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Authors: Ling Chen, Fengna Sun, Yuli Sun, Zheng Xu, Zhan-Jiang Zheng, yuming cui, jian cao, and Li-Wen Xu

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Palladium-Catalyzed Ring-Opening of 2-Alkylidenecyclobutanols: Stereoselective Synthesis of γ,δ -Unsaturated Ketones by C-C Bond Cleavage

Ling Chen,^a Feng-Na Sun,^a Yu-Li Sun,^a Zheng Xu,^a Zhan-Jiang Zheng,^a Yu-Ming Cui,^a Jian Cao,^{a,*} and Li-Wen Xu^{a,*}

^a Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, No 1378, Wenyi West Road, Science Park of HZNU, Hangzhou 311121, People's Republic of China
Fax: (+86)-571-2886-5135; phone: (+86)-571-2886-5135; e-mail: caojian@hznu.edu.cn or liwenxu@hznu.edu.cn

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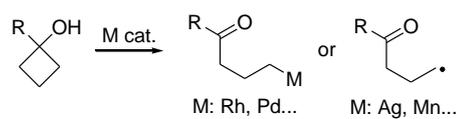
Abstract. A facile synthesis of γ,δ -unsaturated ketones via palladium-catalyzed ring-opening of 2-alkylidenecyclobutanols with organic halides is described. The key step involves C_{sp^3} - C_{sp^2} bond cleavage via palladium-catalyzed β -carbon elimination. The desired γ,δ -unsaturated ketones are obtained in good to excellent yields and broad functional group tolerability. Aryl, heteroaryl, benzyl, and alkynyl halides all readily participate to forge tri-substituted carbon-carbon double bond in a stereoselective manner.

Keywords: C-C activation; palladium-catalysis; β -carbon elimination; C-C coupling

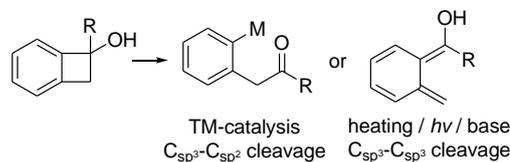
Transition metals catalyzed selective C-C bond cleavage ranks among the most challenging goals in organometallic chemistry.^[1] In this context, small ring organic molecules such as cyclobutanols exhibit unique reactivity towards C-C bond cleavage due to the driving force provided by the release of the inherent ring strain.^[2] Rh- and Pd-catalyzed β -carbon elimination strategy has been shown to be particularly effective for C-C bond cleavage of cyclobutanols.^[3-4] Recently, Ag- and Mn-catalyzed radical-mediated ring-opening of cyclobutanols has also been achieved (Scheme 1, a).^[5] On the other hand, benzocyclobutenols, a special class of cyclobutanol derivatives, undergo C_{sp^3} - C_{sp^2} bond cleavage under Rh- or Pd-catalysis while C_{sp^3} - C_{sp^3} bond cleavage dominates upon heating, photo irradiation, or treatment with a base (Scheme 1, b).^[6] Alkylidenecyclopropane and alkylidenecyclobutane derivatives are interesting structures that have been intensively investigated.^[7] In contrast, 2-alkylidenecyclobutanols, combined with alkylidenecyclobutanes and cyclobutanols, have drawn little attention. In particular, transition metals catalyzed ring-opening of 2-alkylidenecyclobutanols has not been explored. We hypothesize that 2-

alkylidenecyclobutanols would participate Pd-catalyzed cross-coupling with organic halides, leading to γ,δ -unsaturated ketones via selective C_{sp^3} - C_{sp^2} bond cleavage (Scheme 1, c).

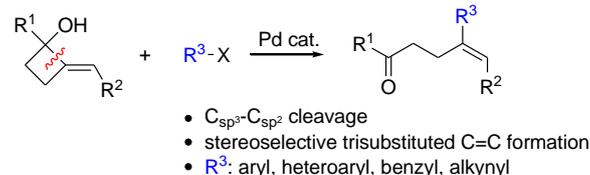
(a) Ring-opening of cyclobutanols



(b) Ring-opening of benzocyclobutenols



(c) This work: Pd-catalyzed ring-opening of 2-alkylidenecyclobutanols



Scheme 1. Ring-opening of cyclobutanol derivatives via C-C bond cleavages.

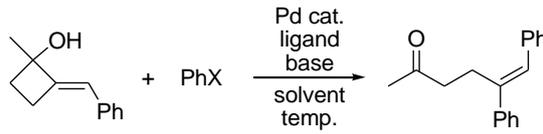
Unsaturated ketones ubiquitously exist in natural products and pharmaceuticals. Compared with α,β - and β,γ -unsaturated ketones, the synthetic routes to access γ,δ -unsaturated ketones are still limited. Conventional approaches to γ,δ -unsaturated ketones involve Claisen-type rearrangements and copper-promoted enone alkenylation.^[8] Several novel methods have been reported recently, such as Ni-catalyzed reductive coupling of enones and alkynes,^[9] Pd-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with allylic alcohols,^[10] and Pd-catalyzed ring-opening of 2-

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alkylidenecyclobutanones with arylboronic acids.^[11] Herein, we report our strategy for the stereoselective synthesis of γ,δ -unsaturated ketones via Pd-catalyzed ring-opening of 2-alkylidenecyclobutanols. Notable features of our tactic include: (a) the starting materials organic halides are commercially available and 2-alkylidenecyclobutanols can be conveniently prepared via addition of Grignard reagents to easily available alkylidenecyclobutanones;^[12] (b) tri-substituted carbon-carbon double bond would be forged in a stereoselective manner; (c) aryl, heteroaryl, benzyl, and alkynyl groups could all be efficiently introduced into the products.

At the outset of our investigation, 2-alkylidenecyclobutanol **1a** and bromobenzene were selected as the model substrates to test our hypothesis. A simple catalyst system involving Pd₂(dba)₃ and XPhos, with Ag₂CO₃ as the base in toluene at 65 °C provided the expected product γ,δ -unsaturated ketone **2a** in good yield (Table 1, entry 1). Screening of the palladium source and ligands demonstrated that Pd(II) catalysts were ineffective (entries 2-3) and XPhos was superior to other common ligands such as BINAP and ^tBu₃P (entries 4-8). Solvents proved to be important as well: toluene was the best choice and other common solvents were not applicable (entries 9-12). Although the combination of Pd₂(dba)₃ and XPhos was effective, the removal of dba (dibenzylideneacetone) from the product **2a** was non-trivial. To circumvent this obstacle, Pd(PPh₃)₄ was chosen as the palladium source instead of Pd₂(dba)₃ without reducing the yield (entry 13). Ag₂CO₃ was found to be the best base although other common base such as KOH and ^tBuOK were also competent (entries 14-20). Further optimization of the reaction temperature showed that 80 °C was the best choice for this transformation and **2a** was obtained in excellent yield (entries 21-23). Use of iodobenzene or chlorobenzene in lieu of bromobenzene resulted in diminished yield (entries 24-25). The configuration of **2a** was assigned as (*E*) by comparison with the reported data^[9-10] and the (*Z*)-isomer was not observed within the detection limit of ¹H NMR, indicating the configurational retention in this ring-opening process.

Table 1. Optimization of the reaction conditions.^[a]

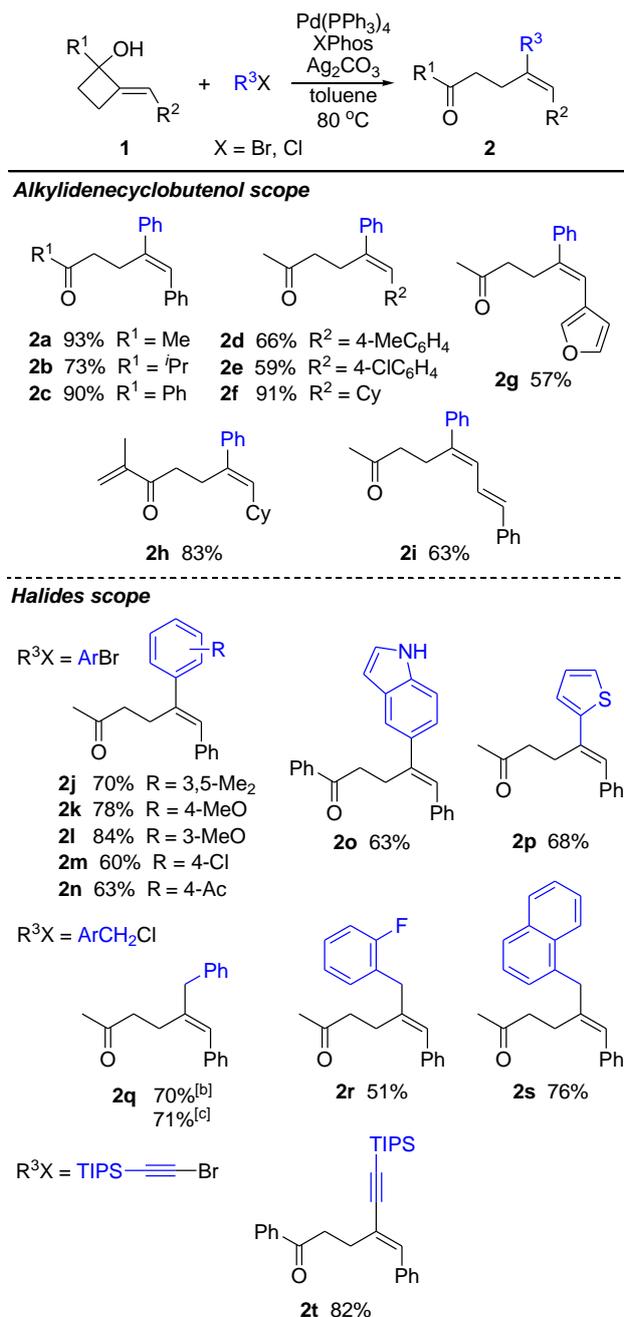


Entry	[Pd]	Ligand	Base	Solvent	Yield (%)
1	Pd ₂ (dba) ₃	XPhos	Ag ₂ CO ₃	toluene	85
2	Pd(OAc) ₂	XPhos	Ag ₂ CO ₃	toluene	NR
3	PdCl ₂	XPhos	Ag ₂ CO ₃	toluene	NR
4	Pd(PPh ₃) ₄	/	Ag ₂ CO ₃	toluene	7

5	Pd ₂ (dba) ₃	PPh ₃	Ag ₂ CO ₃	toluene	6
6	Pd ₂ (dba) ₃	BINAP	Ag ₂ CO ₃	toluene	59
7	Pd ₂ (dba) ₃	TFP	Ag ₂ CO ₃	toluene	NR
8	Pd ₂ (dba) ₃	^t Bu ₃ P	Ag ₂ CO ₃	toluene	NR
9 ^[b]	Pd ₂ (dba) ₃	XPhos	Ag ₂ CO ₃	DCE	0
10 ^[b]	Pd ₂ (dba) ₃	XPhos	Ag ₂ CO ₃	dioxane	0
11	Pd ₂ (dba) ₃	XPhos	Ag ₂ CO ₃	CH ₃ CN	trace
12	Pd ₂ (dba) ₃	XPhos	Ag ₂ CO ₃	DMF	trace
13	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	87
14	Pd(PPh ₃) ₄	XPhos	KOH	toluene	60
15	Pd(PPh ₃) ₄	XPhos	Na ₂ CO ₃	toluene	NR
16	Pd(PPh ₃) ₄	XPhos	^t BuOLi	toluene	13
17	Pd(PPh ₃) ₄	XPhos	^t BuOK	toluene	69
18	Pd(PPh ₃) ₄	XPhos	K ₂ CO ₃	toluene	60
19	Pd(PPh ₃) ₄	XPhos	KF	toluene	12
20	Pd(PPh ₃) ₄	XPhos	DBU	toluene	trace
21 ^[c]	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	7
22 ^[d]	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	93
23 ^[e]	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	73
24 ^[f]	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	71
25 ^[g]	Pd(PPh ₃) ₄	XPhos	Ag ₂ CO ₃	toluene	17

^[a] Unless otherwise specified, the reaction was carried out using **1a** (0.3 mmol), PhBr (0.36 mmol), [Pd] 5 mol%, Ligand 10 mol%, and base (0.33 mmol) in solvent (3 mL) at 65 °C under N₂ for 24 h. ^[b] Mizoroki-Heck product was found in 15~16% yield. ^[c] Room temperature. ^[d] 80 °C. ^[e] 100 °C. ^[f] 80 °C, X = I. ^[g] 80 °C, X = Cl. NR: no reaction.

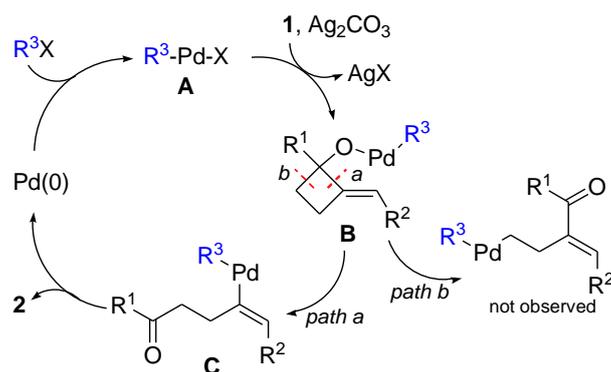
Under the optimal conditions (Table 1, entry 22), the scope and limitations of this ring-opening reaction was then examined using an array of 2-alkylidenecyclobutanols **1**. As depicted in Table 2, aryl, heteroaryl, alkyl and alkenyl groups can all be tolerated at the R¹ and R² positions (**2a-2i**).^[13] Notably, although the starting materials **1** and the products **2** contained internal and even terminal carbon-carbon double bonds, the competitive Mizoroki-Heck reaction was never observed, showing the excellent chemoselectivity of our approach. On the other hand, the scope of organic halides was also screened and a wide variety of organic halides proved to be amenable to this transformation. Aryl bromides bearing both electron withdrawing and donating groups regardless of their positions participated in the ring-opening efficiently to afford the desired products **2j-2n**. Functional groups including chloride, methoxyl and acetyl were well tolerated, thus providing ample room for further functionalization. Heteroaromatics such as unprotected indole and thiophene were compatible (**2o-2p**). To our surprise, benzyl chlorides and alkynyl bromides^[4b] were also competent substrates under the identical conditions, leading to γ -benzyl and γ -alkynyl γ,δ -unsaturated ketones **2q-2t**.

Table 2. Synthesis of γ,δ -unsaturated ketones **2**.^[a]

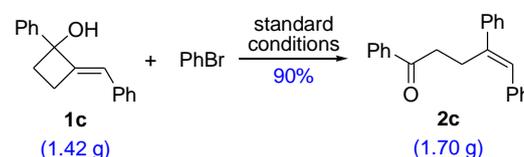
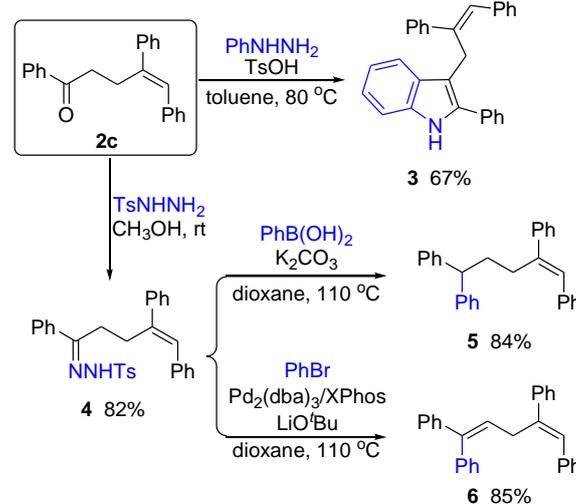
^[a] Unless otherwise specified, the reaction was carried out using **1** (0.3 mmol), R³X (0.36 mmol), Pd(PPh₃)₄ (5 mol%), XPhos (10 mol%), and Ag₂CO₃ (0.33 mmol) in toluene (3 mL) under N₂ for 24 h. ^[b] Pd₂(dba)₃ (2.5 mol%) was used. ^[c] Pd₂(dba)₃ (2.5 mol%) and benzyl bromide were used.

A plausible mechanism was proposed for the coupling-reaction as described in Scheme 2. Initially, an aryl/benzyl/alkynyl palladium species **A** would be formed by oxidative addition of R³X and Pd(0) phosphine complex. Subsequent ligand exchange with 2-alkylidenecyclobutanol **1** affords a palladium alcoholate **B** in the presence of Ag₂CO₃. Selective β -carbon elimination exclusively occurs at C_{sp³}-C_{sp²} bond (path a), leading to the intermediate **C**.^[14] Final

reductive elimination produces the product γ,δ -unsaturated ketone **2** and regenerates Pd(0) catalyst.

**Scheme 2.** Proposed reaction mechanism.

The practicality of our strategy was illustrated by the gram-scale preparation of **2c**, which was readily obtained in 90% yield under the standard conditions (Scheme 3A). The ketone group could be easily converted to various motifs. For instance, Fischer indole synthesis using phenylhydrazine in the presence of *p*-toluenesulfonic acid produced 3-allylindole **3**.^[11] Two-step protocols involving *N*-tosylhydrazone^[15] intermediate **4** lead to multi-substituted alkene **5** and 1,4-diene **6** via metal-free reductive coupling with boronic acid^[16] and Pd-catalyzed cross-coupling with aryl bromide respectively.^[17]

A. Gram-scale preparation**B. Synthetic applications****Scheme 3.** Gram-scale preparation and synthetic applications.

In summary, we have described a novel synthesis of γ,δ -unsaturated ketones via palladium-catalyzed

ring-opening of 2-alkylidenecyclobutanols with organic halides. This strategy features mild reaction conditions and broad functional group tolerability, providing an efficient entrance to aryl, heteroaryl, benzyl, and alkynyl substituted γ,δ -unsaturated ketones with excellent stereoselectivity. A plausible mechanism involving exclusive $C_{sp^3}-C_{sp^2}$ bond cleavage via palladium-catalyzed β -carbon elimination was proposed and various synthetic applications were conducted to provide structurally diverse products.

Experimental Section

Representative Procedure for the Synthesis of γ,δ -unsaturated ketones 2a

A vial was charged with 2-alkylidenecyclobutanol **1a** (52.2 mg, 0.3 mmol), Pd(PPh₃)₄ (17.3 mg, 5 mol%), XPhos (14.3 mg, 10 mol%) and Ag₂CO₃ (90.9 mg, 0.33 mmol) and evacuated under high vacuum and backfilled with N₂. Toluene (3 mL) and PhBr (56.2 mg, 0.36 mmol) were next added and the solution was stirred at 80 °C. Upon reaction completion (24 h, TLC, eluent: hexane-EtOAc, 15:1), the mixture was filtered over a plug of silica gel (washed with 50 mL EtOAc), and the filtrate was concentrated. The mobile phase for flash chromatography: hexane/ethyl acetate = 15:1. Yellow oil (70.0 mg, 93%).

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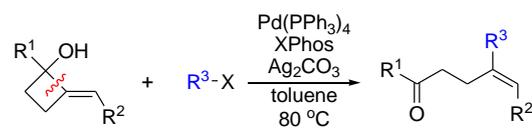
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Palladium-Catalyzed Ring-Opening of 2-Alkylidenecyclobutanols: Stereoselective Synthesis of γ,δ -Unsaturated Ketones by C-C Bond Cleavage

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- C_{sp³}-C_{sp²} cleavage
- stereoselective trisubstituted C=C formation
- R³: aryl, heteroaryl, benzyl, alkynyl