Initiation rates for Grubbs and Grubbs–Hoveyda second generation pre-catalysts have been measured accurately in a range of solvents. Solvatochromic fitting reveals different dependencies on key solvent parameters for the two pre-catalysts, consistent with different mechanisms by which the Grubbs and Grubbs–Hoveyda pre-catalysts initiate.

The alkene metathesis reaction is now a standard transformation in academic laboratories, and has been applied to the synthesis of a wide range of natural and unnatural products, fine chemicals, polymers, and the health and safety implications of transport, transfer, storage and use. There are also sustainability issues raised by projected uncertainty of supply and by legislative changes. These considerations have led major pharmaceutical companies to encourage their discovery chemists to anticipate scale-up on the basis of both chemical efficacy and sustainability, and from a strong experimental starting point. We therefore sought to reveal the effects of solvent on the initiation rates of 1 and 2, which are currently the most popular metathesis pre-catalysts.

Initiation rates were measured for 1 and 2 by reaction of the pre-catalyst with ethyl vinyl ether in a number of solvents. Initiation rates for 1 were obtained following the method of Sanford et al., the rate-determining step in this reaction is known to be dissociation of the phosphane ligand. The integral versus time data was processed using a simple first order treatment (eqn (1)).

\[ \ln[1] = \ln[1]_0 - k_{\text{obs}}t \]  

For solvents where deuterated analogues were unavailable commercially, 10% v/v chloroform-\text{d} was added to enable a deuterium lock.

Initiation rates for pre-catalyst 1 cover only a ca. four-fold spread of values (Table 1), with similar values obtained in MTBE, dimethyl carbonate and DCM. Amongst the most frequently used solvents, the order of initiation rate constants for...
Table 1  Initiation rates for 1 (ca. 5−15 mmol L−1 with 0.5 mol L−1 ethyl vinyl ether) and 2 (0.1 mmol L−1 with 25−200 mmol L−1 ethyl vinyl ether) in various solvents at 298 K, deuterated solvents were used for measurements of the initiation of 1 unless otherwise stated

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( k_{\text{init}} ) in ( s^{-1} )</th>
<th>( k_{\text{rel}} )</th>
<th>( k_{\text{init}} ) in ( \text{mol}^{-1} \text{L} \text{s}^{-1} )</th>
<th>( k_{\text{rel}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>1.0 × 10⁻⁴</td>
<td>0.71</td>
<td>0.0460</td>
<td>1.74</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.5 × 10⁻⁴</td>
<td>0.32</td>
<td>0.0231</td>
<td>0.88</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>1.4 × 10⁻⁴</td>
<td>1.00</td>
<td>0.0264</td>
<td>3.00</td>
</tr>
<tr>
<td>1,2-Difluorobenzene</td>
<td>1.4 × 10⁻⁴</td>
<td>1.00</td>
<td>0.0390</td>
<td>1.48</td>
</tr>
<tr>
<td>Dimethyl carbonate</td>
<td>1.5 × 10⁻⁴</td>
<td>1.07</td>
<td>0.0411</td>
<td>1.56</td>
</tr>
<tr>
<td>Hexafluorobenzene</td>
<td>3.3 × 10⁻⁵</td>
<td>0.24</td>
<td>0.0515</td>
<td>1.95</td>
</tr>
<tr>
<td>Methyl tert-butyl ether</td>
<td>1.3 × 10⁻⁵</td>
<td>0.93</td>
<td>0.0592</td>
<td>2.24</td>
</tr>
<tr>
<td>Toluene</td>
<td>9.2 × 10⁻⁵</td>
<td>0.66</td>
<td>0.0509</td>
<td>1.93</td>
</tr>
<tr>
<td>Trifluorotoluene</td>
<td>1.3 × 10⁻⁵</td>
<td>0.93</td>
<td>0.0446</td>
<td>1.69</td>
</tr>
</tbody>
</table>

\( a \) Relative to the initiation rate in DCM. \( b \) Reported in ref. 26. \( c \) Contained 10% v/v chloroform-d₄ to enable a deuterium lock.

1 was DCM > (benzene ≈ toluene). Metathesis reactions are often conducted in solvents such as DCM or toluene, and DCM has become the default solvent for laboratory scale synthetic applications. It is far from ideal for use on a large scale due to safety, toxicity and environmental concerns whereas MTBE and dimethyl carbonate are not only more industrially acceptable solvents but also support initiation at similar rates to DCM. Notably, the slowest initiation rate was obtained in hexafluorobenzene, which has been reported to be a superior solvent for metathesis reactions (vide infra).\(^{13,14}\)

Initiation rate constants for pre-catalyst 2 were measured (Table 1) according to the published procedure;\(^{17}\) while Plenio et al. have reported non-linear plots of \( k_{\text{obs}} \) versus [substrate] in toluene, all of our plots, which cover the typical concentration range for metathesis (25–200 mmol L⁻¹), were linear.\(^{18}\) A modest (ca. 2-fold) spread of values covered chloroform to MTBE; this represented a range of \( \Delta \varepsilon \) values of only ca. 0.6 kcal mol⁻¹. The order of initiation rate constants for 2 amongst the most frequently used solvents was PhMe > PhH >> DCM and initiation rates in aromatic solvents are typically higher than those in most non-aromatic solvents. In contrast to the results for 1, the initiation rate constant of 2 in hexafluorobenzene is toward the higher end of the range obtained. The trends described here are entirely qualitative (for the PCA context of this work,\(^{19}\) see the ESI!) so we sought a way of correlating measured solvent parameters to initiation rates. Samołowicz et al. attempted to link metathesis performance and solvent dielectric constant\(^{14}\) after suggestions by Sanford et al. that there may be a relationship.\(^{16}\) However, no link could be established; plots of our initiation rates versus solvent dielectric constants\(^{20}\) are scattered and trendless (Fig. 1).

The concept of solvent polarity is a complex one, combining microscopic (such as hydrogen-bond donor or acceptor ability) and macroscopic (such as the dielectric constant) properties of a solvent.\(^{21}\) The \( E_\alpha(30) \) scale\(^{20}\) is based upon the wavelength of absorption of solvatochromatic dye 3 and has found applications in analytical chemistry (where it can be used to predict changes in retention time, and to measure solvent water content)\(^{22}\) and chemical kinetics (to predict changes in the rates of \( S_N2 \) reactions\(^{23}\) and ligand exchange processes\(^{24}\)). \( E_\alpha(30) \) values are available for all nine solvents in which we measured initiation rate constants;\(^{20}\) however, there was no trend at all for pre-catalyst 1 and only a scattered dependence with a negative slope for pre-catalyst 2 (Fig. 2).

The use of Kamlet–Taft–Abboud (TKA) solvatochromatic parameters was explored next;\(^{25}\) this approach was used previously by Adjiman et al.\(^{10}\) but with unreliable rate constants.\(^{26}\) Firstly, we treated the data with eqn (2) but found that poor correlations obtained. Parameters for use in the expanded correlation used by Adjiman are only available for five of the solvents studied here (benzene, chloroform, DCM, HFB and toluene), but all for diethyl carbonate and dimethyl carbonate and methyl tert-butyl ether are used to approximate dimethyl carbonate and methyl tert-butyl ether respectively.\(^{20}\) a linear regression can be performed (eqn (3), Table 2, Fig. 3). Unfortunately, parameters are not available for 1,2-difluorobenzene and trifluorotoluene.

\[
\log_{10}(k) = Aa + Bb + C\pi^* + D
\]

(2)

\[
\log_{10}(k) = Aa + Bb + C\pi^* + D\delta + E(\delta H)^2 + F
\]

(3)
From the coefficients (particularly \(B\) and \(C\)), it appears that the differences in the solvent effects on \(1\) and \(2\) initiation are due to significantly different dependencies on \(\beta\) and \(\pi^*\); \(1\) initiates faster in solvents with a high polarisability and low hydrogen bond donor ability, while for \(2\), these parameters have a much lower influence. Clearly, solvent effects on the initiation of \(2\) are far smaller than those on the initiation of \(1\). These values may also be useful predictively; initiation rate constants of \(2.1 \times 10^{-3}\) s\(^{-1}\) for \(1\) and \(0.039\) L mol\(^{-1}\) s\(^{-1}\) for \(2\) can be calculated in 1,2-dichloroethane, a popular solvent in the synthetic laboratory. This solvent not only offers an extended temperature range over DCM but may also have a higher intrinsic ability to support phosphane dissociation. Adjiman et al. proposed that acetic acid is a particularly effective solvent for metathesis reactions, and has some attractive features for scale-up.\(^{27}\) While vinyl ether and acetic acid are incompatible chemically, preventing the measurement of the initiation rate, the values in Table 2 would predict slow initiation of \(1\) and \(2\), with rate constants of \(1.0 \times 10^{-5}\) s\(^{-1}\) and 0.004 L mol\(^{-1}\) s\(^{-1}\) respectively. This suggests strongly that the successful preparative reaction of diethyl diallylmalonate described by Adjiman et al. is not due to rapid initiation of \(1\). Slow initiation of both pre-catalysts would also be predicted in acetone and ethyl acetate.

There is a consensus that the initiation mechanism of \(1\) involves phosphane dissociation;\(^{16}\) the alkylidene rotates as the Ru⋯P distances increase, according to recent work by Jensen et al.\(^{28}\) The dissociative mechanism for \(2\), for which there is experimental and computational support,\(^{18,29}\) also involves an alkylidene rotation coupled with an extending Ru⋯O distance. The interchange mechanism supported by our computational work\(^{17}\) and also by Plenio’s experimental data,\(^{18}\) is earlier with respect to the Ru⋯O extension, and includes the approach of an alkene molecule towards the Ru centre (EVE in the case of initiation) and some sharing of alkene electron density with the Ru centre. The three types of transition states have different shapes, volumes and polarities so it is not surprising that there is no simple relationship between dielectric constant or \(E_\text{T}(30)\) for either pre-catalyst, and that multi-parameter approaches are required.

The accurate accounting of solvent effects requires that both specific solvation and more continuum-based effects are represented in any model and the KTA empirical approach offers the prospect of revealing these effects. We are not aware of any organometallic reactions to which the approach has been applied so our findings represent a novel use of the methodology. In a more \textit{a priori} approach, Samojłowicz et al. studied the effects of solvent on metathesis reactions;\(^{14}\) the authors noted that the yields of many RCM reactions (with pre-catalysts including \(1\) and \(2\)) were highest in perfluoromeric solvents, followed by aromatic hydrocarbon solvents, followed in turn by chlorinated aliphatic solvents. The authors argued that the facile dissociation/oxidation reaction of the phosphane ligand in \(\text{C}_\text{F}_\text{F}_6\) would allow faster and irreversible formation of catalytically active 14-electron species, which could subsequently be stabilised by \(\pi\)-stacking interactions between solvent molecules and the aryl groups of the NH ligand. Our measured initiation rates are not consistent with faster initiation in the perfluoroarene solvent studied; initiation reactivity decreases in the order DCM ≈ toluene ≈ benzene > hexafluorobenzene for \(1\), though initiation is faster in HFB for \(2\). The differences in rates are relatively modest but even these small rate differences could cause quite large perturbations in reaction yields. Perfluorination is known to increase the solubility of oxygen in solvents; for example, oxygen is approximately twice as soluble in HFB as in benzene itself\(^{10}\) so catalyst decomposition \textit{via} oxidation should be faster in HFB. Grela showed that \(1\) decomposed more rapidly in a mixture of HFB and 1,2-DCE than in 1,2-DCE alone, consistent with this view. In contrast, pre-catalyst \(4\) (known as Umicore M2) was less air sensitive in HFB than in toluene; pre-catalysts of this type are highly robust and typically initiate much more slowly\(^{31}\) than \(1\) or \(2\), so comparisons between the systems may be unsafe, but these contrasting findings do suggest that we need to improve our understanding of pre-catalyst and catalyst concentration behaviour throughout the duration of reactions in addition to quantifying the initiation event accurately.

![Graph](Image)

### Table 2

Results of linear regression for \(1\) and \(2\) initiation rate constants in benzene, chloroform, dichloromethane, diethyl carbonate (for dimethyl carbonate), di-iso-propyl ether (for MTBE), hexafluorobenzene and toluene (see Table 1, eqn (3))

<table>
<thead>
<tr>
<th>Pre-catalyst</th>
<th>(A)</th>
<th>(B)</th>
<th>(C)</th>
<th>(D)</th>
<th>(10^3 E)</th>
<th>(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-0.924 \pm 0.0657)</td>
<td>(0.990 \pm 0.0727)</td>
<td>(1.88 \pm 0.0407)</td>
<td>(-0.170 \pm 0.0278)</td>
<td>(-1.26 \pm 0.118)</td>
<td>(-4.59 \pm 0.0508)</td>
</tr>
<tr>
<td>2</td>
<td>(-0.793 \pm 0.145)</td>
<td>(0.106 \pm 0.161)</td>
<td>(0.0993 \pm 0.0899)</td>
<td>(0.0487 \pm 0.0614)</td>
<td>(-1.13 \pm 0.261)</td>
<td>(-1.04 \pm 0.112)</td>
</tr>
</tbody>
</table>
Conclusions

In conclusion, we have presented accurately measured initiation rate constants for pre-catalysts 1 and 2 in a range of commonly-used solvents. These initiation rates could be used in reaction simulation studies of alkene metathesis, to simulate concentration/time profiles in different solvents. MTBE and dimethyl carbonate, which are much more sustainable solvents, offer faster pre-catalyst initiation than default laboratory solvent DCM. The lack of even a qualitative link between solvent dielectric constant and initiation rate shows that this quantity cannot be used to predict pre-catalyst initiation rates; a KTA solvatochromic treatment has greater potential for this purpose. Further data in a wider variety of solvents, plus a better understanding of how to model the catalyst decomposition event, are required before more concrete conclusions about solvent effects can be made.

Notes and references