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The Heck Reaction in Ionic Liquids: A Multiphasic Catalyst System

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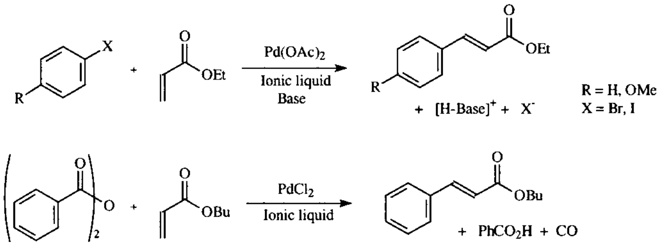
ABSTRACT



Heck coupling of aryl halides or benzoic anhydride with alkenes can be performed with excellent yields in room-temperature ionic liquids, which provide a medium that dissolves the palladium catalyst and allows the product and byproducts to be easily separated. Consequently, the catalyst and ionic liquid can be recycled and reused.

The Heck reaction is of major importance in synthetic organic chemistry, as a carbon−carbon bond-forming reaction.[1] It is often used to functionalize aromatic rings and as an alternate to the Friedel−Crafts reaction.[2] The Heck reaction usually involves the interaction of an aromatic halide[3] or anhydride[4] with an alkene, in the presence of a palladium catalyst at typically a 1−2 mol % concentration, to give an aryl alkene. The reaction normally requires a base to be present,[5,6] particularly in the reactions of aryl halides (but not anhydrides).[4] A major problem with the Heck reaction is that the palladium catalyst is often lost at the end of the reaction.[6] Hence, a process for recycling the catalyst system is of importance.

Room-temperature ionic liquids have been used to great effect as solvents for a number of reactions, for example, Friedel−Crafts reactions,[7] isomerizations of fatty acid derivatives,[8] dimerization reactions of alkenes,[9] Diels−Alder reactions,[10] and hydrogenation reactions.[11] Ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate[12] ([bmim][PF$_6$]) have a particularly useful set of properties, being virtually insoluble in water and alkanes but readily dissolving many transition metal catalysts.[13] Such biphasic

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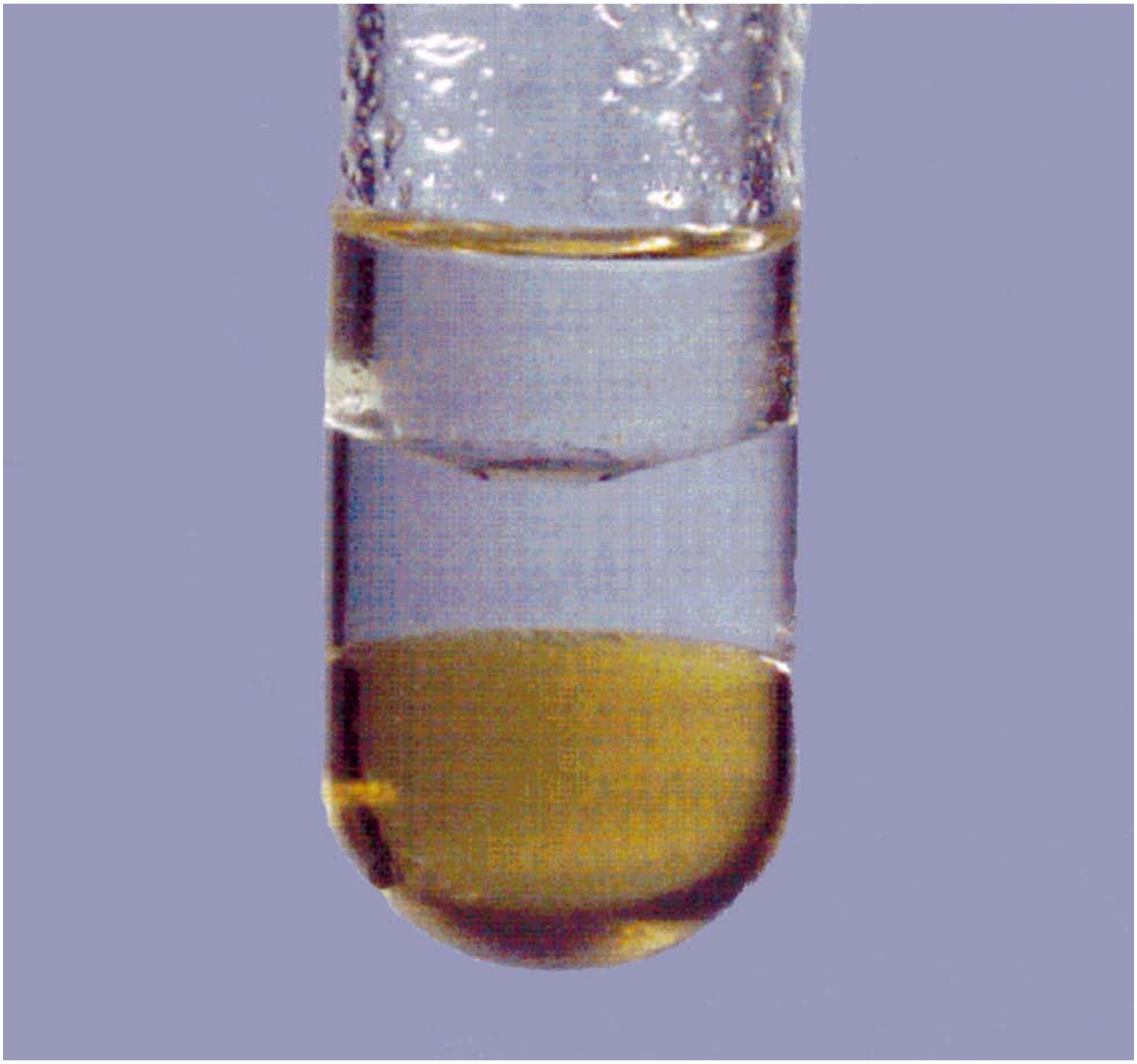

Figure 1. A triphasic mixture of $[bmim]_2[PdCl_4]$ and $P(o\text{-tol})_3$[18] in $[bmim][PF_6]$ (lower layer), water (middle layer), and cyclohexane (top layer).

ionic liquid systems have been used to enable simple extraction of products.[14] Furthermore, if benzoic anhydride is used as a source of aryl moiety, then a base is not required for the reaction (the byproduct in this case is an aryl carboxylic acid which can be recovered at the end of the reaction and converted back to an anhydride).[4]

We have found that the Heck reaction can be performed in a number of low melting point *N*,*N*′-dialkylimidazolium or *N*-alkylpyridinium ionic liquids with halide, hexafluorophosphate, or tetrafluoroborate anions. For our work, we concentrated on using salts with a limited number of anions and cations, so that a correlation between reactivity in the Heck reaction and structural differences in the salts could be determined. For the cation, 1-butyl-3-methylimidazolium ([bmim]), 1-pentyl-3-methylimidazolium ([pmim]), or *N*-hexylpyridinium ($[C_6py]$) species were chosen.[15]

As mentioned above, the high solubility of both $[bmim]_2[PdCl_4]$[13] and $[Pd(OAc)_2(PPh_3)_2]$ in ionic liquids and their low solubility in organic solvents (such as toluene or hexane) enables the products of the reaction to be separated from the ionic liquid and catalyst by solvent extraction with an organic solvent or by distillation from the reaction vessel. Furthermore, if a hydrophobic ionic liquid is chosen (e.g. $[bmim][PF_6]$ or $[C_6py][BF_4]$), then water can also be used

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as an extraction solvent to remove the salt byproducts formed in the reaction. A clear demonstration of this phase behavior is given in Figure 1, where the preferential solubility of the yellow palladium catalyst in the lower ionic phase is clearly apparent.

In the Heck reaction of iodobenzene with ethyl acrylate (Table 1), the reaction proceeds smoothly to produce the expected *trans*-ethyl cinnamate in excellent yields.[16] For reactions carried out in the chloride salts (entries 1, 2, and 6−10), the *N*-hexylpyridinium salts give rise to higher yields than the corresponding reactions in imidazolium salts. The addition of a phosphine ligand to the palladium species in the reaction in the pyridinium salt decreased the yield, and a higher reaction temperature was then required to force the reaction to completion (entries 6 and 7). Several authors have reported that a cosolvent such as DMF or *N*-methylpyrrolidinone (NMP) is required for this reaction;[4,17] however we have found that they are not required and can often decrease the yield of the reaction (entry 10).

Table 1. Heck Reaction of Iodobenzene and Ethyl Acrylate To Give *trans*-Ethyl Cinnamate in Ionic Liquids with 2 mol % of $Pd(OAc)_2$

entry	ionic liquid	additive	base	temp, °C	time, h	yield, %
1	$[C_6py]Cl$	none	Et_3N	40	24	99
2	$[C_6py]Cl$	none	$NaHCO_3$	40	24	98
3	$[C_6py][PF_6]$	none	$NaHCO_3$	80	72	42
4	$[C_6py][BF_4]$	none	$NaHCO_3$	80	72	99
5	$[bmim][PF_6]$	Ph_3P (4 mol %)	Et_3N	100	1	95−99[19]
6	$[C_6py]Cl$	Ph_3P (4 mol %)	$NaHCO_3$	40	24	82
7	$[C_6py]Cl$	Ph_3P (4 mol %)	$NaHCO_3$	100	24	99
8	[pmim]Cl	none	Et_3N	80	72	10
9	[pmim]Cl	none	$NaHCO_3$	100	24	19
10	$[C_6py]Cl$	DMF	$NaHCO_3$	40	24	77

For the reactions carried out in hexafluorophosphate or tetrafluoroborate room-temperature ionic liquids (entries 3 and 4), higher reaction temperatures are needed. Of these two anions, the tetrafluoroborate ionic liquid gives higher yields. In contrast to the chloride-based systems, the addition of a phosphine ligand (such as Ph_3P) was found to promote the reaction in the imidazolium salt $[bmim][PF_6]$ (entry 5). This ionic liquid/catalyst combination can operated under triphasic conditions and give ethyl cinnamate in greater than 95% yield over many reaction cycles,[19] without loss of catalytic activity.

To test whether less reactive aromatic compounds could reliably undergo the Heck reaction, the reaction of 4-bromoanisole (the relative reactivity in the Heck reaction is as follows: $4\text{-}(MeO)C_6H_4Br < C_6H_5Br < 4\text{-}(CHO)C_6H_4Br$)[20] with ethyl acrylate was investigated, in the ionic liquid $[bmim][PF_6]$, using triethylamine as the base and a range of Group 15 ligands (Table 2). The reactions were carried out at two temperatures: 100 °C and 140 °C. As expected, the Group 15 ligand on the palladium catalyst had a significant effect on the yield and conditions required to complete the reaction.

Table 2. Heck Reaction of 4-Bromoanisole and Ethyl Acrylate To Give Ethyl 4-Methoxycinnamate with Various Group 15 Ligands in $[bmim][PF_6]$ with Triethylamine as the Base

entry	Group 15 ligand added (4 mol %)	temp, °C	time, h	yield, %
11	none	100	20	7
12		140	18	94
13	triphenylphosphine	100	72	65
14		140	24	98
15	tri-*o*-tolylphosphine	100	4	55
16		100	24	65
17		140	18	99
18	triphenyl phosphite	100	24	1.5
19		140	24	31
20	1,2-bis(diphenylphosphino)ethane[27]	100	18	<1
21		140	24	13
22	1,1'-bis(diphenylphosphino)ferrocene[27]	100	18	<1
23		140	18	95
24	triphenylarsine	100	12	2
25		140	20	99
26	triphenylstibine	100	72	<1
27		140	24	24

As shown in Table 2, three of the ligands chosen were unsuitable for this reaction, giving poor yields. These were triphenyl phosphite, triphenylstibine, and 1,2-bis(diphenylphosphino)ethane (entries 19, 21, and 27). In the case of triphenylstibine and 1,2-bis(diphenylphosphino)ethane, the

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(16) **General Procedure for the Heck Reaction in Ionic Liquids**. To a round-bottom flask (25 cm^3), equipped with a magnetic stirrer flea and reflux condenser, were added 1-butyl-3-methylimidazolium hexafluorophosphate (5.0 g), palladium(II) acetate (0.045 g, 0.20 mmol), and triphenylphosphine (0.105 g, 0.40 mmol), and the mixture was heated to 80 °C for 5 min with stirring to form the ionic liquid solution of the catalyst. A mixture of triethylamine (1.51 g, 15.0 mmol), iodobenzene (2.04 g, 10.0 mmol), and ethyl acrylate (1.25 g, 12.5 mmol) was added, and the mixture was heated to 100 °C for 1 h. Gas chromatographic analysis of the product showed that no iodobenzene was present. The product was extracted from the reaction vessel by the addition of hexane (10 cm^3), followed by decanting off a hexane solution of the product. This was repeated three further times. The combined hexane extracts were concentrated on a rotary evaporator, and the product was purified by Kugelrohr distillation. This gave 1.67 g of a colorless oil (yield = 95%). The spectroscopic properties of this oil were in accordance with those of authentic *trans*-ethyl cinnamate.

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(18) The catalyst was made by dissolving $[bmim]_2[PdCl_4]$ (1 equiv) and $P(o\text{-}tol)_3$ (2 equiv) in $[bmim][PF_6]$ at 70 °C. For background information of this reaction, see: Herrmann, W. A.; Bohn, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141.

(19) The reaction was carried out six times without loss of activity of the catalyst. The product (*trans*-ethyl cinnamate) was extracted from the reaction vessel with cyclohexane, and the triethylammonium iodide salt was removed by solvent extraction with water. It is important to note that this reaction will work in the presence of a very large excess of water (a 50-fold excess does not hinder this reaction).

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palladium catalyst formed inactive insoluble complexes. As for the other reactions, over 94% yields were readily obtained at 140 °C. Two of ligands gave rise to reactions with rates lower than those in the absence of added ligand (entries 13−17).[21] The ligands triphenylphosphine and tri-*o*-tolylphosphine gave rate enhancements over the absence of Group 15 ligand at 100 °C. It should be noted that in the case of tri-*o*-tolylphosphine, a palladacycle[17b,22] has been observed from the reaction of tri-*o*-tolylphosphine and palladium(II) acetate, and this species may be the active catalyst. These observations appear to show that the electron rich or bidentate ligands reduce the reactivity of the catalyst. In the case where no ligand was present, the reaction was not effective at 100 °C. This is thought to be due to the formation of palladium black. At the higher reaction temperature of 140 °C, the palladium redissolves and the reaction proceeds smoothly. This order of reactivity is summarized in Figure 2.

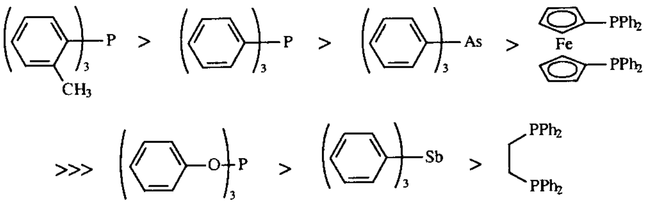

Figure 2. The relative order of reactivity for different ligands in the Heck reaction at 100 °C (Table 2).

The reaction of 4-bromoanisole with alkyl acrylates can give rise to modest yields of the corresponding 4-methoxycinnamates.[20b] Therefore the yield in this reaction is a good test of the performance of the catalyst, solvent, and methodology used. For the reactions of 4-bromoanisole performed in the ionic liquid (Table 2), the yields in this reaction exceed the literature yields.[20b] Furthermore, the product is easily isolated by solvent extraction, and the catalyst and ionic liquid can be recycled.

The reaction of benzoic anhydride with alkenes has also been investigated in ionic liquids in the absence of a base (Table 3). The reaction of butyl acrylate with benzoic anhydride gave *trans*-butyl cinnamate in 90−95% yields.[23] Typically the product and byproduct (benzoic acid) are extracted with ether, and fresh reagents can be added. As can be seen, the reaction works well in chloride salts (entry 28). With the room-temperature ionic liquid $[bmim][BF_4]$, higher reaction temperatures are required (entry 29), but the reaction still works efficiently.

Table 3. Heck Reaction of Benzoic Anhydride and Butyl Acrylate in Ionic Liquids

entry	ionic liquid	catalyst	temp, °C	time, h	yield, %
28	$[C_6py]Cl$	$PdCl_2$ (2 mol %)	160	20	90
29	$[bmim][BF_4]$	$Pd(OAc)2 \cdot 2\ P(o\text{-}tol)_3$ (2 mol %)	200	3	95

In general, there is a considerable difference in reactivity in the Heck reaction between imidazolium and pyridinium ionic liquids. In the case of imidazoium ionic liquids, the 2-H proton is acidic and in the presence of a base can be deprotonated to form a carbene.[24] These imidazolylidine carbenes are known to act as ligands to metals such as palladium(II) and an imidazolylidine-palladium carbeneoid species may be implicated.[25] This may also explain why insoluble palladium black redissolves at above 100 °C in reactions carried out without Group 15 ligands. In the case of reactions carried out in the pyridinium salts (particularly the chloride), phosphine ligands on the palladium catalyst hinder the reaction (see entry 6). It has been suggested that in a chloride (or halide) rich environment, this reaction involves a Pd(II)/Pd(IV) redox cycle,[26] whereas in the cases where the phosphine ligands accelerate the reaction, a mechanism involving Pd(0) and Pd(II) species is involved.[4,17]

In conclusion, ionic liquids such as $[bmim][PF_6]$ are excellent media for the Heck reaction. They can selectively dissolve the palladium catalyst in preference to water or alkane solvents, allowing for ionic liquid and catalyst recycling.

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(23) Owing to the high reaction temperatures (above the boiling point of butyl acrylate), the reaction was carried out in a sealed thick walled glass reaction vessel.

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(27) 2 mol % of ligand was added (4 mol % in P atoms).