

Experimental and Theoretical Study on the Olefin Metathesis of Alkenyl Baylis–Hillman Adducts Using Second-Generation Grubbs Catalyst

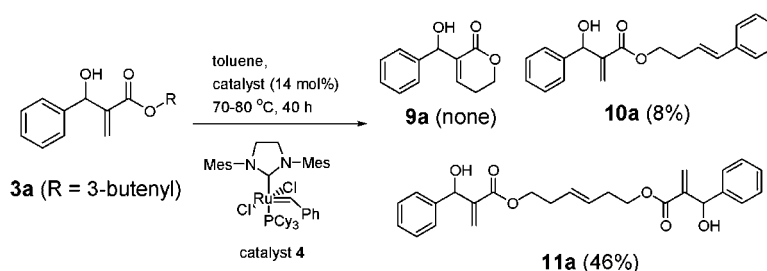
Mi Jung Lee,[†] Ka Young Lee,[†] Jin Yong Lee,^{*,‡} and Jae Nyoung Kim^{*,†}

Department of Chemistry and Institute of Basic Science, Chonnam National University, 300 Yongbong-Dong, Bugku, Gwangju 500-757, Korea, and Institute for Condensed Matter Theory and Department of Chemistry, Chonnam National University, 300 Yongbong-Dong, Bugku, Gwangju 500-757, Korea

jinyong@chonnam.ac.kr; kimjn@chonnam.ac.kr

Received June 28, 2004

ABSTRACT



We have investigated the olefin metathesis from alkenyl Baylis–Hillman adducts using second-generation Grubbs catalyst. In the experiment, the ring-closing metathesis (RCM) product could not be found, while the cross-metathesis (CM) products were found. The computational studies provided consistent explanations for the experimental result. The most limiting factor for the RCM process using second-generation Grubbs catalyst is caused by the high strain and steric effect in the metallacyclobutane intermediates.

Olefin metathesis, termed in 1967 by Calderon and co-workers for the first time,¹ is a powerful method for the formation of carbon–carbon double bonds.² In particular, ring-closing metathesis (RCM) has been used for the synthesis of a variety of cyclic compounds that include carbocyclic, heterocyclic, and fused ring frameworks.^{3,4} However, until several years ago, such reactions were limited because of insufficient catalytic performance. The desire to

apply olefin metathesis to new synthetic challenges has motivated many chemists to improve catalytic performance. The ruthenium complexes have been used as catalysts for a variety of reactions.⁵ The first members of a family of L₂X₂–Ru=CHR (Grubbs catalysts) complexes opened new vistas in olefin metathesis.⁶ Among them, (PCy₃)₂Cl₂Ru=CH₂ has attracted a lot of theoretical interest.⁷ A second-generation Grubbs catalyst where one of the PCy₃ ligands is replaced by an N-heterocyclic carbene (NHC) ligand with a mesityl

[†] Department of Chemistry and Institute of Basic Science.

[‡] Institute for Condensed Matter Theory and Department of Chemistry.

(1) (a) Calderon, N. *Acc. Chem. Res.* **1972**, *5*, 127. (b) Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *34*, 3327.

(2) (a) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990. (c) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

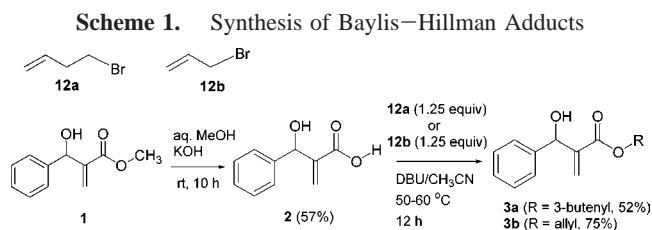
(3) (a) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496. (b) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(4) (a) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (d) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903. (e) Blackwell, H. E.; Sadowsky, J. D.; Howard, R. J.; Sampson, J. N.; Chao, J. A.; Steinmetz, W. E.; O'Leary, D. J.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 5291. (f) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (g) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

group has been shown to have significantly higher activity than that of the parent Grubbs catalyst.^{3b,8}

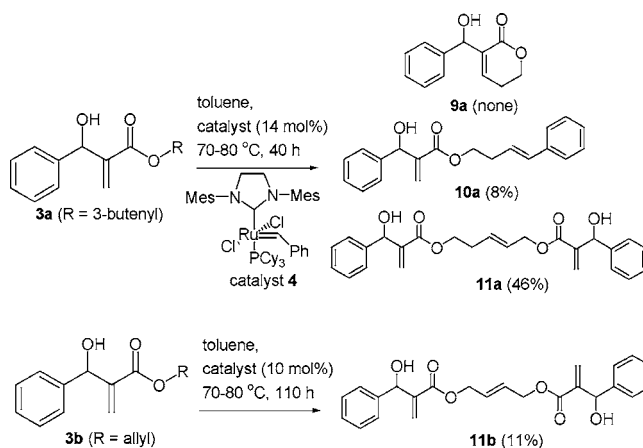
Recently, we synthesized 2,5-dihydrofuran and 2,5-dihydropyrrole skeleta from the Baylis–Hillman adducts of 5,6-dihydro-2*H*-pyran-2-one via the RCM reaction using the Grubbs second-generation catalyst.⁹ The latter catalyst has also been successfully used to synthesize di-, tri-, and tetrasubstituted α,β -unsaturated lactones or lactams of ring size 5–7.¹⁰ There have been several theoretical^{3,7,11} and experimental^{11–13} attempts to explain the mechanism and activity of olefin metathesis with the Grubbs catalyst and its derivatives. Most of the theoretical studies have been carried out on simplified model systems. However, the size of the ligands, their electronic properties, and conformational flexibility are reported to greatly influence the catalytic reactivity.^{13a,14} In this letter, we report a synthetic and theoretical study of the olefin metathesis of two Baylis–Hillman adducts **3a** and **3b** using the second-generation Grubbs catalyst.

We prepared the required starting materials **3a** and **3b** as shown in Scheme 1. The Baylis–Hillman adduct **1** was converted into the acid **2** according to the reported method,¹⁵ and following esterification with **12a** and **12b** using DBU



in acetonitrile, we were able to synthesize the starting materials **3a** and **3b** in moderate yield (Scheme 1). (For the detailed synthesis and spectroscopic data of prepared compounds, see Supporting Information.)

Scheme 2. Possible Products of Olefin Metathesis



With compounds **3a** and **3b** in hand, we examined their RCM reactions with **4** under high-dilution conditions in order to minimize the intermolecular reactions. Initially, we carried out the reaction of **3a** in toluene with 14 mol % catalyst **4** at 70–80 °C for 40 h. Unfortunately, however, we could never detect or isolate the desired RCM product. Instead, the cross-metathesis products **10a** (8%) and **11a** (46%) were isolated along with recovered starting material **3a** (27%).

When we performed the same reaction with **3b**, similar results were obtained. The starting material **3b** was recovered in 45% yield, benzaldehyde in about 40% yield, and the CM product **11b** in 11% yield. Although similar approaches have been successful for the synthesis of five- or six-membered lactones using the RCM reaction has been reported using $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ ^{10b} or $(\text{IMes})(\text{PCy}_3)\text{Cl}_2\text{Ru}=\text{CHPh}$,^{10a} our experiments failed to produce the desired RCM products. During the reaction, we monitored the reaction frequently using TLC to detect the formation of any trace of the RCM product **9a**. The reference sample of **9a** was prepared by the Baylis–Hillman reaction of benzaldehyde and lactone (5,6-dihydro-2*H*-pyran-2-one) derivative according to the

(5) (a) Choi, J. H.; Kim, N.; Shin, Y. J.; Park, J. H.; Park, J. *Tetrahedron Lett.* **2004**, 45, 4607. (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, 69, 1972. (c) Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, 125, 11494. (d) Hinderling, C.; Adlhart, C.; Chen, P. *Angew. Chem., Int. Ed.* **1998**, 37, 2685. (e) Huang, X.; Lin, Z. *Organometallics* **2003**, 22, 5478. (f) Yin, C.; Xu, Z.; Yang, S.-Y.; Ng, S. M.; Wong, K. Y.; Lin, Z.; Lau, C. P. *Organometallics* **2001**, 20, 1216. (g) Wong, W.-Y.; Ting, F.-L.; Lin, Z. *Organometallics* **2003**, 22, 5100. (h) Fung, W. K.; Huang, X.; Man, M. L.; Ng, S. M.; Hung, M. Y.; Lin, Z.; Lau, C. P. *J. Am. Chem. Soc.* **2003**, 125, 11539.

(6) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3974. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, 115, 9858. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem.* **1995**, 107, 2179; *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2039. (d) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, 117, 5503. (e) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, 118, 100.

(7) Aagaard, O. M.; Meier, R. J.; Buda, F. *J. Am. Chem. Soc.* **1998**, 120, 7174.

(8) (a) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, 18, 5375. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953. (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 1751. (d) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, 122, 3783. (e) Ackermann, L.; Furstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, 40, 4787. (f) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 40, 2247.

(9) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, 45, 2805.

(10) (a) Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, 65, 2204. (b) Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, 43, 5393. (c) Gruttadauria, M.; Meo, P. L.; Noto, R. *Tetrahedron Lett.* **2004**, 45, 83.

(11) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, 122, 8204.

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

(13) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, 123, 6543. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, 125, 2546. (c) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, 123, 749. (d) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, 126, 7414. (e) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, 17, 2484. (f) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, 64, 7202.

(14) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, 125, 10103.

(15) (a) Martinez, I.; Andrews, A. E.; Emch, J. D.; Ndakala, A. J.; Wang, J.; Howell, A. R. *Org. Lett.* **2003**, 5, 399. (b) Krishna, P. R.; Kannan, V.; Ilangoan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, 12, 829.

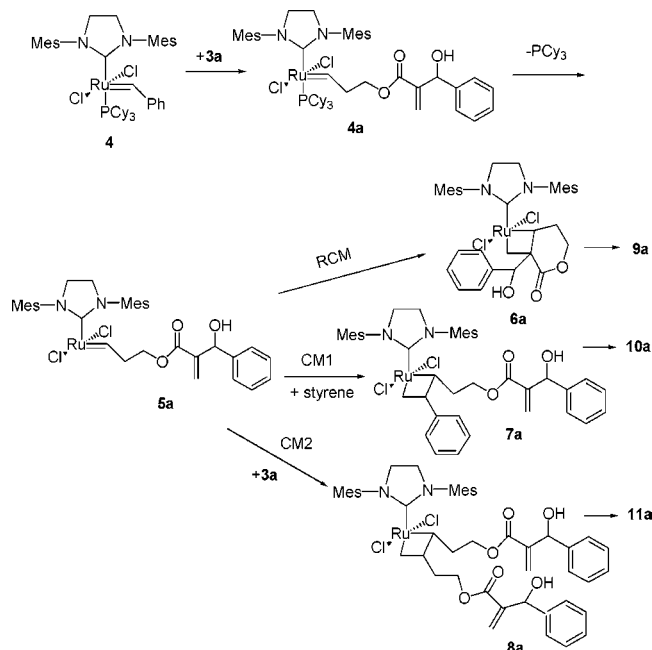


Figure 1. Postulated mechanisms for olefin metathesis.

literature method.¹⁶ Thus, we can exclude the possibility for the formation of the RCM product followed by the conversion to more thermodynamically favorable products over time at high temperature. To find out the effect of hydroxyl group of **3a** on the RCM reaction, we synthesized the MEM-protected **3a** and tried the RCM reaction. Again, we could not obtain the RCM product as before.¹⁷

This may arise from the fact that under the high-dilution conditions for the reaction (favorable for the RCM reaction), the activation energy for forming the desired RCM product is much higher than those for the CM products (**10a** and **11a**). To shed light on these RCM and CM processes, we investigated the conversion of **3a** into **9a**, **10a**, and **11a** by theoretical calculation. Most of the computational studies to date have considered truncated model systems such as PH_3 instead of PCy_3 .^{3,7,11} However, we have included the actual molecular systems in our computations. We compared the relative reaction barriers for the RCM and CM processes using ab initio calculations. All the structures were fully optimized at the Hartree–Fock level of theory with 3-21G basis sets using the Gaussian 98 suite of programs.¹⁸

It has been assumed that the olefin metatheses take place through the dissociation of the PCy_3 ligand followed by the

formation of a π -complex and cyclic four-membered ring intermediates as suggested for the most favored reaction mechanism^{3a,7} (Figure 1). For the olefin metathesis of **3a** with **4**, the catalyst is considered to react first with the monosubstituted terminal double bond of **3a** because it is least electronically deactivated and sterically least hindered.¹⁹ There are three possible products: **9a**, **10a**, and **11a**. Lactone **9a** is the product of ring-closing metathesis (RCM), while **10a** and **11a** are the products of the cross-metathesis (CM) of **5a** with styrene (CM1) and **3a** (CM2), respectively. The relative energies of the three different reaction pathways are shown in Figure 2.

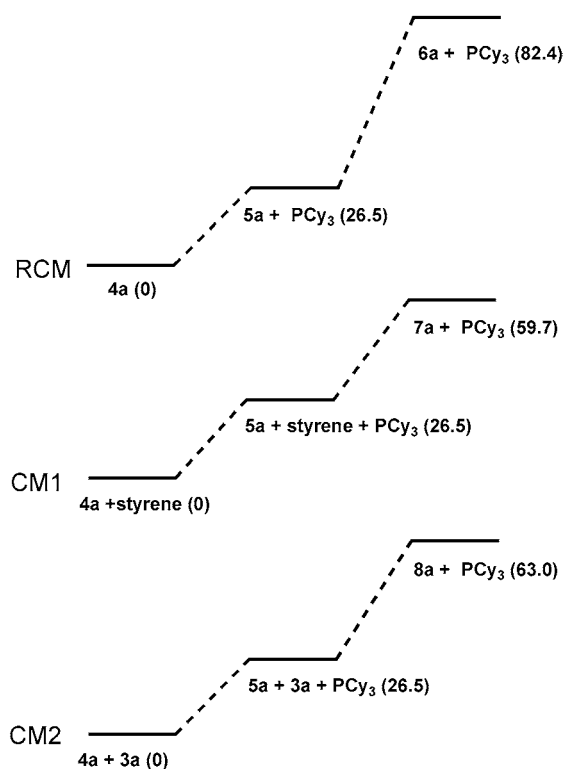


Figure 2. Relative energies (in kcal/mol) along the pathways from **4a** to **6a** (RCM), **7a** (CM1), and **8a** (CM2).

For the RCM pathway, the relative energies of the intermediates, **4a**, **5a** + PCy_3 , and **6a** + PCy_3 , are 0, 26.5, and 82.4 kcal/mol, respectively. For the CM1 pathway, the

(16) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692.

(17) In the reaction, we could isolate the homodimerized product in low yield (9–12%), with abundant starting material being recovered. At the early stage of this project, we examined the reaction of **3a** in CH_2Cl_2 (8% catalyst, reflux, 100 h). We obtained a low yield (7–8%) of **10a**, starting material **3a** (35%), and appreciable amounts of benzaldehyde. Thus, we changed the solvent to toluene as described in this paper. In another substrate, deoxy-**3a**, in toluene, the RCM product was not found either. The benzaldehyde appears to be generated by the retro-Baylis–Hillman (BH) reaction of **3a** and **3b**. The BH reaction, which can be catalyzed by tertiary amines or phosphines, is a reversible process. (Cipane, E. *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350).

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

(19) Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185.

relative energies of the intermediates, **4a** + styrene, **5a** + styrene + PCy₃, and **7a** + PCy₃, are 0, 26.5, and 59.7 kcal/mol, respectively. For the CM2 pathway, the relative energies of the intermediates, **4a** + **3a**, **5a** + **3a** + PCy₃, and **8a** + PCy₃, are 0, 26.5, and 63.0 kcal/mol, respectively. Thus, the reaction barriers for RCM, CM1, and CM2 pathways are 82.4, 59.7, and 63.0 kcal/mol, respectively. These reaction barriers are consistent with the experimental observation that the yields of **10a** and **11a** are 8 and 46%, respectively, while the RCM product **9a** was not obtained. The low yield (8%) of **10a**, despite this reaction pathway being lower in energy than that for **11a**, is presumably due to using a small amount (14%) of ruthenium catalyst, which is the only source of styrene.

The barrier difference for CM1 and CM2 is only 3.3 kcal/mol, but that for CM1 and RCM is 22.7 kcal/mol, which implies that the steric hindrance contributes slightly. Thus, the most dominant factor for the difference in reaction barrier may be the ring strain. The ring strain for **6a** seems to be much higher than that for **7a** and **8a**, where the electronic effect is operating almost equivalently. The electronic effect was previously discussed in detail for various ligands.^{13a}

The RCM of isopentenyl methacrylate gives the corresponding six-membered lactone when it is mediated by **4**.^{10a} The barrier for this reaction has been compared with the barrier for the CM of **3a** and styrene. The barrier difference between the RCM and CM processes is calculated to be about 16.5 kcal/mol, which is much reduced compared with that (22.7 kcal/mol) in our substrates having a ring substituent. Nevertheless, the difference is still very high, which would make it difficult to realize the RCM reactions. The second-generation Grubbs catalyst seems to be inefficient for our RCM reactions, while it seems to be much more efficient for the CM reactions. The main reason for the inefficiency for the RCM reaction may result from the inherent strain and steric effect in the cyclic four-membered ring intermediates. This conclusion applies to the substrates investigated and needs to be further studied for other RCM/CM reactions.

The four membered-ring intermediates **6a**, **7a**, and **8a** may have several different conformers according to the cis or trans conformation for the two chlorines, as well as two substituents constituting the four-membered rings. The X-ray structures of **4**^{5e} and its derivative^{8a} are known. In our calculations, we chose the halide and other ligand orientations

assuming that their orientation did not change after phosphine dissociation despite their exact positions being unknown. For the cyclic intermediate **7a**, we tried to compare the energies of the four different conformers, trans–trans, trans–cis, cis–trans, and cis–cis. We name cis–trans in cases where the two chlorines have a cis conformation and the two substituents (phenyl and ester moieties) have a trans conformation, respectively. The trans–trans conformer is slightly more stable than the trans–cis conformer by 1.45 kcal/mol. In the case of cis conformation for chlorines, we found an interesting behavior. The cis–cis conformer changed into the dissociated complex **5a** and styrene during the geometry optimization. The cis–trans conformer proceeded to the product-like complex. Thus, the metathesis reaction seems to proceed via the configurational exchange from trans to cis for the halides, where the Cl–Ru–Cl is in the trans configuration in the crystal structures. This observation is closely related to the explanation of the catalytic activity by the trans influence of halides, phosphines, and olefins.^{12,13a} Significantly, this configurational exchange is found to be facile even at room temperature from the quantum molecular dynamics study.⁷ The structural details are presented in Supporting Information.

In conclusion, we have investigated the RCM and CM reactions of **3a** with the second-generation Grubbs catalyst **4** both experimentally and theoretically. In the former case, we obtained only CM products and no RCM product even at high-dilution conditions. The experimental results are clearly explained by reaction barrier differences for the RCM and CM reactions based on ab initio calculations for the full molecular systems.

Acknowledgment. This work was supported by Korea Research Foundation Grant (KRF-2002-015-CP0215).

Supporting Information Available: Synthetic details and characterization data and calculated conformations for compounds styrene, PCy₃, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, four configurations (trans–trans, trans–cis, cis–trans, cis–cis) of **7a**, and metallacyclobutane intermediates for RCM and CM processes of isopentenyl methacrylate. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048776I