

Highly Efficient Heck Reactions of Aryl Bromides with *n*-Butyl Acrylate Mediated by a Palladium/Phosphine–Imidazolium Salt System

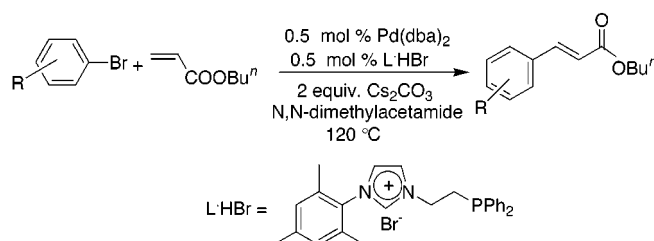
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Received March 12, 2001

ABSTRACT



A new phosphine–imidazolium salt, L·HBr (1, L = (1-ethylenediphenylphosphino-3-(mesityl)imidazol-2-ylidene), has been prepared. A combination of 0.5 mol % of Pd(dba)₂ and 0.5 mol % of L·HBr in the presence of 2 equiv of Cs₂CO₃ as base has proven to be highly efficient in the Heck coupling reactions of aryl bromides (from electron-deficient to electron-rich aryl bromides) with *n*-butyl acrylate.

The use of monodentate phosphines in the Pd-catalyzed Heck reaction provides a most efficient catalytic system for the syntheses of substituted olefins.¹ The primary role of the phosphine ligands is to support palladium in the form of stable PdL₄ or PdL₃ species which can subsequently enter the catalytic cycle and thereby help prevent the formation of inactive palladium black aggregates. Reactions involving the less reactive aryl bromides and aryl chlorides require electron-donating, bulky tertiary phosphines, such as P(*t*-Bu)₃, as supporting ligand in order to assist in the initial oxidative-addition of C–X bonds.² However, under Heck conditions, phosphines and their palladium complexes are

subject to decomposition. Hence, excess phosphine has to be employed. This is undesirable for large-scale applications since phosphines, especially electron-rich phosphines, are expensive. The use of excess ligand also reduces the reaction rates, and in order to counterbalance this negative effect a higher palladium loading is necessary to achieve acceptable catalytic activities.

Bidentate chelating phosphines, in principle, can provide more stable (1:1) Pd(L–L) complexes suitable for Heck reactions and thereby avoid the use of excess phosphine and high loadings of palladium. However, catalytic systems based on bidentate phosphine ligands have displayed limited successes.³

Recently, nucleophilic N-heterocyclic carbenes, or so-called “phosphine mimics”, have attracted a considerable amount of attention.⁴ These ligands are strong σ -donors with negligible π -accepting ability,⁵ and in this respect, they

(1) (a) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Reetz, M. T. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999. (c) Grisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (d) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (e) Link, J. T.; Overman, L. E. *Chemtech* **1998**, *28*, 19. (f) Brase, S.; deMeijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (g) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (h) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

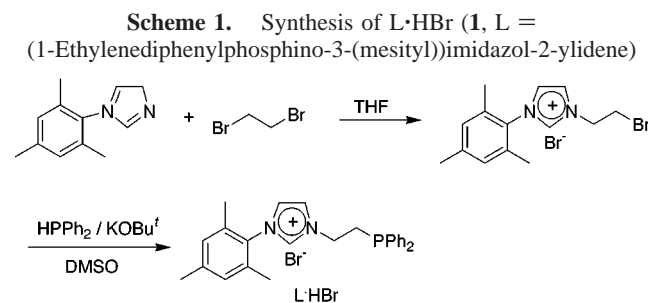
(2) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.

(3) (a) Shaw, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863. (b) Overman, L. E.; Poon, D. J. *Angew. Chem.* **1997**, *36*, 518. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558.

resemble donor phosphines. In contrast to metal phosphine complexes, they form metal complexes that have higher stability toward heat, moisture, and oxygen. Improved catalytic performance has been achieved by the exchange of bulky electron-donating phosphine ligands with nucleophilic carbenes in various catalytic reactions such as Suzuki-type coupling reactions,⁶ amination of aryl chlorides,⁷ olefin metathesis,⁸ and hydrogenations.⁹ The beneficial properties provided by nucleophilic carbene ligands make them a potential ligand family for the Heck reaction. In fact, some early work by Herrmann, Cavell, and others has shown that several Pd carbene complexes were highly efficient in Heck reactions.¹⁰

In view of the general usage of phosphines and the potential of carbene ligands in Heck reactions, we examined mixed phosphine–imidazolium salt bidentate ligands as desirable ligation for Heck chemistry. The chelating phosphine–carbene ligand derived from the imidazolium salt would potentially form a more stable palladium catalyst, so that use of excess ligand and high loadings of palladium might be avoided. Indeed, a recent theoretical calculation shows that a chelating ligand, which consists of a carbene and a phosphine moiety, is suitable for the Pd-catalyzed Heck reaction.¹¹ However, no experimental data have yet been provided to support the calculations. We now report the synthesis of the new phosphine–imidazolium salt L·HBr (**1**, L = (1-ethylenediphenylphosphino-3-(mesityl))imidazol-2-ylidene) and its application in Pd-catalyzed Heck reaction of aryl halides with *n*-butyl acrylate.

The phosphine–imidazolium salt L·HBr (**1**) was prepared in a two-step procedure (Scheme 1). A THF solution of



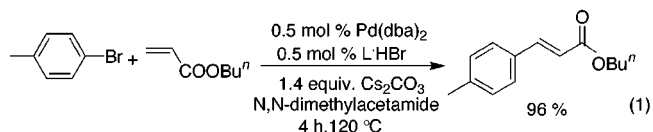
1-(mesityl)imidazole was treated with a 4-fold excess of 1,2-dibromoethane. The intermediate bromine–imidazolium salt slowly precipitated as a white solid during the course of 2 days. Addition of the imidazolium salt to potassium diphe-

(4) (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39, and references therein. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **2000**, *1*, 1751. (c) Schöll, M.; Trmka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (d) Jafarpour, L.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5416. (e) Dullius, J. E. L.; Suarez, P. A. Z.; Einloft, S.; de Souza, R. F.; Dupont, J.; Fischer, J.; De Cian, A. *Organometallics* **1998**, *17*, 815. (f) Aduengo, A. J., III; Krafczyk, R. *Chem. Z.* **1998**, *32*, 6. (g) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162. (h) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725.

(5) Green, J. C.; Scurr, R. G.; Arnold, P. L.; Cloke, G. N. *Chem. Commun.* **1997**, 1963.

nylphosphide, which was prepared in situ by mixing diphenylphosphine and KOBu^t in DMSO, gave the phosphine–imidazolium salt in 91% yield. It should be mentioned that the position of the imidazolium proton was unaffected by the addition of potassium diphenylphosphide.¹²

Recent work in our laboratories has established that active Pd-carbene species can be formed in situ (under basic conditions) from an imidazolium salt in various C–C and C–N coupling reactions.^{6b–d} In our initial experiments, we applied a similar protocol to a catalytic system consisting of 0.5 mol % of Pd(dba)₂, 0.5 mol % of L·HBr (**1**), and 1.4 equiv of Cs₂CO₃, as base, in *N,N*-dimethylacetamide (DMAc) at 120 °C. This system proved to be highly efficient in Heck coupling of 4-bromotoluene with *n*-butyl acrylate. The reaction proceeded very rapidly and reached almost completion in 4 h (eq 1). An independent experiment without the



addition of **1** showed no Heck activity. A recent review addresses conditions for a ligand-free Heck reaction.¹³ The present study involves a ligand-accelerated conversion.

Investigations into the optimum solvent for this reaction showed that reaction rates were significantly enhanced by using polar solvents, with *N,N*-dimethylacetamide being the solvent of choice (Table 1). The reaction rates were also very

Table 1. Effect of the Solvent on the Heck Reaction of 4-Bromobenzene with *n*-Butyl Acrylate^a

entry	solvent	yield ^b (%)
1	THF	8
2	dioxane	27
3	DMF	62
4	DMAc	96

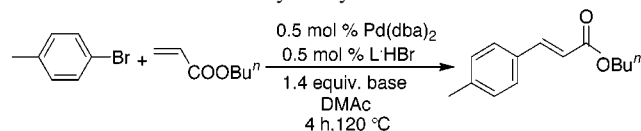
^a Reaction condition: 1 mmol of 4-bromotoluene, 1.4 mmol of *n*-butyl acrylate. ^b GC yield (diethylene glycol di-*n*-butyl ether as GC standard; an average of two runs).

dependent on the base employed (Table 2). A remarkable increase in activity was observed with Cs₂CO₃. The use of 2 equiv, rather than 1.4, was found to be optimal. Other

(6) (a) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186. (b) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (c) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

(7) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307.

(8) (a) Huang, J.; Stevens, E. D.; Nolan, S. P. Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Huang, J.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375.

Table 2. Effect of the Base on the Heck Reaction of 4-Bromobenzene and *n*-Butyl Acrylate^a

entry	base	yield ^b (%)
1	none	0
2	NEt ₃	5 ^c
3	KOBu ^t	0 ^d
4	NaOAc	12
5	K ₂ CO ₃	6
6	Cs ₂ CO ₃	96

^a Reaction condition: 1 mmol of 4-bromotoluene, 1.4 mmol of *n*-butyl acrylate. ^b GC yield (diethylene glycol di-*n*-butyl ether as GC standard; an average of two runs). ^c Biphenyl as major product. ^d Decomposition.

inorganic and organic bases resulted in poorer yields. Substitution of Pd(dba)₂ with Pd(OAc)₂ in the catalytic protocol resulted in a significant decrease in activity with only a 47% yield of the coupled product.

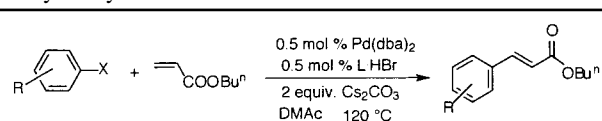
Under our optimized reaction conditions (0.5 mol % of Pd(dba)₂, 0.5 mol % of L·HBr, 2 equiv of Cs₂CO₃, *N,N*-dimethylacetamide, 120 °C), excellent yields of coupled products could be obtained for a wide array of aryl bromides with *n*-butyl acrylate (Table 3). For example, the electron-deficient 4-bromobenzaldehyde was completely converted to the coupled product in ca. 15 min (entry 1). For electron-neutral bromides (bromobenzene, 4-bromotoluene, and 5-bromo-*m*-xylene), complete conversions could also be obtained in less than 2 h (entries 2, 3, and 5). For a sterically congested substrate, 2-bromotoluene, a yield of 35% could be reached in 1 h (entry 4). Longer reaction times afforded a side product resulting from a dehalogenation process. Remarkably, the catalytic system was equally efficient for an electron-donating bromide. A complete conversion could be obtained for 3-bromoanisole and 4-bromoanisole yielding *n*-butyl *trans*-methoxycinnamate in less than 3 h (entries 6 and 7). It should be noted that in all cases only the *trans* products were selectively obtained as confirmed by GC and ¹H NMR. Isolated yields were obtained in certain examples (entries 1, 3, and 6) in order to provide evidence for the practical use of the method.¹⁴

(9) (a) Lee, H. M.; Smith, D. C., Jr.; He, Z.; Stevens, E. D.; Yi, C. S.; Nolan, S. P. *Organometallics* **2001**, *20*, 794. (b) Lee, H. M.; Jiang, T.; Stevens, E. D. Nolan, S. P. *Organometallics* **2001**, *20*, 1255.

(10) (a) Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem. Eur. J.* **2000**, *6*, 1773. (b) Tulloch, A. A. D.; Danopoulos, A. A.; Tooze, R. P.; Cafferkey, S. M.; Kleinhenz, S.; Hursthouse, M. B. *Chem. Commun.* **2000**, 1247. (c) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741. (d) McGuinness, D. S.; Cavell, K. J. *Organometallics* **1999**, *18*, 1596. (e) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772. (f) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371.

(11) Albert, K.; Gisdakis, P.; Rösch, N. *Organometallics* **1998**, *17*, 1608.

(12) The imidazolium salt can be deprotonated by KOBu^t. The bromine-imidazolium salt should be added to a preformed potassium diphenylphosphide solution.

Table 3. Pd/1-Catalyzed Heck Reaction of Aryl Halides with *n*-Butyl Acrylate^a

entry	aryl halide	time (h)	yield ^b (%)
1		0.25	100 (93 ^c)
2		1	100
3		1.5	100 (92 ^c)
4		1	35
5		1	99
6		3	99 (94 ^c)
7		2	99
8		2	13

^a Reaction condition: 1 mmol of aryl halide, 1.4 mmol of *n*-butyl acrylate. ^b GC yield (diethylene glycol di-*n*-butyl ether as GC standard; an average of two runs). ^c Isolated yield.

Attempts had been made to use electron-deficient aryl chlorides as substrates, such as 4-chlorobenzaldehyde and 4-chloroacetophenone. However, no desirable coupled products were obtained. For the electron-neutral chlorobenzene (entry 8) the desired coupling product was obtained, although in a low yield of 13% in 2 h. A prolong reaction time resulted in significant side reaction.

As stated above, a combination of Pd/IMes·HCl (IMes = bis(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene) or IPr·HCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) has proven highly effective in Suzuki-type coupling.⁶ Thus, it was of interest to compare the catalytic performances of **1** with IMes in the Pd-catalyzed Heck reaction of 4-bromotoluene with *n*-butyl acrylate. In fact, our new system involving **1** was much more effective than Pd/IMes, which gave only a yield of 7% of the desired coupled product in 4 h (Pd/1 gave a 96% yield under identical conditions).

(13) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009 and references cited.

(14) **Workup procedure:** Water (50 mL) was added to the reaction mixture, followed by extraction with diethyl ether. The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure to give the crude product. The pure product was obtained by flash chromatography (1/10 ethyl acetate/hexane) on silica gel.

Presumably **1** is deprotonated and forms a chelating phosphine–carbene complex with Pd(dba)₂ in the presence of Cs₂CO₃. The in situ deprotonation and subsequent coordination of the metal center by the phosphine–carbene ligand can be observed by the color change from violet to yellowish brown after the catalytic mixture stirs for 20 min, this prior to the addition of substrate and *n*-butyl acrylate. In the catalytic cycle, Pd/L may proceed via a cationic pathway in which a dissociation of the oxidative-added halide is involved to open up a coordination site for the incoming olefinic substrate. This is in accord with our finding that polar solvents enhanced the reaction rate (vide supra). Mechanistic details are presently being examined.

In summary, a new phosphine–imidazolium salt was prepared and its application in Pd-catalyzed Heck reactions of aryl bromides with *n*-butyl acrylate was investigated and showed that Pd/L·HBr is a highly efficient catalytic system. In fact, a relatively low catalyst loading was sufficient to

mediate the Heck coupling of unactivated aryl bromides with *n*-butyl acrylate in less than 3 h. This initial study shows that chelating phosphine–carbene ligands represent a very promising class of ligand suitable for Heck reactions.¹¹ Investigations into the scope and limitations of the methodology as well as the syntheses of improved ligands including chiral analogues are ongoing.

Acknowledgment. The National Science Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and the Albemarle Corporation are gratefully acknowledged for support of this research.

Supporting Information Available: Experimental procedures, details of reaction conditions, and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL015827S