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Ultrasound promoted Suzuki cross-coupling reactions in ionic liquid at ambient conditions

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Palladium catalyzed Suzuki cross-coupling reactions of halobenzenes including chlorobenzenes with phenylboronic acid have been achieved at ambient temperature (30 °C) in the absence of a phosphine ligand using the ionic liquid 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim][BF_4] with methanol as co-solvent under ultrasonic irradiation.

Among the carbon–carbon bond forming reactions, Suzuki cross-coupling reaction is an extremely versatile methodology for the synthesis of biaryls.[1,2] In recent times, the use of room temperature ionic liquids [I.L.s] as 'Green' solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressures, easy recoverability and reusability.[3] Indeed, Suzuki reactions have been conducted in the I.L. [bmim][BF_4] at 110 °C in the presence of phosphine ligands with a number of advantages.[4] In this investigation, however, chlorobenzene was practically non-reactive affording only traces of biaryl. Very recently, we have reported the ultrasound promoted Heck reaction at ambient temperature conditions using [bbim][BF_4]/[bbim][Br] as newer I.L.s.[5] In continuation of our investigations on sonochemistry in I.L.s, this communication reports for the first time an ultrasound promoted Suzuki cross-coupling reaction of halobenzenes including chlorobenzenes with phenylboronic acid at ambient temperature (30 °C) in the absence of any added phosphine ligand using the I.L. [bbim][BF_4] along with methanol as co-solvent.

The sonochemical reactions were carried out in a thermostated ultrasonic cleaning bath of frequency 50 kHz (Branson 5200). A number of halobenzenes were reacted with phenylboronic acid in I.L. [bbim][BF_4] with methanol as co-solvent using $Pd(OAc)_2$ as catalyst and sodium acetate as base under ultrasonic irradiation as shown in Fig. 1.

As an extension of our previous work,[5] the sonochemical Suzuki coupling reaction of iodobenzene with phenylboronic acid was carried out in the I.L. [bbim][BF_4] as solvent. No reaction was observed even after several hours of sonication both in the presence of air and also when argon was used as a protecting gas. It was observed that phenylboronic acid was insoluble in the I.L. under the reaction conditions. Subsequently, the sonochemical reaction was performed in the I.L. with methanol as co-solvent, which resulted in a homogeneous solution and complete conversion. In air as the ambient gas, the reaction of 4-methoxyiodobenzene with phenylboronic acid showed significant formation of unsubstituted biaryl (20%) due to the homo coupling of phenylboronic acid, which however was not formed in the presence of the inert argon as ambient gas. Consequently, all further reactions were carried out in argon.[6] The results are summarized in Table 1.

As is evident from Table 1, the ultrasound assisted Suzuki coupling reactions proceeded smoothly at 30 °C, with complete conversion for iodobenzenes in 20–30 min, 82–85% conversions for bromobenzenes in 10–45 min and 42–52% conversions for chlorobenzenes in 1–1.5 h. No further conversions were observed beyond the time specified for each substrate in Table 1. It is important to note that under the sonochemical reaction conditions in the I.L., even the normally less or non-reactive chlorobenzenes have shown significant conversions for the Suzuki coupling without the need for the addition of a phosphine ligand. However the reactions with chlorobenzenes needed the stronger sodium methoxide as a base. It is obvious from Table 1 that the process tolerates both electron donating and electron withdrawing substituents on the halobenzenes. The reactants and products could be easily separated from the I.L. by selective extractions.[6] The I.L. recovered in its pure form could be recycled several times. The reaction carried out in this manner also led to the formation of inactive Pd black preventing the recycling of the expensive palladium catalyst. However, the recycling of the catalyst could be achieved by a modified process.

Table 1 Suzuki cross-coupling reaction of halobenzenes with phenylboronic acid in [bbim]$^+$[BF_4]$^-$/MeOH under ultrasonic irradiation

No.	Substrate	Time/min	Yield of biaryls (%)[c]
1	Iodobenzene	20	92[a] (92)
2	4-Methoxyiodobenzene	20	93[b] (92)
3	4-Chloroiodobenzene	30	85[a] (82)
4	4-Nitroiodobenzene	30	82[b] (83)
5	Bromobenzene	45	82[a] (82)
6	4-Methoxybromobenzene	10	85[b] (88)
7	4-Nitrobromobenzene	20	90[b] (88)
8	Chlorobenzene	60	42[a] (43)
9	4-Nitrochlorobenzene	30	65[b] (66)
10	4-Chlorotoluene	60	52[a] (50)
11	2,4-Dinitrochlorobenzene	90	42[b] (39)

[a] Based on GC analysis with external standards. [b] Isolated yields by column chromatography; products fully characterized by mp, MS and elemental analysis. [c] Figures in parentheses are yields obtained using modified procedure.

In the modified process, the Pd–biscarbene complex A [Fig. 2] was preformed as reported earlier[5] and fully characterized.[7] The isolated complex A was then used as the catalyst for the Suzuki coupling reaction using only methanol as solvent under sonochemical conditions.[8] Interestingly, the complete formation of the Pd–biscarbene complex takes 1 h in [bbim][BF_4] as

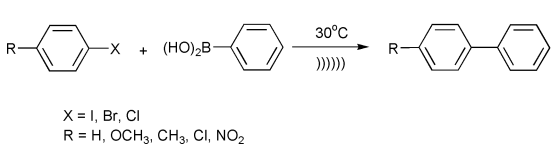

Fig. 1 Sonochemical Suzuki reaction in [bbim][BF_4]/MeOH.

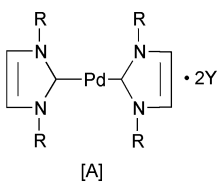

Fig. 2 Pd–biscarbene complex.

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solvent whereas the complex formation is complete in 10 min when methanol is used as the co-solvent. In this methodology, there was no formation of inactive palladium black and the Pd–biscarbene complex could be recovered quantitatively in its pure form. This variant gave more or less similar yields which are indicated in parentheses in Table 1 but with the added advantage that the catalyst could be recycled. In this variant, the reactions could be carried out in either air or argon as ambient gas without formation of palladium black and no homocoupling to biphenyl was observed for the substituted halobenzenes.

The recovered complex from successive recycles was used three times for the sonochemical Suzuki reaction of 4-methoxybromobenzene to afford the 4-methoxybiphenyl in 82%, 80% and 75% yields respectively. These results indicate a marginal progressive loss of the catalytic activity of the complex A for the recycles. With a view to make the recycling step easier, the Suzuki cross-coupling reaction of 4-methoxybromobenzene was performed using complex A as the catalyst in a mixture of I.L. and methanol under ultrasound irradiation conditions. However, the reaction was found to be quite sluggish (20% conversion after 1 h) with complete decomposition of complex A as seen by TLC.

The sonochemical Suzuki coupling reaction at ambient conditions of 4-methoxyiodobenzene with phenylboronic acid in the presence of palladium acetate as catalyst using only methanol as solvent without the I.L. afforded the homocoupled unsubstituted biphenyl in low yields (20%) with no trace of the expected cross coupled 4-methoxybiphenyl even after several hours of sonication. This observation clearly highlights the role of the palladium complex with the I.L. *viz*. complex [A] as the active catalyst in promoting the sonochemical Suzuki cross coupling in the present investigation.

Importantly, the Suzuki coupling reaction of iodobenzene with phenylboronic acid when performed using both the variants at 30 °C but in the absence of ultrasound showed only 25% conversion even after 10 h.

In our previous investigation of ultrasound promoted Heck reaction in I.L. at ambient temperature we have shown the *in situ* formation of clusters of Pd nanoparticles.[5] In an analogous manner, the reaction mixture after a successful Suzuki coupling reaction of iodobenzene with phenylboronic acid was subjected to *in situ* TEM analysis. The TEM image did not show the presence of any colloidal Pd nanoparticles.

In conclusion, in the ultrasound promoted Suzuki cross-coupling reaction described, the use of ultrasound has not only accelerated the formation of the Pd–biscarbene complex A in methanol as co-solvent but also in all probability brought about the *in situ* generation of a zero-valent Pd-species as the active catalyst from [A] in enhanced rates by electron transfer reactions primarily through the phenomenon of acoustic cavitation. It is well known that sonochemical processes proceed through SET (single electron transfer) mechanistic pathway by means of formation and adiabatic collapse of the transient cavitation bubbles.[9,10] It is also highly likely that ultrasound induced secondary reactions in the liquid phase after bubble collapse could be responsible for promoting the oxidative addition, transmetallation and reductive elimination of the catalytic cycle proposed for the Suzuki reaction. Further investigations on these lines taking into account the role of the redox potential of the I.L. and polarity of the medium are in progress.

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6 Typical procedure: a mixture of aryl halide (0.5 mmol), phenylboronic acid (0.5 mmol), [bbim][BF_4] (0.5 g), $Pd(OAc)_2$ (0.001 g) and NaOAc (0.045 g) [NaOMe (0.035 g) for chlorobenzenes] in MeOH (1.0 ml) was sonicated under argon for the specified time. The reactions were monitored by TLC/GC. After completion, water (2 ml) was added and the mixture extracted with ether (2 × 5 ml). The ether layer was separated, dried and the solvent evaporated to leave behind the products and reactants. The amenable product mixtures were subjected to column chromatography to isolate pure products. The rest were subjected to GC analysis using external standards for quantification. The pure I.L. could be quantitatively recovered from the aqueous layer by extraction with DCM and recycled.
7 Pd-Complex [A]—White amorphous powder; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.81(s, 4H), 4.82(t, 8H NCH_2), 2.08(m, 8H NCH_2CH_2), 1.50(m, 8H $NCH_2CH_2CH_2$), 1.01(t, 12H $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.63, 120.28, 50.54, 33.11, 20.11, 13.73. MS: *m*/*z* 466[$M^+ - BF_4$].
8 Modified procedure: a mixture of aryl halide (0.5 mmol), phenylboronic acid (0.5 mmol), NaOAc (0.045 g) [NaOMe (0.035 g) for chlorobenzenes] and Pd–biscarbene complex A (5 mg) in MeOH (1 ml) was sonicated under argon for the specified time. The reactions were monitored by TLC/GC. After completion of the reaction, methanol was evaporated under reduced pressure and the residue was extracted with ether (2 × 5 ml). The ether layer was separated, dried and the solvent evaporated to furnish the products, which were worked up for quantification as mentioned in the first procedure. The residue remaining after the ether extraction was then extracted with EtOAc (2 × 2 ml), washed with water and the solvent evaporated to recover complex A quantitatively for recycling.
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