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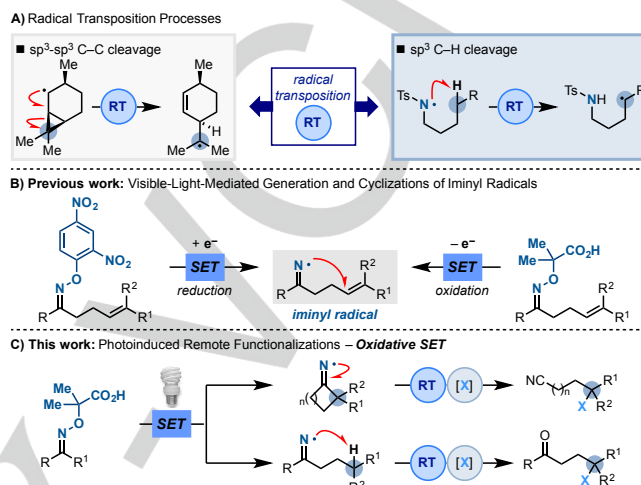
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Photoinduced Remote Functionalizations via Iminyl Radical-Promoted C–C and C–H Bond Cleavage Cascades

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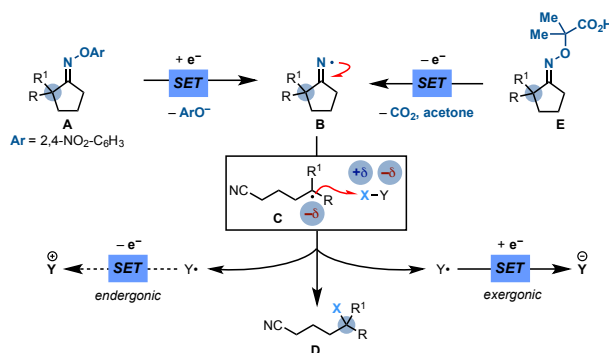
Abstract: A photoinduced cascade strategy leading to a variety of differentially functionalized nitriles and ketones has been developed. These protocols rely on the oxidative generation of iminyl radicals from simple oximes. Radical transposition by sp^3 – sp^3 C–C and sp^3 C–H bond cleavages gives access to distal carbon-radicals that undergo S_H2 -functionalizations. These mild, visible-light-mediated protocols allow remote fluorinations, chlorinations and azidations and have been applied to the modification of bioactive and structurally complex molecules.

The development of methods for the selective functionalization of non-activated sp^3 carbons is a longstanding endeavor in organic synthesis.^[1] Radical strategies are attractive options owing to the ability of odd-electron species to undergo transposition processes.^[2] If a suitably reactive radical is generated in a specific position of an organic molecule, then sp^3 – sp^3 C–C and sp^3 C–H bond cleavages can be triggered leading to remote functionalizations. Classical examples are the ring-opening of α -cyclopropyl radicals (radical clock)^[3] and the 1,5-H-atom abstractions of nitrogen-radicals – the key step of the Hofmann-Löffler-Freytag reaction (HLF)^[4] (Scheme 1A).^[5] We have recently developed two classes of oximes that provide access to iminyl radicals by both reductive and oxidative visible-light-mediated single electron transfers (SETs) and used them in intra-molecular cyclization processes (Scheme 1B).^[6] Whereas amidyl and *N*-Ts-aminy radicals have been extensively exploited in visible-light-mediated transposition reactions,^[5, 7] the implementation of iminyl radicals has been considerably overlooked.^[8] Inspired by the pioneering work of Zard^[8e–g] and Forrester^[8a–c], we wondered if the key transposition steps of the radical clock and the HLF processes could be harnessed as part of a general interrupted cascade strategy from an iminyl radical, leading to a variety of functionalized molecules. Herein, we report the development of two photoinduced manifolds that enable the preparation of remotely functionalized nitriles and ketones via a tandem iminyl radical generation, sp^3 – sp^3 C–C/ sp^3 C–H bond cleavage, functionalization cascade (Scheme 1C). At the outset, we realized that our reductive SET approach for iminyl radical generation and cyclization was electronically mismatched as illustrated in Scheme 2 using a ring-opening–



Scheme 1. Radical transpositions processes and current work using iminyl radicals.

functionalization process. In fact, upon SET reduction and fragmentation of precursor **A**, the iminyl radical **B** should undergo a fast β -fission generating the δ -CN-radical **C**. As this species is expected to be nucleophilic, it benefits from the reaction with polarized SOMOphiles (X–Y) where the X-atom/group has a partial positive character. Following radical atom/group transfer reaction (S_H2), **D** is generated together with the radical Y^\bullet . Owing to its electrophilic nature, a final SET oxidation will be highly endergonic, thus thwarting the development of a redox neutral process. We therefore selected the carboxylic acid-containing oxime **E** as the starting point. We were hopeful that upon deprotonation, a sequence of SET oxidation, followed by CO_2 and acetone extrusion would lead to the formation of **B**. Following β -fission– S_H2 cascade would generate the product **D** and the electrophilic radical Y^\bullet that



Scheme 2. Mechanistic analysis of iminyl radical transposition-functionalization.

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should undergo exergonic SET reduction, ensuring efficient reactivity.

We started our investigation by preparing oxime **1a** by condensation of 2,2-dimethylcyclopentanone with a commercially available hydroxylamine on a gram-scale (Scheme 3A).^[9] Using Fukuzumi's acridinium **2** as the photoredox catalyst ($E^{*}_{1/2} = 2.2$ V vs SCE),^[6b, 10] we evaluated several potential radical fluorinating agents (X–Y),^[11] bases and solvents under blue LEDs irradiation. While NFSI resulted in unreacted **1a** (entry 1), we were pleased to see that using selectfluor the desired iminyl radical generation–ring-opening–fluorination cascade could be achieved albeit in low yield (entry 2). However, by using H₂O as the co-solvent (entry 3) and K₂CO₃ as the base (entry 4), **3a** was obtained in high yield in just 15 minutes. This represents a radical “abnormal” Beckmann fragmentation–fluorination process.^[12] Control experiments confirmed the requirement for base, **2** and continuous blue light irradiation. A quantum yield^[13] $\Phi = 2.8$ was determined for this transformation, which suggests that productive short-lived radical chain propagation processes are operating together with the photoredox pathway.^[9]

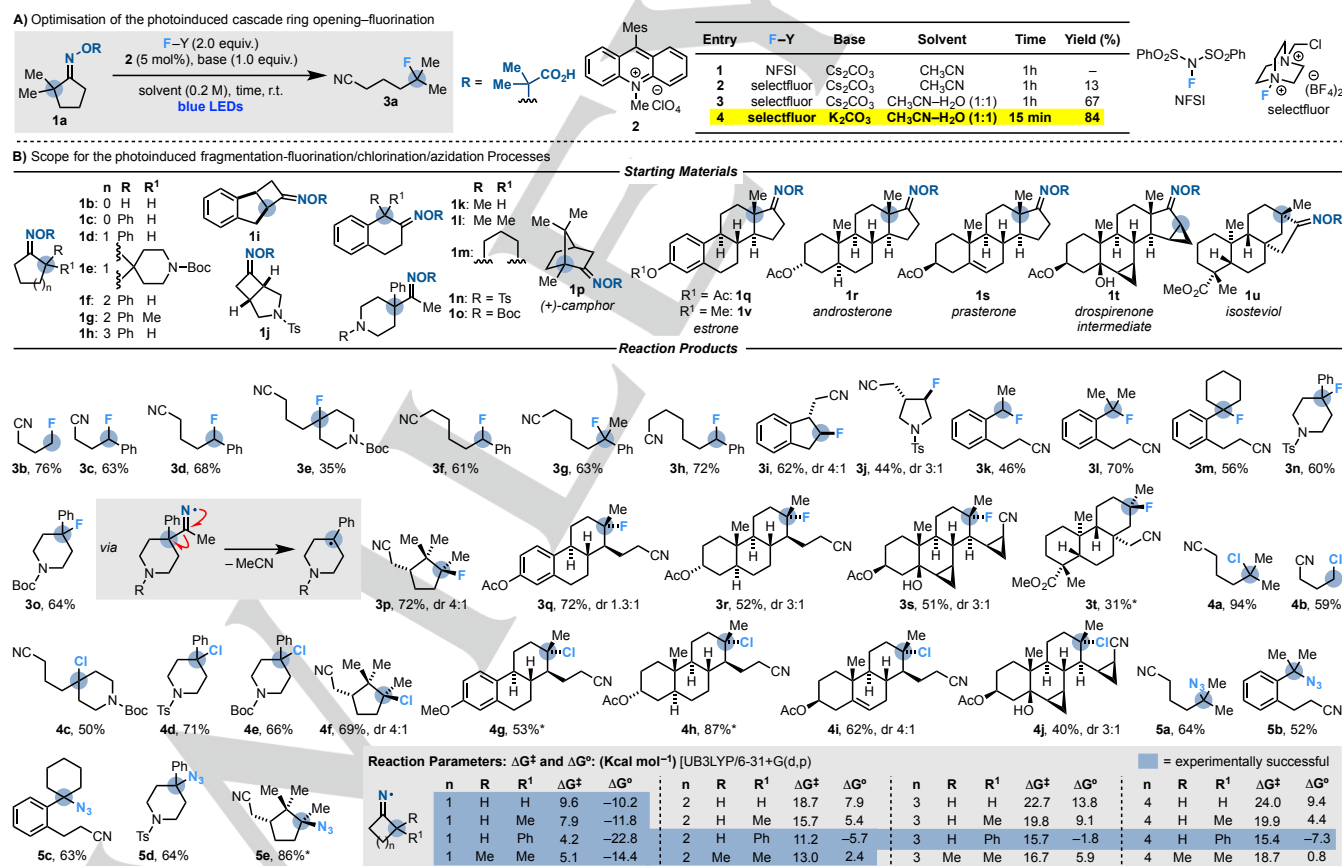
With an optimized set of conditions in hand, the scope of the reaction was evaluated (Scheme 3B). We successfully carried the oxidation–ring-opening–fluorination of oximes deriving from cyclobutanones (**1b,c**→**3b,c** and **1i,j**→**3i,j**), cyclopentanones

(**1d,e**→**3d,e**), cyclohexanones (**1f,g**→**3f–g** and **1k–m**→**3k–m**), and, remarkably, cycloheptanone (**1h**→**3h**), obtaining a broad range of fluorinated products in good yields. The methodology was also implemented as part of a strategy for the preparation of C-4 fluorinated 4-aryl-piperidines (**1n,o**→**3n,o**) that constitute the structural core of many opioid analgesic and antipsychotics such as pethidine and haloperidol. In this case, upon iminyl radical generation the fragmentation process expels acetonitrile.

We were particularly interested in applying this strategy to the structural modification of natural products. As these unique architectures are tuned to allow optimal interactions with specific bio-targets, a methodology enabling access to compounds with natural product-like cores has great promise in phenotypic-based drug discovery.^[14] Pleasingly, we were able to deconstruct and fluorinate (+)-camphor (**13**→**3p**), the steroids estrone (**1q**→**3q**) and androsterone (**1r**→**3r**), a synthetic intermediate of the oral contraceptive drospirenone (**1t**→**3s**) and the diterpene isosteviol (**1u**→**3t**).

Furthermore, *N*-chloro-succinimide (NCS) and tri-*i*-Pr-sulfonyl-azide^[15] were effective among a range of reagents investigated to achieve a novel cascade approach towards chlorinated (**4a–j**) and azidated (**5a–e**) nitriles.^[9] Here, the optimum base and solvent were identified as KOAc–CH₃CN and Cs₂CO₃–CH₂Cl₂ for the chlorination and azidation processes respectively.

By a combination of DFT and experimental studies, we have



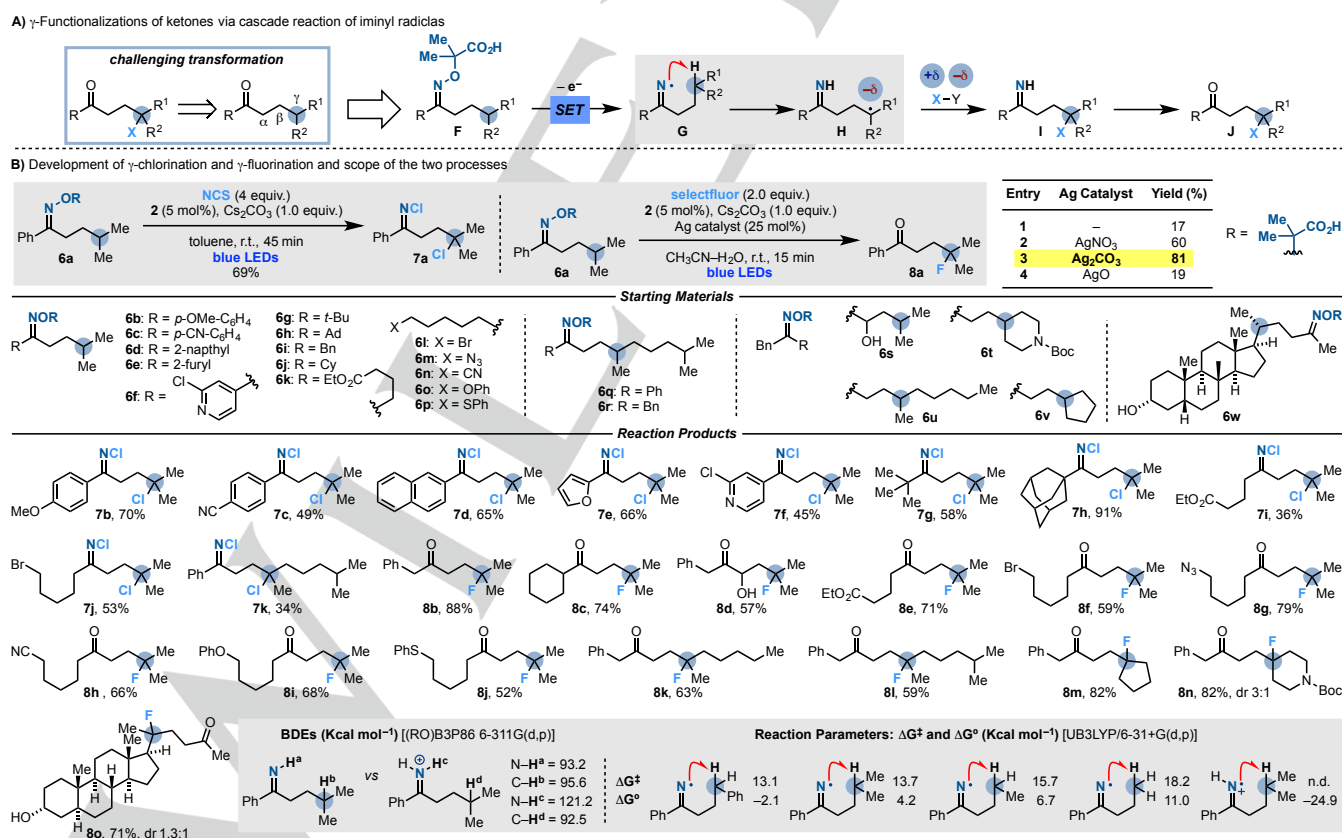
Scheme 3. Development and scope for the photoinduced ring-opening fluorination, chlorination, azidation reactions via iminyl radicals. * = isolated as single diastereomer.

determined that while cyclobutanones derived oximes undergo very facile fragmentation, the radical ring-openings of higher cycles are considerably more difficult. However, by placing either an α -aromatic substituent or two α -alkyl groups (e.g. gem-Me₂), we were able to effectively engage cyclopentanone derivatives. In the case of cyclohexanone and cycloheptanone-derived oximes, the radical fragmentations are increasingly challenging, but could be achieved in good yields when α -aromatic substituents were present.^[9]

Having achieved tandem iminyl radical generation and sp³-sp³ C–C bond fragmentation–functionalization, we evaluated the development of a strategy based on sp³ C–H bond cleavage. Success here would deliver a method for the selective γ -functionalization of ketones^[16] via iminyl radicals that is underdeveloped. Specifically, we envisaged a cascade process starting with the oxidative SET–fragmentation of precursor **F** leading to the iminyl **G**. In this case, as C–C bond fragmentation is not favorable; a 1,5-H-abstraction^[20] would deliver the nucleophilic γ -carbon radical **H** (Scheme 4A). Polarity matched S_H2 reaction with the SOMOphiles (to give **I**) and hydrolysis would provide the γ -functionalized ketone **J** which would be unreactive under classical ionic reactions. We were however concerned by the fact that (i) 1,5-H abstractions involving iminyl radicals are known to require acidic conditions,^[8b, 8c] which would not allow decarboxylation in our system, and (ii) that radical **H** is prone to undergo intramolecular cyclization when R = aromatic as reported by Forrester and Nevado.^[8b, 8c, 8k] Despite these

concerns, we started our investigations by preparing oxime **6a** and exposing it to various SOMOphiles using **2** as the photocatalyst under blue LEDs irradiation (Scheme 4B).^[9] We were pleased to see that in the presence of NCS γ -chlorination occurred smoothly.^[17] However, upon isolation and full characterization of the reaction product we realized that the imine intermediate **I** had reacted with the excess NCS providing the N-Cl imine **7a** which was stable and could be purified by column chromatography.^[18] We then hoped to expand this strategy and develop a sought-after γ -fluorination process. We were particularly interested by the fact that going via an iminyl radical would by-pass some of the limitations of approaches based on the photo-excitation of ketones, which are mostly suited for the fluorination of structurally congested molecules as elegantly demonstrated by Lectka.^[19] In this case however, screening of several radical F-donors, bases, photocatalysts and solvents, lead to very low product formation (entry 1). Pleasingly, by using selectfluor as the F-source and Ag₂CO₃ as a co-catalyst,^[20] γ -fluorinated ketone **8a** was obtained in high yield in just 15 min (entry 3). Control experiments confirmed the necessity of **2**, Ag(I) and continuous blue LEDs irradiation. For this reaction, a calculated quantum yield $\Phi = 4.8$ is consistent with the presence of productive radical chain propagations along with the photoredox manifold.^[9]

With these set of conditions in hand, we evaluated the scope of the processes using a range of oximes with different substitution patterns. This enabled the divergent preparation of a variety of



Scheme 4. Development and scope for the photoinduced γ -chlorination and γ -fluorination reactions via iminyl radicals.

γ -Cl-N-Cl imines (**7b–k**) and -F ketones (**8b–n**) in good yields. Overall, the reactions were largely undeterred by a variety of functionalities as demonstrated by the successful formation of products containing electron rich and poor (hetero)aromatics, nitrile, azide, ester, free alcohol, (thio)ether, and *N*-Boc groups. Furthermore, we were able to apply the -fluorination to the modification of a structurally complex lithocolic derivative (**7o**). The challenges associated to the development of these radical transpositions can be appreciated by evaluating the reaction parameters. According to our calculations, there is a very small gain in BDEs^[21] going from the iminyl **G** to the carbon radical **H** (compare BDE for N–H^a and C–H^b) and these 1,5-abstraction process are generally endergonic (for $\Delta G^\circ = 4.2 \text{ kcal mol}^{-1}$) (Scheme 4).^[9] This is in line with our experimental results showing the ability of these γ -chlorination and γ -fluorination cascades to functionalize tertiary centres, which are the most activated.^[22] Our results also explain while previous methods required a stoichiometric acid that, by protonating the iminyl radical, renders the reaction extremely exergonic and imposes a significant gain in BDEs to the abstraction process (compare BDEs for N–H^c and C–H^d).^[23] In conclusion, we have developed a photoinduced strategy for the preparation of remotely functionalized nitriles and ketones. These protocols are triggered by the organo-photoredox generation of iminyl radicals that, upon transposition via sp³–sp³ C–C or sp³ C–H bond cleavage, give access to distal carbon-radicals.

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Keywords: fluorination • azidation • chlorination • remote radical functionalization cascade • photoinduced

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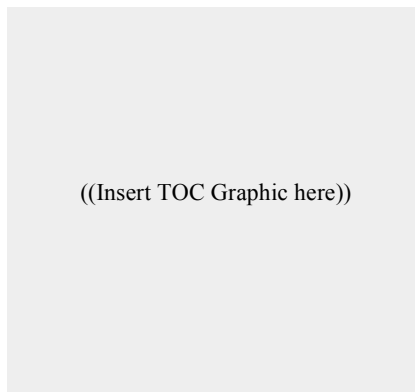
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