Arylation of gem-difluoroalkenes using a Pd/Cu Co-catalytic system that avoids β-fluoride elimination†‡

Kedong Yuan, a Taisia Feoktistova, b Paul Ha-Yeon Cheong b * c and Ryan A. Altman b * c

Pd⁰/Cu¹ co-catalyze an arylation reaction of gem-difluoroalkenes using arylsulfonyl chlorides to deliver α,α-difluorobenzyl products. The reaction proceeds through a β,β-difluoroalkyl-Pd intermediate that typically undergoes unimolecular β-F elimination to deliver monofluorinated alkene products in a net C–F functionalization reaction. However to avoid β-F elimination, we offer the β,β-difluoroalkyl-Pd intermediate an alternate low-energy route involving β-H elimination to ultimately deliver difluorinated products in a net arylation/isomerization sequence. Overall, this reaction enables exploration of new reactivities of unstable fluorinated alkyl-metal species, while also providing new opportunities for transforming readily available fluorinated alkenes into more elaborate substructures.

Introduction

Due to the intrinsic small size and high electronegativity, incorporation of fluorine at specific positions of bio-relevant molecules can improve pharmacokinetic, pharmacodynamic and physicochemical properties, thus facilitating the drug discovery process. For instance, replacing benzylic CH₂ units with CF₂ significantly influences metabolic properties, and strategies that incorporate fluorine directly into these positions aid in accessing the next generation of therapeutic candidates.

Recently, tremendous effort has been devoted to develop diverse reactions for accessing fluorinated drug-like substructures. One important strategy exploits fluorinated synthons, such as gem-difluoroalkenes, as valuable and readily-accessible building blocks for further functionalization. Relative to non-fluorinated alkenes, gem-difluoroalkenes show distinct reactivity trends: (i) reactions typically occur at the electron-deficient gem-difluorinated carbon to deliver α-functionalized products (Scheme 1), (ii) anionic intermediates typically decompose via β-F elimination to generate mono-defluorinated products [Scheme 1A], (iii) organometallic intermediates also decompose via β-F elimination (Scheme 1B). In contrast, transition metal catalysed reactions of gem-difluoroalkenes that avoids β-F elimination are extremely rare. Such a process would require an alternate reaction pathway to avoid β-F elimination and deliver difluoroalkyl substructures (Scheme 1C). Further, a convergent preparation would complement traditional and harsh deoxygenation reactions of ketones that might generate this substructure.

![Scheme 1 Reactivity of gem-difluoroalkenes.](image-url)
To avoid β-F elimination, we sought to offer an alternate route for the z,ω-difluoroalkyl metal intermediate. Specifically, we hypothesized that β-H elimination might outcompete β-F elimination and deliver products containing both fluorine atoms. In practice, we exploited arylsulfonyl chlorides (ArSO2Cl) as readily available aryl reagents that show complementary reactivity and functional group tolerance relative to aryl-halides in cross-coupling and C–H functionalization reactions. These ArSO2Cl generate arylic radicals in the presence of Cu salts at high temperature that might avoid formation of anionic intermediates. Combined, these features inspired us to explore the unique reactivity of ArSO2Cl and gem-difluoroalkenes using a Pd/Cu-based system. Herein, we report a Pd/Cu co-catalyzed arylation-isomerization of gem-difluoroalkenes that avoids β-F elimination.

Results and discussion
Optimization of reaction conditions

Optimal reaction conditions were identified by evaluating the cross coupling of gem-difluoroalkene 1a and ArSO2Cl (2a) to generate difluorobenzyl product 3aa (see ESI Tables 1-7f). Ultimately, a system of Pd(OAc)2/CuCl/Li2CO3 was essential for generating the desired product (Table 1, entry 1), as removal of any individual component drastically decreased the yield of product (entries 2-4). In this reaction, use of an excess of 1a suppressed the formation of side products 4, which likely arose from Heck-arylation of alkene 3aa. Notably, the reaction proceeded well even without ligands (entry 5), though use of an NHC ligand (SIPr·Cl) reduced the yields of side products. Eventually, optimized conditions of 5 mol% Pd(OAc)2, 10 mol% SIPr·Cl, stoichiometric CuCl and Li2CO3 in refluxing 1,4-dioxane coupled 1a (2.5 equiv.) and 2a in 72% isolated yield (entry 6). Under these conditions, the difluorobenzyl group of 3aa did not decompose to a monofluoroalkene, even at high temperature (120 °C).

Table 1: Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard conditions</th>
<th>Conv. (%)</th>
<th>Yield 3aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>100</td>
<td>78 (68)</td>
</tr>
<tr>
<td>2</td>
<td>No Pd(OAc)2</td>
<td>&lt;3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>No CuCl</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>No Li2CO3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>No SIPr·Cl</td>
<td>100</td>
<td>75 (63)</td>
</tr>
<tr>
<td>6</td>
<td>Reaction on 0.5 mmol, 0.33 M</td>
<td>100</td>
<td>76 (72)</td>
</tr>
</tbody>
</table>

Table 2: Scope of arylsulfonyl chlorides

| Conditions: 1a (0.45 mmol), 2a (0.20 mmol), Pd(OAc)2 (0.010 mmol), SIPr·Cl (0.020 mmol), CuCl (0.24 mmol), Li2CO3 (0.40 mmol), 1,4-dioxane (0.50 mL, 0.40 M), N2, reflux for 24 h. Yields determined by GC analysis using dodecane (20 µL) as internal standard. b Mixture of diarylation products (~10%) were observed. Isolated yields are given in parentheses. c 1-(2-Chloro-1,1-difluoro-4-phenylbutyl)-4-methylbenzene and mono-defluorinated arylation products were observed. d Reaction was performed based on 2a (0.30 mol) in 0.33 M solution of 1,4-dioxane. SIPr·Cl = 1,3-bis[2,6-bis[1-methylthyl]phenyl]-1H-imidazolium chloride.

| Conditions: 1a (0.875 mmol), 2 (0.30 mmol), Pd(OAc)2 (0.025 mmol), SIPr·Cl (0.050 mmol), CuCl (0.60 mmol), Li2CO3 (1.0 mmol), 1,4-dioxane (1.5 mL), N2, reflux for 23 h; isolated yields. e Reaction performed on 5.0 mmol scale of 2f. f Li2CO3 (3.0 equiv.). g Start from 4-(bromomethyl)benzenesulfonyl chloride.
diﬂuoroalkenes gave trisubstituted akenes 3ga, 3ha and 3ib in good stereoselectivity. Extension the aliphatic carbon chain slightly decreased the yields (3jb–3lb), though these reactions required additional β-hydride elimination/reinsertion steps to produce the energetically favoured products. Notably, the reaction of cholesterol derivative 1o afforded coupled product 3oa in 61% yield as a mixture of diastereomers (3.6 : 1), of which the relative stereochemistry was determined by X-ray crystallography (CSD: q79h).

Finally, the reaction of 6-chloro-1,1-diﬂuoro-hex-1-ene with 2b afforded diarylation product 3mb, which presumably proceed via a sequence involving arylation-isomerization-arylation (see figure inset).

Mechanistic investigations
A combination of computational and experimental mechanistic studies (see below) and previous literature, support a mechanism involving Pd(II)/Pd(III) intermediates (Fig. 1). The cycle begins with Pd(II) coordinating to the gem-diﬂuoroalkene. Then a combination of the Pd(II) catalyst, CuCl and Li2CO3 activate the ArSO2Cl to generate Ar–Cl, which combines with Pd(II) to generate a Pd(III)–Ar intermediate. β-Migratory insertion of the Ar group into the gem-diﬂuoroalkene would provide a Pd(III)–alkyl intermediate. The Pd(III)–alkyl intermediate undergoes β-H elimination preferentially over β-F elimination to generate alkene-coordinated Pd(III)–H species, and subsequent hydride insertion/elimination transfers the alkene to the thermodynamically stable position, thus delivering the product that retains both ﬂuorine atoms.

Experimental data supports early steps of the proposed cycle. First, the Pd(II) precatalyst, Cu salt, and Li2CO3 are all required to activate the ArSO2Cl, as the absence of any one of these components provides low conversion of ArSO2Cl (2a) to generate Ar–Cl and homocoupling products (Scheme 2A, Table 1, entry 4; see Table ESI-4 for more details). This activation

Table 3 Scope of gem-diﬂuoroalkenes

<table>
<thead>
<tr>
<th>Conditions: 1a (0.875 mmol), 2 (0.50 mmol), Pd(OAc)2 (0.025 mmol), SIPr $\mathrm{Cl}$ (0.050 mmol), CuCl (0.60 mmol), Li2CO3 (1.0 mmol), 1,4-dioxane (1.5 mL), N2 reflux for 21 h; isolated yields; selectivity was determined by 19F NMR and GC analysis of crude mixture.</th>
<th>Yield to Ar–Cl</th>
<th>Yield to Ar–Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Pd, Cu, and Li2CO3 all required to activate ArSO2Cl</td>
<td>100%</td>
<td>37%</td>
</tr>
<tr>
<td>B) Full reaction involves Ar$^+$ intermediate</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>C) Activation of ArSO2Cl involves Ar$^+$ intermediate</td>
<td>56%</td>
<td>25%</td>
</tr>
<tr>
<td>D) Mechanisms proposed for the arylation of gem-diﬂuoroalkenes</td>
<td></td>
<td></td>
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Fig. 1 Plausible mechanism for the arylation of gem-diﬂuoroalkenes.

Scheme 2 Mechanistic experiments to support activation of ArSO2Cl presence of Ar$^+$, and β-hydride elimination.

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contrasts previous Cu\(^1\)-catalyzed reactions of ArSO\(_2\)Cl that generated Ar\(^*\) in the absence of Pd\(^{II}\) or Pd\(^{III}\)/CO\(_2\)\(^{−}\) additives.\(^{10a,b}\) Second, decomposition of ArSO\(_2\)Cl generates ArSO\(_2\)^* and subsequently Ar\(^*\) intermediates, as evidenced by the generation of BHT adducts in both the full reaction (Scheme 2B) and half reaction (Scheme 2C). From this stage, the combination of the Ar\(^*\), Pd\(^{III}\) catalyst, and gem-difluoroalkene could presumably react by multiple pathways (Scheme 2D; see Fig. S1† for more details). According to computations using density functional theory (DFT)-B3LYP-D3BJ/6-31G\(^*\) & LANL2DZ/PCM (1,4-dioxane) at 120 °C, the lowest energy pathway involves a barrierless addition of the Ar\(^*\) to Pd\(^{II}\) to generate a Pd\(^{III}\)-Ar intermediate and subsequent β-migratory insertion of the Ar group into the gem-difluoroalkene. In contrast, antarafacial carboxipalladation of the difluoroalkene is higher in energy by 17.1 kcal mol\(^{−1}\), while direct addition of Ar\(^*\) to the uncoordinated gem-difluoroalkene to generate an unstabilized alkyl radical is 40.3 kcal mol\(^{−1}\) higher in energy.\(^{6c,11}\) Of note, the Pd catalyst plays a key role in generating the unfavorable C-C bond. Specifically, while the disfavored radical attack onto the difluoroalkene (either with or without coordination to Pd\(^{III}\)) would form the new C-C bond through the arene \(\sigma\)-system, the Pd\(^{III}\)-Ar/β-migratory insertion pathway generates the new C-C bond through hybrid orbitals from the arene’s \(\pi\)-system (see Fig. S1† for more details).

Experimental and computational experiments also confirm that β-hydride elimination can outcompete β-fluoride elimination. As evidenced by the deuterium-scrambling reaction of deuterated substrate 1\(q\), the reaction involves a Pd-mediated β-H elimination/reinsertion process that walks the alkene away from the difluorobenzyl moiety (Fig. 2A).\(^{13}\) Computations provided additional insight into these competing processes. Overall comparison of Pd\(^{III}\) and Pd\(^{II}\) mechanisms reveals that the operative mechanism involves Pd\(^{III}\) (see Fig. S2\(†\)): (1) β-H elimination for Pd\(^{III}\) is lower in energy than for Pd\(^{II}\) by 25.1 kcal mol\(^{−1}\); (2) similarly, β-F elimination is favored for Pd\(^{III}\) over Pd\(^{II}\) by 37.1 kcal mol\(^{−1}\). Interestingly, when comparing Pd\(^{III}\) vs. Pd\(^{II}\)-based processes, β-H elimination is consistently favored over β-F elimination for Pd\(^{III}\)- and Pd\(^{II}\)-based mechanisms by 2.5 and 14.5 kcal mol\(^{−1}\), respectively. Overall, for the operative Pd\(^{III}\) mechanism, β-H elimination is favored over β-F elimination by 2.5 kcal mol\(^{−1}\) (Fig. 2B). We also evaluated whether the chemoselectivity is influenced by the homobenzyl and benzyl positions of the H and F atoms by computing the elimination processes for a hypothetical substrate on which the H atoms are benzyl and F atoms are homobenzyl (see Fig. S2–S4\(†\) for more details). In all cases, β-H elimination is markedly preferred over β-F elimination, suggesting that the conjugation effect of the benzyl or the homobenzyl positions are not sufficiently strong to reverse the selectivity. To elucidate the origins of β-H/F elimination selectivity, distortion–interaction analysis revealed that (Fig. 2B): (1) the interaction energies were almost identical in both processes (ca. −54 kcal mol\(^{−1}\)); (2) the Pd\(^{III}\) catalyst was slightly more distorted at the transition state for the favoured β-H elimination (4.7 vs. 1.9 kcal mol\(^{−1}\)); however, (3) the substrate was significantly more distorted at the transition state for the disfavoured β-F elimination (42.7 vs. 36.5 kcal mol\(^{−1}\)), suggesting that the C–F bond is much stronger than the C–H bond (Fig. 2B). These results support the hypothesis that the selectivity arises from strong preference for breaking C–H bond vs. C–F bond.

**Conclusions**

In summary, a Pd\(^{II}/Cu\(^{1}\) co-catalyzed cross-coupling reaction of gem-difluoroalkenes and ArSO\(_2\)Cl react in a net arylation/isomerization sequence that demonstrated good functional group tolerance with respect to both components and provided products bearing the “CF\(_2\)” motif at the benzyl position, which would block radical processes that might activate this position. DFT and mechanistic experiments indicate that Pd plays two key roles in the reaction, first by facilitating the formation of a challenging C–C bond, and second by reacting through a β-H elimination process, which overcomes the favoured metal-mediated β-F elimination process and delivers products bearing both fluorine atoms. These findings should enable the discovery of many complementary reactions for accessing a broad spectrum of fluoroalkyl substructures.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

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Notes and references

The crystal structure for 3oa can be found in the Cambridge Crystallographic Data Centre under code 979bh.


