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Palladium-Catalyzed Multistep Reactions Involving Ring Closure of 2-Iodophenoxyallenes and Ring Opening of Bicyclic Alkenes

Kanniyappan Parthasarathy, Masilamani Jeganmohan, and Chien-Hong Cheng*

Department of Chemistry, National Tsing Hua University, Hsinchu, 30013 Taiwan

chcheng@mx.nthu.edu.tw

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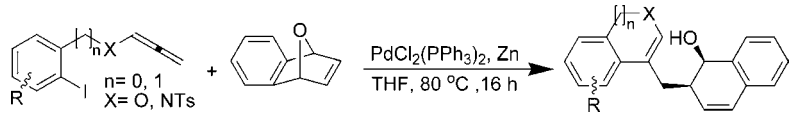
ABSTRACT



An efficient ring closure of 2-iodophenoxy-, 2-iodobenzyloxy-, and 2-iodobenzylaminoallenes followed by ring opening of oxabenzonorbornadienes leading to the synthesis of 2-benzofuranyl, 1*H*-isochromenyl, or 1,2-dihydroisoquinoline methyl-1,2-dihydro-1-naphthalenol derivatives catalyzed by palladium complexes is described.

Multistep reactions in one pot are highly useful synthetic routes in organic synthesis for maximized molecular complexity, minimized organic wastes, and high regio-, stereo-, and chemoselectivity.[1] One of the viable methods to achieve this is via metal-catalyzed multistep reactions, in which an oxidative addition of organic electrophiles to metal, followed by insertion of carbon−carbon multiple bonds and then termination by nucleophiles, is the most common sequence.[2] Various nucleophiles, particularly organometallic reagents, such as organoborates, organosilanes, and organostannanes, have been widely used as the terminating reagents for this type of multistep reaction.[3] However, this type of cross-coupling reaction produces a significant amount of metal salts and organic wastes. Bicyclic alkenes are versatile organic reagents that undergo various types of organic transformations, including metal-catalyzed [2 + 2 + 2] cycloaddition reactions,[4a,b] ring-opening reactions,[4c] and cyclization reactions,[4d,e] but the utility of this reagent as a terminating agent in multistep reactions has not been explored.

Our continuous interest in metal-catalyzed multistep reactions[5] and ring-opening reactions[6] prompted us to explore the possibility of using bicyclic alkenes as a terminating agent for the palladium-catalyzed addition reactions. In this com-

(1) (a) Zhao, L.; Lu, X. *Org. Lett.* **2002**, *4*, 3903. (b) Wu, M.-S.; Rayabrapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12426. (c) Arefalk, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938. (d) Shibata, T.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 1781. (e) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (f) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221. (g) Grigg, R.; Nurnabi, M.; Sarkar, M. R. A. *Tetrahedron* **2004**, *60*, 3359. (h) Negishi, E.; Coperet, C. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vol. 1, p 1431. (i) Coperet, C.; Negishi, E. *Org. Lett.* **1999**, *1*, 165.

(2) (a) Ma, S.; Jiao, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4737. (b) Onitsuka, K.; Suzuki, S.; Takahashi, S. *Tetrahedron Lett.* **2002**, *43*, 6197. (c) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827. (d) Gigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017. (e) Oh, C. H.; Jung, S. H.; Bang, S. Y.; Park, D. I. *Org. Lett.* **2002**, *4*, 3325.

(3) (a) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (b) Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 11940. (c) Yang, F.-Y.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576. (d) Zhou, C. Z.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.

(4) (a) Huang, D.-J.; Sambaiah, T.; Cheng, C.-H. *New J. Chem.* **1998**, *22*, 1147. (b) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 8485. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (d) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286. (e) Rayabarapu, D. K.; Shukula, P.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 4903.

(5) (a) Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 881. (b) Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C.-H. *Chem. Commun.* **2003**, 1746. (c) Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821. (d) Jeganmohan, M.; Cheng, C.-H. *Synthesis* **2005**, *5*, 1693. (e) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921.

(6) (a) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538. (b) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679. (c) Rayabarapu, D. K.; Cheng, C.-H. *Chem.—Eur. J.* **2003**, *9*, 3164. (d) Wu, M.-S.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2005**, *70*, 9545.

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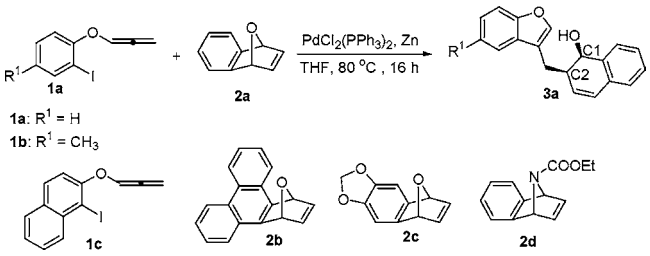
munication, we wish to report a palladium-catalyzed ring closure followed by ring opening of 2-iodophenoxy-, 2-iodobenzyloxy-, and 2-iodobenzylaminoallenes with bicyclic alkenes to give highly regio- and stereoselective benzo[*b*]-furan, 1*H*-isochromenyl, or 1,2-dihydroisoquinoline-substituted 1,2-dihydro-1-naphthalenol derivatives with multiple stereocenters in excellent yields. The skeletons of these products are found in a wide range of naturally occurring compounds that show various biological activities.[7]

When 2-iodophenoxyallene (**1a**) and oxabenzonorbornadiene (**2a**) were heated in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and zinc powder (1.5 equiv) in THF at 80 °C for 16 h, product **3a** involving ring closure of **1a** and ring opening of **2a** was obtained in 85% isolated yield (Scheme 1). Product

Scheme 1



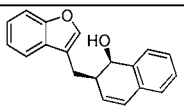
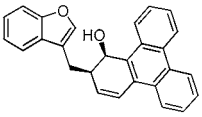
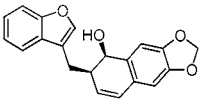
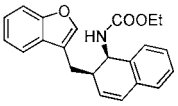
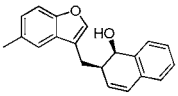
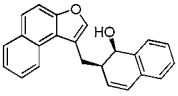
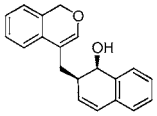
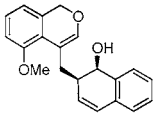
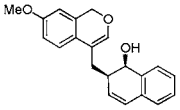
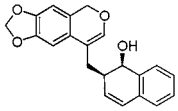
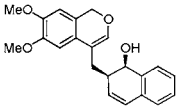
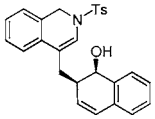
3a was thoroughly characterized by its ^{1}H and ^{13}C NMR and mass data. Control experiments revealed that, in the absence of a palladium catalyst or Zn, no **3a** was obtained. The cis stereochemistry of this product was established based on the coupling constant (~3.5 Hz) of the two protons at C1 and C2.[6]

To optimize the present reaction, the catalytic activity of various palladium complexes was examined for the reaction of **1a** with **2a**. Palladium(0) complexes $Pd(dba)_2$ and $Pd(PPh_3)_4$ in THF were ineffective for the reaction. Pd(II) complexes, such as $PdCl_2(PhCN)_2$ and $PdCl_2(CH_3CN)_2$, were active but gave **3a** in low 30 and 33% yields, respectively, based on the ^{1}H NMR integration method using mesitylene as an internal standard. Monodentate phosphine complex $PdCl_2(PPh_3)_2$ afforded a 90% yield, whereas bidentate phosphine complex $PdCl_2$(dppe) furnished a 35% yield. It appears that $PdCl_2(PPh_3)_2$ is the best catalyst of the palladium complexes tested for the present catalytic reaction. The effect of solvents, including THF, CH_3CN, toluene, ethyl acetate, and DMF, on the yield of the reaction of **1a** and **2a** was also investigated. Of these solvents tested, THF was most effective, affording **3a** in 90% yield, while CH_3CN gave **3a** in 65% yield. The other solvents, toluene, ethyl acetate, and DMF, were totally ineffective for the reaction. On the basis of these optimization studies, we chose $PdCl_2(PPh_3)_2$ as the catalyst and THF as the solvent in the presence of zinc powder for the catalytic reactions described below.

(7) (a) Carter, G. A.; Charnberlain, K.; Wain, R. L. *Ann. Appl. Biol.* **1978**, *88*, 57. (b) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall M. J. *J. Med. Chem.* **1986**, *29*, 1643. (c) Synder, S. E. *J. Med. Chem.* **1995**, *38*, 2395. (d) Perrone, R. J. *J. Med. Chem.* **1995**, *38*, 942.

Under the optimized reaction conditions, bicyclic alkenes **2b**−**2d** were also successfully used for the ring-opening reaction with **1a** (Scheme 1 and Table 1). Thus, 1,4-oxa-

Table 1. Results of Palladium-Catalyzed Ring-Closure and Ring-Opening Reactions[a]

entry	1	2	product	3	yield (%)[b]
1	**1a**	**2a**		**3a**	85 (90)
2	**1a**	**2b**		**3b**	45
3	**1a**	**2c**		**3c**	73
4	**1a**	**2d**		**3d**	86
5	**1b**	**2a**		**3e**	80
6	**1c**	**2a**		**3f**	73
7	**1d**	**2a**		**3g**	87
8	**1e**	**2a**		**3h**	70
9	**1f**	**2a**		**3i**	75
10	**1g**	**2a**		**3j**	71
11	**1h**	**2a**		**3k**	67
12	**1i**	**2a**		**3l**	78

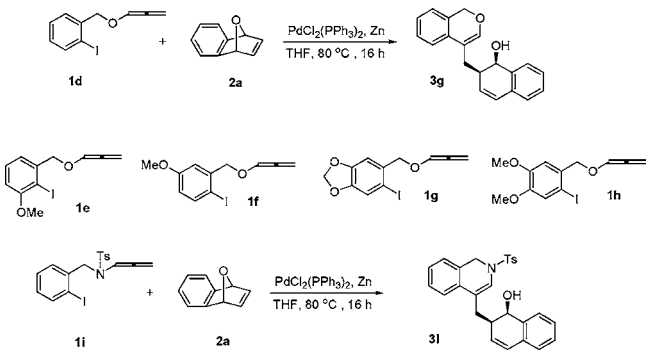
[a] All reactions were carried out using allenes **1** (1.0 mmol), bicyclic alkenes **2** (1.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), Zn (1.50 mmol), and THF (3.0 mL) at 80 °C for 16 h. [b] Isolated yields; yield in the parenthesis was determined by ^{1}H NMR method using mesitylene as an internal standard.

1,4-dihydrotriphenylene **2b** reacted with **1a** to give **3b** in 45% yield (entry 2). The large phenanthrene moiety of **2b** likely inhibits the coordination of this alkene to the bulky palladium center, leading to the observed low yield. Treat-

ment of substituted oxabenzonorbornadiene **2c** having an electron-donating 6,7-methylenedioxy group with **1a** afforded **3c** in 73% yield (entry 3). Similarly, 7-azabenzonorbornadiene **2d** reacted with **1a** to give 1,2-dihydro-1-naphthalenamine **3d** in 86% yield. In addition to **1a**, 2-iodo-4-methylphenoxyallene **1b** and 1-iodo-2-naphthoxyallene **1c** underwent a ring-closure and ring-opening reaction with **2a** to provide **3e** and **3f** in good yields (entries 5 and 6).

As shown in Scheme 2 and entries 7−12 (Table 1), the

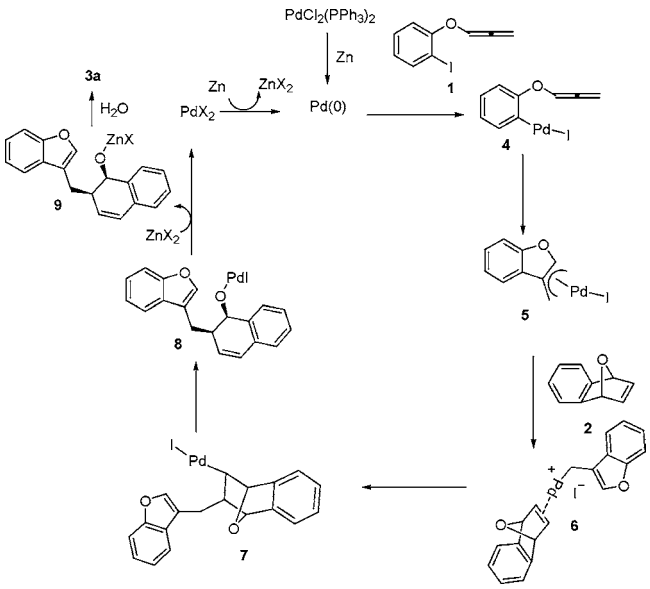
Scheme 2



present protocol can be further extended to substituted 2-iodobenzyloxyallenes **1d**−**h** and 2-iodobenzylaminoallene **1i**. Treatment of 2-iodobenzyloxyallene (**1d**) with **2a** in the presence of $PdCl_2(PPh_3)_2$ and zinc powder afforded 1*H*-isochromene derivative **3g** in 87% isolated yield (Table 1, entry 7). Under similar reaction conditions, electron-donating 3-methoxy- and 5-methoxy-2-iodobenzyloxyallenes **1e** and **1f** on reacting with **2a** provided **3h** and **3i** in 70 and 75% yields, respectively (entries 8 and 9). Highly electron-donating 4,5-methylenedioxa- and 4,5-dimethoxy-2-iodobenzyloxyallenes **1g** and **1h** also underwent ring opening smoothly with **2a** to give **3j** and **3k** in good yields (entries 10 and 11). Further, 2-iodobenzylaminoallene **1i** reacted with **2a** to afford 1,2-dihydroisoquinoline derivative **3l** in 78% yield (entry 12).

On the basis of known palladium-catalyzed allene chemistry and the mechanisms for the catalytic reactions involving π-allylpalladium complexes as key intermediates, a mechanism[5,6] is proposed, as shown in Scheme 3. The reduction of $PdCl_2(PPh_3)_2$ to a Pd(0) by zinc metal likely initiates the catalytic reaction. Oxidative addition of 2-iodophenoxyallene **1** to Pd(0) gives species **4**. Coordination of the allenyl group in **4** to the palladium center followed by insertion into the palladium−carbon bond affords the π-allyl palladium complex **5**. Then, coordination of oxabenzonorbornadiene **2** via the exo face of the carbon−carbon double bond to intermediate **5** gives intermediate **6**. Further insertion of the double bond of **2** into the allylpalladium bond in **6** results in the formation of intermediate **7**. Subsequent β-oxy elimination of **8** and transmetalation with zinc halide leads to intermediate **9** and palladium(II) halide. The latter is then reduced by zinc metal powder to regenerate the Pd(0) catalyst. **9** is hydrolyzed after workup to give the final product **3**.

Scheme 3



The role of zinc metal is crucial in the present catalytic reaction. First, it is used to reduce Pd(II) to Pd(0) to initiate the reaction and as a reducing agent to regenerate the Pd(0) catalyst. Second, the zinc halide produced from the oxidation of zinc metal during the reaction likely acts as a mild Lewis acid to remove a halide from the Pd(II) center and to assist the coordination of the bicyclic alkenes. The role of zinc halide as a Lewis acid in homogeneous catalytic reactions has been proposed.[6] Evidence to support this function came from the observation that the addition of triethylamine, which is expected to form a Lewis acid−base pair with zinc halide, to the catalytic reaction solution of **1a** with **2a** suppressed entirely the formation of **3a**.

In conclusion, we have developed a new palladium-catalyzed multistep reaction involving ring closure of 2-iodophenoxy-, 2-iodobenzyloxy-, and 2-iodobenzylaminoallenes and ring opening of bicyclic alkenes. This method provides the construction of two different and new C−C bonds in one pot and allows an efficient synthesis of various benzo[*b*]furan, 1*H*-isochromenyl, and 1,2-dihydroisoquinoline-substituted 1,2-dihydro-1-naphthalenols in good yields. Further extension of this reaction in an intermolecular way, application of the method in organic synthesis, and detailed mechanistic studies of the catalytic reaction are in progress.

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Supporting Information Available: Preparation details, characterization data of **3a**−**l**, and a copy of the ^{1}H and ^{13}C NMR spectra of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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