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Merging Organocatalysis and Photocatalysis: a New Momentum in Covalent Radical Catalysis

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Abstract: The use of free radicals as organocatalysts constitutes a powerful strategy to activate and functionalize unsaturated carbon chains. Indeed, the unique affinity of open-shell species for alkenes and alkynes can be rerouted to achieve the catalytic covalent activation of the substrate and control a subsequent radical cascade. However, the field of covalent radical catalysis has remained confidential for decades due to important issue in terms of catalyst handling, reaction design and viability. Recently, these pitfalls have been addressed one by one by the use of photocatalysis to control the generation and the reactivity of radical catalysts. This Concept article aims to highlight recent achievements in the field of photocatalyzed covalent radical catalysis and the perspectives offered by such catalytic combinations. The reaction mechanisms and the interconnection between the catalytic cycles are notably discussed with the hope of demonstrating the synthetic potential of this approach and foster a rapid growth of this nascent topic.

1. Introduction

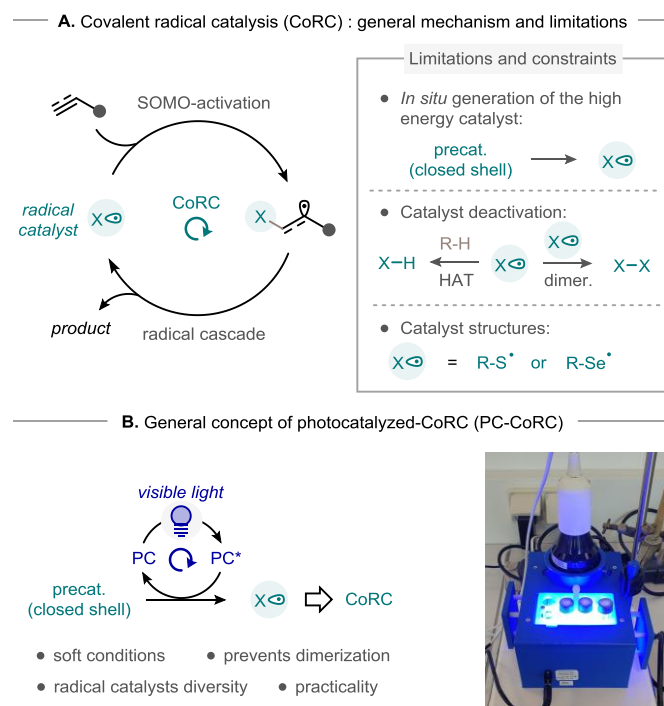
Organocatalysis has a long story in the field of molecular catalysis and provides a powerful tool to access complex molecular architectures. The generic term of organocatalysis actually covers a remarkable diversity of transformations traducing a broad variety of activation modes. However, polar functions on the substrates are generally mandatory to establish covalent or non-covalent interactions with organocatalysts acting as Lewis/Brønsted acids or bases (most organocatalysts).^[1] Consequently, a plethora of poorly functionalized compounds remain out of the scope of traditional organocatalysis. Alternatively, free radicals display a complementary reactivity as compared to closed-shell molecules. Notably, heteroatom-centered radicals demonstrate a unique ability to reversibly add onto C-C multiple bonds to convert non-polarized alkenes and alkynes in highly reactive C-centered radical adduct (SOMO-activation). From this property has emerged covalent radical catalysis (CoRC) in which the selective SOMO activation of alkenes/alkynes by a radical catalyst in the presence of an appropriate reaction partner, triggers a radical cascade resulting in the formation of a new product and the release of the catalyst (Scheme 1A). Hence, CoRC constitutes an efficient strategy to access complex architectures from simple building blocks.

Unlike the other fields of organocatalysis and despite an appealing synthetic potential, CoRC remains seriously underdeveloped more than three decades after Oshima^[2] and Feldman's^[3] pioneering reports. This could be mainly explained by recurrent practical issues related to the challenging design and handling of radical catalysts.^[4] Indeed, free radicals are inherently high-energy species whose lifetime generally does not exceed one millisecond. Consequently, radical catalysts have to be generated *in situ* from appropriate closed-shell precatalysts. Moreover, free radicals can participate in undesired propagation and termination steps constituting troublesome catalyst deactivation pathways. Noteworthy, a fast dimerization of the radical catalyst or a superior ability to promote hydrogen atom transfers (HAT) could completely shut down the covalent activation of substrates. As a consequence of these multiple constraints, CoRC has remained, for years, exclusively confined to sulfur and selenium-centered free radicals. In practice, slow additions of sub-stoichiometric amounts of radical initiators onto (foul-smelling) thiophenols^[2,3,5] and diaryl diselenides,^[6] the design of elaborated hindered thiol precatalysts^[7] and the UV-induced homolytic cleavage of diaryl disulfide S-S bonds,^[8] have been reported to generate open-shell catalysts while limiting dimerization issues in organocatalyzed radical (3+2)-cycloadditions. In the last few years, the release of thiyl radicals by irradiating charge transfer complexes between diaryl disulfide precatalysts and styrene/ phenylacetylene derivatives has been used to achieve the aerobic oxidation of C-C multiple bonds.^[9] However, all these approaches suffer from important restrictions in terms of practicality, scope, functional group tolerance and catalyst diversity.

During the last decade, the use of visible light as a safe and clean energy source for chemical reactions has known intense developments culminating with the advent of visible light photocatalysis. Indeed, photoredox catalysts and photosensitizers able to carry the energy of photons toward photo-inactive substrates respectively by single-electron transfer (SET)^[10] or energy transfer (EnT)^[11] have been extensively used to generate free radicals under soft conditions. Recently, the idea of using photocatalysis to convert photo-inactive precatalysts into high-energy radical catalysts has emerged as an appealing concept (Scheme 1B, *left*). Indeed, the possibility to setup such photocatalyzed CoRC (PC-CoRC) in inexpensive and standardized photoreactors has naturally improved the practical attractiveness of radical catalysis (Scheme 1B, *right*). Moreover, the rich diversity of photocatalysts whose photochemical properties (Figure 1) can be modulated has opened new design.

This Concept article aims to describe how the brand-new field of PC-CoRC brought a new impetus to CoRC. The manuscript is organized according to the classes of radical catalysts

and a strong emphasis has been made on mechanistic discussions in order to provide a comprehensive description of the interconnection between catalytic cycles.



Scheme 1. A) Covalent radical catalysis (CoRC); B) Photocatalyzed-covalent radical catalysis (PC-CoRC) (left) and a standardized HeptatoChem HCK 1006-01-004 PhotoRedOx Box® equipped with a 18 W blue LED HepatoChem® lamp (EvoluChem™ LED 450PF, 450 nm) (right).

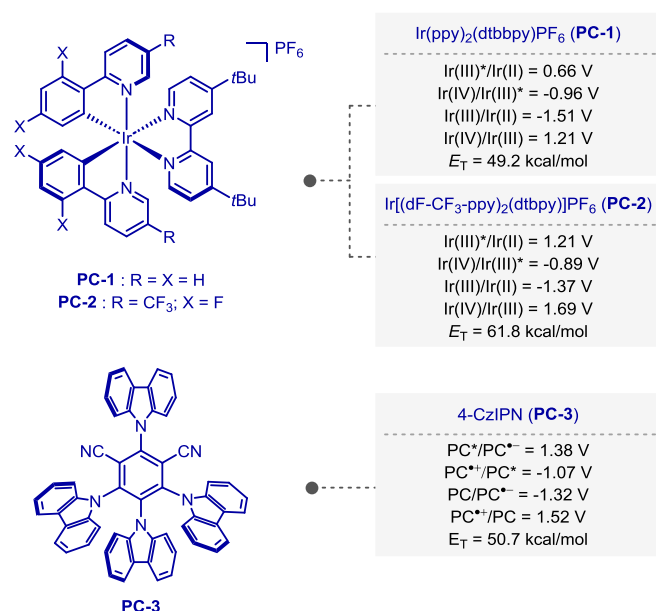
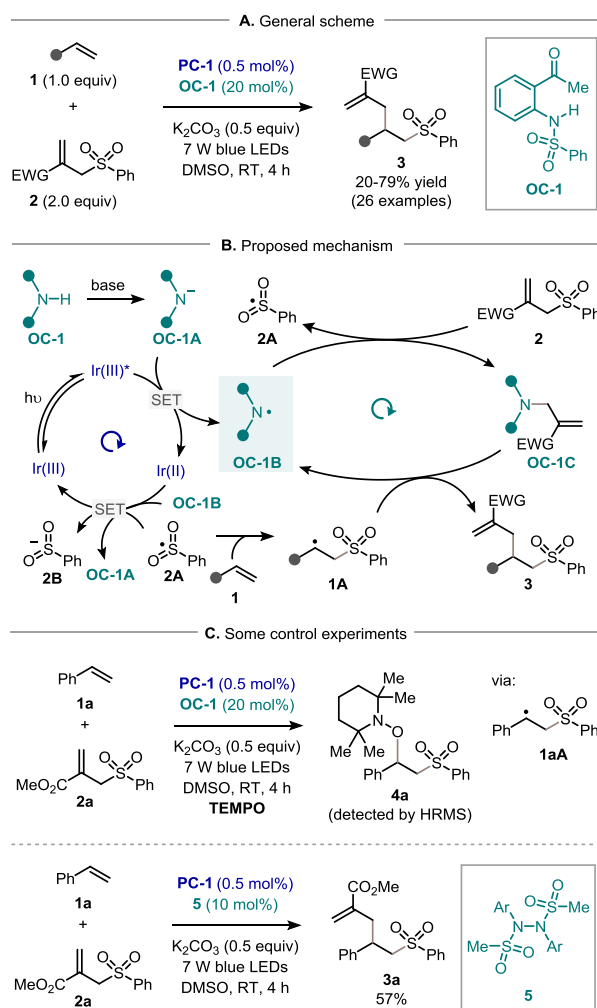


Figure 1. Photocatalysts used in PC-CoRC, Redox potential values are given in MeCN and versus SCE.

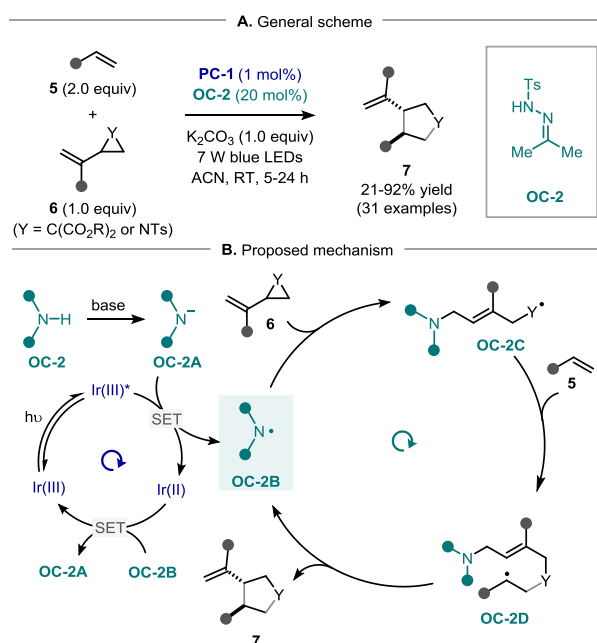
2. Neutral N-centred radical catalysis

The ability of N-centred radicals to add onto alkenes has opened the way to extensive applications in C-N bond formation.^[12] In 2014, Xiao, Chen and co-workers reported a photoredox-catalyzed method to convert N-H tosylhydrazones into N-centred hydrazonyl radicals.^[13] The transformation was described as a stepwise proton-coupled electron transfer involving an N-H deprotonation by NaOH followed by a photocatalyzed single-electron oxidation of the electron-rich nitrogen anion ($E_{ox} = +0.56 \text{ V versus SCE}$)^[14]. A related sequence was then applied to generate N-centred radical catalysts in the first example of PC-CoRC in 2019.^[15] The radical-catalyzed bifunctionalization of alkenes **1** with allylsulfones **2** was then conducted under blue-light irradiation in the presence of iridium complex **PC-1** (Scheme 2A). The reactivity and the stability of the radical catalyst have proved to be influenced by the substitution pattern. The easy modification of *N*-aryl sulfonamides stereo-electronic properties then revealed that *N*-(2-acetylphenyl) benzenesulfonamide **OC-1** was the most efficient precatalyst. The postulated mechanism starts with the deprotonation of **OC-1** and the oxidation of anion **OC-1A**. The subsequent addition of radical **OC-1B** onto allylsulfone **2** initiates the radical cascade and affords intermediates **2A** and **OC-1C** (Scheme 2B). Addition of sulfonyl radical **2A** to olefin **1** results in secondary radical **1A**. The final trapping of **1A** by **OC-1C** delivers product **3** and releases radical catalyst **OC-1B**. The way in which the photoredox cycle is closed remains unclear but could involve a SET between sulfonamidyl radical **OC-1B** or sulfonyl radical **2A** and Ir(II) complex. The radical pathway of the difunctionalization was demonstrated by the detection of product **4a** coming from the trapping of intermediate **1aA** with TEMPO (Scheme 2C). Also, an alternative mechanism involving a S_N2' initiation by **OC-1C** was discarded by the detection, by HRMS, of a dimeric species coming from radical catalyst **OC-1B**. Interestingly, dimer **5** could constitute an efficient precatalyst in the synthesis of **3a** but the mechanism accounting for the N-N bond cleavage was not discussed.

In 2020, Chen and co-workers developed a related catalytic system to promote radical (3+2)-cycloadditions between olefins **5** and vinylcyclopropanes / *N*-tosyl vinylaziridines **6** (Scheme 3A).^[16] In this system, N-H tosylhydrazones have demonstrated higher performances compared to *N*-aryl sulphonamides and **OC-2** was selected as a precatalyst. This reaction affords various vinylcyclopentanes and vinylpyrrolidines **7** and tolerates a broad range of non-acidic functional groups. The authors suggested a mechanism beginning with the addition of radical **OC-2B** onto substrate **6**, followed by the fast opening of the strained cycle (Scheme 3B). A round trip radical cascade between intermediate **OC-2C** and olefin **5** provides desired product **7** and releases the radical catalyst. Closure of the photoredox catalytic cycle was suggested to arise from back electron donation from radical **OC-2B**



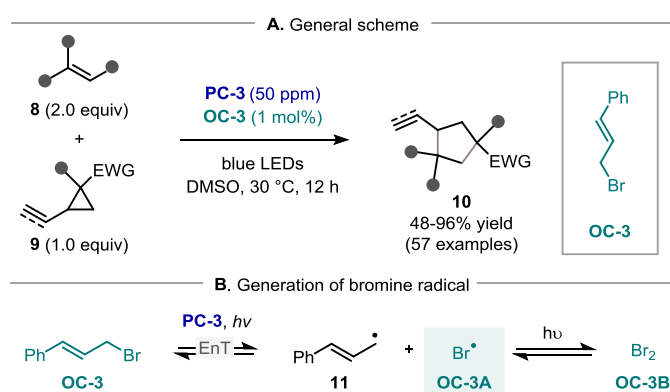
Scheme 2. Difunctionalization of alkenes with allylsulfones by PC-CoRC (Xiao, Chen and co-workers, 2019).



Scheme 3. (3 + 2)-cycloadditions between vinylcyclopropanes and *N*-tosyl vinylaziridines with alkenes by PC-CoRC (Xiao, Chen and co-workers, 2020).

3. Bromine radical catalysis

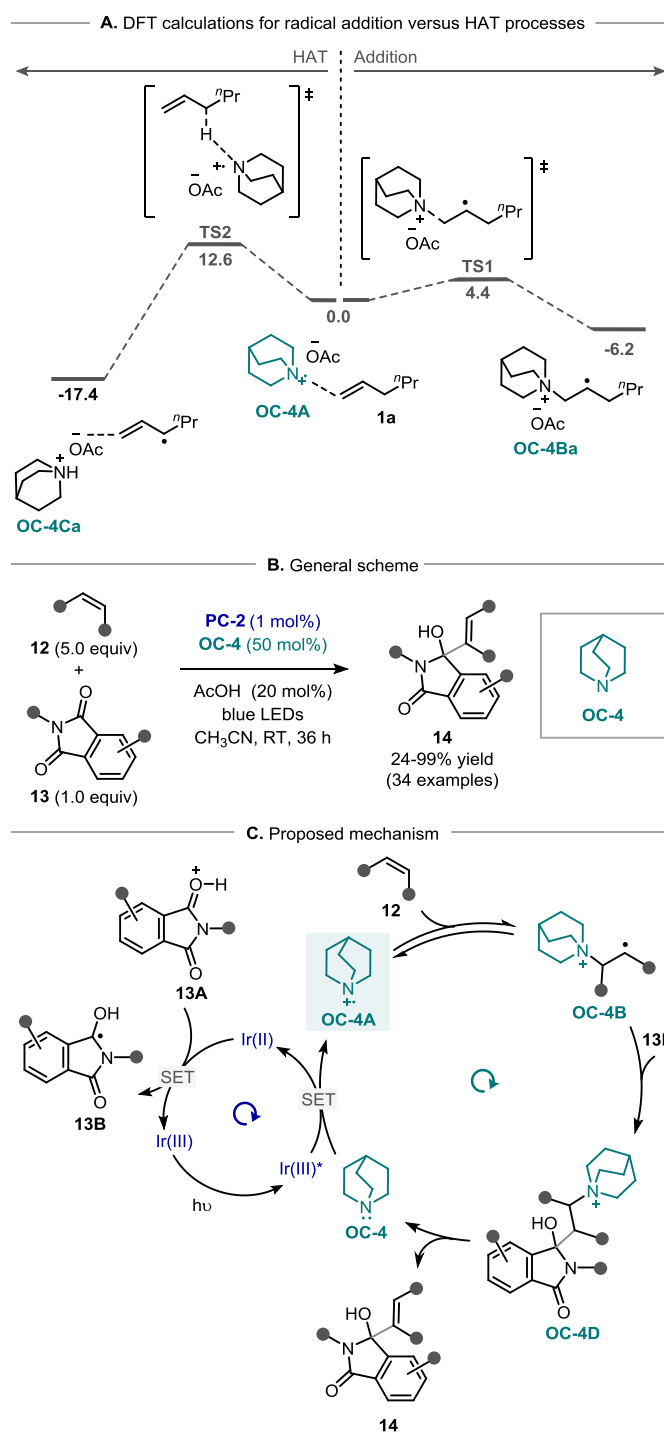
In 2020, Miyake and co-workers explored the possibility to use bromine radical to catalyze (3+2)-cycloadditions between olefins **8** and vinyl- or ethynyl-cyclopropanes **9** (Scheme 4A).^[17] A first strategy aiming at generating the bromine radical by photoredox-catalyzed oxidation of different bromide salts proved to be unsuccessful. A second approach involving the release of the bromine radical by photosensitization of an organic precatalyst was then explored. The combination of cinnamyl bromide **OC-3** and **PC-3**, used in parts per millions (ppm), appeared highly efficient to catalyze the synthesis of vinyl/ethynylcyclopentanes **10** under blue light irradiation. The low photocatalyst loadings ensure that a very low concentration in bromine radical is maintained, which is crucial in order to prevent undesired radical pathways and reach high levels of conversion. *On/off* experiments have revealed that the reaction is paused as soon as the solution is plunged into the dark then discarding a pure radical chain mechanism. The catalyst deactivation is reversible since the catalytic activity is recovered when light irradiation is started again. These results suggest that precatalyst **OC-3**, reformed by recombination of bromine radical **OC-3A** and radical **11**, constitutes the *dark state* of the catalyst (Scheme 4B). Dibromine **OC-3B** could also constitute a dormant catalytic species whose formation can be reversed by homolytic cleavage of the weak Br-Br bond under photochemical conditions. Indeed, the homolysis of Br₂ can occur *via* EnT from the excited photocatalyst (**PC-3***, $E_T = 50.7$ kcal/mol) or can be triggered by direct absorption of blue light by Br₂. From a synthetic point of view, the method described by Miyake and co-workers proceeds under very soft conditions and tolerates a remarkable range of functional groups including alcohols, carboxylic acids, amides and boronic esters. However, the structure of bromine radical is intrinsically not editable which could be an issue to further developments.



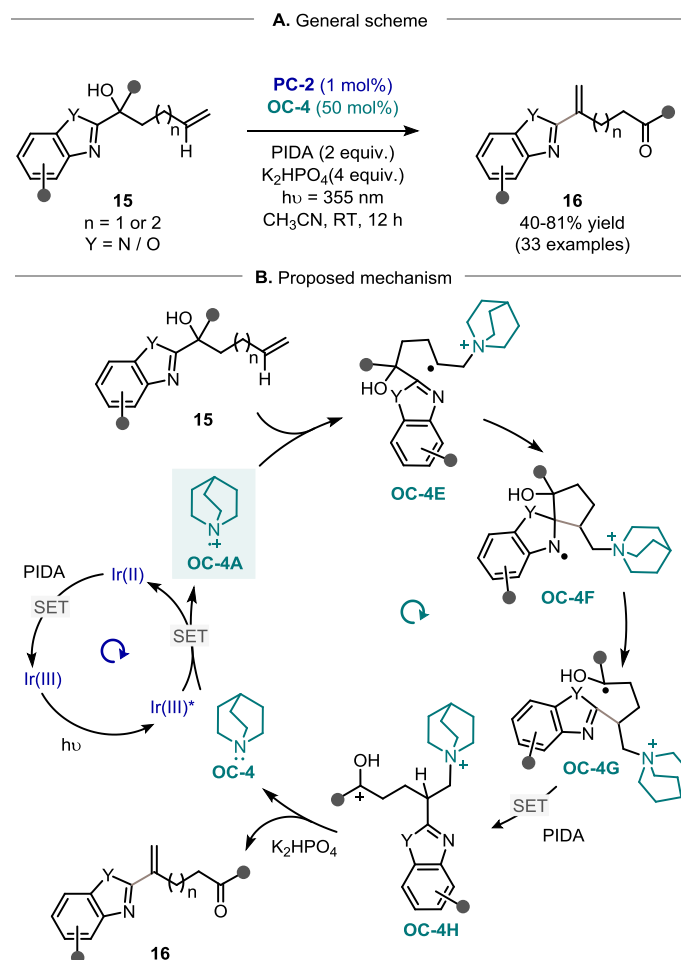
Scheme 4. (3 + 2)-Cycloadditions between vinylcyclopropanes and alkenes catalyzed by bromine radical in PC-CoRC (Miyake and co-workers, 2020).

4. Ammonium radical catalysis

Single-electron oxidation of tertiary amines results in electrophilic ammonium radicals. When presenting α -H atoms, ammonium radicals evolve rapidly into aminyl radicals or iminium salts by deprotonation or HAT, respectively. However, N-bridgehead amines afford more persistent ammonium radicals. Quinuclidine derivatives have then been extensively used as HAT catalysts in photoredox-catalyzed C(sp³)-H bond activations.^[18] However, their ability to participate in reversible radical additions onto alkenes has remained unclear until a recent publication by Shi, Wei and co-workers.^[19] Computational experiments revealed that the addition of quinuclidinium radical **OC-4A** onto 1-hexene **12a** is favored by 8.2 kcal/mol (TS1) over the HAT at the allylic position (TS2) (Scheme 5A). Accordingly, quinuclidinium radical **OC-4A** was used to catalyze a radical version of the venerable Morita-Baylis-Hillman (MBH) reaction. The transformation is orchestrated by a ternary catalytic system and allows the formation of products **14** from various alkenes **12** and phthalimide derivatives **13** (Scheme 5B). Noteworthy, electrophilic radical **OC-4A** selectively adds onto electron-rich olefins and the radical MBH reaction then displays a remarkable complementarity with the traditional two-electron process. This clever example of PC-CoRC relies on the dual role of **PC-2** in: a) the oxidation of precatalyst **OC-4** by reductive quenching of the photoexcited Ir(III)* complex and b) the reduction of the protonated intermediate **13A** into ketyl radical **7B** (Scheme 5C). Consequently, the addition of quinuclidinium radical **OC-4A** to **12** is followed by a radical-radical coupling between **OC-4B** and **13B**. The cationic character of intermediate **OC-4D** allows the release of precatalyst **OC-4** by a β -elimination triggered by AcO⁻. Thereafter, a related strategy was applied to the C(sp²)-H bond functionalization of unactivated alkene **15** via distal heteroaryl *ipso*-migration (Scheme 6A).^[20] If the reaction is similarly initiated by the photoredox-catalyzed oxidation of **OC-4** and the addition of **OC-4A** onto olefin **15**, the subsequent steps are resolutely different (Scheme 6B). Indeed, the formation of radical adduct **OC-4E** is followed by an intramolecular radical addition onto the benzothiazole ring. The radical opening of cyclopentane **OC-4F** and the oxidation of ketyl radical **OC-4G** in the presence of phenyliodine(III)diacetate (PIDA) afford dicationic intermediate **OC-4H**. Ultimately, the deprotonation of **OC-4H** by K₂HPO₄ delivers the desired product and frees precatalyst **OC-4**. Unlike the radical MBH reaction, this transformation is not redox neutral and the photoredox catalyst is only responsible for the oxidation of the quinuclidine precatalyst. Stoichiometric amounts of terminal oxidant are then required to regenerate **PC-2**. Even if quinuclidinium radicals are hardly tunable, their use to orchestrate PC-CoRC has evident practical advantages which are the absence of dimerization of the radical catalyst, a cationic character allowing the design of original catalytic combinations and the commercial availability of quinuclidine **OC-4**.



Scheme 5. Morita-Baylis-Hillman reaction catalyzed by quinuclidinium radical cation in PC-CoRC (Shi and co-workers, 2022)

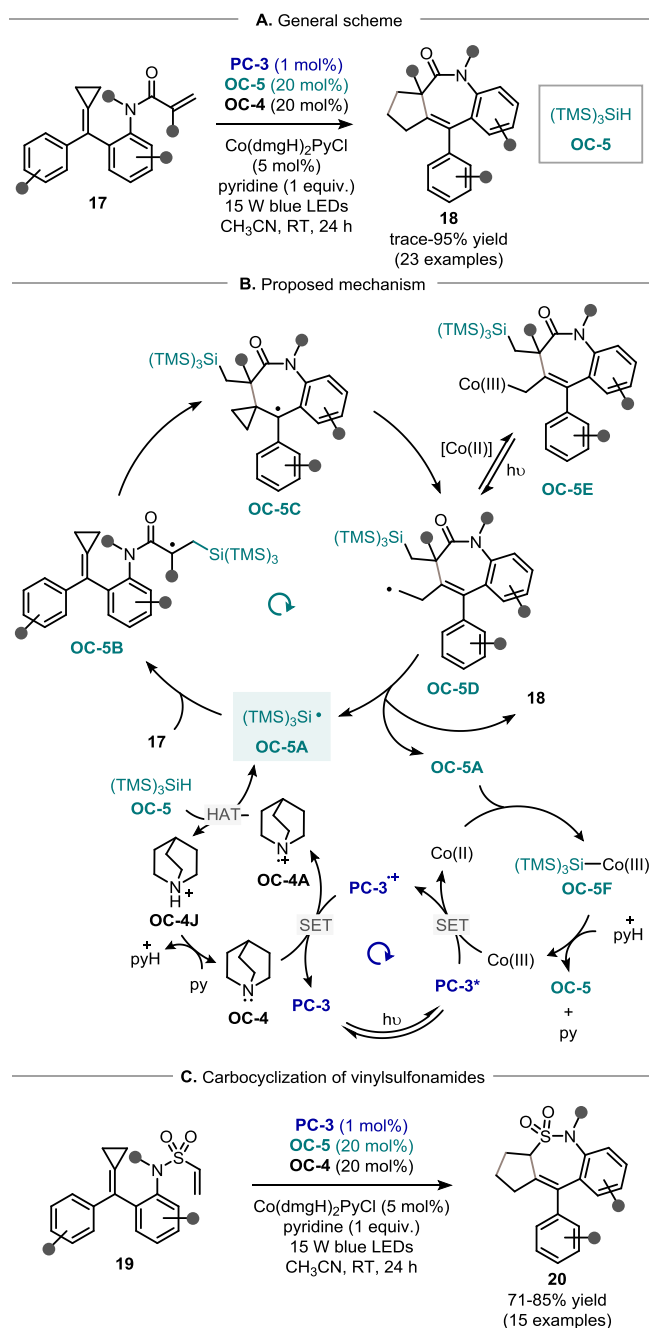


Scheme 6. Intramolecular functionalization of unactivated alkene by PC-CoRC (Shi and co-workers, 2022)

5. Silyl radical catalysis

Silyl radicals are considered as nucleophilic intermediates which preferentially add onto electron-deficient olefins. In 2021, Shi, Wei and co-workers described a carbocyclization of acrylamide-attached alkylidenecyclopropanes **17** initiated by the addition of silyl radical catalyst (Scheme 7A).^[21] The reaction proceeds under the control of a quaternary catalytic system involving **PC-3**, quinuclidine **OC-4**, a silane precatalyst **OC-5** and radical **OC-5A** is indirectly produced by photoredox catalysis. Indeed, the suggested mechanism starts with the oxidative quenching of **PC-3*** by the Co(III) species resulting in a Co(II) complex and the strong oxidant **PC-3**** (Scheme 7B). The oxidation of quinuclidine **OC-4** by **PC-3**** leads to a HAT between quinuclidinium radical **OC-4A** and the hydridic silane **OC-5**. The subsequent CoRC cycle, supported by computational experiments, involves the addition of **OC-5A** onto **17**, followed by the cyclization of electrophilic radical **OC-5B**. Homoallylic radical **OC-5D** arising from the fast cyclopropane radical **OC-5C** can be transiently trapped as the photosensitive alkyl-Co(III) complex **OC-5E** or trigger a 5-*exo tet* cyclization delivering

product **18**. The capture of **OC-5A** by Co(II) species affords silyl-Co(III) complex **OC-5F** which ultimately regenerates the two catalysts after protonation. The reported conditions were also applied with Co^{III}(dmgH)₂PyCl as a co-catalyst. In this complex system, silyl radicals succeed to convert vinyl-sulfonamides **19** into sultam-containing polycyclic compounds **20** in good yields (Scheme 7C).



Scheme 7. Carbocyclization of acrylamide-/vinyl sulfonamide-attached alkylidenecyclopropanes by PC-CoRC (Shi, Wei and co-workers, 2021)

6. Isothiuronium radical catalysis

Recently, Merad and co-workers designed a new class of cationic sulfur-centered radical catalysts generated by photoredox-catalyzed oxidation of thioureas.^[22] The diversity and the accessibility of precatalysts allow a fine tuning of the stereo-electronic properties of the corresponding isothiuronium radical catalysts. The reported binary catalytic system then provides a practical platform to optimize CoRC-based reactions. As a matter of fact, a catalyst screening revealed that *N,N,N,N*-tetrasubstituted thiourea **OC-6** is the most efficient to achieve the synthesis of vinylcyclopentanes **23** from olefins **21** and vinylcyclopropanes **22** (Scheme 8A). Mild reaction conditions including **PC-2** and blue light irradiation demonstrate a broad substrate tolerance and ensure the formation of **23** in only 4 h in MeOH. In accordance with literature precedents,^[23] cyclic voltammetry experiments have demonstrated that the oxidation of thiourea **OC-6** ($E_{\text{ox}} = +0.98$ V in MeOH *versus* SCE) in formation of dimeric species **OC-6B**. Unlike neutral disulfide, dication **OC-6B** is readily reduced back ($E_{\text{red}} = -0.51$ V in MeOH *versus* SCE) to precatalyst **OC-6** and active catalyst **OC-6A** (Scheme 8B). Consequently, the authors postulated a mechanism involving interdependent catalytic cycles involving a dual role of photoredox catalyst **PC-2**. Indeed, the photoexcited iridium complex would trigger the radical cascade by oxidizing precatalyst **OC-6** while maintaining the catalytic activity by reducing dicationic dimer **OC-6Ba** (Scheme 8C). This scenario was supported by the efficient synthesis of **23a** from styrene **21a** and vinylcyclopentane **22a** by using dimer **OC-6Bb** as a precatalyst (Scheme 8D). As an additional proof, the reaction stops as soon as the light is switched off indicating a fully photocatalyzed process.

7. Summary and Outlook

In conclusion, the emerging concept of combining visible-light photocatalysis and organocatalysis has addressed numbers of longstanding issues in CoRC. Indeed, photocatalysts have proved their efficiency in taming the generation and the reactivity of radical catalysts. By this way, the confidential field of CoRC, until recently exclusively restricted to neutral thiyl radicals, have known an extensive diversification of radical catalyst structures. The multiplicity of precatalyst scaffolds have accompanied the development of original strategies to prevent the deactivation of radical catalysts. The use of visible-light as energy source goes with mild reaction conditions and a remarkable functional group tolerance, then contributing to the real synthetic potential of PC-CoRC. For decades, the design of original transformations relying on CoRC was hampered by the necessity to release the radical catalyst by homolysis of a covalent bond. The recent description of cationic radical catalysts has provided new opportunities to solve these limitations since the precatalyst can be ultimately released by heterolytic β -elimination.

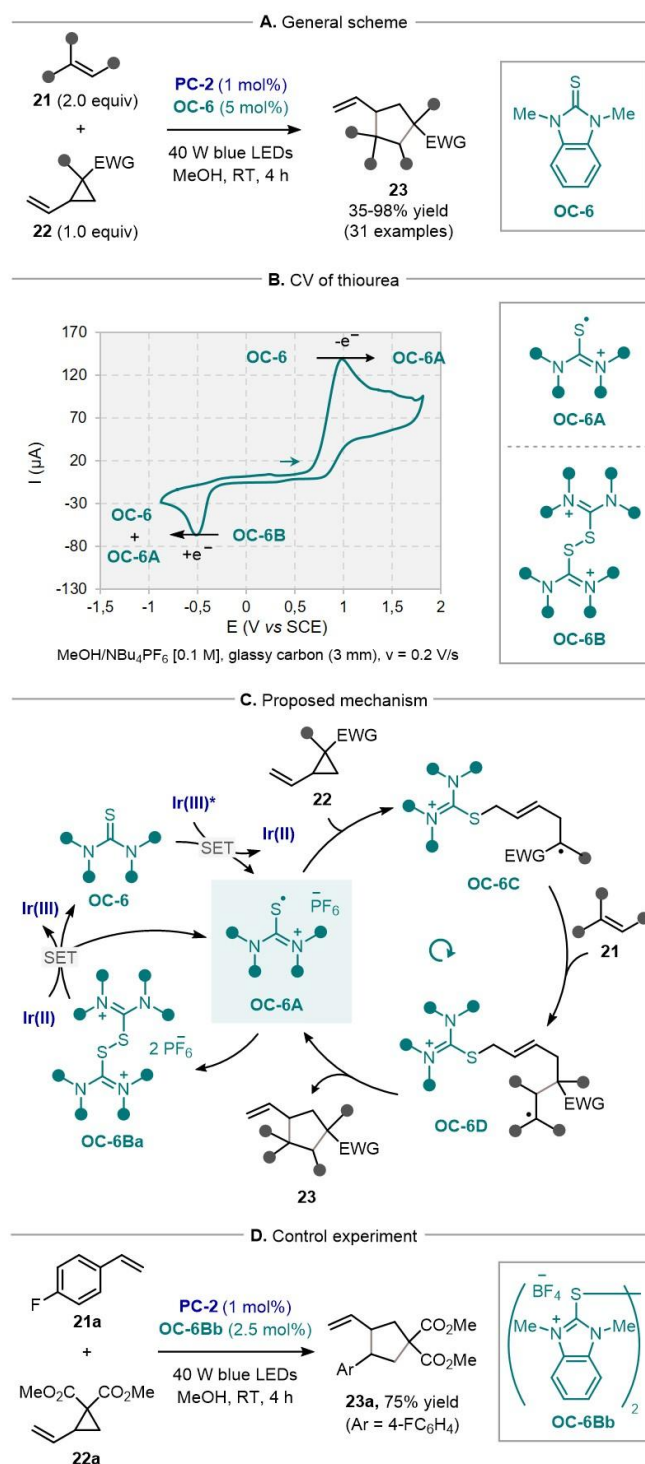
In a near future, the recent field of PC-CoRC has to build on the achievements described above to address new challenges and reach its full maturity. Indeed, some important limitations are still waiting to be knocked down. For instance, PC-CoRC is currently limited to the SOMO activation of olefins and alkynes. The photocatalytic generation of other classes of radical catalysts displaying specific properties (oxophilic, nucleophilic, dicationic) could broadly extend the scope of PC-CoRC (carbonyl, arenes and others). Also, including PC-CoRC in ternary catalytic systems with transition metal catalysts or organocatalysts would constitute a goldmine for the discovery and the design of original transformations. Finally, enantioselective versions of CoRC are extremely scarce and the design of chiral radical catalysts able to ensure enantiocontrol in such reactions has remained a longstanding challenge. In this respect, PC-CoRC could make a huge difference since a greater diversity of radical precatalysts can be used, including a range of readily available homochiral scaffolds.

In closing, we expect that this Concept article will highlight the synthetic potential of PC-CoRC and support the development of this promising but still confidential research area.

Acknowledgements

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Keywords: photocatalysis • organocatalysis • radical chemistry • covalent activation



Scheme 8. (3 + 2)-Cycloadditions between vinylcyclopropanes and alkenes catalyzed by isothiuronium radical cation in PC-CoRC (Merad and co-workers, 2022)

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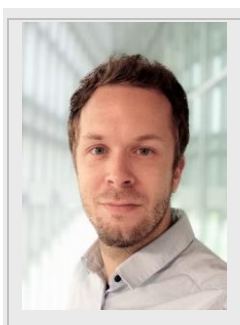
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