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Intramolecular S_N'-Type Aromatic Substitution of Benzylic Carbonates at their Para-Position

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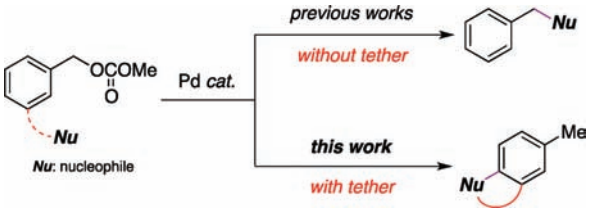
ABSTRACT



The benzylic carbonates, which connect with an active methine through an *o*-phenylene tether at their meta-position, are cyclized by Pd(η^3-C_3H_5)Cp−S-Phos catalyst, yielding 3-methyl-9,10-dihydrophenanthrenes. In the catalytic cyclization, the internal nucleophile attacks not the ortho-carbon but the para-carbon of the benzylic ester. The [3 + 2] cycloaddition of *m*-(silylmethyl)benzyl carbonates with alkylidene malonates was developed from the palladium-catalyzed intramolecular S_N'-type aromatic substitution.

Allylic electrophiles are known to react with nucleophiles at their position γ as well as α to the leaving group.[1] In contrast, the nucleophilic substitution of benzylic electrophiles normally occurs only on the benzylic carbon and is accompanied with no γ-substitution,[2] although the electrophilic substrate can be considered an analog of an allylic compound if its aromatic ring is viewed as an alkene carbon−carbon double bond. Some research groups,[3−7] including us,[8,9] have studied the palladium-catalyzed nucleophilic substitution of benzylic carbonates and carboxylates. The catalytic reaction is believed to proceed through an (η^3-benzyl)palladium(II) intermediate, which is generated from the oxidative addition of the benzylic substrate to palladium(0). Analogous with the Tsuji−Trost reaction,[10] the nucleophile might react with the η^3-benzyl ligand at the γ-position, i.e. ortho-position. Nevertheless, the S_N'-type aromatic substitution has never been reported in the catalytic reactions of benzylic esters to our knowledge.[11]

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(8) (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12104. (b) Kuwano, R.; Kondo, Y. *Org. Lett*. **2004**, *6*, 3545. (c) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett*. **2005**, *7*, 2973. (d) Yokogi, M.; Kuwano, R. *Tetrahedron Lett*. **2007**, *48*, 6109. (e) Kuwano, R.; Kusano, H. *Chem. Lett*. **2007**, *36*, 528. (f) Kuwano, R.; Kusano, H. *Org. Lett*. **2008**, *10*, 1979.

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(11) Palladium-catalyzed aromatic substitutions of benzylic chlorides have been reported by Yamamoto and Bao: (a) Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **2001**, *123*, 759. (b) Lu, S.; Xu, Z.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed*. **2008**, *47*, 4366. (c) Peng, B.; Feng, X.; Zhang, X.; Zhang, S.; Bao, M. *J. Org. Chem*. **2010**, *75*, 2619. (d) Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. *Org. Lett*. **2011**, *13*, 5402. Theoretical study: (e) Ariafard, A.; Lin, Z. *J. Am. Chem. Soc*. **2006**, *128*, 13010.

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In this context, we envisioned that the Pd-catalyzed substitution might occur at the ortho-position if a nucleophilic moiety was installed in the benzylic substrate on its meta-carbon through an appropriate tether (Figure 1). The tether will restrict the intramolecular nucleophilic attack on the benzylic carbon (path a), enforcing the aromatic substitution (path b).[12] This paper describes the reactions of the meta-substituted benzylic carbonates with a Pd catalyst. As we had expected, the Pd catalyst successfully cyclized the substrates through the S_N'-type aromatic substitution. However, the substitution occurred not at the ortho-position but at the para-position.

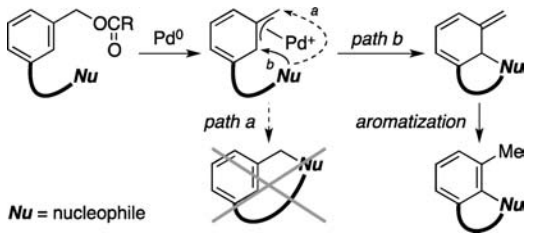
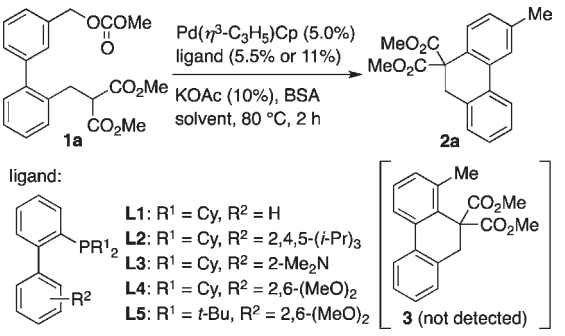


Figure 1. Substrate Design for S_N'-Type Aromatic Substitution.

An *o*-phenylene skeleton would be suitable for the tether because its rigid structure would be favorable for positioning the internal nucleophile around the ortho-position of the benzyl ester. In accordance with the idea, we designed the *m*-substituted benzyl ester **1** to achieve the intramolecular S_N'-type aromatic substitution. The substrate **1a** was heated in THF at 80 °C in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA), potassium acetate, and [Pd(η^3-C_3H_5)Cp]−DPPF catalyst, which is the most effective for the nucleophilic substitution of benzyl carbonates with malonate carbanions in our previous reports (Table 1, entry 1).[8a,b] Contrary to our expection, no formation of the 1-methyl-9,10-dihydrophenanthrene **3** was observed, while the substrate almost disappeared. Compound **1a** mainly underwent the intermolecular nucleophilic substitution to form oligomeric products. To our surprise, a small amount of 3-methyldihydrophenanthrene **2a** was detected in the reaction mixture (Table 1, entry 1). The observation indicates that the internal malonate in **1a** attacks the para-carbon in preference to the ortho-carbon in the case of the intramolecular reaction. With the aim to increase the cyclization, **1a** was heated under various reaction conditions. A more polar solvent seems favorable for the cyclization (entries 1−4). DMF is the solvent of choice for the intramolecular reaction. The selectivity as well as the conversion in the reaction of **1a** is affected by the phosphine ligand on palladium. The DPEphos ligand makes the undesirable oligomerization more predominant (entry 5). The desired cyclization was preferable to the side reaction when DPPB or DPPPent was employed as the spectator ligand (entries 6 and 7). Furthermore, a biaryl monophosphine ligand[13] **L1** was found comparable to DPPF (entry 8). The *o*-phenyl substituent of **L1** may be critical for the S_N'-type aromatic substitution. A Cy_2-PhP−palladium complex, which lacks the *o*-substituent, produced **2a** in only 11% yield (entry 9). The formation of **2a** was remarkably improved by use of biarylphosphine ligands bearing electron-rich substituents on their *o*-aryl group (entries 11−13). In particular, **L3** and **L4**[14] enabled the palladium catalyst to selectively promote the intramolecular S_N'-type aromatic substitution of **1a**, giving **2a** in high yield. Replacing cyclohexyl with *tert*-butyl on the phosphorus of **L4** increased the undesirable intermolecular reaction (entry 14). The catalyst loading can be reduced to

Table 1. Effect of Solvent and Ligand on the Reaction of **1a**[a]



entry	ligand	solvent	convn (%)	yield[b] (%)
1[c]	DPPF[d]	THF	99	15
2[c]	DPPF[d]	toluene	90	6
3[c]	DPPF[d]	1,4-dioxane	76	7
4[c]	DPPF[d]	DMF	>99	52
5[c]	DPEphos[d]	DMF	>99	16
6[c]	DPPB[d]	DMF	>99	78
7[c]	DPPPent[d]	DMF	96	81
8	**L1**	DMF	64	40
9	PCy_2Ph	DMF	48	11
10	PCy_3	DMF	29	0
11	**L2**	DMF	>99	77
12	**L3**	DMF	>99	89
13	**L4**	DMF	>99	88
14	**L5**	DMF	>99	13
15[e]	**L3**	DMF	>99	89[f]
16[e]	**L4**	DMF	>99	97[f]

[a] Reactions were conducted on a 0.1 mmol scale in 0.2 mL of solvent at 80 °C for 2 h. The ratio of **1a**/[Pd]/ligand/BSA/KOAc was 100:5.0:11:110:10. [b] Determined by GC analysis (average of two runs). [c] The ratio of [Pd]/ligand was 1.0:1.1. [d] The structures of the bidentate ligands are shown in Table 3. [e] The reactions were conducted on a 0.4 mmol scale in DMF (0.8 mL) with a 1.0 mol % catalyst loading ([Pd]/ligand = 1.0:2.2). [f] Isolated yield.

(12) A review of aromatic nucleophilic substitution: Burnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

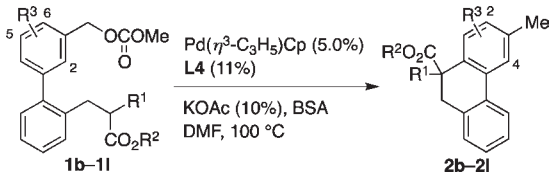
(13) A review for biaryl monophosphine: Surry, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(14) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

1 mol % without degradation of the yield of **2a** (entries 15 and 16).

Substrates **1b**−**1g** bearing an active methine other than dimethyl malonate underwent the intramolecular S_N2'-type aromatic substitution in the presence of the **L4**−Pd catalyst (Table 2, entries 1−6). Ethyl ester **1b** as well as **1a** was cyclized in high yield, although the cyclization of **1b** required a longer reaction time for its completion. In the reaction of isopropyl ester **1c**, the cyclization product **2c** was obtained in only 39% yield with a 1 mol % catalyst loading. Efficient production of **1c** was achieved by increasing the catalyst loading to 5 mol %. The intramolecular nucleophilic attack of the stabilized carbanion to the aromatic ring in **1** may be sensitive to the steric hindrance around the nucleophilic carbon. The Pd-catalyzed cyclization is applicable to the substrates **1d**−**1g** bearing either β-keto- or α-cyanocarboxylate in place of malonate. The benzyl esters **1h** and **1j**, which have a methoxy or fluoro group at their 5-position, also gave the cyclization products **2h** and **2j** in 97% and 67% yields, respectively (entries 7 and 9). Meanwhile, a 5-methyl substituent of **1i** caused the low yield of **2i** (entry 8). The correlation between the yield of **2** and the 5-substituent of **1** indicates that the S_N2'-type aromatic substitution is affected by the steric factor rather than the electronic property of the 5-substituent. 2,3-Dimethyldihydrophenanthrene **2k** was obtained in 60% yield from an *o*-methylbenzyl ester **1k**, while another *o*-methylated substrate **1l** failed to be converted to 3,4-dimethyldihydrophenanthrene **2l** in good yield (entries 10 and 11). The substrate **1** bearing a methyl group at the 4-position was subjected to the Pd-catalyzed reaction to allow the formation of the ortho-substitution product **3**. However, the reaction yielded only oligomers of the *p*-methylated substrate.

Table 2. Intramolecular S_N2'-Type Aromatic Substitution of **1**[a]

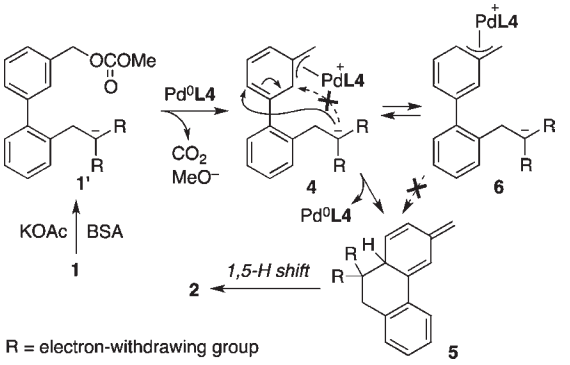


entry	R^1	R^2	R^3	**1**	time (h)	yield[b] (%)
1[c,d]	EtO_2C	Et	H	**1b**	24	98
2[d]	*i*-PrO_2C	*i*-Pr	H	**1c**	6	77
3[d]	MeCO	Et	H	**1d**	4	63
4[d]	*i*-PrCO	Me	H	**1e**	4	74
5	PhCO	Et	H	**1f**	4	86
6	NC	Me	H	**1g**	4	>99
7	MeO_2C	Me	5-MeO	**1h**	6	97
8	MeO_2C	Me	5-Me	**1i**	115	16
9	MeO_2C	Me	5-F	**1j**	2	67
10	MeO_2C	Me	6-Me	**1k**	7	60
11	MeO_2C	Me	2-Me	**1l**	4	25

[a] Reactions were conducted on a 0.2 mmol scale in DMF (0.4 mL) at 100 °C. The ratio of **1**/[Pd]/**L4**/BSA/KOAc was 100:5.0:11:110:10 unless otherwise noted. [b] Isolated yield. [c] The reaction was conducted on a 0.4 mmol scale in DMF (0.8 mL) with a 1.0 mol % catalyst loading. [d] The reactions were conducted at 80 °C.

The Pd-catalyzed intramolecular S_N2'-type aromatic substitution of **1** would proceed through the pathway as shown in Scheme 1. Substrate **1** is deprotonated by BSA and potassium acetate to give its stabilized carbanion **1′** before it reacts with the catalyst. The **L4**−Pd(0) species cleaves the benzylic C−O bond of **1′**, forming zwitterionic (η^3-benzyl)palladium **4**. The carbanion in intermediate **4** is hindered from attacking the ortho-carbon of the η^3-benzyl ligand by the bulkiness of the **L4**-ligated palladium. Therefore, the internal nucleophile reacts with the para-carbon in the manner of an S_N2' pathway. The resulting product **5** is aromatized through a 1,5-hydride shift[15] to produce 3-methyl-9,10-dihydrophenanthrene **2**. The palladium may be possible to form η^3-benzyl complex **6** with the 6-carbon of **1**. However, the intermediate **6** is supposed unfavorable for the intramolecular S_N2'-type reaction, because substrate **1l** gave the cyclization product in lower yield than **1k** (Table 2, entries 10 and 11). The 2-methyl group of **1l** may obstruct the formation of intermediate **4**.

Scheme 1. A Possible Pathway of the Cyclization of **1**

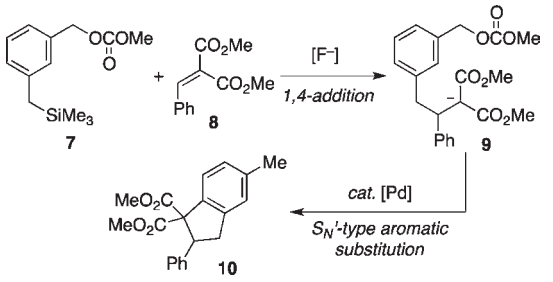


The above S_N2'-type aromatic substitution allowed us to come up with the [3 + 2] cycloaddition of *m*-(silylmethyl) benzyl carbonates **7** and benzylidene malonates **8** (Scheme 2).[16,17] The fluoride-mediated 1,4-addition of the benzylsilane **7** to the α,β-unsaturated carbonyl would afford the benzyl ester **9**,[18] which is tethered to the malonate carbanion with an alkyl chain. The [3 + 2]

(15) Jaeger, C. W.; Kornblum, N. *J. Am. Chem. Soc.* **1972**, *94*, 2545.
(16) The [4 + 2] cycloadditions of *o*-(silylmethyl)benzyl esters with double bonds: (a) Kuwano, R.; Shige, T. *J. Am. Chem. Soc.* **2007**, *129*, 3802. (b) Ueno, S.; Ohtsubo, M.; Kuwano, R. *J. Am. Chem. Soc.* **2009**, *131*, 12904. (c) Ueno, S.; Ohtsubo, M.; Kuwano, R. *Org. Lett.* **2010**, *12*, 4332.
(17) Selected examples of transition-metal catalyzed [3 + 2] cycloaddition with carbon−carbon double bonds giving indan skeletons: (a) Lautens, M.; Mancuso, J. *Org. Lett.* **2002**, *4*, 2105. (b) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 7506. (c) Yu, X.; Lu, X. *Org. Lett.* **2009**, *11*, 4366.
(18) Ricci, A.; Fiorenza, M.; Grifagni, M. A.; Bartolini, G.; Seconi, G. *Tetrahedron Lett.* **1982**, *23*, 5079.

cycloaddition product **10** might be obtained if the in situ generated **9** was cyclized in the same way as **1**.

Scheme 2. Design of the [3 + 2] Cycloaddition of **7** with **8**



A solution of **7** and **8** in DMF was heated at 80 °C for 3 h in the presence of cesium fluoride and the **L4**–palladium catalyst (Table 3, entry 1). Formation of the desired [3 + 2] cycloaddition product **10** was observed in the resulting mixture with GC analysis, but its yield was only 23%. To improve the Pd catalyst, a series of phosphine ligands other than **L4** were evaluated for the reaction of **7** with **8**. In contrast to the cyclization of **1**, bidentate bisphosphine ligands are more suitable for the catalytic cycloaddition than Buchwald-type biarylphosphines. A DPPB–Pd catalyst produced **10** in 42% yield at 3 h (entry 5). The substrate **7** completely disappeared at 3 h, while a longer reaction time led to a higher yield of the cycloaddition product. This suggests that the [3 + 2] cycloaddition proceeds through the sequence of the fluoride-mediated 1,4-addition[18] and the Pd-catalyzed S_N'-type aromatic substitution as shown in Scheme 2. To confirm the pathway, the reaction of **7** with **8** was conducted in the absence of the Pd catalyst (eq 1). As expected, the benzyl silane **7** added to the electron-deficient alkene **8** to give intermediate **9** in 51% isolated yield without formation of **10**. The resulting benzyl ester **9** was cyclized by the DPPB–Pd catalyst to form **10** (eq 2). The cyclization step can proceed in the absence of cesium fluoride, but the fluoride ion works as a base to facilitate the S_N'-type aromatic substitution.

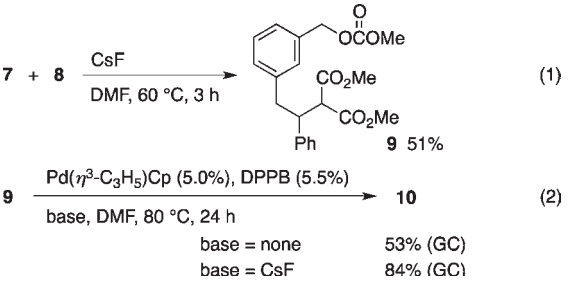
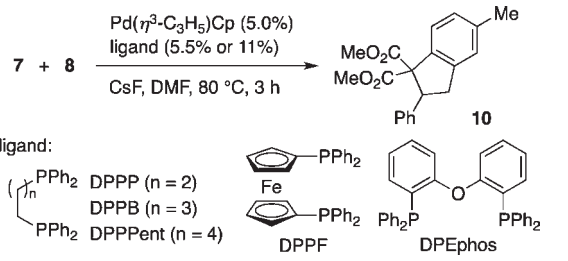


Table 3. Effect of Ligand on the Reaction of **7** with **8**[a]



entry	ligand	yield, %[b]
1[c]	**L4**	23
2[c]	**L3**	33
3[c]	**L2**	35
4	DPPP	31
5	DPPB	42 (57)[d]
6	DPPPent	23
7	DPPF	34
8	DPEphos	37
9[e]	DPPB	49[f]

[a] Reactions were conducted on a 0.1 mmol scale in 0.4 mL of DMF at 80 °C for 3 h. The ratio of **7**/**8**/[Pd]/ligand/CsF was 120:100:5.0:5.5:100. [b] Determined by GC analysis (average of two runs). [c] The ratio of [Pd]/ligand was 1.0:2.2. [d] GC yield at 24 h. [e] The reaction was conducted on a 0.4 mmol scale for 24 h. [f] Isolated yield.

In conclusion, we successfully proved that benzyl carbonates are able to react with a nucleophile on their aromatic ring in the manner of an S_N' pathway in the presence of a palladium catalyst. The aromatic nucleophilic substitution requires an internal nucleophile, which is installed in the electrophilic substrate at the meta-position. The nucleophilic moiety attacks the para-position of the benzyl ester exclusively, giving 3-methyldihydrophenanthrene. Furthermore, the [3 + 2] cycloaddition of a *m*-(silylmethyl)benzyl carbonate with a benzylidene malonate was developed from the palladium-catalyzed S_N'-type aromatic substitution.

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