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Olefin Metathesis Catalyst: Stabilization Effect of Backbone Substitutions of N-Heterocyclic Carbene

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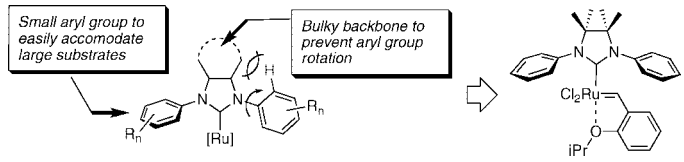
ABSTRACT



Ruthenium olefin metathesis catalysts bearing an *N*-phenyl-substituted N-heterocyclic carbene (NHC) ligand that are resistant to decomposition through C−H activation have been prepared and tested in ring closing metathesis (RCM), cross metathesis (CM), and ROMP reactions. The *N,N′*-diphenyl-substituted NHC complex proved to be one of the most efficient catalysts in RCM to form tetrasubstituted olefins.

Olefin metathesis has become an indispensable tool in making carbon−carbon bonds in organic synthesis.[1] Since the development of well-defined ruthenium-based metathesis catalysts, there has been significant effort directed toward improving the catalyst efficiency. Most notably, the substitution of a phosphine ligand of $RuCl_2(PCy_3)_2(=CHC_6H_5)$ for a bulky, electron-rich N-heterocyclic carbene (NHC) ligand led to metathesis catalysts with enhanced reactivity and stability (Figure 1, **1**).[2]

While the modification of the NHC ligand allowed access to metathesis catalysts suitable for various applications,[3] our group recently demonstrated that decreasing the size of the aryl groups on the NHC ligand by the removal of one ortho substituent was beneficial for the ring closing metathesis (RCM) and cross metathesis (CM) of hindered substrates (Figure 1, **3**).[4]

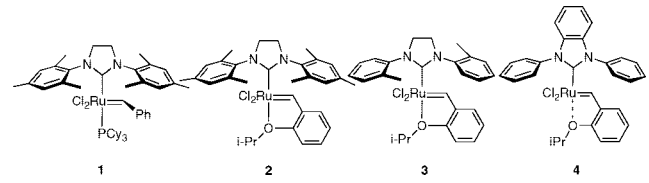


Figure 1. Ruthenium-based olefin metathesis catalysts.

However, attempts to further enhance the efficiency of the catalyst by removing both ortho substituents on the NHC ligand met with either difficulty in synthesis or catalyst instability. For instance, *N,N′*-diphenyl-substituted NHC derived from **5** failed to form a detectable amount of ruthenium complex such as **6** under various conditions (eq

(1) (a) Grubbs, R. H. *Handbook of metathesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (c) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45–52. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013–3043. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.

(2) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.

(3) For examples, see: Deshmukh, P. H.; Blechert, S. *Dalton Trans.* **2007**, 2479–2491, and references therein.

(4) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (c) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

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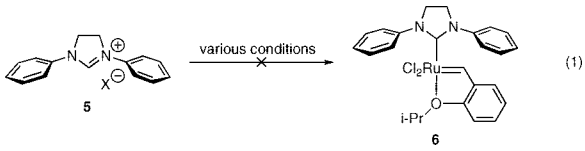
1). It is presumably due to the rapid and irreversible dimerization of the corresponding carbene to form an enetetramine byproduct ("Wanzlick dimerization").[5]



In the case of the 1,3-diphenylbenzimidazol-2-ylidene ligand, the ruthenium complexes were synthesized successfully and shown to have good catalytic activity for hindered olefin synthesis.[6] However, these complexes are rather unstable and decompose to metathesis inactive compounds **7a** and **7b** through the activation of ortho C−H bonds of the *N*-phenyl groups (Figure 2).[7] A related oxidative

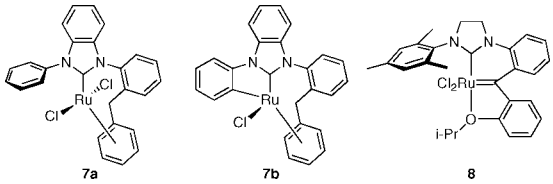


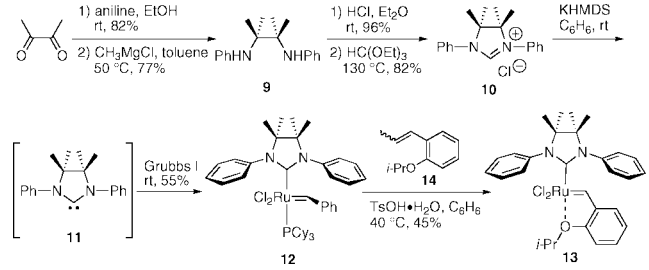
Figure 2. Decomposition of *N*-phenyl-substituted NHC complexes.

degradation product **8** has been reported recently by Blechert's group.[8] These observations suggest *N*-phenyl-substituted NHC complexes are more prone to decomposition in comparison to complexes bearing ortho-substituted N-substituents.[9]

These decomposition pathways are likely facilitated by facile rotation of the *N*-phenyl group relative to bulkier aryl groups, which can bring an aryl C−H bond closer to the ruthenium center. It was therefore anticipated that restriction of the *N*-phenyl ring would raise the barrier for decomposition processes. A straightforward approach to achieve this goal would be to place bulky substituents, such as *gem*-dialkyl groups, on the backbone of the NHC ligand. The backbone substitution was also expected to slow down unfavorable Wanzlick dimerization by providing increased steric hindrance around the carbene.[5d] Furthermore, the substitution on the backbone should affect the electron-donating properties of NHC, since it was conceivable that the direct backbone substitution would have greater influence on the donor ability of NHC than the substitution on the *N*-aryl groups. Herein, we report the synthesis and reactivity of ruthenium complex **13** bearing a tetramethyl-substituted NHC ligand.

The synthesis of **13** began with the condensation of 2,3-butandione with aniline (Scheme 1). Treatment of the

Scheme 1. Synthesis of Ruthenium Complex **13**



resulting diimine with methyl Grignard reagent furnished diamine **9**, which was subsequently converted to imidazolidinium salt **10** in high yield in the presence of excess triethylorthoformate. The corresponding free carbene **11** was generated by treating **10** with potassium hexamethyldisilazide at room temperature, judged by the appearance of the characteristic free carbene ^{13}C NMR signal (245.1 ppm). This carbene displaces a phosphine ligand when mixed with $RuCl_2(PCy_3)_2(=CHC_6H_5)$ at room temperature, affording monophosphine complex **12**, which was promptly transformed to phosphine-free complex **13** by the reaction with **14**.

Compound **13** was stable under air in the solid state and could be purified by flash chromatography. Its structure was fully characterized by NMR and mass spectroscopy as well as single crystal X-ray analysis (Figure 3). The crystal structure shows that the length of the C(1)−Ru is shorter in **13** (1.959 Å) than in **2** (1.980 Å), indicating a stronger NHC−ruthenium interaction. Notably, the two phenyl substituents are slightly tilted away from the neighboring *gem*-dimethyl groups as can be seen from the bond angles C(2)−N(1)−C(8) and C(3)−N(2)−C(14) (124.83° and 121.36°, respectively, compared with 118.33° and 118.22° for **2**).

To the best of our knowledge, **13** is the first stable ruthenium olefin metathesis catalyst bearing *N*,*N*′-diphenyl-substituted NHC with a saturated backbone. It appears that the combination of the shorter NHC−Ru bond and canted *N*-phenyl groups to the metal center helps to stabilize the complex by providing sufficient shielding despite its smaller size.

Encouraged by the successful preparation of **13**, we became curious whether the similar approach could be used to stabilize Blechert's 1-mesityl-3-phenyl-substituted NHC system.[8] Therefore, compound **19** with an unsymmetrically substituted NHC that has a *gem*-dimethyl group adjacent to the *N*-phenyl substituent was synthesized as described in

(5) (a) Wanzlick, H. W.; Schikora, E. *Chem. Ber.* **1961**, *94*, 2389–2393. (b) Liu, Y. F.; Lemal, D. M. *Tetrahedron Lett.* **2000**, *41*, 599–602. (c) Denk, M. K.; Hatano, K.; Ma, M. *Tetrahedron Lett.* **1999**, *40*, 2057–2060. (d) Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2607–2609. (e) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schutz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911.

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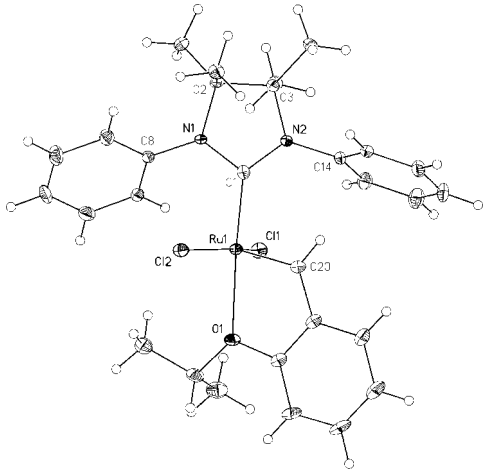
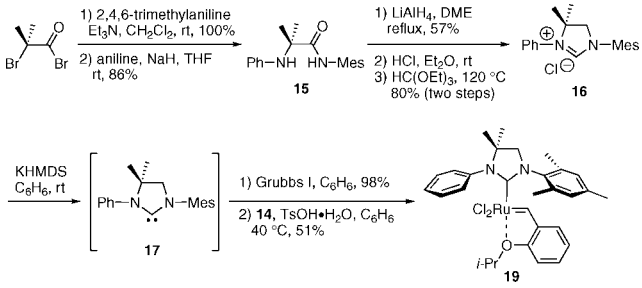


Figure 3. X-ray structure of **13** (ORTEP drawing, thermal ellipsoids are shown at 50% probability). Selected bond length (Å) and angles (°): Ru−C(20) 1.822(2), Ru−C(1) 1.959(2), Ru−O(1) 2.3068(14), Ru(1)−Cl(1) 2.3549(5), Ru−Cl(2) 2.3354(5), Cl(1)−Ru−Cl(2) 157.668(19), C(2)−N(1)−C(8) 124.83(15), C(3)−N(2)−C(14) 121.36(15).

Scheme 2. Compound **19** was isolated as an air-stable crystalline green solid after flash column chromatography,

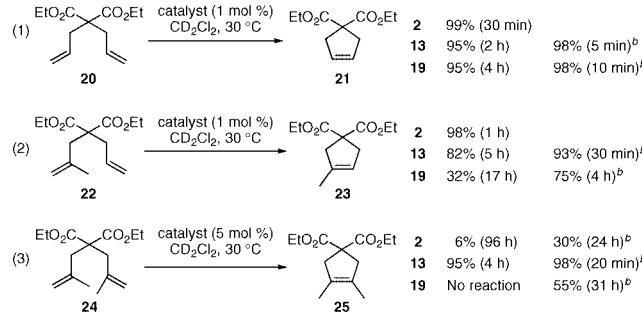
Scheme 2. Synthesis of **19**



and its structure was confirmed by NMR, HRMS, and X-ray analysis. Unlike its parent compound, **19** was quite stable under air and did not readily degrade to the oxidative insertion product analogous to **8**, as judged from the retention of the benzylidene proton signal in the ^{1}H NMR spectrum.[10]

With complexes **13** and **19** in hand, their catalytic activity in various metathesis reactions was tested according to the standard characterization system.[11] First, the catalysts were examined for the ring closing metathesis of diethyl diallylmalonate **20**, diethyl allylmethallylmalonate **22**, and diethyl dimethallylmalonate **24** (Scheme 3). Both **13** and **19** efficiently cyclized **20** in several hours at 30 °C, a slightly

Scheme 3. RCM Reactions with Backbone-Substituted Catalysts[a]



[a]Reactions were performed in NMR tubes with closed caps and conversions were determined by NMR. [b]Reactions were performed at 60 °C in C_6D_6.

slower rate compared to phosphine-free second-generation complex **2**. When more challenging substrate **22** was employed, the RCM proceeded at a noticeably slower rate with **13** or **19**, furnishing the cycloalkene **23** in 82% and 32% yield, respectively, whereas **2** completed the cyclization in one hour. The plots of conversion versus time revealed an induction period with backbone-substituted catalysts. This could originate from different initiation behavior for each catalyst, and indeed **13** initiated about 30% slower than **2** as determined by the irreversible metathesis reaction with *n*-butyl vinyl ether (see Supporting Information).[12]

Remarkably, **13** was highly effective in the ring closing metathesis reaction of **24** forming a tetrasubstituted cycloalkene, completing the cyclization in 4 h at 30 °C. Complex **13** is among the most efficient catalyst in the RCM of **24**. Complexes **3** and **4**, which are also efficient catalysts for hindered substrates, required 15 and 43 h, respectively, to attain 95% (Figure 4).[4a]

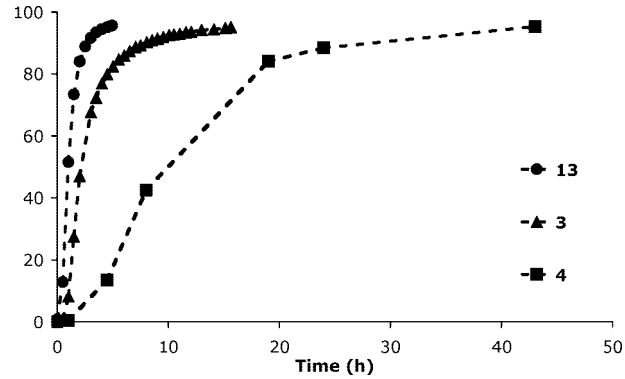


Figure 4. RCM of diethyl dimethallylmalonate (**24**).

Contrary to the high reactivity of **13** in hindered olefin formation, the unsymmetrical complex **19** failed to cyclize

(10) A solution of **19** in CD_2Cl_2 was aerated and subjected to NMR analysis. This was repeated over the period of 4 days without noticeable degradation of the benzylidene signal compared with an internal standard (anthracene).

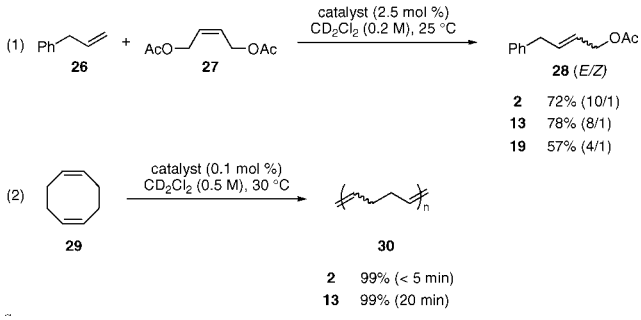
(11) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.

(12) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

24 at 30 °C. However, at higher reaction temperature (60 °C in benzene), **19** afforded **25** in 55% conversion after 31 h.

Next, we examined the catalytic activity of **13** and **19** in the cross metathesis using allylbenzene (**26**) and *cis*-1,4-diacetoxy-2-butene (**27**) (Scheme 4, eq 1).[13] Again, both **13** and **19** catalyzed the reaction at slower rates compared to **2**, but **13** outperformed **2** in terms of overall conversion at the end of the reaction, whereas **19** lost its activity at around 57% conversion. The complex **13** was also an efficient catalyst in the ring opening metathesis polymerization of cyclooctadiene providing **30** cleanly in 20 min at 0.1 mol % of the catalyst loading (Scheme 4, eq 2).

Scheme 4. Cross Metathesis[a] and ROMP[b] with Backbone-Substituted Catalysts



[a]Conversion and *E*/*Z* ratio was determined by GC analysis. [b]Reactions were performed in NMR tubes with closed caps, and conversions were determined by NMR.

While we believe that the observed reactivity difference mainly stems from steric factors, we were interested in the influence of backbone substitution on the electron-donating ability of the NHC, since its strong σ-donating ability is often discussed in conjunction with the catalytic activity of its metal complexes.[14] To evaluate the electronic properties of carbenes **11** and **17**, *cis*-[RhCl(CO)$_2$(NHC)] was prepared via [(NHC)RhCl(COD)] by displacing COD with excess CO.[15] IR carbonyl stretching frequencies show that the electron donor ability of **11** and **17** is comparable to that of H_2IMes, indicating that the backbone substitution contributes to the donor ability of NHC slighltly more than substitution on *N*-aryl groups (Table 1).

Table 1. Carbonyl Frequencies of *cis*-[(NHC)RhCl(CO)$_2$]

NHC	ν_{CO} (cm^{-1})	ref
11	2078, 1996	this work
17	2079, 1996	this work
H_2IMes	2081, 1996	15b

In conclusion, we have successfully prepared a stable ruthenium complex bearing an *N*,*N*′-diphenyl-substituted NHC with a saturated backbone, the synthesis of which has long been elusive. The addition of substituents on the backbone of the NHC ligand, based on our hypothesis that restricting rotation of the *N*-aryl group would prevent catalyst decomposition, allowed access to these species. The catalytic activity of these backbone-substituted complexes was tested in RCM, CM, and ROMP reactions, and **13** emerged as one of the most efficient catalysts in the tetrasubstituted olefin forming RCM reaction. Currently, synthesis of ruthenium-based metathesis catalysts with various substitution patterns on the backbone in combination with different *N*-aryl groups to further enhance the efficiency of olefin metathesis reactions is underway.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. X-ray analysis of compounds **13** and **19**. Procedures for RCM, CM, and ROMP reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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