DOI: 10.1002/ejoc.201101770

Practical Synthesis of Unsymmetrical Diarylacetylenes from Propiolic Acid and Two Different Aryl Bromides

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Keywords: Synthesis design / Palladium / Alkynes / Decarboxylative coupling

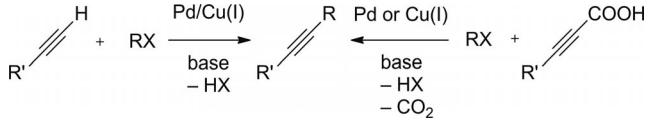
A palladium catalyst that mediates the one-pot sequential Sonogashira and decarboxylative coupling of propiolic acid with two different aryl bromides has been developed. Selective coupling of the first aryl bromide was achieved in the presence of a copper-free, monometallic catalyst generated in situ from allylpalladium chloride dimer and SPhos with tetra-*n*-butylammonium fluoride as the base in an *N*-methyl-2-pyrrolidone/water solvent mixture. Upon addition of another aryl bromide and raising the temperature from 50 to 80 °C, the intermediate arylpropiolic acid underwent decarboxylative coupling to give the corresponding diarylacetylene. Thus, the new system permits a one-pot three-component synthesis of unsymmetrical diarylacetylenes from widely available aryl bromides, rather than expensive aryl iodides, and propiolic acid, rather than (trimethylsilyl)acetylene, as an inexpensive and easy-to-handle acetylene synthon. The process is highly selective, modular, and gives access to a wide range of unsymmetrical diarylacetylenes in good yields.

Introduction

The Cassar–Sonogashira coupling of aryl or alkynyl halides with terminal alkynes is the most effective and widely used method for the formation of C(sp)–C(sp^2) bonds.[1] It has found application in the synthesis of functional materials,[2] pharmaceuticals, and natural products.[3] Traditionally, bimetallic Cu/Pd catalysts are used. The function of the copper cocatalyst is to promote C(sp)–H bond cleavage so that mild amine bases suffice for the generation of alkynyl–metal species. The palladium catalyst promotes the actual cross-coupling by oxidative addition of the aryl halide, transmetallation with the alkynyl–copper species, and reductive elimination of the product.

Four decades after its discovery, the efficiency of Sonogashira catalysts has reached an impressive level. A variety of reaction variants have been developed, which include palladium-free,[4] amine-free,[5] and solvent-free[6] conditions and reactions in aqueous media.[7] A particular focus was set on the development of efficient, reusable Pd catalysts[8] and copper-free reaction protocols[9] as copper promotes unwanted Glaser coupling, and the difficult separation of the two metals complicates the recycling of the palladium catalyst. In copper-free protocols, palladium has the dual role to acidify the acetylenic proton and perform the cross-coupling.

In Sonogashira couplings (Scheme 1), the use of expensive aryl iodides as aryl electrophiles is still the rule rather than the exception, but an increasing number of catalysts allow the use of aryl bromides, triflates, and even chlorides. Examples for such state-of-the-art systems have been described by Herrmann, Plenio, Fu, Buchwald, and Hua, which all feature combinations of palladium precursors with bulky, electron-rich phosphanes.[10]



Scheme 1. Standard vs. decarboxylative Sonogashira couplings.

Sonogashira reactions can also be used for the synthesis of diarylacetylenes from aryl halides and arylacetylenes. However, due to the limited availability of the latter, a more effective synthetic entry consists of the sequential coupling of a first aryl halide with an acetylene synthon and subsequent coupling of the resulting arylacetylene with a second aryl halide. The sequential arylation of acetylene itself is problematic as the intermediate arylacetylenes tend to react faster than the starting acetylene so that product mixtures are obtained, see Scheme 2, (a).[11] The established synthesis of unsymmetrical diarylalkynes thus involves the use of trimethylsilyl (TMS)-acetylene as the acetylene synthon, see Scheme 2, (b). This arylation/deprotection/arylation sequence can be performed in one pot.[12] In the first step,

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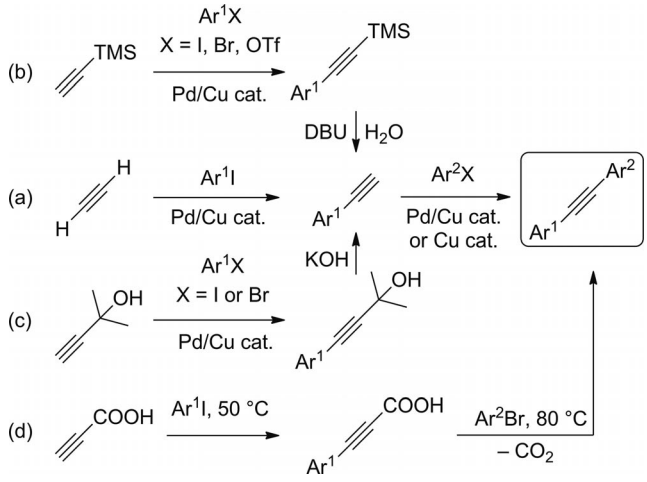
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101770.

TMS-acetylate is coupled with an aryl halide under anhydrous conditions. Subsequent addition of water leads to the cleavage of the TMS group, which permits further coupling with a second aryl halide. In a related strategy, inexpensive 2-methylbut-3-yn-ol is used as the acetylene synthon [Scheme 2, (c)], but in this case the deprotection step requires harsh conditions and fresh catalyst has to be added for the second coupling step.[13]



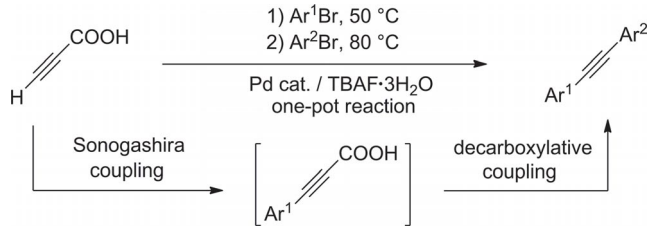
Scheme 2. Concepts for the synthesis of unsymmetrical diarylacetylenes by Sonogashira coupling.

The concept of decarboxylative cross-coupling has recently opened opportunities for a less costly alternative to these established processes.[14] In redox-neutral decarboxylative cross-coupling, nucleophilic organometallic species are generated by the extrusion of CO_2 from carboxylate salts. This strategy was originally described in the context of biaryl synthesis[15] and has subsequently been extended to the formation of carbon–heteroatom bonds,[16] ketone[17] and imine[18] syntheses, (conjugate) addition reactions,[19] and recently Sonogashira couplings.[20] Propiolic acids extrude CO_2 at low temperatures,[21] which has recently been shown to be reversible.[22] In contrast to most other decarboxylative couplings, decarboxylative Sonogashira reactions can thus be performed at remarkably low temperatures. Lee and coworkers have demonstrated that various propiolic acids can be coupled with aryl bromides and iodides at 80 °C using a monometallic palladium catalyst.[23] An alternative procedure for decarboxylative coupling of arylpropiolic acids with aryl bromides, iodides, and triflates using silver and lithium salts as additives has been reported by Kim and Lee.[24] An optimized protocol for decarboxylative coupling of alkynyl carboxylic acids with aryl and benzyl halides with low catalyst loading[25] and a Pd-free decarboxylative cross-coupling catalyzed by copper[26] have also been reported.

Lee and coworkers have utilized decarboxylative Sonogashira coupling for the one-pot synthesis of unsymmetrical diarylacetylenes.[27] When heating a mixture of an aryl iodide, an aryl bromide, and propiolic acid to 50 °C in the presence of a palladium catalyst, the aryl iodide exclusively reacts with the propiolic acid under C–H functionalization. Upon raising the temperature to 80 °C, the resulting arylpropiolic acid underwent decarboxylative coupling with the aryl bromide to yield the corresponding diarylacetylene, see Scheme 2, (d).

Although this process demonstrates that inexpensive propiolic acid can serve as an acetylene synthon in diarylacetylene synthesis, its practicability is limited by the fact that only aryl iodides can be employed in the first coupling step. In order to realize the full potential of this coupling strategy, an extension to the widely available substrate class of aryl bromides is highly desirable.

Herein we present an efficient method for the synthesis of unsymmetrical diarylacetylenes from two different aryl bromides and propiolic acid (Scheme 3).



Scheme 3. One-pot synthesis of diarylacetylenes from aryl bromides and propiolic acid.

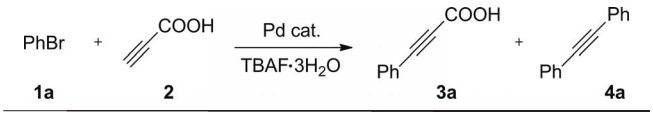
Results and Discussion

In order to establish a sequential one-pot Sonogashira and decarboxylative coupling of propiolic acid starting from aryl bromides, we first needed to identify a catalyst system that would allow the coupling of propiolic acid with an aryl bromide at temperatures sufficiently low to prevent competitive protodecarboxylation and decarboxylative coupling.

As a model for this first coupling step, we chose the Sonogashira reaction of propiolic acid (**2**) and bromobenzene (**1a**) to give phenylpropiolic acid (**3a**, Table 1). The formation of tolane (**4a**) was indicative of unwanted decarboxylative coupling.

As the starting point for catalyst development, the standard conditions reported for the Sonogashira coupling of aryl iodides [5 mol-% of tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) and a triarylphosphane as the catalyst, tetra-*n*-butylammonium fluoride (TBAF) as the base in *N*-methyl-2-pyrrolidone (NMP)] were employed (Table 1).[20] However, no conversion was seen at room temperature for our aryl bromide substrate and only unsatisfactory yields were reached at 60 °C (Entries 1–4). At higher temperatures, rapid protodecarboxylation of **2** and **3a** took place, which precluded selective product formation. In the literature, only one report of the successful coupling of an aryl bromide with **2** was found: Buchwald disclosed that a highly engineered, water-soluble dialkyl-biaryl-phosphane ligand permits the synthesis of 3-methoxyphenylpropiolic acid from the corresponding aryl bromide under special, aqueous conditions.[28] We thus tested various related elec-

Table 1. Synthesis of **3a** from **2** and **1a**.[a]



1a **2** **3a** **4a**

Entry	Ligand [mol-%]	"Pd" [mol-%]	*T* [°C]	Time [h]	Yield [%] **3a**	**4a**
1	PPh_3 (20)	Pd_2dba_3 (10)	60	4	17	0
2	P(*o*Tol)$_3$ (20)	Pd_2dba_3 (10)	60	4	38	0
3	P(*p*Tol)$_3$ (20)	Pd_2dba_3 (10)	60	4	14	0
4	dppf (10)	Pd_2dba_3 (10)	60	4	26	0
5	**L1** (15)	Pd_2dba_3 (10)	60	4	43	4
6	**L2** (15)	Pd_2dba_3 (10)	60	4	49	6
7	**L3** (15)	Pd_2dba_3 (10)	60	4	54	6
8	**L4** (15)	Pd_2dba_3 (10)	60	4	45	23
9	**L3** (7.5)	Pd_2dba_3 (5)	60	4	51	4
10	**L3** (7.5)	Pd_2dba_3 (5)	50	4	42	0
11	**L3** (7.5)	Pd_2dba_3 (5)	50	10	59	2
12	**L3** (7.5)	Pd_2dba_3 (5)	50	16	71	7
13	**L3** (7.5)	Pd_2dba_3 (5)	40	16	61	5
14	**L3** (7.5)	$Pd(OAc)_2$ (5)	50	16	40	4
15	**L3** (7.5)	$[allylPdCl]_2$ (5)	50	16	79	6
16	**L3** (7.5)	$PdCl_2$ (5)	50	16	47	14

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.55 mmol), TBAF·3H_2O (3.00 mmol), NMP (2.5 mL). Yields were determined by GC using *n*-tetradecane as an internal standard after converting **3a** into the methyl ester with MeOTf/K_2CO_3.

tron-rich, sterically demanding dialkyl-biaryl-phosphanes (Figure 1). With these ligands, the activity of the catalyst was substantially improved (Entries 5–8). The highest yield of **3a** was obtained with **L3** (SPhos). **L4** (XPhos) led to a higher conversion of **1a**, but a lower selectivity for **3a** over **4a**.

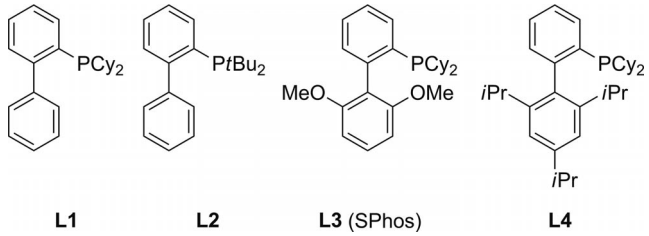


Figure 1. Dialkyl biaryl phosphanes used in this study.

A reduction of the catalyst amount to 2.5 mol-% $Pd_2(dba)_3$ and 7.5 mol-% **L3** did not significantly affect the yield (Entry 9). The selectivity for **3a** over **4a** was improved when the temperature was reduced to 50 °C (Entry 10). At this temperature, complete conversion of the substrate was achieved within 16 h, and **3a** was obtained in 71% yield (Entries 11 and 12). Lower temperatures further slowed the reaction without improving the selectivity (Entry 13). A change of the palladium source to allyl palladium chloride dimer was beneficial, whereas other precursors had a detrimental effect on yield or selectivity (Entries 14–16).

After this first round of optimization, 79% of the product along with 6% of **4a** were obtained using a catalyst generated from allyl palladium chloride dimer (2.5 mol-%) and **L3** (7.5 mol-%) with TBAF as the base in NMP at 50 °C in 16 h (Entry 15).

The reaction conditions were further optimized to improve the yield and selectivity of the reaction (Table 2). The yields dropped in solvents other than NMP (Entries 1–3) and when other bases were used (Entries 4–5), even though these solvents and bases are successfully employed in the Sonogashira coupling of aryl iodides. Other sources of fluoride were also ineffective (Entry 6). A definite improvement was achieved by the addition of water as a cosolvent (Entries 7–9). In a mixture of 9:1 NMP/water, **3a** was obtained in 92% yield along with only 5% of **4a** (Entry 8). Further experiments showed that other proton sources such as methanol were less effective cosolvents than water (Entry 10).

Table 2. Effect of different bases, additives, and cosolvents on the synthesis of **3a**.[a]

Entry	Base [equiv.]	Solvent	Cosolvent [%]	Conv. **1** [%]	Yield [%] **3a**	**4a**
1	TBAF (6)	NMP	–	100	79	6
2	TBAF (6)	THF[b]	–	35	11	1
3	TBAF (6)	DMSO[c]	–	45	0	0
4	Cs_2CO_3 (6)	NMP	–	56	traces	0
5	NEt_3 (6)	NMP	–	74	traces	0
6	CsF (6)	NMP	–	32	4	8
7	TBAF (6)	NMP	H_2O (5)	100	84	3
8	TBAF (6)	NMP	H_2O (10)	99	92	5
9	TBAF (6)	NMP	H2O (15)	92	58	5
10	TBAF (6)	NMP	MeOH (10)	88	62	12

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.55 mmol), TBAF·3H_2O (3.0 mmol), $[allylPdCl]_2$ (2.5 mol-%), **L3** (7.5 mol-%), solvent (2.5 mL), 16 h, 50 °C. Conversions and yields were determined by GC using *n*-tetradecane as an internal standard after converting **3a** into the methyl ester with MeOTf/K_2CO_3. [b] THF = tetrahydrofuran. [c] DMSO = dimethyl sulfoxide.

We next investigated whether this optimized system, which contained $[allylPdCl]_2$/**L3** as the catalyst, TBAF as the base, and a 9:1 mixture of NMP/H_2O, would also promote the second step of our proposed diarylacetylene synthesis: the decarboxylative cross-coupling of arylpropiolic acids. We were delighted to find that the reaction of **3a** and 4-bromotoluene (**1b**) to the desired unsymmetrical diarylacetylene **6a** took place at 70 °C. The yield could be increased to 84% by raising the temperature to 80 °C and extending the reaction time to 14 h (Table 3). Longer reaction times and higher temperatures did not improve the yield any further.

The final step was to combine the two reactions optimized separately into a one-pot protocol (Table 4). Thus, we stirred **1a** with **2** at 50 °C for 16 h in NMP/water (9:1) in the presence of $[allylPdCl]_2$/**L3** and TBAF, then added **1b**, raised the temperature to 80 °C, and continued to stir for 14 h. Under these conditions, the unsymmetrical diarylacetylene **5a** was obtained in high yield (77%) along with only small amounts of the undesired symmetrical products **4a** and **6a**. Control experiments confirmed that such high conversions and selectivities were only be achieved when using $[allylPdCl]_2$ as the catalyst precursor (Entries 1–4), **L3** as the ligand (Entries 1 and 5), and NMP/water (9:1) as the solvent (Entries 1 and 6–8). Under these conditions, the

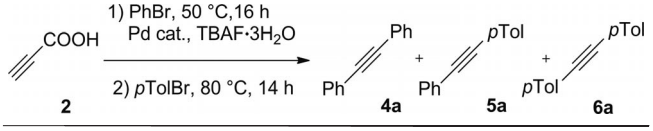
Table 3. Palladium-catalyzed decarboxylative coupling reaction of **3a** and **1b**.[a]

Entry	*T* [°C]	Time [h]	Conversion **1b** [%]	Yield **5a** [%]
1	70	10	69	45
2	80	10	82	71
3	90	10	91	55
4	80	14	92	84

[a] Reaction conditions: **3a** (0.50 mmol), **1b** (0.50 mmol), TBAF·3H_2O (3.00 mmol), NMP/H_2O (2.5 mL, 9:1), [allylPdCl]$_2$ (2.5 mol-%), **L3** (7.5 mol-%). Conversions and yields were determined by GC using *n*-tetradecane as the internal standard.

formation of butadiynes, which is a common side reaction in conventional Sonogashira coupling reactions, was not observed. The reason for the positive influence of water on the reaction outcome could not be unambiguously clarified.

Table 4. One-pot synthesis of **5a**.[a]



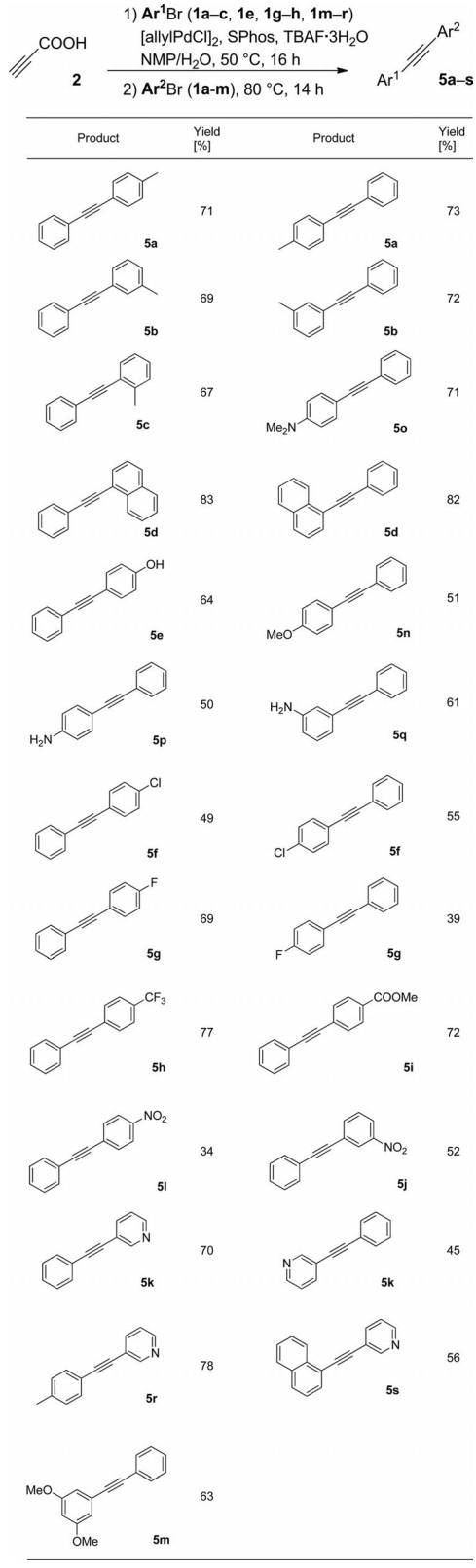
Entry	Ligand	"Pd"	H_2O [%]	Conv. [%] **1a**	Conv. [%] **1b**	Yield [%] **5a**	Yield [%] **4a**	Yield [%] **6a**
1	**L3**	[allylPdCl]$_2$	10	100	98	77	7	5
2	**L3**	[allylPdCl]$_2$	0	91	90	48	7	3
3	**L3**	[allylPdCl]$_2$	5	97	84	61	36	18
4	**L4**	[allylPdCl]$_2$	10	100	92	39	26	19
5	**L3**	$PdCl_2$	10	99	95	37	13	1
6	**L3**	$Pd(OAc)_2$	10	100	88	59	14	0
7	**L3**	$Pd_2(dba)_3$	10	99	94	39	26	14

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.55 mmol), Pd source (5 mol-%), ligand (7.5 mol-%), TBAF·3H_2O (3.0 mmol), NMP/H_2O (2.5 mL), **1b** (0.50 mmol). Conversions and yields were determined by GC using *n*-tetradecane as the internal standard.

Having thus found an effective protocol for the synthesis of unsymmetrical diarylacetylenes from propiolic acid and two different aryl bromides, we next explored its scope. As can be seen from Table 5, the one-pot process is broadly applicable with regard to both aryl bromide coupling partners. Various aryl bromides were successfully employed as substrates for the first arylation step, which include electron-rich, electron-poor, sterically crowded, and heterocyclic derivatives. The best yields were obtained with bromobenzene itself (**5a**–**k**) and with arenes that bear electron-rich substituents (**5a**, **5b**, **5m**, **5o**, **5r**). Substrates that bear electron-withdrawing groups (**5f**, **5g**, **5l**, **5k**) gave slightly lower yields.

Variation of the aryl bromide in the second arylation step revealed that this step also has a broad substrate scope. Interestingly, this decarboxylative coupling seems to be

Table 5. Synthesis of unsymmetrical diaryl alkynes.[a]



[a] Aryl groups Ar^1 that originate from the first arylation are depicted on the left. Reaction conditions: Ar^1Br (0.50 mmol), **2** (0.55 mmol), [allylPdCl]$_2$ (2.5 mol-%), **L3** (7.5 mol-%), TBAF·3H_2O (3.00 mmol), NMP (2.5 mL), 50 °C, 16 h, then addition of Ar^2Br (0.50 mmol), 80 °C, 14 h. Yields refer to isolated products.

more effective with electron-poor than with electron-rich aryl bromides. For the synthesis of unsymmetrical diarylacetylenes with one electron-rich and one electron-poor arene ring, it is thus advisable to introduce the electron-rich arene in the Sonogashira coupling step and the electron-poor one in the decarboxylative coupling step. Performing the coupling steps in reverse usually led to decreased yields. A few substrates, among them aryl bromides that bear nitro or cyano groups, did not give satisfactory yields in the non-decarboxylative coupling with propiolic acid. As a further limitation to our protocol, we found that when using very similar bromoarenes in both steps, e.g. 2-bromotoluene in the first step and bromobenzene in the second, the separation of the desired product from the symmetrical alkynes, which were obtained in small quantities as side products, was problematic.

However, as can be seen from the examples in Table 5, diarylacetylenes that bear various functional groups were tolerated, which include ester, ether, hydroxy, trifluoromethyl, chloro, nitro, and even basic amino groups. Although a lower Pd-loading was employed, the scope and yields are comparable to related methods starting from expensive aryl iodides.[27]

Conclusions

A copper-free, monometallic catalyst generated in situ from allylpalladium chloride dimer and **L3** allows the synthesis of unsymmetrical diarylacetylenes from propiolic acids and two different aryl bromides in the presence of TBAF as the base in an NMP/water solvent mixture. The first step of this one-pot reaction sequence consists of a Sonogashira coupling of the first aryl bromide with propiolic acid to selectively give an arylpropiolic acid. Upon addition of another aryl bromide and raising the temperature from 50 to 80 °C, the corresponding diarylacetylene is formed by decarboxylative coupling. The mild reaction conditions are compatible with various functional groups so that a wide range of diversely substituted diarylacetylenes are conveniently accessible in good yields.

Experimental Section

General Methods: Chemicals and solvents were either purchased from commercial suppliers (puriss. p.A.) or purified by standard techniques. All reactions, if not stated otherwise, were performed in oven-dried glassware under an argon atmosphere with a teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3–30–300/3, 2 min at 50 °C, heating rate 25 °C/min, 3 min at 250 °C). Column chromatography was performed with 230–400 mesh silica gel. NMR spectra were obtained with a Bruker AC 200 spectrometer (200 MHz) using $CDCl_3$ as solvent. Mass spectra were acquired with a Trace GC–MS 2000 ThermoQuest instrument. Melting points were measured with a Büchi 535 apparatus, and IR spectra with a Perkin–Elmer FTIR Spectrum ONE (HeNe 633 nm < 0.4 mW).

General Procedure for the Preparation of Diarylacetylenes 5a–s: A 20 mL Schlenk tube equipped with a magnetic stirrer bar and a rubber septum was charged with allylpalladium(II) chloride dimer (0.025 mmol) and 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl (0.0375 mmol). Aryl bromide **1a**–**c**, **1e**, **1g**, **1h**, or **1m**–**r** (0.50 mmol), **2** (36 μL, 0.55 mmol), and a degassed solution of TBAF·$3H_2O$ (0.95 g, 3 mmol) in NMP/H_2O (9:1, 2.5 mL) were added by syringe. The reaction mixture was stirred at 50 °C for 16 h before aryl bromide **1a**–**m** (0.50 mmol) was added by syringe (solid aryl bromides were added as solution in degassed NMP). The resulting mixture was stirred at 80 °C for 14 h, cooled to room temperature, and diluted with diethyl ether (20 mL). The resulting solution was washed successively with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered, and the solvents were removed in vacuo. The crude product was purified by column chromatography (SiO_2, diethyl ether/cyclohexane gradient) to afford **5a**–**s**.

1-Methyl-4-(2-phenylethynyl)benzene (5a): Compound **5a** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 4-bromotoluene (62 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5a** was isolated as a white solid (68.3 mg, 71%); m.p. 68–70 °C. The NMR spectroscopic data matched those reported in the literature for 1-methyl-4-(2-phenylethynyl)benzene [CAS number 3287-02-3].

Compound **5a** was also prepared according to the general procedure from 4-bromotoluene (62 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5a** was isolated as a white solid (70.2 mg, 73%); m.p. 68–70 °C.

1-Methyl-3-(2-phenylethynyl)benzene (5b): Compound **5b** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 3-bromotoluene (61 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5b** was isolated as a white solid (66.3 mg, 69%); m.p. 28–30 °C. The NMR spectroscopic data matched those reported in the literature for 1-methyl-3-(2-phenylethynyl)benzene [CAS number 14635-91-7].

Compound **5b** was also prepared according to the general procedure from 3-bromotoluene (61 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5b** was isolated as a white solid (69.2 mg, 72%); m.p. 28–30 °C.

1-Methyl-2-(2-phenylethynyl)benzene (5c): Compound **5c** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 2-bromotoluene (60 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5c** was isolated as a colorless oil (64.4 mg, 67%). The NMR spectroscopic data matched those reported in the literature for 1-methyl-2-(2-phenylethynyl)benzene [CAS number 14309-60-5].

1-(2-Phenylethynyl)naphthalene (5d): Compound **5d** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromonaphthalene (70 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5d** was isolated as a colorless oil (94.7 mg, 83%). The NMR spectroscopic data matched those reported in the literature for 1-(2-phenylethynyl)naphthalene [CAS number 4044-57-9].

Compound **5d** was also prepared according to the general procedure from 1-bromonaphthalene (70 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5d** was isolated as a colorless oil (93.6 mg, 82%).

4-(2-Phenylethynyl)phenol (5e): Compound **5e** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 4-bromophenol (86.5 mg, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 2:8), **5e** was isolated as a pale yellow solid (62.1 mg, 64%); m.p. 121–123 °C. The NMR spectroscopic data matched those reported in the literature for 4-(2-phenylethynyl)phenol [CAS number 1849-26-9].

1-Chloro-4-(2-phenylethynyl)benzene (5f): Compound **5f** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromo-4-chlorobenzene (95.7 mg, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5f** was isolated as a white solid (52.2 mg, 49%); m.p. 80–82 °C. The NMR spectroscopic data matched those reported in the literature for 1-chloro-4-(2-phenylethynyl)benzene [CAS number 5172-02-1].

Compound **5f** was also prepared according to the general procedure from 1-bromo-4-chlorobenzene (95.7 mg, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5f** was isolated as a white solid (58.6 mg, 55%); m.p. 80–82 °C.

1-Fluoro-4-(2-phenylethynyl)benzene (5g): Compound **5g** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromo-4-fluorobenzene (55 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5g** was isolated as a white solid (67.7 mg, 69%); m.p. 108–110 °C. The NMR spectroscopic data matched those reported in the literature for 1-fluoro-4-(2-phenylethynyl)-benzene [CAS number 405-29-8].

Compound **5g** was also prepared according to the general procedure from 1-bromo-4-fluorobenzene (55 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5g** was isolated as a white solid (38.3 mg, 39%); m.p. 108–110 °C.

1-(2-Phenylethynyl)-4-(trifluoromethyl)benzene (5h): Compound **5h** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromo-4-(trifluoromethyl)benzene (70 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, cyclohexane), **5h** was isolated as a white solid (94.7 mg, 77%); m.p. 101–103 °C. The NMR spectroscopic data matched those reported in the literature for 1-(2-phenylethynyl)-4-(trifluoromethyl)benzene [CAS number 370-99-0].

Methyl 4-(2-Phenylethynyl)benzoate (5i): Compound **5i** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and methyl 4-bromobenzoate (107.5 mg, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 2:8), **5i** was isolated as a pale yellow solid (85.1 mg, 72%); m.p. 117–119 °C. The NMR spectroscopic data matched those reported in the literature for methyl 4-(2-phenylethynyl)benzoate [CAS number 42497-80-3].

1-Nitro-4-(2-phenylethynyl)benzene (5l): Compound **5l** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromo-4-nitrobenzene (101 mg, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 2:8), **5l** was isolated as a pale yellow solid (37.9 mg, 34%); m.p. 119–121 °C. The NMR spectroscopic data matched those reported in the literature for 1-nitro-4-(2-phenylethynyl)benzene [CAS number 1942-30-9].

1-Nitro-3-(2-phenylethynyl)benzene (5j): Compound **5j** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 1-bromo-3-nitrobenzene (101 mg, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 1:9), **5j** was isolated as a pale yellow solid (58.0 mg, 52%); m.p. 66–68 °C. The NMR spectroscopic data matched those reported in the literature for 1-nitro-3-(2-phenylethynyl)benzene [CAS number 29338-47-4].

3-(2-Phenylethynyl)pyridine (5k): Compound **5k** was synthesized according to the general procedure from bromobenzene (53 μL, 0.50 mmol) and 3-bromopyridine (48 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 3:7), **5k** was isolated as a pale yellow solid (62.7 mg, 70%); m.p. 49–51 °C. The NMR spectroscopic data matched those reported in the literature for 3-(2-phenylethynyl)pyridine [CAS number 1328-38-5].

Compound **5k** was also prepared according to the general procedure from 3-bromopyridine (48 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 3:7), **5k** was isolated as a pale yellow solid (40.3 mg, 45%); m.p. 49–51 °C.

1,3-Dimethoxy-5-(2-phenylethynyl)benzene (5m): Compound **5m** was synthesized according to the general procedure from 1-bromo-3,5-dimethoxybenzene (108.5 mg, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 1:9), **5m** was isolated as a pale yellow oil (75.1 mg, 63%). The NMR spectroscopic data matched those reported in the literature for 1,3-dimethoxy-5-(2-phenylethynyl)benzene.

1-Methoxy-4-(2-phenylethynyl)benzene (5n): Compound **5n** was synthesized according to the general procedure from 4-bromoanisole (63 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 1:9), **5n** was isolated as a pale yellow solid (53.1 mg, 51%); m.p. 53–55 °C. The NMR spectroscopic data matched those reported in the literature for 1-methoxy-4-(2-phenylethynyl)benzene [CAS number 7380-78-1].

4-*N*,*N*-Dimethyl-4-(2-phenylethynyl)aniline (5o): Compound **5o** was synthesized according to the general procedure from 4-bromo-*N*,*N*-dimethylaniline (100 mg, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 3:7), **5o** was isolated as a pale yellow solid (78.6 mg, 71%); m.p. 107–109 °C. The NMR spectroscopic data matched those reported in the literature for 4-*N*,*N*-dimethyl-4-(2-phenylethynyl)aniline [CAS number 14301-08-7].

4-(2-Phenylethynyl)aniline (5p): Compound **5p** was synthesized according to the general procedure from 4-bromoaniline (86 mg, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 4:6), **5p** was isolated as a pale yellow solid (48.3 mg, 50%); m.p. 125–127 °C. The NMR spectroscopic data matched those reported in the literature for 4-(2-phenylethynyl)aniline [CAS number 1849-25-8].

3-(2-Phenylethynyl)aniline (5q): Compound **5q** was synthesized according to the general procedure from 3-bromoaniline (54 μL, 0.50 mmol) and bromobenzene (53 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohex-

ane, 3:7), **5q** was isolated as a pale yellow solid (58.2 mg, 61%); m.p. 43–45 °C. The NMR spectroscopic data matched those reported in the literature for 3-(2-phenylethynyl)aniline [CAS number 51624-44-3].

3-[2-(4-Methylphenyl)ethynyl]pyridine (5r): Compound **5r** was synthesized according to the general procedure from 4-bromotoluene (62 μL, 0.50 mmol) and 3-bromopyridine (48 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 3:7), **5r** was isolated as a white solid (75.3 mg, 78%); m.p. 81–83 °C. The NMR spectroscopic data matched those reported in the literature for 3-[2-(4-methylphenyl)ethynyl]pyridine [CAS number 733035-88-6].

3-[2-(Naphthalen-1-yl)ethynyl]pyridine (5s): Compound **5s** was synthesized according to the general procedure from 1-bromonaphthalene (70 μL, 0.50 mmol) and 3-bromopyridine (48 μL, 0.50 mmol). After purification by flash column chromatography (SiO_2, diethyl ether/cyclohexane, 3:7), **5s** was isolated as a pale yellow oil (64.2 mg, 56%). The NMR spectroscopic data matched those reported in the literature for 3-[2-(naphthalen-1-yl)ethynyl]pyridine [CAS number 950824-89-2].

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data for all reported compounds.

Acknowledgments

We gratefully acknowledge Ministero dell'Università e della Ricerca (MIUR) within the national PRIN framework and Nano-Kat for funding and Umicore for the generous donation of precious metals.

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Received: December 8, 2011
Published Online: January 18, 2012

