4-addition of arylboronic acid **2** to chromone **203a,b,d,e,i-k**. A typical example is the efficient catalyzed asymmetric synthesis of (*S*)- and (*R*)-pinostrobin. This synthesis can be achieved in toluene in the presence of a Rh catalyst with an electron-poor chiral diphosphine MeO-F₁₂-BIPHEP under mild reaction conditions. This catalyst could be applied to the synthesis of several other chiral compounds showing biological properties via asymmetric 1,4-addition (Scheme 100).²⁰⁰

Scheme 100.

Table 63. Stereoselective 1,4-addition of **2** to **203**.

Entry	203	Ar 2	Yield (%)	<i>ee</i> (%)
1	203a	4-MeC ₆ H ₄	205a : 82	99
2	203a	3-MeOC ₆ H ₄	205b : 90	>99
3	203a	2-MeOC ₆ H ₄	205c : 83	>99
4	203a	2-naphthyl	205d : 83	99
5	203a	4-FC ₆ H ₄	205e : 80	>99
6	203a	3-FC ₆ H ₄	205f : 80	99
7	203e	Ph	205g : 86	>99
8	203d	Ph	205h : 81	>99
9	203b	Ph	205i : 87	>99
10	203i	Ph	205j : 90	>99
11	203j	Ph	205k : -	-
12	203k	Ph	205l : 91	99

The Rh-catalyzed 1,4-addition of boronic acids **2** to Michael acceptors such as maleimides **38a-c** is problematic. However, the problem has been circumvented by using the Rh-based catalytic system utilizing electron-deficient MeO-F₁₂-BIPHEP analogues, which allow the reactions to proceed smoothly and cleanly under mild conditions at ambient temperature resulting in the succinimide derivatives **206a-o** in good to excellent yields and *ee*. The key factor to solve the consideration of the vital role of the electronic and steric properties of the diphosphine ligand and the strong boronic acid/ligand reliance in the case of maleimide derivatives. Further study was also devoted to other catalytic applications of trifluoromethyl-substituted ligands based on the MeO-F₁₂-BIPHEP skeleton. Thus the efficiency of the [RhCl(C₂H₄)₂]₂/(*R*)-3,5-(CF₃)₂-MeO-F₁₂-BIPHEP catalytic system on 1,4-addition reactions of diverse boronic acids to maleimides was evaluated (Table 64).²⁰¹

Scheme 101.

Table 64. Substrate Scope of the [Rh]/(*R*)-3, 5-(CF₃)₂-MeO-F₁₂-BIPHEPH system

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1c	4-MeC ₆ H ₄	206a : 80	92
2	1c	4-MeOC ₆ H ₄	206b : 76	85
3	1c	4-BrC ₆ H ₄	206c : 71	70
4	1c	4-FC ₆ H ₄	206d : 74	80
5	1c	4-CF ₃ C ₆ H ₄	206e : 52	82
6	1c	3-MeOC ₆ H ₄	206f : 89	88
7	1c	3-ClC ₆ H ₄	206g : 56	74
8	1c	3-CF ₃ C ₆ H ₄	206h : 73	70
9	1c	3,5-(CF ₃) ₂ C ₆ H ₃	206i : 55	37
10	1c	3,5-(Me) ₂ C ₆ H ₃	206j : 83	58
11	1c	2-MeC ₆ H ₄	206k : 81	40
12	1c	2-naphthyl	206l : 69	80

13	1a	Ph	206m : 68	83
14	1b	Ph	206n : 88	91
15	1b	4-MeC ₆ H ₄	206o : 71	84

Electron-poor SYNPHOS analogues in rhodium-catalyzed stereoselective 1,4-additions of various arylboronic acids **2** to nonsubstituted maleimide substrates **38a** employing the (*R*)-3,5-*di*CF₃-SYNPHOS ligand have been reported to afford 1,4-addition adducts **207a-k**. An outstanding feature of this catalytic system is that it could be conducted at room temperature, while providing a wide range of synthetically and biologically useful chiral 3-substituted succinimide derivatives in pure form, high yields and with excellent enantiomeric excesses of up to >99%, after crystallization. In addition, it is noteworthy that these are the best results reported so far in the literature for this particular family of substrates with atropisomeric diphosphine ligands (Scheme 102).²⁰²

- 207a**: Ar = Ph, yield = 88%, *ee* = 93 (99)%
207b: Ar = 3-FC₆H₄, yield = 81%, *ee* = 89 (99)%
207c: Ar = 3-ClC₆H₄, yield = 75%, *ee* = 87 (99)%
207d: Ar = 3-BrC₆H₄, yield = 81%, *ee* = 80 (97)%
207e: Ar = 4-CF₃C₆H₄, yield = 80%, *ee* = 92 (97)%
207f: Ar = 3-MeC₆H₄, yield = 83%, *ee* = 91 (94)%
207g: Ar = 3-MeOC₆H₄, yield = 85%, *ee* = 90 (99)%
207h: Ar = 4-MeC₆H₄, yield = 80%, *ee* = 91 (97)%
207i: Ar = 4-MeOC₆H₄, yield = 80%, *ee* = 93 (94)%
207j: Ar = C₁₀H₇, yield = 80%, *ee* = 92 (98)%
207k: Ar = 6-MeOC₁₀H₆, yield = 90%, *ee* = 90 (93)%

(Numbers in parentheses indicate the *ee* values after a single crystallization)

Scheme 102. Scope of the stereoselective 1,4-addition reaction of arylboronic acids to maleimide **38a**.

Nevertheless, the addition of arylboronic reagents to aryl nitroalkenes is inefficient in the area of stereoselective catalysis and the development of potent catalysts for this transformation is still in demand.^{203, 204} Excellent progress was accomplished by Lin et al., who employed a C2-symmetric chiral diene as a ligand and potassium trifluoroborates as organoboron reagents,

which were created in situ, to obtain good to excellent *ee*. In this light, a highly efficient transformation was reported regarding the Rh/sulfoxide-phosphine- catalyzed enantioselective addition of diverse arylboronic acids to 2-nitrostyrenes under mild reaction conditions to obtain the desired products with excellent *ee*. Based on this transformation, the first stereoselective total synthesis of cherylline was disclosed.²⁰⁵⁻²¹² An efficient (S/C, substrate/catalyst, up to 500) Rh-catalyzed addition of diverse arylboronic acids **2** to 2-nitrostyrenes **180a-l** under mild reaction conditions was reported, which gave excellent chemical yields (up to 99%) and enantioselectivities (up to 98% *ee*) *via* using *tert*-butanysulfinylphosphine as a ligand. This approach provides a promising route for the synthesis of chiral 2,2-bisarylethylamines **208a-y** with excellent chemical yields and *ee* (Scheme 103).²¹³

Scheme 103.

Table 65. Scope of the Rh-catalyzed stereoselective addition of arylboronic acids to 2-nitrostyrenes.

Entry	R 180	Ar 2	Yield (%)	<i>ee</i> (%)
1	180a : 4-MeOC ₆ H ₄	Ph	208a : 99	95 (<i>R</i>)
2	180b : 3-MeOC ₆ H ₄	Ph	208b : 90	87
3	180c : 2-MeOC ₆ H ₄	Ph	208c : 87	81
4	180a : 4-MeOC ₆ H ₄	2-MeC ₆ H ₄	208d : 81	58
5	180a : 4-MeOC ₆ H ₄	1-naphthyl	208e : 96	72
6	180a : 4-MeOC ₆ H ₄	2-naphthyl	208f : 99	95
7	180a : 4-MeOC ₆ H ₄	4-ClC ₆ H ₄	208g : 99	86

8	180a : 4-MeOC ₆ H ₄	4-FC ₆ H ₄	208h : 99	90
9	180a : 4-MeOC ₆ H ₄	4-MeC ₆ H ₄	208i : 99	97
10	180a : 4-MeOC ₆ H ₄	3-MeC ₆ H ₄	208j : 99	96
11	180a : 4-MeOC ₆ H ₄	3-MeOC ₆ H ₄	208k : 99	95
12	180a : 4-MeOC ₆ H ₄	4- <i>t</i> BuC ₆ H ₄	208l : 99	97
13	180a : 4-MeOC ₆ H ₄	3,5-Me ₂ C ₆ H ₃	208m : 99	96
14	180d : 4-FC ₆ H ₄	Ph	208n : 88	86
15	180e : 4-ClC ₆ H ₄	Ph	208o : 81	82
16	180f : 3,4-(MeO) ₂ C ₆ H ₃	Ph	208p : 99	94
17	180g : 4-Me ₂ NC ₆ H ₄	Ph	208q : 93	97
18	180h : 4-OHC ₆ H ₄	Ph	208r : 99	97
19	180i : 4-MeC ₆ H ₄	Ph	208s : 99	91
20	180j : Ph	4-MeOC ₆ H ₄	208t : 99	96 (<i>S</i>)
21	180h : 4-OHC ₆ H ₄	4-MeOC ₆ H ₄	208u : 92	98
22	180g : 4-Me ₂ NC ₆ H ₄	4-MeOC ₆ H ₄	208v : 95	98
23	180h : 4-OHC ₆ H ₄	4-MOMOC ₆ H ₄	208w : 99	98
24	180k : 4-OH,3-MeOC ₆ H ₃	4-MOMOC ₆ H ₄	208x : 99	97
25	180l : 4-BnO,3-MeOC ₆ H ₃	4-BnOC ₆ H ₄	208y : 99	98

An efficient one-step transformation was reported for the synthesis of 2-arylethanesulfonamides **210a-p** *via* Rh-catalyzed 1,4-conjugate additions of various arylboronic acids **2** to ethane sulfonamides **209a-d**. The amino substituent, the nature of the substituent on arylboronic acid, the type of Rh-catalyst, and the experimental reaction conditions all influenced the reaction outcome.²¹⁴ The yields of the reactions strongly depend on the specific substituent patterns of the reagents used. Although the scope of the reaction requires should be elaborated upon in more detail, this direct strategy allows rapid access to the 2-arylethanesulfonamide chemotype. In spite of their relatively simple chemical structures, all of the depicted 2-arylethanesulfonamides in Table 66, except for **5**,²¹⁵ were claimed as being novel by authors.

Scheme 104.

Table 66. Conjugate addition reactions of arylboronic acids with ethenesulfonamides.

Entry	209	Ar 2	Procedures	Yield (%)
1	209a	3-ClC ₆ H ₄	A	210a: 65
2	209a	4-PhC ₆ H ₄	A	210b: 51
3	209a	naphthalen-2-yl	A	210c: 28
4	209a	naphthalen-2-yl	B	210d: 40
5	209a	Ph	B	210e: 55
6	209b	3-ClC ₆ H ₄	A	210f: 0
7	209b	3-ClC ₆ H ₄	B	210g: 64
8	209b	Ph	B	210h: 48
9	209b	naphthalen-2-yl	B	210i: 46
10	209b	4-PhC ₆ H ₄	B	210j: 33
11	209c	4-PhC ₆ H ₄	B	210k: 40
12	209c	Ph	B	210l: 19
13	209c	3-ClC ₆ H ₄	B	210m: <10
14	209c	naphthalen-2-yl	B	210n: 10
15	209d	3-ClC ₆ H ₄	B	210o: 61
16	209d	4-PhC ₆ H ₄	B	210p: 47

The Rh-catalyzed addition reaction of differently substituted arylboronic acids **2** to various β -aryloxyacrylates and β -phenoxyacrylophenone **211a-c** resulted in the synthesis of 3,3-

diarylpropanoates and 3,3-diarylpropiophenones **212a-c** in satisfactory yields. The double arylation was accomplished by the regeneration of α,β -unsaturated carbonyl compounds via elimination of the β -oxygen (Scheme 105).²¹⁶

Scheme 105. Rhodium-catalyzed reaction of β -aryloxyacrylates **211** with 4-methylphenylboronic acid **2**.

Next, β -(4-acetylphenoxy)acrylate **211c** underwent reaction with differently substituted arylboronic acids **2** to afford the corresponding 3,3-diarylpropanoates **3a-n** in high yields. The results are outlined in Table 67.²¹⁶

Scheme 106.

Table 67. Double arylation of **211c**.

Entry	Ar 2	Temperature	Yield (%)
1	Ph	r.t.	212a: 94
2	4-MeOC ₆ H ₄	r.t.	212b: 91

3	4-AcC ₆ H ₄	reflux	212c : 34
4	3-MeC ₆ H ₄	r.t.	212d : 95
5	4- <i>t</i> -BuC ₆ H ₄	r.t.	212e : 88
6	2-MeC ₆ H ₄	reflux	212f : 91
7	2,4,6-(Me) ₃ C ₆ H ₂	reflux	212g : 0
8	2-naphthyl	r.t.	212h : 63
9	3-MeOC ₆ H ₄	r.t.	212i : 71
10	4-CF ₃ C ₆ H ₄	reflux	212j : 64
11	3-NO ₂ C ₆ H ₄	reflux	212k : 22
12	3-CNC ₆ H ₄	reflux	212l : 14
13	4-FC ₆ H ₄	r.t.	212m : 70
14	3-BrC ₆ H ₄	r.t.	212n : 28

Under certain circumstances, cinnamate **215** can be generated as a by-product. Thus the mechanism for the formation of **211** via double arylation most probably follows a cascade sequence involving 1,4-addition/ β -oxygen elimination²¹⁷⁻²²⁴ to afford **215** with subsequent 1,4-addition/protonation (Scheme 107). The lack of a common 1,4-addition product in the reaction mixture (detected by TLC) confirms that elimination of the β -oxygen smoothly occurs, which in turn indicates the possible protonation of intermediate **213** was completely over ruled. Indeed, this reaction is in contrast to the Rh(I)-phosphane-catalyzed reaction of a β -acetoxycrylate and an arylboronic acid, which can generate a cinnamate as the cross-coupling product.²²⁵

Scheme 107. Possible mechanism.

An effective Rh/diene-catalyzed stereoselective addition of differently substituted arylboronic acids **2** showing steric and electronic diverse properties to α,β -unsaturated γ -lactams **216**, employing chiral diene as ligands, was performed to yield **217a-l**. The results are outlined in Scheme 108.²²⁶ Under the optimized conditions, concluded experimentally; the reaction proceeded smoothly to give the products in excellent chemical yields and enantioselectivities, providing a wide range of synthetically beneficial chiral β -substituted γ -lactams. The supremacy of this strategy is revealed by the brief synthesis of (*R*)-baclofen and (*R*)-rolipram (Figure 10).²²⁶

Figure 10.

- 217a:** Ar = Ph, yield = 99%, *ee* = 98%
217b: Ar = 4-MeOC₆H₄, yield = 99%, *ee* = 98%
217c: Ar = 4-MeC₆H₄, yield = 99%, *ee* = 98%
217d: Ar = 3-MeOC₆H₄, yield = 99%, *ee* = 98%
217e: Ar = 3-MeC₆H₄, yield = 98%, *ee* = 98%
217f: Ar = 2-MeOC₆H₄, yield = 99%, *ee* = 99%
217g: Ar = 2-MeC₆H₄, yield = 99%, *ee* = 99%
217h: Ar = 1-naphthyl, yield = 99%, *ee* = 99%
217i: Ar = 2-naphthyl, yield = 99%, *ee* = 98%
217j: Ar = 4-CF₃C₆H₄, yield = 56%, *ee* = 98%
217k: Ar = 4-ClC₆H₄, yield = 78%, *ee* = 98%
217l: Ar = 4-BrC₆H₄, yield = 72%, *ee* = 97%

Scheme 108. Rhodium-catalyzed stereoselective 1,4-addition reaction of arylboronic acids to **216**.

(*R,R*)-1,2-Bis-(*tert*-butylsulfinyl)benzene is a structurally simple ligand that can be employed in Rh-catalyzed stereoselective 1,4-additions of sodium tetraarylborate reagents **167a-d** to *N*-substituted 2, 3-dihydro-4-pyridones and 4-quinolones **218a-e**. The reactions can be carried out cleanly and smoothly to furnish the respective adducts **219a-m** in high yields (up to 92%) and excellent enantioselectivities (up to 99% *ee*) under mild reaction conditions. Thus, the substrate scope was studied under the optimized conditions. The results are outlined in Table 68. Under these optimized conditions with (*R,R*)-**L41** as a ligand, different sodium tetraarylborates were reacted with substituted 4-pyridones; the phenylation reactions occurred efficiently (87–92% yield, 97–99% *ee*; Table 68).²²⁷

Scheme 109.

Table 68. Stereoselective addition of sodium *tetra* arylborates to 2, 3- dihydro-4-pyridones and 4-quinolones catalyzed by Rh/(*R,R*)-**L41**, 2- bis(*tert*-butylsulfinyl)benzene.

Entry	218	Ar 167	Yield (%)	<i>ee</i> (%)	Config.
1	218a	167a: Ph	219a: 92	99	(<i>R</i>)
2	218a	167b: 4-MeC ₆ H ₄	219b: 91	99	(<i>R</i>)
3	218a	167c: 3-MeC ₆ H ₄	219c: 87	97	(<i>R</i>)
4	218a	167a: Ph	219d: 90	99	(<i>R</i>)
5	218b	167b: 4-MeC ₆ H ₄	219e: 84	98	+
6	218b	167c: 3-MeC ₆ H ₄	219f: 86	99	+
7	218c	167a: Ph	219g: 88	99	+
8	218c	167b: 4-MeC ₆ H ₄	219h: 86	99	+

9	218d	167a : Ph	219i : 70	97	+
10	218d	167b : 4-MeC ₆ H ₄	219j : 75	98	+
11	218e	167a : Ph	219k : 82	98	(<i>R</i>)
12	218e	167b : 4-MeC ₆ H ₄	219l : 80	99	+
13	218b	167d : 4-FC ₆ H ₄	219m : 35	96	+

A series of chiral sulfoxide-olefins was designed and prepared via short reaction pathways; they were used as ligands in Hayashi-Miyaura reactions. By analysis of the results, it was found that vinyl substituents of the ligands had profound affects on the stereocontrolling capability. In particular, either isomer of the adducts can be easily obtained with excellent *ee* by changing the position of the olefin substituents as well as varying the configuration of the C=C bond in the ligands. In 2012, the substrate scope of arylboronic acids and alkenes was clearly demonstrated by using differently substituted phenylboronic acids and alkenes.

The generated Rh-complexes effectively catalyze the 1,4-addition of arylboronic acids **2** to α,β -unsaturated ketones **1a,b** to afford **220a-n**. The vinyl substituents of the ligands with different stereocontrolling capabilities as well as the substrate choice influenced the product *ee*. Both isomers of the product were obtained with good to excellent *ee*'s by using an appropriate olefinic isomer of the ligand.

By using a chiral Rh/sulfoxide-olefin complex as depicted in Scheme 110, a wide range of arylboronic acids were examined in the above reaction. Significantly, the electronic properties of aryl *p*-substituents had only a small effect. Cyclopent-2-enone **1a** can also be used instead of cyclohex-2-en-1-one, giving 84% chemical yield and 92% *ee* (Table 69).²²⁸

Scheme 110.

Table 69. Rh-catalyzed stereoselective 1,4-addition of various arylboronic acids **2** to α,β -unsaturated ketones **1a, b**

Entry	Ar 2	Yield (%)	<i>ee</i> (%)
1	Ph	220a : 98	95(-98) ^a
2	4-MeC ₆ H ₄	220b : 98	94(-97)
3	3-MeC ₆ H ₄	220c : 97	94(-96)
4	4-MeOC ₆ H ₄	220d : 86	88(-98)
5	3-MeOC ₆ H ₄	220e : 90	86(-97)
6	2-MeOC ₆ H ₄	220f : 79	87(-66)
7	4- ^t BuC ₆ H ₄	220g : 95	88(-97)
8	3,5-MeC ₆ H ₃	220h : 99	91(-97)
9	1-naphthyl	220i : 74	29(-92)
10	2-naphthyl	220j : 96	93(-64)
11	4-ClC ₆ H ₄	220k : 93	89(-95)
12	4-FC ₆ H ₄	220l : 90	91(-96)
13	4-CF ₃ C ₆ H ₄	220m : 92	86(-85)
14 ^b	Ph	220n : 84	92(-26)

^a The *ee* values in parentheses, which were obtained when **L58b** was used

^b In the presence of **1a**

The stereochemical routes with Rh/**L59a** were simplified in Figure 11. The initial coordination of the rhodium species more probably leads to a *trans* relationship between the olefinic part of the ligands, and the phenyl group where the substrate 2-cyclohexen-1-one binds to the rhodium center at the position *cis* to the olefinic part of ligands. Due to the steric repulsion between the carbonyl group of the enone and methyl group of the ligands, the carbon-carbon double bond of the substrate binds to the rhodium center with its re-face when the chiral sulfoxide-Z-alkene **L59a** was chosen and employed as the ligand.

Figure 11. Proposed stereochemical pathway.

A wide range of new C1-symmetric chiral diene ligands based on the dicyclopentadiene framework were successfully utilized in the Rh-catalyzed stereoselective 1,4-addition of various arylboronic acids **2** to diverse α,β -unsaturated carbonyl compounds **1a,b,e',g** under mild reaction conditions to obtain **222a-n** in high yields (90–99%) and with excellent enantioselectivities (up to 97% *ee*).

With dicyclopentadiene as the ligand, the substrate scope was studied under the optimized reaction conditions. Selected results are shown in Scheme 111. As indicated in most cases, the desired addition products were produced at ambient temperature in excellent chemical yields and with high enantioselectivities (96–97% *ee*) (Table 70).²²⁹

Scheme 111.

Table 70. Rhodium-catalyzed stereoselective 1,4-additions.

Entry	1	Ar 2	Yield (%)	ee (%)
1	1a	Ph	222a: 98	97
2	1a	4-MeOC ₆ H ₄	222b: 99	96
3	1a	4-MeC ₆ H ₄	222c: 98	96
4	1a	4-BrC ₆ H ₄	222d: 98	97
5	1a	4-CF ₃ C ₆ H ₄	222e: 99	96
6	1a	3-MeOC ₆ H ₄	222f: 98	97
7	1a	3-MeC ₆ H ₄	222g: 99	97
8	1a	3-ClC ₆ H ₄	222h: 97	96
9	1a	2-MeOC ₆ H ₄	222i: 98	87
10	1a	1-naphthyl	222j: 99	85
11	1b	Ph	222k: 94	83
12	1g	Ph	222l: 91	88
13	1e'	Ph	222m: 92	16
14	1e'	2-MeC ₆ H ₄	222n: 90	87

Cyclic β -alkenyl ketones are extensively employed as frameworks in organic synthesis.²³⁰ In this context, the conjugate 1,4-addition of (*E*)-2-phenylethenylboronic acid **223** to cyclic enones **1b** in the presence of tetrahydropentalene ligand (3a*R*,6a*R*)-**L20a-d** was performed as a model reaction. Under mild conditions, this reaction gave ethenylketone **222** with high enantioselectivity up to 87% *ee* and high yields of ethenylketones **224a-c** (Scheme 112). To

establish the generality of method, three different cyclic enones **1a-c** were subjected to 1,4-addition under the same reaction conditions; the configurations of all of the ketones synthesized using (3a*R*,6a*R*)-**L20a-d** were determined to be (*S*). Further investigations revealed that several features affect the selectivity and yields of the products of this approach. It was found that the electronic nature of the aryl substituents in the ligand skeleton had only a tiny effect on the stereocontrol of the addition reaction. On the other hand, steric factors have a significant influence on the enantiomeric purity and chemical yield of the reaction. It was also realized the ligand having nonplanar benzyl substituents was less effective and selective than tetrahydropentalenes with planar aryl groups. It was also understood that the enantioselectivity and productivity of this Rh-catalyst were dependent on the ring size of the cyclic enone. The enantioselectivity in this approach also significantly depends on the nature of the boronic acid employed in the reaction (Table 71).²³¹

While evaluating the catalytic potency of the ligands **L20a-d** with different electronic properties, the observed trend was **L20a** > **L20c** > **L20d** > **L20b** irrespective of the ring size of enone **1a-c**. The structural effect of the enone substrate on the properties of the catalyst in the vinylation reaction was found to be excellent. An increase in the ring size of the cyclic enone **1a-c** resulted in an increase in the productivity and selectivity of the Rh-catalysts, prepared from ligands **L20a-d**.²³¹

Scheme 112. Rh-catalyzed 1,4-addition of boronic acids **223** to cyclic enones **1a-c**

Table 71.

Entry	1	Ln	Yield(%)	<i>ee</i> (%)
1	1b	L20a	224a : 74	70
2	1b	L20b	224a : 51	32
3	1b	L20c	224a : 72	67
4	1b	L20d	224a : 66	76
5	1a	L20a	224b : 80	76
6	1a	L20b	224b : 63	48
7	1a	L20c	224b : 70	76
8	1a	L20d	224b : 65	77
9	1c	L20a	224c : 86	87
10	1c	L20b	224c : 71	58
11	1c	L20c	224c : 80	86
12	1c	L20d	224c : 76	85

Dihydrobenzofuran-based diphosphine ligand (Bicmap) **L61** was employed as a chiral ligand in the Rh(I)-catalyzed stereoselective 1,4-addition of aryl- and alkenylboronic **2** to cyclic enones **1a-c** with up to 99% *ee*. The utilization of [RhCl(C₂H₄)₂]₂ / [Rh(OH)(cod)]₂ / Rh(acac)(C₂H₄)₂ as a Rh source,²³³ along with potassium hydroxide as a base allowed the 1,4-addition to proceed smoothly to afford the corresponding product **225a-m** in 64-98% yield and with good enantioselectivity (89-99% *ee*). It has also been established that the Bicmap-Rh system is an effective catalyst for the 1,4-addition of various alkenylboronic acids to give 2-cyclohexenones with good enantioselectivities (Table 72).²³²

Scheme 113.

Table 72. Rhodium(I)-catalyzed stereoselective 1,4-addition to cyclic enones using (*S*)-**L61**.

Entry	Rh Source	1	Ar 2	Yield (%)	<i>ee</i> (%)
1 ^a	[RhCl(C ₂ H ₄) ₂] ₂	1a	Ph	225a : 91	96
2	[Rh(OH)(cod)] ₂	1a	Ph	225a : 92	95
3	[Rh(acac)(C ₂ H ₄) ₂]	1a	Ph	225a : 98	99
4	[Rh(acac)(C ₂ H ₄) ₂]	1a	4-MeC ₆ H ₄	225b : 80	97
5	[Rh(acac)(C ₂ H ₄) ₂]	1a	3-MeC ₆ H ₄	225c : 89	99
6	[Rh(acac)(C ₂ H ₄) ₂]	1a	2-MeC ₆ H ₄	225d : 50	89
7	[Rh(acac)(C ₂ H ₄) ₂]	1a	3,5-(Me) ₂ C ₆ H ₃	225e : 96	99
8	[Rh(acac)(C ₂ H ₄) ₂]	1a	4-MeOC ₆ H ₄	225f : 64	96
9	[Rh(acac)(C ₂ H ₄) ₂]	1a	4-PhC ₆ H ₄	225g : 93	98
10	[Rh(acac)(C ₂ H ₄) ₂]	1a	4-ClC ₆ H ₄	225h : 31	98
11	[Rh(acac)(C ₂ H ₄) ₂]	1a	3-ClC ₆ H ₄	225i : 61	98
12	[Rh(acac)(C ₂ H ₄) ₂]	1b	Ph	225j : 96	94
13	[Rh(acac)(C ₂ H ₄) ₂]	1c	Ph	225k : 84	95
14	[Rh(acac)(C ₂ H ₄) ₂]	1a	<i>trans</i> -PhCH=CH	225l : 78	89
15	[Rh(acac)(C ₂ H ₄) ₂]	1a	<i>trans-n</i> - C ₆ H ₁₃ PhCH=CH	225m : 79	93

^a 2.3 equiv of KOH was added.

An efficient asymmetric synthesis of flavanone has been successfully carried out *via* Rh(I)-catalyzed stereoselective 1,4-addition of chromone. The reaction of chromone **226** with phenylboronic acid **2** under catalysis of (*S*)-Bicmap **L61** as a chiral ligand (Scheme 114) afforded flavanone **227** in poor yield but with excellent enantioselectivity (99% *ee*).²³²

Scheme 114. Synthesis of flavanone **227**

Chiral phosphorus–olefins (*S*)-**L62a–d** have recently been prepared and the structures of their rhodium complexes were elucidated. These ligands commonly behave as phosphorus–olefin bidentate ligands to rhodium. The Rh-complexes coordinated with the aforementioned ligands act effectively as catalysts in the stereoselective 1,4-additions of differently substituted arylboronic acids **2** to a wide range of α,β -unsaturated ketones **1a–c**, to afford 1,4-adducts **228a–n**. Remarkably, the enantioselectivities were high for cyclic enones and moderate for acyclic enones. It has been proven that ligands (*S*)-**L62a** and (*S*)-**L62d** give the opposite enantiomers of the 1,4-adducts with high *ee* for cyclic enones.²³⁴

2-Cyclohexenone reacted with phenylboronic acid, ligands (*S*)-**L62a–c** showed high catalytic potency to provide (*S*)-3-phenylcyclohexanone with high enantioselectivity (91–94% *ee*). Alternatively, the utilization of ligand (*S*)-**L62d** resulted in the formation of (*R*)-3-phenylcyclohexanone in 98% chemical yield and with high enantiomeric excess (Scheme 115, Table 73).²³⁴

Scheme 115.

Table 73. Rh-catalyzed stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated cyclic ketones.

Entry	1	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	1a	L62a	Ph	228a: 89	94	(<i>S</i>)
2	1a	L62b	Ph	228b: 91	93	(<i>S</i>)

3	1a	L62c	Ph	228c : 81	91	(<i>S</i>)
4	1a	L62d	Ph	228d : 98	97	(<i>R</i>)
5	1a	L62a	4-MeOC ₆ H ₄	228e : 86	96	(<i>S</i>)
6	1a	L62d	4-MeOC ₆ H ₄	228f : 93	97	(<i>R</i>)
7	1a	L62a	4-CF ₃ C ₆ H ₄	228g : 87	94	(<i>S</i>)
8	1a	L62d	4-CF ₃ C ₆ H ₄	228h : 84	97	(<i>R</i>)
9	1a	L62a	2-MeC ₆ H ₄	228i : 92	95	(<i>S</i>)
10	1a	L62d	2-MeC ₆ H ₄	228j : 99	98	(<i>R</i>)
11	1b	L62a	Ph	228k : 92	93	(<i>S</i>)
12	1b	L62d	Ph	228l : 93	95	(<i>R</i>)
13	1c	L62a	Ph	228m : 90	87	(<i>S</i>)
14	1c	L62d	Ph	228n : 87	95	(<i>R</i>)

These phosphorus-olefin ligands were employed in reactions of acyclic enones **229a-c** with phenylboronic acid **2** to afford **230a-f** (Scheme 116).²³⁴

Scheme 116.

Table 74. Rhodium-catalyzed stereoselective 1,4-addition of phenylboronic acid to α,β -unsaturated acyclic ketones.

Entry	R 229	Ln	Yield (%)	<i>ee</i> (%)	Config.
1	229a : Me	L62a	230a : 89	85	(<i>R</i>)
2	229a : Me	L62d	230b : 79	50	(<i>S</i>)
3	229b : <i>n</i> -C ₅ H ₁₁	L62a	320c : 91	83	(<i>R</i>)
4	229b : <i>n</i> -C ₅ H ₁₁	L62d	230d : 73	58	(<i>S</i>)
5	229c : <i>i</i> -Pr	L62a	230e : 93	81	(<i>S</i>)
6	229c : <i>i</i> -Pr	L62d	230f : 79	65	(<i>R</i>)

Based on the results of these 1,4-additions and the characterization of Rh/(*S*)-**L62a** complex by single crystal X-ray crystallography, a stereoselective route was suggested for the 1,4-addition of phenylboronic acid to 2-cyclohexenone under Rh/(*S*)-**L62a** catalysis as illustrated in Figure 12a.²³⁵⁻²⁴¹ As shown, the phenylrhodium species had a *trans*-relationship between the phenyl group and the olefin ligand, while 2-cyclohexenone binds to the rhodium with its *si*-face at the *cis*-position of the olefin ligand, resulting in the formation of the 1,4-adduct with an (*S*)-configuration. The generation of the (*R*)-product utilizing Rh/(*S*)-**L62d** can be explained similarly by the *re*-face coordination of 2-cyclohexenone to rhodium as depicted in Figure 12b.

Figure 12. Proposed stereochemical pathways for the stereoselective 1,4-addition of phenylboronic acid to 2-cyclohexenone catalyzed by Rh/(*S*)-**L62a** (a) and Rh/(*S*)-**L62d** (b).

A series of C1-symmetric chiral bicyclo[2.2.2]octa-2,5-dienes (bod*) **L11** were examined as ligands in Rh-catalyzed arylations of various substrates using differently substituted phenylboronic acids to afford the corresponding products with the highest level of enantioselectivities (up to 99% *ee*) achieved so far with standard diene ligands. A series of dienes **L11** underwent the 1,4-additions of differently substituted arylboronic acids. In this line cyclohex-2-en-1-one, and cyclopent-2-en-1-one **1a** afforded ketones **233a-k** by using chiral dienes **L11a-k**.

The effective catalyst was obtained in situ by mixing chiral ligand **L11** with $[\text{RhCl}(\text{C}_2\text{H}_4)]_2$. Generally, very good enantioselectivities were accomplished with all C1-symmetric chiral bod* dienes **L11**. The highest *ee* (97%) was achieved with the mother bod* **L11c** and with 4-MeO-substituted diaryldiene **L11e** (Scheme 117).²⁴²

Scheme 117.

Table 75. Enantioselective addition of phenylboronic acid to cyclohex-2-en-1-one **1a** catalyzed by chiral Rh/diene **L11a-k** complexes

Entry	Ln	Yield (%)	<i>ee</i> (%)
1	L11a	233a: 75	92
2	<i>ent</i> - L11a	233a: 72	-92
3	L11b	233b: 65	92
4	L11c	233c: 90	97
5 ^a	L11c	233c: 94	97
6	<i>ent</i> - L11c	233c: 70	-97
7	L11d	233d: 86	96
8	L11e	233e: 58	97
9	L11f	233f: 70	96
10	L11g	233g: 79	96

11	L11h	233h : 76	96
12	L11i	233i : 93	91
13	L11j	233j : 97	86
14	L11k	233k : 86	96

^aWith (PhBO)₃ instead of PhB(OH)₂

The same strategy was employed for the addition of phenylboronic acid to cyclopent-2-en-1-one **1b** to give ketones **234a-k** as a model reaction. Generally, high enantioselectivities were accomplished with all C1-symmetric chiral dienes **L11**. The best result (99% *ee*) was obtained with the 4-MeO substituted diaryldiene **L11e**. Using the latter as a Michael acceptor, the bulky ligands **L11i** and **L11j** exhibited high enantioselectivities. The yields of 1,4-adducts **234a-k** were satisfactory (53 -73%) after column chromatography, but were slightly lower than those for adduct **233a-k** (Scheme 118).²⁴²

Scheme 118.

Table 76. Enantioselective addition of phenylboronic acid to cyclopent-2-en-1-one **1b** catalyzed by Rh/diene **L11a-k** complexes.

Entry	Ln	Yield (%)	<i>ee</i> (%)
1	L11a	234a : 95	94
2	<i>ent</i> - L11a	234a : 87	-93
3	L11b	234b : 73	95
4	L11c	234c : 63	98
5	<i>ent</i> - L11c	234c : 71	-98
6	L11d	234d : 75	98
7	L11e	234e : 73	99
8	L11f	234f : 80	98
9	L11g	234g : 55	97
10	L11h	234h : 65	94

11	L11i	234i : 53	97
12	L11j	234j : 60	97
13	L11k	234k : 77	98

The 1,4-addition of (4-methoxyphenyl)boronic acid to the acyclic enone *tert*-butyl cinnamate (= *tert*-butyl (2*E*)-3-phenylprop-2-enoate) **235** was extensively studied. This reaction afforded propanoate **236**. The results are summarized in Table 77. It should be noted that some important and useful drugs can be obtained from chiral diarylmethines of the type of **236**. Carreira *et al.* achieved enantioselectivities of 93% *ee* with the carvone derived dienes. To date, ligands (bod*) had not been examined with cinnamate **235**.²⁴³ The active catalyst was provided by mixing chiral ligand **L11** with [RhCl(C₂H₄)]₂, and about a twofold excess of 4-methoxyphenylboronic acid with respect to **235**. It was then used as an active catalyst in the presence of KOH at 50 °C. The solvent of choice was found to be MeOH/H₂O (10:1). It was found to be superior even compared to dioxane/H₂O. Excellent enantioselectivities (98 –99% *ee*) were accomplished with several bod* ligands **L11a-k**, except for ligands **L11i** and **L11j**, which bear bulky substituents, and the two aryl-alkyl-substituted dienes **L11a** and **L11b**. The use of less equiv. of (4-methoxyphenyl)boronic acid led to a slightly lower yield, but a comparable enantioselectivity (Table 77).²⁴²

Table 77. Enantioselective addition of (4-methoxyphenyl)boronic acid to *tert*-butyl cinnamate **235** catalyzed by Rh/diene **L11a-k** complexes.

Entry	Ln	Conversion [%]	Yield (%)	<i>ee</i> (%)
1	L11a	>95	95	92
2	L11b	60	20	91
3	L11c	>95	78	99

4 ^a	L11c	90	56	98
5	<i>ent</i> - L11c	>95	78	-97
6	L11d	70	56	99
7	L11e	>95	97	99
8	L11f	75	79	98
9	L11g	>95	94	98
10	L11h	>95	30	98
11	L11i	>95	69	93
12	L11j	>95	89	89
13	L11k	>95	63	98

^a With 1.2 instead of 2 equiv. of 4-MeO-C₆H₄B(OH)₂

A novel catalyst system, PQS-Binap Rh **L63** was designed and prepared, and then examined in the stereoselective conjugate additions of arylboronic acids to enones as a homogeneous catalyst. This species is a non-racemic ligated transition metal catalyst-tethered amphiphile. The catalytic activity of the aforementioned catalyst system was evaluated in the stereoselective 1,4-addition reactions of arylboronic acids **2** to acyclic and cyclic enones **1a-c**. The reaction proceeded smoothly in water at room temperature to give the adducts in high yields and with high enantioselectivities. The catalyst system can be recycled without its removal from water in the reaction pot and no loss of appreciable activity. Examples of both cyclic and acyclic enones were used as depicted in Scheme 120. Arylboronic acids bearing either electron-donating and electron-withdrawing groups are well tolerated. This investigation introduced an effective catalyst system as a good alternative to those previously reported recyclable catalysts, particularly those that require long reaction times, and use expensive metals. The stereoselective additions of differently substituted phenylboronic acids to five- and seven-membered cyclic enones were successful, giving satisfactory yields with excellent *ee* (Scheme 120, Table 78).²⁴⁴

Scheme 120. Representative examples using PQS-Binap-Rh as the catalyst for 1,4-addition reactions.

Table 78.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	4-OMeC ₆ H ₄	237a : 99	>99.9
2	1a	4-CF ₃ C ₆ H ₄	237b : 87	99.9
3	1a	2-MeC ₆ H ₄	237c : 80	97.6
4	1b	Ph	237d : 98	78.9
5	1c	Ph	237e : 83	96.3

The conjugate addition of (*E*)-1,2-diphenylethenylboronic acid **239** to 2-cyclohexenone **1a-d**, **238** catalyzed by a diene/rhodium catalyst resulted in a rearrangement that gave products **240a-e** containing a 2-((*E*)-2-phenylethenyl)phenyl group. It has been shown that tandem 1,4-Rh shift/1,4-addition catalyzed Rh/diene reactions take place with high selectivity. It has been suggested that the catalytic cycle involves a 1,4-Rh shift from the 1,2-diphenylethenylrhodium intermediate resulted in another 2-((*E*)-2-phenylethenyl)phenylrhodium intermediate. Thus this high potential activity hidden in the diene/rhodium complexes caused the alkenyl-aryl 1,4-

rhodium shift following with conjugate addition sequence opens a gateway for the applications of chiral diene ligands.^{246, 247} The enantioselectivities for the addition of **239** to **1a** are frequently high (93-98% *ee*) with C2 symmetric dienes (bod*), and those **L64** and **L65** derived from (*R*)-phellandrene. The novel chiral diene **L66**, which is analogous to **L65** but has a more bulky ester motif, exhibited the highest level of enantioselectivity (99% *ee*) (Table 79).²⁴⁵

Table 79. Rhodium/diene-catalyzed stereoselective addition of alkenylboronic acid **239** to enones **1/238**.

Entry	2	Ln	Yield (%)	<i>ee</i> (%)	Config.
1	1a	L11b	240a : 97	96	(<i>R</i>)
2	1a	L11a	240b : 99	95	(<i>R</i>)
3	1a	(<i>R</i>)- L64	240c : 96	93	(<i>R</i>)
4	1a	(<i>R</i>)- L65	240d : 97	98	(<i>R</i>)
5	1a	(<i>R</i>)- L66	240e : 99	99	(<i>R</i>)
6	1b	(<i>R</i>)- L66	240f : 95	96	(<i>R</i>)
7	1c	(<i>R</i>)- L66	240g : 83	95	(<i>R</i>)
8	238	(<i>R</i>)- L66	240h : 93	95	(<i>S</i>)
9	1d	(<i>R</i>)- L66	240i : 73	99	(<i>R</i>)

The generation of the rearranged product **240a** clearly shows that the catalytic cycle proceeds *via* the 1,4-shift of a rhodium from 2-phenylethenyl rhodium(I) intermediate **241** to 2-alkenyl

phenylrhodium(I) **243** most probably in the same way as Rh(III) intermediate **242**; therefore a high selectivity as for **240a** makes it eligible for pushing the 1,4-shift of **241** to **243** faster than the alkenyl rhodation of enone **1a**, resulting in the products formed from the alkenylation of **244a**.²⁴⁸

Scheme 122. A plausible pathway for the rhodium-catalyzed reaction giving **240a** from boronic acid **239** (Rh = [Rh(bod)]).

The Rh/Fc-tfb* catalyst exhibited high catalytic efficiency and enantioselectivity during the addition of *p*-tolylboronic acid **2** to various alkenyl sulfonyl compounds **245a-k** to afford adducts **246a-k** in high yield and with very high *ee* (Scheme 123).²⁴⁹

- 246a:** X = OPh, R = Ph, yield = 98%, *ee* = 96%
246b: X = O(2,6-Me₂C₆H₃), R = Ph, yield = 97%, *ee* = 99%
246c: X = OEt, R = Ph, yield = 84%, *ee* = 97%
246d: X = morpholine, R = Ph, yield = 95%, *ee* = >99.5%
246e: X = 2-benzothiazolyl, R = Ph, yield = 95%, *ee* = >99.5%
246f: X = *p*-tolyl, R = Ph, yield = 92%, *ee* = 99%
246g: X = *p*-tolyl, R = furan, yield = 92%, *ee* = >99.5%
246h: X = *p*-tolyl, R = thiophene, yield = 96%, *ee* = >99.5%
246i: X = *p*-tolyl, R = pyridine, yield = 94%, *ee* = >99.5%
246j: X = *p*-tolyl, R = CH=C(Me)₂, yield = 96%, *ee* = 99%
246k: X = *p*-tolyl, R = Bu, yield = 96%, *ee* = >99.5%

Scheme 123. Rhodium-catalyzed stereoselective addition of *p*-tolylboronic acid **2** to **245a-k**

Stereoselective 1,4-additions of arylboronic acids to α,β -unsaturated sulfonyl compounds **245b** have been conducted in the presence of a Rh catalyst coordinated with a chiral diene ligand to afford adducts **246l-v** in satisfactory chemical yields and with high enantioselectivity (96–>99.5% *ee*). The diene ligand was found to be vital for the generation of the corresponding adduct, whereas the use of a bisphosphine ligand chiefly afforded the *cis*-product. The results obtained from the addition of several arylboronic acids **2** to alkenylsulfonate **245b** are outlined in Scheme 124.²⁴⁹

Scheme 124. Rhodium-catalyzed stereoselective addition of arylboronic acids **2** to **245b**

The stereoselective 1,4-addition of phenylboronic acid **2** to cyclic sulfonate **245l** in the presence of Rh/Fc-tfb* complex proceeded smoothly to afford adduct **246w** in 92% yield and with up to 99.5% *ee* (Scheme 125). The same reaction was also catalyzed by the Rh/binap complex, but preferred the substitution in the reaction of the linear sulfonate **245a**, to provide **246w** in 97% yield and with excellent enantioselectivity (99% *ee*).²⁴⁹

Scheme 125.

A D₂O-labelling experiment revealed the mechanism involved in the protonation step (Scheme 126). The reaction of alkenyl sulfone **245g** with *p*-tolylboroxine **13** in the presence of D₂O, where *p*-tolB(OD)₂ is created in situ, mediated by Rh catalyst and K₃PO₄ at 60 °C afforded the addition product **246x**. The deuterium content at the α-carbon of **246l** was measured as 97% (*dr* = >97:3).²⁴⁹

Scheme 126. A deuterium-labeling experiment

The use of a chiral diene ligand resulted in the Rh-catalyzed stereoselective addition of various arylboronic acids to a wide range of α,β -unsaturated sulfonyl compounds with very high enantioselectivity.

Scheme 127. Rhodium-catalyzed arylation of α,β -unsaturated sulfonyl compounds.

Wan *et al.* in 2012 accomplished and reported an effective Rh/olefin-sulfoxide catalyzed stereoselective conjugate addition of various organo boronic acids **2** to diverse nitroalkenes **180a-n** to afford product **248a-z** in moderate to high yields and with good enantioselectivities (Table 80). Several different nitroalkenes can be successfully used in this process, leading to the corresponding adducts. In particular, alkyl- and heteroaryl substituted nitroalkenes were found to be appropriate substrates for this asymmetric addition in terms of obtained yields and reaction times. The olefin-sulfoxide ligands, which were developed recently, were successfully used in stereoselective additions to nitroalkenes, thus presenting an alternative approach for the synthesis of chiral nitro compounds. 2-Methoxy-1-naphthyl sulfinyl-based olefin ligands were found to be more efficient than the *tert*-butyl sulfinyl-based ones. Generally, it has been found that the electronic properties of the substituent on the substrates do not affect the reaction stereoselectivity in great extent. Nevertheless, the steric hindrance of the substituents on the aromatic ring proved to have a remarkable impact on the activity, but a small effect on the enantioselectivity (Scheme 128).²⁵⁰

Scheme 128.

Table 80. Scope of the Rh-catalyzed stereoselective addition of arylboronic acids to 2-nitroaryalkene.

Entry	R ¹ 180	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	180a : Ph	4-MeOC ₆ H ₄	248a : 89	90	(<i>S</i>)
2	180a : Ph	3-MeOC ₆ H ₄	248b : 85	91	(<i>S</i>)
3	180a : Ph	3-MeC ₆ H ₄	248c : 80	86	(<i>S</i>)
4	180a : Ph	4-FC ₆ H ₄	248d : 85	87	(<i>S</i>)
5	180a : Ph	4- ^t BuC ₆ H ₄	248e : 79	85	(<i>S</i>)
6	180a : Ph	3,4-(Me) ₂ C ₆ H ₃	248f : 86	86	(<i>S</i>)
7	180a : Ph	1-naphthyl	248g : 55	91	(<i>S</i>)
8	180a : Ph	2-naphthyl	248h : 83	88	(<i>S</i>)
9	180b : 2-MeOC ₆ H ₄	Ph	248i : 50	84	(<i>R</i>)
12	180e : 4-MeC ₆ H ₄	Ph	248j : 80	87	(<i>R</i>)
14	180g : 4-ClC ₆ H ₄	Ph	248k : 81	88	(<i>R</i>)
15	180h : 4-CF ₃ C ₆ H ₄	Ph	248l : 79	87	(<i>R</i>)
16	180i : 3,4-(MeO) ₂ C ₆ H ₃	Ph	248m : 87	87	(<i>R</i>)
17	180j : 4-NMe ₂ C ₆ H ₄	Ph	248n : 81	88	(<i>R</i>)
18	180f : 4-FC ₆ H ₄	4-MeOC ₆ H ₄	248o : 90	87	(<i>S</i>)
19	180h : 4-BrC ₆ H ₄	4-MeOC ₆ H ₄	248p : 86	85	(<i>S</i>)
20	180h : 4-CF ₃ C ₆ H ₄	4-MeOC ₆ H ₄	248q : 85	82	(<i>S</i>)
21	180h : 2-naphthyl	4-MeOC ₆ H ₄	248r : 96	90	(<i>S</i>)
22	180i : 3,4-(MeO) ₂ C ₆ H ₃	4-MeOC ₆ H ₄	248s : 92	88	(<i>S</i>)

23	180m : 4-BnO-3-OMeC ₆ H ₃	4-MeOC ₆ H ₄	248t : 77	89	(<i>S</i>)
24	180j : 4-Me ₂ NC ₆ H ₄	4-MeOC ₆ H ₄	248u : 65	90	(<i>S</i>)
25	180n : 3,4-Cl ₂ C ₆ H ₃	4-MeOC ₆ H ₄	248v : 91	89	(<i>S</i>)
26	180i : 3,4-(MeO) ₂ C ₆ H ₃	3-MeOC ₆ H ₄	248w : 84	89	(<i>S</i>)
27	180m : 4-BnO-3-MeOC ₆ H ₃	3-MeOC ₆ H ₄	248x : 80	87	(<i>S</i>)
28	180j : 4-Me ₂ NC ₆ H ₄	3-MeOC ₆ H ₄	248y : 75	91	(<i>S</i>)
29	180n : 3,4-Cl ₂ C ₆ H ₃	3-MeOC ₆ H ₄	248z : 90	85	(<i>S</i>)

The scope of this addition reaction was further defined. The aliphatic nitroalkenes **2** and heteroaryl nitroalkenes **180o-s** were used to afford the corresponding products **249a-p** (Table 81). When aliphatic and hetero aromatic nitroalkenes underwent the conjugate addition, similar levels of enantioselectivity were obtained. It is worthwhile noting that when it comes to problematic aliphatic nitroalkenes, higher enantioselectivities were observed than those similar reactions previously reported (Scheme 129).²⁵⁰

Scheme 129.

Table 81. Scope of the Rh-catalyzed stereoselective addition of arylboronic acids to 2-nitroalkyl styrenes and 2-nitroheteroarylstyrenes.

Entry	R ¹ 180	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	180o : <i>n</i> -Bu	Ph	249a : 61	87	(<i>S</i>)
2	180o : <i>n</i> -Bu	4-MeOC ₆ H ₄	249b : 78	85	(<i>S</i>)
3	180o : <i>n</i> -Bu	4-MeC ₆ H ₄	249c : 85	87	(<i>S</i>)
4	180o : <i>n</i> -Bu	4-FC ₆ H ₄	249d : 83	88	(<i>S</i>)
5	180p : <i>i</i> -Pr	Ph	249e : 70	86	(<i>S</i>)
6	180p : <i>i</i> -Pr	4-MeOC ₆ H ₄	249f : 56	87	(<i>S</i>)
7	180p : <i>i</i> -Pr	4-FC ₆ H ₄	249g : 60	90	(<i>S</i>)
8	180p : <i>i</i> -Pr	4-MeC ₆ H ₄	249h : 85	88	(<i>S</i>)
9	180q : <i>c</i> -C ₆ H ₁₁	Ph	249i : 81	88	(<i>S</i>)

10	180q : <i>c</i> -C ₆ H ₁₁	4-MeOC ₆ H ₄	249j : 65	89	(<i>S</i>)
11	180q : <i>c</i> -C ₆ H ₁₁	4-MeC ₆ H ₄	249k : 71	90	(<i>S</i>)
12	180r : 2-furyl	4-MeOC ₆ H ₄	249l : 57	79	-
13	180s : 2-thienyl	4-MeOC ₆ H ₄	249m : 84	87	-
14	180s : 2-thienyl	3,4-(Me) ₂ C ₆ H ₃	249n : 60	75	-
15	180r : 2-furyl	3,4-(MeO) ₂ C ₆ H ₃	249o : 63	83	-
16	180s : 2-thienyl	3,4-(MeO) ₂ C ₆ H ₃	249p : 74	86	-

The stereochemical outcome of the Rh-complex catalyzed 1,4-addition can be described rationally as illustrated in Figure 13. There is a tendency for π - π stacking between the phenyl moiety of the ligand terminus and the metallated phenyl ring of phenylboronic acid in the transition state of the reaction. The Rh-complex distinguishes the alkene motif of the nitroalkenes due to the steric repulsion between the 2-methoxy-1-naphthyl group of the ligand and the nitro group of the nitroalkene. Therefore, coordination of the nitroalkene from the less steric hindered side occurs more favorably, resulting in the (*S*)-isomer, which is in agreement with the observed stereochemistry.²⁵⁰

Figure 13. Proposed stereochemical pathway for the stereoselective 1,4-addition.

When toluene/isopropanol (20:1) was used as the solvent system and KHF_2 as an appropriate additive, the Rh/diene catalyzed stereoselective arylation 1,4-addition of various arylboronic acids **2** to *N*-Boc-protected α,β -unsaturated δ -lactam or 3-lactam **252**, employing (*S,S*)-Ph-thpe as the ligand proceeded cleanly to give chiral 4-aryl-2-piperidinones **253a-n** with high to excellent chemical yields (up to 94%) and excellent enantioselectivities (up to >99% *ee*).²⁵¹

253a: Ar = Ph, yield = 92%, *ee* = 95%
253b: Ar = 4-MeC₆H₄, yield = 90%, *ee* = 93%
253c: Ar = 4-*t*-BuC₆H₄, yield = 92%, *ee* = 92%
253d: Ar = 4-MeOC₆H₄, yield = 91%, *ee* = 93%
253e: Ar = 4-FC₆H₄, yield = 93%, *ee* = 93%
253f: Ar = 4-ClC₆H₄, yield = 92%, *ee* = 92%
253g: Ar = 4-BrC₆H₄, yield = 80%, *ee* = 93%
253h: Ar = 3-ClC₆H₄, yield = 76%, *ee* = 96%
253i: Ar = 3-MeC₆H₄, yield = 94%, *ee* = 94%
253j: Ar = 3-MeOC₆H₄, yield = 90%, *ee* = 95%
253k: Ar = 2-naphthyl, yield = 85%, *ee* = 96%
253l: Ar = 2-MeOC₆H₄, yield = 84%, *ee* = 96%
253m: Ar = 2-MeC₆H₄, yield = 88%, *ee* = 97%
253n: Ar = 1-naphthyl, yield = 92%, *ee* = >99%

Scheme 130. The Rh/diene catalyzed stereoselective arylation of arylboronic acids to 1-*N*-Boc-2-oxo-5,6-dihydropyridine **252**

Further expansion of this strategy to *N*-Boc-protected α,β -unsaturated-3-lactam **254** was also successful. In this case, boronic acid was required in order to compensate for the low reactivity of the 3-lactam substrate. As illustrated in Scheme 131, the Rh/diene catalyzed stereoselective arylation of 1-naphthyl-boronic acid **2** provided chiral 4-aryl 3-lactam **255** in moderate chemical yield (68%) but with excellent enantioselectivity (98% *ee*).²⁵¹

Scheme 131. The Rh/diene catalyzed stereoselective arylation to 1-*N*-Boc-7-oxo-2,3,4,7-tetrahydro-1*H*-azepine **254**.

Liao *et al.* in 2012 reported the Rh-catalyzed diastereo- and enantioselective Michael addition of diverse arylboronic acids **2** to 3-alkylenyloxindoles **256a-e** using (*R*)-binap **L4** as a ligand. A wide range of the desired functionalized oxindoles **257a-l** were obtained in excellent chemical yields (up to 99%) and with very high enantioselectivities (up to 92% *ee*) as well as high diastereoselectivities (up to 82:18). This strategy provides a facile and efficient approach to synthesize diastereomerically enriched functionalized oxindole derivatives. Then under the already optimized reaction conditions, the substrate scope was studied. The results of this investigation are outlined in Table 82.²⁵²

Scheme 132.

Table 82. Stereoselective conjugate addition of arylboronic acids to 3-alkylenyloxindoles.

Entry	256	Ar 2	Yield (%)	<i>dr</i>	<i>ee</i> (%)
1	256a	Ph	257a: 98	76/24	88
2	256a	4-MeOC ₆ H ₄	257b: 98	70/30	88
3	256a	4-MeC ₆ H ₄	257c: 97	70/30	86
4	256a	4-C(Me) ₃ C ₆ H ₄	257d: 98	67/33	86
5	256a	4-ClC ₆ H ₄	257e: 98	75/25	88
6	256a	4-FC ₆ H ₄	257f: 99	71/29	88
7	256a	3-MeOC ₆ H ₄	257g: 97	69/31	90
8	256a	3-ClC ₆ H ₄	257h: 96	75/25	91
9	256b	Ph	257i: 99	78/22	78

10	256c	Ph	257j : 96	82/18	78
11	256d	Ph	257k : 86	66/34	50
12	256e	Ph	257l : trace	n.d.	n.d.

rRhodium-catalyzed stereoselective conjugate-addition reactions of potassium alkenyl trifluoroborates **28** and α,β -unsaturated carbonyl compounds **1a,b,g,h**, **258a,b** were successfully performed mediated by a Rh-diene complex. Under the optimal reaction conditions, the reactions furnished products **259a-r** with modest to excellent yields and with high degrees of enantioselectivity. The successful application of this strategy was proven by a brief synthesis of (*S*)-pregabalin and (-)- α -kainic acid. The use of substituted alkenyl trifluoroborates afforded products that were obtained generally in higher yields, thus unexpectedly showing that increased steric hindrance was favorable to the reaction (Table 83).²⁵³

Scheme 133.

Table 83. Substrate scope of the rhodium-catalyzed stereoselective alkenylation reaction.

Entry	1/258	R 28	Yield (%)	<i>ee</i> (%)
1	258a	CH=C(Me) ₂	259a : 97	99
2	258a	CMe=CH ₂	259b : 82	99
3	258a	CMe=C(Me) ₂	259c : 93	99
4	258a	CH=CHBn	259d : 43	97
5	258a	CH=CHCy	259e : 55	98
6	258a	CH=CH <i>n</i> Pr	259f : 79	99
7	258a	cyclohexene	259g : 97	99

8	258a	CH=CHPh	259h : 81	99
9	258a	CH=CH(4-MeOC ₆ H ₄)	259i : 85	99
10	258a	CH=CH(4-ClC ₆ H ₄)	259j : 66	99
11	258b	CH=C(Me) ₂	259k : 98	94
12	258b	CMe=CH ₂	259l : 82	94
13	258b	CH=CHPh	259m : 99	91
14	1h	CH=CHPh	259n : 78	99
15	1g	CH=CHPh	259o : 74	93
16	1b	CH=CHBn	259p : 88	98
17	1e	CH=CHPh	259q : 97	99
18	1a	CH=CHPh	259r : 93	78

The conjugate addition reaction of potassium trifluoro-2-(*E*)-phenylethenylborate and [5*H*]-furan-2-one catalyzed by Rh-complex with the ligand (*S,S*)-**L20a** as an example, showed that the alkenyl rhodium intermediate prefers to coordinate to the *Re* face of the lactone to minimize steric repulsions between the phenyl groups on the diene and the lactone, hence resulting in the product **259n** with an (*R*)-configuration (Figure 14). The configuration of other adducts could be assigned as (*R*) by presuming they had a similar pathway.²⁵³

Figure 14. Possible stereochemistry-defining pathway

Recently, several A-B type sterically regular bicyclo[3.3.0]diene-based polymers were prepared as immobilized chiral diene ligands and employed for transition-metal-catalyzed stereoselective reactions by Xu et al.. By employing polymeric diene **L68**, good to excellent enantioselectivities were accomplished in the Rh-catalyzed stereoselective 1,4-addition of arylboronic acids **2** to α,β -unsaturated ketones **1a**, **b**. Products **262a-j** were obtained in satisfactory chemical yields and with good to excellent enantioselectivities (up to 94% *ee*). This work should open a gateway for

the further design and development of new polymeric chiral ligands for stereoselective catalysis (Scheme 134).²⁵⁴

Table 84. Stereoselective 1,4-addition of arylboronic acids catalyzed by Rh/immobilized diene ligand **L68**.

Entry	1	Ar 2	Yield (%)	<i>ee</i> (%)
1	1a	Ph	262a : 94	78
2	1a	1-naphthyl	262b : 91	84
3	1b	Ph	262c : 98	85
4	1b	4-MeOC ₆ H ₄	262d : 94	89
5	1b	4-MeC ₆ H ₄	262e : 92	80
6	1b	4-FC ₆ H ₄	262f : 92	82
7	1b	4-BrC ₆ H ₄	262g : 96	72
8	1b	4-ClC ₆ H ₄	262h : 92	76
9	1b	2-MeOC ₆ H ₄	262i : 96	78
10	1b	1-naphthyl	262j : 94	94

Catalytic enantioselective reactions, particularly enantioselective C-C bond formations, in water as the sole solvent or aqueous media, is currently one of the significant goals for stereoselective synthesis. A green^{255, 256} and highly enantioselective micellar catalytic strategy for the 1,4-

Reaction scheme for the asymmetric allylation of cyclohexenones:

Reaction 1: Cyclohexenone **1a-c, g** reacts with ArB(OH)_2 (2) in the presence of $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2 / \text{L69}$ (surfactant / H_2O (10 : 1), KOH , r.t.) to yield product **263a-l**.

Structure of **L69** (sulfonamido-olefin):

Structure of **SDS** (Sodium Dodecyl Sulfate):

Structure of **PTS** (Poly(2,2,6,6-tetramethyl-1,3-pyridine) Sulfonate):

Structure of **surfactant** (Poly(2,2,6,6-tetramethyl-1,3-pyridine) Sulfonate):

Table 85. Substrate scope of the Rh-catalyzed 1,4-addition of boronic acids to cycloalkenones in H₂O/surfactant media.

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4	1c	PTS	Ph	263d : 100	99
5	1g	SDS	Ph	263e : 85	99
6	1g	PTS	Ph	263f : 100	99
7	1a	SDS	4-MeC ₆ H ₄	263g : 85	76
8	1a	PTS	4-MeC ₆ H ₄	263h : 94	98
9	1a	SDS	3-MeC ₆ H ₄	263i : 57	90
10	1a	PTS	3-MeC ₆ H ₄	263j : 84	94
11	1a	SDS	2-MeOC ₆ H ₄	263k : 99	92
12	1a	PTS	2-MeOC ₆ H ₄	263l : 99	94

To further uncover the scope of the reaction, the stereoselective 1,4-additions of other arylboronic acids bearing electron donating or withdrawing substituents **2** to *N*-Me-maleimide **38a** were conducted at 0 or −10 °C (Table 86). Although the reactions of arylboronic acids required longer reaction times to complete in comparison with those of **2** (= PhB(OH)₂), the yields and enantioselectivities of product **264** were over 90%, even when just 0.5 mol of % Rh/(*R*)-**L27** were utilized. Therefore, it can be concluded that low temperature reactions using the Rh/(*R*)-**L27** catalyst were sufficient for preceding the 1,4-addition of arylboronic acids to *N*-R-maleimides to completion. When the stereoselective 1,4-addition of **2** to *N*-R maleimide (R = Cy **38b**, Bn **38c**, or Ph **38d**) was conducted at −10 °C, products **264i–k** were obtained with over 90% *ee*. Substrates **38bc** and **38d** afforded virtually enantiomerically pure products (Scheme 136, Table 86).²⁶²

Scheme 136.

Table 86. Stereoselective 1,4-addition of arylboronic acids **2** to *N*-R-maleimide **38**.

Entry	38	Ar 2	Temperature	Yield (%)	<i>ee</i> (%)	Config.
1	38a	2-FC ₆ H ₄	0	264a : 99	91	-
2	38a	2-MeOC ₆ H ₄	0	264b : 97	95	-

3	38a	3-FC ₆ H ₄	0	264c : 99	91	(<i>R</i>)
4	38a	3-ClC ₆ H ₄	0	264d : 98	92	(<i>R</i>)
5	38a	3-MeOC ₆ H ₄	-10	264e : 96	94	(<i>R</i>)
6	38a	3-MeC ₆ H ₄	-10	264f : 92	94	(<i>R</i>)
7	38a	3,5-(Me) ₂ C ₆ H ₃	0	264g : 98	94	-
8	38a	4-FC ₆ H ₄	0	264h : 98	95	(<i>R</i>)
9	38c	Ph	-10	264i : 95	95	(<i>R</i>)
10	38b	Ph	-10	264j : 96	99	(<i>R</i>)
11	38d	Ph	-10	264k : 95	99	(<i>R</i>)
12	38e	Ph	-10	264l : 10	-	-
13	38e	Ph	-10	264m : 96	84	(<i>R</i>)
14	38e	Ph	-50	264n : 94	87	(<i>R</i>)
15	38e	Ph	-80	264o : 72	87	(<i>R</i>)

Rh-catalyzed stereoselective 1,4-additions of arylboronic acids **2** to diverse α,β -unsaturated carbonyl compounds **1a** were accomplished at temperatures below 0 °C with Rh/MeO-F₁₂-BIPHEP catalysis. Catalyst Rh/(*R*)-**L27** was beneficial in the stereoselective synthesis of a series of biologically active compounds via stereoselective 1,4-addition reactions under below 0 °C (Scheme 137).²⁶²

Scheme 137. Stereoselective 1,4-addition of **2** to **1a** at 0 °C.

An effective Rh/olefin–sulfoxide catalyzed stereoselective conjugate addition of organoboronic acids **2** to diverse linear unsaturated esters **266** has been developed which afforded moderate to high yields and good enantioselectivities by the utilization of an appropriate 2-methoxy-1-naphthyl sulfinyl functionalized olefin ligands. Furthermore, it was found can be applied to unsaturated methyl esters giving up to 99% yield and 91% *ee*. A wide range of *tert*-butyl-, ethyl-, benzyl-, methyl cinnamates were well tolerated in this process.

With the optimized reaction conditions established, the scope of this reaction was then studied. A wide range of representative boronic acids **2** and unsaturated esters **266** were examined in this reaction under the already concluded optimized conditions. The results are illustrated in Table 87.²⁶³

Scheme 138.

Table 87. Scope of the Rh-catalyzed stereoselective addition of arylboronic acids to unsaturated esters

Entry	266		Ar 2	Yield (%)	<i>ee</i> (%)
	Ar ¹	R			
1	Ph	Me	4-MeOC ₆ H ₄	267a : 85	89
2	Ph	<i>t</i> Bu	4-MeOC ₆ H ₄	267b : 62	87
3	Ph	Et	4-MeOC ₆ H ₄	267c : 81	89
4	Ph	Bn	4-MeOC ₆ H ₄	267d : 83	70
5	Ph	Me	2-MeOC ₆ H ₄	267e : 76	89
6	Ph	Me	4-MeC ₆ H ₄	267f : 92	86
7	Ph	Me	4- ^{<i>t</i>} BuC ₆ H ₄	267g : 91	89
8	Ph	Me	1-naphthyl	267h : 60	83
9	Ph	Me	2-naphthyl	267i : 99	79
10	Ph	Me	3,4-(MeO) ₂ C ₆ H ₃	267j : 95	88
11	Ph	Me	Ph	267k : 93	89
12	Ph	Me	Ph	267l : 88	89
13	Ph	Me	Ph	267m : 73	91

14	Ph	Me	Ph	267n : 92	91
15	4-MeOC ₆ H ₄	Me	Ph	267o : 83	90
16	4-FC ₆ H ₄	Me	Ph	267p : 85	90
17	4-FC ₆ H ₄	Me	Ph	267q : 62	90

Highly enantioselective additions of differently substituted arylboronic acids **2** to diverse β -nitro-based Michael acceptors **180a-i** under the control of a novel and efficient Rh-bicyclo[2.2.1]diene catalyst (S/C (substrate/catalyst) up to 1000) were successfully performed, affording β,β -diaryl nitroethanes **268a-z** in good to high yields (62-99%) and with high to excellent enantioselectivities (85-97% *ee*) (Table **88**).²⁶⁴ This strategy was expanded to 2-heteroarylnitroolefins and 2-alkylnitroolefins, which also gave the desired products with high enantioselectivities and yields via Rh-**L50** complex catalysis. Comparing the use of bicyclo[3.3.0]diene ligands in the stereoselective arylation reaction of some β -nitroolefins and nucleophiles, it can be seen that this system needs lower catalyst loadings at lower temperature to give the desired products with equal or even better enantioselectivity. This strategy was employed for the synthesis of chiral 1-phenyltetrahydro-1H-3-benzazepine effectively (Figure 15). The latter is a well-known intermediate in the synthesis of biologically active *ent*-SKF 38393.²⁶⁴

Figure 15.

Scheme 139.

Table 88. Stereoselective conjugate addition to substituted β -nitrostyrenes **2** catalyzed by $[\text{RhCl}(\mathbf{1d})]_2$.

Entry	R 180	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	180a : 4-MeC ₆ H ₄	Ph	268a : 99	92	(<i>S</i>)
2	180a : 4-MeC ₆ H ₄	4-ClC ₆ H ₄	268b : 84	93	(<i>R</i>)
3	180a : 4-MeC ₆ H ₄	3-NO ₂ C ₆ H ₄	268c : 81	94	(<i>R</i>)
4	180a : 4-MeC ₆ H ₄	4-NO ₂ C ₆ H ₄	268d : 96	94	(<i>R</i>)
5	180a : 4-MeC ₆ H ₄	4-CNC ₆ H ₄	268e : 83	94	(<i>R</i>)
6	180a : 4-MeC ₆ H ₄	4-CF ₃ C ₆ H ₄	268f : 90	93	(<i>R</i>)
7	180a : 4-MeC ₆ H ₄	4-FC ₆ H ₄	268g : 82	95	(<i>R</i>)
8	180a : 4-MeC ₆ H ₄	3-ClC ₆ H ₄	268h : 68	91	(<i>R</i>)
9	180a : 4-MeC ₆ H ₄	3-CF ₃ C ₆ H ₄	268i : 67	93	(<i>R</i>)
10	180a : 4-MeC ₆ H ₄	4- ^t BuC ₆ H ₄	268j : 99	89	(<i>R</i>)
11	180a : 4-MeC ₆ H ₄	3-MeOC ₆ H ₄	268k : 90	91	(<i>R</i>)
12	180a : 4-MeC ₆ H ₄	4-PhC ₆ H ₄	268l : 71	95	(<i>R</i>)
13	180a : 4-MeC ₆ H ₄	1-naphthyl	268m : 90	96	(<i>R</i>)
14	180a : 4-MeC ₆ H ₄	2-naphthyl	268n : 70	91	(<i>R</i>)
15	180b : Ph	4-MeC ₆ H ₄	268o : 85	90	(<i>R</i>)
16	180b : Ph	4-ClC ₆ H ₄	268p : 94	93	(<i>R</i>)
17	180c : 4-ClC ₆ H ₄	4-MeC ₆ H ₄	268q : 81	89	(<i>S</i>)
18	180d : 2-MeOC ₆ H ₄	4-MeC ₆ H ₄	268r : 93	91	(<i>S</i>)
19	180e : 3,4-(MeO) ₂ C ₆ H ₃	Ph	268s : 71	95	(<i>S</i>)
20	180f : 2-furyl	4-MeC ₆ H ₄	268t : 89	89	(<i>R</i>)
21	180f : 2-furyl	4-CNC ₆ H ₄	268u : 92	92	(<i>R</i>)
22	180g : 2-thienyl	4-MeC ₆ H ₄	268v : 99	91	(<i>R</i>)
23	180g : 2-thienyl	4-CNC ₆ H ₄	268w : 94	92	(<i>R</i>)
24	180h : isopropyl	Ph	268x : 81	95	(<i>R</i>)
25	180h : isopropyl	4-MeOC ₆ H ₄	268y : 86	91	(<i>R</i>)
26	180i : cyclohexyl	Ph	268z : 93	89	(<i>R</i>)

An efficient stereoselective addition of arylboronates to aryl-substituted cyclic ketimines proceeded smoothly in the presence of the Rh coordinated chiral diene ligand acting as a chiral catalyst to afford sulfamidates and sulfamides in high yields and with excellent enantioselectivity (up to 99% *ee*). The stereoselective synthesis of *gem*-diaryl substituted sulfamidates and sulfamides *via* the enantioselective addition of a series of arylboronates **270** to cyclic ketimines

269a-k catalyzed by Rh-chiral diene complexes has also been achieved. Using this approach, enantiomerically pure sulfamidates and sulfamide **271a-p** were converted into chiral α -tertiary amine derivatives with no appreciable loss of their enantiomeric excess in high chemical yields. The results are outlined in Table 89 (up to 99% *ee*).²⁶⁵

Scheme 140.

Table 89. Rhodium-catalyzed stereoselective arylation of cyclic ketimines **269**.

Entry	Ar ¹ 269	Ar 270	Yield (%)	<i>ee</i> (%)
1	269a : Ph	4-MeC ₆ H ₄	271a : 98	93
2	269a : Ph	3-MeC ₆ H ₄	271b : 97	92
3	269a : Ph	2-MeC ₆ H ₄	271c : 81	98
4	269a : Ph	4-MeOC ₆ H ₄	271d : 97	92
5	269a : Ph	3,4-(OCH ₂ O) ₂ C ₆ H ₃	271e : 97	92
6	269a : Ph	3,4,5-(OMe) ₃ C ₆ H ₂	271f : 98	94
7	269a : Ph	2-naphthyl	271g : 97	94
8	269a : Ph	4-FC ₆ H ₄	271h : 98	93
9	269a : Ph	4-ClC ₆ H ₄	271i : 98	94
10	269a : Ph	4-CF ₃ C ₆ H ₄	271j : 94	95
11	269a : Ph	1-cyclohexenyl	271k : 92	99
12	269b : 4-MeOC ₆ H ₄	4-MeC ₆ H ₄	271l : 96	94
13	269c : 4-FC ₆ H ₄	4-MeC ₆ H ₄	271m : 97	94
14	269d : 4-ClC ₆ H ₄	4-MeC ₆ H ₄	271n : 99	94
15	269e : 4-BrC ₆ H ₄	4-MeC ₆ H ₄	271o : 93	92
16	269f : 2-furyl	4-MeC ₆ H ₄	271p : 98	91

The reactions of sulfamide ketimines **269g** and **269h** with *p*-tolylboronate **270** mediated by the Rh/(*S,S*)-Fc-tfb***L53** as the catalytic system also proceeded smoothly, resulting in the formation sulfamides **271g** and **271h** in 70% and 78% yields, respectively, and with high enantioselectivity

(Scheme 141). It has also been found that the reaction of cyclic *N*-sulfonylimine **269i** affords the arylation product **271i** in 84% chemical yield and with high enantioselectivity (95% *ee*).²⁶⁵

271g: X = NCO₂-*t*-Bu, Temp = 80 °C, yield = 70%, *ee* = 95%
271h: X = NCO₂CH₂Ph, Temp = 80 °C, yield = 78%, *ee* = 93%
271i: X = CH₂, Temp = 60 °C, yield = 84%, *ee* = 95%

Scheme 141.

Although the use of Rh/(*S,S*)-Fc-tfb***L53** as the catalytic system provided moderate enantioselectivity (56% *ee*) in the reaction of ketimine **1j** under conventional conditions, a higher enantioselectivity was obtained for **269j** when using chiral diene ligand (*R*)-**L71**,²⁶⁶ in the presence K₃PO₄ as a base affording **271j** in 93% yield and 79% *ee* (Scheme 142). In a similar fashion, the reaction of **269k** afforded **271k** with high enantioselectivity (91%).²⁶⁵

Scheme 142.

A novel and direct strategy to obtain enantiomerically pure α -amino phosphonate and phosphinate derivatives employing Rh-catalyzed stereoselective 1,4-additions of potassium trifluoroorganoborates **28** was developed for the synthesis of dehydroamino phosphorus compounds **272a,b** in good chemical yields and with excellent enantioselectivities (up to 96%) utilizing Difluorphos as a chiral ligand. This efficient and facile strategy allows the rapid formation of libraries of such compounds with high levels of enantioselectivity. Several optimizations of the conditions were attempted. After several attempts $[\text{RhCl}(\text{CH}_2\text{CH}_2)_2]_2$ as the Rh catalyst and Difluorphos as the chiral were established as the optimal choices. When isopropanol was used as the solvent and NaHCO_3 as the base, the reaction proceeded smoothly and cleanly to afford α -aminophosphonates **273a-k** with improved yields and with high degrees of enantioselectivity (Table 90).²⁶⁷

Scheme 143.

Table 90. Rhodium-catalyzed addition of potassium aryltrifluoroborates to dehydroaminophosphonates.

Entry	R 272	Ar 28	Yield (%)	<i>ee</i> (%)
1	272a : Ac	Ph	273a : 91	94
2	272a : Ac	Ph	273b : 65	96
3	272b : Bz	Ph	273c : 69	92 ®
4	272a : Ac	4-FC ₆ H ₄	273d : 65	92
5	272a : Ac	4-ClC ₆ H ₄	273e : 72	93
6	272a : Ac	3-ClC ₆ H ₄	273f : 80	94
7	272a : Ac	4-CF ₃ C ₆ H ₄	273g : 86	94
8	272a : Ac	3-CF ₃ C ₆ H ₄	273h : 84	94
9	272a : Ac	4- <i>t</i> -BuC ₆ H ₄	273i : 76	91
10	272a : Ac	4-MeOC ₆ H ₄	273j : 51	94
11	272a : Ac	3-MeOC ₆ H ₄	273k : 77	90

These reaction conditions showed a wide scope and were not limited to the synthesis of enantiomerically pure α -aminophosphonates. Under similar conditions, the addition of potassium phenyltrifluoroborate **272a** to **272c** provided good yields of diastereoisomeric α -amino phosphinates **273l** and **273l'** (Scheme 144) with virtually identical enantiomeric excesses (94% and 92% *ee* respectively).²⁶⁷

Scheme 144.

These conditions were also found to be suitable for the 1,4-addition of differently arylboronic acids, but with a slightly lower enantioselectivity. For instance, the Rh-catalyzed stereoselective 1,4-addition of phenylboronic acid to **272a** gave (*R*)-amino phosphonate **273m** in 92% yield and with 93% ee (Scheme 145).²⁶⁷

Scheme 145.

Xu et al. reported the highly enantioselective synthesis of chiral 3-aryl-1-indanones **275a-o** via a rhodium catalyzed intramolecular 1,4-addition of pinacolboranechalcone derivatives **274a-o** using structurally simple MonoPhos as the chiral ligand under relatively mild reaction conditions. This provided ready access to a wide range of enantiopure 3-aryl-1-indanone derivatives in high yields (up to 95%) and with excellent enantioselectivities (up to 95% ee). Contrary to previously well-established strategies, this stereoselective intramolecular 1,4-addition protocol offers a general and efficient approach with respect to substrate scope and reaction stereocontrol. Furthermore, the use of structurally simple MonoPhos ligand presents outstanding synthetic and economic merits over using expensive and complex bisphosphine ligands. With the optimal conditions in hand the reaction substrate scope using (*R*)-MonoPhos **L2** as the chiral ligand was next investigated. As outlined in Scheme 146, various pinacolborane chalcone derivatives with diverse steric and electronic properties were tested. All substrates were

subjected to a clean and smooth reaction to furnish the desired optically active 3-aryl-1-indanones **275** in high to excellent yields (82–95%) and with high to excellent enantioselectivities (81-95% *ee*) at 80 °C. Interestingly both electron-donating and withdrawing groups substituted on the phenyl rings were well tolerated (Scheme 146).²⁶⁸

- 275a:** R = H, Ar = Ph, yield = 82%, *ee* = 82%
275b: R = H, Ar = 4-FC₆H₄, yield = 93%, *ee* = 88%
275c: R = H, Ar = 4-ClC₆H₄, yield = 95%, *ee* = 94%
275d: R = H, Ar = 3,4-Cl₂C₆H₄, yield = 88%, *ee* = 91%
275e: R = H, Ar = 4-CF₃C₆H₄, yield = 80%, *ee* = 95%
275f: R = H, Ar = 4-MeC₆H₄, yield = 90%, *ee* = 91%
275g: R = H, Ar = 4-^tBuC₆H₄, yield = 86%, *ee* = 89%
275h: R = H, Ar = 4-PhC₆H₄, yield = 92%, *ee* = 95%
275i: R = H, Ar = 2-naphthyl, yield = 95%, *ee* = 94%
275j: R = H, Ar = 2-MeOC₆H₄, yield = 80%, *ee* = 84%
275k: R = H, Ar = 3-MeOC₆H₄, yield = 89%, *ee* = 82%
275l: R = H, Ar = 4-MeOC₆H₄, yield = 92%, *ee* = 95%
275m: R = 4-F, Ar = 4-ClC₆H₄, yield = 90%, *ee* = 94%
275n: R = 5-F, Ar = 4-ClC₆H₄, yield = 92%, *ee* = 93%
275o: R = 5-MeO, Ar = 4-ClC₆H₄, yield = 90%, *ee* = 81%

Scheme 146. [Rh(C₂H₄)₂Cl]₂/L2-catalyzed asymmetric intramolecular 1,4-addition.

The CCC–NHC pincer Rh complex is stable in air and in water. It has successfully catalyzed the 1,4-addition of aromatic boronic acids **2** to cyclic and acyclic α,β-unsaturated enones **1a-c,e,v,t** and enals in methanol and water as solvents in satisfactory yields. The scope of boronic acids was extended to include aromatic heterocyclic compounds. Encouraging results were obtained in the 1,4-addition of nitrogen heterocycles, which frequently show biological activity.^{270, 271} Moreover, high yields were obtained while using ‘green’ alcohol/water systems as solvents (Scheme 147).²⁶⁹

Scheme 147.

Table 91. Scope of cyclohexenone with ArB(OH)₂ and heterocycle boronic acids.

Entry	1	Ar 2	Yield(%)
1	1a	Ph	276a : 92(80°C)
			276a : 99(r.t.)
			276a : 99(50°C)
			276a : 86(50°C)
			276a : 69(50°C)
2	1b	Ph	276b : 78(80°C)
			276b : 99(80°C)
4	1c	Ph	276c : 94(80°C)
			276c : 15(50°C)
			276c : 99(80°C)
5	1e	Ph	276d : 68(80°C)
			276d : 86(50°C)
			276d : 96(80°C)
6	1v	Ph	276e : 40(80°C)
			276e : 20(50°C)
			276e : 99(80°C)
7	1t	Ph	276f : 91(80°C)
			276f : 77(50°C)
			276f : 99(80°C)
9	1a	4-MeC ₆ H ₄	276g : 77(80°C)

			276g: 97(80°C) 276h: 70(80°C) 276h: 99(80°C)
10	1a	2-MeC ₆ H ₄	
11	1a	2,4,6- <i>tri</i> -MeC ₆ H ₂	276i: 76(80°C) 276i: 99(80°C)
12	1a	4- <i>tert</i> -butyl	276j: 81(80°C) 276j: 98(80°C)
13	1a	naphthalen-1-yl	276k: 80(80°C) 276k: 99(80°C)
14	1a	3-BrC ₆ H ₄	276l: 64(80°C) 276l: 62(80°C) 276l: 99(80°C)
15	1a	3,5- <i>di</i> -BrC ₆ H ₃	276m: n.d.(80°C)
16	1a	4-O ₂ NC ₆ H ₄	276n: 34(80°C) 276n: 22(80°C) 276n: 46(80°C)
17	1a	2-OMeC ₆ H ₄	276o: 92(80°C) 276o: 99(80°C)
18	1a	4-O ₂ CMeC ₆ H ₄	276p: 92(80°C) 276p: 99(80°C)
19	1a		276q: 22(80°C) 276q: 77(80°C)
20	1a		276r: 46(80°C) 276r: 69(80°C)
21	1a		276s: n.d.(80°C)
22	1a		276t: 87(80°C) 276t: 99(80°C)
23	1a		276u: 36(80°C) 276u: 83(80°C)
24	1a		276v: n.d.(80°C)

There are remarkable differences in stereoselective inductions for pseudoenantiomeric carbohydrate olefin ligands in Rhodium(I)-catalyzed 1,4-addition reactions. In order to gain further insight, a set of new olefin ligands divergent in the relative configuration and pyranoside configuration were designed and synthesized. It was found that the pseudoenantiomeric ligand pair **L74b** and *ps-ent*-**L74c** always afforded steadily high *ee* values for bulky boronic acids, as well as chiral and achiral enones.²⁷² This fact led to the elucidation of the structural requirements for metal binding, as well as providing a well determined and an enriched alternative for one pseudoenantiomer. Furthermore, an effective kinetic resolution of racemates, *O*-TBS-protected 4-hydroxycyclopentenones via 1,4-addition was performed to recover the starting material with excellent *ee*.²⁷²

The novel ligands for the 1,4-addition reactions were synthesized and used to ligate with rhodium to make a chiral Rh-catalyst, which was employed in order to compare the results with those obtained when *gluco*- and *galacto-eno* Phos were used²⁷³ (Table 92). Experimentally, with cyclohexenone **1a** and phenylboronic acid **2**, **L74d**, **L74f** and *ps-ent*-**L74e** gave excellent *ee* values similar to **L74a** and *ps-ent*-**1a**. Thus, the bulky trityloxy residue of **L74a**, **L74b** and *ps-ent*-**L74c**, is not an essential for an effective stereoselective induction. The origin of the stereoselective induction is the positioning of the 4-phosphinite relative to the plane of the pyranoside. Ligands with a phosphinite oriented below the pyranoside plane gave (*R*)-**277**, rhamno- and galacto-ligands *ps-ent*-**L74e** and *ps-ent*-**L74c** with a phosphinite placed above the pyranoside plane, to afford (*S*)-**277** (Table 92).²⁷²

Scheme 148.

Table 92. 1,4-Additions of boronic acids to enones in the presence of **1a**, **b**, **d**, **f** and *ps-ent*-**c**, **e**

Entry	1	Ln	Ar 2	Yield (%)	<i>ee</i> (%)	Config.
1	1a	<i>cis</i> - L74d	Ph	92	97	(<i>R</i>)
2	1a	<i>trans</i> - L74f	Ph	80	98	(<i>R</i>)
3	1a	<i>trans</i> - L74a	Ph	80	99	(<i>R</i>)
4	1a	<i>ps-ent</i> - L74e	Ph	88	98	(<i>S</i>)
5	1a	<i>ps-ent</i> - L74c	Ph	92	99	(<i>S</i>)
6	1a	<i>cis</i> - L74d	2-MeOC ₆ H ₄	96	95	(<i>R</i>)
7	1a	<i>trans</i> - L74f	2-MeOC ₆ H ₄	78	87	(<i>R</i>)
8	1a	<i>trans</i> - L74b	2-MeOC ₆ H ₄	94	60	(<i>R</i>)
9	1a	<i>ps-ent</i> - L74e	2-MeOC ₆ H ₄	80	66	(<i>S</i>)
10	1a	<i>ps-ent</i> - L74c	2-MeOC ₆ H ₄	96	93	(<i>S</i>)
11	1a	<i>cis</i> - L74d	CH=CH-tol	98	86	-
12	1a	<i>trans</i> - L74a	CH=CH-tol	54	78	-
13	1a	<i>ps-ent</i> - L74e	CH=CH-tol	88	80	+
14	1a	<i>ps-ent</i> - L74c	CH=CH-tol	90	96	+
15	1b	<i>cis</i> - L74d	naphthalen-1-yl	76	92	+
16	1b	<i>trans</i> - L74a	naphthalen-1-yl	37	98	+
17	1b	<i>ps-ent</i> - L74e	naphthalen-1-yl	49	90	-
18	1b	<i>ps-ent</i> - L74c	naphthalen-1-yl	77	94	-
19	1b	<i>cis</i> - L74d	4-CF ₃ C ₆ H ₄	63	92	(<i>R</i>)
20	1b	<i>trans</i> - L74a	4-CF ₃ C ₆ H ₄	34	79	(<i>R</i>)
21	1b	<i>ps-ent</i> - L74e	4-CF ₃ C ₆ H ₄	30	93	(<i>S</i>)
22	1b	<i>ps-ent</i> - L74c	4-CF ₃ C ₆ H ₄	66	92	(<i>S</i>)

When enantioriched enone **8**^{273, 274} (Table 93) was used under substrate control, the 1,4- addition of boronic acid **2** preferentially gave *trans*-**279**. The *fuco*-ligand **L74e**, as well as *gluco*-ligand **L74c**, resulted in the formation of *cis*-**279**, leading to a mismatched incorporation of substrate and catalyst control. Both ligands overpowered the substrate control, but *fuco*-ligand **L74e** was found to be superior by improving the *cis/trans* ratio. When the reaction was performed in the presence of *ps-ent*-**L74c** and *ps-ent*-**L74e**, a matched incorporation of reagent and catalyst control occurred. The *cis/trans* ratio of **279** was virtually identical for both ligands, and *galacto*-enoPhos *ps-ent*-**L74b** afforded a higher chemical yield (Scheme 149).²⁷²

Scheme 149.

Table 93. 1,4-Addition of boronic acid **2** to enone **278**.

Entry	Ln	Rh(I)	Product 279	
			Yield (%) <i>cis</i> / <i>trans</i>	
1	-	[Rh(cod)OH] ₂	93	20:80
2	<i>cis</i> - L74d	[RhCl(C ₂ H ₄) ₂] ₂	92	95:5
3	<i>trans</i> - L74a	[RhCl(C ₂ H ₄) ₂] ₂	78	89:11
4	<i>ps-ent</i> - L74e	[RhCl(C ₂ H ₄) ₂] ₂	79	7:93
5	<i>ps-ent</i> - L74c	[RhCl(C ₂ H ₄) ₂] ₂	86	6:94

The in situ synthesized $[\text{Rh}(\text{OH})_6]^{3-}$ complex interacted into an anion exchangeable Ni–Zn layered hydroxy double salt (Rh/NiZn) was successfully carried out in 2014. The obtained Rh/NiZn efficiency catalyzed the 1,4-addition of divergent enones and differently substituted phenylboronic acids to their respective β -substituted carbonyl compounds. The $[\text{Rh}(\text{OH})_6]^{3-}$ complex preserved its original monomeric trivalent state within the NiZn interlayer following catalysis, due to the strong electrostatic interaction that existed between the NiZn host and anionic Rh(III) complex. The interchelated, monomeric, trivalent Rh hydroxide type was stabilized by the NiZn matrixes, while the reaction could be recycling with no appreciable loss of deactivation. The application of this catalyst in stereoselective 1,4-addition reactions via the hydrophenylation of terminal alkynes with phenylboronic acid **2** led to substituted alkene **1a** (Scheme 150).²⁷⁵

Scheme150. Substrate screening of 1,4-addition reaction with the Rh/NiZn catalyst

It has been revealed that planar-chiral alkenylene-bridged (phosphino- π -arene)-(phosphine)chromium complexes **L75** can coordinate to a Rh(I) cation via a bidentate manner at the (π -arene)-bound phosphorus atom and at the olefin double bond. This was confirmed by NMR and X-ray analysis. The *P*-olefin chelate coordination of **L75** brings about the required chiral environment at the metal center. Thus, these Rh complexes show high performances in different rhodium-catalyzed stereoselective 1,4-addition reactions with differently substituted arylborons as nucleophiles. The controlled experiments indicated that the (η^2 -olefin)-Rh interaction as well as the bridging structure in **L75** play key roles in the induction of high enantioselectivity of these rhodium-catalyzed stereoselective reactions. With the enantioselective chiral ligand **L75b** in hand, its efficiency was tested. The results are illustrated in Scheme 151. Significantly, it was observed that the Michael addition to 2-cyclohexenone could be carried out by using other arylboron nucleophiles, i.e. *p*-tolyl- and *p*-(trifluoromethyl)phenylboronic acids, catalyzed by Rh/(*S*)-**L75b** catalyst, to afford the corresponding (*S*)-**L75a** arylcyclohexanones with excellent enantioselectivities (>97% *ee.*) However, it was observed that the reactions with acyclic enones were challenging (Table 94).²⁷⁶

Scheme 151.

Table 94. Rhodium-catalyzed stereoselective 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds.

Entry	1/38	Ar 2	Ln	Rh-source	Yield (%)	ee (%)	Config.
1	1a	4-MeC ₆ H ₄	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281a : >99	98.4	(S)
2	1a	4-CF ₃ C ₆ H ₄	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281b : 95	97	(S)
3	1b	Ph	(R)- L75a	[RhCl(C ₂ H ₄) ₂] ₂	281c : 95	99.5	(R)
4	1b	Ph	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281d : 92	99.9	(S)
5	1g	Ph	(R)- L75a	[RhCl(C ₂ H ₄) ₂] ₂	281e : 89	99.4	(R)
6	1g	Ph	(S)- L75b	[RhOH(cod)] ₂	281f : 95	99.5	(S)
7	38c	Ph	(R)- L75a	[RhOH(cod)] ₂	281g : 85	81	(R)
8	38c	Ph	(S)- L75b	[RhOH(cod)] ₂	281h : 83	94	(S)
9	1z	Ph	(R)- L75a	[RhCl(C ₂ H ₄) ₂] ₂	281i : 31	57	(S)
10	1z	Ph	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281j : 34	88	(R)
11	1e	Ph	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281k : 4	-	-
12	1e	Ph	(R)- L75a	[RhCl(C ₂ H ₄) ₂] ₂	281l : 13	58	(S)
13	1e	Ph	(S)- L75b	[RhCl(C ₂ H ₄) ₂] ₂	281m : 43	88	(R)

The stereochemical control of this 1,4-addition mediated by Rh/(*R*)-**L75a** is illustrated in Scheme 152. The phenyl rhodium species is positioned to have a *trans*-relationship with the Rh-bonded phenyl group and the olefin ligand, in a way that 2-cyclohexenone binds to the Rh center with its *re* face at the *cis*-position of the olefin ligand. In this way the steric interaction with the chiral ligand is minimized. Insertion of cyclohexenone to the Rh-Ph bond followed by hydrolysis affords an (*R*)-1,4-adduct. In contrast, coordination of cyclohexenone to Rh with the *si* face due to the steric repulsion between the cyclohexene and the methyl group on the olefin tether is disfavored (Scheme 152).²⁷⁶

Scheme 152. Proposed stereochemical pathway for the Rh/(*R*)-**L75a**-catalyzed enantioselective 1,4-addition of phenylboronic acid to 2-cyclohexan-1-one.

The Rh(I)-catalyzed 1,4-addition of aryl and alkenylboronic acids to α,β -unsaturated carbonyl compounds **1a** is a well-known reaction. However, studies regarding the transfer of heteroaryl residues have largely been overlooked. An extensive investigation into heteroarylboronates **285**, **286** in racemic and stereoselective Rh-catalyzed 1,4-additions has been carried out and reported. Several adducts bearing heteroaryl residues were obtained in moderate to excellent yields under racemic conditions. The stereoselective type of the reaction confirmed it to be highly susceptible to the electronic properties of the heteroaryl substituents, with boronates bearing electron-rich residues affording only moderate chemical yields but constantly high enantiomeric excesses (Scheme 153, Table 95).²⁷⁷

Scheme 153.

Table 95. Stereoselective 1,4-addition of heteroaryl MIDA boronates and pinacol boronates to cyclohexenone.

Entry	Ar (285/286)	Ln	Yield (%)	<i>ee</i> (%)	Config.
286a:					
1		L76a	287a: 88	97	(<i>R</i>)
286a:					
2		L76a	287b: 65	91	(<i>R</i>)
286b:					
3		<i>ps-ent</i> - L76c	287c: 56	96	(<i>S</i>)
286b:					
4		L76a	287d: 77	95	(<i>R</i>)
5	286b:	<i>ps-ent</i> - L76c	287e: 56	98	(<i>S</i>)

	286b:				
6		L76a	287f: 33	90	+
	286c:				
7		<i>ps-ent</i> - L76b	287g: 44	94	-
	286c:				
8		L76a	287h: 80	95	+
	286c:				
9		<i>ps-ent</i> - L76b	287i: 37	97	-
	286d:				
10		L76a	287g: 24	91	+
	286d:				
11		<i>ps-ent</i> - L76c	287k: 19	93	-
	285a:				
12		L76a	287l: 37	89	+
	286e:				
13		L76a	287m: 15	90	-
14	286e:	<i>ps-ent</i> - L76c	287n: 10	95	+

	285b:				
15		L76a	287o: 11	93	-
	286f:				
16		L76a	287p: 14	81	-
	286f:				
17		<i>ps-ent</i> - L76c	287q: 16	90	+
	285c:				
18		L76a	287r: 19	71	-
	285d:				
19		L76a	287s: 81	82	+
	285e:				
20		<i>ps-ent</i> - L76c	287t: 56	94	+

A highly regio- and enantioselective Rh-catalyzed 1,4-addition of arylboronic acids **2** to β,γ -unsaturated- α -ketoamides **288a** utilizing a simple novel chiral sulfinylphosphine ligand **L77** has been reported. Using this protocol, excellent chemo-, regio- and enantioselectivities in high yields (up to 93%) and excellent enantiomeric excess (up to 99% *ee*) were achieved. This strategy presents an attractive and facile approach to build up chiral non-racemic γ , γ -diaryl substituted carbonyl compounds. Furthermore, the synthetic application of this method was used in a brief formal synthesis of sertraline and the synthesis of a tetrahydroquinoline-2-carboxyl derivative.

Having established the optimal reaction conditions, the scope of potential substrates was next examined. Scheme 154 depicts various 1,4-adducts **289a-o**, isolated in good to high yields and with excellent enantioselectivities (96–99% *ee*) (Scheme 154).²⁷⁸

- 289a**: Ar = Ph, yield = 91%, *ee* = 98%
289b: Ar = 4-MeC₆H₄, yield = 89%, *ee* = 98%
289c: Ar = 4-CH(Me)₂C₆H₄, yield = 83%, *ee* = 99%
289d: Ar = 4-C(Me)₃C₆H₄, yield = 86%, *ee* = 98%
289e: Ar = 4-OMOMC₆H₄, yield = 75%, *ee* = 98%
289f: Ar = 4-OTBSC₆H₄, yield = 87%, *ee* = 97%
289g: Ar = 4-OBnC₆H₄, yield = 88%, *ee* = 97%
289h: Ar = 4-CF₃C₆H₄, yield = 78%, *ee* = 98%
289i: Ar = 4-ClC₆H₄, yield = 80%, *ee* = 97%
289j: Ar = 3-MeC₆H₄, yield = 90%, *ee* = 99%
289k: Ar = 3-MeOC₆H₄, yield = 89%, *ee* = 98%
289l: Ar = 3-ClC₆H₄, yield = 91%, *ee* = 99%
289m: Ar = 3,4-(Me)₂C₆H₃, yield = 88%, *ee* = 99%
289n: Ar = 3,4-(Cl)₂C₆H₃, yield = 83%, *ee* = 99%
289o: Ar = naphthalene, yield = 91%, *ee* = 96%

Scheme 154. Substrate scope for Rh-catalyzed stereoselective 1,4-addition of various arylboronic acids **2** to β,γ -unsaturated α -ketoamide **288a**

Having recognized the scope of the arylboronic acid reagent, the authors turned their attention to the α -ketoamide. The products obtained from the reactions between various β,γ -unsaturated- α -ketoamide **288a-o** and arylboronic acids **2** are illustrated in Table 96.²⁷⁸

Scheme 155.

Table 96. Substrate scope for Rh-catalyzed stereoselective 1,4-addition of phenylboronic acid **2** to various β,γ -unsaturated- α -ketoamides **288a-o**.

Entry	R 288	Ar 2	Yield (%)	<i>ee</i> (%)
-------	--------------	-------------	-----------	---------------

1	288b : Ph	4-OMeC ₆ H ₄	289a : 84	97
2	288c : 4-MeC ₆ H ₄	Ph	289b : 93	99
3	288d : 4-ClC ₆ H ₄	Ph	289c : 90	99
4	288e : 2-MeC ₆ H ₄	Ph	289d : 91	99
5	288f : 2-MeOC ₆ H ₄	Ph	289e : 89	99
6	288g : 2-NO ₂ C ₆ H ₄	Ph	289f : 87	99
7	288h : 2-FC ₆ H ₄	Ph	289g : 89	98
8	288i : 3-FC ₆ H ₄	Ph	289h : 91	98
9	288j : 4-FC ₆ H ₄	Ph	289i : 90	99
10	288k : 3,4-(Cl) ₂ C ₆ H ₃	Ph	289j : 86	98
11	288l : furan	Ph	289k : 91	97
12	288m : CH=CHMe	Ph	289l : 90	>99
13	288n : CH ₂ CH ₂ Me	Ph	289m : 93	79
14	288o : Me	Ph	289n : 89	83
15	288a : 4-MeOC ₆ H ₄	Ph	289o : 67	67
16	288a : 4-MeOC ₆ H ₄	4- ⁱ PrC ₆ H ₄	289p : 46	76
17	288a : 4-MeOC ₆ H ₄	4- ^t BuC ₆ H ₄	289q : 68	80

Optically active sulfonyl compounds show significant versatility in organic synthesis. They also exhibit interesting biological activity and are useful substances in pharmaceutical chemistry. Among the various protocols introduced for their synthesis, so far the Rh-catalyzed stereoselective 1,4-addition of arylboronic acids **2** to α,β -unsaturated sulfonyl compounds **290a-f** is well established as one of the most practical approaches due to the stability and commercially availability or readily accessibility of the wide range of boronic acid employed as the nucleophile. A series of Rh(I) complexes of bidentate ligands have been prepared for stereoselective 1,4-conjugation addition of α,β -unsaturated sulfonyl compounds. However, some problematic aspects issues remain challenging in terms of improving the efficiency, enantioselectivity and substrate scope. Thus, the development of effective asymmetric catalytic system for the synthesis of chiral sulfonyl compounds is still in much demand and is an essential aim in expanding upon the known and established strategy. Recently a general Rh-catalyzed and highly enantioselective catalytic 1,4-conjugate addition of arylboronic acids to β -aryl- α,β -unsaturated sulfonate has been achieved and reported. The attainment of the process is chiefly

based on the use of outstanding simple chiral phosphite-olefin ligands as bidentate ligands, which present noticeable synthetic and economic merits. Optimization of the reaction conditions showed that the reaction is better run at 50 °C in dioxane and in the presence of $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ and a chiral P/olefin ligand **L78**. This Rh(I) catalyst, which contains a chiral P/olefin ligand, showed a broad substrate scope, as well as tolerating a wide variety of arylboronic acids with diverse electronic and steric demands. This strategy was successfully examined with α,β -unsaturated sulfonates **290a-f**. Significantly, all reactions proceeded smoothly to afford the products in good to very high yields (84%~95%) and with high to excellent enantioselectivities (92%~99% *ee*). The electronic properties of the arylboronic acids did not show any appreciable effect on the reactivity of this reaction. Furthermore, α,β -unsaturated sulfonates **290a-f** with either an electron-donating or electron-withdrawing group on any aromatic carbon were easily subjected to the stereoselective arylation with arylboronic acids, giving chiral sulfonates in high chemical yields and with very high enantioselectivities. The aforementioned reaction offers an operational bench approach to the synthesis of a wide variety of highly enantioenriched *gem*-diaryl substituted sulfonates **291a-t** (Scheme 156).²⁷⁹

Scheme 156.

Table 97. Evaluation of substrate scope

Entry	Ar ¹ 290	Ar 2	Yield (%)	<i>ee</i> (%)
1	290a : Ph	4-MeOC ₆ H ₄	291a : 92	97
2	290a : Ph	4-MeC ₆ H ₄	291b : 92	96

3	290a: Ph	4- ^t BuC ₆ H ₄	291c: 92	99
4	290a: Ph	3-MeC ₆ H ₄	291d: 93	92
5	290a: Ph	2-naphthyl	291e: 91	96
6	290a: Ph	4-ClC ₆ H ₄	291f: 91	94
7	290b: 4-ClC ₆ H ₄	Ph	291g: 85	-92
8	290b: 4-ClC ₆ H ₄	4- ^t BuC ₆ H ₄	291h: 86	99
9	290b: 4-ClC ₆ H ₄	2-naphthyl	291i: 92	97
10	290c: 4-BrC ₆ H ₄	Ph	291j: 90	97
11	290c: 4-BrC ₆ H ₄	4- ^t BuC ₆ H ₄	291k: 91	99
12	290c: 4-BrC ₆ H ₄	2-naphthyl	291l: 95	98
13	290d: 3-ClC ₆ H ₄	Ph	291m: 93	97
14	290d: 3-ClC ₆ H ₄	4- ^t BuC ₆ H ₄	291n: 92	97
15	290d: 3-ClC ₆ H ₄	2-naphthyl	291o: 91	98
16	290e: 2-MeOC ₆ H ₄	Ph	291p: 87	96
17	290e: 2-MeOC ₆ H ₄	4- ^t BuC ₆ H ₄	291q: 90	93
18	290e: 2-MeOC ₆ H ₄	2-naphthyl	291r: 89	98
19	290f: 1-naphthyl	Ph	291s: 84	97
20	290f: 1-naphthyl	4-MeC ₆ H ₄	291t: 89	96

An efficient and highly stereoselective Rh-catalyzed 1,4-selective addition of various arylboronic acids **2** to β,γ -unsaturated α -keto ester **292a-m** was achieved using chiral *tert*-butanesulfinylphosphine as the ligand, giving moderate to excellent 1,4-regioselectivities for **293a-w** (up to 96:4), and good chemical yields (up to 87%), and good to high enantioselectivities (up to 94% *ee*). A detailed mechanism on the 1,4-selectivity and enantioselectivity of this reaction has been not reported yet (Table 98).²⁸⁰

Scheme 157.

Table 98. Substrate scope of stereoselective 1,4-addition to (*E*)-2-oxo-4-arylbut-3-enoate.

Entry	Ar ¹ 292	Ar 2	Yield (%)	<i>ee</i> (%)
1	292a : 4-MeOC ₆ H ₄	Ph	293a : 86	84
2	292b : 4- ⁱ PrC ₆ H ₄	Ph	293b : 87	83
3	292c : 4- ^t BuC ₆ H ₄	Ph	293c : 86	84
4	292d : 4-MeC ₆ H ₄	Ph	293d : 81	80
5	292e : 4-FC ₆ H ₄	Ph	293e : 83	77
6	292f : 4-ClC ₆ H ₄	Ph	293f : 79	73
7	292g : 4-CNC ₆ H ₄	Ph	293g : 70	60
8	292h : 3,4-Cl ₂ C ₆ H ₃	Ph	293h : 82	60
9	292i : 3-ClC ₆ H ₄	Ph	293i : 85	74
10	292j : 3-FC ₆ H ₄	Ph	293j : 78	77
11	292k : 2-ClC ₆ H ₄	Ph	293k : 77	71
12	292l : 2-thiophenyl	Ph	293l : 75	64
13	292m : Ph	4-MeOC ₆ H ₄	293m : 75	71
14	292a : 4-MeOC ₆ H ₄	4- ^t BuC ₆ H ₄	293n : 73	92
15	292a : 4-MeOC ₆ H ₄	4- ⁱ PrC ₆ H ₄	293o : 72	94
16	292a : 4-MeOC ₆ H ₄	4-TBSOC ₆ H ₄	293p : 66	88
17	292a : 4-MeOC ₆ H ₄	4-BnOC ₆ H ₄	293q : 74	80
18	292a : 4-MeOC ₆ H ₄	4-MeC ₆ H ₄	293r : 78	80
19	292a : 4-MeOC ₆ H ₄	4-MeOCH ₂ OC ₆ H ₄	293s : 67	77

20	292a : 4-MeOC ₆ H ₄	4-CF ₃ C ₆ H ₄	293t : 72	54
21	292a : 4-MeOC ₆ H ₄	3-MeOC ₆ H ₄	293u : 87	71
22	292a : 4-MeOC ₆ H ₄	3-ClC ₆ H ₄	293v : 71	74
23	292a : 4-MeOC ₆ H ₄	2-naphthyl	293w : 64	69

Linear (*E*)-enones have been found to be challenging substrates in the Rh-catalyzed stereoselective 1,4-addition of [(ligand)Rh-Ph] to various boronic acids by Qin *et al.*²⁸¹ This reaction is one of the most important catalytic stereoselective methodologies. In this line, the conjugate addition of differently substituted arylboronic acids to 2-cyclohexenone has been extensively investigated as a model reaction, in order to determine the optimized conditions for stereoselective, Rh-catalyzed arylation reactions. Although this reaction study was pioneered by Miyaura *et al.*, Hayashi and Miyaura reported the first stereoselective version by employing a chiral diphosphane ligand, binap. This research group found that while the 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (I; Phbod) showed higher enantioselectivity for 2-cyclohexenone **294a** than acyclic enones such as (*E*)-3-nonen-2-one **294b**, this fashion was reversed when the dibenzyl analogue (II) was used. Recently, Carnell *et al.* examined several bicyclo[2.2.2]octa-2,5-diene ligands in the 1,4-arylation of **294b** and observed a wide range of variation in the enantiomeric excess for bridgehead-substituted Phbod analogues, although the obtained yields were all greater than 92%.²⁸² A Phbod analogue with methyl groups as the substituent at the bridgehead carbon atoms (III) afforded as low as 52% *ee* compared with the unsubstituted Phbod (83% *ee*). These results show why this reaction was a challenge. In most of the reported cases, *ee* values of less than 96% have been claimed.²⁸³⁻²⁸⁹ Apparently, there is no highly enantioselective (> 98% *ee*)^{290, 291} general catalyst for the arylation of acyclic (*E*)-enones, dissimilar to their corresponding cyclic (*Z*)-isomers (Table 99).

Scheme 158. 1,4-Arylation of cyclic (*Z*)- and acyclic (*E*)-α,β-unsaturated ketones catalyzed by RhI complexed with chiral 1,4-diene **L11a-c**

Table 99.

Entry	Ln	Procedure	295a: Yield [%], (<i>ee</i> %, Config)	295b: Yield [%], (<i>ee</i> %, Config)
1	L11a	A	[95], [96, (<i>R</i>)	[90], [83, (<i>S</i>)
2	L11b	A	[97], [95, (<i>R</i>)	[94], [98, (<i>S</i>)
3	L11c	B	[98], [99, (<i>R</i>)	[99], [52, (<i>S</i>)

1,4-Arylations of the γ-branched substrate, (*E*)-5-methyl-3-hexen-2-one (Scheme 159) attached to different ligands **L11b** and **L4** (binap) proceeded smoothly to give the desired products in 85% chemical yields and with 97% *ee*, respectively (Scheme 159). This work as reported by Hayashi et al. in 2003.

Scheme 159. 1,4-Arylation of the γ -branched (*E*)-5-methyl-3-hexen-2-one mediated by RhI ligated with chiral ligands **L11b** and **L4**.

The 1,4-addition of phenyl boronic acid to a linear (*E*)-enone is believed to occur via enantiodiscrimination during the enone binding and carboration stages of the catalytic cycle under the strong influence of conformation (Scheme 160).²⁸¹

Scheme 160. Reaction profile for ligand **L11b**.

A novel and efficient type of achiral diene-Rh-catalyzed stereoselective arylation was developed and reported.²⁹² 3-Sulfolene **300** is in equilibration with 2-sulfolene **301** via base-catalyzed isomerization under Rh-catalyzed arylation conditions. The Rh complex is coordinated with Fc-tfb ligand and is able to catalyze the arylation of 2-sulfolene **301** under isomerization conditions, ultimately consuming all of the sulfolene isomers to provide 3-arylsulfolanes **301** in high chemical yield of the 1,4-conjugate arylation product **302a-o** with high *ee*. This isomerization-stereoselective arylation sequence has also been extended successfully to 6-membered ring and linear allylic sulfones (Scheme 161).²⁹²

302a: Ar = 4-MeOC₆H₄, yield = 90%, *ee* = 98% (*R*)

302b: Ar = Ph, yield = 80%, *ee* = 97% (*R*)

302c: Ar = 4-MeC₆H₄, yield = 67%, *ee* = >99% (*R*)

302d: Ar = 3-MeC₆H₄, yield = 89%, *ee* = 98% (*R*)

302e: Ar = 2-MeC₆H₄, yield = 97%, *ee* = 93% (*R*)

302f: Ar = 4-PhOC₆H₄, yield = 87%, *ee* = 99% (*R*)

302g: Ar = 3-MeOC₆H₄, yield = 95%, *ee* = 98% (*R*)

302h: Ar = 2-MeOC₆H₄, yield = 84%, *ee* = >99% (*R*)

302i: Ar = 4-FC₆H₄, yield = 89%, *ee* = >99% (*R*)

302j: Ar = 4-ClC₆H₄, yield = 90%, *ee* = >99% (*R*)

302k: Ar = 4-BrC₆H₄, yield = 94%, *ee* = >99% (*R*)

302l: Ar = 4-CF₃C₆H₄, yield = 87%, *ee* = >99% (*R*)

302m: Ar = 2-naphthyl, yield = 97%, *ee* = 97% (*R*)

302n: Ar = , yield = 93%, *ee* = 95% (*S*)

302o: Ar = , yield = 61%, *ee* = 91% (*S*)

Scheme 161. Rhodium-catalyzed stereoselective hydroarylation of 3-sulfolene **300** with arylboronic acids

2.

The absolute configuration of product **302k** (Ar = 4-Br-C₆H₄) was defined as (*R*) by analyzing its X-ray crystallographic data. The (*R*)-configuration attained with (*R,R*)-Fc-tfb **L53** was rationalized and understood by the coordination of 2-sulfolene to an aryl-Rh intermediate with its *si* face. The coordination with the opposite face is much less favored because of the steric repulsions that existed between the cyclic alkyl chain of 2-sulfolene and one of the ferrocenyl groups on the diene ligand (Figure 16). All of the obtained products under these conditions with (*R,R*)-Fc-tfb ligand are expected to have the same (*R*)-absolute configuration.

Figure 16. Proposed stereochemical pathway for the stereoselective arylation catalyzed by Rh/(*R,R*)-Fc-tfb

Chromone is known as one of the most problematic substrates in the stereoselective 1,4-additions to α,β -unsaturated carbonyl compounds. However, this problem can be circumvented by using an Rh complex that includes a chiral diene ligand, (*R,R*)-Ph-bod* **L11b**. In this way the 1,4-addition of different arylboronic acids was accomplished to provide high yields of the respective flavanones with excellent enantioselectivities ($\geq 97\%$ *ee*, 99% *ee* for virtually all substrates used). No side products from the ring opening, which could lead to a loss of product enantioselectivity, were observed under the aforementioned reaction conditions.

With the optimized reaction conditions in hand, the efficacy of the catalytic system was studied (Scheme 162). As a result, it was found that the chiral diene ligand (*R,R*)-Ph-bod* can efficiently participate in the Rh-catalyzed 1,4-addition of arylboronic acids **2** to chromones **166** to afford **305a-l** with excellent enantioselectivity ($\geq 97\%$ *ee*). Interestingly by following this strategy, both electron-donating and withdrawing groups on arenes can be efficiently introduced. It is worthwhile noting that the sterically hindered arylboronic acids can also give the desired product in satisfactory chemical yield and with excellent *ee* (Scheme 162).²⁹³

305a: Ph, yield = 94%, *ee* = >99%

305b: 4-MeOC₆H₄, yield = 86%, *ee* = 99%

305c: 3-MeOC₆H₄, yield = 84%, *ee* = >99%

305d: 4-MeC₆H₄, yield = 90%, *ee* = >99%

305e: 3-MeC₆H₄, yield = 84%, *ee* = >99%

305f: 2,4-Me₂C₆H₃, yield = 80%, *ee* = 99%

305g: 4-*t*BuC₆H₄, yield = 93%, *ee* = >99%

305h: 3-FC₆H₄, yield = 72%, *ee* = 98%

305i: 4-FC₆H₄, yield = 66%, *ee* = 98%

305j: 4-CH₂MeC₆H₄, yield = 80%, *ee* = 97%

305k: 1-naphthyl, yield = 91%, *ee* = >99%

305l: 2-naphthyl, yield = 88%, *ee* = >99%

Scheme 162. Rh-catalyzed stereoselective 1,4-additions of arylboronic acids **2** to chromone **166**.

The substrate scope, for this protocol was further studied. A series of 1,4- addition of substituted chromones **166b-i** was examined to arylboronic acids **2** (Scheme 163, Table 100). The results showed no significant electronic effects since most of the desired adducts were provided in satisfactory chemical yields and with excellent enantioselectivities (97–99% *ee*).²⁹³

Scheme 163.

Table 100. Rh-catalyzed 1,4-addition of arylboronic acids to substituted chromones.

Entry	R 166	Ar 2	Yield (%)	<i>ee</i> (%)
1	166b: 6-MeC ₆ H ₄	Ph	305a: 81	99
2	166c: 6,7-Me ₂ C ₆ H ₃	Ph	305b: 72	99
3	166d: 7-MeOC ₆ H ₄	Ph	305c: 81	98

4	166e : 6-Cl-7-MeC ₆ H ₃	Ph	305d : 70	>99
5	166f : 6-FC ₆ H ₄	Ph	305e : 83	97
6	166g : 6-ClC ₆ H ₄	Ph	305f : 77	98
7	166h : 4 <i>H</i> -benzo[h]	Ph	305g : 73	>99
8	166i : 6-MeOC ₆ H ₄	Ph	305h : 76	>99
9	166b : 6-MeC ₆ H ₄	4-MeC ₆ H ₄	305i : 79	98
10	166d : 7-MeOC ₆ H ₄	4-MeC ₆ H ₄	305j : 77	>99

The defined (*R*)-configuration of flavanone **308** using (*R,R*)-Ph-bod* is rationalised by the coordination of chromone to the Rh with its α -*re* face. The coordination with the opposite face is unfavorable due to the steric repulsions between the aromatic motif of chromone and one of the phenyl groups on the chiral diene ligand (Figure 17). All of the products under these conditions with the (*R,R*)-Ph-bod* ligand are expected having the same (*R*)-absolute configuration.

Figure 17. Proposed stereochemical pathway for the stereoselective 1,4-addition to chromone catalyzed by Rh/(*R,R*)-Ph-bod*

7-Azaindoles **2a-j** are versatile frameworks, particularly in the pharmaceutical chemistry, where they can be considered as bioisosteres of indoles or purines. An efficient, novel and highly stereoselective strategy involving Rh-catalyzed stereoselective 1,4-addition of diverse arylboronic acids **2** to 3-benzylidene-1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-ones **309a,b** has been developed. Substrates **309a,b** are known exocyclic methylene lactamyl Michael acceptors. Using this approach, several new original derivatives of 1*H*-pyrrolo[2,3-*b*]pyridin-2(3*H*)-one have been synthesized. Thus, in order to establish the generality of this reaction, the optimized reaction conditions using (*R,R*)-Ph-bod* as the ligand and [(RhCl(C₂H₄)₂)₂] as the catalyst were examined

with differently substituted arylboronic acids added to **309a** and **309b** as the Michael acceptor, which gave the corresponding 1,4-adducts **310a-j** (Table 101).²⁹⁴

Scheme 164.

Table 101. Rhodium-catalyzed 1,4-addition of boronic acids to 7-azaoxindoles **309a** and **309b**.

Entry	R 309	Ar 2	Yield (%)	<i>ee</i> (%)
1	309a : Me	Ph	310a : 93	-
2	309a : Me	4-MeOC ₆ H ₄	310b : 90	92
3	309a : Me	4-CHOC ₆ H ₄	310c : 86	92
4	309a : Me	4-MeC ₆ H ₄	310d : 89	>80
5	309a : Me	4-OCMeC ₆ H ₄	310e : 86	96
6	309a : Me	3-O ₂ NC ₆ H ₄	310f : 73	n.d.
7	309a : Me	(1 <i>H</i> -Indol-5-yl)phenyl	310g : 86	94
8	309a : Me	thiophenyl	310h : 71	n.d.
9	309b : Bn	Ph	310i : 90	-
10	309b : Bn	4-MeOC ₆ H ₄	310j : 90	88

2.2. Organosilicon

A highly enantioselective 1,4-addition of organosiloxanes **1a**, **b**, **d**, **z** to α,β -unsaturated carbonyl compounds **311a-f** was conducted using a chiral Rh-complex created from [Rh(cod)(MeCN)₂][BF₄] and (*S*)-binap **L4'** to give **312a-i**. Using the aforementioned catalyst, both (*E*)- and (*Z*)-1-alkenyl groups and aryl groups were introduced at the α -position of a wide variety of ketones, esters, and amides, with high *ee* (Table 102).²⁹⁵

Scheme 165.

Table 102. Rhodium-catalyzed stereoselective 1,4-addition of organosiloxanes to α,β -enones.

Entry	1	311	Yield (%)	<i>ee</i> (%)	Config.
1	1a	311a	312a: 76	98	(<i>S</i>)
2	1b	311a	312b: 89	94	(<i>S</i>)
3	1z	311a	312c: 90	75	(<i>R</i>)
4	1d	311a	312d: 62	98	-
5	1a	311b	312e: 56	96	-
6	1a	311c	312f: 73	96	-
7	1a	311d	312g: 54	96	(<i>S</i>)
8	1a	311e	312h: 85	91	(<i>S</i>)
9	1a	311f	312i: 88	87	-

The suggested mechanism for this reaction is depicted in Scheme 166. It involves the creation of an organorhodium intermediate **314** via the transmetallation between the silicon reagent **311** and the Rh complex **313** to trigger the addition of the organorhodium intermediate **314** to the α,β -unsaturated carbonyl compound **1**.²⁹⁵⁻²⁹⁷ The stereochemical route of the addition of the Rh-C bond to the enones is similar to that in the stereoselective 1,4-addition of arylboronic acids reported by Hayashi *et al.*²⁹⁸ This is an example of chiral Rh involving a 1:1 complex of Rh and binap. However, the addition of 1.5-fold excess of binap was found to be required to provide high enantioselectivity, which is essential to achieve complexation. In this way, the (*E*)-enones can coordinate to the Rh-(*S*)-binap complex (Figure 18) on their 2-*re* face to prevent the steric

fashion, albeit on their *2si* face to afford the (*S*)-products **312**.²⁹⁵

Scheme 166. Presumed reaction pathway.

Figure 18.

The enantioselective 1,4-addition of organosiloxanes **311a-f** to α,β -unsaturated carbonyl compounds **1a,b,d,z** catalyzed by a chiral Rh complex gave **318a-I** with high enantioselectivity. The chiral Rh complex was created from the reaction of $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$ and (*S*)-binap **L4'**. Both (*E*)- and (*Z*)-1-alkenyl and aryl groups can be introduced with high enantioselectivity into β -position of a wide variety of ketones, esters, and amides (Scheme 167, Table 103).²⁹⁹

Scheme 167.

Table 103. Rhodium-catalyzed stereoselective 1,4-addition of organosiloxanes to α,β -enone.

Entry	1	311	Yield (%)	<i>ee</i> (%)	Config.
1	1a	311a	318a : 76	98	(<i>S</i>)
2	1b	311a	318b : 89	94	(<i>S</i>)
3	1z	311a	318c : 90	75	(<i>R</i>)
4	1d	311a	318df : 62	98	-
5	1a	311b	318e : 56	96	-
6	1a	311c	318f : 73	96	-
7	1a	311d	318g : 54	96	(<i>S</i>)
8	1a	311e	318h : 85	91	(<i>S</i>)
9	1a	311f	318i : 88	87	-

To extend the scope of this reaction, the stereoselective addition of **311a** to α,β -unsaturated esters and amides was tested. It was found that reactions with methyl crotonate **319** and crotonamide **320** proceeded smoothly. The reaction of 3-penten-2-on gave the phenylated (*R*)-adducts, **318j** and **318k**, in acceptable yields and with high enantioselectivity (Scheme 168).²⁹⁹

Scheme 168.

The suggested reaction mechanism is depicted in Scheme 169. It involves the possible formation of an organo rhodium intermediate **322** via transmetallation between the silicon reagent **311** and a Rh complex **321** followed by the addition of organorhodium intermediate **322** to the α,β -unsaturated carbonyl compound **1**. The stereochemical logic of the addition of the Rh-C bond to the enones must be similar to that in the stereoselective 1,4-addition of arylboronic acids reported by Hayashi and Miyaura previously (Scheme 169).²⁹⁹

Scheme 169. Presumed Reaction Pathway

A Rh complex $[\text{Rh}((S)\text{-binap})(\text{MeCN})_2]\text{BF}_4$ catalyzed the hydrosilylation of 1-alkynes with triethoxysilane and the stereoselective 1,4-addition of the obtained alkenylsilanes to give cyclic α,β -unsaturated ketones. This one-pot approach afforded high yields of the respective 1,4-addition products with over excellent enantioselectivity. A one-pot reaction strategy where a $[\text{Rh}((S)\text{-binap})(\text{MeCN})_2]\text{BF}_4$ complex catalyzes successively the hydrosilylation of 1-alkynes with triethoxysilane and the stereoselective 1,4-addition of the obtained alkenylsilanes to cyclic α,β -unsaturated ketones has been reported. Although the regioselectivity at the hydrosilylation stage is not consistently high, the linear alkenylsilanes are more reactive than the branched isomers affording the linear 1,4-addition products with high chemoselectivity. High enantioselectivity was observed ($>90\%$ *ee*) for cyclic enones.

The one-pot protocol starting from phenylacetylene **324a** can be usefully applied to the stereoselective 1,4-addition to cyclic enones, 2-cyclopentenone **1b** and 2-cycloheptenone **1c** yielding the respective (*S*)-3-(*E*)-2-phenylethenylcycloalkanes **327b** and **327c** with high enantioselectivity (90-93% *ee*). The regioselectivity in generating linear or branch alkenylsilane via the Rh-catalyzed hydrosilylation relies on the substituents on the alkyne **324**. Arylacetylenes **324a-e** afforded the hydrosilylation products having 12-25% of branch alkenylsilanes **328**, whereas the linear/ branch ratio for 1-octyne **324f** was approximately one to one. The 1,4-

addition products were not contaminated with those obtained from the branched alkenylsilanes. The highest regioselectivity in generating linear alkenylsilane (*E*)-**326** was obtained in the hydrosilylation of triethylsilylacetylene **324g**, which in its reaction with 2-cyclohexenone **1a** afforded of the 1,4-addition products in high yields and with excellent enantioselectivity (98% *ee*) (Scheme 170, Table 104).³⁰⁰

Scheme 170. Rhodium-catalyzed stereoselective 1,4-addition of alkenylsilanes **326** generated by hydrosilylation of alkynes **324**.

Table 104.

Entry	324	Ratio of (<i>E</i>)- 326 /(<i>Z</i>)- 326 / 328	1	Yield (%)	<i>ee</i> (%)	Config.	Ratio of (<i>E</i>)- 327 /(<i>Z</i>)- 327
1	324a	74:1:25	1a	327a : 89	93	(<i>S</i>)	99:1
2	324a	74:1:25	1b	327b : 74	90	(<i>S</i>)	99:1
3	324a	74:1:25	1c	327c : 79	93	(<i>S</i>)	98:2
4	324a	74:1:25	1d	327d : 76	78	(<i>S</i>)	100:0
5	324b	85:0:15	1a	327e : 66	92	(<i>S</i>)	100:0
6	324c	72:12:16	1a	327f : 65	92	(<i>S</i>)	91:9
7	324d	80:8:12	1a	327g : 67	90	(<i>S</i>)	99:1
8	324e	76:0:24	1a	327h : 70	92	(<i>S</i>)	100:0
9	324f	53:2:45	1a	327i : 73	98	(<i>S</i>)	97:3
10	324g	98:0:2	1a	327j : 85	98	(<i>S</i>)	100:0

A new transition-metal-catalyzed C-Si bond formation mediated by cationic Rh complexes has been reported. The Si-B fragment functions similar to nucleophilic silicon **329**, which is effectively added onto appropriate acyclic and cyclic α,β -unsaturated carbonyl compounds **1a-c,g**. Chiral $[(S)\text{-binap}]\text{Rh}(\text{cod})\text{ClO}_4$ had an unprecedented effect on the stereoselective 1,4-addition to cyclic acceptors and induced high *ees*. This transformation may also result in synthetically useful cascade processes. The enantioselective 1,4-addition of nucleophilic silicon to cyclic substrates **1a-c** catalyzed by chiral $[(S)\text{-binap}]\text{Rh}(\text{cod})\text{ClO}_4$ ^{302, 303} with additives (*S*)-binap and trimethylamine was achieved to give **330a-d** (Scheme 171).³⁰¹

Scheme 171. Catalytic stereoselective conjugate silyl transfer

Highly enantioselective 1,4-additions of aryltrialkoxysilanes **311** to α,β -unsaturated esters **331** and amides **333**, catalyzed by a chiral Rh complex have been reported. The Rh complex was prepared from the reaction of $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$ and (*S*)-binap. In this way aryl groups can be readily and enantioselectively introduced at the β -position of a wide variety of esters and amides. It was found that the enantioselectivity and chemical yield were influenced mainly by the bulkiness of the substituents on the terminal olefin and by the ester or amide group. The reactions of aryltrialkoxysilanes **311a-c** with α,β -unsaturated esters **331a-g** were conducted in the presence of a cationic Rh complex, $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$, and (*S*)-binap in a mixture of 1,4-dioxane/water at 90°C to afford **332a-i** in high chemical yields. The results are outlined in Table 105.³⁰⁴

Scheme 172.

Table 105. Stereoselective 1,4-addition of aryltrialkoxysilanes to α,β -unsaturated esters.

Entry	331	311	Yield (%)	<i>ee</i> (%)	Config.
1	331a	311a	332a: 93	84	(<i>R</i>)
2	331b	311a	332b: 70	89	(<i>R</i>)
3	331c	311a	332c: 76	93	-
4	331d	311a	332d: 70	85	-
5	331e	311a	332e: 76	93	-
6	331f	311a	332f: 36	94	(<i>S</i>)
7	331g	311a	332g: 28	97	(<i>S</i>)
8	331e	311c	332h: 84	88	-
9	331e	311b	332i: 80	93	-

The stereoselective 1,4-addition of aryltrialkoxysilane **311a-c** to α,β -unsaturated amides **333a-e** afforded **334a-g** in high yield. The results are outlined in Scheme 173. Since the reactivities of the α,β -unsaturated amides were found to be slightly lower than those of esters, the yields were lower than those of the esters prepared from the respective carboxylic acids (Scheme 173).³⁰⁴

- 5a:** R¹ = Me, R² = R³ = H, R = Ph, R' = Me, yield = 75%, ee = 81% (*R*)
5b: R¹ = *n*-Pr, R² = R³ = H, R = Ph, R' = Me, yield = 59%, ee = 91% (*R*)
5c: R¹ = *i*-Pr, R² = R³ = H, R = Ph, R' = Me, yield = trace, ee = -
5d: R¹ = R² = R³ = Me, R = Ph, R' = Me, yield = 61%, ee = 72% (*R*)
5e: R¹ = Me, R² = H, R³ = CH₂Ph, R = Ph, R' = Me, yield = 70%, ee = 92%
5f: R¹ = Me, R² = H, R³ = CH₂Ph, R = 4-MeOC₆H₄, R' = Et, yield = 30%, ee = 90%
5g: R¹ = Me, R² = H, R³ = CH₂Ph, R = 4-ClC₆H₄, R' = Et, yield = 54%, ee = 92%

Scheme 173. Stereoselective 1,4-addition of aryltrialkoxysilanes to α,β -unsaturated amides.

Tetraorganosilicon reagents, alkenyl-, aryl-, and silyl[2-(hydroxymethyl)phenyl]dimethylsilanes **336a-g** are stable and recyclable and can be used in 1,4-addition reactions to α,β -unsaturated carbonyl compounds **1a-c**, **g**, **38a**, **b**, **335a-g** under mild Rh-catalysis conditions to afford **337a-t**. All of the reactions make progress with high chemoselectivity under mild conditions to give the corresponding products in satisfactory yields, by utilizing equimolar amounts of the silane reagents. The use of a chiral diene ligand results in the corresponding enantioselective conversions employing the tetraorganosilicon reagents, thus bringing about the silicon-based strategy to optically active ketones and substituted piperidones, which are useful synthetic intermediates in the pharmaceutical industry. The ready availability along with high stability against base, acids, and the moisture of these tetraorganosilicons indicates the superior features of these silane reagents as alternatives to organoboron reagents.

The Rh alkoxide species is proposed to be in charge for the transmetallation step. This has been observed in kinetic resolution of racemic chiral phenylsilane in the asymmetric 1,4-addition reaction catalyzed by an Rh-(chiral diene).³⁰⁵

The equimolar reaction of **336a-g** with **1a-c**, **g**, **38a**, **b**, **335a-g** mediated [Rh(OH)(cod)]₂ in THF at 35 °C afforded **337a-t** in satisfactory yield. The high reactivity of the silicon reagent observed under mild reaction conditions motivated the same research group to further study the features of both silicon reagents and electrophiles (Scheme 174, Table 106).³⁰⁵

Scheme 174.

Table 106. Rhodium-catalyzed 1,4-addition reactions of aryl[2-(hydroxymethyl)phenyl]dimethylsilanes to electron-deficient olefins.

Entry	1/38/335	Ar 336	Yield (%)
1	1b	336a : Ph	337a : 90
2	1b	336a : Ph	337b : 92
3	1a	336a : Ph	337c : 95
4	1c	336a : Ph	337d : 86
5	335a	336a : Ph	337e : 90
6	335b	336a : Ph	337f : 86
7	335c	336a : Ph	337g : 98
8	1g	336a : Ph	337h : 91
9	335d	336a : Ph	337i : 80
10	335e	336a : Ph	337j : 100
11	38a	336a : Ph	337k : 78
12	38b	336a : Ph	337l : 74
13	335f	336a : Ph	337m : 94
14	335g	336a : Ph	337n : 94
15	1b	336b : 4-MeOC ₆ H ₄	337o : 96
16	1b	336c : 4-FC ₆ H ₄	337p : 89
17	1b	336d : 4-BrC ₆ H ₄	337q : 90

18	1b	336e : 4-NCC ₆ H ₄	337r : 93
19	1b	336f : 4-B(pin)C ₆ H ₄	337s : 69
20	1b	336g : 2,4,6-Me ₃ C ₆ H ₂	337t : 85

The 1,4-addition of alkenylsilanes was studied (Scheme 175). The stoichiometric reaction of (*E*)-[2-(hydroxymethyl)phenyl]dimethyl(1-octenyl)silane **336h-w** with **1a-c**, **335g** catalyzed by [Rh(OH)(cod)]₂ in THF at 35 °C afforded the respective adduct **337** in satisfactory yield.³⁰⁵

- 337h: 335g**, R¹ = Hex, R² = H, R³ = H, yield = 67%
337h: 1b, R¹ = Hex, R² = H, R³ = H, yield = 89%
337h: 1a, R¹ = Hex, R² = H, R³ = H, yield = 85%
337h: 1c, R¹ = Hex, R² = H, R³ = H, yield = 78%
337i: 1b, R¹ = (CH₂)₃CN, R² = H, R³ = H, yield = 87%
337j: 1b, R¹ = (CH₂)₃CO₂Me, R² = H, R³ = H, yield = 89%
337k: 1b, R¹ = (CH₂)₃Cl, R² = H, R³ = H, yield = 92%
337l: 1b, R¹ = (CH₂)₃OSiMe₂^tBu, R² = H, R³ = H, yield = 94%
337m: 1b, R¹ = CH₂CH(CO₂Me)₂, R² = H, R³ = H, yield = 91%
337n: 1b, R¹ = CH₂NthPh, R² = H, R³ = H, yield = 84%
337o: 1b, R¹ = CMe₂OH, R² = H, R³ = H, yield = 81%
337p: 1b, R¹ = CMe=CH₂, R² = H, R³ = H, yield = 81%
337q: 1b, R¹ = Ph, R² = H, R³ = H, yield = 87%
337r: 1b, R¹ = H, R² = Me, R³ = H, yield = 77%
337s: 1b, R¹ = H, R² = Ph, R³ = H, yield = 94%
337t: 1b, R¹ = H, R² = H, R³ = Me, yield = 75%
337u: 1b, R¹ = H, R² = H, R³ = Ph, yield = 85%
337v: 1b, R¹ = Me, R² = Me, R³ = H, yield = 79%
337w: 1b, R¹ = H, R² = Pr, R³ = Pr, yield = 90%

Scheme 175. Rhodium-catalyzed 1,4-addition reactions of alkenyl[2 (hydroxymethyl)phenyl]dimethylsilanes to cyclic enones.

Encouraged by the successful 1,4-addition of the silicon reagents under mild reaction conditions along with recent discovery on the use of chiral diene ligands,³⁰⁶⁻³¹⁴ the authors turned their attention to the application of **336** to asymmetric synthesis.

Scheme 176.

Table 107. Rhodium-catalyzed enantioselective 1,4-addition reactions of organo[2-(hydroxymethyl)phenyl]dimethylsilanes.

Entry	1/ 339	Ar 336	Ln	Yield (%)	ee (%)
1	1b	336a : Ph	L11b	337a : 93	97
2	1a	336a : Ph	L11b	337b : 91	99
3	1d	336a : Ph	L11a	337c : 94	97
4	1e	336a : Ph	L11a	337d : 94	97
5	339a	336c : 4-FC ₆ H ₄	L11b	337e : 92	96
6	339b	336x : 4-F-2-MeC ₆ H ₃	L11a	337f : 94	86
7	1b	336p	L11a	337g : 81	91
8	1b	336t	L11b	337h : 85	96
9	1b	336w	L11b	337i : 90	90
10	1b	336y : CH ₂ =CH ₂	L11a	337j : 70	94

This catalyzed reaction originates from the reaction of Rh hydroxide **339** with silane reagent **336** to afford organorhodium intermediate **340** (Scheme 177). In the following Michael addition of R in **340** to an enone, Rh-enolate **341** is obtained, which behaves as a base to react with **336** to provide Michael adduct **337** and Rh-alkoxide **342**. Transmetalation of R from silicon to Rh occurs with the help of the proximal hydroxyl group to recreate **340** to terminate the cycle.³⁰⁵

Scheme 177. Plausible Mechanism

A novel synthetic approach for the synthesis of chiral allylsilanes has been developed via a Rh-catalyzed stereoselective 1,4-addition of alkenyl[2-(hydroxymethyl)phenyl]dimethylsilanes **345a-f** to β -silyl α,β -unsaturated ketones **344a-f** to obtain compounds **346a-k**. By using (*S,S*)-Ph-bod* as a ligand, a wide variety of alkenyl nucleophiles have been assembled to these substrates in high yield and *ee*. The resulting allylsilanes can be employed in the context of stereoselective intramolecular allylation reactions, which can control two adjoining tertiary and quaternary stereogenic centers.

Employing (*S,S*)-Ph-bod* **L11b'** as a ligand, the scope of the substrate and the nucleophile is shown in Table **108**. Therefore, not only a dimethylphenyl silyl group but also other silyl groups i.e., the *tert*-butyldimethylsilyl group, can be used at the β -position of the substrate. With regards to the nature of the substituent adjacent to the carbonyl group, such as primary alkyl, secondary

alkyl, and aryl groups, all are tolerated to afford the respective allylsilanes in satisfactory chemical yields and with high enantioselectivity (Scheme 178, Table 108).³¹⁵

Scheme 178.

Table 108. Rh/(*S,S*)-Ph-bod*-catalyzed stereoselective 1,4-addition of alkenyl[2-(hydroxymethyl)phenyl]dimethylsilanes **345** to β -Silyl α,β -unsaturated ketones **344**.

Entry	344	R 345	Yield (%)	<i>ee</i> (%)
1	344a	345a: Me	346a: 96	93
2	344b	345a: Me	346b: 95	97
3	344c	345a: Me	346c: 91	92
4	344d	345a: Me	346d: 95	97
5	344e	345a: Me	346e: 88	93
6	344a	345b: Ph	346f: 96	93
7	344d	345c: $-(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)-$	346g: 90	92
8	344d	345d: Me ₂	346h: 98	94
9	344e	345d: Me ₂	346i: 92	91
10	344e	345e: di- <i>n</i> -Pr	346j: 92	93
11	344e	345f: di- <i>n</i> -Hex	346k: 91	56

In 2008 Wang *et al.* achieved the rhodium-catalyzed³¹⁶ stereoselective conjugate addition to α,β -unsaturated ketones and related compounds; this is a well-known, efficient protocol for the introduction of aryl and alkenyl motives with high enantioselectivity.³¹⁷ On the other hand, in spite of its high synthetic utility, the stereoselective conjugate addition of an alkynyl group has been largely overlooked.³¹⁸⁻³²¹ A facile and effective method for this type of reaction should be

the addition of terminal acetylenes to enones. However, the terminal acetylenes are more reactive than enone towards the alkynyl rhodium intermediate. Thus the terminal acetylene favors dimerization, which results in the predominant formation of acetylene dimers instead of α -alkynylketones (Scheme 179).³²²⁻³²⁷ This problem can be solved by the rhodium-catalyzed 1,3-rearrangement of an alkynyl group from alkynyl alkenyl carbinols, while the concentration of the acetylene is maintained during the reaction. By using this method, α -alkynylketones can be obtained in high yields.³²⁸ Alternatively, the rhodium-catalyzed stereoselective conjugate alkynylation, can be achieved by using (triisopropylsilyl)acetylene together with a chiral phosphine ligand such as DTBM-segphos.³²⁹ In this light a conjugate addition of (triisopropylsilyl)acetylene **351** to α,β -unsaturated ketones **350a-j** catalyzed by Rh/(*R*)-DTBM-segphos gives **352a-j** with high *ee*. Here, the sterically bulky substituents on the silicon and phosphorus atoms suppress the dimerization of alkynes (Scheme 180).³¹⁶

Scheme 179.

- 352a:** $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, yield = 99%, $ee\% = 91$
352b: $\text{R}^1 = 4\text{-MeOC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$, yield = 89%, $ee\% = 91$
352c: $\text{R}^1 = \text{furan}$, $\text{R}^2 = \text{Me}$, yield = 99%, $ee\% = 93$
352d: $\text{R}^1 = \text{CH=CHPh}$, $\text{R}^2 = \text{Me}$, yield = 78%, $ee\% = 95$
352e: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Me}$, yield = 90%, $ee\% = 95$
352f: $\text{R}^1 = \text{CH}_2\text{Me}$, $\text{R}^2 = \text{Me}$, yield = 92%, $ee\% = 92$
352g: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{CH}_2\text{Me}$, yield = 80%, $ee\% = 89$
352h: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{C}_5\text{H}_{11}$, yield = 90%, $ee\% = 97$
352i: cyclopent-2-enone, yield = 67%, $ee\% = 88$
352j: 1*H*-inden-1-one, yield = 54%, $ee\% = 95$

Scheme 180. Stereoselective conjugate addition of (triisopropylsilyl)acetylene to enones

The Rh(I)-catalyzed activation of a silicon–boron linkage, i.e., the transmetallation of silicon from boron to Rh(I) to form the Rh(I)–OH complex, provides an umpolung, thus facilitating the conjugate addition of nucleophilic silicon **354** onto α,β -unsaturated acceptors **1a-c,f,g**, **353** to provide 1,4-adducts **355a-f**. The stereoselective conjugate silyl 1,4-addition onto electron-poor α,β -unsaturated acceptors is one of the problematic in organosilicon chemistry. A highly enantioselective strategy based on a new activation mode of the silicon-boron linkages has been recently accomplished and reported. Pre- or in situ generated cationic Rh(I)–binap complexes have catalyzed this new carbon–silicon bond generation with excellent enantioselectivity (92 to >99% ee) for a wide range of carboxyl compounds. Notably the enantiomeric excess of >99% ee were observed for acyclic carboxyl compounds. The Rh(I)–**L4'** synthesis of [((*S*)-binap)Rh(cod)]ClO₄ was achieved, which was employed in the stereoselective conjugate silyl transfer to acceptors **1a-c,f,g**, **353** (Scheme 181).³³⁰

Scheme 181. Enantioselective conjugate silyl addition onto cyclic acceptors.

Table 109.

Entry	1/353	Yield (%)	<i>ee</i> (%)	Config.
1	1a	355a : 70	98	(<i>S</i>)
2	1b	355b : 45	96	(<i>S</i>)
3	1c	355c : 22	92	(<i>S</i>)
4	1f	355d : 39	>99	(<i>R</i>)
5	1g	355e : 58	98	(<i>S</i>)
6	353	355f : 9	98	(<i>R</i>)

In the silyl transfer onto *Z*- α,β -unsaturated esters **356**, **357**, **358**, the reduction can still takes place however, it was not predominant, ranging from 10-20%. Virtually all of the acceptors underwent high stereoselective 1,4-addition in satisfactory yields (Scheme 182, Table 110). Excellent enantioselectivities were consistently observed for arylated acceptors, in most circumstances with the branched alkyl chain.³³⁰

Z-356a: R = Ph

Z-356b: R = 4-Me

Z-356c: R = 4-Anisyl

Z-356d: R = 4-ClC₆H₄

Z-356e: R = *n*-Bu

Z-356f: R = *i*-Bu

Z-356g: R = *i*-Pr

Z-357a: R = Ph

Z-357b: R = *n*-Bu

Z-358a: R = Ph

Z-358b: R = *n*-Bu

Scheme 182. Enantioselective silyl transfer onto Z-configured acceptors.

Table 110. Enantioselective conjugate silyl transfer onto acyclic acceptors

Entry	356/357/358	Yield (%)	<i>ee</i> (%)
1	Z-356a	359a: 66	>99
2	Z-356b	359b: 58	>99
3	Z-356c	359c: 50	>99
4	Z-356d	359d: 58	>99
5	Z-356e	359e: 55	>99
6	Z-356f	359f: 44	>99
7	Z-356g	359g: 0	-
8	Z-357a	360a: 65	>99
9	Z-357b	360b: 72	98
10	Z-358a	361a: 60	>99
11	Z-358b	361b: 58	>99

A plausible mechanism, for the Rh(I)-catalyzed 1,4-addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds is shown in Scheme 183. This catalyzed reaction starts with a transmetalation, in which an Rh(I)–OH complex reacts with a C(sp²)–B bond to give the nucleophilic Rh(I)–C(sp²) complex. Consequently, the question arose as to whether the same Rh(I)–OH complex would exhibit the same reactivity toward an Si–B linkage. In this situation (Scheme 183),³³¹ the catalysis starts with the chemoselective coordination of **354**,^{332, 333} to the Rh(I)–OH complex **362**, with the assumption that in **354**, boron is a stronger Lewis acid than silicon (**362**---**363**). Therefore the silicon–boron bond in intermediate **363** is weaker and may be cleaved as illustrated, thus releasing a boric acid **364** and Rh(I)-Si complex **365** (**363**---**365**). The acceptor **366** is then seized by **365**, and conjugate silyl transfer yields Rh(I) enolate **367** (**365**---**367**), which expels the active catalyst **362** under hydrolysis conditions (**367**---**368**).³³⁰

Scheme 183. Tentative catalytic cycle of conjugate silyl transfer.

2.3. Organozincs

An efficient Rh-catalyzed 1,4-addition reaction can be employed to synthesize the biologically active 2-aryl-4-piperidones **370a-f** with high enantioselectivity when organozinc reagents **371a-f** are used as nucleophiles. This protocol was applied to the enantioselective synthesis of the key intermediate in total synthesis of tachykinin antagonists. The applications of this strategy has been further shown both by the electrophilic quench and by the utilization of other α,β -unsaturated substrates **369**. Future investigations revealed further applications of these versatile organozinc reagents as reactive nucleophiles, in Rh-catalyzed 1,4-addition and other associated transformations.³³⁴

The scope of the catalytic stereoselective 1,4-addition of organozinc reagents to **1** is fairly broad. For instance, sterically and electronically diverse arylzinc reagents are well tolerated and afford the products consistently in good yields and with excellent enantioselectivities (Scheme 184).³³⁴

- 371a:** Ar = Ph, yield = 95%, *ee* = >99.5%
371b: Ar = 4-PhC₆H₄, yield = 97%, *ee* = >99.5%
371c: Ar = 4-MeOC₆H₄, yield = 90%, *ee* = 99%
371d: Ar = 4-FC₆H₄, yield = 91%, *ee* = >99.5%
371e: Ar = 3,5-(Me)₂C₆H₃, yield = 87%, *ee* = 99%
371f: Ar = 2-MeC₆H₄, yield = 100%, *ee* = 99%

Scheme 184. Scope of the organozinc reagents in the Rhodium-catalyzed 1,4-addition to **369**.

This 1,4-addition methodology can also be applied to the synthesis of key intermediate **372** for the total synthesis of tachykinin antagonists (Figure 19). In this context, the reaction of **369** with 4-fluoro-2-methylphenylzinc chloride catalyzed by $[\text{RhCl}((R)\text{-binap})]_2$, with subsequent removal of the benzyloxy carbonyl group, provides compound (*R*)-**372** in high yield and enantioselectivity (Scheme 185; 73% yield over two steps, 97% *ee*).³³⁴

Figure 19. Examples of tachykinin antagonists.

Scheme 185.

Hayashi et al. reported on a Rh-catalyzed 1,4-addition reaction to provide 2-aryl-4-piperidones, which are interesting from synthetic and biological points of view. They can be synthesized effectively with high enantioselectivity by the utilization of organozinc reagents as the nucleophilic component. This protocol can also be applied to the enantioselective synthesis of the key intermediate of tachykinin antagonists. The use of this process has been further disclosed by the electrophilic quench and by the utilization of other α,β -unsaturated substrates. The application of the stereoselective 1,4-addition of organozinc reagents mediated by Rh(I)/(*R*)-binap is not restricted to the enantioselective synthesis of 2-aryl-4-piperidones. Therefore, both cyclic and acyclic α,β -enones are enantioselectively arylated under these conditions, to afford β -chiral ketones **373** and **374** in excellent chemical yield and enantioselectivity (Scheme 186).³³⁴

Scheme 186.

A novel and efficient catalytic approach has been developed for the stereoselective synthesis of 2-aryl-2,3-dihydro-4-quinolones **376a-l** involving the Rh-catalyzed 1,4-addition of arylzinc reagents **370** to 4-quinolones **375a-d**. These 1,4-adducts can be obtained with high enantioselectivity by using (*R*)-binap **L4** as a ligand; high yields were obtained by performing the reactions in the presence of chlorotrimethylsilane. Thus the Rh-catalyzed stereoselective 1,4-addition of various arylzinc reagents to 4-quinolones **375**³³⁶⁻³³⁸ in the presence of chlorotrimethylsilane gave the desired compound **376** (Table 111). As illustrated in Table 111, a series of 4-quinolones bearing substituents on the fused benzene ring can be subjected to the 1,4-addition reaction under these conditions. It is noteworthy that not only phenylzinc chloride but also various other arylzinc chlorides, undergo this reaction to give a wide a variety of 2-aryl-2, 3-dihydro-4-quinolones in high yields and with excellent enantioselectivities (72-100% yield, 86-99% *ee*). It was also found that THF was a solvent of choice for this approach; thus a solution of arylzinc chloride and a THF solution of chlorotrimethylsilane were simultaneously added to a mixture of 4-quinolones and Rh/(*R*)-binap catalyst in THF (Scheme 187).³³⁵

Scheme 187.

Table 111. Rhodium-catalyzed stereoselective 1,4-addition of arylzinc reagents to 4-quinolones.

Entry	R 375	Ar 370	Yield (%)	<i>ee</i> (%)	Config.
1	375a : H	370a : Ph	376a : 88	98	(<i>R</i>)
2	375a : H	370e : 3,5-(Me) ₂ C ₆ H ₃	376b : 100	98	(<i>R</i>)
3	375a : H	370f : 2-MeC ₆ H ₄	376c : 74	86	(<i>R</i>)
4	375b : 6-Cl	370a : Ph	376d : 89	99	(<i>R</i>)
5	375b : 6-Cl	370c : 4-MeOC ₆ H ₄	376e : 82	88	(<i>R</i>)
6	375b : 6-Cl	370d : 4-FC ₆ H ₄	376f : 72	95	(<i>R</i>)
7	375c : 6,7-(MeO) ₂	370a : Ph	376g : 87	99	(<i>R</i>)
8	375c : 6,7-(MeO) ₂	370g : naphthalene	376h : 92	98	(<i>R</i>)
9	375c : 6,7-(MeO) ₂	370d : 4-FC ₆ H ₄	376i : 87	97	(<i>R</i>)
10	375d : 8-oxo-[1,3]dioxolo	370 : Ph	376j : 94	94	(<i>R</i>)
11	375d : 8-oxo-[1,3]dioxolo	370g : naphthalene	376k : 87	90	(<i>R</i>)
12	375d : 8-oxo-[1,3]dioxolo	370e : 3,5-(Me) ₂ C ₆ H ₃	376l : 96	97	(<i>R</i>)

The stereochemical results of these 1,4-addition reactions catalyzed by Rh/(*R*)-binap can be understood by the α -*re*-face approach of the substrate that avoids a steric repulsion between the phenyl group on the phosphorus atom of (*R*)-binap **L4** and the benzene ring, which is fused to the substrate (Figure 20).³³⁵

Figure 20. Proposed stereochemical pathway for the stereoselective 1,4-addition to 4-quinolones catalyzed by Rh/(*R*)-binap (R = CO₂Bn).

The highly stereoselective 1,4-addition of arylzinc chlorides **370** to (*E*)-3-arylpropenals **378a-e** occurred under catalysis of rhodium/(*R*)-binap and chlorotrimethylsilane followed by hydrolysis, gave the respective 3,3-diarylpropanals **379a-j** in high yields and with 98–99% *ee*.¹⁴² Some **379a-j** are key intermediates in the synthesis of biologically active compounds.^{339,340} The presence of the chlorosilane is vital for obtaining the 1,4-addition adducts in high yields (Scheme 188).¹⁴²

Scheme 188.

Table 112. Rhodium-catalyzed stereoselective 1,4-addition to enal **378**.

Entry	Ar ¹ 378	Ar 370	Yield (%)	<i>ee</i> (%)	Config.
1	378a :4-MeOC ₆ H ₄	370a : Ph	379a : 80	99	(<i>S</i>)
2	378b :2-MeOC ₆ H ₄	370a : Ph	379b : 74	99	(<i>S</i>)
3	378c :2-MeO-5-MeC ₆ H ₃	370a : Ph	379c : 66	99	(<i>S</i>)
4	378d :4-FC ₆ H ₄	370a : Ph	379d : 80	98	(<i>S</i>)
5	378e :Ph	370c : 4-MeOC ₆ H ₄	379e : 55	99	(<i>R</i>)
6	378e :Ph	370h : 3-MeOC ₆ H ₄	379f : 75	99	(<i>R</i>)
7	378e :Ph	370i : 3,5-Me ₂ C ₆ H ₃	379g : 68	99	(<i>R</i>)

8	378e :Ph	370j : 2-Naphthyl	379h : 75	99	(<i>R</i>)
9	378e :Ph	370k : 4-ClC ₆ H ₄	379i : 79	99	(<i>R</i>)
10	378e :Ph	370l : 3-ClC ₆ H ₄	379j : 79	98	(<i>R</i>)

The stereochemical logic and outcome of the 1,4-addition reaction catalyzed by Rh/(*R*)-binap can be reorganized by the α -si-face attack of the enal, which avoids steric repulsion between the phenyl moiety on the phosphorus atom of (*R*)-binap and the carbonyl group of the enal (Figure 21).

Figure 21. The stereochemical pathway in the rhodium-catalyzed stereoselective 1,4-addition.

Zejschwitz *et al.* reported on the feasibility of kinetic resolutions of racemic monosubstituted cyclohex-2-enones by Rh/binap-catalyzed reactions in 2012. The 1,4-addition of aryl groups resulted in inferior outcomes since either catalyst or substrate control predominated.³⁴¹ It can be stated that the ratio of rate constants $k_{\text{fast}}/k_{\text{slow}}$ is very low in Rh/binap-catalyzed 1,4-additions of aryl groups to chiral cyclohex-2-enones, since catalyst control is very strong when either a 5- or 6-substitution occurs;³⁴²⁻³⁴⁷ substrate control is also very strong when a 4-substitution takes place. In contrast to the conjugate addition, the methyl group can be transformed directly and not through transmetalation to Rh.

When **382** was reacted with PhB(OH)₂ and [Rh(binap)OH]₂, no transformation takes place and a change in color from red to yellow occurs with the decomposition of the catalyst. Transformation with the more reactive PhZnCl **370a** was possible and gave only the *trans*-diastereomer **383a** in satisfactory yield but very low *ee* (Scheme 189). Unsatisfactory results were obtained when using an aryl group; GC analysis of the reaction with PhZnCl disclosed a maximum *ee* of 74% for **383a** at 13% conversion and a maximum *ee* of 15% for **382** at 21% conversion. Therefore the

substrate control of **382** completely prevails over catalyst control, thus making kinetic resolutions improbable (Scheme 189).³⁴¹

383a: Ar = Ph, yield = 79%, *ee* = 13%

383b: Ar = 4-FC₆H₄, yield = 57%, *ee* = <2%

383c: Ar = 4-MeOC₆H₄, yield = 15%, *ee* = 18%

Scheme 189. 1,4-Addition of various aryl groups to enone **382**

To evaluate the substrate control, PhZnCl or PhB(OH)₂ was added to enones **384** to afford 1:1 mixtures of *trans*- and *cis*-**385** with excellent selectivity (Table 113).³⁴¹

Scheme 190.

Table 113. 1,4-Addition of ArZnCl and ArB(OH)₂ to Enones **384a,b**.

Entry	Condition	R 384	Ln	2/370	Yield (%)	<i>trans</i> / <i>cis</i>	<i>ee</i>	<i>ee</i>
							<i>trans</i> (%)	<i>cis</i> (%)
1	A	384a: Me	L4'	PhZnCl	87	1:1	96	>99
2	B	384a: Me	L4	PhB(OH) ₂	82	1:1	97	>99
3	A	384b: <i>i</i> -Pr	L4	PhZnCl	79	1.1:1	97	>99
4	C	384a: Me	L4'	(<i>o</i> -Tol) ZnCl	74	1.2:1	94	>99

5	A	384a : Me	L4'/ L4	PhZnCl	79	7:1	-	-
6	B	384a : Me	L4'/ L4	PhB(OH) ₂	84	4:1	-	-
7	A	384b : <i>i</i> -Pr	L4'/ L4	PhZnCl	79	8:1	-	-
8	C	384a : Me	L4'/ L4	(<i>o</i> -Tol) ZnCl	73	12:1	-	-
9	B	384a : Me	L4'	PhB(OH) ₂	85	1:25	>99	>99

N-Sulfonylimines of cycloalk-2-enones are appropriate substrates for the enantioselective Rh(I)/binap-catalyzed 1,4-additions of arylzinc halides. The cyclic enamides, obtained after quenching, are sensitive to chromatography on silica gel, but can be subjected to diastereoselective reductions to afford *cis*- or *trans*-3-arylcycloalkylamines with five- to seven-membered rings. The 1,4-addition is not affected by the methyl group at C-5 of six-membered rings, thus providing further configurational options. 3-Arylcycloalkylamines are subunits in several bioactive compounds, which can be oxidatively converted into cyclic γ -amino acids.

α,β -Unsaturated *N*-sulfonylimines of cycloalk-2-enones **386** react similarly with the respective carbonyl compounds via Hayashi-Miyaura-type reactions with arylzinc halides **370**. This methodology can be utilized for the enantioselective synthesis of a wide variety of 3-arylcycloalkylamines, with either a *cis*- or *trans*-configuration at the ring, when it is combined with an appropriate reduction method. When cyclohexanone derived imines were used, the stereocontrol by the Rh(I)/binap catalyst can overcome the substrate control due to the stereocenter at C-5 of the ring. Thus, this methodology can be employed for the asymmetric synthesis of all four diastereomers of 3-methyl-5-phenylcyclohexylamine **387a-g**. The introduced aryl rings can be degraded to carboxy groups to give conformationally rigid cyclic γ -aminoacids.

This strategy was also applied to the 1,4-addition of different aromatic residues (Scheme 191). In comparison to the phenyl group, most aryl groups needed a higher catalyst loading to provide high yields, whereas the enantioselectivity was always excellent, independent of the amount of catalyst used. Both electron-donating and electron-withdrawing groups on aryl rings are reactive, although slightly longer reaction times were required for the latter. The steric inference affected the 2-tolyl reagent, however a moderate yield was obtained; good results were observed with 3,5-xylyl or 2-naphthyl groups.³⁴⁸

Scheme 191. 1,4-Addition of various aryl groups.

2.4. Organozirconiums

Highly enantioselective 1,4-additions of alkenyl zirconocene chlorides **389a-e** to α,β -enones **1a** catalyzed by a chiral Rh complex created from [Rh(cod)(MeCN)₂]BF₄ and (*S*)-binap afforded **390** with good *ee* and in satisfactory chemical yield. The reaction could be employed to either cyclic or acyclic enones with up to 99% *ee* being obtained. (*E*)-1-Alkenyl groups can be readily and enantioselectively added at the β -position of various ketones. The reaction mechanism involves transmetallation between the alkenyl zirconocene chloride and the Rh-complex to afford the alkenyl rhodium intermediate which plays a key role (Scheme 192, Table 114).³⁴⁹

Scheme 192.

Table 114. Stereoselective 1,4-addition of alkenylzirconocene chlorides **389** to α,β -enone **1** catalyzed by rhodium-(*S*)-binap **L4'** complexes

Entry	R 389	1	Yield (%)	<i>ee</i> (%)
1	389b : C ₄ H ₉	1a	390a : 83	96
2	389c : C ₅ H ₁₁	1a	390b : 96	99
3	389d : <i>tert</i> -C ₄ H ₉	1a	390c : 49	79
4	389e : Ph	1a	390d : 20	95
5	389a : C ₆ H ₁₃	1b	390e : 99	86 (<i>S</i>)
6	389b : C ₄ H ₉	1b	390f : 93	86
7	389a : C ₆ H ₁₃	1c	390g : 87	97
8	389b : C ₄ H ₉	1c	390h : 63	95
9	389a : C ₆ H ₁₃	1d	390i : 85	72
10	389b : C ₄ H ₉	1d	390j : 82	71
11	389a : C ₆ H ₁₃	1t	390k : 62	79 (<i>S</i>)
12	389b : C ₄ H ₉	1t	390l : 52	80

The reaction mechanism (Scheme 193) most probably involves the creation of an alkenylrhodium intermediate **392** via transmetallation between the alkenylzirconocene chloride **389** and the Rh complex. This reaction route could apply to Rh-catalyzed 1,4-additions of a wide range of organometallic reagents.^{350, 351} Alkenylrhodium **392** can subsequently be added to α,β -enones **1** to afford oxa-*p*-allyl-Rh **393**, followed by reaction with alkenylzirconocene chloride **389** to provide alkenylrhodium intermediate **392** and afford zirconium enolate **394**.³⁴⁹

Scheme 193.

In 2004, Hanzawa *et al.* reported on a highly efficient conjugate addition reactions of alkenyl zirconocene chloride complexes **395** to α,β -enones, α,β -enoic acid esters, and α,β -enoic acid amides **396**, **397**, **398** catalyzed by $[RhCl(cod)]_2$ catalyst to provide 1,4-adducts **399**, **400**, **401** in excellent yields. Significantly, the Rh(I)-catalyst is not restricted by the 1,4-addition of **395a-j** to α,β -enones **396a-d**, and so α,β -enoic acid esters **397a-d** and α,β -enoic acid amides **398** are appropriate for the 1,4-addition. In the reactions of **397**, there is not an appreciable difference in terms of the reactivity of esters **397a-c** with either bulky or small groups. Excellent chemical yield and high diastereoselectivity (95% yield, 90% *de*) were achieved via the reaction of α,β -enoic acid amide derived from Oppolzer's sultam and 2-butenoyl chloride, when the Evans' chiral oxazolidinone, an excellent chiral auxiliary in terms of diastereoselectivity and chemical yield, is employed (98% yield, 26% *de*) (Table 115).³⁵⁰

Scheme 194.

Table 115. [RhCl(cod)]₂-catalyzed 1,4-addition reactions of **395**.

Entry	X	R ¹	R ²	R ³	396/397/398	Yield (%)
1	Ph	Ph	H	H	396a	399a : 93
2	Ph	Me	H	H	396b	399b : 60
3	Ph	H	H	Me	396c	399c : 72
4	Ph	Me	Me	H	396d	399d : 56
5	Ph	H	H	H	396e	399e : 98
6	Me	Ph	H	H	396f	399f : 94
7	<i>n</i> -C ₈ H ₁₇	Me	H	H	396g	399g : 53
8	-	cyclopent-2-enone	H	H	396h	399h : 74
9	-	cyclohex-2-one	H	H	396i	399i : 93
10	-	cyclopent-2-enone	H	H	396j	399j : 91
11	MeO	Ph	H	H	397a	400a : 93
12	<i>i</i> -PrO	Ph	H	H	397b	400b : 90
13	<i>t</i> -BuO	Ph	H	H	397c	400c : 96
14	MeO	<i>n</i> -C ₅ H ₁₁	H	H	397d	400d : 90
15	PhCH ₂ NH ₂	Me	H	H	398a	401a : 68
16	PiperidinyI	Me	H	H	398b	401b : 92
17	oxazolidine-2-one	Me	H	H	398c	401c : 95
18	oxazolidine-2-one	Me	H	H	398c	401d : 85

It is noteworthy that alkyl zirconocene chloride is an ineffective reagent under the present reaction conditions, and the same was noticed in Rh(I)-catalyzed reactions with imines.³⁵²⁻³⁵⁵ Since the transfer of the alkyl group from Zr to Rh is slower than the alkenyl group,³⁵⁶ this 1,4-addition reaction of **1** is expected to involve the creation of alkenyl rhodium species *via* the

transmetallation at the first stage. The overall process is illustrated in Scheme 195, in which the 1,4-adducts are obtained from a catalytic cycle as a Zr-enolate **403**.

Scheme 195. A catalytic cycle for the 1,4-addition reaction of **395**.

The effective additions of **395** to α,β -enoic acid amides **398** under the present conditions encouraged the same research group to test the diastereoselective 1,4-addition of **404a,b** to chiral α,β -enoic acid amides **405a-c**. The diastereoselective 1,4-additions of **395** to chiral α,β -enoic acid amides **405** obtained from 2-butenoyl chloride and chiral amine derivatives are shown in Table 116. However in the present Rh(I)-catalyzed 1,4-addition of the generation of such chelated cationic zirconocene complex, it seems impossible due to the absence of $\text{BF}_3 \cdot \text{OEt}_2$; therefore, the utilization of Evans' chiral oxazolidinone auxiliary only poorly distinguished the diastereoface of the carbon–carbon double bond of **405a,b** to afford 1,4-adducts **406a-d**.³⁵⁰

Scheme 196.

Table 116. Diastereoselective 1,4-addition reactions of **404** to **405**.

Entry	404	R 405	Yield (%)	<i>de</i> (%)
1	404a	405a : <i>t</i> -Bu	406a : 96	11
2	404b	405a : <i>t</i> -Bu	406b : 98	26
3	404c	405a : <i>t</i> -Bu	406c : 92	88
4	404c	405b : <i>n</i> -Bu	406d : 95	90

2.5. Organostannanes

Diene (*R,R*)-**L5** showed excellent capability as a chiral ligand in some catalytic reactions where chiral phosphine ligands could not be employed due to the low catalytic activity of the phosphine complexes. The Rh-catalyzed 1,4-addition of organostannanes is one such example.^{357, 358} The reaction of phenyltrimethylstannane **407** with 2-cyclohexenone **1a** mediated by 3 mol% of the (*R,R*)-**L5**-rhodium catalyst and in the presence sodium methoxide in toluene afforded the stannyl enol ether **408** in high yield (Scheme 197). Upon hydrolysis, (*R*)-**409** was obtained in 80% chemical yield and with 95% *ee*. Under the same conditions, the Rh catalyst, which is coordinated with binap ligand, afforded less than 10% yield of the corresponding 1,4-addition product.⁵²

Scheme 197.

When phenyltributylstannane **411b** was reacted with dehydroalanine **410e** under optimal conditions in the absence of guaiacol, the expected desired product **412d** was obtained in 45% yield and with high enantioselectivity (91% *ee*). These results were comparable to those obtained in the presence of guaiacol (Table 117). Phenol is only useful and needed in the reactions with potassium organotrifluoroborates, but plays a crucial role in the regeneration of the Rh species required for the transmetalation with borane reagents. The suggested mechanism involves a 1,4-addition type reaction of the organometallic reagent with subsequent intramolecular hydride transfer from nitrogen to the neighbouring carbon. It was assumed that the more acidic phenols or even water could act as proton sources. It was also suggested that the Rh enolate species is protonated before the hydride transfer takes place, thus this protonation is not expected to be diastereoselective (Scheme 198, Table 117).¹⁴⁵

Scheme 198.

Table 117. 1,4-Addition/enantioselective protonation using phenylstannane.

Entry	410	R' 411	Yield (%)	ee (%)	Config.
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1	410a	411a: Me	412a: 89	71	<i>R</i>
2	410a	411b: <i>n</i> -Bu	412b: 82	88	<i>R</i>
3	410c	411a: Me	412c: 80	88	<i>R</i>
4	410e	411b: <i>n</i> -Bu	412d: 45	91	<i>R</i>
5	410d	411a: Me	412e: 61	17	<i>S</i>
6	410b	411a: Me	412f: 0	-	-

2.6. Organoaluminiums

It has been found that arylalanes **414** are excellent nucleophiles in the Rh-catalyzed conjugate addition reactions. Elevated temperatures are frequently required for boron nucleophiles, but only 1.2 to 1.5 equivalents of alane gave the same conversion at 5 °C after prolonged reaction time. Significantly, commercially available binap promoted the reaction. The vital electronic effect of the alkyl substituent at the 4-position of trisubstituted enones was realized, and leads to the nucleophilic attack to the 4-position in spite of additional steric hindrance. A wide variety of electron donating and electron-withdrawing substituents were tolerated on the aromatic ring. Furthermore the desired alanes were created from both the respective lithium or Grignard precursors. Ultimately, a wide variety of cyclic and acyclic substrates resulted in excellent *ee* in this transformation.³⁵⁹

The substrate scope was also studied. Scheme 199 indicates that a wide variety of linear and cyclic substrates **413a-f** could be employed in this conversion. In all cases, *ee* were obtained in all reactions, even for the linear substrates. The olefin geometry of the enone can affect the absolute configuration of the product, as *E*- and *Z*-substrates afforded the opposite enantiomers **415a-f** (Scheme 199). Even the normally problematic five-membered-ring substrate showed high reactivity, and virtually perfect selectivity. The reduced yield obtained could be justified by the sensitivity of the product in column chromatography (Scheme 199).³⁵⁹

Scheme 199. Screening of different substrates.

Rhodium(I)/Binap complexes can catalyze highly enantioselective additions of methyl- and arylaluminum reagents **414** to cyclic α,β -unsaturated *N*-tosyl ketimines **416**. These reactions are affected by the choice of solvent and are dependent of the nature of the substituents at the ring. By using an appropriate substrate in a suitable solvent, the reaction takes place in a 1,4-fashion to give the desired 1, 3-substituted cycloalkyl amines **417** after reduction.

In addition, the reversed facial selectivity and the regioselective divergence observed with ketimine (*R*)-**416** allowed the authors to propose reasonable mechanisms for both addition modes (Scheme 200).³⁶⁰

Scheme 200. Regiodivergent reaction on ketimine (*R*)-**416** and 1,4-addition to ketimine **416**.

In the conversions of ketimine **416**, it was observed that the facial selectivity was the same for the addition of both methyl and phenyl groups, which is an indication of similar catalytic cycles. Nevertheless, the facial selectivities of the 1,4-addition are inverted, while the selectivity of the latter is related to that of a standard proposed by Hayashi-Miyaura for the reaction with arylboronic acids and Binap as a chiral ligand.²² Therefore, the 1,4-addition of aluminum reagents may progress via a similar mechanism involving the transmetalation of the carbon nucleophile to rhodium and comprising, in the case of imine (*R*)-**416** and (*R*)-binap, transition state **419** (Figure 22). The observed regiodivergence in the conversion of (*R*)-**416** might then originate from the unfavored steric interactions of the methyl group at the substrate and the binap ligand in the transition state **420**.³⁶⁰

Figure 22. Proposed transition states involved in 1,4- to imine (*R*)-**416** (R = Ph)

3. Miscellaneous

In addition to the reaction of aryltitanium reagents $[\text{ArTi}(\text{OPri})_3]$ providing titanium enolates as 1,4-addition products, the 1,4-addition of lithium aryl(tetraisopropoxy)titanates $[\text{ArTi}(\text{OPri})_4\text{Li}^+]$ mediated by chlorotrimethylsilane afforded silyl enol ethers. The enantiomeric excesses were all high in both reagent systems. The addition of lithium aryl(tetraisopropoxy)titanates $[\text{ArTi}(\text{OPri})_4\text{Li}^+]$ **421a-c** to α,β -unsaturated ketones **1a,b,d** proceeded smoothly resulting in high enantioselectivity (up to 99% *ee*) mediated by an excess amount of chlorotrimethylsilane and a Rh catalyst, created from $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ and (*S*)-binap, in THF at 20 °C to afford the corresponding silyl enolates as 1,4-addition products **423** in high yield. The presence of chlorotrimethylsilane is necessary for the 1,4-addition to occur. It was found that the chemical yields for the addition to 2-cyclopentenone were higher in the present reagent system than in the former system (Scheme 201, Table 118).³⁶¹

Table 118. Stereoselective 1,4-addition of aryltitanate **421** to enone **1** catalyzed by $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ / (*S*)-binap.

Entry	1	Ar 421	Yield (%) of 3	<i>ee</i> (%) of 423
1	1a	421a : Ph	422a : 90	96
2	1b	421a : Ph	422b : 91	99
3	1b	421a : Ph	422c : 85	99
4	1b	421a : Ph	422d : 92	99
5	1b	421b : 4- $\text{CF}_3\text{C}_6\text{H}_4$	422e : 94	97
6	1b	421c : 4-MeOC ₆ H ₄	422f : 83	96
7	1d	421a : Ph	422g : 67	90

The catalytic cycles of the Rh-catalyzed reactions utilizing the two titanium reagents were suggested by analysis of ^{31}P NMR spectra of the Rh intermediate, i.e., **424**, insertion of an enone into arylrhodium species generating (oxa- α -allyl)rhodium intermediate, **425**) silylation of the (oxa- α -allyl)rhodium with chlorotrimethylsilane to provide silyl enolate and a chloro-rhodium complex, and **426**; transmetalation of the aryl group from aryltitanate to the chloro-rhodium created the aryl-rhodium (Scheme 202).³⁶¹

Scheme 202. Catalytic cycle of the 1,4-addition of $\text{PhTi}(\text{OPri})_4\text{Li}^+$ in the presence of ClSiMe_3 .

The Rh-catalyzed reaction of *Sb*-aryl-1,5-azastibocines with α,β -unsaturated ketones and esters **1a, b**, **427a-d** has been achieved and reported (Scheme 203). The corresponding 1,4-conjugate adduct was prepared in aqueous NMP (*N*-methyl-2-pyrrolidinone) under catalysis of $[\text{RhCl}(\text{cod})]_2$; the possible formation of the Heck adduct was not observed under these conditions. Reactions with different enones and enoates were also successfully performed to establish the generality of this 1,4-conjugate addition.

The reactions of enones unsubstituted at the β -position with cyclic enones afforded the expected 1,4-adducts in good yields. Nevertheless, the yields of the 1,4-adduct showed an appreciable decrease in the reactions of enones with bulky substituents at the β -position. However, in the

reaction of enoates, the bulkiness of the ester group did not have any significant affect since methyl, butyl, and *t*-butyl esters gave the respective 1,4-adducts **429a-f** in high yields. However, a substituent on the double bond decreased the yield of the 1,4-addition (Scheme 203).³⁶²

Scheme 203. Reaction of **428** with various enones and enoates

Under the optimal conditions, different Sb-aryl-1,5-azastibocines **428a-d** were reacted with methyl vinyl ketone **335g** (Scheme 204). Irrespective of the electronic nature of the substituent on the aryl group, all of the 1,4-conjugate addition could be performed at 100 °C to obtain the products in satisfactory yields. From these results, it was concluded that 1, 5-azastibocines **428** were good aryl donors in the 1,4-conjugate addition (Scheme 204).³⁶²

Scheme 204. Reaction of various Sb-aryl-1,5-azastibocines **428** with methyl vinyl ketone **335g**

The proposed catalytic cycle for the conjugate addition is similar to the mechanism for the 1,4-addition of organoboronic acid to enones (Scheme 205).^{60, 114, 157} Initially, the aryl group on 1, 5-

azastibocine was transmetallated to a suitable Rh catalyst to provide aryl-rhodium complex **430**. Insertion of an α,β -unsaturated compound to the aryl-Rh bond afforded η^3 -oxa- π -allyl Rh complex **431**, which upon hydrolysis with water present in the aqueous media afforded 1,4-conjugate adduct **432** and rhodium hydroxide **433**. In the aqueous media, the hydrolysis process was expected to be more favorable than the β -elimination process. Thus, the Heck-type adduct **434** was not generated and the formation of 1,4-conjugate adduct **432** was exclusively observed. The rhodium hydroxide **433** was then subjected to transmetallation by 1,5-azastibocine to recreate aryl-rhodium complex **430** (Scheme 205).³⁶²

Scheme 205. Possible catalytic cycle

A novel and efficient Rh-catalyzed conjugate addition of indium reagents to electron deficient olefins was successfully accomplished. The reaction took place in THF/MeOH at 110 °C in the presence of arylindium dichlorides **435a-d**, and Rh(I)-binap complex as an effective catalyst, and α,β -unsaturated ketones and lactones **1a-d,g** to provide **436a-e** in good to high yields. The addition of MeOH is vital for a successful transformation. The NMR spectra indicate that in the catalytic cycle, the indium organometallic is unchanged. Furthermore, when chiral ligands are employed, the conjugate addition reaction proceeds to completion giving only moderate enantioselectivity (Scheme 206, Table 119).³⁶³

Scheme 206.

Table 119. Reaction of arylindium dichlorides with α,β -unsaturated carbonyl compounds

Entry	1	R 435	Yield (%)
1	1a	435a : Ph	436a : 94
2	1a	435b : 4-CF ₃ C ₆ H ₄	436b : 69
3	1a	435c : 4-FC ₆ H ₄	436c : 46
4	1a	435d : 3-FC ₆ H ₄	436d : 66
5	1b	435a : Ph	436e : 80
6	1b	435b : 4-CF ₃ C ₆ H ₄	436f : 57
7	1b	435c : 4-FC ₆ H ₄	436g : 56
8	1c	435a : Ph	436h : 70
9	1c	435b : 4-CF ₃ C ₆ H ₄	436i : 62
10	1d	435a : Ph	436j : 63
11	1d	435b : 4-CF ₃ C ₆ H ₄	436k : 45
12	1g	435a : Ph	436l : 76
13	1g	435b : 4-CF ₃ C ₆ H ₄	436m : 58
14	1g	435c : 4-FC ₆ H ₄	436n : 47
15	1g	435d : 3-FC ₆ H ₄	436o : 56

The effect of MeOH in the reaction mixture was also studied by NMR spectroscopic analysis. In the addition of MeOH, the PhInCl_2 reagent gave the same results as before. The ^{13}C NMR spectra indicated that the reagents $\text{Ph}_2\text{InCl}/\text{PhInCl}_2$ were in the same 7:93 ratio. However, when the reaction mixture was heated at $110\text{ }^\circ\text{C}$, PhInCl_2 was obtained as the sole product. This result is a good indication that the nucleophilic substitution of the chlorine atoms in PhInCl_2 does not occur. This is in agreement with the results reported about the stability of organoindium halides in aqueous media.^{364, 365} Thus it is likely that the role of MeOH in the Rh-catalyzed conjugate addition reactions is connected with the creation of the catalytic species and/or the methanolysis of the oxoallyl rhodium enolate as an intermediate (Scheme 207).³⁶³

Scheme 207. Proposed catalytic cycle for the rhodium-catalyzed conjugate addition of aryliindium dichlorides to enones. Key: (a) Transmetalation. (b) Coordination to the electron-deficient olefin. (c) Alkene insertion into the Rh-Ar bond. (d) Methanolysis of the (oxa- π -allyl)rhodium intermediate.

4. Conclusion

The Rh complex-catalyzed asymmetric 1,4-addition of organoboron reagents, which was discovered by Hayashi and Miyaura in 1998 is a rapidly growing area of research. The reaction can be performed in an aqueous solvent with high enantioselectivity, in most cases up to 90% *ee*, at about 100°C. The receptors for this asymmetric 1,4 addition reaction are mostly α,β -unsaturated ketones, esters, amides, phosphonates, nitroalkenes, etc. This reaction presents the best approach for the enantioselective introduction of aryl and alkenyl groups to the β -position of these electron poor olefins. Regarding the high reactivity of the transition metal -carbon bond towards different classes of carbon-carbon or carbon-heteroatom multiple bonds, the Rh intermediate is added expectedly to some unsaturated bonds besides the electron poor olefins. The addition of organoboron reagents to unactivated alkenes and alkynes, as well as aldehydes and imines by a Rh-complex has also been achieved and reported. The introduction of carbon atoms by this Rh-catalyzed reaction has been found to be restricted to sp^2 carbons. Since the insertion of an olefin into the Rh sp^3 carbon bond occurs in an intramolecular system, the asymmetric 1,4-addition of alkyl groups has so far not been realized. Thus, the catalytic asymmetric introduction of alkynyl groups is another subject which must be attempted. One of the most remarkable recent developments is the 1,4-addition of organosilicon, -tin, and -titanium reagents catalyzed by Rh-complexes. The reactions of aryltitanium reagents in an aprotic solvent are particularly promising, whose catalytic cycle is quite different to that for the reactions in protic solvents such as water. Several novel catalytic reactions of synthetic value have been developed by the incorporation of different types of organometallic reagents and unsaturated molecules. It has been found that some of them can be extended to catalytic asymmetric reactions with high enantioselectivity by the appropriate choice of the chiral ligands.

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Graphical Abstract

In this review, we try to highlight the recent advances in Rh-catalyzed asymmetric 1,4-conjugate addition reactions to α,β -unsaturated carbonyl and related compounds.

Rh-Catalyzed Asymmetric 1,4-Addition reaction to α,β -Unsaturated Carbonyl and related Compounds: An update

Majid M. Heravi,* Mahzad Dehghani, Vahideh Zadsirjan

Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran

*Corresponding author. Fax: + 98 21 88041344; e-mail: mmh1331@yahoo.com (M. M. Heravi)