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Increased Efficiency in Cross-Metathesis Reactions of Sterically Hindered Olefins

Ian C. Stewart, Christopher J. Douglas, and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratory of Chemical Synthesis,
Division of Chemistry and Chemical Engineering, California Institute
of Technology, Pasadena, California 91125

rhg@caltech.edu

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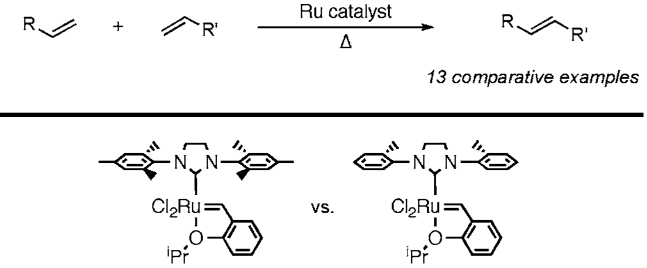
ABSTRACT



Efficiency in olefin cross-metathesis reactions is affected upon reducing the steric bulk of N-heterocyclic carbene ligands of ruthenium-based catalysts. For the formation of disubstituted olefins containing one or more allylic substituents, the catalyst bearing *N*-tolyl groups is more efficient than the corresponding *N*-mesityl catalyst. In contrast, the formation of trisubstituted olefins is more efficient using the *N*-mesityl-containing catalyst. A hypothesis to explain this dichotomy is described.

Olefin cross-metathesis (CM)[1] is a powerful synthetic tool for the preparation of functionalized alkenes due in large part to the advent of catalysts **1**[2a] and **2**[2b] that contain an N-heterocyclic carbene (NHC) ligand (Figure 1).[3] These more active catalysts allow 1,1-disubstituted olefins,[3c] α,*β*-unsaturated carbonyls,[3e] and vinyl phosphonates,[3d] sulfones,[3f] boronates,[3i,j] and silanes[3k] to be utilized as reactive CM partners. We have described a general model for selectivity in CM,[3h] but a number of limitations still hinder its widespread application in organic synthesis. One of those issues is the tolerance of steric conjestion on or around the reactive olefin moiety.[4a] Wagener and co-workers have described the challenge of even simple allylic methyl

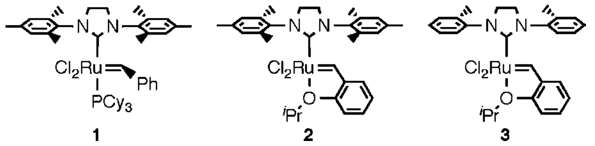


Figure 1. Ruthenium-based olefin metathesis catalysts.

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(1) For recent reviews, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003.

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

(3) For leading references on CM methodology development, see: (a) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (d) Chatterjee, A. K.; Choi, T. L.; Grubbs, R. H. *Synlett* **2001**, 1034−1037. (e) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277−1279. (f) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425−6428. (g) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939−1942. (h) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. (i) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031−6034. (j) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733−7736. (k) BouzBouz, S.; Boulard, L.; Cossy, J. *Org. Lett.* **2007**, *9*, 3765−3768.

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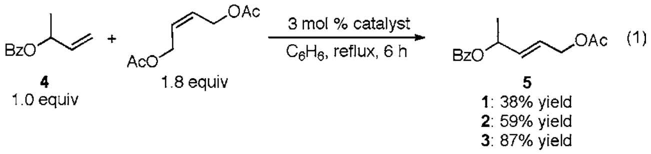
substituents in CM with both Ru- and Mo-based catalysts.[4b] Herein we investigate the effect of reducing the steric bulk of the NHC ligand on the efficiency of sterically challenging CM reactions.

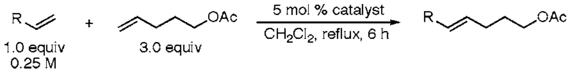
We recently reported the enhanced reactivity of catalyst **3** for the formation of tetrasubstituted olefins by ring-closing metathesis (RCM).[5] On the basis of this improved efficiency we thought that this catalyst, which bears *N*-tolyl rather than *N*-mesityl groups in the NHC ligand, might also exhibit increase efficiency in CM reactions. As an initial assay, we looked at the cross metathesis of but-3-en-2-yl benzoate (**4**) with *cis*-1,4-diacetoxy-2-butene to form allylic benzoate **5** (eq 1). Phosphine-containing catalyst **1** afforded the desired product in only 38% yield,[3h] whereas the phosphine-free catalyst **2** furnished 59% of compound **5**, likely due to increased catalyst lifetime. Catalyst **3**, however, proved to be most active in this series, producing the desired CM product in an impressive 87% yield. With this promising initial result, we embarked on a systematic comparison of catalysts **2** and **3** in a variety of sterically challenging CM reactions.

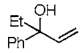
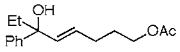
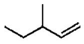
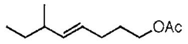
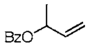
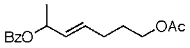
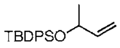
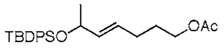
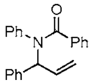
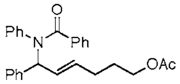


(1)

The formation of disubstituted olefins bearing bulky substituents in the allylic postion proceeds in low yields with phosphine-containing catalyst **1**. Both phosphine-free catalysts **2** and **3** exhibited increased efficiency in CM of a number of challenging substrates with 5-acetoxy-1-pentene (Table 1). Allylic methyl groups have been reported to undergo CM reactions with reduced efficiency,[4] but clearly this substituent is easily tolerated by catalyst **3**, as the desired product is obtained in 98% yield (entry 2). Even the very bulky OTBDPS group is accommodated with this catalyst (entry 4). The allylic amide in entry 5, readily prepared by an Overman rearrangment,[6] was challenging for both catalysts investigated. Notably, catalyst **3** performed better in all cases examined.

Table 1. Formation of Disubstituted Olefins Bearing Allylic Substituents

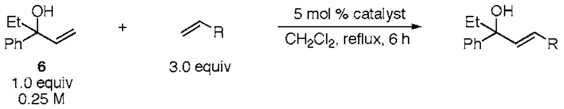


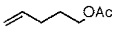
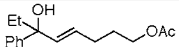
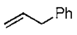
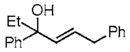
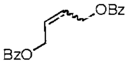
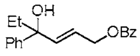
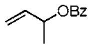
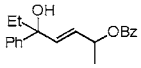
entry	reactant	product[a]	yield (%)[b] 2	yield (%)[b] 3
1			70	89
2			85	98
3			82	93
4			68	91
5			19	30

[a] *E*/*Z* > 20:1 in all cases. [b] Isolated yields.

We next investigated the efficiency of catalysts **2** and **3** in CM reactions of alcohol **6** (Table 2). Good to excellent yields of the cross product were obtained with an allylic phenyl (entry 2) and benzoate substituent (entry 3). Inclusion of additional allylic substituents led to lower yields, but catalyst **3** afforded the densely substituted product in good yield (entry 4). Again, *N*-tolyl catalyst **3** outperformed *N*-mesityl catalyst **2** in all cases.

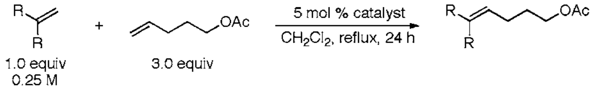
Table 2. CM Reactions of Tertiary Alcohol **6**

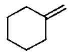
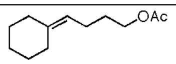
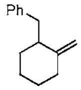
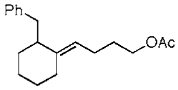
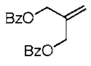
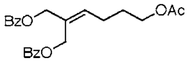


entry	reactant	product[a]	yield (%)[b] 2	yield (%)[b] 3
1			70	89
2			64	91
3			81	98
4[c]			50	66

[a] *E*/*Z* > 20:1 in all cases. [b] Isolated yields. [c] Isolated as a 3:2 mixture of diastereomers.

Table 3. Formation of Trisubstituted Olefins by CM



entry	reactant	product	yield (%)[a] 2	yield (%)[a] 3
1			78	60
2			17	0
3			73	54

[a] Isolated yields.

In stark contrast to the results listed in Tables 1 and 2, the formation of trisubstituted olefins by CM is less efficient using catalyst **3** compared with **2** (Table 3). Reaction of methylenecyclohexane with 5-acetoxy-1-pentene afforded the cross product in 78% and 60% yield with catalysts **2** and **3**,

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[4] (a) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489. (b) Courchay, F. C.; Baughman, T. W.; Wagener, K. B. *J. Organomet. Chem.* **2006**, *691*, 585−594.

respectively (entry 1). The addition of an allylic substituent to the 1,1-disubstituted olefin partner drastically reduced the efficiency of the CM reaction as the desired product was obtained in a mere 17% yield using **2**, whereas **3** afforded none of the trisubstituted olefin in this case.

The divergence in relative efficiencies of these two catalysts for the formation of di- and trisubstituted olefins suggests that at least two parameters are at play here. There are both productive and unproductive olefin metatheses occurring in any given CM reaction. For example, if a 1,2-disubstituted metallacyclobutane is formed, cycloreversion will generate a ruthenium methylidene and the desired CM product (Path A in Figure 2). However, if olefin coordination leads to a 1,3-disubstituted metallacyclobutane (Path B), collapse of this intermediate does not result in a productive CM reaction, but does constitute a catalyst turnover event. *Thus both selectivity of metallacyclobutane formation and the total number of catalyst turnover events* (*i.e.*, *catalyst stability*) *influence the efficiency of cross-metathesis reactions*.

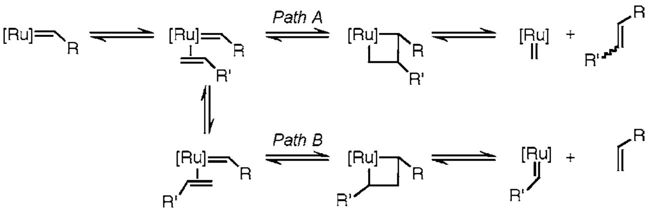


Figure 2. Productive and unproductive CM pathways.

These issues of regioselectivity are especially important in the formation of trisubstituted olefins by CM. While the smaller NHC ligand in **3** allows larger reactants to be accommodated in the formation of disubstituted olefins by CM, it likely also favors unproductive pathways with 1,1-disubstituted olefins. Specifically, the relative selectivity for the formation of π-complex **B** over **A**[7] is likely lower than the selectivity of **D** versus **C** due to the smaller *N*-tolyl containing ligand (Figure 3).[8] In other words, by decreasing the size of the NHC ligand the rate of unproductive cross-metathesis pathways (Path B) may be increased relative to productive pathways (Path A). Catalyst **3** could be performing a similar number of turnovers as **2**, but the smaller *N*-tolyl ligand leads to an increase in the number of unproductive reactions, resulting in lower yields for the desired CM product.

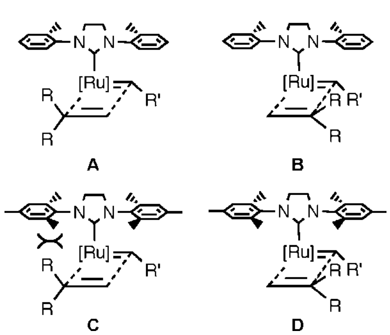
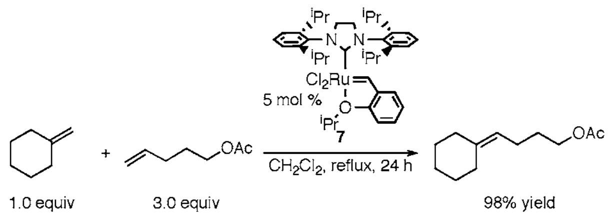


Figure 3. Relevant π-complexes in the formation of trisubstituted olefins by CM. [Ru] = $RuCl_2$.

This steric-based argument suggests that *increasing* the steric bulk of the NHC ligand should increase the yields for the formation of trisubstituted olefins by CM. In support of this hypothesis, catalyst **7**,[9] which displays *N*-2,6-diisopropylphenyl substituents, affords excellent yields, and more importantly higher than those with catalysts **2** or **3**, of the desired products (eqs 2 and 3). The addition of an allylic substituent to a 1,1-disubstituted olefin (e.g., Table 3, entry 2) complicates this trend, from which catalyst **2** emerges as the most efficient (eq 4).



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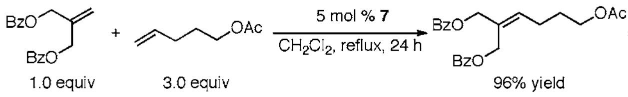

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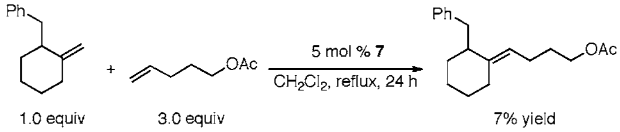

(4)

In summary, by reducing the steric bulk of the NHC ligand in ruthenium-based metathesis catalysts, increased efficiencies for the formation of sterically challenging disubstituted olefins was observed. The formation of trisubstituted olefins by CM, however, is more efficient using bulkier NHC ligands, likely due to the selectivity of productive versus unproductive pathways.

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(5) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589−1592.

(6) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579−586.

(7) For simplicity only the *syn* conformation of the two *N*-tolyl substituents for **A** and **B** is shown in Figure 3.

(8) A cis approach is implied in Figure 3, though aside from the significant increase in reactivity with catalyst **2** compared to **3** in a number of sterically demaning examples, we have no evidence for this geometry in CM reactions. This geometry is supported by isolated π-complexes, for example, see: Anderson, D. R.; Hickstein, D. D.; O'Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 8386−8387. The influence of ligand sterics may also be manifested in ruthenacyclobutane intermediates, but to a lesser extent due to the trans arrangement of metallacycle and the NHC ligand. For pertinent examples, see: Wenzel, A. G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 16048−16049. Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032−5033. Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698−1704.

(9) Courchay, F. C.; Sworen, J. C.; Wagener, K. B. *Macromolecules* **2003**, *36*, 8231−8239.

Acknowledgment. The authors thank the NIH (postdoctoral fellowships to I.C.S. and C.J.D. and Grant 5RO1GM-31332 to R.H.G.), Dr. Patricio Romero (Caltech) for helpful discussions, and Materia Inc. for their generous donation of catalysts used in these studies.

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

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