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Amide-Directed Photoredox Catalyzed C-C Bond Formation at Unactivated sp^3 C-H Bonds

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Abstract

Carbon-carbon (C-C) bond formation is paramount in the synthesis of biologically relevant molecules, modern synthetic materials and commodity chemicals such as fuels and lubricants. Traditionally, the presence of a functional group is required at the site of C-C bond formation. Strategies that allow C-C bond formation at inert carbon-hydrogen (C-H) bonds allow scientists to access molecules which would otherwise be inaccessible and to develop more efficient syntheses of complex molecules.^{1,2} Herein we report a method for the formation of C-C bonds by directed cleavage of traditionally non-reactive C-H bonds and their subsequent coupling with readily available alkenes. Our methodology allows for the selective C-C bond formation at single C-H bonds in molecules that contain a multitude of seemingly indistinguishable such bonds. Selectivity arises through a relayed photoredox catalyzed oxidation of an N-H bond. We anticipate our findings to serve as a starting point for functionalization at inert C-H bonds through a hydrogen atom transfer strategy.

The challenges associated with targeting inert sp^3 C-H bonds for C-C bond formation are their high bond strength and selectivity issues arising from their ubiquitous presence as the scaffolding of organic chemistry (Fig. 1a).³ Sterically accessible C-H bonds, typically termini of alkyl chains, may be activated using Rh or Ir based catalysts in emerging borylation chemistry.⁴ Otherwise, inert sp^3 C-H bonds are nearly impossible to distinguish in a rational and selective way, with few exceptions.^{5–11}

In the context of our work on Rh(III) catalyzed C-H activation,¹² we sought an alternative method to functionalize sp^3 C-H bonds of aliphatic amines. A 1,5-hydrogen atom transfer^{13,14} (1,5 HAT) strategy occurred to us as a potential solution (Fig. 1b). Heteroatom radicals are known to abstract hydrogen atoms through the 1,5-HAT process in a selective way. Given the ubiquity and relevance of nitrogen in molecules of interest, we sought to

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generate nitrogen radicals¹⁵ from highly acidified amidyl N-H bonds¹⁶ using photoredox catalysis¹⁷ to functionalize these distal, unactivated positions, and couple them with a subsequent C-C bond forming step (Fig. 1c). Such a transformation would not require pre-functionalization¹⁸ of the X-H bond and could comprise a net addition of the C-H bond across the alkene, an atom economic process.

We have developed reaction conditions for carbon-carbon bond formation at a tertiary C-H bond that is five bonds away from a nitrogen atom bearing a readily removable trifluoroacetyl group (Fig. 2a and see supplementary information for further details). This group on nitrogen acidifies the N-H bond ($pK_a \sim 13.8$)¹⁹ sufficiently to allow deprotonation using basic K_3PO_4 and providing a driving force for 1,5-HAT. Less acidifying groups on nitrogen such as difluoroacetyl or pentafluorobenzoyl do not lead to desired product. At this point, the excited state of the photocatalyst $[Ir(dF-CF_3ppy)_2dtbbpy]PF_6$ (Fig. 2a) ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}] = +1.21$ V vs SCE in MeCN)²⁰ oxidizes the amidyl anion ($E_p = +0.77$ V vs SCE in MeCN) to generate a nitrogen radical. After 1,5-HAT, a tertiary carbon radical is generated and subsequently trapped with methyl methacrylate. The use of $PhCF_3$ as a solvent and high reaction concentrations (0.4 M) were necessary to achieve high yield (Fig. 2b) (see supplementary information for details).

With the optimized conditions, we investigated the variation in amine molecules with inert C-H bonds and alkenes that are applicable to the developed reaction (Fig. 2b). A range of electron deficient alkenes were successfully trapped by the tertiary radical carbon generated through our photocatalyzed 1,5-HAT methodology using trifluoroacetamide **1a**. Ethyl acrylate **2a**, an alkene devoid of an α -substituent, coupled with trifluoroacetamide **1a** to give the product **3ab** in good yield. These results were mirrored with other acrylate esters such as *t*-butyl and benzyl to give products **3ac** and **3ad** respectively. It should be noted that the reactive benzylic C-H bonds in benzyl acrylate, or in the corresponding product **3ad**, remain intact under the reaction conditions. *N,N*-dimethyl acrylamide **2e**, which has a lower reactivity compared to acrylates, couples with trifluoroacetamide **1a** in reasonable yield. Coupling with vinyl ketones was possible giving products **3af**, **3ag** and **3ah** in good yields. The use of methyl vinyl ketone requires lower reaction concentrations and higher catalyst loading in order to disfavor a competitive aza-Michael reaction pathway, which is formed in >50% conversion in the absence of the photoredox catalyst. Less reactive β -substituted vinyl ketones require a higher alkene concentration. Product **3ai** was obtained in moderate yield using dimethyl maleate.

Variation of the steric environment around the inert C-H bonds had little effect on the outcome of the reaction; products **3ba**, **3ca** and **3dd** were all obtained in good yield (Fig. 2c). Subjection of enantiomerically pure alkane possessing a stereogenic C-H bond results in formation of racemic product **3dd**, consistent with our proposed mechanism. Substrates which bear substituents α to the nitrogen were also competent in the reaction delivering products **3ec** and **3fa** in good yields. In these cases, optimal yields were obtained by switching from $PhCF_3$ to the more polar solvent DMF. Heteroatom functionality including a TBS protected oxygen and a Boc protected amine can be incorporated into the trifluoroacetamide substrate to give products **3gc** and **3hc** in good yields. Importantly, the presence of a Boc protected primary amine in substrate **1h** does not affect the outcome of the

reaction presumably because the Boc-N-H bond is not acidic enough to be deprotonated by the K_3PO_4 . Substrates **1i** and **1j**, with oxygen atoms adjacent to the C-H bond, participate well in the reaction to give products **3ic** and **3ja**. Methylene C-H bonds may also be functionalized using this approach as demonstrated with substrate **1k** to deliver product **3kc** albeit in slightly lower yield. Increased yields are observed using a β -substituted Michael acceptor delivering products such as **3kh**.

Substrates which contain more than one tertiary C-H bond were explored in the reaction (Fig. 3a). Trifluoroacetamide **1l**, which contains two tertiary C-H bonds, can be selectively functionalized at the position proximal to the N-H bond. Functionalization of the remote tertiary C-H bond is not observed. This outcome supports our hypothesis that an intramolecular 1,5-HAT process is operating. When there is potential for a competitive 1,6-HAT,²¹ as in substrates **1m** and **1n**, the 1,5-HAT transfer is favored over 1,6-HAT resulting in products **3mc** and **3nc**. Although 1,5-HAT occurs in preference to 1,6-HAT, products arriving from sequential 1,5-HAT and then 1,6-HAT are observed when reactions are run to completion. Re-subjecting product **3nc** to the reaction conditions but with a different alkene coupling partner results in product **3ncd** in moderate yield. This reaction sequence allows for the coupling of two distinct alkene partners at the two tertiary C-H bonds in substrate **1n** with control over regioselectivity to give a molecule containing two contiguous all-carbon quaternary centers. Medicinally relevant molecules such as Pregabalin²² can also be functionalized (Fig. 3b). Lastly, steroid derived trifluoroacetamide **1p**, a molecule containing six distinct tertiary C-H bonds and three C-H bonds adjacent to heteroatoms, can be selectively functionalized at a single position, determined by its proximity to the N-H bond.

Our mechanistic studies (see supplementary information for a full discussion) suggest that a stepwise deprotonation/oxidation event is at least partly responsible for the generation of the nitrogen radical. Both Cyclic Voltammetry and Stern Volmer studies show that the trifluoroacetamide conjugate base quenches the excited Ir photocatalyst. The close match of trifluoroacetamide and K_3PO_4 pKa under these biphasic conditions means that appreciable amounts of the trifluoroacetamide conjugate base are present in solution. The observation of aza-Michael product with methyl vinyl ketone supports the assertion that the amidyl anion is formed in appreciable amounts. Furthermore, weaker electron withdrawing groups on nitrogen such as difluoroacetyl do not lead to either desired product or aza-Michael adduct implicating the need for the presence of negative charge on nitrogen in order to get desired reactivity. Thus, the bulk of the evidence supports the stepwise pathway is operative. On the other hand, the use of Cs_2CO_3 , a weaker base (pKa = 10.3), also provides the desired product albeit in lower yield. This raises the possibility that the proton-coupled electron transfer pathway^{23,24} can be operative in tandem with the stepwise mechanism.

In summary, we have developed a photoredox catalyzed amide directed selective sp^3 C-H bond functionalization with concomitant carbon-carbon bond formation. The proposed mechanism features the formation of a nitrogen centered radical by photoredox mediated oxidation of an in situ formed amidyl anion, and subsequent 1,5 hydrogen atom transfer to relay the reactive radical species to a specific carbon atom. The subsequent radical can be trapped with a range of electron deficient alkenes. This finding addresses one of the shortcomings in aliphatic C-H bond functionalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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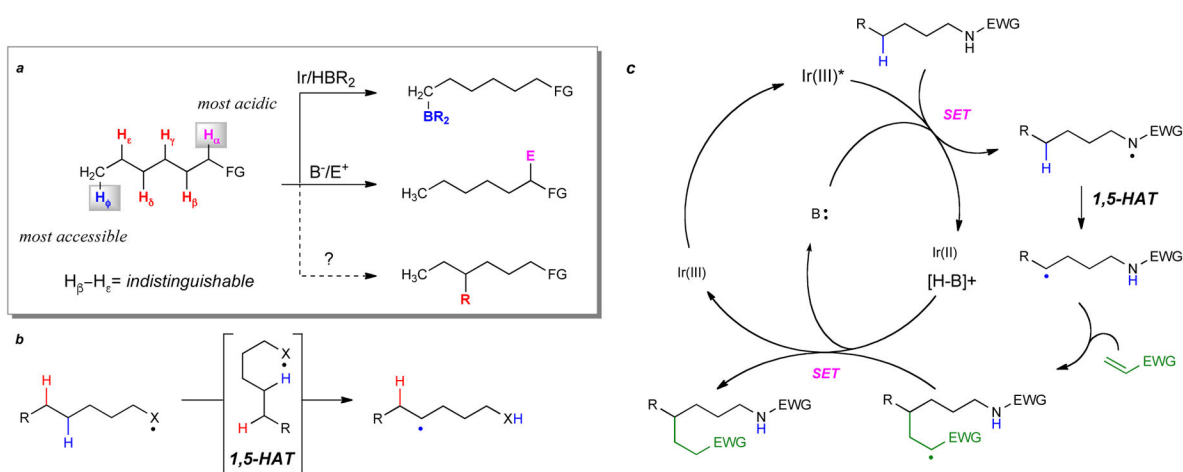
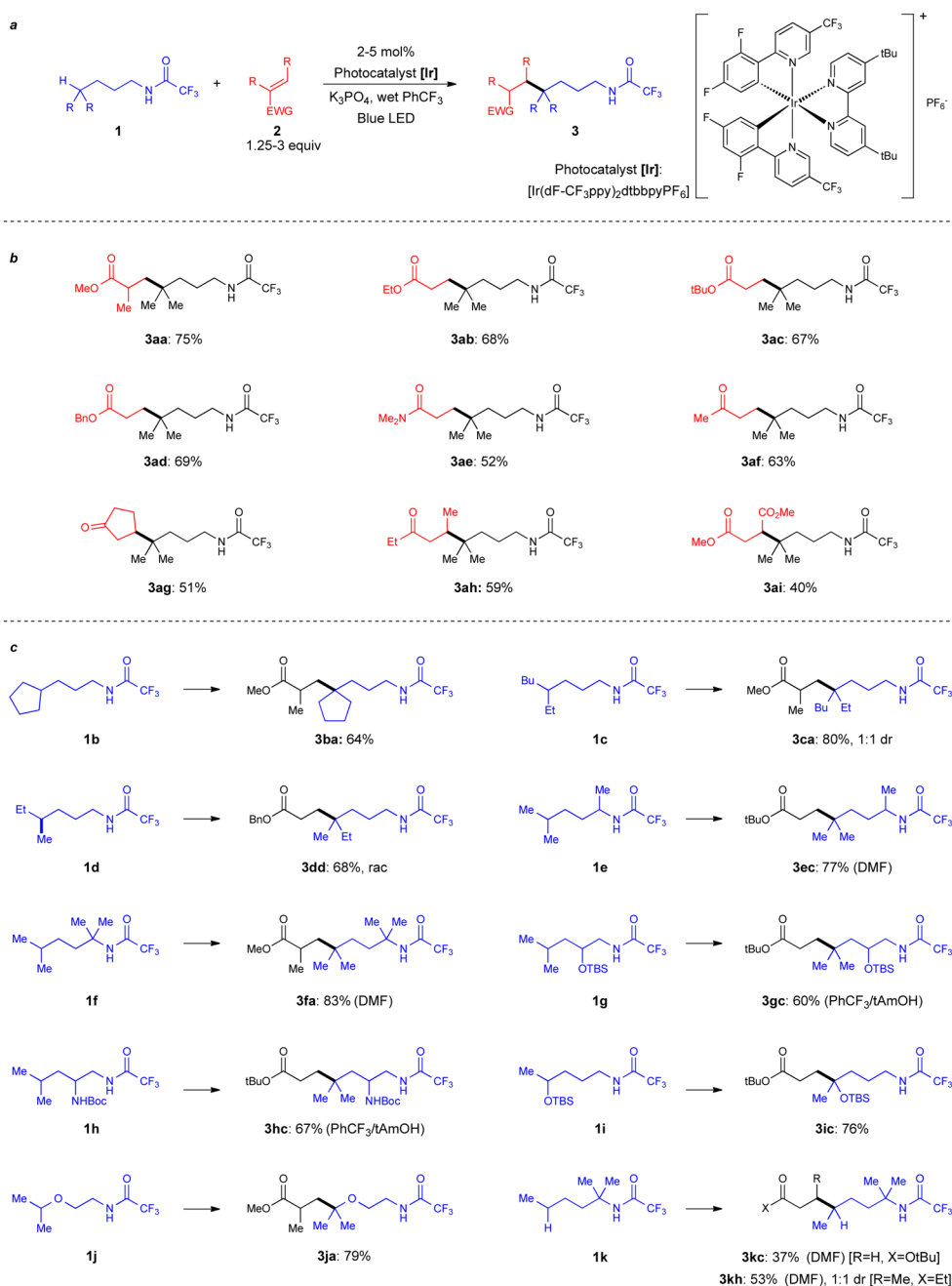


Figure 1.

Selectivity issues with C-H bond functionalization. a, Unactivated sp^3 C-H bonds are similar in electronics and sterics, making them non-trivial to differentiate. b, Our proposed 1,5-hydrogen atom transfer strategy to cleave an unactivated C-H bond with a heteroatom radical. c, Proposed photocatalytic cycle for carbon-carbon bond formation at unactivated C-H bonds. Deprotonation of an acidified N-H bond and in situ oxidation delivers the nitrogen radical with subsequent HAT and functionalization occurring. Upon trapping, the resultant radical is reduced and protonated closing the catalytic cycle and delivering product. EWG: electron-withdrawing group; FG: functional group; HAT: hydrogen atom transfer; SET: single electron transfer.

**Figure 2.**

Photoredox catalyzed C-C bond formation at unactivated sp³ C-H bonds. a, Trifluoroacetamide as the directing group for C-H functionalization. b, Scope of C-C bond formation with respect to the alkene. c, Scope of C-C bond formation with respect to the amine. Solvent is benzotrifluoride unless otherwise indicated. Bn: benzyl; Bu: butyl; dr: diastereomeric ratio; Et: ethyl; Me: methyl; rac: racemic; *t*Bu: *tert*-butyl; TBS: *tert*-butyldimethylsilyl; Boc: *tert*-butyloxycarbonyl; Ph: phenyl; DMF: dimethylformamide; tAmOH: *tert*-amyl alcohol; dF-CF₃ppy: 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy: 4,4'-di-*tert*-butyl-2,2'-bipyridine.

