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In Situ Preparation of a Highly Active N-Heterocyclic Carbene-Coordinated Olefin Metathesis Catalyst

John P. Morgan and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratories for Chemical Synthesis, California Institute of Technology, Pasadena, California 91125

rhg@its.caltech.edu

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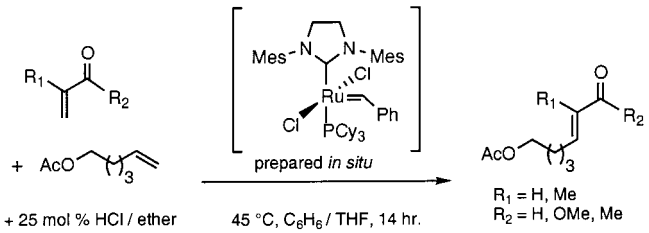
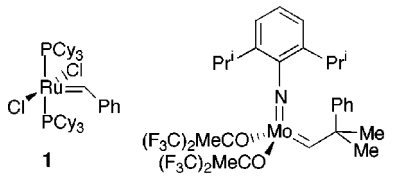
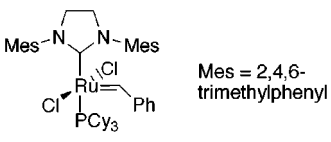
ABSTRACT



Highly active N-heterocyclic carbene-coordinated catalysts may be synthesized and used in situ, without requiring prior isolation of the catalyst. Activation of this in situ catalyst with ethereal HCl dramatically reduces the reaction times required for high conversions. A variety of α,β-unsaturated carbonyl-containing substrates participate readily in cross and ring-closing metathesis reactions using this preparation.

Olefin metathesis with well-defined alkylidene complexes has recently become a widely used carbon−carbon bond-forming method in organic synthesis.[1] In particular, complexes **1**[2] and **2**[3] are now routinely employed in synthesis as both ring-closing (RCM) and crossmetathesis (CM) catalysts. Although catalyst **1** exhibits excellent functional group compatibility, the range of substrates amenable to metathesis has been limited to electronically rich alkenes that are relatively removed from heteroatom functionality. The recent advent of N-heterocyclic carbene-coordinated catalysts,[4,5] such as ruthenium benzylidene **3**, has dramatically alleviated this limitation by performing the metathesis of vinyl siloxanes, fluorinated alkenes, and α,β-unsaturated carbonyl substrates.[6] Catalyst **3** has permitted significant reduction in catalyst loadings and reaction times compared to the parent complex **1**. In addition, **3** demonstrates the high activity of **2** while maintaining the functional group tolerance of **1**.





Currently, the widespread use of **3** is limited due to its relatively difficult preparation. Initial syntheses have utilized the free carbenes of type **4**, which are extremely air and moisture sensitive (Scheme 1).[7] Recent investigations by our group and subsequently by others have demonstrated that the free carbenes can be generated and directly trapped by **1**.[4,5] Despite this simplified ligand preparation, the isolation

(1) For recent reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A-Chem.* **1998**, *133*, 29−40. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*., in press.

(2) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(3) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc*. **1990**, *112*, 8378−8387. (c) Bazan, G. C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899−6907.

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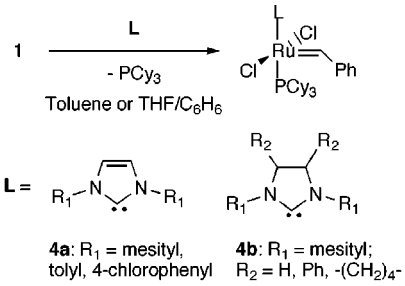
Scheme 1. Synthetic Scope of N-Heterocyclic Carbene-Coordinated Ruthenium Olefin Metathesis Catalysts

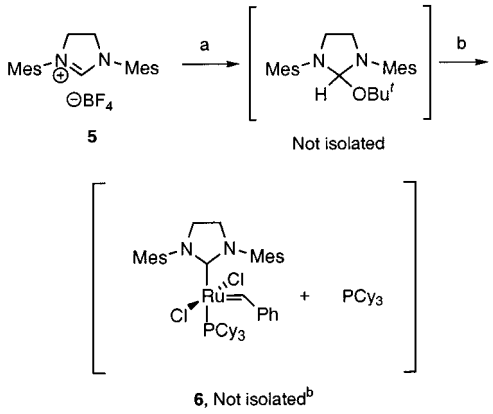


of these new catalysts usually requires air-free, anhydrous conditions and multiple purifications to remove free phosphine generated in the synthesis. It would be highly desirable to obtain a catalyst that has comparable activity to **3** but does not require extensive purification under rigorously air- and moisture-free conditions.

A potential solution to the purification problem would be the production and use of **3** in situ. Although a majority of organometallic reagents are generated in situ, olefin metathesis catalysts prepared in this way are not commonly used by organic chemists.[8] Complexes of high purity are required because productive metathesis using **1** or **3** is inhibited by an excess of free phosphine.[5c,9a] A simple combination of **1** and an N-heterocyclic carbene (or the corresponding alkoxide adduct) is therefore not expected to produce a highly active catalyst, because 1 equiv of free phosphine is generated (Scheme 2).

To overcome potential phosphine inhibition in the in situ generation of **3**, the use of phosphine scavengers is an attractive possibility. Previously studied in our group for **1**,[9a] scavengers are believed to activate the catalyst by removing

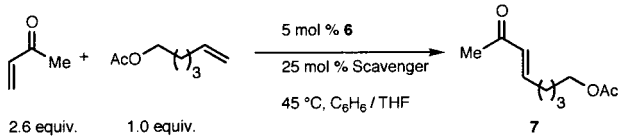
Scheme 2 In Situ Catalyst Synthesis by the Alkoxide Route[a]



[a] Key: (a) KOBu^t, THF, less than 1 min at 25 °C; (b) catalyst **1**, 80 °C, 30 min; (b) **6** refers to the mixture of **3** and 1 equiv of PCy_3.

free phosphine from solution and abstracting bound phosphine from the ruthenium metal center. To probe the efficacy of these processes, a variety of scavengers has been screened in the in situ cross metathesis of methyl vinyl ketone and an unfunctionalized terminal olefin (Table 1). This test reaction

Table 1. Effect of Phosphine Scavenger on the Cross Metathesis of Methyl Vinyl Ketone[a]



entry	scavenger	% yield[b]	time (h)
1	none	92	48
2	HCl/ether	90	14
3	$CuCl_2$	12	14
4	CuCl	42	24
5	$B(C_6F_5)_3$	47	14
6	$Ni(COD)_2$	NA[c]	<1
7	$AlCl_3$	67	14

[a] **6** represents the in situ catalyst preparation described in Scheme 2. COD = cyclooctadiene. See ref 13 for experimental procedure. *E*/*Z* ratios = 14:1. [b] Isolated yields. [c] Yield is negligible; paramagnetic line broadening in ^{1}H NMR.

was chosen because catalyst **1** only produces homodimer of the terminal olefin; thus, no "background" cross metathesis (from unconverted catalyst) will be observed. Additionally, high conversion is obtained at long reaction times even in the absence of a phosphine scavenger (entry 1). The addition of ethereal HCl (entry 2) provides yields and reaction times typical of isolated **3** (i.e., 95% after 14 h for the identical reaction with pure **3**).[6a]

Other phosphine scavengers are much less effective. The generally slow formation of insoluble phosphine−copper adducts may explain the lower yields obtained with copper

(4) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490−2493. Also see corrigenda: *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 262. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (c) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (e) Grubbs, R. H.; Trnka, T. M. *Abstr. Pap. Am. Chem. Soc.* **2000**, 219:130-INORG, Part 1.

(5) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. For related studies with unsaturated imidazol-2-ylidenes, see: (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (c) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517−1519.

(6) For the preparation of 1,3-disubstituted imidazol-2-ylidenes such as **4a** and **4b**, see: (a) Arduengo, A. J.; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027−11028. (b) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523−14534. (c) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

(7) Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055−2057.

(8) In this paper, the phrase "in situ catalyst" refers to a catalyst system that is constructed from many distinct components and then used in the same reaction vessel. It does not refer to single-component catalysts (i.e., allenylidenes), which are thermally or photochemically activated in situ. For the latter cases, see: (a) Picquet, M.; Touchard, D.; Bruneau, C.; Dixneuf, P. H. *New J. Chem.* **1999**, *23*, 141−143. (b) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2249−2250.

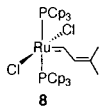
(9) (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897. For the use of HCl as phosphine scavenger, see: (b) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627−1628. (c) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601−6609.

salts (entries 3−4). Another common phosphine scavenger, $B(C_6F_5)_3$, was also ineffective in driving the reaction to desirable yields (entry 5). Using $Ni(COD)_2$ (entry 6) produced a paramagnetic species (as observed by NMR), completely shutting down the reaction. Only the last additive ($AlCl_3$) and HCl provided acceptable metathesis activity.[10]

To ascertain the overall effectiveness of HCl as a phosphine scavenger, NMR-scale experiments were performed.[11] Under the conditions of Table 1, catalyst **1** was observed to completely convert to catalyst **3** and generate 1 equiv of free phosphine. Addition of ethereal HCl (25 mol %) to the NMR sample immediately converted the free phosphine to its phosphonium salt without decomposing **3** (as determined by ^{31}P NMR spectroscopy).

Further optimization of the reaction temperature, loading of HCl, and ruthenium source was then performed (Table 2). Raising the temperature results in catalyst deactivation

Table 2. Variation of Reaction Parameters for the **3**/HCl in Situ System in the Production of **7**[a]

entry	temp. (°C)	mol % HCl	Ru source	% yield of **7**[b]
1	80[c]	25	**1**	trace
2	45	12	**1**	34
3	45	25	 **8**	24

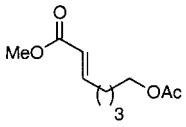
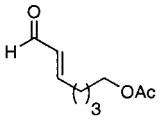
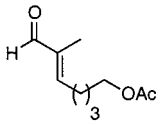
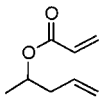
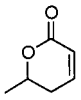
[a] All unspecified conditions are identical to those in entry 2 of Table 1. [b] Isolated yields. [c] Toluene/THF was used as solvent.

(entry 1). Lowering the HCl loading dramatically reduces the yield, although the amount of acid used in this case remains greater than twice that of the catalyst (entry 2).[12]

Switching to the dimethylvinyl carbene **8** as the ruthenium source resulted in reduced yields, apparently arising from the slower initiation of **8** relative to **1**. The most active system is therefore prepared from **1**, **5**, and 25 mol % ethereal HCl at 45 °C.

Preliminary work on a range of CM and RCM substrates indicates that **3** and the **6** + HCl system behave similarly (Table 3).[6a,13] Unsaturated esters and aldehydes readily participate in CM with unfunctionalized terminal olefins (entries 1−2). Even a challenging trisubstituted case (entry

Table 3. Substrate Scope for the 6 + HCl in Situ System[a]

entry	substrate	product	% yield[b]	E:Z
1			98	>20:1
2			52	>20:1[c]
3			82	>20:1
4			83	---

[a] Conditions are identical to entry 2 of Table 1. [b] Isolated yields. [c] The compound originally characterized as the *Z* isomer in ref 5a was later found to be the autoxidized *E* isomer.

3) and a RCM (entry 4) example are successful with this in situ catalyst system. In each case, only small reductions in yield are observed relative to those obtained with pure **3**.

For many applications, the **6** + HCl system offers an advantage over isolated **3**. No organometallic isolation is required. All of the reagents, including the imidazolium salt and the ruthenium benzylidene **1**, are easily obtained and are air stable.[14] The reaction is therefore easily scalable, allowing in situ metathesis to be applied to the early stages of preparative scale syntheses.

In summary, generating **3** in situ and in the presence of HCl is a viable method for achieving high activity similar to that obtained with pure **3**. Further work on N-heterocyclic carbene ligands for in situ catalysis is currently underway.

Acknowledgment. The authors thank the National Institutes of Health for financial support. Dr. Hyunjin Kim is gratefully acknowledged for supplying **5**. Dr. Choon Woo Lee, Dr. Jennifer Love, Melanie Sanford, and Arnab Chatterjee are also acknowledged for helpful discussions and suggestions.

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(10) For a related discussion of HCl, $AlCl_3$, and other Lewis acids as potential phosphine scavengers, see: (a) Sanford, M. S.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 5384−5389. (b) Katayama, H.; Yoshida, T.; Ozawa, F. *J. Organomet. Chem.* **1998**, *562*, 203−206.

(11) NMR tube reactions were prepared under dry nitrogen atmosphere in a Vacuum Atmospheres glovebox and sealed in a J. Young NMR tube. THF-d_8 and C_6D_6 were dried and degassed prior to use and stored over molecular sieves. The concentration of all reagents was identical to those used in the experiments of Table 1. NMR spectra were recorded with Varian VNMR software on an Oxford 300 MHz instrument.

(12) The excess HCl is required to fully protonate the free phosphine. In addition this strong acid may protonate the carbonyl substrates to provide a rate acceleration. A highly oxophilic Lewis acid such as $AlCl_3$ may also play a similar role. For a related example of Lewis acid activation of carbonyl-containing substrates, see: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

(13) A typical experimental procedure is as follows. A suspension of tetrafluoroborate salt **5** (14 mg, 35 μmol) in dry THF (1 mL) was prepared in a flame-dried Schlenk flask under nitrogen. Potassium *tert*-butoxide (4 mg, 35 μmol) was added to the rapidly stirred suspension at room temperature, resulting in the immediate dissolution of **5** to form a yellow solution. After 5 min, a solution of **1** (21 mg, 25 μmol) in dry benzene (2 mL) was added via cannula. The mixture was heated to 80 °C for 35 min and subsequently cooled to room temperature. Methyl vinyl ketone (100 μL, 1.3 mmol), 5-hexenyl acetate (84 μL, 0.5 mmol), and HCl (2.0 M in diethyl ether, 60 μL, 120 μmol) were added to the cooled solution via syringe. The reaction mixture was then heated to 45 °C for 14 h, followed by concentration in vacuo to a brown residue. Purification by silica gel chromatography (9: 1 hexanes: ethyl acetate) yielded 90% of **6** (84 mg, 0.45 mmol) as a clear, yellowish oil.

(14) Catalyst **1** and the imidazolium tetrafluoroborate salt **5** will be available from Strem Chemicals, Inc. soon.