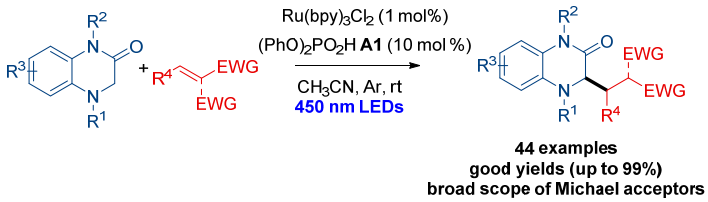
Photocatalytic Giese Addition of 1,4-Dihydroquinoxalin-2-ones to Electron-poor Alkenes Using Visible-light

Jaume Rostoll-Berenguer,[a] Gonzalo Blay,[a] José R. Pedro,*[a] and Carlos Vila*[a]

Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain).

Supporting Information Placeholder

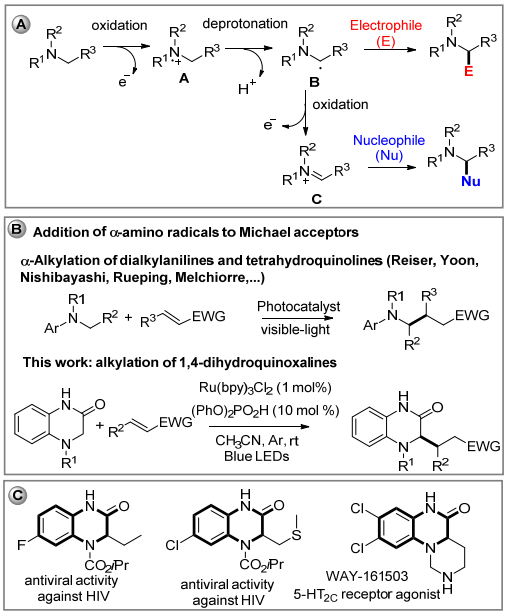


ABSTRACT: The visible-light photoredox-catalyzed coupling of 1,4-dihydroquinoxalin-2-ones and Michael acceptors was achieved using $Ru(bpy)_3Cl_2$ as photocatalyst and $(PhO)_2PO_2H$ as an additive. The optimized reaction conditions provide good yield for the radical conjugate addition products (44 examples) with a wide range of structurally different Michael acceptors. A gram scale reaction using sun-light irradiation is also described. Furthermore, several transformations were carried out with the Giese addition products.

The direct α-alkylation of amines is one of the most important challenges in synthetic organic chemistry, due to the enormous number of biologically active compounds that present nitrogen atoms in their structure.[1] In this context, there are two general methodologies for the oxidative α-functionalization of amines (Scheme 1): (1) several amines can undergo facile one-electron oxidation, affording the nitrogen centered radical cation **A** that deprotonates easily to generate the α-amino radical **B**,[2] (2) which can undergo a second one-electron oxidation to produce iminium ion **C**.[3] The iminium ion **C** can react with nucleophiles, while the α-amino radical **B** can react with electrophiles. The generation of iminium ions by two electron oxidation of amines has been extensively studied because the α-amino radicals are easily oxidized into iminium ions in the presence of stoichiometric amount of oxidants. While the functionalization of amines through α-amino radicals is less studied and there are less reports. Among them, the photoinduced radical formation of **B** is highly desired from the point of view of sustainability and green chemistry.[4] However, high-energy UV irradiation is necessary to generate these intermediates and their applicability is limited.[5] Very recently the emergence of visible-light photoredox catalysis has revolutionized the field of catalysis, and new methodologies have been described for the generation of α-amino radicals and their electrophilic functionalization under mild and sustainable conditions.[6] For example, Pandey, Reiser[7] and Yoon,[8] independently, reported the functionalization of α-amino radicals generated from tetrahydroisoquinolines with α,β-unsaturated ketones. Yoon observed that the addition of a Brønsted acid cocatalyst was beneficial in terms of reactivity and yields of the corresponding products. In 2012, Nishibayashi[9] described the Giese reaction of α-amino radicals generated from *N*,*N*-dimethylanilines to alkylidenemalonates, while in 2013, Rueping[10] described the addition of *N*,*N*-dimethylanilines to arylidenemalononitriles using an iridium photocatalyst in both cases. Li and Xu, described the addition of *N*,*N*-dimethylanilines to acrylate derivatives catalyzed by $Ru(bpy)_3(BF_4)_2$.[11] In 2016, Melchiorre described two elegant methodologies using α-amino radicals, the enantioselective radical conjugate additions of *N*,*N*-dimethylanilines to β,β-disubstituted cyclic enones to obtain quaternary carbon stereocenters with excellent yields and enantioselectivities[12] and the conjugate additions of *N*,*N*-dimethylanilines to alkenylpyridines merging Brønsted acid and visible light photoredox catalysis.[13] While Nicewicz[14] and Ooi, [15] described recently, the alkylation of α-carbamyl radicals with Michael acceptors. Despite of the several successful examples of the Giese addition of α-amino radicals to electron deficient olefins,[16] these reports usually are limited to simple dialkylanilines and tetrahydroisoquinolines

(Scheme 1B). Under these circumstances, we became interesting in the development of our own approach generating α-amino radicals from other tertiary amines such as dihydroquinoxalin-2-ones.[17] In these particular tertiary amines, the generation of a highly stabilized cyclic captodative α-amino radical might be achieved under mild conditions, due to their inherent structure. Moreover, 1,4-dihydroquinoxalinones constitute a prevalent skeleton frequently found in many biologically active compounds (Scheme 1C). Many examples are used as pharmaceuticals, including antiviral compounds used for the treatment of HIV,[18] anticancer compounds,[19] cholesteryl ester transfer protein inhibitors,[20] and antiinflammatory compounds.[21] Therefore, continuing with our interest on the oxidative functionalization of cyclic amines,[22] we described the radical addition of 1,4-dihydroquinoxalin-2-ones to a wide range of electron deficient olefins using a catalytic system formed by $Ru(bpy)_3Cl_2$ and $(PhO)_2PO_2H$ under Blue LEDs irradiation.

Scheme 1. A. Oxidative α-functionalization of amines. B. Addition of α-amino radicals to Michael acceptors. C. Examples of biologically active dihydroquinoxalin-2-ones.

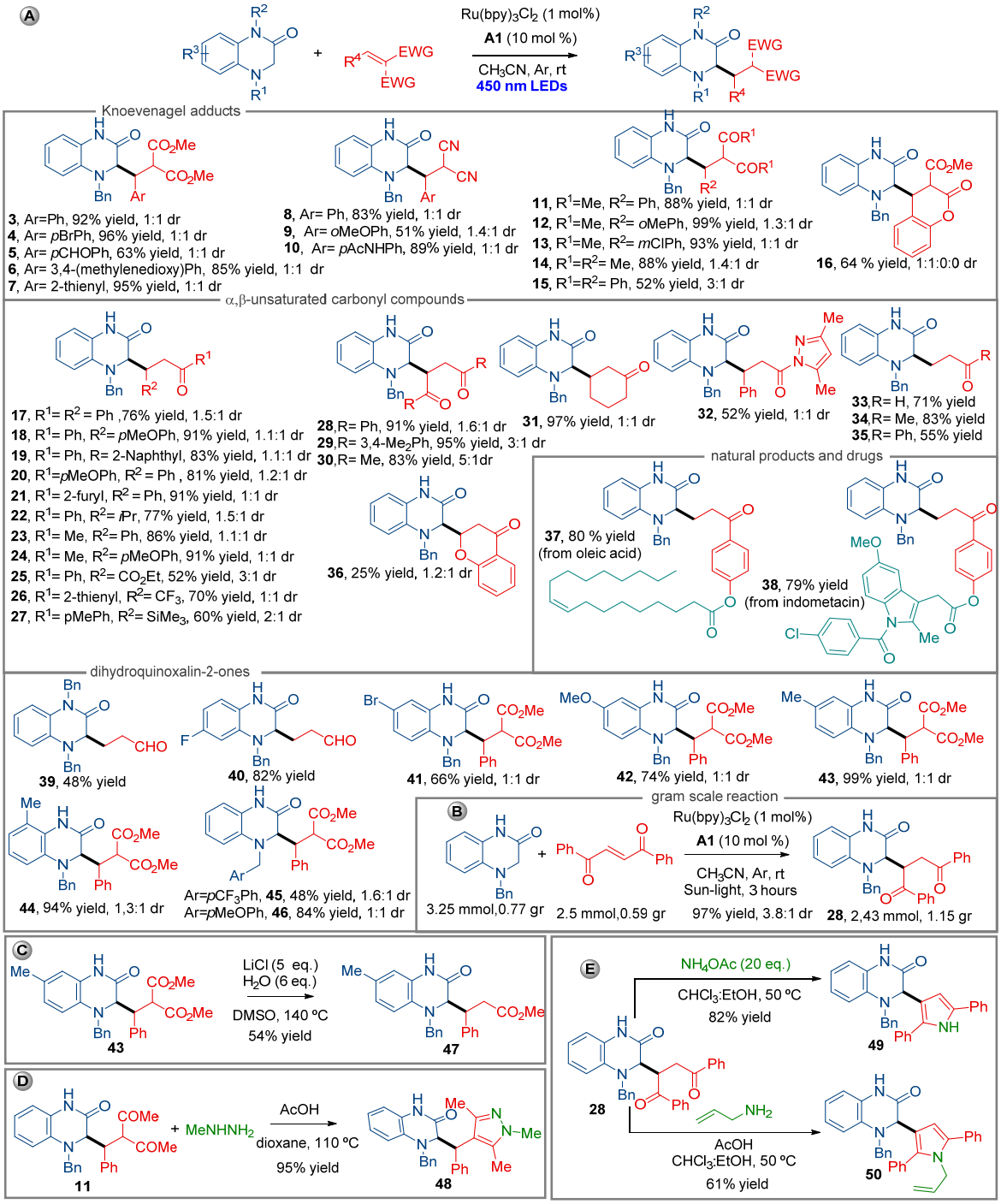


The Giese reaction between 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**1**) and dimethyl 2-benzylidenemalonate (**2**) was selected as the model reaction (Table S1).[23] Compound **1** is a challenging substrate due to the possible formation of two α-amino radicals, in the benzylic position or at α position to the amide. The initial reaction using 1 mol% of $Ru(bpy)_3Cl_2$ under irradiation of 5 W white LEDs, did not gave the corresponding addition product **3** (entry 1), instead we observed the dimerization of **1**. In order to gain more reactivity, we decided to use diphenyl hydrogen phosphate (**A1**) as a Brønsted acid additive as Yoon described.[8] To our surprise, 78% yield of the product **3** was obtained after 48 hours (entry 2). Under blue LEDs irradiation, the reaction was faster and the radical addition product was obtained with higher yield (82%, entry 12).[23] Increasing the amount of 3,4-dihydroquinoxalinone from 1.15 to 1.3 equivalents was beneficial for the speed of the Giese reaction (6 hours), and product **3** was isolated with 92% yield (entry 13).

After identifying the optimized reaction conditions, we set to explore the scope of the radical addition of dihydroquinoxalin-2-ones to Michael acceptors (Scheme 2A). First the versatility of the Michael acceptor was investigated. Different substituted 2-arylidenemalonate bearing aromatic groups with different electronic and steric properties were tested in the reaction with 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**1**) and the corresponding addition products **3–7** could be obtained with excellent yields. 2-arylidenemalonitriles and 2-arylidene-1,3-diketones bearing different substituents in the aromatic ring were also investigated obtaining the corresponding products **8-10** and **11-15**, respectively, with good to excellent yields (51-99%). Interestingly, methyl 2-oxo-2*H*-chromene-3-carboxylate could be used as a radical acceptor obtaining the corresponding product **16** in 64% yield and 1:1 dr. Later, we tested other α,β-unsaturated compounds such as chalcones and other enones as radical acceptors obtaining the corresponding products **17-32** with good yields. Remarkably, a wide range of substitutents are tolerated at β-position of the double bond such as aryl, alkyl, CF_3, $SiMe_3$, ester or ketones. α,β-Unsaturated *N*-acylpyrazoles could be used as radical acceptors, although the corresponding product **32** is obtained with moderate yield (52%). Simpler Michael acceptors such as acrolein, methyl vinyl ketone or acrylophenone as well as other cyclic enones such as chromone could be used, although the corresponding chromanone **36** was obtained with low yield (25%). Next, we demonstrate the synthetic potential of this methodology for the late-stage functionalization of natural products or structurally diverse pharmaceutically relevant substances, including oleic acid and indomethacin, which were well-tolerated (80 and 79% yield, respectively). We next explored the Giese reaction with other 1,4-dihydroquinoxalin-2-ones. For example, 1,4-dibenzyl-3,4-dihydroquinoxalin-2-one could be used under the optimized reaction conditions, although the Giese product **39** was obtained with moderate yield (48%). 3,4-dihydroquinoxalin-2-one bearing electron-donating (Me, MeO) or electron-withdrawing (Br, F) groups at different positions on the aromatic ring furnished the corresponding products **40-44** in good yields (66–99%), regardless of the position or the electronic character of the substituents. Finally, the reaction tolerates different benzylic substituents, affording the corresponding alkylated quinoxalines **45-46** from moderate to good yields. These results are remarkable, because only the oxidation of the endocyclic CH2 was observed.

To further showcase the practicability and scalability of this protocol, we performed the radical conjugate addition at gram scale using sun-light irradiation (Scheme 2B). Under these conditions, the results were similar, in terms of yield, to those obtained on small scale (97% yield), although we observed an enhancement on the diastereoselectivity from 1.6:1 dr, in small scale, to 3.8:1 dr, in a gram scale. Furthermore, we have applied several chemical transformations for the synthesis of interesting

Scheme 2. Scope of the α-alkylation of 1,4-dihydroquinoxalin-2-ones with Michael acceptors.



dihidroquinoxaline derivatives. For example, decarboxylation of **43**, gave the corresponding product **47** smoothly in 54% yield (Scheme 2C). Taking into consideration that the presence of multiple nitrogen heterocycles is very important for drug discovery and medicinal chemistry, we perform several transfor mations taking advantage of the 1,3-dicarbonyl and 1,4-dicarbonyl obtained products. Compound 11 was treated with methylhydrazine in the presence of AcOH in dioxane at 110 ºC, obtaining the corresponding pyrazole functionalized with a quinoxaline moiety (Scheme 2D). Finally, compound **28** was used for the preparation of two substituted pyrroles (**49-50**) by the Paal–Knorr reaction,[24] with good yields (82% and 61% respectively) in both cases (Scheme 2E).

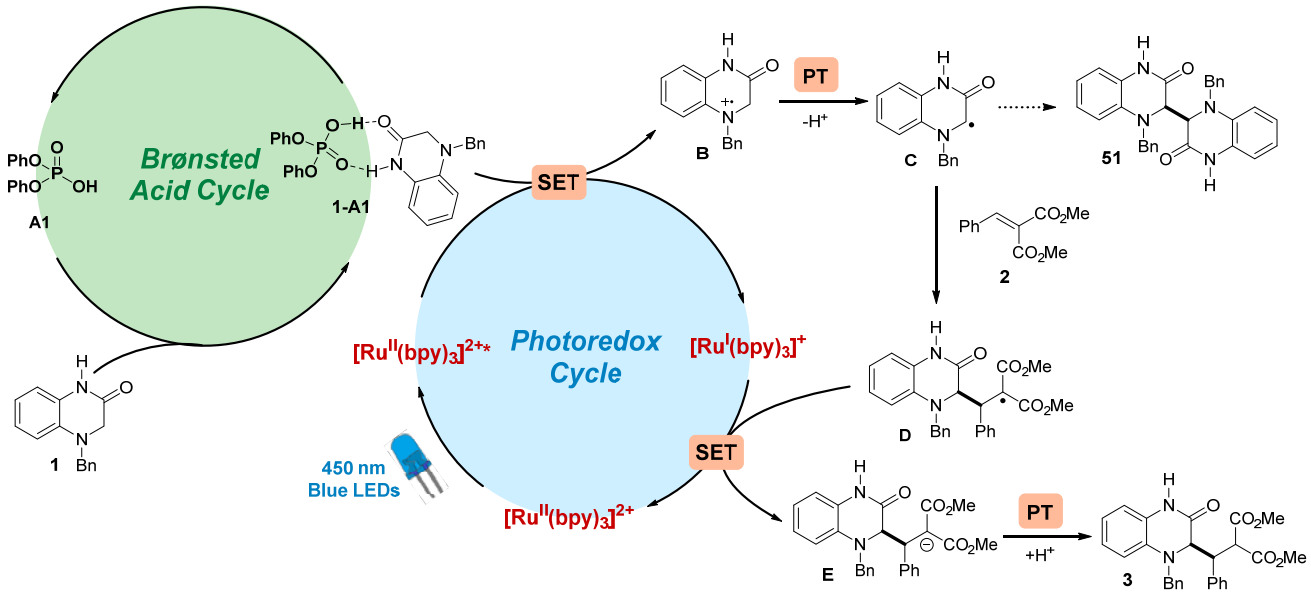
In order to glean insights into the reaction mechanism, we performed a series of experiments. First, we measured the quantum yield (ϕ) of the model reaction, which was found to be as low as 0.15,[23,25] which indicates that a radical chain pathway is not the major pathway in this transfor-

mation, suggesting that the process is governed by a photoredox closed cycle. We also conducted the steady-state Stern–Volmer luminescence quenching experiments summarized in Figure S17.[23] According to these studies, the luminescence emission of $[Ru^*(bpy)_3]^{2+}$ is not decreased by the presence of either **1**, **2** or **A1**. While these experiments were being carried out, we observed that dihydroquinoxalin-2-one **1** has a luminescence emission at 525 nm (Figure S11).[23] This luminesence emission is increased when 10 mol% of **A1** is added (Figure S12). We were interested in this phenomenon and when we performed a UV-vis spectroscopic analysis using a mixture of **1** (1eq.) and **A1** (1.1 eq.), we noticed that this mixture could also absorb light up to λ = 410 nm (Figure S14, purple line).[23] Interestingly, when we performed the luminescence quenching experiments using 1 and 1.1 eq. of **A1**, we observed that both the emission band at 525 nm and the emission band of $[Ru(bpy)_3]^{2+}$ at 600 nm decreased (Figure S13). However, the last one cannot be measured due to the strong emission band at 525 nm. The diminishment of the luminescence at 525 nm is attributed to a self-quenching phenomenon of the emission of complex **1-A1** at high concentrations in CH_3CN (Figure S16), whereas the disappearance of the $[Ru(bpy)_3]^{2+}$ emission band can be ascribed to the quenching by **1-A1** complex, suggesting that the first Single Electron Transfer (SET) should proceed through this way. These data establish that Brønsted acid cocatalyst **A1** and dihydroquinoxalin-2-one **1** may form a highly fluorescent species which have a significant role on the first SET. NMR studies revealed that acidic cocatalyst **A1** could coordinate to dihydroquinoxalin-2-one **1** through the formation of a cyclic two hydrogen-bonded structure.[23] Moreover, we isolated dimer **51**, when we performed the reaction without the Michael acceptor **2**, indicating the presence of α-amino radicals. Additionally, we measured the reduction potential of compound **1** with ($E^o_{1/2}$ (V vs SCE)= +0.80 V) or without ($E^o_{1/2}$ (V vs SCE)= +0.77 V) cocatalyst **A1**, showing that dihydroquinoxalin-2-one **1** is slightly more prone to Single Electron Oxidation in the presence of **A1**.[24] Finally, product **3** was not observed when the reaction was performed under oxygen atmosphere or in the presence of 1.5 eq. TEMPO.[23]

On the basis of these observations, we propose a mechanism by which our transformation should proceed (Scheme 3). Acidic cocatalyst **A1** can act as a bifunctional hydrogen-bonding species to form a cyclic highly-coloured complex through the coordination to dihydroquinoxalin-2-one **1**. This **1-A1** intermediate, which exhibits strong fluorescence emission at 525 nm, can be engaged in a SET with the excited state form of $[Ru(bpy)_3]^{2+}$ resulting of the irradiation with 450 nm Blue LEDs. The SET results in the formation of the corresponding radical cation **B**,[26] which can suffer the loss of a proton to yield the nucleophilic α-amino radical **C**. This radical can participate in an unproductive mechanistic pathway through its self-coupling towards dimer **51**. However, it is nucleophilic enough to react with electron-poor alkene **2** to furnish highly stabilized C-centered radical **D**.[27] A second SET between radical **D** and the Ru(I) complex could occur to regenerate the photocatalyst and provide the enolate **E**, which after a protonation step generates the corresponding Giese product **3**.

In conclusion, we have developed a Giese reaction[28] of 3,4-dihydroquinoxalin-2-one derivatives with a wide range of Michael acceptors using visible-light photoredox catalysis. The corresponding quinoxalin-2-one products (44 examples) were obtained with good yields under mild reaction conditions. The reaction is scalable to one-gram scale using sun-light, obtaining excellent results. Moreover, several transformations have been carried out with the obtained products. Also a series of experiments have been carried out in order to glean insights into the reaction mechanism. Studies to further extend the scope of this redox-neutral photochemical are currently underway in our laboratory.

Scheme 3. Proposed Reaction Mechanism.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, Optimization process, characterization data and NMR spectra of all new compounds. (PDF)

AUTHOR INFORMATION

Corresponding Author

* jose.r.pedro@uv.es
* carlos.vila@uv.es

ACKNOWLEDGMENT

Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (CTQ2017-84900-P) is acknowledged. J.R-B thanks the Ministerio de Ciencia, Innovación y Universidades for a FPU predoctoral contract and C.V. thanks the Agencia Estatal de Investigación (AEI, Spanish Government) for RyC contract (RYC-2016-20187). Access to NMR, MS and X-ray facilities from the Servei Cen-tral de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged

REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardason, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274. (b) Simplício, A. L.; Clancy, J. M.; Gilmer, J. F. Prodrugs for amines. *Molecules*, **2008**, *13*, 519-547. (c) Joule, J. A. Natural products containing nitrogen heterocycles—some highlights 1990–2015. *Adv. Heterocycl. Chem*. **2016**, *119*, 81-106. (d) Pennington, L. D.; Moustakas, D. T. The necessary nitrogen atom: a versatile high-impact design element for multiparameter optimization. *J. Med. Chem*. **2017**, *60*, 3552-3579.

(2) (a) Renaud, P.; Giraud, L. 1-Amino- and 1-Amidoalkyl Radicals: Generation and Stereoselective Reactions. *Synthesis*, **1996**, *36*, 913-926. (b) Dinnocenzo, J. P.; Banach, T. E. Deprotonation of tertiary amine cation radicals. A direct experimental approach. *J. Am. Chem. Soc*. **1989**, *111*, 8646-8653. (c) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. Nonaromatic aminium radicals. *Chem. Rev*. **1978**, *78*, 243-274. (d) Yoon, U. C.; Mariano, P. S. Mechanistic and synthetic aspects of amine-enone single electron transfer photochemistry. *Acc. Chem. Res*. **1992**, *25*, 233-240. (e) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D.; Mariano, P. S. Dynamics of α-CH deprotonation and α-desilylation reactions of tertiary amine cation radicals. *J. Am. Chem. Soc*. **1994**, *116*, 4211-4220. (f) Hoffmann, N.; Bertrand, S.; Marinković, S.; Pesch, J. Efficient radical addition of tertiary amines to alkenes using photochemical electron transfer. *Pure Appl. Chem.* **2006**, *78*, 2227-2246.

(3) (a) Li, C.-J. Cross-dehydrogenative coupling (CDC): exploring C–C bond formations beyond functional group transformations. *Acc. Chem. Res*., **2009**, *42*, 335-344. (b) Murahashi, S. I. Synthetic Aspects of Metal-Catalyzed Oxidations of Amines and Related Reactions. *Angew. Chem. Int. Ed.* **1995**, *34*, 2443-2465.

(4) (a) Ciamician, G. The photochemistry of the future. *Science*, **1912**, *36*, 385-394. (b) Albani, A.; Fagnoni, M. Green chemistry and photochemistry were born at the same time*Green Chem*. **2004**, *6*, 1-6. (c) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects in Visible Light Photocatalysis. *Science*, **2014**, 343, 1239176.

(5) (a) Cookson, R. C.; Costa, S. M. de B.; Hudec, J. Photochemical addition of amines to styrenes. *J. Chem. Soc. D: Chem. Commun.* **1969**, 753-754. (b) Hasegawa, E.; Xu, W.; Mariano, P. S.; Yoon, U.-C.; Kim, J.-U. Electron-transfer-induced photoadditions of the silyl amine, $Et_2NCH_2SiMe_3$, to α,β-unsaturated cyclohexenones. Dual reaction pathways based on ion pair-selective cation-radical chemistry. *J. Am. Chem. Soc*. **1988**, *110*, 8099-8111. (c) Pandey, G.; Reddy, G. D.; Kumaraswamy, G. Photoinduced electron transfer (PET) promoted cyclisations of 1-[*N*-alkyl-*N*-(trimethylsilyl)methyl]amines tethered to proximate olefin: mechanistic and synthetic perspectives. *Tetrahedron* **1994**, *50*, 8185-8194. (d) Das, S.; Kumar, J. S. D.; Thomas, K. G.; Shivaramayya, K.; George, M. V. Photocatalyzed multiple additions of amines to α,β-unsaturated esters and nitriles. *J. Org. Chem*. **1994**, *59*, 628-634. (e) de Alvarenga, E. S.; Cardin, C. J.; Mann, J. An unexpected photoadduct of *N*-carbomethoxymethylpyrrolidine with a chiral butenolide and benzophenone: X-ray structure and synthetic utility. *Tetrahedron* **1997**, *53*, 1457-1466. (f) Bertrand, S.; Hoffmann, N.; Pete, J.-P. Highly Efficient and Stereoselective Radical Addition of Tertiary Amines to Electron-Deficient Alkenes–Application to the Enantioselective Synthesis of Necine Bases. *Eur. J. Org. Chem*. **2000**, 2227-2238. (g) Bauer, A.; Westkamper, F.; Grimme, S.; Bach, T. Catalytic enantioselective reactions driven by photoinduced electron transfer. *Nature* **2005**, *436*, 1139-1140. (h) Harakat, D.; Pesch, J.; Marinkovic, S.; Hoffmann, N. Thiocarbonyl compounds as regulating reagent in the radical addition of tertiary amines with alkenes using photoelectron transfer conditions. *Org. Biomol. Chem*. **2006**, *4*, 1202-1205.

(6) (a) Shia, L.; Xia, W. Photoredox functionalization of C–H bonds adjacent to a nitrogen atom. *Chem. Soc. Rev*. **2012**, *41*, 7687-7697. (b) Nakajima, K.; Miyake, Y.; Nishibayashi, Y. Synthetic utilization of α-aminoalkyl radicals and related species in visible light photoredox catalysis. *Acc. Chem. Res.* **2016**, *49*, 1946-1956. (c) Leitch, J. A.; Rossolini, T.; Rogova, T.; Maitland, J. A. P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal*., **2020**, *10*, 2009-2025.

(7) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. Visible Light Photoredox Catalysis: Generation and Addition of N-Aryltetrahydroisoquinoline-Derived α-Amino Radicals to Michael Acceptors. *Org. Lett*. **2012**, *14*, 672-675.

(8) Ruiz Espelt, L.; Wiensch, E. M.; Yoon, T. P. Brønsted acid cocatalysts in photocatalytic radical addition of α-amino C–H bonds across michael acceptors. *J. Org. Chem*. **2013**, *78*, 4107-4114.

(9) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible-light-mediated utilization of α-aminoalkyl radicals: addition to electron-deficient alkenes using photoredox catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 3338-3341.

(10) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. Oxygen Switch in Visible-Light Photoredox Catalysis: Radical Additions and Cyclizations and Unexpected C–C-Bond Cleavage Reactions. *J. Am. Chem. Soc*. **2013**, *135*, 1823–1829.

(11) Dai, X.; Cheng, D.; Guan, B.; Mao, W.; Xu, X.; Li, X. The Coupling of Tertiary Amines with Acrylate Derivatives via Visible-Light Photoredox Catalysis. *J. Org. Chem.* **2014**, *79*, 7212–7219.

(12) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. Asymmetric catalytic formation of quaternary carbons by iminium ion trapping of radicals. *Nature* **2016**, *532*, 218–222.

(13) Hepburn, H. B.; Melchiorre, P. Brønsted acid-catalysed conjugate addition of photochemically generated α-amino radicals to alkenylpyridines. *Chem. Commun*. **2016**, 52, 3520–3523.

(14) (a) McMans, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and alkylation of α-carbamyl radicals via organic photoredox catalysis. *J. Am. Chem. Soc*. **2018**, *140*, 9056-9060. (b) McManus, J. B.; Onuska, N. P. R.; Jeffreys, M. S.; Goodwin, N. C.; Nicewicz, D. A. Site-Selective C–H Alkylation of Piperazine

Substrates via Organic Photoredox Catalysis. *Org. Lett*. **2020**, *22*, 679-683.

(15) Ohmatsu, K.; Suzuki, R.; Furukawa, Y.; Sato, M.; Ooi, T. Zwitterionic 1,2,3-Triazolium Amidate as a Catalyst for Photoinduced Hydrogen-Atom Transfer Radical Alkylation. *ACS Catal*. **2020**, *10*, 2627-2632.

(16) For decarboxylative Giese addition of amino acid derived α-amino radicals, see: (a) Millet, A.; Lefebvre, Q.; Rueping, M. Visible-Light Photoredox-Catalyzed Giese Reaction: Decarboxylative Addition of Amino Acid Derived α-Amino Radicals to Electron-Deficient Olefins. *Chem. Eur. J.* **2016**, *22*, 13464-13468. (b) Noble, A.; Mega, R. S.; Pflästerer, D.; Myers, E. L.; Aggarwal, V. K. Visible-Light-Mediated DecarboxylativeRadical Additions to VinylBoronic Esters:Rapid Access to g-Amino Boronic Esters. *Angew. Chem. Int. Ed*. **2018**, *57*, 2155-2159. (c) Cai, Y.; Tang, Y.; Fan, L.; Lefebvre,Q.; Hou, H.; Rueping, M. Heterogeneous Visible-Light Photoredox Catalysis with Graphitic Carbon Nitride for α-Aminoalkyl Radical Additions, Allylations, and Heteroarylations. *ACS Catal*. **2018**, *8*, 9471–9476. For selected examples of electrophilic photofunctionalization of tertiary amines, see: (d) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α-amino C-H arylation reaction using the strategy of accelerated serendipity. *Science* **2011**, *334*, 1114-1117. (e) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Direct sp^3 C-H Amination of Nitrogen-Containing Benzoheterocycles Mediated by Visible-Light-Photoredox Catalysts. *Chem.- Eur. J.* **2012**, *18*, 16473-16477. (f) Zhou, H.; Lu, P.; Gu, X.; Li, P. Visible-light-mediated nucleophilic addition of an α-aminoalkyl radical to isocyanate or isothiocyanate. *Org. Lett*. **2013**, *15*, 5646-5649. (g) Zhang, P.; Xiao, T.; Xiong, S.; Dong, X.; Zhou, L. Synthesis of 3-Acylindoles by Visible-Light Induced Intramolecular Oxidative Cyclization of o-Alkynylated N,N-Dialkylamines. *Org. Lett*. **2014**, *16*, 3264–3267. (h) Noble, A.; MacMillan, D. W. C. Photoredox α-Vinylation of α-Amino Acids and N-Aryl Amines. *J. Am. Chem. Soc*. **2014**, *136*, 11602–11605. (i) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of N-Arylaminomethanes with Aldimines. *J. Am. Chem. Soc.* **2015**, *137*, 13768-13771. (j) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. Redox-Neutral α-Allylation of Amines by Combining Palladium Catalysis and Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625-1628. (k) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. A Highly Efficient Gold-Catalyzed Photoredox α-C(sp^3)-H Alkynylation of Tertiary Aliphatic Amines with Sunlight. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046-6050. (l) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals. *Angew. Chem., Int. Ed.* **2016**, 55, 6776-6779. (m) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. Asymmetric Radical–Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis. *Angew. Chem. Int. Ed*. **2016**, 55, 685-688.

(17) (a) Shi, L.; Zhou, H.; Wu, J.; Li, X. Advances in the Chemistry of Quinoxalinone Derivatives. *Mini-Rev. Org. Chem*. **2015**, *12*, 96-112. (b) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. Recent Advances in Photocatalytic Functionalization of Quinoxalin-2-ones. *Eur. J. Org. Chem.*, **2020**, DOI: 10.1002/ejoc.202000746.

(18) (a) Rösner, M.; Billhardt-Troughton, U.-M.; Kirsh, R.; Kleim, J.-P.; Meichsner, C.; Riess, G.; Winkler, I. *U.S. Patent* 5, 723, 461, **1998**. (b) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. Catalytic, Enantioselective Bifunctional Inverse Electron Demand Hetero-Diels–Alder Reactions of Ketene Enolates and o-Benzoquinone Diimides. *J. Am. Chem. Soc.* **2006**, *128*, 13370-13371. (c) Ren, J.; Nichols, C. E.; Chamberlain, P. P.; Weaver, K. L.; Short, S. A.; Chan, J. H.; Kleim, J.-P.; Stammers, D. K. Relationship of Potency and Resilience to Drug Resistant Mutations for GW420867X Revealed by Crystal Structures of Inhibitor Complexes for Wild-Type, Leu100Ile, Lys101Glu, and Tyr188Cys Mutant HIV-1 Reverse Transcriptases. *J. Med. Chem.*, **2007**, 50, 2301-2309. (d) Cass, L. M.; Moore, K. H. P.; Dallow, N. S.; Jones, A. E.; Sisson, J. R.; Prince, W. T. The Bioavailability of the Novel Nonnucleoside Reverse Transcriptase Inhibitor GW420867X Is Unaffected by Food in Healthy Male Volunteers. *J. Clin. Pharmacol.*, **2001**, *41*, 528-535.

(19) (a) Tanimori, S.; Nishimira, T.; Kirihata, M. Synthesis of novel quinoxaline derivatives and its cytotoxic activities. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4119-4121. (b) Abu Shuheil, M. Y.; Hassuneh, M. R.; Al-Hiari, Y. M.; Qaisi, A. M.; El-Abadelah, M. M. Heterocycles [*h*]-Fused onto 4-Oxoqunoline-3-carboxylic Acid, III. Facile Synthesis and Antitumor Activity of Model Heterocycles [*a*]-Fused onto Pyrido[2,3-*f*]quinoxaline-3-carboxylic Acids. *Heterocycles* **2007**, *71*, 2155-2172.

(20) Eary, C. T.; Jones, Z. S.; Groneberg, R. D.; Burgess, L. E.; Mareska, D. A.; Drew, M. D.; Blake, J. F.; Laird, E. R.; Balachari, D.; O'Sullivan, M.; Allen, A.; Marsh, V. Tetrazole and ester substituted tetrahydoquinoxalines as potent cholesteryl ester transfer protein inhibitors. *Bioorg. Med. Chem. Lett*., **2007**, *17*, 2608-2613.

(21) Chen, J. J.; Qian, W.; Biswas, K.; Viswanadhan, V. N.; Askew, B. C.; Hitchcock, S.; Hungate, R. W.; Arik, L.; Johnson, E. Discovery of dihydroquinoxalinone acetamides containing bicyclic amines as potent Bradykinin B1 receptor antagonists. *Bioorg. Med. Chem. Lett*., **2008**, *18*, 4477-4481.

(22) (a) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. 9,10-Phenanthrenedione as Visible-Light Photoredox Catalyst: A Green Methodology for the Functionalization of 3,4-Dihydro-1,4-Benzoxazin-2-Ones through a Friedel-Crafts Reaction. *Catalysts*, **2018**, *8*, 653. (b) Rostoll-Berenguer, J.; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Vila, C. A Combination of Visible-Light Organophotoredox Catalysis and Asymmetric Organocatalysis for the Enantioselective Mannich Reaction of Dihydroquinoxalinones with Ketones. *Org. Lett.*, **2019**, *21*, 6011-6015. (c) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. Copper-Catalyzed Aerobic Oxidative Alkynylation of 3,4-Dihydroquinoxalin-2-ones. *Synthesis*, **2020**, 52, 544-552.

(23) See Supporting Information for further details.

(24) Knorr, L. Synthese von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635-1642.

(25) (a) Cismesiaa, M. A.; Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci*., **2015**, *6*, 5426-5434. (b) Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Ošeka, M.; Melchiorre, P. A Photochemical Organocatalytic Strategy for the α-Alkylation of Ketones by using Radicals. *Angew. Chem. Int. Ed*. **2020**, *59*, 9485-9490.

(26) After the formation of the α-amino radical **C**, it is possible that the phosphoric acid **A-1** is binding **C** in a similar way that in complex **1-A1**.

(27) The Michael acceptor can also be activated by the Brønsted acid catalyst **A-1** to enhance its electrophilicity. We have performed an asymmetric version using a chiral BINOL phosphoric acid catalyst, however we obtained the corresponding Giese product **3** with 1:1 dr and no enantioselectivity (See SI).

(28) During the preparation of the manuscript a regioselective photocatalytic α-funtionalization of acyclic amines has been reported: Leng, L.; Fu, Y.; Liu, P.; Ready, J. M. Regioselective, Photocatalytic α-Functionalization of Amines. *J. Am. Chem. Soc*. **2020**, *142*, 11972–11977.