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REVIEW

Hypervalent iodine reagents for heterocycle synthesis and functionalization

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Abstract: Hypervalent iodine reagents have been vastly applied in many significant oxidative reactions. This surging interest in iodine reagents is mainly due to the very useful oxidizing properties, combined with their benign environmental character and commercial availability. In this review, we focus on the representative transformations that used the common hypervalent iodine reagents as oxidants in heterocycle synthesis and functionalizations, based on the type of the hypervalent iodine reagents.

Keywords: hypervalent iodine reagent, heterocycle synthesis, heterocycle functionalization, oxidative reaction

Introduction

The 1990s witnessed rapid development of hypervalent iodine chemistry. The intense interest is mainly due to the remarkable oxidizing properties of hypervalent iodine reagents and their attractive features such as easy to handle, low toxicity, availability of supply, and environmental benignity.[1–20] Two of their most important synthetic applications are in the constructions of heterocyclic skeletons and functionalization of heterocycles, such as three- to seven-membered rings and spiro compounds, under metal-free reaction conditions. Some representative transformations have been shown in Figure 1. In this review, we summarize, with representative examples, the reactions involving various hypervalent iodine (III) and (IV) reagents used as oxidants for the syntheses and functionalization of heterocyclic compounds. The organization of the presentation is based on the type of the hypervalent iodine reagents.

Hypervalent iodine (III) reagents

The common classification of hypervalent iodine (III) reagents is according to the type of ligands attached to the iodine atom, as shown in Figure 2.[10,16] These broadly applied hypervalent iodine (III) reagents, namely, iodosylarenes **1**, (dichloroiodo) arenes **2a** and (difluoroiodo)arenes **2b**, [bis(acyloxy)iodo]arenes **3**, [hydroxy(tosyloxy) iodo]benzene **4** (Koser's reagent), iodonium salts **5**, iodonium ylides and iodonium imides, and the benziodoxole-based hypervalent iodine reagents **6** and **7** (Togni's reagents), have been found to be powerful and effective oxidants for the synthesis of heterocycles and for facilitating functionalization of heterocyclic compounds via atom transfer reactions.

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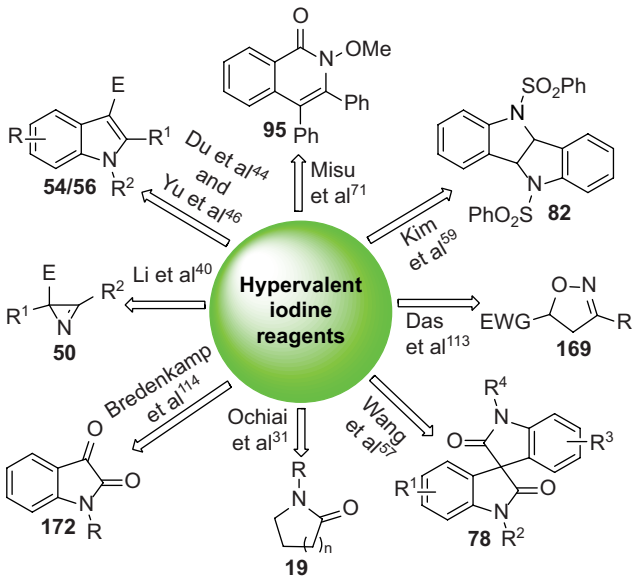

Figure 1 Representative reactions involving hypervalent iodine reagents.

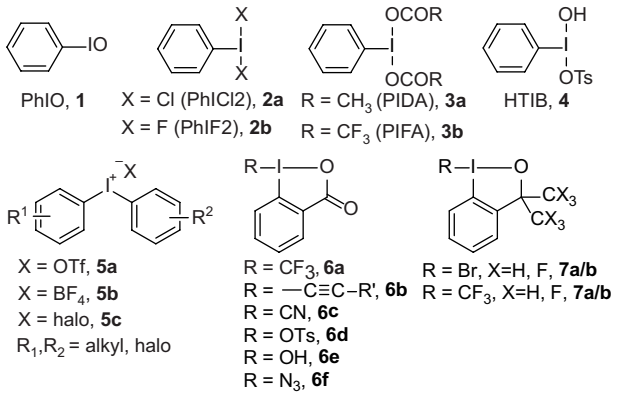

Figure 2 Representative hypervalent iodine (III) reagents.
Abbreviations: PhIO, iodosobenzene; PIDA, phenyliodine diacetate; PIFA, phenyliodine bis(trifluoroacetate); HTIB, [hydroxy(tosyloxy)iodo]benzene.

Iodosylarenes

An important synthetic application of iodosobenzene (PhIO) is promoting oxidative annulation during the construction of heterocyclic framework. For example, Ueno et al[21] reported a direct preparation of heteroaromatic compounds of imidazoles **9a**, thiaozles **9b**, and imidazo[1,2-*a*]pyridines **10** through reactions of alcohol substrates **8** with PhIO catalyzed by *p*-toluenesulfonic acid monohydrate and followed by further reactions with thioamide, benzamidine, and 2-aminopyridine, respectively, under basic conditions (Figure 3).

In 2010, Fan et al[22] described a PhIO-mediated synthesis of the three-membered *N*-benzoyl aziridines **12** and the five-membered oxazolines **13** through an intramolecular oxidative cyclization of substrates **11** in the presence of catalytic amount of *tetra*-butylammonium iodide (Figure 4A-a). Similar conditions were applied to the synthesis of

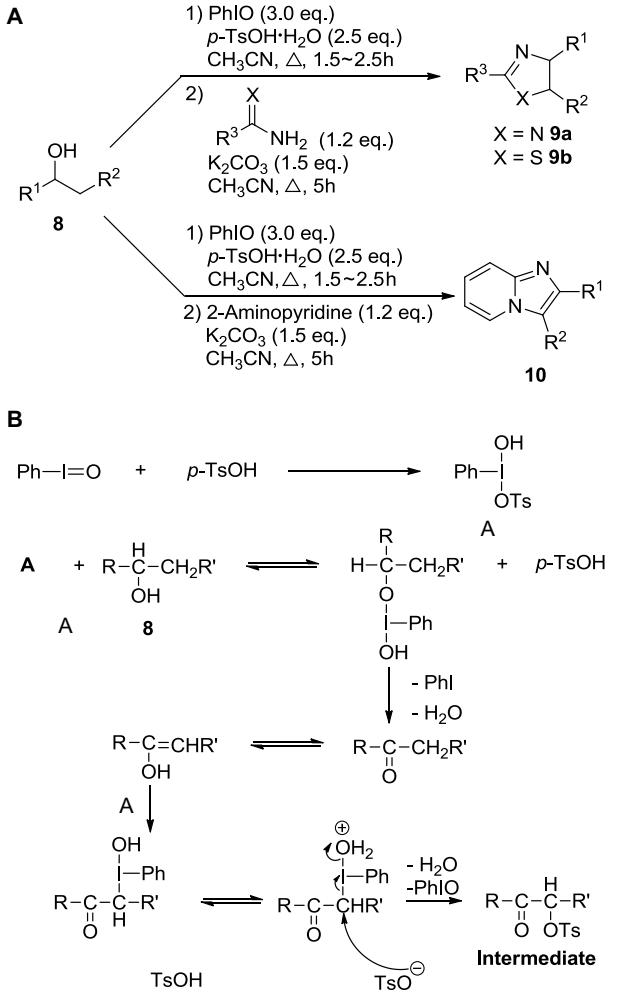

Figure 3 (**A**) PhIO-mediated construction of thiaozles, imidazoles, and imidazo[1,2-*a*]pyridines. (**B**) Proposed mechanism of the oxidation reaction in step I.
Abbreviations: PhIO, iodosobenzene; eq., equivalent; h, hours.

the four-membered oxetanes **15** and azetidines **17** from substrates **14** and **16**, respectively (Figure 4A-b and -c).[23,24] The proposed mechanism has been shown in Figure 4B.

In addition, PhIO can also be used as an efficient oxidant for the functionalization of heterocycles. For example, five- or six-membered lactams **19** could be obtained in moderate yields through the oxidation of cyclic amines **18** with PhIO using H_2O as solvent (Figure 5).[25]

Moriarty et al[26] reported the oxidation of trimethylsilyl ketene acetals of lactones **20** in methanol, mediated by PhIO, to afford the corresponding α-methoxylated carbonyl compounds **21** in good yields (Figure 6). They also found that reaction of dihydropyran **22** with PhIO in H_2O could afford tetrahydro-2-furaldehyde **23** via carbocationic ring contraction (Figure 7). Under the same conditions, cyclohexene and styrene were converted into the corresponding aldehyde products through rearrangement oxidations.[27]

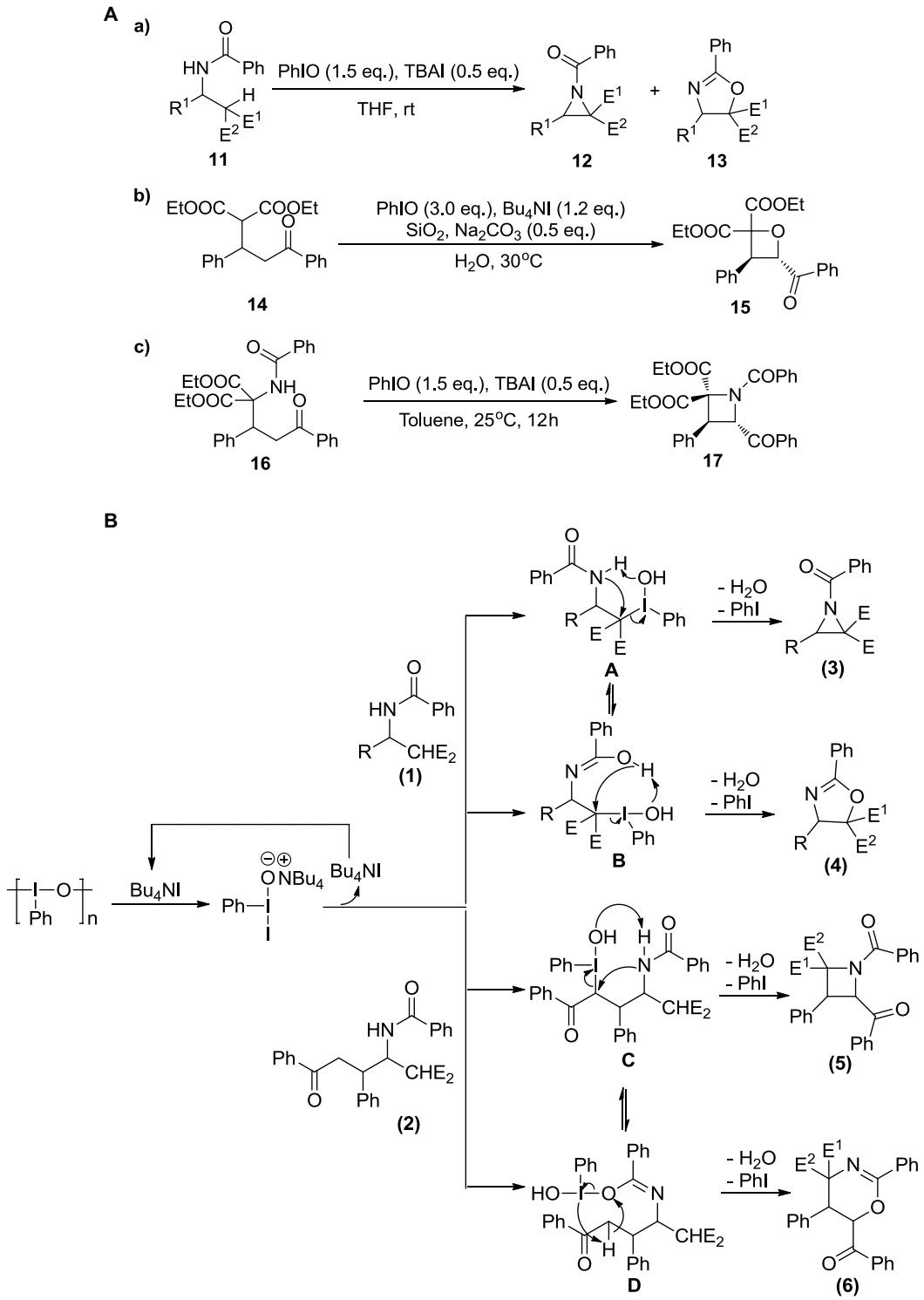

Figure 4 (**A**) (a) PhIO-mediated synthesis of three-membered ring 12 and five-membered ring 13. (b) PhIO-mediated synthesis of oxetane 15. (c) PhIO-mediated synthesis of azetidine 17 (**B**) Proposed mechanism of (a) and (c).
Abbreviations: PhIO, iodosobenzene; eq., equivalent; TBAI, tetra-butylammonium iodide; THF, tetrahydrofuran; rt, room temperature; h, hours.

In the presence of PhIO and I_2, *N*- or *O*-centered radicals could be generated, respectively, from amides or alcohols.[28–30] In 2000, Francisco et al reported the synthesis of homochiral 7-oxa-2-azabicyclo[2.2.1]heptane ring system **28** from specifically protected phosphoramidate derivatives of carbohydrates **24** under the conditions mentioned earlier. Mechanistic studies demonstrated a reaction path involving a hemolytic fragmentation of a hypothetical iodoamide intermediate **26** (Figure 8).[30]

It is worth noting that the applications of PhIO can be significantly restricted in nonpolar solvents due to low

solubility. Therefore, the majority of the known reactions occurs in polar solvents and are catalyzed by a Lewis acid or a transition metal catalyst, with only a few cases reported to be in a nonpolar solvent or without the involvement of a catalyst. One of the rare examples is the formation of lactams **30** in $CHCl_3$ from the cyclic amino acids **29** via initial imine formation followed by oxidative decarboxylation (Figure 9).[31]

(Difluoroiodo)arenes

As fluorinating reagents, (difluoroiodo)arenes ($ArIF_2$) have found many synthetic applications for the syntheses of biologically and pharmaceutically interesting F-containing heterocyclic compounds.[32,33] In 1991, Caddick et al[32] reported the reaction of 1-(arylthio)glycosides **31** with $TolIF_2$, which afforded various 1-fluoroglycosides **32** in moderate-to-good yields (Figure 10).

Upon treating the iodoaldyl substituted four-, five-, and six-membered cyclic ethers **33**–**35** with $TolIF_2$, the five-, six-, and seven-membered cyclic ethers **36**–**38** were stereoselectively synthesized in moderate-to-good yields (Figure 11).[34]

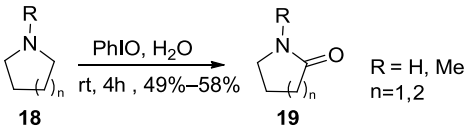

Figure 5 PhIO-mediated functionalization of cyclic amines.
Abbreviations: PhIO, iodosobenzene; rt, room temperature; h, hours.

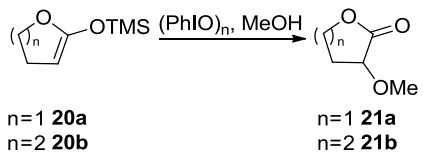

Figure 6 PhIO-mediated oxidation affording α-methoxylated carbonyl compounds.
Abbreviation: PhIO, iodosobenzene.

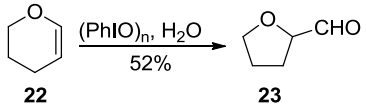

Figure 7 PhIO-mediated oxidation of dihydropyran.
Abbreviation: PhIO, iodosobenzene.

Dichloroiodoarene

(Dichloroiodo)arenes ($ArICl_2$) have been used as chlorinating reagents to carry out modification of various heterocyclic compounds. For example, reaction of *N*-protected pyrrolidine **39** with 4-nitrobenzeneiododichloride afforded α-hydroxy-β,β-dichloropyrrolidine **40** as the main product via a complicated ionic mechanism involving a $C(sp^3)$–H bond activation process (Figure 12). This oxidation gave an α,β,β-oxidation pattern relative to the nitrogen of the heterocycle.[35]

An effective system consisting of a combination of $PhICl_2$ and $Pb(SCN)_2$ was developed by Prakash et al[36] for convenient thiocyanation of various enol silyl ethers **41** (Figure 13).

Recently, Hepples et al[37] reported a Lewis base-catalyzed chlorination method for the diazocarbonyl compound **43a** and isatin-3-hydrazone **43b** by using $PhICl_2$, both of which led to the same product **44** (Figure 14).

The common feature of these reactions is the transfer of the two chlorine ligands from $PhICl_2$ in a germinal fashion rather than vicinal.[37,38]

In 2014, He et al[39] reported a method for the direct synthesis of oxazolidin-2-ones **46** and imidazolidin-2-ones **48** from 1,3-diols **45** and 3-amino alcohols **47** using combined $PhICl_2$ and NaN_3 (Figure 15).

[Bis(acyloxy)iodo]arenes

[Bis(acyloxy)iodo]arenes ($ArI(OCOR)_2$), notably the easily prepared and commercially available phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA), have been widely used as oxidizing reagents in various syntheses of heterocycles. In this review, the applications of PIDA and PIFA are presented based on the type of heterocycles obtained.

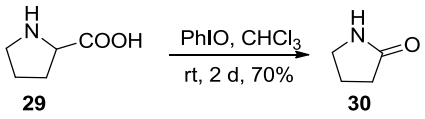

Figure 9 PhIO-mediated conversion of proline into 2-pyrrolidone in nonpolar solvent.
Abbreviations: PhIO, iodosobenzene, rt, room temperature; d, days.

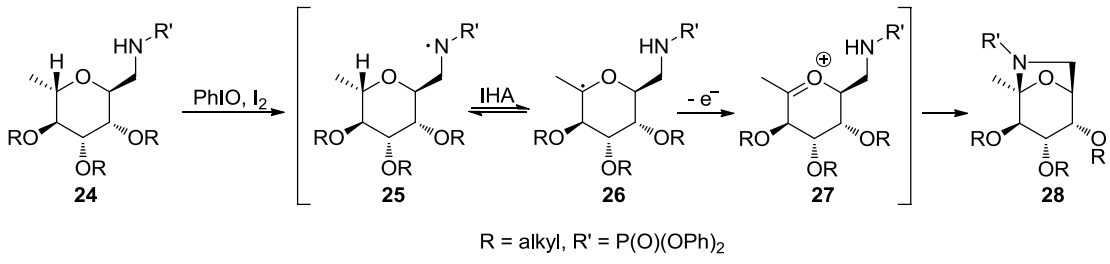

Figure 8 Synthesis of the homochiral 7-oxa-2-azabicyclo[2.2.1]heptane ring system.
Abbreviations: PhIO, iodosobenzene; IHA, intramolecular hydrogen abstraction reaction.

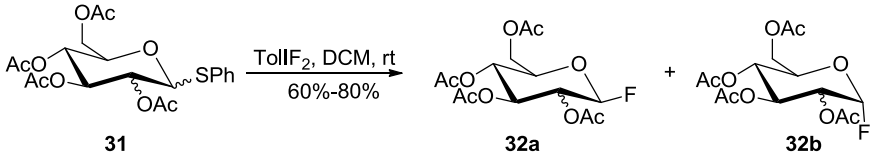

Figure 10 Synthesis of various 1-fluoroglycosides with $TolIF_2$.
Abbreviations: rt, room temperature; DCM, dichloromethane.

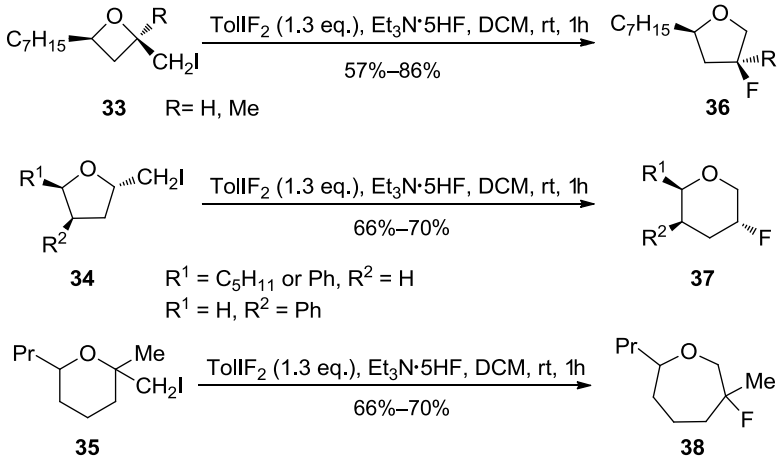

Figure 11 Ring-expansion reactions induced by $TolIF_2$.
Abbreviations: eq., equivalent; rt, room temperature; h, hour; DCM, dichloromethane.

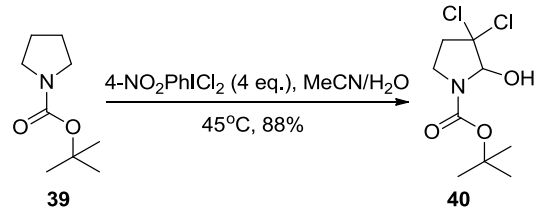

Figure 12 Synthesis of α-hydroxy-β,β-dichloropyrrolidine with $4\text{-}NO_2PhICl_2$.
Abbreviation: eq., equivalent.

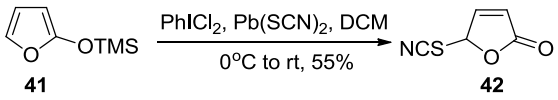

Figure 13 $PhICl_2/Pb(SCN)_2$-mediated thiocyanation of enol silyl ethers leading to lactone **42**.
Abbreviations: rt, room temperature; DCM, dichloromethane.

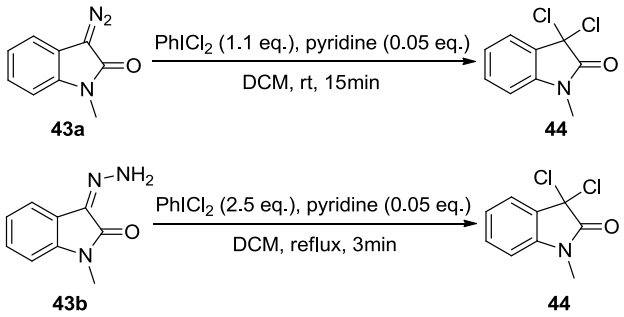

Figure 14 Lewis base-catalyzed chlorination facilitated by $PhICl_2$.
Abbreviations: eq., equivalent; rt, room temperature; min, minutes; DCM, dichloromethane.

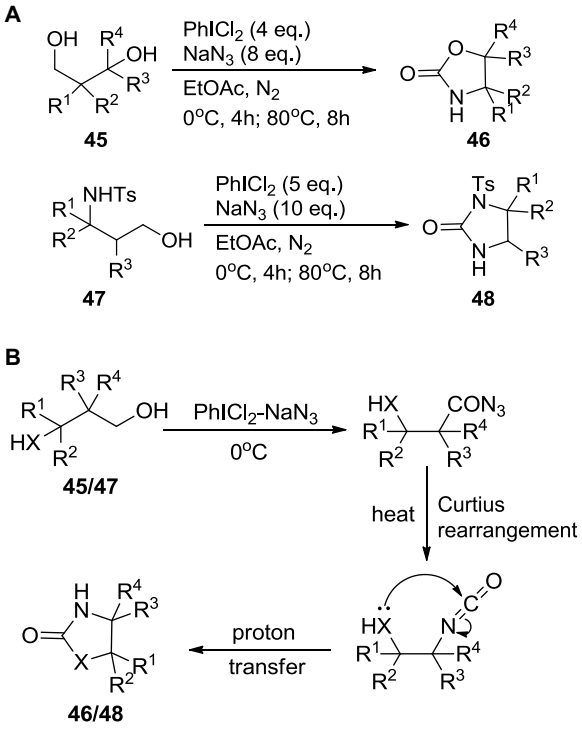

Figure 15 (**A**) Direct synthesis of oxazolidin-2-ones and imidazolidin-2-ones using $PhICl_2$ and NaN_3. (**B**) Proposed mechanism.
Abbreviations: eq., equivalent; h, hours.

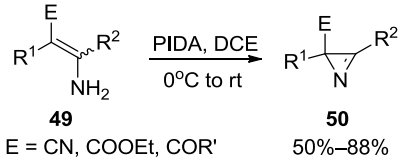

Figure 16 PIDA-mediated synthesis of 2*H*-azirine derivatives from enamines.
Abbreviations: PIDA, phenyliodine diacetate; rt, room temperature; DCE, 1,2-dichloroethane.

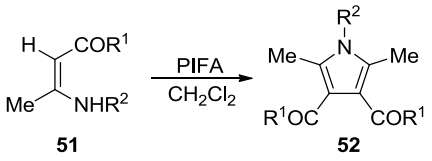

Figure 17 PIFA-mediated synthesis of polysubstituted pyrroles **52**.
Abbreviation: PIFA, phenyliodine bis(trifluoroacetate).

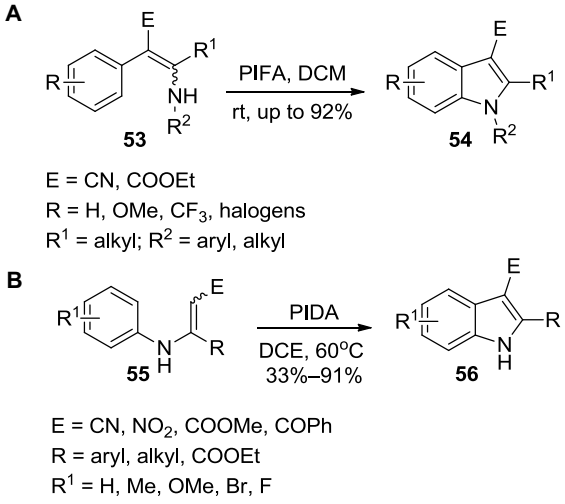

Figure 18 (**A**) I (III)-mediated synthesis of indoles from enamines 53. (**B**) I (III)-mediated synthesis of indoles from enamines 55.
Abbreviations: PIDA, phenyliodine diacetate; PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; DCM, dichloromethane; DCE, 1,2-dichloroethane.

Three-membered heterocyclic products

In 2009, our group reported the synthesis of the smallest unsaturated *N*-containing heterocycle, namely, 2*H*-azirine **50**, via PIDA-mediated intramolecular oxidative azirination of the substituted enamine derivatives **49** under mild conditions (Figure 16).[40] A similar strategy was later applied to the one-pot synthesis of isoxazoles from enaminones.[41]

Five-membered heterocyclic compounds

Pyrrole

Mediated by PIFA, the synthesis of polysubstituted pyrroles **52** was achieved via a tandem dimerization/cyclocondensation of enaminones **51** (Figure 17).[42] Asymmetrical polysubstituted pyrroles were obtained from enamine esters or ketones mediated by PIDA in the presence of $BF_3{\cdot}Et_2O$.[43]

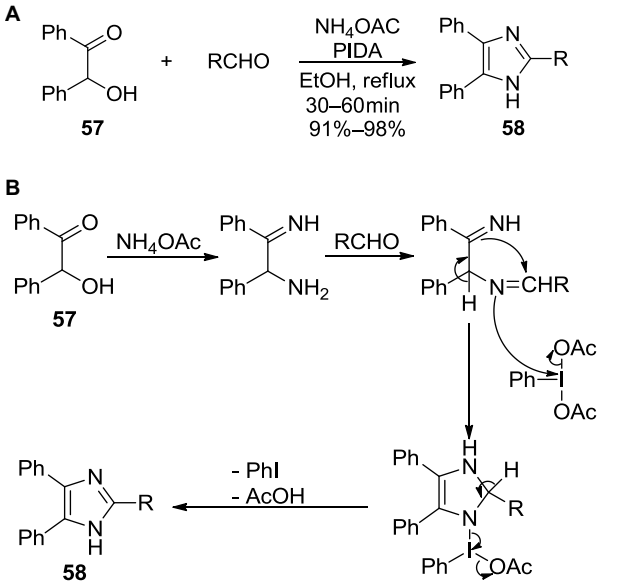

Figure 19 (**A**) PIDA-mediated synthesis of imidazoles via condensation of α-hydroxy ketones with aldehydes and NH_4OAc. (**B**) Proposed mechanism.
Abbreviations: PIDA, phenyliodine diacetate; min, minutes.

Indole

In 2006, the syntheses of *N*-arylated and *N*-alkylated indoles **54** from enamine derivatives **53** were realized through a PIFA-mediated intramolecular oxidative C(sp^2)–N bond formation (Figure 18A).[44] The same strategy was also applied to the synthesis of carbazolones via PIFA-mediated intramolecular cyclization of 2-aryl enaminones.[45] In 2009, a variety of functionalized indoles **56** were synthesized from *N*-aryl enamines **55** via PIDA-mediated oxidative C(sp^2)–C(sp^2) involving no transition metals (Figure 18B).[46]

Azole

In 2007, Das et al[47] reported the condensation of α-hydroxy ketones **57** with aldehydes and ammonium acetate by using PIDA as the sole oxidant. The reaction furnished the cyclized imidazole product **58** through an oxidative C(sp^2)–N bond formation (Figure 19). Various 2-arylbenzimidazoles and benzimidazoles were later synthesized adopting the same methodology.[48]

In 1996, Kotali[49] realized the synthesis of aminoindazole derivatives **60** from the *o*-aminoaryl ketone acylhydrazones **59** via PIDA-mediated N–N bond formation (Figure 20).

In 2012, intramolecular oxidative C–O coupling of *N*-(4-alkoxy-phenyl) and *N*-(4-acetamido-phenyl) benzamides was found to afford the benzoxazole products in high yields under metal-free conditions by using PIFA as an oxidant and TMSOTf as a catalyst (Figure 21).[50]

Upon treating β-monosubstituted enamines **63** with PIFA, an intermolecular cross-coupling occurred and was succeeded by condensation to provide the 4,5-disubstituted 2-(trifluoromethyl)oxazoles **64** (Figure 22).[51] In this approach, the trifluoromethyl moiety in one of the PIFA ligands was incorporated into the final products at the C2 position.

In 2010, Saito et al[52] reported the oxidative cycloisomerization of propargylamide derivatives **65**, mediated by PIDA in AcOH or AcOH-HFIP and affording the corresponding 2,5-disubstituted oxazoles **66** (Figure 23).

Treating anthranilamides **67a** or salicylamides **67b** with PIDA in the presence of potassium hydroxide, the 2-benzimidazolones **68a** and 2-benzoxazolones **68b** were, respectively, obtained in good yields (Figure 24). The postulated mechanistic pathway suggested an initial Hofmann-type rearrangement followed by a sequential intramolecular cyclization of the intermediate isocyanate.[53]

In 2008, PIFA-mediated intramolecular cyclization of the thiobenzamides **69** resulting in the benzothiazoles **70** via reactive intermediates of aryl radical cations was described (Figure 25A).[54] Later on, Kumar et al[55] applied the polymer-supported PIDA to construct the benzothiazoles **73** from the corresponding *o*-amino benzenethiol components **71** and aldehydes **72** (Figure 25B).

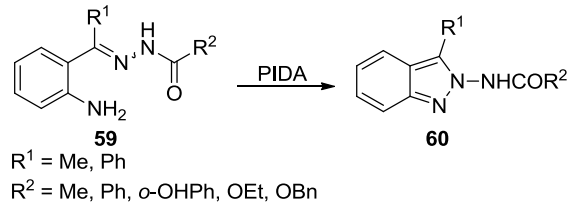

Figure 20 PIDA-mediated synthesis of aminoindazole derivatives.
Abbreviation: PIDA, phenyliodine diacetate.

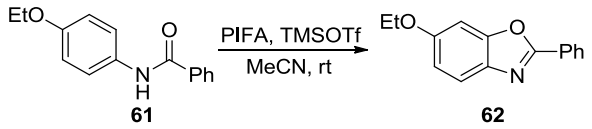

Figure 21 PIFA/TMSOTf-mediated synthesis of benzoxazole derivatives.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; TMSOTf, trimethylsilyl trifluoromethanesulfonate.

Lactone

In 2007, Dohi et al[56] developed a direct construction of the biologically important aryl lactone **76** from carboxylic acid **74** using combined PIDA and KBr (Figure 26). The aryl group in the substrate was understood to be indispensable due to the benzyl radical intermediate **75** as suggested by the mechanism. The aryl lactone product **76** was achieved via hydrogen abstraction and then cyclization.

Spiro heterocycles and bisindolines

In 2012, Wang et al[57] reported a PIFA-mediated synthesis of spirooxindoles **78** from anilide derivatives **77** bearing an appropriate α-arylaminocarbonyl group (Figure 27). These processes feature a metal-free oxidative C(sp^2)–C(sp^3) bond formation, followed by oxidative spirocyclization.

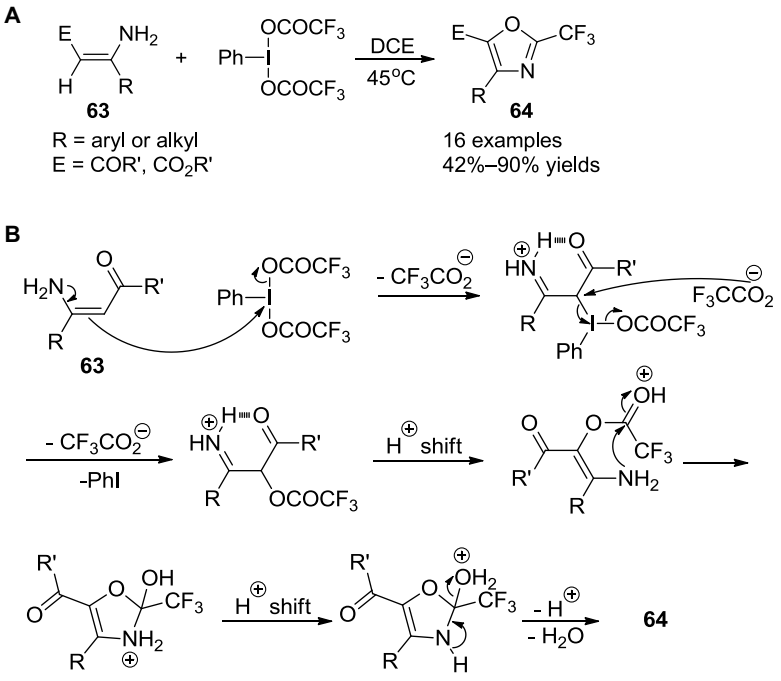

Figure 22 (**A**) PIFA-mediated synthesis of 2-trifluoromethyl oxazole derivatives. (**B**) Proposed mechanism.
Abbreviation: PIFA, phenyliodine bis(trifluoroacetate); DCE, 1,2-dichloroethane.

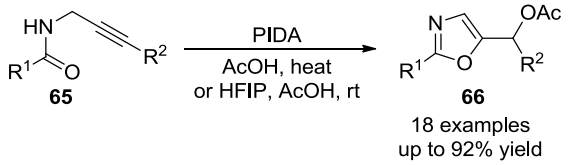

Figure 23 PIDA-mediated synthesis of 2,5-disubstituted oxazoles in AcOH or AcOH-HFIP.
Abbreviations: PIDA, phenyliodine diacetate; rt, room temperature.

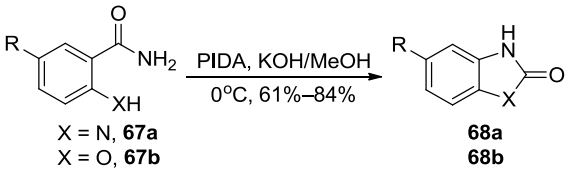

Figure 24 PIDA/KOH-mediated synthesis of 2-benzimidazolones and 2-benzoxazolones.
Abbreviation: PIDA, phenyliodine diacetate.

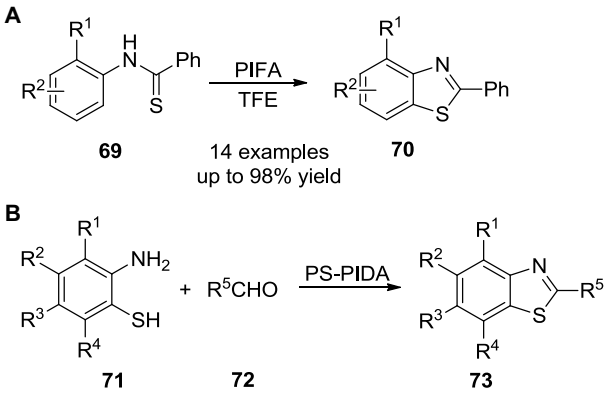

Figure 25 (**A**) PIFA-mediated intramolecular synthesis of benzothiazoles. (**B**) PIDA-mediated intermolecular synthesis of benzothiazoles.
Abbreviations: PIDA, phenyliodine diacetate; PIFA, phenyliodine bis(trifluoroacetate); PS, polymer-supported.

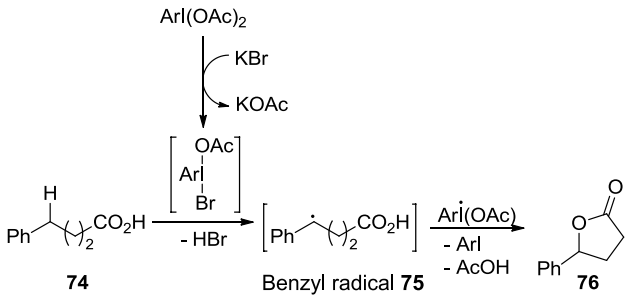

Figure 26 PIDA/KBr-mediated synthesis of aryl lactones.
Abbreviation: PIDA, phenyliodine diacetate.

Recently, Zhang et al[58] reported a PIFA-mediated cascade annulation of internal alkyne **79**, affording the spiro heterocycle **80** (Figure 28). This process encompasses not only two sequential C–N/C–O bond formations but also the insertion of a carbonyl oxygen, all in one pot.

In 2014, Kim et al[59] realized a cascade intramolecular oxidative diamination of olefins **81** by using PIDA as an oxidant and a halide as an additive, leading to the synthesis of a variety of bisindolines **82** (Figure 29).

Six- and seven-membered heterocycles

A PIFA-mediated oxidative C(sp^2)–C(sp^2) bond formation between two aryl rings was reported by Kita et al.[60] Later, this oxidative coupling strategy was widely applied to the conversion of various biaryl substrates tethered by a relatively labile linker attached to the heterocycles, such as a silaketale, sulfide, sulfoxide, sulfone, or dibenzylether.[61–63] For example, Moreno et al[64] described an efficient synthesis of benzo[*c*] phenanthridine **84** and phenanthridinone **86** from properly substituted benzylnaphthylamine **83** and naphthylbenzamide **85**, respectively, through a PIFA-mediated intramolecular oxidative C–C bond formation between the two electron-rich phenyl rings (Figure 30).

Liu et al[65] reported the syntheses of a variety of 3-arylquinolin-2-one compounds **88** from the *N*-methyl-*N*-phenylcinnamamides **87**. The reactions involved an exclusive 1,2-aryl migration along with a metal-free oxidative C–C bond formation, mediated by PIFA in the presence of a Lewis acid (Figure 31).[65]

In 2001, Arisawa et al[66] reported a PIFA-mediated direct intramolecular cyclization of α-(aryl)alkyl-β-dicarbonyl compounds **89** leading to the spirobenzannulated products **90**. Both *meta*- and *para*-substituted phenol ether derivatives containing cyclic or acyclic 1,3-dicarbonyl moieties on the side chain underwent the annulation in a facile manner (Figure 32).

In 1990, Kikugawa and Kawase[67] reported an intramolecular oxidative C(sp^2)–N bond formation in substrates **91**, which contained a methoxyamide side chain on the aromatic ring, to give the *N*-aryl-*N*-methoxyamides **92** (Figure 33) via a nitrenium ion intermediate. This oxidative amidation protocol was later applied in many explorations of novel means to construct heterocyclic framework.[68–70]

Starting from *N*-methoxybenzamide **93** and alkyne **94**, Misu and Togo[71] developed a straightforward synthesis of isoquinolones **95** using PIDA generated in situ through an intermolecular organocatalytic annulation (Figure 34).

The indenocarboxamides **96** could be converted to the fused indeno-1,4-diazepinones **97** through intramolecular oxidative C–N bond formations mediated by PIFA (Figure 35).[72] Moreover, various PIFA-promoted intramolecular amidation reactions have been developed for the formation of five-, six-, and seven-membered heterocycles.[72–75]

In 2014, Zhao and Du described a PIDA-mediated oxidative coupling of the two aryl groups in either 2-acylamino-*N*-phenylbenzamides **98** or 2-hydroxy-*N*-phenylbenzamides

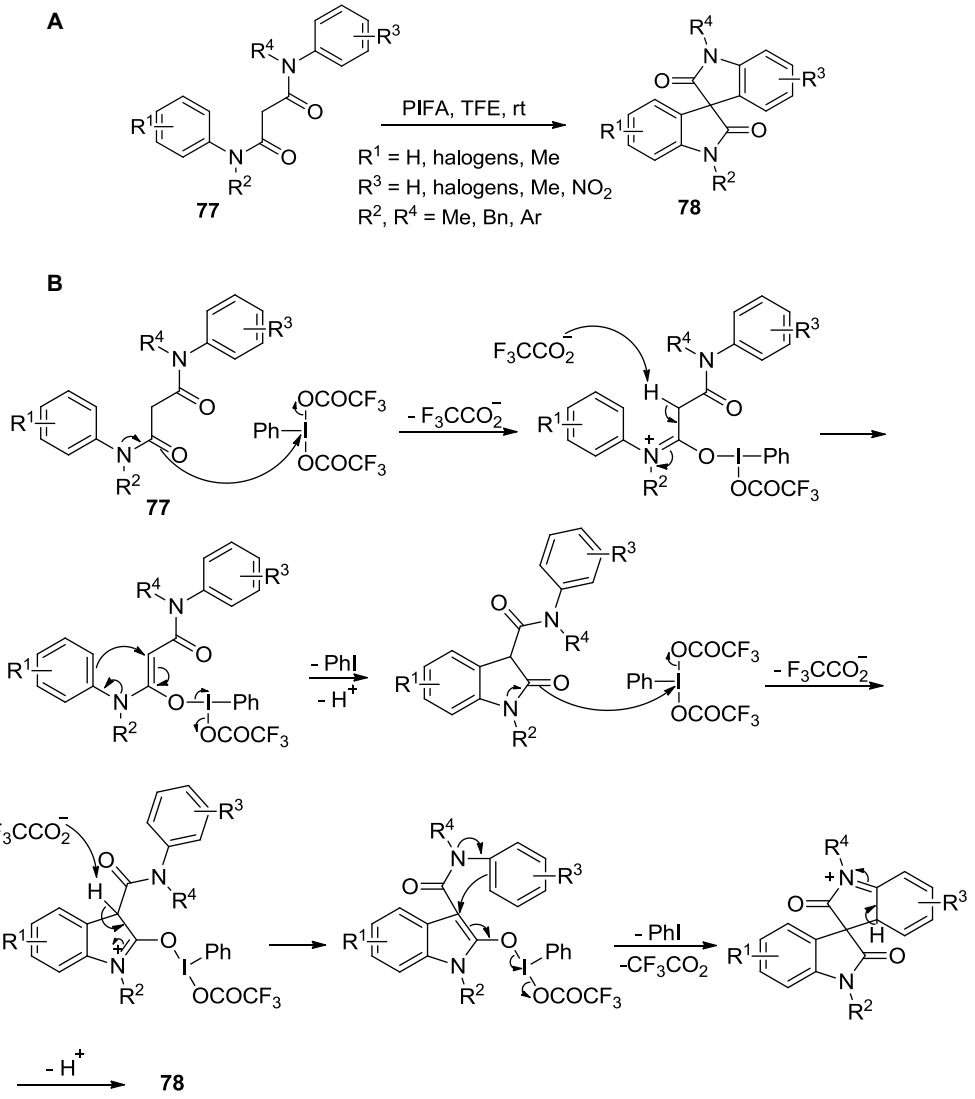

Figure 27 (**A**) Metal-free synthesis of spirooxindoles via PIFA-mediated cascade oxidation. (**B**) Proposed mechanism.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; TFE, 2,2,2-Trifluoroethanol.

100 to afford the dibenzodihydro-1,3-diazepin-2-ones **99** and dibenzo[*d*,*f*][1,3]oxazepin-6(7*H*)-ones **101**, respectively (Figure 36). The reaction sequence involves an oxidative C(sp^2)–C(sp^2) aryl–aryl bond formation, C(sp^2)–C/O bond cleavage, and an intramolecular lactamization/lactonization. The unique feature of this conversion is the concomitant insertion of the *ortho*-substituted *N* or *O* atom into the tether, realized for the first time.[76]

A variety of systems involving PIDA/PIFA have been developed to realize functionalization of heterocyclic compounds. Some representative examples are discussed later.

Iodination

By using a combination of PIFA and I_2, Benhida et al[77] developed an iodination method suitable for electron-deficient heterocyclic compounds including substituted indoles **102** (Figure 37) and coumarins. Moreover, the methodologies offered reaction conditions mild enough to ensure the survival of sensitive protecting group such as acetyl and *tert*-butyldimethylsilyl. The methods were also applied to the iodination of substituted pyrazoles in providing the corresponding 4-iodopyrazole derivatives.[78]

Likewise, PIFA-mediated direct cyanations of various heterocyclic compounds including pyrroles, thiophenes, and indoles were realized using trimethylsilyl cyanide as a source of CN.[79] For example, cyanation of *N*-tosylpyrroles **104** at the C2 position was achieved by using trimethylsilyl cyanide along with PIFA with moderate-to-excellent selectivity (Figure 38).

Bifunctionalization of glycals **106**, including homogeneous azidization and selenylation, has been realized by

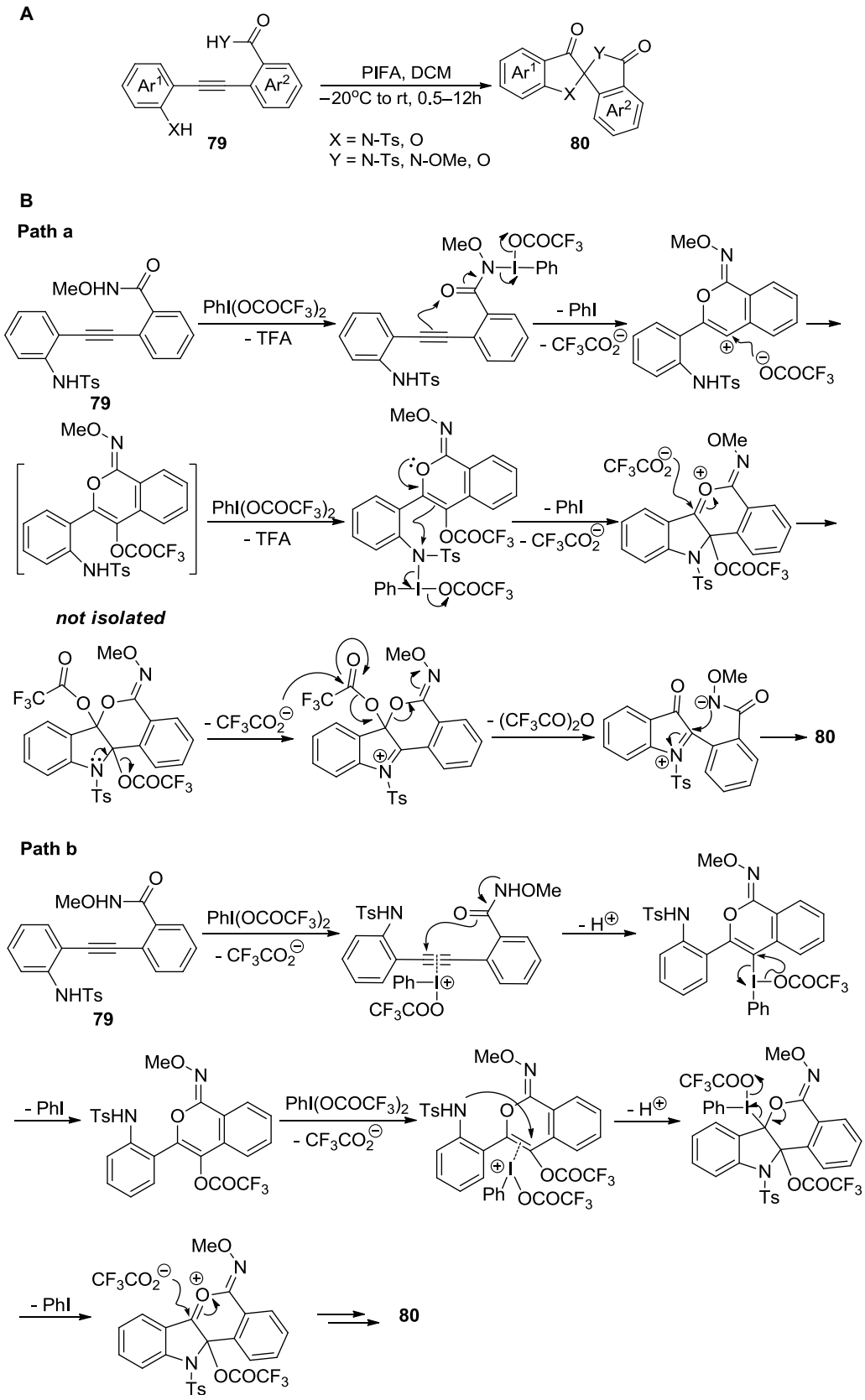

Figure 28 (**A**) PIFA-mediated conversion of internal alkynes to spiro heterocycles via cascade annulation. (**B**) Proposed mechanism.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; h, hours; DCM, dichloromethane.

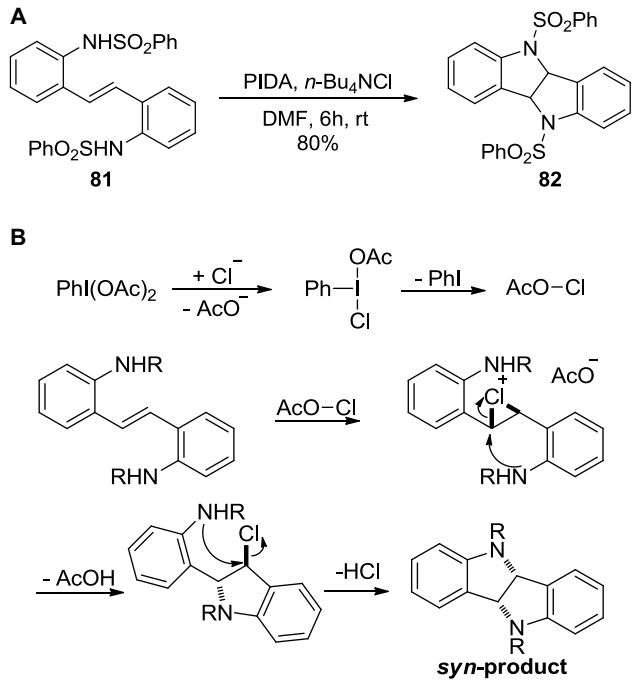

Figure 29 (**A**) PIDA-mediated synthesis of bisindolines via cascade intramolecular oxidative deamination. (**B**) Proposed mechanism.
Abbreviations: PIDA, phenyliodine diacetate; rt, room temperature; h, hours; DMF, N,N-dimethylformamide.

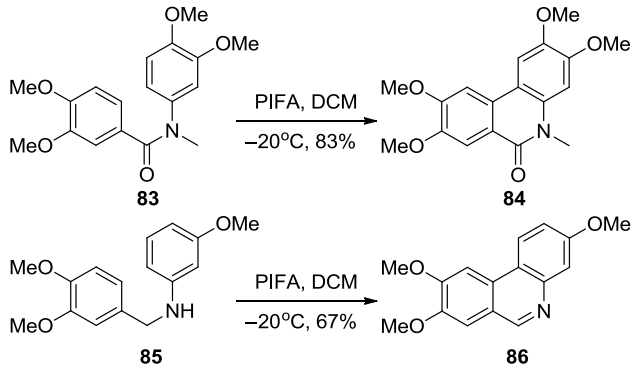

Figure 30 PIFA-mediated synthesis of benzo[*c*]phenanthridine and phenanthridinone.
Abbreviation: PIFA, phenyliodine bis(trifluoroacetate); DCM, dichloromethane.

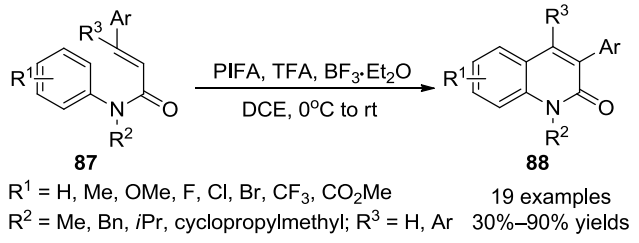

Figure 31 PIFA-mediated synthesis of 3-arylquinolin-2-ones from *N*-methyl-*N*-phenylcinnamamides through oxidative C–C bond formation/1,2-aryl migration.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; TFA, trifluoroacetic acid; DCE, 1,2-dichloroethane.

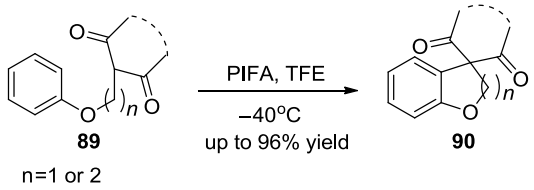

Figure 32 PIFA-mediated direct intramolecular cyclization of α-(aryl)alkyl-β-dicarbonyl compounds.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); TFE, 2,2,2-Trifluoroethanol.

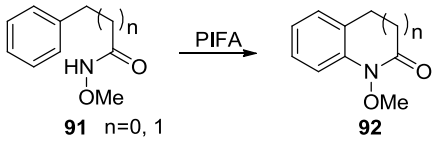

Figure 33 PIFA-mediated synthesis of *N*-aryl-*N*-methoxyamides via an intramolecular oxidative C–N bond formation.
Abbreviation: PIFA, phenyliodine bis(trifluoroacetate).

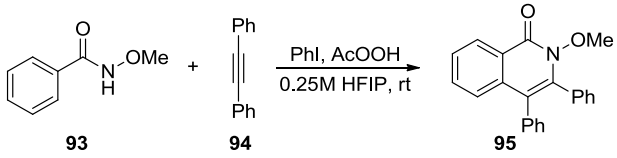

Figure 34 Synthesis of isoquinolones from *N*-methoxybenzamide and diphenyl acetylene mediated by PIDA generated in situ.
Abbreviations: PIDA, phenyliodine diacetate; rt, room temperature.

Mironov et al[80] through the reaction of glycals with PIDA in the presence of $TMSN_3$ and Ph_2Se_2 (Figure 39).

[Hydroxy-(organosulfonyloxy)iodo]arenes

Recently, Kawai et al[81] described a new method for the synthesis of biologically significant trifluoromethyl-2-isoxazoline *N*-oxides **111**. This conversion is realized through the intramolecular oxidative N–O coupling in β-trifluoromethyl-β-hydroxy ketoximes **109**, generated from trifluoromethyl-β-keto alcohols **108**, and mediated by [hydroxy(tosyloxy)iodo]benzene (Figure 40).[81]

Treatment of 2*H*-chromene **112** with [hydroxy(tosyloxy) iodo]benzene in methanol could introduce a methoxyl group at the C4 position to afford 4-methoxy-2*H*-chromene **113** (Figure 41).[82]

Benziodoxole-based hypervalent iodine reagents

During the last decade, studies on the development of the λ^3 iodine benziodoxolone reagents and their applications in facilitating organic transformations have attracted the attention of many synthetic chemists. Some representative examples are presented in this section.

In 2006, Eisenberger et al[83] reported the first use of benziodoxole-derived reagents **5a** and **6b** for CF_3 transfer.

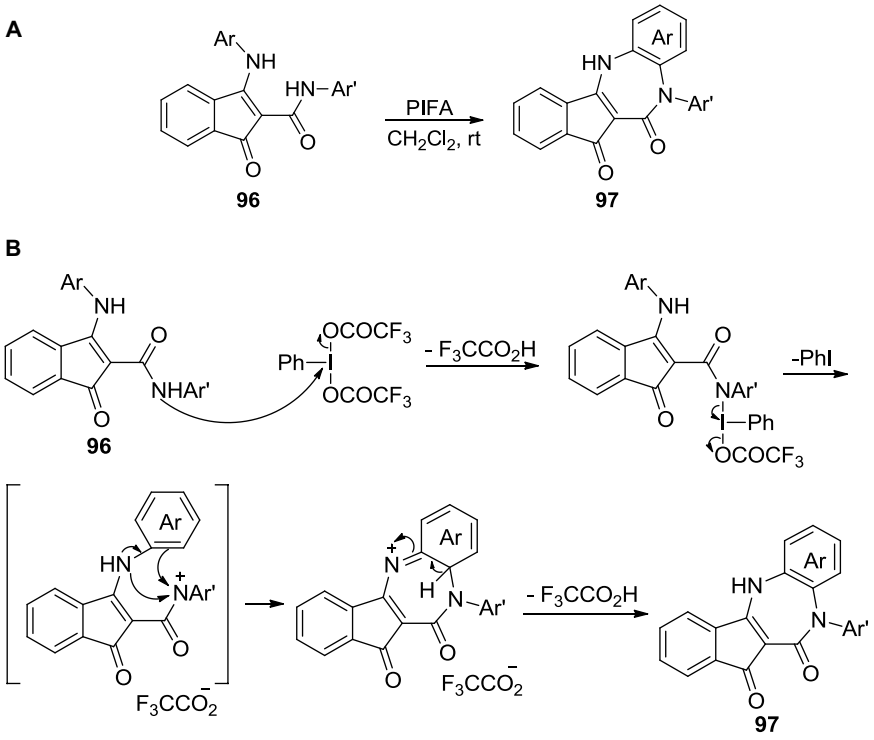

Figure 35 (**A**) PIFA-mediated synthesis of the fused indeno-1,4-diazepinones. (**B**) Proposed mechanism.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature.

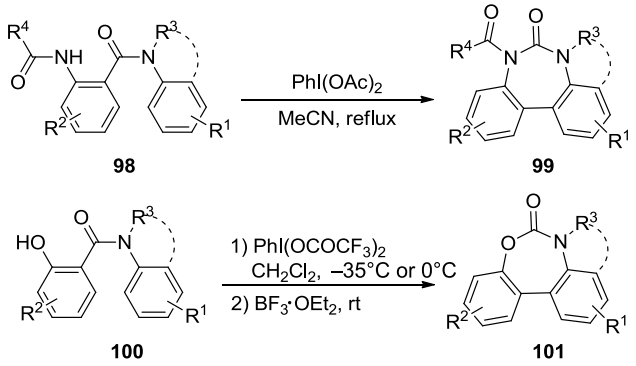

Figure 36 I (III)-mediated formation of dibenzodihydro-1,3-diazepin-2-ones and dibenzo[*d*,*f*][1,3]oxazepin-6(7*H*)-ones.
Abbreviation: rt, room temperature.

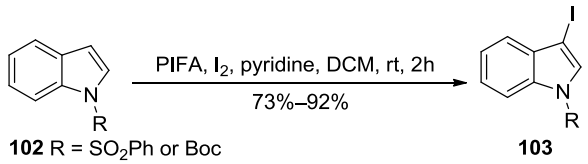

Figure 37 PIFA/I_2-mediated iodination of indole derivatives to 3-iodoindoles **103**.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; h, hours; DCM, dichloromethane.

Later on, many practical applications of this class of hypervalent iodine (III) were developed.[84,85]

In 2014, Wang et al[86] described an intramolecular carbotrifluoromethylation of alkynes **114** by using Togni's reagent in the presence of Cu(I). A variety of trifluoromethylated

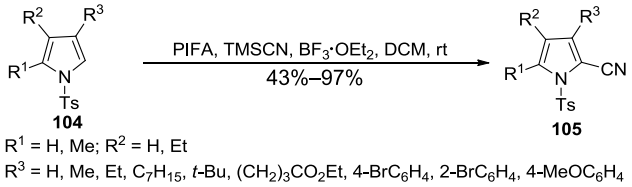

Figure 38 PIFA/TMSCN-mediated selective cyanation of *N*-tosylpyrroles at the C2 position.
Abbreviations: PIFA, phenyliodine bis(trifluoroacetate); rt, room temperature; TMSCN, trimethylsilyl cyanide; DCM, dichloromethane.

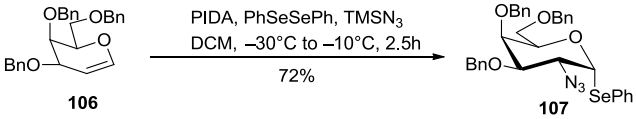

Figure 39 PIDA-mediated homogeneous azidization and selenylation of glycals.
Abbreviations: PIDA, phenyliodine diacetate; h, hours; DCM, dichloromethane.

heterocycles, such as 2*H*-chromene derivatives **115** and **117**, 1,2-dihydroquinoline derivative **116**, and the 2*H*-chromene five-membered cyclic product **118**, were synthesized with great substituent tolerance and high selectivity (Figure 42).

Due to the multiple reactive sites in indoles, trifluoromethylation of indole derivatives presents a challenge in synthetic chemistry. Shimizu et al[87] developed a direct C2-selective trifluoromethylation of indole derivatives **119** with 2-trifluoromethyl indole **120** as the product by using Togni's reagent (Figure 43). Later on, a method for the

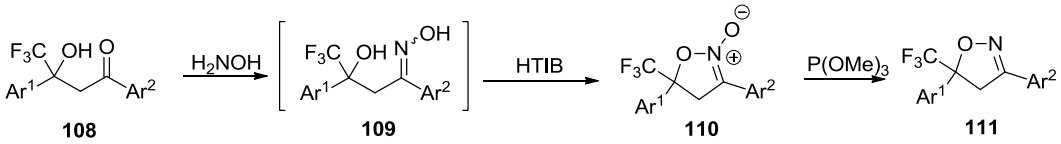

Figure 40 HTIB-mediated synthesis of trifluoromethyl-2-isoxazoline-*N*-oxides.
Abbreviation: HTIB, [hydroxy(tosyloxy)iodo]benzene.

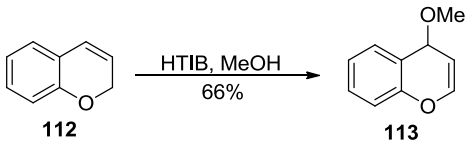

Figure 41 HTIB-mediated synthesis of 4-methoxy-2*H*-chromene.
Abbreviation: HTIB, [hydroxy(tosyloxy)iodo]benzene.

trifluoromethylation of indole compounds to afford the fused tricyclic indoles was established.[88]

In 2014, Zhang and Studer[89] reported a method for the synthesis of the biologically important 1-trifluoromethylated isoquinolines **122**. This transformation starts from the β-aryl-α-isocyano-acrylates **121** and uses Togni's reagent as the CF_3 radical precursor to afford the products in moderate-to-excellent yield, in the absence of any transition metal (Figure 44).

Recently, by using Togni's reagent and a simple catalyst CuI, Wang et al[90] reported an elegant method for the aryltrifluoromethylation of *N*-phenylcinnamamides **123**, where a series of CF_3-containing 3,4-dihydroquinolin-2(1*H*)-ones **124** were obtained regioselectively and diastereoselectively (Figure 45). The same conversion from *N*-arylcinnamamides to CF_3-containing dihydroquinolin-2(1*H*)-ones was also realized under visible light conditions.[91]

Another widely applied benziodoxole reagent is the [(triisopropylsilyl)ethynyl]benziodoxolone (TIPS-EBX) for its role in introducing alkynyl groups. Although TIPS-EBX had been prepared in 1996,[92] the first significant application was not reported until 2009 by Brand et al.[93] Direct alkynylation of indole and pyrrole heterocycles **125** was achieved with good functional group tolerance by using TIPS-EBX in the presence of gold as catalyst (Figure 46).[94]

Recently, cobalt(III)-catalyzed C2-alkynylation of indoles **128** using hypervalent iodine–alkyne reagents was reported (Figure 47).[95] This efficient protocol provided a variety of indole derivatives **129** bearing a C2 alkynyl linker, which can be connected to a series of synthetically useful functional groups such as −F, −Cl, −Br, $-CO_2Me$, or −CN.

Applying TMS-EBX in the presence of tertiary amines, a metal-free alkynylation of various heterocyclic compounds **130**–**133** can be realized under mild conditions and affords the corresponding alkynylated heterocyclic compounds **134**–**137** containing a quaternary carbon in high yields (Figure 48).[96]

In the presence of CsF, cycloaddition between the iodonium ylides **139** and the *ortho*-silyl aryltriflates **138** afforded a series of benzofurans **140** at room temperature in moderate-to-good yields (Figure 49).[97]

Aryliodonium imides in the presence of metal complexes were reported to efficiently introduce another nitrogen atom into the nitrogen-containing heterocycle compounds. Figure 50 depicts the selective addition of the imido moiety to the *N* atom of pyridine rings **141** through a Ru-catalyzed N–N bond formation.[98]

Arylation of heterocycles with diaryliodonium salts, whether at a carbon or a heteroatom, has drawn much attention from synthetic chemists. One of the most representative examples is the arylation of indole derivatives. In 2006, Deprez et al[99] developed a method to carry out arylation of indoles **144** at C2 through a palladium-catalyzed reaction using diaryliodonium salts (Figure 51). This reaction was proven to be compatible with free N–H indoles **144**, such that no by-product from *N*-arylation was observed.

As arylation using diaryliodonium salts would inevitably generate one equivalent of an iodoarene as a side product, it makes this approach unattractive with regard to atom economy. Recently, a Cu-catalyzed tandem C−H/N−H arylation of indoles **146** was discovered, which incorporated both aryl groups from the reagent diaryliodonium salts while providing novel indoles **147** (Figure 52).[100]

A significant amount of efforts have been devoted to the arylation of *N*-containing heterocycles by using diaryliodonium salts and metal catalysts. For example, a Pd-mediated arylation of benzotriazol **148** and a Cu-mediated *N*-arylation of indole **150**, cyclohexylamine **152**, and the four-membered lactam **154** were realized. Selected examples are presented in Figure 53.[101–105]

In 2013, Wang et al[106] realized a $Cu(OTf)_2$-catalyzed regioselective synthesis of polysubstituted quinolines from three components including the diaryliodonium salt **156**, the nitrile **157**, and the alkyne **158** (Figure 54). It is worth noting that the aryl group of the diaryliodonium serves as a C2 building block in this reaction.

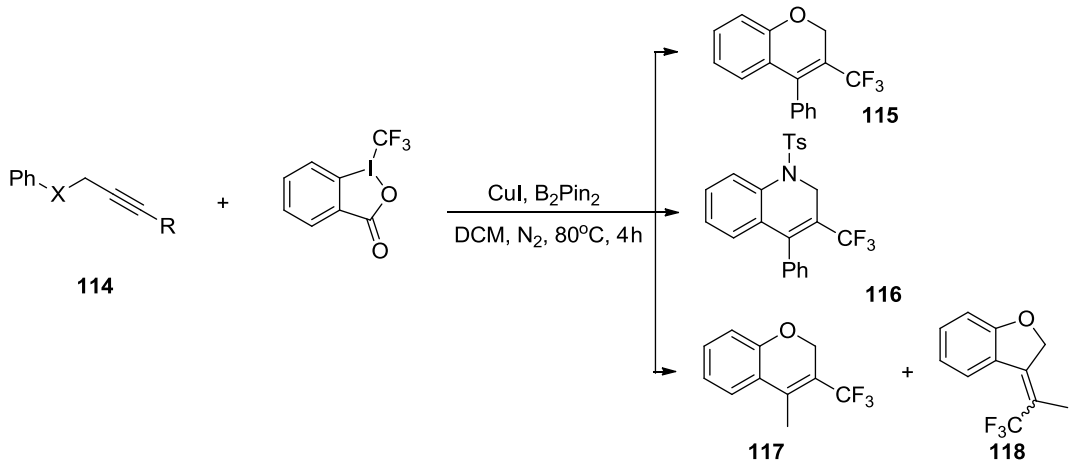

Figure 42 Intramolecular carbotrifluoromethylation of alkynes with Togni's reagent and Cu(I).
Abbreviations: h, hours; DCM, dichloromethane.

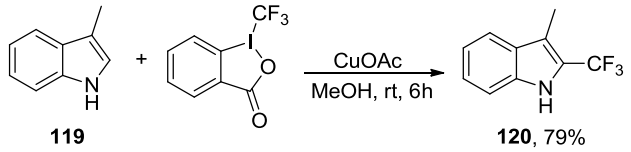

Figure 43 Trifluoromethylation of indole derivatives with Togni's reagent.
Abbreviations: rt, room temperature; h, hours.

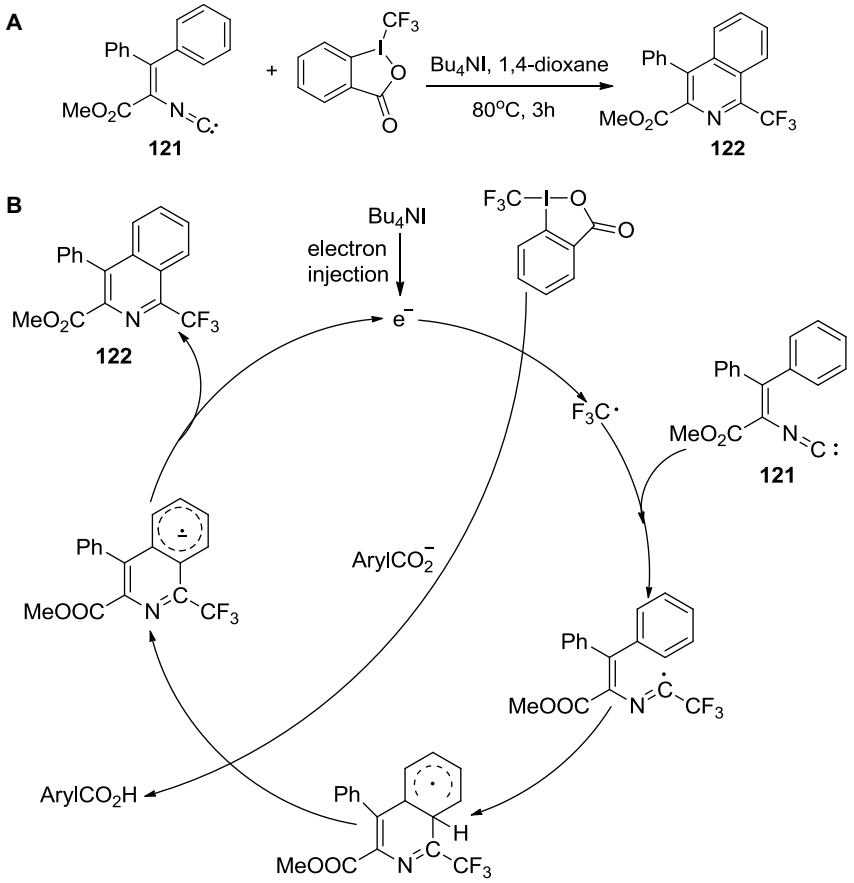

Figure 44 (**A**) Synthesis of biologically important 1-trifluoromethylated isoquinolines with Togni's reagent. (**B**) Proposed mechanism.
Abbreviation: h, hours.

Hypervalent iodine (V) reagents

Among the iodine (V) compounds, Dess–Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX) are the two most practical and therefore most widely applied oxidants for their mild characteristics. A large range of syntheses and functionalization of heterocyclic compounds have been achieved in recent years through the applications of iodine (V) reagents.

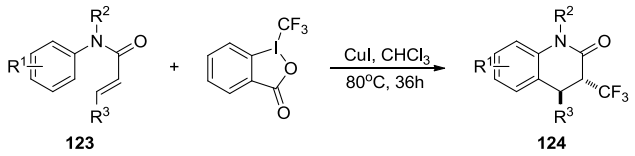

Figure 45 Aryltrifluoromethylation of *N*-phenylcinnamamides by using Togni's reagent and copper catalyst.
Abbreviation: h, hours.

Dess–Martin periodinane

DMP was first introduced in 1984.[107] The most special property of it is its ability to realize selective oxidation of primary and secondary alcohols to their respective aldehydes and ketones.[108,109] Some applications have been formulated based on this property. For example, when treated with DMP in a hydrocarbon solvent, cleavage of the glycol C–C bond in 1,2-diols **160** takes place, leading to the formation of a more complex molecule **162** (Figure 55).[110]

Another example is the synthesis of the 2-substituted benzothiazoles **164** in high yields, which is facilitated by DMP through an intramolecular oxidative cyclization of the thioformanilides **163** in CH_2Cl_2. The mild reaction environment plays a key role as the reaction proceeds via a thiol radical intermediate (Figure 56).[111]

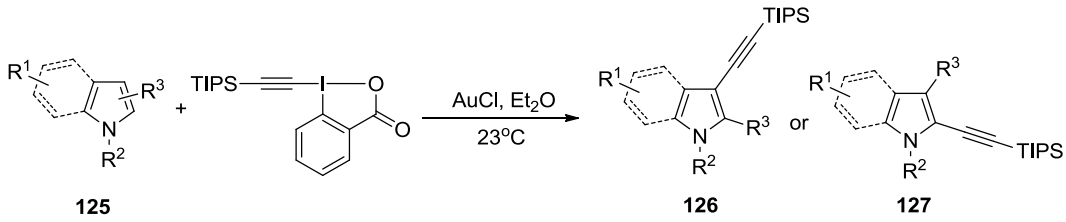

Figure 46 Direct alkynylation of indole and pyrrole heterocycles by using TIPS-EBX.
Abbreviation: TIPS-EBX, [(triisopropylsilyl)ethynyl]benziodoxolone.

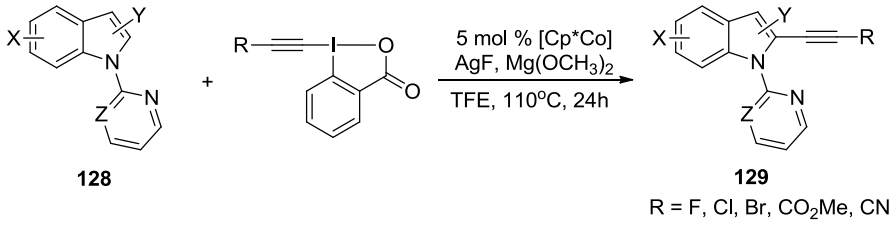

Figure 47 Selective cobalt(III)-catalyzed alkynylation of indoles using hypervalent iodine-alkyne reagents.
Abbreviations: TFE, 2,2,2-Trifluoroethanol; h, hours; Cp*, cyclopentadienyl.

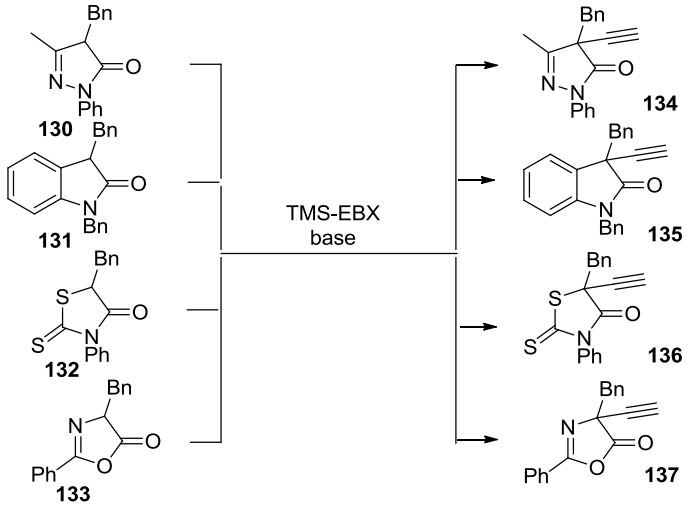

Figure 48 Metal-free alkynylation of various heterocyclic compounds with TMS-EBX.

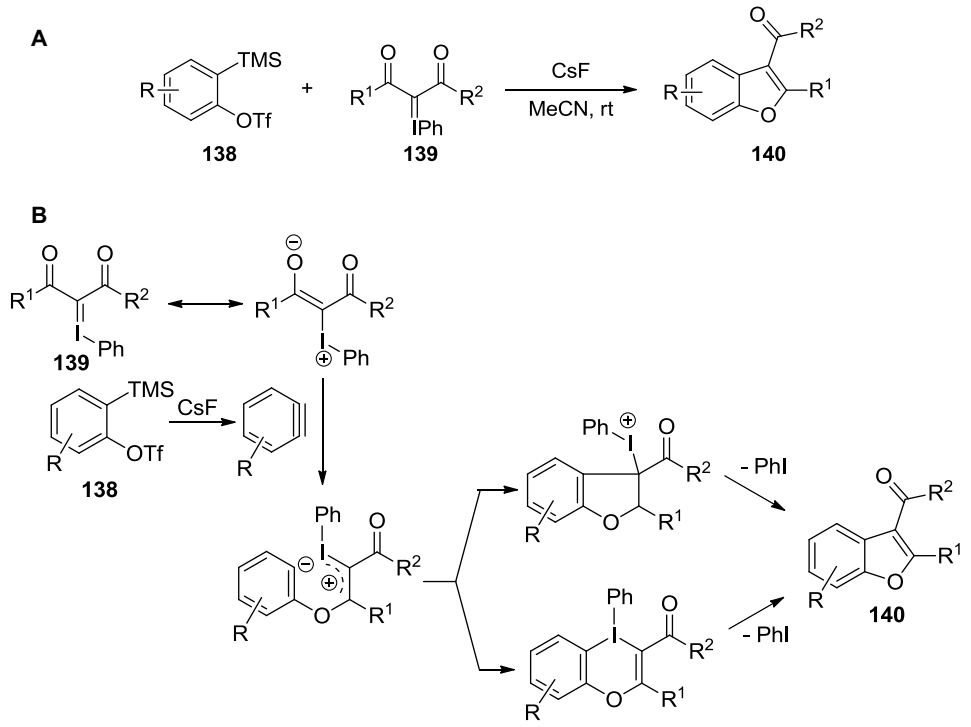

Figure 49 (**A**) Cycloaddition of *ortho*-silyl aryltriflates and iodonium ylides. (**B**) Proposed mechanism.
Abbreviation: rt, room temperature.

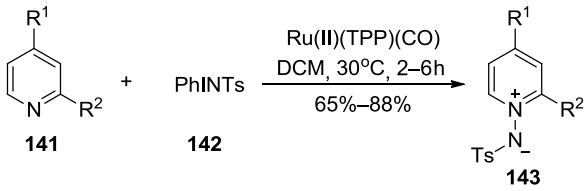

Figure 50 Ru-catalyzed nitrogen atom transfer.
Abbreviations: h, hours; DCM, dichloromethane.

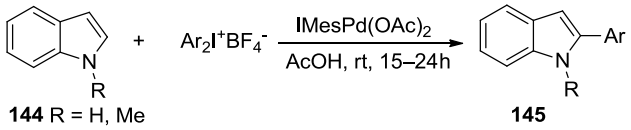

Figure 51 Diaryliodonium salts-mediated arylation of indoles at C2.
Abbreviations: rt, room temperature; h, hours.

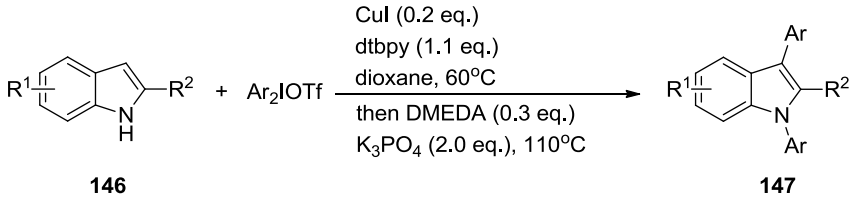

Figure 52 Cu-catalyzed tandem C–H/N–H arylation of indoles with diaryliodonium salts.
Abbreviations: eq., equivalent; DMEDA, N,N'-Dimethyl-1,2-ethanediamine.

Iodoxybenzoic acid

Certain heterocyclic compounds such as isoxazolidines, [1,2]oxazinanes, and 3,5-disubstituted isoxazolines could be synthesized through radical cyclization by using IBX as a single-electron transfer (SET) oxidant. The cyclizations brought about with this protocol could occur in an intramolecular as well as intermolecular manner.

In 2005, Janza and Studer[112] described the generation of alkoxyamidyl radicals initiated by IBX as an SET oxidant from the acylated alkoxyamines **165**. The stereoselective 5-*exo* and 6-*exo* reactions with these *N*-heteroatom-centered radicals led to the isoxazolidines **166a** and the [1,2]oxazinanes **166b** in good-to-excellent yields (Figure 57).

In 2004, Das et al[113] reported the preparation of the 3,5-disubstituted isoxazolines **169**, achieved via an SET reaction consisting of multiple components of **167** and **168** using IBX as an oxidant (Figure 58). The reaction proceeded through a substituted aldoxime intermediate followed by a 1,3-dipolar addition of an alkene.[113]

Recently, Bredenkamp et al[114] reported a new example of IBX-promoted direct functionalization of the indoles **170** to the isatins **172**. The reagent mixture **171** (NaI/IBX-SO_3K containing a substituted sulfonyl of IBX) was employed to trigger this oxidative process (Figure 59).[114]

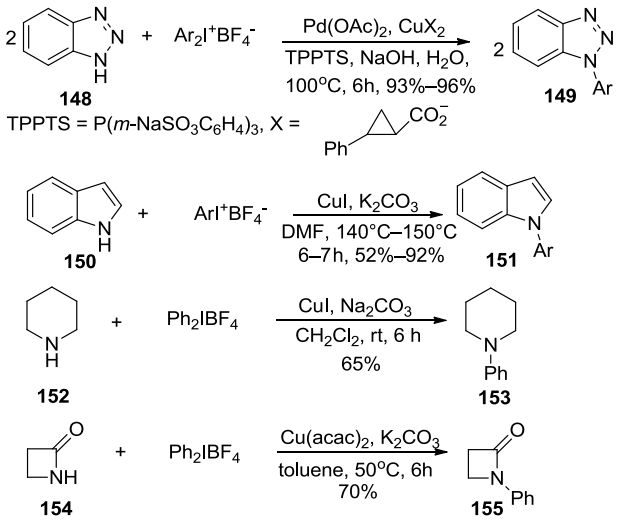

Figure 53 Arylation of *N*-containing heterocycles with diaryliodonium salts.
Abbreviations: rt, room temperature; h, hours.

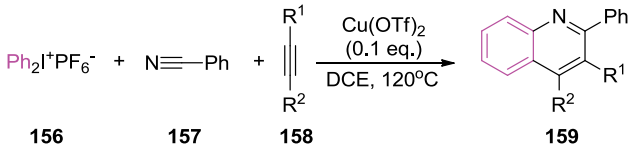

Figure 54 A $Cu(OTf)_2$-catalyzed, three-component regioselective synthesis of polysubstituted quinolones.
Abbreviations: eq., equivalent; DCE, 1,2-dochloroethane.

Conclusion

During the past several decades, hypervalent iodine reagents have been widely used in the syntheses and functionalization of heterocyles. The low production cost has made many of them commercially available, and the low toxicity, being transition metal-free, renders them environmentally friendly. But most importantly, it is their powerful oxidizing properties under mild reaction conditions along with high chemoselectivity that have driven hypervalent iodine chemistry to expand its territory in the field of synthetic chemistry.

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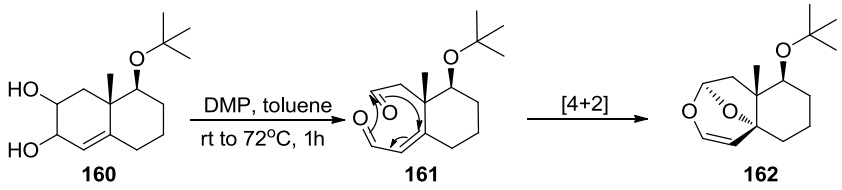

Figure 55 Oxidative cleavage of the glycol C–C bond with DMP.
Abbreviations: DMP, Dess–Martin periodinane; rt, room temperature; h, hours.

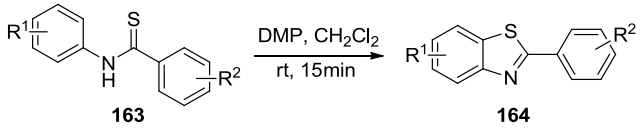

Figure 56 Synthesis of 2-substituted benzothiazoles with DMP.
Abbreviations: DMP, Dess–Martin periodinane; rt, room temperature; min, minutes.

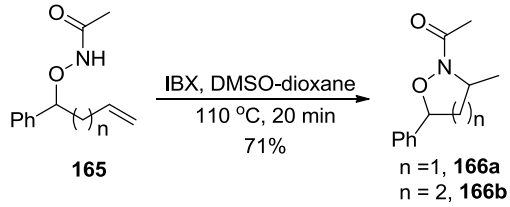

Figure 57 IBX-mediated stereoselective 5-*exo* and 6-*exo* formations of isoxazolidines and [1,2]oxazinanes.
Abbreviations: IBX, 2-iodoxybenzoic acid; DMSO, dimethyl sulfoxide; min, minutes.

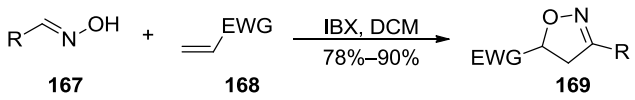

Figure 58 IBX-mediated SET synthesis of isoxazolines involving multiple components.
Abbreviations: IBX, 2-iodoxybenzoic acid; SET, single-electron transfer; DCM, dichloromethane.

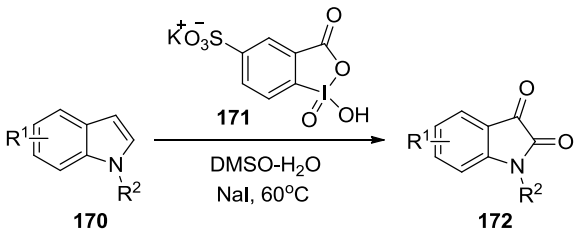

Figure 59 Direct functionalization of indoles to isatins by NaI/IBX-SO_3K.
Abbreviation: DMSO, dimethyl sulfoxide.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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