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12 Hypervalent Iodine Reagents in Photochemistry

Xiaojuan Dong, Hanzhang Qin, and Yiyun Chen

General Introduction

Hypervalent iodine compounds have emerged as powerful and sustainable tools in photochemistry, offering a more ecofriendly alternative to traditional metal-based reagents. Their utility stems from the large atomic radius and high polarizability of the iodine atom, which enable the formation of a unique three-center four-electron (3c–4e) bond (L—I—L). The elongated geometry, weakened strength, and pronounced polarization of this bond give it electrophilic properties similar to those of transition metals. Mechanistically, hypervalent iodine reagents participate in diverse pathways such as oxidative addition, ligand exchange, reductive elimination, ligand coupling, and single-electron transfer. In photochemical reactions, these compounds fulfill six critical roles (Scheme 1):

(1) Direct photoexcitation: absorbing photon energy to populate excited states, initiating downstream reactions.

(2) Photosensitizer quenching: modulating reaction efficiency and selectivity by quenching the excited states of photosensitizers.

(3) Substrate activation: facilitating bond cleavage or functionalization of inert substrates.

(4) Radical chain regulation: mediating radical reactivity via hydrogen-atom transfer (HAT) to initiate or terminate chain processes.

(5) Radical precursors: decomposing to generate reactive radical species.

(6) Radical acceptors: prominent examples include ethynylbenziodoxolones (EBXs) and vinylbenziodoxolones (VBXs). EBXs are mainly used for alkynylation reactions, as discussed in different sections of this chapter. In contrast, VBXs serve as alkenylation reagents, with specific applications detailed in Section 12.3.1.6.

Notably, hypervalent iodine compounds combine low toxicity, mild reaction conditions, and redox versatility, rivaling heavy metals such as mercury or thallium in terms of substrate activation and catalytic efficiency.[1–3] This review explores their dual roles as photoactive reagents and catalysts, emphasizing their direct photoexcitation mechanisms and broader applications in photocatalytic organic synthesis.

This review highlights the applications of hypervalent iodine in photochemical reactions, including direct excitation and photocatalyst quenching (Section 12.1),[4,7,15] substrate activation (Section 12.2),[31,34] targeted functionalization (Section 12.3),[48,69,90] and biocompatible transformations that emphasize its therapeutic potential (Section 12.4).[118]

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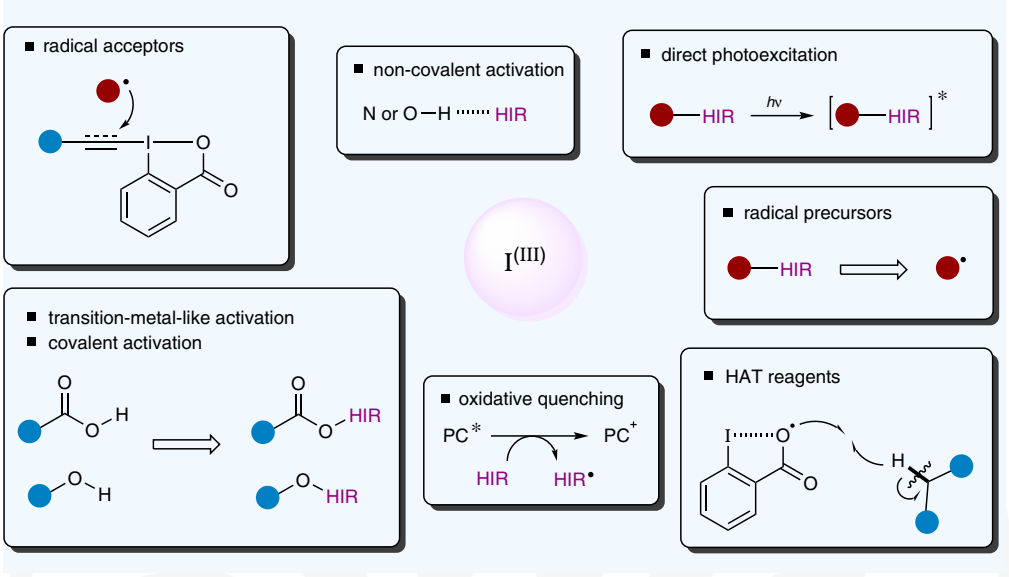
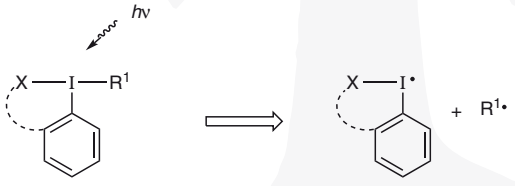
Scheme 1 Reactivity of Hypervalent Iodines in Photochemistry



12.1 Hypervalent Iodine Meets Light Irradiation

The marriage of hypervalent iodine chemistry with photoirradiation unlocks unique reactivity paradigms rooted in the structural duality of these compounds. Central to their photochemical utility is the pronounced *trans*-effect exerted by the ligands, which weakens the opposing I—R^1 bond, rendering it exceptionally labile toward photolytic cleavage (Scheme 2).[4] This bond fragility enables the controlled generation of reactive radical species under mild, often metal-free conditions, which is a hallmark of sustainable synthesis.

Scheme 2 Photoinduced Homolytic Cleavage of Hypervalent Iodine Reagents[4]



Beyond radical initiation, hypervalent iodine reagents can also undergo in situ ligand exchange with substrates, thereby forming transient iodine(III) complexes. These intermediates serve as versatile platforms for photoinduced processes: they can undergo direct photoexcitation to access high-energy states or participate in single-electron-transfer (SET) reactions with photosensitizers, amplifying their role in redox-driven transformations. The interplay of these mechanisms (radical generation, ligand exchange, and photoactivation) creates a dynamic toolbox for precision synthesis, as explored in Section 12.2.

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12.1.1 Direct Photoexcitation

The direct photoexcitation of hypervalent iodine reagents unlocks their innate photochemical potential, enabling bond cleavage and radical generation. This process targets the polarized I—X bond (X = ligand or substituent), which undergoes homolytic or heterolytic cleavage upon light absorption, yielding reactive iodine-centered radicals or electrophilic intermediates. Critically, this activation can occur in two distinct contexts:[1]

(1) Using preformed hypervalent iodine reagents: direct irradiation of reagents such as iodobenzene dicarboxylates triggers I—X bond cleavage, initiating radical cascades.

(2) Using complexes formed in situ: ligand exchange with substrates (e.g., carboxylic acids or amines) forms transient iodine(III) complexes that are photoactive and can be cleaved at particular wavelengths.

This dual activation paradigm offers unparalleled versatility in photochemical designs. Researchers can tailor reagents and pathways to match substrate sensitivity, reaction scale, or sustainability goals. For example, the photoexcitation of preformed hypervalent iodine reagents facilitates rapid fragment coupling under mild reaction conditions,[5,6] whereas in situ formed transient iodine(III) complexes enable late-stage peptide modifications without compromising the integrity of sensitive biomolecules.[7]

The direct photoexcitation strategy bypasses the use of stoichiometric oxidants and harsh conditions, aligning with green chemistry principles. By tuning ligand electronics (e.g., with the presence of electron-withdrawing groups), the photoactivity of the I—X bond can be optimized for specific wavelengths, enhancing energy efficiency. As photochemical methodologies evolve, direct excitation pathways of hypervalent iodine reagents will drive innovations in precision synthesis (e.g., spatiotemporal control in flow reactors) and functional material fabrication (e.g., light-responsive polymers). This adaptability cements their role as indispensable tools in sustainable chemistry.

In 2019, Mal and co-workers introduced a visible-light-mediated method for the dithioacetalization of aldehydes, employing an iodine(III) reagent as photocatalyst (Scheme 3).[8] Upon visible-light irradiation, the iodine(III) reagent **1** undergoes photochemical initiation, generating an acyloxy radical intermediate. This highly reactive intermediate abstracts a hydrogen atom from benzenethiol, resulting in the formation of a thiyl radical. Subsequent reaction of the thiyl radical with the aldehyde forms intermediate **3**. A chain-propagation step ensues, involving hydrogen-atom abstraction from benzenethiol by intermediate **3** to yield the hemithioacetal **4**. This proposed mechanistic pathway, consistent with the findings of Maruoka, Morokuma, and co-workers,[9] suggests that the iodine(III) reagent functions as a photoinitiator, generating the initial radical species that drives the reaction forward. Finally, acid-catalyzed reaction of hemithioacetal **4** with benzenethiol affords the desired dithioacetal product via intermediate **5**. For example, (4-tolylmethylene)bis(phenylsulfane) (**2**) is obtained in 94% yield (Scheme 3).

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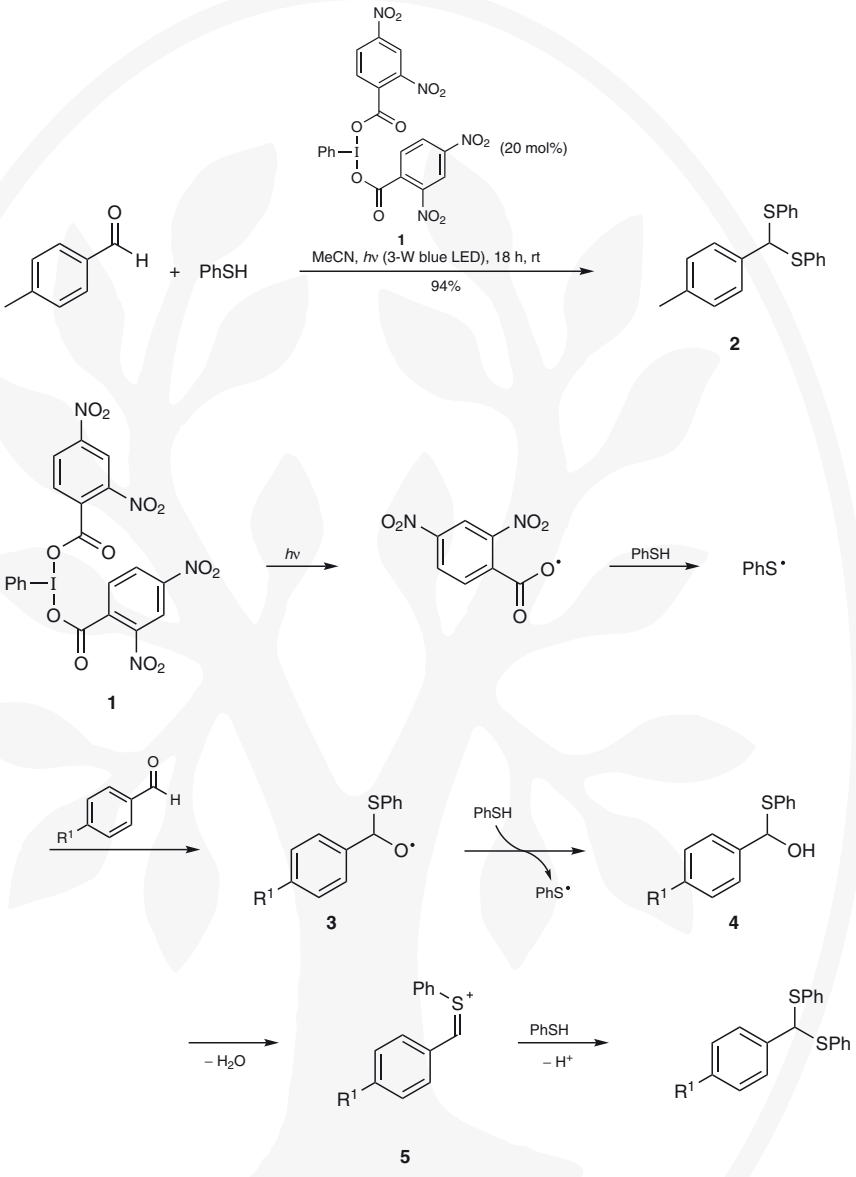
Scheme 3 Synthesis of (4-Tolylmethylene)bis(phenylsulfane) via Photochemical Homolytic Cleavage of an I—O Bond[8]



In 2020, the Bolm group developed a visible-light-mediated protocol for constructing N-α-oxoacylated sulfoximines (e.g., **8**) in high yields by reacting sulfoximidoyl-containing hypervalent iodine reagents (e.g., **6**) with arylalkynes (Scheme 4).[10] The I—N bond formed in the ligand-exchange reaction between the hypervalent iodine(III) reagent hydroxy(tosyloxy)iodobenzene and (methanesulfonylimino)benzene is relatively weak; this characteristic enables homolytic cleavage of the bond under photoexcitation conditions, thereby generating highly reactive aminating agents, which react with the arylalkyne to form vinyl radical species such as **7**. Oxidation of these species with molecular oxygen furnishes the N-α-oxoacylated sulfoximine products via strained 1,2-dioxete intermediates.

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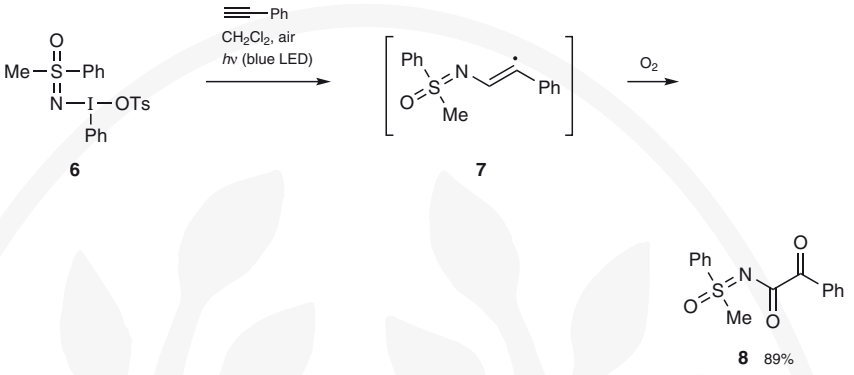
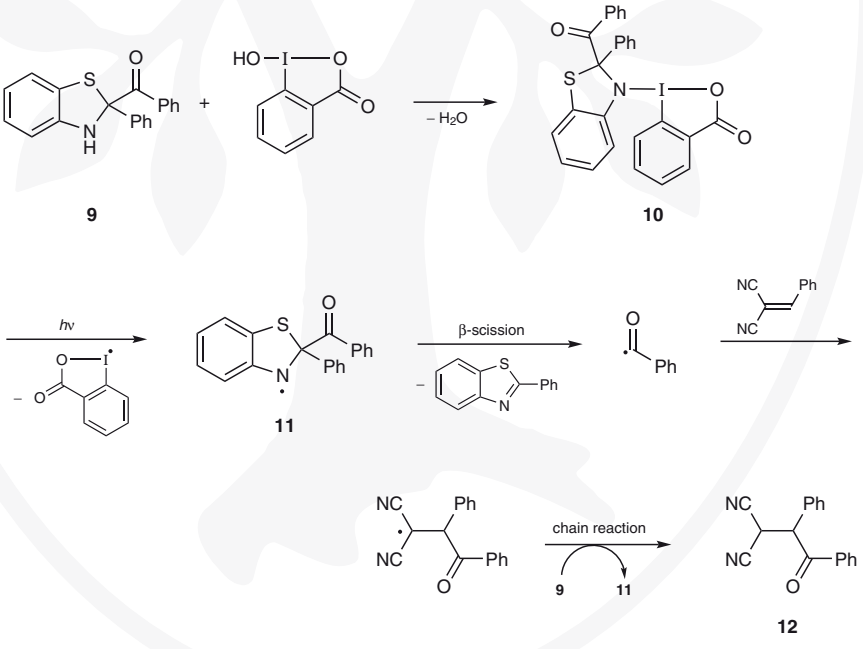
Scheme 4 Visible-Light-Promoted α-Ketoacylation of a Sulfoximine with Phenylacetylene[10]



In 2019, the Zhu group reported a visible-light-mediated approach to generate acyl radicals from 2-acyl-substituted benzothiazolines (Scheme 5).[11] The key step involves photolytic cleavage of the I—N bond of the covalent intermediate **10**, formed between 1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one [1-hydroxy-1,2-benziodoxol-3(1*H*)-one] and a 2-acylbenzothiazoline substrate (e.g., **9**), to generate highly reactive nitrogen-centered radicals (e.g., **11**). Subsequent β-scission of these radicals affords an acyl radical, which serves as a versatile intermediate for a wide range of transformations, including alkylation, alkenylation, and alkynylation. For example, the acyl radicals react with 2-methylenemalononitriles to form 2-(1,2-diaryl-2-oxoethyl)malononitriles (e.g., **12**).

Scheme 5 Acyl Radical Generation Strategy Using 2-Acylbenzothiazolines[11]



Recently, Minakata and co-workers described a method for the photosensitizer-free, visible-light-induced alkylamination of styrenes, employing carboxylic acids and [(diarylmethylene)amino]-benziodoxolones (DABXs) as reagents.[12] Photoexcitation of a DABX reagent **13** triggers homolytic cleavage of the I—N bond, affording an iminyl radical **15** and the iodine radical intermediate **14**. Subsequent single-electron transfer from the carboxylate anion to radical intermediate **14** gener-

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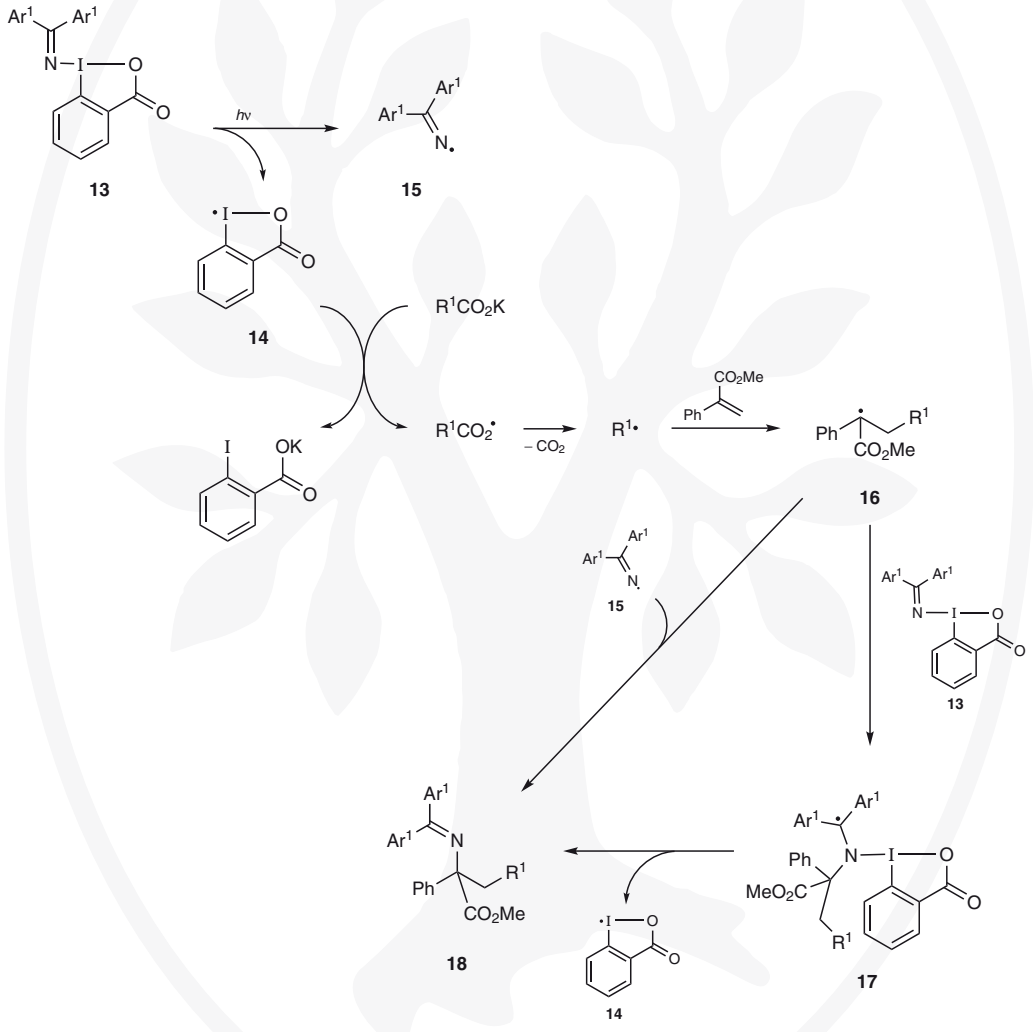
ates a carboxylic acid radical, which undergoes decarboxylative radical addition to an alkene to form a carbon radical **16**. Radical–radical coupling between **16** and **15** yields the desired product **18**. Notably, the higher concentration of the DABX **13** favors its reaction with the carbon radical **16**, regenerating the iodine radical **14** (via formation of carbon radical **17** and subsequent N—I bond cleavage to deliver product **18**), and thus enabling a radical-chain process (Scheme 6). This strategy for photolytic homolysis of the I—N bond not only broadens the application scope of hypervalent iodine reagents in photochemical reactions but also provides an efficient and green pathway for the synthesis of complex organic amine compounds.

Scheme 6 Mechanistic Proposal for Alkylamination of Styrene Derivatives[12]



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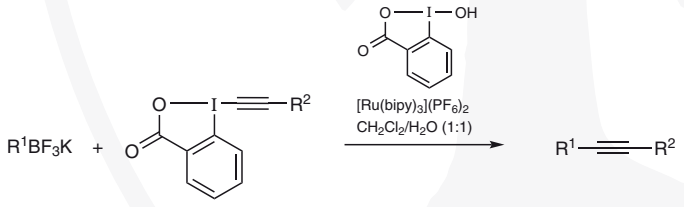
12.1.2 Quenching Agents for Excited Photosensitizers

Hypervalent iodine compounds are emerging as versatile electron-transfer mediators in photochemical reactions, even if they are not directly photoexcitable themselves. Their ability to engage in single-electron transfer (SET) with photoexcited photosensitizers {e.g., $[Ru(bipy)_3]^{2+}$, organic dyes} unlocks pathways to generate reactive intermediates that are critical for catalysis. This SET-driven quenching mechanism converts transient energy from photosensitizers into chemical reactivity, producing hypervalent iodine species (e.g., iodine-centered radicals with lower redox potentials) with increased chemical reactivity.

For instance, the Y. Chen group reported cyclic hypervalent iodine reagents (e.g., 1-hydroxy-1,2-benziodoxol-3-one) that participate in SET with excited photosensitizers. This enables organoboron reagents (e.g., potassium alkyltrifluoroborates or 4,4,5,5-tetramethyl-1,3,2-dioxaborolanes) to be used for alkyl radical generation. This synergy between hypervalent iodine and organoboron reagents enables controlled radical propagation, facilitating transformations such as C—H functionalizations or cross couplings that are otherwise kinetically inaccessible. For example, alkynes **19** are formed by cross coupling of potassium alkyltrifluoroborates and ethynylbenziodoxolones via vinyl radicals **20** (Scheme 7).[13] After optimizing the reaction conditions, such as the amount of photocatalyst, choice of oxidant, solvent system, and addition of base, the optimal conditions include the use of 2 mol% of the photocatalyst and 0.5 equivalents of 1-hydroxy-1λ³-benzo[*d*]-[1,2]iodaoxol-3(1*H*)-one in a 1:1 mixture of dichloromethane and water for 5 hours at 25 °C. The reaction exhibits good compatibility with a variety of substrates, including primary, secondary, and tertiary alkyltrifluoroborates or boronic acids, as well as alkynes with different substituents, and tolerates a range of sensitive functional groups.

Mechanistic studies revealed that $[Ru(bipy)_3]^{2+}$, upon visible-light excitation, forms an excited-state photosensitizer, which is subsequently oxidized by iodine-based radical species **14**, generated in situ from 1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one to form $[Ru(bipy)_3]^{3+}$. $[Ru(bipy)_3]^{3+}$ further oxidizes the alkyl trifluoroborates (or boronic acids) to generate an alkyl radical, which undergoes a radical addition reaction with the ethynylbenziodoxolone reagents (EBXs) to form an alkenyl radical, followed by the release of iodine-centered radical species, ultimately yielding the alkynylated product. Additionally, the application scope of this method was further expanded by performing it in pH 7.4 PBS buffer solution.

Scheme 7 Photocatalytic Chemoselective Deboronative Alkynylation[13]



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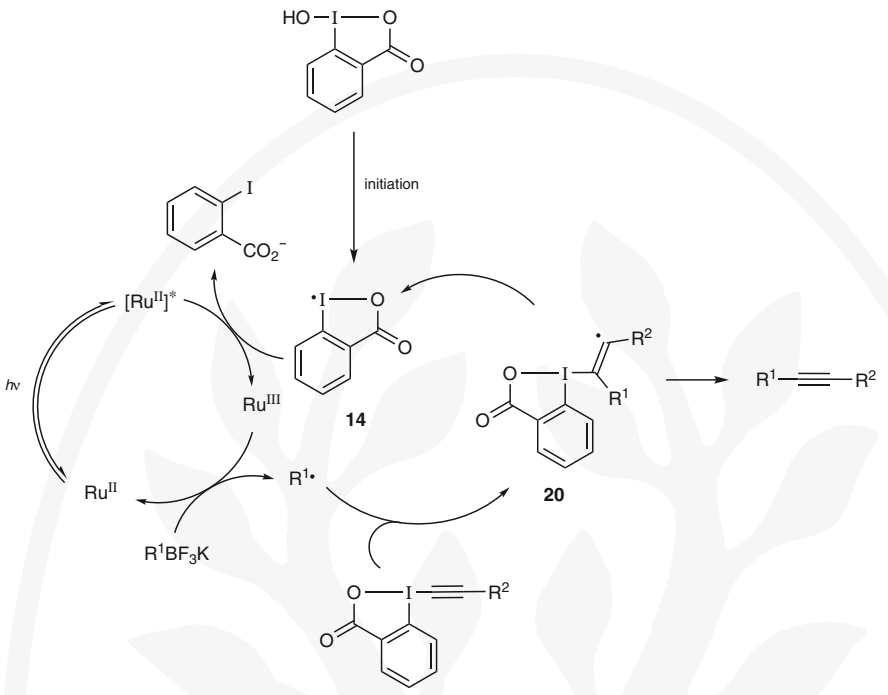

By serving as electron shuttles, hypervalent iodine reagents can amplify the reaction efficiency and selectivity of photoredox cycles. Their tunable redox profiles allow precise matching with photosensitizers, minimizing energy waste and side reactions. This strategy has been leveraged for multi-component reactions requiring sequential SET and bond-forming steps, as well as biocompatible transformations dependent on metal-free conditions. Their dual role as quenchers and reactive intermediates positions them as linchpins in the next generation of photochemical methodologies.

In 2016, the G. Chen group delineated a photoredox-catalyzed Minisci C—H alkylation of N-hetarenes with alkylboronic acids.[14] Based on mechanistic experiments and computational studies, they elucidated that the reaction initiates with a SET event from the photoexcited ruthenium(II) complex to 3-oxo-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate [1-acetoxy-1,2-benziodoxol-3(1*H*)-one; Scheme 8]. The ensuing carboxyl radical species then engages with the alkylboronic acid, yielding an alkyl radical via transient species **21**. This radical undergoes nucleophilic addition to the protonated N-hetarene, resulting in the formation of a nitrogen radical cation (e.g., **22**). The radical cation intermediate is subsequently subjected to single-electron oxidation by ruthenium(III), which is followed by deprotonation to afford the final C—H alkylated product.

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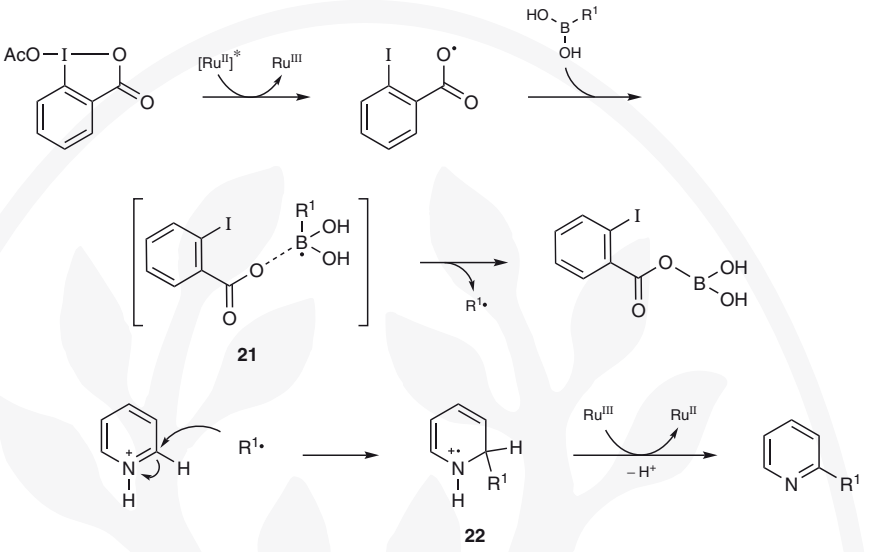
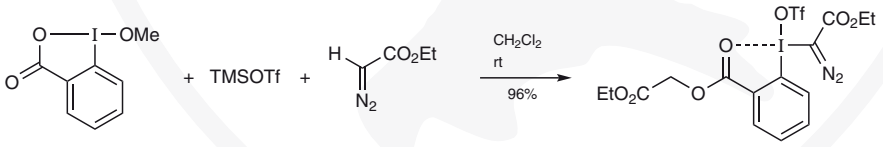
Scheme 8 Minisci C—H Alkylation of N-Hetarenes[14]



Ethyl diazoacetate is a highly reactive compound that is commonly used in a variety of reactions in organic synthesis. Notably, hypervalent iodine compounds containing ethyl diazoacetate can serve as efficient reagents for the transfer of ethyl diazoacetate. In 2018, the Suero group pioneered the utilization of pseudocyclic benziodoxolones (e.g., **23**) adorned with an ethyl diazoacetate group to generate a diazomethyl radical species $N_2{=}C^{\bullet}{-}CO_2Et$ through photoredox catalysis.[15] This method complements existing strategies by enabling the synthesis of *ortho*-substituted and sterically hindered aryl diazo compounds (e.g., **24**), as well as other hard-to-obtain diazo compounds, in a single step without prefunctionalized aromatic starting materials being required (Scheme 9). The underlying mechanism involves the interception of the diazomethyl radical by a (het)arene, culminating in the formation of a cyclohexadienyl radical. This intermediate is subsequently oxidized by ruthenium(III) and deprotonated, yielding the final C—H alkylated product and thereby completing the photoredox cycle. The hypervalent iodine diazo reagent **23** has also been extensively employed under photoredox catalysis conditions in the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles via decarboxylative cyclization of α-oxo carboxylic acids[16] as well as in the [3+2] cyclization of *N*,*N*-dialkylhydrazones[17] or quinoxalinones[18] to afford triazole derivatives.

Scheme 9 Preparation of a Pseudocyclic Benziodoxolone and Its Application in (Het)Arene C—H Diazomethylation by Photoredox Catalysis[15]



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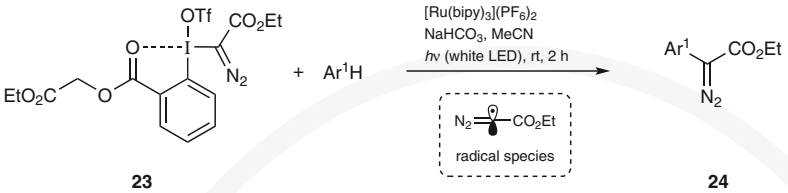
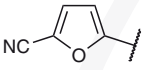
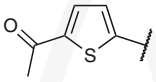
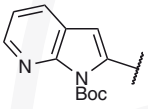
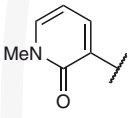
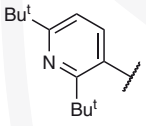
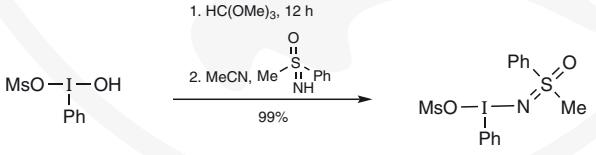


23 24

Ar^1	Yield (%)	Ref
Ph	52	[15]
	68	[15]
	73	[15]
	59	[15]
	70	[15]
	56	[15]

Recognizing the distinctive bioactivities of sulfoximines, their application in both medicinal and agrochemical domains has been extensively explored. In 2018, the Bolm group introduced an innovative photoredox-based catalytic strategy for sulfoximidation reactions employing the sulfoximidoyl-containing hypervalent iodine(III) reagent **25**. This method facilitates the chemoselective oxidation of benzylic C—H bonds under benign conditions, specifically at ambient temperature, thereby expanding the scope of sulfoximine (e.g., **26**) synthesis (Scheme 10).[19]

Scheme 10 Synthesis of a Sulfoximidoyl-Containing Hypervalent Iodine(III) Reagent and Its Application in Photocatalyzed Sulfoximidation[19]



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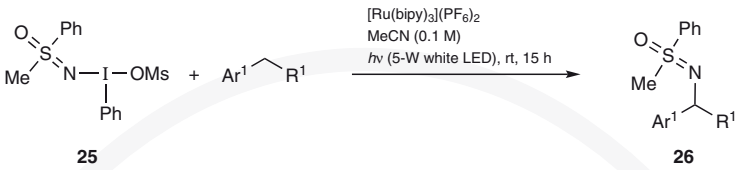

25 26

Ar^1	R^1	Yield (%)	Ref
Ph	4-$MeOC_6H_4$	81	[19]
4-$MeOC_6H_4$	iPr	58	[19]
4-$MeOC_6H_4$	CN	50	[19]
3-thienyl	Me	21	[19]

(1-Diazo-2-ethoxy-2-oxoethyl)[2-(2-ethoxy-2-oxoethoxy)carbonylphenyl]iodonium Trifluoromethanesulfonate (23)**:**[15]
A soln of 1-methoxy-1,2-benziodoxol-3(1*H*)-one (4.0 g, 14.38 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 M) was treated with TMSOTf (2.60 mL, 14.38 mmol, 1.0 equiv) at rt. After 30 min, a cloudy suspension had formed. Subsequently, ethyl diazoacetate (3.3 mL, 31.64 mmol, 2.2 equiv) was added dropwise over 15 min, resulting in evolution of N_2. The mixture was stirred at rt until a clear yellow soln was obtained (typically 3 h). The solvent was removed under reduced pressure and the crude product was recrystallized (Et_2O/CH_2Cl_2 5:1) at −30 °C for 12 h. If necessary, the recrystallization process was repeated to remove impurities. The purified product was isolated by filtration, washed with cold Et_2O (500 mL), and dried under high vacuum. The yellow solid was stored at −30 °C; yield: 8.2 g (96%).

Ethyl 2-(Het)Aryl-2-diazoacetates 24**; General Procedure:**[15]
$[Ru(bipy)_3](PF_6)_2$ (1.7 mg, 2 µmol, 1 mol%), $NaHCO_3$ (50.4 mg, 0.6 mmol, 3.0 equiv), a (het)arene (0.4 mmol, 2.0 equiv), hypervalent iodine reagent **23** (0.2 mmol, 1.0 equiv), and MeCN (2.0 mL; 0.1 M) were added to a 10-mL oven-dried tube equipped with a stirrer bar. The tube was sealed with a septum and degassed by three freeze–pump–thaw cycles under argon. The tube was placed in a photoreactor equipped with white LED strips and the mixture was irradiated at rt. A mini-fan was kept on top to maintain rt. The progress of the reaction was followed by TLC, and after 2 h the mixture was passed through a short pad of silica gel, rinsing with CH_2Cl_2. The solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (silica gel).

Phenyl(*S*-methyl-*S*-phenylsulfoximidoyl)iodonium Methanesulfonate (25)**:**[19]
[Hydroxy(methanesulfonato)iodo]benzene (316 mg, 1 mmol) was stirred in trimethyl orthoformate (1.0 mL) for 12 h. The mixture was concentrated to dryness under reduced pressure, and the resulting residue was used without further purification in the next step. A soln of the residue in MeCN (3.0 mL) was treated with *S*-phenyl-*S*-methyl sulfoximine (155 mg, 1 mmol) at rt, immediately forming a white precipitate. This precipitate was collected by filtration, washed with Et_2O, and dried under reduced pressure to yield spectroscopically pure iodine(III) salt as a white solid; yield: 450 mg (99%).

***N*-[(4-Methoxyphenyl)(phenyl)methyl]-*S*-methyl-*S*-phenylsulfoximine** (26**, Ar^1 = Ph; R^1 = 4-$MeOC_6H_4$); Typical Procedure:**[19]
Phenyl(*S*-methyl-S-phenylsulfoximidoyl)iodonium methanesulfonate (**25**; 91 mg, 0.20 mmol) and $[Ru(bipy)_3](PF_6)_2$ (1.7 mg, 2 µmol, 1 mol%) was added to a flame-dried 15-mL tube equipped with a magnetic stirrer bar. The tube was sealed and then placed under reduced pressure and backfilled with argon three times. Degassed anhyd MeCN (2.0 mL; 0.1 M) was added, followed by 1-benzyl-4-methoxybenzene (0.40 mmol) (**CAUTION:** *carcinogen*). The resulting orange soln was irradiated

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using blue LED strips (5 W) and magnetically stirred. After 15 h, the soln was concentrated and the residue was purified by column chromatography (silica gel, EtOAc/pentane 1:1) to afford a yellow viscous oil; yield: 57 mg (81%).

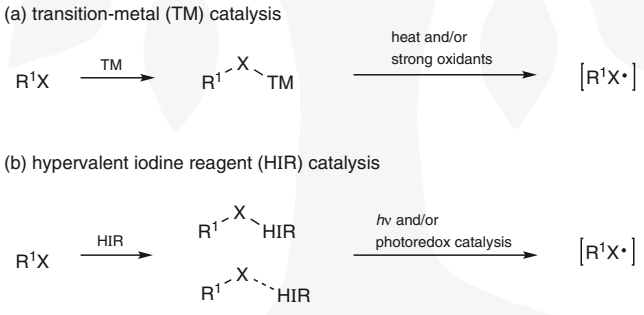
12.2 Hypervalent Iodine Reagents with Activation Roles in Photochemistry

Hypervalent iodine compounds offer a unique opportunity in photochemistry, merging transition-metal-like reactivity with the sustainability of nonmetallic systems. Their ability to engage in ligand exchange with NH and OH functionalities mimics the redox versatility of metals, and their low toxicity aligns with green chemistry principles. This metalloid-like behavior enables the formation of iodine(III) intermediates with lowered redox potentials (Scheme 11), which act as dynamic platforms for photochemical activation. These intermediates reduce energy barriers for bond cleavage or functionalization, rendering traditionally challenging reactions (e.g., inert C—H bond activation, stereoselective cyclizations) kinetically accessible under mild, visible-light-driven conditions. For example, ligand exchange with carboxylic acids generates iodine(III) carboxylate complexes that undergo photolytic homolysis, producing carboxyl radicals for decarboxylative couplings, without the need for high temperatures or toxic oxidants.

The ligand-exchange strategy enhances both efficiency and selectivity across transformations such as C—H functionalization of alkanes and aromatics, and radical–polar crossover reactions enabling multi-step cascades. By circumventing energy-intensive protocols and heavy metals, hypervalent iodine reagents establish themselves as precision-engineered tools for modern synthesis. Their compatibility with photoredox catalysis further amplifies their utility, enabling atom-economical bond formations in pharmaceuticals (e.g., kinase inhibitors), agrochemicals, and functional materials. Moreover, hypervalent iodine reagents can noncovalently activate inert substrates to facilitate a range of transformations under mild conditions.

As mechanistic insights deepen, hypervalent iodine reagents are poised to redefine sustainable industrial chemistry, from electrocatalysis to biocompatible photoredox platforms.

Scheme 11 Metalloid Properties of Hypervalent Iodine Reagents



12.2.1 Covalent Activation

Traditional methods for generating carboxyl radicals from carboxylic acids rely on harsh conditions, such as high temperatures, strong oxidants, and toxic reagents, limiting their utility in sensitive synthetic contexts. Transition-metal catalysts can activate carboxylic acids via metal–carboxylate complexation, but these systems often suffer from metal leaching, toxicity, and incompatibility with biomolecular substrates. Hypervalent iodine reagents circumvent these limitations through a mild, metal-free strategy:

(1) Ligand exchange: carboxylic acids undergo ligand substitution with hypervalent iodine reagents (e.g., iodobenzene dicarboxylates), forming stabilized iodine(III) carboxylate complexes.

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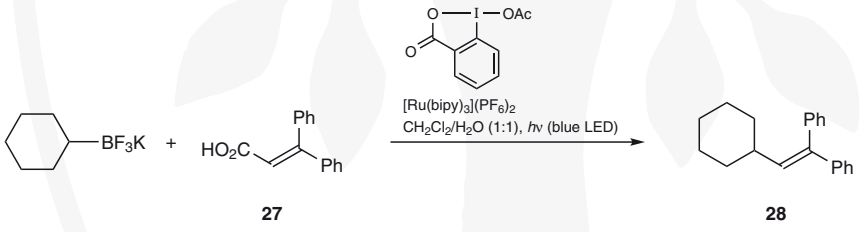
(2) Photochemical cleavage: under light irradiation, these complexes undergo homolytic bond cleavage (direct photolysis) or photoredox-mediated single-electron transfer (SET), liberating reactive carboxyl radicals.

This dual activation pathway combines operational simplicity with precise control, enabling carboxyl radical generation under ambient conditions without stoichiometric oxidants. The resulting radicals participate in decarboxylative couplings, C—H functionalizations, and cyclizations, streamlining access to complex architectures in pharmaceuticals, agrochemicals, and functional polymers. By merging sustainability with synthetic efficiency, hypervalent iodine reagents redefine carboxyl radical chemistry for the modern era.

12.2.1.1 Carboxylic Acid Activation

α,β-Unsaturated carboxylic acids covalently coordinate with hypervalent iodines to effectively accept alkyl radicals. In 2014, the Y. Chen group developed a visible-light-induced deboronative/decarboxylative alkenylation, representing the first hypervalent-iodine-enabled C(sp^3)—C(sp^2) coupling of alkyltrifluoroborates and alkenes, utilizing aryl- or acyl-substituted vinyl carboxylic acids (e.g., **27**) to afford alkylated alkenes (e.g., **28**) (Scheme 12).[6] The proposed mechanism involves in situ formation of a benziodoxolone vinyl carboxylic acid complex **29** from the α,β-unsaturated carboxylic acid and 1-acetoxy-1,2-benziodoxol-3(1*H*)-one. This complex undergoes carbon radical addition to form radical intermediate **30**, which subsequently undergoes benziodoxolone-facilitated decarboxylation, releasing the benziodoxolone radical and yielding the alkylated alkene product. Compared to traditional alkyl Heck-type reactions, this C(sp^3)—C(sp^2) coupling reaction demonstrates superior chemoselectivity under mild conditions and can be applied to effectively synthesize aryl- and acyl-substituted alkylalkenes containing sensitive functional groups.

Scheme 12 Vinyl Carboxylic Acid Activation as Radical Receptor by a Hypervalent Iodine, and Associated Mechanism[6]



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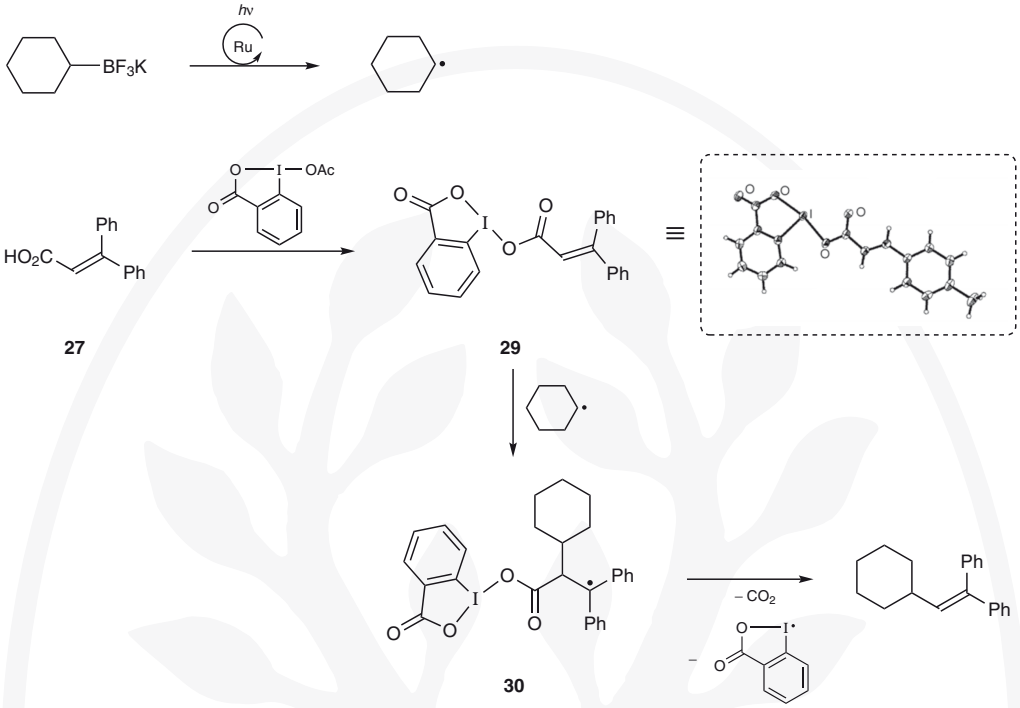

Alkynyl-coordinated cyclic hypervalent iodine reagents can also serve as radical acceptors. In 2015, the Y. Chen group introduced a protocol combining dual hypervalent iodine(III) reagent and photoredox catalysis for decarboxylative alkynylation.[20] This method represents the first instance of hypervalent iodine reagent/photoredox dual catalysis for generating acyl radicals from an in situ formed complex (e.g., **34**) of α-oxo acids (e.g., **31**) and 1-acetoxy-1,2-benziodoxol-3(1*H*)-one, followed by an unprecedented acyl radical addition to an alk-1-ynylbenziodoxolone (e.g., **32**) to afford alk-1-ynyl ketones (e.g., **33**) (Scheme 13). In this process, the alk-1-ynylbenziodoxolone serves two roles: it functions as a radical acceptor, and the alk-1-ynylbenziodoxolone generated radical (e.g., **35**) acts as an oxidative quencher for the photoredox catalysis. In addition, 1-acetoxy-1,2-benziodoxol-3(1*H*)-one acts as the covalent activator for the oxo acid, thereby lowering the redox potential of the substrate. Notably, the efficient construction of an mGlu5 receptor inhibitor under neutral aqueous conditions suggests promising applications in visible-light-induced biological systems. Notably, the reaction proceeds smoothly in phosphate-buffered saline (PBS; pH 7.4), giving the product in 83% yield, even in the presence of complex biomolecule mixtures such as cell lysates (Scheme 13). This visible-light-induced method offers efficient reaction kinetics under neutral aqueous conditions, making it promising for biological studies.

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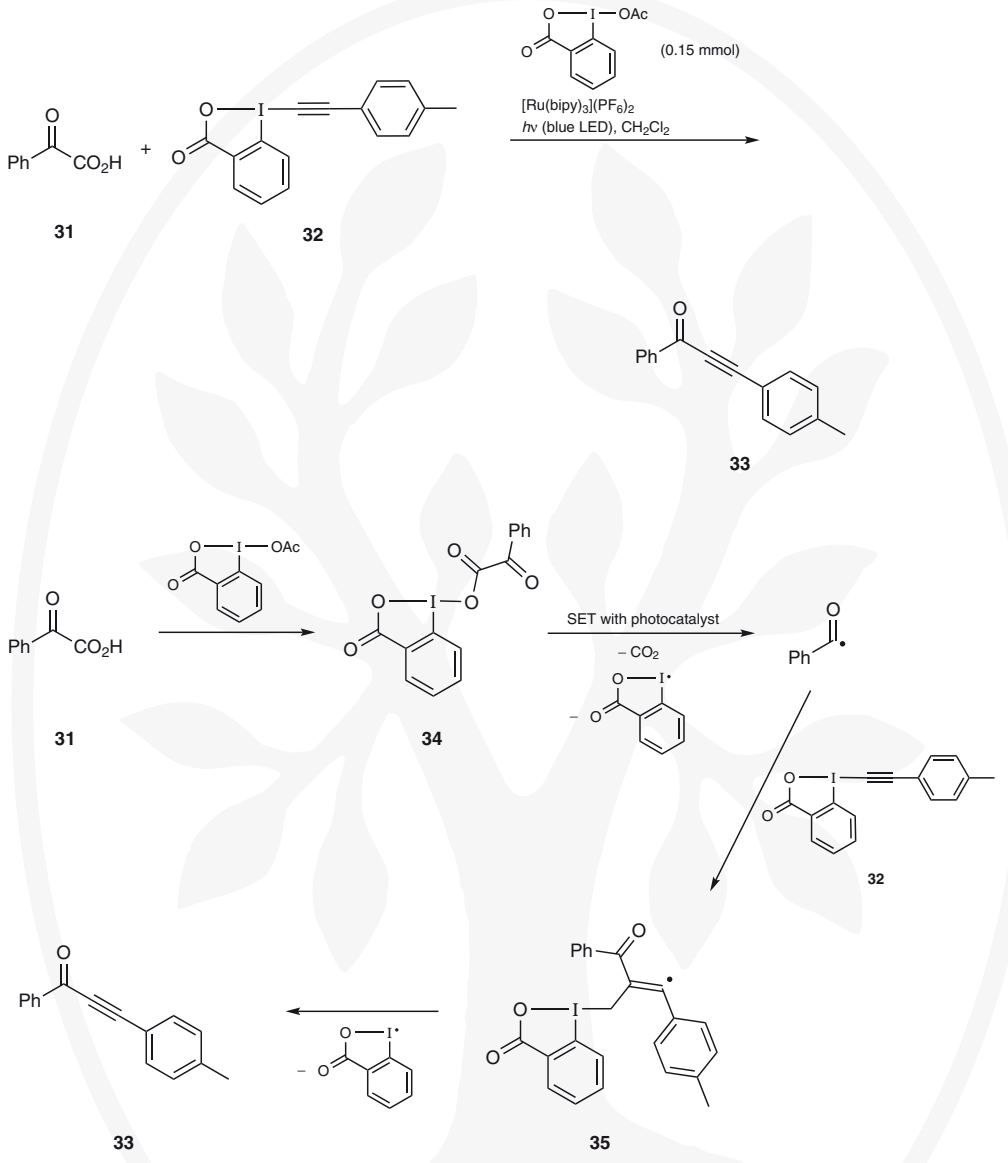
Scheme 13 Decarboxylative Alkynylation of α-Oxo Acids via SET of a Hypervalent Iodine Complex with a Photocatalyst[20]



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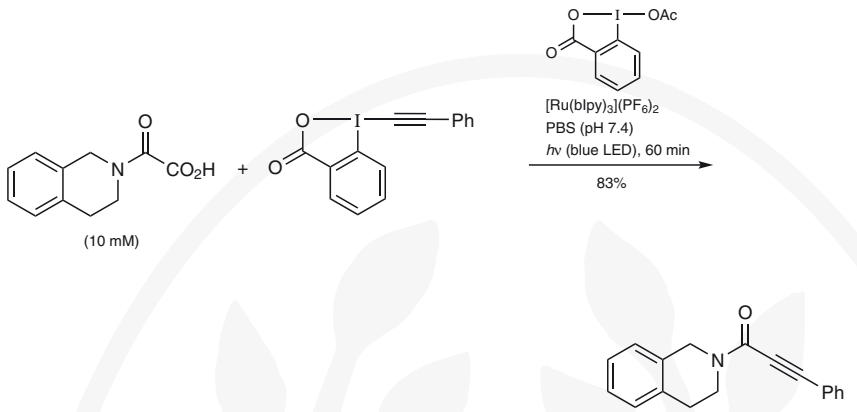
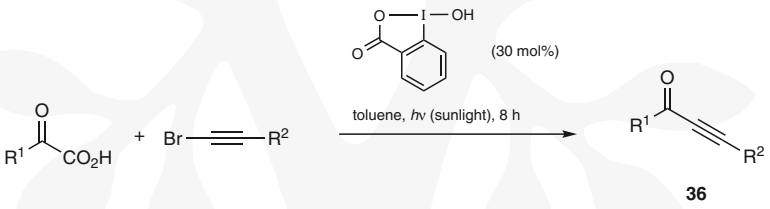


Wang and co-workers have reported a method for the decarboxylative alkynylation of oxo acids using bromoacetylenes, enabled by hypervalent iodine(III) reagents under sunlight irradiation at room temperature, to afford alk-1-ynyl ketones **36** (Scheme 14).[5] Experiments demonstrated comparable results using blue light (λ = 450–455 nm), suggesting that the reaction is primarily driven by light. The authors propose that an alk-1-ynylbenziodoxolone is a potential intermediate in the reaction.

Scheme 14 Synthesis of Alk-1-ynyl Ketones[5]



R^1	R^2	Yield (%)	Ref
Ph	Ph	62	[5]
iBu	Ph	69	[5]
4-$MeOC_6H_4$	$(CH_2)_4Me$	44	[5]

This activation strategy can be extended to α,α-difluoroarylacetic acids. In 2016, the Qing group developed a visible-light-induced protocol for preparing difluoroalkylated arenes (e.g., **38**) through the hydroaryldifluoromethylation of alkenes using α,α-difluoroarylacetic acids (Scheme 15).[21] The in situ generated hypervalent iodine activated carboxylic acid intermediate exhibits a reduced redox potential, facilitating single-electron transfer with the photoexcited iridium photosensitizer **37**. Subsequent radical addition and hydrogen-atom transfer (HAT) processes afford the desired hydroaryldifluoromethylated products under mild conditions.

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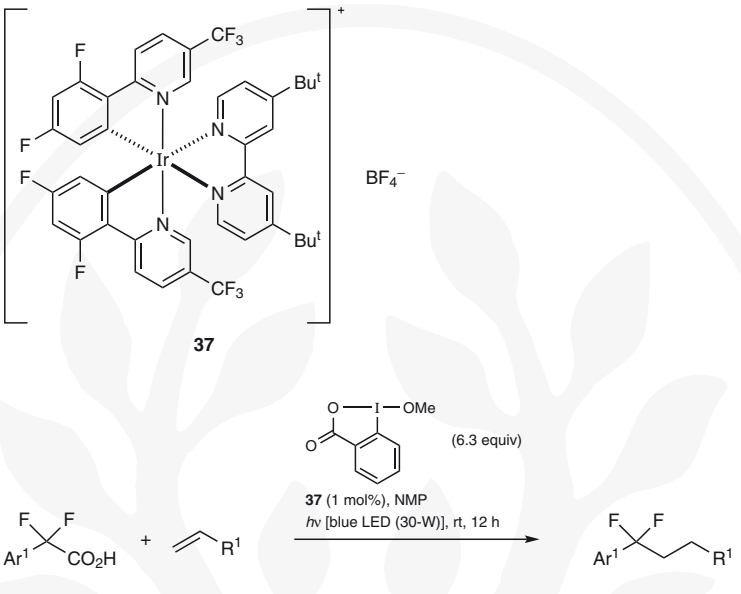
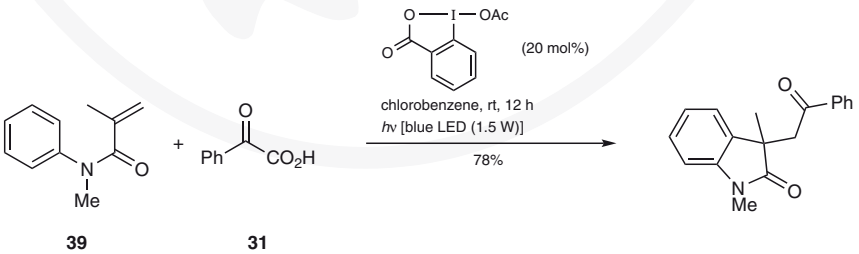
Scheme 15 Photoredox-Catalyzed Hydroaryldifluoromethylation of Alkenes[21]



Ar^1	R^1	Yield	Ref
4-$F_3CC_6H_4$	$(CH_2)_2Ph$	71	[21]
4-$F_3CC_6H_4$	$CH_2P(O)(OEt)_2$	54	[21]
4-iPrC_6H_4	SO_2Ph	63	[21]

In 2015, Wang and co-workers reported a direct decarboxylative acylarylation of acrylamides (e.g., **39**) with α-oxo carboxylic acids (e.g., **31**) (Scheme 16).[22] This process, catalyzed by 1-acetoxy-1,2-benziodoxol-3(1*H*)-one and driven by visible light, proceeds via a photoredox mechanism without the need for an external photocatalyst. The reaction cascade involves decarboxylative radical addition and cyclization, ultimately releasing carbon dioxide and molecular hydrogen. Building on this work, the same group later developed a similar approach for the synthesis of 3-acylated coumarins (e.g., **40**).[23] In 2023, the Banerjee group expanded the scope of this strategy to include the synthesis of dihydroquinolinone scaffolds (e.g., **41**) through a visible-light-promoted, metal- and photocatalyst-free radical cascade cyclization of cinnamamides with α-oxo carboxylic acids.[24] This method offers a sustainable and efficient route to these valuable compounds under mild conditions.

Scheme 16 Photocatalyzed Tandem Decarboxylative Annulations Using Hypervalent Iodine Reagents[22–24]



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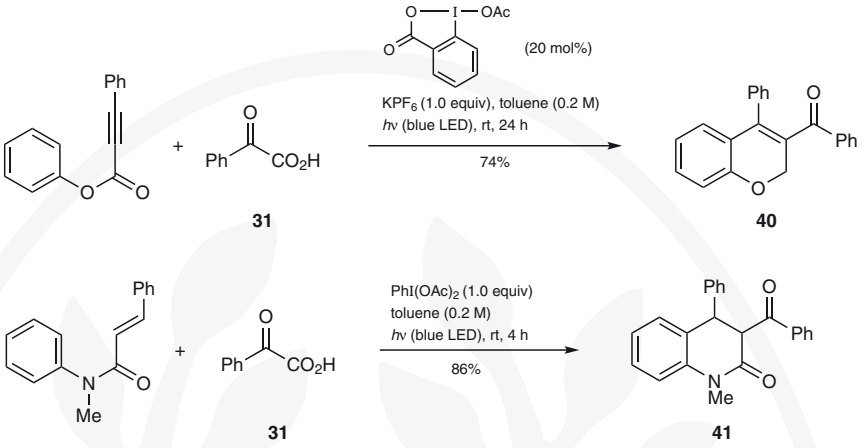
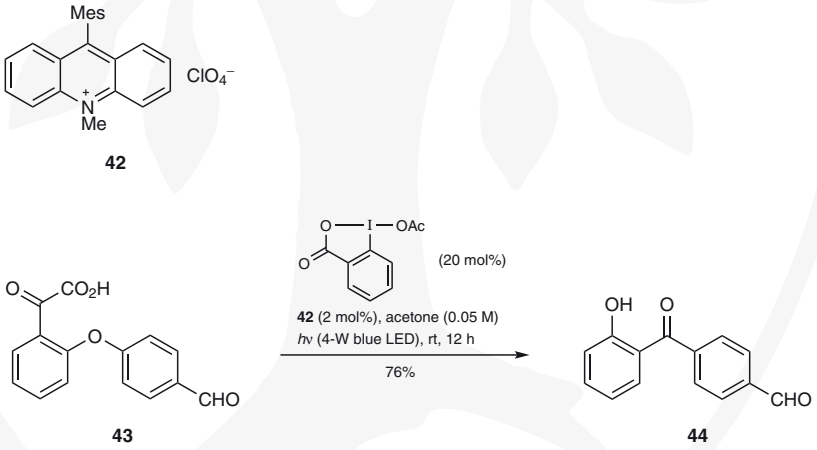


α-Oxo acids and hypervalent iodine can synergistically facilitate rearrangement reactions under mild conditions. In a significant advancement reported in 2019, the Y. Chen group pioneered a radical Smiles rearrangement using a dual hypervalent iodine(III)/photoredox catalytic system. This innovative approach enables the efficient transformation of various biaryl ethers (e.g., **43**) into hydroxybenzophenones (e.g., **44**) using 9-mesityl-10-phenylacridin-10-ium perchlorate (**42**) as photocatalyst and a catalytic amount of 1-acetoxy-1,2-benziodoxol-3(1*H*)-one (Scheme 17).[25] Notably, the reaction proceeds smoothly in phosphate-buffered saline (PBS; pH 7.4) solutions with a stoichiometric amount of 1-acetoxy-1,2-benziodoxol-3(1*H*)-one, highlighting its potential for biocompatible applications.

Scheme 17 Smiles Rearrangement by Dual Hypervalent Iodine(III)/Photoredox Catalysis[25]



Alkyl radicals generated via activation by hypervalent iodine complexation readily undergo 1,5-hydrogen-atom transfer (1,5-HAT) under mild conditions. The Y. Chen group synthesized iminophenylacetic acid derivatives to facilitate alkoxyl radical generation using alk-1-ynylbenziodoxolone hypervalent reagents (e.g., **32**) (Scheme 18).[26] Mechanistic investigations and X-ray crystallography revealed the structure of the crucial alkoxyl benziodoxolone iminophenylacetic acid complex (as analogue **46**). Such complexes have a significantly reduced oxidation potential, enabling efficient single-electron oxidation. This approach selectively functionalizes δ-C(sp^3)—H bonds through alkynylation, leading to the synthesis of diverse δ-alkynols (e.g., **45**).

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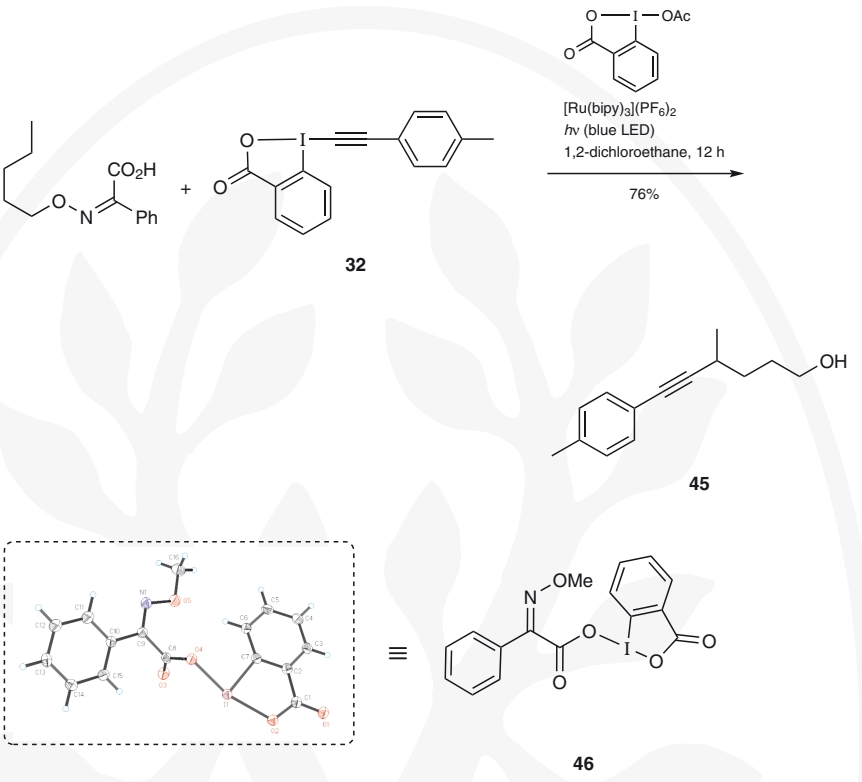
Scheme 18 Synthesis of δ-Alkynols by 1,5-Hydrogen-Atom Transfer[26]



Oxamic acids can undergo oxidative decarboxylation when activated by a hypervalent iodine reagent. In 2018, Landais and co-workers developed a photocatalytic method to synthesize urethanes and ureas from oxamic acids using 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN; **47**) as photocatalyst (Scheme 19).[27] Intermediate trapping experiments suggest that 1-acetoxy-1,2-benziodoxol-3(1*H*)-one, acting as the terminal oxidant, reacts with the oxamic acid to form an unstable benziodoxolone oxamic acid complex. This complex generates an amidocarboxyl radical, which is subsequently oxidized by the photocatalyst radical cation to form the corresponding protonated isocyanate. The protonated isocyanate then either loses a proton to yield an isocyanate or reacts in situ with alcohols and amines to produce urethanes and ureas, respectively.

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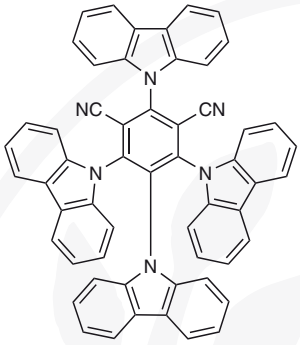
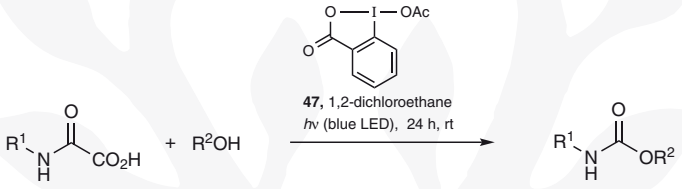
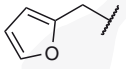
Scheme 19 Synthesis of Urethanes by Visible-Light Photocatalyzed Oxidative Decarboxylation of Oxamic Acids[27]



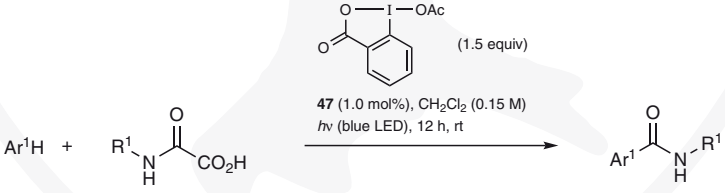
47



R^1	R^2	Yield (%)	Ref
CHPhMe	Et	86	[27]
Bn	CH_2CF_3	48	[27]
	Et	40	[27]
1-adamantyl	1-adamantyl	68	[27]

Using a similar photocatalytic approach, the same group achieved the addition of carbamoyl radicals to N-heterocycles under metal-free conditions (Scheme 20).[28]

Scheme 20 Addition of Carbamoyl Radicals to N-Heterocycles[28]



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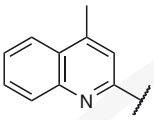
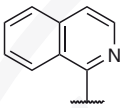
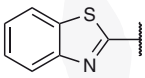
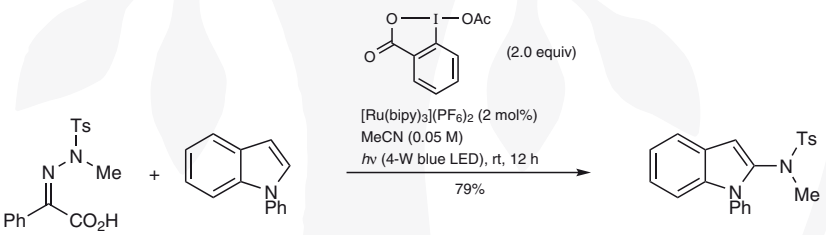
Ar^1	R^1	Yield (%)	Ref
	$(CH_2)_5Me$	90	[28]
	Cy	80	[28]
	CHPhMe	93	[28]

Sulfonamides are ubiquitous in a wide range of bioactive molecules. They play a crucial role in various biological processes and have found extensive applications in medicine, agriculture, and materials science. C(sp^2)—H sulfonamidation is a valuable approach for introducing sulfonamide groups into (het)arenes. In 2022, the Y. Chen group reported the synthesis of *N*-(het)arylsulfonamides (e.g., **49**) through C(sp^2)—H amidation using bench-stable amidyl iminophenylacetic acids (e.g., **48**) (Scheme 21).[29] The hypervalent iodine reagent 1-acetoxy-1,2-benziodoxol-3(1*H*)-one covalently activates the iminophenylacetic acid, facilitating the generation of sulfonamidyl radicals under mild photocatalytic oxidative conditions. A wide range of indoles, pyrroles, imidazopyridines, and fused arenes undergo C(sp^2)—H amidation with exceptional chemo- and regioselectivity.

Scheme 21 Synthesis of *N*-Methyl-*N*-(1-phenyl-1*H*-indol-2-yl)-4-toluenesulfonamide via C(sp^2)—H Amidation of 1-Phenyl-1*H*-indole with an Amidyl Iminophenylacetic Acid[29]



Significant advancements in photoredox-mediated alkylation of aromatic heterocycles have reshaped the field, with multiple research groups pioneering novel methods that leverage hypervalent iodine reagents and visible-light irradiation. Early work, dating back to 1991, demonstrated the alkylation of aromatic heterocycles using bis(trifluoroacetoxy)iodobenzene under UV-light irradiation, facilitated by hypervalent iodine(III) coordinated carboxylates.[30] In 2018, the Zhang group developed a method for direct decarboxylative coupling of carboxylic acids with N-heterocycles under visible-light irradiation (Table 1, entry 1).[31] This reaction, remarkable for its simplicity, proceeds without the need for a photocatalyst or additional acid additives. The mechanism involves a ligand exchange between [bis(trifluoroacetoxy)iodo]benzene and the alkyl carboxylic acid. Concurrently, the Frenette group introduced another innovative protocol for visible-light C—H alkylation of heteroaromatics via hypervalent iodine promoted decarboxylation, using 9-mesityl-10-phenylacridin-10-ium perchlorate (**50**) as photocatalyst (entries 2–4).[32] Additionally, the G. Chen group reported a photoredox-mediated Minisci alkylation of N-hetarenes (entry 5).[33] This method, employing tris(2,2′-bipyridyl)ruthenium(II) chloride {$[Ru(bipy)_3]Cl_2$} as the photocatalyst

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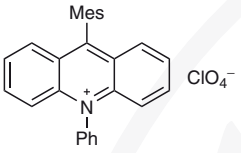
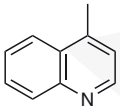
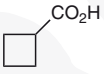
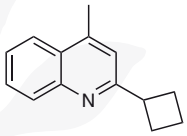
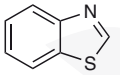
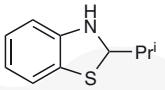
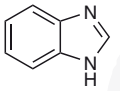
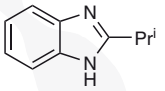
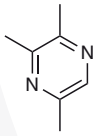
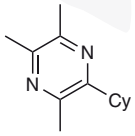
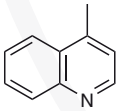
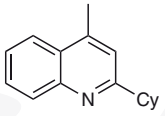
and 1-acetoxy-1,2-benziodoxol-3(1*H*)-one as the oxidant, enables efficient incorporation of a diverse range of primary, secondary, and tertiary alkyl groups into various electron-deficient N-heterarenes.

Table 1 C—H Alkylation of Heteroaromatics via Hypervalent Iodine Promoted Decarboxylation[31–33]



50



Entry	Hetarene	Carboxylic Acid	Conditions	Product	Yield (%)	Ref
1			$PhI(O_2CCF_3)_2$ (2 equiv), acid (4 equiv), MeCN, *hv* (12-W blue LEDs), rt, N_2, 12 h		82	[31]
2		$iPrCO_2H$	**50** (1 mol%), $PhI(O_2CCF_3)_2$ (2 equiv), acid (3 equiv), MeCN, *hv* (32-W blue LEDs), rt, 16 h		69	[32]
3		$iPrCO_2H$	**50** (1 mol%), $PhI(O_2CCF_3)_2$ (2 equiv), acid (3 equiv), MeCN, *hv* (32-W blue LEDs), rt, 16 h		52	[32]
4		$CyCO_2H$	**50** (1 mol%), $PhI(O_2CCF_3)_2$ (2 equiv), acid (3 equiv), MeCN, *hv* (32-W blue LEDs), rt, 16 h		78	[32]
5		$CyCO_2H$	$[Ru(bipy)_3]Cl_2$ (1 mol%), 1-acetoxy-1,2-benziodoxol-3(1*H*)-one (2.0 equiv), $(CF_3)_2CHOH$, *hv* (18-W CFL), 30 °C, 8 h		80	[33]

1,3-Diphenylprop-2-yn-1-one (36, **$R^1 = R^2 =$ Ph); Typical Procedure:**[5]
A 5-mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with 2-oxo-2-phenylacetic acid (0.60 mmol, 3 equiv), (bromoethynyl)benzene (0.20 mmol), 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (0.06 mmol, 30 mol%), and toluene (1.0 mL) under air. The mixture was exposed to sunlight at rt for 8 h. After completion of the reaction, the mixture was concentrated. The crude product was further purified by flash chromatography (silica gel, petroleum ether/EtOAc 15:1 to 30:1); yield: 25.6 mg (62%).

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2-Cyclobutyl-4-methylquinoline (Table 1, Entry 1):[31]
4-Methylquinoline (0.4 mmol, 1.0 equiv), cyclobutanecarboxylic acid (1.6 mmol, 4.0 equiv), and $PhI(O_2CCF_3)_2$ (0.8 mmol, 2.0 equiv) were placed in a dry 10-mL Schlenk tube under N_2. Anhyd MeCN (4.0 mL) was added by syringe. The mixture was stirred and irradiated using 12-W blue LEDs at rt for 12 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2 and washed with sat. aq $NaHCO_3$. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude product was purified by flash column chromatography (silica gel); yield: 65 mg (82%).

12.2.1.2 Alcohol Activation

The direct generation of alkoxyl radicals from alcohols offers the most straightforward and efficient approach for the formation of such radical species. However, the high bond-dissociation energy of the O—H bond in alcohols poses a significant thermodynamic and synthetic challenge for homolytic cleavage. Recent advancements have enabled the generation of alkoxyl radicals from alcohol compounds through hypervalent iodine activation. These reactive alkoxyl radical intermediates can undergo β-scission or 1,5-hydrogen-atom transfer (1,5-HAT), etc., leading to a variety of synthetically useful transformations.[34]

In 2017, the Y. Chen group pioneered a visible-light-induced method for generating alkoxyl radicals from both strained cycloalkanols (Table 2, entries 1 and 2)[34] and linear alcohols (entries 3–5)[35] with cyclic hypervalent iodine(III) reagents. This approach facilitates selective $C(sp^3)$—$C(sp^3)$ bond cleavage and subsequent alkynylation reactions using alk-1-ynylbenziodoxolones (e.g., **32**) as radical acceptors. This activation mode is extended to P(O)—$C(sp^3)$ bond cleavage for phosphine radical generation and the further radical alkynylation of α-phosphorus alcohols, enabling the efficient synthesis of phosphonoalkynes (entries 6–8).[36] The use of alcohols as radical precursors enables radical addition reactions through a mechanism analogous to the activation of carboxylic acids by hypervalent iodine(III) reagents.

for references see p 520

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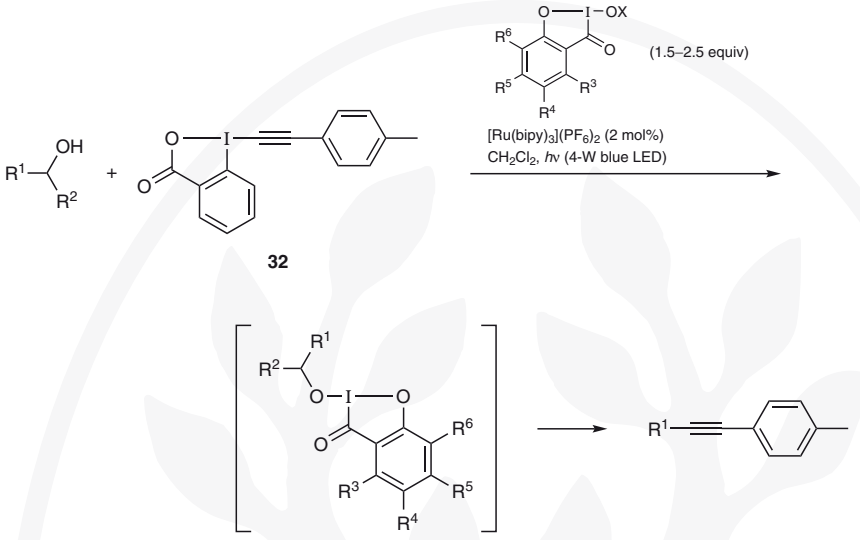
Table 2 Alkynylation by Activation of Alcohols with Cyclic Hypervalent Iodine Reagents[34–36]



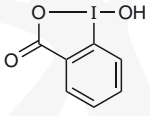
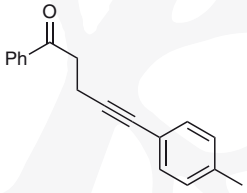
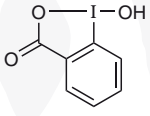
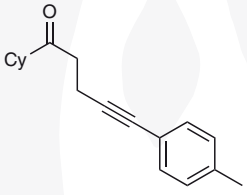
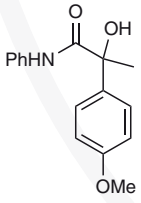
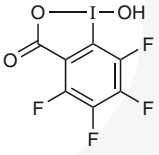
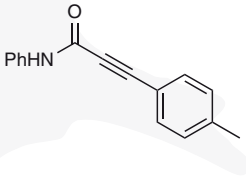
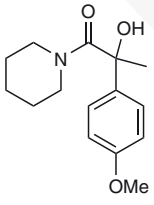
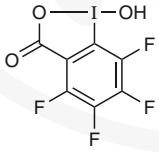
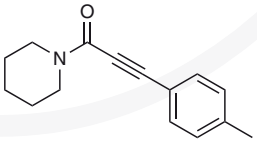
Entry	Alcohol	Additive	Product	Yield (%)	Ref
1		 (2.5 equiv)		85	[34]
2		 (2.5 equiv)		69	[34]
3		 (2.0 equiv)		76	[35]
4		 (2.0 equiv)		89	[35]

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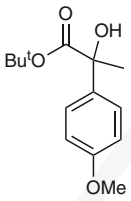
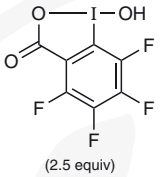
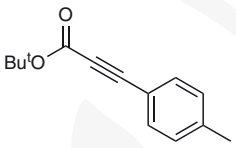
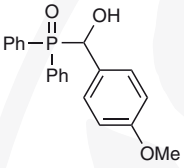
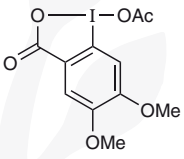
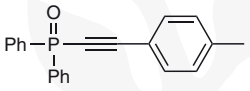
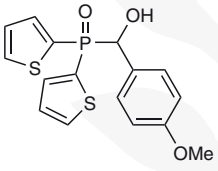
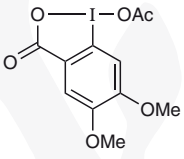
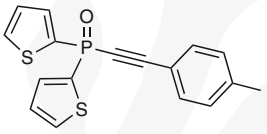
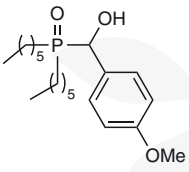
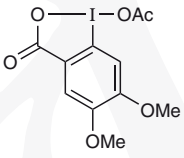
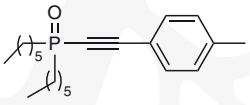
Table 2 (cont.)

Entry	Alcohol	Additive	Product	Yield (%)	Ref
5		 (2.5 equiv)		73	[35]
6		 (1.5 equiv)		83	[36]
7		 (1.5 equiv)		76	[36]
8		 (1.5 equiv)		77	[36]

In 2019, the Liu group reported a method for the precise cleavage of C—C bonds in alcohols. This method exhibits broad functional-group tolerance, accommodating a wide range of primary, secondary, and tertiary alcohols, including saccharides and steroids, regardless of ring strain or steric hindrance. For example, the C—H alkylation of lepidine with a range of primary, secondary, and tertiary alcohols affords 2-alkyl-4-methylquinolines **51** (Scheme 22).[37]

for references see p 520

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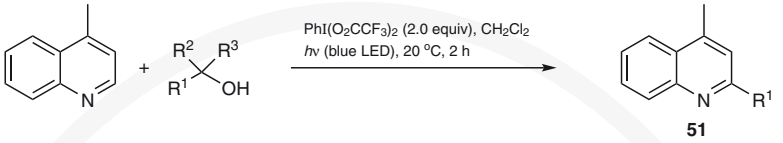
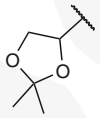
Scheme 22 Synthesis of 2-Alkyl-Substituted Quinoline Derivatives[37]

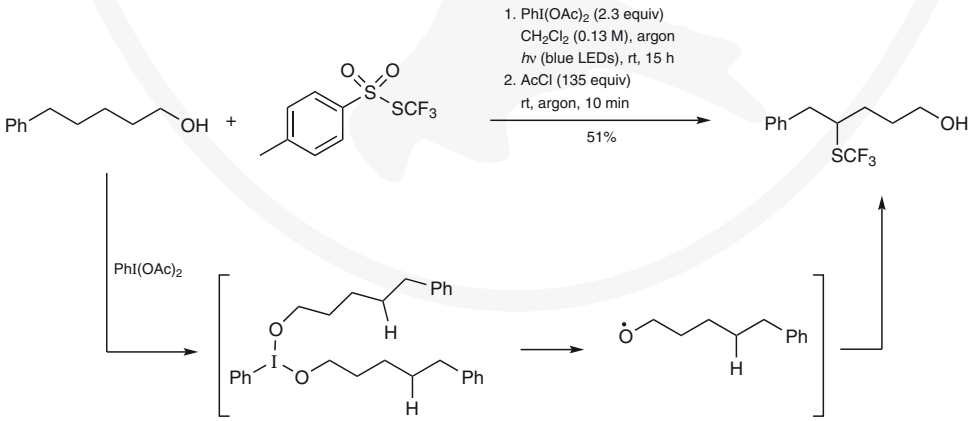


R^1	R^2	R^3	Yield (%)	Ref
MOM	H	H	39	[37]
cyclopentyl	H	H	85	[37]
t-Bu	H	H	95	[37]
	H	H	74	[37]
iPr	Me	H	85	[37]
Bz	Me	Me	75[a]	[37]

[a] Reaction time was 12 h.

The 1,5-hydrogen-atom abstraction process, which can be achieved under a variety of reaction conditions, enables a range of significant transformations. Besset and co-workers developed a methodology allowing for the remote and direct construction of a C(sp^3)—SCF_2R^1 bond on aliphatic alcohols through 1,5-hydrogen-atom transfer (Scheme 23).[38] This transition-metal-free approach provides access to fluorinated molecules that are otherwise challenging to synthesize. A variety of fluorinated moieties are successfully incorporated with complete regioselectivity at a distal position on primary, secondary, and even tertiary alcohols, in the presence of the hypervalent iodine reagent (diacetoxyiodo)benzene [phenyliodine(III) diacetate, PIDA] and readily available *S*-fluoroalkyl 4-toluenesulfonothioate reagents. Key features of this transformation include the use of free alcohols, the absence of photocatalysts or transition-metal-catalysts, the versatility and applicability of the method toward various SCF_2R^1 [R^1 = H, F, CO_2Et, and $PO(OEt)_2$] groups, and the precise control of regioselectivity for the δ-position. By addressing an unmet synthetic challenge, the approach opens new pathways to synthetic routes for fluorinated scaffolds and significantly expands the repertoire of aliphatic SCF_2R^1 containing molecules.

Scheme 23 Synthesis of a (Trifluoromethyl)sulfanyl-Containing Alcohol[38]



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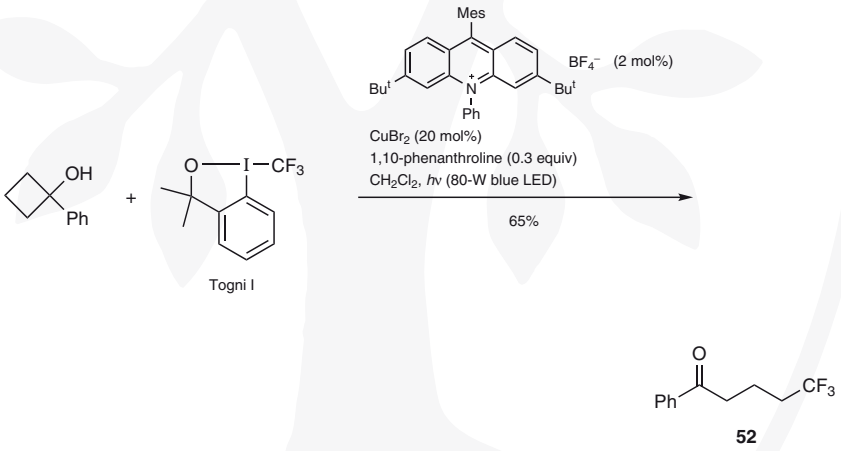
The presence of a perfluoroalkyl group at the terminal position of drug molecules increases the lipophilicity and metabolic stability. In 2021, the Y. Chen group developed a convenient method for the selective introduction of terminal trifluoromethyl groups onto aryl and alkyl ketones at the γ, δ, ε, or more distant positions through the selective cleavage of C—C bonds in cycloalkanols (Scheme 24).[39] This transformation is enabled by synergistic noncovalent interactions between the alcohol and the hypervalent iodine(III) reagent, facilitating the activation of both the alcohol and the Togni reagent I [1,3-dihydro-3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole] within a dual photoredox/copper catalytic system, using 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate as photocatalyst. For example, 5,5,5-trifluoro-1-phenylpentan-1-one (**52**) is obtained from 1-phenylcyclobutan-1-ol in 65% yield under these conditions. The scalability of this reaction, demonstrated by a gram-scale synthesis, and its effectiveness in the trifluoromethylation of structurally complex steroids highlight its potential for practical applications.

In 2023, the Y. Chen group presented a protocol for synthesizing distal amido ketones and nitrogen-functionalized ketones from alcohols and NH nucleophiles, leveraging dimethyl benziodoxoles (Scheme 24).[40] The method involves dual activation of alcohols and various NH nucleophiles through the formation of crucial dimethyl benziodoxole complexes, by reaction with 3,3-dimethyl-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-ol. Commonly available NH nucleophiles such as imides, sulfonamides, carbamates, triazoles, indazoles, and sulfoximines participate in photoredox/copper catalysis to afford distal amido ketones and nitrogen-functionalized ketones (e.g., **53**) with exceptional regio- and chemoselectivity. This scalable protocol is applicable for late-stage modifications of complex molecules, streamlining synthetic pathways. One dimethyl benziodoxole complex with an NH nucleophile was characterized via X-ray crystallography and computationally investigated.

Scheme 24 Distal Functionalization of Cycloalkanols for Ketone Synthesis[39,40]



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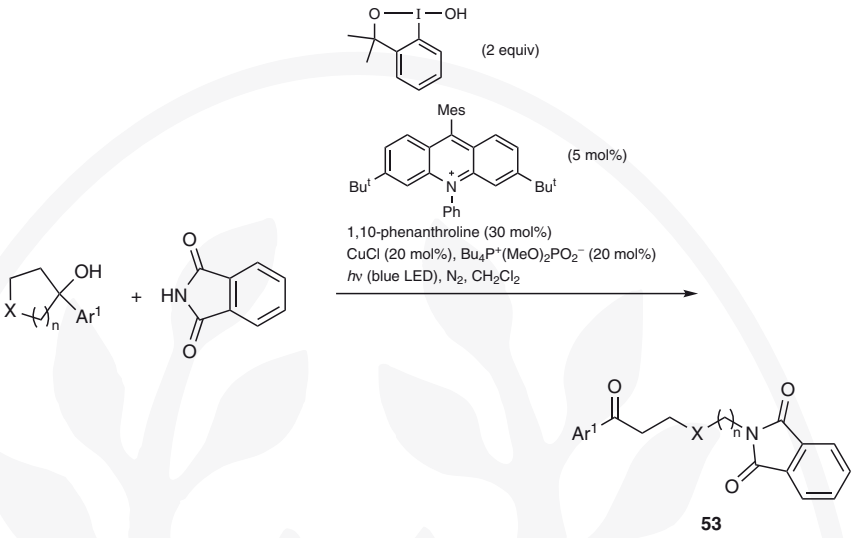
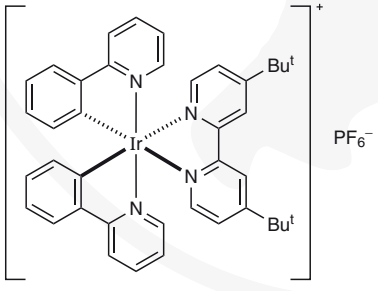


Ar^1	X	n	Yield (%)	Ref
4-Tol	CH_2	1	76	[40]
4-$MeOC_6H_4$	CH_2	1	77	[40]
4-$MeOC_6H_4$	O	2	79	[40]
4-$MeOC_6H_4$	CH_2	8	75	[40]

The same group has also reported that cyclic iodine(III) reagents facilitate the synthesis of cyclopentanones, cyclohexanones, and dihydrofuranones bearing α-quaternary centers via photoredox catalysis using iridium complex **54** {[$Ir(ppy)_2(dtbbpy)$]PF_6} as photocatalyst (Scheme 25).[41] The reaction proceeds through the formation of complexes of a cyclic iodine(III) reagent with allylic alcohols, enabling the first alkylboronate addition/semipinacol rearrangement of allylic alcohols with dual activation of both the alcohol and the double bond. Tertiary carbon centers play a crucial role in bioactive small molecules, yet their efficient construction remains a formidable synthetic challenge. This method offers significant progress in overcoming this challenge. The same activation mode can be applied in amide compounds.[11]

Scheme 25 Cyclic Iodine Reagent Enabled Alkylboronate Addition/Rearrangement of Allylic Alcohols under Photoredox Catalysis[41]



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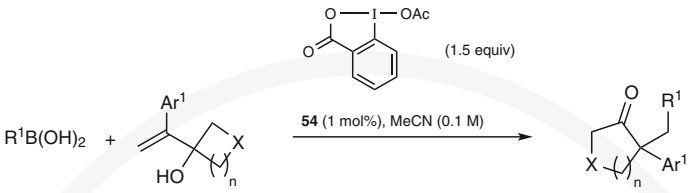
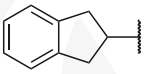
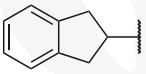


R^1	Ar^1	X	n	Yield (%)	Ref
	4-PhC_6H_4	CH_2	1	70	[41]
Cy	4-PhC_6H_4	CH_2	1	75	[41]
s-Bu	4-PhC_6H_4	CH_2	1	63	[41]
Cy	4-ClC_6H_4	O	1	73	[41]
	4-Tol	CH_2	2	75	[41]

5,5,5-Trifluoro-1-phenylpentan-1-one (52)**:**[39]
1-Phenylcyclobutan-1-ol (22 mg, 0.15 mmol, 1.5 equiv), Togni reagent I (33 mg, 0.1 mmol, 1.0 equiv), 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (1.1 mg, 2 µmol, 2 mol%), $CuBr_2$ (4.5 mg, 0.02 mmol, 20 mol%), and 1,10-phenanthroline (5.4 mg, 0.03 mmol, 30 mol%) were placed in a 4-mL clear-colored glass vial equipped with a magnetic stirrer bar. Degassed CH_2Cl_2 (2.0 mL) was added and the vial was sealed under N_2, and then the stirred mixture was exposed to irradiation by an 80-W LED light bulb, positioned 5-cm away from the vial, at rt for 2 h. After TLC indicated the complete consumption of starting materials, the mixture was concentrated and the residue was directly purified by column chromatography (petroleum ether/EtOAc) to afford a white solid; yield: 14 mg (65%).

2-[5-Oxo-5-(4-tolyl)pentyl]isoindoline-1,3-dione (53**, X = CH_2; n = 1); Typical Procedure:**[40]
3,6-Di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate (2.8 mg, 5 µmol, 5 mol%) and 1,10-phenanthroline (5.4 mg, 0.03 mmol, 30 mol%), CuCl (2.0 mg, 0.02 mmol, 20 mol%), phthalimide (0.1 mmol, 1.0 equiv), 3,3-dimethyl-1λ³-benzo[*d*][1,2]iodaoxol-1(3*H*)-ol (55.6 mg, 0.2 mmol, 2.0 equiv), tetrabutylphosphonium dimethyl phosphate (7.7 mg, 0.02 mmol, 20 mol%), and 1-(4-tolyl)cyclopentan-1-ol 1 (35.2 mg, 0.2 mmol) were added to a 4-mL flask equipped with a stirrer bar. The flask was sealed and evacuated and backfilled with N_2 three times. CH_2Cl_2 (2 mL) was added and the stirred mixture was irradiated with an 80-W blue LED light bulb, positioned 5-cm away from the vial, for 12 h. The crude product was purified by flash column chromatography to afford a white solid; yield: 24.4 mg (76%).

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12.2.2 Noncovalent Activation

While covalent activation dominates current applications of hypervalent iodine reagents, noncovalent activation represents an underexplored frontier with transformative potential. Hypervalent iodine reagents can engage substrates through noncovalent interactions, such as hydrogen bonding, halogen bonding, or electron donor–acceptor (EDA) complexation, with molecules containing N—H/O—H bonds, π-systems, or electron-deficient groups. These interactions transiently polarize substrates or stabilize transition states, lowering activation barriers and enabling reactions under mild conditions.

For example, EDA complexes formed between iodine(III) reagents and electron-rich aromatics facilitate direct C—H functionalization without covalent activation.[42] By circumventing stoichiometric metal catalysts or harsh reagents, noncovalent activation aligns with green chemistry principles and opens pathways for biocompatible synthesis.

12.2.2.1 Amine Activation

Cyclopropyl amide derivatives, characterized by their relatively high redox potentials, are less likely to undergo efficient single-electron transfer (SET) with photochemically excited sensitizers, thereby limiting their utility in photochemical transformations. Nevertheless, through noncovalent activation by cyclic hypervalent iodine(III) reagents, effective photocatalytic transformations of these substrates can be realized.

In 2021, the Y. Chen group reported the synthesis of aminoalkynes (e.g., **56**) from alk-1-ynylbenziodoxolone reagents (e.g., **55**) under mild catalytic photoredox conditions using 9-mesityl-10-phenylacridin-10-ium tetrafluoroborate as photocatalyst (Scheme 26).[43] The method utilizes *N*-cyclopropyl- and *N*-cyclobutylamides as radical precursors, and the alk-1-ynylbenziodoxolone reagent as a radical acceptor. It efficiently constructs γ- and δ-aminoalkynes via selective β-bond fragmentation of the amidyl radical (e.g., **58**), followed by alkyl radical addition to the alkyne. Various α-amino substituents can be further introduced into the aminoalkynes by nucleophilic trapping of oxygen, sulfur, and carbon nucleophiles. The resulting aminoalkynes serve as versatile precursors for the synthesis of diverse bioactive fused azacycles.

Significantly, this work unveiled the noncovalent activation of hypervalent iodine(III) reagents with *N*-cycloalkylamides, a departure from the covalent activation observed with carboxylates and alcohols. The 5,6-dimethoxy-3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate reagent engages *N*-cyclopropylamide substrates via intermolecular hydrogen bonding and halogen bonding (as shown in adduct **57**), thereby lowering the activation energy barrier of the substrate. Notably, the 5,6-dimethoxy-3-oxo-1λ^3-benzo[*d*][1,2]iodaoxol-1(3*H*)-yl acetate reagent adopts dual roles: it acts as a hydrogen-bond acceptor, forming an AcO···H—N interaction with the amide NH group, while simultaneously functioning as a halogen-bond donor to the carbonyl oxygen (I···O═C). This cooperative bonding mechanism greatly enhances the activation efficacy of the reagent.

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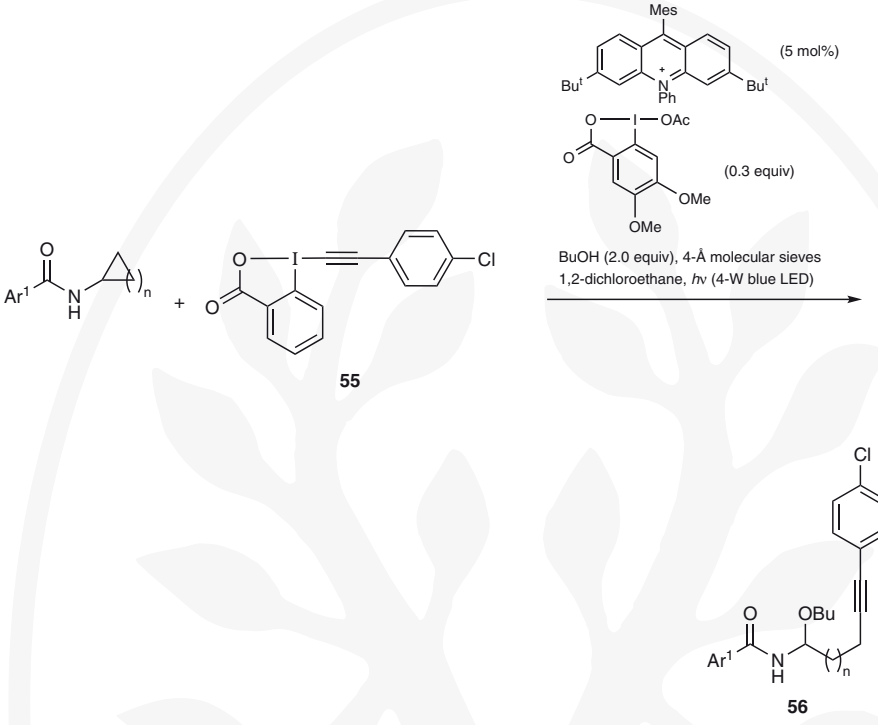
Scheme 26 Synthesis of an Aminoalkyne by Selective C(sp^3)—C(sp^3) Cleavage/Alkynylation of an *N*-Cyclopropylamide[43]



Ar^1	n	Yield (%)	Ref
4-Tol	1	80	[43]
3,4,5-$(MeO)_3C_6H_2$	2	71	[43]

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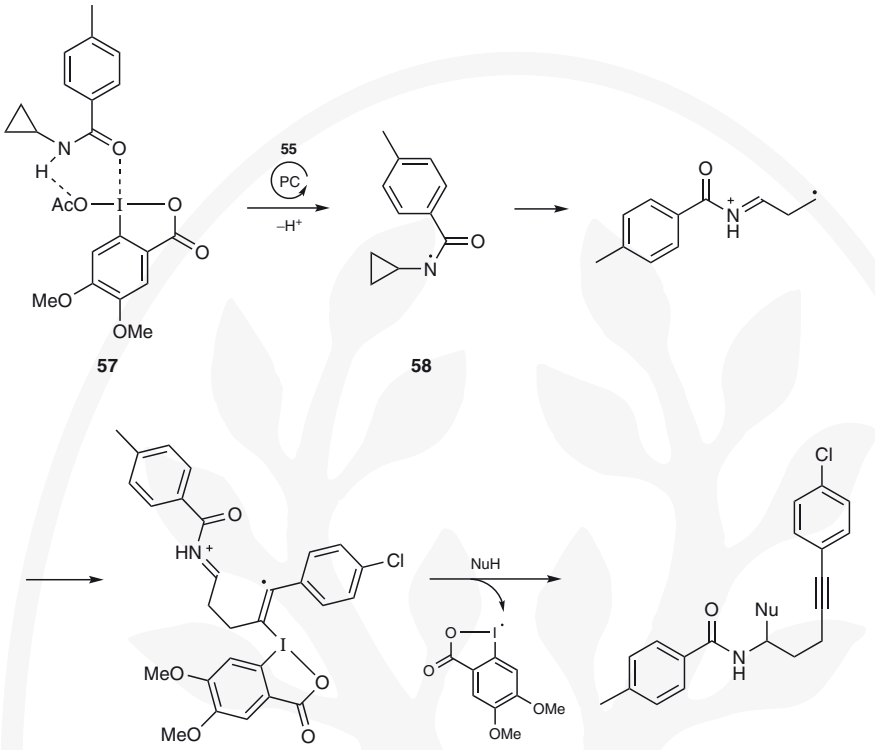
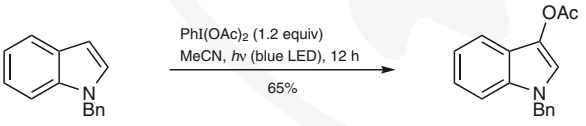


12.2.2.2 Activation by Electron Donor–Acceptor (EDA) Complex Formation

A noncovalent activation mode can also be achieved via formation of an EDA complex between a hypervalent iodine reagent and a substrate. Such complexes can readily undergo transformation under mild conditions, without the need for an external photosensitizer. The essence of the reaction mechanism lies in the formation of the EDA complex, which promotes activation of the substrate through an electron-transfer process, thereby enabling efficient light-induced electron-transfer processes. In 2023, Yadav and co-workers reported an efficient visible-light-mediated photochemical transformation of indoles into the corresponding 3-acetoxylated derivatives (e.g., **59**) under photocatalyst-free conditions at ambient temperature (Scheme 27).[42] An EDA complex (e.g., **60**), formed between the indole and a hypervalent iodine compound such as (diacetoxyiodo)-benzene, undergoes light-induced electron-transfer processes upon visible-light excitation. This single-electron-transfer (SET) event generates synthetically useful intermediates for the regioselective acetoxylation of indoles.

Scheme 27 Synthesis of 3-Acetoxylated Indole Derivatives and a Possible Mechanism[42]



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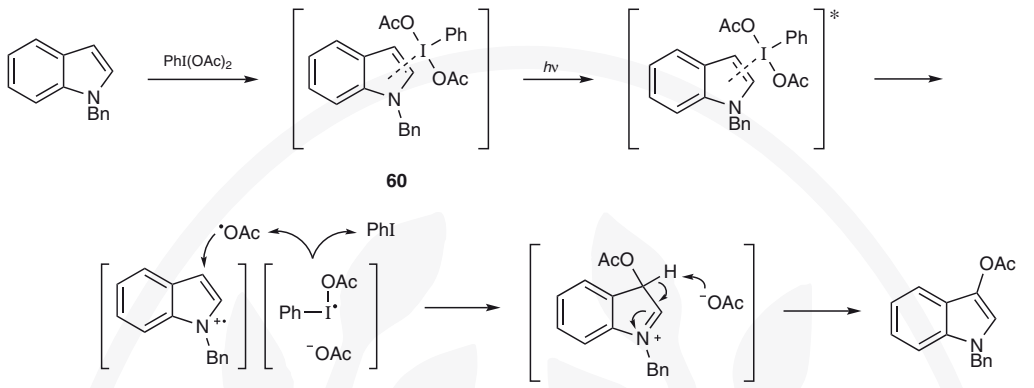

12.3 Hypervalent Iodines as Functionalization Reagents in Photochemistry

Radical reactions have garnered considerable interest in organic synthesis for their single-electron mechanistic pathways and diverse substrate compatibility. In recent years, hypervalent iodine reagents have established themselves as versatile radical precursors, operating under mild conditions while exhibiting exceptional functional-group tolerance. These reagents combine environmental benignity with operational simplicity, generating diverse reactive radicals via single-electron transfer (SET) or photoinduced homolysis under mild conditions. The resulting radicals participate in high-yielding additions, cyclizations, and cross couplings, while the tunable ligand frameworks enable precise control over site-selective azidation, diazomethylation, amination, and fluoroalkylation. Their enhanced selectivity and superior atom economy render such radical species indispensable for constructing intricate molecular architectures, particularly in natural product synthesis. Furthermore, the inherent green chemistry advantages (low toxicity, minimal byproduct generation, and energy-efficient activation) position this approach as a cornerstone tool for sustainable synthesis. This section reviews advancements in hypervalent iodine reagents as photochemical radical precursors, detailing their mechanistic underpinnings (e.g., SET, bond homolysis) and synthetic applications.

12.3.1 Radical Precursors

Hypervalent iodine reagents have emerged as tunable photochemical radical precursors, merging atom-efficient radical generation with unmatched versatility, while advancing sustainable synthetic strategies. Under visible-light irradiation, these reagents generate organic radicals through two distinct pathways:

(1) Single-electron transfer (SET): stabilizes charge-separated intermediates, enabling redox-neutral transformations.

(2) Polarized I—L bond homolysis: exploits the weakened I—L bond to produce radicals via clean, light-driven cleavage.

The resulting radicals participate in intermolecular additions, cyclizations, and cross couplings, achieving high regioselectivity and functional-group tolerance.[44] For instance, this reactivity has been harnessed to assemble polycyclic drug candidates and agrochemical intermediates in fewer steps than traditional methods.

This versatility of the dual pathway allows hypervalent iodine reagents to operate under mild, metal-free conditions, circumventing toxic byproducts and energy-intensive protocols. Their compatibility with visible light, including sunlight in some cases, aligns with green chemistry principles, minimizing waste while maximizing atom economy. By enabling the synthesis of complex

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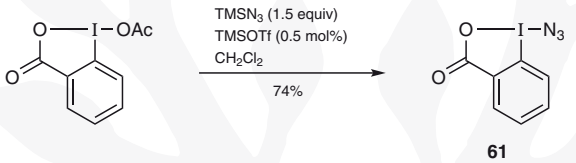
scaffolds (e.g., heterocycles, stereodefined alkenes), these reagents are redefining workflows in pharmaceutical development (e.g., kinase inhibitors).[45–47] As the demand for sustainable methodologies grows, hypervalent iodine stands at the forefront of precision synthesis, bridging efficiency with environmental stewardship.

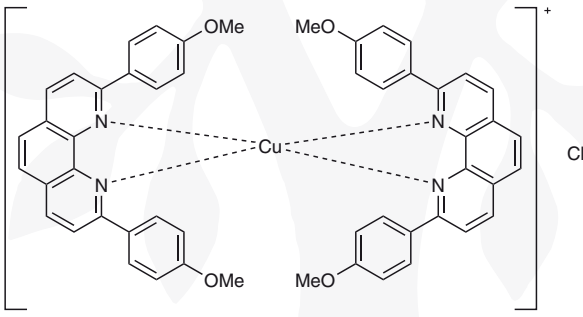
12.3.1.1 Azidation Reagents

The use of photoredox catalysis to activate 1-azido-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**61**; Zhdankin reagent) for enhanced azidation has emerged within the past decade. In 2013, Greaney and co-workers employed copper–2,9-bis(4-methoxyphenyl)-1,10-phenanthroline complex **62** in combination with the Zhdankin reagent to catalyze various azidation reactions (Scheme 28).[48,49] The azidation of styrene-type double bonds can be controlled by the light: visible-light irradiation favors oxoazidation to form monoazide products **63** (X = OMe), whereas dark conditions lead to diazidation products **63** ($X = N_3$).

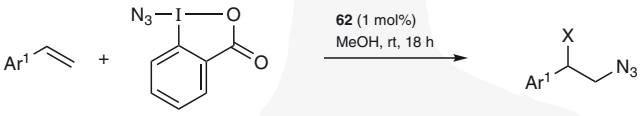
Scheme 28 Preparation of the Zhdankin Reagent, and Its Application in Light-Switchable Azidation of Styrenes[48,49]



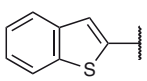
61



62



61 **63**

Ar^1	X	Conditions	Yield (%)	Ref
Ph	OMe	*hν* (30-W fluorescent bulb)	60	[49]
Ph	N_3	in the dark	96	[49]
4-BrC_6H_4	N_3	in the dark	97	[49]
2-naphthyl	N_3	in the dark	92	[49]
	OMe	*hν* (30-W fluorescent bulb)	80	[49]

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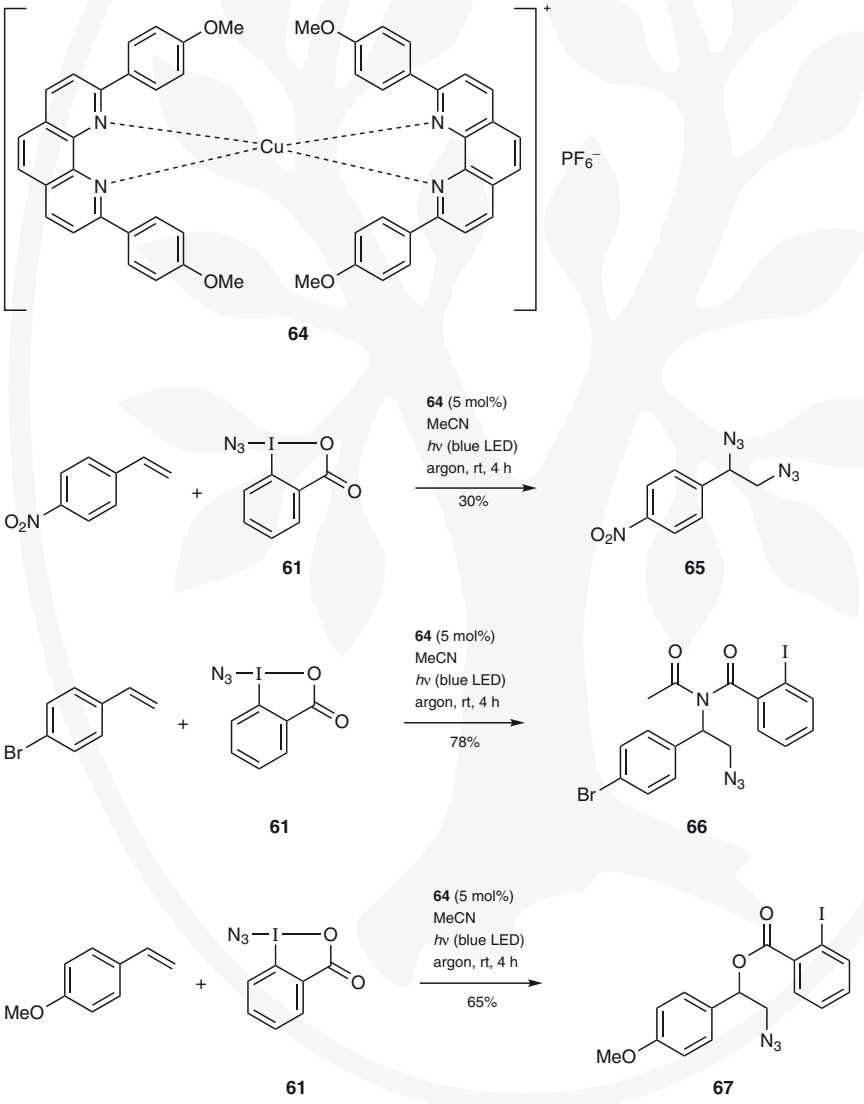
Yu and co-workers used the copper–2,9-bis(4-methoxyphenyl)-1,10-phenanthroline complex **64** as a photocatalyst for the reaction of styrenes with the Zhdankin reagent under visible-light irradiation. The outcome of the reaction was shown to depend on the electronic nature of the substrate; diazidation products (e.g., **65**) are obtained with electron-deficient substrates, amidoazidation products (e.g., **66**) with electronically less biased substrates, and benzoyloxyazidation products (e.g., **67**) with electron-rich substrates (Scheme 29).[50] Tang and co-workers employed trifluoromethyl 4-toluenesulfonate and the Zhdankin reagent to achieve azidotrifluoromethoxylation of styrenes through synergistic visible-light-mediated photoredox and silver catalysis in the presence of 4,4′,4″-tri-*tert*-butyl-2,2′:6′2″-terpyridyl to afford, for example, 2-azido-1-phenyl-1-(trifluoromethoxy)ethane (**68**) in 58% yield.[51]

Scheme 29 Photocatalytic Azidations of Styrenes[50,51]



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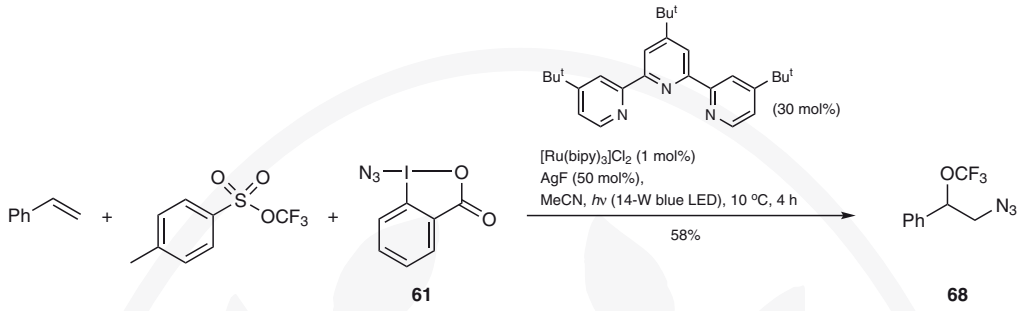
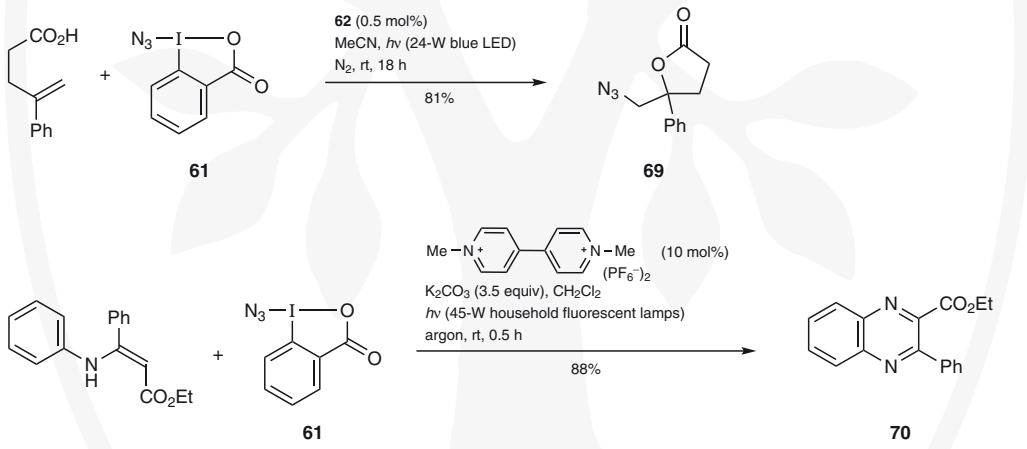


61 68

The azidyl radical generated from the Zhdankin reagent in combination with copper–2,9-bis-(4-methoxyphenyl)-1,10-phenanthroline complex **62** can also be used in tandem addition/cyclization reactions. Waser and co-workers reported a general and versatile synthesis of azidolactones starting from alkene-containing carboxylic acids. A range of 1,1- and 1,2-azidolactones (e.g., **69**) are obtained selectively in high yields with broad functional-group tolerance (Scheme 30).[45] In addition, Yu and co-workers reported the conversion of *N*-arylenamines into quinoxalines (e.g., **70**) via tandem azidation/intramolecular C—H amination under visible-light irradiation, using the Zhdankin reagent as the azidating agent in the presence of a catalytic amount of methyl viologen hexafluorophosphate.[52]

Scheme 30 Photocatalytic Tandem Addition/Cyclization Reactions[45,52]



Recent advances in C—H azidation strategies have included significant progress in the functionalization of both aromatic and aliphatic C—H bonds. The Greaney group reported a benzylic C—H azidation of alkylarenes, under similar copper catalysis conditions, to afford corresponding benzylic azides (e.g., **71**) (Scheme 31).[53] The Chen group reported a new strategy for the C—H azidation of aliphatic substrates, using the Zhdankin reagent under tris(2,2′-bipyridyl)ruthenium(II) chloride {[Ru(bipy)$_3$]Cl$_2$} catalysis and visible-light irradiation, to give C—H functionalization products (Scheme 31).[54] Here, the Zhdankin reagent was used to generate a radical for the azidation of tertiary aliphatic C—H bonds to afford, for example, the tertiary alkyl azide **72** in 80% yield; however, they also found that the addition of a nucleophilic chloride or bromide source gives halogenated products (e.g., **73** and **74**). These reactions are efficient, selective, and compatible with complex substrates.

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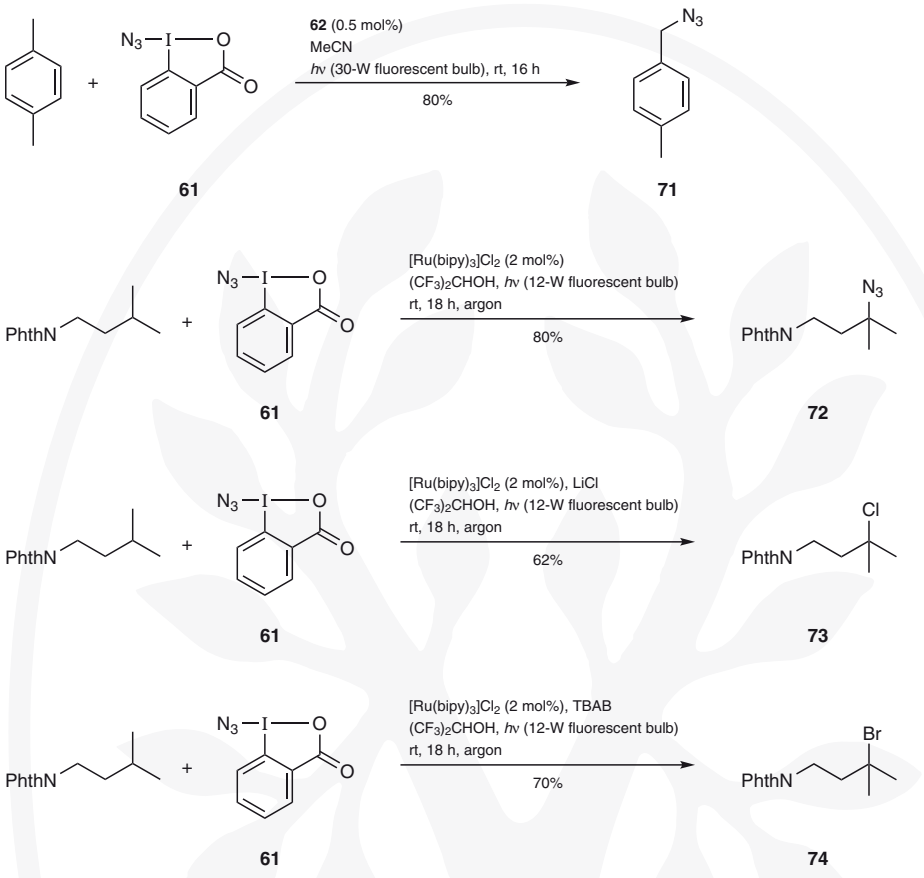
Scheme 31 Photocatalytic C—H Azidation and Halogenation Reactions[53,54]



The Zhdankin reagent can be considered a valuable azide source, but safety concerns have prompted the development of alternatives such as the azidobenziodazolone reagent **75**. The latter has been successfully employed in established photoredox- and metal-mediated azidation reactions.[55] The Waser group utilized **75** as an azidyl radical source to achieve a novel ring-expansion of silylated cyclobutanols to azidated cyclopentanones[55] and the synthesis of quinolines from cyclopropenes.[56] In 2023, they then reported an azidoalkynylation of alkenes, enabling straightforward access to homopropargylic azides **76** by combining **75** and alkynyltrifluoroborate salts (Scheme 32).[57] Under blue-light irradiation, the excited-state ruthenium(II) catalyst reduces **75**, generating the azidyl radical. Subsequently, the azidyl radical adds to the styrene and the resulting carbon radical is oxidized to a benzyl carbocation intermediate (e.g., **77**), which reacts with a nucleophilic alkynyltrifluoroborate salt to yield the product. A variety of homopropargylic azides bearing electron-rich or electron-poor aryl, heterocyclic, or ether substituents could be synthesized in up to 84% yield.

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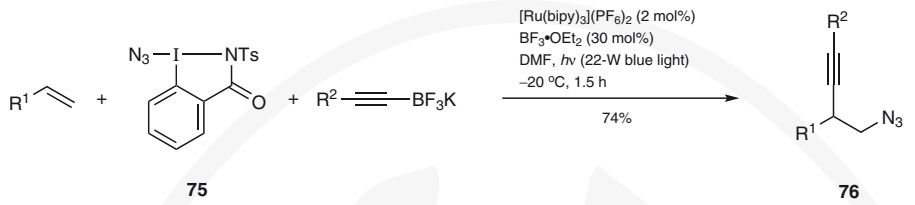
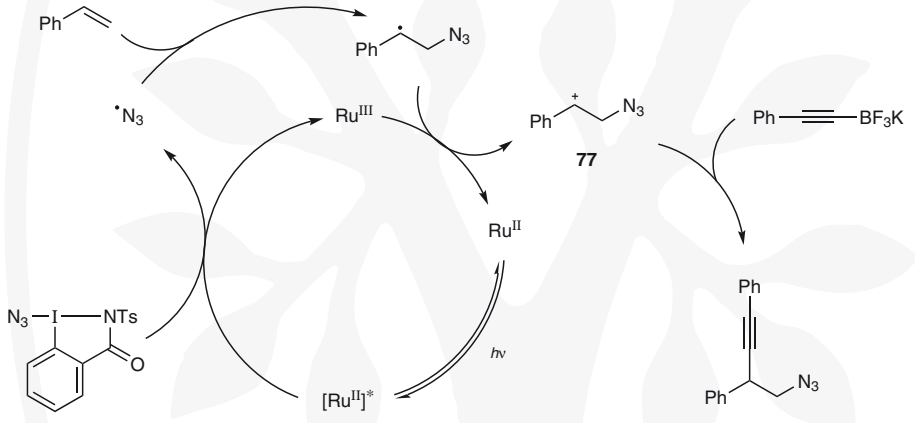
Scheme 32 Photocatalytic Azidoalkynylation of Alkenes[57]



R^1	R^2	Yield (%)	Ref
Ph	Ph	73	[57]
4-$MeOC_6H_4$	Ph	84	[57]
C≡CPh	Ph	44	[57]
4-$AcOC_6H_4$	4-FC_6H_4	67	[57]
4-$MeOC_6H_4$	Me	54	[57]



Additionally, Du and co-workers achieved the synthesis of aryl azides in high yields through a cross-coupling reaction of arylboronic acids with azidobenziodazolone reagent **75** catalyzed by copper powder.[58] This ligand- and base-free transformation exhibits good functional-group tolerance, with **75** serving as a bifunctional reagent, acting as both an oxidant and an azide source.

1-Azido-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (61; Zhdankin Reagent):[48]
1-Acetoxy-1,2-benziodoxol-3(1*H*)-one (1.0 g, 3.28 mmol, 1.0 equiv) was stirred in anhyd CH_2Cl_2 (3 mL). $TMSN_3$ (0.66 mL, 4.9 mmol, 1.5 equiv) was cautiously added. A catalytic amount of TMSOTf (3 µL, 0.02 mmol, 0.5 mol%) was added and the mixture was stirred at rt for 30 min. The mixture was then dried under reduced pressure to give a yellow precipitate, which was washed a few times with hexanes to give the product as pure pale-yellow crystals; yield: 0.70 g (74%).

1-(Azidomethyl)-4-methylbenzene (71):[53]
A vial equipped with a stirrer bar and sealable with a septum was charged with copper–2,9-bis-(4-methoxyphenyl)-1,10-phenanthroline complex **62** (2.2 mg, 2.5 µmol, 0.5 mol%) and 1-azido-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**61**; 145 mg, 0.50 mmol, 1.0 equiv). The vial was purged under a stream of N_2. A degassed mixture of MeCN (2.5 mL) and *p*-xylene (40 equiv, 20 mmol, 2.5 mL) was added and the vial was sealed and positioned 1-cm away from a 30-W fluorescent bulb. The stirred mixture was irradiated at rt for 16 h, and then loaded directly on a column and

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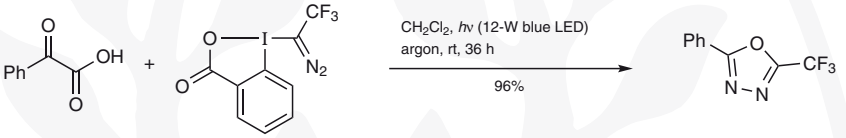
subjected to column chromatography (hexane/CH_2Cl_2 mixtures) to afford a colorless oil; yield: 59 mg (80%).

12.3.1.2 Diazomethylation Reagents

Cyclic iodine(III) diazo reagent **79** and acyclic iodine(III) diazo reagent **81** have been utilized as precursors for generating diazo-2,2,2-trifluoroethyl and diazo(ethoxycarbonyl)methyl radicals. Han and co-workers reported a visible-light-induced [3+2] cycloaddition of the cyclic iodine(III) diazo reagent **79** with α-oxo acids (e.g., **78**) for the construction of 5-(trifluoromethyl)-1,3,4-oxadiazoles (e.g., **80**) (Scheme 33).[46]

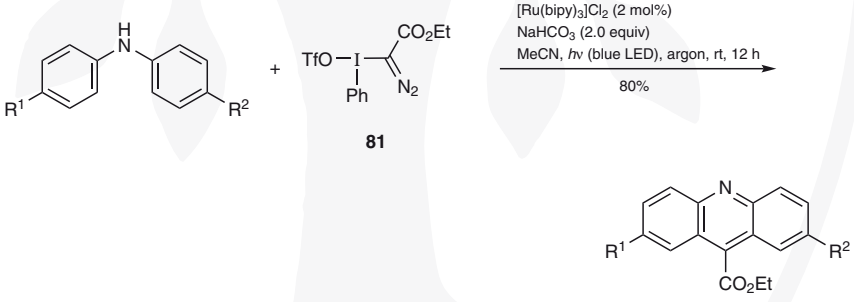
Scheme 33 Photocatalytic Tandem Addition/Cyclization Reaction of 2-Oxo-2-phenylacetic Acid with a Cyclic Iodine(III) Diazo Reagent[46]



78 **79** **80**

Liu, Li, and co-workers reported an efficient synthesis of substituted acridines, through double C—C bond formation via C(sp^2)—H bond activation of diarylamines with hypervalent iodine(III) reagents (e.g., **81**) (Scheme 34).[59] The reaction introduces a diazo group onto the diarylamine and enables subsequent late-stage functionalization with the diazonium unit.

Scheme 34 Photocatalytic Tandem Addition/Cyclization Reaction of Diarylamines with an Acyclic Iodine(III) Diazo Reagent[59]



81

R^1	R^2	Yield (%)	Ref
H	H	80	[59]
H	OMe	71	[59]
Me	Me	89	[59]
Cl	Me	67	[59]

for references see p 520

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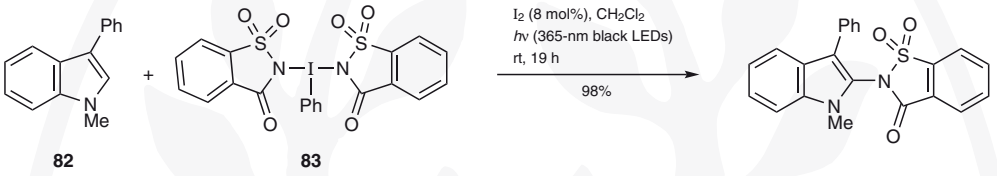
12.3.1.3 Amination Reagents

Amine derivatives coordinated to hypervalent iodine compounds serve as effective aminating agents. The synthesis of acyclic iodane, benziodoxolone, and benziodoxole reagents bearing saccharin moieties was accomplished by Muñiz and co-workers (Scheme 35).[60] The iodine(III) reagent **83** can be used in a novel light-induced C—H amination of hetarenes such as N-protected indoles (e.g., **82**) as the combined oxidant and nitrogen source. The C—H selective amidation occurs under black LED irradiation with molecular iodine as radical initiator, affording products in yields of up to 98%. The methodology has been extended to other heterocycles.

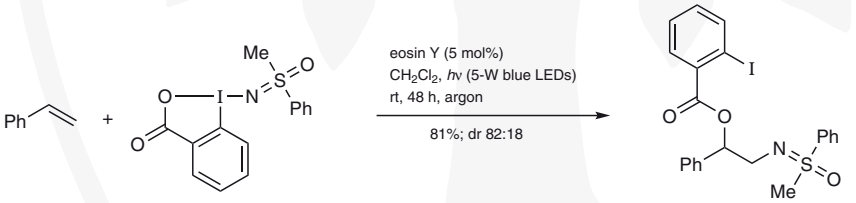
Scheme 35 Photocatalytic C—H Amination of an N-Protected Indole[60]



82 **83**

Bolm and co-workers prepared 1-sulfoximidoyl-1,2-benziodoxoles (e.g., **84**) and investigated their photocatalytic reactivity with styrenes. Under blue LED irradiation, the organic dye eosin Y is the most suitable photocatalyst for achieving diastereoselectivity in the process and affords sulfoximidoylethyl 2-iodobenzoates (e.g., **85**) in up to 81% yield and with up to 88:12 diastereoselectivity (Scheme 36).[61] Upon photoexcitation, eosin Y (EY) is converted into its triplet state (EY*). The 1,2-benziodoxole **84** oxidatively quenches the excited-state photocatalyst EY* via single-electron transfer (SET), yielding the radical cation $EY^{+\bullet}$ while simultaneously generating an N-centered sulfoximidoyl radical and 2-iodobenzoate. The N-centered sulfoximidoyl radical adds to a styrene to form a benzyl radical (e.g., **87**), which is subsequently oxidized to a carbocation (e.g., **86**). Finally, the carbocation intermediate reacts with 2-iodobenzoate to produce the desired product.

Scheme 36 Photocatalytic Sulfoximidation of Styrene[61]



84 **85**

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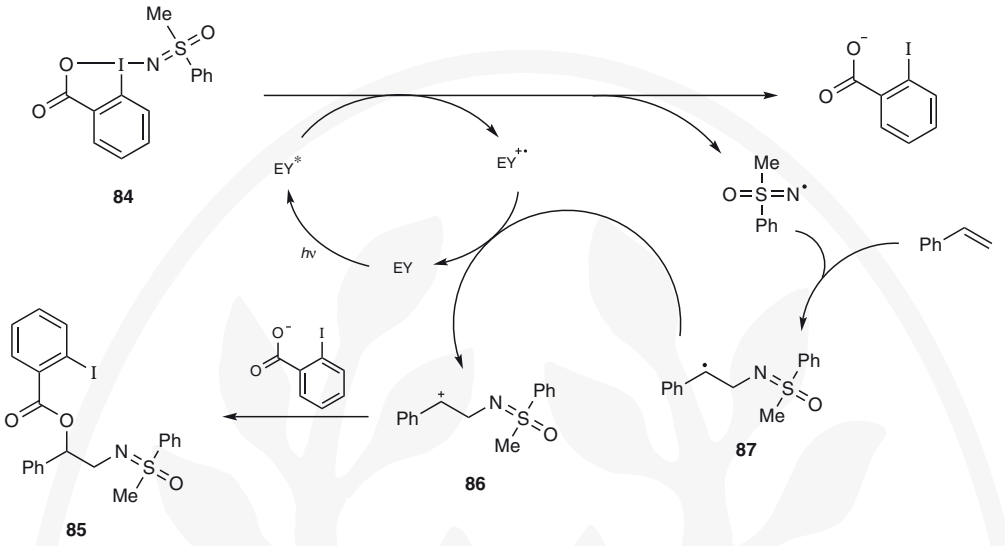
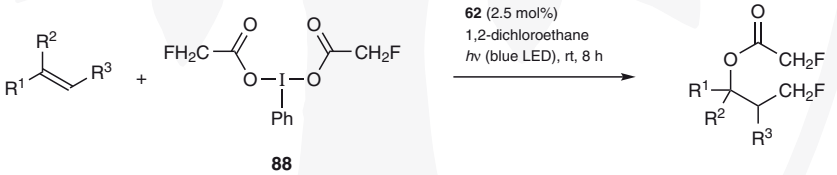
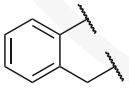


12.3.1.4 Fluoroalkylation Reagents

In recent years, significant advancements have been made in the development of mild and efficient methods for the fluoromethylation of alkenes and hetarenes using hypervalent iodine reagents. Veliks and co-workers reported the oxymonofluoromethylation of alkenes utilizing hypervalent iodine reagent **88** as a bifunctional reagent, copper(I) photocatalyst **62**, and blue light (Scheme 37).[62] The direct oxymonofluoromethylation of a broad scope of alkenic substrates was reported. Characterized by mild reaction conditions, operational simplicity, and a wide range of applications, this methodology provides a convenient route to monofluoromethyl-containing molecules, enhancing their utility in medicinal chemistry and drug discovery.

Scheme 37 Photocatalytic Monofluoroalkylation of Alkenes[62]



R^1	R^2	R^3	Yield (%)	Ref
4-Tol	H	H	81	[62]
4-$F_3CC_6H_4$	H	H	68	[62]
Ph	H	CO_2Me	66[a]	[62]
		H	57[b]	[62]
Ph	Me	H	64	[62]

for references see p 520

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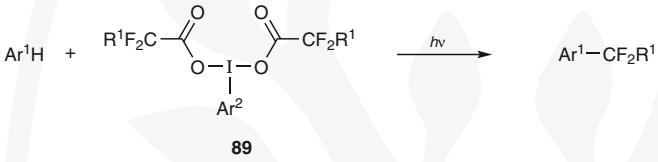
R^1	R^2	R^3	Yield (%)	Ref
(*E*)-CH=CHPh	H	H	79	[62]
OBz	H	H	37	[62]
NPhth	H	H	69	[62]

[a] dr 1:1.2.
[b] dr 4:1.

In recent years, visible-light-mediated methods have emerged to facilitate difluoromethylation of diverse scaffolds. Hypervalent iodine(III) reagents containing difluoroacetoxy groups are widely employed for mild, efficient, and cost-effective generation of difluoromethyl radicals. Maruoka and co-workers pioneered a photocatalytic method for the C—H difluoromethylation of hetarenes, employing hypervalent iodine(III) reagents **89** (R^1 = H) with difluoroacetoxy ligands (Table 3, Entry 1).[63]

Table 3 Visible-Light-Induced C—H Difluoroalkylation of (Hetero)Aromatics and Enamides[63–67]



89

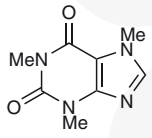
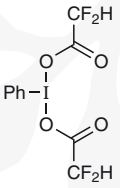
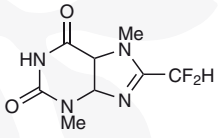
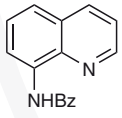
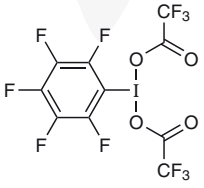
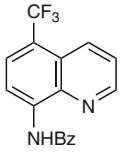
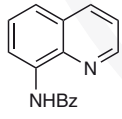
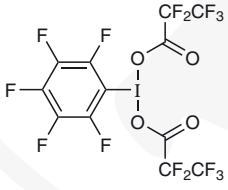
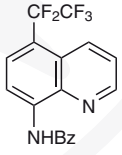
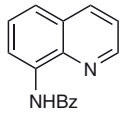
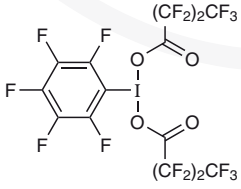
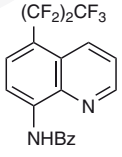
Entry	Substrate	Hypervalent Iodine Reagent	Conditions	Product	Yield (%)	Ref
1			$CDCl_3$, *hv* (400 nm light), rt, 24 h		48	[63]
2			$[Ru(phen)_3]Cl_2$ (2 mol%), MeCN, *hv* (12-W blue LEDs), rt, 12 h		79	[64]
3			$[Ru(phen)_3]Cl_2$ (2 mol%), MeCN, *hv* (12-W blue LEDs), rt, 12 h		81	[64]
4			$[Ru(phen)_3]Cl_2$ (2 mol%), MeCN, *hv* (12-W blue LEDs), rt, 12 h		75	[64]

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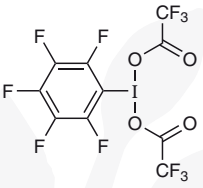
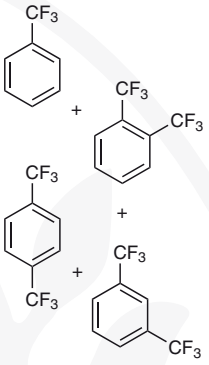
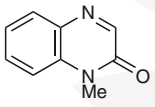
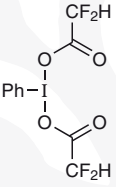
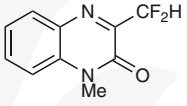
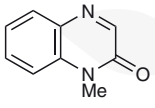
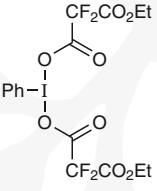
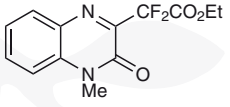
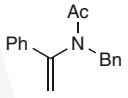
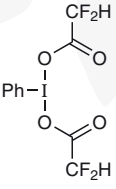
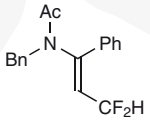
Table 3 (cont.)

Entry	Substrate	Hypervalent Iodine Reagent	Conditions	Product	Yield (%)	Ref
5			$[Ru(bipy)_3](PF_6)_2$ (2 mol%), MeCN, *hv* (blue LEDs), 35 °C, 12 h		88[a]	[64]
6			1,2-dichloroethane, *hv* (24-W blue LED), 40 °C, 12 h		67	[65]
7			$PhI(O_2CCF_3)_2$ (1.5 equiv), THF, *hv* (blue LED), 40 °C, 12 h		65	[66]
8			$[Ru(bipy)_3]Cl_2•6H_2O$ (5 mol%), DMF, *hv* (30-W blue LED), rt, 12 h		62	[67]

[a] Ratio (mono/*o*/*p*/*m*) 47:10:18:13.

A diverse range of acyclic hypervalent iodine(III) reagents, bearing various fluoroalkyl ligands, could be prepared. These reagents serve as versatile precursors for generating a variety of fluorinated alkyl radicals under similar visible-light conditions, enabling a wide range of fluoroalkyl radical mediated C—H bond transformations across diverse substrates (Table 3, entries 2–8).[64–67]

Mechanistically, the easily prepared [bis(difluoroacetoxy)iodo]benzene reagents (e.g., **88**) smoothly generate a carboxyl radical **90** and an iodanyl radical **91** upon irradiation with visible light (λ = 400 nm) in the absence of an additional reagent or a catalyst. Subsequent decarboxylation of **90** affords a difluoromethyl radical, which reacts with the (het)arene to generate a radical intermediate (e.g., **92**). Oxidation and deprotonation of this intermediate furnishes the desired product (Scheme 38).

for references see p 520

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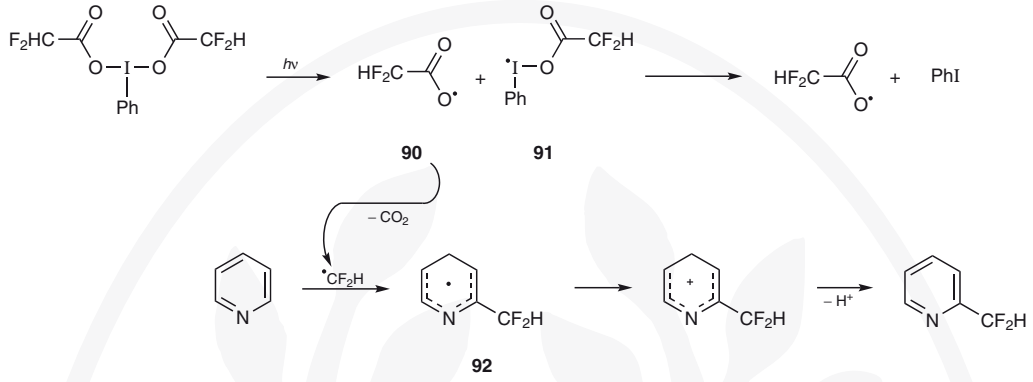
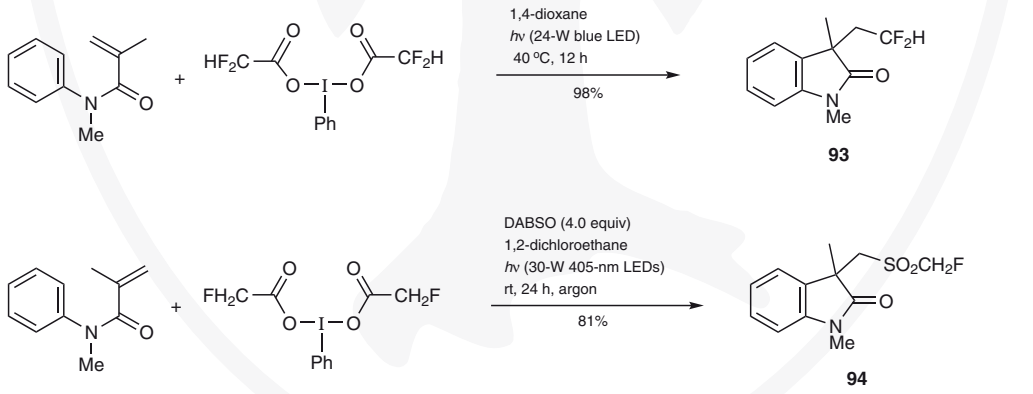
Scheme 38 Mechanism of Visible-Light-Induced C—H Difluoroalkylation of Aromatics[63]



Difluoromethylation cascade reactions mediated by visible light have emerged as powerful tools for the construction of complex organic backbones incorporating a difluoromethyl group. Notably, the intermediates generated upon addition of the difluoromethyl group can be exploited for subsequent cyclizations. Lu and co-workers reported a cascade difluoromethylation/cyclization of *N*-arylacrylamide substrates to afford difluoromethylated 2-oxindoles (e.g., **93**) in high yields without the need for exogenous oxidants or photocatalysts (Scheme 39).[68] In addition, Yang and co-workers developed a visible-light-induced radical-relay strategy for synthesizing heterocycles with a monofluoromethylsulfonyl group (Scheme 39).[69] This method uses [bis(difluoroacetoxy)-iodo]benzene and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) as precursors, achieves excellent yields of oxindole products (e.g., **94**), and features mild conditions and broad functional-group compatibility. Similar difluoromethylation methods can afford a variety of heterocyclic derivatives with fluorine substitutions.[70–73] Alternatively, a photocatalyst-mediated reduction was shown to facilitate the generation of difluoromethyl radicals following decarboxylation, as demonstrated by Zhu, Wu, and co-workers in the synthesis of difluoromethylated dibenzazepines (e.g., **95**).[74]

Scheme 39 Visible-Light-Induced Tandem Difluoromethyl Addition/Cyclization Reactions[68,69,74]



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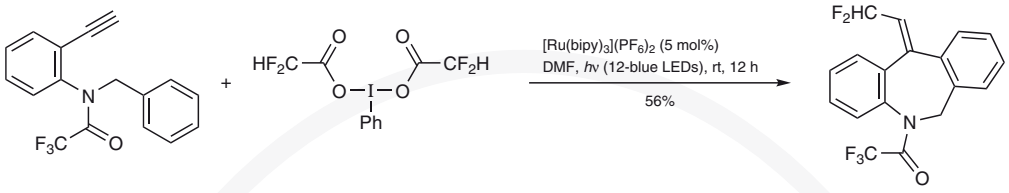
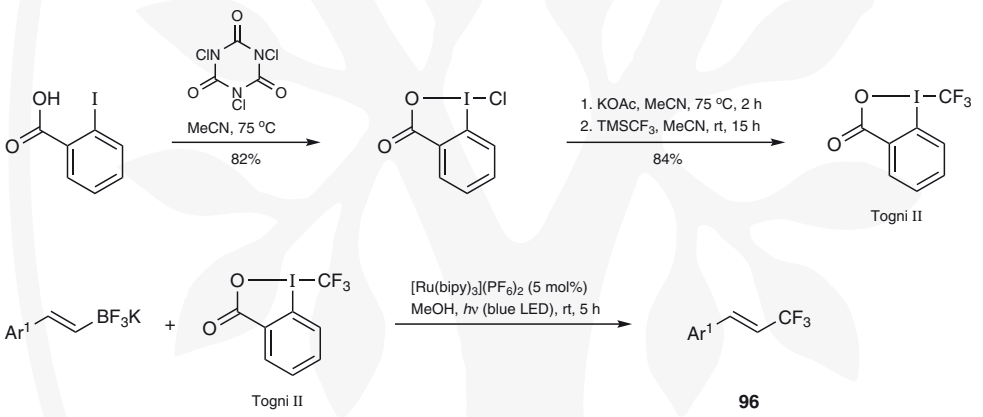


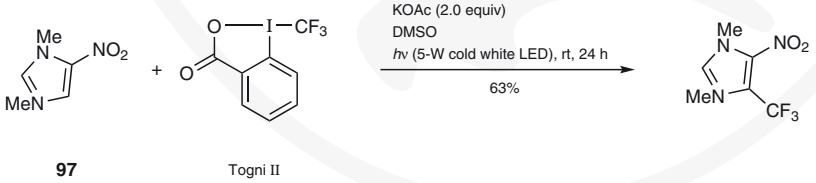
95

The cyclic Togni reagents have emerged as a versatile source of trifluoromethyl radicals. In 2013, Akita, Koike, and co-workers reported the trifluoromethylation of vinyltrifluoroborates using the Togni reagent II [1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one] under ruthenium photoredox catalysis to afford trifluoromethylated alkenes (e.g., **96**) (Scheme 40).[75,76] The Zhang group subsequently demonstrated the direct trifluoromethylation of nitroimidazoles (e.g., **97**) with the Togni reagent II via photoredox catalysis.[77] Furthermore, Wu and co-workers reported a nickel-catalyzed synthesis of 2-trifluoromethylated pyridine *N*-oxides under mild conditions with moderate functional-group compatibility.[78]

Scheme 40 Preparation of the Togni Reagent II, and Its Application in Photocatalytic C—H Trifluoromethylation[75–77]



Ar^1	Yield (%)	Ratio (*E*/*Z*)	Ref
Ph	87	98:2	[75]
4-Tol	81	92:8	[75]
4-MeOC_6H_4	88	99:1	[75]



97 Togni II

MacMillan and co-workers have developed a streamlined photoredox/copper dual catalytic system for the direct decarboxylative trifluoromethylation of carboxylic acids with the Togni reagent I, using iridium complex **98** as photocatalyst, copper(I) cyanide as the copper source, bathophenanthroline as the ligand, and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine as base. The addition of 30

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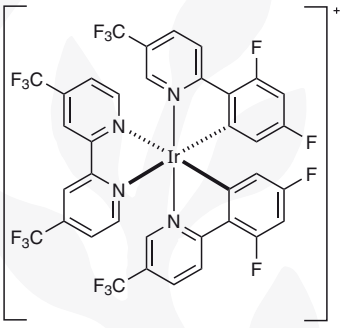
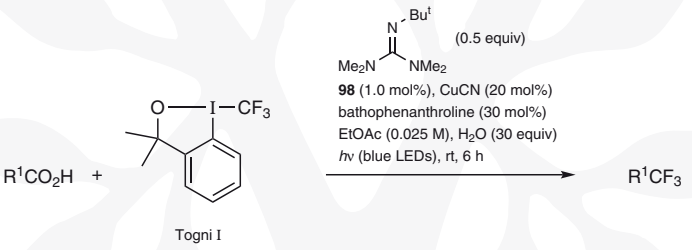
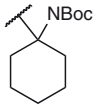
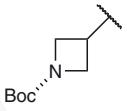
equivalents of water further improves the reaction efficiency (Scheme 41).[79] This method exhibits broad functional-group tolerance, accommodating heterocycles, alkenes, alcohols, and strained rings. Moreover, it is compatible with primary, secondary, and tertiary carboxylic acids. This powerful transformation enables the late-stage trifluoromethylation of diverse carboxylic acid derived natural products and pharmaceuticals.

Scheme 41 Photocatalytic Decarboxylative Trifluoromethylation of Carboxylic Acids Using the Togni Reagent I[79]



98



R^1	Yield (%)	Ref
2-BrC_6H_4	63	[79]
	65	[79]
	75[a]	[79]

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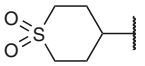
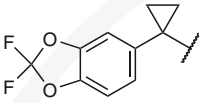
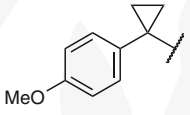
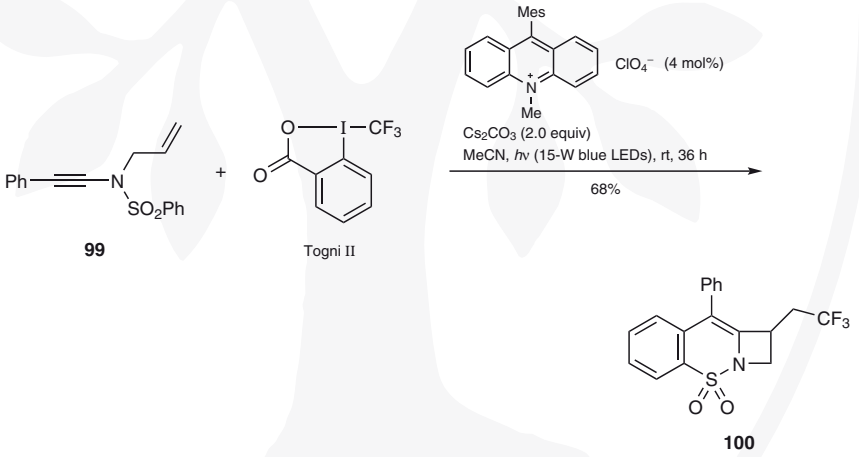
R^1	Yield (%)	Ref
	79	[79]
	82	[79]
	82	[79]

[a] dr 2:1.

The Togni reagent II has also found extensive application in trifluoromethyl radical triggered intramolecular cyclizations. Bai, Yuan, Zhu, and co-workers reported a cascade trifluoromethylation/cyclization of *N*-allyl-*N*-(arylethynyl)benzenesulfonamides (e.g., **99**) using the Togni reagent II and an organophotocatalyst, to afford trifluoromethyl-containing azetidine-fused tricyclic compounds (e.g., **100**). This transformation constitutes a rare example of a 4-*exo*-*dig* radical cyclization, proposed to proceed via an alkenyl radical intermediate generated upon radical addition (Scheme 42).[80]

Scheme 42 Photocatalytic Tandem Addition/Cyclization Reaction of an *N*-Allyl-*N*-(arylethynyl)benzenesulfonamide[80]



Shi and co-workers reported the synthesis of trifluoromethylated 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole derivatives using the Togni reagent II under blue-light irradiation.[81] Similarly, Zhu and co-workers employed the Togni reagent II to achieve a tandem trifluoromethylation/cyclization/remote oxidation of 1,6-dienes, affording trifluoromethyl-containing tetrahydrofurans and tetrahydropyrroles.[82] Duan and co-workers developed a photoredox catalytic system for the synthesis of 3-trifluoromethylated and 3-difluoroacetylated coumarins.[83] Finally, the X. Chen group demonstrated the synthesis of trifluoromethylated azaspiro[4.5]trienones.[84]

These methods not only expand the substrate scope of fluoralkylation reactions but also enhance the selectivity and compatibility of the reactions, providing new pathways for the construction of complex organic molecules.

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1-(Trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (Togni Reagent II, Scheme 40):[76]
A suspension of 2-iodobenzoic acid (30.0 g, 121 mmol, 1.0 equiv) in MeCN (225 mL) was heated to 75 °C. A soln of trichloroisocyanuric acid (9.46 g, 40.7 mmol, 1.01 Cl^+ equiv) in MeCN (45 mL) was added in one portion and the mixture was heated at 75 °C for 10 min. The resulting mixture was diluted with MeCN (150 mL) and vacuum-filtered over an oven-preheated, sintered glass funnel. The filter cake was rinsed with additional hot MeCN (150 mL). The filtrate was concentrated under reduced pressure to near dryness, and the resulting yellow solid was collected by filtration and washed with cold MeCN. The mother liquor from filtration was partially concentrated under reduced pressure, giving a second crop of crystals. The combined crops were dried under reduced pressure overnight to afford 1-chloro-1,2-benziodoxol-3(1*H*)-one as a slightly yellow crystalline solid; yield: 28.0 g (82%).

KOAc (10.8 g, 0.11 mol, 2.0 equiv) was dried under reduced pressure at 150 °C for 30 min and then cooled to rt. 1-Chloro-1,2-benziodoxol-3(1*H*)-one (15.6 g, 55.1 mmol, 1.0 equiv) and MeCN (155 mL) were added and the mixture was stirred at 75 °C for 2 h. The mixture was cooled to rt. $TMSCF_3$ (8.97 mL, 60.7 mmol, 1.10 equiv) was added in one portion and the mixture was stirred at rt for 15 h. MeCN (100 mL) was added and the brown mixture was heated to 75 °C, and then the hot mixture was filtered through a pad of Celite. The filtrate was concentrated to about 50 mL end volume and then cooled to −20 °C. The crystals were collected by filtration, washed with cold (−20 °C) MeCN (50 mL), and dried under reduced pressure. The mother liquor was again concentrated to approximately 15 mL end volume and cooled to 20 °C. The crystals were collected by filtration and washed with cold (−20 °C) MeCN (10 mL). Both crystalline fractions were dried under high vacuum to afford a white crystalline solid; yield: 14.6 g (84%).

1-Aryl-3,3,3-trifluoroprop-1-enes 96**; General Procedure:**[75]
A 20-mL Schlenk tube was charged with the Togni reagent II (0.275–0.30 mmol, 1.1 equiv-1.2 equiv), $[Ru(bipy)_3](PF_6)_2$ (10.7 mg, 12.5 µmol, 5 mol%), a potassium (2-arylvinyl)trifluoroborate (0.25 mmol, 1.0 equiv), and MeOH (5.0–10.0 mL) under N_2. The vinylborate was dissolved with ultrasonic bath. The tube was placed at a distance of 2–3 cm from a 3-W blue LED lamp (λ = 425 ±15 nm). The red soln was stirred at rt (water bath) under visible-light irradiation for 5 h. Sat. aq $NaHCO_3$ was added and the resulting mixture was extracted with Et_2O or pentane. The extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel).

12.3.1.5 Alkylation Reagents

Alkylation reactions hold significant value in chemical synthesis and industrial applications, yet their efficient and selective realization still faces numerous challenges, necessitating continuous exploration of new reaction mechanisms and catalytic strategies. The Jamison group reported a photoredox decarboxylative radical cyclization of *ortho*-heterocycle-substituted aryl isocyanides (e.g., **101**) with phenyliodine(III) dicarboxylates (e.g., **102**) as alkyl radical sources to access 4-alkylated heterocycle-fused quinoxalines (e.g., **103**), using tris[2-(2-pyridyl)phenyl]iridium(III) [*fac*-$Ir(ppy)_3$] as photocatalyst (Scheme 43).[85] Upon irradiation, the excited-state catalyst $[Ir^{III}(ppy)_3]^*$ initiates a single-electron transfer (SET) process with phenyliodine(III) dicarboxylates **102**, generating a cyclohexyl radical and $Ir^{IV}(ppy)_3$ as the strong oxidant. Subsequent radical addition to the aryl isocyanide forms imidoyl radical **105**, which undergoes intramolecular homolytic aromatic substitution (Hirashima reaction) with the adjacent pyrrole ring to yield radical intermediate **104**. Oxidation of **104** by $Ir^{IV}(ppy)_3$ generates a cationic intermediate **106** and regenerates the catalyst [*fac*-$Ir(ppy)_3$]. Deprotonation of the cation by the carboxylate anion affords the final pyrrolo[1,2-*a*]quinoxaline product.

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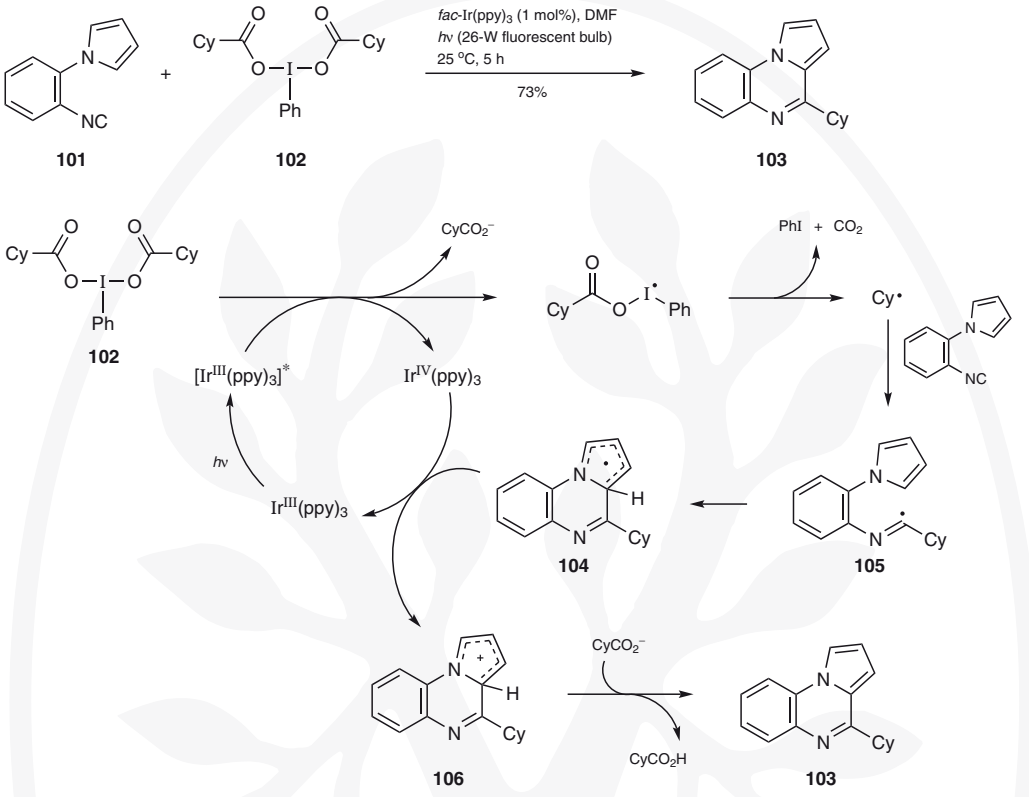
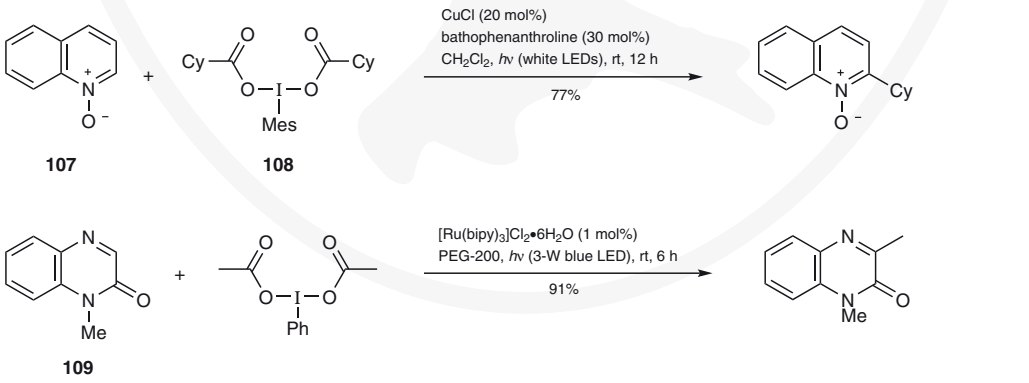
Scheme 43 Photocatalytic Tandem Alkyl Addition/Cyclization Reaction of 1-(2-Isocyanophenyl)-1*H*-pyrrole[85]



Tian, Loh, and co-workers employed hypervalent iodine(III) dicarboxylate reagent **108** to achieve visible-light/copper-catalyzed decarboxylative C—H alkylation of hetarene *N*-oxides (e.g., **107**) (Scheme 44).[86] By varying the carboxylate ligand on the hypervalent iodine(III) reagent, diverse alkyl radicals can be generated under photocatalytic conditions. He and co-workers further reported visible-light-initiated decarboxylative alkylation of quinoxalin-2(1*H*)-ones (e.g., **109**) with phenyliodine(III) dicarboxylates [e.g., $PhI(OAc)_2$] in photoredox catalysis.[87]

Scheme 44 Photocatalytic C—H Alkylation of Quinoline 1-Oxide and 1-Methylquinoxalin-2(1*H*)-one[86,87]



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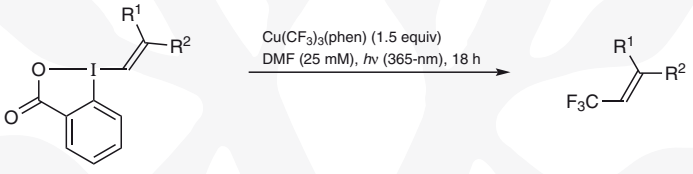
12.3.1.6 Alkenylation Reagents

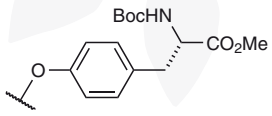
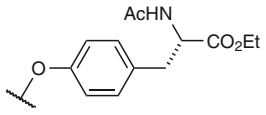
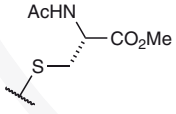
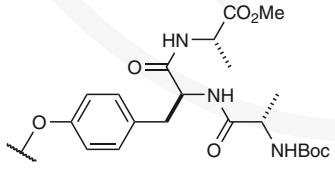
Alkenylation reactions hold significant importance in organic synthesis, as they not only install carbon–carbon double bonds but also enable the synthesis of complex molecular structures. Such transformations find broad applications in the synthesis of natural products, pharmaceuticals, and materials science. Vinylbenziodoxolone (VBX) reagents facilitate the alkenylation of various compounds under mild reaction conditions (see Section 7), yet their involvement in photochemical reactions is relatively limited.[88]

In 2023, Waser and co-workers introduced a novel trifluoromethylation method employing vinylbenziodoxolone reagents as radical acceptors, utilizing high-valent copper(III) complexes such as (1,10-phenanthroline)tris(trifluoromethyl)copper(III) [$Cu(CF_3)_3$(phen)], to achieve the synthesis of trifluoromethylated alkenes under thermal conditions or UV irradiation (Scheme 45).[89] This method is stereoselective and applicable to a wide range of vinylbenziodoxolones **110**, including those derived from amino acids, peptides, vinyl (thio)ethers, and enamides. The resulting trifluoromethylated alkenes can be further functionalized through reactions such as reduction or epoxidation. The method is scalable for large-scale synthesis and can also be conducted under visible-light irradiation, offering a new route for the synthesis of polysubstituted trifluoromethylated compounds.

Scheme 45 Synthesis of Trifluoromethylated Alkenes[89]



110

R^1	R^2	Yield (%)	Ref
	Ph	80	[89]
	Me	36	[89]
	$(CH_2)_2N_3$	71	[89]
	Ph	63	[89]

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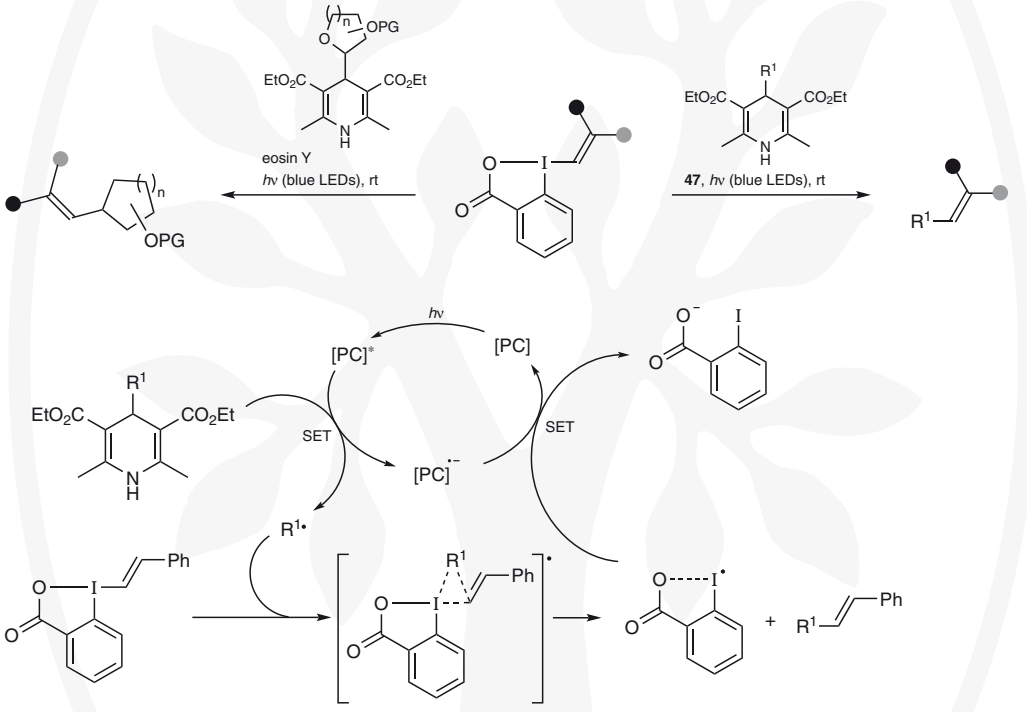
In the same year, the Olofsson group reported a photoredox-catalyzed C—C coupling reaction, employing 4-alkyldihydropyridines as radical precursors and vinylbenziodoxolones as radical acceptors to achieve the stereospecific synthesis of functionalized alkenes and *C*-glycosides.[90] This method is transition-metal-free, features mild reaction conditions, and exhibits excellent tolerance of common functional groups. It allows for the synthesis of the corresponding alkenes in good yields with complete retention of the alkene configuration using 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN; **47**) as photocatalyst (Scheme 46). Additionally, the method has been applied to the diastereoselective C-glycosylation of 4-glycosyldihydropyridines using eosin Y as photocatalyst, yielding *C*-vinyl glycosides with superior *E*/*Z* ratios. Preliminary mechanistic studies suggest that the C—C bond formation is stereospecific and proceeds through a concerted transition state (Scheme 46).

Scheme 46 Vinylbenziodoxolones as Acceptors of Alkyl Radicals Derived from 4-Alkyldihydropyridines[90]



12.3.1.7 Alkynylation Reagents

Alkyne groups are used in organic synthesis to construct complex molecular skeletons and provide synthetic diversity. They improve target selectivity, increase structural diversity, and enhance metabolic stability. In addition, alkynes have important uses in materials science and industrial applications (such as metal processing and chemical industry). Alk-1-ynylbenziodoxolone reagents can be used to introduce alkyne groups under mild reaction conditions. Some studies on the use of alk-1-ynylbenziodoxolone reagents as radical acceptors have been mentioned in the preceding sections and will not be repeated here. Moreover, reactions that are compatible with alk-1-ynylbenziodoxolone reagents often tolerate vinylbenziodoxolone reagents and/or 3-oxo-1λ³-benzo[*d*][1,2]iodaoxole-1(3*H*)-carbonitrile as well.[43,91]

In one example, discussed in detail in Section 12.1.2 (Scheme 7), the Y. Chen group has pioneered a visible-light-induced deboronative alkynylation reaction, using tris(2,2′-bipyridyl)ruthe-

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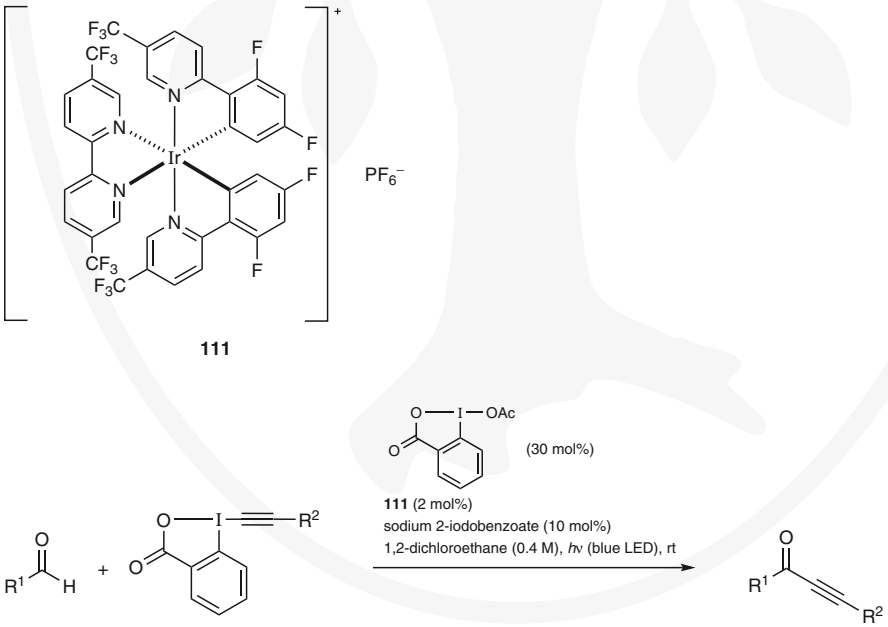
nium(II) hexafluorophosphate as the photocatalyst and 1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one [1-hydroxy-1,2-benziodoxol-3(1*H*)-one] as the oxidant; here, they achieved efficient coupling of alkyltrifluoroborates (Scheme 7) or boronic acids with alk-1-ynylbenziodoxolones.[13]

12.3.2 Hydrogen-Atom-Transfer Reagents

Hypervalent iodine reagents may also serve as versatile hydrogen-atom-transfer (HAT) mediators in photochemical reactions. Through single-electron transfer (SET) or homolytic/heterolytic cleavage, these reagents generate reactive radicals capable of selectively abstracting hydrogen atoms from specific C—H bonds. This HAT reactivity enables the direct functionalization of inert substrates under mild, redox-neutral conditions, bypassing the need for directing groups or harsh conditions.

A seminal study by Glorius and co-workers exemplified this strategy. Using a photoredox-mediated HAT process, they achieved the regio- and chemoselective synthesis of ynones, ynamides, and ynoates via direct aldehyde C—H bond activation using the iridium photocatalyst **111** (Scheme 47).[92] The mechanism involves (1) photoexcitation of a photosensitizer, which transfers an electron to the 2-iodobenzoic acid anion, generating a 2-iodobenzoyloxyl radical; (2) radical-mediated HAT from the aldehyde C—H bond of the substrate, producing a stabilized acyl radical; (3) radical addition to an alk-1-ynylbenziodoxolone reagent; and (4) elimination of a benziodoxolonyl radical to release the desired product. This cascade operates under ambient conditions, achieving high yields and selectivity without the need for stoichiometric oxidants. The synergy of photoredox catalysis and the HAT capabilities of hypervalent iodine reagents underscore the potential of this strategy for C—H bond diversification in complex molecular settings. By merging HAT efficiency with the tunable reactivity of hypervalent iodine reagents, this approach opens avenues for late-stage functionalization of pharmaceuticals, natural products, and biomolecules.

Scheme 47 Synthesis of Ynones, Ynamides, and Ynoates[92]



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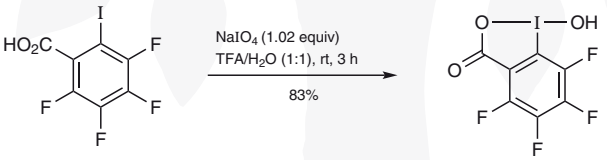
R^1	R^2	Yield (%)	Ref
iPr	Ph	75	[92]
cyclopropyl	Ph	80	[92]
cyclohex-1-enyl	Ph	70	[92]
Ph	Ph	72	[92]
NPhMe	TIPS	56	[92]
piperidino	Ph	65	[92]
OPh	Ph	46	[92]
OBu	Ph	51	[92]

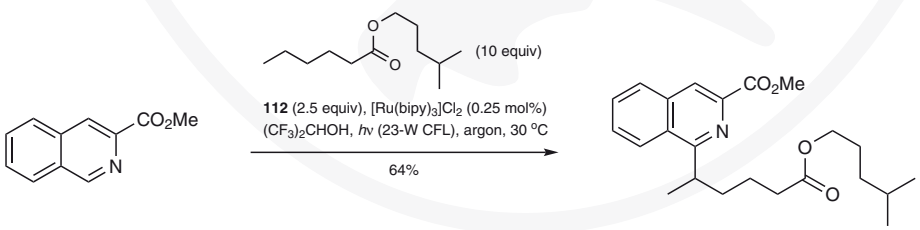
Generally, traditional alkylation reactions preferentially target the weaker, tertiary C—H bonds in alkanes. Overcoming this thermodynamic bias to selectively functionalize the stronger, more abundant methylene C—H bonds would significantly expand the scope of alkane C—H functionalization. In 2017, the G. Chen group reported a highly efficient photoredox-mediated Minisci-type alkylation of N-hetarenes (e.g., **113**) with various alkane substrates under reagent control of the hypervalent iodine oxidant 4,5,6,7-tetrafluoro-1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**112**) (Scheme 48),[93] demonstrating excellent methylene selectivity (Scheme 49).[94] The proposed mechanism begins with **112** undergoing single-electron transfer (SET) with the excited-state photocatalyst, thereby generating the corresponding aryl carboxyl radical. This aryl carboxyl radical subsequently engages in hydrogen-atom abstraction (HAT) from the alkyl substrate to afford a secondary alkyl radical. The addition of the secondary alkyl radical to **113**, followed by a subsequent SET process, furnishes the final target product **114** (Scheme 49). Notably, secondary carbon radicals readily undergo radical addition with aromatic heterocycles, whereas tertiary carbon radicals are more prone to oxidation by photoredox catalysts, leading to cation formation.

Scheme 48 Synthesis of 4,5,6,7-Tetrafluoro-1-hydroxy-1λ³-benzo[*d*]-[1,2]iodaoxol-3(1*H*)-one[93]



112

Scheme 49 Selective Activation of C—H Bonds Mediated by 4,5,6,7-Tetrafluoro-1-hydroxy-1λ³-benzo[*d*]-[1,2]iodaoxol-3(1*H*)-one[94]



113 **114**

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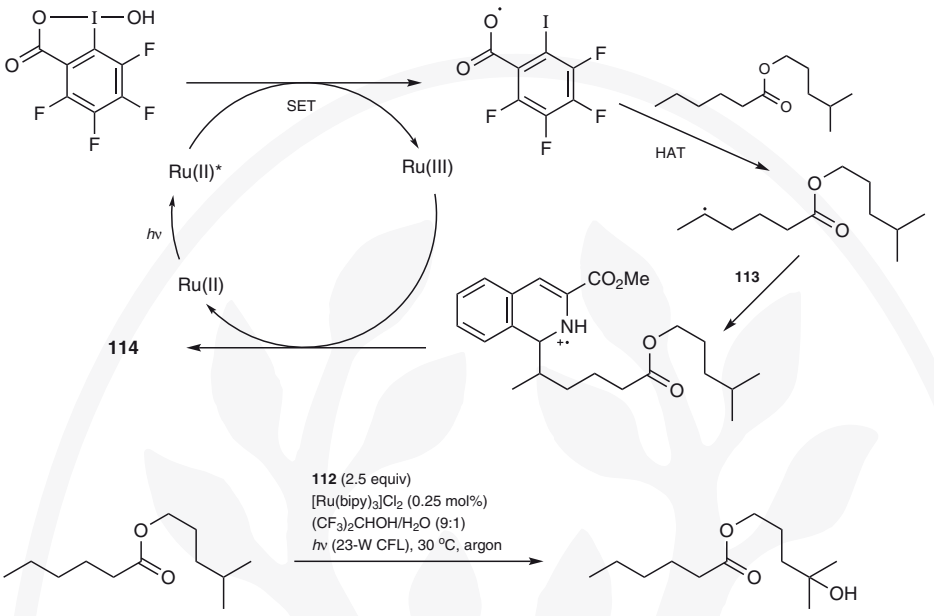

In 2019, Cai and co-workers reported a catalytic photoredox method for the oxidative cross coupling of alkenes with dialkylformamides.[95] Here, an in situ generated diaryliodonium salt **115** is quenched by photoexcited 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN; **47**), yielding the key iodanyl radical **116**. Subsequent hydrogen-atom transfer between this radical and dimethylformamide generates a highly reactive carbamoyl radical **117** and 2-iodo-1,3,5-trimethoxybenzene. The carbonyl radical adds to a 1,1-diarylethylene, forming a radical adduct that undergoes single-electron transfer with the radical cation of the photocatalyst to give the alkyl cation **118**. Finally, β-hydrogen elimination of the alkyl cation facilitated by potassium carbonate affords an α,β-unsaturated amide product **119** (Scheme 50). In the same year, the same group developed a visible-light-promoted oxidative alkylarylation of *N*-aryl- and *N*-benzoyl-substituted acrylamides through direct C—H bond functionalization.[96]

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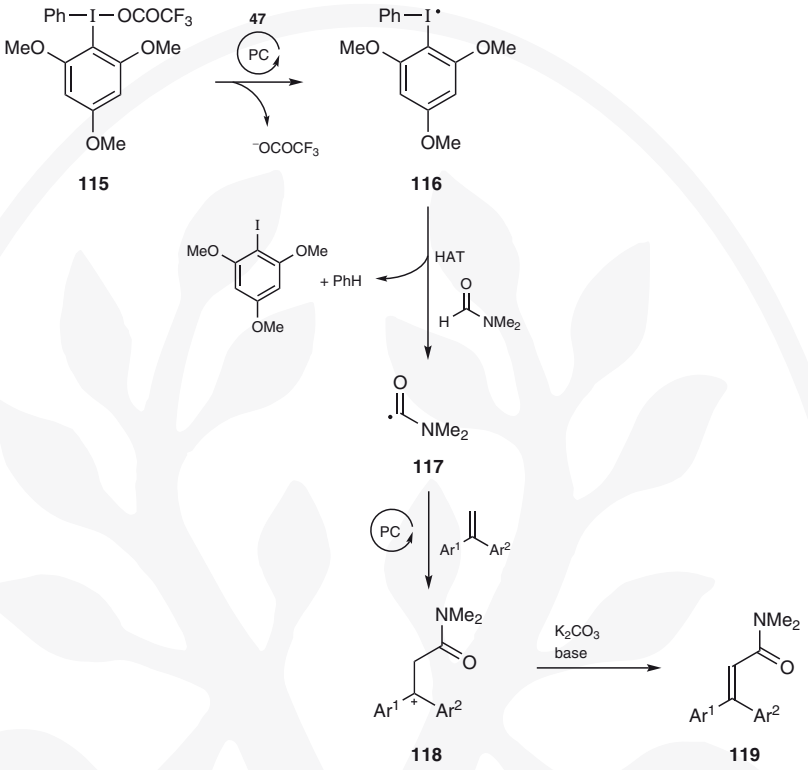
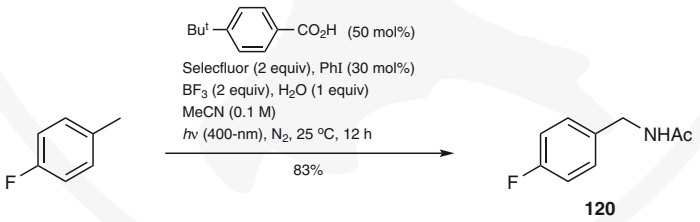
Scheme 50 Photocatalyzed Synthesis of α,β-Unsaturated Amides[95]



A trivalent iodine intermediate **121** is generated in situ by oxidation of iodobenzene with Selectfluor, with 4-*tert*-butylbenzoic acid serving as a ligand (Scheme 51).[97] Complexation with boron trifluoride enhances the oxidation properties of complex **121**. Visible-light-induced homolysis of the I—O bond generates a 4-*tert*-butylbenzoic carboxyl radical, which abstracts a hydrogen atom from a substrate such as 1-fluoro-4-methylbenzene. The resulting carbon radical is oxidized by the remaining iodine species to form a carbocation. The carbocation undergoes a Ritter-type reaction to yield amine derivatives (e.g., acetamide **120**).

Scheme 51 C(sp^3)—H Ritter Amination via Excitation of In Situ Formed Boron Trifluoride–Iodine(III) Complexes[97]



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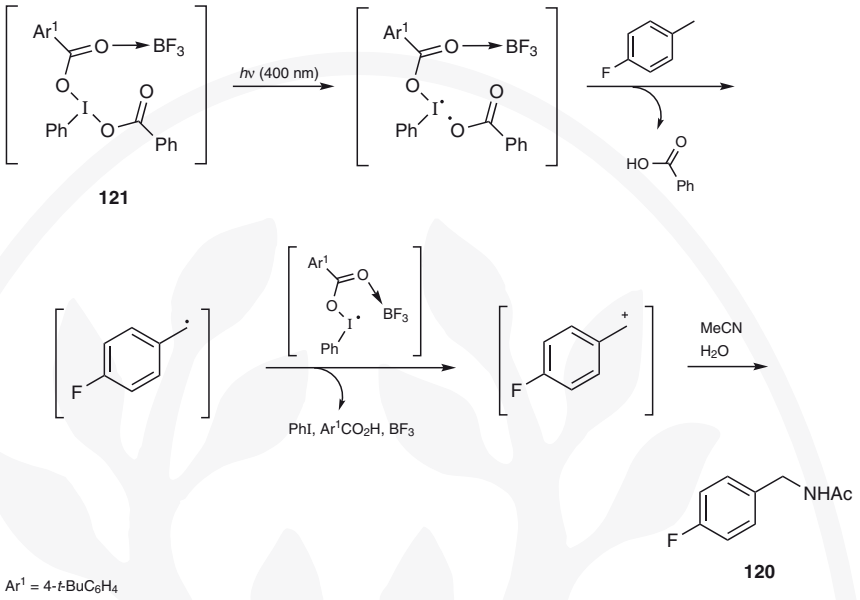
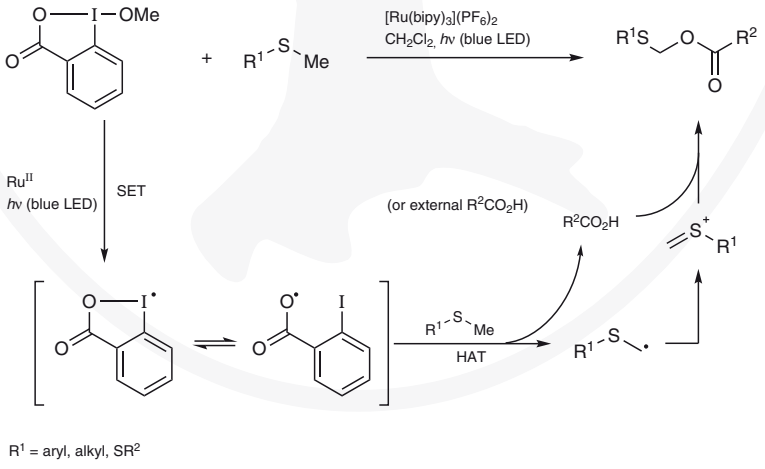


Direct α-C—H functionalization of sulfides via hydrogen-atom transfer, without the use of strong oxidants, is highly desirable. However, the similar bond-dissociation energies of α-C—H bonds in sulfides (93 kcal·mol^{-1}) and ethers/amines (92 kcal·mol^{-1}) pose a significant challenge for selective functionalization. A potential solution involves rapid oxidation of α-thioalkyl radicals using a mild oxidant, to selectively form sulfonium intermediates, enabling α-C—H acyloxylation of sulfides. In 2023, Chen and Wu demonstrated the α-C—H acyloxylation of sulfides using hypervalent iodine(III) reagents under photoredox catalysis (Scheme 52).[7] 1-Methoxy-1,2-benziodoxol-3(1*H*)-one derivatives serve as the HAT agent, mild oxidant, and source of the carboxylate group in this reaction. Additionally, external carboxylate nucleophiles can also be introduced into α-C—H bonds of sulfides. This method exhibits broad applicability to aryl and alkyl sulfides, including methionine peptide derivatives.

Scheme 52 Hypervalent Iodine as a HAT Reagent and Nucleophile Source for Selective C—H Acyloxylation of Sulfides/Disulfides[7]



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4,5,6,7-Tetrafluoro-1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (112)**:**[93]
$NaIO_4$ (1.1 g, 5.1 mmol, 1.02 equiv) and 2,3,4,5-tetrafluoro-6-iodobenzoic acid (1.6 g, 5 mmol, 1.0 equiv) were added at rt to a mixture of TFA in H_2O (1:1; 20 mL). The resulting suspension was vigorously stirred and heated at reflux for 3 h, and then cooled to rt, and poured into cold H_2O (5 mL). The resulting mixture was cooled to rt and the product was collected by filtration, washed with H_2O and hexane, and dried under high vacuum in the dark to afford 4,5,6,7-tetrafluoro-1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**112**) as a white solid; yield: 1.4 g (83%).

Methyl 1-[6-(4-Methylpentoxy)-6-oxohexan-2-yl]isoquinoline-3-carboxylate (114)**:**[94]
Methyl isoquinoline-3-carboxylate (**113**; 0.2 mmol, 1.0 equiv), 4-methylpentyl hexanoate (10 equiv), and 4,5,6,7-tetrafluoro-1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (**112**; 0.5 mmol, 2.5 equiv) were added to a soln of $[Ru(bipy)_3]Cl_2$ (0.5 µmol, 0.25 mol%) in $(CF_3)_2CHOH$ (2.5 mL). The vial was purged with argon for 1 min and the mixture was stirred at 30 °C under fluorescent-light irradiation (23-W) for 30 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (3 mL). K_2CO_3 (ca. 80 mg) was added and the resulting mixture was vigorously stirred for 5 min and then filtered through a pad of Celite, rinsing with CH_2Cl_2. The filtrate was concentrated under reduced pressure and the residue was purified by preparative TLC or flash chromatography (silica gel) to afford the colorless product; yield: 49 mg (64%).

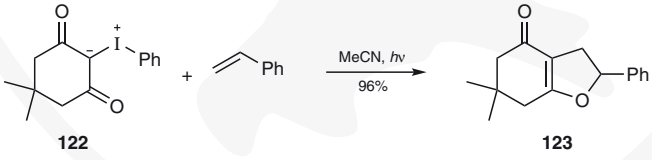
12.3.3 Iodonium Ylides

Iodonium ylides stand at the forefront of photochemical innovation, enabling a diverse spectrum of bond-forming and redox-driven reactions through their unique radical-generating capabilities.[98] Upon photoexcitation, these reagents participate in single-electron-transfer (SET) processes, producing transient radical intermediates that drive transformations such as C—C bond construction via radical addition or cyclization, oxidative functionalization of alkenes and alkynes, and elimination pathways yielding unsaturated scaffolds.[44]

Notably, these processes occur under mild, oxidant-free conditions, circumventing the need for toxic or energy-intensive reagents. This operational simplicity, combined with their ability to orchestrate both radical and polar reactivity, positions iodonium ylides as multifunctional tools in organic synthesis. Their compatibility with photoredox catalysis further amplifies their utility, enabling cascade reactions and stereoselective transformations with precise spatiotemporal control.

In 2000, Hadjiarapoglou and co-workers reported a method for the synthesis of substituted dihydrofurans via [3+2] cycloaddition of iodonium ylide **122** with alkenes such as styrene upon irradiation with a mercury lamp to give, for example, cyclic product **123** in 96% yield (Scheme 53).[99]

Scheme 53 Synthesis of a Substituted Dihydrofuran via [3+2] Cycloaddition of a Iodonium Ylide with Styrene[99]



122 **123**

In 2019, Murphy and co-workers developed a visible-light-mediated synthesis of doubly activated cyclopropanes from alkenes and β-dicarbonyl-derived iodonium ylides (Table 4).[100] Computational analysis attributed the observed high selectivity to exclusive HOMO–LUMO excitation rather than free carbene generation.

for references see p 520

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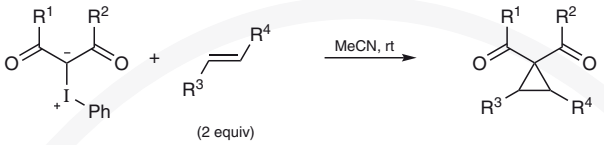
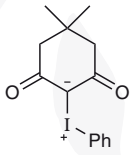
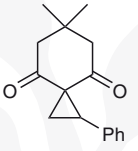
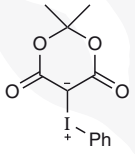
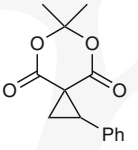
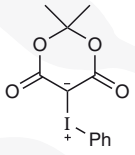
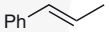
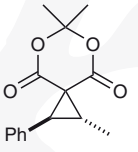
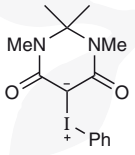
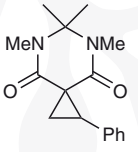
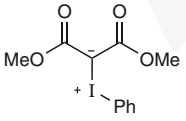
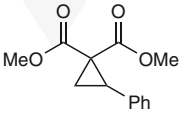
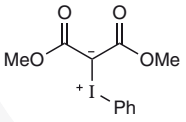
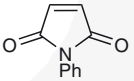
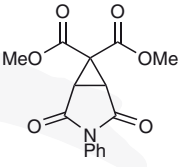
Table 4 Iodonium Ylides for Cyclopropanation with Alkenes[100]



Iodonium Ylide	Alkene	Time (h)	Product	Yield (%)	Ref
		1.5		95	[100]
		24		96	[100]
		24		85	[100]
		30		85	[100]
		3		81[a]	[100]
		7		46	[100]

[a] 20 equiv of the alkene was used.

12.3.4 Aryliodonium Salts

Diaryliodonium salts are highly versatile compounds, widely employed in organic synthesis as arylating agents for diverse nucleophilic groups. At room temperature, they are typically solid, exhibit good thermal stability, and remain inert toward oxygen and water. But, they are photosensitive and gradually decompose upon prolonged light exposure; therefore, they should be stored in the absence of light.[101] The selective functionalization of C—H bonds and the addition of aryl groups to unsaturated bonds via aryl-λ³-iodine reagents provide efficient routes to novel molecu-

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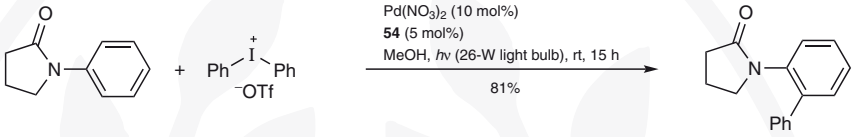
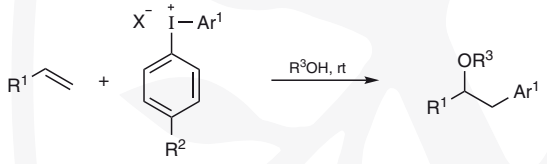
lar architectures. In 2012, Sanford and co-workers reported a significant acceleration of palladium-catalyzed C—H arylation using diaryliodonium salts and the iridium photocatalyst **54** {[Ir(ppy)$_2$(dtbbpy)]PF$_6$} (Scheme 54).[102] Since then, aryliodonium salts have been extensively utilized as radical precursors in photochemical reactions to generate aryl radicals and facilitate C—H arylation of diverse substrates.[103–109]

Scheme 54 Photocatalytic C—H Arylation of 1-Phenylpyrrolidin-2-one[102]



The Greaney group has achieved the oxyarylation of styrenes by photoredox catalysis (Scheme 55).[110] Aryl radicals, generated from suitable hypervalent iodine(III) reagents, undergo addition to the styrene double bond, forming a benzyl radicals. Subsequent oxidation of the benzyl radicals generates benzylic cations, which react with nucleophiles to form a C—O bond. The Glorius[111] and Li[112] groups have also reported methods for the addition of aryl radicals generated from hypervalent iodine reagents to alkenes (Scheme 55).

Scheme 55 Photocatalytic Oxyarylation of Alkenes[110–112]



R^1	R^2	X	Ar^1	R^3	Conditions	Yield (%)	Ref
Ph	H	BF_4	Ph	Me	Ir(ppy)$_3$ (1 mol%), Zn(OAc)$_2$ (20 mol%), MeOH, *hν* (30-W light bulb), 18 h	70	[110]
$(CH_2)_5Me$	H	BF_4	Ph	Me	[Au(PPh$_3$)]NTf$_2$ (10 mol%), **54** (5 mol%), MeOH, *hν* (blue LEDs), 20 h	82	[111]
Ph	SF_5	OTs	Mes	H	[Ru(bipy)$_3$](PF$_6$)$_2$ (1 mol%), acetone/H$_2$O, *hν* (blue LEDs), 18 h	65	[112]

Yu and co-workers employed a similar phenyliodine(III) activation strategy to generate alkyl radicals for photoredox-catalyzed addition/cyclization reactions with aryl isocyanides (e.g., **124**) to afford isoquinolines (e.g., **125**) (Scheme 56).[113] The integration of in-line isocyanide formation and photochemical cyclization within a three-step continuous flow system enabled the efficient synthesis of polycyclic compounds. Furthermore, this approach has been applied to diverse cyclization reactions.

for references see p 520

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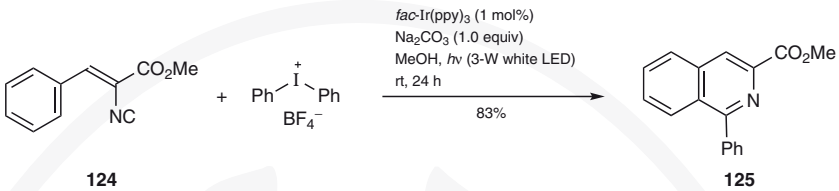
Scheme 56 Tandem Photocatalytic Addition/Cyclization Reaction of an Aryl Isocyanide[113]



124 **125**

The Denton group reported a regiospecific coupling reaction between phosphines and aryl radicals derived from diaryliodonium salts, under photoredox conditions, to afford quaternary arylphosphonium salts **126** (Scheme 57).[114] Visible-light excitation of tris(2,2′-bipyridyl)ruthenium(II) chloride populates the excited state, which undergoes reductive quenching by the phosphine to generate a phosphoniumyl radical cation **128**. The resulting ruthenium(I) species subsequently reduces the iodonium salt, leading to fragmentation and formation of an aryl radical and an iodobenzene. Addition of the aryl radical to the phosphoniumyl radical cation affords the desired product. Alternatively, the reaction can be initiated by the addition of an aryl radical to the phosphine substrate, generating a phosphoranyl radical intermediate **127**. Subsequent oxidation of this radical by the iodonium salt produces the phosphonium salt product and propagates the radical chain.

Notably, the reaction proceeds even in the absence of the ruthenium photocatalyst under visible-light conditions. A proposed mechanism for this reaction involves the formation of a charge-transfer complex between the phosphine and the iodonium salt, facilitating electron transfer and generating the phosphoniumyl radical cation and an aryl radical. Karchava and Bugaenko have demonstrated this catalyst-free visible-light-mediated synthesis of unsymmetrical tertiary arylphosphines for a wide range of phosphines with diaryliodonium salts.[115]

Scheme 57 Photocatalytic Arylation of Phosphines, and Proposed Mechanism Using a Ruthenium Photocatalyst[114,115]



126

R^1	R^2	R^3	Ar^1	Ar^2	Conditions	Yield (%)	Ref
Ph	Ph	Ph	Ph	Ph	$[Ru(bipy)_3]Cl_2$ (10 mol%), *hv* (10-W lamp), 20 min	85	[114]
Ph	Ph	Ph	Ph	Ph	*hv* (10-W lamp), 20 min	12	[114]
Ph	Ph	2-pyridyl	Ph	Ph	$[Ru(bipy)_3]Cl_2$ (10 mol%), *hv* (10-W lamp), 20 min	82	[114]
Ph	Ph	Ph	Ph	Mes	MeCN, 400–410 nm LEDs, rt, 2 h	90	[115]
Ph	Ph	Ph	Mes	Mes	MeCN, 400–410 nm LEDs, rt, 5 h	72	[115]
Ph	Ph	Ph	2-$O_2NC_6H_4$	Mes	MeCN, 400–410 nm LEDs, rt, 2 h	94	[115]
Bu	Bu	Ph	2-Me-3-$O_2NC_6H_3$	Mes	MeCN, 400–410 nm LEDs, rt, 2 h	66	[115]

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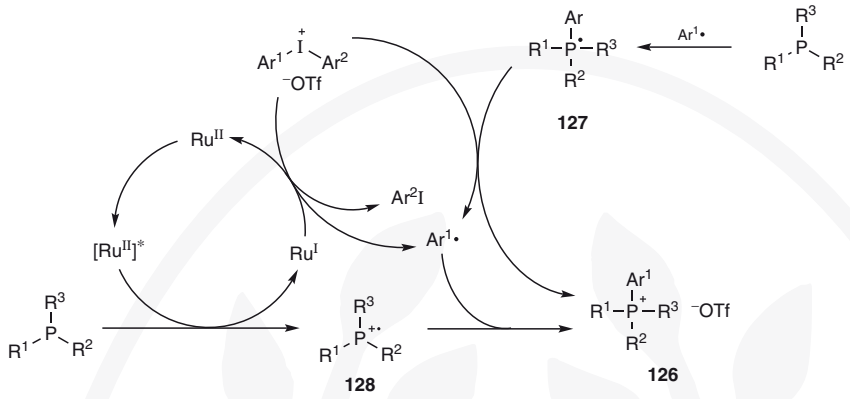
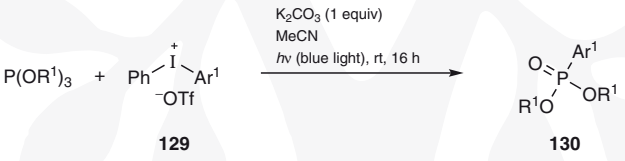


Lakhdar and co-workers reported a straightforward approach to access valuable organophosphorus molecules via photoredox coupling of diaryliodonium salts **129** and phosphites under blue-light irradiation (Scheme 58).[116] Diaryliodonium salts bearing electron-withdrawing or electron-donating groups react efficiently to afford the corresponding arylphosphonates (e.g., **130**) in excellent yields. The reaction demonstrates compatibility with triethyl, triisopropyl, and trimethyl phosphites, which react smoothly with diaryliodonium salts to yield the arylated phosphonates in satisfactory to excellent yields.

Scheme 58 Metal-Free Visible-Light-Mediated Synthesis of Arylphosphonates[116]



R^1	Ar^1	Yield (%)	Ref
Et	Ph	83	[116]
Et	4-$MeOC_6H_4$	83	[116]
Et	4-$F_3CC_6H_4$	84	[116]
Me	Ph	94	[116]
iPr	Ph	91	[116]

12.4 Biocompatible Photochemistry of Hypervalent Iodine Reagents

Hypervalent iodine reagents have recently emerged as pivotal tools in biocompatible photochemistry, driving significant advancements in peptide and protein functionalization. The unique synergy that they offer in terms of mild reaction conditions, exceptional functional-group tolerance, and visible-light responsiveness enables the generation of reactive intermediates in aqueous or physiological environments, which is crucial for biomolecular applications.[117] These reagents facilitate site-specific modifications, allowing the introduction of fluorophores, bioconjugates, and functional groups without compromising biomolecular integrity. This precision, combined with their metal-free nature, positions hypervalent iodine chemistry as a transformative tool for chemical biology, drug discovery, and the development of targeted therapeutics.

The serendipitous discovery of biocompatible hypervalent iodine reactions underscores their untapped potential. A landmark study in 2014 by the Y. Chen group introduced a visible-light-in-

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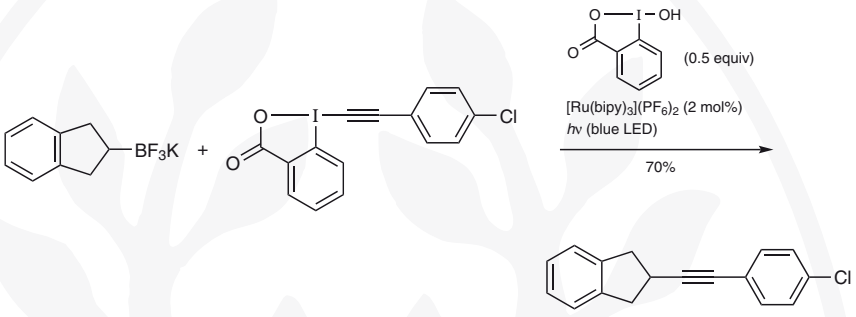
duced deboronative alkynylation using the tris(2,2′-bipyridyl)ruthenium(II)/1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one [1-hydroxy-1,2-benziodoxol-3(1*H*)-one] catalytic system (Scheme 59; see also Scheme 7).[13] Operable under neutral aqueous conditions, this method achieves unprecedented chemoselectivity across biomolecular substrates, including amino acids, nucleosides, nucleic acids, and even bacterial cell lysates, all without observable biomolecular interference.

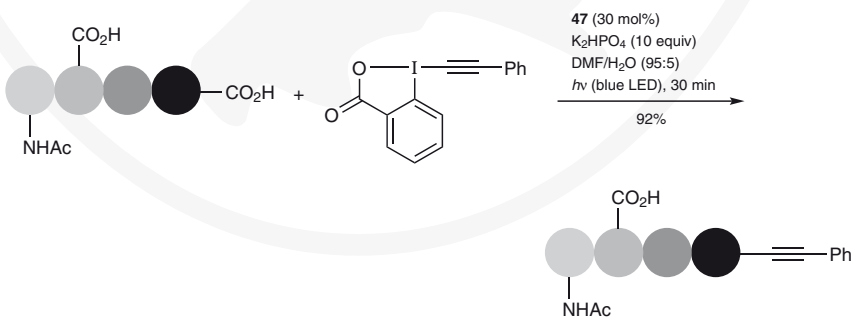
Scheme 59 Deboronative Alkynylation under Biocompatible Conditions[13]



Building on this breakthrough, the Y. Chen group and others expanded the scope to deboronative alkenylation (see Scheme 12),[6] decarboxylative alkynylation (see Scheme 13),[20] and aryl amidation (see Scheme 21),[29] leveraging the adaptability of hypervalent iodine reagents to forge diverse bonds under biocompatible conditions. The reactions demonstrate exceptional tolerance toward a wide array of sensitive functional groups, proceeding efficiently even in the presence of biomolecules such as amino acids, nucleosides, oligosaccharides, nucleic acids, proteins, and cell lysates. This robust functional-group compatibility highlights the versatility of these reactions as a transformative tool for biomolecular modifications in complex biological environments, including late-stage diversification of bioactive molecules and precision labeling in cellular contexts. As mechanistic insights grow, so does the potential to design "smart" reagents for in vivo applications, bridging synthetic chemistry with biological complexity.

Hypervalent iodine reagents have become indispensable for late-stage peptide and protein functionalization, combining low toxicity, broad functional-group tolerance, and stability in biocompatible environments. A landmark study in 2019 by the Waser group exemplifies their potential: leveraging 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN; **47**) as a metal-free photocatalyst, they achieved C-terminal selective alkynylation of peptides via photoredox-catalyzed decarboxylative coupling (Scheme 60).[118] This method operates under ambient conditions, is complete within 30 minutes, and accommodates hexameric peptides with diverse C-terminal residues, showcasing both efficiency and scalability.

Scheme 60 C-Terminal Selective Bioconjugation of Peptides[118]



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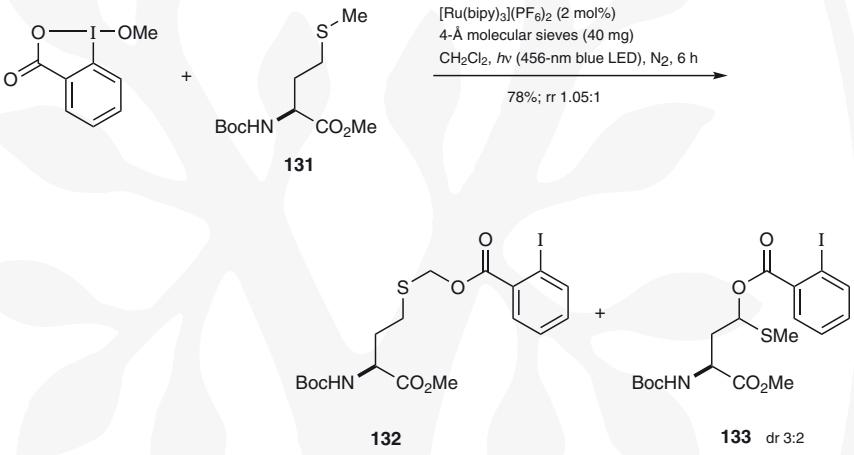
While alk-1-ynylbenziodoxolone reagents are still underexplored in biomolecular contexts, their success in small-molecule alkynylation suggests untapped potential for site-specific bioconjugation. As mechanistic understanding grows, these reagents are poised to revolutionize applications ranging from antibody–drug conjugate (ADC) synthesis to real-time biomolecular tracking, bridging synthetic chemistry with biological complexity.

Hydrogen-atom-transfer (HAT) processes mediated by hypervalent iodine reagents offer a unique combination of site-selective reactivity and mild, biocompatible conditions, which is particularly advantageous for applications involving biomolecules. In 2023, Chen and Wu demonstrated this potential by achieving C—H acyloxylation of sulfides (see Scheme 52), a method that could be extended to methionine derivative **131**, whose sulfur α-positions can be modified to obtain the corresponding products **132** and **133** in a total yield of 78%, a regioisomeric ratio (**132**/**133**) of 1.05:1, and a diastereomeric ratio of 3:2 for **133** (Scheme 61).[7] Remarkably, dipeptide methionine derivatives exhibit exceptional reactivity under these conditions, underscoring the compatibility of the method with structurally complex biomolecules.

Scheme 61 C—H Acyloxylation of Methionine Derivatives[7]



These breakthroughs cement the role of hypervalent iodine reagents as a linchpin in biocompatible photoredox catalysis, offering precise tools for peptide and protein engineering, targeted drug discovery, and ultrasensitive biosensing. By enabling covalent modifications in biologically relevant settings, these reagents bridge synthetic chemistry with biomolecular complexity. Future innovations will likely expand their utility to in vivo labeling, prodrug activation, and dynamic biomaterial assembly, solidifying the role of hypervalent iodine reagents at the forefront of chemical biology.

12.5 Conclusions

Hypervalent iodine(III) compounds are increasingly recognized as valuable tools in photochemistry, owing to their combination of mild reactivity, low toxicity, and sustainable profiles. These reagents serve as both oxidants and radical precursors, enabling a wide range of bond-forming processes including arylations, alkynylations, and C-H functionalizations. Their structural modularity allows fine-tuning of reactivity, while their compatibility with visible-light photoredox systems has expanded the scope of mild and selective transformations. Importantly, the integration of hypervalent iodine chemistry with photocatalysis has shifted their role from traditional stoichiometric oxidants toward catalytic partners, improving atom economy and reducing waste.

Looking ahead, the development of hypervalent iodine based photochemical methods is likely to continue influencing synthetic methodology, particularly in the areas of sustainable synthesis

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and late-stage functionalization. Their compatibility with biomolecular environments, demonstrated in peptide functionalization and protein engineering, signals untapped potential for in vivo applications, targeted drug delivery, and diagnostic probe development. As mechanistic insights deepen, these reagents will bridge disciplines, offering sustainable solutions to challenges in organic synthesis, chemical biology, and materials science. The future of photochemistry is bright and hypervalent iodine reagents shine at its forefront.

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