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Review

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Aqueous-mediated hypervalent iodine chemistry: from green reaction medium to reactivity modulator

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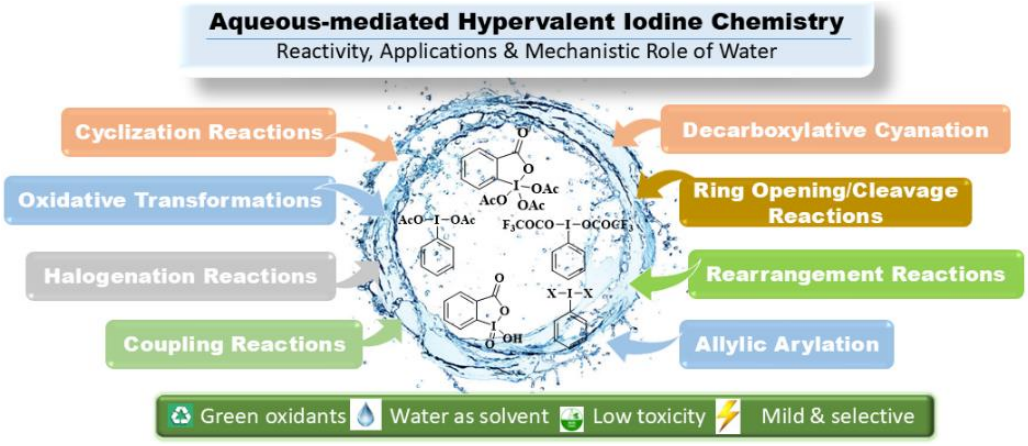
Abstract

Hypervalent iodine reagents are widely recognized as highly versatile, efficient, economic and eco-friendly alternatives in carrying out various organic transformations, viz., carbon-carbon and carbon-heteroatom (C-N, C-O, C-S, C-F) bond formation, halogenation, rearrangement, α-functionalization of carbonyl compounds, oxidation reactions, etc., under mild and operationally simple conditions. The utility of water as a solvent in biological reactions, along with its unique characteristics, makes it an ideal solvent from economic and environmental perspectives. In the present review article, we attempted to provide a comprehensive discussion of the synthetic utility of hypervalent iodine reagents in aqueous media, highlighting mechanistic insights, merits and demerits, and up-to-date methodological developments.



Keywords: Hypervalent iodine chemistry; aqueous media; green chemistry; sustainable organic synthesis; iodine (III) reagents; iodine (V) reagents.

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1. Introduction

Iodine, a naturally occurring non-metallic element, owing to its low electronegativity and high polarizability, exhibits variable oxidation states, -1, +1, +3, +5, +7, resulting in the synthesis of stable polycoordinate complexes. The first hypervalent organoiodine compound, (dichloroiodo)benzene [$PhICl_2$], was discovered in 1886[1], and since then, multiple polyvalent iodine compounds have been discovered and extensively explored as environmentally benign stoichiometric catalysts and electrophilic reagents in synthetic organic chemistry[2-7]. These reagents exhibit similar chemical properties and reactivity toward transition metals. The greater versatility, selectivity, recyclability, mild reaction conditions, easy handling, biodegradability, reduced toxicity, and low cost of hypervalent iodine compounds make them excellent, environmentally friendly, and relatively low-cost alternatives to transition-metal-based reagents. Over the past few decades, hypervalent iodine catalysis has been extensively explored for various organic transformations[2-4,8], viz., carbon-carbon and carbon-heteroatom (C-N, C-O, C-S, C-F) bond formation, halogenation, rearrangement, α-functionalization of carbonyl compounds, oxidation reactions, etc., under mild, operationally simple conditions. Some of the commonly used hypervalent iodine reagents are: phenyliodine(III) diacetate (PIDA) **1**, phenyliodine(III) bis(trifluoroacetate) (PIFA) **2**, [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) **3**, iodobenzenedichloride/bromide (IBD) **4**, Dess-Martin periodinane (DMP) **5**, 2-iodoxybenzoic acid (IBX) **6**, etc (Figure 1).

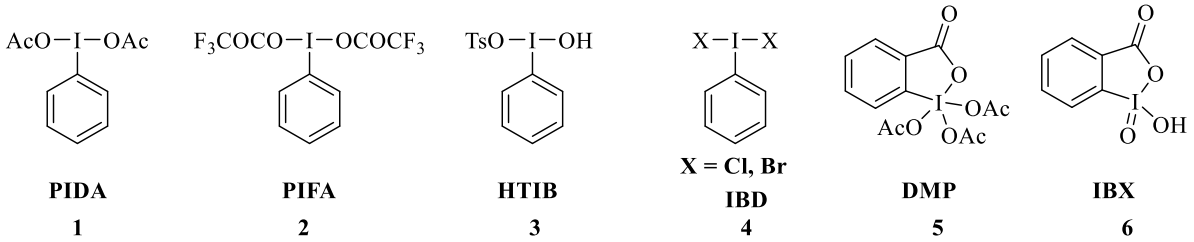


Figure 1. Structure of commonly used hypervalent iodine reagents.

Traditionally, organic synthesis is carried out in organic solvents such as MeOH, EtOH, DMSO, DCM, $CHCl_3$, etc. The growing awareness of environmental concerns relating to solvent toxicity and waste generation has inspired synthetic chemists to explore water as a greener alternative to halogenated and polar aprotic solvents.[9,10] Initially, aqueous media was considered incompatible for organic synthesis due to solubility issues. However, Breslow succeeded in conducting Diels-Alder cycloaddition in aqueous medium[11,12], and since then organic chemists have shown interest in conducting organic reactions in water. The unique characteristics of water, viz., high dielectric constant, high viscosity, high surface tension, high heat of vaporization, amphoteric nature, large temperature range, etc., make it an ideal solvent from economic and environmental perspectives[13]. Recent research has established that water actively influences selectivity, reactivity, and reaction rates by stabilizing transition states.[14]

Though, in many reported protocols, water is not only the principal solvent system but is introduced as a minor additive in largely organic solvent systems. While such reaction medium cannot strictly be considered as fully aqueous reaction conditions, the presence of water often plays a crucial mechanistic role in deciding the outcome of the protocol. Water can participate in proton transfer processes, effecting the formation and stability of iodine(III) intermediates, and facilitate nucleophilic trapping processes during oxidative transformations[15]. These effects are especially significant in rearrangements and oxidative coupling reactions where minute changes in the reaction conditions can dramatically change the distribution of products. Mechanistic studies have therefore highlighted that water often serves not only as a green solvent but also as a reactivity-modulating element that plays a decisive role in product distribution of many hypervalent iodine-mediated reactions. Therefore, the development of water or water-assisted synthetic protocols has become significant research direction in sustainable organic synthesis. This combination of hypervalent iodine catalysis in aqueous media or mixed aqueous systems has shown promising applications in the synthesis of complex organic compounds, such as pharmaceuticals, natural products, and functional materials.

Numerous review articles, book chapters and patents were published on hypervalent iodine chemistry[15-31]. However, there is limited discussion in the scattered literature on hypervalent iodine catalysis in aqueous or combined aqueous media. Given the growing interest in ecofriendly synthetic methodologies, an updated comprehensive overview of aqueous and water-assisted hypervalent iodine reactions is timely. In the present article, we aim to provide a focused and inclusive discussion of the application of hypervalent iodine reagents in aqueous media in organic synthesis, highlighting mechanistic insights, merits and demerits, and up-to-date methodological developments. This review covers the literature published from 2021 to 2025. This article emphasized the dual role of water, both as a green reaction medium and as a mechanistically important component in governing reactivity and selectivity in hypervalent iodine chemistry.

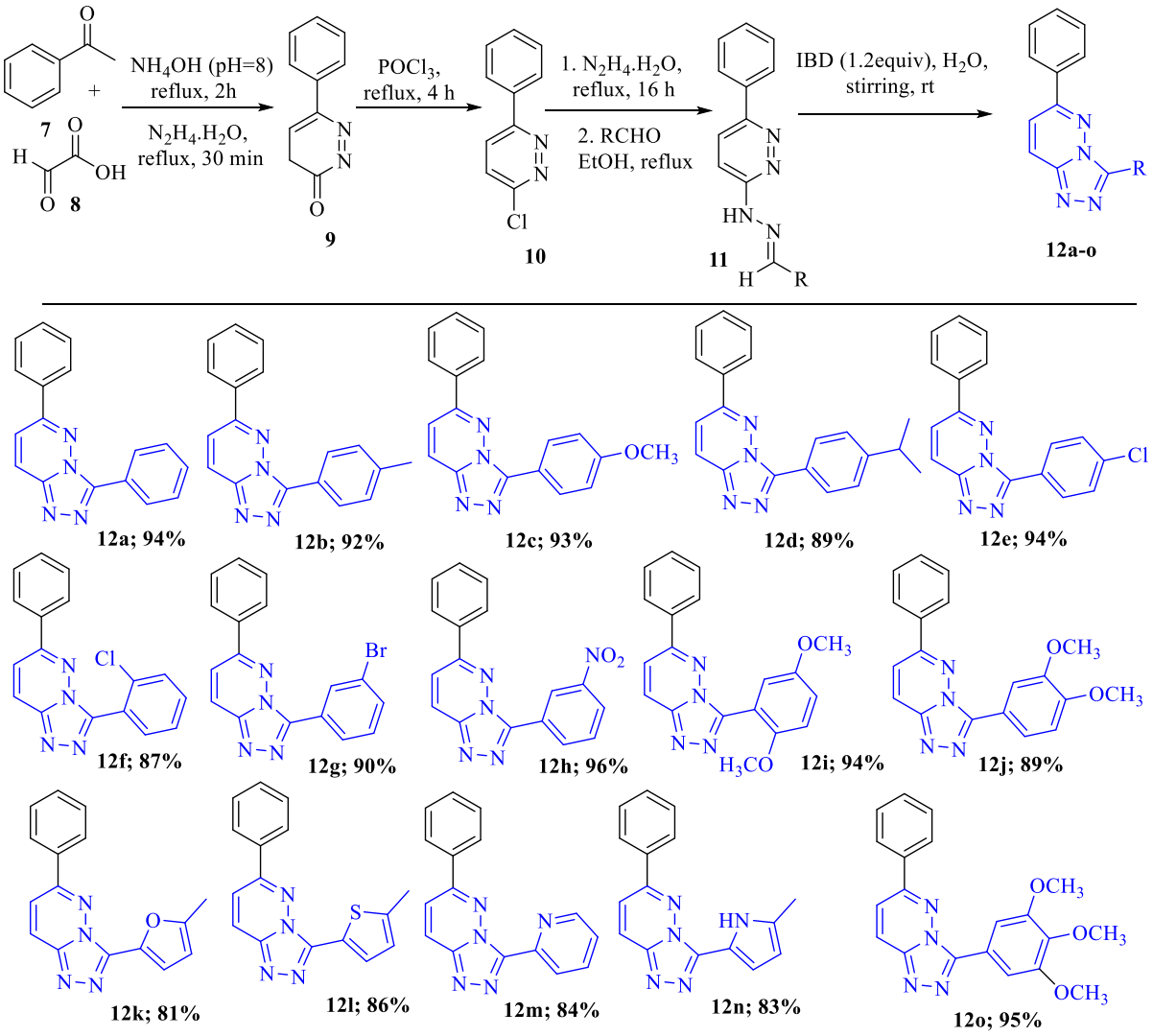
2. Synthetic Applications of Hypervalent Iodine Reagents under Aqueous Conditions

Hypervalent iodine reagents tolerate aqueous conditions well and are used to carry out a diverse range of transformations. The synthetic applications of these reagents are described below:

2.1. Cyclization reactions

Sihag and coworkers reported an efficient synthesis of 1,2,4-triazolo[4,3-*b*]pyridazine analogues **12a-o** *via* hypervalent iodine(III)-assisted oxidative cyclization of pyridazinyl hydrazones under aqueous conditions[32] (Scheme 1). Mechanistically, the reaction proceeds through iodine(III)-mediated oxidation of the hydrazone, followed by cyclization to afford the fused triazoles. Synthesized derivatives were assessed for their cytotoxic

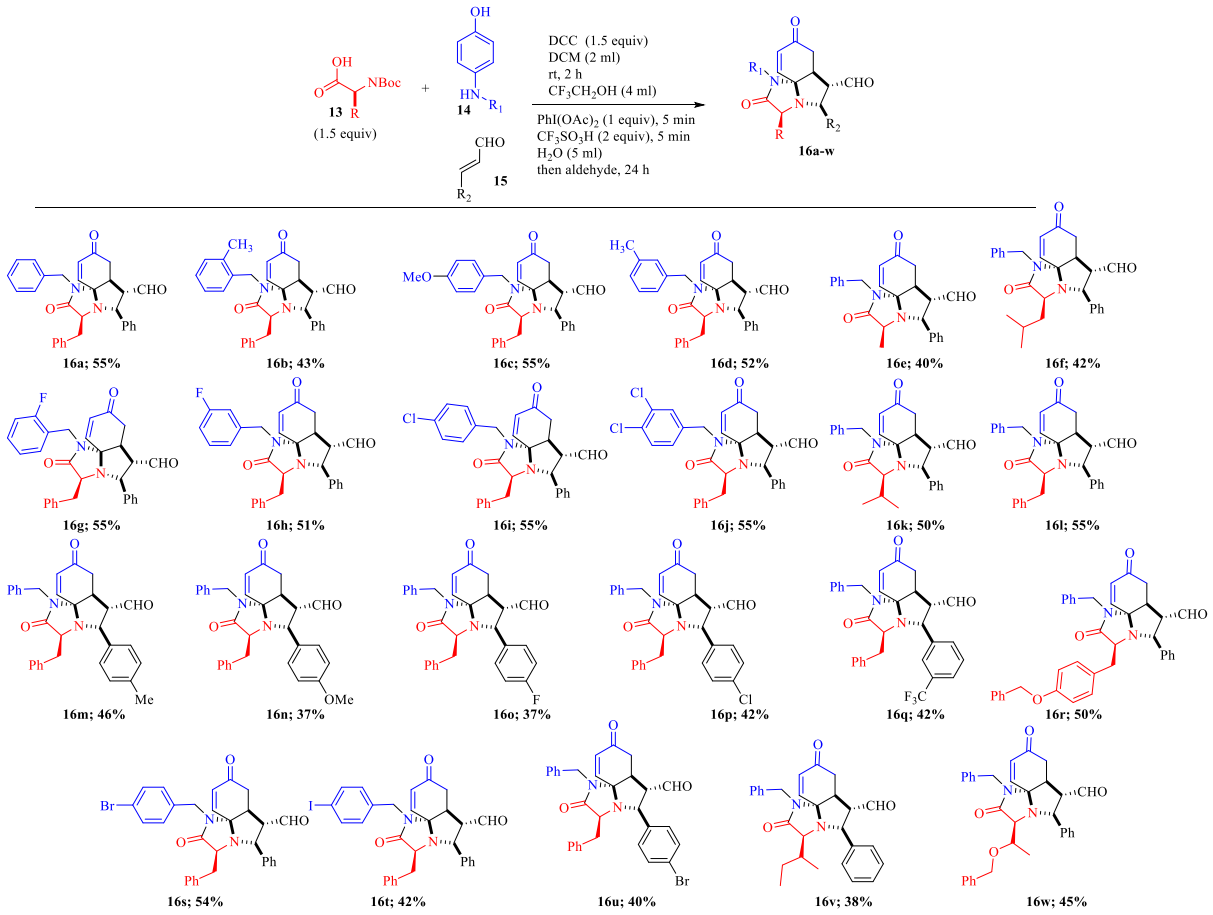
and anticancer potential against the breast cancer cell line MCF-7, and several analogues displayed significant activity, as validated by molecular docking studies. The protocol demonstrated large functional group tolerance, water as green solvent and use of green reagent; IBD as oxidant, highlighting aqueous hypervalent iodine chemistry as a promising platform for heterocycle synthesis.



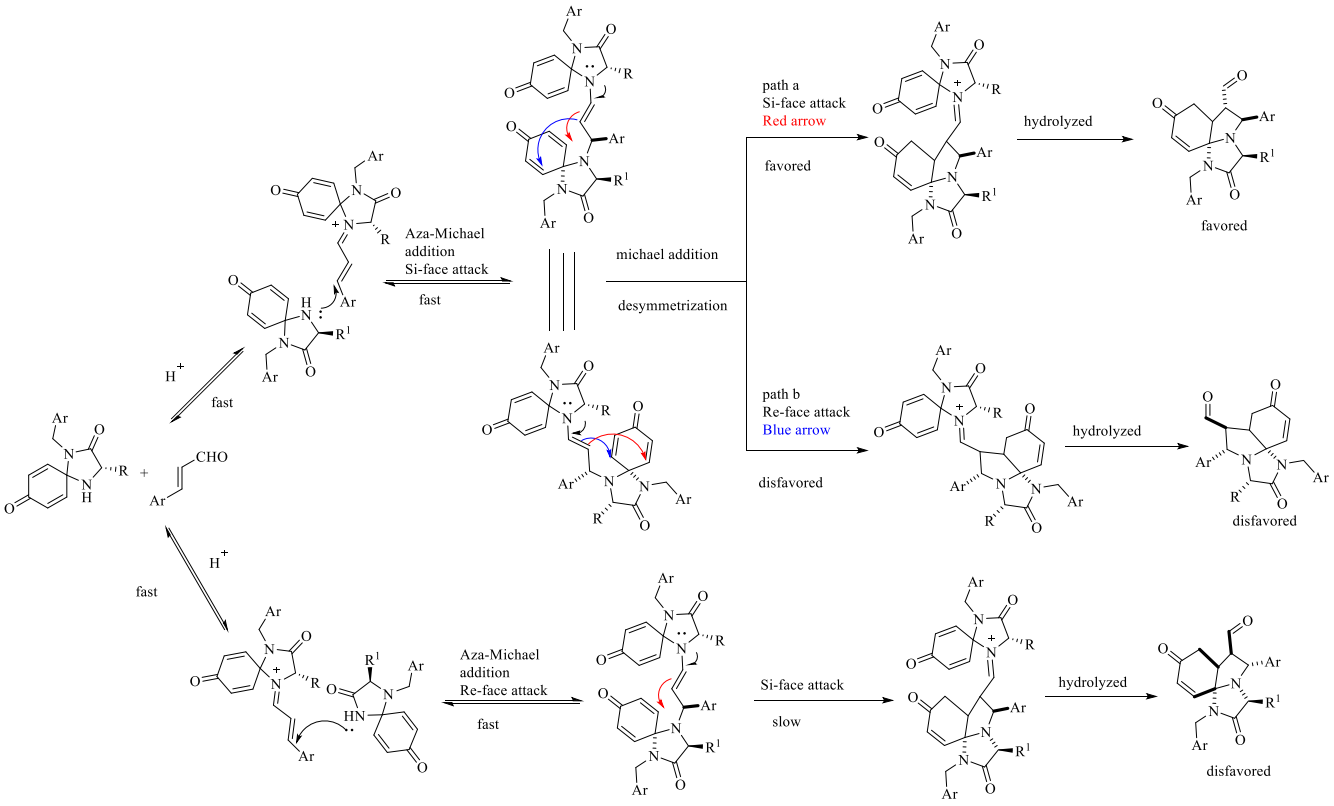
Scheme 1. Hypervalent iodine (III) assisted oxidative cyclization.

Do[33] reported an efficient one-pot multicomponent methodology for the construction of chiral aza-tricyclic molecules **16a-w** with excellent diastereoselectivity (>20:1 dr) (Scheme 2). This protocol employed readily accessible chiral *N*-Boc-protected amino acid, *N*-alkylated p-aminophenol, and α,β-unsaturated aldehyde derivatives and involved a series of bond-forming steps, amide coupling, hypervalent iodine–mediated oxidative dearomatization, and acid-catalyzed aza-Michael/Michael cascade steps in aqueous environments. The developed protocol tolerated a wide range of aminophenols, amino acids, and cinnamaldehyde derivatives, yielding the chiral spiro-imidazolidinone cyclohexenones in moderate to good yields. The stereocontrol in this approach relies solely on the amino acid precursor (Scheme 3). The controlled addition of water facilitated efficient cyclization under eco-friendly conditions, suppressing side reactions.

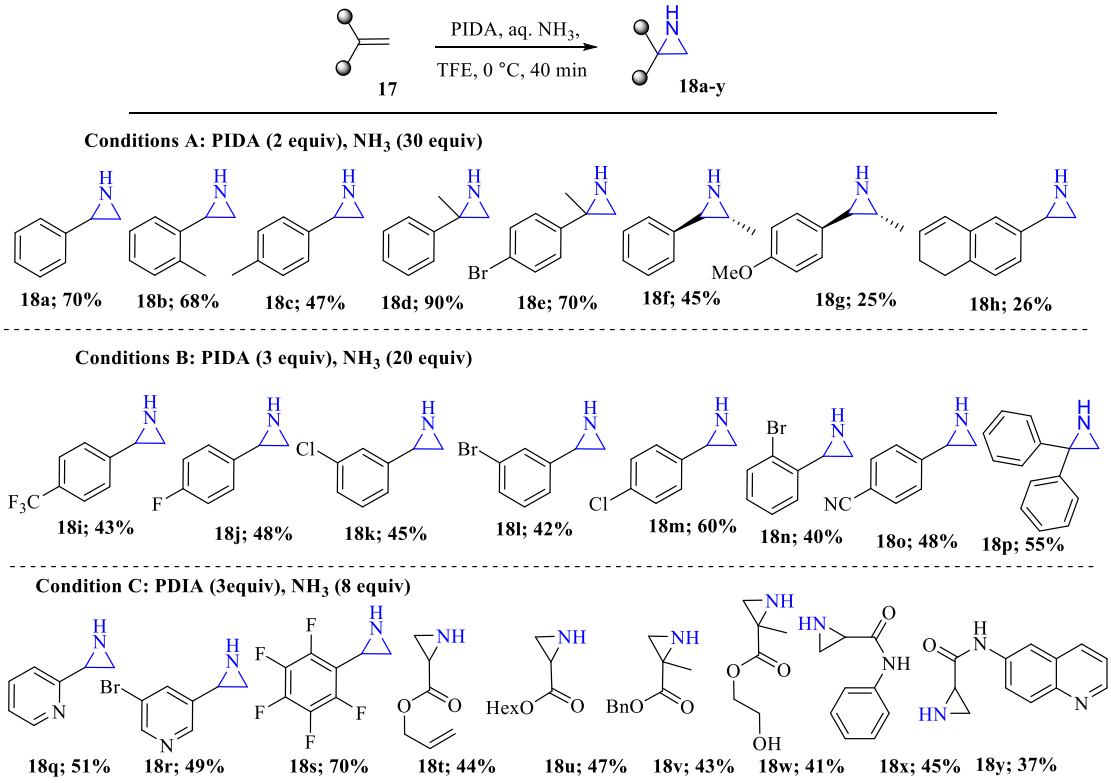
A series of aziridines **18a-y** has been synthesized by Gelato and coworkers from a large number of alkenes **17** using aqueous ammonia and (diacetoxyiodo)benzene (PIDA) under mild conditions[34] (Scheme 4). Optimization investigations revealed that electronically distinct alkenes required distinct combinations of reagents to furnish the corresponding aziridines. The proposed mechanism involves the in situ formation of an iodonitrene intermediate, which, upon electrophilic addition to alkenes, affords *N*-iodonium aziridines. Judicious control of pH and ammonia concentration was found to be critical for directing selectivity toward the desired aziridines rather than rearranged nitriles. The proposed strategy recognized aqueous ammonia as a green nitrogen source, offering a metal-free platform for direct NH-aziridination of alkenes.



Scheme 2. One-pot multicomponent synthesis of chiral aza-tricyclic molecules.

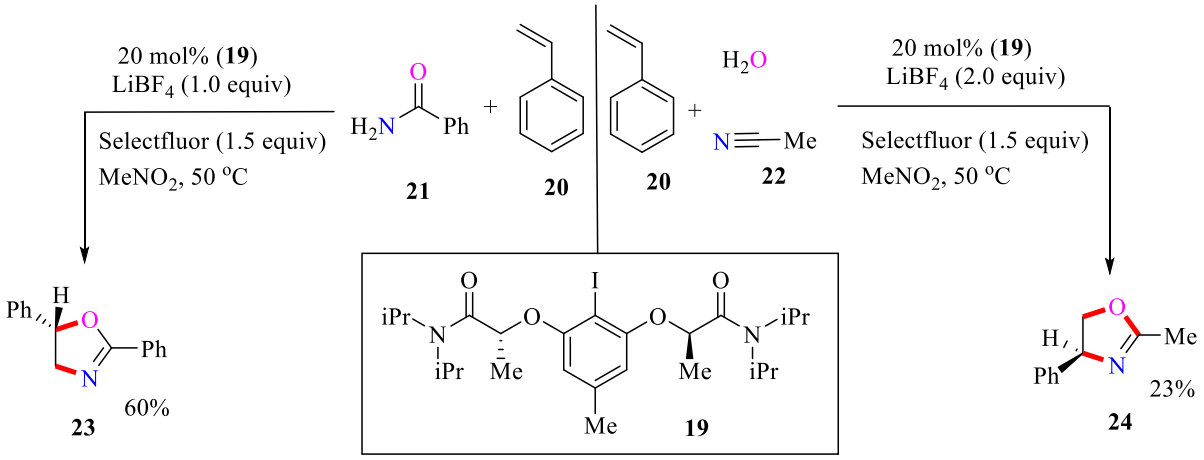


Scheme 3. Plausible mechanism for one-pot multicomponent synthesis of chiral aza-tricyclic molecules.



Scheme 4. PIDA-mediated synthesis of aziridines.

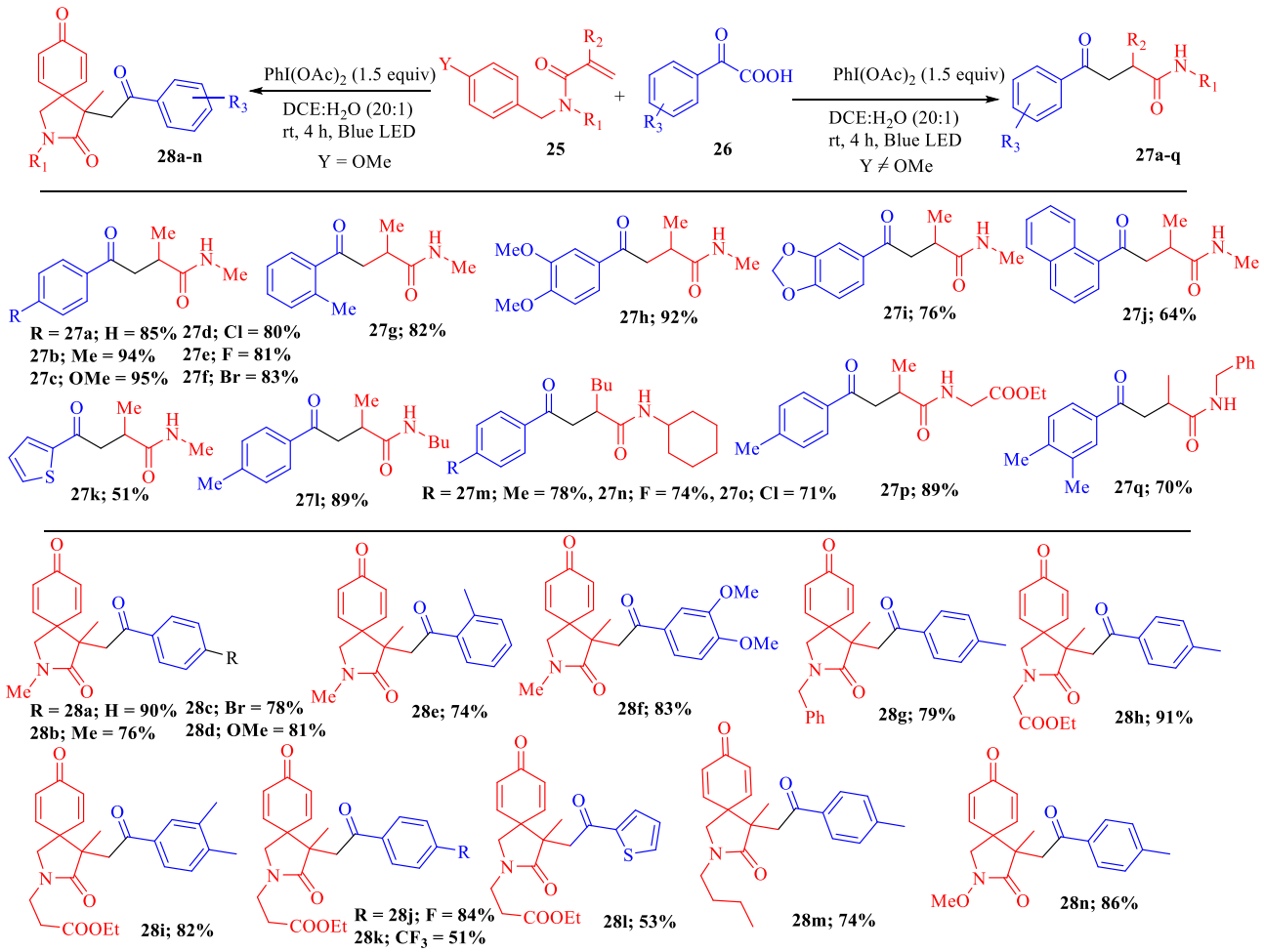
Wu and coauthors[35] reported a regiodivergent method for alkene oxyamination reaction. Initially, the chiral hypervalent iodine catalyst **19** was oxidized with selectfluor and then treated with $LiBF_4$ to produce iodine(III) species (Scheme 5). The authors used amide **21** as the N,O source to produce oxazoline **23** as the product. In contrast, in a Ritter-type reaction with CH_3CN **22** and H_2O, the product was obtained with opposite regioselectivity in 23% yield **24** and 87:13 e.r. Oxazoline derivatives can be converted into various oxazoles and amino alcohol derivatives.



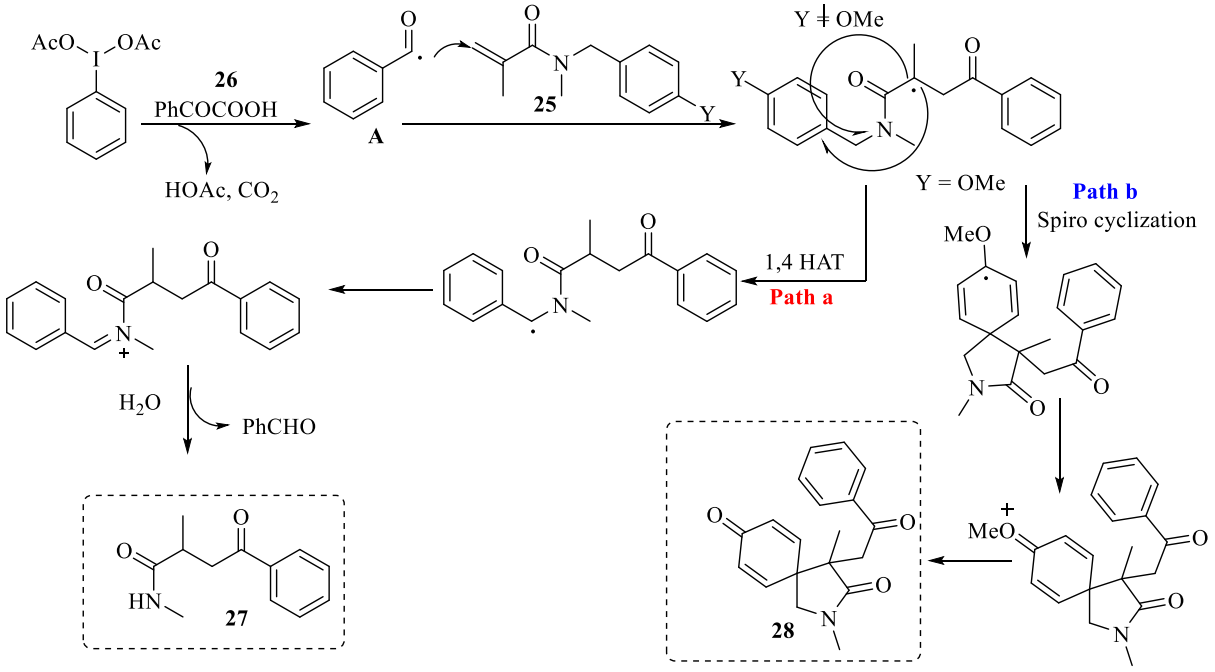
Scheme 5. Asymmetric olefin oxyaminations.

An efficient, metal- and photocatalyst-free synthesis of γ-ketoamides **27a-q** and 2-azaspiro[4.5]decanes **28a-n** (Scheme 6) was reported by Nishad and coworkers *via* visible-light-assisted 1,4-hydrogen-atom transfer and dearomative spirocyclization of *N*-benzylacrylamides in high yields[36]. Mechanistic investigation found that the reaction is initiated by the selective activation of α-oxocarboxylic acids **26** to afford acyl radicals **A** *via* homolytic cleavage of the I-O bond under LED irradiation. Thereafter, addition to acrylamides **25** and deviation via 1,4-hydrogen-atom transfer (**Path a**) or dearomative spirocyclization (**Path b)** afforded γ-ketoamides **27** and azaspiro[4.5]decanes **28**, respectively, as final products (Scheme 7). Water was found crucial for selective transformations by enabling the hydrolysis of intermediates (iminium/oxonium ions) and by stabilizing reactive species. Control experiments and radical-trapping methods validated the involvement of a free-radical pathway.

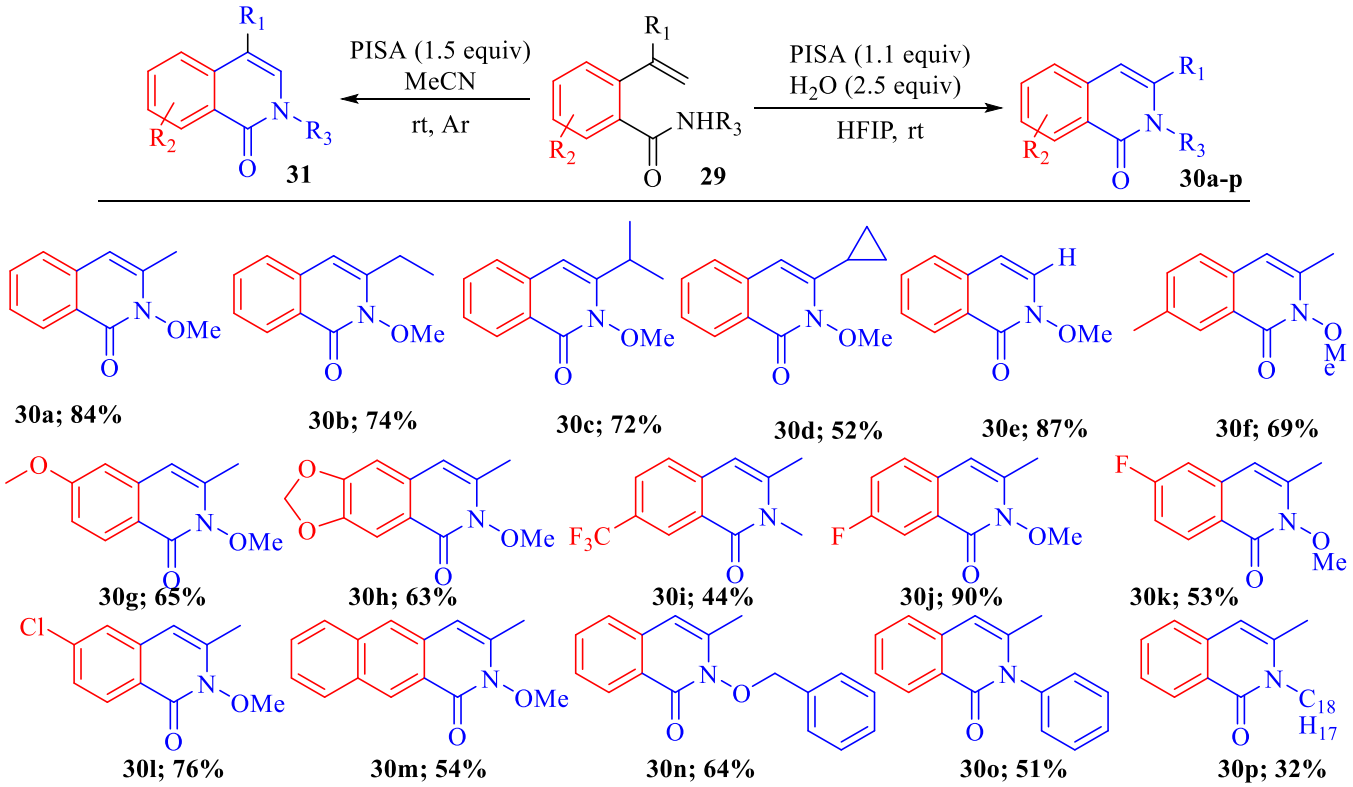
The PISA (phenyliodonio) sulfamate-mediated synthesis of isoquinolinone analogues **30**, **31** from o-alkenylbenzamides **29** was reported by Hu and coworkers (Scheme 8)[37]. Optimization studies established that under aqueous conditions, PISA chemo selectively facilitates the intramolecular C-H amination to yield 3-substituted isoquinolinones **30a-p**, while changing the solvent to anhydrous acetonitrile completely transformed the reaction pathway, affording 4-substituted isoquinolinones **31** as the final product. Mechanistic studies found that the reaction is initiated by the interaction of the olefin moiety **29** with the central iodine(III) atom of PISA, affording intermediate **A**, which H_2O attacks at the benzylic carbon, leading to intermediate **B**. Thereafter, an intramolecular proton shift followed by phenyl migration, reductive elimination, and successive cyclization and dehydration yielded the final product **30** (Scheme 9). Overall, the present protocol highlighted the importance of water control in steering the reactivity of hypervalent iodine(III) reagents.



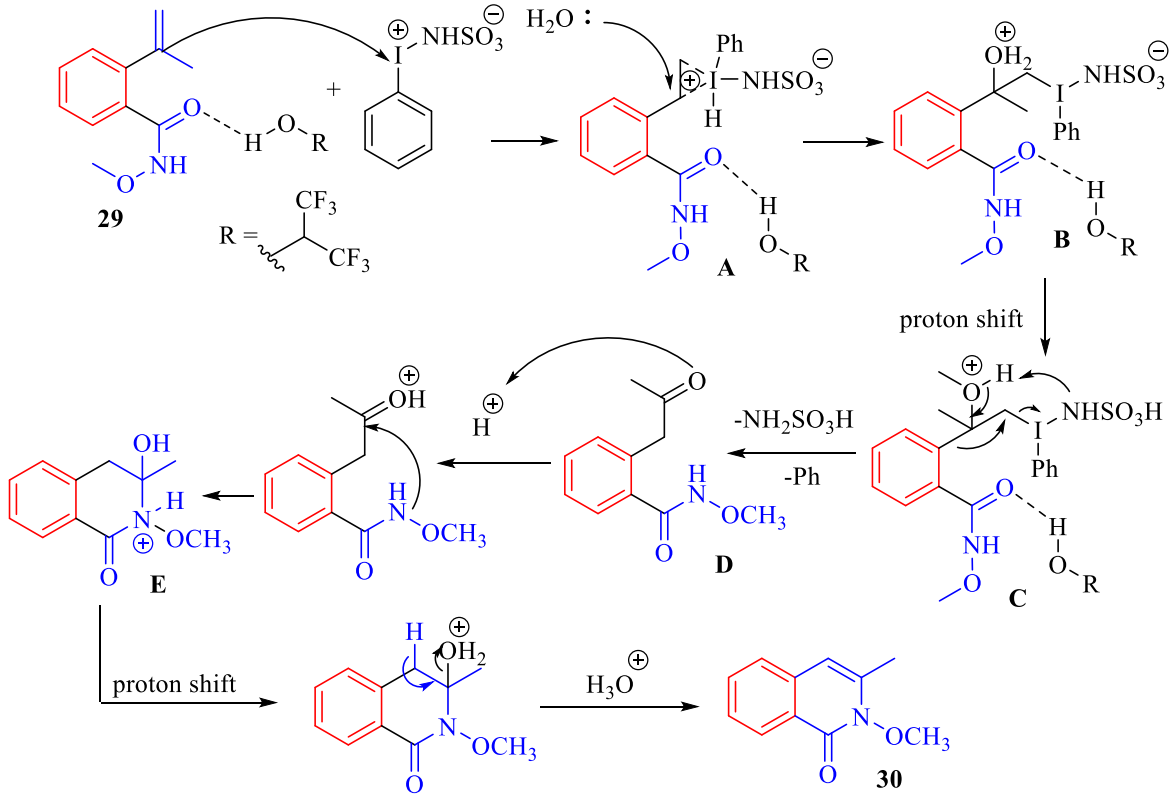
Scheme 6. PIDA-mediated synthesis of γ-ketoamides and 2-azaspiro[4.5]decanes.



Scheme 7. Plausible mechanism for PIDA-catalysed synthesis of γ-ketoamides and 2-azaspiro[4.5]decanes.



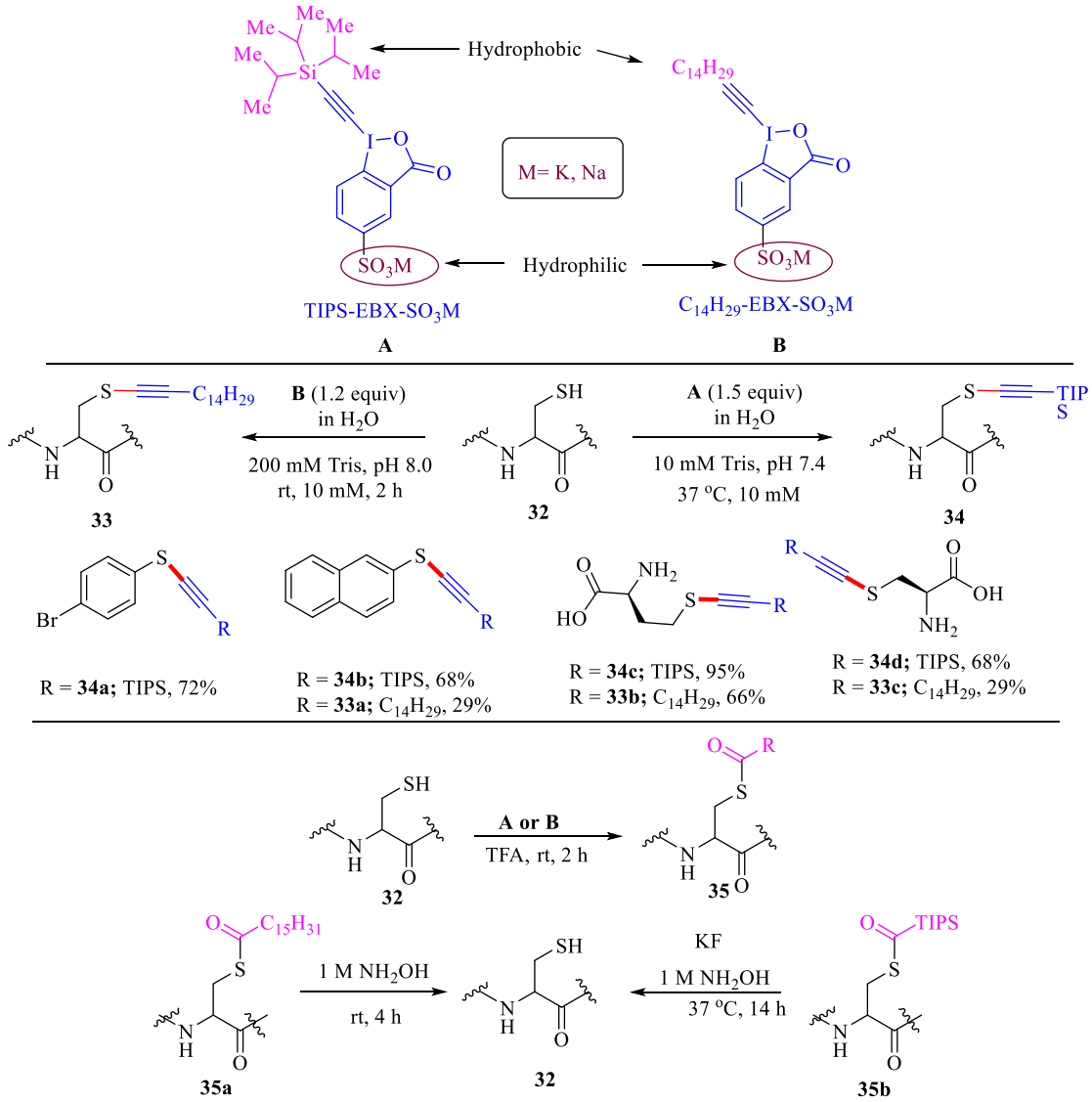
Scheme 8. PISA-mediated synthesis of isoquinolinone analogues.



Scheme 9. Plausible mechanism for PISA-mediated synthesis of isoquinolinone analogues.

2.2. Coupling reactions

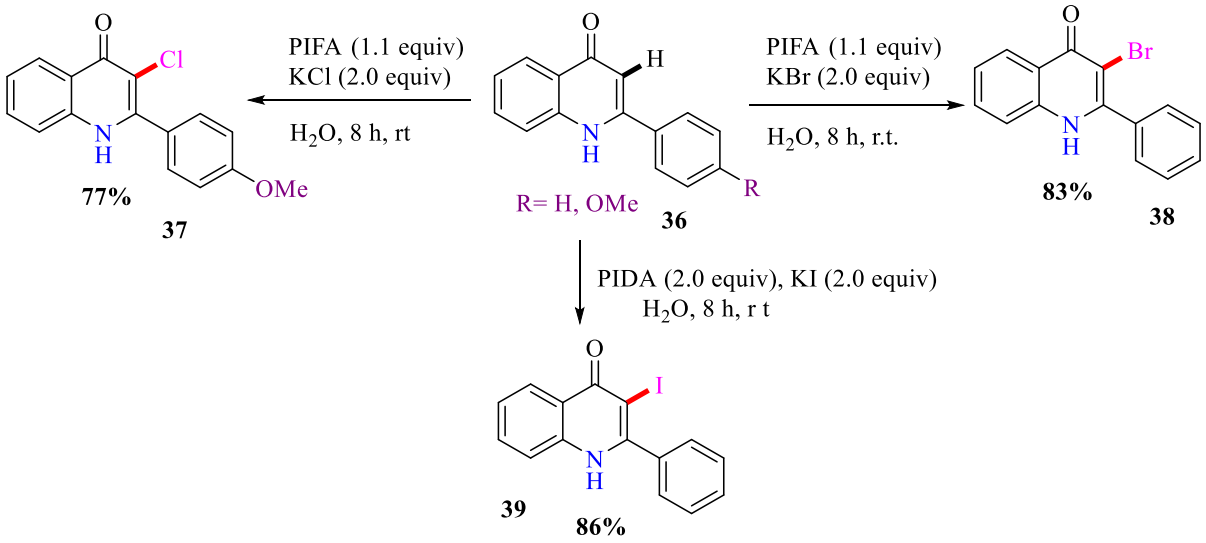
Mishra and coworkers introduced an aqueous-mediated selective lipophilization of cysteine groups **32** with a silyl **34a-d** or an alkyl substituted **33a-c** alkynes using amphiphilic ethynylbenziodoxolone (EBX) iodine(III) reagents, under physiological conditions (pH 6 to 9, 37 °C or room temperature)[38]. Sulfonylated EBXs **A** and **B** (Scheme 10) were synthesized and applied for the functionalization of peptide chains without organic co-solvents, inert atmosphere, or protecting groups. The reported methodology exhibited good chemoselectivity for cysteine in the presence of other nucleophilic amino acid side chains and showed a broad substrate scope, including aromatic thiols, cysteine, homocysteine, small and longer peptides, and even His–Cys-ubiquitin. RP-HPLC retention times and LogP measurements indicated that alkynylation significantly increased lipophilicity in peptide chains. Notably, thioalkynes can be converted into thioesters **35** under acidic conditions, giving access to cleavable or permanent lipidation motifs. The present study marked a significant advance in aqueous hypervalent iodine chemistry and provided a versatile, mild method for the functionalization of peptide and protein chains.



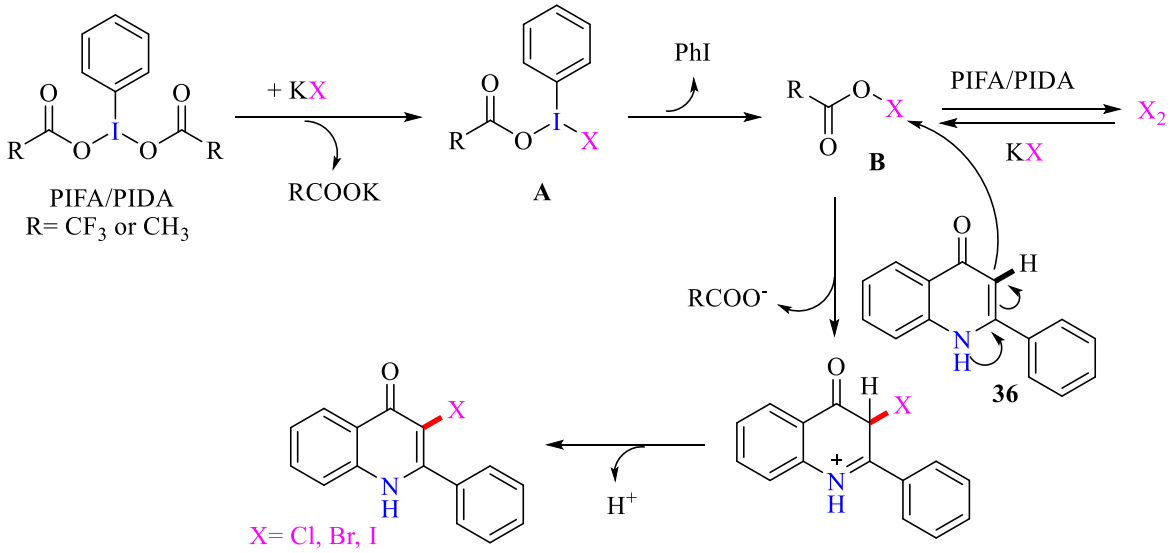
Scheme 10. Application of EBX iodine(III) reagents in alkynylation of peptide chains, thioester formation and cleavage.

2.3. Halogenation reactions

Yang et al.[39] developed an efficient and sustainable gram-scale protocol for the regioselective halogenation of 4-quinolones **36** in aqueous media (Scheme 11). Gram-scale halogenation was achieved using PIFA/PIDA as a stoichiometric oxidant, in combination with potassium halide salts, at room temperature in H_2O. Potassium halide salts, KCl, KBr, and KI were used selectively for chlorination, bromination and iodination, respectively. Mechanistic investigations showed that PIFA/PIDA and KX reacted to form a hypervalent iodine intermediate **A**, which produced hypohalite salt **B** that served as the active electrophilic halogenation species (Scheme 12). Finally, a halogenated product was produced by electrophilic attack at C3 of **36** followed by rearomatization. This protocol could be employed for the late-stage functionalization of potential bioactive molecules containing 4-quinolone skeletons in aqueous media.

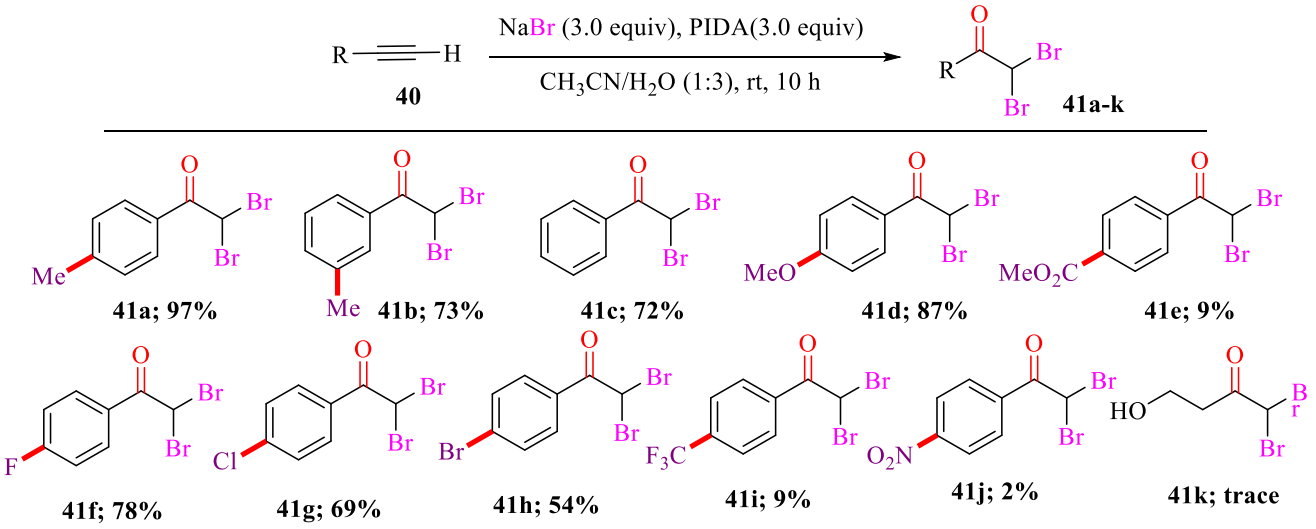


Scheme 11. Gram-Scale preparation of 3-halo-4-quinolones in water.



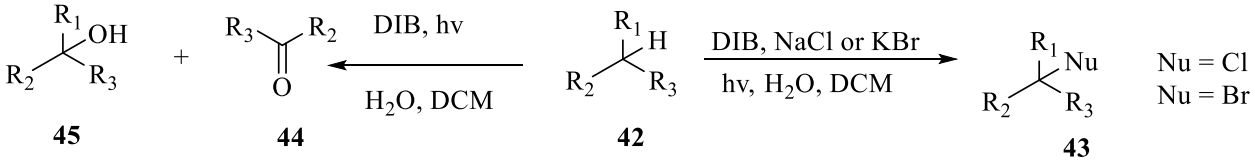
Scheme 12. Plausible mechanism for the synthesis of 3-halo-4-quinolones in water.

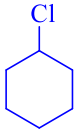
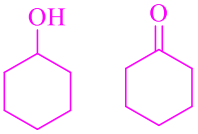
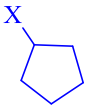
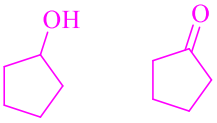
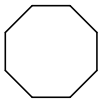
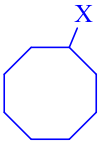
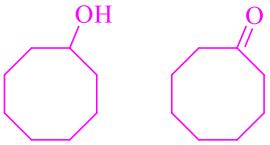
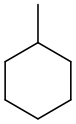
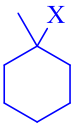
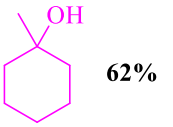
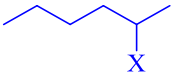
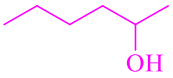
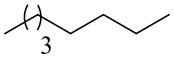
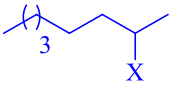
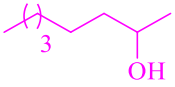
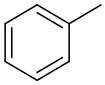
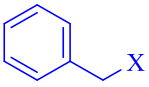
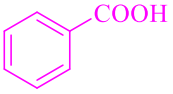
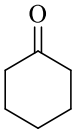
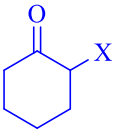
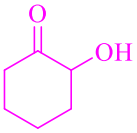
Li and coworkers[40] reported an efficient methodology for the chemoselective oxidative bromination of terminal alkynes **40** by exploring hypervalent iodine chemistry. The authors employed a combination of PIDA ((diacetoxyiodo)benzene) and NaBr in the CH_3CN to carry out vicinal debromination. However, adding H_2O to the system led to the synthesis of α,α-dibromoketones **41a-k** with excellent chemoselectivity and yields (Scheme 13). H_2O plays an important role in furnishing the brominated ketone, as it leads to the in-situ formation of HOBr. A diverse range of electron-releasing and halogen substituents on aromatic alkynes was well tolerated. However, the protocol proved limited in its utility for electron-withdrawing substituents. This methodology offered a mild, efficient, eco-friendly one-pot strategy for the chemoselective synthesis of bromide derivatives.



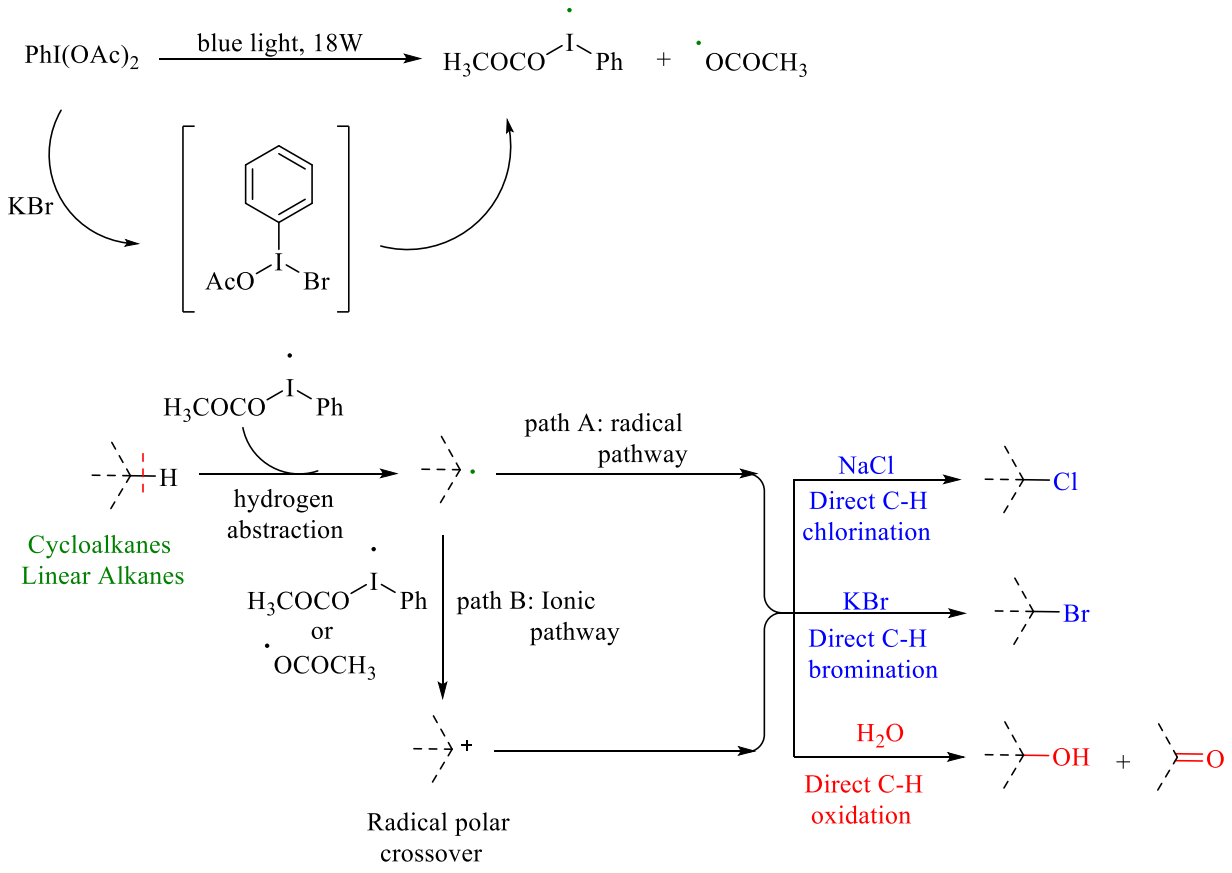
Scheme 13. Bromination of terminal alkyne with hypervalent iodine reagents.

Jia and coworkers[41] disclosed a visible-light-mediated, metal-free and environmentally friendly approach for the functionalization of unactivated C(sp^3)-H bonds **42** by employing (diacetoxyiodo)benzene (DIB) in aqueous media (Scheme 14). Visible light irradiation of PIDA produced iodanyl and acetoxy radicals that abstracted hydrogen from alkanes, resulting in the formation of alkyl radicals that were captured by different coupling partners. In this strategy, H_2O served a dual role, solubilizing inorganic materials and acting as an oxygen source. This protocol was employed for the selective functionalization, viz., chlorination, bromination, or oxidation, of unactivated C-H bonds to synthesize alkyl halides **43**, alcohols **45**, or ketones **44** in moderate to excellent yields (Scheme 15). Overall, this approach enabled the site-selective C-H functionalization by incorporating water in the hypervalent iodine chemistry.



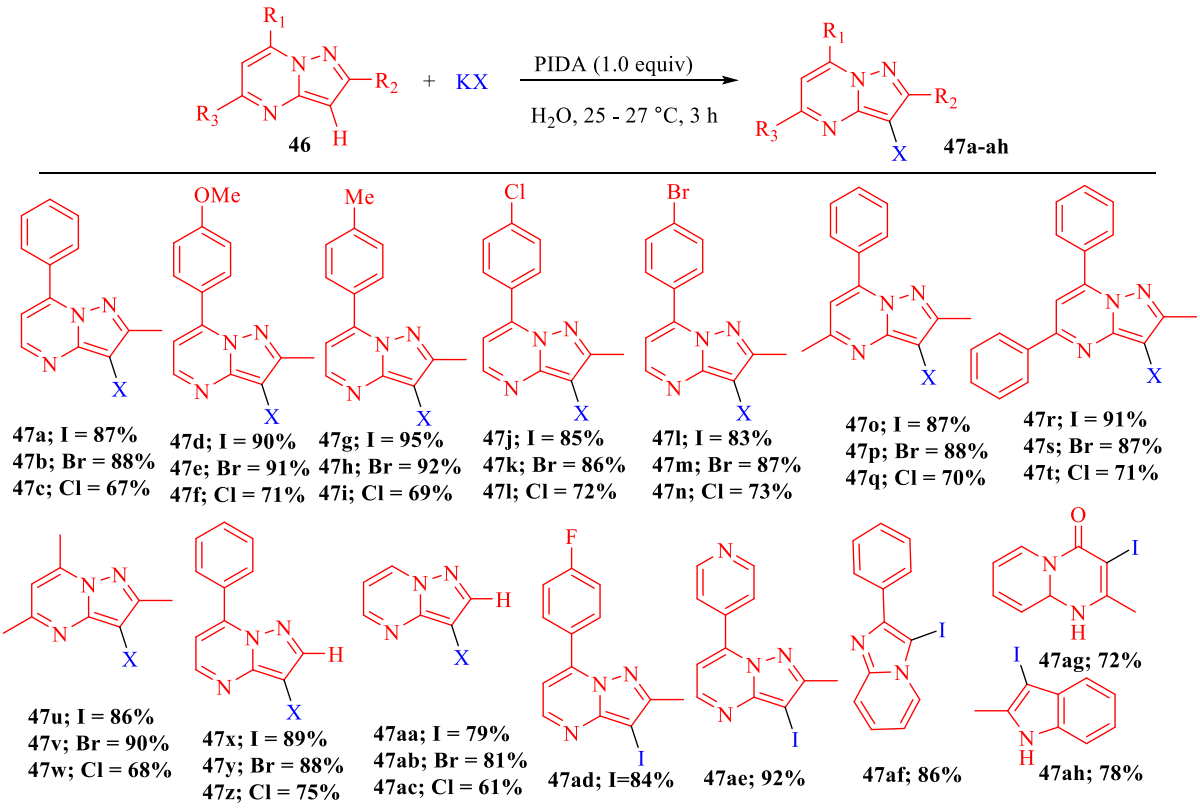
Sr. No.	Substrate	Halogenation	oxidation
1.		 X = Cl, **80%** X = Br, **64%**	 **69% (1.56 : 1)**
2.		 X = Cl, **70%** X = Br, **62%**	 **59% (1.46 : 1)**
3.		 X = Cl, **93%** X = Br, **80%**	 **99% (1 : 1.5)**
4.		 X = Cl, **53%** X = Br, **31%**	 **62%**
5.		 X = Cl, **52%** X = Br, **61%**	 **55%**
6.		 X = Cl, **99%** X = Br, **96%**	 **54%**
7.		 X = Cl, **41%** X = Br, **59%**	 **85%**
8.		 X = Cl, **24%** X = Br, **21%**	 **48%**

Scheme 14. PIDA mediated functionalization of unactivated C(sp^3)-H bonds.

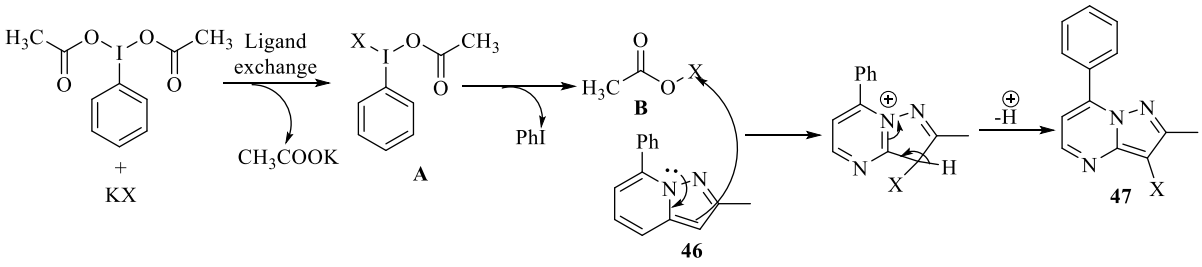


Scheme 15. Proposed mechanism for the PIDA mediated functionalization of unactivated C(sp3)-H bonds.

Chillal and coworkers have discovered (diacetoxyiodo)benzene (PIDA) mediated regioselective C(sp^2)-H halogenation of pyrazolo[1,5-*a*]pyrimidines **46** using readily available potassium halide salts (KI, KBr, KCl) under aqueous conditions (Scheme 16)[42]. The reaction is initiated by ligand exchange of PIDA with a halide salt, leading to the formation of intermediate **A**, which undergoes a transformation to an electrophilic hypohalite species, **B**. Thereafter, electrophilic aromatic substitution leads to the synthesis of the desired products in good to excellent yields **47a-ah** (Scheme 17).



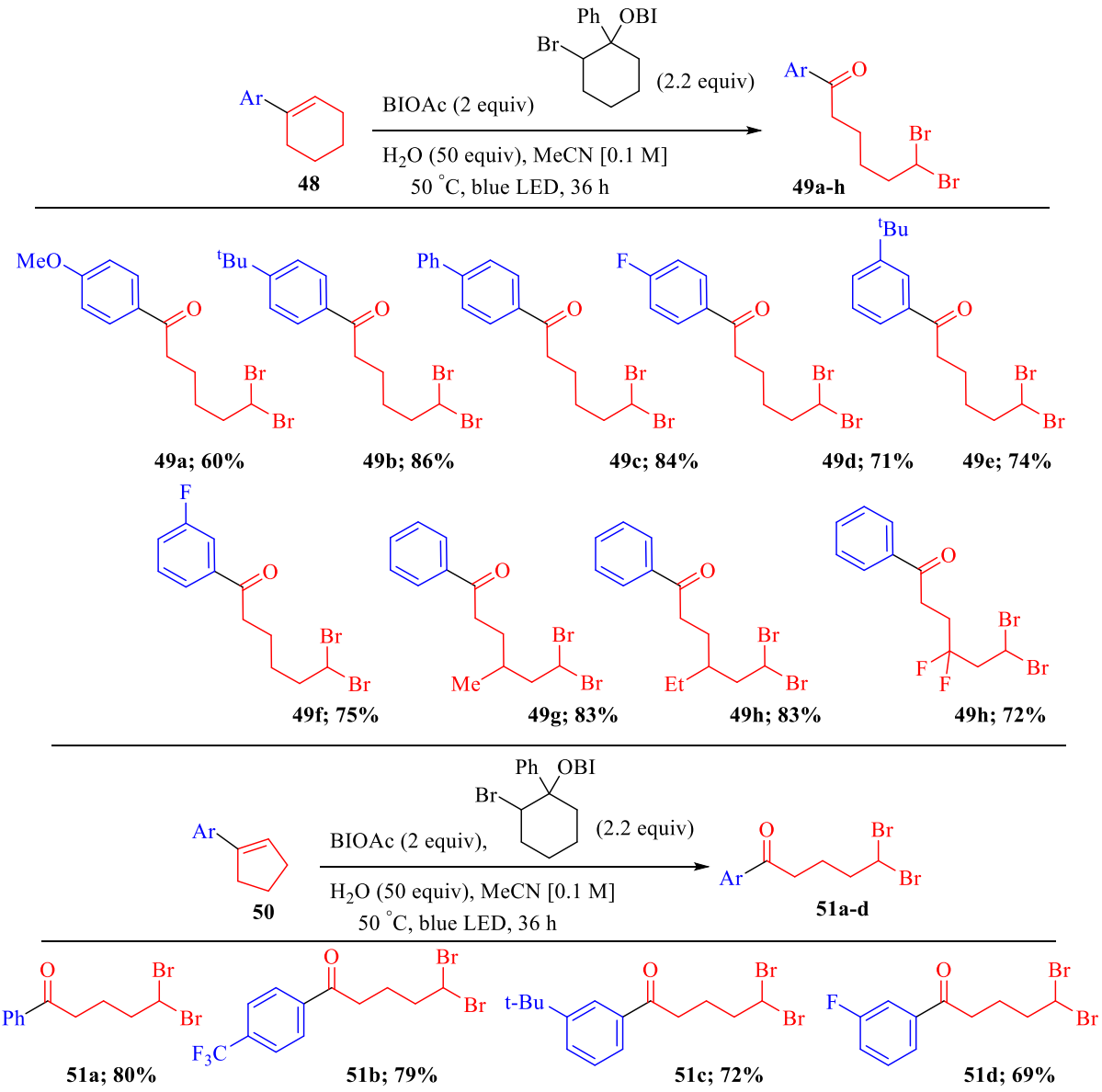
Scheme 16. PIDA-mediated regioselective C(sp²)-H halogenation.



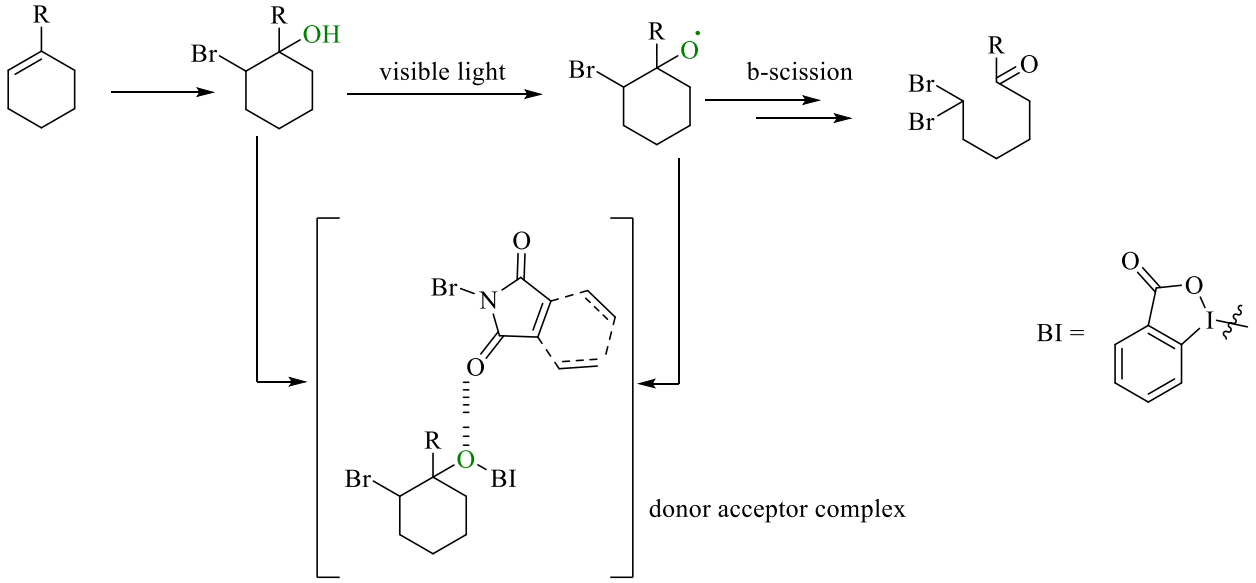
Scheme 17. Plausible mechanism for PIDA-mediated regioselective C(sp²)-H halogenation.

2.4. Ring opening/cleavage reactions

Wei and coworker[43] reported a visible-light-driven approach for the ring-opening of olefins **48, 50**, resulting in gem-dibromination **49, 51** in the presence of hypervalent iodine(III) species and water as the reaction components (Scheme 18). Iodine (III) benziodoxole precursor and *N*-bromoimides constitute a donor-acceptor complex that undergoes homolytic cleavage on visible light irradiation, forming alkoxy radicals. A stoichiometric excess of H_2O was required to furnish bromohydrin intermediates that produced alkoxy radicals.



Scheme 18. Gem-dibromination in the presence of hypervalent iodine (III) reagent.

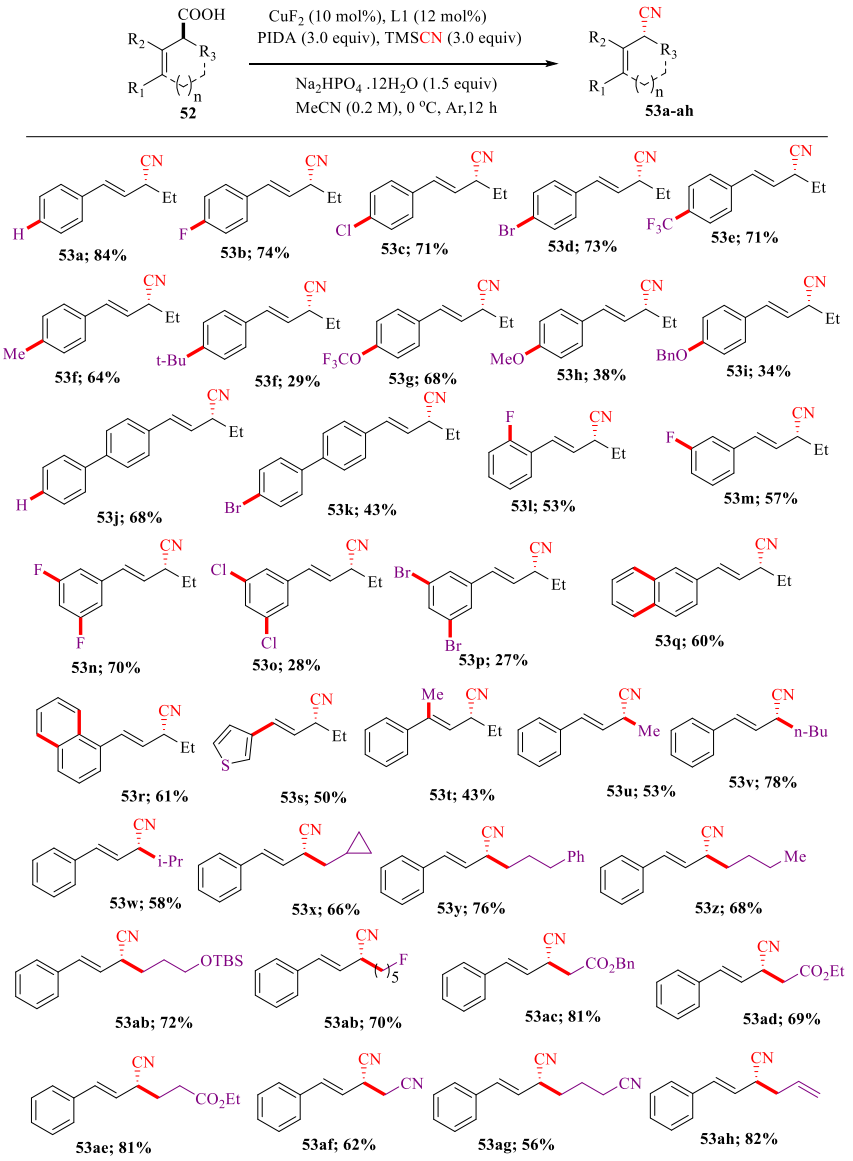


Scheme 19. Proposed mechanism for the gem-dibromination in the presence of hypervalent iodine (III) reagent.

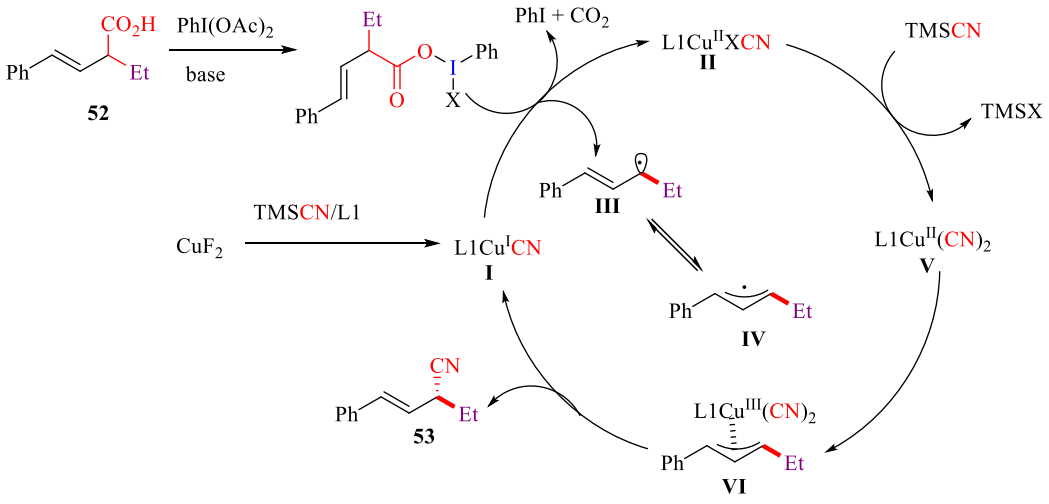
These radicals underwent β-cleavage to give ring-opened geminal dibromoketones in good yields. Deconstructive functionalization of alkenes is explored in cyclohexenes, cyclopentenes, and acyclic trisubstituted alkenes, resulting in the formation of geminal dibromides (Scheme 19). TEMPO experiments and light-switch-on/off experiments established radical pathways, whereas UV-Vis and Jørgensen plots corroborated donor-acceptor complex formation. The investigation enabled the investigation of photochemical radical cascades under aqueous conditions.

2.5. Decarboxylation/ decarboxylative cyanation

Zhang and coworkers reported the highly regio and enantioselective synthesis of chiral allyl nitriles **53a-ah** from copper-catalyzed enantioselective cyanation of β, ϒ-unsaturated carboxylic acids **52** using hypervalent iodine(III) reagent[44]. The mechanistic approach involves iodine(III)-mediated decarboxylation followed by enantioselective cyanation *via* a Cu(III) intermediate (Scheme 20). Control experiments supported the involvement of the radical pathway and confirmed the essential presence of the copper catalyst, ligand, and PIDA, while the use of $Na_2HPO_4 \cdot 12H_2O$ significantly improved reaction efficiency. Key features of the procedure include mild reaction conditions and broad functional group tolerance (Scheme 21).

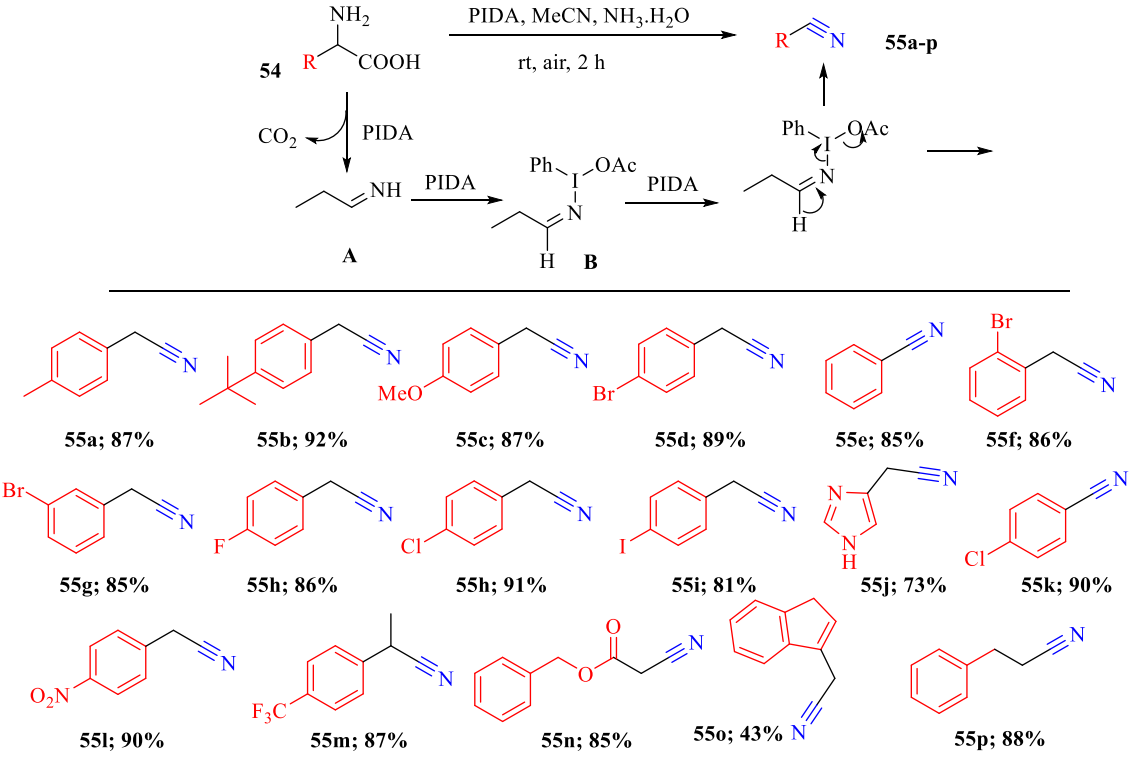


Scheme 20. Enantioselective decarboxylative cyanation.



Scheme 21. Proposed mechanism for enantioselective decarboxylative cyanation.

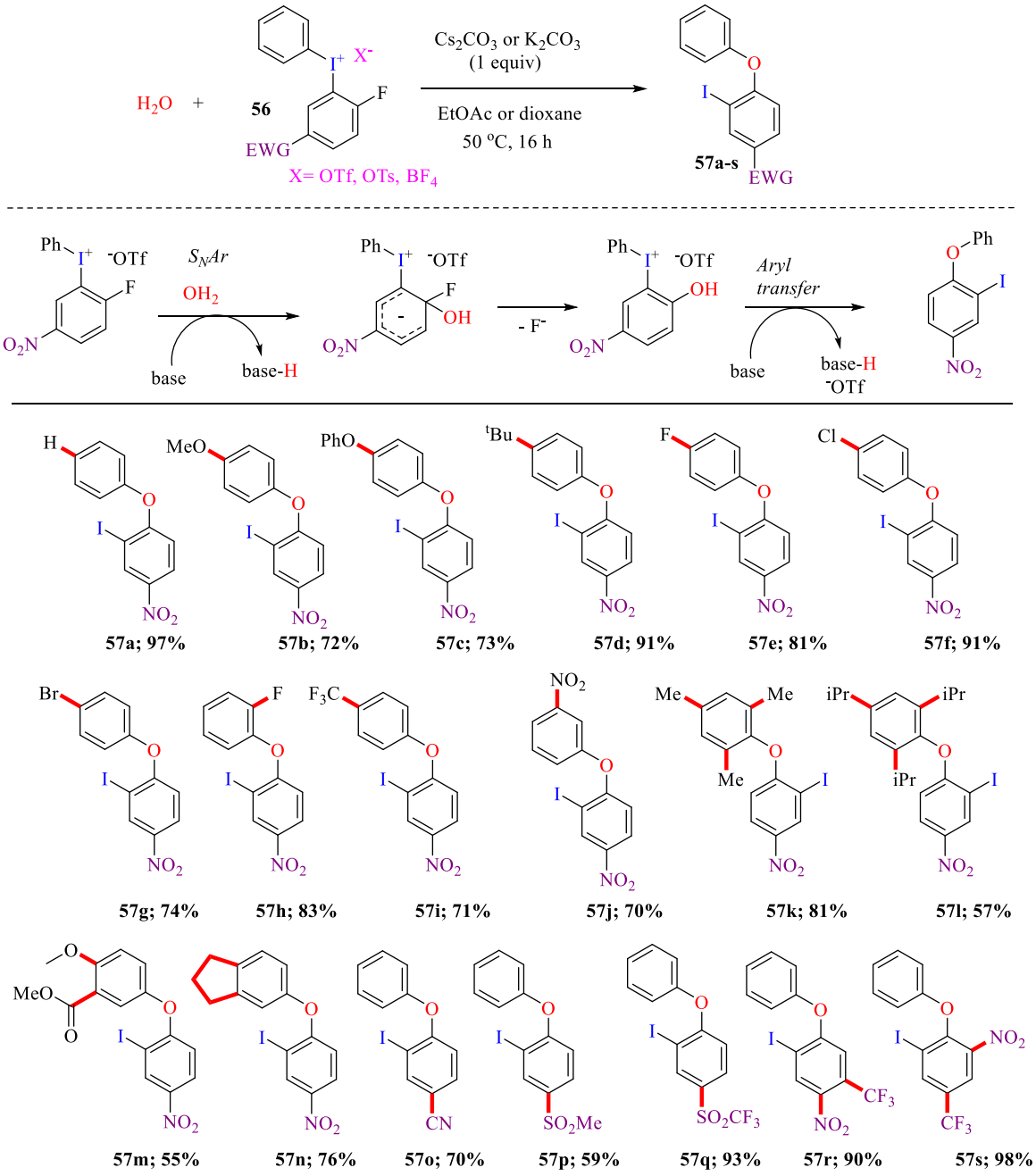
Li and coworkers have reported an efficient synthesis of nitriles **55a-p** *via* bis(acetoxy)iodobenzene (PIDA)-assisted decarboxylative cyanation of α-amino acids **54** in aqueous ammonia, yielding high yields[45]. Mechanistic studies revealed that the reaction is initiated by PIDA-assisted decarboxylation of an α-amino acid to afford imine intermediate **A**, which again reacts with PIDA to afford intermediate **B**. Thereafter, an intramolecular pathway with removal of iodobenzene and acetic acid afforded the nitriles as the final products (Scheme 22). Studies found that water plays a crucial role in maintaining equilibrium between imine intermediates and their corresponding hydrolysis products, thereby overwhelming side reactions and ensuring selective nitrile formation. The strategy demonstrated a broad substrate scope, tolerating a wide range of amino acids with electron-withdrawing as well as electron-releasing groups, and avoiding the use of hazardous materials.



Scheme 22. PIDA-assisted decarboxylative cyanation of α-amino acids.

2.6. Rearrangement reactions

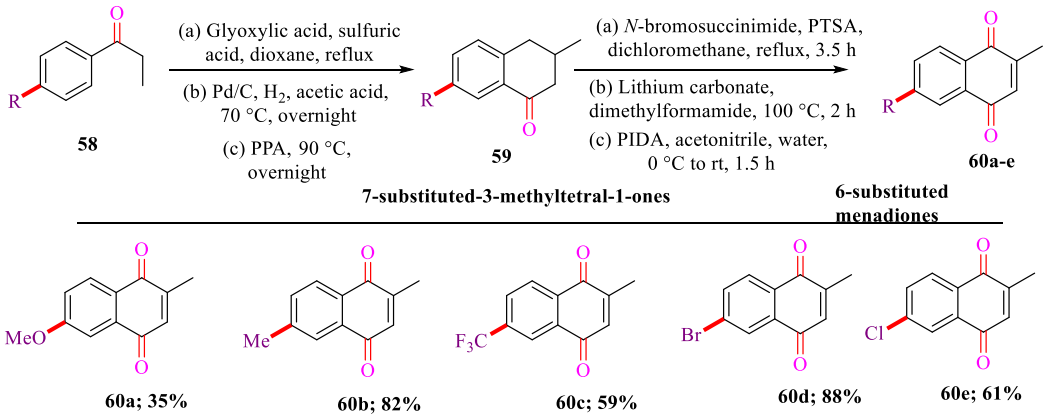
Linde and coworkers reported transition-metal-free diarylation **57a-s** of various heteroatom nucleophiles with significant compatibility toward water as both solvent and nucleophile, aided by ortho-fluorinated diaryliodonium salts **56**[46]. The developed protocol combines the reactivity of aromatic nucleophilic substitution with iodine(III)-mediated aryl transfer in a single step, allowing the simultaneous installation of two different aryl groups under environmentally benign conditions (Scheme 23). Notably, the reaction continued efficiently under aqueous conditions, with water itself serving as a nucleophile to yield diaryl ethers in high yields. Key highlights of the methodology involve broad functional-group tolerance, high atom economy and mild reaction conditions. A mechanistic study revealed that water initially attacks the ortho-fluorinated diaryliodonium salt, yielding a hydroxy-substituted iodine(III) intermediate, which then undergoes intramolecular aryl migration, providing the diaryl ether as the final product.



Scheme 23. Diarylation of water with substrate scope and proposed mechanism.

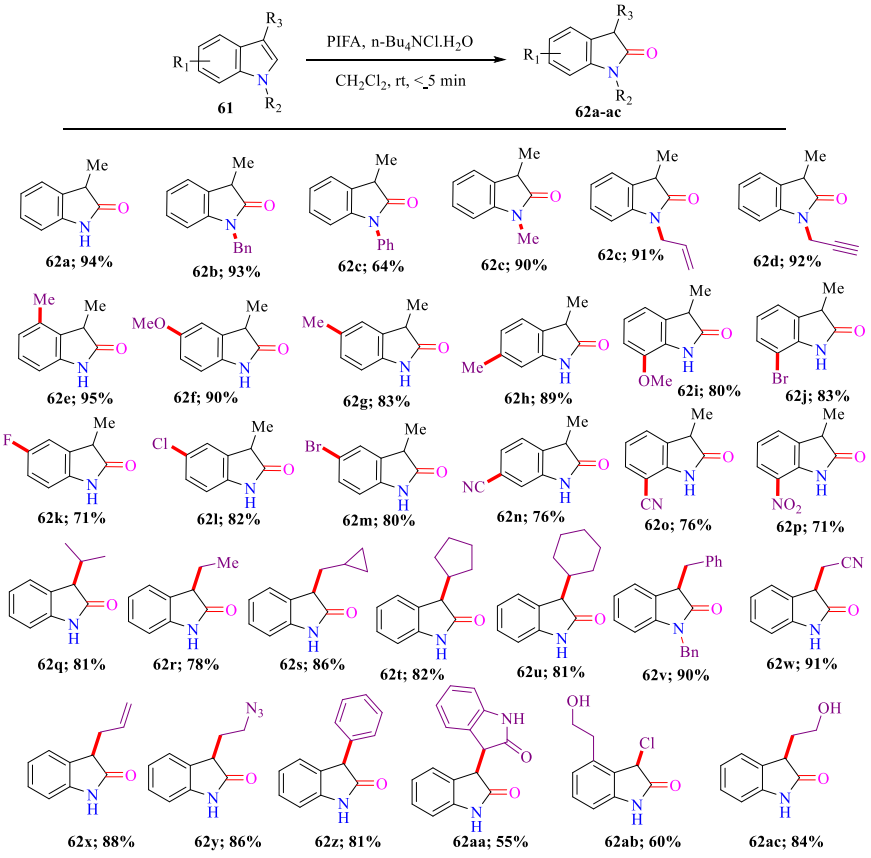
2.7. Oxidation reactions

Trometer and coworkers established a scalable multigram synthetic protocol for 7-substituted-3-methyltetral-1-ones **59** and 6-substituted menadiones **60**, active intermediates for biologically potent molecules (Scheme 24)[47]. The synthetic protocol involves initial condensation of 4'-substituted propiophenones **58** with glyoxylic acid, followed by palladium-catalyzed hydrogenation and acid-assisted intramolecular cyclization to yield tetralone intermediates. Thereafter, α-bromination using mild N-bromosuccinimide and base-induced aromatization to naphthols, followed by hypervalent iodine(III)-assisted oxidation (PIDA), afforded the final products **60a-e** in good yields.



Scheme 24. Synthesis of 7-substituted-3-methyltetral-1-ones **59** and 6-substituted menadiones **60**.

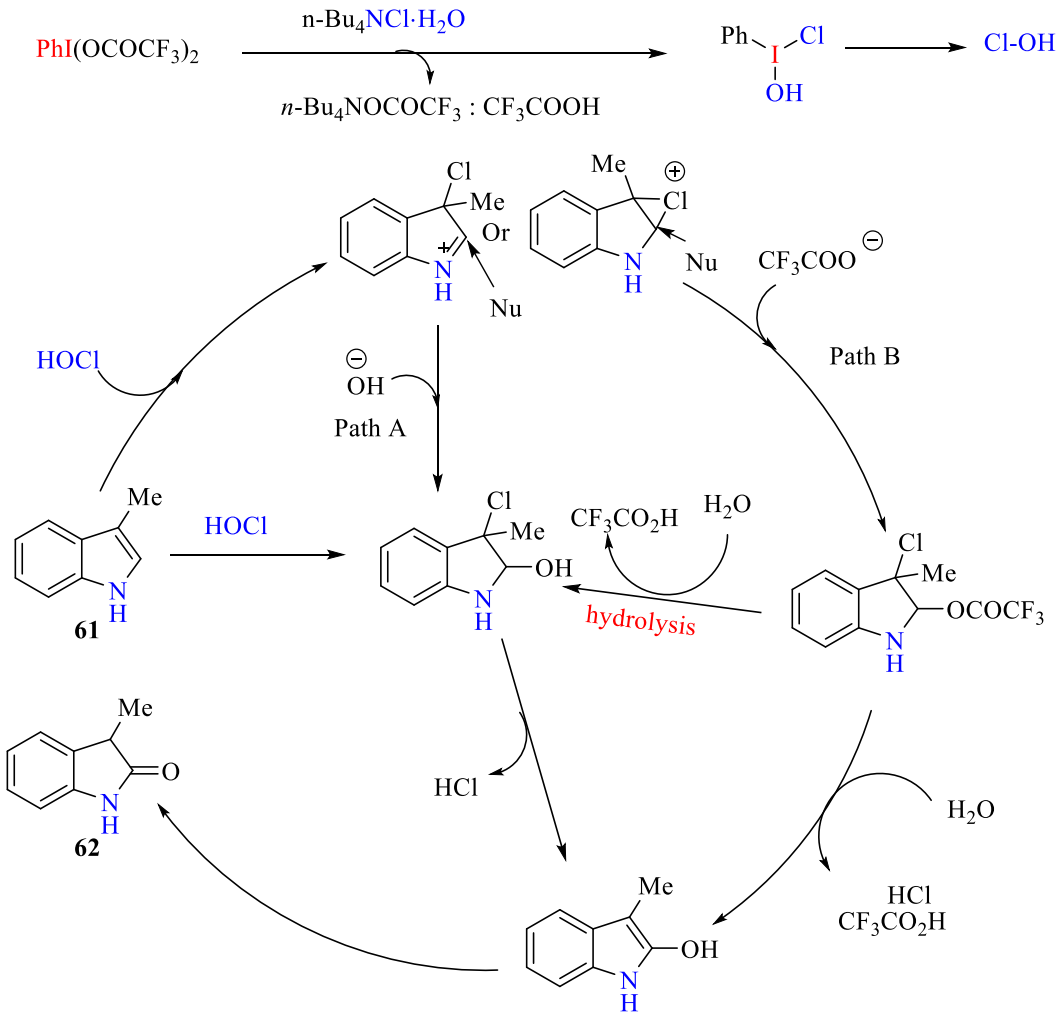
Liang and coworkers reported a series of 3-substituted 2-oxindoles **62a-ac** *via* PIFA/n-$Bu_4NCl{\cdot}H_2O$ system-assisted oxidation of indoles **61** (Scheme 25)[48].



Scheme 25. Synthesis of 3-substituted 2-oxindoles from the oxidation of indoles.

The protocol progressed under mild conditions, yielding desired products in high yields (up to 95%) within a short reaction time and tolerating a wide range of functional groups, demonstrating the practicality of water-assisted hypervalent iodine oxidation chemistry. Mechanistic investigation found the *in-situ* formation of HOCl from the reaction of PIFA with chloride under aqueous conditions. Thereafter, electrophilic chlorohydroxylation

of the indole and elimination lead to the formation of the oxindole framework (Scheme 26). Isotope labelling validated water as the oxygen source.

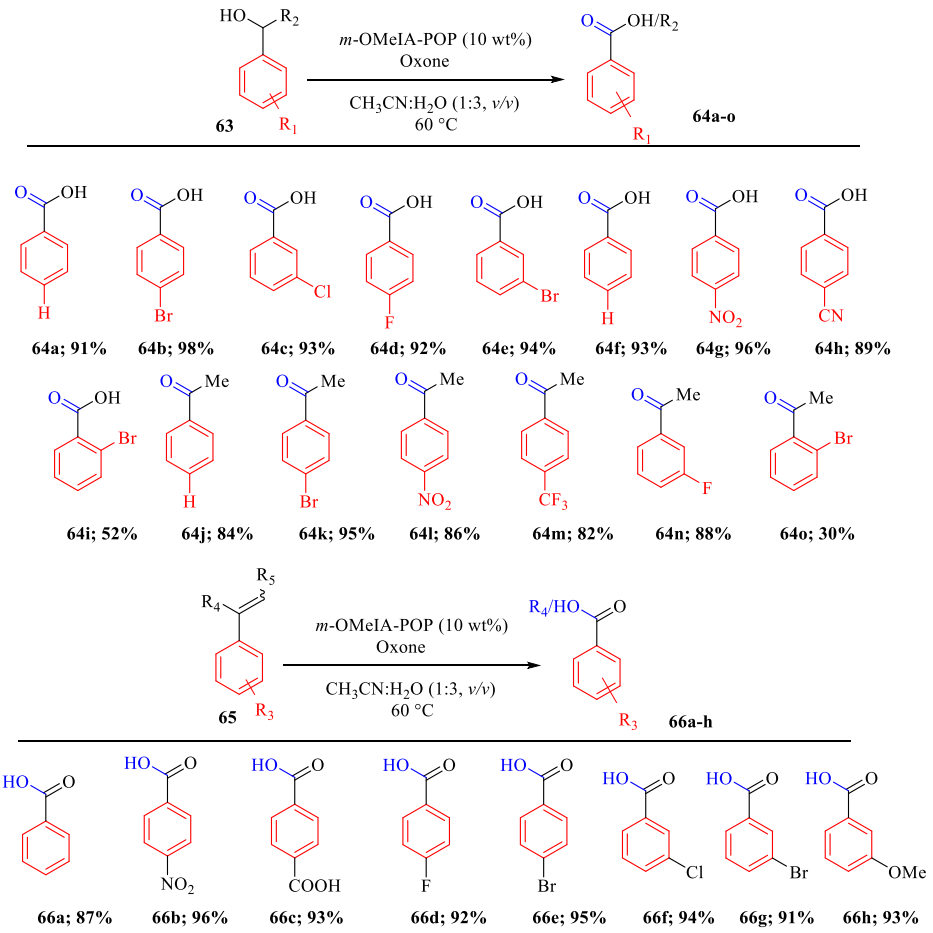


Scheme 26. Proposed mechanism for the PIFA-mediated oxidation of indole.

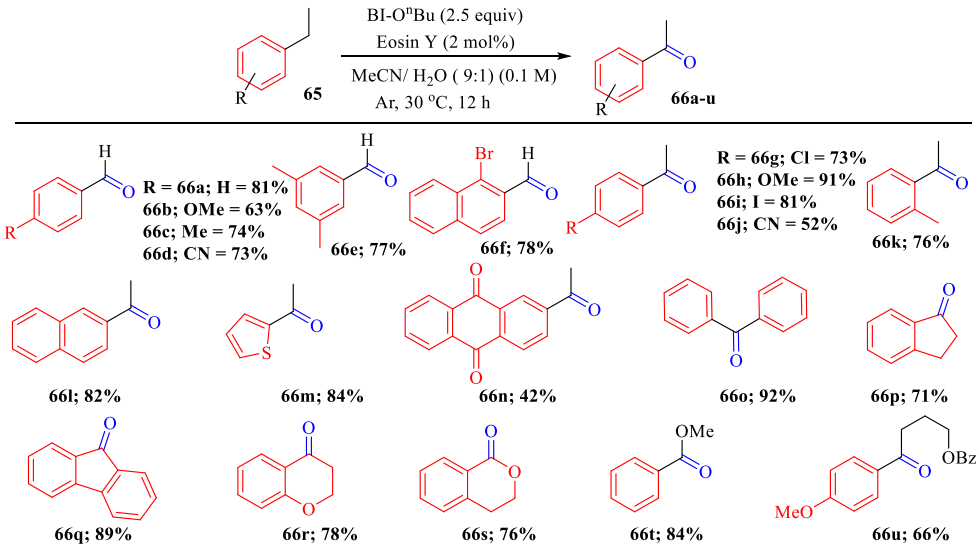
Tamuly and coworkers synthesized porous organic polymers (POPs) featuring biaryl building blocks with inbuilt o-iodobenzoic acid (IA) moieties and employed these heterogeneous precatalysts for the oxidation of alcohols **63**, vicinal diols, and acyloins, and for the cleavage of olefins **65**[49]. Synthesized organic polymers with *o*-iodobenzoic acid oxidized using Oxone under aqueous-organic media [CH_3CN/H_2O (1:3)] to afford catalytically active, λ^5-iodane o-iodoxybenzoic acid (IBX) (Scheme 27). Key features of the developed protocol include the reuse of the catalyst without significant loss of activity and the in situ generation of λ^5-iodane, which avoids the handling and isolation of explosive iodine(V) reagents.

He and coworkers discovered a photocatalyst, eosin Y-mediated benzylic C-H oxidation of a variety of alkyl arenes **65** and *N*-heteroarenes to corresponding aldehydes and ketones **66a-u** assisted by hypervalent iodine reagents under water-assisted conditions (Scheme 28)[50]. Mechanistic studies revealed that the activation of Eosin Y initiates a reaction to generate Eosin Y*, which undergoes single-electron transfer with hypervalent iodine(III) reagent to afford BI radical **B.** Tautomeric conversion of **A** and **B** enabled hydrogen atom transfer, producing benzylic radical **C**. Further, oxidative radical-polar crossover with Radical **C** and Eosin $Y^{\bullet+}$, affording benzyl carbocation intermediate **D**, which is trapped by water as the nucleophilic oxygen source, providing

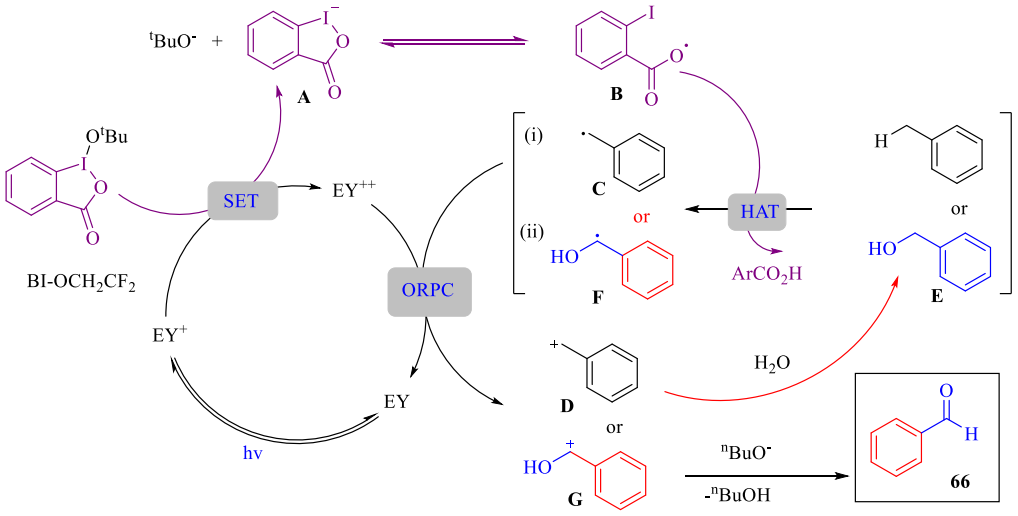
benzyl alcohol intermediates and finally aldehydes or ketones as the desired product (Scheme 29). Overall, the present work emphasized the synergistic interaction among photoredox activation, hypervalent iodine catalysis, and controlled water participation for selective benzylic oxidation.



Scheme 27. Heterogeneous catalyzed oxidation of alcohols, vicinal diols, acyloins and cleavage of olefins.

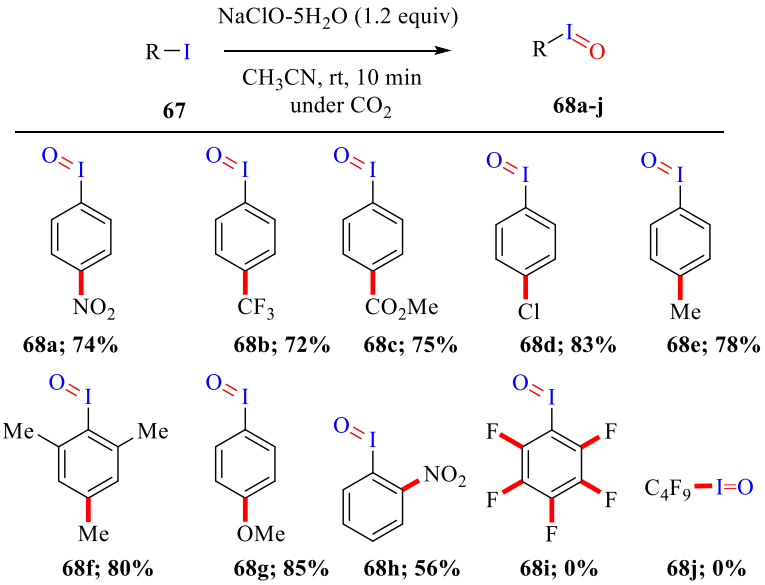


Scheme 28. Photocatalytic benzylic C-H oxidation using hypervalent iodine (III).

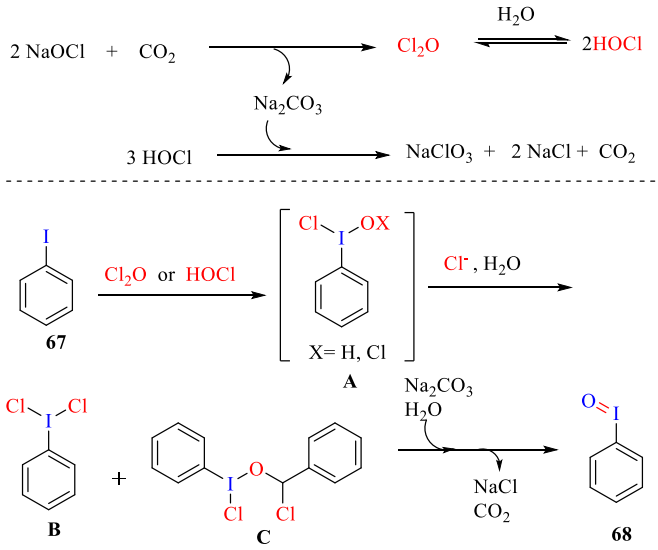


Scheme 29. Plausible mechanism for Photocatalytic benzylic C-H oxidation using hypervalent iodine (III).

Miyamoto and coworkers[51] developed a one-pot oxidative protocol for the synthesis of iodosylarene (ArIO) derivatives **68a-j** using NaOCl·5H_2O under a CO_2 atmosphere (Scheme 30). The targeted oxidation products were obtained in excellent yields by stirring diversely functionalized iodoarenes **67** with NaOCl·5H_2O in CH_3CN under 1 atm. CO_2 at ambient temperature for 10 minutes. This protocol was operationally simple, eco-friendly, and economic, and tolerated a wide range of substrates, including electron-rich and electron-deficient substrates; however, highly deactivated iodoarenes, such as pentafluoroiodobenzene **68i** and nonafluorobutyl iodide **68j**, remain unreactive. The one-pot base-free conditions enabled diverse oxidative transformations, including the synthesis of imino-λ^3-iodane, iodonium ylide, sulfoxides, pentavalent λ^5-bismuthane, and benzynes. Mechanistic investigation showed that a CO_2 atmosphere promotes the formation of oxo species (Cl_2O or HOCl), which serve as the active oxidant for iodoarenes. Initially, iodobenzene attacked Cl_2O or HOCl, leading to the formation of a transient iodine (III) intermediate **A** that rapidly undergoes ligand exchange to form $PhICl_2$ **B** or a μ-oxo dimer **C** that furnished the iodosylbenzene **68** precipitates (Scheme 31).

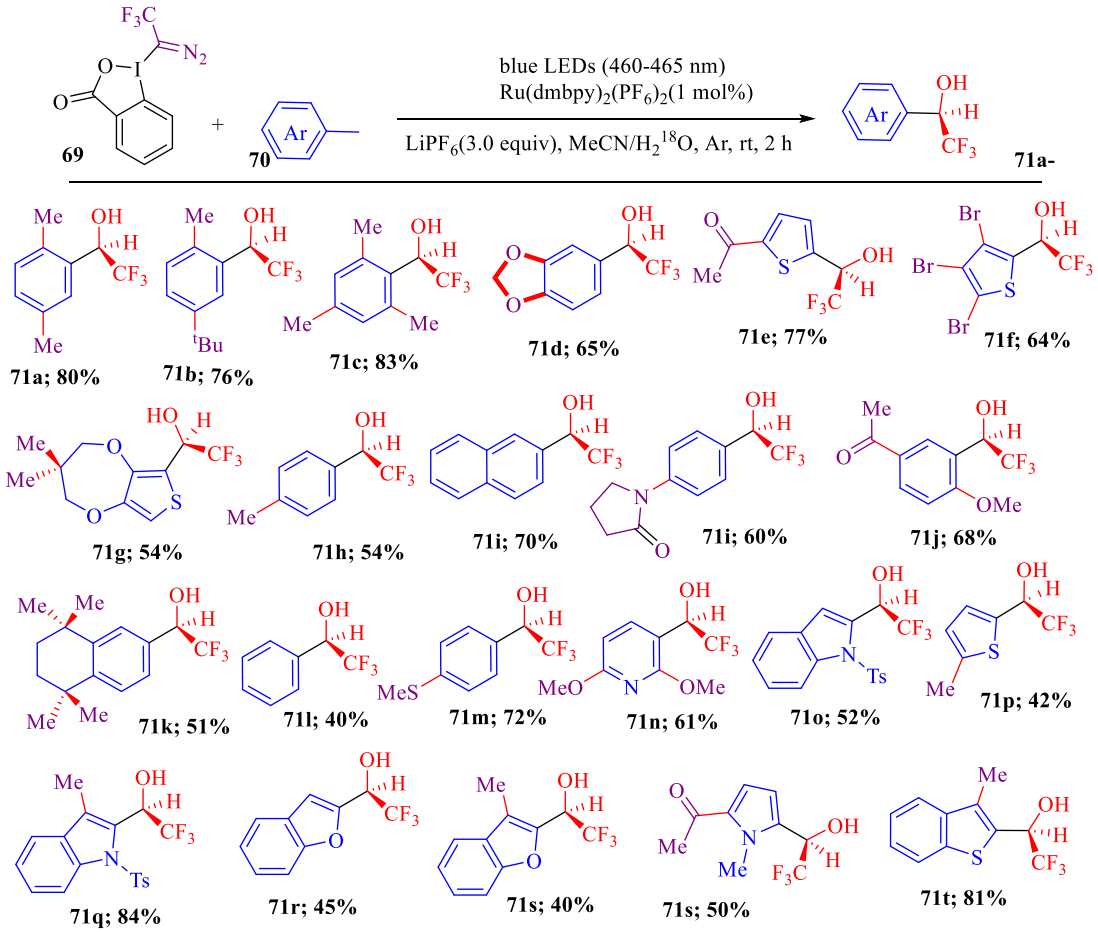


Scheme 30. Synthesis of iodosylarene.



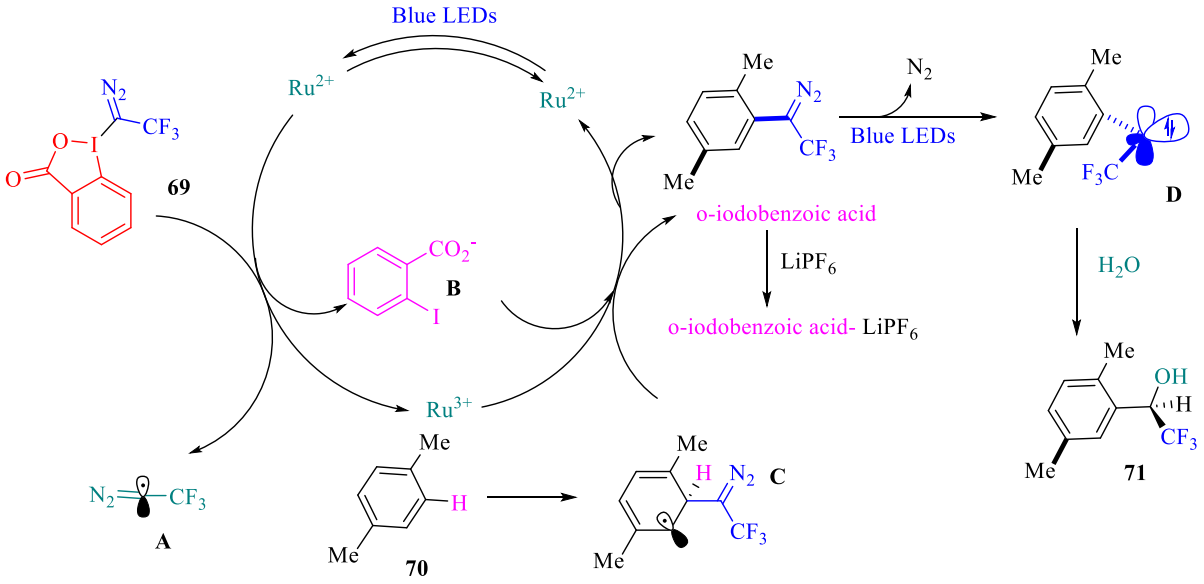
Scheme 31. Proposed mechanism for oxidation of Iodoarenes.

Tian and coworkers reported a photocatalytic approach for the trifluoromethylcarbinolation of arenes **70** assisted by hypervalent iodine(III) reagents bearing a diazotrifluoromethyl group **69** under aqueous conditions (Scheme 32)[52].



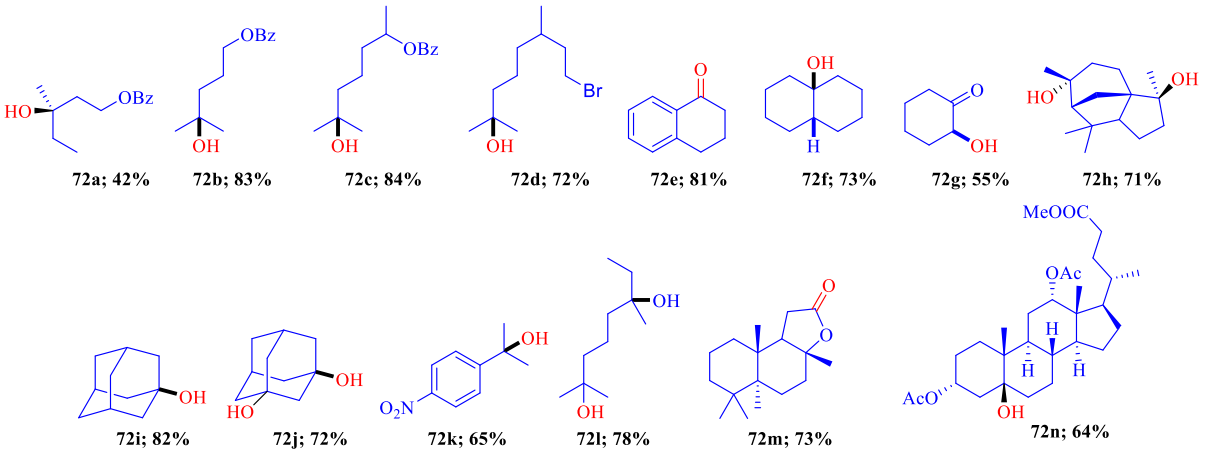
Scheme 32. Hypervalent iodine(III) mediated trifluoromethylcarbinolation of arenes.

Iodine(III) reagent on visible-light irradiation generated diazotrifluoroethyl radical **A** in the presence of a Ru-based photocatalyst, which facilitates regioselective C(sp^2)-H functionalization of arenes to give aryl(trifluoromethyl) diazo intermediates **C**. Further on, nitrogen removal led to the formation of singlet trifluoromethyl carbenes **D**, which on reaction with water lead to insertion of the O-H bond, delivering α-(het)aryl trifluoromethylcarbinols **71** as the final product (Scheme 33). The use of deuterated water confirms that water serves as the oxygen source.



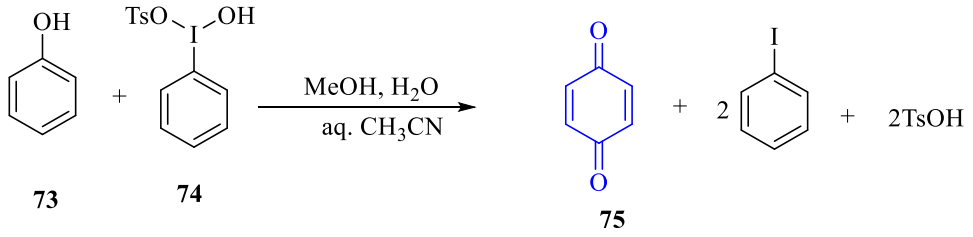
Scheme 33. Plausible mechanism for Hypervalent iodine(III) mediated trifluoromethylcarbinolation of arenes.

Uchida[53] investigated a non-heme-type glycine-based ruthenium complex, Ru(bpga), for the specific chemoselective C-H oxygenation employing hypervalent iodine reagent as the terminal oxidant and water molecules as the oxygen source (Scheme 34). The Ru(bpga) catalyst, $PhI(OBz\text{-}F_5)_2$, and water as the oxygen source, various C-H bonds were transformed **72a-n** in a site-selective manner. The oxygenation reactions under these conditions tolerated various functional groups, viz., bromine, ester, alcohol, and nitro groups, and retained stereochemistry in the case of chiral substrates **72a-n**. This eco-friendly strategy achieved success in synthesizing isotopic-oxygen-labelled compounds, site-selective late-stage C-H oxidations with excellent chemoselectivity, functional group tolerance and broad substrate scope under acidic conditions. Mechanistic studies revealed the reversible hydrolysis of $PhI(OCOR)_2$ under aqueous acidic conditions, with the O-atom of water serving as the source of the C-O oxygen.



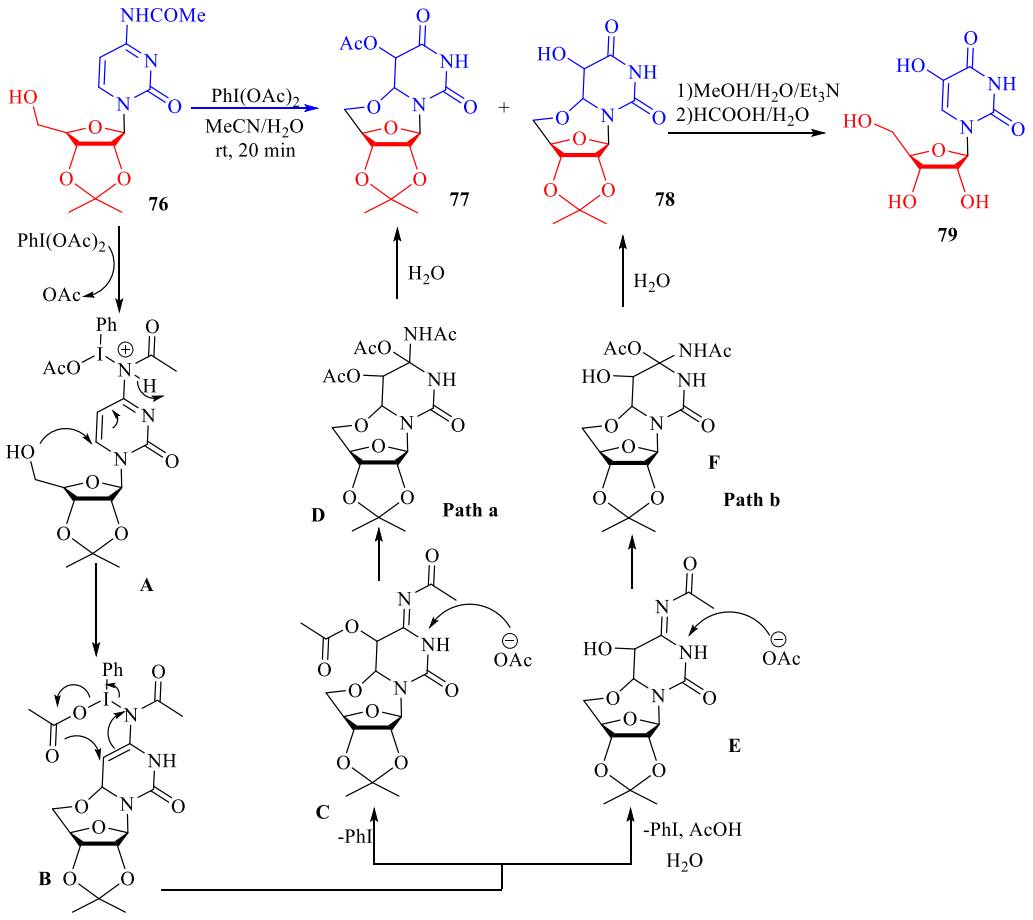
Scheme 34. Chemoselective C-H oxygenation using Ru(bpga), and sPhI(OBz-F_5)$_2$ in water.

Bennett and coworkers[54] examined the oxidation of phenolic compounds, viz., phenol, hydroquinone, catechol, and resorcinol, using the hypervalent iodine(III) reagent [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) under aqueous conditions (Scheme 35). Hydroquinone and catechol were oxidized to benzoquinone and *o*-quinone using a 2:1 HTIB: substrate ratio, whereas phenol and resorcinol required higher HTIB loadings at a 6:1 ratio. The oxidizing behaviour of phenol and resorcinol produced different oxidation products and was more complicated than that of hydroquinone and catechol, which could not be electrochemically reduced. In this oxidative strategy, water served as the proton source and reaction medium. Comparative analysis revealed the effect of solvent composition on quinone selectivity (benzoquinone vs o-quinone). This work highlighted the application of aqueous hypervalent chemistry for the electrochemical detection of phenolic pollutants.



Scheme 35. HTIB mediated oxidation of phenol.

An efficient synthesis of 5-hydroxyuridine **79** via hypervalent iodine(III)- assisted oxidative cyclization of 2′,3′-O-isopropylidene-N^4-acetylcytidine **76** under aqueous conditions was reported by Maverick and coworkers[55] (Scheme 36).

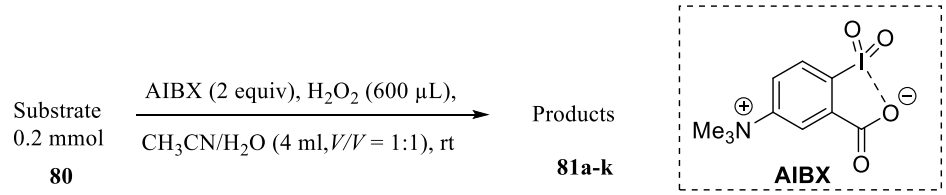


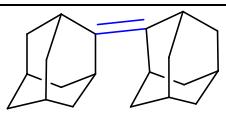
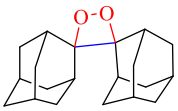
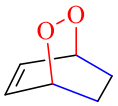
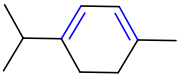
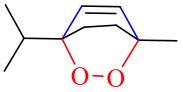
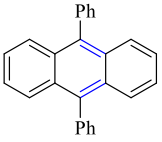
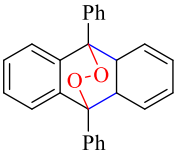
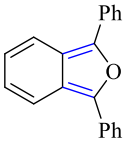
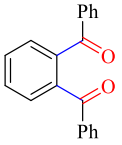
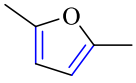
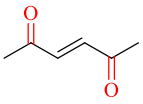
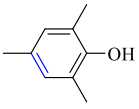
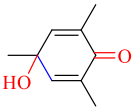
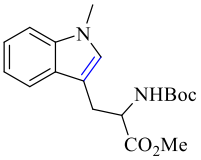
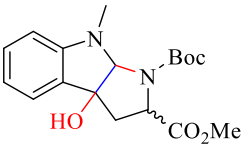
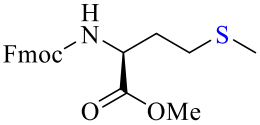
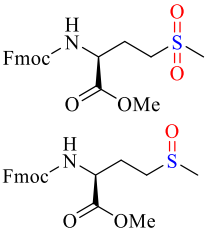
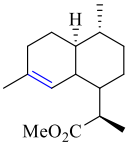
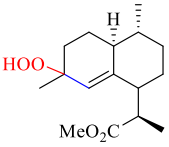
Scheme 36. Hypervalent iodine(III)-assisted synthesis of 5-hydroxyuridine.

Reaction of protected cytidine **76** with iodobenzene diacetate generate ammonium intermediate **A**, which facilitate the cyclization through an attack of the 5′-hydroxyl group at position C_6 to afford intermediate **B**. **Path a** involved the intramolecular acetylation at C_5 generates imine **C**. Thereafter, acetate attacked at the α-position of imine to form a hemiaminal ether intermediate **D**, which is hydrolyzed in water to yield 5-acetoxy-5′-*O*,6-cyclo-5,6-dihydro-2′,3′-*O*-isopropylidene uridine **77**. Whereas in **path b, B** is directly attacked by water at position C_6, followed by removal of iodobenzene and acetic acid to form imine **E**, which undergoes the same reaction sequence as **F** to give compound 5-hydroxy-2′,3′-*O*-isopropylidene uridine **78**. Succeeding mild basic opening of the cyclonucleosides, followed by aqueous deprotection, afforded 5-hydroxyuridine **79** in good yield.

2.8. Miscellaneous reactions

Shen and coauthors[56] developed an aqueous-mediated methodology for singlet oxygen generation employing a combination of the hypervalent iodine reagent AIBX and H_2O_2 (Scheme 37). The developed system was successfully employed for carrying out characteristic singlet oxygen reactions *viz*. [2 + 2]/[4 + 2] cycloadditions, Schenck ene reactions, and heteroatom oxidation reactions. This strategy was successfully employed for the key step, the ene reaction, in the synthesis of the antimalarial drug artemisinin, outperforming conventional methods. AIBX could be efficiently regenerated by reoxidation with dimethyldioxirane. Overall, this work presented aqueous-mediated hypervalent iodine(V) chemistry as a practical, eco-friendly, and scalable methodology for diverse oxidative transformations.

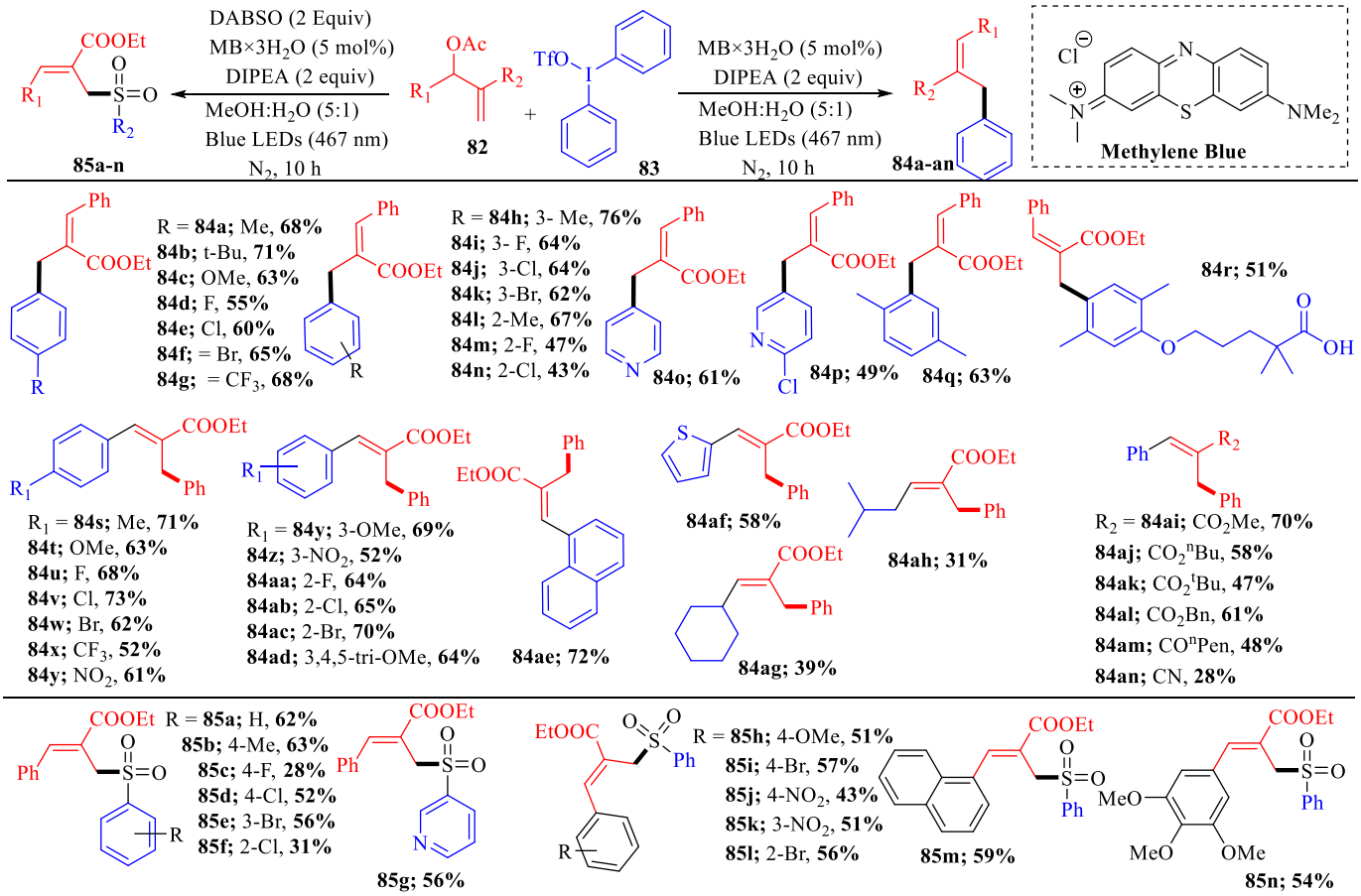


Sr. No.	Substrate	Product	Time (h)	Yield (%)
a.			48	79
b.			12	62
c.			7	87
d.			48	50
e.			48	84
f.			12	50
g.			36	40
h.			72	27
i.	PPh_3	$O{=}PPh_3$	0.5	95
j.			7	91.5 + 8.5
k.			48	66

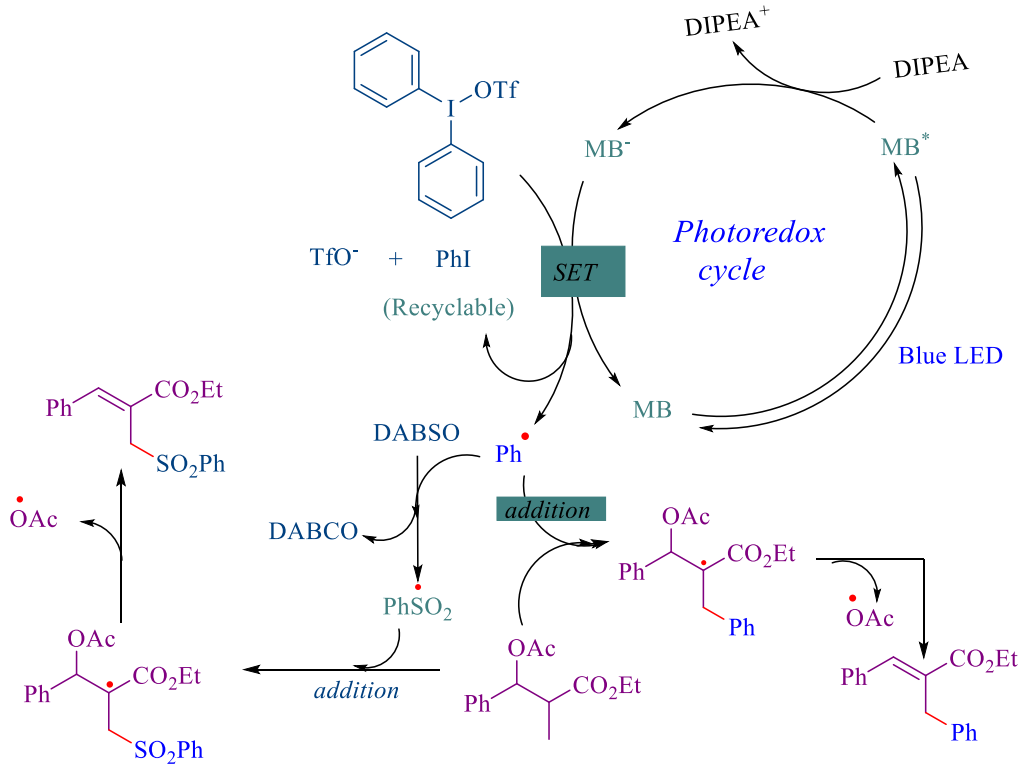
Scheme 37. Synthetic utility of singlet oxygen generated from the AIBX and H_2O_2 system.

Senapati *et al.*[57] reported stereoselective allylic arylation **84a-an** and aryl sulfonylation **85a-n** of Morita–Baylis-Hillman (MBH) acetates employing an organophotoredox-catalyst and diaryliodonium triflates **83** as aryl radical precursors (Scheme 38). Visible irradiation of MBH acetates in MeOH/H_2O solvent mixture in the presence of methylene blue and DIPEA afforded trisubstituted alkenes with high E-selectivity. The authors further extended the protocol to three components by including 1, 4-diazabicyclo [2.2.2] octane bis (sulfur dioxide) adduct (DABSO) leading to the synthesis of allylic aryl sulfones under operationally simple, mild and aqueous lenient environment. Mechanistic investigations showed aryl radical generation from diaryliodonium salts, followed by olefin addition and acetoxy radical elimination (Scheme 39). Overall, this work provided an efficient, sustainable approach for selective allylic functionalization, displaying a synergistic combination of hypervalent iodine chemistry in aqueous media with visible-light photoredox catalysis.

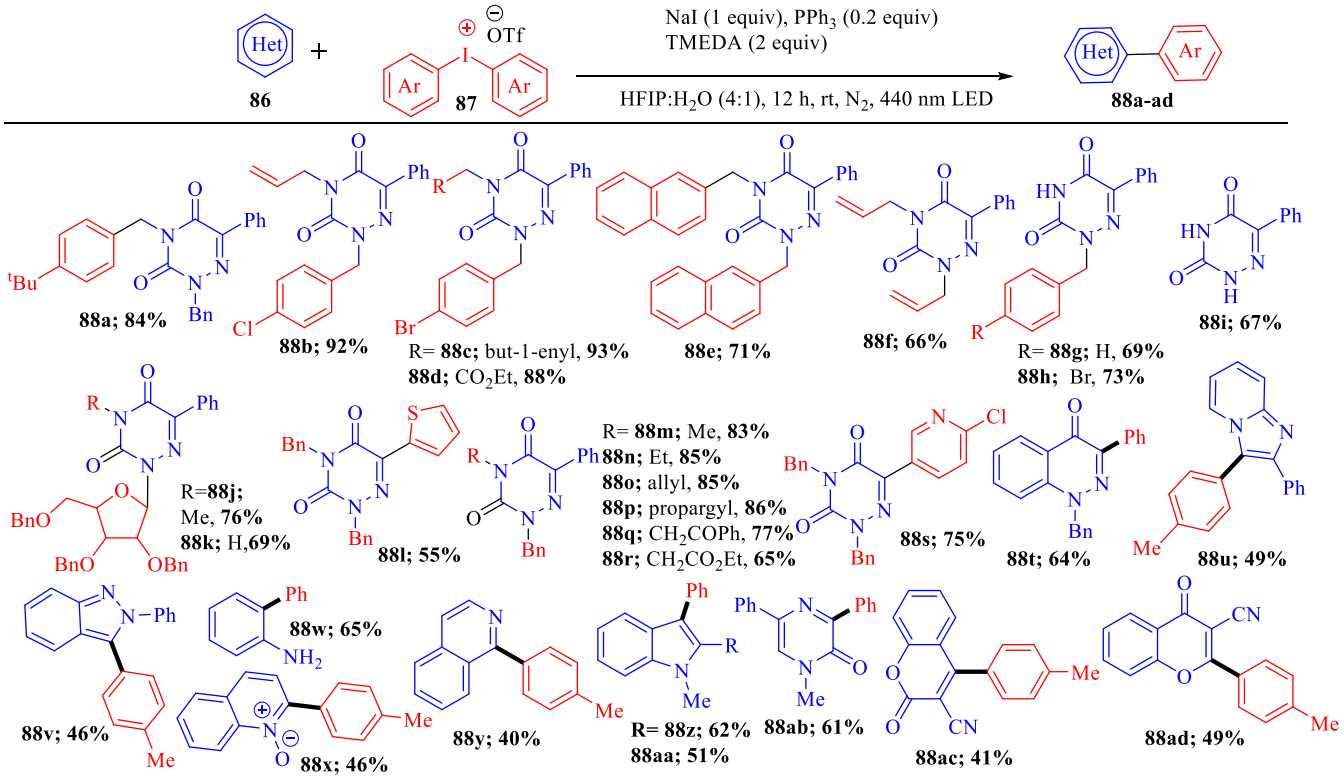
Meher *et al.*[58] developed a transition-metal-free arylation strategy for twelve different classes of heterocyclic compounds **86** by employing a photoredox system comprising a self-assembled tetrameric electron donor-acceptor (EDA) complex of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), sodium iodide, triphenyl phosphine, and diaryliodonium reagents (DAIRs) (Scheme 40). This tetrameric complex, upon visible-light irradiation, released aryl radicals that enabled the arylation of diverse heterocycles. A variety of heterocycles **88a-ad**, viz., electron-rich, electron-deficient, aromatic, and non-aromatic, were arylated in moderate to good yields using the newly developed approach. Trapping experiments and photophysical and DFT-based studies were consistent with the formation of an electron donor-acceptor (EDA) complex. This approach tolerated diverse functionalities and could be used for late-stage functionalization of pharmaceutically significant compounds.



Scheme 38. Organophotoredox-catalyzed selective allylic functionalization of MBH Acetates.

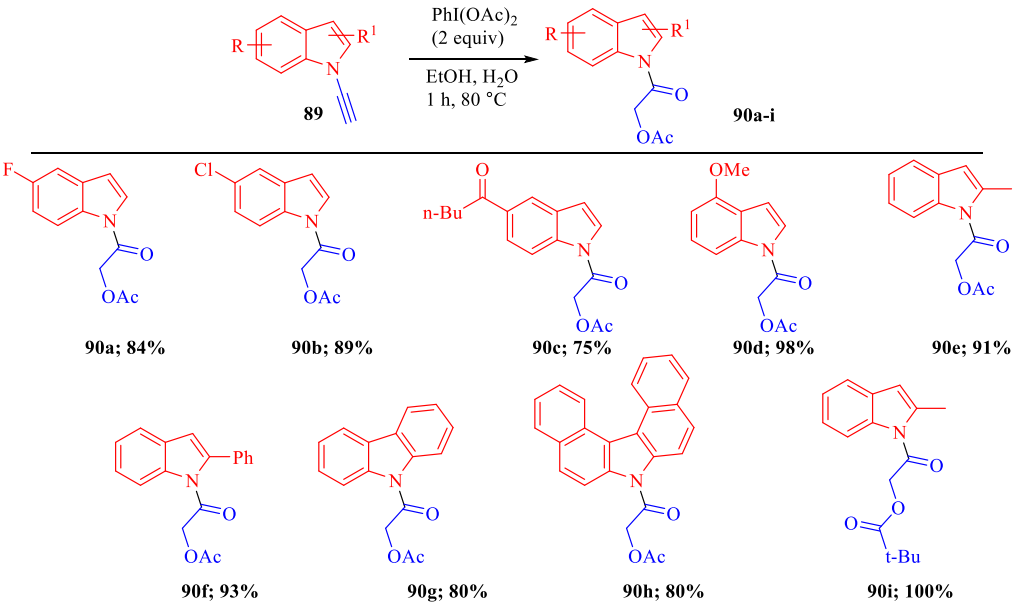


Scheme 39. Plausible mechanism for the organophotoredox-catalyzed selective allylic functionalization of MBH Acetates.

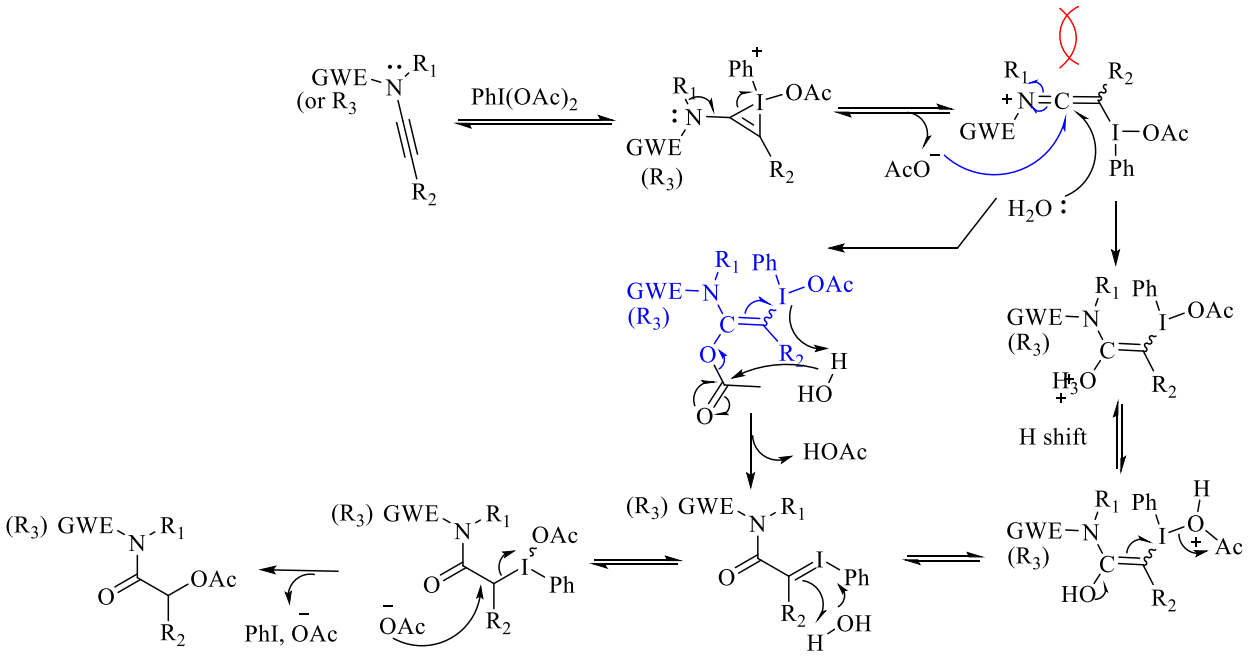


Scheme 40. Visible light-mediated arylation of diverse heterocycles.

Long et al.[59] developed a metal-free protocol for oxyacetoxylation of aryl nitriles **89** using $PhI(OAc)_2$ as the catalyst in a polar protic solvent (EtOH), furnishing good yields of α-acetoxy amides **90a-l** with high chemo- and regioselectivity (Scheme 41). The methodology tolerated diverse functionalities, including intact *N*-heteroaryl moieties. Mechanistic examination revealed that the transformation proceeded via alkyne activation by PIDA, leading to the formation of a cyclopropenyl iodonium species, which subsequently fragmented to give a β-iodo keteneiminium intermediate (Scheme 42). The involvement of H_2O and PIDA as oxygen sources was evidenced by isotopic labelling experiments. Overall, this protocol provided a mild, chemo- and regioselective strategy for the oxyacetoxylation of arylamines under economic, sustainable conditions.



Scheme 41. PIDA mediated metal-free oxyacetoxylation of arylamines **89.**



Scheme 42. Plausible mechanism for the PIDA mediated metal-free oxyacetoxylation of arylamines **89**.

3. Conclusions

Hypervalent iodine chemistry has attracted researchers for carrying out sustainable organic synthesis, with water serving a multifaceted role far beyond that of a simple reaction medium. The excellent compatibility of hypervalent iodine reagents with aqueous media enabled the development of various metal-free, mild, operationally simple, economic, and eco-friendly methodologies that align well with green chemistry principles. Not all hypervalent iodine-mediated reactions benefited from water, as specific reactions involving radical pathways showed inhibitory effects, necessitating careful protocol design and mechanistic understanding. In various instances, water improved reaction efficiency, scalability and selectivity. The integration of water-compatible hypervalent iodine reagents with electrochemical, photochemical, and flow systems further expands their synthetic utility and sustainability. These reagents exhibited exceptional chemoselectivity, regioselectivity and stereoselectivity in a diverse array of transformations like cyclization, halogenation, ring opening/cleavage, oxidation, couplings, C-H functionalization, carbonylation, and many more. Hypervalent iodine chemistry is a rapidly growing field, with significant growth, showing promising potential for future applications in sustainable synthesis. This review article will help researchers working in sustainable organic synthesis by exploring aqueous hypervalent iodine chemistry.

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