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Cross-Coupling

Palladium-Catalyzed Defluorinative Coupling of Difluoroalkenes and Aryl Boronic Acids for Ketone Synthesis

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Abstract: The transition-metal-catalyzed carbonylation reaction is a useful approach for ketone synthesis. However, it is often problematic to use exogenous carbonyl reagents, such as gaseous carbon monoxide. In this manuscript, we report a novel palladium-catalyzed coupling reaction of *gem*-difluoroalkenes and aryl boronic acids that yields bioactive indane-type ketones with an all-carbon α-quaternary center. Characterization and stoichiometric reactions of the key intermediates RCF_2Pd^{II} support a water-induced defluorination and cross-coupling cascade mechanism. The vinyl difluoromethylene motif serves as an in situ carbonyl precursor which is unprecedented in transition-metal-catalyzed coupling reactions. It is expected to raise broad research interest from the perspectives of ketone synthesis, fluoroalkene functionalization, and rational design of new synthetic protocols based on the unique reactivity of difluoroalkyl palladium(II) species.

Introduction

Ketones are ubiquitous and essential modules in natural products and synthetic functional molecules (Figure 1a). The modern synthesis of ketones takes advantage of transition-metal catalysis to forge direct incorporation of carbonyl motif into targeted skeletons. And carbonylation by using carbon monoxide has occupied a central position.[1] However, it is often problematic to transport, store, and handle the toxic gaseous CO reagent, especially when high pressure must be applied. Alternative strategies to address this issue use liquid or solid CO surrogates, such as formic acid derivatives and metal carbonyls.[2] But these surrogates might not be well-tolerated by other reaction components. Another solution is the two-chamber system to separate the generation and subsequent use of carbon monoxide into two reactors.[3] The CO gas generated ex situ is diffused from one reactor to the other through a channel connected on the top. Despite these advancements, new reagents and mild protocols for ketones synthesis remain highly demanded.

On the other hand, although there are a few reports on the transition-metals-catalyzed synthesis of α-quaternary ketones,[4] little attention has been paid to the bioactive indane-type skeletons (Figure 1a).[5,6] The intramolecular Heck annulation of alkenes followed by an intermolecular coupling reaction is attractive in preparing such cyclic compounds.[7] Merging carbonylation into the catalytic cycle allows for the synthesis of all-carbon quaternary centers at the β position of ketones,[8] however, not at the α position (Figure 1b). Herein, we report these ketones could be

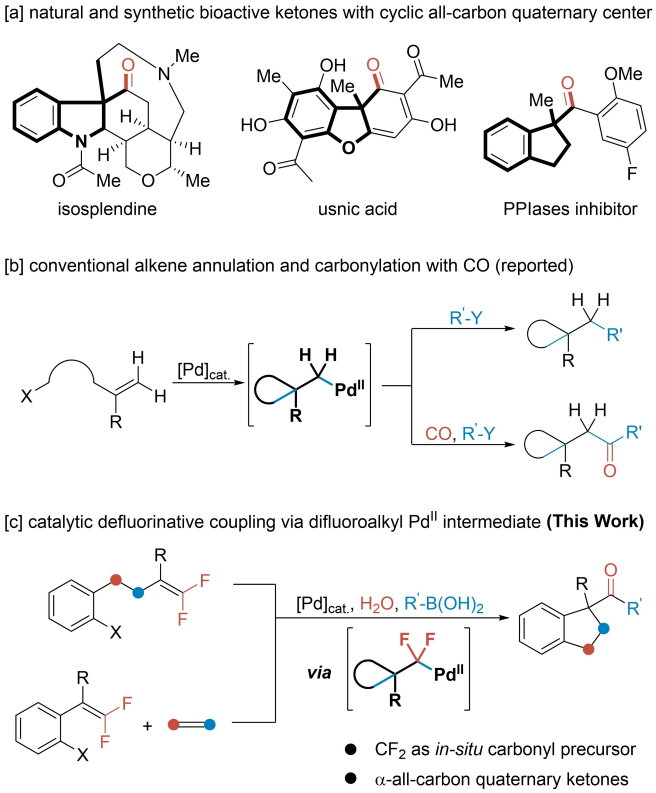

Figure 1. Representative examples of bioactive ketones, carbonylative alkene difunctionalizations, and our design.

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prepared by a palladium-catalyzed reaction of *gem*-difluoroalkenes with aryl boronic acids (Figure 1c). The carbonyl motif is derived in situ from the water-induced defluorination of difluoroalkyl palladium intermediate RCF_2Pd^{II} under mild reaction conditions, instead of using any exogenous carbonyl sources.

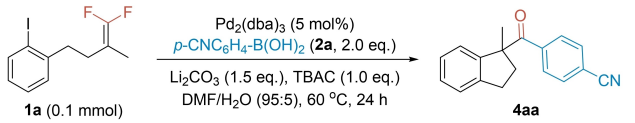
This unprecedented defluorinative cross-coupling reaction was developed from serendipitous discovery. Previously, we reported a AgF-mediated coupling reaction between the *gem*-difluoroalkenes and non-fluorinated alkenes.[9] We learned that the electron density of *gem*-difluorovinyl motif was biasedly distributed due to fluorine substitutions. When $R^1R^2C{=}CF_2$ was subjected to intermolecular migratory insertion with an active R^3–M species, the nucleophilic R^3 group would intrinsically favor the electrophilic difluoromethylene side while the metal resided on the other side, affording complex $R^3CF_2CR^1R^2$–M (Figure 2). This species might undergo subsequent cross-coupling with another reagent,[10] or β-fluoride elimination to monofluoroolefin.[11] At the onset of this project, our initial design was to alter the previous regioselectivity by a confined intramolecular 5-*exo*-trig migratory insertion (Figure 1c). And RCF_2–Pd^{II} species could be obtained that might enable new downstream cross-coupling reactions. To our surprise, the RCF_2–Pd^{II} was found unique and better suited for in situ defluorination as a carbonyl precursor.

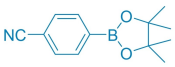
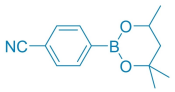
Results and Discussion

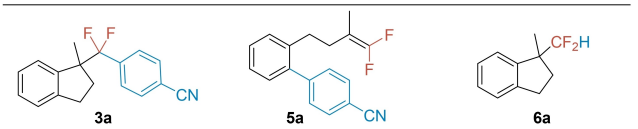
Based on our initial design, *gem*-difluoroalkene **1a** was used as the model substrate and the palladium as catalyst. Capture of the RCF_2–Pd^{II} intermediate by aryl boronic acid **2a** was expected to afford RCF_2Ar **3a** (Table 1). However, preliminary investigations indicated ketone **4aa** was the major product (structure confirmed by X-ray analysis, Table 2), while only a trace amount of **3a** was detected. Other by-products included the Suzuki coupling product **5a** and the protonation product **6a**. The yield of **4aa** was significantly improved by adding water as co-solvent, and a 5% volume in DMF was optimal (entry 1–4). Other catalysts including $PdCl_2$ and $Pd(PPh_3)_4$ were much less effective (entry 5, 6). Ligands were also investigated as they might help stabilizing the organometallic intermediate and controlling the stereoselectivity. But we found the bidentate ligands were deleterious to this reaction (entry 7, 8), while the monodentate pyridine showed moderate improvement (entry 9, see Supporting Information). Since fluoroalkenes were relatively weak ligands for coordination to transition metals,[12] we envisioned the strong chelating ligands would hamper the coordination and insertion of *gem*-difluorovinyl motif at the Pd^{II} center. This was partly confirmed in the mechanism study section. Instead, DMF solvent might act as a detachable ligand in the related process. On the other hand, Li_2CO_3 was crucial as the base. The yield of the Suzuki coupling product **5a** increased when other bases were screened (entry 10–11). And Ag_2O should be used without *tetra*-butyl ammonium chloride (TBAC) to avoid the formation of AgCl salt (entry 12). In other cases, TBAC was still necessary (entry 13). We reasoned slow transmetalation of aryl boronic acid to the palladium intermediate would favor sufficient intramolecular migratory insertion of the *gem*-difluorovinyl motif into Ar–Pd^{II}.[13] TBAC might help tuning the *p*H of the reaction mixture by interaction with Li_2CO_3, which was important to the transmetalation. The different transmetalation rates might also explain why aryl boronic esters afforded slightly decreased yields while aryl trifluoroborate salt was completely ineffective (entry 14–16).

Under the established reaction condition, the substrate scope of the organoboronic acids was studied (Table 2, top).

Table 1: Reaction development.



entry	variation of reaction conditions	yield (%, **4aa**)[a]
1	standard	86 (75%[b])
2	DMF	19
3	$DMSO/H_2O$ (95:5)	45
4	NMP/H_2O (95:5)	82
5	$PdCl_2$ as catalyst (5 mol%)	24
6	$Pd(PPh_3)_4$ as catalyst (5 mol%)	10
7	xantphos as ligand (12 mol%)	trace
8	2, 2'-bipyridine as ligand (12 mol%)	8
9	pyridine as ligand (22 mol%)	62
10	K_2CO_3 as base (1.5 eq.)	23
11	Cs_2CO_3 as base (1.5 eq.)	33
12	Ag_2O as base (1.5 eq.)	57[c]
13	without TBAC	42
14	*p*-CNC_6H_4-BF_3K	trace
15		65
16		71



Standard condition: **1a** (0.10 mmol), **2a** (0.20 mmol), $Pd_2(dba)_3$ (5 mol%), Li_2CO_3 (0.15 mmol), and TBAC (0.10 mmol) in DMF/H_2O (95:5, 2.0 mL) at 60 °C. [a] ^1H NMR yields with CH_2Br_2 as internal standard. [b] isolated yield. [c] no TBAC.

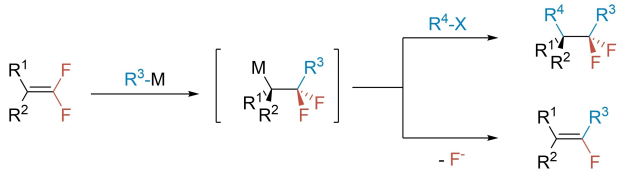
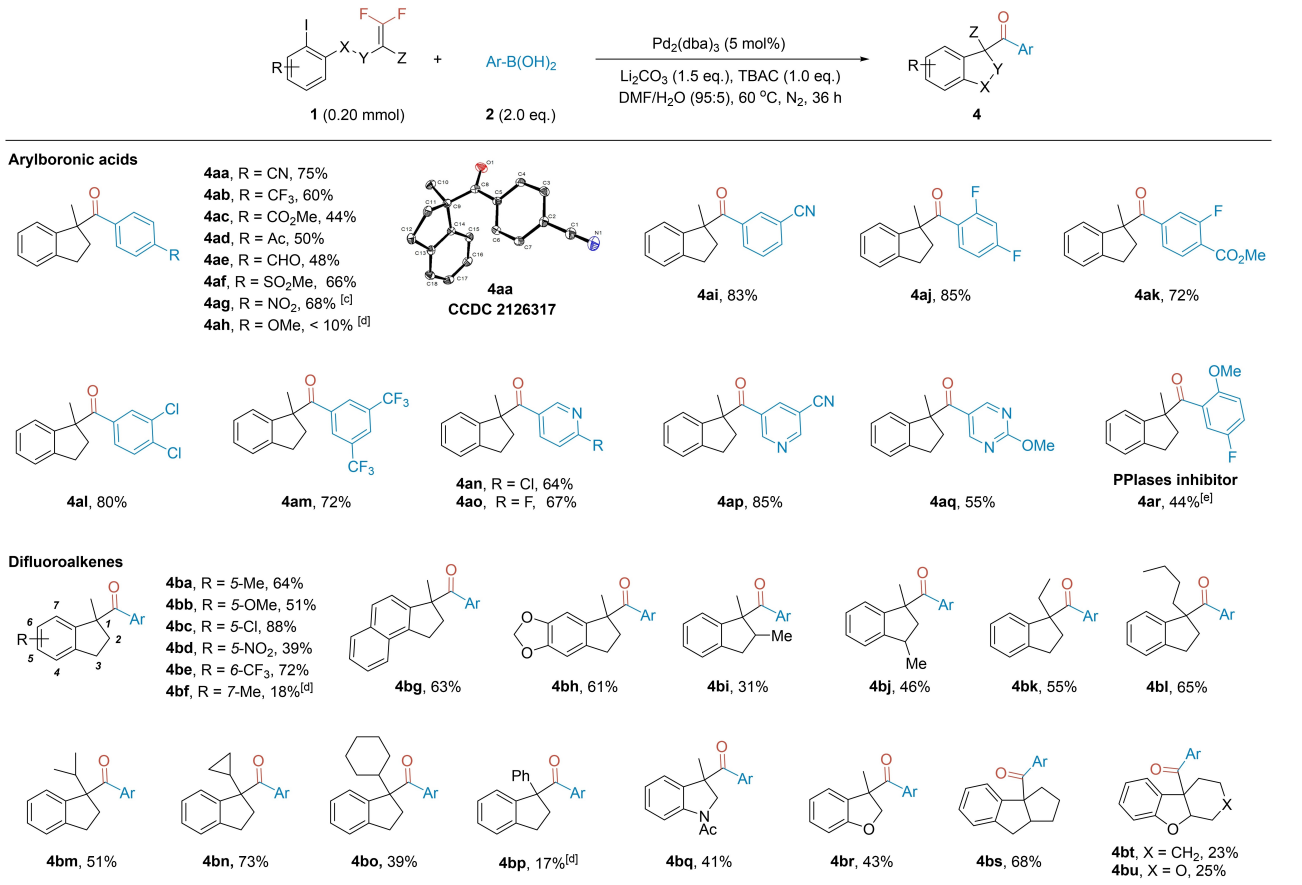


Figure 2. Conventional functionalizations of *gem*-difluoroalkenes.

Table 2: Scope of aryl boronic acids and *gem*-difluoroalkenes.[a,b]

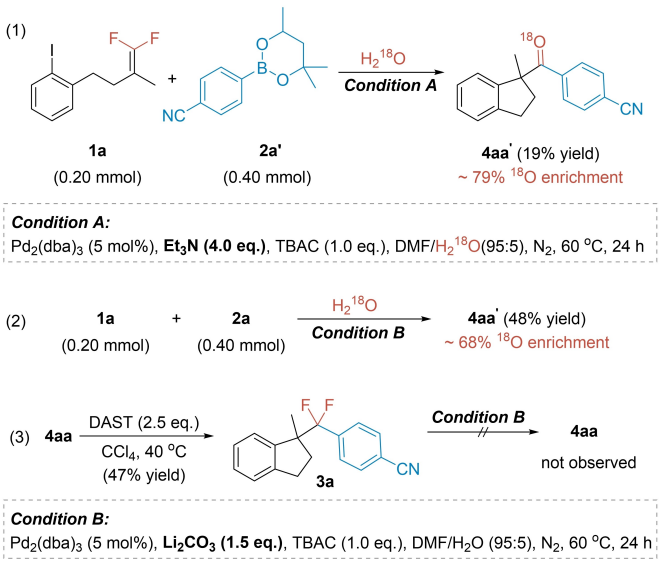


[a] reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Pd_2(dba)_3$ (5 mol%), Li_2CO_3 (0.30 mmol), TBAC (0.20 mmol) in DMF/H_2O (95 : 5, 4.0 mL) at 60 °C. (Ar = *p*-CNC_6H_4–). [b] isolated yields. [c] 4,4,6-trimethyl-2-(4-nitrophenyl)-1,3,2-dioxaborinane was used instead of boronic acids. [d] determined by ^{1}H NMR and GC-MS without isolation due to low yield. [e] DIPEA as a base (6.0 eq.).

Reaction time might vary depending on specific substrates and was recorded in Supporting Information. This reaction worked better for electron-deficient aryl boronic acids (**4aa**–**4ag**), but was less efficient for the electron-rich ones (**4ah**). Several parameters might affect such a delicate tandem reaction, and we thought the transmetalation step remained one of the key factors. Functional group tolerance was quite good. The carboxylic ester (**4ac**, **4ad**), aldehyde (**4ae**), sulfonate (**4af**), nitro (**4ag**), cyanide (**4ai**), and halogens (**4aj**, **4al**) were all compatible and offered satisfactory yields. It's noteworthy that heteroaryl boronic acids including pyridine and pyrimidine afforded related ketones in good yields (**4an**–**4aq**). A peptidyl prolyl *cis*/*trans* isomerase (PPIases) inhibitor **4ar** could also be readily obtained with our method.[6k]

Variations of the *gem*-difluoroalkenes were also studied (Table 2, bottom). Substituents of different electron properties on the *meta* and *para* positions were well-tolerated (**4ba**–**4be**, **4bg**, **4bh**). But the reaction was found sensitive to substituent *ortho* to the aryl iodide, probably due to the steric hindrance (**4bf**). An additional methyl group on the tethering methylene chain between the aryl and vinyl motifs resulted in decreased yields (**4bi**, **4bj**). The reaction was also sensitive to the steric hinderance of the vinyl substituents. Linear ethyl and butyl motifs gave acceptable yields (**4bk**, **4bl**). The *i*-Pr substitution resulted in 51 % yield, while its cyclic analogue gave 73 % yield (**4bm**, **4bn**). A more congested vinyl cyclohexyl group made the reaction less effective with only 39 % yield (**4bo**). Aryl substituent was just not good (**4bp**). To our delight, this method could be extended to the preparation of indoline and coumaran derivatives (**4bq**, **4br**), which were essential building blocks of many bioactive molecules.[6a–j] It was also useful to construct fused polycyclic ketones by employing related *gem*-difluoroalkenes as starting materials (**4bs**–**4bu**).

Control experiments were carried out to figure out when the defluorination took place and where the carbonyl oxide motif came from. There were three suspect oxygen donors in the reaction system, namely water, boronic acid, and Li_2CO_3. To rule out potential oxygen exchange among these three reagents in the ^{18}O labeling experiment, condition A was used by replacing aryl boronic acid **2a** and Li_2CO_3 with boronic ester **2a′** and Et_3N (Scheme 1). Although this was not an optimal condition that gave ketone in low yield, product **4aa′** was successfully labeled in about 79 % ^{18}O enrichment when $H_2{}^{18}O$ was the only oxygen source



Scheme 1. Control experiments.

(Scheme 1-1). The labeling ratio slightly dropped to about 68 % when **2a** and Li_2CO_3 were used with $H_2{}^{18}O$ (Scheme 1-2). On the other hand, compound **3a** was prepared from the post-fluorination of ketone **4aa**.[14] It was then subjected to the standard catalytic reaction conditions, but no conversion to **4aa** was detected (Scheme 1-3). Therefore, the carbonyl motif of ketone products in our reaction was probably derived from the difluoromethylene hydrolysis by water in the palladium-mediated catalytic coupling cycle, not from the post-defluorination of **3a** off the cycle.

Further studies of the related organometallic complexes and elementary steps were conducted to gain deep insight into the transformations. Oxidative addition of Pd^0 to aryl iodide **1a** in the presence of ligands gave complexes **7a**–**7c** respectively (Figure 3A, no reaction without ligand in THF). X-ray analysis of their structures revealed the difluorovinyl motif was away from the Pd^{II} center without any interaction. Heat **7a**–**7c** in various organic solvents did not give alkene insertion products. Also, their direct reactions with model substrate **2a** under the catalytic reaction conditions only gave trace amounts of ketone **4aa**, whereas the Suzuki product **5a** was mainly obtained with **7b** and **7c** (the reaction with **7a** gave fluoroolefin **11b** which was observed and depicted in Figure 3C). $AgBF_4$ was therefore added to force the release of a coordination site by abstracting iodide. Consequently, complex **7a** bearing a phenanthroline (Phen)

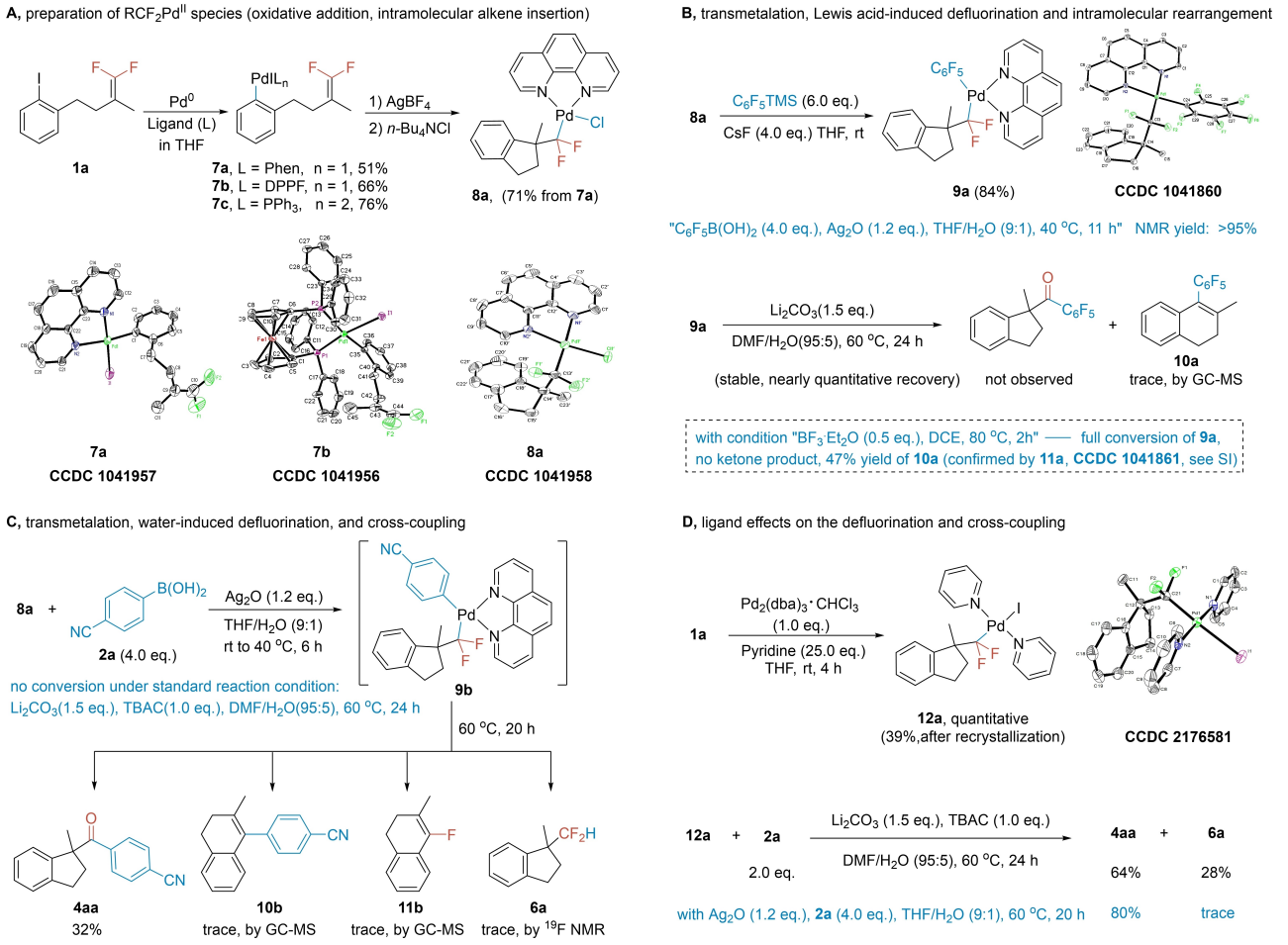


Figure 3. Preparation, characterization, and transformations of key organopalladium intermediates potentially involved in the catalytic reactions.

ligand was cyclized and subsequently converted to a more stable chloride complex **8a**. But **7b** and **7c** remained inefficient for cyclization, ending up with defluorination or protonation to **6a** (minor). We envisioned the phosphine-ligated palladium(II) center was too congested, whereas the Phen analogue with a planar skeleton was more open for coordination and insertion of the vinyl motif. **8a** was a stable orange crystalline solid that remained in good quality for months in the dry box. It adopted a rigid square planar geometry with a *cis* alignment of ligand RCF_2– and chloride. The two fluorines of difluoromethylene motif were inequivalent with varied C–F bond lengths (1.390 Å vs 1.398 Å).

Transmetalation with complex **8a** was next explored (Figure 3B). We used C_6F_5TMS as the aryl source at the very beginning. Because the reaction was easy to monitor by ^{19}F NMR and gave the desired adduct **9a** in dry THF that was stable for purification and characterization (**9a** was later found also available from $C_6F_5B(OH)_2$ and Ag_2O in THF/H_2O). To our surprise, neither reductive elimination to $RCF_2C_6F_5$ nor defluorinative coupling to ketone was observed by treating **9a** with the catalytic reaction conditions. Only a trace amount of ring-expansion product **10a** was detected by GC-MS. In recent studies of the CF_3–$Pd^{II}R$ and $ArCF_2$–$Pd^{II}R$ species,[15] Lewis acids were more robust to induce the defluorination that afforded metal fluorocarbene intermediates. These species were liable to nucleophilic addition by exogenous reagents or 1,1-insertion by the pre-ligated R group on Pd^{II}, yielding RCF_2–Pd^{II} or $RArCF$–Pd^{II} respectively. In this context, we investigated the reaction of **9a** with boron trifluoride. Exhaustive defluorination took place immediately. Again, only **10a** was afforded in 47 % isolated yield (structure confirmed by further derivation to a crystalline compound **11a**, see Supporting Information for X-ray analysis). These results provided two important messages. Firstly, a C_6F_5– derived metal complex was reluctant to defluorination and reductive elimination under the catalytic reaction conditions. Secondly, the ring-expansion coupling pathway was favored instead of ketone formation, if defluorination was triggered under forcing reaction conditions. It was probably because the pentafluorophenyl palladium was thermodynamically inert for bond dissociation.[16] This might explain the failure of $C_6F_5B(OH)_2$ as a substrate in the catalytic reactions.

Therefore, we continued the transmetalation study of **8a** with the model substrate, aryl boronic acids **2a** (Figure 3C). The two substrates were incubated under the standard catalytic reaction conditions (Li_2CO_3/DMF), however, no conversion was observed. Prolonged reaction time at a higher temperature only resulted in complete decomposition. To facilitate the transmetalation, Ag_2O was employed as the promoting reagent instead of Li_2CO_3. A new group of peaks appeared on the ^{19}F NMR spectrum, and it was tentatively assigned to **9b** (Figure 3C, also see Figure S6 in Supporting Information). Attempts to isolate this new species failed and led to complete defluorination. Careful analysis of the resulting mixture revealed ketone **4aa** was the major product (32 % yield, on 0.10 mmol scale), along with trace amounts of **10b**, **11b**, and **6a**. These results implied that RCF_2–$Pd^{II}Ar$ (**9**) might be the key intermediate, from which defluorination and ketone were derived.

To further elucidate the ligand effect and mimic the catalytic reaction system more precisely, we decided to use pyridine as a weak coordination ligand instead of Phen for the stoichiometric organometallic reactions (Figure 3D). Indeed, palladium(0) reacted with substrate **1a** in the presence of pyridine that directly gave alkene insertion product **12a** in a single step. Unlike complex **8a** which was relatively inert, **12a** underwent a fast reaction with **2a** to give ketone **4aa**, under either the standard catalytic reaction conditions (64 % yield) or the Ag_2O-mediated condition (80 % yield). No transmetalation intermediate was observed during the process, due to the accelerated defluorinative cross-coupling. Therefore, we envisioned bidentate ligands not only hampered the migratory insertion of *gem*-difluorovinyl motif, but also were unfriendly to the transmetalation and defluorination. A vacant coordination site was essential to the catalytic defluorinative coupling reaction. This was in good agreement with the results observed in the reaction development section. For comparison, **12a** was separately treated with C_6F_5TMS/CsF, $C_6F_5B(OH)_2$/AgO, and $C_6F_5B(OH)_2$/Li_2CO_3 under related reaction conditions. We still did not observe any ketone product in these cases, except for trace amounts of **10a**, **11b**, and **6a** (Figure S7 in Supporting Information).

Taken together with all the above results, a mechanism for the catalytic cycle was tentatively proposed in Figure 4 (**1a** as model substrate). Starting from the oxidative addition of palladium(0) to substrate **1a** and followed by intramolecular alkene insertion, the difluoroalkyl palladium(II) intermediate **II** was obtained. Subsequently, it underwent transmetalation with aryl boronic acids to afford **III**. The previously reported $RCF_2Pd^{II}Ar$ species mainly had a

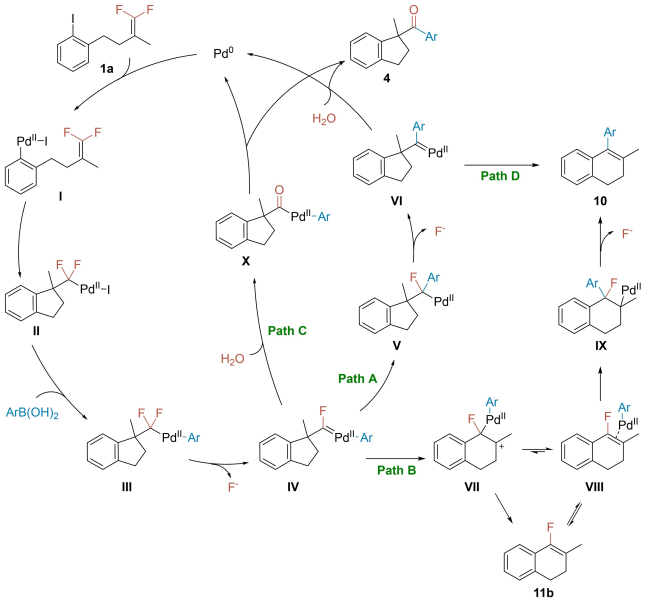


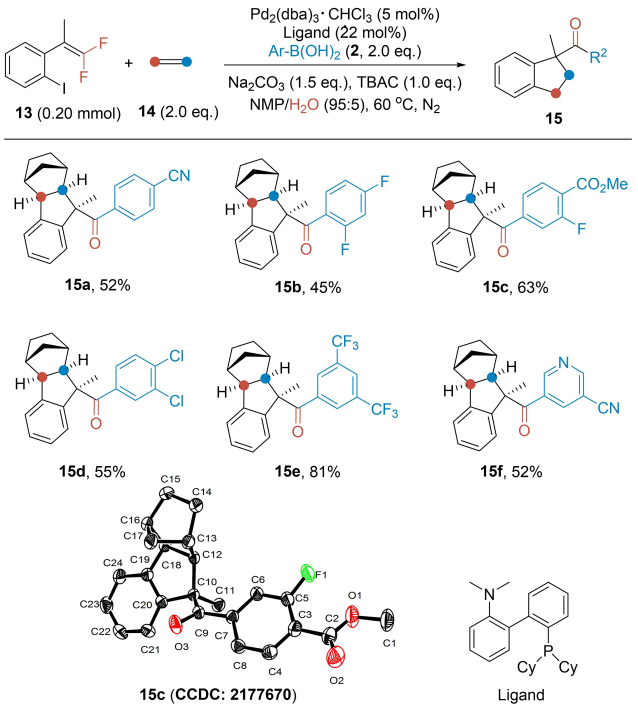
Figure 4. Proposed catalytic cycle (Notes: potential coordination(s) of halide or solvent to Pd^0 or Pd^{II} in the related metal complexes were omitted for clarity).

supporting group R in stabilizing the related complexes and facilitating the subsequent cross-couplings, through either π-conjugation or strong σ-induction effects, such as aryl or carbonyl groups.[17] Therefore, reductive elimination to RCF_2Ar was favored, rather than defluorination. In very few cases, strong Lewis acids were applied to forge the defluorination, and these transformations could only be carried out in stoichiometric amounts with palladium complexes.[15d] The sp^3-hybridized quaternary carbon, herein, could hardly provide an extra bonus for stabilizing this difluoroalkyl palladium(II), except for preventing itself from the β-elimination. Therefore, **III** was more liable to defluorination, and even water could induce this process. Detachable weak-coordinated ligands, such as pyridine or DMF, would benefit the defluorination by releasing a vacant coordination site on Pd^{II} (Figure 3C, D). Finally, the *trans*-effect of Ar group might also have an impact on the defluorination to some degree, as we found the C_6F_5– ligated complex exhibited higher stability than the nonfluorinated analogues (Figure 3B).

There were three possible downstream reaction pathways for fluorocarbene metal intermediate **IV** derived from defluorination of **III**.[18] One was the 1,1-insertion of Ar from Pd^{II} center to carbene (Path A).[15] The resulting intermediate **V** then underwent a second defluorination via a similar approach and probably yielded intermediate **VI**. **VI** was further quenched by water to afford ketone **4**, or rearranged to olefin **10** in the absence of exogenous nucleophiles (Path D). The second pathway for **IV** was more likely to proceed if Ar was an inert ligand, such as C_6F_5– (Path B). Intramolecular aryl rearrangement from the five-membered cyclic quaternary carbon to carbene would then become kinetically favored than 1,1-insertion, giving ring-expansion complex **VII**. **VII** underwent elimination to alkene **11b** and Ar–Pd^{II}. Meanwhile, the Ar–Pd^{II} might be in active equilibrium of coordination with **11b** through complex **VIII**. And it was possible for **VIII** to undergo alkene insertion to **IX**. Finally, β-fluoride elimination of **IX** would give **10**. Besides, the third pathway could not be ruled out currently (Path C). The water-induced carbonyl formation might occur at the very early stage to afford intermediate **X**, which yielded ketone **4** via reductive elimination.

Based on the mechanism, the catalytic paradigm was further extended to a more complex multi-component reaction (Table 3). We hypothesized the *gem*-difluorinated styrene analogue **13** derived palladium(II) complex might firstly allow an intermolecular insertion of alkene, which then underwent intramolecular insertion of the *gem*-difluorovinyl motif. The resulting annulation adduct would follow the general protocol of defluorinative cross-coupling with aryl boronic acid. However, there were several challenges in the designed catalytic cycle. First, the palladium complex derived from substrate **13** might take direct cross-coupling with aryl boronic acid, in competition with the alkene insertion. Second, suppose the desired intermolecular alkene insertion worked well and gave a new palladium(II) intermediate, then potential side reactions such as β-elimination and arylation with boronic acid must be addressed. After an extensive survey, we found the reaction could be enabled by norbornene (**14**).[19] And an exogenous ligand was helpful in suppressing these side reactions (Table 3). It was generally applicable to a range of electron-deficient aryl boronic acids. Related ketones **15** were obtained in good to excellent yields. Other alkenes afforded more complicated reaction mixtures that remains under optimization at the current stage.

Table 3: The four-component catalytic reaction for ketone synthesis.



[a] **13** (0.20 mmol), **14** (0.40 mmol), **2** (0.40 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mol%), Ligand (22 mol%), Na_2CO_3 (0.30 mmol), TBAC (0.20 mmol) in NMP/H_2O (95:5, 4.0 mL) at 60 °C for hours under nitrogen atmosphere.

Conclusion

In summary, a new palladium-mediated catalytic paradigm for ketones synthesis is developed from *gem*-difluoroalkenes, aryl boronic acids, and water. The vinyl difluoromethylene serves as an in situ carbonyl precursor instead of using any exogenous carbonyl sources. Related organometallic intermediates and species in/off the catalytic cycle have been fully studied that offers reasonable information for understanding the mechanism. The principle of defluorinative cross-coupling could be further extended to multi-component reactions in preparing ketones of more complex structures.

This study is important and expected to draw broad research interest from several perspectives. 1) It provides an alternative protocol for ketones synthesis, especially the α-all-carbon quaternary ketones bearing indane-type skeletons. And the use of exogenous carbonyl sources is avoided.

2) It unfolds the unique reactivity and utility of the difluoroalkyl palladium(II) RCF_2–Pd^{II} species. While previous studies mainly use supporting group R to enhance the balance of stability and reactivity (R = aryl, allylic, carbonyl, etc.),[17] the unactivated RCF_2–Pd^{II} is rarely studied (R = alkyl, no π conjugation or strong σ inducing effect). We get the first well-defined structure of such type of species, and disclose their catalytic defluorination reaction as in situ carbonyl precursors under mild conditions. Although the difluoromethylene hydrolysis by strong acids is known,[20] these forcing reaction conditions could hardly be incorporated into transition-metal-mediated catalytic cycle. 3) It exemplifies a novel strategy for the difunctionalization of fluoroalkenes. Alter the intrinsic reactivity of fluoroalkenes in the reaction with organometallic species allows for the rational design of new catalytic paradigms for divergent synthesis.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Boronic Acids · Defluorination · Fluoroalkenes · Ketones · Palladium

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