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Synthesis of 2-Alkylidenecyclopentanones via Palladium-Catalyzed Cross-Coupling of 1-(1-Alkynyl)cyclobutanols and Aryl or Vinylic Halides

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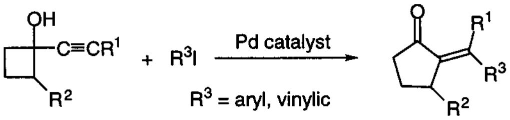
ABSTRACT



The palladium-catalyzed cross-coupling of aryl or vinylic halides and 1-(1-alkynyl)cyclobutanols affords good yields of stereoisomerically pure 2-arylidene- or 2-(2-alkenylidene)cyclopentanones, respectively, by a process involving (1) oxidative addition of the organic iodide to Pd(0), (2) carbopalladation of the triple bond of the 1-(1-alkynyl)cyclobutanol, (3) regio- and stereoselective ring expansion to form a novel palladiacycle, and (4) reductive elimination to the 2-alkylidenecyclopentanone with simultaneous regeneration of the Pd(0) catalyst.

The synthesis of 2-alkylidenecyclopentanones is important, because some natural products bearing this functionality exhibit significant biological activity.[1] A number of reactions of palladium reagents and four-membered ring compounds have been previously shown to undergo novel processes to produce ketones. For example, methylenecyclobutanes undergo palladium(II)-catalyzed ring expansion to cyclopentanones.[2] The reaction of cyclobutanols and catalytic amounts of Pd(OAc)$_2$ generates 3-alkenones.[3] The analogous palladium(0)-catalyzed reaction of cyclobutanols and aryl halides affords 4-arylalkanones.[4] Recently, 1-vinylcyclobutanols or the corresponding silyl ethers have been shown to react with palladium(II) salts to produce ring-expanded palladiocyclopentanones, which undergo either hydride elimination to unsaturated cyclopentanones[5] or further cyclization to produce unsaturated bicyclic ketones.[6] 2-(1-Alkynyl)-2-hydroxycyclobutanones undergo palladium(II)-catalyzed ring expansion to 2-alkylidene-1,3-cyclopentanediones.[7] 1-(3-Methoxycarbonyloxy-1-propynyl)cyclobutanols undergo palladium(0)-catalyzed ring expansion in the presence of phenols to produce 2-(1-aryloxyvinyl)cyclopentanones.[8] Finally, 1-allenylcyclobutanols react with aryl or vinylic halides in the presence of a palladium catalyst by a

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[1] See: Liebeskind, L. S.; Chidambaram, R.; Mitchell, D. *Pure Appl. Chem*. **1988**, *60*, 27 and references therein.

[2] Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1977**, 583.

[3] Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645.

[4] Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010.

[5] (a) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503. (b) Demuth, M.; Pandey, B.; Wietfeld, B.; Said, H.; Viader, J. *Helv. Chim. Acta* **1988**, *71*, 1392. (c) de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177. (d) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2329. (e) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74. (f) Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363. (g) Nemoto, H.; Miyata, J.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1933.

[6] (a) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett* **1994**, 599. (b) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850. (c) Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 907.

[7] (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Liebeskind, L. S.; Chidambaram, R.; Mitchell, D.; Foster, B. S. *Pure Appl. Chem.* **1988**, *60*, 27. (c) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291.

[8] Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583.

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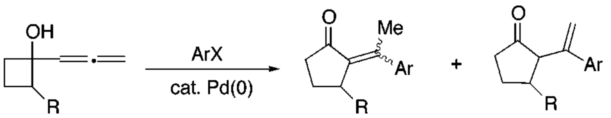
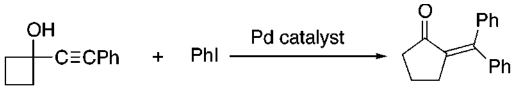
process involving carbopalladation of the allene and subsequent ring expansion of the resulting π-allylpalladium intermediate to generate unsaturated cyclopentanones (eq 1).[9]



(1)

Despite the fact that we have carried out a large number of carbopalladation reactions on 1-(1-alkynyl)cycloalkanols bearing five- or six-membered rings without any involvement of the carbocyclic ring, this latter process involving allenylcyclobutanols encouraged us to examine the possibility that 1-(1-alkynyl)cyclobutanols might undergo an analogous cross-coupling process with aryl or vinylic halides to afford 2-alkylidenecyclopentanones. We now wish to report the success of that process.

With a wide variety of 1-(1-alkynyl)cyclobutanols readily available, we focused our initial studies on the reaction of 1-(phenylethynyl)cyclobutanol (**1**) and iodobenzene as our model system (eq 2). An examination of the effect of several different palladium catalysts [Pd(PPh$_3$)$_4$, Pd(OAc)$_2$, and Pd(dba)$_2$], various inorganic and organic bases, two different chloride sources [LiCl and n-Bu$_4$NCl (TBAC)], and the ligand PPh$_3$ on the yield of cyclopentanone **2** afforded the following optimized procedure: 10 mol % of Pd(OAc)$_2$, 20 mol % of PPh$_3$, 2 equiv of aryl or vinylic iodide, 2 equiv of diisopropylethylamine as the base, and 2 equiv of n-Bu$_4$NCl are allowed to react in DMF as the solvent at 80 °C. This procedure afforded a 70% yield of cyclopentanone **2** after a 12 h reaction time (Table 1, entry 1).

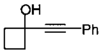
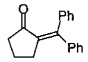
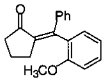
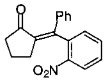
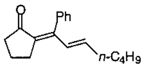
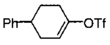
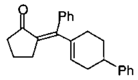
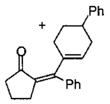
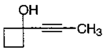
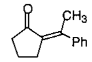
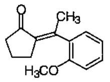
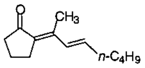
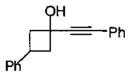
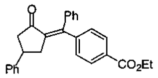
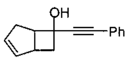
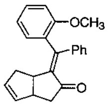
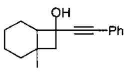
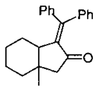


1 **2** (2)

With a standard procedure in hand, we explored the scope and limitations of this novel route to 2-alkylidenecyclopentanones by examining a wide variety of 1-(1-alkynyl)cyclobutanols and aryl or vinylic iodides as shown in Table 1. The reaction of 1-(phenylethynyl)cyclobutanol (**1**) and the electron-rich o-iodoanisole provided the corresponding 2-arylidenecyclopentanone as a single stereoisomer in good yield (entry 2). A high yield was also obtained from the electron-poor o-iodonitrobenzene (entry 3). Neither electronic effects nor steric hindrance thus appear to cause any problems. Under our standard reaction conditions for aryl iodides, phenyl triflate failed to produce any of the expected cyclopentanone product.

We also examined the possibility of employing vinylic iodides in this process. The reaction of 1-(phenylethynyl)cyclobutanol (**1**) and (E)-1-iodo-1-hexene under our standard conditions afforded the single isomeric product **5** in 40%

Table 1. Palladium-Catalyzed Cross-Coupling of 1-(1-Alkynyl)cyclobutanols and Aryl or Vinylic Iodides[a]

entry	1-(1-alkynyl)-cyclobutanol	organic iodide	product(s)	% isolated yield
1	 **1**	C_6H_5I	 **2**	70
2		o-$CH_3OC_6H_4I$	 **3**	74
3		o-$NO_2C_6H_4I$	 **4**	70
4		E-n-C_4H_9CH=CHI	 **5**	40
5			 **6a**	36
			 **6b**	35
6	 **7**	PhI	 **8**	60
7		o-$CH_3OC_6H_4I$	 **9**	63
8		E-n-C_4H_9CH=CHI	 **10**	35
9	 **11**	p-$IC_6H_4CO_2Et$	 **12**	64
10	 **13**	o-$CH_3OC_6H_4I$	 **14**	52[b]
11	 **15**	PhI	 **16**	60

[a] Unless otherwise stated, all reactions were carried out under an argon atmosphere using 1 equiv of cyclobutanol (0.5 mmol), 2 equiv of organic halide (1.0 mmol), 10 mol % of Pd(OAc)$_2$ (0.05 mmol), 20 mol % of PPh$_3$ (0.1 mmol), 2 equiv of n-Bu$_4$NCl (TBAC, 1.0 mmol), 2 equiv of i-Pr$_2$NEt (1.0 mmol), and DMF (5 mL) at 80 °C for 12 h. [b] These reactions were carried out for 6 h at 80 °C.

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[9] (a) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (b) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089.

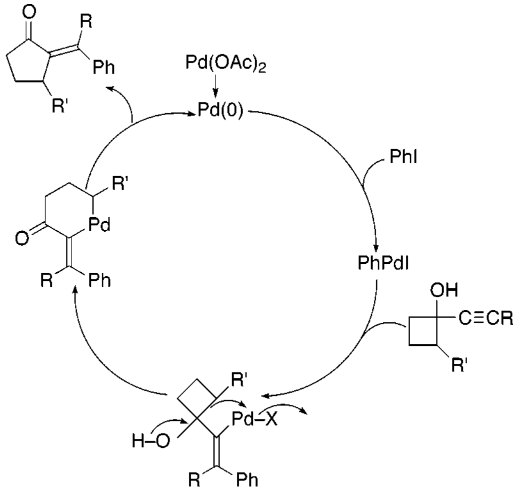
yield (entry 4). The 2D NOSEY spectrum of the product was only consistent with the carbonyl group and the new vinylic moiety being trans to each other. Surprisingly, the analogous reaction with the vinylic triflate 4-phenylcyclohex-1-enyl triflate afforded a higher yield, but the product was a 1:1 mixture of stereoisomers, which proved to be rather unstable (entry 5).

The reaction of 1-(prop-1-ynyl)cyclobutanol (**7**) and iodobenzene under our standard conditions again gave the single isomer product **8** (Table 1, entry 6). The product was characterized by 1D and 2D NMR HMQC, COSEY, and NOSEY spectroscopy. The spectra are only consistent with the structure **8** with the phenyl group trans to the carbonyl. Further examples of the reaction of 1-(prop-1-ynyl)cyclobutanol (**7**) and an aryl iodide or a vinylic iodide produced analogous ring-expanded products in slightly lower yields than those obtained with 1-(phenylethynyl)cyclobutanol (**1**) (entries 7 and 8). In both cases, a single stereoisomeric product was obtained. Good results were also obtained in the reaction between 3-phenyl-1-(phenylethynyl)cyclobutanol (**11**) and the electron-deficient aryl iodide ethyl *p*-iodobenzoate (entry 9).

To gain a better mechanistic understanding of this interesting process, we carried out reactions with two unsymmmetrical bicyclic alkynols. The reaction between 6-(phenylethynyl)bicyclo[3.2.0]hept-2-en-6-ol (**13**) and *o*-iodoanisole under our standard reaction conditions gave the single regioisomeric product **14** in good yield whose spectra are only consistent with an electron-deficient intermediate being generated in which the more substituted carbon of the cyclobutanol has undergone migration (entry 10). Similarly, the reaction of 1-methyl-7-(phenylethynyl)bicyclo[4.2.0]-octan-7-ol (**15**) and iodobenzene gave a good yield of the bicyclononanone **16** in which the more substituted neighboring carbon of the cyclobutanol has undergone exclusive migration.

On the basis of the above results and previous work,[8,9] we believe that this novel ring expansion process proceeds as shown in Scheme 1 by a sequence involving (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the aryl or vinylic iodide or triflate to Pd(0), (3) vinylic or arylpalladium coordination to the carbon−carbon triple bond of the alkynylcyclobutanol and subsequent regio- and stereoselective insertion of the alkynylcyclobutanol to form a vinylpalladium intermediate, (4) release of the cyclobutane ring strain by migration of the more highly substituted, electron-rich carbon of the cyclobutanol to palladium to produce a palladiacyclohexanone, and (5) reductive elimination to afford a single stereoisomeric 2-alkylidenecyclopentanone with simultaneous regeneration of the Pd(0) catalyst. Ring expansion to a palladiacycle nicely explains the fact that the aryl or vinylic group arising from the organic iodide always ends up trans to the carbonyl carbon. Were the cyclobutanol carbon to migrate so as to effect a direct backside displacement of the vinylic palladium, one would expect the opposite stereochemistry in the final product.

Scheme 1



In conclusion, a variety of highly substituted 2-alkylidenecyclopentanones have been prepared by the reaction of aryl or vinylic iodides and 1-(1-alkynyl)cyclobutanols in the presence of a palladium catalyst. These products are formed regio- and stereoselectively in moderate yields. The process appears to involve a novel ring expansion to a palladiacyclohexanone and subsequent reductive elimination. It would be quite difficult to prepare such products by any other present methodology.

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Supporting Information Available: The preparations of all starting 1-(1-alkynyl)cyclobutanols, the standard palladium-catalyzed cross-coupling procedure, and ^1H and ^{13}C NMR spectra for all starting cyclobutanols and cyclopentanone products in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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