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Improvement in Olefin Metathesis Using a New Generation of Ruthenium Catalyst Bearing an Imidazolylidene Ligand: Synthesis of Heterocycles

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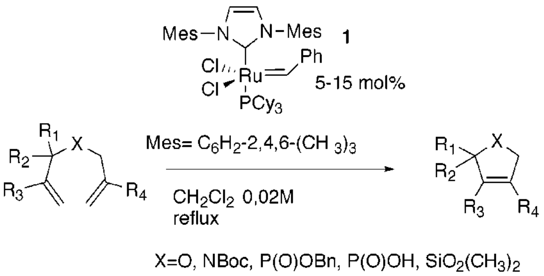
ABSTRACT



A number of heterocycles have been prepared in very good yields using 1,3-dimesitylimidazol-2-ylidene ruthenium benzylidene 1. This catalyst displays increased activity for ring-closing metathesis of some hindered heterodienes which did not cyclize using the Grubbs catalyst 2. The scope of the olefin metathesis has been expanded.

Ring-closing metathesis (RCM) has been shown to be a highly effective and practical method in organic synthesis. It has emerged as an efficient strategy to prepare, usually in excellent yields, various functionalized carbocycles and heterocycles from acyclic dienes precursors.[1] This success hinges on the development of stable metal carbenes as olefin metathesis catalysts. The benzylidene ruthenium carbene initiator **2** developed by Grubbs[2] and the alkoxy imido molybdenum catalyst **3** developed by Schrock[3] have proven to be the best suited and the most widely used systems to perform RCM. The ruthenium complex exhibits greater functional group tolerance and higher moisture and atmospheric oxygen stability relative to those of the extremely sensitive molybdenum system. Nevertheless, this latter

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(1) For recent reviews on olefin metathesis, see the following and references cited within these articles: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.

(2) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(3) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(4) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310−7318.

(5) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375−5380. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207.

(6) (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (b) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890.

(7) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309.

(8) (a) For the first carbene of this type, see: Wanzlick, H.-W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75−80. (b) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

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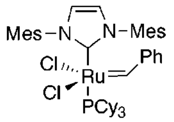
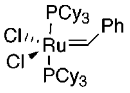
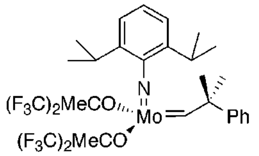
exhibits better reactivity toward a broad range of substrates with important steric and electronic demands.[4]



1



2



3

Further advances in catalyst development leading to complexes with enhanced activity and stability are expected to extend the scope of the RCM reaction. Recent investigations in this area have led to the development of a new generation of catalysts. Catalyst precursors bearing nucleophilic N-heterocyclic carbene ligands have been introduced. As reported by Nolan and co-workers, the use of these versatile imidazol-2-ylidenes ligands, so-called “phosphine mimics”, has opened new opportunities in optimizing the efficiency of catalyst able to mediate RCM[5] as well as C−C[6] and C−N[7] bond formation. Indeed, the 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene ligand (IMes) developed by Arduengo et al.[8] not only stabilizes the catalyst **1** but also enhances its catalytic activity toward RCM, as shown in early experiments.[5,9] This new ruthenium derivative has also been reported to display improved thermal stability compared to existing initiators.[5b] These attractive improvements prompted us to examine the scope and the potential of RCM reactions mediated by this new catalyst **1**.

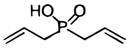
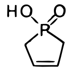
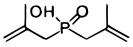
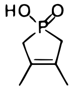
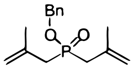
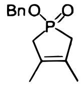
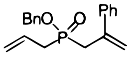
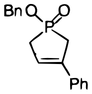
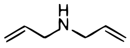
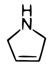
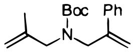
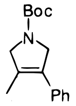
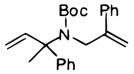
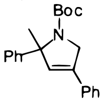
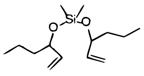
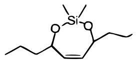
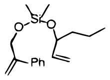
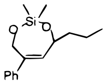
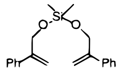
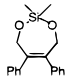
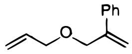
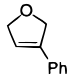
Grubbs and co-workers have explored the reactivity of 1,3-dimesitylimidazol-2-ylidene ruthenium benzylidene **1** with some sterically demanding dienes. Submitted to cyclization in the presence of **1**, diverse substrates afford carbocycles that could not be obtained with catalyst **2**.[10a] Similarly, the 4,5-dihydroimidazol-2-ylidenes ruthenium derivative has been shown to also exhibit high olefin metathesis activity.[10b]

Herein we report the use of initiator **1** in RCM as a new route to prepare various substituted heterocycles.

We intended to test the selectivity and the limitation of the reactivity displayed by benzylidene **1** compared to its parent complex **2**. The present study aims at providing some guidelines for the use of this new catalyst in the preparation of polyfunctionalized molecules.

As shown in Table 1 we initially investigated the activity of benzylidene **1** in the RCM of phosphinic acids (entry 1). Whereas the diallylphosphinic acid did not undergo cyclization with catalysts **2** and **3**, the use of 5% of **1** led to a quantitative conversion to the desired heterocycle within 4 h. However, benzylidene **1** failed to promote the cyclization of a phosphinic acid to form a tetrasubstituted double bond (entry 2), although it permits cyclization to the corresponding benzyl phosphinate (entry 3).

Table 1. Results of Ring-Closing Metathesis[11] Using the New Generation Initiator **1** and the Initial Grubbs Catalyst **2**

Entry	Substrate	Product	Yield using **2** [%cat., time]	Yield using **1** [%cat., time]
1			no rcm[d]	quantitative [5%, 4h]
2			no rcm	no rcm
3			no rcm[d]	88% (81%) [5%, 60h]
4			no rcm	quantitative (92%) [10%, 12h]
5			no rcm	no rcm
6			no rcm	83% (76%) [14%, 72h]
7			no rcm	no rcm
8			57% [10%, 24h]	quantitative [5%, 2h]
9			no rcm	90% [7.5%, 24h]
10			no rcm	no rcm
11			dimerization [3%, 3h]	85% [5%, 6h]

[a] Reaction conditions: 0.02 M in refluxing dichloromethane. [b] Yields in parentheses are isolated. [c] No RCM means that no RCM product could be detected after several days by ^{1}H NMR and starting materials were recovered. [d] Neither substrates of entries 1 and 3 undergo cyclization with the Schrock catalyst **3**. [12]

With another sterically demanding phosphinate bearing a double bond containing a phenyl group (entry 4), catalyst **1** has shown interesting RCM activity compared to that of **2** which proved inactive. The reaction required 10 h and 10 mol % of catalyst to proceed to completion.

As far as amino templates are concerned, benzylidene **1** was unable to cyclize free amine (entry 5). Nevertheless,

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(9) Similar results were reported by the Grubbs laboratory.

(10) (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

ring closure of an N-protected substrate leading to a five-membered structure with a tetrasubstituted double bond proved feasible (entry 6). The compatibility with additional steric bulk of phenyl and methyl groups was quite surprising and underlines the efficiency of this catalytic system (requiring however the protection of the amino moiety). In entry 7 no reaction occurred with allylic disubstituted carbamate. It can be assumed that either the diene conformation is not favorable for the cyclization or the initiation reaction of the benzylidene with the monosubstituted olefin remains impossible due to steric hindrance.

To illustrate another useful application, the closing of some silaketals has been investigated (entries 8−10) to prepare precursors to allylic diols. The use of silicon tethering methodology with RCM has already been reported. [13] With the silaketals studied here, we intended to underscore the new possibilities opened in this field by initiator **1**. The substrates chosen include sterically hindered structures. Only the substrate outlined in entry 8 underwent cyclization with Grubbs catalyst **2** in 57% yield, while the other substrates proved inactive (entries 9 and 10). With initiator **1**, the cyclization in entry 8 proceeded in quantitative yield after 2 h with 5% catalyst. Moreover, ring closure could be achieved in 90% yield with the substrate from entry 9 leading to a seven-membered ring containing a trisubstituted double bond and an alkyl residue in the allylic position. Not surprisingly, the substrate presented in entry 10 failed to cyclize. These results are very promising for the temporary silicon-tethered methodology and for the preparation of asymmetric alkene-1,4-diols, which are useful for the elaboration of asymmetric catalysts or chiral auxiliaries.[14]

Finally we examined one example of ether (entry 11) to show the selectivity displayed by catalyst **1**. Whereas we observed only a dimerization product using Grubbs catalyst **2**, the cyclized product was the only one obtained in good yield with the new catalyst.

Herein we have presented a brief survey of the behavior of ruthenium catalyst **1** bearing an imidazolylidene ligand. Various heterodienes, which failed to react with Grubbs catalyst, cyclize in good to excellent yields through RCM. Even with the Schrock catalyst **3**, substrates from entries 1 and 3 failed to react, proving the high potential of this new initiator. The improvement in catalyst activity appears to be sufficient to overcome some steric deactivation and the inhibition effect of some functional groups. Moreover, the catalyst displays a remarkable thermal stability compared to that of existing initiators and proves to be easy to handle. Hence this complex could provide new access to polysubstituted targets and widen the scope and synthetic applications of the RCM reaction. Ongoing efforts are directed toward the use of catalyst **1** in various RCM protocols.

Acknowledgment is made to Hoechst Marion Roussel for financial support to M.B., to the National Science Foundation (CHE-9985213) and the Louisiana Board of Regents for support to S.P.N., and to A. Valleix for obtaining mass spectra.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Representative procedure**: In a typical reaction a stirred solution of diene (typical concentration 0.02 M) in dry dichloromethane with a catalytic amount of ruthenium benzylidene (3−15 mol %) was heated to reflux. The reaction was followed by TLC or ^{1}H NMR monitoring the disappearance of the starting material. After heating, the reaction mixture was concentrated under vacuum. Purification was performed by chromatography on silica gel providing the desired cycloadduct in yields indicated in Table 1.

(12) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119−2123.

(13) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769.

(14) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519. (b) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409−418.