

Palladium Catalyzed Suzuki Cross-coupling Reaction in Molten Tetra-*n*-butylammonium Bromide

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A practical procedure for palladium catalyzed Suzuki cross-coupling reaction of arylboronic acids with aryl halides, including aryl chlorides in molten tetra-*n*-butylammonium bromide (TBAB) was developed. The reaction exhibits high efficiency and functional group tolerance. The recovery of the catalyst and molten *n*-Bu₄NBr was also investigated.

Keywords palladium, tetra-*n*-butylammonium bromide, arylboronic acids, Suzuki coupling, biaryl

Introduction

The Suzuki cross-coupling reaction¹ has become an important synthetic method for carbon-carbon bond formation utilizing aryl or alkenyl boronic acids and aryl or alkenyl halides. Recently, application of the reaction to alkyl-alkyl² coupling and perfluoroalkyl-aryl³ coupling has expanded its scope considerably. Ma *et al.*⁴ developed a general route to synthesize 4-aryl-2(5*H*)-furanones using the Suzuki coupling of 4-halo-2(5*H*)-furanones and arylboronic acids. However, some problems are still incurred with the reaction. For example, the reaction generally employs expensive substrates such as aryl iodides or bromides as well as expensive palladium complex catalysts. Both the manipulation and recovery of the catalysts were of difficulty. Considerable efforts have been made to modify the performance in various directions. A number of catalysts have been developed which promoted the Suzuki coupling of aryl chlorides with arylboronic acids.⁵

Over the past few years, ionic liquids and molten salts have become an efficient solution for catalyst separation and recycling in many metal-catalyzed reactions.⁶ The Suzuki cross-coupling reaction involving the use of ionic liquids like imidazolium⁷ ionic liquids and phosphonium⁸ salt ionic liquids can be conducted under mild conditions. However, it has been reported that one potential disadvantage of using ionic liquids containing the counter ion of PF₆⁻ or BF₄⁻ is that they react with traces of water to give species such as O₂PF₂⁻ and the very highly reactive and corrosive HF, which destroy the catalyst.⁹

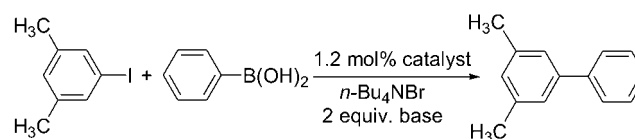
A literature survey exhibits that a few organic reactions have been carried out in more readily available quaternary ammonium salts with high melting point such as tetra-*n*-butylammonium bromide, which has

been widely used as a phase transfer catalyst in many organic reactions. Muzart *et al.*¹⁰ successfully employed molten *n*-Bu₄NBr without water as solvents in palladium chloride catalyzed oxidation of alcohols. In recent years, several palladium catalysts have been successfully used for the Heck reaction in molten *n*-Bu₄NBr.¹¹ On the other hand, *n*-Bu₄NBr was an important additive in "ligandless" palladium catalyzed Suzuki cross-coupling reactions.¹² This leads us to envisage the Suzuki cross-coupling reaction using palladium complexes as catalyst in molten *n*-Bu₄NBr medium.

Results and discussion

Our initial studies involved the coupling of phenylboronic acid with 5-iodo-*m*-xylene in the presence of 1.2 mol% of palladium species under different conditions. The results are summarized in Table 1.

Table 1 Suzuki cross-coupling reaction of 5-iodo-*m*-xylene with phenylboronic acid in molten *n*-Bu₄NBr



Entry	Catalyst	Base	Reaction time/min	Yield ^a /%
1	Pd(PPh ₃) ₄	K ₂ CO ₃ (aq.)	10	81
2	Pd(PPh ₃) ₄	None	240	0
3	Pd(PPh ₃) ₄	K ₂ CO ₃	240	0
4	Pd(PPh ₃) ₂ Cl ₂	K ₂ CO ₃ (aq.)	10	53
5	Pd(OAc) ₂	K ₂ CO ₃ (aq.)	10	60
6	Pd black	K ₂ CO ₃ (aq.)	10	37

^a Isolated yield determined by ¹H NMR (500 MHz).

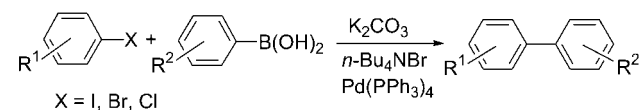
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It was found that using 1.2 mol% of Pd(PPh₃)₄ as catalyst and two equivalents of aq. K₂CO₃ as base in molten *n*-Bu₄NBr, 3,5-dimethylbiphenyl was obtained in 81% yield after 10 min heating at 120 °C (Table 1, Entry 1). Notably, addition of base and water to the reaction mixture was obligatory in this method. Without base (Table 1, Entry 2) or water (Table 1, Entry 3), the reaction did not occur. This suggests that water plays an important role for solubility of base and for removal of the by-products KHCO₃ and K[XB(OH)₃] generated in the reaction. Other palladium species such as Pd(PPh₃)₂Cl₂ (Table 1, Entry 4), Pd(OAc)₂ (Table 1, Entry 5) and palladium black (Table 1, Entry 6) can also catalyze the reaction in molten *n*-Bu₄NBr in the presence of water. But they all give lower yields than Pd(PPh₃)₄. Next a range of aryl halides including less reactive aryl chlorides were screened for the Suzuki reaction using the optimized condition.

All reactions proceeded in 1 : 1.1 stoichiometric ratio of aryl halide and boronic acid using 2 mol · L⁻¹ aq. K₂CO₃ as base in exposure to air and without degassing the molten *n*-Bu₄NBr. The results are summarized in Table 2.

Table 2 Pd(0) mediated Suzuki cross-coupling reaction of aryl halides with boronic acids in molten *n*-Bu₄NBr



Entry	X	R ¹	R ²	Reaction time/min	Isolated yield ^a /%
1	I	3,5-Me ₂	H	10	81
2	I	4-MeO	H	10	70
3	I	H	H	10	93
4	I	4-Iodo	H	10	56 ^b
5	Br	H	H	10	91
6	Br	4-Ac	H	10	92
7	Br	4-Ac	4-Me	10	87
8	Br	4-Ac	3,5-Me ₂	10	92
9	Br	4-Ac	4-MeO	10	90
10	Cl	H	H	30	64
11	Cl	4-Ac	H	30	70
12	Cl	4-Ac	4-Me	30	69
13	Cl	4-Ac	3,5-Me ₂	30	78
14	Cl	4-NO ₂	H	30	74

^a Average of two runs, purities >95% (determined by 500 MHz ¹H NMR). ^b The product was *p*-terphenyl.

The reaction exhibits high efficiency and functional group tolerance. The cross-coupling reaction of iodo-benzenes (Table 2, Entries 1—4) including a rather electron-rich one (Table 2, Entry 2) with phenylboronic acid proceeded efficiently in molten *n*-Bu₄NBr and were all complete within 10 min at 120 °C. In addition, 1,4-diiodobenzene can react with two equivalents of

phenylboronic acid furnishing *p*-terphenyl in an acceptable yield (Table 2, Entry 4).

Bromobenzene exhibited comparable reactivity toward coupling with phenylboronic acid (Table 2, Entry 5). Then the scope of the reaction was expanded by altering the arylboronic acid partner using 4'-bromoacetophenone as aryl halide (Table 2, Entries 6—9). The cross-coupled biaryl products can be furnished in high yields.

In particular, aryl chlorides can efficiently react with arylboronic acids under the present condition (Table 2, Entries 10—14). The reaction of chlorobenzene with phenylboronic acid underwent smoothly affording biphenyl with 64% yield in 30 min (Table 2, Entry 10). In contrast to this result, chlorobenzene behaves sluggishly in the ionic liquid [bmim][BF₄] thermally.⁷

The recovery of the catalyst and molten *n*-Bu₄NBr was also investigated. It was found that the palladium catalysts were fairly stable after the coupling reaction even exposure to air. Then the coupling of phenylboronic acid with 5-iodo-*m*-xylene was examined in the presence of 1.2 mol% of Pd(PPh₃)₄ to study the recovery of the catalyst and solvent (Table 3).

Table 3 Suzuki cross-coupling of 5-iodo-*m*-xylene and phenylboronic acid for catalysts recycling

Cycle	Reaction temperature/°C	Time/min	Yield ^a /%
1	120	10	81
2	80	10	93
3	80	10	91

^a Isolated yield determined by ¹H NMR (500 MHz).

After completing the reaction, it was found that when extracting with diethyl ether and cooling the reaction mixture to room temperature, a tri-phasic system with water and diethyl ether can be effected. Isolation of the biaryl product layer can be achieved without apparent leaching of palladium species into the product. The bottom aqueous phase was removed and discarded leaving the middle orange-colored molten *n*-Bu₄NBr catalyst layer (crystallization did not occur even after 48 h settling at room temperature).

n-Bu₄NBr was not lost in the water layer to an appreciable degree. The reason may be that the aqueous phase has almost been saturated with the by-products KHCO₃ and K[XB(OH)₃] generated in the reaction. So the resulting orange-colored molten *n*-Bu₄NBr was re-used for the next run. By using this ambient liquid *n*-Bu₄NBr, the reaction temperature could decrease to 80 °C. To suppress the formation of the by-products, the arylboronic acid was added over a period of time at ambient temperature. As shown in Table 3, the yields of 3,5-dimethylbiphenyl seem to be higher after the first cycle.

In summary, a practical procedure for palladium catalyzed Suzuki cross-coupling reaction was developed by use of molten *n*-Bu₄NBr and water. The results demonstrated that the molten *n*-Bu₄NBr and water bi-

phasic system could stabilize the active catalytic species and showed a dramatic increase in activity especially with respect to aryl chloride without any additives. At the end of the first run the catalyst in molten *n*-Bu₄NBr could be easily recycled and the *homo*-coupled products could be inhibited to a negligible extent by modification of the manner of recharging arylboronic acid.

Experimental

All reactions were carried out in open air. Unless otherwise specified, all materials were used as purchased. Arylboronic acids were prepared by reported method.¹³ The yields are usually the average of two runs. The purities of isolated products were determined by ¹H NMR spectra which were recorded on a 500 MHz Bruker instrument using CDCl₃ as solvent. IR spectra were recorded on an AVATAR 360 FTR instrument. Elemental analysis was performed on a 240 CHN instrument.

General procedure for the biaryl preparation

In a three-necked round-bottomed flask (25 mL) equipped with a reflux condenser, palladium catalyst (0.016 mmol) was heated with aryl halide (1.25 mmol) in *n*-Bu₄NBr (1.5 g) at 120 °C with vigorous stirring until a dark brown solution emerged where the temperature was kept at 120 °C, arylboronic acid (1.37 mmol) and an aqueous solution of K₂CO₃ (0.365 g, in 1.25 mL of water) was added sequentially. After heating for 10–30 min, the reaction mixture was cooled to about 60 °C while the reaction mixture still remained in a liquid phase. Diethyl ether (10 mL) was added cautiously through the top of the condenser. The mixture was stirred for a few minutes and cooled to room temperature. The middle molten *n*-Bu₄NBr layer maintained a liquid phase and the top diethyl ether layer was separated. After extraction with diethyl ether (2 × 10 mL), the combined extracts were washed successively by 1 mol · L⁻¹ NaOH (10 mL), and water (2 × 10 mL) and dried (Na₂SO₄). Filtration through a small pad of silica and evaporation to dryness afford the biaryl product.

3,5-Dimethylbiphenyl¹⁴ It was prepared from 5-iodo-*m*-xylene and phenylboronic acid in 81% isolated yield as a colorless liquid. ¹H NMR (CDCl₃, 500 MHz) δ: 7.57 (d, *J*=7.3 Hz, 2H), 7.42 (t, *J*=7.7 Hz, 2H), 7.31 (t, *J*=7.4 Hz, 1H), 7.21 (s, 2H), 6.99 (s, 1H), 2.38 (s, 6H); IR (neat) *v*: 3030, 1602, 849, 760 cm⁻¹.

4-Methoxybiphenyl¹⁵ It was prepared from 4-iodo-anisole and phenylboronic acid in 70% isolated yield as a white solid. m.p. 84–85 °C (lit.¹⁵ m.p. 87 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 7.52–7.59 (m, 4H), 7.41 (t, *J*=7.5 Hz, 2H), 7.30 (t, *J*=7.1 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 2H), 3.85 (s, 3H); IR (KBr) *v*: 2959, 1602, 834, 759 cm⁻¹.

Biphenyl¹⁶ It was prepared from iodobenzene, bromobenzene or chlorobenzene with phenylboronic acid in 64%–93% isolated yield as a white solid. m.p. 64–65 °C (lit.¹⁶ m.p. 70 °C); ¹H NMR (CDCl₃, 500

MHz) δ: 7.59 (d, *J*=7.6 Hz, 4H) 7.44 (t, *J*=7.6 Hz, 4H), 7.35 (t, *J*=7.4 Hz, 2H); IR (KBr) *v*: 3058, 1569, 903, 728, 696 cm⁻¹.

***p*-Terphenyl¹⁷** It was prepared from 1,4-diiodobenzene and phenylboronic acid in 56% isolated yield as a white solid. m.p. 210–212 °C (lit.¹⁷ m.p. 209–212 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 7.64–7.68 (m, 8H), 7.46–7.49 (m, 4H), 7.36 (m, 2H); IR (KBr) *v*: 1480, 1451, 836, 747 cm⁻¹.

4-Acetylbiphenyl¹⁸ It was prepared from 4'-bromoacetophenone or 4'-chloroacetophenone and phenylboronic acid in 70%–92% isolated yield as a white solid. m.p. 116–118 °C (lit.¹⁸ m.p. 121 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 8.03 (d, *J*=8.4 Hz, 2H), 7.68 (d, *J*=8.4 Hz, 2H), 7.62 (d, *J*=7.6 Hz, 2H), 7.40–7.49 (m, 3H, 3ArH), 2.64 (s, 3H); IR (KBr) *v*: 3000, 2961, 1679, 1602, 833, 765 cm⁻¹.

4-Acety-4'-methylbiphenyl¹⁹ It was prepared from 4'-bromoacetophenone or 4'-chloroacetophenone and 4-methylphenylboronic acid in 71%–87% isolated yield as a white solid. m.p. 110–113 °C (lit.¹⁹ m.p. 121–122 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 8.01 (d, *J*=8.3 Hz, 2H), 7.67 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.1 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H); IR (KBr) *v*: 3033, 2962, 1681, 803 cm⁻¹.

4-Acety-3',5'-dimethylbiphenyl It was prepared from 4'-bromoacetophenone or 4'-chloroacetophenone and 3,5-dimethylphenylboronic acid in 78%–92% isolated yield as a white solid. m.p. 83–85 °C; ¹H NMR (CDCl₃, 500 MHz) δ: 8.01 (d, *J*=8.3 Hz, 2H) 7.66 (d, *J*=8.3 Hz, 2H), 7.24 (s, 2H), 7.04 (s, 1H), 2.63 (s, 3H), 2.39 (s, 6H); IR (KBr) *v*: 2912, 1677, 1602, 826 cm⁻¹. Anal. calcd for C₁₆H₁₆O: C 85.68, H 7.19; found C 85.47, H 7.16.

4-Acety-4'-methoxybiphenyl²⁰ It was prepared from 4'-bromoacetophenone and 4-methoxyphenylboronic acid in 90% isolated yield as a white solid. m.p. 153–155 °C (lit.²⁰ m.p. 153–154 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 8.00 (d, *J*=8.3 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 6.99 (d, *J*=8.6 Hz, 2H), 3.87 (s, 3H), 2.63 (s, 3H).

4-Nitrobiphenyl²¹ It was prepared from 4-chloronitrobenzene and phenylboronic acid in 74% isolated yield as a yellow solid. m.p. 110–112 °C (lit.²¹ m.p. 114–114.5 °C); ¹H NMR (CDCl₃, 500 MHz) δ: 8.29 (d, *J*=8.8 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 2H), 7.62 (d, *J*=7.6 Hz, 2H), 7.45–7.50 (m, 3H); IR (KBr) *v*: 3075, 2961, 1595, 853, 740 cm⁻¹.

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