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

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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 physiochemical 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 synths, such as gem-difluoroalkenes, as valuable and readily-accessible building blocks for further functionalization. Relative to non-fluorinated alkene, 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 deoxyfluorination 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 α,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 aryl 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 1–7). Ultimately, a system of Pd(OAc)₂/CuCl/Li₂CO₃ was essential for delivering 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 aryl 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.

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Evaluation of substrate scope

The reaction conditions tolerated a broad scope of ArSO₂Cl bearing many important functional groups (Table 2). A variety of para-substituted ArSO₂Cl were tolerated, including halogenated groups that are not tolerated by many Pd-catalyzed coupling reactions (I, Br, Cl; 3ab–3ad) and electron withdrawing groups (CN, NO₂, CO₂Me; 3af–3ah). Interestingly, benzyl chloride product 3ai was formed in moderate yield from reaction of 4-(bromomethyl)benzenesulfonyl chloride and 1a through an extra halogen exchange step. This benzyl electrophile would be useful for further synthetic elaboration. Fluorinated ArSO₂Cl reacted smoothly to give the corresponding arylation product in good yields (3aj–3an). Ortho-substituted ArSO₂Cl coupled effectively (3al–3ao), and heteroarylsulfonyl chlorides were tolerated albeit with reduced yields of product (3aq–3as). Notably, reactions of electron-rich (e.g. OMe, SMe, NHAc and N-heteroaryl (pyridine, imidazole, pyrazole, quinoline) sulfonyl chlorides reacted in lower yield or with poor selectivity due to competing defluorination. The reaction proceeded on well on larger scales, with 3aj obtained on 5 mmol scale without decreasing the reaction yield.

The catalytic system also coupled various aryl-substituted gem-difluoroalkenes (Table 3) and afforded 3ba–3da, 3eg and 3fa in good yields. Reaction of alkyl-substituted gem-
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 1oa 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 proceeds 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,10–12 support a mechanism involving PdII/PdIII intermediates (Fig. 1). The cycle begins with PdII coordinating to the gem-diﬂuoroalkene. Then a combination of the PdII catalyst, CuCl and Li2CO3 activate the ArSO2Cl to generate Ar, which combines with PdII to generate a PdIII–Ar intermediate. β-Migratory insertion of the Ar group into the gem-diﬂuoroalkene would provide a PdIII–alkyl intermediate. The PdIII-alkyl intermediate undergoes β-H elimination preferentially over β-F elimination to generate alkene-coordinated PdIII-H species,14 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 PdII 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

| Conditions: 1a (0.875 mmol), 2 (0.50 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 21 h; isolated yields; selectivity was determined by 19F NMR and GC analysis of crude mixture. b 1b, 1.75 equiv. c 110 °C, reﬂux for 38 h. X-ray structure of 3oa provided.

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contrasts previous CuI-catalyzed reactions of ArSO2Cl that generated Ar in the absence of PdII or PdII/CO3 additives. Second, decomposition of ArSO2Cl generates ArSO2 instead of BHT adducts in both the full reaction (Scheme 2B) and half reaction (Scheme 2C). From this stage, the combination of the Ar, PdII 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 PdII to generate a PdIII·Ar intermediate and subsequent β-migratory insertion of the Ar group into the gem-difluoroalkene. In contrast, antarafacial carboxylation 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. 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 PdII) would form the new C·C bond through the arene σ-system, the PdIII·Ar·β-migratory insertion pathway generates the new C·C bond through hybrid orbitals from the arene’s π-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 1q, the reaction involves a Pd-mediated β-H elimination/reinsertion process that walks the alkene away from the difluorobenzyl moiety (Fig. 2A).†† Computations provided additional insight into these competing processes. Overall comparison of PdII and PdIII mechanisms reveals that the operative mechanism involves PdII (see Fig. S2††): (1) β-H elimination for PdII is lower in energy than for PdII by 25.1 kcal mol⁻¹; (2) similarly, β-F elimination is favored for PdII over PdII by 37.1 kcal mol⁻¹. Interestingly, when comparing PdII vs. PdIII-based processes, β-H elimination is consistently favored over β-F elimination for PdII and PdII-based mechanisms by 2.5 and 14.5 kcal mol⁻¹, respectively. Overall, for the operative PdII mechanism, β-H elimination is favored over β-F elimination for 2.5 kcal mol⁻¹ (Fig. 2B). We also evaluated whether the chemoselectivity is influenced by the homobenzylic and benzylic positions of the H and F atoms by computing the elimination processes for a hypothetical substrate on which the H atoms are benzylic and F atoms are homobenzylic and vice versa (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 benzylic or the homobenzylic 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 PdII 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 PdII/CuI co-catalyzed cross-coupling reaction of gem-difluoroalkenes and ArSO2Cl react in a net arylation/isomerization sequence that demonstrated good functional group tolerance with respect to both components and provided products bearing the “CF2” motif at the benzylic 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.

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§ The crystal structure for 3oa can be found in the Cambridge Crystallographic Data Centre under code q79h.

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