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Recent advances in visible light-driven phosphine-mediated transformations

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The literature on the use of trivalent phosphines in the activation of electrophilic unsaturated reagents is large. However, the application of such derivatives for the generation of radical intermediates has received attention only in the past decade. This review provides a detailed description of the phosphine-mediated-photocatalyzed and photoredox-catalyzed protocols for the formation of carbon–carbon and carbon–heteroatom bonds proposed in the last decade.

1. Introduction

Since the seminal experiments published in the early-1960s, the potential of trivalent phosphines as organocatalysts in synthesis has been intensively exploited.[1] However, in a large part of the literature available, the nucleophilic addition of the phosphine moiety on an electrophilic reactant (*e.g.* olefins, alkynes or allenes) promotes the formation of a reactive zwitterion species, which is then converted into the desired product[2–10] *via* electron-pair-transfer reactions. On the other hand, only a few strategies based on a single-electron-transfer (SET) mechanism have been proposed.[11] However, these SET strategies are based on the successful application of phosphines as redox active cocatalysts in photoredox-catalyzed processes.[12] Such premises have increased attention on the development of phosphine-promoted visible light-driven protocols, enabling chemical paths that are poorly or not accessible *via* thermal approaches. As described in Scheme 1, phosphine photo-organocatalysis has been reported to occur *via* three paths, namely:

(a) β-Scission of a phosphoranyl radical (path a). Trivalent phosphine undergoes photoinduced SET and the resulting radical cation $PR_3^{\bullet+}$ is trapped by a suitable (thio)alcohol R–XH. The resulting phosphoranyl radical releases a carbon-centred radical *via* β-scission of the C–X bond. The process is thermodynamically driven by the stoichiometric formation of a stable phosphine oxide or sulfide as the byproduct.

(b) α-Scission of a phosphoranyl radical (path b). The α-scission occurring in the phosphoranyl radical described in path b releases, *via* C–P bond homolytic cleavage, a carbon-centred radical. Such behavior is kinetically favored by the presence of an unpaired electron occupying a P–X antibonding

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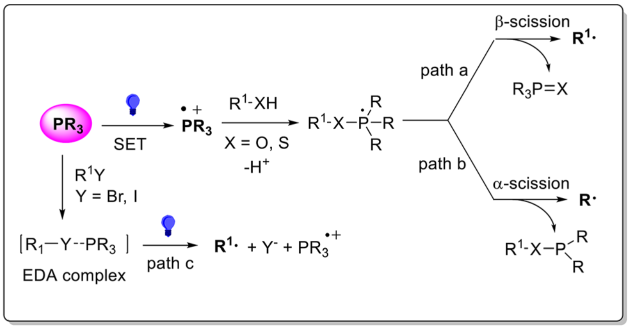
Luca Nicchio was born in 1998 in Peschiera del Garda, Italy. In 2020, he received his Master's degree in Chemistry at the University of Pavia (Italy) under the supervision of Prof. Maurizio Fagnoni (Photogreen Lab). Luca is currently a PhD student in a joint PhD program between Université Paris-Saclay and University of Pavia (Université Paris-Saclay International Joint PhD Program-Cotutelle 2022), under the supervision of Luc Neuville (DR2) and Prof. Stefano Protti. His research is focused on the development of new and green synthetic approaches through visible-light generation of radical intermediates from arylazo sulfones and arylazo sulfonates.



Scheme 1 Conceptual overview of phosphine-mediated photoredox processes.

orbital. The competition between paths a and b was described to depend strictly on the relative bond strengths of C–X and P–C bonds.[13]

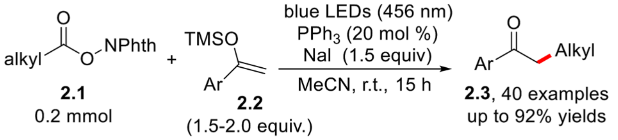
(c) Formation of an electron donor acceptor (EDA) complex. In some cases, a visible light-absorbing EDA complex[14] could be formed *via* the *in situ* interaction of electron-poor alkyl halides (*e.g.*, perfluoroalkyl iodides) and trivalent phosphines *via* SET. The photoinduced homolytic cleavage of the C–halogen bond then affords the desired alkyl radical.[14]

As all the examined paths have been applied to organic synthesis, we aim to provide an overview of the most recent applications of phosphines in the visible light-driven formation of carbon–carbon and carbon–heteroatom bonds. The classification is based on the first chemical bond formed, in accordance with the proposed mechanism. The use of continuous flow conditions as well as the application of the developed procedures in late-stage functionalization approaches have been considered and discussed in the following sections.

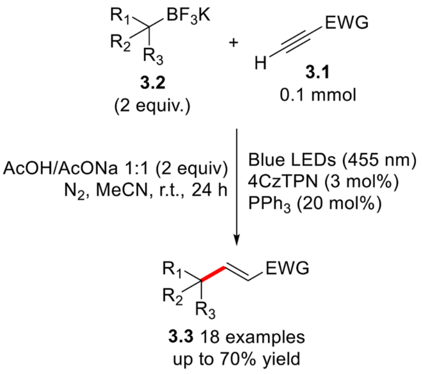
2. Formation of carbon–carbon bonds

2.1. Hydroalkylation reactions

The photocatalytic NaI-PPh_3 mediated decarboxylative alkylation of silyl enol ether **2.2** and redox-active esters **2.1** affords α-substituted acetophenones **2.3** in discrete-to-satisfactory yield. The reaction occurs under transition metal-free conditions (Scheme 2) in the presence of a stoichiometric excess of NaI.[15] The same strategy also promotes the Minisci-type alkylation of N-heterocycles and an analogous enantioselective α-amino alkylation with the assistance of a chiral phosphoric acid in catalytic amounts.



Scheme 2 Light-driven, photocatalytic NaI-PPh_3-mediated decarboxylative alkylation of silyl enol ethers and nitrogen-based heterocycles.



Scheme 3 Giese-like functionalization of ynoates **3.2** by dual phosphine organocatalysis and photoredox catalysis.

Shi and co-workers applied a photoredox-promoted hydroalkylation strategy to the preparation of a library of DNA-tagged alkenes using xanthates as the alkyl radical precursors in the presence of $Ir[FCF_3(CF_3)ppy]_2(dtbbpy)PF_6$ as the photoredox catalyst.[16] Phosphine organocatalysis was merged with photoredox catalysis in the conversion of ynoates **3.1** to electron-poor olefins **3.3** under metal-free conditions, as described in Scheme 3.[17] The procedure involves a Giese-like coupling of **3.1** with alkylating agents trifluoroborate salts **3.2** in the presence of 4-CzTPN as the photoredox catalyst.

Recently, mercaptans **4.2** have been proposed as electron-deficient precursors of carbon-centred radicals in the hydroalkylation of styrenes **4.1** under blue-light irradiation and in the presence of transition metal-based species $[Au_2(\mu\text{-dppm})_2]Cl_2$ (Scheme 4a).[18] Such a versatile strategy was successfully applied to the functionalization of small amino-acid fragments as well as the preparation of polymers (an example is given in Scheme 4b). The same target was achieved under photocatalyst-free conditions by Su and co-workers.[19] They exploited the partial oxidation of triphenyl phosphine to the corresponding triphenylphosphine oxide which, in turn, forms an EDA complex with the yet unreacted PPh_3; the species is

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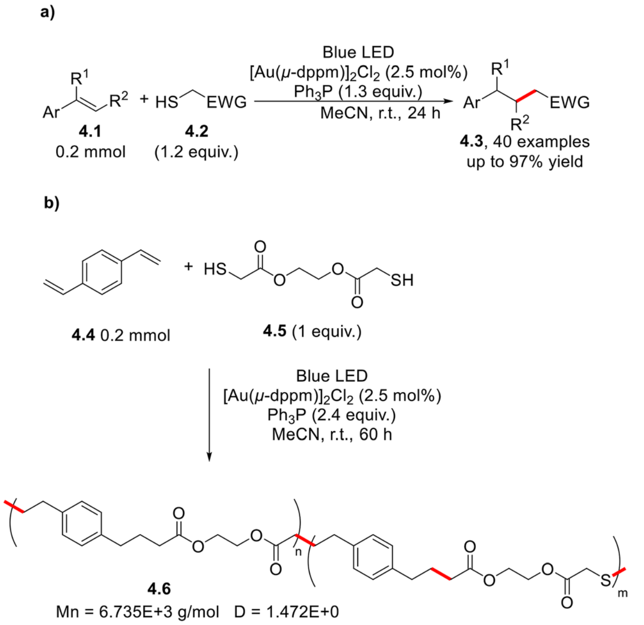
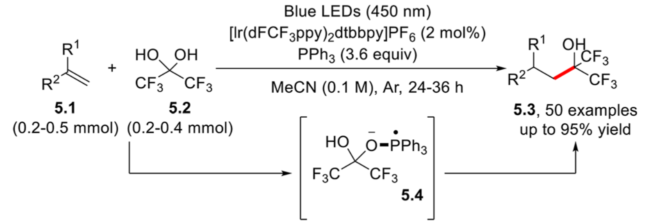
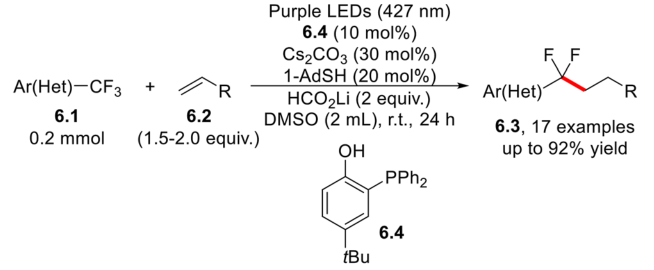


Scheme 4 Visible light-driven gold-catalyzed hydroalkylation of styrenes **4.1** in (a) synthesis and (b) polymerization processes.



Scheme 5 Photoredox-catalyzed phosphine-mediated bifunctionalization of electron-deficient alkenes.



Scheme 6 Photoredox-organocatalyzed difluoro(hetero)arylation and difluoroalkylation of non-activated olefins.

responsible for both the absorption of light and initiation of the radical chain process.[19]

Perfluoroalkyl radicals have been generated and, in turn, employed for the hydroalkylation of electron-poor olefins (including fluoxetine and sertraline derivatives) from the hydrated form of hexafluoroacetone (**5.2**, Scheme 5) and trifluoro-acetaldehyde.[20] In this case, a key role is played by the phosphoranyl radical **5.4**, arising from the coupling between the triphenylphosphine radical cation and **5.2**.[20]

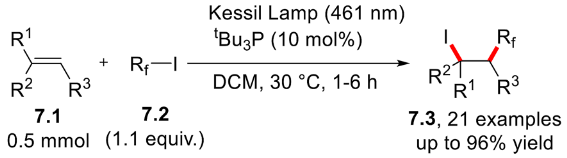
In situ deprotonation of phenol **6.4** generates the *o*-phosphinophenolate anion, which acts as a photoredox organocatalyst for activating trifluoromethyl groups in trifluoroacetamides, acetates, trifluoromethyl (hetero)arenes (**6.1**, Scheme 6) and even trifluoroalkanes. This approach enables the difluoroalkylation of non-activated alkenes and polyfunctionalized aromatics, including the antipsychotic compound trifluoroperazine.[21]

The difunctionalization of multiple bonds is one of the most widely adopted approaches for constructing structurally complex molecules.[22–25] In this context, the 1,2-iodoperfluoroalkylation of alkenes *via* C–C and C–I bond formation was described to occur under visible light (461 nm) irradiation of a mixture of olefin **7.1** (Scheme 7), perfluoroiodoalkanes **7.2** and a catalytic amount of tri-tertbutylphosphine. The reaction mechanism involves an atom-transfer radical addition (ATRA) chain path initiated by the formation of an EDA complex between **7.2** and the $^t\mathrm{Bu}_3\mathrm{P}$ organocatalyst.[26] The same synthetic target was achieved by having recourse to a merged photoredox/copper catalysed strategy, in the presence of *fac*-Ir(ppy)$_3$ as the photoredox catalyst and Cu(MeCN)$_4^-$ as the cocatalyst, respectively.[27]

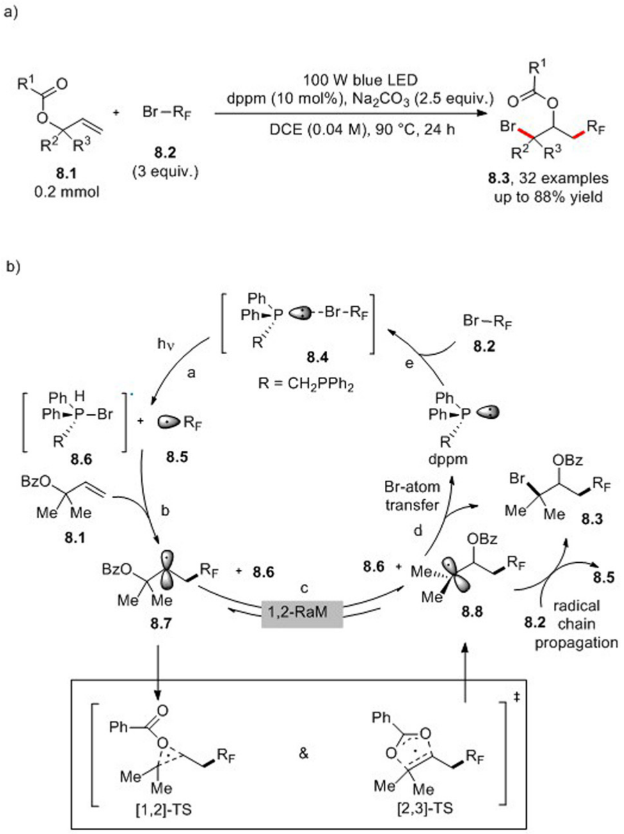
A 1,3-carbobromination strategy for the conversion of allyl carboxylates **8.1** to isopropyl carboxylates (sIPC) **8.3** was reported recently in the literature (Scheme 8a).[28] The suggested non-chain-radical mechanism is shown in Scheme 8b. It involves the formation of a visible light-absorbing EDA complex **8.4** between the phosphine (dppm) and **8.2.** Upon

Kui Lu was born in Jiangxi Province, China, in 1981. He received his BS degree from China Agricultural University in 2002 and then a Ph.D. degree in organic chemistry from Peking University, China, in 2007 under the supervision of Professor Zhen Yang. After postdoctoral research in the laboratory of Professor Ohyun Kown at the University of California, Los Angeles, U.S.A., he came back to China and worked as a group leader of medicinal chemistry in Bioduro Co., Ltd. In 2011, he started his independent career as an associate professor at Tianjin University of Science & Technology and was promoted to full professor in 2020. His research involves photochemistry, organosulfur chemistry and organofluorine chemistry.

Stefano Protti completed his PhD in Pavia (2007). Later he moved to LASIR Laboratory (Lille, France) at the iBitTec-S laboratory (CEA Saclay, France) carrying out studies on photocatalyzed oxidation reactions for energy storage; then, he moved to the University of Pavia, where he has served as Associate Professor since 2018. His research is mainly focused on the development of synthetic strategies driven by visible light.



Scheme 7 Visible light-induced photochemical 1,2-iodoperfluoroalkylation of alkenes.



Scheme 8 Photoinduced and phosphine-catalyzed difunctionalization of allyl carboxylates.

irradiation, **8.4** decompose in the bromo-phosphine **8.6** and alkyl radical **8.5** (path a). The latter is trapped by the olefin moiety in allyl carboxylate **8.1** (path b). The obtained secondary alkyl radical **8.7** undergoes 1,2-radical migration (1,2-RaM) to generate the more stable intermediate **8.8** (path c). Subsequently, bromo-atom transfer from **8.6** to **8.8** affords the desired product (path d).[28]

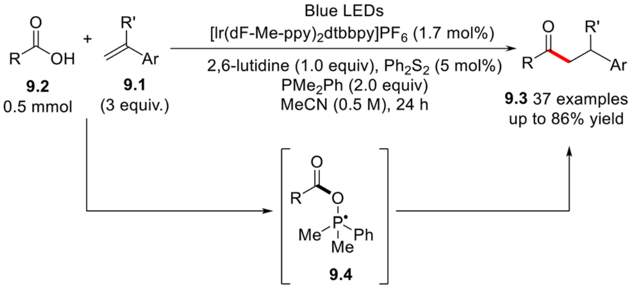
Xia Zhao was born in Tianjin, China, in 1983. She received her BS degree from Nan Kai University in 2006, and then a Ph.D. degree in organic chemistry from Peking University, China, in 2011 under the supervision of Professor Jianbo Wang. After that she started her independent career as an assistant professor at Tianjin Normal University and was promoted to full professor in 2021. Her research interests focus on photochemistry and organosulfur chemistry.

2.2. Acylation reactions

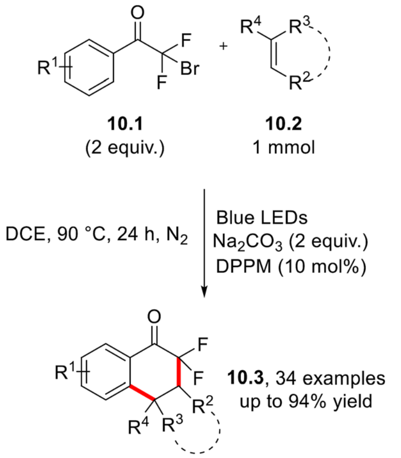
Aliphatic ketones play a crucial part in post-transformation and late-stage functionalization processes, making them privileged targets in organic synthesis.[29,30] Symmetric and asymmetric dialkyl ketones **9.3** have been obtained *via* Ir(III)-photocatalyzed hydroacylation of styrenes (**9.1**, Scheme 9) by aliphatic acids **9.2** in the presence of diphenyl methyl phosphine, as reported in Scheme 9.[31] In this case, a key role is played by the phosphoranyl radical **9.4** which, in turn, undergoes β-scission to release the desired acyl radical. Analogously, aromatic carboxylic acids have been employed as precursors of acyl radicals in the preparation of α,α′-diaryl carbonyls *via* photoredox-catalyzed acylation 1,6-conjugate addition to *p*-quinone derivatives.[32] By following an analogous pathway, acyl oximes have been employed as the acyl radical precursors in the hydroacylation of 1,1-diarylethylenes and α-trifluoromethyl styrenes.[33]

The photoinduced phosphine-catalyzed cyclization of bromodifluoroacyl arenes **10.1** with olefins has been applied recently to the preparation of a wide range of cyclic *gem*-difluoroacyl compounds **10.3** under photocatalyst-free conditions (Scheme 10).[34]

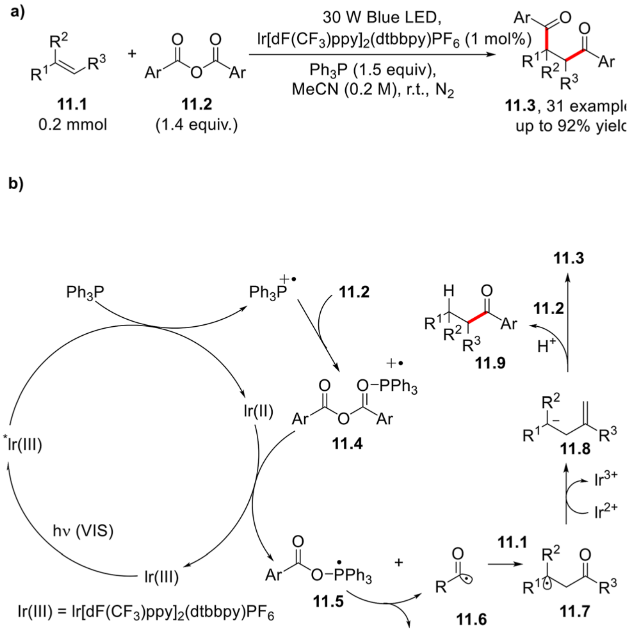
Anhydrides **11.2** have been employed as acylating radical agents in the photocatalyzed conversion of alkenes **11.1** into 1,4-dicarbonyl derivatives (**11.3**, Scheme 11). In the proposed mechanism, the photoexcited photocatalyst ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$)* undergoes reductive quenching by triphenyl phosphine. Then, the resulting radical cation $PPh_3^{•+}$ is trapped by **11.2** to form the complex **11.4**, which allows the otherwise unfavorable reduction of the carboxylic moiety in **11.2** ($E_{1/2}^{red}$ = −1.41 V *vs.* SCE) by Ir(II). The acyl radical **11.6** arising from the decomposition of intermediate **11.5** is, in turn, trapped by the C=C double bond of **11.1**. The resulting radical **11.7** undergoes reduction to carbanion **11.8**, which reacts with another molecule of **11.2** to form the diacylated product. In the presence of a proton source (*e.g.*, water), **11.8** is finally converted into the corresponding hydroacylated derivative **11.9**.[35]



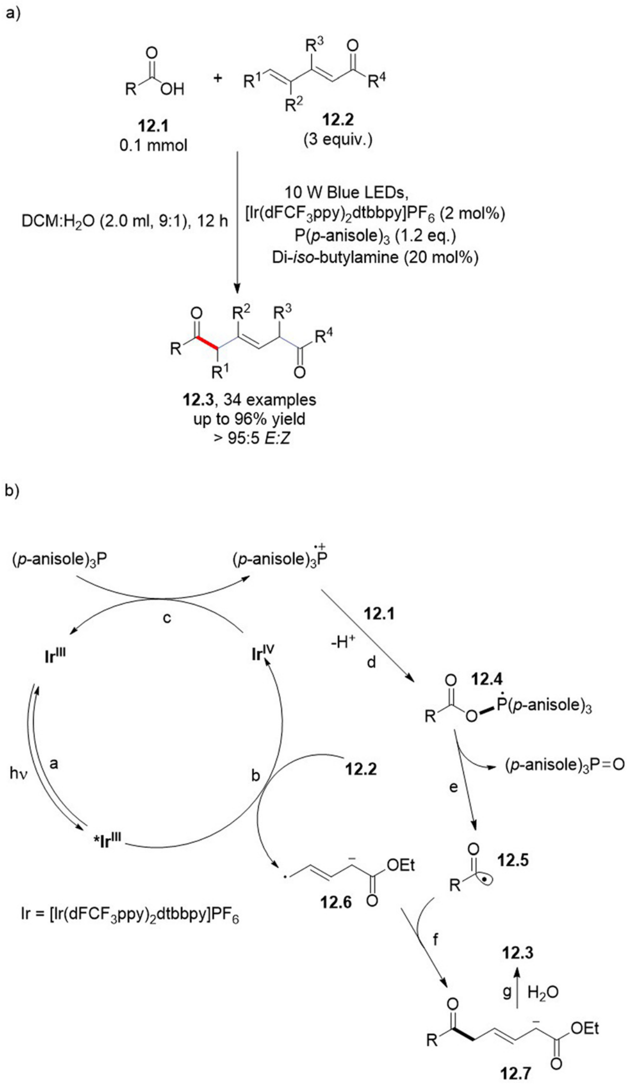
Scheme 9 Hydroacylation of styrenes **9.1** by carboxylic acids.



Scheme 10 Blue light-mediated, photocatalyst-free preparation of cyclic ketones **10.3**.



Scheme 11 (a) Visible light-driven photoredox-catalyzed 1,2-difunctionalization of olefins. (b) Suggested mechanism.



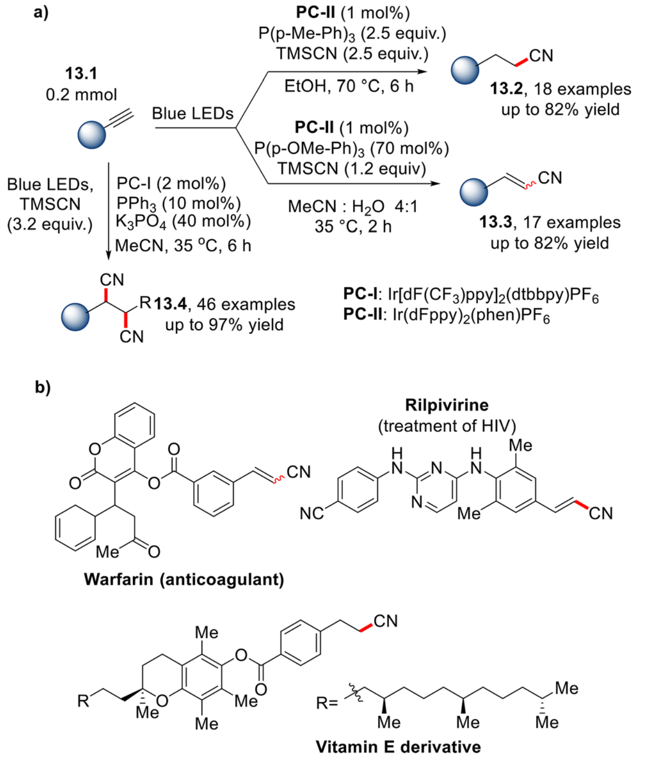
Scheme 12 Regioselective, photoredox-catalyzed decarboxylative acylation of electron-poor 1,3-dienes **12.2**.

1,6-Dicarbonyl derivatives **12.3**[36–38] are suitable, *via* a regioselective 1,6-addition of acyl radicals (in turn generated from carboxylic acids **12.1** under Ir(II) photoredox-catalyzed conditions), onto electron-deficient 1,3-dienes (**12.2**, Scheme 12a).[39] If exposed to visible light, the excited photoredox catalyst undergoes oxidative quenching by **12.2**, generating the radical anion **12.6** (Scheme 12b, paths a and b). As a result, triarylphosphine is oxidized through a SET, while restoring the starting photoredox catalyst (path c). The resulting phosphoranyl radical intermediate **12.4** (path d) decomposes and releases the acyl radical **12.5** (path e), which then couples with **12.6** (path f). Protonation of the so-generated carbanion **12.7** by water (path g) affords the desired product **12.3**.[39]

A divergent approach for the selective preparation of alkyl nitriles (**13.2**, Scheme 13a), alkenyl nitriles (**13.3**) and alkyl dinitriles (**13.4**) from alkynes has been proposed by Chu and co-workers.[40] As shown in Scheme 13a, the choice of phosphine is critical in determining the reaction outcome. Notably, a wide range of polyfunctionalized substrates, including warfarin analogues, pharmaceutics, sugars and vitamin E, can be selectively functionalized under the tunable conditions (some examples are depicted in Scheme 13b).

2.3. Arylations

The incorporation of fluorine atoms and fluorine-containing functional groups into complex (hetero)aromatic cores is a flourishing research area in view of the opportunity to “fine

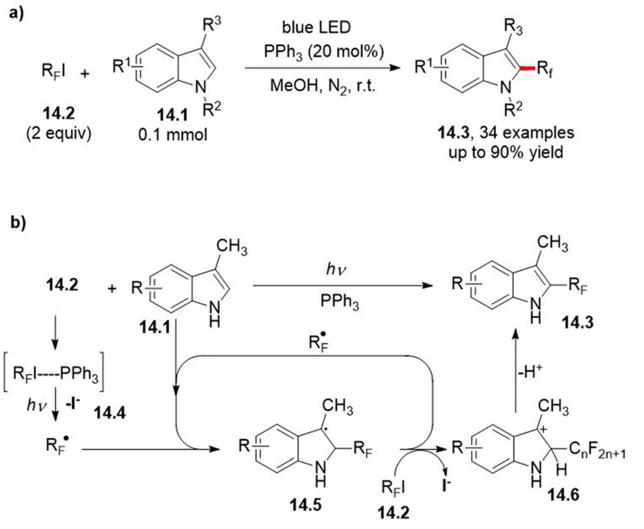


Scheme 13 (a) Phosphine/photoredox-catalyzed divergent cyanation of alkynes and (b) selected applications.

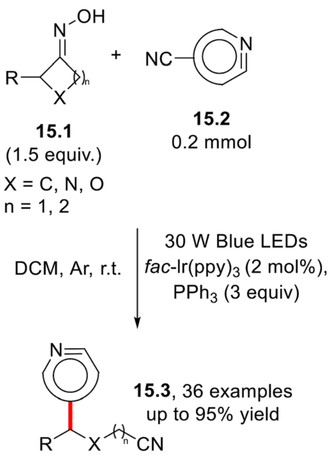
tune" key physicochemical properties, including (among others), solubility, metabolic stability and bioavailability.[41–48] In this context, the use of phosphine as a radical initiator in the perfluoroalkylation of electron-rich heterocycles **14.1** (including indoles) has been proposed only recently. In the case described by Jin and co-workers,[49] and suitable for Scheme 14a, an EDA complex (**14.4**) between the chosen perfluoroalkyl iodide **14.2** and the phosphine catalyst is involved. Visible light-irradiation promotes a SET, and the so generated perfluoroalkyl radical $\mathbf{R_F}^{\bullet}$ which is, in turn, trapped by the heteroaromatic core. Thus, obtained radical species **14.5** is oxidized by another molecule of **14.2** to release, after deprotonation of the Wheland intermediate **14.6**, the desired product **14.3** and so restarting, simultaneously, the radical chain. The protocol was found to be successful also when starting from indoles conjugated to bioactive fragments such as zomipitran and melatonine.[49]

Analogously, the introduction of a *gem*-difluoromethyl group into alkenes and (hetero)cyclic cores (including dimethyl uracil) has been reported to occur *via* a visible light-promoted phosphine-catalyzed difluoroalkylation strategy.[50]

As mentioned above, nitrile is one of the most prevalent and versatile units in organic synthesis, acting as a precursor of different functional groups, including amines, aldehydes, amidines, ketones, carbamates and carboxylic acids.[51] The research group of Yi accomplished an intriguing photoredox-neutral ring-opening pyridylation of cyclic oximes **15.1**



Scheme 14 Visible light-driven phosphine-catalyzed perfluoroalkylation of indoles.



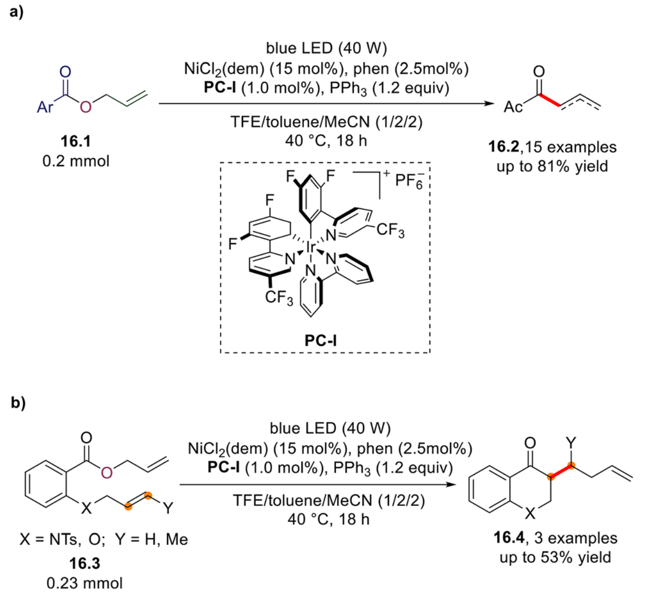
Scheme 15 Photoredox-neutral ring-opening pyridylation of cyclic oximes.

(Scheme 15) by cyanopyridines **15.2** to afford a wide array of pyridyl-alkylnitriles **15.3** with satisfactory selectivity (Scheme 15).[52]

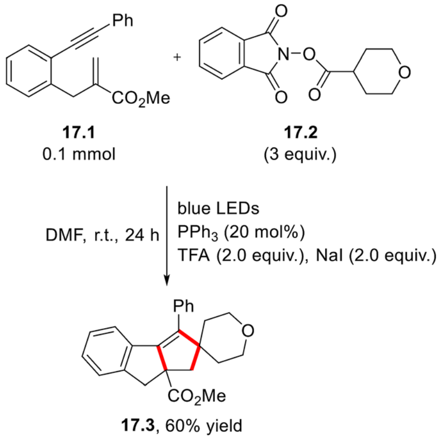
2.4. Extrusion reactions

In 2023, Tobisu and co-workers described a nickel/Ir(II) photoredox/phosphine-promoted intramolecular C–C coupling occurring in allyl esters **16.1** for the preparation of asymmetric ketones **16.2.** in good yield (Scheme 16a).[53] The same conditions have been applied to obtain a cyclic ketone (**16.4**, Scheme 16b) *via* functionalization of allyl esters bearing a tethered alkene moiety (**16.3**).[53]

In 2019, Xu and co-workers described a single example of phosphine/iodide-based photocatalytic decarboxylative [2 + 2 + 1] annulation of 1,6-enynes and *N*-hydroxyphthalimide esters,



Scheme 16 Nickel/photoredox/phosphine-catalyzed preparation of ketones from allyl esters.



Scheme 17 Preparation of spyroderivative **17.3** *via* phosphine/iodide-based photocatalytic decarboxylative [2 + 2 + 1] annulation.

providing the corresponding cyclopenta[*a*]indene **17.3** in 60% yield (Scheme 17). The procedure can be considered to be a transition metal-free alternative to *fac*-Ir(ppy)$_3$-catalyzed approach described in the same study.[54]

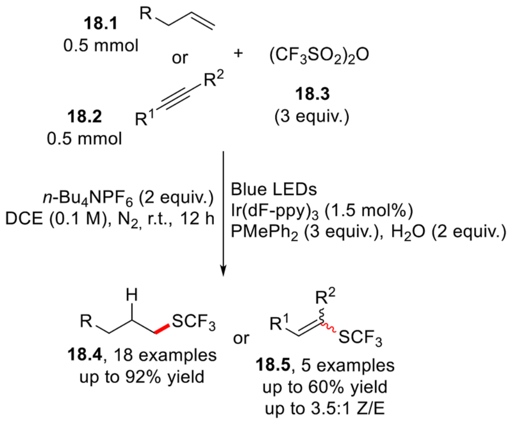
3. Formation of carbon–heteroatom bonds

3.1. C–S bond formation

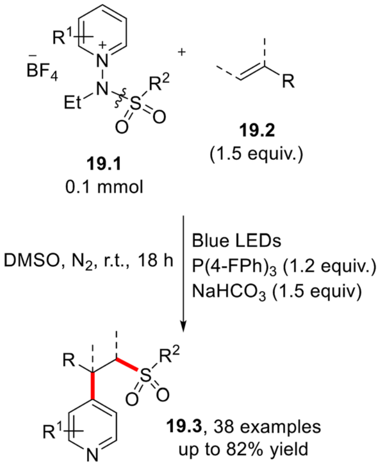
The incorporation of a trifluoromethylthio moiety (–SCF$_3$) in pharmaceuticals and agrochemicals enables fine tuning of their lipophilicity and electronic properties.[44,47,55] Qing and co-workers disclosed a facile and mild strategy for the Ir(III)-photoredox-catalyzed hydrotrifluoromethylthiolation of unactivated alkenes (**18.1**) or alkynes (**18.2**) using trifluoromethanesulfonic anhydride (Tf$_2$O) as the SCF$_3$ radical precursor in the presence of H$_2$O as the proton source (Scheme 18).[56]

The visible light-induced hydrosulfonylation of alkenes in the presence of *N*-amidopyridium salts **19.1** as precursors of the sulfonyl radical has recently been proposed in a photocatalyst-free fashion *via* the formation of a photoreactive EDA complex between **19.1** and triphenyl phosphine (or HCO$_3^-$ anion, Scheme 19). Notably, the protocol was extended to the functionalization of bioactive molecules such as estrone and fructopiranose.[57]

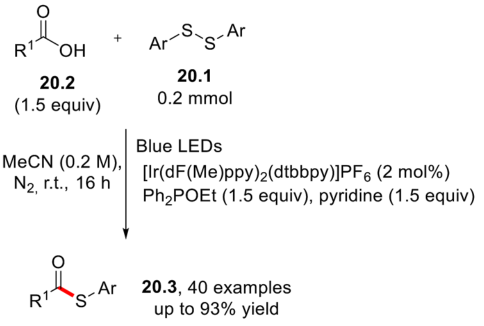
Disulfides **20.1** have been employed as the sulfur source in the photoredox-catalyzed, alkoxy phosphine-mediated thioesterification of carboxylic acids **20.2** that was successfully applied to the functionalization of complex pharmaceutical-derived carboxylic acids, including the cholesteryl ester transfer protein inhibitor dalcetrapib (Scheme 20).[58]



Scheme 18 Visible light-mediated hydrotrifluoromethylthiolation of unactivated alkenes and alkynes.



Scheme 19 1,2-Difunctionalization of olefins *via* blue light-driven C–aryl and C–S bond formation.



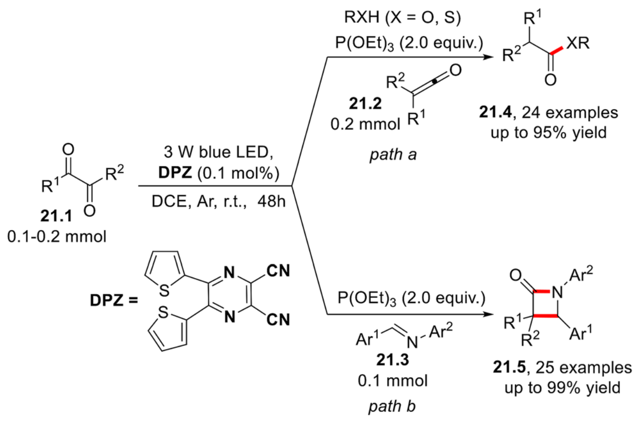
Scheme 20 Phosphine-mediated thioesterification of carboxylic acids **20.2**.

In 2021, Jiang and co-workers reported the photoredox catalytic phosphite-mediated deoxygenation and Wolff rearrangement of 1,2-diketones *via* ketenes to afford the corresponding (thio)esters (**21.4**, Scheme 21, path a) using the pyrazine derivative DPZ as the visible light-absorbing photocatalyst.[59] The same approach is on the basis of the preparation of β-lactams **21.5** (path b) *via* a Staudinger [2 + 2] cycloaddition with imines.[60]

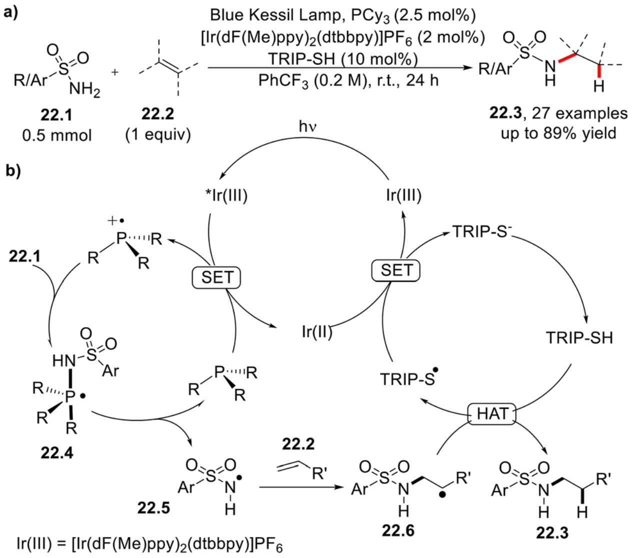
3.2. C–N bond formation

A photoredox-catalyzed anti-Markovnikov hydroamination of olefins **22.2** by sulphonamides **22.1** in the presence of tricyclohexylphosphine and TRIP-SH as the cocatalysts was described recently (Scheme 22a).[61] As illustrated in Scheme 22b, the mechanism involves a merged photoredox/hydrogen atom transfer (HAT)/phosphine organocatalysis cycle. The P–N bond α-cleavage occurring in the radical intermediate **22.4**, in turn generated by coupling of $PCy_3^{\bullet+}$ with **22.1**, plays a key role in the generation of the amido radical **22.5** which, in turn, is trapped by **22.2** to afford the intermediate **22.6**. The latter undergoes HAT with TRIP-SH to release the desired product.[61] A similar visible light-driven anti-Markovnikov hydroamination of alkenes (including cyclic olefins and vinyl ethers) was carried out using *N*-hydroxyphthalimide as the functionalizing agent and triethyl phosphite as the cocatalyst.[62]

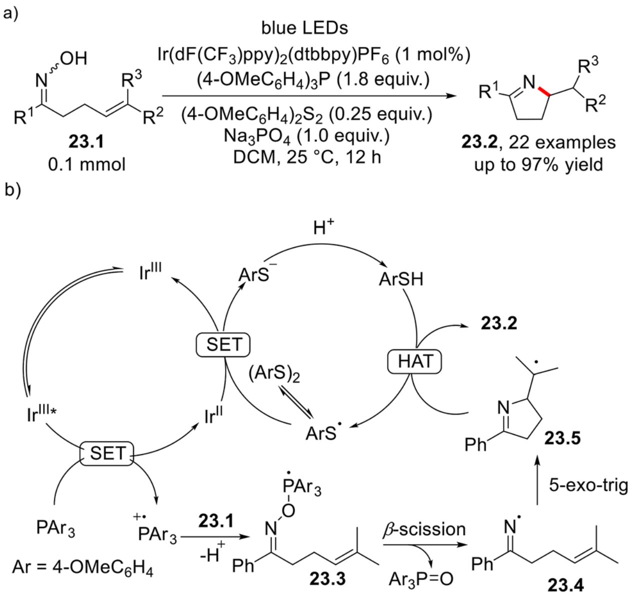
The synthesis of pyrrolines from γ,δ-unsaturated oximes (Scheme 23) was recently described to take place in the presence of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, tris(4-methoxyphenyl) phosphine and 4-methoxyphenyl disulphide as the photoredox catalysts and cocatalysts, respectively.[63] This strategy is based on the reductive quenching of the photoexcited iridium catalyst by tris(4-methoxyphenyl)phosphine ($E_{p/2}[Ar_3P^{\bullet+}/Ar_3P]$ = +0.87 V *vs.* SCE), which is converted to the corresponding radical cation and adds itself onto the oxime moiety. The so-



Scheme 21 Photoredox catalytic phosphite-mediated deoxygenation and Wolff rearrangement of α-diketones.



Scheme 22 Visible light-driven anti-Markovnikov hydroamination of olefins.



Scheme 23 Light-driven intramolecular hydroimination of oximes **23.1**.

generated phosphoranyl radical **23.3** undergoes N–O bond β-cleavage to deliver the iminyl radical **23.4** which, in turn, undergoes intramolecular 5-*exo*-trig cyclization. HAT from 4-methoxythiophenol (arising from the corresponding disulfide) to the carbon-centered radical **23.5** affords the desired product.

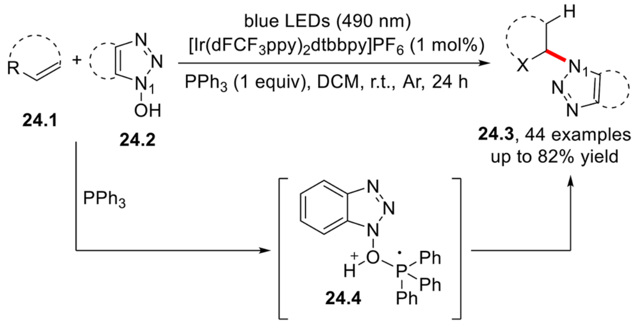
N-Hydroxyl azoles **24.2** (Scheme 24) were successfully employed in the regioselective hydroazolylation of alkenes under Iridium photoredox catalysis in the presence of triphenylphosphine. The N–O bond cleavage that occurs in the phosphoranyl radical cation **24.4** has been suggested to be the key step in the reaction mechanism. An analogous mechanism was exploited for the preparation of *N*-arylphthalimides *via* the photocatalyzed radical *N*-arylation of (hetero)aryl derivatives by *N*-hydroxyphthalimides.[64]

The development of innovative strategies for the amidation of carboxylic acids is of interest in organic synthesis due to the widespread presence of amide moieties in fine chemicals, peptides, as well as in polymeric materials.[65–70]

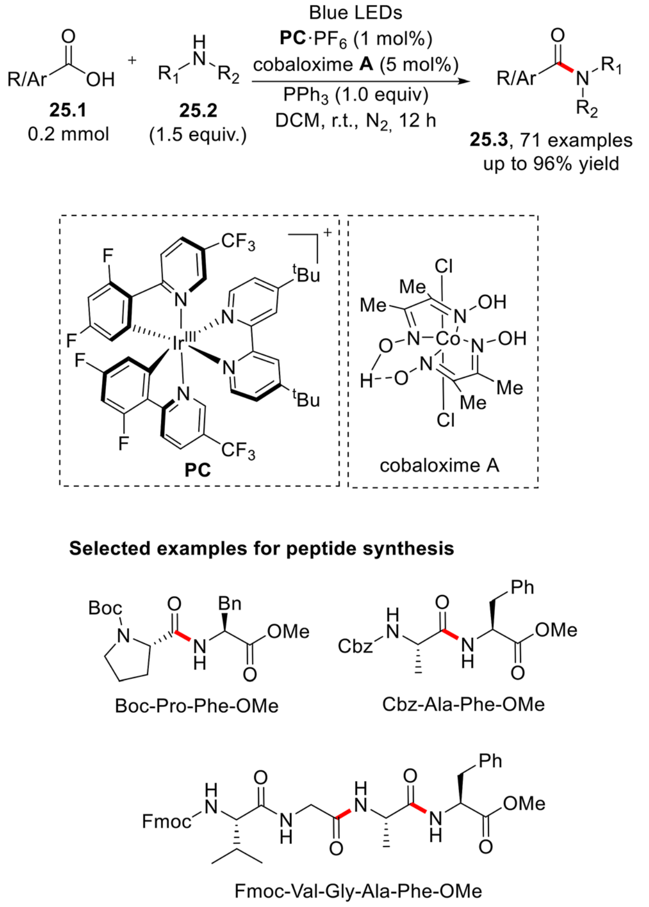
In this context, we noted the preparation of differently substituted amides *via* a merged photoredox/cobaloxime-catalyzed deoxygenative activation of carboxylic acid.[71] The protocol, which requires PPh_3 as the redox active cocatalyst, has been employed on different biorelevant substrates and was considered for late-stage functionalization. Furthermore, the process has been optimized under continuous-flow conditions for the preparation of peptides in satisfactory yield (Scheme 25).[71,72] Carboxylic acids have been used also as the acyl radical precursor in the preparation of differently substituted acyl hydrazides by deoxygenative hydroacylation of azobenzenes.[73]

3.3. Carbon–halogen bond formation

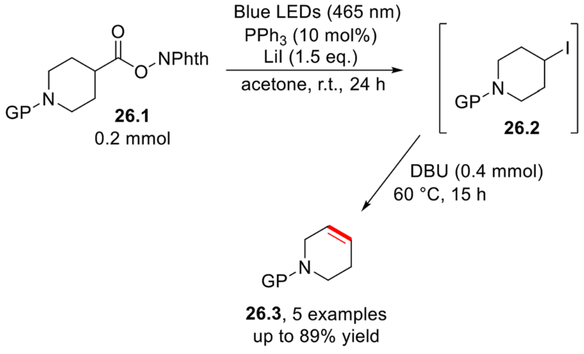
Carboxylic acid derivatives have been employed in the preparation of halogenated substrates *via* an acyl radical. *N*-(Acyloxy) phthalimides have been subject to triphenylphosphine-photocatalyzed iododecarboxylation using lithium iodide as the iodine source to afford a wide range of both cyclic and acyclic alkyl iodides (**26.2**, Scheme 26).[74] Notably, if an organic base (DBU) is added, **26.2** undergoes elimination to afford the corresponding alkene in a one-pot fashion.[74]



Scheme 24 Photoredox-catalyzed hydroazolylation of alkenes.



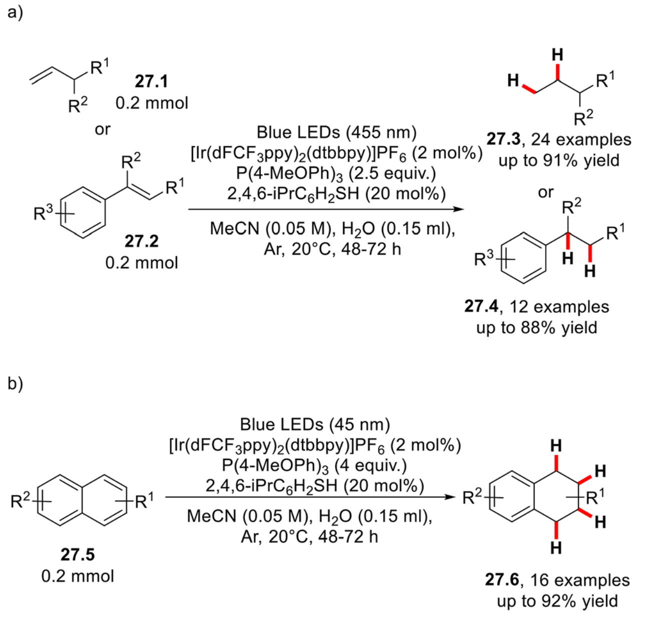
Scheme 25 Merged photoredox and cobaloxime preparation of amides *via* deoxygenative amidation of carboxylic acids.



Scheme 26 Triphenylphosphine-photocatalyzed iododecarboxylation of *N*-(acyloxy)phthalimide.

3.4. Carbon–hydrogen bond formation

In 2023, Studer and co-workers established the photocatalyzed activation of water by the interaction of a phosphine radical, which could provide an H atom to react further with alkenes (**27.1** or **27.2**) under mild conditions (Scheme 27).[75] This transfer hydrogenation methodology has been applied to the reduction of naphthalenes **27.5**. Furthermore, photochemical



Scheme 27 Photocatalyzed activation of water and further application.

skeletal editing of 2-substituted quinolines can be achieved to afford 2,3-disubstituted indoles *via* a hydrogenative rearrangement in slightly modified conditions.[75]

4. Conclusions

In recent years, radical phosphine chemistry has emerged as an elegant and prominent strategy for broadening the horizons of (visible) light-driven methodologies. Attention has been focused on the design of late-stage functionalization protocols for pharmaceutical design and synthesis of bioactive and natural molecules. Despite the advancements reported in the literature, there are several drawbacks that have not been solved. This is because the design of stereoselective processes is still underdeveloped and the use of triarylphosphines in stoichiometric excess[56,75] involves the release of rather noxious phosphorous-based byproducts. In this context, research should focus on methodologies that employ trisubstituted phosphines as effective organocatalysts (*e.g.*, where an EDA complex with an electron poor alkyl halide is formed)[28] as a promising strategy to overcome these limitations.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts of interest to declare.

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