HYPERVALENT IODINE(III) REAGENTS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Rajnish Budhwan[a], Gaurav Garg[a], Irishi N. N. Namboothiri*[b], Sandip Murarka*[a]

[a]*Indian Institute of Technology Jodhpur, 342037 Karwar, Jodhpur District, Rajasthan, India*

[b]*Indian Institute of Technology Bombay, Powai, 400076 Mumbai, Maharashtra, India*

(email: sandipmurarka@iitj.ac.in, irishi@chem.iitb.ac.in)

Abstract. *Hypervalent iodine(III) reagents have profound applications in a range of facile and novel synthetic methodologies primarily due to their remarkable oxidizing property, robust synthetic utility, environmentally benign nature and easy availability. This chapter emphasises mainly on the various transition metal-free reactions of hypervalent iodine(III) reagents for the construction of a diverse range of heterocyclic compounds.*

Contents

1. Introduction

Heterocyclic compounds are embedded in many natural products and are of high pharmaceutical relevance due to their presence in a diverse array of biologically active compounds and drug candidates.[1-3] The chemistry of hypervalent iodine compounds have witnessed a tremendous advancement in the last couple of decades and it has received wide applications towards the synthesis of a profusion of bioactive heterocyclic compounds.[4-8] The versatile oxidative properties in combination with their easy availability, ease of handling, nontoxicity, environmentally benign nature and impressive functional group tolerance have immensely contributed towards the popularity of this class of reagents.

The common hypervalent iodine(III) reagents, such as (diacetoxyiodo)benzene (PIDA), (bis(trifluoroacetoxy)iodo)benzene (PIFA), iodosobenzene (PhIO), [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) have found widespread synthetic utility in the formation of carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds leading ultimately to a diverse collection of heterocycles (Figure 1).[9-11] Moreover, hypervalent iodine(III) compounds have emerged as an attractive surrogate of transition-metal catalysts in traditional oxidative cross coupling reactions and demonstrate comparable

efficiency.[9,12,13] This chapter summarizes the progress made, especially in the last decade, in the field of transition-metal-free hypervalent iodine(III) chemistry involving de novo synthesis of a plethora of heterocycles through a diverse range of intra- and intermolecular oxidative annulations (Figure 2).

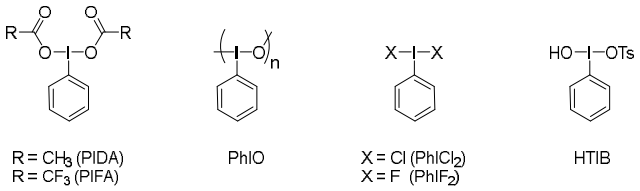


Figure 1. Commonly employed hypervalent iodine(III) reagents.

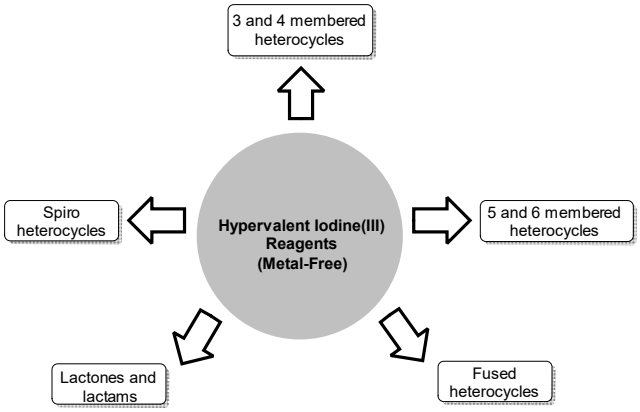


Figure 2. Transition-metal free synthesis of heterocycles involving hypervalent iodine(III) reagents.

2. *De novo* synthesis of heterocycles with hypervalent iodine(III) reagents

This section describes the transition-metal-free synthesis of a range of heterocycles through hypervalent iodine(III) catalyzed/mediated oxidative annulations and is categorized according to the ring size and nature of heterocycles obtained.

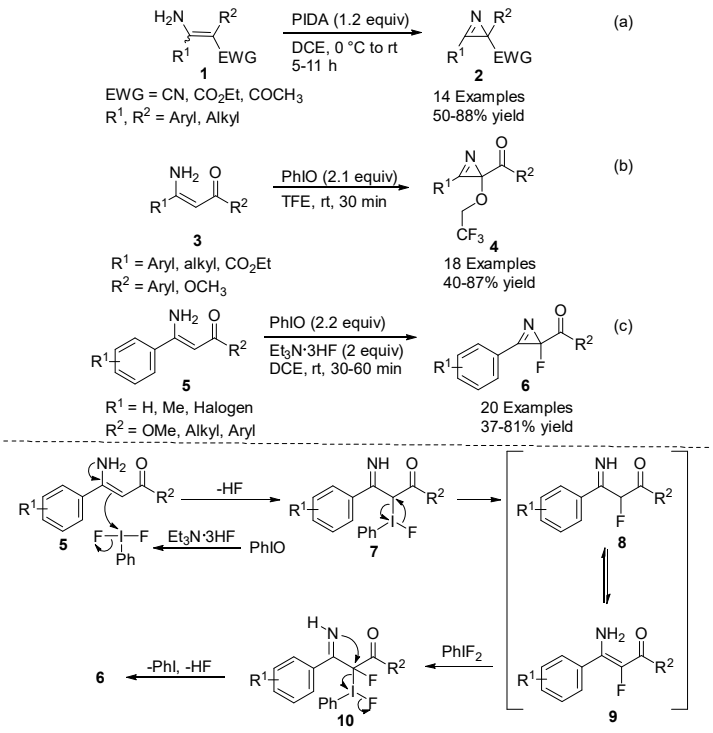
2.1. Synthesis of three and four membered heterocycles

Three and four membered heterocycles have found many applications both as synthons in the synthesis of more elaborate structures and as valuable targets in synthesis due to their interesting physical and stereoelectronic properties.[14] Here in this section, we demonstrate various synthetic methodologies available for the construction of these heterocycles using metal-free hypervalent iodine(III) reagents.

2.1.1. Synthesis of azirines, aziridines, diaziridines and azetidines

2*H*-Azirines are smallest unsaturated *N*-heterocyclic compounds where a C=N bond is incorporated within a three-membered ring, which makes it highly strained and reactive. In 2009, Zhao and coworkers successfully converted enamine derivatives **1** to the corresponding azirines **2** in moderate to good yields using PIDA as an oxidant (Scheme 1a).[15] Importantly, the method worked well for α-substituted enamine compounds and the final 2-aryl-2*H*-azirines were successfully converted to the useful indole-3-carbonitriles through a known thermal rearrangement process. Following this, the same group reported a similar method where α-unsubstituted enamine compounds **3** were transformed to trifluoroethoxylated 2*H*-azirines **4** using PhIO oxidant and trifluoro ethanol (TFE) as a solvent as shown in Scheme 1b.[16] A range of enaminones and enamine carboxylic esters were converted to biologically relevant 2*H*-azirines in good yields.

Mechanistically, it is proposed that the reaction proceeds through an intermolecular oxidative C-O bond formation to afford trifluoroethoxylated enamine intermediates, which subsequently undergoes intramolecular azirination to deliver the final products. More recently, Du and coworkers synthesized fluorinated azirines *via* domino fluorination/azirination reaction sequence of enamine derivatives.[17] A variety of α-unsubstituted enamines **5** reacted with *in situ* generated $PhIF_2$ under metal-free conditions to afford a diverse range of fluorinated 2*H*-azirines **6** (Scheme 1c). The postulated mechanism of authors begins with *in situ* generation of $PhIF_2$ species, which reacts with enaminone substrate **5** to give α-iodo imine **7**, followed by the formation of imine **8** through reductive elimination of PhI from **7**. Subsequently, **8** undergoes tautomerization to afford **9** which upon reaction with second equivalent of $PhIF_2$ forms **10**. Finally, intramolecular cyclization of intermediate **10** leads to azirine compound **6.**

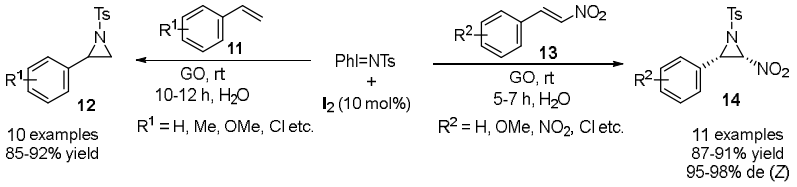


Scheme 1. Iodine(III) mediated synthesis of azirines from enamines and enaminones.

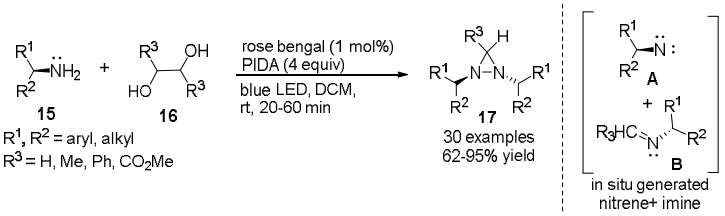
Due to the strained skeleton, aziridines have high synthetic potential towards acting as intermediates in the synthesis of various heterocyclic compounds. Moreover, in the presence of a suitable nucleophile, they participate in a variety of synthetic transformations giving rise to ring opening products.[18] (Diacetoxyiodo)benzene-mediated aziridination of alkenes proceeding *via* generation of aminoiodanes represents one of the most popular synthetic routes towards the synthesis of aziridines.[19] In 2017, Rai and coworkers[20] disclosed a green methodology for the construction of various tosylaziridines **12**, **14** in good yields using PhI=NTs as a nitrene source and graphene oxide (GO) as the catalyst. The reaction was carried out in water at room temperature and proposed to proceed through the insertion of nitrene into various alkenes **11, 13** (Scheme 2).

Similar to aziridines, diaziridines are also three membered heterocycles which contain two nitrogen atoms connected with a single bond. Recently, Maiti and coworkers[21] developed a PIDA mediated photocatalytic approach to synthesize substituted diaziridines **17** in good to excellent yields (Scheme 3). The

reaction was carried out using aliphatic amines **15** and 1,2-diols **16** in the presence of a blue LED, rose bengal as an organic photocatalyst and PIDA as an oxidant. The reaction was proposed to proceed through *in situ* generation of nitrene and imine intermediates which ultimately produced the desired diaziridines *via* insertion of nitrenes into imines. Interestingly, authors extended the scope to optically active diaziridines by utilizing chiral amines as well as amino acids as one of the starting precursors.

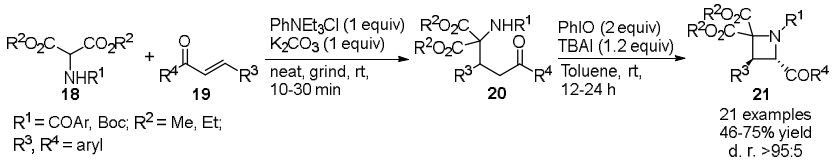


Scheme 2. Synthesis of aziridines using hypervalent iodine(III) reagent.



Scheme 3. $PhI(OAc)_2$ mediated photocatalytic synthesis of substituted diaziridines.

Azetidines are strained four membered azacycles and undergo a wide range of transformations to afford several nitrogen containing compounds. In 2010, Fan and coworkers[22] showed the construction of highly functionalized azetidines **21** *via* a PhIO/TBAI mediated oxidative cyclization of **20**, which in turn was prepared by a controlled Michael addition of aminomalonates **18** to chalcones **19** (Scheme 4). Highly substituted azetidines **21** were obtained in good yields and high diastereoselectivities (>95:5).

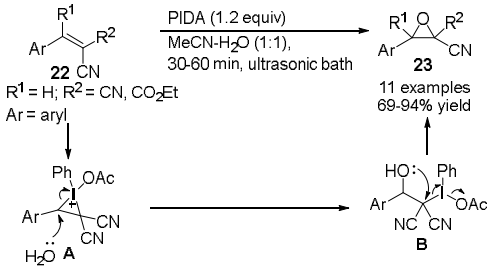


Scheme 4. PhIO mediated diastereoselective synthesis of substituted azetidines.

2.1.2. Synthesis of oxiranes and oxetanes

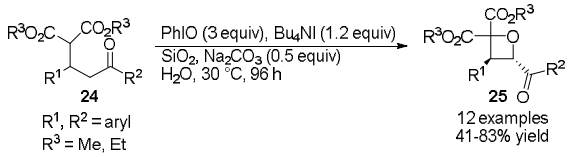
Hypervalent iodine reagents have been successfully utilized in the synthesis of oxiranes and oxetanes, representing small size oxygen heterocycles and are embedded in many FDA approved pharmaceuticals.[23] Ochiai et al.[24] had discovered that hypervalent λ^3-iodane prepared by reaction of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with tetra-*n*-butylammonium fluoride under nitrogen atmosphere can oxidize *α,β*-unsaturated carbonyl compounds to the corresponding oxiranes in moderate yields at room temperature. In 2006, MacMillan and coworker[25] demonstrated an organocatalytic asymmetric synthesis of oxiranes from *α,β*-unsaturated aldehydes by using imidazolidinone catalyst and iminoiodinane as the oxidant. Through NMR studies, it was revealed that iminoiodinanes serve as an 'internal syringe pump' towards the slow release of iodosobenzene which is absolutely crucial to obtain reaction efficacy and high enantiocontrol. Very recently, Singh et al.[26] reported a novel and efficient PIDA assisted methodology to synthesize *β*-cyanoepoxides **23** in moderate to good yields from *β*-cyanostyrenes **22** using ultrasonic bath

(Scheme 5). Mechanistically the reaction begins with the formation of a three membered iodonium intermediate **A** through activation of the double bond in styrene **22** by PIDA. Then the opening of the three membered ring of intermediate **A** by water gives intermediate **B**, which subsequently undergoes intramolecular cyclization to deliver the desired epoxides **23**.



Scheme 5. PIDA-mediated synthesis of *β*-cyanoepoxides.

Fan and coworkers[27] successfully adopted their azetidine synthesis protocol for the synthesis of medicinally important oxetanes. The Michael adducts **24** were transformed to substituted oxetanes **25** in good yields through a solvent controlled oxidative cyclization using a combination of iodosobenzene and tetrabutylammonium iodide (Scheme 6). Interestingly, water as a solvent was crucial to the formation of oxetanes, as switching the solvent from water to methanol led to the divergent formation of substituted cyclopropanes as the major product.



Scheme 6. Synthesis of substituted oxetanes using a combination of PhIO/Bu_4NI.

2.2. Synthesis of five and six membered heterocycles

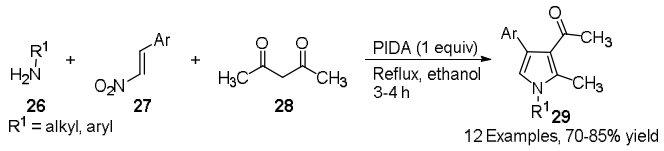
Five membered heterocyclic compounds belong to the privileged class of heterocycles due to their omnipresence in several biologically active compounds and huge demand in pharmaceutical industries.[2] Over the last two decades, hypervalent iodine(III) reagents have played crucial role in the synthesis of several five membered heterocycles, including pyrrole, imidazole, oxazole, isoxazole, pyrrolidine etc. In this section we will summarize all these remarkable transition metal free synthetic strategies documented for the construction of five-membered heterocycles using hypervalent iodine(III) reagents.

2.2.1. Synthesis of pyrroles, pyrrolidines, imidazoles and pyrazoles

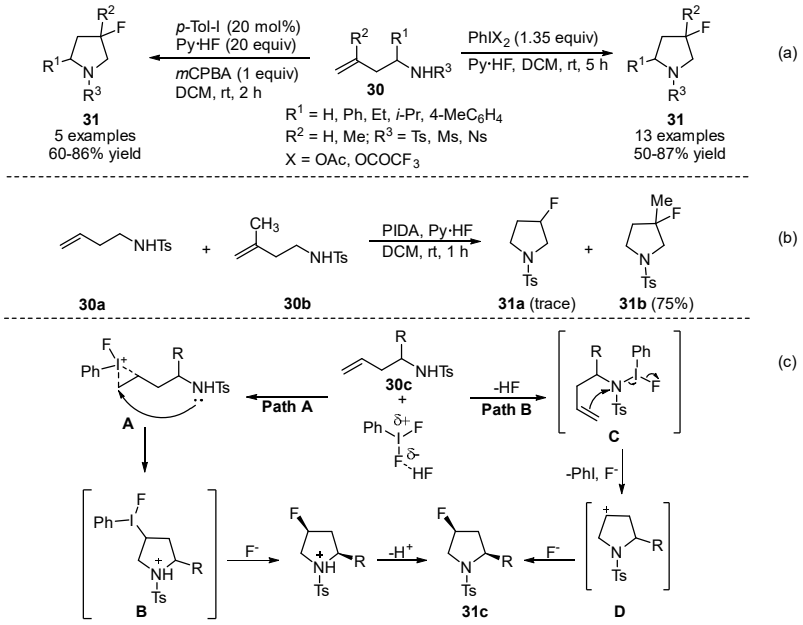
In 2001, Chen and Zhang demonstrated a PIFA mediated dimerization/cyclocondensation cascade of enaminones for the synthesis of polysubstituted pyrroles.[28] Following this, Yu and coworkers[29] reported an oxidative homocoupling of enamine esters and ketones in the presence of PIDA and BF_3•Et_2O to afford symmetric polysubstituted pyrroles in moderate to good yields. In 2013, Telvekar and coworkers[30] reported a facile three-component coupling of readily available amines **26**, nitrostyrenes **27** and acetylacetones **28** using PIDA in ethanol at reflux temperature to furnish substituted pyrroles **29** (Scheme 7). The method was found to be quite robust and a diverse range of nitrostyrenes and amines participated to give the corresponding pyrrole derivatives in good yields.

Recently, Kitamura et al. showcased a PIDA mediated aminofluorination of homoallylamine derivatives **30** using Py•HF as the fluorinating agent to give tosylated 3-fluoropyrrolidines **31** in good yields (Scheme 8a).[31] Interestingly, the catalytic version of the reaction was shown to be working using

p-iodotoluene as the catalyst and *m*CPBA as the terminal oxidant. Through competition experiment between homoallylamines **30a** and **30b**, authors successfully demonstrated that the presented aminoflurocyclization reaction is selective towards highly electron rich double bonds (Scheme 8b). Based on the high reactivity of homoallylamine **30b** and preferential formation of **31b** in the competition experiment, authors proposed that the reaction may proceed through path A. Accordingly, initially formed difluoroiodobenzene gets activated by HF, which then forms the iodonium intermediate **A** by reacting with homoallylic amine **30a**. Subsequently, the intermediate **A** undergoes intramolecular ring opening by the pendant nitrogen atom leading to the formation of **B**, which upon substitution by fluoride and deprotonation furnishes the desired fluoropyrrolidine **31c**. However, authors could not discard the possibility of an alternative mechanism proceeding through the formation of aminofluoroiodonium intermediate **C** following reaction of difluoroiodobenzene with tosyl amino group (path B). Subsequent to its generation intermediate **C** reacts with the double bond to form carbocation **D**, which then gets attacked by fluoride anion to afford **31c**. Interestingly, the methodology was extended to fluorocyclization of homoallylic substrates with oxygen-centered nucleophiles giving rise to fluorinated tetrahydrofuran and butyrolactone derivatives in acceptable yields.



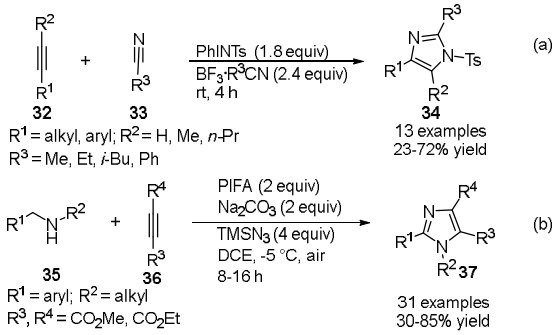
Scheme 7. PIDA Mediated three component synthesis of substituted pyrroles.



Scheme 8. Aminofluorination for the synthesis of 3-fluoropyrrolidines.

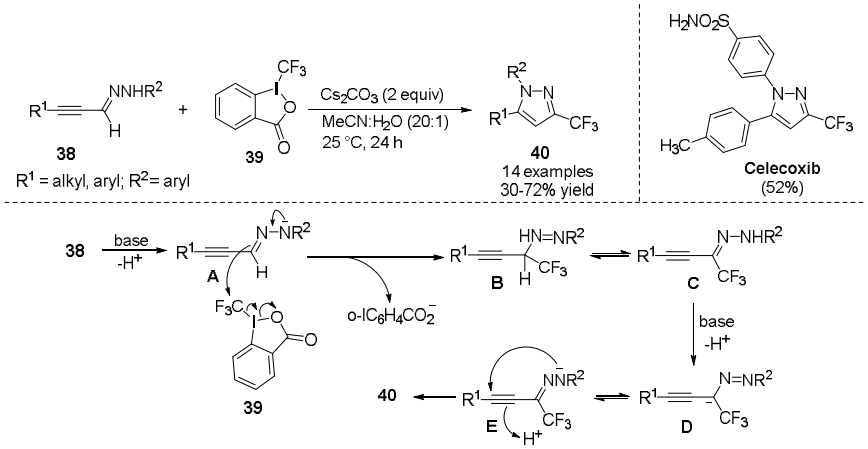
Saito et al. recently developed a metal free boron trifluoride nitrile complex promoted [2+2+1] annulation of nitriles **33**, alkynes **32** and iminoiodanes to synthesize 2,4-disubstituted and 2,4,5-trisubstituted *N*-tosyl-imidazoles **34** in moderate yields (Scheme 9a).[32] Very recently, Sharada's group[33] reported a PIFA

promoted intermolecular cycloaminative strategy for the synthesis of various imidazole derivatives **37** (Scheme 9b). To this end, several secondary cyclic and acyclic amines reacted with a range of electron deficient terminal and internal alkynes in the presence of PIFA and trimethylsilylazide to undergo a hydroamination-azidation-cyclization sequence delivering imidazole derivatives in moderate to good yields.



Scheme 9. Synthesis of substituted imidazole derivatives using iodine(III) reagents.

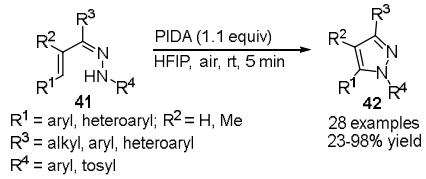
Pyrazole moiety represents an important motif found in many pharmaceuticals and agrochemicals and hence has attracted the attention of synthetic community. In 2014, Wang and coworkers[34] reported an efficient and novel process to synthesize 3-trifluoromethyl pyrazoles **40** through a successive trifluoromethylation/cyclization sequence of α,β-alkynic hydrazones **38** under transition metal free conditions (Scheme 10). The method was found to be quite robust and the anti-arthritic drug Celecoxib was successfully prepared in 52% yield. Based on several mechanistic studies, authors proposed that the reaction is initiated by the deprotonation of alkynic hydrazone **38** to yield the intermediate **A**, which then reacts with highly electrophilic **39** to give either **B** or **C** through the formation of C-CF_3 bond. Hence formed intermediate **C** then undergoes deprotonation/cyclization/protonation sequence to afford desired pyrazoles **40**. However, the authors could not rule out the intermediacy of radicals in this reaction.



Scheme 10. Synthesis of 3-trifluoromethyl pyrazoles.

Hypervalent iodine mediated/catalyzed oxidative heterocyclizations represent a powerful strategy towards the synthesis of heterocycles. Along these lines, Zhu and coworker[35] developed an additive free PIDA mediated cycloamination of vinyl hydrazones **41** for the efficient synthesis of pyrazole derivatives **42**

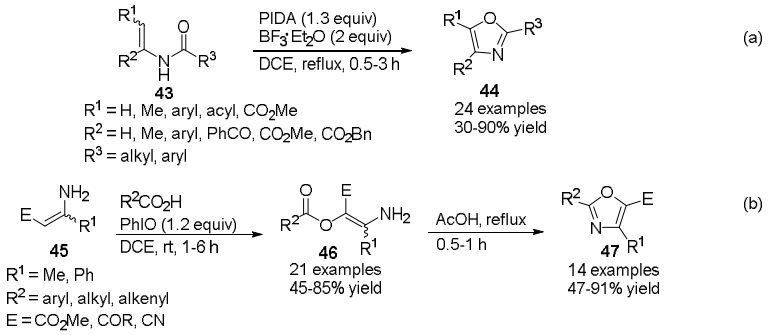
(Scheme 11). A similar hypervalent iodine(III) enabled oxidative annulation strategy was adopted by Chiba et al.[36] for the synthesis of dihydroimidazoles through aminooxygenation and diamination of *N*-allylamidines.



Scheme 11. PIDA assisted synthesis of pyrazoles.

2.2.2. Synthesis of oxazoles, isoxazoles, oxazolines and isooxazolines

In analogy to their synthesis of *N*-tosyl-imidazoles **34** (as described in Scheme 9a), Saito, Hanzawa and coauthor[37] showed that various ketones and nitriles in the presence of iodosobenzene and trifluoromethanesulfonic acid or bis(trifluoromethanesulfonyl)imide leads to the formation of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles under mild conditions. Meanwhile, Zhao, Du and coworkers[38] applied iodine(III)-promoted intramolecular oxidative heterocyclizations for the construction of C-O bonds. To this end, a range of enamides **43** were successfully converted to the corresponding oxazoles **44** in the presence of PIDA and BF_3•OEt_2 (Scheme 12a). Contemporaneously, the same research group developed an iodosobenzene promoted cross-coupling of enamines **45** and carboxylic acids leading to the formation of *β*-acyloxy enamines **46**, which upon treatment with acetic acid underwent intramolecular cyclization to afford di-and tri-substituted oxazoles **47** in good to excellent yields (Scheme 12b).[39]

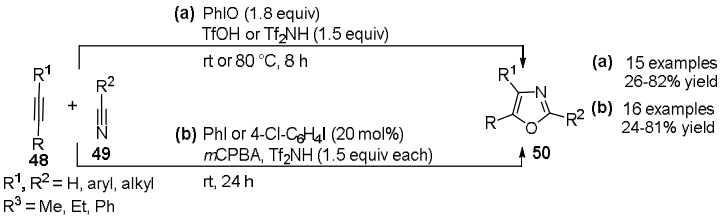


Scheme 12. Synthesis of substituted oxazoles.

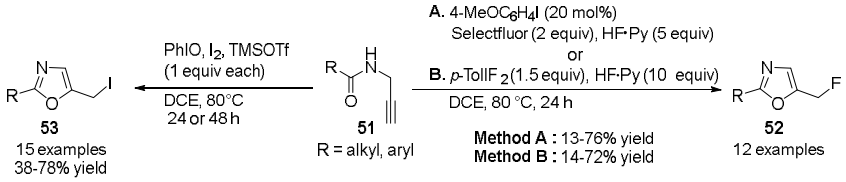
In 2013, Saito et al.[40] developed a transition metal free [2+2+1] annulation of nitriles, alkynes and iodosobenzene to furnish substituted oxazoles with high regioselectivity using triflic acid or triflic imide as a Brønsted acid. Both terminal and internal alkynes **48** and a range of nitriles **49** participated in this transformation giving rise to 2,4-di- and 2,4,5-trisubstituted oxazoles **50** in moderate to good yields (Scheme 13a). The Authors successfully synthesized a non-steroidal anti-inflammatory drug, Oxaprodine in two steps from commercially available starting materials by applying their multicomponent annulation strategy. Later, in 2017, the same group[41] went ahead and developed the corresponding catalytic version of their cycloaddition protocol, where iodine(III) catalyst was generated *in situ* by using iodoarene as a precatalyst and meta-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant (Scheme 13b).

In 2010 Saito's group[42] reported an iodine(III)-promoted oxidative cycloisomerization of propargylamides **51** in AcOH or AcOH-HFIP leading to the formation of 2,5-disubstituted oxazoles in good yields. Recently, the authors extended their methodology to a cyclomerization-halogenation sequence to prepare fluorinated[43] and iodinated[44] oxazoles **52**, **53** respectively, using hypervalent iodine(III) reagents

(Scheme 14). A mixture of iodosylbenzene, iodine and trimethylsilyl methanesulfonate (TMSOTf) was found to be effective for the preparation of iodinated oxazoles **53**; whereas, a combination of difluoroiodoarene and HF•Py in refluxing dichloroethane was suitable for the cyclomerization-fluorination sequence on propargylamides **51** (Scheme 14). Importantly, the authors demonstrated that fluorooxazoles **52** can also be prepared by *in situ* generating iodine(III) catalyst from iodoarene using Selectfluor as a fluorinating oxidant in the presence of HF•Py.



Scheme 13. Synthesis of multisubstituted oxazoles by formal [2+2+1] cycloaddition.



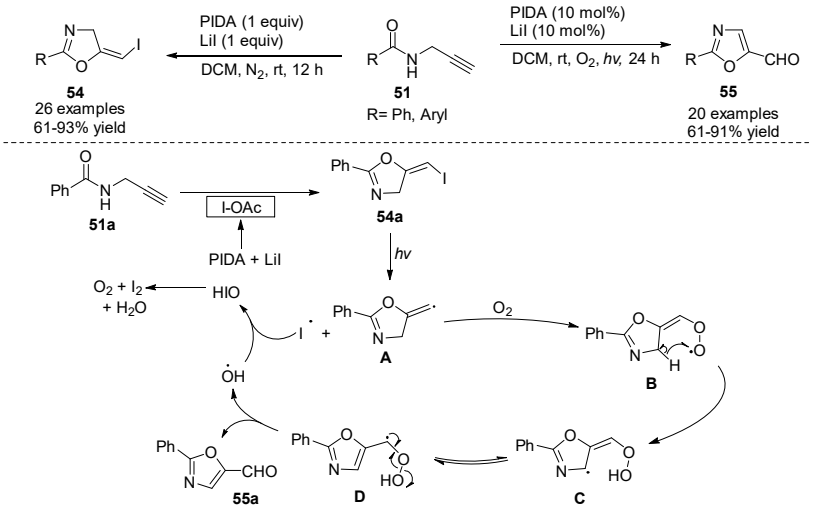
Scheme 14. One step synthesis of fluorinated and iodinated oxazole.

Recently, Liu and coworkers[45] developed a PIDA mediated iodooxygenation of propargylamides **51** to synthesize (*E*)-5-iodomethylene-2-oxazolines **54** in good to excellent yields using lithium iodide as the iodine source (Scheme 15). Interestingly, authors showed that *N*-propargylamides can also be converted to oxazole-5-carbaldehydes **55** under visible light irradiation using PIDA/LiI system and dioxygen (Scheme 15). The proposed mechanism begins with the generation of iodoacetic acid (IOAc) intermediate through the PIDA promoted oxidation of iodide anion (Scheme 15). Subsequent to its generation, IOAc induces the intramolecular electrophilic cyclization of *N*-propargylamide **51a** to give 5-iodomethylene-2-oxazoline **54a**. Irradiation under visible light leads to the homolytic cleavage of carbon-iodine bond in **54a** with concomitant generation of radical species **A**, which subsequently reacts with oxygen to afford peroxy radical **B**. **B** then undergoes radical translocation through a six-membered transition state to give **C**, which is essentially a resonance structure of radical species **D**. Finally, release of hydroxyl radical from **D** delivers desired aldehyde **55a** and the resulting hydroxyl radical combines with iodine radical to produce HIO, which further decomposes into iodine radical and gets enrolled in the next catalytic cycle.

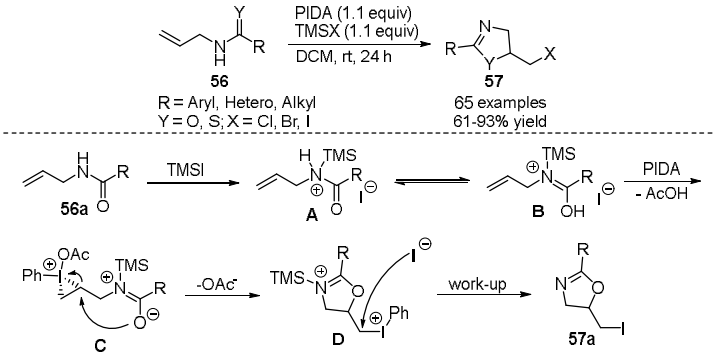
A similar oxidative cyclization strategy was adopted by Harned and coworker[46] in the PIDA mediated synthesis of oxazolines starting from *N*-allylamide. In this reaction BF_3•OEt_2 was used to facilitate the generation of highly electrophilic iodine(III) intermediate that can trigger the intramolecular cyclization event. Recently, Li group[47] demonstrated a more general intramolecular halooxygenation and halothionation of *N*-allylcarboxamides/*N*-allylcarbothioamides **56** using PIDA as an oxidant and halotrimethylsilane as the halogen source to furnish corresponding 5-halomethyloxazolines/5-halomethylthiazolines **57** in good to excellent yields (Scheme 16). Based on several control experiments, authors proposed that initial interaction of TMSI and **56a** generates intermediate **A**, which then tautomerizes to **B** (Scheme 16). Following which, the carbon-carbon double bond in **B** gets activated by PIDA to form the cyclic iodonium intermediate **C**, which subsequently undergoes intramolecular attack by oxygen atom to afford intermediate **D**. The final halooxygenated product **57a** was obtained after the work up of **D**.

In 2009, Ciufolini[48] developed an efficient and novel PIDA-mediated synthesis of isoxazolines using olefins and nitrile oxides. The nitrile oxides were generated *in situ* through rapid oxidation of oximes using

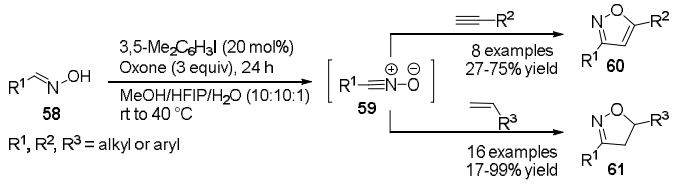
PIDA and substoichiometric amount of trifluoroacetic acid. Subsequently, Delft and coauthors[49] demonstrated PIFA assisted oxidation of aldoximes to nitrile oxides, which were then trapped with alkynes to furnish isoxazoles in good yields. Meanwhile, Zhdankin and coworkers[50] demonstrated that nitrile oxides **59** can also be generated by hypervalent iodine(III) catalyzed oxidation of oximes **58** using catalytic iodoarene and oxone as a terminal oxidant (Scheme 17).



Scheme 15. PIDA Mediated intramolecular cyclization for the synthesis of oxazoles and oxazolines.



Scheme 16. Synthesis of 5-halomethyl-2-oxazolines.

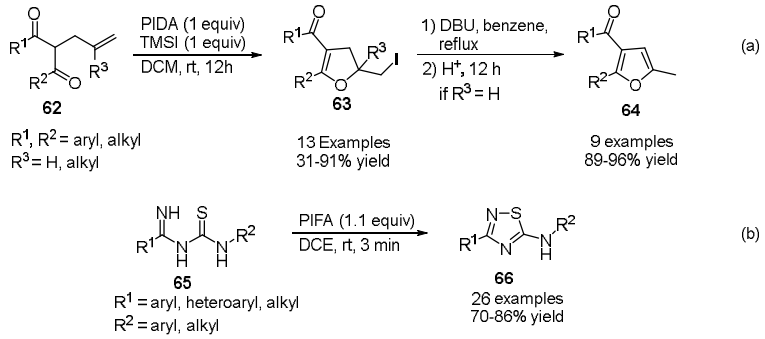


Scheme 17. Iodine(III)-catalyzed synthesis of isoxazoles and isoxazolines.

Hence generated nitrile oxides successfully reacted with a range of alkenes and alkynes affording corresponding isoxazoles **60** and isoxazolines **61** in good yields. In subsequent years, iodine(III) reagents received wide applications in the synthesis of isoxazoles,[51] 2-oxazolines[52] and dihydroxazoles.[53]

2.2.3. Synthesis of furans, oxadiazoles and thiadizoles

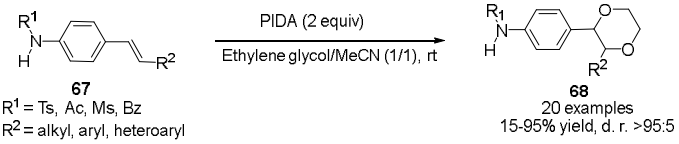
Very recently, Ling, Liu and coworkers reported a PIDA promoted haloenolcyclization of 2-allyl-1,3-diketones **62** using trimethylsilyliodide as the iodine source leading to the smooth formation of a wide variety of 5-iodomethyl-4,5-dihydrofurans **63** in good to excellent yields (Scheme 18a).[54] The resulting dihydrofurans **63** were successfully transformed to substituted furan derivatives **64** by treatment with a non-nucleophilic hindered base DBU, followed by an acid catalyzed rearrangement process (Scheme 18a). Besides pyrazoles and oxazoles, iodine(III)-mediated intramolecular oxidative heterocyclizations have also been successfully applied in the synthesis of oxadiazoles and thiadiazoles. Kumar et al. developed a PIDA promoted oxidative dimerization of indole-3-thiocarboxamides to afford 3,5-bis(indolyl)-1,2,4-thiadiazoles and several of these thiadiazoles exhibited antitumor activity against a panel of cancer cell lines.[55] In 2013, Shah, Kumar and coworkers[56] documented that acylthiosemicarbazides readily undergo oxidative desulfurization in the presence of PIDA to furnish a range of 2-arylamino-5-(3'-indolyl)-1,3,4-oxadiazoles in good yields. Along these lines, Muthusubramanian group[57] demonstrated a PIFA mediated transition-metal-free and efficient intramolecular oxidative process to forge S-N bond in imidoyl thioureas **65** furnishing 3-substituted-5-arylamino-1,2,4-thiadiazoles **66** in good to excellent yields (Scheme 18b).



Scheme 18. PIDA promoted synthesis of furans and thiadiazoles.

2.2.4. Synthesis of six membered heterocycles

In 2017, Fan, He and coworkers synthesized a range of 2,3-disubstituted 1,4-dioxanes **68** in good yields and with excellent diastereoselectivities by a novel PIDA-mediated dialkoxylation of 4-aminostyrenes **67** using ethylene glycol (Scheme 19).[58] The reaction was proposed to proceed through an oxidative dearomatization-induced nucleophilic attack and subsequent aromatization-induced 1,6-conjugated addition.



Scheme 19. Synthesis of 2,3-disubstituted 1,4-dioxanes.

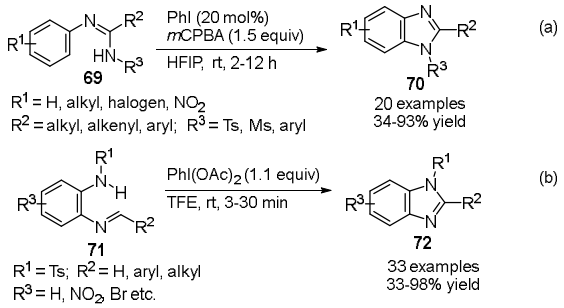
2.3. Synthesis of fused heterocyclic compounds

Fused heterocyclic compounds are the heterocyclic ring systems that are derived through fusion with either carbocycles or heterocycles. Due to the presence of this class of heterocycles in a variety of pharmacologically active compounds, they have attracted attention of numerous synthetic chemists over the

last few decades. This section is dedicated to the synthetic methodologies employing hypervalent iodine(III) chemistry that have been applied to the synthesis of a series of fused heterocycles, such as, indoles, indolines, benzimidazoles, carbazoles, quinolinones, quinoxalines etc.

2.3.1. Synthesis of substituted benzimidazoles

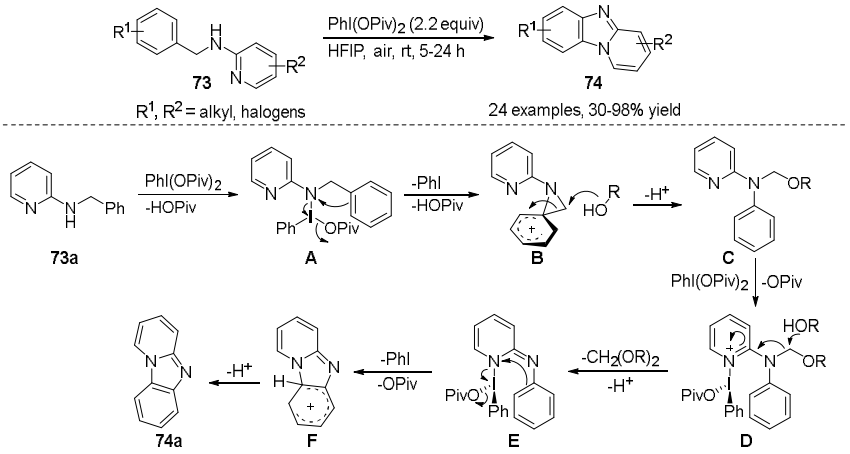
Zhu and coworkers[59] showed that biologically important 2-substituted benzimidazole **70** can effectively be synthesized *via* PIDA promoted intramolecular C–N bond annulation of readily available *N*-arylamidines. The authors also extended their method for the synthesis of tricyclic 2-alkyl-fused benzimidazoles. Meanwhile Punniyamurthy and coworkers[60] reported the organocatalytic version of such an intramolecular oxidative amination process. To this end, amidines **69** were oxidatively cyclized to the corresponding *N*-tosyl and *N*-aryl benzimidazoles **70** in good yields using iodobenzene as a catalyst and *meta*-chloroperbenzoic acid as the terminal oxidant (Scheme 20a). Later on, Maiti and Mal[61] reported an elegant methodology to synthesize 1,2-substituted benzimidazoles *via* metal free C(sp)^2–H amidation. The method was found to be quite robust and a range of disubstituted benzimidazoles **72** were prepared in good yields using PIDA as an oxidant **(**Scheme 20b). More recently, Das and coworkers[62] reacted 2-aminobenzylamine with easily available aldehydes/arylamines in the presence of PIDA/iodine reagent system to synthesize 2-substituted benzimidazoles through a ring distortion strategy.



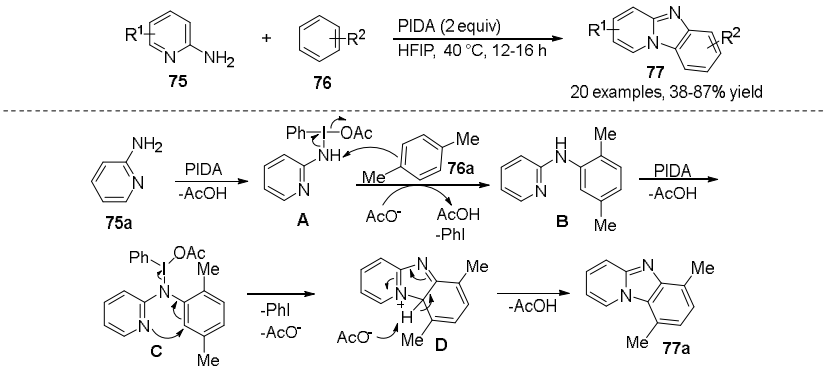
Scheme 20. Iodine(III)-mediated synthesis of substituted benzimidazoles.

In 2013, Zhu's group[63] demonstrated a hypervalent iodine(III) catalyzed intramolecular cycloamination of *N*-benzyl-2-aminopyridines to afford pyrido[1,2-a]benzimidazoles **74** in good yields. The iodine(III) species was generated *in situ* from iodobenzene and peracetic acid. Contemporaneously, the same group[64] showed that pyridobenzimidazoles **74** can also be synthesized from *N*-benzyl-2-aminopyridines **73** in the presence of stoichiometric amount of PhI(OPiv)$_2$ in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent through an intriguing tandem demethylenation/cycloamination reaction sequence (Scheme 21). The proposed mechanism of the authors begins with the formation of an electrophilic *N*-iodo species **A** through coordination of PhI(OPiv)$_2$ with **73a**, which then generates a Wheland intermediate **B** following an *ipso*-S$_E$Ar reaction on the phenyl ring. Subsequently, nucleophilic addition of HFIP on **B** leads to the cleavage of C-C bond and forms another intermediate **C**, which upon reaction with a second equivalent of PhI(OPiv)$_2$ furnishes **D**. Then a nucleophilic substitution by HFIP and an electrophilic annulation on the pyridine nitrogen generates intermediate **F**, which ultimately delivers pyridobenzimidazole **74a** following the deprotonation of **F**.

Meanwhile, Antonchick's group[65] reported an efficient PIDA-mediated intermolecular synthesis of pyrido[1,2-a]benzimidazole **77** using 2-aminopyridines **75** and commercially available arenes **76** (Scheme 22). The authors performed several mechanistic experiments and proposed that an initial reaction of PhI(OAc)$_2$ with **75a** produces intermediate **A**, which upon attack by the arene ring **76a** produces **B**. **B** then reacts with the second equivalent of PhI(OAc)$_2$ and undergoes intramolecular cycloamination with concomitant elimination of PhI and AcOH to deliver product **77a**. The authors successfully extended their method for the synthesis of benzo[4,5]imidazo[1,2-a]quinolines by reacting 2-aminoisoquinolines with arenes.



Scheme 21. Iodine(III) mediated synthesis of pyridoimidazoles.



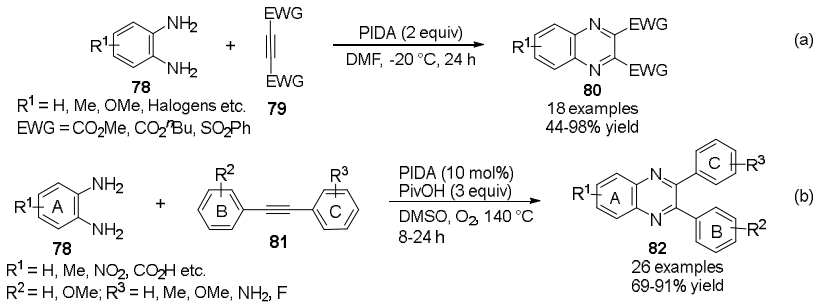
Scheme 22. Intermolecular annulation towards the synthesis of pyrido[1,2-a]benzimidazoles.

2.3.2. Synthesis of substituted quinoxalines, quinolinones and isoquinolinones

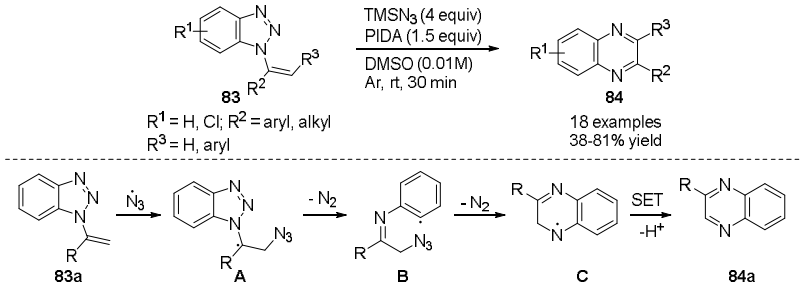
Minakata and coworkers[66] reported the direct synthesis of medicinally relevant quinoxalines **80** using 1,2-diaminobenzenes **78** and electron deficient alkynes **79** through a formal [4+2] oxidative annulation using PIDA as an oxidant (Scheme 23a). At the same time, Chung, Wang and coworkers[67] developed an oxidative annulation between substituted 1,2-diamino benzenes **78** and internal alkynes **81** using PIDA and PivOH to afford the corresponding substituted quinoxaline derivatives **82** in good yields (Scheme 23b). Importantly, in this process, the actual oxidant $PhI(OPiv)_2$ is generated *in situ* in a catalytic manner through the reaction of PIDA and PivOH.

In 2015, Shi and coworkers[68] demonstrated the first example of a radical mediated triazole ring opening towards the synthesis of various quinoxalines **84** through azide radical addition on vinyl substituted triazole derivatives **83** (Scheme 24). Importantly, the reaction was found to be reagent controlled as quinoxalines were obtained specifically under neutral conditions and upon carrying out the reactions under basic conditions corresponding nitriles were delivered. The reaction was proposed to occur *via* radical pathway that begins with the addition of azide radical on the alkene in **83a** to generate intermediate **A**. Subsequent triazole ring opening through elimination of nitrogen provides radical intermediate **B**, which then undergoes addition on azide to form intermediate **C**. Finally, oxidation and deprotonation event on **C** delivers the final product **84a**. Subsequently, Sharada's group[69] presented a PIDA-promoted azidation of

N-aryl vinylogous carbamates and concurrent intramolecular coupling through nitrogen-incorporation for the synthesis of quinoxaline diesters *via* the formation of two C(sp^2)–N bonds.



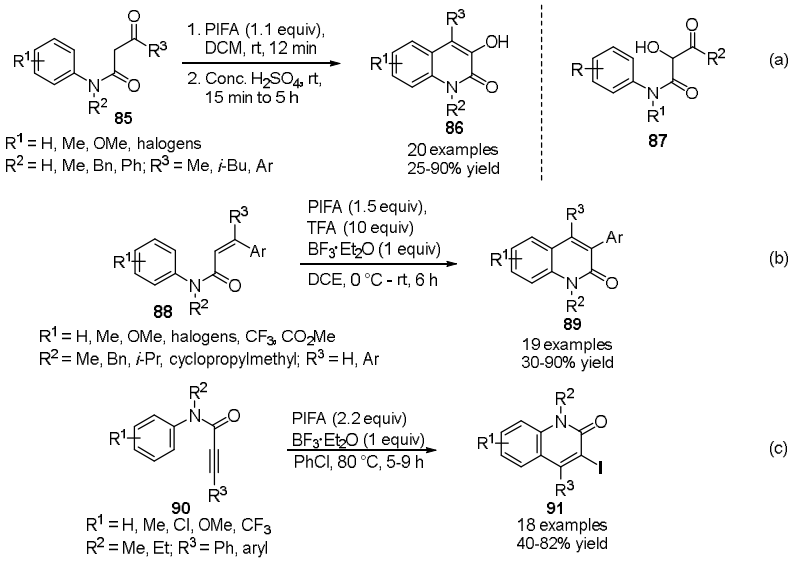
Scheme 23. Synthesis of quinoxaline derivatives.



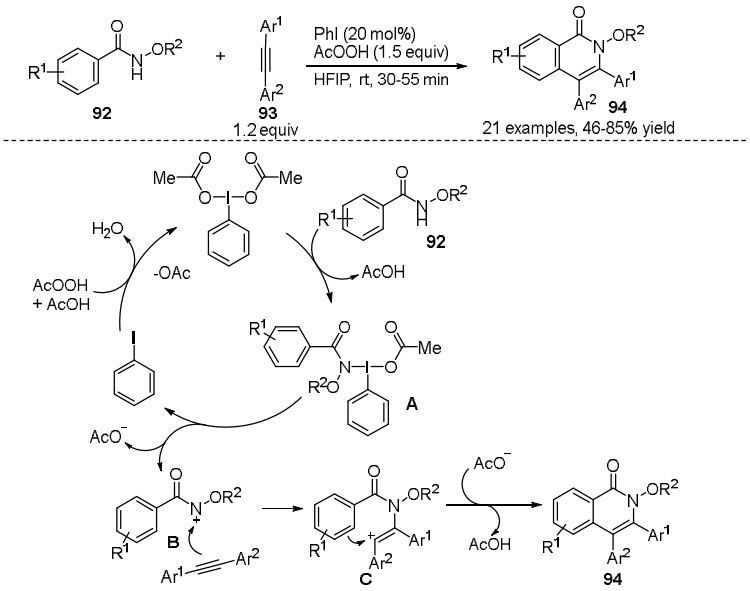
Scheme 24. Synthesis of substituted quinoxalines through radical mediated triazole ring opening.

Zhao, Du and coauthors[70] realized a one pot two-step synthesis of 3-hydroxy quinolinones **86** starting from *N*-phenylacetoacetamides **85** (Scheme 25a). The reaction proceeded through a PIFA-mediated *α*-hydroxylation to give intermediate **87**, which subsequently underwent sulfuric acid promoted intramolecular dehydrative cyclization reaction sequence to the desired quinolones **86**. Concurrently, the same research group[71] demonstrated a mechanistically different PIFA mediated synthesis of 3-arylquinolin-2-ones **89** proceeding through an intramolecular oxidative C(sp^2)–C(sp^2) coupling of *N*-alkyl-*N*-arylcinnamamides **88** in the presence of BF_3•Et_2O as a Lewis acid (Scheme 25b). Subsequently, the authors studied the reaction in detail and by combined experimental and theoretical experiments they found that the reaction occurs by a highly regioselective 1,2-aryl migration process.[72] Recently in 2017, Du and coworkers[73] presented a novel iodocyclization of *N*-arylpropynamides **90** using PIFA as an oxidant as well as an iodinating agent to synthesize iodinated quinoline-2-ones **91** in moderate to good yields (Scheme 25c).

In 2014, Antonchick's group developed an unprecedented organocatalytic regioselective synthesis of diverse isoquinolone derivatives **94** through an intermolecular oxidative annulation of symmetrical and non-symmetrical internal alkynes **93** with *N*-alkoxybenzamide derivatives **92** using a combination of catalytic amount of iodobenzene and peracetic acid **(**Scheme 26).[74] The authors proposed that *in situ* generated PIDA initially reacts with **92** to generate nitrenium intermediate **B**, which then reacts with internal alkyne to form vinyl carbocation **C**. Finally, **C** undergoes intramolecular annulation to furnish isoquinolinone derivatives **94**. Subsequently, Zheng, Zhu and coworkers[75] reported a similar intermolecular coupling towards the synthesis of isoquinolinones using PIFA as a stoichiometric oxidant. Meanwhile Zhao, Du and coworkers demonstrated an intramolecular cyclization of *o*-(1-alkynyl)benzamides followed by an oxidative hydroxylation to synthesize 3-hydroxy-2,3-dihydroisoquinolin-1,4-dione derivatives using PIFA as an oxidant.[76]



Scheme 25. Synthesis of 3,4-disubstituted quinoline-2-ones.

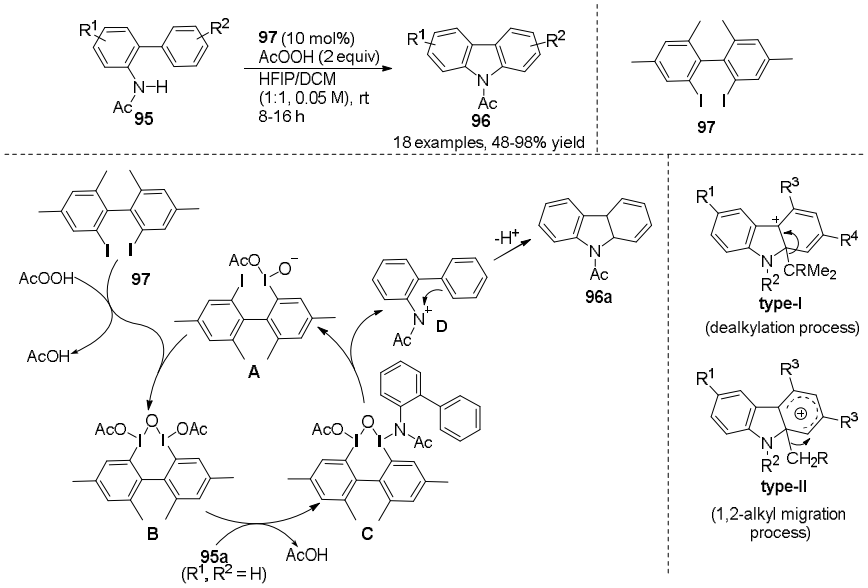


Scheme 26. Novel intermolecular annulation for the synthesis of isoquinolinone derivatives.

2.3.3. Synthesis of substituted carbazoles

In 2011, Antonchick and coauthors[77] developed a very efficient and novel *in situ* generated hypervalent iodine(III) catalyzed synthesis of substituted carbazoles **96** through intramolecular amination of *N*-acetaminobiphenyls **95**. The required iodine(III) catalyst was generated using aryl iodide **97** in the presence of peracetic acid (Scheme 27). Prior to this, Chang et al.[78] had reported a similar intramolecular cycloaminative synthesis of carbazoles either by a copper-catalyzed process using PIDA as an oxidant or

through a transition-metal-free protocol using stoichiometric PIFA as an oxidant. Importantly, the yield of the Cu-catalyzed protocol was significantly higher as compared to the PIFA mediated process and the reaction was proposed to proceed through the intermediacy of radicals. On the contrary, Antonchick and coworkers excluded the possibility of radicals in their organocatalytic process. They proposed that their reaction involves an initial formation of oxo-bridged hypervalent iodine species **B** by the reaction of diiodoarene and peracetic acid, which then reacts with acetaminobiphenyl **95a** to form **C**. **C** then undergoes cleavage to generate nitrenium intermediate **D**, which finally affords the desired carbazole **96a** through an intramolecular C-N bond formation. **A** then gets reoxidized to the μ-oxo-bridged active iodine(III) catalyst **B** and further participate in the catalytic process**.** More recently, Mal's group showed that following the Friedel-Crafts type annulation on the initially generated nitrenium ion of type **D**, the re-aromatization leading to carbazoles can take place in potentially two ways depending on the substituent attached to the phenyl ring of aminobiphenyl derivatives. The rearomatization can take place either through a retro-Friedel-Crafts type dealkylation process[79] (**type-I**; in case of resulting stable secondary/tertiary carbocation such as, $^{+}CRMe_2$) or through a 1,2-alkyl (methyl, ethyl) migration process[80] (**type-II**).



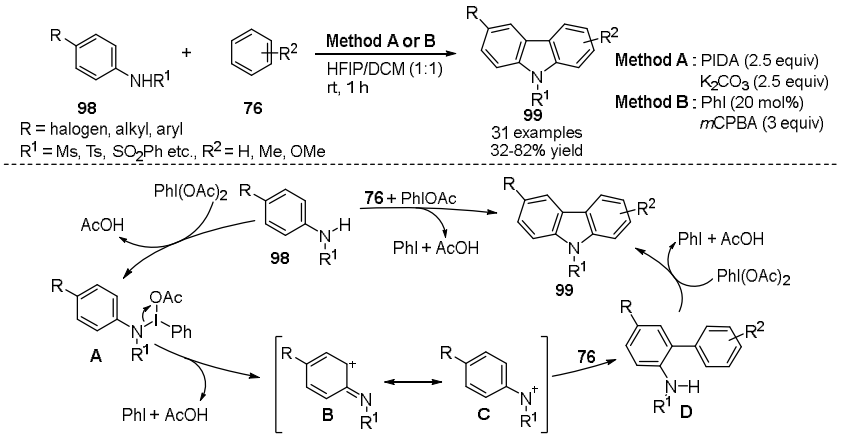
Scheme 27. Synthesis of carbazoles by intramolecular cycloamination process.

Besides these reports, Mal's group disclosed an efficient and novel methodology for the synthesis of various carbazoles **99** using preformed or *in situ* generated hypervalent iodine(III) reagent. In their report[81] they showcased fusion of unactivated arenes **76** and anilides **98** through an intermolecular dehydrogenative annulation process with the formation of C–C and C–N bonds to afford multisubstituted carbazoles **99** in moderate to good yields (Scheme 28). According to the proposed mechanism, the reaction begins with the generation of nitrenium ion **C**, which is stabilized through charge delocalization and forms intermediate **B**. The carbenium ion **B** leads to the formation of intermediate **D** by forming C-C bond upon reaction with **76**. **D** then further reacts with iodine(III) reagent through an oxidative cycloamination process to ultimately lead to the desired carbazole compounds **99**.

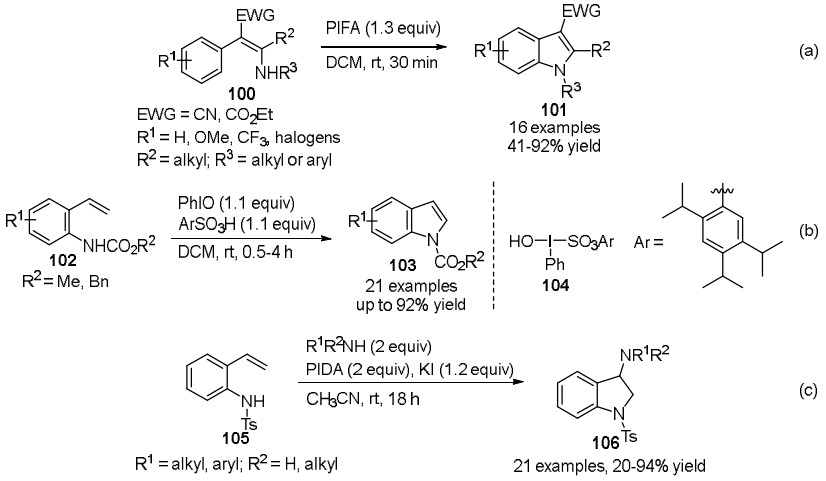
2.3.4. Synthesis of indoles and indolines

Zhao and coworkers showed that enamine derivatives can be oxidatively cyclized to biologically important indoles *via* intramolecular amidation through either $C(sp^2)$-$C(sp^2)$ or $C(sp^2)$-N bond stitching. They developed a PIFA-mediated intramolecular C-N bond forming cyclization of enamine derivatives **100**

towards the synthesis of *N*-arylated and *N*-alkylated indoles **101** (Scheme 29a).[82] Later they disclosed that *N*-aryl enamines undergo oxidative C-C bond formation in the presence of PIDA to furnish a variety of substituted indoles.[83] Recently, Muñiz group developed a modified Koser reagent **104** mediated intramolecular oxidative cyclization of 2-amino styrenes **102** to afford corresponding indoles **103** in good yields (Scheme 29b).[84] The modified Koser reagent **104** was generated *in situ* either in a stoichiometric fashion by reacting 2,4,5-tris-isopropylbenzene sulfonic acid with iodosobenzene or in a catalytic manner using *m*CPBA as the terminal oxidant. Similarly, Johnston and Hong[85] reported an operationally simple PIDA-mediated synthesis of 3-aminoindolines **106** from tosyl-protected 2-vinyl anilines **105** that occurs through concurrent intra- and intermolecular oxidative diamination of terminal alkenes (Scheme 29c). In 2014, Chang and coworkers documented an intramolecular diamination of olefins using PIDA as an oxidant and tetrabutylammonium iodide as an additive to synthesize a variety of bisindolines in good yields.[86]



Scheme 28. Carbazole synthesis through iodine(III)-assisted/catalyzed dehydrogenative annulations.

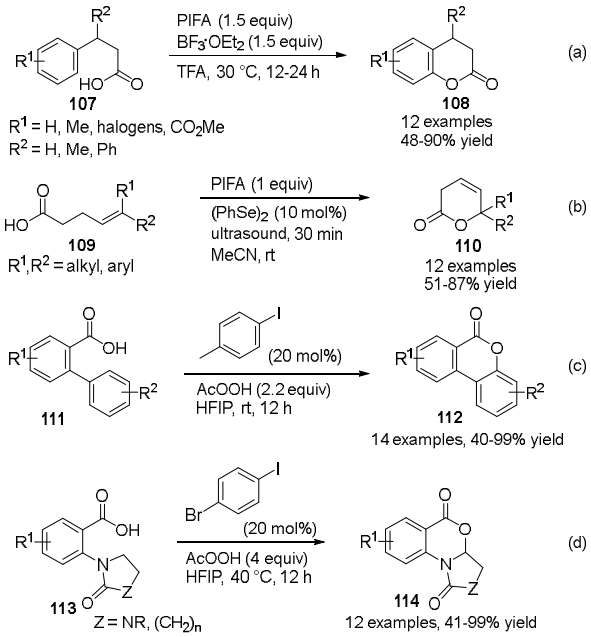


Scheme 29. Synthesis of indoles and indolines through oxidative cyclizations.

2.4. Synthesis of lactones and lactams

2.4.1. Racemic synthesis of substituted lactones

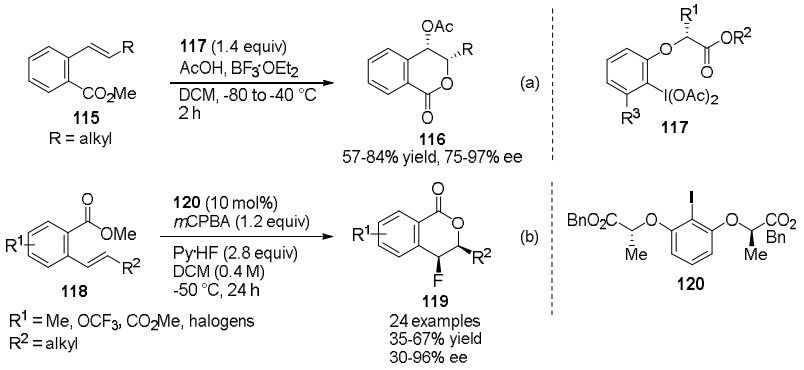
Intramolecular C(sp^2/sp^3)-H lactonization of carboxylic acids by using hypervalent iodine reagents is a fruitful strategy for the synthesis of lactones. In 2010, Gu et al.[87] developed a PIFA induced oxidative cyclization of 3-aryl propionic acids **107** to synthesize 3,4-dihydrocoumarins **108** (Scheme 30a). The reaction was proposed to proceed through the intermediacy of radical cations. Subsequently, Wirth and Singh[88] demonstrated a very convenient diphenylselenide catalysed regioselective synthesis of 3,6-dihydro-2*H*-pyran-2-ones **110** through an oxidative lactonization of *γ,δ*-unsaturated pentenoic acids **109** using PIFA as a stoichiometric oxidant (Scheme 30b). Recently the same research group extended their method to the oxidative cyclization of malonate derivatives using PIDA as an oxidant.[89] In this process double bonds are dioxygenated to afford five membered lactones in moderate yields. Martin group[90] reported an elegant intramolecular oxidative coupling that proceeds through a tandem C(sp^2)-H functionalization/C-O bond formation event to furnish benzolactones **112** in good yields (Scheme 30c). The reaction occurs in the presence of 4-iodotoluene as the catalyst and peracetic acid as a terminal oxidant. The authors successfully extended their method for C(sp^3)-H functionalization affording a diverse range of substituted benzoxazinones **114** using 4-bromotoluene as the catalytic hypervalent iodine precursor (Scheme 30d).



Scheme 30. Intramolecular lactonization of carboxylic acids using Iodine(III) reagents.

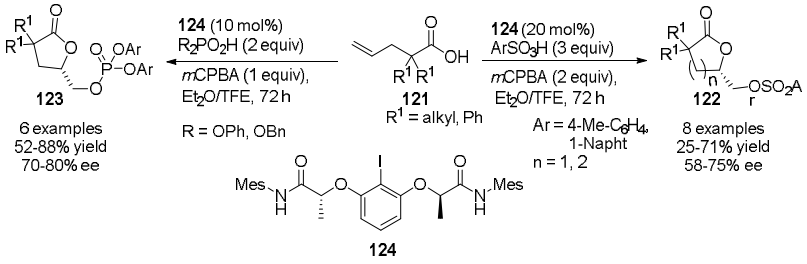
2.4.2. Enantioselective synthesis of lactones

Enantioselective synthesis of lactone moiety is of high importance as many chiral lactones have been used to synthesize natural products and bioactive compounds. Fujita and coworkers[91,92] demonstrated a catalytic enantioselective oxylactonization of *ortho*-alkenylbenzoates **115** using lactate-derived chiral hypervalent iodine reagents **117** to synthesize 4-acetoxyisochroman-1-one derivatives **116** with high endo selectivity and up to 97% ee (Scheme 31a)**.** In 2016, Jacobsen and coworkers developed an enantio- and diastereoselective fluorolactonization towards the synthesis of optically pure 4-fluoroisochromanones **119**.[93] To this end, several alkenyl benzoates **118** underwent smooth lactonization in the presence of readily available chiral aryl iodide catalyst **120**, *m*CPBA as terminal oxidant and HF•Py as the nucleophilic fluoride source.



Scheme 31. Enantioselective oxy- and fluoro-lactonizations of alkenylbenzoates.

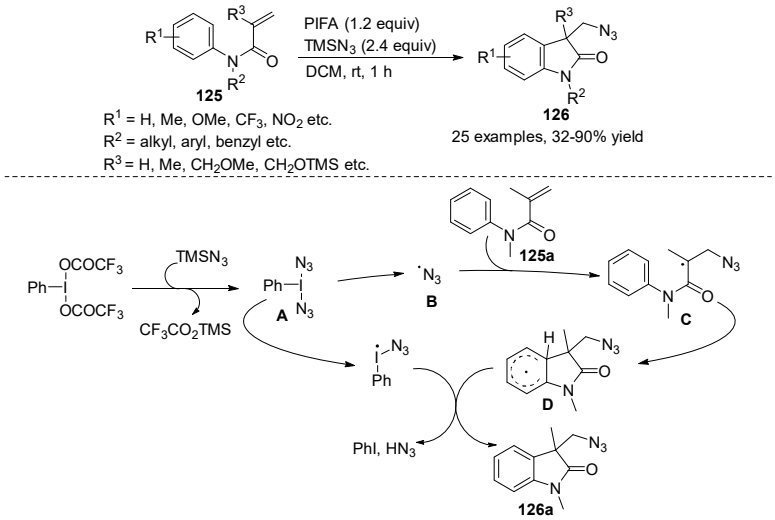
In 2016, Masson et al.[94] demonstrated an enantioselective chiral hypervalent iodine-catalyzed oxylactonization of 4-pentenoic acids **121** to afford sulfonyloxy- and phosphoryloxy-γ-butyrolactones **122** and **123** respectively, in moderate yields and enantioselectivities (Scheme 32). The hypervalent iodine reagent was generated *in situ* through the reaction of chiral iodoarene **124** and *m*CPBA.



Scheme 32. Catalytic enantioselective synthesis of sulfonyloxy- and phosphoryloxy-γ-butyrolactones.

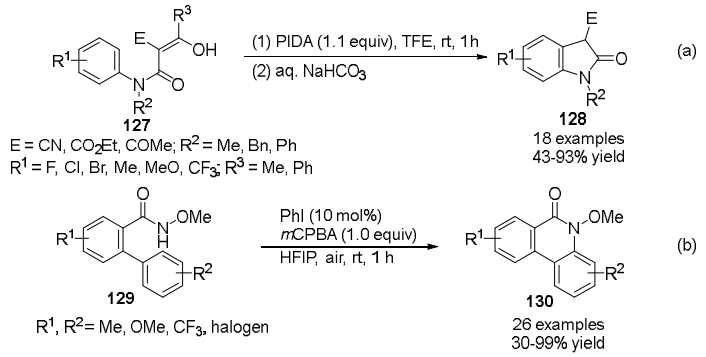
2.4.3. Synthesis of lactams using hypervalent iodine reagents

In 2013, Antonchick and coworkers[95] demonstrated a novel and efficient azidoarylation of alkenes for the construction of biologically appealing 2-oxindoles **126** framework by using stoichiometric amount of PIFA and $TMSN_3$ (Scheme 33). The method was found to be highly robust and several oxindoles were prepared in good to excellent yields. Mechanistically, the authors proposed that an initial ligand exchange between PIFA and $TMSN_3$ generates intermediate **A** that following fragmentation leads to azidyl radical **B**. Subsequently, it undergoes addition on substrate **125a** to form carbon-centered radical **C**, which then undergoes radical nucleophilic aromatic substitution to provide **D**. Finally, product **126a** is obtained through an oxidation/deprotonation sequence of **D**. Soon after this report, Liu, Tan and coworkers reported on carbotrifluoromethylation of alkenes using PIDA as an oxidant and $TMSCF_3$ as the trifluoromethyl source to furnish trifluoromethylated oxindoles.[96] Mechanistically, the reaction proceeds through the generation of trifluoromethyl radical and subsequent addition to the alkene in a similar fashion to that of azidoarylation method. More recently, Maruoka group[97] reported a similar iodine(III)-mediated radical acylarylation of *N*-arylacrylamides with aliphatic aldehydes to synthesize a variety of carbonyl group bearing 2-oxindoles. In this case the required acyl radical was generated from the corresponding aliphatic aldehydes under photolysis conditions. Along these lines, Zhou's group[98] documented on PIDA-mediated oxidative cyclization of 2-isocyanobiphenyls with $TMSCF_3$ towards the synthesis of 6-(trifluoromethyl)phenanthridines that are embedded in many naturally occurring alkaloids.



Scheme 33. PIFA mediated synthesis of oxindoles.

Hypervalent iodine(III)-mediated oxidative functionalization of enolizable carbonyl compounds represent a powerful strategy for the formation of C-C bonds.[7] Accordingly, Zhao and Du group[99] developed a PIFA-mediated oxidative $C(sp^2)$-$C(sp^3)$ bond annulation technology to successfully transform anilides to the corresponding 3-hydroxy-2-oxindoles. Subsequently, the same research group extended their methodology to forge $C(sp^2)$-$C(sp^2)$ bond and accordingly anilides **127** underwent smooth intramolecular annulation and subsequent deacylation in the presence of PIDA to furnish 2-oxindole derivatives **128** in good yields (Scheme 34a).[100] Iodine(III)-promoted intramolecular amidation has also been applied in the synthesis of lactams. In 2017, Xue group[101] developed an efficient iodobenzene catalyzed synthesis of phenanthridinones **130** from *N*-methoxybenzamides **129** under mild conditions using *m*CPBA as a terminal oxidant (Scheme 34b). Previously, a similar intramolecular amidation strategy was applied in the synthesis of indoloquinolinones[102] and 1,4-benzodiazepines.[103]

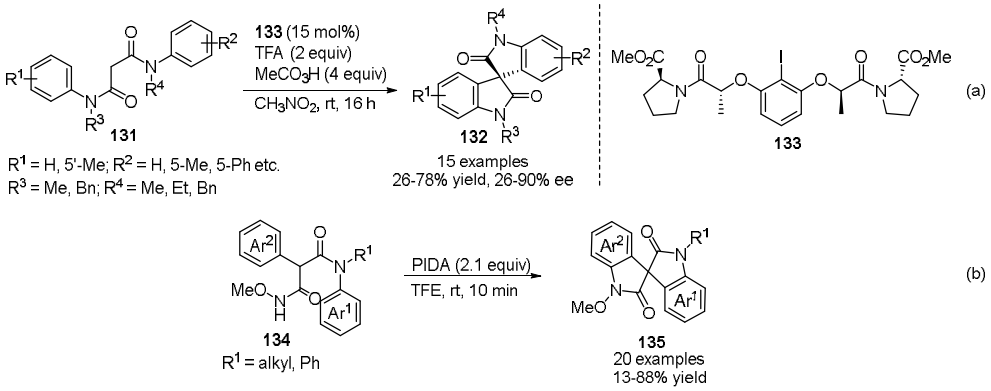


Scheme 34. Iodine(III)-mediated/catalyzed synthesis of 2-oxindoles and phenanthridinones.

2.5. Synthesis of spiro-heterocycles

Spiro heterocyclic compounds have received immense applications in the field of medicinal chemistry and drug discovery. Biologically active spiro heterocyclic scaffolds are the subunits of many antibiotics,

antimicrobial and antitumor drugs.[104,105] In this section we present several useful methods for the synthesis of these particular class of scaffolds using hypervalent iodine(III) reagents under transition-metal-free conditions.[106] Zhao group[99] developed an intramolecular dual $C(sp^2)$-$C(sp^3)$ coupling of diphenylmalonamides **131** using PIFA to access a range of spirooxindole compounds. Later, in 2014, Gong group[107] successfully demonstrated the corresponding enantioselective version allowing access to optically active spirooxindoles **132** in good yields and high enantioselectivities (Scheme 35a). The required chiral hypervalent iodine reagent was generated *in situ* by using chiral aryl iodide **133** and peracetic acid. After that the same group[108] developed another chiral iodine(III)-catalyzed C-C bond forming asymmetric oxidative dearomatizative spirocyclization of 1-hydroxy-N-aryl-2-naphthamide derivatives enabling synthesis of spirooxindoles and its analogues in high enantioselectivities. Recently, Du et al.[109] presented a novel PIDA-mediated synthesis of C_3-unsymmetric spiro-oxindoles **134** from diphenylmalonamides **135** that proceeds through the oxidative formation of C-C bond preceding an oxidative C-N bond annulation (Scheme 35b).

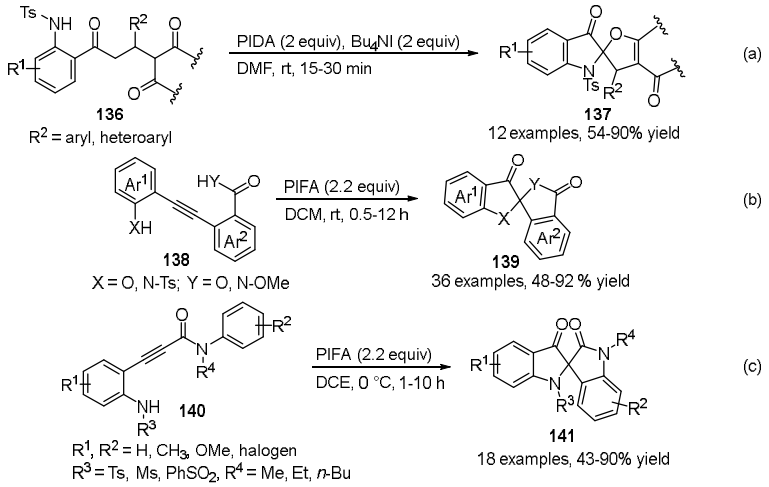


Scheme 35. Synthesis of *N*-containing spirocyclic compounds through C-C and C-N bond formation.

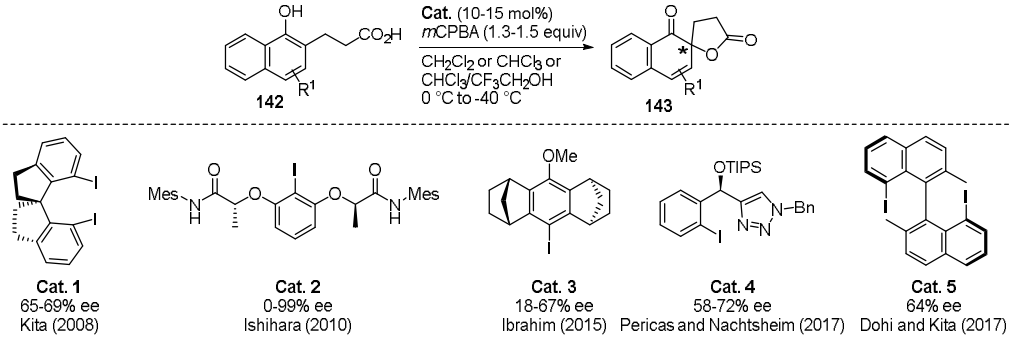
In 2011, Fan and coauthors[110] reported an efficient method for the synthesis of oxa-aza spirobicyclic compounds **137** using a combination of PIDA and tetrabutylammonium iodide (Scheme 36a). To this end, a range of N-protected substrates **136** underwent tandem C-H bond oxidation to yield the desired oxa-azaspirobicycles **137** with concomitant C-O and C-N bond formation. In 2015, Du and coworkers[111] developed a PIFA mediated cascade annulation process comprising two sequential C-N and C-O bond formation to convert diortho-substituted diarylacetylenes **138** to various spirocycles containing an N,O- or O,O-ketal **139** in moderate to good yields (Scheme 36b). Subsequently, authors presented a similar iodine(III)-mediated *trans*-aminocarboxylation and oxaminocarboxylation of alkynes for the synthesis of spiro-heterocyclic compounds.[112] In 2017, Du's group[113] developed a PIFA-mediated transition-metal-free cascade annulation of 2-sulfonamido-N-phenylpropiolamides **140** that occurs through sequential $C(sp^2)$-C(sp) and $C(sp^2)$-N bond formation and concurrent incorporation of carbonyl oxygen leading to the formation of functionally orchestrated 2-spiropseudoindoxyl derivatives **141** in moderate to good yields (Scheme 36c).

In 2008, Kita and co-workers developed a catalytic asymmetric spirolactonization of 1-naphthol derivative **142** utilizing a structurally rigid C_2-symmetric 1,1'-bisindane based iodoarene **Cat. 1** to give the corresponding spirolactones **143** with moderate enantioselectivity (Scheme 37).[114] Subsequently, Ishihara disclosed a lactate derived conformationally flexible C_2-symmetric iodoarene **Cat. 2** to furnish the desired spirolactones with excellent enantioselectivities.[115] Following these initial articles, the field of asymmetric oxidative spirocyclization of naphthol carboxylic acids **142** giving rise to the corresponding dearomatized spirolactones **143** have attracted much attention. Several chiral iodide based reagents, such as Ibrahim's dimethanoanthracene based iodoarene **Cat. 3**,[116] Pericàs and Nachtsheim's C_1-symmetric

triazole-functionalized chiral iodoarene **Cat. 4**[117] and Dohi and Kita's atropisomeric 8,8'-diiodobinaphthalene **Cat. 5**[118] have been introduced since then. All these chiral iodides delivered the desired spirolactones **143** with moderate enantioselectivities in the presence of *m*CPBA as the terminal oxidant (Scheme 37).

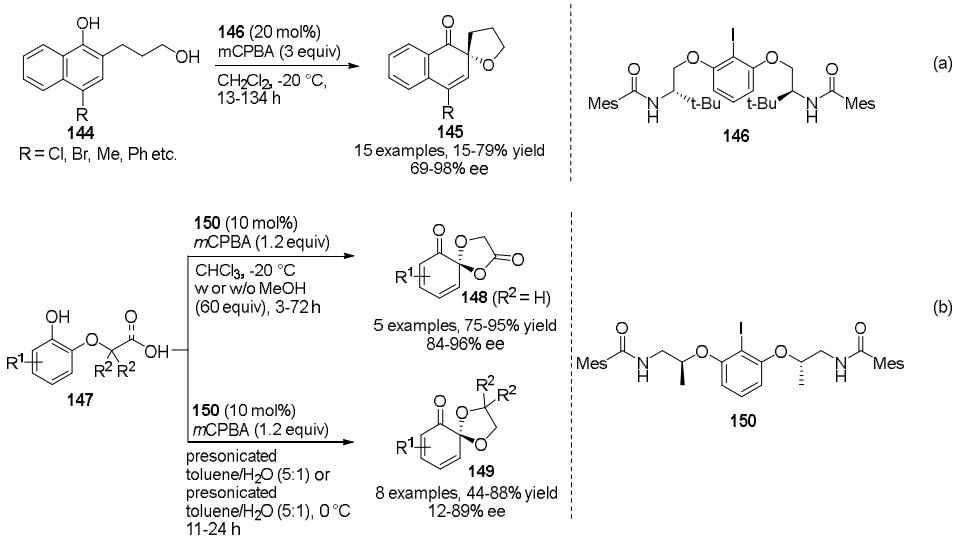


Scheme 36. Synthesis of aza- and oxa-aza spirocyclic compounds.



Scheme 37. Asymmetric synthesis of spirolactones through dearomatization of a phenolic group.

An enantioselective dearomatizing oxidative spirocyclization of naphthol-derived noncarboxylic acid substrates have also been studied in recent past. Accordingly, Ciufolini group developed an enantioselective, hypervalent iodine promoted oxidative cycloetherification reaction of naphtholic alcohols **144** using modified Uyanik-Ishihara chiral iodide **146** to afford the desired spiroheterocycles **145** in good to excellent enantioselectivity (Scheme 38a).[119] Authors successfully applied their protocol in the enantioselective cyclization of naphtholic sulfonamides as well. Moreover, Ishihara and coworkers documented a chiral organoiodine(III) **150** catalyzed oxidative dearomatization of ortho-hydroquinone derivatives **147** O-tethered to an acetic acid or ethanol unit at the ortho-positions to furnish the corresponding masked ortho-benzoquinones (MOBs) in moderate to high yields with high to excellent enantioselectivities (Scheme 38b).[120] Importantly, the enantioselective method was equally effective towards the oxidative dearomatization of para-hydroquinone derivatives O-tethered to an acetic acid and the corresponding masked para-benzoquinones (MPBs) were obtained with moderate to high enantioselectivities.



Scheme 38. Asymmetric Synthesis of oxa-spiroheterocycles through oxidative dearomatization.

3. **Conclusions**

In this chapter we have summarized the transition-metal-free hypervalent iodine(III)-mediated/catalyzed synthetic methods that have been developed mostly in the last decade and successfully applied in the construction of a plethora of heterocyclic compounds. The current decade has witnessed the demand of green, economic, less waste generating and sustainable synthetic approaches and hypervalent iodine(III) reagents are proving to be apt for sustainable synthesis. Owing to their easy availability, environmentally benign nature, non-toxicity, good functional group tolerance and excellent oxidizing properties, these classes of reagents have evolved as potential transition metal surrogates and received wide applicability in the field of synthetic chemistry. Considering the ever-growing demand, application of these classes of reagents in the achiral/chiral synthesis of hitherto unknown or pre-existing bioactive heterocyclic compounds can be anticipated.

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