Ring-Closing Metathesis in Methanol and Water

Thomas A. Kirkland, David M. Lynn, and Robert H. Grubbs*

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

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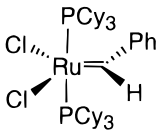
The ring-closing metathesis (RCM) of acyclic dienes in both methanol and water has been achieved through the use of water-soluble ruthenium alkylidenes. These alkylidenes react readily with acyclic olefins in protic solvents, but they do not cyclize α,ω-dienes because of the instability of the resulting methylidene. Successful cyclization has been achieved through simple substrate modification—incorporation of an olefin substituent allows cyclization to proceed in good yield. A methyl-substituted substrate was cyclized in 60% conversion in methanol, and the incorporation of a phenyl substituent resulted in nearly quantitative cyclization. Phenyl-substituted substrates are best suited for the reaction, as a more stable, active catalyst is regenerated upon each catalyst turnover. Using this methodology, 90% conversion of a water-soluble substrate to a substituted cyclopentene has been achieved in aqueous solution. This methodology has also been successfully applied to increase RCM yields in organic solvents.

Introduction

Ring-closing metathesis (RCM) has emerged as a useful method for the synthesis of carbocycles and heterocycles.[1] Although several early transition metal alkylidenes are highly active for RCM,[2] their use in organic synthesis is limited by their intolerance to protic functional groups and impurities.[1a,3] In contrast, ruthenium alkylidene **1** is stable and active in the presence of polar and protic moieties such as alcohols, aldehydes, ketones, carboxylic acids, esters, amides, and water.[3c,4] Although this increased functional group tolerance has enabled the application of RCM to densely functionalized substrates,[5] many interesting substrates are derived from biological systems and therefore are insoluble in organic solvents. Although alkylidene **1** is active in the presence of protic solvents such as water and methanol, it is completely insoluble in these solvents.[6]



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Recently, several techniques have been developed for the metathesis of water-soluble substrates. Aqueous emulsions have allowed the ring-opening metathesis polymerization (ROMP) of water-soluble monomers with alkylidene **1**.[7] The use of MeOH/CH_2Cl_2 blends has also allowed the ROMP of monomers that are insoluble in CH_2Cl_2.[7a] However, the successful application of these methods to RCM has not been reported. Current methods of applying RCM to biologically relevant substrates focus on rendering the substrate soluble in organic solvents, either by extensive substrate protection[5b,8] or binding of the substrate to solid support.[5b,9] However, the use of organic solvents can alter or destroy important higher-order structures that these substrates typically display in water.[10] The development of a methodology that enables efficient carbon−carbon bond formation in aqueous media would allow the synthesis of a variety of interesting compounds with biological applications. To this end, the RCM of *unprotected substrates in water* has remained an important goal.[11]

Metathesis in water was initially demonstrated with ill-defined catalysts such as $RuCl_3$ and $Ru(H_2O)_6tos_2$ (tos = *p*-toluenesulfonate), which were shown to ROMP strained, cyclic olefins in aqueous media.[7c,12] Although these complexes do not contain a formal alkylidene, small amounts of alkylidenes are generated *in situ* in the

(1) For recent reviews on RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056. (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452.

(2) For examples of RCM with tungsten and molybdenum alkylidenes, see: (a) Leconte, M.; Salvatore, P.; Mutch, A.; Lefebvre, F.; Basset, J. M. *Bull. Soc. Chem. Fr.* **1995**, *132*, 1069−1071. (b) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992−8998. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427.

(3) (a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: London, 1997. (b) Kirkland, T. A.; Grubbs R. H. *J. Org. Chem.* **1997**, *62*, 7310−7318. (c) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H.; *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.

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

(5) For additional examples of the functional group tolerance of **1**, see (a) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorenson, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733−2734. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614.

(6) Alkylidene **1** is inactive in polar, aprotic solvents such as DMSO and DMF.

(7) (a) Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931−9932, and references therein. (b) Lynn, D. M.; Kanaoka, S.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 784−790. (c) Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248−7255.

(8) (a) Blackwell, H. E.; Grubbs, R. H., **1998**, unpublished work. (b) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926−10927. (c) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547−550. (d) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364−12365.

(9) For general references on solid supported RCM, see: (a) Peters, J.-U.; Blechert, S. *Synlett.* **1997**, 348−350. (b) Pernerstorfer, J.; Schuster, M.; Blechert, S. *J. Chem. Soc. Chem. Commun.* **1997**, 1949−1950. (c) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143−7146. (d) van Maarseveen, J. H.; den Hartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249−8252. (e) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979−1980.

(10) Blackwell, H. E.; Grubbs, R. H. Unpublished results.

(11) For general reviews of other carbon−carbon bond forming processes in water, see: (a) Li, C. J. *Tetrahedron* **1996**, *52*, 5643−5668. (b) Breslow, R. A. *Acc. Chem. Res.* **1991**, *24*, 159−164.

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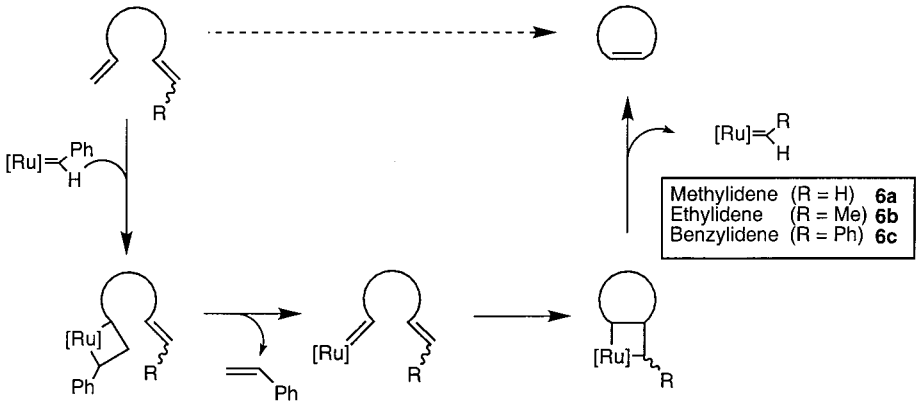
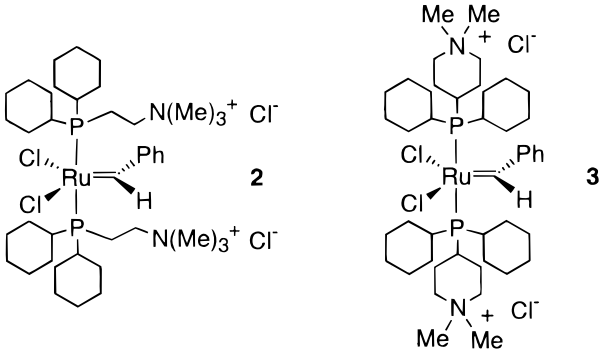
Scheme 1. The First Turnover Step of RCM

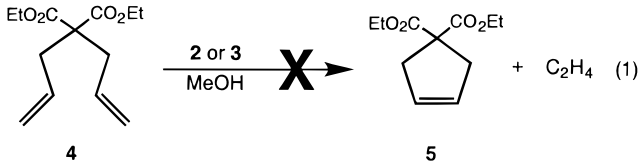


presence of strained, cyclic olefins. Limited reaction with acyclic olefins has been observed during ROMP,[12d,13] but no RCM in methanol or water has been observed.[13] We recently reported the synthesis of well-defined, water-soluble alkylidenes **2** and **3**,[14] which are highly active in the ROMP of strained, cyclic olefins in both methanol and water.[15] In this contribution, we report that these alkylidenes are active for both acyclic olefin metathesis and RCM in water and methanol.



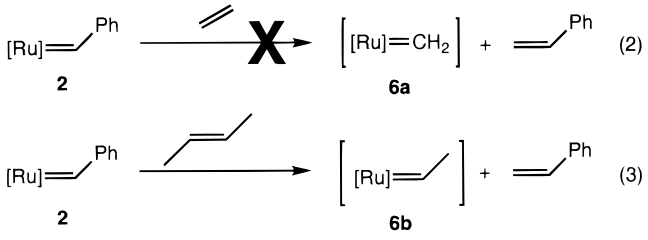
Results and Discussion

Initial Studies. Initial attempts to probe the activities of **2** and **3** toward RCM centered upon the cyclization of α,ω-dienes such as diethyl diallylmalonate (**4**). Alkylidene **1** cyclizes **4** rapidly and quantitatively to cyclopentene diester **5** in organic solvents.[16] However, the treatment of diene **4** with a catalytic amount of alkylidenes **2** or **3** in methanol gives no product (eq 1).[17]



During the first turnover in the successful RCM of α,ω-dienes, a benzylidene (Scheme 1, **6c**) reacts with the diene to generate an equivalent of cyclized product, styrene and a methylidene (Scheme 1, **6a**). This methylidene is the true catalytic species. Although the methylidene derived from **1** is stable under a variety of conditions,[4b] the instability of other transition metal methylidenes is often a limiting factor in RCM.[18] When alkylidene **2** or **3** is reacted with an α,ω-diene, styrene is observed by ^{1}H NMR spectroscopy but the methylidene is not. This indicates that **2** and **3** react with the substrate but the methylidene that is formed decomposes before reentering the catalytic cycle.

Further evidence that methylidene instability was preventing RCM was obtained through reaction of alkylidenes **2** and **3** with simple acyclic olefins. Whereas reaction of **1** with ethylene proceeds quantitatively to the expected methylidene,[4b] the reaction of **2** with ethylene results in rapid decomposition (eq 2). Alkylidene **2** does react with either propene or *trans*-2-butene to yield a new resonance at 19.3 ppm in the ^{1}H NMR, which was assigned as an ethylidene (eq 3).



The increased stability of the ethylidene prompted us to examine RCM substrates containing substituted olefins. In the RCM of dienes containing one terminal olefin and one internal olefin (Scheme 1, R ≠ H), metathesis occurs initially at the terminal olefin[3b,19] and the olefin substituent is transferred to the alkylidene upon cyclization. Therefore, we reasoned that the incorporation of a methyl substituent into a model diene would result in the generation of a more stable catalytic species. Our initial studies focused on the diethyl diallylmalonate system as a scaffold. In this case, the cyclopentene diester

(12) (a) Hillmyer, M. A.; Lepetit, C.; McGrath, D. V.; Novak, B. M.; Grubbs, R. H. *Macromolecules* **1992**, *25*, 3345−3350. (b) Feast, W. J.; Harrison, D. B. *J. Mol. Catal.* **1991**, *65*, 63−72. (c) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542−7543. (d) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960−961.

(13) Novak, B. M. Ph.D. Thesis, California Institute of Technology, 1989.

(14) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317−4325.

(15) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627−1628.

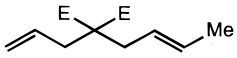
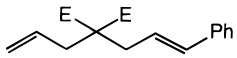
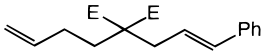
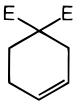
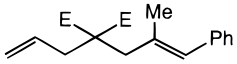
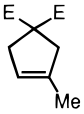
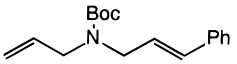
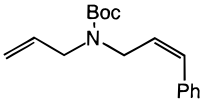
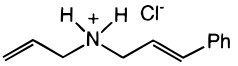
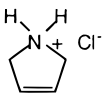
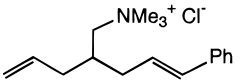
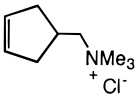
(16) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897.

(17) In certain cases, the use of 5 mol % **2** in the RCM of **4** gives up to 5% product. The use of alkylidene **3** or increased loading of alkylidene **2** affords no increase in conversion.

(18) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427, and references therein.

(19) Kim, S. H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073−1081.

Table 1. RCM of Functionalized Dienes Initiated by Alkylidenes 2 and 3[a]

Substrate[b]		Product		Solvent	Conversion[c,d]
	**7**		**5**	MeOH	30% (**2**)[e] 60% (**3**)[e]
	**8**		**5**	MeOH	80% (**2**) 95% (**3**)
	**10**		**16**	MeOH	45% (**2**)[f] 55% (**3**)[f]
	**11**		**17**	MeOH	>95% (**3**)
	**12**		**18**	MeOH	40% (**2**) 90% (**3**)
	**13**		**18**	MeOH	30% (**2**) >95% (**3**)
	**14**		**19**	MeOH H_2O H_2O	75% (**2**) 10% (**2**) 5% (**3**)
	**15**		**20**	MeOH H_2O H_2O	90% (**3**) 60% (**3**) 90% (**3**)[g]

[a] The following conditions were used unless otherwise noted: 5 mol % catalyst (**2** or **3**), 0.37 M substrate, 45 °C. [b] E = CO_2Et. [c] Conversions were determined by ^1H NMR. [d] Number in parentheses indicates alkylidene used. [e] Substrate conc. = 0.24 M. [f] Substrate conc. = 0.1 M. [g] 10 mol % **3** used.

is kinetically favored by the Thorpe-Ingold effect,[20] analogues are easily synthesized, and the conversion of these substrates to cyclized product is easily monitored by ^1H NMR.

RCM of Substituted Olefins in Methanol. Methyl-substituted diene **7** was synthesized through the reaction of crotyl bromide with the anion of diethyl allyl malonate.[21] Treatment of **7** with 5 mol % alkylidene **2** or **3** in methanol gives 60% conversion to cyclic diester **5** (Table 1). The catalytic ethylidene was clearly observed by ^1H NMR spectroscopy during these reactions. The reactions were clean, consisting primarily of cyclic product and unreacted starting material. It should be noted that although replacement of a terminal olefin with an internal olefin in a RCM substrate alters the structure of the catalytically active alkylidene, the structure of the desired cyclized products remains unaffected.

Although the increased stability of the generated ethylidenes allows for RCM with alkylidenes **2** and **3**, catalyst stability is still a limiting factor because the ethylidene is observed to completely decompose before the starting material is consumed. This problem is further amplified by the decreased rate of olefin metathesis that accompanies increasing steric bulk around the olefin, allowing the rate of catalyst decomposition to be more competitive with the rate of RCM. After considering the greater reactivity and stability of benzylidene **1** compared with analogous methylidenes and ethylidenes,[4b] we examined a phenyl-substituted substrate.

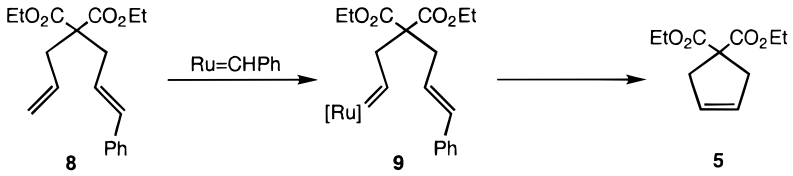
Phenyl-substituted diene **8** was synthesized in an analogous manner to **7** using cinnamyl bromide. Incorporation of a phenyl substituent proved to be highly effective, as treatment of **8** with alkylidene **2** resulted in 80% conversion to cyclopentene **5**. Furthermore, cyclization proceeded nearly quantitatively in the presence of alkylidene **3**. Although some alkylidene decomposition is evident, alkylidene **3** is still observed after all of diene **8** is converted to cyclic product. Alkylidenes **2** and **3** are regenerated in the RCM of phenyl-substituted substrates, and are therefore true catalysts.

The reason for the decomposition of benzylidenes **2** and **3** in the RCM of **8** is unclear, as they are stable for days in either methanol or water at 45 °C. Styrene generated in the RCM of a phenyl-substituted diene could react with

(20) 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*, 10978−10980 and references therein.

(21) For a general procedure for malonate alkylation, see: Gilman, H.; Blatt, A. H. *Organic Syntheses*, Coll. Vol. I; John Wiley and Sons: New York, 2nd ed., 250−251.

Scheme 2



a benzylidene to generate an unstable methylidene, although control reactions of alkylidenes **2** and **3** with styrene indicate that this is not a significant decomposition pathway. Another consideration is the decomposition of transitional alkylidene **9**, which is generated upon initial reaction of the catalyst with substrate **8** (Scheme 2). The stability of such an alkylidene is unknown but is expected to be similar to the analogous ethylidene.

Alkylidene **3** is a significantly more active catalyst than alkylidene **2** in these cyclizations. This difference in reactivity can be explained through an analysis of phosphine electronic parameters.[16] For alkylidenes of the type $(PR_3)_2Cl_2Ru{=}CHR$, metathesis activities generally increase as the phosphine ligands become larger and more electron-rich.[16] Although the phosphines coordinated to **2** and **3** are sterically similar, the phosphines in **3** are more electron-rich.[15] Whereas differences in the activities of these alkylidenes have not been noted for ROMP, the RCM of substrate **7** allows for a qualitative assessment of their relative activities. The treatment of **7** with alkylidene **2** results in 30% conversion after 1.5 h, whereas the use of alkylidene **3** results in 85% conversion over the same time period. This result is in accord with theoretical predictions.[15] A quantitative assessment of catalyst activities was not attempted because of alkylidene decomposition over the course of the reaction.

Formation of cyclohexene diester **16** was achieved *via* cyclization of phenyl-substituted diene **10** with **2** and **3** in methanol (Table 1). The slower formation of a six-membered ring relative to a five-membered ring is believed to be responsible for the lower conversion.[22] The decreased cyclization rate allows decomposition of the intermediate alkylidene that is analogous to **9** to be more competitive with the rate of RCM (Scheme 2).[23] Surprisingly, the cyclization of methyl-substituted diene **11** does not suffer from this rate decrease. Although ruthenium alkylidenes typically react sluggishly with trisubstituted olefins, the cyclization of **11** to cyclopentene **17** proceeds quickly and quantitatively.[24]

Olefin geometry also has a significant impact on cyclization rates. For example, the cyclization of *trans*-substituted substrate **12** with alkylidene **3** requires 30 h to reach 90% conversion, whereas cyclization of the *cis*-substituted derivative **13** proceeds quantitatively in 2 h (Table 1). This effect is not surprising, as *cis*-substituted olefins are able to coordinate to the metal center better than *trans*-olefins.[3a] The dramatic rate increase provided by the inclusion of *cis*-olefins can be an effective method for improving the overall conversion by increasing the rate of cyclization relative to the rate of alkylidene decomposition.

RCM in Water. Having demonstrated the RCM of several substrates in methanol, we turned our attention to homogeneous RCM in water. Model substrates examined initially were based on a diallylamine hydrochloride framework[25] because analogues are easily synthesized and conversions are easily monitored by ^{1}H NMR. Phenyl-substituted diene **14** was synthesized from allylamine and cinnamyl bromide, and cyclized with alkylidene **3** in methanol to give pyrroline hydrochloride **19** in 75% conversion (Table 1). Although the RCM of this substrate in water only proceeds to 5−10% conversion with both alkylidenes, these reactions represent the first observation of RCM in water. The cyclization of a *cis*-substituted analogue yielded similar results, giving 15% conversion in the presence of catalyst **3**.

Catalysts **2** and **3** are active in the presence of acid[15] and have been shown to polymerize monomers containing amine hydrochlorides without loss of activity,[26] suggesting that the ammonium functionality was not degrading the alkylidene. Failure of the *N*,*N*-dimethyl analogue of **14** to cyclize under the same conditions further suggested that other factors were responsible for these low conversions. Because alkylidene **1** reacts slowly with electron-deficient olefins,[27] we considered that the strongly electron-withdrawing nature of the ammonium group was deactivating these dienes for RCM.

To circumvent this possibility, a water-soluble substrate was designed with the quaternary ammonium functionality further removed from the olefins. Diene **15** was synthesized through functional group manipulation of malonate **8**. This new substrate showed a dramatic increase in conversion in both water and methanol. Treatment of ammonium salt **15** with alkylidene **3** gives cyclopentene **20** in 60% conversion in water and 90% in methanol (Table 1). Although conversions in water are lower than in methanol, excellent conversions in either solvent can be achieved through an increase of the catalyst loading. The increase in conversion observed with this increase in catalyst loading indicates that catalyst decomposition is still a limiting factor in these reactions. For example, in the presence of 10 mol % **3**, cyclization of **15** *proceeds to 90% conversion in aqueous solution* (eq 4).

(22) For a discussion of the effects of substrate homologation on intramolecular cyclizations, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232 and references therein.

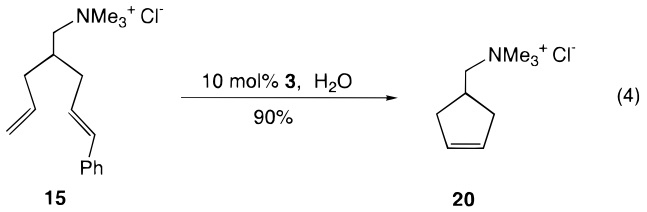
(23) Another factor that should be considered is substrate dimerization, but this does not appear to be significant in the RCM of **10** as conversion is not dependent on substrate concentration.

(24) In the synthesis of unsymmetrical olefins with this methodology, it is critical that the phenyl substituent be placed on the more substituted olefin as in substrate **11**. If the phenyl substituent is placed on the less substituted olefin, the ruthenium carbene will preferentially react with the 1,2-disubstituted olefin, then react with the gem-disubstituted olefin intramolecularly, giving one equivalent of cyclized product and the unstable methylidene.

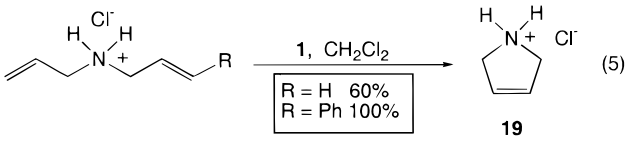
(25) Chlorides were used exclusively, as exposure of ruthenium alkylidenes of the type $(PR_3)_2Cl_2Ru{=}CHR$ to other coordinating anions such as Br^- results in fast anion exchange, typically yielding a significantly less active catalyst. This effect is not observed for very weakly coordinating anions such as SO_3-. See ref 16.

(26) Lynn, D. M.; Grubbs, R. H. Unpublished results.

(27) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 7, in press.



Applications to Organic Systems. The beneficial effects of diene substitution are not limited to RCM with alkylidenes **2** and **3**. Even though the methylidene derived from **1** is quite robust, under certain reaction conditions its instability can limit conversion. For example, RCM of diallylamine hydrochloride with 5 mol % alkylidene **1** only proceeds to 60% conversion in methylene chloride (eq 5). RCM of the readily synthesized phenyl-substituted analogue **14**, however, gives pyrroline hydrochloride (**19**) *quantitatively* under the same conditions with minimal decomposition of the catalytic benzylidene. This simple modification of the starting material greatly improved the yield of the desired product, and could be applied generally to increase RCM yields with **1** in organic solvents.



Conclusions

We have demonstrated the first examples of RCM in water and methanol. Although alkylidenes **2** and **3** do not promote the RCM of α,ω-dienes, simple olefin substitution allows for successful RCM to afford the desired cyclic product. We have determined several factors that influence the success of these reactions. In particular, the choice of olefin substituent is important because it directly affects the stability and reactivity of the resultant catalytic alkylidenes. Phenyl substituents have proven to be the most effective, allowing for quantitative conversions to cyclized product in methanol. Additionally, dienes containing *cis*-olefins cyclize considerably faster than those containing *trans*-olefins. This methodology describes an efficient, metal-catalyzed, carbon−carbon bond-forming process that proceeds to high conversion *in aqueous media*. It has also been extended to increase conversions in RCM catalyzed by **1** in organic solvents. The incorporation of substituted olefins in complex, water-soluble dienes may allow for the construction of biologically interesting architectures in aqueous media.

Experimental Section

General Considerations. All manipulations and reactions involving ruthenium alkylidenes were performed in a nitrogen-filled dry box or by use of standard Schlenk techniques under an atmosphere of argon. Distilled deionized water and reagent-grade methanol were used for these reactions, and were rigorously degassed by purging with argon and stirring under high vacuum before use. All other reagents were used without further purification unless otherwise noted. Alkylidenes **1**,[4b] **2**,[14] **3**,[14] substrates **7**,[28] **8**,[29] **14**,[30] and products **5**,[2b] **16**,[31] **17**,[32] **18**,[3c] **19**,[33] and **20**[34] have been previously prepared and reported. Substrate **4** is commercially available and was degassed before its use. Argon was purified by passage through columns of BASF R3−11 catalyst (Chemalog) and 4 Å molecular sieves (Linde). Analytical TLC was performed with silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed with silica gel 60 (230−400 mesh) from EM Science.[35]

General RCM Procedure. In a typical reaction, substrate **8** (35 mg, 0.11 mmol) was placed in a vial and dissolved in CD_3OD (0.15 mL). In a separate vial, **2** (5.0 mg, 5.54 μmol) was placed in a vial and dissolved in CD_3OD (0.15 mL). The catalyst and substrate solutions were combined, placed in an NMR tube, and the tube was sealed with a rubber septum. The reaction was heated to 45 °C, and monitored by ^{1}H NMR. Conversion to product (80%) was determined *via* integration of the methylene protons α to the olefin in the cyclized product (2.95 ppm, s) relative to the methylene protons of the uncyclized substrate (2.68 ppm, dd).

Reaction of Alkylidene 2 with Acyclic Olefins (General Procedure). A solution of alkylidene **2** (10 mg, 0.11 mmol) in CD_3OD (0.5 mL) was placed in a NMR tube that was sealed with a rubber septum. This solution was heated to 45 °C and purged with propene, resulting in a rapid color change from deep purple to orange. After 15 min, the reaction was monitored by ^{1}H NMR. An alkylidene resonance for **2** was observed at 19.94 ppm, as well as a new alkylidene resonance at 19.29 ppm. Styrene was also observed in the reaction mixture. The generation of a new alkylidene species was also confirmed by ^{31}P NMR (33.3 ppm, s). Evaporation of solvent yielded an orange powder, but rapid decomposition precluded isolation.

4,4-Dicarboethoxy-1-phenyl-1,7-octadiene (10). Diester **10** was synthesized from 1,1-dicarboethoxy-4-pentene and cinnamyl bromide according to a previously published procedure.[36] 1,1-Dicarboethoxy-4-pentene was synthesized according to the same method. Diester **10** was isolated as a clear, colorless oil (33%, two steps): ^{1}H NMR δ ($CDCl_3$) 7.32−7.17 (m, 5H), 6.44 (d, J = 7.8 Hz, 1H), 6.11−6.00 (m, 1H), 5.84−5.73 (m, 1H), 5.04 (d, J = 8.6 Hz, 1H), 4.96 (d, J = 5.1 Hz, 1H), 4.19 (q, J = 5.3 Hz, 4H), 2.06−2.03 (m, 4H), 1.24 (t, J = 4.8 Hz, 6H); ^{13}C NMR δ ($CDCl_3$) 170.8, 137.3, 136.8, 133.5, 128.2, 127.1, 125.9, 123.8, 114.8, 61.0, 57.3, 36.2, 31.6, 28.2, 13.9; HRMS calcd for $C_{20}H_{26}O_4$ (M^+) 330.1831, found 330.1825.

4,4-Dicarboethoxy-1-phenyl-2-methyl-1,6-heptadiene (11). Diester **11** was synthesized from diethyl allylmalonate and 3-bromo-1-phenyl-2-methyl-2-propene in an analogous manner to substrate **10**. 3-Bromo-1-phenyl-2-methyl-2-propene was synthesized from the commercially available alcohol in an analogous manner to *cis*-cinnamyl bromide. Diester **11** was isolated as a clear, colorless oil (12%, two steps): ^{1}H NMR δ ($CDCl_3$) 7.32−7.27 (m, 3H), 7.19 (d, J = 4.0 Hz, 2H), 6.35 (s, 1H), 5.79−5.68 (m, 1H), 5.13 (d, J = 5.0 Hz, 1H), 5.09 (s, 1H), 4.22−4.14 (m, 4H), 2.86 (s, 2H), 2.73 (d, J = 3.4 Hz, 2H), 1.79 (s, 3H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR δ ($CDCl_3$) 171.2, 137.9, 133.7, 132.8, 130.4, 129.0, 128.1, 126.4, 119.1, 61.3, 57.7, 43.4, 37.2, 18.7, 14.2.

***N*-Boc-*N*-allyl-*trans*-cinnamylamine (12).** Allylamine (10.9 g, 0.191 mol) and di-*tert*-butyl dicarbonate (13.9 g, 63.6 mmol) were dissolved in CH_2Cl_2 (250 mL) at 0 °C and allowed to stir for 8 h. The solution was then washed with water (100

(28) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans.* **1984**, 1745−1754.

(29) Hanessian, S.; Leger, R. *J. Am. Chem. Soc.* **1992**, *114*, 3115−3117.

(30) Crozet, M. P.; Kaafaran, M.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1984**, 390−398.

(31) Bachman, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 493−501.

(32) Schweizer, E. E.; O'Neill, G. J. *J. Org. Chem.* **1965**, *30*, 2082−2083.

(33) Gajda, T.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 992−1002.

(34) Tropsha, A. E.; Nizhinni, S. V.; Yaguzhinskii, L. S. *Bioorg. Khim.* **1985**, *11*, 1931−1941.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(36) Gilman, H.; Blatt, A. H. *Org. Synth.* **1935**, *Collect. Vol. 1*, 250−251.

mL), dried with $MgSO_4$, and concentrated to give *N*-Boc-allylamine as a pale yellow solid (9.7 g, 97%), which was used without further purification.

N-Boc-allylamine (2.88 g, 18.29 mmol) was allowed to react with NaH (0.48 g, 20.12 mmol) in DMF (50 mL) for 15 min. Then *trans*-cinnamyl bromide (3.97 g, 20.12 mmol) was added and the solution was heated to 60 °C. After stirring for 16 h, the reaction was quenched with water (50 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried over $MgSO_4$, concentrated, and purified on silica gel (5% EtOAc in hexanes) to yield **12** as a clear, colorless oil (3.98 g, 80%): ^{1}H NMR δ ($CDCl_3$) 7.42−7.21 (m, 5H), 6.46 (d, J = 7.9 Hz, 1H), 6.20−6.11 (m, 1H), 5.85−5.76 (m, 1H), 5.18−5.12 (m, 2H), 3.96 (br s, 2H), 3.87 (br s, 2H), 1.49 (s, 9H). ^{13}C NMR δ ($CDCl_3$) 155.5, 136.9, 134.1, 131.8, 128.7, 127.7, 126.5, 125.7, 116.8, 79.8, 48.8, 48.4, 28.6; HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1730.

***N*-Boc-*N*-allyl-*cis*-cinnamylamine (13).** *Cis*-cinnamyl alcohol (2.07 g, 15.4 mmol), which was prepared as previously reported,[37] was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. To this solution was added PPh_3 (6.07 g, 23.1 mmol) and CBr_4 (7.66 g, 23.1 mmol). After 1 h the solvent was removed in vacuo, the solid residue was taken up in hexanes, and filtered through a plug of silica. This afforded *cis*-cinnamyl bromide (1.8 g, 60%), which was used without further purification.[38]

Substrate **13** was then synthesized in a manner similar to **12** using *cis*-cinnamyl bromide. It was isolated as a clear, colorless oil (74%): ^{1}H NMR δ ($CDCl_3$) 7.38−7.19 (m, 5H), 6.57 (d, J = 5.9 Hz, 1H), 5.74−5.61 (m, 2H), 5.01 (d, J = 4.9 Hz, 1H), 4.91 (d, J = 8.6 Hz, 1H), 4.12 (br s, 2H), 3.75 (br s, 2H), 1.44 (s, 9H). ^{13}C NMR δ ($CDCl_3$) 155.5, 136.8, 133.9, 131.2, 129.4, 128.9, 128.3, 126.5, 116.7, 79.8, 49.1, 44.3, 28.6; HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1729.

2-Allyl-5-phenyl-4-penten-1-ol. To a solution of diester **8** (3.14 g, 9.92 mmol) in DMSO (20 mL) was added H_2O (0.67 g, 37.22 mmol) and NaCl (0.70 g, 12.41 mmol). This was heated at reflux for 90 h, quenched with H_2O (75 mL), extracted with ether (3 × 40 mL), and dried over $MgSO_4$. After removal of solvent and elution of the resulting black oil through a pad of SiO_2 (10% EtOAc in hexanes), a yellow, clear oil was obtained (1.31 g), which was used without further purification.

Dropwise addition of this oil dissolved in THF (10 mL) to a suspension of $LiAlH_4$ (0.41 g, 10.7 mmol) in THF (20 mL), which was at 0 °C, was completed over 30 min. After this solution had stirred for 2 h it was quenched with H_2O (1 mL), followed by 15% NaOH (5 mL). Removal of the resulting solids by filtration, removal of solvent in vacuo, and purification of the resultant oil on silica gel gave the known alcohol in good accordance with literature values (0.93 g, 49%, two steps).[39]

1-(*N*,*N*,*N*-Trimethylammonium chloride)-2-allyl-5-phenyl-4-pentene (15). A solution of tosyl chloride (0.55 g, 2.89 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. 2-Allyl-5-phenyl-4-penten-1-ol (0.50 g, 2.63 mmol) and NEt_3 (0.40 g, 3.94 mmol) were added and the solution was allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with water (25 mL), extracted with CH_2Cl_2 (25 mL), and dried over $MgSO_4$. The resulting oil was carried on without further purification.

This tosylate (1.26 g, 3.66 mmol) was added to a solution of LiBr (0.95 g, 10.97 mmol in acetone) (20 mL) and the reaction mixture was refluxed. After 12 h, the reaction was quenched with water (25 mL), extracted with pentane (3 × 25 mL), and dried over $MgSO_4$. The resulting oil was added to a flask containing MeOH (15 mL), which had been purged with NMe_3 for 5 min. This reaction mixture was heated to 50 °C for 24 h, and then all of the solvent was removed to give a brown solid. This solid was eluted through a column packed with Amberlite IRA-400 Cl^- ion-exchange resin with MeOH, then triturated with Et_2O to yield **15** as a white crystalline solid (53%, three steps): ^{1}H NMR δ ($CDCl_3$) 7.38−7.18 (m, 5H), 6.48 (d, J = 7.9 Hz, 1H), 6.27−6.17 (m, 1H), 5.86−5.77 (m, 1H), 5.17 (d, J = 4.4 Hz, 1H), 5.13 (d, J = 5 Hz, 1H), 4.14 (s, 2H), 3.45 (s, 9H), 2.44−2.16 (m, 5H); ^{13}C NMR δ ($CDCl_3$) 136.8, 134.6, 134.2, 128.9, 127.8, 126.4, 125.9, 119.5, 69.8, 53.9, 38.5, 37.7, 33.5; HRMS calcd for $C_{17}H_{26}ClN$ (M-Cl^+) 244.2065, found 244.2060.

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Supporting Information Available: ^{1}H NMR spectra and IR data for **11**, **12**, **13**, **15** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981678O

(37) Davis, F. A.; Reddy, R. T. *J. Org. Chem.* **1992**, *57*, 2599−2606.

(38) The quick isomerization of this compound resulted in the presence of <10% **11** in **10**, as determined by ^{1}H NMR. This did not affect the behavior of **11** and was discounted.

(39) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1135−1145.