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Trityl isocyanide as a general reagent for visible light mediated photoredox-catalyzed cyanations†

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A photoredox catalytic strategy has been developed to enable the functionalization of a variety of commercially available, structurally different radical precursors by the use of a bench-stable isonitrile as an efficient cyanating reagent. Specifically, a radical-based reaction has provided a mild and convenient procedure for the cyanation of primary, secondary and tertiary radicals derived from widely accessible sp^3-hybridized carboxylic acids, alcohols and halides under visible light irradiation. The reaction tolerates a variety of functional groups and it represents a complementary method for the cyanation of structurally different scaffolds that show diverse native functionalities, expanding the scope of previously reported methodologies.

Introduction

Aliphatic nitriles are ranked among the most common functional groups in bioactive molecules.[1] The anticancer agent ruxolitinib, the antihyperglycemic vildagliptin and the antibacterial cefmetazole are examples of commercialized drugs containing alkyl cyanides. Additionally, nitriles are versatile synthetic handles used to introduce a broad variety of functional groups in organic molecules, and prevalent intermediates in the synthesis of heterocycles (Fig. 1).[2]

Traditionally, alkyl halides have been used to prepare aliphatic nitriles through a S_N2 or S_N1 reaction. Some drawbacks of this approach are the need to prepare the alkyl halides, the use of toxic cyanide salts, high temperatures and competing elimination reactions.[3] To complement this polar strategy different radical approaches have been developed, based on the generation of a nucleophilic radical from a suitable precursor followed by reaction with a cyanating reagent. With the expansion of photoredox catalysis[4] and electrochemistry,[5] radical approaches have become attractive ways to prepare alkyl nitriles from native and abundant functional groups under extremely mild conditions,[6] complementing the use of transition metals and avoiding high temperatures.[7] Carboxylic acids,[8–10] redox-active esters,[11] alkyl halides,[12,13] trifluoroborate salts,[14] and specific C–H bonds[10,15] have been used as carbon-centered alkyl radical precursors in photoredox-catalyzed and electrochemical cyanation reactions. The cyanating reagents used in these transformations include tosyl and trimethylsilyl cyanide, cyanobenziodoxolone, 4-cyano pyridine and inorganic salts such as sodium and potassium cyanides (Scheme 1). All of them are cyanide-containing reagents often used in superstochiometric amounts. The introduction of cyanide-free reagents that could promote general photoredox catalyzed cyanations would be a convenient addition to the toolbox that chemists have at disposal to prepare aliphatic nitriles.

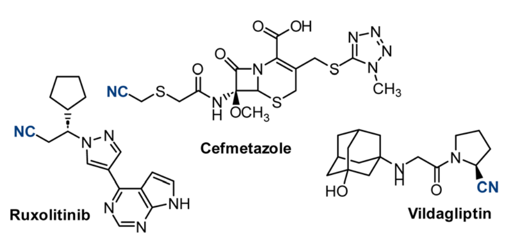

Fig. 1 Selected pharmaceuticals containing aliphatic nitriles.

Our group recently demonstrated that isonitriles can unlock hydro- and deuterodeamination reactions under extremely mild conditions.[16] Indeed, isonitriles can intercept visible light-generated silyl radicals to give an imidoyl radical intermediate that enables a β-scission, provoking the C–N bond fragmentation. Based on these results, we reasoned that a tunable isonitrile could intercept carbon-centered radicals generated under photoredox catalysis to provide a unified strategy for the cyanation of common functional groups.

Although isonitriles have been used as efficient radical traps[17] and suitable reagents in radical cyanations,[18] the nitrile

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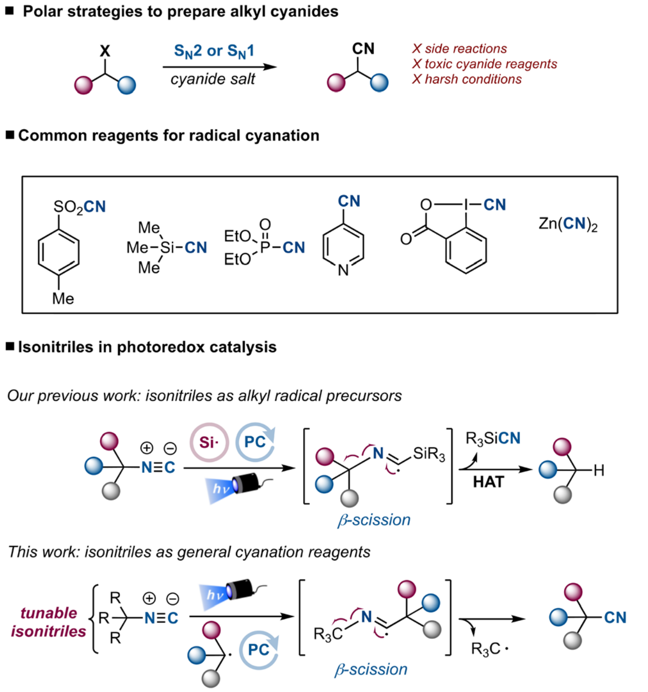
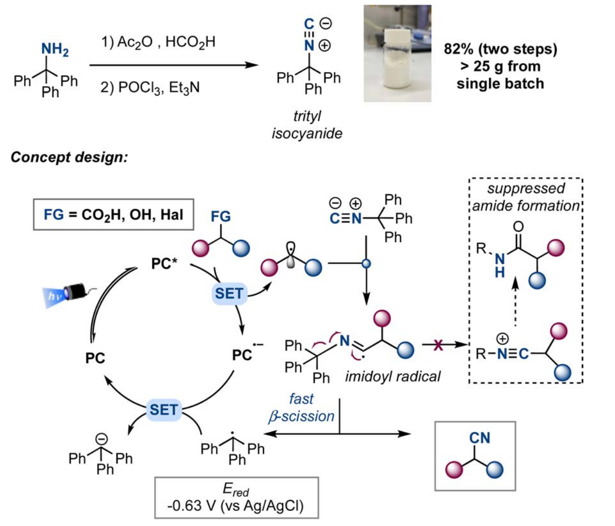


Scheme 1 Common reagents used for radical cyanation of aliphatic precursors. Dual use of isonitriles in photoredox catalysis: alkyl radical precursors and cyanation reagents.



Scheme 2 Trityl isocyanide as a general reagent for photoredox catalyzed cyanation.

product usually competes with the formation of an amide, through the *in situ* generation of a nitrilium ion or a ketenimine.[19] We envisioned that trityl isocyanide, a bench stable solid easily prepared from trityl amine,[20] could be used as a selective cyanating reagent for precursors capable to provide alkyl radicals through a photoredox reductive quenching cycle (Scheme 2). Among the class of compounds that could generate alkyl radicals through a reductive quenching cycle, carboxylic acids, alcohols and alkyl halides (*via* an alpha-amino radical-mediated halogen atom transfer) attracted our interest as they are commercially available abundant building blocks.[21] Once generated, the alkyl radical would add to trityl isocyanide to form an imidoyl radical.[22] Subsequent β-fragmentation would afford the nitrile product and a trityl radical that could be easily reduced to the stabilized trityl anion through a single-electron reduction [$E_{red} = -0.63$ V *vs.* Ag/AgCl],[23] regenerating the photocatalyst. Key in our design is the fact that the stability of the trityl radical would favour a fast β-scission, therefore avoiding the nitrilium ion formation through single-electron oxidation,[24] and shifting the selectivity towards the nitrile formation. During the preparation of this manuscript Procter reported the synthesis of aliphatic nitriles from alkyl iodides using a sulfonium salt as a halogen atom transfer reagent precursor and an α-amide isocyanide as cyanating reagent.[25] Herein, we present the use of trityl isocyanide as a general cyanating reagent for alkyl carboxylic acids, alcohols and halides. This reagent allows the use of widely accessible sp^3-hybridized building blocks, providing a straightforward access to structurally different nitriles under mild conditions (Scheme 2).

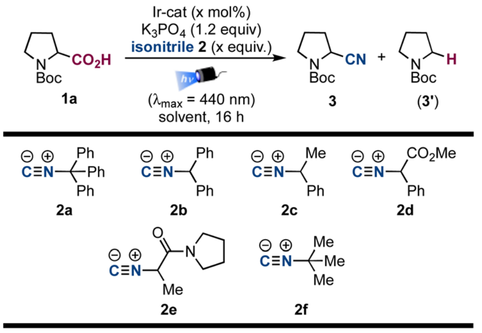
Results and discussion

We started our investigations choosing carboxylic acids **1** as building blocks that could generate carbon-centered radicals by established photoredox catalysis *via* the corresponding carboxylates [$E_{ox} \approx +1.2$ V *vs.* SCE] upon deprotonation and subsequent decarboxylation.[26,27]

As preliminary conditions, we employed [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$] (Ir-cat) as the photoredox catalyst [$E^*_{red}(Ir^{III*}/Ir^{II}) = +1.21$ V *vs.* SCE],[28] K_3PO_4 as base, acetonitrile as solvent and we irradiated the reaction with a blue 440 nm Kessil PR160L LED lamp. On the other hand, isonitrile **2a** (3.0 equiv.) was chosen since we envisioned that the corresponding trityl radical that would be obtained after β-scission would be easily reduced to regenerate the ground state photocatalyst. Indeed, we were delighted to observe an efficient decarboxylation of carboxylic acid **1a** and the concomitant formation of product **3** in 68% yield (Table 1, entry 1). Next, we evaluated different isonitriles (**2b–f**) as alternative cyanating reagents (entries 2–6), observing a diminished reactivity which indicated that the stability and redox potential of the intermediate isocyanide-derived radical play a crucial role. Moreover, different amounts of decarboxylative product **3′** were obtained, observing a lower ratio with isonitrile **2a**, presumably due to the easy β-scission that leads to the highly stabilized trityl radical. Switching the solvent to DMSO led to an improvement of the yield (entry 7) and after some further optimization (see ESI† for additional details) the desired product could be obtained in 82% yield, employing 1.0 mol% of catalyst loading, 2.5 equiv. of isonitrile and performing the reaction on a 0.20 mmol scale (entry 11).

To enhance the synthetic utility of the isonitrile-enabled photocatalytic cyanation, we decided to expand the scope of the reaction by tackling a similar transformation starting from widely accessible aliphatic alcohols **4** as radical precursors. To achieve the required radical deoxygenation, we relied on

Table 1 Optimization of the photocatalytic decarboxylative cyanation with isonitriles[a]



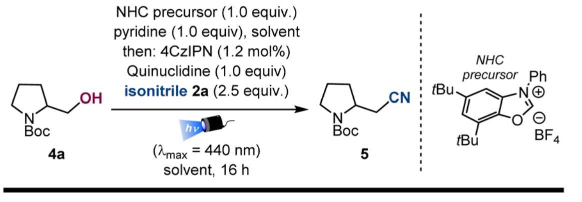
Entry	Solvent	2 (equiv.)	Ir-cat (mol%)	Yield 3 (3′) %
1	MeCN	**2a** (3.0)	2	68 (14)
2	MeCN	**2b** (3.0)	2	55 (35)
3	MeCN	**2c** (3.0)	2	30 (5)
4	MeCN	**2d** (3.0)	2	48 (52)
5	MeCN	**2e** (3.0)	2	24 (0)
6	MeCN	**2f** (3.0)	2	4 (12)
7	DMSO	**2a** (3.0)	2	74 (12)
8	DMF	**2a** (3.0)	2	60 (14)
9	DCM	**2a** (3.0)	2	0 (5)
10	$PhCH_3$	**2a** (3.0)	2	36 (30)
11[b,c]	DMSO	**2a** (2.5)	1	82 (8)
12[d]	DMSO	**2a** (2.5)	1	0
13[e]	DMSO	**2a** (2.5)	1	0

[a] The reactions were performed on a 0.10 mmol scale and the yields were determined by ^{1}H NMR with CH_2Br_2 as an internal standard. [b] The reaction was performed on a 0.20 mmol scale. [c] Yield determined after isolation by column chromatography purification. [d] The reaction was performed in the absence of light. [e] The reaction was performed in the absence of photocatalyst. See ESI for further details.

a recently developed strategy that, upon oxidation of an alcohol-NHC (N-heterocyclic carbene) adduct [$E_{ox} \approx +0.6$ V *vs.* SCE], allows an efficient C–O bond homolysis.[29] Slightly adapting this methodology to our envisioned cyanation strategy, we obtained a promising 30% yield (Table 2, entry 1) when 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was used as the photoredox catalyst [E^{*}_{red}(4CzIPN*/4CzIPN$^{\bullet-}$) = +1.35 V *vs.* SCE].[30] The use of MTBE or 1,4-dioxane as solvents improved the yields (entries 2 and 3), obtaining the product in 75% yield when a 1 : 1 mixture of dioxane and DMSO was employed (entry 4). After some additional optimization (see ESI† for further details) the reaction could be scaled up to 0.2 mmol with a 2.0 mol% of photocatalyst, delivering the desired nitrile **5** in a slightly diminished yield (60%, entry 5).

Next, with the aim of developing a complementary method that could provide an alternative to nucleophilic substitution reactions, we evaluate the possibility to exploit a halogen atom transfer (XAT) photocatalytic strategy to generate a carbon-centered radical from alkyl halides **6** (Table 3).[31] Specifically, the photoredox catalyst engages in a SET with triethylamine [E_{ox} = +0.77 V *vs.* SCE] by a reductive quenching cycle to deliver an α-amino alkyl radical as a powerful XAT reagent that abstract the iodine atom to deliver a new carbon-centered radical.

Table 2 Optimization of the photocatalytic deoxygenative cyanation with isonitriles[a]

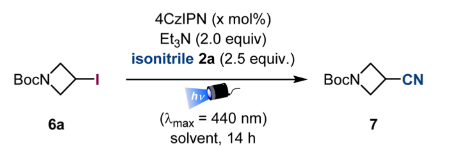


Entry	Solvent	4CzIPN (mol%)	Yield %
1	MTBE : DMA (1 : 1)	1.2	30
2	MTBE	1.2	46
3	Dioxane	1.2	52
4	Dioxane : DMSO (1 : 1)	1.2	75
5[b]	Dioxane : DMSO (1 : 1)	1.2	60
6[c]	Dioxane : DMSO (1 : 1)	1.2	0
7[d]	Dioxane : DMSO (1 : 1)	—	0

[a] The reactions were performed on a 0.10 mmol scale and the yields were determined after isolation by column chromatography purification. [b] The reaction was performed on a 0.20 mmol scale. [c] The reaction was performed in the absence of light. [d] The reaction was performed in the absence of photocatalyst. See ESI for further details.

Gratifyingly, adding isonitrile **2a** to the reaction mixture, the transiently generated radical could be efficiently trapped to furnish the corresponding isonitrile **7** in 88% yield (Table 3, entry 1). Decreasing the photocatalyst loading to 2.0 mol% afforded the product in 91% yield (entry 2), whereas different

Table 3 Optimization of the photocatalytic XAT-enabled cyanation with isonitriles[a]



Entry	Solvent	4CzIPN (mol%)	Yield %
1	MeCN	5.0	88
2	MeCN	2.0	91
3	DMSO	2.0	50
4	Acetone	2.0	69
5[b]	MeCN	2.0	0
6[c]	MeCN	2.0	0
7[d]	MeCN	—	0

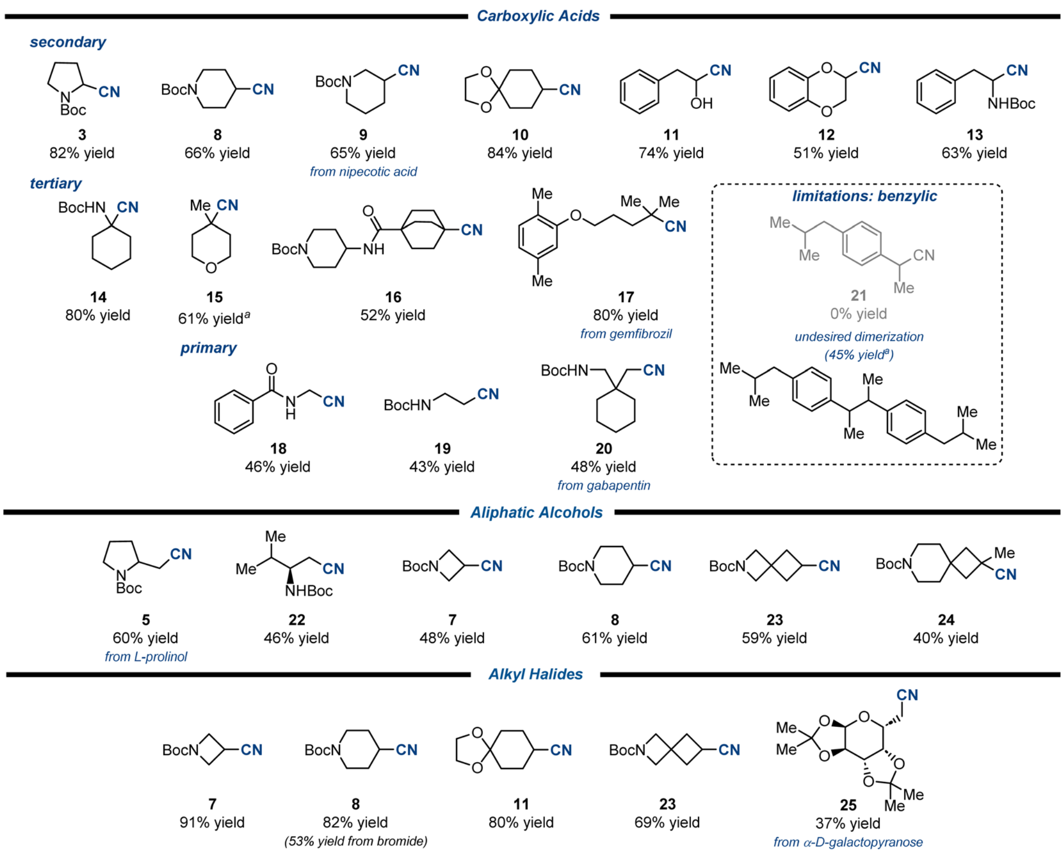
[a] The reactions were performed on a 0.20 mmol scale and the yields were determined after isolation by column chromatography purification. [b] The reaction was performed in the absence of triethylamine. [c] The reaction was performed in the absence of light. [d] The reaction was performed in the absence of photocatalyst. See ESI for further details.

solvents than acetonitrile led to diminished yields (entries 3 and 4). Even in this case, the presence of all the reaction components was necessary for a successful reaction since it did not proceed in the absence of XAT reagent, light or photocatalyst.

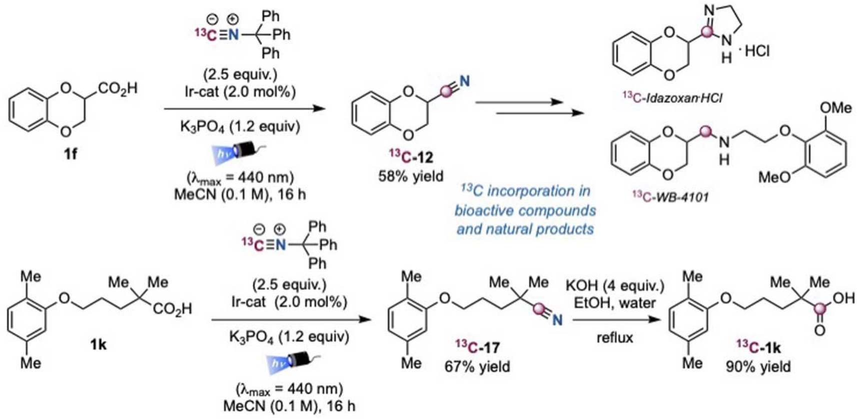
With the optimized conditions in hand for the three different radical precursors, we evaluated the scope of the photocatalytic cyanation reaction, employing a variety of carboxylic acids **1**,[8–10] aliphatic alcohols **4**, and alkyl halides **6** (Table 4).[12,13,25] *N*-Boc-piperidine-containing secondary carboxylic acids delivered the corresponding nitriles **8** and **9** in 66% and 65% yield. Acetal-, hydroxy- and catechol-containing products (**10–12**) were obtained in moderate to high yields, highlighting the functional group compatibility of the method. On the other hand, *N*-boc phenylalanine derived nitrile **13** was isolated in 63% yield, showcasing that *N*-protected α-amino acids are suitable substrates. Next, we employed tertiary carboxylic acids to study the influence of the radical stability and of its steric hindrance on the outcome of the reaction. We were pleased to observe high reactivity in all the cases, indicating an efficient β-scission of the imidoyl radical upon radical addition on isonitrile **2a**. Indeed, products **14–17** were obtained, allowing the introduction of a nitrile functionality at the bridgehead position of a bicyclo[2.2.2]octane and the modification of the lipid-regulating agent gemfibrozil. Stabilized and not stabilized primary radicals could be employed, resulting in the formation of nitriles **18–20**, albeit with slightly lower yields. The general reactivity observed with primary, secondary and tertiary aliphatic carboxylic acids is striking as most previous examples are limited to carboxylic acids carrying an α-heteroatom.[8–10] On the other hand, benzylic carboxylic acids were not suitable for this reaction. Indeed, although efficiently decarboxylated, the corresponding nitrile **21** was not observed and only a dimeric compound was detected (45% NMR yield of a 50% maximum theoretical yield), presumably due to a reluctance of the (more stable) benzyl radical to undergo radical addition to the isonitrile or to a more favourable and undesired α-scission of the transiently formed imidoyl radical.

Subsequently, we evaluated the scope of the reaction employing aliphatic alcohols as radical precursors. Different β-amino alcohols, which are derived from ubiquitous α-amino acids and that present a primary alcohol as functional group, could be employed, delivering products **5** and **22** in 60% and 46% yield, respectively. Secondary aliphatic alcohols furnished a variety of cyclic nitriles (**7**, **8**, and **23**) with different ring size or a spirocyclic scaffold. Moreover, a tertiary alcohol was amenable to this transformation, delivering the spirocyclic tertiary nitrile **24** in 40% yield. To the best of our knowledge our protocol

Table 4 Reaction scope of the photoredox-catalyzed cyanation[a,b]



[a] The reactions were performed on a 0.20 mmol scale and the yields were determined after isolation by column chromatography purification. [b] The yield was determined by ^{1}H NMR with CH_2Br_2 as internal standard. See ESI for further details.



Scheme 3 Incorporation of ^{13}C in bioactive compounds and natural products.

represents the first example of photoredox-catalyzed direct cyanation of aliphatic alcohols.

Next, we explored the possibility to carry out a photocatalytic cyanation starting from alkyl halides **6**.[12,13,25] A variety of structurally different secondary iodides could be employed, obtaining nitriles **7**, **8**, **11**, and **23** in excellent yields. In addition, the same reaction could be performed over secondary bromides, despite a diminished yield in comparison with the parent iodide (53% *vs.* 82% yield). Primary halides were also suitable for this transformation, as exemplified by the α-D-galactopyranose-containing product **25**, which demonstrated the feasibility to employ more complex scaffolds and natural product cores. These results are comparable to those obtained using TMS-CN as cyanating reagent.[12]

Moreover, we decided to prepare the ^{13}C-labelled analogous of trityl isocyanide **2a**, employing ^{13}C-formic acid for its synthesis. Indeed, the use of this ^{13}C-labelled cyanating reagent would enable access to the corresponding isotopic nitrile analogues through functionalization of widely available carboxylic acids, aliphatic alcohols and alkyl halides, allowing the efficient incorporation of a carbon isotope starting from diversified starting materials. As representative examples, we chose to prepare the isotopic analogues of products **12** and **17**. When the photocatalytic reaction was performed in the presence of isonitrile **^{13}C-2a** as a trapping agent, we smoothly observed the formation of compounds **^{13}C-12** and **^{13}C-17** in 58% and 70% yield (Scheme 3). Therefore, this labelling strategy could enable the synthesis of ^{13}C-labelled analogous of bioactive compounds such as idazoxan hydrochloride and WB-4101.[32] Moreover, the potential of this methodology was showcased by the facile hydrolysis of **^{13}C-17**, which allowed to access a ^{13}C-labelled gemfibrozil analogue **^{13}C-1k** in 90% yield.

Conclusion

In summary, we have developed a general photocatalytic cyanation reaction employing trityl isocyanide as selective cyanating reagent. The use of a photoredox reductive quenching strategy, along with a judicious choice of the more appropriate isonitrile, avoids the formation of undesired nitrilium ions, shifting the transformation towards the nitrile product. The suitability of carboxylic acids, aliphatic alcohols and alkyl halides as radical precursors enables a straightforward transformation from widely accessible building blocks. Besides enabling access to alkyl nitriles from common and diversified precursors, this methodology represents a valuable alternative to polar cyanation strategies that allows the easy preparation of isotopic analogues, avoiding the use of cyanide-containing reagents.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

M. T. conceived and designed the project. I. Q., M. M., C. P.-S., and T. R. performed all optimization studies and photocatalytic reactions. M. T. and T. R. wrote the manuscript with the contribution of all the authors.

Conflicts of interest

There are no conflicts to declare.

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