

Non-Metathetic Behavior Patterns of Grubbs' Carbene

Benito Alcaide*^[a] and Pedro Almendros*^[b]

Abstract: Grubbs' carbene complex $[\text{Cl}_2(\text{Cy}_3\text{P})_2\text{Ru}=\text{CHPh}]$ and its second-generation counterpart $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$ have demonstrated remarkable efficiency metathesizing olefins. Furthermore, a growing number of newly discovered catalytic processes mediated by this complex broaden its synthetic utility beyond olefin metathesis. In addition, the ready availability of these stable ruthenium-based catalysts coupled with their tolerance toward a wide variety of common functional groups make Grubbs' catalysts very convenient synthetic tools. This paper presents recent advances in the non-metathetic behavior patterns of Grubbs' carbene.

Keywords: carbenes • heterogeneous catalysis • metathesis • ruthenium • synthetic methods

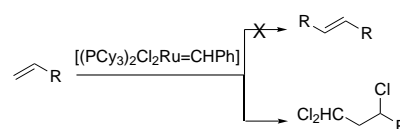
Introduction

The area of metal-catalyzed olefin metathesis reactions is a remarkable topic in current chemistry because of its relevance as an efficient and elegant method to form carbon-carbon double bonds.^[1] Over the past decade, well-defined ruthenium-based catalysts have been developed which combine high activity and excellent tolerance to many common functional groups. Grubbs et al. introduced the first such catalyst with the general formula $[(\text{PR}_3)_2\text{X}_2\text{Ru}=\text{CHR}]$,^[2] the most prominent example being $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ (**1**).^[3] The replacement of one trialkylphosphane ligand by an N-heterocyclic carbene (NHC) has led to a new class of metathesis catalysts with the general formula $[(\text{PR}_3)(\text{NHC})\text{X}_2\text{Ru}=\text{CHR}]$ which are even more active than the original Grubbs

complexes; the most representative of these second-generation compounds is the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (Im) substituted ruthenium-based catalyst $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$ (**2**).^[4] Furthermore, a growing number of newly discovered catalytic processes mediated by Grubbs' carbene complex broaden its synthetic utility beyond olefin metathesis. The aim of this concept article is to summarize these advances, with special focus on practical concerns.

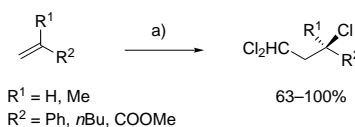
Discussion

Snapper et al. reported in 1999 that the classical Grubbs' ruthenium benzylidene complex $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ catalyzes the chemo- and regioselective addition of chloroform across mono- and 1,1-disubstituted olefins.^[5] In fact, during an investigation on cross-metathesis, they isolated a product derived not from olefin metathesis but from a metal-catalyzed addition of CHCl_3 across an alkene (Scheme 1).



Scheme 1. New reactivity of Grubbs' ruthenium benzylidene complex as catalyst for Kharasch addition.

In comparison to previously described ruthenium-based Kharasch catalysts, the mild conditions under which Grubbs' carbene affects the addition of CHCl_3 are particularly noteworthy (Scheme 2). The ability of Grubbs' carbene to catalyze the Kharasch addition of CHCl_3 across various olefins was contrasted to the known catalyst $[\text{Cl}_2\text{Ru}(\text{PPh}_3)_3]$. While higher temperatures ($> 120^\circ\text{C}$) and prolonged reaction times



Scheme 2. Grubbs' carbene as mild catalyst for the metal-promoted addition of CHCl_3 across alkenes. a) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, CHCl_3 , $45-65^\circ\text{C}$, 2–12 h.

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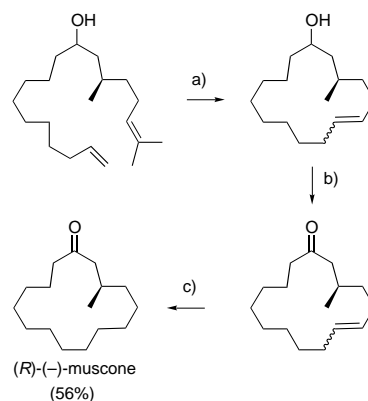
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(> 8 h) were usually required under $[\text{Cl}_2\text{Ru}(\text{PPh}_3)_3]$ catalysis, exposure of styrene to CHCl_3 in the presence of $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ for only 2 h at 65°C resulted in a quantitative yield of Kharasch product. The same reaction conditions with $[\text{Cl}_2\text{Ru}(\text{PPh}_3)_3]$ provided <5% of the addition product. However, it was noted that in CHCl_3 under Grubbs' carbene catalysis, readily metathesizable olefins, such as unhindered alkenes, are susceptible to both reactions pathways. Whereas the specific structures and events in the catalytic cycle are unclear for alkylidene complex **1**, some experiments support the ruthenium-mediated radical nature of the reaction.

The ability to control molecular architecture constitutes a major challenge for synthetic polymer chemistry. Transition metal species have been introduced in controlled radical polymerization systems, a methodology which goes by the name of atom transfer radical polymerization (ATRP). Demonceau et al. tested Grubbs' carbene as a catalyst for the ATRP of methyl methacrylate in the presence of ethyl 2-bromo-2-methylpropionate as the polymerization initiator.^[6, 7] Complex **1** was found to be even more active ($k_{\text{app}} = 1.95 \times 10^{-4} \text{ s}^{-1}$) than the exceptionally efficient $[\text{RuCl}_2(p\text{-cymene})(\text{PCy}_3)]$ ($k_{\text{app}} = 1.05 \times 10^{-4} \text{ s}^{-1}$), $[\text{RuCl}_2(p\text{-cymene})(\text{P}i\text{Pr}_3)]$ ($k_{\text{app}} = 5.65 \times 10^{-5} \text{ s}^{-1}$), or $[\text{RuCl}_2(p\text{-cymene})(\text{PPhCy}_2)]$ ($k_{\text{app}} = 5.2 \times 10^{-5} \text{ s}^{-1}$), but to the detriment of polymer control ($M_w/M_n = 1.28$; $f = 0.60$).^[7]

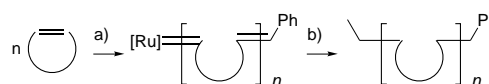
It has been reported that complex **1**, or its more active second generation imidazolidine derivative **2**, is also useful mediating a variety of catalytic hydrogenation reactions that include regiospecific ketone and olefin reductions, transfer hydrogenations of ketones, and dehydrogenative oxidations of alcohols.^[8] As synthetic application of these catalytic reactions outlined above, a one-pot tandem metathesis transfer dehydrogenation–hydrogenation procedure was developed and used for the total synthesis of the natural product (*R*)-(-)-muscone in 56% overall yield from the acyclic precursor (Scheme 3).^[8]

Ring-opening metathesis polymerization (ROMP) of cycloolefins, followed by hydrogenation, enables synthesis of high-molecular-weight, narrow-polydispersity polyolefins with desirable optical characteristics. It has been reported recently a tandem ROMP-hydrogenation via a single Ru precursor, namely complex **1**, permitting catalytic reduction of ROMP polymers under exceptionally mild, homogeneous conditions (1 atm of H_2 , 60°C). Repeated catalyst cycling between



Scheme 3. A one-pot/three-step synthesis of (*R*)-(-)-muscone catalyzed by the second generation Grubbs' carbene. a) $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 40°C . b) NaOH , 3-pentanone, 80°C . c) H_2 , 70°C .

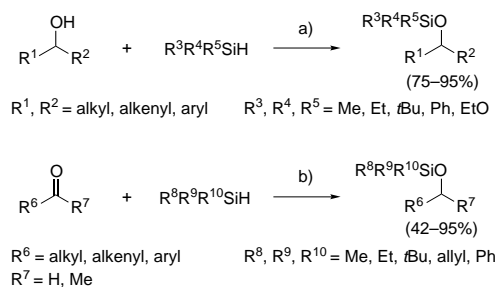
metathesis and hydrogenation chemistry is effected in a one-pot procedure (Scheme 4).^[9]



Scheme 4. Grubbs' carbene-catalyzed tandem ROMP-hydrogenation. a) $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$, CH_2Cl_2 , RT. b) Et_3N , 1 atm of H_2 , 60°C .

Silyl ethers comprise one of the most widely used classes of protecting groups in synthetic chemistry. Although the conventional silylation procedure is straightforward and dependable, it usually needs environmentally undesirable solvents such as CH_2Cl_2 and DMF as well as excess of amine bases. In this context, it has been recently reported a greener methodology to silyl ethers promoted by complex **1**. On investigating the activation of silicon-hydrogen bonds by a variety of transition metal complexes, Lee et al. found that Grubbs' carbene is an effective catalyst for the condensation of alcohols and silanes, showing no indication of competing olefin metathesis even with a terminal alkene.^[10] In addition to the above dehydrogenative condensation, the same authors described the ability of $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ to accomplish the hydrosilylation of carbonyls (Scheme 5). Silanes in both hydrosilylation and dehydrogenative condensation reactions showed similar reactivity profiles. In general, dialkyl aryl and

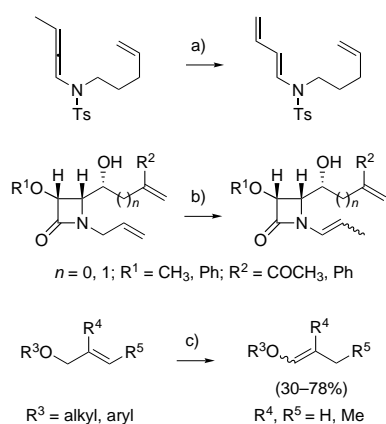
Abstract in Spanish: *El carbeno de Grubbs $[\text{Cl}_2(\text{Cy}_3\text{P})_2\text{Ru}=\text{CHPh}]$ y su homólogo de segunda generación $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$ han demostrado una elevada efectividad en la metátesis de olefinas. Además, el descubrimiento de un amplio abanico de nuevos procesos catalíticos inducidos por este complejo ha traspasado su utilidad sintética más allá de la metátesis de olefinas. La asequibilidad y estabilidad de este catalizador de rutenio unidas a su compatibilidad con los grupos funcionales más comunes, convierten al carbeno de Grubbs en una herramienta sintética muy útil. Este artículo recoge avances recientes acerca de comportamientos no metatéticos del carbeno de Grubbs.*



Scheme 5. Activation of silanes by Grubbs' carbene: dehydrogenative condensation of alcohols and hydrosilylation of carbonyls. a) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, $25\text{--}55^\circ\text{C}$, neat. b) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, $50\text{--}80^\circ\text{C}$, neat.

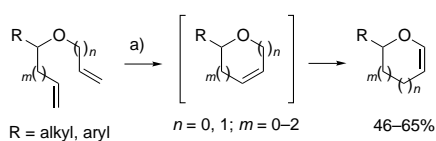
alkyl diaryl silanes react more efficiently than either trialkyl or trialkoxy silanes.

Grubbs' carbenes **1** and **2** must be added to the list of various metal complexes which act as efficient catalysts for the isomerization of unsaturated oxygen and nitrogen containing compounds. Rutjes et al. encountered an interesting ruthenium-induced isomerization of allenamides to dienamides catalyzed by complex **2** (Scheme 6) in the ring-closing metathesis reactions of olefin containing-enamides.^[11] In a different study, it has been outlined that in some cases the isomerization to the internal double bond in a N-allyl β -lactam is favored versus ring-closing metathesis under Grubbs' carbene catalysis (Scheme 6).^[12] Similarly, Cossy et al. reported in 2002 that the second-generation Grubbs' carbene **2** mediates efficiently the isomerization of β,γ -unsaturated ethers to the corresponding vinyl ethers (Scheme 6).^[13]



Scheme 6. Grubbs' catalyst-promoted isomerization of allenamides, allylamides, and allyl ethers. a) $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$, ethylene dichloride, 84 °C. b) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, CH_2Cl_2 , 40 °C. c) $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$, CH_2Cl_2 , RT.

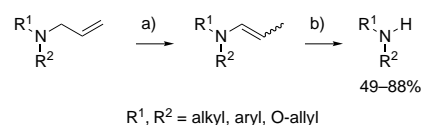
Snapper et al. described a new preparation of cyclic enol ethers through a tandem RCM-olefin isomerization catalyzed by Grubbs' carbene **2** (Scheme 7).^[14] The authors suggested that the isomerization is sensitive to steric factors because it was unable to generate trisubstituted enol ethers.



Scheme 7. Preparation of cyclic enol ethers through a Grubbs' carbene-catalyzed tandem RCM-olefin isomerization. a) $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$, CH_2Cl_2 , 45–70 °C.

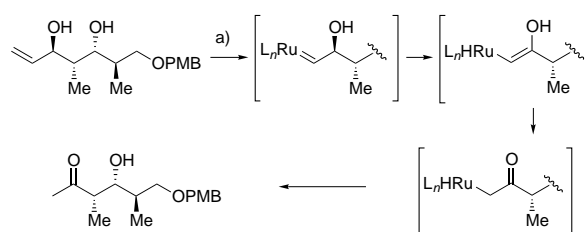
We have reported in 2001 a novel application of Grubbs' carbene **1**, namely, the first examples accounting for the catalytic deprotection of tertiary allylic amines by using reagents different from palladium catalysts.^[12] Significantly, the catalytic system directs the reaction toward the selective deprotection of allylamines in the presence of allylic ethers. This ruthenium-promoted method is more convenient, che-

moselective, and operationally simple in comparison to the conventional palladium-catalyzed method. The current mechanistic hypothesis invokes a nitrogen-assisted ruthenium-catalyzed isomerization, followed by hydrolysis of the enamine intermediate (Scheme 8).



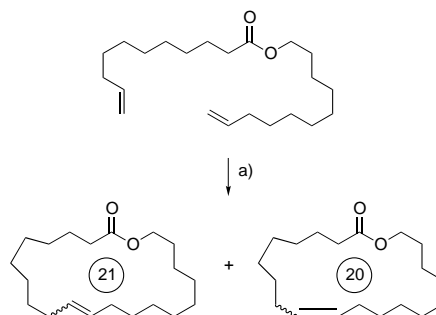
Scheme 8. Grubbs' carbene-catalyzed deprotection of allylic amines. a) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, toluene, 110 °C. b) Chromatographic workup.

Hoye and Zhao reported that alk-1-en-3-ols under exposure to complex **1** give an allylic alcohol–methyl ketone transformation.^[15] The possible intermediates accounting for this cleavage reaction are shown in Scheme 9.



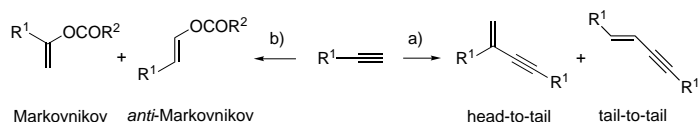
Scheme 9. Alkenol-methyl ketone transformation induced by complex **1**. a) $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$, CDCl_3 , RT.

Similar C=C bond isomerizations have been also described by Fürstner et al. for unsubstituted olefins.^[16] The authors found an intrinsic bias of a 1,22-diene for ring contraction under RCM conditions. Thus, treatment of the terminal 1,22-diene with the second generation Grubbs' carbene **2** leads to essentially complete consumption of the starting material, but yields significant amounts of the 20-membered ring in addition to the desired 21-membered lactone (Scheme 10). The 21-membered macrocycle likely results from an initial isomerization of one of the double bonds in the starting diene, followed by elimination of propene instead of ethylene during ring closure.



Scheme 10. Second-generation Grubbs' carbene-catalyzed tandem isomerization/ring contraction. a) $[\text{Cl}_2(\text{Im})(\text{Cy}_3\text{P})\text{Ru}=\text{CHPh}]$, toluene, 80 °C.

Recent research by Verpoort et al. described the catalytic activity of Grubbs' first-generation catalyst towards the dimerization, vinylation or nucleophilic attack of carboxylic acids on terminal alkynes (Scheme 11).^[17] The preference for dimerization or vinylation is strongly dependent on the nature of the terminal alkyne. Aliphatic alkynes produce only vinylation products, with a high regioselectivity for Markovnikov addition. Dimerization only takes place with a conjugate arylacetylene. In addition, the acidity of the carboxylic acid plays a key role in the preference of terminal alkynes towards dimerization or towards vinylation of the triple bond: vinylation is preferred at low pK_a , but at increasing pK_a the selectivity changes towards the formation of dimeric products.



Scheme 11. Vinylation or dimerization on terminal alkynes mediated by Grubbs' catalyst. a) $[\text{PCy}_3]_2\text{Cl}_2\text{Ru}=\text{CHPh}$, toluene, 110°C . b) $[\text{PCy}_3]_2\text{Cl}_2\text{Ru}=\text{CHPh}$, $\text{R}^2\text{-COOH}$, toluene, 110°C .

Conclusion

The metathetic ability of Grubbs' ruthenium-based catalyst is known for a decade and extensive studies have been devoted over these years. However, non-metathetic behavior patterns have appeared very recently that deserves special attention.^[18] Complex **1** has been shown to catalyze the Kharasch addition, the removal of allyl groups from amines, the atom transfer radical polymerization, the hydrogenation of olefins, the transfer hydrogenation of ketones, the dehydrogenative oxidation of alcohols, the dehydrogenative condensation of alcohols, and the hydrosilylation of carbonyls. Therefore, this growing number of newly discovered catalytic processes mediated by Grubbs' carbene complex broaden its synthetic utility beyond olefin metathesis. Tuning and new uses of this ruthenium-based catalyst are likely, and will contribute to its relevance as a versatile and effective tool in organic and organometallic chemistry.

Acknowledgement

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- [1] For selected reviews, see: a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; c) M. R. Buchmeiser, *Chem. Rev.* **2000**, *100*, 1565; d) K. J. Irvin, J. C. Mol, *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Diego, **1997**; e) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem. Int. Ed.* **1997**, *36*, 2036.
- [2] S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974.
- [3] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.
- [4] M. Scholl, S. Ding, W. C. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
- [5] J. A. Tallarico, L. A. Malnick, M. L. Snapper, *J. Org. Chem.* **1999**, *64*, 344.
- [6] a) F. Simal, A. Demonceau, A. F. Noels, *Angew. Chem.* **1999**, *111*, 559; *Angew. Chem. Int. Ed.* **1999**, *38*, 538; b) F. Simal, S. Delfosse, A. Demonceau, A. F. Noels, K. Denk, F. J. Kohl, T. Weskamp, W. A. Herrmann, *Chem. Eur. J.* **2002**, *8*, 3047.
- [7] Grubbs et al. prepared a new difunctional ruthenium complex from $[(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}]$ and allyl 2-bromo-2-methylpropionate which was able to mediate both ring-opening metathesis polymerization (ROMP) and ATRP simultaneously. This domino reaction afforded well-defined block copolymers. See: C. W. Bielawski, J. Louie, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 12872.
- [8] J. Louie, C. W. Bielawski, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 11312.
- [9] S. D. Drouin, F. Zamanian, D. E. Fogg, *Organometallics* **2001**, *20*, 5495.
- [10] S. V. Maifeld, R. L. Miller, D. Lee, *Tetrahedron Lett.* **2002**, *43*, 6363.
- [11] S. S. Kinderman, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045.
- [12] B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Org. Lett.* **2001**, *3*, 3781.
- [13] C. Cadot, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2002**, *43*, 1839.
- [14] A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390.
- [15] T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 169.
- [16] A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204.
- [17] K. Melis, T. Opstal, F. Verpoort, *Eur. J. Org. Chem.* **2002**, 3779.
- [18] For a recent review on non-metathetical transformations of organic substrates catalyzed by various ruthenium complexes, see: B. M. Trost, D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.