RECENT DEVELOPMENT IN PALLADIUM-MEDIATED SYNTHESIS OF OXYGEN HETERO CYCLES

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Abstract - This review describes the synthesis of oxygen heterocycles by palladium-mediated cyclization published during 2003 to 2007.

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1. INTRODUCTION

The unusual growth of worldwide demand of heterocyclic compounds due to their pharmacological and biological activities have attracted organic chemists for continuous research directed towards the development of novel and more effective synthetic strategies. Many of these strategies involve the formation of either carbon-carbon or carbon-heteroatom bond from the corresponding acyclic precursors.
Among several newly developed methodologies, the employment of palladium catalysis in oxygen heterocycles synthesis have proven its efficiency and importance to the level where this is now routinely considered in strategy level planning of complex targets.

Last decade has encountered an overwhelming development in the field of palladium chemistry and its significant contributions in the synthesis of heterocycles and have brought renaissance in chemical laboratories as well as industries. A wealth of books and reviews covering particular and limited aspects of organopalladium chemistry are available. The wide utility of palladium in organic synthesis is evident from the large number of name reactions where the deep influences of this versatile transition metal enable it in the formation of C-C, C-O, C-N and even C-S bond under relatively mild conditions. The catalytic requirement and excellent tolerance of functional groups avoiding the protection-deprotection chemistry has made possible the use of palladium in the synthesis of small to large ring heterocyclic compounds. Moreover, the development of asymmetric transformation using chiral ligand is a major break through in the palladium-catalyzed synthesis of heterocycles. In addition, the Pd-catalyzed domino multiple transformation, in recent years, have been the general need both from economical and ecological ground.

Palladium metal being a member of the late transition series in the periodic table forms stable palladium complexes of oxidation state: Pd(0), Pd(II) and Pd(IV). Different synthetic strategies employing both Pd(0)-complexes and Pd(II)-salts have been developed and facile reversible redox process due to small energy difference between these two preferred oxidation states have enriched the organic chemistry especially heterocyclic chemistry. Although catalytic amount of palladium is required for successful conversion, the catalyzed processes are in fact strongly dependent on other factors eg. base, ligand, temperature, additives and solvents. A tunable reaction conditions enable the palladium chemistry more flexible for the future endeavors of novel and exciting chemistry, despite the vast amounts of studies reported so far.

The search for various heterocycles and many new methodologies involving palladium has been the central goal in recent years. Our prime objective is to provide a complete and updated summary of palladium-catalyzed approaches for the preparation of oxygen heterocycles developed from 2003 onwards with the emphasis on the underlying principle following each synthetic procedure and the reliance of the results on the appropriate choice of reaction conditions. As industrial preparations of many heterocyclic compounds have only been reported as patents outlining only the manufacturing route, a thorough review of the patent literature, which is often difficult to interpret, is beyond the scope of this review. Procedures where palladium-catalysis are not involved in the final construction of heterocyclic ring has not been included in this review.

2. INTRAMOLECULAR REACTIONS WITH ALKYNES, ALKENES, ALLENES, ARENES AND HETEROARENES: HECK, SUZUKI, STILLE AND SONOGASHIRA TYPE REACTIONS
The potentiality of C-C unsaturated bond as carbon source to get coupled with aryl- and vinyl halides or organometallics in a palladium mediated reaction is well documented. Heck reaction is of particular prominence in the synthesis of heterocycles. The intramolecular version of this reaction with aryl or vinyl halides generally proceeds through a sequence of oxidative addition to C-X (X = halogen) bond, insertion and β-elimination (for olefins) or protonolysis (for alkynes) to generate the heterocycles ranging from small to macrocyclic compounds. The observed rate of oxidative addition with C-X bonds decreases according to the following order: C-I > C-Br > C-Cl > C-F. The reactivity of aryl triflates is in between that of aryl iodides and aryl bromides. Additives also play a significant role in controlling the reaction outcome of palladium-catalyzed reactions. Recently intramolecular reactions have been developed involving related carbopalladation reactions followed by trapping with nucleophilic reagents.

For macrocyclization via C-C bond formation with olefin or alkyne, the well-known Heck, Suzuki, Sonogashira and Stille reactions are now routinely considered. A different approach to C-C bond formation involving the palladium-catalyzed intramolecular reaction of enolate derived from ketones, esters and amides with aryl or vinyl halide or oxidative coupling with olefin has been utilized for the synthesis of five- and six-membered heterocyclic compounds. It is well established that for small sized ring the intramolecular Heck reaction usually favours exo-cyclization as due to steric reason endo-cyclization, which generate energetically favorable substituted alkene product, is less probable. By contrast, macrocycle formation proceeds through a favourable endo-cyclization pathway.

2.1. REACTIONS OF ARYL HALIDES

In palladium-catalyzed Heck reaction, aryl iodide has been found to be the most commonly used halide source. However, the use of aryl bromide or aryl chloride for the construction of heterocycles would be very much interesting from the synthetic point of view. In an investigation, Liu et al. reported the use of aryl bromide for the synthesis of 2,3-dihydrobenzofurans under ligand free Pd(OAc)$_2$–catalyzed reductive Heck cyclization (Scheme 1). However, an excellent improvement in the yield of 2 (87%) was observed under the Buchwald condition. By employing various palladium complexes [([t-Bu]$_2$P(OH))$_2$-PdCl$_2$], [([t-Bu]$_2$P(OH)(t-Bu))$_2$-PdCl$_2$] and [([t-Bu]$_2$P(OH)-PdCl$_2$)$_2$] developed by Li, a 70% yield of 2 was obtained.

![Scheme 1](image_url)

The efficiency of the methodology was explored by the synthesis of chromans and isochromans in excellent yields. Quite interestingly, the greater propensity of formation of normal Heck product instead of reductive cyclization product from the ether, under reductive Heck condition, clearly indicated...
faster $\beta$-H elimination in comparison to competing hydride reduction to 5. The exo-alkene intermediate 6 isomerized under the reaction conditions to afford thermodynamically more stable 7 in 74% isolated yield (Scheme 2).

![Scheme 2](image)

A systematic study to account for the conformational effects on the intramolecular Heck reactions of ether and ester tethered aryl iodides were carried out by Branchaud et al.\textsuperscript{19} Allyl-2-iodobenzyl ether 8 when subjected to established Heck condition (Scheme 3, condition A) afforded the six-membered products 6 and 7 (82:18) in good yields.

![Scheme 3](image)

**Conditions A:** Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), Et$_3$N (2 equiv.), AgNO$_3$ (1 equiv.), MeCN, 80 °C

**Conditions B:** Styrene (3 equiv.), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), Et$_3$N (2 equiv.), AgNO$_3$ (1 equiv.), MeCN, 80 °C

In contrast to ether, the intramolecular Heck reaction\textsuperscript{20} cyclohexyl-2-iodobenzoate 9 suffered from a competition between cyclization over deiodination leading to the product 12 predominated over exo-cyclization and afforded cyclized products 10 + 11 in poor yields (Scheme 4).

![Scheme 4](image)

**Condition C:** Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), Et$_3$N (2 equiv.), MeCN, 80 °C

**Condition D:** Pd(OAc)$_2$ (10 mol%), KOAc (2 equiv.), n-Bu$_4$NBr (1 equiv.), 4 Å MS, DMF, 80 °C

The use of ionic liquids\textsuperscript{21} in PdCl$_2$-catalyzed intramolecular Heck reaction for the synthesis of benzofuran derivative 14 was demonstrated by She et al.\textsuperscript{22} The ionic liquid, [bmim]BF$_4$ was utilized to conduct the reaction and compound 14 was obtained from o-iodophenyl allyl ether 13 (Scheme 5).
Lautens and Fang reported\textsuperscript{21} that the catalytic combination of Pd\(_2\)(dba)\(_3\)/HP(t-Bu)\(_3\)BF\(_4\) and DABCO in dioxane afforded an unusual intramolecular Heck reaction with dihydronaphthalene substrates 15 yielding formal \textit{anti}-hydroly de elimination\textsuperscript{24} products 16 via 17 in good-to-excellent yields under mild conditions. It is easily understood that the base removed a proton from the benzylic palladium intermediate 17 in an antiperiplanar fashion in the rate determining step\textsuperscript{25} (Scheme 6).

The Pd(OAc)\(_2\)-catalyzed asymmetric allylic alkylation of chiral \(\sigma\)-bromoarylcyclohexenyl ethers 18a,b for the construction of tricyclic benzofuran moieties 19a,b was described.\textsuperscript{26} Utilizing Jeffery condition\textsuperscript{27} and also in the presence of monodentate ligand P\(\sigma\)-tol), the cyclization is always accompanied by competitive ionization product. At this point different ligand was used to get more Heck reaction product. It is observed that in presence of Pd(OAc)\(_2\)/bis(1,4-diphenylphosphino)propane(dppp) and silver carbone the enantiopure \(\sigma\)-bromoarylcyclohexenyl ethers 18a,b give corresponding Heck product 19a,b in excellent yield (Scheme 7).

Pattenden and co-workers in an investigation towards the formation of quarternary stereocenter and heterocyclic core of diazonide A, reported that iodoalkene 20, as a 3:1 mixture of \(Z\)- and \(E\)-isomers, when subjected to Pd(OAc)\(_2\) in DMF in the presence of Ag\(_2\)CO\(_3\) and PPh\(_3\) for 4 days underwent \(5\)-exo-\(trig\) cyclization to afford benzodihydrofuran 21 in 72\% yield (Scheme 8).\textsuperscript{28} The same catalytic combination in THF when applied to the mixture of \textit{syn} and \textit{anti} diastereomers 22, gave spiro chromene products 23 and
24, resulting from a 6-exo-trig cyclization. However, in \(N,N\)-dimethylacetamide at higher temperature (85–90 °C), a small amount (~ 8%) of the corresponding isomeric ether 25, resulting from a competing 7-endo-trig cyclization, was produced concurrently (Scheme 8).

A similar intramolecular 5-exo-trig cyclization to generate quarternary stereocenter was also observed during the synthesis of tyrosine derived model benzofuranone 27.\(^{29}\) The intramolecular Heck reaction of benzoate 26 in the presence of \(\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3\) catalyst, (S)-BINAP as ligand and \(\text{Ag}_3\text{PO}_4\) as additive afforded the cyclized product 27 as a 3:2 mixture of diastereomers (Scheme 9).

Norbornene-mediated \(\text{Pd(OAc)}_2\)-catalyzed reaction of \(\text{o-iodo alkenyl ether 28 in the presence of different alkyl bromides 29 afforded chromene-4-ylidines 30 and 1-benzoxepin-5-ylidines 31 (Scheme 10).}^{30}\) The ring forming step involves the palladium-catalyzed \(\text{ortho-alkylation with an intramolecular exo-trig Heck type cyclization where two carbon-carbon bonds (of which one from an unactivated aryl C-H bond) are formed in one-pot.}\)}
Methyl-1,2-dihydro-1-naphthalenol substituted benzofuran and 1H-isochromene derivative 34 were prepared by a palladium-catalyzed cascade ring closure/ring opening reaction. By using Pd(PPh₃)₂Cl₂ as catalyst and Zn metal as mild Lewis acid, 2-iodophenoxyallenes 32a and 2-iodobenzyloxyallenes 32b in the presence of oxabenzonorbornadienes 33 generated the desired cyclized products 34a,b in good yields (Scheme 11). The reaction also works well when X = NTs affording corresponding nitrogen heterocycles in good yields.31

![Scheme 11](image)

We have reported the synthesis of medium-sized naphthalene based oxygen heterocycles by intramolecular Heck reaction.32 The Pd(OAc)₂-catalyzed reaction of 2- and 1-naphthyl ethers 35 afforded eight-membered oxa-cycle 36 in good yield via 8-exo-trig cyclization. The 9-endo product 37 was isolated in 20% yield only in the case of ether 35a (Scheme 12).

![Scheme 12](image)

Intramolecular hydroarylation reaction of the homopropargyl ether 38 with Pd(OAc)₂ catalyst was reported to afford the chromene 39 along with inseparable alkyne byproduct 40 (Scheme 13).33

![Scheme 13](image)

We have utilized the Jeffery’s two-phase protocol for the construction of a number of tetracyclic coumarin- and quinolone-annulated oxygen heterocycles 42 and 44 (Scheme 14).34 The process is quite general, regioselective and afforded the desired products in good-to-excellent yields. Here it is observed
that for quinolone moiety the reaction yield is slight lower than that for corresponding coumarin moiety. By using Pd(OAc)$_2$ as catalyst, KOAc as base, and $n$-Bu$_4$NBr as additive in DMF a series of coumarin and quinolone derivatives 42a-d and 44a-d were synthesized.

$\text{Scheme 14}$

2.2 REACTIONS OF VINYL HALIDES

Intramolecular reactions of vinyl halides with C-C unsaturated bond have also been applied to the construction of heterocyclic compounds. The intramolecular Heck reaction of compound (+)-45 with Pd(OAc)$_2$ afforded 8-exo-trig and 9-endo-trig cyclzed products 46 and 47$^{35}$ (Scheme 15).

$\text{Scheme 15}$

In an attempt to synthesize highly strained polyunsaturated macrolactone, parent moiety of the natural product oximidine II,$^{36}$ employing intermolecular transesterification and Suzuki type cross-coupling$^{10}$ between trifluoroborate 48 and secondary alcohol 49, the 11-membered macrolactone 50 bearing an exo-methylene moiety was obtained in 7% isolated yield (Scheme 16).$^{37}$ The base lability of 49 in DMF, wherein the vinyl bromide is prone to dehydrohalogenation to give enyne 51, was responsible for the formation of 50. Intramolecular carbometalation of 51 generated 52 which after protonolysis led to the contracted macrolactone 50.
2.3 REACTIONS OF ENOLATES

Palladium-catalyzed coupling between ketone enolate and aryl or vinyl halides is regarded as a viable route for α-arylation or α-alkenylation of ketones. Thus the intramolecular coupling reaction of tethered vinyl or aryl halides and ketone enolates provides a useful route to a wide variety of heterocycles.

The enolate generated from the γ-heteroalkenyl β-keto amides underwent oxidative coupling with the tethered alkene when subjected to Pd(MeCN)₂Cl₂ and Yb(OTf)₃ in dry THF under 1 atm O₂ as terminal oxidant. A variety of six-, seven- and eight-membered oxygen heterocycles were synthesized regioselectively from the heteroalkenyl β-ketoamides in excellent yields (Scheme 17). The added Yb(OTf)₃ in this reaction acted as a Lewis acid and enhanced the enol formation and the intramolecular attack of the nucleophilic enol toward Pd(II)-activated olefin.

3. CYCLIZATION VIA C-H BOND FUNCTIONALIZATION

Palladium-catalyzed functionalization of C-H bond has undergone a rapid development over the past decade. The potentiality of this excellent protocol has proven to be extremely useful for the synthesis of a wide variety of N- and O-heterocycles under mild conditions. In general the cyclization via aromatic C-H functionalization proceeds through Pd(IV) intermediate generated by electrophilic palladation on second aromatic or heteroaromatic ring followed by reductive elimination of palladium to afford the heterocycles. However, with unactivated alkanes, the functionalization reaction depends on less clearly defined substrate catalyst interactions. Both intra- and intermolecular versions of this reaction are discussed in the following section.
3.1 FUNCTIONALIZATION OF ALKANE C-H BONDS

The development of catalytic system for direct functionalization of alkane sp\(^3\) C-H bond is of considerable interest.\(^{47}\) The sp\(^3\) C-H bond adjacent to amines are relatively activated and can be functionalized under special condition.\(^{48}\) Recently, a new and exciting methodology for the Pd-catalyzed intramolecular alkylations with aryl bromides and chlorides has been developed.\(^{50}\) The Pd(OAc)\(_2\)/PCy\(_3\)/HBF\(_4\)/Cs\(_2\)CO\(_3\)/pivalic acid catalyzed reaction, involving sp\(^3\) C-H cleavage/functionalization, of ether 55 resulted in complete and clean conversion to 56 in 97\%, \(X = \text{Br}\) and 77\%, \(X = \text{Cl}\) (Scheme 18).

Density functional theory (DFT) calculations\(^{49}\) indicated that a concerted palladation-deprotonation pathway enabled by the presence of three-center agostic interactions at the transition state\(^{50}\) 61, 62 and 63 accounts for the formation of compounds 56a,b. Furthermore, higher \(\Delta G^\ddagger\) value leading to 59 (reaction at secondary carbon atom) compared to that leading to 58 (reaction at methyl carbon atom) might be responsible for the experimentally observed selectivity for the reaction at the methyl group. The reaction at more remote position leading to 60 is also kinetically and thermodynamically disfavoured (Scheme 19).

3.2 FUNCTIONALIZATION OF AROMATIC C-H BONDS

3.2.1 DIRECT FUNCTIONALIZATION REACTIONS
The palladium-catalyzed direct functionalization of aromatic or heteroaromatic C-H bond via C-H activation is a versatile way to generate a wide variety of O-heterocycles under mild conditions. The added advantage of this exciting protocol is the rapid access to target molecules without any activating group. The intramolecular biarylation of aryl benzyl ether 64 was successfully accomplished by the catalyst generated in situ from Pd(OAc)$_2$ and ligand, 2-(diphenylphosphino)-2-(N,N-dimethylamino)-biphenyl 67 with low catalyst loading. An excellent yield of dibenzopyran 65 (96%) along with 4% of debrominated product 66 was obtained with 5 mol% Pd(OAc)$_2$ and 10 mol% 67 (Scheme 20).

![Scheme 20](image)

Fagnou et al. reported that by employing a single catalytic system Pd(OAc)$_2$/P(t-Bu)$_3$-HBF$_4$/K$_2$CO$_3$ in the presence of styrene, compound 68 underwent domino intramolecular Heck reaction and direct arylation reaction to give the products 70a in one pot (Scheme 21). A $p$-acetoxy group on the styrenyl component becomes cleaved under the reaction conditions.

![Scheme 21](image)

Palladium-catalyzed intramolecular biaryl coupling of phenyl benzoate derivatives 71a,b was investigated. The reactions of 71a,b in the presence of Pd(OAc)$_2$, P(n-Bu)$_3$ and K$_2$CO$_3$ in DMA under refluxing condition proceeded smoothly to give benzo[c]chromen-6-ones 72a,b (Scheme 22).

![Scheme 22](image)

A microwave-assisted, palladium-catalyzed, norbornene-mediated domino process involving two intramolecular ortho alkylations of aromatic C-H bonds followed by an intermolecular Heck reaction was
The interesting feature of this reaction is that two alkyl-aryl bonds and one alkenyl-aryl bond were formed in one-pot. Using various olefins as Heck acceptor and lengthening the bromoalkyl chain of the aryl iodide 73, the syntheses of [5,6,5] ring, symmetrical [6,6,6]- and unsymmetrical [5,6,6; 7,6,7] systems were achieved. The primary differences in their preparation were the reaction time, which was longer for the higher membered ring system (Scheme 23).

Scheme 23

For the synthesis of sulfur and nitrogen heterocycles, slight modification of the reaction conditions (increased the catalyst loading to 20 mol%) was required to obtain a modest yield of the cyclized products.

An extensive work on the palladium-catalyzed domino three C-H functionalization for the synthesis of polycyclic heterocycles has recently been reported. The norbornene-mediated and Pd(OAc)2-catalyzed reaction of 77 and 76 afforded tricyclic heterocycle containing benzoxepine moiety 78 in moderate to excellent yield 35-80%. The yield affected when the newly formed ring size increase (Scheme 24).

Scheme 24

The addition of aryl boronic acid to phenoxyacetonitrile 80 under the catalysis of cationic palladium complex [(bpy)Pd^+/(μ-OH)]_2[(OTf)_2] (catalyst B) or [(bpy)Pd^{2+}](H_2O)_2][(OTf)_2] (catalyst C) afforded 3-substituted benzofuran derivatives 81 and the byproduct 82. Nitromethane is the choice of solvent for achieving the desired cyclization (Scheme 25).

Scheme 25

**Condition A**: ArB(OH)_{2} (1.5 mmol), 80 (0.5 mmol), catalyst B (5 mol%) in MeNO_{2} (2.0 mL) at 80 °C

**Condition B**: ArB(OH)_{2} (0.3 mmol), 80 (0.2 mmol), catalyst C (5 mol%) in MeNO_{2} (1.0 mL) at reflux
The reactions were performed under two different conditions (condition A and condition B). Aryl boronic acid with electron-donating groups gave better yields than those with electron-withdrawing groups. However, excellent yields were obtained using α-substituted 3,5-dimethoxyphenoxyacetonitrile 80b as the substrate than using 80a. The catalyst C was more effective than the catalyst B in this reaction. The catalyzed reaction is assumed to proceed through the initial generation of ketone 82, which in the presence of cationic palladium species generated the benzofuran derivatives via C-H activation and dehydration. An alternative Friedel Crafts pathway is also probable for the formation of the benzofuran derivatives.

Tanaka et al. reported direct construction of fused aromatic ring systems by palladium-catalyzed “zipper-mode” double C-H bond activation process. Treatment of (Z)-3-bromo-2-methylphenyl-(2-bromo-3-phenylprop-2-enyl)ether derivative 83 with a catalytic amount of Pd(OAc)\(_2\) and PCy\(_3\).HBF\(_4\) in the presence of Cs\(_2\)CO\(_3\) in dioxane afforded 5H-phenanthro[1,10-bc]furan derivative 84 (Scheme 26).

3.2.2 CYCLIZATION VIA 1,4-PALLADIUM MIGRATION

Excellent ability of palladium to insert into unactivated C-H bond is of great interest as it affords wide variety of useful synthetic processes. The through-space palladium rearrangement with simultaneous C-H activation provides a novel way to introduce palladium into a specific location within organic molecules. These novel palladium migration process are not only mechanically important but also synthetically useful because they afford an alternative way to introduce a palladium moiety into an organic molecule.

Recently, Larock et al. have applied their vinylic to aryl palladium migration strategy for the synthesis of substituted dibenzofurans, although Pd-O coordination would be expected to be much weaker than Pd-N coordination. A series of 3-iodophenyl phenyl ether 85 reacted with various internal alkynes under the reaction conditions Pd(OAc)\(_2\), bis(diphenylphosphino)methane (dpdm) and CsO\(_2\)CCMe\(_3\) (CsPiv) in DMF at 100 °C to afford two isomeric dibenzofurans 87a and 87b in moderate to excellent yield. The efficiency of the reaction is highly dependent on the nature of the group attached to the aromatic ring as more electron rich aromatic ring facilitate the vinyl to aryl palladium migration (Scheme 27).
A novel methodology based on C-H activation via 1,4-palladium alkyl to aryl migration followed by intramolecular arylation providing an expedient route to fused ring systems has been reported. Under the optimized reaction conditions aryl halides afforded the compounds (Scheme 28).  

![Scheme 28](image)

4. CYCLIZATION OF 1,n-UNSATURATED SYSTEMS: CYCLOISOMERIZATION AND CASCADE ADDITION-CYCLIZATION REACTIONS

Cyclization of 1,n-unsaturated systems catalyzed by palladium has emerged as a convenient way for the preparation of heterocyclic compounds. The reactions are broadly classified into two major categories: (a) cycloisomerization reaction and (b) cascade addition-cyclization reaction. The cyclization reaction usually proceeds through the generation of vinyl or alkyl palladium species either via hydro metallation pathway (for cycloisomerization) or via addition of species to carbon-carbon triple bond (cascade addition-cyclization reaction). In both categories the heterocycles are formed via carbon-carbon bond formation.

4.1 CYCLOISOMERIZATION REACTIONS

Palladium-catalyzed cycloisomerization reaction has proven as one of the versatile process to construct cyclic compounds from the acyclic 1,n-unsaturated precursors. In general, 1,6-unsaturated system affords five-membered cyclic product. The cycloisomerization of enyne in the presence of palladium source Pd(dba)$_3$.CHCl$_3$/PPh$_3$/AcOH afforded five-membered heterocycles (Scheme 29). By utilizing this protocol, a number of five-membered oxygen heterocycles were synthesized.

![Scheme 29](image)

Zhang and collaborators extensively investigated the palladium-catalyzed domino cycloisomerization/Suzuki coupling of 1,6-enynes. By utilizing Pd(PPh$_3$)$_4$ as catalyst, both electron rich (93a) and electron poor (93b) enynes underwent this cascade cyclization-coupling reaction to afford five-membered heterocycles 94a and 94b with an exo double bond (Scheme 30).
2-Methylenecyclopropanyl ketones **95a** owing to the presence of the *exo*-cyclic C=C bond and the strained cyclopropane, underwent highly selective ring-opening cycloisomerization using Pd(MeCN)_2Cl_2 as catalyst to afford 4*H*-pyrans **96** ([Scheme 31](#)). Interestingly, the reaction of the cyclopropyl ketones **95b** in the presence of NaI with the same catalyst afforded substituted furan derivatives **97**.

The cycloisomerization of [1'-1''-cyclopropylideneethyl]cyclopropylmethyl)(prop-2'-ynyl)ether **98** having a terminal cyclopropane unit, when subjected to Pd_2(dba)_3.CHCl_3, P(o-tol)_3 and AcOH in PhH gave two products, a non cross conjugated triene, seven-membered oxacycle **99** and an intermolecular coupling product trienyne **100**, the ratio of which depended on the dilution of the starting material ([Scheme 32](#)).

The oligounsaturated open chain compounds **101** also underwent palladium-catalyzed oligocyclization for the construction of an elegant and efficient assembly of oligocyclic systems. Thus enediyne **101** under the same reaction conditions as above afforded cross conjugated tetraene **102** with Z-configured double bond between the two rings ([Scheme 33](#)).
A new palladium-catalyzed chemoselective cycloisomerization of cis-2,4-diene-1-als 103 to 4-alkylidene-3,4-dihydro-2'H-pyrans 104 and 3-cyclopentenones 105 was reported by Liu et al. The reaction was carried out in the presence of Pd(PhCN)2Cl2 in PhMe efficient for efficient construction of 2'H-pyran derivatives 104 except only for three substrates [(i) R1 = Me, R2 = Et; (ii) R1 = Me, R2 = i-Pr; (iii) R1 = R2 = -{CH2}4-] where 3-cyclopentenones 105 were formed as major products. This chemoselectivity problem was circumvented by using 2,6-lutidine (5%) as additive and in such cases 2'H-pyran derivatives 104 were obtained exclusively in 75-78% yields (Scheme 34).

Mechanistically the cis-2,4-dien-als 103a were expected to follow the pathway 106→107→108→109. The added 2,6-lutidine accelerated the deprotonation reaction of intermediate 108 and preferably gave 2'H-pyrans 104a with the change of chemoselectivity (Scheme 35).

4.2 CASCADE ADDITION-CYCLIZATION REACTIONS
The divalent palladium-catalyzed intramolecular enyne coupling reaction initiated by acetoxypalladation and halopalladation of alkyne was developed for the construction of a wide variety of five-membered oxygen and nitrogen heterocycles. An assays of oxygen- tethered enynes 110 on treatment with Pd(OAc)2 and 2,2'-bipyridine in AcOH at 80-100 °C were converted to five-membered oxygen heterocycles 111 bearing γ,δ-unsaturation in moderate-to-excellent yields (Scheme 36). The reactions were highly stereoselective as all the products contained Z-configured double bonds.
An expedient route to the synthesis of stereo-defined $\alpha$-halomethylene-$\gamma$-butyrolactones, lactams and tetrahydrofurans via PdCl$_2$-catalyzed cis-chloropalladation-cyclization of 1,6 enynes 112a in AcOH was developed by Zhang et al.$^{81}$ The reaction showed excellent stereoselectivity ($E$/Z > 99/1) as only five membered ($E$)-113 were obtained in good yields. The halopalladation-cyclization of 1,6-enynes 112b using PdBr$_2$ as catalyst was somewhat less selective as compared to PdCl$_2$ as both ($E$) and ($Z$) isomers 114 were produced during cyclization. The trans-bromopalladation to ($Z$) product is due to the increased polarity of Pd-Br bond (Scheme 37).

Cationic Pd(II)-catalyzed$^{82}$ intramolecular cyclization of aroylmethyl 2-alkynoates 115 initiated by carbopalladation of alkynes with arylboronic acids was reported by Lu et al.$^{83}$ In the presence of [(dppp)-Pd(H$_2$O)$_2$](OTf)$_2$ as catalyst the reaction between 115 and arylboronic acids afforded $\alpha$-alkylidene-$\beta$-hydroxy-$\gamma$-lactones 116 in excellent yields with $E$-configured exocyclic double bond. The asymmetric version of this reaction was conducted using Pd(CF$_3$CO$_2$)$_2$/(S,S)-BDPP catalyst-(117) which gave the hydroxylactone 116 with high ee value. It is noteworthy that the reaction proceeded under mild condition without a Pd(II)/Pd(0) redox system with high enantioselectivity. It is proposed that the high Lewis acidity of the Pd center in the cationic species-118 activated the carbonyl group by coordination with the unshared electron pairs on the oxygen atom to facilitate the cyclization and enantioface discrimination of ketones resulting in high ee values (Scheme 38).$^{85}$
Lewis acid additive showed high influence on the diastereoselectivity of the intramolecular allyl transfer reaction of allenic aldehydes 119 with hexamethylditin catalyzed by \((\pi\text{-allyl})_2\text{PdCl}_2\) (Scheme 39).\(^{86}\) Moderate-to-good yields of *trans*-products 121 were obtained by using B\((\text{C}_6\text{F}_5)_3\) as Lewis acid additive. In the absence of any additive *cis*-products 120 were obtained in good yields. Mechanistically, the *cis*-isomer formation proceeds through the transition state 122 where as a reverse \(\pi\)-facial selectivity to yield *trans*–121 may proceed via 123.

\[
\begin{align*}
\text{Me}_3\text{SnSnMe}_3 & \to (\text{p-allyl})_3\text{PdCl}_2 (1 \text{ mol%}) & \text{Me}_3\text{SnSnMe}_3 & \to (\text{p-allyl})_3\text{PdCl}_2 (2 \text{ mol%}) \\
\text{Me}_3\text{SnSnMe}_3 & \to \text{Me}_3\text{SnSnMe}_3 & \text{Me}_3\text{SnSnMe}_3 & \to \text{Me}_3\text{SnSnMe}_3 \\
\text{Me}_3\text{SnSnMe}_3 & \to \text{Me}_3\text{SnSnMe}_3 & \text{Me}_3\text{SnSnMe}_3 & \to \text{Me}_3\text{SnSnMe}_3
\end{align*}
\]

Scheme 39

5. CYCLOADDITION REACTIONS

5.1. [3+2] CYCLOADDITION REACTIONS

Palladium-catalyzed [3+2] cycloaddition\(^{82}\) reaction is an efficient method to prepare five-membered heterocycles. A number of oxazolidine\(^{88}\) and imidazolidine\(^{89}\) derivatives were synthesized by [3+2] cycloaddition between oxiranes and aziridines with heterocumulenes. An extensive investigation on the palladium-catalyzed [3+2] cycloaddition reaction between 2-(acetoxymethyl)-3-(trimethylsilyl)propene 124a and carbon dioxide was reported by Greco *et al.*\(^{90}\) The reaction is presumed to proceed via the in situ generation of \(\eta^2\)-Pd trimethylenemethane (TMM) complex-(A), the three atom partner, which underwent [3+2] cycloaddition with carbon dioxide to afford \(\gamma\)-butylo lacone 125 as the major product along with acetylated compound 126 (Scheme 40).
5.2 [4+2] CYCLOADDITION (DIELS-ALDER REACTION)

A palladium-catalyzed endo-cycloaddition reaction has recently been demonstrated. Two equivalent of ethyl vinyl ether, a commonly used dienophile in cycloaddition reactions, was subjected to cycloaddition reaction with o-vinylphenol 128 using Pd[(-)-Sparteine]Cl$_2$ as catalyst to afford the endo-product 129 as a single diastereomer (Scheme 41). The yield of the product 129 could be increased to 30% when 10% Et$_3$N was added to the reaction. The formation of the compound 129 is assumed to proceed via in situ generation of o-quinone methide which undergoes cycloaddition with ethyl vinyl ether in an endo manner.

5.3. [4+3] CYCLOADDITION REACTIONS

First example of palladium-catalyzed [4+3] intramolecular cycloaddition of alkylidenecyclopropanes and dienes has recently been reported. The reaction is successfully carried out in the presence of Pd$_2$(dba)$_3$ as catalyst in dioxane using phosphine ligand 133 or 134 and dienylidenecyclopropanes 130. Here the cisoid-diene activated by the presence of electron-withdrawing CO$_2$Et group gave stereochemically rich 5,7-fused bicyclic compounds 131 predominantly along with very little amount of 5,5-fused bicyclic compounds 132. The terminally phenyl-substituted substrate 130b also underwent the cycloaddition providing the adduct 131b. Interestingly, the nonactivated diene also underwent this cycloaddition reaction. The selectivity ratio (seven versus five) was found better using ligand 134 (Scheme 42).

It is envisaged that in the presence of conjugated diene, a π-allyl rearrangement might be responsible for the formation of the seven-membered ring. With transoid diene 130a, cycloaddition reaction afforded the epimeric cycloadduct 131a with poor selectivity of the seven- over the five-membered cycloadduct (Scheme 43).
5.4. [2+2+1] CYCLOADDITION REACTIONS

Transition metal-catalyzed [2+2+1] cycloaddition, in particular Pauson-Khand reaction, between two olefin units with carbon monoxide have been well investigated and is considered to be a general method for the construction of five-membered ring compounds containing carbonyl groups. In comparison to extensive utilization of Co, Ti, Ni, Ru, Rh, and Ir complexes in Pauson-Khand reaction, very few successful examples of palladium-catalyzed Pauson-Khand reaction are available. Yang et al. reported successful application of the palladium catalysis in the [2+2+1] cycloaddition reaction for the construction of bicyclic oxygen and nitrogen heterocycles. Different allylpropargyl ethers when subjected to Pauson-Khand reaction utilizing PdCl$_2$ as catalyst and tetramethyl thiourea (tmtu) as additive in the presence of CO using THF as solvent at 50 °C produced the desired cycloadducts in moderate yields (Scheme 44). In absence of tmtu the Pd(II)-catalyst was precipitated immediately. The yield of the reaction was poor for allylpropargyl ethers compared to allylpropargyl amines.

\[
\text{Scheme 42}
\]

\[
\text{Scheme 43}
\]

\[
\text{Scheme 44}
\]
6. HETEROCYCLIZATION REACTIONS: CYCLIZATION VIA CARBON-HETEROATOM BOND FORMATION

6.1. INTRAMOLECULAR ADDITION OF O-H, C=O BONDS ACROSS ALKENE, ALLENE AND ALKYNE

The applications of Pd catalysis in the formation of carbon-heteroatom bond via intramolecular addition of heteroatom nucleophiles on to carbon-carbon unsaturated bond have turned out to be the most attractive and important tools in the transition metal-catalyzed synthesis of heterocycles. From the synthetic point of view, these reactions employing various nucleophiles like amines, alcohols, carboxylic acids, esters, amides, carbonyl and imines are very important as the addition reactions can be performed with excellent atom efficiency without any waste formation. In the presence of higher valent Pd(II) the reaction proceeds with the initial formation of π-complex through the coordination of nucleophile to the C-C unsaturated bond followed by intramolecular nucleophilic addition to the electron deficient unsaturated bond.

6.1.1. ADDITION TO ALKENE

Alkene appended heteroatom nucleophiles have been found to undergo palladium(II)-catalyzed heterocyclization to produce a variety of heterocyclic compounds. Both activated and unactivated double bonds can react with the nucleophiles. The synthesis of a number of five- and six-membered oxygen heterocycles has been reported via oxidative cyclization of a variety of nucleophiles such as phenol onto unactivated double bonds catalyzed by Pd(CF\(_3\)CO\(_2\))\(_2\) and pyridine in the presence of molecular oxygen as the sole stoichiometric oxidant in a nonpolar solvent (PhMe) (Scheme 45).

![Scheme 45](image)

The asymmetric version of this reaction was successfully carried out by using pre-synthesized Pd(CF\(_3\)CO\(_2\))\(_2\) complex and 100 mol% of (-)-sparteine. Under the optimized reaction conditions, phenol 139a was cyclized to provide dihydrobenzofuran (+)-140a’ in 72% yield with 76% ee (Scheme 46).

![Scheme 46](image)
Quite similarly, 1,7-dien-3-ol 141 on treatment with Pd(PhCN)₂Cl₂ and BQ as oxidant underwent 6-exo Wacker-type oxidative cyclization, followed by alkene migration to the more highly substituted position to afford hexahydrochromene derivative 142 (Scheme 47). However, 1,5-dien-3-ols 143a,b under the same reaction conditions reacted rapidly to give aromatized products 144a,b.

The stereo- and regioselectivity of the intramolecular palladium(II)-catalyzed 1,4-oxidation reactions of 1,3-dienes bearing a side chain with a carboxylic or alcoholic nucleophiles 145a and 145b, were highly affected by the presence of additives and solvent composition (AcOH/acetonitrile) (Scheme 48). The carboxylic acid 145a gave cis-isomer of δ-lactone 146a as the major product along with 147b when the reaction was conducted in AcOH/acetone (1:4) in the absence and presence of LiCl and LiOAc. However, in the absence of LiCl and LiOAc the cis-isomer was formed exclusively in 53% yield. 1,4-Oxidation of alcohol when performed in AcOH without the addition of MnO₂ also followed the same pathway.

![Scheme 47](image)

The use of chiral bisoxazoline ligands based on binaphthyl and biphenyl backbone in the Pd(II)-catalyzed enantioselective Wacker-type cyclization of α-allylphenols has been well documented. In a related study, C₂-asymmetric bisoxazoline ligand bearing an axis-unfixed biphenyl backbone-151 was utilized in highly enantioselective Pd(II) catalyzed Wacker-type cyclization of 2-allylphenols 149 (Scheme 49). The reactions were catalyzed by Pd(II)-151 complex generated in situ by mixing Pd(CF₃CO₂)₂ with bisoxazoline-151 (Pd/ligand 1:2) and BQ to afford the corresponding chiral 2,3-dihydrobenzofuran 150 with excellent enantioselectivity (90-98% ee).
Asymmetric cyclization of 2-(3-methylbut-2-enyl)phenol 152 with a chiral ligand and catalytic palladium afforded\textsuperscript{105} both the desired product 2-isopropenyl-2,3-dihydrobenzofuran 153 and the unwanted pyran derivative 154 (Scheme 50). However, the reaction suffered from poor conversion and poor enantioselectivity. Koning et al. showed that Trost condition for the synthesis of chiral 2-substituted-2-vinyl chromans using chiral ligand (157a)\textsuperscript{106} and catalytic Pd(dba)\textsubscript{2} furnished the required volatile 2-isopropenyl-2,3-dihydrobenzofuran 156a\textsuperscript{107} from the alcohol 155a. The opposite enantiomer of 156b was also synthesized by similar treatment of 155b with Pd(dba)\textsubscript{2} using the opposite Trost chiral ligand (157b).

Trost and collaborators demonstrated a highly efficient and atom economic dual catalytic approach comprised of two distinctly separate reaction strategy (i) Ru-catalyzed intermolecular enyne cross-coupling\textsuperscript{108} to 1,4-diene followed by (ii) intramolecular nucleophilic trapping of \( \pi \)-alkylpalladium species, in a one-pot reaction sequence for the synthesis of enanto- and diastereo pure \( \pi \)-heterocycles.\textsuperscript{109} A different catalytic combination Pd\textsubscript{2}(dba)\textsubscript{3}, CHCl\textsubscript{3}, and L-1 were employed for the enantioselective \( \pi \)-heterocyclization. The furan and pyran rings 160 were formed in good yields, with pyran affording the highest enantioselectivity. The enantioselectivity of the furan ring synthesis was slightly improved (79\%) by the addition of tetrabutyl ammonium chloride. The seven-membered ring formation was also unsuccessful under this condition due to competitive formation of the triene product (Scheme 51).
It is worthwhile to note that oxygen and nitrogen nucleophiles showed opposite selectivity in the enantioselective heterocyclization reaction. In case of sulfonamide substrates, the enantiodetermining\textsuperscript{110} matched ionisation\textsuperscript{111} was followed by fast intramolecular mismatched nucleophilic addition. As the rate of mismatched attack becomes faster than the equilibration of 163, the (S)-stereochemistry is predicted from the (R,R)-ligand though the ring closure involves a mismatched event. On the contrary, if the rate of addition in the cyclization of alcohol nucleophile 161b is slower than equilibration of the palladium-allyl diastereomer, the nucleophilic addition becomes enantiodetermining. Hence, the 1,4-diene 161b undergoes a matched ionization followed by rapid equilibration of 164 and 165. Matched nucleophilic attack through 165 leads to 162b when (R,R)-ligand is utilized (Scheme 52).

\begin{equation}
\text{Sulfonamides: ionisation is enantiodetermining}
\end{equation}

\begin{equation}
\text{Oxygen nucleophiles: nucleophilic addition is enantiodetermining}
\end{equation}

\textbf{Scheme 52}

Wolfe et al. reported that the reaction between 4-penten-1-ol 166 and 2-naphthylbromide 167 employing a combination of Pd\textsubscript{2}(dba)\textsubscript{3}/dpe-phos/NaO\textsubscript{t}-Bu catalysts presumably proceeded via palladium(aryl) (alkoxide) intermediate\textsuperscript{112} 169 which underwent intramolecular insertion of the alkene into the Pd-O bond\textsuperscript{113} followed by reductive elimination to afford the 2-naphthyltetrahydrofuran 168 (Scheme 53).\textsuperscript{114} It
is evident from the mechanism that the generation of palladium(aryl)(alkoxide) intermediate 169 and intramolecular insertion of olefin into Pd-O bond are the controlling steps of this catalytic transformation. A precise mechanistic detail of the alkene insertion into the Pd-O bond is depicted in Scheme 53. The most likely pathways involved either direct insertion of alkene via five-coordinated intermediate 174 (Scheme 53, path A)\textsuperscript{113a} or insertion through four-coordinated intermediate 172, formed by an associative ligand substitution process that too proceeds through the five-coordinated complex 170.\textsuperscript{115}

The stereochemical outcome of the carboetherification and carboamination\textsuperscript{116} reactions of γ-hydroxy 166 and 167 with tethered aryl bromides are highly influenced by the nature of the heteroatom and added ligand. Phosphine ligand controls the syn- versus anti-addition pathways in the catalytic cycle, which allows for stereoselective construction of either of the two possible product diastereomers from a given substrate. For example, the (1S\textsuperscript{*},2R\textsuperscript{*})-2-indan-1-yl tetrahydrofuran 168 (51%, syn addition product) was synthesized in 51% and 60% yields from both E- and Z-alkene alcohols (166 and 167) via the Pd\textsubscript{2}(dba\textsubscript{3}/PCy\textsubscript{3},HBF\textsubscript{4} and Pd\textsubscript{2}(dba\textsubscript{3})(\pm)-BINAP-catalyzed syn- and anti-additions respectively (Scheme 54).\textsuperscript{117} Similarly, both the syn- and anti-additions are observed during the preparation of (1S\textsuperscript{*},2S\textsuperscript{*})-isomer 170 from both the alkenes (166 and 167) by changing from chelating dppb to monodentate [\text{Pp(MeO)xC\textsubscript{6}H\textsubscript{4}}]\textsubscript{3} keeping the other condition fixed. Substrates bearing tertiary alcohols also behave similarly to afford products of either syn- or anti-addition.

As predicted, the catalyst-induced change in stereochemistry is likely due to a change in the reaction mechanism in the carboetherification reaction. The syn-addition products are assumed to be derived from an unexpected transannular alkene insertion of an 11-membered Pd(Ar)OR complex 181 where as
Wacker-type anti-oxypalladation,\textsuperscript{118} i.e. via the ordered intermediate 184 gives anti-addition product. The stereochemistry around the tetrahydrofuran ring is dictated by non-bonding interactions in the transition state with a preference for pesudoequatorial orientation of substituents. The intramolecular carboamination reaction may proceed via a mechanism similar to that for syn-addition reactions of alcohol substrates involving a transannular alkene insertion of an 11-membered palladium (aryl)(amido) intermediate through transition state 186 or 187 (Scheme 55).

Scheme 54
Palladium-catalyzed enantioselective C-3 allylation of 3-substituted-1H-indoles using trialkylboranes was developed by Trost et al.\textsuperscript{119} Indoles with pendant alcohols 188a,b and allylic alcohol when treated with Pd\(_2\)(dba)\(_3\).CHCl\(_3\), 189 as ligand and 9-BBN-(C\(_6\)H\(_{13}\)) as promoter afforded cis-5,5- and 5,6-fused heterocycles 190a-e. The selectivity is highly dependent on the borane reagent used in the reaction as in addition to promoting the ionization of allyl alcohol,\textsuperscript{120} 9-BBN-(C\(_6\)H\(_{13}\)) is directly involved in the enantiodiscriminating step (Scheme 56).

![Scheme 56](image)

The stereoselective palladium-catalyzed cyclization of THP ether 191 gave four diastereomeric 2,4,6-trisubstituted tetrahydropyrans 192a and 192b of which the 4,6-cis-isomer was produced as the major product.\textsuperscript{121} The cyclization was carried out employing different alcohol using Pd(PhCN)\(_2\)Cl\(_2\) as catalyst. In the case of 2\(\alpha\) and 2\(\beta\) products, major products were 2\(\beta\) isomer and the stereoselectivity (2\(\beta\):2\(\alpha\)) was almost 3:1-2:1 (Scheme 57).

![Scheme 57](image)

The above reaction may proceed through the formation of hemiacetal intermediate. Four possible conformations (A-D) are assumed which allow the alcohol of the hemiacetal to attack the olefin. The 4,6-cis products are predominantly formed from the chair-like transition state A and B with the allylic alcohol equatorially oriented. The conformations C and D, where the allylic alcohol is in the axial position, causing destabilization by 1,3-diaxial interactions may afford the 4,6-trans product. The hemiacetal reacts intramolecularly with palladium-coordinated olefin shown in A to result in the observed major 2\(\beta\)-isomer 192aa (Scheme 58).
6.1.2. ADDITION TO ALLENE

The transition metal-catalyzed cyclization of functionalized allenes has caught the attention of many synthetic chemists due to its unique reactivity and stereoselectivity. Palladium-catalyzed addition of heteroatom nucleophiles to allenes followed by trapping of the intermediate alkenyl palladium intermediate by proton or any electrophilic species has found extensive applications in the synthesis of heterocycles.

In particular, the reaction between two same or differently functionalized allenes, i.e, homodimerization reaction of functionalized allenes and is of considerable interest. Hasmi et al. reported the homodimerization reaction of allenyl ketone. The intermolecular dimerization of 2,3-allenoic acids using PdCl$_2$ as catalyst afforded bicyclic butenolide. Moreover, in the heterodimerization the reactions between 2,3-allenoic acids or 2,3-allenamides and 1,2-allenyl ketones, both allenes were cyclized to form products with two different rings. An interesting $\beta$-hydroxy elimination to dienyl unit was observed during the palladium-catalyzed cyclization of 2,3-allenoic acids in the presence of 2,3-allenols. Alcaide and co-workers also reported similar cross-coupling cyclization reactions of R-allenols in the presence of 2,3-allenyl carboxylates (Scheme 59).

Intermolecular cross coupling reaction between 2,3-allenoic acids and simple allenes by Pd(OAc)$_2$ and BQ afforded highly substituted furan-2(5$H$)-ones Z-198 (Scheme 60). The catalytic cycle that leads to furan-2(5$H$)-ones is suggested to proceed via initial cyclic oxypalladation of 2,3-allenoic acids with Pd(II) to generate furanonyl palladium intermediates which is trapped by the simple allenes to afford $\pi$-allylic intermediates (Scheme 61).
The synthesis of sterically congested bicyclic tetrahydrofurans 201a,b from allenyltetrahydroxyfurans 200a,b by palladium-catalyzed sequential cyclization-coupling reactions has recently been reported.\textsuperscript{130} The PdCl$_2$-CuCl$_2$-catalyzed reaction showed excellent results for the construction of bicyclic tetrahydrofurans 201a (98%) (Scheme 62).
6.1.3. ADDITION TO ALKYNE

The palladium-catalyzed reaction of alkyne with proximate nucleophilic center represents a useful reaction to afford products via intermolecular nucleophilic attack at the \( \pi \)-palladium alkyne complex, which is generated in situ by the coordination of Pd(II) to carbon-carbon triple bond\( \textsuperscript{1,2} \). This provides a straightforward approach to the synthesis of a large number of oxygen heterocycles.

A base free palladium-catalyzed heterocyclization of 2-alkynylphenols for the synthesis of 2-substituted 3-halobenzo[\( b \)]furans 204a,b\textsuperscript{131} has been reported by employing two different catalytic combinations (condition-A: PdCl\( _2 \)-CuCl\( _2 \) and condition-B: PdBr\( _2 \)-CuBr\( _2 \)) to afford 2-phenyl 3-bromobenzo[\( b \)]furan 204a and 2-phenyl 3-chlorobenzo[\( b \)]furan 204b by treating 202 to condition-A and B respectively. The dehalogenated product 203 in 17% yields was obtained as a byproduct when the reaction was performed under condition-B (Scheme 63). It is suggested that HEt\( _3 \)NX, employed in the reaction, may labilize the palladium-carbon \( \sigma \)-bond, thereby converting palladium into a good leaving group.\textsuperscript{132}

\[
\begin{align*}
\text{Condition A: (0.3 mmol), PdCl}_2 (5 \text{ mol%), CuCl}_2 (3 \text{ equiv}) \\
\text{HEt}_3\text{NI (0.2 equiv), DCE (5 mL), rt}
\end{align*}
\]

\[
\begin{align*}
\text{Condition B: (0.3 mmol), PdBr}_2 (5 \text{ mol%), CuBr}_2 (3 \text{ equiv}) \\
\text{HEt}_3\text{NI (0.2 equiv), DCE (5mL), rt}
\end{align*}
\]

Scheme 63

The combination of PdI\( _2 \)/KI catalyst has been found to be quite effective for the divergent synthesis of (Z)-1-alkylidene-1,3-dihydroisobenzofurans 206 and 1\( H \)-isochromenes 207 via 5-\( \textit{exo-dig} \) or 6-\( \textit{endo-dig} \) cyclization of 2-alkynylbenzyl alcohols 205 (Scheme 64).\textsuperscript{133}

\[
\begin{align*}
\text{Scheme 64}
\end{align*}
\]

Electronic factors show high impact on the regioselectivity of the palladium-catalyzed hydroalkoxylation of alkylnols by controlling the mode of cyclization i.e. 5-\( \textit{exo-dig} \) versus 6-\( \textit{endo-dig} \).\textsuperscript{134} This is in contrast to the base promoted cyclization where the cyclization proceeds through 5-\( \textit{exo-dig} \) mode exclusively.\textsuperscript{135} In the Pd(MeCN)\( _2 \)Cl\( _2 \) mediated cycloisomerization of sugar acetylenic derivatives 208a-e both 5-\( \textit{exo-dig} \) and 6-\( \textit{endo-dig} \) cyclizations were observed depending on the nature of the substituent on the aromatic ring leading to the formation of products 209 and 210 in poor to excellent yields.\textsuperscript{136} It is interesting to note that electron-donating group attached to the aromatic ring favors a 6-\( \textit{endo-dig} \) while electron attracting group...
favors a 5-exo-dig mode of cyclization. The formation of ketals 209a, 210b and 210e occur due to further cyclization of the free hydroxyl group at C₆ (Scheme 65).

Palladium-catalyzed cyclization and subsequent conjugate addition of the carbopalladium intermediates have been achieved by successive hydroalkoxylation of 212 with Pd(MeCN)₂Cl₂, conjugate addition with acrolein and LAH reduction in one-pot to give a mixture of compounds 213 and 214 (Scheme 66).

3,3,3-Trifluoroprop-1-en-2-yl substituted furans 215 were efficiently synthesized by Pd(MeCN)₂Cl₂-catalyzed cyclization-isomerization of 1,1,1-trifluoro-2-[t-butyldimethylsilyl oxy]-methyl]-3-alkynylbut-2-en-1-ols (Scheme 67). The catalysts like Pd(OAc)₂, Pd(PPh₃)₄, Pd₂(dba)₃ and Pd(PPh₃)₂Cl₂ were found to be inactive under the reaction conditions. The formation of the furan ring may be easily explained by considering a 5-endo-dig ring closure of the hydroxyl group at the activated alkyne.

Substituted 2,3-dihydrofurans 218 were synthesized by the palladium-catalyzed reaction of propargylic carbonate 217 containing a homopropargylic hydroxyl group with different phenols (Scheme 68). The reaction was carried out using Pd₂(dba)₃.CHCl₃-dppf catalytic system in dioxane.
The hydroxypalladation-reductive elimination reaction between o-alkynylcardanol 219 and iodobenzene utilizing Pd(db)3, 2,2'-bipyridyl (bpy) and K2CO3 in acetonitrile at 50 °C afforded 2,3-disubstituted benzo[b]furan derivative 220 (Scheme 69).139

Gouverneur et al. devised a palladium(II)-catalyzed Wacker-Heck reaction involving the union of structurally diversified hydroxy-ynones 221 and ethyl acrylate, two electron deficient species. The reaction, generally, proceeds through intramolecular hydroxylation to generate the σ-alkenyl palladium intermediate which may be trapped by olefin intramolecularly.140 An optimization studies for the ring closure of 221 into 222 revealed that the choice of catalyst and additive play an important role on the success of this cascade process. It was observed that except in two cases when the reaction was carried out in 10 mol% of Pd(MeCN)4(BF4)2, K2CO3, PPh3, Cu(OAc)2-H2O or in 10 mol% of Pd(MeCN)4(BF4)2, K2CO3 respectively, the desired product was obtained exclusively along with side product 223 due to the protonolysis of the σ-alkenyl palladium intermediate. Interestingly, addition of LiBr minimised the formation of 223 and increased the yield of 222 to 43%. The best result with an improved 58% yield of 222 was obtained when the reaction was carried out in the presence of 10 mol% of Pd(MeCN)2Cl2, Cu(OAc)2, PPh3 and 20 mol% of LiBr in DME at 65 °C under an atmospheric pressure of oxygen (Scheme 70).

Gabriele et al. recently developed a PdI2-catalyzed new, selective and atom economical methodology for the synthesis of 2-[(dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]dioxine 225 starting from 2-prop-2-ynyloxyphenols 224 as a mixture of E- and Z-isomers of which Z-isomer was produced
The methodology was also extended to other secondary amines such as morpholine where also Z-isomers were formed as the major products (Scheme 71).

A similar sequential oxidative aminocarbonylation-intramolecular conjugate addition-cyclization was observed during the synthesis of 2-[(dialkylcarbamoyl)methylene]tetrahydrofuran derivatives starting from pent-4-yn-1-ols 226, under the aforesaid reaction conditions (Scheme 72).

Gabriele et al. recently reported palladium-catalyzed oxidative aminocarbonylation of various substituted alkynols for the construction of different heterocyclic skeletons. The product formation depends on the position of the OH group with respect to the triple bond. The alkynols 228 were reacted with PdI₂, KI and amine in dioxane under CO/air (4:1) to afford the 6-hydroxy-2-ynamide 229 along with the formation of furan derivatives 230. The reaction follows two sequential processes – a palladium-catalyzed oxidative aminocarbonylation of the triple bond, followed by a 5-exo-dig cyclization leading to the formation of dihydrofuran derivatives 230 (Scheme 73).

Bioactive benzofurans 232 were synthesized by sequential homobimetallic from precursors 231 using Pd(PPh₃)₄ and PdI₂ (homobimetallic catalyst) and KI (excess) as the catalytic system. The major products 232 in this reaction were obtained along with small amount of byproducts 233, 234 and 235 (Scheme 74).
An efficient general synthesis of 2-benzofuran-2-ylacetamides \(^{147}\) \(238\) starting from 1-(2'-allyloxyaryl)-2-yn-1-ols \(236\), amines \(237\) and CO with Pd\(_2\)-PPh\(_3\)-KI has been developed utilizing sequential homobimetallic concept (Scheme 75).

The scope of the oxidative carbonylation-cyclization protocol was further extended \(^{148}\) by synthesizing benzofurans \(240\) and benzopyran \(241\) derivatives (Scheme 76).

Propargylic esters \(242\) in the presence of Pd(MeCN)\(_2\)Cl\(_2\)/BQ underwent oxidative cyclization-carbonylation reaction to afford methoxycarbonylated orthoester \(243\) (Scheme 77). \(^{149}\) The uncyclized product \(244\) was obtained only when R\(^1\) is p-methoxyphenyl. Very poor yield of the compound \(244\) was observed only with the benzoate having electron-attracting group attached to the para-position of the aromatic ring.
Wu et al. reported Pd(0)-catalyzed cascade addition-oxidation reaction of 2-alkynylbenzaldehyde with aryliodides in methanol. The one-step reaction afforded the regio- and stereoselective synthesis of stereoisomeric methyl-2-(2,2-disubstituted-vinyl) benzoates along with the addition product. The exclusive formation of the products was observed only when electron-withdrawing substituent was present in the aromatic ring. This regio- and stereoselective domino process simultaneously coupled the oxidation of an aldehyde to an ester with the hydroarylation of an alkyne to an alkene (Scheme 78).

![Scheme 78](image)

The reaction of alkenyl aldehydes with methanol in the presence of Pd(II) catalyst to afforded a mixture of five- and six-membered alkenyl ethers. However with alkynyl benzaldehyde, the cyclization in the presence of Pd(OAc)$_2$, BQ and MeOH gave exclusively six-membered product in moderate yield. In this transformation Pd(OAc)$_2$ acted as dual role catalyst exhibiting both as a Lewis acid for enhancing the electrophilicity of aldehyde as well as a transition metal catalyst for enhancing the electrophilicity of the alkyne bond, for constructing the R-methoxycyclic alkenyl ether from the o-alkynylaryl aldehyde (Scheme 79).

![Scheme 79](image)

Oxidative carbonylation of the substrate was carried out with PdI$_2$ catalyst with KI leading to complete conversion of the substrate with the formation of products and the benzoxazine derivative. The product is formed by a 6-exo-dig mode of cyclization (Scheme 80). The dihydroindolone derivative is formed due to in situ formation of 2-ethynylaniline by cleavage of the amide bond.
This protocol was further extended to the synthesis of tetrahydrofuran derivatives\(^{153}\) with fair diastereoselectivity. The compounds 253 when subjected to oxidative carbonylation-cyclization by PdI\(_2\) and KI afforded 2-methoxy-5-[methoxycarbonyl)methylene]tetrahydrofurans 254 and 255 and respectable diastereoselectivity (Scheme 81).

Palladium-catalyzed cyclization of the dihydroxy pyrrole 256 with propargylic carbonate 257 afforded 2-alkyldenepyrrolo[c]-1,4-dioxane derivatives 258 and 259 with around 85:15 regioselectivity (Scheme 82).\(^{154}\) The reactions of alkynes 257a,c,d were conducted using Pd(PPh\(_3\))\(_4\) and dppb to afford dioxane compounds 258a,c,d in excellent yields along with traces of compounds 259a,c,d where as excellent yields of 259b,e were obtained from alkynes 257b,e.

\[
\begin{align*}
R^1 & \quad R^2 & \quad R^3 \\
HETEROLOGY, Vol. 81, No. 3, 2010 & \quad CO + 2\text{MeOH} + (1/2)\text{O}_2 & \quad \text{PdI}_2\text{-KI} \\
253a. R^1 = \text{Me}, R^2 = \text{H}, R^3 = -\text{CO}_2\text{Me} & \quad \text{MeOH}/\text{MeCN} & \quad 65-100\degree\text{C} \\
253b. R^1 = \text{Me}, R^2 = \text{Et}, R^3 = -\text{CO}_2\text{Me} & \quad 24-36\text{ h} & \quad 254a-g (33-89\%) \\
253c. R^1 = \text{Me}, R^2 = \text{Bn}, R^3 = -\text{CO}_2\text{Me} & & \quad 255a-g (0-30\%) \\
253d. R^1 = \text{Me}, R^2 = \text{Et}, R^3 = -\text{COMe} & & \\
253e. R^1 = \text{R}^2 = -\text{CH}_2\text{Ph}, R^3 = -\text{CO}_2\text{Et} & & \\
253f. R^1 = \text{Ph}, R^2 = R^3 = \text{H} & & \\
253g. R^1 = \text{Ph}, R^2 = \text{Me}, R^3 = \text{CO}_2\text{Me} & & \\
\end{align*}
\]

Scheme 81

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Bn} \\
\text{256} & \quad \text{MeO}_2\text{CO} \\
\text{EtO}_2\text{C} & \quad \text{Bn} \\
\text{257a}. R^1 = R^2 = \text{H} & \quad \text{258a} (85\%) \\
\text{257b}. R^1 = \text{H}; R^2 = \text{Me} & \quad \text{258b} (\text{traces}) \\
\text{257c}. R^1 = \text{Me}; R^2 = \text{H} & \quad \text{258c} (95\%) \\
\text{257d}. R^1 = \text{Et}; R^2 = \text{H} & \quad \text{258d} (95\%) \\
\text{257e}. R^1 = \text{H}; R^2 = \text{Et} & \quad \text{258e} (\text{traces}) \\
\end{align*}
\]

Scheme 82

6.2. INTRAMOLECULAR COUPLING OF OH WITH ARYL HALIDE

Pd-catalyzed cross-coupling between Csp\(^2\)-halides or triflates represent some of the most powerful and versatile tools for the construction of C-N and C-O bonds in modern synthetic organic chemistry.\(^1\) Methodologies for the construction of this type of bonds intramolecularly have become extraordinarily popular, as they represent a very efficient entry into different types of important nitrogenated and oxygenated heterocyclic compounds.\(^2\)

A palladium-catalyzed highly efficient enantioselective synthesis of chiral substituted 2-methylchromans was developed\(^{155}\). The product distribution in this reaction is controlled by the steric environment adjacent to the alcohol. Thus from the substrate having both primary and secondary alcohol at the
tethering under the Buchwald condition employing Pd(OAc)₂/ligand-263 afforded exclusively the six-membered oxacycle 261a (Scheme 83). In contrast, the substrate 260b bearing both tertiary and primary alcohol at the tethering under the same reaction conditions found to afford the chroman along with seven-membered oxacycle 261c. This regioselectivity may be due to the propensity for forming a seven-membered palladacycle 262a, versus an eight-membered palladacycle 262b.

Scheme 83

Synthesis of ladder-type furan rings, dibenzo[d,d’]benzo[1,2-b:4,5-b’]difurans 265a-c was achieved by Pd(OAc)₂-catalyzed intramolecular O-arylation of 264a-c using 2-di-tert-butylphosphino-2’-methylbiphenyl (L₁) as ligand and 2,6-di-tert-butyl-4-methylphenol (BHT) as additive. A substantial base and solvent effect on the O-arylation was observed and the compounds 265a-c were obtained. Substitution on the aryl rings affect the reaction yields and in case of electron-withdrawing group this effect increases (Scheme 84).

Scheme 84

6.3. CYCLOCARBONYLATION AND CYCLOCARBOXYLATION REACTIONS

The palladium-mediated carbonylation and carboxylation reactions have been extensively employed in the synthesis of heterocycles. Ma et al. reported a mild and efficient Pd-catalyzed carbonylation of propargylic alcohols with various structural patterns for the synthesis of (Z)-R-chloroalkylidene-β-lactones selectively. In the presence of PdCl₂-CuCl₂ catalytic system and carbon monoxide optically
active propargylic alcohols 266 allowed a convenient synthesis of the corresponding (Z)-α-chloroalkylidene-β-lactones 267 with high ee values (Scheme 85).

\[
\text{R}^1 \text{C} (= \text{O}) \text{R}^2 \xrightarrow{\text{PdCl}_2(10 \text{ mol\%}), \text{CuCl}_2(5 \text{ equiv})} \text{THF, CO (20 atm)} \xrightarrow{30 \degree \text{C}, 4 \text{ h}} \text{267}
\]

Scheme 85

The reaction between 2-methylbut-3-yn-2-ol 268 and thiophenol in the presence of Pd(OAc)$_2$, PPh$_3$, $p$-TsOH and CO afforded thiolactonization product 269 as the major product along with mono- and dithiocarboxylation products 270 and 271 (Scheme 86).$^{160}$

\[
\text{HO} \xrightarrow{\text{Pd(OAc)$_2$/PPh$_3$, p-TsOH}} \xrightarrow{400 \text{ psi CO, THF}} \text{268} \text{ SPh} \xrightarrow{120 \degree \text{C}, 48 \text{ h}} \text{269} 58\% + \text{270} 13\% + \text{271} 7\%
\]

Scheme 86

Palladium-catalyzed annulation of internal alkynes by $o$-iodophenol in the presence of CO employing Pd(OAc)$_2$, pyridine, and $n$-Bu$_4$NCl afforded coumarin derivative 274$^{161}$ (Scheme 87).

PdI$_2$-catalyzed oxidative aminocarbonylation of the terminal alkynes 275 has been described as a facile route for the synthesis of five-membered oxygen heterocycles 276$^{162}$ Thus, propargyl alcohol and amine when subjected to PdI$_2$, carbon monoxide and oxygen in the presence of secondary amine afforded 4-dialkylamino-5$H$-furan-2-ones 276 by a sequential oxidative aminocarbonylation-intramolecular conjugate addition-cyclization route (Scheme 88). The reaction also works well when hetero atom is nitrogen giving corresponding N-heterocycles.

\[
\text{R}^1 \text{C} (= \text{O}) \text{R}^2 \xrightarrow{\text{PdI}_2 \text{ cat}} \xrightarrow{\text{CO, R}_2\text{NH, O}_2} \text{275}
\]

Scheme 88

Another interesting example of palladium-catalyzed cyclocarbonylation reaction was encountered during the synthesis of the lactone ring of (+)-Ricciocarpin A$^1$ 279$^{163}$ The lactone ring (+)-279 was constructed via intramolecular carbonyl insertion of the alcohol (-)-277 in the presence Pd(OAc)$_2$ and
triarylphosphine. Reduction of compound 278 with sodium borohydride resulted in the formation of (+)-ricciocarpin 279 (Scheme 89).

\[
\begin{align*}
\text{(-)-277} & \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{CO, Et}_3\text{N}, \text{DMPU}} \text{MeOH, 55 °C, 24 h, 89\%} \\
\text{(+)-278} & \xrightarrow{\text{NaBH}_4, \text{pyridine}} \text{rt, 6 h, 76\%} \\
\text{ (+)-279}
\end{align*}
\]

Scheme 89

It was observed that palladium-catalyzed cyclocarbonylation and thiocarbonylation reaction of enynols with thiols gave usually thioester-containing 6-membered-ring lactones 281 using THF as the solvent. Similar reaction of enynols 280 with a variety of thiols when conducted with 500 psi carbon monoxide in the presence of a catalytic amount of Pd(OAc)$_2$ (2 mol\%) and PPh$_3$ (8 mol\%) in ionic liquid [bmim]PF$_6$ or [bmim][Tf$_2$N], exhibited excellent chemoselectivity and resulted in the formation of the monocarbonylated product 281 (Scheme 90).

\[
\begin{align*}
\text{R}^1 = & \text{H, Ph, p-MeC}_6\text{H}_4, p-\text{EtC}_6\text{H}_4, m-\text{MeOC}_6\text{H}_4 \\
\text{R}^2 = & \text{R}^3 = \text{H, -(CH}_2\text{)}_2- \\
\text{R}^4 = & \text{Ph, -OC}_6\text{H}_4, p-\text{FC}_6\text{H}_4, 2-\text{naphthyl, C}_9\text{H}_17, i-\text{Pr}
\end{align*}
\]

Scheme 90

The reaction of chiral propargylic carbonates 282a,b was shown to proceed in a highly enantiospecific manner to give chiral cyclic carbonates 283 via an overall cascade chirality transfer process (Scheme 91).

\[
\begin{align*}
\text{(S)-282a, R = Me} & \xrightarrow{\text{Pd}_2(\text{dba})_3, \text{CHCl}_3 (5 \text{ mol\%}) \text{ ligand (20 mol\%)}} \text{dioxane, 50 °C} \\
\text{8-24 h, CO}_2 \text{ atm} & \xrightarrow{} \text{(Z,S)-283aa-283ae} \\
\text{(S)-282b, R = pentyl} & \xrightarrow{} \text{(E,R)-283aa-283ae}
\end{align*}
\]

Scheme 91

The enantiospecificity of this cascade reaction, performed by using Pd$_2$(dba)$_3$,CHCl$_3$ as catalyst is highly dependent on the choice of phosphine ligand. Thus, by using dppe as a ligand enantiomerically enriched chiral propargylic carbonate 282a afforded both cyclic carbonate (Z,S)- and (E,R)-283aa in a 10:1 ratio
with 95% enantiomeric excess for each product. The same reaction with (S)-282a in the presence of dppp selectively afforded (E,R)-283aa without any loss of enantiomeric purity or dppe as ligand in the presence of phenol as nucleophile afforded both (Z,S)- and (E,R)-283 in high enantiomeric purity. A similar highly enantiospecific cascade reaction occurred between 282a,b and various phenols to afford the corresponding cyclic carbonates (Z,S)- and (E,R)-283ab-ae.

7. CYCLIZATION VIA CASCADE CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION: HETEROCYCLIZATION REACTIONS

7.1 HETEROCYCLIZATION REACTIONS WITH ALKYNES

Palladium-catalyzed intermolecular heterocyclization of alkynes has emerged as an accomplished route to the synthesis of large varieties of heterocycles. Depending upon the nature of the alkynes employed, the annulation proceeds through two distinctively different mechanistic pathways. For terminal alkynes, widely popular Sonogashira coupling and base mediated cyclization approach afford the heterocycles. However, intermolecular addition of the nucleophile to C-C triple bond followed by intramolecular reaction appeared to be a convenient pathway for the heterocyclization with internal alkynes. An interesting substituent effect on the mode of cyclization during palladium-catalyzed domino Sonogashira cross coupling cyclization of o-iodocardanol 288 was reported. Substituent effect was found to be very effective for the synthesis of lipophilic benzo[b]furans 290 from terminal alkynes and o-iodophenols. With (2-methoxyethoxy)methyl protected 2-methylbut-3-yn-2-ol utilized as terminal alkyne precursor, chroman-4-one 292 was produced presumably via initially formed cross-coupling reaction.
intermediate, addition of water to carbon-carbon triple bond, an elimination step and conjugate addition of the phenolic oxygen to the resultant \( \alpha,\beta \)-unsaturated carbonyl compound. However, 2-methylbut-3-yn-2-ol afforded the benzo\([b]\)furan derivative 290 low yield along with the acetophenone derivative 291 as the major product (Scheme 93). In the latter case, instead of conjugate addition, removal of hydroxy group as acetone through retroaldol reaction led to the formation of acetophenone derivative 291. Apparently, the addition of water to the C-C triple bond of the coupling intermediate in these cases is faster than the desired intramolecular cyclization onto the phenolic oxygen. An improved reaction conditions utilizing \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) (0.02 equiv), \( \text{CuI} \) (0.04 equiv), \( \text{Et}_2\text{NH} \) (2 equiv) in DMF at 60 °C was found to be effective for the preparation of 2-substituted benzo\([b]\)furans in good-to-excellent yields.

Regio- and stereocontrolled synthesis of stannylated butenolides was achieved through palladium-catalyzed domino cross-coupling/cyclization reaction of tributylstannyl (Z)-3-substituted iodopropenoate with tributylstannylacetylene. \(^{172}\) \( \text{Pd(PPh}_3\text{)}_4 \) is an efficient catalyst for the preparation of (E)-5-tributylstannymethylidene-5\( H \)-furan-2-ones 294a-e (Scheme 94).

\[
\begin{align*}
\text{R}^1 & = \text{H, Me, MeOCH}_2\text{, Ph, Me}_3\text{Si} \\
\text{Bu}_3\text{Sn} & \xrightarrow{25 \degree \text{C}, 16 \text{ h}, \text{DMF}} \text{Bu}_3\text{Sn} \\
\text{294a-e} & \text{ (62-70\%)}
\end{align*}
\]

(2\( E \))-2,3-Difluoro-3-iodoacrylic acid 295 underwent coupling-cyclization with terminal alkyne under co-catalysis of \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \) (2 mol\%) and \( \text{CuI} \) (5 mol\%) to provide 3,4-difluoro-6-substituted-2-pyrone 296 in 43-71% yields. \(^{173}\) The formation of the compound 296 (when \( \text{R} = \text{Ph} \)) was assumed to involve in situ generation of yneenoic acid. Interestingly, exclusive formation of the six-membered pyrone ring may be due to the partial polarization of the triple bond by the two fluorine atoms facilitating the attack of the carboxylate anion at the partial positive charged carbon atom (Scheme 95).
Heterogenous catalyst, Pd/MgLa mixed metal oxide has been utilized to conduct the copper free Sonogashira coupling between o-halogenated phenols and phenylacetylene. The reaction is efficient only in the case of 2-iodophenol giving the 2-arylbenzofuran derivative 299 while with bromo- and chloro-compounds due to low reactivity afforded the desired benzofuran derivative in low yield (Scheme 96).

One pot synthesis of diverse 2-substituted furo[3,2-c]quinoline derivatives based on domino coupling-cyclization between 3-iodoquinoline-4-ones 300 and terminal acetylenes afforded the compounds 301 in excellent yields (Scheme 97).

### 7.1.2. REACTIONS WITH INTERNAL ALKYNES

Double annulation of bis(allyloxy)bis(alkynyl)benzene 302 in the presence of Pd$_2$(dba)$_3$.CHCl$_3$ catalyst and PPh$_3$ as ligand afforded the tetrasubstituted benzodifuran 303 in 71% yield along with a trace amount of 304 (Scheme 98).
7.2 HETEROCYCLIZATION REACTIONS WITH ALKENES

Pd(II)-catalyzed oxidative annulation of alkenes with oxygen nucleophiles, commonly known as Oshima Utimoto reaction,\textsuperscript{178a} has received much attention in synthetic organic chemistry. The use of Pd(II)-catalyst along with large amount of Cu(II) as promoter of the catalyst in the oxidative addition of allylic alcohol to olefin has been well established.\textsuperscript{178} Mechanistically, the reaction proceeds via oxypalladation followed by 5-\textit{exo} cyclization and $\beta$-hydrogen elimination to give the cyclic ether 309 (Scheme 99).

\[
\begin{align*}
\text{R} & \quad \text{O}\quad \text{R} \\
\text{OH} & \quad \text{OR} \quad \text{PdX}_2 + \text{HX} \rightarrow \text{R} & \quad \text{PdX} \quad \text{OR} \quad \text{Pd(0)} + \text{HX} \\
\text{305} & \quad \text{306} & \quad \text{5-exo} & \quad \text{308} & \quad \text{309} \\
\text{Pd(0)} & \quad 2\text{HX} \quad \text{<OX>} & \quad \text{PdX}_2 & \quad \text{<OXH}_2>
\end{align*}
\]

Scheme 99

Recently, Pd(II)-Cu(II) catalysis has been utilized in the synthesis of 2-alkoxytetrahydrofurans 310 from allylic alcohols and vinyl ethers. Using catechol as an activator, the reaction afforded cyclic ethers in moderate-to-excellent yields (Scheme 100).\textsuperscript{179} The role of catechol may be in (i) enhancement of catalyst stability by construction of a Pd-Cu heterometallic species bearing catechol as ligand of Cu (II) effective capture of O$_2$ by its activator by the Cu-catechol moiety. The occurance of 5-\textit{exo} cyclization of the oxypalladium intermediate 307 rather than 6-\textit{endo} cyclization may be due to conformational compatibility of the oxypalladation adduct 307 for undergoing the cyclization towards the internal alkene, which must coordinate to Pd(II). It has been observed that the rate of cyclization depends on the Ph-group attached and thus the presence of electron-withdrawing group retards the reaction.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\text{OH} & \quad \text{O} \\
\text{(1 mmol)} & \quad \text{Cu(OAc)$_2$(0.05 mmol)} \quad \text{O$_2$, MeCN, rt, 3 h} \\
\text{305} & \quad \text{306a} & \quad \text{Pd(OAc)$_2$(0.05 mmol)} & \quad \text{310} \\
\text{Pd:Cu: GC yield (%)} & \quad 1:1:1 & \quad 48 \\
\text{1:1:2} & \quad 82 \\
\text{1:1:4} & \quad 84(82)$^a$ \\
\text{1:1:4} & \quad 79 \\

\text{[a] Isolated yield}
\end{align*}
\]

Scheme 100

Palladium-catalyzed stereoselective Oshima-Utimoto reaction was successfully achieved for the construction of five-membered oxacycle 312 employed for the preparation of lactone ring in the asymmetric synthesis of (-)-11R,1,3-dihydroxanthatin.\textsuperscript{180} The allylic alcohol 311 on treatment with Pd(OAc)$_2$/Cu(OAc)$_2$ catalytic system in acetonitrile afforded the tetrahydrofuran derivative in 68% yield and with $>$12:1 1,2-stereoisinduction (Scheme 101). Presumably, the Pd-catalyzed process proceeded via
the chair like transition state 313 and was found to result in a separable 1:1 mixture of α and β anomers. The target compound was subsequently synthesized in few steps in 66% yield.

The allylic alcohol 314 and vinyl ether 306b, when subjected Oshima-Utimoto reaction under the conditions 10 mol% Pd(OAc)$_2$, 2.5 equiv Cu(OAc)$_2$ in MeCN at 55 °C for 15 h afforded the furan derivative 315 in 69% yield with >15:1 1,2 diastereoinduction (Scheme 102).

Stereocontrolled synthesis of tricyclic core cis-lactone 317 of the natural product (-)-panacene 765 via intramolecular alkoxy carbonylation-lactonization protocol was achieved\textsuperscript{182} by Pd(OAc)$_2$-catalyzed domino cyclization of the phenol 316. The natural (-)-panacene 318 was then synthesized from the tricyclic lactone 317 (Scheme 103).

Catalytic amounts of Pd(II), H$_4$PMo$_{11}$VO$_{40}$.28H$_2$O (HPMo$_{11}$V), and Lewis acid-like CeCl$_3$\textsuperscript{183} were found to be very effective for the construction of ethyl-5-methyl-3-furoate 321 in 86% yield from ethyl acrylate 319 and propanaldehyde 320.\textsuperscript{184} The reaction was conducted in the presence of 1 atmosphere of oxygen
using solvent mixture (MeOH-AcOH). It is proposed that the acrylate initially formed acetal 322 or its synthetic equivalent 323 may undergo aldol type condensation with 320 by CeCl₃ to give an α,β-unsaturated carbonyl condensate 326 which on subsequent enolization by Pd(II) followed by intramolecular cyclization may produce ethyl furoate 321 through Pd-H elimination from a dihydrofuran intermediate 329. Finally, the reduced Pd(0) was reoxidized to Pd(II) by the action of HPMo₁₁V/O₂ reoxidation system (Scheme 104).³⁸⁵

\[ \text{Scheme 104} \]

7.3. HETEROCYCLIZATION REACTIONS WITH DIENES

Larock et al. reported an efficient approach to biologically interesting dihydrofuroflavonoids 332 via palladium-catalyzed annulation of 1,3-dienes by o-iodoacetoxyflavonoids 330.³⁸⁶ The regioselective reaction was accomplished by employing catalyst Pd(dba)₂/dppe and base Ag₂CO₃ in dioxane/H₂O as solvent (4:1) to afford compound 332 (Scheme 105).

\[ \text{Scheme 105} \]

In the case of cyclic 1,3-dienes 334, an increase in the ring size of the cyclic 1,3-diene led to a significantly lower yield of annulation products 335 (Scheme 106).³⁸⁷
8. PALLADIUM-CATALYZED MULTI-COMPONENT REACTION

Recently there is flurry of activities in the development of efficient synthetic procedure that can affect multiple chemical reactions in a one-pot event.\(^{188, 189}\) The ability of the palladium-catalysts to affect multicomponent reactions has enable to rapidly generate the libraries of heterocyclic compounds.\(^{1, 190}\) The reactions are highly chemo-, regio- and stereoselective and show excellent tolerance of functional groups.

8.1. PALLADIUM-CATALYZED THREE-COMPONENT REACTION

Three-component reaction between 1,3-diketone with terminal alkyne in the presence of carbon monoxide was effected in the presence of Pd(PPh\(_3\)\(_2\))Cl\(_2\) as catalyst and dppp as ligand in ionic liquid [bmim][Tf\(_2\)N] gave highly substituted endocyclic enol lactones 338 in moderate-to-good yields (Scheme 107).\(^{191}\) The reaction is assumed to proceed via the generation of alkoxy- and acyl palladium complex 339 and 340. Regioselective intramolecular acylpalladation of the latter and subsequent reductive elimination may produce the linear precursor 341 and regenerate the palladium(0) species. An intramolecular cyclization of the vinyl acetate with the activated double bond may then give the 6-membered enol lactone 338.

Meijere \textit{et al.} developed a Pd(0)-catalyzed novel multicomponents queuing cascade reaction for the construction of spiro-annulated five- and six-membered heterocycles.\(^{192}\) The three-component cross coupling reactions of bicyclopropyldene 342 with \textit{with} \textit{o}-iodophenols were investigated using various catalytic conditions. However for \textit{o}-iodophenol this condition favored the formation of 345 (24%) over 344 (11%). The formation of the product 345 was avoided by protecting the OH group with TMS, which gave the product 344 (29%) (Scheme 108). The reaction also works well when heteroatom is nitrogen affording corresponding nitrogen heterocycles.
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9. MISCELLANEOUS

9.1 INTRAMOLECULAR HECK REACTION

The syntheses of the macrocyclic taxoids \(^{193}\) \(352\) and \(352\) from \(351\) and \(351\) were achieved by using the catalysts Pd(PPh\(_3\)) and Pd\(_2\)(dba)/AsPh\(_3\) respectively by an exclusive exo-cyclization mode (Scheme 111). Likewise, the macrocycles \(354\) were also obtained in good yields.

\[ \text{Scheme 111} \]
Synthesis of a range of highly constrained cyclic tripeptides, a mimic of vancomycin’s carboxylate-binding pocket, via intramolecular Sonogashira coupling as the ring-closing reaction was reported by Liskamp and co-workers. The linear precursors 355a-c when subjected to Pd(PPh$_3$)$_4$, CuI and Et$_2$NH furnished the cyclic peptides 356a-c. Interestingly, increasing steric bulk (leucine, 355c) or the absence of a turn-inducing motif (glycine, 355a) resulted in a lower yield of cyclization and formation of undesired byproducts (nonstrained diynes 357) and cyclic dimer 358 were obtained along with the strained 15-membered peptide macrocycles 356 (Scheme 112).
9.2. CYCLOADDITION REACTIONS

The behavior of oxime ether in the presence of palladium catalyst is quite interesting. It has been observed that the oxime O-allyl ether 359 in the presence of Pd(MeCN)₂Cl₂ as catalyst in CHCl₃ at 60 °C underwent formal [2,3] sigmatropic rearrangement to generate unstable nitrone intermediate 360 which could be trapped by 1,3-dipolar cycloaddition with dipolarophiles like maleimide 361 to give the cycloadduct 361a (Scheme 113). This reaction is nonselective as diastereomeric mixture is obtained.

![Scheme 113](image)

To test the intramolecular nature of the nitrone formation, a cross over experiment was set to allow scrambling of the partners (Scheme 114). However, after 72 h the formation of products 361b and 363 clearly indicate that the nitrone formation proceeds completely in an intramolecular fashion.

![Scheme 114](image)

9.3. INTRAMOLECULAR ADDITION OF N-H BONDS ACROSS ALKENE

Domino N-arylation/cyclization/C-arylation of O-homoallylhydroxylamines 364 with aryl bromides in the presence of Pd₂(dba)₃, x-phos and NaOt-Bu afforded cis-disubstituted isoxazolidine derivatives 366 (Scheme 115).

![Scheme 115](image)
A highly diastereoselective Pd(0)-mediated cascade C-C and C-N bond formation was achieved in a one-pot event for the synthesis of isoxazolidine derivatives 368. The reactions of O-homoallyl hydroxylamines 367 with aryl iodides were best carried out in the presence of Pd$_2$(dba)$_3$, P(o-tol)$_3$ and Cs$_2$CO$_3$ in refluxing PhMe for 20 h to afford the isoxazolidine derivatives 368 together with normal Heck coupling adducts 369 (Scheme 116). The effect of base and reaction time on the enantioselectivity of the palladium-catalyzed asymmetric domino allylic substitution of (Z)-1,4-diacyloxy- and (Z)-1,4-bis(alkoxycarbonyloxy)-2-butene 370a-c using 2-(phosphinophenyl)pyridine (375) as chiral ligand have been reported. All the reactions were carried out using [Pd(C$_3$H$_5$Cl)] as catalyst in CH$_2$Cl$_2$ at room temperature employing various nucleophiles. For 2-(benzylamino)phenol and 2-(benzylamino)ethanol, excellent yields and good enantioselectivities were observed when the reaction was carried out for 72 h using KF as a base where as the reaction with 1,2-bis(benzylamino)ethane was best effected with K$_2$CO$_3$ as the base with good enantioselectivity. In all the cases the products 373 and 374 were formed with R-configuration (Scheme 117).

Formation of the products 373 and 374 proceeds via π-allylpalladium complexes. The possible diastereomic π-allylpalladium complexes (376, 377, 379 and 380) are assumed to be in rapid equilibrium. The strong trans-effect of phosphorous causing preferential attack of the carbon trans to P-atom along with rotation of allyl system in the direction causing less steric repulsion during nucleophilic attack might be responsible for exclusive formation of the R-product via intermediate 378 (Scheme 118).
Palladium(0)-catalyzed regiospecific domino allylation of 2-aminophenols with 2-butene-1,4-diol produced two cyclized compounds 384 and 385 in comparable yields. The reaction was carried out in the presence of Pd(OAc)$_2$, PPh$_3$ and Ti(O$i$-Pr)$_4$. Interestingly, formation of the compound 385 was not observed in case of aromatic ring containing strongly electron-withdrawing group (NO$_2$). The addition of Ti(O$i$-Pr)$_4$ in this reaction promoted the allyl-OH bond cleavage, thus enhancing the rate of the reaction and the yield (Scheme 119). The same reaction was also applicable to the diamino substrates.

The reaction of 2-aminophenols with cyclic $meso$-allylic diacetates 387 catalyzed by Pd(dba)$_2$/PPh$_3$ gave phenoxazines 388 (Scheme 120). Based on well-known $\pi$-allylpalladium chemistry it is assumed that the relative stereochemistry of the morpholine ring and cyclopentene and / or the cyclohexene ring should be $cis$. 

Scheme 118

![Scheme 118](image)

Scheme 119

![Scheme 119](image)

Scheme 120

![Scheme 120](image)
9.4. INTRAMOLECULAR COUPLING OF NH AND OH WITH ARYL HALIDE

The Pd-catalyzed intramolecular arylamination and aryl etherification on carbohydrate derived substrates by using bulky biarylphosphine ligands has been reported. A variety of highly functionalized cis-fused tricyclic furobenzoazocines were prepared from D-glucose-derived substrates utilizing Pd(dba)₃ as catalyst and (±)-BINAP as ligand. KOt-Bu + K₂CO₃ was found to give excellent results for the bromo substrates while the iodo substrate afforded better result with Cs₂CO₃ (Scheme 121).

![Reaction Scheme 121]

An efficient synthetic protocol for the synthesis of a wide range of N-arylated 5-, 6- and 7-membered heterocycles involving palladium-mediated sequential intramolecular and intermolecular arylamination reactions has been reported. The use of an in situ generated Pd(0) catalyst associated to N-heterocyclic carbene, N,N-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidine (SIPr) as ligand, NaOt-Bu and Pd(OAc)₂ was found to be effective. This diarylation protocol was also applied to the synthesis of benzoxazines and benzoxazepines from 391 by employing the same conditions (Scheme 122).

![Reaction Scheme 122]

Ma et al. reported the synthesis of oxazepine ring containing pyridazinone moiety via palladium catalyzed intramolecular coupling of an aryl bromide with an alcohol. The pyridazinone when treated with Pd(OAc)₂ and (dppf) afforded the product. The reaction is assumed to proceed via palladium oxapalladacycle followed by C-O bond forming reductive elimination (Scheme 123).

![Reaction Scheme 123]
Palladium-catalyzed intramolecular cycloamination strategy for the synthesis of an assembly of oxazepine 396a and thiazepine ring 396b systems were carried out using Pd\(_2\)(dba)\(_3\), P(t-Bu)\(_3\) and NaOt-Bu or with K\(_2\)CO\(_3\) in PhMe. In general this worked well for the substrates, 2-[(2-bromobenzyloxy]aniline hydrochloride 395a and 2-[(2-bromobenzyl)thio]aniline hydrochloride 395b to give the desired substituted oxazepine and thiazepine tricyclic core (Scheme 124).

9.5. CYCLOCARBONYLATION AND CYCLOCARBOXYLATION REACTIONS

Gabriele et al. reported that a combination of PdI\(_2\) and KI in DME exhibited excellent catalytic efficiency in the oxidative cyclocarbonylation reaction of \(\beta\)-amino alcohols and 2-aminophenol (Scheme 125)

9.6. HETEROCYCLIZATION REACTION WITH ALKYNE

A palladium-catalyzed one-pot heterocyclization for the construction of polycyclic indole derivatives 400 starting from 2-chloroanilines 399 bearing tethered acetylenes was achieved by using Dt-BPF as ligand, K\(_2\)CO\(_3\) as base and NMP as solvent at 130 °C (Scheme 126). The reaction is also applicable when X = nitrogen affording corresponding nitrogen heterocycles.
9.7. PALLADIUM-CATALYZED FOUR-COMPONENT REACTION

Gabriele et al. reported an efficient concatenation of aminocarbonylation and cyclocarbonylation for the synthesis of 2-oxazolidinones 403a,b.\(^{212}\) The one-pot method consists of the reaction of \(\alpha,\alpha\)-disubstituted 2-ynylamines with CO, \(\text{O}_2\), and morpholine in the presence of catalytic amounts of PdI\(_2\) in conjunction with KI and H\(_2\)O (PdI\(_2\)/KI/1/2/H\(_2\)O molar ratio1:10:500: 500), in DME as the solvent at 100 °C under 20 atm of a 4:1 mixture of CO/air to afford 403 in excellent yield. The reaction in the presence of secondary amine like piperidine and diethyl amine also proceeded smoothly with good yield of oxazolidinones. In the case \(\alpha\)-monosubstituted propargylamine, such as benzyl-[1-(1-ethylpropyl)prop-2-ynyl]amine under the same reaction conditions, the initially formed oxazolidinone underwent a spontaneous double bond shift with the formation of 3H-oxazol-2-one derivative 403b (Scheme 127).

9.8. CLAISEN REARRANGEMENT

Pd-catalyzed domino Claisen rearrangement\(^{213}\)/oxidative cyclization of allyl aryl ethers 404 into benzofurans 405 was investigated by Youn et al.\(^{214}\). The scope of this sequential process was tested with different allyl aryl ethers in the presence of Pd(MeCN)\(_2\)Cl\(_2\) as catalyst, Na\(_2\)CO\(_3\) as base and BQ as oxidant in dioxane to afford benzofuran derivatives. This reaction is facile for the electron rich arenes where as for the electron deficient arenes higher catalysts loading and increased temperatures are required (Scheme 128).

9.9. ELECTROCYCLIZATION REACTION

Stoltz et al. developed a diastereoselective tandem Stille-oxa-electrocyclization reaction to generate the pyran ring.\(^{215}\) A combination of catalytic Pd(PPh\(_3\))\(_4\), CuI and DMF with exclusion of light facilitated coupling of 407 with 406 to yield the furan appended tricyclic spiro compound 409 (Scheme 129).
The presence of light and CuI is very much essential for this domino Stille-oxa-electrocyclization reaction. However, in the presence of light only Stille coupling occurs along with cis-trans isomerization, resulting in the formation of trans-dienone 410.

10. CONCLUSION
Synthetic strategies involving palladium is highly desirable due to its versatility in catalyzing a broad spectrum of chemical transformations under mild conditions and tolerance of functional groups. Heterocyclic compounds are widely used in chemical, pharmaceutical and agricultural industries. The applications of palladium catalysis in the synthesis of heterocyclic compounds are now at its premium level of achievement. In this review, we have demonstrated an enclave of novel and exciting palladium chemistry, which has now become a powerful tool in the synthesis of heterocycles.

Strategically, palladium-catalysis in the synthesis of oxygen heterocyclic compounds is very important, as this constitute an efficient strategy for carbon-carbon and carbon-heteroatom bond formation. Although significant contributions have already been made in this area, new challenges are continuously forthcoming. Proper tuning of the reaction conditions will lead to the development of new methodologies that can widen the scope of the application of palladium-catalysts even for the synthesis of complex biologically active molecules. We hope that this review will be useful to the synthetic chemists in general and heterocyclic and medicinal chemists in particular.

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