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Acid-mediated activation of modified ring-closing metathesis catalysts

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ABSTRACT

To improve the reactivity of Grubbs catalyst, novel ligands were designed and synthesized which possess nitrogen-containing heterocycles such as imidazole and pyridine. The modified catalysts were treated with a range of acids and the acid salt forms were used as catalysts for ring-closing metathesis (RCM) reactions. As a result, reactions employing the acid-modified catalysts showed considerable reactivity enhancement in RCM.

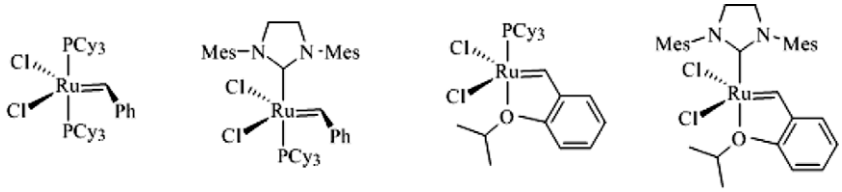
In regard to the construction of five- to seven-membered and macrocyclic rings, ring-closing metathesis (RCM) has become an indispensable tool to organic chemists. The RCM has been widely utilized as a key step in the synthesis of many natural products (see Fig. 1).[1]

In recent years, a large number of metathesis catalysts have been reported by several research groups. Among several catalysts for the RCM, ruthenium–benzylidene[2] pre-catalysts have been the most widely used due to their stability and tolerance toward many functional groups. After the development of Grubbs first generation catalyst (**1**) and *N*-heterocyclic carbene-based second generation catalyst (**2**),[3] boomerang-type pre-catalysts were reported.[4] Among them, Grubbs–Hoveyda catalysts **3a** and **3b** equipped with a chelating ether moiety have shown superior stability compared to prior Grubbs catalysts and are even recoverable by column chromatography.[2g,5] However, though reactions employing the catalysts **3** show great performance, their initial reaction rates proved to be slower than those employing catalyst **2**, probably as a result of steric and electronic factors caused by isopropoxy group.[6] Therefore, many research groups tried to come up with new catalysts that exhibit improved reactivity while preserving stability observed in the Hoveyda-type catalysts (see Fig. 2).

In recent years, a range of Hoveyda-type ruthenium precatalysts were reported based upon various ligand modifications. These approaches involve structural modification of *N*-heterocyclic carbene moiety[7] as well as changes on the benzylidine structure as shown in catalysts **4a**–**e**.[8,9] Among various ligand-modification strategies, we focused on the tuning of the benzylidine moiety with an electron-density monitoring group. For example, introduction of electron-withdrawing nitro or ester group as in **4c** and **4d**, respectively, led to enhancement of the leaving group properties and showed increased catalyst activities.[9b,c]

In relation with this approach, Grela and co-workers reported a new Hoveyda-type catalyst containing diethylamine-substitution on the aromatic ring (**4e**).[9d] They utilized the amino group in the catalyst for both anchoring and activation of the catalyst. In the reactions employing this catalyst, enhanced reactivity was observed when it was anchored onto sulfonic acid resin.

Based on the improved results of the RCM employing catalyst **4a**–**e**, one can assume that decreasing the electron density on the



1 **2** **3a** **3b**

Figure 1. Commonly used ruthenium olefin metathesis catalysts. Cy = cyclohexyl, Mes = mesitylene.

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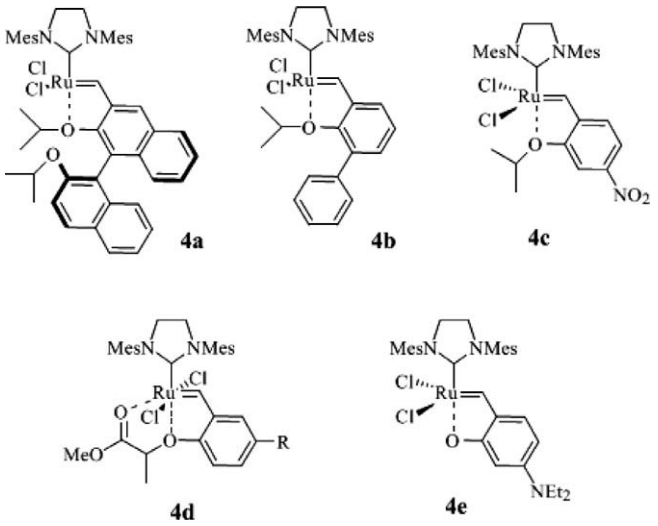
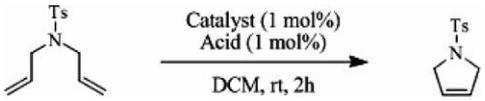


Figure 2. Benzylidine-modified olefin metathesis catalysts.

oxygen atom of the isopropyl fragment and increasing the steric bulk of the Hoveyda-type ruthenium carbene complex result in an increase in catalytic activity. Therefore, we envisioned that electron-withdrawing imidazolium or pyridinium salts attached to the benzylidine part of the catalyst would weaken ruthenium–oxygen chelation and facilitate the initiation of the catalytic cycle. Though pyridine and imidazole moieties were embedded in a few modified Grubbs catalysts[10] and in derivatives for ionic liquid application,[11] there was no report on the acid-mediated activation of the catalysts using the imidazole or pyridine moieties to the best of our knowledge. Herein, we report on the synthesis of modified Grubbs catalyst and results of RCM with such acid-activated catalysts.

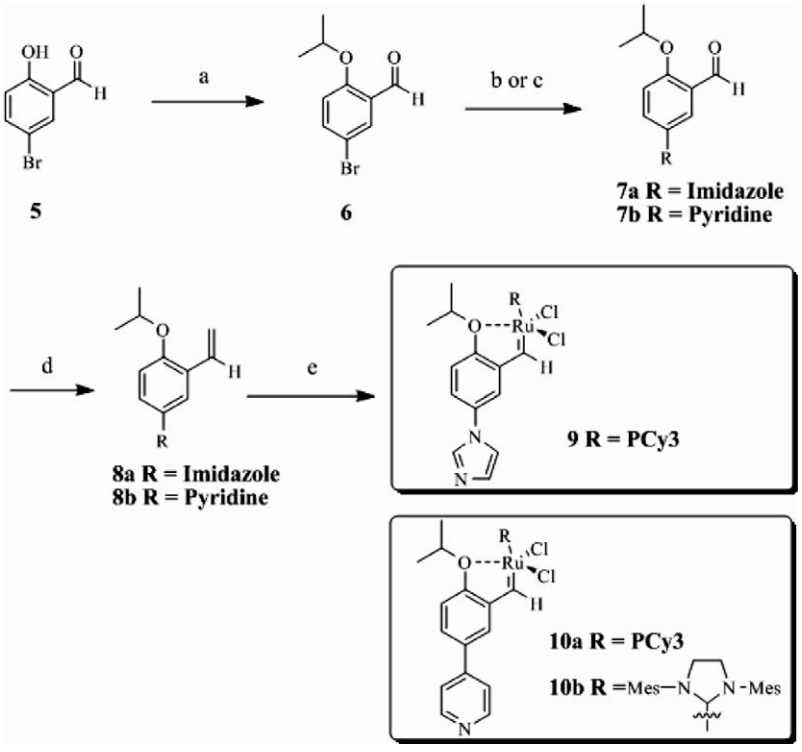
Synthesis of the heterocycle-containing ligands is depicted in Scheme 1. From commercially available 3-bromosalicylaldehyde **5**, compound **7a** was obtained through etherification followed by Ullmann-type coupling. For the preparation of pyridine-containing ligand **7b**, Suzuki–Miyaura coupling of **5** with 4-pyridylboronic acid was carried out. Resulting aldehyde **7** was converted to vinyl derivative **8** through Wittig reaction. To generate ruthenium–carbene complex, **8** was treated with Grubbs catalyst in the presence of copper(I) chloride. Detailed reagents and yield of each step are described in Scheme 1.

Table 1
Results of RCM with various acid-activated catalysts[a]



Entry	Catalyst	Acid	Conversion[b] (%)
1	**9**	None	45
2		HCl[c]	99
3		TFA	95
4		PTSA	89
5		Perfluoropropanoic acid	77
6		Triflic acid	60
7		CSA	55
8	**10a**	None	48
9		HCl[c]	97
10		TFA	99
11	**10b**	None	99
12		HCl[c]	96
13		TFA	24

[a] Catalyst activation with acids was performed through stirring the catalyst with an acid for 30 min prior to RCM reaction.
[b] Conversions were determined from GC analysis.
[c] A 4 N solution in 1,4-dioxane was used.



Scheme 1. Reagents and conditions: (a) 2-iodopropane, Cs_2CO_3, K_2CO_3, DMF, rt, 12 h, 99%; (b) imidazole, CuI, Cs_2CO_3, *N*,*N*′-dimethylethylene-diamine, 170 °C, 48 h, 87%; (c) 4-pyridylboronic acid, $Pd(dppf)Cl_2$, Na_2CO_3, DME/H_2O = 3:1, reflux, 3 h, 80%; (d) methyltriphenyl-phosphonium bromide, LHMDS, THF, 0 °C→rt, 12 h, 86%; (e) Grubbs catalyst, CuCl, CH_2Cl_2, reflux, 2 h, 55–60%.

With the new catalysts in hand, RCM reactions using various acids were carried out for 2 h with 1 mol % of catalyst and equivalent amount of acids. The results are summarized in Table 1 and Figure 3. When catalyst **9** was tested with various acids, the catalyst bearing electron-donating imidazole group showed low activity in RCM (entry 1), which bodes well with our assumption. However, the in situ-formed imidazolium salts obtained by treatment with acids showed enhanced activity to the same reaction. It is of particular note that, when HCl or trifluoroacetic acid (TFA) was used as additives, the reaction reached over 95% conversion within 2 h (entries 2 and 3). Moreover, the initial rate of the reaction using HCl salt was faster than that of the reaction using pristine Grubbs–Hoveyda first generation catalyst. In cases of other acid salts, relatively lower levels of activation were observed.

In the case of pyridine-containing catalyst **10a**, it was observed that the propagation rate of the reaction is almost same as that of imidazole-containing catalyst system (less than 60% of conversion after 150 min, Fig. 4). However, reactions using acid-activated catalyst such as HCl or TFA salt proceeded very rapidly (entries 9 and 10 of Table 1 and Fig. 4). It is interesting to note that, in case of pyridine-substituted catalyst **10a**, reaction using TFA salt proceeded faster than that of an HCl salt (Fig. 4).

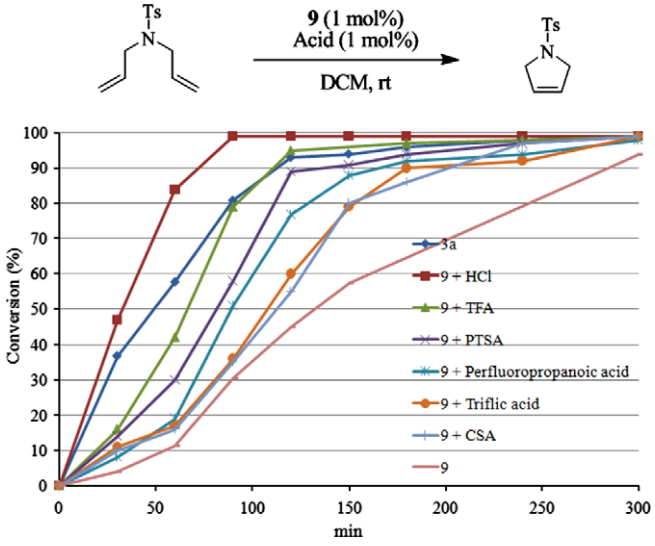


Figure 3. RCM using various acid-activated catalysts **9** compared with parent Hoveyda catalyst.

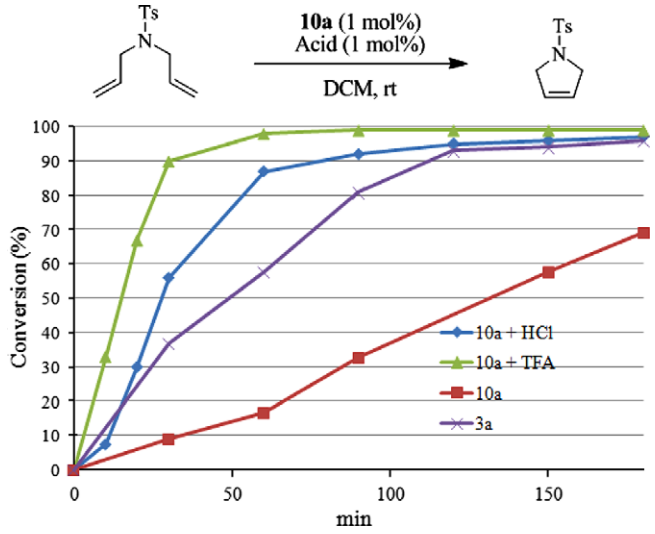


Figure 4. RCM with activated pyridine catalyst **10a**.

We also prepared a pyridine-containing carbene complex **10b** because it was expected to lead to a more reactive catalytic system. The reaction was completed within 30 min even without HCl treatment. Though initiation rate was found to be greatly enhanced in the case of HCl treated **10b**, the conversions were almost same after 20 min in either HCl activated or non-activated case. However, when TFA was used instead of HCl, the reaction stopped at around 25% conversion (Fig. 5). In the case of pyridine catalyst **10b**, the acid-activation process may render the catalyst too active and thus it may decompose during the activation and reaction. This was verified in part from the fact that the reaction using the acid-

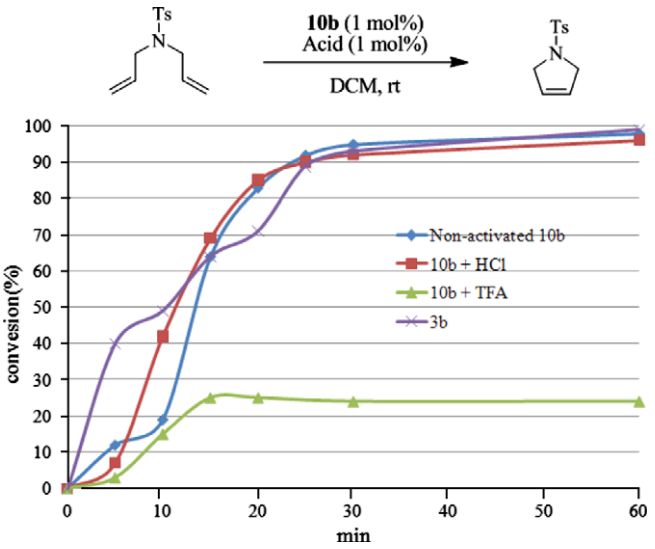
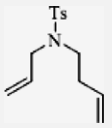
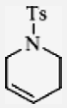
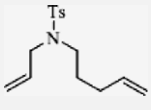
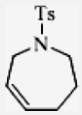
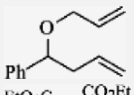
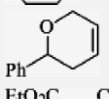
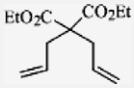
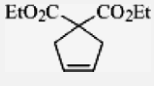
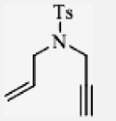
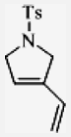


Figure 5. RCM with activated catalyst **10b**.

Table 2
Results of RCM with pyridine ligands **10a** and **10b**[a]

Entry	Substrate	Product	Yield[b] (%)		
			10a·TFA	**10b**·HCl	**10b**
1			99	60 (69)[d]	84
2			99	84	90
3			99	78	99
4			99	66	99
5			46 (80)[c]	n.r.	n.r.

[a] All the reactions were carried out with 1 mol % catalyst and 1 mol % acid in dichloromethane at room temperature for 2 h.
[b] Isolated yields.
[c] Value in parentheses is yield after 20 h.
[d] The acid and the catalyst were added together without prior stirring for 30 min.

activated catalyst without 30 min prior activation gave slightly better yield after 2 h (Table 2, entry 1, number in parentheses).

Since the rates of reactions employing the pyridine catalyst **10a** is slightly faster than those of the imidazole-containing catalyst **9**, the scope of substrates in the reactions employing the pyridine catalyst **10a** was explored using various substrates under the acid-activated conditions. The results are summarized in Table 2. To a 1 mol % of pyridine catalyst **10a** and **10b**, the same amount of hydrochloric acid (for **10a**) or trifluoroacetic acid (for **10b**) was added and the mixture was stirred for 30 min. With the pyridinium–TFA salt from **10a**, all the di-substituted substrates were cyclized smoothly within 2 h at room temperature. When the TFA–**10a** salt was employed in an enyne metathesis, only 46% cyclization was observed in 2 h, but longer reaction time increased the yield to 80% (Table 2, entry 5).

Meanwhile, reactions involving catalyst **10b** showed relatively low yields compared to **10a**. Most of the reactions showed high conversion at early stage. However, as in the case of TFA-activated catalyst **10b** in Figure 5, the reactions did not proceed further after 2 h and the starting materials remained. We assumed that activation of the pyridine catalyst **10b** with HCl renders the catalyst too unstable to proceed within the given reaction time. To confirm this hypothesis, we carried out same series of reactions with non-activated catalyst **10b** and obtained much higher yields of the products as shown in Table 2.

To see if the pyridine-containing catalyst **10a** is stable toward the acid, it was treated with an equiv of TFA in an nmr tube for one day and RCM was carried out using this acid-treated catalyst. As shown in Figure 6, the RCM of *N,N*-diallyl *p*-toluenesulfonamide using this TFA-treated catalyst proceeded at the same rate as the one using the catalyst treated with TFA for 0.5 h, both of which are much faster than the reaction using unactivated catalyst **10a**.

That the activation of the catalyst **10a** was truly due to the activation of the pyridine ring rather than other parts of the catalyst was confirmed by the following experiments: RCMs using catalyst **3a** were carried out after activation with an acid for 0.5 or 24 h. As shown in Figure 7, RCMs using **3a** activated with HCl for 0.5 h proceeded slightly faster, but the reaction using **3a** activated with TFA for 0.5 h was somewhat slower than the one using untreated **3a**. When the reactions were carried out using **3a** treated with an acid for a day, they were considerably slower presumably due to the decomposition of the catalyst by the acids.

In conclusion, we have modified the Grubbs catalyst by adding a nitrogen-containing heterocycle onto the ligand and activation of

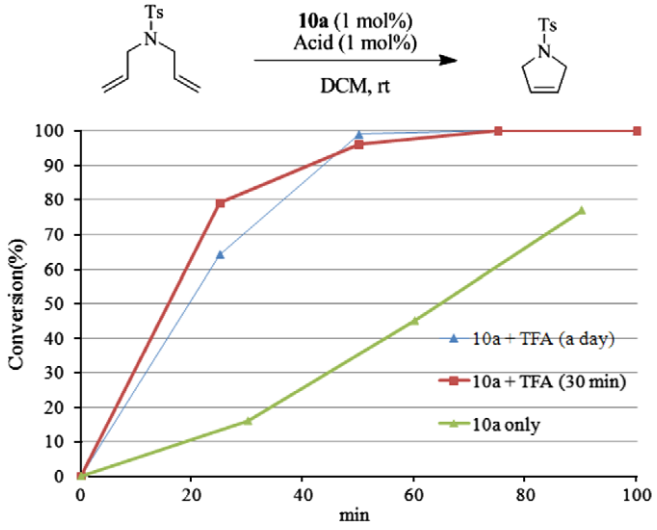


Figure 6. RCM with TFA-activated catalyst **10a**.

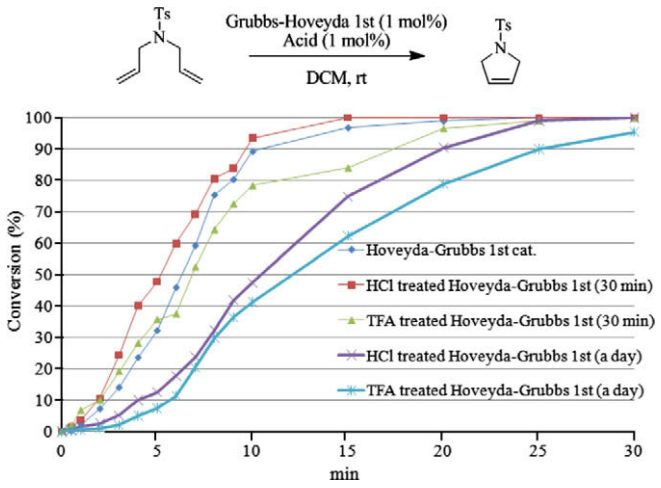


Figure 7. Results of RCM using acid-treated Grubbs–Hoveyda catalyst (**3a**).

the catalyst with an acid was shown to be an efficient way to enhance activity of the catalytic system. Compared to classical Hoveyda-type catalyst, some of our acid-activated catalysts showed enhanced activity toward RCM while retaining stability Figure 7. RCM with acid-treated Grubbs–Hoveyda first catalyst.

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