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Protonolysis of a Ruthenium−Carbene Bond and Applications in Olefin Metathesis

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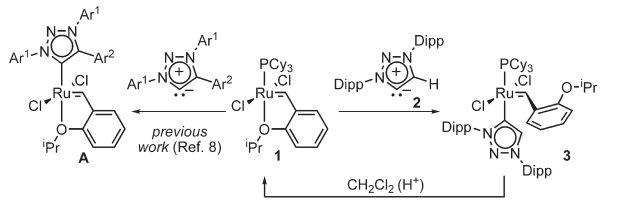
S Supporting Information

ABSTRACT: The synthesis of a ruthenium complex containing an N-heterocylic carbene (NHC) and a mesoionic carbene (MIC) is described wherein addition of a Brønsted acid results in protonolysis of the Ru−MIC bond to generate an extremely active metathesis catalyst. Mechanistic studies implicated a rate-determining protonation step in the generation of the metathesis-active species. The activity of the NHC/MIC catalyst was found to exceed those of current commercial ruthenium catalysts.

Olefin metathesis has gained widespread use as a robust method for the formation of C−C double bonds, largely as a result of the development of increasingly powerful catalysts.[1] Key to a catalyst's efficiency are its activity and stability, which can be tuned through a judicious choice of ligands. Specifically, the stability of a ruthenium-based catalyst can be improved by preventing decomposition pathways that rely on nucleophilic attack by a dissociated ligand.[2] For instance, replacing a dissociating phosphine ligand by a chelating ether moiety results in a catalyst that is more stable under metathesis reaction conditions.[3] A second N-heterocyclic carbene (NHC) may be used in place of a phosphine, and in fact, complexes such as this were among the first metathesis catalysts to incorporate NHCs.[4] However, because of the low dissociation rate of NHCs on ruthenium, all bis-NHC complexes require thermal activation at temperatures well above room temperature (RT).[4] Nevertheless, these catalysts are still effective in a variety of metathesis transformations and have the added benefit of initiating only in response to an external stimulus (latent catalysis), a behavior which is critical in materials science applications.[5,6] We report herein that ruthenium complexes incorporating a traditional NHC and a mesoionic carbene (MIC)[7] may be activated by the addition of a Brønsted acid. The resulting catalyst combines the stability and latency of bis-NHC complexes while maintaining low activation temperatures. Furthermore, we demonstrate that in some reactions, the performance of this catalyst surpasses that of the best commercially available catalysts.

We previously reported the synthesis and activity of ruthenium olefin metathesis catalysts of type **A** bearing MICs in place of more traditional NHCs (Scheme 1).[8] In our attempts to prepare analogues bearing the unhindered H-substituted MIC **2** from **1**, we observed the formation of **3**. We noted that in the

Scheme 1. Initial Discovery of Acid-Induced Dissociation of MIC 2 from 3 (Dipp = 2,6-Diisopropylphenyl)



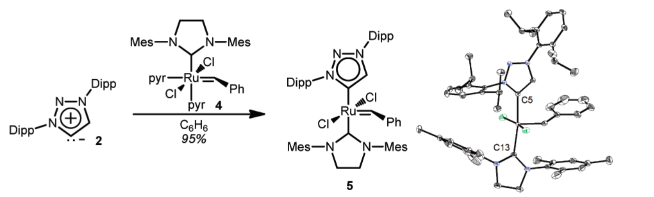


Figure 1. (left) Synthesis of **5** and (right) its solid-state structure with 50% probability ellipsoids. H atoms have been omitted for clarity. Selected bond lengths (Å) and angle (deg): C13−Ru, 2.086; C5−Ru, 2.097; C13−Ru−C5, 169.34.

presence of a solvent containing acidic impurities, the transformation of **3** to **1** occurred. Although relatively rare, protonolysis reactions of metal−NHC bonds have been observed for ruthenium[9] and other late metals.[10] Given these precedents, we concluded that MIC **2** is acid-labile and imagined that it could be incorporated into a metathesis catalyst as a dissociating ligand.

Combining free MIC **2** with **4** in C_6H_6 resulted in the new complex **5**, which was isolated in excellent yield after washing with cold pentane (Figure 1). The solid-state structure of **5** is consistent with those of analogous bis-NHC complexes.[4c]

Initial metathesis screens revealed that **5** is completely inactive at RT. For instance, 1 mol % **5** in C_6H_6 was unable to polymerize 1,5-cyclooctadiene (COD) to any detectable extent within a period of 12 h at RT.[11] Some minimal conversion was observed after extended periods, presumably as a result of very slow catalyst initiation due to the acidic glassware or acid impurities. Under similar reaction conditions, <5% conversion of the ring-

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Table 1. RCM of 7 with 5 (1 mol %) and Acid (20 mol %) in C_6D_6 (0.1 M)

entry	acid	time (h)	conv. (%)[a]
1	none	18+	<5
2	HCl (1 M in Et_2O)	0.3	>95
3	perchloric (70%)	4	73
4	trifluoroacetic	0.3	>95
5	acetic	18	20
6	formic (88%)	18	91
7	hydrobromic (48%)	4	>95
8	hydroiodic (57%)	4	>95
9	HBF_4 (Et_2O)	1	16
10	BH_3 (THF)	18	19
11	$B(C_6F_5)_3$	17	33
12	$ZnCl_2$	1	>95
13	$SnCl_4$	18	<5

[a] Measured by ^{1}H NMR spectroscopy.

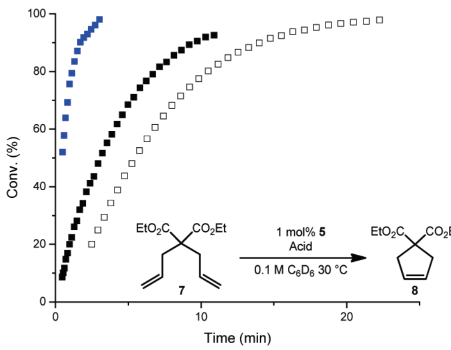

Figure 2. RCM of 7 with 5 and TFA (blue) or HCl (black) and RCM of 7 with NHC complex 6 (white). Conditions: 7 (0.08 mmol), 5 or 6 (0.0008 mmol), and HCl (1 M in Et_2O, 31 equiv., 0.025 mmol) or TFA (16 equiv., 0.013 mmol) in C_6D_6 (0.8 mL) at 30 °C. Conversion was measured by ^{1}H NMR spectroscopy.

closing metathesis (RCM) substrate diethyl diallylmalonate (7) was observed over a period of several weeks at RT. In contrast, addition of HCl (1 M in Et_2O) resulted in complete and immediate conversion of 7 to the RCM product 8 within 20 min (Table 1, entry 2). Having established the feasibility of our initial hypothesis, we set about studying the protonolysis reaction in greater detail.

Our initial efforts focused on the effect of different acids on the RCM of 7 (Table 1). Strong acids (entries 2–4, 7, and 8) were found to be the most effective and were capable of initiating the reaction even when added as aqueous solutions. However, the identity of the conjugate base was also important, as HBF_4 performed poorly (entry 9) in comparison with acids with similar pK_a's. Weaker acids (entries 5 and 6) were less efficient and reached full conversion only after several hours or not at all. Interestingly, some Lewis acids were also capable of affecting the transformation. For instance, addition of $ZnCl_2$ resulted in complete conversion within 2 h at RT, while addition of $B(C_6F_5)_3$ resulted in only 33% conversion after several hours. Other Lewis acids such as $SnCl_4$ were found to be even less effective. In general, Brønsted acids significantly outperformed Lewis acids.

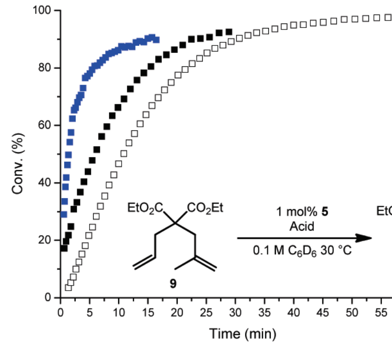

Figure 3. RCM of 9 with 5 and TFA (blue) or HCl (black) and RCM of 9 with NHC complex 6 (white). Conditions: 9 (0.08 mmol), 5 or 6 (0.0008 mmol), and HCl (1 M in Et_2O, 31 equiv., 0.025 mmol) or TFA (16 equiv., 0.013 mmol) in C_6D_6 (0.8 mL) at 30 °C. Conversion was measured by ^{1}H NMR spectroscopy.

Because of their proficiency in activating 5, HCl and trifluoroacetic acid (TFA) were chosen to investigate the RCM of 7 to 8 more closely. Under standard RCM screening conditions, a mixture of 5 and either HCl or TFA showed complete conversion of 7 to 8 within 10 min at 30 °C (Figure 2). The reaction with TFA was particularly fast, reaching 100% conversion within only a few minutes. Catalyst 5 also excelled at the RCM of trisubstituted substrate 9 (Figure 3). Notably, under the above RCM reactions, catalyst 5 was found to be superior to commercial catalysts such as $(H_2IMes)Cl_2Ru({=}CHPhO^iPr)$ (6; H_2IMes = 1,3-dimesitylimidazolidin-2-ylidene).[12] As expected on the basis of these results, 5 also performed well at ring-opening metathesis polymerization (ROMP) with both HCl and TFA [see the Supporting Information (SI)].

After the activation of 5 with acid had been established, additional experiments were performed with the two best acid activators, TFA and HCl, to study the mechanism of activation in greater detail. The benzylidene proton resonance of 5 was monitored by ^{1}H NMR spectroscopy following addition of varying amounts of TFA. A plot of the observed rate constant (k_{obs}) versus concentration of TFA in C_6D_6 displayed a second-order dependence on TFA (Figure S10 in the SI). This behavior is consistent with protonation of 5 by an acid dimer instead of an acid monomer.[13] In order for the above situation to be plausible, however, protonation must be involved in the rate-determining step of the reaction. To probe this possibility and also to simplify the acid—base chemistry of the system, we decided to monitor the initiation of 5 in CD_3CN rather than in C_6D_6.

If protonation is involved in the rate-determining step of the initiation reaction, a plot of k_{obs} versus acid concentration should be linear *at constant pH*.[14] This would parallel the behavior of general acid-catalyzed reactions, although in this case, kinetic runs were conducted under pseudo-first-order conditions. Indeed, when an initiation study was performed with TFA in CD_3CN using potassium trifluoroacetate to maintain an approximately constant pH, a linear plot was obtained (Figure S12). Further evidence of the involvement of acid in the rate-determining step was provided by a Brønsted plot (Figure 4), which displays a linear relationship between the pK_a of the acid in CD_3CN and the logarithm of the initiation rate of 5.[15] Finally, a plot of log(k_{obs}) versus the pH of the solution exhibited behavior characteristic of the involvement of acid in the rate-determining step (Figure S15). When HCl was used in place of

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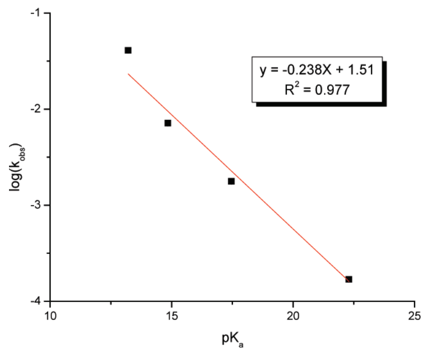
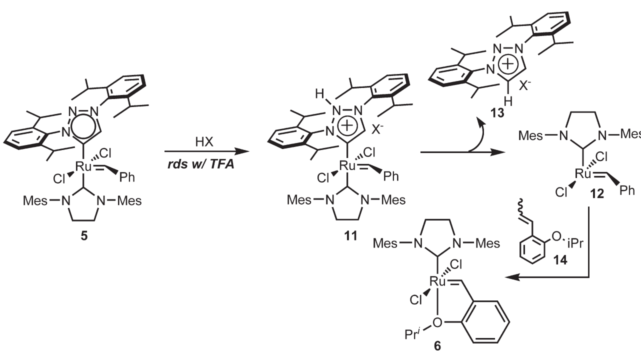


Figure 4. Brønsted plot for initiation of **5** at RT in CD_3CN. Conditions: **5** (0.003 mmol) and acid (0.045 mmol) in CD_3CN (0.6 mL). Acids were acetic acid, Cl_2HCCO_2H, F_3CCO_2H, and CH_3SO_3H.

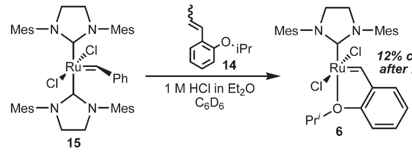
Scheme 2. Proposed Mechanism for Initiation of 5



TFA in CD_3CN, a first-order dependence on HCl concentration was observed (Figure S17). All of the above results are strong indications that a protonation event rather than dissociation is the rate-determining step in catalyst activation.

The initiation kinetics of **5** in the presence of inorganic acids in solvents of lower polarity (C_6D_6, toluene-d_8) are more intricate and likely involve poorly understood solvation and/or counter-ion effects, as suggested from the screening of acid initiators. For instance, the reaction of **5** in C_6D_6 following the addition of excess HCl (>15 equiv) revealed a decrease in the benzylidene proton signal intensity that followed clean first-order kinetics. A plot of k_{obs} versus HCl concentration displayed saturation kinetics, which is inconsistent with a protonation event being rate-determining under these conditions and *may* be indicative of a pre-equilibrium step (Scheme 2 and Figure S3). Monitoring the growth of product **6** after treatment of **5** with acid in the presence of varying amounts of **14** showed no dependence on the chelating olefin concentration (Scheme 2 and Figure S5).[16] Therefore, any reaction with an olefin must take place after the rate-determining step. The above experiment with **14** also allowed us to identify **13**, which precipitated from solution. Taken together, the formation of **6** and **13** suggest that protonation of **5** generates catalytic intermediate **12**, which is the same active species that is postulated to follow thermally induced ligand dissociation in common ruthenium metathesis catalysts.[17] An Eyring plot of the activation reaction with HCl in toluene-d_8 under *saturation conditions* (Figure S5) yielded the values $\Delta H^{\ddagger} = 11.9 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = -33.3 \pm 0.7$ eu. The value of $\Delta H^{\ddagger}$ for **5** is ~10 kcal/mol less than those for comparable phosphine-based catalysts, while the value of $\Delta S^{\ddagger}$ is much larger in magnitude and negative.[17] The negative $\Delta S^{\ddagger}$ is inconsistent with a rate-limiting dissociative step. Therefore, a simple interpretation of the above saturation kinetics as a fast protonation equilibrium followed by slow ligand dissociation is inaccurate. However, any conclusions based on $\Delta S^{\ddagger}$ alone are complicated by the likely formation of charged transition states in solvents that are largely incapable of stabilizing them (e.g., C_6D_6).[18] Nevertheless, the observed initiation rate of **5** in C_6D_6 under saturation conditions at RT (0.0011 s^{-1}) is slightly higher than that of $(H_2IMes)(PCy_3)Cl_2Ru(=CHPh)$ (0.00046 s^{-1} at 35 °C),[17] which explains the superior performance of **5** in RCM.[19]

Scheme 3. Initiation study of 15[a]



[a] Conditions: **15** (0.0032 mmol), **14** (0.032 mmol), and HCl (0.05 mmol) in C_6D_6.

A complete proposed mechanism for the initiation event of **5** is shown in Scheme 2. Although our mechanistic studies could not definitively establish the nature of the protonation event, the fact that some Lewis acids also activated the catalyst strongly suggests that the unsubstituted nitrogen (N2) on the MIC ligand (**2**) plays an important role. Previously reported density functional theory calculations on free MICs (e.g., **2**) suggest that N2 has the second-highest proton affinity after the carbene itself, meaning that protonation at this position is plausible.[8] Thus, it is likely that initiation entails protonation at the MIC N2 in **5** to give **11**, followed by dissociation with a concomitant 1,3-proton shift to give **13** and **12**, both of which were observable by mass spectrometry (see SI). This mechanism is consistent with our experimental results to date, but at this time we cannot definitively rule out other possibilities.

A final question we wished to answer was whether the behavior of **5** was due to the unique nature of the MIC ligand or if other conventional NHCs (e.g., H_2IMes) would act in a similar manner. In order to determine this, $(H_2IMes)_2Cl_2Ru(=CHPh)$ (**15**) was added to **7**, and no RCM activity was observed at RT.[20] Upon addition of HCl (10 equiv), no immediate activity was detected either. However, after a period of ~12 h at RT, ~70% conversion to **8** was observed by NMR spectroscopy. When HCl was added to a mixture of **15** and **14** in order to approximate the extent of catalyst initiation, only ~12% conversion to catalyst **6** was achieved after a period of 24 h (Scheme 3). This result is in contrast to that observed for **5**, which was able to achieve complete conversion to **6** within a matter of minutes. Thus, although **15** is capable of being activated by acid, this occurs much less efficiently than for **5**.

In summary, we have demonstrated that in the presence of acid, a MIC ligand may act as a leaving group, allowing an otherwise inactive metathesis complex (**5**) to enter the metathesis catalytic cycle. Furthermore, under standard metathesis reactivity screening conditions, **5** is superior to the latest commercial catalysts and can complete RCM reactions within a matter of minutes at RT. A mechanistic study of the initiation mechanism concluded that protonation is rate-determining with the most efficient initiator, TFA, but that the activation step is strongly influenced by the identity of the acid and solvent. With strong-acid initiators, **5** is able to quickly and efficiently access the same reactive intermediate as other catalysts (e.g., **12**) and thus combines latency with exceptional reactivity at RT. Finally, we have established that the observed protonolysis behavior of **5** can also occur, but only to a limited extent, in other bis-NHC complexes, enabling the incorporation of these activation mechanisms in future generations of metathesis catalysts.

■ ASSOCIATED CONTENT

S Supporting Information. NMR spectra, kinetic data, mechanistic analysis, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Protonolysis of a Ruthenium−Carbene Bond and Applications in Olefin Metathesis [*Journal of the American Chemical Society* **2011**, *133*, 8498–8501 DOI: 10.1021/ja203070r]. Benjamin K. Keitz, Jean Bouffard, Guy Bertrand, and Robert H. Grubbs*

Page 8499. In the captions of Figures 2 and 3, there is an error regarding the amount of trifluoroacetic acid (TFA) added. The actual amount added, 10 μL, amounts to 160 equiv and 0.13 mmol, not 16 equiv and 0.013 mmol.

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