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Directed γ-C(sp^3)–H Alkylation of Carboxylic Acid Derivatives through Visible Light Photoredox Catalysis

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Supporting Information

ABSTRACT: Visible light photoredox catalysis enables direct γ- C(sp^3)–H alkylation of saturated aliphatic carbonyl compounds. Electron-deficient alkenes are used as the coupling partners in this reaction. Distinguished site selectivity is controlled by the predominant 1,5-hydrogen atom transfer of an amidyl radical generated *in situ*.

Strategies that selectively functionalize unactivated C(sp^3)–H bonds in the presence of multiple other sites are of intense current interest.[1] Directed reactions are common in this milieu, often via transition-metal catalysis.[2] Among diverse functionality capable of directing C–H activation, carbonyls are attractive due to their ubiquity and versatility. β-Functionalization of aliphatic carbonyl compounds has been facilitated by robust organo-[3] or transition-metal catalysis.[4] Although some progress has been made, γ-C–H functionalization remains a formidable challenge. A literature survey disclosed two strategies for addressing this issue. First, Corey,[5] Chatani,[6] Chen,[7] and Yu[8] pioneered primary γ-C–H arylation, alkynylation, olefination, and intramolecular amination reactions based on sterically controlled formations of six-membered metallacycles (Figure 1a). Methylene and methine groups are not amenable to these reactions. Second, intramolecular hydrogen atom abstraction by an amidyl radical,[9] in a 1,5-fashion (i.e., modified Hofmann–Löffler–Freytag reaction[10]), generates a γ-carbon-centered radical. These radicals largely end up as halogenated[11] or cyclized product,[12] due to high reactivity of the excess halogen reagents within the systems.

Very recently, we[13] and Knowles[14] reported selective C(sp^3)–H bond abstraction and alkylation with electron-deficient alkenes relying on photoredox catalysis[15] with selectivity governed by a 1,5-hydrogen atom transfer (HAT)[16] reaction (Figure 1b). The reacting center was thus delivered from a pendant amine functionality which was oxidized by the excited state of the photocatalyst. The net transformation may be viewed as remote functionalization of an aliphatic amine. With this success, we turned our attention to remote functionalization of other aliphatic systems using complementary functional groups to deliver selectivity.

We anticipated that the formation of an amide bond on a carboxylic acid would afford an opportunity to create a different N-centered radical after oxidation, but it still might allow for selective 1,5-HAT to activate remote sites. The immediate challenge was that a trifluoroacetamide, which we used in our amine-directed functionalization, could not be used for carboxyl-directed functionalization. At the outset of this work, it was not clear what functionality would be required since it would have to fulfill several criteria in the successful generation/translocation of nitrogen radicals. It is well documented[16] that the high electrophilic character of the amidyl radical[9] is crucial for hydrogen atom abstraction. Therefore, an appropriate protecting group (usually electron-deficient) on nitrogen is required for three reasons: (1) to acidify the N–H proton to enable mild deprotonation, (2) to give the resulting amidyl anion reasonable oxidation potential for single electron transfer (SET), and (3) to provide a higher N–H bond dissociation energy (BDE)[17] relative to that of C(sp^3)–H bonds, ultimately allowing for efficient abstraction.

An initial survey of common N-protecting groups on 4-methylpentanamide revealed ethoxycarbonyl as being optimal (see SI for details). Methyl methacrylate (MMA) was used as

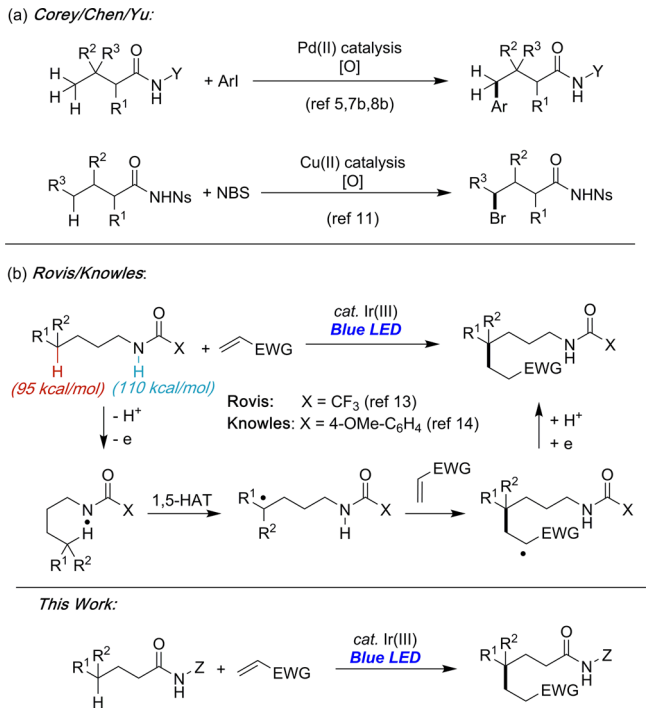

Figure 1. Remote C(sp^3)–H functionalization.

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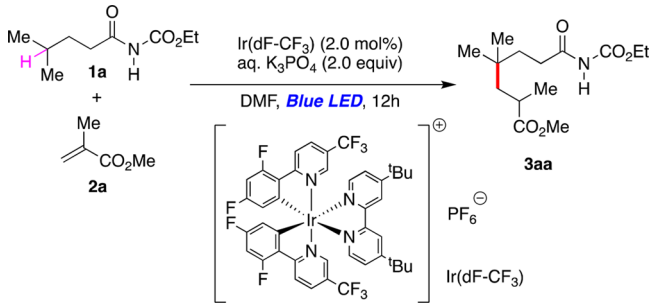
the alkene coupling partner, and Ir[(dF-CF_3)ppy]$_2$(dtbbpy)]-PF_6 ((dF-CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine)[18] was chosen as the photocatalyst. We were delighted to find that the reaction of **1a** in the presence of saturated aq. K_3PO_4 and blue light provided the desired product **3aa** in 76% NMR yield (Table 1, entry 1). Superior yield (74% isolated, entry 5)

Table 1. Optimization[a]



entry	base	solvent	yield (%)[b]
1	K_3PO_4	DMF	76
2	Cs_2CO_3	DMF	66
3	quinuclidine	DMF	0
4	K_3PO_4[c]	DMF	83
5[d]	K_3PO_4[c]	DMF/*t*-AmylOH (1:1)	84(74[e])
6[d,f]	K_3PO_4[c]	DMF/*t*-AmylOH (1:1)	0

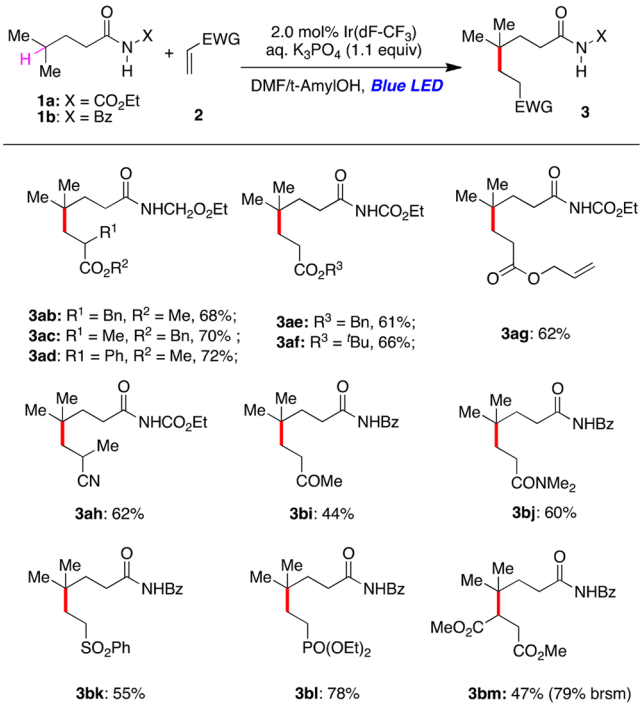
[a]Ir(dF-CF_3) (2.0 mol%), aq. K_3PO_4 (2.0 equiv), **1a** (1.0 equiv), **2a** (5.0 equiv), DMF, 34 W blue LED, ~40 °C, 12 h. [b]Yield determined by ^{1}H NMR using trimethoxybenzene as the internal standard. [c]1.1 equiv. [d]3.0 equiv of **2a**. [e]Isolated yield. [f]No photocatalyst. Similarly, there was no product formation when either light or base was excluded.

was obtained by using 1.1 equiv of K_3PO_4 and 1:1 mixed DMF/*t*-AmylOH. Control experiments suggested that the photocatalyst, base, and light were all essential for a successful γ-C−H alkylation reaction of carbamate **1a** (entry 6).

With optimized conditions in hand, we next investigated the alkene scope with amide **1a** or **1b** as the substrate (Scheme 1). Reactions of **1a** with acrylates bearing α-substituents, including alkyl and aryl groups, proceed well, delivering products **3ab**−**3ad** in good yields (68−72%). Acrylates without α-substituents couple with **1a** providing products **3ae** and **3af** in slightly lower yields, likely a consequence of competitive aza-Michael addition as well as oligomerization (see SI for details). Allyl acrylate engages in reactivity as the desired product **3ag** is exclusively obtained in 62% isolated yield. Methacrylonitrile is also a suitable partner for this reaction (**3ah**, 62% yield). This protocol was then successfully applied to other electron-deficient alkenes, such as methyl vinyl ketone, acrylamide, vinyl sulfone, and vinyl phosphonate, when amide **1b** is used. Products **3bi**− **3bl** were isolated in moderate to good yields. β-Substituents on more electron-deficient alkenes (e.g., dimethyl maleate) result in an incomplete reaction, as **3bm** was obtained in only 47% yield.

The amide scope was examined next (Scheme 2). Substrates with tertiary γ-C−H bonds (BDE ≈ 95 kcal/mol) are well tolerated, giving alkylated products **3cf**−**3ge** in good yields (Scheme 2a). Tunable mono- or dialkylation of substrates bearing activated secondary C−H bonds (BDE ≈ 90 kcal/mol) is also possible (**3ie**−**3je′**). This could be achieved by simply altering the ratio between the amide and

Scheme 1. Alkene Scope[a,b]



[a]Conditions: Ir(dF-CF_3) (2.0 mol%), K_3PO_4 (1.1 equiv), **1** (1.0 equiv), **2** (1.2−3.0 equiv), 1:1 mixed DMF/*t*-AmylOH, 34 W blue LED, ~40 °C, 12 h. [b]Isolated yields are given.

alkene starting materials. A pharmacologically relevant γ-aminobutyric acid derivative gives monoalkylated product **3kl** in moderate yield (38%). Unactivated secondary C−H bonds remain a challenge (**3hi**, 14% yield). Next, amide substrates possessing two or more potential hydrogen abstraction sites were examined (Scheme 2c). Gratifyingly, 1,5-HAT process was found to outcompete other pathways.[19] As a result, products **3lf**−**3rf** are formed in moderate to good yields. Functional groups such as chloride (**3ee**), BocN-H (**3ne**), and acetal (**3se**) are also tolerated. A steroidal derivative with multiple stereogenic centers and tertiary C−H bonds exclusively furnishes product **3ue** in moderate yield. It is noteworthy that a glucose-derived radical intermediate undergoes alkylation with modest diastere oselectivity (**3tl**).

We further interrogated the selectivity of 1,5-HAT when presented with two distinct tertiary C−H bonds (eqs 1−3). In all cases investigated, regioselectivity is high. With substrates **1v** and **1w**, HAT occurs on the C−H bond distal to the σ-withdrawing oxygen functionality, presumably for electronic reasons. Substrate **1x**, on the other hand, has two electronically similar tertiary C−H bonds (eq 3). HAT is still completely selective, delivering product **3xe** in 54% yield. The two competitive HAT reactions presumably proceed via bicyclic transition states ([4.4.0] and [3.3.1]), with the former being preferred for reasons of ring strain.[20]

A possible mechanistic pathway is shown in Figure 2. Deprotonation of **1a** (pK_a ≈ 11.0 in H_2O, pK_a ≈ 16.5 in DMSO)[21] with K_3PO_4 (pK_a ≈ 12.4 in H_2O)[22] provides potassium amide **I**. A Stern−Volmer experiment (see SI for details) reveals the feasibility of single-electron oxidation of **I** ($E_{1/2}^{red}$ = +1.04 V vs saturated calomel electrode (SCE) in DMF) by the excited state of Ir[(dF-CF_3)ppy]$_2$(dtbbpy)]PF_6

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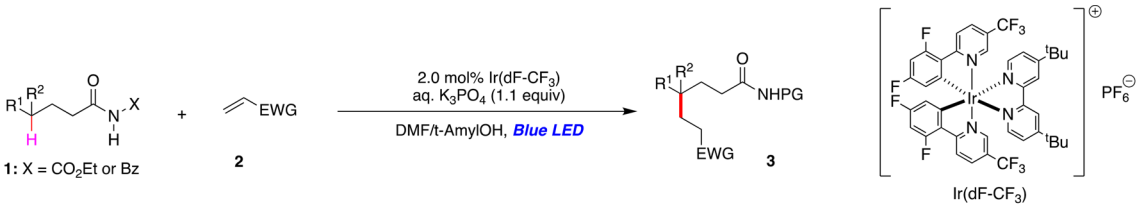
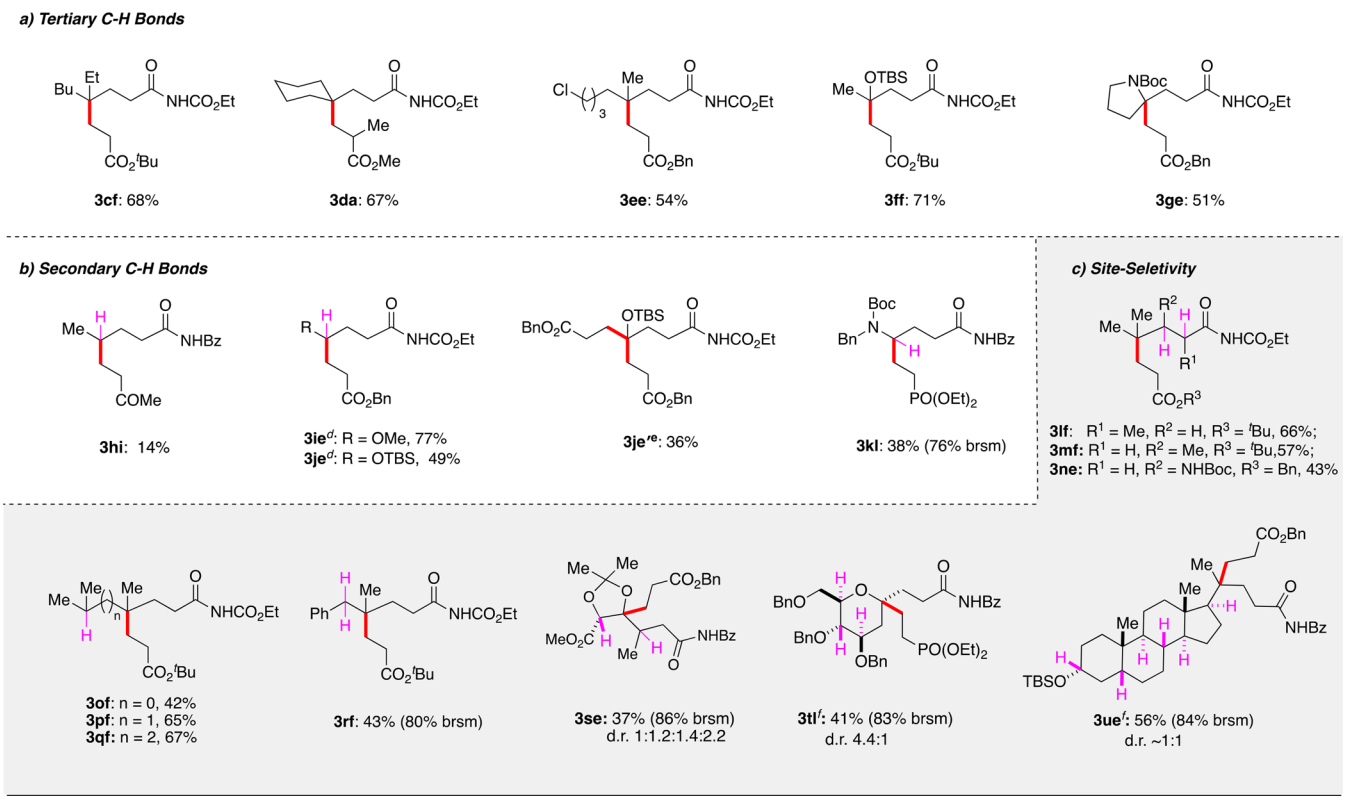
Scheme 2. Amide Scope[a,b,c]





[a]Conditions: Ir(dF-CF_3) (2.0 mol%), K_3PO_4 (1.1 equiv), **1** (1.0 equiv), **2** (1.2–3.0 equiv), 1:1 mixed DMF/*t*-AmylOH (1.0 mL), 34 W blue LED, N_2, ~40 °C, 12 h. [b]Isolated yields are given. [c]dr was determined by the crude ^{1}H NMR. [d]1.2 equiv of amide and 1.0 equiv of benzyl acrylate were used. [e]2.0 equiv of benzyl acrylate was used. [f]4.0 mmol% of Ir(dF-CF_3) was used. Ir(dF-CF_3) = Ir[(dF-CF_3)ppy]$_2$(dtbbpy)PF_6.

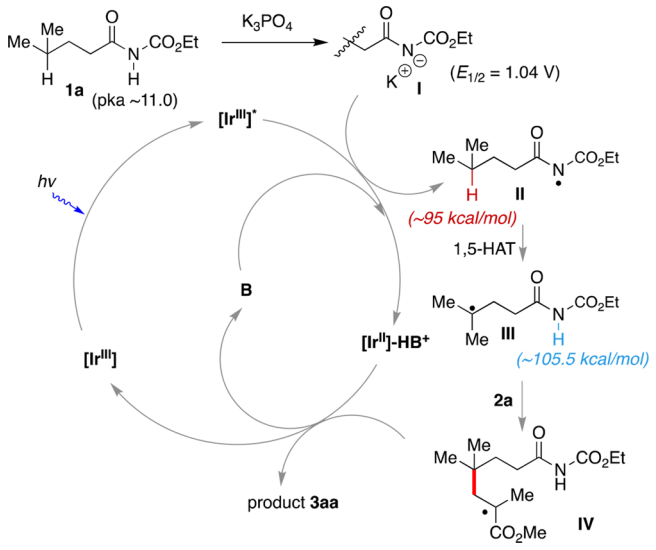


Figure 2. Proposed mechanism.

($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V vs SCE in MeCN),[18] which furnishes amidyl radical **II**. A subsequent energetically favorable 1,5-HAT (N–H BDE ≈ 105.5 kcal/mol[23] vs tertiary γ-C–H BDE ≈ 95 kcal/mol) gives nucleophilic γ-carbon radical **III**, which is then trapped by electron-deficient alkenes (e.g., methyl methacrylate), leading to the formation of a new carbon radical **IV**. Single-electron reduction of **IV** ($E_{1/2}^{red}$ = −0.73 to −0.59 V vs SCE in MeCN)[24] by the Ir^{II} species ($E_{1/2}^{red}$[Ir^{III}/Ir^{II}] = −1.37 vs SCE in MeCN),[18] followed by protonation, affords product **3aa**, thereby also regenerating the ground-state Ir^{III} catalyst.[25]

In summary, we have developed a visible light photoredox-catalyzed γ-alkylation of saturated aliphatic carboxylic acid derivatives with a variety of electron-deficient alkenes. Efficient *in situ* generation of the amidyl radical, and subsequent translocation in a 1,5-fashion, ensures excellent site-selectivity. We have further delineated substrate scope and shown that synthetically useful levels of regioselectivity may be attained for more complex substrates.

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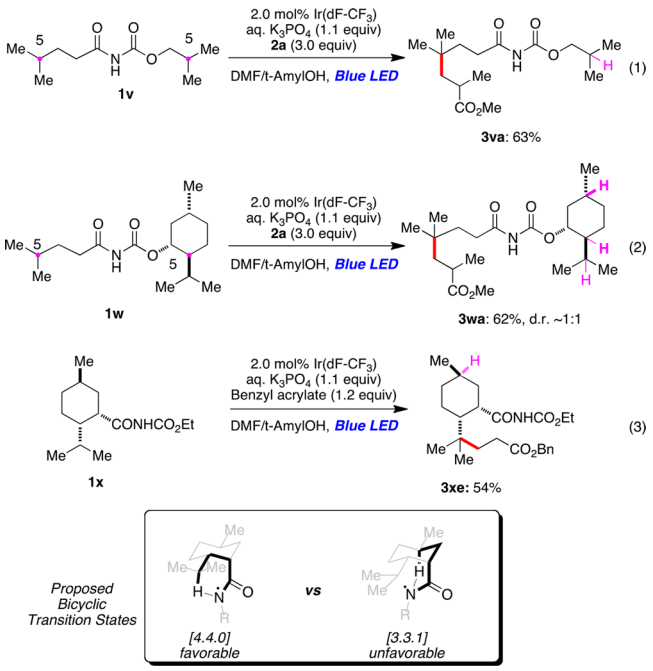

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09306.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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