An Improvement of the Palladium-Catalyzed [4+2] Cycloaddition of *o*-(Silylmethyl)benzyl Carbonates with Alkenes

Yushu Jin,^a Kentaro Ishizuka,^b Ryoichi Kuwano*a,c

^a Department of Chemistry, Graduate School of Sciences, and International Research Center for Molecular Systems (IRCMS), Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

- ^b Education Center for Global Leaders in Molecular Systems for Devices, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan
- ^c JST ACT-C, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan Fax +81(92)6422572; E-mail: rkuwano@chem.kyushu-univ.jp

Received: 12.06.2014; Accepted after revision: 01.08.2014

Abstract: The palladium complex, which is generated in situ from $Pd(\eta^3-C_3H_5)Cp$ and tris(4-methoxy-3,5-dimethylphenyl)phosphine, catalyzed the [4+2] cycloaddition of *o*-(silylmethyl)benzyl carbonates with alkenes. The reaction of the benzyl esters with methyl crotonate gave methyl 3-methyltetralin-2-carboxylate in 84% yield with 2% catalyst loading.

Key words: catalysis, cycloaddition, *o*-quinodimethanes, alkenes, palladacycles

The Diels-Alder reaction of o-quinodimethanes with alkenes is a powerful approach for constructing benzofused six-membered carbocycles.¹ The [4+2] cycloaddition is often used for the synthesis of natural products,² medicines,³ and π -conjugated materials.⁴ We have developed the palladium-catalyzed [4+2] cycloadditions of o-(silylmethyl)benzyl carbonates 1 with alkenes,⁵ imines,⁶ and ketones.⁷ The catalytic cycloaddition is based on the nucleophilic benzylic substitution through palladium catalysis, in which the palladium(0) species cleaves the benzylic C-O bond of benzyl ester to form the $(\eta^3$ -benzyl)palladium(II) intermediate.⁸ In the course of our studies on the catalytic substitution of benzyl esters, bidentate bisphosphines were mainly used as the spectator ligand for the homogeneous palladium catalyst. The use of bisphosphine ligand facilitates the palladium(0) to undergo the oxidative addition of the benzylic C-O bond. As with the benzylic substitution, bisphosphine ligands were used for the above palladium-catalyzed cycloadditions of 1.5-7

Recently, we reported the intramolecular $S_N 2'$ -type aromatic substitution of benzylic carbonates, which are tethered to a nucleophile at their *meta* positions.⁹ The cyclization of the benzylic substrates efficiently took place in the presence of a palladium catalyst bearing biaryldicyclohexylphosphine, SPhos (L1).¹⁰ The usefulness of the monophosphine for the reaction of the benzylic substrates stimulated us to evaluate various monophosphine ligands for the catalytic [4+2] cycloaddition of 1 with

SYNLETT 2014, 25, 2488–2492 Advanced online publication: 25.08.2014 DOI: 10.1055/s-0034-1379014; Art ID: st-2014-u0511-1 © Georg Thieme Verlag Stuttgart · New York alkenes.¹¹ Herein, we report an improvement of the palladium catalyst for the cycloaddition.

Various monophosphines were evaluated for the cycloaddition of **1a** with methyl crotonate (**2a**). The results are summarized in Table 1. First, a mixture of 1a and 2a was treated with $Pd(\eta^3-C_3H_5)Cp-L1$ catalyst in DMSO at 120 °C. Disappointingly, the desired tetralin 3a was obtained in only 33% yield (Table 1, entry 1). The yield value was comparable to that of the reaction using Ph_3P ligand (Table 1, entry 2). Bulky trialkylphosphine-palladium complexes could catalyze the cycloaddition, but the bulkiness of the ligand caused slight deterioration of the palladium catalysis (Table 1, entries 3 and 4). Next, a series of *para*-substituted triarylphosphines L2-L5 were employed as the ligand for the catalytic cycloaddition. The formation of **3a** is considerably affected by the electronic property of the substituents. Use of electron-deficient ligands L2 and L3 led to significant decrease in the yield of 3a (Table 1, entries 5 and 6). In particular, no product 3a was formed and the substrate 1a remained intact in the reaction employing L2. The electron density of the metal atom in the L2-palladium(0) complex may be insufficient for the oxidative addition of the benzylic C-O bond of 1a. Ligand L4 was similar in the yield to Ph₃P (Table 1, entry 7). The catalyst efficiency was remarkably improved by using triarylphosphine L5 bearing methoxy groups (Table 1, entry 8). However, such improvement was not observed when the reaction of 1a with 2a was conducted with ortho-substituted ligand L6 or L7 (Table 1, entries 9 and 10). The electronic effect of the methoxy substituents may be canceled by their steric hindrance. The yield of 3a was somewhat enhanced by installing methyl groups at the meta positions of L5 (Table 1, entry 11). Tris(4-methoxy-3,5-dimethylphenyl)phosphine (L8) is the best ligand for the palladium-catalyzed cycloaddition of 1a with 2a. The *meta* substituent influences the cycloaddition electronically rather than sterically, because the meta phenyl groups of L9 caused a slight decrease in the yield (Table 1, entry 12). Further improvement of the catalytic cycloaddition was not achieved by more electron-rich ligand L10 (Table 1, entry 13). Replacing one or two of the electron-donating aryl substituents of L8 by phenyl group caused decrease in the yield of **3a** (Table 1, entries 14 and 15).



	Fable 1	Optimization	of Reaction	Conditions ^a
--	---------	--------------	-------------	--------------------------------

\ R ^a	² / _n L1:	$/_n$ L12 : R ¹ = OMe, R ² = Me, n = 1			
Entry	Ligand	Temp (°C)	Yield (%) ^b		
1	L1	120	33		
2	Ph ₃ P	120	32		
3	Cy ₃ P	120	29		
4	$(t-\mathrm{Bu})_3\mathrm{P}$	120	22		
5	L2	120	0		
6	L3	120	18		
7	L4	120	34		
8	L5	120	51		
9	L6	120	31		
10	L7	120	29		
11	L8	120	62		
12	L9	120	48		
13	L10	120	46		
14	L11	120	49		
15	L12	120	49		
16	L8	100	70		
17	L8	80	0		
18 ^c	L8	100	84 ^d		

^a Reactions were conducted on a 0.2 mmol scale in DMSO (0.5 mL) for 24 h unless otherwise noted. The molar ratio of $1a/2a/Pd(\eta^3-C_3H_5)Cp/ligand$ was 20:24:1.0:2.0.

^b GC yield (average of two runs).

^c The reaction was conducted on a 0.5 mmol scale in DMSO (1.0 mL) for 48 h. The molar ratio of $1a/2a/Pd(\eta^3-C_3H_5)/ligand$ was

50:100:1.0:2.0.

^d Isolated yield.

As a result of further optimization of reaction conditions with ligand L8, the cycloadduct 3a was obtained in higher yield from the reaction of 1a with 2a at 100 °C (Table 1, entry 16). Furthermore, use of an excess amount of dienophile **2a** allowed the **L8**–palladium catalyst to produce **3a** in 84% yield with 2% catalyst loading (Table 1, entry 18). The cycloaddition proceed with complete stereospecificity, because no *cis* isomer of **3a** was detected in the reaction mixture.

The optimized palladium catalyst promoted the cycloaddition of the o-(silylmethyl)benzyl carbonate (1a) with various conjugated alkenes 2 as shown in Table 2. Methyl methacrylate (2b) reacted with 1a to give tetralin 3b in 55% yield (Table 2, entry 1). The L8-palladium catalyst promoted the cycloadditions of 1a with α,β -unsaturated ketones 2c and 2d, but the ketone substrates required higher temperature for affording 3c and 3d (Table 2, entries 2 and 3). It is noteworthy that the use of the monophosphine allows the cycloaddition of 2d to proceed in moderate yield, while the cyclic enone scarcely reacted with **1a** in the presence of $Pd(\eta^3-C_3H_5)Cp-DPPE$ catalyst.⁵ Furthermore, the reaction was accompanied by the epimerization at the α -carbon of the ketone, giving 3d without formation of the *cis* isomer. A series of *p*-substituted styrenes work as the alkene substrate in the catalytic cycloaddition (Table 2, entries 4-6). Electron-donating and electron-withdrawing substituents did not cause significant decrease in the yields of the cycloadducts. Tetralin **3h** was also obtained in good yield from the reaction of *trans*-stilbene (2h) through the L8-palladium catalyst (Table 2, entry 7). 1,1-Diphenylethene and *trans*-β-methylstyrene are possible to react with 1a, but the corresponding cycloadducts were obtained in 27% and 38% yield, respectively. To our surprise, little formation of the desired tetralin was observed in the reaction of 1a with methyl acrylate (2i) or cinnamate (2j, Scheme 1).





The L8–palladium catalyst was applied to the reaction of substituted o-(silylmethyl)benzyl esters **1b-d** (Table 3). As with 1a, the methyl-substituted analogue 1b reacted with 2a and 2e to give the corresponding cycloadducts in 77% and 65% yield, respectively (Table 3, entries 1 and 2). However, the palladium catalyst failed to control the regiochemistry of the cycloaddition. The reactions of 1c with 2a, 2b, and 2e also produced regioisomeric mixtures of the cycloadducts in good or moderate yield (Table 3, entries 3–5). The methyl group at the 6-position of 1c scarcely obstructed the activation of the benzylic C-O bond with the palladium catalyst and slightly affected the ratio of 3 to 3'. The ratio was not significantly affected by the olefinic substrates. The palladium catalyst is useful for the reaction of the benzofused substrate 1d, which failed to form **3n** through the DPPE-palladium catalyst (Table 3, entry 6).

The low regioselectivities in the reactions of **1b** and **1c** suggest that the present catalytic cycloaddition proceeds through the pathway involving a 2-palladaindane **4** (Scheme 2). The benzylic C–O bond of **1** is cleaved by the **L8**–palladium(0) **5** to give the (η^3 -benzyl)palladium(II) **6** and/or (η^1 -benzyl)palladium(II) **7**. The following intramolecular transmetalation between the silyl group and methoxy ligand in **7** forms the palladaindane **4**, in which the two Pd–C bonds are almost equivalent. The insertion of alkene **2** into one of the Pd–C bonds and the following reductive elimination yield the tetralin **3** and palladium(0) (**5**). The catalytic cycle is similar to the mechanism proposed in our previous reports, where a bisphosphine-chelating palladium complex was used as the catalyst.⁵ The

DPPE-palladium catalyst allowed methyl acrylate (2i) and cinnamate (2j) to react with 1, while these olefinic substrates failed to form the desired cycloadduct in the presence of the L8-palladium complex. The interaction between 5 and these π -accepting alkenes might obstruct the approach of 1 to the palladium(0), because 2i and 2j are stronger in affinity for low-valent metal than other alkenes 2a-h.¹² In the DPPE-palladium catalyst, the bisphosphine tightly chelates the metal atom through its two phosphorus atoms to create stiff steric hindrance around the catalytic center. The steric hindrance may weaken the coordination of 2i or 2j to the palladium. Meanwhile, the coordination of L8 to the palladium in 5 is looser than that of DPPE. The monodentate ligand furnishes less crowded

SiMe ₃ OCOMe +	$\begin{array}{c} R^{4} \\ R^{2} \\ R^{2} \\ \textbf{2b-h} \end{array} \overset{Pd(\eta^{3}-C_{3}H_{5})Cp (2.0 \text{ mol\%})}{L8 (4.0 \text{ mol\%})} \\ \hline \\ DMSO, 48 \text{ h} \end{array}$	$\xrightarrow{R^3}_{3b-h} R^1$		
Entry	Alkene 2	Temp (°C)	Product 3	Yield (%) ^b
1	CO ₂ Me Me	100	Me CO ₂ Me	55
2		120	3b COEt	68
3	2d	120		50
4	Ph 2e	100	3d Ph 3e	72
5	2f	100	C ₆ H ₄ -4-(<i>t</i> -Bu)	59
6°	CF3	100	C ₆ H ₄ -4-CF ₃	62
7	2g Ph Ph 2h	100	3g Ph 3h	65

 Table 2
 Cycloaddition of 1a with Alkenes 2^a

^a Reactions were conducted on a 0.5 mmol scale in DMSO (1.0 mL) for 48 h unless otherwise noted. The molar ratio of $1a/2/Pd(\eta^3-C_3H_5)Cp/L8$ was 50:100:1.0:2.0.

^b Isolated yield.

^c The reaction was conducted for 24 h.

Synlett 2014, 25, 2488-2492

 $\ensuremath{\mathbb{C}}$ Georg Thieme Verlag Stuttgart \cdot New York



Table 3Cycloadditions of 1b-d with 2a or 2e^a

^a Reactions were conducted on a 0.5 mmol scale in DMSO (1.0 mL) at 100 °C for 48 h unless otherwise noted. The molar ratio of $1a/2/Pd(\eta^3-C_3H_5)Cp/L8$ was 50:100:1.0:2.0.

^b The ratio was determined by NMR analysis.

^c Isolated yield of the mixture of regioisomers.

^d The reaction was conducted at 120 °C.

reaction field to the catalyst than DPPE. Therefore, in the cycloaddition thorough **L8**–palladium catalyst, the olefinic substrates strongly interact to the metal atom as compared with the reaction using DPPE ligand.

In conclusion, we found that some electron-rich triarylphosphines are useful as the spectator ligand for the palladium-catalyzed [4+2] cycloaddition of *o*-(silylmethyl)benzyl carbonates **1** with alkenes **2**. In particular, Pd(η^3 -C₃H₅)Cp-tris(4-methoxy-3,5-dimethylphenyl)phosphine (**L8**) catalyst give the desired cycloadducts in up to 84% yield. The observation indicates that triarylphosphine-ligated palladium(0) complex is possible to activate the benzylic C–O bond when the ligand has appropriate elec-



Scheme 2 A possible pathway of the catalytic cycloaddition of 1 with 2 $\,$

tron-donating substituents. The L8–palladium catalyst allows 2-cyclohexenone (2d) and stilbene (2h) to react with 1, while these alkenes failed to form the cycloadduct with 1 through DPPE–palladium catalyst in our previous report.⁵ Further improvement of the catalytic cycloaddition of 1 is in progress.

Acknowledgment

This work was supported by ACT-C (JST) and KAKENHI (Nos. 24655085 and 24106732). We thank the Cooperative Research Program of 'Network Joint Research Center for Materials and Devices' for HRMS measurement.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/ 10.1055/s-00000083.

References

- Reviews: (a) Segura, J. L.; Martín, N. Chem. Rev. 1999, 99, 3199. (b) Charlton, J. L.; Alauddin, M. M. Tetrahedron 1987, 43, 2873.
- (2) Selected examples: (a) Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett.* **1990**, *31*, 6205. (b) Matsuya, Y.; Itoh, T.; Nemoto, H. *Eur. J. Org. Chem.* **2003**, 2221. (c) Nicolaou, K. C.; Gray, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 607. (d) Nicolaou, K. C.; Gray, D. L.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613. (e) Dubois, S.; Rodier, F.; Blanc, R.;

- Parrain, J. L. Org. Biomol. Chem. 2012, 10, 4712.
 (3) Yoshida, H.; Yoshida, R.; Mukae, M.; Ohshita, J.; Takaki, K. Chem. Lett. 2011, 40, 1272.
- (4) Selected examples: (a) Kaur, I.; Stein, N. N.; Kopreski, R. P.; Miller, G. P. J. Am. Chem. Soc. 2009, 131, 3424.
 (b) Kaur, I.; Jazdzyk, M.; Stein, N. N.; Prusevich, P.; Miller, G. P. J. Am. Chem. Soc. 2010, 132, 1261. (c) Liang, Z.; Tang, Q.; Liu, J.; Li, J.; Yan, F.; Miao, Q. Chem. Mater. 2010, 22, 6438. (d) Purushothaman, B.; Bruzek, M.; Parkin, S. R.; Miller, A. F.; Anthony, J. E. Angew. Chem. Int. Ed. 2011, 50, 7013. (e) Mughal, E. U.; Eberhard, J.; Kuck, D. Chem. Eur. J. 2013, 19, 16029.
- (5) Kuwano, R.; Shige, T. J. Am. Chem. Soc. 2007, 129, 3802.
- (6) Ueno, S.; Ohtsubo, M.; Kuwano, R. J. Am. Chem. Soc. 2009, 131, 12904.
- (7) Ueno, S.; Ohtsubo, M.; Kuwano, R. Org. Lett. 2010, 12, 4332.
- (8) (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. J. Am. Chem. Soc. 2003, 125, 12104. (b) Kuwano, R. Synthesis 2009, 1049.
- (9) Ueno, S.; Komiya, S.; Tanaka, T.; Kuwano, R. Org. Lett. 2012, 14, 338.
- (10) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. Angew. Chem. Int. Ed. 2004, 43, 1871.
- (11) Other examples of the palladium-catalyzed reactions of benzylic esters using monophsophine ligand: (a) Hikawa, H.; Matsuda, N.; Suzuki, H.; Yokoyama, Y.; Azumaya, I. *Adv. Synth. Catal.* 2013, *355*, 2308. (b) Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* 2012, *354*, 2465.
- (12) Tolman, C. A. J. Am. Chem. Soc. 1974, 96, 2780.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.