Photocatalysis

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Visible-Light Photoredox-Catalyzed C–H Difluoroalkylation of Hydrazones through an Aminyl Radical/Polar Mechanism

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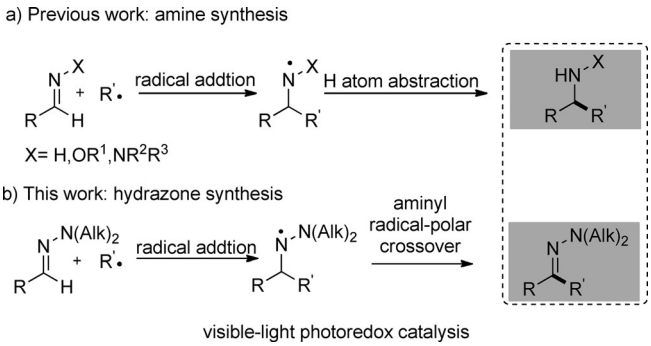
Abstract: *An unprecedented visible-light-induced direct C–H bond difluoroalkylation of aldehyde-derived hydrazones was developed. This reaction represents a new way to synthesize substituted hydrazones. The salient features of this reaction include difluorinated hydrazone synthesis rather than classical amine synthesis, extremely mild reaction conditions, high efficiency, wide substrate scope, ease in further transformations of the products, and one-pot syntheses. Mechanistic analyses and theoretical calculations indicate that this reaction is enabled by a novel aminyl radical/polar crossover mechanism, with the aminyl radical being oxidized into the corresponding aminyl cation through a single electron transfer (SET) process.*

The incorporation of a difluoromethyl group (CF_2) into organic molecules is particularly intriguing because of its significant applications in the life sciences.[1] It is indeed well-established that the strategic introduction of a difluoromethyl group can improve the physicochemical properties of organic compounds. For example, the CF_2 group can act as a bioisostere for an oxygen atom or a carbonyl group, and also serve as a lipophilic hydrogen-bond donor.[2] For these reasons, substantial effort has been devoted to the development of synthetic methods for the incorporation of the CF_2 group.[3]

Over the past five years, the addition of a CF_2 radical to a π acceptor has been developed as one of the most straightforward methods to access structurally diverse difluorinated compounds.[4] Nevertheless, despite these important progress, existing methods for radical-type difluoroalkylation are extremely limited to carbon–carbon π bonds (alkene, alkyne, or arene). In contrast, and to the best of our knowledge, no direct difluoroalkylation of carbon–nitrigen π bonds has been reported. The most common and venerable synthetic application of radical addition to imine functional groups is reductive addition for the synthesis of amines (Scheme 1a).[5,6] In this generic reaction manifold, radical addition to a C=N bond first generates an aminyl radical, which then readily undergoes H atom abstraction from the solvent or another hydrogen source. Here we wondered whether this regular pattern could be intercepted, through a radical-polar crossover strategy,[7] thus considerably expanding the synthetic utility of imino compounds.



Scheme 1. Radical addition to carbon–nitrigen π bonds.

Visible-light photoredox catalysis has recently emerged as a powerful tool in synthetic organic chemistry and features the unique ability to facilitate radical/polar crossover reactions.[8] We envisioned that the aminyl radical could undergo a stepwise single-electron oxidation and deprotonation process mediated by visible-light photoredox catalysis (Scheme 1b). Such a process would restore the imino group and exploit new methodology for C–H bond functionalization of aldehyde-derived imino compounds. As a part of our recent ongoing efforts on visible-light-promoted direct difluoroalkylation,[4j,k] we report below the first successful development of visible-light-induced C–H difluoroalkylation of aldehyde-derived hydrazones. To our knowledge, the visible-light photoredox-catalyzed aminyl radical/polar crossover reaction has not been reported so far, thus representing a challenge.

To validate the feasibility of this aminyl radical/polar process, the readily accessible aldehyde hydrazone **1a** was chosen as the substrate on account of its quick radical addition rate relative to that of oxime ethers or imines (Table 1).[9] In an initial test, **1a** was reacted with $BrCF_2CO_2Et$ (**2a**) in acetonitrile (0.1 M) under visible-light irradiation from a 25W fluorescent light bulb in the presence of *fac*-[Ir(ppy)$_3$] and Na_2HPO_4 (Table 1, entry 1). Delightfully,

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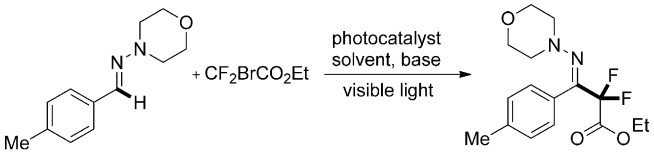
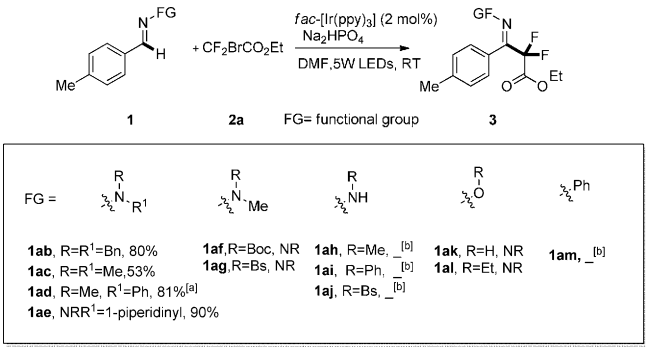
Table 1: Optimization studies.[a]



Entry	Photocatalyst	Base	Solvent	Yield [%][b]
1	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	CH_3CN	58
2	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	CH_2Cl_2	40
3	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	DMSO	80
4	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	DMF	86
5	[Ir(ppy)$_2$(dtbpy)$_3$]PF_6	Na_2HPO_4	DMF	83
6	[Ru(bpy)$_3$]$(PF_6)_2$	Na_2HPO_4	DMF	52
7	*fac*-[Ir(ppy)$_3$]	–	DMF	20
8	*fac*-[Ir(ppy)$_3$]	KOAc	DMF	52
9	*fac*-[Ir(ppy)$_3$]	Na_2CO_3	DMF	72
10[c]	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	DMF	92
11	–	Na_2HPO_4	DMF	0
12[d]	*fac*-[Ir(ppy)$_3$]	Na_2HPO_4	DMF	0

[a] The reactions were carried out with **1a** (0.1 mmol), CF_2BrCO_2Et (0.15 mmol, 1.5 equiv), base (0.15 mmol, 1.5 equiv), photocatalyst (0.002 mmol, 2 mol%), solvent (1 mL), at room temperature, 25W fluorescent light bulb, 12 h. [b] Yield of isolated product. [c] 5W LEDs. [d] In dark. bpy = bipyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, ppy = phenylpyridine, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.



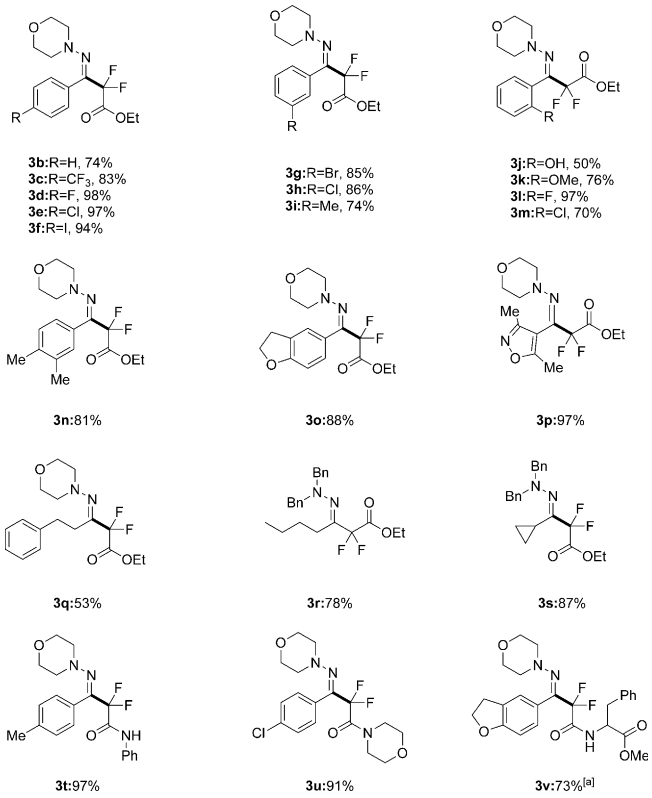
Scheme 2. Investigation of the effect of the N-substituent. Reaction conditions: **1** (0.1 mmol), **2a** CF_2BrCO_2Et (0.15 mmol, 1.5 equiv), Na_2HPO_4 (0.15 mmol, 1.5 equiv), *fac*-[Ir(ppy)$_3$] (0.002 mmol, 2 mol%), DMF (1 mL), at room temperature, 5W LEDs, 12 h. The *E*-configured products are shown and the yields are those of the isolated product. [a] 1.2 equiv CF_2BrCO_2Et were used. Trace amounts of the aromatic C–H difluoroalkylation product were detected. [b] Starting materials were consumed and a complex mixture of products were obtained. Boc = *tert*-butoxycarbonyl, Bs = benzenesulfonyl.

the desired product **3a** was isolated with a satisfactory yield of 58%. After solvent screening, strong polar solvents, such as DMF and DMSO, were found to be more suitable for this reaction (entries 2–4). The catalysts [Ir(ppy)$_2$(dtbpy)$_3$]PF_6 and [Ru(bpy)$_3$]$(PF_6)_2$ showed inferior reactivity toward the conversion of **1a** (entries 5 and 6). The addition of a base is essential for this reaction and its role is to neutralize the byproduct HBr. Further screening showed other bases, such as KOAc and Na_2CO_3, gave lower yields of this reaction (entries 7–9). Furthermore, it was found the highest yield of **3a** (92%) was obtained when 5W LEDs were adopted instead of a 25 W fluorescent light bulb (entry 10). Control experiments showed the reaction could not proceed in the absence of either visible-light irradiation or the photocatalyst (entries 11 and 12). It is worth mentioning that no difluorinated hydrazones were detected in any of the above cases.

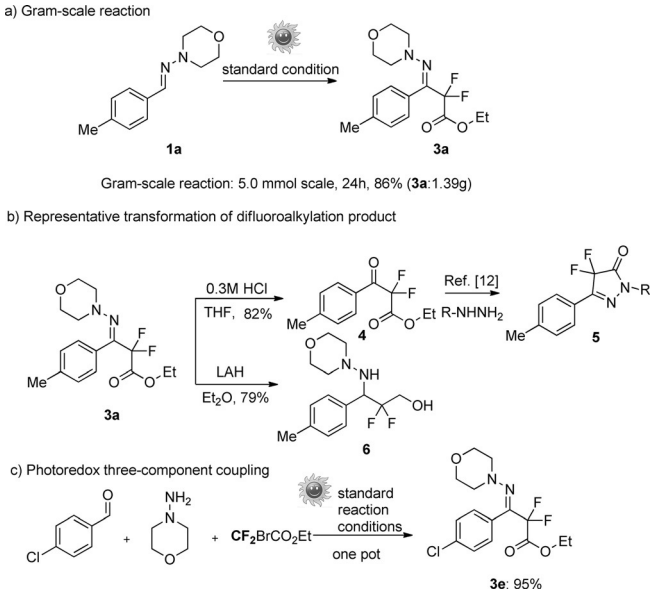
With the preliminary realization of visible-light-induced C–H difluoroalkylation of **1a**, we next investigated the effect of the N-substituent (**1ab–aj**; Scheme 2). The reaction of **1ab–ae** all furnished the desired products with moderate to good yields (53–90%), whereas the *N*-Boc and *N*-Bs hydrazones, **1af** and **1ag**, respectively, failed to give the desired product. Additionally, this reaction did not tolerate secondary amino groups as a complex mixture of products was obtained in the cases of **1ah–aj**, eventhough the starting materials were consumed. These experimental results indicated that the N,N-dialkyl structural motif is crucial for this transformation. We speculated that this activity difference may be explained by the three-electron π-bond interaction between amino radical with the adjacent nitrogen atom. This interaction could affect stabilization of the transition state. Oxime ethers and imines are other radical acceptors containing a C=N group. However, no reaction occurred when either oxime ethers (**1ak** and **1al**) or an imine (**1am**) were used as the substrates.

With these results in hand, we turned our attention to explore the scope with respect to N,N-dialkyl hydrazones under the optimized reaction conditions. The representative examples are shown in Scheme 3. (Hetero)aryl aldehyde-derivied hydrazones bearing either electron-donating (methyl, methoxy) or electron-withdrawing (trifluoromethyl, fluoro) substituents furnished the corresponding products with good to excellent yields (**3b–p**). The position of the substitutents on the phenyl ring has no effect on this reaction. Remarkably, the C–H difluoroalkylation reaction of heterocyclic hydrazones also proceeded well to give the desired products in good yields (**3o–p**). Encouraged by the successful difluoroalkylation of (hetero)aryl aldehyde-derived hydrazones, we tried to extend the scope of this reaction to aliphatic aldehyde-derived hydrazones. To our delight, the difluoroalkylation proceeded well, thus giving the desired product in moderate to good yields (**3q–s**). Bromodifluoroacetamides were studied as difluorinating reagents,[10] and they proved to be suitable substrates, thus providing the corresponding difluorinated hydrazone with excellent yields (**3t–u**). Additionally, the phenylalanine-derived bromodifluoroamide also reacted smoothly, thus offering facile access to complex fluorinated compounds (**3v**). To clarify, the main product in the target hydrazones was determined to be *E* configured by a ^1H–^1H NOESY NMR experiment (see the Supporting Information for details).[11] In addition, we found that slow *E*/*Z* isomerization is affected by both solvent and temperature.

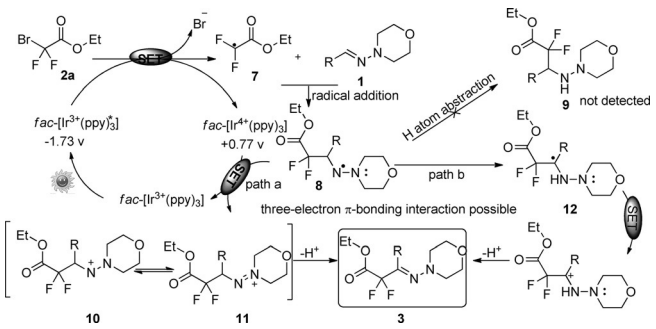
To demonstrate the synthetic utility of this visible-light-promoted difluoroalkylation reaction, a gram-scale reaction was carried out under standard reaction conditions. We were delighted to find that the synthesis of **3a** proceeded smoothly with a good yield of 86% on a 5 mmol scale (Scheme 4a). Hydrazones are significant and versatile reagents in organic chemistry. Simple acidic treatment of **3a** readily delivered the



Scheme 3. Scope of N,N-dialkyl hydrazones in the difluoroalkylation reaction. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol, 1.5 equiv), Na_2HPO_4 (0.15 mmol, 1.5 equiv), *fac*-[Ir(ppy)$_3$] (0.002 mmol, 2 mol%), DMF (1 mL), at room temperature, 5W LEDs, 12–24 h. The *E*-configured products are shown and the yields are those of the isolated products. [a] 3 equiv phenylalanine derived bromodifluoroamide **2d** were used.



Scheme 4. Synthetic utility of methodology. LAH = lithium aluminum hydride.



Scheme 5. Plausible mechanism.

corresponding difluorinated β-ketoester, which could react with hydrazines toward biologically active 4,4-difluoropyrazol-5-ones (Scheme 4b).[12] In addition, difluorinated hydrazine could be easily obtained in 79% yield by reduction of **3a** with lithium aluminum hydride in diethyl ether (Scheme 4b). Integration of multistep chemical reactions into a one-pot reaction represents an atom- and step-economical process. We wished to incorporate the aldehyde, hydrazine, and $BrCF_2CO_2Et$ in a highly efficient one-pot condensation/C–$C(CF_2)$ bond-forming reaction. Most remarkably, the one-pot three-component coupling reaction proceeded smoothly to give an excellent yield (95%) of product **3e**, thus making the present photoredox catalysis strategy more attractive and robust (Scheme 4c).

A plausible aminyl radical/polar mechanism is proposed, but a precise reaction mechanism awaits further study. Under visible-light irradiation, the photocatalyst *fac*-[$Ir^{3+}(ppy)_3$] undergoes a metal to ligand charge-transfer (MLCT) process to produce the strongly reducing excited state Ir^{3+}* (−1.73 V vs. SCE in CH_3CN; Scheme 5). Then a SET process from this species to **2a** generates the CF_2 radical precursor **7** and Ir^{4+} (+0.77 V vs. SCE in CH_3CN).[4] It was found no product was detected when the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added to the reaction system, thus further implying a radical reaction. Subsequent radical addition to the C=N bond leads to the aminyl radical intermediate **8**, which should be stabilized by the adjacent nitrogen atom through a possible three-electron π-bonding interaction. At this point, **8** does not undergo H atom abstraction to generate corresponding hydrazine **9**. Instead, a key aminyl radical/polar crossover step proceeds between **8** and Ir^{4+}, thus regenerating the photocatalyst and either the aminyl cation **10** or **11** (path a). Further tautomerization and deprotonation of aminyl cation would give the product **3**. Alternatively, a light on/off experiment verified the necessity of continuous irradiation of visible light and suggested that chain propagation is not the predominant mechanistic pathway (Figure 1).

In addition to the aminyl radical/polar mechanism (Scheme 5, path a), another possible carbon radical/polar process is depicted (Scheme 5, path b). As the oxidation potential of radical intermediate cannot be measured, DFT calculations were performed to explore the Gibbs free-energy profiles of the two different reaction paths (Figure 2). In path b, the conversion of the aminyl radical **8** into the carbon radical **12** for substrates **1a**, **1af**, **1ag**, and **1al** is endothermic

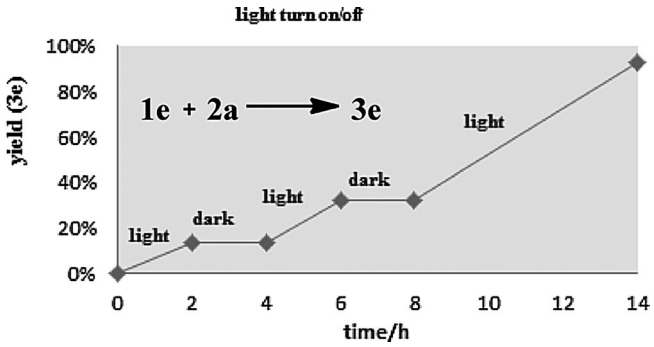


Figure 1. Time profile of difluoroalkylation of **1e** with and without light.

by 6.1, 3.4, 1.3, and 7.1 kcal mol^{-1}, respectively. Although the conversion of **8** into **12** for substrates **1af** and **1ag** is thermodynamically more favorable than that of substrate **1a**, both **1af** and **1ag** exhibit no reactivity experimentally. Hence, the path b can be excluded. On the contrary, for path a, the SET step in the conversion of **8** into **11** for substrate **1a** is exothermic by 13.2 kcal mol^{-1}. However, for the substrate with the electron-withdrawing substituent **1ag**, the formation of the aminyl cation is only exothermic by 0.4 kcal mol^{-1}, and for substrates **1af** and **1al**, the corresponding process is endothermic by 1.6 and 17.9 kcal mol^{-1}, respectively. Hence, the formation of **11** from **1a** is more favorable than the processes from the other three substrates. These results can account for the fact that only **1a** exhibits the reactivity experimentally. Therefore, the aminyl radical/polar mechanism (path a) is responsible for the visible-light photoredox-catalyzed difluoroalkylation of aldehyde-derived hydrazones.

In conclusion, we have successfully developed the visible-light photoredox-catalyzed C–H difluoroalkylation of aldehyde-derived hydrazones for the first time. In addition, the current method is further highlighted by the feasibility of the one-pot synthesis of a difluorinated hydrazone. More importantly, this unprecedented photoredox protocol for C–H bond functionalization of hydrazones is enabled by a novel aminyl radical/polar crossover mechanism. We anticipate this new mode of intrinsic reactivity, revealed by the aminyl radical/polar crossover process, will be used for more transformations of carbon–nitrogen π bond bonds.

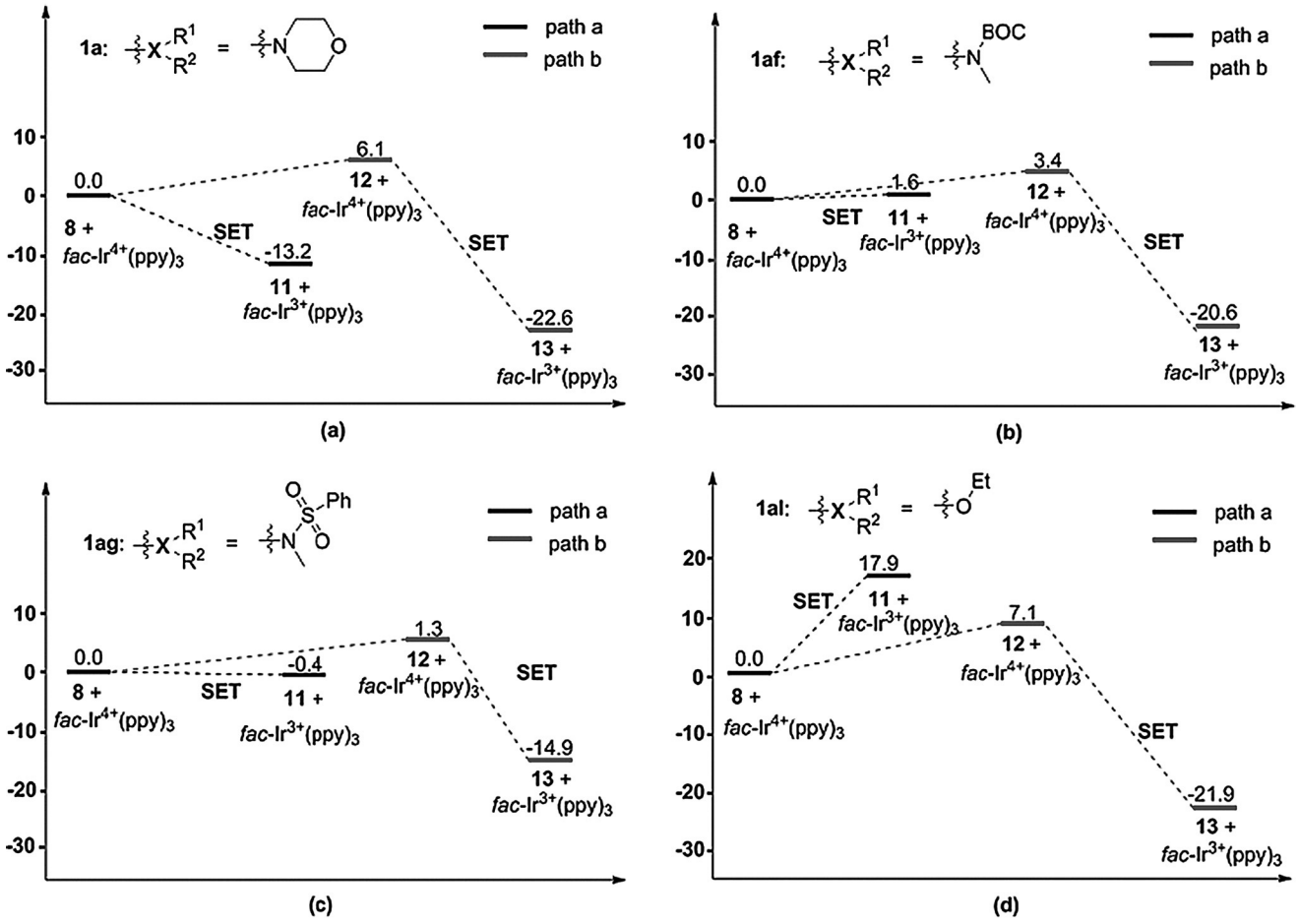


Figure 2. Computed Gibbs free-energy (in kcal mol^{-1}) profiles for visible-light photoredox-catalyzed difluoroalkylation of aldehyde-derived hydrazones.

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Keywords: fluorine · hydrazones · imines · photocatalysis · radical reactions

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