ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

An Efficient Protocol for the Cross-Metathesis of Sterically Demanding Olefins

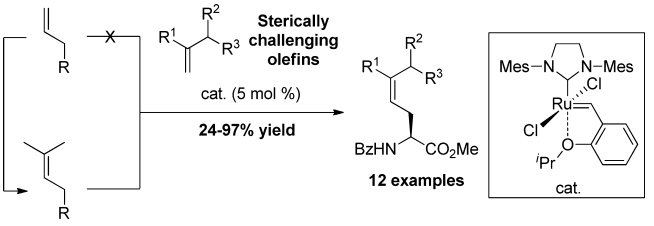
Zhen J. Wang, W. Roy Jackson, and Andrea J. Robinson*

School of Chemistry, Monash University, Clayton 3800, Victoria, Australia

Andrea.Robinson@monash.edu

Received April 28, 2013

ABSTRACT



Cross-metathesis of a wide range of previously unreactive, sterically demanding alkenes can be achieved in fair to excellent yield using a commercially available catalyst by a facile strategy involving reversal of steric preference.

Ruthenium alkylidene catalyzed cross-metathesis (CM) has been used as an efficient C=C bond forming reaction in many syntheses.[1] To date, however, CM of sterically demanding substrates remains a challenge. In particular, one class of alkenes that possesses 1,1-disubstitution *and* allylic branching, generically depicted by structure **1**, performs poorly in CM reactions (Figure 1a). A literature survey of CM reactions involving this olefin subclass[2] reveals that only a few ring strained examples lead to viable reaction yields using Ru-alkylidene catalysts **2**–**4** (Figure 1b).[2d,3] Hence, this olefin class regularly falls into the type IV classification, namely as spectators to CM,[4] and appear to be beyond the scope of existing, commercially available catalysts such as **2**–**4**. In order to address this deficiency, catalysts designed with decreased steric crowding around the Ru-center, such as **4**, have been investigated but success to date has been limited (Figure 1b).[2b,5]

Herein, we report a facile methodology to perform efficient CM reactions involving sterically challenging cross

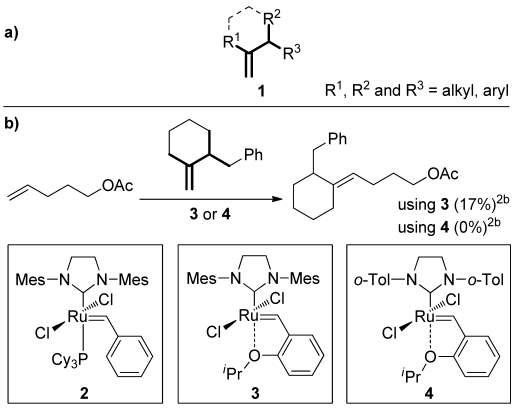


Figure 1. Difficult CM reactions. (a) Generic structure of unreactive CM substrates. (b) Example of poor yields observed for CM reactions involving olefins with general structure **1**.

(1) (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753. (b) 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*, 58–71. (c) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750. For a review, see: (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (e) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (f) Vougloukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787. (g) Prunet, J.; Grimaud, L. Cross-metathesis in Natural Products Synthesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*; Cossy, J., Arseniyadis, S., Meyer, C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp 287–312.

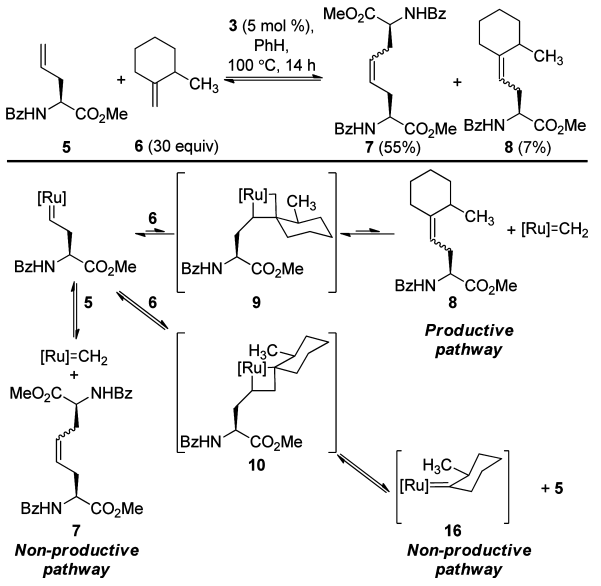
(2) (a) Lee, M. J.; Lee, K. Y.; Lee, J. Y.; Kim, J. N. *Org. Lett.* **2004**, *6*, 3313–3316. (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444. (c) Barile, F.; Bassetti, B.; D'Annibale, A.; Gerometta, R.; Palazzi, M. *Eur. J. Org. Chem.* **2011**, 6519–6526. (d) Plummer, C. W.; Soheili, A.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2462–2464.

(3) Raju, R.; Howell, A. R. *Org. Lett.* **2006**, *8*, 2139–2141.

(4) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

10.1021/ol401194h

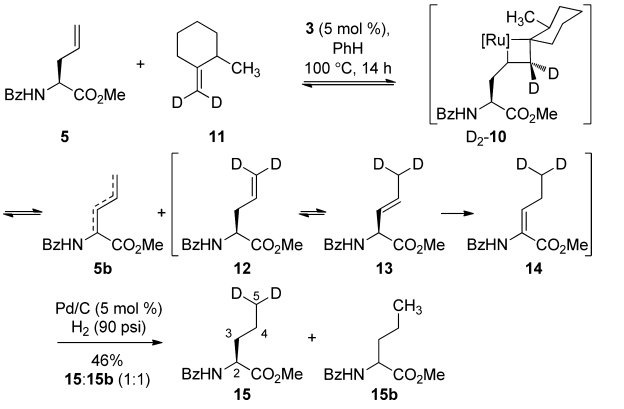
Scheme 1. Catalytic Pathways for the CM Reaction between **5** and **6**[6]



partners conforming to the general structure **1** using commercially available catalyst **3**. Our study began with an in-depth analysis of a representative reaction between **5** and **6** (Scheme 1). The reaction gave starting material **5** as a mixture of regioisomers (38% combined yield),[7,8] the dimer **7** (55%), and the desired cross product **8** in only 7% isolated yield. A possible explanation for the observed product distribution can be provided by examining the *productive* and *nonproductive* metathesis pathways within the catalytic cycle (Scheme 1). These pathways are characterized by the intermediate metallocyclobutanes **9** and **10**.[9] The 1,2-metallocyclobutane **9** can ring open in a productive fashion to give the desired cross product **8**, whereas the 1,3-metallocyclobutane **10** can only undergo nonproductive Ru-alkylidene exchange reactions. We hypothesized that the steric bulk imposed by the hindered olefinic substrate **6** disfavors the formation of the 1,2-metallocyclobutane **9** and, therefore, results in a poor yield of **8**.[10,11] The reason for the poor reactivity was initially unclear to us. The sterically hindered olefin **6** could be acting predominantly as a spectator, or the reaction could be preferentially cycling through the nonproductive intermediate **10**. Both of these explanations would result in low conversion of the starting materials. Furthermore, a secondary catalytic cycle involving the self-metathesis of allylglycine **5** to give byproduct **7** also competes with the process of the desired CM reaction (Scheme 1). As a result, despite catalyst turnover, only small quantities of the desired cross product **8** are generated.

In order to acertain whether the metathesis reaction was cycling through the nonproductive intermediate **10**, a deuterium-labeled crossover experiment was conducted (Scheme 2). CM between allylglycine derivative **5** and the

Scheme 2. Deuterium Crossover Experiment for CM Reaction between **5** and **11**



dideutero-cross partner **11** was performed under identical reaction conditions to those depicted in Scheme 1. This resulted in a mixture of dideutero-crossover product **12**, isomerized analogues **13** and **14**, and isomerized starting material **5b**.[12] Subsequent hydrogenation of the mixture gave the expected deuterium-labeled compound **15** and **15b** in a 46% combined yield as a 1:1 mixture. Exclusive deuterium incorporation was observed at the C5 position, and the label did not scramble despite the isomerization process. This crossover experiment therefore supports the formation of the *nonproductive* 1,3-metallocyclobutane intermediate **10** during the CM reaction between **5** and **6**.[13] More importantly, these results show that the catalyst **3** *is* reactive toward sterically hindered olefins such as **6** but almost exclusively in a *nonproductive* fashion. This result

(5) (a) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arit, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652–13653. (b) Chung, C. K.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2693–2696. (c) Kuhn, K. M.; Bourg, J. B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313–5320. (d) Vorfalt, T.; Leuthäußer, S.; Plenio, H. *Angew. Chem.* **2009**, *121*, 5293–5296.

(6) It should be noted that an alternative pathway to product **8** exists *via* reaction of intermediate **16** with **5**.

(7) During CM, concomitent isomerization of **5**, but not **6**, is observed. The resultant internal C2 and C3 olefins do not undergo CM under the reaction conditions employed.

(8) (a) McNaughton, B. R.; Bucholtz, K. M.; Camaaño-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733–736. (b) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(9) (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999. (b) Stewart, I. C.; Keitz, B. K.; Kuhn, K. M.; Thomas, R. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 8534–8535. (c) Wenzel, A. G.; Blake, G.; VanderVelde, D. G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 6429–6439.

(10) To further support this steric argument, the nor-methyl analogue of **6**, methylenecyclohexane, can undergo CM with **5** in 98% isolated yield. The dramatic difference in yield arising from CM of methylenecyclohexane and **6** under identical experimental conditions can only be attributed to the steric crowding imposed by the methyl group in the allylic position of **6**.

(11) Up to eight possible diastereoisomers of **9** (and **10**) could be formed during the CM reaction. The reaction equilibrium, however, would favor the formation of diastereoisomers of **10** over diastereoisomers of **9** to avoid adverse steric interaction.

(12) The dimer **7** and trace amounts of cross product **8** (< 5%) were also isolated.

(13) Whilst it is possible to also obtain **15** *via* the productive pathway, the observed level of deuterium incorporation (46%) exceeds the theoretical yield *via* this pathway (5%).

also supports the formation of the intermediate **16** in a system where more reactive olefins such as **5** and **7** are present (Scheme 1).

Following from this experiment we hypothesized that strategies which promoted cycling through the *productive* 1,2-metallocycle, rather than increasing catalyst reactivity, would be more successful in achieving efficient CM. Toward this end, we investigated the effect of adding additional substitution to the reactive type I cross partner. The addition of two terminal methyl groups to olefin **5** generates the trisubstituted olefin **17** and causes steric reversal within the molecule; that is, the terminus of the olefin becomes more sterically encumbered (Figure 2).[14,15] We postulated that this key structural alteration would reorient olefin binding at the ruthenium center and promote formation of a productive metallocyclobutane over a nonproductive metallocyclobutane. Importantly, the *same* product would be generated from the terminal alkene (e.g., **5**) and its prenylated derivative (e.g., **17**) following the CM reaction.

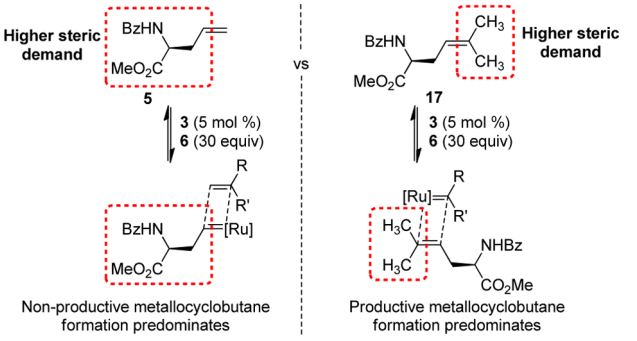
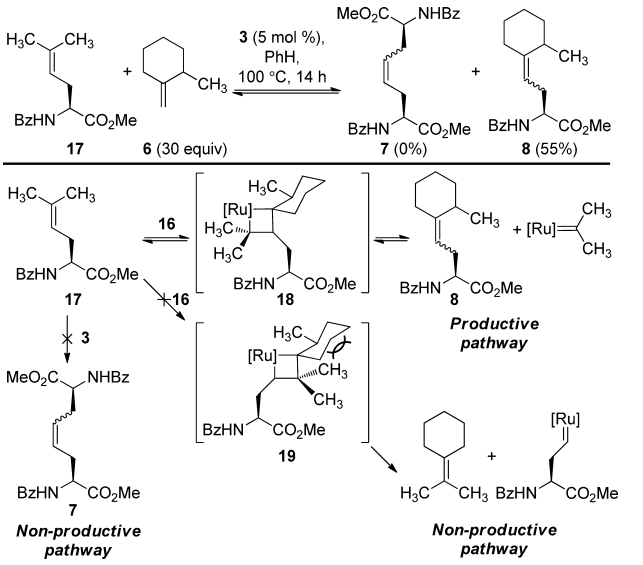


Figure 2. Comparison of relative steric demand in **5** and **17** showing steric reversal across the alkene bond.

To examine this hypothesis, the CM of the prenylglycine derivative **17** with **6** was performed under identical reaction conditions to those previously described (Scheme 3). This time, however, the elusive cross product **8** was isolated in 55% yield. Notably, the previously observed isomerization was eliminated when using the prenylated analogue **17**. Furthermore, the required product **8** was not accompanied by the dimer **7**. This result is consistent with previous work by us showing that under analogous metathesis conditions prenylglycine does not self-dimerize.[16] Hence, the steric reversal modification promotes cycling through the previously disfavored *productive* pathway (that is, cycling through **18** is now favored over **19**). In conclusion, with this simple structural modification, the synthesis of **8** could finally be achieved using an unmodified, commercially available catalyst **3** at a 5 mol % loading.

Scheme 3. Catalytic Pathways for the CM Reaction between **17** and **6**



The scope of this approach was explored *via* the CM of the geminal dimethyl analogues **17** and **20** with hindered exocyclic and aliphatic olefins of the generic structure **1** bearing increasing steric bulk in the vicinity of the reacting olefin (Figure 3). Each of these reactions was first performed with the corresponding unsubstituted, terminal equivalents of **17** and **20** (i.e., **5** and pent-4-en-1-yl acetate respectively), and in *every* case, nonviable yields of the desired cross product were obtained (Figure 3, entries in parentheses (0−17% yield)). Similarly, the crotylglycine derivative **21** also failed to react with **6** to generate the target product **8** (Scheme 4). In conclusion, trisubstituted olefins are required to facilitate the steric reversal, and prenylation of terminal olefins readily accomplishes this end.

Gratifyingly, the geminal dimethyl analogue **20** reacted with a hindered exocyclic and functionalized aliphatic olefin to provide cross products **22** and **23** in excellent yield (90 and 87% respectively). A direct comparison of the yield obtained for compound **22** with previous results summarized in Figure 1b shows the significant improvement in the CM efficiency. A regioselective CM was also achieved between α-benzyl methylenecyclohexane and geranyl acetate to give **24** in 53% yield (Figure 3).[17]

The use of the prenylglycine analogue **17** also led to synthetically viable CM yields with various hindered olefinic cross partners (compounds **8** and **25**–**32**, Figure 3). Unavoidably, in all cases except compounds **28** and **29**, an inseparable mixture of *E*- and *Z*-isomers was obtained. Additionally, in the cases where racemic cross partners were used (compounds **8**, **25**, **26**, and **32**), a mixture of epimers was obtained. Compounds **28** and **29**, on the other hand, were obtained as single stereoisomers possessing the

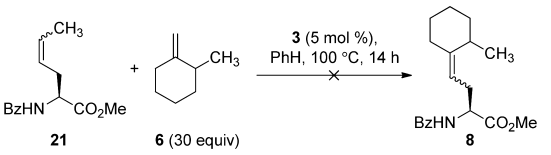
(14) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942.

(15) Transformation of terminal olefins into trisubstituted analogues is readily achieved *via* CM with isobutylene or 2-methyl-2-butene.

(16) Robinson, A. J.; Elaridi, J.; Patel, J.; Jackson, W. R. *Chem. Commun.* **2005**, 5544–5545.

(17) (a) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465–3467. (b) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448–1452.

Scheme 4. Attempted Screening for an Alternative Cross Partner



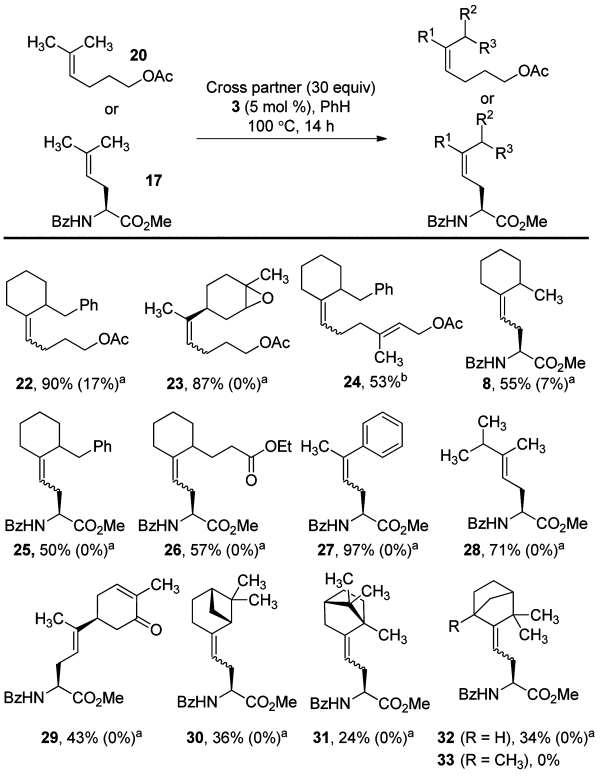
E-configuration (determined by NOESY experiments) in 71% and 43% yield respectively.

Pleasingly, several highly hindered terpenes, such as *β*-pinene, camphene, and methylenecamphor, also participated in productive catalyst turnovers, albeit in lower yield, to generate olefins **30**–**32** respectively.[17,18] The limit of this steric reversal strategy was finally reached when a highly hindered cross-coupling partner, a tetra-allylic substituted methylenefenchone derivative, was employed (compound **33**, Figure 3).

In all cases, the desired cross product was the only olefin generated in each of these reactions; the presence of tetrasubstituted olefins was undetected under the new reaction conditions suggesting that the active metathesis catalyst was unable to cycle *via* the nonproductive intermediate (such as **19**). In each of the reactions, excess starting material was recovered unchanged and in high yield (90–95%) upon completion of the reaction for recycling in subsequent reactions. Attempts were made to lower the equivalents of the excess cross partner; however a decline in yield was observed.

In conclusion, previous work by others has shown that CM of sterically demanding 1,1-disubstituted, allylic branched olefins under Ru-alkylidene catalysis is challenging. Close examination of the catalytic cycle of these substrates has enabled us to achieve viable CM yields with these olefins using second generation Hoveyda–Grubbs catalyst (**3**) *via* a steric-reversal strategy driven by minor modification of the starting type I olefin. This work therefore extends the scope of this already remarkable catalyst and facilitates the expedient synthesis of highly substituted and functionalized olefins. This CM approach is currently being exploited for the synthesis of tricyclic marine alkaloids.

(18) The cross partners used to synthesize **31** and **32** were generated from camphor and fenchone, respectively, using forcing Wittig olefination reaction conditions.



[a] Yields in parentheses obtained when terminal olefins **5** and pent-4-en-1-yl acetate were used as starting materials. [b] Geranyl acetate was used as the starting material.

Figure 3. Scope of CM reaction involving hindered olefins.

Acknowledgment. The authors wish to acknowledge the financial support of the Australian Research Council and the award of a postgraduate research award to Z.J.W. The authors acknowledge Nicolas D. Spiccia (Monash University) for prior contributions and discussions.

Supporting Information Available. Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.