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

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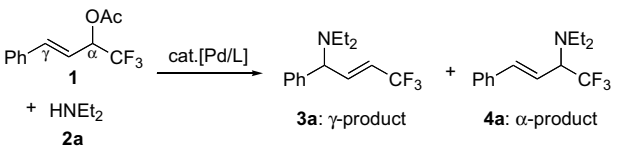
Abstract

The palladium-catalyzed regioselective allylic amination of α-trifluoromethylated allyl acetate occurred using $Pd(OAc)_2$/DPPE and $[Pd(\pi\text{-allyl})(cod)]BF_4$/DPPF. The selective formation of the γ-product was attained by $Pd(OAc)_2$/DPPE, while the α-product was obtained using $[Pd(\pi\text{-allyl})(cod)]BF_4$/DPPF.

Keywords: Palladium; Allylic amination; Regioselectivity; Fluorine

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 aminations 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 $Pd_2(dba)_3$ or $[Pd(\pi\text{-allyl})Cl]_2$ 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 $Pd(OAc)_2$ and $[Pd(\pi\text{-allyl})(cod)]BF_4$ 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 $Pd(OAc)_2$ with PPh_3 (4 equiv to Pd), but the reaction rate was low (entry 1).



Scheme 1.

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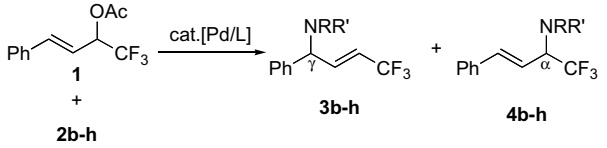
Table 1
Palladium-catalyzed allylic amination of **1** with diethylamine **2a**[a]

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 PPh_3) 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)]BF_4 (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)]BF_4 also catalyzed the allylic amination of **1**. Again, the γ-selective amination was observed in the reaction using PPh_3 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 summarized 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)]BF_4/DPPF catalyst exhibited an 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)]BF_4/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,



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

Scheme 2.

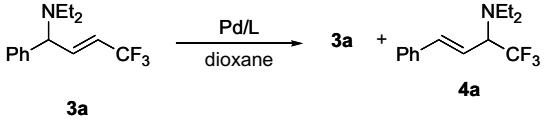
Table 2
Palladium-catalyzed allylic amination of **1** with amines **2b–h**[a]

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)]BF_4 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.

but the yield was very low (12% NMR yield), and the reaction using [Pd(π-allyl)(cod)]BF_4/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 $Pd(OAc)_2$/DPPE, though the yield was low (entry 9). On the other hand, the reaction with [Pd(π-allyl)(cod)]BF_4/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 $Pd(OAc)_2$ catalyst exhibited the perfect γ-selectivity (entry 13), and the [Pd(π-allyl)-(cod)]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 $Pd(OAc)_2$/DPPE. In contrast, it is unclear whether or not the selective substitution occurred during the reaction of the [Pd(π-allyl)(cod)]BF_4/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 [Pd(π-allyl)(cod)]BF_4/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 % [Pd(π-allyl)(cod)]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 [Pd(π-allyl)(cod)]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 [Pd(π-allyl)(cod)]BF_4/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 and Table 3). On the other hand, we also confirmed that the $Pd(OAc)_2$/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 [Pd(π-allyl)(cod)]BF_4/DPPF catalyst.



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	[Pd(π-allyl)(cod)]BF_4	—	>80	Trace
2	[Pd(π-allyl)(cod)]BF_4/DPPF	—	>99	52
3	[Pd(π-allyl)(cod)]BF_4/DPPF	1.5 equiv	>99	73
4	$Pd(OAc)_2$/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.

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 $Pd(OAc)_2$/DPPE catalyst, and the unusual α-product was obtained using the [Pd(π-allyl)(cod)]BF_4/DPPF catalyst. We also revealed that the γ-product was easily isomerized to the α-product under the [Pd(π-allyl)(cod)]BF_4/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 PPh_3, 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)]BF_4 (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 $MgSO_4$, and evaporated. The NMR yield (95%, trioxane as a internal standard) and diastereomeric ratio were determined by 400 MHz ^{1}H NMR for crude material. The residue was purified by silica gel column chromatography (hexane/EtOAc/Et_3N = 97:2:1) to give 46 mg (87%) of **4a** (α-product) as a colorless oil. Compound **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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. ^{19}F NMR (470 MHz, $CDCl_3$): δ −70.7 (d, J = 11.5 Hz). Anal. Calcd for $C_{14}H_{18}F_3N$: C, 65.35; H, 7.05; N, 5.44. Found: C, 65.24; H, 7.14; N, 5.40. Regioisomer **3a** (γ-product): ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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). ^{19}F NMR (470 MHz, $CDCl_3$): δ −63.7. Anal. Calcd for $C_{14}H_{18}F_3N$: C, 65.35; H, 7.05; N, 5.44. Found: C, 65.26; H, 7.17; N, 5.31.
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