Palladium-catalyzed Nucleophilic Substitution of Diarylmethyl Carbonates with Malonate Carbanions

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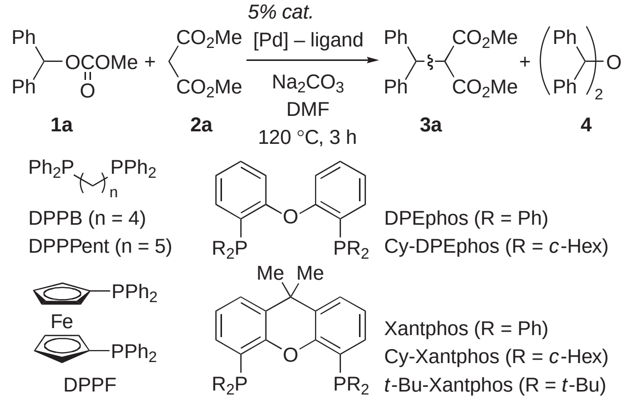
The nucleophilic substitution of diarylmethyl carbonates with malonate carbanions proceeded in the presence of [Pd(π-C_3H_5)(cod)]BF_4–Cy-Xantphos, giving the desired (diarylmethyl)malonates in up to 90% yield. The yield was extremely affected by choice of the phosphine ligand.

Nucleophilic substitution is a fundamental reaction in organic synthesis.[1] Alkyl halides or sulfonates have been chosen for an electrophilic substrate commonly. Carboxylate functionality has seldom been utilized as a leaving group on the electrophilic substrate because of its low reactivity. Anomalistically, substitution of allylic carboxylates has often been utilized in organic synthesis by means of homogeneous palladium catalysis.[2] Palladium(0) cleaves the allylic C–O bond to form (π-allyl)palladium intermediate, which readily reacts with various nucleophiles. Meanwhile, we reported recently that a palladium-catalyzed nucleophilic substitution of benzylic carbonates.[3–5] As with the catalytic allylic substitution, the benzylic C–O bond was activated by palladium(0) to provide (π-benzyl)palladium intermediate. However, the substrates for the catalytic benzylic substitution have been limited to benzylic esters having no α-substituent, with the exception of 1-(naphthyl)ethyl acetates.[4,6] This paper describes a palladium-catalyzed nucleophilic substitution of benzylic carbonates possessing an aryl substituent at the α-position, i.e. diarylmethyl esters.

Reaction of diphenylmethyl carbonate **1a** with malonate **2a** was attempted under various reaction conditions. The desired (diphenylmethyl)malonate **3a** was obtained in 80% yield when the reaction was conducted in DMF at 120 °C in the presence of sodium carbonate and 5 mol % of the palladium complex generated from [Pd(π-C_3H_5)(cod)]BF_4 and a bidentate ligand Cy-Xantphos (Table 1, Entry 8). The choice of ligand on palladium is crucial for the benzylic substitution of **1a**. Triphenylphosphine–palladium catalyst produced no **3a** and a small amount of bis(diphenylmethyl) ether (**4**) (Entry 1). The production of **3a** was not achieved by using chelate ligands bearing two diphenylphosphino groups (Entries 2–5). Only Xantphos[7] gave **3a** in recognizable yield (10%), but **4** was obtained preferentially (Entry 6). The undesirable formation of **4** was successfully evaded with cyclohexyl-substituted bisphosphine ligands (Entries 7 and 8). Cy-Xantphos afforded **3a** in 80% yield at 24 h. However, the benzylic substitution of **1a** was remarkably hindered by bulky *tert*-butyl groups of *t*-Bu-Xantphos (Entry 9). The palladium catalysis was strongly affected by base and solvent. Sodium carbonate is the base of choice. Potassium carbonate could give **3a** but seemed to cause decomposition of the palladium catalyst (Entry 10). Use of nitrogen compounds as a base obstructed consumption of **1a** (Entry 11). Methoxide librated from **1a** might be possible to serve as a base for generating malonate carbanion, but **3a** was obtained in 3% yield with no base.[8] The reaction of **1a** with **2a** barely proceeded in solvents other than DMF. Base and solvent did not affect the production of the side product **4** much. The catalytic alkylation of **2a** with **1a** proceeded with 1% catalyst loading, affording **3a** in 90% isolated yield (Table 2, Entry 1).

Table 1. Effect of phosphine ligand on the reaction of **1a** with **2a**[a]

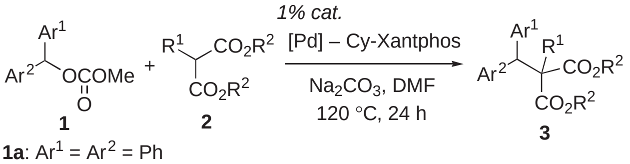


Entry	Ligand	Yield (**3a**)/%[b]	Yield (**4**)/%[b]
1	PPh_3[c]	0	6
2	DPPB	1	12
3	DPPPent	2	13
4	DPPF	2	23
5	DPEphos	2	9
6	Xantphos	10	26
7	Cy-DPEphos	10	7
8	Cy-Xantphos	31 (80)	3 (8)
9	*t*-Bu-Xantphos	2	0
10[d]	Cy-Xantphos	38 (44)	3 (8)
11[e]	Cy-Xantphos	9	6

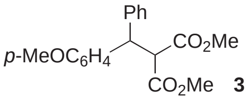
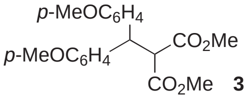
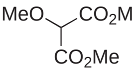
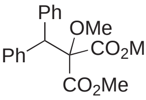
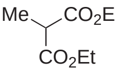
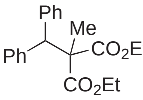
[a] Reactions were conducted in DMF (1.0 mL). [Pd(π-C_3H_5)(cod)]BF_4 was used as a palladium catalyst precursor. The ratio of **1a** (0.20 mmol):**2a**:Na_2CO_3:[Pd]:ligand was 20:30:30:1:1.1. [b] GC yield at 3 h (average of two runs). GC yields at 24 h were given in parentheses. [c] The ratio of [Pd]:PPh_3 was 1:2.2. [d] K_2CO_3 was used in place of Na_2CO_3. [e] DBU was used in place of Na_2CO_3.

As shown in Table 2, the benzylic substitutions of other diarylmethyl carbonates with malonates were attempted under the reaction conditions optimized above. Electron-rich substrate **1b**, which have a methoxy group, was converted into **3b** in 55% yield (Entry 2). Further introduction of a methoxy group on another benzene ring of **1** resulted in remarkable decrease in the yield of **3** (Entry 3). The electron-donating group caused the formation of diarylmethyl methyl ether, which was generated through thermal decarboxylation. In contrast, no reactions were

Table 2. Benzylic substitution of **1** with malonate carbanions[a]



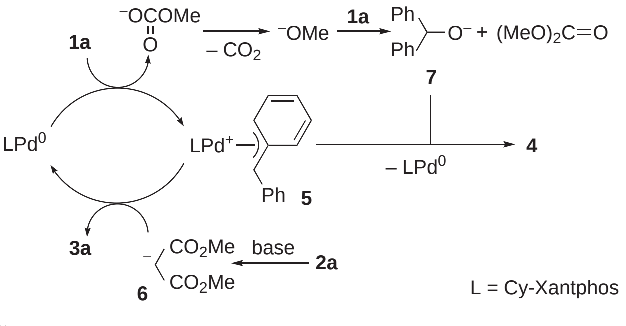
1a: Ar^1 = Ar^2 = Ph
1b: Ar^1 = Ph, Ar^2 = p-MeOC$_6$H$_4$
1c: Ar^1 = Ar^2 = p-MeOC$_6$H$_4$

Entry	1	2	Product (3)	Yield/%[b]
1[c]	**1a**	**2a**	**3a**	90
2	**1b**	**2a**	 **3b**	55
3	**1c**	**2a**	 **3c**	25
4	**1a**	 **2b**	 **3d**	86
5[d]	**1a**	 **2c**	 **3e**	57

[a] Reactions were conducted in DMF (1.0 mL) for 24 h. [Pd(π-C$_3$H$_5$)(cod)]BF$_4$ was used as a palladium catalyst precursor. The ratio of **1** (1.0 mmol):**2**:Na$_2$CO$_3$:[Pd]:ligand was 100:120:130:1:1.1. [b] Isolated yields. [c] The reaction was conducted for 16 h. [d] The reaction was conducted in 0.2 mmol scale with 5% palladium loading.

observed in the case of diarylmethyl carbonate possessing an electron-withdrawing group, such as trifluoromethyl and alkoxycarbonyl. Several α-substituted malonates underwent the reaction with **1**. Carbonate **1a** was reacted with dimethyl methoxymalonate (**2b**), giving **3d** in high yield (Entry 4). The reaction of methylmalonate **2c** required 5% palladium loading for the production of **3e** (Entry 5). Diethyl phenylmalonate scarcely reacted with **1a**. The reactivity of **2** was strongly affected by the steric hindrance of the α-substituent.

A possible reaction pathway of the catalytic benzylic substitution of diarylmethyl carbonates is shown in Scheme 1. The benzylic C–O bond of **1a** undergoes the oxidative addition to Cy-Xantphos–palladium(0), forming (π-benzyl)palladium **5**. The intermediate **5** reacts with malonate carbanion **6** to afford the alkylated product **3a**. The formation of the side product **4** is rationalized as follows: the methoxide liberated from **1a** through the oxidative addition or water contained in reagents may bring about the solvolysis giving diarylmethoxide **7**, which can attack the π-benzyl ligand on palladium of **5**. The steric hindrance of cyclohexyl group of Cy-Xantphos might suppress the nucleophilic attack of **7** as well as accelerating that of **6**. t-Bu-Xantphos would be too bulky for **1a** to react with palladium(0).



Scheme 1. Possible reaction pathway of the benzylic substitution of **1a**.

We developed the palladium-catalyzed alkylation of malonate carbanions with diarylmethyl carbonates, which are one of α-substituted benzylic esters. The catalytic nucleophilic substitution proceeded efficiently in the presence of [Pd(π-C$_3$H$_5$)(cod)]BF$_4$–Cy-Xantphos catalyst. Phosphine ligand extremely affected the catalysis. Unfortunately, the optimal palladium catalyst failed to bring about the nucleophilic substitution of α-alkylated benzylic esters. Investigation of the reaction is in progress.

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References and Notes

1 M. B. Smith, J. March, in *March's Advanced Organic Chemistry*, 5th ed., John Wiley & Sons, Inc., New York, **2001**, Chap. 10, p. 389.
2 G. Hata, K. Takahashi, A. Miyake, *J. Chem. Soc., Chem. Commun.* **1970**, 1392; K. E. Atkins, W. E. Walker, R. M. Manyik, *Tetrahedron Lett.* **1970**, *11*, 3821; B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; J. Tsuji, in *Palladium Reagents and Catalysts*, John Wiley & Sons, Inc., West Sussex, **2004**, Chap. 4, p. 431.
3 R. Kuwano, Y. Kondo, Y. Matsuyama, *J. Am. Chem. Soc.* **2003**, *125*, 12104; R. Kuwano, Y. Kondo, *Org. Lett.* **2004**, *6*, 3545; R. Kuwano, Y. Kondo, T. Shirahama, *Org. Lett.* **2005**, *7*, 2973.
4 J.-Y. Legros, J.-C. Fiaud, *Tetrahedron Lett.* **1992**, *33*, 2509; J.-Y. Legros, M. Toffano, J.-C. Fiaud, *Tetrahedron* **1995**, *51*, 3235; M. Toffano, J.-Y. Legros, J.-C. Fiaud, *Tetrahedron Lett.* **1997**, *38*, 77; J.-Y. Legros, G. L. Primault, M. Toffano, M.-A. Rivière, J.-C. Fiaud, *Org. Lett.* **2000**, *2*, 433; M. Assié, J.-Y. Legros, J.-C. Fiaud, *Tetrahedron: Asymmetry* **2005**, *16*, 1183.
5 H. Narahashi, A. Yamamoto, I. Shimizu, *Chem. Lett.* **2004**, *33*, 348; Y.-S. Lin, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 723.
6 Recently, Yasuda and Baba reported that indium chloride was an effective catalyst for the nucleophilic substitution of α-substituted benzylic alcohols, see: M. Yasuda, T. Somyo, A. Baba, *Angew. Chem., Int. Ed.* **2006**, *45*, 793.
7 M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.
8 Pd(Cp)(η^3-C$_3$H$_5$) was used as a palladium source for the reaction.
9 Supporting information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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