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Palladium and copper co-catalyzed chloroarylation 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 (NO₂⁻) additive to avoid the favorable β -F elimination pathway that forms monofluorinated products, instead delivering difluorinated products.

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 molecules3-5 (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 gemdifluoromethylene-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 CF2-Carvl bond would reveal a nucleophilic aryl species and a gemdifluoroalkene 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-CF2 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 gemdifluoroalkenes that proceed through 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 C(Aryl)-CF2 bondformation, 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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A. Retrosynthetic Disconnection of ArCF2-R

$$R \xrightarrow{Ar} R \xrightarrow{\lambda_1 Ar} R \xrightarrow{\delta^+} F + \underbrace{ \left[\begin{array}{c} \lambda_1 \\ F \end{array} \right]} R$$

B. Metal-Catalyzed C-F Functionalization of gem-Difluoroalkenes

$$R = \text{aryl, alkyl} \quad X = B(OH)_2, MgX$$

$$I, SiR_3$$

$$I = DG$$

$$IRh], [Co], [Mn]$$

$$IRh]$$

$$IRh], [Co], [Mn]$$

C. Arylation of $\emph{gem-D}$ ifluoroalkenes Through β -Hydride Elimination

$$R = \text{aryl, alkyl}$$

$$R = \text{aryl, alkyl}$$

$$R = \text{aryl, alkyl}$$

D. 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). The However, substrates lacking β -H atoms, such as gem-difluorostyrenes, readily underwent β -F elimination. Herein, we report a F-retentive Pd/Cu cocatalyzed regioselective difunctionalization reaction of gem-difluoroalkenes, which convergently generates new C_{alkyl} -Cl and CF_2 -aryl bonds and increases complexity (Scheme 1D). Notably, the reaction exploits an uncommon nitrite (NO $_2$ -) 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 electrondonating 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*-difluor-oalkene **1a** with electron deficient aryl-sulfonyl chloride **2a** to form chloro-arylated product **3aa** was facilitated under anaer-obic 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 $\neg NO_2$ 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	\mathbf{A}^b	\mathbf{B}^{b}	\mathbf{C}^{b}	\mathbf{D}^{b}
1	4-CN-Ph	4-NO ₂ -Ph	60	29	28	_	_
2	3,4,5-tri-OMe-Ph	$4\text{-NO}_2\text{-Ph}$	>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% $CuCl_2$, 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*-diffuorostyrene **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 $^-\text{NO}_x$, 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 chloroarylated 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 19 F NMR of the crude reaction mixtures. Overall, exhaustive screening demonstrated the ability of $^-\text{NO}_2$ additives to facilitate formation of the C–Cl bonds and minimize β-fluoride elimination.

Further studies more rigorously established the ability of NO_2^- to control the selectivity for promoting chlorination over β -F elimination. Specifically, increasing the equivalents of $NaNO_2$ from 0 to 1.0 systematically increased the selectivity from 1.3:1 to 11:1 (entries 11–17), and 1.0 equiv. $NaNO_2$ was selected for further studies. Similarly, the use of $NaNO_3$ followed a similar trend, albeit with lower maximum selectivity (up to 3.9:1, ESI Table S2†). The use of $NaNO_2$ 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 $NaNO_2$ could be lowered to 25% with no reduction in selectivity or yield; at these scales, the use of stoichiometric $NaNO_2$ 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 electronrich *gem*-difluorostyrenes containing ethers and alkyl groups afforded products in moderate yields (3ba-3fa). Electrondeficient *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 chloroarylated 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

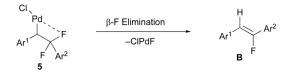
 $Ar^2 = 4-NO_2-Ph; 4qa, 61\%$

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 [\mathbf{A} : (\mathbf{B} + \mathbf{C} + \mathbf{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 \mathbf{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 deoxyfluorinating reagents that react preferentially with carbonyls (**4qc**). Additionally, aryl sulfonyl chlorides bearing halogens

A. β-F Elimination Pathway



B. Nitrite Supresses β-F Elimination

$$\begin{array}{c|c}
CI & CI & CI \\
Pd & NO_2 \\
Ar^1 & F & F
\end{array}$$

$$\begin{array}{c|c}
CI & NO_2 \\
Ar^1 & F \\
\hline
Ar^2
\end{array}$$

$$\begin{array}{c|c}
CuCl_2 & CI \\
CuCl & F & F
\end{array}$$

Fig. 2 Proposed mechanisms by which ${}^{-}NO_2$ 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-4qi). 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(II) 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, O_2CCF_3 , BF_4 , PF_6 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†.

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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 Calkyl-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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