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Palladium-Catalyzed Formal [4+2] Cycloaddtion 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 developed[6] 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-C_3H_5)Cp and a bidentate ligand DPPE[12] (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 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 ^{1}H 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]

Scheme 1

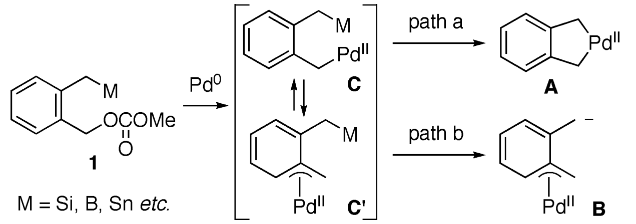
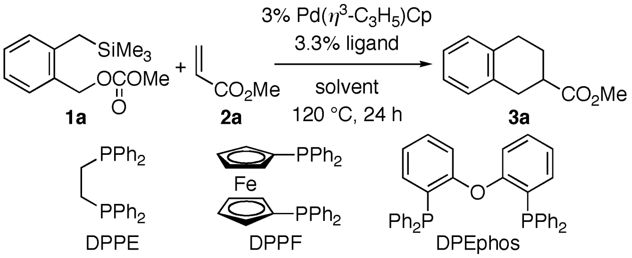
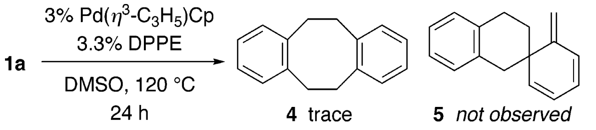


Table 1. Effect of Solvent and Ligand on Cycloaddition of **1a** with **2a**[a]



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.



(1)

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,

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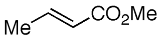
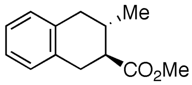
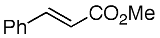
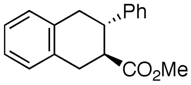
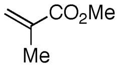
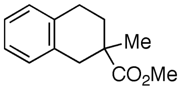
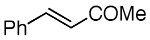
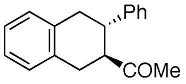
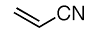
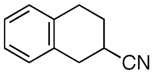
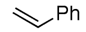
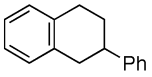
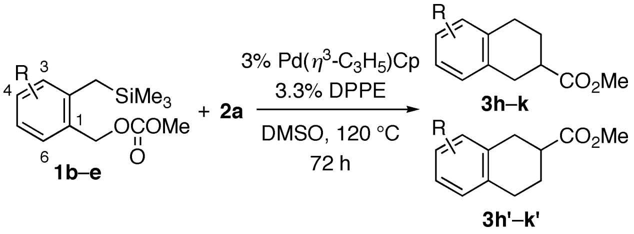
Table 2. Palladium-Catalyzed Cycloaddition of **1a** with Olefins (**2**)[a]

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 ^{1}H 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-Me$_2$ (**1e**)	**3k**, **3k′**	60:40	51

[a] The detail of reaction conditions was given in Supporting Information. [b] The ratio was determined with ^{1}H 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.

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(12) DPPE = 1,2-bis(diphenylphosphino)ethane.

(13) Although DPPE was inefficient for the catalytic substitution of benzylic carbonates in our previous report (ref 9a), DPPE−[Pd(η^3-C_3H_5)(cod)]BF$_4$ 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.

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(16) *β-cis*-Methylstyrene reacted with **1a** to afford the cis-cycloadduct stereospecifically. However, yield of the product was low (14%).

(17) The electron-deficient olefins may bind tightly to palladium(0) to obstruct the interaction of **1a** and catalyst.

(18) No cycloadduct was obtained from the reaction of the substrate **1** having a methyl on its α-position of the carbonate group.

(19) Each reaction of **1c** and **1d** gave the same major regioisomers to the fluoride-induced *o*-xylylene [4+2] cycloaddtion in ref 6h (**1c**, major/minor = 52:48; **1d**, major/minor = 55:45).

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