



Double amination of 2-fluoroallylic acetates by palladium catalysts

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ARTICLE INFO

Article history:

Received 20 January 2018

Revised 14 February 2018

Accepted 19 February 2018

Available online 20 February 2018

Keywords:

Palladium

Fluorine

Amination

Sulfonamide

C–F bond activation

ABSTRACT

We accomplished the palladium-catalyzed double substitution of 2-haloallylic acetates with nitrogen nucleophiles. During the Pd₂(dba)₃/DPPE-catalyzed reaction of 2-fluoroallylic acetates with *N*-substituted-*p*-toluenesulfonamide, two equivalents of nitrogen nucleophiles were introduced to the allyl unit with a *Z*-selectivity through the carbon–fluorine bond cleavage. We further demonstrated the reaction of 2-chloroallylic acetates, and succeeded in obtaining the same doubly-substituted products in good yields with a high *Z*-selectivity.

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The palladium-catalyzed reaction of allylic esters with nucleophiles generally provides allylic-substituted products or cyclopropane derivatives,^{1,2} but there is an alternative reaction process for the reaction of 2-haloallylic compounds, and the reaction mainly affords doubly-substituted products. For example, the palladium-catalyzed double-substitution reactions of 2-chloro or 2-bromoallylic compounds with oxygen or carbon nucleophiles were reported by three research groups.^{3–5} On the other hand, during the course of our recent study of the palladium-catalyzed reaction of fluorine-containing allylic compounds with nucleophiles,^{6–8} we also developed the double-substitution reaction of 2-fluoroallylic esters with several nucleophiles.⁶ For example, we demonstrated the double-substitution reactions of 2-fluoroallylic acetates with several types of nucleophiles, such as malonate,^{6a} phenoxide^{6b} or hydride,^{6c} and we recently examined the reaction with nitrogen nucleophiles.^{6e} However, when the imides were employed as nitrogen nucleophiles for the reaction of 2-fluoroallylic esters, phenols are essential for progress of the reaction, and both the nitrogen and oxygen nucleophiles were introduced to the allylic unit.^{6e} This result indicates that there is still no report about the double-substitution reaction of 2-fluoroallylic esters with two equivalents of nitrogen nucleophiles. Based on this background, we examined the palladium-catalyzed reaction of 2-fluoroallylic acetates with several types of nitrogen nucleophiles, and we revealed that the sulfonamide analogues afford the desired doubly-substituted product, which was two

nitrogen nucleophiles being introduced to the allylic unit, as the major product.

To realize the intended double-substitution reaction of 2-fluoroallylic acetate **1a** with *N*-methyl-*p*-toluenesulfonamide (**2a**) (3 equiv. to **1a**), we examined the reactions with several palladium catalysts in the presence of Cs₂CO₃ (2 equiv. to **1a**).

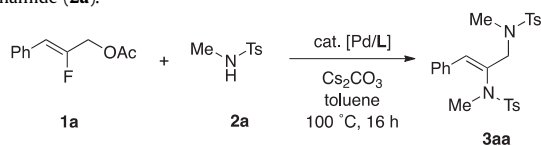
The reaction by Pd(PPh₃)₄, which was an effective catalyst for the double-etherification reaction of **1a** with phenols, gave the intended doubly-substituted products **3aa**,⁹ but the yield was moderate and the *Z/E* ratio of the product was very low (Table 1, entry 1). We next tried the reaction by [Pd(C₃H₅)Cl]₂ with PPh₃ or DPPE as a ligand, then confirmed that the reaction with [Pd(C₃H₅)Cl]₂/DPPE afforded **3aa** in a good yield with a high *Z*-selectivity (entries 2 and 3). To increase both the yield and *Z/E* ratio, we further investigated the reaction by Pd(OAc)₂ or Pd₂(dba)₃ (entries 4 and 5), and revealed that Pd₂(dba)₃/DPPE (Pd/L = 1/1) produced **3aa** in 90% NMR yield with an 88% *Z*-selectivity (entry 5). Furthermore, we revealed that the reaction also proceeded with a reduced amount of the palladium catalyst from 5 mol% to 0.5 mol% (entry 6), and the best result (93% NMR yield, 80% isolated yield with 91% *Z*-selectivity) was obtained when the reaction was conducted at 80 °C (entry 7).

With the optimal reaction conditions in hand, we examined the palladium-catalyzed reaction of **1a** with other *N*-substituted-*p*-toluenesulfonamides **2b–k**. As shown in Table 2, the palladium-catalyzed reaction of **1a** with *N*-ethyl-*p*-toluenesulfonamide (**2b**) smoothly proceeded, and provided the intended doubly-substituted products **3ab** in 88% with a 95% *Z*-selectivity. The reaction with **2c** also gave the desired product **3ac** in a good yield with a

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Table 1
Palladium-catalyzed reaction of 2-fluoroallylic acetate (**1a**) with *N*-methyl-*p*-toluenesulfonamide (**2a**).^a



Entry	[Pd] (mol%)	L (mol%)	Yield ^b (%) of 3aa	Z:E ^c
1	Pd(PPh ₃) ₄ (10)	–	61	41:59
2	[Pd(C ₃ H ₅ Cl) ₂] ₂ (5)	PPh ₃ (30)	62	38:62
3	[Pd(C ₃ H ₅ Cl) ₂] ₂ (5)	DPPE (10)	82	83:17
4	Pd(OAc) ₂ (10)	DPPE (10)	68	87:13
5	Pd ₂ (dba) ₃ (5)	DPPE (10)	90	88:12
6	Pd ₂ (dba) ₃ (0.5)	DPPE (1)	84	88:12
7 ^d	Pd ₂ (dba) ₃ (0.5)	DPPE (1)	93 (80) ^e	91:9

^a Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), [Pd], L, and Cs₂CO₃ (0.50 mmol) in toluene (2.5 mL) at 100 °C for 16 h.

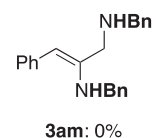
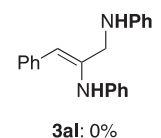
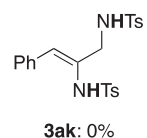
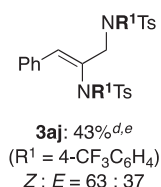
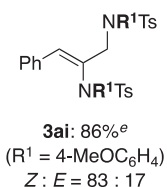
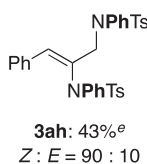
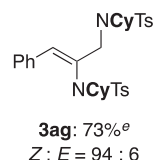
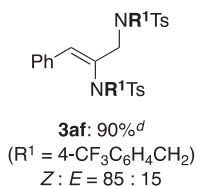
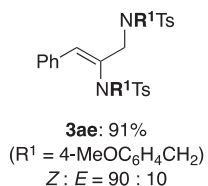
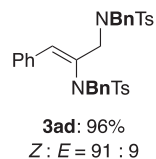
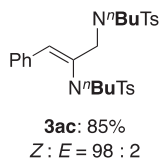
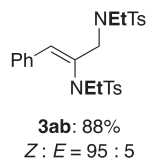
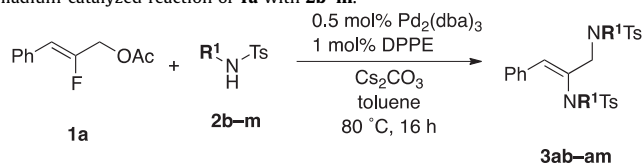
^b The yields were determined by ¹H NMR of crude materials using an internal standard (phenanthrene).

^c Z/E ratios were determined by ¹H NMR of crude materials.

^d Reaction was conducted at 80 °C.

^e Isolated yield is shown in parentheses.

Table 2
Palladium-catalyzed reaction of **1a** with **2b–m**.^{a,b,c}



^aReaction conditions: **1a** (0.25 mmol), **2b–m** (0.75 mmol), Pd₂(dba)₃ (0.5 mol%), DPPE (1.0 mol%), and Cs₂CO₃ (0.50 mmol) in toluene (2.5 mL) at 80 °C for 16 h.

^bThe yields are isolated yields after silica gel column chromatography.

^cRatios were determined by ¹H NMR of crude materials.

^d5.0 mL of toluene was used.

^e5 mol% of Pd₂(dba)₃ and 10 mol% of DPPE were used.

high Z/E ratio. We next investigated the reactions of **1a** with *N*-benzyl-*p*-toluenesulfonamide analogues **2d–f**, and succeeded in obtaining corresponding products **3ad–af** in good yields with good Z-selectivities. Although the reaction required 5 mol% of Pd₂(dba)₃ and 10 mol% of DPPE,¹⁰ the reaction of **1a** with *N*-cyclohexyl-*p*-toluenesulfonamides (**2g**) gave the corresponding product **3ag** in 73% yield with a 94% Z-selectivity. We next examined the reactions of *N*-aryl-*p*-toluenesulfonamide analogues **2h–j**, and confirmed that the reaction with **2i** (R¹ = 4-MeOC₆H₄) provided **3ai** in good yield. However, both reactions of **1a** with **2h** and **2j** (R¹ = 4-CF₃C₆H₄) resulted in moderated yields (43%), respectively. We also confirmed that the reactions with *p*-toluenesulfonamide (**2k**), aniline (**2l**), or benzylamine (**2m**) did not occur. These results indicated that the alkyl group substituted *p*-toluenesulfonamides are more suitable nitrogen nucleophiles for the present palladium-catalyzed double substitution reaction compared to the other types of *p*-toluenesulfonamides, and the reaction is also sensitive to the steric factor of the alkyl group on the nitrogen.

We further investigated the reactions of other 2-fluoroallylic acetates **1b–j**, which possess several substituents at the C-4 position of the allylic acetates, with **2a** or **2d**, and the results are summarized in Table 3. We first, we examined the reaction of **1b–j** with *N*-methyl-*p*-toluenesulfonamide (**2a**) using the optimized reaction conditions. The reactions of **1b** and **1c**, which possess an electron-donating group on the benzene ring at the C-4 position, gave the desired products **3ba** and **3ca** in 93% and 94% yields with a 90% Z-selectivity, respectively. The reaction of **1d** and **1e**, which possesses an electron-withdrawing group on the benzene ring, also produced **3da** and **3ea** in 94% with 89% and 87% Z-selectivity, respectively. The *o*-tolyl or 1-naphthyl group substituted allylic acetates **1f** and **1g** smoothly reacted with **2a** to provide the expected doubly substituted products **3fa** and **3ga** in 92% and 98% yields, respectively. We also examined the reaction of the alkyl group substituted allylic acetates **1h** and **1i** with **2a**, and succeeded in obtaining the desired doubly-substituted products **3ha** and **3ia** in good yields, but unfortunately the Z/E ratios were low. Furthermore, we attempted the reaction of the 2-thienyl group substituted allylic acetate **1j**, and revealed that the reaction produced the desired product **3ja** in 70% yield with an 83% Z-selectivity. Furthermore, we investigated the palladium-catalyzed reactions of **1b–j** with *N*-benzyl-*p*-toluenesulfonamide (**2d**). Some yields and Z/E ratios of the reaction with **2d** were lower than the results of the reaction with **2a**, but we succeeded in obtaining the corresponding products in moderate to good yields, although the reaction with **1c** with **2d** gave **3cd** in very low yield (27%). For example, the reactions of the aryl group substituted allylic acetate **1b** and **1d–g** with **2d** provided **3bd** and **3dd–gd** in the range of 62–94% yields with 90–96% Z-selectivities. Although the Z/E ratios were low again, we confirmed that the reaction of the alkyl group or 2-thienyl group substituted allylic acetate **1h–j** with **2d** produced the doubly-substituted products **3hd–jd** in moderate to good yields, respectively.

We also examined the reaction of the 2-chloro- or 2-bromoallylic acetates **4** and **5** with **2a** using the optimized reaction conditions, and confirmed that the reaction of 2-chloroallylic acetate **4** afforded the doubly-substituted product **3aa** in 86% yield with an 89% Z-selectivity, but the reaction of the 2-bromoallylic acetate **5** resulted in a low yield (Scheme 1, (1)). These results suggest that the 2-chloroallylic acetate is also an available substrate for the present palladium-catalyzed double-substitution reaction with *N*-methyl-*p*-toluenesulfonamides **2**. Furthermore, in support of the possible reaction mechanism, we attempted the reactions of the (*E*)-2-fluoroallylic acetate ((*E*)-**1a**) and 2-fluoro-1-phenylallylic acetate **6** with **2a** under the optimized palladium-catalyzed conditions (Scheme 1, (2) and (3)), and confirmed that both reactions provided the same doubly-substituted products **3aa** in 90% and

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