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Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations

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1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) is a typical donor–acceptor fluorophore, with carbazolyl as an electron donor and dicyanobenzene as an electron acceptor. It has emerged as a powerful organophotocatalyst since 2016. Excellent redox window, good chemical stability and broad applicability make 4CzIPN an attractive metal-free photocatalyst. In this review, the recent advances of the application of 4CzIPN as a photoredox catalyst in the past three years (2016–2018) for various organic reactions are summarized.

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1. Introduction

From the standpoint of green and sustainable chemistry, the development of clean, economical and efficient chemical processes has attracted extensive interest from both academia

and industry.¹ Over the past few decades, radical chemistry has emerged as a powerful tool for the rapid construction of complicated organic molecules due to the formation of versatile open shell reactive species.² Accordingly, a plethora of methods could be applied to trigger radical reactions, such as thermolysis, radiation, photolysis, electrolysis and redox systems.³ Among these strategies, photocatalysis has been regarded as one of the most clean and promising methods, which has been extensively applied in radical chemistry.⁴ In particular, the past few years have witnessed the significant renaissance of photocatalysis in the field of organic chemistry since the pioneer works reported by MacMillan⁵ and Yoon⁶ in 2008. Despite the classic photoredox catalysts like ruthenium and iridium polypyridyl complexes displaying tremendous potential in organic synthetic chemistry,⁷ inexpensive and transition-metal-free organic photocatalysts also revealed extensive utilities. Notably,

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Scheme 1 Structure of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).

recent reviews on organic photoredox catalysis have summarized the synthetic applications of Eosin Y, 9-mesityl-10-methylacridinium ions, and other organic dyes.⁸ Recently, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was found to be a versatile photocatalyst for various reactions (Scheme 1). As this is a fast-growing field, a summary of 4CzIPN for organic transformation is highly desired. In this article, the recent trend of using 4CzIPN as a visible-light photocatalyst in organic synthesis is reviewed.

2. Properties of 4CzIPN

The family of carbazolyl dicyanobenzenes (CDCBs), with carbazolyl (Cz) as an electron donor and dicyanobenzene as an electron acceptor, were first reported as highly efficient light harvesters for organic light-emitting diodes by Adachi and co-workers in 2012.⁹ Among these, 4CzIPN is one of the most promising compounds for photocatalysis. As shown in Fig. 1, the carbazolyl groups are



Fig. 1 (A) HOMOs of 4CzIPN; (B) LUMOs of 4CzIPN; (C) UV-visible and photoluminescence spectra of 4CzIPN. Reprinted in part with permission from ref. 9a. Copyright 2012 Springer Nature Publishers Limited.

remarkably distorted from the dicyanobenzene ring with a large dihedral angle of about 60° due to the steric hindrance. Density functional theory (DFT) calculations reveal that the highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) of 4CzIPN are localized on the donor moiety Cz and acceptor moiety dicyanobenzene, respectively (Fig. 1A and B). The separated HOMOs and LUMOs give rise to a small energy gap (ΔE_{ST}) between S_1 and T_1 states. Consequently, the non-overlapping frontier molecular orbitals (FMOs) make 4CzIPN an efficient thermally activated delayed fluorescence (TADF) material. More importantly, the spatially separated HOMOs and LUMOs allow an independent fine tuning of both orbitals through the modification of both the electron donor and electron acceptor moieties of the cyanobenzene scaffold, by which their photophysical and electrochemical properties can be tuned for specific catalytic purposes.¹⁰

In addition, the ultraviolet-visible absorption spectrum and the photoluminescence spectrum of 4CzIPN in toluene are presented in Fig. 1C, suggesting a maximum emission at 507 nm. Importantly, a high photoluminescence quantum yield (up to 94.6%) and a long life-time in the excited state (5.1 μ s) were observed. The photoredox potentials of 4CzIPN were also reported^{9a,11} (see Table 1).

Photocatalysts such as organic dyes (e.g., Eosin Y, Rose Bengal) and polypyridyl complexes (e.g., *fac*-Ir(ppy)₃, [Ir(dF(CF₃))₂(dtbbpy)](PF₆), and [Ru(bpy)₃](PF₆)₂) have found tremendous applications for photocatalytic transformations in recent decades. These compounds are excellent photocatalysts for various organic transformations. They are poor single-electron oxidants/reductants in the ground states; however, the excited states under visible-light irradiation are potent single electron transfer reagents. Generally, wide redox potential windows, long-lived excited states, and high fluorescence quantum yields of the photocatalysts might be beneficial to their catalytic activities.

As summarized in Table 1, the redox potentials and excited state lifetime of the above-mentioned photocatalysts were compared with those of 4CzIPN. Despite being an inexpensive organic molecule, 4CzIPN shares several common photophysical features with Ru- and Ir-polypyridyl catalysts such as long excited state lifetime, wide redox window, and high fluorescence quantum yield. For example, 4CzIPN bears both oxidation and reduction potentials similar to that of the Ir-catalyst [Ir(dF(CF₃))₂(dtbbpy)](PF₆), rendering it a highly desirable photocatalyst.

Table 1 Comparison of the redox potentials and excited state lifetime of common photocatalysts^a

Name	$E_{1/2}(P^+/P^*)$ (V)	$E_{1/2}(P^*/P^-)$ (V)	$E_{1/2}(P^+/P)$ (V)	$E_{1/2}(P/P^-)$ (V)	τ (μ s)	Ref.
4CzIPN	-1.04	+1.35	+1.52	-1.21	5.1	9a
EY	-1.11	+0.83	+0.78	-1.06		8c
RB	-0.99	+0.66	+0.78	-1.11		12
Ir-1	-1.73	+0.31	+0.77	-2.19	1.9	13
Ir-2	-0.89	+1.21	+1.69	-1.37	2.3	14
Ru-1	-0.81	+0.77	+1.29	-1.33	1.1	15

^a All potentials are given in volts *versus* the saturated calomel electrode (SCE). Measurements were performed in acetonitrile at room temperature. EY = Eosin Y. RB = Rose Bengal. Ir-1 = *fac*-Ir(ppy)₃. Ir-2 = [Ir(dF(CF₃))₂(dtbbpy)](PF₆). Ru-1 = [Ru(bpy)₃](PF₆)₂. τ = excited state lifetime.

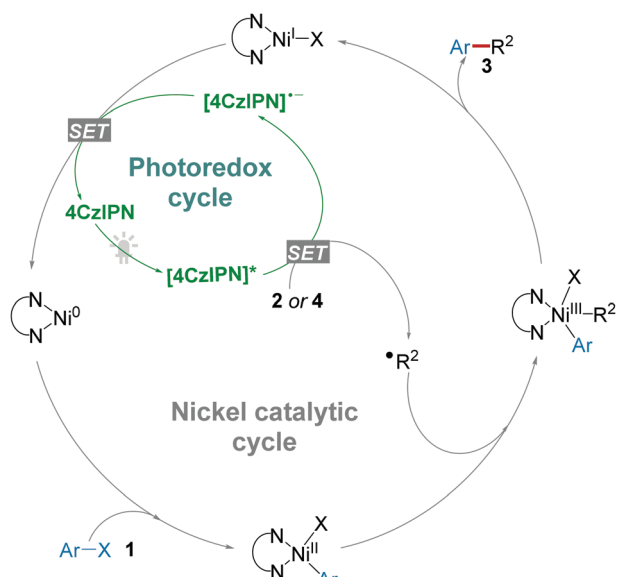
Moreover, the redox properties of 4CzIPN analogues could also be easily tuned by deliberate molecular design and modifications of the electron donor and acceptor moieties according to the established structure–property relationships.^{10b} Overall, the above-mentioned unique properties make 4CzIPN not only a metal-free alternative to transition metal photocatalysts but also an irreplaceable powerful photocatalyst in modern synthesis.

3. 4CzIPN/metal (Ni or Pd) dual-photoredox systems

3.1 4CzIPN in radical generation and metal catalyst regeneration

The application of 4CzIPN as a photocatalyst for organic reactions just started in 2016 by Zhang and co-workers.¹¹ For the energetically demanding photoredox/Ni dual catalytic decarboxylative arylation, the suggested reaction mechanism (Scheme 2) revealed that a photocatalyst with high oxidative potential ($>+1.1$ V) was necessary for the generation of reactive radical $\cdot R^2$ via a single electron transfer (SET) from the precursors like carboxylic acids **2**, alkyltrifluoroborates **4**, silicates **8**, and glyoxylic acid monohydrate **14**, *etc.*¹⁶ On the other hand, reduced photocatalyst $[4CzIPN]^{*-}$ underwent a SET to regenerate the Ni(0) catalyst species. Accordingly, reactions following this general mechanism will be summarized in this section.

Given that the reductive potential of photoexcited 4CzIPN ($[4CzIPN]^*$) is +1.35 V (*vs.* SCE), while the oxidative potential of amino acid *N*-*tert*-butoxycarbonyl-proline (*N*-Boc-pro) is +0.95 V (*vs.* SCE), it should be feasible for $[4CzIPN]^*$ to obtain an electron from *N*-Boc-pro. After the evaluation of rationally designed CDCB-based donor–acceptor (D–A) fluorophores, 4CzIPN was demonstrated to be a stable and active photoredox catalyst for the photoredox/Ni dual catalytic decarboxylative arylation of aryl



Scheme 2 The proposed mechanism of photoredox/Ni dual catalytic decarboxylative arylation.

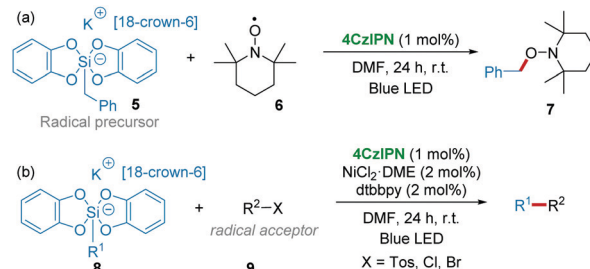


Scheme 3 4CzIPN/Ni catalyzed arylation of aryl halides with carboxylic compounds and alkyltrifluoroborates.

halides **1** and carboxylic compounds **2** (Scheme 3a) and cross-coupling of alkyltrifluoroborates **4** with aryl halides (Scheme 3b) under light irradiation from a compact fluorescence lamp (CFL).

Subsequently in 2016, the group of Ollivier and Fensterbank¹⁷ found that the photooxidation of benzyl bis(catecholato)silicates **5** ($E_{1/2}(\text{Ox/red}) = +0.3$ to $\sim +0.9$ V *vs.* SCE) with 4CzIPN ($E_{1/2}([4CzIPN]^*/[4CzIPN]^{*-}) = +1.35$ V *vs.* SCE) was possible to generate benzyl radical, which could be trapped by TEMPO **6** (2,2,6,6-tetramethyl-1-piperidinyloxy) affording **7** under the irradiation of blue LED light (Scheme 4a). Therefore, a 4CzIPN/Ni dual-catalytic system was applied for the reaction of various alkyl bis(catecholato)silicates **8** as radical precursors with radical acceptors **9** such as allylsulfones, alkenyl halides, β -bromostyrene, *etc.* (Scheme 4b).

Having known that aryl–Ni^{II} complexes, formed from aromatic halides and nickel catalysts (Scheme 2), are good radical acceptors for the *in situ* generated radicals from carboxylic acids, alkyltrifluoroborates, and silicates, some other approaches were also developed by using the 4CzIPN/Ni system for the construction of C–C bonds. For instance, Molander's group reported that the 4CzIPN/Ni dual-catalytic system could be utilized in the synthesis of natural and unnatural flavanones **12** from trifluoroboratochromanones **11** with aryl and heteroaryl bromides **10** under



Scheme 4 4CzIPN/Ni catalyzed arylation of aryl halides with silicates.

Highlight



Scheme 5 4CzIPN/Ni catalyzed arylation of aryl bromides with trifluoroborates.

mild conditions (weak base, ambient temperature, and visible-light) (Scheme 5).¹⁸

Moreover, glyoxylic acid monohydrate **14** was successfully applied as a formyl radical precursor *via* photoinduced decarboxylation, which then coupled with aryl iodides/bromides **13** to synthesize various arene and heteroarene carbaldehydes **15** under the dual catalysis of 4CzIPN/Pd (Scheme 6).¹⁹ A plausible reaction mechanism was proposed, which is similar to the mechanism of the 4CzIPN/Ni system shown in Scheme 2. This procedure provides a practical method for the construction of aryl aldehydes under mild conditions.

In 2017, Mariano and Wang *et al.*²⁰ demonstrated that readily available 2,2-diethoxyacetic acid **16** has a low oxidative potential (+0.95 V vs. SCE, Cs salt of **16** in CH₃CN), which should be a promising radical precursor in the presence of photoexcited 4CzIPN ([4CzIPN]*). Furthermore, studies established a formylation of organic (pseudo)halides with **16** as a radical precursor to generate $\cdot\text{CH}_2(\text{OEt})_2$ radical **18** by the catalysis of the 4CzIPN/Ni dual-catalytic system under the irradiation of blue LED light (Scheme 7a). As shown in the proposed mechanism



Scheme 6 4CzIPN/Pd catalyzed formylation of aryl halides.

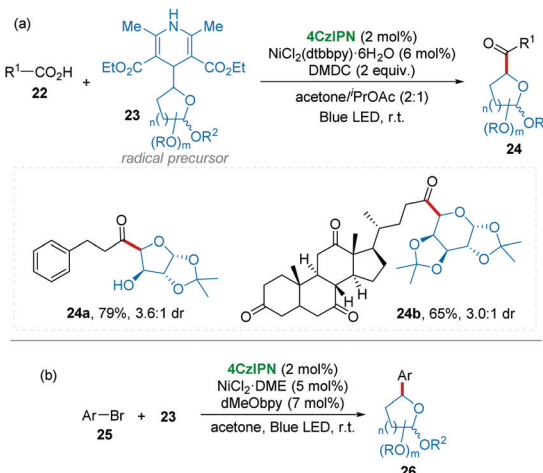


Scheme 7 4CzIPN/Ni catalyzed formylation of aryl halides and triflates.

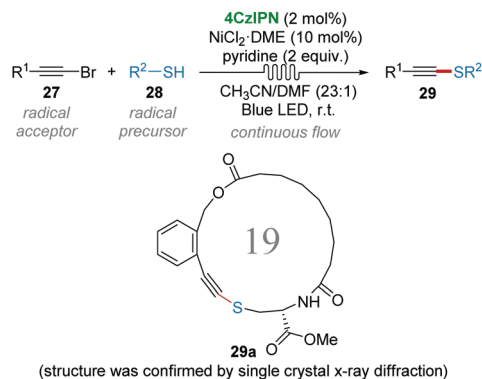
(Scheme 7b), the reaction of radical **18** and the Ni(0) complex produced diacetal-nickel(i) intermediate **19**, followed by an oxidative addition of **1** affording Ni(III) complexes **20**. After the reductive elimination, aryl diacetal **21** was obtained, which could then be converted into aryl aldehyde **17** by acidic workup. This work represents a cost-effective formylation strategy for the synthesis of aromatic aldehydes starting from substantial aryl chlorides and avoiding the use of toxic CO and tin compounds under extremely mild conditions.

In medicinal chemistry, the introduction of *C*-glycoside moieties into drug molecules has become an effective strategy for the development of novel pharmaceutical compounds, which may display unique activities as antitumor and antibiotic agents.²¹ In particular, *C*-acyl-glycoside is one of the most attractive compounds towards complex bioactive molecules.²² However, the direct synthesis of *C*-acyl-glycoside using easily available carboxylic acid as an acyl source is very challenging.²³ Recently, Molander and co-workers²⁴ used high-throughput experimentation techniques demonstrating that dimethyl dicarbonate (DMDC) is a good activator for various carboxylic acids for the formylation reaction, in which glycosyl substituted 1,4-dihydropyridines **23** were employed as radical precursors²⁵ under blue LED light with 4CzIPN/Ni dual catalysis (Scheme 8a). Notably, a free hydroxy group and steroidal moieties (**24a** and **24b**) can be well tolerated in this elegant procedure. Subsequently, a similar strategy was applied to the arylation of highly functionalized saccharides **26** from aryl bromide **25** and glycosyl substituted 1,4-dihydropyridines **23** with 4CzIPN/Ni dual catalysis under visible-light irradiation (Scheme 8b).²⁶

The construction of the C–S bond has been an important issue in heteroatom chemistry, material science and medicinal chemistry.²⁷ Alkynyl sulphides could be obtained by using umpolung-type strategies including sulfur umpolung and alkyne umpolung.²⁸ However, methods for the direct synthesis of alkynyl sulphides are rare, because the direct reaction of thiols and terminal alkynes generally gives the thiol-yne click reaction products.²⁹ In 2017, Collins and co-workers realized the oxidative coupling of bromoalkynes **27** and thiols **28** to synthesize thioalkynes



Scheme 8 4CzIPN/Ni catalyzed synthesis of acylated/arylated glycosides.



Scheme 9 4CzIPN/Ni catalyzed synthesis of thioalkynes.

29 using continuous flow techniques involving 4CzIPN/Ni dual photocatalysis.³⁰ It is believed that the thiyl radical is generated from thiols **28** under the catalysis of 4CzIPN under LED light. The procedure was highly efficient (30 min, 50–96% yields) and showed high reproducibility (gram scale). In particular, 19-membered macrocyclic alkyne sulphide **29a** could be synthesized, albeit in 28% yield under flow conditions, *via* an intramolecular coupling by using this dual photocatalytic system (Scheme 9).

In 2018, direct C–H oxidation of 2-arylpyridines and 2-arylbenzothiazoles **30** towards phenols **31** with the metallaphotoredox system under visible-light with O₂ as a green oxidant was reported by Singh's group (Scheme 10).³¹ In this protocol, BrCCl₃ and toluene (or cyclohexane) were found to be significant for this transformation. It was proposed that $\cdot\text{CCl}_3$ radical **35** was first produced from BrCCl₃ catalyzed by 4CzIPN, which then induced benzyl radical **36** (or cyclohexyl radical **37**) from toluene (or cyclohexane). Subsequently, radical **36** (or **37**) was trapped by O₂ to produce intermediate peroxy radical **38** (or **39**), which then released hydroxyl radical **40** (HO \cdot).



Scheme 10 4CzIPN/Pd catalyzed hydroxylation.

3.2 4CzIPN in photocatalytic metal catalyst regeneration

The transformation of carbon dioxide (CO₂) into valuable products under mild conditions has drawn huge attention in the past few decades.³² Selective hydrocarboxylation of styrenes with CO₂ is one of the most challenging reactions.³³ Recently, König and co-workers reported a ligand-controlled selective Markovnikov and anti-Markovnikov hydrocarboxylation of styrenes with CO₂ under mild conditions. As shown in Scheme 11a, the hydrocarboxylation products could be tuned by using different ligands.³⁴ For example, when 1,4-bis-(diphenylphosphino)butane (dppb, **L1**) as a ligand gave anti-Markovnikov product **42** (linear/branched $\geq 97:3$), neocuproine (**L2**) as a ligand afforded Markovnikov product **43** (branched/linear = 100:0) by 4CzIPN/Ni dual catalysis.

In the mechanistic studies, it was found that radical inhibitors could not inhibit the reaction, suggesting that radical intermediates are not essential. On this basis, a possible mechanism with two pathways was proposed as shown in Scheme 11b. For the anti-Markovnikov reaction, the Ni(0) species might first coordinate with CO₂ generating Aresta's complex **44**,³⁵ which was followed by alkene insertion affording 5-membered nickelalactone **45**. After a SET step, nickel carboxylate **46** was produced, and then anti-Markovnikov product **42** was released *via* a subsequent reduction (nickel catalytic cycle I). On the other hand, H₂ was detected in the reaction indicating that a nickel hydride intermediate (H–Ni^{II}) was plausible. For the Markovnikov reaction, the reaction pathway (nickel catalytic cycle II) involving nickel hydride intermediate **47** was also reasonable.

Scheme 11 4CzIPN/Ni catalyzed hydrocarboxylation of styrene with CO₂.

4. Metal-free catalytic system

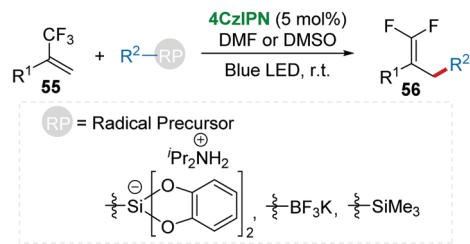
Compared with the classic photocatalysts with strong excited state reduction potential (*i.e.* Ru/Ir complexes), 4CzIPN has prominent features such as low cost and easy preparation.^{9a,11} Therefore, 4CzIPN was applied as an excellent organophotocatalyst for various transformations under the irradiation of visible-light. With the catalysis of 4CzIPN, radical precursors could be converted into reactive radicals, which could be trapped by organic substrates, such as unsaturated C=C or C=N bonds, rendering metal-free photocatalytic approaches. Therefore, reactions employing 4CzIPN as the sole metal-free photocatalyst are summarized in this section.

4.1 Reactions involving C=C bonds

After demonstrating that 2,2-diethoxyacetic acid **16** as a radical precursor could generate $\cdot\text{CH}_2(\text{OEt})_2$ radical **18** by 4CzIPN catalysis under the irradiation of blue LED light (Scheme 7a),²⁰ the research group of Mariano and Wang³⁶ subsequently developed a regioselective hydroformylation reaction of aryl olefins with diethoxyacetic acid **16** as the formylation reagent using a continuous flow system (Scheme 12). In their proposed mechanism, relatively stable benzylic radical **52** was produced *via* the anti-Markovnikov addition of radical **18** to the C=C bond, which then underwent a SET process affording anion **53**. Anion **53** was easily converted into the desired aldehyde **51** by protonation and acid catalyzed hydrolysis.

Almost at the same time, Molander's group disclosed a mild and efficient method for the construction of *gem*-difluoroalkenes **56** from trifluoromethyl-substituted alkenes **55** which underwent radical defluorinative alkylation with the photocatalysis of 4CzIPN (Scheme 13).³⁷ Various radical precursors including alkyl bis(catecholato)silicates, organotrifluoroborate, and α -silylamine were investigated in this procedure. Key intermediate **58** was formed *via* the radical addition and the SET process, followed by an E1cB-type fluoride elimination delivering *gem*-difluoroalkenes **56**.

Considering the importance of cyclopropyl in pharmaceutical active molecules, direct cyclopropanation from easily available compounds is highly valuable. Consequently, Molander's group³⁸

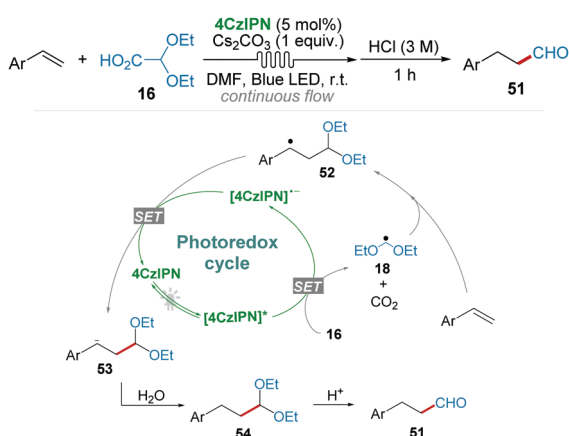


Scheme 13 4CzIPN catalyzed defluorinative alkylation.

developed a radical cyclopropanation reaction of alkenes **59** *via* a single-electron photocatalysis approach with 4CzIPN catalysis under visible-light (Scheme 14). In this work, triethylammonium bis(catecholato)iodomethylsilicate **60** was applied as a cyclopropanating reagent, which generated a halomethyl radical in the reaction. The mechanistic studies revealed that the addition of this halomethyl radical to **59** was followed by a SET process using 4CzIPN, which converted the resulting radical adduct **62** to an anion **63** that undergoes anionic 3-*exo*-tet cyclization producing the product **61**.

Subsequently, the 4CzIPN photocatalytic system was further applied to the cyclopropanation reaction of homoallylic tosylate **64** and radical precursors **65** under blue light (Scheme 15).³⁹ This method is a more general cyclopropanation strategy because various radicals are applicable for the radical addition with the C=C bond of **64**.

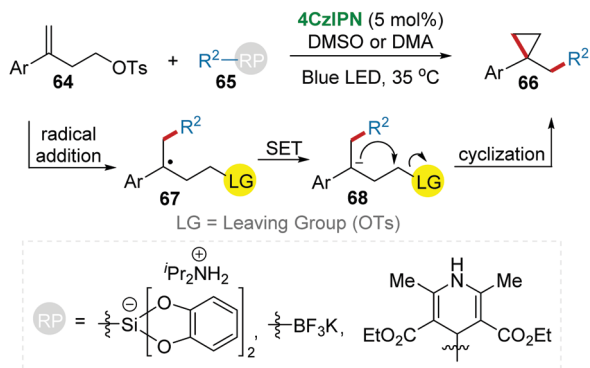
Due to the similar bond dissociation energies (BDEs) of Si-H and C-H bonds, the selective activation of Si-H bonds is challenging.⁴⁰ Recently, Wu and co-workers⁴¹ demonstrated that the combination of photocatalyst 4CzIPN and hydrogen atom transfer (HAT) catalysts **72** and **73** was an efficient catalytic system for the hydrosilylation of alkenes through Si-H activation (Scheme 16). As Si is more electropositive than C,



Scheme 12 4CzIPN catalyzed hydroformylation reaction of aryl olefins.



Scheme 14 4CzIPN catalyzed cyclopropanation of alkenes.

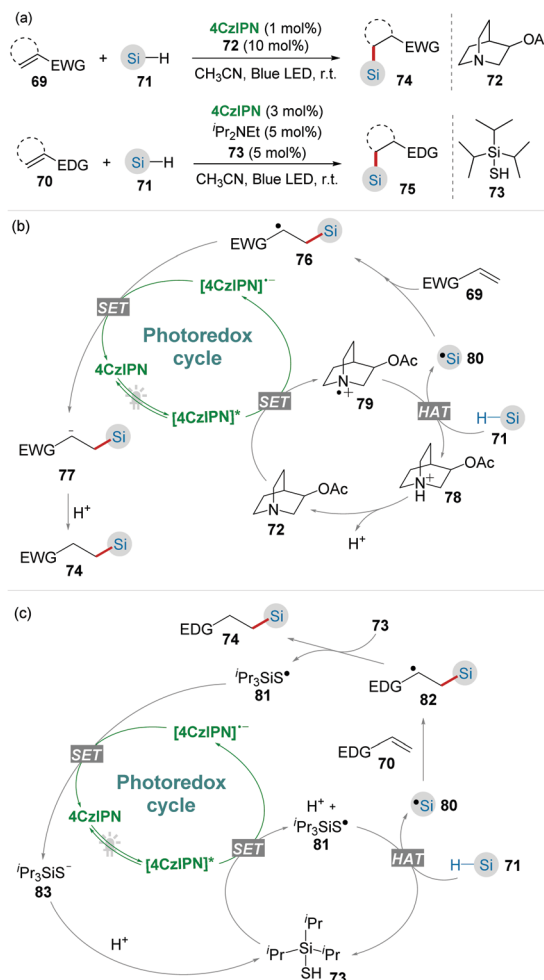


Scheme 15 4CzIPN catalyzed radical/polar annulation reactions of homoallylic tosylate.

Si–H bonds are generally more hydridic than C–H bonds. Therefore, it is feasible to generate silyl radicals *via* selective Si–H activation by using a highly electrophilic HAT catalyst.⁴² In this work, the hydrosilylation of both electron-deficient **69** and electron-rich alkenes **70** toward the corresponding products **74** and **75** was achieved by using different HAT catalysts **72** or **73** incorporated with 4CzIPN under mild blue light irradiation.

CO₂ is an abundant, renewable C1 feedstock, and an important electrophile for organic synthesis. Transformations of CO₂ under mild conditions have drawn considerable attention in the past few decades.⁴³ In the proposed reaction pathway of combined photoredox system (4CzIPN/HAT) catalyzed hydrosilylation of olefins (Scheme 16b), silyl radical addition adduct **76** underwent a single-electron reduction giving the corresponding nucleophilic anion **77**. Inspired by this key step, Wu's group⁴⁴ realized the silacarboxylation of alkenes **84** with silane and CO₂ under similar photocatalytic conditions (Scheme 17). Significantly, the unfunctionalized C(sp³)–H alkanes also proceeded smoothly to react with alkene and CO₂ under identical conditions delivering the important γ -amino acid motifs as products.

Cascade radical reactions have emerged as a powerful method for the rapid construction of complex scaffolds in the past few decades.⁴⁵ In particular, photocatalysis methods are powerful and sustainable synthetic protocols to initiate the radical cascade reactions.⁴⁶ Very recently, the research group of Cai reported a series of visible-light promoted radical cascade reactions using 4CzIPN as a metal-free photocatalyst (Scheme 18). For example, the trifluoromethylation/aryl migration reaction of α,α -diaryl allylic alcohols **86** and CF₃SO₂Na (Langlois reagents) **87** with 4CzIPN photocatalysis produced β -trifluoromethyl- α -aryl ketones **88** as products (Scheme 18a).⁴⁷ This method avoids the use of transition metal catalysts, expensive trifluoromethyl sources and strong oxidants.⁴⁸ Similarly, the same catalytic system could also be applied to the reaction of *N*-arylacrylamides **89** and Langlois reagent **87**, affording CF₃-containing oxindoles (Scheme 18b).⁴⁹ In addition, using dimethyl sulfoxide **91** as a radical precursor, α -aryl- γ -methylsulfinyl ketones **92** were constructed from α,α -diaryl allylic alcohols **86** by 4CzIPN photocatalysis. In this work, phenyliodonium bis(trifluoroacetate) (PhI(OCOCF₃)₂, PIFA) and 1,3,5-trimethoxybenzene were added to form the hypervalent iodine(III) compound intermediate as an oxidant. The kinetic



Scheme 16 4CzIPN/HAT catalyzed hydrosilylation of alkenes.



Scheme 17 4CzIPN/HAT catalyzed silacarboxylation of alkenes with silane and CO₂.



Scheme 18 4CzIPN catalyzed radical cascade reactions.

isotope effect demonstrated that C–H bond cleavage might be the rate-determining step (Scheme 18c).⁵⁰

Highlight



Scheme 19 4CzIPN catalyzed 1,2-amidoalkynylation of unactivated alkenes.

Very recently, Studer's group reported the 1,2-amidoalkynylation of unactivated alkenes **93** with 4CzIPN photocatalysis.⁵¹ Troc-protected α -aminoxy acids **94** (Troc = 2,2,2-trichloroethoxy-carbonyl) were used as precursors for the formation of amidyl radicals **99**. The nucleophilic addition of N-radicals **99** with alkenes **93** afforded the adduct radicals **100**, which were then trapped by hypervalent iodine(III) compounds to eventually provide amidoalkynylation products **96** (Scheme 19). Notably, various mono-, di- and trisubstituted unactivated alkenes are employed as substrates for the construction of diverse β -alkynylated Troc-amides under mild conditions.

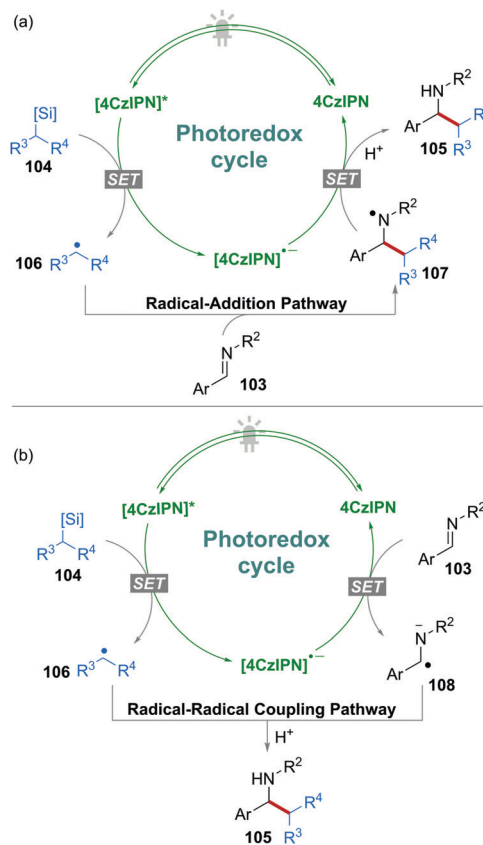
4.2 Reactions involving C=N bonds

Besides the above-mentioned unsaturated C=C bonds, the C=N bonds were also reported as radical acceptors for novel transformations under 4CzIPN photocatalysis. On the other hand, it is also possible to generate α -amino radical anions from C=N bonds *via* a SET process, rendering a possible radical-radical coupling reaction. For instance, Molander's group reported a C-C bond formation reaction from imines **103** and ammonium alkyl bis(catecholato)silicates **104** using 4CzIPN as the sole photocatalyst in DMSO without any additives (Scheme 20).⁵²

In this procedure, the single-electron oxidation of silicates **104** produced C-centered radicals **106**. Subsequently, two reaction pathways should be possible (Scheme 21): (a) The addition of radical **106** to imine **103**, followed by a single-electron reduction of the resulting N-centered radical **107**; or (b) a "persistent radical", *i.e.*, α -amino radical anion **108** was produced by the single-electron reduction of **103**, followed by a radical-radical coupling with



Scheme 20 4CzIPN catalyzed alkylation of imines.



Scheme 21 Two possible reaction pathways.

radical **106**. In the two possible pathways, although the reduction of imine **103** to the corresponding α -amino radical anion **108** was unfavourable, pathway b could not be excluded in this process.

In 2018, the group of Weng and Lu⁵³ disclosed 4CzIPN-catalyzed decarboxylative benzylation of imines **109** under the irradiation of visible-light (Scheme 22). A variety of primary, secondary, and tertiary arylacetic acids **110** were successfully applied as precursors of benzyl radicals, enabling the facile benzylation of a variety of imines affording diverse β -aryl-ethylamines **111**. In the mechanistic studies, some imine reduction and imine dimer by-products were observed, thus ruling out the radical-addition pathway.

In 2018, Yu's group developed the 4CzIPN-catalyzed hydrocarboxylation of imines (or enamides) **112** with a CO₂ atmosphere to synthesize α,α -disubstituted α -amino acids **113** under irradiation of visible-light (Scheme 23).⁵⁴ The traditional umpolung hydrocarboxylation of imines with CO₂ is very challenging;⁵⁵ however, it is hypothesized that α -amino carbanions **114** could be generated by the visible-light-driven reduction of imines **112**, followed by the nucleophilic addition of CO₂ to give carboxylates **115**.



Scheme 22 4CzIPN catalyzed decarboxylative benzylation of imines.



Scheme 23 4CzIPN catalyzed hydrocarboxylation of imines.

Scheme 24 4CzIPN catalyzed one-pot synthesis of α,α -difluoroketone hydrazones.

The research group of Zhou and Wang⁵⁶ used the one-pot approach to realize the synthesis of α,α -difluoroketone hydrazones **119** from aldehydes **116**, hydrazines **117**, and bromodifluorinated reagents **118** *via* visible-light photoredox catalysis (Scheme 24). The condensation of aldehydes **116** and hydrazines **117** produced the corresponding hydrazones **120**, followed by a single-electron oxidation to generate radical **121** or **122**. On the other hand, the single-electron reduction of BrCF_2R^4 **118** under photoredox conditions afforded radical **123**. The radical addition of **122** and **123** furnished intermediate **124**, which then converted into the desired product **119** by deprotonation.

Sherwood *et al.* reported an improved, one-pot Minisci reaction using carboxylic acids and N-containing heterocycles including quinoline, pyridine, quinaldine, isoquinoline, quinazolinone, purine, phthalazine, quinoxaline, 7-azaindoles, benzimidazole, benzothiazole, caffeine, nebularine, *etc.* with the 4CzIPN photocatalysis system (Scheme 25).⁵⁷ Carboxylic acids **126** first undergo *N*-(acyloxy)phthalimides (NAPs) **128** formation in the presence of *N*-hydroxyphthalimide (NHPI) and *N,N'*-diisopropylcarbodiimide (DIC) and DMAP. Subsequently, the NAPs generate the alkyl radical releasing CO_2 and phthalimide under photocatalytic conditions, followed by radical addition with heterocycles **125** giving the C–C bond formation product **127**.



Scheme 25 4CzIPN catalyzed one-pot Minisci reaction.



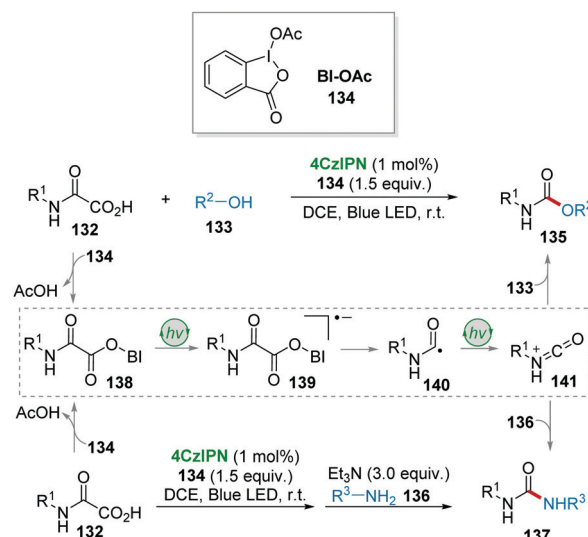
Scheme 26 4CzIPN catalyzed direct C–H functionalization.

In Molander's recent report, 4CzIPN was also found to be an efficient photocatalyst for the direct C–H functionalization of heteroarene **129** with *tert*-butyltrifluoroborate **130** affording product **131** in the presence of $\text{K}_2\text{S}_2\text{O}_8$ and trifluoroacetic acid (TFA) (Scheme 26).⁵⁸ However, when primary alkyltrifluoroborate was employed as a substrate, the yield was very poor, probably due to the extremely high oxidation potential of primary alkyltrifluoroborates.

4.3 Miscellaneous reactions

In 2018, the group of Cramail and Landais described a 4CzIPN photocatalyzed oxidative decarboxylation of oxamic acids **132** with alcohol **133** or amine **136** to synthesize urethanes **135** and ureas **137** (Scheme 27).⁵⁹ In this strategy, a hypervalent iodine reagent (BI-OAc, **134**) was employed as an oxidant. Adduct **138**, resulting from **132** and **134**, underwent a free-radical decarboxylation under visible-light, generating carbamoyl radical **140**, followed by oxidation which furnished the key isocyanate intermediate **141**. Finally, the addition of alcohol **133** or amine **136** to **141** delivered the corresponding products urethanes **135** and ureas **137**.

Due to the importance of deuterium- and tritium-labelled pharmaceutical compounds for drug discovery, in 2017 MacMillan and co-workers⁶⁰ reported an efficient dual photo-/HAT-catalysis system for the installation of deuterium (D) and tritium (T) at the α -amino $\text{C}(\text{sp}^3)\text{-H}$ of 18 drug molecules in a single step using isotopically labelled water (D_2O or T_2O) as the source of the hydrogen isotope (Scheme 28). For example, commercially available antidepressant drug clomipramine **142** was deuterated to give the corresponding product **143** in 76% yield using 4CzIPN as a photocatalyst and thiol **73** as a HAT catalyst.



Scheme 27 4CzIPN catalyzed oxidative decarboxylation coupling.

Highlight



Scheme 28 Dual photo-/HAT-catalysis system for C(sp³)-H deuteration (gram scale).



Scheme 29 Trifluoromethylthiolation of tertiary ethers.

Recently, the research group of Xie and Zhu disclosed an elegant synergistic photo-/HAT-catalysis system to realize the transition-metal-free, site-specific trifluoromethylthiolation of tertiary ethers **144** with 4CzIPN as a photocatalyst and BINOL-based phosphorothiol **146** as a HAT catalyst (Scheme 29).⁶¹ Based on the calculation of singly occupied molecular orbital (SOMO) energies of several kinds of thiyl radicals, compound **146** with significantly high electrophilic reactivity was proved to be a potential HAT catalyst. Under photocatalysis, **146** was converted into a thiyl radical to abstract the most hydridic C-H bond of the ether providing radical **148**. Radical **148** underwent a homolytic cleavage of the C-O bond forming tertiary alkyl radical **149**, which then reacted with **145** resulting in product **147** via the radical-radical pathway or the radical-addition pathway.

Leonori and co-workers⁶² described a 4CzIPN-involved photocatalysis approach for the remote C(sp³)-H functionalization of amides and amines **150** with polarized SOMOphiles (X-Y) **151** (Scheme 30). Substrate **150** suffered from a SET oxidation and



Scheme 30 4CzIPN-catalyzed remote C(sp³)-H functionalization.

fragmentation giving amidyl radical **153**, followed by enthalpy-favorable 1,5-HAT resulting in the key radical **154**. Then, the S_H2 reaction between **154** and SOMOphiles **151** furnished the targeted products **152**. This procedure provides an efficient method for the incorporation of F, Cl, SPh, CN, and alkyne functionalities into amides and amines *via* a cascade process of 1,5-HAT and S_H2-functionalization.

5. Conclusions

Visible-light promoted organic synthesis with metal complexes (Ru and Ir, *etc.*) as photocatalysts has gained huge attention in the past few decades. To a great extent, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) is an excellent and inexpensive metal-free alternative for those noble photocatalysts. In this review, the recent advances of the application of 4CzIPN as a photoredox catalyst for the generation of various radicals in organic reactions were summarized. For instance, benzyl radicals, formyl radicals, •CH₂(OEt)₂ radical, •CCl₃ radical, silyl radicals, amidyl radicals, alkyl radicals, carbamoyl radicals, thiyl radicals, *etc.* from many different precursors could be achieved *via* 4CzIPN photocatalysis. However, 4CzIPN photocatalysis offers far more than a metal-free alternative to the classic noble complexes. As a typical donor-acceptor molecule, 4CzIPN has shown an excellent redox window, good chemical stability and broad applicability. It is convenient for researchers to modify the charge transfer characteristics of 4CzIPN analogues with specific redox potentials by changing the donors and acceptors.¹⁰ Overall, 4CzIPN has been used as a photocatalyst for organic transformation just since 2016. The application of simple and economical 4CzIPN as a metal-free photocatalyst will open new avenues for the exploration of novel visible-light-promoted transformations.

Conflicts of interest

There are no conflicts to declare.

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