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Development and Mechanistic Investigations of a Base-Free Suzuki-Miyaura Cross-Coupling of α,α-Difluoroacetamides via C–N Bond Cleavage.

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ABSTRACT: This study describes the development and understanding of a palladium-catalyzed cross-coupling of fluoroacetamides with boronic acids, under base-free conditions, to selectively give valuable α,α-difluoroketone derivatives. Detailed mechanistic studies were conducted to assess the feasibility of each elementary step, i.e C(acyl)–N bond oxidative addition, followed by base-free transmetallation and reductive elimination. These investigations allowed the structural characterization of palladium(II) fluoroacyl intermediates derived from C–N bond oxidative addition of an amide electrophile. They also revealed the high reactivity of these intermediates for transmetallation with boronic acids without exogenous base. The mechanistic studies also provided a platform to design a practical catalytic protocol for the synthesis of a diversity of α,α-difluoroketones, including CF_2H-ketones. Finally, the synthetic potential of this fluoroacylation methodology is highlighted in sequential, orthogonal C–Br and C–N bond functionalization of an α-bromo-α,α-difluoroacetamide with a focus on compounds of potential biological relevance.

KEYWORDS: cross-coupling, palladium catalysis, mechanism, transmetallation, synthetic method, difluoroketone

INTRODUCTION

Nowadays, the *gem*-difluoromethylene (CF_2) group is well established as a key structural unit in many compounds of pharmaceutical and agrochemical interest due to the recognition of its significant impact on chemical and biological activity.[1] Rapid progress in the strategic incorporation of CF_2-containing functional groups into high-value scaffolds is therefore extremely desirable to satisfy the supreme demand for new drug candidates. For instance, the past recent years have seen tremendous advances in the development of efficient catalytic strategies for the *gem*-difluoroalkylation of unsaturated organic substrates including cross-coupling reactions or direct C–H bond functionalization via transition metal (TM)[2] or visible light-driven photoredox catalysis.[3] In this area, functionalized difluoromethyl halides (e.g., Hal-CF_2-FG, with FG = CO_2R, $CONR_2$, SO_2Ph, $PO(OR)_2$) have been established as privileged reagents in that they are readily available, robust and practical.[4] These substrates proved to be efficient coupling partners in metal-catalyzed fluoroalkylation reactions, *via* C–halogen bond activation (**I**, Figure 1A).[2c] These reactions give access to a broad range of *gem*-difluorinated products containing functional groups that can provide opportunities for further downstream elaboration. In this context, α,α-difluoroacetamide derivatives (**II**, Figure 1A) are particularly appealing because they open access to high-value α,α-difluoroketones (**III**), which are privileged substructures in chemical biology and drug design.[5] However, the rare derivatization methods rely on nucleophilic additions of highly reactive organolithium and Grignard reagents that need to be prepared and handled under inert conditions.[6]

On the other hand, carboxylic acid derivatives such as amides, esters and acyl fluorides have been recently recognized as suitable electrophilic partners for catalytic cross-coupling reactions via C–N, C–O or C–F bond activation, respectively.[7] Amides, which are present in a wide range of important natural and synthetic molecules, have long been regarded as inert substrates to catalytic transformations. But they have received considerably more attention, over the last few years, as a new type of electrophiles in cross-coupling reactions. Notably, in 2015, Szostak,[8] Zou,[9] and Garg[10] independently reported the palladium- or nickel-catalyzed Suzuki-Miyaura-type (SM) cross-coupling of these C_{acyl}–N electrophiles, making it a valuable addition to the repertoire of acylative methods for ketone synthesis.[11] However, this methodology has not been explored so far as a tool to perform *gem*-difluoroacylation of a specific substrate.[12]

Within this context, the development of a palladium-catalyzed cross-coupling of α,α-difluoroacetamides with organoboron compounds would provide a valuable strategy for the direct and simple preparation of diversely substituted difluoroketones. It would also generate significant synthetic perspectives for halodifluoroacetamides as dual-function templates. Selective orthogonal connective pathways could be envisioned with these substrates acting alternatively as difluoroalkylating and difluoroacetylating reagents (Figure 1A).

Importantly, fluoroacetylation methodologies are very rare compared to fluoroalkylation protocols. A recent successful

strategy, reported independently by the groups of Skrydstrup[13] and Zhang,[14] relies on carbonylative Suzuki-Miyaura substitution of functionalized difluoromethyl halides (Figure 1B, left). The reaction proceeds via the generation of a palladium-fluoroalkyl intermediate ensuing from C–Br bond activation, followed by insertion of carbon monoxide and carbon-carbon bond reductive elimination. The main challenge of this approach is the intrinsic reluctance of strong metal-fluoroalkyl bonds to undergo carbon monoxide insertion.[14a,15,16] Moreover, this approach was typically applied for the synthesis of α,α-difluorinated 1,3-dicarbonyl compounds.

We envisioned that the direct difluoroacetylative approach using difluoroacetamide electrophiles (Figure 1B, right) via C–N bond cleavage could provide a valuable complementary strategy to directly introduce $C(O)CF_2$ moiety. Besides the development of a practical catalytic protocol, we were also eager to address fundamental mechanistic questions about this transformation. From a mechanistic point of view, the information about the C–N bond activation of amides with palladium complexes is scarce, and the transient difluoroacyl palladium(II) intermediates have never been structurally characterized. Other critical aspects to consider are the stability and the reactivity of the putative difluoroacyl intermediate towards organometallic nucleophiles, and finally, the adjustment of suitable conditions with compatible reactants to allow selective formation of the desired ketone under catalytic conditions.

Herein, we disclose our investigations going from stoichiometric organometallic studies to the development of a practical and robust catalytic protocol for the synthesis of α,α-difluoroketones. The most significant features of our mechanistic studies include the first structural characterization of key difluoroacyl palladium intermediates and evidences for their ability to undergo base-free transmetallation with arylboronic acid. These mechanistic investigations served as a basis for the discovery of a base-free palladium-catalyzed cross-coupling reaction of amide electrophiles under mild conditions to yield a variety of α,α-difluorinated (hetero)aryl ketones, including alkylCF_2- and CF_2H-ketones. Finally, the synthetic potential of this methodology was highlighted by addressing the challenges associated with orthogonal reactivity of α-halo-α,α-difluoroacetamides.

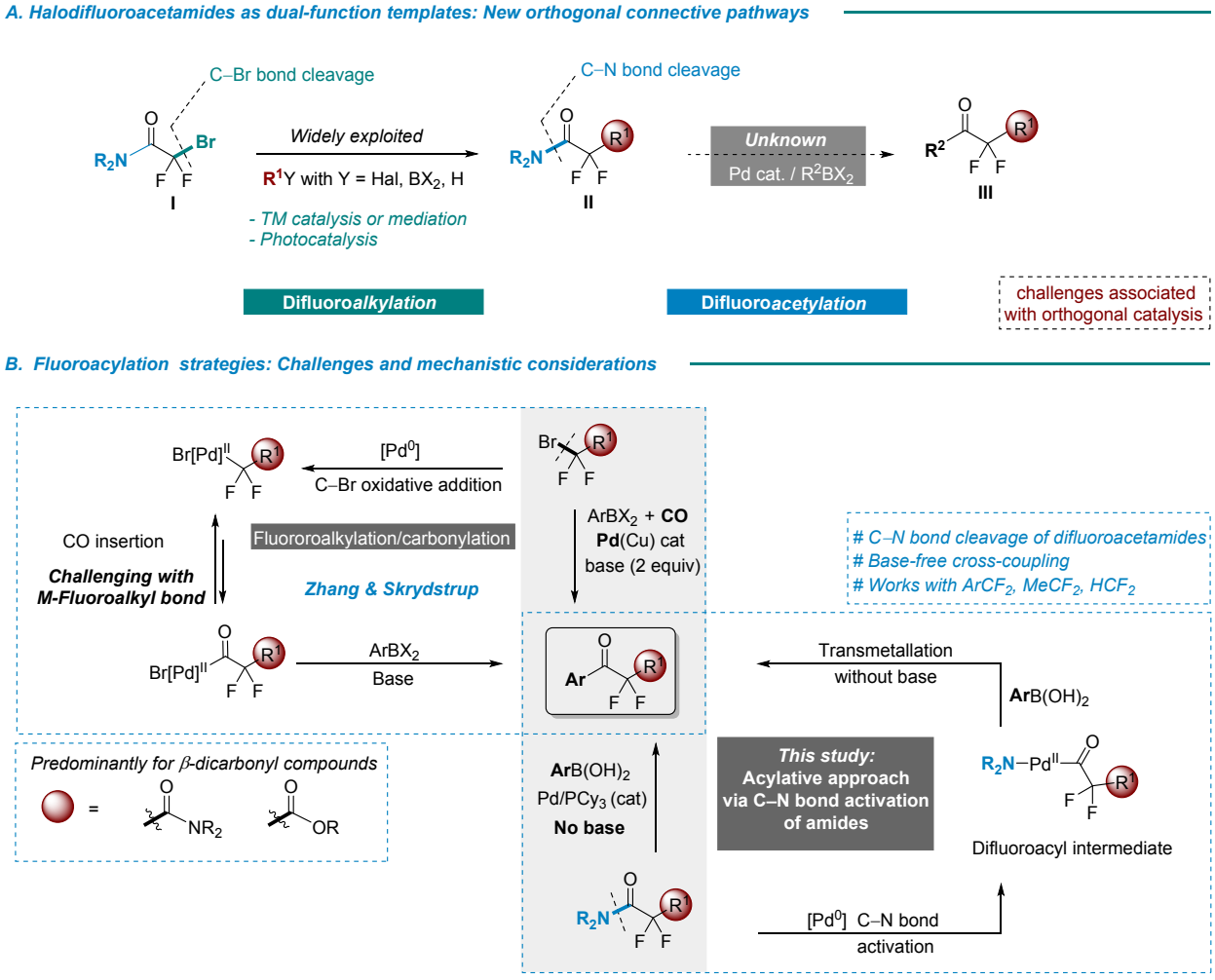


Figure 1. (A) New strategy towards α,α-difluoroketones exploiting the orthogonality of difluoroalkylative and difluoroacetylative reactions of halodifluoroacetamides. (B) Recent catalytic developments in the synthesis of difluorocarbonyl compounds via a carbonylative approach, and proposed novel approach with mechanistic considerations.

RESULTS AND DISCUSSION

To evaluate the feasibility of this new protocol we decided to use *N*-(difluoroacetyl)-glutarimide **1a** as a model substrate. This twisted amide handle, introduced by Szostak,[8, 17] has been shown to be a versatile and robust precursor in metal-catalyzed cross-coupling reactions involving C_{acyl}–N bond activation. The glutarimide function is easily installed starting from readily available carboxylic acids to afford the corresponding, bench-stable difluoroacetamide in multigram scale.

Stoichiometric investigations

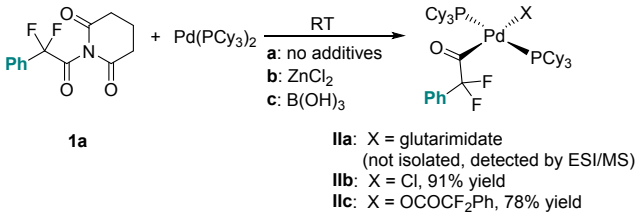
Preliminary experiments exploring the palladium-catalyzed cross-coupling of *N*-(difluoroacetyl)-glutarimide **1a** with phenylboronic acid using catalytic conditions classically reported for the SM cross-coupling of amides[8, 17] resulted in complete degradation of the starting reactant. Rapid control experiments indicated that compound **1a** decomposes over time in the presence of inorganic bases. Thus, stoichiometric studies were first conducted to set-up suitable conditions allowing efficient coupling of **1a** with phenylboronic acid without the addition of exogenous base. Gratifyingly, the cross-coupling reaction in the presence of stoichiometric amount of $Pd(PCy_3)_2$ in toluene proceeded at room temperature to give the corresponding difluoroketone **2a** in 89% yield, as determined by ^{19}F NMR spectroscopy, after 10 min.

The development of SM cross-coupling reactions without exogenous base is of high interest in regards to sustainable catalysis, furthermore, it will allow to extend the scope to base sensitive compounds. Very few reports describe efficient base-free methodologies for SM reactions.[18,19] Two main strategies have been recently developed to by-pass the requirement for stoichiometric amount of exogenous base. The first one relies on the use of pre-designed cationic palladium complexes.[18] The second one is based on the generation of metal-fluoride intermediates by oxidative addition of C–F bonds, that are highly reactive towards transmetallation without additives.[7i, 19] Taking into account these considerations, we were keen to get more insight into the structure of the palladium intermediate generated by oxidative addition of the difluoroacetamide and its subsequent reactivity with boronic acids.

Oxidative addition of C_{acyl}–N bond of difluoroacetamide to generate palladium(II) difluoroacyl complexes

In the context of recent developments of palladium-catalyzed cross-coupling reactions of amides, acylpalladium-amidate species are proposed as key intermediates, but their isolation and characterization have not been reported.[20,21] With this information in mind, we first investigated the C_{acyl}–N bond activation step. The reaction of **1a** with $Pd(PCy_3)_2$ was carried out under the same conditions as the cross-coupling reaction. Surprisingly, monitoring of the reaction by ^{19}F NMR spectroscopy indicated that after 20 min only trace amount of the starting amide is converted to a species that appears as a broad signal ($\delta^{19}F = -90.8$ ppm). After few days of reaction, the conversion slowly reaches a maximum of 40% that do not evolve with time unless to give decomposition products. ^{31}P NMR monitoring revealed that the starting $Pd(PCy_3)_2$ also slowly converts to unidentified species.[22] ESI mass spectroscopy analyses of the reaction mixture clearly indicated the formation of a cationic difluoroacyl palladium intermediate (mass peak at 821.3978 m/z for $[C_{44}H_{71}F_2OP_2Pd^+]$), but all attempts to isolate and further characterize the corresponding complex were unsuccessful. The slow reactivity of **1a** towards Pd(0) compared to the cross-coupling reaction rate may suggest that the transient difluoroacyl palladium intermediate rapidly reacts with boronic acid to drive the reaction towards the formation of the final difluoroketone. Willing to isolate and characterize the difluoroacyl palladium intermediate, we studied the oxidative addition reaction in the presence of additives such as LiCl, $ZnCl_2$ or $B(OH)_3$ in order to facilitate the oxidative addition of the C_{acyl}–N bond.[23-24] Gratifyingly, the reaction of **1a** with $Pd(PCy_3)_2$ in the presence of $ZnCl_2$ or $B(OH)_3$ proceeded smoothly to give difluoroacyl palladium(II) complexes **IIb** ($\delta^{31}P\{^1H\} = 22.4$ ppm) and **IIc** ($\delta^{31}P\{^1H\} = 21.8$ ppm) as major phosphorus-containing compounds, in 91% and 78% spectroscopic yield, respectively (Scheme 1).[22]

Scheme 1. C–N bond oxidative addition of 1a to $Pd(PCy_3)_2$.



1a

IIa: X = glutarimidate (not isolated, detected by ESI/MS)
IIb: X = Cl, 91% yield
IIc: X = $OCOCF_2Ph$, 78% yield

Most diagnostic NMR data are the $^{13}C\{^1H\}$ NMR signals of the fluoroacyl ligand. The $^{13}C\{^1H\}$ NMR resonances of **IIb** and **IIc** corresponding to the carbonyl moiety are shifted downfield upon oxidative addition from 171.5 ppm (for **1a**) to 234.8 (**IIb**) and 229.0 ppm (**IIc**), which is typical for fluoroacyl-palladium species.[25] The signals corresponding to the CF_2 moiety appear as triplet of triplets due to coupling to fluorine and phosphorus atoms. Also, the ^{19}F NMR resonance of fluoroacyl moiety is shifted downfield from –102.3 (for **1a**) to –90.1 (**IIb**) and –89.8 ppm (**IIc**). For complex **IIc**, the ^{19}F and ^{13}C NMR spectra display additional signals corresponding to a difluoroacetate ligand bound to Pd.[22] The molecular structures of **IIb** and **IIc** were unambiguously confirmed by single crystal X-Ray diffraction analysis (Figure 2). The palladium center adopts a square planar environment and is ligated by two phosphorus atoms and a difluoroacyl ligand in each case. The coordination sphere is completed by a chlorine atom in complex **IIb** and by a difluoroacetate ligand in **IIc**. The formation of complex **IIc** is proposed to occur via a ligand exchange between the transient amidate complex **IIa** and difluorophenylacetic acid generated in situ in the presence of $B(OH)_3$. In line with this proposition, the formation of the same complex is observed when the oxidative addition reaction is carried out in the presence of difluorophenylacetic acid instead of $B(OH)_3$. Notably, complexes **IIb** and **IIc** represent the first examples of fluoroacyl palladium complexes structurally characterized, and their formation provides direct evidence for the C_{acyl}–N bond oxidative addition to Pd(0).[26,27]

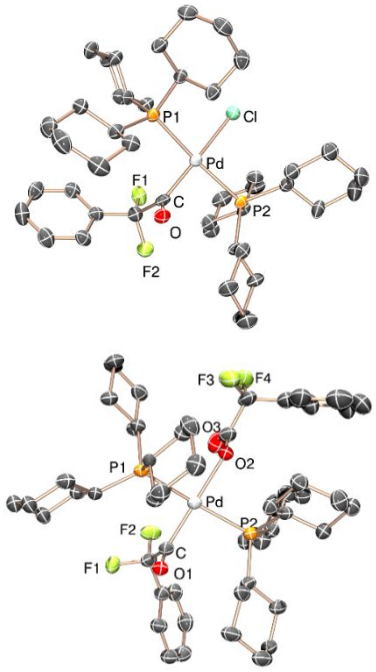
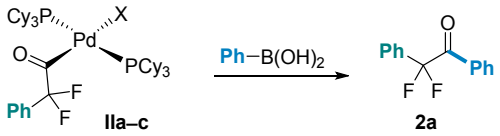


Figure 2. Molecular structures of the Pd(II) difluoroacyl complexes **IIb** (top) and **IIc** (bottom). Hydrogen atoms and solvent molecules are omitted for clarity; one crystallographic independent molecule is shown.

Transmetallation reactivity of palladium(II) difluoroacyl intermediates with phenylboronic acid

Next, we investigated the reactivity of complexes **IIa–c** with phenylboronic acid to compare the ability of the difluoroacyl palladium(II)–X intermediates (X = glutarimidate, fluoroacetate, chloride) to undergo transmetallation reaction without exogenous base (Scheme 2). The reaction of **IIa**, in situ generated, with $PhB(OH)_2$ proceeded very rapidly at room temperature to give directly the difluoroketone product in 89% yield after 10 min. No intermediate is detected indicating that the carbon-carbon bond reductive elimination is significantly faster than transmetallation. The difluoroacetate complex **IIc** also reacts with $PhB(OH)_2$ but at lower rate (73% yield after 1.5 h at 80 °C). In contrast, no reaction was observed between the chloro complex **IIb** and $PhB(OH)_2$ under the same conditions. When 2 equivalents of K_2CO_3 were added and the reaction mixture was heated to 80 °C for 48 h, the desired product **2a** was formed in 65% yield, along with side products.[28] These results highlight the key role of the amidate ligand in the reactivity of the difluoroacyl palladium(II) intermediate towards transmetallation with boronic acids and confirm its ability to undergo the reaction under base-free conditions.

Scheme 2. Reactivity of difluoroacyl palladium complexes with phenylboronic acid.



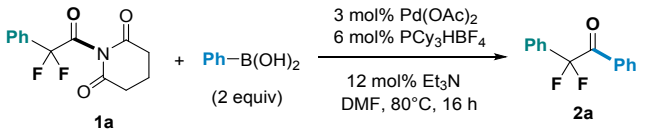
IIa: X = glutarimidate, *in situ generated*		89% (10 min, RT)
IIb: X = Cl	w/o base	1.5% (1.5 h, 80 °C)
	with K_2CO_3 (2 equiv)	65% (48 h, 80 °C)
IIc: X = $OCOCF_2Ph$		73% (1.5 h, 80 °C)

Overall, these stoichiometric studies clearly substantiate the C–N bond oxidative addition of a fluoroacetamide to palladium to form a fluoroacyl intermediate that is highly reactive towards transmetallation with phenylboronic acid without the requirement of exogenous base. Furthermore, these results provide interesting insights that may be of high relevance to cross-coupling reactions of amides involving the formation of acyl-metal amidate intermediates. Next, we were eager to translate these mechanistic insights into the development of a palladium-catalyzed difluoroacetylation of boronic acids with difluoroacetamide electrophiles.

Catalytic optimization studies

First, we assessed the feasibility of the cross-coupling reaction under base-free conditions using 3 mol% of $Pd(PCy_3)_2$. The coupling product **2a** was formed in quantitative yield after 18 h at 80 °C, as indicated by ^{19}F NMR spectroscopy. Difluoroacetylation of phenylboronic acid with **1a** proceeded equally well at 80 °C in various solvents (*N,N*-dimethylformamide, 1,4-dioxane, toluene) by using 3 mol% of $Pd(OAc)_2$ in combination with 6 mol% of PCy_3 as an optimal catalyst system (Table S2 in Supporting Information). Then, we were keen to set up catalytic conditions with an emphasis on the identification of catalysts and reaction conditions amenable to standard bench-top protocols obviating the need for Schlenk or glovebox techniques (Table 1). Importantly, the reaction proved amenable to set-up on the bench top, using $Pd(OAc)_2$ with the air-stable $PCy_3{\cdot}HBF_4$ salt in the presence of triethylamine (12 mol%) that releases the free phosphine. The desired ketone was formed in 94% yield after 18 h at 80 °C in DMF. A screening of the solvents indicated that DMF was the best solvent for carrying out the cross-coupling reaction without the use of any air-free techniques. Other solvents, including 1,4-dioxane and toluene, provide much lower conversions (Table 1, entries 4–7).[29] Notably, further screening of Pd-based catalysts and ligands including phosphorous and nitrogen-based bidentate ligands did not allow for the identification of other effective catalytic systems (Table 1, entries 10–14). Lastly, neopentyl phenylboronic ester was also evaluated but proved unreactive under these conditions (Table 1, entry 15). However, the same cross-coupling reaction proceeded efficiently in the presence of 2 equivalents of $B(OH)_3$ (Table 1, entry 16).[8a]

Table 1. Selected optimization experiments for difluoroacetylation of phenylboronic acid with 1a under bench-top conditions.[a]



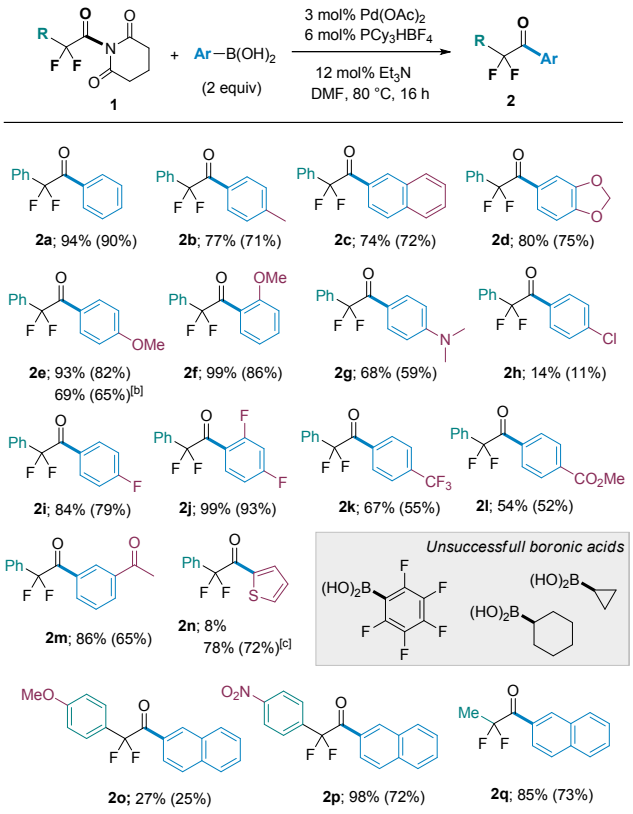
Entry	Deviation from standard conditions	Yield (%)[b]
1	None	94 (99)
2	PCy_3 instead of $PCy_3{\cdot}HBF_4/Et_3N$	<5 (99)
3	Without $PCy_3{\cdot}HBF_4/Et_3N$	31 (65)
4	1,4-dioxane instead of DMF	24 (97)
5	Toluene instead of DMF	8 (90)
6	NMP instead of DMF	19
7	MeCN, THF, DMSO, or DMAc instead of DMF	<5
8	1 equiv of Et_3N	36
9	25 °C instead of 80 °C	10
10	$nBu_3P{\cdot}HBF_4$ instead of $PCy_3{\cdot}HBF_4$	<5
11	Dcype·2HBF_4 (3 mol%) instead of $PCy_3{\cdot}HBF_4$	<5
12	PPh_3 instead of $PCy_3{\cdot}HBF_4/Et_3N$	<5
13	Pd-PEPPSI-IPr instead of $Pd(OAc)_2/PCy_3{\cdot}HBF_4/Et_3N$	<5
14	Bipy (3 mol%) instead of $PCy_3{\cdot}HBF_4/Et_3N$	<5
15	PhBnep/$Pd(PCy_3)_2$ (5 mol%) instead of $PhB(OH)_2/Pd(OAc)_2/PCy_3{\cdot}HBF_4/Et_3N$	(1.5)
16	PhBnep/$B(OH)_3$ (2 equiv)/$Pd(PCy_3)_2$ (5 mol%) instead of $PhB(OH)_2/Pd(OAc)_2/PCy_3{\cdot}HBF_4/Et_3N$	(87)

[a] Reactions performed on 0.5 mmol scale in 2 mL of solvent. Yields were determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. Dcype = 1,2-Bis(dicyclohexylphosphino)ethane; bipy = 2,2'-bipyridine; Pd-PEPPSI-IPr = [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (3-chloropyridyl)palladium(II) dichloride; nep = neopentyl glycolato. [b] Yields in parentheses refer to reactions performed under inert atmosphere of a glovebox (0.25 mmol scale; 1 mL of solvent)

Scope and limitations of the protocol

Having established optimal reaction conditions, we screened the scope of the reaction (Table 2). The cross-coupling reaction proceeded well with a diversity of arylboronic acids bearing electron-donating and electron-withdrawing groups (**2a**-**2m**). Remarkably, the yields were not affected by the steric hindrance of *ortho*-substituted substrates. Various substituents and functional groups were tolerated, including carboxylic ester and ketone, thus offering opportunities for further diversification. The reactivity of halide-substituted arylboronic acids was also examined, including base-sensitive[19a] polyfluorophenyl derivatives. Pleasingly, mono- and bis-fluorinated arylketones (**2i** and **2j**, respectively) were formed in high yield, but production of the corresponding pentafluoroaryl derivative proved unsuccessful. One notable exception to the general good behavior of arylboronic acids in this reaction was the *p*-chloro-substituted derivative that only afforded low yields of the desired arylketone (**2h**).[22] Gratifyingly, inherently unstable 2-heterocyclic boronic acids[30] also proved suitable substrates under inert atmosphere as illustrated with the synthesis of 2-thiophenyl ketone **2n**. Disappointingly, however, alkylboronic acids remained reluctant to participate in the cross-coupling reaction. Next we briefly investigated the scope of *N*-(α-arylacetyl)-glutarimides with a special emphasis on the effect of *para* substituents in the α-aryl moiety. Notably, substrates with electron-withdrawing *para* substituents afforded the products (**2p**) in higher yields than those bearing electron-donating substituents (**2o**). Remarkably, an α-alkyl amide (see **2q**) participated as well in the cross-coupling reaction. Overall, the method holds promise as a direct connective approach to difluoroketones that tolerates diverse substitution patterns not always accessible by other methods, notably those employing stoichiometric organometallic reagents. Finally, the robustness of this transformation was demonstrated by performing the synthesis of **2e** on a gram scale (65% isolated yield).

Table 2. Scope of the reaction.[a]



[a] Reactions performed on 0.5 mmol of **1** in 2 mL of DMF. Yields were determined by ^{19}F NMR of the crude reaction mixture using fluorobenzene as an internal standard. Isolated yields are given in parentheses. [b] Yield of gram-scale reaction. [c] Reaction performed using $Pd(PCy_3)_2$ as catalyst in toluene under inert atmosphere of a glovebox.

Synthetic potential: orthogonal functionalization

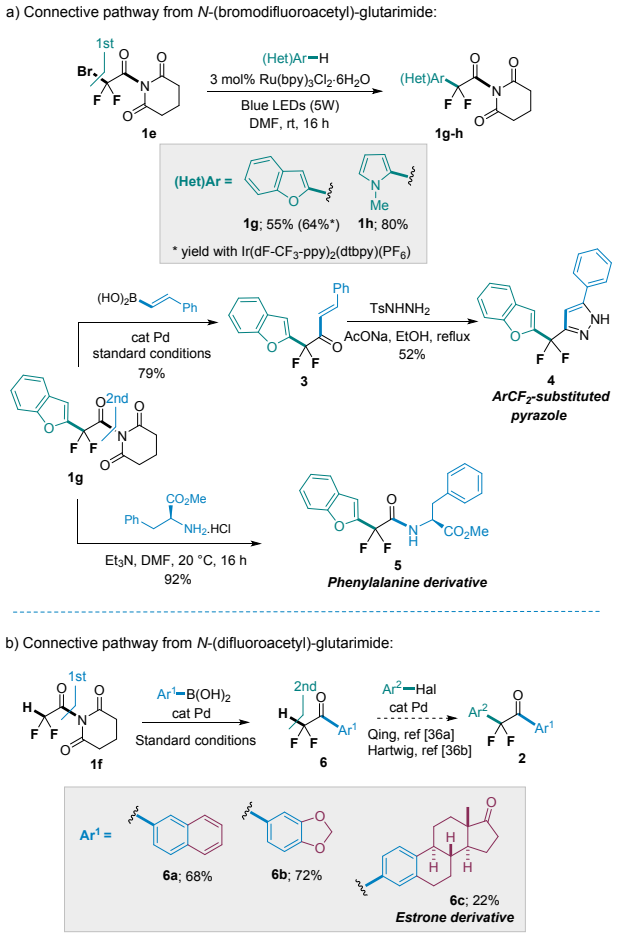
As a broader perspective in the cross-coupling reactions of α,α-difluoroacetamides, we conceived that *N*-(bromodifluoroacetyl)-glutarimide (**1e**) could possibly serve as a useful template that would offer orthogonal connective pathways to α-(hetero)aryl-α,α-difluoroketones by combining alkylation and acetylation steps through successive C–Br and C–N bond cleavage processes (Scheme 3a). To evaluate the feasibility of this design, we selected as first strategic bond

connecting pathway the photo-induced CF_2 radical-based approach that will ensure mechanistic discrimination between the two reactive sites through selective activation of the C–Br bond. Most delightedly, exploratory experiments indicated that *N*-glutarimide-derived bromodifluoroacetamide **1e** could be used as an effective difluoroalkylation reagent of 2,3-benzofuran and *N*-methylpyrrole, and most importantly under base-free conditions.[31] A brief optimization study revealed that the C–H bond *gem*-difluoroalkylation of these heteroarenes with **1e** proceeds selectively in DMF as the solvent using either Ru- or Ir-based photocatalysts (*i.e.,* $Ru(bpy)_3Cl_2{\cdot}6H_2O$; $Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)(PF_6)$) under the illumination of 5W blue light-emitting diodes (LEDs) to give access to the desired *N*-(α-heteroaromatic α,α-difluoroacetyl)-glutarimide derivatives (**1g-h**).

Further reactivity and synthetic applications of the difluorinated *N*-acylglutarimides were then investigated with a particular focus on target compounds of potential biological relevance (Scheme 3a). For instance, α-fluorinated α',β'-unsaturated ketones have recently attracted much interest as advanced intermediates for the synthesis of fluoroalkyl-substituted heterocycles, and most notably pyrazole-based drugs and agrochemicals. However, methods to access these compounds remain sporadic and often rely on multiple-step pathways combined with the use of specialized reagents.[32] Pleasingly, the successful participation of *trans*-β-styrylboronic acid in the cross-coupling reaction with **1g** through $C_{(acyl)}$–N bond activation provides a straightforward access to α,α-difluorinated enone **3** in good yield. The synthetic interest of 2-benzofuryl derivative **3** was illustrated by reaction with *N*-tosylhydrazine[33] to furnish valuable CF_2-linked bis-heteroarene **4**. Notably, bis-(hetero)arene difluoromethane derivatives are currently being considered as possible lipophilic, metabolically stable replacements for bis-(hetero)arene methanes in medicinal chemistry.[34] Importantly, **1g** also displayed further interesting reactivity towards catalyst-free direct transamidation reactions. These methods have recently emerged as the most attractive, though the most challenging, for amide synthesis.[35] For instance, interconversion of glutarimide to L-phenylalanine methyl ester proceeded smoothly at room temperature under catalyst-free conditions, to yield difluoroacetyl phenylalanine derivative **5**.

Finally, we envisioned that *N*-(difluoroacetyl)-glutarimide (**1f**) could also prove useful as an alternative platform for orthogonal functionalization through sequential cross-coupling connective pathways involving here C–H and C–N bond cleavage processes. Indeed, the Pd-catalyzed Buchwald-Hartwig type α-arylation of α,α-difluoroketones (HCF_2COR, **6**) with haloarenes has recently been established as a new method to access α-aryl-α,α-difluoroketones (**2**).[36] We reasoned that *N*-(α,α-difluoroacetyl)-glutarimide **1f** could then serve as a valuable synthetic precursor of the starting α,α-difluoroketones, and thereby offer a first catalytic connective pathway toward bis-arylated difluoroketones via C–N bond cleavage (Scheme 3b). To showcase the feasibility and the potential of this pathway, the cross-coupling of CF_2H-containing amide **1f** was carried out with selected examples of boronic acids, affording aryl ketones **6**, including estrone derivative **6c**. This brief survey represents, to the best of our knowledge, the first demonstration of a catalytic process allowing transfer of an intact $COCF_2H$ group from a reagent to an (hetero)arene.[37]

Scheme 3. Orthogonal functionalization as a new perspective, and synthetic applications.



CONCLUSIONS

In summary, we have developed a novel and simple synthetic access to diversely substituted α,α-difluoroketones based on palladium-catalyzed cross-coupling of difluoroacetamides with boronic acids. The mechanism of the reaction has been thoroughly investigated to gain a clear understanding of the catalytic cycle. The first step involves C–N bond oxidative addition of difluoracetamide to give difluoroacyl palladium intermediates that have been structurally authenticated. Then, the difluoroacyl palladium-amidate intermediate has been shown to rapidly undergo base-free transmetallation with boronic acids, followed by C–C bond reductive elimination to yield the desired difluoroketone selectively. The reaction proceeds under mild conditions on the bench top to provide structurally diverse α,α–difluoroketones, including $MeCF_2$- and HCF_2-ketones that are not easily accessible by other reported methodologies. We also demonstrated the synthetic potential and complementarity of this protocol by highlighting orthogonal C–Br and C–N bond functionalization of readily available α-bromo-α,α-difluoroacetamide substrates, which bring new opportunities to the field of synthetic organofluorine chemistry. Current work in our laboratory is seeking to generalize this methodology to other difluorinated carboxylic acid derivatives and to investigate the application of this approach to the development of decarbonylative cross-coupling of difluorocarbonyl substrates.

EXPERIMENTAL SECTION

Preparation of α-(hetero)aryl-α,α-difluoroketones 2. A 10 mL microwave reaction vial equipped with a magnetic stir bar was charged with palladium acetate (3 mol%; 0.015 mmol; 3.2 mg), $PCy_3{\cdot}HBF_4$ (6 mol%; 0.03 mmol; 11 mg), the selected *N*-(α-(hetero)aryl-α,α-difluoroacetyl)-glutarimide derivative (1.0 equiv; 0.5 mmol), the selected boronic acid (2.0 equiv; 1.0 mmol), triethylamine (12 mol%; 0.06 mmol; 8 µL) and dry DMF (2 mL; 0.25 M). The vial was flushed with argon and capped, and the reaction mixture was stirred for 16 h at 80 °C (aluminum heating block). The mixture was then cooled to room temperature, diluted with dichloromethane (10 mL) and washed with HCl 1N (3 x 10 mL). The organic phase was then dried over $MgSO_4$, concentrated under vacuum, and the residue subjected to silica gel flash chromatography to afford the corresponding α,α-difluoroketone.

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ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, spectral and analytical data including NMR spectra (PDF)
Crystallographic data for IIb (CIF)
Crystallographic data for IIc (CIF)

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REFERENCES

(1) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley: Chichester, 2009. (b) O'Hagan, D. Understanding Organofluorine Chemistry. An Introduction to the C–F Bond. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in Medicinal Chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (d) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. (e) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking beyond Intuition. *Science* **2007**, *317*, 1881–1886. (f) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591. (g) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acenã, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518.

(2) Selected reviews: (a) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264. (b) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. Difluoromethylation Reactions of Organic Compounds. *Chem. Eur. J.* **2017**, *23*, 14676–14701. (c) Feng, Z.; Xiao, Y.-L.; Zhang, X. Transition-Metal (Cu, Pd, Ni)-Catalyzed Difluoroalkylation via Cross-Coupling with Difluoroalkyl Halides. *Acc. Chem. Res.* **2018**, *51*, 2264–2278. For an illustrative example from our laboratory, see: (e) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. Palladium-Catalyzed $C(sp^2)$−H Alkylation of Aldehyde-Derived Hydrazones with Functionalized Difluoromethyl Bromides. *Angew. Chem. Int. Ed.* **2016**, *55*, 1885–1889.

(3) (a) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. Controlled Fluoroalkylation Reactions by Visible-Light Photoredox Catalysis. *Acc. Chem. Res.* **2016**, *49*, 2284–2294. (b) Lemos, A.; Lemaire, C.; Luxen, A. Progress in Difluoroalkylation of Organic Substrates by Visible Light Photoredox Catalysis. *Adv. Synth. Catal.* **2019**, *361*, 1500–1537.

(4) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress toward the Introduction of Functionalized Difluoromethylated Building Blocks onto $C(sp^2)$ and C(sp) Centers. *Chem. Eur. J.* **2015**, *21*, 12836–12865.

(5) For an up-to-date overview of the preparation, use, and biological activity of α,α-difluoroketones, see: Pattison, G. Methods for the Synthesis of α,α-Difluoroketones. *Eur. J. Org. Chem.* **2018**, *2018*, 3520–3540.

(6) For illustrative examples, see: (a) Arlow, S. I.; Hartwig, J. F. Synthesis of Aryldifluoroamides by Copper-Catalyzed Cross-Coupling. *Angew. Chem. Int. Ed.* **2016**, *55*, 4567–4572. (b) Ge, S.; Arlow, S. I.; Mormino, M. G.; Hartwig, J. F. Pd-Catalyzed α-Arylation of Trimethylsilyl Enolates of α,α-Difluoroacetamides. *J. Am. Chem. Soc.* **2014**, *136*, 14401–14404. (c) Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. Concise Preparation of 2,2-Difluorohomopropargyl Carbonyl Derivatives. Application to the Synthesis of 4,4-Difluoroisoquinolinone Congeners. *J. Org. Chem.* **2008**, *73*, 2656–2661.

(7) For selected reviews on C–N and C–O bond activation, see: (a) Meng, G.; Shi, S.; Szostak, M. Cross-Coupling of Amides by N–C Bond Activation. *Synlett* **2016**, *27*, 2530–2540. (b) Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc. Rev.* **2017**, *46*, 5864–5888. (c) Dander, J. E.; Garg, N. K. Breaking Amides Using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413–1423. (d) Guo, L.; Rueping, M. Decarbonylative Cross-Couplings: Nickel Catalyzed Functional Group Interconversion Strategies for the Construction of Complex Organic Molecules. *Acc. Chem. Res.* **2018**, *51*, 1185–1195. (e) Liu, C.; Szostak, M. Decarbonylative Cross-Coupling of Amides. *Org. Biomol. Chem.* **2018**, *16*, 7998–8010. (f) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)–NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N–C/O–C Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589–2599. (g) Chaudhari, M. B.; Gnanaprakasam, B. Recent Advances in the Metal-Catalyzed Activation of Amide Bonds. *Chem. Asian J.* **2019**, *14*, 76–93. (h) Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. *N* -Boc-Amides in Cross-Coupling Reactions. *Chem. Eur. J.* **2019**, *25*, 2663–2674. For C–F bond activation: (i) Keaveney, S. T.; Schoenebeck, F. Palladium-Catalyzed Decarbonylative Trifluoromethylation of Acid Fluorides. *Angew. Chem. Int. Ed.* **2018**, *57*, 4073-4077. (j) Blanchard, N.; Bizet, V. Acid Fluorides in Transition-Metal Catalysis: A Good Balance between Stability and Reactivity. *Angew. Chem. Int. Ed.* **2019**, *58*, 6814–6817.

(8) (a) Meng, G.; Szostak, M. Sterically Controlled Pd-Catalyzed Chemoselective Ketone Synthesis via N–C Cleavage in Twisted Amides. *Org. Lett.* **2015**, *17*, 4364–4367. (b) Meng, G.; Szostak, M. Palladium-Catalyzed Suzuki-Miyaura Coupling of Amides by Carbon-Nitrogen Cleavage: General Strategy for Amide N–C Bond Activation. *Org. Biomol. Chem.* **2016**, *14*, 5690–5707.

(9) Li, X.; Zou, G. Acylative Suzuki Coupling of Amides: Acyl-Nitrogen Activation via Synergy of Independently Modifiable Activating Groups. *Chem. Commun.* **2015**, *51*, 5089–5092.

(10) Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-Catalysed Suzuki-Miyaura Coupling of Amides. *Nat. Chem.* **2016**, *8*, 75–79.

(11) For a recent review of acylative Suzuki-Miyaura cross-coupling reactions, see: Buchspies, J.; Szostak, M. Recent Advances in Acyl Suzuki Cross-Coupling. *Catalysts* **2019**, *9*, 53.

(12) It is of note that the reactivity of perfluoroacetic anhydrides and aryl esters towards Pd and Ni complexes has been investigated through stoichiometric studies: (a) Maleckis, A.; Sanford, M. S. Catalytic Cycle for Palladium-Catalyzed Decarbonylative Trifluoromethylation Using Trifluoroacetic Esters as the CF_3 Source. *Organometallics* **2014**, *33*, 2653–2660. (b) Maleckis, A.; Sanford, M. S. Synthesis of Fluoroalkyl Palladium and Nickel Complexes via Decarbonylation of Acylmetal Species. *Organometallics* **2014**, *33*, 3831–3839. (c) Nagayama, K.; Shimizu, I.; Yamamoto, A. Oxidative Addition of Aryl and Benzyl Trifluoroacetates to Zerovalent Palladium Complexes with Two Modes of C–O Bond Cleavage Processes. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799–803. For a single report of a catalytic process dealing with perfluoroacetylation, see: (d) Kakino, R.; Shimizu, I.; Yamamoto, A. Synthesis of Trifluoromethyl Ketones by Palladium-Catalyzed Cross-Coupling Reaction of Phenyl Trifluoroacetate with Organoboron Compounds. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371–376.

(13) (a) Andersen, T. L.; Frederiksen, M. W.; Domino, K.; Skrydstrup, T. Direct Access to α,α-Difluoroacylated Arenes by Palladium-Catalyzed Carbonylation of (Hetero)Aryl Boronic Acid Derivatives. *Angew. Chem. Int. Ed.* **2016**, *55*, 10396–10400. (b) Yin, H.; Kumke, J. J.; Domino, K.; Skrydstrup, T. Palladium Catalyzed Carbonylative Coupling of Alkyl Boron Reagents with Bromodifluoroacetamides. *ACS Catal.* **2018**, *8*, 3853–3858.

(14) (a) Zhao, H.-Y.; Feng, Z.; Luo, Z.; Zhang, X. Carbonylation of Difluoroalkyl Bromides Catalyzed by Palladium. *Angew. Chem. Int. Ed.* **2016**, *55*, 10401–10405. For a more recent example using Ni catalysts that operate via a distinctive pathway, see: (b) Zhao, H.-Y.; Gao, X.; Zhang, S.; Zhang, X. Nickel-Catalyzed Carbonylation of Difluoroalkyl Bromides with Arylboronic Acids. *Org. Lett.* **2019**, *21*, 1031–1036. For seminal work by Zhang on the cross-coupling of difluoroalkyl halides with boronic acids, see : c) Xiao, Y.-L.; Guo, W.-H.; He, G.-Z.; Pan, Q.; Zhang, X. Nickel-Catalyzed Cross-Coupling of Functionalized Difluoromethyl Bromides and Chlorides with Aryl Boronic Acids: A General Method for Difluoroalkylated Arenes. *Angew. Chem. Int. Ed.* **2014**, *53*, 9909–9913.

(15) Fu, X.-P.; Xue, X.-S.; Zhang, X.-Y.; Xiao, Y.-L.; Zhang, S.; Guo, Y.-L.; Leng, X.; Houk, K. N.; Zhang, X. Controllable Catalytic Difluorocarbene Transfer Enables Access to Diversified Fluoroalkylated Arenes. *Nat. Chem.* **2019**, *11*, 948–956.

(16) Cordaro, J. G.; Bergman, R. G. Dissociation of Carbanions from Acyl Iridium Compounds: An Experimental and Computational Investigation. *J. Am. Chem. Soc.* **2004**, *126*, 16912–16929.

(17) (a) Meng, G.; Szostak, M. General Olefin Synthesis by the Palladium-Catalyzed Heck Reaction of Amides: Sterically Controlled Chemoselective N–C Activation. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518–14522. (b) Shi, S.; Meng, G.; Szostak, M. Synthesis of Biaryls through Nickel-Catalyzed Suzuki-Miyaura Coupling of Amides by Carbon-Nitrogen Bond Cleavage. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959–6963. (c) Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Structures of Highly Twisted Amides Relevant to Amide N−C Cross-Coupling: Evidence for Ground-State Amide Destabilization. *Chem. Eur. J.* **2016**, *22*, 14494–14498. (d) Shi, S.; Szostak, M. Efficient Synthesis of Diaryl Ketones by Nickel-Catalyzed Negishi Cross-Coupling of Amides by Carbon-Nitrogen Bond Cleavage at Room Temperature Accelerated by a Solvent Effect. *Chem. Eur. J.* **2016**, *22*, 10420–10424. (e) Szostak, R.; Szostak, M. *N*-Acyl-Glutarimides: Resonance and Proton Affinities of Rotationally-Inverted Twisted Amides Relevant to N–C(O) Cross-Coupling. *Org. Lett.* **2018**, *20*, 1342–1345. (f) Meng, G.; Szostak, M. *N*-Acyl-Glutarimides: Privileged Scaffolds in Amide N–C Bond Cross-Coupling. *Eur. J. Org. Chem.* **2018**, *2018*, 2352–2365 (review).

(18) For SM cross-coupling reactions with aryl diazonium electrophiles, see: Chen, L.; Sanchez, D. R.; Zhang, B.; Carrow, B. P. "Cationic" Suzuki–Miyaura Coupling with Acutely Base-Sensitive Boronic Acids. *J. Am. Chem. Soc.* **2017**, *139*, 12418–12421.

(19) For SM cross-coupling reactions with acyl or vinyl fluoride electrophiles, see: (a) Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. Base-Free Nickel-Catalysed Decarbonylative Suzuki–Miyaura Coupling of Acid Fluorides. *Nature* **2018**, *563*, 100–104. (b) Ohashi, M.; Saijo, H.; Shibata, M.; Ogoshi, S. Palladium-Catalyzed Base-Free Suzuki-Miyaura Coupling Reactions of Fluorinated Alkenes and Arenes via a Palladium Fluoride Key Intermediate. *Eur. J. Org. Chem.* **2013**, *2013*, 443–447.

(20) Mechanistic information on the amide C–N bond oxidative addition with palladium rely on computational studies, see: (a) Li, G.; Lei, P.; Szostak, M.; Casals-Cruañas, E.; Poater, A.; Cavallo, L.; Nolan, S. P. Mechanistic Study of Suzuki-Miyaura Cross-Coupling Reactions of Amides Mediated by [Pd(NHC)(Allyl)Cl] Precatalysts. *ChemCatChem* **2018**, *10*, 3096–3106. (b) Zhou, T.; Ji, C. L.; Hong, X.; Szostak, M. Palladium-Catalyzed Decarbonylative Suzuki-Miyaura Cross-Coupling of Amides by Carbon-Nitrogen Bond Activation. *Chem. Sci.* **2019**, *10*, 9865–9871 or in-situ MS-experiments, see ref [8a].

(21) For computational investigations with nickel, see: (a) Ji, C.-L.; Hong, X. Factors Controlling the Reactivity and Chemoselectivity of Resonance Destabilized Amides in Ni-Catalyzed Decarbonylative and Nondecarbonylative Suzuki-Miyaura Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 15522–15529. A single example of structural characterization of acyl nickel(II) complex ensuing from acyl C–N bond activation has been reported, see: (b) Hu, J.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. Nickel-Catalyzed Decarbonylative Borylation of Amides: Evidence for Acyl C−N Bond Activation. *Angew. Chem. Int. Ed.* **2016**, *55*, 8718–8722.

(22) See Supporting Information for details.

(23) Base-free Suzuki reaction of N,O-acetals has been shown to proceed via a boronic acid-assisted oxidative addition, see: Sylvester, K. T.; Wu, K.; Doyle, A. G. Mechanistic Investigation of the Nickel-Catalyzed Suzuki Reaction of *N,O* -Acetals: Evidence for Boronic Acid Assisted Oxidative Addition and an Iminium Activation Pathway. *J. Am. Chem. Soc.* **2012**, *134*, 16967–16970.

(24) In the context of SM cross-coupling reactions with *N*-acyl-glutaramides, Szostak and co-workers observed a beneficial impact of $B(OH)_3$ additive, which was proposed to facilitate the C–N bond cleavage via Lewis acidic assistance, see ref [8a].

(25) NMR data consistent with those of previously reported fluoroacyl-Pd complexes. See refs [12a, 12c], and Nagayama, K.; Kawataka, F.; Sakamoto, M.; Shimizu, I.; Yamamoto, A. Preparation of Acyl(Carboxylato)Bis(Tertiary Phosphine)Palladium(II) Complexes by C–O Bond Cleavage of Carboxylic Anhydrides on Interaction with Palladium(0) Complexes. Catalytic Hydrogenation of Carboxylic Anhydrides to Aldehydes by Palladium Complexes. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 573–580.

(26) A single example of Platinum(II) perfluoroacyl complex has been structurally characterized, see: Wicht, D. K.; Glueck, D. S.; Liable-Sands, L. M.; Rheingold, A. L. Terminal Platinum(II) Perfluoroacyl Phosphido Complexes: Synthesis and Dynamic Processes. *Organometallics* **1999**, *18*, 5130–5140.

(27) CCDC 1958225 (**IIb**) and CCDC 1958226 (**IIc**) contain the supplementary crystallographic data for this paper. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(28) Notably, in these conditions the product of decarbonylative cross-coupling was detected in 29% spectroscopic yield, see SI.

(29) For a discussion on the beneficial effect of DMF solvent on the generation and stabilization of Pd(0) species see: Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slattery, J. M. Solvent Effects in Palladium Catalysed Cross-Coupling Reactions. *Green Chem.* **2019**, *21*, 2164–2213.

(30) (a) Billingsley, K.; Buchwald, S. L. Highly Efficient Monophosphine-Based Catalyst for the Palladium-Catalyzed Suzuki−Miyaura Reaction of Heteroaryl Halides and Heteroaryl Boronic Acids and Esters. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963 and references cited therein.

(31) For a previous report on the photo-catalyzed (hetero)arylation of halodifluoroacetamides, see: Wang, L.; Wei, X.-J.; Jia, W.-L.; Zhong, J.-J.; Wu, L.-Z.; Liu, Q. Visible-Light-Driven Difluoroacetamidation of Unactive Arenes and Heteroarenes by Direct

C–H Functionalization at Room Temperature. *Org. Lett.* **2014**, *16*, 5842–5845.

(32) (a) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. Synthesis of Diversely Fluorinated Pyrazoles as Novel Active Agrochemical Ingredients. *J. Fluorine Chem*. **2013**, *152*, 2–11. (b) Fustero, S.; Simón-Fuentes, A.; Delgado, O.; Román, R. Fluorinated Pyrazoles and Indazoles. In *Fluorine in Heterocyclic Chemistry;* Nenajdenko, V., Ed.; Springer: Cham, *Vol 1*, **2014**, pp 279–321. (c) Sloop, J. C.; Holder, C.; Henary, M. Selective Incorporation of Fluorine in Pyrazoles. *Eur. J. Org. Chem.* **2015**, *2015*, 3405–3422. (d) Schmitt, E.; Rugeri, B.; Panossian, A.; Vors, J.-P.; Pazenok, S.; Leroux, F. R. In Situ Generated Fluorinated Iminium Salts for Difluoromethylation and Difluoroacetylation. *Org. Lett.* **2015**, *17*, 4510–4513. See also: (e) Trost, B. M.; Tracy, J. S.; Yusoontorn, T. Vanadium-Catalyzed Coupling of Allenols with Electrophilic Halide Sources for the Formation of α-Halo-α′,β′-Unsaturated Ketones. *Org. Lett.* **2019**, *21*, 1207–1211 and references cited therein.

(33) Wang, Y.; Han, J.; Chen, J.; Cao, W. An Efficient Route to 3-Trifluoromethylpyrazole via Cyclization/1,5-H Shift and Its Applications in the Synthesis of Bioactive Compounds. *Tetrahedron* **2015**, *71*, 8256–8262.

(34) (a) Geri, J. B.; Wade Wolfe, M. M.; Szymczak, N. K. The Difluoromethyl Group as a Masked Nucleophile: A Lewis Acid/Base Approach. *J. Am. Chem. Soc.* **2018**, *140*, 9404–9408 and references cited therein. (b) Peterson, E. A.; Teffera, Y.; Albrecht, B. K.; Bauer, D.; Bellon, S. F.; Boezio, A.; Boezio, C.; Broome, M. A.; Choquette, D.; Copeland, K. W.; Dussault, I.; Lewis, R.; Jasmine Lin, M.-H.; Lohman, J.; Liu, J.; Potashman, M.; Rex, K.; Shimanovich, R.; Whittington, D. A.; Vaida, K. R.; Harmange, J.-C. Discovery of Potent and Selective 8-Fluorotriazolopyridine c-Met Inhibitors. *J. Med. Chem.* **2015**, *58*, 2417–2430. (c) Storer, R. I.; Brennan, P. E.; Brown, A. D.; Bungay, P. J.; Conlon, K. M.; Corbett, M. S.; DePianta, R. P.; Fish, P. V.; Heifetz, A.; Ho, D. K. H.; Jessiman, A. S.; McMurray, G.; de Oliveira, C. A. F.; Roberts, L. R.; Root, J. A.; Shanmugasundaram, V.; Shapiro, M. J.; Skerten, M.; Westbrook, D.; Wheeler, S.; Whitlock, G. A.; Wright. J. Multiparameter Optimization in CNS Drug Discovery: Design of Pyrimido[4,5-*d*]Azepines as Potent 5-Hydroxytryptamine 2C (5-HT_{2C}) Receptor Agonists with Exquisite Functional Selectivity over 5-HT_{2A} and 5-HT_{2B} Receptors. *J. Med. Chem.* **2014**, *57*, 5258–5269.

(35) For leading references, see: (a) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N–C/O–C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161–11172. (b) Li, G.; Szostak, M. Highly Selective Transition-Metal-Free Transamidation of Amides and Amidation of Esters at Room Temperature. *Nat. Commun.* **2018**, *9*, 4165. (c) Liu, Y.; Achtenhagen, M.; Liu, R.; Szostak, M. Transamidation of N-Acyl-Glutarimides with Amines. *Org. Biomol. Chem.* **2018**, *16*, 1322–1329.

(36) (a) Guo, C.; Wang, R.-W.; Qing, F.-L. Palladium Catalyzed Direct α-Arylation of α,α-Difluoroketones with Aryl Bromides. *J. Fluorine Chem.* **2012**, *143*, 135–142. (b) Ge, S.; Chaładaj, W.; Hartwig, J. F. Pd-Catalyzed α-Arylation of α,α-Difluoroketones with Aryl Bromides and Chlorides. A Route to Difluoromethylarenes. *J. Am. Chem. Soc.* **2014**, *136*, 4149–4152.

(37) Another direct, catalytic access to α,α-difluoromethyl aryl ketones ($ArCOCF_2H$) from arylboronic acids has just been reported, based on the use of diethyl bromodifluoromethylphosphonate as a fluorine source: see ref [15].

Abstract:

Difluoroacetamides are established as difluoroacetylation reagents through Pd-catalyzed C_{acyl}–N bond cleavage, and effectively participate in base-free SM cross-coupling reactions to afford high-value α,α-difluoroketones. Mechanistic studies allowed the structural characterization of oxidative addition-derived fluoroacyl-Pd^{II} intermediates. Insight into possible applications to orthogonal C–Br and C–N bond functionalization of α-bromodifluoroacetamides is also provided.