Desulfonative Suzuki–Miyaura Coupling of Sulfonyl Fluorides

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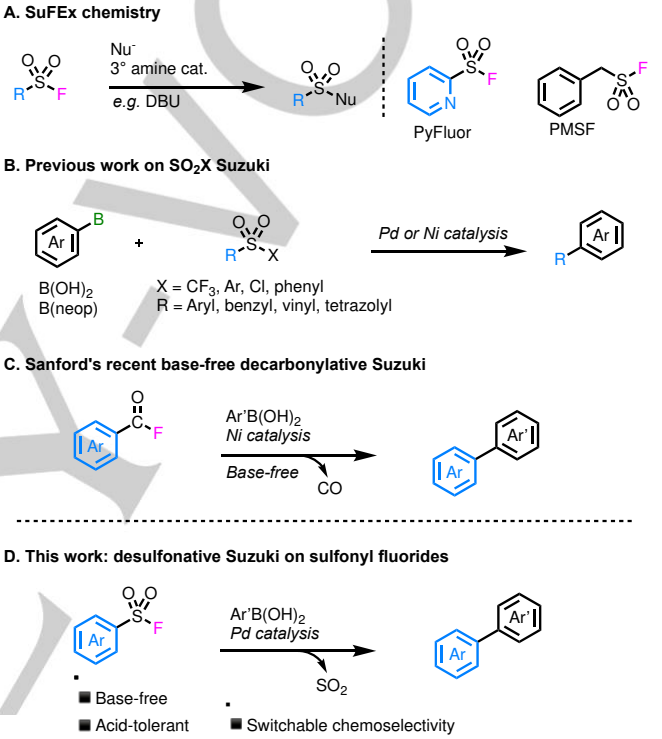
COMMUNICATION

Desulfonative Suzuki-Miyaura Coupling of Sulfonyl Fluorides

Paul Chatelain[a], Cyprien Muller[a], Abhijit Sau[a], Daria Brykczyńska[a], Maryam Bahadori,[b] Christopher N. Rowley[b] and Joseph Moran[a]*

Abstract: *Sulfonyl fluorides have emerged as powerful "click" electrophiles to access sulfonylated derivatives. Yet, they are relatively inert towards C–C bond forming transformations, notably under transition-metal catalysis. Here, we describe conditions under which aryl sulfonyl fluorides act as electrophiles for the Pd-catalyzed Suzuki-Miyaura cross-coupling. This desulfonative cross-coupling occurs selectively in the absence of base and, unusually, even in the presence of strong acids. Divergent one-step syntheses of two analogues of bioactive compounds showcase the expanded reactivity of sulfonyl fluorides to encompass both S-Nu and C-C bond formation. Mechanistic experiments and DFT calculations suggest oxidative addition occurs at the C-S bond followed by desulfonation to form a Pd-F intermediate that facilitates transmetalation.*

Sulfonyl fluorides have received significant attention since their recent re-discovery by Sharpless as "click-able" reagents in SuFex chemistry, which has been described as one of the most powerful reactions in click chemistry.[1,2] Despite their structural similarity to sulfonyl chlorides, the stronger S–F bond confers sulfonyl fluorides with a unique reactivity.[3] They undergo rapid and selective nucleophilic substitution under specific reaction conditions, leading to their use as chemical probes for biology (e.g. PMSF), as fluorinating reagents (e.g. Doyle's PyFluor) or simple sulfonylating agents (Scheme 1A).[1,3–5] As highlighted in Sharpless' and Arvidsson's recent reviews, sulfonyl fluorides are largely inert to hydrolysis, reduction, and transition metal catalysis.[1–3] The SO_2F group is often installed through transition-metal catalyzed processes,[6–18] and has been reported to be inert under Suzuki-Miyaura coupling (SMC) conditions.[3,19–21] As a result, while sulfonyl fluorides are a powerful tool to access sulfonylated derivatives, their use as SMC electrophiles to form C–C bonds would significantly broaden their synthetic utility. However, despite the importance of the SO_2F group and substantial efforts to widen the scope of the SMC reaction to include sulfones and sulfonyl chlorides,[22–31] a method for C-C cross-coupling of sulfonyl fluorides has yet to be developed (Scheme 1B).[21] Inspired by Ogoshi's proof of concept that palladium fluorides can undergo transmetalation with boron compounds under base-free conditions, and by Sanford's subsequent work on the base-free Ni-catalyzed decarbonylative Suzuki coupling of carbonyl fluorides (Scheme 1C),[32,33] we envisaged that sulfonyl fluorides could react in an analogous desulfonative pathway under Pd-catalysis (Scheme 1D). Here we describe the discovery and development of the SMC reaction of aryl sulfonyl fluorides, which can undergo cross-coupling under base-free or, unusually, under highly acidic conditions. Experiments and DFT calculations suggest the mechanism involves oxidative addition into the C–S bond, followed by desulfonation, rather than addition into the S–F bond. The reaction enables SMC reactivity that is orthogonal to that of aryl chlorides and positions the SO_2F group as a point of divergence between S–Nu and C–C bond formation.



Scheme 1. Context for the development of the SMC reaction of aryl sulfonyl fluorides.

We started by investigating the SMC of 2-pyridylsulfonylfluoride (PyFluor), a commercially available fluorinating agent. When RuPhos was used as ligand with catalytic $Pd(acac)_2$, PyFluor underwent coupling with 4-methoxyphenylboronic acid to provide the corresponding biaryl **1** in 97% yield without addition of any base at 130 °C (Table 1, entry 1). Lowering the temperature led to decreased yields (entry 2; see also Graph S1). $Pd(PPh_3)_4$, previously used in the SMC of sulfonyl chlorides,[23] was less effective than the combination of $Pd(acac)_2$ and RuPhos (entry 3). Changing the Pd source to $Pd(OAc)_2$ led to a significant decline in yield (entry 4). The ligand loading was also an important feature of this reaction: lowering it below 20 mol% (as compared to 5 mol% Pd) led to decreased yield (entry 5). Other Buchwald ligands, such as SPhos and XPhos, did not improve the reactivity (entries 6 and 7). The use of toluene as a solvent proved less effective (entry 8), whereas trifluorotoluene was an acceptable substitute for 1,4-dioxane (entry 9).

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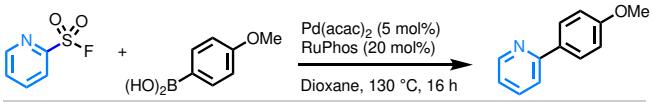
Table 1: Evaluation of reaction parameters



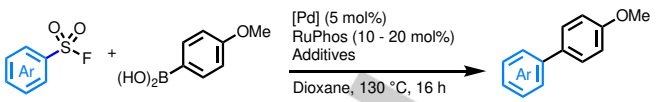
Entry	Variations from standard conditions	Yield **1** (%)
1	None	97
2	120 °C instead of 130 °C	81
3	$Pd(PPh_3)_4$ as only catalyst	49
4	$Pd(OAc)_2$ instead of $Pd(acac)_2$	57
5	RuPhos 15 mol% instead of 20 mol%	77
6	SPhos instead of RuPhos	67
7	XPhos instead of RuPhos	59
8	Toluene instead of dioxane	67
9	$PhCF_3$ instead of dioxane	90
10	Addition of camphor sulfonic acid (1 equiv)	65
11	Addition of trifluoroacetic acid (1 equiv)	77
12	Addition of trifluoroacetic acid (1.5 equiv)	46

Reaction conditions: 0.2 mmol 2-$PySO_2F$, 0.3 mmol 4-MeOPhB$(OH)_2$, $Pd(acac)_2$ (5 mol%), RuPhos (20 mol%), Dioxane 1 mL, 130 °C (internal temperature), pressure tubes, 16 h. acac = acetylacetone; RuPhos = 2-dicyclohexyl-phosphino-2′,6′-diisopropoxybiphenyl.

Unusually for a Pd-catalyzed cross-coupling, the reaction still occurred in good yields even in the presence of CSA or TFA (entries 10-12). Existing SMC reactions operating in the presence of external Brønsted acids employ reactive aryl diazoniums (in the presence of AcOH)[34] or aryl hydrazines (in the presence of PivOH)[35] as electrophiles. Both of those acids are considerably weaker than the ones employed here.

Additives were found to be beneficial for some substrates. Under standard conditions, the more hindered 6-Me derivative of PyFluor reacted modestly (Table 2, entry 1). Cu(IPr)Cl was therefore investigated as an additive due to its positive effect on the SMC of sulfones.[28] Combined with potassium bifluoride, Cu(IPr)Cl led to cross-coupling in near quantitative yields for this more challenging substrate (entry 2). We then oriented our efforts towards lowering the ligand loading.

Table 2: Additives and alternative catalysts for challenging substrates



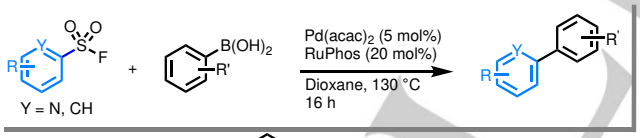
Entry	Substrate	Conditions	Product	Yield (%)
1		**A** (base-free)	**12**	30
2		**B**	**12**	98
3		**C**	**12**	>99
4		**A** (base-free)	**20**	65
5		**B**	**20**	74
6		**C**	**20**	62

General reaction conditions: 0.2 mmol $ArSO_2F$, 0.3 mmol 4-MeOPhB$(OH)_2$, Dioxane 1 mL, *catalysts* 130 °C, 16 h. **A:** $Pd(acac)_2$ (5 mol%) + RuPhos (20 mol%), no additives. **B:** Same as **A** with Cu(IPr)Cl (2.5 mol%) and KHF_2 (50 mol%). **C:** PdG3-RuPhos (5 mol%) + RuPhos (10 mol%), same additives as **B**. Cu(IPr)Cl = Chloro[1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene]copper(I); PdG3 = 2-(2-amino-1,1-biphenyl)]palladium(II) methanesulfonate.

A smaller excess of RuPhos (10 mol%) could be used with PdG3-RuPhos (5 mol%) as the pre-catalyst instead of $Pd(acac)_2$ (entry 3). This suggests that some excess ligand is probably required to reduce the Pd(II) pre-catalyst to an active Pd(0) species. Further experimental support is provided in Table S4. The benefit of adding Cu(IPr)Cl and KHF_2 was less pronounced for simple carbocyclic aromatic sulfonyl fluorides, such as 2-CN(C_6H_4)SO_2F (entries 4 and 5). For this substrate, PdG3-RuPhos furnished lower yields (entry 6).

The optimized conditions were then applied to a variety of aryl sulfonyl fluorides and aryl boronic acids (Scheme 2). Electron donating or withdrawing groups were well-tolerated on the boronic acid. 2-Benzothienyl boronic acid was also well-tolerated (**2**) but pyridyl boronic acids were unreactive. Steric congestion in 2-naphthyl boronic acid did not impair reactivity (**3**). Other functional groups on the boronic acid were also found to be tolerated, including vinyl substitution (**5**), aromatic amines (**6**), benzyl ethers (**8**, **17**, **24**), aldehydes (**10**), and dioxy methylene groups (**14**). Pyridyl sulfonyl fluorides substituted with electron-donating or electron-withdrawing groups displayed good reactivity using

Scheme 2: Substrate scope.



a: 6 h. b: additives: Cu(IPr)Cl (2.5 mol%), KHF_2 (50 mol%). c: *b* using PdG3-RuPhos (5 mol%), RuPhos (10 mol%) as catalysts. d: *b* using $Co(acac)_3$ instead of Cu(IPr)Cl. e: *d* using PdG3-RuPhos (5 mol%), RuPhos (10 mol%) as catalysts.

Cu(IPr)Cl and KHF_2 as additives (**12** – **21**). Substitution *ortho* to the sulfonyl fluoride leaving group was tolerated (**19**). Unsuccessful attempts to couple other heterocyclic sulfonyl fluorides are documented in Table S5. Finally, coupling an alkenyl boronic acid also afforded good yields under standard base-free conditions (**22**). Replacing the boronic acid coupling partner with the analogous trifluoroborate did not significantly impact reactivity. Under otherwise identical conditions, 4-MeO(C_6H_4)BF_3K was successfully coupled to 4-CN(C_6H_4)SO_2F, yielding **28** in 69% yield (versus 68% yield for the boronic acid under the conditions described in Scheme 3, footnote d).

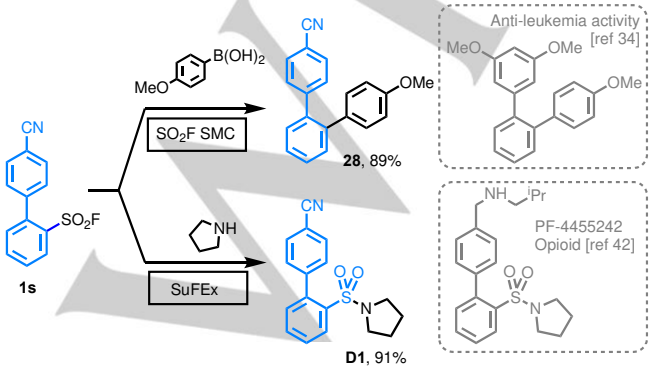
Carbocyclic aryl sulfonyl fluorides cross-coupled in good yields when substituted with cyano or aryl groups (Scheme 2, **23** – **31**). Unfortunately, nitro and ester groups were not tolerated (Table S5). *Para*-cyanobenzene sulfonyl fluoride reacted sluggishly under either aforementioned conditions, but gave 68-72% yield when $Co(acac)_3$ was used as an additive instead of Cu(IPr)Cl (**28**). Cobalt complexes have previously been implicated in the reduction of sulfones via C-S oxidative addition, which might explain the benefit of this cobalt additive.[36] Supporting this hypothesis, $Co(acac)_3$ furnished a small amount of cross coupling product even in the absence of the Pd catalyst in the case of PyFluor (Table S1). Nevertheless, most substrates benefitted more from the addition of Cu(IPr)Cl than from $Co(acac)_3$.

Based on the observation that PdG3-RuPhos could catalyze the reaction with lower ligand loading, we then investigated its use with more challenging substrates. In general, it led to similar or slightly higher yields (Scheme 2, **12**, **15**, **18** – **20**, **23**, **24**), with the 4-picolyl derivative being an exception (**21**).

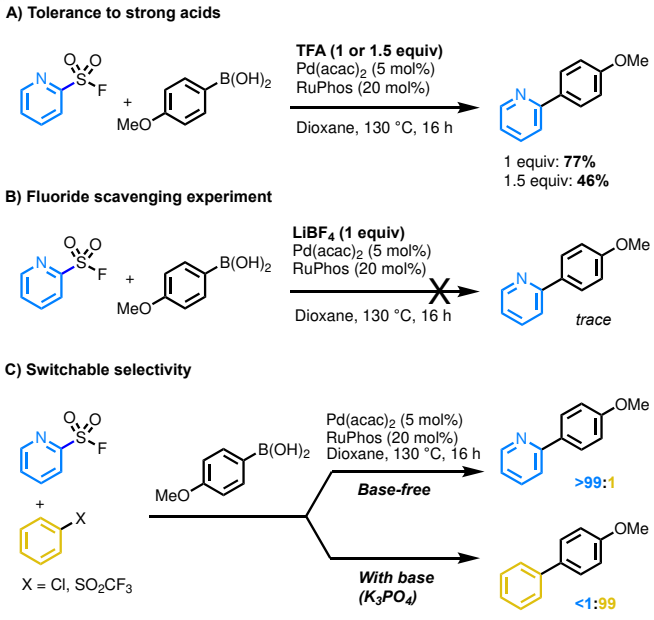
In an attempt to access terphenyl structures, a motif present in many bioactive molecules,[37] *ortho*-aryl substitution on the sulfonyl fluoride was investigated. Satisfyingly, these sterically hindered substrates were well tolerated (**29** – **31**) and yielded terphenyl structures analogous to known medicinally relevant compounds.[38] This similarity was exploited in the representative divergent synthesis shown in Scheme 3. Starting from biphenyl **1s**, conveniently prepared from the commercial 2-Br(C_6H_4)SO_2F, SMC can be undertaken to create an analogue of an anti-leukemia compound,[38] whereas SuFEx chemistry afforded an analogue of the novel opioid antidepressant PF-4455242 under development by Pfizer.[39]

Experiments were carried out to probe the mechanism. Unusually for a Pd catalyzed cross coupling, the reaction still occurred in good or moderate yields even in the presence of stoichiometric or superstoichiometric TFA (Scheme 4A and Table 1, entries 11-12; see also Table S3). This unusual acid tolerance is in accord with our initial hypothesis that a Pd-F intermediate capable of transmetalation is generated as a result of oxidative addition and subsequent desulfonylation, without the need for an external base. In further support of this hypothesis, the addition of 1 equiv of the fluoride scavenger $LiBF_4$ was found to inhibit the reaction (Scheme 4B). Excess gas pressure was observed to be released upon opening the sealed reaction vessel after it had cooled to room temperature, indicating the release of SO_2 during the reaction. 2-Fluoropyridine was found to be unreactive under standard coupling conditions, highlighting the importance of the SO_2 moiety.

Next, competition experiments were carried out. Subjecting an equimolar mixture of PyFluor with another SMC electrophile, either PhCl or $PhSO_2CF_3$, led only to coupling of PyFluor, with the other electrophiles remaining unreacted. In contrast, the identical competition experiment, but in the presence of K_3PO_4 as base, led to exclusive coupling at PhCl or $PhSO_2CF_3$, leaving PyFluor intact (Scheme 4C). Similar base-free intermolecular competition experiments between PyFluor and PhBr resulted in no cross coupling for either substrate. These experiments suggest that the pyridyl group on the substrate or product does not act as a base to facilitate transmetalation, further supporting the intermediacy of a Pd-F species.[40] It also suggests that fluoride is not exchanged between intermediates generated from oxidative addition (i.e. between Py-Pd-F and Ph-Pd-Cl), or that it at least happens significantly more slowly than a subsequent transmetalation event. To track the fate of the leaving group, a typical crude reaction mixture (specifically, that described in Table 1, entry 1) extracted with D_2O revealed the presence of $B(OH)_3$, $BF_3{\bullet}H_2O$ and BF_4^- as the only compounds visible by ^{11}B NMR. ^{19}F NMR of the same extracts confirmed the presence of these species along with a small amount of SO_2F^-[41] and other unidentified peaks. HRMS analysis confirmed the presence of fluorosulfite ions and several several fluoroborates ($BF(OH)_3^-$, $BF_2(OH)_2^-$, $BF_3(OH)^-$, BF_4^-). This indicates that the fluoride ions are mostly scavenged from the Pd-F intermediates by boron during or after transmetalation.



Scheme 3. Representative example of a divergent synthesis utilizing the SO_2F Suzuki method



Scheme 4. Mechanistic experiments.

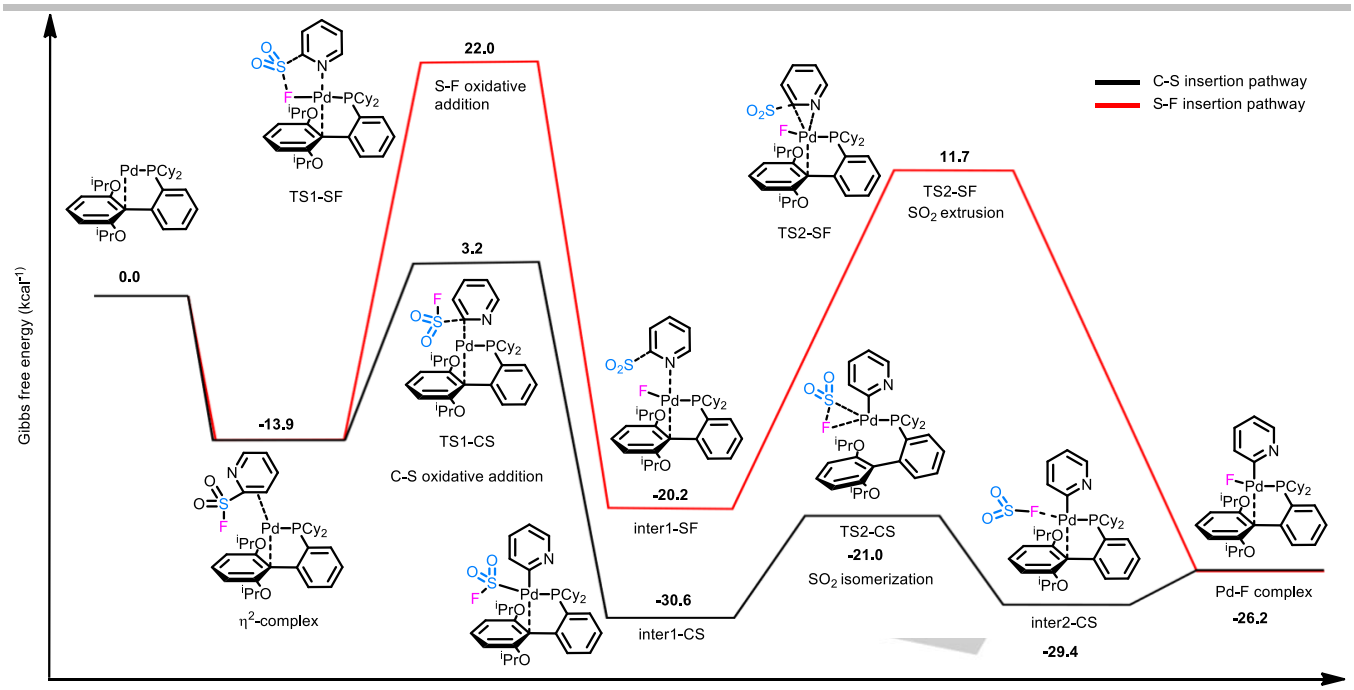
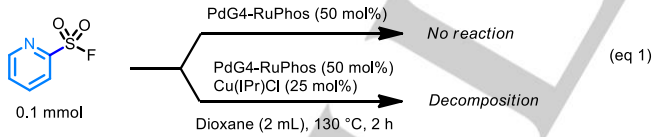


Figure 1. Calculated Gibbs energies for the oxidative addition of sulfonyl fluorides to Pd(0)-RuPhos (kcal/mol) through the C-S bond (black) and through the S-F bond (red).

To investigate the role of the copper additive, the reactivity of PyFluor was evaluated without boronic acid in the presence and absence of Cu(IPr)Cl (25 mol%) (eq. 1). For these investigations, PdG4-RuPhos, which is also a useful pre-catalyst (Table S4), was used instead of PdG3 to avoid an interfering amination stemming from PdG3's carbazole group. In the absence of Cu(IPr)Cl, PyFluor largely remained intact under the reaction conditions, as revealed by ^{19}F NMR after 2 h. However, in the presence of Cu(IPr)Cl, PyFluor rapidly decomposed, with no 2-fluoropyridine observed. Without PdG4-RuPhos, Cu(IPr)Cl does not lead to decomposition, suggesting a synergistic effect between the two species. Based on these observations, it can be inferred that Cu(IPr)Cl becomes involved in a step prior to transmetalation; either during oxidative addition or desulfonation. Indeed, the reductive desulfonation of vinyl sulfonyl fluorides using a copper catalyst and B_2Pin_2 as a reductant has been described.[42]



(eq 1)

DFT calculations were undertaken to address two remaining mechanistic question regarding the SMC of aryl sulfonyl fluorides: 1) whether oxidative addition proceeds through the C-S bond or the S-F bond, and 2) the mechanism of SO_2 release (Figure 1). As transmetalation from aryl palladium fluoride complexes with aryl boronic acids and the subsequent reductive elimination are known to occur in the absence of base under much milder conditions than those required for the present reaction,[33,40,43,44] it is highly likely that the turnover-limiting step in this case is oxidative addition, in agreement with studies on the SMC of aryl sulfones.[22] Computational investigations therefore focused only on the oxidative addition step. As expected for a conventional oxidative addition mechanism into the C–S bond, the arene substrate was found to preferentially coordinate to the metal in an η^2 fashion. Oxidative addition of the metal to the C–S bond yields a Pd(SO_2F)(2-Py) intermediate (TS1-CS). In principle, the SO_2F group could immediately be exchanged with the aryl borate in a salt metathesis reaction, but the $LiBF_4$ inhibition and SO_2 release suggests the formation of a Pd–F bond. We identified a facile transition state (TS2-CS) for the transfer of F from sulfur to the metal in which the F bridges Pd and SO_2. Loss of SO_2 yields an aryl-Pd-F complex. For PyFluor, the oxidative activation step is rate limiting, with a modest barrier (17.1 kcal/mol relative to the substrate/catalyst complex; 3.2 kcal/mol absolute). A potential mechanism was also calculated for S-F insertion, in which the pyridine nitrogen of PyFluor coordinates to Pd, followed by fluoride transfer to Pd (TS1-SF), leading to intermediate inter1-SF. A second transition state where SO_2 is eliminated yields the Pd(2-Py)F intermediate (TS2-SF). The calculated activation energy for this mechanism (35.9 kcal/mol relative to the substrate/catalyst complex; 22.0 kcal/mol absolute) is significantly higher than for the C–S activation mechanism, so it is not likely to contribute significantly. The experimentally observed trend that electrophiles bearing electron-withdrawing groups ortho and para to the leaving group are more reactive is typical for oxidative addition reactions involving an electron-rich Pd(0) species.[45] This trend is also in qualitative agreement with the calculated barrier to C-S oxidative addition for a selection of substrates (see SI). However, consideration of this step alone does not account for the entirety of limitations in substrate scope, indicating that other mechanistic factors are also at play.

In summary, despite their widely reported stability in the face of transition-metal catalysis, aryl sulfonyl fluorides can be used as electrophiles in the SMC reaction. Coupling can occur without any exogenous base and, unusually, even in the presence of strong acids. Mechanistic experiments and DFT calculations suggest that the reaction proceeds through an oxidative addition of palladium into the C-S bond, rather than the S-F bond, followed by desulfonation to form a Pd-F intermediate. This mechanism allows aryl sulfonyl fluorides to undergo base-free SMC in the presence of aryl chlorides or sulfones. By complementing well-

established S-Nu bond forming SuFEx chemistry, the sulfonyl fluoride group can now also be used as a tool for C-C bond formation, enabling further developments in divergent synthesis.

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Notes

The authors declare no competing financial interest.

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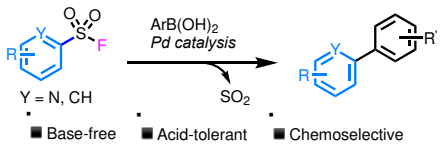
Entry for the Table of Contents:

COMMUNICATION



Aryl sulfonyl fluorides, typically inert to transition metal catalysis, undergo a Pd-catalyzed desulfonative Suzuki-Miyaura coupling. The reaction can occur without added base and turns the -SO_2F group into a divergent handle for C-C or S-Nu coupling.

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Desulfonative Suzuki-Miyaura Coupling of Sulfonyl Fluorides