

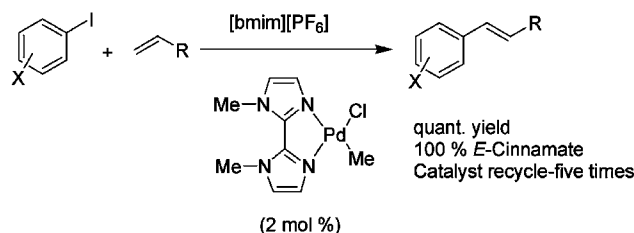
Highly Efficient, Recyclable Pd(II) Catalysts with Bisimidazole Ligands for the Heck Reaction in Ionic Liquids

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ABSTRACT



New Pd(II) complexes with bisimidazole ligands were prepared and proved to be effective catalysts for the Heck reaction under phosphine-free conditions using ionic liquids as solvents. This system could be recycled five times without any loss of catalytic activity.

Palladium-catalyzed $C_{sp^2}-C_{sp^2}$ coupling reactions are widely used for organic synthesis. For instance, vinyl substitution (Heck reaction) is one of the most important, reliable, and general reactions for C–C bond formation with applications in the areas of bioactive compounds, natural products, and high-performance materials.¹ The Heck reaction is usually carried out in the presence of bulky phosphine ligands, which give Pd(0) species and accelerate the reaction rate. However, many phosphines can be sensitive to air and moisture with conversion to, for example, phosphine oxide species. The latter can poison the metal leading to catalyst decomposition. In such cases, catalyst reuse can be difficult.² Hence, the development of phosphine-free recycling catalytic systems is of importance for the Heck reaction.³ There are also significant economical and environmental reasons for developing recyclable catalytic reactions from both academic and industrial perspectives.

As an extension to our research in “recyclable catalytic systems”,⁴ we became interested in the use of nonvolatile room-temperature ionic liquids as reaction media.⁵ We now wish to report preliminary results demonstrating the significant enhancement of reactivity in the Heck reaction using

ionic liquids. Since 1996, there have been extensive studies on the palladium–phosphine-catalyzed Heck reactions in ionic liquids.⁶ It is important to note the remarkable work reported by Seddon and co-workers on the use of [bmim]-[PF₆] or [bmim][BF₄] with PdCl₂ or Pd₂(dba)₃ as a catalyst, tri-*o*-tolylphosphine or triphenylphosphine as a ligand, and Et₃N or NaHCO₃ as a base.^{7,8} Surprisingly, little attention has been paid to phosphine-free Heck reactions.⁹

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Our goal was to employ palladium complexes under phosphine-free conditions to effect the Heck reaction on a recyclable basis. Ionic liquids were chosen because of their recyclability and reusability. The organic products can be easily separated from the transition metal catalysts dissolved in ionic liquids by simple extraction with normal organic solvents. We reasoned that if the ligand has an imidazole moiety, it will have high solubility in ionic liquids having the imidazole skeleton. The ligands **1** and **2** were prepared in 40 and 50% isolated yield by Ullmann coupling of 2-iodo-1-methylimidazole and 2-iodo-1-methylbenzimidazole, respectively, and copper metal. New Pd(II) **1a** and **2a** were obtained in 96% yield from the reaction of Pd(cod)ClMe¹⁰ with equimolar amounts of **1** or **2** in dichloromethane for 2 h at 25 °C.

The complexes are insensitive to oxygen or moisture; no change of their activity was observed when they were exposed to an open system in the Heck reaction. When Pd(cod)Cl₂ or Pd₂(dba)₃ was employed, palladium black or an insoluble solid was observed after an extended reaction time. The catalytic activity of new Pd(II) complexes was examined for the Heck reaction of bromobenzene and *n*-butyl acrylate (Table 1). Using 2 mol % Pd(II) **1** and 2 g of [bmim][PF₆],

Table 1. Heck Coupling of Bromobenzene with *n*-Butyl Acrylate in [bmim][PF₆]^a




entry	base (equiv)	temp (°C)	time (h)	yield (%) ^b
1	NaOAc (1.3)	120	12	12
2	Na ₂ CO ₃ (1.5)	140	12	4
3	Et ₃ N (1.5)	160	12	69
4	first recycle		24	17
5	DIEA (1.5)	160	12	100
6	first recycle		24	32
7 ^c	DIEA (1.5)	160	24	100
8	first recycle		24	37

^a All reactions were carried out using 3 mmol of bromobenzene, 1.25 equiv of *n*-butyl acrylate, 1.5 equiv of Et₃N, 2 mol % **1a**, and 2 g of the ionic liquid. ^b ¹H NMR yield. ^c 4-Bromoanisole was used.

we found that Et₃N or DIEA is an efficient base without the need for an extra ligand such as triphenylphosphine. Unfortunately, it was difficult to recycle the catalyst because it was slowly deactivated at high temperatures (160 °C) and long reaction times (1 day). Below 160 °C, the reaction was too sluggish to be of value. When the more active iodoben-

Table 2. Recyclable Heck Coupling of Iodobenzene with *n*-Butyl Acrylate in [bmim][PF₆]^a



entry	cycle no. ^b				
	1	2	3	4	5
1	>99	>99	>99	>99	>99
2 ^c	>99	>99			
3 ^d	<5				
4 ^e	>99	98	96		

^a All reactions were carried out using 3 mmol of iodobenzene, 1.25 equiv of *n*-butyl acrylate, 1.5 equiv of Et₃N, 2 mol % **1a**, and 2 g of ionic liquid, 120 °C, 1 h. ^b Values given for each cycle are isolated yields (%). ^c Performed with 0.2 mol % catalyst. ^d Performed with 0.02 mol % catalyst. ^e Performed with 2 mol % of **2a**.

zene was coupled with the same acrylate (Table 2), the reaction proceeded to completion at 120 °C within 1 h and afforded only (*E*)-cinnamate in quantitative yield.

We were gratified to observe that the catalyst could be recycled five times without any loss of activity. Furthermore, the reaction was also successful using lower catalytic loading (0.2 mol %), but reactions did not proceed at very low catalyst concentrations (0.02 mol %). For comparison, when we tried the same reaction under fixed conditions (2 mol % catalyst, 120 °C, 1 h) in various organic solvents, the reaction rates were significantly enhanced by using a polar solvent (yield of 4-methyl-*trans*-cinnamic acid *n*-butylester; toluene (17%), dioxane (49%), acetonitrile (71%), DMSO (98%), NMP (99%), DMF (100%), [bmim][BF₄] (99%)). In an organic solvent, excellent catalytic activity is shown in DMSO, NMP, and DMF. MeCN provides good results, but dioxane and toluene are unsatisfactory. Since the catalyst was decomposed in the workup step, it was impossible to recycle the catalyst in all of these solvents. The reaction was followed over a 1 h period, to determine the extent of conversion as a function of time (see Figure 1 in Supporting Information). It is noteworthy that the reaction reached 84% conversion within 5 min and nearly all of the starting material was converted to product after 30 min. This means that the new Pd(II) catalyst is highly efficient for the Heck reaction in ionic liquids. The reaction of iodoarenes containing electron-withdrawing or electron-donating substrates with *n*-butyl acrylate was then run under the optimized conditions, and the results are described in Table 3. All of the coupling reactions proceeded smoothly to give the corresponding (*E*)-cinnamates, with reuse of the catalyst without any loss of activity. Small steric effects were found to be of importance for complete conversion. A 1,1'-bisthiophene (ca. 20%) was the side product of the reaction of 2-iodothiophene with *n*-butyl acrylate, thus reducing the yield of the desired product.¹¹ A more versatile and practical test of the recyclability of the catalyst was examined, wherein each subsequent cycle was carried out with a different substrate. Starting

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


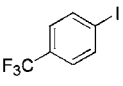
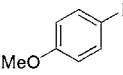
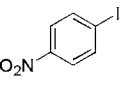
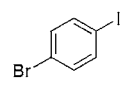
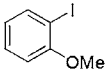

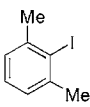

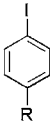
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Table 3. Heck Coupling of Iodoarenes with *n*-Butylacrylate in [bmim][PF₆]^a

$$\text{Ar-I} + \text{CH}_2=\text{CHCO}_2^t\text{Bu} \longrightarrow \text{Ar-CH}=\text{CHCO}_2^t\text{Bu}$$

entry	substrates	recycle no.	time (h)	conv. (%)	yield (%) ^b	entry	substrates	recycle no.	time (h)	conv. (%)	yield (%) ^b			
1		1	1	>99	70 ^c	7		1	1.5	>99	76 ^d			
		2	1	>99	70			2	1.5	80	56 ^e			
		3	1	>99	74			8		1	>99	>99		
		4	1	>99	73					9	>99	>99		
		5	1	>99	73					10		1	>99	>99
2		1	1	>99	94	11		1	>99			98		
		2	1	>99	94			12				24	33	33 ^e
		3	1	>99	91									
		4	1	>99	91									
		5	1	>99	91									
3		1	1	>99	>99	4		1	2	82	82			
		2	1	>99	>99			2	2	73	70			
		3	1	80	76			3	2	38	38			
		4	2	>99	>99			4	15	94	94			
		5	3	>99	>99			5		20	86	85		
4		1	2	82	82	6				0.5	>99	>99		
		2	2	73	70									
		3	2	38	38									
		4	15	94	94									
		20	86	85										

(R = Me, Et)

^a All reactions were carried out under the following conditions: 3 mmol of iodoarenes, 1.25 equiv of *n*-butyl acrylate, 1.5 equiv of Et₃N, 2 mol % **1a**, and 2 g of the ionic liquid, 120 °C. ^b Isolated yield. ^c Bisthiophene was also formed in ~20% yield. ^d 1-Bromo-(*E*)-cinnamate/1-iodo-(*E*)-cinnamate = 3/1. ^e Reactant began to sublime at 120 °C.

with 2 mol % catalyst, five Heck reactions were carried out on a sequential basis (X = H, CF₃, CH₃, NO₂, OCH₃), with the products isolated by ethyl ether extraction, and the ionic liquid was washed with water to remove the amine salt. The recovered ionic liquid layer was reused without any pre-treatment. No loss of catalytic activity was observed in this reaction, thus making the process of potential use to industry (Table 4).

To examine the versatility of this method, the Heck reaction was effected with iodoarenes with containing electron-withdrawing or electron-donating substituents. The results in Table 3 show that the conversions, regioselectivities, and yields were satisfactory within short reaction times. Several other Heck reactions were examined, including ones leading to lactone or lactam; specifically, *ortho*-hydroxy or amino iodobenzene was reacted with *n*-butyl or methyl acrylate under standard reaction conditions, affording products in quantitative yield.¹² Each of the resulting *ortho*-substituted (*E*)-cinnamates were then subjected to cyclization to heterocycles, by refluxing in glycerol for 12 h, 60–99% yield (see Scheme 2 in Supporting Information).

To determine the scope of this catalytic system with other vinyl substrates, 4-iodoanisole was reacted with different unsaturates under identical conditions. Excellent results were obtained for acrylates, butyl vinyl ether,¹³ and styrenes (Table 5). On the basis of the high catalytic activity of the new Pd(II) complex, we also attempted a double-Heck reaction¹⁴

Table 4. Subsequent Recyclable Heck Reaction with Different Iodoarenes^a

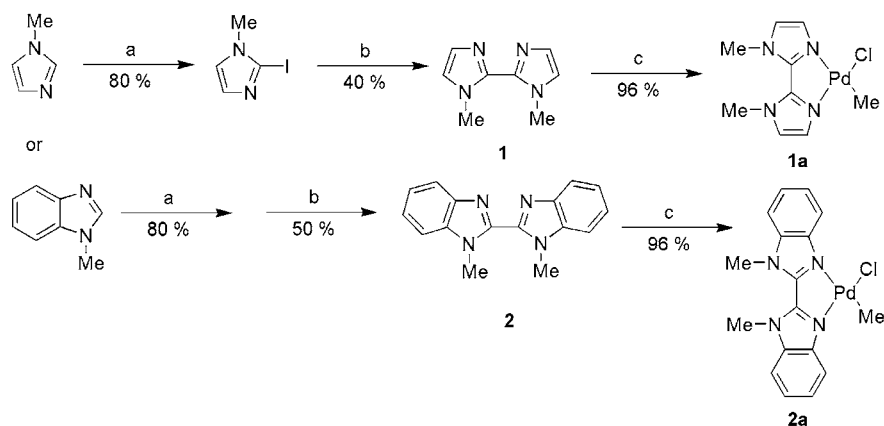
$$\text{X-C}_6\text{H}_4\text{-I} + \text{CH}_2=\text{CHCO}_2^t\text{Bu} \longrightarrow \text{X-C}_6\text{H}_4\text{-CH}=\text{CHCO}_2^t\text{Bu}$$

cycle no.	X	time (h)	conversion (%)	yield (%)
1	H	1	>99	>99
2	CF ₃	1	95	95
3	CH ₃	1	>99	98
4	NO ₂	2	93	93
5	OCH ₃	1	>99	98

^a All reactions were carried out using 3 mmol of the iodoarene, 1.25 equiv of *n*-butyl acrylate, 1.5 equiv of Et₃N, 2 mol % **1a**, and 2 g of the ionic liquid, at 120 °C.

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Scheme 1. Synthesis of Bisimidazole Ligands and Palladium Complexes^a



^a Conditions: (a) MeLi, I₂, THF, -78 °C then rt; (b) Cu, DMF, reflux, 4 h; (c) Pd(cod)ClMe, CH₂Cl₂, rt, 2 h.

by using an excess of iodoarene. β,β -Diphenylacrylates were successfully synthesized with high conversion under standard reaction conditions.¹⁵ The extent of reaction was dependent on the catalyst loading and electronic factors. For example,

Table 5. Heck Coupling of 4-Iodoanisole with Vinyl Compounds^a

entry	X	conversion (%)	yield (%)
1	CO ₂ Me	99	98
2	CO ₂ tBu	99	98
3	O ^t Bu	85 ^b	80 ^b
4	Ph	99	99
5	4-Cl-Ph	97	95

^a All reactions were carried out using 3 mmol of 4-Iodoanisole, 1.25 equiv of the vinyl compound, 1.5 equiv of Et₃N, 2 mol % **1a**, and 2 g of the ionic liquid, at 120 °C, 1 h. ^b α -Adduct/ β -adduct = 9/1.

12% conversion was observed with 2 mol % catalyst (Table 6, entry 1), but 74% conversion was achieved with 10 mol % catalyst (entry 3). The iodoarene, 4-CF₃C₆H₄I, containing the electron-withdrawing CF₃ group, gave mono-Heck reaction in >99% yield with only the biaryl as the side product (53% yield, entry 6). However, iodoarenes with electron-donating groups gave diarylacrylates in excellent conversion in 4 h (entries 4 and 5). Furthermore, it was possible to do

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(15) Initially, Ar¹-I (1.0 equiv) was added to the reaction mixture to give the monoarylated product (1 h) in situ, and then Ar²-I (3.0 equiv) was added to the mixture with stirring for 3 h at 120 °C.

a sequential double-Heck reaction with different kinds of iodoarenes (entries 7 and 8). These results are significant, demonstrating the high reactivity of the catalyst system for disubstitution.

Table 6. Double-Heck Coupling with Iodoarenes with *n*-Butyl Acrylate in [Bmim]PF₆^a

entry	Ar ₁ -I (equiv)	Ar ₂ -I (equiv)	time (h)	conversion (%)	yield (%)
1 ^b	PhI (3)		30	12	8
2 ^c	PhI (3)		24	41	30
3	PhI (3)		24	74	65
4	4-MeO-PhI (4)		4	88	80
5	4-Me-PhI (4)		4	81	80
6	4-CF ₃ -PhI (4)		4	<i>d</i>	
7	4-Me-PhI (1)	PhI (3)	4	76 ^e	70
8	4-MeCOPhI (1)	PhI (3)	4	67 ^f	60

^a Unless otherwise indicated, all reactions were carried out using 3 mmol of *n*-butyl acrylate, 5 equiv of Et₃N, and 10 mol % of **1a** at 120 °C.

^b Performed with 2 mol % of **1a**. ^c Performed with 5 mol % of **1a**. ^d Double-Heck product was not detected; dimer product was produced in 53% yield on the basis of iodoarene. ^e E/Z = 6/4. ^f E/Z = 7/3.

In summary, efficient Heck reactions have been realized using ionic liquids and new Pd(II) catalysts. The Pd(II) complexes having imidazole-like ligands were sufficiently soluble in ionic liquids, enabling excellent and efficient Heck reactions with various iodoarenes and vinyl moieties.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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