# Pd-Catalyzed Three-Component Coupling of Terminal Alkynes, Arynes, and Vinyl Cyclopropane Dicarboxylate

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S *Supporting Information*

ABSTRACT: A palladium-catalyzed three-component coupling involving *in situ* generated arynes, terminal alkynes, and vinyl cyclopropane dicarboxylate has been developed. The process demonstrates the first example of aryne chemistry combined with the ring opening of vinyl cyclopropanes. This efficient method using readily available starting materials generates two new carbon−carbon bonds in one pot.
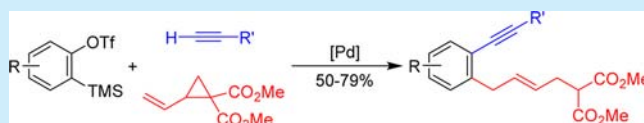
Aryne chemistry has become an important pillar for the facile 1,2-bifunctionalization of arene units in recent years.[1] The aryne precursor 2-trimethylsilylphenyl triflate (**1a**) can be functionalized under mild reaction conditions via cycloaddition reactions or multicomponent reactions.[2] The three-component coupling involves the addition of a nucleophile and an electrophile to the *in situ* formed aryne moiety (Scheme 1).[3] The use of carbon nucleophiles such as

Scheme 1. Three-Component Coupling of Arynes
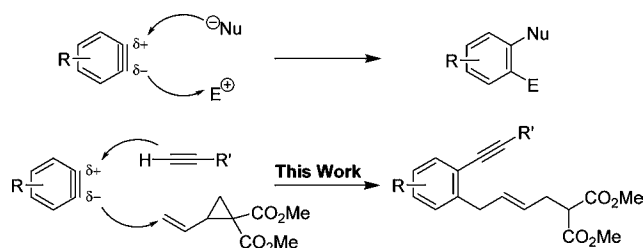
alkenes, alkynes, or allenes and carbon electrophiles such as allyl or vinyl moieties generates two new carbon−carbon bonds in one pot.[4] Also the addition of singly bonded metal−carbon species as C−Si[5] or C−Sn[6] in a nucleophilic manner was reported. If the electrophile and nucleophile are not linked, a very efficient one-pot three-component reaction can occur. Aryne chemistry has also been shown to be compatible with Pd catalysis.[7,8] The palladium could either interact directly with the highly strained C−C triple bond of the aryne resulting in a carbopalladation process[7] or activate the electrophile (e.g., by formation of a Pd-allyl complex).[8] Due to our strong interest in the chemistry of donor−acceptor−cyclopropanes,[9] we envisioned utilizing vinyl cyclopropane dicarboxylate as the electrophile for the general process shown in Scheme 1. Such a three-membered ring is known to be easily activated by transition metal catalysts.[10] This activated complex was planned to be intercepted by the adduct of aryne and acetylide acting as the nucleophile.

At the outset of our studies aryne precursor **1a**, phenylacetylene **2a**, and vinyl cyclopropane **3** were reacted under

Table 1. Optimization of the Reaction Conditions[a]
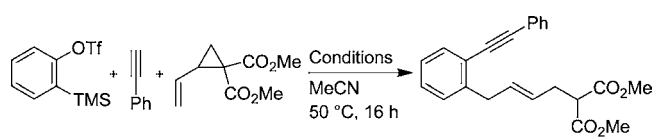
entry	catalyst (10 mol %)	ligand (10 mol %)	fluoride source	yield [%]
1	−	−	CsF	0[b]
2	Pd(PPh₃)₄	−	CsF	27[c]
3	Pd(PPh₃)₄ + CuI	−	CsF	51[c]
4	Pd(OAc)₂	XantPhos	CsF	0
5	Pd(dba)₂	dppp	CsF	42
6	Pd(dba)₂ + CuI	dppp	CsF	59
7	Pd(dba)₂ + CuI	dppe	CsF	52
8	Pd(dba)₂ + CuI	dppf	CsF	25
9	Pd(dba)₂ + CuI	dppp	KF + 18C6	73
10	Pd(dba)₂ + CuI	dppp	KF + 18C6	13[d]
11	Pd(dba)₂ + CuI	dppe	KF + 18C6	65
12	Pd(dba)₂ + CuI	dppp	KF + 18C6	49[e]
13	CuI	dppp	KF + 18C6	0

[a]Conditions: **1a** (204 μmol), **2a** (136 μmol), **3** (177 μmol), CsF or KF with 18C6 (408 μmol), MeCN (4 mL) at 50 °C for 16 h. [b]Reaction temperature 50 and 80 °C. [c]E/Z ratio of 9:1. [d]Reaction was carried out in THF. [e]Reaction was carried out in MeCN/toluene 1:1.

standard conditions commonly employed in aryne chemistry using CsF and acetonitrile at 50 °C (Table 1, entry 1). As expected, even after heating up to 80 °C, the desired coupling product could not be observed (Table 1, entry 1). To activate the vinyl cyclopropane the application of Pd(PPh₃)₄ as the catalyst yielded 27% of product **4aa** with concomitant formation of triphenylene[11] as a major side product (Table 1, entry 2).

The addition of copper iodide to activate the terminal alkyne increased the yield to 51% (Table 1, entry 3). In both cases a mixture of E/Z isomers was observed with the E-isomer as the

major isomer (ratio of 9:1). Fortunately, changing the catalyst to Pd(dba)$_2$/dppp led to further improvement of the yield and complete *E* selectivity of the desired product **4aa** (Table 1, entry 5, dba = dibenzylideneacetone, dppp = 1,3-bis(diphenylphosphanyl)propane). Again adding 10 mol % of CuI afforded the coupling product in 59% yield (Table 1, entry 6). The use of dppe (1,2-bis(diphenylphosphanyl)ethane) or dppf (1,1′-bis(diphenylphosphino)ferrocene) slightly decreased the yield (Table 1, entries 7, 8, and 11). The best result was obtained by performing the reaction with potassium fluoride instead of cesium fluoride in the presence of 18-crown-6 (18C6) affording **4aa** in 73% yield (Table 1, entry 9). In the absence of the palladium complex the hydroalkynylation product was detected as the sole product (Table 1, entry 13).

With the optimized reaction conditions in hand we started to examine the reaction scope (Scheme 2). In total, we subjected 14 different alkyne derivatives to the reaction conditions.

Various electron-donating and electron-withdrawing aryl acetylenes were exposed to the reaction. The electron-donating methoxy group attached to the aryl moiety improved the yield to 79% (**4ab**). Methyl substituents in *meta-* and *para-*positions to the alkyne provided **4ac** and **4ad** in 66% and 62% yields, respectively. Also electron-withdrawing alkynes such as 1-ethynyl-4-nitrobenzene and 4-ethynylbenzonitrile afforded **4ae** and **4af** in 60% and 57% yields. The coupling with 3-ethynyl thiophene, a heterocyclic alkyne, proceeded smoothly in 76% yield (**4ag**). Besides aryl acetylenes, we also employed weakly electron-donating aliphatic groups. 1-Hexyne and the sterically encumbered 3,3-dimethylbut-1-yne reacted to afford **4ah** and **4ai** in 64% and 65% yield, respectively.
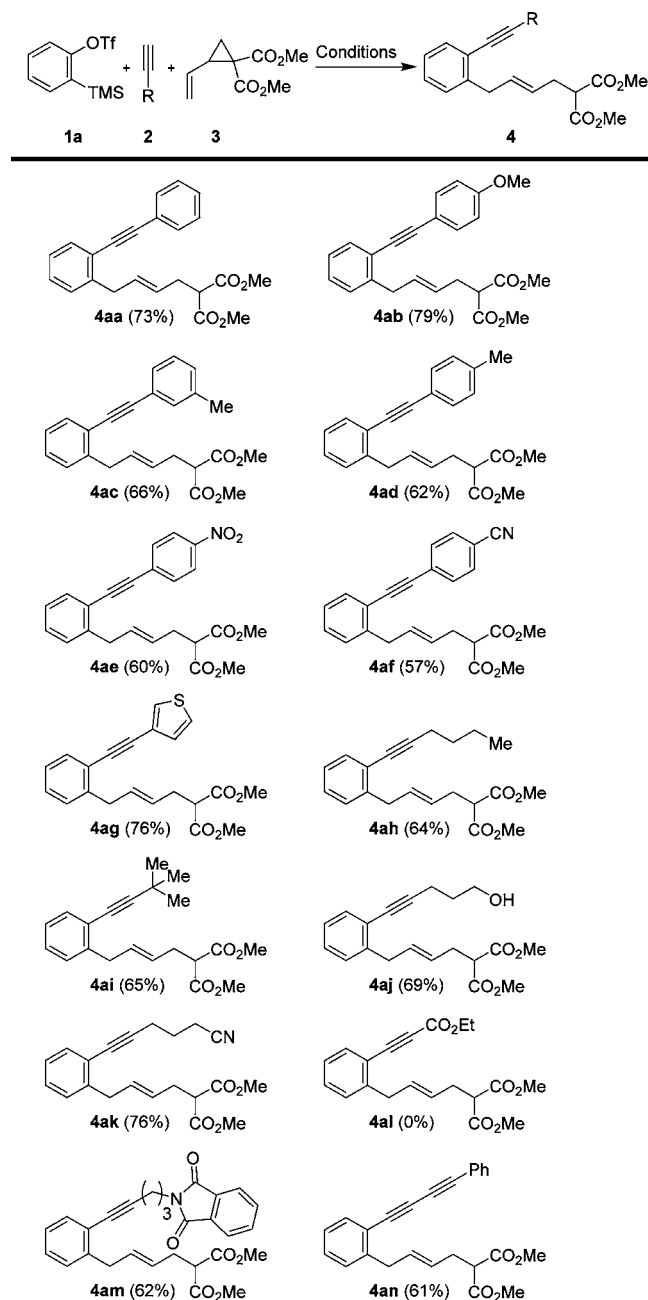
It is literature-known that primary and secondary alcohols react with arynes to produce aryl ethers.[12] Nevertheless, in our case the use of 4-pentyn-1-ol showed only coupling at the terminal alkyne to form a new C–C bond. The corresponding primary alcohol **4aj** was obtained in 69% yield. Also nitrile and phthalimide derivatives delivered the corresponding products in yields of 76% (**4ak**) and 62% (**4am**). Even diyne units were tolerated; phenyldiacetylene afforded the desired product **4an** in 61% yield. The installation of an electron-withdrawing group such as an ester directly attached to the alkyne moiety strongly reduces the nucleophilicity of the acetylide. As a result, the C–C coupling was completely prevented and **4al** was not obtained.

Afterward, we extended the scope of the three-component reaction with respect to the aryne (Table 2).

Gratefully, a broad spectrum of arynes including electron-rich, electron-deficient and arynes with extended π-systems could be transformed. The indane aryne precursor **1b** and the 3,4-dimethoxy derivative **1c** accomplished **4ba** and **4ca** in 76% and 70% yields, respectively. Naphthalene precursor **1d** led to the corresponding coupling product **4da** in 58% yield (Table 2, entry 3). Unfortunately, when using the aryne precursor **1e** bearing two fluorine substituents the desired coupling product **4ea** was obtained in only 11% yield (Table 2, entry 4) although **1e** was entirely consumed. In addition, when unsymmetrical aryne precursors were employed regioisomeric mixtures resulted in 50% up to 78% yields (Table 2, entries 5–8). Noteworthy, in the case of **1f** the chlorine substituent has a strong electronic influence on the aryne system leading to a regioisomeric ratio of 5:1. In contrast, we did not observe any regioselective preference in the formation of **4ha** with a methyl group at the same position.[13]

On the basis of these results, we propose a possible mechanism for the palladium-catalyzed three-component

Scheme 2. Scope with Respect to Alkyne[a]

[a]Conditions: **1a** (204 μmol), **2** (136 μmol), **3** (177 μmol), Pd(dba)$_2$ (13.6 μmol), dppp (13.6 μmol), KF (408 μmol), 18C6 (408 μmol), MeCN (4 mL) at 50 °C for 16 h; all yields represent isolated coupling products.

coupling (Scheme 3). Initially, copper acetylide **2a′** is generated by deprotonation of the terminal alkyne **2a** using CsF and CuI. Acetylide **2a′**, acting as a nucleophile, couples to the in situ generated benzyne **1a′** affording the highly nucleophilic copper intermediate **5**. Simultaneously, vinyl cyclopropane **3** is activated by the Pd(0) catalyst to form π-allyl palladium complex **3′**. This complex is intercepted by the nucleophilic intermediate **5** at the least hindered carbon of **3′** to form complex **4aa′**. The regeneration of the active palladium catalyst closes the catalytic cycle and affords the desired coupling product **4aa**.

Table 2. Scope with Respect to Aryne[a]

entry	aryne precursor	product	yield[b] (%)
1	1b	4ba	76
2	1c	4ca	70
3	1d	4da	58
4	1e	4ea	11
5	1f	4fa1/4fa2 4-Cl/5-Cl	63[c,f]
6	1g	4ga1 + 4ga2	50[d]
7	1h	4ha1/4ha2 4-Me/5-Me	78[d]
8	1i	4ia1/4ia2 3-Me/6-Me	77[e,f]

[a]Conditions: **1** (100 μmol), **2a** (76.9 μmol), **3** (100 μmol), Pd(dba)$_2$ (7.69 μmol), dppp (7.69 μmol), KF (231 μmol), 18C6 (231 μmol), MeCN (2 mL) at 50 °C for 16 h. [b]All yields represent isolated compounds. [c]Ratio of regioisomers 5:1. [d]Ratio of regioisomers 1:1. [e]Ratio of regioisomers 2:1. [f]Due to strongly overlapping signals, we were unable to determine which regioisomer is favored.

In conclusion, we have developed a palladium-catalyzed three-component coupling of arynes with terminal alkynes and vinyl cyclopropane dicarboxylate. The present process demonstrates the first example of aryne chemistry combined with the ring-opening of vinyl cyclopropanes. This protocol provides a straightforward access to 1-allyl-2-alkynylbenzenes from readily available terminal alkynes and aryne precursors. Future studies will elucidate whether other types of donor−acceptor cyclopropanes might be incorporated in a similar process.

Scheme 3. Plausible Reaction Mechanism of the Palladium-Catalyzed Three-Component Coupling Reaction
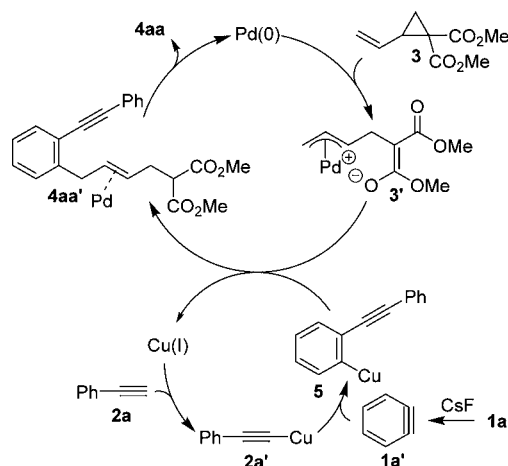
■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental details, and NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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