# Supported ionic liquid catalyst (Pd-SILC) for highly efficient and recyclable Suzuki–Miyaura reaction

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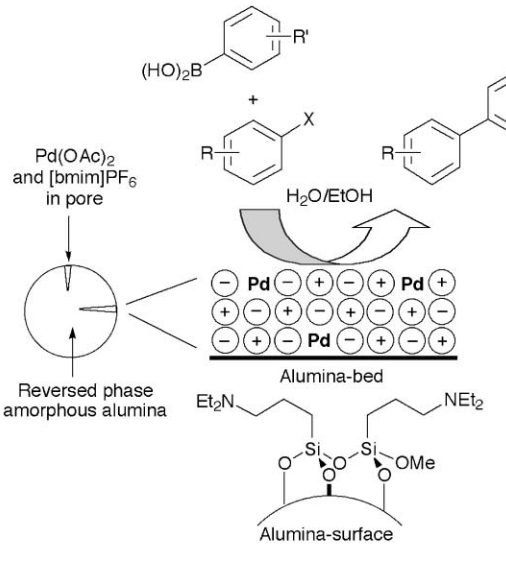
**Highly efficient Suzuki–Miyaura coupling of aryl halides with arylboronic acid was realized in 50% aqueous ethanol at room temperature employing $Pd(OAc)_2$ immobilized in diethylaminopropylated (NDEAP) alumina pores with the aid of $[bmim]PF_6$, which enabled recycle use up to five times in 95% average yield and turnover number of two million.**

The Suzuki–Miyaura reaction is one of the most powerful cross coupling reactions not only for various biaryls but also for arylolefinic compounds.[1] Owing to wide applicability towards a variety of substrates, the reaction has been applied to process chemistry, in which more mild, and efficient protocols are desired.[2] In designing such protocols, room-temperature ionic liquids have played important roles as a liquid support,[3] which gives stability and recyclability to the catalyst.[4] In order to improve the cost and handling of the catalyst in recycle use, the catalyst supported by an ionic liquid was further supported on a porous solid such as silica or molecular sieves.[5] The present paper describes highly efficient Suzuki–Miyaura reaction in 50% ethanol catalysed by immobilized $Pd(OAc)_2$ on reversed phase alumina with the aid of an ionic liquid (Pd-SILC) (Scheme 1).



Scheme 1 Suzuki–Miyaura reaction catalyzed by immobilized Pd catalyst on reversed phase alumina.

Immobilization of $Pd(OAc)_2$ on amorphous silica or alumina with the aid of an ionic liquid was carried out in the same manner as described previously.[5d] Since the choice of solvent was very important, we focused initially on the effect of solvent in the coupling reaction of *p*-bromoacetophenone with phenylboronic acid, and the results of investigations are shown in Table 1. In entries 1–5 and 8–10, a large amount of *p*-bromoacetophenone was recovered. However, we happened to find that the reaction occurred essentially instantaneously in 50% aqueous ethanol[6] as shown in entries 11 and 12, in which the ethanol : water ratio was critical for rapid reaction. A larger amount of ethanol slowed down the reaction (entries 7, 13 and 14). On the other hand, a higher water content caused separation of the ionic liquid layer from the alumina (entry 15).

Since the reaction of *p*-bromoacetophenone with phenylboronic acid was so promising in 50% aqueous ethanol, the reaction of *p*-bromoanisole was employed as a probe to tune further reaction conditions.

An optimum support for $Pd(OAc)_2$ was investigated in 50% aqueous ethanol and the results are shown in Table 2. Silica grafted octyltrimethoxysilane did not immobilize $Pd(OAc)_2$ even with ionic liquid.[5e,7] Thus, surfaces of silica and alumina were grafted with amino groups, and their capability as reversed phase

**Table 1** Solvent effect in the reaction of *p*-bromoacetophenone with phenylboronic acid

| Entry[a] | Solvent | Time/min | Yield[b] (%) |
|---|---|---|---|
| 1[c,f] | $Et_2O$ | 100 | 0 |
| 2[c] | $CH_3CN$ | 90 | 43 |
| 3[c] | DMF | 90 | 55 |
| 4[c] | AcOEt | 90 | 61 |
| 5[c] | Acetone | 90 | 67 |
| 6[c,f] | PEG | 180 | 100 |
| 7[c,f] | EtOH | 90 | 100 |
| 8[d] | THF–$H_2O$ (1 : 1) | 180 | 38 |
| 9[d] | PEG–$H_2O$ (1 : 1) | 180 | 43 |
| 10[d,g] | *t*-BuOH–$H_2O$ (1 : 1) | 180 | 55 |
| 11[c] | EtOH–$H_2O$ (1 : 1) | <1 | 100 |
| 12[c] | EtOH–$H_2O$ (1 : 1) | <1 | 100 |
| 13[e] | EtOH–$H_2O$ (3 : 1) | 180 | 77 |
| 14[e] | EtOH–$H_2O$ (22 : 1) | 180 | 53 |
| 15[e,h] | EtOH–$H_2O$ (1 : 3) | 10 | — |

[a] Reaction was carried out at room temperature with two equivalents of potassium carbonate employing 0.05 equivalents of $Pd(OAc)_2$ immobilized on solid support with the aid of $[bmim]PF_6$. [b] Yield is for isolated pure product and based on *p*-bromoacetophenone. [c] 0.25–0.3 mmol of Pd/g of $SiO_2$ was used as catalyst. [d] 0.02–0.025 mmol of Pd/g of $Al_2O_3$ was used as catalyst. [e] 0.25–0.3 mmol of Pd/g of $Al_2O_3$ was used as catalyst. [f] Pd was reduced before the reaction by refluxing in *n*-hexane. [g] Reaction was carried out at 50 °C. [h] Leaching of ionic liquid layer occurred.

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**Table 2** Examination of optimum support for $Pd(OAc)_2$ in the reaction of *p*-bromoanisole and phenylboronic acid

| Entry[a] | Support | Yield[b] (%) |
|---|---|---|
| 1 | Polyimino-$SiO_2$ | 3 |
| 2 | Ethylenediamino-$SiO_2$ | 24 |
| 3 | NDEAP-$SiO_2$[c] | 64 |
| 4 | NDEAP-$Al_2O_3$ | 83 |
| 5 | [bmim]$PF_6$-NDEAP-$SiO_2$ | 83 |
| 6 | [bmim]$PF_6$-NDEAP-$Al_2O_3$ | 83 |
| 7 | [bmim]$NTf_2$-NDEAP-$Al_2O_3$ | 75 |

[a] Reaction was carried out at room temperature for 3 h in EtOH–$H_2O$ (1 : 1); Pd loading was 0.29 mmol $g^{-1}$. [b] Yield is for isolated pure product and based on *p*-bromoanisole. [c] NDEAP = *N*,*N*-diethylaminopropylated

solid supports was examined. In entries 1 and 2, $Pd(OAc)_2$ was not reduced to Pd(0) and thus a large amount of *p*-bromoanisole was recovered. While $Pd(OAc)_2$ immobilized on *N*,*N*-diethylaminopropylated alumina or silica with or without [bmim]$PF_6$ gave the best results (entries 4–6), immobilization with the aid of an ionic liquid was desirable especially to inhibit leaching of $Pd(OAc)_2$ in recycle use.[5b] Among solid supports, alumina was preferable due to its stability towards aqueous basic reaction conditions (entries 5 and 6). [Bmim]$PF_6$ was superior to [bmim]$NTf_2$ (entries 6 and 7).

de Vries and Reetz reported that low Pd loading (0.01–0.1 mol%) was more effective for homogeneous catalytic reaction, since aggregation of Pd nanoparticles into less reactive clusters could be prevented.[8] Actually, $Pd(OAc)_2$ at low concentration in silica pores exhibited higher reactivity in our previous Mizoroki–Heck reaction in water.[5e] To this end, an immobilized catalyst of low concentration (0.020–0.025 mmol $g^{-1}$ of alumina) was used for further reactions. Actually, leaching of $Pd(OAc)_2$ was observed in the reaction of higher loading catalyst (0.25–0.3 mmol $g^{-1}$) in aqueous ethanol.

The other parameter is the choice of a base. After screening several different bases, it was found that the reaction was dependent on base, among which two equivalents of potassium carbonate was optimum as shown in Table 3, entry 6. The efficiency of potassium carbonate is yet to be discussed.

Based on the optimized reaction conditions (Table 3, entry 6),[9] the Suzuki–Miyaura coupling of a variety of aryl halides with arylboronic acid was investigated and the results are shown in Table 4. Aryl halides having both electron withdrawing and donating substituents provided the coupling products in satisfactory yields (entries 1–4). The electronic nature of the arylboronic acid also did not affect the efficiency of the reaction (entries 5 and 6).

**Table 3** Effect of base in the reaction of *p*-bromoanisole and phenylboronic acid

| Entry[a] | Base | Amount (equiv.) | Yield[b] (%) |
|---|---|---|---|
| 1 | $Na_2CO_3$ | 2 | 39 |
| 2 | $K_3PO_4$ | 2 | 46 |
| 3 | $Cs_2CO_3$ | 2 | 58 |
| 4[c] | DBU | 1 | 77 |
| 5 | $K_2CO_3$ | 1 | 37 |
| 6 | $K_2CO_3$ | 2 | 83 |
| 7 | $K_2CO_3$ | 3 | 40 |

[a] Reaction was carried out at room temperature for 3 h in EtOH–$H_2O$ (1 : 1). Pd loading on [bmim]$PF_6$–NDEAP–$Al_2O_3$ was 0.020–0.025 mmol $g^{-1}$. [b] Yield is for isolated pure product and based on *p*-bromoanisole. [c] Leaching of ionic liquid layer occurred.

**Table 4** Coupling of a variety of aryl halides with phenylboronic acids

| Entry[a] | Aryl halide and arylboronic acid | Time/min | Yield[b] (%) |
|---|---|---|---|
| 1 | R = *p*-Ac, X = Br, R′ = H | 1 | 100 |
| 2 | R = *p*-$NO_2$, X = Br, R′ = H | 60 | 92 |
| 3 | R = *p*-MeO, X = Br, R′ = H | 180 | 83 |
| 4 | R = *p*-Me, X = Br, R′ = H | 100 | 61 |
| 5 | R = *p*-Ac, X = Br, R′ = *p*-MeO | 15 | 98 |
| 6 | R = *p*-Ac, X = Br, R′ = *p*-Ac | 10 | 96 |
| 7 | R = *p*-Ac, X = I, R′ = H | 40 | 97 |
| 8 | R = *p*-MeO, X = I, R′ = H | 15 | 78 |
| 9 | R = *p*-Cl, X = Br, R′ = H | 30 | 93 |
| 10 | R = *p*-$EtO_2C$, X = Br, R′ = H | 240 | 100 |
| 11 | R = *p*-$HO_2C$, X = Br, R′ = H | 180 | 84 |
| 12[c] | 3-Bromopyridine, R′ = H | 30 | 92 |

[a] Reaction was carried out under the optimized reaction conditions as described in ref. 9 employing low loading Pd catalyst (0.020–0.025 mmol $g^{-1}$). [b] Yield is for isolated pure product and based on aryl halide. Purity of the product was determined by NMR spectroscopy. [c] Reaction was carried out under microwave heating at 75 °C.

The catalyst was re-used up to five times in 95% average yield, though catalytic activity gradually was lost during recycle use (Table 5).

**Table 5** Recycle of the catalyst in the reaction of *p*-bromoacetophenone and phenylboronic acid

| Entry | Time/min | Yield[a] (%) |
|---|---|---|
| 1 | <1 | 100 |
| 2 | 2 | 90 |
| 3 | 15 | 92 |
| 4 | 45 | 96 |
| 5 | 60 | 97 |

[a] Yield is for isolated pure product and based on *p*-bromoacetophenone.

High efficiency of the present catalytic system was exemplified by a remarkably high turnover number of 2 million and high turnover frequency of 30 thousand (Table 6, entry 5).[10] For each reaction, a new flask was employed to avoid the possibility of Suzuki–Miyaura reaction catalyzed by Pd contamination.[11]

**Table 6** Performance of the catalyst in the reaction of *p*-bromoacetophenone and phenylboronic acid[a]

| Entry | Catalyst (eq.) | Time | Yield (%) | TON | TOF/$h^{-1}$ |
|---|---|---|---|---|---|
| 1 | $4 \times 10^{-3}$ | 5 min | 100 | 250 | $3 \times 10^{3}$ |
| 2 | $5 \times 10^{-4}$ | 30 min | 100 | $2 \times 10^{3}$ | $4 \times 10^{3}$ |
| 3 | $5 \times 10^{-5}$ | 30 min | 100 | $2 \times 10^{4}$ | $4 \times 10^{4}$ |
| 4 | $5 \times 10^{-6}$ | 11 h | 100 | $2 \times 10^{5}$ | $2 \times 10^{4}$ |
| 5 | $5 \times 10^{-7}$ | 70 h | 98 | $2 \times 10^{6}$ | $3 \times 10^{4}$ |

[a] A new reaction vessel was employed for each run.

In summary, we have developed highly efficient Suzuki–Miyaura coupling of aryl halides with arylboronic acids in 50% aqueous ethanol employing $Pd(OAc)_2$ immobilized in NDEAP-alumina pores with the aid of an ionic liquid, [bmim]$PF_6$. The reaction proceeded without a phosphine ligand at room temperature in a short period of time. The immobilized catalyst was re-used up to five times in 95% average yield. The highest turnover number of two million exemplified high efficiency of the protocol.

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