Cross Metathesis Allowing the Conversion of a Ruthenium Indenylidene Complex into Grubbs' Catalyst

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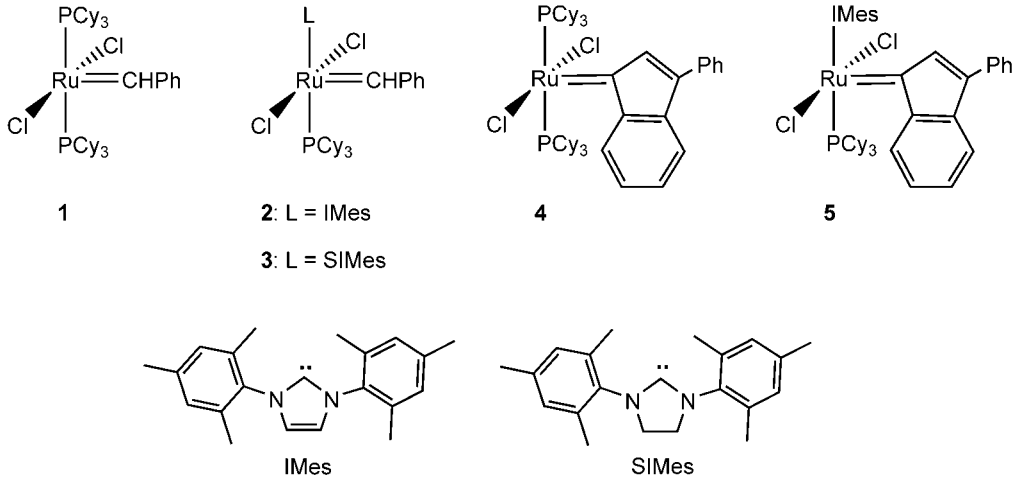
Abstract: The active metathesis catalyst $(PCy_3)_2Cl_2$Ru(3-phenylinden-1-ylidene) (**4**) was obtained in high yield using a simple one-pot procedure. The initial reaction of $RuCl_2(PPh_3)_3$ with 1,1-diphenyl-2-propyn-1-ol gave $(PPh_3)_2Cl_2$Ru(3-phenylinden-1-ylidene) (**6**). *In situ* exchange of PPh_3 with PCy_3 led to the isolation of **4** in >90% yield. Whereas complex **6** did not show any activity in the cross metathesis reaction with styrene, reaction of compound **4** with excess styrene gave Grubbs' catalyst, $(PCy_3)_2Cl_2Ru$=C(H)Ph (**1**), dichloro(phenylmethylene)bis(tricyclohexylphosphane)ruthenium(II), in nearly quantitative yield. This two-step procedure yielded complex **1** in 88% overall yield starting from inexpensive and commercially available materials. The widely used metathesis catalyst **1** was also obtained in good yield in one single step, that is, without isolation of compound **4**, making this a simple and safe synthetic route to Grubbs' catalyst.

Keywords: cross metathesis; Grubbs' catalyst; homogeneous catalysis; metal carbenes; ruthenium

The advent of well-defined, highly reactive catalysts for olefin metathesis (ring-closing metathesis, RCM; ring-opening metathesis polymerization, ROMP; cross metathesis, CM; and their combinations) has made this technique a powerful tool in organic synthesis and polymer chemistry.[1,2] Especially valuable was the introduction of late-transition metal ruthenium catalysts which display excellent tolerance towards polar functional groups.[3] Several modifications of the original catalyst precursor $(PCy_3)_2Cl_2Ru$=C(H)Ph [**1**, Grubbs' catalyst, dichloro(phenylmethylene)bis(tricyclohexylphosphane)-ruthenium(II)],[4] have appeared in the last decade. These include highly active and stable 'second-generation' catalysts, modified with *N*-heterocyclic carbenes, such as $(PCy_3)(IMes)Cl_2Ru$=C(H)Ph (**2**),[5] and (PCy_3)-$(SIMes)Cl_2Ru$=C(H)Ph (**3**),[6] [IMes = 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene; SIMes = 1,3-bis(2,4,6-trimethylphenyl)tetrahydroimidazol-2-ylidene]. We have also shown that complexes of unsaturated "C_α" ligands other than these alkylidenes such as $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (**4**) and $(PCy_3)(IMes)Cl_2Ru$(3-phenylinden-1-ylidene) (**5**) are active catalyst precursors in the ring-closing metathesis of dienes (Scheme 1).[7]



Scheme 1.

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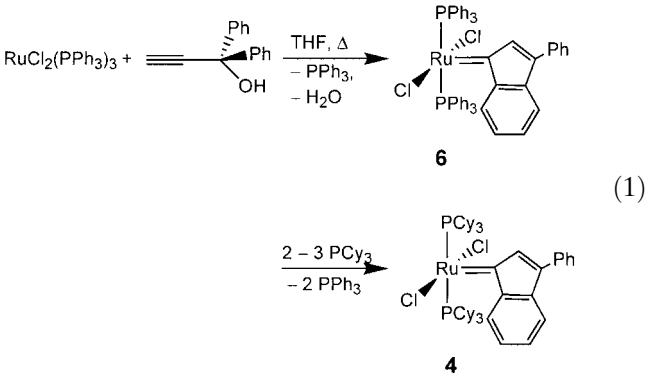
The major drawback of the highly popular complexes **1**, **2** and **3** are the synthetic procedures available for their synthesis. In the most widely used preparation route, complexes **1**–**3** are synthesized by reaction of the inexpensive and commercially available $RuCl_2(PPh_3)_3$ with a diazo compound. However, the instability of diazo compounds and safety issues associated with handling the diazo compounds leaves room for improvement. An alternative method using *in situ* generated sulfur ylides as carbenoid precursors has appeared recently.[8]

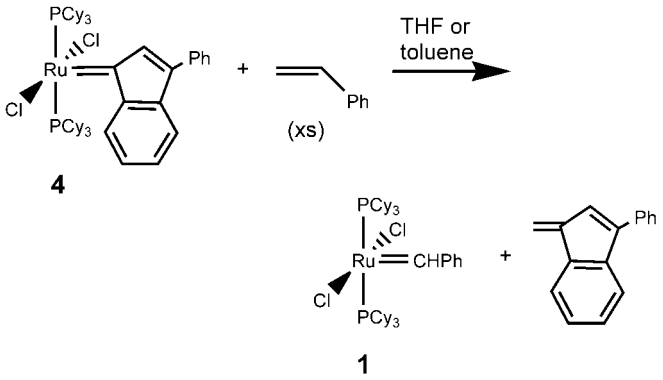
Here, we present an alternative synthetic route leading to complex **1** in high yield starting from $RuCl_2(PPh_3)_3$, PCy_3, a commercially available alkynol and styrene. For this, we capitalize on the activity of the indenylidene complex **4** which, through a cross metathesis reaction, yields the desired compound $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (**1**). The present study also shows that the active metathesis catalyst **4** can be obtained in high yield in a single synthetic step.

The phenylindenyl complex **4** has been synthesized in the past using a two-step procedure. The first step consists of reacting 1,1-diphenyl-2-propyn-1-ol with $RuCl_2(PPh_3)_3$ in refluxing THF and results in the formation of $(PPh_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (**6**) according to Eq. (1).[9] The second step involves a simple ligand substitution of PPh_3 with PCy_3 in CH_2Cl_2 and gives complex **4** in 80% overall yield. We wanted to devise a simpler, one-pot method to the catalytically active compound **4**. Indeed, when the reaction mixture in THF is treated directly with a slight excess of PCy_3 (2.7 equivs.), clean formation of **4** was detected as shown by ^{31}P NMR spectroscopy. Subsequent work-up yielded pure complex **4** in 90–95% yield. As confirmed by ^{31}P NMR, a single signal for the two equivalent phosphine ligands is observed at 34.30 ppm. ^1H NMR data are in accord with the reported chemical shift values for **4**.



(1)

Next, the feasibility of the cross-metathesis of compound **4** with styrene was examined, a reaction that would lead to complex **1** according to Eq. (2). Therefore, we performed small-scale experiments using complex **4** in the presence of 20 equivs. of styrene in either THF or toluene solutions.



(2)

The mixture was vigorously stirred at room temperature, the appearance of product **1** was followed by ^{31}P NMR. Both solvents showed the reaction to proceed in nearly identical reaction times, with completion of the reaction in one day (see Table 1 and Experimental Section). This is somewhat surprising and indicates no effective binding of THF to the catalytically active monophosphine species.[10] Substantially longer reaction times, both in THF and toluene, were observed in the presence of 5 or 10 equivs. of styrene under the same reaction conditions. Complex **6** did not show any activity in this cross metathesis reaction. Surprisingly, the indenylidene complexes with either IMes, $[(PCy_3)(IMes)Cl_2Ru$(3-phenylinden-1-ylidene)] (**5**), or SIMes, $[(PCy_3)$-$(SIMes)Cl_2Ru$(3-phenylinden-1-ylidene)] (**7**), did not show good reactivity toward the cross metathesis with styrene. Interestingly, clean formation of complex **1** was observed after only 90 min when a THF solution containing **4** and 20 equivs. of styrene were heated under an argon flow (oil bath temperature; 70 °C). Although complex **1** is notoriously unstable at high temperature, no decomposition was observed under these conditions.[11] We believe that the excess styrene present in the cross-metathesis reaction efficiently retards decomposition of complex **1**. Using this reaction protocol on a preparative scale with subsequent work-up in pentane led to the isolation of Grubbs' catalyst (**1**) in nearly quantitative yield (96%) starting from complex **4**. Overall, this two-step procedure involving commercially available materials [i.e., $RuCl_2(PPh_3)_3$, 1,1-diphenyl-2-propyn-1-ol, styrene] gave complex **1** in 88% overall yield.

Finally, we wanted to examine the feasibility of the cross-metathesis reaction when excess phosphine was present in the reaction mixture, as would be the case in a one-pot synthesis of **1** starting directly from $RuCl_2(PPh_3)_3$. For this purpose, we reacted compound **4** with excess styrene (20 equivs.) in the presence of either 2 equivs. PPh_3 or 2 equivs. PCy_3. The results of this series of experiments are listed in Table 1 (Experimental Section, entries 4 and 5) and show that while PPh_3 retards

the reaction, the presence of 2 equivs. of free PCy_3 completely shuts down the activity of **4**.[1b] These experiments encouraged us to attempt the preparation of **1** in a one-step preparative scale (1 gram) by slightly modifying our reaction conditions. Phosphine exchange was performed using only 2.05 equivs. of PCy_3 (instead of 2.7 equivs.). Due to the presence of free phosphine ligands, (3 equivs. PPh_3, 0.05 equivs. PCy_3) the cross-metathesis reaction required 3 h at 70 °C to reach completion, as monitored by ^{31}P NMR. In addition, more styrene was added during the transformation in order to accelerate the reaction and prevent decomposition of **1** (see above). Despite the fact that some of the compound was lost during work-up (mostly because of the presence of several organic byproducts), $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (**1**) was recovered in 80% overall yield. Spectroscopic data (^1H and ^{31}P NMR) of the purple compound confirmed the clean formation of Grubbs' catalyst.

In summary, a new, synthetically simple and safe method for the synthesis of the widely used metathesis catalyst $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (**1**, Grubbs' catalyst) is described. The method involves reaction of $RuCl_2(PPh_3)_3$ with commercially available 1,1-diphenyl-2-propyn-1-ol in a THF solution, *in situ* substitution of the PPh_3 ligands by PCy_3 and subsequent cross-metathesis of the indenylidene compound **4** with excess styrene. The procedure may be performed in a single step or alternatively, using a two-step procedure with isolation of compound **4**. Both methods yield the desired complex $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (**1**) in good yield and high purity. The described method appears to be general, allowing the synthesis of various alkylidenes. These and related experiments are currently ongoing in our laboratories.

Experimental Section

General Remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of dry argon or in an MBraun glovebox containing dry argon. Solvents were distilled from appropriate drying agents or were passed through an alumina column in an MBraun solvent purification system. Other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Solvents for NMR spectroscopy were degassed with argon and dried over molecular sieves. 1,1-Diphenyl-2-propyn-1-ol (Aldrich, 99%) and $RuCl_2(PPh_3)_3$ (Strem, 99%) were used as received. Styrene (Fluka, 99%) was degassed and kept in the freezer (−50 °C). Complexes $(PCy_3)(IMes)Cl_2Ru$(3-phenylinden-1-ylidene) (**5**) and $(PCy_3)(SIMes)Cl_2Ru$(3-phenylinden-1-ylidene) (**7**) were synthesized according to published procedures.[7] NMR spectra were recorded on a 400 MHz Varian Gemini spectrometer.

Synthesis of $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (4) from $RuCl_2(PPh_3)_3$

$RuCl_2(PPh_3)_3$ (5.00 g, 5.215 mmol) and 1,1-diphenyl-2-propyn-1-ol (1.63 g, 7.823 mmol) were dissolved in THF (170 mL) and the red solution was heated at reflux for 3 h. Subsequently, the solution was cooled to room temperature, PCy_3 (3.95 g, 14.081 mmol) was added as a solid and the reaction mixture was stirred overnight at room temperature. The volatiles were removed, the sticky red solid suspended in diethyl ether (100 mL) and stirred for an additional 15 min. The suspension was filtered; the filtrate was washed with diethyl ether (2 × 5 mL) and pentane (2 × 5 mL) and dried under vacuum giving the product as a brick-red solid. An additional crop of product was obtained by cooling the mother liquor in the freezer (−50 °C) overnight, filtering the precipitate formed and washing with cold pentane (2 × 10 mL). Overall yield: 4.43 g (92%). ^{31}P and ^1H NMR (C_6D_6) showed clean formation of $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (**4**).

Synthesis of $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (1) from $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (4)

A THF solution (60 mL) containing $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (**4**, 539 mg, 0.583 mmol) was heated under argon (oil bath temperature: 70 °C) with stirring. After 5 min, styrene (1.34 mL, 11.665 mmol) was added *via* syringe and the red solution was stirred at 70 °C under argon for 100 minutes. During this time, the Schlenk flask was purged 4 times by applying vacuum for 1 second. Subsequently, the volatiles were removed under vacuum. The solid was suspended in pentane (70 mL), stirred for 10 min, concentrated to 30 mL and put into the freezer for 1 hour (−50 °C). The purple precipitate was filtered, washed with cold pentane (−50 °C, 2 × 10 mL) and dried under vacuum. Yield: 459 mg (96%). ^{31}P and ^1H NMR (C_6D_6) showed clean formation of $(PCy_3)_2Cl_2Ru[{=}C(H)Ph]$ (**1**).

Table 1. *In situ* follow-up by ^{31}P NMR of the formation of $(PCy_3)_2Cl_2Ru[{=}C(H)Ph]$ (**1**) from **4** [conditions: **4** (100 mg), styrene (20 equivs.), solvent (10 mL)].

Entry	Solvent	Added PR_3	T [°C]	Conversion at 1.5 h	Conversion at 3.5 h	Conversion at 7 h	Conversion at 24 h
1	Toluene	–	rt	16%	25%	40%	100%
2	THF	–	rt	14%	21%	35%	100%
3	THF	–	70	100%	–	–	–
4	THF	2 PPh_3	70	72%	100%	–	–
5	THF	2 PCy_3	70	<5%	<10%	<10%	–

Synthesis of $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (1) from $RuCl_2(PPh_3)_3$.

$RuCl_2(PPh_3)_3$ (1000 mg, 1.043 mmol) and 1,1-diphenyl-2-propyn-1-ol (282 mg, 1.356 mmol) were dissolved in THF (50 mL) and the red solution was heated at reflux for 3 h. Subsequently, the solution was cooled to room temperature, PCy_3 (600 mg, 2.138 mmol) was added as a solid and the reaction mixture was stirred overnight at room temperature. Styrene (2.39 mL, 20.86 mmol) was added *via* syringe and the reaction mixture was heated under argon (oil bath temperature: 70 °C) with stirring. In the course of the reaction additional styrene was added after one hour and again after two hours (2.39 mL each). Completion of the reaction was observed after 3 h. During this time, the Schlenk flask was purged every 30 min by applying vacuum for 1 second. Subsequently, the volatiles were removed under vacuum leaving a sticky dark-red solid. The solid was suspended in an acetone/pentane mixture (1:10; 150 mL overall), stirred for 10 min, concentrated to 50 mL and put into the freezer for 3 hours (− 50 °C). The purple precipitate was filtered, washed with cold pentane and acetone (− 50 °C, 2 × 5 mL each) and dried under vacuum. An additional crop of product was obtained by leaving the mother liquor in the freezer (− 50 °C) overnight, filtering the precipitate formed and washing with cold pentane (2 × 5 mL). Overall yield: 686 mg (80%). ^{31}P and ^{1}H NMR (C_6D_6) showed clean formation of $(PCy_3)_2Cl_2Ru{=}C(H)Ph$ (**1**).

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[10] ^{31}P NMR showed no peak for free phosphine during the transformation indicating that dissociation/association of phosphine is too fast for detection by NMR spectroscopy.

[11] Formation of a black precipitate, probably containing metallic ruthenium, was observed when heating the solution for more than 2 hours.

