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Palladium-Catalyzed Oxidative Alkynylation of Alkenes via C–C Bond Cleavage under Oxygen Atmosphere

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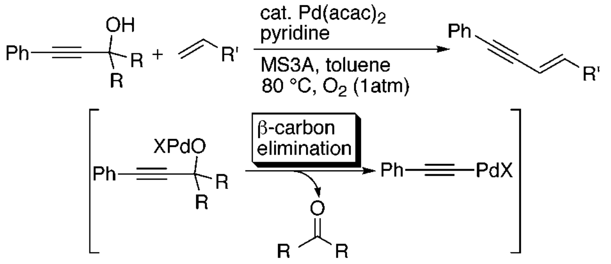
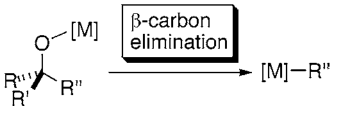
ABSTRACT



Palladium-catalyzed oxidative alkynylation of alkenes using *tert*-propargylic alcohols as alkynylation reagents via C–C bond cleavage under an oxygen atmosphere affords the corresponding ene-yne compounds.

The dealkylation reaction of a late transition metal alcoholate via *β*-carbon elimination is one of the unique processes to produce alkylmetal species for successive reactions such as *β*-hydrogen elimination and C−C bond formation affording useful organic compounds (Scheme 1). Although many reports of the C−C bond cleavage reaction have appeared in recent years,[1] examples of such dealkylation reactions catalyzed by a late transition metal are still few in number.[2] Recently, an important study by Miura and co-workers reported the arylation reaction of simple *tert*-alcohols such as α,α-dialkylarylmethanols with aryl halides using palladium catalyst, providing the corresponding biaryls via selective Csp^3−Csp^2 bond cleavage.[3]

Scheme 1



Recently, we have succeeded in the aerobic oxidation of primary and secondary alcohols to aldehydes and ketones in a Pd(OAc)$_2$/pyridine/MS3Å system.[4] We also reported the oxidative transformation[5] and arylation of *tert*-cyclobutanols[6] involving C−C bond cleavage reaction, in which *β*-carbon elimination from the palladium alcoholate is the key step.

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[1] For reviews of C−C bond cleavage reactions, see: (a) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (e) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, 1999; pp 97−129.

[2] (a) Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2352. (b) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587. (c) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147. (d) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.

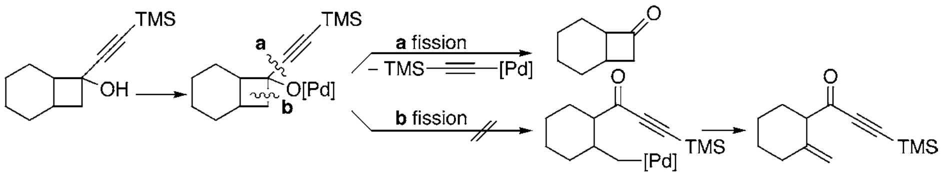
[3] Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

[4] (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750.

[5] (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455.

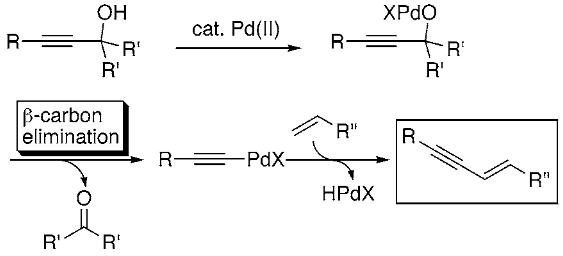
10.1021/ol0348405 CCC: $25.00

Scheme 2



In the course of the studies on the oxidative transformation of *tert*-cyclobutanols, we found the Csp^3−Csp bond cleavage (**a** fission) occurred in preference to Csp^3−Csp^3 bond cleavage (**b** fission) of the cyclobutane ring as shown in Scheme 2. Here, it is expected that an alkynylpalladium species might be produced, which may be employed for some useful organic transformations. Now we wish to report the novel palladium-catalyzed oxidative reaction of *tert*-propargylic alcohols with several alkenes to afford ene-yne compounds via selective Csp^3−Csp bond cleavage under an oxygen atmosphere as shown in Scheme 3.

Scheme 3. Working Hypothesis of Oxidative Alkynylation via C−C Bond Cleavage



First, the reaction of *tert*-alcohol **1a** or **1b** in toluene with ethyl acrylate was carried out using some palladium(II) salts in the presence of pyridine and MS3Å under oxygen (Scheme 4, Table 1). Among some palladium salts, Pd(acac)$_2$ (acac = acetylacetonate) was found to be the most effective catalyst to give the desired ene-yne-carbonyl compound **2**[7] in moderate yields (entries 3 and 5). Pyridine was the base of choice, and the presence of at least 2 equiv of pyridine to a substrate was essential for efficient reaction without the formation of metallic palladium.[5,8] That is, the reaction without pyridine did not give the desired product at all (entry 7). Furthermore, oxygen was indispensable for this oxidative reaction (entry 8).[5,8] Among the solvents examined, DMF (*N*,*N*-dimethylformamide) was useful for obtaining **2** in good yield (entry 9). It was also confirmed that the propargylic alcohol **1a** was not deprotected without palladium catalysts.

Scheme 4

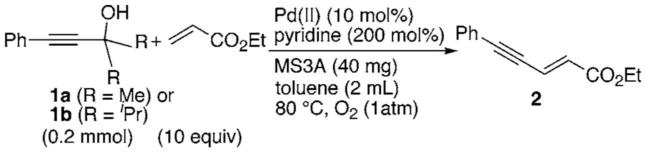


Table 1. Effect of Pd(II) Salts

entry	substrate	Pd(II) salt	time (h)	GLC yield (%)
1	**1a**	Pd(OAc)$_2$	24	30[a]
2	**1a**	PdCl$_2$	24	tr
3	**1a**	Pd(acac)$_2$	25	49[a]
4	**1b**	Pd(OAc)$_2$	48	41
5	**1b**	Pd(acac)$_2$	48	57
6	**1a**	Pd(acac)$_2$	48	57
7[b]	**1a**	Pd(acac)$_2$	24	0
8[c]	**1a**	Pd(acac)$_2$	24	4
9[d]	**1a**	Pd(acac)$_2$	48	61

[a] Isolated yield. [b] In the absence of pyridine. [c] Under N$_2$. [d] DMF was used as a solvent.

Next, several propargylic alcohols were tested to use as alkynylation reagents. Typical results are listed in Table 2. Alcohols **1a**−**e** having different substituents at the propargylic position could be used for obtaining **2** in moderate yields (Table 2, entries 1−6). In the case of the reaction of alcohols **1d** and **1e**, the formation of the eliminated ketone (3-phenylcyclobutanone or benzophenone, respectively) was confirmed (entries 5 and 6).[9] It should be noted that the Csp^3−Csp bond cleavage occurs prior to the cleavage of the *endo*-carbon of the strained cyclobutane ring (entry 5).[10] Interestingly, **2** was formed from secondary alcohol **1f**, although its yield was lower.[11] This result suggests that the Csp^3−Csp bond can be cleaved competitively with the fast β-hydrogen elimination.[12]

The alkynylation of several alkenes by propargylic alcohol **1a** was carried out (Table 3). The reaction with alkyl

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(6) (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. (b) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (c) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 3037.

(7) Other methods for the synthesis of these ene-yne carbonyl compounds have been reported. For example, see: (a) Jeffery, T. *Synthesis* **1987**, 70. (b) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558.

(8) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179.

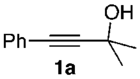
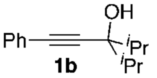
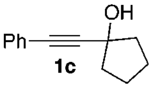
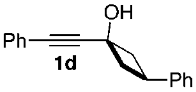
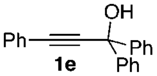
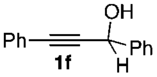
(9) Isolated yield; 3-phenylcyclobutanone (59%), benzophenone (59%).

(10) In the ring cleavage reaction of *tert*-cyclobutanols, the Csp^3−Csp^3 bonds of the cyclobutane ring were more easily and selectively cleaved than the Csp^3−Csp^2 or Csp^3−Csp^3 bond of substituents on the ring; see refs 5 and 6.

(11) The formation of 1,3-diphenyl-2-propyn-1-one was detected by GC/MS. The isolation of it was not carried out because of its instability under these reaction conditions.

(12) The fast β-carbon elimination of an alkynyl group is probably due to the strong precoordination of the π-bond of an alkyne with palladium.

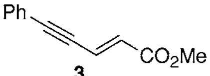
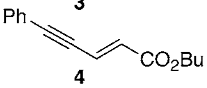
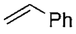
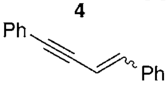
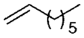
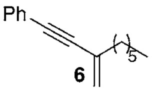
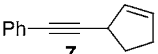
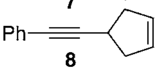
Table 2. Pd(II)-Catalyzed Reaction of Several *tert*-Propargylic Alcohols with Ethyl Acrylate

entry	alcohol	GLC yield (%) of **2**
1 2	 **1a**	57 61[a]
3	 **1b**	57
4	 **1c**	45
5	 **1d**	60[b,c]
6	 **1e**	52[c]
7 8	 **1f**	26 32[a]

[a] DMF was used as a solvent. [b] Isolated yield. [c] The formation of the corresponding eliminated ketone was also confirmed.

acrylates gave the corresponding ene-yne-carbonyl compounds **3** and **4** in moderate yields (entries 1 and 2), whereas the use of styrene gave **5** in 54% yield as an isomeric mixture. In the case of 1-octene, alkynylation occurred at an internal position of the alkenic moiety to give **6** in 33% yield. The reaction of cyclopentene gave a mixture of **7** and **8**, in which isomerization of **7** to **8** might occur by the in situ formed palladium hydride species.

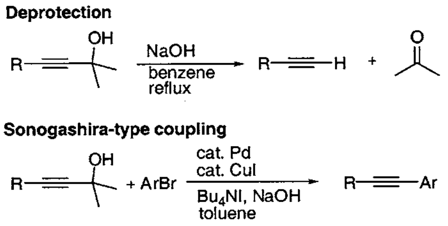
Table 3. Pd(II)-Catalyzed Reaction of **1a** with Several Alkenes[a]

entry	alkene	product	isolated yield (%)
1		 **3**	49
2		 **4**	57
4		 **5**	54[b] (*cis*/*trans* = 1/4)
5		 **6**	33[b]
6		 **7**  **8**	40 (**7**/**8** = 2/1)

[a] Reaction conditions: Pd(acac)$_2$ (10 mol %), pyridine (0.8 mmol), **1a** (0.4 mmol), alkene (4 mmol), and MS3Å (80 mg) in toluene (4 mL) at 80 °C for 48 h under O$_2$ (1 atm). [b] In DMF (4 mL).

tert-Propargylic alcohols such as 2-(2-hydroxylpropyl)-alkynes have been used as a convenient source of acetylene, because the elimination of terminal alkyne in the presence of base occurs accompanied with the formation of acetone (Scheme 5).[13] Therefore, a palladium-catalyzed Sonogashira-type reaction of aryl halides with 2-(2-hydroxylpropyl)-acetylene has been accomplished by utilizing this reactivity of 2-(2-hydroxylpropyl)alkynes, in which in situ formation of the terminal alkyne might be involved in the presence of base (Scheme 6).[14] On the other hand, our findings clearly indicate that the β-carbon elimination from the palladium alcoholate of *tert*-propargylic alcohols occurs, and to the best of our knowledge this reaction is the first example to show a Csp^3−Csp bond cleavage by palladium catalysis.[15]

Scheme 5



In summary, we demonstrated that the palladium-catalyzed oxidative alkynylation of an alkene via a Csp^3−Csp bond cleavage proceeded to afford an ene-yne compound. This oxidative reaction proceeds by the use of molecular oxygen as the sole oxidant. Although as a synthetic method our system has some substrate limitations at this stage, the present results offer a new synthetic method for ene-yne compounds by the use of C−C bond cleavage reaction.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (14750680) from the Ministry of Education, Culture, Sports, Science, Technology, Japan.

Supporting Information Available: Standard experimental procedure and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] For examples, see: (a) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763. (b) Swindell, C. S.; Fan, W.; Klimko, P. G. *Tetrahedron Lett.* **1994**, *35*, 4959. (c) Rodriguez, J. G.; Martin-Villamil, R.; Cano, F. H.; Fonseca, I. *J. Chem. Soc., Perkin Trans. 1* **1997**, 709.

[14] (a) Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337. (b) Choi, C.-K.; Tomita, I.; Endo, T. *Chem. Lett.* **1999**, 1253. (c) Chow, H.-F.; Wan, C.-W.; Low. K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910. β-Carbon elimination step might be partly involved in these reactions.

[15] Al(III)- and Zr(IV)-mediated Meerwein−Ponndorf−Verley alkynylation of aldehydes using a *tert*-propargylic alcohol has been reported, in which the reaction proceeds via a direct migration of the alkynyl moiety to a carbonyl carbon atom. (a) Ooi, T.; Miura, T.; Maruoka, K. *J. Am. Chem. Soc.* **1998**, *120*, 10790. (b) Ooi, T.; Takaya, K.; Miura, T.; Maruoka, K. *Synlett* **2000**, 69. (c) Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H.; Maruoka, K. *Tetrahedron* **2001**, *57*, 867.