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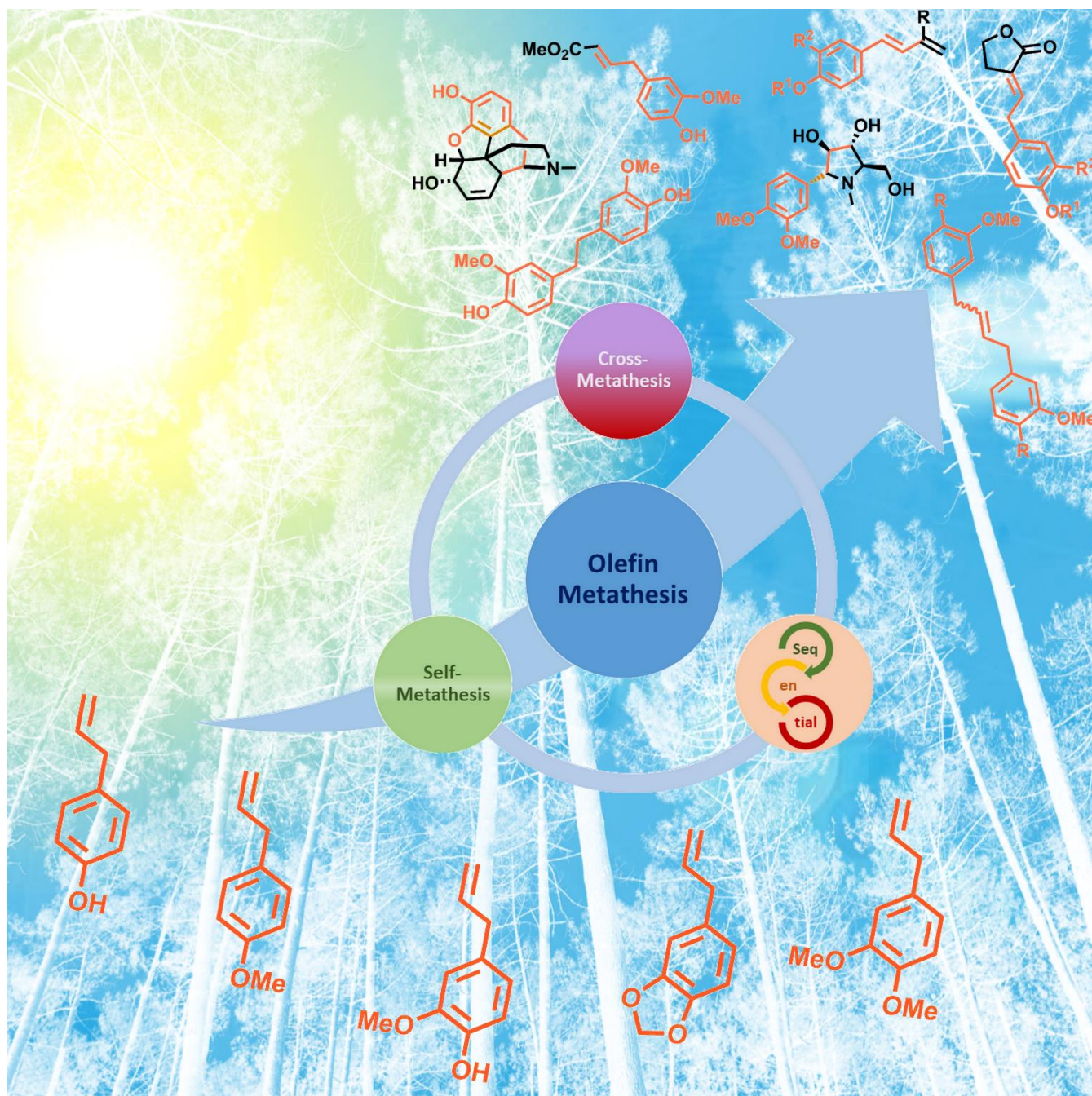
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REVIEW

Transformations of bio-sourced 4-hydroxyphenylpropanoids based on olefin metathesis

Hallouma Bilel,^[a] Naceur Hamdi,^[b] Cédric Fischmeister,^[c] and Christian Bruneau*^[c]

Dedicated to Prof. Pierre H. Dixneuf for his meaningful contribution to organometallic chemistry and ruthenium catalysis



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Abstract: 4-Hydroxyphenylpropanoids represent an important class of natural products directly extracted from plants or derived from lignocellulosic materials. They are phenol derivatives equipped with a terminal propenyl group, which is perfectly suited for applications involving olefin metathesis processes. In this review, we show that conditions have been found to achieve their self-metathesis, cross metathesis as well as some sequential transformations with metathesis as a key step with high yields and controlled stereoselectivities. Some applications in multi-step synthesis of biological relevant natural products involving metathetic transformations of 4-hydroxyphenylpropanoids are also reported.

1. Introduction

Besides fossil resources, which have been extensively used in petrochemical industry for the production of a variety of products ranging from fuels for energy purposes to commodity and specialty products during the twentieth century, the contribution of renewable natural resources is now considerably increasing with objectives of sustainable development.^[1-7] All classes of abundant natural products including carbohydrates,^[8] oils and fats,^[9] terpenes,^[10] and lignocellulosic materials^[11] have potential applications in fine chemistry, especially *via* simple catalytic transformations. In this review, we focus on the utilization of phenylpropanoids, which constitute one of the most representative family of aromatic bio-sourced feedstocks. They can be obtained from lignin biomaterials and also exist as well-defined molecules extracted from plants. Among them, 4-allylphenol derivatives such as eugenol, estragole, safrole, ... have interesting properties for applications in cosmetic, pharmaceutical as well as flavor and fragrance industry.^[12] Because these molecules contain a terminal propenyl group and a phenol functionality, they have already served as substrates or intermediates in the construction of more complex molecules of interest.^[12a,b,13] Since the discovery of efficient and robust catalysts, olefin metathesis has been extensively used as a direct transformation adding value to bio-sourced feedstocks such as unsaturated fats and oils,^[14] terpenes,^[15] and natural vinylphenols,^[16] containing internal or terminal carbon-carbon double bonds. Similarly, straightforward and clean transformations of the terminal double bond of the propenyl group of phenylpropanoids by cross metathesis with

other olefins has enabled the preparation of functionalized phenol derivatives that are challenging to prepare by other synthetic routes. In this review, self-metathesis and cross metathesis reactions of 4-allylphenol derivatives with various types of olefins will be reported and some applications in synthesis described in details.

1.1. Substrates and catalysts

The most common 4-allylphenol derivatives found in nature that have been evaluated in olefin metathesis transformations are listed in Figure 1. Apart from estragole (**2**) and chavicol (**4**), which are simple 4-allylphenol derivatives, the others are members of the eugenol family.

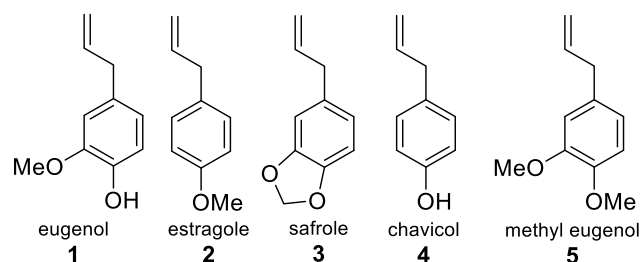


Figure 1. Main 4-allylphenol derivatives of this review

Then it must be noted that most of the metathesis transformations we have found in the literature have been performed with ruthenium catalysts (Figure 2).

2. Self-metathesis

Eugenol (**1**) has been extensively used as model substrate of functionalized phenylpropanoids in olefin metathesis reactions. Its self-metathesis was initially achieved in the presence of the first generation Grubbs catalyst **Ru1**.^[17,18] Without solvent, in the presence of 0.3 mol% of catalyst, the self-metathesis product **6** was isolated in 71% yield as a mixture of stereoisomers in a *EZ* ratio of 5.9:1. The formed ethylene was removed from the liquid phase by applying an initial static vacuum (Scheme 1) and the structure of the major symmetrical olefin (*E*)-(**6**) isolated as a solid was confirmed by X-ray crystallography.^[19]

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Dr. C. Bruneau graduated in chemistry from the Institut National Supérieur de Chimie Industrielle de Rouen (France, 1974) and got his PhD at the University of Rennes (1979). He obtained a CNRS position in 1980 and since 1986 has been working in the field of transition metal catalysis at the University of Rennes. He has been mainly involved in ruthenium and recently iridium-catalyzed selective transformations (olefin metathesis, allylation, sp^2 and sp^3 C-H bond activation and functionalization, hydrogen transfer, asymmetric catalysis, additions to alkynes, bio resources transformations). From 2000 to 2011, he was the head of the CNRS–University of Rennes research group “Organometallics and Catalysis”. He is the recipient of the prize of the Coordination Chemistry Division (2008) and Le Bel prize (2016) from the French Chemical Society, and Paul Langevin prize (2012) from the French Academy of Sciences.



Dr. Cédric Fischmeister received his PhD degree in 1998 from the University of Montpellier II working on the synthesis of hybrid organic-inorganic materials under the supervision of Profs. Robert Corriu and Geneviève Cerveau. He then joined the group of Prof. Régis Réau in Rennes to work on phosphole-containing conjugated molecules for light emitting materials. After spending 16 months as a post-doc research associate in the group of Prof. Andrew Holmes at the Melville Laboratory for polymer synthesis in Cambridge UK, working on the synthesis of PPVs for LEDs, he was appointed in 2001 as a CNRS research engineer in the group of Dr. Christian Bruneau and Prof. Pierre Dixneuf, and obtained the “Habilitation à Diriger des Recherches” in 2008. His research interests concern organometallic chemistry and homogeneous catalysis applied to the transformation and valorization of renewable materials using essentially olefin metathesis and reduction

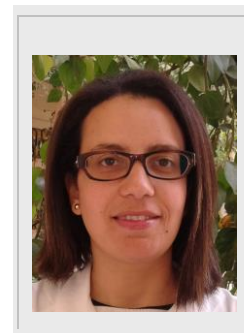


transformations. He is also interested in future energy carriers such as hydrogen and in the implementation of sustainable chemical transformations and processes.

Prof. Naceur HAMDI is currently holding a position of Professor of Chemistry at the University of Carthage in Tunisia. Actually he is in Saudi Arabia in the framework of a technical cooperation. He has experience of more than 15 years working in the field of organic and organometallic chemistry as well as in homogeneous catalysis and is well connected to the international inorganic and organometallic communities. He has produced more than 70 publications in peer-reviewed international journals plus 5 contributions to books. With more than 1000 citations, he is currently ranked by ISI Web of Science with an h-index of 20. He has presented his work in approximately 70 extramural seminars in academic and industrial research institutions worldwide by their invitation.



Dr. Hallouma Bilel was born in Tunis (Tunisia) in 1984. She obtained a PhD from the University of Rennes 1 – France and the University of Carthage- Tunisia in 2015 under the supervision of Dr. Christian Bruneau and Dr. Naceur Hamdi. During this period she was trained in catalytic transformations of natural products by metathesis reactions, using ruthenium catalysts under the guidance of Dr. Cédric Fischmeister. In 2015, she joined the University of Gafsa-Tunisia as assistant professor. She is currently faculty member at Jouf University – KSA. Her current researches include synthesis of products with high added value.



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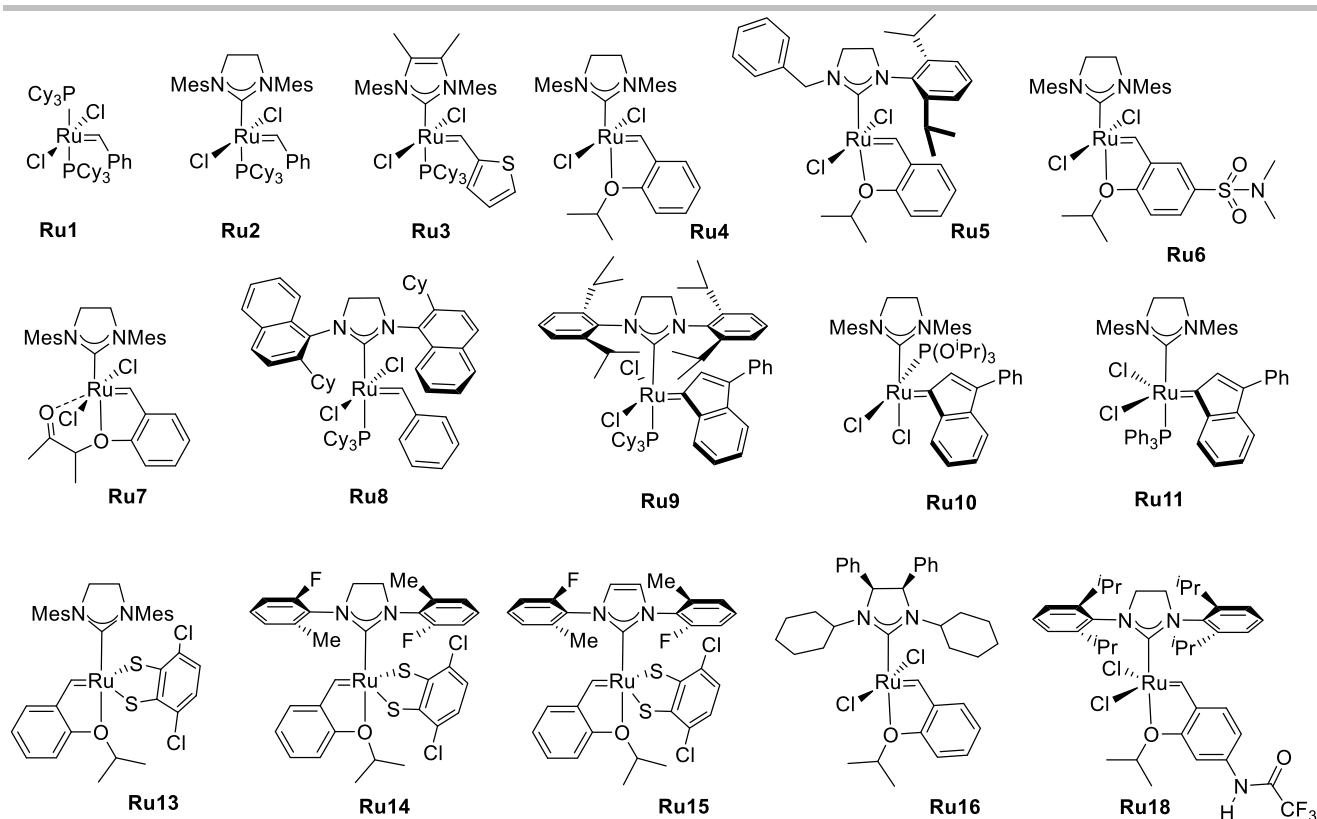
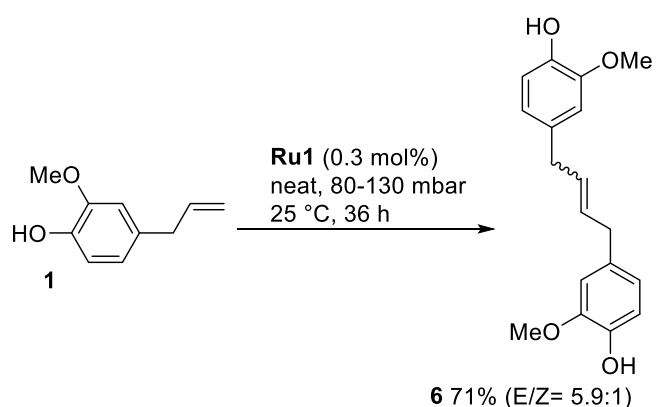


Figure 2. Ruthenium catalysts used in this review



Scheme 1. Self-metathesis of eugenol

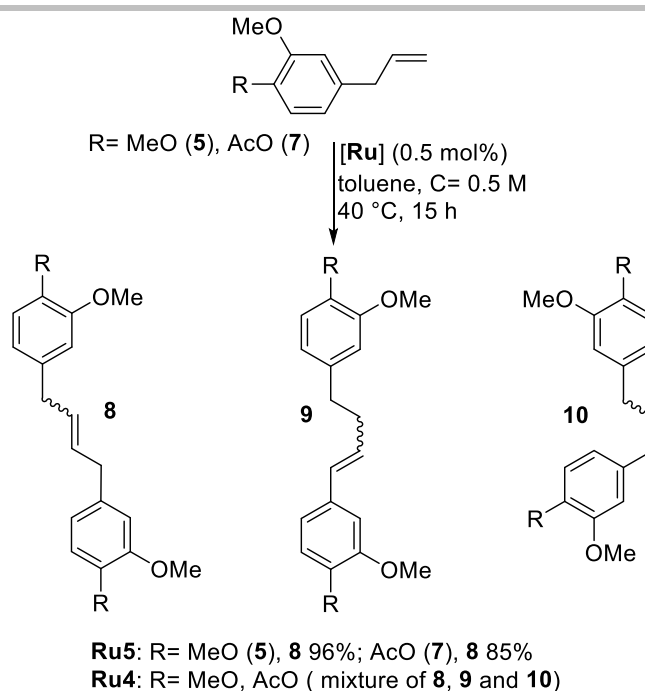
The isolated yield of (**6**) was increased to 93% when the reaction was carried out during 48 h under a reduced pressure of 27 mbar with a higher loading of 1 mol% of **Ru1**.^[20] After hydrogenation of the double bond the corresponding saturated bis(phenol) was converted by standard reaction with CNBr into a bis(cyanate) that polymerized upon thermal treatment to give a renewable thermosetting resin. The self-metathesis of estragole (**2**) was successfully achieved in refluxing dichloromethane ($c=0.3$ M) in

the presence of 2.5 mol% of **Ru1**. The corresponding 1,4-di(4-methoxyphenyl)but-2-ene was isolated in 97% yield with a *E:Z* ratio of 6.2:1.^[21] The self-metathesis of (**1**) was also successfully achieved in the presence 1 mol% of the second generation ruthenium complex **Ru2**^[22] in dichloromethane as solvent ($c=0.4$ M). After 5 h at 25 °C, (**6**) was isolated in 63% yield as a mixture of *E* and *Z* isomers.^[23] It was also shown that when this catalyst **Ru2** was occluded in polydimethylsiloxane and used in a protic MeOH/H₂O mixture (90:10 vol%) as solvent, the metathesis catalyst properties were lost and new properties of double bond isomerization appeared. Thus, the reaction of eugenol in this mixed solvent ($c=0.9$ M) at 100 °C for 20 h in the presence of 1 mol% of occluded **Ru2** catalyst did not provide the self-metathesis product (**6**) but only isoeugenol, the corresponding β -methylstyrene derivative in 82% yield.^[23] With a catalyst loading of 0.5 mol%, the catalyst **Ru3** (Figure 2) was found to be moderately active at room temperature for the self-metathesis of **1** leading to 48% conversion in toluene ($c=0.45$ M) within 1 h but no information about yield and stereoselectivity was given. This conversion could be improved to 60% by increasing the temperature to 80 °C, and even better to

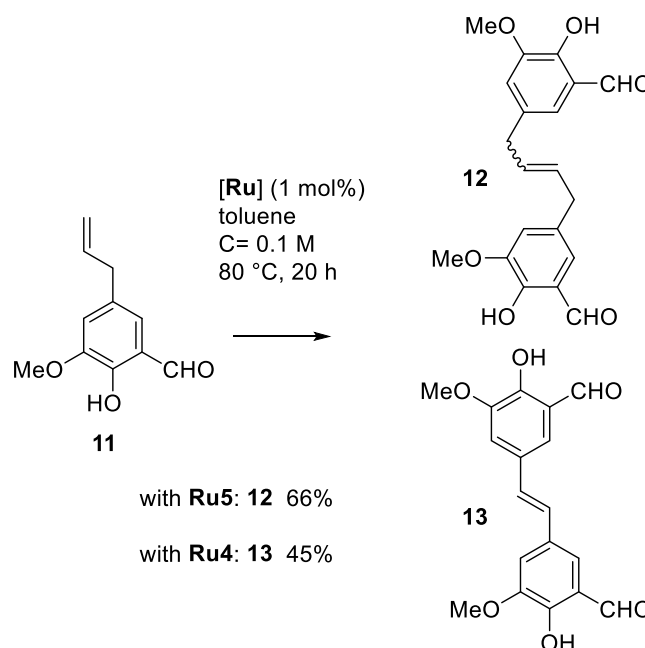
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93% when a second dose of 0.5 mol% of **Ru3** was added after 1 h and the reaction prolonged for another 1 h.^[24] It is surprising to observe that no reaction took place when dimethyl carbonate was used as solvent.^[25] With the second generation Hoveyda catalyst **Ru4**^[26] the possibility of competing reactions involving double bond migration either before or after the metathesis reaction was disclosed with methyl eugenol (**5**) and the protected eugenol (**7**) (Scheme 2).^[27] With these substrates, the reaction at 40 °C in toluene (*c*= 0.5 M) for 15 h in the presence of 0.5 mol% of **Ru4** gave an inseparable mixture of stereoisomers of the self-metathesis product (**8**), its isomer (**9**) resulting from post-migration of the double bond from (**8**), and (**10**) with a shorter link between the two aryl groups arising from a double bond migration/cross metathesis sequence. Interestingly, under similar catalytic conditions the utilization of the catalyst **Ru5** equipped with an unsymmetrical *N*-heterocyclic carbene ligand led to selective self-metathesis affording (**8**) in 96% (*E/Z*= 5.3:1) and 85% (*E/Z*= 4.9:1) isolated yield, from (**5**) and (**7**), respectively.

The self-metathesis of (**11**), a phenylpropanoid derivative functionalized with a formyl functionality in *meta*-position of the allyl group of eugenol was also efficiently and selectively carried out with catalyst **Ru5** to give the sole self-metathesis product (**12**) in 66% yield but required higher catalyst loading and reaction temperature (Scheme 3). By contrast, the Hoveyda catalyst **Ru4** did not give self-metathesis of (**11**) but prior isomerization of the propenyl group into a β -methylstyryl group followed by cross metathesis leading to the formation of the (*E*)-stilbene (**13**) in 45% yield.^[27] These two examples illustrate the drastic influence of the catalyst on the fate of the competing metathesis and isomerization reactions and highlight the absence of isomerizing properties brought by the unsymmetrical NHC ligand in **Ru5**. The high propensity of allylbenzene derivatives including 4-hydroxyphenylpropanoids to isomerize in the presence of ruthenium olefin metathesis and other metal catalysts has been extensively studied and recently reviewed by van Otterlo.^[12a]



Scheme 2. Self-metathesis competing with isomerization/metathesis

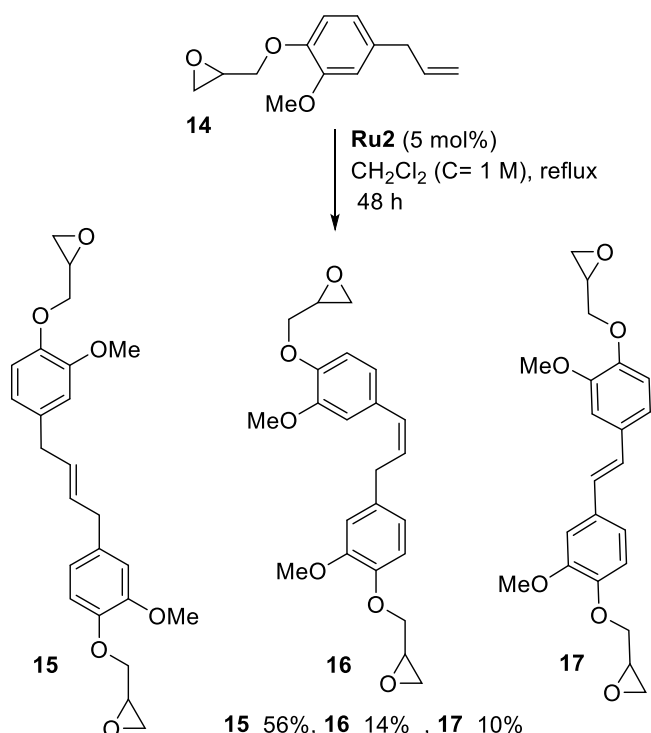


Scheme 3. Different reactivities of **Ru4** and **Ru5** in metathesis transformations of (**11**)

The second generation Grubbs catalyst **Ru2**, which as **Ru4** is equipped with a symmetrical *N*-heterocyclic carbene ligand also gave isomerization of the propenyl into the β -methylstyryl group as exemplified in the metathesis of the *O*-protected eugenol (**14**) in refluxing dichloromethane, which besides the self-metathesis product (**15**) obtained in 56%, provided the products (**16**) (14%) and (**17**) (10%), arising from cross metathesis of the initial

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substrate with its *in situ* generated styrene isomer and self-metathesis of this styrene, respectively (Scheme 4).^[28]



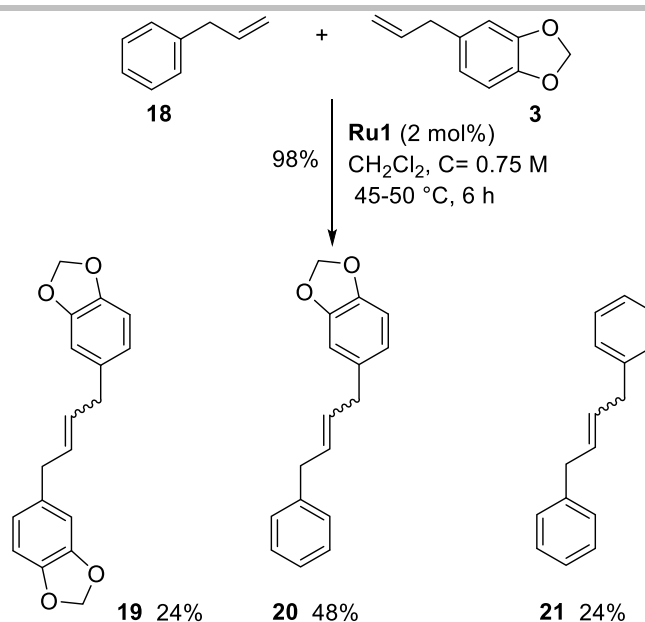
Scheme 4. Self-metathesis of O-protected eugenol in the presence of **Ru2** catalyst

Finally, Re(VII) oxide supported on mesoporous alumina has been successfully used in self-metathesis of estragole (**2**) with excellent selectivity at 25 °C under heterogeneous conditions.^[29]

3. Cross metathesis

3.1. Cross metathesis with styrenes

A library of internal olefins has been constructed by cross metathesis of allylbenzene (**18**) with various terminal olefins in order to further prepare databases of diols using the Sharpless dihydroxylation reaction.^[30] Among the olefin partners, safrole (**3**) was used in a particular cross metathesis reaction involving two allylbenzene derivatives.^[31] In the presence of 2 mol% of **Ru1**, almost full conversion of the two substrates was obtained within 6 h at 45-50 °C in CH₂Cl₂. As expected the two self-metathesis (**19**) and (**21**) and the cross metathesis (**20**) products were obtained in a statistical ratio (Scheme 5). With the first generation Grubbs catalyst **Ru1**, which is not prone to promote double bond migration, only 1,4-diarylbut-2-enes were produced.



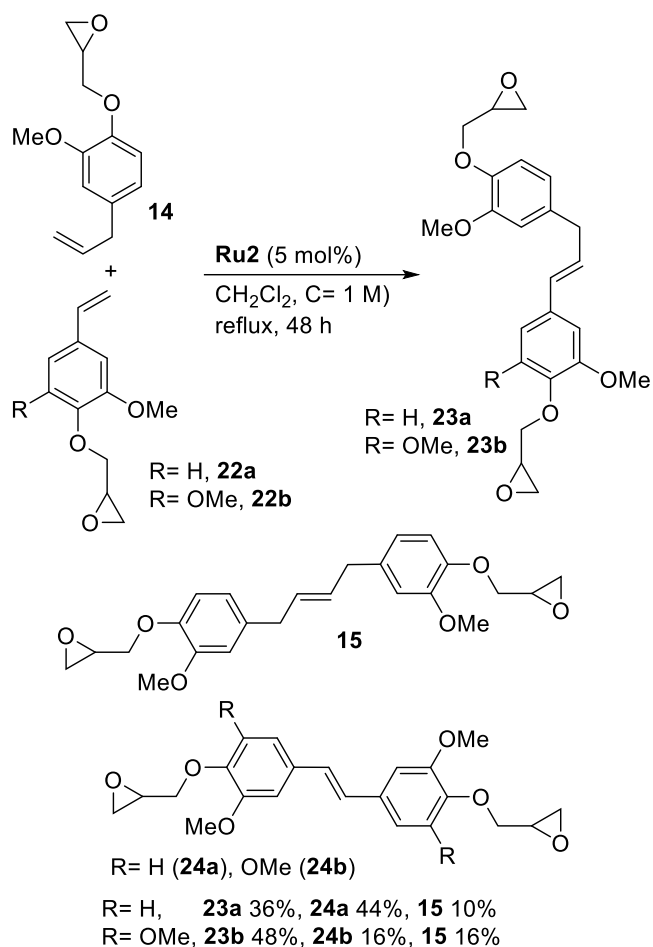
Scheme 5. Cross metathesis of allylbenzene **14** with safrole **3**

Based on the general model for selectivity in olefin cross metathesis with **Ru1** and **Ru2** proposed by Grubbs in 2003, it appears that both aliphatic terminal olefins and styrenes with low steric hindrance in *ortho*-positions of the vinyl group have a propensity to give self-metathesis.^[32] This was indeed observed when the O-glycidylated eugenol (**14**) was reacted with 4-vinyl guaiacol (**22a**) in refluxing dichloromethane for 48 h in the presence of 5 mol% of **Ru2** (Scheme 6).^[28] The cross-metathesis product (**23a**) was obtained in 36% yield together with the self-metathesis products of the styrene (**22a**) ((**24a**), 44% yield) and the allylphenol derivative (**14**) ((**15**), 10% yield). The transformation by self-metathesis of the more bulky 4-vinyl syringol (**22b**) was less important leading to (**24b**) in 16% yield, whereas the formation of the cross-metathesis product (**23b**) became more favoured (48% yield). It is noteworthy that (**15**) was also formed in 16% yield and that another unsymmetrical stilbene arising from cross-metathesis of the styrene (**22b**) with the isomerized starting eugenol was formed in 5% yield. After hydrolysis into diols, all these new glycidylated compounds arising from natural resources were evaluated for their binding affinity to the estrogen receptor α .^[28]

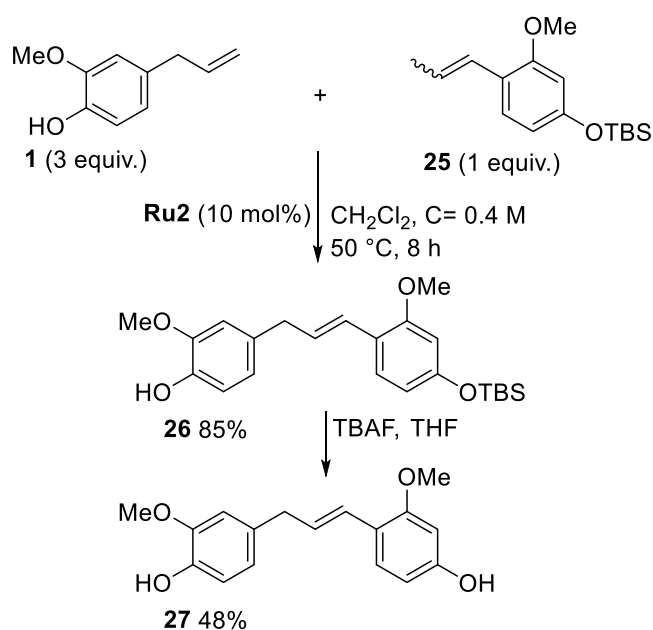
The cross metathesis of eugenol (**1**) with the disubstituted double bond of the *ortho*-methoxy- β -methylstyrene (**25**) was more selective due to the lower self-metathesis ability of (**25**) and the excess of (**1**). The metathesis carried out in dichloromethane at 50 °C for 8 h with a (**1**)/(**25**) ratio of 3 afforded the cross metathesis product (**26**) in 85% yield with high selectivity but required the presence of 10 mol% of **Ru2** (based on (**25**)) (Scheme 7).^[33]The

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fully deprotected phenol (**27**) was then involved in the preparation of santalin B, one of the major colorant of red sandalwood



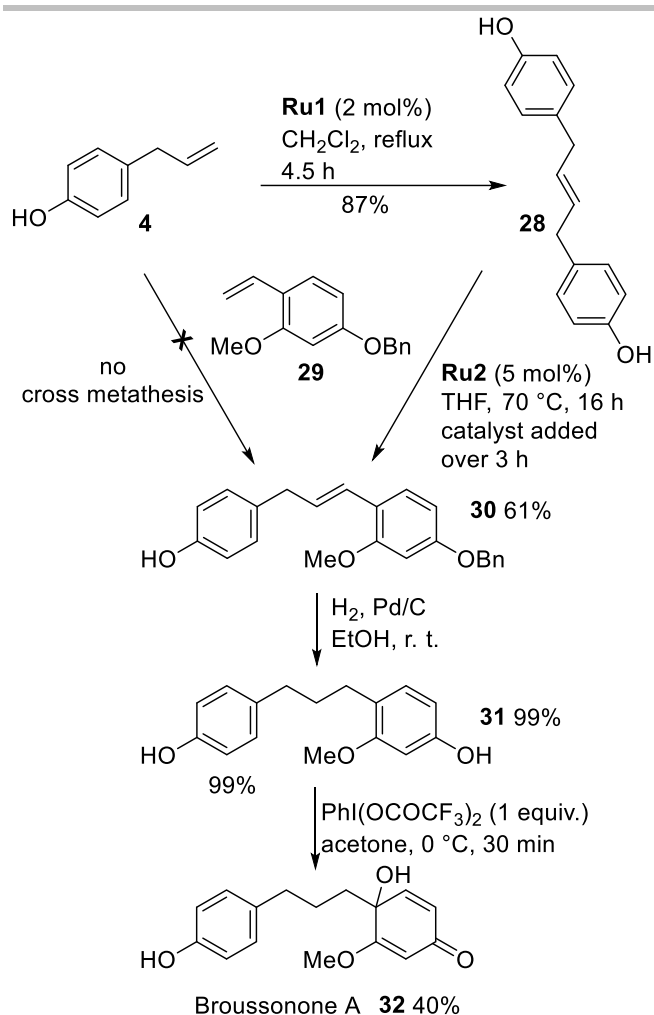
Scheme 6. Cross metathesis of allyl and vinyl guaiacols



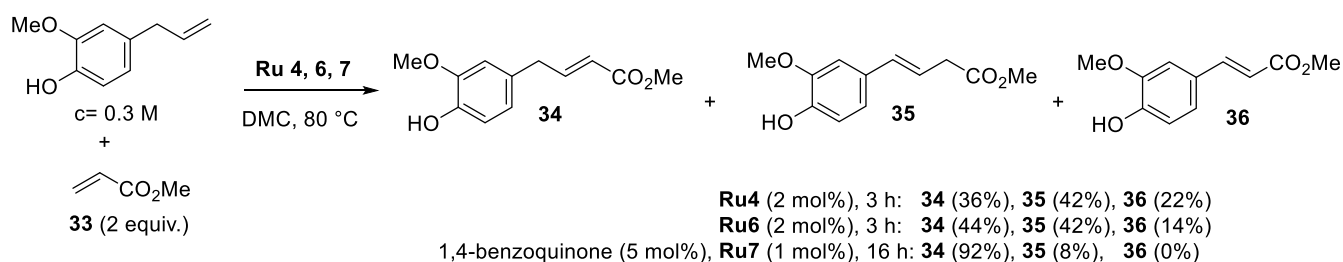
Scheme 7. Preparation of bis-phenol (**27**) via cross metathesis from eugenol

The cross metathesis of chavicol (**4**) with the 2-methoxy-4-benzyloxystyrene (**29**) was unproductive and only self-metathesis of (**4**) was observed^[34] in line with general results obtained with diversely substituted alkoxyallylbenzenes in the presence of **Ru1** or **Ru2** in refluxing CH_2Cl_2 .^[22] However, the expected product (**30**) was obtained when (**28**) featuring an internal olefin was used as cross metathesis partner (Scheme 8). The best conditions consisted in using 5 mol% of **Ru2** slowly added over 3 h in the reaction mixture containing 2 equivalents of (**28**) with respect to (**29**) in THF. The slow addition preserved the integrity of the catalyst and made possible the cross metathesis with (**4**), which was in unfavorable competition with the self-metathesis of (**4**) in the initial trials. The efficiency of such a strategy based on the use of an internal olefin rather than the terminal one has been demonstrated in previous cases of difficult direct cross metathesis with sterically hindered terminal olefins.^[19,35] Further hydrogenation of the internal double bond of (**30**) and hydroxylation provided a straightforward synthesis of the natural Broussonone A (**32**). It can also be noted that a variety of allylbenzenes substituted by alkoxy groups in *ortho*-, *meta*- or *para*-position were reactive in self-metathesis and cross metathesis with styrene partners,^[22,36] whereas *ortho*-substituted styrenes were generally less reactive with terminal olefins.

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Scheme 8. Synthesis of Broussonone A (32) from chavicol (4)

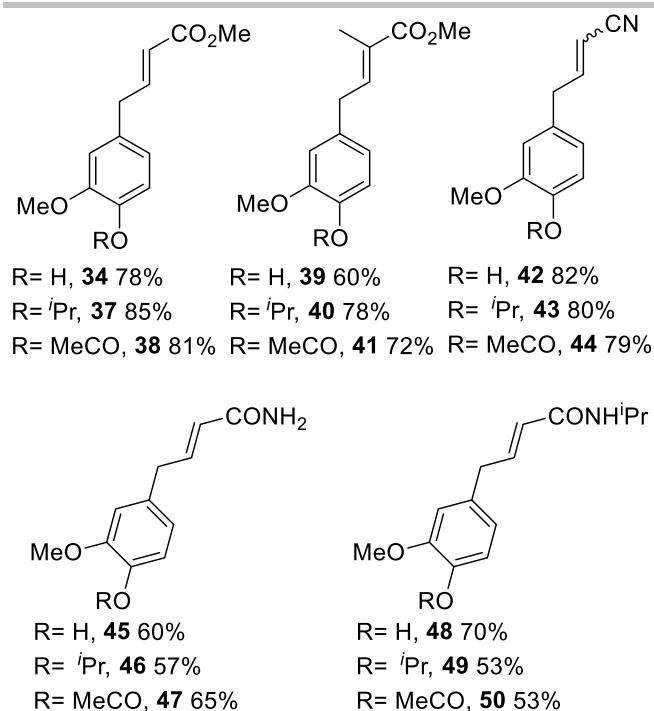


Scheme 9. Cross metathesis of eugenol (1) with methyl acrylate (33)

3.2. Cross metathesis with electron-deficient olefins

The electron-deficient olefins that are considered in this paragraph essentially include acrylic esters and nitriles, which are olefins of type II.^[32] They are less prone to self-metathesis and thus the cross metathesis reaction is favored. The self-metathesis of 4-allylphenol derivative leads to an internal double bond (§ 2) that can further give cross metathesis with the electron-deficient olefin leading to the cross metathesis product in a cascade sequence. The cross metathesis of eugenol with methyl acrylate was efficient at 80 °C with the second generation ruthenium catalysts **Ru4**, **Ru6** and **Ru7** but was highly affected by the formation of byproducts resulting from sequential cross metathesis/double bond migration and double bond migration/cross metathesis as illustrated by the formation of products (**35**) and (**36**), respectively (Scheme 9).^[37] The limitation of the formation of byproducts could be achieved by using 5 mol% of 1,4-benzoquinone in the presence of 1 mol% of **Ru7**, which allowed to reach full conversion of (1) with a selectivity of 92% in favor of the expected product (**34**) isolated in 78% yield as the (*E*)-isomer.^[38]

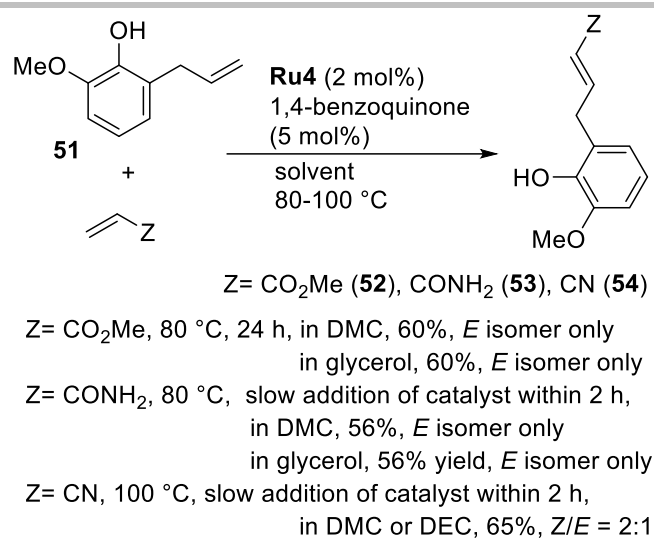
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Scheme 10. Cross metathesis of eugenol derivatives with electron-deficient olefins

This catalytic system was applied to other electron-deficient partners such as methyl methacrylate, acrylonitrile and acrylamides, each partner requiring specific experimental conditions (Scheme 10).^[37,39] From methyl methacrylate, the best yield in (**39**) (60%) was obtained with 2 mol% of **Ru4** at 90 °C in the presence of 5 mol% of 1,4-benzoquinone in neat methyl methacrylate (~30 equiv.). From acrylonitrile, it was necessary to heat up to 100 °C in diethyl carbonate using a protocol of slow addition of the catalyst, which allowed to reach 82% yield of (**42**) in a *Z/E* ratio of 2:1. The 1,2-disubstituted acrylic amides (**45**) and (**48**) were obtained in satisfactory yields at 80 °C in dimethyl carbonate also using the slow addition of catalyst protocol. When the phenol group of eugenol was protected either as an ether with an isopropyl group or as an acetate, the cross metathesis with the same acrylic olefins was achieved under similar catalytic conditions and led to isolated yields of the expected products ((**37**), (**40**), (**43**), (**46**), (**49**) and (**38**), (**41**), (**44**), (**47**), (**50**)) located in the same range as those obtained from eugenol, always with high (*E*)-stereoselectivity except with acrylonitrile that furnished mostly the (*Z*)-isomers.

The substitution pattern close to the propenyl group did not induce a strong effect on the cross metathesis since with the same acrylic olefins, under identical or related experimental conditions, *o*-eugenol (**51**) led to the cross metathesis products (**52**)-(54) with similar yields and stereoselectivities as those observed with eugenol (Scheme 11).^[37,40]

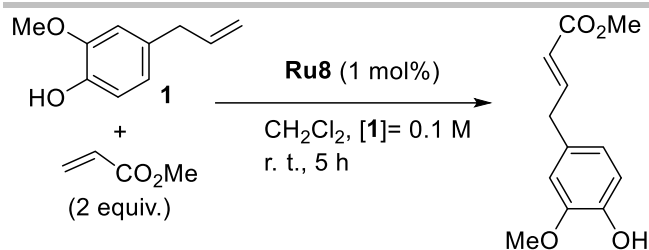


Scheme 11. Cross metathesis with *o*-eugenol and electron-deficient olefins

The cross metathesis of estragole (**2**) with a fourfold excess of methyl acrylate was optimized in 1,2-dichloroethane ([**2**] = 0.125 M) in the presence of 0.5 mol% of **Ru4** at 70 °C for 4 h to give the expected product in 79% yield with a limited amount of double bond migration of about 10%.^[41] It was observed that the self-metathesis of (**2**) was more important in concentrated solution reaching 14-16% ([**2**] = 0.25 M or without solvent) and that the migration towards a styryl derivative was favoured by a higher catalyst loading. The nature of the solvent was crucial for the selectivity of the cross metathesis reaction and considering productivity and selectivity aspects, *p*-cymene was found to be an excellent solvent leading to 95% conversion of (**2**) into the cross metathesis product in 93% yield. It must be pointed out that the advantage of *p*-cymene as an inhibitor of double migration was also observed with other ruthenium catalysts, but did not prevent the self-metathesis of estragole in the presence of some other ruthenium catalysts.

The isomerization and self-metathesis products that could be formed from eugenol became very minor when a second generation Grubbs ruthenium catalysts such as **Ru8** bearing a bulky naphthyl *N*-heterocyclic carbene ligand was used under very mild conditions in dichloromethane at room temperature (Scheme 12).^[42] It was thus possible to isolate (**34**) in 92% yield with extremely high stereoselectivity.

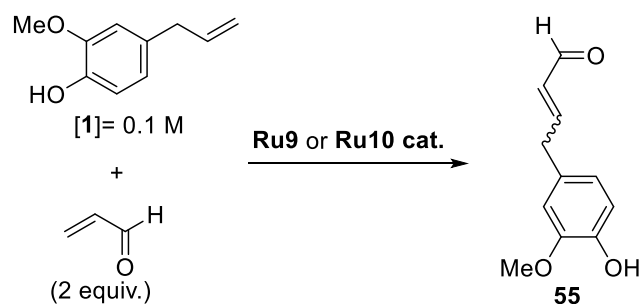
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34 92% ($E/Z > 20:1$)

Scheme 12. Cross metathesis of eugenol with sterically hindered ruthenium catalysts

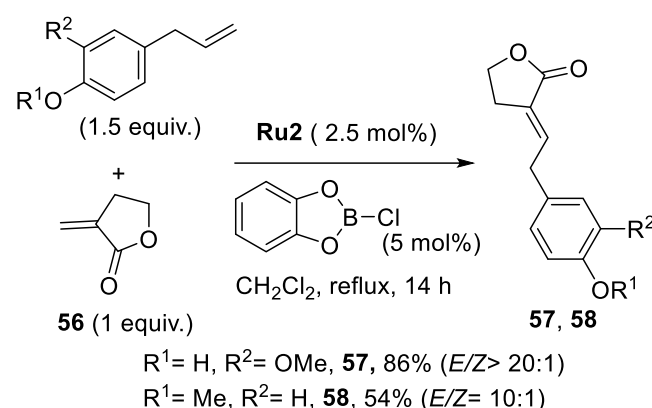
The cross metathesis of eugenol with acrolein was less efficient than starting from an acrylate but could be achieved in satisfactory yields with the help of the indenyl ruthenium catalysts **Ru9**^[43] and **Ru10**^[44] (Scheme 13). With this cross metathesis partner, the stereoselectivity in favour of the (*E*)-isomer was not as good as with acrylates or acrylamides. It can be noted that the cross metathesis of the hydroxy-protected safrole (**3**) with acrolein has been carried out in 46% yield in the presence of 2.5 mol% of **Ru4** in dichloromethane at room temperature for 1 day,^[45a] and that the utilization of crotonaldehyde led to the same final product in 75% yield when the reaction was performed during 16 h in refluxing dichloromethane in the presence of 2 mol% of **Ru4** added in 2 equal portions, the second half being introduced after 5 h of reaction.^[45b] With the ruthenium indenylidene complex **Ru11** equipped with a triphenylphosphine ligand, the cross metathesis of estragole (**2**) with acrylic acid took place in dichloromethane at room temperature for 3 h with a catalyst loading of 1 mol% to give the 3-substituted acrylic acid in 76% yield with a E/Z ratio higher than 20:1 together with 16% of the estragole self-metathesis product.^[46] By contrast, the cross metathesis of isopropylacrylamide with the more sterically hindered *o*-allylphenol provided only 23% yield ($E/Z = 8:2$) of the expected product.



Ru9 (5 mol%), CH_2Cl_2 , 40 °C, 8 h, **55** 37% ($E/Z = 10:1$)
Ru10 (2 mol%), toluene, 80 °C, 5 h, **55** 62% ($E/Z = 6:1$)

Scheme 13. Cross metathesis of eugenol with acrolein

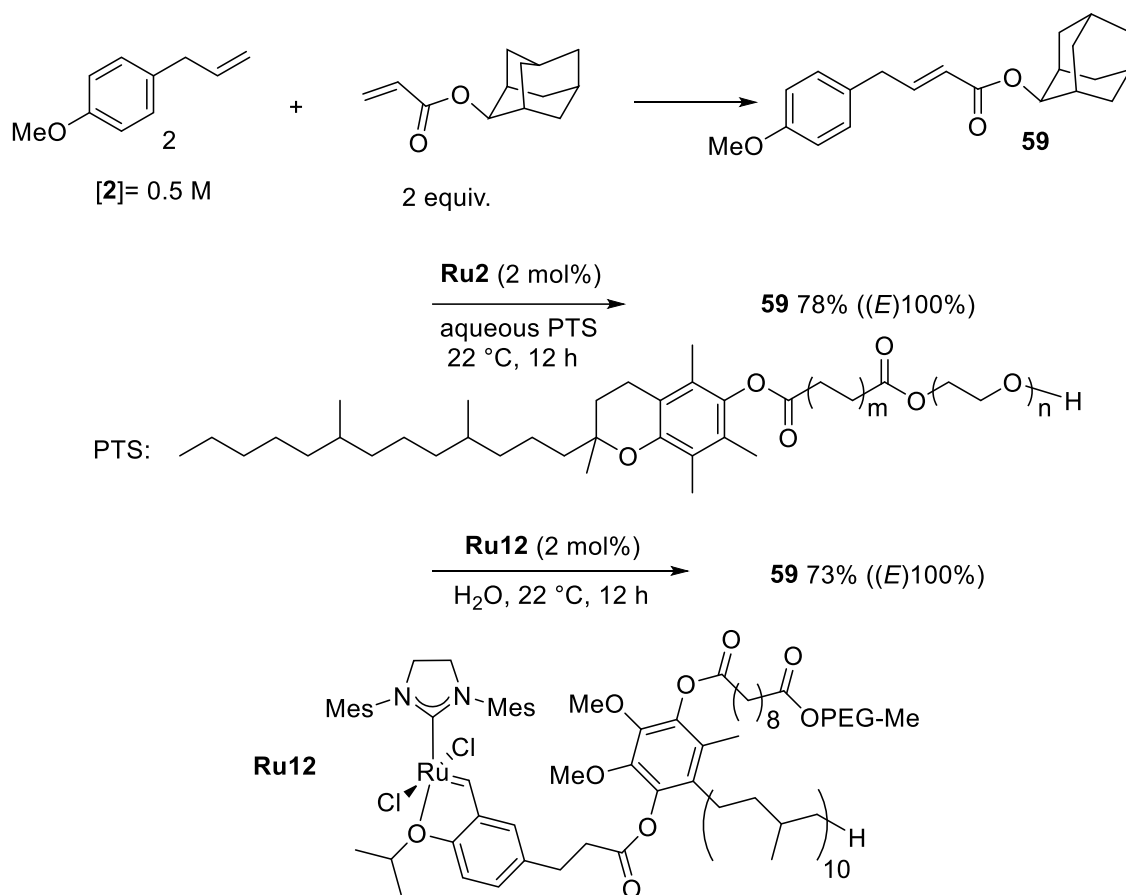
The cross metathesis of the α -methylene- γ -butyrolactone (**56**) with terminal olefins has been performed with **Ru2** as catalyst but this reaction required the presence of an additive in order to reduce the formation of the lactone resulting from double bond migration from *exo* to *endo*-cyclic position. 2,6-Dichlorobenzoquinone was efficient to play this role with some olefins but chlorocatecholborane was found to have a broader scope. Thus in the presence of 2.5 mol% of **Ru2** and 5 mol% of chlorocatecholborane in refluxing dichloromethane, eugenol and estragole were converted into (**57**) and (**58**) in 86 and 54% yield, respectively (Scheme 14).^[47]



Scheme 14. Cross metathesis between α -methylene- γ -butyrolactone (**56**) and eugenol and estragole

Interestingly, it was shown that the cross metathesis of estragole **2** with alkyl acrylates could be efficiently achieved in water at room temperature. This was made possible either by using **Ru2** (2 mol%) in water containing 2.5% of the amphiphilic surfactant^[48] or the PQS-attached Hoveyda catalyst **Ru12** (Scheme 15).^[49] The bulky adamantyl acrylate (**59**) was thus obtained in good yields with complete (*E*)-stereoselectivity with both catalytic systems.

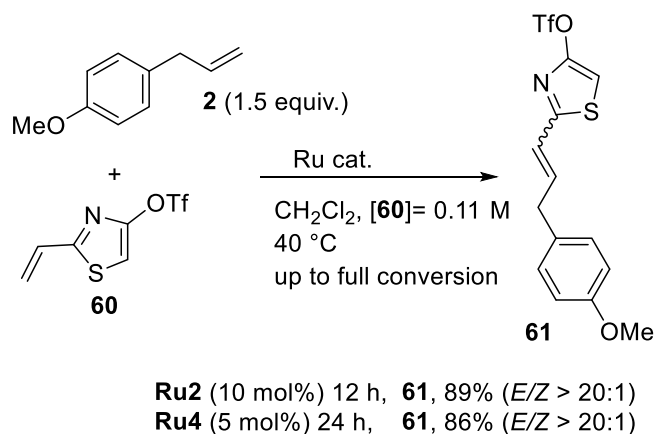
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Scheme 15. Cross metathesis of estragole in water

3.3 Cross metathesis with functional vinylic partners

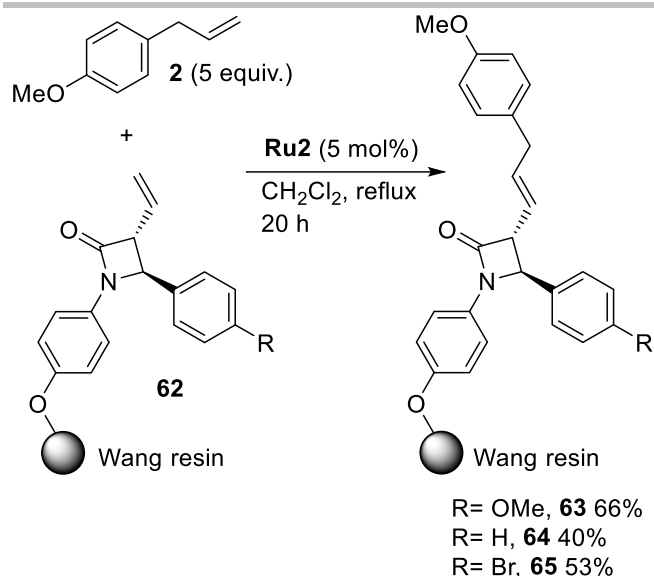
The cross metathesis of estragole with the 4-vinylthiazole product (**60**) has been conducted successfully in refluxing dichloromethane to give (**61**) with excellent stereoselectivity but with relatively high catalyst loading (Scheme 16).^[50]



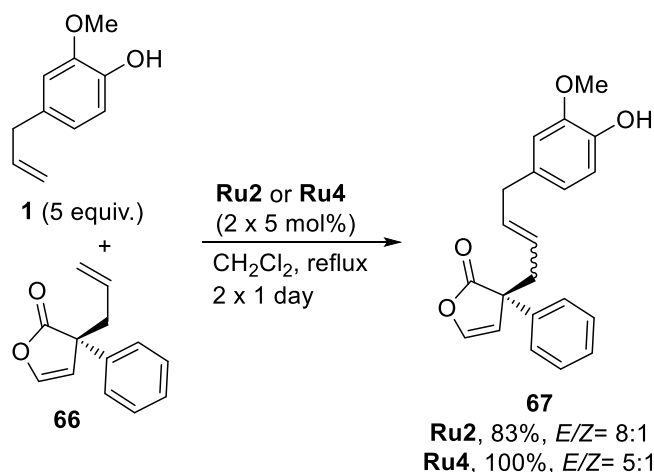
Scheme 16. Cross metathesis of estragole with a 4-vinylthiazole

β -Lactams analogues of cholesterol absorption inhibitors have been prepared by cross metathesis of supported vinyl β -lactams with substituted styrenes and allylbenzene derivatives. With this solid support strategy, the resin-bound olefin was much less prone to self-metathesis and the olefin in solution could be used in excess in order to reach higher conversion. In the presence of 5 mol% of **Ru2**, the products (**63**)–(**65**) were isolated in good yields and perfect (*E*)-stereoselectivity from estragole and the Wang resin-bound substrate (**62**) (Scheme 17).^[51]

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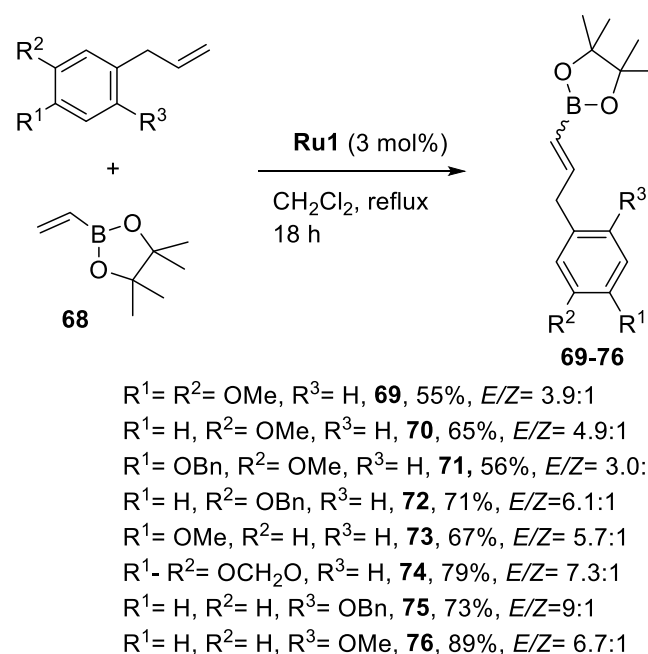
Scheme 17. Cross metathesis of estragole with β -lactam

The cross metathesis of (3*S*)-3-Phenyl-3-(prop-2-en-1-yl)-2,3-dihydrofuran-2-one (**66**) with eugenol was achieved with the second generation catalysts **Ru2** and **Ru4** in excellent yields with retention of configuration of the initial butenolide.^[52] This transformation however required a large excess of eugenol (5 equiv.), high amount of catalyst (10 mol%) and a long reaction time probably due to the high coordination ability of substrate **66** (Scheme 18). Further [3,3]-sigmatropic Cope rearrangement led to the diastereoselective synthesis of γ -butenolides with two controlled adjacent stereogenic centers and a terminal allylic group.

Scheme 18. Cross metathesis of eugenol with the dihydrofuranone (**66**)

Vinyl boronates represent a useful class of substrates that have been extensively used in cross coupling reactions. The synthesis of 3-aryl-1-propenyl boronates (**69**)-(76) has been attempted from allylbenzene derivatives and the pinacol vinyl boronate (**68**) via cross metathesis with ruthenium catalysts. Second generation

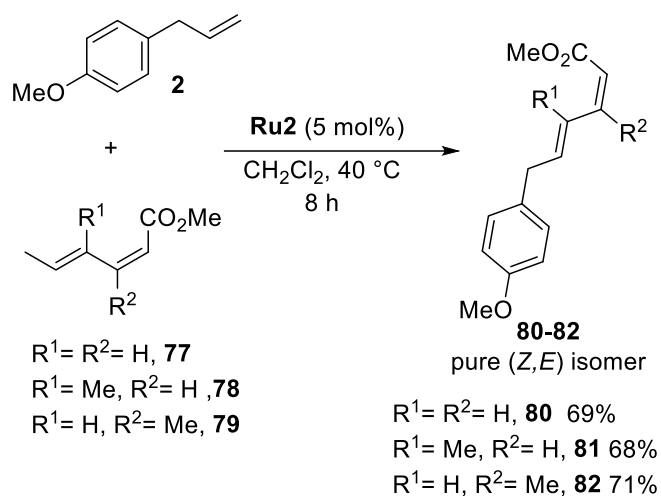
catalysts such as **Ru2** or **Ru4** provided full conversion of the allylbenzene substrates but the main product was the styrene arising from isomerization of the propenyl group without incorporation of the vinyl boronate substrate. On the other hand, the reaction of methyleugenol performed in the presence of 3 mol% of the first generation **Ru1** catalyst in refluxing dichloromethane for 18 h provided the expected product (**69**) with high selectivity and an *E/Z* ratio of 4:1 (Scheme 19).^[53] It is noteworthy that the isomerization with second generation catalysts could be reduced by addition of 1,4-benzoquinone but this procedure did not compete with the protocol based on the utilization of **Ru1** without additive. This reaction was applied to methyl eugenol (**69**) benzyl eugenol (**71**), estragole (**73**) and safrole (**74**). It can be noted that the (*E*)-stereoselectivity was improved when the allylbenzene substrate was substituted in *ortho*-position.

Scheme 19. Cross metathesis with vinyl boronate (**68**)

Cross metathesis involving a conjugated diene as partner has not been studied extensively as compared to monoolefins.^[54] However, the cross metathesis of terminal olefins with methyl (2*Z*,4*E*)-hexadienoate (**77**) has been shown to selectively involve its 4,5 double bond leading to the formal introduction of a new substituent at C5. When equimolar amounts of (**2**) and (**77**), (**78**) or (**79**) were treated in dichloromethane at 40 °C for 8 h in the presence of 5 mol% of **Ru2**, the new dienes (**80**)-(82) were produced in about 70% yield as pure stereoisomers together with

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small amounts of the self-metathesis product of (**2**) (Scheme 20).^[55]



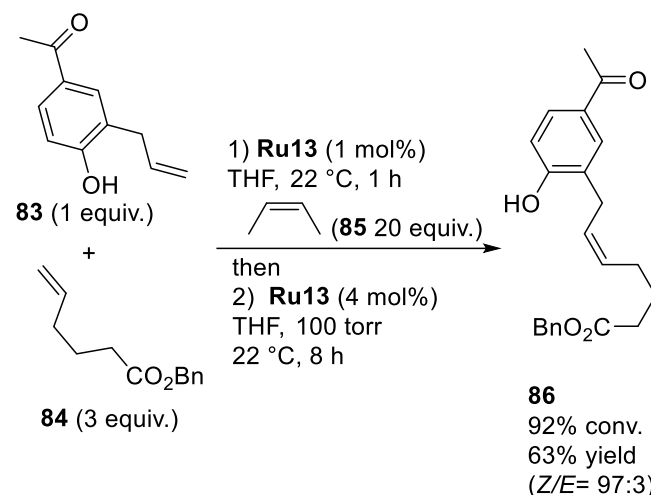
Scheme 20. Cross metathesis with dienes

3.4 (Z)-Stereoselective cross metathesis

The more thermodynamically stable (*E*)-carbon-carbon double bond isomers were usually obtained upon cross metathesis of olefins with the commercially available catalysts such as **Ru1**, **Ru2**, **Ru4** (see § 3). Then, so called (*Z*)-selective molybdenum, tungsten and ruthenium catalysts were designed on purpose to favor the formation of (*Z*)-isomers *via* a kinetically selective process. This was achieved by controlling the orientation of the substituents on the intermediate metallacyclobutane of the Chauvin mechanism,^[56] which is critical for determining the stereochemistry of the newly formed double bonds.^[57] Several preparations and modifications of natural products presenting a defined (*Z*)-carbon-carbon double bond have then been developed based on the discovery of catalysts enabling (*Z*)-selective cross metathesis with a variety of functional substrates.^[58] More recently, new stereoretentive catalysts have been developed that are able to kinetically produce (*Z*)- and (*E*)-double bonds with excellent selectivities *via* cross metathesis of pure (*Z*)- and (*E*)-olefins.^[59] The first and most active catalysts able to achieve this performance were ruthenium dithiolate catalysts such as **Ru13**, **Ru14** and **Ru15** presented in Figure 2.^[60] These catalysts are (*Z*)-selective, stereoretentive and tolerant to a variety of functional groups but are not suited for metathesis transformations of terminal alkenes because the *in situ* generated ruthenium methylidene species are too unstable.^[61] A successful strategy was designed based on introducing in the reaction

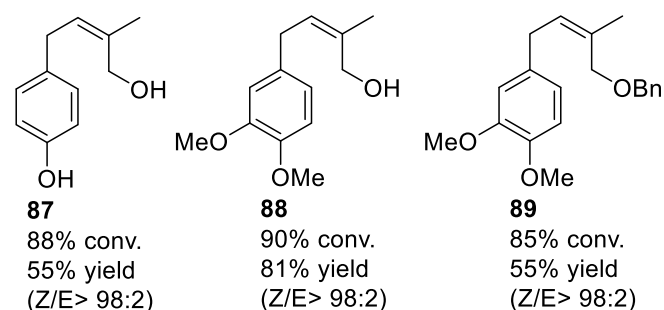
mixture a sacrificial olefin, namely (*Z*)-but-2-ene, which rapidly generated internal (*Z*)-olefins *via* cross metathesis with the terminal double bonds of the substrates before starting stereoretentive cross metathesis with another internal olefin. The protocol was made more efficient by removal of the excess of (*Z*)-but-2-ene and formed propene under vacuum (133 mbar).

The *o*-allylphenol (**83**) was thus reacted with benzyl hex-5-enoate (**84**) in two steps in the presence of **1** and then 4 mol% of **Ru13** in THF at 22 °C to produce (**86**) in 63% isolated yield with excellent (*Z*)-stereoselectivity (Scheme 21).^[61]



Scheme 21. Stereoretentive cross-metathesis of *o*-allylphenol (**83**) with the olefin (**84**)

With the same strategy, chavicol (**4**) and methyl eugenol (**5**) were transformed into the corresponding allyl alcohol derivatives (**87**)-(89) in the presence of **1** and then 5 mol% of **Ru14** at 22 °C using (*Z*)-butene (**85**) as methylene capping agent and (*Z*)-2-methyl but-2-enol or its benzyl ether as coupling partner (Scheme 22).^[62]



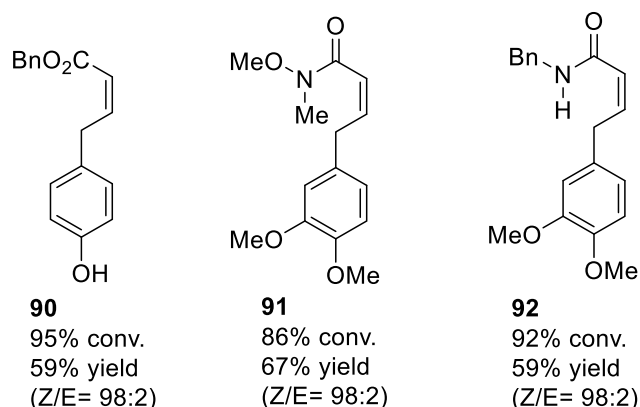
Scheme 22. Stereoretentive cross metathesis with (*Z*)-trisubstituted allylic alcohol substrates

In all the examples of cross metathesis with electron-deficient olefins reported in § 3.2, the (*E*)-selectivity was predominant, except in the case of acrylonitrile.^[63] It has now been shown that the use of ruthenium catecholthiolate make possible the selective

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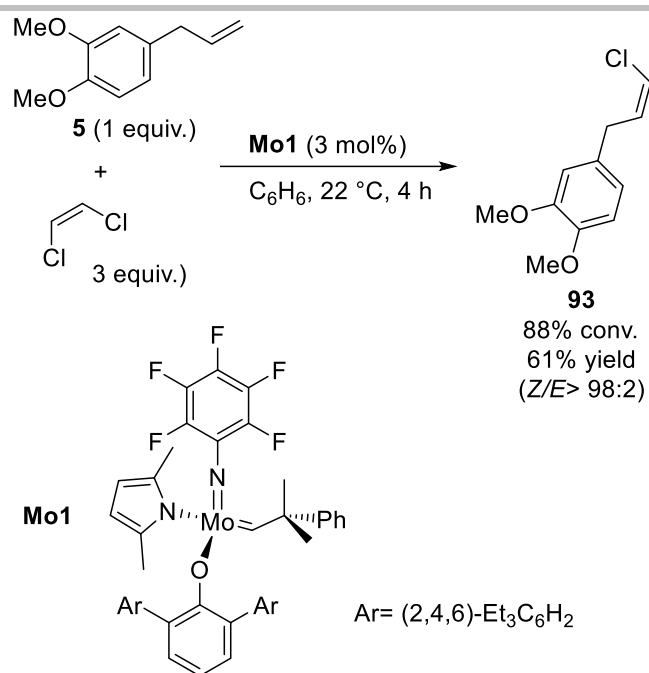
formation of (*Z*)-isomers with high yields and stereoselectivity based on the same principle of capping the terminal double bond in order to make possible the stereoretentive cross metathesis with a (*Z*)-olefin partner.

This is illustrated by the synthesis of (**90**)-(b92) upon cross metathesis of chavicol (**4**) with benzyl (*Z*)-but-2-enoate, and methyl eugenol (**5**) with (*Z*)-*N*-methoxy-*N*-methylbut-2-enamide and *N*-benzyl-*i*-but-2-enamide, respectively (Scheme 23).^[64] In all cases, the (*Z*)-isomers were obtained with almost perfect stereoselectivity with a total amount of 9 mol% of catalyst **Ru15**. It can be noted that *o*-allylphenol reacted similarly.



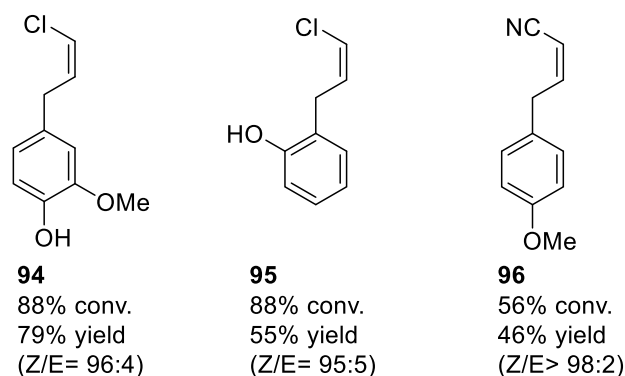
Scheme 23. Stereoretentive cross metathesis with (*Z*)-acrylic substrates

Recently, a breakthrough was made by the discovery of molybdenum catalysts able to promote cross metathesis involving 1,2-dihaloalkenes. Thus, the cross metathesis of methyl eugenol (**5**) was achieved with (*Z*)-1,2-dichloroethene in the presence of 3 mol% of catalyst **Mo1** at 22 °C within 4 h with almost complete (*Z*)-selectivity for (**93**) (Scheme 24).^[65] This catalytic system presents a wide scope of applications and applies for the synthesis of (*Z*)-alkenyl chlorides, bromides and fluorides.



Scheme 24. Synthesis of (*Z*)-alkenyl halides by (*Z*)-selective cross metathesis

Since hydroxy or carboxylic acid groups are not well tolerated for this (*Z*)-selective cross metathesis, the use of pinacolborane (HB(pin)) was envisioned as a traceless protection of alcohols and phenols. Indeed, the protection of the hydroxy group took place within a few minutes at room temperature and the cross metathesis with a 1,2-dihaloethene could be readily performed in the presence of catalytic amounts of **Mo1**. Further chromatography over silica gel directly afforded the (*Z*)-alkenyl halide with the deprotected hydroxyl group. In the presence of 5 mol% of **Mo1** at 22 °C in C₆H₆ for 4 h, eugenol **1** and *o*-allylphenol were successfully converted into the corresponding (*Z*)-3-chloroallyl derivatives (**94**) and (**95**) in 88% conversion and a *Z*/*E* ratio of 95:5 (Scheme 25).^[66]



Scheme 25. (*Z*)-Alkenes via cross metathesis with **Mo1** as catalyst

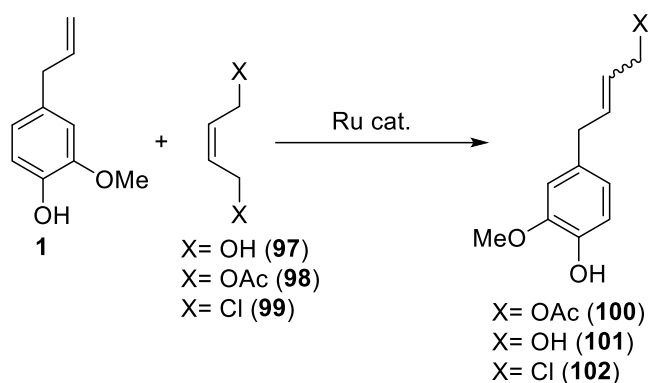
Finally, **Mo1** exhibits much higher efficiency in the (*Z*)-selective cross metathesis of acrylonitrile or maleonitrile with terminal

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olefins than all other second generation ruthenium catalysts. This is exemplified by cross metathesis of estragole **2** with acrylonitrile in the presence of 5 mol% of **Mo1** in C₆H₆ at 22 °C for 4 h, which provided (**96**) in 46% yield but with extremely high (*Z*)-selectivity (Scheme 25).^[67]

3.5. Cross metathesis with internal symmetrical olefins

Cross metathesis with symmetrical internal olefins presents the interest of limiting the formation of ruthenium methylidene carbene intermediates, which are most often source of decomposition of the catalytic species or poorly reactive resting states. The first report on cross metathesis of estragole (**2**) with *cis*-but-2-enediol diacetate (**98**) described the use of a recyclable polymer-supported first generation Hoveyda catalyst^[68] in 5 mol% loading that operated in refluxing dichloromethane for 9 h and led to the formation of a modest 33% of the acetate (**100**) and 18% of the estragole self-metathesis product.^[69] Later on it was shown that the second generation catalysts were more efficient and that complete conversion of 4-hydroxyphenylpropanoids could be obtained (Scheme 26).



Scheme 26. Cross metathesis with *cis*-but-2-ene derivatives

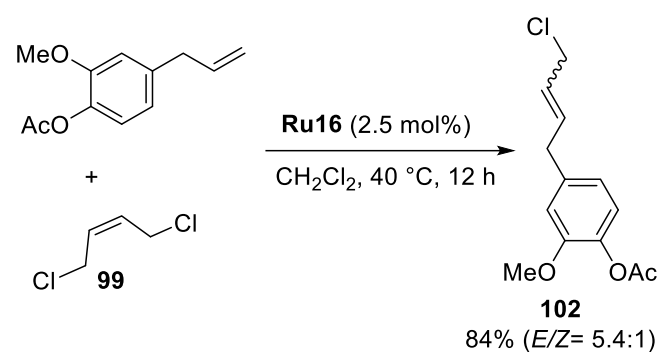
In particular Grubbs catalyst **Ru2** embedded in paraffin wax has been used to produce (**101**) in good yields from eugenol and the diol (**97**) (Table 1, entries 1, 2).^[70,71] The catalysts **Ru8** and **Ru11** were also suitable for the cross metathesis of (**1**) with *cis*-but-2-enediol diacetate (**98**) and the reaction carried out in dichloromethane at room temperature with 1 mol% of catalyst for 1-5 h led to high yield of (**100**) with a *E/Z* ratio of 10:1 (Table 1, entries 3, 4) accompanied by the formation of variable amounts of the self-metathesis product (**6**).^[42,46]

Table 1. Room temperature cross metathesis of eugenol (**1**) with *cis*-but-2-ene derivatives

Olefin	Cat. (mol%)	t (h)	Yield (%)	<i>E/Z</i>	ref.
(97)	Ru2* (3.5)	12	98	ND	[71]
(97)	Ru2* (2)	23	86	ND	[70]
(100)	Ru11 (1)	1	71	9:1	[46]
(100)	Ru8 (1)	5	86	10:1	[42]

Ru2*: **Ru2** in paraffin wax, ND: not determined

Another representative of the 4-hydroxyphenylpropanoid family, eugenol acetate was reacted with *cis*-1,4-dichlorobut-2-ene (**99**) with the catalyst **Ru16** (2.5 mol%) in dichloromethane at 40 °C for 12 h to give **102** in 84% yield with a *E/Z* ratio of 5.4:1 without detection of self-metathesis product (Scheme 27).^[72]



Scheme 27. Cross metathesis with *cis*-1,4-dichlorobut-2-ene (**99**)

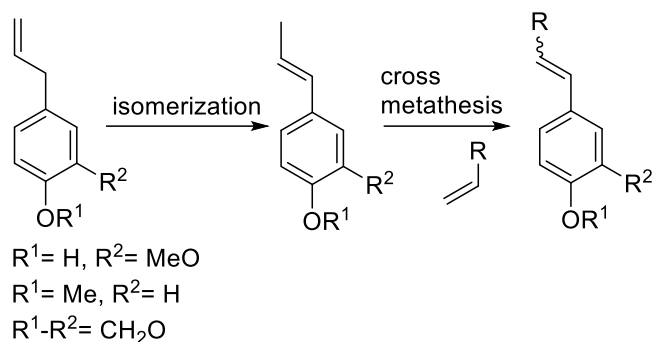
4. Sequential transformations involving a metathesis step

4.1 Isomerization and cross metathesis

We have seen in § 2 and 3, that the migration of the allylic double bond of phenylpropanoids from 2-propenyl to 1-propenyl explained the lack of selectivity in some self- and cross-metathesis reactions. As soon as the ruthenium-based olefin metathesis catalysts were introduced in synthesis, a relationship between ruthenium-carbene and ruthenium-hydride complexes was rapidly disclosed. It was shown that metal-hydride species could indeed result from metal-carbene decomposition and induce double bond isomerization, in competition or in combination with olefin metathesis reactions.^[12a,73] Even though the involvement of these ruthenium-hydride species is not certain,^[74] olefin migration was avoided or limited by the presence of additives such as 1,4-benzoquinone, the use of first generation ruthenium catalysts and more recently by the design of catalysts with no isomerizing properties.^[75] It is also noteworthy that as observed in many metathesis transformations, the catalysts and

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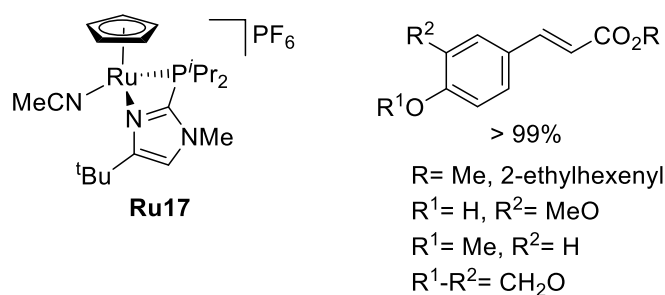
substrates impurities can be source of isomerization reactions.^[73b] On the other hand, advantage could be taken from this facile double bond migration to further generate functional styrene derivatives upon subsequent cross metathesis (Scheme 28).



Scheme 28. General scheme for isomerization/cross metathesis sequence

The isomerising catalysts **Ru17** and $[PdBr(P^tBu_3)_2]$ have been used to achieve the first step of the transformation.

Thus, the one-pot isomerization/cross metathesis in toluene was successfully achieved *via* first complete isomerization of the renewable phenylpropanoids (**1**)-(3) in the presence of 0.1 mol% of **Ru17** during 0.5 h followed by cross metathesis with methyl and 2-ethylhexenyl acrylate in the presence of 0.5 mol% of **Ru4** at 70 °C for 6 h. Under these conditions quantitative yields of the corresponding cinnamates were produced (Scheme 29).^[76]

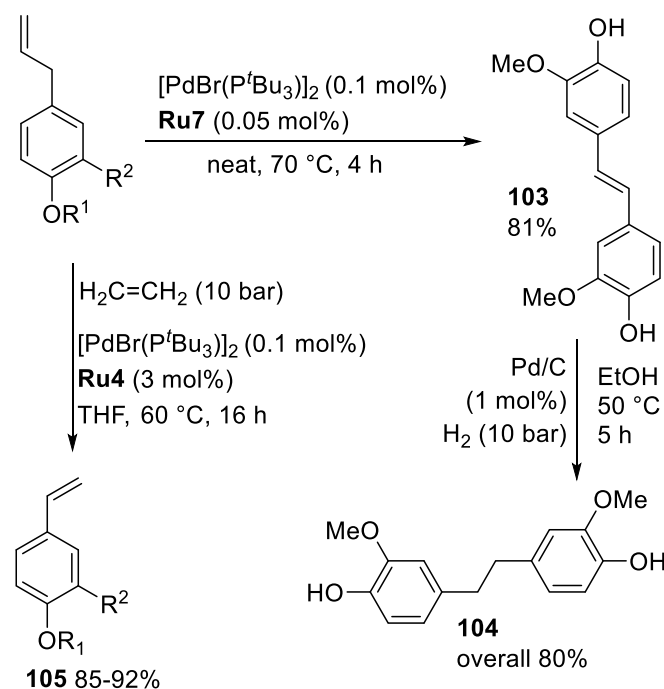


Scheme 29. Ruthenium-catalyzed isomerization/cross metathesis

With the palladium catalyst, it was possible to introduce both catalysts at the outset of the reaction and perform orthogonal catalysis.^[77] The (*E*)-styrene (**103**) was thus produced from eugenol in very high isolated yield at 30 mmol scale showing that the tandem isomerization/self-metathesis was also realistic. In addition a subsequent hydrogenation under 10 bar of hydrogen in the presence of palladium on charcoal led to an overall yield of the (**104**) in 80% yield (Scheme 30).^[78] When ethylene was introduced as a cross metathesis partner, the ethenolysis^[79] of the 2-propenyl intermediate took place leading to the formation of the desired styrenes (**105**) from eugenol, estragole, safrole, methyl eugenol in more than 85% yield.^[80]

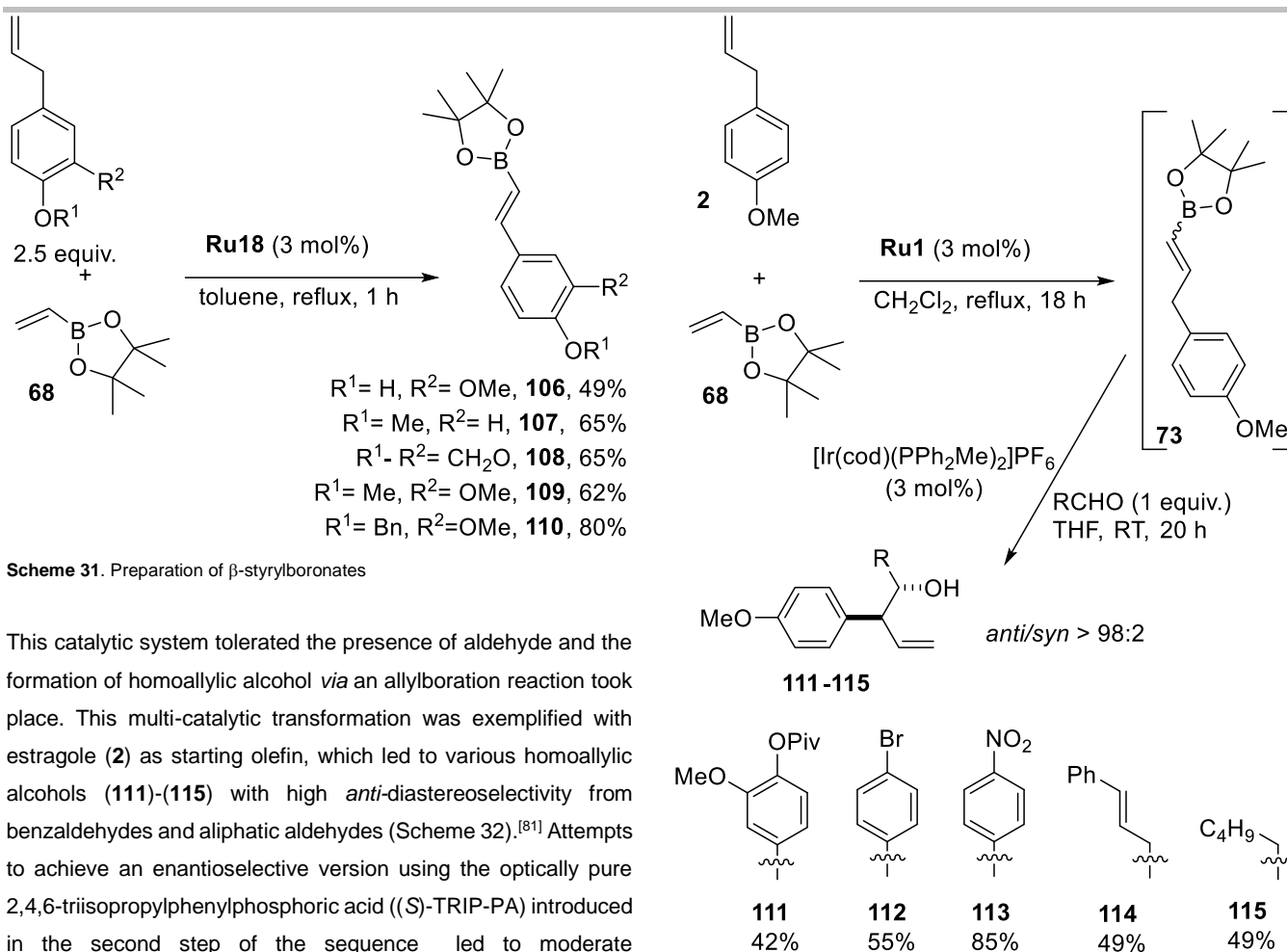
Whereas the cross metathesis of the vinylboronate (**68**) with allyl-substituted aromatics in the presence of the first generation **Ru1** catalyst selectively led to alkenylboronates (Scheme 19)^[53] the introduction of the *bis*-(2,6-diisopropylphenyl)imidazolinyldene ligand (SIPr) in the second generation Hoveyda type catalyst **Ru18** changed the course of the reaction leading to the selective formation of β -styrylboronates resulting from an isomerization/cross metathesis sequence (Scheme 31).^[81]

In the presence of 3 mol% of **Ru18** after 1 h of reaction in refluxing toluene, all the new vinylboronates (**106**)-(110) arising from eugenol, estragole, safrole, methyl eugenol and benzyl eugenol were obtained as a single (*E*)-stereoisomer in 49, 65, 65, 62, and 80% yield, respectively. In this sequence, both isomerization and cross metathesis were promoted by the same catalyst precursor giving rise to an auto-tandem catalysis process.^[76] Advantage has also been taken from the selective cross metathesis reaction of allylbenzene derivatives with vinyl pinacol borate in the presence of **Ru1** to further perform double bond migration and allylboration from aldehydes. Following the cross metathesis of estragole with the vinylborate (**68**) leading to (**73**) in good yield (Scheme 19), the isomerization of the created double bond to form a styrene intermediate was efficiently and stereoselectively achieved at room temperature in the presence of 3 mol% of $[Ir(cod)(PPh_2Me)_2]PF_6$ initially activated by dihydrogen to give the (*E*)-isomer.



Scheme 30. Palladium-catalyzed isomerization followed by cross-metathesis

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Scheme 31. Preparation of β -styrylboronates

This catalytic system tolerated the presence of aldehyde and the formation of homoallylic alcohol *via* an allylboration reaction took place. This multi-catalytic transformation was exemplified with estragole (**2**) as starting olefin, which led to various homoallylic alcohols (**111**)-(115) with high *anti*-diastereoselectivity from benzaldehydes and aliphatic aldehydes (Scheme 32).^[81] Attempts to achieve an enantioselective version using the optically pure 2,4,6-triisopropylphenylphosphoric acid ((*S*)-TRIP-PA) introduced in the second step of the sequence led to moderate enantioselectivities located in the range 56-82%.^[82]

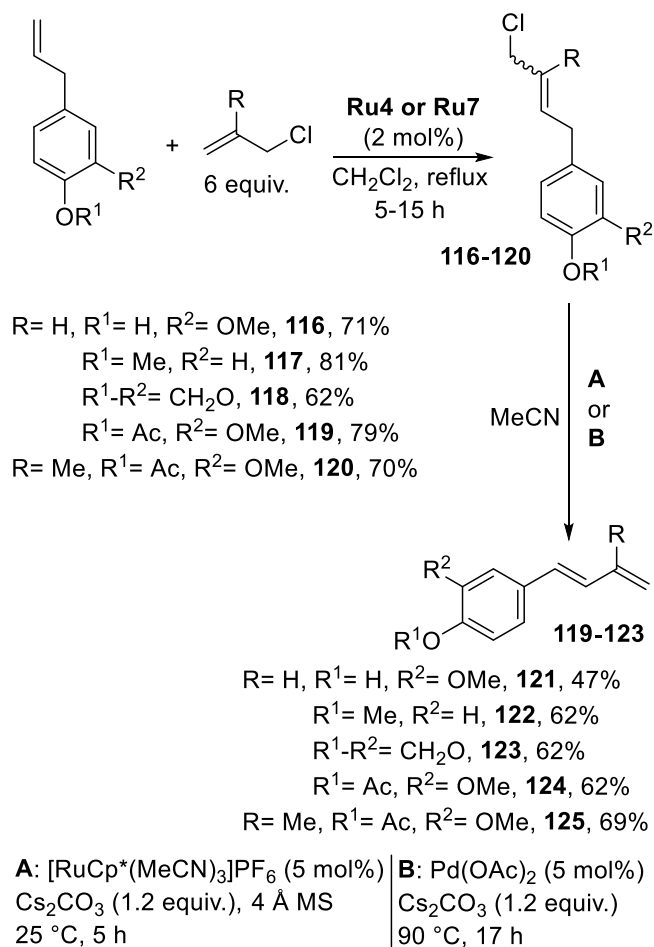
Scheme 32. Preparation of homoallylic alcohols

4.2 Cross metathesis and elimination

Conjugated dienes have been prepared in a sequential transformation of terminal olefins involving cross metathesis with an allylic chloride followed by an elimination reaction catalysed by ruthenium or palladium. The metathesis reaction was carried out in dichloromethane with 2 mol% of **Ru4** or **Ru7** and led to the allylic chlorides (**116**)-(120) in good yields with (*E*)-selectivity (Scheme 33).^[83,84] Two protocols were suitable for the elimination step. One involved the dehydrochlorination in the presence of $[\text{RuCp}^*(\text{MeCN})_3]\text{PF}_6$ as catalyst and was performed in acetonitrile at room temperature, the other was based on the use of $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ to promote the same reaction at 90 °C. In both cases, the dienes resulting from renewable 4-hydroxyphenylpropanoids were obtained in satisfactory yields as the (*E*)-isomers only. The dienes arising from allyl chloride and estragole (**2**), safrole (**3**), eugenol (**1**) and eugenol acetate were thus obtained in two steps in 50% (**122**), 38% (**123**), 33% (**121**) and 49% (**124**), respectively (Scheme 33). The bio-sourced

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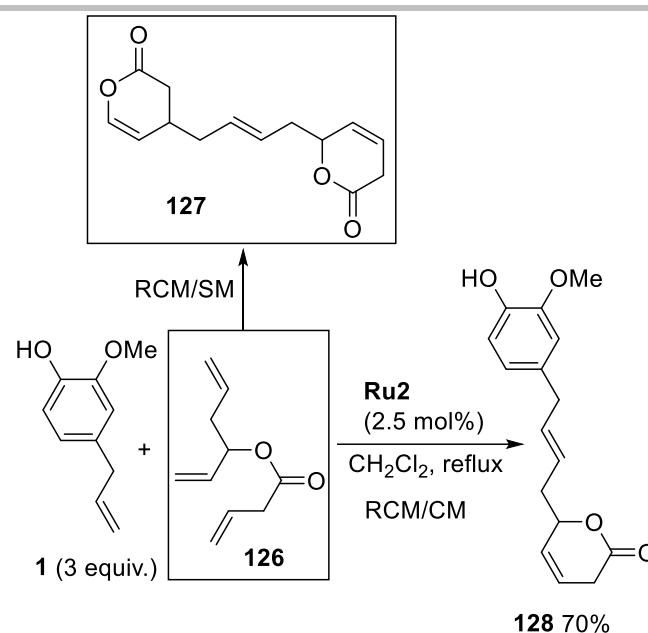
dienes (**121**)-(123) have then been used to study their rhodium-catalyzed hydroformylation.^[84]



Scheme 33. Preparation of dienes

4.3 Ring closing and cross metathesis

When the triene (**126**) was treated with 2.5 mol% of **Ru2** in refluxing dichloromethane, the symmetrical bis-(3,6-dihydropyranone) (**127**) resulting from regioselective ring closing metathesis/self-metathesis (RCM/SM) was formed in 81% yield (Scheme 34).^[85] In the presence of an additional terminal olefin including eugenol (**1**), it was shown that the ring closing metathesis was followed by cross metathesis (RCM/CM) with the external alkene to give the unsymmetrical internal olefin (**128**). Under the above conditions, with a threefold excess of (**1**), the reaction was stopped after complete conversion of the ester **126** and the final product (**128**) was isolated in 70% yield as the sole (*E*)-isomer. It must be noted that this catalytic sequence was achieved with only one ruthenium catalyst and that it required very high dilution conditions ([**126**] = 0.01 M).^[85]



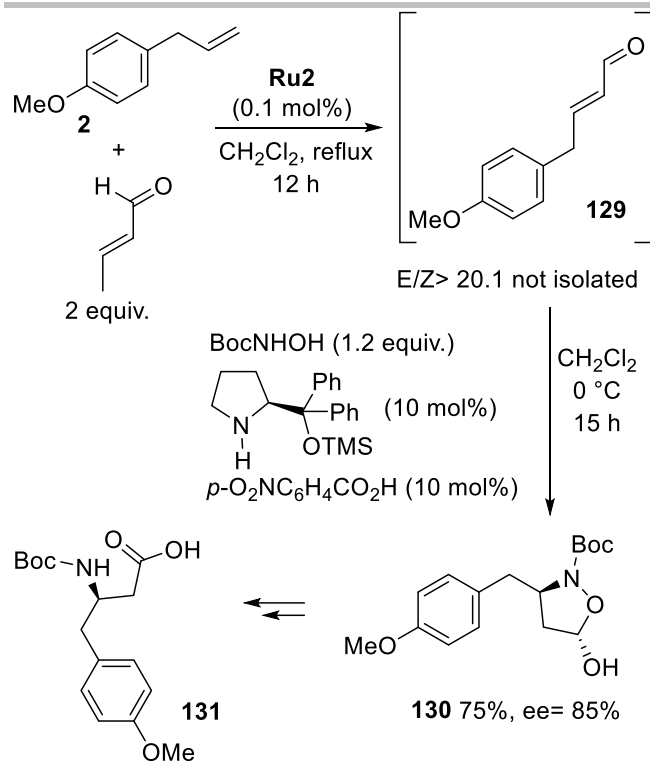
Scheme 34. Preparation of functionalized pyrones

4.4 Cross metathesis, conjugate addition

The reaction of (*E*)-4-phenylbut-2-enals with *N*-BocNHOH in the presence of a Bronsted acid and a chiral base was shown to give the conjugate addition product of type (**130**) in high yield and very good enantioselectivity (Scheme 35). Based on the possibility of producing the (*E*)-4-arylbut-2-enals by cross metathesis of allylarenes with a conjugated enal, estragole together with crotonaldehyde were used for this purpose. Thus, the one-pot cross metathesis in the presence of 0.1 mol% of **Ru2** in refluxing dichloromethane followed by organocatalytic conjugate addition with *N*-BocNHOH at 0 °C in the presence of *p*-nitrobenzoic acid and (*S*)-diphenylprolinol-TMS produced the (*3R*)-*tert*-butyl 3-arylmethyl-5-hydroxyisoxazolidine carboxylate (**130**) in 75% yield with 85% enantioselectivity.^[86] Further oxidation of the hydroxy group of **130** by NaClO₂/H₂O₂ followed by hydrogenolysis of the N-O bond by dihydrogen catalysed by palladium gave the optically active β-amino acid derivative (**131**).

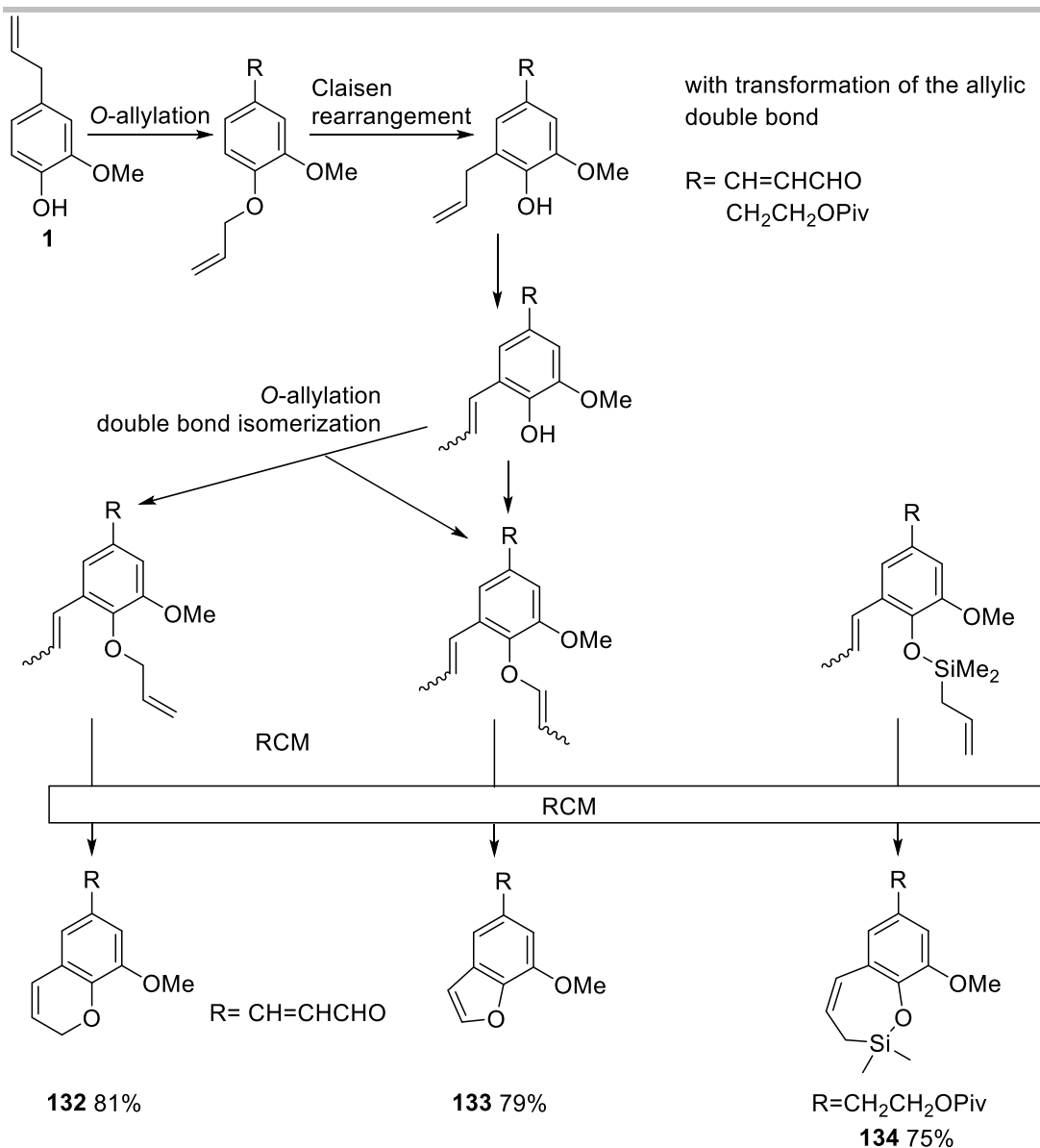
It is also worth mentioning a few examples involving eugenol as starting material, which after a few transformations such as *O*-allylation, Claisen rearrangement or double bond isomerization led to dienes substrates, which were cyclized by ring closing metathesis. As shown in Scheme 36, the initial allylic double bond of eugenol is not involved in the metathesis transformations. The ring closing metathesis reactions have been carried out with **Ru2** as catalysts and have led to the bicyclic products (**132**),^[87] (**133**)^[88] and (**134**)^[89] in 81, 79 and 75% yield, respectively (Scheme 36).

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Scheme 35. Cross metathesis/conjugate addition sequence

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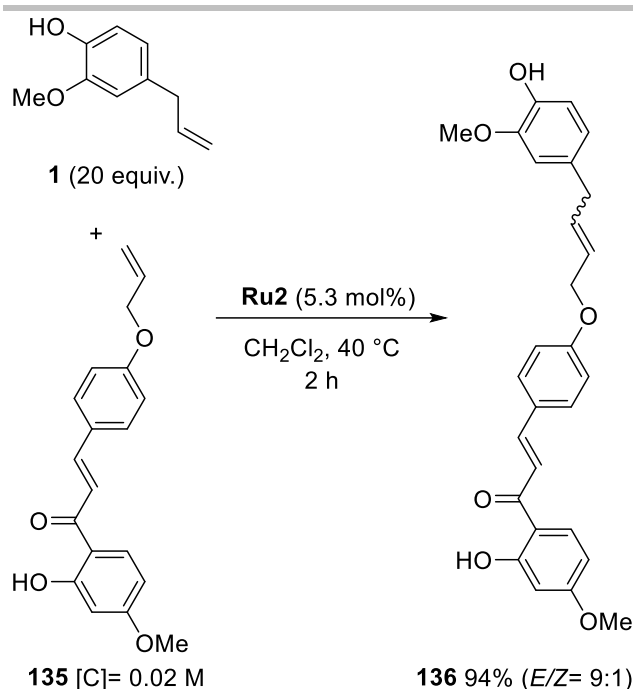
Scheme 36. Ring closing metathesis of modified eugenol

5. Applications in synthesis

In this final paragraph are reported some preparations of natural products and biologically active molecules involving at least a cross metathesis reaction with a 4-hydroxyphenylpropanoid substrate.

In a program aiming at producing a library of compounds for antibacterial screening, the chalcone (**135**) was reacted with a large excess of eugenol (**1**) in a diluted solution of dichloromethane in the presence of 5.3 mol% of **Ru2** for 2 h. The new hybrid molecule (**136**) was isolated in 94% yield with a *E/Z* ratio of 9:1 (Scheme 37).^[90]

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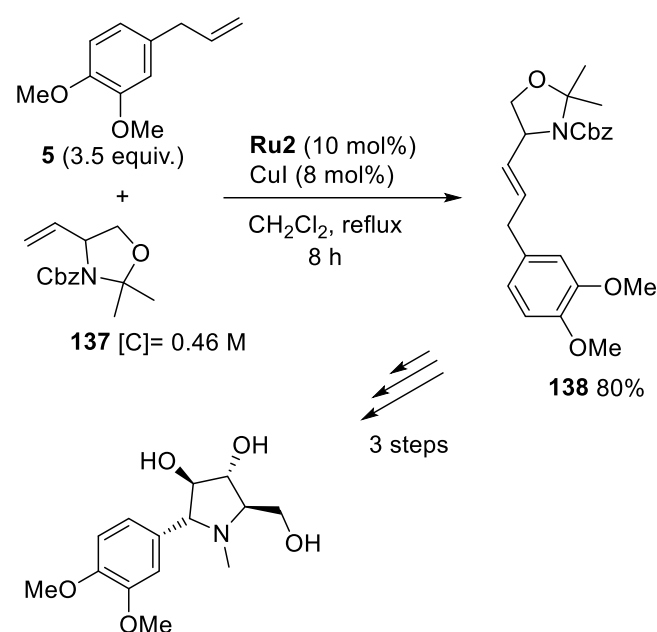


Scheme 37. Preparation of a hybrid eugenol-chalcone molecule

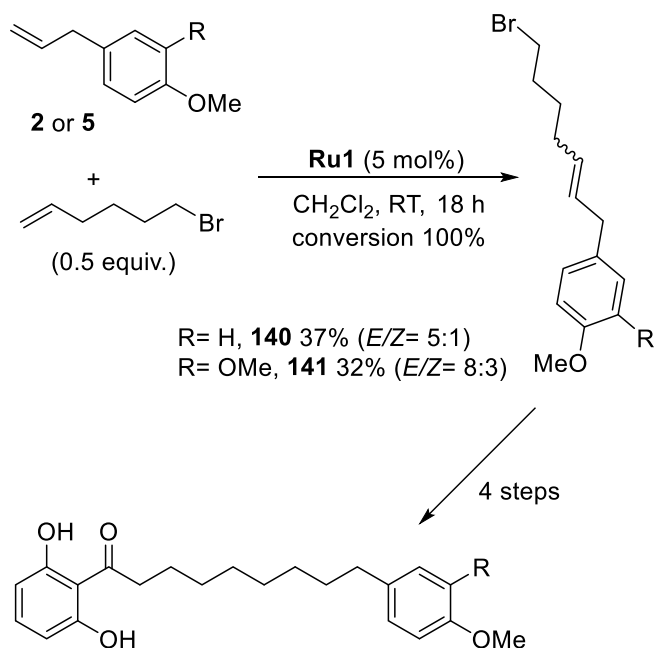
(-)-Codonopsinol (**139**), isolated from *C. clementidea* presents inhibitory activity against α -glycosidase of yeast and *Bacillus stearothermophilus* lymph.^[91] A synthesis was envisioned based on the cross metathesis of methyl eugenol **5** with the olefin (**137**) as the first step (Scheme 38). Indeed, the cross metathesis carried out in refluxing dichloromethane with 10 mol% of **Ru2** and 8 mol% of **CuI** acting both as a co-catalyst bringing a stabilizing effect due to the iodide ion and as phosphine scavenger,^[92] exclusively led to the (*E*)-olefin (**138**) in 80% isolated yield. Then a few more steps including osmium-catalyzed enantioselective dihydroxylation followed by ring opening, acetylation, DDQ-catalyzed cyclization and deprotection gave (-)-codonopsinol (**139**) in an overall yield of 52%.

Malabaricones B and C are natural diarylnonanoid products isolated from the *Myristicaceae* family of plants displaying numerous biological properties. A straightforward synthesis of these molecules was proposed, which involved as the first step the cross metathesis of estragole (**2**) or methyl eugenol (**5**) with 6-bromohex-1-ene (Scheme 39).^[93] The first generation **Ru1** catalyst made the cross metathesis possible producing (**140**) and (**141**) with moderate yields due to important self-metathesis of the substrates and also low stereoselectivities, which was not a problem since the following step was the hydrogenation of the double bond under 1 bar of hydrogen in the presence of 3 mol% of **Pd/C**. After coupling with a dimethoxyphenyl β -keto ester introducing the other terminal aryl group and further steps, the malabaricones B (**143**) and C (**142**) were isolated in 11.7 and

8.5% yield, respectively, in 6 steps from the phenylpropanoid, 6-bromohex-1-ene and 2',6'-dimethoxyacetophenone.^[93]



(-)-codonopsinol (**139**) 52% yield from **5** and **137**

Scheme 38. Synthesis of (-)-Codonopsinol (**139**) from methyl eugenol

R= H, Malabaricone C, **142** overall yield 8.5%
R= OMe, Malabaricone B, **143** overall yield 11.7%

Scheme 39. Synthesis of Malabaricones B and C

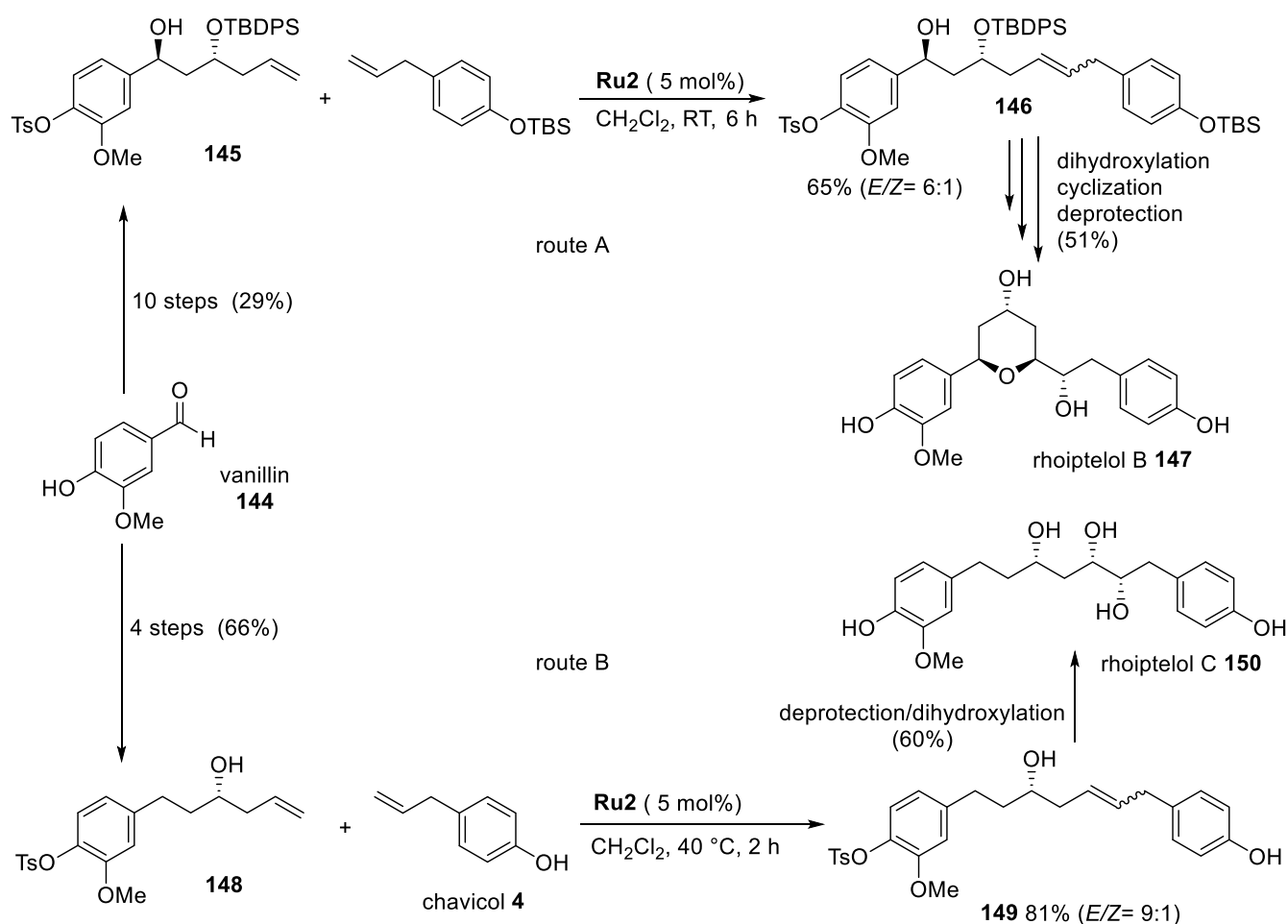
Rhoiptelols are 1,7-diarylheptanoids with biological activities that have been extracted from Asian plants. Their structure is based on a seven carbon chain with a linear or a cyclic arrangement

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capped with two phenolic groups. Their total synthesis starting from 4-hydroxyphenylpropanoids represents a very suitable method. The preparations of Rhoiptelol B and C were thus successfully achieved independently starting from vanillin and involving in their synthesis sequence a cross metathesis reaction with a chavicol substrate. Before the cross metathesis step, vanillin (**144**) was transformed into the homoallylic alcohol derivative (**145**), and cross metathesis with TBS-protected chavicol in the presence of 5 mol% of **Ru2** gave the olefin (**146**) in 65% yield with a *E/Z* ratio of 6:1 (Scheme 40 – route A).^[94] Enantioselective dihydroxylation of double bond followed by

cyclization and deprotection led to the rhoiptelol B (**147**) in 9.5% yield from vanillin in 14 steps.

In the synthesis of rhoiptelol C, vanillin was first transformed into the homoallylic alcohol (**148**), which served as cross metathesis partner of chavicol to give (**149**) in 81% yield with a *E/Z* ratio of 9:1 (Scheme 40 – route B).^[95] Then, phenol deprotection and enantioselective Sharpless dihydroxylation led to rhoiptelol C (**150**) in 32% yield from vanillin in 7 steps.



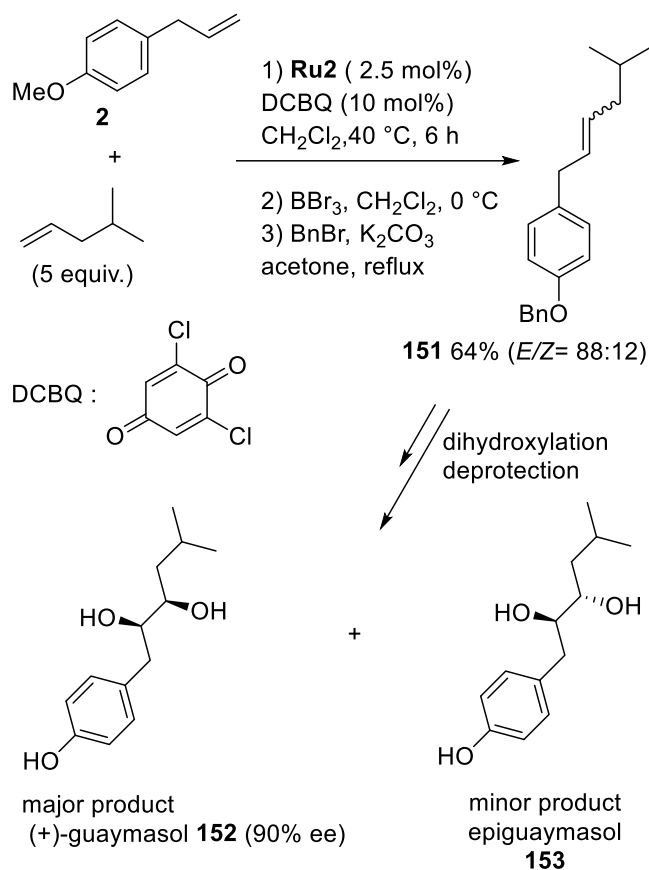
Scheme 40. Preparations of rhoiptelols B and C

Other 1,7-diarylheptanoids featuring a non-functionalized seven carbon linear tether (or containing only one double bond) have been prepared using cross metathesis of 6-arylhex-1-ene with estragole and methyl eugenol in the presence of the first generation **Ru1** catalyst. Modest yields were obtained when the aryl group of 6-arylhex-1-ene contained an unprotected phenolic hydroxyl group,^[96] but a yield of 62% was obtained with a protected phenol.^[97]

The synthesis of the natural product (+)-guaymasol, has been achieved from estragole by using a sequence combining a cross metathesis and an enantioselective dihydroxylation. Treatment of estragole with 4-methylpent-1-ene in the presence of 2.5 mol% of **Ru2** and 10 mol% of dichlorobenzoquinone (DCBQ) limiting isomerization of double bonds and byproducts formation, delivered a 88:12 mixture of *E* and *Z* isomers of estragole derivatives. Unfortunately, after dihydroxylation, it was not possible to cleave the methoxy group by treatment with BBr_3 or

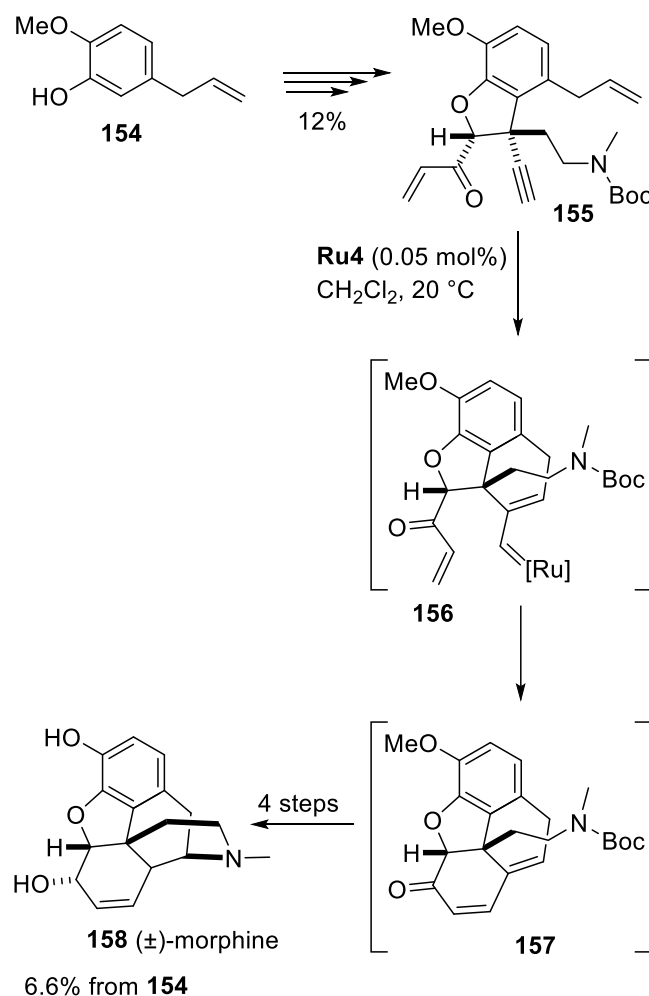
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TMSI. To circumvent this failure, the methoxy group was changed to a benzyl group after cross metathesis to give (**151**) in 64% yield with the same isomeric ratio. Then, asymmetric dihydroxylation with AD-mix- β /MeSO₂NH₂ in ^tBuOH/H₂O at 0 °C gave (+)-guaymasol (**152**) as the major product with 90% ee together with the minor epiguaymasol (**153**) (Scheme 41).^[98]



Scheme 41. Preparation of (+)-guaymasol (**152**) from estragole

The preparation of (\pm)-morphine according to the procedure outlined in Scheme 42 represents a rare example of involvement of the estragole derivative (**155**) equipped with two double and one triple bond affording a polycyclic product *via* a domino sequence of enyne-ene ring closing metathesis.^[99] With a low loading of catalyst **Ru4** in dichloromethane at 20 °C, the intramolecular enyne metathesis of the triple bond with the allyl fragment formally leads to the intermediate ruthenium carbene (**156**), which then interact with the acrylic double to give the polycyclic product (**157**). Without isolation, (**157**) was deprotected, rearranged to form a polycyclic amine, and subsequent selective reduction of the carbonyl group by NaBH₄ and deprotection of the methoxy group by BBr₃ led to (\pm)-morphine (**158**) in 6.6% overall yield from 2-hydroxy estragole (**154**).^[100]

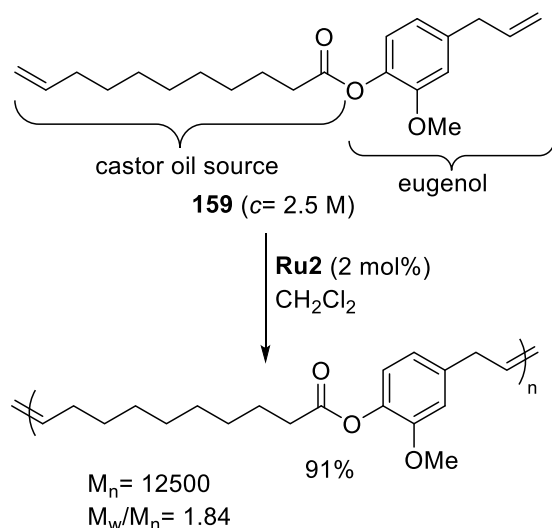


Scheme 42. Preparation of (\pm)-morphine

Recently, novel applications have emerged based on combination of different types of bio-sourced and natural molecules in order to generate unprecedented functionalized molecules and materials. For instance, a new polyester has been produced by acyclic diene metathesis polymerization (ADMET) of the monomer (**159**) resulting from condensation of eugenol with 10-undecenoyl chloride derived from castor oil. Starting from a 2.5 M solution of monomer in dichloromethane at 50 °C for 12 h in the presence of 2 mol% of **Ru2**, a polymer with unimodal molecular weight distribution ($M_n = 12700$, $M_w/M_n = 1.85$) was isolated in 91% yield (Scheme 43).^[101] Other examples involving the cross metathesis of eugenol with renewable unsaturated fatty acid esters has been reported. The cross metathesis of (**1**) with methyl oleate was thus explored with the ruthenium catalysts **Ru1**, **Ru2** and **Ru4**. The most efficient one was **Ru2**, which allowed the selective cross metathesis in more than 90% yield with very low formation of self-metathesis products.^[102] Indeed the selectivity towards the formation of the four cross metathesis products *versus* self-metathesis of the two substrates was very high (> 98%) when the

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reaction was performed with an excess of eugenol (20 equiv.) in a protic solvent such as ethanol with a high oleate concentration of 10 M at 50 °C for short reaction time (less than 1 hour) with a catalyst loading of 0.1 mol%. These conditions were also successfully applied to methyl petroselinate and erucate.^[101a]



Scheme 43. ADMET polymerization of (**159**)

6. Conclusion

The allyl group of 4-hydroxyphenylpropanoids arising from natural products has been involved in a variety of olefin metathesis reactions from self-metathesis to cross metathesis with functional olefins. The selectivity of these reactions is mainly affected by the deleterious possibility of double bond migration in the phenylpropanoid substrate or the cross metathesis partner, which leads to undesired products. The migration of the double bond in the final cross metathesis product is also a possibility, which leads to a double bond position isomer. These side reactions can be avoided or at least limited by the use of additives or the selection of appropriate metathesis catalysts that do not promote double bond migration. With the first generations of ruthenium catalysts, the stereoselectivity of the formed double bond was mostly in favour of the (*E*)-isomer except in the case of acrylonitrile that always favoured the formation of (*Z*)-isomers. More recently, ruthenium dithiolate and molybdenum pyrrolide catalysts have shown their high efficiency to produce (*Z*)-olefins in high yields and stereoselectivities. We have shown that cross metathesis reactions could represent key steps of sequential transformations to reach specific targets.

Finally, it appears that metathesis transformations of 4-hydroxyphenylpropanoids have been used in some synthesis of natural products and in the preparation of hybrids of renewable

products upon combination with fatty acid derivatives. These preliminary results reveal that olefin metathesis involving phenylpropanoids offers straightforward and green processes for the access to value-added products from bio-sourced substrates extracted from renewables and that future applications have to be discovered, including couplings with other unsaturated natural resources. This review also clearly shows that intramolecular enyne or intermolecular ene-yne metathesis have been neglected and should be considered in further investigations.

Keywords: phenylpropanoids • olefin metathesis • bioresources

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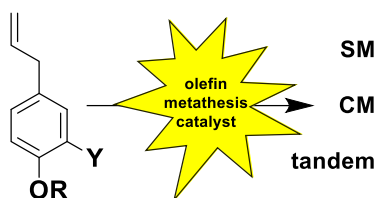
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REVIEW

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In this review are gathered transformations of 4-hydroxyphenypropanoids involving olefin metathesis catalyzed by ruthenium and molybdenum catalysts. Model reactions of self- and cross-metathesis point out the problems of selectivity due to possible concurrent double bond migration reactions and the recent progress in controlled stereoselectivity with the help of new catalysts. Applications in synthesis are also presented.