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Palladium/Imidazolium Salt Catalyzed Coupling of Aryl Halides with Hypervalent Organostannates

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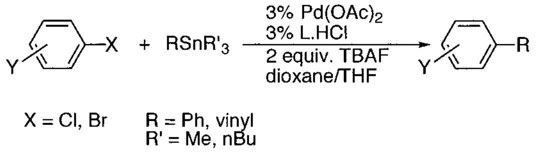
ABSTRACT

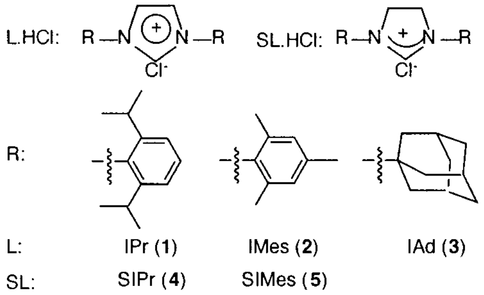


A Pd(OAc)$_2$/imidazolium chloride system has been used to mediate the catalytic cross-coupling of aryl halides with organostannanes. The imidazolium salt IPr·HCl (IPr = 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene) in combination with TBAF (^{n}Bu$_4$NF) was found to be most effective for the cross-coupling of aryl bromides and electron-deficient aryl chlorides with aryl and vinyl stannanes.

Cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] The Stille reaction,[2] where tin reagents are employed as a coupling partner with aryl, vinyl or allyl halides (or pseudohalides) to form C−C bonds, belongs to a larger family of palladium- and nickel-catalyzed reactions. These coupling reactions alternatively make use of a variety of transmetalating agents such as organoboron,[3] organomagnesium,[4] organosilicon,[5] and organozinc[6] reagents. Usually, metal−phosphine complexes are commonly employed as ancillary ligands in such systems.[1a,7] The use of organostannanes as coupling partners has attracted much attention as a result of their availability and air- and moisture-stability, as well as compatibility with a variety of functional groups. However, the difficulties associated with tin removal from the product and tin toxicity represent major limitations/concerns associated with the Stille reaction.

Nucleophilic *N*-heterocyclic carbenes[8] represent a versatile class of ligands able to mimic tertiary phosphines which are widely used in homogeneous catalysis.[7] (Scheme 1)

Scheme 1. Imidazolium Salts



Recently, we and others have found that the combination of Pd(dba)$_2$ or Pd(OAc)$_2$ with electron-rich and sterically

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(1) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987. (c) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 799−938.

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(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. In *Metal-Catalyzed Cross-Couplings Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97 and references therein.

(4) (a) Yamamura, M.; Moritani, I.; Murahashi, S. *J. Orgamomet. Chem.* **1975**, *91*, C39−C42. (b) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268−9269. (c) Sekia, A.; Ishikawa, N. *J. Organomet. Chem.* **1976**, *118*, 349−354

(5) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845−853.

(6) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.

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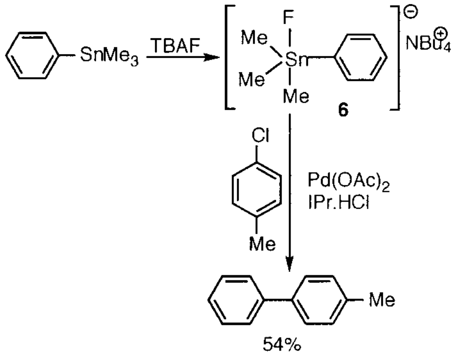
demanding IPr·HCl (**1**) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) or IMes·HCl (**2**) (IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene) mediates the couplings of aryl halides with amines,[9] organomagnesium,[10] organoboron.[11] and organosilicon[12] reagents. On the basis of these observations and the fact that organostannanes are isoelectronic with organosilicon compounds, it was of interest to examine whether this palladium/imidazolium salt system could catalyze the Stille reaction. We now wish to report the use of Pd(II)/IPr·HCl and TBAF (^{n}Bu$_4$NF) as a base in the cross-coupling reaction of aryl halides with organostannane reagents.

It is well-known that, like silicon,[13] tin is fluorophilic.[14] Consequently, the resulting hypervalent organostannate species generated in the reaction of the organostannane with the fluoride anion are more labile with regard to the transmetalation reaction.[15] Kosugi et al. have reported[16] that $Pd(dba)_2/PPh_3$/TBAF does not catalyze the Stille coupling of aryl chlorides. In an effort to overcome the limitations of the Stille reaction, e.g., slow transmetalation step and removal of tin byproducts, the use of hypervalent stannate species was investigated.

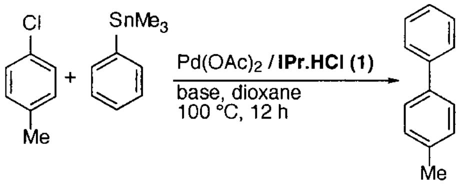
We have found that treatment of 1.1 equiv of Me_3PhSn with 2 equiv of TBAF resulted in the formation of a hypervalent fluorostannate anion (Scheme 2).[17]

Scheme 2. Hypervalent Stannate Intermediate



The stannate **6** coupled with 4-chlorotoluene in the presence of the Pd(II)/IPr·HCl catalyst. In turn, CsF, a very effective additive for $Pd_2(dba)_3/P^tBu_3$ catalyzed Stille reaction[18] proved to be less effective (Table 1, entry 2). However, when a Pd/IPr·HCl ratio of 1:2 was used, the reaction of 4-chlorotoluene with Me_3PhSn led to a 74% yield of the cross-coupling product (Table 1, entry 3).[19] Attempts to couple other aryl halides using CsF as an additive/base were unsuccessful. Other bases such as Cs_2CO_3, KO^{t}Bu, and NaOH proved to be ineffective for the cross-coupling of 4-chlorotoluene with $PhSnMe_3$ (Table 1, entries 4, 5, and 7). The role of the TBAF additive (base) in these transformations is 3-fold: the strong base F$^-$ [20] initially deprotonates the imidazolium chloride to form the free carbene ligand in situ, which coordinates to Pd. It also facilitates the transmetalation step by forming the more reactive hypervalent tin species, and finally it helps the removal of tin byproducts from the reaction mixture.

Table 1. Effect of Base on $Pd(OAc)_2$/IPr·HCl Catalyzed Cross-Coupling of 4-Chlorotoluene with Phenyl(trimethyl) Tin[a]



entry	base	yield (%)[b]
1	none	<5
2	CsF	22
3	CsF	74[c]
4	KO^{t}Bu	30
5	Cs_2CO_3	7
6	TBAF	54
7	NaOH	32

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.1 mmol of arylstannane, 2 mmol of TBAF, 3.0 mol % $Pd(OAc)_2$, 3.0 mol % IPr·HCl, 1 mL of dioxane, 100 °C. [b] GC yields. Yields are average of two runs. [c] Pd(II)/2IPr·HCl ratio was used.

Investigation of other imidazolium salts as ligand precursors led to the observation that the bulkier and less electron-donating IAd·HCl[21] was also an effective ligand for the cross-coupling of 4-chlorotoluene and Me_3PhSn (Table 2, entry 4). Unlike its performance in the Suzuki cross-coupling,[11]

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(7) Applications of phosphine ligands in homogeneous catalysis: (a) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; Wiley and Sons: New York, 1992. (b) *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983.

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(9) (a)Huang, J.; Grasa, A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 2053−2055. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett*, **2000**, *2*, 1423−1426.

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(11) (a) Zhang, C.; Huang, J.; Trudell, M. T.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (b) Böhm, V. P. W.; Gstömayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.*, **2000**, *595*, 186−190.

(12) (a) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 1307−1309. (b) For palladium phosphine mediated process, see for example: Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688.

(13) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140.

(14) Smith, P. J. *Chemistry of Tin*; Blackie: New York, 1998.

(15) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc*, **1998**, *120*, 8978−8985

(16) Fugami, K.; Ohnuma, S.-Y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63−64.

(17) (a) ^{19}F NMR spectrum of 2 equiv of TBAF/THF and 1 equiv of Me_3PhSn in DMSO-d_6 after heating to 45 °C for 24 h shows the presence of a new peak (in C_6D_6: −144.8 ppm vs $CFCl_3$) due to the formation of $[Me_3PhSnF]^-[Bu_4N]^+$ species. (b) For an example of hypervalent organostannane, see: Mallella, S. P.; Yap, S.; Sama, J. R.; Aubke, F. *Inorg. Chem.* **1986**, *25*, 4074−4080. (c) For a silicon analogue, see: Handy, C. J.; Lam, Y.-F.; DeShong, P. *J. Org. Chem.* **2000**, *65*, 3542−3543.

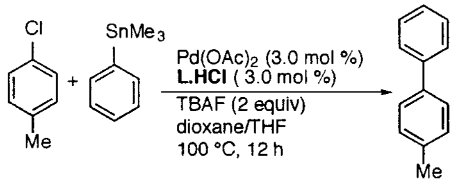
(18) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413.

(19) The reasons why varied Pd to L ratios lead to different catalytic performance are under study.

(20) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429−452.

(21) (a) Huang, J,; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370−2375. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

Table 2. Effect of the Ligand on Pd(OAc)$_2$/L·HCl Catalyzed Cross-Coupling of 4-Chlorotoluene with Phenyl(trimethyl) Tin[a]

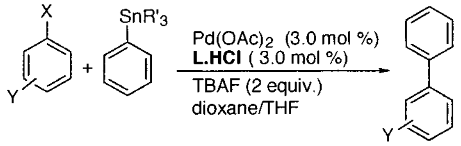


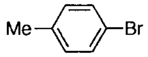
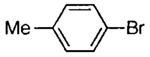
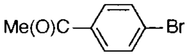
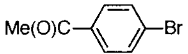
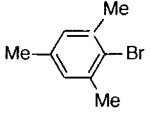
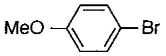
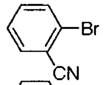
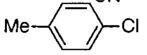
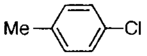
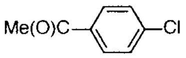
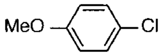
entry	L	yield (%)[b]
1	none	11
2	IPr (**1**)	54
3	IMes (**2**)	26
4	IAd (**3**)	64
5	SIPr (**4**)	8
6	SIMes (**5**)	20

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.1 mmol of arylstannane, 2 mmol of TBAF, 3.0 mol % Pd(OAc)$_2$, 3.0 mol % L·HCl, 1 mL of dioxane, 100 °C. [b] GC yields. Yields are average of two runs.

IMes·HCl was found to be an ineffective ligand for the Stille reaction (Table 2, entry 3).

Table 3. Pd(OAc)$_2$/L·HCl Catalyzed Cross-Coupling of Aryl Halides with Arylstannanes[a]



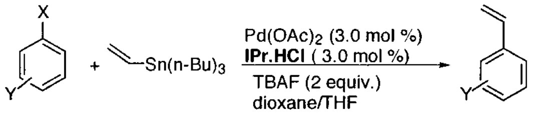
entry	aryl halide	tin reagent	L	time (h)	yield(%)[b,c]
1		Me$_3$PhSn	IPr.HCl	1.5	90
2		Ph(n-Bu)$_3$Sn	IAd.HCl	3	91
3		Me$_3$PhSn	IPr.HCl	0.5	92
4		Me$_3$PhSn	IAd.HCl	1	86
5		Me$_3$PhSn	IPr.HCl	48	86
6		Me$_3$PhSn	IPr.HCl	2	92
7		Me$_3$PhSn	IPr.HCl	48	80
8		Me$_3$PhSn	IPr.HCl	24	54
9		Ph(n-Bu)$_3$Sn	IAd.HCl	12	45
10		Me$_3$PhSn	IPr.HCl	1	91
11		Me$_3$PhSn	IPr.HCl	48	35

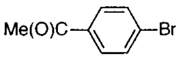
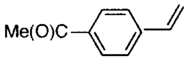
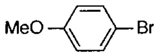
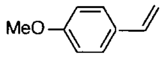
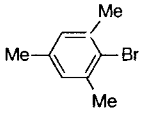
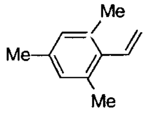
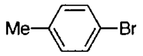
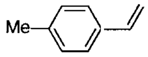
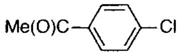
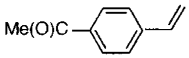
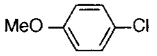
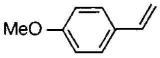
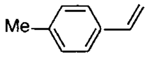
[a] Reaction conditions: 1.0 mmol of aryl halide, 1.1 mmol of arylstannane, 2 mmol of TBAF, 3.0 mol % Pd(OAc)$_2$, 3.0 mol % L·HCl, 1 mL of dioxane, 80 °C for aryl bromides (100 °C for aryl chlorides). [b] Isolated yields. [c] All reactions were monitored by GC. Yields are average of two runs.

Both Pd(II)/IPr·HCl and Pd(II)/IAd·HCl were found to be effective catalytic systems for the cross-coupling of electron-neutral and electron-defficient aryl bromides with either PhSnMe$_3$ or PhSn(^{n}Bu)$_3$ (Table 3). The electron-rich 4-bromoanisole coupled rapidly only with the more reactive PhSnMe$_3$ using IPr·HCl as ligand (Table 3, entry 6) leading to a 92% isolated yield. Ortho-substituted aryl bromides required longer reaction times when reacted with Me$_3$PhSn (Table 3, entries 5 and 7). These results illustrate that, generally, aryl bromides are the optimal electrophiles in coupling reactions involving various organostannanes.

A survey of catalytic cross-coupling of aryl chlorides with arylstannanes using IPr·HCl as the supporting ligand is provided in Table 3 (entries 8−11). Similar to reactions involving organosilicon coupling reagents,[12] the catalyst/ligand system was not found suitable for couplings involving electron-neutral and electron-rich aryl chlorides (Table 3, entries 8, 9, and 11). A similar catalytic behavior was observed for the coupling of aryl halides with vinylstannanes (Table 4). Unlike aryl bromides that reacted easily with tributylvinylstannane (Table 4, entries 1 and 4), only the electron-deficient 4-chloroacetophenone converted to the coupling product in a moderate yield (Table 4, entry 5). The results in Tables 3 and 4 suggest that the coupling of aryl chlorides requires more vigorous conditions and is facilitated by electron-withdrawing substituents. This observation would suggest that the oxidative addition of aryl halides (or vinyl halides) is the rate-determining step of the reaction.

Table 4. Pd(OAc)$_2$/IPr·HCl Catalyzed Cross-Coupling of Aryl Halides with Vinylstannane[a]



entry	aryl halide	product	time (h)	yield(%)[b,c]
1			3	92
2			48	69
3			48	25
4			48	98
5			3	83
6			24	15
7			12	41

[a] Reaction conditions: 1.0 mmol of aryl halide, 1.1 mmol of vinylstannane, 2 mmol of TBAF, 3.0 mol % Pd(OAc)$_2$, 3.0 mol % IPr·HCl, 1 mL of dioxane, 80 °C for aryl bromides (100 °C for aryl chlorides). [b] GC yields. [c] All reactions were monitored by GC. Yields are average of two runs.

A major difficulty in working up reaction mixtures from

Stille cross-couplings is the removal of tin byproducts. In the present case, TBAF serves not only as base and tin transfer reagent but also as fluorous medium for tin extraction. This makes possible the removal of tin by simple water extraction.

In summary, a palladium/imidazolium salt system was determined to be efficient in the cross-coupling of electron-neutral and electron-poor aryl halides with organotin reagents. Moreover, the use of the Pd/IPr•HCl system has been extended to the Stille reaction and now clearly demonstrates the efficiency and generality of this class of ligands for cross-coupling reactions involving aryl halides and a variety of transmetallating organometallic reagents.

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Supporting Information Available: Experimental procedures and references to known compounds are provided. This material is free of charge via the Internet at http://pubs.acs.org.

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