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Effect of Water on the Heck Reactions Catalyzed by Recyclable Palladium Chloride in Ionic Liquids Coupled with Supercritical CO₂ Extraction

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The Heck coupling of iodobenzene with olefins occurs with high efficiencies at low temperatures in imidazolium-based ionic liquids catalyzed by PdCl₂/Et₃N, and the catalyst can be recycled after extraction of the products by supercritical CO₂. The coupling efficiency is dependent on water content of the ionic liquid. With a low water content (<50 ppm) in the ionic liquid, the Heck coupling reaction would proceed with >90% yield at room temperature using this catalytic system.

Introduction

The palladium-catalyzed carbon–carbon (Csp²–Csp²) coupling reaction is an important contemporary organic synthetic process that is known as the Heck reaction. The reaction is usually performed using a catalytic amount of a palladium complex, often with phosphine ligands, in a polar solvent at moderately high temperatures. One problem with the Heck reaction in conventional solvents is the loss of the palladium catalyst after the reaction. Several strategies have been reported in the literature for recycling the catalyst. Carmichael et al. reported the use of ionic liquids as media with palladium acetate Pd(OAc)₂ and a base for the Heck reaction.¹ Using the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆] as a medium, the Pd(OAc)₂ catalyst (2 mol %) with triphenyl phosphine (Ph₃P, 4 mol %) as an additive and Et₃N as the base, the coupling of iodobenzene and ethyl acrylate to *trans*-ethyl cinnamate gave a yield of 95%–99% after 1 h at 100 °C. For the *N*-hexylpyridinium (C₆py)-based ionic liquid [C₆py][PF₆] with Pd(OAc)₂ and NaHCO₃ without a phosphine, the same reaction gave a 42% yield after 72 h of reaction at 80 °C. Hexane was used to extract the reaction products. Because the products could be separated by solvent extraction, recycling of the catalyst was possible, although no experimental data were given. In another report, Park and Alper showed that bis-(imidazole)Pd(II) complexes in [bmim][PF₆], in the presence of Et₃N, gave a quantitative yield for the Heck coupling of iodobenzene and *n*-butyl acrylate at 120 °C after 1 h of reaction.² The product was extracted with ethyl ether, and the catalyst could be reused five times without losing activity.

The advantages of combining supercritical CO₂ and ionic liquids for chemical separations were discussed by Blanchard and co-workers.^{3,4} Brown et al. reported that the product of an asymmetric hydrogenation in [bmim][PF₆] could be extracted by supercritical CO₂, and the catalyst Ru(O₂CMe)₂((*R*)-tolBINAP) could be reused without losing activity for five cycles.⁵ Chiappe et al. investigated the Stille cross-coupling reaction catalyzed by Pd(OAc)₂ in different ionic liquids and found loss of catalytic activity due to precipitation of Pd⁽⁰⁾ at the end of the extraction process.⁶ Recently, we have investigated Heck coupling of iodobenzene and olefins using a simple PdCl₂ and Et₃N catalytic system in [bmim][PF₆]. Supercritical fluid CO₂ was used to remove reaction products from the ionic liquid,

and recycling of the catalyst was evaluated. The Heck reaction in the ionic liquid showed high yields at room temperature; however, the coupling efficiency was determined to be dependent on water content of the ionic liquid. Our preliminary results and explanation regarding the effect of water on the Heck coupling reactions are given in this article.

Experimental Section

The ionic liquid used in this study, [bmim][PF₆], was prepared via the metathesis of [bmim]Cl with aqueous NaPF₆, extraction with methylene chloride, and drying under high vacuum for several hours at 50 °C. The [bmim]Cl was produced from butyl chloride and methyl imidazole and recrystallized from ethyl acetate/acetonitrile at –20 °C. Complete metathesis and extraction of NaCl was established by testing aqueous extracts of the ionic liquid, in methylene chloride, with AgPF₆ solution until no cloudiness due to AgCl could be observed. The imidazolium-based bis(trifluoromethylsulfonyl)imide ionic liquid ([bmim][Tf₂N]) was also prepared by metathesis of [bmim]Cl with aqueous lithium bis(trifluoromethylsulfonyl)imide, extraction with methylene chloride, and drying under high vacuum for several hours at 50 °C.

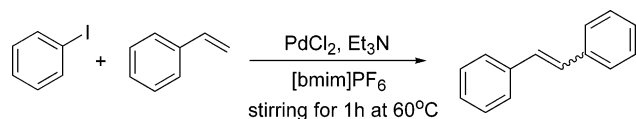
The procedure of the Heck reaction is given as follows. A 10 mL stainless steel high-pressure reactor equipped with a glass cup (2 cm in diameter and 2 cm in height) containing a stirring bar was charged with PdCl₂ (0.001 g, 0.006 mmol), Et₃N (0.043 mL, 0.3 mmol), and [bmim][PF₆] (1 g, density of 1.36 g/mL) and stirred for 10 min. Iodobenzene (0.022 mL, 0.2 mmol) and styrene (0.024 mL, 0.21 mmol) were added to the reaction vessel and stirred for 1 h at 60 °C. After the reaction, a small sample of the ionic liquid was taken for analysis and the products in the ionic liquid phase were extracted with supercritical CO₂.

For the supercritical fluid CO₂ extraction, liquid CO₂ was pressurized by an ISCO pump (model 260D) up to 100 atm and flowed into the reaction vessel that contained the ionic liquid at 40 °C. After a static extraction of 1 h, CO₂ was allowed to flow through the reactor at a constant pressure of 100 atm. The dynamic extraction was controlled with a 0.5 mL/min flow at 40 °C for ~1 h. The products dissolved in the CO₂ phase were trapped in a collection vessel for spectroscopic and chromatographic analyses. After the supercritical CO₂ extraction, the ionic liquid that contained the palladium catalyst was reused for another experiment. Nuclear magnetic resonance (300 MHz ¹H NMR, Bruker model AMX300), high-performance liquid chromatography (HPLC) (ThermoFinnigan SpectraSYSTEM), and gas chromatography/mass spectroscopy (GCMS) (Shimadzu models GC-17A and GCMS-QP5050) were used for sample analysis.

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Scheme 1. Heck Coupling of Iodobenzene and Styrene in [bmim][PF₆]

The water contents in the ionic liquid were analyzed by Karl Fischer titration (Mettler Toledo, model DL36). The chlorine contents of the ionic liquids were determined by neutron activation analysis. The samples were sealed in polyethylene vials and irradiated in a 1 MW TRIGA reactor with a steady neutron flux of 6×10^{12} neutrons cm⁻² s⁻¹. The radioisotope ³⁸Cl produced by the neutron capture of ³⁷Cl has a half-life of 37.3 min and emits gamma rays with energies of 1.60 and 2.15 MeV that were used for the identification and quantification of chlorine in the samples.

Results and Discussion

The coupling of iodobenzene with styrene to give *trans*-stilbene, as shown in Scheme 1, was studied in [bmim][PF₆] at different temperatures using PdCl₂ as the catalyst. PdCl₂ itself does not dissolve in [bmim][PF₆]; however, in the presence of a base such as Et₃N, it dissolves easily. Several bases were tested for the PdCl₂ catalyst, and Et₃N was determined to be the most effective. One interesting observation made from our experiments is that the amount of water in the ionic liquid is important for the coupling efficiency. Using a relatively pure [bmim][PF₆] with a low water content (<50 ppm), the Heck coupling reaction could occur even at room temperature (25 °C) with >90% yield. However, after storage of the same ionic liquid for a couple of months under ambient atmosphere, a higher temperature was required to obtain the same coupling yield, even though the ionic liquid remained colorless visually. According to Blanchard et al.,⁷ [bmim][PF₆] has a tendency to absorb moisture when it is exposed to the atmosphere and a small amount of water impurity can affect the phase behavior of the ionic liquid. Ionic liquids are not as stable as we generally think. The instability of hexafluorophosphate-containing ionic liquids has been reported recently.⁸ Commercially available [bmim][PF₆] from Aldrich has a slight yellow color and is labeled as 95% pure. Using the commercial [bmim][PF₆], Scheme 1 would not occur at room temperature and would require at least 5 h at 70 °C to achieve a coupling yield of >80%.

It is difficult to keep the water content of [bmim][PF₆] at <50 ppm under ambient atmosphere for repeated experiments. In this study, the coupling of arylhalides with styrene and with methyl acrylate catalyzed by PdCl₂/Et₃N was tested at 60 °C with 318 ppm of water in [bmim][PF₆]. At this temperature, a slight change in the water content of the ionic liquid did not seem to show a noticeable effect on the coupling reactions, which proceeded with high efficiencies, as shown in Table 1. The coupling reactions were virtually complete after 1 h at 60 °C. This temperature is lower than the temperatures reported previously for the Heck coupling reactions in ionic liquids using different forms of palladium catalysts. The conversion yields including the isomers of each product were quantitative after extraction with supercritical CO₂. The isomers of *trans*-stilbene and *trans*-methylcinnamate were <1% of the major product, based on the detection limits of the NMR, GCMS, and HPLC peaks of the isomers. In the case of the Heck reaction of cyclohexene with arylhalides, the conversion is known to be difficult.⁹ The PdCl₂/Et₃N-catalyzed coupling of iodobenzene with cyclohexene in the ionic liquid required a longer time, ~20

Table 1. Coupling of Arylhalides and Olefins Catalyzed by PdCl₂/Et₃N in [bmim][PF₆]^a

arylhalide	olefin	time (h)	temp (°C)	conversion ^b (%)
iodobenzene	styrene	1	60	99
iodobenzene	styrene	1	50	88
iodobenzene	styrene	1	40	75
iodobenzene	methyl acrylate	1	60	99
iodobenzene	cyclohexene ^c	20	100	90 ^d
1-iodo-4-nitrobenzene	styrene	1	100	97
1-iodoanisole	styrene	1	100	98
bromobenzene	styrene	1	100	91

^a Molar ratio of iodobenzene/olefin/PdCl₂ = 1.00/1.05/0.03 and 1 mL of ionic liquid (0.0318% of water in [bmim][PF₆]) used as solvent at 60 °C. ^b Conversion yield was determined via HPLC with a C₁₈ column, based on peak area measurement. ^c Five equivalents of cyclohexene, relative to iodobenzene. ^d 1-Phenylcyclohexene isomers.

Table 2. Comparison of Catalytic Activity of the Heck Reaction (see Scheme 1) in Imidazolium-Based Ionic Liquids with Different Water Contents at 25 °C

ionic liquid	H ₂ O Content		[Pd]/[H ₂ O] ratio	time (h)	catalytic activity ^a
	(wt %)	(ppm)			
1	0.0042 ^b	42 ^b	2.420	3	9.9
2	0.0049 ^c	49 ^c	2.072	3	8.5
3	0.0318 ^b	318 ^b	0.318	5	7.0
4	0.0500 ^c	500 ^c	0.203	7	0.0
5	0.0900 ^b	900 ^b	0.113	7	0.5
6	0.6900 ^b	6900 ^b	0.015	12	0.0

^a A catalytic activity of 10 means a quantitative conversion of starting material and all reactions occurs in a N₂ atmosphere. ^b The compound [bmim][PF₆] was preserved under an argon atmosphere. ^c The compound [bmim][Tf₂N] was preserved under an argon atmosphere.

h, to achieve >90% conversion, and Table 1 gives the summary of our experimental data.

The conversion yield of the Heck reaction at room temperature changed drastically with water content in the [bmim][PF₆]. In a freshly prepared [bmim][PF₆], Karl Fischer analysis of the ionic liquid showed 0.0042 wt % (42 ± 5 ppm) of residual water. The catalytic activity of PdCl₂ for the Heck reaction in this relatively dry [bmim][PF₆] was excellent at room temperature (25 °C; see Table 2). As the amount of water in the ionic liquid increased, the coupling rate began to slow. At 0.69 wt % water in [bmim][PF₆], the Heck coupling reaction would not occur at 25 °C. If the temperature was increased to 120 °C, the reaction would proceed partially (~30% conversion after 1 h) with 0.69% water in the ionic liquid.

In previous studies, water was used as an extraction solvent in the ionic liquid-mediated Heck coupling reaction to remove salt byproducts¹ and also was used as a second solvent in ionic liquid biphasic catalytic hydrogenations.¹⁰ According to Tran et al., the properties of room-temperature ionic liquids are dependent on the amount of water dissolved in the system and the kinetics of water absorption by ionic liquids are not only relatively complex but also dependent on the concentration of water.¹¹ Single-crystal X-ray diffraction (XRD) of 1-butyl-3-methylimidazolium fluoride monohydrate, [bmim]F·H₂O, was reported by Swatoski et al. as a decomposition product from the hydrolytic degradation of [bmim][PF₆].^{8b} In our NMR measurements, the water that was dissolved in the ionic liquids (samples 4 and 6 in Table 2) was observed in proton NMR (300 MHz, CDCl₃) at a resonance peak of $\delta = 2.1867$ (singlet) for [bmim][Tf₂N] and $\delta = 2.1899$ (singlet) for [bmim][PF₆], which were different from the peak for bulk water droplets at $\delta = 4.7019$. The shift in proton NMR of water in ionic liquid is an indication that the water molecules are bound to the ionic liquid. Sample 6 shows at least 0.69% of the dissolved water is

Table 3. Conversion of Iodobenzene and Styrene to *trans*-Stilbene Catalyzed by PdCl₂/Et₃N in [bmim][PF₆] (see Table 1), as a Function of the Number of Cycles

entry	catalyst solution	conversion ^a (%)
1	fresh	99
2	recycled from entry 1 ^b	98
3	recycled from entry 2 ^b	97
4	recycled from entry 3 ^b	97

^a Conversion yield was determined via GC and HPLC, based on peak area measurement. ^b Includes an addition of 0.20 mmol of iodobenzene, 0.21 mmol of styrene, and 0.30 mmol of Et₃N to the ionic liquid at 60 °C, with a water content of 318 ppm.

virtually all bound to the ionic liquid [bmim][PF₆]. Cammarata et al. reported that the molecules of water dissolved in ionic liquids were associated with anions such as PF₆[−] or Tf₂N[−] and the strength of the interaction between water molecules and the anions increases in the following order, based on IR spectroscopic studies: PF₆[−] < BF₄[−] < Tf₂N[−].¹² Water that was associated with PF₆[−] or Tf₂N[−] could lead to the formation of HF, which would increase the acidity of the system, leading to a retardation of the Heck reaction. Water could also be associated with the imidazolium ion via hydrogen bonding to the acidic proton of the heterocyclic ring and could inhibit a carbene formation mechanism, which was probably responsible for the stability of the palladium catalyst, as discussed later in this paper. The catalytic activity of the Heck reaction in [bmim][Tf₂N] (samples 2 and 4 in Table 2) seemed to show a greater effect by water, compared with that observed in [bmim][PF₆]. For example, with 500 ppm of water, the Heck reaction would not occur in [bmim][Tf₂N] but would still proceed with 5% conversion in [bmim][PF₆] with the same amount of PdCl₂/Et₃N at 25 °C. Our NMR results also indicated that the extraction of the product and the reactant from [bmim][PF₆] by supercritical CO₂ at 40 °C was not affected by water amounts up to 0.69%, as shown by sample 6 in Table 2.

The amount of chloride in our [bmim][PF₆] was determined by neutron activation analysis (NAA) that was performed at the Nuclear Radiation Center at Washington State University (Pullman, WA). According to the nondestructive NAA result, the chlorine content of our ionic liquid was 70 ppm and remained constant over several weeks of storage. Chloride contamination of the ionic liquid does not seem to be a problem for the Heck coupling reactions that have been described in this paper.

We chose to evaluate the recyclability of the palladium catalyst using the coupling in [bmim][PF₆] at 60 °C that has been depicted by Scheme 1 for this study. After supercritical CO₂ extraction of the product, the reaction in the ionic liquid was repeated under the same conditions. The results of repeated use of the PdCl₂/Et₃N catalyst in [bmim][PF₆] for the Heck coupling scheme (Scheme 1) are given in Table 3. The catalyst was recycled four times without losing activity.

The mechanism of PdCl₂/Et₃N-catalyzed Heck reaction in [bmim][PF₆] is not well-known. According to the literature, the acidic proton on the heterocyclic ring of the imidazolium ionic liquid can be removed by a base, leading to the formation of a carbene.¹⁴ McGuinness et al. reported that these carbenes acted as ligands to transition metals.¹⁵ In many transition metal-catalyzed processes, ligands are known to have a key role in stabilizing the transition state or the intermediate and affecting the electronic and steric properties of the metal. Strong donor heterocyclic carbene ligands have been reported to have a role similar to that for tertiary phosphine ligands.¹⁶ According to the results of Herrmann et al.¹⁶ and McGuinness et al.,¹⁵ imidazolium carbene-palladium complexes can be prepared from Pd(OAc)₂ and 1,3-dimethyl imidazolium iodide or 3,3'-dimethyl-

1,1'-methylene imidazolium diiodide. The palladium complexes showed remarkable activities for the Heck reaction, suggesting that the carbenes derived from imidazole could stabilize Pd²⁺ and Pd⁰ complexes that are involved in the catalytic reaction cycle. A possible carbene-palladium complex could be derived from [bmim][PF₆] under our experimental conditions, similar to the [PdBr₂(carbene)₂] species in [bmim]Br, as reported by Xu et al.¹⁷ Note that we also examined the coupling of iodobenzene and styrene in the ionic liquids [bmim][BF₄] with sodium tetrachloropalladate (Na₂PdCl₄) at 60 °C. The yield of the coupling reaction in [bmim][BF₄] was similar to that described for the PdCl₂/Et₃N-catalyzed reaction in [bmim][PF₆].

Conclusions

We have demonstrated that the Pd(II)/Et₃N-catalyzed Heck reactions in imidazolium-based ionic liquid [bmim][PF₆] can proceed with high efficiencies at room temperature if the solvent is relatively free of water. Supercritical CO₂ can be used to extract the coupling products, and the catalyst can be reused without losing its activity for at least four cycles. This ionic liquid/supercritical CO₂ coupled reaction-separation process, which involves two environmentally sustainable solvents to achieve high reaction efficiency and facile separation of the catalyst and products, represents an example of the green synthetic techniques that are desirable for future chemical manufacturing processes. Potential applications of this simple palladium-catalyzed Heck reactions in imidazolium-based ionic liquids for other organic syntheses are currently under investigation.

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