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Review

Synthesis of Conjugated Dienes in Natural Compounds

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Abstract: This review describes the various synthetic methods commonly used to obtain molecules possessing conjugated dienes. We focus on methods involving cross-coupling reactions using various metals such as nickel, palladium, ruthenium, cobalt, cobalt/zinc, manganese, zirconium, or iron, mainly through examples that aimed to access natural molecules or their analogues. Among the natural molecules covered in this review, we discuss the total synthesis of a phytohormone, Acid Abscisic (ABA), carried out by our team involving the development of a conjugated diene chain.

Keywords: diene compounds; cross-coupling reactions; Mizoroki–Heck; natural products; abscisic acid

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1. Introduction

Conjugated dienes or, more generally, polyenic scaffolds are present in many biologically interesting natural molecules (Figure 1) [1,2]. Developing new approaches to design these structures is therefore of great synthetic interest. The olefination reaction is often associated with the uncontrolled production of E and Z isomers, which may require careful purification [3]. Currently, a large number of reactions can be used to obtain this motif, in particular cross-coupling reactions [4,5]. This review will focus on these coupling reactions using various metals.

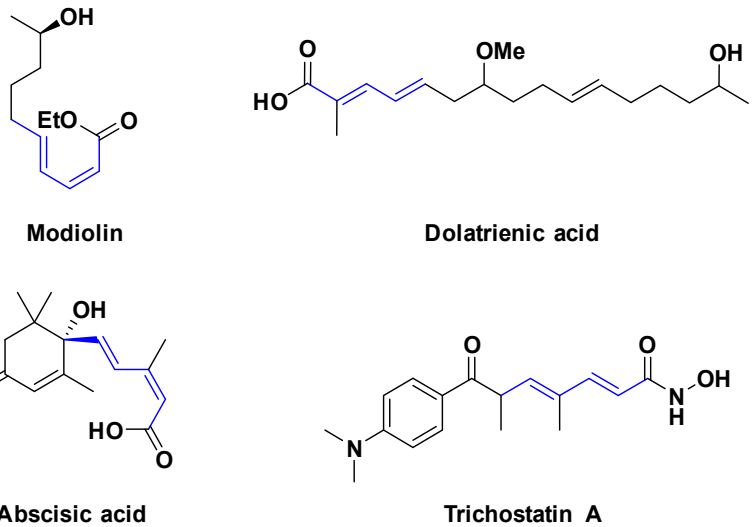


Figure 1. Examples of natural products containing a conjugated diene moiety.

2. Coupling Reactions

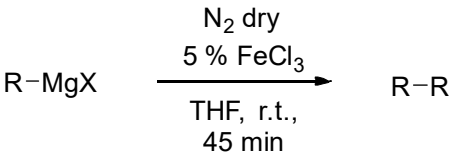
2.1. Homocoupling Reactions

Generally, homocoupling is a side reaction of a cross coupling between two chemical species catalyzed by a metal and is not used for the synthesis of natural molecules. However, it is possible to promote this type of coupling with some metals or even by reacting only

one reagent to be coupled and can be useful for generating intermediate reactants for the more complex synthesis of interesting molecules depending on the starting material.

Conjugated dienes can be obtained by homocoupling reactions. Cahiez's team recently developed two homocoupling conditions from organomagnesium derivatives [4]. Their first condition used iron (III) chloride as the catalyst. This method proved to be very effective on aryl compounds (Table 1, entries 1 and 2) and showed interesting activity on alkene compounds. In fact, the homocoupling of (E)-styrylmagnesium bromide on itself mainly led to the compound (E/E), with a yield of 68% (Table 1, entry 4).

Table 1. Homocoupling of organomagnesium compounds in the presence of $FeCl_3$.



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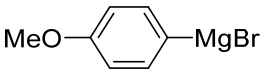
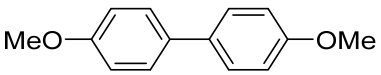
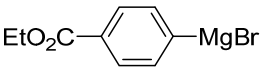
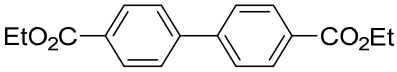
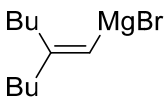
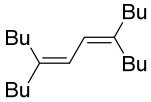
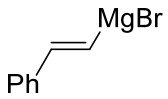
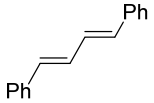
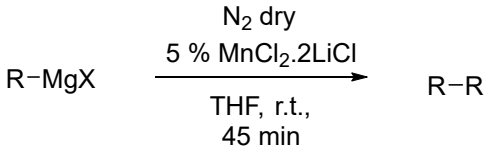
1			88
2			70
3			60
4			68

This method is efficient for homocoupling between sp^2 carbons but is inefficient on sp carbons. Cahiez's team then set up a second methodology using a manganese derivative: manganese (II) chloride [4], since it turned out that these compounds had similar behavior to the coupling of organomagnesium compounds. The conditions of the previous homocoupling were applied with manganese and led to very good results. Upon applying this method to the aryl compound, better yields were obtained (Table 2, entries 1 and 2). This trend was confirmed on the diene compounds, with an increase in yield of nearly 30% on the di-butyl compound (Table 2, entry 3 versus Table 1, entry 3). It is interesting to note that this homocoupling reaction preserved the Z or E configuration of the starting organomagnesium compounds since after the reaction, the main compound that was obtained corresponded to the conjugated diene of the (E/E) or (Z/Z) configuration (Table 2, entries 4 and 5). This method was extended to the synthesis of alkyne compounds, and various products were obtained with very good yields (Table 2, entries 5 and 6). These conjugated dienes can be advantageously reduced to conjugated dienes.

Table 2. Homocoupling of organomagnesium compounds in the presence of $MnCl_2$.



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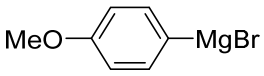
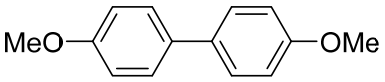
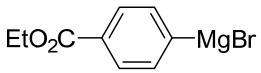
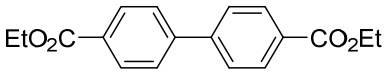
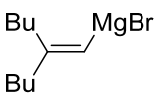
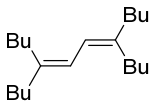
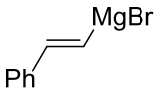
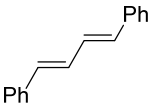
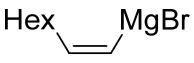
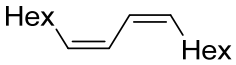
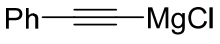
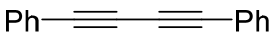
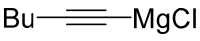
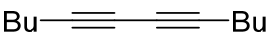
1			95
2			80
3			88
4			90
5			92
6			89
7			91

2.2. Metal Catalyzed Reactions

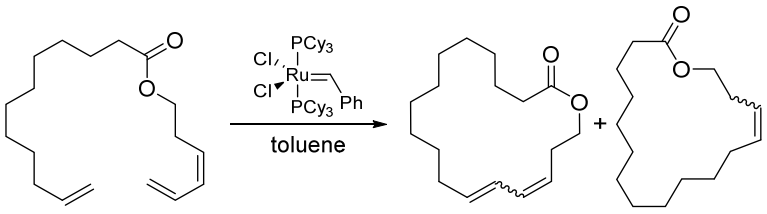
2.2.1. Reactions Catalyzed by Ruthenium

Metathesis

Metathesis, a coupling reaction between two vinyl units, is catalyzed by a metal complex, such as Grubbs or Schrock catalysts [4,6–8]. This "Ring-Closing Metathesis" reaction makes it possible to form 1,3-diene compounds. Several teams have developed methods to obtain 1,3-diene compounds and have been more or less successful. During the last decade, however, Fürstner's team developed an efficient method to generate conjugated diene compounds with stereoselectivity control [9].

First, they observed the low selectivity of the (E,Z) isomer towards the other two possible isomers through the use of the first-generation Grubbs catalyst. In addition, they observed a parasitic ring contraction reaction, which resulted in a single alkene 3 (Table 3).

Table 3. Metathesis by ring closure with the 1st generation Grubbs catalyst.

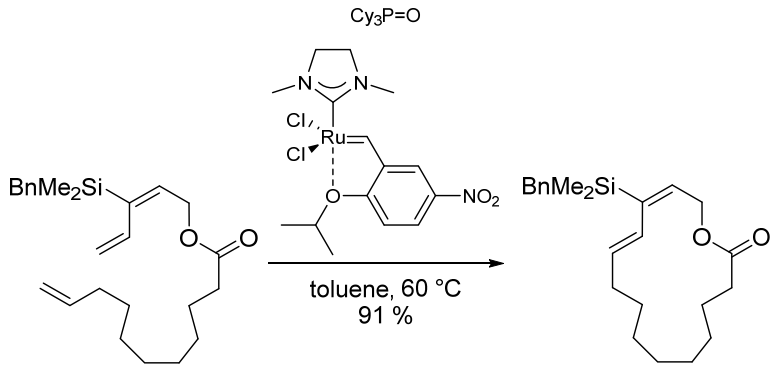


1 **2** **3**

Entry	Catalyst	Temperature (°C)	t (h)	2 (dr)	3 (dr)
1	Grubbs I	20	24	86% (3:1:1)	14% (5:1)
2	Grubbs I	110	22	91% (2.7:1:1)	9% (5:1)
3	Grubbs II	20	24	<5%	95% (7:1)
4	Grubbs II	110	22	12% (1:3:4)	88% (6:1)

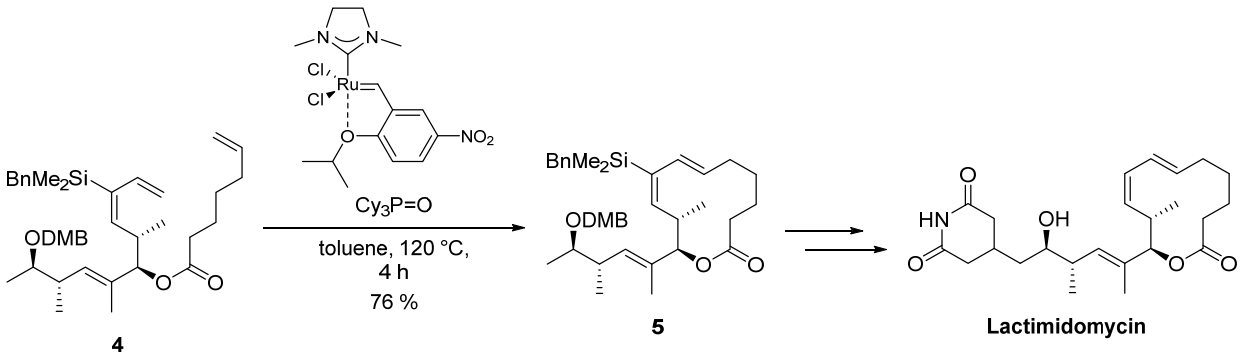
Using the first-generation catalyst at 20 °C, compound **2** was formed in yields of up to 86%, but the expected compound E, Z was mixed with minor by-products (Table 3, entry 1). By increasing the temperature to 110 °C, and in the presence of $Cy_3P(O)$, the yield was slightly improved but to the detriment of compound (E,Z), which decreased compared to the other compounds (Table 3, entry 2). Interestingly, the use of the second-generation Grubbs catalyst promoted cycle contraction at the expense of compound 2 (entries 3 and 4).

In view of this selectivity problem, Fürstner's team proposed the use of a silyl group on the diene in order to promote ring closure in favor of the compound (E,Z) (Scheme 1).



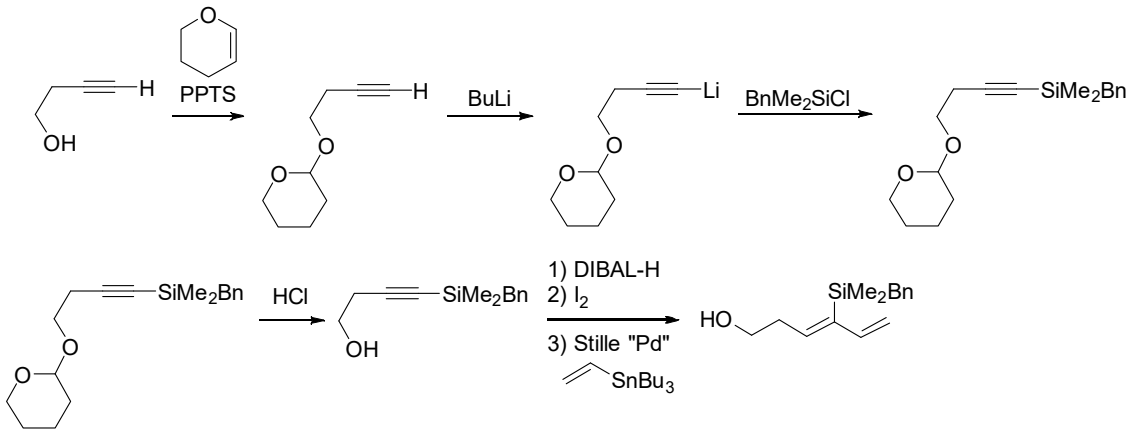
Scheme 1. Conditions of metathesis cyclization favoring the compound E, Z.

With this approach, a lactimidomycin synthetic pathway was established (Scheme 2) using compound 4 in the reaction described above, leading to compound 5 in a 76% yield. Lactidomycin is a macrolide antibiotic that is a potent inhibitor of cell proliferation or cell migration and also demonstrates antifungal properties [10].



Scheme 2. Synthesis of lactimidomycin by metathesis.

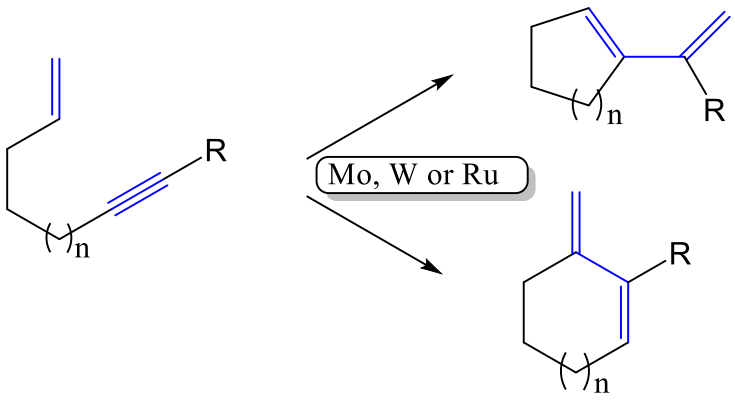
Silylated compounds are readily available via the nucleophilic substitution of the chlorine atom of an alkylsilyl chloride derivative with an alkyne that has been previously deprotonated at −78 °C in THF and that has been allowed to obtain the desired compound. In the present case, the compound has an alcohol function protected by the action of 2,3-dihydro-2H-pyrane. Subsequently, the alkyne function was protected by benzyldimethylsilyl chloride. The alcohol was deprotected using hydrochloric acid. The triple bond was selectively reduced to the trans compound, which was iodinated and used in a Stille coupling reaction with tributyl (vinyl) tin. Under these conditions, the compound that was obtained is a conjugated diene with a silyl group in position 3 (Scheme 3).



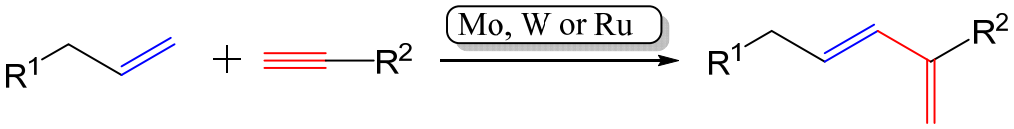
Scheme 3. Synthesis of a silylated derivative.

Enyne Metathesis

Ring-closing enyne metathesis (RCEYM) is C–C bond formation that leads to 1,3-diene via two possible mechanisms: metal salt catalyzed enyne bond reorganization and carbene-mediated enyne metathesis [11]. This reaction can be intra or intermolecular and is favored by transition metals such as molybdenum or tungsten and more frequently by ruthenium (Schemes 4 and 5).

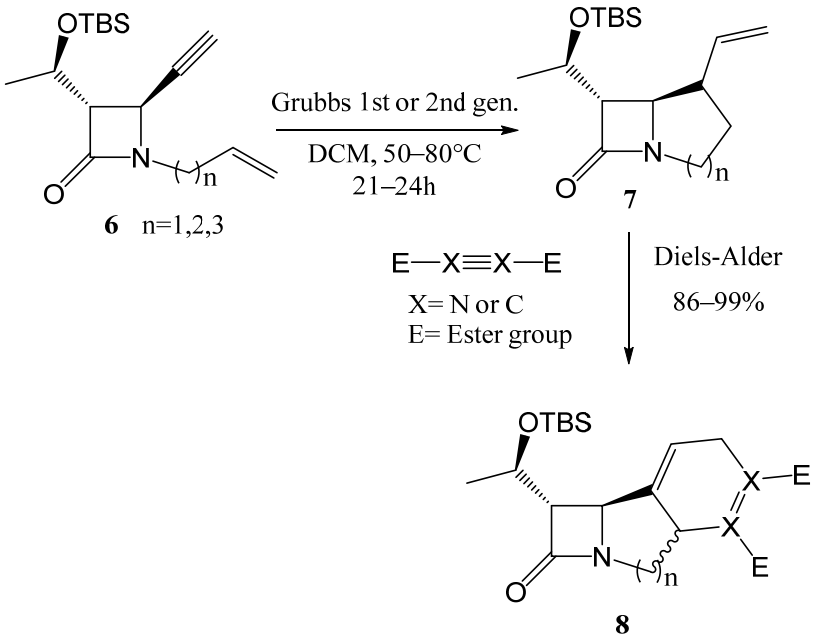


Scheme 4. Intramolecular RCEYM.



Scheme 5. Intermolecular RCEYM.

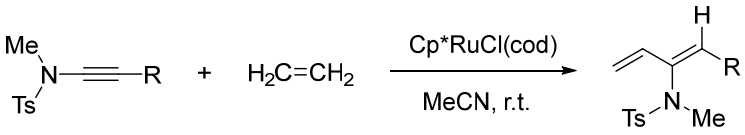
Access to a family of polycyclic β-lactams 8 has been described by Genêt et al. [12] and involves the RCEYM reaction followed by Diels–Alder final cyclization, producing annulated β-lactams compounds with an interesting antibacterial activity (Scheme 6).

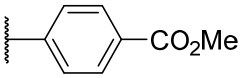
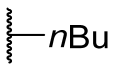
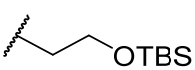


Scheme 6. Annulated β-Lactams synthesis by RCEYM followed by Diels–Alder.

Sato's group used ynamides and ethylene [13]. For this coupling, the amine must be protected by an electron withdrawing group, such as a tosyl. However, the alkyne can be substituted with various groups such as benzyl methanoate, which resulted in the coupled compound in a quantitative yield in just 2 h (Table 4, entry 1). When the ynamide was substituted by an n-butyl group, the reaction time increased considerably to 19 h, but the yield was still very good (Table 4, entry 2). When the group carried by the triple bond was a silyl ether, the yield dropped to 20% for 21 h of reaction time, but the starting compound was recovered in a yield of 57% (Table 4, entry 3). With an ynamide terminal, the reaction did not take place, and only 45% of the starting material was recovered. The same thing occurred when the ynamide was substituted with a TMS group, but in this case, 85% of the starting material was recovered.

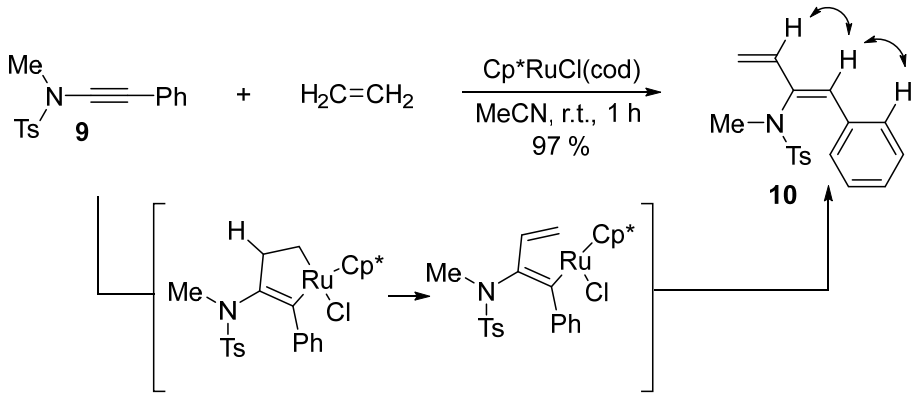
Table 4. Obtaining various dienes substituted by Sato.



Entry	R	t (h)	Yield [a]	Ynamide [a]
1		2	quant.	0
2		19	80	0
3		21	20	57

[a] isolated compound.

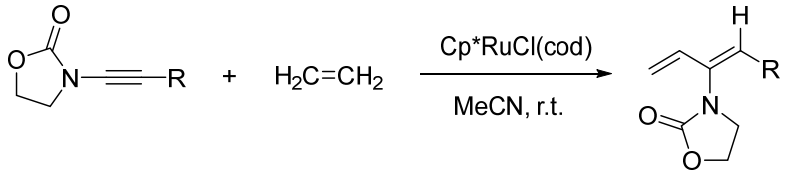
The regioselectivity of the reaction comes from the addition of the catalyst to the ynamide, to which the ethylene was coupled. This is because the three compounds formed a five-member metallo ring with nitrogen in trans compared to ruthenium. β elimination then led to the conjugated diene compound systematically with the Z stereochemistry. This stereochemistry was verified by NOE coupling on test molecule 10, which was obtained from compound 9 (Scheme 7).

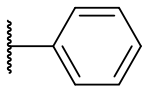
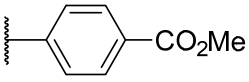
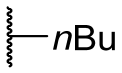


Scheme 7. Mechanism for the reaction described by Sato.

Sato and his team transposed their reaction to an oxazolidinone substituted on nitrogen by an alkyne. Various alkyne derivatives were used to obtain results that were very similar to those obtained with the ynamides (Table 5, entries 1 and 2). Nevertheless, the use of a butyl derivative was not efficient because only 10% of the coupling compound was obtained against the 80% that had been obtained previously (Table 5, entry 3).

Table 5. Coupling to oxazolidinone.

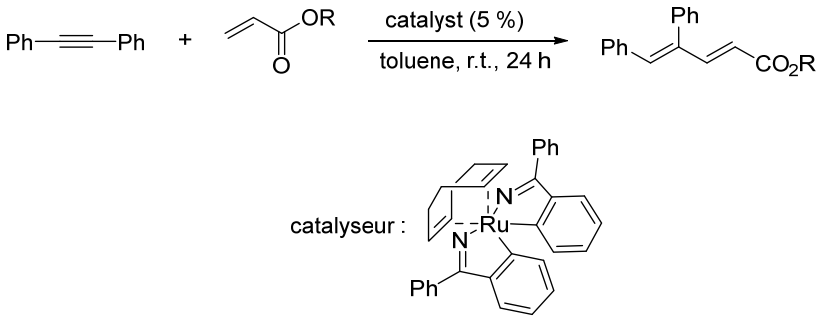


Entry	R	t (h)	Yield [a]	Ynamide [a]
1		2	86	0
2		2	87	0
3		25	10	80

[a] isolated compound.

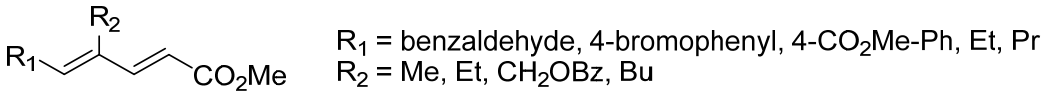
In 2014, Zhao's group developed a coupling from diphenylethyne and acrylate derivatives in toluene at room temperature [14]. They obtained conjugated diene compounds with an (E,Z) configuration. Different esters were used with very good yields. For example, the use of methyl or ethyl acrylate allowed them to obtain coupling products with yields of 98% and 99%, respectively (Table 6, entries 1 and 2). The yield remained excellent when the ester was an isomer of butane, such as *tert* or *n*-butyl (Table 6, entries 3 and 4).

Table 6. Alkyne–acrylate coupling according to Zhao's group.



Entry	R	Yield (%)
1	Me	98
2	Et	99
3	*n*Bu	98
4	*t*Bu	90

This efficient method was generalized to a large number of alkynes, as phenyls were not necessary to ensure the success of the reaction. Various substituents of the alkyne led to the desired alkenes (Scheme 8).

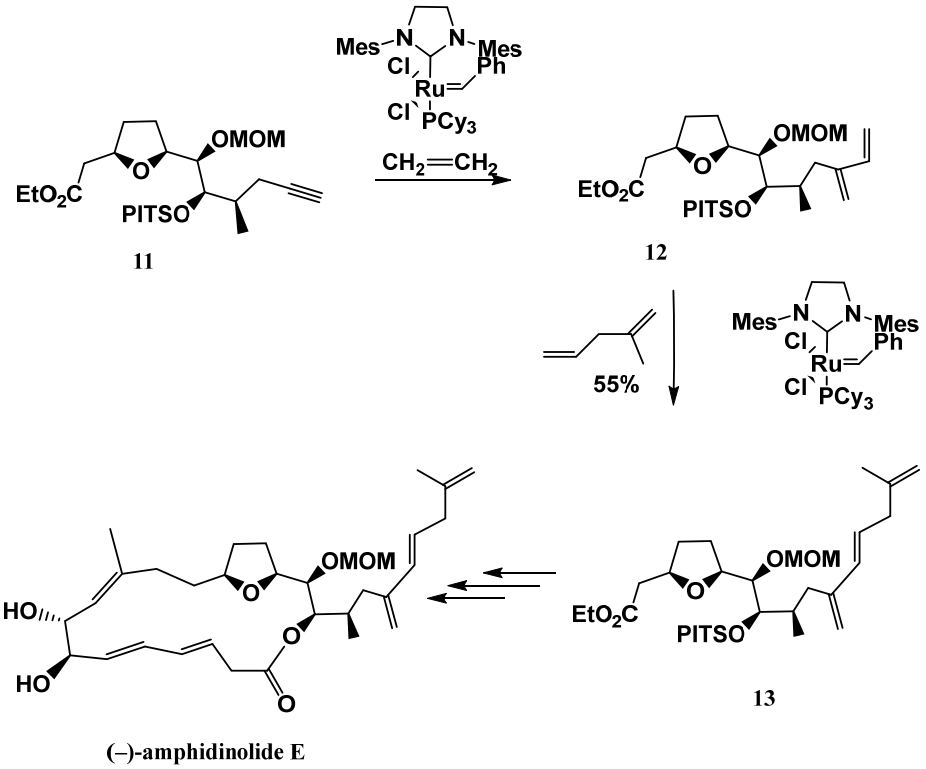


Scheme 8. Generalization of the method by Zhao's group.

An application of an intermolecular enyne metathesis followed by a diene cross metathesis was used as the key steps in the total synthesis of (−)-amphidinolide E described by Lee et al. [15]. This compound is a part of natural macrolides family and possesses a high cytotoxicity against various cancer cell lines. They successfully used the second generation of the Grubbs catalyst to generate diene 12 and then the required triene 13 using a cross-metathesis step. Subsequent standard modifications led to the expected (−)amphidinolide E (Scheme 9).

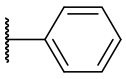
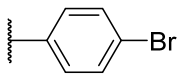
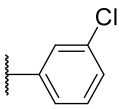
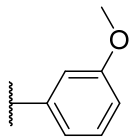
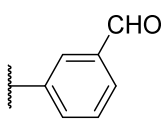
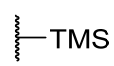
2.2.2. Example of Analog Cobalt Catalyzed Coupling

In 2010, Cheng's group developed a reaction to obtain 1,3-diene derivatives from vinyl compounds in the presence of a cobalt catalyst [16]. When the diphenylethyne was placed in the presence of styrene, the diene was obtained at a 97% yield (Table 7, entry 1). The reaction was also effective with para bromostyrene (Table 7, entry 2) or with the use of donor groups in the meta position of styrene, which led to the corresponding products in very good yields (Table 7, entries 3 to 5). When trimethylsilylethylene was used, the coupling took place, but moderately, even when the reaction time was increased to 36 h (Table 7, entry 6).

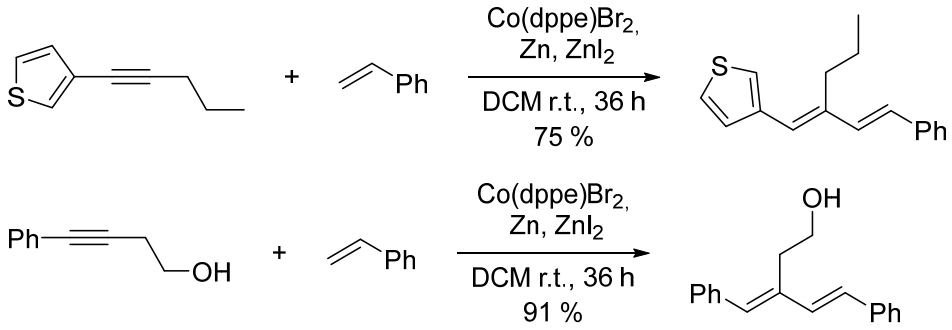


Scheme 9. Synthesis of (−)-amphidinolide E via an intermolecular enyne metathesis.

Table 7. Cheng et al.'s cobalt coupling.

Entry	R	Yield (%)
1		97
2		92
3		94
4		88
5		85
6		64

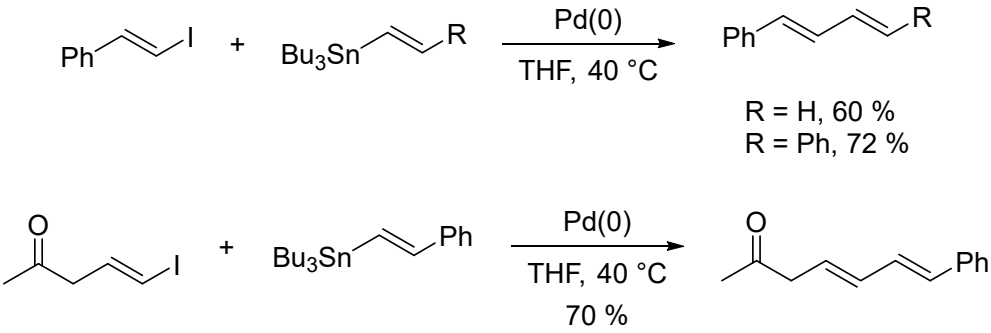
After varying the vinyl compound, Cheng et al. used different alkyne compounds in the presence of styrene, such as 3-pentynylthiophene or 4-phenylbut-3-yn-1-ol. However, with CoI_2, dppp, (1,3-bis (diphenylphosphino) propane), the coupling compounds were not obtained. Cheng opted for a catalyst with a lower steric hindrance due to its ethane and non-propane ligand ($Co(dppe)Br_2$) as well as the presence of bromine atoms that were smaller than iodine atoms. Under these conditions, the coupling products were successfully obtained, with yields of 75% and 91%, respectively (Scheme 10).



Scheme 10. Extension of cobalt coupling according to Cheng.

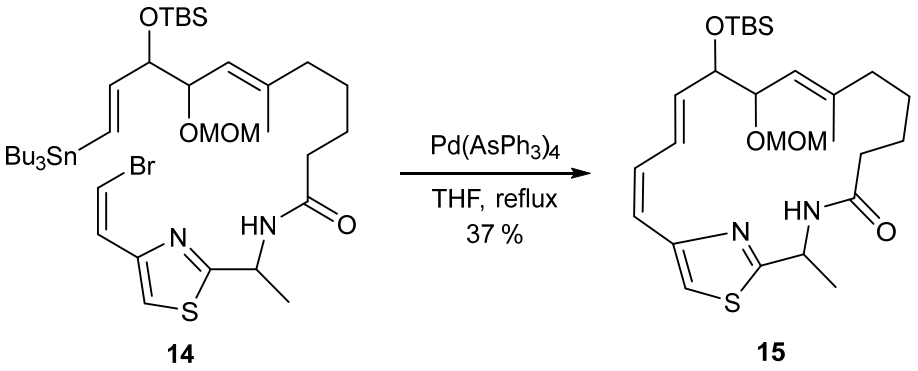
2.2.3. The Stille Reaction

The Stille reaction, a palladium-catalyzed cross-coupling reaction between an organostannane and a halide, was first described by Stille in 1985 [17] and was illustrated through numerous examples. Herein, we will focus on those that led to conjugated dienes. The coupling between the (E)-(iodovinyl) benzene and a stannyl derivative successfully resulted in the corresponding 1,3-diene compound. It is important to note that the reaction exclusively kept the stereochemistry of the reactants involved. This reaction is of great synthetic interest because a compound with a trans stereochemistry will lead to a trans diene (Scheme 11) [18,19].



Scheme 11. Stille coupling to generate conjugated dienes.

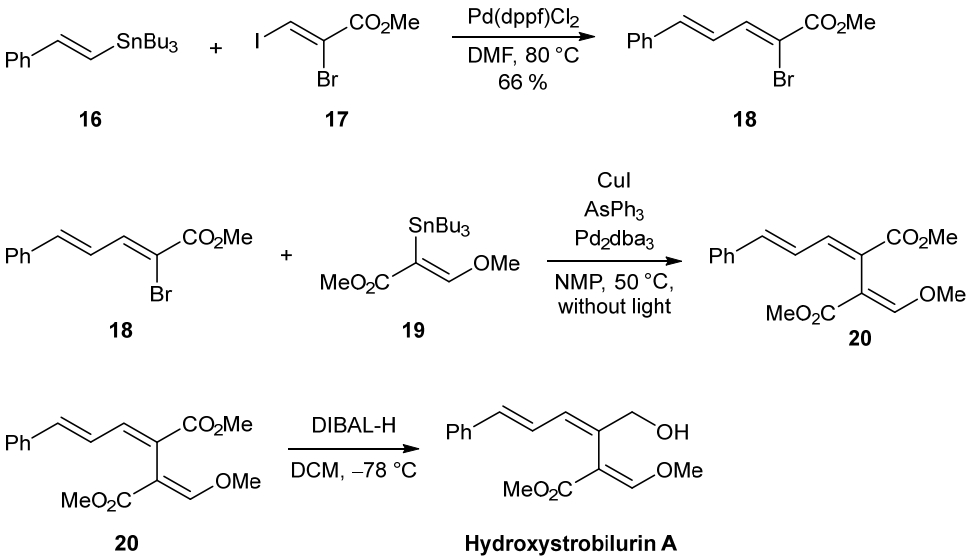
In 2001, Pattenden's team proposed the total synthesis of natural molecules comprising a conjugated diene moiety via the Stille coupling reaction [20]. Their work began with the application of Farina's conditions, i.e., the use of palladium tetrakistriphenylarsine in THF at reflux, which enabled them to obtain compound 15 via the intramolecular cyclization of compound 14 at a 37% yield (Scheme 12) [21].



14 **15**

Scheme 12. Intramolecular cyclization by Stille coupling.

Several years later, Morris' group attempted to obtain hydroxystrobilurin A (methyl (2E,3Z,5E)-3-(hydroxymethyl)-2-(methoxymethylidene)-6-phenylhexa-3,5-dienoate), with Stille coupling as a key reaction [22]. Hydroxystrobilurin A has the same biological activity of other strobilurins or oudemansins. It exhibits antifungal activities but no antibacterial activity compared to strobilurin [23]. Compound 16 was coupled with the iodine derivative 17 in the presence of $Pd(dppf)Cl_2$ in anhydrous DMF. Compound 18, which is a conjugated diene, was obtained at a yield of 66%. The coupling turned out to be selective at the iodine level as expected, leaving the possibility of carrying out another coupling on the bromine atom. This is, moreover, the continuation of the strategy envisaged by this team (Scheme 13).

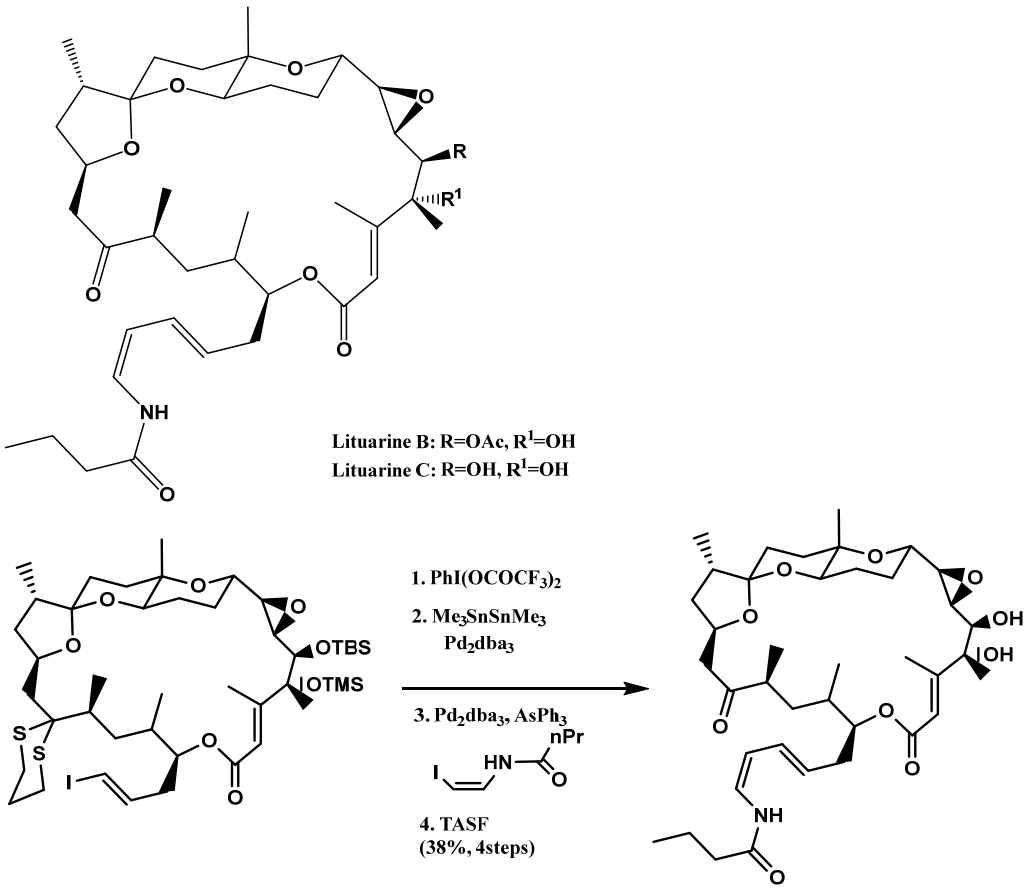


Scheme 13. Total synthesis of hydroxystrobilurin A by the Morris group.

Compound 18 was coupled with compound 19 in the presence of CuI, triphenylarsine and Pd_2dba_3 in N-methylpyrolidine at 50 °C and was protected from light. The compound 20 thus obtained at an 86% yield was then reduced by the action of DIBAL-H on the α,β-unsaturated methyl ester. A 12% yield of hydroxystrobilurin A was thus obtained. In this case, the coupling took place on the bromine atom unlike the previous reaction. This may be due to the use of CuI, which activates the C-Br bond by the complexation of the latter, and then via transmetalation with palladium, it initiates the catalytic cycle of the coupling.

Stannylated compounds, although easily accessible, remain extremely toxic. Despite the effectiveness of this coupling, it is therefore necessary to consider its environmental impact during total synthesis. In addition, if this coupling is used for the synthesis of active compounds, slight traces of tin could still be present in the final formulation.

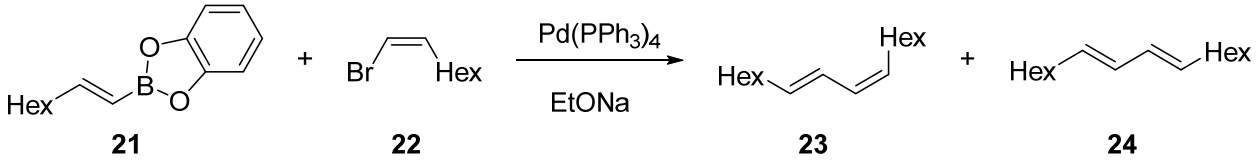
Amos B. Smith et al. [24] described the total synthesis of the Lituarines B and C macrocyclic lactones involving the formation of (E/Z)-dienamide side chain with cis-vinyl stannane by the Stille coupling reaction (Scheme 14). These compounds are present in biologically active marine natural products. Cytotoxic and antineoplastic activities were observed.



Scheme 14. Lituarines B and C and stannylation of the vinyl iodide moiety.

2.2.4. The Suzuki–Miyaura Reaction

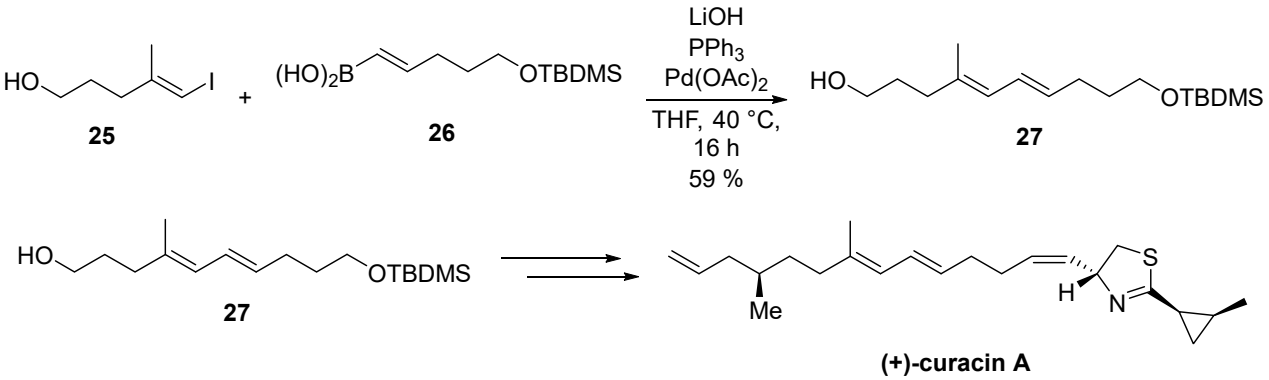
In 1979, the Suzuki team [25–27] published a coupling reaction between a boronic acid derivative and a vinyl bromide in the presence of a base and palladium (Scheme 15) [28].



Scheme 15. Suzuki coupling reaction.

Historically, the first coupling was carried out between the compounds 21 and 22 in the presence of palladium tetrakistriphenylphosphine and sodium ethanoate, leading to the conjugated diene derivatives 23 and 24 in respective yields of 47% and 41%.

This reaction opened the way to numerous total syntheses, such as that described by Pattenden's group for the synthesis of (+)-curacin A in 2002 (Scheme 16) [29]. Curacin has been reported to be a potent antiproliferative cytotoxic compound for several cancers, including renal, colon, and breast cancers [30–33]. Curacin A interacts with binding sites that inhibit the microtubule polymerization involved in cell division and proliferation processes.



Scheme 16. Suzuki coupling used for the synthesis of (+)-curacin A.

Compounds 25 and 26 were placed in the presence of palladium acetate, triphenylphosphine, and lithium hydroxide in degassed THF at 40 °C for 16 h to lead to the single isomer (E,E) of compound **27** in a 59% yield.

In 2004, Molander's group developed [34] a total synthesis of oxymidine II, which demonstrated potent antitumor activity [35] and used the Suzuki reaction as the key step for the formation of the macrocycle (Figure 2).

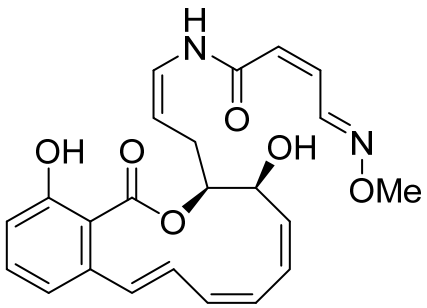
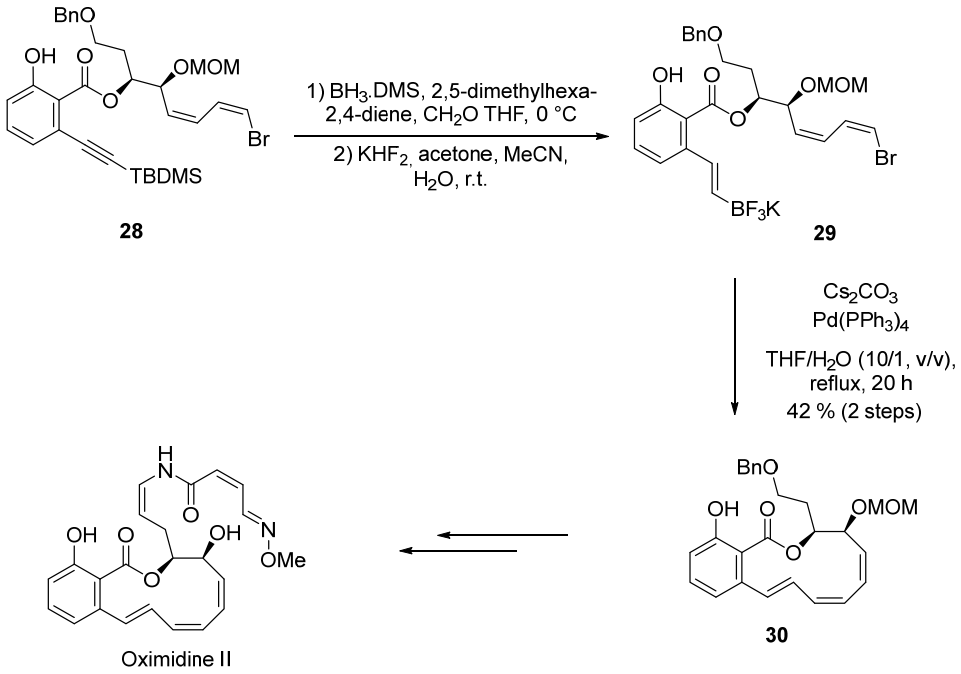


Figure 2. Target molecule of the Molander group.

This macrocyclization was carried out intramolecularly on molecule 21 (Scheme 17) in the presence of $Pd(PPh_3)_4$ derived from cesium carbonate in a THF/H_2O (10/1, *v*/*v*) mixture at the reflux temperature for 20 h. Compound 30 was obtained in a 42% yield in two steps from alkyne 28.

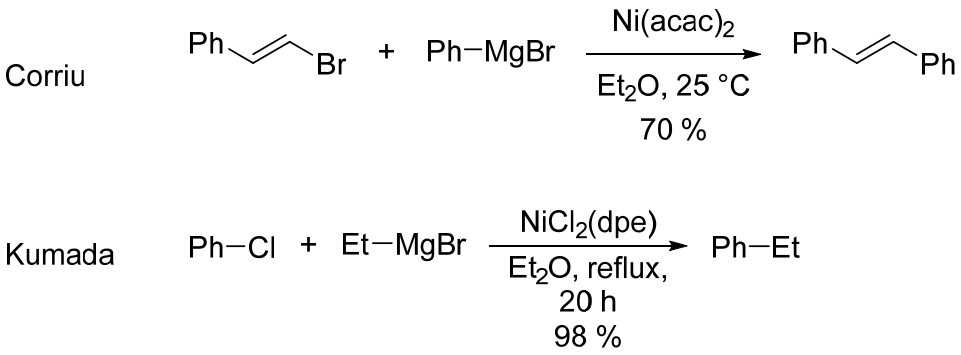


Scheme 17. Suzuki coupling performed by Molander's group.

Suzuki coupling yields, among other things, conjugated diene and triene compounds from simple and easily accessible reagents. However, boronic acid derivatives comprising several chemical functions are generally expensive when they are commercially available.

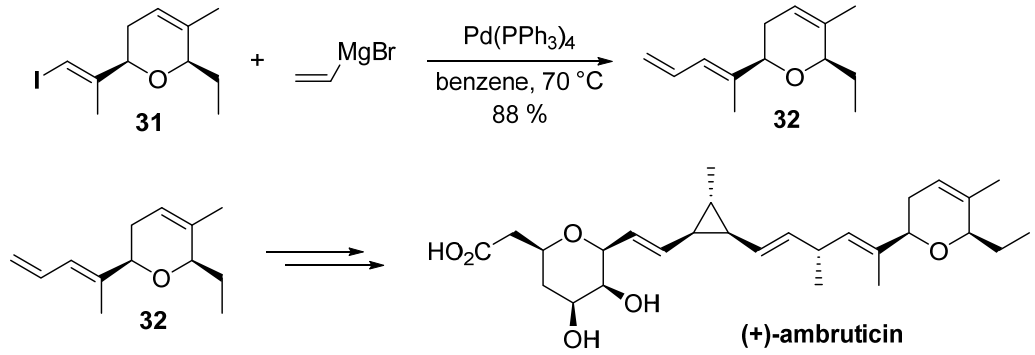
2.2.5. The Kumada-Corriu Reaction

In 1972, both Kumada's team and Corriu's team reported the coupling reaction between an aryl halide and an organomagnesium compound in the presence of nickel as the catalyst [36,37]. In a solution in diethyl ether with a very low catalyst load, between 0.1 and 0.2%, the coupled compounds were obtained in very good yields (Scheme 18).



Scheme 18. Historical reactions of Kumada and Corriu.

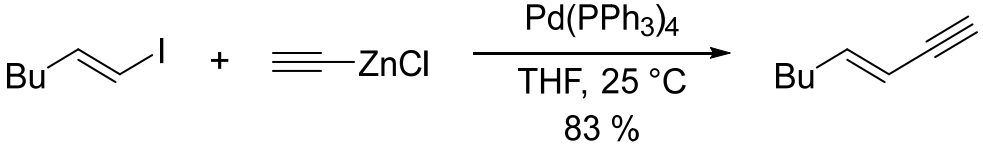
Although initially developed with nickel, this reaction can take place in the presence of palladium. In fact, Jacobsen's group used this type of catalyst in their Kumada-Corriu reaction for the total synthesis of Ambruticin in 2001. This natural product exhibits potent antifungal activity [38,39]. Compound 31 was placed in the presence of palladium tetrakistriphenylphosphine and vinylmagnesium bromide in benzene under reflux to lead to conjugated diene 32 with the correct conformation. During this coupling, the stereochemistry of the compounds was preserved (Scheme 19).



Scheme 19. Total synthesis of (+)-ambruticin according to Jacobsen.

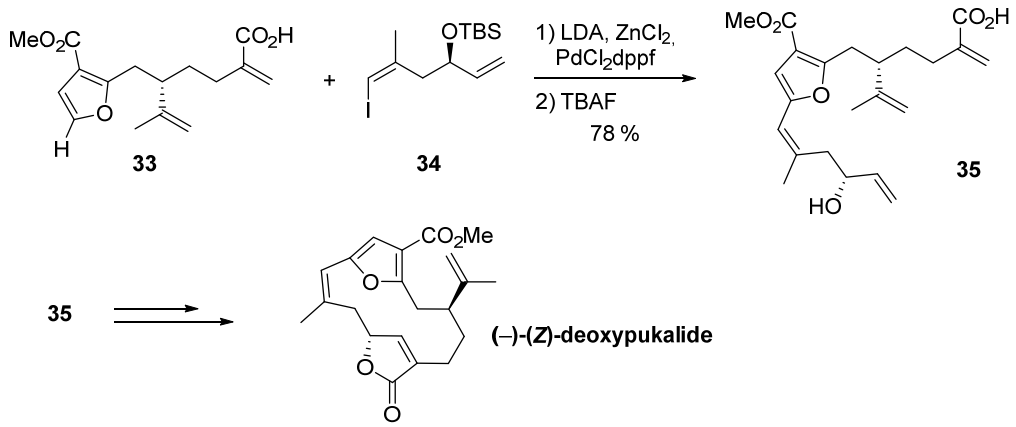
2.2.6. The Negishi Reaction

During the reaction developed in 1977 by Negishi, halogenated compounds were coupled with organozinc derivatives [40–42]. Historically, the first coupling was carried out between (E)-1-iodohex-1-ene and ethynylzinc chloride, which was prepared in situ by adding a solution of $ZnCl_2$ in THF to a solution of ethynyl lithium. The reaction was carried out at room temperature in THF in the presence of $Pd(PPh_3)_4$ as a catalyst to yield the desired coupling compound in a yield of 83% (Scheme 20).



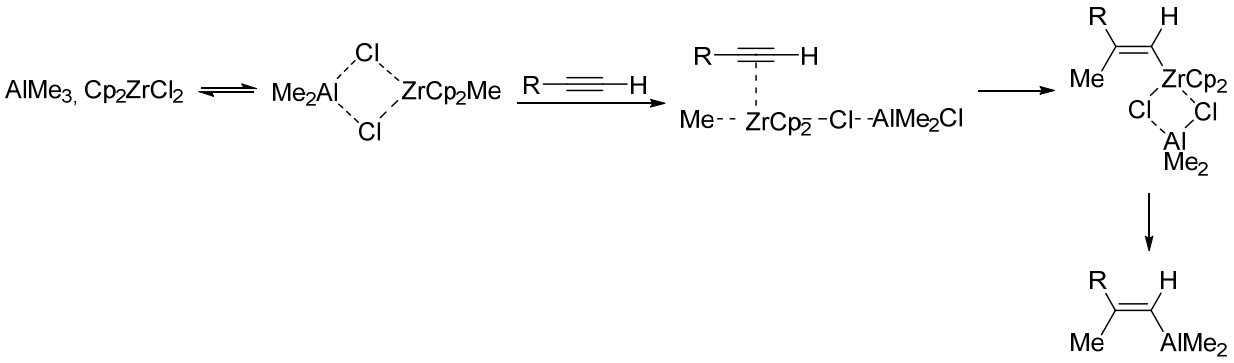
Scheme 20. Historical coupling of the Negishi reaction.

In 2008, Kershaw's team used Negishi coupling as one of the key reactions to synthesize a naturally occurring compound isolated from corals, the deoxypukalide that is obtained by the desoxygenation of pukalide [43]. The synthesis was performed from compound 33 with 2.3 equivalents of LDA to tear the acidic proton from the cycle, leading to the lithiated derivative udnergoing transmetalation in the presence of zinc chloride. The latter compound underwent Negishi coupling in the presence of compound 34 and a ferrocene palladium complex. The alcohol that was obtained was deprotected in the presence of TBAF, leading to compound 35 with a global yields of 78% in two steps. Then, various subsequent reactions led to the expected natural compound (Scheme 21).



Scheme 21. Synthesis of deoxypukalide via Negishi coupling.

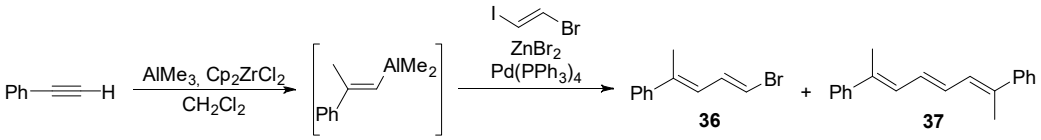
Another alternative to obtain organozinc compounds was used by Negishi during the total synthesis of vitamin A in 2001 [44]. In this case, the necessary terminal alkyne was placed in the presence of trimethylaluminum and a zirconium complex (Cp_2ZrCl_2) in dichloromethane to generate the corresponding alkenylalane. Firstly, the trimethylaluminum and Cp_2ZrCl_2 complex chelated via a non-binding doublet of the chlorine atoms and exchanged a methyl group. Then, the triple bond on the electronic vacancy of the zirconium incorporated the methyl at the same time. The triple bond was reduced by electronic transfer. Subsequently, transmetalation took place between the zirconium and the aluminum, leading to the alkenylalane compound (Scheme 22).



Scheme 22. Preparation of the alkenylalane compound for the Negishi reaction.

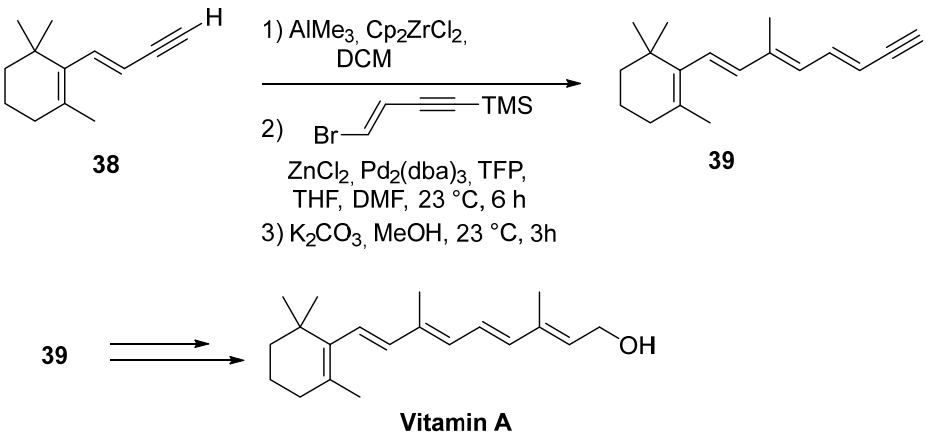
In this case, Negishi sought to optimize the coupling between the organozinc and the compound (E)-1-bromo-2-iodo-ethene while promoting the addition on the iodine atom as well as reducing the possibility of having a second coupling on the bromine atom. A search for the best solvent (Table 8) showed that a DMF/THF mixture (2/1, *v/v*) was the best combination, as it favored the mono-coupling with iodine with only traces of compound 37. DMF had a very significant impact on the reaction because when the coupling was carried out in THF, the yield of compound 36 dropped to 20% without increasing the proportion of 37. However, after 12 h of reaction time, they observed the formation of compound 37 with a yield of up to 10%.

Table 8. Solvent optimization.



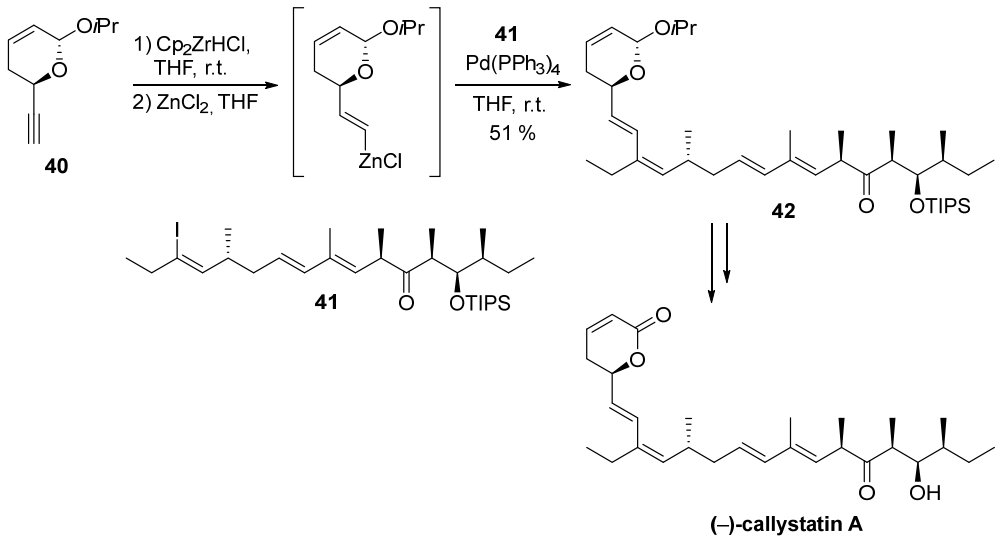
Solvent	t (h)	36 (%)	37 (%)
DMF/THF (2/1, *v/v*)	1	84	Traces
THF	1	20	Traces
THF	12	30	10

This process was used to synthesize vitamin A by reacting compound 38 under the conditions described above. The deprotection of the alkyne was then carried out to lead to conjugated compound 39 at a yield of 70% (Scheme 23).



Scheme 23. Synthesis of vitamin A via the Negishi reaction.

In 2004, Panek's group developed the total synthesis of Callystatin A through a Negishi coupling reaction [45]. Callystatin exhibits anti-tumor activity, and this antibiotic blocked some of the molecules involved in the cellular processes of proliferation, differentiation, development, and hormone action [46] To achieve this, alkyne 40 was brought into contact with the zirconium complex at room temperature. The advantage of using Cp_2ZrHCl, also called Schwartz's reagent, is that it adds a proton to the triple bond and not a methyl, which was the case previously [47]. The addition of zinc chloride in THF led to organozinc, which was immediately engaged in the Negishi coupling reaction with iodine compound 41 to generate compound 42 at a 51% yield. Various deprotection reactions then led to the target natural molecule (Scheme 24).

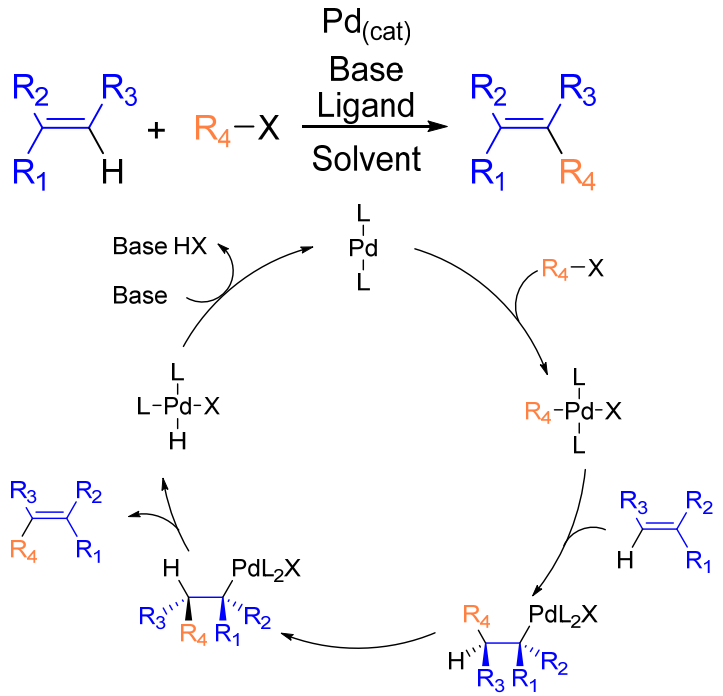


Scheme 24. Synthesis of callystatin A by Panek's group.

2.2.7. The Mizoroki–Heck Reaction

Heck–Mizoroki coupling is one of the most convenient methods for carbon–carbon double bond formation in small organic molecules. Here, we report the state-of-the art of conditions leading to conjugated diene compounds in general and an application of the synthesis to a natural molecule.

In 1971, Mizoroki's team published work to bound phenyl iodide and vinyl bromide in the presence of palladium and potassium carbonate [48]. In 1972, Heck's group described the same coupling but applied these conditions to various substrates [49]. This reaction, called the Heck–Mizoroki reaction (Scheme 25), is commonly used in organic synthesis, as the required building blocks are easy to access and are generally inexpensive.



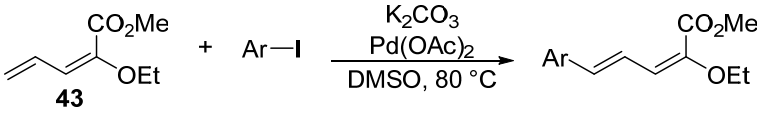
Scheme 25. General scheme and mechanism of the Heck–Mizoroki reaction.

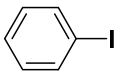
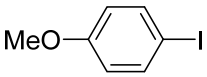
The mechanism of this reaction is now well known [50]. To improve the environmental impact of its use, some studies have introduced improvements, for example the work by Hallberg's team in 2002, which describes a methodology for this coupling using microwaves as a thermal source [51]. The advantage of using this type of heating is that it reduces the reaction time considerably compared to conventional heating because microwaves heat the reaction media to the core. The coupling compounds that were obtained were all of configuration (E). The use of microwave irradiation did not modify the stereochemistry of the double bond since although isomerization occurred by the thermal effect, the products formed in these examples were thermodynamic products and not kinetic products. It should be noted that these conditions required high heating, with temperatures reaching up to 180 °C. This may not be tolerated by certain functions or even by complex molecules such as certain sugars, as it can lead to degradation and side products.

In 2012, the Lamaty team published coupling conditions in a solvent that had the particularity of being solid at room temperature: PEG2000 [52]. As before, the stereochemistry of the compounds was exclusively of group (E), and no isomerization was observed. In 2016, our team showed that Mizoroki–Heck coupling can also be conducted in an environmentally sound manner in PEG 400 [53]. In 2008, Han and his team developed a solvent-free Heck–Mizoroki coupling procedure with a catalyst supported by SBA-15 silica grafted with 1,1,3,3-tetramethylgaunidinium (TMG) [54]. Compounds were obtained in very good yields while only using a tiny amount of catalyst (0.001 mol%). In 2017, Jagtap published an interesting review on the different conditions that can be used for the Heck coupling reaction, but it did not deal with the formation of conjugated dienes [55].Application of Mizoroki–Heck coupling to the synthesis of diene compounds.

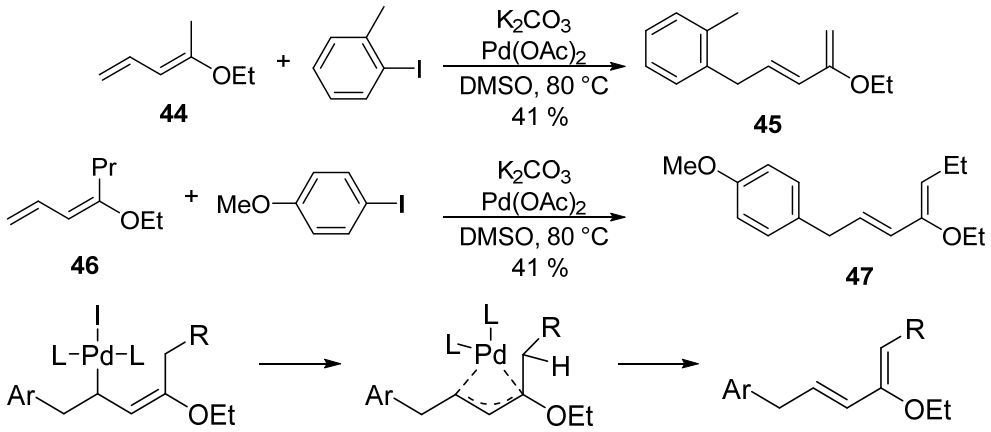
In 2003, the Venturello team reported the coupling of conjugated diene compounds with aromatic iodine derivatives [56]. The yields obtained in these conditions were moderate, but the isolated compounds retained the stereochemistry (E,E) of the starting diene compound 43 (Table 9).

Table 9. Heck coupling according to Venturello's group.



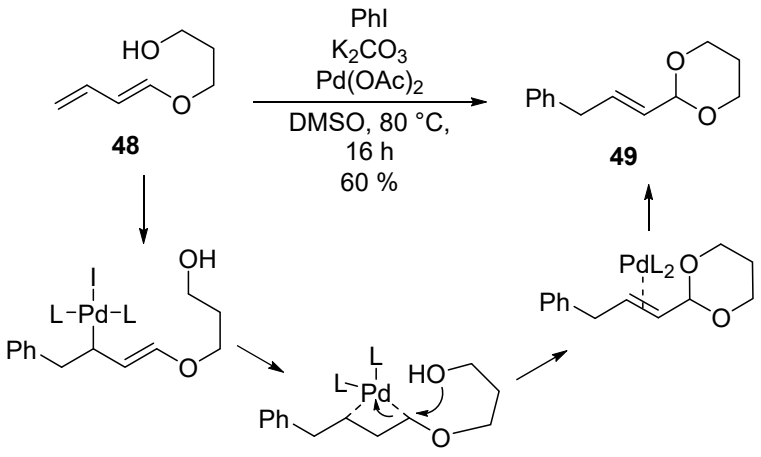
Entry	Ar-I	Yield (%)
1		43
2		48

However, in these conditions, when the diene did not have an ester function but instead had an alkyl substituent such as a methyl 44 or a propyl 46, the isomerization of the double bonds belonging the coupling product (45,47) was observed (Scheme 26).



Scheme 26. Mizoroki–Heck coupling with isomerization of double bonds and mechanism.

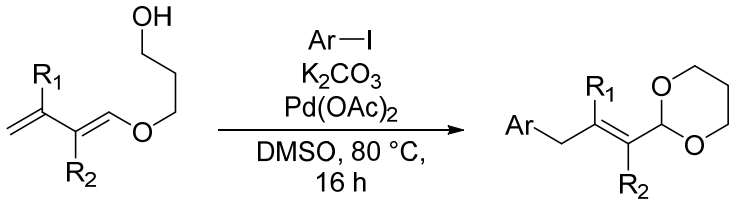
When this team used diene 48 in the previously described coupling conditions, isomerization was observed, and a cyclized compound was isolated. This intramolecular cyclization was the result of the addition of alcohol to the diene complexed with palladium. Finally, the catalyst was decomplexed from the alkene to lead to compound 49 (Scheme 27). The conformation of the compound obtained was exclusively (E).

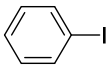
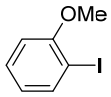
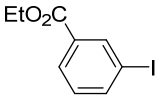
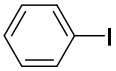
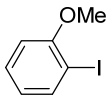
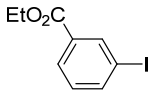
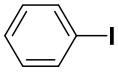


Scheme 27. Reaction mechanism of compound 49 synthesis.

From this result, the Venturello team generalized their method using various iodine compounds and various substituted dienes. When the diene was not substituted, the yields ranged between 60% and 73% depending on the aromatics used, with one (E) configuration only (Table 10, entries 1 to 3). Substitution on the 3′ position of the diene used with a methyl group did indeed lead to the expected coupling compound, but a second isomer was observed (Table 10, entries 4 and 6). However, it was shown that when aryl is hindered in the ortho position, only compound (E) was isolated (entry 5). If the diene was substituted with a methyl at the 2′ position, then compound (Z) was not observed in favor of compound (E) (Table 10, entry 7).

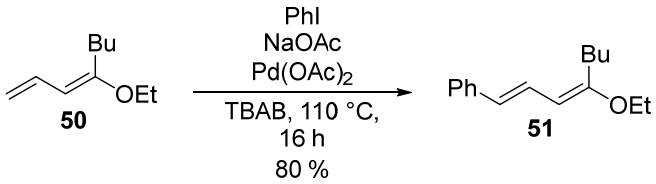
Table 10. Generalization of cyclizing Heck conditions.



Entry	R_1	R_2	Ar-I	Yield (*E*)/(*Z*) (%)
1	H	H		60/0
2	H	H		68/0
3	H	H		73/0
4	Me	H		42/8
5	Me	H		79/0
6	Me	H		53/17
7	H	Me		65/0

The compounds that were thus isolated were of great synthetic interest because in the presence of an acid catalyst, it would be possible to regenerate an α,β-unsaturated aldehyde by deprotection of the acetal function of the molecule.

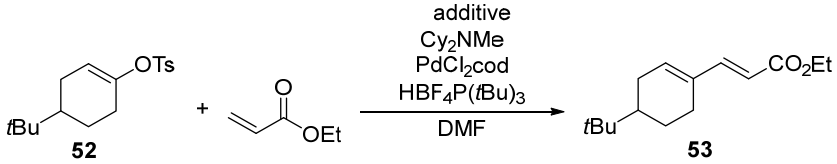
In 2006, the same team developed conditions leading to dienes without any isomerization [57]. The base changed, but the most important variation was the replacement of DMSO by an ionic liquid, tetrabutylammonium bromide (Scheme 28). The compound obtained was a conjugated diene with an exclusive (E,E) 51 stereochemistry.



Scheme 28. Heck coupling in ionic solvent by Venturello.

In 2006 Skrydstrup's group developed a new methodology to generate conjugated diene compounds [58]. They started from tosylate compounds 52 instead of the usually used iodine compounds in the presence of $PdCl_2cod$ as the catalyst. The phosphine was present in the form of a salt and was prepared according to the method described by Fu, with dicyclohexylmethylamine as a base in the medium [59]. These conditions required 1 equivalent of lithium chloride (50%, Table 11, entry 2) and an increase in the reaction temperature to 100 °C to be efficient (66%, Table 11, entry 3).

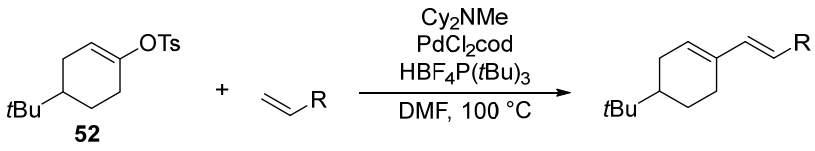
Table 11. Optimization of the coupling conditions by Skrydstrup et al.



Entry	Additive	Temperature (°C)	t (h)	Yield (%)
1	-	85	24	5
2	LiCl	85	24	50
3	LiCl	100	24	66

A generalization of the method was carried out. When styrene was used, coupling took place within 17 h, with a yield of 96% (Table 12, entry 1). The result was even better with 4-vinyl-1,1′-biphenyl (Table 12, entry 2). The reaction was tolerant to many compounds, such as 4-vinylpyridine: the coupling compounds were obtained in a yield of 88% (Table 12 entry 3).

Table 12. Generalization of the method by Skrydstrup's group.



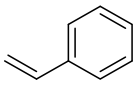
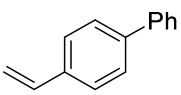
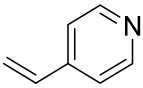
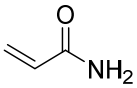
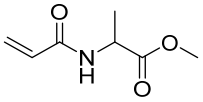
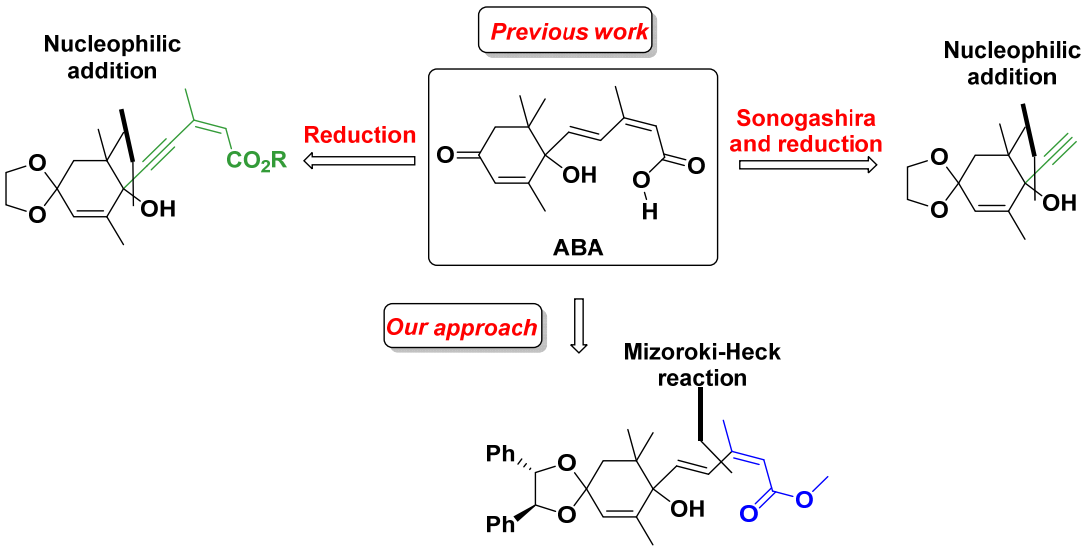
Entry	R	t (h)	Yield (%)
1		17	96
2		16	99
3		17	88

Table 12. *Cont.*

Entry	R	t (h)	Yield (%)
4		17	92
5		23	64

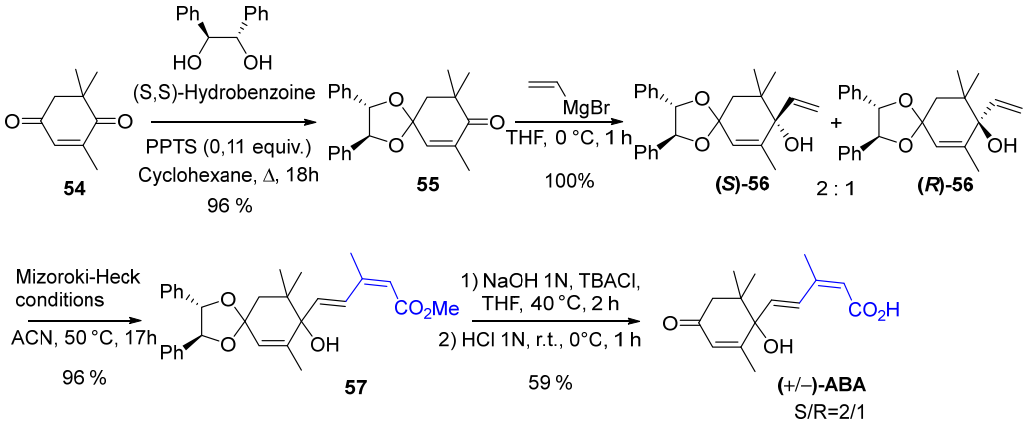
In the context of applications for the synthesis of natural products, Dounay and Overmann reported an asymmetric intramolecular Heck reaction in the total synthesis of natural products [50], and other teams reported other total synthesis reactions [60–62]. To achieve our goal concerning natural products possessing a conjugated diene, in 2018, our team applied the Mizoroki–Heck reaction to synthetize abscisic acid (ABA) (Scheme 29) in an environmentally sound manner [63]. ABA is an important phytohormone [64–70] that has been reported to have interesting properties [71,72]. After having considered the different synthesis strategies reported in the literature [73–81], the Mizoroki–Heck reaction conditions were optimized with methyl (2Z)-3-iodobut-2-enoate and various allylic cyclohexenols and cyclohexanols.



Scheme 29. Retrosynthetic approaches used by our team for the successful synthesis of ABA.

We succeeded in controlling the configuration of the double bonds, and no isomerization was observed. Our methodology was based on the association of simple terminal olefins with methyl (2Z)-3-iodobut-2-enoate in optimized solvent-free conditions in the presence of palladium acetate under air but without any ligand.

The expected (E/Z)-diene 57 was isolated in a 96% yield without racemization, and the *R*/*S* ratio was maintained during the formation of the diene. After a final saponification followed by an acidic treatment, abscisic acid synthesis was carried out. The ABA enantiomerically enriched in its *S* isomer was therefore synthetized in four steps, achieving a global yield of 54% (Scheme 30) [63].



Scheme 30. ABA synthesis in four steps.

3. Conclusions

We have presented some reactions described since the 2000s that have been conducted to obtain alkene compounds and, in particular, conjugated diene compounds. These reactions are very diverse and require, for the most part, a large number of precautions. The most important issue, however, is the toxicity of most of the catalysts required to accomplish the previously described couplings in the synthesis of these molecules of interest. That may be problematic for the production of these molecules on a large scale and should commit the scientific community to investing in all sustainable synthetic routes.

As diene moieties are often present in natural compounds, it is therefore necessary to develop or improve the conditions for these coupling reactions in an environmentally sound manner, as the use of chlorinated solvents, or even benzene, is still too widespread and should be optimized in favor of reactions that can be conducted without the use of solvent or with green solvents.

Author Contributions: Conceptualization and methodology, G.D. and S.B.-R.; investigation and data curation, G.D. and S.B.-R.; writing—original draft preparation, G.D. and S.B.-R.; writing—review and editing, S.B.-R.; supervision, project administration, and funding acquisition, S.B.-R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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