Cross-Coupling

DOI: 10.1002/ange.201000472

Sonogashira Cross-Coupling of Arenediazonium Salts**

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Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

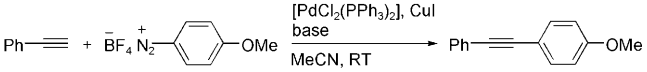
Arenediazonium salts represent an attractive alternative to aryl halides or triflates because of their higher reactivity, their tolerance of milder conditions, their availability from inexpensive anilines, and because additional base is not required in several applications. Arenediazonium salts have been used in a variety of palladium-catalyzed reactions, including Mizoroki–Heck reactions, Suzuki–Miyaura and Stille cross-coupling reactions, and carbonylation reactions, in the synthesis of sulfinic acids and boronic esters;[1] their use in hydroarylation reactions has also been described.[2] Nevertheless, the alkynylation of arenediazonium salts continues to represent a challenge. After the seminal works of Sonogashira et al., Heck and Dieck, and Cassar on the alkynylation of aryl iodides and bromides,[3] a great deal of work has been done to extend the scope of the reaction to include an even wider range of reactants;[4] however, the extension of the reaction to arenediazonium salts remains unresolved.

To the best of our knowledge, the sole attempt to involve arenediazonium salts in the formation of arylacetylenes was made by Genêt and co-workers,[5] who obtained only small amounts of the desired cross-coupling derivative by palladium-catalyzed reaction of potassium 1-hexenyltrifluoroborate with *para*-toluenediazonium tetrafluoroborate. We investigated the reaction using phenylacetylene (**1a**) and 4-methoxybenzenediazonium tetrafluoroborate (**2a**) as the model system. No evidence of the formation of cross-coupling product **3a** was found using $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) or $Pd(OAc)_2$ with a variety of phosphine (PPh_3, Xphos, $HP(tBu)_3BF_4$) or carbene ligands, generated from 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride in the presence of base;[6] a screen of different solvents (MeOH, THF, DME, DMF), in the presence or absence of base (iPr_2NEt, K_2CO_3, Bu_4NOAc) and CuI at temperatures ranging from room temperature to 60 °C also afforded no cross-coupled product. In all cases, complex reaction mixtures were obtained, and anisole and 1,4-diphenyl-1,3-diyne were frequently the main by-products.

To overcome this limit of the palladium-based chemistry of arenediazonium salts, we reasoned that a strategy in which arylacetylenes are formed by an iododediazoniation reaction, followed by a Sonogashira cross-coupling might be successful. Iododediazoniation is a well-established reaction, and recently remarkable advances have been reported in this area.[7] Nevertheless, no examples of its utilization in a sequential process with a palladium-catalyzed reaction have yet been described. Herein, we show that such a sequential process is indeed possible and report the first utilization of arenediazonium salts in Sonogashira cross-coupling reactions.

An initial screen using $[PdCl_2(PPh_3)_2]$, CuI, and Et_2NH in MeCN at room temperature showed that **3a** could be isolated in 48% yield in the presence of nBu_4NI (1.5 equiv) or NaI (2 equiv; Table 1, entries 1 and 2). Optimization studies were then performed by changing the nature and number of equivalents of the base.

Table 1: Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Base	Added salt (equiv)	*t* [h]	Yield of **3a** [%][b]
1	Et_2NH	nBu_4NI (1.5)	1.5	48
2	Et_2NH	NaI (2.0)	9	48
3	Et_2NH	nBu_4NI (2.0)	1	78
4	Et_2NH	nBu_4NI (2.6)	1.5	67
5	iPr_2NH	nBu_4NI (2.0)	1	79
6	Et_2NH	NaI (2.0)/nBu_4NI (0.2)	5	81
7	Et_2NH	nBu_4NI (2.0)	9	–[c]
8	–	nBu_4NI (2.0)	6	–[d]
9	Et_2NH	nBu_4NI (0.2)	1.5	trace

[a] Unless otherwise stated, reactions were carried out at room temperature on a 0.5 mmol scale in 3 mL of MeCN using 2 equiv of **1a**, 1 equiv of **2a**, 10 equiv of base, 0.02 equiv of $[PdCl_2(PPh_3)_2]$, 0.04 equiv of CuI, and nBu_4NI or NaI. [b] Yields are given for isolated products. [c] Omitting CuI. [d] Omitting Et_2NH.

These investigations revealed that when 2 equivalents of nBu_4NI were used, **3a** was isolated in a satisfactory 78% yield after 1 hour (Table 1, entry 3). Increasing the number of equivalents of nBu_4NI led to a lower yield (Table 1, entry 4), whereas comparable results were obtained by substituting iPr_2NH for Et_2NH (Table 1, entry 5) or using 2 equivalents of NaI in the presence of 0.2 equivalents of nBu_4NI (Table 1, entry 6). No cross-coupled product was formed when CuI (Table 1, entry 7) or Et_2NH were omitted from the reaction (Table 1, entry 8).

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[**] We gratefully acknowledge GlaxoSmithKline for their generous financial support and a fellowship position as well as Dr. Alcide Perboni and Dr. Paolo Stabile of GlaxoSmithKline for valuable discussions. We are also indebted to MURST and to La Sapienza, University of Rome.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000472.

The scope and generality of the process was explored next using the conditions from Table 1, entry 3, although the conditions described in Table 1, entries 5 and 6 provided similar results. As shown in Table 2, electron-rich and electron-poor arenediazonium tetrafluoroborates react with phenylacetylene to give the corresponding cross-coupling products in good to excellent yields. The reaction tolerates a variety of substituents including chloro, bromo, keto, ester, cyano, and nitro groups. Substituents in the *ortho* position are also tolerated (Table 2, entries 2, 4, 6, and 12).

The extension of the reaction to a variety of terminal alkynes was also examined. Our initial results are summarized in Table 3.

Formation of **3f**, **3l**, and **3v–x** is particularly noteworthy given that alkynylarenes that contain 2-halo- and 2-aminoaryl moieties have been widely used for the preparation of indoles,[6,8] and that those containing 2-hydroxyaryl moieties are useful intermediates for the synthesis of benzo[*b*]furans using transition-metal-catalyzed cyclization reactions.[9] This chemistry might provide an exceedingly useful tool for appending heterocyclic rings to aniline fragments.

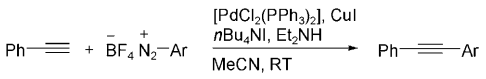
As an example, we explored the formation of 2-phenylindole from 2-ethynylaniline (**1g**) and benzenediazonium tetrafluoroborate (**2c**) through a process that would omit the isolation of the cross-coupling intermediate. After some experimentation, we were pleased to find that adding 5 mol% of $NaAuCl_4$ and MeCN to the crude product mixture after work-up of the Sonogashira reaction gave the desired indole product in 64% overall yield after 12 hours at 60°C.

The entire diazonium salt synthesis/iododediazoniation/cross-coupling sequence can also be performed in a one-pot domino process, omitting the isolation of the intermediate arenediazonium salt (Scheme 1).[10] The best results were obtained when the reagents required for the alkynylation step were added to a crude mixture following the preparation of the diazonium salts that had been concentrated under reduced pressure.

A plausible mechanism for this alkynylation reaction involves the initial iododediazoniation of the arenediazonium salt, followed by formation of a σ-aryl palladium iodide by oxidative addition, subsequent reaction of σ-aryl palladium iodides with copper acetylides that are formed in situ, and reductive elimination of the resultant σ-alkyne–σ-aryl palladium complexes to give the cross-coupling product **3** and regenerate the active catalyst species.

The intervention of an alternative mechanism that involves the formation of σ-aryl palladium iodides from the reaction pathway outlined in Scheme 2 has been ruled out on the basis of the following experiments: The reaction of **1a** with **2c** was carried out under standard conditions using nBu_4NBr instead of nBu_4NI. If σ-aryl palladium bromides were generated by trapping σ-aryl palladium cations (**C**)[11] with bromide anions, the traditional reluctance of aryl bromides to undergo oxidative addition with palladium catalysts that are coordinated to triphenylphosphine[12] should be circum-

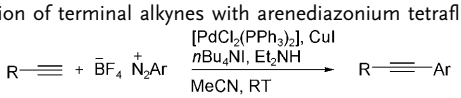
Table 2: Reaction of phenylacetylene with arenediazonium tetrafluoroborates.[a]

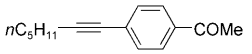
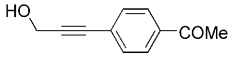
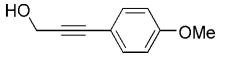
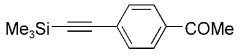
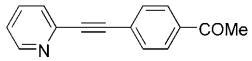
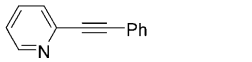
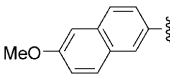
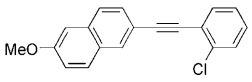
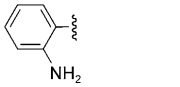
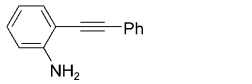
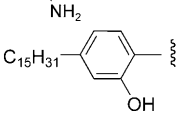
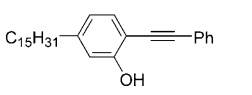


Entry	Ar	2	t [h]	Product	Yield [%][b]
1	4-$MeOC_6H_4$	**2a**	1	**3a**	78
2	2-$MeOC_6H_4$	**2b**	1.5	**3b**	66
3	Ph	**2c**	1.5	**3c**	91
4	2,4-$Me_2C_6H_3$	**2d**	2	**3d**	75[c]
5	4-ClC_6H_4	**2e**	2	**3e**	77
6	2-ClC_6H_4	**2f**	2	**3f**	85
7	3,4,5-$MeOC_6H_2$	**2g**	1.5	**3g**	90
8	4-$MeCOC_6H_4$	**2h**	0.5	**3h**	85
9	3-$MeOC_6H_4$	**2i**	2	**3i**	79
10	4-$MeO_2CC_6H_4$	**2j**	1	**3j**	78
11	4-BrC_6H_4	**2k**	2	**3k**	83
12	2-BrC_6H_4	**2l**	2	**3l**	74
13	4-NCC_6H_4	**2m**	1	**3m**	86
14	3-$CF_3C_6H_4$	**2n**	2	**3n**	90
15	4-$O_2NC_6H_4$	**2o**	1.5	**3o**	91

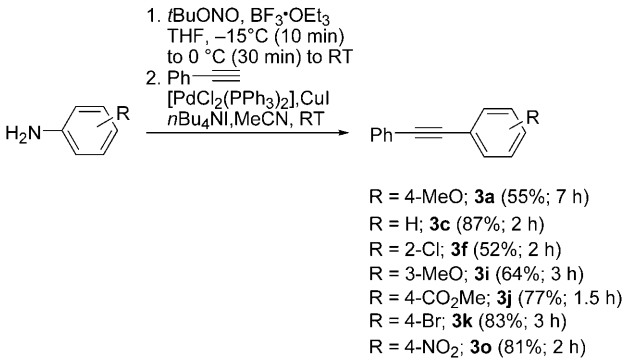
[a] Unless otherwise stated, reactions were carried at room temperature out on a 0.5 mmol scale in 3 mL of MeCN using 2 equiv of **1a**, 1 equiv of **2**, 10 equiv of Et_2NH, 0.02 equiv of $[PdCl_2(PPh_3)_2]$, 0.04 equiv of CuI, and 2 equiv of nBu_4NI. [b] Yields are given for isolated products. [c] At 60°C using $(iPr)_2NH$.

Table 3: Reaction of terminal alkynes with arenediazonium tetrafluoroborates.[a]

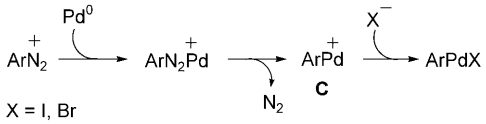


Entry	R	1	2	Product (t [h])		Yield [%][b]
1	nC_5H_{11}	**1b**	**2h**		**3p** (2 h)	75
2	$HOCH_2$	**1c**	**2h**		**3q** (3 h)	78
3	$HOCH_2$	**1c**	**2a**		**3r** (2 h)	72
4	Me_3Si	**1d**	**2h**		**3s** (2 h)	72
5	2-pyridyl	**1e**	**2h**		**3t** (1.5 h)	87
6	2-pyridyl	**1e**	**2c**		**3u** (2 h)	92
7		**1f**	**2f**		**3v** (2 h)	63
8		**1g**	**2c**		**3w** (6 h)	82
9		**1h**	**2c**		**3x** (4 h)	92

[a] Unless otherwise stated, reactions were carried at room temperature out on a 0.5 mmol scale in 3 mL of MeCN using 2 equiv of **1**, 1 equiv of **2**, 10 equiv of Et_2NH, 0.02 equiv of $[PdCl_2(PPh_3)_2]$, 0.04 equiv of CuI, and 2 equiv of nBu_4NI. [b] Yields are given for isolated products.



Scheme 1. One-pot domino cross-coupling of anilines with phenyl acetylene.



Scheme 2. Formation of ArPdX through the reaction of halide anions with $ArPd^+$ intermediates.

vented, and formation of cross-coupling products should be observed. No evidence for the formation of compound **3a** was found after 5 hours at room temperature, whereas bromobenzene was obtained in 90% yield,[13] suggesting that the bromodediazoniation process is faster than the reaction shown in Scheme 2. To consider whether the lack of cross-coupling product in the presence of nBu$_4$NBr might be due, at least in part, to a different reactivity of σ-arylpalladium iodide and bromide intermediates towards copper acetylides, we explored the reactions of preformed [PhPdI(PPh$_3$)$_2$][14] and [PhPdBr(PPh$_3$)$_2$][15] with phenylacetylene at room temperature.[16] As shown in Figure 1, the bromide complex shows a higher reactivity in the initial phases of the reaction, which in both cases led to approximately 42% yield of **3a** after 2 hours. If σ-aryl palladium bromides were generated by trapping σ-aryl palladium cations **C** with bromide anions, the corresponding cross-coupling product should then form. Taken together, these results strongly support the view that the Sonogashira cross-coupling of arenediazonium salts with terminal alkynes in the presence of nBu$_4$NI proceeds through a domino process that starts with the iododediazoniation step.

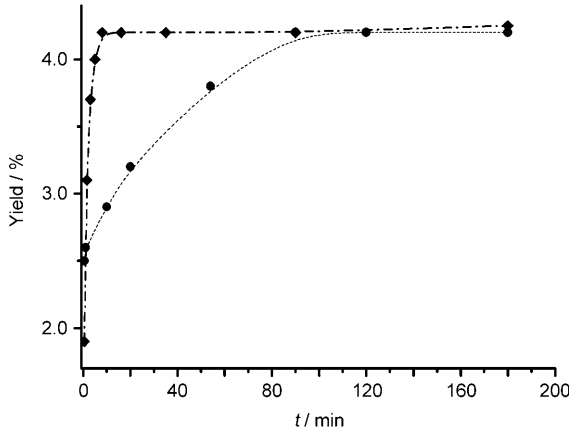


Figure 1. Reaction of [PhPdI(PPh$_3$)$_2$] (●) and [PhPdBr(PPh$_3$)$_2$] (◆) with phenylacetylene in the presence of CuI and Et$_2$NH in MeCN at room temperature.

In conclusion, the efficient cross-coupling of terminal alkynes with arenediazonium salts has been developed. To the best of our knowledge, this transformation is the first example of the alkynylation of arenediazonium salts. The reaction occurs under mild conditions in the presence of nBu$_4$NI and proceeds through a domino iododediazoniation/Sonogashira cross-coupling sequence. Good to excellent yields are usually obtained. A variety of alkyl, aryl, and heteroaryl substituents on the alkyne substrate can be used and many useful functionalities including bromo, chloro, keto, ester, ether, cyano, and nitro substituents on the arenediazonium salt are also tolerated. *ortho* Substituents, both in the arenediazonium salt and the alkynylarene, are also tolerated. The formation of alkynylarenes bearing 2-chloro-, 2-bromo-, 2-amino-, and 2-hydroxyaryl moieties may be exceedingly useful for appending heterocyclic rings to aniline fragments. The entire arenediazonium salt synthesis/iododediazoniation/cross-coupling sequence can also be performed as a one-pot domino process, omitting the isolation of the arenediazonium salt.

Received: January 26, 2010
Revised: March 5, 2010
Published online: April 26, 2010

Keywords: arenediazonium salts · cross-coupling · domino reactions · homogeneous catalysis · palladium

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