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Palladium-Catalyzed Fluoroalkylative Cyclization of Olefins

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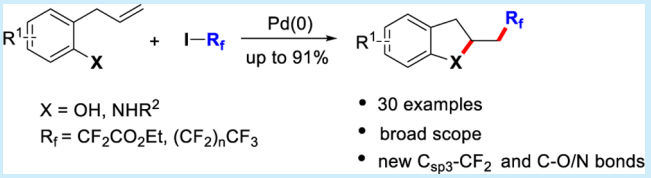
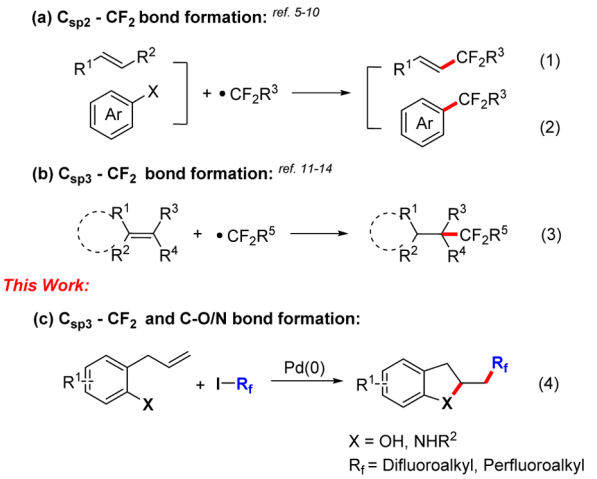
Supporting Information

ABSTRACT: A palladium-catalyzed fluoroalkylative cyclization of olefins with readily available R_f—I reagents to afford the corresponding fluoroalkylated 2,3-dihydrobenzofuran and indolin derivatives with moderate to excellent yields is reported. This novel procedure provides an efficient method for the construction of C_{sp^3}—CF_2 and C—O/N bonds in one step. A wide range of functional groups are tolerated. It is proposed that a radical/SET (single electron transfer) pathway proceeding via the fluoroalkyl radical may be involved in the catalytic cycle.



Motivated by diverse applications in agrochemistry, pharmacy, and materials science, substantial efforts have been dedicated to the development of efficient protocols of organofluorine compounds.[1] Among the commonly encountered fluoroalkyl groups, the difluoromethylene (CF_2) moiety has been tremendously investigated in recent years owing to its unique applications in drug discovery and life science.[2,3] For instance, it can be served as a potential bioisostere of hydroxyl or thiol groups, as well as a carbonyl group.[3] Given the importance of the CF_2 functional moiety in synthetic and medicinal chemistry, significant recent efforts have been reported for the new synthetic procedures.[4] Recently, the transition-metal based protocols have been focused on the exploration of the efficient C_{sp^2}—CF_2 bond formation via cross-coupling with aryl boronic acid,[5] aryl halides,[6] heteroaryl C—H bonds,[7] styrenes,[8] and α,β-unsaturated carboxylic acids (Scheme 1, eqs 1 and 2).[9] More recently in 2016, elegant works of different transition-metals-induced C_{sp^2}—H difluoromethylation of aldehyde-derived hydrazones to afford the functionalized difluoromethylketone hydrazones have been reported, with some evidence for a SET-initiated radical process.[10] Compared with interest in the construction of C_{sp^2}—CF_2 bonds, method development for C_{sp^3}—CF_2 bond generation has received less attention (Scheme 1, eq 3).[11] In 2013, Wolf and co-workers documented that copper(II)-induced addition of α,α-difluoroenolates to aldehydes with high yields and *ee* values.[12] Efficient Mukaiyama—Michael addition of fluorinated enol silyl ethers to tetrasubstituted olefins catalyzed by a chiral secondary amine phosphoramide was proposed by Zhou group in 2015.[13] Previously, the silver-mediated C_{sp^3}—CF_2 bond formation procedure has been investigated by the Hao group.[14] However, despite a variety of significant advances for the construction of C_{sp^2}—CF_2 (or C_{sp^3}—CF_2) bonds, there are fewer protocols for C—CF_2 and C—X (X = heteroatom) bonds in a one-step synthesis. In 2015, the Stephenson group established a new approach for the halodifluoromethylation of alkenes via visible light photoredox catalysis.[15] Afterward, an efficient intramolecular amino- and oxydifluoromethylation process of unactivated alkenes with HCF_2SO_2Cl as the HCF_2 radical source by photoredox-catalyzed was proposed by the Dolbier group.[16] Hence, it is highly desirable to explore a general and practical method for construction of C—CF_2 and C—C/X bonds.

Scheme 1. Methods for Incorporation of Fluoroalkyl Groups



Inspired by these advances and based on our previous work,[17] we envisioned that since oxidative addition of iododifluoromethyl reagents to Pd(0) is feasible, then electrophilic palladation of alkenes with the resulting Pd(II) complex by a subsequent nucleophile reaction might represent a possible alternative strategy to realize the construction of C_{sp^3}—CF_2 and C—O/N bonds in a one-step manner. Fortunately, a palladium-catalyzed

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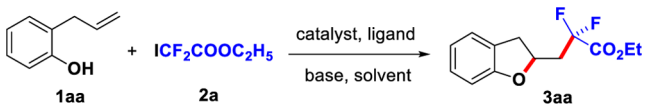
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	base	solvent	yield[b] (%)
1	$Pd_2(dba)_3$	Xantphos[c]	K_2CO_3	dioxane	31
2	$PdCl_2(CH_3CN)_2$	Xantphos	K_2CO_3	dioxane	48
3	$PdCl_2(PPh_3)_2$	Xantphos	K_2CO_3	dioxane	28
4	$Pd(PPh_3)_4$	Xantphos	K_2CO_3	dioxane	50
5	$Pd(PPh_3)_4$	DPEPhos[d]	K_2CO_3	dioxane	55
6	$Pd(PPh_3)_4$	PPh_3	K_2CO_3	dioxane	56
7	$Pd(PPh_3)_4$	dppe[e]	K_2CO_3	dioxane	60
8	$Pd(PPh_3)_4$	dppf[f]	K_2CO_3	dioxane	65
9	$Pd(PPh_3)_4$	dppf	Cs_2CO_3	dioxane	54
10	$Pd(PPh_3)_4$	dppf	*t*-BuOK	dioxane	10
11	$Pd(PPh_3)_4$	dppf	Et_3N	dioxane	65
12	$Pd(PPh_3)_4$	dppf	CF_3CO_2Na	dioxane	25
13	$Pd(PPh_3)_4$	dppf	NaOAc	dioxane	28
14	**$Pd(PPh_3)_4$**	**dppf**	**KOAc**	**dioxane**	**78**
15	$Pd(PPh_3)_4$	dppf	K_3PO_4	dioxane	69
16	$Pd(PPh_3)_4$	dppf	CsOAc	dioxane	57
17	$Pd(PPh_3)_4$	dppf	LiOAc	dioxane	trace

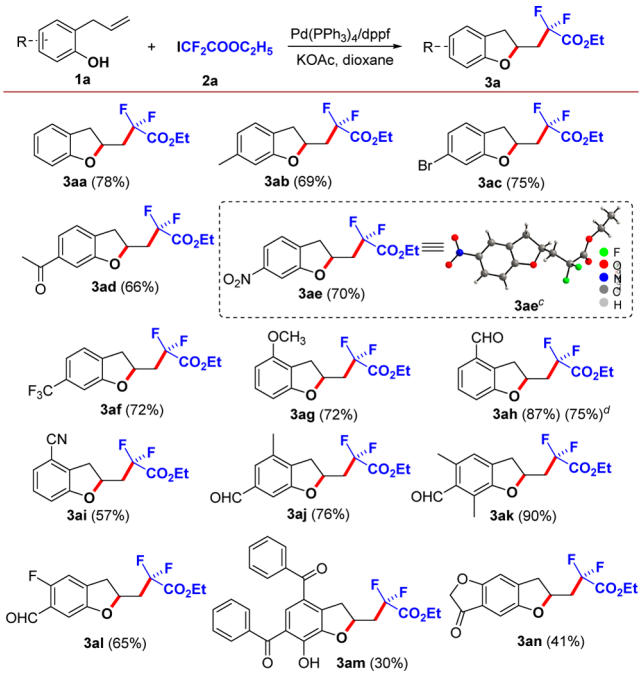
[a]A mixture of **1aa** (0.15 mmol, 1 equiv), **2a** (0.3 mmol, 2 equiv), base (0.3 mmol, 2 equiv), catalyst (7.5 mol %), ligand (15 mol %), and solvent (3 mL) were sealed in a 25 mL Schlenk tube at 80 °C for 20 h under N_2. [b]Yields of the isolated product. [c]Xantphos = dimethylbisdiphenylphosphinoxanthene. [d]DPEPhos = bis[2-(diphenylphosphino)phenyl] ether. [e]dppe = 1,2-bis(diphenylphosphino) ethane. [f]dppf = 1,1′-bis(diphenylphosphino) ferrocene.

coupling of alkenes with iodofluoroalkylated reagents which affords a variety of dihydrobenzofuran and indoline derivatives has been developed (Scheme 1, eq 4).

We initiated our investigations using 2-allylphenol **1aa** with ethyl iododifluoroacetate **2a** as the substrates. The combination of **1aa**, $Pd_2(dba)_3$, Xantphos, and K_2CO_3 in dioxane at 80 °C for 20 h under a nitrogen atmosphere afforded a modest yield (31%) of the desired product **3aa** (Table 1, entry 1). And the major byproduct of this transformation is unreacted starting material. To improve the yield of **3aa**, various catalysts were screened. Delightfully, the use of $Pd(PPh_3)_4$ was more effective with the moderate yield of 50% (Table 1, entry 4). Using dppf as a ligand, the optimal ligand for this transformation still provided the desired **3aa** in moderate yield (Table 1, entry 8). To complete the difluoroalkylative cyclization synthesis, a base is necessary to neutralize the acid generated in the reaction system. Thus, a range of salts were also screened. Significantly, KOAc was selected as the optimal base, giving a good yield of **3aa** (78%) (Table 1, entry 14). Additionally, the reaction is very sensitive to solvent and dioxane is much better than other solvents (see Supporting Information).

With the optimal conditions established, the remaining substrates were screened to probe the generality of the new protocol. Gratifyingly, a broad substrate scope was compatible with the method and displayed excellent chemoselectivity (Scheme 2). Good yields were obtained with *para*- and *ortho*-substituted aryls. Notably, substrates with both electron-withdrawing and -donating substituents afforded the products **3aa**−**ai** in good to excellent yields. Versatile functional groups, such as halogens, acetyl, nitro, formyl, cyano, hydroxyl, and ether were tolerated, thus offering opportunities for further transformations. Significantly, product **3ae** proved to be crystalline.[18] The relative stereochemistry of these difluoromethylative cyclization 2,3-dihydrobenzofuran derivatives were determined by means of crystallographic analysis. Notably, the multisubstituted aryls

Scheme 2. Substrate Scope of 2-Allylphenols[a,b],



[a]Reaction conditions: **1aa** (0.15 mmol, 1 equiv), **2a** (0.3 mmol, 2 equiv), KOAc (0.3 mmol, 2 equiv), $Pd(PPh_3)_4$ (7.5 mol %), dppf (15 mol %), and dioxane (3 mL) was sealed in a 25 mL Schlenk tube at 80 °C for 20 h under N_2. [b]Isolated yields based on **1a**. [c]ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3ae**. [d]Isolated yields based on **1ah** at the 1 mmol scale.

proceeded smoothly to give the corresponding products (**3aj**−**al**). Notably, the product of **3ak** has an excellent yield of up to 90%. However, the steric effect of the substituent seemed to have

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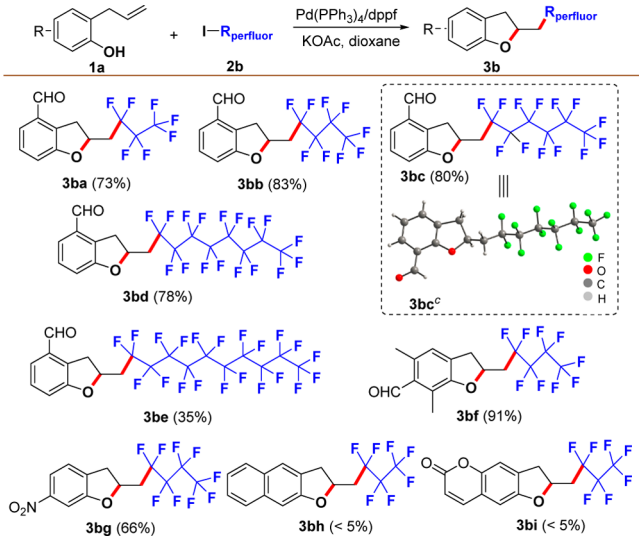
some influence on the reaction (**3am**). Importantly, the hetroaryl substrate was also compatible with the transformation (**3an**).

In view of the importance of perfluoroalkyl moieties, the possible incorporation of such groups into substrates was screened (Scheme 3). In general, perfluoroalkylated products

Scheme 3. Substrate Scope of Iodoperfluoroacetates[a,b]



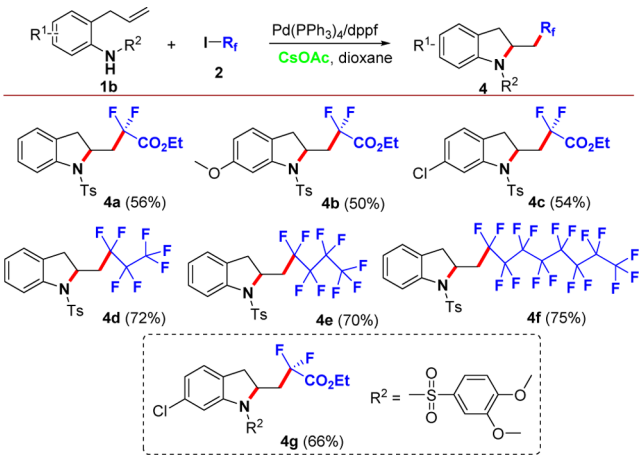
[a]Reaction conditions: **1aa** (0.15 mmol, 1 equiv), **2b** (0.3 mmol, 2 equiv), KOAc (0.3 mmol, 2 equiv), $Pd(PPh_3)_4$ (7.5 mol %), dppf (15 mol %), and dioxane (3 mL) were sealed in a 25 mL Schlenk tube at 80 °C for 20 h under N_2. [b]Isolated yields based on **1a**. [c]ORTEP representation with 50% probability thermal ellipsoids of a crystal structure of **3bc**.

could react efficiently in moderate to good yields (**3ba**–**be**) (structure **3bc** was confirmed by X-ray crystallography).[19] Interestingly, a multisubstituted aryl was successfully prepared in 91% yield (**3bf**). However, there was less tolerance for condensed ring and condensed heterocyclic substrates (**3bh**, **3bi**).

To further diversify the protocol, the substrate scope was expanded to different substituted 2-allylanilines (Scheme 4). Pleasingly, the difluoroalkylative cyclization of 2-allylanline **1ba** could undergo this transformation with a 40% yield under the optimal conditions. To complete the indolin synthesis, addition of a range of acetates was screened, which deeply affected the transformation (see Supporting Information). Ultimately, CsOAc was selected as the optimal base. With the optimized reaction conditions in hand, we assayed the reaction against a number of substituted 2-allylanlines and were pleased to observe successful fluoroalkylative cyclization products (**4a**–**4f**). Surprisingly, steric hindrance in terms of R^2-substitution also underwent the conversion smoothly to afford product **4g**.

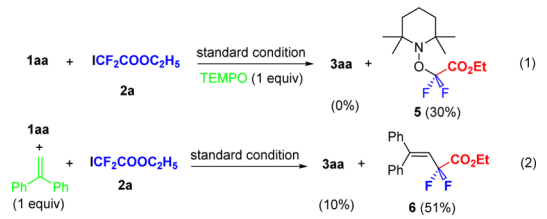
To gain some insight into the mechanism of our reaction, several control experiments were performed to investigate the possibility of a radical/SET pathway. Our standard coupling reaction of **1aa** with **2a** (78%) was thus repeated in the well-known radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 1 equiv). Interestingly, formation of product **3aa** was totally inhibited, and the TEMPO–CF_2CO_2Et adduct **5** was formed in 30% yield as estimated by ^1H, ^{13}C, and ^{19}F NMR spectroscopy (Scheme 5, eq 1). The reaction was also performed in the presence of butylated hydroxytoluene (BHT, 1 equiv) which furnished **3aa** in a diminished yield of 27% (see Supporting

Scheme 4. Substrate Scope of 2-Allylanilines[a,b]



[a]Reaction conditions: **1b** (0.15 mmol, 1 equiv), **2** (0.3 mmol, 2 equiv), CsOAc (0.3 mmol, 2 equiv), $Pd(PPh_3)_4$ (7.5 mol %), dppf (15 mol %), and dioxane (3 mL) were sealed in a 25 mL Schlenk tube at 80 °C for 20 h under N_2. [b]Isolated yields based on **1b**.

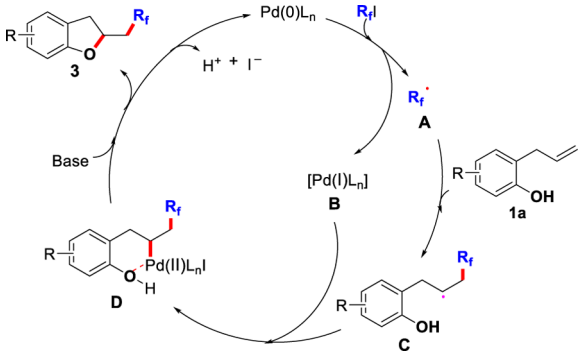
Scheme 5. Preliminary Mechanistic Studies



Information). Moreover, when 1,1-diphenylethylene (1 equiv) was used as a radical scavenger in this reaction, the product **3aa** underwent a dramatic drop in yield of 10%, with the formation of **6** in 51% yield (determined by NMR spectroscopy) (Scheme 5, eq 2). These preliminary experiments seem to confirm that a free CF_2CO_2Et radical is generated under our standard reaction conditions.

In light of these experimental results and previous work,[6−10] a plausible radical/SET pathway is outlined in Scheme 6. The

Scheme 6. Possible Mechanism



process would begin with the formation of an electrophilic fluoroalkyl radical (**A**) via a radical/SET pathway from a Pd(0) complex to ICF_2CO_2Et with concomitant generation of Pd(I) complex **B**. Subsequent electrophilic radical addition of **A** across the C=C bond of the olefins was a key step and led to the formation of the carbon free radical **C**. Further oxidation of the

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radical complex **C** with Pd(I) would lead to the Pd(II) complex **D**. Finally, reductive elimination of **D** from the α-OH group afforded the coupling product **3** and recycled the active Pd(0) catalytic species. However, an alternative pathway with Pd(0) as a radical initiator followed by an intramolecular SN_2 substitution was also possible (see Supporting Information for details). 2-Allylaniline substrates would undergo a similar mechanism.

In summary, we have presented a practical Pd(0)-catalyzed fluoroalkylative cyclization reaction of unactivated olefins from readily available ICF_2CO_2Et reagent. This novel procedure provided an efficient method for the construction of functionalized fluoroalkylation 2,3-dihydrobenzofuran and indolin derivatives in moderate to excellent yields. Remarkably, we have realized an efficient construction of C_{sp^3}–CF_2 and C–O/N bonds in a one-step manner through the straightforward conversion of olefins, and the TEMPO–CF_2CO_2Et adduct was successfully isolated. Further efforts into the mechanistic details as well as explorations of medical applications of the products are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03865.

Typical experimental procedure, characterization for all products (PDF)

Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1503833 (**3ae**) contains the supplementary crystallographic data. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(19) CCDC 1503834 (**3bc**) contains the supplementary crystallographic data. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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