Organofluorine Compounds

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Activation of Allylic C–F bonds: Palladium-Catalyzed Allylic Amination of 3,3-Difluoropropenes**

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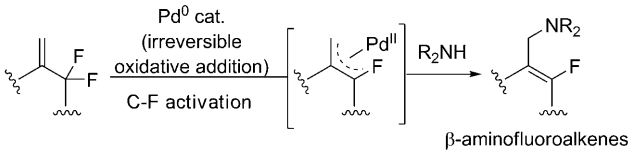
There is currently great interest in the activation of C–F bonds using transition metals such as nickel, palladium, and rhodium, which play a central role in mediating reactivity.[1] In palladium-catalyzed systems, aryl fluorides are typically used as substrates for C–F activation; the use of aliphatic fluorides, and in particular allylic fluorides, is far less common.[1e,2] In this context, the oxidative insertion of a palladium catalyst into an allylic C–F bond, first reported by Togni and co-workers, was particularly significant.[2b] Based upon this pioneering work, Gouverneur et al. recently reported the palladium-catalyzed allylic alkylation reaction of allylic fluorides in which the C–F bond is replaced by a C–C bond, affording non-fluorinated products.[2e]

In light of the interest in the development of procedures for the synthesis of fluorinated molecules,[3,4] we envisioned that the oxidative addition[5] of a 3,3-difluoropropene derivative to a palladium(0) catalyst could generate an unusual fluorinated π-allyl palladium complex (Scheme 1).[6] Nucleophilic attack on the allyl ligand would afford a fluorinated product in which one of the C–F bonds would be replaced by a C–Nu bond whilst keeping one C–F bond intact. Furthermore, the use of amines would result in the unique and valuable preparation of β-aminofluoroalkenes, which are themselves versatile synthetic precursors for further functionalization.[7] As well as being an important class of fluorinated molecules, fluoroalkenes have been studied for potential applications as a peptide isostere[8] or in liquid-crystalline materials.[9]

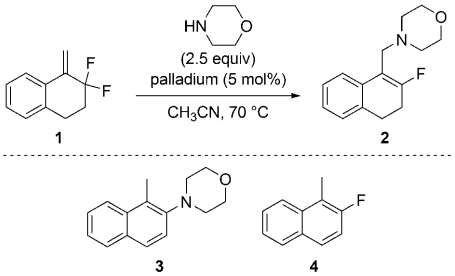
Herein, we report our initial studies towards a general synthesis of β-aminofluoroalkenes using the palladium-catalyzed allylic amination of 3,3-difluoropropenes by an allylic C–F bond activation.



Scheme 1. Palladium-catalyzed allylic amination of 3,3-difluoropropenes using allylic C–F activation.

2,2-Difluoro-1-methylene tetrahydronaphthalene (**1**) was selected as the substrate for optimization of the reaction conditions (Table 1) because of its straightforward preparation and its potential susceptibility to oxidation, which we hoped would allow us to perform the desired coupling under

Table 1: Reaction optimization for the allylic amination of **1**.[a]



Entry	Catalyst	*t* [h]	Yield [%][b]	**2**/**3**/**4**[c]
1	–	16	0	–
2	$[Pd(PPh_3)_4]$	6	31	93:4:3
3[d]	$[Pd(PPh_3)_4]$	0.25	34	77:20:3
4	$[Pd(PPh_3)_2Cl_2]$	3.5	traces	–
5	$Pd(OAc)_2/PPh_3$ (1:2)	6	52	86:11:3
6[e]	$[Pd_2(dba)_3]/tBu_3P$ (1:2)	6	12	95:2:3
7	$[Pd_2(dba)_3]/Cy_3P$ (1:2)	6	26	90:10:0
8	$[Pd_2(dba)_3]$/dppe (1:2)	6	44	97:3:0
9	$[Pd_2(dba)_3]$/dppp (1:2)	6	62	93:7:0
10	$[Pd_2(dba)_3]$/dppf (1:2)	6	63	95:5:0
11	$[Pd(dppf)Cl_2]\cdot CH_2Cl_2$	3.5	68	100:0:0
12[f]	$[Pd(dppf)Cl_2]\cdot CH_2Cl_2$	22	72	100:0:0
13[g]	$[Pd(dppf)Cl_2]\cdot CH_2Cl_2$	60	70	100:0:0

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of isolated **2**. [c] Estimated by ^1H and ^{19}F NMR spectroscopy of the crude reaction mixture. [d] 160 °C; microwave irradiation. [e] $tBu_3PH\cdot BF_4$ was used as the tBu_3P source and Cy_2NMe as an external base. [f] 2.5 mol% catalyst. [g] 0.5 mol% catalyst. dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane, 1,1′-bis(diphenyl-phosphino)ferrocene.

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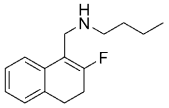
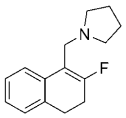
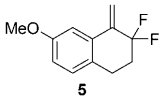
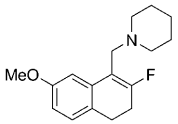
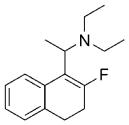
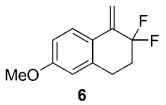
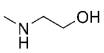
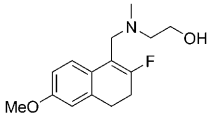
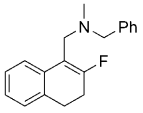
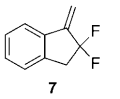
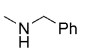
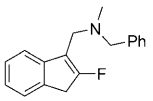
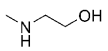
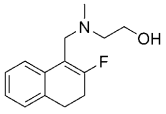
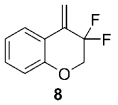
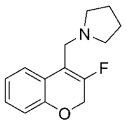
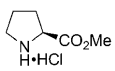
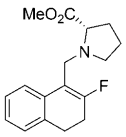
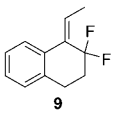
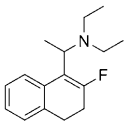
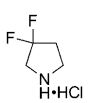
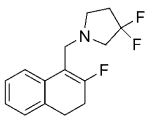
mild conditions.[10] Although no reaction was observed in the absence of palladium, we were pleased to observe the formation of the desired product **2** when $[Pd(PPh_3)_4]$ was used as the catalyst, albeit in low yield (31%; Table 1, entry 2). Aminonaphthalene **3** (ca. 4%) and 2-fluoro-1-methylnaphthalene (**4**)[11] (ca. 3%) were also observed in the crude reaction mixture using ^1H and ^{19}F NMR spectroscopy. Performing the reaction at a higher temperature using microwave irradiation resulted in a similar isolated yield of **2** (34%), along with a much greater amount of aminonaphthalene **3** side-product (ca. 20%; Table 1, entry 3). The reaction was found to be sensitive to the nature of the catalyst, as only trace amounts of **2** were observed in the presence of $[Pd(PPh_3)_2Cl_2]$ (Table 1, entry 4), whilst a moderate yield of **2** was obtained with $Pd(OAc)_2/PPh_3$ (1:2), albeit with good selectivity (Table 1, entry 5). Monodentate electron-rich ligands, such as tBu_3P and Cy_3P, led to low yields of **2** (12% and 26%, respectively; Table 1, entries 6 and 7); more encouraging results were obtained with bidentate ligands (Table 1, entries 8–10). The use of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ as the catalyst provided the desired product in 68% yield and excellent selectivity (100:0:0) in a shorter reaction time (3.5 h; Table 1, entry 11). The catalyst loading was successfully reduced to 0.5 mol% with a comparable isolated yield of **2** (70%; Table 1, entry 13) over a longer reaction time (60 h). For practical reasons, 2.5 mol% $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ was used in acetonitrile at 70°C for 22 h as the standard conditions for the rest of the study (Table 1, entry 12).[12]

Preliminary evaluation of the scope of this transformation on cyclic 3,3-difluoropropenes was then performed (Table 2). A variety of secondary amines reacted successfully under the reaction conditions, including pyrrolidine, diethylamine, and *N*-methylbenzylamine (Table 2, entries 2–4).[13] Interestingly, when 2-(methylamino)ethanol was used as the nucleophile, protection of the alcohol functionality was not necessary, as only the N-alkylation product was isolated (70%; Table 2,

Table 2: Allylic amination of cyclic 3,3-difluoropropenes.[a]

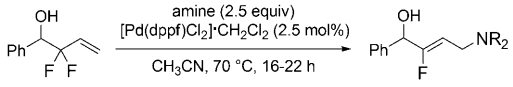
Entry	Substrate	Amine	Product	Yield [%][b]	Entry	Substrate	Amine	Product	Yield [%]
1	**1**		**2**	72	8[f]	**1**			70
2[c]	**1**			72	9	 **5**			65
3[c]	**1**			85	10	 **6**			70
4	**1**			80	11	 **7**			74
5	**1**			70	12[c]	 **8**			77
6[d]	**1**			65	13[g]	 **9**			63
7[c,e]	**1**			53					

[a] Reaction conditions: $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (2.5 mol%), amine (2.5 equiv), acetonitrile, 70°C, 14–22 h. [b] Yield of isolated products. [c] 5.0 equivalents of amine added. [d] 3 equivalents of iPr_2EtN added. [e] iPr_2EtN (5 equiv) was also added. [f] $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (5 mol%), *n*-butylamine (10 equiv), acetonitrile, 70°C, 90 min. [g] $[\{Pd(allyl)Cl\}_2]$ (5 mol%), (*rac*)-binap (10 mol%), diethylamine (5.0 equiv), acetonitrile, 50°C, 60 h. binap = 2,2-bis(diphenylphosphanyl)-1,1-binaphthyl.

entry 5). Amine hydrochloride salts could be used as nucleophiles in the reaction in the presence of a non-nucleophilic amine base to capture the HCl. Thus, both L-proline methyl ester hydrochloride salt (Table 2, entry 6) and 3,3-difluoropyrrolidine hydrochloride (Table 2, entry 7) reacted successfully to afford their respective amination derivatives. Primary amines, such as *n*-butylamine, led to mixtures of mono- and bis(alkylated) products under the standard reaction conditions. However, using a larger excess of the amine (10 equiv) resulted in the isolation of the monoalkylated product in good yield (70%; Table 2, entry 8). Isomeric methoxy-substituted 3,3-difluoropropenes **5** and **6**, 2,2-difluoro-1-methylene-2,3-dihydro-1H-indene (**7**), and 3,3-difluoro-4-methylenechroman (**8**) reacted equally well, providing the desired fluorinated products in 65–77% yield (Table 2, entries 9–12). Finally, 1-methyl-3,3-difluoropropene (**9**) successfully afforded the fluoroalkene product in 63% yield (Table 2, entry 13). In this case, a stereocenter is created during the reaction, thus opening up the possibility of an asymmetric transformation.

Acyclic 3,3-difluoropropenes were also accessed in a straightforward manner by the indium-mediated allylation of aldehydes in water using bromodifluoropropene.[14] Treatment of homoallylic alcohol **10** with *N*-methylbenzylamine, diethylamine, or 3,3-difluoropyrrolidine hydrochloride, under our optimized conditions, led to the formation of (*Z*)-fluoroalkenes **11**–**13** in excellent yields (86%, 97%, and 90% yield, respectively) with *Z* stereoselectivities greater than 20:1 (Table 3). The formation of such diverse synthons using this allylation/amination sequence exemplifies the synthetic opportunities offered by this method.

Table 3: Allylic amination of acyclic 3,3-difluoropropenes.[a]

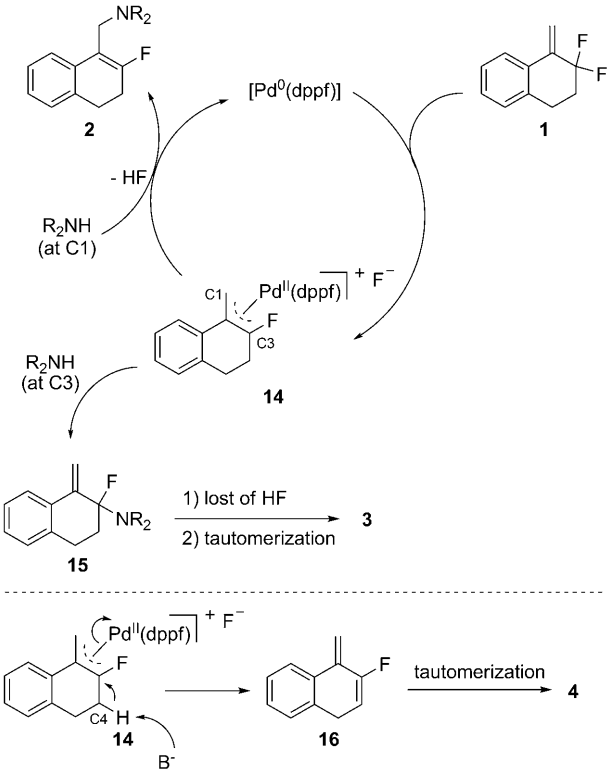


10 11-13

Entry	Amine	Product	Yield [%][b]
1		**11**	86
2[c]		**12**	97
3[c,d]		**13**	90

[a] Reaction conditions: $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (2.5 mol%), amine (2.5 equiv), CH_3CN, 70°C, 16–22 h. [b] Yield of isolated product. [c] 5.0 equivalents of amine added. [d] 5 equivalents of iPr_2EtN added.

A possible mechanism for the formation of the observed products is shown in Scheme 2.[15,16] Initial oxidative addition of an allylic C–F bond[2b,d,e] to the palladium(0) catalyst would generate fluorinated palladium π-allyl complex **14**.[17–19] Interestingly, the formation of **14** is thought to be irreversible (i.e., the reductive elimination of a F–Pd^{II}–allyl complex is kinetically disfavored),[2b,20] which would make this system



Scheme 2. Plausible mechanistic pathway for the formation of **2**, **3**, and **4**. R_2NH = morpholine, $B^- = F^-$ or morpholine.

analogous to the established decarboxylative allylation system developed by Tsuji and co-workers.[21] We expect that the palladium atom in complex **14** would lie closer to C3 than C1, because C3 bears an electron-withdrawing fluorine substituent.[22] Thus, external nucleophilic attack[22a] of the amine at C1, which is less strongly bound to the metal but also more sterically accessible, would afford the desired fluoroalkene **2**.[15,16,22,23] Alternative external nucleophilic attack[22a] of the amine at C3 would initially generate gem-fluoroamine **15**, the latter would subsequently undergo rapid amine-assisted elimination of HF followed by tautomerization to generate the isolated aminonaphthalene **3**. The formation of 2-fluoro-1-methylnaphthalene (**4**)[11] may be explained by the base-elimination (for example, a fluoride ion or an amine) of a proton at C4 from fluorinated palladium π-allyl complex **14** to afford **16**, followed by tautomerization.[2b,24] Detailed mechanistic studies to investigate these proposed pathways are currently underway.

In summary, we have developed a palladium-catalyzed allylic amination reaction of 3,3-difluoropropenes. Notably, the key fluorinated palladium π-allyl intermediate is generated using an allylic C–F bond activation. This reaction allows the efficient synthesis of β-aminofluoroalkenes from readily available 3,3-difluoropropenes and amines. Extension of the procedure to other nucleophiles (carbon, oxygen) and detailed mechanistic studies will be reported in due course. The simplicity of the reaction and the availability of its precursors should make this methodology appealing in the context of diversity-oriented synthesis.

Experimental Section

Typical procedure: A solution of **1** (50 mg, 0.28 mmol), and morpholine (60 μL, 0.69 mmol, 2.5 equiv) in acetonitrile (1 mL) was added to a round-bottom flask containing $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.6 mg, 6.9 μmol, 2.5 mol%) in acetonitrile (0.4 mL). The resulting mixture was stirred at 70°C for 22 h. Water was added, and the mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography of the crude residue on silica gel with 20% Et_2O/hexanes gave **2** (48 mg, 72%) as a colorless oil.

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[18] Because chloride ions are present, η^3-π complex **13** may exist as η^1-σ complex, see: a) C. Amatore, A. Jutand, M. A. M'Barki, G. Meyer, L. Mottier, *Eur. J. Inorg. Chem.* **2001**, 873 – 880; b) T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365 – 376. Studies to determine the exact nature of palladium complex **14** are underway.

[19] The fluoride counter ion in complex **14** is unlikely to be "naked" and is presumably stabilized by hydrogen bonding with an amine, HF produced in the reaction and/or adventitious water. The exact nature of the fluoride ion is not known at present.

[20] For the recent report on the reductive elimination of Ar-F from Ar-Pd^{II}-F, see: D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J.

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