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Redox-Divergent Synthesis of Fluoroalkylated Pyridines and 2-Pyridones via Cu-Catalyzed N-O Cleavage of Oxime Acetates

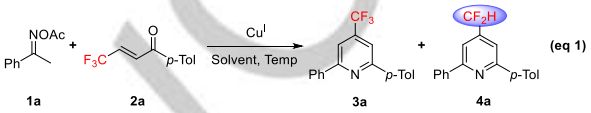
Dachang Bai,[a] Xueli Wang,[b] Guangfan Zheng,[b] Xingwei Li[a,b]*

Abstract: Cu-catalyzed redox-divergent [3+3] couplings of oxime esters with β-CF_3 enones and acrylates are described. The redox-neutral coupling with such enones and acrylates afforded trifluoromethylated pyridines and pyridones, respectively. Under reductive conditions, difluoromethylated pyridines, difluoromethylated pyridones, and trifluoromethylated dihydropyridones were selectively obtained. The reactions occurred under mild conditions with broad substrate scope and regio/redox-selectivity.

Organofluorine compounds are of vital significance in pharmaceutical, agrochemical, and material studies, as introduction of F atoms into organics has a profound impact on their metabolic stability, solubility, and lipophilicity.[1] In particular, the CF_2H group serves as a bioisostere of hydroxyl and thiol groups and a lipophilic hydrogen bond donor. Selective introduction of CF_2H into aromatics can also remarkably improve these properties, which has received considerable attention.[2] However, compared to the well-established trifluoromethylation systems, methods of difluoromethylation remain limited.[3] On the other hand, pyridines and pyridones are prevalent structural motifs in natural products and bioactive molecules.[4] The introduction of fluoroalkyls into these heterocycles can modulate their basicity and binding properties.[1-2,5] Consequently, fluorinated heteroarenes possess beneficial properties of both units and are a promising family of pharmacores. For example, Mefloquine is used to prevent or treat malaria, and Fluazinam is a broad-spectrum fungicide.[1,6]

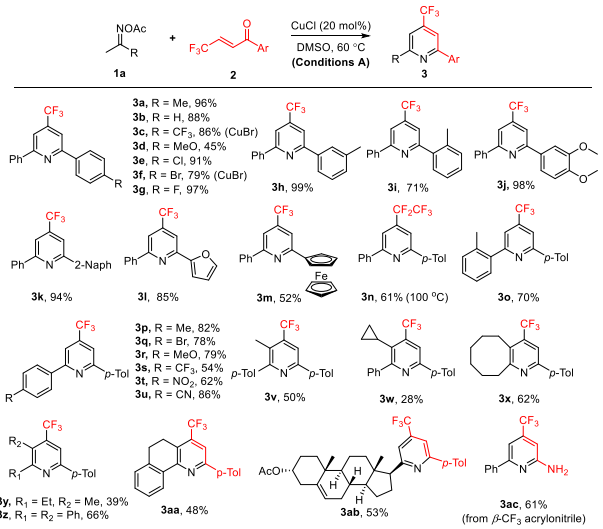
Recently, tremendous effort has been made in metal-catalyzed synthesis of pyridines.[7] The strategy of using readily available oximes to construct heterocycles is appealing.[8] Recent advancements in Cu-catalyzed [3+3]/[3+2] annulation of oxime esters with activated π-bonds, which proceeds via a nucleophilic Cu(II)-enamide, provided new routes for heterocycle synthesis, as has been reported by Guan, Yoshikai, Jiang, Wei, and others.[9,10] Recently, Yoshikai developed Cu-catalyzed synthesis of alkyl/aryl-substituted pyridines starting from oxime esters and α,β-unsaturated aldehydes/ketimines.[9c,i] However, methods for synthesis of fluoroalkylated pyridines/pyridones have been rather limited. In addition, all these systems are limited to redox-neutral or oxidative conditions.[8f] Reductive coupling of oximes remains underexplored, which substantially limited the accessible patterns of heterocycle products. We now report redox-divergent synthesis of five classes of heterocycles via Cu-catalyzed [3+3] annulation of oxime acetates with β-CF_3-substituted enones/acrylates.

We commenced our investigation with optimization studies on the coupling of oxime acetate **1a** and β-CF_3 enone **2a**[11] (eq 1 and Table S1). It was found that 4-trifluoromethylpyridine **3a** was isolated in 96% yield when simply catalyzed by CuCl in DMSO at 60 °C (Conditions A). To our surprise, the CF_2H-analogue **4a** was obtained in 68% yield when catalyzed by $CuBr/PPh_3$ in the presence of ^{t}BuOK with ^{i}PrOH as a reducing agent (Conditions B).



	1a	2a	3a	4a
Conditions A: CuCl (20 mol%), DMSO, 60 °C, 24 h			98%	nd
Conditons B: CuBr (20 mol%)/PPh_3 (25 mol%) , ^{i}PrOH (2 equiv), ^{t}BuOK (4.4 equiv), THF, 25 °C, 24 h			nd	68%

With the optimized conditions in hand, we next investigated the scope of the coupling systems (**Scheme 1**). The conditions A turned out to be broadly applicable for enones bearing diverse electron-donating and -withdrawing groups at the *para* position of the benzene ring (**3a-g**, 45-97%). The reaction also worked well for *meta*- and *ortho*-tolyl enones (**3h**, **3i**) and for various other (hetero)aryl enones (**3j-m**). Replacement of the CF_3 group in the enone by C_2F_5 also led to smooth coupling, albeit at elevated temperature (**3n**). In several cases, CuBr exhibited higher activity than CuCl (**3c**,**f**). The scope of the oxime ester was next examined in the coupling with a *p*-tolyl-substituted enone. A variety of electronically and sterically different acetophenone oximes reacted smoothly (**3o−3aa**), including those bearing an α-substituent (**3v-3aa**). This protocol is also applicable to the late-stage functionalization of a natural product. Besides enones, β-CF_3 acrylonitrile also coupled smoothly to afford a 2-aminopyridine (**3ac**) in good yield.



Scheme 1. Pyridine synthesis via condensation of oxime esters with β-fluoroalkylated enones (Conditions A). See Supporting Information for details.

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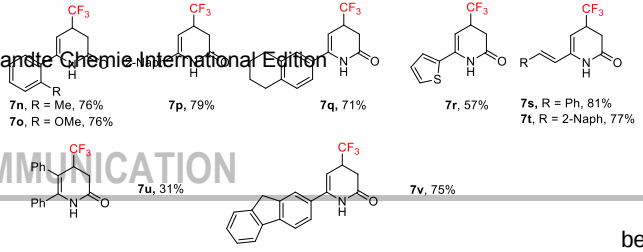
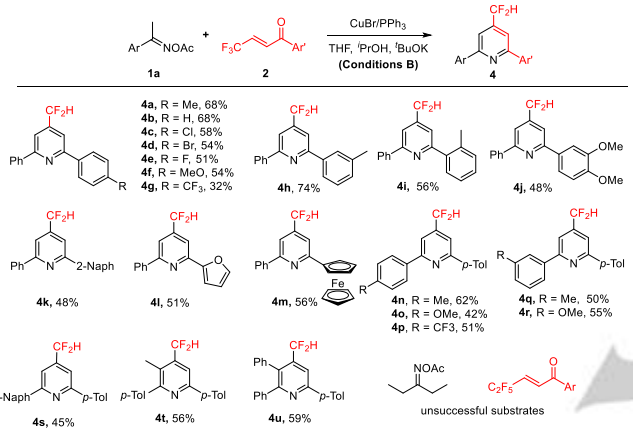


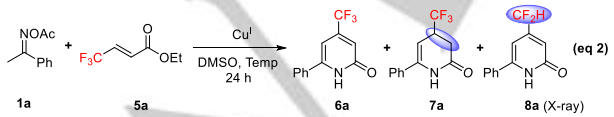
We next investigated the scope of reductive synthesis of 4-difluoromethylpyridines (Scheme 2). CF_3-substituted enones bearing various electron-donating and -withdrawing groups at the *para* position were fully tolerated (**4a-4g**, 32-68%). The reaction also tolerated enones bearing *o*-Me, *m*-Me, 2-Naph, and dimethoxy substituents (**4h**-**4k**). The coupling of 2-furyl and ferrocenyl-substituted enones also proceeded smoothly (**4l** and **4m)**. Regarding the scope of oxime esters, introduction of EDGs and EWGs to different positions of the oxime ester is tolerated (**4n-4s**). Incorporation of a Me or Ph group to the α-position of the acetophenone oxime also allowed synthesis of tetra-substituted pyridines (**4t**, **4u**). In contrast to viability of β-C_2F_5 enone and the oxime ester derived from 3-pentanone and in Scheme 1 (**3n** and



3x), no reaction occurred under the current conditions.

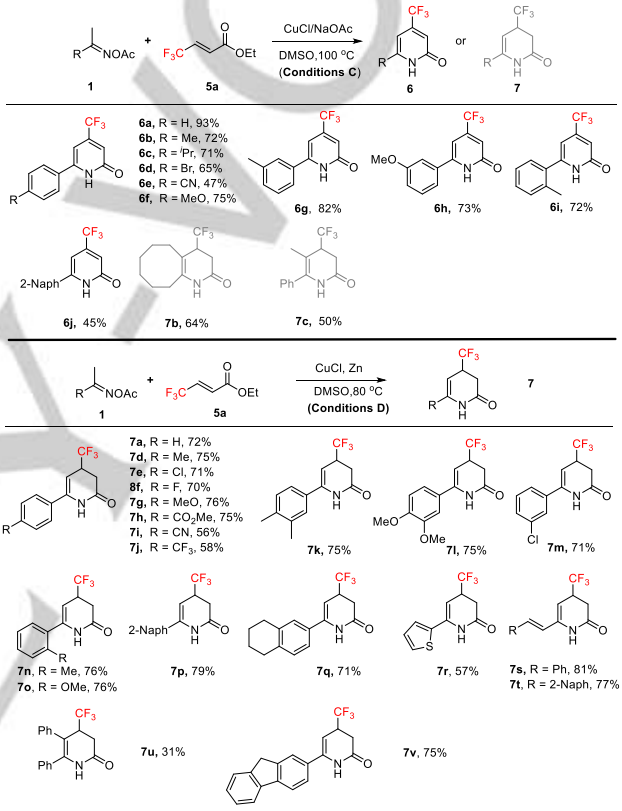
Scheme 2. Reductive coupling of oxime esters with *β*-CF_3 enones. Conditions B: **1a** (0.2 mmol), **2** (0.3 mmol), CuBr (0.04 mmol), PPh_3 (0.05 mmol), ^{i}PrOH (2.0 equiv), ^{t}BuOK (4.4 eq) in THF (2.0 mL), isolated yields.

To better define the scope of the present [3+3] annulation reaction, we next examined the annulation using a less electrophilic β-trifluoromethylated acrylate (**5a**) as a coupling partner (eq 2 and Table S2). Extensive screening of the solvent, temperature, base, and reductant revealed that redox-neutral annulation occurred with NaOAc as an additive to give 4-CF_3 pyridine **6a** in high yield (Conditions C). Application of Zn as a reductant afforded CF_3-retentive reduction product **7a** (Conditions D). In addition, 4-CF_2H-substituted pyridone **8a** (X-Ray analysis) [12] was isolated as the major product when DBU was employed as a base as well as a reductant (Conditions E).



	6a	7a	8a (X-ray)
Conditions C: CuCl (20 mol%), NaOAc (2 equiv), 100 °C	93%	nd	nd
Conditions D: CuCl (10 mol%), Zn (25 mol %), 80 °C	< 5%	72%	< 5%
Conditions E: CuCl (20 mol%), DBU (2 euiv), 120 °C	< 5%	< 5%	83%

Synthesis of 4-trifluoromethylated pyridones was then explored (Scheme 3). Various oximes derived from acetophenones exhibited good functional group tolerance, regardless of the presence of halogens, EWGs, and EDGs in the benzene ring (**6a-6j**, 47-93%). Introduction of an alkyl group to the α-position of the oxime, surprisingly, shifted the selectivity to the reduction product (dihydropyridones **7b**, **7c**). It is likely that the steric effect of these alkyl groups inhibits oxidative aromatization. To highlight synthesis of dihydropyridones, the conditions **D** were adopted. It was found that a truly large scope of oxime esters coupled with **5a** in good to excellent yield, with full compatibility with EDGs and EWGs (**7a-7r, 7v**) and tolerance of steric and electronic effects of the oxime ester substrate. The reaction was equally efficient for alkenyl-substituted oxime esters (**7s, 7t**). Introduction of a phenyl group to the α-position of oxime is also tolerated, albeit with lower yield (**7u**).



Scheme 3. CF_3-retentive annulation of oxime esters with a β-CF_3 acrylate Reaction. Conditions C: oxime **1** (0.2 mmol), **5a** (0.4 mmol), CuCl (0.04 mol), NaOAc (0.40 mmol), and DMSO (2.0 mL), 100 ℃, 24 h. Conditions D: **1** (0.2 mmol), **5a** (0.4 mmol), CuCl (0.02 mol), Zn (25 mol%), DMSO (3.5 mL), 80 ℃, 24 h.

The scope of the fifth class of product, 4-difluomethylpyridone, was accordingly examined under conditions E with DBU (Scheme 4). In line with the scope of other coupling systems, oxime esters derived from acetophenones and other ketones all underwent smooth coupling with acrylate **2a** to afford the desired products in moderate to excellent yield, although oxime esters bearing an α-alkyl/aryl group tend to react in lower efficiency (**8k**, **8l**).

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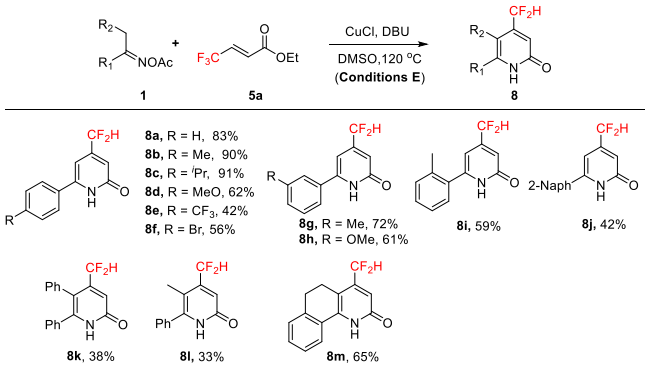
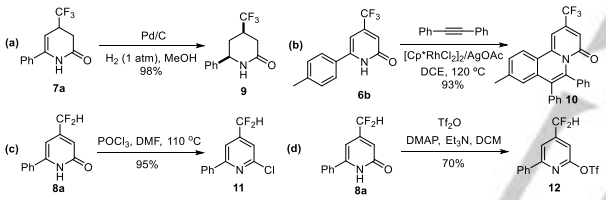


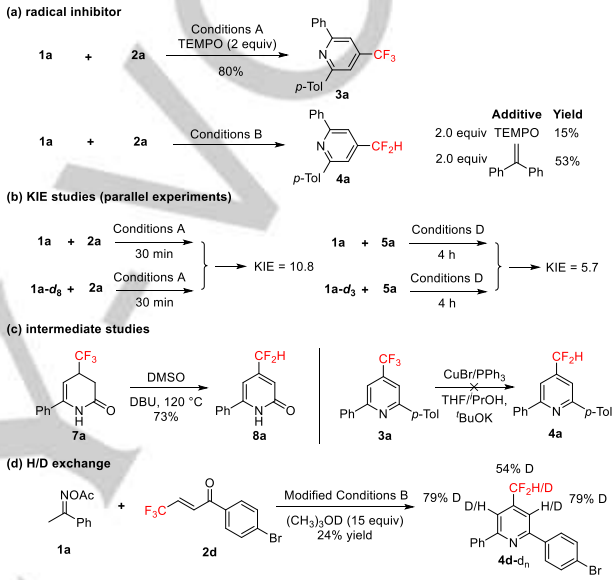
Scheme 4. Dehydrofluorinative coupling of oxime esters with a β-CF_3 acrylate Conditions E: **1** (0.2 mmol), **5a** (0.4 mmol), CuCl (0.04 mol), DBU (0.40 mmol), DMSO (2.0 mL), 120 ℃, isolated yields.

The synthetic utility of (dihydro)pyridones has been briefly demonstrated (Scheme 5). Hydrogenation of dihydropyridone **7a** afforded lactam **9** as a single diastereomer in nearly quantitative yield. In addition, Rh(III)-catalyzed oxidative [4+2] coupling between NH pyridone **6b** and diphenylacetylene afforded a fused heterocycle (**10**) in excellent yield.[13] 2-Chlorination of **8a** gave **11**, and the *O*-triflation of **8a** yielded **12**. The presence of Cl and OTf group allows further manipulation.

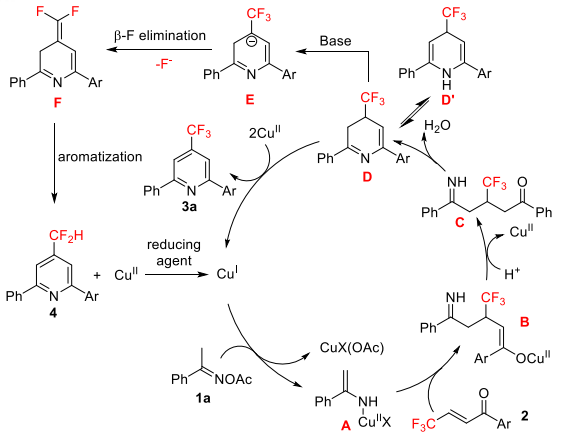


Scheme 5. Derivatization Reactions.

Several experiments have been performed to probe the mechanism of these coupling systems (Scheme 6). Addition of TEMPO to the coupling of **1a** and **2a** caused no inhibition toward formation of **3a** (conditions A), indicating an ionic pathway. In fact, this conclusion is consistent with observation of product **3w** (Scheme 1), as a radical pathway would lead to ring scission.[10a] While formation of CF_2H-substituted pyridine **4a** was retarded with addition of TEMPO (conditions B), the reaction was only slightly affected when 1,1-diphenylethylene was introduced (Scheme 6a), so no solid conclusion on C-centered α-imino radical can be drawn. Parallel reactions were then conducted using **1a** and labeled **1a**-d_8 or **1a**-d_3 for KIE studies. Significant kinetic isotope effects have been observed for the coupling with an enone (KIE = 10.8, conditions A) or with an acrylate (KIE = 5.7, conditions D). These results suggest that cleavage of the α-C-H bond is involved in the turnover-limiting step (Scheme 6b). To identify intermediates during the formation of 4-CF_2H pyridone **8a**, 4-CF_3-functinalized dihydropyridone **7a** was treated with DBU in DMSO, which led to clean formation of **8a** (Scheme 6c), suggesting that it was generated via elimination of HF followed by tautomerization. In contrast, **3a** proved not to be an intermediate for the formation of **4a** since no conversion of **3a** was observed (GC-MS) under conditions B. Likewise, **4a** is likely generated via dehydrofluorination of a CF_3-functionalized 3,4-dihydropyridine. We also performed H/D exchange experiment for the coupling of **1a** and enone **1d** with ^{t}BuOD as a deuterium source (Conditions B). NMR analysis of the isolated product revealed that both the 3- and 5-positions are equally deuterated (79% D), and significant H/D exchange was also detected at the difluoromethyl position (Scheme 6d), which agrees with intermediacy of a CF_3-dihydropyridine (see Scheme 7) with subsequent tautomerization[14] (Note that no post-coupling H/D exchange was observed for **4d** under the standard conditions with CD_3OD or ^{t}BuOD, as confirmed by our control experiments).



Scheme 6. Mechanistic studies.



Scheme 7. Proposed Mechanism.

On the basis of our studies and reports on Cu-catalyzed coupling of oximes, a plausible pathway is given for formation of pyridines (Scheme 7).[9c,i] Oxidation of Cu(I) by oxime ester **1** gives a copper(II) enamide **A** together with a Cu(II) species. Conjugate addition of **A** to enone **2a** then yields an enolate species **B**, and subsequent protolonysis leads to ketone **C**. Dehydrative cyclization would produce a dihydropyridine intermediate **D**, and

further oxidation of **D** by two copper(II) species furnishes CF_3-pyridine product **3** with regeneration of the copper(I) catalyst. In presence of a suitable base and reductant, **D** undergoes $E1_{cb}$ to afford intermediate **F**, which then isomerizes to the 4-CF_2H-pyridine product **4**. Meanwhile, the Cu(I) catalyst is regenerated by further reduction of Cu(II). The coupling with a β-CF_3 acrylate likely follows the same mechanism except that the cyclization process forms an amide bond. Following this cyclization, the dihydropyridone species is either released, oxidized by Cu(II), or undergo elimination of HF under condition control, and the last pathway is favored for DBU, a stronger base and reductant.

In summary, we have demonstrated redox-divergent access to five classes of fluoroalkylated heterocycles via copper-catalyzed [3+3] coupling of oxime acetates with β-trifluoromethylated enones/acrylates. Under redox-neutral conditions, the coupling afforded 4-CF_3-pyridines and -pyridones. The coupling using ^{i}PrOH, Zn, and DBU as a reductant led to selective formation of 4-CF_2H pyridines, 4-CF_3-dihydropyridones, and 4-CF_2H pyridones, respectively. The coupling systems cover a particularly broad range of oxime acetates derived from aryl-alkyl and dialkyl ketones in acyclic as well as cyclic settings. The redox-diversity and elegant control of reaction selectivity may provide insight for future studies of other Cu-catalyzed systems, which are currently underway in our laboratories.

Acknowledgements ((optional))

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Keywords: Copper • Pyridine • Pyridone • Oxime• Fluoroalkyl

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[12] CCDC-1824515 (**8a**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

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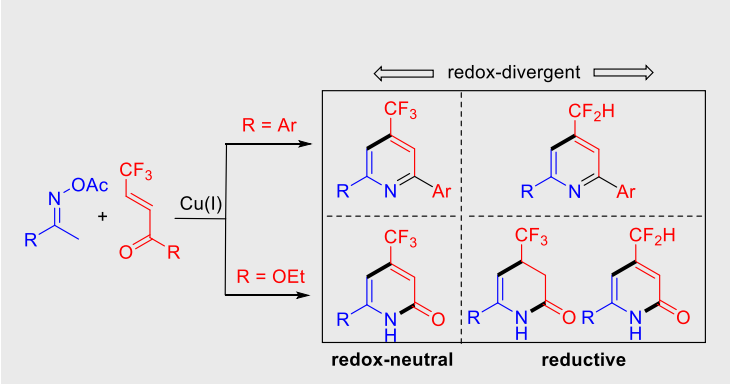

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Redox-Divergent Synthesis of Fluoroalkylated Pyridines and 2-Pyridones via Cu-Catalyzed N-O Cleavage of Oxime Acetates

Redox-divergent Cu-catalyzed coupling of oxime acetates with β-CF_3-substituted enones/acrylates led to selective synthesis of fluoroalkylated pyridines and (dihydro)pyridones via substrate control and redox-control.