

Article

NHC Ligand Effects on Ru-Catalyzed Cross-Metathesis of Renewable Materials

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Abstract: As petrochemical resources become increasingly scarce and expensive, much attention has been focused on renewable resources from biomass as alternative options for producing basic building blocks for chemical manufacturing. Catalytic olefin metathesis represents a powerful tool to transform biosourced structural motifs in valuable commodity, fine, and specialty chemicals. In that respect, the appropriate choice of the catalyst is the key issue of each metathesis transformation. The current study examines the influence of different *N*-heterocyclic carbene (NHC) ligands containing one or two *N*-alkyl substituents on the efficiency of Hoveyda–Grubbs-type catalysts in the cross-metathesis reaction of ethyl oleate with *cis*-1,4-diacetoxy-2-butene and cross-metathesis of eugenol acetate with *cis*-1,4-dichloro-2-butene. Interestingly, the introduction of alkyl *N*-substituents in the NHC ligand was revealed as beneficial for catalytic performances in the examined cross-metathesis (CM) reactions, leading to higher activity and/or selectivity than those observed in the presence of the classical, commercially available Hoveyda–Grubbs second generation catalyst (HGII).

Keywords: cross-metathesis; renewable resources; NHC ligands; ruthenium catalysts; fatty acid esters; phenylpropenoids

1. Introduction

Olefin metathesis is a highly versatile method for the construction of new carbon–carbon double bonds, which finds important applications in the synthesis of pharmaceuticals, petrochemicals, polymers, and specialty chemicals [1–3].

In recent years, the gradual depletion of fossil resources and the strong need to limit the adverse environmental and health impacts of petroleum-based chemicals have pushed towards the use of renewable natural resources as green alternatives [4]. In the olefin metathesis field, readily available and inexpensive plant-derived molecules containing carbon–carbon double bonds are currently considered ideal raw materials to be employed for the synthesis of valuable compounds for the chemical industry [5–11]. Among all renewable raw materials, unsaturated fatty acid esters from vegetable oils, such as methyl or ethyl oleate, emerge as the most attractive chemical platforms for olefin metathesis. These compounds, in fact, can be easily transformed in a variety of high-value products via cross-metathesis (CM) with both unfunctionalized and functionalized olefins [12–23]. For instance, the CM of unsaturated fatty acid esters with various functional groups offers a versatile route for the synthesis of α,ω -difunctional compounds, which serve as chemical intermediates and polymer precursors.

Another class of renewable compounds that are particularly suitable for olefin metathesis transformations is represented by phenylpropenoids, such as safrole, eugenol, and estragole, typically found in essential oils. This class of compounds have been employed in CM reactions with different cross-partners to produce polyfunctional olefins, which can be successively transformed

in many types of useful chemicals [24–30]. The increasing interest in metathesis applications involving molecules from renewable resources is strictly related to the development of highly efficient catalysts with improved functional group tolerance. The right choice of the catalyst is one of the key issues to render such processes attractive and viable for industrial use. In this view, easy-handling, stable olefin metathesis ruthenium-based catalysts coordinated with *N*-heterocyclic carbene (NHC) ligands are considered as good candidates for applications involving renewable feedstocks as substrates [21,25–29,31–33].

Recently, we have reported on Hoveyda–Grubbs-type catalysts bearing backbone-substituted symmetrical and unsymmetrical NHCs, characterized by at least one *N*-alkyl moiety. These complexes were found to be efficient catalysts for specific metathesis applications, proving to be in some cases more active and/or selective than the traditional, commercially available **HGII** (Figure 1) [34–39]. To get a deeper picture of the catalytic potential of this class of complexes and their applicability in the field of olefin metathesis with renewable chemicals, we herein describe two CM reactions, namely the CM of ethyl oleate with *cis*-1,4-diacetoxy-2-butene, and the CM of eugenol acetate with *cis*-1,4-dichloro-2-butene, promoted by *N,N'*-dialkyl (**Ru1** and **Ru2**) and *N*-alkyl, *N'*-aryl (**Ru3** and **Ru4**) NHC Ru-complexes depicted in Figure 1. *N,N'*-dialkyl complexes **Ru1** and **Ru2** differ from each other in the bulkiness of the alkyl substituent, whereas *N*-alkyl, *N'*-aryl **Ru3** and **Ru4** in that of the aryl substituent. The influence of the nature of *N*-substituents as well as of backbone configuration of NHC ligands in determining catalyst efficiency is therefore discussed.

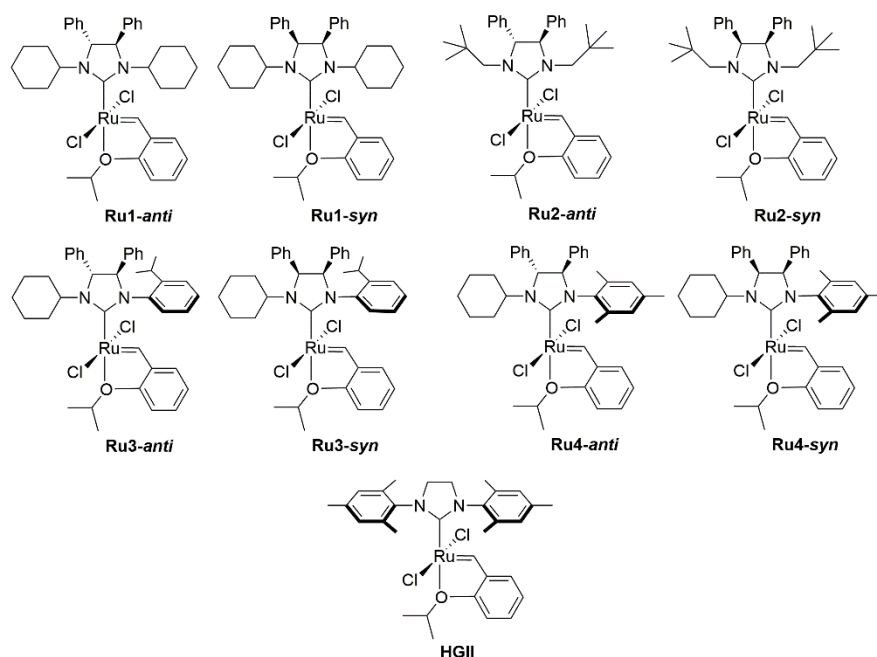


Figure 1. The Hoveyda–Grubbs second generation catalysts used.

2. Results and Discussion

2.1. Cross-Metathesis of Ethyl Oleate with *Cis*-1,4-Diacetoxy-2-Butene

The synthesis of **Ru1–Ru4** was carried out as previously described [34,36,38]. In order to provide a comprehensive picture of the catalytic behavior of **Ru1–Ru4**, some key characterization data of these complexes are summarized in Table 1 [36,38]. In this table, the thermal stabilities displayed by **Ru1–Ru4** are quantified as the percentage of undecomposed catalyst in C₆D₆ after 1 day, 2 days, and 14 days at 60 °C under nitrogen; furthermore, the steric demand of the NHC ligands of **Ru1–Ru4** is described by the percentage buried volume (%*V*_{bur}) [40,41], while their electron-donating properties by the Ru(II)/Ru(III) redox potentials [42]. As a general trend, catalysts possessing *anti*-related phenyl

groups on the backbone turn out as more stable than the corresponding *syn* isomers and possess higher %V_{Bur} values. Moreover, *N,N'*-dialkyl catalysts are found to be less stable than *N*-alkyl, *N'*-aryl complexes, with cyclohexyl substituted catalysts **Ru1-anti** and **Ru1-syn** emerging as the less stable and the less encumbered catalysts in the series.

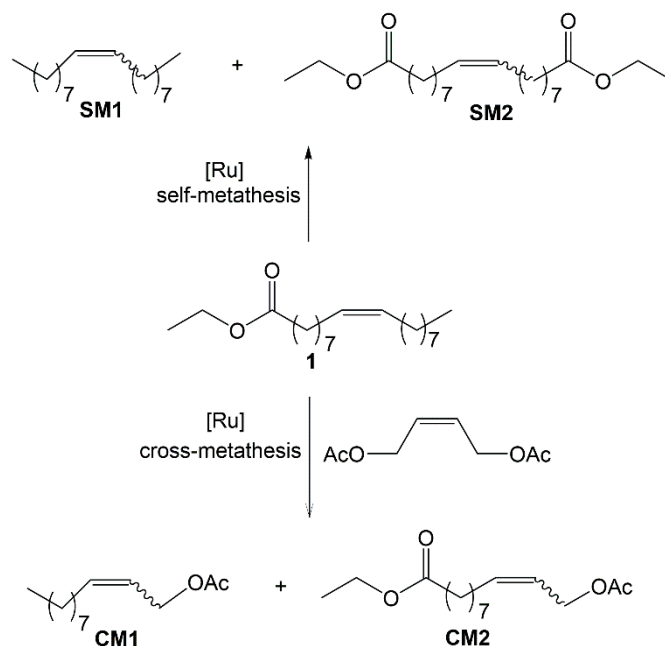
Table 1. Percentage of undecomposed complex, %V_{Bur} values, and redox potentials for **Ru1–Ru4** ¹.

Catalyst	%Catalyst Left			%V _{Bur}	$\Delta E_{1/2}$ (V)
	(1 Day)	(2 Days)	(14 Days)		
Ru1-anti	98	98	25	28.9	0.950
Ru1-syn	79	66	21	28.7	0.972
Ru2-anti	93	92	33	31.0	1.00
Ru2-syn	82	73	33	30.9	0.996
Ru3-anti	100	100	42	31.0	0.960
Ru3-syn	82	74	32	30.5	0.947
Ru4-anti	100	100	100	31.8	0.950
Ru4-syn	100	100	100	31.5	0.961
HGII	86	84	83	32.9	0.860

¹ For **Ru1** and **Ru2**, see Reference [38]; for **Ru3**, **Ru4**, and **HGII**, see Reference [36].

Of note, both *syn* and *anti* isomers of **Ru4** displayed higher stability than commercial catalyst **HGII**, chosen as benchmark. All the NHC ligands of **Ru1–Ru4** display lower electron-donating properties than the symmetrical *N,N'*-diaryl NHC of **HGII**, as suggested by the higher values of the Ru(II)/Ru(III) redox potentials. This difference can be related to the presence of phenyl groups on the NHC backbone, regardless of their relative orientation. No other substantial effect can be appreciated, except that deriving from the presence of neopentyl *N*-substituents, which impart lower electron-donor abilities to the corresponding NHCs.

Ru1–Ru4 were first tested in the CM of ethyl oleate (**1**) with *cis*-1,4-diacetoxy-2-butene (**2**) (Scheme 1).



Scheme 1. Cross-metathesis (CM) of ethyl oleate (**1**) with *cis*-1,4-diacetoxy-2-butene (**2**).

This CM transformation was chosen because it allows us to obtain valuable commodity chemicals from relatively inexpensive substrates. The desired cross-metathesis products, namely undecen-2-enyl

acetate (**CM1**) and ethyl 11-acetoxyundec-9-enoate (**CM2**), are both interesting substrates for several syntheses and for the preparation of short chain polymer precursors [9,22,43]. Moreover, undecen-2-enyl acetate (**CM1**) can be transformed, under appropriate conditions, into polyallylic alcohols [44].

The CM reactions were conducted in toluene at 50 °C with a catalyst loading of 2.5 mol%. A fivefold excess of **2** is used to restrict the undesirable concurrent self-metathesis reaction of ethyl oleate leading to the secondary metathesis products octadec-9-ene (**SM1**) and diethyl octadec-9-enedioate (**SM2**).

The results are presented in Table 2. The ethyl oleate conversion, the reaction selectivity, and the yield of cross- and self-metathesis products were determined by gas chromatography (GC) with dodecane as an internal standard, wherein *E* and *Z* isomers were counted together. Each product was identified by gas chromatography-mass spectrometry (GC-MS) and its structure and configuration confirmed by ¹H NMR spectroscopy.

Table 2. CM of **1** with **2** in the presence of **Ru1–Ru4** and **HGII** ¹.

Entry	Catalyst [mol%]	Conversion ² [%]	Selectivity ² [%]	Yield ² [%]			
				CM1	CM2	SM1	SM2
1	Ru1-anti (2.5)	61	87	53	40	3	4
2	Ru1-syn (2.5)	90	96	57	40	1	2
3	Ru2-anti (2.5)	90	92	51	45	1	3
4	Ru2-syn (2.5)	-	-	-	-	-	-
5	Ru3-anti (2.5)	89	95	51	47	1	1
6	Ru3-syn (2.5)	-	-	-	-	-	-
7	Ru4-anti (2.5)	-	-	-	-	-	-
8	Ru4-syn (2.5)	-	-	-	-	-	-
9	HGII (2.5)	90	94	51	46	1	2
10	Ru1-anti (1.0)	-	-	-	-	-	-
11	Ru1-syn (1.0)	76	94	53	44	1	2
12	Ru2-anti (1.0)	67	90	52	43	2	3
13	Ru3-anti (1.0)	84	94	51	46	1	2
14	HGII (1.0)	59	89	52	42	3	3

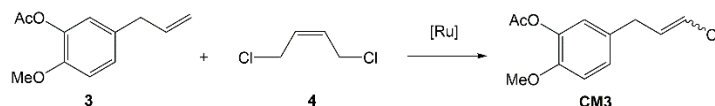
¹ Reaction conditions: [**1**] = 0.14 M in toluene, 5 eq. **2**, 50 °C, 12 h; ² determined by GC, using dodecane as an internal standard.

As can be seen from Table 2, very different results were registered. *N,N'*-dialkyl catalysts (entries 1–4) were found to be competent in this CM reaction, only **Ru2-syn** with neopentyl *N*-groups failed (entry 4), while *N*-alkyl, *N'*-aryl catalysts turned out to be practically inactive (entries 5–8), the only exception being **Ru3-anti** (entry 5). In all cases, yield of both desired cross-metathesis products, namely **CM1** and **CM2**, was similar, and slightly better for **CM1**. Other products from side-reactions or double-bond isomerization were not observed. Even if the selected CM is a quite demanding reaction, we were quite surprised to find that it was prohibitive for complexes such as *N*-alkyl, *N'*-aryl catalysts **Ru4-anti** and **Ru4-syn**, that, on the contrary, were revealed as highly performing catalysts in the cross-metathesis of ethyl oleate with ethylene (ethenolysis) [36]. Interestingly, the presence of symmetrically substituted *N*-alkyl NHCs coordinated to the metal seems to favor the formation of more reactive catalytic species, especially when the alkyl group is a cyclohexyl (entries 1 and 2). In fact, in this case, both *anti* and *syn* isomers of **Ru1** can promote the reaction, with the *syn* catalyst showing higher conversion than the *anti* congener (90% vs. 61%). It is also worth to note, that these two catalysts are the least bulky and stable in the series (see Table 1). The replacement of a cyclohexyl *N*-substituent in the NHC by the bulky mesityl group is deleterious for the catalytic activity of both *anti* and *syn* isomers of **Ru4** (entries 7 and 8), which, by the way, are the most bulky and stable in the series (see Table 1). Except for **Ru1-anti** (entry 1), all the catalysts able to promote the reaction showed high conversions, comparable to those observed with commercial catalyst **HGII** (entry 9). Selectivity of the cross-metathesis reaction was in the range 87–96%. The best selectivity was observed when **Ru1-syn** was used (96%, entry 2). No trend in the electronic influence of the NHC ligand could be found.

Ru1, **Ru2-anti**, and **Ru3-anti** were then tested at lower catalyst loading (1.0 mol%, entries 10–14), as described by Behr [19] and Grela [21] for the CM of methyl oleate with **2**. All the catalysts gave still satisfactory results in terms of conversion, with one exception, **Ru1-anti**, which was already less effective, and in these reaction conditions became inactive (entry 10). Notably, **Ru1-syn**, **Ru2-anti**, and **Ru3-anti** outperformed commercially available **HGII**, which showed a significant drop in conversion, from 90 to 59% (entry 14). As for selectivity, in all cases a similar level (around 90%) was maintained.

2.2. Cross-Metathesis of Eugenol Acetate with *Cis*-1,4-Dichloro-2-Butene

The reactivity of the different catalysts was next studied in the CM of eugenol acetate (**3**) with *cis*-1,4-dichloro-2-butene (**4**) (Scheme 2). Eugenol acetate belongs to the family of phenylpropenoids, which are considered as important fine-chemical building blocks. It is one of the key constituents of clove essential oil, together with eugenol, from which it can be easily obtained by direct acetylation with acetic anhydride. It has been widely used as a food and flavor ingredient and has also been recognized for its antibacterial, antioxidant, and antivirulence activities. The CM of **3** with **4** affords the allylic chloride derivative **CM3**, which represents a useful intermediate for the synthesis of polymers and chemicals.



Scheme 2. CM of eugenol acetate (**3**) with *cis*-1,4-dichloro-2-butene (**4**).

This transformation was carried out in CH_2Cl_2 at 40 °C using 2.5 mol% catalyst loading and 3 equivalents of **4** to minimize self-metathesis of **3**. The catalytic performance of **Ru1–Ru4** was compared to that of commercially available **HGII** and the results are summarized in Table 3.

Table 3. CM of **3** with **4** in the presence of **Ru1–Ru4** and **HGII** ¹.

Entry	Catalyst	Yield ² [%]	<i>E</i> : <i>Z</i> ³
1 ⁴	Ru1-anti	77	5.4
2 ⁴	Ru1-syn	84	5.4
3 ⁴	Ru2-anti	70	3.2
4 ⁴	Ru2-syn	88	2.8
5	Ru3-anti	77	9.0
6	Ru3-syn	60	2.0
7	Ru4-anti	75	7.0
8	Ru4-syn	54	3.2
9	HGII	50	7.4

¹ Reaction conditions: [**3**] = 0.2 M in methylene chloride, 3 eq. **4**, 40 °C, 12 h; ² isolated yield; ³ *E*:*Z* ratios were determined by ¹H NMR spectroscopy; ⁴ see ref. [38].

In all cases, no undesired side-products arising from self-metathesis and/or double bond migration reactions were observed. The only exception is the CM promoted by **Ru3-syn**, in which the formation of unidentified side-products was observed. All the eight catalysts were found to be more efficient than **HGII**, with **Ru2-syn** emerging as the most active among the examined catalysts. These results clearly indicate that the introduction of alkyl *N*-substituents is particularly advantageous for this CM reaction. As for the NHC backbone configuration, *syn* isomers of *N,N'*-dialkyl catalysts resulted as more active than their *anti* counterparts (entries 1–4), while the reverse behavior was observed in the group of *N*-alkyl, *N'*-aryl catalysts (entries 5–8). As for selectivity, no remarkable difference was noticed in the case of *N,N'*-dialkyl catalysts **Ru1** and **Ru2** (entries 1–4), for which both the isomers gave almost the same *E/Z* ratios and a slightly increased *Z*-selectivity was observed when *N,N'*-neopentyl catalysts

Ru2 were used. On the contrary, in the case of **Ru3** and **Ru4**, decorated with *N*-alkyl,*N'*-aryl NHC, differences in *E/Z* ratios were evident (entries 4–8). *Anti* isomers were indeed more selective than their *syn* congeners towards the formation of the desired CM product with a *Z* double bond. In general, as observed in the previous CM reaction, less stable catalysts with lower bulkiness of the NHC ligand turned out as the best performing catalysts. Unfortunately, no trend in the electronic influence of the NHC ligand could be established.

3. Materials and Methods

3.1. General Considerations

All reactions with Ru-based compounds were carried out under nitrogen using standard Schlenk and/or Glove-box techniques. Toluene and dichloromethane were purchased from Merck (Germany) and distilled before used. Ethyl oleate was purified through a column of neutral, activated alumina before use. All the other solvents and reagents were purchased from Merck or TCI Chemicals Europe (Belgium) and used as received. Catalysts **Ru1–Ru4** were synthesized according to literature procedures [34,36,38]. GC analysis was performed on Agilent Technologies 7890 A instrument equipped with a HP5MSUI column (60 m 25 mm) using the following temperature program: 100 °C for 20 min, then 15°/min until 300 °C, and finally 300 °C for 8 min. The NMR spectra were recorded on BrukerAM 300 spectrometer (300 MHz for ¹H; 75 MHz for ¹³C) or BrukerAVANCE 400 spectrometer (400 MHz for ¹H; 100 MHz for ¹³C). The NMR samples were prepared dissolving about 10 mg of compound in 0.5 mL of the deuterated solvent.

3.2. Procedures for the CM of Ethyl oleate (**1**) and Cis-2,4-Diacetoxy-2-Butene (**2**)

Under a nitrogen atmosphere, **1** (75 µL) and dodecane (50 µL) were introduced. At this point, the *t*₀ sample was prepared. After that, **2** (165 µL) was added and the mixture was transferred into a toluene solution of the catalyst (2.5 mol %). The reaction was placed in an oil bath at 50 °C for 14 h and then cooled in an ice bath and quenched with ethyl vinyl ether. After that, the GC sample was prepared in hexane. The samples were stored at −20 °C until GC analysis. For a representative chromatogram of the reaction mixture, see the supporting information (Figure S1).

The conversion was determined through comparison of the areas of **1** and of dodecane in the sample containing the aliquot of the crude reaction mixture (sample *t*) and in the a *t*₀ sample using the following equation:

$$\text{Conversion (\%)} = \left(1 - \frac{\text{Area (1)}_t * \text{Area (dodecane)}_{t_0}}{\text{Area (1)}_{t_0} * \text{Area (dodecane)}_t} \right) * 100$$

In order to calculate selectivity, response factors (rf) of all the components of the reaction mixture with respect to **1** (to which a rf = 1 was arbitrarily attributed) were determined. Starting from the areas in the chromatogram and the abovementioned rfs, selectivity and yield toward each (*i*) component were calculated as follows:

$$\alpha(i) = \frac{\text{Area}(i)}{\text{rf}(i) * \text{MW}(i)}$$

$$\text{Selectivity (\%)} = \frac{\alpha(\text{CM1}) + \alpha(\text{CM2})}{\alpha(\text{CM1}) + \alpha(\text{CM2}) + 2 * [\alpha(\text{SM1}) + \alpha(\text{SM2})]} * 100$$

$$\text{Selectivity}(i)(\%) = \frac{\alpha(i)}{\alpha(\text{CM1}) + \alpha(\text{CM2}) + 2 * [\alpha(\text{SM1}) + \alpha(\text{SM2})]} * 100$$

$$\text{Yield}(i)(\%) = \frac{\text{Selectivity}(i)(\%) * \text{Conversion}(\%)}{100}$$

3.3. Procedures for the CM of Eugenol Oleate (3) and Cis-1,4-Dichloro-2-Butene (2)

Under a nitrogen atmosphere, 47 μL of **3** and 77 μL of **4** were added simultaneously to a solution of the catalyst (2.5 mol%) in dry methylene chloride. The reaction mixture was refluxed under nitrogen overnight and then purified by column chromatography with hexane/ethyl acetate 9/1 as the eluent. The CM product (**CM3**) was obtained as a transparent oil. The *E/Z* ratios were determined by ^1H NMR through integration of the methylene ($\text{CH}-\text{CH}_2-\text{Cl}$) signals at δ 4.19 (*Z*) and δ 4.06 (*E*). For a representative ^1H NMR spectrum, see the supporting information (Figure S2).

4. Conclusions

A series of ruthenium catalysts containing backbone-substituted symmetrical *N,N'*-dialkyl and unsymmetrical *N*-alkyl, *N'*-aryl NHC ligands were compared in two CM reactions of renewable substrates. Improved activities and selectivities, with respect to the commercially available HGII, were observed in both the reactions. Although the catalytic performances of the examined complexes are not easily rationalized in relation to the NHC ligand architecture, these results encourage further efforts towards the development of new catalysts containing *N*-alkyl substituents, since they seem to be suitable for several specific olefin metathesis applications, in which the general purpose NHC Ru catalysts are less competent.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/8/904/s1>. Figure S1: Representative chromatogram of the crude reaction mixture from the CM of **1** and **2**, Figure S2: Representative ^1H NMR spectrum of the CM product (**CM3**) from reaction of **3** and **4** (CDCl_3 , 400 MHz).

Author Contributions: F.G. conceived and designed the experiments; V.P. and R.C. performed the syntheses, and the chromatographic and spectroscopic experiments; V.P. and F.G. analyzed the data; F.G. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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