

Highly Efficient Ruthenium Catalysts for the Formation of Tetrasubstituted Olefins via Ring-Closing Metathesis

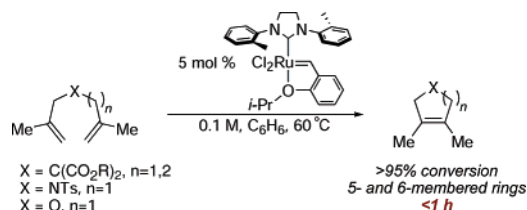
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Received February 28, 2007

ABSTRACT



A series of ruthenium-based metathesis catalysts with N-heterocyclic carbene (NHC) ligands have been prepared in which the *N*-aryl groups have been changed from mesityl to mono-*ortho*-substituted phenyl (e.g., tolyl). These new catalysts offer an exceptional increase in activity for the formation of tetrasubstituted olefins via ring-closing metathesis (RCM), while maintaining high levels of activity in ring-closing metathesis (RCM) reactions that generate di- and trisubstituted olefins.

The formation of carbon–carbon bonds by olefin metathesis has become one of the most powerful and broadly applicable synthetic tools of modern chemists.¹ In particular, ring-closing metathesis (RCM) reactions promoted by ruthenium-based catalysts have been widely utilized by synthetic organic chemists in the construction of small, medium, and large ring systems from acyclic precursors.² The formation of cyclic, disubstituted olefins from terminal dienes is generally effectively catalyzed by diphosphine ruthenium complexes,³

and the synthesis of cyclic trisubstituted olefins can be readily achieved using second-generation systems such as **1** (Figure

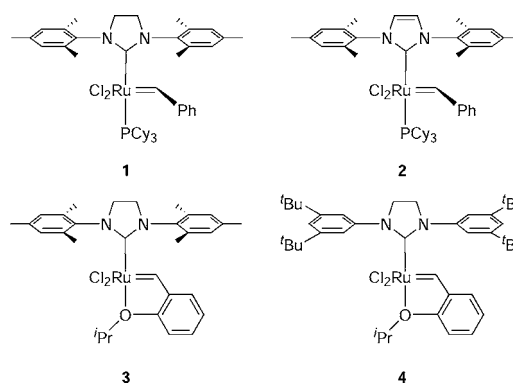


Figure 1. Ruthenium-based olefin metathesis catalysts.

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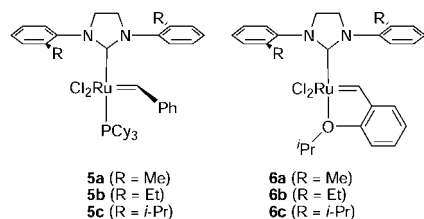
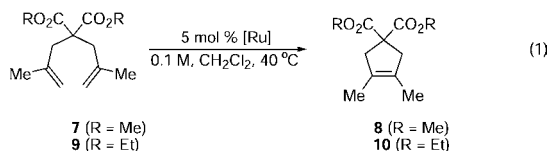


Figure 2. Ru catalysts with mono-ortho-substituted NHCs.

1).⁴ However, a ruthenium catalyst capable of producing ring structures that contain a tetrasubstituted carbon–carbon double bond with high efficiency remains elusive.^{5,6} Recent efforts toward this goal have focused on the development of N-heterocyclic carbene (NHC) ruthenium complexes where both ortho positions of the *N*-aryl rings are substituted with small atoms (e.g., H).⁷ Although these new catalysts, including compound **4**, are more efficient than previous ruthenium-based systems in the formation of cyclic tetrasubstituted olefins, they tend to require long reaction times and their production is difficult and not economical on a large scale.⁸

In pursuit of more efficient and more easily prepared catalysts, we continued to investigate the effects of the *N*-aryl group substitution patterns on the catalytic activity of the corresponding ruthenium complexes. Because removing both ortho substituents of the *N*-aryl ring (e.g., **4**) led to a large increase in reactivity for the formation of tetrasubstituted olefins, we were interested in studying catalysts derived from NHC ligands with only one ortho substituent on the aryl rings (Figure 2).⁹

A series of catalysts (**5a–c** and **6a–c**) were synthesized, and their activity was initially tested in the ring closing of dimethylallylmalonates **7** and **9** (eq 1).¹⁰ Phosphine-based catalysts **5a–c** gave high conversions to **8** under mild



conditions within very short reaction times (Table 1, Figure 3). Methyl-substituted catalysts **5a** and **6a** performed better

Table 1. RCM to Form Tetrasubstituted Olefin **8**

catalyst	time (h)	conv. (%) ^a	time (h)	conv. (%) ^a
1	1	4	24	50
2	1	9	24	40
3	1	0	24	0
4	1	0	20	24
5a	0.25	81	1	86
5b	0.25	62	1	71
5c	0.25	72	1	74
6a	1	45	24	70
6b	1	22	24	59
6c	1	16	24	33

^a Monitored by GC. See Supporting Information for additional details and time points.

than their ethyl- and isopropyl-substituted analogues, respectively.

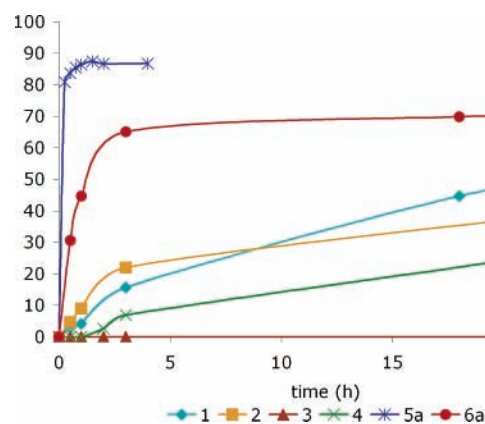


Figure 3. RCM to form tetrasubstituted olefin **8**.

Ether-based systems¹¹ **6a–c** were found to require longer reaction times than phosphine-based systems **5a–c** under the same conditions (Table 1). The kinetics of RCM to form tetrasubstituted olefins were monitored for catalysts **5a** and

(9) Chiral ruthenium metathesis catalysts have been reported with only one ortho substituent on each N-bound aryl ring. These catalysts are significantly less efficient for the preparation of tetrasubstituted olefins by RCM than the catalysts reported in this communication. See ref 7.

(10) The optimum temperature for RCM reactions using catalyst **4** is 60 °C; see ref 7.

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6a by NMR spectroscopy in closed tubes according to our recently published standard characterization system.¹² The results indicated that catalyst **5a** initiates rapidly but also decomposes readily under the reaction conditions.¹³ We believe that the build-up of ethylene in this closed system increases the concentration of intermediate ruthenium methyldiene complexes, which are susceptible to decomposition upon attack by free PCy₃.¹⁴ The analogous ether-based catalyst **6a** appeared to initiate more slowly but was longer-lived.

Increasing the temperature at which the metathesis reaction was run led to sufficient initiation rates. When run at 60 °C, catalyst **6a** quantitatively afforded tetrasubstituted product **10** within 30 min. Unreacted or regenerated **6a** was detected by ¹H NMR spectroscopy upon completion of the RCM reaction, suggesting that the catalyst loading could likely be decreased. Indeed, the ring closure of **9** was accomplished in >95% conversion *within 1 h using only 2.5 mol % of catalyst 6a* in C₆D₆ at 60 °C. The addition of water or performing the reactions in air did not significantly affect the yields of the RCM.

We propose that the remarkable increase in catalytic activity of **6a** compared to **3** in the RCM of **7** results from the significantly more open steric environment around the ruthenium center, which allows the catalytic site to accommodate larger organic fragments. The X-ray crystal structure of **6a** illustrates the reduced steric hindrance around the metal compared to that in **3** (Figure 4).^{11b} Interestingly, two

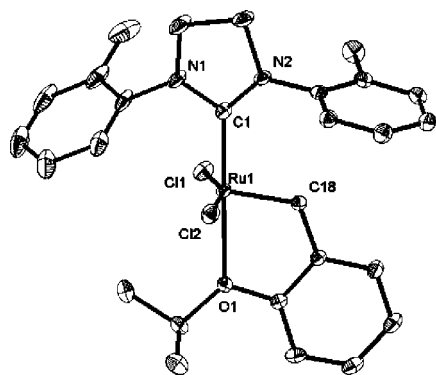


Figure 4. ORTEP diagram of **6a**.

conformers are present in the single crystal in a 91:9 ratio. The major conformer corresponds to the complex where the *o*-tolyl substituents of the NHC ligand adopt a syn conformation, whereas the *o*-tolyl substituents of the minor conformer have an anti conformation. It is not clear whether the syn or the anti conformer is more active in RCM. Studies related to the conformation of catalysts **5a–c** and **6a–c** in solution are underway.


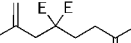

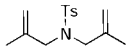
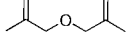
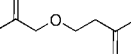
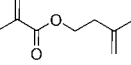
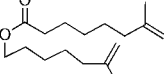
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Catalyst **6a** efficiently affords a variety of five-, six-, and seven-membered tetrasubstituted RCM products within much shorter reaction times than **3** (Table 2). Diene **11** was

Table 2. RCM Reactions Using Catalysts **3** and **6a**

substrate ^a		conv. (%)	
	3	6a	
	30, 24 h	>95, <1 h 100 ^b	
	>95, 24 h	>95, <1 h 100 ^b	
	50, 24 h	87 ^c , 24 h	
	85, 24 h	>95, <1 h	
	>95, 24 h	>95, <1 h	
	43, 24 h	88, 11 h	
	n.r.	n.r.	
	n.r.	n.r.	

^a E = CO₂Et. ^b Isolated yield. ^c Performed in an open system. Conversion in a closed system (NMR tube) was 62%.

quantitatively cyclized within 1 h, and full conversion was also achieved within 1 h in the RCM of sulfonamide **13** and ether **14**. Ring closing of **12**, which generates a seven-membered ring, was most efficient when ethylene was removed from the system. However, despite the higher reactivity of **6a**, the ring closing of ester **16** or the macrocyclization of ester **17** was not realized.

A rather simple modification, removal of an ortho substituent from the *N*-aryl ring of the NHC ligand, has resulted in a complex that efficiently catalyzes the formation of tetrasubstituted olefins by ring-closing metathesis. The synthesis of these catalysts can be performed on a large scale, and metathesis reactions do not require any special handling, a hallmark of ruthenium-based metathesis catalysts. In contrast to expectations, these less-substituted systems were sufficiently stable to provide efficient conversion to highly substituted products. A com-

plete discussion of catalyst development and reaction condition optimization will be reported in due course. The application of these catalysts to other metathesis reactions is ongoing in our laboratories.

Acknowledgment. We gratefully acknowledge financial support from NIH Grant 5RO1GM31332 to R.H.G. and an NIH postdoctoral fellowship to I.C.S. We thank Larry

Henling and Dr. Michael Day (California Institute of Technology) for X-ray structural analysis.

Supporting Information Available: Experimental procedures and characterization for catalysts **5a–c** and **6a–c** and procedures for the RCM reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0705144