

Palladium-Catalyzed Formal [4+2] Cycloaddition of *o*-Xylylenes with Olefins

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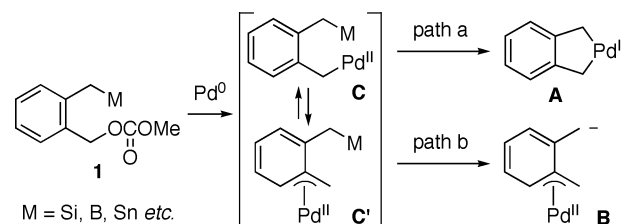
Diels–Alder reaction, that is, [4+2] cycloaddition of 1,3-dienes with alkenes, is an attractive method to construct 6-membered carbocycles.¹ The reaction generally requires high temperature to obtain the desired cycloadduct in high yield.² The cycloaddition is known to accelerate in the presence of varied metal complexes.³ The metal-mediated methodology has contributed to the advance of stereoselective cycloaddition.⁴ Meanwhile, *o*-xylylenes, which are 1,3-cyclohexadienes having two exomethylenes at the 5- and 6-positions, have a remarkable reactivity for Diels–Alder reaction as a diene.⁵ Various methods for in-situ generation of *o*-xylylene have been developed⁶ and utilized for the syntheses of natural products.⁷ However, it is hard to control the intermolecular reaction of *o*-xylylene because of its violent reactivity.⁸ This paper describes a new organometallic methodology for generating an *o*-xylylene equivalent, which reacted with various conjugated olefins to yield the [4+2] cycloadduct.

We have developed the palladium-catalyzed nucleophilic substitutions of benzylic carbonates recently.⁹ The catalytic reaction proceeds through the benzylic C–O bond activation by palladium(0). As shown in Scheme 1, we envisioned that the *o*-xylylene equivalent **A** or **B** would be generated from *o*-(metalated-methyl)-benzyl carbonate **1**^{6f,10} through the C–O bond cleavage leading to (benzyl)palladium **C**. The M and palladium(II) of **C** would undergo intramolecular transmetalation leading to 2-palladaindane **A** (path a),¹¹ which might give the tetralin cycloadduct through olefin insertion followed by reductive elimination. Alternatively, the benzylic carbon bound to M would behave as a carbanion (path b). The carbanion of **B** might undergo 1,4-addition to an α,β -unsaturated carbonyl compound, and then the resulting enolate might attack the η^3 -benzyl on palladium(II). The above hypothesis stimulated us to attempt the reaction of *o*-[(trimethylsilyl)methyl]-benzyl carbonate **1a** with methyl acrylate **2a** in the presence of a palladium(0) complex.

A mixture of **1a** and **2a** in DMSO was heated at 120 °C for 48 h in the presence of 3% palladium catalyst prepared from Pd(η^3 -C₃H₅)Cp and a bidentate ligand DPPE¹² (Table 1, entry 1). Tetralin-2-carboxylate **3a**, which is the cycloadduct of *o*-xylylene with **2a**, was obtained in 78% isolated yield. The use of a Lewis basic solvent is crucial for the catalytic reaction. The desired product **3a** was obtained in reasonable yield when the reaction was conducted in DMF as well as in DMSO (entry 2). In contrast, **1a** was hardly consumed in 1,4-dioxane or toluene (entries 5, 6). The yield of **3a** was significantly affected by the ligand on palladium. The use of bisphosphine DPPF and DPEphos, which were effective for the palladium-catalyzed nucleophilic substitution of benzylic esters,^{9,13} slowed the production of **3a** (entries 7, 8). The monophosphine-ligated palladium did not work as a catalyst for the cycloaddition very well (entry 9). No **3a** was obtained from the reaction of **1a** and **2a** with DPPE in the absence of palladium.

The mixture of **1a** and DPPE–palladium catalyst in DMSO was heated to 120 °C for 24 h in the absence of **2a**, affording a trace

Scheme 1

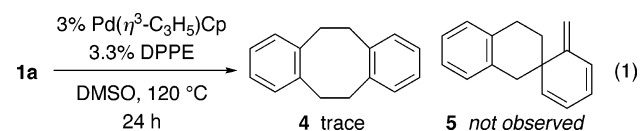
Table 1. Effect of Solvent and Ligand on Cycloaddition of **1a** with **2a**^a

entry	solvent	ligand	yield (%) ^b
1 ^c	DMSO	DPPE	78 ^d
2	DMSO	DPPE	60
3	DMF	DPPE	72
4	MeCN	DPPE	45
5	1,4-dioxane	DPPE	7
6	toluene	DPPE	5
7	DMSO	DPPF	32
8	DMSO	DPEphos	30
9	DMSO	2 PPh ₃	10

^a Reactions were conducted in 1 mL of solvent. The ratio of **1a** (0.15 mmol)/**2a**/[Pd]/ligand was 100:120:3:3.3. ^b GC yield (average of two runs).

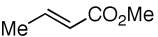
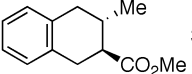
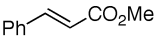
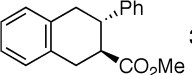
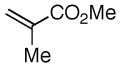
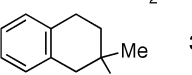
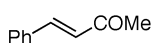
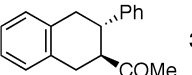
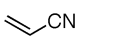
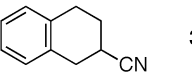
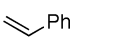
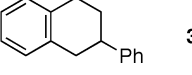
^c The reaction was conducted by using 0.5 mmol of **1a** in 1 mL DMSO for 48 h. ^d Isolated yield.

amount of [2,2]orthocyclophane **4** (<3%), which might have formed through Hiyama cross-coupling of two **1a** (eq 1).¹⁴ No formation of *o*-xylylene dimer **5** was detected in the resulting mixture by GC and ¹H NMR analysis.¹⁵ This observation may rule out the reaction pathway involved with palladium-mediated generation of free *o*-xylylene and its pericyclic cycloaddition with the dienophile. The cycloaddition of **1a** with **2a** occurred on the DPPE-ligated palladium atom and proceeds through either reactive intermediate **A** or **B**.¹³

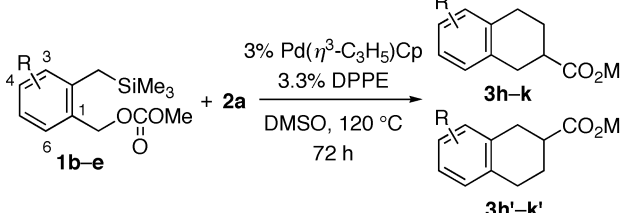


Various conjugated olefins **2** underwent the catalytic formal [4+2] *o*-xylylene cycloaddition (Table 2). The *o*-xylylene precursor **1a** reacted with acrylates substituted at the trans or geminal position,

Table 2. Palladium-Catalyzed Cycloaddition of **1a** with Olefins (**2**)^a

entry	olefin (2)	product (3)	yield, % ^b
1	 2b	 3b	58
2	 2c	 3c	79
3	 2d	 3d	47
4	 2e	 3e^c	71 ^d
5 ^e	 2f	 3f	42
6	 2g	 3g	62

^a The detail of reaction conditions was given in Supporting Information.^b Isolated yield. ^c A small amount of *cis*-**3e** (*trans/cis* = 93:7) was detected in ¹H NMR analysis of the crude product. ^d Isolated yield of pure *trans*-**3e**.^e The reaction was conducted at 140 °C.**Table 3.** Palladium-Catalyzed Cyclization of **1b–e** with **2a**^a

				
entry	R (1)	product (3)	ratio ^b	yield (%) ^c
1	4-MeO (1b)	3h, 3h'	60:40	42
2	4-Me (1c)	3i, 3i'	54:46	72
3	3-Ph (1d)	3j, 3j'	55:45	92
4	4,6-Me₂ (1e)	3k, 3k'	60:40	51

^a The detail of reaction conditions was given in Supporting Information.^b The ratio was determined with ¹H NMR analysis. It is uncertain which is the major product, **3** or **3'**. ^c Yield of a mixture of **3** and **3'**.

yielding the corresponding tetralin products (entries 1–3). No formation of *cis*-2,3-disubstituted tetralins was detected in the catalytic cycloadditions of *trans*-dienophiles **2b** and **2c**.¹⁶ Olefins conjugated with ketone, nitrile, and benzene worked as a dienophile (entries 4–6). However, the palladium catalysis failed to react **1a** with strongly electron-deficient olefins, such as maleate and fumarate,¹⁷ as well as cyclic ones.

As shown in Table 3, the DPPE–palladium complex was effective for the reaction of compounds **1b–e** bearing substituents on the aromatic ring.¹⁸ For example, 3-phenyl-substituted **1d** reacted with **2a** to give the desired tetralins in 92% yield (entry 3). The substituent at the 6-position of **1e** barely hindered the catalytic cycloaddition (entry 4). In all cases, cycloaddition products were obtained as a regioisomeric mixture of **3h–k** and **3h'–k'** (54:46–60:40).¹⁹ The low regioselectivity indicates that the cycloaddition of **1** proceeds through intermediate **A** in Scheme 1. If the reaction was involved with path b, tetralin **3h–k** would be obtained with perfect regioselectivity.

In conclusion, we developed the palladium-catalyzed [4+2] cycloaddition of *o*-(silylmethyl)benzylic carbonates with olefins. The desired tetralin products were obtained with good yield when

the reaction was conducted in Lewis basic solvent, as well as by using a DPPE–palladium catalyst. The present catalytic reaction is equivalent to the [4+2] *o*-xylylene cycloaddition with dienophiles. Use of a chiral ligand in place of DPPE may lead to a catalytic asymmetric cycloaddition of *o*-xylylenes with olefins.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Reviews: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115. (c) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779–4807.
- Oppolzer, W. Intermolecular Diels–Alder Reactions. In *Comprehensive Organic Synthesis Vol. 5: Combining C–C π -Bond*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; pp 315–399.
- (a) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965–4966. Review: (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.
- (a) McKinsty, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145–6154. (b) Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077–10088. (c) Heath, H.; Wolfe, B.; Livinghouse, T.; Bae, S. K. *Synthesis* **2001**, 2341–2347. Review of asymmetric Diels–Alder reaction using Lewis acid catalyst: (d) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
- Reviews: (a) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873–2889. (b) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199–3246.
- Selected examples of in-situ generation of *o*-xylylenes: (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833–3834. (b) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609–7622. (c) Askari, S.; Lee, S.; Perkins, R. R.; Scheffer, J. R. *Can. J. Chem.* **1985**, *63*, 3526–3529. (d) Sano, H.; Ohtsuka, H.; Migita, T. *J. Am. Chem. Soc.* **1988**, *110*, 2014–2015. (e) Lenihan, B. D.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 2072–2085. (f) Fleming, I.; Morgan, I. T.; Sarkar, A. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2749–2746. (g) Kakiya, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2139–2147. (h) Kuwano, R.; Shige, T. *Chem. Lett.* **2005**, *34*, 728–729.
- (a) Nicolaou, K. C.; Gray, D. L. *F. J. Am. Chem. Soc.* **2004**, *126*, 607–612. (b) Matsuya, Y.; Sasaki, K.; Nagaoka, M.; Kakuda, H.; Toyooka, N.; Imanishi, N.; Ochiai, H.; Nemoto, H. *J. Org. Chem.* **2004**, *69*, 7989–7993.
- Bach achieved a highly enantioselective cycloaddition of an *o*-xylylene by using an excess of a chiral template. (a) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Massa, W.; Bach, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3693–3696. (b) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Kaneda, M.; Wada, T.; Inoue, Y.; Bach, T. *Chem.–Eur. J.* **2004**, *10*, 2179–2189.
- (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104–12105. (b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545–3547. (c) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973–2975.
- Yoshida and Kunai used **1** (M = Si) for the palladium-catalyzed distannylation of *o*-xylylene. They conducted the reaction in the presence of KF in order to generate a free *o*-xylylene from **1**. The free *o*-xylylene reacted with hexabutyltin activated by palladium(0). Yoshida, H.; Nakano, S.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Org. Lett.* **2006**, *8*, 4157–4159.
- Tanaka reported an enantioselective rhodium-catalyzed [4+2] carbocyclization of 2-alkynylbenzaldehydes. The authors proposed 2-metallaindane intermediate for the catalytic reaction. Tanaka, K.; Hagiwara, Y.; Noguchi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7260–7263.
- DPPE = 1,2-bis(diphenylphosphino)ethane.
- Although DPPE was inefficient for the catalytic substitution of benzylic carbonates in our previous report (ref 9a), DPPE–[Pd(η^3 -C₃H₅)(cod)]BF₄ catalyst could activate the benzylic C–O bond and catalyze the reaction of methyl *o*-methylbenzyl carbonate with dibutylamine in DMSO at 120 °C, giving the benzylated tertiary amine in 42% yield.
- Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.
- Errede, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 949–954.
- β -*cis*-Methylstyrene reacted with **1a** to afford the *cis*-cycloadduct stereospecifically. However, yield of the product was low (14%).
- The electron-deficient olefins may bind tightly to palladium(0) to obstruct the interaction of **1a** and catalyst.
- No cycloadduct was obtained from the reaction of the substrate **1** having a methyl on its α -position of the carbonate group.
- Each reaction of **1c** and **1d** gave the same major regioisomers to the fluoride-induced *o*-xylylene [4+2] cycloaddition in ref 6h (**1c**, major/minor = 52:48; **1d**, major/minor = 55:45).

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