Copper-Promoted C−N Bond Cross-Coupling with Hypervalent Aryl Siloxanes and Room-Temperature N-Arylation with Aryl Iodide

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Received April 14, 2000

The formation of C−N bond via cross-coupling reactions[1−3] represents an important addition to the synthetic methodologies for the preparation of nitrogen-containing compounds in pharmaceuticals, crop-protection chemicals and material sciences. In contrast to the powerful C−C bond cross-coupling reactions of Suzuki[4a] and Stille,[4b] a need remains for mild (weak base and room temperature) and general C−N bond cross-coupling reactions for a wide variety of N−H-containing substrates. In recent years, Buchwald[1a] and Hartwig[1b] have pioneered palladium-catalyzed C−N cross-couplings of aryl halides with amines, anilines, mono-nitrogen azoles and carbamates, in general involving either strong base (*t*-BuONa) or elevated temperatures. Arylbismuths[1c−d] and arylleads[1e] have been demonstrated to undergo copper-promoted N-arylation also at elevated temperatures. More recently, the copper-promoted N-arylation with arylboronic acids for diverse N−H-containing substrates was discovered by Chan[2] and Lam.[3] This methodology was further extended to include, with limited success, arylstannanes.[3b] In further pursuit of an optimum arylmetalloid for this versatile copper-promoted N-arylation reaction, we would like to report that hypervalent aryl siloxanes are an efficient alternative to arylboronic acids for C−N bond formation. This new discovery offers the advantage of performing a one-pot room-temperature N-arylation in the absence of strong base, starting with aryl iodide, via the in situ generation of aryl siloxanes. Organosilicon compounds have recently been shown[5−7] to be effective reagents for C−C bond cross-couplings.

Scheme 1. N-Arylation with Aryl Trimethylsiloxane

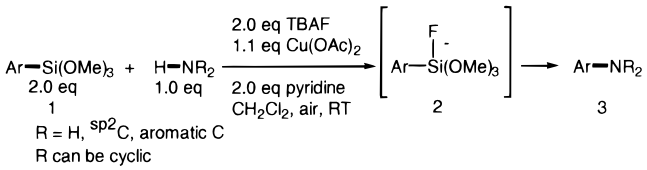
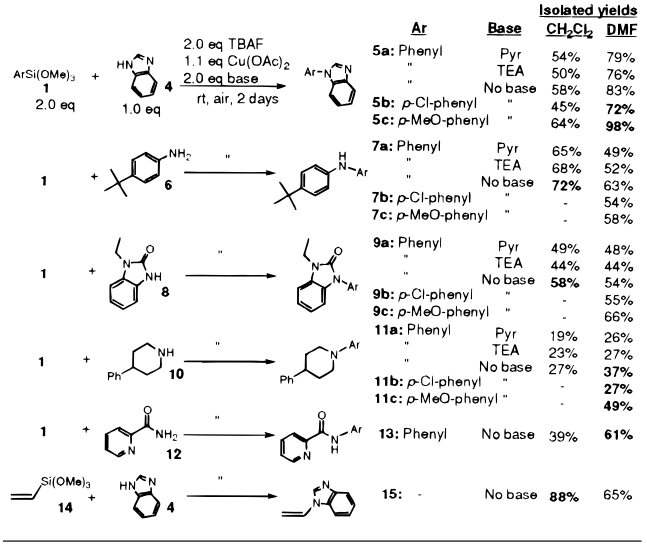


Table 1. N-Arylation of N−H-Containing Substrates with Hypervalent Aryl Siloxanes



	Ar	Base	Isolated yields CH_2Cl_2	DMF
	5a: Phenyl	Pyr	54%	79%
	"	TEA	50%	76%
	"	No base	58%	83%
	5b: *p*-Cl-phenyl	"	45%	**72%**
	5c: *p*-MeO-phenyl	"	64%	**98%**
1 + 6	**7a:** Phenyl	Pyr	65%	49%
	"	TEA	68%	52%
	"	No base	**72%**	63%
	7b: *p*-Cl-phenyl	"	-	54%
	7c: *p*-MeO-phenyl	"	-	58%
1 + 8	**9a:** Phenyl	Pyr	49%	48%
	"	TEA	44%	44%
	"	No base	**58%**	54%
	9b: *p*-Cl-phenyl	"	-	55%
	9c: *p*-MeO-phenyl	"	-	66%
1 + 10	**11a:** Phenyl	Pyr	19%	26%
	"	TEA	23%	27%
	"	No base	27%	**37%**
	11b: *p*-Cl-phenyl	"	-	**27%**
	11c: *p*-MeO-phenyl	"	-	**49%**
1 + 12	**13:** Phenyl	No base	39%	**61%**
14 + 4	**15:** -	No base	**88%**	65%

Addition of an equimolar amount[8] of tetrabutylammonium fluoride (TBAF) to phenyl trimethylsiloxane (**1**) generates a hypervalent siloxane species **2** (Scheme 1).[5] This silicate species is a very efficient arylating agent for N−H-containing substrates in the presence of cupric acetate[9] at room temperature under atmospheric air to generate N-arylated cross-coupled product **3**. For example, for benzimidazole **4** in DMF, 83% isolated yield of **5a** was obtained (Table 1). The reaction is very fast with the rate of the consumption of benzimidazole (90% in 10 min in methylene chloride) an order of magnitude faster for siloxane than was observed for boronic acid.[3b]

Previously when employing arylboronic acids as arylating agent, it was essential to add base/ligand (either pyridine or triethylamine, depending on the substrate).[2,3] However, we found that no base/ligand was necessary for N-arylations with aryl siloxane (Table 1).[10]

A variety of other N−H-containing substrates can be arylated (Table 1). 4-*tert*-Butylaniline **6** gave 72% yield of **7a** in CH_2Cl_2.[11] *N*-Ethylbenzimidazolidinone **8** can be N-phenylated to give 58% yield of **9a** in CH_2Cl_2. 4-Phenylpiperidine **10** also undergoes cross-coupling to give 37% of **11a**. Interestly, 2-picolinamide **12** can be N-phenylated (61%) in DMF.[12] In terms of the electronic

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(1) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron* **1997**, *53*, 4137−4144. (d) Fedorov, A. Y.; Finet, J.-P. *Tetrahedron Lett.* **1998**, *39*, 7979−7982. (e) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678−5682.

(2) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (b) For an improved version of the related O-arylation see also: Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

(3) (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2937−2940. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K.; Chan, D. M. T.; Combs, A. P. *Synlett* **2000**, 674−676. (c) For solid-phase version of N-arylation see: Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623−1626. (d) Combs, A. P.; Rafalski, M. *J. Combinatorial Chem.* **2000**, *2*, 29−32.

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

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(7) For transmetalation from silicon to copper see: (a) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780−1787 (ref 18, 20 therein). (b) Ito, H.; Hosomi, A. *J. Synth. Org. Chem.* **2000**, *58*, 274. (c) Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985−990. (d) Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196−11197. (e) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893−7896.

(8) Excess TBAF (50% equivalent excess) did not affect the yield.

(9) Cupric acetate, the best copper salt used previously[2,3] in the N-arylation of arylboronic acid is required. No product was obtained in its absence.

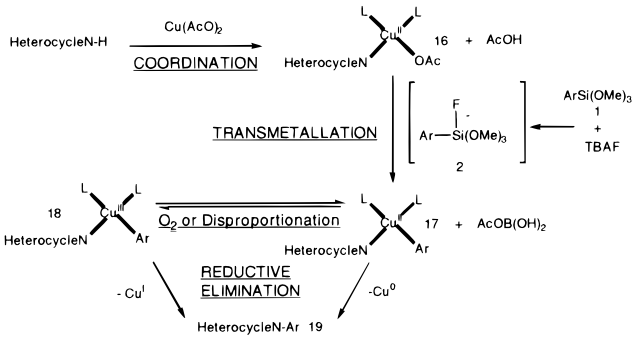
(10) We believe tetra-*n*-butylammonium fluoride is not the base since in theory all fluoride is consumed stoichiometrically by the formation of Si−F bond with aryl trimethylsiloxane.

(11) In an attempt to increase the yield for *tert*-butylaniline, phenyl tris-(2,2,2-trifluoroethyl)siloxane,[5] a more reactive siloxane was used, but the yield remained the same. The use of phenyl triethylsiloxane instead of phenyl trimethylsiloxane also gave similar yields in the case of benzimidazole.

(12) On the contrary, benzamide gave only 9% N-arylation after heating at 70 °C. We are currently investigating the significance and utility of this chelating effect of α-heteroatoms on N-arylation. We thank Dr. Elizabeth Hauptman of DuPont CR&D for this observation.

10.1021/ja001305g CCC: $19.00
Published on Web 07/20/2000

Scheme 2. Possible Mechanism of N-Arylation with Hypervalent Aryl Siloxane



effect of the substituents on aryl siloxane, the yield is in the following descending order: *p*-methoxy > phenyl > *p*-chloro. In general, DMF is the preferred solvent for **4**, **10**, and **12**. CH_2Cl_2 is the preferred solvent for **6** while **8** works equally well in either DMF or CH_2Cl_2.

That the reaction involves a hypervalent siloxane species is evident by the fact that no **5a** was obtained in the absence of fluoride. The hypervalent siloxane species can also be preformed prior to the addition of benzimidazole and cupric acetate with no change in yields. Water does not appear to interfere with the reaction as the commercial solution of TBAF in THF contains 5% water. Addition of 4 Å molecular seives thus provides no change in the yield of *N*-phenylbenzimidazole. This is again in contrast to the copper-promoted N-arylation using arylboronic acids where the use of 4 Å molecular sieves is reported to improve the yield.[2b−3]

We have also discovered that N-vinylation is possible. For example, benzimidazole can be vinylated by vinyl trimethylsiloxane **14** in CH_2Cl_2 to give 88% yield of *N*-vinylbenzimidazole **15**. We are currently investigating the scope and utility of this novel N-vinylation reaction.[13]

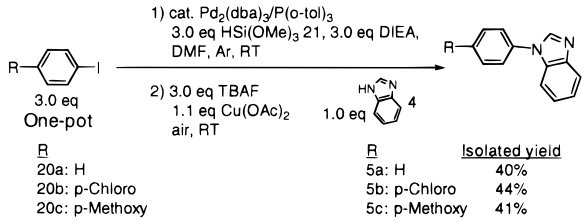
We believe the mechanism (Scheme 2) is similar to that postulated for N-arylation with arylbismuths[1c−d] or arylboronic acids.[2,3] Copper(II) acetate is insoluble in CH_2Cl_2. The first step[3b] involves the rapid coordination and dissolution of copper(II) acetate by heterocycle such as benzimidazole to form heterocycle•copper(II) complex **16**. The second step involves the transmetalation[7] of the pentavalent aryl silicate **2** formed by the addition of fluoride to aryl trimethoxysiloxane **1**[5−7] with **16** to give heterocycle•copper(II)•aryl complex **17**. Complex **17** can undergo reductive elimination to give **19**. Alternatively, **17** can undergo air oxidation or disproportionation to yield the corresponding higher oxidation-state copper(III) complex **18** which can be more efficiently reductive eliminate to afford **19**. A free radical mechanism is ruled out since the addition of 1,1′-diphenylethylene has no effect on the reaction.

The ultimate goal of our investigation is to perform a one-pot N-arylation of benzimidazole using iodobenzene **20a** as the arylating agent via in situ generation of phenyl trimethylsiloxane. Masuda had recently reported the palladium-catalyzed formation of phenyl trimethylsiloxane from **20a** and trimethoxysilane **21** at room temperature.[14] We were attracted to the mild condition of this aryl siloxane formation reaction. The mild siloxane formation reaction of Masuda appears to complement our mild siloxane arylation reaction for a combined one-pot reaction (Scheme 3).

(13) N-vinylation has not been reported by Buchwald/Hartwig.[1a−b]

(14) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569−8571.

Scheme 3. One-Pot N-Arylation with Iodobenzene



Iodobenzene was reacted with trimethoxysilane in the presence of catalytic $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ and *i*-Pr_2EtN in DMF[15] under argon at room temperature. After 12 h, benzimidazole, cupric acetate and TBAF were added and stirred in air until the starting material is consumed. *N*-phenylbenzimidazole **5a** was obtained in 40% isolated yield. This accomplished a one-pot N-arylation of benzimidazole with iodobenzene at room temperature, in the absence of strong base. 4-Chlorophenyl siloxane **20b** and 4-methoxyphenyl siloxane **20c** gave 44 and 41% yields, respectively. That the palladium catalyst from the siloxane formation first step is not involved in the N-arylation second step was demonstrated by the same yield of *N*-phenylbenzimidazole when palladium was removed with Chelex (Bio-Rad) after the first step.

In summary, we have discovered the copper-promoted C−N cross-coupling reaction with hypervalent aryl or vinyl siloxane and a variety of N−H-containing substrates and the extension to a room-temperature one-pot N-arylation, in the absence of strong base, with aryl iodide via in situ generation of siloxane. To the best of our knowledge, this is *the first example of room-temperature N-arylation with aryl iodide in the absence of strong base*.[16] The mild condition of the reaction is analogous to that of amide C−N bond formation and can potentially tolerate most base-sensitive functional groups. We are currently investigating the general scope of this reaction, in particular, other N−H-containing substrates, the use of aryl bromides/chlorides, catalytic copper[17] and applications in generating heterocycle-containing libraries.

Acknowledgment. We thank Dr. Paul S. Anderson and Dr. Ruth R. Wexler for their support of this research.

Note Added in Proof. Replacing the ligand from P(*o*-tol)$_3$ to 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) in the one-pot reaction increases the yield of **5a** from 40 to 53% (We thank Professor Nolan for a sample of the ligand: Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055).

Supporting Information Available: Experimental details for the general procedure, ^{1}H spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001305G

(15) Preliminary investigation of solvent preferences for the one-pot N-arylation is as follow: DMF, NMP > DMAC ≫ EtOAc, dioxane, THF. CH_2Cl_2 gave no product.

(16) In general, N-arylation using Buchwald and Hartwig chemistry requires either elevated temperature or strong base (N*a*t-BuO). During the course of this work, we became aware that some room-temperature N-arylation of Buchwald/Hartwig chemistry is possible, although still in the presence of stong base Na *t*-BuO. (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (b) Hartwig, J. P.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

(17) Modifying Collman's recent procedure, we found that 0.1 equiv of $[Cu(OH)•TMEDA]_2Cl_2$ catalyzes the N-phenylation of benzimidazole with hypervalent phenyl trimethoxysiloxane (69% yield) at 50 °C in DMF (Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236).