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Liquid/Solid Phase Transfer Activation of Grubbs-Type Alkene Metathesis Catalysts; Application of Silver Salts of Sulfonated Polystyrene[†]

Zhenxing Xi,[a] Hassan S. Bazzi,[*b] John A. Gladysz[*a]

Abstract. Alkene metatheses catalyzed by $(H_2IMes)(Cy_2PCH_2CH_2N(CH_3)_3^+)(Cl)_2Ru(=CHPh)$ Cl^-, an analog of Grubbs' second generation catalyst with an ammonium-salt containing phosphine, are dramatically accelerated when conducted in the presence of the insoluble resin PS-SO_3Ag (PS = polystyrene). A mechanism involving ionic and covalent phosphine binding (PS-$SO_3Ag \cdot PCy_2CH_2CH_2N(CH_3)_3^+$ PS-SO_3^-) with concomitant formation of AgCl is proposed. Grubbs' second generation catalyst exhibits a modest rate enhancement, believed to reflect the generation of PS-$SO_3Ag \cdot PCy_3$.

Keywords: alkene metathesis, ruthenium, polystyrene, phosphine ligand, silver, phase transfer

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[†] Electronic supplementary information (ESI) available: Experimental procedures.

In previous papers, we have developed the concept of "phase transfer activation" of metal based catalysts.[1-4] This technique is applicable when a ligand (L) must first dissociate in an initial or "k_1" step to generate the active catalyst (Scheme 1).[5,6] This step is often reversible, with recapture of the ligand by the catalyst faster than subsequent binding of substrate ($k_{-1}[L] \gg k_2[\text{substrate}]$). As can be derived from the full rate expression given in Scheme 1, this serves to lower the velocity of the reaction as compared to the opposite limit with $k_{-1}[L] \ll k_2[\text{substrate}]$ (compare red box vs. green box).
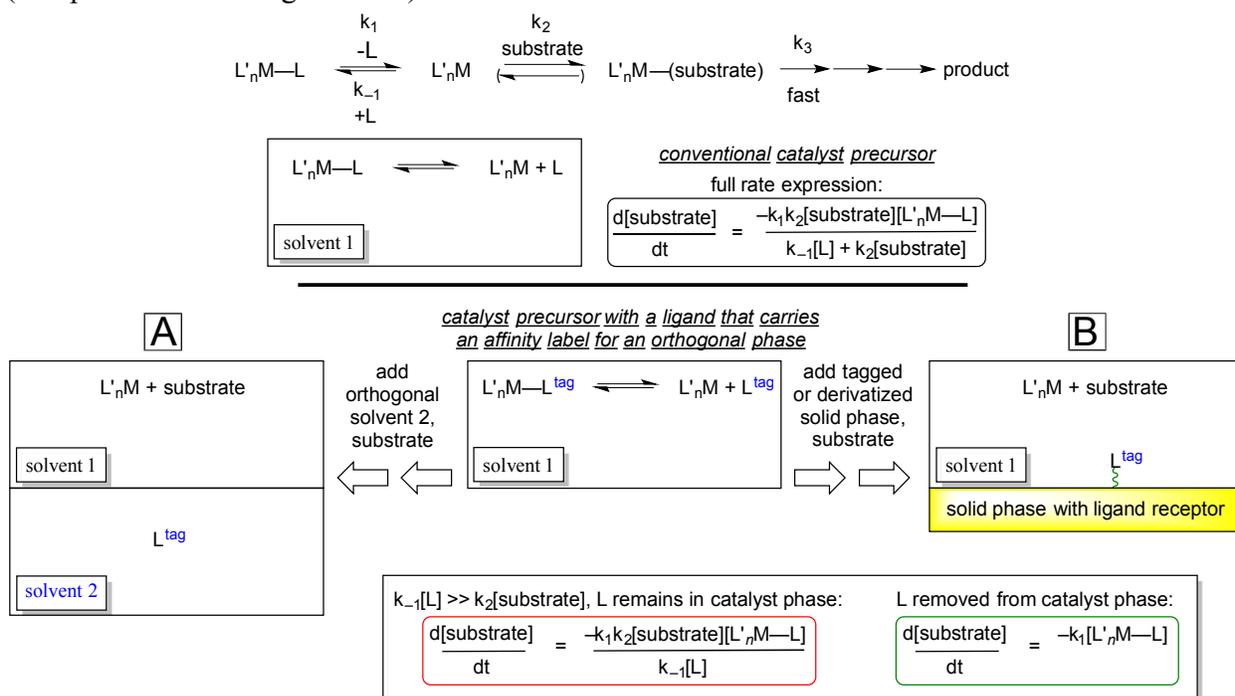

Scheme 1. General principles of phase transfer activation.

Hence, we have sought catalyst precursors with ligands that are phase or affinity labeled such that they will rapidly transfer to an orthogonal (immiscible) phase, as shown in Scheme 1-A for liquid/liquid biphase systems. In earlier publications, we have prepared derivatives of Grubbs' second generation alkene metathesis catalyst (**1a**) with fluorophilic and hydrophilic phosphine ligands (**1b**,**c**; see Scheme 2).[1-4] These afforded marked rate enhancements of ring closing reactions (RCM) under aqueous/organic and fluorous/organic liquid/liquid biphase conditions, as compared to organic monophase conditions.

In the preceding protocols, no binding site has been provided for the phase labeled ligand

in the orthogonal phase. Thus, phase transfer will be governed by a partition coefficient. We wanted to expand this strategy in two conceptual directions. First, we were attracted to the idea of using orthogonal <u>solid</u> phases, of which numerous hydrophilic, fluorophilic, and lipophilic varieties are available. Among other attributes, this would greatly decrease solvent demand. Second, given that many solid materials are easily functionalized – e.g., polystyrene (PS)[7] – we set out to build in possible phase, ionic, or covalent interactions to enhance phase transfer, as exemplified in Scheme 1-B.
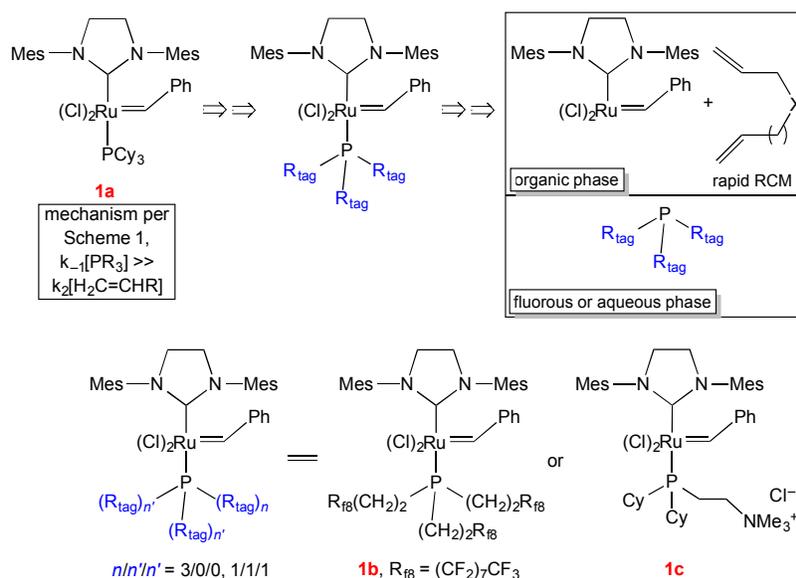
Scheme 2. Liquid/liquid phase transfer activation using analogs of Grubbs' second generation alkene metathesis catalyst (**1a**) with phase labeled phosphine ligands (**1b,c**).

As noted above, dramatic rate accelerations are observed when catalyst **1c**, which features a phosphine with a hydrophilic tetraalkylammonium chloride moiety, is applied under aqueous/organic biphase conditions. We wondered whether the positively charged ligand might rapidly adsorb onto a negatively charged polystyrene, for example readily available sulfonated derivatives as represented by the Amberlyst family.[8] We furthermore speculated that using a silver salt of a sulfonated polystyrene (PS-SO$_3$Ag)[9] would provide additional driving forces. As sketched in Scheme 3-A,[10] a thermodynamically favorable AgCl precipitation would generate the requisite number of anionic binding sites, while the remaining PS-SO$_3$Ag moieties could covalently bind to the trivalent phosphorus atom. This polymer was first reported by Bergbreiter, together with a

variety of data involving PPh$_3$ binding in solution.[9]
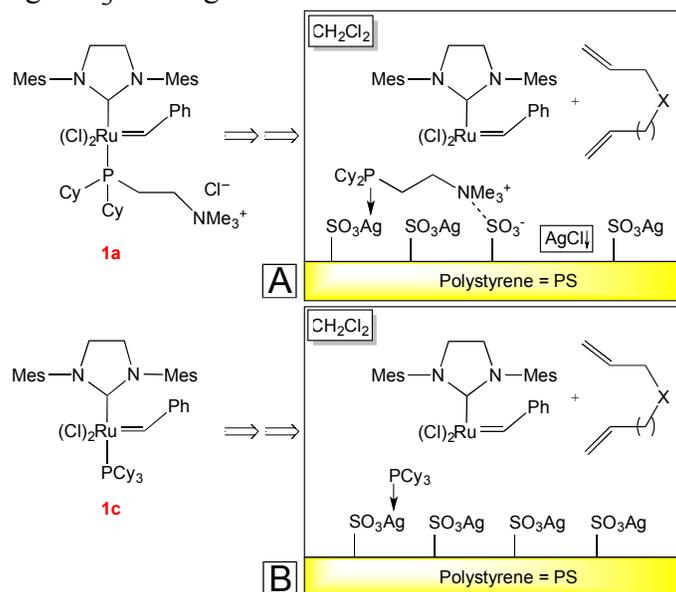
Scheme 3. Proposed mechanisms of catalyst activation.

Commercial Amberlyst 15 (PS-SO$_3$H; 4.7 mmol H$^+$/g of polymer) was converted to the silver salt PS-SO$_3$Ag as previously reported,[11] and standardized by a gravimetric method (HNO$_3$/NaCl; 1.5 mmol Ag$^+$/g of polymer).[9a,12] In an initial series of experiments, the polymer loading was optimized with respect to the catalyst/substrate charge, using *N*-allyl-*N*-methallyl-*p*-tosyl-amide (**2**) as shown in Scheme 4. Thus, a series of Schlenk tubes was charged with **1c** (0.0025−0.0028 mmol; 2.5−2.8 mol%), tridecane internal standard, 2.0 mL of a 0.049−0.050 M CH$_2$Cl$_2$ solution of **2** (0.099-0.102 mmol), and varying amounts of the PS-SO$_3$Ag resin per Figure 1 (0.015, 0.030, 0.045, 0.060, 0.075, 0.150 mmol Ag$^+$ or 6-60 equiv with respect to **1c**). Aliquots were periodically removed and quenched with ethyl vinyl ether, and the rate of formation of the RCM product **3** (Scheme 4) assayed by GC. The best results were obtained with a 0.045 mmol loading (18 equiv; magenta inverted triangles), although data were comparable with 0.030 and 0.060 mmol loadings. The 0.045 mmol charge was used for all subsequent experiments.

The rate profile with the 0.045 mmol PS-SO$_3$Ag loading is repeated in Figure 2 (magenta inverted triangles), and compared with that of a new experiment without the PS-SO$_3$Ag, but with the same reactant/solvent quantities and catalyst charge (blue diamonds). The latter reaction is dramatically slower. For comparison, two experiments were conducted with orthogonal liquid
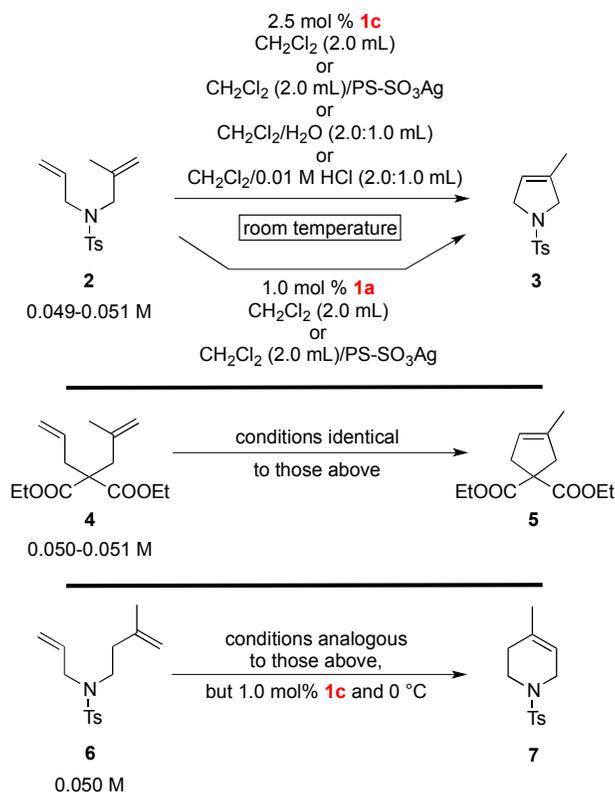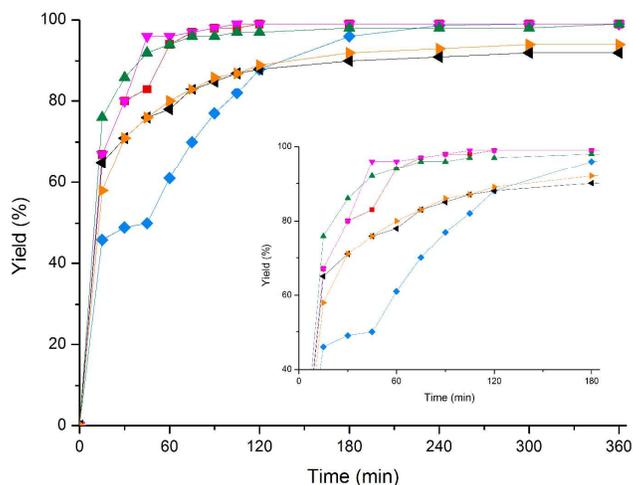
Scheme 4. Ring closing metatheses studied.

Figure 1. Rates of formation of **3** (room temperature, $[\mathbf{2}]_0$ = 0.049−0.051 M, 2.5 mol% **1c**) in 2.0 mL CH_2Cl_2 in the presence of PS-SO$_3$Ag resin. Resin loading: ◆ 0.010 g (0.015 mmol Ag$^+$); ■ 0.020 g (0.030 mmol Ag$^+$); ▼ 0.030 g (0.045 mmol Ag$^+$); ▲ 0.040 g (0.060 mmol Ag$^+$); ◀ 0.050 g (0.075 mmol Ag$^+$); ▶ 0.100 g (0.150 mmol Ag$^+$).

phases. In the first, water (1.0 mL) was added to the CH_2Cl_2 solution, giving a biphasic organic/ aqueous system per Figure 2 (orange squares). In the second, 0.01 M aqueous HCl (1.0 mL) was added (green triangles). Both of these experiments, which have been reported earlier,[2] afforded

faster rates than the monophasic CH_2Cl_2 conditions. The latter, in which the phosphine ligand is protonated by HCl concomitantly with phase transfer, was more rapid. However, both remained slower than the liquid/solid biphase conditions with $PS-SO_3Ag$. Hence, liquid/solid biphase conditions can be superior for phase transfer activation.
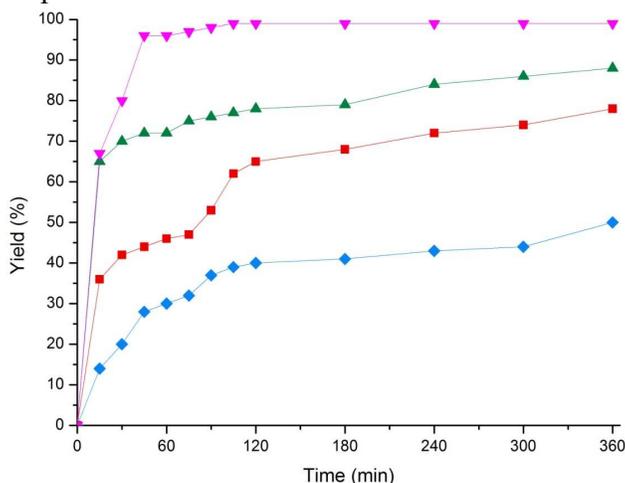

Figure 2. Rates of formation of **3** (room temperature, $[2]_0 = 0.049–0.051$ M, 2.5 mol% **1c**). Solvent systems: ◆ CH_2Cl_2 (2.0 mL); ■ CH_2Cl_2/H_2O (2.0 mL/1.0 mL); ▲ $CH_2Cl_2/0.01$ M aqueous HCl (2.0 mL/1.0 mL); ▼ CH_2Cl_2 (2.0 mL) with 0.030 g PS-SO_3Ag resin (0.045 mmol Ag^+).

In order to establish the generality of these phenomena, experiments analogous to those in Figure 2 were conducted with two additional substrates, diethyl 2-allyl-2-methallylmalonate (**4**) and the allyl/homoallyl N-tosylamide **6** (Scheme 4).[13] As illustrated in Figures 3-A and 3-B, the liquid/solid biphase conditions gave much faster RCM rates than the liquid monophase conditions (magenta inverted triangles vs. blue diamonds). However, here the liquid/liquid biphase conditions involving aqueous HCl (green triangles) exhibited slightly faster rates at low conversions (15-30 min).

With regard to the catalyst activation mechanism sketched in Scheme 3-A, Grubbs' second generation catalyst **1a** would not be expected to give comparable rate accelerations. Thus, in experiments analogous to those in Figure 1, Schlenk tubes were charged with **1a** (0.0010 mmol), tridecane internal standard, 2.0 mL of a 0.051 M CH_2Cl_2 solution of **4** (0.101 mmol), and varying amounts of the PS-SO_3Ag resin. These conditions employ a lower catalyst loading and less reactive RCM substrate than in Figure 1, apropos to the intrinsically higher reactivity of **1a** vs. **1c**
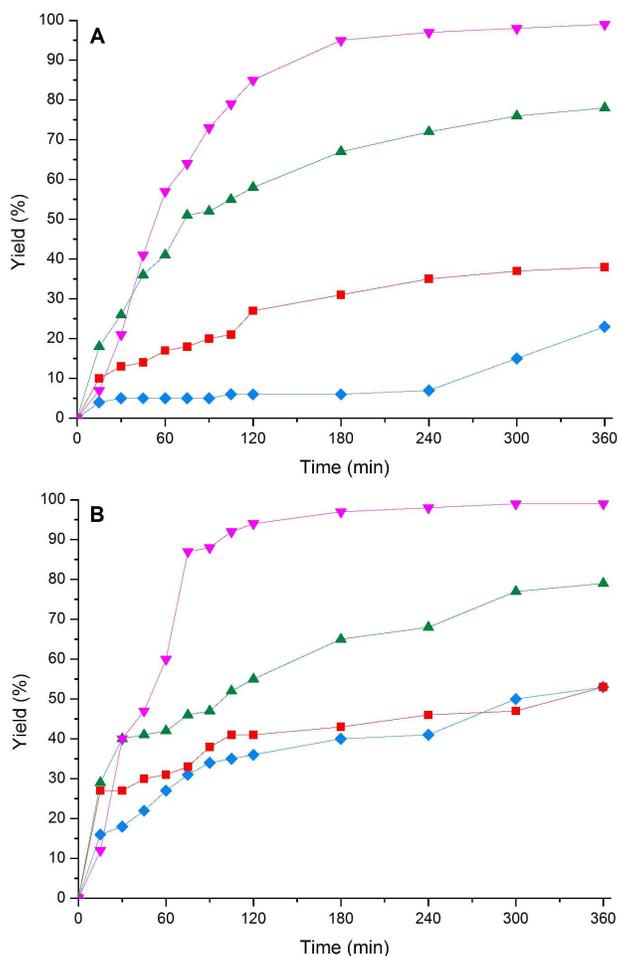
Figure 3. **A**. Rates of formation of **5** (room temperature, $[4]_0 = 0.050−0.051$ M, 2.5 mol% **1c**). Solvent systems: ◆ CH_2Cl_2 (2.0 mL); ■ CH_2Cl_2/H_2O (2.0 mL/1.0 mL); ▲ $CH_2Cl_2/0.01$ M aqueous HCl (2.0 mL/1.0 mL); ▼ CH_2Cl_2 (2.0 mL) with 0.030 g PS-SO_3Ag resin (0.045 mmol Ag^+). **B**. Rates of formation of **7** (0 °C, $[6]_0 = 0.050$ M, 1.0 mol% **1c**). Solvent systems: ◆ CH_2Cl_2 (4.0 mL); ■ CH_2Cl_2/H_2O (4.0 mL/2.0 mL); ▲ $CH_2Cl_2/0.01$ M aqueous HCl (4.0 mL/2.0 mL); ▼ CH_2Cl_2 (4.0 mL) with 0.024 g PS-SO_3Ag resin (0.036 mmol Ag^+).

established earlier.[2] As shown in Figure s1, the rate depended upon the PS-SO_3Ag loading. That with 0.015 mmol Ag^+ proved optimum and was used in subsequent experiments.

The rate profile for this PS-SO_3Ag loading is repeated in Figure 4 (solid red squares), together with data for an analogous experiment in the absence of the resin (solid blue diamonds). A rate enhancement is evident under liquid/solid biphase conditions, but is less dramatic. Similar effects were seen with the other substrates **2** (Figure 4; note faster reaction) and **6** (not depicted).

Accordingly, we suggest two mechanisms for liquid/solid phase transfer of the phosphine ligands, as sketched in Scheme 3. In the first and originally envisioned scenario, the PS-SO_3Ag resin and the tetraalkylammonium chloride containing phosphine generate AgCl and the surface
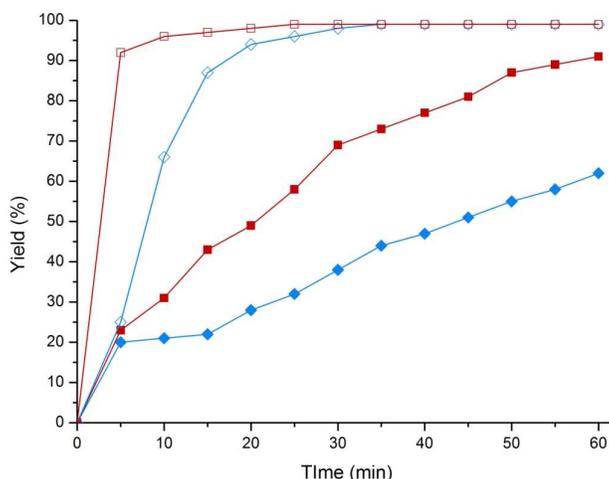
Figure 4. Rates of formation RCM products (room temperature, [substrate]$_0$ = 0.050−0.051 M, 1.0 mol% **1a**). Substrate/product, solvent systems: ◆ **4/5**, CH$_2$Cl$_2$ (2.0 mL); ■ **4/5**, CH$_2$Cl$_2$ (2.0 mL) with 0.010 g PS-SO$_3$Ag resin (0.015 mmol Ag$^+$); ◇ **2/3**, CH$_2$Cl$_2$ (2.0 mL); □ **2/3**, CH$_2$Cl$_2$ (2.0 mL) with 0.010 g PS-SO$_3$Ag resin (0.015 mmol Ag$^+$).

assembly PS-SO$_3$Ag·PCy$_2$CH$_2$CH$_2$N(CH$_3$)$_3$$^+$ PS-SO$_3$$^-$, which features ionic and covalent inter-actions. In the second, applicable to neutral trialkylphosphines such as PCy$_3$, a more weakly bound covalent adduct is generated (e.g., PS-SO$_3$Ag·PCy$_3$). Although many silver(I) phosphine adducts have been characterized, they are generally labile, with low barriers to phosphine ex-change (typically 11-13 kcal/mol) suggestive of weak silver-phosphorus bonds.[14]

Finally, the ability of the PS-SO$_3$Ag resin to adsorb the free phosphines Cy$_2$PCH$_2$CH$_2$N-Me$_3$$^+$ Cl$^-$ and PCy$_3$ was tested. For solubility reasons, the former could not be assayed in the re-action solvent (CH$_2$Cl$_2$), so methanol was employed, with the idea that the more polar solvent would decrease the driving force for adsorption and provide a lower limit for rates and equilibria in less polar solvents. Thus, NMR tubes were charged with standard solutions of the phosphines in CD$_3$OD or CD$_2$Cl$_2$ (0.40 M; 0.40 mL, 0.160 mmol) and capillaries containing the internal standard ClPPh$_2$. A reference ^{31}P{^{1}H} NMR spectrum was recorded, and the PS-SO$_3$Ag resin (0.0342-0.0322 mmol Ag$^+$, ca. 20 mol% compared to phosphine) was added with shaking. The amount of adsorbed phosphine was assayed every 30-60 min, as diagrammed in Figure 5. Inter-estingly, the theoretical amount of the cationic phosphine was adsorbed (Ag$^+$ limiting, 1:1 stoi-chiometry), and at approximately twice the rate of PCy$_3$.[15]
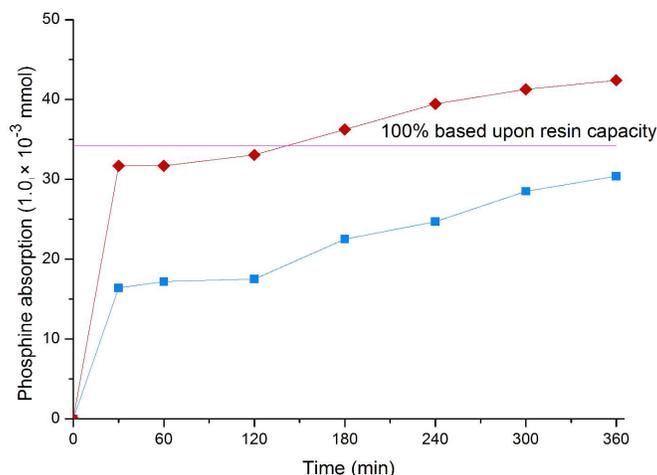
Figure 5. Phosphine absorbed by 0.0215−0.0228 g of PS-SO$_3$Ag resin (1.5 mmol Ag$^+$/g): ($\blacklozenge$) Cy$_2$PCH$_2$CH$_2$NMe$_3^+$ Cl$^-$ from a CD$_3$OD solution (0.40 M, 0.400 mL); ($\blacksquare$) PCy$_3$ from a CD$_2$Cl$_2$ solution (0.40 M, 0.400 mL).

Various additives have previously been noted to enhance the rates of alkene metatheses with Grubbs type catalysts. These include a variety of copper(I) salts.[16] However, we are unaware of any prior data with silver(I) species. Importantly, Bergbreiter tested the effect of PS-SO$_3$Ag upon rates of alkene hydrogenations with Wilkinson's catalyst some time ago.[9,11] No acceleration was noted, and only very modest enhancements were observed with ruthenium catalysts of the type RuHX(PPh$_3$)$_3$ (X = H, OAc, Cl; 1.1-1.8 fold).[9,11] However, a poorly active catalyst precursor, RuCl$_2$(PPh$_3$)$_3$, did exhibit a 15 fold rate increase.[9b,11] All of these results, and others involving inhibition of phosphine poisoning, were interpreted from the standpoint of covalent phosphine binding to the resin.

In summary, this study has expanded the scope of phase transfer activation, as applied to alkene metathesis using Grubbs-type catalysts, from liquid/liquid biphase to liquid/solid biphase conditions. These new solvent-leaner protocols incorporate attractive bonding interactions between the solid phase and the ligands undergoing phase transfer, thereby providing the most pronounced rate accelerations observed to date. Future reports will extend the utility of phase transfer activation to other types of catalytic reactions.

Notes and References

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(10) This model presupposes that the silver loading is greater than the catalyst loading.

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(12) The conversion of PS-SO$_3$H to PS-SO$_3$Ag sites is ca. 32%. Incomplete conversions of functionalized polystyrenes are often attributed to groups that reside in less accessible interior domains.

(13) A reviewer has inquired about data with other solid supports. Two acidic resins, Dowex 50WX2 (Aldrich) and Nafion (Alfa Aesar) were also investigated under the conditions of Figure 2 (but without silver derivatization). These were only moderately effective, with rates intermediate between the monophase (CH$_2$Cl$_2$) and liquid/liquid organic/aqueous biphase (CH$_2$-Cl$_2$/H$_2$O) conditions.

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(15) A reviewer has asked about the ability of the PS-SO$_3$Ag resin to adsorb catalyst **1c**. An experiment comparable to those in Figure 5 was carried out, but with a higher silver loading to further promote catalyst adsorption (0.50 mL of 0.044 M **1c** in CD$_2$Cl$_2$; 0.0475 g PS-SO$_3$Ag, 0.0712 mmol Ag$^+$). Based upon a slight diminution of the catalyst ^{31}P NMR signal relative to that of the standard, an upper limit of ca. 5% adsorption (0.021 mmol, 1% based upon Ag$^+$; measured after ca. 2 min) could be set. There was no further change after 4 h.

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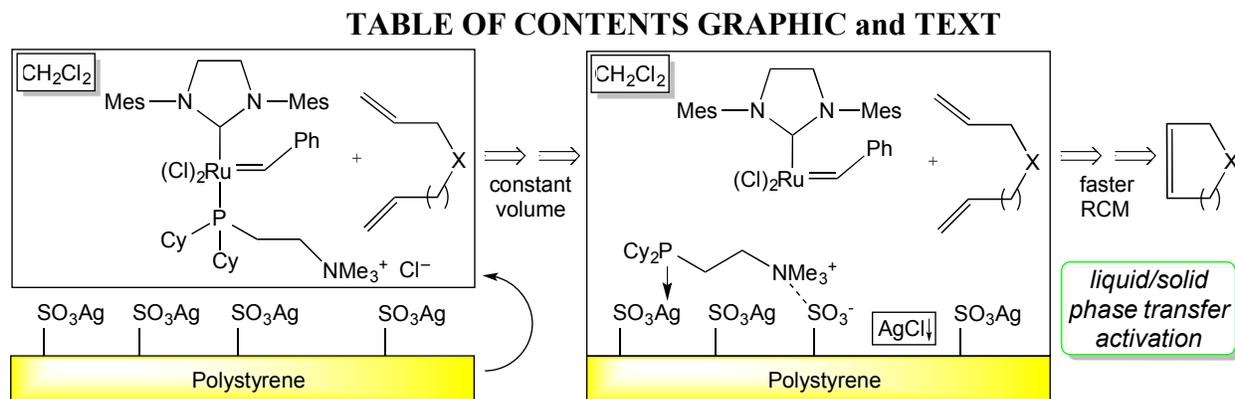
An analog of Grubbs' second generation catalyst with a tetralkylammonium chloride containing phosphine exhibits faster rates in the presence of polystyrene-SO_3Ag.

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Scheme 2. Liquid/liquid phase transfer activation using analogs of Grubbs' second generation alkene metathesis catalyst with phase labeled phosphine ligands.

Scheme 3. Proposed mechanisms of catalyst activation.

Scheme 4. Ring closing metatheses studied.

Figure 1. Rates of formation of **3** (room temperature, $[2]_0 = 0.049-0.051$ M, 2.5 mol% **1c**) in 2.0 mL CH_2Cl_2 in the presence of PS-SO_3Ag resin. Resin loading: ◆ 0.010 g (0.015 mmol Ag^+); ■ 0.020 g (0.030 mmol Ag^+); ▼ 0.030 g (0.045 mmol Ag^+); ▲ 0.040 g (0.060 mmol Ag^+); ◀ 0.050 g (0.075 mmol Ag^+); ▶ 0.100 g (0.150 mmol Ag^+).

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Figure 5. Phosphine absorbed by 0.0215-0.0228 g of PS-SO_3Ag resin (1.5 mmol Ag^+/g): (◆) $Cy_2PCH_2CH_2NMe_3^+$ Cl^- from a CD_3OD solution (0.40 M, 0.400 mL); (■) PCy_3 from a CD_2Cl_2 solution (0.40 M, 0.400 mL).

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