ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2019, **6**, 1757

Received 3rd February 2019,
Accepted 29th March 2019

DOI: 10.1039/c9qo00192a

rsc.li/frontiers-organic

Pd-Catalyzed coupling reaction of cyclobutanols with propargylic carbonates†

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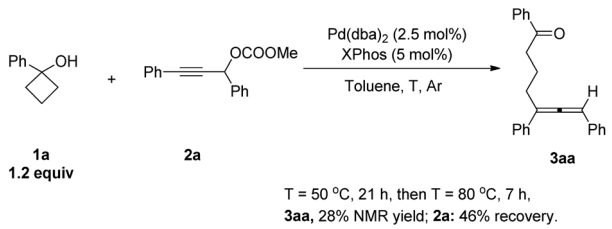
An efficient approach of Pd-catalyzed ring opening coupling reaction of cyclobutanols with propargylic carbonates was realized to provide a series of multisubstituted δ-allenyl ketones. The reaction had a wide substrate scope with tolerance to different functional groups.

Introduction

An allene unit is an important type of molecular structure and found widespread in numerous natural products and bioactive molecules.[1] Thus, the synthesis of differently substituted allenes has attracted a lot of attention.[2] The coupling reaction of propargylic carbonates with different metal regents was an efficient method for the construction of multi-substituted allenes.[3] Recently, we found that cyclopropanols may be used as an efficient coupling reagent with propargylic carbonates for the synthesis of different substituted allenes. The reaction has a wide substrate scope under mild reaction conditions.[4] To expand the scope of such a reaction, we envisioned that cyclobutanols which are easily available from cyclobutanones[5] could also be used in this type of coupling reaction *via* Pd catalysts as pioneered by Uemura.[6,7] In this paper, we report a general method for the synthesis of different substituted δ-allenyl ketones from propargylic carbonates.

Firstly, standard reaction conditions with cyclopropanols were used for the coupling reaction of cyclobutanol **1a** with propargylic carbonate **2a**. Unfortunately, the reaction mixture was stirred at 50 °C for 21 h and then 80 °C for 7 h to afford the desired allene product **3aa** in only 28% NMR yield with 46% of carbonate **2a** being recovered (Scheme 1). These results revealed that the reactivity of cyclobutanol was much lower than the cyclopropanol, which was possibly due to their different ring strains (the ring strains of cyclopropane and cyclobutane are 29.0 and 26.3 kcal mol^{-1}, respectively[8]).



Scheme 1 Reaction of cyclobutanol **1a** with propargylic carbonate **2a** under the standard conditions of cyclopropanol.

Results and discussion

Based on these results, we decided to further screen the reaction conditions with cyclobutanol **1a** and propargylic carbonate **2a** as the model substrates. Firstly, different carbonate salts were added in toluene at 80 °C with $Pd(dba)_2$ and XPhos as the catalysts. K_2CO_3 and Cs_2CO_3 provided the highest yields (Table 1, entries 1–4). $K_3PO_4{\cdot}3H_2O$ had almost the same effect (Table 1, entry 5). Other bases such as *t*-BuOK, $NaHCO_3$, CsOPiv, DIPEA, and Et_3N were also tested demonstrating inferior results (Table 1, entries 6–10). Finally, we also found that the very freshly prepared carbonate **2a** can be used directly to give the corresponding allene **3aa** in 80% NMR yield without the addition of any base (Table 1, entry 11). However, 1.0 equiv. of base was required for the (slightly) aged **2a**.

Then, a range of different phosphine ligands were screened. The use of PPh_3 and dppp led to complicated results (Table 2, entries 1 and 2). When other phosphine ligands such as PCy_3, dppf, dppm, LB-Phos and Gorlos-Phos were used, the starting material **2a** was recovered in 36–75% with no product **3aa** being observed (Table 2, entries 3–7). Fortunately, SPhos and *rac*-BINAP resulted in a moderate yield of product **3aa** with 5–10% yield of **2a** remaining (Table 2, entries 8 and 9). Finally, it was observed that XPhos was still the best ligand, which provided the allene product in 80% yield and no **2a** was recovered (Table 2, entry 10).

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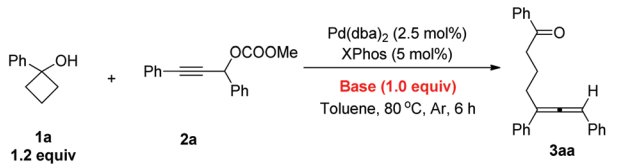
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9qo00192a

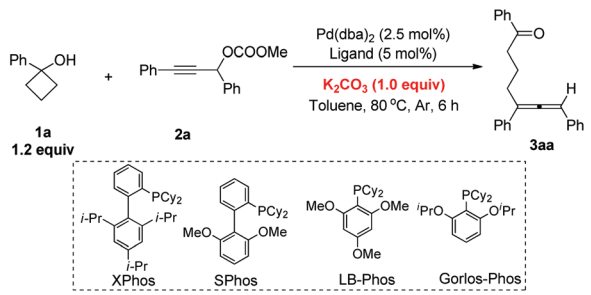
Table 1 The effect of base[a]



Entry	Base	NMR yield of **3aa** [b] (%)	Recovery of **2a** [b] (%)
1	Li_2CO_3	59	3
2	Na_2CO_3	54	10
3	K_2CO_3	80	0
4	Cs_2CO_3	80	0
5	$K_3PO_4{\cdot}3H_2O$	79	0
6	*t*-BuOK	Complicated	—
7	$NaHCO_3$	55	12
8	CsOPiv	0	96
9	DIPEA	51	12
10	Et_3N	61	3
11[c]	—	80	0

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and base (1.0 equiv.) in toluene (1.0 mL) at 80 °C. [b] NMR yield with CH_2Br_2 as the internal standard. [c] The carbonate **2a** was used immediately after chromatography on silica gel; reaction time: 3 h.

Table 2 The effect of ligand[a]



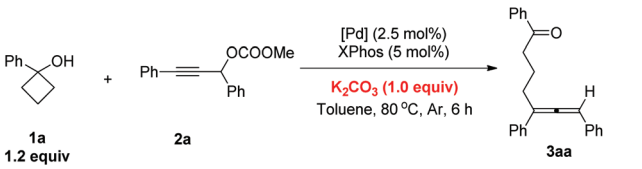
Entry	Ligand	NMR yield of **3aa** [b] (%)	Recovery of **2a** [b] (%)
1	PPh_3	Complicated	—
2	dppp	Complicated	—
3	PCy_3	0	75
4	dppf	0	74
5	dppm	0	36
6	LB-Phos	0	63
7	Gorlos-Phos	0	39
8	SPhos	56	10
9	*rac*-BINAP	63	5
10	**XPhos**	**80**	**0**

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (2.5 mol%), ligand (5.0 mol%), and K_2CO_3 (1.0 equiv.) in toluene (1.0 mL) at 80 °C. [b] NMR yield with CH_2Br_2 as the internal standard.

Subsequently, with XPhos as the optimal ligand, Pd(II) salts were tested. Different Pd(II) sources such as $Pd(OAc)_2$, $PdCl_2$ and $Pd(TFA)_2$ gave 9–28% yields of product **3aa** with 31–81% recovery of the starting material **2a** (Table 3, entries 2–4).

Considering the convenience, $K_3PO_4{\cdot}3H_2O$ was used as the base for further study. Solvents were further screened. THF, dioxane, CH_3CN and DCM all gave the desired product **3aa** albeit with lower yields (49–69%, Table 4, entries 2–5). When DMF was used, the reaction was complicated and 14% of **3aa** was observed (Table 4, entry 6).

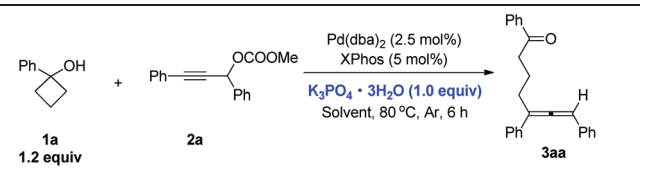
Table 3 The effect of Pd-catalyst[a]



Entry	[Pd]	NMR yield of **3aa** [b] (%)	Recovery of **2a** [b] (%)
1	**$Pd(dba)_2$**	**80**	**0**
2	$Pd(OAc)_2$	28	31
3	$PdCl_2$	13	73
4	$Pd(TFA)_2$	9	81

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), [Pd] (2.5 mol%), XPhos (5.0 mol%), and K_2CO_3 (1.0 equiv.) in toluene (1.0 mL) at 80 °C. [b] NMR yield with CH_2Br_2 as the internal standard.

Table 4 The effect of solvent[a]



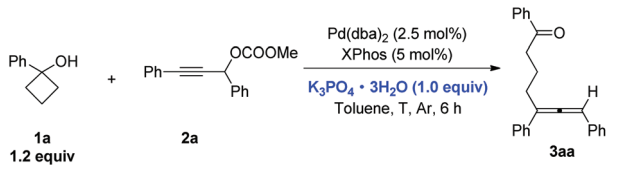
Entry	Solvent	NMR yield of **3aa** [b] (%)	Recovery of **2a** [b] (%)
1	**Toluene**	**79**	**0**
2	THF	69	0
3	Dioxane	61	0
4	CH_3CN	56	0
5	DCM	49	0
6	DMF	14	—

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and K_2CO_3 (1.0 equiv.) in solvent (1.0 mL) at 80 °C. [b] NMR yield with CH_2Br_2 as the internal standard.

Finally, lowering the temperature to 70 °C or 60 °C can both provide 81% yield of **3aa** (Table 5, entries 2 and 3). However, the reaction at 60 °C on 1 mmol scale led to the minor recovery of the propargylic carbonate **2a**. Decreasing the temperature further to 50 °C resulted in a lower yield of **3aa** with 53% recovery of the starting material **2a** (Table 5, entry 4).

With the optimized reaction conditions above (Table 5, entry 2), the substrate scope of various cyclobutanols **1** with the propargylic carbonates **2a** was investigated. All the reactions were carried out on 1 mmol scale and the results are summarized in Scheme 2. When R^1 is an aryl group, besides phenyl, the substituent group on the phenyl group can be either an electron-withdrawing group (F, Cl) or an electron-donating group (OMe), providing the allene products in 50–79% yields (Scheme 2, **3aa–3ga**). In addition, the substituents on the phenyl rings at the *ortho*, *meta*, and *para* positions

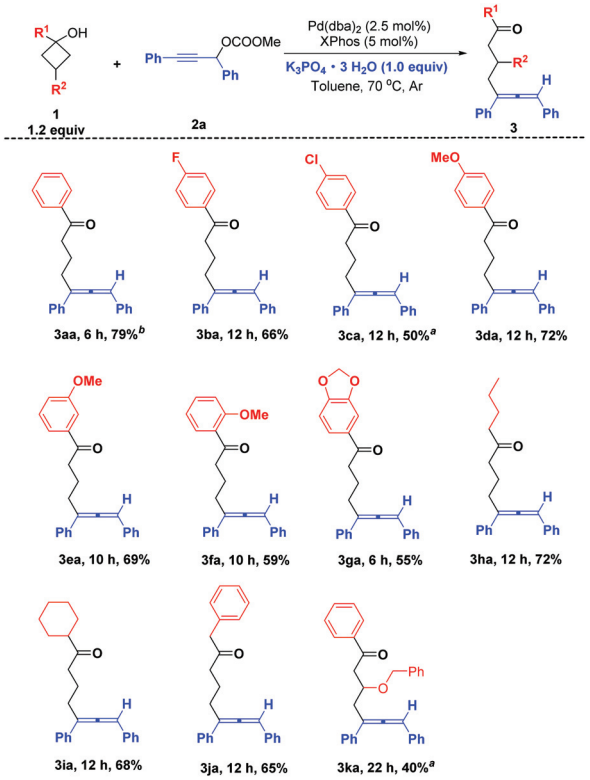
Table 5 The effect of temperature[a]



Entry	Temperature	NMR yield of **3aa** [b] (%)	Recovery of **2a** [b] (%)
1	80	79	0
2	**70**	**81**	**0**
3	60	81	0
4	50	31	53

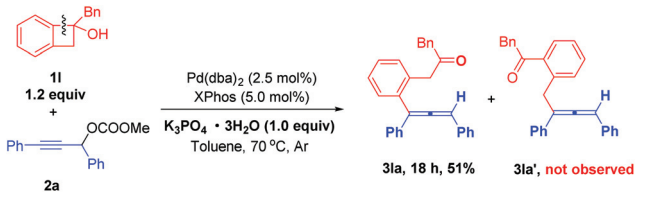
[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and K_2CO_3 (1.0 equiv.) in toluene (1.0 mL). [b] NMR yield with CH_2Br_2 as the internal standard.

may all be tolerated (Scheme 2, **3da–3fa**). And the piperonyl group can be tolerated well providing 55% yield of **3ga**. Except for the aryl group, R^1 can be different alkyl groups such as *n*-butyl, cyclohexyl and benzyl to provide the desired allene products in 65–72% yields (Scheme 2, **3ha–3ja**). The reaction also worked with a cyclobutanol with an additional substituent group at the 3-position providing the expected product **3ka** with 40% yield (Scheme 2).



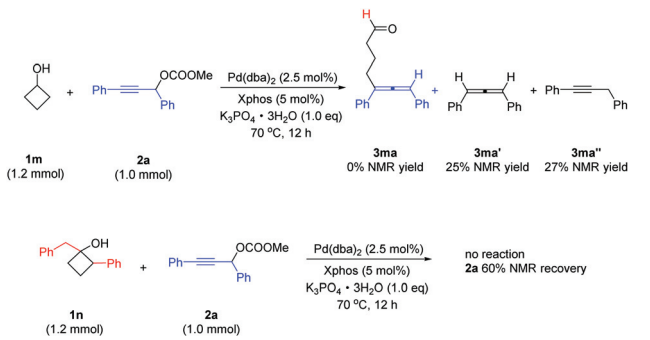
Scheme 2 Substrate scope with respect to cyclobutanols. Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and $K_3PO_4{\cdot}3H_2O$ (1.0 equiv.) in toluene (5.0 mL) at 70 °C. [a] $Pd(dba)_2$ (5.0 mol%) and XPhos (10.0 mol%) were used. [b] Byproduct, 1,3-dipenylpropadiene, was formed in 4% NMR yield.

Notably, when benzocyclobutanol **1l** was used in the reaction, product **3la** with the cleavage of the proximal bond was selectively generated in 51% yield, and the distal bond cleavage product **3la′** was not observed (Scheme 3).



Scheme 3 The reaction of benzocyclobutanol. Reaction conditions: **1l** (1.2 mmol), **2a** (1.0 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and $K_3PO_4{\cdot}3H_2O$ (1.0 equiv.) in toluene (5.0 mL) at 70 °C.

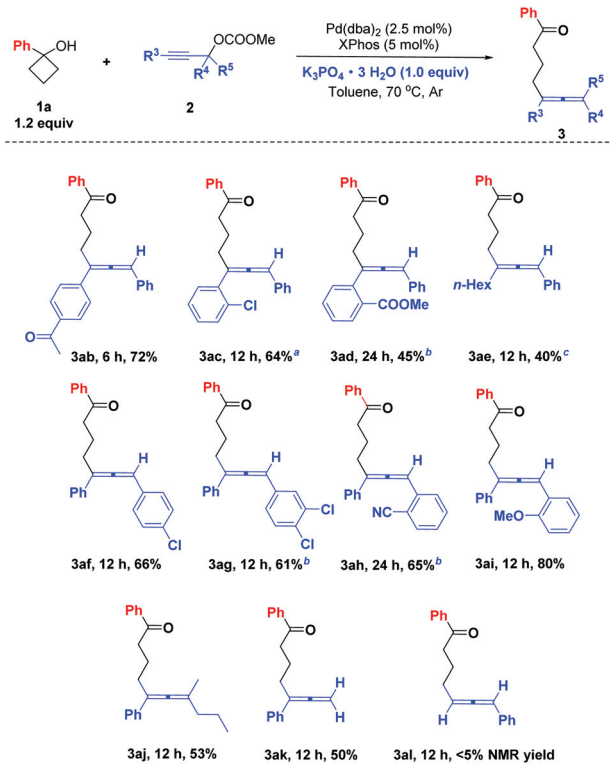
However, when R^1 = H, the reaction did not provide the expected product **3ma**, instead, by-products 1,3-diphenylpropadiene **3ma′** and 1,3-dipenylpropyne **3ma″** were formed in 25% and 27% NMR yields, respectively.[4] The reaction of the cyclobutanol **1n**, which has an additional substituent at the 2-position, gave no allene product with 60% recovery of the starting material **2a** (Scheme 4).



Scheme 4 Failed substrates of cyclobutanols.

Next, the scope of propargylic carbonates **2** was also tested. When R^5 is H, R^3 and R^4 substituents can be different aryl or alkyl groups. For example, 4-acetyl, 2-chloro, and 2-methoxycarbonyl substituted phenyls at the R^3 position were tolerated providing the allene products **3ab–3ad** in 45–72% yields. When R^3 was *n*-hexyl, it could result in 40% yield of **3ae** by decreasing the amount of **1a** to 1.0 mmol and increasing the amount of propargylic carbonate **2e** to 1.5 mmol. And 4-chloro, 3,4-dichloro, 2-cyano and 2-methoxy substituted phenyls could be introduced successfully to the R^4 position to give the final products **3af–3ai** in 61–80% yields. It should be noted that the catalyst loading should be improved to 5 mol% for **3ac**, **3ad**, **3ag** and **3ah** to make sure the complete consumption of the starting carbonates. Notably, besides the secondary propargylic carbonates, tertiary propargylic carbonates (R^2 = Ph, R^3 = ^{n}Pr, R^4 = Me) could also be used to afford the

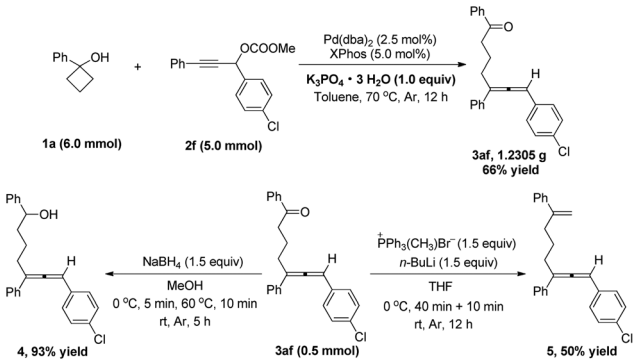
fully substituted allene product **3aj** in a moderate yield. Besides, when $R^4 = R^5 = H$, the reaction afforded **3ak** with 50% yield. However, when $R^3 = H$, the corresponding allene product **3al** was formed in a very low yield (<5% by ^1H NMR) (Scheme 5).



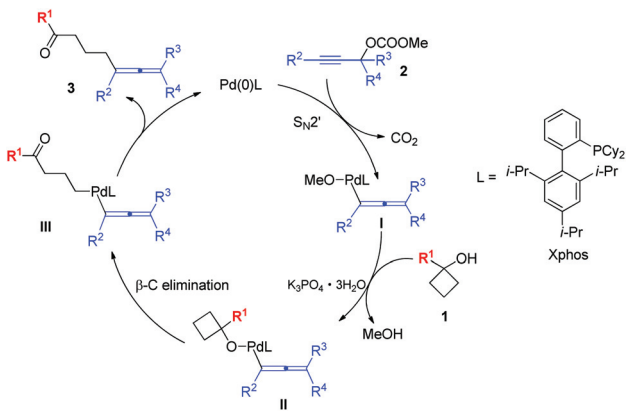
Scheme 5 Substrate scope with respect to propargylic carbonates. Reaction conditions: **1a** (1.2 mmol), **2** (1.0 mmol), $Pd(dba)_2$ (2.5 mol%), XPhos (5.0 mol%), and $K_3PO_4{\cdot}3H_2O$ (1.0 equiv.) in toluene (5.0 mL) at 70 °C. [a] **1a** (1.0 mmol), **2** (1.2 mmol), $Pd(dba)_2$ (5.0 mol%) and XPhos (10.0 mol%) were used. [b] $Pd(dba)_2$ (5.0 mol%) and XPhos (10.0 mol%) were used. [c] **1a** (1.0 mmol) and **2** (1.5 mmol) were used.

In order to demonstrate the synthetic utility and practicality of the method, the allene product **3ab** was synthesized on a gram scale. A 5.0 mmol scale reaction was carried out providing 1.2305 g of the desired product **3ab** in 66% isolated yield. And the allene product **3ab** can be subjected to some transformations. For example, it can be reduced to the secondary alcohol **4** with $NaBH_4$, and reacted with the Wittig reagent producing product **5** (Scheme 6).

Based on the previous experimental results and knowledge,[4,9] a possible mechanism was proposed as shown in Scheme 7. Firstly, the propargylic carbonate **2** reacted with Pd(0) *via* S_N2'-type oxidative addition together with the elimination of a molecule of CO_2, which leads to the allenyl palladium methoxide intermediate **I**. Then intermediate **I** underwent ligand exchange with cyclobutanol **1** generating intermediate **II**, which would provide intermediate **III** by β-C elimination. Intermediate **III** delivered the final product **3** *via* reductive elimination and regenerated the Pd(0) species completing the catalytic cycle.



Scheme 6 Gram-scale reaction and synthetic utility.



Scheme 7 The proposed mechanism.

Conclusions

In summary, an efficient method to synthesize different multi-substituted δ-allenyl ketones *via* palladium-catalyzed ring opening of cyclobutanols and oxidative addition of propargylic carbonates was developed. This reaction had a wide substrate scope with tolerance to different functional groups, and this method may be easily expanded to gram scale synthesis with potential synthetic utility.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Basic Research Program of China (2015CB856600) and the National Natural Science

Foundation of China (21502020) is greatly appreciated. We thank Yifan Cui of our group for reproducing the results of **3ca**, **3ga**, and **3ab** represented in this study.

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