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One-Pot Synthesis of Symmetrical and Unsymmetrical Bisarylethynes by a Modification of the Sonogashira Coupling Reaction

Matthew J. Mio,[†] Lucas C. Kopel,[†] Julia B. Braun,[†] Tendai L. Gadzikwa,[†] Kami L. Hull,[†] Ronald G. Brisbois,[*,†] Christopher J. Markworth,[‡] and Paul A. Grieco[*,‡]

Department of Chemistry, Macalester College, 1600 Grand Avenue,
St. Paul, Minnesota 55105, and Department of Chemistry and Biochemistry,
Montana State University, Bozeman, Montana 59717

brisbois@macalester.edu

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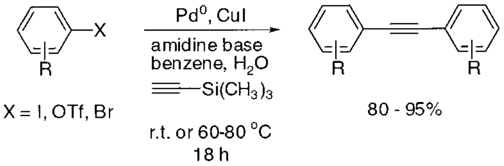
ABSTRACT



A modification of the Sonogoshira coupling reaction employing an amidine base and a substoichiometric amount of water generates symmetrical and unsymmetrical bisarylethynylenes in one pot through in situ deprotection of trimethylsilylethynylene-added intermediates.

The Sonogashira palladium-catalyzed cross-coupling reaction[1] has proven to be a powerful method for the formation of shape-persistent arylethynylenes.[2] Whether employed in the generation of scaffolds leading to molecular electronic devices,[3] dendrimers,[4] dehydrobenzannulenes,[5] foldamers,[6] or polymers,[7] the Sonogashira cross-coupling has proven to be a reliable, high-yielding reaction that is tolerant of a wide variety of functional groups. However, use of the Sonogashira reaction to effect iterative synthesis often requires systematic silane protection/deprotection of terminal ethynylenes.[8] Although a variety of strategies for in situ base-mediated deprotection and cross coupling have been reported, all such methods require prior installation of protecting groups and/or supplementary reagents.[9] Our immediate need for efficient syntheses of a wide range of bisarylethynylenes[10] derives from efforts focused on supramolecular self-assembly, in which Co-mediated [2 + 2] annulation of alkynes

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[†] Macalester College.

[‡] Montana State University.

(1) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(2) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402.

(3) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791.

(4) (a) Pugh, V. J.; Hu, Q.-S.; Zuo, X.; Lewis, F. D.; Pu, L. *J. Org. Chem.* **2001**, *66*, 6136. (b) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528.

(5) Wan, W. B.; Haley, M. M. *J. Org. Chem.* **2001**, *66*, 3893.

(6) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.

(7) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605.

(8) (a) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1965**, *4*, 217. (b) Eastmond, R.; Johnson, T. R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 4601. (c) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10.

(9) (a) Denmark, S. E.; Sweis, R. *J. Am. Chem. Soc.* **2001**, *123*, 6439. (b) Pugh, C.; Percec, V. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 1101. (c) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910. (d) Shultz, D. A.; Gwaltney, K. P.; Lee, H. *J. Org. Chem.* **1998**, *63*, 4034. (e) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.

(10) While several procedures for generating bisarylethynylenes using alkynylmetal reagents are known, we only compare our method to similar Pd- and Cu-based strategies. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5. (b) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1995.

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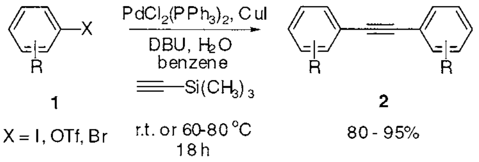
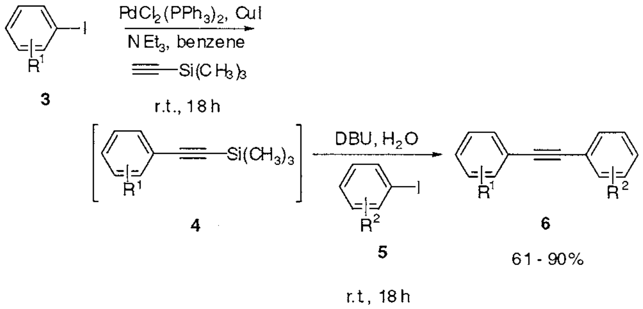
Scheme 1

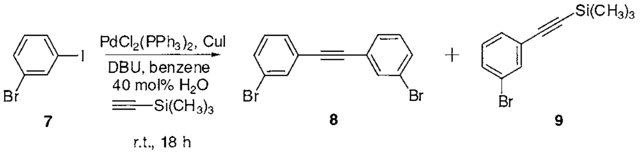


Scheme 2



provides CpCoCb-bridged ligands or ligand precursors.[11] Herein, we report on a modification of the Sonogashira reaction that allows for the one-pot generation of symmetrical (Scheme 1) and unsymmetrical bisarylethynylenes (Scheme 2). Central to the synthetic protocol is the utilization of an amidine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the presence of substoichiometric amounts of water, in addition to Pd^0 catalyst, CuI, and organic solvent.[12]

Table 1. Study of Symmetrical Bisarylethynylene Formation under a Variety of Modified Sonogashira Reaction Conditions[a]



entry	catalyst	base	solvent	yields[b] (%)		
				7	8	9
1	$PdCl_2(PPh_3)_2$	DBU	benzene	trace	99	0
2	$PdCl_2(PPh_3)_2$	DBU	toluene	8	92	0
3	$PdCl_2(PPh_3)_2$	DBU	dioxane	5	95	0
4	$PdCl_2(PPh_3)_2$	DBU	THF	6	94	0
5	$PdCl_2(PPh_3)_2$	DBU	DMF	4	96	0
6	$PdCl_2(PPh_3)_2$	DBU	CH_3CN	trace	99	0
7	$PdCl_2(PPh_3)_2$	TEA	benzene	44	0	56
8	$PdCl_2(PPh_3)_2$	DABCO	benzene	18	0	82
9	$PdCl_2(PPh_3)_2$	DBN	benzene	14	84	1
10	$PdCl_2(PPh_3)_2$	GUAN	benzene	38	62	trace
11	$Pd_2(dba)_3$[c]	DBU	benzene	9	91	trace
12	$Pd(PPh_3)_4$	DBU	benzene	2	98	trace
13	$PdCl_2dppf$	DBU	benzene	7	93	trace
14	$PdCl_2(PhCN)_3$[d]	DBU	benzene	85	9	5

[a] All reactions were carried out in the absence of light for 18 h with a 0.2 M solution of **1** in the indicated solvent using 6 mol % catalyst, 10 mol % CuI, 6.0 equiv of base, 40 mol % water, and 0.5 equiv of trimethylsilylethynylene (all relative to 1 equiv of **1**). [b] GC yields based on **1**. [c] 10 mol % PPh_3 added. [d] 6 mol % $P(t\text{-}Bu)_3$ added.

As outlined in Scheme 1 and detailed in Table 1 (entries 1−6), symmetrical bisarylethynylene **8** is produced in excellent yield in a variety of solvents when 6.0 equiv of DBU and 40 mol % water are used (along with 6 mol % $PdCl_2(PPh_3)_2$ and 10 mol % CuI). In addition to varying the solvent, extensive studies were conducted to optimize these reaction conditions for the formation of **8** by varying the amount of added water, base, Pd^0 catalyst, and the steric bulk of the silane protecting group. Modulating the quantity of added water between 0 and 100 mol % (relative to 1 equiv of **7**) showed a plateau effect at 40 mol %; thus, we chose that amount for our protocol (see the Supporting Information). The significance of DBU was demonstrated when triethylamine (TEA) and DABCO were employed as the base in benzene containing 40 mol % water: bisarylethynylene **8** was not be detected by GC analysis, and only standard Sonogashira product **9** was obtained (Table 1, entries 7 and 8). Use of amidines 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,3,4,6,7,8-hexahydro-2*H*-pyrimido(1,2-*a*)pyrimidine (GUAN) in benzene containing 40 mol % water provided **8** in yields ranging from 84% (DBN; Table 1, entry 9) to 62% (GUAN; Table 1, entry 10). Interestingly, the terminal ethynylene analogue of **9** was observed in trace amounts when DBN was used in conjunction with no added water (see the Supporting Information).[13] Optimized results were obtained with DBU, benzene, and 40 mol % water (Table 1, entry 1). Various palladium catalysts [$PdCl_2(PPh_3)_2$, $Pd_2(dba)_3/PPh_3$, $Pd(PPh_3)_4$, $PdCl_2dppf$ and $PdCl_2(PhCN)_3/P(t\text{-}Bu)_3$] were examined using these optimal reaction conditions. Yields ranged from 90 to 99% (Table 1, entries 1, 11−14) in all cases but $PdCl_2(PhCN)_3/P(t\text{-}Bu)_3$. A survey of different protecting alkylsilanes was also performed under optimized reaction conditions, with data conforming to known reactivities as they relate to steric bulk. Whereas excellent yields were possible using DBU, benzene, and 30 mol % water when trimethylsilylethynylene was used, triethylsilylethynylene and *tert*-butyldimethylsilylethynylene gave only a trace or none of product **8**, respectively.

Based on these results and previous reports from the literature,[9] we conjectured that the operative coupling mechanism in the Sonogashira modification features a protodesilylation to effect in situ silane deprotection. This conclusion is based on three points: (1) Clearly, the in situ silane deprotection step must be amidine base-dependent, but it is also copper(I)-dependent. Reactions executed with no added CuI resulted in complete recovery of starting material, indicating Cu^+ association is a reaction necessity and ruling out nucleophilic activation involving silicon and the amidine

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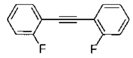
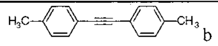
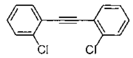
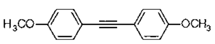
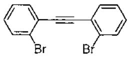
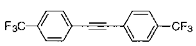
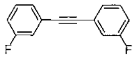
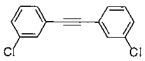
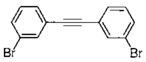
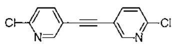
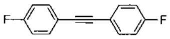
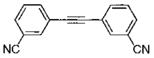
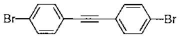
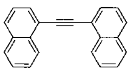
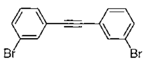
(11) Johannessen, S. C.; Brisbois, R. G.; Fischer, J. P.; Grieco, P. A.; Counterman, A. E.; Clemmer, D. E. *J. Am. Chem. Soc.* **2001**, *123*, 3818.

(12) Use of DBU in Sonogashira-type couplings has been previously reported: Bodwell, G. J.; Miller, D. O.; Vermeij, R. J. *Org. Lett.* **2001**, *3*, 2093.

base (see the Supporting Information). (2) Silicate pathways for silane deprotection (both with and without added Cu^+)[9a,d,e,14] are invalidated by the almost quantitative bisarylethyne product yields observed when reactions were performed with substoichiometric (40 mol % relative to **7**) amounts of added water (Table 1). In addition, yields are depressed when no water was purposefully added, suggesting the involvement of adventitious moisture.[15] (3) Bisarylethyne yield suppression was observed under "protonless" reaction conditions (mixtures of **7**, **9**, DBU, benzene, $PdCl_2(PPh_3)_2$, CuI, and no added trimethylsilylethynylene or water; see the Supporting Information). Moreover, the addition of catalytic HI[16] to anhydrous reactions such as those listed in Table 1 show good yields of bisarylethyne **8** (see the Supporting Information). Taken together, these three results indicate the amidine base is acting as a proton shuttle. In support of this determination, the literature reinforces the invocation of a DBU salt in the organic reaction mixture,[17] and DBU has been used catalytically in the nucleophilic addition of acyldiazomethanes to aldehydes and imines.[18] Therefore, we speculate that after proceeding through the commonly accepted cross-coupling chemistry, the silane-protected arylethynylene converges with Cu^+ and a water/DBU salt, resulting in protodesilylation to yield the terminal ethynylene. Consequently, the aryl-substituted terminal ethynylene is resubmitted to the cross-coupling cycle, generating the bisarylethynyl product after a second pass.

Table 2. Synthesis of Symmetrical Bisarylethynylenes from Aryl Halides and Aryl Triflates[a]

product	temp.	yield (%)[b]	product	temp.	yield (%)[b]
	60	93[c]		60	93[c]
	60	87[c]		60	71[c]
	60	92[c]		r.t.	93[c]
	r.t.	97[c]		r.t.	91[c]
	r.t	93[c]		r.t.	90[c]
	r.t.	96[c]		r.t.	95[c]
	60	89[c]		80	67[d]
	r.t.	99[c]		80	88[d]
	r.t.	89[c]		80	69[d]
	r.t.	69[c]		60	84[e]
	r.t.	88[c]		60	48[e]

[a] All reactions were carried out in the absence of light for 18 h with a 0.2 M solution of aryl halide/triflate in benzene using 6 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI, 6.0 equiv of DBU, 40 mol % water, and 0.5 equiv of trimethylsilylethynylene (all relative to 1 equiv of aryl halide/triflate). [b] Isolated yield based on average of two runs. [c] From the precursor iodide. [d] From the precursor bromide. [e] From the precursor triflate.

Using the optimized protocol detailed above (Scheme 1; Table 1, entry 1), several symmetrical bisarylethynylenes were prepared (Table 2). Similar procedures yielding such symmetrical products have been reported; however, these employ the in situ elimination of acetone under basic conditions[9b,c] or the use of acetylene gas.[19] Aryl iodides, triflates, and bromides are all reactive and give rise to the symmetrical bisarylethynylenes. Of particular note is the substituent effect observed for both iodides and bromides. Iodides with electron-withdrawing groups (acetyl, methoxycarbonyl, and trifluoromethyl) give excellent yields of their respective bisarylethynes at room temperature. In contrast, iodides with electron-donating groups such as methoxy and methyl require elevated temperatures (60 °C) to proceed in good yield. The same applies to the more sterically hindered *o*-iodohalide substrates; in comparison to reactions run at 60 °C, reduced yields were observed at room temperature. Triflates follow this pattern as well. Aryl iodides 2-chloro-5-iodopyridine, 1-iodonaphthalene, and 2-iodothiophene gave high yields of their respective symmetrical bisarylethynylene analogues at room temperature employing the standard protocol. Additionally, room-temperature iodides are easily scaled up into the 2 g range (see the Supporting Information). In general, aryl bromides required elevated temperatures (80 °C) for complete conversion.[20]

Unsymmetrical bisarylethynylenes were also prepared using a one-pot base toggle protocol (Scheme 2; Table 3). Addition of benzene to a flask containing 6 mol % $PdCl_2$-

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(13) We ascribe this observation to the known comparison of the reaction rates of DBU (faster) and DBN (slower) in elimination reactions. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995.

(14) (a) Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159. (b) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449 and references therein.

(15) Without intentional addition of water, we always isolated **8** as the major product, although rigorously purified solvents and reagents were used as well as careful syringe transfer techniques. For example, we observed 72% yield of **8** (by GC−MS analysis) using a 0.20 M benzene solution of 1 equiv of 1-bromo-3-iodobenzene (**7**), 6.0 equiv of DBU, 0.5 equiv of trimethylsilylethynylene, 6.0 mol % $PdCl_2(PPh_3)_2$, and 10 mol % CuI.

(16) Grieco, P. A.; Markworth, C. J. *Tetrahedron Lett.* **1999**, *40*, 665.

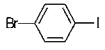
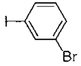
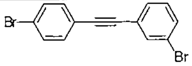
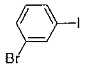
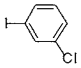
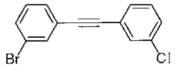
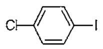
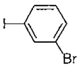
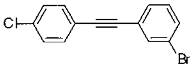
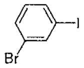
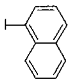
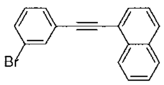
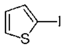
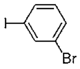
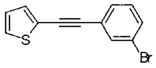
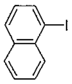
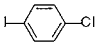
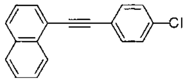
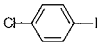
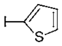
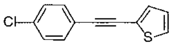
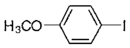
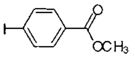
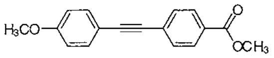
(17) Values of pK_a in water for triethylamine (the most common base used for Sonogashira couplings) have been measured at 10.8. In organic solvents, this value is known to decrease (in DMSO, $pK_a = 9.00$). Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. With DBU, on the other hand, the exact opposite is observed. In water, the pK_a of DBU has been measured at 11.0. In DMSO, this value rises to 12.0, but a recent investigation of this amidine in acetonitrile has produced a pK_a of 24. Kalijurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202.

(18) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285.

(19) Li, C.-J.; Chen, D.-L.; Costello, C. W. *Org. Process Res. Dev.* **1997**, *1*, 325.

(20) 4-Bromobenzonitrile gave only a trace (<1%) of the bisarylethyne product, and complete recovery of starting material was observed for 4-bromo-*N*,*N*-dimethylaniline and 4-bromobiphenyl. Other unsuccessful attempts suggest that a detrimental single-electron-transfer pathway may take precedence over cross-coupling in certain substrates. Two iodides we investigated (1-iodo-4-nitrobenzene and 1-iodo-3,5-dinitrobenzene) and two bromides (4-bromobenzophenone and 5-bromopyrimidine) gave no discernible products when subjected to our reaction conditions.

Table 3. Synthesis of Unsymmetrical Bisarylethynylenes from Aryl Iodides[a]

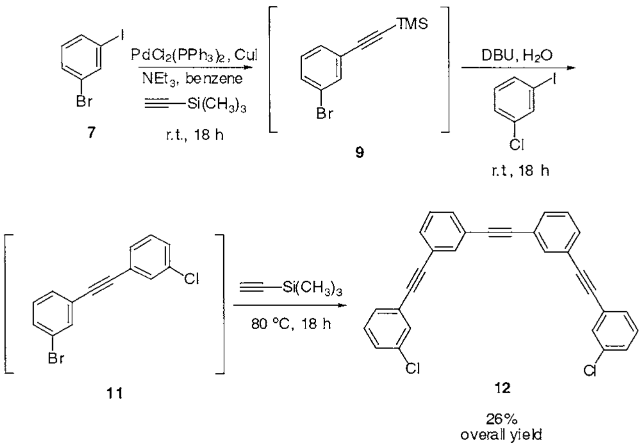
first aryl iodide	second aryl iodide	product	yield (%)[b]
			61
			79
			90
			81
			62
			64
			62
			71

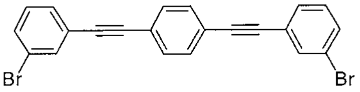
[a] All reactions were carried out in the absence of light at room temperature with a 0.2 M solution of the first aryl iodide (1 equiv) in benzene using 6 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI, 6.0 equiv of NEt_3, and 1.05 equiv of trimethylsilylethynylene. After 18 h, 1.0 equiv of the second aryl iodide, 12.0 equiv of DBU, and 40 mol % water were added (all relative to 1 equiv of first aryl iodide). Reactions were then allowed to stir an additional 18 h before workup. [b] Isolated yield based on an average of two runs.

$(PPh_3)_2$, 10 mol % CuI, and a first aryl iodide **3** followed by addition of 6.0 equiv of Et_3N and trimethylsilylethynylene provided standard Sonogashira product **4** in situ, after vigorous stirring in the dark for 18 h. Sequential addition of 1.0 equiv of a second aryl iodide (**5**), 12.0 equiv of DBU, and 40 mol % water (relative to 1 equiv **3**) gave rise to unsymmetrical bisarylethynylene **6** after 18 h at room temperature (61−90% isolated yield; Table 3).

In addition, this one-pot base toggle procedure was used to generate the symmetrical triarylethynylene **10**, prepared in 63% isolated yield from 1,4-diiodobenzene (first aryl iodide) and **7** (second aryl iodide). Similarly, tetraarylethynylene compound **12** was prepared in one pot by using a combination base *and* temperature toggle procedure as illustrated in Scheme 3 in fair yield. Such convergency is an excellent harbinger of applications where the solid-phase generation of discrete oligomers is inconvenient or expensive.[21]

Scheme 3





10

In conclusion, we have demonstrated an innovative modification for the Sonogashira coupling reaction to generate symmetrical and unsymmetrical bisarylethynes in one pot. Combination of the amidine DBU as base and a substoichiometric amount of water is critical to the featured reactivity. Our continuing efforts are aimed at determining the utility of our methodology in the efficient construction of diverse oligo- and polymeric structures, encouraging implications for which derive from convergent syntheses of **10** and **12**. We shall report on such work in due course.

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Supporting Information Available: General experimental details, general synthetic procedures, detailed results of the optimization (water, solvent, base, catalyst, ethynylsilane) study, and physical characterization data of all symmetrical and unsymmetrical bisarylethynes. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Huang, S.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4908.