Fluorous phase-transfer activation of catalysts: application of a new rate-enhancement strategy to alkene metathesis†

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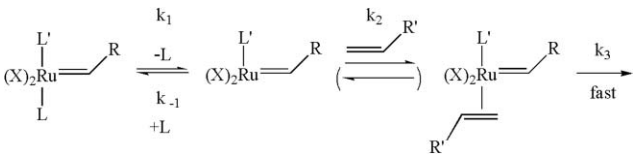
Reactions of the bis(pyridine) complex $(H_2IMes)(Py)_2(Cl)_2Ru(=CHPh)$ and fluorous phosphines $P(CH_2CH_2R_{fn})_3$ (n = a, 6; b, 8; c, 10; $R_{fn} = (CF_2)_{n-1}CF_3$) give $(H_2IMes)(P(CH_2CH_2R_{fn})_3)(Cl)_2Ru(=CHPh)$ (2a–c, 64–73%), which are analogs of Grubbs' second generation catalyst and effective alkene metathesis catalysts under organic monophasic and fluorous/organic biphasic conditions. The latter give rate accelerations, which are believed to arise from phase transfer of the dissociated fluorous phosphine.

Since the first report in 1994,[1] fluorous catalysis has primarily been regarded as a method for catalyst recovery.[2] However, it seemed to us that fluorous techniques might also be used for catalyst *activation*. For example, there are many metal-based catalyst precursors from which a ligand must first dissociate before the catalytic cycle can be entered. The reverse reaction often slows the overall rate. Thus, if the ligand could be efficiently scavenged, faster reactions would occur. Most scavenging strategies involve chemical derivatization, but fluorous methodologies could bring phase transfer into play.

A case in point would be the ruthenium alkene metathesis catalysts developed by Grubbs.[3] As summarized in Scheme 1, the dissociation of a phosphine L (k_1 or initiation step) can be followed either by recoordination (k_{-1} step) or alkene binding (k_2 step). Rate studies have identified many catalysts, including the commercially available first and second generation systems, for which $k_{-1} > k_2$.[3] We wondered whether rate enhancements might be realized when catalysts bearing fluorous phosphines were employed under organic/fluorous liquid/liquid biphasic conditions. As illustrated in Scheme 2, fluorous phosphines can have high thermodynamic affinities for fluorous phases, whereas the active catalyst and alkenes would have high thermodynamic affinities for organic phases.



Scheme 1 Initiation sequence for a Grubbs-type ruthenium alkene metathesis catalyst.

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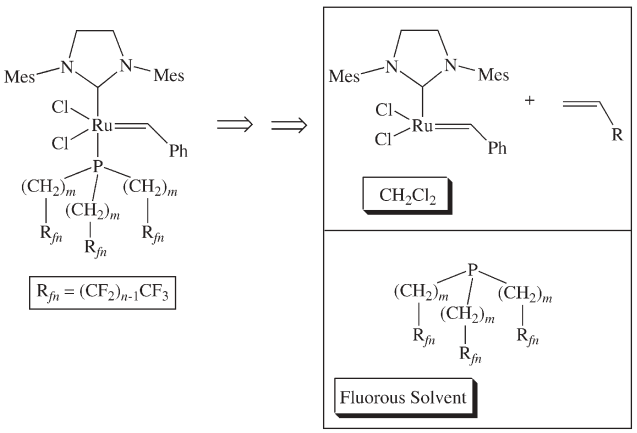
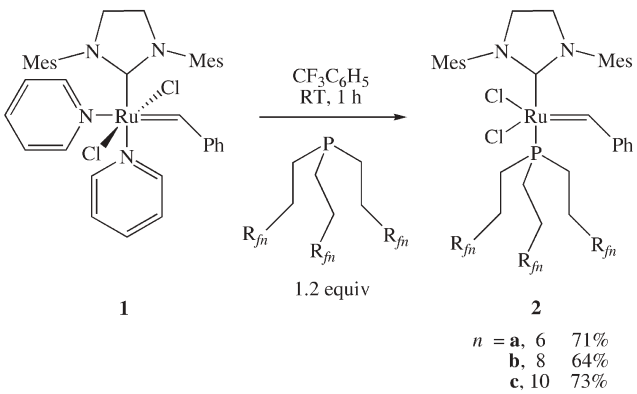


Scheme 2 Proposed fluorous phase-transfer catalyst activation.

Fluorous versions of Grubbs' catalysts are known,[4] but they have been prepared for purposes of catalyst recovery, and carry ponytails or tags on either non-dissociating or "boomerang" carbene ligands. Since we wanted to evaluate systems with a spectrum of phase properties, the series of fluorous aliphatic phosphines $P(CH_2CH_2R_{fn})_3$ (n = **a**, 6; **b**, 8; **c**, 10) was selected.[5] All exhibit partition coefficients that are highly biased for fluorous phases ($CF_3C_6F_{11}$–toluene: 98.8 : 1.2, >99.7 : <0.3, >99.7 : <0.3).[5] As shown in Scheme 3, reactions with the ruthenium bis(pyridine) benzylidene complex **1**[6] gave the target complexes **2a–c** as analytically pure pink solids in 64–73% yields. They were characterized by NMR spectroscopy (^1H, ^{13}C, ^{31}P, ^{19}F) and mass spectrometry, as summarized in the supporting information.†

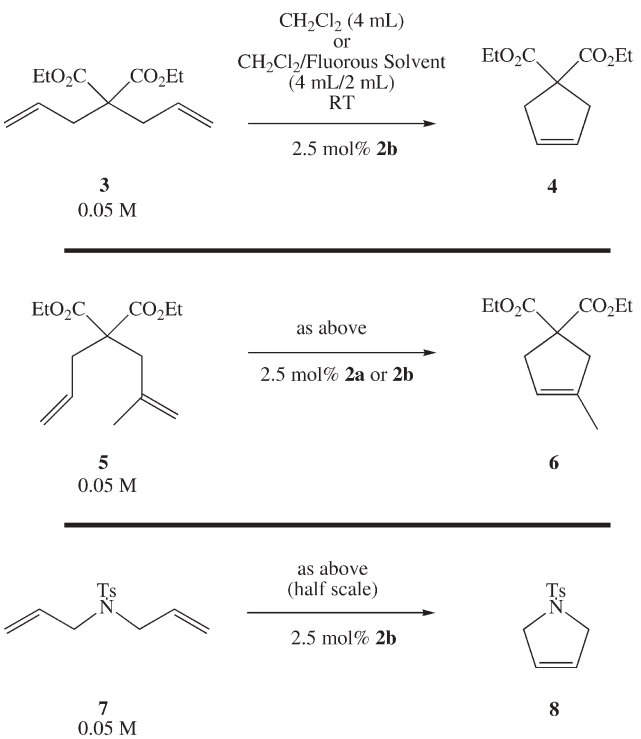


Scheme 3 Synthesis of ruthenium metathesis catalysts with fluorous phosphines.

Complexes **2a**, **b** were soluble in CH_2Cl_2, benzene, hexane, and pentane. Paralleling the effect of the R_{fn} ponytail length in the free phosphines, **2c** was only slightly soluble. The $CF_3C_6F_{11}$–toluene partition coefficients of **2a–c** were measured by HPLC.† The values, 13.2 : 86.8, 39.6 : 60.4 and 77.6 : 22.4, exhibited the expected trend. When toluene is replaced by a solvent of greater polarity (*e.g.*, CH_2Cl_2), the proportions of **2a**, **b** in the non-fluorous phase should increase. Since even non-polar alkenes greatly prefer the non-fluorous phase ($CF_3C_6F_{11}$–toluene $<5 : >95$ for $\geqslant C_{10}$),[7] the partitioning of some catalyst precursor into the fluorous phase is deleterious for the rate. However, the much more biased partitioning of the fluorous phosphine should often compensate.

Complexes **2a–c** were screened in standard metathesis reactions, and found to be effective catalyst precursors, as will be detailed in future publications. To address the theme of this communication, the ring-closing metathesis of diethyl-2,2-diallylmalonate (**3**)[8] was investigated under various conditions using **2b** (Scheme 4). Two side-by-side reactions were conducted using 4 mL of CH_2Cl_2 (0.00125 M in **2b**, 0.05 M in **3**). In one case, 2 mL of $CF_3C_6F_{11}$ was added. Based upon the partitioning data noted above,[7] this should not affect the concentration of **3** in the CH_2Cl_2 phase. The concentration of **2b** should be reduced by less than 19.8% (*i.e.*, 39.6/2 due to the 2 : 1 volume ratio, and still less due to the substitution of toluene by CH_2Cl_2). The formation of the cyclopentene product **4** was monitored by GC in the presence of an internal standard, and the results are depicted in Fig. 1.

Fig. 1 shows that the initial rate of metathesis was markedly enhanced in the presence of the fluorous solvent. After 1 and 2 h the yields of **4** were 23% and 44%, as opposed to 6% and 16% in CH_2Cl_2 alone. An analogous experiment was conducted with perfluoro(2-butyltetrahydrofuran). This solvent is somewhat less



Scheme 4 Test reactions for fluorous phase transfer activation.

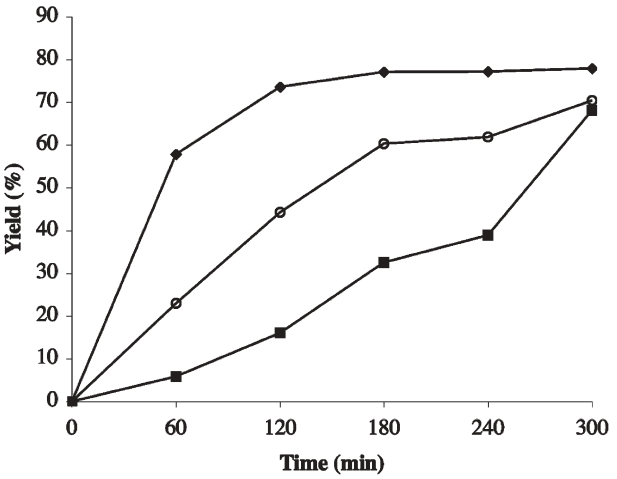


Fig. 1 Rates of formation of **4** in Scheme 4. Solvent systems: ♦ CH_2Cl_2–perfluoro(2-butyltetrahydrofuran) (4 mL/2 mL); ○ CH_2Cl_2–$CF_3C_6F_{11}$ (4 mL/2 mL); ■ CH_2Cl_2 only (4 mL).

viscous than $CF_3C_6F_{11}$,[9] which we imagined might aid diffusion across the phase boundary. Interestingly, a significantly greater rate enhancement was observed, with **4** present in 58% and 74% yields after 1 and 2 h. To confirm that these phenomena were not unique to a single substrate, diethyl-2-allyl-2-methallylmalonate (**5**) and *N*,*N*-diallyltosylamide (**7**) were similarly reacted (Scheme 4). Analogous rate enhancements were observed for the formation of **6** (Figure 2s,† CH_2Cl_2–$CF_3C_6F_{11}$) and **8** (Figure 4s,† CH_2Cl_2–perfluoro(2-butyltetrahydrofuran)). The latter was particularly dramatic (58% *vs.* 2% and 91% *vs.* 4% after 1 and 2 h). Reaction of **5** with the less fluorophilic catalyst **2a** gave similar results (Figure 3s†).

In biphasic fluorous/organic systems, a small amount of fluorous solvent typically partitions into the organic solvent, and *vice versa*. Therefore, there remains some possibility that the preceding trends might (in part) represent solvent effects. Hence, analogous experiments were conducted with Grubbs' second generation catalyst $(H_2IMes)(PCy_3)(Cl)_2Ru(=CHPh)$—a non-fluorous system. As illustrated in the supporting information, the initial rates of formation of **4** and **8** were virtually identical in CH_2Cl_2 and CH_2Cl_2–perfluoro(2-butyltetrahydrofuran); that of **4** was only very slightly faster in CH_2Cl_2–$CF_3C_6F_{11}$ (Figures 5s–7s†). However, the rates of metathesis were greater than those with **2b** (for **4**, 44–50% and 77–88% yields in CH_2Cl_2 after 15 and 60 min).[10]

Other additives that might inhibit the k_{-1} step in Scheme 1 have been investigated. Grubbs,[11] Nolan,[12] and Blechert[13] have reported various types of copper species and Lewis or Brønsted acids that are believed to bind the phosphine L and lead to rate accelerations in certain cases. In a complementary approach, Piers has developed a novel class of highly active fourteen-valence-electron catalyst precursors that *lack* any ligand L.[14] Phenol additives can also have positive effects, but other mechanisms are thought to be involved.[15] Importantly, the dissociated PCy_3 ligand is intimately involved in the decomposition of Grubbs' second generation catalyst.[16] Therefore, another advantage of the phase transfer activation in Scheme 2 may be longer-lived catalysts. Finally, fluorous/organic biphasic conditions have also been found to give enhanced rates with hetereogenized rhodium

hydrogenation catalysts.[17] However, another activation mode is believed operative.

In summary, the data presented in this communication are consistent with a new catalyst activation strategy that uses phase transfer to fluorous media to remove dissociated ligands that can compete with substrate molecules for binding to a reactive metal center. Note that this modus, which we view as "passive transport", might be coupled with a binding or derivatization event in the fluorous phase—an enhancement that might be termed "active transport".[18] Hence, there are tantalizing possibilities for future extensions. In any event, experiments are in progress to further probe the mechanism of activation of **2a**, **b** under fluorous/organic liquid/liquid biphasic conditions, as well as their recyclability. These will be detailed in future publications.

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Notes and references

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10 In Scheme 1, triarylphosphine ligands (L) with electron withdrawing substituents give greater k_1 values.[3b] The electron withdrawing effects of the R_{fn} segments are strongly felt at the phosphorus atoms of **a–c** (H. Jiao, S. Le Stang, T. Soós, R. Meier, K. Kowski, P. Rademacher, L. Jafarpour, J.-B. Hamard, S. P. Nolan and J. A. Gladysz, *J. Am. Chem. Soc.*, 2002, **124**, 1516). Hence, **2a–c** would be expected to be faster initiating catalysts than tri-*n*-alkylphosphine analogs. However, overall rates are a function of many additional factors[3].

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