

The use of calcium carbide in one-pot synthesis of symmetric diaryl ethynes†

Weiwei Zhang, Huayue Wu, Zhiqing Liu, Ping Zhong, Lin Zhang, Xiaobo Huang and Jiang Cheng*

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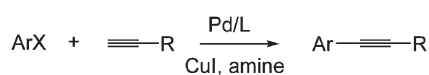
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An efficient Pd-catalyzed copper and amine free coupling reaction of acetylene and aryl bromides was achieved with calcium carbide as an acetylene source, using inorganic base and easily prepared, air-stable aminophosphine ligand in common organic solvents, providing symmetric diaryl ethynes in one-pot with yields ranged from moderate to excellent.

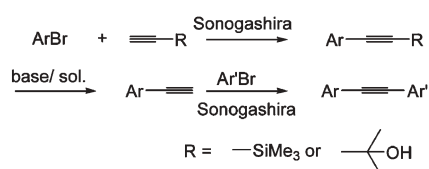
Palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl halides is one of the most straightforward methods for the preparation of aryl alkynes and conjugated enynes (Scheme 1).^{1,2}

Such reactions can not only serve as a powerful synthetic method in constructing complex systems including natural products,³ but also as a powerful tool to synthesize conjugated oligomers or polymers with interesting physical properties in material science.⁴ Such a method for efficient synthesis of diarylacetylenes has also been applied for supramolecular self-assembly construction.⁴ Usually, biaryl ethynes can be obtained by two ways. One is by using a protected acetylene (Scheme 2).⁵ However, this three-step procedure is circuitous and often leads to modest overall yields of the desired diaryl ethyne. The other one is using acetylene gas, which is a very economical way to deliver a triplet C–C bond moiety to organic substrates.⁶ But it often requires Cu(I) salt or amine to synthesize biaryl ethyne from acetylene gas and the procedures are not well documented. The Cu(I) acetylides formed *in situ* can undergo oxidative dimerization



R = aryl, alkyl, X = I, Br, Cl

Scheme 1



Scheme 2

College of Chemistry & Material Science, Wenzhou University, Mid. Xueyuan Rd., Wenzhou, 325027, China.

E-mail: shchengjiang@yahoo.com.cn; Fax: 86-577-88156826;

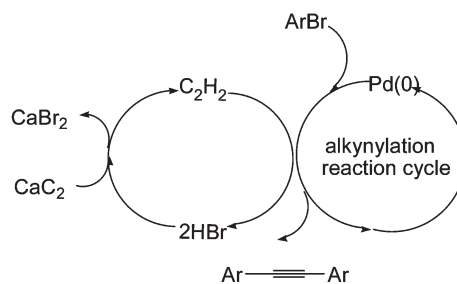
Tel: 86-577-88156826

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to give diaryldiacetylenes when exposed to air or an oxidant, which is known as the Glaser coupling.⁷ The methods mentioned above have the following disadvantages: 1) The yield is often not very high. 2) By-products are generally difficult to separate from the desired products. 3) The copper acetylide is potentially an explosive reagent.⁸ 4) The use of amine as solvent is not environmental friendly. 5) Only the expensive, highly active aryl iodides are proper substrates when acetylene gas is employed. 6) This procedure, especially in a large scale preparation, is not experimentally facile because acetylene is a gas. Considering this, we explored the use of the inexpensive, easily handled and commercially available calcium carbide as the acetylene source to synthesize some biaryl ethynes. Herein, we report a copper and amine free alkynylation reaction between aryl bromides and acetylene, which was derived from calcium carbide *in situ*, affording the biaryl ethynes in one-pot with moderate to excellent yields. Aminophosphines were employed as ligands in the procedure, which were air-stable, easily prepared and showed high activity in the Suzuki reaction as well as in copper and amine free alkynylation reaction.⁹

At the very beginning, we noted that two molecules of HBr were released in the alkynylation reaction cycle. So we reasoned, if the released HBr could react with calcium carbide to produce acetylene, the added base would remain untouched. Thus, the alkynylation reaction of aryl bromides with acetylene (derived from calcium carbide *in situ*) would run in the presence of only a catalytic amount of base and water (Scheme 3). We first chose *p*-bromoanisole as a substrate and ¹Pr₂NPPH₂ (**L1**) as a ligand to investigate the alkynylation reaction in the absence of a copper salt.

Much to our disappointment, treatment with a mixture of calcium carbide **1** (256 mg, 4 mmol), *p*-bromoanisole **2h** (374 mg, 2 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), K₂CO₃ (10 mol% and 50 mol%) and **L1** (43 mg, 0.15 mmol) in undried THF (5 mL) at 65 °C under an inert atmosphere for 12 hours only afforded the



Scheme 3

desired product **3h** in 32% and 36% yields, respectively. Therefore, we tested a series of parameters, which may play important roles in the reaction. Firstly, we studied the influence of the ratio of the base. It was pleasing to find that the combination of **1** (256 mg, 4 mmol), **2h** (374 mg, 2 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), K₂CO₃ (552 mg, 4 mmol) and **L1** (43 mg, 0.15 mmol) in undried THF (5 mL) gave the product in 79% yield.¹⁰ When the amount of K₂CO₃ was increased to 300 mol%, the product was obtained in 80% yield. Since no significant increase in the yield was found by increasing the amount of base, we chose to use 200 mol% of K₂CO₃ in the reaction to reduce the waste. We then turned our attention to the screening of ligands. On considering the electronic effect and steric hindrance in ligand designing in the transition metal catalyzed-coupling reaction,¹¹ we tested some other aminophosphine ligands, which are all easily synthesized (Fig. 1). Only a trace amount of desired product was detected when **L2**, which was a high activity ligand in the Suzuki reaction, was employed. The ligand **L3** gave 30% yield of the product. Since an increase of the electron density in the P atom usually facilitates the oxidative addition step in the catalytic cycles, we introduced methoxy group in the *para* position of the phenyl in **L1**. However, the yield was only slightly increased to 82% when **L4** was applied instead of **L1**. We therefore decided to use the easily prepared ligand **L1** in the reaction and optimized the base and solvent conditions by screening. Finally the optimized reaction conditions were as follows: **1** (256 mg, 4 mmol), **2h** (374 mg, 2 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), K₂CO₃ (552 mg, 4 mmol) and **L1** (43 mg, 0.15 mmol) in undried THF (5 mL). With the optimized reaction conditions in hand, a series of aryl bromides were tested under these conditions. The results are summarized in Table 1.¹²

The aryl bromide substrates worked well under the reaction conditions in the absence of CuI or amine. For example, although aryl bromides containing electron-donating substituents were usually found to be reluctant in taking part in oxidative addition to Pd(0), yet in our system, products **3b**, **3h**, **3i** were obtained in 97%, 79% and 67% isolated yield, respectively (Table 1, Entries 2, 8, 9). The *ortho* group in the aryl bromide was found to have some effect in the reaction, and the yields were slightly decreased to 75% for *o*-bromotoluene (**2c**), 69% for 2,6-dimethylphenyl bromide (**2f**) and 62% for 2,4,6-trimethylphenyl bromide (**2g**) (Table 1, Entries 3, 6, 7). As for the 3-bromothiophene (**2m**), maybe owing to the possibility of the sulfur atom coordinating with the palladium atom, the yield was slightly decreased to 44% (Table 1, Entry 13). It is noteworthy that the aryl bromides containing electron-withdrawing substituents afford the desired products in low yield. A 56% yield of the product was obtained for 3-bromobenzaldehyde (**2j**) and no reaction takes place for 1-bromo-4-nitrobenzene (**2o**) (Table 1, Entries 10, 15). However, when the carbonyl group in 4-bromobenzaldehyde (**2k**) was protected by ethylene glycol, the yield of the coupling product **3p** dramatically increased to 56% (Table 1, Entry 16). This seems to be somewhat contradictory to

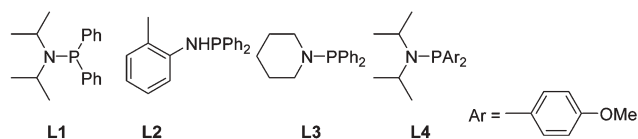


Fig. 1 The screened ligands.

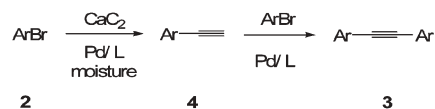
Table 1 Alkynylation reaction of aryl bromides and acetylene using calcium carbide as acetylene source^a

ArBr + CaC ₂		Pd(OAc) ₂ /L1 K ₂ CO ₃ , undried THF	Ar—C≡C—Ar	
2	1		3	
Entry	Aryl bromide		Product	Yield (%) ^b
1	Bromobenzene (2a)		3a	83
2	1-Bromonaphthalene (2b)		3b	97
3	<i>o</i> -Bromotoluene (2c)		3c	75
4	<i>m</i> -Bromotoluene (2d)		3d	76
5	<i>p</i> -Bromotoluene (2e)		3e	78
6	2,6-Dimethylphenyl bromide (2f)		3f	69
7	2,4,6-Trimethylphenyl bromide (2g)		3g	62
8	<i>p</i> -Bromoanisole (2h)		3h	79
9	<i>m</i> -Bromoanisole (2i)		3i	67
10	3-Bromobenzaldehyde (2j)		3j	56
11	4-Bromobenzaldehyde (2k)		3k	14
12	3-Bromopyridine (2l)		3l	72
13	3-Bromothiophene (2m)		3m	44
14	5-Bromobenzo[<i>d</i>][1,3]dioxole (2n)		3n	56
15	1-Bromo-4-nitrobenzene (2o)		3o	N. R.
16	2-(4-Bromophenyl)-1,3-dioxolane (2p)		3p	56
17	4-Bromo <i>N,N</i> -dimethylaniline (2q)		3q	65

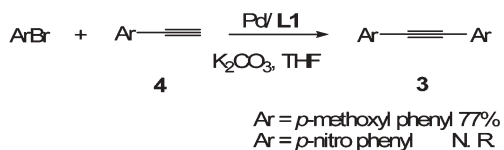
^a All reactions were run with aryl bromide (2 mmol), CaC₂ (236 mg, 4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), **L1** (43 mg, 0.15 mmol) and K₂CO₃ (552 mg, 4 mmol) in 5 ml of undried THF at 65 °C for 12 h.
^b Isolated yield.

the general considerations in the transition metal catalyzed coupling reaction. We propose that the reactions proceed in two steps: 1) The aryl acetylene's formation. 2) The Sonogashira reaction of aryl acetylene with aryl bromide (Scheme 4).

When *p*-nitrobromobenzene (**2o**) was used as the substrate, the reaction could not proceed and the starting materials were almost quantitatively recovered without the formation of product **4**. This implies that during the course of forming symmetric diarylacetylenes, the second reaction serves as the driving force for the first reaction. Although *p*-nitrobromobenzene may take part in the first reaction more facily than *p*-bromoanisole, in the primary product **4**, the terminal triple bond in *p*-nitrophenylacetylene (**4o**) has much less electron density than in *p*-methoxyphenylacetylene (**4h**) owing to the presence of the strongly electron withdrawing nitro group. It is known that in Sonogashira reactions, alkynes with low electron density in the terminal triple bond are less active. For example, trifluoromethylethyne and ethyl propionate are not good substrates in Sonogashira reactions.¹³ We suspected that this electron deficiency in the terminal triple bond in **4o** was the reason for the lack of reactivity of **2o** in the reactions mentioned above.¹⁴ To support this hypothesis, we have found in control experiments that *p*-bromoanisole (**2h**) reacts with *p*-methoxyphenylacetylene smoothly in the presence of palladium acetate and the ligand **L1** to give the symmetric diarylethyne in 77% yield, while **2o** can not react with *p*-nitrophenyl acetylene under the same conditions (Scheme 5).



Scheme 4



Scheme 5

In conclusion, we have developed an efficient, copper and amine free alkynylation reaction using calcium carbide and aryl bromides with easily prepared, air-stable aminophosphine as ligand. The mild reaction conditions, the use of undried solvent, the obviation of copper salt as co-catalyst and amine as solvent, as well as the utilization of cheap inorganic base and calcium carbide all contribute to making this a most attractive reaction.

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 - 12 General procedure: Under nitrogen atmosphere, a Schlenk reaction tube was charged with calcium carbide **1** (236 mg, 4 mmol), aryl bromide **2** (2 mmol), K₂CO₃ (552 mg, 4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), ligand (0.15 mmol) and undried THF (5 mL). The reaction tube was purged with N₂ under a dry ice bath. After the mixture was heated at 65 °C for 12 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel to give the product **3**. **3h** 1,2-bis(4-methoxyphenyl)ethyne ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, *J* = 9.0 Hz, 4H), 6.85 (d, *J* = 9.0 Hz, 4H), 3.81 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 159.4, 132.8, 115.8, 114.0, 87.9, 55.3.
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 - 14 The charge of the terminal carbon atom is calculated to be –0.272825 and –0.227259 for **4h** and **4o**, respectively by DFT method at the B3LYP-6-31G level (Gaussian 98).