Catalytic Fluorination

DOI: 10.1002/anie.201007307

Palladium-Catalyzed Allylic Fluorination**

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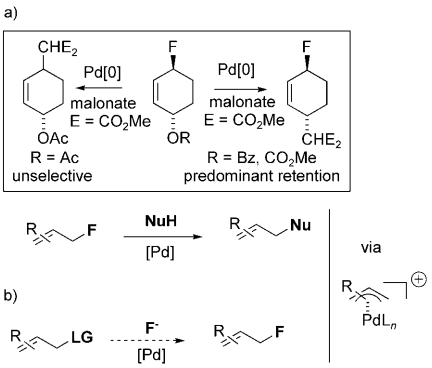
Transition metal catalyzed allylic substitution is a powerful method for carbon–carbon and carbon–heteroatom bond formation and plays a pivotal role in modern organic synthesis.[1] These reactions encompass a wide variety of heteroatoms (N, O, S, Si, P) as nucleophiles. A transition metal catalyzed allylic fluorination would unveil new synthetic approaches towards highly valuable fluorinated compounds such as fine pharmaceuticals or ^{18}F-labeled radiotracers for positron emission tomography (PET). The conceptual difficulties in developing such a reaction are, however, numerous and have been well documented. Togni and co-workers concluded that this process is thermodynamically unfavorable, as a result of unsuccessful attempts to trap cationic η^3-(1,3-diphenylallyl)palladium diphosphine complexes with fluoride ions.[2] The use of the fluoride ion as the nucleophilic component presents a series of challenges, including the potential reversibility of the reaction.[3] Solvation can dramatically decrease the reactivity of the fluoride ion and in its desolvated form it becomes a strong Brønsted base favoring elimination instead of substitution.[4] The low intrinsic nucleophilicity of the fluoride ion is demonstrated by its frequent use as an additive to modulate catalytic reactivity or product distribution.[5]

In previous work, we demonstrated that allyl fluorides are reactive under Tsuji–Trost allylic alkylation conditions, and that the reaction deviates from the expected stereochemical course, with much higher levels of inversion being observed than with the standard carboxylate or carbonate leaving groups.[6] Critically, a reactivity order was established by internal competition, in which fluoride was demonstrated to be a superior leaving group to acetate, but inferior to methyl carbonate (Scheme 1). Based on this recent discovery, and by applying the principle of microscopic reversibility, we considered that the catalytic allylic substitution by fluoride ions would be achieved by a judicious choice of the allylic leaving group, the fluoride source, and the ligand. The catalytic formation of C_{sp^3}–F bonds is uncommon,[7,8] which is in contrast with the intense output of catalytic routes to C_{sp^2}–F bonds.[9]



Scheme 1. a) The palladium-catalyzed allyl fluoride alkylation[6] and b) the palladium-catalyzed allyl fluoride formation. Bz = benzoyl.

Initial investigations focused on the palladium-catalyzed fluorination of simple allylic carbonates derived from 1- or 2-arylprop-2-en-1-ols. The results derived from 2-(4-(*tert*-butyl)phenyl)allyl methyl carbonate (**1a**) are shown in Table 1. This model substrate was selected for the conceptual validation because it does not allow for competitive elimination and the desired allylic fluoride **2** has distinctive ^{1}H NMR ($\delta = 5.27$ ppm, dd, $J = 47$ Hz, 6 Hz, CH_2 in $CDCl_3$) and ^{19}F NMR spectra ($\delta = -212.7$ ppm, td, $J = 47$ Hz, 3 Hz) that permit easy tracking. The choice of carbonate as the leaving group was driven by its established superior reactivity compared with fluoride in the Tsuji–Trost alkylation; a crucial requirement to overcome the competing C–F displacement.[6] Early screening experiments that employed CsF in THF with 5 mol % [$Pd(dba)_2$] and 15 mol % PPh_3 revealed the presence of the desired product **2** in a trace amount (entry 1). When TBAF rather than CsF was used, the complete consumption of the starting material led disappointingly to the allylic alcohol **3** as the main product (entry 2). It is well known that tetra-alkylammonium fluorides are notoriously difficult to maintain in their dehydrated state owing to

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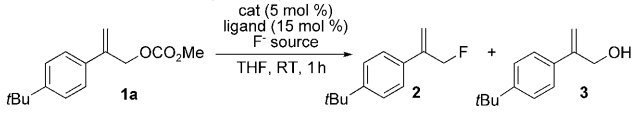
[**] We thank Dr. S. Fletcher for very helpful discussions. This research was financially supported by the EPSRC (C.H., A.H., M.T.), GSK (M.H.), the CRUK (M.T.), the European Union FP7-ITN-238434 (E.B.), and the Leverhulme Trust (J.M.B.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007307.

Table 1: Palladium-catalyzed allylic fluorination of **1a**.



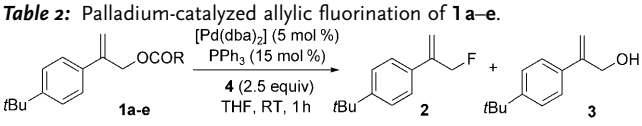
Entry	Catalyst	Ligand	Fluoride Source	**1a/2/3**[a]	Yield **2** [%][b]
1	$[Pd(dba)_2]$	PPh_3	CsF	1:0.02:0.4	–
2	$[Pd(dba)_2]$	PPh_3	TBAF	0:1:12	–
3	$[Pd(dba)_2]$	PPh_3	**4**[c]	1:4:4	30
4	$[Pd(OAc)_2]$	PPh_3	**4**[c]	1:3:5	–
5	$[Pd(PPh_3)_4]$	–	**4**[c]	1:5:2	–
6	$[Pd(C_3H_5)(PPh_3)_2]^+$[d]	–	**4**[c]	1:2:5	–
7	–	–	**4**[c]	1:0:0	–

[a] Ratio determined on crude reaction mixture by using ^{1}H NMR spectroscopy. [b] Yield of the isolated product. [c] **4** is TBAF·(tBuOH)$_4$. [d] Used as BF_4^- salt. dba = dibenzylideneacetone, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

their very high hygroscopicity. We therefore turned to tetra-*n*-butylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride [TBAF·(tBuOH)$_4$; **4**]; a reagent that possesses low hygroscopicity and is reported to display good nucleophilicity and low basicity (entries 3–7).[10] A substantial improvement was observed when using this anhydrous crystalline reagent. Under the most favorable reaction conditions, the allylic fluoride **2** was isolated in a 30% yield, in addition to the undesired allylic alcohol **3** (entry 3). Importantly, control reactions that were run in the absence of a palladium catalyst did not result in formation of the fluoride **2** (entry 7).

At this stage the viability of catalytic allylic fluorination had been demonstrated. Under the chosen reaction conditions, persistent competition from side reactions in which allyloxy-type compounds were formed, was unavoidable. To assess the extent to which the methylcarbonate leaving group is responsible for these undesired processes,[11] alternative reactive leaving groups were investigated (Table 2). The acetate **1b** and trifluoroacetate **1c** were subjected to the reaction conditions, but only the starting material or the allylic alcohol were observed by ^{1}H NMR spectroscopy (entries 2 and 3). With benzoate **1d**, allylic fluoride **2** was formed in low conversion (entry 4). We then turned to 2-(4-(*tert*-butyl)phenyl)allyl 4-nitrobenzoate (**1e**); *p*-nitrobenzoate is rarely used as a leaving group in palladium catalysis.[12] Pleasingly, we found that fluorination of **1e** with 2.5 equivalents of TBAF·(tBuOH)$_4$ in the presence of 5 mol% of $[Pd(dba)_2]$ and 15 mol% PPh_3 for one hour at room temperature, led to the isolation of the allylic fluoride **2** in quantitative yield (entry 5). A control experiment confirmed that the presence of the catalyst is essential for the fluorination to proceed (entry 6). This further optimization study indicated that among the esters investigated, the substrate releasing the stronger carboxylic acid is not the one that leads to successful fluorination (pK_a (H_2O) = −0.25 for CF_3COOH, 4.20 for PhCOOH, 3.44 for $pNO_2C_6H_4COOH$, and 3.18 for HF).

Table 2: Palladium-catalyzed allylic fluorination of **1a–e**.

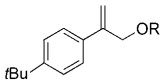
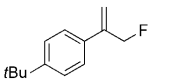
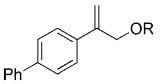
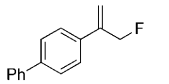
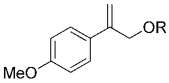
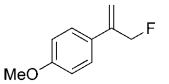
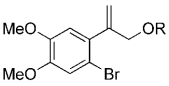
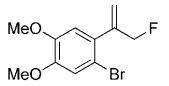
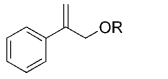
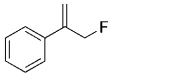
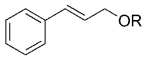
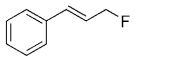
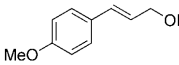
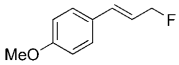
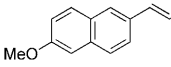
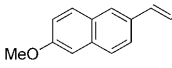
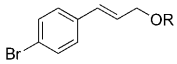
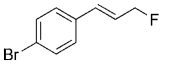
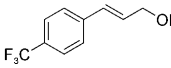
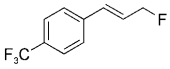
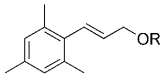
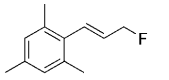
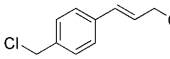
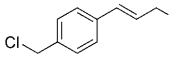


Entry	**1a–e**	R	**1/2/3**[a]	Yield **2** [%][b]
1	**1a**	OMe	1:4:4	30
2	**1b**	Me	100:0:0	–
3	**1c**	CF_3	0:0:100	–
4	**1d**	Ph	80:20:0	–
5	**1e**	p-$NO_2C_6H_4$	0:100:0	> 95
6[c]	**1e**	p-$NO_2C_6H_4$	100:0:0	–

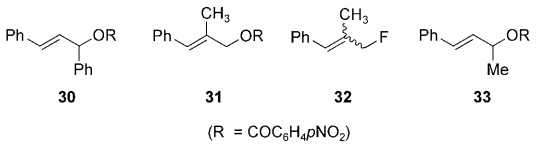
[a] Ratio determined by ^{1}H NMR spectroscopy. [b] Yields of the isolated product. [c] Reaction run in the absence of palladium catalyst.

The identification of a leaving group leading exclusively to the formation of the desired allylic fluoride **2** enabled us to examine the scope of this new allylic fluorination protocol. Our results are summarized in Table 3. Various 2-substituted propenyl fluorides (**19**–**21**), which are structurally related to **2**, were obtained in high yields (> 80%; entries 1–4). The reaction to form the parent compound **22** is comparably efficient, but the volatility of this product attenuates the yield of isolated product (entry 5). The reaction is not limited to 2-propenyl esters (**5**–**8**). Under these reaction conditions, cinnamyl fluoride (**23**) was isolated in high yield (entry 6). This result indicated that the conditions of allylic fluorination are sufficiently mild to prevent decomposition of **23**, which is known to be unstable upon standing at room temperature.[13] The branched regioisomer 3-fluoro-3-phenylpropene that arises from fluorination at the benzylic position, and is easily differentiated by ^{19}F NMR spectroscopy, was not detected. This result contrasts with the fluorination of cinnamyl alcohol carried out using diethylaminosulfur trifluoride (DAST); a reaction that gives a mixture of regioisomers, with the branched product being formed predominantly (linear/branched 1:1.75).[14] The procedure was successful for several other linear allyl *p*-nitrobenzoates (**10**–**15**), although the yields were generally lower (entries 7–12). For the formation of the electron-rich allyl fluorides **24** and **25**, the reaction was efficient and rapid, but the products were sensitive to the work-up conditions (entries 7 and 8).[15] Formation of 4-bromocinnamyl fluoride (**26**) and more particularly the 4-trifluoromethyl analogue **27** were slower, and in the latter case required heating to 40 °C (entries 9 and 10, respectively). The sterically hindered mesityl ester **14** also required heating to 40 °C (entry 11); palladium coupling chemistry has not previously been observed in a 2,6-disubstituted arylallyl ester.[16] Formation of the 4-chloromethyl derivative **29** indicates that the incorporation of a sensitive and easily manipulated functional group is feasible under these mild reaction conditions (entry 12). As anticipated, an attempt to form the allyl fluoride from ester **30** (Scheme 2) was not possible under our standard reaction conditions.[2] Substrate **31** was reactive, and in this case a mixture of stereoisomers of **32** was formed together with traces of the benzylic regioisomer (21% yield determined by ^{19}F NMR spectroscopy). One limitation of the current protocol is a propensity for the competing elimination to give diene products, when possible. For example, reactant **33** gives approximately 5% of the desired allyl fluoride, as well as the

Table 3: Fluorination of 2- and 3-substituted propenyl esters.[a]

Entry	Ester (R = $COC_6H_4pNO_2$)		Allyl Fluoride		Yield [%][b]
1		**1e**		**2**	>95
2		**5**		**19**	95
3		**6**		**20**	85
4		**7**		**21**	84
5		**8**		**22**	66
6		**9**		**23**	>95
7[c]		**10**		**24**	39
8		**11**		**25**	46
9		**12**		**26**	53
10[d]		**13**		**27**	35
11[d]		**14**		**28**	65
12		**15**		**29**	60

[a] Reaction conditions: **4** (2.5 equiv), $[Pd(dba)_2]$ (5 mol%), PPh_3 (15 mol%), THF, RT, 1 h. [b] Yield of the isolated product. [c] Reaction run for 1 h at RT and 20 min at 40°C. [d] Reaction run at 40°C for 4 h; **27** is unstable.

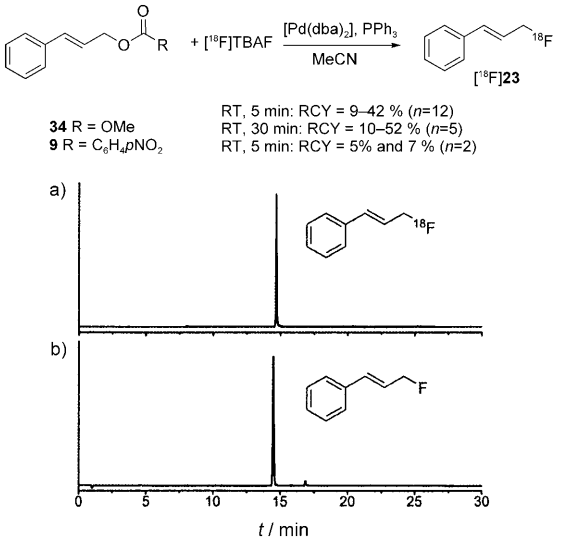


Scheme 2. Fluorination of **30**, **31**, and **33**.[25]

diene that is formed by formal loss of *p*-nitrobenzoic acid and the unreacted starting material.[17]

The reactivity of the substrate in allylic fluorination is very responsive to carbocation stabilizing substituents in the substrate at the 1- and 2-positions of the allyl moiety. This observation militates in favor of the involvement of an η^3-allylpalladium cation in the catalytic cycle, and places emphasis on factors that facilitate its formation, rather than the subsequent trapping with a fluoride ion.[18]

At this stage, we were poised to investigate whether this new reaction would proceed with [^{18}F]fluoride because PET can only benefit from the availability of a wider range of radiosynthetic methods for ^{18}F labeling.[19] The very mild conditions required for the palladium-catalyzed allylic fluorination to proceed, and the prospect to include transition-metal-based chemistry in the portfolio of radiosynthetic transformations available for ^{18}F–C bond construction, prompted us to study the ^{18}F-fluorination of a representative allylic precursor. This investigation started with the preparation of the no-carrier-added reagent [^{18}F]TBAF.[20] A solution of [^{18}F]TBAF in anhydrous acetonitrile was added to a large excess of cinnamyl methyl carbonate **34** (Scheme 3), $[Pd(dba)_2]$, and triphenylphosphine in anhydrous acetonitrile. The mixture was stirred at room temperature for either 5 or 30 minutes. After quenching with water, radio-HPLC analysis of the reaction mixture indicated the formation of [^{18}F]-labeled cinnamyl fluoride ([^{18}F]**23**; Scheme 3a), the identity of which was confirmed by coelution with the "cold" reference compound (Scheme 3b). The decay-corrected radiochemical yield (RCY) was 9–42% ($n = 12$) for reactions quenched after 5 minutes. No significant improvement was observed after 30 minutes (RCY = 10–51%, $n = 5$). Control experiments in the absence of $[Pd(dba)_2]$ did not lead to the formation of [^{18}F]**23** at room temperature or upon heating at 110°C for 20 minutes; a result indicating that the transition metal is essential for ^{18}F-fluorination to proceed. The *p*-nitrobenzoate group of **9** was successfully displaced with [^{18}F]TBAF in the presence of $[Pd(dba)_2]$ but this process was much less efficient with a RCY not exceeding 7%. This result indicates that because of the constraints imposed by ^{18}F-fluorination, tailored optimization is required. This new labeling protocol was compared with conventional direct S_N2 ^{18}F-fluorination.[21] We examined the reactivity of cinnamyl chloride and cinnamyl bromide with [^{18}F]TBAF. After 5 minutes at room temperature, cinnamyl chloride remained intact; cinnamyl bromide was successfully fluorinated leading to [^{18}F]**23** with a RCY not exceeding



Scheme 3. Palladium-mediated ^{18}F–C bond formation. a) Ordinate HPLC-radioactivity of [^{18}F]-**23**. b) Ordinate HPLC-UV (254nm) spectrum of **23**. n = number of experiments conducted.

20% ($n = 3$). Under forcing conditions (110 °C, 20 min), both cinnamyl chloride and bromide delivered [^{18}F]**23** with a RCY of 40% and 42%, respectively.[22]

In conclusion, this paper describes a palladium-catalyzed method for the formation of allylic C–F bonds from allyl *p*-nitrobenzoate, including "hot" fluoride.[23] This method is significant, as halides are typically categorized as unsuitable nucleophiles for transition metal catalyzed allylic substitution. Ongoing efforts seek to expand the scope of this reaction to more challenging substrates such as those prone to elimination and to validate a catalytic asymmetric variant of this new fluorination reaction. To our knowledge, this work demonstrates for the first time that ^{18}F–C bond formation is feasible using a mild and rapid palladium-based protocol.[24] The way is paved towards organotransition-metal ^{18}F-radiochemistry.

Experimental Section

General procedure: [Pd(dba)$_2$] (6 mg, 0.01 mmol) and PPh_3 (8 mg, 0.03 mmol) were added to a solution of 2-(4-*tert*-butylphenyl)prop-2-en-1-yl-4-nitrobenzoate (68 mg, 0.2 mmol) in THF (2 mL). TBAF·(*t*BuOH)$_4$ (279 mg, 0.5 mmol) was then added in one portion. The reaction was stirred at RT for 1 h. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O (2 × 5 mL), and then the combined organic extracts were washed with NH_4Cl (2 × 10 mL), H_2O (1 × 5 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the crude reaction mixture was purified by using silica gel column chromatography with 100% petroleum ether (b.p. 30–40 °C) eluent.

Received: November 20, 2010
Published online: February 8, 2011

Keywords: allylic fluorination · fluorides · homogeneous catalysis · palladium · positron emission tomography

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