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Photoredox-Catalyzed Tandem Insertion/Cyclization Reactions of Difluoromethyl and 1,1-Difluoroalkyl Radicals with Biphenyl Isocyanides

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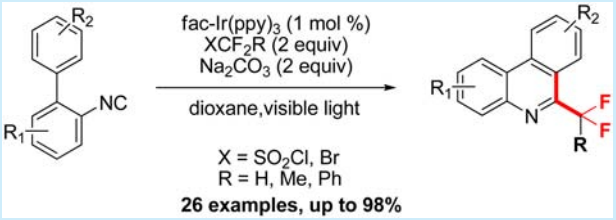
Supporting Information

ABSTRACT: Using visible-light photoredox conditions, difluoromethylation and 1,1-difluoroalkylation of biphenyl isocyanides have allowed the synthesis of a series of 6-(difluoromethyl)- and 6-(1,1-difluoroalkyl)phenanthridines via tandem addition/cyclization/oxidation processes. The reactions are carried out in wet dioxane at room temperature using *fac*-Ir(ppy)$_3$ as catalyst to form a large variety of substituted phenanthridine products in good to excellent yield.

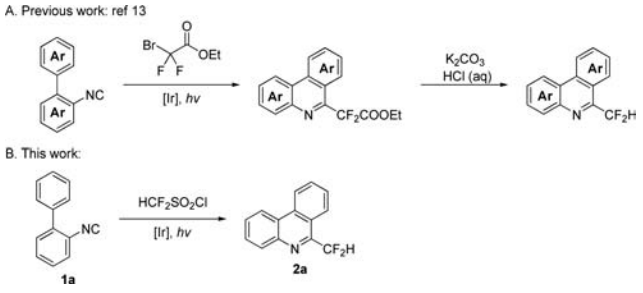


The introduction of fluorine-containing alkyl groups into molecules has attracted researchers' interest for several decades because of the beneficial properties that their presence can bestow, including enhanced reactivity, lipophilicity, and bioactivity.[1] A host of elegant approaches have been developed to introduce fluoro substitutents and fluorinated alkyl groups; in particular, the trifluoromethyl group, into diverse skeletons.[2] However, methodologies to introduce CF_2H have been considerably less studied.[3,4] Traditional methods for the synthesis of difluoroalkylated molecules generally involved the use of expensive and highly reactive reagents such as SF_4, (diethylamino)sulfur trifluoride (DAST), and other related reagents to carry out deoxyfluorination of aldehydes and ketones.[5] In addition to the many undesirable aspects of these methodologies, they also generally suffer from poor functional group tolerance. Therefore, the development of new methods for introduction of CF_2H and other *gem*-difluoroalkyl groups into organic compounds remains a challenging and worthwhile endeavor.

Recently, there has been much excellent work in the area of direct introduction of the difluoromethyl group into aromatic and heteroaromatic compounds mainly via radical processes or cross-coupling reactions.[6−8] For instance, in 2012, Baran's group developed a new reagent $Zn(SO_2CF_2H)_2$ which under oxidative conditions generates the difluoromethyl radical that will allow difluoromethylation of heterocycles.[6] In the same year, Hartwig and Prakash independently reported copper-mediated difluoromethylation of aryl iodides using (trimethylsilyl)difluoromethane ($TMSCF_2H$) and tributyl(difluoromethyl)stannane (n-Bu_3SnCF_2H), respectively, as their sources of difluoromethyl.[7] Shen and his co-workernd co-workers realized difluoromethylation of aryl iodides and bromides using $TMSCF_2H$ with copper and silver as cocatalyst.[8] The Goossen group also reported Sandmeyer difluoromethylation of aryl diazonium salts.[9]

The phenanthridine core occurs widely in natural products and biological molecules.[10] One effective method for preparing phenanthridines bearing substituents at the 6-position has involved reactions of various radicals, including trifluoromethyl, with 2-isocyano-1,1′-biphenyl.[11,12] With respect to the difluoromethyl group, thus far, only Yu's group has reported a method for difluoromethylation of isocyanides, in his case using a stepwise strategy involving initial reaction with the carboethoxydifluoromethyl radical (Scheme 1 (a)).[13] The *direct* difluoromethylation of isocyanides is still unreported.

Scheme 1. Preparation of 6-(Difluoromethyl)phenanthridine



In recent work, our group has demonstrated that, under photoredox catalysis, CF_2HSO_2Cl can be a very good difluoromethyl radical precursor, with the generated radical showing good reactivity toward both electron-rich and electron-poor double bonds.[14] We envisioned that a similarly generated CF_2H radical would react with 2-isocyano-1,1′-biphenyl (**1a**), with the intermediate radical then cyclizing with subsequent oxidation and deprotonation to form 6-(difluoromethyl)-phenanthridine (Scheme 1 (b)).

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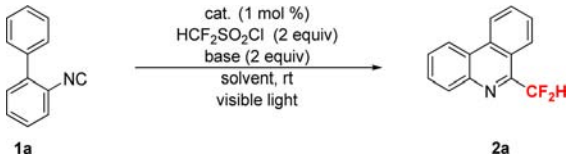
To test our hypothesis, **1a** was used as substrate under the photoredox conditions that we had used previously to generate the difluoromethyl radical, using *fac*-Ir(ppy)$_3$ as catalyst with 1 mol % loading. Considering their previously determined significance, several bases were examined (Table 1). Unfortunately, only trace amounts of product were detected when using Na_2CO_3 and K_2HPO_4 (entries 1 and 2), and looking at a few other bases did not improve the situation, with **1a** largely remaining unreacted (entries 3–7). Solvent dependence was then examined. Using K_2HPO_4 as base, highly polar solvents were found to be ineffective (entries 8–10), but combining dioxane with a small amount of water led to 54% of the desired product (entry 11). Other Ir photoredox catalysts gave similar results (entry 12 and 13). However, changing the base to Na_2CO_3 led to an increase in yield to 84%, which was considered to be satisfactory (entry 14). It should be mentioned that only 20% of product was obtained in the absence of water (entry 15). The exact effect of water is still unclear, but it is probable that water promotes the solubility of the base in dioxane.

Table 1. Screening Conditions[a,b]



1a 2a

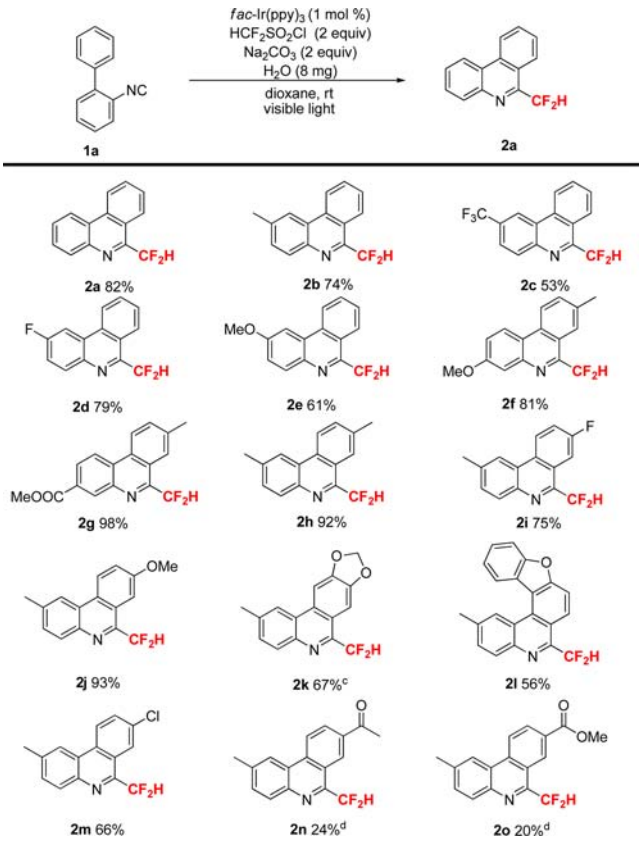
entry	catalyst	solvent	base	yield (%)
1	Ir(ppy)$_3$	CH_3CN	Na_2CO_3	trace
2	Ir(ppy)$_3$	CH_3CN	K_2HPO_4	trace
3	Ir(ppy)$_3$	CH_3CN	Ag_2CO_3	ND
4	Ir(ppy)$_3$	CH_3CN	K_2CO_3	ND
5	Ir(ppy)$_3$	CH_3CN	K_3PO_4	ND
6	Ir(ppy)$_3$	CH_3CN	KOAc	ND
7	Ir(ppy)$_3$	CH_3CN	NaOAc	ND
8	Ir(ppy)$_3$	DMF	K_2HPO_4	ND
9	Ir(ppy)$_3$	DMAc	K_2HPO_4	ND
10	Ir(ppy)$_3$	NMP	K_2HPO_4	ND
11[c]	Ir(ppy)$_3$	dioxane	K_2HPO_4	54
12[c]	[Ir{df(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$	dioxane	K_2HPO_4	63
13[c]	[Ir(dtbpy) (ppy)$_2$]PF$_6$	dioxane	K_2HPO_4	56
14[c]	Ir(ppy)$_3$	dioxane	Na_2CO_3	84
15	Ir(ppy)$_3$	dioxane	Na_2CO_3	20

[a]Reactions were run with 0.1 mmol of **1a**, 0.2 mmol of HCF_2SO_2Cl, 0.2 mmol of base, and 0.001 mmol of catalyst in 1 mL of solvent under visible light. [b]All yields were based on **1a** using fluorobenzene as internal standard. [c]4–6 mg of water as additive

To study the scope of the reaction, various biarylisonitriles were tested (Scheme 2). A variety of substituents, both electron rich and electron poor, on the isonitrile arene moiety, including methyl (**1b**), carbomethoxy (**1g**), methoxy (**1e**, **1f**), fluoro (**1d**), and CF_3 (**1c**), produced the corresponding products in good to excellent yields. Substitution on the other phenyl ring indicated that the reaction did not tolerate electron-poor substituents on this ring, with compounds **2n** and **2o** being formed in poor yield. Otherwise, it appears that this reaction is quite versatile with respect to substitution and multisubstitution of the two phenyl rings.

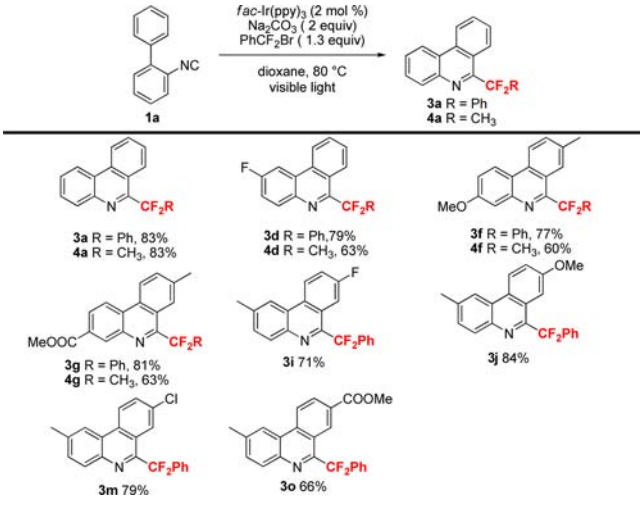
To further explore the application of the tandem reaction, RCF_2X was employed under the optimized conditions (Scheme 3). Since the $PhCF_2Br$ is liquid and easier to prepare than the respective sulfonyl chloride, it was used as the precursor of the $PhCF_2$ radical instead of the sulfonyl chloride. Using a higher

Scheme 2. Substrates Scope of Difluoromethylation of Isocyanides[a]



[a]Reactions were run with 0.2 mmol of **1a**, 0.4 mmol of HCF_2SO_2Cl, 0.4 mmol of base, and 0.002 mmol of catalyst in 2 mL of dioxane with 8 mg water under visible light. [b]Isolated yield. [c]Regioselectivity (2.6:1) [d]Yields were determined by ^{19}F NMR using fluorobenzene as internal standard.

Scheme 3. Substrate Scope of Other *gem*-Difluoroalkylations of Isocyanides



[a]Reactions were run with 0.1 mmol of **1a**, 0.13 mmol of $PhCF_2Br$, 0.2 mmol of base, and 0.002 mmol of catalyst in 1 mL of solvent under visible light. [b]Isolated yield.

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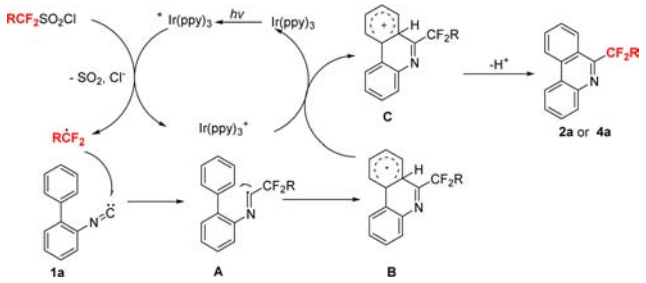
temperature and 2% loading of catalyst, very good yields were able to be obtained for a variety of substrates.

Additionally, $CH_3CF_2SO_2Cl$ proved effective as a source of 1,1-difluoroethyl radical for addition to the isocyanides, leading to formation of the corresponding phenanthridine products (**4**) in good yield.

A photoredox catalytic cycle was proposed as the mechanism of these reactions, based on precendent (Scheme 4). First, the

Scheme 4. Proposed Mechanism



excited Ir catalyst reduces the sulfonyl chloride to form the difluoromethyl radical, which then adds to the isonitrile to generate the imidoyl radical **A**, which cyclizes on the arene to give cyclohexadienyl radical **B**. Then **B** is oxidized by the high-valent catalyst to form cationic intermediate **C** with regeneration of catalyst. Finally, intermediate **C** is depronated to form the product.

In conclusion, the first example of difluoromethyl and 1,1-difluoroalkyl radical isonitrile insertion reactions which afford phenanthridine derivatives under mild conditions is reported. The difluoromethyl radical as well as α,α-difluorobenzyl or 1,1,-difluoroethyl radicals exhibited excellent reactivity with isonitriles. The respective sulfonyl chlorides were excellent precursors for the difluoromethyl and 1,1-difluoroethyl radicals, whereas (bromodifluoromethyl)benzene proved effective as the precursor for the α,α-difluorobenzyl radical.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02061.

Experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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