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Palladium-Catalyzed Oxidative Carbonylative Coupling of Arylboronic acids with Terminal Alkyne to Alkynones

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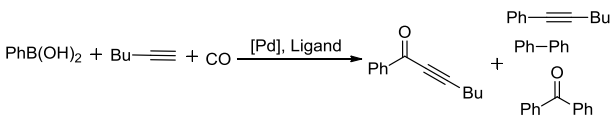
Abstract. We describe here an interesting palladium-catalyzed oxidative carbonylation of arylboronic acids with terminal alkyne. By the proper combination of palladium salt, ligand, and oxidant, the desired alkynones were isolated in moderate to good yields. Notably, all the reactions were performed at room temperature and moisture and air can be tolerated by this procedure. More importantly, this is the first example of oxidative carbonylative coupling of arylboronic acids with alkynes which filled the missed link in carbonylative coupling reactions.

Palladium-catalyzed carbonylation reactions have already become a true toolbox in modern organic synthesis. These transformation allow for the straightforward preparation of aromatic carboxylic acid derivatives both on laboratory and industrial scale.[1] Among the developed palladium-catalyzed carbonylative transformations of aryl halides, carbonylative Sonogashira reaction can give alkynones as their products which are important compounds for heterocycles synthesis.[2] In all the known carbonylative Sonogashira reactions, ArX (X = I, Br, OTf, N_2OAc) are the commonly applied substrates.[3] With the concept of oxidative coupling, two nucleophiles are coupled together in the presence of a suitable oxidant, the carbonylative coupling of arylboronic acids with alkynes offers another possibility.[4] Notably, the formation of the respective arylpalladadium(II) complex as a crucial intermediate can be achieved under milder conditions, because the related oxidative addition to aryl halides is somehow challenge in the presence of CO.

As early as in 1981, Suzuki and co-workers reported the first oxidative methoxycarbonylation of alkenylboron compounds.[5a, 5b] Later on, Uemura and co-workers showed the methoxycarbonylation of phenylboronic acid in methanol in the presence of $Pd(PPh_3)_4$ and NaOAc as catalytic system. Here, methyl benzoate was obtained in 58% yield together with benzophenone and biphenyl.[5c, 5d] Recently, Yamamoto reported the oxidative alkoxycarbonylation of arylboronates using a $Pd(OAc)_2/PPh_3$ catalyst and stoichiometric amount of benzoquinone as oxidant.[5f] The desired products were obtained in good yields, and DFT as well as MP2 calculations were carried out to understand the reaction mechanism. Soon later, Lei and co-workers developed an elegant methodology using air as benign oxidant in the presence of NEt_3 as base.[5g] More recently, our group reported the oxidative carbonylation of arylboronic acids with styrenes.[5h] Chalcones were produced in good to excellent yields by using air as the oxidant. As our continuing interests in this area, here, we wish to report our recent achievements on the oxidative carbonylation of arylboronic acids with alkynes. By the proper combination of catalyst system and oxidant, the desired alkynones were isolated in moderate to good yields. Notably, this is the first example on oxidative carbonylative Sonogashira reaction.

Based on our experience on the oxidative carbonylation of arylboronic aicds with styrenes, we started our investigation with ligands testing (Table 1, entries 1-6). By using $Pd(OAc)_2$ as the catalyst, Ag_2O as the oxidant and NaOAc as the base, 42% of the desired alkynone was formed with DPPP as the ligand (Table 1, entry 2). And NaOAc was found to be the best base for this transformation after testing several other typical bases (Table 1, entries 7-11). Hex-1-yn-1-ylbenzene was detected as the main by-product in all the cases.

Table 1. Pd-catalyzed oxidative carbonylation of phenylboronic acid with 1-hexyne: Ligands and bases testing.[a]

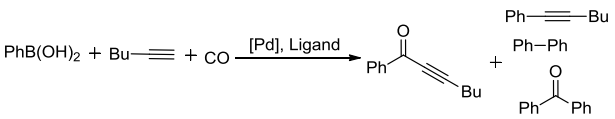


Entry	Ligand	Base	Yield[b]
1	DPPE	NaOAc	5%
2	DPPP	NaOAc	42%
3	DPPB	NaOAc	8%
4	DPPF	NaOAc	2%
5	BINAP	NaOAc	0%
6	$BuPAd_2$	NaOAc	2%
7	DPPP	*t*BuOK	14%
8	DPPP	Cs_2CO_3	<1%
9	DPPP	Na_2CO_3	0%
10	DPPP	K_2CO_3	4%
11	DPPP	NEt_3	12%

[a] $Pd(OAc)_2$ (2 mol%), Ligand (4 mol%), base (2 equiv.), Ag_2O (1.5 equiv.), acetone (1 mL), CO (8 bar), phenylboronic acid (0.5 mmol), 1-hexyne (1.2 equiv.), RT, 12h. [b] Yields were determined by GC using hexadecane as internal standard, calculated based on phenylboronic acid.

Then different solvents were checked subsequently (Table 2, entries 1-6), but no improved yield could be observed. The commonly applied palladium salts were tested as well (Table 2, entries 7-11), to our delight, 63% of 1-phenylhept-2-yn-1-one was formed by using $Pd(TFA)_2$ as the catalyst (Table 2, entry 11). Notably, the reaction was tested at 0°C or 60°C as well, but no better yield was detected. It's important to mention that, in addition to the testing listed in Tables 1 and 2, DPPM, DPPPe, Xantphos, DPEPhos, PPh_3, PCy_3, Bipyridine, 1,10-phen as ligand; CuO, Cu_2O, Fe_2O_3, $Cu(OAc)_2$, BQ, TBHP (in decane), TBP, UHP (Urea hydrogen peroxide), Ag_2CO_3, AgOAc, $AgNO_3$, Ag_3PO_4, AgTFA as oxidant; Cs_2CO_3, *t*BuOK, NEt_3, $NaHCO_3$, KOAc as base; CO pressure up to 40 bar were all tested with different combination, but no improved results were given.

Table 2. Pd-catalyzed oxidative carbonylation of phenylboronic acid with 1-hexyne: Solvents and palladium salts testing.[a]

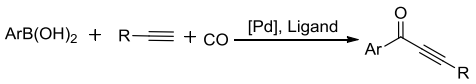


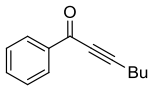
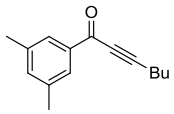
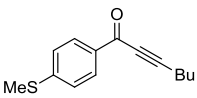
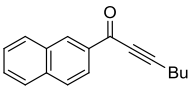
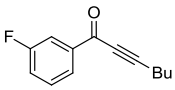
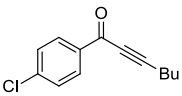
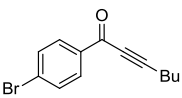
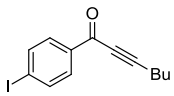
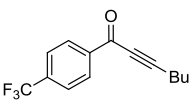
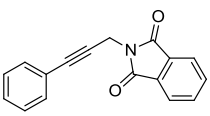
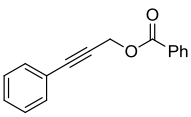
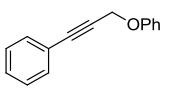
Entry	[Pd]	Solvent	Yield[b]
1	$Pd(OAc)_2$	MeCN	<1%
2	$Pd(OAc)_2$	DMF	0%
3	$Pd(OAc)_2$	THF	23%
4	$Pd(OAc)_2$	EtOAc	<1%
5	$Pd(OAc)_2$	dioxane	<1%
6	$Pd(OAc)_2$	DCM	<1%
7	$Pd_2(dba)_3$	acetone	13%
8	$Pd(MeCN)_2Cl_2$	acetone	5%
9	$Pd(PPh_3)_2Cl_2$	acetone	<1%
10	$PdCl_2$	acetone	28%
11	$Pd(TFA)_2$	acetone	63%[c]

[a] [Pd] (2 mol%), DPPP (4 mol%), NaOAc (2 equiv.), Ag_2O (1.5 equiv.), solvent (1 mL), CO (8 bar), phenylboronic acid (0.5 mmol), 1-hexyne (1.2 equiv.), RT, 12h. [b] Yields were determined by GC using hexadecane as internal standard, calculated based on phenylboronic acid. [c] $Pd(TFA)_2$ (5 mol%), DPPP (10 mol%).

With the best reaction conditions in hand, we carried out the substrates testing (Table 3). The challenge of this transformation was further proved by the difficulty in substrates testing. Among the around thirty examples of $Ar(hetero)B(OH)_2$ tested (listed in SI), in most of the cases, the direct oxidative coupling of arylboronic acids with 1-hexyne are the main products formed.[6] Several selected examples are listed, however, the successful examples shown excellent functional group tolerance and moderate yields of the alkynones were isolated. Methylthio as potentially oxidizable functional group can be tolerated under this oxidative coupling conditions (Table 3, entry 3). Aryl halides, especially aryl iodides and aryl bromides, are typical substrates applied in palladium-catalyzed coupling reactions.[7] To our surprise, not only (4-chloroophenyl)boronic acid but also (4-bromophenyl)boronic acid and (4-iodophenyl)boronic acid can be applied as substrates here, the corresponding alkynones were isolated in 49-62% yields (Table 3, entries 6-8). Instead of arylboronic acids, $PhBF_3K$ and phenylboronic acid pinacol ester were tested with 1-hexyne under our conditions as well. Unfortunately, only trace of the desired alkynone was formed and mainly resulted non-carbonylative coupling product. Additionally, several propargylic substrates and phenyacetylenes were subsequently tested. But only the direct oxidative coupling products were formed and isolated in good yields (Table 3, entries 10-12).

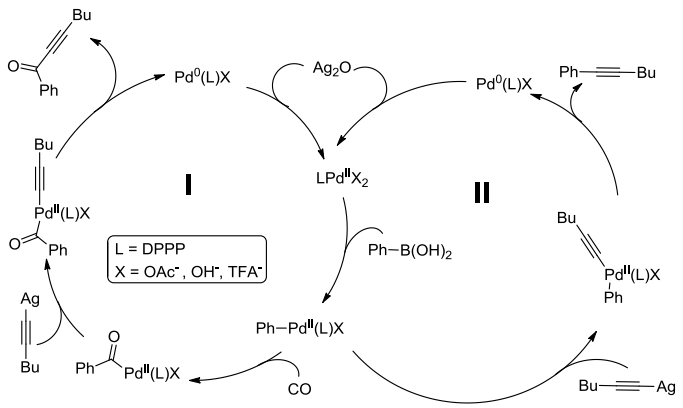
Table 3. Pd-catalyzed oxidative carbonylation of arylboronic acid with alkynes: Substrates scope.[a]



Entry	Products	Yield[b]
1		54%
2		52%
3		58%
4		47%
5		61%
6		49%
7		56%
8		62%
9		51%
10		73%
11		67%
12		78%

[a] $Pd(TFA)_2$ (5 mol%), DPPP (10 mol%), NaOAc (2 equiv.), Ag_2O (1.5 equiv.), acetone (1 mL), CO (8 bar), arylboronic acid (0.5 mmol), alkyne (1.2 equiv.), RT, 12h. [b] Isolated yields.

Regarding the reaction mechanism, a possible reaction pathway is been proposed in Scheme 1. The reaction started with Pd(II), the acylpalladium was formed after transmetalation with phenylboronic acid and insertion of CO. After an exchange of the anion by phenyl acetylide, the desired product was eliminated by reductive elimination. The Pd(0) then been oxidized back to Pd(II) by Ag_2O and get ready for next cycle. The cycle **II** gave the non-carbonylative coupling product. Here, the transmetalation of the *in situ* generated alkynylsilver with organopalladium species is too much fast even at room temperature which may explain the non-carbonylative products are the dominant products in most of the cases. At the end of the reactions, metallic silver ball and silver mirror can be observed.



Scheme 1. Proposed reaction mechanism.

In conclusion, an interesting palladium-catalyzed oxidative carbonylation of arylboronic acids with alykne to give alkynones has been developed. By the proper combination of palladium catalyst, oxidant and base, the desired alkynones were isolated in moderate yields. Notably, this is the first example of oxidative carbonylative coupling of arylboronic acids with alkynes which filled the missed link in carbonylative coupling reactions.

General information

Reactions were run under an air atmosphere with exclusion of moisture from reagents and autoclaves. All substrates were purchased from Sigma-Aldrich and were used as received. Solvents were dried from molecular sieves and kept under argon. NMR spectra were recorded on the Bruker AV 300 spectrometers. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane (δ 0.0 for ^{1}H NMR in DMSO-d_6, $CDCl_3$) and *d*-solvent peaks (δ 77.00 for ^{13}C NMR, chloroform and for DMSO-d_6, δ 40.00), respectively. All measurements were carried out at room temperature unless otherwise stated. Mass spectra were recorded on an AMD 402/3 or a HP 5989A mass selective detector. Gas chromatographic analysis was performed on an Agilent HP-5890 instrument with an FID detector and an HP-5 capillary column (poly(dimethylsiloxane) with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 mm film thickness) with argon as the carrier gas.

Experimental section

The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for six 4 mL Wheaton vials. $Pd(TFA)_2$ (5.0 mol%), DPPP (10.0 mol%), Ag_2O (2 equiv.), phenylboronic acid (0.5 mmol), NaOAc (2 equiv.) and a magnetic stir bar were placed in each vials under air, which were then capped with a septum equipped with an inlet needle. Then 1-hexyne (1.2 equiv.) and acetone (1 mL) were added to the vial *via* syringe. The vials were placed in an autoclave, filled with 8 bar of CO at room temperature and keep the reaction at room temperature for 12 h. After the reaction was completed, the autoclave was vented to discharge N_2. The product was extracted with ethyl acetate (5×3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. The purification occurred by flash chromatography on silica gel (eluent: heptane/EtOAc 95:05).

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Notes and references*:*

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Electronic Supplementary Information (ESI) available: [analytic data and NMR spectrum]. See DOI: 10.1039/c000000x/

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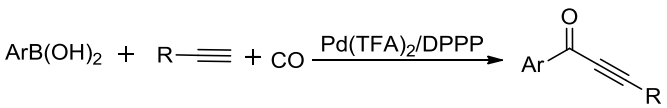

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