JOC Article

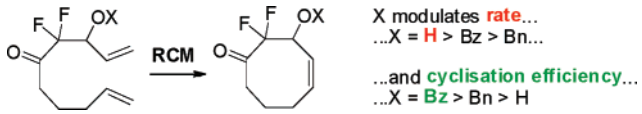
Selected Substituent Effects on the Rate and Efficiency of Formation of an Eight-Membered Ring by RCM

Lisa Mitchell,[†,‡] John A. Parkinson,[‡] Jonathan M. Percy,*[,‡] and Kuldip Singh[†]

Department of Chemistry, University of Leicester, University Road, Leicester LE1 7RH, United Kingdom, and Department of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow G1 1XL, United Kingdom

jonathan.percy@strath.ac.uk

Received December 21, 2007



Studies of a range of reactions forming cyclooctenones highlight a discrepancy between cyclization rate and cyclization efficiency. Cyclization rates change modestly as the oxygen function at the allylic position is varied, and increase upon *gem*-dimethylation. Cyclization efficiency has also been quantified for four substrates, revealing a range of effective molarities (EMs) of 2 orders of magnitude that are substituent dependent. The most efficient cyclization appears to result from suppression of the cross-metathesis pathway through which oligomerization begins, rather than from a particularly rapid cyclization reaction. In the presence of a Ti(IV) cocatalyst, diene monomers transform smoothly to eight-membered-ring products without the intermediacy of dimers or other oligomers, indicating that the cyclizations are kinetically and not thermodynamically controlled. The *gem*-dialkyl effect is also shown to be kinetic.

Introduction

The ring closing metathesis (RCM) reaction has changed the way we think about the synthesis of cyclic molecules, leading to the award of the Nobel Prize to the three chemists most responsible for the major strategic advances in the area.[1] The direct synthetic connection of an α,ω-diene to a cyclic alkene or unsaturated heterocycle in the presence of numerous functional groups of a wide range of types and at high density can be achieved routinely by using commercially available and easy-to-handle Ru catalysts. Total syntheses of many complex natural products[2] have been planned and executed by using the RCM as a strategic event.[3] The tolerance of the reaction to variations in ring size is remarkable, with even rings that are usually difficult to make, like medium rings,[4] being formed in high yield (if appropriate substitution patterns are present). Though Fürstner[5] inter alia has outlined a number of extremely useful general ideas that explain the success of RCM reactions, our detailed knowledge of the interplay of structure and efficiency in the RCM is limited.[6] Some detailed computational studies of very simple prototypical reactions[7] and of relatively complex cyclization systems[8] have been carried out, but there seem to be relatively few general computational insights concerning cyclization.

[†] University of Leicester.
[‡] University of Strathclyde.

(1) For the award lectures from the three Laureates, see: (a) Chauvin, Y. *Angew. Chem., Int. Edit.* **2006**, *45*, 3740. (b) Schrock, R. R. *Angew. Chem.-Int. Ed.* **2006**, *45*, 3748. (c) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760. For a recent overview, see: *Chem. Eng. News* **2007**, *85*, 37. For a recent review, see: Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.

(2) For recent examples, see: (a) Klar, U.; Buchmann, B.; Schwede, W.; Skuballa, W.; Hoffinann, J.; Lichtner, R. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 7942. (b) Hong, Z. Y.; Liu, L.; Hsu, C. C.; Wong, C. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7417. (c) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (d) Furstner, A.; Nevado, C.; Tremblay, M.; Chevrier, C.; Teply, F.; Aissa, C.; Waser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5837. (e) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547. (f) Inoue, M.; Sato, T.; Hirama, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4843. (g) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383. (h) Hong, S. W.; Yang, J. H.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2078. (i) Bohrsch, V.; Neidhofer, J.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1302.

(3) For an elegant and comprehensive recent review, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(4) (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(5) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

(6) (a) For an excellent overview, see: Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.* **2006**, *10*, 185. Enyne metathesis has received much more detailed scrutiny; see: (b) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55. (c) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442.

(7) (a) Cavallo, L. *J. Am. Chem. Soc.* **2002**, *124*, 8965. (b) Tsipis, A. C.; Orpen, A. G.; Harvey, J. N. *Dalton Trans.* **2005**, 2849. (c) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496. (d) Fomine, S.; Vargas, S. M.; Tlenkopatchev, M. A. *Organometallics* **2003**, *22*, 93.

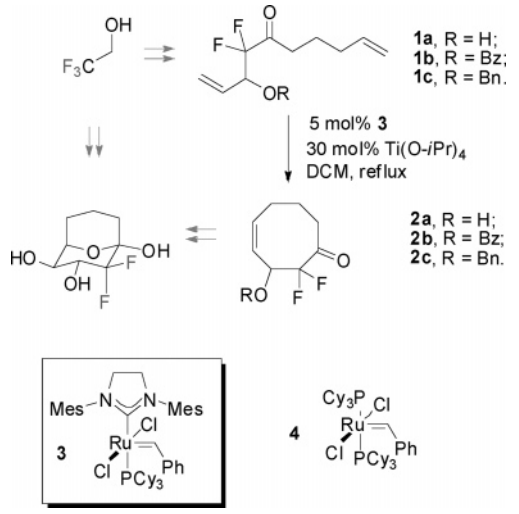
10.1021/jo702726b CCC: $40.75
Published on Web 02/14/2008

Two classic reviews by Mandolini[9] summarized a large set of data derived from lactonizations, intramolecular etherifications, and C−C bond-forming reactions, and reported the relationship between cyclization efficiency and ring size. Medium rings represent some of the most difficult challenges for cyclization strategies; the combination of developing ring strain and the requirement to restrict rotations around 7−9 flexible bonds ensures unfavorable enthalpic and entropic[10] contributions to $\Delta G^{\ddagger}$; cyclization reactions that form medium rings are therefore often relatively slow. High dilution (or Ziegler) conditions are often employed to reduce the rate of competing oligomerization pathways, because relatively inefficient cyclization is anticipated.

The RCM reaction converts a diene precursor to two alkene molecules, one of which is volatile ethylene in most synthetic sequences, allowing the unfavorable $\Delta S^{\ddagger}$ (and $\Delta H^{\ddagger}$) associated with cyclization to be compensated for entropically. Nevertheless, RCM reactions that form medium rings, for example, cyclooctannulation,[11] which is severely enthalpically and entropically disadvantaged, are reported to require high catalyst loading, high dilution, long reaction times, and importantly some degree of "gearing" of appropriately placed substituents[12] to deliver acceptable yields of cycloalkene products. These factors combine to severely restrict scaleability (in principle). Almost all our insights concerning RCM efficiency come from yield measurements; there are very few kinetic studies of the RCM reactions and those that are published involve the formation of five-membered rings and cyclization is not rate-determining.[13] There are no *measured* effective molarities in the literature; Fogg has presented a number of *expected* values of RCM EMs based on ring size but we are unaware of any experimental determinations of EM for RCM reactions.[14]

In the absence of quantitative information about a wide range of systems, the optimization of RCM reactions remains a matter of trial and error rather than one of rational design based on a *detailed* understanding of the underlying principles.

SCHEME 1



Recently, we showed how we could use metalated difluoroalkene chemistry to advance trifluoroethanol rapidly to deliver a number of sugar-like systems and a glycosyl phosphate analogue; the synthesis of a cyclooctenone template **1** by RCM[15] was a key step (Scheme 1).[16]

We wished to optimize the RCM reaction by varying the reaction solvent and temperature and the loading of the Ruthenium catalyst and by the correct choice of protection (R in **1**) for an allylic hydroxyl group, reporting the results of qualitative studies in our full synthetic paper. We now wish to report the results of a study in which substituent effects on RCM are quantified for the first time, with the two fluorine atoms acting as reporter groups for the various constituents within complex reaction mixtures.

A number of authors have reported that allylic substituents can exert large effects on RCM reaction yield[17] and regiochemical outcome.[18] In the most cited paper in the area, Hoye and

(8) (a) Vyboishchikov, S. E.; Thiel, W. *Chem.-Eur. J.* **2005**, *11*, 3921. (b) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem.- Eur. J.* **2005**, *12*, 51.

(9) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117.

(10) Buszek and co-workers have measured very small $\Delta S^{\ddagger}$ values for a series of lactonisations forming eight-membered rings; see: Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781.

(11) For a recent review, see: Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740.

(12) The literature describes a number of failed attempts to cyclize simple (often geminally disubstituted) cyclooctene precursors; however, Taylor and Crimmins found that precursors with appropriately placed vicinal substituents could be cyclized successfully. For successful examples demonstrating the importance of substituent patterns or gearing, see: (a) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (b) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473. (c) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267. For unsuccessful attempts to cyclize less substituted systems, see: (d) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (e) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309. For the ROMP of cyclooctene with tungsten alkylidene catalysis, see: (f) Kress, J. *J. Mol. Catal. A* **1995**, *102*, 7. The copious ROMP literature for cyclooctenes is well reviewed by Ivin; see: (g) Ivin, K. J. *Olefin Metathesis*; Academic Press: New York, 1983.

(13) Most of the quantitative studies deal with simple 5- and 6-ring-forming reactions: (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Bassetti, M.; Centola, F.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Organometallics* **2003**, *22*, 4459. See also: (c) Basu, K.; Cabral, J. A.; Paquette, L. A. *Tetrahedron Lett.* **2002**, *43*, 5453. (d) Guo, X.; Basu, K.; Cabral, J. A.; Paquette, L. A. *Org. Lett.* **2003**, *5*, 789. (e) Paquette, L. A.; Basu, K.; Eppich, J. C.; Hofferberth, J. E. *Helv. Chim. Acta* **2002**, *85*, 3033.

(14) For a study that begins to examine a much wider range of systems and discusses cyclization efficiency, see: Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Pamas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024.

(15) (a) Miles, J. A. L.; Mitchell, L.; Percy, J. M.; Singh, K.; Uneyama, E. *J. Org. Chem.*, **2007**, *72*, 1575−1587. (b) For a related system, see: Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N.; Uneyama, E. *Org. Biomol. Chem.* **2005**, *3*, 2701.

(16) For examples of RCM-based syntheses of selectively fluorinated molecules, see: (a) Butt, A. H.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **2000**, 1691. (b) Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528. (c) Audouard, C.; Fawcett, J.; Griffith, G. A.; Kerouredan, E.; Miah, A.; Percy, J. M.; Yang, H. L. *Org. Lett.* **2004**, *6*, 4269. (d) Fustero, S.; Catalan, S.; Piera, J.; Sanz-Cervera, J. F.; Fernandez, B.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 4010. (e) Fustero, S.; Sanchez-Rosello, M.; Jimenez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 2706. (f) Fustero, S.; Bartolome, A.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Soler, J. G.; de Arellano, C. R.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523. (g) De Matteis, V.; van Delft, F. L.; Jakobi, H.; Lindell, S.; Tiebes, J.; Rutjes, F. *J. Org. Chem.* **2006**, *71*, 7527. (h) De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. *Eur. J. Org. Chem.* **2006**, 1166. (i) Yang, Y. Y.; Meng, W. D.; Qing, F. L. *Org. Lett.* **2004**, *6*, 4257. (j) You, Z. W.; Wu, Y. Y.; Qing, F. L. *Tetrahedron Lett.* **2004**, *45*, 9479.

(17) For reports of significant substitutent effects on RCM outcomes, see: (a) Castoldi, D.; Caggiano, L.; Bayon, P.; Costa, A. M.; Cappella, P.; Sharon, O.; Gennari, C. *Tetrahedron* **2005**, *61*, 2123. (b) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Tesler, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913. (c) Kaliappan, K. P.; Kumar, N. *Tetrahedron* **2005**, *61*, 7461. (d) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263. (e) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.

SCHEME 2

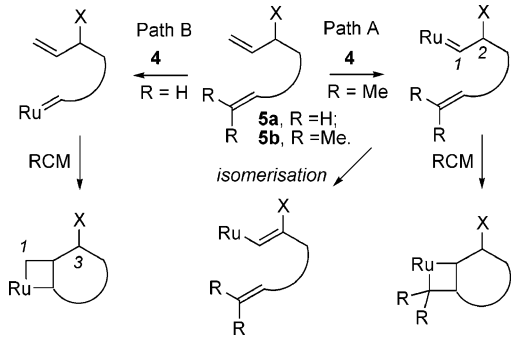
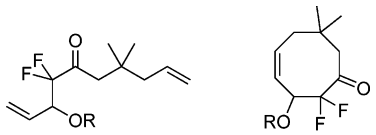


CHART 1



6a, R = H;
6b, R = Bz;
6c, R = Bn.

7a, R = H;
7b, R = Bz;
7c, R = Bn.

Zhao[19] studied the effect of allylic substitutents on the rate ofcyclopentannulation (Scheme 2, path A) using Grubbs' first generation catalyst **4** and concluded that "free allylic hydroxyl groups exerted a large *activating* effect upon the initial carbene exchange reaction with an adjacent vinyl group...". They also observed that "secondary hydroxyl groups are a liability in RCM reactions because of a net fragmentation reaction that consumes ruthenium alkylidene species" (this arises via the isomerization pathway shown in the scheme). Hoye's system (**5b**) sterically commits the active catalyst to react at the allylic alcohol terminus (Path A).[20] The published papers that cite Hoye and Zhao usually refer to another order of events which is path B (substrate **5a** would react by this pathway).

The large effects in Hoye's system presumably arise because of the orientation of the addition of the starting alkylidene across the alkenyl group of the allylic fragment. To start the reaction, the metal must add close to the substituent (the fragmentation reaction can then proceed from this pathway) and significant steric effects would be expected because the coordination sphere around ruthenium is compressed by bulky ligands. Hoye concludes that the large effect observed arises from a difference in the rate of alkylidene transfer, rather than cyclization (a conclusion overlooked by most of the authors citing the paper). In the case of **1a**−**c** and **6a**−**c** (Chart 1), reaction would be expected to initiate at the terminal Type I alkenyl group. Though *gem*-dimethylation at the homoallylic position is likely to reduce the rate of initiation in the more substituted species slightly,[21] we would expect the rate retarding effect of an allylic oxygen function to be bigger than the more remote steric effect.

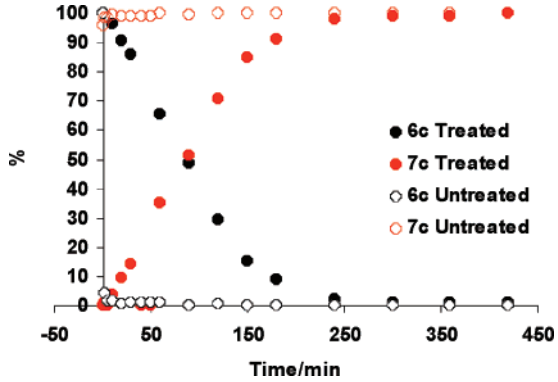


FIGURE 1. Substrate consumption appears instantaneously in the absence of sample treatment. RCM of **6c** (0.01 M in DCM, 1 mol % **3**, 30 mol % Ti(O-*i*Pr)$_4$, 25 ± 0.1 °C).

This range of substrates will allow us to begin to quantify both the effects of the free hydroxyl group and commonly used protected forms at the allylic position in path B and the *gem*-dialkyl effect on the rate and efficiency of the cyclization reaction.

Results and Discussion

Development of a Sampling Protocol for RCM Reactions. We developed a protocol to follow RCM directly (2% precatalyst **3**, 30% Ti(O*i*-Pr)$_4$ cocatalyst, 10 mM in substrate in dry degassed CH_2Cl_2 at room temperature or above), in which aliquots were withdrawn by syringe and passed through C-18 silanized solid-phase extraction (SPE) tubes that had been preconditioned with wet acetonitrile. Each sample was eluted with acetonitrile into a GC vial. This protocol ensured that the alkylidene catalyst was destroyed very close to the time of sampling and gave reproducible results for all substrates. Figure 1 shows the effects of aliquot treatment on the cyclization of **6c**; in the untreated experiment, the consumption of precursor appears to be instantaneous. Samples removed from reactions which were transferred straight to GC vials for analysis without treatment and the queued for GC analysis gave unreproducible and misleading results as the RCM continued in the GC vial, despite addition of wet CH_2Cl_2.[22]

The apparent rapid consumption of starting material can be shown to be an experimental artifact by ^{19}F NMR analysis, in which starting material can be seen to be the major species present in untreated aliquots taken close to the beginning of the reaction. The profiles arising from the treated samples show the smooth conversion of diene monomer into eight-membered-ring product, without the formation of other products (detectable by GC-MS or ^{19}F NMR). The product formation curve mirrors precursor consumption; response factors were determined for all precursors and products. We also checked the composition of product mixtures before and after passage through the SPE media; there was no perturbation of the composition, indicating that there was no selective retention of products or precursors

(18) Allylic substituents appear to modulate the competition between RCM reactions that form 5- and 6-membered rings; see: (a) Schmidt, B.; Nave, S. *Chem. Commun.* **2006**, 2489. (b) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143.

(19) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.

(20) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(21) (a) Homoallylic methylation lowers the rate of alkylidene transfer by ca. 50%; see: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484. (b) For a recent investigation of related effects, see: Courchay, F. C.; Baughman, T. W.; Wagener, K. B. *J. Organomet. Chem.* **2006**, *691*, 585.

(22) A landmark paper describes the scale-up of a synthetic campaign in which RCM delivers a macrocycle. Analysis is secured by using a sulfur nucleophile to sequester and deactivate the Ru-catalyst: Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X. J.; Wei, X. D.; Simpson, R. D.; Feng, X. W.; Fuchs, V.; Xu, Y. B.; Tan, J.; Zhang, L.; Xu, J. H.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133.

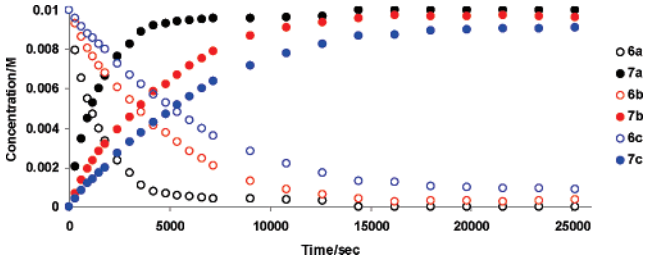


FIGURE 2. Competitive RCM between substrates **6a**, **6b**, and **6c** (0.01 M in each substrate in DCM, 2 mol % **3**, 30 mol % Ti(O-*i*Pr)$_4$ per substrate, 25 ± 0.1 °C, treated aliquots).

(see the Supporting Information for details). Carrying out the reactions at higher concentration leads to the formation of more complex reaction mixtures, as discussed later in the paper ({^{1}H}^{19}F NMR spectra for simple and complex RCM product mixtures and characterization studies are presented in the Supporting Information).

Kinetic Profiling of the RCM Reactions. A competition experiment was carried with **6a**−**c** in the same reactor to investigate the relationship between cyclization reactivity and allylic functional group. The reactions were run in degassed CH_2Cl_2 at 298 K with **3** at 2 mM (2 mol %) and Ti(O-*i*Pr)$_4$ (30 mol %) per substrate (each substrate present at 10 mM) to maintain a constant ratio of catalyst to total substrate.

Data showed a relatively low degree of scatter suggesting that the sampling and preparation routine was reliable and reproducible. None of the reactions could be fitted to first-order kinetic plots.[23] The nature of the allylic substituent exerted a decisive effect on the rate of consumption of precursor as shown in Figure 2 (and on product formation which mirrors the precursor consumption profile in each case); the order of reactivity is **6a** > **6b** > **6c**.[24] The approximate half-lives of the three substrates are 1200, 3500, and 5400 s. There is no obvious explanation for this difference in reactivity but a number of authors have commented on remote substituent effects on RCM reactions.[25,26] The steric sizes of −OH, −OBn, and −OBz substituents as measured by their *A*-values are all rather similar so significant steric effects seem unlikely.

The reactions continue to different extents, with **6a** reaching 100% conversion, **6b** ca. 97%, and **6c** 90%. Diene and cycloalkene concentration can be measured reproducibly to ±4% so the slower reaction has clearly failed to reach completion.[27]

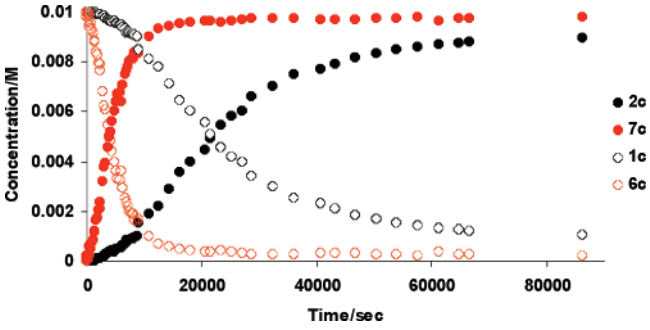


FIGURE 3. Competitive RCM between *gem*-dimethylated **6c** and less substituted **1c** (0.01 M in each substrate in DCM, 2 mol % **3**, 30 mol % Ti(O-*i*Pr)$_4$ per substrate, 25 ± 0.1 °C, treated aliquots).

We cannot explain these data by postulating the existence of an equilibrium reaction between diene and a mixture of cycloalkene and ethylene, because ethylene has very low solubility in the reaction solvent and is free to depart the open system.[9f] As cyclooctenol formation accurately mirrored diene consumption, we are not observing an equilibrium reaction between oligomers and cyclooctenol (several aliquots were concentrated after analysis to look for oligomers by ^{19}F NMR, and none were found). Synthetic reactions run at higher initial concentrations reach completion indicating that inhibition by reaction product is not responsible for the establishment of an equilibrium reaction under these conditions. Instead, it appears that the loss of activity of **3** appears to be significant at room temperature in CH_2Cl_2 even on the relatively short time scale of 10 h, with major implications for the conduct of slow RCM reactions with **3** (see the Supporting Information for the procedure used to establish this and the experimental data). To our knowledge, the rates of decomposition of **3**, the active benzylidene, or the methylidene formed upon turnover have not been reported under *synthetic* conditions,[28] though some computational studies have been carried out.[29]

The *gem*-Dialkyl Effect on the RCM. Figure 3 shows the competition between **1c** and **6c** in CH_2Cl_2 at 298 K under the usual conditions and with the same sampling protocol as described previously. The reaction of **6c** is dominated by the rapid cyclization with no visible induction period. The reaction end-point lies within experimental error of 100% completion. The failure of the slower reaction of **1c** to complete is believed to be due to the decomposition of catalyst on this time scale; this reaction also appears to have a distinct induction period, where relatively little substrate is turned over.

The exaggerated induction phase in the decay curve is presumably due to competition between the two substrates. The consumption of **1c** speeds up significantly once most of **6c** has been consumed; this would be consistent with intermediate alkylidene exiting more rapidly through cyclization in the *gem*-dialkylated case. The approximate half-lives of the reactions are 3900 and 21600 s, corresponding to an approximate rate

(23) Bassetti and co-workers (ref 9b) followed the formation of a 5-membered ring by RCM and noted that precursor consumption was not first order in some circumstances. The kinetic regime can include catalyst formation from precatalyst and a number of other events in addition to cyclization. We have established that the range and order of reactivity is correct by repeating the experiments with only a single substrate present. The detailed kinetic analysis will be reported elsewhere.

(24) A referee suggested that the competition between the three substrates may lead to perturbation of the profiles for the slower substrates. However, the purpose of the experiment is to show the rank order of reactivity, and the approximate range from highest to lowest, that the profiles from the competition reaction do successfully. The order of reactivity is not changed from single substrate experiments.

(25) (a) Aissa, C.; Riveiros, R.; Ragot, J.; Furstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512. (b) Meng, D. F.; Su, D. S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y. H.; Chou, T. C.; He, L. F.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733.

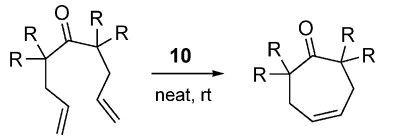
(26) For effects due to hydrogen bond formation, see: (a) Vassiliko-giannakis, G.; Margaros, L.; Tofi, M. *Org. Lett.* **2004**, *6*, 205. Furstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731.

(27) Detection limits were estimated based on response factor measurements and we estimate that ±4% is a reasonable estimate of the accuray of individual concentration measurements at 10 mM starting concentration.

(28) Ulman and Grubbs studied the lifetimes of a range of precatalyst systems; the imidazolidinylidene-based precatalyst related to **3** was studied but no data were reported for **3** (the dihydroimidazolidinylidene-based precatalyst). See: Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202. Grubbs and co-workers recently examined the decomposition of the relevant phosphine complexes in the presence of ethene: Hong. S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961.

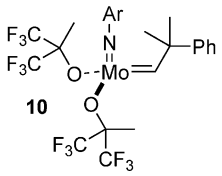
(29) (a) van Rensburg, W. J.; Steynberg, P. J.; Kirk, M. M.; Meyer, W. H.; Forman, G. S. *J. Organomet. Chem.* **2006**, *691*, 5312. (b)

SCHEME 3



8a, R = H
8b, R = Me.

9a, R = H, 0%;
9b, R = Me, 95%.

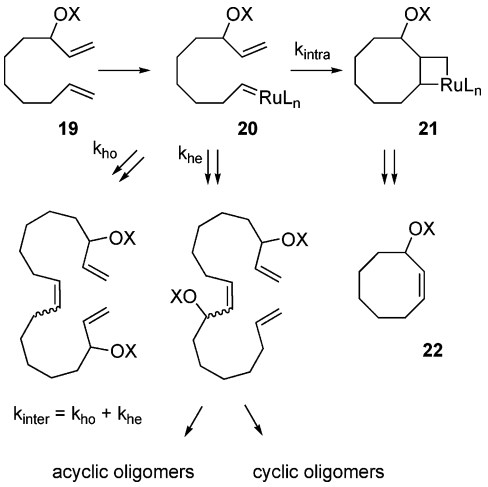


difference of less than an order of magnitude, which is a typical *gem*-dialkyl effect. The *gem*-dialkyl effect has been studied extensively but the acceleration of medium ring formation has not been quantified. The recent review by Jung and Piizzi[30] includes a single example of an RCM subject to a *gem*-dialkyl effect; *gem*-dimethylation on both sides of a midchain ketonic carbonyl group (a major structural perturbation) changes the outcome of a solvent-free metathesis reaction catalyzed by **10** completely from oligomerization to cycloheptannulation (Scheme 3).[31]

Forbes[31] attributed the outcome to significant thermodynamic destabilization of the acyclic ketone **8b** relative to **9b** caused by the mutual proximity of two quaternary centers.[32] As the reactive Schrock catalyst is capable of catalyzing the ROMP of neat **9b**, the outcome would appear to be under thermodynamic control. Our observed rate increase represents the only observation of a *kinetic gem*-dialkyl effect on an RCM to our knowledge; the origin of the effect will be explored elsewhere.

Measurement of Effective Molarities for Cyclooctannulations. Scale-up requires reactions that can be run at concentrations approaching 0.01 M or higher, or the volumes of solvent required become prohibitive for normal laboratory equipment.[22] We therefore sought to explore the effects of concentration upon the metathesis outcomes quantitatively.[33] In synthetic work, we found that the RCM of benzoate **1b** could be carried out successfully up to 20 mM concentration (100% conversion, 46% isolated purified yield, losses being incurred during removal of ruthenium residues) with catalyst **3** (5 mol %) and a Ti(IV) cocatalyst, with products resulting from cross metathesis forming at higher concentrations. Discrete oligomer signals cannot be identified by $\{^1H\}^{19}F$ NMR under these conditions, as the fluorine environments are too similar, resulting in overlapping signals with a chemical shift similar to that of the starting diene, indicating an acyclic species. The synthetic concentration for RCM of **1b** is a relatively high concentration compared to most of those used in the literature for 8-membered-ring RCM. Higher

SCHEME 4



dilution was required for benzyl ether **1c** (2.5 mM) and alcohol **1a** (1 mM); significant quantities of cross metathesis products were formed at 20 mM with these substrates, suggesting that the allylic substituent modulates cyclization *efficiency* significantly. We also noted that the synthesis of **6a** could be carried out at 10 mM without formation of other products, suggesting that *gem*-dialkylation increases cyclization efficiency over cross metathesis.

The effective molarity[10,34] (EM, k_{intra}/k_{inter}) measures the relative efficiency of the cyclization rate (k_{intra}) compared to the most chemically congruent dimerization (k_{inter}). Scheme 4 shows how the total yields of cyclized and oligomerized products were used to estimate k_{intra} and k_{inter}.

This mechanism assumes that the RCM of **19** will always initiate most rapidly on the Type I alkene leading to the formation of new alkylidene **20**, which closes affording metallocyclobutane **21**. Varying the diene concentration and exploiting the *gem*-difluoro group in the system by integrating the $\{^1H\}^{19}F$ NMR spectra should allow the EM to be determined from a linear plot between the intramolecular:total intermolecular product ratio and the reciprocal diene concentration, assuming that this ratio accurately represents the partitioning of **20** between oligomerization and cyclization pathways, because

$$\%_{intra}\text{ (yield of cyclic product }\mathbf{22}) = k_{intra}[\mathbf{20}]$$

and

$$\%_{inter}\text{ (total yield of other products)} = k_{inter}[\text{diene }\mathbf{19}][\mathbf{20}]$$

so

$$\%_{intra}/\%_{inter} = k_{intra}[\mathbf{20}]/k_{inter}[\text{diene }\mathbf{19}][\mathbf{20}] = \text{EM}(1/[\text{diene }\mathbf{19}])$$

The analysis assumes that ROMP (or ring opening then ADMET) of the cycloalkene product **22** is slow under these conditions. We have re-exposed **2b** and **7b** to **3** under *synthetic* conditions (0.02 M) and failed to observe any change in the ^{19}F NMR spectrum of the mixture after 24 h, vide supra. However, under *more concentrated* conditions (1 M), we can observe slow ring opening and oligomerization for **2b** and **7b**. Alkenes within large rings are known to isomerize under

(30) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(31) (a) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978. (b) Murphy has suggested that a single methyl substituent facilitates a macrocyclization by RCM; to our knowledge, these represent the sole examples and neither has been quantified; see: Commereuc, A. G. J.; Murphy, J. A.; Dewis, M. L. *Org. Lett.* **2003**, *5*, 2785.

(32) Alder, R. W.; Allen, P. R.; Anderson, K. R.; Butts, C. P.; Khosravi, E.; Martin, A.; Maunder, C. M.; Orpen, A. G.; St Pourcain, C. B. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2083.

(33) An interesting qualitative study is described by: Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297.

(34) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

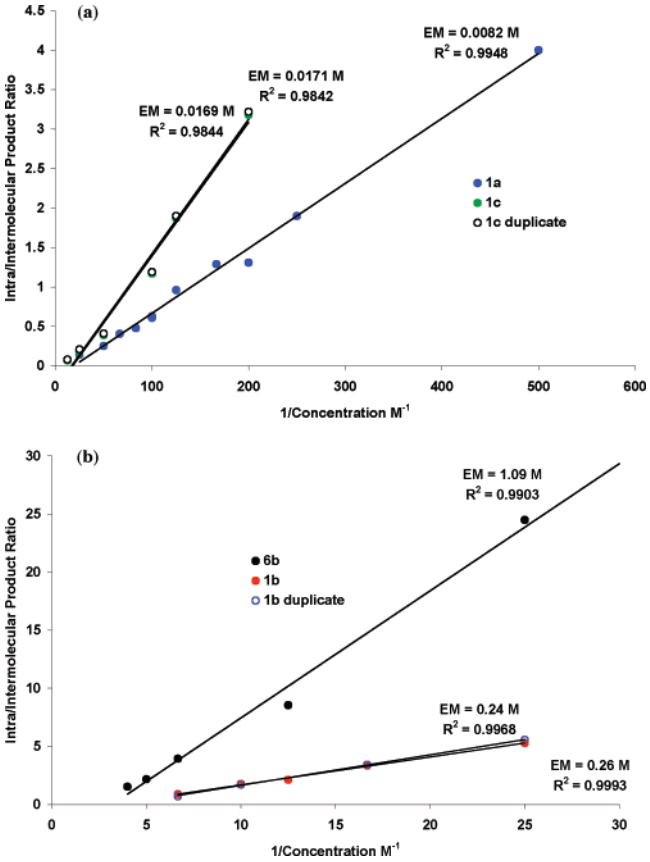


FIGURE 4. Determination of effective molarities for the RCMs of (a) **1a** and **1c** and (b) **1b** and **6b** (DCM, 5 mol % **3**, 30 mol % Ti(O-iPr)$_4$, reflux, 18 h).

thermodynamic control[35] in the presence of **3** but our cyclizations appear to be under kinetic control. These results will be discussed more fully elsewhere.

Fortunately we observed excellent dispersion between **2b** and other products in the $\{^1H\}^{19}F$ NMR spectra of product mixtures from **1b**, with the majority of the which, larger products (other than oligomers) being formed having discrete signals, that could be paired up using $^2J_{F-F}$ coupling constants and via correlation spectra ($^{19}F-^{19}F$ COSY).[36] Spectra were determined initially with a default relaxation delay, then re-recorded (duplicate determinations) with a relaxation delay (D_1) equal to $5T_1$ (T_1 values were measured) to ensure reliable integration. Full sweep width (0 to −300 ppm) spectra were also recorded to exclude the possibility of peaks wrapped or folded into the window used for integration.

In some cases, we were able to observe oligomers as distinct ions in the electrospray mass spectra. We also synthesized an acyclic heterodimer from **1a**, and (16-membered) cyclic dimers of **1a** and **1b**; these results are described fully in the Supporting Information.

The correlation between intramolecular:intermolecular product ratio and the reciprocal concentration is excellent (Figure 4) affording an EM of 0.25 M, which is high for the formation of an eight-membered ring from a highly flexible system. Since

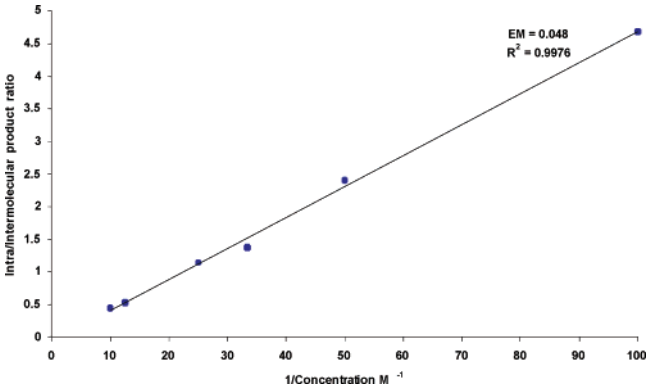


FIGURE 5. Determination of effective molarities for the RCMs of **1b** in the absence of the Ti(IV) cocatalyst (DCM, 5 mol % **3**, reflux, 18 h).

the synthesis of **7a** can be carried out at higher concentration than that for **2a**, we also determined an EM for **6b**. The $\{^1H\}^{19}F$ NMR spectra at 218 K (the cyclooctenones are fluxional at 300 K) again showed good dispersion between an eight-membered ring and side products, affording an EM of 1.09 M, which is high for a reaction forming an eight-membered ring.

EMs of 0.017 and 0.008 M were obtained for the cyclizations of **1c** and **1a**, respectively, using this method. These EM values are more typical of reactions forming eight-membered rings.[10a,34,37]

EMs for the formation of eight-membered rings range from 0.001 to 0.1 M with the larger values obtaining for heteroannelations of systems that have one or more rotors removed.[38] The nature of the allylic functional group clearly exerts a significant effect on the *relative efficiencies* of the cyclization and competing oligomerization.[39]

We also determined the EM of the cyclization of **1b** in the absence of the Ti(IV) cocatalyst (Figure 5). The cyclization is five times less efficient in the absence of the cocatalyst, but is still more efficient than any of the cocatalyzed cyclizations of the other substrates. Exploration of the role of the Ti(IV) cocatalyst falls outside of the scope of this paper and will be reported elsewhere.[40]

Most other discussions of substituent effects on RCM outcomes derive exclusively from measurements of yields or percent conversions that are assumed to correlate with reaction

(35) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.

(36) The possibility of alkene (positional) isomerization before cyclization was also examined explicitly; we found no evidence for the formation of seven-membered-ring products under conditions that might promote isomerization (see the Supporting Information for details).

(37) Fogg and co-workers (ref 14) quote EMs for the formation of rings of a range of sizes which are for etherifications and C−C bond forming reactions of various types, rather than RCMs.[9f] While it is true to say that EMs for a given ring size fall within a particular band, some of those bands are quite wide. There are a number of significant changes in geometry on the pathway from acyclic diene to cycloalkene that may be represented well or poorly by the enthalpic and entropic properties of the product cycloalkene. We would argue that the EMs for non-RCM reactions are at absolute best a guideline, rather than a reliable predictor of cyclization efficiency.

(38) For a remarkably effective RCM forming an 8-membered ring, see: Chavan, S. P.; Thakkar, M.; Jogdand, G. F.; Kalkote, U. R. *J. Org. Chem.* **2006**, *71*, 8986.

(39) The relative effect of ether and ester allylic functionality on cross-metathesis rate has not been quantified but there are a number of publications that claim that chelation between ester carbonyl oxygen and Ru disables cross-metathesis events. For example, see: (a) McNaughton, B. R.; Bucholtz, K. M.; Camaano-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733. (b) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513. (c) Sheddan, N. A.; Arion, V. B.; Mulzer, J. *Tetrahedron Lett.* **2006**, *47*, 6689.

(40) Lewis acids are known to facilitate RCM; see: (a) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101. (b) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. The two papers describe quite different scenarios. In the former, a crown ether is synthesized efficiently via a Group I metal-templated RCM. The

rates.

However, since allylic protecting groups slow down the rate of cyclization modestly, the assumption that these substrates are less efficient or do not work may be misleading if analyses were made on the same time scale as the reaction of the free allylic alcohol. It is possible that many of the reactions for which very low yields have been reported with protected allylic alcohols were not left for an adequate amount of time before carrying out a conversion or yield analysis, or that inappropriate reaction concentrations were employed.

Conclusions

At the appropriate concentrations, all the diene substrates studied converted smoothly and directly to their corresponding cyclooctenones, apparently without the intermediacy of oligomers, though cyclic and acyclic oligomers were detected at higher concentrations (and characterized fully in some cases). Reaction rate is affected modestly by *gem*-dialkylation and the nature of allylic oxygen functions, in stark contrast to many qualitative observations from the synthetic literature where reaction yields can vary from >50% for free alcohols to zero for derivatives.

The first EMs have been *measured* for RCM reactions; while the values are typical for cyclooctannelation, there is remarkable sensitivity to the nature of the allylic substituent. The high EM for benzoate **1b** appears to arise from relatively low CM rates for this substrate; *the substrate that cyclizes most rapidly* is not necessarily the one that *cyclizes most efficiently*.

These results indicate strongly that substituent effects on CM must be considered in addition to the likely rate of cyclization when planning or evaluating an RCM reaction or outcomes. Quantification of the interplay of structure and reactivity will aid rational activity and efficiency-based design of RCM substrates, especially for challenging synthetic targets. The overall equilibrium constant for the process is important, but the reaction outcome is determined by a wider range of subtle factors, which we hope to understand more fully through electronic structure calculations and detailed study of reaction kinetics.

Experimental Section

Full preparative and characterization details for all compounds are reported in the Supporting Information.

Procedure for Determining Reaction Concentration/Time Profiles. Titanium(IV) isopropoxide (30 mol %) was added to a 0.01 M solution of dienes **1a**−**c** and **6a**−**c** in dry, degassed dichloromethane and the solution was stirred in a jacketed flask connected to a circulating chiller to maintain constant temperature (25.0 ± 0.1 °C) under an atmosphere of nitrogen. An aliquot (0.2 mL) was removed from the reaction and transferred to a GC vial before the addition of a solution of Grubbs' second generation precatalyst **3** (2 mol %) in CH_2Cl_2 (0.2 mL); aliquots were then withdrawn from the reaction at varying intervals throughout. Prior to starting the experiment, Supelco 1 mL C-18 solid-phase extraction tubes were preconditioned with 1 mL each of 20% water/acetonitrile. Each aliquot subsequently withdrawn from the reaction was passed through one of these tubes. Samples were eluted with 1 mL each of acetonitrile into GC vials for analysis.

Procedure for Determining Effective Molarity. Titanium isopropoxide (0.3 equiv) was added to solutions of **1a** in dry, degassed CH_2Cl_2 in dry reactor tubes and the solutions were refluxed under nitrogen for 30 min; **3** (5 mol %) was added and the solution refluxed overnight. These samples were not SPE treated on the basis that catalyst activity is likely to be minimal after $>6 \times 10^4$ s at reflux in CH_2Cl_2 so there is no issue arising from further reaction during sample concentration.

All spectra for the experiment upon repetition were run with $D_1 = 5$ s ($5T_1$, longest T_1 measured at 1 s) to ensure no slow relaxing signals were unresolved within the spectral time scale. The spectral window was set to 40 ppm (between −100 and −140 ppm, centered at −120 ppm), and 1024 scans were recorded. Folding/wrapping was interrogated recording the full spectral window (0 to −300 ppm) in 100 ppm increments ($D_1 = 5$ s, 256 scans per experiment). No folding or wrapping was observed into the product spectral window.

Each solution was cooled and the solvent carefully distilled off at atmospheric pressure to prevent loss of volatile **2a**. The crude products were analyzed by $\{^1H\}^{19}F$ NMR and ES-MS. Larger products were not characterized from these mixtures but a series of larger rings were identified in the ES^- mass spectrum; 16-membered-ring species were synthesized by another route (vide infra).

Duplicate EM Determination for 1a with Modified Product Isolation. Experiments were run between 5 and 40 mM, this time leaving weaker solutions (5−10 mM) to evaporate at room temperature at atmospheric pressure. ^{19}F NMR spectra were obtained directly from the stronger solutions (15−40 mM) to confirm that **2a** was not lost during slow evaporation. All spectra for these experiments were run with $D_1 = 5$ s (vide infra) to ensure no slow relaxing signals were unresolved within the spectral time scale.

Acknowledgment. We thank the EPSRC and the University of Leicester (DTG studentship for L.M.), and the University of Strathclyde for affording visitor status to L.M. We also wish to acknowledge the use of the EPSRC's (Engineering and Physical Sciences Research Council) National Mass Spectrometry Service Centre, University of Wales Swansea.

Supporting Information Available: Synthetic procedures and characterization data for kinetic substrates, kinetic data and details of EM determination, oligomer characterization, and synthesis of 16-membered products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702726B

latter paper describes the facilitation by a Ti(IV) cocatalyst of an RCM catalyzed by **4**. However, the lower Lewis acidity of **3** is expected to diminish the effect of chelate formation on RCM; see: Furstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331.