First determination of the rate acceleration of a palladium-catalysed coupling reaction by use of high pressure

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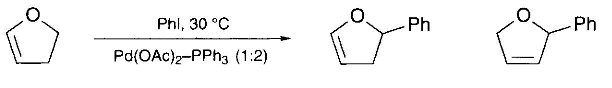
The activation volume, $\Delta V^\ddagger$, reflecting the rate acceleration by pressure, of the coupling reaction between 2,3-dihydrofuran and iodobenzene is determined as -12 ± 2 cm^{-3} by kinetic measurements at pressures between 1 bar and 8 kbar; moreover, our kinetic data suggest that the rate-determining step is not the oxidative addition of iodobenzene to the palladium catalyst.

High pressure in liquid phases has been traditionally used to accelerate organic reactions.[1–3] Pressure can be expected to cause a rate enhancement when the activation volume, $\Delta V^\ddagger$, *i.e.* the difference of the volume of the transition state and the starting materials, is < 0. This can be easily understood to be the case in addition reactions, and probably best known is the application of pressure in Diels–Alder reactions.

A transition–metal catalysed process typically consists of a number of reaction steps, consequently, to predict the net effect of pressure in such a reaction is difficult. High-pressure organometallic chemistry has not been widely studied so far,[4] but very recently there have been some accounts on palladium catalysed reactions in this context.[5–8] While qualitatively an acceleration by pressure in Heck type reactions has been observed,[6,7] in Pd-catalysed [3 + 2] cycloadditions, pressure caused a rate decrease.[8] To gain more specific insights about the role of pressure in transition-metal catalysed reactions, we have for the first time determined the volume of activation of such a process. As a model we have chosen the palladium-catalysed cross-coupling of iodobenzene and 2,3-dihydrofuran **1**,[9,10] which has attracted considerable interest over recent years since it offers the possibility of carrying out this reaction asymmetrically,[11,12] as well as providing an indirect access to acetate[13] and antialdol products.[14]

Initially, we tried to monitor the reaction under pressure directly by IR or UV spectroscopy, however, the changes in absorbance between starting materials and products proved to be insufficient. Therefore, all kinetic measurements under pressure had to be carried out in separate runs, monitoring the consumption of iodobenzene and the formation of **2** and **3** by GC analysis.†



1 **2** (4:1) **3**

Fig. 1 shows the kinetic data obtained for reactions carried out at 30.0 °C at various pressures. Using a catalyst formed from Pd(OAc)$_2$–PPh$_3$ (1 : 2), a mixture of **2** and **3** (3–4 : 1) is formed. The ratio of the regioisomers showed erratic behaviour (ranging from 73 : 27 to 81 : 19), but was independent of the pressure applied. The following analysis is proposed in terms of consumption of starting material, which leads to the same results as the analysis for the formation of **2** or **3**.

The reaction is not greatly but is still significantly accelerated by pressure, showing a 23-fold rate increase from 1 bar to 8 kbar. Plotting ln k *vs.* p gives a typical curve expected in kinetics of Diels–Alder reactions under pressure[15] with a linear dependence in the low-pressure region which levels off at higher pressures as the increased viscosity of the solvent becomes important in determining the rate of reaction (Fig. 2). From these data, the activation volume is determined to be $\Delta V^\ddagger = -12 \pm 2$ cm^{-3}, which is not as high as for Diels–Alder reactions (typically $\Delta V^\ddagger = -25$ to -45 cm^{-3}), but nevertheless indicates the potential benefits of pressure in transition-metal catalysed reactions.

To predict which reaction steps are accelerated by pressure to account for the overall rate enhancement is difficult. So far it has been postulated that oxidative additions and complexation

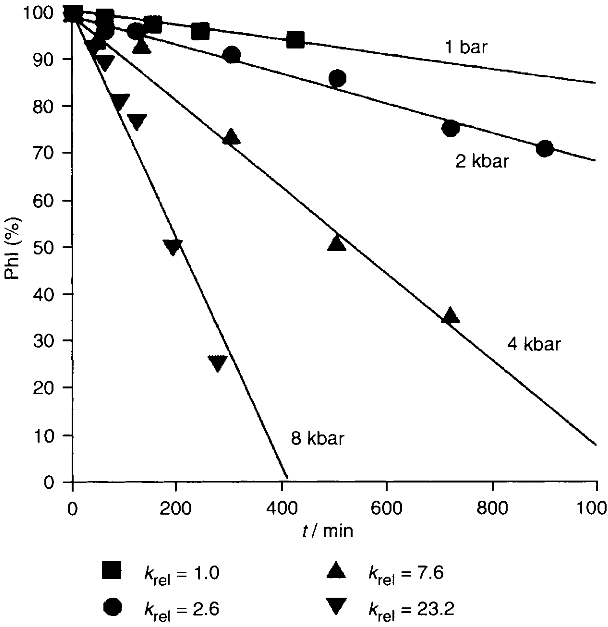


Fig. 1 Effect of pressure upon the reaction of PhI with **1**

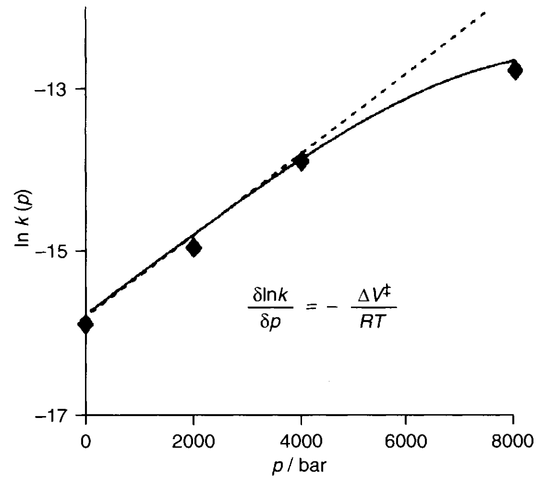
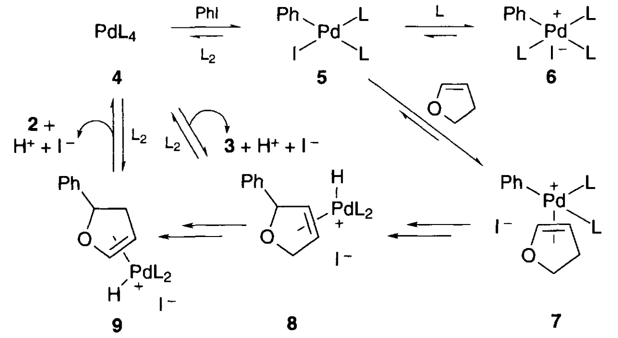


Fig. 2 ln$k(p)$ = $a + bp + cp^2$ with $\Delta V^\ddagger = -bRT$

are favoured, while elimination and decomplexation reactions are disfavoured and insertion, migration and deinsertion are independent of pressure.[7] In general, oxidative addition of aryl halide to the palladium centre is considered to be the rate-determining step in the Heck reaction,[16] although different conclusions have also been drawn.[17] As can be seen from Fig. 1, the rate of the coupling reaction investigated here is independent of the concentration of iodobenzene, revealing that the rate-determining step cannot be the formation of **5** by oxidative addition of iodobenzene to the palladium catalyst **4** (Scheme 1). Consequently it must be concluded that the oxidative addition step is not accelerated by pressure. Reactions can also be accelerated by pressure if ions are formed; such processes can have activation volumes of up to -100 cm^3 mol^{-1}.[18] Therefore, displacement of the halide in **5** by a neutral ligand leading to **6** or directly to **7** should be favoured by increased pressure due to electrostrictive effects.[19] Moreover, ligand exchange (*e.g.* **6**→**7**) in organometallic complexes has been shown to proceed by an associative substitution made in many cases, which is generally accelerated by pressure.[20] A series of intramolecular insertion steps and migration steps occur leading mainly to the thermodynamically favoured complex **9** which should not be influenced by pressure (*cf.* ref. 7). In agreement with this analysis we found that the regioisomeric ratio of **2** and **3** is independent of pressure at low triphenylphosphine concentrations. Most difficult is the analysis for the decomplexation of **8** or **9**. It is not clear at all that such a reaction step should be disfavoured by increased pressure (*cf.* ref. 7) since the decomplexation most likely takes place by a ligand displacement, *e.g.* by the solvent, occurring through an associative mechanism.[21] Finally, the liberation of H^+I^- should be greatly enhanced by pressure.

In conclusion, we have demonstraterd quantitatively that high pressures can accelerate a transition-metal catalysed reaction. Further investigations into the generality of this effect are under way.



Scheme 1

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Footnote

† All samples were prepared simultaneously and subsequently deep frozen in liquid air prior to use: to a solution of iodobenzene (0.2 mmol), 2,3-dihydrofuran (2 mmol), triethylamine (0.6 mmol) in 1.5 ml thf–MeCN (1 : 1) was added a catalyst solution of $Pd(OAc)_2$ (3 mol%) and PPh_3 (6 mol%) in 1 ml thf–MeCN (1 : 1), which was previously heated to 50 °C for 10 min. Sum of iodobenzene, **2** + **3** >99% (GC, pentamethylbenzene as internal standard), linear correlation coefficient for the consumption of iodobenzene >0.98 for all pressures. 10^7k l mol^{-1} s^{-1}: 1 bar, 1.34; 2 kbar, 3.47; 4 kbar, 10.2; 8 kbar, 31.1.

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