Palladium-Catalyzed Substitution and Cross-Coupling of Benzylic Fluorides
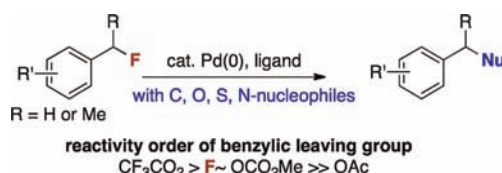
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ABSTRACT

Benzylic fluorides are suitable substrates for Pd(0)-catalyzed Tsuji–Trost substitution using carbon, nitrogen, oxygen, and sulfur nucleophiles and for cross-coupling with phenylboronic acid. For the bifunctional substrate 4-chlorobenzyl fluoride, fine-tuning of the reaction conditions allows for the regioselective displacement of either the chlorine or fluorine substituent. The leaving group ability of fluoride vs other groups displaced in substitution is $CF_3CO_2 \approx p\text{-}NO_2C_6H_4CO_2 \approx OCO_2CH_3 > F > CH_3CO_2$, a ranking similar to allylic fluorides under Pd catalysis.

The number of active pharmaceutical and agrochemical ingredients that contain a benzylic fluoride or a fluorine substituent directly adjacent to a heteroaryl motif is significant, with growth to be expected through the 21st century.[1] Benzylic fluorination may be performed by halide exchange with TBAF·3H$_2$O or TBAF·4tBuOH,[2] or dehydroxy-fluorination of benzylic alcohols with diethylaminosulfur trifluoride DAST.[3] The Ru-catalyzed nucleophilic fluorination of benzylic bromides by halide exchange with thallium fluoride was reported in 2001.[4]

More recently, Sanford,[5] Vigalok,[6] and Gagné[7] described cases of Pd- or Pt-mediated benzylic electrophilic fluorination. In contrast to benzylic C–F bond formation, the reactivity of benzylic fluorides in transition metal catalyzed substitution or cross-coupling reactions is unknown. This piece of information is however critically important, given the widespread and increasing use of organofluorine compounds in medicine and biology and the importance of catalytic pathways to aryl and benzyl fluorides in their synthesis (Figure 1).

Figure 1. Palladium-catalyzed substitution of allyl fluoride[8] (eq 1) and benzyl fluoride (eq 2).

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Herein, we report a series of Pd-catalyzed reactions that provide foundations for benzylic C−F substitution. The reactivity of fluorides vs other benzylic leaving groups is discussed, as well as the stereochemical course of substitution in one case. By analogy with our previous work on allylic C−F substitution[8] and allylic fluorination,[9] this study will facilitate development of the reverse reaction, catalytic benzylic fluorination. The ability of benzylic carbonates and carboxylates to undergo nucleophilic substitution or cross-coupling is very well documented, following the early work of Legros and Fiaud,[10] and is thought to proceed via an η^3-benzyl metal complex.[11] Nucleophilic addition typically occurs regioselectively at the benzylic carbon, but substitution in the ring by a tethered group has been observed.[12] An instructive example of noncatalytic Ir-mediated carbon fluorine activation at a benzylic carbon is available.[13] This process does not occur *via* direct oxidative addition of the C−F bond to iridium but is initiated instead by reversible C−H bond cleavage. Our studies began with efforts to identify suitable conditions for Pd-catalyzed substitution via C−F activation using 2-(fluoromethyl)naphthalene **1a** (Table 1).

This model substrate does not allow for competitive elimination and is more reactive than the benzyl analogue.[10,15] Dimethyl malonate (pK_a = 15.9 in DMSO) and Meldrum's acid (pK_a = 7.3 in DMSO)[16] were examined under basic conditions. For both nucleophiles, Pd(η^3-C₃H₅)(COD)·BF₄ (5 mol %) was the catalyst of choice when used in combination with the bidentate phosphine

Table 1. Effect of Pd Source and Ligand on the Reactivity of **1a** with Dimethyl Malonate **I** or Meldrum's Acid **II**[14]

entry	catalyst ligand[a]	NuH[b]	solvent base	time, temp	conv[c]
1	**A**	**I**	THF, NaH	48 h, 60 °C	38%
2	**B**	**I**	EtOH, K₂CO₃	16 h, 75 °C	>95%[d]
3	**C**	**II**	DMSO, Et₃N	48 h, 60 °C	66%[e,f]
4	**B**	**II**	DMSO, NaH	8 h, 60 °C	81%[e,f]
5	**B**	**II**	EtOH, Et₃N	16 h, 50 °C	57%[e,f]
6	–	**II**	DMSO, Et₃N	24 h, 60 °C	0%[g]
7	**D**	**II**	DMSO, Et₃N	24 h, 60 °C	0%[g]

^{a}**A**: 5 mol % Pd₂(dba)₃−dppe (Pd/L = 1:1.5). **B**: 5 mol % Pd(η^3-C₃H₅)(COD)·BF₄−DPEPhos (Pd/L = 1:2). **C**: 5 mol % Pd(η^3-C₃H₅)-(COD)·BF₄−dppf (Pd/L = 1:2). **D**: No Pd, 10 mol % dppf. ^{b}**I**: Dimethyl malonate. **II**: Meldrum's acid. ^{c}Conversion determined by ¹H NMR. ^{d}Mixture of methyl and ethyl malonate. ^{e}Isolated yield. ^{f}Dialkylated product. ^{g}Recovery of starting material. DPEPhos = bis(2-diphenyl-phosphinophenyl)ether; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

ligand DPEPhos (10 mol %) (entries 2 and 4). EtOH and DMSO are suitable solvents, but for subsequent studies involving less reactive starting materials, EtOH was found to be superior, as polar protic solvents are better able to sequester the fluoride leaving group through hydrogen bonding.[17] Control reactions in the absence of a Pd catalyst failed to produce more than traces of product (entries 6−7).

These results encouraged a study with a wide range of substrates and nucleophiles (Figure 2). The favored conditions used with Meldrum's acid coupling proved effective for **1a**. For this substrate, the reactions were conducted using 5 mol % Pd(η^3-C₃H₅)(COD)·BF₄ and 10 mol % of DPE-Phos in DMSO at 60 °C for 24 h. For all other substrates, EtOH was a superior solvent. Morpholine, aniline, phenol, and sodium benzenesulfinate all displace fluoride under Pd catalysis; for **2c−e**, the best yields were obtained using 20 mol % of *t*BuXPhos; the products were isolated with yields ranging from 41% to 95%. The fluoromethylated quinoline **3a**, indole **4a**, benzofuran **5a**, and benzothiophene **6a** also underwent successful substitution with yields above 75%; control experiments ruled out the possibility of an uncatalyzed pathway for **1a** and **2a**; some background reactivity was however observed for the heteroaromatic systems **3a**, **4a**, **5a**, and **6a** (maximum 9% yield for **6a**).

Pd-catalyzed substitution of monocyclic benzylic fluorides is more challenging (attenuation of aromaticity on π-allyl formation) and typically required extended times at 70 or 75 °C to proceed efficiently using the same catalyst and reagents. The data summarized in Scheme 1 indicate that the reaction tolerates benzylic fluorides with *p*-phenyl, *p*-nitro, *p*-chloro, and *p*-bromo substituents and

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(15) η^3-α-Arylalkyl complexes derived from (*R*)-Binap react faster than η^3-allyl complexes. The relative order of reactivity towards aniline was naphthylmethyl > naphthylethyl > benzyl > 1,1- dimethylallyl > allyl; see: Johns, A. M.; Tye, J. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 16010.

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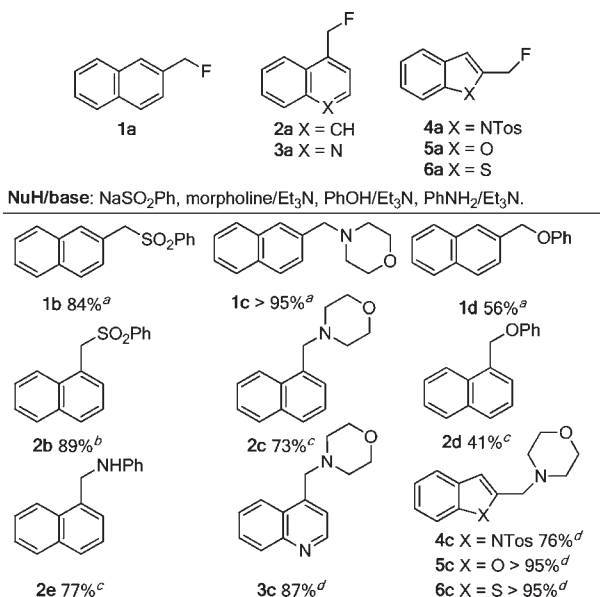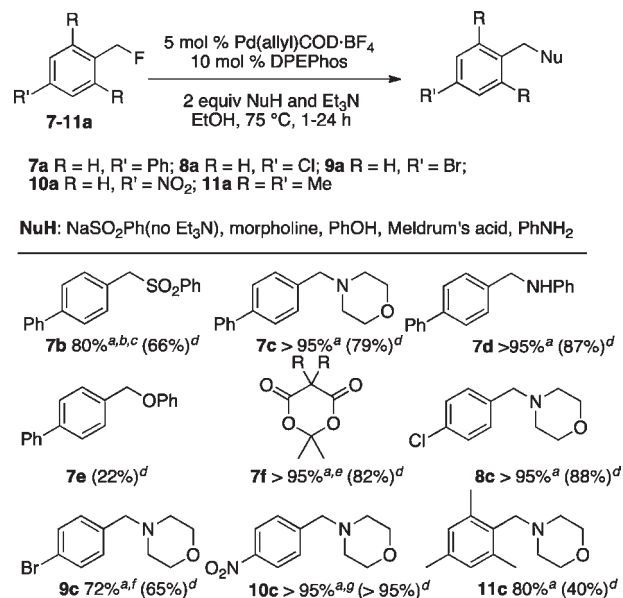
Figure 2. Pd-catalyzed substitution of bicyclic aromatics **1−6a**. [a]5 mol % Pd(allyl)COD·BF$_4$, 10 mol % DPEPhos, DMSO, 60 °C, 24 h, 1.5−2 equiv of NuH. [b]5 mol % {(η^3-C$_3$H$_5$)PdCl}$_2$, 10 mol % DPEPhos, EtOH, 20 °C, 24 h, 1.5−2 equiv of NuH. [c]5 mol % Pd(allyl)COD·BF$_4$, 20 mol % tBuXPhos, EtOH, 75 °C, 24 h, 1.5−2 equiv of NuH. [d]5 mol % Pd(allyl)COD·BF$_4$, 10 mol % DPEPhos, EtOH, 75 °C, 24 h, 1.5−2 equiv of NuH.

is compatible with a range of C-, N-, O-, and S-nucleophiles. Local optimization was also performed to maximize conversion to product with alternative ligands such as XantPhos and tBuXPhos used when necessary.[14] Site selectivity in favor of benzylic fluoride displacement was observed for the bifunctional substrates **8a** and **9a**. Substitution of the sterically demanding fluoride **11a** with morpholine was also successful, but full conversion to **11c** was not reached despite using 20 mol % of tBuXPhos.

We also examined the reactivity of **1a** and **8a** in Pd-catalyzed Miyaura−Suzuki cross-coupling with phenylboronic acid (Scheme 2). The reaction of benzyl halides other than fluoride, benzyl carbonates, and benzyl acetates with arylboronic acids, aryltrifluoroborates, or arylstannanes is documented in the literature, inclusive of studies examining selectivity issues for benzylic substrates with *p*-chloro- or *p*-bromoaryl substitution.[10] The Miyaura−Suzuki coupling of 2-(fluoromethyl)naphthalene **1a** with 2 equiv of phenylboronic acid and K$_3$PO$_4$ was successfully performed using the Pd(η^3-C$_3$H$_5$)COD·BF$_4$−DPEPhos system in DMSO leading to **1g** in 67% yield. Site selectivity was examined with the bifunctional 4-chlorobenzyl fluoride **8a**. The best result was observed using 5 mol % of Pd(η^3-C$_3$H$_5$)COD·BF$_4$ and 20 mol % of XPhos. The reaction led exclusively to 4-(fluoromethyl)-1,1′-biphenyl **7a** in > 95% conversion (78% isolated yield). In contrast, using the bidentate DPEPhos under protic conditions, the benzylic coupling product **12** predominated (64% yield). In a previous example of Suzuki−Miyaura reactions with 4-chlorobenzyl bromide,

Scheme 1. Pd-Catalyzed Substitution of **7−11a**

7a R = H, R' = Ph; **8a** R = H, R' = Cl; **9a** R = H, R' = Br; **10a** R = H, R' = NO$_2$; **11a** R = R' = Me

NuH: NaSO$_2$Ph, morpholine, PhOH, Meldrum's acid, PhNH$_2$

[a]Conversion to product. [b]Solvent: EtOH/H$_2$O (5/1). [c]10 mol % tBuXPhos. [d]Isolated yields. [e]R″ = (1,1′-biphenyl-4-yl)methyl. [f]Reaction in *n*PrOH at 95 °C, 10 mol % Pd, 20 mol % DPEPhos. [g]20 mol % of tBuXPhos.

benzylic coupling was observed; in contrast aryl coupling was seen for 4-bromo- or 4-iodobenzyl bromide.[18] The reversal of regioselectivity between eqs 4 and 5 reflects the known enhancement of aryl chloride reactivity in Pd-coupling by very bulky electron-rich monophosphines.[19]

Scheme 2. Miyaura−Suzuki Cross-Coupling of 2-Fluoromethyl Naphthalene **1a** and Benzylic Fluoride **8a**
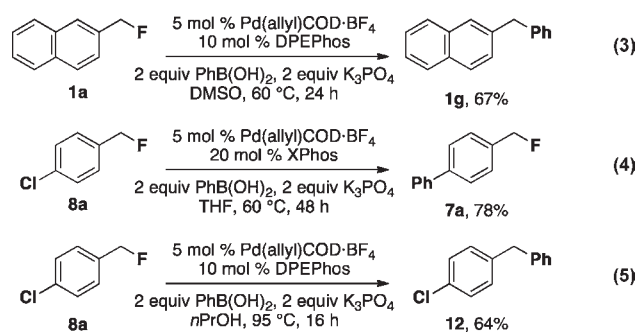
The relative leaving group ability of fluoride versus carbonate, acetate, trifluoroacetate, and *p*-nitrobenzoate was determined by performing a set of competition experiments. A 1:1 mixture of **2a** and the competing substrate **2h−2k** was subjected to Pd-catalyzed substitution by

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sodium benzenesulfinate. Compounds **2i**, **2j**, and **2k** were more reactive than the fluoride **2a**, but **2h** was clearly less reactive. The product distribution presented in Table 2 indicates that the reactivity order is $CF_3CO_2 \approx p\text{-}NO_2C_6H_4CO_2 \approx OCO_2CH_3 > F > CH_3CO_2$. This ranking is similar to allylic fluorides under Pd catalysis.[8,20]

Table 2. Competition Experiments: F versus CH_3CO_2, $p\text{-}NO_2C_6H_4CO_2$, CH_3OCO_2, and CF_3CO_2

2a

2h, R = COCH₃
2i, R = OCOCH₃
2j, R = COCF₃
2k, R = COC₆H₄NO₂

1 equiv of each

2b

+ recovered reactant(s)

5 mol % [Pd(allyl)Cl]₂
11 mol % DPEPhos

1.5 equiv PhSO₂Na
DMSO, 60 °C, 24 h

entry	RO	RO	F	SO₂Ph	OH
1	CH_3CO_2	29^a	0	71	0
2	$p\text{-}NO_2C_6H_4CO_2$	0	18	78	4
3	CF_3CO_2	7	22	69	2
4	CH_3OCO_2	0	29	71	0

^{a} All numbers refer to normalized ratios of products determined by ^{1}H NMR of the crude reaction mixture.

The configuration at the benzylic carbon was used to gain insight into the reaction mechanism. This study examined the reactivity of the secondary 2-(1-fluoroethyl)naphthalene **13a** with morpholine under our standard reaction conditions (Scheme 3). In this system, β-hydride elimination becomes possible. This competing pathway was predominant with the bulky monophosphine *t*BuX-Phos (> 95% alkene) but significantly minimized (86% of substitution) when using bidentate DPEPhos in ethanol. Enantioenriched (*S*)-1-(1-fluoroethyl)naphthalene **13a** (71% ee)[14] was substituted giving (*S*)-**13c** in 38% ee and 82% yield (Scheme 3, A). The major product is formed with overall retention, but with significant erosion of enantiomeric purity, an observation suggesting preferential outer sphere attack of the nucleophile on the (η^3-benzyl)Pd complex with inversion of configuration.[21]

(20) For a study of allylic fluoride substitution under Pt catalysis, see: Benedetto, E.; Massaba, K.; Tredwell, M.; Hollingworth, C.; Brown, J. M.; Gouverneur, V. *Organometallics* **2012**, *31*, 1408.

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Scheme 3. Pd-Catalyzed Substitution of (*S*)-**12a** with Morpholine[14]

5 mol % Pd(allyl)COD·BF₄
10 mol % DPEPhos

2 equiv morpholine/Et₃N
EtOH, rt, 48 h

A: (S)-13a 71% *ee*
B: (S)-13a 77% *ee*, 5 fold dilution

A: (S)-13c 82%, 38% *ee*
B: (S)-13c 64%, 66% *ee*

In further experiments carried out at higher dilution the product ee is higher (Scheme 3, B). One could therefore account for the erosion of ee by a mechanism similar to the one advanced for classical Tsuji−Trost allylic substitution (second order dependence on Pd concentration),[22] whereby an [L₂Pd(0)] species attacks the cationic (η^3-benzyl)Pd-(II)complex with inversion of configuration. Attempts to minimize erosion by adding tetrabutylammonium fluoride or lithium chloride were not successful.[23]

In summary, we have demonstrated that benzylic fluorides can be transformed under transition metal catalysis. The first examples of Pd-catalyzed substitution and cross-coupling of benzylic fluorides and various derivatives with C-, N-, O-, and S-nucleophiles and with phenylboronic acid are disclosed. Competition experiments indicate that for this class of substrates, trifluoroacetate, carbonate, and *p*-nitrobenzoate are better leaving groups than fluoride but fluoride is superior to acetate, a ranking order mirroring the reactivity of allyl derivatives. Enantioenriched 2-(1-fluoroethyl)naphthalene was successfully substituted with morpholine but with substantial erosion of ee. Mechanistic studies with isolation of discrete complexes are in progress.

Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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