ORGANIC LETTERS

2011
Vol. 13, No. 23
6188–6191

Analogs of Grubbs' Second Generation Catalyst with Hydrophilic Phosphine Ligands: Phase Transfer Activation of Ring Closing Alkene Metathesis

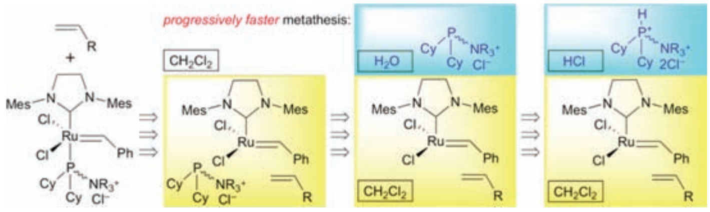
Zhenxing Xi,[†,‡] Hassan S. Bazzi,[*,†] and John A. Gladysz[*,‡]

Department of Chemistry, Texas A&M University at Qatar, P.O. Box 23874, Doha, Qatar, and Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012, United States

gladysz@mail.chem.tamu.edu; bazzi@tamu.edu

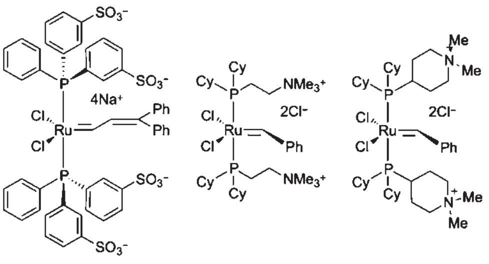
Received September 25, 2011

ABSTRACT



Analogs of Grubbs' second generation catalyst with hydrophilic phosphine ligands are synthesized, and those with $Cy_2PCH_2CH_2N(CH_3)_3{}^+$ Cl^- and $Cy_2P\overline{CHCH_2CH_2N(CH_3)_2{}^+CH_2CH_2}$ Cl^- give much faster ring closing metatheses under CH_2Cl_2/aqueous or CH_2Cl_2/aqueous HCl biphasic as opposed to CH_2Cl_2 monophasic conditions. This is attributed to rapid phase transfer of the dissociated ligand to the aqueous phase, where under acidic conditions it is protonated.

Hydrophilic ligands are usually employed to solubilize a metal complex, typically a catalyst or precatalyst, in water.[1] Particular attention has been given to hydrophilic phosphine ligands.[2] Accordingly, several water-soluble analogs of Grubbs' first generation alkene metathesis catalyst (**1**)[3] and related species[4] have been reported and employed in aqueous phase chemistry. Some examples are depicted in Figure 1. Additional types of water-soluble ruthenium metathesis catalysts, and metatheses carried out in or in the presence of water, have been reviewed.[5]



1a **1b** **1c**

Figure 1. Some water-soluble ruthenium metathesis catalysts.

However, there are further potential applications for ligands that are soluble in water or a phase orthogonal to the reaction medium. For example, with many metal-based catalyst precursors, a ligand must first dissociate before the catalytic cycle can be entered. The reverse reaction often

---

[†] Texas A&M University at Qatar.

[‡] Texas A&M University.

(1) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643.

(2) (a) Pinault, N.; Bruce, D. W. *Coord. Chem. Rev.* **2003**, *241*, 1. (b) Präsang, C.; Bauer, E. B. In *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Vol. 3, p 917. (c) Snelders, D. J. M.; van Koten, G.; Klein Gebbink, R. J. M. *Chem.—Eur. J.* **2011**, *17*, 42.

(3) (a) Grubbs, R. H. In *Aqueous Organometallic Chemistry and Catalysis*; Horváth, I. T., Joó, F., Eds.; Kluwer: The Netherlands, 1995; p 15. (b) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601.

(4) (a) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577. (b) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508.

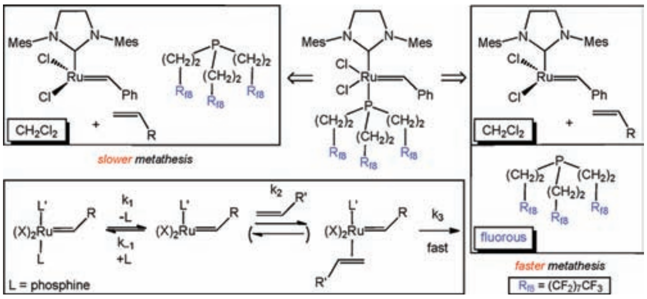
(5) Burtscher, D.; Grela, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 442; *Angew. Chem.* **2009**, *121*, 450.

10.1021/ol202548q

slows the overall rate. Thus, if the ligand could be efficiently scavenged, faster reactions would occur. Most scavenging strategies involve chemical trapping.[6] However, phase transfer into an orthogonal solvent represents another possibility. Toward this end, a biased partition coefficient is also required.

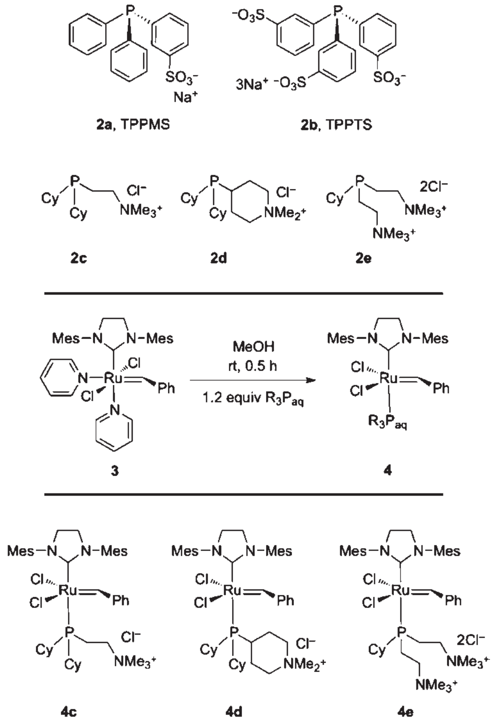
Extensive studies have established the initial steps depicted in Scheme 1 (bottom) for the mechanism of Grubbs' first and second generation metathesis catalysts.[7] In a previous study, we showed that significant rate accelerations occurred when analogs of Grubbs' second generation catalyst with fluorous phosphines $P((CH_2)_mR_{fn})_3$ ($R_{fn} = (CF_2)_{n-1}CF_3$) were conducted under organic/fluorous biphasic conditions as opposed to organic monophasic conditions (Scheme 1, right vs left).[8] This was attributed to rapid transfer of the dissociated phosphine to the fluorous phase, which effectively eliminated competition of nonproductive phosphine reassociation (k_{-1} step, Scheme 1) with productive alkene binding (k_2 step).

Scheme 1. Phase Transfer Activation of Analogs of Grubbs' Second Generation Alkene Metathesis Catalyst with Fluorous Phosphines under Organic/Fluorous Liquid/Liquid Biphase Conditions



Since we were unaware of any additional examples of such "phase transfer activation" of catalysts in the literature, further validation of the concept was sought. Accordingly, in this communication we extend Scheme 1 to aqueous/organic biphase systems using analogs of Grubbs' second generation catalyst with water-soluble phosphines. Furthermore, we find that even more pronounced rate accelerations occur when aqueous HCl is employed as the orthogonal phase, presumably due to protonation of the dissociated ligand.[9]

Scheme 2. Water-Soluble Phosphines and Ruthenium Complexes Thereof Used in This Study



The phosphines depicted in Scheme 2 (top) were purchased or synthesized by literature procedures.[10] Two series were investigated. The first featured a triphenylphosphine core in which one or three phenyl groups were functionalized by a sodium sulfonate moiety in a meta position (TPPMS, TPPTS; **2a**,**b**). This provides steadily increasing hydrophilicity. The second featured trialkyl phosphines containing one or two tetraalkylammonium halide groups (**2c**–**e**).

As shown in Scheme 2 (middle), the ruthenium bis(pyridine) benzylidene complex $(H_2IMes)(Py)_2(Cl)_2Ru(=CHPh)$ (**3**; H_2IMes = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene)[11] and the phosphines were combined under homogeneous conditions in the polar solvent methanol. NMR analyses of the reaction with **2a** showed only 10% conversion to a new benzylidene complex, and no conversion was observed with **2b**. However, workups of the reactions with **2c**–**e** gave the new complexes **4c**–**e** (Scheme 2, bottom) as analytically pure brownish solids in 85–65% yields.

The new complexes were characterized by NMR spectroscopy (^1H, ^{13}C, ^{31}P), as summarized in the Supporting Information (SI). All features were routine, with the ^1H and ^{13}C NMR data sharing many features with those of Grubbs' second generation catalyst. Since CH_2Cl_2 is a common solvent for alkene metathesis, H_2O/CH_2Cl_2 partition coefficients for the complexes and phosphine ligands were determined as described in the experimental section (SI) and summarized in Table 1. Surprisingly, there appear to be little quantitative data on the *relative* aqueous/organic

---

(6) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324.

(7) (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103.

(8) (a) Corrêa da Costa, R.; Gladysz, J. A. *Chem. Commun.* **2006**, 2619. (b) Corrêa da Costa, R.; Gladysz, J. A. *Adv. Synth. Catal.* **2007**, *349*, 243.

(9) For Brønsted basicities of phosphines, see the following recent articles and earlier references therein: (a) Streitwieser, A.; McKeown, A. E.; Hasanayn, F.; Davis, N. R. *Org. Lett.* **2005**, *7*, 1259. (b) Pestovsky, O.; Shuff, A.; Bakac, A. *Organometallics* **2006**, *25*, 2894.

(10) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317.

(11) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314.

Table 1. Partition Coefficients (H_2O/CH_2Cl_2, 24 °C) for Water-Soluble Phosphines and Their Corresponding Grubbs' Catalysts

phosphine	partition coefficient	ruthenium complex	partition coefficient
2a	>99.9:<0.1	--	--
2b	>99.9:<0.1	--	--
2c	92.8:7.2 (>99.9:<0.1)[a]	**4c**	<0.1:>99.9
2d	80.7:19.3 (>99.9:<0.1)[a]	**4d**	<0.1:>99.9
2e	>99.9:<0.1	**4e**	>99.9:<0.1

[a] 0.10 M aqueous HCl used in place of H_2O; analysis after addition of base.

solubilities of hydrophilic phosphines in the literature. In accord with the coloration of the biphasic mixtures, the monotetraalkylammonium salts **4c**,**d** partitioned exclusively into the organic phase, and the bis(tetralkylammonium) salt **4e** exclusively into the aqueous phase.

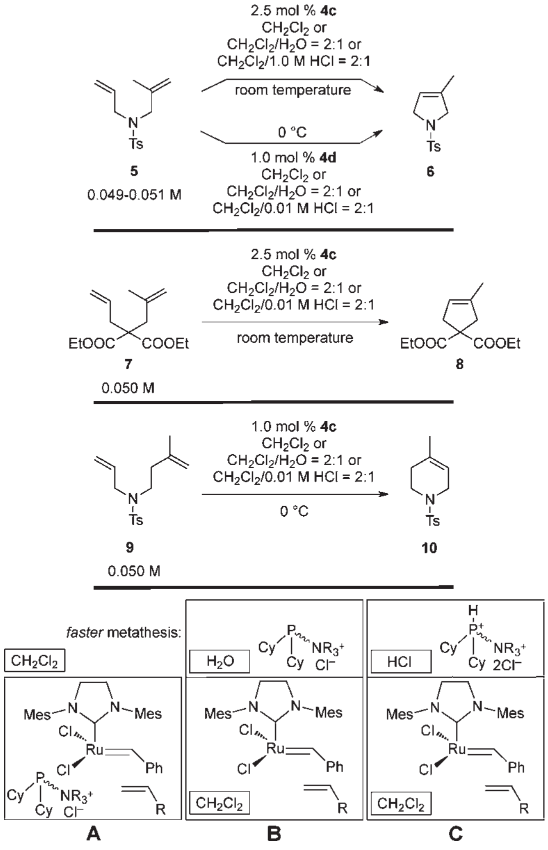
The data in Table 1 help to identify the most promising catalyst systems for aqueous/organic phase transfer activation of alkene metathesis. Complex **4e** is too hydrophilic and will be orthogonal to the reactant phase. With the lipophilic complexes **4c**,**d**, both phosphine ligands preferentially partition into the aqueous phase, but that in **4c** to a somewhat greater extent.

Substrates that would react at convenient time scales between room temperature and 0 °C were sought, and based upon screening experiments the reactions depicted in Scheme 3 were selected. The ring closing metathesis of *N*-allyl-*N*-methallyltosylamide (**5**) to **6** was conducted using 2.0 mL of a 0.050 M CH_2Cl_2 solution and 2.5 mol % of **4c**. The rate of conversion of **5** was monitored by GC with reference to a tridecane internal standard. Data are summarized in Figure 2. Then an otherwise identical reaction was conducted in the presence of water (1.0 mL), corresponding to **B** in Scheme 3 (bottom). As shown in Figure 2, a significant rate acceleration was observed.

Next, an otherwise identical reaction was conducted in the presence of 1.0 M aqueous HCl (1.0 mL; **C** in Scheme 3). Now a more dramatic rate acceleration was observed. This is consistent with protonation of the phosphine ligand **2c** following phase transfer,[9] and the much more biased partition coefficient that results (Table 1). Grubbs has also observed faster metatheses in the presence of HCl in systems that do not involve phase transfer.[3b,12]

In another series of experiments (SI), the concentration of HCl in the aqueous phase was varied. Comparable rate data were obtained with 1.0, 0.10, and 0.010 M aqueous HCl (Figure s1). Hence, the latter was used in subsequent experiments below. Also, when the catalyst loading in the H_2O/CH_2Cl_2 experiment was decreased to 1.0 mol %, there was a corresponding decrease in rate. However, the rate was essentially unchanged when the catalyst loading was increased to 5.0 mol % (Figure s2).

Scheme 3. Phase Transfer Activation of Analogs of Grubbs' Second Generation Alkene Metathesis Catalyst with Water-Soluble Phosphines under Organic/Aqueous Liquid/Liquid Biphase Conditions



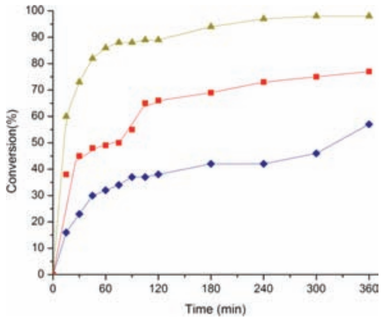


Figure 2. Rates of formation of **6** (room temperature, $[\mathbf{5}]_0$ = 0.049−0.050 M, 2.5 mol % **4c**). Solvent systems: A (blue,◆) CH_2Cl_2 (2.0 mL); B (red,■) CH_2Cl_2/H_2O (2.0 mL/1.0 mL); C (gold,▲) CH_2Cl_2/1.0 M aqueous HCl (2.0 mL/1.0 mL).

The generality of these phenomena was tested with other catalysts and substrates. Figure 3 depicts a series of experiments similar to those in Figure 2, but using complex **4d**. This catalyst was intrinsically more active, so the

---

(12) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153.

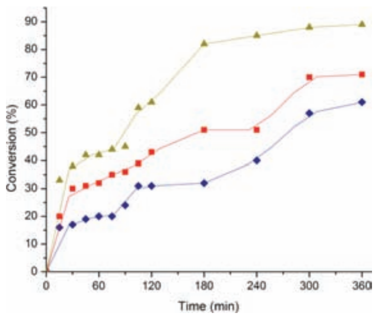


Figure 3. Rates of formation of **6** (0 °C, $[\mathbf{5}]_0$ = 0.050−0.051 M, 1.0 mol % **4d**). Solvent systems: A (blue,◆) CH_2Cl_2 (4.0 mL); B (red,■) CH_2Cl_2/H_2O (4.0 mL/2.0 mL); C (gold,▲) CH_2Cl_2/0.010 M aqueous HCl (4.0 mL/2.0 mL).

metathesis was conducted at 0 °C with a 1.0 mol % loading. Parallel effects were observed, although the magnitudes of the rate accelerations were less, possibly due in part to the less biased partition coefficient of the dissociating phosphine **2d**.

Next, a series of experiments comparable to those in Figure 2 was conducted with catalyst **4c** and diethyl 2-allyl-2-methallylmalonate (**7**; Scheme 3). As shown in Figure 4, analogous rate accelerations were realized under biphasic conditions, with aqueous HCl being more effective than water alone. Similar results were obtained with the *N*-tosylamide **9** (Scheme 3), which affords the six-membered heterocycle **10**, as summarized in Figure 5.

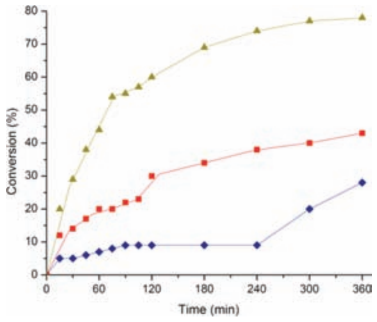


Figure 4. Rates of formation of **8** (room temperature, $[\mathbf{7}]_0$ = 0.050 M, 2.5 mol % **4c**). Solvent systems: A (blue,◆) CH_2Cl_2 (2.0 mL); B (red,■) CH_2Cl_2/H_2O (2.0 mL/1.0 mL); C (gold,▲) CH_2Cl_2/0.010 M aqueous HCl (2.0 mL/1.0 mL).

As a control experiment, the reaction conducted in CH_2Cl_2 in Figure 2 was compared with one conducted under otherwise identical conditions, but in the presence of the fluorous solvent perfluoro(2-butyltetrahydrofuran) (FC-75; 1.0 mL). A slight rate decrease was noted (Figure s3). Finally, when Grubbs' second generation catalyst was employed in place of **4c** in Figure 2 (monophasic conditions), a much faster reaction occurred. Hence, **4c** and **4d** are intrinsically less active metathesis catalysts.

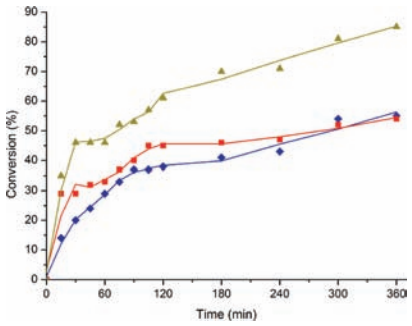


Figure 5. Rates of formation of **10** (0 °C, $[\mathbf{9}]_0$ = 0.050 M, 1.0 mol % **4c**). Solvent systems: A (blue,◆) CH_2Cl_2 (4.0 mL); B (red,■) CH_2Cl_2/H_2O (4.0 mL/2.0 mL); C (gold,▲) CH_2Cl_2/0.010 M aqueous HCl (4.0 mL/2.0 mL).

In summary, we have established that the new catalysts **4c** and **4d** can effect a variety of ring closing metatheses and that these reactions are significantly accelerated when conducted in the presence of water or aqueous HCl. These data are consistent with a phenomenon that can be termed "phase transfer activation", whereby the hydrophilic phosphine ligand is rapidly transferred to the aqueous phase, diminishing competition from the nonproductive k_{-1} step in the mechanism sketched in Scheme 1. In the case of aqueous HCl, the phosphine ligand is furthermore protonated, which further decreases the equilibrium concentration of the phosphine in the reaction phase and may kinetically assist crossing the phase boundary. There are a number of attractive possibilities for extending this concept,[13] and additional examples will be reported in due course.

Acknowledgment. We thank the Qatar National Research Fund for support (Project No. 08-607-1-108).

Supporting Information Available. Details of the synthesis and characterization of **4c**−**e**, catalysis experiments, and partition coefficient measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(13) For example, analogs of Grubbs' second generation catalyst have been prepared with imidazolium containing phosphine ligands, which impart high affinities for imidazole based ionic liquids: Consorti, C. S.; Aydos, G. L. P.; Ebeling, G.; Dupont, J. *Org. Lett.* **2008**, *10*, 237.