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The $Cl_2(PCy_3)(IMes)Ru(=CHPh)$ catalyst: olefin metathesis versus olefin isomerization

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Abstract

While investigating RCM of substrates requiring elevated temperatures and extended reaction times, significant isomerization of one of the double bonds in the starting diene was observed with the recently developed [**RuIMes**] catalyst. This isomerization appeared as an important drawback of the catalyst, but a judicious selection of solvent and additive can completely eliminate this side reaction. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The strong impact of ring-closing metathesis (RCM) on organic synthesis has led to the development of several new catalysts, recently culminating in the use of nucleophilic carbenes as supporting ligands [1]. In this paper, we wish to focus on an important side-reaction, olefin isomerization, observed in the course of RCM studies using one of the new-generation catalysts.

We recently developed in our laboratories a ruthenium–carbene catalyst bearing one bis-mesityl imidazolinylidene ligand [2] ([**RuIMes**], Fig. 1), and we have employed it in the synthesis of eight-membered carbocycles for the RCM key step [3]. Based on the later study and several recent reports [4], the new catalyst [**RuIMes**] is as stable and easy to use as Grubbs' ruthenium catalyst [5] ([**Ru**], Fig. 1), and its reactivity is comparable to that of Schrock's molybdenum catalyst [6] ([**Mo**], Fig. 1).

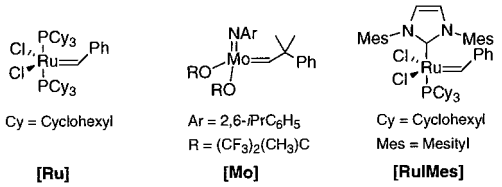

Fig. 1. RCM catalysts.

RCM of substrates **1a**–**c** with [**RuIMes**] proceeded in yields ranging from 86 to 91% (Scheme 1, Table 1) [3]. These results are noteworthy considering the elaborate substitution pattern of cyclooctenes adducts **2a**–**c**. However, a by-product was also obtained, and although it was in small quantity (5–10%), it rendered purification difficult. This by-product was not detected in the crude reaction mixtures of RCM performed with [**Mo**].

Careful analysis of ^{1}H-NMR spectra of crude RCM mixtures led us to believe that this by-product resulted from the migration of the less hindered double bond of **1** to an internal position. An independent synthesis of this compound was necessary for unambiguous identification. Thus, ketone **3**, an intermediate in the synthesis of products **1a**–**c**, was quantitatively converted to isomeric ketone **4** using $RhCl_3$ in ethanol (Scheme 2). The synthesis of the isomeric carbonate **6a** was then accomplished following the route used for **1a**–**c**, [3] as described in Scheme 2.

The isomerization of the starting olefin during reaction with [**RuIMes**] catalyst was then fully secured by

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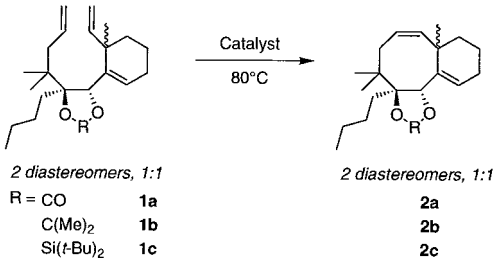
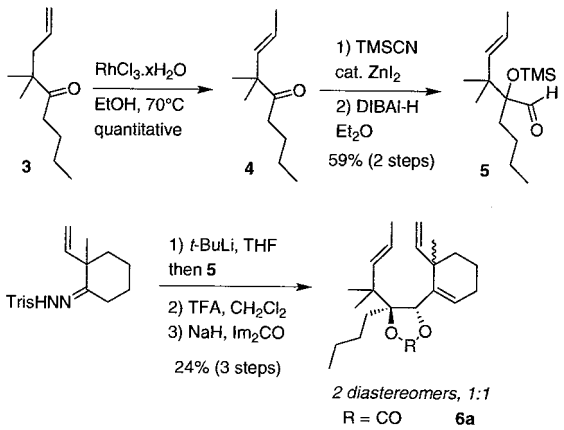


Scheme 1.

Table 1
Synthesis of cyclooctenes by RCM

Substrate	Catalyst	Time	Yield (%)
1a	**[Ru]**	8 days	34 [a]
	[Mo]	3 days	41 [a]
	[RuIMes]	15 h	86
1b	**[Ru]**	8 days	0
	[Mo]	3 days	93
	[RuIMes]	15 h	86
1c	**[Ru]**	8 days	0
	[Mo]	3 days	96
	[RuIMes]	20 h	91

[a] In this case, only one isomer reacts, and the product is the *trans* cyclooctene (see Ref. [3]).



Scheme 2. Preparation of isomerized RCM precursor.

comparison of the ^{1}H-NMR spectra of pure **6a** and of the crude products of RCM of **1a**. The seven-membered ring product corresponding to the RCM of **6a** is not observed, because its formation would result from a reaction between two double bonds located in a neopentylic position [7].

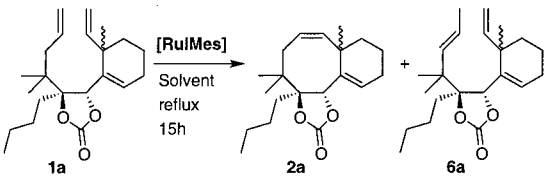
Olefin isomerization with ruthenium derivatives is a well-known process [8]. However, there are only a few mentions in the literature of this reaction as a side-reaction during olefin metathesis. The isomerization can result from the decomposition products of the **[Ru]** catalyst [9], and has been observed after a prolonged reaction time [10], or during purification by distillation [11]. In both cases, the amount of isomerized product is negligible, and far less than what was observed in the present system.

Taylor reported an olefin isomerization during the synthesis of an oxocene by RCM with **[Ru]** in dichloromethane, and attributed it to the residual acidity of the solvent: replacing dichloromethane by diethyl ether prevented isomerization [12]. We discarded the possibility of a residual acidity in the solvent: the addition of $NaHCO_3$ did not modify the outcome of the reaction.

We therefore, suspected this particular reactivity to be attributable to the **[RuIMes]** catalyst itself. The ligand exchange (IMes vs. PCy_3) must increase the catalyst propensity towards isomerization. This hypothesis was recently confirmed in a report from the Fürstner laboratory describing the synthesis of a 21-membered macrolactone by RCM using **[RuIMes]** as catalyst [13]. The corresponding 20-membered ring lactone was also obtained as a by-product, and the authors invoke a RCM with loss of propylene, which could result from an isomerization of the starting material.

In order to gain further understanding of the increased reactivity displayed by the new generation catalyst **[RuIMes]**, we focused our attention on this isomerization reaction. The carbonate protected substrate **1a** was chosen for a full study as the isomerization was more prevalent in this case. Furthermore, we found significant lack of reproducibility in the RCM reaction involving **1a** with **[RuIMes]** in benzene: isomerization occurred to the extent of 30–50%.

The solvent selection proved crucial in influencing the product distribution of the reaction (Scheme 3, Table 2).

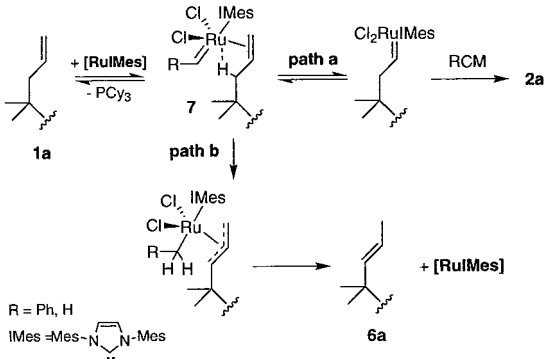


Scheme 3.

Table 2
Influence of the solvent on the product distribution

Solvent	b.p. (°C)	Cyclization (**2a**) (%)	Isomerization (**6a**) (%)
Benzene	80	50–70	30–50
Toluene	110	20	80
DCE	83	90	10
DME	85		100

The ratios of the different products were determined by integration of the ^{1}H-NMR spectra of the crude reaction mixtures.



Scheme 4. Postulated mechanism of the isomerization process.

We propose the mechanism in Scheme 4 for the isomerization process. The ruthenium catalyst coordinates to the less sterically crowded olefin. Complex **7** can then react along two different pathways. Along path a, the classical carbene exchange for metathesis occurs via a metallacyclobutane intermediate, enabling the generation of the RCM adduct **2a**. This step is an equilibrium [14]. Along path b, the deprotonation at the allylic position leads to a π-allyl complex, responsible for the double bond migration.

We envisage that the allylic proton is trapped by the carbene carbon, considering that the high oxidation state of the ruthenium in complex [**RuIMes**] will not favor the formation of a hydride complex. Furthermore, the IMes ligand, a strong σ-donor, will increase the basicity of the carbene. Also, an agostic interaction between the 16-electron transition metal complex and the allylic hydrogen, could help the process.

Assuming this mechanism, the solvent influence can be rationalized in terms of coordination ability. The more coordinating the solvent, the more it will prevent the second double bond from coordinating the ruthenium center, which is necessary to achieve the RCM process, so isomerization will be favored.

This proposed mechanism is in agreement with the observation that isomerization has only been noticed with substrates which react slowly by RCM. In the case of compounds **1a**–**c**, the high temperature of 80 °C and an extended reaction time are necessary to overcome the high energy of activation of the reaction. In the case of a macrocycle formation, the two reacting double bonds are also far away from the reacting center [15]. But in the case of dienes leading to 'easy' RCM, e.g. which do not need a high temperature or an extended reaction time, the coordination to the second double bond will be rapid enough to avoid the slower isomerization process. For instance, the RCM with [**RuIMes**] of a diene analogous to **1**, but leading to a cycloheptene, showed similar reactivity in DME and in benzene.

More interestingly, we noticed that in some cases there was no isomerization during the RCM of **1a** with [**RuIMes**] in benzene. This was observed when the starting diene had been previously subjected to Grubbs' catalyst. Although purified, this product might have been contaminated with catalyst decomposition products. This was also noticed when fresh [**RuIMes**] catalyst was added to the crude product resulting from a RCM performed under oxygen atmosphere, for which the conversion rate was very low.

A systematic study of different additives was then conducted on the RCM involving carbonate **1a**. All reactions were carried out under an argon atmosphere in degassed DCE at reflux, with 5% of [**RuIMes**] catalyst at a 0.02 M concentration [16]. Results are summarized in Scheme 5 (Table 3).

The RCM reaction is very sensitive to additives as illustrated by the significantly more sluggish reaction when small amounts (5%) of tricyclohexylphosphine (PCy_3) or water are added [17]. Tricyclohexylphosphine oxide ($OPCy_3$) finally emerged as the reagent responsible for isomerization inhibition. Here the isomeric adduct **6a** is not detected by TLC and ^{1}H-NMR in the crude reaction product. The fact that even a catalytic quantity (10% respective to the catalyst) is sufficient to inhibit the isomerization is in agreement with the hypothesis of a trace of phosphine oxide present along with unreacted **1a** recovered after reaction with [**Ru**].

Tricyclohexylphosphine oxide, $O{=}PCy_3$, is generated from the oxidation of PCy_3 and is a very weakly binding and bulky ligand. We presume that it is able to coordinate to the intermediate complex **7**, enough to prevent proton abstraction and π-allyl formation, or by hindering the agostic interaction, but weakly enough to exert no influence on the metallacyclobutane formation and the RCM process. The lack of influence of triphenylphosphine oxide ($O{=}PPh_3$) demonstrates the subtlety of the observed effects, and more work remains to be performed to confirm the proposed mechanism.

Interestingly, water has very little effect on the RCM reactions described here. This result, linked with the reaction carried out under an oxygen atmosphere, clearly illustrates that the ruthenium-based catalysts are only sensitive to oxygen, and not to water. Therefore, we routinely carry out reactions for synthetic purposes in DCE (min purity 99%) without any precaution but argon degassing.

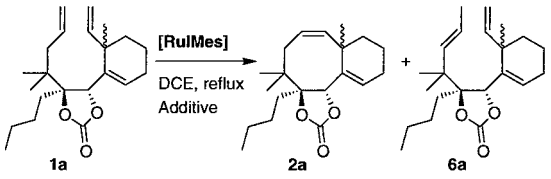
In conclusion, we document here a new aspect of the stable carbene ligand-based ruthenium metathesis catalysts. We have illustrated that olefin isomerization may be a competitive process to RCM when these reactive ruthenium species are used in the case of slow-reacting substrates. The importance of a weakly coordinative ligand has been established, and this opens new perspectives for RCM. A complete mechanistic investigation of the isomerization versus metathesis process is under investigation, as well as the isomerization of simple olefins with [**RuIMes**].

2. Experimental

2.1. General methods

All air and/or water sensitive reactions were carried out under an Ar atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was oven dried (110 °C) and/or carefully dried in line with a flameless heat gun. Unless otherwise stated.

^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker WP 200 (200 MHz) or on a Bruker AM 400 (400 MHz) instrument. The chemical shifts are expressed in parts per million (ppm) referenced to residual $CHCl_3$ (7.27 ppm). Data are reported as follows: δ, chemical shift; multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet and m, multiplet), coupling constants (J in hertz, Hz), integration and assignment. H,H-COSY and H,H-NOESY experiments were routinely carried out to ascertain H–H connections and configuration assignments, respectively. ^{13}C-NMR spectra were recorded on the same instruments at 50.3 and 100.6 MHz, respectively. ^{13}C-NMR chemical shifts are expressed in parts per million (ppm), reported from the central peak of deuterochloroform (77.14 ppm). J-modulated spin-echo technique (J-mod) experiments were used for evaluating CH multiplicities.



Scheme 5.

Mass spectra (MS) were obtained on a Hewlett–Packard HP 5989B spectrometer via either direct introduction (chemical ionization, CI, NH_3) or GC–MS coupling with a Hewlett–Packard HP 5890 chromatograph. Infrared spectra (IR) were obtained on a Perkin–Elmer FT 1600 instrument using NaCl salt plates (thin film) and are reported in terms of frequency of absorption (ν, cm^{-1}). Microanalyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, CNRS, F-91198, Gif sur Yvette. Flash chromatography was performed on E. Merck Silica Gel Si 60 (40–63 mm, Ref. 9385).

Tetrahydrofuran (THF) and Et_2O were distilled from sodium–benzophenone, MeOH from CH_3OMg.

2.2. 2-Butyl-3,3-dimethyl-2-trimethylsilyloxyhex-4-enal (5)

To a solution of ketone **3** (400 mg, 2.4 mmol) in EtOH (6 ml) was added $RhCl_3 \cdot x H_2O$ (40 mg, 3 mol%), and the resulting red solution was heated at 70 °C for 6 h, then cooled to room temperature (r.t.), filtered through a pad of silica gel and concentrated in vacuo. Part of the resulting crude product (300 mg, 75%) were then diluted in 10 ml of dry CH_2Cl_2 at 25 °C, and a catalytic pinch of ZnI_2 was added, and then 360 μl (2.7 mmol, 1.5 equivalents) of Me_3SiCN. The resulting mixture was heated at reflux for 2 h, then cooled to r.t. and concentrated in vacuo (with a NaOCl–NaOH trap). The crude product was filtered through a pad of silica gel, and the silica gel was washed three times with Et_2O–pet. ether 1:1 (50 ml). The cyanhydrine thus obtained was concentrated in vacuo and used crude for the following step: it was diluted with 10 ml of Et_2O, and the resulting solution was cooled to −78 °C. A

Table 3
Influence of additives on the product distribution

Additive	Time (h)	SM (**1a**) (%)	Cyclization (**2a**) (%)	Isomerization (**6a**) (%)
Decomposition [Ru] [a]	15		100	
Decomposition [**Mo**] [a]	12	5	85	10
O_2	15	90	10	
PCy_3, 5%	60	40	60	
PCy_3, 0.5%	72	10	70	20
H_2O, 5%	20	30	60	10
H_2O, traces [b]	12	10	80	10
Styrene, 5%	15	5	90	5
Et_3N, 5%	72		50	50
Et_3N, 0.5%	72		75	25
$OPCy_3$, 5%	15		100	
$OPCy_3$, 0.5%	15		100	
$OPPh_3$, 5%	12	10	80	10
$[RuCl_2(p\text{-Cy})]_2$, 5%	15	30	35	35

The ratios of the different products were determined by integration of the ^{1}H-NMR spectra of the crude reaction mixtures.

[a] The starting diene (two diastereomers) was subjected to the specified catalyst ([**Ru**] or [**Mo**]), and the purified unreacted diastereomer, presumably containing traces of decomposition products of the RCM catalyst, was reacted with [**RuIMes**].

[b] In this case, the solvent was not distilled, and the glassware was not dried, but no other water was added.

solution of DIBAL-H (1 M in hexanes) (3.8 ml, 3.8 mmol, 2.2 equivalents) was added, and the reacting mixture was stirred at −78 °C for 2 h, then 30 min at 0 °C, and finally quenched with 2 ml of EtOAc. The mixture was then diluted with 100 ml Et_2O, warmed to r.t. and 10 g of silica gel were added. The resulting suspension was vigorously stirred for 6 h, and then filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (Et_2O–pet. ether 2:98) yielded 284 mg (59%) of aldehyde **5** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.56 (s, 1H), 5.58 (d, 1H, $J = 15.2$ Hz), 5.43 (dq, 1H, $J = 15.2$, 6.4 Hz), 1.88–1.58 (m, 3H), 1.68 (dd, 3H, $J = 6.4$, 0.7 Hz), 1.35–1.22 (m, 3H), 1.02, 0.99 (2s, 6H), 0.87 (t, 3H, $J = 7.1$ Hz), 0.15 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ (ppm) 205.0, 136.7, 123.4, 87.8, 43.3, 31.6, 26.2, 23.1, 23.0, 18.2, 13.9, 2.8.

IR (film): ν 2960, 1734, 1468, 1380, 1248, 1159, 1086 cm^{-1}.

MS (IC, NH_3): m/z 288 (MNH_4^+), 271 (MH^+), 253, 241, 181.

2.3. 4-Butyl-4-(1,1-dimethyl-but-2-enyl)-5-(6-methyl-vinylcyclohex-1-enyl)-[1,3]dioxolan-2-one (**6a**)

To a solution of triisopropylbenzenesulfonylhydrazone derived form 2-methyl-2-vinylcyclohexanone (75 mg, 180 μmol) in 1 ml of THF at −78 °C was added dropwise over 3 min a *t*-BuLi solution (1.7 M in C_6H_{14}, 220 μl, 400 μmol, 2.2 equivalents). The resulting red solution was stirred at −78 °C for 20 min, during which time it turned dark red. Temperature was then quickly raised to 0 °C for 1 min causing intense bubbling and decoloration to light yellow, then set back down to −78 °C. A solution of aldehyde **5** (55 mg, 200 μmol, 1.1 equivalents) in 0.5 ml of THF was then added via cannula to the vinyl anion solution prepared above, and the resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was then quenched at −78 °C by 5 ml of a saturated aq. $NaHCO_3$ solution and allowed to warm to r.t., then diluted with ether (50 ml). The layers were separated, and the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product was diluted with 2 ml of CH_2Cl_2 and four drops of trifluoroacetic acid were added. The solution turned yellow and was stirred at r.t. for 5 min, after which time it was concentrated in vacuo. The crude product was then diluted in dry DMF (1 ml), and NaH was added portionwise (80% in oil, 3 mg, 380 μmol, 2.1 equivalents). The resulting suspension was vigorously stirred at r.t. for 15 min, and then carbonyldiimidazole (35 mg, 800 μmol, 5.0 equivalents) was added. The resulting mixture was stirred at r.t. for 3 h, then diluted with 50 ml of Et_2O and quenched with a saturated NH_4Cl solution (5 ml). The layers were separated, and the organic layer was washed successively with water (3 × 10 ml) and brine (10 ml), and dried over $MgSO_4$ then concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel (Et_2O–pet. ether 10:90) to give 15 mg (24%) of a 1:1 mixture of the two diastereomers of **6a** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz, *taxol numbering*): δ 5.92 (t, 0.5H, $J = 4.1$ Hz), 5.84 (t, 0.5H, $J = 3.9$ Hz), 5.74 (dd, 0.5H, $J = 17.6$, 10.6 Hz), 5.68 (dd, 0.5H, $J = 17.6$, 10.6 Hz), 5.58–5.46 (m, 2H), 5.12 (d, 0.5H, $J = 10.6$ Hz), 5.09 (d, 0.5H, $J = 10.6$ Hz), 5.01 (d, 1H, $J = 17.6$ Hz), 4.80 (s, 0.5H), 4.79 (s, 0.5H), 2.20–2.13 (m, 2H), 1.81–1.15 (m, 10H), 1.70 (d, 3H, $J = 6.4$ Hz), 1.28, 1.07, 1.06, 1.04 (4s, 9H), 0.87 (t, 1.5H, $J = 7.0$ Hz), 0.86 (t, 1.5H, $J = 7.7$ Hz).

^{13}C-NMR ($CDCl_3$, 100.6 MHz, *taxol numbering*): δ 155.7, 155.6, 145.5, 144.9, 138.6, 137.4, 134.6, 131.4, 130.1, 126.2, 125.5, 114.3, 113.7, 91.0, 90.7, 80.4, 79.5, 45.6, 45.5, 40.9, 40.2, 37.7, 37.0, 31.0, 30.7, 27.4, 27.2, 25.4, 25.2, 24.0, 23.8, 23.1, 22.7, 22.5, 21.8, 20.9, 18.2, 17.8, 13.7.

IR (film): ν 2964, 2935, 2874, 1800, 1454, 1375, 1323, 1199, 1124, 1045, 1045 cm^{-1}.

MS (IC, NH_3): m/z 364 [MNH_4^+], 349 [MH^+], 303, 285, 219, 151.

Acknowledgements

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[16] We have also shown that a fivefold increase or a decrease of the concentration is without any influence on the outcome of the reaction, when suspecting the impurity to be the dimer resulting from cross metathesis of **1a** with itself.

[17] This point has been extensively studied by Grubbs on the [**Ru**] catalyst (see Ref. [14]), and by Nolan on the [**RuIMes**] catalyst (see Ref. [2b]).