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Palladium-Catalyzed Nucleophilic Benzylic Substitutions of Benzylic Esters

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η^3-Allyl-metal complex **1** is a key intermediate of many organic reactions employing transition metal complexes. Palladium-catalyzed allylic substitution of allylic esters is representative of the reactions mediated by **1**.[1] The analogous η^3-benzyl-metal complex intermediate **2**[2] has often been cited in rationalization of regioselectivities in catalytic additions to vinylarenes using a transition metal complex.[3] However, palladium-catalyzed nucleophilic benzylic substitution of benzylic esters has not been well-established despite its potential usefulness. Fiaud and Legros had reported that a DPPE-palladium complex displayed catalytic activity for benzylic substitutions of naphthylmethyl and quinolylmethyl esters.[4] The palladium catalyst, however, failed to promote reaction of benzyl acetate.[4a] This paper discloses that a palladium complex is a good catalyst for benzylic substitutions of benzyl esters with malonates and amines. The palladium catalyst is applicable to reaction with a wide range of benzylic esters.

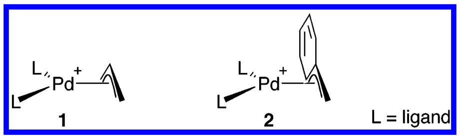
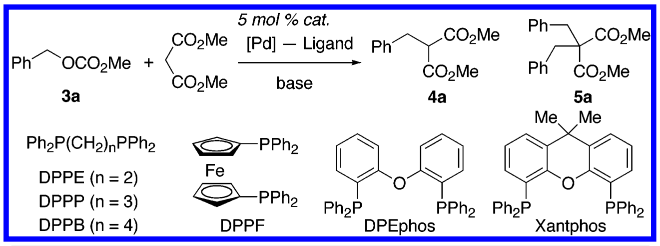


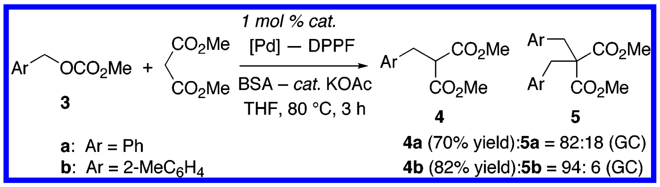
Table 1. Benzylic Alkylation of **3a** with Dimethyl Malonate[a]



entry	[Pd][b]	ligand	base[c]	convn (**3a**), %[d]	yield (**4a**), %[d]	**4a**:**5a**[e]
1	A	DPPF	BSA	20	16	
2	B	DPPF	BSA	34	27	71:29
3	C	DPPF	BSA	99	74	77:23
4	C	DPPF	DBU	23	13	
5	C	DPPF	KO(*t*-Bu)	49	23	69:31
6	C	DPPF	Cs_2CO_3	29	19	
7	C	2 PPh_3	BSA	0	0	
8	C	DPPE	BSA	3	2	
9	C	DPPP	BSA	16	10	
10	C	DPPB	BSA	39	41	88:12
11	C	DPEphos	BSA	74	62	83:17
12	C	Xantphos	BSA	71	62	86:14

[a] Reactions were conducted in THF (1.0 mL) at 80 °C for 3 h. The ratio of **3a** (0.2 mmol):dimethyl malonate:base:Pd:ligand = 20:30:30:1:1.1. [b] A, $Pd(dba)_2$; B, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$; C, $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$. [c] KOAc (15 μmol) was added to the reaction mixture when BSA was used as a base. [d] Determined by GC. [e] The ratios were calculated from the GC areas.

Scheme 1



Various palladium catalyst precursors, ligands, bases, and solvents were evaluated for the reaction of benzyl methyl carbonate (**3a**) and dimethyl malonate. Selected results are shown in Table 1. The combination of $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$, DPPF, and BSA provided the desired product **4a** in the highest yield.[5] The rate of the reaction was heavily affected by the base and precursor of palladium catalyst. The appropriate choice of the ligand on palladium is also important for catalysis. Palladium complex containing monodentate phosphine promoted no benzylic alkylation. DPPE, which had been used for benzylic substitution of naphthylmethyl esters,[4] was ineffective in the catalytic benzylic alkylation of **3a**. Increasing the ligand bite angle enhanced the reaction rate.[6] The highest conversion of **3a** and yield of **4a** was observed in a reaction using DPPF ligand. However, DPEphos and Xantphos, providing a larger P−Pd−P angle, were less effective than DPPF.[7]

The amount of the palladium catalyst was reduced to 1 mol % without a significant loss of yield of **4a** (Scheme 1). Although considerable formation of **5a** was observed in the reaction of **3a**, the *ortho*-substituent of the benzylic ester suppressed the formation of a dibenzylated product. The benzylic alkylation of **3b** produced the monoalkylated malonate **4b** in 82% isolated yield with a small amount of **5b**.

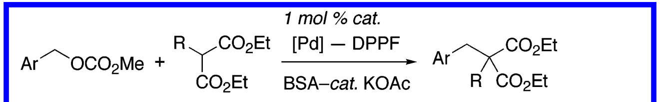
Reactions of various combinations of benzylic carbonate **3** and substituted malonates **6** were conducted in the presence of 1 mol % of the $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$−DPPF catalyst, providing the corresponding benzylated products **7** in high yields as shown in Table 2. The *ortho*-substituent on an aromatic ring of **3** did not hinder the alkylation of **6**. Both electron-rich and electron-poor benzylic esters, **3c** and **3e**, respectively, underwent benzylic alkylation without deterioration in the reaction rate. The catalytic reaction possesses high functional group compatibility. The benzylations of acetamido- (**6c**) and methoxymalonate (**6d**) proceeded with no deactivation of the palladium catalyst to produce α-heterosubstituted benzylmalonates in high yields. The former reactions may provide a good synthetic approach to functionalized phenylalanine derivatives.[8] Reactions of naphthylmethyl esters were completed within 1 h to give the coupling products **7p** and **7q** in high yields.

To clarify the substituent effect of **3** on the reaction rate, reactions of **6b** with equimolar mixtures of **3a** and **3c**, **3a** and **3e**, and **3c** and **3e** were conducted, and the results of these experiments are shown in Scheme 2. Both *p*-methoxy and *p*-trifluoromethyl groups accelerated the benzylic substitution. The findings indicate that the inductive effect of the substituent on the aromatic ring may control the reaction rate rather than the resonance effect.

A palladium complex generated from $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$ and a bidentate phosphine ligand exhibited high catalytic activity for

10.1021/ja037735z CCC: $25.00

Table 2. Catalytic Benzylations of 2-Substituted Malonates[a]



3a: Ar = Ph
3b: Ar = 2-MeC$_6$H$_4$
3c: Ar = 4-MeOC$_6$H$_4$
3d: Ar = 4-MeC$_6$H$_4$
3e: Ar = 4-CF$_3$C$_6$H$_4$
3f: Ar = 4-ClC$_6$H$_4$
3g: Ar = 4-MeO$_2$CC$_6$H$_4$
3h: Ar = 1-Naphthyl
3i: Ar = 2-Naphthyl

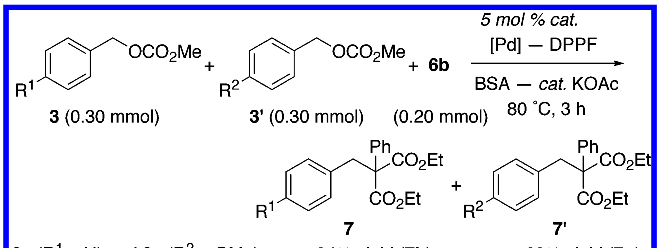
6a: R = Me
6b: R = Ph
6c: R = AcNH
6d: R = MeO

7a: Ar = Ph, R = Me
7b: Ar = Ph, R = Ph
7c: Ar = Ph, R = AcNH
7d: Ar = Ph, R = MeO
7e: Ar = 2-MeC$_6$H$_4$, R = AcNH
7f: Ar = 2-MeC$_6$H$_4$, R = MeO
7g: Ar = 4-MeOC$_6$H$_4$, R = Ph
7h: Ar = 4-MeOC$_6$H$_4$, R = AcNH
7i: Ar = 4-MeOC$_6$H$_4$, R = MeO
7j: Ar = 4-MeC$_6$H$_4$, R = Ph
7k: Ar = 4-MeC$_6$H$_4$, R = AcNH
7l: Ar = 4-CF$_3$C$_6$H$_4$, R = Ph
7m: Ar = 4-CF$_3$C$_6$H$_4$, R = MeO
7n: Ar = 4-ClC$_6$H$_4$, R = Ph
7o: Ar = 4-MeO$_2$CC$_6$H$_4$, R = Ph
7p: Ar = 1-Naphthyl, R = Me
7q: Ar = 2-Naphthyl, R = Me

entry	**3**	**6**	time, h	product	yield, %[b]
1[c]	**3a**	**6a**	48	**7a**	61
2	**3a**	**6b**	24	**7b**	95
3	**3a**	**6c**	48	**7c**	89
4	**3a**	**6d**	48	**7d**	88
5	**3b**	**6c**	48	**7e**	84
6	**3b**	**6d**	24	**7f**	92
7	**3c**	**6b**	4	**7g**	94
8	**3c**	**6c**	24	**7h**	>99
9	**3c**	**6d**	24	**7i**	94
10	**3d**	**6b**	24	**7j**	98
11	**3d**	**6c**	48	**7k**	89
12	**3e**	**6b**	48	**7l**	78
13	**3e**	**6d**	48	**7m**	83
14	**3f**	**6b**	48	**7n**	79
15	**3g**	**6b**	24	**7o**	86
16	**3h**	**6a**	1	**7p**	92
17	**3i**	**6a**	1	**7q**	92

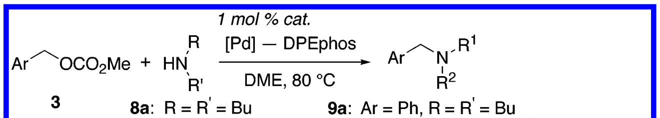
[a] Reactions were conducted in THF (1.0 mL) at 80 °C. The ratio of **3** (1.0 mmol):**6**:base:KOAc:[Pd(η^3-C$_3$H$_5$)(cod)]BF$_4$:DPPF was 100:110:110:7.5:1:1.1 unless otherwise noted. [b] Isolated yield. [c] 1.5 mmol of **6a** and BSA was used.

Scheme 2



	7	**7'**
3a (R^1 = H) and **3c** (R^2 = OMe)	34% yield (**7b**)	68% yield (**7g**)
3a (R^1 = H) and **3e** (R^2 = CF$_3$)	24% yield (**7b**)	63% yield (**7l**)
3c (R^1 = OMe) and **3e** (R^2 = CF$_3$)	43% yield (**7g**)	58% yield (**7l**)

Table 3. Catalytic Benzylic Amination of Benzylic Esters[a]



8a: R = R' = Bu
8b: morpholine
8c: R = Ph, R' = H

9a: Ar = Ph, R = R' = Bu
9b: Ar = 2-MeC$_6$H$_4$, R = R' = Bu
9c: Ar = 4-MeOC$_6$H$_4$, R = R' = Bu
9d: Ar = 4-CF$_3$C$_6$H$_4$, R = R' = Bu
9e: Ar = 4-MeO$_2$CC$_6$H$_4$, R = R' = Bu
9f: Ar = 1-Naphthyl, R = R' = Bu
9g: Ar = 1-Naphthyl, R, R' = O(CH$_2$CH$_2^-$)$_2$
9h: Ar = 1-Naphthyl, R = Ph, R' = H

entry	**3**	**8**	time, h	product	yield, %[b]
1	**3a**	**8a**	96	**9a**	73
2[c]	**3b**	**8a**	24	**9b**	80
3[c]	**3c**	**8a**	24	**9c**	90
4	**3e**	**8a**	3	**9d**	88
5[c]	**3g**	**8a**	1	**9e**	96
6	**3h**	**8a**	1	**9f**	93
7	**3h**	**8b**	1	**9g**	98
8	**3h**	**8c**	24	**9h**	94

[a] Reactions were conducted in DME (1.0 mL) at 80 °C. The ratio of **3** (1.0 mmol):**8**:[Pd(η^3-C$_3$H$_5$)(cod)]BF$_4$:DPEphos was 100:110:1:1.1 unless otherwise noted. [b] Isolated yield. [c] 2 mol % of catalyst was used.

benzylic amination of benzylic esters as well as alkylation. DPEphos ligand is superior to DPPF in the reaction of **3a** with dibutylamine (**8a**).[9,10] The scope of the benzylic amination using the palladium-DPEphos catalyst is shown in Table 3. A wide range of benzylic amines can be prepared by the palladium-catalyzed reaction. Of note is that the benzylations of amines proceeded with no base to give the desired products in high yields, while common benzylations of amines with benzylic halides have required a stoichiometric amount of base for neutralization of hydrogen halide. The reaction may be useful for benzyl protection of amino groups in base-sensitive compounds.

In conclusion, palladium complexes with a bisphosphine ligand bearing an appropriate bite angle were found to catalyze nucleophilic benzylic substitution of benzylic esters with high generality. This finding may prove the usefulness of (η^3-benzyl)palladium as an intermediate in catalytic processes such as that of the (η^3-allyl)palladium complex.

Acknowledgment. This work was supported by the Kurata Memorial Hitachi Science and Technology Foundation.

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

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(5) The reaction of **3a** employing Pd(dba)$_2$ or [Pd(η^3-C$_3$H$_5$)(cod)]BF$_4$−DPPF catalyst yielded neither **4a** nor **5a** in the absence of base.
(6) Bite angles of DPPE, DPPP, DPPB, and DPPF in the palladium dichloride complexes are 86°, 91°, 95°, and 99°, respectively: (a) Steffen, W. L.; Palenik, G. J. *Inorg. Chem.* **1976**, *15*, 2432−2439. (b) Makhaev, V. D.; Dzhabieva, Z. M.; Konovalikhin, S. V.; D'yachenko, O. A.; Belov, G. P. *Russ. J. Coord. Chem.* **1996**, *22*, 563−567. (c) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.
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(9) We evaluated DPPF, DPEphos, and Xantphos for the reaction of **3a** and **8a** with 5 mol % of catalyst. GC yields (3 h) were 7%, 23%, and 8%, respectively.
(10) No benzylic amine **9f** was detected by GC analysis in the reaction of **3h** and **8a** at 80 °C in DME without the palladium catalyst.

JA037735Z