ORGANIC LETTERS

2007
Vol. 9, No. 7
1339−1342

Ruthenium-Catalyzed Ring-Closing Metathesis to Form Tetrasubstituted Olefins

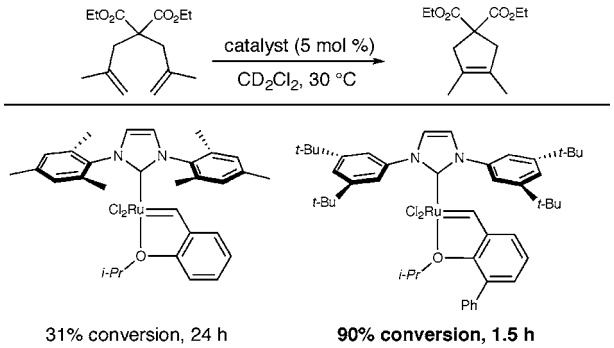
Jacob M. Berlin, Katie Campbell, Tobias Ritter, Timothy W. Funk, Anatoly Chlenov,† and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

rhg@caltech.edu

Received January 25, 2007

ABSTRACT



31% conversion, 24 h **90% conversion, 1.5 h**

Increased efficiency for ring-closing metathesis to form tetrasubstituted olefins using N-heterocyclic carbene ligated ruthenium catalysts was achieved by reducing the size of the substituents at the ortho positions of the N-bound aryl rings.

Olefin metathesis has emerged as a versatile and powerful tool for organic and polymer chemistry.[1] Ruthenium-based N-heterocyclic carbene complexes, such as **2**−**4**, possess activity similar to molybdenum-based complexes, such as **1**, yet display high functional group tolerance and air and moisture stability (Figure 1).[2] Nevertheless, there remain transformations for which molybdenum-based catalysts are significantly more efficient, such as ring-closing metathesis (RCM) to form tetrasubstituted olefins.[3] In this communication, we present new ruthenium complexes with increased efficiency for this transformation.

† Current address: Materia, Inc. 12 N. Altadena Dr., Pasadena, California 91107.

(1) For recent reviews on olefin metathesis, see: (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(2) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416. (c) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (d) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.−Eur. J.* **2001**, *7*, 3236.

(3) For progress toward efficient ruthenium-catalyzed RCM to form tetrasubstituted olefins, see: (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (b) Clavier, H.; Audic, N.; Guillemin, J.-C.; Mauduit, M. *J. Organomet. Chem.* **2005**, *690*, 3585. (c) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.−Eur. J.* **2001**, *7*, 3236. (d) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (e) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000. (f) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (g) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Hermann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. (h) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (i) Jafarpour, L.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 4075. (j) Louie, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 247. (k) Yao, Q. *Org. Lett.* **2002**, *4*, 427. (l) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74. (m) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (n) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875. (o) Yao, Q.; Motta, A. R. *Tetrahedron Lett.* **2004**, *45*, 2447.

10.1021/ol070194o CCC: $37.00
Published on Web 03/08/2007

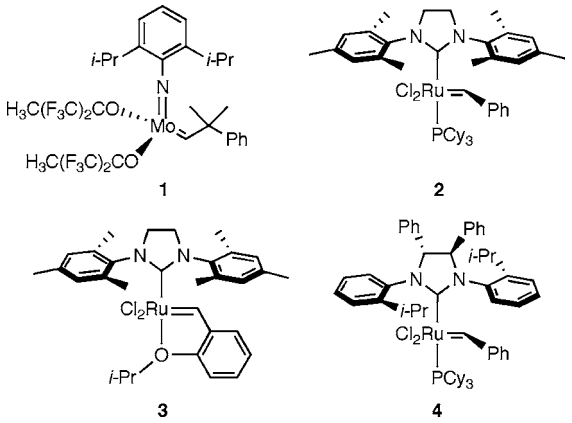
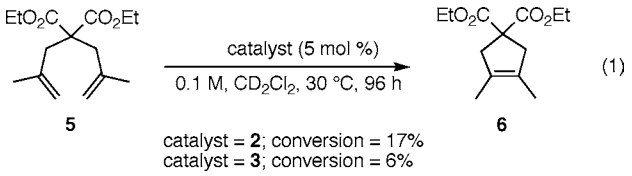
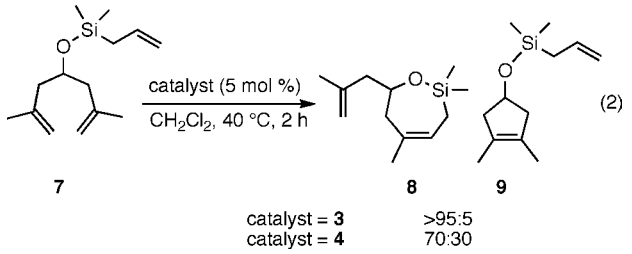


Figure 1. Olefin metathesis catalysts **1**−**4**.

Recently, we developed a standard set of activity comparisons for olefin metathesis catalysts.[4] During this work, it was observed that diethyl dimethallylmalonate (**5**) is a very challenging substrate for catalysts **2** and **3** (eq 1).



In the course of our recent work on ruthenium-catalyzed enantioselective metathesis, a five-membered ring containing a tetrasubstituted olefin was unexpectedly isolated from the asymmetric ring-closing reaction of triene **7** catalyzed by complex **4** (eq 2).[5]



When triene **7** was treated with achiral catalyst **3**, only the trisubstituted olefin **8** was observed. However, when catalyst **4** was used, a 70:30 ratio of **8** to the tetrasubstituted olefin **9** was obtained. We hypothesized that the absence of one ortho substituent on each N-bound aryl ring of catalyst **4** resulted in the additional space necessary for formation of the more sterically demanding tetrasubstituted olefin.

It was proposed that catalysts with even less bulk at the ortho positions than the isopropyl/proton combination of **4** would be effective for the preparation of tetrasubstituted olefins. Thus, three catalysts (**10**−**12**, Figure 2) were

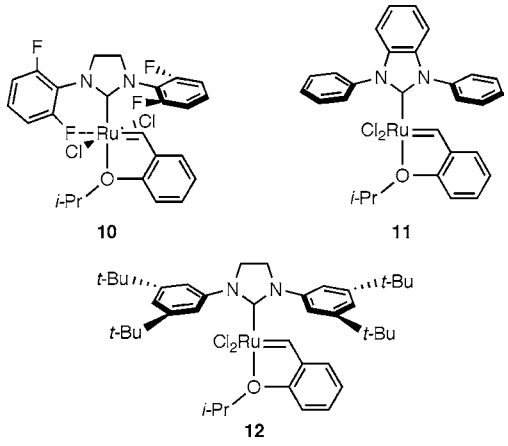


Figure 2. Catalysts **10**−**12**, which show increased efficiency for RCM to form tetrasubstituted olefins.

prepared with reduced bulk at the ortho positions of the N-bound aryl rings. Catalyst **10** possesses fluorines at all four ortho positions.[6] Striving to place the smallest possible substituents at the ortho positions, **11** and **12** were prepared containing *ortho*-hydrogens at those positions.[7]

To compare catalysts **10**−**12** to catalysts **2** and **3**, the ring-closing reaction of diene **5** using these catalysts was monitored over time (Figure 3). These reactions were

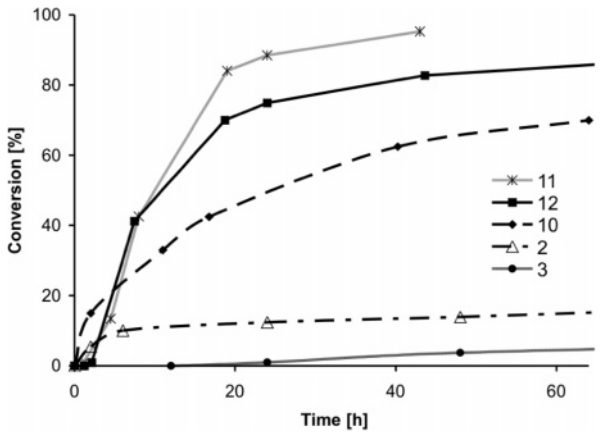


Figure 3. RCM of diethyl dimethallylmalonate (**5**) at 30 °C.

performed under the conditions developed for standard activity comparisons (eq 1). All three of the new catalysts performed significantly better in this reaction than either **2** or **3**. Catalysts **10**−**12** all eventually reached similar conver-

(4) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740.

(5) (a) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (b) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591.

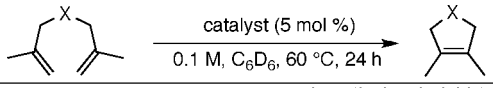
(6) Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768.

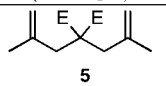
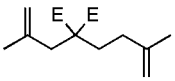
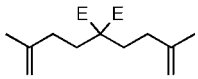
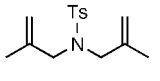
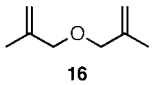
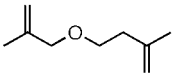
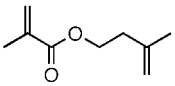
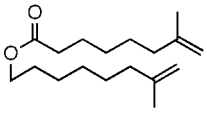
(7) Attempts to replace the *tert*-butyl groups in **12** with smaller substituents have resulted in unsuccessful catalyst synthesis.

sions. When the reaction temperature was increased to 60 °C, the ring-closing reactions of **5** using catalysts **10**−**12** reached their maximal conversions in under 24 h.

Using these conditions, catalysts **10**−**12** were compared to catalyst **3** for a number of substrates (Table 1). Substrate

Table 1. RCM to Form Tetrasubstituted Olefins*



substrate (E =CO_2Et)	conversions (isolated yields) with catalysts **3**, **12**, **11**, **10** [%] **3**	**12**	**11**	**10**
 **5**	30	93 (86)	>95	88[a]
 **13**	>95	>95 (99)	>95	>95[a]
 **14**	50	51 (47)	36[b]	34[a]
 **15**	85	>95 (99)	>95	>95[a]
 **16**	>95	>95[c]	55	>95[a]
 **17**	43[d]	78[c,e]	NR	43[a]
 **18**	NR	NR	NR	NR[a]
 **19**	NR	NR	NR	NR[a]

* NR = no reaction. [a] $CDCl_3$ used as solvent due to the poor solubility of **10** in aromatic solvents. [b] Reaction time: 96 h. [c] Isolated yield not determined due to product volatility. [d] 75% consumption of **17**. [e] 10% 2,6-dichlorobenzoquinone was added. Without 2,6-dichlorobenzoquinone: 60% conversion to RCM product, 95% consumption of **17**.

5 proved to be uniquely challenging for catalyst **3**; for all of the other substrates, **3** performed in a more similar fashion to **10**−**12**. None of the catalysts showed any conversion for **18** or **19**, precursors to an electron-deficient tetrasubstituted olefin and a tetrasubstituted olefin in a macrocycle, respectively.[8] Substrate **17** warrants further discussion. Use of catalyst **3** gave a mixture of three compounds, with 43% conversion to the ring-closed product, 32% conversion to a rearranged byproduct, and 25% remaining starting material (**17**). Use of catalyst **12** resulted in complete consumption of **17**, but with only 60% conversion to the ring-closed product and 40% conversion to the rearranged byproduct. Interestingly, catalyst **10** gave 43% conversion to the ring-closed product and no byproduct formation. Ruthenium hydride species formed from the decomposition of ruthenium olefin metathesis catalysts are known to catalyze the migration of olefins at 40 °C in CD_2Cl_2.[9] Repeating the reactions using **3** and **13** with 10% 2,6-dichloroquinone added to consume any hydride formed,[10] catalyst **3** gave very poor conversion, but catalyst **12** gave 78% conversion to the ring-closed product with no byproduct formation. Overall, catalyst **12** performed as well as or better than **3** for all of the substrates.

One concern that remained was the prolonged reaction time and elevated temperature necessary for these ring-closing reactions. As can be seen in Figure 3, the ring-closing reaction of **5** with catalyst **12** displays an induction period, illustrated by the "S"-shaped reaction profile. This induction period is even more evident in ring-closing reactions of less-hindered substrates.[11] It was thus proposed that slow initiation was the primary challenge to catalyst **12**'s activity and was responsible for the need for elevated temperature and prolonged reaction time.

It is well-known that the initiation rates of catalysts such as **12** can be altered by varying the ligand trans to the NHC.[12] Unfortunately, efforts to vary this position for **12** have been unsuccessful thus far; however, the unsaturated NHC analogue of **12** is able to accommodate a variety of ligands trans to the NHC (Figure 4).

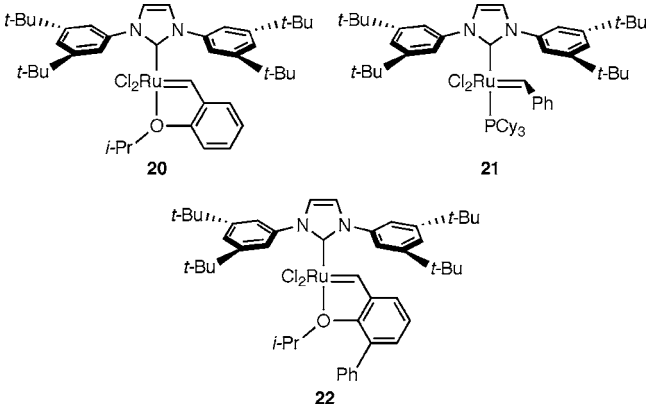


Figure 4. Unsaturate NHC analogues of **12**.

Indeed, the three catalysts **20**−**22** show dramatically different reaction profiles (Figure 5). Catalyst **20** performs the reaction more slowly than **12**, as was expected because the unsaturated analogue of the parent catalyst **2** is less active

(8) In reference 3f, it was reported that **17** could be ring closed in 43% yield using the variant of **3** where the NHC is unsaturated. Despite efforts to reproduce this result under conditions identical to those reported, no conversion was observed.

(9) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

(10) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(11) See Supporting Information for graphs.

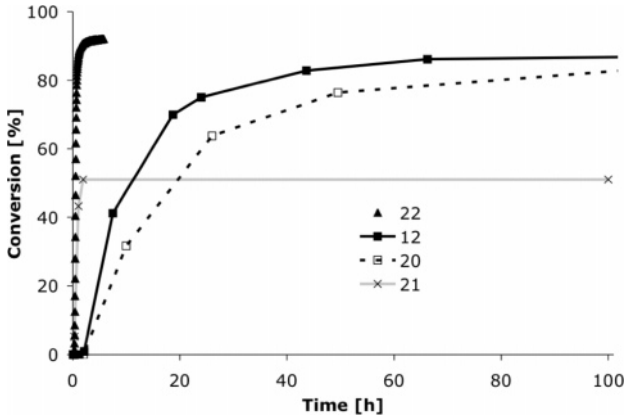


Figure 5. Comparison of catalysts **20**, **21**, and **22** to **12** for RCM of diethyl dimethallylmalonate (**5**) at 30 °C.

than **2**.[13] Catalyst **21** displayed a dramatically enhanced rate of initiation, reaching 43% conversion in just 1 h, but this catalyst also displayed dramatically reduced stability, as the maximal conversion was only 51%. Catalyst **22** was prepared to test a rapidly initiating catalyst that lacked phosphine, and pleasingly rapid initiation and good stability were observed as 90% conversion was achieved in just 1.5 h![14]

On the basis of an unexpected result from enantioselective ring-closing metathesis, three new catalysts (**10**−**12**) were prepared with reduced bulk at the ortho positions of the N-bound aryl rings. All three catalysts performed more efficiently than known catalysts in the standard ring-closing reaction of **5** to prepare a tetrasubstituted olefin (**6**). A brief examination of other substrates demonstrated that catalyst **12** is the most promising of the new catalysts. Continued modification of catalyst **12** led to catalyst **22**, which shows extremely promising reactivity for RCM to prepare tetrasubstituted olefins.

Acknowledgment. We gratefully acknowledge Alexandre Pletnev of Materia, Inc. for work on the synthesis of **12** and Jean Li of The California Institute of Technology for preparing **14** and **18**. T.R. thanks the German Academic Exchange Service (DAAD) for a postdoctoral fellowship. K.C. thanks the NSERC for a postdoctoral fellowship.

Supporting Information Available: Synthesis, characterization, and NMR spectra of new compounds and further activity plots for **10**−**12** and **20**−**22**. Reaction conditions for RCM are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070194O

(12) (a) Hejl, A.; Day, M. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 6149. (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (c) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103. (d) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

(13) For example, see: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(14) A more detailed graph for the use of catalyst **22** is included in the Supporting Information.