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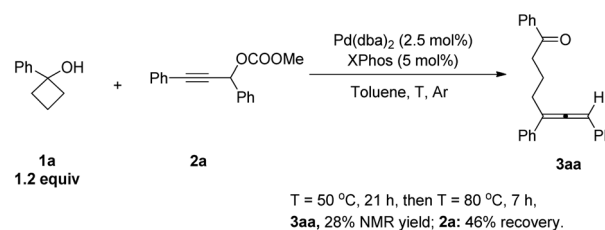
Pd-Catalyzed coupling reaction of cyclobutanols with propargylic carbonates†

Penglin Wu,^a Minqiang Jia^{*a} and Shengming Ma  ^{*a,b}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 reagents 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 cyclobutanones⁵ 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, respectively⁸).

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

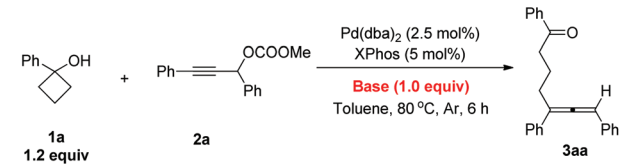
Results and discussion

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. K₂CO₃ and Cs₂CO₃ provided the highest yields (Table 1, entries 1–4). K₃PO₄·3H₂O had almost the same effect (Table 1, entry 5). Other bases such as *t*-BuOK, NaHCO₃, CsOPiv, DIPEA, and Et₃N 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 PPh₃ and dppp led to complicated results (Table 2, entries 1 and 2). When other phosphine ligands such as PCy₃, 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).

^aResearch Center for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P. R. China^bState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China. E-mail: masm@sioac.ac.cn

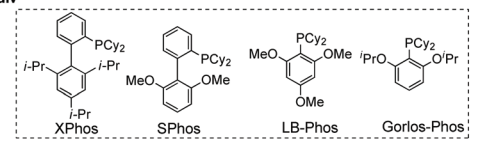
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9qo00192a

Table 1 The effect of base^a


Entry	Base	NMR yield of 3aa ^b (%)	Recovery of 2a ^b (%)
1	Li ₂ CO ₃	59	3
2	Na ₂ CO ₃	54	10
3	K ₂ CO ₃	80	0
4	Cs ₂ CO ₃	80	0
5	K ₃ PO ₄ ·3H ₂ O	79	0
6	<i>t</i> -BuOK	Complicated	—
7	NaHCO ₃	55	12
8	CsOPiv	0	96
9	DIPEA	51	12
10	Et ₃ N	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 CH₂Br₂ 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

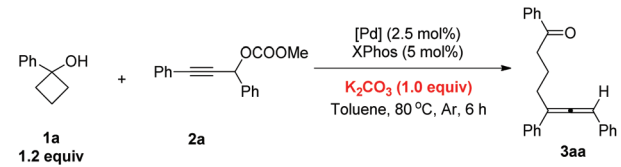


Entry	Ligand	NMR yield of 3aa ^b (%)	Recovery of 2a ^b (%)
1	PPh ₃	Complicated	—
2	dppp	Complicated	—
3	PCy ₃	0	75
4	dppf	0	74
5	dppm	0	36
6	LB-Phos	0	63
7	Gorlos-Phos	0	39
8	SPhos	56	10
9	<i>rac</i> -BINAP	63	5
10	XPhos	80	0

^a Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), Pd(dba)₂ (2.5 mol%), ligand (5.0 mol%), and K₂CO₃ (1.0 equiv.) in toluene (1.0 mL) at 80 °C. ^b NMR yield with CH₂Br₂ 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, PdCl₂ 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).

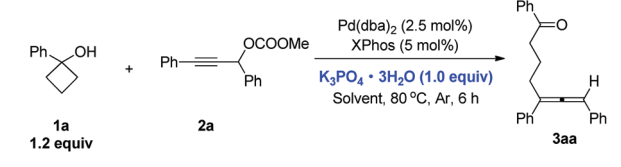
Considering the convenience, K₃PO₄·3H₂O was used as the base for further study. Solvents were further screened. THF, dioxane, CH₃CN and DCM all gave the desired product **3aa**

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 K₂CO₃ (1.0 equiv.) in toluene (1.0 mL) at 80 °C. ^b NMR yield with CH₂Br₂ as the internal standard.

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).

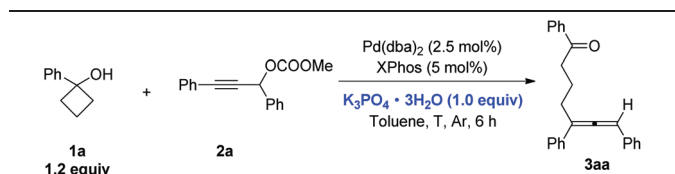
Table 4 The effect of solvent^a


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 ₃ CN	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 K₂CO₃ (1.0 equiv.) in solvent (1.0 mL) at 80 °C. ^b NMR yield with CH₂Br₂ 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).

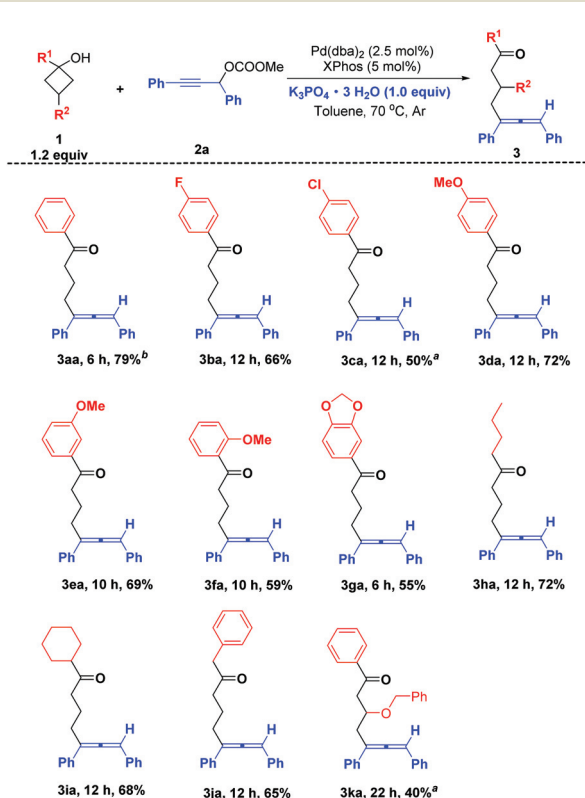
With the optimized reaction conditions above (Table 5, entry 2), the substrate scope of various cyclobutanols **1** with the propargylic carbonates **2a** was investigated. All the reactions were carried out on 1 mmol scale and the results are summarized in Scheme 2. When R¹ is an aryl group, besides 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

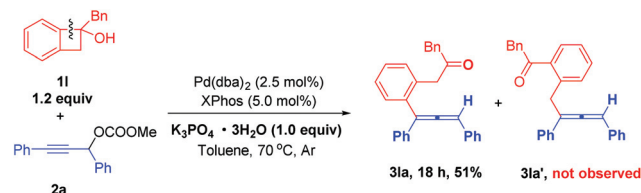
^a Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), Pd(dba)₂ (2.5 mol%), XPhos (5.0 mol%), and K₂CO₃ (1.0 equiv.) in toluene (1.0 mL). ^b NMR yield with CH₂Br₂ as the internal standard.

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, R¹ 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).



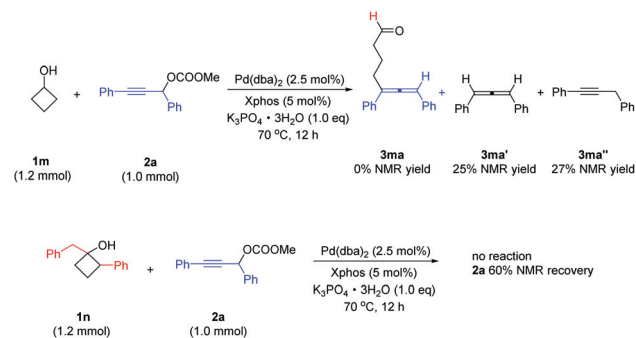
Scheme 2 Substrate scope with respect to cyclobutanols. Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), Pd(dba)₂ (2.5 mol%), XPhos (5.0 mol%), and K₃PO₄·3H₂O (1.0 equiv.) in toluene (5.0 mL) at 70 °C. ^a Pd(dba)₂ (5.0 mol%) and XPhos (10.0 mol%) were used. ^b Byproduct, 1,3-diphenylpropadiene, 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 K₃PO₄·3H₂O (1.0 equiv.) in toluene (5.0 mL) at 70 °C.

However, when R¹ = H, the reaction did not provide the expected product **3ma**, instead, by-products 1,3-diphenylpropadiene **3ma'** and 1,3-diphenylpropyne **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 R⁵ is H, R³ and R⁴ substituents can be different aryl or alkyl groups. For example, 4-acetyl, 2-chloro, and 2-methoxycarbonyl substituted phenyls at the R³ position were tolerated providing the allene products **3ab–3ad** in 45–72% yields. When R³ 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 R⁴ 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 (R² = Ph, R³ = ⁿPr, R⁴ = 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).



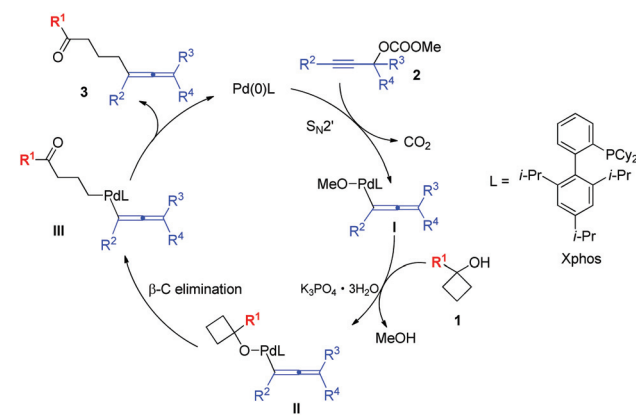
Scheme 5 Substrate scope with respect to propargylic carbonates. Reaction conditions: **1a** (1.2 mmol), **2** (1.0 mmol), Pd(dba)₂ (2.5 mol%), XPhos (5.0 mol%), and K₃PO₄·3H₂O (1.0 equiv.) in toluene (5.0 mL) at 70 °C. ^a **1a** (1.0 mmol), **2** (1.2 mmol), Pd(dba)₂ (5.0 mol%) and XPhos (10.0 mol%) 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 NaBH₄, 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 CO₂, 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



Scheme 6 Gram-scale reaction and synthetic utility.



Scheme 7 The proposed mechanism.

reductive elimination and regenerated the Pd(0) species completing the catalytic cycle.

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

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Notes and references

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