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The Generation of Efficient Supported (Heterogeneous) Olefin Metathesis
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- Executive Summary.

Over the past decade, a new family of homogeneous metathesis catalysts has been developed that will tolerate most organic functionalities as well as water and air. These homogeneous catalysts are finding numerous applications in the pharmaceutical industry as well as in the production of functional polymers. In addition the catalysts are being used to convert seed oils into products that can substitute for those that are now made from petroleum products. Seed oils are unsaturated, contain double bonds, and are a ready source of linear hydrocarbon fragments that are specifically functionalized. To increase the number of applications in the area of biomaterial conversion to petrol chemicals, the activity and efficiency of the catalysts need to be as high as possible. The higher the efficiency of the catalysts, the lower the cost of the conversion and a larger number of practical applications become available. Active supported catalysts were prepared and tested in the conversion of seed oils and other important starting materials. The outcome of the work was successful and the technology has been transferred to a commercial operation to develop viable applications of the discovered systems. A biorefinery that converts seed oils is under construction in Indonesia. The catalysts developed in this study will be considered for the next generation of operations.

- Accomplished objectives and goals.

The goal of the research was to develop olefin metathesis catalysts that were highly efficient to be used in the conversion of seed oils into chemical and fuels. We proposed to accomplish this goal by the use of a combination of approaches, increasing the stability of the basic catalysts, isolating them on a surface to slow decomposition and provide a easy mode of isolation and then the development of methods for the reactivation of the supported catalysts should result in a major increase in catalyst efficiency and utility. These catalysts will then have much broader applications in the conversion of naturally occurring olefins into useful products and provide a bio-renewable source of organic molecules. During the

support period, a number of supported catalysts were prepared and studied in detail. The utility was sufficiently high that the systems were transferred to a commercial group that is developing applications for the new catalysts. Patented processes were developed and are moving toward commercialization. Through the use of modified ligands, more active and stable catalysts were prepared. These systems have provided a basis for further development of highly active catalyst systems. Some progress was made toward the reactivation of the catalysts. Unfortunately, the funding was completed before that work was finished. It is being carried on using other funds. In addition to the proposed areas, we explored the use of the catalysts in microfluidic systems to explore the possibility of increasing their activity by using high surface area reactors and rapid mixing.

- Summary of activities.

The original proposal was that supported catalysts would be more efficient than homogeneous systems.¹ The required supported metathesis catalysts were prepared during the funding period and tested for activity. A variety of systems were produced and examined under a variety of reaction conditions. It was found that in some cases, the supported systems did show higher activity and productivity. However, the early stages of development left the question of whether the increased effort required for supporting the system and the recovery of the metal afterward from the support was overcome by the utility. These questions will be answered in the future when the systems are optimized. A family of new ligands was prepared that allowed for the NHC ligands on the most active metathesis catalysts to be made more rigid. It was found through a series of studies that these new ligand systems showed higher activity in many cases and will have applications in specialized areas of olefin metathesis. The ligand synthesis and systematic study will aid others in the design of efficient catalytic systems.² In the final proposed study, efforts were made to recover and to reactivate the spent catalyst. Methods were found that will allow ruthenium to be recovered efficiently after a reaction but an efficient method to convert the spent system back to an active catalyst was not completed. That work is ongoing. Through a collaboration with another group, we explored the use of these catalysts in microfluidic systems. In many of the reactions, gas is given off or absorbed. It was hoped that the use of microfluidics would allow for increased intersurface area and more efficient gas transfer. These systems continue to be developed.³

1. "Well-defined Silica-supported Olefin Metathesis Catalysts." D. P. Allen, M. M. Van Wingerden, and R. H. Grubbs, *Org. Lett.* **2009**, *11*, 1261-1264.
2. "The Effects of NHC-Backbone Substitution on Efficiency in Ruthenium-based Olefin Metathesis." K. M. Kuhn, J-B. Bourg. C. K. Chung, S. C. Virgil, R. H. Grubbs, *J. Amer. Chem. Soc.* **2009**, *131* (14), 5313-5320. "Low Catalyst Loadings in Olefin Metathesis: Synthesis of Nitrogen Heterocycles by Ring-Closing Metathesis." K. M. Kuhn, T. M. Champagne, S. H. Hong, W-H. Wei, A. Nickel, C. W. Lee, S. C. Virgil, R.H. Grubbs, R. L. Pederson, *Org. Lett.* **2010** *12* (5), 984-987. "Olefin Metathesis Catalyst: Stabilization Effect of Backbone Substitutions of N-Heterocyclic Carbene." C. K. Chung, R. H. Grubbs, *Org. Lett.* **2008**, *10* (13), 2693-2696.

3. "Low Pressure Ethenolysis of Renewable Methyl Oleate in a Microchemical System." C. P. Park, M. M. Van Wingerden, S. Y. Han, D. P. Kim, R. H. Grubbs, *Org. Lett.* **2011**, 13 (9), 2398-2401.

- Product Development under the Award.

During the term of the funding period, a number of papers were published to transfer the information the academic community and to allow those groups to build on the our results. After the funding period was complete, the technology was transferred to the company that was founded to commercialize the ruthenium technology. They have tested the materials in real commercial applications and they have filed for patents on those applications.

- Publications.

1. "Well-defined Silica-supported Olefin Metathesis Catalysts." D. P. Allen, M. M. Van Wingerden, and R. H. Grubbs, *Org. Lett.* **2009**, 11, 1261-1264. DOI: 10.1021/ol9000153
2. "The Effects of NHC-Backbone Substitution on Efficiency in Ruthenium-based Olefin Metathesis." K. M. Kuhn, J-B. Bourg. C. K. Chung, S. C. Virgil, R. H. Grubbs, *J. Amer. Chem. Soc.* **2009**, 131 (14), 5313-5320. DOI: 10.102/ja900067c
3. "Low Catalyst Loadings in Olefin Metathesis: Synthesis of Nitrogen Heterocycles by Ring-Closing Metathesis." K. M. Kuhn, T. M. Champagne, S. H. Hong, W-H. Wei, A. Nickel, C. W. Lee, S. C. Virgil, R.H. Grubbs, R. L. Pederson, *Org. Lett.* **2010** 12 (5), 984-987. DOI: 10.1021/ol9029808
4. "Low Pressure Ethenolysis of Renewable Methyl Oleate in a Microchemical System." C. P. Park, M. M. Van Wingerden, S. Y. Han, D. P. Kim, R. H. Grubbs, *Org. Lett.* **2011**, 13 (9), 2398-2401. DOI: 10.1021/ol200634y

- Web site or other Internet sites that reflect the results of this project.

None

- Networks of collaborations fostered.

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- Technologies/Techniques.

None

- Inventions/Patent Applications, licensing agreements and other products.

None

Well-Defined Silica-Supported Olefin
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ABSTRACT

Two triethoxysilyl-functionalized *N*-heterocyclic carbene ligands have been synthesized and used to prepare the corresponding second-generation ruthenium olefin metathesis catalysts. These complexes were then grafted onto silica gel, and the resulting materials were efficient heterogeneous catalysts for a number of metathesis reactions. The solid-supported catalysts were shown to be recyclable over a number of reaction cycles, and no detectable levels of ruthenium were observed in reaction filtrates (ruthenium concentration of filtrate <5 ppb).

Olefin metathesis has emerged as a unique and powerful transformation for the interconversion of olefinic hydrocarbons in both organic and polymer chemistry.¹ The development of well-defined ruthenium-based catalysts (**1–3**, Figure 1)² has greatly expanded the scope and applications of this process due to their increased tolerance of organic functionality, moisture, and oxygen.³ However, even with the advances in this area, catalyst lifetime and efficiency can

Figure 1. Ruthenium-based olefin metathesis catalysts.²

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(1) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997.

(2) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(3) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (c) Schrod, Y.; Pederson, R. L. *Aldrichim. Acta* **2007**, *40*, 45–52. (d) Grubbs, R. H. *Adv. Synth. Catal.* **2007**, *349*, 34–40.

represent a major limiting factor in the further advancement of this technology. Thus, over the past decade, significant emphasis has been placed on gaining a fundamental understanding of the various decomposition pathways leading to catalyst deactivation.⁴ This has led to the advent of new catalyst architectures that provide improved reactivity and/or methods for eliminating or reducing particular decomposition pathways such as C–H activation of *ortho* *N*-aryl substituents.⁵

Several decomposition pathways involve bimetallic species due to the propensity for ruthenium to dimerize via thermodynamically stable chloride (**4** and **6**) or carbide bridges (**5**) (Figure 2).^{4b–c} One approach to prevent these undesirable

Figure 2. Various dimeric ruthenium decomposition products.⁴

bimolecular decomposition pathways is to immobilize the catalyst onto a solid support that inhibits intermolecular catalyst–catalyst interactions via site isolation.⁶ Furthermore, supported catalysts have the added advantages of generating products free of ruthenium contamination and possess the ability to be recovered and subsequently recycled. A number of reports have been published employing various strategies to obtain solid-supported olefin metathesis catalysts.⁷ These consist of anchoring the catalytic moiety, via a number of positions within the catalyst framework, to a variety of solid supports, such as organic polymers or inorganic oxides. Of the various strategies, immobilization through a chelating benzylidene has been the most widely employed. These catalysts operate via a release/return phenomenon⁸ with all the catalytic activity arising from a homogeneous species, which is susceptible to the same bimetallic decomposition pathways. Likewise, such systems

cannot realize all the benefits of solid-phase catalysis, such as desirable continuous flow processes.

Scheme 1. Synthesis of Ruthenium Complexes **15** and **16**

(4) (a) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207. (b) Amoroso, D.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2002**, *21*, 3335–3343. (c) Amoroso, D.; Snelgrove, J. L.; Conrad, J. C.; Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. *Adv. Synth. Catal.* **2002**, *344*, 757–763. (d) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (e) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. (f) Hong, S. H.; Chlenow, A.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5148–5151. (g) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.

(5) (a) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenow, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339–1342. (b) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (c) Anderson, D. R.; Lavallo, V.; O’Leary, D. J.; Bertrand, G.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7262–7265. (d) Vougioukalakis, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 2234–2245. (e) Chung, C. K.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2693–2696.

(6) (a) Collman, J. P.; Belmont, J. A.; Brauman, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 7288–7294. (b) Drago, R. S.; Pribich, D. C. *Inorg. Chem.* **1985**, *24*, 1983–1985. (c) Tollner, K.; Popovity-Biro, R.; Lahav, M.; Milstein, D. *Science* **1997**, *278*, 2100–2102. (d) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147–4154.

(7) For recent review articles, see: (a) Buchmeiser, M. R. *New. J. Chem.* **2004**, *28*, 549–557. (b) Coperet, C.; Basset, J.-M. *Adv. Synth. Catal.* **2007**, *349*, 78–92. (c) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786–6801.

Other strategies involve immobilization via alternative X-type ligands that replace the ancillary chlorides, such as fluorinated carboxylates,⁹ or via functionalized NHC ligands.¹⁰ The latter is a very attractive approach as the NHC forms a strong bond to the ruthenium center and is the most substitutionally inert ligand within the catalyst coordination sphere.¹¹ Herein, we report the syntheses of two triethoxysilyl functionalized NHC ligands (**10** and **13**) and their use in the generation of ruthenium complexes **15** and **16**.¹² The subsequent grafting of these complexes onto silica is described and the utility of the silica-supported analogues as heterogeneous catalysts is evaluated.

The synthesis of **10** began with the allylation of bisimine **7** followed by reduction to furnish diamine **8**. This was treated with HCl and triethyl orthoformate to generate the imidazolium

(8) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799. (b) Hoveyda, A. H.; Gillingham, D. G.; van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23.

chloride **9**. A Pt(0)-catalyzed hydrosilylation of **9** using HSiCl₃ and subsequent treatment with ethanol/NEt₃ produced the triethoxysilyl backbone functionalized NHC salt **10**. A similar strategy was used to prepare NHC salt **13**. Diamine **11** was prepared in three steps from commercially available starting materials (see the Supporting Information) and used to generate *p*-allyl NHC salt **12**. This was transformed to the triethoxysilyl-functionalized NHC salt **13** via the Pt(0)-catalyzed hydrosilylation procedure described above. Ruthenium complexes **15** and **16** were subsequently prepared by deprotonation of the respective NHC salts, **10** and **13**, with potassium bis(trimethylsilyl)-amide and treatment of the resulting free carbene with ruthenium complex **14**.

Next, solutions of **15** and **16** were stirred with silica at 25 °C for 72 h to obtain the corresponding silica-supported catalysts **15-SiO₂** and **16-SiO₂** (Figure 3). At this time, the ruthenium-

Figure 3. Silica-supported catalysts **15-SiO₂** and **16-SiO₂**.

loaded material was transferred to a Soxhlet extraction thimble and continuously extracted with CH₂Cl₂ for 48 h. This step was necessary to remove any traces of **15** or **16** that were not covalently immobilized to the silica support.

With silica-supported analogues **15-SiO₂** and **16-SiO₂** in hand, we first wanted to gauge their catalytic activity, along with determining their degree of heterogeneity. This was necessary to ensure that the catalytic activity arises from the supported catalyst and not from some *active* species leaching from the solid support. This was done by performing a split or hot-filtration test.¹³ We examined the RCM of diethyl-diallyl malonate at 60 °C for both supported catalysts, where, after 10 min half of the reaction was filtered at a conversion of 67% (**15-SiO₂**) and 31% (**16-SiO₂**), respectively. After

an additional 50 min reaction time, the silica-supported catalyst containing suspensions proceeded to >95% (**15-SiO₂**) and 86% (**16-SiO₂**), whereas the filtered portions showed no further reactivity (Figure 4). Thus, the catalytic activity

Figure 4. Split tests to determine the degree of catalyst heterogeneity for **15-SiO₂** and **16-SiO₂**. Reactions were performed in C₆D₆ (0.1 M) using 0.25–0.5 mol % of catalyst and percent conversion determined by ¹H NMR.

arises from the supported complex and not from catalyst that leached from the solid support. Also worth noting is that the filtered reaction mixture involving **15-SiO₂** was analyzed for ruthenium content and contained <5 ppb ruthenium contamination (below detection limit of ICP-MS).

With the positive results obtained from the split tests, the catalysts were next examined in a series of RCM reactions as displayed in Table 1. The results show that both catalysts are

Table 1. RCM Reactions Employing **15-SiO₂** and **16-SiO₂**

R = H, Me

entry	RCM substrate	catalyst	time	conversion (%) ^a
1		15-SiO₂	1 h	> 95
		16-SiO₂	1 h	84
2		15-SiO₂	2 h	> 95 ^b
		16-SiO₂	2 h	85 ^b
3		15-SiO₂	1 h	83
		16-SiO₂	1 h	13
4		15-SiO₂	4 h	> 95
		16-SiO₂	4 h	55

^a Reactions were not run to completion, rather only for the allotted time. Percent conversions determined by ¹H NMR. ^b ICP-MS analysis of the RCM product isolated by filtration and concentration indicated <5 ppb ruthenium contamination.

(9) For a representative example, see: Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, 70, 4687–4694.

(10) For representative examples, see: (a) Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, 39, 3898–3901. (b) Mayr, M.; Buchmeiser, M. R.; Wurst, K. *Adv. Synth. Catal.* **2002**, 344, 712–719. (c) Prühs, S.; Lehmann, C. W.; Fürstner, A. *Organometallics* **2004**, 23, 280–287.

(11) For evidence of exchange between the X-type ligands, see: Tanaka, K.; Böhm, V. P. W.; Chadwick, D.; Roepert, M.; Braddock, D. C. *Organometallics* **2006**, 25, 5696–5698.

(12) Merck & Co., Inc. have filed patents in this research area. For a representative patent see: Koehler, K. Immobilizable N-heterocyclic Carbene Metal Complexes with Alkoxy-silyl Groups International Patent No. WO 2007/017047 A1.

(13) Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, 31, 485–493.

competent, even at the low catalyst loadings employed (0.4 mol %); however, in all cases the NHC backbone functionalized **15-SiO₂** outperforms the *p*-*N*-aryl-derived **16-SiO₂**.¹⁴

Next, the supported catalysts were screened for the cross-metathesis reaction between allylbenzene (**21**) and *cis*-1,4-diacetoxy-2-butene (**22**) (eq 1).¹⁵ Again, **15-SiO₂** outperformed **16-SiO₂** supplying the cross product in 80% versus 30% yield after 2 h. However, **16-SiO₂** did continue to turnover, reaching a maximum of 53% conversion after 24 h.¹⁶

The reason for the greater reactivity of **15-SiO₂** compared to **16-SiO₂** is unknown; however, it is speculated to arise from an interaction between the ruthenium active site and the silica surface that is present in the case of **16-SiO₂** but is blocked by the steric bulk of the NHC ligand in the case of **15-SiO₂**. RCM studies involving the homogeneous complexes **15** and **16** were performed in hopes of gaining insight into this matter and revealed that **16** had a slightly longer induction period compared to **15**, however this does not appear to account for the sometimes dramatic differences in activity observed for the supported analogues (see the Supporting Information). The difference then is most likely a function of the silica support.

We were next interested in gaining some information into the recyclability of the supported catalysts. Due to the increased reactivity of **15-SiO₂**, it was utilized for a recycling experiment involving the RCM of diethylallylmethylallyl malonate (**20**). The results are depicted in Figure 5 and show

(14) A direct comparison between the better heterogeneous catalyst **15-SiO₂** and the corresponding homogeneous catalyst **3** was not performed, but it is estimated that **3** is approximately 2–3 times more active in terms of reaction rate.

(15) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, 25, 5740–5745.

(16) It was hoped that the bulky steric nature of the silica support may influence the *E/Z* selectivity of **23**; however, a plot of the *E/Z* ratio vs percent conversion of **23** employing **15-SiO₂** and **16-SiO₂** reveals that the supported catalysts behave similarly to homogeneous catalysts **1–3** (see the Supporting Information).

Figure 5. Recycling of **15-SiO₂** for RCM of substrate **20**. Reactions were performed in C₆H₆ (0.1 M) using 0.75 mol % of **15-SiO₂**/cycle and percent conversions determined by ¹H NMR. Each cycle was 2 h except for no. 5, which was run for 12 h.

that the catalyst was effectively recycled multiple times with an eventual gradual decrease in activity.

In conclusion, we have successfully synthesized two triethoxysilyl-functionalized NHC ligands and the corresponding second-generation olefin metathesis catalysts which were anchored onto silica to furnish silica-supported catalysts **15-SiO₂** and **16-SiO₂**. These species were shown to be competent catalysts for a variety of olefin metathesis reactions, mimicking their homogeneous counterparts. Likewise, the activity of the supported catalysts is truly heterogeneous in nature as revealed by split tests and they can be recycled multiple times. Most importantly, the catalysts do not leach ruthenium under the standard reaction conditions as revealed by ICP-MS analysis of filtered reaction solutions (ruthenium concentration of filtrate <5 ppb in all cases).

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Supporting Information Available: Experimental procedures and characterization data for new compounds and all procedures for catalytic studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Effects of NHC-Backbone Substitution on Efficiency in Ruthenium-Based Olefin Metathesis

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Abstract: A series of ruthenium olefin metathesis catalysts bearing N-heterocyclic carbene (NHC) ligands with varying degrees of backbone and *N*-aryl substitution have been prepared. These complexes show greater resistance to decomposition through C–H activation of the *N*-aryl group, resulting in increased catalyst lifetimes. This work has utilized robotic technology to examine the activity and stability of each catalyst in metathesis, providing insights into the relationship between ligand architecture and enhanced efficiency. The development of this robotic methodology has also shown that, under optimized conditions, catalyst loadings as low as 25 ppm can lead to 100% conversion in the ring-closing metathesis of diethyl diallylmalonate.

Introduction

Olefin metathesis has emerged as a valuable tool in both organic and polymer chemistry.¹ Ruthenium-based catalysts, in particular, have received considerable attention because of their tolerance to moisture, oxygen, and a large number of organic functional groups.² Following the report of the increased activity of complex **1** (H₂IMes)(PCy₃)Cl₂Ru=CHPh (H₂IMes = 1,3-dimesitylimidazolizidine-2-ylidene),³ and Hoveyda's subsequent exchange of the phosphine ligand with a chelating ether moiety (**2**),⁴ many researchers have focused on increasing catalytic activity, selectivity and stability through modification of the N-heterocyclic carbene (NHC) ligand.⁵

As ligand modification has led to improved catalyst activity, a variety of applications have become possible, including ring-closing metathesis (RCM), cross metathesis (CM), ring-opening cross metathesis (ROCM), acyclic diene metathesis polymerization (ADMET), and ring-opening metathesis polymerization (ROMP). Among those metathesis reactions, ring-closing metathesis has become the most commonly employed metathesis reaction in organic synthesis.⁶ For this transformation, NHC catalysts, such as **1**, **2**, and more recently **3**, have allowed both high activity and increased catalyst lifetime to be realized (Chart 1).^{3,4,5c}

Chart 1. Representative NHC-Bearing Olefin Metathesis Catalysts

Despite these advances, still more efficient catalysts are sought to increase the applicability of RCM in industry. In many cases, olefin metathesis is still plagued by catalyst deactivation and the requirement of high catalyst loadings.⁶ Furthermore, decomposition products of olefin metathesis catalysts have been shown to be responsible for unwanted side reactions such as olefin isomerization.⁷ Increased catalyst loading could also potentially increase the level of residual ruthenium impurities

[†] Caltech Center for Catalysis and Chemical Synthesis.

- (1) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003, and references cited therein. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (c) Schrod, Y.; Pederson, R. L. *Aldrichim. Acta* **2007**, *40*, 45–52. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013–3043.
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Chart 2. *N*-Phenyl Substituted Complexes

in the final products, which becomes especially critical where reaction products are intended for pharmaceutical use.⁸ Collectively, these issues have a direct influence on the operational cost of metathesis transformations. With these factors in mind, the next challenge in RCM is to substantially decrease the catalyst loading, thereby reducing both reaction cost and the challenges in product purification. To this effect, our goal has been to increase catalyst efficiency by developing even more stable and robust catalysts that still retain a high catalytic activity.

Recently, studies by our group and others have unveiled the decomposition pathways at play during metathesis reactions.⁹ Among other degradation products, complexes derived from C–H activation of *N*-aryl substituents were reported. Since the NHC ring and the aryl substituent must approach coplanarity for C–H activation, it was anticipated that decomposition via C–H activation processes might be slowed by restriction of *N*-aryl group rotation of the NHC ligand, and this might be achieved by placing sterically hindered groups on the NHC backbone. This hypothesis was confirmed by successfully preparing *N*-phenyl complexes **4** and **5** that are more resistant to the decomposition initiated by C–H activation (Chart 2).^{5a,b} Having unsubstituted *N*-phenyl groups, these complexes display good and exceptional reactivity, respectively, in the formation of highly substituted olefins. Despite these improvements, complexes **4** and **5** are more prone to decomposition than **1** and **2**.¹⁰

To address and further understand the balance between activity and stability of **5**, we sought to investigate a homologous series of ruthenium catalysts bearing NHCs with varying degrees of backbone and aryl substitution. Molecular modeling and the calculations of Jensen et al. suggest that a catalyst bearing an NHC with mesityl groups at nitrogen and a fully methylated backbone would be an improvement over existing catalysts.¹¹ We expected that the degree of substitution could be central to increased activity and catalyst lifetimes.

Chart 3. Imidazolinium Salts

Herein, we report the preparation and characterization of a series of catalysts bearing NHCs with varying degrees of backbone and aryl substitution. Initial evaluation of their performance in olefin metathesis demonstrated that the common assays were not effective at measuring the relative efficiencies of these catalysts at standard catalyst loadings.¹² While the standard conditions are excellent in evaluating the activity of new catalysts, they are not sensitive to small variations in the efficiency profile accompanying subtle modification in catalyst architecture.

In order to examine these small changes, we have developed a highly sensitive ppm level assay utilizing the precision and consistency of Symyx robotic technology. We utilized these techniques to examine the activity and stability of these catalysts in RCM at low catalyst loadings, providing increased insight into the relationship between ligand architecture and catalyst efficiency. The development of this methodology has also shown that, under optimized conditions, complete conversion in the RCM of diethyl diallylmalonate is observed with catalyst loadings as low as 25 ppm (0.0025 mol%).

Results and Discussion

Catalyst Syntheses. The preparation of the 1,1'-dimethyl- and 1,2-dimethyl-substituted imidazolinium chlorides **6** and **7** (Chart 3) have been previously reported by Bertrand and Çetinkaya, respectively.¹³ Under analogous experimental conditions, imidazolinium chlorides **9** and **10**, featuring 2-methylphenyl (*o*-tolyl) groups, were obtained in good yields. Unfortunately, separation of the *syn*- and *anti*- isomers of **10** proved to be extremely difficult, requiring the mixture to be carried forward.

Following the procedures previously reported by our group to access the NHC of complex **5**, we then attempted the preparation of the highly substituted imidazolinium salts bearing four methyl substituents.^{5a} While imidazolinium chloride **11** was prepared without incident, we were unable to synthesize the intermediate tetramethylated diamine **13** of the corresponding *N*-mesityl analogue under various conditions (Scheme 1). Considering the trimethylated NHC to be sufficiently encumbered to prevent *N*-aryl rotation, we prepared **8** instead by Grignard addition followed by reduction and imidazolinium salt formation.

With precursors **6**–**11** in hand, the corresponding free carbenes were generated by treatment of the imidazolinium salts

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Scheme 1. Synthesis of Imidazolium Chloride **8**

	Ar	R ¹	R ²	R ³	R ⁴	% Yield
15	Mesityl	H	H	Me	Me	49
16	Mesityl	Me	H	H	Me	54
17	Mesityl	H	Me	Me	Me	44
18	<i>o</i> -Tolyl	H	H	Me	Me	57
19^a	<i>o</i> -Tolyl	H (Me)	Me (H)	H	Me	38
20	<i>o</i> -Tolyl	Me	Me	Me	Me	72

^a Backbone methyl groups are a mixture of *syn*- and *anti*- isomers.

Figure 1. Synthesis of ruthenium complexes **15–20**.

with potassium hexamethyldisilazide (KHMDS) at room temperature (Figure 1). These carbenes (prepared in situ) were reacted with commercially available (PCy₃)RuCl₂=CH(*o*-OiPrC₆H₄) at 70 °C, affording the phosphine-free chelating ether complexes **15–20**. These complexes were isolated as crystalline green solids after flash column chromatography, and as solids are both air- and moisture-stable under standard conditions.

Structural Analyses. To probe the electronic and steric effects of backbone substitution, crystals of **17** and **20** were grown and their molecular structures were confirmed by single-crystal X-ray crystallographic analysis (Figure 2). The complexes exhibit a distorted square pyramidal geometry with the benzylidene moiety occupying the apical position. When compared with its unsubstituted analogue **2**, the backbone substitution of **17** results in significant differences in three key structural parameters summarized in Table 1: (1) Ru–C(1) bond length, (2) C(1)–Ru–C(25) bond angle, and (3) the C(3)–N2–C(16) bond

Chart 4. IR Carbonyl Stretching Frequencies of *cis*-[RhCl(CO)₂(NHC)] Complexes **21–23**

	21	22	23
ν_{CO} (cm ⁻¹)			
sym	2081	2079	2077
asym	1996	1995	1994

Table 1. Selected X-Ray Data for **2**, **17**, **3**, and **20^a**

	2^b	17	3^c	20
Bond length (Å)				
Ru–C(1)	1.980	1.968	1.962	1.964
Ru–C(25)	1.824	1.840	1.823	1.835
Ru–O	2.262	2.255	2.244	2.261
Bond angles (deg)				
C(3)–N(2)–C(16)	118.22	122.60	119.91	119.82
C(2)–N(1)–C(7)	118.32	123.82	120.69	120.26
C(1)–Ru–C(25)	101.60	103.08	102.48	103.14
Cl(1)–Ru–Cl(2)	156.42	161.26	159.49	160.80

^a For a complete list of bond lengths and angles for **17** and **20**, refer to the Supporting Information. ^b See ref 4. ^c See ref 5c.

angle. Surprisingly, there are no major differences between the solid-state structures of complexes **3** and **20**.

The crystal structure of complex **17** suggests that the backbone methyl substituents push the *N*-mesityl groups toward the ruthenium center and as a result the NHC–Ru–benzylidene bond angle is also increased. However, the bond distance between the NHC carbene carbon and the Ru center is shorter in **17** (1.968 Å) than in **2** (1.980 Å). This effect can be explained by noting that the backbone methyl substituents increase the electron-donating ability of the NHC ligand. This effect is also seen in the IR carbonyl stretching frequencies of the *cis*-[RhCl(CO)₂(NHC)] complexes **21–23** (Chart 4), where increased substitution resulted in lower frequencies.¹⁴ These structural differences should have a significant impact on the efficiency of the different catalysts.

Ring-Closing Metathesis (RCM) Activity. RCM is widely used in organic synthesis and serves as a standard assay to evaluate the relative efficiency of most ruthenium-based catalysts.^{6,12} With this in mind, we began our metathesis activity studies by focusing on the catalytic activity of the *N*-mesityl series (**2**, **15–17**) in the RCM of diethyl diallylmalonate **24** to cycloalkene **25**. The reactions, utilizing 1 mol% catalyst in

Figure 2. X-ray crystal structures of complexes **17** and **20** are shown. Displacement ellipsoids are drawn at 50% probability. For clarity, hydrogen atoms have been omitted.

Figure 3. RCM of dienes **24**, **26**, and **28** to di-, tri-, and tetrasubstituted cycloalkenes **25**, **27**, and **29**, respectively, using catalysts **2** and **15–17**.

CD_2Cl_2 at 30°C , were monitored by ^1H NMR spectroscopy (Figure 3). Interestingly, the plots of cycloalkene **25** concentration vs time (Figure 3) revealed that the complexes effect the cyclization of **24**, but with slower reaction rates as backbone substitution is increased. The same trend was observed for the cyclization of diethyl allylmethylmalonate **26** to form trisubstituted cyclic olefin **27**. However, in the very challenging RCM of diethyl dimethylmalonate **28**, using 5 mol% catalyst in C_6D_6 at 60°C , increased substitution resulted in increased catalyst lifetimes and higher conversions to tetrasubstituted cyclic olefin **29**.

Several explanations could exist to explain these contradictory results. Along with decreased initiation rate, increased backbone substitution could also alter propagation rate, stability, or a combination of both. In any case, the results indicate that the assays reported by Ritter, et al., while useful for evaluating the activity of new catalysts,¹² do not distinguish between catalysts that are both highly active¹⁵ and stable.¹⁶ Future improvements in, and understanding of, olefin metathesis catalysts will require a more sensitive assay to evaluate small variations in the efficiency profile accompanying subtle modification in catalyst architecture.

Development of a ppm Level Assay. To study subtle differences in activity and stability, the standard RCM reactions should be observed at the lower limit of productive catalyst loading and under optimized conditions. With this in mind, new techniques were developed using a Symyx robotic system to maintain a high degree of precision and consistency when working with ultralow catalyst loadings. Our group has recently

Figure 4. RCM of diene **24** to disubstituted cycloalkene **25**, using catalyst **2** in a variety of solvents.

used these robotic systems to optimize reaction conditions and investigate new applications in olefin metathesis.¹⁷ Similarly, utilizing an automated Vantage system, Grela et al. recently reported the successful RCM of **24** at just 0.02 mol% **2**.¹⁸

A robotic assay was developed utilizing the RCM of diene **24** by complex **2**. Stock solutions of catalyst and substrate were prepared in a nitrogen-filled glovebox. While substrate stock solutions could be stored in septum-topped vials, catalyst

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Figure 5. RCM of diene **24** to disubstituted cycloalkene **25**, using catalyst **2**.

solutions were prepared immediately prior to use. The Symyx core module was utilized to add all solutions to reaction vessels as well as to sample the reaction mixtures at programmed time intervals. Aliquots were added into ethyl vinyl ether solution at $-20\text{ }^{\circ}\text{C}$,¹⁹ and then analyzed by gas chromatography with dodecane as an internal standard, measuring the change in the amounts of substrate and product with time. With minimal deviation in reaction results, 1 M (1 mL vials) and 0.1 M (20 mL vials) concentrations were employed depending on reaction scale and glassware to minimize substrate usage. The large vials were used in experiments where aliquots were withdrawn over the course of the reaction.

For practical reasons, most standard metathesis assays are performed in a closed system under inert atmosphere.^{12,18} However, we have observed variations in reaction rate and total conversion depending on the headspace of the reaction vessel. To circumvent this problem, reactions were carried out in open vials. Additionally, in order to minimize the potential for

decomposition pathways related to oxygen, all reactions were conducted in a nitrogen-filled glovebox. While ruthenium-based catalysts are relatively stable under ambient conditions, at low catalyst loadings oxygen related decomposition becomes relevant. Control reactions were completed on a Symyx core module open to atmosphere, confirming the importance for oxygen-free reaction conditions (Figure 4).

Other reaction considerations, including temperature and solvent, were optimized based on our recent complementary studies on the RCM of diallylamines with low catalyst loadings.^{17a} A solvent screen identified toluene as the optimal solvent for RCM of these diallyl substrates (Figure 4). Toluene as solvent also allowed for an increased temperature of $50\text{ }^{\circ}\text{C}$. While increased temperatures have previously been shown to increase metathesis reaction rates,^{18,20} temperatures above $50\text{ }^{\circ}\text{C}$ decreased assay consistency and resulted in significant solvent losses throughout the course of the reaction. The use of methylene chloride, the solvent most commonly used for RCM, resulted in considerable solvent loss even at $30\text{ }^{\circ}\text{C}$. Furthermore, its use resulted in decreased conversions, relative to other solvents. The RCM of **24** was then monitored over a variety of catalyst loadings to calibrate the new assay (Figure 5). Under optimized conditions (0.1 M, toluene, $50\text{ }^{\circ}\text{C}$), complex **2** afforded almost quantitative yields of **25** after 1 h at just 50 ppm.

Under the optimized conditions, trimethylated complex **17** required only 25 ppm to reach full conversion to disubstituted cycloalkene **25**; a catalyst loading near pharmaceutical impurity limits.⁸ In order to directly compare the *N*-mesityl series (**2** and **15–17**), catalyst loadings were further decreased to 15 ppm to ensure that no reactions would reach completion before the catalyst had completely decomposed. Again, at very low catalyst loadings, increased backbone substitution resulted in higher conversions to cyclic olefin **25**. When conversions were monitored over the course of the reaction, the effects of backbone substitution became evident (Figure 6a). The data suggest that the higher conversions are a direct result of longer catalyst lifetimes. However, as observed during the NMR studies, increased backbone substitution decreases catalyst reaction rate. These results were supported through observation

Figure 6. Plot of the RCM of diene **24** to disubstituted cycloalkene **25**, with conversion monitored over 24 h: (a) using catalysts **2** and **15–17**. The inset depicts a plot expansion over 1 h of the reaction; (b) using catalysts **3** and **20**.

Figure 7. RCM of diene **26** to disubstituted cycloalkene **27**, using catalyst **2**.

of the same trends when complexes **3** and **20** were studied using the same assay (Figure 6b).²¹

The catalyst efficiency assay was then expanded to study the RCM of **26** to give trisubstituted cycloalkene **27**. Calibration using the more sterically challenging substrate revealed that significantly more catalyst is necessary to effect full conversion to **27**, with complex **2** affording yields over 90% at 400 ppm catalyst loadings (Figure 7). The increase in required catalyst loading due to the addition of a single methyl group demonstrates the importance and effect of the olefin substrates steric environment.

Catalyst comparison reactions, performed at 200 ppm, reveal that the addition of substituents to the NHC ligands has greater impact on the efficiency of the metathesis catalysts than with the previous substrate, with **17** and **20** both outperforming their unsubstituted analogues (Figure 8). Notably, the RCM of **26** also clearly highlights the difference in stability between the *N*-mesityl (**2** and **17**) and the *N*-*o*-tolyl catalysts (**3** and **20**). For this trisubstituted olefin substrate, catalyst stability is more significant than activity for success in RCM. Complex **5** is the most active ruthenium-based catalyst to date, but not particularly stable under prolonged reaction conditions. As expected, while **5** performs exceptionally well at standard loadings (1 mol%), it falters at low catalyst loadings.

Finally, the ring-closing metathesis of **28** to tetrasubstituted cycloalkene **29** was examined using the same catalyst assay. Continuing the trend, at 0.2 mol% loading, complex **17** outperforms **2**, yielding just 15% and 7% of the tetrasubstituted cycloalkene respectively (Figure 9). Despite the expected low yields, the result reaffirmed the conclusion that backbone substitution increases the stability of the resulting complex. In the case of the *N*-mesityl series, this increase in stability has not resulted in a detrimental decrease in activity.

Figure 8. RCM of diene **26** to trisubstituted cycloalkene **27**, using catalysts **2**, **3**, **5**, **17**, and **20**.

Figure 9. RCM of diene **28** to tetrasubstituted cycloalkene **29**, using catalysts **2**, **3**, **17**, and **20**.

Figure 10. RCM of diene **28** to tetrasubstituted cycloalkene **29**, using catalysts **3**, **5**, and **20**.

Surprisingly, the *N*-*o*-tolyl series does not continue in the expected trend. Complexes **3** and **20** were compared at 0.2 mol% catalyst loading (Figure 9), revealing complex **3** to be the most efficient catalyst for this tetrasubstituted olefin. To confirm this result, complexes **3**, **5**, and **20** were tested at a lower loading of 0.1 mol% and the reactions were monitored over time (Figure 10). At this loading, the effectiveness of the catalysts to complete the RCM dropped significantly, providing a reminder that more efficient catalysts still need to be developed.

Complex **3** outperformed both the more stable **20** and the more active **5**. At low catalyst loadings, the decreased stability of **5** becomes a larger factor than its increased activity. Complex **20** faces the opposite challenge of substantially decreased activity. The differences between **3**, **5**, and **20** suggest that increased activity becomes more important than, but does not negate, increased stability for the RCM of very challenging substrates. While conversions were low, the experiment gives a clear result and is a reminder that the key to catalyst efficiency is the ratio of the rate of productive olefin metathesis relative to the rate of catalyst decomposition.

Conclusions

In summary, we describe the synthesis and characterization of a series of ruthenium-based olefin metathesis catalysts bearing NHCs with varying degrees of backbone and aryl substitution.

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- (21) Complexes **15**, **16**, **18**, and **19** underwent no further testing as experimentation continually demonstrated that complexes bearing disubstituted backbone ligands consistently gave results between the two extremes.

In order to study their subtle differences in activity and stability, a highly sensitive assay was developed to operate at the lower limit of productive catalyst loading. These techniques were developed using a Symyx robotic system to maintain a high degree of precision and consistency when working with ultralow catalyst loadings.

The development of this highly sensitive assay has provided increased insight into the relationship between ligand architecture and efficiency. In this study, both backbone and aryl substitution were found to significantly impact catalyst stability and activity. Whereas low *N*-aryl bulk on the NHC ligands led to increased activity, it also decreased stability. Increased backbone substitution, however, led to increased catalyst lifetimes and decreased reaction rates. Furthermore, it was found that the relative importance of stability and activity on efficiency is dependent on the steric encumbrance of the RCM reaction. For substrates with low steric demands, catalyst stability is quite important for success at low catalyst loadings. For sterically encumbered substrates, catalyst activity becomes much more important than increased stability. The ability to study the relationship between small changes in ligand architecture and efficiency will allow us to better explore new opportunities in catalyst design.

Experimental Section

General Information. NMR spectra were recorded using a Varian Mercury 300 or Varian Inova 500 MHz spectrometer. NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^1H and ^{13}C . Spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. IR spectra were recorded on a Perkin-Elmer Paragon 1000 Spectrophotometer. Gas chromatography data was obtained using an Agilent 6850 FID gas chromatograph equipped with a DB-Wax Polyethylene Glycol capillary column (J&W Scientific). High-resolution mass spectroscopy (FAB) was completed at the California Institute of Technology Mass Spectrometry Facility. X-ray crystallographic structures were obtained by the Beckman Institute X-ray Crystallography Laboratory of the California Institute of Technology. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K., and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers 670930 (**17**) and 651007 (**20**).

All reactions involving metal complexes were conducted in oven-dried glassware under a nitrogen atmosphere with anhydrous and degassed solvents, using standard Schlenk and glovebox techniques. Anhydrous solvents were obtained via elution through a solvent column drying system.²² Silica gel used for the purification of organometallic complexes was obtained from TSI Scientific, Cambridge, MA (60 Å, pH 6.5–7.0). $\text{RuCl}_2(\text{PCy}_3)(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$, **2**, and **3** were obtained from Materia, Inc. Unless otherwise indicated, all compounds were purchased from Aldrich or Fisher and used as obtained. The compounds **6**,^{13a} **7**,^{13b} **12**,^{13b} **21**,¹⁴ **24**–**29**,¹² have been described previously and were prepared according to literature procedures or identified by comparison of their spectroscopic data. The initial screening of the catalysts, in RCM via ^1H NMR spectroscopy was conducted according to literature procedures.¹²

Low ppm Level Assays. Experiments on the RCM of **24**, **26**, and **28** using the catalysts described were conducted using a SymyxTM Technologies Core Module (Santa Clara, CA) housed in a Braun nitrogen-filled glovebox and equipped with Julabo LH45 and LH85 temperature-control units for separate positions of the robot tabletop.

For experiments where aliquots were not taken during the course of the reaction, up to 576 reactions (6×96 well plates) could be performed simultaneously in 1 mL vials by an Epoch software-based protocol as follows. To prepare catalyst stock solutions (0.25 mM), 20 mL glass scintillation vials were charged with catalyst (5 μmole) and diluted to 20.0 mL total volume in THF. Catalyst solutions, 6 to 800 μL depending on desired final catalyst loading, were transferred to reaction vials and solvent was removed via centrifugal evaporation. The catalysts were preheated to the desired temperature using the LH45 unit, and stirring was started. Substrates (0.1 mmol), containing dodecane (0.025 mmol) as an internal standard, were dispensed simultaneously to 4 reactions at a time using one arm of the robot equipped with a 4-needle assembly. Immediately following substrate addition, solvent was added to reach the desired reaction molarity, generally 1 M. All reactions were quenched by injection of 0.1 mL 5% v/v ethyl vinyl ether in toluene at a preprogrammed time. Samples were then analyzed by gas chromatography.

Alternatively, where aliquots were taken during the course of the reaction, the entire operation was performed on 12 reactions simultaneously (4 catalyst loadings in triplicate or 2 catalysts at 3 catalyst loadings in duplicate) by an Epoch software-based protocol as follows. To prepare catalyst stock solutions (1.0 mM), 20 mL glass scintillation vials were charged with catalyst (5 μmole) and diluted to 5.0 mL total volume in toluene. Catalyst solutions, 10 to 400 μL depending on desired final catalyst loading, were transferred to glass 20 mL scintillation vials each capped with a septum having a 3 mm hole for the purpose of needle access, and were diluted to 10 mL total volume in toluene. The catalysts were preheated to 50.0 °C using the LH45 unit and stirred. Substrates (1 mmol), containing dodecane (0.25 mmol) as an internal standard, were dispensed simultaneously to 4 reactions at a time using one arm of the robot equipped with a 4-needle assembly. After the 2 min required for completion of the transfer, 50 μL aliquots of each reaction were withdrawn using the other robot arm and dispensed to 1.2 mL septa-covered vials containing 5% v/v ethyl vinyl ether in toluene cooled to –20 °C in two 96 well plates. The needle was flushed and washed between dispenses to prevent transfer of the quenching solution into the reaction vials. Sixteen time points were sampled at preprogrammed intervals and the exact times were recorded by the Epoch protocol. Samples were then analyzed by gas chromatography.

General Procedure for the Preparation of Catalysts 15–20.

To a solution of imidazolinium salt in toluene (or benzene) was added KHMDS, and the resulting solution was stirred at room temperature for a few minutes. $\text{RuCl}_2(\text{PCy}_3)(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$ was then added, and the mixture was stirred for the designated time and temperature (*vide infra*). After cooling to room temperature, the mixture was purified by column chromatography on TSI silica (eluent: hexane/diethyl ether = 2/1 $\rightarrow$ 1/1) to give the titled compounds as a green solid.

$\text{RuCl}_2(4,4\text{-dimethyl-1,3-dimesityl-imidazolin-2-ylidene})(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$ (15**).** **6** (200 mg, 0.54 mmol), potassium hexamethyldisilazide (140 mg, 0.70 mmol), and $\text{RuCl}_2(\text{PCy}_3)(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$ (250 mg, 0.42 mmol) was reacted according to the general procedure (stirred for 2 h at 70 °C) to give the desired ruthenium complex **15** as a green powder (135 mg, 0.21 mmol, 49%).

^1H NMR (500 MHz, CD_2Cl_2 , 25 °C): δ 16.46 (br s, 1H), 7.55 (ddd, J = 8.3 Hz, 2.0 Hz, 1H), 7.10 (br s, 2H), 7.05 (br s, 2H), 6.95 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.86 (sept, J = 6.1 Hz, 1H), 3.93 (s, 2H), 2.50–2.25 (m, 18H), 1.47 (s, 6H), 1.21 (d, J = 6.1 Hz, 6H).

^{13}C NMR (125 MHz, C_6D_6): δ 293.3 (m), 213.3, 153.0, 146.4, 141.3, 139.0, 138.6, 130.7, 130.0, 129.3, 122.7, 122.5, 113.6, 75.4, 68.2 (br), 65.6 (br), 28.1, 21.8, 21.5, 21.4.

HRMS Calcd for $\text{C}_{33}\text{H}_{42}\text{Cl}_2\text{N}_2\text{ORu}$: 654.1718. Found: 654.1725.

$\text{RuCl}_2(1,3\text{-dimesityl-4,5-dimethyl-imidazolin-2-ylidene})(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$ (16**).** **7** (100 mg, 0.27 mmol), potassium hexamethyldisilazide (70 mg, 0.35 mmol), and $\text{RuCl}_2(\text{PCy}_3)(=\text{CH-}o\text{-OiPrC}_6\text{H}_4)$ (250 mg, 0.42 mmol) was reacted according to the general procedure (stirred for 2 h at 70 °C) to give the desired ruthenium complex **16** as a green powder (135 mg, 0.21 mmol, 49%).

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OiPrC₆H₄) (100 mg, 0.17 mmol) was reacted according to the general procedure (stirred for 2 h at 70 °C) to give the desired ruthenium complex **16** as a green powder (60 mg, 0.092 mmol, 54%).

¹H NMR (500 MHz, C₆D₆, 25 °C): δ 16.74 (s, 1H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 (ddd, *J* = 7.5, 1.5 Hz, 1H), 7.00 (br s, 4H), 6.65 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 4.49 (sept, *J* = 6.1 Hz, 1H), 4.12 (s, 2H), 3.00–2.30 (br s, 12H), 2.25 (s, 6H), 1.31 (br s, 6H), 0.81 (d, *J* = 6.5 Hz, 6H).

¹³C NMR (125 MHz, C₆D₆): δ 293.8, 213.4, 153.0, 146.4, 140.7, 138.7, 130.2, 129.9, 128.8, 122.8, 122.5, 113.6, 75.3, 62.4 (br), 21.8, 21.4, 13.9 (br).

HRMS Calcd for C₃₃H₄₂Cl₂N₂ORu: 654.1718. Found: 654.1738.

RuCl₂(1,3-dimesityl-4,4,5-trimethyl-imidazolin-2-ylidene)(=CH-*o*-OiPrC₆H₄) (17). **8** (200 mg, 0.46 mmol), potassium hexamethyldisilazide (120 mg, 0.60 mmol), and RuCl₂(PCy₃)(=CH-*o*-OiPrC₆H₄) (200 mg, 0.33 mmol) was reacted according to the general procedure (stirred for 2.5 h at room temperature and 4 h at 60 °C) to give the desired ruthenium complex **17** as a green powder (97 mg, 0.15 mmol, 44%). Crystals suitable for X-ray crystallography were grown at room temperature by slow diffusion of pentane into a solution of **17** in benzene.

¹H NMR (500 MHz, C₆D₆, 25 °C): δ 16.65 (br s, 1H), 7.13–7.07 (m, 3H), 6.94 (br m, 3H), 6.63 (td, *J* = 7.6, 0.8 Hz, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 4.46 (sept, *J* = 6.1 Hz, 1H), 4.20 (br s, 1H), 2.85–2.47 (m, 12H), 2.24 (s, 3H), 2.21 (s, 3H), 1.28 (d, *J* = 6.1 Hz, 6H), 1.15 (br s, 3H), 0.88 (br s, 3H), 0.69 (br d, *J* = 6.9 Hz, 3H).

¹³C NMR (125 MHz, C₆D₆): δ 293.8 (m), 213.4 (br), 152.9, 146.5, 140.7, 138.7, 138.6, 130.9, 130.6, 130.3, 129.4, 122.7, 122.4, 113.6, 75.3, 71.0 (br), 68.4 (br), 25.1, 23.1 (br), 21.8, 21.5, 21.4, 12.1. HRMS Calcd for C₃₄H₄₄Cl₂N₂ORu: 668.1875. Found: 668.1898.

RuCl₂(1,3-ditolyl-4,4-dimethyl-imidazolin-2-ylidene)(=CH-*o*-OiPrC₆H₄) (18). **9** (190 mg, 0.60 mmol), potassium hexamethyldisilazide (157 mg, 0.78 mmol), and RuCl₂(PCy₃)(=CH-*o*-OiPrC₆H₄) (200 mg, 0.33 mmol) was reacted according to the general procedure (stirred for 2 h at 70 °C) to give the desired ruthenium complex **18** as a green powder (112 mg, 0.19 mmol, 57%).

¹H NMR (500 MHz, CD₂Cl₂, 25 °C): δ 16.41 (br s, 0.40H), 16.24 (br s, 0.60H), 8.59 (br s, 1.20H), 8.59 (br s, 0.80H), 7.60–7.20 (m, 7H), 6.88–6.81 (m, 3H), 4.91 (m, 1H), 4.40–3.60 (m, 2H), 2.62–2.40 (m, 6H), 1.64–1.07 (m, 12H).

¹³C NMR (125 MHz, CD₂Cl₂): δ 232.5, 152.2, 144.3, 141.9, 138.6, 134.3, 132.5, 131.4, 129.9, 129.5, 129.2, 128.9, 128.8, 127.6, 126.9, 122.3, 122.0, 121.8, 112.9, 74.8, 68.1, 66.6, 29.7, 27.3, 27.0, 26.9, 26.3, 24.6, 23.9, 21.5, 19.5.

HRMS Calcd for C₂₉H₃₄Cl₂N₂ORu: 598.1092. Found: 598.1064.

RuCl₂(1,3-ditolyl-4,5-dimethyl-imidazolin-2-ylidene)(=CH-*o*-OiPrC₆H₄) (19). **10** (100 mg, 0.32 mmol), potassium hexamethyldisilazide (70 mg, 0.35 mmol), and RuCl₂(PCy₃)(=CH-*o*-OiPrC₆H₄) (100 mg, 0.17 mmol) was reacted according to the general

procedure (stirred for 2 h at 70 °C) to give the desired ruthenium complex **19** as a green (39 mg, 0.065 mmol, 38%).

¹H NMR (500 MHz, C₆D₆, 25 °C): δ 16.64–16.41 (m, 1H), 9.00 (br s, 2H), 7.11–6.71 (m, 8H), 6.65 (m, 1H), 6.42 (t, *J* = 7.8 Hz, 1H), 4.57 (sept, *J* = 6.4 Hz, 1H), 4.29–3.55 (m, 2H), 2.65–2.25 (m, 6H), 1.20–1.60 (m, 6H), 1.05–0.60 (m, 6H).

¹³C NMR (125 MHz, C₆D₆): δ 291.7, 290.9, 232.5, 210.74, 152.8, 144.2, 140.0, 139.6, 138.6, 137.4, 132.4, 132.2, 131.5, 131.3, 130.6, 130.3, 121.9, 121.8, 113.0, 112.8, 74.4, 61.1, 61.0, 60.4, 21.7, 21.6, 13.2, 12.9.

HRMS Calcd for C₂₉H₃₄Cl₂N₂ORu: 598.1092. Found: 598.1097.

RuCl₂(1,3-ditolyl-4,4,5,5-tetramethyl-imidazolin-2-ylidene)(=CH-*o*-OiPrC₆H₄) (20). **11** (41 mg, 0.12 mmol), potassium hexamethyldisilazide (24 mg, 0.12 mmol), and RuCl₂(PCy₃)(=CH-*o*-OiPrC₆H₄) (60 mg, 0.1 mmol) was reacted according to the general procedure described above to give the desired ruthenium complex **20** as a green powder as a ca. 3:1 mixture of isomers (45 mg, 0.072 mmol, 72%). Crystals suitable for X-ray crystallography were grown at room temperature by slow diffusion of pentane into a solution of **20** in benzene.

¹H NMR (500 MHz, C₆D₆, 25 °C): δ 16.64 (s, 0.75H), 16.33 (s, 0.25H), 8.89 (d, *J* = 7.7 Hz, 0.75H), 8.84 (d, *J* = 7.9 Hz, 0.25H), 7.43–7.25 (m, 4H), 7.20–7.05 (m, 4H), 6.99–6.94 (m, 1H), 6.70–6.62 (m, 1H), 6.34 (d, *J* = 8.3 Hz, 1H), 4.45 (sept, *J* = 6.1 Hz, 1H), 2.74 (s, 0.75H), 2.68 (s, 2.25H), 2.47 (s, 0.75H), 2.44 (s, 2.25H), 1.38–1.20 (m, 10H), 1.04 (s, 2H), 0.76–0.70 (m, 6H).

¹³C NMR (125 MHz, C₆D₆): δ 214.0, 211.5, 153.1, 153.0, 145.8, 143.3, 143.2, 141.6, 140.8, 140.3, 139.8, 137.3, 136.5, 136.0, 134.7, 134.4, 132.3, 132.2, 131.9, 129.6, 129.5, 129.4, 129.1, 128.9, 127.6, 127.3, 126.9, 126.6, 122.7, 122.6, 122.6, 122.5, 113.5, 75.2, 75.1, 72.3, 71.8, 71.7, 71.4, 24.9, 24.3, 24.1, 23.9, 22.7, 22.5, 22.4, 22.2, 22.1, 22.0, 20.3, 20.1, 19.7, 19.4, 19.3.

HRMS Calcd for C₃₁H₃₈Cl₂N₂ORu: 626.1405. Found: 626.1427.

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Supporting Information Available: Detailed experimental procedures and characterization data. Crystallographic details for **17** and **20** are provided in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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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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(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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Low Pressure Ethenolysis of Renewable Methyl Oleate in a Microchemical System

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ABSTRACT

A microchemical system for ethenolysis of renewable methyl oleate was developed, in which the dual-phase, microfluidic design enabled efficient diffusion of ethylene gas into liquid methyl oleate through an increased contact area. The increased mass transfer of ethylene favored the formation of desired commodity chemicals with significantly suppressed homometathesis when compared to the bulk system. In addition to higher selectivity and conversion, this system also provides the typical advantages of a microchemical system, including the possibility of convenient scale-up.

The generation of useful, low molecular weight chemicals from renewable natural resources is an important research topic throughout the fields of chemistry and chemical engineering. Because of environmental challenges and potential economic advantages, the search for new feedstock sources and the development of chemical and biological processes to utilize the new feedstocks are the focus of much research.¹ Ruthenium catalysts, which have become useful for organic synthesis and polymer chemistry, have been tested in the olefin metathesis of internal olefins with ethylene, known as

ethenolysis, which can be used to produce the desired low molecular weight products from renewable seed oils (eq 1).²

Early studies of the ethenolysis of natural seed oils showed promise but was limited by the high sensitivity of the traditional molybdenum, tungsten, and rhenium catalysts. The advent of ruthenium catalysts with low sensitivity but high activity has spurred a renewed interest in ethenolysis, but limited selectivity and conversion have hampered progress to commercially viable processes. Homometathesis continues to be a troubling competing reaction which reduces the yield.

Microchemical systems have provided new strategies and new challenges as new process techniques.³ The benefits of precise control of reaction variables and high surface area-to-volume ratios are manifest in reduced

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waste, higher yield, and reduced reaction times. Furthermore, the difficulties of scale-up can largely be avoided by simple parallelization of small-scale microfluidic test reactors. In addition to traditional, one-step microchemical reactions, several consecutive reactions, including separation, purification, and detection, have been successfully integrated as complete microchemical processes.⁴

A particularly challenging type of microchemical system is the heterogeneous reaction involving any combination of the gas, liquid, and solid phases.⁵ The heterogeneous reactions between gas and liquid are mainly conducted with two main modes of contact:⁶ one with the two phases flowing in contact in parallel, the other with alternative bands of gas bubbles and liquid slugs. In a recent report we described a microchemical system with the former mode of contact mediated by a PDMS (polydimethylsiloxane) membrane.⁷ As an alternative to this strategy, however, we feel the segmented mode of contact has its own unique advantages due mainly to the simple, convenient setup and a broader choice of available capillary materials, allowing better chemical stability and mechanical strength even at high pressure. Herein, we report a facile and efficient microchemical ethenolysis under various reaction conditions, through the continuous segmented flow of ethylene and methyl oleate in a capillary tube with a 0.5 mm inner diameter. Moreover, the reaction was performed nearly solvent-free, except for a minimum amount of toluene to dissolve the catalyst (1.0 mg of catalyst in 2.0 mL of toluene), which avoids the use of excess organic solvent to facilitate the dissolution of ethylene gas as has been reported.⁸ The poor solubility of ethylene in methyl oleate (mole fraction of ethylene/methyl oleate = 0.108, 60 psi)^{2a}

and the slow diffusion of ethylene into the solution favor homometathesis instead of the desirable ethenolysis. Overcoming the bias for homometathesis suggests two straightforward strategies: developing catalysts with a high kinetic selectivity for ethenolysis, or engineering processes to drive ethylene into the reaction. The engineering approach was the main strategy of this work and was accomplished by increasing the contact area between methyl oleate and ethylene, thereby maximizing the transfer of the ethylene into the methyl oleate phase with high diffusion efficiency.⁶

Figure 1. (A) Microchemical ethenolysis of methyl oleate (MO) with Ru catalyst (1.0 mg/2 mL toluene). (B) Segmented flow of ethylene and methyl oleate in a capillary microreactor.

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In the initial design a mode of merging phases which is a general approach for reactions of this type was adopted (see Supporting Information for the system, Figure 1SA). Ethylene gas and methyl oleate were mixed in the first T-junction where slugs of liquid formed in the gas flow. In the second T-junction the flow was merged with the catalyst solution to form larger liquid slugs in the gas flow. However, this system resulted in an irregular distribution of catalyst in the methyl oleate due to slight variations in the flow rate between the two T-junctions. Because of the unsatisfactory results, the mixing order was changed so that the catalyst (at 1.0 µL/min) and substrate (at 5.7 µL/min) were mixed first and the ethylene gas was added second (Figure 1). This created the potential for a deleterious side reaction when the catalyst and substrate were mixed with no ethylene, but this was mitigated by lowering the temperature in the section between the T-junctions. The lower temperature also was expected to facilitate the diffusion of ethylene into solution. The cooled mixture of catalyst and methyl oleate was quickly saturated with ethylene injected in the second T-junction and then heated to start the reaction, taking advantage of the rapid heat transfer of microchemical systems.³ The flow rate of the solution, and consequently the retention time, was finely controlled by a peristaltic pump instead of the more general approach of regulating the back pressure.

A noticeable shortening of the length of ethylene bubbles was observed through the length of the microreactor, a not unexpected observation as ethylene is consumed during the reaction.⁹ The pressure drop across the length of the microreactor caused by the increased friction of the segmented liquid flow was worrisome because of the potentially variable solubility of ethylene, but the pressure at the exit was measured to be 56 psi when the inlet pressure was set to 60 psi. The pressure differential and corresponding solubility difference were thus concluded to be negligible.

Figure 2. Ethenolysis under different temperature and pressure conditions. Catalyst **6** (300 ppm) was used. (a) Yield (%) = conversion $\times$ selectivity = $(1 - \text{final moles of } \mathbf{1} / \text{initial moles of } \mathbf{1}) \times \{(2 - 3) / (2 - 3 - 4 - 5)\} \times 100$. Conversion and selectivity were determined by GC analysis. (b) Selectivity after 120 min retention time.

As the effects of pressure and temperature in the batch system were well documented in previous reports,² the same variables were carefully studied in the microchemical system. With 300 ppm of catalyst **6**, the pressure was varied from 15 to 60 psi and the temperature was varied from 20 to 40 °C. The results illustrate that the pressure of ethylene has a direct impact on the yield (Figure 2).¹⁰ Elevating the temperature over 30 °C resulted in a 5% loss in the net yield after 120 min, due to the decreased selectivity (30 psi and 40 °C: 48% conversion, 85% selectivity, 30 psi and 40 °C: 50% conversion, 72% selectivity). These good results at low temperature and high pressure are well consistent with the batch studies, where the same factors increase the selectivity and yield of ethenolysis.²

For the ethenolysis of methyl oleate **1**, six ruthenium catalysts were selected: first generation catalysts **6** and **7**; second generation catalysts **8**, **9**, and **10**; and cyclic alkyl-amino carbene (CAAC)-based catalyst **11**¹¹ (Figure 3). Each catalyst was screened at a variety of catalyst loadings, and the results were tabulated (Table 1). When catalyst **6** was used at 0 °C only a negligible amount of product was formed, confirming that no olefin metathesis occurs in the first cooled mixing zone as was expected in the redesigned system (entry 1). When the first mixing section was not

Figure 3. Ruthenium catalysts for ethenolysis of methyl oleate.

cooled, an increase in homometathesis was observed as expected (entry 3). Hoveyda-type catalyst **7** was slightly more effective than catalyst **6** (entries 4 and 5), and the typical second generation catalyst **8** gave the poorest results in selectivity and yield, although the more active catalyst required less time than catalysts **6** and **7** to achieve a similar conversion (entries 6–8). The second generation catalysts **9** and **10**, which contain a sterically hindered NHC ligand, also gave lower yields than PCy₃-based catalysts **6** and **7** (entries 9–12), even though it is known that catalysts with NHC ligands have better stability and activity toward olefin metathesis than catalysts with PCy₃ ligands. In this case the homocoupling reaction, while not significant for phosphine-based catalysts **6** and **7**, accounted for about half the activity of the NHC-based

Table 1. Ethenolyses of Methyl Oleate **1** in the Microchemical System^a

	cat. (ppm)	t (°C)	time (min)	conv (%) ^c	select (%) ^d	yield (%) ^e	TON ^f
1	6 (150)	0	180	3	99	3.0	600
2	6 (300)	30	120	65	96	62.4	5800
3	6 ^b (300)	30	120	66	91	60.1	5600
4	7 (100)	30	120	39	94.8	37.0	7500
5	7 (300)	30	120	69	93.7	64.7	4400
6	8 (50)	40	60	58	45	26.1	11 000
7	8 (100)	30	120	59	43.5	25.7	5400
8	8 (100)	40	60	61	41	25.0	5300
9	9 (50)	40	60	54	52	28.1	13 500
10	9 (100)	40	60	57	50	28.5	6800
11	10 (50)	40	40	61	58	35.4	22 300
12	10 (100)	40	40	63	55	34.7	10 900
13	11 (50)	40	60	80	87	69.6	27 200
14	11 (100)	40	60	81	84	68.0	13 300
15	11 (100)	40	30	72	88	63.4	12 400

^a General reaction conditions: 60 psi ethylene, the microchemical system described in Figure 1A. Conversion and selectivity were determined by GC analysis. ^b No cooling of the mixing zone. ^c Conversion = $(1 - \text{final moles of } \mathbf{1} / \text{initial moles of } \mathbf{1}) \times 100$. ^d Selectivity (%) = $(2 - 3) / (2 - 3 - 4 - 5) \times 100$. ^e Yield (%) = conversion $\times$ selectivity/100. ^f TON = yield / [(initial moles of **1**) / (moles of cat.)].

(9) In addition to the higher surface area-to-volume ratio, the microfluidic system is free from pressure drop, even though much of the gas is consumed, which is a property not found in batch systems.

(10) Conversion and selectivity for each condition are in the Supporting Information, Table 1S.

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catalysts **8**, **9**, and **10**. The result from catalyst **11** is the most noteworthy as the catalyst is currently the most selective catalyst known for ethenolysis among the NHC-based catalysts. Catalyst **11** gives the highest yield in this study, even when compared with phosphine-based catalysts **6** and **7**. Catalyst **11** gave a 69.6% yield with only 50 ppm catalyst and a 60 min retention time (entry 13). The selectivity is comparable to the result of the batch reaction tested at higher pressure (selectivities up to 83% were measured at 150 psi), but because of the higher conversion the yield was higher in the microchemical system.^{2b} Additionally, the selectivities of catalysts **6**, **7**, **8**, **9**, and **10** are superior in the microchemical system at 60 psi compared to the batch reaction at 150 psi.

In conclusion, a microchemical system for gas–liquid dual-phase reactions was developed which was applied to the ethenolysis of methyl oleate. The results at 60 psi

of ethylene were comparable to the results of batch reactions at 150 psi of ethylene. This is expected to be due to the high surface area-to-volume ratio suitable for fast mass transfer of the gas into the solution phase. The sterically hindered CAAC-based ruthenium catalyst **11** gave 80% conversion and 87% selectivity with only 50 ppm catalyst.

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