Spectroscopic Investigation of the Remote C–H Allylation of Amides via Photoredox and Nickel Dual Catalysis

Céline Bourgois[a]
Simon De Kreijger[a]
Bin Xu[b]
Uttam K. Tambar*[b]
Ludovic Troian-Gautier*[a,c]

[a] Université catholique de Louvain (UCLouvain). Institut de la Matière Condensée et des Nanosciences (IMCN), Molecular Chemistry, Materials and Catalysis (MOST). Place Louis Pasteur 1, bte L4.01.02, 1348 Louvain-la-Neuve, Belgium

[b] Department of Biochemistry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, United States

[c] Wel Research Institute, Avenue Pasteur 6, 1300 Wavre; Belgium

Ludovic.Troian@uclouvain.be,
Uttam.Tambar@utsouthwestern.edu

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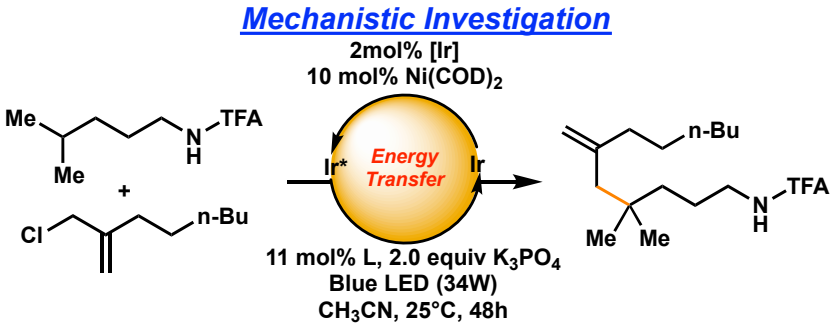

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Abstract The mechanistic details of a reported allylation reaction were investigated by means of Stern-Volmer experiments and nanosecond transient absorption spectroscopy. Both reference substrates, *i.e.* allylic chloride and trifluoroacetamide, were inefficient quenchers but large quenching rate constants were observed upon the addition of $Ni(COD)_2$ and bisoxazoline. The large quenching rate constants and absence of observable photoproducts were consistent with a mechanism that operates by energy transfer between the excited-state iridium photosensitizer and the nickel complex.

Key words Photoredox, Energy Transfer, Mechanism, Iridium, Transient Absorption, Quenching, Stern-Volmer

Given the ubiquity of nitrogen atoms in medicinal chemistry and other molecular sciences,[1] the selective functionalization of nitrogen containing molecules is an essential tool in chemical synthesis. The allylation of amines and amides is particularly useful, because the resulting allylic amines are synthetically versatile building blocks that can be converted into a broad range of products.[2] Recently, Tambar and co-workers reported a direct allylation of unactivated C(sp^3)–H bonds in unfunctionalized amides with simple allylic chlorides using Ir/Ni dual photoredox catalysis (**Figure 1**).[3]

A 1,5-HAT process was triggered by photoredox-generated amidyl radicals that led to various allyl-substituted amides isolated in good yields, high δ-selectivity, and high functional group tolerance.[3] Over 25 examples with yields ranging from 38% to 76% were reported.[3] At that time, the proposed mechanism based on several control experiments and on established literature, the authors proposed a mechanism where the reaction proceeded through the oxidation of a deprotonated amide via an excited Ir(III) photosensitizer, $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ (**Figure 2**). The corresponding amidyl radical would then undergo a 1,5-hydrogen atom transfer, leading to the scission of the C(sp^3)-H bond. The carbon radical could then react with allylic chloride to yield the desired product and a chlorine radical that, as a very potent oxidant,[4] was used to oxidize Ir(II) back to its ground-state product.

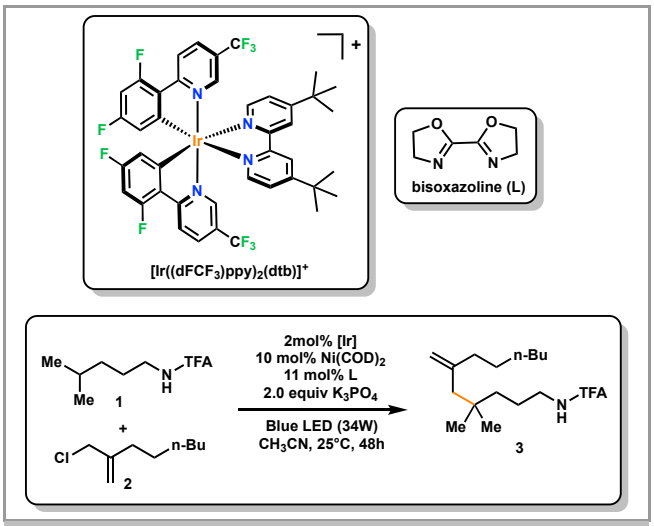

Figure 1 Prototypical reaction for the direct allylation of unactivated C(sp^3)-H bonds in unfunctionalized amides as reported by Tambar and co-workers. [3]

Herein, we investigated the mechanism of this reaction by means of steady-state and time-resolved spectroscopic techniques and offer an alternative mechanism that is proposed to occur via energy transfer rather than electron transfer.[5]

The absorption and photoluminescence spectra of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ were first recorded in acetonitrile (**Figure 3**). Properties typical of Ir(III) compounds with low-lying metal-to-ligand charge transfer (^{3}MLCT) excited states were observed, *i.e.* moderate absorption in the visible range and room temperature photoluminescence centered at 470 nm was observed with an excited-state lifetime of 2.5 µs.[6] Similar

measurements were performed on mixtures of $Ni(COD)_2$ and bisoxazoline (**L**) dissolved in acetonitrile in the presence of allylic chloride (**2**) or mixtures of trifluoroacetamide (**1**) and **2** (**figure 3**). The *in situ* generated nickel complexes absorbed up to 450-550 nm, which overlapped with the steady-state photoluminescence spectra of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$. Note that the absorbance of $Ni(COD)_2$ in the presence of bisoxazoline is not shown as it yielded a black solution with a precipitate that induced some additional scattering.

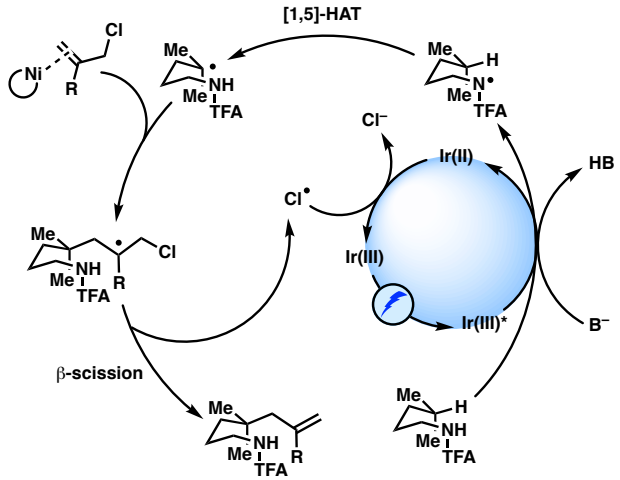

Figure 2 Proposed mechanism for the direct allylation of unactivated $C(sp^3)$-H bonds in unfunctionalized amides as reported by Tambar and co-workers. [3]

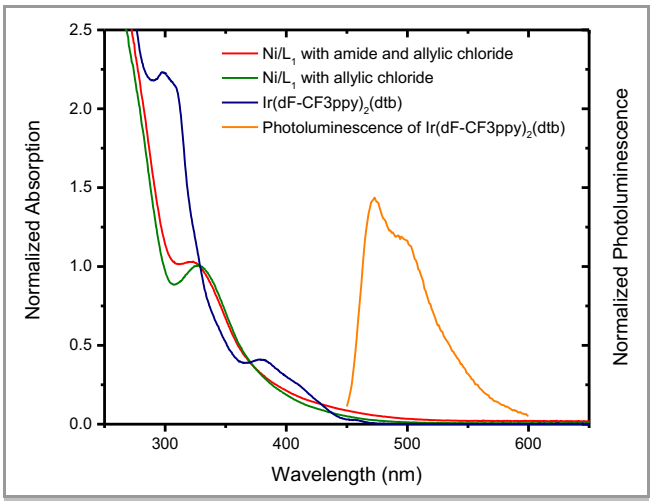

Figure 3 Absorption spectra of the different nickel derivatives as well as the absorption and photoluminescence spectra of $[Ir(dF\text{-}CF_3ppy)_2(dtb)]^+$ recorded in argon purged acetonitrile at room temperature.

The excited-state reactivity of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ with a series of potential quenchers, namely compounds **1** and **2**, was then investigated. Overall, the excited-state quenching data was well described by the Stern-Volmer model that provided the corresponding quenching rate constants.[4, 5b, 7] Excited-state quenching by trifluoroacetamide occurred in a dynamic fashion and proceeded with an overall small quenching rate constant, k_q = (2.30±0.10) x10^6 $M^{-1}s^{-1}$ (**Figure S2**). Importantly, the presence of K_3PO_4 did not influence the trifluoroacetamide quenching rate constant, suggesting that a proton-coupled mechanism does not occur, and that the addition of base is not assisting excited-state quenching. In addition, this quenching rate constant was about an order of magnitude smaller than that determined using the allylic chloride derivative, k_q = (1.49±0.12) x10^7 $M^{-1}s^{-1}$ (**Figure S3**). Both quenching rate constants are still two to three orders of magnitude smaller than diffusion limited processes and are therefore not very likely to occur or to lead to the efficient generation of products.[8] This is in line with the moderate yields of 48% that were obtained after 48h of irradiation in the absence of nickel catalyst.[3] At this stage, it is complicated to propose a mechanism for the reaction taking place in the absence of Nickel based on spectroscopic measurements alone. A mechanism based on the oxidation of the amine, as proposed in the first step of **figure 2**, could be operative.[9] Indeed, excited-state oxidation of triethylamine (TEA) or N,N-diisopropylethylamine (TEA), for example, is known to operate, albeit with small quenching rate constants.[10] With nickel, this yield rose to 76% and as such, we decided to investigate the excited-state quenching of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ using *in situ* generated Ni complexes. Excited-state quenching by the Ni^0L species (k_q = (1.46±0.08) x10^9 $M^{-1}s^{-1}$) was around 1.5 x10^9 $M^{-1}s^{-1}$ (**Figure S4**). An upward curvature was observed in the Stern-Volmer plot using the steady-state photoluminescence (PLI_0/PLI) measurements. We believe however that this upward curvature is a result of the competitive absorption by Ni^0L that absorbs light between 400 and 800 nm. The excited-state quenching by $Ni^{II}L$(**2**), the proposed complex generated from $Ni(COD)_2$, bisoxazoline, and allyl chloride **2** was very efficient, with a quenching rate constate k_q = (1.29±0.07) x10^9 $M^{-1}s^{-1}$ determined from the time-resolved data (**Figure 4a-b**). The excited-state quenching by $Ni^{II}L$(**2**) occurred through a combination of both dynamic and static quenching with the corresponding static constant of K_s = 5900 M^{-1} (**Figure 4c-d**).

The Stern-Volmer experiments indicate that the excited-state quenching occurs more efficiently with *in situ* generated nickel complexes than with allylic chloride or trifluoroacetamide. Although it is tempting to assign large quenching rate constants with efficient excited-state electron transfer, such mechanisms can only be proved by transient absorption spectroscopy or other spectroscopic techniques that clearly identify spectral signatures that are unambiguously ascribed to oxidized or reduced species.[5b, 7a] Hence, the absorption spectra of the excited, reduced, and oxidized states of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ was first characterized by transient absorption spectroscopy . using pulsed 420 nm light excitation in argon purged acetonitrile. [5b, 11] The excited-state absorption spectra of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ showed the absence of isosbestic points and only excited-state absorption features with a maximum centered at 480 nm (**Figure S8**). The spectrum of the reduced photosensitizer was determined by performing nanosecond transient absorption experiments of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ in the presence of tri-*p*-tolylamine; TTA (**Figure S6**). This light-mediated reaction generated the mono-reduced Ir(II) photosensitizer and the corresponding oxidized $TTA^{\bullet+}$ radical cation. The spectral signature of this species is unambiguous, and its molar absorption coefficient can then be used to determine the absorption spectra of the reduced Ir(II) species.[12] Finally, the spectra of the oxidized Ir(IV) complex was determined using methyl viologen as electron acceptor (**Figure S7**). In this case as well, the spectral signature of the

singly reduced $MV^{\bullet+}$ radical cation led to the extrapolation of the absorption spectra of the oxidized iridium photosensitizer.

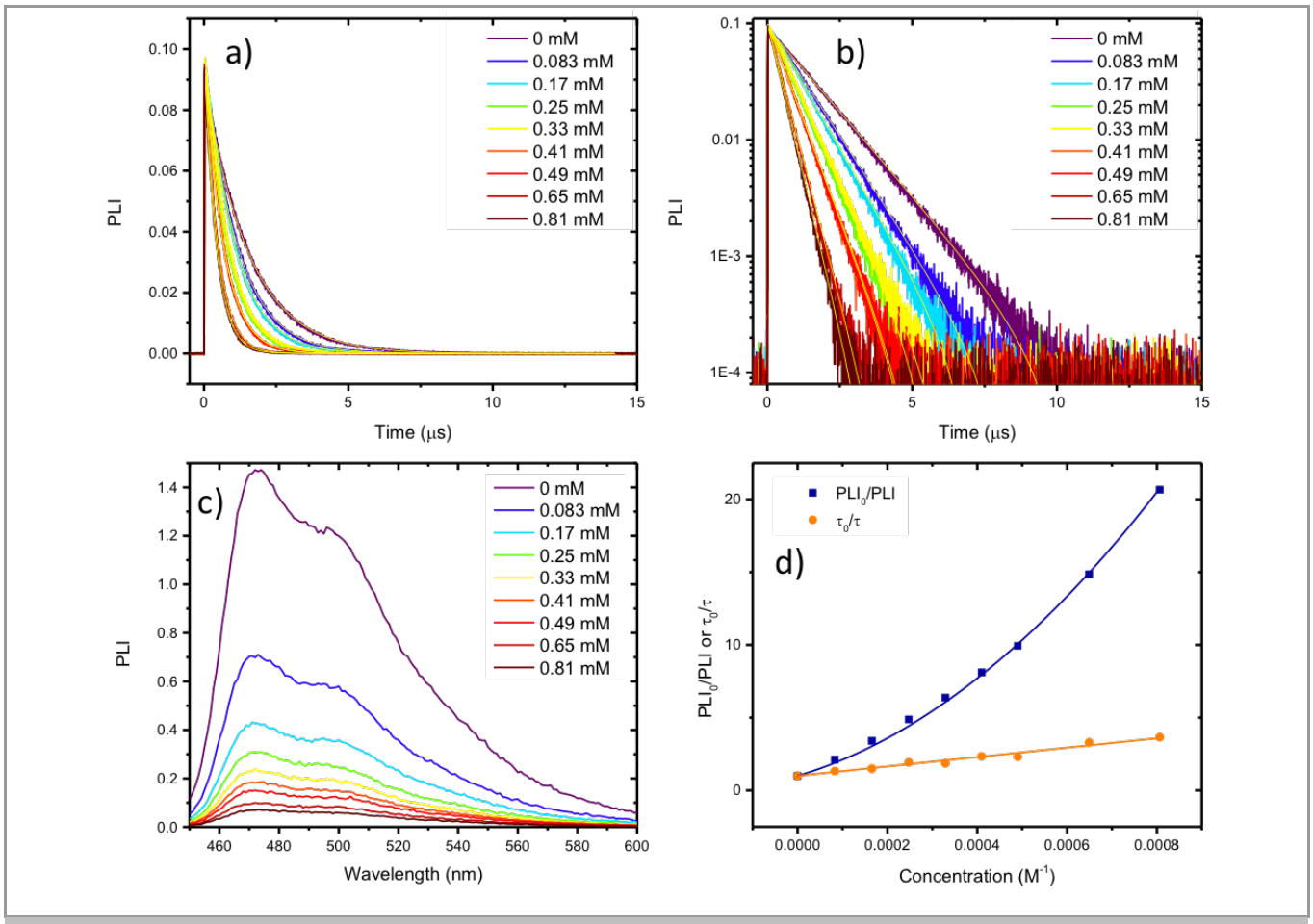

Figure 4 Evolution of the time-resolved (a and b) and steady-state (c) photoluminescence in the presence of increasing amount of $Ni^{II}L(Cl)(Allyl)$ in argon purged acetonitrile at room temperature. The corresponding Stern-Volmer plot is represented in panel (d).

With a clear spectral signature of the iridium photosensitizer in different oxidation states, we decided to perform transient absorption spectroscopy using compounds **1**, **2**, $Ni^{0}L$, and $Ni^{II}L$(**2**). Using compounds **1** and **2**, only the excited state of $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ was observed by transient absorption spectroscopy, with no evidence for the formation of the mono-reduced or mono-oxidized iridium photosensitizer (**Figure S11-S12**). This was in line with the low quenching rate constants determined previously that probably stems from an uphill driving force for electron transfer. Oxidative quenching of $Ni^{0}L$ was clearly observed by nanosecond transient absorption spectroscopy through the persistent absorption spectra attributed to the mono-reduced $[Ir(dF(CF_3)ppy)_2(dtb)]$ (**Figure S9**). However, it should be noted that this Ni^{0} species was not expected to be present during photocatalysis due to the large excess of **2**. The most significant quenching was observed with $Ni^{II}L$(**2**), yet, no photoproducts were observed by transient absorption spectroscopy (**Figure S13**). Had oxidative or reductive excited-state quenching occurred with even low cage escape yields, then the Ir complex would have reported on the redox chemistry, contrary to what was observed.[10b, 13] Cage-escape yields as low as 5% can routinely be determined[10b, 13a, 13b, 13d, 14] and hence our inability to observe reaction products implies either electron transfer with very rapid geminate recombination occurring below our instrument's response or energy transfer. Energy transfer from ^{3}MLCT states to Ni(II) catalysts has previously been proposed by McCusker and MacMillan as well as by Molander,[15] which differ significantly from proposed reductive quenching mechanisms. An energy transfer mechanism taking place between $[Ir(dF(CF_3)ppy)_2(dtb)]^+$ and cinnamyl chloride derivatives was recently proposed by our groups.[11] An iridium photosensitizer triplet–triplet energy transfer was also recently reported for the photoinduced *trans–cis* isomerization of cinnamic acid derivatives.[16]

In here, energy transfer to the *in situ generated* $Ni^{II}L$(**2**) species is proposed (**Figure 5**). In the original report describing this reaction, a mechanism that did not proceed through a Ni(II) (η3)allyl-π-complex was proposed based on deuterium-labeled experiments in the presence and absence of nickel.[3] However, based on UV-Vis measurement and Stern-Volmer quenching studies with the proposed Ni(II) complex generated from $Ni(COD)_2$, bisoxazoline, and allyl chloride, we now propose the formation of Ni(II) (η^3)allyl-π-complex that undergoes regioselective reductive elimination to yield the observed productive distribution in the original deuterium-labeled experiments.[3] Additionally, we did not observe any electron

transfer products that might have resulted from a Ni(III)/Ni(I) cycle, even though such electron transfer products should have been observed even if they proceeded with cage-escape yields as low as 5%. Direct evidence for energy transfer was also not observed but this is not surprising as the excited-state lifetime of the excited nickel complex is expected to be very short.[17] Energy transfer is expected to yield a ligand-field excited state of the Ni^{II}* catalyst. After energy transfer, the excited $Ni^{II}L(\mathbf{2})^*$ undergoes chlorine atom (Cl•) release, consistent with metal localized excited-states that are antibonding in character with respect to metal-ligand bonds.[18] The chlorine atom is then proposed to abstract a hydrogen atom from trifluoroacetamide **1**, yielding the amide radical that undergoes a subsequent 1,5-hydrogen-atom-transfer. Insertion of this rearranged radical leads to a $Ni^{II}L$(amide)(allyl) complex. The final reductive elimination with light is proposed to yield the desired product.

A test of this energy transfer mechanism is to generate the Ni^{II}* ligand field excited state by direct excitation with light, *i.e.* in the absence of the iridium photosensitizer. However, under such conditions, there was no evidence for photocatalysis under the 48 hours of illumination that were typically employed. Other groups have also reported that direct excitation of a well-defined nickel catalyst was far less efficient than excitation with an iridium photosensitizer.[15c, 15d] It is not obvious why Ir* photosensitized reactions in this dual catalyst manifold are so much more efficient than direct excitation. We propose that the spin state of the catalyst may play a role in the photocatalysis that involves energy transfer. Four-coordinate Ni^{II} complexes are often square planar with a singlet $^1A_{1g}$ ground state. In contrast, octahedral Ni^{II} complexes are typically $^3B_{1g}$ triplets and hence spin allowed energy transfer acceptors for Ir* ^{3}MLCT excited state. Energy transfer to a $^3B_{1g}$ ground state with reductive elimination from a triplet excited state would be more efficient than that for the corresponding singlet states. Future studies with well-defined Ni^{II} square planar and octahedral catalysts are expected to provide valuable new insights.

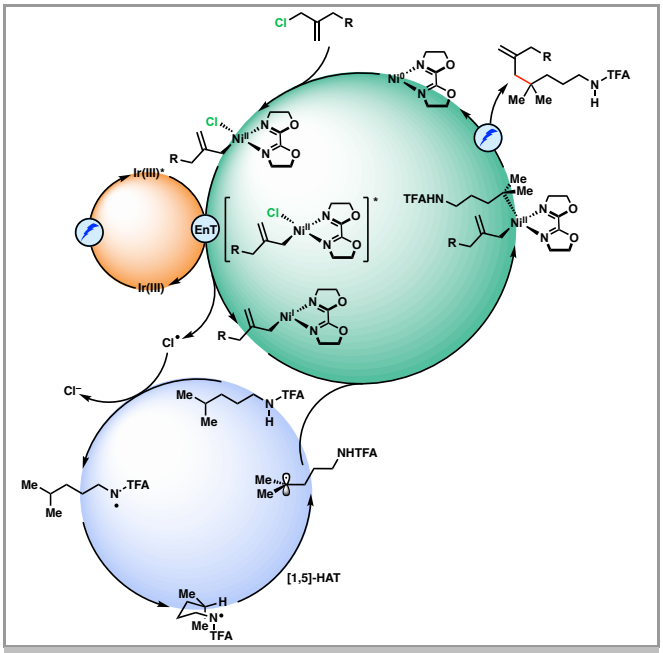

Figure 5 Proposed mechanism for the chemoselective and regioselective remote C-H allylation of amide via energy transfer from Ir* to a nickel(II) catalyst.

In conclusion, an alternative, yet complementary, mechanism for blue-light induced δ-selective allylation of amides through a remote sp^3 C–H functionalization is proposed. Steady-state and time-resolved photoluminescence quenching experiments coupled to nanosecond transient absorption spectroscopy are in line with an excited-state quenching process that is most consistent with energy transfer rather than electron transfer. Such studies, and other in the fields, highlight the necessity to join efforts between research communities to try and reach consensus for potential mechanisms.

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Supporting Information

Yes

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

Biography

Ludovic Troian-Gautier received his B.S. (2008), M.S (2010) and Ph.D. in chemistry (2014) from the Université libre de Bruxelles (ULB – Belgium) under the supervision of Pr. C. Moucheron and guidance of Pr. A. Kirsch-De Mesmaeker. He undertook post-doctoral research at X4C, a new start-up, under the supervision of Pr. I. Jabin and Dr. A. Mattiuzzi where he worked on surface modification using calix[4]arene derivatives. Between 2015 and 2019, he performed research within the Alliance for Molecular PhotoElectrode Design for Solar Fuels directed by Prof. G. J. Meyer at UNC-Chapel Hill. In May 2019, he started a Chargé de Recherches position (F.R.S.-FNRS) at ULB and, in October 2022, he was promoted to Chercheur Qualifié F.R.S.-FNRS at UCLouvain where he pursues his research endeavors on mechanistic photoredox catalysis and energy related challenges. Photo Credit: Eric Herchaft.

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