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Solvent-Free Mizoroki-Heck Reaction Applied to the Synthesis of Abscisic Acid and Some Derivatives

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Abstract: Abscisic acid (ABA) is a natural product, which is a well-known phytohormone. However, this molecule has recently exhibited interesting biological activities, emphasizing the need for a simple and direct access to new analogues based on the ABA framework. Our strategy relies on a pallado-catalyzed Mizoroki-Heck cross-coupling as key reaction performed in solvent and ligand free conditions. After a careful optimization, we succeeded in accessing various (*E*/*Z*)-dienes and (*E*/*E*/*Z*)-trienes in moderate to good yields without isomerization and applied the same approach to the synthesis of ABA in an environmentally sound manner.

Keywords: Mizoroki-Heck; abscisic acid; solvent-free

1. Introduction

Polyenic scaffolds constitute an important functionality among organic compounds and have a high synthetic interest since medicinally relevant molecules and natural products exhibit diene fragments (Figure 1) [1].

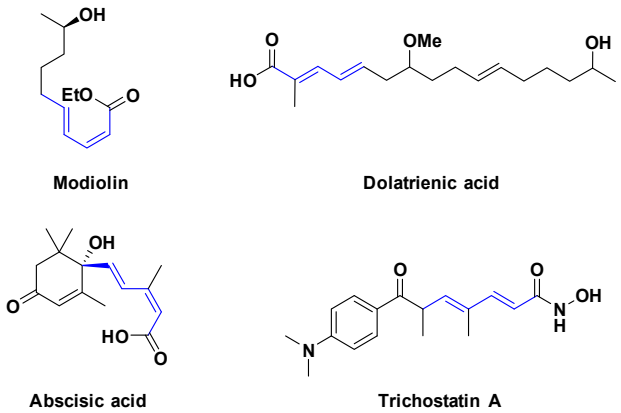


Figure 1. Examples of biologically active natural products containing diene moieties.

Several synthetic methods have therefore been developed to obtain these carotenoid moieties in iterative process or in convergent methods [2]. Traditionally, the olefination reaction was extensively used. However, it is often associated with the uncontrolled production of E and Z isomers which may require careful purification [3]. Then transition metal-catalyzed cross-coupling reactions galvanized the synthesis of these complex conjugated molecules. Catalysts such as ruthenium [4], zirconium [5–7], zinc [8] and nickel [9] were successfully used. The use of palladium has been widely reported with

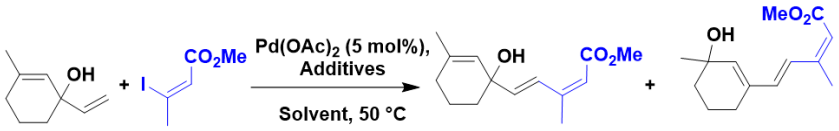
Negishi [10,11], Stille [12–15], Suzuki-Miyaura [16–18], Sonogashira [19], Kumada-Tamao [20] and Mizoroki-Heck [21–25] cross-coupling reactions [26–28]. Lately, the use of single unsaturated units as building blocks was promoted to respond to the challenging but crucial control of the configuration of the double bond generated [29–33]. In our effort to develop environmentally benign tools [34–36], we herein report the use of the Mizoroki-Heck reaction, which requires simple and directly accessible starting materials to build stereocontrolled dienes and trienes. Unlike other cross-coupling approaches, which may require several steps to install the pre-activated partners, the Mizoroki-Heck reaction enables the direct formation of dienes from terminal olefin substrates. The efficiency of our method was then evaluated in the synthesis of abscisic acid, an important phytohormone [37–43] which has been recently reported to have interesting biological effects [44,45].

2. Results and Discussion

2.1. Optimization of the Mizoroki-Heck Reaction

To achieve the optimized conditions, the cross-coupling reaction of 1-ethenyl-3-methylcyclohex-2-en-1-ol **1** with methyl (2*Z*)-3-iodobut-2-enoate **2** was selected as the model reaction under the standard conditions previously described by Cossy and co-workers (Table 1, entry 1) [46]. Surprisingly, only degradation was observed. Since conjugated products are prompted to make versatile rearrangement [47,48], the reaction was next performed in a flask protected from natural light. A small amount of the expected product **3a** was isolated along with the side product **4** (entry 2). The formation of **4** can be explained by a 1,3-rearrangement of the allylic alcohol, a transformation previously described by Qu and co-workers under a thermal activation in water [48]. The use of acetonitrile moreover of an additional ligand induced no positive change (entries 3 and 4) [49]. However, a significant improvement was obtained by replacing silver acetate by silver carbonate and 1.5 equiv. of silver carbonate proved to be the optimized amount (entries 5–7). A moderate heating is recommended since the formation of **3a** was significantly reduced at 80 °C.

Table 1. Optimization of the Mizoroki-Heck reaction between **1** and **2**.



1 **2** **3a** **4**

Entry	**1** (equiv.)	**2** (equiv.)	Additive (equiv.)	Solvent	Time (h)	Yield **3**:**4** (%)
1	1.2	1	AgOAc (1.1)	DMF	17	0:0 [a]
2	1.2	1	AgOAc (1.1)	DMF	17	5:4 [b]
3	1.2	1	AgOAc (1.1)	MeCN	17	9:0 [b]
4	1.2	1	AgOAc (1.1) $P(o\text{Tol})_3$ (0.1)	MeCN	17	9:20 [b]
5	1.2	1	Ag_2CO_3 (1.5)	MeCN	17	63:0 [b,c]
6	1.2	1	Ag_2CO_3 (2)	MeCN	17	63:0 [b,c]
7	1.2	1	Ag_2CO_3 (1.1)	MeCN	17	54:0 [b,c]
8	1.2	1	Ag_2CO_3 (1.5)	MeCN	17	10:0 [b,c,d]
9	1.2	1	Ag_2CO_3 (1.5)	none	1	63:0 [b,c]
10	1	2	Ag_2CO_3 (1.5)	none	1	60:0 [b,c]
11	1	1 + 1	Ag_2CO_3 (1.5)	none	1	50:0 [b,c]
12	1.2	1	Ag_2CO_3 (1.5)	none	1	62:0 [b,d]

[a] The reaction was performed under natural light. [b] Reaction performed protected from natural light. [c] Reaction performed under air. [d] The reaction temperature was set at 80 °C. [e] Reaction performed under inert atmosphere.

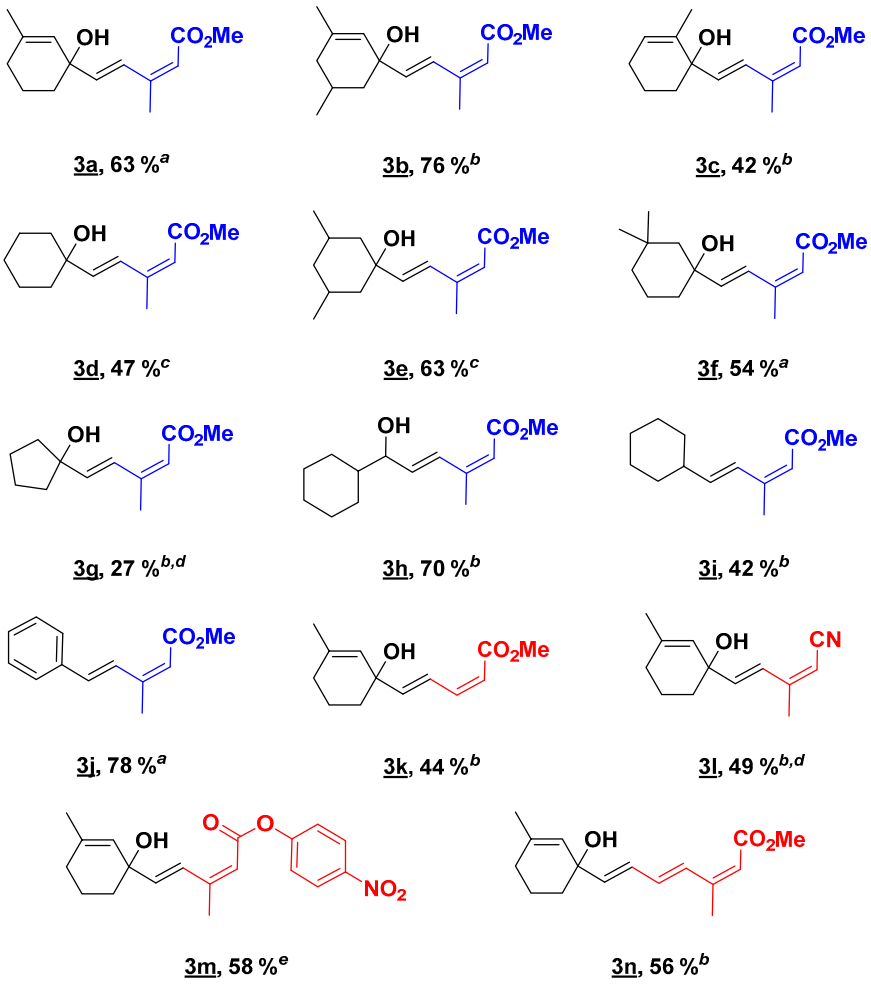
Next, neat conditions were tried, and even if the reaction mixture was a thick paste, the expected product **3a** was isolated in similar yield (63%) in a considerably shorter time (1 h vs. 17 h). To the best

of our knowledge, this is the first example of neat Mizoroki-Heck reaction for the formation of dienes. The vinylation of acrylic substrates has been already reported in solvent-free conditions but it usually requires the use of a ligand, palladium supported catalyst, palladium nanocatalyst or microwave activation [50–57]. Finally, **2** was introduced in excess, in one portion or in sequential addition, without improving the yield (entries 10 and 11). Hence the optimized reaction conditions were as follows: in a flask protected from light, **1** (1.2 equiv.) and **2** (1 equiv.) in presence of $Pd(OAc)_2$ (5 mol %) and Ag_2CO_3 (1.5 equiv.) at 50 °C for 1 h. It should be noted that working under an inert atmosphere did not improve the yield of the products **3a** and **4** (entry 12).

2.2. Substrate Scope

A diversity of terminal olefin substrates was tested in the coupling reaction with methyl (2*Z*)-3-iodobut-2-enoate **2**. The results are reported in Scheme 1. Various allylic cyclohexenols and cyclohexanols were examined and the expected dienes were obtained in moderate to good yields **3a**–**3f**. The presence of an unsaturation and/or different methyl substituents on the ring had little influence on the efficiency of the reaction. The variation of the yield observed was more substrate-dependent since **3c** and **3d** appeared to be very unstable and degraded spontaneously if not stored at low temperature in dark conditions. For these compounds, the reaction was tried at room temperature; however, the cross-coupling reaction failed completely. The stability issue was even more pronounced for 1-ethenylcyclopentan-1-ol, since its formation from cyclopentanone was difficult. The cross-coupling reaction was performed on the crude starting material, which could explain the low yield observed. Surprisingly, the resulting product **3g** was completely bench stable. Satisfyingly, sterically hindered secondary alcohols **3h** and sensitive tertiary alcohols (**3a**–**3g**) were well tolerated under our optimized conditions. Even the volatile ethenylcyclohexane, which required working in a sealed tube, and the unstable styrene led to the corresponding dienes **3i** and **3j** in 42% and 78% yields. It is worth noting that all the coupling products were obtained as pure (*E*,*Z*)-dienes. The configuration of the diene was confirmed by ^{1}H NMR (Supplementary Materials: Figure S1). The chemical shift of the hydrogen alpha to the ester moiety is in accordance with the values reported in the literature for a (*E*/*Z*)-diene, around 5.5 ppm (vs. 6.0 ppm for a *E*/*E* fragment) [58].

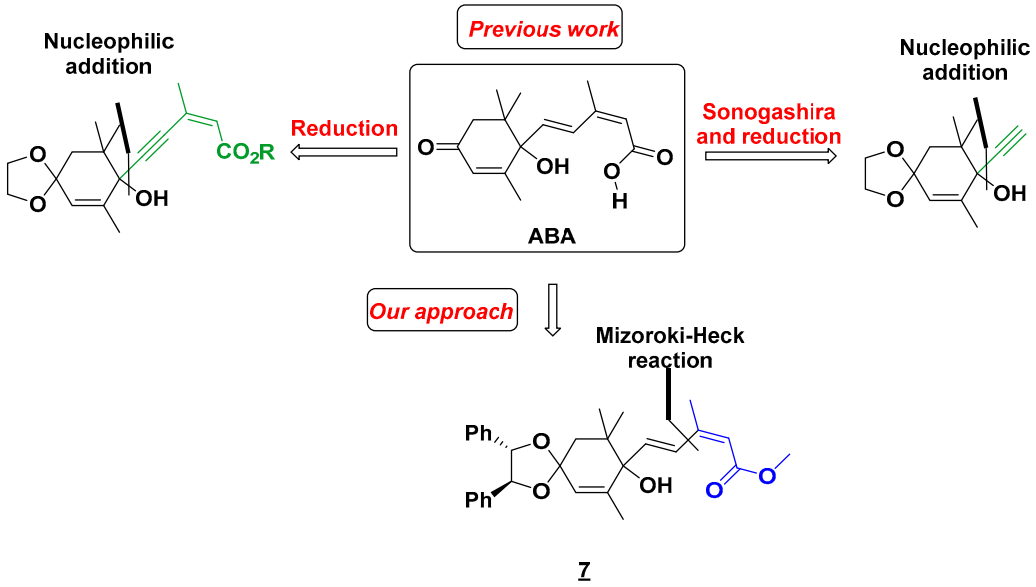
Finally, different vinylic iodides were submitted to our solvent-free Mizoroki-Heck conditions. (2*Z*)-3-iodobut-2- enenitrile **2a**, Methyl (2*Z*)-3-iodoacrylate **2b**, and 4-nitrophenyl(2*Z*)-3-iodobut-2-enoate **2c** were successfully introduced on 1-ethenyl-3-methylcyclohex-2-en-1-ol **1** leading to expected compounds (**3k–3m**). Compound **3k** appeared to be more sensitive to degradation than **3a**, but the (*E*,*Z*) configuration remained unchanged. The reaction conditions were then extended to the formation of (*E*,*E*,*Z*) tertiary trienol **3n**, using Methyl (2*Z*,4*E*)-5-iodo-3-methylpenta-2,4-dienoate (**2e**), which was isolated in 56% yield.



Scheme 1. Scope of substrates. [a] 1 h of reaction time. [b] 2 h of reaction time. [c] 1 h 40 min was required for the reaction time. [d] sealed tube. [e] 40 min of reaction time.

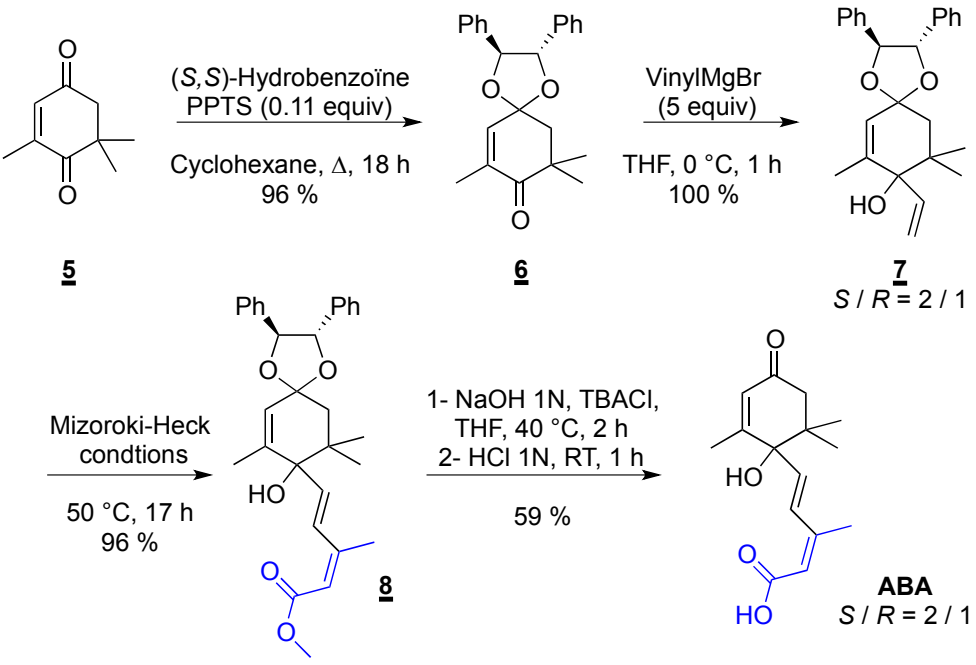
2.3. Synthesis of ABA

Having a method to obtain the diene scaffold in hand, we focused on the synthesis of abscisic acid (ABA). Several syntheses have already been reported in the literature [59–61]. Most of them are based on the introduction of the carbon skeleton of the side chain via the corresponding alkyne in one step [62–65] or with trimethylsilylacetylene [66,67], which is then functionalized by a Sonogashira reaction (Scheme 2). Our strategy requires a reduction step to obtain the final (*E*,*Z*) diene fragment. Our approach is based on the introduction of the side chain with our solvent-free Mizoroki-Heck reaction between methyl (2*Z*)-3-iodobut-2-enoate **2** and **7**. Our key cross-coupling precursor was straightforwardly obtained from the commercially available 2,6,6-trimethylcyclohex-2-ene-1,4-dione **5**.



Scheme 2. Retrosynthetic approaches for the synthesis of ABA.

First, the mono protection of the diketone **5** was tried following the conditions described by Ferrer and co-workers (Scheme 3) [68]. (*S*,*S*)-hydrobenzoin, our chiral auxiliary, was heated in presence of a catalytic amount of *p*TsOH in benzene. However only the degradation of the hydrobenzoin into benzaldehyde was observed. We then decided to use pyridinium *p*-toluenesulfonate (PPTS), which is a milder acidic catalyst [69].



Scheme 3. Synthesis of ABA.

This time, in benzene the desired product **6** was isolated after 5 days in a promising 24% yield. A survey of different solvents was made and fortunately, the environmentally sound cyclohexane significantly improved the yield and the reaction time since **6** was obtained in 96% yield after 18 h. Next, the Grignard reaction with an excess of vinylmagnesium bromide gave quantitatively **7** as a

mixture of inseparable diastereoisomers. The *R*/*S* ratio of the newly formed center was determined by HPLC. Disappointingly, working at a lower temperature (−20 °C or −78 °C) did not improve this ratio much while it considerably reduced the formation of **7**. Nevertheless, our key step was performed on the mixture of both isomers and the expected (*E*/*Z*)-diene **8** was isolated in 96% yield without racemization, the *R*/*S* ratio remained unchanged during the formation of the diene **8**. A saponification followed by an acidic treatment enabled the formation of abscisic acid with the same *R*/*S* ration and therefore enantiomerically enriched in its *S* isomer. The final product was synthetized in four steps from **5** in 54% global yields.

3. Conclusions

To conclude, we managed to develop an efficient, environmentally sound method to synthetize delicate dienes and trienes via a Mizoroki-Heck reaction. The configuration of the double bonds was controlled, and no isomerization was observed. The salient features of our approach are the association of simple terminal olefins with various vinylic iodides, palladium acetate under air without any ligand or solvent. Our optimized solvent-free Mizoroki-Heck reaction was next successfully applied to the synthesis of ABA. This method offers a short new pathway where solvents and reagents were chosen to give an environmentally friendlier alternative to the synthesis already available in the literature.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/8/3/115/s1, Figure S1: ^{1}H NMR and ^{13}C NMR Spectra of all compounds.

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Author Contributions: Sabine Berteina-Raboin conceived and designed the experiments. Geoffrey Dumonteil performed the experiments. Geoffrey Dumonteil, Marie-Aude Hiebel and Sabine Berteina-Raboin analyzed the data and wrote the paper.

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

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