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Ruthenium Carbene Complexes with *N*,*N*′-Bis(mesityl)imidazol-2-ylidene Ligands: RCM Catalysts of Extended Scope

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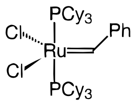
The ruthenium carbene complexes **3a**,**b** bearing imidazol-2-ylidene ligands constitute excellent precatalysts for ring-closing metathesis (RCM) reactions allowing the formation of tri- and tetrasubstituted cycloalkenes. They also apply to annulations that are beyond the scope of the standard Grubbs carbene **1** as well as to ring-closing reactions of acrylic acid derivatives even if the resulting α,*β*-unsaturated lactones (or lactams) are tri- or tetrasubstituted. The reactivity of **3a** was found to be highly dependent on the reaction medium: particularly high reaction rates are observed in toluene, although this solvent also leads to an increased tendency of the catalyst to isomerize the double bonds of the substrates.

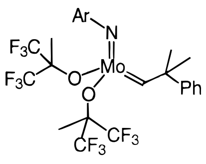
Introduction

The ruthenium carbene $(PCy_3)_2Cl_2Ru{=}CHPh$ **1** and derivatives thereof developed by Grubbs et al. set the standard in the field of olefin metathesis and have rapidly evolved into versatile and reliable tools for advanced organic chemistry.[1,2] They exhibit a remarkably wide scope and are distinguished by an excellent compatibility with many functional groups. Among the few limitations that infringe upon this superb overall application profile, the limited thermal stability of **1** and its sensitivity toward the substitution pattern of the substrates are most noteworthy. Specifically, this complex mediates the formation of trisubstituted olefins by ring-closing metathesis (RCM) only in special cases and usually fails for tetrasubstituted ones.[3]

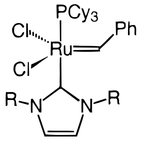
A very recent development, however, promises to fill this gap. Thus, replacement of one of the PCy_3 groups of **1** by sterically encumbered N,N′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene ligands (or their fully saturated analogues)[4] does not only impart a significantly increased stability of the active species in solution but also seems to bring more highly substituted products within reach.[5,6,7] All examples reported so far are highly promising; a final conclusion, however, cannot yet be drawn since the number of applications is still rather limited. Therefore, we undertook a more comprehensive investigation of this important facet, which is summarized below. It corroborates the notion that the benzylidene carbene complex **3a** and its phenylindenylidene analogue **3b** represent RCM catalysts of extended scope that apply to many ring-closure reactions that cannot be effected by **1** itself and that have therefore been a domain of the more active but quite sensitive Schrock alkylidene catalyst **2**.[8]



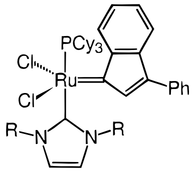
1



2



3a



3b

Results and Discussion

During the course of our investigation, we noticed a pronounced solvent dependence of the reactivity of complex **3a** (R = mesityl) (originally and almost simultaneously described by the groups of Nolan and Grubbs).[5,6] As can be seen from the results compiled in Schemes 1 and 2, reactions in toluene are substantially faster than those in CH_2Cl_2, and this increased activity is not simply an effect of the higher reaction temperature in this medium. Specifically, the tetrasubstituted cyclohexene derivative **5** (which cannot be obtained with the parent Grubbs catalyst **1**) is formed in essentially quantitative yield after only 15 min (!) if the reaction is carried out in toluene. The reaction requires 2−3 h in CH_2Cl_2 solution to reach completion. This striking influence of the medium has only been observed for the ruthenium

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(1) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

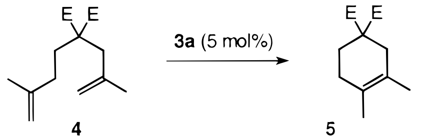
(2) For recent reviews see the following for leading references: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(3) For a detailed study on the effects of substitution on RCM, see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(4) Review on N-heterocyclic carbenes: Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162.

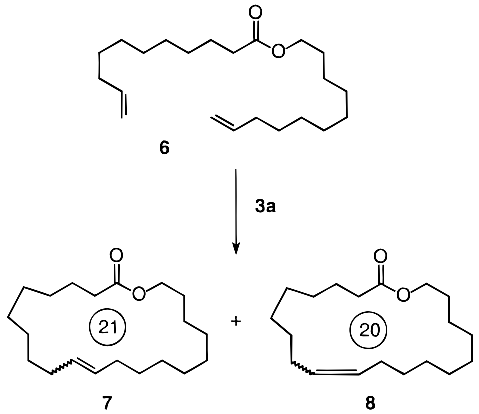
10.1021/jo9918504 CCC: $19.00

Scheme 1



CH_2Cl_2	40°C	60 min	54%
toluene	80°C	15 min	98%

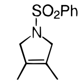
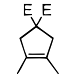
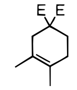
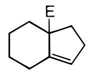
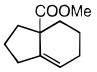
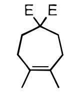
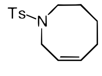
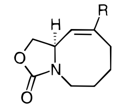
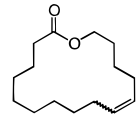
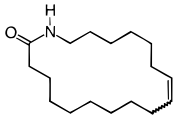
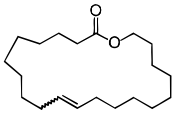
Scheme 2



Solvent	T (°C)	Catalyst (mol%)	t (h)	GC 7	GC 8
toluene	80	1.2	0.8	67	12
toluene	40	1.2	6.5	65	10
CH_2Cl_2	40	4	23	71[a]	2
$ClCH_2CH_2Cl$	80	1.2	12	23	2

[a] Isolated Yield

Table 1. RCM Catalyzed by 3a,b in Refluxing CH_2Cl_2 (E = COOEt)

Entry	Product		Catalyst (mol%)	Yield (%)[a]
1		14	**3a** (2.5%)	96[b]
2			**3b** (2.5%)	97[b]
3		15	**3a** (8%)	77[b]
4		5	**3b** (2.5%)	89[b]
5		16	**3a** (5%)	98
6		17	**3a** (5%)	93
7		18	**3b** (5%)	71
8		19	**3a** (1%)	64
9		20a	**3a** (1%)	62 (R = H)
10		20b	**3a** (5%)	95 (R = Me)
11		21	**3a** (2%)	72
12		22	**3a** (3%)	82
13		7	**3a** (4%)	71

[a] Isolated yield. [b] The reaction was carried out in toluene at 80 °C.

carbene complexes bearing *N-mesityl* substituents on their imidazol-2-ylidene ligands. Related complexes with *N*-cyclohexyl or *N*-isopropyl groups do not show this effect.[7] Unfortunately, however, this unprecedented reactivity of **3a** in toluene is impaired by a pronounced tendency of the active species to isomerize the double bonds of the substrate. Thus, treatment of diene **6** with as little as 1.2 mol % of **3a** in toluene leads to essentially complete consumption of the starting material within 45 min[9] but delivers significant amounts of the 20-membered ring **8** in addition to the desired 21-membered lactone **7** (Scheme 2). Compound **8** likely results from an initial isomerization of one of the double bonds in **6** followed by elimination of propene instead of ethylene during ring closure.[10] This intrinsic bias for ring contraction cannot be suppressed by lowering the reaction temperature. In stark contrast, however, only minute amounts of **8** are detected if the reaction is performed in CH_2Cl_2.

As can be seen from the results compiled in Table 1, the reactivity of **3a**,**b** in CH_2Cl_2 is sufficiently high to allow the preparation of di-, tri-, and even tetrasubstituted cycloalkenes in good to excellent yields. All ring sizes including medium and macrocyclic ones can be accessed. Note that most of these cyclizations cannot be effected if carbene **1** is used as the catalyst. This holds true for *all* tetrasubstituted cases (entries 1−4 and 7), the trisubstituted eight-membered ring **20b** shown in entry 10, as well as for annulation reactions depicted in entries 5 and 6. Although the macrocyclic products

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(5) For R = mesityl see ref 6 and the following paper: Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(6) For R = mesityl see ref 5 and the following paper: (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. For "saturated" carbene analogues thereof see: (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

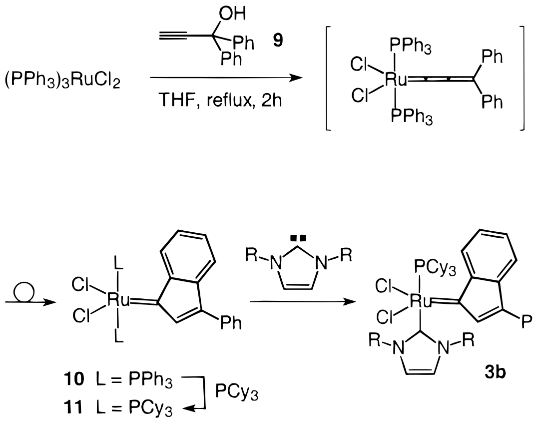
(7) For R = isopropyl, cyclohexyl, −CHMePh, −CHMe(naphthyl), and mesityl, see: (a) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (b) Weskamp, T.; Kohl, F. J.; Gleich, D.; Herrmann, W. A. *Angew. Chem.* **1999**, *111*, 2573. (c) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron*, in press.

(8) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Review: Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1.

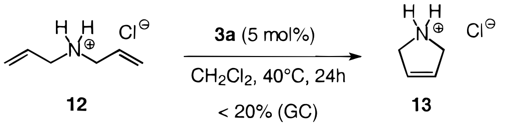
(9) Note that the same reaction catalyzed by **1** (5 mol %) requires ≥24 h!

(10) In some cases, alkene isomerizations have also been observed with more conventional catalysts, cf.: (a) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635. (b) Marciniec, B.; Foltynowicz, Z.; Lewandowski, M. *J. Mol. Catal.* **1994**, *90*, 125. (c) Thorn-Csanyi, E.; Dehmel, J.; Luginsland, H.-D.; Zilles, J. U. *J. Mol. Catal. A* **1997**, *115*, 29.

Scheme 3



Scheme 4

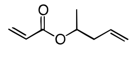
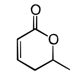
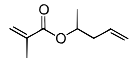
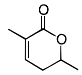
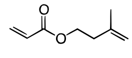
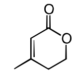
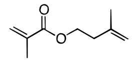
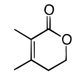
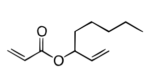
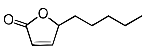
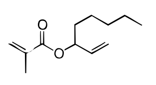
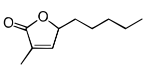
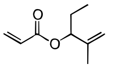
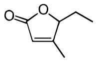
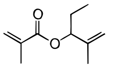
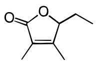
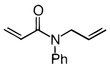
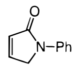
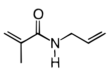
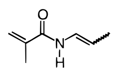
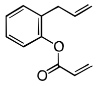
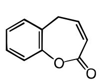
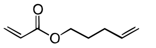
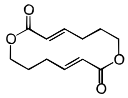
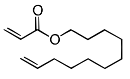
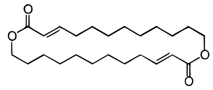


(entries 11−13) can also be obtained with **1**,[11] the use of **3a** results in shorter reaction times and/or allows us to employ lower catalyst loadings. This aspect is particularly relevant with respect to pentadec-10-enolide **21** (entry 11) which is converted into the valuable, musk-odored perfume ingredient Exaltolide (= pentadecanolide) upon simple hydrogenation.[11a,b]

As can be deduced from the results in Table 1, complex **3a** bearing a benzylidene carbene moiety and complex **3b** with a phenylindenylidene unit are essentially equipotent precatalysts. The latter compound is particularly attractive for its convenient preparation using commercially available propargyl alcohol **9** as the carbene source (Scheme 3).[12,13]

One important limitation for RCM reactions catalyzed by **3a**, however, was encountered during this investigation. All attempts to convert bisallylamine·HCl **12** into dihydropyrrole **13** resulted in low conversions, although ammonium salts were previously reported to be compatible with the standard Grubbs carbene **1** (Scheme 4).[14] We suppose that this shortcoming is caused by the increased basicity of the imidazol-2-ylidene ligand[15] as compared to that of PCy_3, which may be protonated off the metal center by the ammonium salt. NMR inspections of the crude mixture support this interpretation.

Table 2. RCM of α,β-Unsaturated Esters and Amides Catalyzed by 3a[a]

Entry	Substrate		Product		c (mmol/l)	t (h)	Yield (%)
1		**23**		**24**	20	2	95
2		**25**		**26**	20	24	79
3		**27**		**28**	100	20	73
4		**29**		**30**	100	40	42
5		**31**		**32**	20	2	93
6 7 8		**33**		**34**	40 40 40	2 2 2	92[b] 79[c] 48[d]
9		**35**		**36**	40	12	78
10		**37**		**38**	100	40	63
11		**39**		**40**	20	3	82
12		**41**		**42**	13	24	71
13		**43**		**44**	4	12	89[e,f]
14		**45**		**46**	4	1	62
15		**47**		**48**	4	3	77

[a] All reactions are carried out with 5 mol % of catalyst **3a** in toluene at 80 °C unless stated otherwise. [b] Using 5 mol % of the catalyst. [c] Using 1 mol % of the catalyst. [d] Using 0.1 mol % of the catalyst. [e] In refluxing CH_2Cl_2. [f] When carried out in toluene, the product formed is partly isomerized to the corresponding styrene derivative.

The high reactivity of **3a**,**b** allows us to overcome another limitation of the parent Grubbs carbene **1**. Electron-deficient alkenes are known to be rather poor substrates for metathesis reactions catalyzed by this complex. Although scattered reports on RCM of acrylates can be found in the literature,[16] such transformations are far from being general and often require assistance by Lewis acidic additives such as $Ti(OiPr)_4$ to reach a preparatively useful level.[17,18] To the best of our knowledge, direct formations of tri- or tetrasubstituted acrylic acid derivatives via olefin metathesis have previously not yet been accomplished.[19] As can be seen from the results

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(11) (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (c) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (d) Fürstner, A., Grabowski, J.; Lehmann, C. W. *J. Org. Chem*. **1999**, *64*, 8275. (e) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (f) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746. (g) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010. (h) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem*. **1999**, *64*, 2361. (i) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (j) Fürstner, A.; Müller, T. *J. Org. Chem*. **1998**, *63*, 424.

(12) (a) Originally it had been believed that the species formed from $(PPh_3)_3RuCl_2$ and $HC{\equiv}CCPh_2OH$ is the diphenylallenylidene complex depicted in Scheme 3, cf.: Harlow, K. J.; Hill, A. F.; Winton-Ely, J. D. E. T. *J. Chem. Soc., Dalton Trans*. **1999**, 285. More detailed studies, however, have shown that the stable product formed in this reaction is the rearranged product, i.e., the indenylidene ruthenium complex **10**, cf.: Hill, A. F.; Fürstner, A.; Liebl, M.; Mynott, R.; Gabor, B., Jafarpour, L.; Nolan, S. P. Manuscript in preparation. (b) The preparation and X-ray structure of **3b** are described in: Jafarpour, L.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5416.

(13) Fürstner, A.; Hill, A. F.; Liebl, M.; Wilton-Ely, J. D. E. T. *Chem. Commun*. **1999**, 601.

(14) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(15) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370.

compiled in Table 2, the use of the "second-generation" carbene complex **3a** allows for the first time to access di-, tri-, and even tetrasubstituted α,*β*-unsaturated lactones of ring size 5−7 in good to excellent yields. Tertiary acrylic acid amides also participate in RCM (entry 11), whereas a residual H-atom on nitrogen leads to exclusive isomerization as can be seen from entry 12. Attempts to form larger cycles, however, failed so far and resulted in the formation of the cyclic dimers **46** and **48**. The fact that each of them is obtained as a single isomer with head-to-tail connected monomer units and *E*-configurated double bonds indicates highly organized reactive intermediates along the RCM pathway. This unexpected feature is currently under investigation in our laboratory.

In summary, we have shown that the ruthenium carbene complexes **3a** and **3b** bearing *N*,*N′*-bis(mesityl)-2,3-dihydro-1*H*-imidazol-2-ylidene ligands are excellent precatalysts for RCM which are effective in many cases that are beyond the scope of the classical Grubbs carbene **1**. In particular, this refers to the preparation of tri- and tetrasubstituted cycloalkenes, RCM involving highly substituted acrylates, as well as annulation reactions. The unique combination of high activity, remarkable stability, ease of synthesis and an excellent application profile renders these compounds highly attractive for applications to advanced organic synthesis. Further studies aimed at probing the general use of these catalysts in a variety of RCM reactions are ongoing.

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Supporting Information Available: The entire Experimental Section including adequate characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For reports on RCM involving α,*β*-unsaturated carbonyl compounds see the following for leading references: (a) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem.* **1998**, *110*, 1975. (b) Krikstolaitytè, S.; Hammer, K.; Undheim, K. *Tetrahedron Lett.* **1998**, *39*, 7595. (c) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem.* **1996**, *108*, 2111. (d) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (e) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547.

(17) The beneficial effect of $Ti(OiPr)_4$ on RCM was demonstrated for the first time in: (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. Subsequently, this system turned out ot be highly useful in applications to acrylates and other handicaped cases, cf.: (b) Dirat, O.; Kouklovsky, C.; Langlois, Y.; Lesot, P.; Courtieu, J. *Tetrahedron Asymmetry* **1999**, *10*, 3197. (c) Grossmith, C. E.; Senia, F.; Wagner, J. *Synlett* **1999**, 1660. (d) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743. (e) Wipf, P.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321. (f) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199. (g) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187. (h) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (i) Ghosh, A. K.; Hussain, K. A. *Tetrahedron Lett.* **1998**, *39*, 1881.

(18) Recently, a cationic ruthenium−carbyne complex has been developed that exhibits high reactivity in cross-metathesis reactions involving acrylates;, cf.: Stuer, W.; Wolf, J.; Werner, H.; Schwab, P.; Schulz, M. *Angew. Chem.* **1998**, *110*, 3603. RCM of acrylic acid derivatives with this catalyst have not been reported.

(19) For a trisubstituted case, an indirect two-step procedure comprising RCM and allylic oxidation has recently been described, cf.: Carda, M.; Castillo, E.; Rodriguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639.