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# A chronicle review: Regioselective synthesis of trifluoromethyl group containing allylic amines using palladium-catalyzed allylic amination pathway

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ABSTRACT

Palladium-catalyzed regioselective allylic amination of the α-trifluoromethyl group-substituted allyl acetate has been accomplished using $Pd(OAc)_2$/DPPE and $[Pd(\pi\text{-allyl})(cod)]BF_4$/DPPF as catalysts. The selective formation of the γ-product was attained by the use of $Pd(OAc)_2$/DPPE, while the α-product was obtained in the presence of $[Pd(\pi\text{-allyl})(cod)]BF_4$/DPPF. We also succeeded in synthesizing optically active allylic amines using $Pd(OAc)_2$/DPPE and $[Pd(\pi\text{-allyl})(cod)]BF_4$/BINAP began from optically active trifluoromethyl-substituted allyl acetate. Furthermore, we established that kinetic resolution of two types of allylic amines was possible using enantioselective isomerization by the $[Pd(\pi\text{-allyl})(cod)]BF_4$/(*S*)-BINAP catalyst.

## 1. Introduction

Fluorine substituted organic compounds have attracted strong interest in the field of medicinal chemistry and material sciences because of their unique properties due to the strong electron withdrawing nature of fluorine, while the atomic size of fluorine is believed to be similar to that of hydrogen. For example, the replacement of hydrogen atoms by fluorine atoms in organic molecules causes a relatively small steric change, but leads to major changes in the electron character of the molecules. Also, some compounds containing fluorines sometimes exhibit an unusual stereoselectivity under standard organic reaction conditions [1]. Therefore, the development of efficient means of preparing fluorinated compounds is one of the important subjects in organic chemistry [1].

The transition metal-catalyzed allylic amination reaction of allyl esters is a versatile method of producing allylic amines, and several transition metal catalysts have been employed to realize these reactions [2,3]. However, most of them were reactions involving non-fluorinated substrates, and there had been reported only limited examples of the palladium-catalyzed reaction of α-trifluoromethyl-substituted allyl substrates when we launched the present project [4]. Konno et al. demonstrated the first example of the palladium-catalyzed regioselective (γ-selective) allylic amination of α-trifluoromethyl-substituted allyl mesylate, and in 2002 established that the reaction produced the γ-product as a single regioisomer [5]. Okano and co-workers demonstrated regioselective palladium-catalyzed allylic substitution reaction with a malonate in 2003, though the authors demonstrated no allylic amination [6] (Fig. 1).

We have been investigating the possibility of palladium-catalyzed allylic amination and established several reactions in this field: regiocontrol of allylic amination, isomerization of the amino group of the allylic position, kinetic resolution of allylic amines *via* chiral palladium complex, and finally, accomplishment of enantioselective allylic amination [7–9]. In this chronicle, we report studies on the palladium-catalyzed regioselective allylic amination of α-trifluoromethyl-substituted allyl esters with amines, including the synthesis of the trifluoromethyl group containing optically active allylic amines. We also report the achievement of enantioselective Pd-catalyzed α-amination of α-trifluoromethyl-substituted allyl ester with various types of amines.

## 2. Regiostereocontrol of allylic amination

We examined the allylic amination of (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-yl acetate (**1a**) with diethylamine using several

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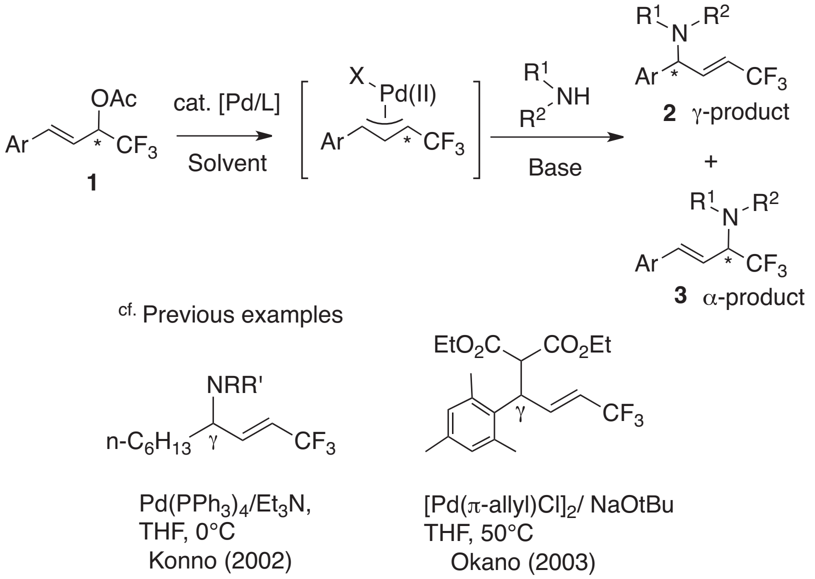

**Fig. 1.** Regioselective Pd-catalyzed allylic substitution reaction of 1,1,1-trifluoro-4-arylbut-3-en-2-yl acetate.

palladium/phosphine catalysts (Fig. 2) and we found that $Pd(OAc)_2$ and $[Pd(\pi\text{-allyl})(cod)]BF_4$ exhibited a catalytic activity for this intended reaction [7,8]. On the contrary, palladium catalysts, which were generated from $Pd_2(dba)_3$ or $[Pd(\pi\text{-allyl})Cl]_2$ with several phosphine ligands, showed no catalytic activity toward the desired amination reaction or resulted in a low conversion of the substrate **1a** (<20%). Furthermore, it was established that the regioselectivity significantly depended on the ligand system. Initially, we conducted the reaction using $Pd(OAc)_2$ with $PPh_3$ (4 equiv. *versus* Pd), and a poor reaction rate was recorded. After evaluation of six types of phosphine ligands: which included 1,1-bis(diphenylphosphino)methane (DPPM), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), and (diphenylphosphino)ferrocene (DPPF), we succeeded in controlling regioselectivity of the reaction. The results obtained for the palladium-catalyzed allylic amination of **1a** with diethylamine (**2a**) are summarized in Table 1.

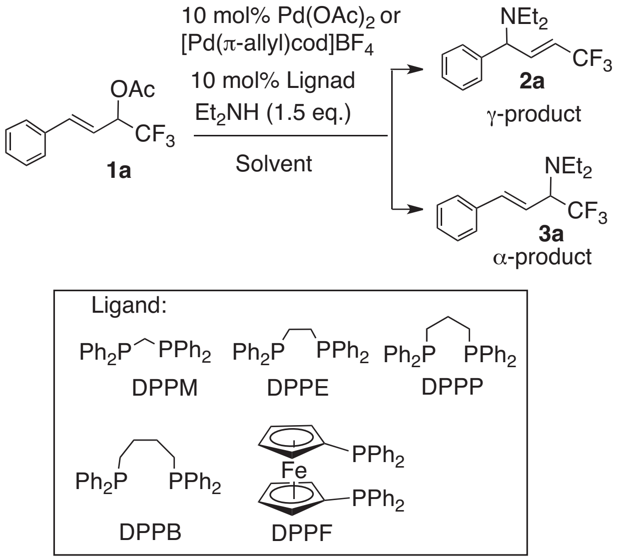

**Fig. 2.** Regioselective allylic amination of 1,1,1-trifluoro-4-phenylbut-3-en-2-yl acetate using various Pd-catalyst systems.

It was found that DPPE [1,2-bis(diphenylphosphino)ethane] (1 equiv. to Pd) worked as an effective ligand for the allylic amination of **1a**, and allyl amine **2a** (γ-product) was obtained as a single regioisomer in 86% isolated yield when the reaction was carried out in THF at 60 °C (entry 1). $[Pd(\pi\text{-allyl})(cod)]BF_4$ [10] also catalyzed the allylic amination of **1a** using dioxane as solvent but in different modes (entries 3–6). The γ-selective aminated product **2a** was obtained for the reaction using DPPE ligated palladium catalyst with very poor yield (entry 2). The regioselectivity depended on the ligand, and α-selectivity was improved by increased distance between two diphenylphosphino groups. DPPB ligated Pd-catalyst gave α-product **3a** preferentially (entry5), and **3a** was obtained as a sole product (>98%) in 95% yield when the reaction was carried out in the presence of DPPF ligand at 100 °C using dioxane as solvent (entry 6).

We thus established regioselective allylic amination of **1** with several amines using these two types of palladium catalyst systems (Condition A and B) (Fig. 3). The results of Pd-catalyzed regioselective allylic amination are summarized in Table 2, where we described our control of the regioselectivity of allylic amination of **1** using two types of Pd-catalyst systems: $Pd(OAc)_2$/DPPE mediated reactions exhibited perfect γ-selectivity and trifluoromethyl-substituted allyl amine **2** was produced as a sole product (Table 2). Reactions of **1a** with various amines, such as morpholine, *N*,*N*-dibutylamine, *N*-butylamine, or benzylamine were conducted under condition A, to give γ-products **2b**, **2c**, **2d**, **2e**, and **2g** with perfect selectivity in high to acceptable yields (entries, 1, 3, 5, 7, 9, and 11). However, the reaction with aniline gave **2f** poor yield while excellent regisoelectivity was still obtained (entry 9). On the

**Table 1**
Regioselective amination of 1,1,1-trifluoro-4-phenylbut-3-en-2-yl acetate.

| Entry | Pd cat.[a] | Ligand | Solvent | Temp (°C) | Yield [b] (%) | γ:α[c] |
|---|---|---|---|---|---|---|
| 1 | A | DPPE | THF | 60 | 86 | >98:<2 |
| 2 | B | DPPM | dioxane | 100 | 11 | >98:<2 |
| 3 | B | DPPE | dioxane | 100 | 43 | 60:40 |
| 4 | B | DPPP | dioxane | 100 | 67 | 69:31 |
| 5 | B | DPPB | dioxane | 100 | 53 | 15:85 |
| 6 | B | DPPF | dioxane | 100 | 95 | <2:>98 |

[a] Pd cat. A: 10 mol% $Pd(OAc)_2$, B: 10 mol% $[Pd(\pi\text{-allyl})cod][BF_4]$.
[b] Isolated yield.
[c] The ratio of diastereoisomers are determined by $^1H$ NMR analysis.