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Visible-light-induced alkoxy radical generation for inert chemical bond cleavage/functionalization

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Inert chemical bond cleavage and functionalization reactions provide expedient synthetic routes and are fundamental in organic synthesis. Alkoxy radicals enable inert chemical bond cleavages by hydrogen atom transfer and β -fragmentation reactivity; however their further synthetic transformations and functional group compatibility are limited by traditional alkoxy radical generation methods. Recently, visible-light-induced alkoxy radical generation methods have emerged and led to new advancements in inert chemical bond cleavage reactions and subsequent functionalization, with excellent chemoselectivity and functional group compatibility. In this Feature Article, the generation of alkoxy radicals by different visible-light-induced methods and their common or distinct reactivity are discussed, which are categorized by $C(sp^3)-H$, $C(sp^3)-C(sp^3)$, and $C(sp^3)-X$ bond cleavages and subsequent transformations.

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Introduction

The $C(sp^3)-H$ and $C(sp^3)-C(sp^3)$ bonds widely exist in organic compounds, and their intrinsic inertness with high bond energies makes their selective cleavage reactions difficult.^{1–5} To tackle this, the highly reactive alkoxy radicals provide a unique

approach with hydrogen atom transfer and β -fragmentation reactivity for inert $C(sp^3)-H$ and $C(sp^3)-C(sp^3)$ bond activations (Fig. 1a).^{6–8} However, their further synthetic transformation and functional group compatibility are limited due to the relatively harsh reaction conditions such as strong oxidants, heating, and UV light irradiation (Fig. 1b).^{9,10}

In the past decade, the visible-light-induced reactions have emerged as a powerful and mild radical initiation method with excellent chemoselectivity and potential biomolecular applications.^{11–14} However, the first visible-light-induced

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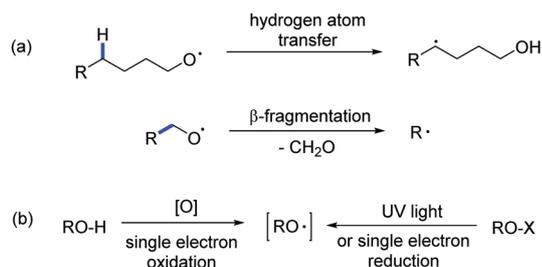


Fig. 1 The inert chemical bond cleavage by alkoxy radicals and traditional generation conditions.

alkoxy radical generation was not revealed until 2015.¹⁵ Since then, a wave of visible-light-induced alkoxy radical generation for inert chemical bond cleavage/functionalization has been reported. In this Feature Article, the common or distinct reactivity of alkoxy radicals and also different visible-light-induced generation methods are discussed, which are categorized by $C(sp^3)\text{-H}$, $C(sp^3)\text{-C}(sp^3)$, and $C(sp^3)\text{-X}$ bond cleavages and subsequent transformations.

$C(sp^3)\text{-H}$ bond cleavage/functionalization enabled by alkoxy radicals

The inert $C(sp^3)\text{-H}$ bonds without adjacent activating groups are difficult targets for selective cleavage and functionalization.^{16–18} The 1,5-hydrogen atom transfer (1,5-HAT) reaction of alkoxy radicals provides a regioselective approach for inert $C(sp^3)\text{-H}$ bond activation and the resulting alkyl radical is suitable for further functionalization (Fig. 2).¹⁰ While the 1,5-hydrogen atom transfer reaction of alkoxy radicals is considered slower than β -fragmentation in most cases, the rate constants vary significantly with different alkoxy radical structures.^{7,8}

The first report of visible-light-induced alkoxy radical generation was revealed in 2015 which enabled $C(sp^3)\text{-H}$ bond activation and intermolecular allylation/alkenylation with *N*-alkoxyphthalimides.¹⁵ The subsequent asymmetric $C(sp^3)\text{-H}$ bond Michael addition was achieved by the combination of *N*-alkoxyphthalimides with chiral Lewis acids in 2016.¹⁹ After that, the $C(sp^3)\text{-H}$ arylation and di-*tert*-butyl azodiformate addition with unprotected alcohols were accomplished using proton-coupled electron transfer (PCET) and cerium chlorides.^{20,21}

N-alkoxyphthalimides were previously reported to generate alkoxy radicals in the presence of azodiisobutyronitrile/tributyltin hydride;²² however the first attempt under photoredox catalysis conditions in 2011 only yielded aldehydes after

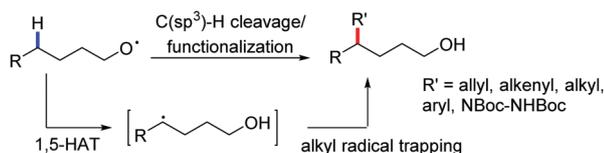


Fig. 2 The $C(sp^3)\text{-H}$ bond cleavage by alkoxy radicals for new C–C and C–N bond formation.

intramolecular fragmentation, and the alkoxy radical was not obtained (Fig. 3a).²³ In 2015, the Chen group reported the first visible-light-induced alkoxy radical generation with *N*-alkoxyphthalimides enabled by Hantzsch esters (Fig. 3b).¹⁵ The regioselective $C(sp^3)\text{-H}$ bond cleavage/functionalization was achieved by 1,5-HAT reaction of alkoxy radicals to yield the alkyl radical, followed by reaction with allyl sulfones or vinyl sulfones for intermolecular allylation/alkenylation. While the alkoxy radical generation under previous conditions enabled $C(sp^3)\text{-H}$ bond activation, the trapping of the alkyl radical for intermolecular C–C bond formation is difficult and limited.^{24–27}

The photocatalytic system is initiated by the photoexcitation of *fac*-Ir(ppy)₃ to generate Ir(III)*, which is reduced by Hantzsch ester to yield Ir(II) (Fig. 3c). The Ir(II) undergoes single-electron transfer with *N*-alkoxyphthalimides to yield the *N*-alkoxyphthalimide radical anion, which is further protonated by the Hantzsch ester radical cation to facilitate the alkoxy radical formation. The protonation of the *N*-alkoxyphthalimide radical anion is similar to the coordination by tributyltin in the AIBN/Bu₃SnH system to prevent the intramolecular fragmentation. Finally, the alkoxy radical undergoes 1,5-HAT reaction and subsequent intermolecular alkyl radical trapping to yield the C–C bond formation adduct. The reaction mechanism is further supported by the reaction of 1-naphthalene-substituted *N*-alkoxyphthalimide

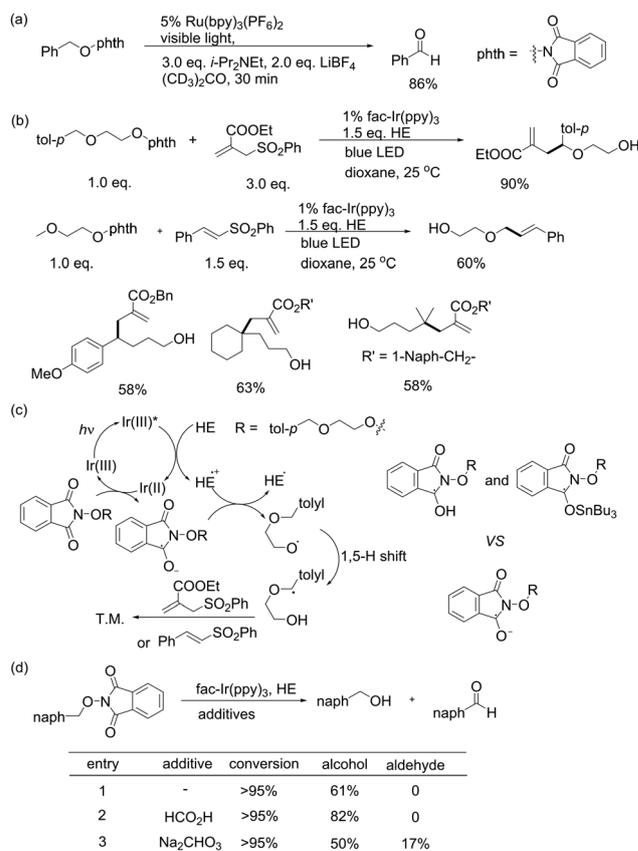


Fig. 3 The $C(sp^3)\text{-H}$ bond cleavage and allylation/alkenylation by Hantzsch ester.

without δ -C(sp³)-H bonds (Fig. 3d). In the absence of radical acceptors, 1-naphthalenylmethanol was obtained as the hydrogenation adduct. When formic acid was added, the yield of 1-naphthalenylmethanol was increased to 82%. When sodium carbonate was added, the yield of 1-naphthalenylmethanol was decreased to 50%, and 1-naphthaldehyde derived from intramolecular fragmentation was observed in 17% yield.²³ In the photoredox system, the Hantzsch ester is crucial for both the electron transfer and proton transfer of the reaction.

In 2016, the Meggers group reported the first asymmetric C(sp³)-H bond Michael addition by combining 1,5-HAT reaction from visible-light-induced alkoxy radical generation with catalytic asymmetric C-C bond formation (Fig. 4a).¹⁹ The alkoxy radical was generated by *N*-alkoxyphthalimides facilitated by Hantzsch ester, and the authors ingeniously used *N,O*-rhodium-coordinated *N*-acylpyrazole substrates for asymmetric Michael addition (Fig. 4b).²⁸ The observed high enantioselectivity demonstrates that the chiral Lewis acid is compatible with visible-light-induced alkoxy radical generation conditions and accelerates the radical addition to outcompete the prevailing racemic background reaction. It is worth noting that *N*-acylpyrazoles are useful precursors for converting to other functionalities such as amides and diols (Fig. 4c).

In 2017, the Zhu group reported C(sp³)-H bond heteroarylation guided by tertiary alcohols (Fig. 5a).²⁰ The use of Ir[dF(CF₃)ppy]₂-(dtbbpy)PF₆ as the photocatalyst and persulfates as the oxidant enabled alkoxy radical generation from tertiary alcohols. The photocatalytic system is initiated by the photooxidation of alcohols to yield alkoxy radicals, though the exact oxidative species was not specified (Fig. 5b). After the 1,5-HAT reaction, the resulting alkyl radical undergoes *ipso*-addition to the heterocycle, which yields the C(sp³)-H bond heteroarylation

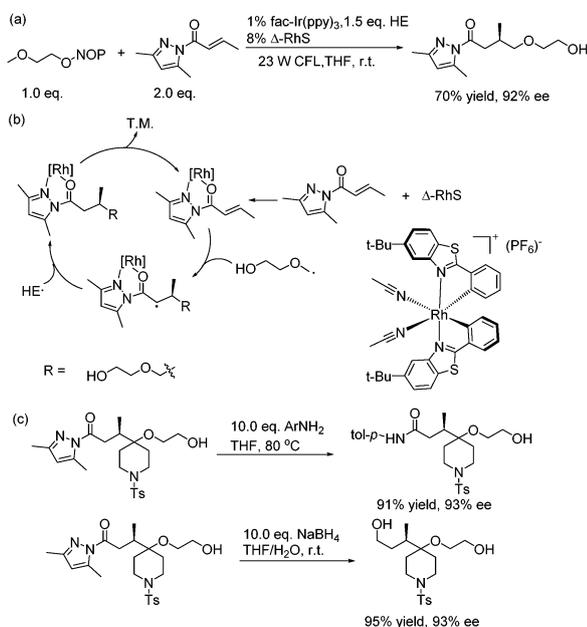


Fig. 4 The asymmetric C(sp³)-H bond cleavage and Michael addition by chiral Lewis acids.

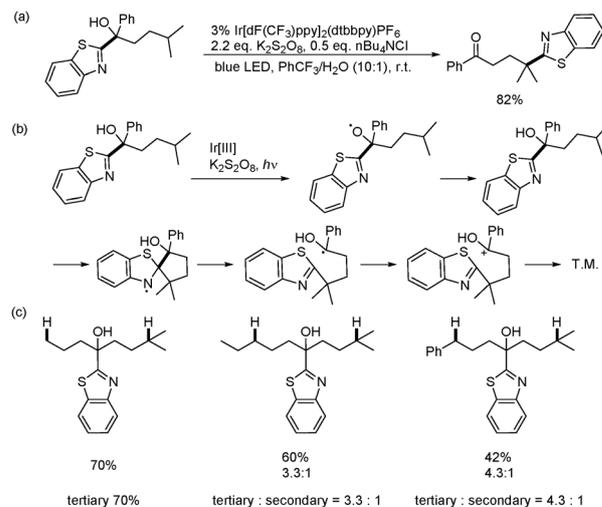


Fig. 5 The C(sp³)-H bond cleavage and aryl migration by PCET.

adduct after the heteroaryl migration and oxidative elimination.²⁹ The reactivity order of different C(sp³)-H bonds (tertiary C(sp³)-H > secondary C(sp³)-H \approx benzylic > primary C(sp³)-H) agrees with the relative bond dissociation energies (BDE) (Fig. 5c).

In 2018, the Zuo group reported the C(sp³)-H bond cleavage and C-N bond formation of alcohols with a coordination-LMCT-homolysis mechanism (Fig. 6a).²¹ Using CeCl₃ as the photocatalyst, the alkoxy radical generation is enabled by primary, secondary, and tertiary alcohol oxidation for the first time. The reaction is initiated by the formation of the alkoxy-Ce(III)Ln complex, which is oxidized by the nitrogen radical to the alkoxy-Ce(IV)Ln complex (Fig. 6b).³⁰⁻³² The homolysis of alkoxy-Ce(IV)Ln under visible light irradiation provides the alkoxy radical and recovers Ce(III)Ln. The alkyl radical from the 1,5-HAT reaction of alkoxy radicals undergoes

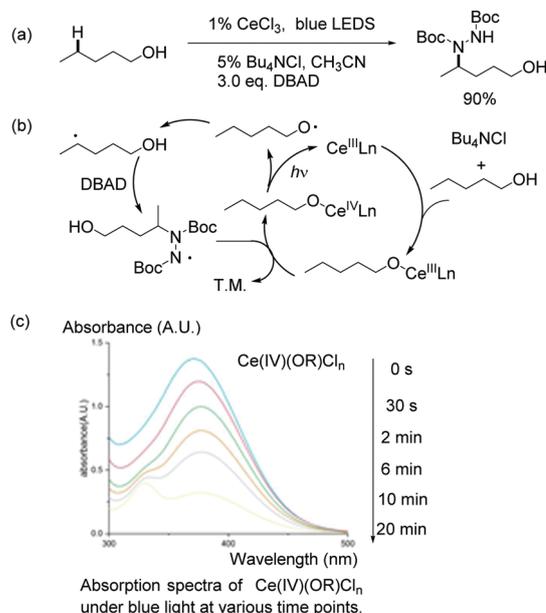


Fig. 6 The C(sp³)-H bond cleavage and C-N bond formation by Ce(III).

radical addition to di-*tert*-butyl azodiformate (DBAD) to yield the nitrogen radical, which subsequently oxidizes alkoxy-Ce(III)Ln and yields the C–N bond formation adduct. The absorption spectra of the alkoxy-Ce(IV)Ln complex overlap with blue LED, and the increase of absorbance in the 360–370 nm range in the first 30 minutes suggests the build-up of catalytic quantities of Ce(IV), which gradual shift to $\lambda_{\text{max}} = 330$ nm upon irradiation indicated the photoinduced homolysis to generate alkoxy-Ce(III)Ln (Fig. 6c).

C(sp³)–C(sp³) bond cleavage/functionalization enabled by alkoxy radicals

The regioselective and chemoselective cleavage of inert C(sp³)–C(sp³) bonds is difficult but very valuable for expedient synthesis.^{33–35} The β -fragmentation of alkoxy radicals provides a unique approach to generate the alkyl radical with C(sp³)–C(sp³) bond cleavage and the alkyl radicals are suitable for further transformations (Fig. 7).^{7,8} Under the traditional alkoxy radical generation methods such as by using silver salts, persulfates, or manganese acetates, the ring-opening C(sp³)–C(sp³) bond cleavage of strained cycloalkanols has been accomplished; however the application of unstrained linear alcohols has not been reported.^{36–41}

The first report of visible-light-induced C(sp³)–C(sp³) bond cleavage of cycloalkanols/linear alcohols and subsequent alkylation/alkenylation was presented in 2016 by using cyclic iodine(III) reagents.⁴² Afterwards, the C(sp³)–C(sp³) bond cleavage and hydrogenation of alcohols was enabled by the proton-coupled electron transfer approach, and C(sp³)–C(sp³) bond cleavage and di-*tert*-butyl azodiformate addition of cycloalkanols was fulfilled by the cerium chloride method.^{43,44} In 2017, the first metal-free alkoxy radical generation enabled C(sp³)–C(sp³) bond cleavage and allylation/alkenylation with a donor–acceptor complex approach using *N*-alkoxyphthalimides and Hantzsch esters.⁴⁵

In 2016, the Chen group reported the first visible-light-induced alkoxy radical generation from alcohol oxidation by cyclic iodine(III) reagents (Fig. 8a).⁴² The selective C(sp³)–C(sp³) bond cleavage/functionalization is realized by β -fragmentation of alkoxy radicals to yield the alkyl radical, followed by reaction with alkynyl benziodoxoles or vinyl carboxylates for alkylation/alkenylation. The reaction is initiated by the oxidation of the photoexcited Ru(II)* to Ru(III) with acetoxyl benziodoxoles (BIOAc) or its resulting benziodoxole radical (Fig. 8b).⁴⁶ The Ru(III) then oxidizes the cyclic iodine(III)-coordinated hydroxylate

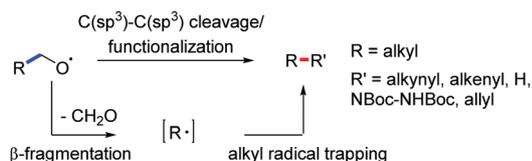


Fig. 7 The C(sp³)–C(sp³) bond cleavage by alkoxy radicals for new C–C, C–H, and C–N bond formation.

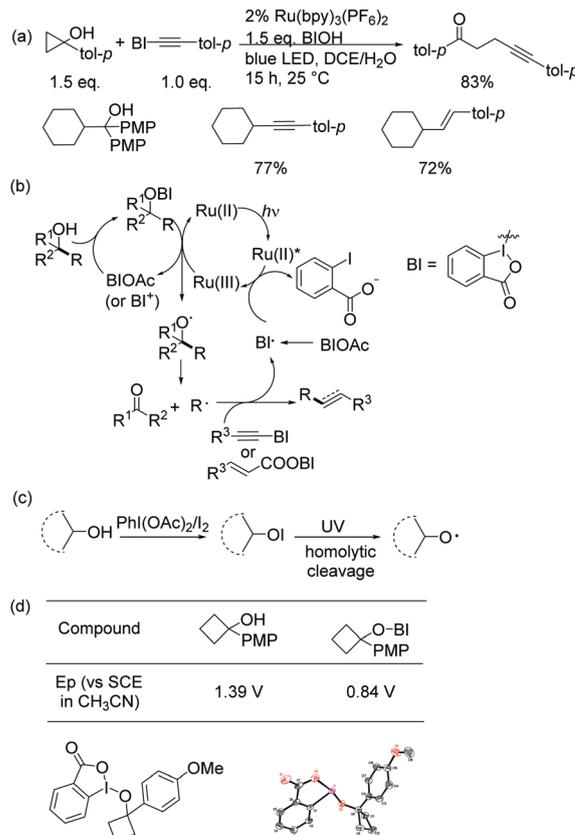


Fig. 8 The C(sp³)–C(sp³) bond cleavage and alkylation/alkenylation by cyclic iodine(III) reagents (CIR).

complex formed *in situ* to generate the alkoxy radical, which then undergoes β -fragmentation to yield the alkyl radical for subsequent alkylation/alkenylation.

In previously reported methods using iodine and iodoso-benzene diacetate (PhI(OAc)₂) for alkoxy radical generation, the *in situ* formed iodine(I)-bound hydroxylate from alcohols undergoes homolytic I–O bond cleavage upon UV light irradiation or heating to yield the alkoxy radical (Fig. 8c).⁹ In this reaction, the formation of the cyclic iodine(III)-coordinated hydroxylate complex significantly decreased the oxidation potential of the cyclobutanol from 1.39 V to 0.84 V (vs. SCE in MeCN), and facilitated the electron transfer for alcohol oxidation (Fig. 8d). Various strained cycloalkanols, and for the first time linear alcohols, underwent the selective C(sp³)–C(sp³) bond cleavage and intermolecular C–C bond formation reactions.^{47,48}

In 2016, the Knowles group reported the visible-light-induced alkoxy radical generation by direct homolytic activation of the alcohol O–H bond for the first time (Fig. 9a).⁴³ The C(sp³)–C(sp³) bond cleavage of cycloalkanols by alkoxy radicals yielded the alkyl radical for subsequent ring-opening hydrogenation. The reaction is initiated by the electron-rich arene oxidation with Ir(III)* to a radical cation, whose one-electron reduction in concert with Brønsted base catalyst enabled the alkoxy radical generation due to the intramolecular PCET reaction (Fig. 9b).^{49,50} The subsequent β -fragmentation of the alkoxy radical yields the alkyl radical, which is trapped by thiophenol to yield the

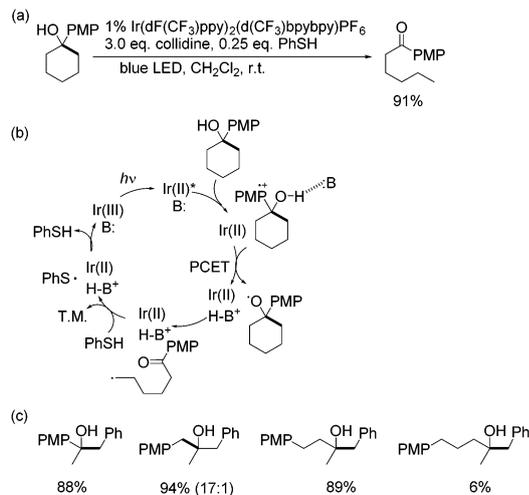


Fig. 9 The $C(sp^3)-C(sp^3)$ bond cleavage and hydrogenation by PCET.

hydrogenation adduct. The electron-rich arene and the hydroxyl group can be distanced by one to three carbon atoms (Fig. 9c).

In 2016, the Zuo group reported the visible-light induced alcohol oxidation to generate alkoxy radicals by $CeCl_3$ catalysis (Fig. 10a).⁴⁴ This methodology represents the first example of application of unstrained secondary cycloalkanols for $C(sp^3)-C(sp^3)$ bond cleavage and functionalization under visible light irradiation. The reaction is initiated by the photoexcitation of the alkoxy- $Ce(III)Ln$ complex formed *in situ* [alkoxy- $Ce(III)Ln$]^{*}, which is subsequently oxidized by the nitrogen radical to the alkoxy- $Ce(IV)Ln$ complex (Fig. 10b).^{30–32} The decomposition of alkoxy- $Ce(IV)Ln$ provides the alkoxy radical, which then undergoes β -fragmentation to yield the alkyl radical to react with di-*tert*-butyl azodiformate (DBAD). While $CeCl_3$ and the alkoxy- $Ce(III)Ln$

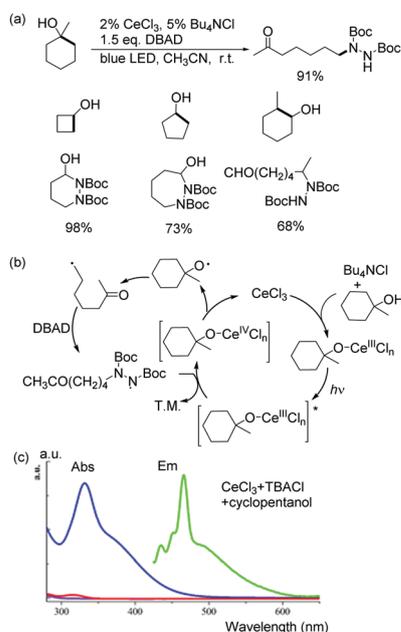


Fig. 10 The $C(sp^3)-C(sp^3)$ bond cleavage and $C-N$ bond formation by $Ce(III)$.

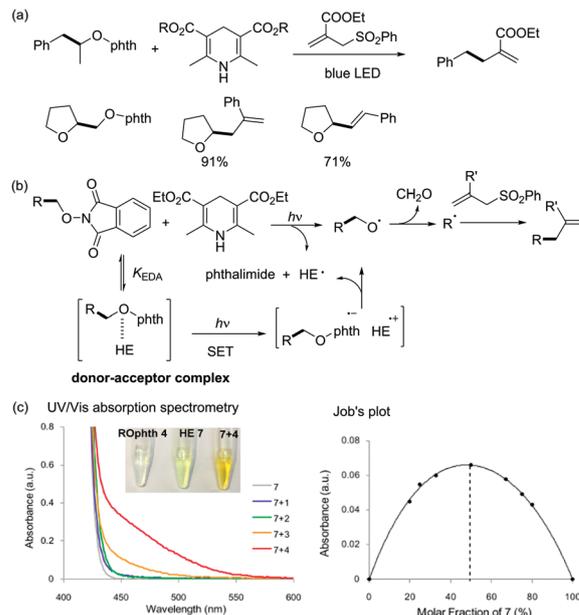


Fig. 11 The $C(sp^3)-C(sp^3)$ bond cleavage and allylation by the donor-acceptor complex.

complex only exhibit weak absorption in the 300–400 nm range, the addition of extraneous chlorides induces absorption up to 470 nm, which suggests that the extraneous chlorides lead to more efficient photoexcitation for catalytic efficiency (Fig. 10c).

In 2017, the Chen group reported the first donor-acceptor complex-enabled alkoxy radical generation under metal-free reaction conditions induced by visible light (Fig. 11a).⁴⁵ Selective $C(sp^3)-C(sp^3)$ bond cleavage and allylation/alkenylation was demonstrated using this photocatalyst-free approach with primary, secondary, and tertiary alkoxy radicals for the first time. The reaction is initiated by the formation of the donor-acceptor complex between Hantzsch esters and *N*-alkoxyphthalimides *in situ*, which leads to red-shift to the visible light absorption (Fig. 11b).^{51,52} After visible-light-induced electron transfer, the *N*-alkoxyphthalimide radical anion is formed and eliminates phthalimides to generate the alkoxy radical. The resulting alkoxy radical undergoes β -fragmentation to yield the alkyl radical and is trapped by allyl or vinyl sulfones for radical allylation/vinylation. The UV/Vis absorption experiments suggest red-shifts of the donor-acceptor complex, and the Job's plot indicates 1:1 ratio of Hantzsch esters and *N*-alkoxyphthalimides for donor-acceptor complex formation (Fig. 11c).

$C(sp^3)-X$ bond cleavage/functionalization enabled by alkoxy radicals

The selective cleavage of inert $C(sp^3)-X$ ($X \neq H$ or $C(sp^3)$) bonds is an unusual reactivity of alkoxy radicals. Traditional generation of β -carbonyl alkoxy radicals requires the addition of the alkyl radical to diketones or the homolytic cleavage of the peroxide bonds, while the formation of α -phosphorus alkoxy

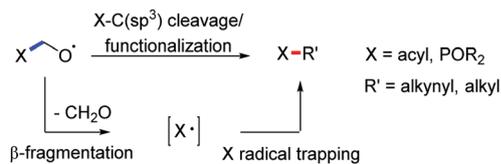


Fig. 12 The C(sp³)-X bond cleavage by alkoxy radicals for new X-C bond formation.

radicals requires intramolecular alkyl radical addition to acylphosphine oxides.⁵³⁻⁵⁵ In addition, the β-fragmentation of alkoxy radicals to yield X (X = acyl or POR₂) radicals for subsequent X-C bond formation has not been achieved by traditional alkoxy radical generation methods (Fig. 12).^{7,8} With the mild radical initiation conditions induced by visible light, the underexplored reactivity of alkoxy radicals for C(sp³)-X bond cleavage/functionalization is revealed. The first report of C(sp³)-X bond cleavage by cyclic iodine(III) reagents for C(sp³)-carbonyl cleavage and alkylation from β-carbonyl alcohols was presented in 2017.⁵⁶ In 2018, the first C(sp³)-P bond cleavage and alkylation/Michael addition from α-phosphorus alcohols was reported.⁵⁷

In 2017, the Chen group reported the first C(sp³)-carbonyl bond cleavage/alkynylation reaction by alkoxy radicals with photoredox catalysis (Fig. 13a).⁵⁶ The β-amide, β-ester, and β-ketone alcohols yielded ynamides, ynoates, and ynones, respectively, for the first time, with excellent regio- and chemo-selectivity under mild reaction conditions. The use of novel cyclic iodine(III) reagents (CIR) is essential for β-carbonyl

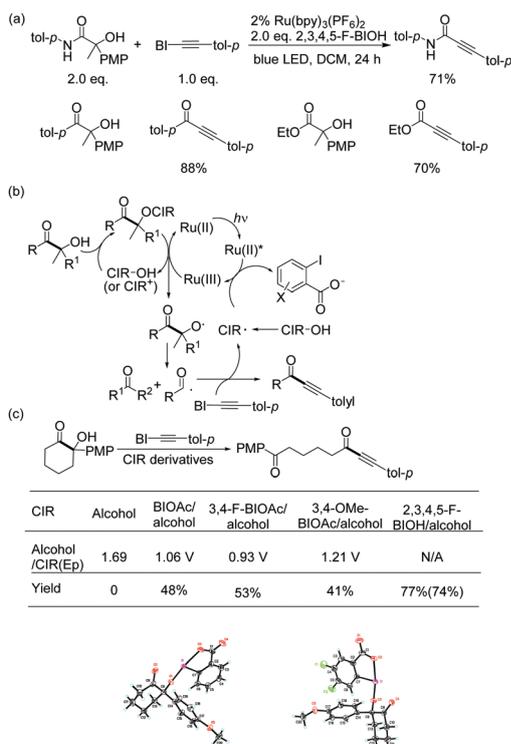


Fig. 13 The C(sp³)-carbonyl bond cleavage and alkylation by cyclic iodine(III) reagents.

alkoxy radical generation from β-carbonyl alcohols. The reaction is initiated by the oxidation of the photoexcited Ru(II)* to Ru(III) by either the CIR or its decomposing CIR radical adduct (Fig. 13b). The Ru(III) then oxidizes the β-carbonyl alcohol/CIR complex formed *in situ* and releases the CIR cation (CIR⁺) for the new CIR catalytic cycle. The alkoxy radical undergoes β-C(sp³)-carbonyl bond cleavage reaction to yield the carbamoyl, alkoxy-carbonyl, or acyl radical, and finally forms ynamides, ynoates, or ynones by radical addition to alkynyl benziiodoxoles.^{53,54} The electron-deficient benziiodoxoles are beneficial for the reaction due to (i) the decreased oxidation potential of the cyclic iodine(III) reagent-alcohol complex, and (ii) the increased oxidative quenching efficiency for photoexcited Ru(II)* (Fig. 13c).

In 2018, the Chen group reported the first C(sp³)-P bond cleavage reaction by alkoxy radicals with dual photoredox/CIR catalysis (Fig. 14a).⁵⁷ Various α-phosphorus alcohols including arylphosphinoyl, alkylphosphinoyl, phosphonate, and phosphonic amide alcohols undergo C(sp³)-P bond cleavage and radical alkylation to generate phosphonoalkynes.⁵⁵ The reaction is initiated by the formation of the benziiodoxole/α-phosphorus alcohol complex *in situ*, which yields the alkoxy radical upon oxidation by Ru(III). The alkoxy radical undergoes C(sp³)-P bond cleavage to yield the phosphorus radicals including the previously inaccessible phosphonic diamide radicals, and further undergoes radical α-addition to the alkynyl benziiodoxole to yield the phosphonoalkyne for the first time. Acylphosphine oxide or H-phosphonate is not reactive under the reaction conditions, which suggests that they are not reaction intermediates of the reaction (Fig. 14c). In addition, the unreactive hydroxyl-protected α-diarylphosphinoyl alcohol suggests the critical role of the CIR coordination to the free hydroxyl group.

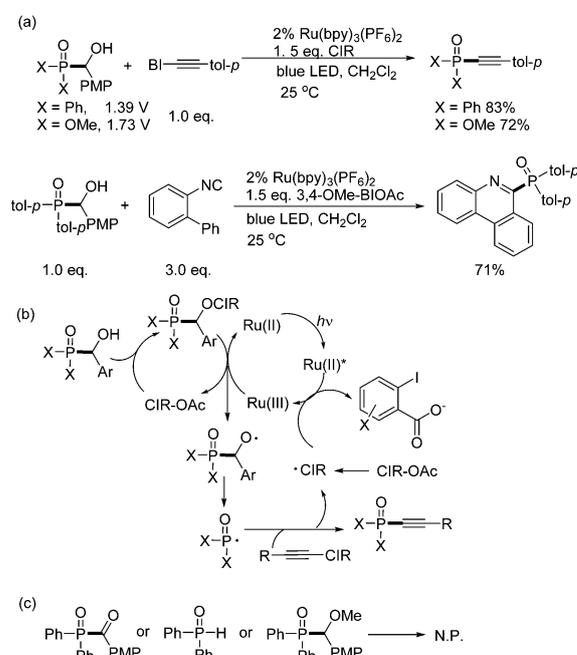


Fig. 14 The C(sp³)-phosphorus bond cleavage and alkylation by cyclic iodine(III) reagents.

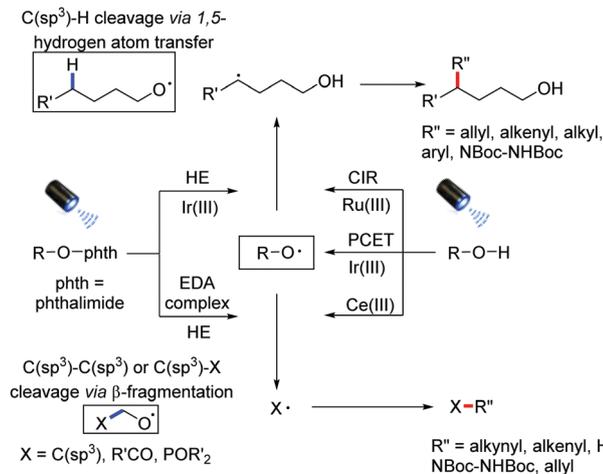


Fig. 15 Summary of visible-light-induced alkoxy radical generation methods and reactivity.

Conclusion

N-alkoxyphthalimides and unprotected alcohols have been reported to generate alkoxy radicals under visible-light-induced reaction conditions (Fig. 15). The *N*-alkoxyphthalimides undergo single electron reduction by photoredox catalysis or the donor-acceptor complex formation for alkoxy radical generation, in which the Hantzsch ester plays critical roles in both processes. The alcohols undergo single electron oxidation by photoredox catalysis facilitated by cyclic iodine(III) reagents, proton-coupled electron transfer mechanism, or cerium chlorides to yield alkoxy radicals. Compared with traditional alkoxy radical generation methods, the visible-light-induced methods do not require strong oxidants, heating or UV light irradiation, and bring excellent chemoselectivity and functional group compatibility.

The inert C(sp³)-H, C(sp³)-C(sp³), and C(sp³)-X bond cleavage/functionalization is enabled by alkoxy radicals under visible-light-induced conditions with 1,5-hydrogen atom transfer or β-fragmentation reactivity. The alkyl radicals resulting from C(sp³)-H or C(sp³)-C(sp³) bond cleavage undergo allylation, alkenylation, alkynylation, hydrogenation, arylation, or addition to di-*tert*-butyl azodiformates resulting in new bond formation. The acyl or phosphorus radical resulting from C(sp³)-X bond cleavage undergoes X-C bond formation which is unknown with previous alkoxy radical generation methods. With the emerging reports on different visible-light-induced alkoxy radical generation methods and reactivity, we envision that exciting new results on novel inert chemical bond cleavage/functionalization by alkoxy radicals will be forthcoming soon.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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