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Palladium–Imidazolium Carbene Catalyzed Aryl, Vinyl, and Alkyl Suzuki–Miyaura Cross Coupling

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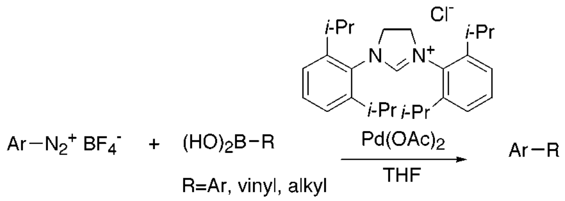
ABSTRACT



_N_,_N_-Bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride with palladium(II) acetate (2 mol %) was used as catalyst, without added base, to efficiently cross couple aryl, vinyl, and alkyl boronates and boronic acids with aryldiazonium tetrafluoroborate substrates. The reactions were performed at 0 °C or rt, giving product in 2 to 4 h with 80 to 90% yields for isolated materials. Diazonium ions, formed in situ, also cross couple under these conditions.

The Suzuki−Miyaura reaction, the palladium-catalyzed cross coupling of boranes, boronic esters, and boronic acids with sp^2 halides and pseudohalogens, continues to attract new methodology, development, and applications.[1] Recent developments by Buchwald and Fu and co-workers include new palladium catalysts with phosphine ligands that can be used at rt.[2] Copper carboxylate additives, reported by Liebeskind et al., can also be used at lower temperatures and have the advantage of being used without added base.[3] Nolan and co-workers have reported imidazolium and diazabutadiene ligands with Pd$_2$(dba)$_3$ forming catalysts that couple the most difficult aryl chloride substrates with added cesium carbonate in refluxing dioxane.[4] Couplings have been reported using aryldiazonium ions, more active substrates, using 10 mol % of palladium(II) acetate without added base in refluxing methanol.[5] We now report dihydroimidazolium carbene−palladium acetate catalyzed couplings that are active from 2 to 0.01 mol % of catalyst loading with aryldiazonium ions and aryl, vinyl, and alkyl boron substrates. These reactions can be performed at 0 °C or rt without added base. An efficient one-pot in situ diazonium formation cross coupling starting with an aniline is also reported using this active catalyst system.

Arduengo-type imidazolium carbene ligands with palladium and other transition metals have recently found many applications as catalysts for palladium cross couplings and ruthenium-based olefin metathesis.[6] The most active bis-2,6-diisopropylphenyl ligand in the series was selected for this investigation. A catalytic amount of the imidazolium chloride (2 mol % based on the substrate), readily prepared according to literature references,[7] was treated with palladium(II)

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(1) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(2) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L *J. Am. Chem. Soc.* **1999**, *121*, 9550. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(3) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (b) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149.

(4) (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (b) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077.

(5) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405.

(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.

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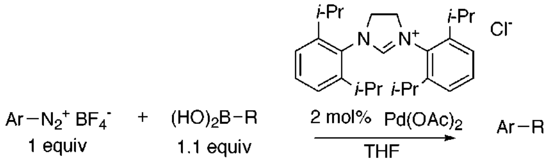
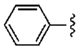
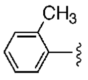
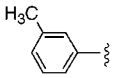
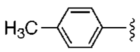
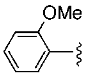
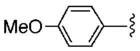
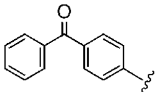
acetate (2 mol %) in THF. Initially it was thought that added base would be needed to form the active palladium carbene complex. Others have shown that added base, *tert*-butoxide,[8] carbonate,[9] or fluoride, is required.[10] Cavell has shown that palladium carbenes can be formed by treating imidazolium salts first with silver(I) oxide followed by transfer to palladium acetate without additional base.[11] Couplings were then performed, but added base was needed for successful coupling transformations in this case. Initially, base free conditions were investigated and were found to be successful for the diazonium Suzuki–Miyaura couplings now reported. Biaryl compounds were formed from various aryldiazonium tetrafluoroborates coupled with aryl boronic acids (Table 1).[12] After 3 h TLC indicated consumption of the starting materials and products were isolated in the 80 to 90% range using silica gel chromatography. In cases performed on a larger scale (10 mmol), the yields further improved to the high 90% range. Electron-rich methoxy-substituted substrates allowed for the use of even lower temperature at 0 °C and the yields remained high. The electron-deficient benzophenone diazonium ion was equally efficient with the various boronic acids investigated.

Control experiments included leaving out the imidazolium salt ligand. Use of either palladium(II) acetate or tetrakis(triphenylphosphine) palladium alone as catalysts in THF or toluene, without added imidazolium chloride, resulted in no product formation at rt over an extended 36 h time period. Acetate appears to function as base in this case to generate the active palladium carbene catalyst under the conditions investigated. 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] Homocoupling of phenylboronic acid, when used alone without added diazonium salt, is not observed at 0 °C. Only at rt after 16 h was a significant 37% yield of biphenyl product obtained when the diazonium tetrafluoroborate was left out.

The biphenyl reaction was explored in various solvents at a 2 mol % load level, and the isolated yields remained high. Only methanol lowered the yield somewhat to 82% (Table 2). THF was found to be best at 95%. Catalyst loading of this system was also investigated with various reactions performed in THF at rt for 3 h (Table 2). The reaction

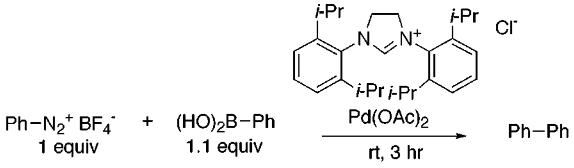
Table 1. Suzuki Coupling with Palladium–Imidazolium Catalysis



Ar-[a]	-R	temp,°C	time, h	product,Ar-R	yield, %[b]
	-Ph	23	3	Ph–Ph	95(98)
	-Ph-4-*t*-Bu	23	3.5	Ph–Ph-4-*t*-Bu	91(95)
	-Ph-4-OMe	0	2.5	Ph–Ph-4-OMe	94(96)
	-Ph	23	3	2-MePh–Ph	81
	-Ph-4-*t*-Bu	23	3	2-MePh–Ph-4-*t*-Bu	85
	-Ph-4-OMe	0	2.5	2-MePh–Ph-4-OMe	89
	-Ph	23	3	3-MePh–Ph	85
	-Ph-4-*t*-Bu	23	3	3-MePh–Ph-4-*t*-Bu	80
	-Ph-4-OMe	0	2.5	3-MePh–Ph-4-OMe	87
	-Ph	23	3	4-MePh–Ph	86(91)
	-Ph-4-*t*-Bu	23	3	4-MePh–Ph-4-*t*-Bu	87(91)
	-Ph-4-OMe	0	2.5	4-MePh–Ph-4-OMe	89
	-Ph	0	2.5	2-MeOPh–Ph	84
	-Ph-4-*t*-Bu	0	2.5	2-MeOPh–Ph-4-*t*-Bu	86
	-Ph-4-OMe	0	2.5	2-MeOPh–Ph-4-OMe	79
	-Ph	0	2.5	4-MeOPh–Ph	93(97)
	-Ph-4-*t*-Bu	0	2	4-MeOPh–Ph-4-*t*-Bu	93
	-Ph-4-OMe	0	2.5	4-MeOPh–Ph-4-OMe	92(96)
	-Ph	23	3	4-PhCOPh–Ph	83
	-Ph-4-*t*-Bu	23	2.5	4-PhCOPh–Ph-4-*t*-Bu	86
	-Ph-4-OMe	0	2.5	4-PhCOPh–Ph-4-OMe	88

[a] Reactions were perfomed on a 0.1 mmol scale at 0.2 M concentration. [b] Yields are reported for isolated, chromatographed materials. Numbers in parentheses are for 10 mmol scale reactions.

Table 2. Effect of Solvent and Substrate/Catalyst Ratio



solvent	mol% catalyst	S/C[a]	yield, %[b]
THF	2	50	95
CH_2Cl_2	"	"	88
PhH	"	"	88
diox.	"	"	90
MeOH	"	"	82
THF	1	100	92
"	0.5	200	89
"	0.2	500	88
"	0.1	1,000	86
"	0.01	10,000	68

[a] Substrate (0.1 mmol) to catalyst mole ratio. [b] Yields are reported for isolated, chromatographed materials.

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(7) (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.

(8) Herrmann, W. A.; Goossen, L. J.; Spiegler, M. *Organometallics* **1998**, *17*, 2162.

(9) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

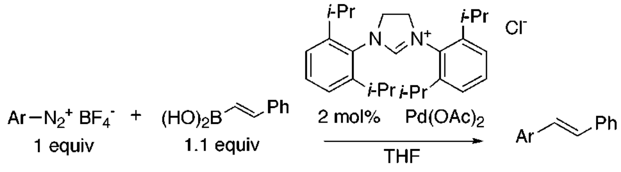
(10) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

(11) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741.

(12) **General procedure:** To a flask containing magnetically stirred dry THF (3 mL) under nitrogen at the indicated temperature were added arenediazonium tetrafluoroborate (0.1 mmol), arylboronic acid (0.11 mmol), $Pd(OAc)_2$ (2 mol %), and *N*,*N*-bis(2,6-diisopropyl)dihydroimidazolium chloride (2 mol %). Stirring was continued for the indicated time until TLC analysis revealed consumption of the starting materials. The reaction was worked up with ether and brine, dried over magnesium sulfate, and purified by silica gel chromatography. All products, all of which are known, were characterized by ^{1}H NMR and MS.

(13) The imidazolium ligand and palladium acetate were mixed at rt 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 active catalyst in this case will be reported elsewhere.

Table 3. Suzuki Coupling with Styryl Boric Acid



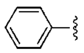
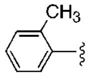
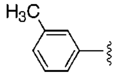
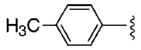
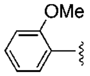
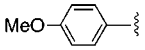
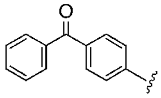
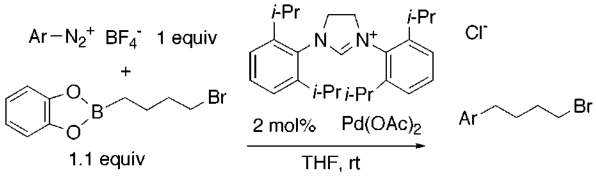
Ar-	temp. °C	time, hr	yield, %
	rt	3.5	83
	rt	3.5	68
	rt	3.5	86
	rt	3.5	86
	0	3.0	87
	0	2.5	87
	rt	3.0	85

Table 4. Alkyl Catecol Borane Coupling



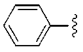
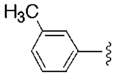
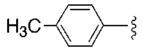
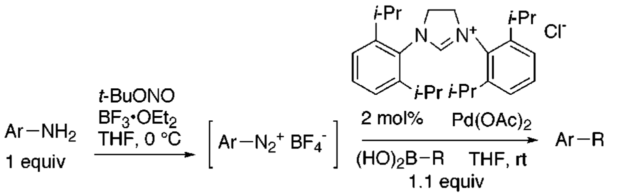
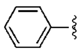
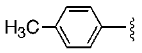
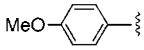
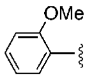
Ar-	time, hr	yield, %
	4.5	61
	4.0	81
	4.0	80

Table 5. In Situ Aniline Suzuki Coupling



Ar-[a]	-R	time, hr	product,Ar-R	yield, %[b]
	-Ph	5	Ph−Ph	76
	-Ph-4-*t*-Bu	5.5	Ph−Ph-4-*t*-Bu	61
	-Ph-4-OMe	4.5	Ph−Ph-4-OMe	61
	-Ph	4.5	4-MePh−Ph	68
	-Ph-4-*t*-Bu	6.5	4-MePh−Ph-4-*t*-Bu	61
	-Ph-4-OMe	4	4-MePh−Ph-4-OMe	62
	-Ph	4	4-MeOPh−Ph	70
	-Ph-4-*t*-Bu	5.5	4-MeOPh−Ph-4-*t*-Bu	57
	-Ph-4-OMe	5.5	4-MeOPh−Ph-4-OMe	66
	-Ph	4	2-MeOPh−Ph	53

[a] Substrate (0.1 mmol) to catalyst mole ratio. [b] Yields are reported for isolated, chromatographed materials.

remained highly efficient even when performed at 0.1 mol %, with a 1000:1 substrate-to-catalyst ratio, giving product with a yield of 86%. Only at 0.01 mol % did the yield fall off to a moderate 68% yield after 3 h. Longer reaction times may further extend the load level to even higher substrate to catalyst levels with this active ligand system.

Vinyl cross coupling was explored using this catalyst system with β-styryl boronic acid (Table 3). In all cases good yields in the 80% range were obtained. Again, the more electron rich methoxy substrates allowed for efficient reactivity at 0 °C. Only the more hindered *o*-methyldiazonium tetrafluoroborate substrate gave product with lower yield at 68% in this case.

Suzuki−Miyaura coupling is unique in that alkyl boron compounds, both alkylboranes and boronic esters, are known to participate in coupling reactions to produce alkyl-sp^2 linked products. Usually this transformation requires a more active catalyst, excess substrate, and higher temperatures.[14] Using this palladium acetate−imidazolium carbene catalyst (2 mol %), 4-bromo-1-catecolboranylbutane coupled with aryldiazonium tetrafluoroborates at rt to give arylalkanes in good yields. Phenyl coupling gave 61% yield while the more electron rich substrates generated product in 80% yield after 4 h (Table 4).

The utility of this system is further illustrated by the flexibility of being able to start with an aniline substrate and employ an in situ diazonium formation step.[15] The anilines indicated were treated with *tert*-butyl nitrite followed by boron trifluoride etherate at 0 °C in THF for 30 min according to the procedure of Doyle (Table 5).[16] To this mixture were added the imidazolium chloride and palladium(II) acetate (2 mol %) followed by addition of the aryl boronic acid. The reaction was warmed to rt and TLC was again used to monitor consumption of the starting materials.

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(14) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. (c) Furstner, A.; Seidel, G. *SynLett* **1998**, 161.

(15) Doyle, M. P.; Siegfreid, B.; Elliot, R. C.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2431.

(16) **General in situ procedure:** To a flask containing stirred, dry THF at 0 °C (2 mL) was added the aniline compound (0.2 mmol) followed by BF_3•OEt_2 (22.7 mg, 0.2 mmol), diluted with THF (2 mL). Following stirring for 15 min, to the solution was added *tert*-butyl nitrite (23 mg, 0.22 mmol) diluted in THF (2 mL) and stirring was continued for 30 min. To the mixture were added arylboronic acid (0.2 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), and *N*,*N*-bis(2,6-diisopropyl)dihydroimidazolium chloride (1.2 mg, 0.004 mmol) diluted in THF (5 mL). Stirring continued and the reaction was worked up at the indicated time. The product was isolated and characterized as before.

Somewhat longer reaction times were needed. Yet, in all cases the products were isolated in good yield, in the 60 to 70% range. Only the *o*-methoxy substrate was lower yielding at 53%.

With ease and flexibility, this new active palladium acetate−imidazolium catalyst system readily cross couples aryl, vinyl, and alkyl boron reagents with aryldiazonium ions in high yield at rt. Added base is not needed, and a two-step, single flask operation is productive using simple aniline starting materials. Acetate appears to function as base in this case, producing the active palladium catalyst. When the ligand is removed, the reaction does not occur. Very high turnover numbers are possible in some cases, giving high yields with as little as 0.01 mol % of catalyst. The system should find applications with more complex targets that contain base-sensitive functionality. It should also be applicable to the development of asymmetric versions[17] due the high reaction rates now demonstrated at lower temperatures.

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

OL016724C

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[17] (a) Herrmann, W. A.; Goossen, L. J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805. (b) Herrmann, W. G.; Goossen, L. J.; Spiegler, M. *Organomet.* **1998**, *17*, 2162.