ORGANIC LETTERS

2002
Vol. 4, No. 12
2079−2082

Palladium–Imidazolium Carbene Catalyzed Mizoroki–Heck Coupling with Aryl Diazonium Ions

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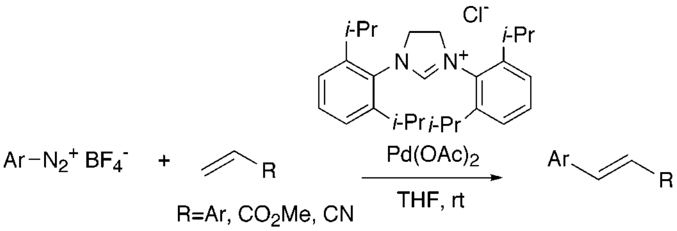
Received April 2, 2002

ABSTRACT



Catalyst formed from *N*,*N*-bis(2,6-diisopropylphenyl)dihydroimidazolium chloride and palladium(II) acetate (2 mol %) was used, without added base, to efficiently produce Heck coupled products with olefins and aryl diazonium tetrafluoroborate substrates. The reactions were performed at room temperature, giving product in 2–4 h with 80–90% yields for isolated materials. Diazonium ions, formed in situ directly from anilines, also couple under these conditions.

The palladium-catalyzed Mizoroki−Heck reaction using aryl halides and olefins has become a powerful and versatile means of carbon−carbon bond formation.[1] Yet limitations remain; in particular, conditions commonly require elevated temperatures with added base. Mixed products often suffer from olefin migration following insertion, and substrate generality in asymmetric versions is poor. Recent developments by Fu and Littke using *tert*-butylphosphine as a ligand with $Pd_2(dba)_3$ and dicyclohexylmethylamine base allow for the use of aryl bromides and electron-poor aryl chlorides at room temperature.[2] Typical conditions employ palladium(II) acetate with triarylphosphine and carbonate base at temperatures above 100 °C. Use of silver and thallium salt additives can lead to increased activity and often improve selectivity, most notably in intramolecular examples.[3] Aryl diazonium salts are typically more reactive than aryl iodides and have been used for palladium-catalyzed Heck couplings in good yields under refluxing methanol or ethanol conditions without added base.[4] Added base, in this case, can also give products with less alkene migration.[5] We now report that dihydroimidazolium−palladium catalyzed Heck couplings are active from 2 to 0.1 mol % catalyst loading with aryl diazonium fluoroborate and various olefin substrates performed at room temperature without added base in THF. Also, an efficient one-pot in situ diazonium formation−Heck coupling protocol starting from an aniline is also successful using this active catalyst system.

Nonphosphine imidazolium carbene ligands with palladium and other transition metals have recently been used

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[1] (a) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449−7476. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

[2] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000. Use of *tert*-butylphosphine at elevated temperature: Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123−2132.

[3] (a) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Grigg, R.; Longanathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687−690.

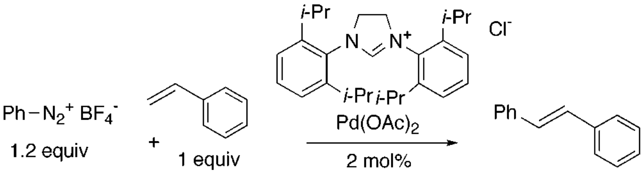
[4] (a) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y. *J. Org. Chem.* **1980**, *45*, 2359−2364. (b) Kikukara, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31−35. (c) Sengupta, S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1943−1947.

[5] (a) Brunner, H.; Le Cousturier de Courcy, N.; Genet, J. P. *Tetrahedron Lett.* **1999**, *40*, 4815−4818. (b) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039−3042.

10.1021/ol025961s CCC: $22.00

as catalysts for cross coupling and olefin metathesis reactions.[6] We recently reported a highly efficient Suzuki–Miyaura boron crossed coupling method with aryl diazonium fluoroborates under imidazolium–palladium catalysis at low temperature.[7] The most active bis-2,6-diisopropylphenyl dihydroimidazolium chloride ligand in that series was selected for this Heck coupling investigation. A catalytic amount of the 4,5-dihydroimidazolium chloride (2 mol % based on the substrate), readily prepared according to the literature,[8] was treated with palladium(II) acetate (2 mol %) in THF. Added base was not needed to form the active palladium carbene complex as found previously for the Suzuki reaction.[7] Others have shown that added base, *tert*-butoxide,[9] carbonate,[10] or fluoride is required.[11] Alternatively, Cavell has shown that palladium carbenes can be formed by treating imidazolium salts first with silver(I) oxide followed by transfer of the carbene ligand to palladium acetate without additional base being added.[12] Couplings were reported, but added base was needed for successful outcomes in that case. Stilbene was now formed from phenyl diazonium fluoroborate and styrene (Table 1) after 4.5 h at room temperature in the presence of the imidazolium–palladium catalyst. TLC indicated consumption of the starting materials, and the product was isolated in 77% yield following silica gel chromatography. When the analogous aromatic (4,5-dihydro) bis-2,6-diisopropylphenyl imidazolium ligand was used, the product yield was significantly lower at 57%. Recently Nolan and co-workers reported the use of a chelating phosphine–imidazolium–palladium catalyst that required carbonate base in *N*,*N*-dimethylacetamide at 120 °C using less reactive aryl bromides.

Table 1. Effect of Solvent and Ligand



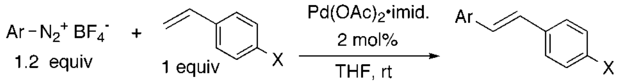
solvent	time, h	temp, °C	yield, %[a]
THF	4.5	rt	77 (57)[b]
toluene	6	rt	46
toluene	5	110	57
dioxane	7	rt	57
ether	6	rt	61
MeOH	5	rt	5Y

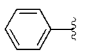
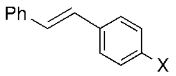
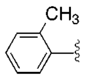
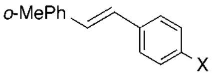
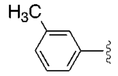
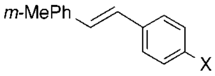
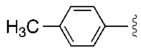
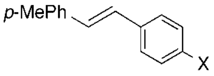
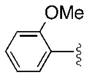
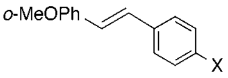
[a] Yields are reported for isolated, chromatographed materials. [b] The analogous dehydroimidazolium chloride lignad was used.

Palladium(II) acetate (2 mol %) used alone without added imidazolium ligand, in THF at room temperature for 12 h, gave a much reduced 21% yield of stilbene product. Use of tetrakis(triphenylphosphine) palladium as catalyst in THF or toluene, resulted in no product formation even after an extended 36 h time period and gave only a 12% yield of product after 12 h in THF at reflux. Acetate appears to function as base in this case to generate the active palladium carbene catalyst under the conditions investigated. As previously reported,[7] an equimolar $CDCl_3$ solution (0.8 M) of the imidazolium chloride and palladium acetate monitored by ^{1}H NMR showed complete disappearance of the diagnostic proton located on the iminium carbon found at 8.15 ppm.[13] Use of toluene and the other solvents shown gave product with lower yields, including methanol, previously the solvent of choice for diazonium couplings.[4,5]

Reaction conditions were explored with various aryl diazonium fluoroborates and two styrenes (X = H, −OMe) at 1.2:1 stoichiometry (Table 2). The catalyst load could be lowered to 0.1% without significant loss in yield in the

Table 2. Heck Coupling with Styrene



Ar-[a]	X	time, h	product	yield, %
	-H	5		77(72)[b]
	-OMe	4.5		78
	-H	5		75
	-OMe	4		67
	-H	5		80
	-OMe	3.5		77
	-H	4.5		86
	-OMe	4.5		81
	-H	4.5		81
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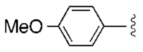
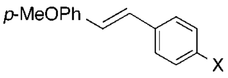
	-H	4.5		88 (87)[b]
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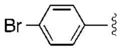
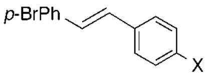
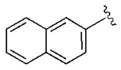
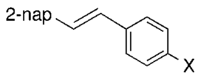
	-H	4		91
	-OMe	3		87
	-H	4		80
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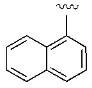
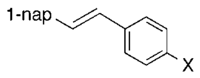
	-H	4		87
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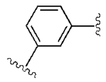
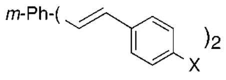
	-H	4		57
	-OMe	4		32

[a] Reactions were performed on 0.1 mmol scale at 0.2 M concentration. [b] Isolated yields using 0.1 mol % palladium acetate–imidazolium catalyst.

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(6) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (c) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511. (d) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292.

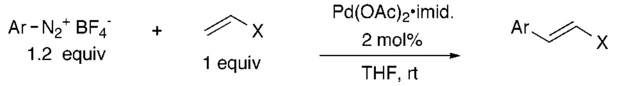
(7) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761–3764.

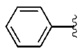
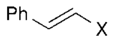
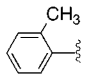
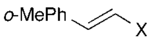
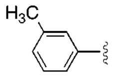
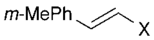
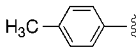
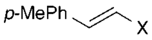
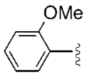
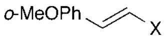
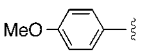
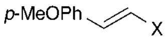
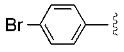
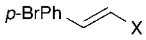
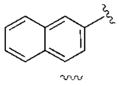
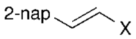
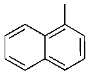
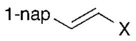
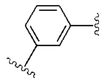
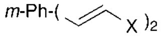
(8) (a) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J. Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523. (b) Saba, S.; Brescia, A. M.; Kaloustian, M. K. *Tetrahedron Lett.* **1991**, *32*, 5031.

phenyl and the *p*-methoxyphenyl diazonium ion cases. All substitution patterns gave product in useful yields, including *o*-methyl, methoxy, and 1-naphthyl substrates. The *p*-bromophenyl diazonium ion example showed complete chemoselectivity with exclusive reaction via the diazonium group in excellent 91% yield. Only with the 1,3-bis-phenyl diazonium ion in a double reactivity mode using 2.2 equiv of styrene were the yields lowered to 57% and 32%. The more reactive *p*-bis-phenyl diazonium ion in this case turned dark instantly and gave no yield of Heck coupling products under these conditions. Only homocoupling was evident using LC-MS analysis. The ligand-to-metal ratio was explored at 2:1 and 3:1 ratio using 4 and 6 mol % amounts of dihydroimidazolium ligand. With the first entry substrates (Table 2), phenyl diazonium fluoroborate and styrene under identical conditions and time, the isolated yields remained the same at 78% and 77%, respectively. Ligand and palladium acetate at 1:1 ratio increased in amount to 15 mol % improved the yield only slightly to 81% in this case.

Methyl methacrylate and acrylonitrile in THF at room temperature were also used under the new Heck arylation conditions (Table 3). In general, longer reaction times were needed and lower yields were found using acrylonitrile. Only with the *p*-bromophenyl diazonium ion was a reasonable 61% yield obtained. As seen before, the more electron-rich methoxyphenyl ions gave higher yields, in this case 51% and 58%. Methacrylate gave moderate to good yields across the range of substrates, including all *ortho*-substituted ions. Again, only the bis-*m*-phenyl diazonium was poor at 32%. All of these examples were again performed at 1.2:1 stoichiometry. Presumably the reaction rates and yields could be further improved using a higher relative amount of either coupling partner.

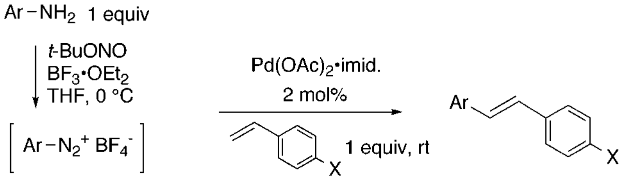
Table 3. Heck Coupling with Acrylates

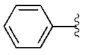
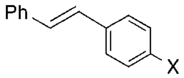
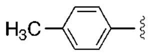
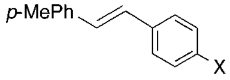
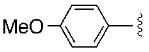
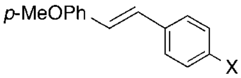
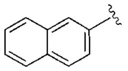
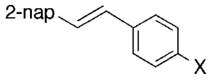


Ar-	X	time, h	product	yield, %
	-CO$_2$Me -CN	3 4.5		68 47
	-CO$_2$Me -CN	3 5		66 42
	-CO$_2$Me -CN	3 4.5		64 41
	-CO$_2$Me -CN	3 4.5		65 48
	-CO$_2$Me -CN	2.5 4		70 51
	-CO$_2$Me -CN	2 4		71 58
	-CO$_2$Me -CN	2.5 3.5		81 61
	-CO$_2$Me -CN	2.5 4		71 39
	-CO$_2$Me -CN	2.5 3.5		77 37
	-CO$_2$Me	3		32

The utility of this system is further illustrated by the flexibility of being able to directly start with an aniline substrate employing an in situ generated diazonium fluoroborate.[14] This approach was previously found to be applicable to low-temperature Suzuki couplings with this catalyst.[7] The anilines indicated were treated with *tert*-butyl nitrite followed by addition of boron trifluoride etherate at 0 °C in THF according to the procedure of Doyle (Table 4).[15] The imidazolium chloride and palladium(II) acetate, both at 2 mol %, were added followed by addition of the indicated styrene coupling partner. The reaction was warmed to room

Table 4. In Situ Aniline Coupling



Ar-	X	time, h	product	yield, %
	-H -OMe	7 6		58 51
	-H -OMe	6 6		61 58
	-H -OMe	6 6		21 17
	-H -OMe	6 5		62 53

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(13) The imidazolium ligand and palladium acetate were mixed at room temperature for 2 h to generate a homogeneous, pale yellow solution. A portion was analyzed by ^{1}H NMR (300 MHz). When sodium *tert*-butoxide and ligand were mixed under similar conditions, a black precipitate resulted. Further studies to establish the structure of the actual catalyst in this case will be reported elsewhere.

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(15) The aniline compound was reacted with BF$_3$•OEt$_2$ in THF and *tert*-butylnitrite for 30 min at 0 °C. Styrene, Pd(OAc)$_2$, and *N*,*N*-bis(2,6-diisopropyl)dihydroimidazolium chloride were added, and the reaction was allowed to warm. The product was isolated and characterized as before. See the Supporting Information for details.

temperature, and TLC was again used to monitor consumption of the starting material. Somewhat longer reaction times were needed. Yet, in all cases the products were isolated in moderate yield, in the 50−60% range. Surprisingly, the more electron-rich *p*-methoxy ion now was the lowest yielding substrate at 21% and 17%.

With ease and flexibility this new active palladium acetate−imidazolium catalyst system with aryl diazonium ions at 1:1.2 stoichiometry readily arylates olefin substrates in high yield at room temperature. Added base is not needed either to form the carbene catalyst or for alkene product formation. Acetate appears to function as base in this case, producing the active palladium catalyst. Following oxidative insertion and loss of nitrogen, apparently the intermediate cationic palladium species readily inserts olefin and turns over without the need of added base. When the ligand is omitted, the reaction occurs at a very slow rate at this temperature and with very low yield. When using as little as 0.1 mol % catalyst, high turnover numbers were demonstrated in some cases. Also, a direct, single-flask operation was developed and found to be efficient with aniline substrates. This imidazolium−palladium catalyst−diazonium ion system should find applications with more complex targets that contain base-sensitive functionality. It can also be applied to the development of asymmetric versions[16] as a result of high reaction rates now operative at lower temperatures.

Acknowledgment. We are grateful for support provided by Brigham Young University and the National Institutes of Health (GM57275). We also thank Bruce Jackson for help with the MS analyses.

Supporting Information Available: Analytical data for the known product compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025961S

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