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Photoinduced Remote Functionalization of Amides and Amines Using Electrophilic Nitrogen-Radicals

Sara P. Morcillo,[a]# Elizabeth M. Dauncey,[a]# Ji Hye Kim,[a] James J. Douglas,[b] Nadeem S. Sheikh[c] and Daniele Leonori*[a]

Abstract: The selective functionalization of sp^3 C–H bonds at distal positions to functional groups is a challenging task in synthetic chemistry. Here we report a photoinduced radical cascade strategy for the divergent functionalization of amides and protected amines. The process is based on the oxidative generation of electrophilic amidyl radicals and their following transposition via 1,5-HAT resulting in remote fluorination, chlorination and, for the first time, thioetherification, cyanation and alkynylation. The process is tolerant of most common functional groups, and delivers useful building blocks that can be further elaborated. The utility of this strategy is demonstrated through the late-stage functionalization of aminoacids and a dipeptide.

The selective functionalization of sp^3 C–H bonds is a long sought-after goal in synthetic chemistry.[1] In general, when a directing group is present, products of α- and β-functionalization are easy to access through ionic (e.g. enolate chemistry, 1,4-addition) and transition metal-mediated reactivity (e.g. directed metallation) (Scheme 1A). Targeting more distal positions, such as the γ and δ, is more difficult.[2] One way of achieving this is to use nitrogen radicals harnessing their ability to undergo transposition processes by 1,5-H atom transfer (1,5-HAT).[3] This reactivity constitutes the key step of the name reaction developed by Hoffman and Löffler[4] and has been pioneered in classical radical processes by Forrester,[5] Minisci,[6] Suarez[7] and others.[8] More recently, the advent of visible-light photocatalysis[9] has propelled the development of milder ways for exploring this reactivity. For example, Muñiz[10] has identified an array of protocols for the preparation of nitrogen heterocycles using catalytically generated N–I and N–Br amides. Nagib[11] has used N–I imine-type derivatives to access 1,2-amino-alcohols and Nevado[12] has employed electron poor *O*-acyl oximes in the assembly of tetralones. Most relevant here is the work of Knowles[13] and Rovis[14] which, through proton-coupled electron transfer, have generated amidyl radical from amides and developed cascades based on 1,5-HAT and following radical addition to Michael acceptors.

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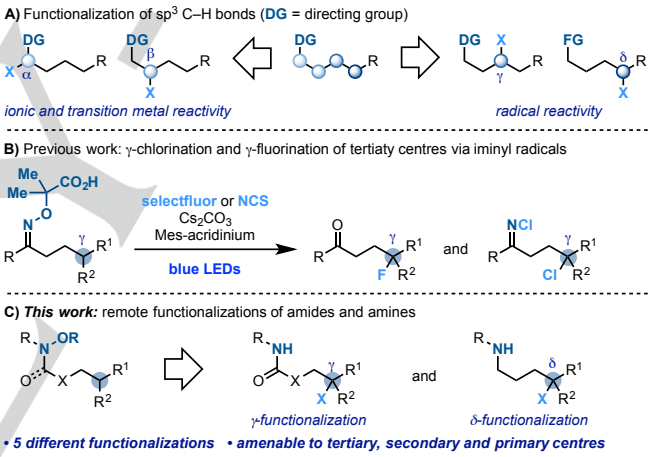
We and the group of Studer have recently developed a reaction for the oxidative generation of iminyl radicals and the following 1,5-HAT–functionalization (Scheme 1B).[15] In our hand this process enabled γ-chlorination and γ-fluorination but was only feasible on tertiary centres, thus limiting the synthetic applicability to a narrow range of substrates. In this paper we demonstrate how changing the nature of the nitrogen radical to amidyl and *N*-protected aminyl radicals unlocks distal functionalizations of amides, carbamates and amines (Scheme 1C). This methodology targets tertiary, secondary and even primary centres and has been applied to five different functionalizations spanning distal C–X (X = heteroatom) and C–C bond formation.

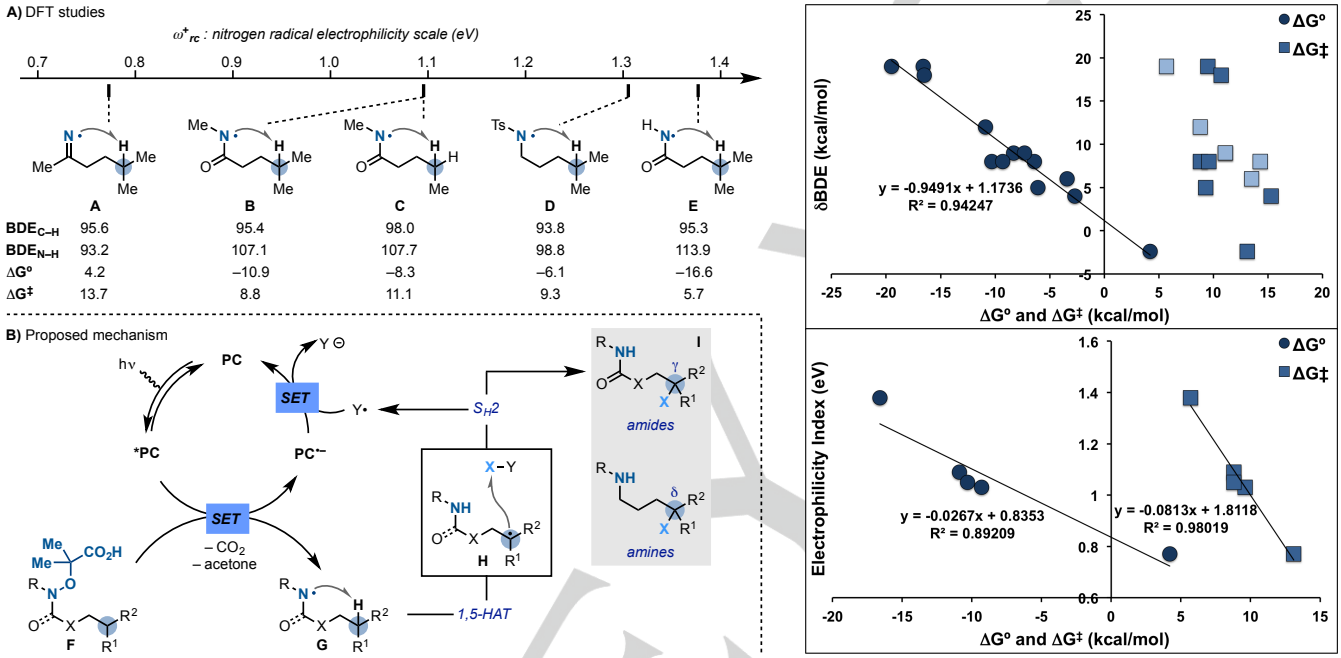


Scheme 1. A) Ionic versus radical reactivity for the functionalization of sp^3-C–H bonds. B) γ-Fluorination and chlorination of tertiary centres via 1,5-HAT of iminyl radicals. C) γ- and δ-Functionalizations via 1,5-HAT of amidyl radicals.

At the outset of our work, we surmised that to achieve efficient 1,5-HAT–functionalization cascades at room temperature, both enthalpic and polar effects had to be maximized.[16] We therefore turned our interest towards the use of amidyl radicals because of their high electrophilic character[17] and the strong N–H bonds of the corresponding amides. These properties were expected to synergistically render the reaction exothermic ($\Delta G^\circ < 0$; enthalpic contribution) and lower the activation barrier ($\Delta G^\ddagger$; polar effects contribution). To obtain more information on these aspects, we have conducted computational studies on a range of model 1,5-HAT processes spanning amidyl, carbamoyl, *N*-Ts-aminyl and iminyl radicals (Scheme 2A).[18] For example, while 1,5-HAT of iminyl radical **A** is endothermic, amidyls (**B**, **C** and **E**) and *N*-Ts-aminyl radical **D** are ought to undergo exothermic abstraction of H-atoms on tertiary, secondary and even primary positions. Indeed, a good correlation was found between the variation of bond dissociation energies (BDEs)[19] between the incipient N–H bond and the γ-sp^3 C–H bond ($\delta BDE = BDE_{N-H} - BDE_{C-H}$) and the ΔG° of the processes. Correlation between the

δBDE and the activation barrier for 1,5-HAT ($\Delta G^{\ddagger}$) was less obvious but a clear trend was observed within the amidyl series (γ-abstractions, light blue squares). The high exothermicity characterizing these reactions means that early transition states are likely operating[20] which makes the reaction parameters sensitive to polar effects. Indeed, a good correlation between the nitrogen-radical electrophilicity indeces (ω^{+}_{rc}) and both $\Delta G°$ and $\Delta G^{\ddagger}$ was observed. These results make the evaluation of this parameter of relevance when planning similar reactions.

Our mechanistic proposal was centered on a photoredox cycle generating an amidyl (or an *N*-protected aminyl) radical (**G**) via SET oxidation and fragmentation of the precursor **F** (Scheme 2B). At this point, enthalpy-favorable 1,5-HAT would deliver the distal radical **H**, which should display nucleophilic character. Homolytic atom/group-transfer (e.g. S_H2 reaction) with a polarized SOMOphile (X–Y) would furnish the targeted amides and protected amines **I** as well as the electron poor radical Y• that ought to close the photoredox cycle by SET with the $PC^{\bullet-}$.[21]



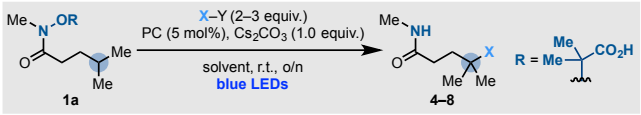
Scheme 2. A) DFT studies on the 1,5-HAT of nitrogen-radicals and correlations with the reaction parameters ($\Delta G°$ and $\Delta G^{\ddagger}$). B) Proposed mechanism for the divergent remote functionalization of amides and amines.

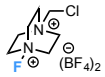
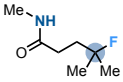
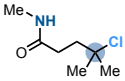
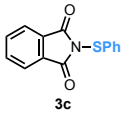
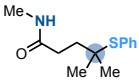
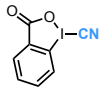
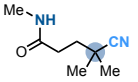
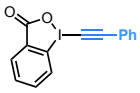
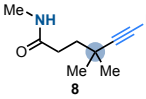
Initial efforts focused on the development of γ-fluorinations using amide **1a**, which was prepared on gram scale (Scheme 3).[18] Pleasingly, blue LEDs irradiation of **1a**, Fuzukumi's acridinium (**2a**) as the photocatalyst ($*E^{ox}$ = +2.1 V vs SCE),[22] selectfluor[23] (**3a**) as the SOMOphile, Cs_2CO_3 as the base in CH_3CN–H_2O gave the desired product **4** in 36% yield (entry 1). By changing the photocatalyst to the more chemically robust Ir(III) complex **2b** the yield was improved to 87% (entry 2). Using NCS (**3b**) as the SOMOphile, we developed a γ-chlorinating process (**5**). Also in this case, the use of photocatalyst **2b** led to better results than **2a** (entries 3 and 4), and the organic dye **2c** was identified as optimum for this transformation (entry 5). A similar trend in photocatalyst-based efficiency was observed for the γ-thioetherification using the S-donor **3c**, which lead to the formation of **6** in high yield (entries 6–8). Finally, by employing the IBX-reagents **3d**[24] and **3e**,[25] in the presence of **2c** as the photocatalyst, we developed cascade reactions resulting in sp^3 γ-cyanation (**7**) and γ-alkynylation (**8**). It is worth mentioning that while the γ-fluorination of amides has been developed using Fe-catalysts,[26] and γ-chlorinations have been reported using *N*-Cl-amides via radical chain propagations,[27] γ-thioetherification, γ-cyanation and γ-alkynylation are, to the best of our knowledge, unprecedented.

In order to obtain mechanistic insights we conducted luminescence-quenching studies (Stern-Volmer analysis) which showed that **1** (as its Cs salt) quenches all three photocatalysts **2a**–**c** at significant higher rates than all the other SOMOphiles **3a**–**e**.[18] Quantum yields (Φ) were determined for all optimized reactions (Scheme 3). The very low values obtained in these studies suggest that mechanisms based on radical chain propagations (dark reactivity) should not account for the full reaction productivity thus corroborating our proposed mechanism.[18]

We then evaluated the scope for this divergent functionalization strategy using a host of functionalized amides and *N*-protected-amines (**1a**–**z** and **1aa**–**ae**) (Scheme 4). In accordance with our computational studies, we were able to perform γ-fluorination at tertiary (**4**) and both secondary alkyl (**9**) and benzylic (**10**) positions. The process could also be expanded to γ-terminal centres via the generation of a primary radical albeit in lower yield (**11**). The *N*-substitution was also evaluated and we successfully engaged amide precursors with a removable *N*-Bn

group (**12**) as well as an unprotected substrate, which gave the corresponding fluorinated primary amide **13** in good yield.



Entry	X–Y	PC	Solvent	Yield (%)	Product	Φ
1	 3a	2a	$CH_3CN–H_2O$	36	 4	
2		2b	**$CH_3CN–H_2O$**	**87**		0.08
3	 3b	2a	CH_3CN	39	 5	
4		2b	CH_3CN	55		
5		2c	**CH_3CN**	**76**		0.06
6	 3c	2a	CH_2Cl_2	32	 6	
7		2b	CH_2Cl_2	69		
8		2c	**CH_2Cl_2**	**71**		0.02
9	 3d	2a	CH_2Cl_2	42	 7	
10		2b	CH_2Cl_2	21		
11		2c	**CH_2Cl_2**	**97**		0.02
12	 3e	2c	**CH_2Cl_2**	**80**	 8	0.06

2a: Mesityl acridinium (ClO_4); **2b**: Ir[dF(CF_3)ppy]$_2$(dtbpy)(PF_6); **2c**: 4CzIPN

Scheme 3. Optimization of the divergent radical functionalization strategy using **1a**.

The possibility to engage carbamoyl radicals was investigated next but in this case, the reaction was found feasible only on a tertiary centre (**14** vs **15**).

As further element of substrate scope investigation, we evaluated the development of δ-fluorination of *N*-protected amines. We quickly discovered that commonly used *N*-protecting groups like Cbz (**16**), Boc (**17**) and Ts (**18**) were compatible and provided the desired δ-fluoro amines in good yields.[28] The process was also extended to the functionalization of δ-secondary alkylic (**19**), benzylic (**20**) as well as primary centres (**21**).

In general, 1,5-HAT processes are favoured over 1,6-HATs due to their optimum chair-like six-membered cyclic transition state. Nevertheless, 1,6-translocations could be efficiently achieved by providing an enthalpic bias to the system.[20, 29] As demonstrated by the formation of **22** and **23**, there is a preference for 1,6-HAT when this position is a tertiary centre. This is in line with an energetically more favourable reaction profile: $\Delta\Delta G°(1,6^{tert} – 1,5^{sec})$ = –4.7 kcal mol^{-1} and $\Delta\Delta G^{‡}(1,6^{tert} – 1,5^{sec})$ = –2.4 kcal mol^{-1}.[18] The increased chain flexibility of *N*-Boc-amine however, resulted in mixtures of 1,5- (δ) and 1,6-(ε)-fluorination (**24**).

The γ-chlorination (**5**, **25**–**28**), γ-thioetherification (**6**, **29**–**31**), γ-cyanation (**7**, **32**, **33**) and γ-alkynylation (**8**, **34**–**37**) were also attempted on the same precursors and, much to our liking, were successful on secondary alkyl centres. The functionalization of γ-secondary benzylic and primary positions was in general less efficient.

The possibility of using SOMOphile **3b**–**e** to obtain δ-functionalized amines was evaluated next and found feasible in good to moderate yields (**38**, **39** and **41**) with the exception of the cyanation process (**40**) that consistently resulted in complex mixtures.

More structurally diverse starting materials were then evaluated with the intention of accessing complex building blocks and obtain information on the functional groups compatible with the process. We were able to selective functionalise unsymmetrical tertiary centres (**42**–**44**), as well as γ-carbons embedded into cyclic motifs like the rigid norbornene (**45**–**49**) and the cyclopentyl-ring (**50**–**53**). This procedure also streamlined access to several C–4 functionalized *N*-Boc-piperidines (**54**–**57**) that are valuable building blocks with frequent applications in medicinal chemistry.[30] The successful formation of **58**–**61** showed that alkyl halides as well as protected alcohols are tolerated, thus giving access to products with handles for further functionalization.

Strategies for the selective modification of natural aminoacid side chains are a valuable tool to access novel and high value chemotypes.[31] In general, this is achieved by oxidation followed by stepwise functionalization and several strategies based on selective H-atom abstraction have been reported.[16, 32] Using a range of differentially protected leucine derivatives we were able to perform γ-fluorination (**62**–**64**) and γ-alkynylation (**65**). The γ-fluorination could also be achieved on an unprotected substrate (**66**) albeit in low yield. The successful γ-alkynylation might have applications given the importance of preparing side chain-modified aminoacids with functional groups that undergo click type reactions like azide-alkyne cycloaddition and thiol-yne reaction.[33] Pleasingly, this strategy could be extended to the selective late-stage modification of L-isoleucine (**67**, **68**) and L-lysine (**69**), which normally give isomeric-mixture under other protocols. Finally, the L-leucine γ-functionalizations was also expanded to a dipeptide building block (**70**, **71**) in good yield.

In conclusion, we have developed a divergent strategy for the selective functionalization of amides, carbamates and amines at distal positions. The methodology involves the photoinduced SET oxidation of α-oxiamido acids to generate electrophilic amidyl radicals. Through a cascade of 1,5-HAT and S_H2-functionalization, fluorine, chlorine, SPh, cyano and alkyne functionalities can easily be installed. Applications to the selective modification of aminoacids and a dipeptide highlight the compatibility of this approach to medicinal chemistry-relevant motifs.

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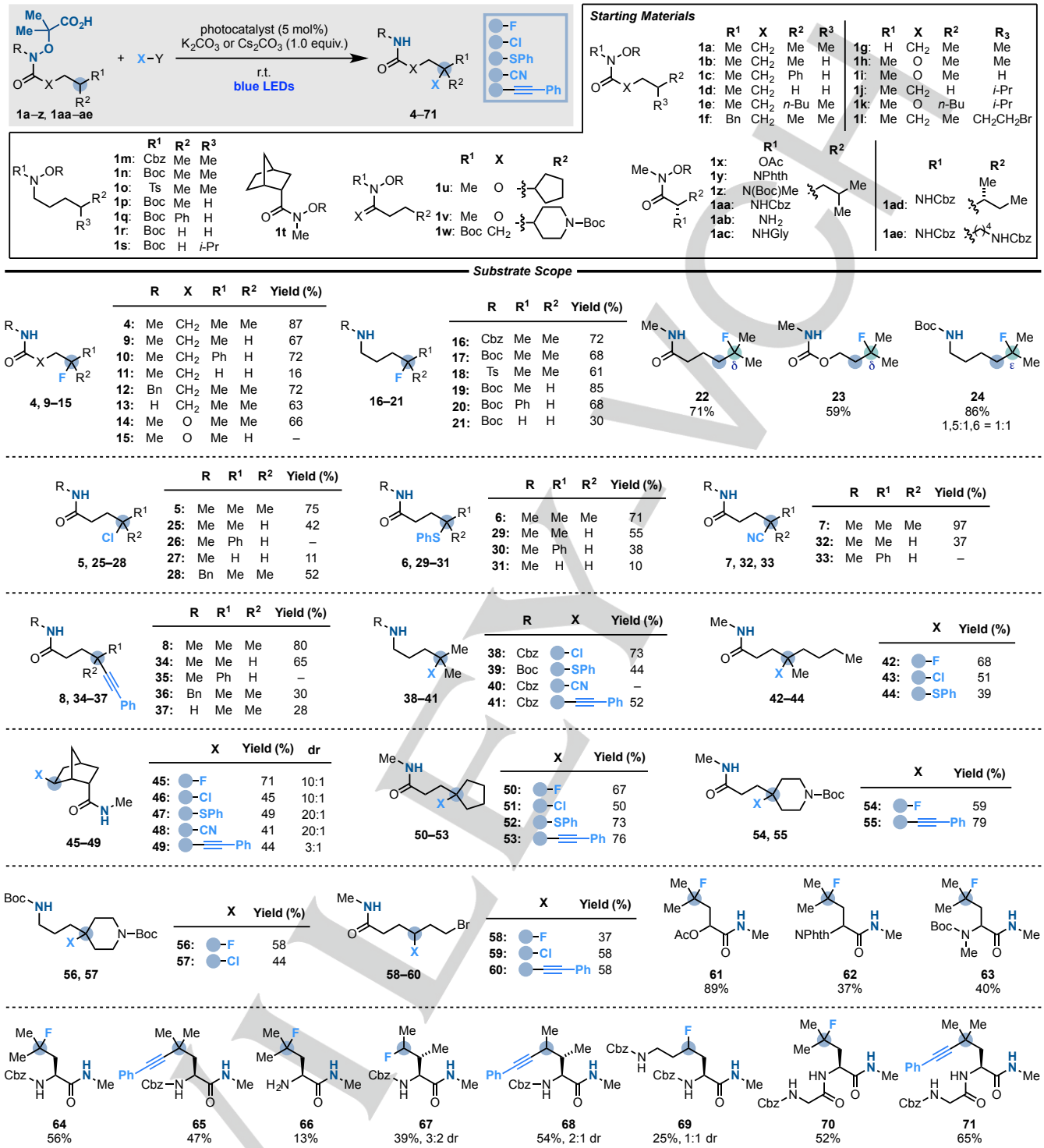

Scheme 4. Substrate scope for the divergent remote functionalization of amides and amines.

Keywords: remote functionalization • photoinduced • nitrogen radical • late-stage modification • peptide

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