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Flash Generation of a Highly Reactive Pd Catalyst for Suzuki–Miyaura Coupling by Using a Flow Microreactor

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Recently, we proposed the concept of flash chemistry,[1] in which extremely fast reactions are conducted in a controlled manner by using flow microreactors;[2–4] unstable reactive species are generated quickly and are used in a subsequent reaction before they decompose by virtue of their short residence time.[5] Herein, we show an application of flash chemistry in catalyst generation. A highly reactive short-lived catalyst precursor is generated by using a flow microreactor in the absence of substrates, and it is transferred, before it decomposes, to a reaction vessel, in which a catalytic reaction is conducted. The concept has been successfully applied to the generation of an extremely efficient Pd catalyst for Suzuki–Miyaura coupling.[6–7]

It is known that generation of monoligated [Pd^{0}L] species (L = phosphine ligand) plays an important role in the Suzuki–Miyaura coupling reactions, because coordinatively unsaturated [Pd^{0}L] species are highly reactive towards oxidative addition of aryl halides (ArX) to produce [Pd(Ar)X(L)], a key intermediate in the coupling.[8] However, [Pd^{0}L] is highly unstable, and its generation at high concentrations is very difficult. We envisioned that the flash method involving 1:1 mixing of Pd^{II} and L in flow microreactor enables the generation of unstable monoligated [Pd^{II}L] species as a precursor at high concentrations in the absence of coupling substrates. In the next step, [Pd^{II}L] species is transferred, before it decomposes, to a reaction vessel for coupling reactions, in which it may be reduced to give highly reactive [Pd^{0}L].

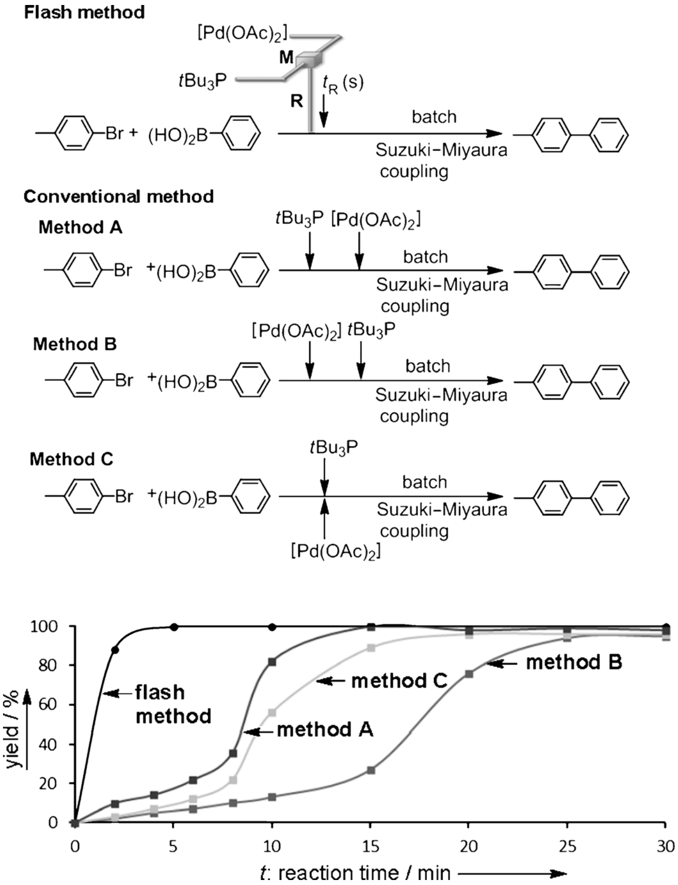

Figure 1. Suzuki–Miyaura coupling of *p*-bromotoluene and phenylboronic acid in the presence of KOH catalyzed by [Pd(OAc)$_2$]–*t*Bu$_3$P. Flash method: solutions of [Pd(OAc)$_2$] (1 mol%) and *t*Bu$_3$P (1 mol%) were introduced to micromixer (M) and microtube reactor (R; residence time: $t_R = 0.65$ s), and the resulting solution was dropped into a vessel, in which the coupling reaction was conducted. Conventional method A: a solution of *t*Bu$_3$P (1 mol%) was added to a reaction vessel. After 10 s, a solution of [Pd(OAc)$_2$] (1 mol%) was added. Conventional method B: a solution of [Pd(OAc)$_2$] (1 mol%) was added to a reaction vessel. After 10 s, a solution of *t*Bu$_3$P (1 mol%) was added. Conventional method C: a solution of [Pd(OAc)$_2$] (1 mol%) and a solution of *t*Bu$_3$P (1 mol%) were simultaneously added to a reaction vessel. Progress of the coupling reaction was monitored by GC analysis.

We chose to use tri-*tert*-butylphosphine (*t*Bu$_3$P), which is one of the most powerful phosphine ligands.[9] A catalyst was prepared by using a flow microreactor system[10] at room temperature (flash method, Figure 1). A solution of [Pd(OAc)$_2$] (2.67 mM) in THF and that of *t*Bu$_3$P (2.67 mM) in THF were introduced to a T-shaped micromixer (M) (inner diameter 250 μm) by syringe pumps (flow rate of both solutions 4.5 mL min^{-1}). The resulting solution was passed through a microtube reactor (R; inner diameter 500 μm, length 50 cm, residence time $t_R = 0.65$ s). After a steady state was reached, the resulting solution was dropped into a 20 mL vessel (1.5 mL) containing a solution of *p*-bromotoluene (0.200 mol), phenylboronic acid (0.240 mmol), and potassium hydroxide (0.256 mmol) in THF/H$_2$O (4.25 mL; 2.25:2) for 10 s. After addition was complete, the

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mixture in the reaction vessel was stirred at 24 °C. The progress of the coupling reaction was monitored by GC.

For comparison, three conventional methods were examined (Figure 1). In method A, a solution of tBu$_3$P in THF (2.67 mM, 0.75 mL) was added to a reaction vessel, and after 10 s, a solution of [Pd(OAc)$_2$] in THF (2.67 mM, 0.75 mL) was added. In method B, a solution of [Pd(OAc)$_2$] was added, and after 10 s, a solution of tBu$_3$P was added. In method C, both solutions were added simultaneously to a reaction vessel (10 s). In all cases, 1 mol % of [Pd(OAc)$_2$] and 1 mol % of tBu$_3$P based on p-bromotoluene were introduced to the reaction vessel. Notably, the catalytic activity strongly depends on the way of addition of [Pd(OAc)$_2$] and tBu$_3$P. As shown in Figure 1, the reaction was complete within 5 min in the case of the flash method. However, in all conventional methods, the reaction took much longer time to reach completion. The extremely high reactivity observed for the catalyst generated by the flash method seems to be attributed to the quick generation of a highly unstable reactive catalyst precursor by fast micromixing of [Pd(OAc)$_2$] and tBu$_3$P in the absence of coupling substrates and potassium hydroxide, and its transfer to the reaction vessel before it decomposes by virtue of the short residence time in the flow system.[11]

The importance of the residence time in the flash method is also noteworthy as shown in Figure 2. The rate of the coupling reaction increases with an increase in the residence time in the microtube reactor ($t_R < 0.33$ s), presumably because of the progress of the formation of an effective catalyst precursor. However, further increase in t_R causes a decrease in the rate of the coupling, presumably because of decomposition of the catalyst precursor.

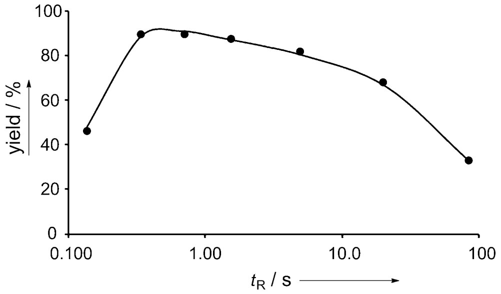

Figure 2. Effect of the residence time (t_R) for preparing the catalyst from [Pd(OAc)$_2$] and tBu$_3$P. Plots of the yield of the coupling product (reaction time = 2 min) against t_R.

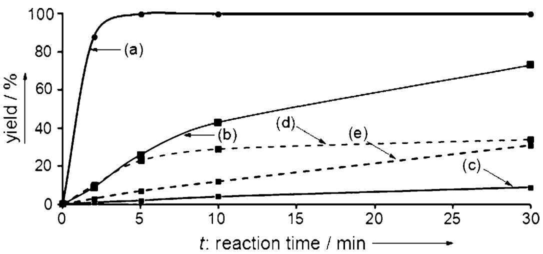

Figure 3. Comparison of the catalytic activity of [Pd–tBu$_3$P] complexes generated by various methods. a) Flash method: solutions of [Pd(OAc)$_2$] (1 mol %) and tBu$_3$P (1 mol %) were reacted in a flow microreactor, and then the resulting solution was introduced to a reaction vessel for the coupling reaction (t_R = 0.65 s). Conventional method: b) [Pd(tBu$_3$P)$_2$] (1 mol %). c) [Pd$_2$(dba)$_3$] (0.5 mol %) and tBu$_3$P (1 mol %) were mixed and the mixture was stirred for 2 h. The resulting solution was used for the coupling reaction. d) [(η^3-allyl)Pd(tBu$_3$P)Cl] (1 mol %). e) Palladacycle **2** (1 mol %).

To gain a deeper insight into the nature of the species generated by the flash method, its catalytic activity was compared with those of other Pd catalysts containing tBu$_3$P generated by the conventional method (Figure 3). Commercially available [Pd(tBu$_3$P)$_2$][12] was less active, presumably because coordination of two tBu$_3$P ligands reduces the catalytic activity (Figure 3 b). Therefore, we assume that a 1:1 complex of [Pd(OAc)$_2$] and tBu$_3$P (**1**) was generated by the flash method and that palladium(II) species **1** was reduced to monoligated palladium(0) species, that is, [Pd(tBu$_3$P)] in the reaction vessel.[13] A 1:1 mixture of [Pd$_2$(dba)$_3$] (dba = dibenzylideneacetone) and tBu$_3$P,[14] which may generate [Pd(tBu$_3$P)], was also less reactive than **1**, presumably because of the coordination of dba (Figure 3 c). π-Allyl palladium chloride with tBu$_3$P was also less reactive than **1** (Figure 3 d).

An in-line flow FTIR spectroscopic analysis[16] (ATR method) was performed to characterize **1** (see the Supporting Information for details). As shown in Figure 4, [Pd(OAc)$_2$] showed two strong IR bands at $\tilde{\nu}$ = 1429 and 1614 cm^{-1} that are assigned to the carboxylate ion. The IR spectrum of the species obtained by the flash method (t_R = 0.55 s) showed four major bands at $\tilde{\nu}$ = 1290, 1430, 1620, and

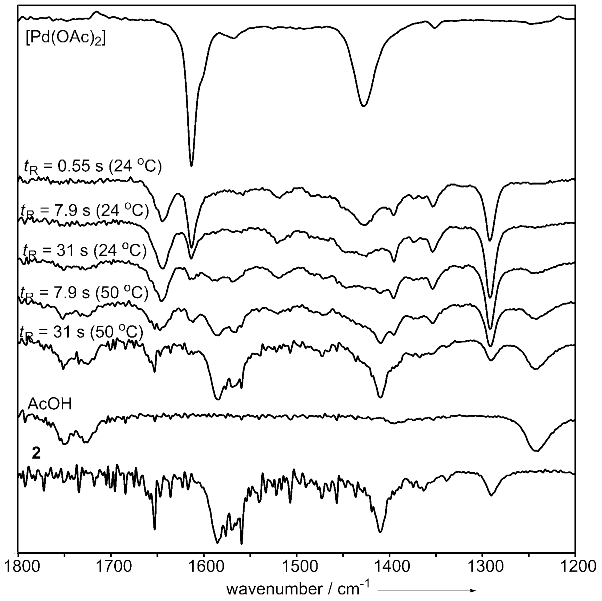

Figure 4. The in-line flow FTIR spectroscopic analysis. Solutions of [Pd(OAc)$_2$] and tBu$_3$P were mixed in a micromixer (M) and were allowed to react in a microtube reactor (R); the resulting solution was introduced to the in-line flow cell of the FTIR.

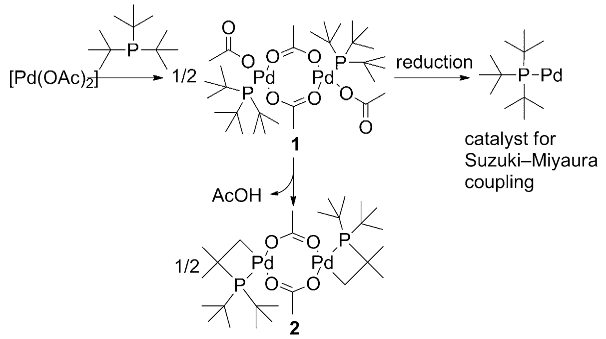

Figure 5. Generation of $[t\mathrm{Bu_3PPd^0}]_2$ (**1**) from $[\mathrm{Pd(OAc)_2}]$ and $t\mathrm{Bu_3P}$ and formation of palladacycle **2**.

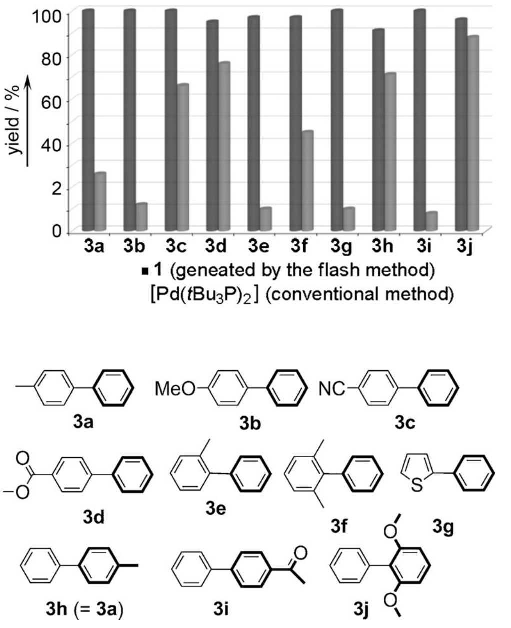

Figure 6. Comparison of the yields of the coupling products by using **1** generated by the flash method and those by using $[\mathrm{Pd}(t\mathrm{Bu_3P})_2]$ (conventional method). The aryl or heteroaryl groups derived from the corresponding boronic acids are indicated in bold line. The reactions were carried out at 24 °C for 5 min.

1640 $\mathrm{cm^{-1}}$, which are very similar to those reported for $[\mathrm{Pd(OAc)_2Ph_3P}]_2$ ($\tilde{\nu}=1314$, 1411, 1580, and 1629 $\mathrm{cm^{-1}}$) with both bridged and monodentate carboxylate groups.[17] Therefore, the formation of $[\mathrm{Pd(OAc)_2}t\mathrm{Bu_3P}]_2$ is strongly suggested (Figure 5). Further increase in t_R caused a decrease in the intensities of these bands and an increase in the intensity of other bands at $\tilde{\nu}=1550$–1600 $\mathrm{cm^{-1}}$, which seemed to indicate the formation of palladacycle **2** (Figure 5). In fact, the spectrum of the complex obtained at longer t_R at 50 °C looks very similar to that of **2**. The intensity of bands at $\tilde{\nu}=1720$–1750 and 1420 $\mathrm{cm^{-1}}$ also increased, indicating simultaneous formation of AcOH.

The present flash method enables the use of commercially available, less expensive, and air-stable $[\mathrm{Pd(OAc)_2}]$ to generate a highly reactive catalyst precursor. As stated above, the coordination of $t\mathrm{Bu_3P}$ to $[\mathrm{Pd(OAc)_2}]$ takes place in the microtube reactor to give $[\mathrm{Pd(OAc)_2}t\mathrm{Bu_3P}]_2$ (**1**). Compound **1** is quickly transferred to the reaction vessel before the formation of palladacycle **2** and then is reduced in the reaction vessel to give catalytically active monoligated palladium(0) species, $[\mathrm{Pd}(t\mathrm{Bu_3P})]$. However, prolonged residence time in the microtube led to the formation of palladacycle **2**,[15] which is less catalytically active as shown in Figure 3 e.

By using the optimized conditions for the flash generation of **1**, the Suzuki–Miyaura coupling reactions of several aryl halides with arylboronic acids were examined. As shown in Figure 6, the reactions were extremely fast even at room temperature, and the corresponding coupling products were obtained within 5 min in high yield. Notably, **1** was much more reactive than $[\mathrm{Pd}(t\mathrm{Bu_3P})_2]$ in all cases examined. The reaction can be performed at low catalyst loading. For example, the coupling of *p*-bromotoluene and phenylboronic acid gave the product in 95 % yield in 18 h at room temperature with 0.01 mol % of the catalyst.

Arylboronic acids that quickly undergo deboronation under basic conditions are challenging coupling partners for Suzuki–Miyaura reactions. For example, perfluorophenyl-, 2-furyl-, and 2-thienylboronic acids are known to decompose easily by deboronation under the standard conditions of Suzuki–Miyaura coupling.[18] Because the use of flash-generated **1** enables the reactions to proceed under much milder conditions (lower temperatures and shorter reaction time), we envisioned that the flash method would solve the problem. As shown in Figure 7, the coupling of 2-thienyl-, 2-furyl-, 2-benzothienyl-, 2-benzofuryl-, and 2,6-difluorophenylboronic acids with bromobenzene, *p*-methoxybromobenzene, and unprotected 5-bromoindole proceeded to give the corresponding coupling products in good yields.

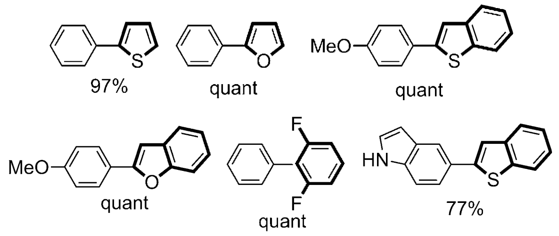

Figure 7. Coupling of aryl halides and arylboronic acids, which easily decompose under the standard conditions. The aryl or heteroaryl groups derived from the corresponding boronic acids are indicated in bold line. The reactions were complete within 5 min at 24 °C.

In summary, we found that fast 1:1 micromixing of $[\mathrm{Pd(OAc)_2}]$ and $t\mathrm{Bu_3P}$, and its quick transfer to the reaction vessel by using the flow system enabled the use of highly reactive unstable species as a catalyst precursor for Suzuki–Miyaura coupling. The coupling reactions could be complete within 5 min even at room temperature. Aryl- or heteroarylboronic acids, which quickly deboronate under basic conditions, could be also used as coupling partners, because the reactions can be conducted at lower temperatures and in a short time. The present observations open a new possibility for not only Suzuki–Miyaura coupling, but also other catalytic reactions. It is hoped that on-site on-demand generation of a catalyst or its precursor by using the flash method will greatly enhance the possibility of catalytic reactions.

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Keywords: cross-coupling · microreactors · Suzuki–Miyaura coupling · palladium

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Cross-Coupling

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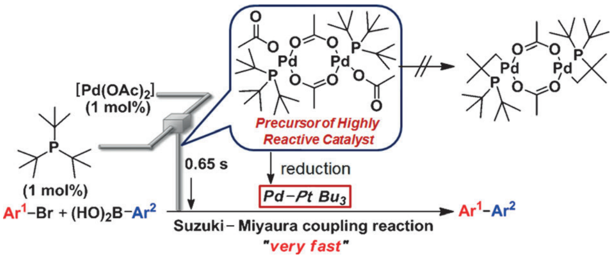
Flash Generation of a Highly Reactive Pd Catalyst for Suzuki–Miyaura Coupling by Using a Flow Microreactor



Superflash! The flash chemistry enables the use of highly reactive unstable species as catalysts for chemical synthesis. Fast micromixing of a solution of [Pd(OAc)$_2$] and that of tBu$_3$P in 1:1 mole ratio gave a solution of a highly reactive unstable species, which was immediately transferred to a vessel by using a flow microreactor, in which Suzuki–Miyaura coupling was conducted (see scheme).