Palladium-Catalyzed Organic Reactions Involving Hypervalent Iodine Reagents

Samata E. Shetgaonkar 1, Ritu Mamgain 1, Kotaro Kikushima 2, Toshifumi Dohi 2,* and Fateh V. Singh 1,*

1 Chemistry Division, School of Advanced Sciences (SAS), Vellore Institute of Technology-Chennai, Chennai 600127, Tamil Nadu, India; samata.shetgaonkar@gmail.com (S.E.S.); ritu.mamgain@vit.ac.in (R.M.)
2 College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu 525-0058, Shiga, Japan; kixy@okayama-u.ac.jp
* Correspondence: td1203@ph.ritsumei.ac.jp (T.D.); fatehveer.singh@vit.ac.in (F.V.S.)

Abstract: The chemistry of polyvalent iodine compounds has piqued the interest of researchers due to their role as important and flexible reagents in synthetic organic chemistry, resulting in a broad variety of useful organic molecules. These chemicals have potential uses in various functionalization procedures due to their non-toxic and environmentally friendly properties. As they are also strong electrophiles and potent oxidizing agents, the use of hypervalent iodine reagents in palladium-catalyzed transformations has received a lot of attention in recent years. Extensive research has been conducted on the subject of C—H bond functionalization by Pd catalysis with hypervalent iodine reagents as oxidants. Furthermore, the iodine(III) reagent is now often used as an arylating agent in Pd-catalyzed C—H arylation or Heck-type cross-coupling processes. In this article, the recent advances in palladium-catalyzed oxidative cross-coupling reactions employing hypervalent iodine reagents are reviewed in detail.

Keywords: palladium; hypervalent iodine reagents; oxidant; catalyst; bond formation

1. Introduction

Polyvalent iodine compounds have become popular in organic synthesis as they have been proven to be efficient and eco-friendly reagents [1–3]. Furthermore, these reagents are non-toxic, quite stable, simple to prepare, and a viable alternative to metal-derived oxidants or catalysts in a variety of oxidative reactions [4–9]. Various scientific papers, book chapters, and review articles have been published on the chemistry of hypervalent iodine.[10–18]. The functionalization of carbonyl compounds [19,20], cyclization [21–24], oxidative rearrangements [25–27], alkene difunctionalizations [28–31], and atom-transfer reactions [32], in the presence of hypervalent iodine compounds as reagents or catalysts, is now well established. The capacity of hypervalent iodine reagents to operate as both oxidant and ligand transfer reagents is the key to the substantial success made in this area [33,34].

Palladium, on the other hand, has emerged as a versatile catalyst. It is an essential component of several coupling reactions, such as Stille coupling and the Suzuki–Miyaura, Heck, Buchwald–Hartwig, Sonogashira, and Negishi, resulting in a broad variety of useful compounds [35]. The effect of hypervalent iodine in palladium-catalyzed reactions has received a great deal of attention over the years. In 2007, Sanford and colleagues published the first review paper addressing the unusual reactivity of hypervalent iodine reagents in Pd-catalyzed reactions [36]. Wengrynuk’s group later published a piece of a review in 2017 that outlines the critical significance of polyvalent iodine reagents in high-valent palladium chemistry [37]. Polyvalent iodine compounds react efficiently with palladium complexes due to their electrophilic nature and oxidizing property, promoting reactions through Pd(0/II) and Pd(II/IV) catalytic cycles [38]. Furthermore, a handful of these se compounds are used as aryl, alkyaryl, and heteroatom ligand sources.
in several Pd-catalyzed ligand transfer processes. The commonly used hypervalent iodine(III)/(V) reagents in palladium-catalyzed reactions are listed in Figure 1. Hypervalent iodine(III)/(V) reagents, such as phenyliodine(III) diacetate 1 (PIDA), phenyliodine(III) bis(trifluoroacetate) 2 (PIFA), phenyliodine(III) dipivaloate 3 (PIDP), and Dess–Martin periodinane 4 (DMP), are frequently employed oxidants in palladium-catalyzed reactions. Apart from this, cyclic hypervalent iodine(III) reagents 5 and 6 are also used as oxidants, whereas 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one 7 (TIPS-EBX) is widely explored as an alkylating reagent. Owing to their highly electrophilic nature, diaryliodonium salts 8 are excellent arylation reagents in palladium-catalyzed reactions.

**Figure 1.** Examples of hypervalent iodine(III)/(V) reagents 1–8.

In comparison to the Pd(0/II) redox cycle, substantial progress has been achieved in the chemistry of Pd(II/IV)-catalyzed reactions over the last several decades. In this context, the current review focuses on recent progress in palladium-catalyzed transformations utilizing hypervalent iodine reagents, emphasizing possible synthetic applications and mechanistic features. The article is categorized based on the bonds generated, which include C—O, C—N, C—C, C—Si, C—B, and C—halogen bonds, as well as alkene difunctionalization.

### 2. C—O Bond Formation

Palladium-catalyzed, ligand-mediated C—H functionalization has been known to be one of the most effectual, atom-efficient, and cost-effective methods for introducing different functional groups to unactivated arene and alkane C—H bonds in organic synthesis. Several research groups have conducted extensive studies on the formation of the C—O bond, using palladium catalysis involving hypervalent iodine reagents as the oxidant or heteroatom ligand. Pd-catalyzed C—H oxidative cyclization, C—H acyloxylation, C—H alkoxylation, and allylic oxidation are significant methods in C—O bond formation that are guided by directing functional groups such as oxime ether, oxazoline, amide, pyridine, pyrimidine, and so on.

#### 2.1. C—H Cyclization

Significant progress has been made in the field of palladium-catalyzed oxidative cyclization processes employing hypervalent iodine reagents, which allow access to a variety of oxygen-containing heterocycles. For instance, Yu and co-authors developed a novel method for the construction of dihydrobenzofurans 10 via the palladium-catalyzed C—H activation/C—O cyclization reaction [39]. In the presence of (diacetoxyiodo)benzene 1 as the terminal oxidant and Pd(OAc)$_2$ as the catalyst, a series of tertiary alcohols 9 were efficiently converted into targeted cyclized products 10 in moderate to good yields (Scheme 1).
Moreover, the scope of the reaction was extended for the preparation of important scaffolds such as spirocyclic dihydrobenzofurans.

Scheme 1. Pd-catalyzed synthesis of dihydrobenzofurans 10 via hydroxyl-group directed C—H activation/C—O cyclization reaction of 9 using Phl(OAc)_2 1 as terminal oxidant.

The catalytic cycle for the preparation of dihydrobenzofurans 10 was initiated by the palladium-catalyzed C—H activation of substrate 9 to give intermediate 11, followed by subsequent oxidation using Phl(OAc)_2 1 to give Pd(IV) intermediate 12. Finally, the reductive elimination of 12 gives cyclized product 10 along with the regeneration of the Pd(II) catalytic species to continue the catalytic cycle (Scheme 2).

Later, Gevorgyan and coworkers achieved the intramolecular silanol group-directed C—H oxygenation of arenes 13 using PIDA 1 as an oxidant in the presence of a palladium catalyst [40]. These reactions begin with the production of cyclic silicon-protected catechols 14, which are then desilylated with TBAF/THF to yield substituted catechols 15 (Scheme 3). The reaction featured excellent site selectivity and broad substrate scope, particularly as electron-rich substrates react much faster and provide high yields.
Scheme 3. Pd(II)-catalyzed synthesis of substituted catechols 15 from silanols 13 using Phl(OAc)₂ 1 as oxidant.

The probable catalytic cycle begins with the coordination of Pd with silanols 13 to generate palladacycle 16, followed by PPh₃-mediated oxidation to produce Pd(IV)-intermediate 17. The intermediate 17 is then reductively acetoxylated into intermediate 19 and regenerates the palladium catalyst. Finally, acid-catalyzed transesterification of 19 yields 21 and loses acetic acid to generate cyclic silyl-protected catechols 14, which are then desilylated with Tetrabutylammonium fluoride (TBAF) 18 to yield catechols 15. Based on ^18O-labeling experiments, the production of product 14 by direct C—O reductive cyclization was ruled out (Scheme 4).

Scheme 4. Plausible catalytic cycle for the synthesis of substituted catechols 15 via C—H oxygenation of silanols 13 using oxidant Phl(OAc)₂ 1.

Another interesting work published by Gevorgyan’s research group is a convenient method for the synthesis of oxasilacycles 23 and 25 from benzyl-silanol 22 and 24, respectively, using a combination of Pd(OAc)₂ and Phl(OAc)₂ 1 via C—H oxygenation strategy [41]. Under the optimized conditions, a variety of silanol-directed aromatic substrates 22 and 24 bearing alkyl and aryl substituents were transformed into the corresponding cyclic products in significant yields (Scheme 5). Gratifyingly, the oxasilacycles were found...
to be valuable intermediates as they contained an easily removable or modifiable Si—O bond and thus could be converted into useful functionality. The reactions include the well-known Tamao oxidation, Hiyama–Denmark cross-coupling, and nucleophilic addition, as well as the novel Meerwein salt-mediated oxasilacycle ring-opening and nitrene synthesis from the benzylsilane and nitroso compound. The desilylation of the cyclic product in the presence of CsF in DMF to give phenol in good yield is an example of the synthetic usefulness of oxasilacycles.

![Scheme 5. Pd(II)-catalyzed C—H oxygenation of benzylsilanol](image)

Furthermore, Dong and colleagues reported the production of cyclic ethers 27 by palladium-catalyzed oxime-masked-alcohol-directed dehydrogenative annulation of the substrates 26 sp³ C—H bonds using (diacetoxyiodo)benzene 1 as an oxidant [42]. Under normal circumstances, the reaction proceeds preferentially at the β position, and the substrates 26 with the primary, secondary, and tertiary hydroxyl groups perform extremely well (Scheme 6). The process might continue through C—H palladation, followed by Pd oxidation, to a higher oxidation state and an intramolecular S_N2 reaction to generate oxonium intermediate 29. Finally, cyclic ethers 27 were synthesized through deprotonation or debenzylation and used to renew the Pd catalyst.

Shi and colleagues demonstrated the Pd-catalyzed intramolecular lactonization of, α, α-disubstituted arylacetic acids 30 in the presence of Ph(OAc)₂ 1 and Ac—Gly—OH as the required ligand to obtain a variety of, α, α-disubstituted benzofuran-2-ones 31 in varying yields [43]. The catalytic system is made up of Pd(OAc)₂ and a mixture of NaOAc, CsOAc, and AgOAc as the most efficacious bases (Scheme 7). Wang et al., in 2013, proposed a similar C—H activation/C—O production technique for constructing functionalized benzofuranones [44].

The proposed mechanistic approach for the lactonization of acids 30 is outlined in Scheme 8. The reaction begins with the deprotonation of acid 30 under the basic condition to form carboxylate salt 32, which further coordinates with the Pd catalyst to give intermediate 33, followed by C—H cleavage via concerted metalation deprotonation to form Pd(II) intermediate 34. Six-membered palladacycle 34 underwent oxidation with Phl(OAc)₂ 1 to give Pd(IV) intermediate 35, which underwent final reductive elimination to release product 31 via path ‘a’ or formed acetoxylated product 36, which then condensed to give anticipated product 31 (path ‘b’).
Scheme 6. Pd(II)-catalyzed preparation of cyclic ethers 27 from oxime-masked alcohols 26 using PhI(OAc)$_2$ 1 oxidant.

Scheme 7. Pd(II)-catalyzed direct lactonization of acids 30 to synthesize benzofuranones 31 using PhI(OAc)$_2$ 1 as an oxidant.

Subsequently, a novel route to construct biaryl lactones 38 from biaryl carboxylic acids 37 via palladium-catalyzed C—H activation/C—O cyclization, using PhI(OAc)$_2$ 1 as an effective oxidant, was developed [45]. The presence of acetyl-protected glycine (15 mol% Ac—Gly—OH) as a ligand, along with base KOAc and solvent t-BuOH, provided the best results for the desired products 38 (Scheme 9). Both the electron-rich and the electron-deficient substituents were well tolerated on the aryl rings. Furthermore, the present protocol was successfully utilized for the total synthesis of the natural product cannabinol in a 72% yield.
Scheme 8. The catalytic cycle for the intramolecular lactonization of acids 30 to synthesize benzofuranones 31 using PhI(OAc)$_2$ 1 as an oxidant.

Scheme 9. Pd(II)-catalyzed C–H activation/C–H cyclization of biaryl carboxylic acids 37 to afford biaryl lactones 38 using PhI(OAc)$_2$ 1.

Shi’s group, in 2016, revealed a straightforward method for the synthesis of γ-lactones 40 via the Pd(II)-catalyzed 2-pyridinylisopropyl (PIP) auxiliary-directed intramolecular cyclization of unactivated C(sp$^3$)—H bonds, utilizing the oxidant PIDA 1 [46]. The lactonization of aliphatic acids 39 with different substituents on the alkyl chain went exceptionally well, yielding γ-lactones 40 in 32—77% yields (Scheme 10).

Scheme 10. Pd(II)-catalyzed synthesis of γ-lactones 40 through PIP auxiliary-directed intramolecular lactonization of aliphatic acids 39 using PhI(OAc)$_2$ 1 as oxidant.

The formation of a five-membered palladacycle 41 via Pd-catalyzed C—H activation facilitated by bidentate auxiliary is the most plausible pathway for the lactonization of
aliphatic acids. In the presence of PhI(OAc)$_2$, palladacycle 41 was oxidized to provide Pd(IV) intermediate 42, which was then ligand exchanged to generate 43 and was further reductively eliminated to liberate target product 40 and a Pd(II) catalyst to sustain the catalytic cycle (Scheme 11). Another route to lactone 40 is by a direct $S_N2$-type attack by the carboxylate group on the Pd(IV)—C bond of 42.

Scheme 11. Plausible catalytic cycle for the synthesis of γ-lactones 40.

2.2. $C({sp^2/sp^3})-H$ Acylxylation

Over the years, C—H acylxylation has gained considerable attention because it introduces ester functionality on the aromatic and aliphatic substrates. Using palladium catalysts and iodine(III) reagents as oxidants, notable progress has been achieved in transmuting $sp^2$ and $sp^3$ hybridized C—H bonds into useful C—O bonds. In the next section, we will discuss the recent developments made in C—H acyloxylation reactions employing different directing groups.

2.2.1. $C({sp^2})-H$ Acylxylation

Several ligand-directed $C({sp^2})-H$ acylxylation reactions have been developed, giving facile access to valuable oxygenated arenes. In 2009, Chen and co-authors published the Pd(II)-catalyzed pyrimidine-directed ortho-acetoxylation of phenol derivatives 44 in the presence of PhI(OAc)$_2$ 1 as an efficient oxidant in combination with the Ac$_2$O/AcOH solvent system [47]. The reaction proceeded through the Pd-catalyzed ortho C—H activation of pyrimidyl ethers 44, resulting in the formation of six-membered palladacycles which, upon functionalization, furnished acetoxyalted products 45 in variable yields (Scheme 12). However, the substrates 44 with electron-withdrawing groups or with ortho-/meta-substituents reacted slowly and gave the desired products in moderate yields.

Scheme 12. Pd(II)-catalyzed pyrimidine-directed ortho-acetoxylation of phenol derivatives 44 using PhI(OAc)$_2$ 1 as an oxidant to form acetoxyalted products 45.
Later, Liang and his co-workers employed the bidentate ligand system for the Pd(II)-catalyzed C—H activation/C—H acetoxylation of amide substrates 46 and 48 [48]. Under the optimized conditions, various pyridines 46 and 8-aminoquinoline 48 derivatives were converted to the desired acetoxylated products 47 and 49, respectively, in the presence of PhI(OAc)₂ 1 as an oxidant as well as an acetate source (Scheme 13).

The plausible catalytic cycle for the ortho-acetoxylation of arenes is outlined in Scheme 14. The reaction begins with the coordination of amide substrates 46 with a Pd(II) catalyst to give 5-membered fused palladacycles 50, followed by oxidation with PhI(OAc)₂ 1 to form an unstable Pd(IV) intermediate 51, which subsequently undergoes reductive elimination to give acetoxylated products 47.

Scheme 13. Pd(II)-catalyzed bidentate ligand-directed C—H activation/C—H acetoxylation of amide substrates 46 and 48 using PhI(OAc)₂ 1 to give products 47 and 49, respectively.

Scheme 14. Plausible catalytic cycle for the Pd(II)-catalyzed ortho-acetoxylation of arenes 46 to 47 using PhI(OAc)₂ 1 as an oxidant.
In 2010, Sanford and co-author employed in situ-generated O-acetyl oxime as an efficient directing group for the sp² C—H acetoxylation of 52 [49]. The reaction involves the O-acetylation of oximes 52, occurring upon treatment with AcOH/\(\text{Ac}_2\text{O}\) for 2 h at 25 °C, to form O-acetylated products 53, which further direct C—H acetoxylation in the presence of \(\text{Pd(OAc)}_2\) and \(\text{PhI(OAc)}_2\) 1 to afford mono-ortho-oxygenation products 54 (Scheme 15). Furthermore, the synthesized compounds were readily transformed into valuable compounds such as ketones, amines, alcohols, and heterocycles using different reaction conditions.

Scheme 15. Pd(II)-catalyzed O-acetyl oxime-directed C(sp²)—H acetoxylation of 52 to give acetoxylated product 54 using \(\text{PhI(OAc)}_2\) 1.

Later, Gevorgyan and co-workers described the pyridyldiisopropylsilyl (PyDipSi)-directed C—H acetoxylation/pivaloxylation of arenes through palladium catalysis [50]. Arylsilanes 55 reacts in the presence of hypervalent iodine(III) reagents \(\text{PhI(OAc)}_2\) 1 or \(\text{PhI(OPiv)}_2\) 56 in 1,2-dichloroethane (DCE) to yield monoacetoxylated or pivaloxylated products 57 in a good yield (Scheme 16). Both of the hypervalent iodine(III) reagents act as oxidants as well as the source of the acyloxyl group. The reaction possessed an easily removable directing group, and it possessed remarkable functional group tolerance and excellent site selectivity.

Scheme 16. Pd(II)-catalyzed pyridyldiisopropylsilyl-directed C—H acyloxylation of arylsilanes 55 using \(\text{PhI(OAc)}_2\) 1 or \(\text{PhI(OPiv)}_2\) 56 as an oxidant and acyloxyl group source.

Furthermore, the same group performed double C—H pivaloxylation of the 2-pyrimidyldiisopropylsily (PyrDipSi)-directed arenes 58 to afford bispivaloxylated products 59, using the \(\text{Pd(OAc)}_2/\text{PhI(OPiv)}_2\) 56 catalytic system [51]. Additionally, the ortho-substituted arenes 60 smoothly transformed into monopivaloxylated products 61 in good yields under similar conditions (Scheme 17). Finally, the PyrDipSi group was easily removed to yield protected resorcinols or was converted into useful synthetic products.

In 2013, Shi and co-workers employed 1,2,3-triazoles-pyridine (TA-Py) as a directing group in the Pd(II)-catalyzed selective ortho-C—H activation of arenes 62 for the first time, using oxidant \(\text{PhI(OAc)}_2\) 1 and co-oxidant \(\text{AgOAc}\) [52]. The reaction scope was examined with various TA-Py amides 62 to furnish the desired oxidized products 63 in useful yields (Scheme 18). In the case of the meta-substituted arenes, excellent regioselectivity (dr > 20:1) was achieved with acetoxylation, taking selectively at less sterically hindered carbon. A
further TA-Py group also promoted the acetoxylation of unactivated sp$^3$ C—H substrates under identical conditions.

Scheme 17. Pd(II)-catalyzed 2-pyrimidylisopropylsil-directed C—H oxygenation of arenes 58 and 60 to products 59 and 61, respectively, using PhI(OPiv)$_2$ 56 as an oxidant.

Scheme 18. Pd(II)-catalyzed C—H activation of TA-Py-directed 62 to afford acetoxylated products 63 using PhI(OAc)$_2$ 1.

In 2015, Dong’s team published the Pd-catalyzed dimethoxybenzaldoxime-directed ortho-acetoxylation of arenes 64, using oxidant PIDA 1 [53]. Both the primary and the secondary masked alcohol-derived substrates 64 smoothly underwent ortho-acetoxylation to yield acetoxylated products 65 in good to excellent yields (Scheme 19). The substrates 64 with ortho- or meta-substituents gave mono-oxidation products, while the symmetrical substrates formed bis-oxidation products.

Scheme 19. Pd(II)-catalyzed dimethoxybenzaldoxime-directed ortho-acetoxylation of arenes 64 to produce acetoxylated products 65 using PhI(OAc)$_2$ 1 as an oxidant.
In addition, a regioselective approach, including the Pd(II)-catalyzed C—H benzoxylation of 2-arylpyridines 66, yielded mono-benzoxylation products 68 in moderate to good yields [54]. They used the easily accessible iodonbenzene dibenzoate derivatives 67 as an oxidant and benzoxy group source (Scheme 20). Furthermore, the current benzoxylation process was effectively employed for the benzoxylation of 2-thienyl pyridines 69 to obtain 3-benzyoxylated thiophenes 70 in a high yield.

Scheme 20. Pd(II)-catalyzed ortho C—H benzoxylation of 66 and 69 using substituted iodonbenzene dibenzoates derivatives 67 as oxidant and source of benzoxy group.

Scheme 21 depicts a probable mechanism for the ortho C—H benzoxylation process. Initially, the substrates 66 are activated using a palladium catalyst to generate complex 71, which is then oxidatively added to 67 to form complex 72 in a high oxidation state Pd(IV) or a Pd(III)-Pd(III) intermediate [55]. Finally, the reductive elimination of 72 yields the desired product 68 and regenerates the palladium catalyst, bringing the catalytic cycle to a close.

The Pd-catalyzed C—H oxygenation of simple arenes devoid of directing groups remains a challenge as it leads to the formation of mixtures of isomers. Sanford and colleagues discovered the nonchelated-aided Pd-catalyzed C—H acetoxylation of simple arenes, utilizing pyridine as a ligand [56]. Later, the same research group studied the use of the oxidant and ligand in controlling the site selectivity in the Pd-catalyzed C—H acetoxylation of multi-substituted arenes 73 [57] (Scheme 22). Under ligand-free conditions and in the presence of PhI(OAc)2, 71, the C—H acetoxylation of arenes 73 gave a modest yield of products 75 with the selectivity dominated by electronic effects, resulting in preferential acetoxylation at the electron-rich sites (Conditions A). On the other hand, the use of acridine (1.5 mol%) as an ancillary ligand in combination with that of Pd(OAc)2 and MesI(OAc)2 74 showed sterically controlled selectivity (Conditions B).

Furthermore, the regioselective C—H functionalization of indoles has been discovered to be a simple approach for obtaining physiologically relevant 3-acetoxyindoles. Suna’s and Kwong’s groups both separately reported the synthesis of 3-acetoxyindoles 77 by the Pd(II)-catalyzed direct C3-oxidation of indole derivatives, employing PhI(OAc)2 1 as an efficient terminal oxidant [58, 59]. In addition, Lei and colleagues used PhI(OAc)2 1 and KOH as bases to establish a comparable Pd-catalyzed method for the selective C3-acetoxylation.
of substituted indoles 76 [60]. Mechanistic studies indicated that electrophilic pallada-
tion occurs at the C3 position of indole to form a Pd(II) species, which is oxidized to a
Pd(IV) intermediate and then reductively eliminated to provide matching C3-acetoxylated
indoles 77. (Scheme 23).

Scheme 21. Plausible catalytic cycle for the Pd(II)-catalyzed ortho-C—H benzoxylation of 66 using
iodobenzene dibenzoates 67.

Scheme 22. Pd-catalyzed site-selective C—H acetoxylation of multi-substituted arenes 73 using
oxidant PhI(OAc)2 1 or MesI(OAc)2 74.

Scheme 23. Pd(II)-catalyzed C3-acetoxylation of substituted indoles 76 to afford C3-acetoxylated
indoles 77 using PhI(OAc)2 1.
Szabó and co-workers presented an excellent example for the preparation of allylic acetates or benzoates via the Pd-catalyzed allylic C—H acetoxylation/benzoyloxylation of alkenes, using hypervalent iodine reagent as an oxidant [61]. The reactions were carried out in AcOH or MeCN solvent in the presence of bases KOAc and LiOBz. The catalytic process involved the formation of (η³-allyl)palladium intermediate, which was confirmed through deuterium-labelling studies. Moreover, the reaction worked perfectly well for both the internal and the terminal alkenes to provide an exclusively trans product. (Scheme 24).

**Scheme 24.** Pd(II)-catalyzed C—H acetoxylation/benzoyloxylation of alkenes to furnish allylic acetates or benzoates using iodonium salts as oxidants.

Later, the same group described the conversion of functionalized cyclic or acyclic alkenes into allylic trifluoroacetates via Pd-catalyzed C—H trifluoroacetoxylation, employing PhI(OCOCF₃)₂ as the oxidant and trifluoroacetoxy source [62]. Excellent regioselectivity (d.r: > 95:5) and diastereoselectivity were observed in the case of the monosubstituted cycloalkanes. Furthermore, the cyclic alkenes reacted much faster than the acyclic ones, and therefore, the addition of LiOCOCF₃ was necessary in the case of substrates (Scheme 25).

**Scheme 25.** Pd(II)-catalyzed C—H trifluoroacetoxylation of allylic alkenes using PhI(OCOCF₃)₂ as an oxidant and trifluoroacetoxy source.

### 2.2.2. C(sp³)—H Acyloxylation

Another major approach in regioselective C—O bond formation is the acyloxylation of aliphatic C(sp³)—H bonds. Simple methods for activating a suitable C—H bond have been designed, utilizing various directing groups. In 2010, a new chelation-assisted Pd(OAc)₂-catalyzed C(sp³)—H acyloxylation of 8-methylquinoline was established in
the presence of a stoichiometric amount of the oxidant PhI(OAc)$_2$ 1 [63]. The reaction scope was investigated using a wide variety of carboxylic acids 87 to obtain mono-acyloxylation products 88 in moderate to good yields (Scheme 26).

The authors proposed a mechanism for this C(sp$^3$)—H acyloxylation reaction, which is outlined in Scheme 27. The reaction began with the chelation-assisted activation of the benzylic C—H bond of 86 to form a cyclopalladated intermediate 89, which underwent further oxidation with PhI(OCOR)$_2$ 90 (formed in situ by the reaction of PhI(OAc)$_2$ 1 and RCOOH 87 to form Pd(IV) intermediate 91). Finally, the reductive elimination of 91 gave the desired product 88.

In 2010, Neufeldt and Sanford also reported the Pd-catalyzed in situ-generated O-acetyl oxime-directed sp$^3$ C—H acetoxylation of dialkyl oximes 92 to afford acetoxylated products 94 in useful yields [49]. The acetoxylation reaction was compatible with different functional groups, such as alkyl chlorides, protected amines, and benzylic C—H bonds (Scheme 28). Moreover, the acetoxylation occurs selectively at primary β sp$^3$ C—H bonds, in comparison to the analogous secondary sites.
Scheme 28. Pd(II)-catalyzed O-acetyl oxime-directed sp³ C—H acetoxylation of 92 to give acetoxylated products 94 using PhI(OAc)₂ as oxidant.

Using oxime as the directing group, the acetoxylation of β C—H bond of substrates 95 was performed, employing Pd(OAc)₂ and PhI(OAc)₂ [64]. The catalytic reaction was expected to generate a five-membered exo-palladacycle 96, which on oxidation gives masked 1,2-diols 97 (Scheme 29). Moreover, the selective functionalization of the β-methylene (CH₂) and β-methine (CH) groups in cyclic substrates was also carried out under the same reaction conditions. Furthermore, the deprotection of the DG and acetyl groups was conducted by using Zn/AcOH and K₂CO₃/MeOH, respectively, to yield diols in excellent yields.

Scheme 29. Pd(II)-catalyzed site-selective C(sp³)—H acetoxylation of 95 to provide protected 1,2-diols 97 using oxidant PhI(OAc)₂ 1.

An elegant protocol employing S-methyl-S-2-pyridyl-sulfoximine (MPyS) as the directing group for the selective catalytic oxidation of the unactivated primary β-C(sp³)—H bond of the amide substrates 98 at room temperature was developed [65]. In the presence of Pd(OAc)₂ and PhI(OAc)₂ 1, the preparation of β C—H acetylated products 100 was achieved using carboxylic acids 87 as the solvent and acetate source (Scheme 30). Furthermore, the diacetoxylation of the β, β'-C(sp³)—H bonds of amides 99 was also investigated under the modified conditions to afford diacetoxylated products 101.

Later, the benzylic C(sp³)—H bonds of 102 were subjected to Pd-catalyzed acetoxylation, using picolinamide and quinoline-2-carboxamide as efficient directing groups in the presence of PhI(OAc)₂ 1 as the oxidant and acetate source [66]. This oxidative transformation furnishes acetylated products 103 with excellent functional group compatibility and broad substrate scope (Scheme 31). Furthermore, the amide auxiliary was removed through base hydrolysis to give 2-aminobenzyl alcohols in a high yield.
Scheme 30. Pd(II)-catalyzed C(sp$^3$)—H acyloxylation of MPyS-N-amides substrates 98 or 99 using carboxylic acid 87 as the acetate source and PhI(OAc)$_2$ 1 as the oxidant.

Scheme 31. Pd(II)-catalyzed acetoxylation of benzylic C—H bond of substrates 102 to afford acetoxylated products 103 using PhI(OAc)$_2$ 1 as the oxidant and acetate source.

The proposed mechanism for this reaction is depicted in Scheme 32. The reaction was initiated by the coordination of 102 with the Pd(II) catalyst to form palladacycle intermediate 104 via directed C—H activation, followed by oxidation in the presence of PhI(OAc)$_2$ 1 and Ac$_2$O to form Pd(IV) intermediate 105. Finally, the reductive elimination of 105 gave the desired products 103 and the regenerated Pd catalyst to continue the catalytic cycle.

Scheme 32. Plausible catalytic cycle for the acetoxylation of benzylic C—H bonds of 103 using PhI(OAc)$_2$ 1.
In 2014, Chen and colleagues accomplished the Pd(OAc)$_2$-catalyzed acetoxylation of the C(sp$^3$)–H bond of simple alkylamines 106 guided by picolinamide (PA), utilizing PhI(OAc)$_2$ 1 as an oxidant and under an argon atmosphere [67]. The procedure makes it simple to obtain acetoxylated compounds 107 in a high yield. Furthermore, under these conditions, the C–H acetoxylation of the methyl group of arylamines 108 progressed easily, yielding acetoxylated compounds 109. The addition of Li$_2$CO$_3$ was crucial as it suppressed the formation of cyclic azetidine through intramolecular C–H amination (Scheme 33).

![Scheme 33](image)

Stambuli and co-workers reported a Pd-catalyzed PhI(OAc)$_2$-mediated allyllic oxidation of cis-vinylsilanes 110, using PIDA 1 to give the corresponding cis-silyl allylic acetate 111 as the major product [68]. This ligand-free approach required lower catalyst loading and exhibited good substrate scope, and the oxidation products were isolated in moderate to good yields (Scheme 34).

![Scheme 34](image)

Recently, in 2021, Punji and coworkers reported the palladium-catalyzed chemoselective C(sp$^2$)–H and C(sp$^3$)–H acetoxylation of tertiary amides through coordinated O–chelation under mild conditions [69]. On screening the reaction parameters, the best results were found on reacting substituted tertiary amide 112 with diaacetxyiodobenzene 1 (3.0 equiv.) in the presence of 1 mol% Pd(OAc)$_2$ as a catalyst, dissolved in hexafluoroisopropanol (HFIP)/Ac$_2$O at 80 °C for 20 h (Scheme 35). On performing the reaction in acetic acid at 120 °C, the mono-acetoxylated product 113, along with the diaacetoxylated product, was obtained, but on reducing the temperature to 80 °C and performing the reaction in HFIP/AC$_2$O, a high selectivity of monoacetoxylation was observed. The mild inorganic oxidants, such as Na$_2$S$_2$O$_8$, K$_2$S$_2$O$_8$, and AgOAc, were found to be less effective in comparison to the PhI(OAc)$_2$. The amides with cyclic substituents, as well as simple dialkyl amides with different steric properties, were found to be well-tolerated and yielded
the desired acetoxylated compounds in good to excellent yields. Under the optimized conditions, the acetoxylation of the methylene C(sp\(^3\))—H bond on the tertiary and cyclic amides failed to occur. Similarly, simple carboxylic acid and ester could not afford the acetoxyalted products.

Scheme 35. Pd-catalyzed acetoxylation of C(sp\(^2\))—H and C(sp\(^3\))—H bonds of tertiary amides 112 to corresponding product 113 in presence of Phl(OAc)\(_2\).

The possible catalytic cycle for the acetoxylation of tertiary amide is given in Scheme 36. The reaction is assumed to start with the coordination of tertiary amide 112 to the Pd(II) species via carbonyl oxygen, which is followed by C—H cleavage, resulting in an alkyl-Pd(II) intermediate 114. Furthermore, the intermediate 115 was obtained as the outcome of Pd(II) to Pd (IV) oxidation by Phl(OAc)\(_2\). Finally, the reductive elimination step results in the formation of the product as well as the regeneration of the Pd(II) catalyst for the next cycle.

Ariafard and co-workers recently described the mechanism of the Pd(OAc)\(_2\)-catalyzed alkoxylation of butyramide derivatives facilitated by hypervalent iodine(III) reagents, with the help of density functional theory (DFT) calculations. The calculations led to the result that the process consists of four basic steps: (i) C(sp\(^3\))—H bond activation, (ii) oxidative addition, (iii) reductive elimination, and (iv) active catalyst regeneration. The first step
completes through a concerted metalation–deprotonation (CMD) mechanism. Furthermore, the oxidative addition begins with the transfer of an X ligand from a hypervalent iodine reagent (ArIX2) to Pd(II) to create a square pyramidal complex with an iodonium at the apical position. The Pd(II) oxidation is triggered by a straightforward isomerization of the consequent five-coordinate complex. As a result, moving the ligand trans to the Pd—C(sp3) bond to the apical position enhances the electron transfer from Pd(II) to iodine(III). This leads to the iodine(III) reduction accompanied by the release of the second ligand as a free anion. The C—O reductive elimination of the generated Pd(IV) complex is accomplished by the nucleophilic attack of the solvent (alcohol) on the sp3 carbon through an outersphere SN2 mechanism aided by the X anion. The oxidative addition and reductive elimination activities occur with a relatively low activation barrier (DG‡ 0–6 kcal mol⁻¹). Due to the coordination between the alkoxylated product and the Pd(II) center, the regeneration of the active catalyst is endergonic. Thus, the subsequent catalytic cycles proceed with a substantially greater activation barrier in comparison to the initial catalytic cycle [70].

2.3. C(sp²/sp³)—H Alkoxylation

Another intriguing Pd-catalyzed reaction that allows the synthesis of C—O bonds is the -CH alkoxylation of sp² and sp³ bonds, utilizing hypervalent iodine reagents as an oxidant. In 2012, Chen’s group reported a Pd(OAc)₂/PhI(OAc)₂ catalytic method featuring the alkoxylation of the C(sp³)—H bonds of picolinamide-coupled amines 116 at γ or δ positions, employing alcohols 118 as a source of the alkoxy group [71]. A series of alkyl ether products 119 were isolated in 42–95% yields with excellent functional group tolerance (Scheme 37). In addition, the C(sp²)—H alkoxylation of arenes 117 was also investigated to yield mono- or bisalkoxylated products 120 in variable yields. Finally, the picolinamide auxiliary could be easily removed by treatment with an aqueous HCl/MeOH solution.

In 2013, Shi and co-workers developed a classic Pd-catalyzed method, in which a pyridine-based bidentate auxiliary enabled C—H alkoxylation of the methylene and methyl C(sp³)—H bonds of 121, employing different alcohols 118 as the source of the alkoxyl group mediated by PhI(OAc)₂ 1 [72]. Moreover, this catalytic oxygenation route was successfully applied to the alkoxylation of the β and γ C(sp²)—H bonds of arenes 123. A facile synthesis of alkyl ethers 122 and aryl alkyl ethers 124 was achieved with good yields (Scheme 38). Additionally, the directing group can be removed via nitrosylation and hydrolysis to yield β-methoxycarboxylic acid, which can be used for further transformation to various functional groups.
Scheme 38. Pd(II)-catalyzed Phl(OAc)$_2$-mediated C--H alkoxylation of unactivated C(sp$^3$)--H and C(sp$^2$)--H bond of substrates 121 and 123 to alkoxylated products 122 and 124, respectively.

Later, Sun et al. reported the azo group-directed selective C(sp$^2$)--H alkoxylation of azobenzene compounds 125 with alcohols 118, utilizing palladium catalysis [73]. Using this method, the synthesis of ortho-alkoxy aromatic azo scaffolds 126 was prepared with moderate to good yields, using both primary and secondary alcohol 118 as the alkoxylation reagents (Scheme 39). However, alkoxylation occurred only with meta-substituted azobenzenes, while the ortho- and para-substituted azobenzenes gave the desired products in traces.

Scheme 39. Palladium-catalyzed Phl(OAc)$_2$-mediated C(sp$^2$)--H alkoxylation of azobenzene derivatives 125 to afford ortho-alkoxylation products 126.

The proposed catalytic pathway for the o-alkoxylation of azobenzene derivatives 125 is depicted in Scheme 40. Initially, the substrates 125 coordinate with the Pd catalyst which results into the formation of palladacycle 127 via C--H activation. Next, the PIDA-induced oxidation in the presence of alcohols 118 gave Pd(IV) intermediate 128, which underwent reductive elimination to afford targeted products 126 and regenerated the palladium catalyst.

Subsequently, Rao and his co-workers reported the first example of employing cyclic hypervalent iodine(III) reagents 130 as efficient oxidants in the Pd-catalyzed C(sp$^3$)--H bond alkoxylation of unactivated methylene and methyl groups [74]. A series of 8-aminoquinoline-derived carboxylic acid substrates 129 and 132 were converted into the β-alkylated products 131 or 133, respectively, by utilizing a variety of alcohols 118 as an alkoxy source (Scheme 41). Furthermore, the synthetic application of the current approach for the alkoxylation of several Ibuprofen analogues, such as Naproxen, Ketoprofen, and Flurbiprofen, to obtain alkoxylated compounds in varying yields, was proven.
Scheme 40. The plausible catalytic cycle for the palladium-catalyzed C(sp\(^3\))—H-alkoxylation of azobenzene derivatives 125 using Phl(OAc)\(_2\) 1.

Scheme 41. Pd-catalyzed C(sp\(^3\))—H bond alkoxylation of aminoquinoline-derived substrates 129 and 132 to β-alkoxylated products 131 and 133, respectively, by using cyclic hypervalent iodine(III) reagents 130.

Later, the same research group established a similar approach for producing symmetrical acetals 137 through the Pd-catalyzed regioselective double C(sp\(^3\))—H bond alkoxylation of 8-aminoquinoline-derived substrates 125 with the alcohols 118, using cyclic iodine(III) reagent 130 as an oxidant [75]. However, in the case of unsymmetrical acetals, as per the
previous condition, the premixture of both alcohols 118 and 136 would give symmetric acetal as the major product (Scheme 42). Therefore, a modified two-step protocol was developed wherein, initially, the monoalkoxylation of 134 with ROH 118 was carried out at 80 °C for 2–6 h, followed by the addition of R²OH 136 and the oxidant 130 to yield unsymmetric acetals 138 in good yields.

Scheme 42. Pd(II)-catalyzed double C(sp³)–H alkoxylation of 8-aminoquinoline-derived substrates 134 to acetals 137 and 138 using cyclic iodine(III) reagent 130 as an oxidant.

In 2014, Zhang and Sun demonstrated the regioselective alkoxylation ortho C(sp²)–H bond of 2-aryloxyopyridines 139 to provide ortho-alkoxylation products 140 in the presence of a catalytic amount of Pd(OAc)₂ and oxidant PhI(OAc)₂ 1 [76]. The reaction employed 2-pyridyloxyl as an easily transformable directing group and alcohols 118 as a source of the alkoxy group (Scheme 43). Electron-rich substrate-bearing groups, such as alkoxy and methyl, gave the best results, whereas the electron-deficient substrates led to the lowering in yields.

Scheme 43. Pd(II)-catalyzed ortho-alkoxylation of 2-aryloxyopyridines 139 using alcohols 118 as source of an alkoxy group and PhI(OAc)₂ 1 as an oxidant.

2.4. C(sp²)–H Oxidation

Bigi and White transformed terminal olefins 141 into α,β-unsaturated ketones 142 via the Wacker oxidation–dehydrogenation process, employing the Pd(II)/PhI(OAc)₂ cocatalytic system in the presence of 1,4-benzoquinone as an oxidant [77]. Interestingly,
PhI(OAc)$_2$ 1 played a crucial role as a dehydrogenation catalyst and not as a terminal oxidant. The reaction occurred under mild conditions (35 °C), tolerating a wide range of functional groups, and α, β-unsaturated ketones 142 were obtained in good yields (Scheme 44).

![Scheme 44](image)

**Scheme 44.** Pd(II)/Iodine(III)-catalyzed Wacker oxidation–dehydrogenation of olefins 141 to afford α,β-unsaturated ketones 142 using PhI(OAc)$_2$ 1 as a cocatalyst.

Later, similar to Wacker-type oxidation, Fernandes’s research group developed a procedure to convert different aliphatic and aromatic terminal alkenes 143 into functionally diverse methyl ketones 145 using Dess–Martin Periodinane (DMP) 144 as an oxidant under a nitrogen atmosphere [78]. Furthermore, a variety of allylic or homoallylic compounds 146 were examined under similar olefin oxidation conditions to produce substantial quantities of methyl ketones 147. This approach has several benefits, including excellent functional group compatibility with a wide range of substrates and high yields with complete Markovnikov selectivity (Scheme 45).

![Scheme 45](image)

**Scheme 45.** Pd(II)-catalyzed Wacker-type oxidation of alkenes 143 and 146 to ketones 145 and 147, respectively, using DMP 144 as an oxidant.

2.5. C—H Phosphorylation/Sulfonation

Huang and colleagues recently demonstrated the Pd(II)-catalyzed sulfonation and phosphorylation of the unactivated benzyl C(sp$^3$)—H bonds of 8-methylquinolines 148, using sulfonate or organophosphorus hypervalent iodine(III) reagents 149 as an oxidant as well as a functional group source [79]. Using this technique, the desirable products 150 or 151 were produced in moderate to high yields over a wide range of substrates (Scheme 46). Additionally, the same approach was applicable for the pyridyl-directed C(sp$^2$)—H hydroxylation and arylation of arenes.
Scheme 46. Pd-catalyzed C(sp³)—H phosphorylation/sulfonation of methylquinolines 148 to afford products 150 or 151 using organophosphorus and sulfonate hypervalent iodine reagents 149.

2.6. Miscellenous

In 2015, Kitamura and his research group disclosed a novel route to accessing acyloxyarenes 153 from trimethylsilyl-arenes 152 via a Pd(OAc)₂-catalyzed desilylative acyloxylation strategy, using the easily available terminal oxidant PhI(OCOCF₃)₂ (PIFA) 82 in AcOH [80]. The reaction scope was explored by varying the substituents on arenes as well as by using different carboxylic acids 87 as a source of the acyl group (Scheme 47). Additionally, the hydrolysis of acetoxylated products gave access to phenol derivatives, which further extended the synthetic utility of this method.

Scheme 47. Pd(II)-catalyzed desilylative acyloxylation of trimethylsilylarenes 152 using PhI(OCOCF₃)₂ 82 as an oxidant to afford acetoxyarenes 153.

A striking example to prepare α-acetoxylated enones 155 from alkynes 154 was developed by Backvall and co-workers via Pd-catalyzed oxidative acetoxylation in the presence of terminal oxidant PhI(OAc)₂ 1 in DMSO. The addition of 10 mol% of benzoquinone (BQ) elevated the yields of the anticipated products 155 [81]. The reaction scope was explored by varying the substituents at the propargylic position and also on the arene unit (Scheme 48). Further experimental studies using ¹⁸O-labeled DMSO revealed that the ketonic oxygen atom in the final product originates from dimethylsulfoxide.
Zhu and his co-workers developed a highly efficient and simple route for the synthesis of three types of 2-aminofurans via the Pd-catalyzed cycloisomerization of polysubstituted homoallenyl amides 156, using hypervalent iodine(III) reagents as the oxidant [82]. The Pd(II)-catalyzed acetoxylative cycloisomerization of 156 was carried out by employing the oxidant PhI(OCOR)\textsubscript{2} in MeCN under an inert atmosphere to give the desired acetoxylated products 157 in variable yields. When alcohols 118 were used as coupling partners in the presence of oxidant PIFA 82, the corresponding alkoxylated products 158 were isolated via the alkoxylative cycloisomerization of 156. Moreover, the hydroxylation of homoallenyl amides 156 under basic conditions furnished the hydroxylated products 159 in significant yields (Scheme 49).

3. C—C Bond Formation

C—H functionalization using a palladium catalyst is an essential technique in C—C bond-forming reactions. A variety of catalytic reactions involving hypervalent iodine(III) reagents as oxidants have been discussed in this section.

3.1. Via Oxidative Cyclization

Li and his colleagues developed an intriguing domino process showcasing the Pd-catalyzed C—H functionalization of N-arylpropiolamides 160, utilizing iodine(III) reagent 161 as an aryl source [83]. This ingenious procedure resulted in 3-(1-aryl methylene)oxindoles 162 (Scheme 50). Furthermore, the study was conducted to find the effect of several
electron-rich and electron-deficient substituents on the aryl ring and the terminal triple bond. It was also reported by the group that substrates 160 with the N-acetyl or N-H group were unsuitable for the present reaction. Later, the synthesis of (E)-(2-oxindolin-3-ylidene)phthalimides and (E)-(2-oxoindolin-3-ylidene)methyl acetates by the palladium-catalyzed C—H functionalization of N-arylpropiolamides with phthalimide and carboxylic acids as nucleophiles was also reported by Tang et al. [84,85].

Scheme 50. Pd(II)-catalyzed synthesis of 3-(1-arylmethylene)oxindoles 162 via C—H functionalization of N-arylpropiolamides 160 with iodine(III) reagent 161 as an aryl source.

Tong et al. used PIDA 2 as an oxidant to perform the first Pd-catalyzed oxidative cyclization of 1,6-enynes 163 into the corresponding bicyclo [3.1.0] hexane derivatives 165 [86]. Later, Sanford and Tong’s research teams also developed procedures for the synthesis of multi-substituted bicyclo [3.1.0] ring systems by employing bipyridine as a ligand [87–89]. Furthermore, Tsujihara et al. reported the enantioselective synthesis of bicyclic lactones 165 from 1,6-enynes 163 in variable yields with up to 95% enantiomeric excess, using asymmetric Pd(II)/Pd(IV) catalysis [90]. The reaction employs chiral ligand spiro bis(isoxazoline) 164 (abbreviated as SPRIXs), a preformed Pd-SPRIX 164 complex as a catalyst, and PhI(OAc)2 1 as a terminal oxidant (Scheme 51).

Scheme 51. Pd-catalyzed enantioselective oxidative cyclization of enynes 163 to prepare corresponding bicyclic lactones 165 using PhI(OAc)2 1 as an oxidant.

In 2012, the palladium-catalyzed PhI(OAc)2-mediated intramolecular trifluoromethylation of alkenes 165 was achieved using TMSCF3 166 as an efficient trifluoromethyl source [91]. This method provided easy-to-access CF3-substituted oxindoles 168 at room temperature (Scheme 52). The presence of nitrogen-containing ligand 167 and Lewis acid Yb(OTf)3 was necessary to obtain the best results for the cyclization reaction. This reaction probably occurs via the arylpalladation of olefins, followed by the nucleophilic attack of arene to generate Pd(II) intermediate 169, which, upon oxidation and reductive elimination, forms Csp3—CF3 bond.

Tong and co-authors in 2019 developed an outstanding example of a Pd(II/IV)-catalyzed intramolecular cycloaddition of propargylic alcohol or amine and alkene of substrates 170 through an acetoxylative (3 + 2) annulation approach to afford bicyclic
heterocycles 171 in a good yield [92]. A further reaction of enynes 172 in the presence of ligand 1,10-phenanthroline gave cyclopropane products 174 through the formation of 1,10-phenligated Pd(IV) intermediate 173 (Scheme 53).

Scheme 52. Pd(II)-catalyzed intramolecular trifluoromethylation activated alkenes 165 with TMSCF$_3$ 166 as trifluoromethyl source to deliver CF$_3$-substituted oxindoles 168.

Scheme 53. Pd(II)-catalyzed synthesis of bicyclic heterocycles 171 and 174 from 1,6-enynes 170 and 172, respectively, using PhI (OAc)$_2$ 1.

The possible catalytic cycle for this oxidative cycloaddition reaction is given in Scheme 54. The reaction starts with acetoxypalladation, which produces alkenyl-Pd(II)
intermediate 175, which, through chair-like transition state (TS) 176, is then transformed into alkyl-Pd(II) intermediate 177. Following that, the Phl(OAc)_2-mediated oxidation yields bicyclic Pd(IV) intermediate 178, which is then converted to 179 by AcOH loss. Finally, intermediate 179 is subjected to direct C—O reductive elimination to provide product 171 and to renew the palladium catalyst, allowing the catalytic cycle to continue.

Scheme 54. The catalytic cycle for the Pd(II)-catalyzed synthesis of bicyclic heterocycles 171 from 1,6-enynes 170 using Phl(OAc)_2 1.

3.2. Via C—H Bond Arylation

In 2011, Mao and colleagues reported an in-situ Heck-type coupling reaction between olefins 143 and iodobenzene, using hypervalent iodine reagents 180 [93]. The reaction was carried out in an open environment at 40–60 °C using Pd(OAc)_2 (4 mol%), K_2CO_3 as a base, and PEG-400 solvent media. The expected coupling products 181 were obtained in an excellent yield (Scheme 55). The catalytic system was devoid of any ligands and had good catalyst recyclability. Magedov and colleagues discovered a comparable Pd-catalyzed Heck-type arylation of terminal alkenes with aryliodine(III) diacetates [94].

Scheme 55. Pd(II)-catalyzed Heck-type coupling reaction of terminal olefins 143 with hypervalent iodine(III) reagents 180 to give coupling products 181.
Under the optimized reaction conditions, a number of iodobenzene diacetates 183 bearing various functional groups were coupled with benzoxazoles derivatives 182 to efficiently furnish the corresponding arylation products 184 in modest to excellent yields (Scheme 56) [95]. A further reaction with iodobenzene instead of PIDA 1 gave a trace amount of the arylation products monitored by GC-MS, which indicates that ArI is not the possible intermediate in the present reaction.

Scheme 56. Palladium-catalyzed C—H arylation of benzoxazoles derivatives 182 employing iodobenzene diacetates 183 as an arylating reagent.

Cai and colleagues used aryliodine(III) diacetates 183 as a coupling partner in the Pd-catalyzed C—H arylation of polyfluoroarenes 185 [96]. The described protocol exhibits excellent substrate scope and tolerates a wide range of functional groups. The reaction mechanism indicates the in situ formation of aryliodides from ArI(OAc)_{2} 183 under basic conditions, resulting in moderate to excellent yields of desirable polyfluorobiaryls 186 (Scheme 57).

Scheme 57. Pd(OAc)_{2}-catalyzed C—H arylation of polyfluoroarenes 185 using aryliodine(III) diacetates 183 as aryl source to afford coupled products 186.

### 3.3. Via C—H Fluoroalkenylation

Liu et al. published the Pd-catalyzed C—H trifluoromethylation of indoles substituted at C3 position 187 in the presence of terminal oxidant PhI(OAc)_{2} 1, using the Ruppert–Prakash reagent, TMSCF_{3} 166 [97]. The reaction involves the in situ generation of CF_{3} from the reaction of TMSCF_{3} 166 and CsF, which later reacts with indole 187 to afford the desired trifluoromethylated products 188 in variable yields (Scheme 58). Meanwhile, the addition of TEMPO and bidentate ligand 167 significantly enhances the product yields. The reaction proposed proceeds via a Pd(II)/Pd(IV) pathway involving the initial electrophilic palladation of a C—H bond of indole to form complex 189, followed by PIDA-induced oxidation to yield Pd^{IV} intermediate 190, which finally undergoes reductive elimination to furnish the desired products 188.

Recently in 2021, Chen et al. reported the Pd-catalyzed chlorodifluoroethylation of various aromatic amides 191 dissolved in DCE with a new 2-chloro,2,2-difluoroethyl(mesityl)iodonium salt (CDFI) 192 in the presence of trifluoroacetic acid (TFA) additive. The reaction was found to be well tolerated in the presence of electron-withdrawing and electron-donating substituents on the aryl ring, affording the chlorodifluoroethylated product 193 in a good to excellent yield. Furthermore, it was observed that adding 4 equiv. of DBU to the DCE solution of the chlorodifluoroethylated substrates obtained from the above
reaction resulted in the formation of dehydrochlorination products 194 in high yields at room temperature [98] (Scheme 59).

![Scheme 58. Pd-catalyzed C—H trifluoromethylation of 187 to yield trifluoromethlated products 188 using TMSCF$_3$ 166 as CF$_3$ source and PhI(OAc)$_2$ 1 as an oxidant.](image1)

Scheme 59. Pd-catalyzed synthesis of difluoroethyl 193 and difluorovinyl 194 compounds from substituted aromatic amides 191 using chlorodifluoroethyl iodonium salt (CDFI) 192.

The possible catalytic cycle for chlorodifluoroethylation is given in Scheme 60. First, the palladium acetate activation procedure starts the reaction in the presence of trifluoroacetic acid (TFA). The palladium species then builds a cyclometalated intermediate 194 in the presence of the directing group. The complex 194 is then chlorodifluoroethylated by CDFI 192 to give the intermediate 195. Next, the chlorodifluoroethyl group on the Pd(IV) center is transferred to the aromatic ring to generate intermediate 196, which finally un-
dergoes the elimination reaction to provide the product 193 and renew the active Pd(II) species for the next catalytic cycle.

Scheme 60. A plausible mechanism for Pd-catalyzed synthesis of difluoroethyl from substituted aromatic amides 191 using CDFI 192.

Furthermore, in the same year, Novák and coworkers developed Pd-catalyzed ortho C—H activation of the aromatic and heteroaromatic system (Scheme 61). Various directing groups (DG), such as the secondary and tertiary amides of anilides, ureas, benzamide derivatives, or ketones, resulted in stereoselective fluorovinylation under mild reaction conditions [99]. The tetrafluoropropenylation reaction of substituted acetanilide 197 with mesityl-(tetrafluoropropenyl) iodonium triflate 198 at 25 °C in the presence of 7.5 mol% palladium(II) acetate catalyst and 2 equiv. trifluoroacetic acid (TFA) dissolved in DCM completed in 4 h to obtain the 2,3,3,3-tetrafluoropropenylated 199 with Z selectively in a high yield. The reaction was observed to be tolerant towards various types of substituents.

Scheme 61. Pd-catalyzed C—H fluorovinylation of 197 to yield 2,3,3,3-tetrafluoropropenylated 199 using aryl(fluoroalkenyl)-iodonium salts as fluoroalkenylating agents.

Besset and coworkers reported an additive-free direct 2,2,2-trifluoroethylation of aryl acrylamides 200 derived from the 8-aminoquinoline as a directing group (DG) by Pd-catalyzed C—H bond activation in the presence of fluorinated hypervalent iodine.
reagent at room temp. (Scheme 62) [100]. The mesityl(trifluoroethyl)iodonium triflate 192, a hypervalent iodine reagent developed by the Novák group, was used as the coupling partner. The products obtained had a moderate to good yield with stereoselectivity towards the formation of Z-isomers. Under the given reaction conditions, it was observed that the aromatic substitution pattern did not affect the reaction yield. The reaction was well tolerated by a wide range of functional groups, including ester and halogens (Cl, Br, and even I). On changing the directing group, a drastic change in the yield of the products was observed. On using 5-methoxy-8-aminoquinoline as a directing group, the yield of the corresponding product dropped to 18%, while the styrene-directing group resulted in no reaction. Thus, it was concluded that the directing group played an important role in the transformation.

Scheme 62. Pd-catalyzed 2,2,2-trifluoroethylation of acrylamides to afford 2,2,2-trifluoroethylated product in presence of mesityl(trifluoroethyl)iodonium triflate 192.

3.4. Via C—H Alkynylation

Waser and colleagues, in 2013, reported the regioselective C2-alkynylation of N-alkylated indoles 202 in the presence of a palladium catalyst and TIPS-EBX 203, an alkynylation reagent [101], for the first time. The process provided a good yield of 2-alkynylated indoles 204 at room temperature (Scheme 63). A variety of substituents, including Cl, Br, F, and I, remained an integral part of the end products, allowing for additional synthetic modifications.

Scheme 63. Pd(II)-catalyzed regioselective C2-alkynylation of N-alkylated indoles 202 using TIPS-EBX 203 as an alkynylation reagent.

The speculated mechanism for this alkynylation reaction is shown in Scheme 64. The reaction initiates by palladation taking place either at the C2 position to form intermediate 206 via concerted metalation–deprotonation (path a) or at the C3 position via electrophilic palladation to provide intermediate 205, which further undergoes Pd migration to give 206 (path b). Next, the intermediate 206 undergoes oxidative alkynylation using TIPS-EBX 203 to afford Pd(IV) intermediate 207, which gives the desired product 204 upon undergoing reductive elimination.
Scheme 64. The proposed catalytic cycle for Pd-catalyzed C2-alkynylation of 202 to afford alkynylated products 204.

3.5. Via Coupling

In 2015, Cai and co-workers reported the first example of the Pd-catalyzed homo-coupling of aryliodine(III) diacetates 208 towards the synthesis of synthetically useful symmetrical biaryls 209 [102]. The reaction worked remarkably well under aerobic conditions, required a shorter reaction time, and tolerated a reasonable range of functional groups with good chemoselectivity (Scheme 65). Preliminary mechanistic studies revealed in situ generations of aryl iodide through the base-mediated thermal degradation of 208, accompanied by an Ullmann-type homocoupling to give the desired products 209.

Scheme 65. Pd(II)-catalyzed homocoupling of aryliodine(III) diacetate 208 to furnish desired biaryls 209.

In 2016, Huang and co-workers illustrated the use of easily available hypervalent iodine(III) compounds 211 as efficient arylating reagents in the preparation of arylated N-heteroaromatic compounds 212 using palladium catalysis [103]. A variety of N-heteroaromatic bromides 210 were successfully coupled to afford aromatic-substituted pyridines and quinolones in moderate to good yields (Scheme 66). Furthermore, the substrates with electron-donating groups showed higher reactivity as compared to their counterparts.
Scheme 66. Pd(II)-catalyzed arylation of N-heteroaromatic bromides 210 to access arylated heteroaromatic compounds 212 using hypervalent iodine(III) reagents 211.

The proposed mechanism was studied by taking an example of 3-bromopyridine 210, and it is shown in Scheme 67. The reaction begins with the oxidative addition of 210 with the palladium catalyst to form pyridyl-Pd(II)-Br species 213, which reacts with the aryl iodide 214 obtained by the thermal degradation of 211 to give intermediate 215. The reductive elimination of 215 yields coupling product 212 and regenerates the Pd(0) catalyst to continue the catalytic cycle.

Scheme 67. The proposed Pd(0)/Pd(II)-catalytic cycle for the arylation of heteroaromatic compounds 210 using hypervalent iodine(III) compounds 211.

Recently, in 2020, Song and co-workers reported a C—H arylation reaction of heterocycle compound 216 in the presence of 5 mol% Pd nanoparticle catalyst 217 and 1.3 equiv. hypervalent iodine reagent, [Ph2]BF4 218, as an oxidant at 60 °C (Scheme 68) [104]. The arylation specifically occurred at the C2 position of the heterocyclic compounds, such as indole and furanes, with a high yield of arylated product 119; only sulphur-containing heterocycles benzothiophene and the substituted thiophene provided C3-arylated products. It was also observed that the yield of the arylated product increased by adding water to the reaction. The Pd nanoparticles used as the catalyst were easily recovered after the reaction.
and were reutilized five more times. The recycled catalyst provided the arylated product in an 80–86% conversion for up to six cycles.

\[
\begin{align*}
\text{Scheme 68.} & \quad \text{Pd nanoparticle catalyzed arylation of heterocyclic compounds}\ 216 \text{ with a hypervalent iodine reagent, } [\text{Ph}_2\text{I}]\text{BF}_4. \quad 217.
\end{align*}
\]

4. C—N Bond Formation

In recent times chemists have shown a lot of interest in catalytic C—H activation/C—N bond formation as it is a robust method for making N-containing aliphatic/aromatic heterocycles. Many methodologies are reported for the C—H aminations of unactivated sp\(^3\) and sp\(^2\) C—H bonds employing palladium species as the catalyst and hypervalent iodine reagents as oxidants. In the next section, we will discuss various intra- and intermolecular C(sp\(^2\)/sp\(^3\))—H bond functionalization reactions reported in the last decade using this strategy.

4.1. Via Intramolecular C(sp\(^2\)/sp\(^3\))—H Bond Functionalization

In 2008, Gaunt and co-workers reported an elegant approach for the synthesis of carbozoles 221 at room temperature \[105\]. The reaction involves the intramolecular C—H amination of N-substituted biphenyls 220 using Pd(OAc)\(_2\) and PhI(OAc)\(_2\) \[1\] as a catalyst and oxidant, respectively (Scheme 69). The possible strategy designed for this reaction involves the coordination of Pd to the amine 220, cyclopalladation, oxidation, and reductive elimination to afford cyclic products 221. Further preparation and isolation of the trinuclear carbopalladation complex confirm that the reaction follows the Pd(II)/Pd(IV) catalytic cycle. Furthermore, the potential scope of this method was extended for the synthesis of N-glycosyl carbozoles, a basic skeleton found in many natural products.

\[
\begin{align*}
\text{Scheme 69.} & \quad \text{Pd(II)-catalyzed intramolecular C—H amination of } 220 \text{ using oxidant PhI(OAc)}_2 \text{ to form carbozoles } 221.
\end{align*}
\]

Yu and colleagues exhibited that the intramolecular C—H activation/C—H cyclization of phenethylamine derivatives 222 with 2-pyridinesulfonyl as an efficient directing group in the presence of oxidant PhI(OAc)\(_2\) \[1\] affords a variety of functional diverse indoline derivatives 223 in moderate to high yields (Scheme 70) \[106\]. Furthermore, 2-pyridinesulfonyl moiety was removed easily under mild conditions by treating with magnesium in MeOH at 0 °C. Similar intramolecular C—H amination reactions to prepare indolines were previously reported by Daugulis and Chen’s research groups independently, using a Pd(OAc)\(_2\)/PhI(OAc)\(_2\) \[1\] catalytic system \[107,108\].
Scheme 70. Pd(II)-catalyzed synthesis of indolines 223 via C—H activation/C—H cyclization of phenethylamine derivatives 222 using PhI(OAc)_2 as an oxidant.

The plausible catalytic cycle for the intramolecular C—H amination of 222 is depicted in Scheme 71. Initially, the amine and pyridyl moiety of 222 coordinates with the Pd(II) catalyst to form complex 224, which undergoes a selective ortho-C—H cleavage to form complex 225, which, on subsequent oxidation with PhI(OAc)_2, gives Pd(IV) species 226. The reductive elimination of complex 226 forges the desired cyclic products 223 and regenerates the palladium catalyst.

Scheme 71. Plausible catalytic cycle for the Pd(II)-catalyzed C—H activation/C—H cyclization of 222 into the corresponding indoline products 223.

Later, Shi and his research group used 1,2,3-triazoles-4-carboxylic acid as an effective directing group for the palladium-catalyzed C(sp^2)—H activation of arenes 227 to afford cyclization products 228, using oxidant PhI(OAc)_2 [52]. With both sp^2 and sp^3 C—H bonds at the γ-positions of the substrate, the activation occurs selectively at the sp^2 C—H bond. Moreover, the TAA-directed activation of the methyl sp^3 C—H bonds of substrates 229 was achieved under the modified condition in the presence of acetic acid to furnish azetidines 230 with a high diastereoselectivity (Scheme 72).
Chen’s research group reported the synthesis of heterocyclic amines 232 and 234 by intramolecular C—H amination reactions in toluene, using Pd(OAc)$_2$ as catalysts and PhI(OAc)$_2$ 1 as an oxidant, under an inert environment [109]. A series of picolinamide (PA)-directed amine substrates 231 and 233 bearing γ- and δ-C(sp$^3$)—H bonds were cyclized smoothly to afford azetidines 232 and pyrrolidines 234, respectively, in significant yields with high diastereoselectivity (Scheme 73). Gratifyingly, PA can be removed easily under acidic conditions at room temperature.

Liu and co-workers disclosed the Pd-catalyzed intermolecular oxidative C—H amination of unactivated terminal olefins 235, using O-alkyl N-sulfonylcarbamates 236 as nitrogen nucleophiles and employing PhI(OPiv)$_2$ 56 as a terminal oxidant and 1,4-naphthoquinone as an additive [110]. This oxidative amination protocol leads to the efficient synthesis of valuable allylic amines 237 in useful yields (Scheme 74). In addition, the present catalytic system provides products in improved yields as compared to previously reported aerobic oxidative protocols.
Scheme 74. Pd(II)-catalyzed intermolecular C—Hamination of unactivated olefins 235 with O-alkyl N-sulfonylcarbamates 236 using Phl(OPiv)$_2$ 56 as oxidant.

Hartwig and colleagues discovered another intriguing approach using the Pd-catalyzed regioselective intermolecular C—Hamination of multi-substituted arenes 238 utilizing phthalimide 239 as the source of nitrogen supply [111]. The reactions require the sequential addition of oxidant Phl(OAc)$_2$ 1 at 9 and 24 h as it reverts Pd black formed into soluble palladium species, thereby increasing product yields. A series of N-aryl phthalimides 240 were synthesized in moderate to good yields with sterically controlled regioselectivity (Scheme 75).

Scheme 75. Pd(II)-catalyzed intermolecular C—Hamination of multi-substituted arenes 238 with phthalimide 239 using Phl(OAc)$_2$ 1 as an oxidant.

5. C—B, C—Si, and C—Halogen Bond Formation

For the first time, Szabó and coworkers reported the selective C—H borylation of simple alkenes, using a palladium pincer complex as an efficient catalyst and Phl(OCCOCF$_3$)$_2$ 82 as an essential oxidant [112]. A series of cyclic 241 and acyclic alkenes 245 were reacted with bis(pinacolato)diboron (B$_2$pin$_2$) 243 as a boronate source to provide valuable organoboronates 244 and 246, respectively, in moderate to good yields (Scheme 76). Furthermore, the reaction was examined with Pd(OAc)$_2$ as a catalyst; however, the products were obtained with lower yields. Except for cycloheptane, which gave allylic compounds preferentially, the subsequent borylation process proceeded with great vinylic selectivity.

Scheme 77 depicts the plausible catalytic cycle for the C—H borylation of alkenes 245. Initially, Phl(OCCOCF$_3$)$_2$ 82 oxidized Pd(II) complex 243 into electrophilic Pd(IV) complex 247, which underwent further trans-metalation with B$_2$pin$_2$ 243 to give complex 248. After that, alkene 242 coordinated with complex 248 to form 249, which, on subsequent Bpin ligand insertion into the double bond, gave complex 250. Finally, the reductive elimination–decomplexation of 250 gave targeted products 246 with the regeneration of catalyst 242.
Scheme 76. Palladium-catalyzed C—H borylation of olefins 241 and 245 with B₂pin₂ 243 using PhI(OCOCF₃)₂ 82 as an oxidant.

Scheme 77. Catalytic cycle for the palladium pincer complex-catalyzed C—H borylation of olefins 245 using PhI(OCOCF₃)₂ 82 as an oxidant.

Szabó and colleagues pioneered the first oxidative allylic C—H silylation of terminal olefins 235 with hexamethyldisilane 251 as the silyl source, yielding allylsilanes 254 [113]. This catalytic process employed hypervalent iodine(III) reagent 253 as an oxidant and a Pd(OAc)₂ or a nitrogen- and selenium-based palladium catalyst 252 (Scheme 78). More-
over, the functional groups, such as ester, benzyl, and amide were well tolerated under the oxidizing conditions, and the anticipated products were obtained with high regio- and stereoselectivity.

Scheme 78. Pd-catalyzed C—H silylation of terminal alkenes 235 using hexamethyldisilane 251 as the silyl source to provide allylsilanes 254.

The catalytic cycle for the Pd(II)-catalyzed C—H silylation of olefins 235 initiated with the oxidation of a Pd(II) catalyst by 253 to form Pd(IV) complex 255, followed by the coordination with alkene 235 to give complex 256, which underwent internal deprotonation to deliver allylpalladium complex 257. Next, complex 257 underwent transmetalation with hexamethyldisilane 251 to give 258, which, upon reductive elimination, afforded the final product allylsilanes 254 (Scheme 79).

Scheme 79. Catalytic cycle for the Pd(II)-catalyzed C—H silylation of terminal alkenes 235 to afford allylsilanes 254.
The conversion of a C—H bond into a C—Halogen bond, catalyzed by palladium, is an appealing approach for obtaining valuable aryl halides. However, only a few experiments have been conducted in C—H halogenation reactions using high-valent palladium catalysis in the past. Sanford and colleagues presented the very first study on Pd-catalyzed C—H fluorination using AgF as the fluoride source and PhI(OPiv)$_2$ as the oxidant [114]. A variety of 8-methylquinoline analogues with variable substituents were transformed successfully into fluorination products in moderate to good yields (Scheme 80). Further substrates bearing electron-withdrawing groups produced better results than those with electron-donating groups.

Scheme 80. Pd(II)-catalyzed C—H fluorination of 8-methylquinoline analogues to give fluorination products using AgF and PhI(OPiv)$_2$.

Rao’s research group demonstrated the ortho C—H iodination of phenol carbamates in DCE/TfOH at room temperature using palladium catalysis and cyclic hypervalent reagent as an iodine source and oxidant [115]. The reaction might follow a Pd(II)/(IV) pathway involving the formation of a cyclopalladium(II) intermediate, oxidation to Pd(IV) intermediate, and a C—I bond reductive elimination to furnish a variety of ortho-iodinated masked phenols with excellent regioselectivity (Scheme 81).

Scheme 81. Pd(II)-catalyzed ortho C—H iodination of phenol carbamates to give ortho-iodinated phenols using Togni’s reagent as a source of iodine.

6. Alkene Difunctionalization

The palladium-catalyzed difunctionalization of simple alkenes using hypervalent iodine reagents has emerged as a powerful method in organic synthesis. Various 1,1- and 1,2-difunctionalization protocols have been developed by several researchers for preparing a diverse array of useful molecules from alkenes. A general mechanism for the Pd-catalyzed oxidative functionalization of alkenes is shown in Scheme 82. These transformations often proceed through the formation of δ-alkyl Pd$^\text{II}$ intermediate, obtained via olefin insertion into the aryl-Pd bond. Such an oxidative Heck intermediate undergoes β-hydride elimination to form Heck product, and the resulting -HPdLn-species readds to give benzylic Pd(II) intermediate, which can be intercepted to furnish
1,1-difunctionalized products 267. Moreover, Heck intermediates could be oxidatively functionalized into the 1,2-difunctionalized products 268 in the presence of a suitable oxidant.

**Scheme 82.** Plausible mechanism for the Pd(II)-catalyzed difunctionalization of alkenes 143.

### 6.1. Pd(II)-Catalyzed 1,1-Difunctionalization of Alkenes

The Pd-catalyzed hypervalent iodine-mediated 1,1-difunctionalization of alkenes is rare, and only a few examples are available in the literature. Moran and co-author published an article highlighting the 1,1-difunctionalization of acrylate derivatives 270 using palladium catalysis [116]. This reaction involves a three-component coupling of substituted arenes 269, activated alkenes 270, and hypervalent iodine(III) reagent 271 in acetic acid (Scheme 83). The reaction possibly involves the formation of Heck intermediates 264, which are subsequently functionalized with an acetate ion to give aldol-type products 272.

**Scheme 83.** Pd(II)-catalyzed 1,1-difunctionalization of activated olefins 270 with substituted arenes 269 using oxidant 3-NO$_2$C$_6$H$_4$I(OAc)$_2$ 271.

Later, Sanford and co-workers disclosed the similar 1,1-aryloxygenation protocol, wherein arylstannanes 273 were successfully coupled with terminal olefins 143 in the presence of hypervalent iodine reagents (PhI(OCOR')$_2$ 180 as an oxidant [117]. This catalytic approach enabled a simultaneous generation of C—C and C—O bonds in a single step, furnishing 1,1-arylacetoxylated products 275 in significant yields (Scheme 84). However, the formation of Heck and 1,1-arylchlorinated products was observed under these conditions.
Scheme 84. Pd(II)-catalyzed 1,1-arylacetoxylation of olefins 143 with ArSnBu$_3$ 273 using hypervalent iodine reagent 180 as an oxidant.

6.2. 1,2-Difunctionalization of Alkenes

Significant progress has been made in Pd-catalyzed olefin bis-functionalization, using different hypervalent iodine reagents. Based on this technique, a variety of intra- and intermolecular transformations have also been devised, including dimation, dioxygenation, aminoacetoxylation, fluoroamination, oxidative amination, etc.

6.2.1. Intramolecular 1,2-Difunctionalization of Alkenes

One of the most potent methods for constructing aromatic and aliphatic cyclic compounds containing heteroatom is the catalytic intramolecular difunctionalization of alkenes. The Pd-catalyzed intramolecular oxidative amination for the production of tetrahydrofurans utilizing the PIDA 1 as an oxidant was reported by Sanford and colleagues [118]. Muñiz’s research group then used a palladium catalyst for intramolecular catalytic alkene dimation for the synthesis of bisindoline and cyclic urea scaffolds [119–121]. Furthermore, Oshima and co-workers disclosed a novel intramolecular carboacetoxylation protocol for the oxidative cyclization of 4-pentetyl-substituted malonate esters 276, employing oxidant Phl(OAc)$_2$ 1 to afford acetoxymethyl-substituted cyclopentane derivatives 277, along with bicyclic lactones 278 (Scheme 85) [122]. Additionally, the carboacetoxylation products 277 could be easily converted into bicyclic lactones 278 by treating with sulfuric acid under a reflux condition in isopropyl alcohol.

Scheme 85. Pd(II)-catalyzed intramolecular cyclization of olefins 276 to afford cyclopentane derivatives 277 using Phl(OAc)$_2$ 1 as an oxidant.

At the same time, Zhu et al. reported the domino carboacetoxylation of N-aryl acrylamides 279 for the synthesis of 3,3′-disubstituted oxindoles 280 in AcOH at 100 °C, using the catalytic quantity of Pd(OAc)$_2$ and Phl(OAc)$_2$ 1 as an oxidant [123]. Interestingly, when substrate 279 ($R^2 = H$) was subjected to domino carboacetoxylation, the expected oxindole was isolated along with spirooxindole 282. Thus, the authors re-evaluated the present condition and synthesized spirooxindoles 282 from alkenes 281 via a carboamination process under modified conditions, employing the PdCl$_2$ catalyst in acetonitrile at 80 °C (Scheme 86).
Scheme 86. Pd(II)-catalyzed synthesis of oxindoles 280 and spirooxindoles 282 from N-aryl acrylamides 279 and 281, respectively, using PhI(OAc)2 oxidant.

The intramolecular oxyalkynylation of nonactivated terminal alkenes employing hypervalent iodine reagent was reported by Waser and co-workers in 2010 for the first time [124]. Phenol 283 and aliphatic or aromatic acid derivatives 285 in the presence of Pd(hfacac)2 as a Pd catalyst and hypervalent iodine(III) reagent derived from benziodoxolone 192 as an acetylene transfer reagent in DCM resulted in a good yield of cyclic ethers 284 and γ-lactones 286, respectively (Scheme 87).

Scheme 87. Pd-catalyzed intramolecular oxyalkynylation of phenols 283 and carboxylic acids 285 to cyclic ethers 284 and cyclic lactones 286, respectively, by using hypervalent iodine(III) reagent 192 as an acetylene source.
Later, in 2011, the same research group synthesized 4-propargyl lactams 288 by the intramolecular aminoalkynylation of activated olefins 287, using TIPS-EBX 192 as an alkynylation agent. The catalyst used for the reaction was lithium palladate, Li\(_2\)[PdCl\(_4\)], which was generated in situ [125]. Additionally, the present protocol was successfully utilized for the synthesis of 4-propargyl oxazolidinone and imidazolidinones 290 through the cyclization of allyl carbamates or allyl urea 289 (Scheme 88). Furthermore, the synthetic utility of this reaction was extended towards the synthesis of the bicyclic heterocycles pyrrolizidine and indolizidine and also in the total synthesis of the natural product (±)-trachelanthamidine.

![Scheme 88. Pd(II)-catalyzed intramolecular aminoalkynylation of activated olefins 287 and 289 to cyclic products 288 and 290, respectively, by using TIPS-EBX 192 as an alkynylation agent.](image)

Liu and co-workers achieved the Pd-catalyzed intramolecular aminofluorination of unactivated alkenes 291 to fluorine-containing cyclic amines 292 in moderate to high yields [126]. The reaction employed AgF as a fluorinating agent and PhI(OOC\(_\text{tBu}\))\(_2\) 56 as a terminal oxidant (Scheme 89). These transformations proceeded via a Pd(II/IV) catalytic cycle involving the trans-aminopalladation of olefins mediated by Pd, oxidation by PhI(OPiv)\(_2\), and a final reductive elimination, giving aminofluorination products.

![Scheme 89. Pd(II)-catalyzed intramolecular aminofluorination of olefins 291 to afford cyclic amines 292 using oxidant PhI(OOC\(_\text{tBu}\))\(_2\) 56.](image)

**6.2.2. Intermolecular 1,2-Difunctionalization of Alkenes**

Muñiz and colleagues pioneered intermolecular diamination of terminal alkenes in the presence of a Pd catalyst, using saccharin and bissulfonimides as nitrogen donors.
and iodosobenzene dipivalate 56 as an oxidant [127]. Later, Martinez and Muñiz used a Pd/Phl(OPiv)_2 catalytic system to effectively perform an intermolecular vicinal diamination of internal alkenes 293 with phthalimide 239 and bissulfonimides 294 as nitrogen sources [128]. The limiting reagent in this reaction was alkene, and the anticipated diamination products 295 were obtained in a variable yield with perfect regio- and diastereoselectivity (Scheme 90).

![Scheme 90. Pd(II)-catalyzed intermolecular 1,2-diamination of internal alkenes 293 with phthalimide 239 and bissulfonimides 294 as a nitrogen source to desired products 295.](image)

The mechanistic approach towards the intermolecular diamination of alkenes is shown in Scheme 91. Initially, alkene 293 coordinates with the Pd catalyst followed by the subsequent aminopalladation involving the nucleophilic addition of 239 trans stereochemistry to form δ-alkylpalladium complex 296. The rapid oxidation of complex 296 gives Pd(IV) intermediate 297, which is attacked by bissulfonimides 294 to provide desired products 295 with a net inversion of configuration at the benzylic position.

![Scheme 91. Proposed catalytic cycle for the Pd-catalyzed intermolecular vicinal diamination of internal alkenes 293.](image)

Similarly, the allylic ethers 298 underwent a catalytic intermolecular 1,2-diamination reaction in the presence of phthalimide 239 and N-fluoro-bis(phenylsulfonyl)imide 299 as nitrogen sources [129]. In the presence of oxidant iodosobenzene dipivalate 56, the diamination proceeded smoothly with complete regio- and chemoselectivity to furnish the 1,2,3-trisubstituted amination products 300 in good yields (Scheme 92).
In continuation, Muñiz and co-workers reported the synthesis of new palladium-phthalimidato complexes 302 and demonstrated their broad applicability as catalysts in the vicinal diamination of allyl ethers 301 and alkenes 235, using phthalimide 239 and tetrafluorophthalimide as nitrogen sources [130]. The treatment of phthalimide 239 with Pd(OAc)$_2$ in nitrile solution at room temperature resulted in the formation of palladium-phthalimidato complexes 302. The air-stable preformed phthalimidato complexes, which proved to be versatile catalysts for the present diamination reaction, providing the desired products 303 and 304 in useful yields (Scheme 93). Furthermore, the same research group synthesized other bissaccharido palladium(II) complexes and investigated their applications in the catalytic regioselective diamination and aminooxygenation of alkenes [131].
The dioxygenation of vicinal alkene is a critical step in the preparation of valuable 1,2-dioxygenated scaffolds. Dong et al. and Shi’s research group simultaneously reported Pd-catalyzed vicinal dioxygenation of olefins using hypervalent iodine reagent as the terminal oxidant through a unique Pd(II)/Pd(IV) mechanism [132,133]. Later, Sanford’s group developed the chiral oxime-directed asymmetric 1,2-dioxygenation of alkenes in the presence of Pd(II) catalysts, using Phl(OBz)_2 as an oxidant and benzoyloxy source [134]. Various chiral allyl oxime ethers were tested, and the results showed that menthione-derived substrates had the highest reactivity and diastereoselectivity. This method allows the efficient preparation of dibenzyolated compounds with a disterioisomeric ratio up to 90:10. (Scheme 94).

![Scheme 94. Pd(II)-catalyzed oxime-directed asymmetric 1,2-dioxygenation chiral oxime allyl ether with Phl(OBz)_2.](image)

Sorensen and Stahl’s groups concurrently reported the Pd-catalyzed aminoacetoxylation of alkenes, using 1 equiv. of nitrogen nucleophiles and 2 equiv. of olefin [135,136]. Muñiz and colleagues later disclosed a modified approach for the intermolecular aminoacetoxylation of internal/terminal alkenes that allowed the alkene substrate to be used as a limiting reagent [137]. Using phthalimide as a nitrogen source, a variety of alkenes, such as allyl ethers, allyl benzenes, (Z)—methylstyrene, etc., were oxidized and transformed into an aminoacetoxylated product. (Scheme 95). Based on the results of the experiments, it was shown that Phl(OAc)_2 alters the stereochemical aspect of the aminoacetoxylation process, favoring the trans-aminopalladation route.

![Scheme 95. Pd(II)-catalyzed intermolecular amioacetoxylation of alkenes using Phl(OAc)_2.](image)

Szabó and colleagues, in 2016, reported the Pd-catalyzed iodofluorination of alkenes using fluoroiodane reagent as an iodine and fluorine source [138]. Pd(BF)_2(MeCN)_4 or PdCl_2(MeCN)_2 or Pd(OAc)_2 in CDCl_3 were used in the reaction. The reaction was planned to proceed to intermediate, which, following C(sp^2)—I bond breakage, would produce iodofluorinated compounds in moderate to excellent yields (Scheme 96). Some alkenes, on the other hand, underwent allylic rearrangement, followed by iodofluorination, to produce internally iodofluorinated compounds. Simple cycloalkenes also produced an iodofluorinated product, but at low yields.

In 2015, Liu and co-workers demonstrated an efficient and simple palladium-catalyzed protocol for the synthesis of β-amino acid derivatives via an intermolecular aminocarbonylation reaction [139]. An array of aliphatic or aromatic terminal alkenes were reacted with either 2-oxazolidone or with phthalimide under a carbon monoxide atmosphere in the presence of a hypervalent iodine(III) reagent.
as an oxidant (Scheme 97). The reaction possessed excellent regioselectivity, broad substrates scope, and remarkable functional group tolerance. Further experimental evidence revealed that the iodine(III) reagent plays a crucial role in accelerating the intermolecular aminopalladation process.

Scheme 96. Pd(II)-catalyzed intermolecular iodofluorination of alkenes 308 using PhI(OAc)$_2$ 1.

Scheme 97. Pd(II)-catalyzed aminocarbonylation of alkenes 143 for the synthesis of $\beta$-amino acid 313 and 315 using iodine(III) reagent as an oxidant.

Using PIDA 2 as an oxidant, the same research group devised a new Pd-catalyzed intermolecular oxycarbonylation of terminal 316 or internal alkenes under a CO atmosphere [140]. This difunctionalization procedure allows for the simple synthesis of different oxycarboxylic acids 317 and 319 with high functional group compatibility, regioselectivity, and diastereoselectivity (Scheme 98). This method’s potential was expanded to the synthesis of a natural product, (+)-honaucin C, in a 48% yield, up to 99% ee.
Scheme 98. Pd(II)-catalyzed oxycarbonylation of alkenes 316 and 318 using Phl(OAc)$_2$ 1 as oxidant.

7. Miscellaneous

Das et al., in 2020, introduced an interesting Pd-catalyzed ortho-C(sp$^2$)–H variation of (NH)-free 2-substituted benzimidazole, quinazoline, imidazopyridine core as the directing group 320 in the presence of PIDA 1 as a key reagent under mild conditions [141]. Four different functional groups, acetoxy, aryl, iodide, and nitro groups, were installed concurrently on the single substrate by changing the inorganic additives in the presence of PIDA under aerobic conditions. PIDA, a hypervalent iodine catalyst, serves as an oxidant and a source of functional groups in all of the four reactions. In absence of any additive, the acetoxy group becomes attached to the ortho position of the phenyl to give 321, whereas, in the presence of Cs$_2$CO$_3$, I$_2$, and NaNO$_2$, the additives in acetonitrile solvent aryl, iodide, and the nitro group attach at the ortho position to give products 322, 323, 324, respectively (Scheme 99). The reactions complete in 3-6 h and are found to be functional-group tolerant.

Scheme 99. Pd-catalyzed C(sp$^2$)–H functionalization of benzothiazole/benzoxazole/benzimidazole 320 using PIDA 1 as an oxidant.
8. Conclusions

This review explored the various palladium-catalyzed reactions mediated by hypervalent iodine compounds. Hypervalent iodine compounds have emerged as versatile oxidants, with a wide range of reactivity under mild conditions, and at the same time are non-toxic, environmentally friendly, inexpensive, and easy-to-handle reagents in organic synthesis. In recent years, the use of hypervalent iodine reagents in palladium-catalyzed transformations has received a lot of attention as they are strong electrophiles and powerful oxidizing agents. Together, they act as a powerful tool for the diversification of C—H bonds. The intrinsic oxidizing character and specific reactivity with palladium catalysts have successfully synthesized various useful scaffolds through C—O, C—N, C—C, C—Si, C—B, and C—halogen bond formation reactions. In addition, a variety of Pd-catalyzed alkene difunctionalization processes utilizing hypervalent iodine reagents have recently been established. In future, an intriguing area of investigation would be the use of recyclable polymer-supported hypervalent iodine reagents in palladium-catalyzed processes.

Author Contributions: S.E.S. has covered the literature and compiled regarding the C—O bond formations, including the generation of the chem draw files. R.M. devoted efforts for the compilation of C—C and C—N bond formation reactions. K.K. compiled C—X and alkene difunctionalization reactions. The editing of the review manuscript was conducted by F.V.S. and T.D. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded by JSPS KAKENHI (Grant Number 19K05466) and the Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: R.M. acknowledges the support from the Department of Science and Technology, New Delhi, India, for WOS-A project SR/WOS-A/CS-107/2018. F.V.S. acknowledges support from CSIR New Delhi, India (Grant Number: 02/(0330)/17-EMR-II). T.D. acknowledges support from JSPS KAKENHI (Grant Number 19K05466) and the Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Not applicable.

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