Note

Synthesis of 1-Tetrasubstituted 2,2,2-Trifluoroethylamine Derivatives *via* Palladium-Catalyzed Allylation of sp^3 C–H Bonds

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This note describes the construction of tetrasubstituted carbon stereocenters *via* palladium-catalyzed allylation of sp^3 C–H bonds of 2,2,2-trifluoroethylamine derivatives. The presence of 2-pyridyl group of the imines derived from 1-substituted-2,2,2-trifluoroethylamine was key to promoting the reaction efficiently, allowing an access to a variety of 1-allylated 2,2,2-trifluoroethylamine derivatives with tetrasubstituted carbon stereocenters.

Key words allylation; tetrasubstituted carbon; palladium catalysis; 2,2,2-trifluoroethylamine

2,2,2-Trifluoroethylamines are important structures in organic molecules[1] and pharmaceuticals because they improve bioactivities compared with the corresponding ethylamine derivatives.[2,3] Thus, the development of synthetic methods for 1-tetrasubstituted-2,2,2-trifluoroethylamines that cannot be accessed by hydrogenation of imines and reductive amination of ketones is an important challenge.[4,5] Catalytic nucleophilic addition to trifluoromethyl ketimines to gain access to these structures has been extensively studied over the last decade (Chart 1, Eq. a).[4,5]

On the other hand, the reaction of 2,2,2-trifluoroethylamine derivatives with electrophiles is a complementary approach for the synthesis of 1-substituted-2,2,2-trifluoroethylamines (Chart 1, Eq. b).[6–12] This reaction comprises one of these steps toward functionalization of 2,2,2-trifluoroethylamines when combining condensation with carbonyl compounds and subsequent hydrolysis. Very recently, several groups reported ketimines derived from 2,2,2-trifluoroethylamine as a pronucleophile. In these reactions, azomethine ylides are formed as nucleophiles through deprotonation of the sp^3 C–H bond of 2,2,2-trifluoroethylamines. The scope of these reactions is mostly limited to unsubstituted 2,2,2-trifluoroethylamines (R^1=H), however, and reported reactions with 1-substituted-2,2,2-trifluoroethylamines mostly have an electron-withdrawing group as the substituent.[13–15] In addition, most of the reported reactions are limited to 1,3-dipolar cycloaddition with electron-deficient olefins,[6–8,10,11] and these cyclized products are not readily transformed into *N*-unprotected 2,2,2-trifluoroethylamines.[16]

To overcome these limitations, herein we report our preliminary studies on Pd-catalyzed allylation of sp^3 C–H bonds of 1-mono-substituted 2,2,2-trifluoroethylamines, providing a variety of 1-allylated 2,2,2-trifluoroethylamines with tetrasubstituted carbon stereocenters. Our results demonstrated that the cooperative activation of 2,2,2-trifluoroethylamines and allyl carbonate using Pd catalysts is important for promoting the reaction. In addition, the product was readily transformed into *N*-unprotected 2,2,2-trifluoroethylamine.

The design of our reaction is depicted in Chart 2. We selected Pd-catalyzed allylation of the sp^3 C–H bond of *N*-(1-substituted-2,2,2-trifluoroethyl)aldimine (**1**) with allyl *tert*-butyl carbonate (**2**) for the following reasons: 1) the *tert*-butoxide anion generated from **2** and Pd(0) would work as a base for the deprotonation of **1**; 2) the coordination of **1** to the palladium catalyst would allow for facile deprotonation of the sp^3 C–H bond to generate the azomethine ylide intermediate; and 3) soft electrophilic (π-allyl)Pd would promote the reaction with the generated azomethine ylide without concomitant 1,3-cycloaddition reactions.[17,18]

To evaluate whether the hypothetical catalytic cycle described above would work as expected, we performed the reaction with imine **1a** and **2** in the presence of 2.5 mol% of the allylpalladium(II) chloride dimer (5 mol% for Pd) with 10 mol% of PPh_3, and the desired product **3a** was obtained in 25% yield in 2 h at room temperature (Table 1, entry 1). When the reaction time was prolonged to 20 h, most of substrate **1a** was consumed and the yield was increased to 82% (entry 2). Reactions without PPh_3 or with 5 mol% of PPh_3 did not afford **3a**, suggesting the importance of PPh_3 for promoting the reaction (entries 3, 4). The use of 5 mol% of tetrakis(triphenylphosphine)palladium(0) as the catalyst

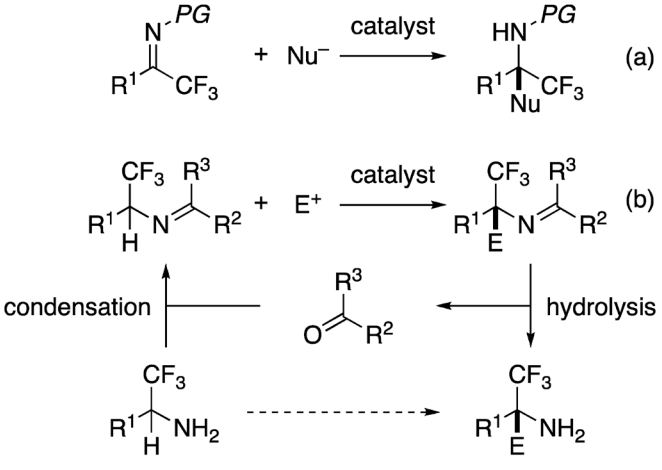

Chart 1. Approaches to 1-Substituted 2,2,2-Trifluoroethylamines

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improved the reactivity (entry 5), producing 88% yield of **3a** when the reaction was performed over 24 h (entry 6), and this reaction condition was selected as optimal. An elevated reaction temperature did not improve the yield of **3a** (entry 7). Addition of base did not change the reactivity (entry 8), whereas performing the reaction without the Pd catalyst did not afford the product at all (entry 9). These results suggest that deprotonation of **1a** was likely promoted by *tert*-butoxide anions generated from **2** through the formation of the (π-allyl)Pd(II) species.

With the optimized conditions in hand, we investigated the substrate scope of imine **1** (Table 2). The desired product **3a** was isolated in 66% yield after silica gel column chromatography without significant decomposition. The reduced isolated yield was due to the difficulties in separating the product **3a** from byproducts.[19] Imines with an electron-donating and -withdrawing group on the arene ring were also applicable to the reaction, affording the product **3b**–**d** in moderate to good isolated yields. *meta*-Substituted imine **1e** also gave the products **3e** in 68% isolated yield. 1-Alkyl-substituted imine **1f**, a more challenging substrate due to possible isomerization, was applicable to the reaction but afforded **3f** in a reduced yield,

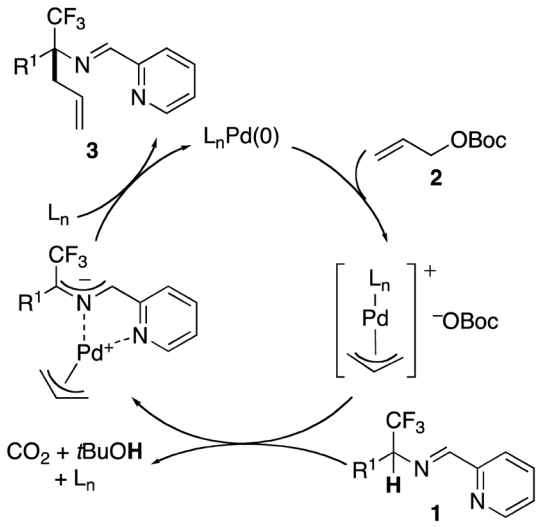
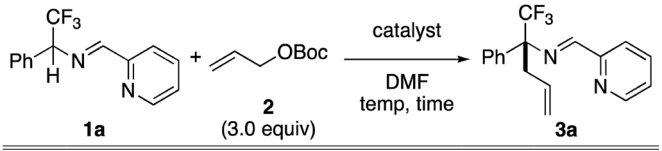


Chart 2. Design of Our Reaction

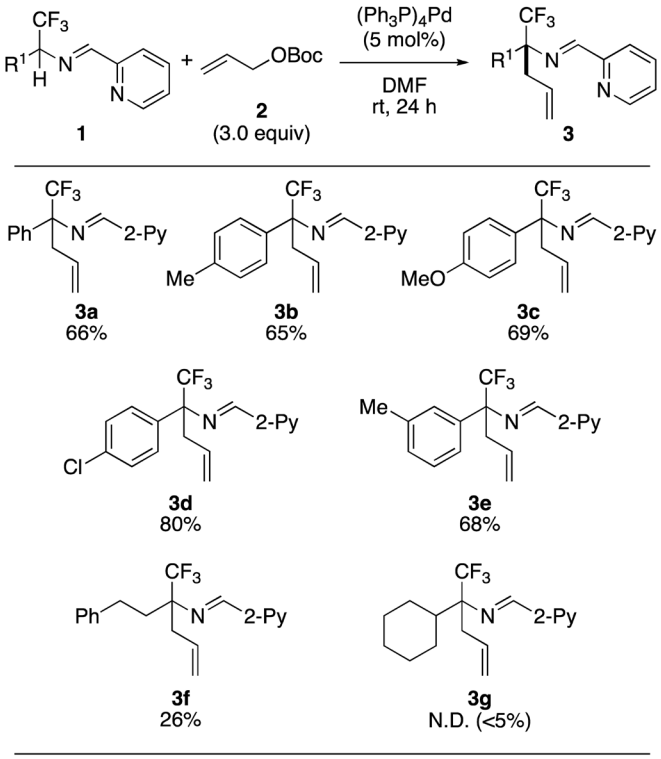
Table 1. Optimization of Reaction Conditions



Entry	Catalyst	Temp. (°C)	Time (h)	Yield (%)[a]
1	2.5 mol% of $[Pd(allyl)Cl]_2$ + 10 mol% of PPh_3	r.t.	2	25
2	2.5 mol% of $[Pd(allyl)Cl]_2$ + 10 mol% of PPh_3	r.t.	20	82
3	2.5 mol% of $[Pd(allyl)Cl]_2$	60	2	<5
4	2.5 mol% of $[Pd(allyl)Cl]_2$ + 5 mol% of PPh_3	60	2	<5
5	5 mol% of $Pd(PPh_3)_4$	r.t.	2	58
6	5 mol% of $Pd(PPh_3)_4$	r.t.	24	88
7	5 mol% of $Pd(PPh_3)_4$	60	2	85
8	5 mol% of $Pd(PPh_3)_4$ + 20 mol% of KO*t*Bu	60	2	86
9	20 mol% of KO*t*Bu	60	2	<5

a) Determined by ^{19}F-NMR analysis of the crude mixture. r.t., room temperature.

Table 2. Scope and Limitations of Substrates[a]



a) Isolated yield was reported unless otherwise noted. Yield in parenthesis was determined by ^{19}F-NMR analysis of the crude mixture.

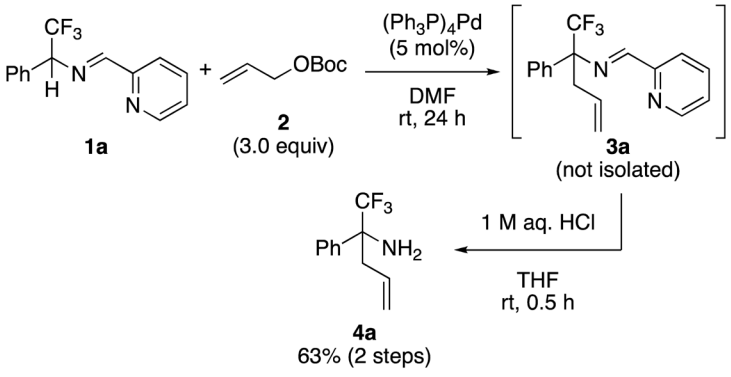


Chart 3. Access to *N*-Unprotected 1-Tetrasubstituted 2,2,2-Trifluoroethylamine

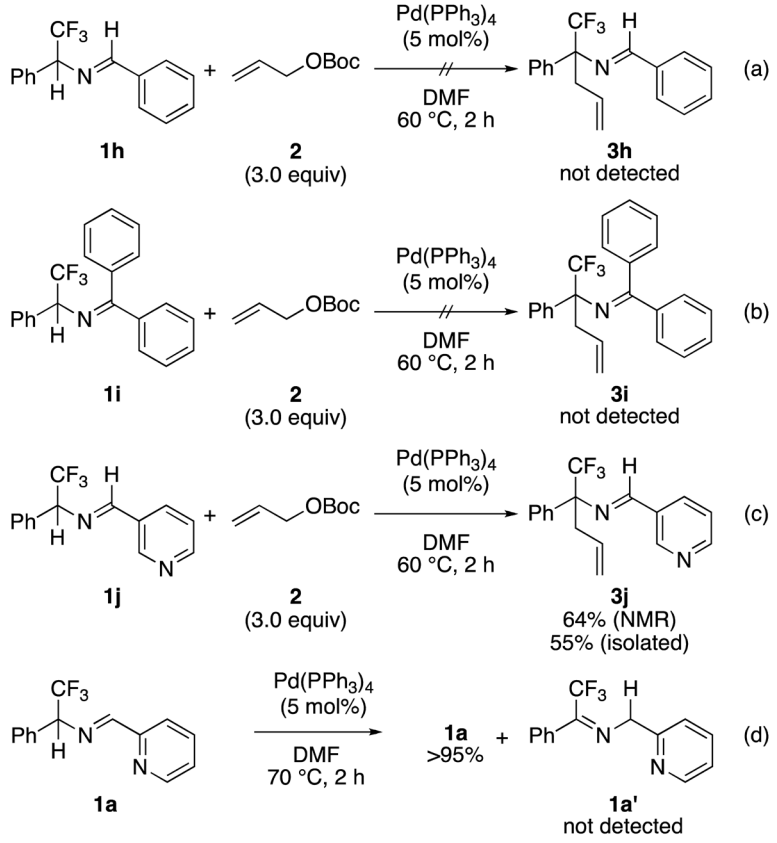


Chart 4. Control Experiments

while more sterically demanding 1-cyclohexyl-substituted imine **1g** did not provide the product **3g** at all, and **1g** remained unchanged even at higher temperatures. The reaction with **1a** and **2** and subsequent hydrolysis of **3a** yielded *N*-unprotected 1-allylated 2,2,2-trifluoroethylamine **4a** in 63% yield in two steps (Chart 3).

To gain mechanistic insight into the catalytic system, we performed several control experiments. Imines **1h** and **1i** derived from benzaldehyde and benzophenone did not provide the allylated products (Chart 4, Eqs. a, b), and both imines **1h** and **1i** remained unchanged. Replacement of the 2-pyridyl moiety with 3-pyridyl group reduced the reactivity (Eq. c).[20] These results indicated that both the electron-withdrawing nature and the coordinating ability of the imine moiety are important to promote the reaction efficiently, although bidentate chelation may not be indispensable. In addition, treatment of **1a** in the absence of **2** resulted in the recovery of **1a** with no formation of isomerized **1a′** (Eq. d), supporting the assumption that *tert*-butoxide anion generated from **2** promotes the deprotonation of **1a**.

In conclusion, we developed a palladium-catalyzed allylation of the sp^3 C–H bonds of *N*-(1-substituted-2,2,2-trifluoroethyl)-aldimines, affording 1-allylated 2,2,2-trifluoroethylamine derivatives with tetrasubstituted carbon stereocenters. *In situ* generation of *tert*-butoxide anion and coordination of the imines was important for promoting the reaction. Further studies to improve the scope of the reaction and application to one-pot sp^3 C–H bond functionalization of *N*-unprotected amines in the presence of catalytic amounts of coordinating aldehydes are ongoing in our laboratory.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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17) For a selected example of transition metal-catalyzed allylation with azomethine ylide, see: Liu J., Cao C.-G., Sun H.-B., Zhang X., Niu D., *J. Am. Chem. Soc*., **138**, 13103–13106 (2016).
18) For a selected example of transition metal-catalyzed allylation with azomethine ylide, see: Su Y.-L., Li Y.-H., Chen Y.-G., Han Z.-Y., *Chem. Commun*., **53**, 1985–1988 (2017).
19) Although the identification of the byproducts was not possible, we assume that imidazolidine derivatives resulted from dimerization of the imine **1a** *via* 1,3-cycloaddition are the possible byproducts. Such dimerization of the imines are known in the literature: Grigg R., Donegan G., Gunaratne H. Q. N., Kennedy D. A., Malone J. F., Sridharan V., Thianpatanagul S., *Tetrahedron*, **45**, 1723–1746 (1989).
20) We also tried the reaction of **1k** with 4-pyridyl group instead of 2-pyridyl moiety, and the desired product **3k** was observed in 35% yield based on ^{19}F-NMR analysis of the crude mixture. Due to the difficulty of separating the byproduct, however, we were unable to isolate **3k** in pure form.