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Palladium-Catalyzed Dehydrogenative Fluoroalkoxylation of Benzaldehydes

Long Jin, Xing-Long Zhang, Rui-Li Guo, Meng-Yue Wang, Ya-Ru Gao, and Yong-Qiang Wang*

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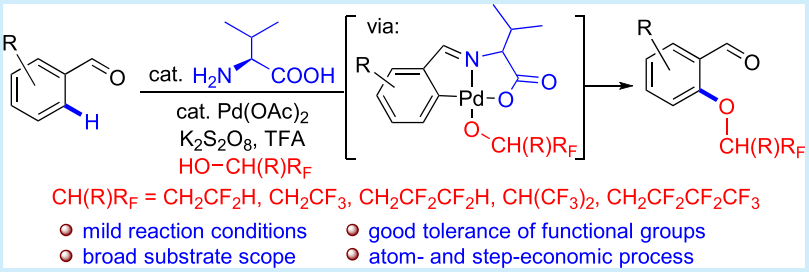

ABSTRACT: A direct and efficient palladium-catalyzed oxidative dehydrogenative fluoroalkoxylation of benzaldehydes is reported here for the first time. The method features mild reaction conditions, good tolerance of functional groups, and a broad substrate scope. The protocol employs the transient directing group strategy, thereby avoiding the additional installation and removal of directing groups, endowing the method with great advantages of atom and step economy. The approach should find broad applications in drug synthesis and discovery processes.

Fluorine-containing compounds, on the basis of their unique special pharmacokinetic and physicochemical properties, play important roles in the fields of pharmaceuticals, agrochemicals, and materials science.[1] Among fluorine-containing compounds, fluoroalkyl aryl ethers are widely used in medicinal chemistry due to the high metabolic stability, electron-withdrawing effect, and increasing lipophilicity of fluoroalkoxy groups.[2] Representative examples include the multibillion-dollar proton pump inhibitor lansoprazole, the antiarrhythmic flecainide, the antibenign prostatic hyperplasia silodosin, and idalopirdine (Figure 1).[3] Consequently, it is highly desirable to develop an efficient synthetic method for fluoroalkyl aryl ethers.[4,5] Traditionally, fluoroalkyl aryl ethers have been prepared via nucleophilic substitution or transition-metal-mediated cross-coupling of phenols or aromatic halides with fluorine partners (Figure 2a).[4] Recently, Ji and Li et al. realized the trifluoroethoxylation of benzamides through a C−H bond activation strategy with amide groups as the directing groups (Figure 2b).[5] Compared with traditional methods, direct C−H bond functionalization has obvious benefits in terms of step and atom economy. However, the existing methods require preinstallation of amide-based directing groups. Furthermore, the amide groups are generally removed under strong acid (e.g., aq. HCl[5a]) or base (e.g., NaOH,[5c,d] LiOH[5b,g]) conditions, which greatly limits the application of the method, in particular, in the late-stage transformation of advanced synthetic intermediates.

Benzaldehydes, as common organic chemicals, are the key starting materials for the synthesis of many biologically active compounds and functional materials.[6] Therefore, the development of the direct C−H functionalization of benzaldehydes is extremely valuable. But such a promising transformation is a challenge due to the aldehyde's susceptibility toward oxidation[7] and undesired reactions of the acyl C−H bond

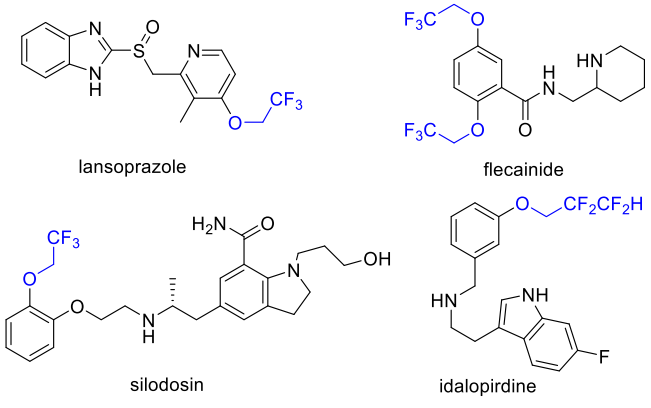

Figure 1. Drugs containing fluorinated alkyl aryl ethers.

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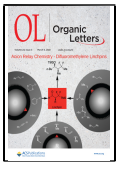

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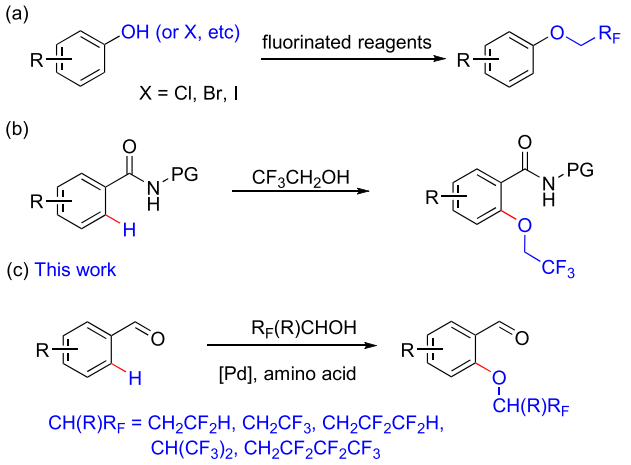


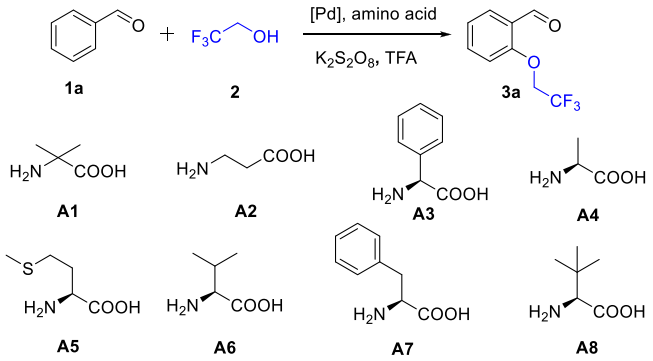
Figure 2. Synthetic methods of the fluoroalkyl aryl ethers.

(e.g., metal insertion).[8] Herein we disclose an efficient palladium-catalyzed direct C−H oxidative fluoroalkoxylation of benzaldehydes (Figure 2c). This approach exploits a transient directing group (TDG) strategy, thereby avoiding additional installation and removal steps of the directing group.[9] To our knowledge, this is the first report of the efficient dehydrogenative fluoroalkoxylation of benzaldehydes with fluorinated alcohols.[10]

Our study began with extensive transient directing amino acid screening with benzaldehyde (**1a**) and trifluoroethanol (TFE, **2**) as the model substrates, $Pd(OAc)_2$ as the catalyst, and $K_2S_2O_8$ as the oxidant (Table 1). First, 2-aminoisobutyric acid was investigated at 80 °C. Unfortunately, no obvious reaction was observed (entry 1). Considering that trifluoroacetic acid (TFA) and $Pd(OAc)_2$ can facilely generate a more active $[Pd(II)O_2CCF_3]^+$ species,[14a] TFA (2.0 equiv) was added to the reaction system. To our delight, the reaction gave the desired trifluoroethoxylated product **3a** in 31% isolated yield (entry 2). Then, other amino acids were tested. No reaction occurred with β-amino acid **A2** (entry 3). All α-amino acids **A3**−**A8** could give the product **3a**, and **A6** afforded the best result (entries 4−9). More amino acids and other types of transient directing reagents were tested but gave inferior yields. (See the Supporting Information (SI).) Then, we tested different oxidants and found that $K_2S_2O_8$ was still the best (entry 10). Different types of palladium sources have been examined successively (entries 11−15). $Pd(TFA)_2$ and $Pd(OAc)_2$ provided similar results. In view of the cost, we still chose the more economical $Pd(OAc)_2$. When TFA was replaced by the same amount of AcOH, the reaction could not proceed, demonstrating the importance of TFA (entry 16). The amounts of **A6** and TFA had a significant effect on the reaction, and **A6** (50 mol %) and TFA (2.0 equiv) were still preferred. (See the SI.) Increases or decreases in the reaction temperature led to an obvious drop in the yield. (See the SI.) Finally, the amount of $Pd(OAc)_2$ was investigated. $Pd(OAc)_2$ (15 mol %) could provide the desired product **3a** in 71% isolated yield, and more $Pd(OAc)_2$ loading did not lead to a clear improvement in yield (entries 17−19). Accordingly, the optimized reaction conditions were determined to be as follows: $Pd(OAc)_2$ (15 mol %), amino acid **A6** (50 mol %), $K_2S_2O_8$ (2.0 equiv), and TFA (2.0 equiv) at 80 °C.

With the optimal reaction conditions in hand, the direct C−H oxidative trifluoroethoxylation was applied to different

Table 1. Optimization of Reaction Conditions[a]



entry	Pd source	amino acid	oxidant	yield (%)[b]
1[c]	$Pd(OAc)_2$	**A1**	$K_2S_2O_8$	0
2	$Pd(OAc)_2$	**A1**	$K_2S_2O_8$	31
3	$Pd(OAc)_2$	**A2**	$K_2S_2O_8$	0
4	$Pd(OAc)_2$	**A3**	$K_2S_2O_8$	20
5	$Pd(OAc)_2$	**A4**	$K_2S_2O_8$	28
6	$Pd(OAc)_2$	**A5**	$K_2S_2O_8$	12
7	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	61
8	$Pd(OAc)_2$	**A7**	$K_2S_2O_8$	21
9	$Pd(OAc)_2$	**A8**	$K_2S_2O_8$	46
10[d]	$Pd(OAc)_2$	**A6**	other oxidants	<32
11	$Pd(TFA)_2$	**A6**	$K_2S_2O_8$	62
12	$PdCl_2$	**A6**	$K_2S_2O_8$	36
13	PdI_2	**A6**	$K_2S_2O_8$	15
14	$Pd(PPh_3)_2Cl_2$	**A6**	$K_2S_2O_8$	0
15	$Pd(OH)_2$	**A6**	$K_2S_2O_8$	21
16[e]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	0
17[f]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	38
18[g]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	71
19[h]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	72

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.8 mL, 11 mmol), [Pd] (10 mol %), amino acid (50 mol %), oxidant (0.4 mmol), TFA (2 equiv), and open to air for 12 h. [b]Isolated yield. [c]Without TFA. [d]Other oxidants: $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, *p*-benzoquinone (BQ), $PhI(OAc)_2$, Ag_2CO_3, and O_2 (1 atm). [e]2.0 equiv of AcOH was added, without TFA. [f]$Pd(OAc)_2$ (5 mol %). [g]$Pd(OAc)_2$ (15 mol %). [h]$Pd(OAc)_2$ (20 mol %).

benzaldehydes (Scheme 1). We were delighted to find that various para substituents (alkyl groups, halides, phenyl, ether, trifluoromethyl, and ester) with various steric and electronic properties were well tolerated, affording the desired products in good yields (**3a**−**3l**). It should be mentioned that benzaldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups. Satisfactory results were also obtained with Me, Cl, Br, CF_3, NO_2, and CO_2Me substituted at the meta position of benzaldehydes (**3m**−**3r**). It is noteworthy that a derivative of the biologically active L-menthol also afforded the corresponding product in good yield (**3s**). Benzaldehydes substituted at the ortho position, which usually were difficult substrates because of steric hindrance, were also well tolerated, providing the products in 51−80% yields (**3t**−**3x**). Gratifyingly, disubstituted and trisubstituted benzaldehydes were also suitable substrates, affording corresponding products in moderate to good yields (**3y**−**3af**). Interestingly, 2-naphthylaldehydes gave normal 3-trifluoroethoxylation products (**3ag**, **3ah**), whereas 1-naphthylaldehyde afforded 8-trifluoroethoxylation product (**3ai**). Both kinds of naphthylaldehyde substrates presented complete respective

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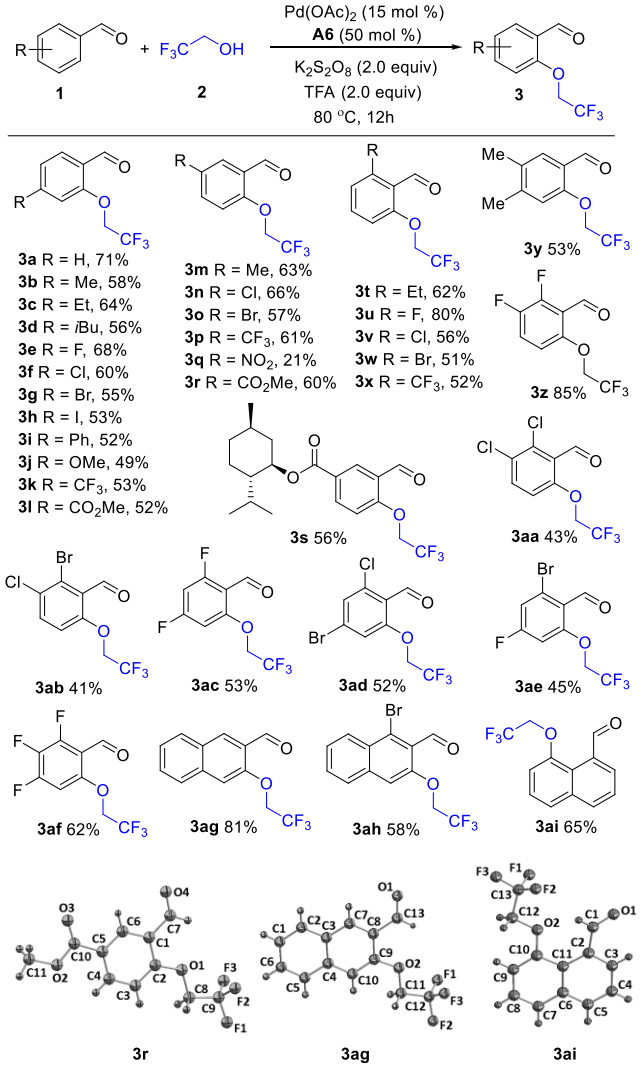
Scheme 1. Scope of Aldehydes[a]

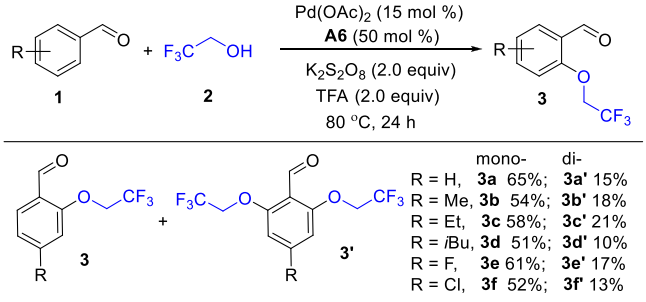


[a]Reaction conditions: **1** (0.4 mmol), **2** (1.6 mL, 22 mmol), $Pd(OAc)_2$ (0.06 mmol), amino acid (0.2 mmol), oxidant (0.8 mmol), and TFA (0.8 mmol) under air at 80 °C for 12 h. All yields given are those for the isolated products.

regioselectivity. The structures of **3r**, **3ag**, and **3ai** were confirmed by single-crystal X-ray diffraction. (See the SI.)

It is worth mentioning that ortho functionalization of arenes generally suffers from poor mono- versus diselectivity.[11] In this dehydrogenative fluoroalkoxylation of benzaldehydes, we found that the extension of the reaction time to 24 h would lead to the formation of a small amount of the difluoroalkoxylation products **3a′−3f′** for substrates **1a−1f** (Scheme 2; it did not improve the yields of **3a′−3f′** for longer than 24 h), and the yield of the monofluoroalkoxylation products **3a−3f** was decreased accordingly. For other substrates, difluoroalkoxylation products could not be detected, even when extending the reaction time to 72 h. Moreover, we found that the diarylation could not be improved by increasing the amount of oxidant or alcohol, demonstrating that the approach possessed good selectivity for the monoarylation. Although the exact reason for the monofluoroalkoxylative selectivity was not clear, we suspected that it might be ascribed to the reaction mechanism of the concerted metalation−deprotonation (CMD; see later). The fluoroalkoxyl group is an electron-

Scheme 2. Difluoroalkoxylation[a]

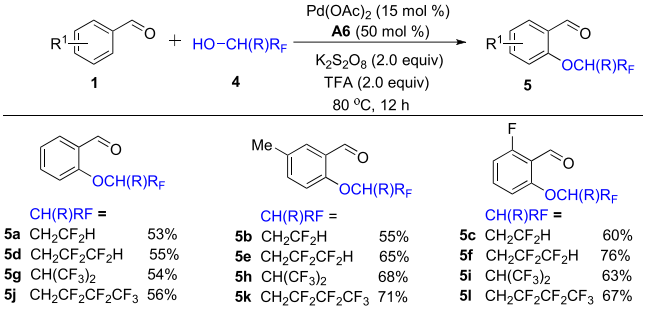


[a]Reaction conditions: **1** (0.4 mmol), **2** (1.6 mL, 22 mmol), $Pd(OAc)_2$ (0.06 mmol), amino acid (0.2 mmol), oxidant (0.8 mmol), and TFA (0.8 mmol) under air at 80 °C for 24 h. All yields given are those for the isolated products.

rich group; therefore, it is unfavorable for the second fluoroalkoxylation.

Next, we moved on to test other fluorinated alcohols with benzaldehyde, *m*-methylbenzaldehyde, and *o*-fluorobenzaldehyde as the partners (Scheme 3). To our delight, these

Scheme 3. Fluoroalkoxylation with Other Fluorinated Alcohols[a]



[a]Reaction conditions: **1** (0.4 mmol), **4** (1.6 mL), $Pd(OAc)_2$ (0.06 mmol), amino acid (0.2 mmol), oxidant (0.8 mmol), and TFA (0.8 mmol) under air at 80 °C for 12 h. All yields given are those for the isolated products.

benzaldehydes could react smoothly with 2,2-difluoroethanol, 2,2,3,3-tetrafluoro-1-propanol, 1,1,1,3,3,3-hexafluoro-2-propanol, and 2,2,3,3,4,4,4-heptafluoro-1-butanol under the optimal reaction conditions, generating the corresponding fluoroalkoxylated products in 53−76% yields (**5a−5l**). In these reactions, we could not detect a difluoroalkoxylation product in the reaction system. More valuable fluorinated alcohols, such as 2,2,3,3-tetrafluoro-1-propanol and 2,2,3,3,4,4,4-heptafluoro-1-butanol, possess higher boiling points, and their amount could be decreased to 1.0 mL for 0.4 mmol of **1** without a reduction in yield. Note that nonafluoro-*tert*-butanol was not a suitable substrate, probably due to the steric hindrance effect. It should be mentioned that 2-fluoroethanol and nonfluorinated alcohols, such as methanol and ethanol, could not afford the corresponding alkoxylative products under the current reaction conditions.[12,13] Furthermore, it is noteworthy that although the current reaction conditions were oxidative, the oxidized product of fluorinated alcohols, such as trifluoroacetaldehyde and heptafluorobutyraldehyde, could not be detected in all reaction systems.

To test the practicality of the developed oxidative dehydrogenative fluoroalkoxylation, we conducted the reaction

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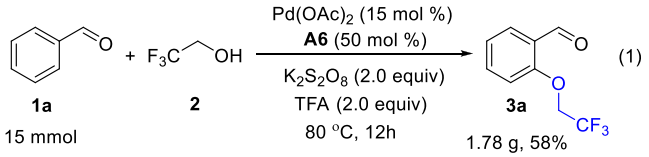
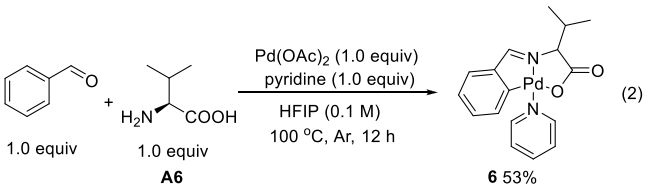
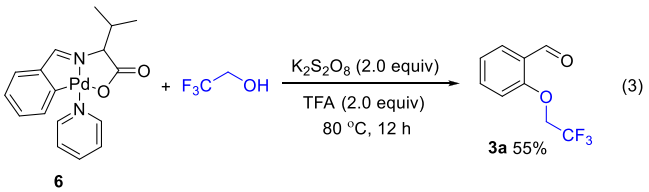
on 15 mmol of **1a** to couple to **2**, and 1.78 g (58% yield) of product **3a** was isolated (eq 1).

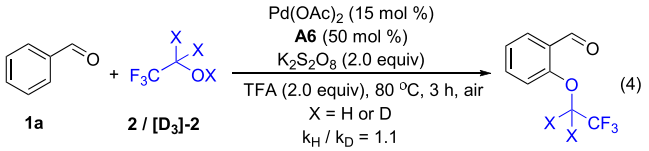


To gain insight into the reaction mechanism, we independently synthesized the putative palladacycle intermediate (eq 2). Pleasingly, the cyclopalladium intermediate **6**

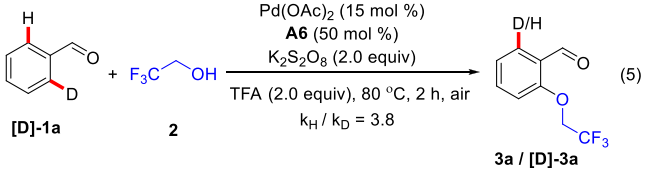


was isolated from the reaction system of benzaldehyde with stoichiometric $Pd(OAc)_2$, pyridine, and **A6**.[14d,15] Then, the cyclopalladium intermediate **6** was treated with TFE, $K_2S_2O_8$, and TFA to give **3a** in 55% yield (eq 3). Subsequently, kinetic





isotope effect (KIE) experiments were performed (eqs 4 and 5). The KIE value of two parallel reactions of **1a** with **2** and



$[D_3]$-**2** was found to be 1.1, and the intramolecular KIE value for the reaction of [D]-**1a** was 3.8, indicating the cleavage of the C−H bond of the aromatic ring involved in the rate-determining step. As previously mentioned, electron-deficient substrates **1** reacted faster than electron-rich substrates, and only a few cases found a small amount of difluoroalkoxylation products. These results and the intramolecular KIE value (3.8) showed that the mechanism was likely a CMD process but not an electrophilic aromatic palladation.[14b]

On the basis of the above results and related literature,[5g,15,16] a possible mechanism for the palladium-catalyzed C−H oxidative fluoroalkoxylation of benzaldehydes was proposed (Figure 3). First, benzaldehyde and amino acid **A6** reversibly form imine intermediate **A**.[15] Meanwhile, the active Pd(II)

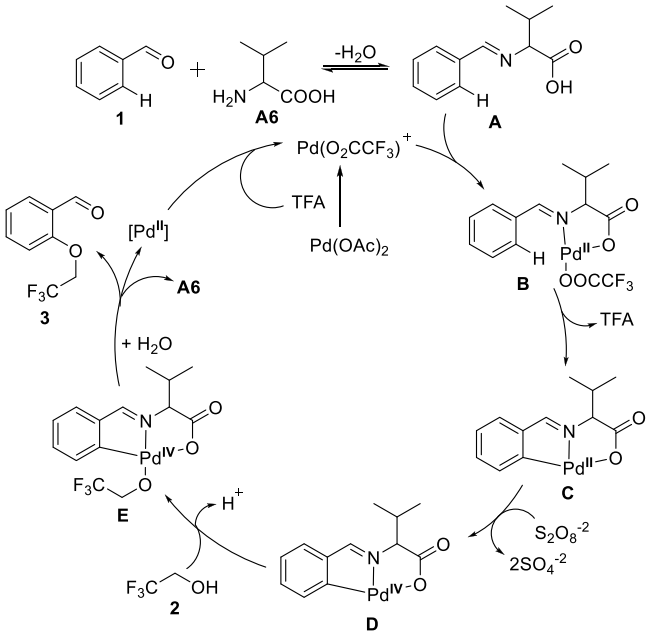


Figure 3. Proposed mechanism.

species is generated in situ from $Pd(OAc)_2$ with TFA.[14] The coordination of an α-imino acid **A** to a Pd(II) species generates a palladium complex **B**.[17] The five-membered ring intermediate **C** is formed by an intramolecular C−H bond activation of the intermediate **B**, probably through a CMD process.[14b,18] The intermediate C is oxidized by persulfate to generate the Pd(IV) species **D**, which is fluoroalkoxylated by fluorinated alcohol to provide intermediate **E**;[19] then, the following reductive elimination results in product formation and Pd catalyst regeneration.

In summary, an efficient protocol for the synthesis of fluoroalkyl aryl ethers was developed by using the palladium-catalyzed dehydrogenative fluoroalkoxylation of benzaldehydes with fluorinated alcohols. The synthetic method features mild reaction conditions, good tolerance of functional groups, and a broad substrate scope. The approach employs a transient directing group strategy, thereby possessing the advantages of atom and step economy. Given the importance of the fluoroalkyl aryl ether motif in medicinal chemistry, the approach should find broad applications in drug synthesis and discovery processes.[20] Detailed mechanism and application studies are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00365.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 2038545−2038547 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Author

Yong-Qiang Wang − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China;* orcid.org/0000-0002-2774-3248; Email: wangyq@nwu.edu.cn

Authors

Long Jin − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China*

Xing-Long Zhang − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China*

Rui-Li Guo − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China*

Meng-Yue Wang − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China*

Ya-Ru Gao − *Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710069, China;* orcid.org/0000-0002-6057-1652

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00365

Notes

The authors declare no competing financial interest.

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(13) The different reactivities of fluorinated and non-fluorinated alcohols were partially attributed to their different p*K*a values, which had a marked impact on the nucleophilicity of alcohol (e.g. CF_3CH_2OH, p*K*a = 12.37; CH_3OH, p*K*a = 15.09). For the concerted p*K*a values, see: Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. Calculation of the p*K*a Values of Alcohols from σ^* Constants and from the Carbonyl Frequencies of Their Esters. *J. Org. Chem.* **1971**, *36*, 1205−1209.

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