Synthesis of spirocyclic scaffolds using hypervalent iodine reagents

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Abstract
Hypervalent iodine reagents have been developed as highly valuable reagents in synthetic organic chemistry during the past few decades. These reagents have been identified as key replacements of various toxic heavy metals in organic synthesis. Various synthetically and biologically important scaffolds have been developed using hypervalent iodine reagents either in stoichiometric or catalytic amounts. In addition, hypervalent iodine reagents have been employed for the synthesis of spirocyclic scaffolds via dearomatization processes. In this review, various approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents are covered including their stereoselective synthesis. Additionally, the applications of these reagents in natural product synthesis are also covered.

Review
1. Introduction
The chemistry of spirocyclic compounds is a well established research area of organic and medicinal chemistry [1-5]. These scaffolds are common structural motifs found in various classes of naturally occurring systems [6-8]. More importantly, various natural and synthetic products containing a spirocyclic ring are currently used as commercial drugs for the treatment of several health problems [9,10]. Annosqualine (1) is an isouquinoline-cored alkaloid and it was isolated in 2004 from the stem of Annona squamosa [11] (Figure 1). Griseofulvin (2) is a spirobenzofuranone-based naturally occurring compound which was isolated from Penicillium griseofulvum in 1939 [12]. In 1959, it was launched in the market as an antifungal agent for the treatment of ringworm in human beings and animals [4,13]. Stepharine (3) is a member of the proaporphine alkaloid family and isolated from an angiosperm Stephania glabra [14]. Tofogliflozin (4) is a synthetic spirocyclic glycoside that was launched as antidiabetic agent in 2012 in Japan [15]. Rolapitant (5) is a marketed drug that was ap-
Figure 1: The structures of biologically active natural and synthetic products having spirocyclic moiety.

proved in 2015 for the treatment of nausea and vomiting [16]. Compound 6 is a spiropyrimidinetrione analogue which is currently in clinical trials for the treatment of gonorrhea [17]. There are several ways available in literature for the synthesis of spirocyclic compounds but most of them are associated either with transition metals or hypervalent iodine reagents [1-3].

Hypervalent iodine reagents provide various functional group transformation opportunities in organic chemistry. Their environment-friendly nature and mild reaction conditions makes them more attractive candidates for the replacements of various toxic metals in organic synthesis [18-31]. These reagents are more popular for their oxidizing properties [32-38] and electrophilic nature of different iodine(III) reagents has been explored to developed various synthetic transformations including rearrangements [39-62]. Hypervalent iodine chemistry has now become a well-established research area and various book chapters [19,20,27] and review articles [21-24,31-35,60,63,64] appeared to explain the chemistry of these reagents. In the past two decades, a number of organic chemists used these reagents for the construction of a variety of spirocyclic scaffolds. In 2008, Quideau and co-workers published a nice review article where they have described various spirocyclization reactions using hypervalent iodine reagents via deoxidations of aromatic phenolic species [32]. This review article is quite useful for readers who want to know the chemistry involved during the dearylation of phenols and to find the relevant literature available until 2008. In this review article, various approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents are covered including stereoselective reactions.

Hypervalent iodine reagents are mainly popular for their oxidative properties but various iodine(III) reagents have been used as electrophiles. Numerous iodine(III) reagents have been successfully used to achieve diverse spirocyclic scaffolds. Phenols 7 or 11 having an internal nucleophile at ortho- or para-position can be used as starting material for the synthesis of ortho- and para-spiroyclic compounds in the presence of iodine(III)-based electrophiles (Scheme 1). Phenolic oxygen of compound 7 attacks to the iodine of 8 to form intermediate 9. Furthermore, on nucleophilic attack of the internal nucleophile to the ortho-position intermediate 9 converts to ortho-spiroyclic compound 10 with the elimination of the hypervalent iodine moiety. Similarly, para-spiroyclic compounds 13 can be achieved starting from compounds 11 and iodine(III) reagent 8 (Scheme 1). The synthesis of spirocyclic compounds can be achieved using stoichiometric or catalytic amounts of iodine(III) reagents. According to literature reports, both heterocyclic and carbocyclic spirocyclic compounds can be achieved using these reagents [27,32].

2. Synthesis of spirilactones
2.1. Using stoichiometric amounts of iodine(III) reagents

The history of the utility of hypervalent iodine reagents in the synthesis of spirocyclic compounds is going to become quite old now. Initially, iodine(III) reagents were applied for synthesis of spirocyclic in 1990s [65,66]. In 1991, Kita and co-workers [67] established the synthesis of spirohexadiones from N-acyltryramines using iodine(III) reagent. After these reports, numerous hypervalent iodine-mediated spirocyclizations were investigated and phenolic oxidations of substrates
have been explored for the construction of spirodienone motifs [21,64].

In 1993, Wipf and Kim [68] employed PIDA (15) for spirocyclization of N-protected tyrosine 14 to spirolactone 16. The spirocyclization reaction was carried out in methanol using stoichiometric amounts of PIDA (15) and spirolactone 16 was isolated in 35% yield (Scheme 2). Probably, the cyclization reaction proceeded via dearomatization of phenolic substrate 14 followed by nucleophilic attack of the carbonyl moiety of carboxylic group.

Furthermore, Giannis and co-workers [69] reported the synthesis of novel aminomethylpolystyrene-supported (di-acetoxyiodo)benzene (PSDIB) reagents 17a and 17b starting from aminomethylated polystyrene with 4-iodobenzoic acid and 4-iodophenylacetic acid in two steps (Figure 2).

Both polymer-supported reagents 17a and 17b were used in similar spirocyclizations of tyrosine 14. Both tyrosine 14a and N-protected tyrosine derivatives 14b,c were used as starting material and results of their spirolactonization are summarized in Table 1 (Scheme 3).

Numerically, Giannis and co-workers [69] reported the synthesis of novel aminomethylpolystyrene-supported (di-acetoxyiodo)benzene (PSDIB) reagents 17a and 17b starting from aminomethylated polystyrene with 4-iodobenzoic acid and 4-iodophenylacetic acid in two steps (Figure 2).

The spirolactonization products 16 were isolated in excellent yields when reactions were performed with substrates 14
Table 1: Spirolactonization of substrates 14 to spirolactones 16 using polymer-supported reagents 17a and 17b.

| entry | substrate 14 | PS-iodine(III) reagent | 16 yields (%) |
|-------|--------------|------------------------|---------------|
| 1     | 14a: R = NH₂  | 17a                    | 82            |
| 2     | 14a: R = NH₂  | 17b                    | 80            |
| 3     | 14b: R = Cbz-NH | 17a          | 25            |
| 4     | 14b: R = Cbz-NH | 17b          | 26            |
| 5     | 14c: R = Boc-NH | 17a          | 24            |
| 6     | 14c: R = Boc-NH | 17b          | 25            |

(R = NH₂) having free amino group (Table 1, entries 1 and 2). Notably, the poor yields were observed during the spirolactonization of N-protected tyrosine derivatives 14b and 14c (Table 1, entries 3–6). The advantage of this reaction is that the polymer-supported reagent can be regenerated and reused without loss of any significant activity [69].

In 2010, Kita and co-workers [70] developed another approach for PIDA-mediated spirolactonization of 1-(p-hydroxyaryl)cyclobutanols 18 to spirolactones 19 in good yields (Scheme 4). The reaction was initiated with formation of an intermediate 20 by the oxidation of the phenolic hydroxy group of 18, which rearranged to compound 21. Furthermore, water attacks the ketone moiety of 21 to form para-substituted phenol 22. The phenolic intermediate 22 is further oxidized with another molecule of PIDA (15) to form intermediate 23, which yielded the final product 19 on intramolecular cyclization [70].

Furthermore, Kita and his research group [71] reported an iodine(III)-mediated cyclization of arylalkynes 24 to spirocyclic products 26 by in situ-generated active hypervalent iodine species. In this report, para-substituted esters 24 were cyclized to corresponding spirolactones 26 using stoichiometric amount of bis(iodoarene) 25 with terminal oxidant mCPBA in the presence of TsOH·H₂O in TFE (Scheme 5). In this reaction, active hypervalent iodine species was generated in situ by the oxidation of bis(iodoarene) 25 using mCPBA as terminal oxidant.

In 2011, Kita and co-workers [72] investigated a more reactive µ-oxo bridged hypervalent iodine(III) reagent used in the spirocyclization of phenolic substrates 27 to spirolactones 29. The reaction products were obtained in excellent yields using 0.55 equivalents of bridged iodine(III) reagent 28 in acetonitrile at room temperature (Scheme 6). Furthermore, a comparative study was done between bridged iodine(III) reagent 28 with PIFA. It was found that the reaction products 29 were obtained in higher yield using the bridged iodine(III) reagent compared to that using PIFA. Probably, the iodine-OCOCF₃ bond of the bridged compound 28 has a significant ionic character as

![Scheme 4: PIDA-mediated spirolactonization of 1-(p-hydroxyaryl)cyclobutanols 18 to spirolactones 19.](image-url)
Scheme 5: Iodine(III)-mediated spirocyclization of aryl alkynes 24 to spirolactones 26 by the reaction with bis(iodoarene) 25 in the presence of mCPBA.

| R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | mCPBA (1.1 equiv) |
|------------|------------|------------|-----------------|
| H, OMe     |            |            | 86–99%          |

6 examples
R<sup>1</sup> = H, OMe; R<sup>2</sup> = Me, t-Bu, Cl; R<sup>3</sup> = Ph, 4-OMeC<sub>6</sub>H<sub>4</sub>

Scheme 6: Bridged iodine(III)-mediated spirocyclization of phenols 27 to spirodienones 29.

| R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | OCOCF<sub>3</sub> |
|------------|------------|------------|-----------------|
| H, OMe, Me, Br | R<sup>2</sup> = H, Me; R<sup>3</sup> = H, Me | 80–99% |

8 examples
R<sup>1</sup> = H, OMe, Me, Br; R<sup>2</sup> = H, Me; R<sup>3</sup> = H, Me

the iodine–oxygen bond distance is larger than in PIFA which intends to make it more reactive than PIFA.

PIFA (31) is a more electrophilic iodine(III) reagent than PIDA (15) due to the presence of two trifluoroacetoxy groups. There are some approaches for the synthesis of spirocyclic compounds where PIFA (31) is used as electrophile.

Recently, Lewis and co-workers [73] reported the conversion of arnottin I (30) to its spirocyclic analogue arnottin II (32) by reaction with LiOH followed by PIFA (31). The spirocyclic product arnottin II (32) was isolated in 56% yield (Scheme 7). This approach is based on a tandem oxidative deaomratization process and will be quite useful for the conversion of functionalized benzocoumarins to spirocyclic lactones.

In 2015, Du and co-workers [74] reported a spirocyclization of diarylacetylenes to fused spiro polycyclic compounds through a hypervalent iodine-mediated cascade annulation reaction. In this reaction, the Lewis acid BF<sub>3</sub>·Et<sub>2</sub>O acts as catalyst which activates the substrate. A further treatment with PIDA (15) forms the spirocyclic products through intramolecular cyclization.

Scheme 7: Iodine(III)-mediated spirocyclization of arnottin I (30) to its spirocyclic analogue arnottin II (32) using stoichiometric amount of PIFA (31).

1. LiOH·H<sub>2</sub>O, THF/MeOH/H<sub>2</sub>O (3:1:1), 50 °C, 2 h
2. PIFA (31), HFIP, 0 °C, 12 h

32: 56%
2.2. Using hypervalent iodine reagents as catalyst

The hypervalent iodine-catalyzed synthesis of spiroyclic compounds can be achieved either by using catalytic amounts of a hypervalent iodine species or by generation of a similar active catalytic species in situ by the oxidation of iodoarene using a terminal oxidant. More commonly, m-chloroperbenzoic acid (mCPBA) and oxone are used as oxidant to generate the hypervalent iodine species in situ via oxidation of iodoarenes. In 2014, Singh and Wirth have compiled a review article where they have covered various aspects of hypervalent iodine catalyzed reactions [75].

In 2005, Kita and his research group investigated a hypervalent iodine-catalyzed spirocyclization reaction by generating the catalytic hypervalent iodine species via in situ oxidation of iodoarene using mCPBA as terminal oxidant [76]. In this report, p-substituted phenols 27 were cyclized to the corresponding spirolactones 29 using iodotoluene 33 as precatalyst, mCPBA as oxidant and TFA as an additive. The spirolactones 29 were isolated as reaction products in excellent yields (Scheme 8). Probably, the iodine(III) species was generated in situ as the active catalytic species that was playing the key role for the dearomatization of phenol. In addition, a similar reaction was also achieved by using various PIFA analogues as catalyst directly in the presence of 1.5 equivalents of mCPBA. Since this report, several iodine(III)-catalyzed oxidative spirocyclization reactions have been successfully developed.

In 2009, Ishihara and co-workers [77] developed an oxylactonization of ketocarboxylic acid 34 to spirolactone 36 using 10 mol % of iodobenzene (35) as precatalyst, 20 mol % of TsOH·H₂O as additive and 1.8 equivalents of mCPBA as oxidant. The catalytic reaction was carried out in nitromethane at 50 °C for 23 h and spirolactone 36 was isolated in 74% yield (Scheme 9). It was noted that 20 mol % of additive was essential to initiate the reaction efficiently. The reaction was quite slow when 10 mol % of additive was used. Once again, iodine(III) species was generated in situ which was probably working as active catalytic species.

2.3. Stereoselective synthesis of spirolactones

Recently, Kita and co-workers [78] reported a new type of biphasyl-based chiral iodine(III) species 38 and its efficient utilization in the spirocyclization of naphthols containing carboxylic acids. 1-Naphthol-2-propionic acids 37 were cyclized to corresponding spirolactone derivatives 39 using chiral-8,8'-diiodonaphthyl reagent 38 as precatalyst, mCPBA as an oxidant in chloroform at low temperature. The reaction products 39 were isolated in good yields with more than 78% enantiomeric excess (Scheme 10). The active catalytic hypervalent iodine species was generated in situ by oxidation of optically active iodoarene 38 using mCPBA as an oxidant.

2.4. Application of spirolactones in natural products synthesis

In 2005, Wipf and Spencer [79] reported the first total synthesis of the Stemona alkaloid (−)-tuberostemonine (40). In this report, PIDA (15) was used as an electrophile for the synthesis of spirolactone 16 in 35% yield by the cyclization of L-tyrosine 14 in nitromethane at room temperature for 2.5 h (Scheme 11).
3. Synthesis of spirolactams

3.1. Using stoichiometric amounts of iodine(III) reagents

In 1998, Ciufolini and co-workers [80] reported the oxidative cyclization of tyrosine derivatives to spirolactams using iodine(III) reagents. In this reaction, oxazoline derivatives 41 were cyclized to spirocyclic products 42 using PIDA (15) as an electrophile in trifluoroethanol at room temperature for 30 minutes. The desired products 42 were isolated in moderate yields (Scheme 12).

Additionally, the same research group [81] reported the oxidative cyclization of a phenolic substrate to a spirolactam using PIDA as electrophile. In this methodology, oxazoline 43 was cyclized to spirolactam 44 in 50% yield using PIDA (15) in trifluoroethanol at room temperature (Scheme 13). Furthermore, spirolactam was used as intermediate in the synthesis of tricyclic compound 43 possessing a similar structure like that of the naturally occurring heterocyclic compound FR901483 [82].

Wardrop and co-workers [83] developed a new method for the preparation of 1-azaspiranes 47 by treatment of α- and β-substituted 3-(methoxyphenyl)-N-methoxypropionamides 46 with [bis(trifluoroacetoxy)iodo]benzene (PIFA, 31) in dichloro-
methane (Scheme 14). The reactions were carried out at low temperature and spiro lactams 47 were achieved in high yields with up to 96% enantiomeric excess. Furthermore, these compounds have been employed as important synthetic intermediates for the construction of biologically active molecules such as histrionicotoxins and the cytotoxic marine alkaloid fasicularin [84].

In 2010, Honda [85] reported the synthesis of isoquinoline alkaloids possessing spirocyclic framework using PIDA (15) as an electrophile in hexafluoroisopropanol solvent. The $p$-substituted phenolic compound 48 was used as starting material for the construction of spiro lactam 49 in 69% yield (Scheme 15). This is an important intermediate in the synthesis of various naturally occurring alkaloids such as TAN1251A, TAN1251C and TAN1251D [86].

Wardrop and Burge [87] reported a iodine(III)-mediated oxidative spirocyclization of hydroxamates 50. The azaspirans 51 containing quaternary carbon centers were synthesized in good to excellent yields on treating substrates 50 with PIFA (31) in dichloromethane/methanol (1:1, Scheme 16). The reaction products (spiro lactams 51) were obtained as inseparable mixture of anti- and syn-diastereomers.

Haroutounian and co-workers [88] investigated a PIFA-mediated synthesis of spirocyclic lactam 54 as side product by treating substrate 52 with 1.5 equivalents of PIFA (31) in presence of 3.0 equivalents of TFA as an additive in dichloro methane (Scheme 17). The fused tricyclic compound 53 was obtained as major product in 55% yield along with the spiro compound 54 as a minor product in 8% yield.

In 2009, Zhang and co-workers [89] reported an efficient method for the synthesis of spiro $\beta$-lactams via oxidative dearomatization reactions. In this report, the synthesis of spiro $\beta$-lactams 56 were achieved successfully by the oxidative cyclization of $p$-substituted phenols 55 using PIDA (15) as an electrophile and copper(II) sulfate pentahydrate as an additive in the presence of DMAP base. The spirocyclization reactions were performed in MeOH for 2 h at 0 °C and spirocyclic products 56 were isolated in good yields (Scheme 18). Additionally, fused bicyclic compounds 57 were also observed in few reactions in traces. The structure of the spiro $\beta$-lactam was confirmed by single crystal X-ray crystallography.
Dong and co-workers [90] developed a novel way for the synthesis of five-membered spiro pyrazolin-5-ones using amide and amine-containing precursors. Herein, five-membered azaheterocyclic derivatives were synthesized efficiently in presence of PIFA and with TFA as an additive.

Furthermore, Kita and his research group [71] displayed a method for the cyclization of alkyne derivative 58 to spiro lactam 59 by an in situ-generated active hypervalent iodine species. In this method, para-substituted amide 58 was cyclized to the corresponding spiro lactam 59 in 92% yield using a stoichiometric amount of bis(iodoarene) 25 with the terminal oxidant mCPBA in the presence of TsOH·H₂O in TFE (Scheme 19).

In 2012, Zhao and co-workers [91] developed a new approach for the construction of spirooxindoles 61 through tandem cascade oxidation of substituted anilides 60. In this methodology, anilide derivatives 60 were reacted with [bis(trifluoroacetoxy)iodo]benzene (31, PIFA) in TFE at room temperature to afford functionalized lactams 61 in good yields (Scheme 20). Various electron-donating and withdrawing groups at the phenyl ring in anilides were successfully tolerated.

Furthermore, Sunoj and Sreenithya [92] developed a metal-free approach for the synthesis of 1,1'-dimethyl-3,3'-spirobi[indoline]-2,2'-dione (61) from N₁,N₃-dimethyl-N₁,N₃-diphenylmalonamide (60) using PIFA (31) in trifluoroethanol at room temperature. The spiro lactam 61 was isolated in 75% yield.
Scheme 19: Iodine(III)-mediated spirocyclization of para-substituted amide 58 to spirolactam 59 by the reaction with bis(iodoarene) 25 in the presence of mCPBA.

Scheme 20: Iodine(III)-mediated synthesis of spirolactams 61 from anilide derivatives 60.

(Scheme 21). According to the proposed mechanistic pathway, the reaction was initiated with formation of an intermediate 63 by the attack of the carbonyl oxygen to electrophilic iodine(III) reagent 31 which could be rearranged to compound 64. Finally, the acetate anion attacks the β-hydrogen of 64 to form spirolactam product 61.

Scheme 21: PIFA-mediated oxidative cyclization of anilide 60 to bis-spirobisoxindole 61.
In 2014, Xu and Abdellaoui [93] reported a nucleophilic intra-molecular cyclization of phenylacetamides 65 to spirocyclic lactams 66 via iodine(III)-mediated spirocarbocyclizations. In literature, there are limited methods available for the synthesis of spiro-β-lactam-3-carbonitrile which is widely used as an antibiotic [94]. In this methodology, N-(p-hydroxyphenyl)cyanoacetamides 65 were cyclized to corresponding 4-spiro-β-lactam-3-carbonitriles 66 in useful yields using PIDA (15) as an electrophile in the presence of KOH as base in anhydrous ethanol at room temperature (Scheme 22).

In 2014, Fan and co-workers [95] investigated an efficient approach for the synthesis of a spirocyclic-skeleton-containing dieniminium moiety. Herein, arylamines 67 were cyclized to spirocyclic dieniminium salts 68 using PIFA (31) as an electrophilic species in nitromethane (Scheme 23). All the reactions were completed within a minute and desired lactams were isolated in good yields. The presence of electron-withdrawing groups at the aromatic ring shows a negative effect on the yield while the presence of electron-enriched groups afforded the products 68 in high yields.

In addition, Zhu and co-workers [96] developed another hypervalent iodine-mediated intermolecular spirocarbocyclization approach for synthesis of spirolactam. In this approach, N-methoxybenzamide 69 and diphenylacetylene (70) were treated in presence of PIFA (31) in dichloromethane to corresponding spirodienone compound 71 in 48% yield (Scheme 24). Additionally, trifluoroacetic acid (TFA) was used as an additive in the reaction.

In 2015, Wang’s group [97] reported an iodine(III)-mediated approach for the intermolecular spirocyclization of amides 72 with sulfonylhydrazides 73 to spirolactams 75. In this method,
functionalized amides 72 containing an alkyne moiety and sulfonylhydrazides 73 undergo intermolecular spirocyclization in presence of I$_2$O$_5$/TBHP oxidative system to give the sulfonated spirolactams 75 in high yields (Scheme 25). This oxidative system found to be more efficient and could sustain the presence of diverse functional groups. The structure of 75 was confirmed by single crystal X-ray crystallography.

3.2. Using hypervalent iodine reagents as catalysts

In 2007, Kita and co-workers [98] investigated the first iodoarene-catalyzed spirocyclization of functionalized amides 76 to spirocyclic systems 77 by carbon–nitrogen bond formation using 10 mol % of iodotoluene 33 as precatalyst, 1.0 equivalent of CF$_3$COOH as an additive and mCPBA as terminal oxidant in trifluoroethanol (Scheme 26). The spirocyclic compounds 77 were isolated in high yields. The cyclization reaction was probably initiated by in situ generated active iodine(III) species by the oxidation of iodotoluene 33 in the presence of mCPBA.

In 2010, Zhu’s research group [99] achieved a Pd-catalyzed synthesis of spirolactams 80 by the cyclization of functionalized amides 78 using 10 mol % PdCl$_2$ (79) in presence of Ph(OAc)$_2$ (15) in acetonitrile solvent at 80 °C. The spirocyclic products 80 were obtained in moderate yields (Scheme 27). It was observed that the introduction of electron-donating group at para-position in substrates 78 gave the desired products in good yields whereas introduction of strong electron with-
Kita and co-workers [100] developed another catalytic approach for the cyclization of amides 76 to spirolactams 77. In this approach, 2 mol % of bis(iodoarene) 81 was used as precatalyst and peracetic acid (PAA) as an oxidant instead of mCPBA, which plays an important role in generation of active iodine(III) species. The bis(iodoarene) 81 was oxidized to a unique μ-oxo-bridged hypervalent iodine(III) species in situ, wherein PAA is used as extremely green oxidant which releases non-toxic co-products (Scheme 28).

In 2011, Yu and co-workers [101] developed an intramolecular lactonization of p-substituted phenols 82 to spirooxindoles 83 using 10 mol % of iodobenzene (35) as precatalyst, mCPBA as an external oxidant and TFA as additive. All the catalytic reactions were performed in dichloromethane and spirolactams 83 were isolated in good to excellent yields (Scheme 29). It was noted that mCPBA/TFA combination did not work well for some transformations and it was replaced with oxidant urea·H₂O₂ and TFAA as an additive.

3.3. Stereoselective synthesis of spirolactams

Gong and co-workers [102] efficiently cyclized 1-hydroxy-N-aryl-2-naphthamides 84 to corresponding spirolactam derivatives 86 using chiral iodoarene 85 as a catalyst, mCPBA as an oxidant and TFE as an additive. The presence of 10.0 equivalents of H₂O₂ was required to get the reaction products in high yields with up to 92% ee (Scheme 30). The chiral hypervalent-λ³-iodanes were generated in situ by the oxidation of the chiral C₂-symmetric iodoarene 85 that was playing the key role for the oxidative spirocyclization of phenols.

In addition, N-methyl-N-(2-naphthyl)-2-naphthamides 87 were also cyclized to corresponding spiro compounds 88 in high yields and with up to 84% enantiomeric excess (Scheme 31). Furthermore, the absolute configuration of 88 was assigned by its single crystal X-ray analysis.

3.3. Application of spirolactams in natural product synthesis

In 2001, Ciufolini and co-workers [103] employed PIDA (15) as an electrophile during the synthesis of naturally occurring tricyclic azaspirane derivative TAN1251C. In this report,
Scheme 30: Iodine(III)-mediated asymmetric oxidative spirocyclization of phenols 84 to spiro lactams 86 using chiral iodoarene 85 as precatalyst.

Scheme 31: Iodine(III)-catalyzed asymmetric oxidative spirocyclization of N-aryl naphthamides 87 to spirocyclic compounds 88 using chiral iodoarene 85 as precatalyst.

Scheme 32: Cyclization of p-substituted phenolic compound 89 to spirolactam 90 using PIDA (15) in TFE.

Phenolic 3-arylpropionamide 89 was cyclized to spirolactam 90 in 41% yield using PIDA (15) as an electrophile in the presence of NaHCO₃ in trifluoroethanol (TFE) at room temperature followed by addition of acetic anhydride and pyridine in the presence of 10 mol % DMAP (Scheme 32). In addition, spirocyclic product 90 was used as key precursor in the synthesis of naturally occurring tricyclic azaspirane derivative TAN1251C 91 in a sequence of steps.
Furthermore, PIDA (15) was used as an electrophile during the synthesis of biologically active molecule FR901483 by the same research group [104]. In this report, spirocyclic oxazoline 93 was prepared by starting from para-substituted phenolic compound 92 under the reaction conditions mentioned in Scheme 32 (Scheme 33).

In 2002, Honda and co-workers [105] reported the synthesis of naturally occurring (−)-TAN1251A (95) employing an oxidation of phenols via an dearomatization process. In this report, para-substituted phenolic compound 48 was cyclized to spirocyclic lactam 49 using PIDA (15) as an electrophile. The spirocyclic compound 49 was achieved in 69% yield (Scheme 34). Additionally, synthesized spirocyclic compound 49 was converted to natural product 95 in few chemical steps.

4. Synthesis of spirocarbocycles

4.1. Using stoichiometric amounts of iodine(III) reagents

Furthermore, O-silylated phenolic compound 96 was spirocyclized to spirocarbocyclic compound 97 in 95% yield using bridged iodine(III) reagent 28 as an electrophile and trifluoroethanol (TFE) as the solvent at room temperature (Scheme 35). Compound 97 was further used as substrate for the synthesis of discorhabdin alkaloids [106,107].

In 1996, Kita and co-workers [108] developed an intramolecular cyclization of ortho-substituted phenols 98 to aza-spirocarbocyclic compounds 101 via hypervalent iodine-mediated spirocarbocyclization reactions using 31 as an electrophile. In this methodology, ortho-substituted phenolic derivatives 98 were
Like PIDA and PIFA, Koser reagents are other iodine(III) reagents known to behave as electrophiles. In 2000, Spyroudis and co-workers [109] reported the spirocyclization of para-substituted phenols 102 to corresponding spirocarbocyclic derivatives 104 via dearomatization process using Koser reagent. In this reaction, substrates 102 were reacted with a stoichiometric amount of [(hydroxy)(tosyloxy)iodo]benzene (103) in dichloromethane at 0 °C. The spirocyclic products 104 were obtained in poor yields (Scheme 37).

Furthermore, Kita and his research group [71] reported the synthesis of spirocarbocyclic compounds 106 from arylalkynes 105 using a hypervalent iodine reagent generated in situ by the oxidation of bis(iodoarene) 25 in the presence of mCPBA as an terminal oxidant (Scheme 38).
Wang and co-workers [110] developed a hypervalent iodine-mediated synthesis of ortho-spirocarbocyclic compounds via dearomatization of ortho-substituted phenols. In this reaction, ortho-substituted phenols 107 were cyclized to form spirocarbocyclic compounds 109 in useful yields. All the reactions were performed in a CF₃CH₂OH/CH₂Cl₂ (1:1) solvent combination using PIDA (15) as an electrophile at −40 °C for 10–15 minutes (Scheme 39). This is an example of an ortho-oxidative phenol dearomatization reaction wherein there is the formation of the steriogenic center at the spiro-ring junction. This approach provides an easy and direct method for the construction of ortho-spirocarbocyclic compounds which is broadly found to originate in most of bioactive natural products [111,112].

4.3. Application of spirocarbocyclic compounds in natural product synthesis

In 2003, Kita and co-workers [113,114] employed an iodine(III) reagent during the total synthesis of sulfur-containing alkaloid 112. Initially, the substrates 110 were cyclized to spirodienone derivatives 111 in useful yields using PIFA (31) as source of electrophile in trifluoroethanol at room temperature (Scheme 40). Furthermore, synthesized compounds 111 were converted into the natural product discorhabdin A (112).

In 2006, Honda and co-workers [115] reported the total synthesis of spiro-isoquinoline alkaloid (±)-anosqualine (1). In this report, the substrate 113 was cyclized to form spirocyclic compound 114 via desilylation with TBAF in THF followed by reaction with n-BuLi in hexafluoroisopropanol using PIDA (15) at 4 °C (Scheme 41). This oxidative cyclization of enamide substrate 113 afforded synthetically useful spiroenamide 114, which was used as key intermediate for total synthesis of anosqualine (1). The synthesis of natural product 1 was achieved in two steps starting from synthesized compound 114.

Honda and Shieghisa [116] reported the total synthesis of naturally occurring compound stepharine (3) starting from aro-
matic aldehyde 115. Initially, substituted phenolic compound 116 was prepared in seven steps from aldehyde 115. Furthermore, the synthesized compound 116 was converted into the natural product stepharine (3) by reaction with PIDA (15) in trifluoroethanol (TFE) followed by the reduction with NaBH₄. The synthesis of the natural product stepharine (3) was obtained in 90% yield by starting from phenolic substrate 116 (Scheme 42).

In 2008, Kita and co-workers [117] developed an iodine(III)-catalyzed approach for the spirocyclization of p-substituted phenols 117 to spirocarbocyclic products 119 in good yields using a catalytic amount of iodoarene 118 and urea·H₂O₂ as an oxidant. Probably, the active hypervalent iodine(III) species was generated in situ by the oxidation of iodoarene 118 in the presence of urea·H₂O₂ oxidant (Scheme 43). Furthermore, the synthesized spirocyclic compounds were used as synthetic intermediate for the synthesis of biologically active natural product amaryllidaceae alkaloids such as (±)-maritidine (120) [118-120].

In 2009, Kita and co-workers [121] reported the synthesis of various oxygen analogues of naturally occurring compound discorhabdin A starting from substrate 110 in few chemical steps. Discorhabdin A is an alkaloid that shows various biological activities including strong cytotoxic activity [122]. During the first step, starting substrates 110 were cyclized to spirocyclic compounds 111 in useful yields using PIFA (31) in presence of montmorillonite K10 in trifluoroethanol (Scheme 44). Furthermore, synthesized spirocyclic compounds 111 were used as key precursors for the synthesis of oxygen analogues of discorhabdin A (121).
Scheme 43: Iodine(III)-catalyzed spirocyclization of phenols 117 to spirocarbocyclic products 119 using iodoarene 118 in the presence of the oxidant urea H$_2$O$_2$.

Scheme 44: PIFA-mediated spirocyclization of 110 to spirocyclic compound 111 using PIFA (31) as electrophile.

Scheme 45: PIDA-mediated spirocyclization of phenolic sulfonamide 122 to spiroketones 123.

5. Synthesis of miscellaneous spirocyclic compounds

5.1. Using stoichiometric amounts of iodine(III) reagents

In 2002, Ciufolini and co-workers [123] reported the spirocyclization of various phenolic sulfonamides 122 to spiropyrrolidines 123 using PIDA (15). In this reaction, sulfonamides 122 undergo N-acylation, wherein various homotyramine sulfonamides were treated with electrophile PIDA (15) in hexafluoroisopropanol to give the spirocyclic products 123 in high yields (Scheme 45). However, the similar spirocyclization could not successfully applied for the construction of six-membered spiropiperidine systems.

In 2015, Jain and Ciufolini [124] developed PIDA-mediated spirocyclization of 2-naphtholic sulfonamides 124 to spiro-
The spirocyclization reactions were carried out by treating N-sulfonamide substrates 124 with (di-acetoxyiodo)benzene (15) in trifluoroacetic acid (TFA) and spiropyrrolidines 125 were isolated in good to excellent yields (Scheme 46). However, the presence of an electron-donating functionality at para-position to the phenolic group induced no spirocyclization product.

In 2016, Bray and Shirley [125] reported the oxidative spirocyclization of meta-substituted phenol 126 to tricyclic spiroketals 127 in 56% yield using PIDA (15) as electrophilic species in acetonitrile at room temperature (Scheme 47). The mixture of both isomers was separated by flash column chromatography and the stereochemistry of major isomer 127a was assigned on the basis of NOE. This spirocyclic functionality is the basic nucleus found in the phorbaketal family of natural products.

5.2. Stereoselective synthesis of chiral spirocyclic ketals

Recently, Ishihara and co-workers [126] synthesized chiral C2-symmetric iodoarene 129a and 129b (Figure 3) in few steps and used as precatalyst in iodine(III)-catalyzed enantioselective synthesis of spiroketals with high selectivities.

In this report, substrates 128 were reacted with 10 mol % of chiral iodoarene 129a and 129b in the presence of mCPBA oxidant in chloroform at 0 °C. The desired ortho-spirocyclic ketals 130 were obtained in high yields with more than 93% enantiomeric excess (Scheme 48). Interestingly, the higher selectivities were observed with chiral hypervalent iodine(III) reagent 129b compared to 129a.

5.3. Application of miscellaneous spirocyclic compounds in natural product synthesis

Various hypervalent iodine reagents have been proved as vital reagents during the synthesis of several natural products containing spirocyclic skeleton. In 1999, Ley and co-workers [127] used polymeric PIDA reagent 132 to achieve the synthesis of spirocyclic core of natural product (+)-epidihydromaritidine (134). In this report, para-substituted phenol 131 was cyclized to spirodienone 133 using polymer supported (diacetoxy)iodobenzene reagent 132 (Scheme 49). The desired product 133 was
Scheme 48: Iodine(III)-catalyzed oxidative spirocyclization of substituted phenols 128 to spirocyclic ketals 130.

Scheme 49: Oxidative spirocyclization of para-substituted phenol 131 to spirodienone 133 using polymer supported iodine(III) reagent 132.

obtained in 70% yield without conventional work-up procedure and purification by chromatographic technique. Furthermore, synthesized spirocyclic compound 133 was converted into the alkaloid (+)-epidihydmoritidine (134) in three chemical steps.

Furthermore, Wipf and co-workers [128] reported a new synthetic route for the synthesis of deoxypreussomerin A (137) and palmarumycin CP1 (138). During the first step, the synthesis of spirocyclic compound 136 was achieved in 87% yield by the reaction of PIDA (15) with the naphthol derivative 135 in trifluoroethanol at room temperature. Additionally, synthesized compound 136 was used as key intermediate in the total synthesis of natural products 137 and 138 (Scheme 50). Additionally, more analogues of palmarumycin CP1 were synthesized later.

Scheme 50: Oxidative cyclization of bis-hydroxy-naphthyl ether 135 to spiroketal 136 using PIDA (15) as an electrophile.
which were showing good thioredoxin–thioredoxin reductase (Trx-1/TrxR) inhibitory activity [129]. It was observed that the introduction of enone functionality in naphthoquinone spiroketal enhances the biological activity of palmarumycin 138.

Furthermore, Ley and co-workers [130] employed polymer-supported iodine(III) reagent during the total synthesis of Amaryllidaceae alkaloid (+)-plicamine (141). In this report, spirodienone 140 was synthesized in 82% yield by the oxidative spirocyclization of p-substituted phenolic substrate 139 using polymer-supported iodonium diacetate 132 in 2,2,2-trifluoroethanol/DCM at −10 °C (Scheme 51). Additionally, the synthesized functionalized spirodienone 140 was used as precursor for the synthesis of (+)-plicamine (141).

In 2002, Quideau and co-workers [131] developed the synthesis of marine sesquiterpenoid (+)-puupehenone starting from catechol derivative 142. Marine sesquiterpenoids are mainly known for their biological importance such as antitumor, antiviral and antibiotic properties [132]. In this report, the catechol-derived starting substrate 142 was cyclized to spirocyclic product 143 in 67% yield using PIFA (31) as suitable electrophile in dichloromethane at −25 °C (Scheme 52). Furthermore, the spirocyclic product 143 assists as the key synthetic intermediate in the synthesis of the marine natural product (+)-puupehenone (144).

In 2005, Marco and co-workers [133] reported the synthesis of naturally occurring spiroacetals aculeatin A (146a) and
aculeatin B (146b) and iodine(III) reagent was used as an electrophile in one step during their synthesis. In this report, p-substituted phenolic substrate 145 was directly cyclized to naturally occurring spirocyclic optical isomers 146a and 146b using PIFA (31) in solvent combination of CH$_3$COCH$_3$/H$_2$O (9:1) at room temperature for 24 h. The spirocyclic compound 146 was obtained as two optical isomers in 5.5:1 ratio with overall 65% yield (Scheme 53).

Furthermore, Peuchmard and Wong [134] developed a new synthetic route for the total synthesis of the natural product (±)-aculeatin starting from substrate 147. (±)-Aculeatin and its derivatives possessing spirocyclic skeleton are known for their antibacterial and antiprotozoal properties [135]. In this report, substrate 147 was cyclized to spiroketals, i.e., (−)-aculeatin (146a) and (+)-aculeatin (146b) in 3:2 ratio. Herein, 1.0 equivalent of PIFA (31) was used as an electrophile, 0.4 equivalents of TFA as nonnucleophilic counter anion in solvent combination of Me$_2$CO/H$_2$O (10:1) at room temperature for 15 minutes (Scheme 54). The reaction proceeds through phenolic oxidative cyclization of phenolic substrate 147 which is the key step in the overall synthesis. The absolute configuration of the synthesised compound was determined by comparing the optical rotary values with that of natural compound (−)-aculeatin (146a) and (+)-aculeatin (146b).

In the continuation to previous work, the same research group [136] reported the synthesis of aculeatin D. In this report, the p-substituted phenolic compound 148 was directly cyclized to natural product aculeatin D (149) in 77% yield using PIFA (31) (Scheme 55).

In 2006, Ley and co-workers [137] reported the total synthesis of natural product (±)-oxomaritidine (151) starting from phenolic substrates and polymer-supported hypervalent iodine reagent was used in one step. In this report, p-substituted phenolic compound 131 was cyclized to spirocyclic compound 133 in 50% yield containing a seven membered ring system. The cyclization reaction was carried out using polymer-supported PIFA reagent 150 as an electrophile and trifluoroacetic anhydride (TFAA) as an additive at 80 °C in a microreactor without using any solvent (Scheme 56). Additionally, synthesised compound 133 was used as precursor for the synthesis of (±)-oxomaritidine (151).
In 2007, Lalic and Corey [138] reported the synthetic pathway for the synthesis of the naturally occurring antibiotic platensimycin (154) which is isolated from Streptomyces platensis. In this report, 6-methoxy-1,4-naphthoquinone-4-ethylene ketal (153) was synthesized by intermolecular oxidative cyclization of 7-methoxy-α-naphthol (152) with ethylene glycol in the presence of PIFA (31) in acetonitrile. The reaction product 153 was isolated in 80% yield (Scheme 57). Additionally, the synthesized compound 153 was converted into the antibiotic platensimycin (154) after nine chemical steps.

Furthermore, the same electrophilic species 15 was used to cyclize ortho-substituted phenolic compounds 155 to spiroketalts 156 by Quideau and co-workers [139]. The cyclization reactions were performed in trifluoroethanol and spirocyclic ketalts 156 were isolated in useful yields (Scheme 58). Additionally, the synthesized spiroketal 156 (R = iPr; R^1 = iPr) was used as substrate for the synthesis of natural product (+)-biscarvacrol (157).

Koag and Lee [140] reported the synthesis of a spiroketal by radical cyclization of a steroidal alkylamine in presence of PIDA (15) as oxidant and molecular iodine in dichloromethane at low temperature. It is an example of hypiodite-mediated radical cyclization wherein the oxazaspiroketal moiety is formed which is further used as key intermediate for the synthesis of the natural product cephalostatin.

Additionally, spiroketalts 159 were also synthesised by enatioselective spirocyclization of ortho-substituted phenols 158 using similar chiral auxiliaries 129a or 129b under similar reaction conditions mentioned in Scheme 48. Furthermore, the synthesized spiroketal 159 (R^2 = iPr; R^3 = SiMe3) was used as synthetic intermediate for enantioselective synthesis of natural product (−)-biscarvacrol [8] (Scheme 59). Additionally, Parra and Reboredo compiled a review article where authors have covered various aspects of stereoselective spirocyclizations using chiral hypervalent iodine reagents [44]. This review article would be more interesting for readers and provides some significant
information about the utility of chiral iodine(III) reagents in enantioselective spirocyclizations with suitable detail.

**Conclusion**

In this review article, we have summarized different approaches for the synthesis of spirocyclic scaffolds using hypervalent iodine reagents in stoichiometric or catalytic amounts. Various iodine(III) reagents such as (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene and Koser’s reagent have been used to achieve a variety of spirocyclization reactions under mild reaction conditions. Various hypervalent iodine-catalyzed spirocyclization of functionalized phenols and aromatic amines have been successfully developed using iodoarenes as precatalyst in the presence of terminal oxidants. In addition, this review highlights various stereoselective spirocyclizations using chiral hypervalent iodine reagents. Finally, the recent applications of hypervalent iodine reagents in natural product synthesis are also covered.

**Acknowledgements**

Fateh V Singh is thankful to the DST New Delhi for providing Start-Up Research Grant (SB/FT/CS-068/2014) as financial support. All the authors are thankful to the chemistry division, VIT University, Chennai Campus, Chennai.

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