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Brønsted Guanidine Acid–Base Ionic Liquids: Novel Reaction Media for the Palladium-Catalyzed Heck Reaction

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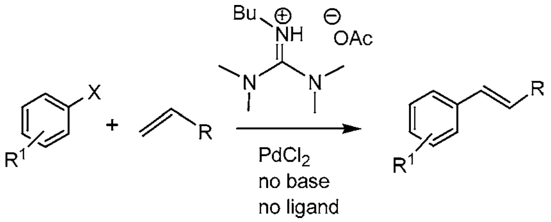
ABSTRACT



Brønsted acid–base ionic liquids (GILs) based on guanidine and acetic acid are efficient reaction media for palladium-catalyzed Heck reactions. They offer the advantages of high activity and reusability. GIL2 plays multiple roles in the reaction: it could act as solvent, as a strong base to facilitate *β*-hydride elimination, and as a ligand to stabilize activated Pd species.

The palladium-catalyzed couplings of olefins with aryl or vinyl halides, known as the Heck reaction,[1] have attracted increasing attention due to their synthetic versatility. The recent development of many efficient procedures involving Pd catalyst precursors, such as those associated with carbenes,[2] N-, S-, P-, and Se-containing palladacycles,[3] and even ligand-free approaches,[4] are quite impressive. However, most of them are homogeneous systems and share common drawbacks; that is, catalyst/product separation and catalyst reuse are difficult. This problem has been solved by the immobilization of Pd catalysts[5] and by using heterogeneous catalysts.[6] However, these systems do not reach the high activities of homogeneous catalysts and often suffer from

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substantial Pd leaching.[7] Therefore, finding more simple, efficient, and reusable catalytic systems for the Heck reaction is of importance practically and is still in demand.

Ionic liquids (ILs), known for their nonvolatile, nonflammable, and thermally stable properties, have recently been used in the Heck reaction under the catalysis of palladium with or without a phosphine ligand.[8] As an alternative to a volatile, toxic, organic solvent, ILs can serve as an excellent medium and as a mobile support for Pd catalysts. To avoid catalyst leaching in IL systems, some efforts have been made by introducing functional groups into the ionic liquid which can complex with metal centers.[9] Another way is the introduction of imidazolium tags into a metal complex to enhance the solubility of the catalyst in ionic liquids.[10] However, the syntheses of functionalized ionic liquids or ionic metal complexes are rather complicated and multistep procedures have to be used.

The essential requirement for the Heck reaction includes a base, a ligand-stabilized active Pd species, and a reaction medium. Guanidine is a strong organic base and is able to form a complex with a Pd(II) salt. It is also known that ionic liquids based on guanidinium salts are excellent reaction media for organic reactions.[11] Herein, we wish to report that Brønsted guanidine acid−base ionic liquids (GILs) are efficient media for the Heck reaction. To the best of our knowledge, the guanidine acid−base ionic liquid is one of the simplest catalyst systems, which could be used not only as a solvent but also as a ligand and a base and offers the advantage of high activity and reusability without the need of a phosphine ligand.

GILs1−3 (Figure 1) were prepared by neutralizing guanidine with acetic acid or HPF_6, respectively. The GIL1 and GIL3 are white solids, and GIL2 is a colorless liquid at room temperature.

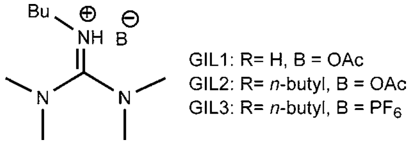
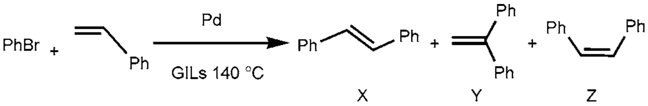


Figure 1. Structures of GILs1−3.

Table 1. Palladium-Catalyzed Heck Reaction of Bromobenzene and Styrene[a]



entry	GIL	catalyst	*t* (h)	yield (%)[b]	TON
1	GIL1	$PdCl_2$	20	99	620
2	GIL2	$Pd(OAc)_2$	2	99	620
3	GIL2	$PdCl_2$	0.25	99	620
4	GIL3	$Pd(OAc)_2$	4	0	0
5[c]	GIL2	$PdCl_2$	20	98	9800
6[d]	GIL2	$PdCl_2$	48	34	340000

[a] Unless otherwise indicated, the reaction conditions were as follows: bromobenzene (5 mmol), styrene (6 mmol), GIL (6 mmol), $PdCl_2$ (0.16 mol %) or $Pd(OAc)_2$ (0.16 mol %), 140 °C. [b] Average of isolated yields of two runs. [c] Catalyst (0.01 mol %). [d] Catalyst (0.0001 mol %).

The coupling reactions of bromobenzene (5 mmol) with styrene (6 mmol) in different GILs (6 mmol) at 140 °C in a sealed flask were investigated, in which $Pd(OAc)_2$ or $PdCl_2$ was used as the catalyst. As can be seen from the data in Table 1, the catalyst system based on GIL2 displayed excellent activity. Quantitative conversion was achieved within 0.25 h when 0.16 mol % of $PdCl_2$ was applied, and the selectivity for *trans*-stilbene was 98% (X/Y/Z = 98:1.7:0.3); the same conversion in GIL1 could only be gained by prolonging the reaction time to 20 h (Table 1, entry 1). Decreasing the catalyst loading to 0.01% still resulted in quantitative conversion and high selectivity, even though the reaction times were prolonged to 20 h (Table 1, entry 5). Attempts to decrease the catalyst loading even further, to 0.0001 mol % Pd, resulted in the incomplete conversion of bromobenzene, but a moderate yield could still be obtained after prolonged heating (entry 6, TON = 340 000). $PdCl_2$ was more efficient than $Pd(OAc)_2$ in this reaction. There was no detectable conversion when the reaction was performed in GIL3 (Table 1, entry 4). In GIL1 and GIL2, a homogeneous yellow solution was formed during the reaction. However, in GIL3, palladium black slowly precipitated,

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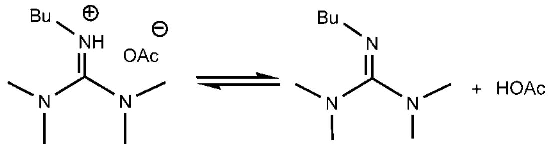
which indicated the decomposition of active palladium species.

Dupont et al. reported that ionic liquids based on dialkylimidazolium were capable of stabilizing the catalytically active Pd nanoparticles[12] in the Heck reaction. However, the Heck reaction of bromobenzene and olefins performed in imidazolium-based ionic liquids proceeded very slowly with a low yield. This is in contrast to the present work performed in a guanidinium ionic liquid catalyst solution where the reaction was completed within 0.25 h in a high yield. The result clearly indicates the significant enhanced effect of the guanidinium salts on the rate. In a previous paper, we reported that tetramethylguanidine was an efficient ligand for palladium-catalyzed Heck reactions.[13] In the present study, GILs1−2 consisted of a strong organic guanidine base and an organic weak acid. At an elevated reaction temperature (140 °C), GILs may dissociate into guanidine and acetic acid (Scheme 1), so the generated guanidine acts as a base and a ligand for active Pd species. The efficiency of this catalyst system would contribute to the stabilization of the Pd by the guanidine or GILs[14] and to the very fast PdH neutralization by the strong guanidine base. TGA analysis showed (Figure 2) that the GILs1−2 indeed decomposed into guanidine and acetic acid, and the GIL3 is stable below 200 °C. This could explain why GIL3 was not active for the Heck reaction under these reaction conditions. The difference between the catalytic activities of GIL1 and GIL2 should come from that of Pd(II) complexes based on tetramethylguanidine and 2-butyl-1,1,3,3-tetramethylguanidine. To prove this assumption, the complex (1) L_2PdCl_2[15] (L = 2-butyl-1,1,3,3-tetramethylguanidine) was prepared by a similar procedure for the preparation of tetramethylguanidine Pd(II) complex 2.[13] Its molecular structure is shown in Figure 3. It is known that four molecules of tetramethylguanidine can coordinate simultaneously to a Pd(II) center in complex 2.[13] As shown in Figure 3, however, only two 2-butyl-1,1,3,3-tetramethylguanidine molecules and two chloride ions coordinated to the Pd(II) center. The active catalyst involved in the arylation is generally believed to be the 14 e species $L_2Pd(0)$.[1] We used 0.1 mol % of complex 1 to catalyze the reaction between bromobenzene and styrene in DMA. We observed the complete conversion to stilbene after 2 h at 140 °C. This activity was higher than that of complex 2.[13]

Scheme 1. Equilibrium Reaction of GIL2 in the Sealed Flask



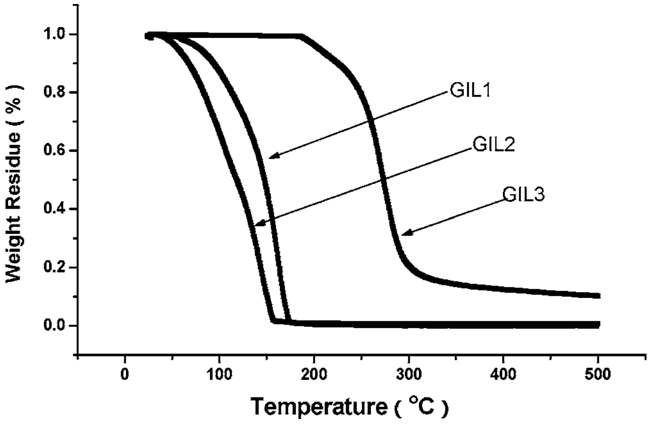


Figure 2. TGA curves of GILs1−3.

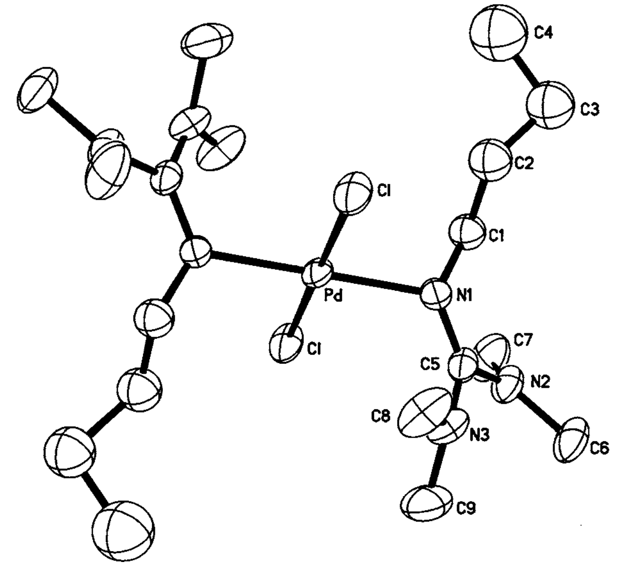


Figure 3. Molecular Structure of L_2PdCl_2; L = 2-*n*-butyl-1,1,3,3-tetramethylguanidine.

To examine the versatility of this method, several representative aryl halides with electron-withdrawing or electron-donating substituents were tested in GIL2. The results in Table 2 show that the regioselectivities and yields were satisfactory within a short reaction time. The results indicate that the GIL2/$PdCl_2$ system is efficient for the Heck reaction.

The described GIL2 protocol is of further advantage because the catalyst and the GILs could be recycled. The

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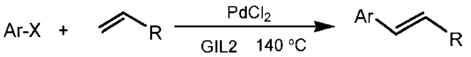
[15] Crystal data: $C_{18}H_{42}Cl_2N_6Pd$ (L_2PdCl_2), M = 519.88, triclinic space group $P\bar{1}$, $a = 8.528(2)$ Å, $b = 8.709(2)$ Å, $c = 9.053(2)$ Å, $\alpha = 76.742(4)°$, $\beta = 85.015(5)°$, $\gamma = 88.705(4)°$, $V = 651.9(3)$ Å^3, $T = 293(2)$ K, final R indices [$I > 2\sigma(I)$], R1 = 0.0604, wR2 = 0.1499.

Table 2. $PdCl_2$/GIL2-Catalyzed Heck Reaction of Aryl Halides and Olefins[a]



entry	aryl halide	R	*t* (h)	yield (%)[b]
1	C_6H_5I	Ph	0.25	99
2	C_6H_5I	CO_2Bu	0.25	100
3	*p*-MeC_6H_4I	Ph	0.5	96
4	*p*-MeC_6H_4I	CO_2Bu	0.5	98
5	*p*-MeC_6H_4Br	Ph	1	96
6	*p*-MeC_6H_4Br	CO_2Bu	1	98
7	*p*-$MeOC_6H_4Br$	Ph	2	92
8	*p*-$MeOC_6H_4Br$	CO_2Bu	2	93
9	*p*-(CHO)C_6H_4Br	Ph	0.25	99
10	*p*-(CHO)C_6H_4Br	CO_2Bu	0.25	100
11	*p*-$NO_2C_6H_4Br$	Ph	0.25	99
12	*p*-$NO_2C_6H_4Br$	CO_2Bu	0.25	100
13	3-Br−Pyridine	Ph	0.5	98
14	3-Br−Pyridine	CO_2Bu	0.5	99
15	*p*-$NO_2C_6H_4Cl$	Ph	1.0	95
16	*p*-$NO_2C_6H_4Cl$	CO_2Bu	1.0	96
17	*p*-(CHO)C_6H_4Cl	Ph	1.0	94
18	*p*-(CHO)C_6H_4Cl	CO_2Bu	1.0	97
19	C_6H_5Cl	Ph	5.0	10
20	C_6H_5Cl	CO_2Bu	5.0	12

[a] Unless otherwise indicated, the reaction conditions were as follows: aryl halide (5 mmol), olefin (6 mmol), GIL2 (6 mmol), $PdCl_2$ (0.16 mol %), 140 °C. [b] Average of isolated yields of two runs.

Figure 4. Biphasic mixture of $PdCl_2$ in GIL2 (bottom layer) and toluene/hexane (top layer).

Heck reaction of bromobenzene (2 mmol) with styrene (2.2 mmol) was carried out in GIL2 (10 mmol). Upon the completion of the reaction, the products were separated via simple extraction with toluene/hexane (1:1). A clear demonstration of this phase behavior is given in Figure 4, where the preferential solubility of the yellow palladium catalyst in the lower ionic phase is clearly apparent. After the extraction of the product of the first-time reaction, bromobenzene and styrene were added again in the same ionic liquid. At this stage, the ionic liquid solution contained GIL2 and guanidinium bromide. This ionic liquid mixture was still active until all acetate converted to bromide. The catalytic system was reused five times, and it proceeded well without the loss of activity. The amount of palladium that remained in GIL2 was determined by means of ICP-AES. The concentration of palladium in GIL2 was 0.45 mg/g, which was slightly decreased in comparison with the original loading (0.49 mg/g).

In summary, the basic guanidine-based room-temperature ionic liquid (GIL2) was successfully used in the palladium catalytic Heck reaction. GIL2 played multiple roles in this system. First, it offered ligands to stabilize the activated Pd(0) during the reaction. Second, it offered a strong base to favor the competitive β-hydride elimination, and finally, it offered a high polar solvent to increase the reaction rate. The catalyst and the GIL2 could be recycled at least five times without the loss of catalytic activity.

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Supporting Information Available: Analytical data and spectra (^1H NMR) for all the products; typical procedure for the preparation of the GIL, as well as X-ray crystallographic data for complex 1 (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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