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Cleavage of C-C and C-O Bonds to Form C-C Bonds: Direct Cross-coupling Between Acetylenic Alcohols and Benzylic Carbonates

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Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday.

Abstract:

A Palladium catalyzed cross-coupling reaction between C(sp) and C(sp^3) centers was achieved via the C-C bond cleavage in acetone protected terminal alkynes and C-O bond cleavage in benzylic carbonates. Good to excellent yields are observed for 24 examples. This procedure uses the relatively stable acetylenic alcohols, a widely used alkynyl reagent in laboratory synthesis, instead of the unstable and volatile terminal alkynes as the reactant. The employment of benzylic carbonates has also avoided the involvement of lachrymatory benzyl halides, making this method more practical in synthesis. Ligands play an important role in the procedure. K_2CO_3 is proved to be able to accelerate the reaction.

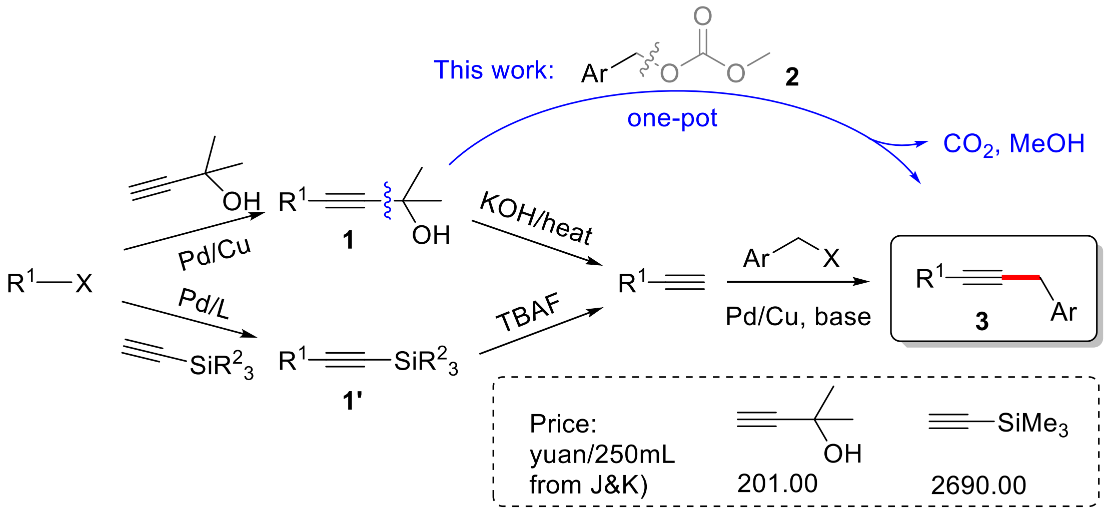
Key words:

Acetylenic alcohols, benzylic carbonates, C-C bond forming, cleavage of C-C bonds.

Introduction:

Acetylene moieties are one of the most important structures in organic synthesis[1-3]. Cross-coupling of terminal alkynes with other structures represent one of the most useful and efficient method to introduce the acetylene moieties into the target molecules[4-6]. Over the past several decades, the coupling reactions involving terminal alkynes have been well studied[7, 8], as known as the Sonogashira type coupling reactions, and also have been widely applied in organic synthesis from laboratory preparation to industrial scaled-up production. However, only simple terminal alkynes are commercially available. For more complex structures containing terminal alkyne moieties in laboratory synthesis, they are often prepared from the cross-coupling between electrophiles with acetylenic alcohols[9] or silanes, as shown in Scheme 1. For acetylenic silanes, the high cost has restricted their applications in scaled-up preparation. Although the acetylenic alcohols are usually of much lower cost, the generation and isolation of terminal alkynes may cause extra effort and waste. Thus it would be much more efficient if the relative cheap acetylenic alcohols (**1** in Scheme 1) could be directly used as the alkynyl sources in cross-coupling reactions with other substrates, as shown in Scheme 1.

Scheme 1. Methods to introduce the acetylenic moieties into benzylic structures



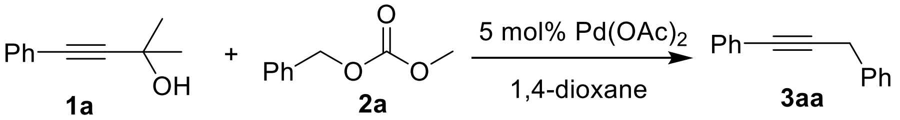
There have already a few reports that employed acetylenic alcohols as the alkyne source in coupling reactions. Chow et al. reported an early example of Pd/Cu catalyzed coupling between aryl halides with acetylenic alcohols under phase transfer conditions[10]. Similar work using acetylenic alcohols as the source of alkynes were reported respectively by several team, include Tsai[11], Wu[12, 13], Chang[14], Wen[15], Uemura[16], Endo[17] and Gu[18]. It is noted that most of these reports have employed aryl halides or alkenes as the other coupling reagents, forming a $Csp\text{-}Csp^2$ bond.

There are also several reports that focus on the coupling reactions between terminal alkynes and benzyl halides to form the $Csp\text{-}Csp^3$ bond. Pérez et al. have described the cross-coupling reaction of indium acetylides as nucleophiles with benzyl bromine.[19] Deepak and co-workers reported an nickel catalyzed coupling reaction between benzyl bromine and aluminum acetylides.[20] Meanwhile, researchers also obtained benzylic alkynes through breakage of C-H bond in terminal alkynes instead breakage of C-M(In, Zn, Al).[21-24] Zhang has also disclosed an example of decarboxylative cross-coupling between alkynyl carboxylic acids and benzyl halides for the synthesis of benzylic alkynes[25]. Considering about the lachrymatory property of benzyl halides, using the easy-handling benzylic carbonates instead may represent a better choice. Hirano et al. have reported that diaryl methyl carbonates could undergo cross-coupling with terminal alkynes smoothly, with moderate to good yields[26]. However, simple diphenylmethyl carbonate did not perform well, and another limitation was that arylacetylenes, like phenylacetylene, did not react under this condition. A very recent report by Chatani et al. reveals a Rh-catalyzed C-O bond alkynylation using aryl carbamates with propargyl alcohols[27], indicating the importance of the acetylenic alcohols in organic synthesis. However, to our best knowledge, there is no report that realized the cross-coupling between benzylic carbonates and acetylenic alcohols directly till now. Based on these discoveries and our earlier study on the preparation of terminal alkynes from acetylenic alcohols[9], we wish to report our latest discoveries on the formation of $C(sp)\text{-}C(sp^3)$ bonds through the cleavage of $C(sp)\text{-}C(sp^3)$ bonds in aryl propargyl alcohols and $C(sp^3)\text{-}O$ in benzylic carbonates.

Results and Discussion:

We initiate our model reaction exploration utilizing benzylic carbonate **2a** as the electrophile in the presence of Pd catalyst, as shown in Table 1. By employing 5 mol% of $Pd(OAc)_2$ and 5 mol% phosphine ligand, the reaction did merely occur (entries 1-7). Screening of the bases (entries 8-12) or increasing the catalyst loading (entry 13) did not improve the yield either. To our delight, excess of ligand over the Pd catalyst have reversed the reaction, and satisfactory results were achieved when 10 mol% $Pd(OAc)_2$ with 20 mol% of dppb (1,4-Bis(diphenylphosphino)butane) as the ligand (99%, entry 15) was employed. Stoichiometric amount of base was required, while decreasing the amount of base may lead to lower yields (entries 17-19). It is also noteworthy that this reaction could occur effectively in air atmosphere (entry 16).

Table 1. Condition optimization for the cross-coupling of acetylenic alcohols with benzylic carbonates



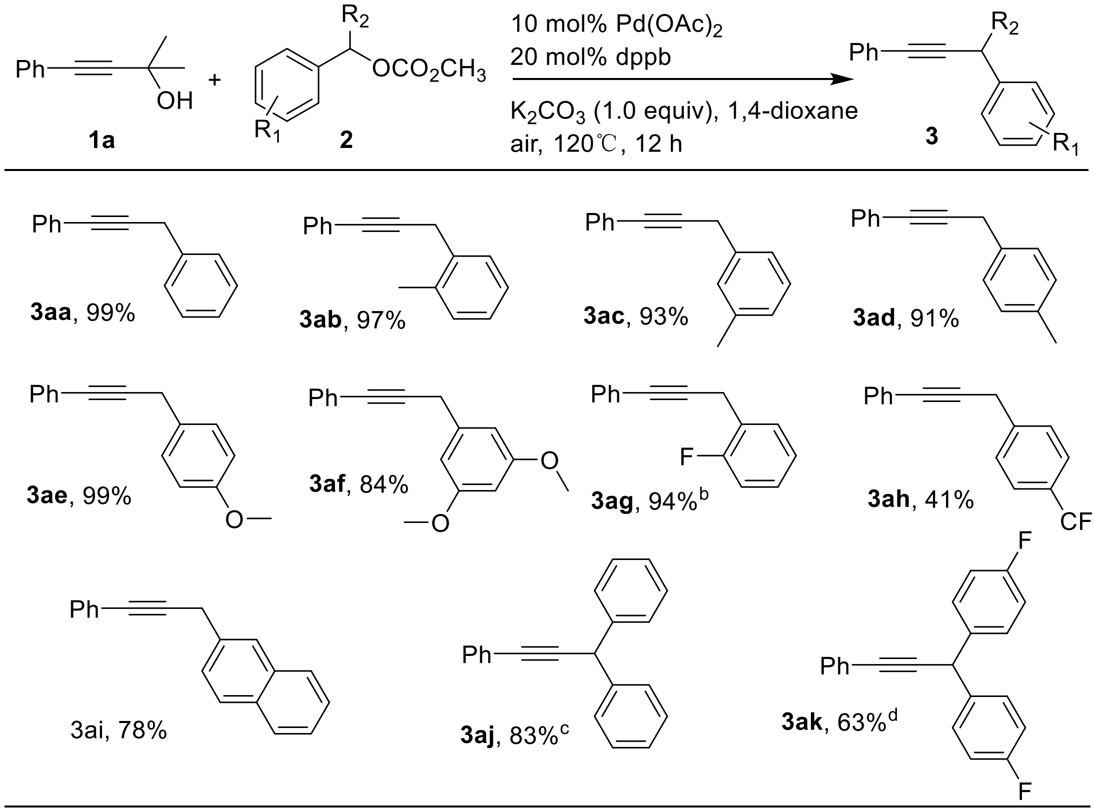
Entry[a]	Ligand	Base	Yield(%)[b]
1	Xantphos	K_2CO_3	trace
2	dppf	K_2CO_3	none
3	DPPphos	K_2CO_3	trace
4	DPPPent	K_2CO_3	trace
5	Xphos	K_2CO_3	trace
6	PCy_3	K_2CO_3	trace
7	dppb	K_2CO_3	trace
8	DPPphos	K_3PO_4	trace
9	DPPphos	KO^tBu	none
10	DPPphos	pyridine	none
11	DPPphos	KOH	none
12	DPPphos	Ag_2CO_3	none
13[c]	dppb	K_2CO_3	trace
14[d]	dppb	K_2CO_3	93
15[e]	dppb	K_2CO_3	99
16[ef]	dppb	K_2CO_3	99
17[ef]	dppb	none	none
18[ef]	dppb	K_2CO_3 (0.1eq)	5
19[ef]	dppb	K_2CO_3 (0.5eq)	89

[a] **1a** 0.25 mmol, **2a** 0.25 mmol, $Pd(OAc)_2$ 0.0125 mmol, Ligand 0.0125 mmol, Base 0.25 mmol, solvent 3 mL, 120°C, 12 h, Ar. [b] GC yield. [c] $Pd(OAc)_2$ 0.025 mmol, Ligand 0.025 mmol. [d] $Pd(OAc)_2$ 0.0125 mmol, Ligand 0.025mmol. [e] $Pd(OAc)_2$ 0.025 mmol, Ligand 0.05 mmol. [f] Air atmosphere.

With the optimized conditions in hand (Table 1, entry 16, 99%), we then examined the cross-coupling reaction of acetylenic alcohol **1a** with a variety of benzylic carbonates for the synthesis of benzylic alkynes, as shown in Table 2. Satisfactory results were obtained using this method. The model reaction initiate from **1a** and **2a** gave 99% isolated yield of the product **3aa**.

The electronic properties of the substitute group on aryl moiety of the benzylic carbonates did not affect the reaction, with the exception of trifluoromethyl group, of which only 41% product (**3ah**) was obtained. NMR analysis showed the tautomeric transformation of the product **3ah** between alkyne form and allene form[21]. Furthermore, the secondary benzyl carbonates also worked well under this condition (**3aj** and **3ak**).

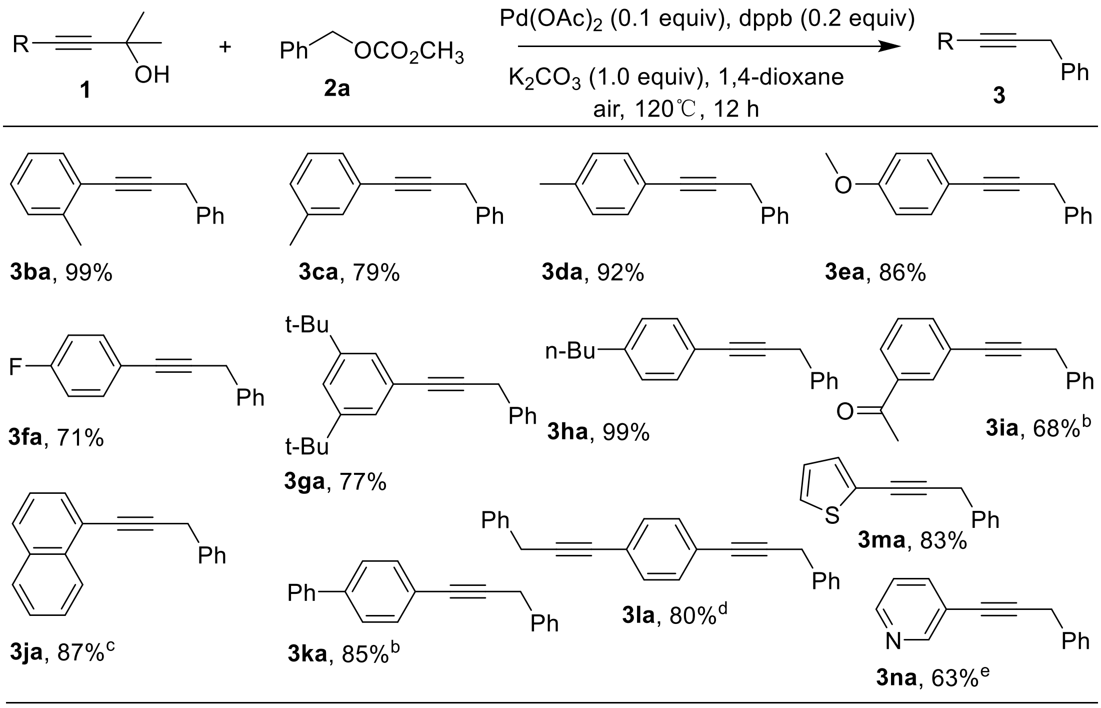
Table 2. Substrate scope of benzylic carbonates [a]



[a] Isolated yields. Conditions: **1a** (0.25 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), dppb (0.2 equiv), K_2CO_3 (1.0 equiv), 1,4-dioxane (3 mL), air, 120℃, 12 h. [b] **1a** (1 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), dppb (0.2 equiv), K_2CO_3 (1.0 equiv), 1,4-dioxane (3 mL), air, 120℃, 12 h. [c] **2** (5.0 equiv). [d] **2** (3.0 equiv).

We have also examined the substrates scope of different acetylenic alcohols and the results were shown in Table 3. A series of aryl propargylic alcohols were proved to be compatible, generating the products in good to excellent yields. Ortho-, meta- and para-substituents on the phenyl ring of the aryl propargylic alcohols were tolerated and all gave good yields (**3ba**~**3da**). Aryl propargylic alcohols bearing electron-donating or electron-withdrawing substituents also gave acceptable yields of the corresponding products. Naphthalene and heterocyclic aromatic substituents were also tolerated in this reaction (**3ja**, **3ma** and **3na**).

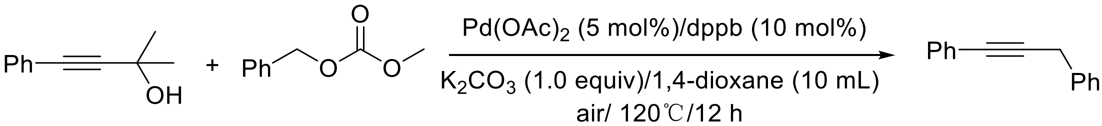
Table 3. Substrate scope of acetylenic alcohols [a]



[a] Isolated yields. Conditions: **1** (0.25 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), dppb (0.2 equiv), K_2CO_3 (1.0 equiv), 1,4-dioxane (3 mL), air, 120℃, 12 h. [b] **2** (5.0 equiv). [c] **1a** (1 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), dppb (0.2 equiv), K_2CO_3 (1.0 equiv), 1,4-dioxane (3 mL), air, 120℃, 12 h. [d] **2** (6.0 equiv), 3.5 h. [e] **1a** (0.5 mmol), **2** (2.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dppb (0.2 equiv), K_2CO_3 (1.0 equiv), 1,4-dioxane (3 mL), air, 120℃, 12 h.

A scaled up experiment under similar condition has also been taken, employing 5 mmol of the acetylenic alcohol **1a** and equal amount of benzylic carbonate **2a** to yield the product **3aa** in 86% isolated yield. It is notable that in this gram scale reaction the catalyst loading of $Pd(OAc)_2$ could be halved into 5 mol%, as shown in Scheme 2.

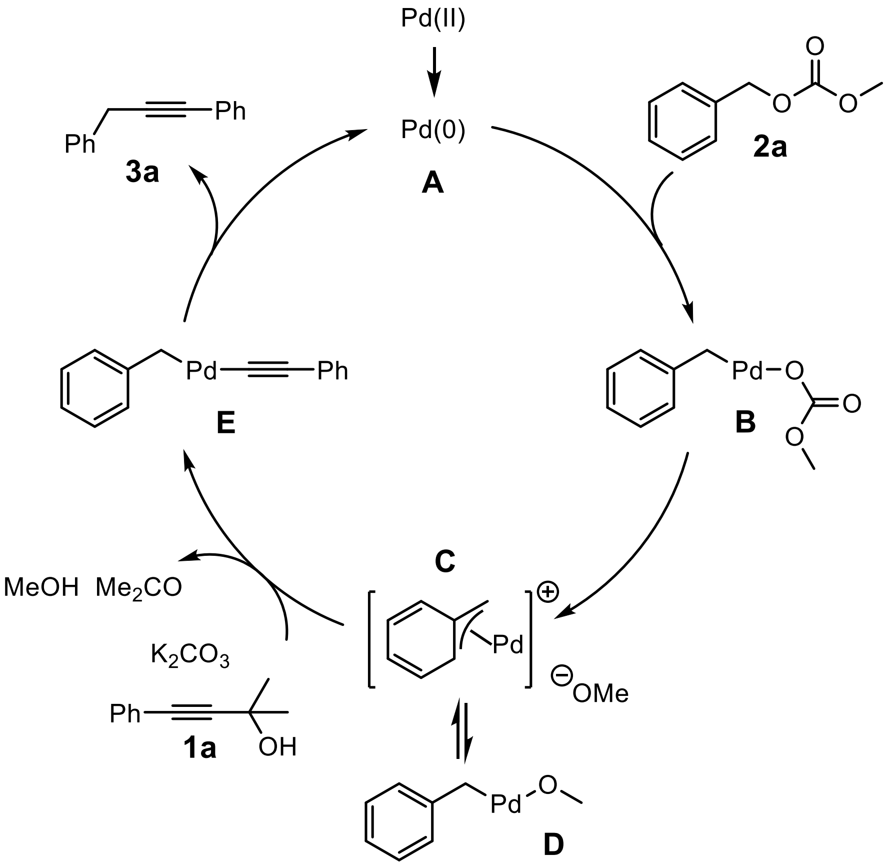
Scheme 2. Gram scale synthesis of **3aa**



1a, 5.0 mmol **2a**, 5.0mmol **3aa**, 86%

A proposed mechanism of this transformation is shown in Scheme 3. Firstly, Pd(II) is reduced to form an active species Pd(0) , which then goes through the oxidative addition step by **2a** to generate **B**. **B** could easily undergo the decarboxylation step to form the intermediate **C**, which could interconvert with its tautomer, (η^1-benzyl)(alkoxo)-palladium (**D**), and further reacts with **1a** in the presence of K_2CO_3 to form the Pd(II) intermediate **E** via a deacetonative step[28-30]. Finally, the desired product **3a** together with the active catalyst center Pd(0) is generated through reductive elimination of **E** to fulfill the catalytic cycle.

Scheme 3. Proposed mechanism



Conclusions:

In summary, we have developed a palladium-catalyzed deacetonative cross-coupling reaction between aryl propargyl alcohols with benzylic carbonates, which involves the breakage of C(sp)-C(sp^3) bonds in aryl propargyl alcohols and C(sp^3)-O bonds in benzylic carbonates for the formation of C(sp)-C(sp^3) bonds in benzylic alkynes. This reaction avoids the employment of more expensive terminal alkynes and lachrymatory benzyl halides, and could proceed smoothly in moderate to good yields in air atmosphere with a broad substrate scope in both propargyl alcohols and benzylic carbonates.

Experimental Section

General procedure for preparation of benzylic alkynes

To a solution of 1,4-dioxane (3 mL) in a flame dried flask were sequentially added propargyl alcohol **1** (0.25 mmol), benzyl carbonate **2** (0.375 mmol), $Pd(OAc)_2$ (0.025 mmol), dppb (0.05 mmol) and K_2CO_3 (0.25 mmol). After stirring under 120℃ for 12 h, the reaction mixture was carefully quenched with 20 mL of brine and extracted by EtOAc (6 mL × 2), dried over anhydrous Na_2SO_4 and concentrated. Finally, the residue was purified by a flash chromatograph on silica gel to give the desired product.

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