

Low Catalyst Loadings in Olefin Metathesis: Synthesis of Nitrogen Heterocycles by Ring-Closing Metathesis

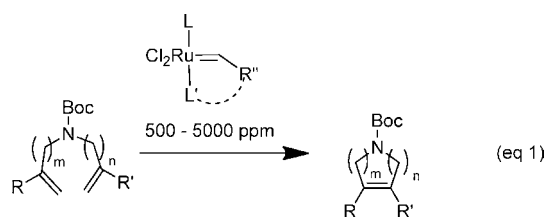
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ABSTRACT



A series of ruthenium catalysts have been screened under ring-closing metathesis (RCM) conditions to produce five-, six-, and seven-membered carbamate-protected cyclic amines. Many of these catalysts demonstrated excellent RCM activity and yields with as low as 500 ppm catalyst loadings. RCM of the five-membered carbamate series could be run neat, the six-membered carbamate series could be run at 1.0 M, and the seven-membered carbamate series worked best at 0.2–0.05 M.

Olefin metathesis has become an indispensable tool for the formation of new carbon–carbon bonds; its success in organic synthesis and materials chemistry has been driven by the development of increasingly efficient catalysts.¹ Ruthenium-based catalysts have received considerable attention because of their tolerance to moisture, oxygen, and a large number of organic functional groups.² Ring-closing metathesis (RCM), in particular, has become the most commonly employed metathesis

reaction in organic synthesis.³ RCM has had an especially large impact on the pharmaceutical industry because the reaction allows for an efficient and direct formation of heterocycles from acyclic dienes.^{3h,j}

The evolution of ruthenium-based catalysts (Figure 1) from first generation catalyst **1** to the highly active catalyst complex **10** bearing a tetramethyl-substituted NHC ligand has been driven by a continued need for increasingly efficient catalysts. Generally, phosphine-ligated catalysts, such as **1** and **3**, have been suitable for the formation of disubstituted cyclic olefins.⁴ The increased activity of H₂IMes-ligated catalyst complexes (H₂IMes = 1,3-dimesitylimidazolidine-2-ylidene), such as **2**, **4**, **5**, and **6**, has allowed for the facile production of trisubstituted olefins.⁵ More recently, deca-

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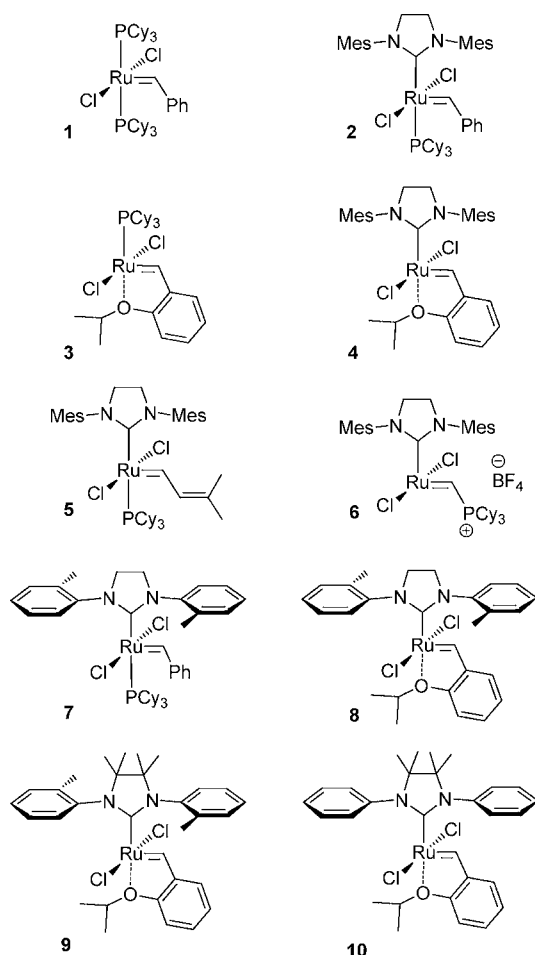


Figure 1. Ruthenium-based olefin metathesis catalysts (Mes = 2,4,6-trimethylphenyl).

ing *N*-aryl steric bulk (**7** and **8**) on the *N*-heterocyclic carbene (NHC) and adding methyl groups to the backbone (**9** and **10**) have greatly increased activity and stability, allowing for efficient synthesis of highly hindered olefin products.^{5d,e,6}

Despite their effectiveness, the use of homogeneous olefin metathesis is limited by high catalyst costs and the often difficult purification of products from residual ruthenium.⁷ A unified approach to address both of these issues is to use lower catalyst loadings in the metathesis event. Herein we report our studies

aimed at dramatically decreasing catalyst loadings for the synthesis of carbamate-protected cyclic amines from the typically reported 2–5 mol %^{1g,4} (i.e., 20,000–50,000 ppm) to as low as 500 ppm. In order to examine the widest possible variety of catalysts and conditions, we have utilized the precision and consistency of Symyx robotic technology to quickly screen a large number of RCM reactions using ppm catalyst loadings.⁸ Several groups have recently demonstrated the value of robotic systems to study catalyst efficiencies, reaction conditions and new applications in olefin metathesis.⁶ Aiming to limit the economic and environmental costs of the process, we performed our screening in as concentrated a state as possible, up to the use of neat reagents.

Due to the wide variety of catalysts now available, the judicious choice of one catalyst for any particular application can be a daunting challenge. There are many substrate-dependent variables as well as catalyst stability, activity, and initiation rate considerations that determine catalyst efficiency for a given reaction. Therefore, it is important to examine and understand trends in relative catalyst efficiencies based on both reaction conditions and substrate design. With this in mind, several commercially available catalysts along with recently reported variants were utilized in this study (Figure 1), reaffirming the notion that no single catalyst is best for all olefin metathesis applications.^{1f,6c,d}

Our research focused on the RCM of carbamate-protected acyclic amines to form the corresponding di-, tri-, and tetrasubstituted five-, six-, and seven-membered carbamate-protected cyclic amines (eq 1); where *m* and *n* = 1 or 2, which are valuable intermediates in organic synthesis and pharmaceuticals.^{3h,j}

Initial reaction parameters were chosen on the basis of the results from a recent complementary study on catalyst efficiency.^{6a} In that work methylene chloride, a solvent often used in olefin metathesis reactions, was shown to greatly decrease catalyst efficiency and was therefore not utilized in our experiments.^{6a} Instead, methyl *tert*-butyl ether (MTBE) and toluene were utilized. Both solvents consistently provided excellent yields throughout our studies. MTBE, in particular, is a prudent alternative to chlorinated solvents and other peroxide-forming ethers.

While increased temperatures have previously been shown to improve metathesis efficiency,^{6c,3h} temperatures above 55 °C decreased assay consistency and resulted in solvent losses.

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(7) Governmental recommendations for residual ruthenium in pharmaceuticals are now routinely less than 10 ppm. For recent guidelines, see: (a) Zaidi, K. *Pharmacoepial Forum* **2008**, *34*, 1345–1348. (b) Criteria given in the EMEA Guideline on the Specification Limits for Residues of Metal Catalysts, available at www.emea.europa.eu/pdfs/human/swp/444600.pdf.

(8) See Supporting Information for details on the use of the Symyx robot. Ethylene was vented to the glovebox in these reactions.

To minimize introducing experimental errors into the system, all assays were carried out at 50 °C, which was the best compromise between fast reaction rates and solvent loss.

The choice of substrate, substrate concentration, solvent, and catalyst had an effect on RCM yields. For example, five-membered rings can be formed neat. Notably, RCM yields of five-membered rings were comparable when run neat or in 1.0 M concentrations (see Table 1 and Figure 5); reactions were not optimized.

Table 1. Effects of Concentration on the Formation of Di-substituted Five-, Six-, and Seven-Membered Carbamate-Protected Cyclic Amines by Catalyst Complex **4**

substrate	product	concn [M]	yield (%)
 11	 12	neat	87
		1 M	>99
		0.2 M	>99

 13	 14	1 M	96
		0.2 M	>99
		0.05 M	92

 15	 16	1 M	46
		0.2 M	82
		0.05 M	90

Under these reaction conditions, 500 ppm catalyst loadings of **4** afforded excellent yields (87%) of **12** when run neat and >99% yields at 1 M; **14** was produced in 96% yields when run at 1 M and >99% yields at 0.2 M. Not too surprisingly, as the ring size increased from five to seven, more dilute substrate concentrations were needed to produce 82% yields of **16** at 0.2 M and 90% yields at 0.05 M, as shown in Table 1.

Having determined that concentrated reactions (neat to 1 M) will produce 87–99% yields of **12**, with 500 ppm of catalyst **4**, we sought to compare **4** to a range of other commonly used ruthenium metathesis catalysts; see Figure 2. The results indicated that catalysts **3** and **4** performed this RCM most efficiently. Lower yields were attained with catalysts containing a labile phosphine (**1**, **2**, **5**, and **7**) compared to Hoveyda and Piers type catalysts (**3**, **4**, **6**, **8**, **9**, and **10**). The lower yields with **1**, **2**, **5**, and **7** may be a result of competitive phosphine-based decomposition pathways.

Excellent yields (95% to >99%) of **14** were produced using 1 M solutions of **13** in MTBE with 500 ppm catalyst loadings of **2**, **3**, **4**, and **5**. More variation in yields were seen using **19**, a more sterically hindered substrate than **13**; see Figure 3. Catalyst **5** performed exceptionally well by producing >99% yield of **20**, compared to 88% yield with **2** and 68% yield with **4**.

While disubstituted cyclic olefins were easily formed by a variety of catalysts, NHC-bearing catalysts were required

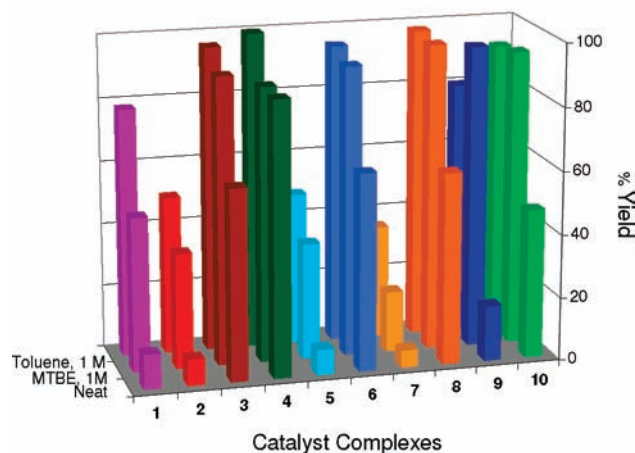
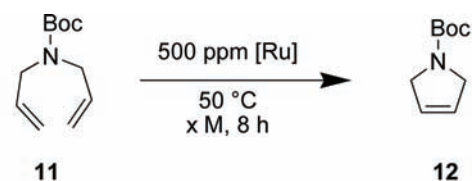


Figure 2. RCM of **11** to **12** utilizing catalyst complexes **1**–**10**.

to produce trisubstituted cyclic olefins at low catalyst loadings, as seen in Figure 4 by the failure of **1** and **3** to perform the ring-closing of substrate **17**. This highlights the general trend that NHC-ligated catalysts display increased activity compared to their non-NHC counterparts.

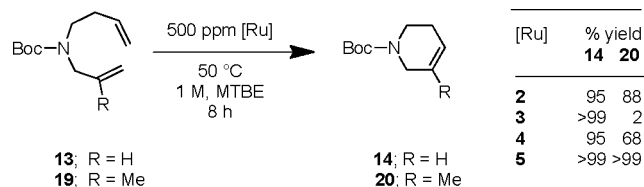


Figure 3. RCM of **13** and **19** utilizing catalyst complexes **2**–**5**.

Changes in a substrate's sterics or chain length can have a dramatic effect in catalyst efficacies. This is evident from the results in Figures 2, 3, and 4 which reinforce the axioms that metathesis catalysts need to be screened to determine the best catalyst for a reaction and more importantly that not one catalyst is best for every reaction.

Recent catalyst design and synthesis has focused on increasing the utility of olefin metathesis when working with highly hindered substrates.^{5d,e,6a} We began a study to determine catalyst trends in the RCM of sterically hindered **23** to **24**, utilizing 1000 ppm catalyst loadings (see Figure 5). Changes in concentration had a negligible effect on the yields of **24**. As in previous examples, the Grubbs–Hoveyda catalysts (**8**–**10**) outperformed the phosphine variant (**7**).

The RCM of **25** using 1000 ppm catalyst loadings of **8** and **9** produced 17% and 34% of **26**, respectively. Thus

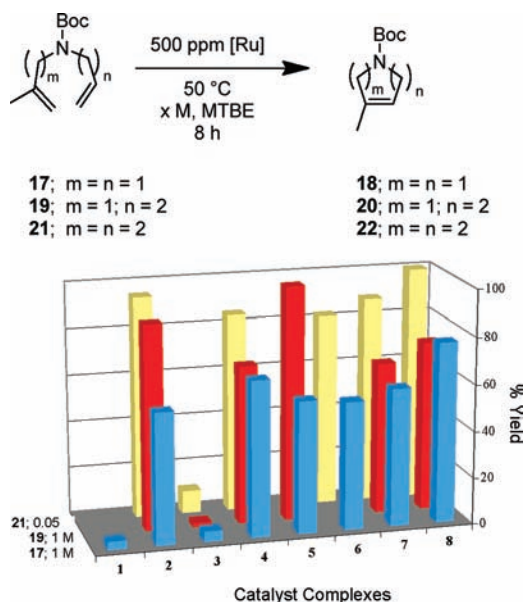


Figure 4. RCM of 17, 19, and 21 utilizing catalyst complexes 1–8.

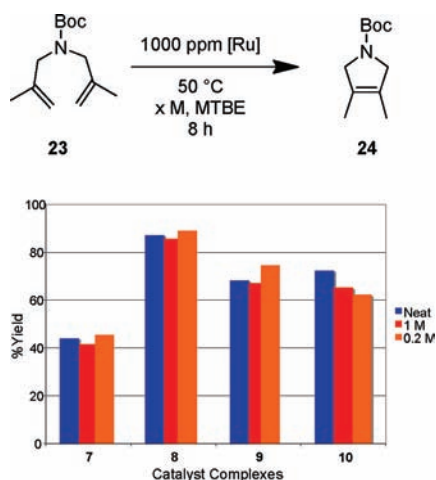


Figure 5. RCM of 23 with 1000 ppm of catalyst complexes 7–10.

catalyst loadings of 5000 ppm were needed to produce >90% yields of 26 and 28; see Figure 6. The 52% yield of 26 was

suspected to be an anomaly since the yield of 28, the more challenging product, was 98%. Furthermore, only catalysts 8, 9, and 10 were found to effectively accomplish this RCM reaction, providing a reminder that more efficient catalysts still need to be developed.

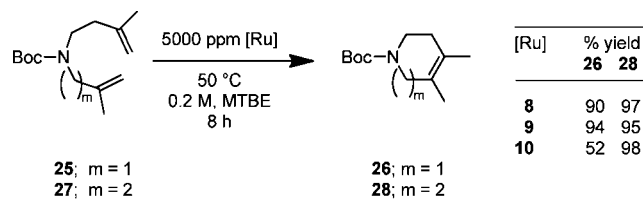


Figure 6. RCM of 25 and 27 utilizing catalyst complexes 8–10.

In conclusion, we have synthesized di-, tri-, and tetrasubstituted five-, six-, and seven-membered carbamate-protected cyclic amines via RCM using as low as 500 ppm of ruthenium metathesis catalysts. This method has provided an overall assessment of metathesis catalyst activities with nine carbamate substrates. In general, every carbamate-protected cyclic amine in this study could be produced in >90% yields using catalyst loadings of 500 ppm for the di- and trisubstituted five- and six-membered carbamate-protected cyclic amines and 1000–5000 ppm catalyst loadings for the more demanding tetrasubstituted five-, six- and seven-membered carbamate-protected cyclic amines. Two final observations were that the five-membered carbamate-protected cyclic amines could be run neat and that MTBE was a practical solvent in these RCM reactions.

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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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