

# Palladium-Catalyzed Isobenzofuran Generation under Neutral Conditions via Oxidative Addition to Lactol Methyl Ether

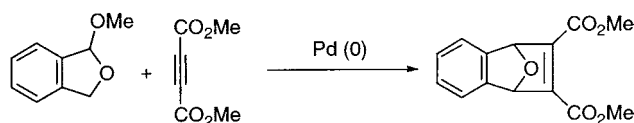
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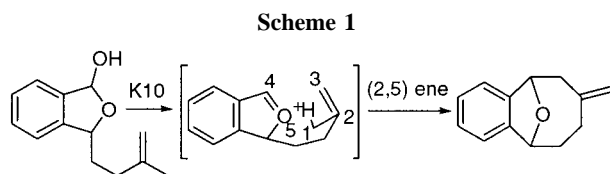
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## ABSTRACT



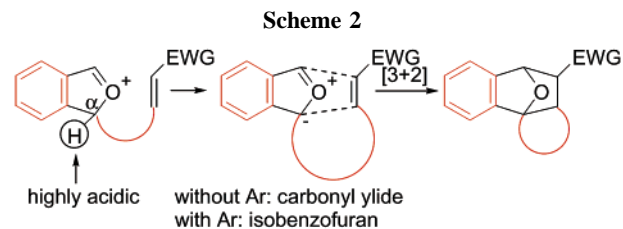
A novel method for generation of isobenzofuran is developed from lactol methyl ether using palladium catalysts. This reaction can be carried out under neutral conditions and hence improves on the precedent methods under acidic or basic conditions and at high temperatures. Furthermore, this Pd-catalyzed isobenzofuran generation suggests the involvement of oxidative addition of Pd catalyst into benzylic or allylic methyl ethers.

Several excellent methods for isobenzofuran generation<sup>1,2</sup> have been developed.<sup>3</sup> However, these are still limited by the reaction conditions (acidic or basic) or applicable substrates. Therefore, new generation methods are desirable especially under neutral conditions. Recently, we reported the example of (2,5)-ene cyclization<sup>4</sup> using an oxonium ion intermediate as an enophile (Scheme 1).<sup>5–7</sup> It is expected



that the  $\alpha$ -proton of this oxonium intermediate is very acidic and therefore may easily be abstracted in the presence of

base leading to isobenzofuran (Scheme 2). Herein we report a novel method for isobenzofuran generation from lactol methyl ether using palladium catalysts under neutral conditions via oxidative addition to the methyl ether followed by sequential<sup>8</sup> deprotonation.

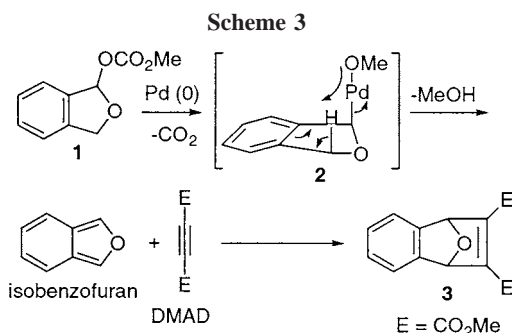


There is a pioneering work by Tsuji in which Pd(0) catalysts undergo oxidative addition to allylic carbonate to form the  $\pi$ -allylpalladium intermediate accompanied by decarboxylation.<sup>9,10</sup> The resultant alkoxide on Pd acts as a

(1) Reviews: (a) Haddadin, M. J. *Heterocycles* **1978**, *9*, 865. (b) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (c) Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*, 53. (d) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093.

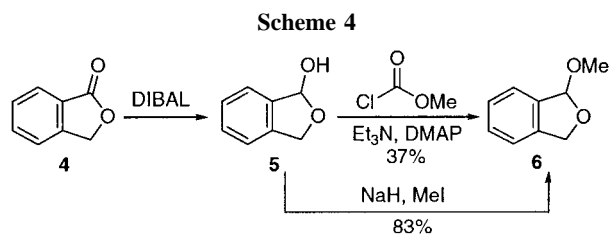
(2) (a) Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 2081; (b) *Can. J. Chem.* **1965**, *43*, 1599.

base to abstract hydrogen from an active methylene compound to generate a carbanion that attacks  $\pi$ -allylpalladium to form a carbon–carbon bond. We applied this reaction to isobenzofuran generation using benzylic carbonate **1** as a substrate (Scheme 3). First, alkyl palladium species **2** would



be generated from **1**. The alkoxide on Pd might act as a base to abstract a benzylic proton to generate isobenzofuran that could be trapped in situ by dimethyl acetylenedicarboxylate (DMAD) affording the adduct **3**.<sup>11</sup>

To prepare **1**, lactone **4** was treated with DIBAL to give lactol **5** followed by the addition of methyl chloroformate (Scheme 4). As a result, lactol methyl ether **6** was obtained



presumably via **1** because of its lability (Supporting Information). Methyl ether **6** was prepared separately by treatment with sodium hydride followed by methyl iodide.

Interestingly, **6** was found to give isobenzofuran by treatment with Pd(0) catalyst (Scheme 5). In the absence of

(3) (a) Pyrolysis at 650 °C: Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347. (b) Acidic conditions: Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354. (c) Basic conditions: Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849. (d) Use of diazo compound: Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. (e) Basic and acidic conditions: Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689.

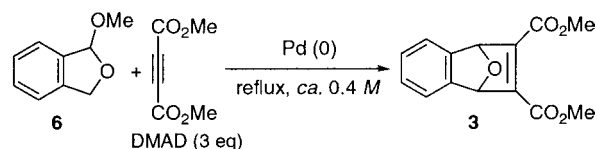
(4) (2,5)-Ene cyclization: (a) Ohmura, H.; Smyth, G. D.; Mikami, K. *J. Org. Chem.* **1999**, *64*, 6056. (b) Ohmura, H.; Mikami, K. *Tetrahedron Lett.* **2001**, *42*, 6859.

(5) Review on l-(m,n) terminology: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(6) Account on l-(m,n)-ene cyclizations: Sarkar, T. K. *J. Indian Inst. Sci.* **1994**, *74*, 329.

(7) Recent examples of l-(m,n)-ene cyclization: (a) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669. (b) Okano, T.; Nakagawa, K.; Kubodera, N.; Ozono, K.; Isaka, A.; Osawa, A.; Terada, M.; Mikami, K. *Chem. Biol.* **2000**, *7*, 173. (c) Mikami, K.; Osawa, A.; Isaka, A.; Sawa, E.; Shimizu, M.; Terada, M.; Kubodera, N.; Nakagawa, K.; Tsugawa, N.; Okano, T. *Tetrahedron Lett.* **1998**, *39*, 3359. (d) Noguchi, M.; Mizukoshi, T.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2201.

**Scheme 5**



Pd(0) catalyst, no generation of isobenzofuran was observed up to 100 °C. Generation of isobenzofuran was further investigated using Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(OAc)<sub>2</sub> + dppp, and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> as Pd(0) species in several solvents (Table 1).

**Table 1.** Choice of Pd(0) Catalysts<sup>a</sup>

entry	Pd(0)	solvent	time (days)	yield of <b>3</b> (%)
1		CH <sub>2</sub> Cl <sub>2</sub>	1	nr
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	1	nr
3	(8 mol %)	CH <sub>3</sub> CN	4	17 (30) <sup>c</sup>
4		THF	1.5	nr
5		CH <sub>2</sub> Cl <sub>2</sub>	1.5	nr
6		C <sub>6</sub> H <sub>6</sub>	20 h	0 <sup>d</sup>
7	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub>	CH <sub>3</sub> CN	1	30 <sup>d</sup>
8	(4 mol %)	CH <sub>3</sub> CN <sup>b</sup>	3	21 (45) <sup>e</sup>
9		THF	20 h	0 <sup>d</sup>
10		CH <sub>2</sub> Cl <sub>2</sub>	1	nr
11	Pd(OAc) <sub>2</sub> (4 mol %)	C <sub>6</sub> H <sub>6</sub>	2	0 <sup>f</sup>
12	DPPP (8 mol %)	CH <sub>3</sub> CN	2	27 <sup>g</sup>
13		THF	2	<10 (<20) <sup>h</sup>

<sup>a</sup> All reactions were carried out using a catalytic amount of palladium complex in the presence of DMAD (3 equiv) under reflux at 0.4 M. <sup>b</sup> DPPP (16 mol %) was added. <sup>c</sup> Based on recovery of starting material **6**: 46%. <sup>d</sup> All starting material **6** was consumed. <sup>e</sup> Based on recovery of starting material **6**: 54%. <sup>f</sup> Product was detected by TLC after 1 day. <sup>g</sup> Recovery of starting material **6**: 66%. <sup>h</sup> Based on recovery of starting material **6**: 48%.

As a result, the desired DMAD adduct of isobenzofuran **3** was obtained in CH<sub>3</sub>CN with all Pd(0) species. Above all, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> was found to be the best in terms of catalytic activity and the yield of **3** (entry 7).<sup>12</sup> The addition of phosphine ligand lowered the catalytic activity of Pd(0) species and the yield of **3** (entry 8). The sterically bulky phosphine ligand might interrupt the deprotonation by methoxide. Therefore, further investigation was carried out without phosphine ligand in various solvents.

(8) Reviews on sequential reactions: (a) Nakai, T.; Mikami, K. *Kagaku no Ryoiki* **1982**, *36*, 661; *Chem. Abstr.* **1982**, *96*, 16001. (b) Ziegler, F. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon Press: Oxford, 1991; Vol. 5, p 875. (c) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (d) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (e) Special issue on frontiers in organic reaction sequence: Wender, P. A. *Chem Rev.* **1996**, *96*, 1.

(9) Reviews: (a) Tsuji, J. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 1036. (b) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (c) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

(10) General reviews on Pd chemistry: (a) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; Wiley & Sons: Chichester, UK, 1995. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.

(11) For the spectral data of **3**, see: Sambaiah, T.; Huang, D.-J.; Cheng, C.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 195.

(12) Adduct **3** was scarcely obtained without palladium complex.

The catalytic activity of Pd species turned out to depend on the solvent employed (Table 2). The most suitable solvent

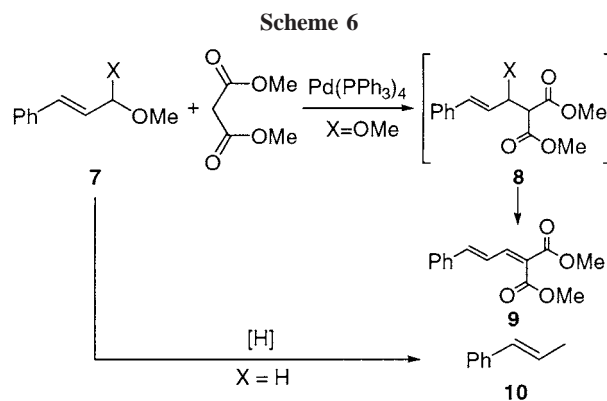
**Table 2.** Effect of Solvent<sup>a</sup>

entry	solvent	time	yield of <b>3</b> (%)
1	DMSO	15 min	71
2	DMSO	45 min	65
3	DMSO	1.5 h	53
4	DMA	2.5 h	68
5	DMA	13 h	52
6	DMF	7 h	46
7	1,4-dioxane	7 h	0

<sup>a</sup> All reactions were carried out using 4 mol % Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in the presence of DMAD (3 equiv) at 100 °C.

was DMSO, which gave **3** in 71% yield within 15 min (entry 1). However, prolonged reaction time resulted in a lower yield, possibly because of decomposition of **3** (entries 2 and 3). The cycloadduct **3** was also obtained using DMA and DMF in reasonably good yields (entries 4 and 6). We speculate that the reason polar solvents such as DMSO, DMA, and DMF are suitable for this reaction is that coordinating solvents could stabilize the polarized palladium intermediate. Moreover, dissociation of methoxide was facilitated and the basicity of methoxide was increased in polar solvents.

The results shown in Tables 1 and 2 imply that the oxidative addition of Pd catalyst to benzylic methyl ether does take place. In general, this type of oxidative addition of Pd catalyst to methyl ether has been considered to be difficult.<sup>13</sup> However, there was a report that allylic methyl ether with Pd(PPh<sub>3</sub>)<sub>4</sub> in the presence of hydride gave a demethylated reduction product as shown in our own product **10**.<sup>14</sup> This type of product was reported to be generated by the oxidative addition of Pd to the methyl ether. In a similar reaction with β-methoxymethyl styrene (**7**: X = H), we obtained the demethylated product, β-methyl styrene **10** (22%). Furthermore, treatment of β-(dimethoxymethyl)-



styrene **7** (X = OMe), which has a structure similar to **6**, with Pd(PPh<sub>3</sub>)<sub>4</sub> in the presence of dimethylmalonate, produced conjugate ester **9** (Scheme 6). These results support the oxidative addition of Pd catalyst into allylic or benzylic methyl ether.

In summary, a novel method of generating isobenzofuran from lactol methyl ether using palladium catalysts has been developed. This reaction can be carried out under neutral conditions and, hence, is of greater advantage than the precedent methods of isobenzofuran generation under acidic or basic conditions and at high temperature.<sup>1-3</sup> Furthermore, this Pd-catalyzed isobenzofuran generation suggests the involvement of oxidative addition of Pd catalyst into benzylic or allylic methyl ether.

**Supporting Information Available:** Preparative methods, spectral and analytical data, and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) Oxidative addition of Pd(0) species was reported in dioxane on allylic phenyl ethers but not on methyl ether: Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075. Enantiospecific Pd(0)-catalyzed substitution of acetates and carbonates of 1-naphthylethanol: Legros, J. Y.; Toffano, M.; Fiaud, J. C. *Tetrahedron* **1995**, 51, 3235.

(14) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, 47, 4380.