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Hydrofurylation of Alkylidenecyclopropanes Catalyzed by Palladium

Itaru Nakamura, Shinichi Saito, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science
and Research Center for Organic Resource
and Material Chemistry
Institute for Chemical Reaction Science
Tohoku University, Sendai 980-8578, Japan

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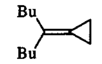
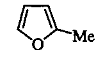
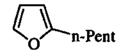
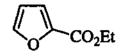
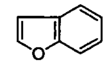
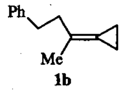
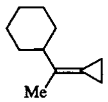
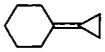
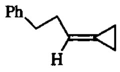
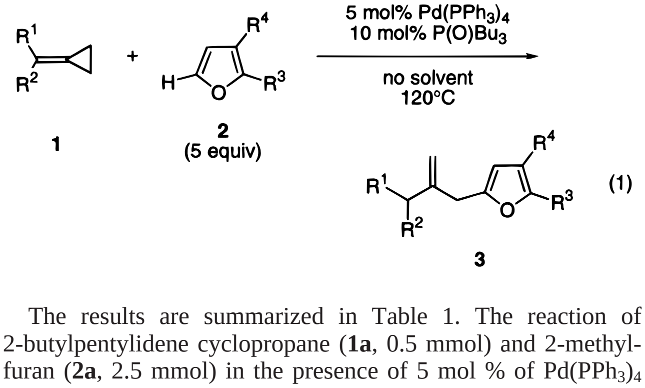
Table 1. Pd-Catalyzed Hydrofurylation of Alkylidenecyclopropanes **1**[a]

entry	1	2	time / h	3	yield[b] / %
1	 **1a**	 **2a**	28	**3a**	70
2	**1a**	 **2b**	34	**3b**	70
3	**1a**	 **2c**	19	**3c**	77
4	**1a**	 **2d**	21	**3d**	63
5	 **1b**	**2d**	28	**3e**	35
6	**1b**	**2a**	15	**3f**	68
7	 **1c**	**2a**	39	**3g**	74
8	 **1d**	**2a**	21	**3h**	65
9	 **1e**	**2a**	17	**3i**	43[c]

[a] The reaction of **1** (0.5 mmol) and **2** (2.5 mmol) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of tributylphosphine oxide without solvent at 120 °C. [b] Isolated yield based on **1**. [c] As a byproduct, $PhCH_2CH{=}CH(CH_3)C{=}CH_2$ **4** was formed in 20% yield.

The carbon−carbon bond forming reaction is one of the most important reactions in organic synthesis. Especially, addition of a carbon−hydrogen bond to a carbon−carbon unsaturated bond, so-called hydrocarbonation, is the most desirable method for this purpose, since it is an atom-economic and ecological process. Recent researches revealed that transition metal catalyst had a high potential to promote addition of a carbon−hydrogen bond of various pronucleophiles,[1] such as active methyne compounds,[2,3] aldehydes,[4] terminal alkynes,[5] and functionalized aromatic rings.[6] In continuation of our search for new hydrocarbonation reactions, we found that the carbon−hydrogen bond at the 2-position of furan derivatives can undergo the addition to the double bond of alkylidenecyclopropanes (so-called *hydrofurylation*). Previously, the C−H activation of furans with $Rh_4(CO)_{12}$ catalyst was reported,[7a] but a large excess of furans, significantly high CO pressures, and very high reaction temperatures were required. Herein, we report that palladium-catalyzed hydrofurylation of alkylidenecyclopropanes[3,8] **1** affords 2-allylfuran derivatives **3** regioselectively in good to high yields under milder conditions (eq 1).



The results are summarized in Table 1. The reaction of 2-butylpentylidene cyclopropane (**1a**, 0.5 mmol) and 2-methylfuran (**2a**, 2.5 mmol) in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of tributylphosphine oxide proceeded smoothly at 120 °C without solvent to give the corresponding 2-allylfuran derivative **3a** in 70% yield (entry 1). Other catalysts such as Pd2-

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(2) For a review, see: (a) Radhakrishnan, U.; Yamamoto, Y. *Chem. Soc. Rev.* **1999**, *28*, 199. For 1,3-dienes, see: (b) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1183. (c) Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta Chem. Scand. Ser. B* **1986**, *40*, 184. (d) Baker, R.; Popplestone, R. J. *Tetrahedron Lett.* **1978**, *38*, 3575. (e) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771. (f) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831. For allenes, see: (g) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (h) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. (i) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. For 1,3-enynes, see: (j) Gevorgyan, V.; Kadowaki, C.; Salter, M. M.; Kadota, I.; Saito, S.; Yamamoto, Y. *Tetrahedron* **1997**, *53*, 9097. For propargyl compounds, see: (k) Kadota, I.; Shibuya, A.; Gyoung, Y.-S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. For alkynes, see: (l) Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477.

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(7) (a) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, 507. A mixture of internal acetylenes, furans, and $Rh_4(CO)_{12}$ (0.05 mmol) was heated at 220 °C for 7 h under pressure of CO (25 kg/cm^2 at room temperature), giving the hydrofurylation products arising from addition of the C−H at the 2-position to the alkyne triple bond. (b) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, *40*, 2699. Furans reacted with α,β-unsaturated carbonyl compounds in the presence of $Pd(OCOR)_2$/*tert*-butyl perbenzoate to give the oxidative coupling products derived from formal dehydrogenation of the C−H at the 2-position and vinylic hydrogen.

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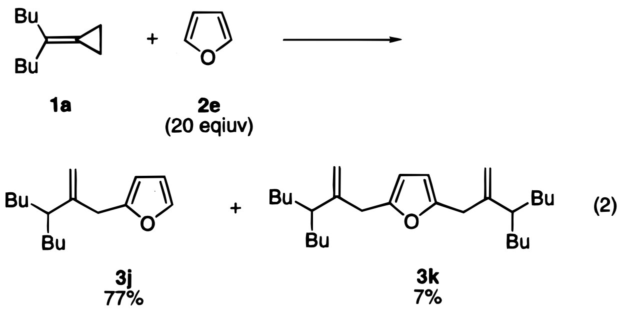
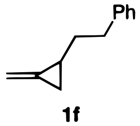
(dba)$_3$·CHCl$_3$, Pd(OAc)$_2$, and Pt(PPh$_3$)$_4$ did not promote the reaction at all. The choice of phosphine ligands is very important. Among numerous phosphine ligands examined, *tributylphosphine oxide* gave the best result; the use of other ligands afforded unsatisfactory results, and in the absence of tributylphosphine oxide the reaction was very slow. Normally, 5 equiv of furans were used. When 3 equivs of **2a** was used, the yield of **3a** decreased to 63% yield. The reaction of **1a** with 2-pentylfuran (**2b**) and ethyl 2-furoate (**2c**) gave **3b** and **3c**, respectively, in good to high yields (entries 2 and 3). The reaction of benzofuran with **1a** or 1-methyl-3-phenylpropylidenecyclopropane (**1b**) produced **3d** or **3e** in 63 or 35% yield, respectively (entries 4 and 5). The reaction of **1b**, 1-cyclohexylethylidenecyclopropane (**1c**), and cyclopropylidenecyclohexane (**1d**) with **2a** produced **3f**, **3g**, and **3h** in 68%, 74%, and 65% yield, respectively (entries 6−8). The reaction of **1e** and **2a** gave **3i** in 43% yield together with 2-methyl-5-phenyl-1,3-pentadiene (**4**) (20%, entry 9).

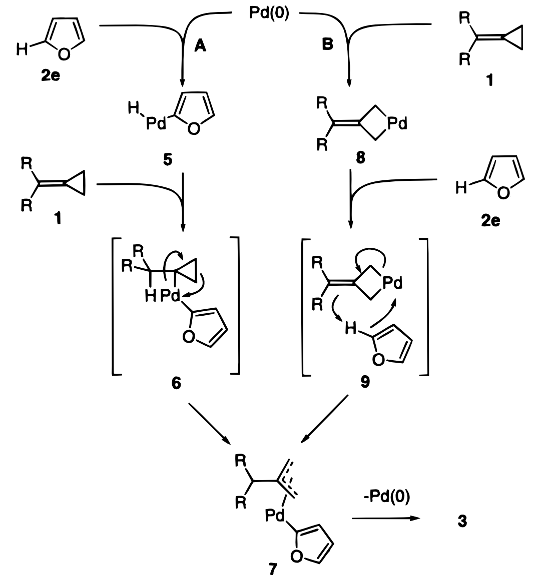
The reaction of **1a** with furan (**2e**) itself (20 equiv) afforded the monoallylated furan **3j** in 77% yield along with a small amount (7%) of the diallylated furan **3k** (eq 2). The use of 5 equiv of **2e** gave 64% of **3j** and 11% of **3k**. The reaction of the methylenecyclopropane (**1f**), which had a substituent on the ring, with **2a** did not afford any adducts at all.





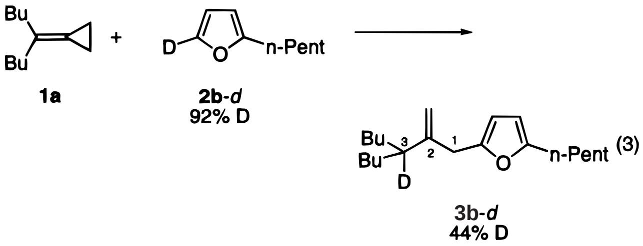
1f

Scheme 1



Plausible mechanisms for the hydrofurylation reaction are shown in Scheme 1. The oxidative addition of palladium(0) to the carbon−hydrogen bond of furan **2e** would lead to the hydride−palladium complex **5** (route **A**). Hydropalladation of a double bond of **1** followed by the distal bond cleavage of the cyclopropane ring would afford the π-allylpalladium intermediate **7**.[9] Reductive elimination of palladium(0) from **7** would give **3**. Another possibility is that Pd(0) would insert to a distal bond of **1** forming palladacyclobutane (**8**).[10] Since **8** is a sort of σ-allylpalladium species, a pallada-ene reaction with **2** may take place as shown in **9**, giving the π-allylpalladium species **7**.

To know the fate of the C−H at the 2-position of furans, we carried out the reaction of 2-deuterio-5-pentylfuran (**2b**-*d*, D content 92%) with **1a** under the same conditions as above. The monodeuterated **3f**-*d*, in which the deuterium content at the C-3 position was 44%, was obtained in 66% yield (eq 3). No multideuterated products and the monodeuterated product, in which deuterium was attached to the carbon atoms other than the C-3 position, were obtained at all. The formation of the C-3 deuterated product **3b**-*d* can be explained by both mechanisms (**A** and **B**). Rather low deuterium content seems to suggest that mechanism **A** is operative, but at the present time we cannot completely eliminate the possibility of participation of route **B**.



Irrespective of the precise mechanism, we are now in a position to carry out the hydrofurylation reaction in good yields under the reaction conditions which can be manipulated without using high temperatures and pressures. The palladium-catalyzed hydrofurylation was tried with diphenylacetylene, instead of with alkylidenecyclopropanes. However, no adducts were obtained and the starting substrates were recovered. Perhaps the formation of rather stable π-allylpalladium intermediate **7** becomes a key for inducing the hydrofurylation of **1** (see Scheme 1). The structure framework of multisubstituted furans is often found in important natural products, such as furanocembranes,[11] furan fatty acids,[12] and calicogorgins.[13] The present methodology may be applicable to the synthesis of those furan families.

Supporting Information Available: Experimental Information including experimental procedure (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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