Palladium-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with arylboronic acids†

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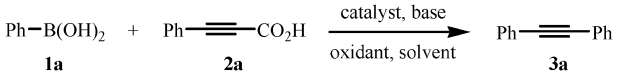
A highly efficient and mild palladium-catalyzed decarboxylative cross-coupling of aryl boronic acids and alkynyl carboxylic acids for the synthesis of unsymmetrical substituted alkynes is described for the first time.

The unsymmetrically substituted alkyne moiety is an important structural motif in many biologically active natural products and pharmaceutical compounds.[1] Therefore, the development of efficient methods to construct unsymmetrical alkynes is highly desirable. In recent years, many methods have been developed to target the synthesis of the unsymmetrical alkyne moiety.[2] Among them, the Sonogashira reaction is one of the most powerful and straightforward methods involving the coupling of sp C–H and sp^2 C–X.[3] Generally, one of the byproducts formed in the Sonogashira reaction is butadiyne, a homo-coupling product resulting from the oxidative dimerization of the terminal alkyne.[4] For the synthesis of unsymmetrical alkynes many modifications of the Sonogashira reaction have been made, for example, using silane protected alkynes[5] or 2-methylbut-3-yn-2-ol[6] as coupling reagents, which allow further elaboration after the first coupling, thus producing the desired unsymmetrical alkynes. Inspired by the work of Lee *et al.* on the decarboxylative coupling of alkynyl carboxylic acids with aryl halides,[7] we envisage that the carboxylic acid could serve as a latent protecting group for the coupling reaction which allows access to a wide variety of unsymmetrical alkynes. However, reported coupling reactions employing carboxylic acids are conducted under harsh reaction conditions such as high temperature, need of phosphine ligands and high catalyst loading.[8] Therefore, it will be a challenge to develop a new type of coupling reaction involving alkynyl carboxylic acid for the efficient synthesis of unsymmetrical alkynes under mild reaction conditions. Herein, we report the first example of palladium-catalyzed highly efficient synthesis of substituted alkynes *via* decarboxylative cross-coupling of carboxylic acids and arylboronic acids under mild reaction conditions.

Initially, the coupling reaction between phenylboronic acid and phenylpropiolic acid was chosen as model reaction to optimize the reaction conditions. Different catalysts, solvents, oxidants and bases were screened. As shown in Table 1, when copper(I) iodide was used, no reaction occurred at room temperature (Table 1, entry 1). When the catalyst was changed to copper(II) acetate, still no desired product was obtained while the homo-coupling product, 1,4-diphenylbuta-1,3-diyne, was detected as the major product (Table 1, entry 2). No product was furnished when one equiv. palladium acetate was used, and the major product was biphenyl, indicating that the decarboxylation process was suppressed under the sole effect of palladium acetate (Table 1, entry 3). Gratifyingly, when Ag_2O was added, almost quantitative yield of the target product was obtained (Table 1, entry 4). After screening various solvents, it was found that dichloromethane is the best solvent for the reaction (Table 1, entries 4–6). The use of other oxidants, such as copper(II) triflate, *p*-benzoquinone, resulted in homo-coupling product (Table 1, entries 7–8). Further examination of various bases and catalysts proved that KOAc and $Pd(OAc)_2$ is the optimal combination(Table 1, entries 9–14). In addition, it is noteworthy that when the catalyst loading was decreased from 5 mol% to 1 mol%, there was almost no deleterious effect on the yield, which further demonstrates the high efficiency of this reaction (Table 1, entry 15). However, from a consideration of the scale of the reaction and convenience of handling, we continued with 5 mol% of catalyst for the subsequent investigations.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Oxidant	Base	Yield (%)[b]
1	CuI	MeCN	O_2	—	NR
2	$Cu(OAc)_2$	toluene	O_2	—	0[c]
3	$Pd(OAc)_2$	CH_2Cl_2	—	KOAc	0[d]
4	$Pd(OAc)_2$	CH_2Cl_2	Ag_2O	KOAc	93
5	$Pd(OAc)_2$	MeCN	Ag_2O	KOAc	69
6	$Pd(OAc)_2$	THF	Ag_2O	KOAc	55
7	$Pd(OAc)_2$	MeCN	$Cu(OTf)_2$	KOAc	0[c]
8	$Pd(OAc)_2$	MeCN	BQ	KOAc	0[c]
9	$Pd(OAc)_2$	CH_2Cl_2	Ag_2O	NaOAc	85
10	$Pd(OAc)_2$	CH_2Cl_2	Ag_2O	K_2CO_3	80
11	$Pd(OAc)_2$	CH_2Cl_2	Ag_2O	KO^{t}Bu	73
12	$PdCl_2$	CH_2Cl_2	Ag_2O	KOAc	90
13	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	Ag_2O	KOAc	84
14	—	CH_2Cl_2	Ag_2O	KOAc	Trace
15	$Pd(OAc)_2$	CH_2Cl_2	Ag_2O	KOAc	92[e]

[a] Unless otherwise noted, the reactions were carried out at room temperature using phenylboronic acids (0.2 mmol), phenylpropiolic acid (0.24 mmol), base (0.3 mmol), oxidant (0.3 mmol), catalyst (5 mol%), dichloromethane (1 mL), 4 Å MS (0.1 g) for 12 h under air atmosphere. [b] Isolated yields. [c] No desired product was obtained and 1,4-diphenylbuta-1,3-diyne was detected as the major product. [d] One equiv. palladium acetate was used and biphenyl was obtained as the major product. [e] Using 1 mol% of catalyst.

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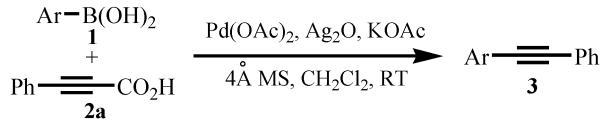
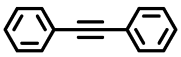
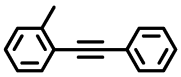
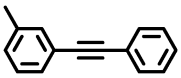
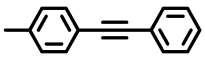
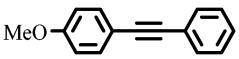
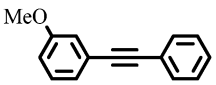
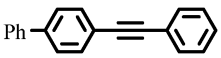
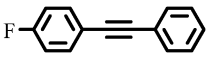
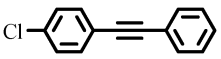
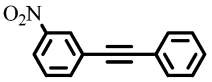
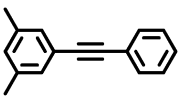
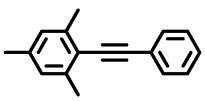
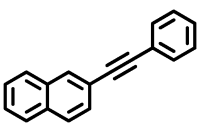
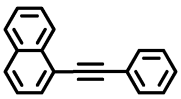
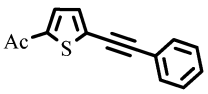
With the optimized conditions in hand, we next investigated the scope of the reaction using various arylboronic acids. As shown in Table 2, all the substrates examined under the standard conditions afforded the corresponding coupling products in good to excellent yields. The coupling appears to be invariant to the electronic properties of the substrates as the reactions with both electron-rich and electron-poor arylboronic acids all proceeded efficiently. When *m*-nitrophenylboronic acid (Table 2, entry 10) and 5-acetyl-2-thiopheneboronic acid (Table 2, entry 15) were employed as coupling partners, slight decreases in yields were revealed, which may due to competitive complexation with the palladium catalyst. In addition, arylboronic acids with differing positions of substituent also exhibited different reactivities, which is mainly due to steric hindrance.

Next, the scope of this decarboxylative cross-coupling reaction was explored by using different alkynyl carboxylic acids with 4-methoxyphenyl boronic acid under the aforementioned optimized conditions. As shown in Table 3, all the reactions using various alkynyl carboxylic acids proceeded efficiently to afford the desired arylated alkyne **3** in good to excellent yields. Aromatic alkynyl carboxylic acids substituted at the phenyl ring with MeO, Ac, NO_2, CN, I and Br were all converted into the corresponding products efficiently, indicating no remarkable electronic effects of the substituents on the reaction (Table 3, entries 1–6). It is noteworthy that the reaction using 4-halophenyl propiolic acid occurred selectively at the carboxylic acid group, without any coupling product at the aromatic ring detected (Table 3, entries 5, 6). With regard to aliphatic

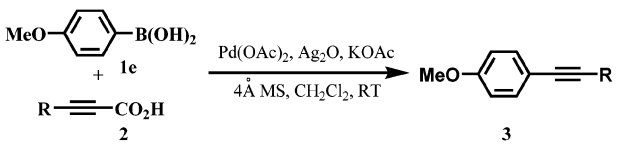
Table 2 Decarboxylative coupling of phenylpropiolic acid with arylboronic acids[a]

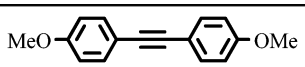
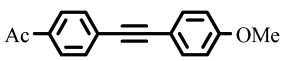
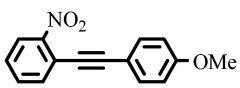
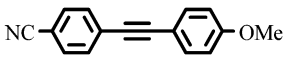
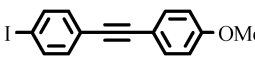
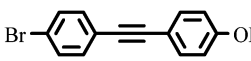
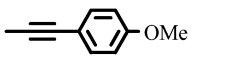
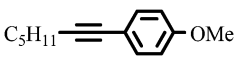
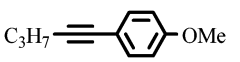
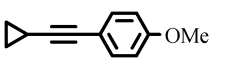


Entry	Product **3**		Yield (%)[b]
1		**3a**	93
2		**3b**	83
3		**3c**	87
4		**3d**	91
5		**3e**	94
6		**3f**	89
7		**3g**	86
8		**3h**	99
9		**3i**	90
10		**3j**	79
11		**3k**	84
12		**3l**	41
13		**3m**	92
14		**3n**	81
15		**3o**	76

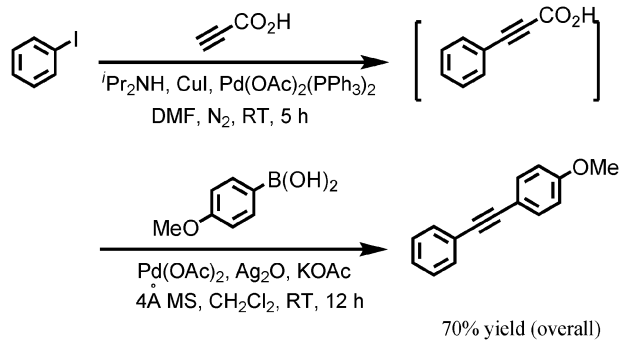
[a] Unless otherwise noted, the reactions were carried out at room temperature using arylboronic acid (0.2 mmol), phenylpropiolic acid (0.24 mmol), KOAc (0.3 mmol), Ag_2O (0.3 mmol), $Pd(OAc)_2$ (5 mol%), dichloromethane (1 mL), 4 Å MS (0.1 g) for 12 h under air atmosphere. [b] Isolated yields.

Table 3 Decarboxylative coupling of alkynyl carboxylic acids with 4-methoxyphenyl boronic acids[a]



Entry	Product **3**		Yield (%)[b]
1		**3p**	99
2		**3q**	99
3		**3r**	72
4		**3s**	70
5		**3t**	81
6		**3u**	89
7		**3v**	50
8		**3w**	89
9		**3x**	94
10		**3y**	87

[a] Unless otherwise noted the reactions were carried out with 4-methoxyphenylboronic acid (0.2 mmol), alkynyl carboxylic acids (0.24 mmol), KOAc (0.3 mmol), Ag_2O (0.3 mmol), $Pd(OAc)_2$ (5 mol%), dichloromethane (1 mL), 4 Å MS (0.1 g) for 12 h under air atmosphere. [b] Isolated yields.

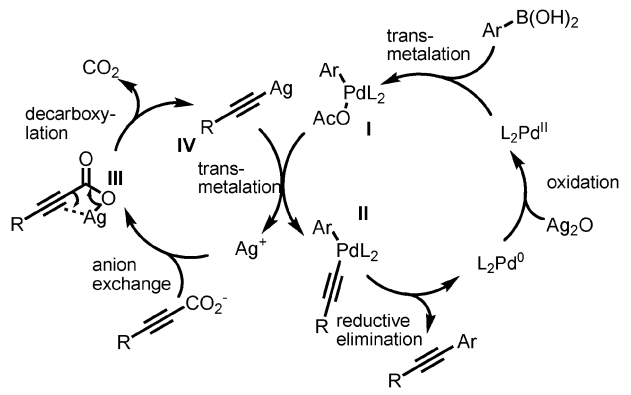


Scheme 1 Consecutive reactions for the synthesis of unsymmetrical diarylalkyne.

alkynyl carboxylic acids, both cyclic and acylic substrates can be effectively coupled to furnish the desired products in good to excellent yields (Table 3, entries 7–10). Owing to the difficulty of direct introduction of the 1-propynyl group, it is worth mentioning that the reaction employing 2-butynoic acid as the coupling partner can also afford the corresponding product, albeit in moderate yield (Table 3, entry 7).

To demonstrate the efficiency of this method for the synthesis of unsymmetrical alkynes, Sonogashira reaction followed by our decarboxylative coupling method was attempted using iodobenzene, propiolic acid and 4-methoxyphenyl boronic acid as substrates. After simple workup of the reaction between iodobenzene and propiolic acid (without purification), the intermediate was subjected directly to the decarboxylative coupling to provide the desired unsymmetrical alkyne in 70% overall yield (Scheme 1).

A proposed mechanism based on our results is shown in Scheme 2.[9] First, transmetalation between arylboronic acids and palladium acetate occurs to form aryl palladium species **I**. Then the alkynyl group is transfered from the metal–silver species to the metal–palladium species to form the intermediate **II** which contains two organic ligands in the coordination sphere of the palladium center. Reductive elimination ensues



Scheme 2 Proposed reaction mechanism.

to form the product and palladium(0) species, which is then oxidized by silver(I) to regenerate the palladium(II) to complete the catalytic cycle. As can be seen in Scheme 2, the silver oxide plays two different roles in the catalytic cycle: first as the oxidant to oxidize the palladium(0); and second as the decarboxylative agent to generate the desired alkynyl metal species.

In conclusion, an efficient palladium-mediated decarboxylative coupling of aryl boronic acids with alkynyl carboxylic acids was successfully established. The reaction described here is mild, general, and efficient. This method provides easy access to a wide variety of unsymmetrical alkynes.

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