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Palladium-Catalyzed [4 + 2] Cycloaddition of *o*-(Silylmethyl)benzyl Esters with Ketones: An Equivalent to Oxo-Diels−Alder Reaction of *o*-Xylylenes

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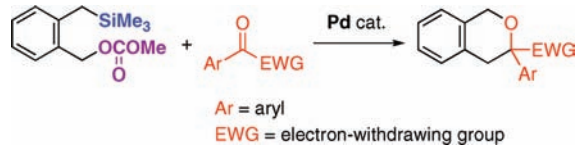
ABSTRACT



o-(Silylmethyl)benzyl carbonates reacted with various electron-deficient ketones in the presence of a palladium catalyst, affording the [4 + 2] cycloaddition products, isochromanes, in high yields. The palladium-catalyzed cycloaddition is equivalent to the oxo-Diels−Alder reaction of *o*-xylylene with ketones. The regioselectivities were extraordinarily affected by the structures of the *o*-xylylene precursors and ketones. The unusual regiochemistry may support two competitive reaction pathways in the catalytic reaction.

The [4 + 2] cycloaddition of *o*-xylylenes with carbonyl groups offers an attractive access to isochromane frameworks, which are often seen in various biologically active compounds.[1] Several methods have been developed to perform the oxo-Diels−Alder reaction.[2,3] However, the *o*-xylylene substrates have required an electron-donating group on their exomethylenes in order to react with the carbon−oxygen double bonds in good yield. No report has been made on the successful cycloaddition of electron-neutral and -deficient *o*-xylylenes with ketones or aldehydes.[4] Previously, we reported that *o*-(silylmethyl)benzyl carbonates act as equivalents to *o*-xylylenes in the presence of a palladium catalyst, reacting with alkenes[5] or imines[6] to form the [4 + 2] cycloaddition products. In this context, we envisioned that the palladium catalysis might lead to the successful oxo-Diels−Alder reaction of *o*-xylylenes.

(1) Examples of biologically active isochromane compounds: (a) Kock, I.; Draeger, S.; Schulz, B.; Elsasser, B.; Kurtan, T.; Kenez, A.; Antus, S.; Pescitelli, G.; Salvadori, P.; Speakman, J.-B.; Rheinheimer, J.; Krohn, K. *Eur. J. Org. Chem.* **2009**, 1427–1434. (b) Shishido, Y.; Wakabayashi, H.; Koike, H.; Ueno, N.; Nukui, S.; Yamagishi, T.; Murata, Y.; Naganeo, F.; Mizutani, M.; Shimada, K.; Fujiwara, Y.; Sakakibara, A.; Suga, O.; Kusano, R.; Ueda, S.; Kanai, Y.; Tsuchiya, M.; Satake, K. *Bioorg. Med. Chem.* **2008**, *16*, 7193–7205. (c) Tobe, M.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Tetrahedron* **2007**, *63*, 9333–9337. (d) Chen, G.; Lin, Y.; Vrijmoed, L. L. P.; Fong, W.-F. *Chem. Nat. Compd.* **2006**, *42*, 138–141. (e) Ogawa, A.; Murakami, C.; Kamisuki, S.; Kuriyama, I.; Yoshida, H.; Sugawara, F.; Mizushima, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3539–3543.

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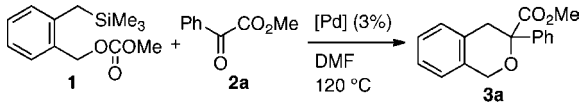
A mixture of *o*-[(trimethylsilyl)methyl]benzyl carbonate **1** and phenylglyoxylate **2a** was heated at 120 °C in the presence of Pd(η^3-allyl)Cp−DPPPent,[7] which is the most effective catalyst for our previous [4 + 2] cycloaddition of **1** with imines (Scheme 1).[6] The desired isochromane **3a** was

Scheme 1. Cycloaddition of **1** with **2a**

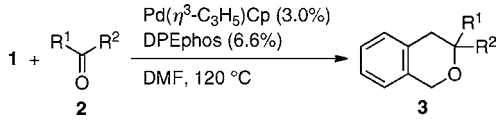


[Pd] = Pd(η^3-allyl)Cp – DPPPent 42% (at 1 h)
[Pd] = Pd(η^3-allyl)Cp – DPEphos 75% (at 1 h)
90% (at 3 h)

formed in 42% GC yield after 1 h. The activity of the palladium catalyst was enhanced using DPEphos[8] in place of DPPPent. The DPEphos−palladium catalyst completed the desired reaction within 3 h and produced **3a** in 90% isolated yield. No formation of **3a** was detected when the mixture of **1** and **2a** was treated with potassium fluoride in the absence of DPEphos−palladium, although the fluoride source was known to generate *o*-xylylene from **1** with no palladium.[9,10] In the reaction, **1** completely disappeared at 3 h and was converted into *o*-xylylene oligomers. The observation may suggest that free *o*-xylylene fails to undergo the oxo-Diels−Alder reaction. The palladium catalysis would be crucial for the formation of the isochromane skeleton through the reaction of **1** with ketones.

The DPEphos−palladium catalyst allows a variety of arylglyoxylates **2b**−**h** to react with the *o*-xylylene equivalent **1** (Table 1, entries 1−7). The electron-donating methoxy

Table 1. Cycloaddition of **1** with Ketones **2**[a]



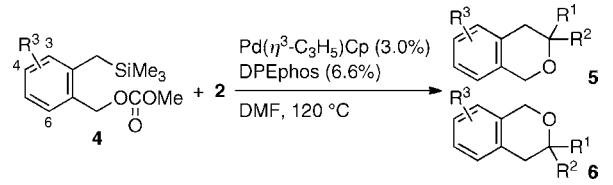
entry	R^1	R^2	**2**	time, h	product (**3**)	yield,[b] %
1	Ph	CO_2Et	**2b**	3	**3b**	93
2	4-$MeOC_6H_4$	CO_2Et	**2c**	12	**3c**	41
3	4-$CF_3C_6H_4$	CO_2Et	**2d**	3	**3d**	81
4	2,4-$Me_2C_6H_3$	CO_2Me	**2e**	24	**3e**	35
5	1-naphthyl	CO_2Et	**2f**	3	**3f**	67
6	2-naphthyl	CO_2Et	**2g**	3	**3g**	93
7	2-furyl	CO_2Me	**2h**	4	**3h**	93
8	$-C_6H_4N(Bn)C(O)-$		**2i**	24	**3i**	92
9	Ph	C(O)Ph	**2j**	6	**3j**	85
10	Ph	CF_3	**2k**	24	**3k**	93

[a] All reactions were conducted in DMF (3.0 mL). The ratio of **1**/**2** (0.45 mmol)/Pd(η^3-C_3H_5)Cp/DPEphos was 150:100:3.0:6.6. [b] Isolated yield.

group in **2c** caused a decrease in the reactivity of the carbonyl substrate (entry 2). In contrast, the electron-deficient substrate **2d** showed reactivity comparable to **2b** (entry 3). The *ortho*-substituent in **2e** hindered the catalytic cycloaddition (entry 4). The reactions of poly- and heterocyclic aromatic substrates **2g** and **2h** produced isochromanes **3g** and **3h** in high yields, while **2f** reacted with **1** in moderate yield because of the steric hindrance of its 1-naphthyl group (entries 5−7). As with the α-keto esters, isatin **2i** or 1,2-diketone **2j** also served as a dienophile in the palladium-catalyzed [4 + 2] cycloaddition (entries 8 and 9). Furthermore, the palladium catalysis is effective for the reaction of trifluoromethyl ketone **2k** (entry 10). However, acetophenone and methyl pyruvate remained intact in the reactions with **1**. The observations indicate that the ketonic substrate requires an aryl and electron-withdrawing group on each side of its carbonyl carbon in order to react with **1** to form the desired isochromane product.

Next, we directed our attention to the regiochemistry in the catalytic cycloadditions of substituted *o*-(silylmethyl)-benzyl carbonates **4a**−**e** (Table 2). The reactions of **4a** and

Table 2. Cycloaddition of Substituted *o*-(Silylmethyl)benzyl Carbonates **4** with Ketones **2**[a]



entry	R^3 (**4**)	**2**	time, h	product	**5**/**6**[b]	yield,[c] %
1	6-Ph (**4a**)	**2k**	24	**5a**, **6a**	85:15	82
2	3-Ph (**4b**)	**2k**	6	**5b** (= **6a**), **6b** (= **5a**)	16:84	92
3	6-Me (**4c**)	**2k**	24	**5c**, **6c**	35:65	86
4	3-Me (**4d**)	**2k**	6	**5d** (= **6c**), **6d** (= **5c**)	68:32	80
5	**4b**	**2a**	4	**5e**, **6e**	52:48	63[d]
6	**4c**	**2a**	24	**5f**, **6f**	13:87	74
7	**4d**	**2a**	20	**5g** (= **6f**), **6g** (= **5f**)	90:10	75
8	**4d**	**2i**	24	**5h**, **6h**	91: 9	69
9	**4d**	**2j**	6	**5i**, **6i**	88:12	73
10	4-MeO (**4e**)	**2k**	9	**5j**	>99:1	70

[a] All reactions were conducted in DMF (3.0 mL). The ratio of **1**/**2** (0.45 mmol)/Pd(η^3-C_3H_5)Cp/DPEphos was 150:100:3.0:6.6. [b] Determined by the ^{1}H NMR analyses of crude products. [c] Isolated yield of a mixture of **5** and **6** unless otherwise noted. [d] Combined yield of **5e** and **6e**, which were isolated in 30% and 33% yields, respectively.

4b with trifluoromethyl ketone **2k** were similar in regioselectivity to the corresponding reactions with *N*-tosylimine in our previous report (entries 1 and 2).[6] Both reactions afforded the mixture of two regioisomers **5a** and **6a** with the same molar ratio. The observed regioselectivities suggest that **4a** and **4b** were transformed into identical intermediates in the course of the cycloaddition. The substrates **4c** and **4d**, which have a methyl group at the 6- or 3-position, also underwent the cycloaddition with **2k** in good yields (entries

3 and 4). The decrease in the size of the 6- or 3-substituent brought about the reversed regioselectivities as well as the lower ratios of **5** to **6**. Furthermore, the reversed regioselectivities rose to 16:84 or 86:14 when α-keto ester **2a** was used in place of **2k** (entries 6 and 7). Preferential formation of **5** from **4d** was observed in the reactions with **2i** and **2j**, which have a 1,2-dicarbonyl skeleton (entries 8 and 9). It is noteworthy that 4-methoxy-substituted **4e** was transformed into **5j** with no formation of **6j** (entry 10).

In order to rationalize the unexpected correlation of regioselectivity with substrate structure, we envision two competitive reaction pathways as shown in Figure 1. One is

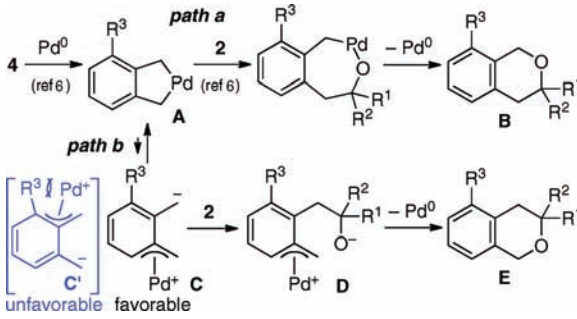


Figure 1. Two competitive pathways for the cycloaddition of **4** with **2**.

similar to the pathway proposed for the cycloaddition of **1** or **4** with imine in our previous report (path a).[6] An *o*-(silylmethyl)benzyl ester reacts with palladium(0) to form 2-palladaindan **A**. The 1,2 insertion of **2** occurs at one of the C−Pd bonds as the ketone avoids the steric hindrance of R^3, leading to the preferential formation of cycloaddition product **B**.[11] In another pathway (path b), **A** is in equilibrium with (η^3-benzyl)palladium **C** through $\eta^1-\eta^3$ isomerization.[12] The formation of regioisomeric **C′** is hindered by the repulsion between R^3 and palladium. The benzylic anion in zwitterionic **C** attacks on the carbonyl carbon of **2** to form intermediate **D**. The intramolecular nucleophilic attack of the alkoxide on the η^3-benzyl in **D** forms the regioisomeric product **E**. The regioselectivities in the reactions of **4c** or **4d** with α-keto ester **2a** indicate that these cycloadditions would proceed through path b in preference to path a. The *o*-phenyl group in **4a** or **4b** may obstruct the nucleophilic attack of **C** on **2**, allowing these substrates to react with **2a** through path a. Hence, the reaction of **4b** with **2a** gave an equimolar mixture of **5e** and **6e**. Furthermore, the trifluoromethyl group in **2k** may be advantageous to path a because its bulkiness makes the ketonic substrate less reactive to the nucleophilic attack of **C**.[13] Synergistic effects of the trifluoromethyl in **2k** and the phenyl group in **4a** or **4b** would lead to the selective formation of **5a** in entries 1 and 2 of Table 2. In the reaction of **4e**, the benzylic anion would be preferentially generated at the *meta* position of the methoxy substituent in zwitterionic **C** due to resonance effects. The resulting intermediate would lead to the exclusive formation of **5j**.

In conclusion, electron-deficient ketones **2** react with (*o*-silylmethyl)benzyl carbonates in the presence of the DPEphos−palladium catalyst, affording 3,3-disubstituted isochromanes in high yields. The catalytic cycloaddition is equivalent to the oxo-Diels−Alder reaction of *o*-xylylenes with ketones. The regioselectivity of the cycloaddition was extraordinarily sensitive to the structures of both substrates. The observations suggest that the present catalytic cycloaddition may proceed through two competitive reaction pathways.

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

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