

MINI REVIEW

View Article Online  
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Cite this: *Ind. Chem. Mater.*, 2024, 2, 276

Received 16th July 2023,  
Accepted 15th August 2023

DOI: 10.1039/d3im00078h

rsc.li/icm

# Palladium-catalyzed carbonylation of activated alkyl halides *via* radical intermediates

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Palladium-catalyzed carbonylation is an efficient approach to prepare carbonyl-containing compounds with high atomic economy in synthetic organic chemistry. However, in comparison with aryl halides, carbonylation of alkyl halides is relatively challenging due to the decreased stability of the palladium intermediates. Carbonylation of activated alkyl halides is even more difficult, as nucleophilic substitution reactions with nucleophiles occur more easily with them. In this article, we summarize and discuss recent achievements in palladium-catalyzed carbonylative reactions of activated alkyl halides. The transformations proceed through radical intermediates which are generated in various manners. Under a relatively high pressure of carbon monoxide, the corresponding aliphatic carboxylic acid derivatives were effectively prepared with various nucleophiles as the reaction partners. Besides alcohols, amines and organoboron reagents, four-component reactions in combination with alkenes or alkynes were also developed. Case-by-case reaction mechanisms are discussed as well and a personal outlook has also been provided.

**Keywords:** Carbonyl group; Palladium catalysis; Carbonylation; Activated alkyl halides; Radical intermediates.

## 1 Introduction

Carbon monoxide (CO) is an inexpensive and abundant one-carbon source in chemical synthesis, and employing it to undertake the carbonylative process is a direct and efficient way to construct valuable carbonyl-containing compounds.<sup>1,2</sup> Remarkable progress has been made in transition-metal-

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Xiao-Feng Wu

Xiao-Feng Wu was born in China. He was educated at Zhejiang Sci-Tech University (bachelor, 2003–2007, China), Rennes 1 University (Master, 2007–2009, France) and the Leibniz-Institute for Catalysis-Rostock University (PhD, 2009–2012, Germany). Then, he started his independent research at LIKAT and ZSTU where he was promoted to professor in 2013 and defended his Habilitation from Rennes 1 University (2017, France). In 2020, he joined Dalian Institute of Chemical Physics (DICP). Xiao-Feng has authored >550 publications in international journals; meanwhile, he is also the editor or author of over 10 books.



catalyzed carbonylation reactions after decades of development. This kind of transformation has now become one of the most powerful methods for the synthesis of carbonylated compounds and has also been successfully used as a key step in the total synthesis of many natural products.<sup>3,4</sup> More importantly, many carbonylative procedures have been industrialized. For instance, the catalytic double carbonylative reaction of benzyl halides and the carbonylation of epoxides have been performed at large scale, and the Monsanto or Cativa processes make the majority of the world's acetic acid production through methanol carbonylation.<sup>2,5,6</sup>

Palladium-catalyzed carbonylative reactions have experienced rapid development during past decades. In 1974, Heck and co-workers reported the first palladium-catalyzed carbonylation reaction of aryl halides and benzyl halogenated compounds.<sup>7</sup> Then, Ryu and co-workers reported their study on the free-radical-mediated carbonylation of unactivated alkyl halides in 1990.<sup>8</sup> The same group also reported a Pd/light-induced multicomponent carbonylative coupling reaction of activated halides with alkenes in 2011.<sup>9</sup> In 2020, Arndtsen and co-workers developed a seminal strategy that exploits simple visible-light excitation of palladium to drive both oxidative addition and reductive elimination with low barriers. Both aryl halides and unactivated halides can be effectively converted into the corresponding carbonylated compounds (Scheme 1).<sup>10</sup>

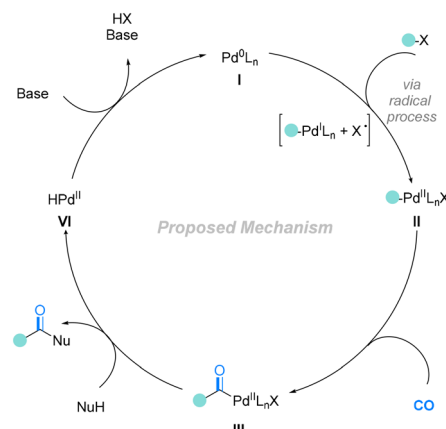
In synthetic chemistry, the efficient assembly of complex compounds from simple starting materials is a challenging and long-standing goal. In this article, we summarize and discuss recent studies on palladium-catalyzed carbonylative transformations of activated alkyl halides which are able to construct a wide variety of carbonylated compounds and their derivatives with valuable functional groups, including fluorinated groups, cyano groups, and ester groups. The contents are mainly categorized according to two aspects: i) palladium-catalyzed direct carbonylation of activated alkyl halides with nucleophiles (Scheme 2); ii) palladium-catalyzed carbonylation of activated alkyl halides and nucleophiles with alkenes or alkynes (Scheme 3).

## 2 Palladium-catalyzed direct carbonylation of activated alkyl halides with nucleophiles

Organic fluorides play a vital role in medical chemistry, and materials science due to their special physical and chemical properties. The introduction of a fluorine atom into organic



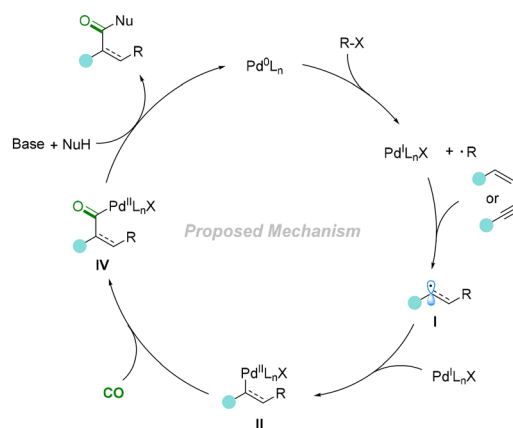
**Scheme 1** Landmarks of palladium-catalyzed carbonylative transformations of various halides.



**Scheme 2** Palladium-catalyzed direct carbonylation of activated alkyl halides with nucleophiles.

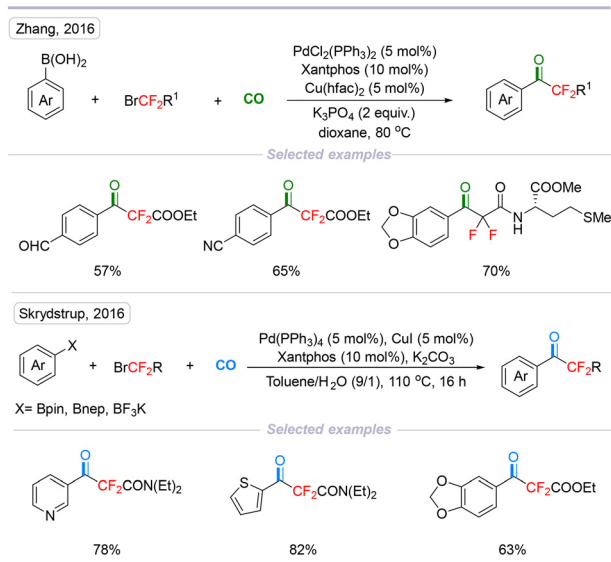
molecules could change their biological activity and physical properties.<sup>11–14</sup> On the other hand, employing commercially available fluorine-containing activated halides to introduce fluorine atoms into molecules is an efficient method to construct fluorine-containing compounds. In 2016, Zhang's group<sup>15</sup> and Skrydstrup's group<sup>16</sup> reported elegant transformations of Pd-catalyzed carbonylative coupling reactions of difluoroalkyl bromides. The main challenge is that the reaction intermediates ( $R_F-M$ ) are less prone to undergoing carbonyl insertion because the  $\sigma$ -bonds between fluoroalkyl groups and transitional metals are stronger than their normal hydrocarbon counterparts. This transformation not only provides us with a new way of viewing palladium-catalyzed fluoroalkylative carbonylation but also inspires us to probe this strategy to build up some valuable bioactive molecules (Scheme 4).

Later, in 2018, Skrydstrup's group provided a direct route to construct  $\alpha,\alpha$ -difluoro- $\beta$ -alkyl- $\beta$ -ketoamides *via* Pd-catalyzed carbonylative coupling between bromo-difluoroacetamides and alkyl boron reagents.<sup>17</sup> This transformation has good chemoselectivity and provided a broad



**Scheme 3** Palladium-catalyzed carbonylation of activated alkyl halides and nucleophiles with alkenes or alkynes.



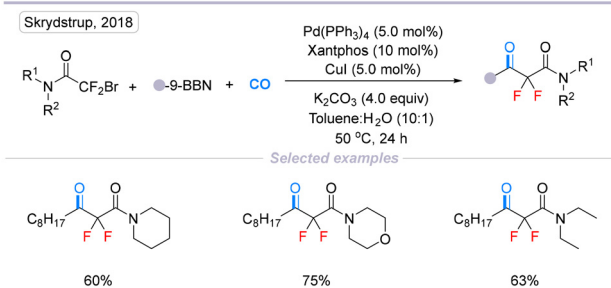


**Scheme 4** Palladium-catalyzed direct carbonylation of difluoroalkyl bromides and aryl boron reagents.

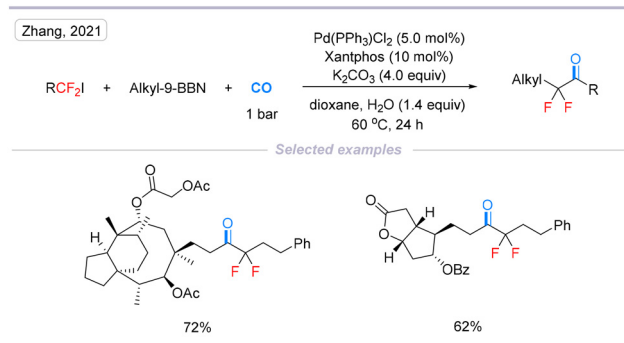
selection of  $\alpha,\alpha$ -difluoro- $\beta$ -alkyl- $\beta$ -ketoamides which are suitable for further synthetic manipulation (Scheme 5).

In 2021, Zhang's group reported a palladium-catalyzed carbonylative cross-coupling of difluoroalkyl halides with alkyl-9-BBN under 1 bar of CO.<sup>18</sup> The reaction overcomes the hydrodehalogenation and  $\beta$ -hydride elimination of unactivated difluoroalkyl halides, representing the first example of catalytic carbonylation of unactivated difluoroalkyl halides (Scheme 6).

In 2023, our group developed a novel palladium-catalyzed carbonylative procedure for bromoacetonitrile using amines, phenols, and alcohols as the nucleophiles *via* a radical intermediate. A variety of valuable 2-cyano-*N*-acetamide and 2-cyanoacetate products were obtained in excellent yields under mild reaction conditions. Additionally, a scale-up reaction was performed smoothly with low catalyst loading. Moreover, this transformation can be carried out under atmospheric pressure and provide alternative routes to 7 drug precursors. This transformation overcame the challenge that activated haloalkanes are prone to undergoing nucleophilic substitu-



**Scheme 5** Palladium-catalyzed direct carbonylation of difluoroalkyl bromides and alkyl boron reagents.

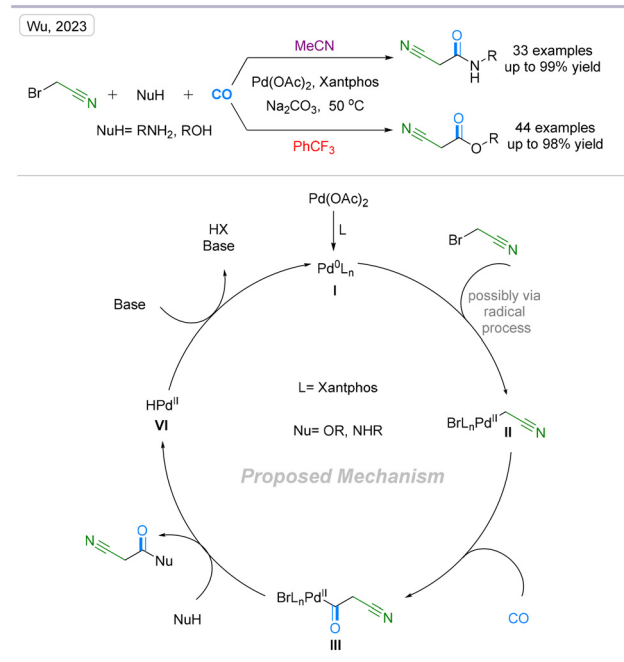


**Scheme 6** Palladium-catalyzed direct carbonylation of unactivated difluoroalkyl halides with alkylboranes.

tion reactions with strong nucleophiles and tend to be reduced by dehalogenation (Scheme 7).<sup>19</sup>

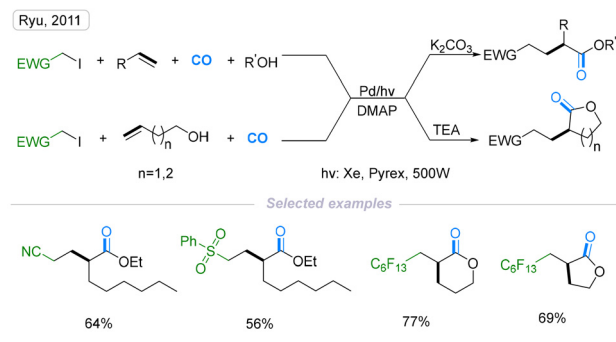
### 3 Palladium-catalyzed carbonylation of activated alkyl halides and nucleophiles with alkenes or alkynes

Multicomponent reactions (MCRs), in which three or more reactants are combined in a single reaction vessel ending up with one main product, is an efficient way to synthesize highly functionalized molecules from readily available synthons. Carbon monoxide (CO) is a cheap industrial raw material, and employing it in multicomponent reactions to



**Scheme 7** Palladium-catalyzed direct carbonylation of bromoacetonitrile to synthesize 2-cyano-*N*-acetamide or 2-cyanoacetate compounds.



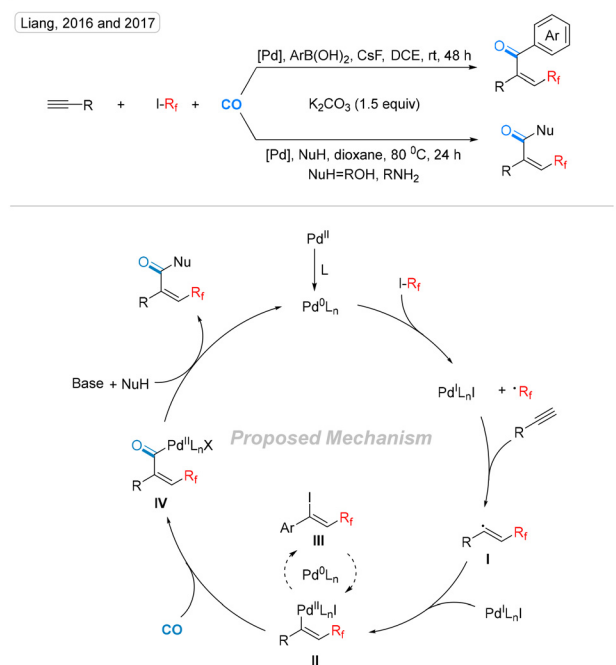


**Scheme 8** Palladium-catalyzed four-component fluoroalkylative carbonylation.

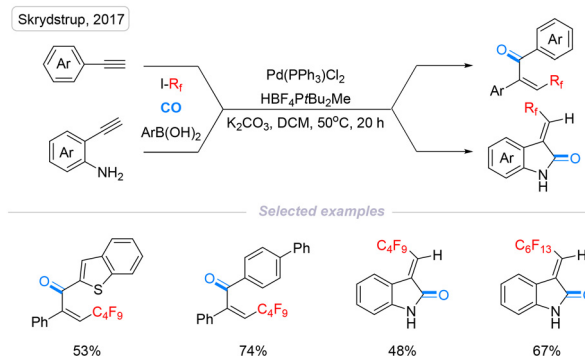
build up some valuable scaffolds is an efficient and attractive method.<sup>20–23</sup>

In 2011, Ryu's group developed a pioneering and interesting carbonylative four-component transformation comprising  $\alpha$ -substituted iodoalkanes, alkenes, and alcohols. The reaction proceeded smoothly to give functionalized esters in good yields under photoirradiation conditions using xenon light, and a three-component coupling reaction accompanied by intramolecular esterification proceeded to give lactones in good yields (Scheme 8).<sup>9</sup>

In 2016, Liang's group reported a Pd-catalyzed four-component radical carbonylation and difluoroalkylation reaction utilizing ethyl difluoroiodoacetate as a  $\text{CF}_2$  radical precursor under a low pressure of CO in a single step using alcohols, phenols, and amines as nucleophiles.<sup>24</sup> In 2017, the same



**Scheme 9** Palladium-catalyzed four-component fluoroalkylative carbonylation of aryl alkynes.

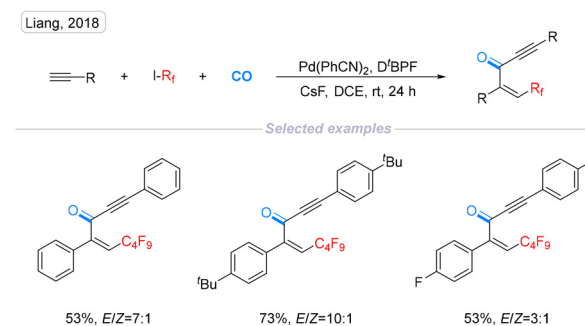


**Scheme 10** Palladium-catalyzed perfluoroalkylative carbonylation of alkyne to synthesize perfluoroalkyl-substituted enones and indolin-2-ones.

group developed a Pd-catalyzed four-component perfluoroalkylative carbonylation by using arylboronic acids as carbon nucleophiles under 1 bar of CO at room temperature (Scheme 9).<sup>25</sup>

In 2017, Skrydstrup's group reported a convenient method to access perfluoroalkyl-substituted enones using a four-component palladium-catalyzed carbonylative coupling of aryl boronic acids together with terminal alkynes and perfluoroalkyl iodides in the presence of CO. A wide range of highly functionalized enones can be prepared in a single operation in good yields. With 2-aminophenyl alkynes as the substrates, intramolecular aminocarbonylation proceeded smoothly to provide the desired indolin-2-one framework. Finally, the authors expanded the two-chamber technology to synthesize the target compounds with  $^{13}\text{C}$ -isotope labeling (Scheme 10).<sup>26</sup>

In 2018, Liang's group reported a palladium-catalyzed perfluoroalkylative/difluoroalkylative carbonylation of alkyne with alkyne as the nucleophile. This interesting transformation proceeded under atmospheric pressure at room temperature (Scheme 11).<sup>27</sup>

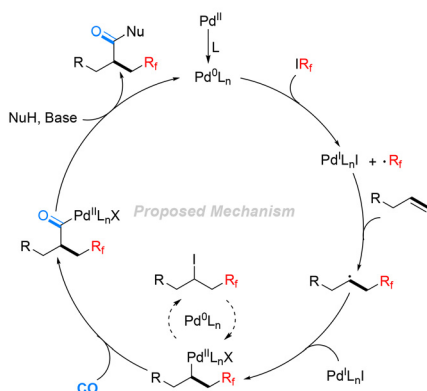
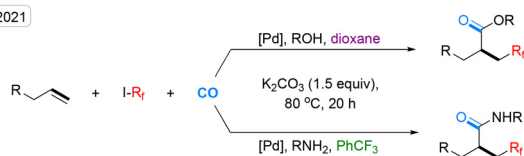


**Scheme 11** Palladium-catalyzed perfluoroalkylative and difluoroalkylative carbonylation of alkyne using alkyne as a nucleophile.





Wu, 2021

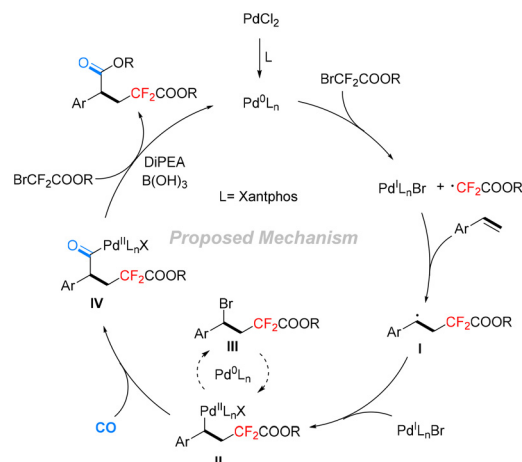
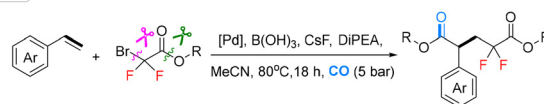


**Scheme 12** Palladium-catalyzed perfluoroalkylative carbonylation of unactivated alkenes to synthesize  $\beta$ -perfluoroalkyl esters and amides.

In 2021, our group reported a palladium-catalyzed four-component perfluoroalkylative carbonylation of unactivated alkenes with perfluoroalkyl halides, amines, or phenols (Scheme 12). With dioxane as a solvent, we got  $\beta$ -perfluoroalkyl esters while  $\beta$ -perfluoroalkyl amides were obtained with benzotrifluoride as the solvent. This transformation proceeded under mild conditions and is suitable for the modification of pharmaceutical and drug molecules. Furthermore, a wide range of substrates, including phenols, anilines, alkylamines, sulfonamides, and hydrazines, are suitable reaction partners for this catalyst system, resulting in various  $\beta$ -perfluoroalkyl amides with good functional-group tolerance and excellent chemoselectivity.<sup>28,29</sup> In 2022, our group reported a novel palladium-catalyzed procedure for the difluoroalkylative carbonylation of aryl olefins (Scheme 13).<sup>30</sup>

The catalytic cycle was initiated from the active catalyst  $\text{Pd}^0\text{L}_n$  species, which was produced from the  $\text{PdCl}_2$  pre-catalyst. Then, the  $\text{Pd}^0\text{L}_n$  complex induced an SET (single-electron transfer) process of bromodifluoroacetate to give the corresponding difluoroacetate radical and a  $\text{Pd}^{\text{I}}\text{L}_n\text{X}$  species, followed by the addition of the difluoroacetate radical to aryl alkenes to give a secondary benzylic radical **I**. Then, the  $\text{Pd}^{\text{I}}\text{L}_n\text{X}$  species was reincorporated with carbon radical **I** to obtain the vital intermediate **II**. It should be mentioned that complex **II** could be converted into **III** through reductive elimination. However, the reaction is reversible, and compound **III** could react with the reactive  $\text{Pd}^0\text{L}_n$  species and reconverted into **II**. After the insertion of CO, complex **II** will be transformed into intermediate **IV**. Finally, complex **IV** reacts with another molecule of bromodifluoroacetate and gives the final product after reductive elimination. Meanwhile, in the presence of DiPEA,  $\text{Pd}^0\text{L}_n$  will be regenerated for the next catalytic cycle.

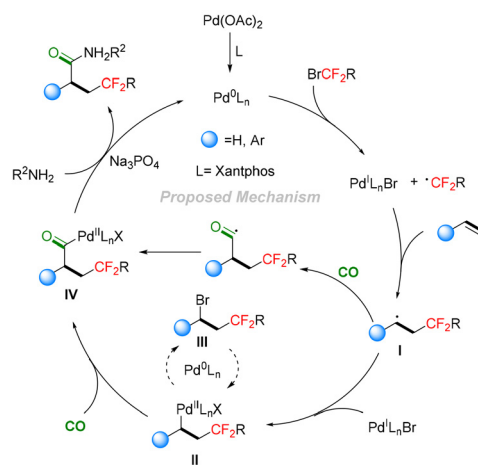
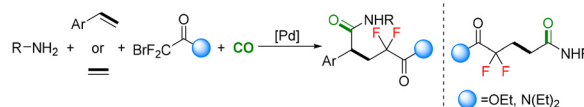
Wu, 2021



**Scheme 13** Palladium-catalyzed difluoroalkylative carbonylation of aryl alkenes toward corresponding difluoropentanedioates.

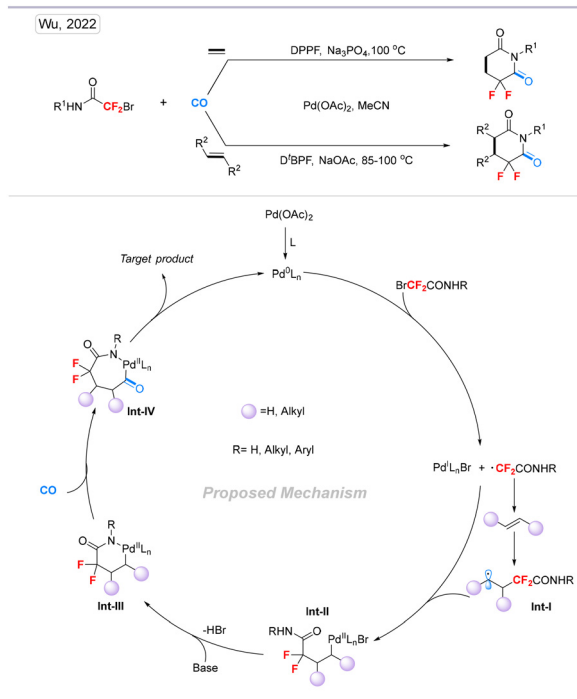
In the same year, we developed a palladium-catalyzed four-component difluoroalkylative carbonylation of aryl olefins. Notably, ethylene gas, as an original C2 synthon, can also be transformed into the corresponding products with moderate yields (Scheme 14).<sup>31</sup>

Wu, 2021



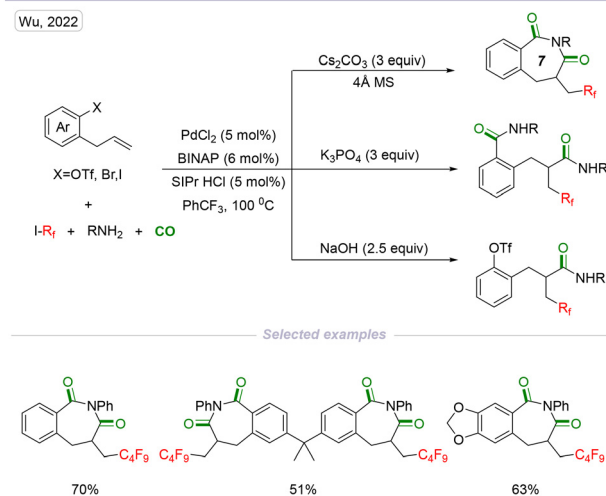
**Scheme 14** Palladium-catalyzed four-component difluoroalkylative carbonylation of aryl alkenes and ethylene gas.



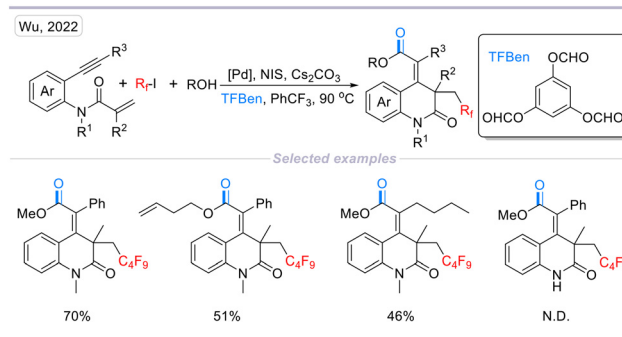


**Scheme 15** Palladium-catalyzed difluoroalkylative carbonylation of alkenes to carbonyl difluoro-containing heterocycles.

In 2022, we developed a difluoroalkylative carbonylative cyclization of unactivated alkenes and ethylene gas enabled by palladium catalysis (Scheme 15). This transformation proceeded in mild conditions with good functional-group and heterocyclic compatibility, which is suitable for late-stage functionalization. Moreover, this procedure can also be applied to the synthesis of gemigliptin, which is a medicine approved for the treatment of type 2 diabetes mellitus.<sup>32</sup>



**Scheme 16** Palladium-catalyzed perfluoroalkylative carbonylation of 2-allylaryl trifluoromethanesulfonates.

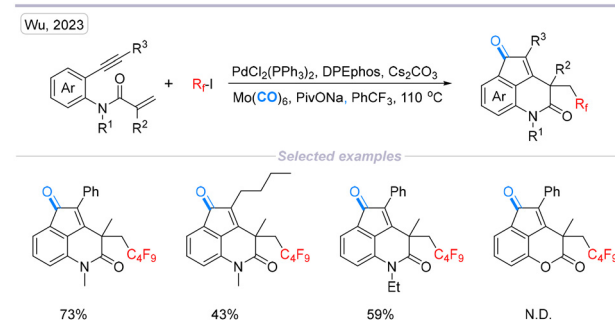


**Scheme 17** Palladium-catalyzed cascade carbonylative synthesis of perfluoroalkyl and carbonyl-containing 3,4-dihydroquinolin-2(1H)-ones.

In 2022, our group reported an efficient palladium-catalyzed multicomponent perfluoroalkylative carbonylation to synthesize various amides, and 2-allyl trifluoromethanesulfonates, perfluoroalkyl halides and amines were applied in this tandem process to get the corresponding  $\beta$ -perfluoroalkyl amides with good functional-group tolerance and high chemoselectivity (Scheme 16). The various final products were controlled by the different bases applied.<sup>33</sup>

In the same year, a palladium-catalyzed cascade radical cyclization and carbonylation of 1,7-enynes with perfluoroalkyl iodides and alcohols was developed by our group (Scheme 17). This method provides a facile and efficient route for the construction of 3,4-dihydroquinolin-2(1H)-one scaffolds by applying benzene-1,3,5-triyl triformate (TFBen) as the CO source. This method enables the incorporation of both perfluoroalkyl and carbonyl units into the 3,4-dihydroquinolin-2(1H)-one scaffolds, providing different 3,4-dihydroquinolin-2(1H)-one derivatives in moderate to high yields with excellent *E/Z* selectivity.<sup>34</sup>

In 2023, a one-pot two-step radical-mediated carbonylative cyclization of 1,7-enynes with perfluoroalkyl iodides catalyzed by palladium was developed, and a variety of polycyclic 3,4-dihydroquinolin-2(1H)-one derivatives containing perfluoroalkyl and carbonyl units were obtained in good yields (Scheme 18).<sup>35</sup>



**Scheme 18** Palladium-mediated cascade carbonylative synthesis of perfluoroalkyl and carbonyl-containing polycyclic 3,4-dihydroquinolin-2(1H)-one derivatives.



## 4 Summary and outlook

In conclusion, this review has surveyed recent advances in the area of palladium-catalyzed carbonylative coupling conversion of activated alkyl halides *via* radical intermediates. These transformations can be performed under a low pressure of CO, unlike traditional free radical carbonylation reactions. More importantly, these methods provide alternative routes to construct some bioactive drug molecules due to the introduction of some interesting functional groups. Although palladium-catalyzed carbonylative coupling reactions of activated alkyl halides have developed very well, several interesting directions still need to be probed: i) employing cheaper metal catalysts to achieve these transformations; ii) improving these interesting methods to synthesize some useful drug molecules or bioactive compounds with shorter steps; iii) developing a novel catalyst system to achieve the enantioselective carbonylation reaction of activated alkyl halides. Finally, we hope that this review will inspire future developments in this area.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the financial support from DICP and K. C. Wong Education Foundation (GJTD-2020-08).

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