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Palladium and copper co-catalyzed chloro-arylation of *gem*-difluorostyrenes – use of a nitrite additive to suppress β -F elimination†

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The installation of fluorine and fluorinated functional groups in organic molecules perturbs the physicochemical properties of those molecules and enables the development of new therapeutics, agrichemicals, biological probes and materials. However, current synthetic methodologies cannot access some fluorinated functional groups and fluorinated scaffolds. One such group, the *gem*-difluorobenzyl motif, might be convergently synthesized by reacting a nucleophilic aryl precursor and an electrophilic *gem*-difluoroalkene. Previous attempts have relied on forming unstable anionic or organometallic intermediates that rapidly decompose through a β -F elimination process to deliver monofluorovinyl products. In contrast, we report a fluorine-retentive palladium and copper co-catalyzed chloro-arylation of *gem*-difluorostyrenes that takes advantage of a nitrite (NO_2^-) additive to avoid the favorable β -F elimination pathway that forms monofluorinated products, instead delivering difluorinated products.

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Introduction

The introduction of fluorine and fluorinated functional groups into organic molecules is a prominent strategy to perturb a molecule's physicochemical properties relevant to the development of therapeutics, agrichemicals, biological probes, and materials.^{1,2} One important functional group, the *gem*-difluorobenzyl motif, is typically used by medicinal chemists to block metabolically labile benzylic positions on drug candidates from benzylic oxidation by P450s, to reduce arene epoxidation by P450s by decreasing the electron density of the aromatic π system, or as a replacement for a labile oxygen atom.^{1,2} Such *gem*-difluoromethylene groups are most commonly accessed by deoxyfluorination reactions of carbonyl-containing molecules^{3–5} (Scheme 1A, Blue) that typically require reagents that can exhibit poor functional group compatibility (Deoxo-Fluor, XtalFluor, and Fluolead)^{3,5} or that, for many substrates, can competitively form monofluorovinyl side products (DAST and Deoxofluor).^{6,7} To complement this functional group interconversion strategy, alternative approaches to generate *gem*-

difluoromethylene-containing compound might enable access to more elaborate substructures through convergent bond-forming processes.

As a complementary strategy to access *gem*-difluorobenzyl substructures, retrosynthetic disconnection of the $\text{CF}_2\text{-C}_{\text{aryl}}$ bond would reveal a nucleophilic aryl species and a *gem*-difluoroalkene that bears electrophilic character at the terminal difluorinated carbon⁸ (Scheme 1A, Red). However, nucleophilic addition reactions of *gem*-difluoroalkenes that occur under basic conditions typically proceed through unstable anionic intermediates that decompose to form vinyl fluorides *via* β -F elimination pathways.^{9–12} Though some net nucleophilic hydrofunctionalization reactions have been developed using a variety of heteroatom nucleophiles,^{13–18} fluorine-retentive functionalization reactions of *gem*-difluorinated alkenes to generate new C– CF_2 bonds remains limited.^{18–27} Instead, reactions of *gem*-difluoroalkenes with aryl nucleophiles typically proceed through unstable organometallic intermediates that also decompose *via* β -F elimination to form monofluorovinyl products (Scheme 1B).^{9–11,28–42}

In contrast to these previous two-electron approaches, we have recently focused on functionalization reactions of *gem*-difluoroalkenes that proceed through radical intermediates,^{27,43–47} thus avoiding unstable anionic or organometallic intermediates that undergo β -fluoride elimination.^{9–11,20,30–39,41,42,48,49} With respect to $\text{C}_{(\text{Aryl})}\text{-CF}_2$ bond-formation, a fluorine-retentive Pd/Cu co-catalyzed arylation of *gem*-difluoroalkenes with aryl sulfonyl chlorides proceeded through Pd-alkyl intermediates bearing β -F atoms, but avoided β -F elimination by offering the metal a kinetically favorable β -H

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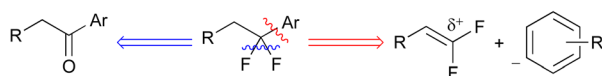
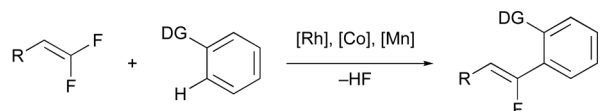
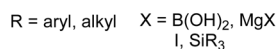
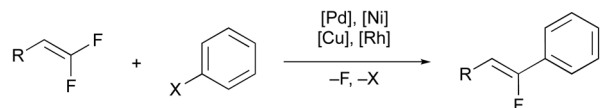
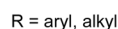
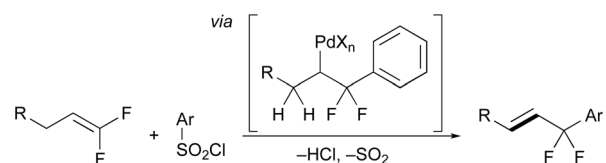
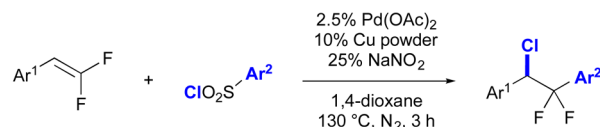
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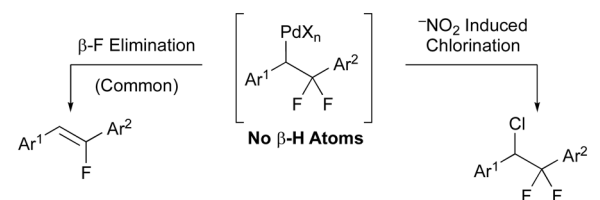
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A. Retrosynthetic Disconnection of ArCF₂-RB. Metal-Catalyzed C-F Functionalization of *gem*-DifluoroalkenesC. Arylation of *gem*-Difluoroalkenes Through β -Hydride EliminationD. Pd/Cu Co-Catalytic Chloro-Arylation of *gem*-Difluoroalkenes

Nitrite additive improves reductive elimination process

E. Mechanistic Hypothesis: Facilitate Reductive Elimination



Scheme 1 Metal catalyzed arylation reactions of *gem*-difluoroalkenes typically proceed through organometallic intermediates prone to undergo β -fluoride elimination, which can be overcome using a nitrite additive.

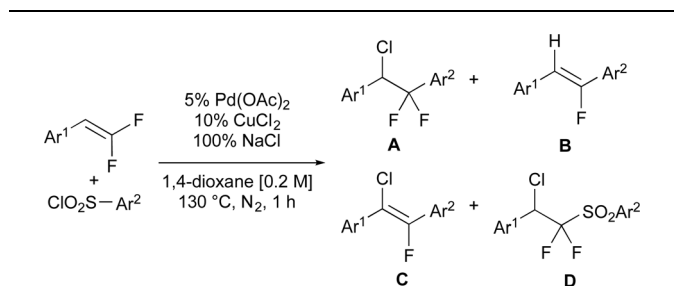
elimination pathway (Scheme 1C).⁵⁰ However, substrates lacking β -H atoms, such as *gem*-difluorostyrenes, readily underwent β -F elimination. Herein, we report a F-retentive Pd/Cu co-catalyzed regioselective difunctionalization reaction of *gem*-difluoroalkenes, which convergently generates new C_{alkyl}-Cl and CF₂-aryl bonds and increases complexity (Scheme 1D). Notably, the reaction exploits an uncommon nitrite (NO₂⁻) additive to promote the reductive elimination of a C_{alkyl}-Cl bond, thus avoiding the kinetically facile β -F elimination pathway (Scheme 1E).

Results and discussion

In early explorations, modification of our previously reported conditions²⁷ delivered mixtures of desired chloro-arylated product (A), β -F elimination side products (B and C), and a chloro-sulfonylated product (D) in a substrate-dependent manner (Table 1). Reactions of electron-deficient *gem*-difluorostyrenes with electron-deficient aryl sulfonyl chlorides formed products A and B in equal quantities (entry 1); however, when the aryl ring of either substrate bore neutral or electron-donating substituents, side product B or D typically formed in 10–12% yield along with trace quantities of C (entries 2–5). To avoid competing β -F elimination processes, we initially explored conditions that facilitate reductive elimination of Pd complexes to form new C-X bonds by changing the properties of the ligand,⁵¹ using weaker coordinating solvents,⁵² exploiting additives that generate high-valent palladium species [Pd(II)/(IV) cycle] under anaerobic (e.g. PhICl₂, PhI(OAc)₂, Ph₂ICl, Umemoto's reagent)^{53–56} or aerobic (e.g. PhICl₂, PhI(OAc)₂, ⁻NO₃, ⁻NO₂)^{57–62} conditions.

Eventually, the reaction of electron-deficient *gem*-difluoroalkene 1a with electron deficient aryl-sulfonyl chloride 2a to form chloro-arylated product 3aa was facilitated under anaerobic conditions in good selectivity in the presence of nitrite additives (Table 2, entries 1 and 2). With this improvement in hand, an additive screen demonstrated the unique ability of ⁻NO₂ to minimize formation of monofluoroalkene 3aa'. As a control experiment, the reaction run without any additives formed chloro-arylated product 3aa in modest yield and poor selectivity (entry 1). However, addition of 25% sodium nitrite [NaNO₂] dramatically increased selectivity for 3aa over 3aa' (entry 2), though the addition of sodium nitrate [NaNO₃] only

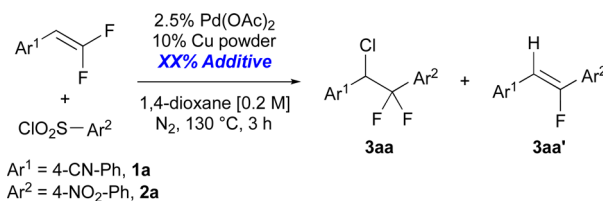
Table 1 Various side products observed during early reaction development^a



Entry	Ar ¹	Ar ²	Conv. ^b	A ^b	B ^b	C ^b	D ^b
1	4-CN-Ph	4-NO ₂ -Ph	60	29	28	—	—
2	3,4,5-tri-OMe-Ph	4-NO ₂ -Ph	>95	73	10	4	—
3	4- ^t Bu-Ph	4-NO ₂ -Ph	63	13	10	3	—
4	3,5-di-Me-Ph	4-NO ₂ -Ph	40	15	12	1	—
5	4-OMe-Ph	4-OMe-Ph	91	17	1	2	11

^a Unless otherwise stated, all reactions were carried out with *gem*-difluorostyrene (0.20 mmol), aryl sulfonyl chloride (0.40 mmol), 5% Pd(OAc)₂, 10% CuCl₂, NaCl (0.20 mmol) and heated for 1 h under an atmosphere of nitrogen. ^b Yields were determined by ¹⁹F NMR using α,α,α -trifluorotoluene as an internal standard.



Table 2 NO_x additives increase selectivity^a

Entry	Additive	% Additive	Conv. ^b	3aa ^b	3aa' ^b	3aa/3aa'
1 ^c	None	0	>95	32	25	1.3
2	NaNO ₂	25	>95	56	6	9.3
3	NaNO ₃	25	>95	41	16	2.5
4	KNO ₂	25	>95	61	7	8.7
5	KNO ₃	100	>95	60	17	3.5
6	NaCl, NaBr, NaI	25	40–94	0–26	0–21	0–1.2
7	NaOAc, NaTFA, NaOTf	25	88–98	24–36	16–20	1.5–2
8	NaPF ₆ , NaBF ₄	25	>95	34	17–19	1.8–2
9	Na ₂ CO ₃ , NaHCO ₃	25	>95	33–35	18–21	1.6–1.9
10	Na ₃ PO ₄ , Na ₂ HPO ₄	25	>95	31–35	14–15	2.1–2.5
11 ^c	NaNO ₂	2.5	>95	41	18	2.2
12 ^c	NaNO ₂	5	>95	42	17	2.5
13 ^c	NaNO ₂	10	>95	52	12	4.4
14 ^c	NaNO ₂	20	>95	50	11	4.7
15 ^c	NaNO ₂	50	>95	53	8	6.3
16 ^c	NaNO ₂	75	>95	51	7	7.7
17 ^c	NaNO ₂	100	>95	51	5	11

^a Unless otherwise stated, all reactions were carried out with *gem*-difluorostyrene **1a** (0.20 mmol), aryl sulfonyl chloride **2a** (0.40 mmol), 2.5% Pd(OAc)₂, 10% Cu powder, XX% additive and heated for 3 h under an atmosphere of nitrogen. ^b Yields were determined by ¹⁹F NMR using α,α,α -trifluorotoluene as an internal standard. ^c All reported yields and selectivities represent an average of three independent runs.

provided a more modest improvement in selectivity relative to NaNO₂ (entry 3). The increase in selectivity was not dependent on Na⁺ and instead dependent on ⁻NO_x, as KNO₂ and KNO₃ provided comparable yield and selectivity to their Na⁺ counterparts (entries 4–5). Additionally, other Na-based additives, including halogens (entry 6), O-based anions (entry 7), non-coordinating ions (entry 8), anionic bases (entries 9 and 10) did not significantly increase selectivity for forming chloro-arylated product over β -F elimination product (for individual yields, see ESI Table S1[†]). In this screen, β -F elimination product **C** and chloro-sulfonylated product **D** were generally each detected in <2% quantities by ¹⁹F NMR of the crude reaction mixtures. Overall, exhaustive screening demonstrated the ability of ⁻NO₂ additives to facilitate formation of the C–Cl bonds and minimize β -fluoride elimination.

Further studies more rigorously established the ability of NO₂⁻ to control the selectivity for promoting chlorination over β -F elimination. Specifically, increasing the equivalents of NaNO₂ from 0 to 1.0 systematically increased the selectivity from 1.3 : 1 to 11 : 1 (entries 11–17), and 1.0 equiv. NaNO₂ was selected for further studies. Similarly, the use of NaNO₃ followed a similar trend, albeit with lower maximum selectivity (up to 3.9 : 1, ESI Table S2[†]). The use of NaNO₂ also improved the yield and selectivity for a wide range of Pd-based (ESI Table S3[†]) and Cu-based (ESI Table S4[†]) catalyst systems, with the

combination of Pd(OAc)₂ and Cu powder performing best. Interestingly, on 1.0 and 5.0 mmol scales, the loading of NaNO₂ could be lowered to 25% with no reduction in selectivity or yield; at these scales, the use of stoichiometric NaNO₂ did not provide additional benefits to yield or selectivity. For this reaction, routine evaluation of solvent, temperature, and time indicated 130 °C/1,4-dioxane/3 h as optimal conditions (ESI Tables S5–S7[†]). In general, lower temperatures and shorter reaction times delivered less product, while hotter or longer reaction times provided no benefit (ESI Tables S6 and S7[†]).

The optimized conditions enabled coupling of a wide range of *gem*-difluorostyrenes with aryl sulfonyl chlorides to deliver chloro-difluorinated products (Fig. 1). Reactions of electron-rich *gem*-difluorostyrenes containing ethers and alkyl groups afforded products in moderate yields (**3ba–3fa**). Electron-deficient *gem*-difluorostyrenes containing O-benzyl, phenyl ester, trifluoromethyl, nitrile, tosylate and methyl ester groups (**3aa**, **3ga–3ka**), and *gem*-difluorostyrenes bearing halogen atoms (**3la–3na**) also reacted efficiently to deliver the chloro-arylated products in moderate yields. Substrates containing heterocyclic moieties including *N*-benzenesulfonyl indole and benzofuran moieties were also compatible in this system (**3oa–3pa**). However, non-styrenyl *gem*-difluoroalkenes and *gem*-difluoroalkenes containing N–H and thioethers were not tolerated. Importantly, the selectivity for chloro-arylated products



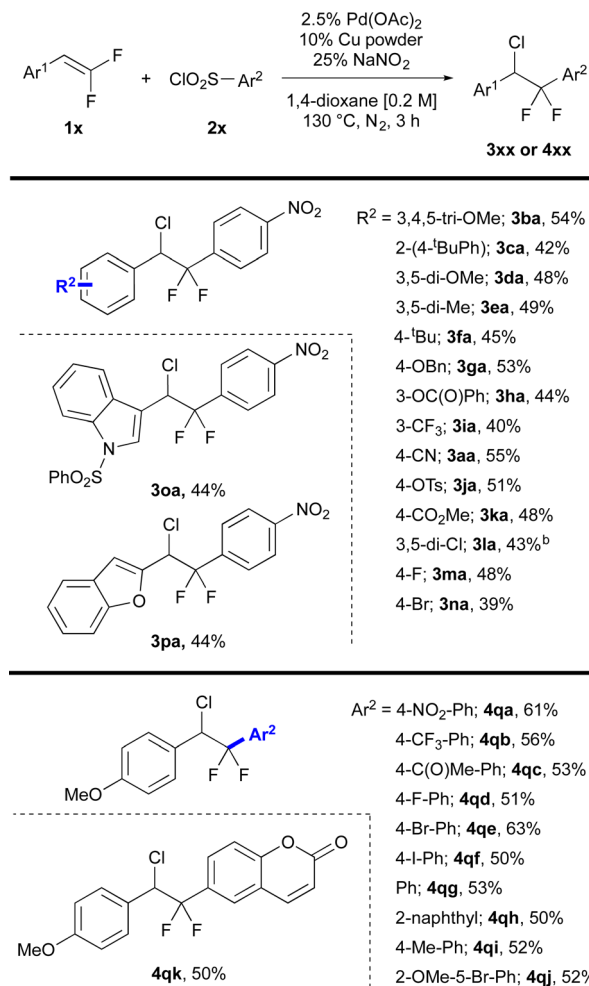
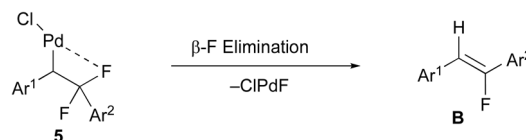


Fig. 1 Scope of *gem*-difluorostyrenes and aryl sulfonyl chlorides. ^aUnless otherwise stated, all reactions were carried out with *gem*-difluorostyrene (1.0 mmol), aryl sulfonyl chloride (2.0 mmol), 2.5% Pd(OAc)₂, 10% Cu powder, 25% NaNO₂, 1,4-dioxane (5.0 mL) and heated at 130 °C for 3 h under an atmosphere of nitrogen. ^b5% mmol Pd(OAc)₂. All reported yields and selectivities represent an average of two independent runs.

was not influenced by the electronic character of either aryl ring, with selectivities >9 : 1 [A : (B + C + D)] as determined by ¹⁹F NMR of the crude reaction mixture], except for one outlier (entry 7, 5 : 1, ESI Table S8[†]). Moreover, the NaNO₂ additive suppressed β-F elimination, with yields of B averaging at or below 4% (as determined by ¹⁹F NMR of the crude reaction mixture), except for one outlier with 6% (entry 7, ESI Table S8[†]).

A series of aryl sulfonyl chlorides bearing a range of electronic characters were coupled with *gem*-difluorostyrene **1q** to deliver chloro-arylated products (Fig. 1). Aryl sulfonyl chlorides containing strong electron-withdrawing nitro, trifluoromethyl and ketone groups reacted smoothly to deliver chloro-arylated products in fair to good yields (**4qa–4qb**). Notably, an aryl sulfonyl chloride containing a ketone group successfully delivered the chloro-arylated product, which contrasts with deoxy-fluorinating reagents that react preferentially with carbonyls (**4qc**). Additionally, aryl sulfonyl chlorides bearing halogens

A. β-F Elimination Pathway



B. Nitrite Suppresses β-F Elimination

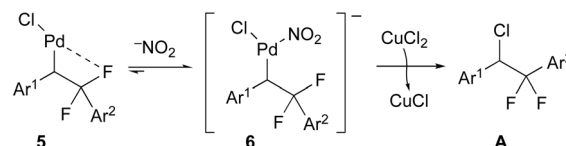


Fig. 2 Proposed mechanisms by which ⁻NO₂ prevents β-F elimination.

provided the corresponding chloro-arylated products in moderate to good yields (**4qd–4qf**). Moreover, such examples that tolerate aryl iodides and bromides suggest that the catalytic cycle does not involve Pd(0) intermediates. Aryl sulfonyl chlorides bearing electronically neutral phenyl and naphthyl groups (**4qg–4qh**) as well as electron-donating alkyl and ether groups also provided chloro-arylated products in moderate yields (**4qi–4qj**). Finally, a coumarin-derived aryl sulfonyl chloride reacted smoothly to deliver the chloro-arylated product in moderate yield (**4qk**). For this series, reactions of electronically neutral or rich aryl sulfonyl chloride proceeded in slightly lower selectivity 5 and 6 : 1 [A : (B + C + D)] as determined by ¹⁹F NMR of the crude reaction mixture], solely due to an increase of product D, which likely derives from slow desulfination, not from an increase in β-F elimination (entries 24, 26 and 27, ESI Table S8[†]). Finally, aryl sulfonyl bromides were not compatible with this system, instead delivering aryl bromides as the predominant side product (detected *via* GC-MS).

⁻NO_x additives have served unique and modestly understood roles in many Pd-catalyzed processes,^{57,60,62–65} though the ability of the additives to influence β-elimination *vs.* reductive elimination processes show no precedent.⁶⁶ With respect to the immediate reaction, the ability of ⁻NO₂ to influence the selectivity for difluorobenzyl *vs.* monofluorovinyl products (A *vs.* B) could result from multiple different phenomena. First, coordination of ⁻NO₂ to the putative Pd(Cl)(alkyl) intermediate 5 might block the binding site typically populated by the vicinal F atom, thus precluding the β-F elimination process (Fig. 2A). Second, binding of ⁻NO₂ might accelerate the reductive elimination process to form the C–Cl bond *via* intermediate 6, as the π-back bonding interaction between Pd(IV) and ⁻NO₂ pulls electron density away from the metal,⁶⁷ thus destabilizing the higher oxidation state form and reducing the energy barrier for reductive elimination (Fig. 2B), as has been demonstrated for reductive elimination of C–F bonds from Pd(IV) complexes.⁶⁸ In contrast, other anions tested (*e.g.* halogens, ⁻OTf, ⁻OAc, ⁻O₂CCF₃, ⁻BF₄, ⁻PF₆) do not engage in strong π-back bonding interactions that might help avoid β-F elimination. For a proposed mechanism and mechanistic studies, see the ESI (Fig. S1, Tables S9 and S10[†]).



Conclusion

In conclusion, a palladium and copper co-catalyzed reaction utilizes aryl sulfonyl chlorides to add both aryl and chlorine groups across *gem*-difluoroalkenes in a regioselective difunctionalization reaction. Notably, this reaction exploited NaNO₂ as a critical additive that enabled formation of the C_{alkyl}-Cl bond and reduced the common β-F elimination pathway, thus improving selectivity for generating difluorobenzyl products over monofluorovinyl products, and we speculate that such additives might prove more generally useful at perturbing rates of reductive elimination and/or β-F elimination processes. Ongoing investigation to further understand the unique role of nitrite in this reaction will be reported in due time.

Data availability

The data underlying this study are available in the published article and its ESI.†

Author contributions

K. Y. and R. A. conceived the project. A. J. I., C. Z. W., and R. T. L. carried out the experiments. A. J. I. and R. A. A. wrote the manuscript, and all authors revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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