Palladium-Catalyzed Skeletal Reorganisation of Cyclobutanones Invoving Successive C-C Bond/C-H Bond Cleavage

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Abstract

The utilization of cyclobutanones as the synthon in transition metal catalysis has been made great success. Because C(carbonyl)-C bond of cyclobutanones can be cleaved through strain release. Despite those advancements, the main catalysts in literature are Rh catalysts or Ni catalysts and the reaction with C–H bond is still underdeveloped. Herein, we realized the first palladium-catalyzed skeletal reorganisation of cyclobutanones invoving successive cleavage of C(carbonyl)-C bonds and C-H bond cleavage, which con-stitutes an rapid access to diverse indanones.

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Palladium-Catalyzed Skeletal Reorganisation of Cyclobutanones Invoving Successive C-C Bond/C-H Bond Cleavage

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Comprehensive Summary

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Keywords

Cyclobutanones | C-C Bond Cleavage | C-H bond cleavage | Palladium Catalysis | ring expansion

Background and Originality Content

Cyclobutanones have served as unique building blocks in organic synthesis because it is strained and possesses high ring strain energy.[1] Low valent transition metals can easily insert into their C(carbonyl)-C bonds to form 5-membered metallacyclopentanones, which are capable of performing various synthetic transformations to access diverse complex skeletons.[2] A well-known reactivity of the metallacyclopentanones involves the migratory insertion of π-systems such as alkynes, akenes and carbonyl functionality (Scheme 1a).

Scheme 1 Strategies for transition-metal-catalyzed C-C σ-bond activation of cyclobutanones

Despite many efforts have been made in discovery of new reactvities of cyclobutanones, there are some limitations: (1) the main catalysts enabling the oxidative cleavage of C(carbonyl)-C bonds of cyclobutanones in literature are Rh catalysts or Ni catalysts,[3,4] which hampered the exploitation of new synthetic reactions; and (2) the reaction of C–H bond with cyclobutanones under the transition metal-catalytic condition is still underdeveloped. As shown in Scheme 1b, Matsuda and co-workers presented the only example on the reaction of C–H bond with cyclobutanones involving oxidative addition of C(carbonyl)-C bond and sequential intramolecular C–H bond cleavage by use of expensive Rh-catalyst in 2015.[5] To ensure the reaction, as high as 150 °C is needed and a sub- or stoichiometric pyridine was added to serve as a directing group in situ. Their deuterium experiments proved that C–H bond cleavage step under the reaction involved intramolecular σ-complex-assisted metathesis. Encouraged by our group and Murakami's recent work on palladium-catalyzed ring expansion reactions of benzocyclobutenones that involves the oxidative addition of the C–C bond directly[6] and the versatility of Pd catalyst in C–H bond activation,[7] we wonder if C(carbonyl)-C bonds of cyclobutanones can be selectively cleaved by palladium(0) catalyst in the absence of directing group to form the five-membered palladacyclopentanones, which would trigger the successive intramolecular C–H bond activation, delivering ring expansion product. With this idea in our mind, herein, we realized the first palladium-catalyzed skeletal reorganisation of phenyl cyclobutanones involving successive cleavage of C(carbonyl)-C bonds and C-H bond cleavage, which constitutes a rapid access to diverse indanones.[8,9] Our further study indicates that the Pd-catalytic system in this reaction involves different C–H bond mechanism from Matsuda's Rh-catalytic system with different scope of substrates.

Results and Discussion

Results

We commenced the optimization of reaction conditions using diphenylcyclobutane **1a** as standard substrate (Table 1). Based on the previous works, we first evaluated transition metal catalysts that are capable of activating C-C bond of cyclobutanones in the previous works. $Rh(PPh_3)_3Cl$ and $Ni(cod)_2$ with the ligand PCy_3 or IPr were inactive in the absence of directing group (entries 1–3). We also use $Pd(OAc)_2$ as a catalyst to screen different ligands. Phosphine ligands didn't show any reactivity (entries 4–6). Encouragingly, when the NHC ligand IPr, generated in situ by the deprotonation of IPr·HCl with KO^t Bu, was used, the reaction afforded the desired product **2a** in 73% yield (entry 7). Using IMes as the ligand diminished the yield to 45% (entry 8). When $Pd(OAc)_2$ was replaced with $[Pd(allyl)Cl]_2$ or $Pd(P^t Bu_3)_2$, the yields dropped to 70% and 10%, respectively (entries 9 and 10). $Pd(PPh_3)_4$ as the catalyst would shut down the reaction (entry 11). Utilization of (IPr)Pd(allyl)Cl as the catalyst delivered product **2a** in 73% yield (entry 12). Replacing the base with NaO^t Bu or LiO^t Bu didn't promote the reactivity (entries 13 and 14). K_3PO_4 showed better activity, providing **2a** in 76% yield (entry 15). Increasing the loading of K_3PO_4 to 50 mol% improved the yield to 81% (entry 16). Reducing the amount of (IPr)Pd(allyl)Cl to 5 mol% only led to the slightly decrease of the yield (entry 17).

Table 1 Optimization of the Reaction Conditions[a]

Entry	[M]	Ligand	Base	Yield/%[b]
1	$Rh(PPh_3)_3Cl$	-	-	N.P.
2	$Ni(cod)_2$	20 mol% PCy_3	-	N.P.
3	$Ni(cod)_2$	12 mol% IPr·HCl	KO^tBu	N.P.
4	$Pd(OAc)_2$	20 mol% PCy_3	-	N.P.
5	$Pd(OAc)_2$	20 mol% PPh_3	-	N.P.
6	$Pd(OAc)_2$	20 mol% SPhos		N.P.
7	$Pd(OAc)_2$	12 mol% IPr·HCl	KO^tBu	73%
8	$Pd(OAc)_2$	12 mol% IMes·HCl	KO^tBu	45%
9	$[Pd(allyl)Cl]_2$	12 mol% IPr·HCl	KO^tBu	70%
10	$Pd(P^tBu_3)_2$	12 mol% IPr·HCl	KO^tBu	10%
11	$Pd(PPh_3)_4$	12 mol% IMes·HCl	KO^tBu	N.P.

Entry	[M]	Ligand	Base	Yield/%[b]
12	(IPr)Pd(allyl)Cl	-	KO^{t}Bu	73%
13	(IPr)Pd(allyl)Cl	-	NaO^{t}Bu	41%
14	(IPr)Pd(allyl)Cl	-	LiO^{t}Bu	N.P.
15	(IPr)Pd(allyl)Cl	-	K_3PO_4	76%
16[c]	(IPr)Pd(allyl)Cl	-	K_3PO_4	81%[d]
17[e]	(IPr)Pd(allyl)Cl	-	K_3PO_4	62%

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), metal catalyst (10 mol%), ligand (12-20 mol%), base (20 mol%) at the 100 °C for 24 h. N.P. = No Product.[b] Yields were determined by^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.[c] 50 mol% K_3PO_4 was added.[d] Isolated yield is given after chromatography.[e] 5 mol% (IPr)Pd(allyl)Cl was used.

With the optimal reaction condition in hand, we investigated the substrates scope of this reaction (Scheme 2). Cyclobutanones bearing two same aryl groups at the 3-position underwent the ring expansion reaction smoothly, affording **2a**–**c** in 81%–92% yields. When one of the phenyl rings was changed to thienyl ring, the C–H bond activation selectively occurred at more electron-rich thienyl rings instead of phenyl ring. Cyclobutanones possessing phenyl ring and methyl group were well suitable. Substrates with electron-donating or electron-withdrawing groups at *para* or *ortho* -position of phenyl ring furnished the desired products **2g**–**f** in 42–84% yields. The phenyl ring can be replaced with 1-naphthyl ring to give **2j** in 62% yield, wherein the C–H bond at 2-position of the naphthyl ring was activated. Besides, the methyl group can also be replaced with ethyl and benzyl groups as well, providing the indanones **2k**–**m** . The cyclobutanones bearing a hydrogen atom and a phenyl ring at the 3-position also underwent the desired transformation to offer**2n**–**s** in 30%–56% yields. Compared to the **2n** , introducing electron-donating (**2o** and **2p**) or electron-withdrawing groups (**2r** and **2s**) at*para* -position of phenyl ring could promote the reactivity. Interestingly, when the two substituents at 3-position are benzyl group, the cyclobutanone would undergo ring expansion from a four-membered ring to form a six-membered ring and gave 1-tetralone **2t** in 74% yield, which indicates the process involving C–H bond activation occurred at the *ortho* -position of phenyl ring of benzyl group.

Scheme 2 Substrate scope for this reaction. Unless otherwise specified, the reaction was performed under optimized condition: diphenylcyclobutane **1a** (0.2 mmol, 1.0 equiv.), (IPr)Pd(allyl)Cl (0.02 mmol, 10 mol%), K_3PO_4 (0.1 mmol, 50 mol%) in PhMe (2 mL) at 100 degC for 24 h.[a] 120 degC. [b] 20 mol% K_3PO_4 was used.

To investigate the reaction mechanism, we performed several control experiments. **1a-d_{10}** with two fully deuterated phenyl rings was subjected to the standard condition and 2a-d10 was obtained in 65% yield (Scheme 3a). The deuterium atom at the ortho-position of phenyl rings didn't transferred to the methyl group of**2a-d_9** , which isn't consistent with the previous Rh-catalytic system. Therefore, the pathway involving intramolecular C–C/C–H σ-bond metathesis could be excluded. Next, we performed the reaction in the presence of D_2O, the mixture of four products was obtained in 75% total yield (Scheme 3b). It indicates that the reaction may undergo protodemetalation process, the proton on methyl comes from the reaction system. The competition experiment was also conducted between **1a** and **1a-d_{10}**(Schem 3c). This weak kinetic isotope effect implied that C-H activation might be not the rate-determining step. It is worth mentioning that when cutting the reaction time to 5 h, no product was detected. It might can attribute to the need of a long induction period for C-C bond cleavage.

Scheme 3 Mechanistic experiments.

On the basis of deuterization experiments and litereature's reports, we propose that the reaction is initiated by the oxidative C–C bond cleavage of clobutenone **1a** to give a five-membered palladacycle**A** , which would undergo an intramolecular electrophilic C-H activation to give bridged bicyclic intermediate **B** . Subsequent facile C(sp^2)-C(sp^2) reductive elimination gives the alkylpalladium species **C** , followed by protodemetalation to deliver the final product **2** .

Scheme 4 Proposed catalytic cycle.

Conclusions

In conclusion, this work for the first time demonstrates that Pd-catalyst is also capable of cleavage of C(carbonyl)-C bonds of cyclobutanones via oxidative addition, which would provide chance to find new transformations based on cyclobutanones. According to Pd-catalyzed condition, we realized the skeletal reorganisation of cyclobutanones invoving successive cleavage of C(carbonyl)-C bonds and C-H bond cleavage, delivering diverse indanones. In contrast to the previous Rh-catalytic system, the Pd-catalytic system herein involves different mechanism and features several advantages: 1) no need of directing group to facilitate the C(carbonyl)-C bond cleavage; 2) much milder reaction condition and 3) simplified work-up.

Experimental

General procedure for Palladium-catalyzed skeletal reorganisation of cyclobutanones: In an N_2-filled glovebox, an oven-dried 25-mL Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged successively with (IPr)Pd(allyl)Cl (11.4 mg, 0.02 mmol, 10 mol%), K_3PO_4 (21.2 mg, 0.1 mmol, 0.5 equiv.), cyclobutanones **1** (0.2 mmol, 1.0 equiv. If the compound is an oil, then it will be injected into the reaction after adding the solvent) and PhMe (2 mL). The tube then was sealed with a Teflon screw cap, moved out of the glovebox, and reacted at the assigned temperature with vigorous stirring. After 24 h, the reaction mixture was cooled to room temperature, and the solvent was evaporated under vacuum to give the crude product. The resulting residue was purified by silica gel flash column chromatography to afford the corresponding indanones**2** .

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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