Efficient Sonogashira Reactions of Aryl Bromides with Alkynylsilanes Catalyzed by a Palladium/Imidazolium Salt System

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Summary: A palladium/imidazolium chloride system has been used to mediate the cross-coupling reaction of aryl halides with alkynylsilanes. The combination of 3 mol % $Pd(OAc)_2$ and 6 mol % IMes·HCl in the presence of Cs_2CO_3 as base proves to be a highly efficient system in assisting coupling of aryl bromides with alkynylsilanes.

Increasing attention has focused on the synthesis of arylalkynes and conjugated enynes as these play an important role in the assembly of bioactive natural molecules and new materials.[1] The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides provides a most straightforward and powerful method for such synthetic strategies.[1,2] Usually, the Sonogashira reaction is mediated by a palladium−phosphine complex and copper(I) iodide as a cocatalyst. Recently, a palladium system modified by a bulky, electron-rich phosphine ligand, P^tBu_3, has been reported to display unusually high activity in Sonogashira coupling of aryl bromides.[3]

Nucleophilic N-heterocyclic carbenes have attracted considerable attention.[4] These ligands are strong σ-donors with negligible π-accepting ability and in this regard resemble tertiary phosphines.[5] High catalytic activities have been achieved using nucleophilic carbenes in a variety of catalytic reactions which include the Suzuki−Miyaura reaction,[6] the Kumada−Tamao−Corriu reaction,[7] the Heck reaction,[8] aryl amination involving aryl chlorides,[9] olefin metathesis,[10] and olefin hydrogenation.[11] The use of nucleophilic carbenes in Sonogashira coupling has so far resulted in limited success.[12] To the best of our knowledge, only four examples of the Sonogashira reaction mediated by palladium N-heterocyclic carbene complexes have been reported. Furthermore, the protocol used only dealt with activated arylbromides (4-bromoacetophenone and 4-bromofluorobenzene) as substrates.[13] In this contribution, we wish to report a very efficient Sonogashira reaction involving various arylbromides and alkynylsilanes catalyzed by the palladium/imidazolium salt system.

We have established that Pd-carbene species can be formed *in situ* from a palladium precursor with imidazolium salts in various C−C coupling reactions under basic conditions.[6b,c,7] In initial experiments, a catalytic system consisting of 2 mol % $Pd(OAc)_2$ and 4 mol % IMes·HCl with 2 equiv of Cs_2CO_3 as base in *N,N*-dimethylacetamide (DMAc) at 80 °C was used in an attempt to mediate the coupling of 4-bromotoluene (1 mmol) with phenylacetylene (1.4 mmol). Using this protocol, the desired product was obtained in 80% yield (GC yield based on 4-bromotoluene). However, a side-product, 1,1′-(1-buten-3-yne-1,4-diyl)bis(4-methylbenzene), obtained from the dimerization of phenylacetylene, was also obtained. The ratio of side-product to

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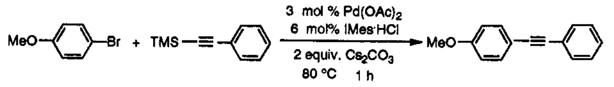
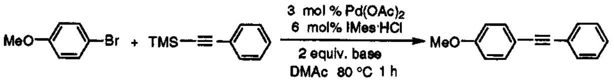
Table 1. Effect of the Solvent on Pd(OAc)$_2$/IMes·HCl-Catalyzed Sonogashira Reaction of 4-Bromoanisole with 1-Phenyl-2-(trimethylsilyl)acetylene[a]



entry	solvent	yield (%)[b]
1	THF	48
2	dioxane	37
3	CH_3CN	68
4	DMF	60
5	DMAc	87

[a] Reaction conditions:1.0 mmol of 4-bromoanisole, 1.4 mmol of 1-phenyl-2-(trimethylsilyl)acetylene, 2 mL of DMAc. [b] GC yields based on 4-bromoanisole (average of two runs).

Table 2. Effect of the Base on Pd(OAc)$_2$/IMes·HCl-Catalyzed Sonogashira Reaction of 4-Bromoanisole with 1-Phenyl-2-(trimethylsilyl)acetylene[a]



entry	base	yield (%)[b]
1	none	0
2	Et_3N	0
3	TBAF	9
4	CsF	13
5	K_2CO_3	29
6	Cs_2CO_3	87

[a] Reaction conditions:1.0 mmol of 4-bromoanisole, 1.4 mmol of 1-phenyl-2-(trimethylsilyl)acetylene, 2 mL of DMAc. [b] GC yields based on 4-bromoanisole (average of two runs).

Scheme 1. Structure of Imidazolium Salts

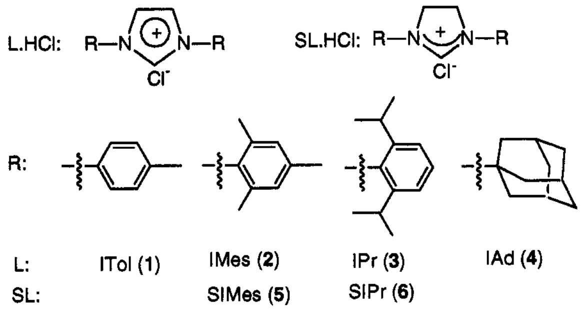
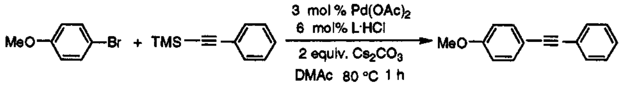


Table 3. Sonogashira Reaction of 4-Bromoanisole with 1-Phenyl-2-(trimethylsilyl)acetylene Using Pd(OAc)$_2$ with Different Imidazolium Chlorides[a]



entry	L	yield (%)[b]
1	none	32[c]
2	ITol (1)	62
3	IMes (2)	87
4	IPr (3)	80
5	IAd (4)	56
6	SIMes (5)	66
7	SIPr (6)	60

[a] Reaction conditions:1.0 mmol of 4-bromoanisole, 1.4 mmol of 1-phenyl-2-(trimethylsilyl)acetylene, 2 mL of DMAc. [b] GC yields based on 4-bromoanisole (average of two runs). [c] Reaction time 6 h.

desired coupling product was 1:3 (based on GC analysis). To suppress the side-reaction, 1-phenyl-2-(trimethylsilyl)acetylene was used as coupling partner with arylbromides.[14] The catalytic system proved to be highly efficient in coupling 4-bromotoluene with 1-phenyl-2-(trimethylsilyl)acetylene. The reaction proceeded very rapidly and afforded the desired product in 90% yield in 1 h. Only traces (<6%) of the dimerization product were observed. The dimerization side-reaction involving 1-phenyl-2-(trimethylsilyl)acetylene was almost completely inhibited.

In optimization studies, the deactivated 4-bromoanisole was used as test substrate. A search for the best solvent for this system showed that polar solvents (such as acetonitrile, DMF, and DMAc) could be used. *N*,*N*-Dimethylacetamide was selected as the optimum solvent (Table 1). The reaction rates also proved to be significantly influenced by the identity of the base used in the reaction (Table 2). The highest activity was achieved with Cs_2CO_3 as the base. The base typically used in Sonogashira reaction, triethylamine, did not lead to active systems. Other inorganic or organic bases resulted in lower yields. We view the role of the base as twofold: it initially deprotonates the imidazolium chloride to form the free carbene ligand, which can coordinate to palladium.[15] Second, it assists in the deprotection of 1-phenyl-2-(trimethylsilyl)acetylene to generate the silicon-free phenylacetylene intermediate.[16] Thus this reactive species should be present in low concentration in the reaction mixture, suppressing the intermolecular dimerization of phenylacetylene.[16,17]

In an effort to select the most effective imidazolium salts, a series of 1,3-disubstituted imidazolium chlorides (Scheme 1) was used in the test reaction (Table 3). The imidazolium chlorides investigated were all active in the catalytic system. The use of IMes (**2**) or IPr (**3**) led to highly efficient Sonogashira reactions. Substitution of IMes, IPr with more electron-donating SIMes (**5**), SIPr(**6**), respectively, resulted in a decrease in activity.

Under optimized conditions (3 mol % Pd(OAc)$_2$, 6 mol % IMes·HCl, with or without 2 mol % CuI, 2 equiv of Cs_2CO_3, *N*,*N*-dimethylacetamide, 80 °C) excellent product yields could be obtained from a wide array of arylbromides with 1-phenyl-2-(trimethylsilyl)acetylene in a very short time (Table 4). The electron-deficient 4-bromobenzaldyde was completely converted to product in less than 15 min (entry 1). For electron-neutral aryl bromides, complete or near complete conversions could be reached in 30 min (entries 2, 3). This catalytic system was equally efficient for electron-rich arylbromides. An 82% yield could be reached from 4-bromoanisole in 30 min (entry 6). It is noteworthy that the above-mentioned

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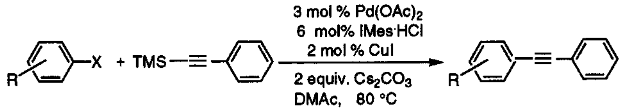
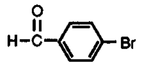
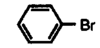
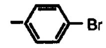
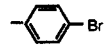
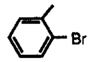
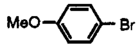
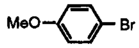
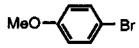
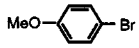
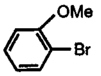
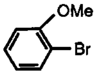
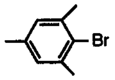
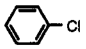
Table 4. Pd(OAc)$_2$/L·HCl-Catalyzed Sonogashira Reaction of Aryl Halide with 1-Pheyl-2-(trimethylsilyl)acetylene[a] [17]

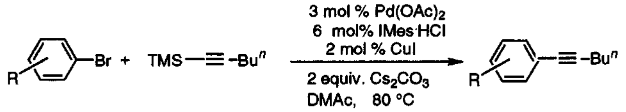


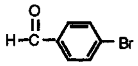
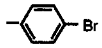
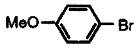
entry	aryl halide	time (h)	yield (%)[b]
1		0.25	100 (92)[c]
2		0.5	100 (91)[c]
3		0.5	96 (86)[c]
4		0.5	99
5		0.5	100 (93)
6		0.5	82[c]
7		3	94[d]
8		0.5	96 (88)
9		1	43[c], [e]
10		0.5	100 (93)
11		0.5	95[f]
12		1	90 (82)
13		1	51

[a] Reaction conditions:1.0 mmol of aryl halide, 1.4 mmol of 1-phenyl-2-(trimethylsilyl)-acetylene, 2 mL of DMAc. [b] GC yields based on aryl halide; number in parentheses is isolated yield (average of two runs). [c] Without CuI. [d] Reaction temperature 60 °C. [e] 3 mol % Pd(dba)$_2$ as Pd source. [f] 6 mol % IPr·HCl as ligand.

high activities were achieved under copper-free conditions. The addition of 2 mol % CuI as cocatalyst can increase reaction rates (entries 4, 8). This effect is more remarkable with deactivated arylbromides. A nearly complete conversion was observed for 4-bromoanisole (entry 8) using this protocol.[18] The catalytic system was also highly efficient for sterically encumbered substrates. (entries 5, 10, and 12). Remarkably, the catalytic system was effective for chlorobenzene in moderate yield (entry 13).

Table 5. Pd(OAc)$_2$/L·HCl-Catalyzed Sonogashira Reaction of Aryl Bromide with 1-Trimethylsilyl-1-hexyne[a]



entry	aryl bromide	time (h)	yield (%)[b]
1		1	100
2		1	71
3		1	55

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.4 mmol of 1-trimethylsilyl-1-hexyne, 2 mL of DMAc. [b] GC yields based on aryl bromide (average of two runs).

To evaluate the scope of this method, we also performed coupling reactions involving arylbromides and 1-trimethylsilyl-1-hexyne (Table 5). The electron-deficient 4-bromobenzaldyde was completely converted to the coupled product in 1 h (entry 1). For electron-neutral and electron-donating arylbromides, moderate to good yields could be obtained (entries 2, 3).

In summary, a palladium/imidazolium chloride system has been successfully applied to the cross-coupling of arylhalides with alkynylsilanes. The Pd(OAc)$_2$/IMes·HCl has proven to be a highly efficient catalytic system in the cross-coupling reactions of a variety of arylbromides with alkynylsilanes. The coupling reaction proceeds rapidly under copper-free conditions, although the addition of CuI as cocatalyst can facilitate the reaction especially for deactivated arylhalides. This system also proves to be tolerant of sterically hindered substrates. Preliminary results show this system to be promising in mediation of the Sonogashira reaction involving aryl chlorides. Usually, a trimethylsilyl group is used as a protective group in the synthesis of precursors used in the Sonogashira reaction.[14] This work, representing a synthetic simplification, presents a significant advantage in not requiring the deprotection of silyl-protected alkynes prior to performing the Sonogashira coupling and in most instances does not require the presence of a copper cocatalyst. Studies aimed at developing protocols for use of aryl chlorides in the Sonogashira reaction are ongoing.

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Supporting Information Available: Experimental details are available free of charge via the Internet at http://pubs.acs.org.

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(18) In a typical catalytic run, a scintillation vial equipped with a screw-cap and a septum was charged with Pd(OAc)$_2$ (0.03 mmol), IMes·HCl (0.06 mmol), Cs$_2$CO$_3$ (2.0 mmol), and 2.0 mL of *N*,*N*-dimethylacetamide in a glovebox. The mixture was stirred for 15 min outside the glovebox. Then 1.0 mmol of aryl halide and 1.4 mmol of 1-phenyl-2-(trimethylsilyl)acetylene were added to the vial. The reaction mixture was allowed to stir in an oil bath at 80 °C. The product yields were monitored and determined by GC analysis. In some cases, the products were isolated by column chromatography and identified by GC−MS and ^{1}H NMR. The workup procedure was as follows: 50 mL of water was added to the reaction mixture, followed by extraction with diethyl ether. The combined organic layer was dried over MgSO$_4$ and filtered, and ether was evaporated to give a crude product. The pure product was obtained by flash chromatography (1:30 ethyl acetate/hexane).