A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201811004
Angew. Chem. 10.1002/ange.201811004

Link to VoR: http://dx.doi.org/10.1002/anie.201811004
http://dx.doi.org/10.1002/ange.201811004

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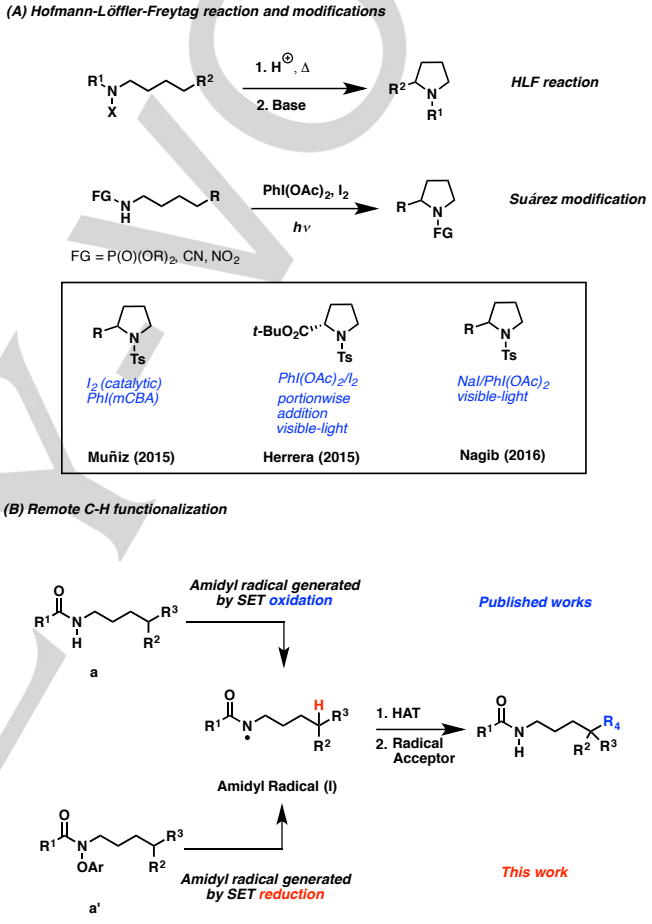
Amidyl Radical Directed Remote Allylation of Unactivated sp^3 C-H Bonds via Organic Photoredox Catalysis

Kui Wu[+], Lushun Wang[+], Sonivette Colón-Rodríguez, Gerd-Uwe Flechsig*, and Ting Wang*

Abstract: *The development of visible-light-mediated allylation of unactivated sp^3 C-H bonds is reported. The remote allylation was directed by the amidyl radical, which was generated by photocatalytic fragmentation of a pre-functionalized amide precursor. Both aromatic and aliphatic amide derivatives could successfully deliver the remote C-H allylation products in good yields. A variety of electron deficient allyl sulfone systems could be used as δ-carbon radical acceptor.*

The selective functionalization of unactivated sp^3 carbon-hydrogen (C-H) bond is a long-standing challenge in modern organic synthesis.[1],[2] Hydrogen atom transfer (HAT) catalysis[3] has shown its advances in regioselective activation of an inert C-H bond for direct formation of new carbon-carbon (C-C) bonds and carbon-heteroatom (C-O, C-N, C-X) bonds.[4] Particularly, the 1,5-hydrogen atom abstraction of nitrogen radicals, the key step of the Hofmann-Loffler-Freytag (HLF) reaction[5], has been widely used in the synthesis of heterocyclic compounds and natural products (Scheme 1A).[6] A major milestone in the development of HLF reaction is Suárez modification[7], which precludes the requirement of the pre-formed haloamine (Scheme 1A). In addition, Muñiz[4f], Herrera[4m], and Nagib[4e] have also reported their discoveries toward the HLF reaction (Scheme 1A). Recently, visible-light photoredox catalysis has been leading efficient accesses to N-radicals under mild conditions.[8] Abstraction of the δ C-H followed by coupling with radical acceptors realized the remote functionalization of unactivated C-H bonds (Scheme 1B).[9]-[12] Particularly, Knowles[9] and Rovis[10] reported their works on direct homolysis of N-H bonds of amides via a single-electron-transfer (SET) process[13]. The challenging SET oxidation was realized by Ir(III) photocatalyst, generating the electrophilic amidyl radical (I)[14] smoothly. However, due to the difficulty of direct homolysis of N-H bonds, the amide substrates were relatively limited (R^1=aryl or CF_3) in order to keep the high efficiency of the transformation[15]. Taking advantage of the pre-functionalized amide (**a'**),[16] the amidyl radical (I) could be readily accessible through a SET reduction. Subsequent 1,5-HAT and intermolecular radical addition would realize the remote functionalization of unactivated sp^3 C-H bonds. This synthetic strategy would potentially broaden the amide substrate scope for such transformation. In our previous studies[17], we have found that electron-deficient allyl sulfones[18],[19] could be a suitable radical acceptor in such transformation. Applying such radical acceptors into the HAT reaction system, we herein report an amidyl radical directed remote allylation of unactivated sp^3 C-H bonds via an amidyl radical promoted radical cascade reaction.



Scheme 1. Remote C-H functionalization.

Inspired by Leonori's pioneer studies on the aryloxy amides[16],[20], we began our reaction condition optimization with amide substrate **1**, allyl sulfone **2** as radical coupling partner, organic photocatalyst eosin Y, and green light-emitting diode (LED) irradiation (Table 1). A careful survey of various bases demonstrated that DIPEA serves best in this reaction (Table 1, entries 1-4). In addition, CH_2Cl_2 was found to be the optimal solvent after careful screening of various solvents (CH_2Cl_2, MeOH, CF_3CH_2OH, CH_3CN, DMF, DMSO, and 1,4-dioxane) (Table 1, entries 5-10). It is worth mentioning that, since the reaction was very sensitive to oxygen, degas procedure (freeze-pump-thaw) was necessary for the success of such transformation. With the optimized condition, **3** was generated in 75% yield after 12 hours at room temperature (Table 1, entry 2). Control experiments (Table 1, entries 11-13) verified that the

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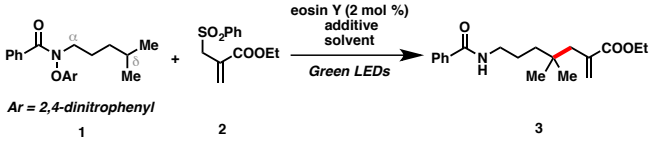
additive, photocatalyst, and light irradiation are necessary for the success of this transformation. Light on-off experiments (Supporting Information) showed continuous light irradiation is necessary for the reaction to reach completion.

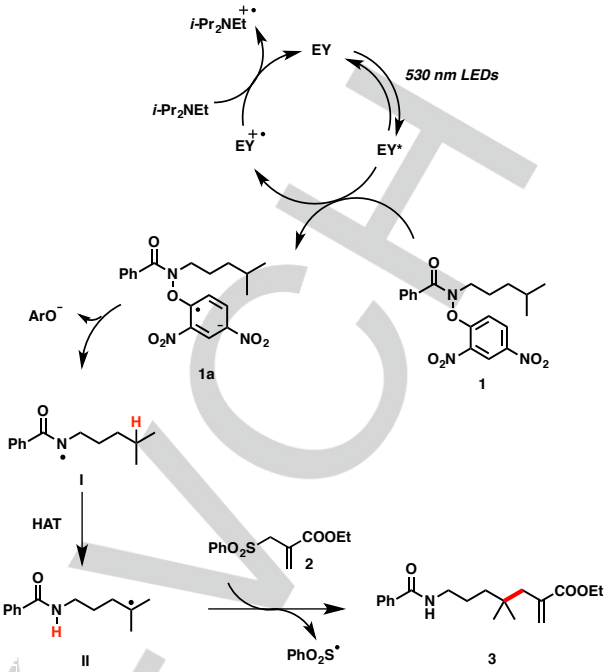
Table 1. Reaction Condition Optimizations[a]



entry	additive	solvent[b]	yield (%)[c]
1	Et_3N	CH_2Cl_2	61
2	**DIPEA**	**CH_2Cl_2**	**75**
3	DMAP	CH_2Cl_2	55
4	DABCO	CH_2Cl_2	0
5	DIPEA	MeOH	70
6	DIPEA	CF_3CH_2OH	15
7	DIPEA	CH_3CN	56
8	DIPEA	DMF	23
9	DIPEA	DMSO	25
10	DIPEA	1,4-dioxane	34
11	--	CH_2Cl_2	0
12[d]	DIPEA	CH_2Cl_2	0
13[e]	DIPEA	CH_2Cl_2	0

[a] Reactions conducted by irradiating **1** (1 equiv), **2** (2 equiv), additive (2 equiv), and photocatalyst (2 mol %) in solvent (0.05 M) with two 6 W, 530 nm light-emitting diode (LED) flood lamps for 12 h. [b] All solvents was degassed via Freeze-Pump-Thaw procedure for 3 times. [c] Isolated yields. [d] Reaction conducted in the dark. [e] Reaction conducted without photocatalyst.

Mechanistically, although DIPEA was known to be able to reductively quench excited eosin Y (EY*), our Stern-Volmer emission quenching studies suggested that reactant aryloxy-amide **1** quenches EY* at a significantly higher rate (Supporting Information). The evidence validated that the catalyst eosin Y ($E_{1/2,}^{red}$ = -1.06 V vs SCE), upon photo excitation, would reduce the aryl unit of **1** ($E_{1/2,}^{red}$ = -0.925 vs SCE) to generate **1a**, which would deliver the amidyl radical **I** through a fragmentation. The electrophilic amidyl radical **I** promoted a 1,5-hydrogen atom transfer, affording nucleophilic carbon radical **II**. The subsequent intermolecular radical addition to allyl sulfone (**2**) would afford the remote allylation product **3** by extruding the $PhSO_2$•. The photoactive catalyst (**EY**) is likely to be regenerated by oxidizing a molecule of DIPEA (Scheme 2).



Scheme 2. Proposed mechanism.

We next focused our attention on exploring the scope of the photocatalytic cascade reaction. Scheme 3 summarizes experiments probing a range of amides substrates. We were pleased to find that a variety of tertiary C-H bonds could be selectively functionalized by the optimized conditions, furnishing **3-8** in good yields (56%-78%). Substituted benzoyl amides and other aromatic amides could also deliver the corresponding products **9-12** in good yields (62%-77%). Since an aryloxy group is pre-installed for the generation of the amidyl radical, the scope of amide was not limited to aryl amides or strong electron-withdrawing substituted alkyl amides. In fact, N-acetyl substrate **13s** ($E_{1/2,}^{red}$ = -0.885 V vs SCE) tends to be easier reducible than N-Benzoyl substrate **1** ($E_{1/2,}^{red}$ = -0.925 V vs SCE). Excitingly, N-acetyl, N-isobutyryl, N-pivaloyl, and N-cyclopentylcarbonyl substrates (**13s**, **14s**, **15s**, and **16s**) reacted smoothly under these conditions, providing the corresponding products **13-16** in the yields of 63%, 73%, 58%, and 64% respectively. Moreover, this radical process is compatible with a variety of functional groups, such as ester (**17**), silyl ether (**18**), alkene (**19**), and oxalate (**20**). Carbamate derivative **21s** could also be used as starting material, furnishing corresponding allylation product **21** in excellent yield (84%). More excitingly, a variety of secondary C-H bonds could also be selectively functionalized, affording corresponding products **22-26** in moderate to good yields (42%-74%). The excellent scope of the reaction would potentially broaden the synthetic application of such remote C-H functionalization strategy.

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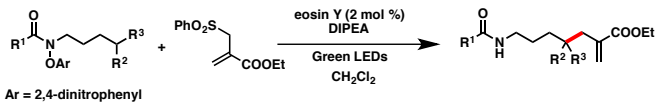
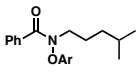
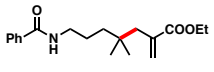
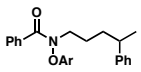
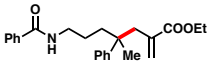
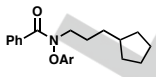
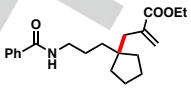
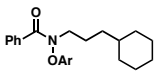
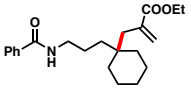
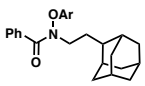
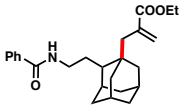
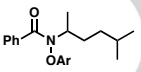
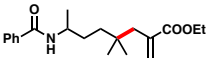
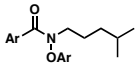
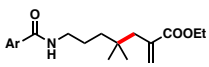
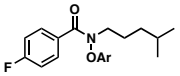
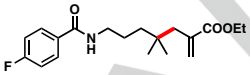
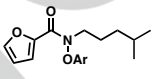
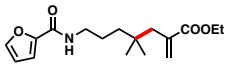
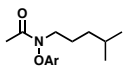
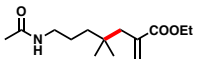
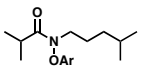
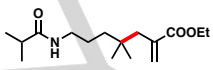
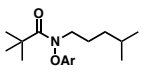
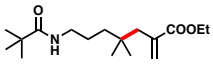
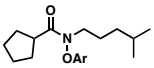
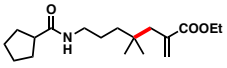
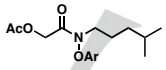
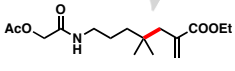
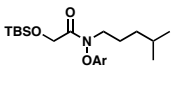
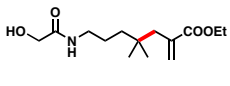


Tertiary C-H Bonds

R¹ = aromatics

Substrates	*Products*	*Substrates*	*Products*	*Substrates*	*Products*
					
1	**3** 75%	**4s**	**4** 75%	**5s**	**5** 56%
$E_{1/2}^{red}$ = -0.925 V vs SCE		$E_{1/2}^{red}$ = -0.900 V vs SCE			
					
6s	**6** 65%	**7s**	**7** 73%	**8s**	**8** 78%
					
9s. Ar = 4-methylphenyl **10s.** Ar = 4-methoxyphenyl	**9.** Ar = 4-methylphenyl, 72% **10.** Ar = 4-methoxyphenyl, 62%	**11s**	**11.** 67%	**12s**	**12** 77%
		$E_{1/2}^{red}$ = -0.880 V vs SCE		$E_{1/2}^{red}$ = -0.890 V vs SCE	

R¹ = aliphatics

Substrates	*Products*	*Substrates*	*Products*	*Substrates*	*Products*
					
13s	**13** 63%	**14s**	**14** 73%	**15s**	**15** 58%
$E_{1/2}^{red}$ = -0.885 V vs SCE					
					
16s	**16** 64%	**17s**	**17** 65%	**18s**	**18** 60%[a]
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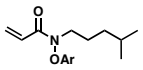
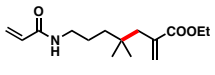
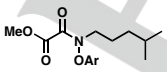
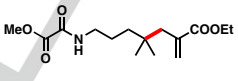
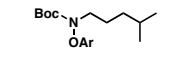
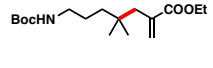
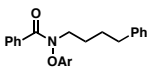
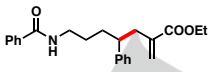
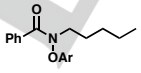
					
19s	**19** 55%	**20s**	**20** 50%	**21s**	**21** 84%
$E_{1/2}^{red}$ = -0.890 V vs SCE		$E_{1/2}^{red}$ = -0.895 V vs SCE		$E_{1/2}^{red}$ = -0.938 V vs SCE	

Secondary C-H Bonds

Substrates	*Products*	*Substrates*	*Products*	*Substrates*	*Products*
					
22s	**22** 74%	**23s**	**23** 66%	**24s**	**24** 67%
$E_{1/2}^{red}$ = -0.905 V vs SCE					
25s	**25** 51%	**26s**	**26** 42%[b], *d.r.* = 1:1		
$E_{1/2}^{red}$ = -0.900 V vs SCE					

Scheme 3. Reaction Scope. [a] Yield was obtained after removal of TBS group. [b] Yield was obtained after removal of Bz group.

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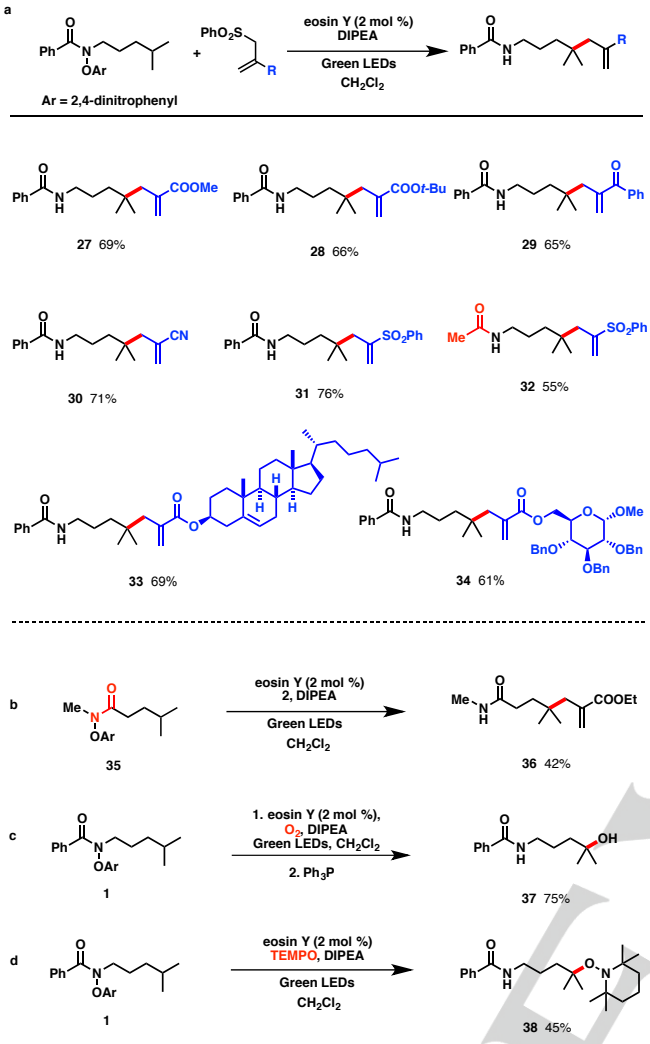

Scheme 4. Reaction Scope: a) radical acceptor scope; b) remote allylation of C-H bond at Cγ position; c) Oxygen as radical acceptor; d) TEMPO (2 equiv) as radical acceptor.

Next, we evaluated the scope of radical acceptor that can participate in this process. A variety of allyl sulfone[16],[17] bearing different electron-withdrawing-group (i.e. ester, ketone, nitrile, sulfone) could be used as radical acceptor, reacting smoothly under the optimized reaction conditions to afford **27-32** in good yields (55%-76%). In addition, the strategy could be successfully utilized in more complex molecular settings, such as steroid (**33**, 69%) and carbohydrate (**34**, 61%). Moreover, the carboxylic acid derived aryloxy amide **35** could also undergo the corresponding remote functionalization of C-H bond at γ position, furnishing **36** in 42% yield (Scheme 4, eq b). Beside electron-deficient alkene system, O_2 and TEMPO could also be used as radical acceptor, offering the opportunity to functionalize the tertiary C-H as an alcohol (Scheme 4, eq c) or marked C-O bond (Scheme 4, eq d).

In summary, we have developed an organic photocatalytic method for the radical allylation of unactivated sp^3 C-H bonds via an amidyl radical promoted 1,5-hydrogen atom transfer/intermolecular radical addition cascade. A range of amide substrates, both aromatic amides and aliphatic amides, are suitable for this transformation. A variety of electron deficient allyl sulfone system could be used as δ-carbon radical acceptor. Moreover, the strategy could be also applied on functionalization of γ-carbon of amides, and oxidation of C(δ)-H bond of amines. Applications of this synthetic strategy in more complicated molecular settings are ongoing in our laboratory.

Acknowledgements

We are grateful to the University at Albany, State University of New York, for financial support. We thank Prof. Alexander Shekhtman (SUNY-Albany) and Prof. Zhang Wang (SUNY-Albany) for NMR assistance.

Keywords: photoredox catalysis • metal free • amidyl radical • Unactivated C-H Bonds • eosin Y

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