

Regioselective synthesis of trifluoromethyl group substituted allylic amines via palladium-catalyzed allylic amination

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Abstract

The palladium-catalyzed regioselective allylic amination of α -trifluoromethylated allyl acetate occurred using $\text{Pd}(\text{OAc})_2/\text{DPPE}$ and $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$. The selective formation of the γ -product was attained by $\text{Pd}(\text{OAc})_2/\text{DPPE}$, while the α -product was obtained using $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$.

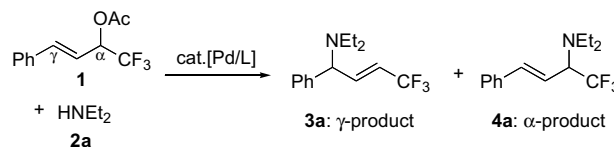
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The transition metal-catalyzed allylic substitution of allyl esters is one of the most efficient means for realizing carbon–carbon and carbon–heteroatom bond formation reactions in organic synthesis.¹ Especially, there are several excellent stereoselective allylic substitutions, including allylic amination,^{2,3} that have been reported using palladium catalysts.⁴ Although there have been numerous examples of reactions of *non-fluorinated* substrates, only a few reports about the palladium-catalyzed allylic substitution reaction using *fluorinated* substrates have been reported.⁵ To the best of our knowledge, there is only one example of the transition metal-catalyzed allylic amination of the α -trifluoromethylated allyl substrate, which was reported by Konno et al. in 2002.^{5e} They demonstrated the palladium-catalyzed allylic amination of α -trifluoromethylated allyl mesylate, and found that the reaction produced the γ -product as a single regioisomer. With this result in mind, we started to investigate other palladium catalyst systems, which would give the other regioisomer (α -product). We now report both the α -selective and γ -selective allylic amin-

ations of α -trifluoromethylated allyl acetate using two types of palladium catalysts.

We examined the allylic amination of the α -trifluoromethylated allyl acetate **1** with diethylamine (**2a**) using several palladium/phosphine catalysts (Scheme 1). Based on the initial screening, we confirmed that some palladium catalysts, which were generated from $\text{Pd}_2(\text{dba})_3$ or $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ with several phosphine ligands,⁶ did not catalyze the desired amination reaction nor resulted in the low conversion of substrate **1** (<20%). On the other hand, we found that the $\text{Pd}(\text{OAc})_2$ and $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4$ exhibited a catalyst activity for this intended reaction. The results obtained for the palladium-catalyzed allylic amination of **1** with diethylamine (**2a**) are summarized in Table 1.⁷ We first conducted the reaction using $\text{Pd}(\text{OAc})_2$ with PPh_3 (4 equiv to Pd), but the reaction rate was low (entry 1).



Scheme 1.

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Table 1
Palladium-catalyzed allylic amination of **1** with diethylamine **2a**^a

Entry	[Pd/L]	Solvent	Temp (°C)/time (h)	Yield ^b of 3a + 4a (%)	3a : 4a ^c
1	Pd(OAc) ₂ /PPh ₃	THF	60/12	20	>98:2
2	Pd(OAc) ₂ /DPPE	THF	60/12	86 (80) ^d	>98:2
3	Pd(OAc) ₂ /DPPF	THF	60/12	64 (58) ^d	>98:2
4	Pd(OAc) ₂ /DPPE	Dioxane	100/12	68	>98:2
5	[Pd(π-allyl)(cod)]BF ₄ /PPh ₃	THF	60/12	12	>98:2
6	[Pd(π-allyl)(cod)]BF ₄ /DPPE	THF	60/12	17	>98:2
7	[Pd(π-allyl)(cod)]BF ₄ /DPPF	THF	60/12	56	68:32
8	[Pd(π-allyl)(cod)]BF ₄ /DPPF	Dioxane	60/12	78	69:31
9	[Pd(π-allyl)(cod)]BF ₄ /DPPF	Dioxane	100/9	95 (87) ^d	2:>98
10 ^e	[Pd(π-allyl)(cod)]BF ₄ /DPPF	Dioxane	100/12	66	73:27
11	[Pd(π-allyl)(cod)]BF ₄ /DPPF	Dioxane	100/0.5	68	61:39

^a All reactions were carried out with **1** (0.20 mmol), **2a** (0.31 mmol), palladium (0.020 mmol), and ligand (0.021 mmol for DPPE and DPPF, 0.084 mmol for PPh₃) in solvent (1.0 mL) under nitrogen unless otherwise noted.

^b The yields were determined by ¹H NMR.

^c The ratio was determined by 400 MHz ¹H NMR spectral analysis of the crude materials.

^d Isolated yield by silica gel column chromatography in parentheses.

^e [Pd(π-allyl)(cod)]BF₄ (0.010 mmol) and DPPF (0.010 mmol) were used.

Fortunately, we found that DPPE [1,2-bis(diphenylphosphino)ethane] (1 equiv to Pd) is an effective ligand for the allylic amination of **1**, and the γ-trifluoromethyl group substituted allyl amine **3a** (γ-product) was obtained as a single regioisomer in 80% isolated yield (entry 2). We also examined the reaction with DPPF, but the yield was lower (entry 3). A further investigation revealed that [Pd(π-allyl)(cod)]BF₄ also catalyzed the allylic amination of **1**. Again, the γ-selective amination was observed in the reaction using PPh₃ and DPPE ligated palladium catalyst, but the yield was very low (entries 5 and 6). Interestingly, the palladium catalyst, which coordinated with DPPF, exhibited a higher reactivity and gave a mixture of two diastereoisomers **3a** and **4a** (α-product) in the ratio of 68:32 (entry 7). This α-selectivity was improved by elevating the reaction temperature to 100 °C in dioxane, and **4a** was obtained as a single regioisomer in 87% isolated yield (entry 9). It was found that several other reaction conditions, such as a lower temperature (60 °C) (entry 8), reduced the catalyst amount (5 mol % of Pd and DPPF) (entry 10) or shorter reaction times (30 min) (entry 11), decreased this α-selectivity and produced the γ-product as the major product.

We applied these two catalyst systems to the reaction with other amines (Scheme 2), and the results are summa-

rized in Table 2. The reaction with aliphatic secondary amines, such as morpholine (**2b**) and dibutylamine (**2c**), proceeded with the same regioselective trend as the reaction with **2a**. For example, the Pd(OAc)₂/DPPE catalyzed reaction of **1** with **2b** or **2c** formed the γ-product (**3b** or **3c**) as a single regioisomer (entries 1 and 3). On the other hand, the [Pd(π-allyl)(cod)]BF₄/DPPF catalyst exhibited another regioselectivity and produced the α-products **4b** and **4c** as the major regioisomers (entries 2 and 4). Unfortunately, these palladium-catalyzed allylic aminations with both Pd(OAc)₂/DPPE and [Pd(π-allyl)(cod)]BF₄/DPPF are very sensitive to the steric factor of the amines. As shown in entries 5 and 6, the reaction with *N*-ethylisopropylamine using Pd(OAc)₂/DPPE proceeded with a >98% γ-selectivity,

Table 2
Palladium-catalyzed allylic amination of **1** with amines **2b–h**^a

Entry	2	Condition ^b	Yield ^c of 3 + 4 (%)	3 : 4 ^d
1	2b	A	92 (99) ^e	97:3
2		B	75 (79) ^e	7:93
3	2c	A	64 (72) ^e	>98:2
4		B	80	2:>98
5	2d	A	(12) ^e	>98:2
6		B	(15) ^e	75:25
7	2e	A	0	—
8		B	0	—
9	2f	A	54 (56) ^e	>98:2
10		B	61 (66) ^e	2:>98
11	2g	A	66 (68) ^e	>98:2
12		B	79 (80) ^e	2:>98
13	2h	A	(22) ^e	>98:2
14		B	58 (60) ^e	2:>98

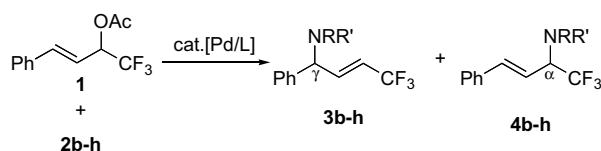
^a All reactions were carried out with **1** (0.20 mmol) and **2** (0.31 mmol) in solvent (1.0 mL) for 12 h under nitrogen unless otherwise noted.

^b Condition A: 10 mol % Pd(OAc)₂ and 10 mol % DPPE in THF at 60 °C. Condition B: 10 mol % [Pd(π-allyl)(cod)]BF₄ and 10 mol % DPPF in dioxane at 100 °C.

^c Isolated yield by silica gel column chromatography.

^d The ratio was determined by 400 MHz ¹H NMR spectral analysis of the crude materials.

^e The NMR yield in parentheses.

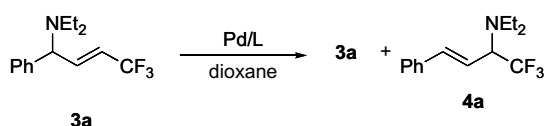


2b: morpholine
2c: dibutylamine
2d: *N*-ethylisopropylamine
2e: diisopropylamine
2f: *n*-butylamine
2g: benzylamine
2h: aniline

Scheme 2.

but the yield was very low (12% NMR yield), and the reaction using $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ gave a mixture of two diastereoisomers, **3d** and **4d**, in the ratio of 75:25. The reaction with diisopropylamine (**2e**) resulted in no reaction (entries 7 and 8). We also demonstrated the reaction with the primary amines **2f** and **2g**, and obtained the expected results. We observed the perfect γ -selectivity in the reaction of **2f** using $\text{Pd}(\text{OAc})_2/\text{DPPE}$, though the yield was low (entry 9). On the other hand, the reaction with $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ produced the α -product in moderate yield (61% isolated yield) as a single regioisomer (entry 10). Similar results were obtained for the reaction with benzylamine (**2g**) (entries 11 and 12). This trend in regioselectivity was again observed in the reaction with an aromatic amine **2h**; the $\text{Pd}(\text{OAc})_2$ catalyst exhibited the perfect γ -selectivity (entry 13), and the $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4$ catalyst again selectively produced the α -product (entry 14).

We next studied the reaction mechanism and/or pathway for the regioselective substitution especially for the unusual selective formation of the α -product. Generally, the palladium catalyst forms the π -allylpalladium intermediate and nucleophiles attack the π -allyl terminus. According to the report about the allylic substitution of α -trifluoroalkylated allyl mesylates by Konno et al.,^{5d} the allyl substrate easily formed the π -allylpalladium complex, and nucleophiles selectively attacked the less sterically hindered π -allyl terminus to form the γ -product.⁸ We believe that the same mechanism is applicable to the reaction of **1** with **2** by $\text{Pd}(\text{OAc})_2/\text{DPPE}$. In contrast, it is unclear whether or not the selective substitution occurred during the reaction of the $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ catalyst because, as we previously mentioned, the γ -product was obtained as the major product under several different conditions (Table 1, entries 8, 10, and 11). Based on these results, we assumed that $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ had also selectively formed γ -product, thus causing isomerization to provide the α -product under the given reaction conditions.^{3f,g,9} To prove these hypotheses, the γ -product **3a** was treated with the palladium catalyst and the ^1H NMR spectrum measured. When the reaction was carried out with 10 mol % $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4$ (without DPPF) in dioxane at 100 °C for 12 h, we confirmed the >80% conversion of **3a**, but a complex mixture was produced. However, the reaction with 10 mol % of $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4$ and 10 mol % of DPPF indicated the formation of α -product **4a** (52% NMR yield), which suggested that **3a** was isomerized to **4a** by $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$.¹⁰ Furthermore, the addition of excess Et_2NH (1.5 equiv to **3a**) increased the formation of **4a** up to a 73% NMR yield (Scheme 3



Scheme 3.

Table 3

The reaction of γ -product **3a** using the palladium catalyst^a

Entry	[Pd/L]	Et_2NH	Conversion ^b of 3a (%)	Yield ^b of 4a (%)
1	$[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4$	—	>80	Trace
2	$[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$	—	>99	52
3	$[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$	1.5 equiv	>99	73
4	$\text{Pd}(\text{OAc})_2/\text{DPPE}$	1.5 equiv	0	0

^a All reactions were carried out with **3a** (0.20 mmol), palladium (0.020 mmol), and ligand (0.021 mmol) in dioxane (1 mL) at 100 °C for 12 h under nitrogen.

^b Determined by 400 MHz ^1H NMR spectral analysis of the crude materials.

and Table 3). On the other hand, we also confirmed that the $\text{Pd}(\text{OAc})_2/\text{DPPE}$ did not catalyze the isomerization of **3a** to **4a** under the same conditions. These results strongly support the idea that the γ -product was selectively formed at first, then it was isomerized to the α -product by the $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ catalyst.

In conclusion, we have demonstrated the regioselective formation of both the α - and γ -trifluoromethyl group-substituted allyl amines via the palladium-catalyzed allylic amination of α -trifluoromethylated allyl acetate. The conventional γ -product was obtained using the $\text{Pd}(\text{OAc})_2/\text{DPPE}$ catalyst, and the unusual α -product was obtained using the $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ catalyst. We also revealed that the γ -product was easily isomerized to the α -product under the $[\text{Pd}(\pi\text{-allyl})(\text{cod})]\text{BF}_4/\text{DPPF}$ catalyzed reaction conditions, then concluded that the α -product was formed by the isomerization of the γ -product.

Acknowledgments

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6. We examined PPh₃, DPPE, and DPPF as a phosphine ligand.
7. General Procedure of palladium-catalyzed allylic amination. The reaction conditions and results are shown in Tables 1 and 2. A typical procedure is given for the reaction of **1** with **2a** (Table 1, entry 9). To a solution of [Pd(π -allyl)(cod)]BF₄ (7.0 mg, 0.020 mmol) and DPPF (11.4 mg, 0.021 mmol) in dioxane (1.0 mL) were added allyl acetate **1** (50 mg, 0.20 mmol) and amine **2a** (23 mg, 0.31 mmol) at room temperature. The resultant mixture was stirred at 100 °C for 9 h. The reaction mixture was quenched with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous MgSO₄, and evaporated. The NMR yield (95%, trioxane as a internal standard) and diastereomeric ratio were determined by 400 MHz ¹H NMR for crude material. The residue was purified by silica gel column chromatography (hexane/EtOAc/Et₃N = 97:2:1) to give 46 mg (87%) of **4a** (α -product) as a colorless oil. Compound **4a**: ¹H NMR (500 MHz, CDCl₃): δ 1.08 (t, J = 7.1 Hz, 6H), 2.79 (dq, J = 6.4, 7.1 Hz, 2H), 2.64 (dq, J = 6.4, 7.1 Hz, 2H), 3.77–3.86 (m, 1H), 6.22 (dd, J = 8.1, 15.7 Hz, 1H), 6.68 (d, J = 16.1 Hz, 1H), 7.23–7.41 (m, 5H). ¹³C NMR (125 MHz, CDCl₃): δ 14.0, 44.8, 63.8 (q, J_{CF} = 27.5 Hz), 120.1, 126.3 (q, J_{CF} = 285.3 Hz), 126.6, 128.2, 128.6, 136.2, 136.4. ¹⁹F NMR (470 MHz, CDCl₃): δ –70.7 (d, J = 11.5 Hz). Anal. Calcd for C₁₄H₁₈F₃N: C, 65.35; H, 7.05; N, 5.44. Found: C, 65.24; H, 7.14; N, 5.40. Regioisomer **3a** (γ -product): ¹H NMR (500 MHz, CDCl₃): δ 0.99 (t, J = 6.9 Hz, 6H), 2.53 (q, J = 7.0 Hz, 4H), 4.27 (d, J = 8.2 Hz, 1H), 5.77–5.84 (m, 1H), 6.50–6.56 (m, 1H), 7.26–7.36 (m, 5H). ¹³C NMR (125 MHz, CDCl₃): δ 11.8, 43.1, 66.6, 119.3 (q, J_{CF} = 33.6 Hz), 122.9 (q, J_{CF} = 269.3 Hz), 127.6, 128.1, 128.6, 140.3, 141.4 (q, J_{CF} = 6.1 Hz). ¹⁹F NMR (470 MHz, CDCl₃): δ –63.7. Anal. Calcd for C₁₄H₁₈F₃N: C, 65.35; H, 7.05; N, 5.44. Found: C, 65.26; H, 7.17; N, 5.31.
8. The electronic effect of trifluoromethyl group is also important for this regioselectivity.
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