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Palladium-Catalyzed Double Alkylation of 3-Aryl-2-fluoroallyl Esters with Malonate Nucleophiles through the Carbon−Fluorine Bond Cleavage

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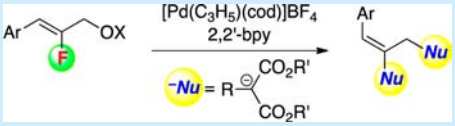
Supporting Information

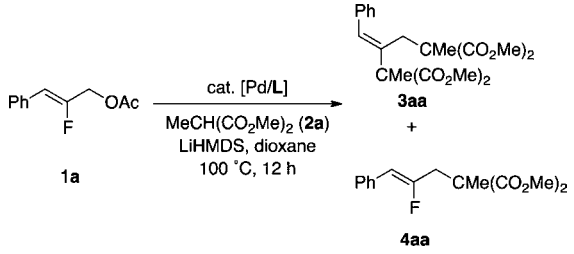
ABSTRACT: The alkylation of (*Z*)-3-aryl-2-fluoroallyl acetate with the malonate anion by the $[Pd(C_3H_5)(cod)]BF_4$/2,2′-bpy catalyst proceeds through the carbon−fluorine bond cleavage, and 2 equiv of the malonate nucleophile was introduced to the allyl substrate.



It is well-known that the palladium-catalyzed allylic alkylation of allyl esters usually proceeds through π-allyl palladium intermediates, and nucleophiles generally attack the terminal carbon atom of the π-allyl group to produce the allylic alkylated compounds.[1] On the other hand, as an alternative reaction process, nucleophilic attack at the central carbon atom of the π-allyl moiety provides cyclopropane derivatives under the appropriate reaction conditions.[2] Furthermore, three groups have discovered that the disubstituted products, in which nucleophiles attack both the terminal and central carbon atoms of the π-allyl palladium complex, were obtained from the reaction of 2-haloallyl compounds.[3−5] In 1995, Bäckvall reported the double alkylation of the 2-chloro-π-allyl palladium complex with sodium dialkyl methylmalonate.[3] The palladium-catalyzed double etherification of 2,3-dibromo-1-propene with sodium phenoxide was demonstrated by Organ's group in 1997.[4] They further succeeded in obtaining the doubly alkylated product as a major product from the reaction with malonate nucleophile, but the reaction required a catalytic amount of phenoxide and detectable amount of doubly substituted products by both the malonate and phenoxide anions. Murai et al. also reported that the palladium-catalyzed reaction of 2-chloroallyl compounds provides doubly substituted products with two different nucleophiles.[5] Although they previously discovered that the platinum catalyst gave a doubly alkylated product with the malonate anion,[6] to the best our knowledge, there is no example of the selective formation of the doubly alkylated product by palladium catalyst without phenoxide. Furthermore, these examples of the double substitution reactions were limited to the reaction of the 2-bromo- or 2-chloroallyl compounds. However, during the course of our study on the palladium-catalyzed allylic substitutions of fluorine-contained allyl compounds,[7] we found that the double alkylation of 2-fluorocinnamyl acetate with malonate nucleophiles proceeded through the carbon−fluorine bond cleavage.[8] We now report the $[Pd(C_3H_5)(cod)]$-BF_4/2,2′-bipyridine-catalyzed stereoselective double alkylation of 3-aryl-2-fluoroallyl esters with malonate nucleophiles.

We initially examined the palladium-catalyzed allylic alkylation of (*Z*)-2-fluoro-3-phenylallyl acetate ((*Z*)-**1a**) with the lithium dimethyl methylmalonate, which was generated in situ from dimethyl methylmalonate and LiHMDS. As shown in Table 1, the reaction of (*Z*)-**1a** with **2a** without palladium catalyst did not give any substituted products (entry 1), and the reactions of (*Z*)-**1a** by palladium acetate with PPh_3 gave the

Table 1. Palladium Catalysts for the Alkylation of 1a with 2a[a]



entry	[Pd] (mol %)	L (mol %)	yield (%)[b] 3aa	4aa
1			0	0
2	$Pd(OAc)_2$ (10)	PPh_3 (20)	0	97
3	$Pd(OAc)_2$ (10)	dppe (10)	22	44
4	$Pd(OAc)_2$ (10)	dppp (10)	18	52
5	$Pd(OAc)_2$ (10)	bpy (10)	34	<2
6	$Pd_2(dba)_3$ (5)	bpy (10)	46	<2
7	$[PdCl(C_3H_5)]_2$ (5)	bpy (10)	52	<2
8	$[Pd(C_3H_5)(cod)]BF_4$ (10)	PPh_3 (20)	0	99
9	$[Pd(C_3H_5)(cod)]BF_4$ (10)	dppe (10)	36	54
10	$[Pd(C_3H_5)(cod)]BF_4$ (10)	dppp (10)	13	61
11	$[Pd(C_3H_5)(cod)]BF_4$ (10)	bpy (10)	86 (90)[c]	<2
12	$[Pd(C_3H_5)(cod)]BF_4$ (10)	tmeda (10)	35	12
13	$Pd(dppp)_2$ (10)		37	41

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), [Pd] (5 or 10 mol %), **L** (10 or 20 mol %), LiHMDS (2.8 equiv, 1.0 M in THF), dioxane (5.0 mL). [b]The yields were determined by ^1H NMR. [c]Isolated yield is shown in parentheses.

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usual linear-type allylic alkylation product **4aa** (entry 2). However, when the phosphine ligand was changed from PPh_3 to dppe or dppp, we detected the formation of the doubly alkylated product (tetraester) (*E*)-**3aa** together with **4aa** (entries 3 and 4). The selective formation of the doubly alkylated product (*E*)-**3aa** was attained using 2,2′-bipyridine (bpy) as a ligand, but the yield was poor (entry 5). To improve the yield of (*E*)-**3aa**, we screened several palladium precatalysts, such as $Pd_2(dba)_3$, $[PdCl(C_3H_5)]_2$, or $[Pd(C_3H_5)(cod)]BF_4$. The reactions using $Pd_2(dba)_3$ or $[PdCl(C_3H_5)]_2$ with bpy gave the desired product (*E*)-**3aa** in 46% and 52% yields, respectively (entries 6 and 7). To our delight, the highest yield (86% NMR yield, 90% isolated yield) was obtained by the combination of $[Pd(C_3H_5)(cod)]BF_4$ with bpy (entry 11). The exact structure, including olefin geometry, of product (*E*)-**3aa** was determined by an X-ray crystallographic analysis (Figure 1).[9,10] We also examined the reaction using $[Pd(C_3H_5)(cod)]$-

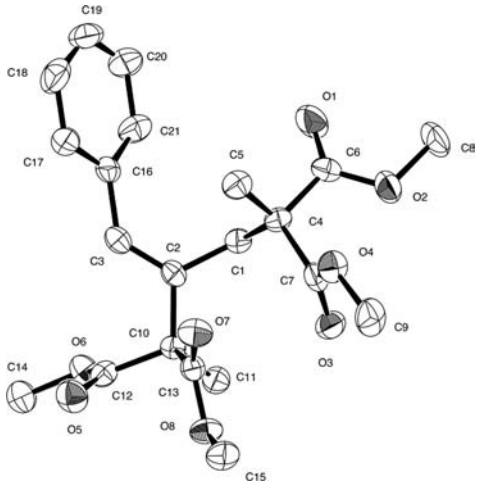
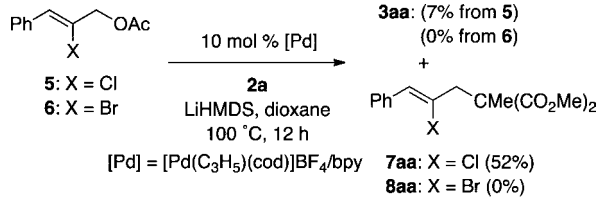


Figure 1. X-ray crystal structure of **3aa**.

BF_4/tmeda (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)[3] or Pd-(dppp)$_2$,[4] but both catalysts gave a mixture of **3aa** and **4aa** with low yields (entries 12 and 13). We further confirmed that the reaction of 2-chlorocinnamyl acetates (**5**) provide **7aa** as a major product and the reaction of 2-bromocinnamyl acetates (**6**) did not gave any doubly alkylated product **3aa** under optimized conditions (Scheme 1).[11] Those results indicate that

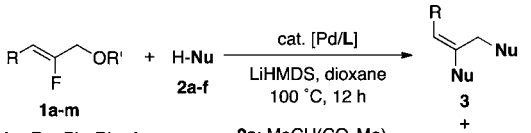
Scheme 1. Palladium-Catalyzed Reaction of 2-Halocinnamyl Acetates 5 and 6



the fluorine atom of **1a** stabilizes positive charge at C-2 carbon of the π-allylpalladium intermediate more strongly than chlorine or bromine atom, and nucleophiles selectively attack at the C-2 carbon bearing a fluorine atom.

We next investigated the $[Pd(C_3H_5)(cod)]BF_4$/bpy-catalyzed double alkylation of several 2-fluoroallyl esters with malonate anions, and the results are summarized in Table 2.

Table 2. $[Pd(cod)(C_3H_5)]BF_4$/bpy-Catalyzed Double Alkylation of 1 with 2



1a: R = Ph, R' = Ac
1a': R = Ph, R' = CO_2Me
1b: R = 4-$MeOC_6H_4$, R' = Ac
1c: R = 4-$CF_3C_6H_4$, R' = Ac
1d: R = 4-ClC_6H_4, R' = Ac
1e: R = 2-MeC_6H_4, R' = Ac
1f: R = 1-naphthyl, R' = Ac
1g: R = 2-naphthyl, R' = Ac
1h: R = $PhCH_2CH_2$, R' = Ac
1i: R = cyclohexyl, R' = Ac
1j: R = H, R' = Ac
1k: R = 2-furyl, R' = Ac
1l: R = 2-(*N*-methylpyrrolyl), R' = Ac
1m: R = 2-thienyl, R' = Ac

2a: $MeCH(CO_2Me)_2$
2b: $MeCH(CO_2Et)_2$
2c: $CH_2(CO_2Me)_2$
2d: $CH_2(CO_2Et)_2$
2e: $CH_2(CO_2{}^tBu)_2$
2f: $Me(O)CH_2CO_2Et$

entry	1	2	yield[a] (%) of 3
1	**1b**	**2a**	72 (**3ba**)
2	**1c**	**2a**	80 (**3ca**)
3	**1d**	**2a**	89 (**3da**)
4	**1e**	**2a**	37 (**3ea**)
5[b]	**1e**	**2a**	78 (**3ea**)
6	**1f**	**2a**	67 (**3fa**)
7	**1g**	**2a**	80 (**3ga**)
8	**1h**	**2a**	10 (**3ha**)[c]
9	**1i**	**2a**	0 (**3ia**)[d]
10	**1j**	**2a**	76 (**3ja**)
11	**1k**	**2a**	69 (**3ka**)
12	**1l**	**2a**	60 (**3la**)
13	**1m**	**2a**	74 (**3ma**)
14	**1a**	**2b**	66 (**3ab**)
15	**1a**	**2c**	29 (**3ac**)
16[b]	**1a'**	**2c**	74 (**3ac**)
17[b]	**1a'**	**2d**	76 (**3ad**)
18	**1a'**	**2e**	<10 (**3ae**)
19	**1a**	**2f**	0 (**3af**)

[a]Isolated yield. [b]10 equiv of **2** was used. [c]**4ha** (61%) was obtained. [d]**4ia** (26%) was obtained.

Typically, the reaction was carried out as follows: 10 mol % of $[Pd(C_3H_5)(cod)]BF_4$, 10 mol % of bpy, allylic acetate **1**, malonic ester **2** (3.0 equiv), and LiHMDS (2.8 equiv) were mixed in dioxane at 0 °C, and the reaction mixture was stirred at 100 °C for 12 h. The reactions of the 3-aryl-2-fluoroallyl acetates **1b**−**d**, which contained electron-donating or -withdrawing groups on the aromatic ring, smoothly proceeded and gave the desired doubly alkylated product (**3ba**, **3ca**, and **3da**) in good yield (entries 1−3). The *o*-tolyl-substituted 2-fluoroallyl acetate **1e** produced **3ea** in poor yield (37%), but an acceptable yield (78%) was obtained by increasing the amount of methyl dimethylmalonate (**2a**) from 3 to 10 equiv (entries 4 and 5). The reaction of the naphthyl-substituted allyl acetates **1f** and **1g** also required an excess of nucleophiles to obtain the desired products **3fa** and **3ga** in moderate to good yield (entries 6 and 7). Unfortunately, the reaction of the alkyl-substituted 2-fluoroallyl acetate **1h** resulted in a 10% yield, the monoalkylated linear type product **4ha** was formed as a major product (entry 8), and **1i** did not provide any of the desired doubly alkylated product (entry 9). On the other hand, reactions of heteroaromatic-substituted acetates, such as **1k**−**m**, provided the desired products **3ka**−**ma** over 60% yield (entries

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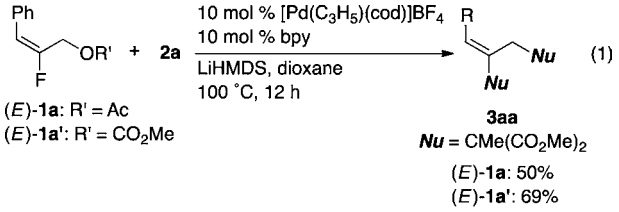
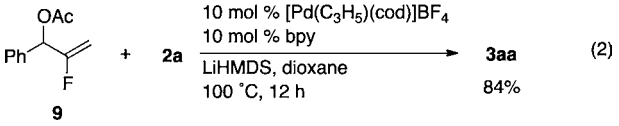
11−13). As shown in entries 14−18, the reactions with other malonic esters (**4b**−**e**) were also examined, and we confirmed that the reaction with **2b**, which has a methyl group on the α-carbon of the malonic ester, gave the doubly alkylated product **3ab** in 66% yield (entry 14). The reaction with a dialkyl malonate, such as **2c**, resulted in a low yield (29%) under the optimized catalyst conditions (entry 15). However, changing the leaving group of an allyl substrate from acetate (**1a**) to methyl carbonate (**1a′**) and using a large excess (10 equiv) of dialkyl malonate effectively improved the yield of the desired doubly alkylated product **3ac** to 74% yield (entry 16). The reaction with diethyl malonate (**2d**) also smoothly proceeded (entry 17), but the reaction with di-*tert*-butyl malonate (**2e**) resulted in a low yield (entry 18). We also examined the reaction with ethyl acetoacetate (**2f**), but the reaction gave furan derivatives[5,6,13] in 78% yield instead of doubly alkylated product (entry 19).

We further examined the reaction of (*E*)-2-fluoro-3-phenylallyl acetate ((*E*)-**1a**) and 2-fluoro-1-phenylallyl acetate (**9**) with the anion of **2a**. The reaction of (*E*)-**1a** produced (*E*)-**3aa**, which is the same product from the reaction of (*Z*)-**1a**, but the yield was slightly lower (eq 1). Again, changing the leaving

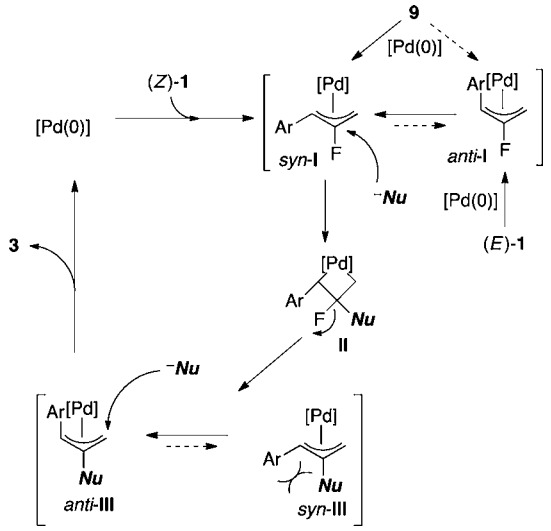




group from acetate to methyl carbonate effectively increased the yield to 69%, and the acetate **9** also afforded (*E*)-**3aa** in 84% yield (eq 2). The fact that the same doubly alkylated product was obtained in the reaction of the 2-fluoroallyl esters (*E*)-**1**, (*Z*)-**1** and **9** suggests that the reaction proceeds through the same reaction intermediate, which is likely to be a 2-fluoro-π-allyl palladium complex. Unfortunately, our several trials for observing and/or isolating the 2-fluoro-π-allyl complexes failed, and the details of the reaction mechanism have not yet been clarified. However, we currently believe that the reaction proceed with a similar pathway as the reported for the double substitution reaction of the 2-bromo- or 2-chloroallyl esters.[3−5]

Based on these observations and in accordance with previous reports, we propose a possible reaction mechanism in Scheme 2. The 2-fluoro-π-allylpalladium intermediate resulting from (*Z*)-**1** should be *syn*-2-fluoro-π-allylpalladium (*syn*-**I**), which contains the aromatic substituent at the *syn* position with respect to the fluorine atom at the 2 position of the π-allyl group. On the other hand, (*E*)-**1** selectively forms *anti*-**I**, and **9** forms both *syn*-**I** and *anti*-**I** in a certain ratio,[14] with the sterically more stable *syn*-**I** being predominant. After the isomerization from *anti*-**I** to the thermodynamically more stable *syn*-**I** occurred, the nucleophile first attacks at the central carbon atom of the π-allyl moiety and provides palladacyclobutane **II**[2−5,12] followed by the C−F bond cleavage, which affords the 2-alkylated π-allypalladium complex **III**. In the palladium complex **III**, *anti*-**III** is assumed to be more stable than *syn*-

Scheme 2. Proposed Reaction Mechanism



III due to the steric repulsion between two the substituents on the C-1 and C-2 carbons of the π-allyl group. Finally, a second nucleophile attacks the C-3 carbon of the *anti*-**III** to produce the doubly alkylated product (*E*)-**3**.

In summary, we have demonstrated the palladium-catalyzed alkylation of 3-aryl-2-fluorinated allyl esters with malonate nucleophiles and found that 2 equiv of malonate nucleophiles were introduced to the allyl substrate through the carbon−fluorine bond cleavage. Reaction results of three regioisomeric 2-fluorinated allyl esters suggest that the reaction proceeded via same reaction intermediates, such as 2-fluoro-π-allylpalladium, palladacyclobutane, and 2-alkylated-π-allylpalladium. Further studies to reveal the details of the reaction mechanism, and reaction with other fluorinated allyl substrates and nucleophiles are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) See the Supporting Information for details.

(10) The reaction proceeded with >98% *E*-selectivity, and it was determined by ^{1}H NMR of the crude materials.

(11) Reactions of **5** and **6** by Pd(dppe)$_2$ catalyst gave **3aa** in 11% and 0% NMR yield, respectively.

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