

Note

Phosphine-free Suzuki cross-coupling reactions under ultrasound

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Abstract

Suzuki cross-coupling reaction was successfully carried out in ethylene glycol under phosphine-free conditions to obtainment of biaryls using ultrasonic irradiation. High yields were obtained using different palladium and bases sources. The catalyst was recycled up to three times with good to moderate activity.

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1. Introduction

Palladium-catalyzed cross-coupling reactions [1] via Suzuki [2], Heck [3], Stille and coworkers [4], Negishi et al. [5] and Sonogashira [6] protocols are powerful methods for C–C bond formation. These reactions are still under investigation by several groups interested in more environmentally compatible processes [7].

The Suzuki cross-coupling reaction is an extremely versatile methodology for generation of carbon–carbon bonds and is employed most successfully in the synthesis of biaryls [8], this reaction is very attractive due to the stability of precursors, boronic acids, and facility of work up [9].

To avoid the use of flammable, hazardous and/or non-renewable solvents, the use of ionic liquids, fluorinated solvents, supercritical fluids and PEGs has been extensively reported in organic synthesis, in particular in Pd(0) catalyzed C–C bond formation [10]. Recently, ionic liquids have gained prominence as attractive alternatives to volatile organic solvents for catalytic reactions and separation processes. Suzuki reactions in ionic liquids, in particular those involving dialkylimidazolium salts, have vastly been

reported [11]. Phosphine ligands, ammonium and phosphonium halides and quaternary ammonium salts have been found to stabilize the Pd-catalysts *via* formation of zero-valent Pd species and accelerate the coupling in the reaction [12]. Phosphine-free or ligand-free catalytic systems are economically profitable and environmentally friendly have received that in increasing interest.

Suzuki coupling for the production of biaryls has been claimed to be possible under microwave [13] or ultrasonic irradiation [14]. Both conditions, in general lead to reduction of reaction times, clean media and generally high yields are obtained.

In the present paper, our results concerning the use of ethylene glycol as solvent, phosphine-free system, in Suzuki cross-coupling reaction under ultrasonic irradiation are disclosed. The sonochemical reactions were carried out in a thermostated ultrasonic cleaning bath at 47 kHz (Branson 1210).

2. Results and discussion

Our initial investigation started with the cross-coupling reaction of iodobenzene and phenylboronic acid as a model system. The reaction was carried out in the presence of different palladium sources (PdCl₂ or Pd₂(dba)₃), triphenylphosphine, tetrabutylammonium bromide (TBAB) as

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additive, base (KF, NaHCO₃ or K₂CO₃) and ethylene glycol as solvent under ultrasound. The results are summarized in Table 1.

Using ethylene glycol as solvent moderate to high yields were obtained. Moderate yields were obtained with KF and NaHCO₃ (entries 1 and 2) while K₂CO₃ associated to PdCl₂ 5% mol (entry 3) lead to the highest yields. Using this base (K₂CO₃) the amounts of PdCl₂ were reduced to 2.5 and 1% mol (entries 4 and 5) but lower yields were obtained. When Pd₂(dba)₃ was used high yields were obtained using 5% and 2.5% mol (entries 6 and 7). Reduction on Pd₂(dba)₃ (entry 8), to 1% mol, resulted in poor yield. Using Pd₂(dba)₃ at 2.5% mol, the reaction was tested out under thermal condition at 55 °C for 3 h and the result was very good (entry 9). However, at room temperature (entry 10) the reaction yield was not very satisfactory showing that energy is necessary to carry out the reaction. A mixture of ethylene glycol/water (entry 11) was tested furnishing a moderate yield, while in water (entry 12) surprisingly good yield was obtained. The reactions were carried out under phosphine-free conditions in 3 h (entry 13) and 4 h (entry 14), the results obtained were still good, demonstrating that there is no need to use phosphine in this reaction. A reaction using this media, phosphine-free

condition, in 4 h under thermal condition (entry 15) was carried out furnishing 71% of conversion, the reaction under sonochemical condition (entry 14) was much better. Reaction without TBAB was carried out and gave 89% (entry 16) showing that TBAB is important to reaction, probably it stabilize the palladium. The products could be easily separated from the catalyst by extraction with chloroform.

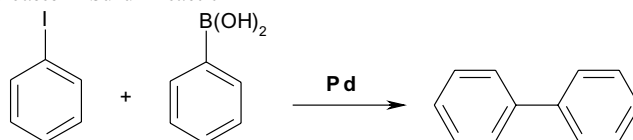
To generalize our method, other substrates were successfully tested (Table 2). Using different aryl halides and boronic acids, K₂CO₃ as base, Pd₂(dba)₃ 2.5% mol, TBAB 5% mol and ethylene glycol under ultrasound for 4 h, biaryls were obtained with yields between 77% and 96%.

To prove the efficiency of the ultrasonic effect, some reactions of Table 2 were carried out under thermal condition, but the yields were worse. The products 1-biphenyl-4-yl-ethanone (entry 2) and 4-fluoro-biphenyl (entry 4) furnished 81% and 84%, respectively.

We noticed a insignificant Ullmann-type homocoupling reaction between aryl halides, typical of coupling reaction under ultrasound. The ultrasound effect on this type of coupling is described in the literature [14b].

The ability to isolate product and recover and recycle the catalyst solution permits repetitive catalytic runs. The

Table 1
Effect of different palladium sources and bases in Suzuki reaction



Entry	Catalyst	Base	Solvent	Yield (%) ^a
1 ^b	PdCl ₂ 5%	KF	Ethylene glycol	59
2 ^b	PdCl ₂ 5%	NaHCO ₃	Ethylene glycol	70
3 ^b	PdCl ₂ 5%	K ₂ CO ₃	Ethylene glycol	100
4 ^b	PdCl ₂ 2.5%	K ₂ CO ₃	ethylene glycol	25
5 ^b	PdCl ₂ 1%	K ₂ CO ₃	Ethylene glycol	14
6 ^b	Pd ₂ (dba) ₃ 5%	K ₂ CO ₃	Ethylene glycol	100
7 ^b	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	99
8 ^b	Pd ₂ (dba) ₃ 1%	K ₂ CO ₃	Ethylene glycol	55
9 ^c	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	91
10 ^d	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	20
11 ^e	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol/water	66
12 ^b	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Water	80
13 ^f	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	86
14 ^g	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	96
15 ^{g,c}	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	71
16 ^{g,h}	Pd ₂ (dba) ₃ 2.5%	K ₂ CO ₃	Ethylene glycol	89

^a Determined by gas chromatography.

^b 1.0 mmol iodobenzene, 1.0 mmol phenylboronic acid, 3 mmol base, 3 g solvent, 5% mol PPh₃ and 5% mol TBAB under ultrasound (55 °C) for 3 h.

^c Thermal condition (55 °C).

^d Room temperature.

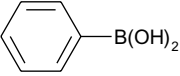
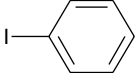
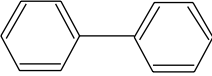
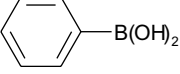

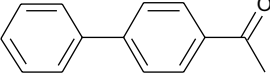
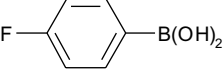

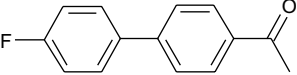
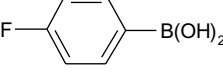
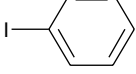
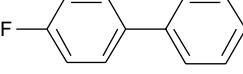
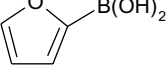
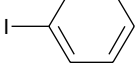
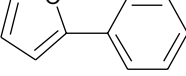
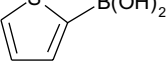
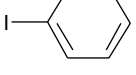
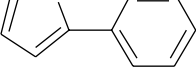
^e Mixture ethylene glycol/water 0.5 mL/2.5 mL.

^f Phosphine-free in 3 h reaction time.

^g Phosphine-free in 4 h reaction time.

^h Without TBAB.

Table 2
Phosphine-free Suzuki reaction of different aryl halides and boronic acids^a

Entry	Boronic acid	Aryl halides	Product	Yield (%) ^b
1				94
2				92
3				96
4				94
5				77
6				79

^a 1.0 mmol aryl halide, 1.0 mmol boronic acid, 2.5% mol Pd₂(dba)₃, 5% mol TBAB, 3 mmol K₂CO₃, 3 g ethylene glycol under ultrasound (55 °C) for 4 h.

^b Isolated yields.

Table 3
Effect of catalytic runs in Suzuki reaction^a

Entry	Run	Yield (%) ^b
1	1st	91
2	2nd	85
3	3rd	53

^a 1.0 mmol iodobenzene, 1.0 mmol phenylboronic acid, 2.5% mol Pd₂(dba)₃, 5% mol TBAB, 3 mmol K₂CO₃, 3 g ethylene glycol under ultrasound (55 °C) for 4 h.

^b Determined by GC.

catalyst was recycled under phosphine-free conditions (Table 3) by extraction of the solution with chloroform. The catalyst solution was reused three times with good to moderate activity in the reaction of iodobenzene with phenylboronic acid.

3. Conclusion

In summary, our reaction media using Pd₂(dba)₃ 2.5% mol, K₂CO₃, TBAB 5% mol and ethylene glycol as solvent proved to be a suitable phosphine-free media for Suzuki cross-coupling reaction under ultrasound. We have obtained biaryls of a simplest manner with high yields. The catalyst was recycled up to three times with good activity in the first and second run. Ethylene glycol proved to be a great eco-friendly solvent to Suzuki cross-coupling reaction, it is cheap and recoverable.

4. Experimental

The ¹H NMR and ¹³C NMR spectra were recorded on Bruker 200 and 50 MHz NMR spectrometer in CDCl₃. The mass spectra were obtained using Shimadzu instrument GCMS-26542. Ultrasonication was performed in a thermostated Branson 1210 ultrasonic cleaner with a frequency of 47 kHz and a normal power of 250 W. The reagents were obtained from commercial sources and used without purification.

4.1. General procedure

In a 25 mL reaction flask equipped with iodobenzene (1 mmol, 0.204 g), phenylboronic acid (1 mmol, 0.1219 g) and Pd₂(dba)₃ (2.5% mol, 0.023 g), K₂CO₃ (3 mmol, 0.414 g), TBAB (5% mol, 0.0161 g) were suspended in 3 g of ethylene glycol heating to 55 °C under ultrasonic irradiation for 4 h. The reactional mixture was extracted with chloroform. The organic phase was washed with water and brine and dried over anhydrous magnesium sulphate. Solution was filtered, solvent was evaporated and product was purified by flash chromatography (hexane/ethyl acetate 3:7).

Biphenyl. White solid, 0.145 g (94%). M.p.: 70–71 °C. ¹H NMR (CDCl₃, 200 MHz) δ 7.56 (d, 2H), 7.40 (d, 2H), 7.29 (d, 2H). ¹³C NMR (CDCl₃, 50 MHz) δ 140.8, 128.4, 126.9, 126.8. GC–MS: 154 *m/z*, 77 *m/z*.

1-Biphenyl-4-yl-ethanone. White solid, 0.180 g (92%). M.p.: 121–122 °C. ¹H NMR (CDCl₃, 200 MHz) δ 8.09 (d, 2H), 7.63 (d, 2H), 7.58 (d, 2H), 7.40 (dd, H), 7.37 (dd, H), 2.63 (s, 1H). ¹³C NMR (CDCl₃, 50 MHz) δ 197.7, 145.7, 139.8, 135.9, 128.9, 128.1, 127.3, 26.2. GC–MS: 196 *m/z*, 181 *m/z*, 153 *m/z*, 77 *m/z*, 43 *m/z*.

1-(4'-Fluoro-biphenyl-4-yl)-ethanone. White solid, 0.205 g (96%). M.p.: 109–110 °C. ¹H NMR (CDCl₃, 200 MHz) δ 8.00 (d, 2H), 7.63 (d, 2H), 7.59–7.57 (m, 2H), 7.17 (t, 2H), 2.64 (s, 3H). ¹³C NMR (CDCl₃, 50 MHz) δ 197.7, 164.2, 161.7, 144.7, 135.9, 135.8, 129.0, 128.9, 127.0, 116.1, 115.9, 26.7. GC–MS: 214 *m/z*, 199 *m/z*, 171 *m/z*, 94 *m/z*, 77 *m/z*.

4-Fluoro-biphenyl. White solid, 0.162 g (94%). M.p.: 75 °C. ¹H NMR (CDCl₃, 200 MHz) δ 7.56–7.53 (m, 4H), 7.40 (t, 2H), 7.33 (t, 1H), 7.15 (t, 2H). ¹³C NMR (CDCl₃, 50 MHz) δ 163.7, 161.3, 140.3, 137.4, 137.3, 128.8, 128.7, 128.6, 127.3, 127.0, 115.7, 115.5. GC–MS: 172 *m/z*, 153 *m/z*, 95 *m/z*, 77 *m/z*.

2-Phenylfuran. Colorless liquid, 0.111 g (77%). ¹H NMR (CDCl₃, 200 MHz) δ 7.68 (t, 2H), 7.44 (d, 1H), 7.39–7.24 (m, 3H), 6.64 (d, 1H), 6.45 (dd, 1H). ¹³C NMR (CDCl₃, 50 MHz) δ 154.2, 142.3, 131.1, 128.9, 127.5, 124.0, 111.8, 105.1. GC–MS: 144 *m/z*, 115 *m/z*, 77 *m/z*, 65 *m/z*.

2-Phenylthiophene. Colorless liquid, 0.126 g (79%). ¹H NMR (CDCl₃, 200 MHz) δ 7.61 (d, 1H), 7.37–7.16 (m, 5H), 7.02–6.99 (m, 2H). ¹³C NMR (CDCl₃, 50 MHz) δ 128.9, 127.9, 127.9, 127.4, 125.9, 124.8, 123.0, 29.7. GC–MS: 160 *m/z*, 82 *m/z*, 77 *m/z*.

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