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How to cite: Angew. Chem. Int. Ed. **2021**, 60, 8818–8822
International Edition: doi.org/10.1002/anie.202017365
German Edition: doi.org/10.1002/ange.202017365

Pd/Cu-Catalyzed Defluorinative Carbonylative Coupling of Aryl Iodides and *gem*-Difluoroalkenes: Efficient Synthesis of α-Fluorochalcones

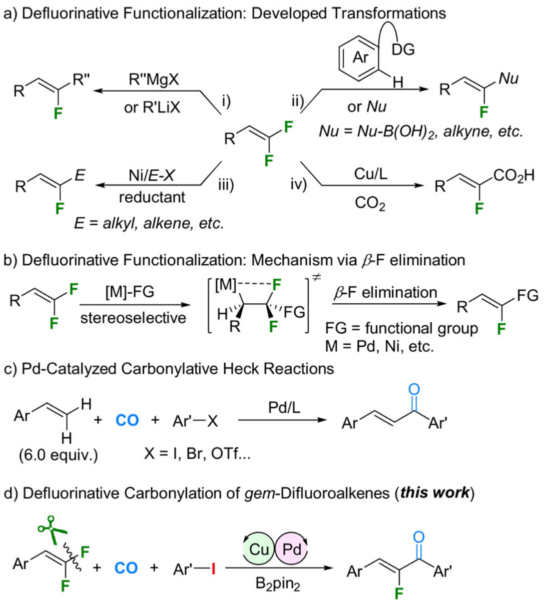
*Fu-Peng Wu, Yang Yuan, Jiawang Liu, and Xiao-Feng Wu**

Dedicated to Professor Ilhyong Ryu on the occasion of his 70th birthday

Abstract: *An unprecedented and challenging defluorinative carbonylation was achieved. Enabled by a Pd/Cu cooperative catalyst system, the first example of defluorinative carbonylative coupling has been established. With gem-difluoroalkenes and aryl iodides as the substrates, this methodology offers flexible and facile access to privileged α-fluorochalcones under mild reaction conditions in moderate-to-excellent yields. Mechanistic studies indicated transmetalation between palladium and copper intermediates as a crucial step of the catalytic cycle.*

The incorporation of a fluorine or fluorine-containing fragment into organic molecules can generally have a positive influence on physical and biological properties, such as increasing the solubility, lipophilicity, and metabolic stability of the parent molecules.[1] In particular, monofluoroalkenes have attracted considerable interests from chemical community as monofluoroalkenes exhibit a similar electronic and steric properties as amide bonds, which means fluoroalkenes are excellent mimics of peptide bonds. Monofluoroalkenes mimic of bioactive amides have been widely used to enhance biological properties.[2] However, the synthesis of monofluoroalkenes is not a trivial task.[3] In recent years, *gem*-difluoroalkene moiety has been used as an ideal precursor for the preparation of monofluoroalkenes via defluorinative functionalization.[4] For example, Fu and co-workers realized a nickel-catalyzed defluorinative reductive cross-coupling of alkyl halides with *gem*-difluoroalkenes in 2017.[5] Additionally, several other original transformation on defluorinative functionalization of *gem*-difluoroalkenes were established independently, including defluorinative nucleophilic addition,[6] cross-coupling via C–H/C–F activation,[7] reductive coupling of electrophile[8] and Cu-catalyzed defluorinative carboxylative reaction[9] [Scheme 1, Eq. (a)]. One of the key steps in these transformations is the activation of the C–F bond by β-F elimination or oxidative insertion under the assistant of directing group.[7o,p,q] To the best of our knowledge, despite these successful examples, carbonylation of C–F bond has not been realized yet. Therefore, developing a new method of defluorinative carbonylation is still desirable.

According to our research experience on carbonylation,[10] under the atmosphere of CO, the oxidative addition of C–F bond with metal center[11] usually is challenge due to the inhibitory influence of CO coordination to the metals and also the strong C–F bond energy[12] (120–129 kcal mol^{-1} for olefinic C–F bonds). More recently, Toste and their coworkers reported a palladium-catalyzed defluorinative coupling of difluoroalkenes and boronic acids.[7f] This reaction was postulated to proceed via the insertion of aryl-Pd complex into a *gem*-difluoroalkene to produce alkyl-Pd intermediate, which could deliver the final alkene product after β-F elimination [Scheme 1, Eq. (b)]. Similarly, carbonylative Heck reaction was developed and also undergo the insertion of acyl-Pd intermediate into olefin and followed by β-H elimination to give the final product [Scheme 1, Eq. (c)].[13] However, a large excess of olefins (at least 6 equiv) is typically required. Based on the above mechanistic considerations, we speculate that carbonylation of C–F bond



Scheme 1. Defluorinative functionalization.

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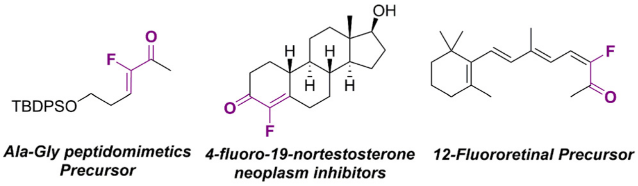


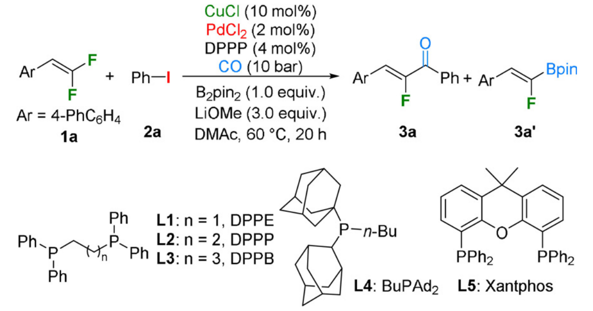
Scheme 2. Selected examples of bioactive α-fluorinated enone derivatives.

can potentially be achieved via β-F elimination with *gem*-difluoroalkenes as the substrates [Scheme 1, Eq. (d)].

On the other hand, as the products, α-fluorinated enones represent an important molecular skeleton with potent biomedical applications (Scheme 2).[14] Herein, we report a Pd/Cu catalyzed defluorinative carbonylative coupling of aryl iodides and gem-difluoroalkenes to access single isomer of α-fluorochalcones under mild reaction conditions. It is noteworthy that despite great achievements in the carbonylative coupling reactions, this work represents the first example on defluorinative carbonylation.

We commenced our studies with 4-(2,2-difluorovinyl)-1,1′-biphenyl (**1a**) and iodobenzene (**2a**) as the model substrates and the influence of all reaction parameters were systematically evaluated (see Supporting information for details). After intensive investigations, we found that the desired α-fluorochalcone **3a** can be obtained in 74% yield when CuCl/PdCl$_2$ as the catalyst, DPPP as the ligand and LiOMe as the base in presence of B$_2$pin$_2$ at 60 °C under 10 bar CO atmosphere was applied (Table 1, entry 1). The *Z*-fluorinated vinylboronate ester **3a′** was the main by-product during the process of our studies. In our control experiments, copper, palladium, and ligand were proven all essential for the success of this transformation (Table 1, entry 2). The role of B$_2$pin$_2$ and base in the reaction can not be replaced by the other reductants such as Zn or Mn (Table 1, entry 3).[7k,n] In the testing of various phosphine ligands, DPPP was found to be superior to the other tested ligands (Table 1, entries 4–7). Increasing the load of the dppp inhibited the reaction, indicating that the ligand only coordinates with palladium metal. With increased loading of phosphine ligand can improve the reaction outcome significantly, due to that excess phosphine ligand (Pd/P = 1:4) may be used to reduce Pd^{II} to Pd^0 and stabilize the active palladium species. Furthermore, different Pd and Cu precursors were studied as well. Palladium precursors have little influence on the reaction result while a slightly decreased yield was observed the other tested copper salts (Table 1, entries 9–13). The loading of B$_2$pin$_2$ is critical to the reaction, and only stoichiometric amount of B$_2$pin$_2$ can promote the catalytic cycle (Table 1, entries 14 and 15). Excess amount of B$_2$pin$_2$ can significantly reduce the yield of product **3a**, because **3a** will further react with excess B$_2$pin$_2$ to give a complexed reaction mixture (see supporting information). To our delight, 63% yield of **3a** can still be obtained under 5 bar of CO (Table 1, entry 16). Notably, this formal defluorinative carbonylation proceeded with high efficiency and high selectivity, only (*Z*)-isomer product can be detected here and confirmed by ^{19}F NMR.

Table 1: Optimization of reaction conditions.[a]

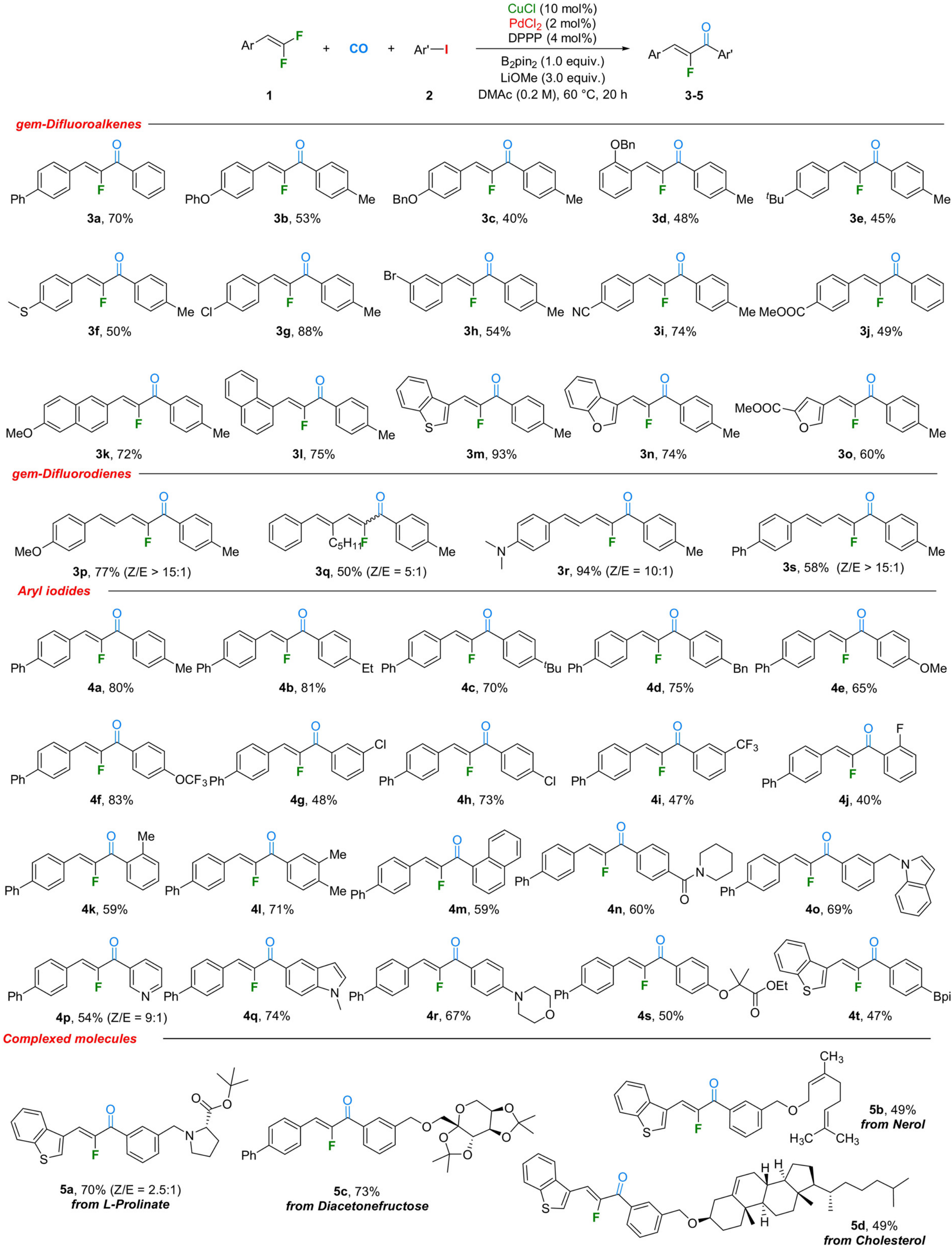


Entry	Variations from standard conditions	Yield [%][b]
1	none	74(0)
2	w/o CuCl or PdCl$_2$ or DPPP	0(31)
3	Mn or Zn instead of B$_2$pin$_2$/LiOMe	0(25)
4	**L1** instead of **L2**	27(15)
5	**L3** instead of **L2**	4(38)
6	**L4** instead of **L2**	8(16)
7	**L5** instead of **L2**	3(35)
8	DPPP (10 mol%) instead of DPPP (4 mol%)	56(21)
9	Pd(OAc)$_2$ instead of PdCl$_2$	70(0)
10	[Pd(η^3-C$_3$H$_5$)Cl]$_2$ instead of PdCl$_2$	70(0)
11	CuTc instead of CuCl	66(0)
13	CuOAc instead of CuCl	62(0)
14	0.5 equiv B$_2$pin$_2$ instead of 1.0 equiv B$_2$Pin$_2$	19(15)
15	1.5 equiv B$_2$pin$_2$ instead of 1.0 equiv B$_2$Pin$_2$	12(20)
16	CO (5 bar) instead of CO (10 bar)	63(6)

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), CuCl (10 mol%), PdCl$_2$ (2 mol%), DPPP (4 mol%), B$_2$pin$_2$ (1.0 equiv), LiOMe (3.0 equiv), CO (10 bar), DMAc (0.2 M), 60 °C, 20 h, yields were determined by GC using hexadecane as the internal standard. [b] Yield of **3a′** shown in parentheses. DMAc: *N*,*N*-dimethylformamide.

With the optimized reaction conditions in hand, we examined the scope of *gem*-difluoroalkenes and aryl iodides for this transformation. As shown in the Table 2, *gem*-difluoroalkenes spanning a range of electronic properties were tested for this process. *gem*-Difluoroalkenes bearing electron-donating groups such as *tert*-butyl, ether and sulfide afforded the corresponding α-fluorochalcones in moderate yields (**3b**–**3f**). In contrast, chloro, bromo, cyano, ester, thiophene and furan were compatible better with the reaction conditions to produce the target products in moderate to excellent yields (**3g**–**3o**). Importantly, the more challenging *gem*-difluorodienes were also suitable starting materials here, afforded the desired products with good regio- and stereoselectivity, thus greatly expanding the applicability of the reaction. Subsequently, a scope of iodobenzenes was performed. Iodobenzenes with electron-donating substituent show excellent reactivity, afforded the corresponding products in excellent yields (**4a**–**4f**). In addition, iodoarenes substituted with electron-withdrawing group such as Cl and CF$_3$ groups were also tolerated in this process, delivered the desired products in moderate yields (**4g**–**4j**). Functional groups, such as amide (**4n**), indole (**4o**, **4q**), pyridine (**4p**), morphine (**4r**) and Bpin (**4t**) were all compatible in this transformation. PhN$_2$BF$_4$, PhBr, and PhOTf was tested instead of PhI was well, but no desired product could be detected. More complexed substrates were successfully trans-

Table 2: Substrate scope of gem-difluoroalkenes and iodobenzenes.[a]



3a, 70%; **3b**, 53%; **3c**, 40%; **3d**, 48%; **3e**, 45%

3f, 50%; **3g**, 88%; **3h**, 54%; **3i**, 74%; **3j**, 49%

3k, 72%; **3l**, 75%; **3m**, 93%; **3n**, 74%; **3o**, 60%

3p, 77% (Z/E > 15:1); **3q**, 50% (Z/E = 5:1); **3r**, 94% (Z/E = 10:1); **3s**, 58% (Z/E > 15:1)

4a, 80%; **4b**, 81%; **4c**, 70%; **4d**, 75%; **4e**, 65%

4f, 83%; **4g**, 48%; **4h**, 73%; **4i**, 47%; **4j**, 40%

4k, 59%; **4l**, 71%; **4m**, 59%; **4n**, 60%; **4o**, 69%

4p, 54% (Z/E = 9:1); **4q**, 74%; **4r**, 67%; **4s**, 50%; **4t**, 47%

5a, 70% (Z/E = 2.5:1) ***from L-Prolinate***

5b, 49% ***from Nerol***

5c, 73% ***from Diacetonefructose***

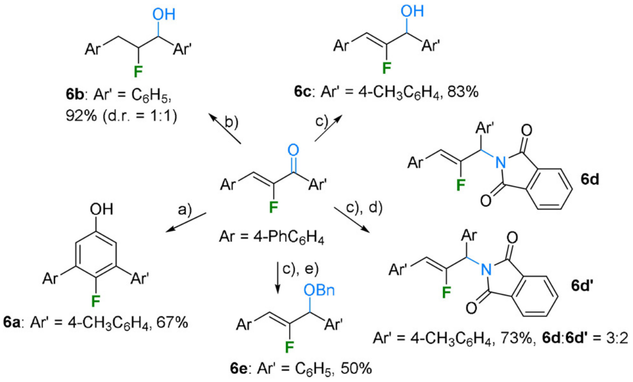
5d, 49% ***from Cholesterol***

[a] Reaction conditions: *gem*-difluoroalkenes (0.2 mmol), iodobenzenes (1.2 equiv), CuCl (10 mol%), $PdCl_2$ (2 mol%), DPPP (4 mol%), B_2pin_2 (1.0 equiv), LiOMe (3.0 equiv), CO (10 bar), DMAc (0.2 M), 60°C, 20 h, isolated yields.

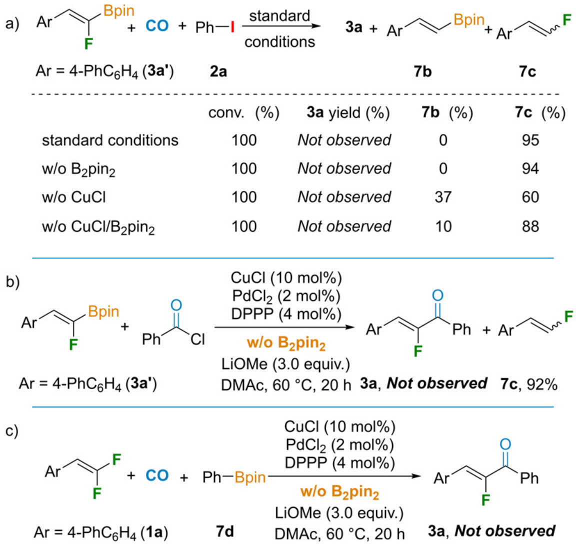
formed under our standard conditions as well, delivered the target products in moderate to good yields (**5a**–**5d**). Aliphatic *gem*-difluoroalkenes failed to deliver the corresponding product (see supporting information for more details).

In order to further demonstrate the synthetic value of this procedure, transformations of α-fluorochalcone were carried out (Scheme 3).[15] α-Fluorochalcone can be transformed into 3,5-disubstituted phenols **6a** in an one-pot manner.[15a] Furthermore, α-fluorochalcone can be reduced to alkyl alcohol **6b** or allyl alcohol **6c** under Pd/H_2 or $NaBH_4$ conditions. In addition, α-allyl alcohol can be further transformed into α-fluoroallyl amine **6d**/**6d′** and α-fluoroallyl ether **6e** in moderate yields. Good stereoselectivity were observed in these cases.

For a better mechanistic understanding of this Pd/Cu catalyzed defluorinative carbonylation, several control experiments were performed (Scheme 4). Since we observed *Z*-fluorinated vinylboronate ester **3a′** in this transformation, we are wondering whether **3a′** acts as an intermediate of the reaction. Therefore, **3a′** was prepared and subjected to the standard conditions, the desired product **3a** was not observed; instead, we detected 95 % yield of protodeboronation product **7c**. Moreover, in the case of absence of B_2pin_2/CuCl, the target product was not formed neither and trace protodefluorination product **7b** was obtained [Scheme 4, Eq. (a)]. In addition, **3a′** and benzoyl chloride failed to deliver the target product which further ruled out **3a′** as the reaction intermediate [Scheme 4, Eq. (b)]. No desired product could be detected when phenyl borate **7d** was tested with or without B_2pin_2 [Scheme 4, Eq. (c)]. These results of the experiments indicate that **3a′** and **7d** were not intermediates of the reaction. Therefore, the possibility of cascade processes seems to be ruled out. Subsequently, we speculated **7e** might be the intermediate of the reaction. Surprisingly, when **7e** was subject to this defluorinative carbonylation, the product **7f** was delivered in 40 % yield under our standard conditions (Table 3). CO/B_2pin_2 were proven to be necessary for this process. This leads to the conclusion that alkene which inserts into the acyl-Pd^{II}X species.



Scheme 3. Derivatization of α-fluorochalcone. Reaction conditions: a) ethyl 2-fluoro-3-oxobutanoate, Cs_2CO_3, MeCN, 120 °C, 4 h. b) Pd/C, H_2 (1 bar) EtOH/THF, rt, 12 h. c) $NaBH_4$ MeOH, rt, 0.5 h. d) PPh_3, imide, DIAD, THF, rt, 3 h. e) NaH, BnBr, Bu_4NI, THF, rt, 5 h.

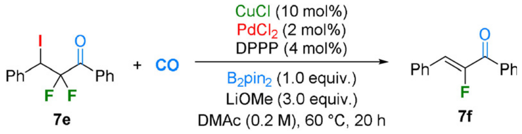


	conv. (%)	3a yield (%)	7b (%)	7c (%)
standard conditions	100	*Not observed*	0	95
w/o B_2pin_2	100	*Not observed*	0	94
w/o CuCl	100	*Not observed*	37	60
w/o CuCl/B_2pin_2	100	*Not observed*	10	88

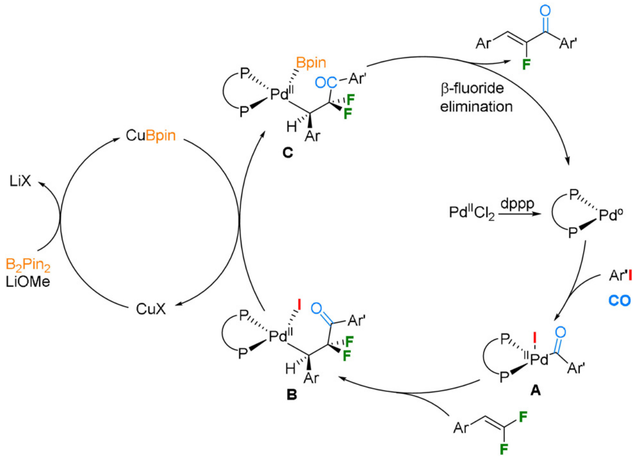
Scheme 4. Control experiments.

Based on the above experimental results and related literatures,[4–10] we proposed a possible reaction pathway for this transformation (Scheme 5). The catalytic cycle consists of two individual cycles involving copper and palladium catalysts. In the palladium cycle, under the reduction of phosphine ligand, catalytically active **L**Pd^0 complex can be produced in situ. Oxidative addition of aryl iodide to **L**Pd^0, followed by CO coordination and insertion, leads to the key acyl-Pd^{II}I intermediate **A**. Subsequently, the alkyl-Pd^{II}I species **B** was formed after a migratory insertion into the double bond. Afterwards, the alkyl-Pd^{II}I complex **B** reacts with CuBpin

Table 3: Mechanistic study.



Entry	Variations from standard conditions	Yield [%]
1	none	40
2	w/o B_2pin_2	0
3	w/o CO	0
4	w/o CuCl	< 5
5	w/o $PdCl_2$ and DPPP	< 5



Scheme 5. Plausible reaction mechanism.

species via transmetalation to give intermediate **C**; CuBpin was generated from LiOMe, B_2pin_2 and CuX in the copper cycle. Promoted by boron, intermediate **C** undergoes β-fluoride elimination to deliver the desired α-fluorochalcone with only Z-isomer and regenerate the catalytically active LPd^0 catalyst after reductive elimination.

In summary, we have developed the first example on defluorinative carbonylation. Catalyzed by Pd/Cu co-catalysts, the carbonylative cross-coupling between aryl iodides and *gem*-difluoroalkenes occurred. A variety of valuable α-fluorochalcones were obtained in good yields under mild conditions. Diverse functional group were well tolerated in this process. Synthetic transformations of the obtained α-fluorochalcones product clearly demonstrate the value of this process.

Acknowledgements

We thank the China Scholarship Council for a Ph.D. Scholarship. We appreciate the analytical department of the Leibniz-Institute for Catalysis at the University of Rostock for their assistance.

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation · copper · coupling reactions · palladium · α-fluorochalcones

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Manuscript received: December 31, 2020
Accepted manuscript online: February 4, 2021
Version of record online: March 9, 2021