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Palladium-Catalyzed Hydroalkylation of Alkynes with Cyclopropanols: Access to γ,δ-Unsaturated Ketones

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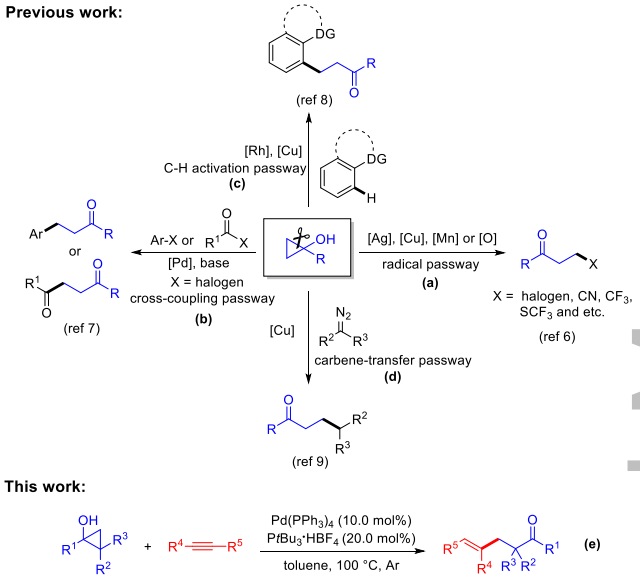
Abstract: A palladium-catalyzed hydroalkylation of alkynes with cyclopropanols has been developed. This reaction provided a straightforward way to the synthesis of γ,δ-unsaturated ketones in moderate to good yields, exhibiting high atom economy and *Z/E* selectivity. Deuterated tri-substituted alkenes could also be expediently produced by using deuterium oxide as a co-solvent.

Keywords: palladium-catalyzed; hydroalkylation; alkynes; cyclopropanols; γ,δ-unsaturated ketones

The ongoing development of transition-metal-mediated selective C-C bonds activation/cleavage methods can offer plenty of opportunities to implement novel synthetic strategies, because C-C bonds are ubiquitous in organic molecules.[1] However, the activation of C-C bonds remains challenging due to the highly inert nature of C-C bonds, resulting in an energetically unfavorable reaction compared to the activation of C-H bonds.[2] Over the past decades, considerable attention has been focused on searching for new means of activating C-C bonds.[3] By taking advantage of the inherent ring-strain in small rings, researchers acquired an efficient method of achieving this goal.[4]

Cyclopropanols[5] are readily available three-membered-ring structure which can be considered as the equivalents of homoenolates. They have been used in many cross-coupling reactions to construct β-functionalized ketones through C-C bonds cleavage. In this context, the radical meditated ring-opening reaction of cyclopropanols was widely explored to construct C-C, C-N and C-X (X = S, halogen) bonds (Scheme 1a).[6] Transition-metal-catalyzed cross-coupling reactions of cyclopropanols with aryl halides, benzyl halides, and acyl halides have been achieved



Scheme 1. Ring-opening transformation of cyclopropanols

by Orellana, Walsh and Cha, respectively (Scheme 1b).[7] Li and coworkers described a rhodium-catalyzed C-H activation of arenes with cyclopropanols (Scheme 1c).[8] Copper-catalyzed carbene-transfer coupling reaction of cyclopropanols with diazoesters has been realized by Wang and co-workers (Scheme 1d).[9] These pioneering works will encourage chemists to exploit more transformations of cyclopropanols, broadening their synthetic scope and functionality. To the best of our knowledge, no related work on the transition-metal-catalyzed hydroalkylation of alkynes with cyclopropanols has been realized. Functionalization of alkynes is a familiar and fundamental objective in organic synthesis, because of the availability of alkynes, as well as the widespread application of functionalized alkenes.[10] As a part of our continuous efforts to explore various transformations of alkynes,[11] herein, we will describe our latest work on the palladium-catalyzed hydroalkylation of alkynes with

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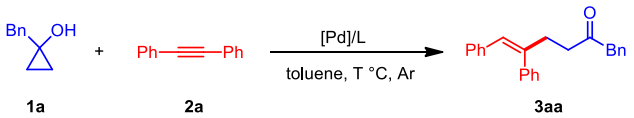
cyclopropanols to access γ,δ-unsaturated ketones (Scheme 1e).

Table 1. Optimization of reaction conditions.[a]



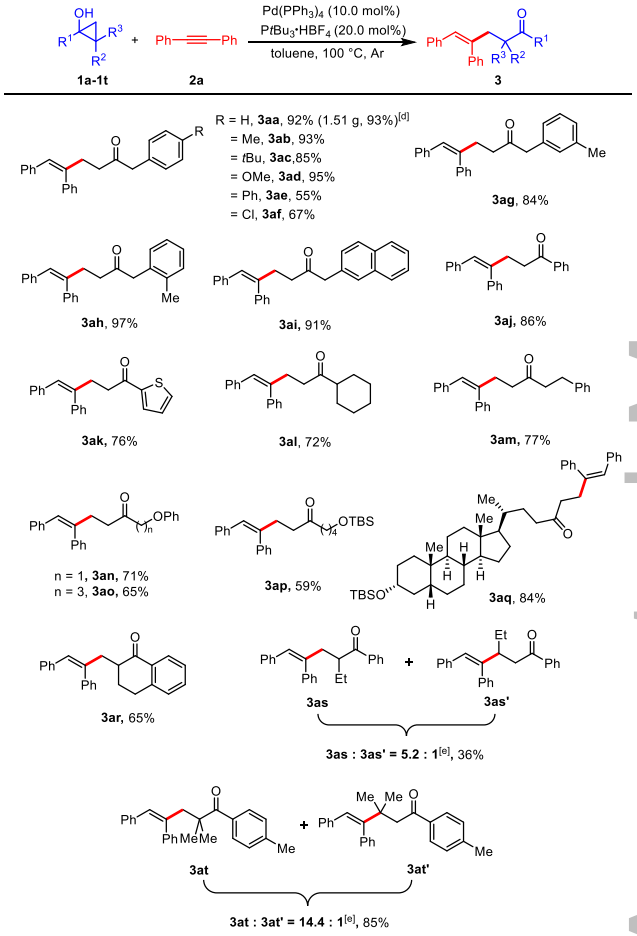
1a **2a** **3aa**

Entry	Catalyst	T	Ligand	Yield (%)[b]
1[c]	$Pd(PPh_3)_4$	80	/	26[d]
2[c]	$Pd_2(dba)_3$	80	/	trace
3[c]	$PdCl_2$	80	/	trace
4[c]	$Pd(OAc)_2$	80	/	trace
5[c]	$[Pd(allyl)Cl]_2$	80	/	trace
6[c]	$Pd(PPh_3)_4$	100	/	66
7[c]	$Pd(PPh_3)_4$	120	/	65
8	$Pd(PPh_3)_4$	100	/	79
9	$Pd(PPh_3)_4$	100	PPh_3	55
10	$Pd(PPh_3)_4$	100	Cy-JohnPhos	93
11	$Pd(PPh_3)_4$	100	dppm	N.D.
12	$Pd(PPh_3)_4$	100	dppb	<10
13	$Pd(PPh_3)_4$	100	PCy_3	89
14	$Pd(PPh_3)_4$	100	P*t*Bu$_3$·HBF$_4$	96(92)[d]
15	$Pd(OAc)_2$	100	P*t*Bu$_3$·HBF$_4$	14
16	$Pd(TFA)_2$	100	P*t*Bu$_3$·HBF$_4$	21
17	$PdCl_2(PPh_3)_2$	100	P*t*Bu$_3$·HBF$_4$	<10
18[e]	$Pd(PPh_3)_4$	100	P*t*Bu$_3$·HBF$_4$	92
19[f]	$Pd(PPh_3)_4$	100	P*t*Bu$_3$·HBF$_4$	85
20	/	100	P*t*Bu$_3$·HBF$_4$	N.D.
21	/	100	HBF_4	N.D.

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), [Pd] (10.0 mol%), ligand (20.0 mol%) in 1.0 mL toluene under argon for 24 h. N. D. = no detected.
[b] The yield was determined by ^{1}H NMR analysis.
[c] **1a** (0.25 mmol) and **2a** (0.25 mmol) were used.
[d] Isolated yield.
[e] 7.5 mol% catalyst and 15.0 mol% ligand were used.
[f] 5.0 mol% catalyst and 10.0 mol% ligand were used.

We initiated our study with 1-benzylcyclopropanol **1a** and diphenylacetylene **2a** as the model substrates. The desired coupling product **3aa** was isolated in 26% yield with $Pd(PPh_3)_4$ as the catalyst at 80 °C in toluene under an argon atmosphere (Table 1, entry 1). Other catalysts such as $Pd_2(dba)_3$, $PdCl_2$, $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$ were ineffective (Table 1, entries 2-5). Increasing the temperature resulted in higher yields (Table 1, entries 6 and 7). The product **3aa** could be achieved in 79% yield when the ratio of **1a** and **2a** was improved to 2:1 (Table 1, entry 8). Screening of additional ligands revealed that P*t*Bu$_3$·HBF$_4$ performed best and further improved the yield to 96% (Table 1, entries 9-14). When the reaction was carried out with other Pd sources and P*t*Bu$_3$·HBF$_4$, the yield of **3aa** decreased obviously (Table1, entries 15-17).[12] Decreasing the catalyst loading negatively impacted the reaction efficiency (Table 1, entries 18 and 19). The reaction did not occur under catalyst free conditions (Table 1, entries 20 and 21). Other solvents such as DMF, MeCN, THF and DMSO were inferior to toluene (see the Supporting Information (SI) for more details on the optimization of reaction conditions). The configuration of **3aa** was assigned as (*Z*) by NOE analysis and the (*E*)-isomer was not observed in the ^{1}H NMR (see SI for details).

Table 2. Substrate scope of cyclopropanols.[a, b, c]



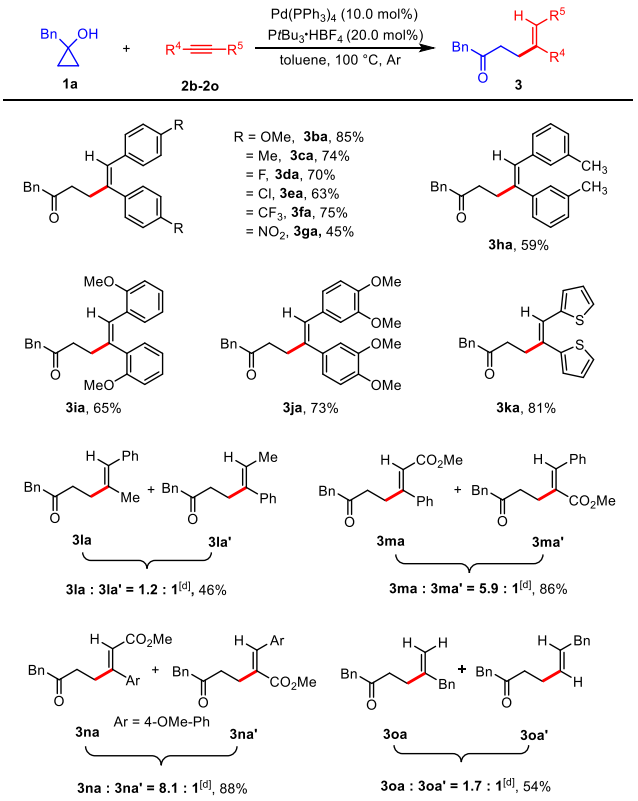
[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.25 mmol), $Pd(PPh_3)_4$ (10.0 mol%), P*t*Bu$_3$·HBF$_4$ (20.0 mol%) in 1.0 mL toluene under argon at 100 °C for 24 h.
[b] Isolated yields.
[c] *Z*/*E* ratios were determined by ^{1}H NMR analysis, *Z*/*E* > 50:1.
[d] 10.0 mmol scale.
[e] The ratio of isomers was determined by ^{1}H NMR analysis.

10.1002/adsc.201800200

With the optimized conditions in hand, we then investigated the substrate scope and generality of this reaction with a series of cyclopropanols. Results of the tests were summarized in Table 2. Benzylcyclopropanols with electron-donating or electron-withdrawing groups at the *para*-position of the benzene ring produced **3aa-3af** in moderate to good yields. The steric hindrance did not affect the reactivity, and the products **3ag** and **3ah** with a methyl group at the *meta*- or *ortho*-positon of the benzene ring were obtained in 84% and 97% yields. Product **3ai** with 2-naphthyl group was achieved in 91% yield. Phenyl-, 2-thienyl-, cyclohexyl- and phenethyl-substituted cyclopropanols all coupled with **2a** in good efficiency (**3aj-3am**). The cyclopropanols **1n-1p** containing phenyl and TBS ether groups reacted smoothly to deliver **3an**, **3ao** and **3ap** in 71%, 65% and 59% yield, respectively. Notably, lithocholic acid-derived cyclopropanol was also viable, affording **3aq** in 84% yield, which provided an efficient platform for the further functionalization of complex molecules. The bicyclic substrate **1r** underwent selective C-C bond cleavage to provide **3ar** in 65% yield. When multisubstituted cyclopropanols **1s** and**1t** were tested, a mixture of **3as**/**3as'** was achieved in 36% yield (5.2:1), and **3at**/**3at'** could be furnished in 85% yield (14.4:1). To gain insight into the utility and efficiency of the reaction, a gram-scale experiment was carried out, and the product **3aa** (1.51 g) could be achieved in 93% yield on 10.0 mmol scale.

After checking the scope and generality of the cyclopropanols, we then shifted our attention to investigating the substrate scope of alkynes (Table 3). Alkynes bearing both electron-donating and electron-withdrawing groups produced **3ba-3ga** in moderate to good yields. Products **3ha-3ja** with *meta*-methyl, *ortho*-methoxy and dimethoxy groups were achieved in 59%-73% yields. Replacing the benzene ring with thiophene ring, **3ka** was achieved with 81% yield. Moreover, asymmetric internal alkynes **2l** and **2m** were used to figure out the regioselectivity of this reaction, leading to a mixture of **3la**/**3la'** in 46% yield (1.2:1), and **3ma**/**3ma'** in 86% yield (5.9:1). Asymmetric alkyne **2n** with a methoxy group at the *para*-position of the benzene ring afforded **3na**/**3na'** in 88% yield (8.1:1). Terminal alkyne **2o** was also compatible in this reaction and offered **3oa**/**3oa'** in 54% yield (1.7:1). Aliphatic internal alkynes were inactive substrates and could not realize the transformation under the standard reaction conditions.

Table 3. Substrate scope of alkynes. [a, b, c]

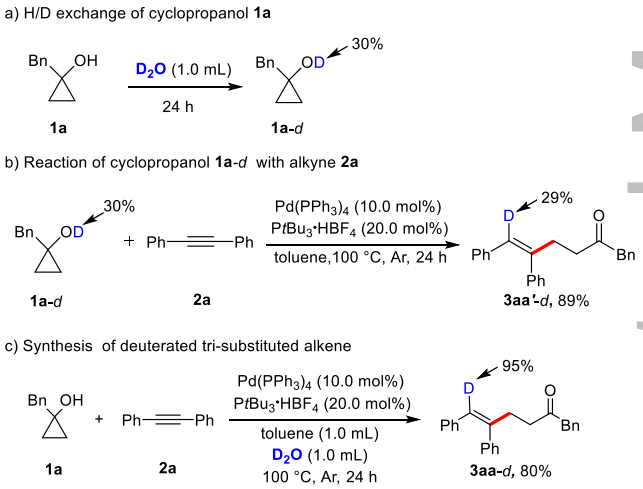


[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.25 mmol), $Pd(PPh_3)_4$ (10.0 mol%), $PtBu_3{\cdot}HBF_4$ (20.0 mol%), in toluene (1.0 mL) at 100 °C for 24 h under argon.

[b] Isolated yields.

[c] *Z*/*E* ratios were determined by ^1H NMR analysis, *Z*/*E* > 50:1.

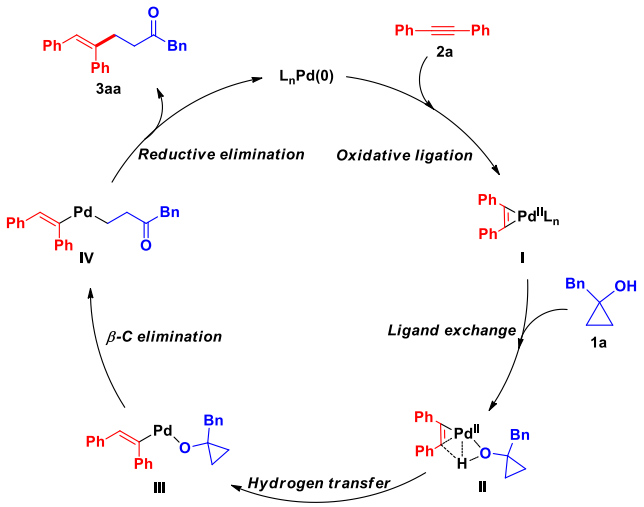
[d] The ratio of isomers was determined by ^1H NMR analysis.



Scheme 2. Further studies of the reaction.

To gain some mechanistic insight into this reaction, a deuterium-labeling experiment with cyclopropanol **1a** was performed and the deuterium ratio at the hydroxyl of cyclopropanol **1a**-*d* was 30% after stirred with deuterium oxide (D_2O) for 24 h (Scheme 2a). The reaction of **1a**-*d* (30% D) and **2a** led to the formation of **3aa'**-*d* in 89% yield with 29% deuterium ratio (Scheme 2b). When D_2O was used as a co-solvent, the deuterated product **3aa**-*d* was obtained in 80% yield with 95% deuterium ratio (Scheme 2c). We speculated that the coordination of oxygen to palladium catalyst could improve the efficiency of the H/D exchange.

On the basis of the above results of the deuterium-labeling experiments and previous works,[5d, 5e, 13] a plausible catalytic cycle of this reaction was proposed as shown in Scheme 3. Initially, the oxidative ligation of alkyne **2a** to the Pd(0) catalyst forms the complex **I**.[13e] Ligand exchange of cyclopropanol **1a** with complex **I** affords the intermediate **II**, which subsequently undergoes hydrogen transfer to afford vinylpalladium species **III**.[14] β-Carbon elimination of cyclopropanol generates homoenolate **IV**.[7a, 7c, 8] Finally, reductive elimination produces the product γ,δ-unsaturated ketone **3aa** and regenerates Pd(0) catalyst to the next catalytic cycle. Further studies to determine the mechanism are in progress in our laboratory.



Scheme 3. Proposed mechanism.

In summary, we have developed a palladium-catalyzed hydroalkylation of alkynes with cyclopropanols to construct γ,δ-unsaturated ketones through a sequence of hydrogen transfer and ring opening pathway. Various functionalized γ,δ-unsaturated ketones were obtained in moderate to good yields with high atom economy and *Z/E* selectivity. This method also provided a practical and convenient route for the assembly of deuterated tri-substituted alkenes by using D_2O as a co-solvent. Studies toward expanding the class of cyclopropanols to further diversify molecular frameworks are ongoing in our laboratory.

Experimental Section

General procedure for the synthesis of γ,δ-unsaturated Ketones: A sealed tube was charged with cyclopropanols **1** (0.5 mmol, 2.0 equiv.), alkynes **2** (0.25 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (0.025 mmol, 10.0 mol%), $PtBu_3{\cdot}HBF_4$ (0.05 mmol, 20.0 mol%), and toluene (1.0 mL). The tube is thoroughly flushed with argon. Then the reaction mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of Celite. The solution was concentrated in *vacuo* and purified by careful chromatography on silica gel with PE/EA (*v*/*v* = 100:1) to afford the desired products **3**.

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[12] When the reaction was carried out using $Pd(OAc)_2$ with different loading amounts of $Pt\mathit{Bu}_3{\cdot}HBF_4$ or $Pt\mathit{Bu}_3$, **3aa** was achieved in 14%-22% yield. When $Pd(t\mathrm{Bu}_3P)_2$ was used as a single catalyst, **3aa** could be achieved in 86% yield (see the Supporting Information (SI) for more details on the optimization of reaction conditions).

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UPDATE

Palladium-Catalyzed Hydroalkylation of Alkynes with Cyclopropanols: Access to γ,δ-Unsaturated Ketones

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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