Transcript:  

**Introduction**

The directed activation of carbon–hydrogen bonds (C–H) is a topic of increasing importance with a wide range of applications in organic synthesis.¹ However, one of the major challenges in selective catalytic functionalization of C–H bonds is to enable the use of native substrates without covalently installing external directing groups. Transient directing groups (TDGs), which form reversible linkages with the substrates in situ, complement a promising alternative approach to direct metal-catalysed or -mediated C–H functionalization, thereby avoiding the additional installation and removal of directing groups.² While most of the achievements for TDG-mediated and Pd-catalyzed C(sp²)–H functionalization are restricted in C(sp²)–H arylation,³ alkylation,⁴ and alkenylation,⁵ efforts to develop Pd-catalyzed C(sp³)–O and C(sp³)–N bond forming reactions have recently afforded new advances.⁶ Recently, the seminal examples of these rare reactions, which were reported by Erik J. Sorensen and co-workers, featured the utilization of 4-chloroanthranilic acid as the bidentate transient directing group (BiTDG), and 1-fluoro-2,4,6-trimethylpyridinium triflate as the bystanding oxidant.⁷ Soon after, ortho-C–H methoxylation and fluoroalkoxylation of benzaldehydes were also realized by employing monodentate directing groups⁸ and BiTDG respectively which form N, O-bis-coordinated complexes with Pd(II) catalyst and promote the C–H activation process.⁹

Nevertheless, mild and selective transformations of this type are still largely undeveloped and the new catalytic TDGs, e.g., N, N-bidentate coordination, remain to be further exploited. Therefore, the investigation of new TDGs allowing flexible and diverse reactivities is of great importance and highly desirable.

The use of the peptide backbone in site-selective C–H oxygenations of tripeptides presented catalytic action by N, N-bidentate coordination of amide groups with Pd (Scheme 1A).⁹ Significantly, a bulky, amino amide transient directing group was developed to selectively promote the benzylic C(sp³)–H acetoxylation with low yield (29%) (Scheme 1B).¹⁰ Based on this particular investigation and our previous studies of using

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**Scheme 1** Controlled site-selective C–H bond oxygenation.
To establish the viability of the C(sp^2)–H oxygenation of benzaldehydes, diverse molecules containing amino groups were investigated their role in palladium-catalyzed oxygenation of benzaldehydes, diverse molecules containing amino groups. Herein, we report an amino amide as catalytic transient directing group enabled C(sp^2)–H oxygenation of broad range of benzaldehydes and benzylic amines and alcohols via C–O bond formation at the unactivated positions.

| Entry | Oxidant | TFA (equiv.) | Yield(%) |
|-------|---------|-------------|----------|
| 1     | F1      | 2           | 88       |
| 2     | F2      | 2           | 60       |
| 3     | F3      | 2           | 45       |
| 4     | F4      | 2           | 60       |
| 5     | Other oxidants | 2         | <30      |
| 6     | F1      | 0           | 30       |
| 7     | F1      | 1           | 50       |
| 8     | F1      | 3           | 80       |
| 9     | F1      | 5           | 78       |
| 10    | F1      | 10          | 78       |
| 11    | F1      | 2           | 75       |
| 12    | F1      | 2           | 60       |
| 13    | F1      | 2           | Trace    |
| 14    | F1      | 2           | 30       |
| 15    | F1      | 2           | Trace    |
| 16    | F1      | 2           | Trace    |
| 17    | F1      | 2           | 25       |
| 18    | F1      | 2           | 35       |
| 19    | F1      | 2           | 30       |
| 20    | F1      | 2           | 72       |
| 21    | F1      | 2           | N.R.     |
| 22    | —       | 2           | N.R.     |

Table 2 Optimization of the reaction conditions

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2, entries 11 and 12). Compared with trifluoroethanol, other solvents, such as toluene and dichloromethane, were not applicable to the reaction (Table 2, entries 13–17). Additionally, 2-aminopropanoic acid was used as a contrast TDG under the optimum conditions, only 35% yield was achieved (Table 2, entry 18). Therefore, it can be presumed that the short peptides rather than its hydrolysate can coordinate with Pd(II) entry 18). Therefore, it can be presumed that the short peptides optimum conditions, only 35% yield was achieved (Table 2, 2-aminopropanoic acid was used as a contrast TDG under the
electron-rich methoxy group substituents were well tolerated to benzaldehydes bearing the alkyl group, halogen and the
results were also obtained (3b, 3c, 3g and 3h). It is noteworthy that 2-ethylbenzaldehyde also showed reaction activity in spite of the steric hindrance effect, affording the corresponding product in moderate yields (3d). Whereas, strong electron-deficient benzaldehydes with ester and nitro substituents only provided trace amounts of the product (3j and 3k). Furthermore, we also screened the other fluorinated alcohols under the standard conditions for obtaining fluorinated compounds. Gratifyingly, polyfluoroalkoxylation of benzaldehyde with other polyfluoro-alcohols proceeded smoothly with completely selectivity in moderate yields (3l–3n). Significantly, the ortho-C–H di-polyfluoroalkoxylation products could not be detected, demonstrating that the transformation showed good selectivity for the mono-fluoroalkoxylation. Moreover, 3-methylbenzaldehyde and 3, 4-dimethoxy-benzaldehyde also afforded the corresponding mono-polyfluoroalkylated products in 49–64% yields (3o, 3p and 3q). Notably, secondary fluorinated alcohols such as 1,1,1,3,3,3-hexafluoro-2-propanol were also effective nucleophiles towards the benzaldehyde with steric hindrance, affording the highly hindered fluoroalkyl ethers in 55% isolated yields (3r).

Since the current reaction conditions were oxidative, we next wondered whether benzylic amines could be oxidized and serve as effective coupling partners for this reaction. Benzylamine instead of benzaldehyde was used as a substrate, and reacted with trifluoroethanol under the optimal reaction conditions (Table 3). To our delight, the C–N and ortho-C(sp²)–H consecutive oxidation of benzylamine could also be accomplished in one pot, albeit with lower efficiency (Table 3, entries 1). Upon evaluation of various oxidants, we discovered that although the [F+] bystanding oxidants gave inferior yields of the corresponding products in less than 10% (Table 3, entry 3–5), K2S2O8 was identified as potentially effective oxidant for this reaction, affording the desired product in 70% yield (Table 3, entry 2). Interestingly, the reaction with dual oxidant (F1/F4) system

Under optimal conditions, we next investigated the substrate scope of substrates of benzaldehydes and fluorinated alcohols (Scheme 2). Firstly, the substrate scope of the various benzaldehydes was examined for the C(sp²)–H bond trifluoroethoxylation. We were delighted to find that different benzaldehydes bearing the alkyl group, halogen and the electron-rich methoxy group substituents were well tolerated to give the desired products in moderate to good yields (3a–3l).

When we changed the placement of the methyl or methoxy group from the para-position to the meta-position, satisfactory results were also obtained (3b, 3c, 3g and 3h). It is noteworthy that 2-ethylbenzaldehyde also showed reaction activity in spite

Scheme 2 Scope of aldehydes and fluorinated alcohols.a  a Reaction conditions: 1 (0.2 mmol), fluorinated alcohols (2 mL), Pd(OAc)2 (10 mol%), A9 (50 mol%), F1 (0.4 mmol), TFA (2 equiv.) and stirred at 80 °C for 12 h. All yields given are those for the isolated products.

Table 3 Optimization of the consecutive oxidation of benzylamine

| Entry | Oxidant | Temperature(°C) | Yieldb (%) |
|-------|---------|----------------|------------|
| 1     | F1      | 80             | 18%        |
| 2     | K2S2O8  | 80             | 70%        |
| 3     | F2      | 80             | Trace      |
| 4     | F3      | 80             | Trace      |
| 5     | F4      | 80             | 10%b (86%) |
| 6c    | F1+ K2S2O8 | 80     | 78%        |
| 7d    | F1+ F4  | 80             | 80%        |
| 8d    | F1+ F4  | 60             | 70%        |
| 9d    | F1+ F4  | 50             | 55%        |
| 10d   | F1+ F4  | 80             | 78%        |

a Isolated yields. b Benzaldehyde was formed as major product. c F1 (0.2 mmol), K2S2O8 (0.2 mmol), under air. d F1 (0.2 mmol), F4 (0.2 mmol), under air. e F1 (0.2 mmol), F4 (0.2 mmol), under N2.
could be further optimized up to 80% isolated yield (Table 3, entry 6–10).

On the basis of this strategy, a variety of amines were investigated under new conditions. N-benzyl primary amines having methyl group, halogens and the electron-rich methoxy group on the aromatic ring all underwent the desired oxidation reaction in 45–80% yields (Scheme 3, entry 1–6). Unfortunately, N-benzyl secondary amines, such as N-methyl-1-phenylmethanamine and N-benzylpropan-1-amine, only provided trace amounts of yield, which indicated that the secondary amines are not suitable for this process (Scheme 3, entry 7–10). Remarkably, N-benzyl tertiary amines were competent to undergo the reaction in moderate yields (Scheme 3, entry 11–17).

Based on our experiments and related literature, a plausible mechanism was proposed for the palladium-catalyzed ortho-C(sp2)–H oxidation of benzaldehydes (Scheme 4). Benzyl amines get converted into imine intermediate by the [F+] bystander oxidant, which in turn could be hydrolyzed to the aldehydes. Condensation of benzaldehydes with the ligand 2-(2-amino-propanamido)propanoic acid provides the imine intermediate A. Coordination of this imine to a palladium species followed by cyclopalladation process generates the [5, 5]-bicyclic palladium intermediate C via a site-selective C–H bond activation process, and oxidative addition of the intermediate C with fluorinating bystander oxidant generates the palladium(IV) species D. Next, the fluoride anion is displaced by the fluorinated alcohol to provide intermediate E. Reductive elimination of this palladium complex followed by a ligand dissociation process provides the α-imino amide, which releases the desired product, and ligand 2-(2-aminopropanamido)propanoic acid.

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**Scheme 3** Scope of benzylic amines. Reaction conditions: 4 (0.2 mmol), TFE (2 mL), Pd(OAc)2 (10 mol%), A9 (50 mol%), F1 (0.2 mmol), F4 (0.2 mmol), TFA (2 equiv.) and stirred at 80 °C for 12 h. All yields given are those for the isolated products.

**Scheme 4** Proposed mechanism.
Conclusions

In summary, we have developed a general method for the C(sp^3)-H fluoroalkoxylation of benzaldehydes and benzylic amines using 2-(2-aminopropanamido)propanoic acid as the transient directing group and the [F^+] bystanding oxidant. Moderate to good yields were obtained for a broad substrate scope under mild conditions. Given the efficient and selective processes for the functionalization of C(sp^3)-H bonds, the approach will greatly enrich the toolbox and provide alternative method for transformation of advanced synthetic intermediates in a single step. More importantly, the approach should find broad applications in synthesis of ubiquitous structural units in biologically active natural products and pharmaceuticals. Detailed mechanistic studies and new applications of this TDG strategy are underway in our laboratory.

Experimental

Typical procedure for palladium-catalyzed C(sp^3)-H polyfluoralkoxylation of benzaldehydes

An 8 mL vial equipped with a stir bar was charged with Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol, 10 mol%), A9 (16.0 mg, 0.1 mmol, 50 mol%), 1-fluoro-2,4,6-trimethylpyridinium triflate (F1) (90.8 mg, 0.4 mmol, 2.0 equiv.), and benzaldehydes (0.2 mmol, 1.0 equiv.), followed by the addition of chloroform (2.0 mL) and TFA (2.0 equiv.). The flask was then sealed and the mixture was stirred at 80 °C for 30 min, followed by the addition of Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol, 10 mol%) and benzaldehydes (0.4 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 10 min before being heated to 80 °C for 12 h. The reaction mixture was cooled to room temperature, followed by the addition of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous MgSO\(_4\), followed by the addition of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous MgSO\(_4\), followed by the addition of water and ethyl acetate. The residual was purified through column chromatography on silica gel to give the desired products.

Typical procedure for the C-N and ortho-C(sp^3)-H consecutive oxidation of benzyamines

Selectfluor (F4) (70.8 mg, 0.2 mmol, 1.0 equiv.) and 1-fluoro-2,4,6-trimethylpyridinium triflate (F1) (90.8 mg, 0.2 mmol, 1.0 equiv.) were added to a solution of benzyamines (0.2 mmol, 1.0 equiv.) in chloroform (2.0 mL). The reaction mixture was stirred at 80 °C for 30 min, followed by the addition of Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol, 10 mol%), A9 (16.0 mg, 0.1 mmol, 50 mol%), and TFA (2.0 equiv.). The reaction mixture was stirred at the same temperature for 12 h. Upon completion, the reaction mixture was cooled to room temperature, followed by the addition of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous MgSO\(_4\), followed by the addition of water and ethyl acetate. The residual was purified through column chromatography on silica gel to give the desired products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was financially supported by the Scientific Research Foundation of Yunnan Provincial Education Department (No. 2019J1061), Applied Basic Research Project of Yunnan (No. 202001AU070096).

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Nonfluorinated alcohols and other long chain fluorinated alcohols, such as methanol, ethanol, and 3,3,3-trifluoropropan-1-ol, not suitable substrates under the current reaction conditions, probably due to their different pKₐ values.