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REVIEW

Strategy of total synthesis based on the use of Rh-catalyzed stereoselective 1,4-addition.

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In 1998, Hayashi and Miyaura reported the first asymmetric conjugate addition of aryl- and alkenyl- boronic acids to α,β-unsaturated ketones using chiral rhodium complexes as catalysts. During the last decade, this reaction has been developed quickly and the enantioselectivity was significantly improved with the emergence of new phosphine ligands. In addition to the methodological work, this reaction was applied as a key step in the total synthesis of natural compounds. The purpose of this paper focuses on examples of the use of this reaction to prepare elaborated chiral molecules with high diastereoselectivies and/or enantioselectivities.

1. Introduction

The stereoselective 1,4-addition of carbon nucleophile to enones is a widely used strategy for carbon-carbon bond formation affording chiral β-substituted ketones and is one of the most important methods for the preparation of optically active natural and pharmaceutical products. There are many examples reported in the literature employing a stoichiometric process either using a covalently bound chiral auxiliary or stoichiometric ligand coordinated to the counterion of the carbon nucleophile. Over the 3 last decades, considerable efforts have been made to propose efficient catalytic systems for enantioselective conjugate addition to α,β-unsaturated carbonyl derivatives. In 2010, the most significant methods - catalytic processes using chiral organometallic complexes and small chiral organic molecules - have been gathered into a textbook.[1] Among these methods promoting or catalyzing the stereoselective conjugate reactions, the use of rhodium-catalyst for the addition of boron derivatives to enones appears as a powerful synthetic tool for establishing new carbon-carbon bonds with high stereoselectivities. The purpose of this paper focuses on the use of this methodology for the total synthesis of natural and/or bioactive compounds.

Since the publication of the seminal work in 1997[2] of Miyaura and coworkers, both alkyl- and arylboronic derivatives (boronic acids or esters) have been extensively used as valuable coupling reagents in the presence of rhodium complexes to catalyze conjugate additions. Shortly afterwards, the first asymmetric 1,4-addition to enones has been published, the addition of phenylboronic acid to 2-cyclohexenone with the use of $[Rh(acac)(C_2H_4)_2]$ as rhodium source and in the presence of (*S*)-BINAP as chiral ligand in dioxane/H_2O at 100 °C afforded the 1,4-addition product with 97% ee and high yield (Scheme 1).[3] This new asymmetric rhodium-catalyzed reaction has been then quickly developed during the last decade and in particular to identify the best catalytic system (combination Rh/chiral ligand) aiming to generate the new chiral center in high enantioselectivity.[4] Among the large number of chiral ligands tried out, chiral dienes, chiral sulfoxides and chiral phosphoramidites have been employed successfully and these results have been recently combined into one review.[5]

In 2002, a catalytic cycle has been proposed by Hayashi and coll. according to NMR spectroscopic studies for the asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexenone catalyzed by the combination of Rh complex with (*S*)-BINAP (Scheme 2). The catalytic cycle follows a classical process corresponding to (i) a transmetalation step of the aryl group from boron to rhodium to form the phenylrhodium species **B**, (ii) an insertion of enone into the aryl-rhodium bond to generate the oxo-π-allylrhodium **C**, and finally (iii) hydrolysis of this rhodium enolate affording the product **3** and the hydroxorhodium species **A**. It is interesting to note that rhodium remains in the same oxidation state (+1) all along the catalytic cycle.

Shortly before, the same group proposed a stereochemical pathway for the enantioselective reaction according to the highly skewed structure known for metal coordinated with BINAP.[7] The Figure 1 discloses the formation of the product with (*S*) configuration. The 2-cyclohexenone coordinates to rhodium preferentially with its 2*si* face rather than its 2*re* face as the upper part of the (*S*)-BINAP-rhodium complex is blocked by one of the phenyl rings of the bidentate ligand. The following addition by insertion of the carbon-carbon double bond into the rhodium-phenyl bond leads to the formation of the stereogenic center with the absolute configuration (*S*).

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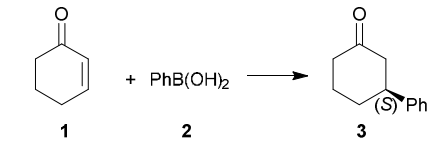
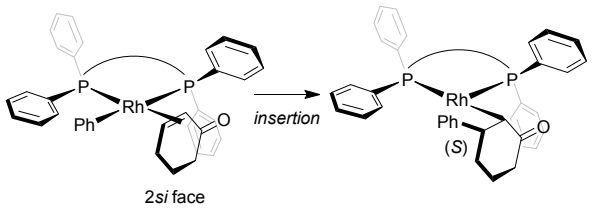


ketone / boronic acid (1 : 1.4)
3 mol% [Rh(acac)(CO)$_2$] / (*S*)-BINAP,
dioxane / H_2O (10 : 1), 100 °C, 5 h = 15% yield, 43% ee
3 mol% [Rh(acac)(C_2H_4)$_2$] / (*S*)-BINAP,
dioxane / H_2O (10 : 1), 100 °C, 5 h = 64% yield, 97% ee
ketone / boronic acid (1 : 2.5)
3 mol% [Rh(acac)(C_2H_4)$_2$] / (*S*)-BINAP,
dioxane / H_2O (10 : 1), 100 °C, 5 h = 93% yield, 97% ee

Scheme 1



2*si* face

Fig. 1 Stereochemical justification for the enantioselective addition of a phenylboronic acid to 2-cyclohexenone with Rh[(*S*)-BINAP] complex.

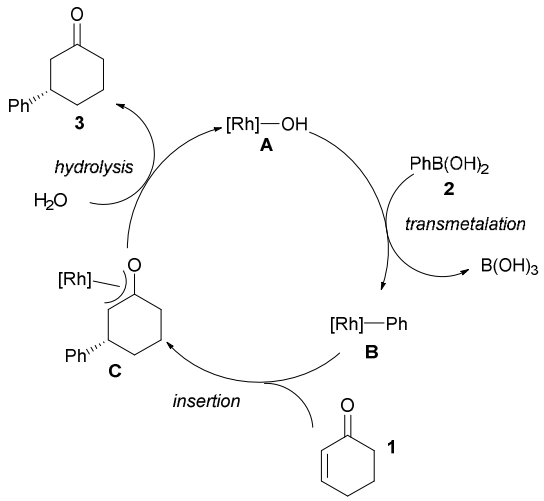
In addition to methodological works, this reaction was applied as a key step in the total synthesis of natural products. The purpose of this paper focuses on examples of the use of this reaction to prepare elaborated chiral compounds with high diastereoselectivies and/or enantioselectivities.

Among the various examples of total synthesis using the rhodium catalyzed stereoselective addition of a boron derivative to an enone as key step, two different approaches have to be distinguished. The first one is the diastereoselective approach in which the configuration of the newly stereogenic center, created in this 1,4-addition, is controlled due to the presence of another chiral center in one of the reagents (boronic species or α,β-enone). Thus the reaction is carried out with an achiral catalyst system and leads to one stereoisomer. In the second approach, called enantioselective, the formation and the control of the stereogenic center is dependent of the use of a chiral catalyst system and affords one enantiomer.The main text of the article should appear here with headings as appropriate.

2. Diastereoselective approaches

2.1. Total synthesis of (+)-brefeldin A (2008)

Brefeldin A (BFA, 7) is a lactone antibiotic first isolated in 1958 from the fungus Eupenicillium brefeldianum. BFA inhibits the transport of proteins from endoplasmic reticulum (ER) to Golgi apparatus and leads to protein accumulating in ER.



Scheme 2

Prolonged blocking of protein transport by BFA results in ER stress and apoptosis through multiple cellular events. Since its isolation, many approaches have been proposed to prepare this compound in the most efficient way, but also to provide access to analogs for biological studies. Among them, in 2008, Wu and coll.[8] reported a strategy based on the use of a diastereoselective Hayashi-Miyaura reaction. This synthesis started by the preparation of the chiral 4-substituted-cyclopentenone **4** in 8 steps starting from 4-pentyn-1-ol. A second chiral alkenyl side chain was then diastereoselectively introduced to the enone **4** via the Michael addition of the vinyl boronic acid compound **5** mediated by a rhodium catalyst relying to the previously reported Csaky's conditions.[9] The product **6** of this Hayashi-Miyaura reaction was obtained as a single stereoisomer in high yield (Scheme 3). Initially, the authors tried to introduce a simplified side chain to the enone **4** by the use of [Rh(acac)(CO)$_2$]/dppb as catalytic system in aqueous dioxane at 100 °C. Only *ca.* 15% of the Michael product was formed indicating the significance of the presence of a mineral base as LiOH in the reaction mixture, leading Wu and coll. to use the sensitive lithium-mediated reaction conditions from vinyl iodide derivative to accomplish the Michael addition.[8c]

Then, after modifying functional groups and ring closing by macrolactonization reaction using Shiina's anhydride, the synthesis of BFA has been completed.

2.2. Total synthesis of (-)-7-oxamuricatacin analogs (2009)

Csaky and coll.[10] reported the development of an efficient rhodium-catalyzed diastereoselective addition of boronic acids to α,β-unsaturated lactones to prepare chiral δ-hydroxy-γ-butenolide derivatives that are widely found in many biologically active natural products. The reaction occurs in high yield and high *trans*-diastereoselectivity when a mineral

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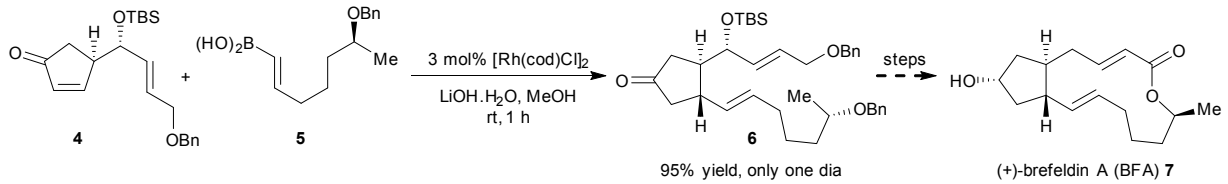
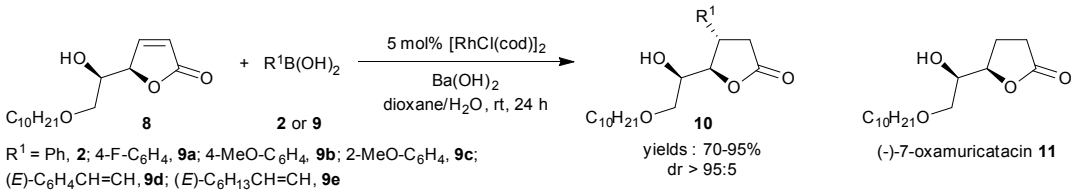


Scheme 3



Scheme 4

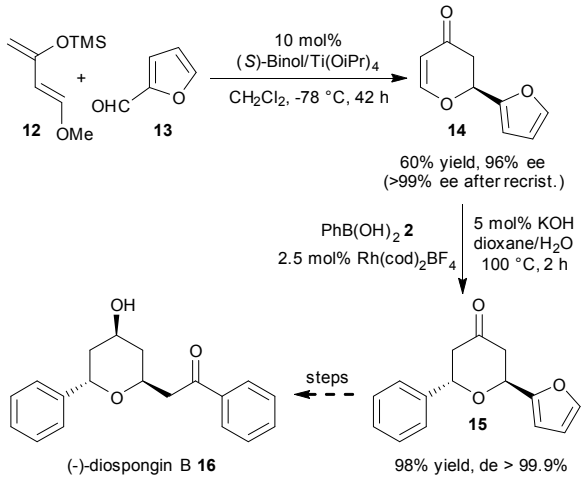
base is used, the better results being obtained in the presence of barium hydroxide in combination with $[RhCl(cod)]_2$ as catalyst. The stereoselectivity of this reaction is the outcome of the addition of the rhodium complex on the less hindered face of the carbon-carbon double bond of the lactone **8**. From thisobservation, various boronic acid derivatives have been engaged to afford (-)-7-oxamuricatacin analogs **10** (Scheme 4).

2.3. Total synthesis of (-)-diospongin B (2009)

Diospongins A and B (**16**) were isolated from the rhizomes of *Diocorea spongiosa* through a bioassay-guided fractionation with promising antiosteoporotic activity. Despite their structural similarity, they exhibit remarkable differences in their biological profile. Diospongin B displays potent inhibitory activity on bone resorption induced by parathyroid hormone, which is comparable to that of calcitonin, a drug used clinically for osteoporosis while diospongin A did not show any activity. The strategy, adopted here by Kumaraswamy and coll.,[11] consisted first in forming the oxacycle through an enantioselective Diels-Alder reaction and then to introduce diastereoselectively the phenyl moiety thanks to a Hayashi-Miyaura reaction (Scheme 5). The later was initially accomplished following classical reaction conditions (rhodium complex as catalyst with phenylboronic acid in aqueous dioxane at reflux) but only a small amount of the expected product **15** was obtained. The addition of a catalytic amount of KOH in the reaction system led to a complete conversion of the starting material to afford finally the product **15** with an excellent yield and a very high diastereomeric excess after isolation (Scheme 6). This approach was also used for the syntheses of the diospongin A as well as enantiomers of diospongins A and B in high yields and stereoselectivities.

2.4. Total synthesis of (-)-anisatin (2012)

The works of Csaky[10] having demonstrated the efficiency of the Hayashi-Miyaura reaction for the synthesis of chiral butenolides, Fukuyama and coll.[12] decided to start their total synthesis of (-)-anisatin **20**, a natural sesquiterpen, according to this reaction (Scheme 6). The 1,4-addition was achieved in the presence of a catalytic amount of rhodium complex and a mineral base (NaOH) in aqueous THF at room temperature.



Scheme 5

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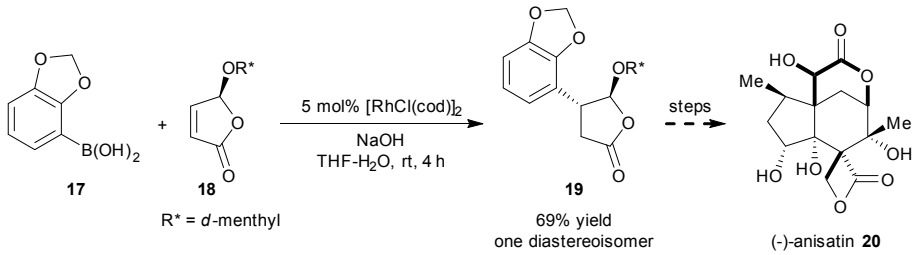


Scheme 6

Once again, the addition of the aryl boronic acid derivative **17** to the chiral butenolide **18** afforded the expected product **19** with complete diastereoselectivity and good yield.

2.5. Total synthesis of (-)-isoschizogamine (2012)

Isoschizogamine **24**, a hexacyclic indolin alkaloid, was first isolated in 1963 from the twigs of the East African monotypic shrub *Schizozygia caffeoides.* The fascinating structure of this compound has attracted the attention of numerous groups of synthetic chemists, and the single total asymmetric synthesis was disclosed by Fukuyama and coll. in 2012.[13] To introduce the dimethoxy aryl group, the authors chose the rhodium-catalyzed 1,4-addition between the corresponding aryl boronic acid and the enantiopure α,β-unsaturated lactone **21** (Scheme 7). On the contrary of the above described syntheses where the reaction into the Michael product **23**, this step was here accomplished in the presence of triethylamine as base. The product **23** was formed as a single diastereoisomer and isolated with an excellent yield. The total synthesis was then achieved in 16 steps from **23** including lactone opening using allylamine followed by lactamization and ring closing metathesis and then introduction of a nitrogen function on the aromatic ring allowing the generation of the pentacyclic aminal moiety.

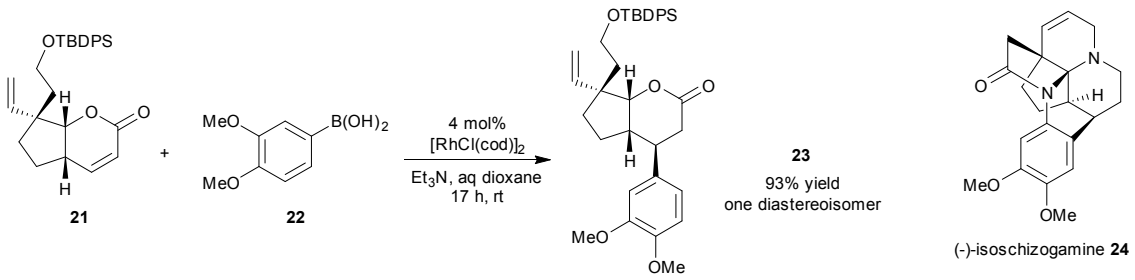
3. Enantioselective approaches

3.1. Formal synthesis of (-)-parotexine (2001)

The efficiency and stereoselectivity of the addition of aryl groups to *N*-benzyl-5,6-dihydro-2(1*H*)-piperidone using asymmetric Hayashi-Miyaura reaction was studied for the synthesis of chiral 4-aryl-2-piperidinones. The findings of this methodological study can be summarized as follow: i) the use of arylboroxines with 1 equiv of water is the best agreement according to conversion and enantioselectivity compared with the use of arylboronic acids, ii) the best reaction temperature is 40 °C, iii) the enantioselectivity is essentially the same whatever the BINAP derivatives used as ligand. With these conclusions in hand, Hayashi and coll.[14] prepared their key intermediate **27** from 5,6-dihydro-2(1*H*)-piperidone **25** for a formal synthesis of the (-)-paroxetine **28**, a potent antidepressant drug (Scheme 8). The absolute configuration of the arylation product was determined by correlation to the known Boc-protected piperidone derivative.

3.2. Methodology toward the synthesis of steroids (2004)

Krische and coll. developed a catalytic diastero and enantioselective tandem conjugate addition-aldol cyclization of keto-enones, the conjugate addition being the chiral



Scheme 7

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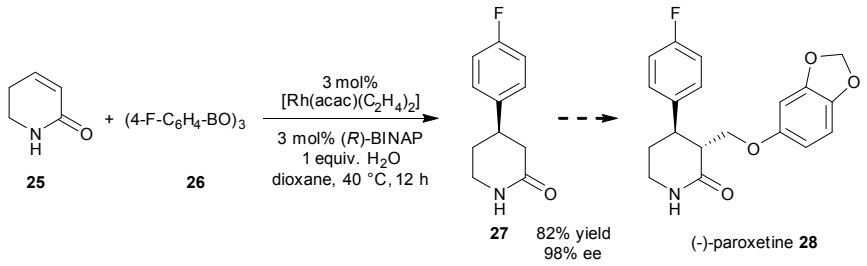
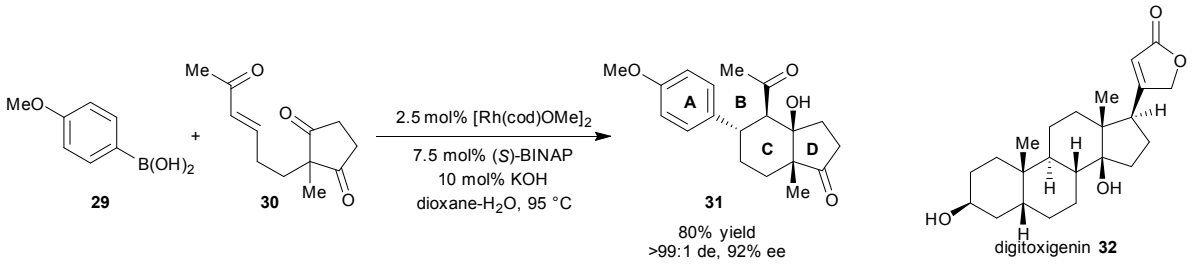


Scheme 8



Scheme 9

discriminating step. This efficient new methodology has been used further to prepare optically enriched *seco*-B ring steroids as found in digitoxigenin **32**, a naturally cardiotonic steroid derived from digitalis.[15] Based on their previous works[16] consisting in the synthesis of five- and six-membered ring products from aromatic and aliphatic mono-enone mono-ketone precursors, they started their studies with the use of $[RhCl(cod)]_2$ as precatalyst. Although this rhodium complex afforded the desired products with excellent levels of selectivity, the chemical yields were non reproducible and highly variable. The reactions were achieved in the presence of $[Rh(cod)OMe]_2$, a rhodium complex known to be more resistant to oxidation, leading to the tandem conjugate addition-aldol cyclization products in high diastereo- and enantioselectivities and reproducible high yields (Scheme 9).

Note that the formation of the four contiguous chiral centers with high stereoselectivity during this process is likely the result of the combination of the stereoselective conjugate addition of the boronic acid with the formation of a strained intermediate as depicted in Figure 2.

3.3. Formal synthesis of (-)-indatraline (2011)

During their studies consisting in the preparation and identification of chiral dienes to form diene-rhodium precatalysts for asymmetric Hayashi-Miyaura reactions, Wu and coll. evaluated the efficiency of these ligands for conjugate addition reactions of arylboronic acids to acyclic α,β-unsaturated carbonyl derivatives.[17] The diene in hand, the authors found that **34** give the products in high yield and excellent enantioselectivity. The optimization of the reaction conditions has shown that the combination of Et_3N as base and ethanol as solvent in the presence of $[RhCl(C_2H_4)_2]_2$ as precatalyst afforded the expected products with better results. Based on the optimal reaction conditions, the formal synthesis of (-)-indatraline **37** was engaged (Scheme 10). The conjugate addition of phenylboronic acid to the unsaturated ester **33** led to the compound **35** in high ee which was then easily converted without racemization into the previously reported precursor **36** of the title natural product **37**.

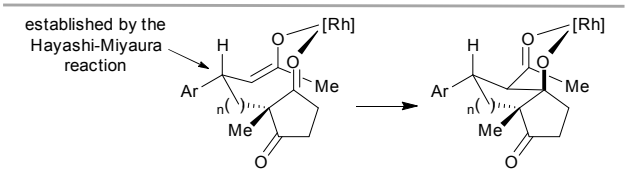


Fig. 2 Explanation of the control of the 4 contiguous stereocenters in the total synthesis of digitoxigenin.

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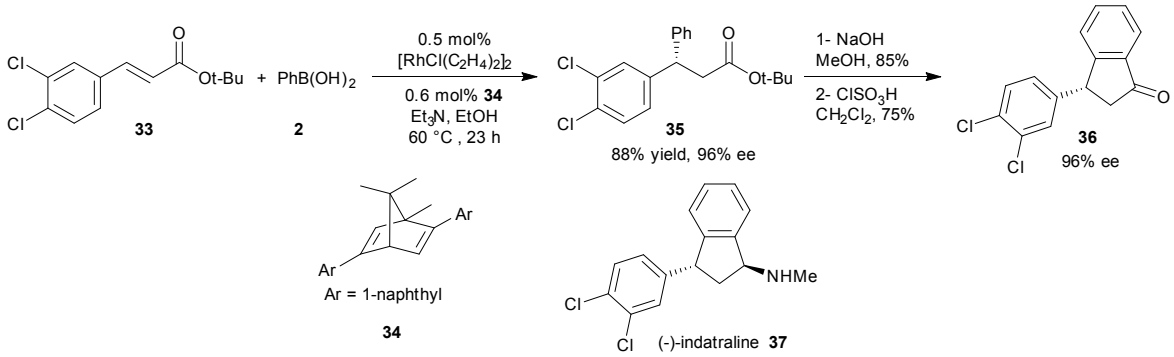
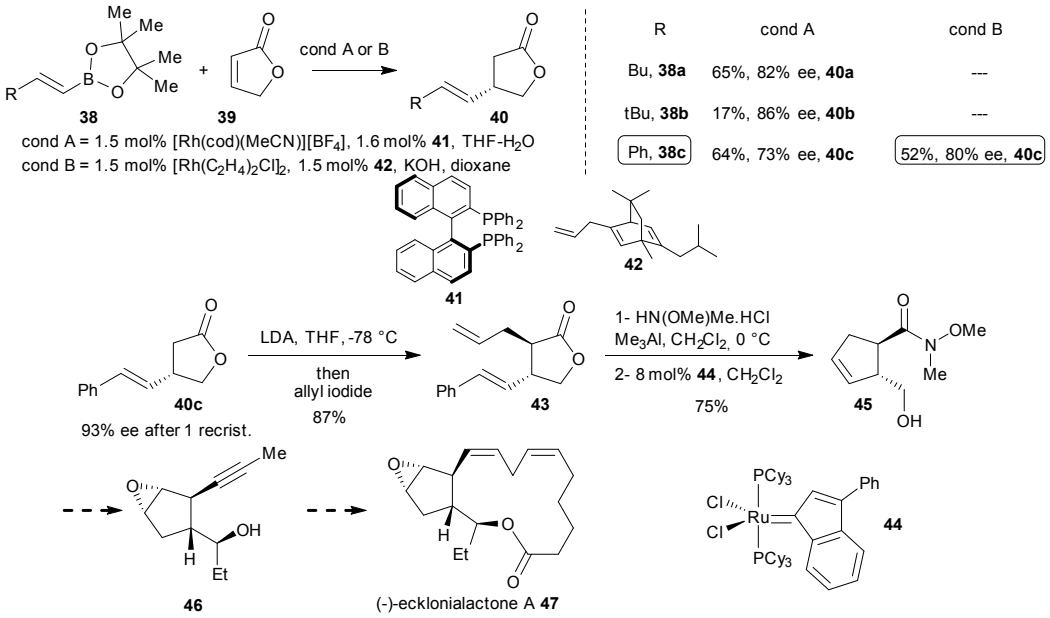


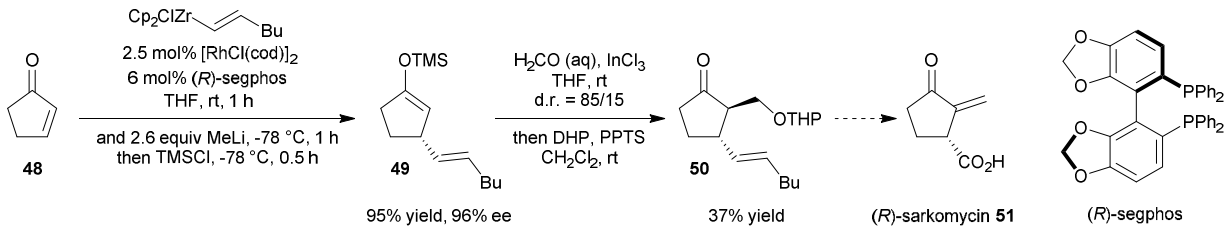
Scheme 10

3.4. Total synthesis of ecklonialactones (2011)

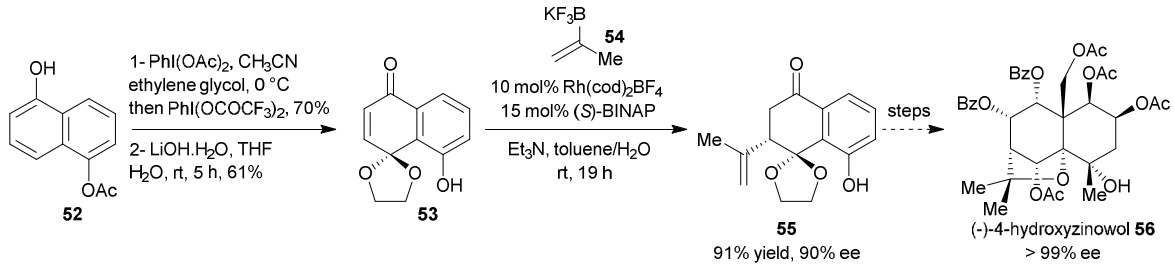
By the use of the asymmetric Hayashi-Miyaura reaction, Fürstner and coll. proposed a concise and protecting-group free total synthesis of enantiopure ecklonialactones A, B and C.[18] Because the conjugate addition of vinyl boronic derivatives to α,β-unsaturated lactones are still rare, different reaction including various ligands have been tested (Scheme 11). Finally the best compromise in terms of yield and enantioselectivity has been found to be the use of the chiral diene **42** as ligand with $[Rh(C_2H_4)_2Cl]_2$ as precatalyst in the presence of KOH as base in aqueous dioxane at room temperature. Note that the (*S*)-BINAP **41** and the diene **42** used as chiral ligands afforded the same enantiomer **40c**. Finally the product **40c** was isolated in 93% ee after recrystallization and then further functionalized - allylation, Weinreb amide formation and RCM – consisting in the conversion of **43** into the cyclopentene **45**. The latter led to (-)-ecklonialactone A **47** obtained after an eight-step sequence.



Scheme 11



Scheme 12



Scheme 13

3.5. Total synthesis of (*R*)-sarkomycin (2013)

In 2013 the group of von Zezschwitz *et al.* published the total synthesis of (*R*)-sarkomycin **51**, a secondary metabolite isolated from *Streptomyces erythrochromogenes*, based on a rhodium catalyzed 1,4-addition as a key step.[19] This natural product has shown antibiotic activity but also strong anticancer activity against various cell lines. Unlike the above mentioned examples, the coupling reaction was accomplished via the conjugate addition of alkenylzirconocene in place of boronic acid derivative to cyclopentenone. The reaction was realized in the presence of $[RhCl(cod)]_2$ as precatalyst and the chiral biphosphine (*R*)-segphos (Scheme 12). As previously shown by the authors,[20] it is then possible to generate in situ the trimethylsilyl enol ether by successive additions of MeLi aiming to convert first the zirconium enolate into lithium then Me_3SiCl which afforded the expected product **49** with high yield and 96% ee. In the absence of MeLi, only the corresponding ketone was obtained. The following steps has been accomplished without observation of racemization to give (*R*)-sarkomycin **51** with 96% ee and 19% overall yield.

3.6. Total synthesis of (-)-4-hydroxyzinowol (2014)

Among the most biologically active compounds isolated from the South American medical plant *Zinowoewia costaricensis*, the (-)-4-hydroxyzinowol **56** has shown a potent anticancer activity with a strong P-gp inhibitory activity.[21] This compound belong to the sesquiterpene family that possesses a *trans*-decalin core and a tetrahydrofuran heterocycle (Scheme 13). The total synthesis of **56** remains still challenging due to the nine consecutive stereogenic centers on the *trans*-decalin backbone. The proposed total synthesis by Inoue and coll. was designed so as to be based on the first chiral center formed with high enantioselectivity in order to continue the synthesis only via diastereoselective reactions. The use of the Hayashi-Miyaura reaction to generate this first chiral center appeared to the authors as an obviousness due to the well-known effectiveness of this reaction. The asymmetric addition of potassium 2-propyl trifluoroborate **54**[22] to the naphthoquinone monoketal **53** with $Rh(cod)_2BF_4$ and (*S*)-BINAP as chiral ligand led to the expected 1,4-addition product **55** with high yield and 90% ee. From this resulting chiral compound **55**, the authors achieved the total synthesis after 33 remaining steps.

4. Conclusions

This paper has summarized the use of the stereoselective conjugate addition of aryl- and alkenyl- boronic acids to α,β-unsaturated ketones with rhodium complexes in formal and total synthesis of natural compounds. The diversity of rhodium sources, the numerous boronic acid derivatives available (or easy to prepare), the different possibilities of chiral ligands and mild reaction conditions make this reaction compatible with numerous functional groups and sensitive compounds. Although this Hayashi-Miyaura reaction was not extensively employed in total synthesis, the first results described here have shown its versatility. Whether in diastereoselective conditions or in its enantioselective version with a chiral rhodium complex, the 1,4-additions occurred with good to high stereoselectivity. Therefore it is likely that in the future this reaction should be more frequently used at the heart of total synthesis strategies.

Acknowledgements

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