HETEROCYCLES, Vol. 81, No. 3, 2010, pp. 517 - 584. © The Japan Institute of Heterocyclic Chemistry
Received, 20th October, 2009, Accepted, 25th December, 2009, Published online, 28th December, 2009
DOI: 10.3987/REV-09-662-1

RECENT DEVELOPMENT IN PALLADIUM-MEDIATED SYNTHESIS OF OXYGEN HETEROCYCLES

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

CONTENTS

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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[1] and reviews[2] 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.[3] In addition, the Pd-catalyzed domino multiple transformation, in recent years, have been the general need both from economical and ecological ground.[4]

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.

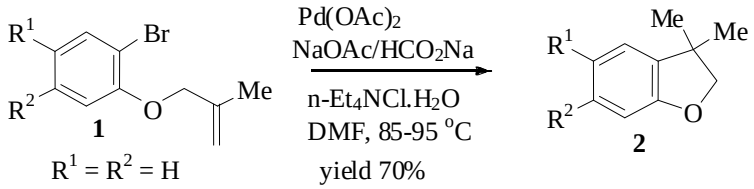
The search for various heterocycles and many new methodologies involving palladium has been the central goal in recent years. Our prime objective is to provide a complete and updated summary of palladium-catalyzed approaches for the preparation of oxygen heterocycles developed from 2003 onwards with 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.[2,5] Heck reaction[1a,2a,6] 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.[7] 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.[8] Recently intramolecular reactions have been developed involving related carbopalladation reactions followed by trapping with nucleophilic reagents.[9] For macrocyclization via C-C bond formation with olefin or alkyne, the well-known Heck, Suzuki, Sonogashira and Stille reactions are now routinely considered.[10] 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[11] or oxidative coupling with olefin[12] 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.[2a] By contrast, macrocycle formation proceeds through a favourable *endo*-cyclization pathway.[10]

2.1. REACTIONS OF ARYL HALIDES

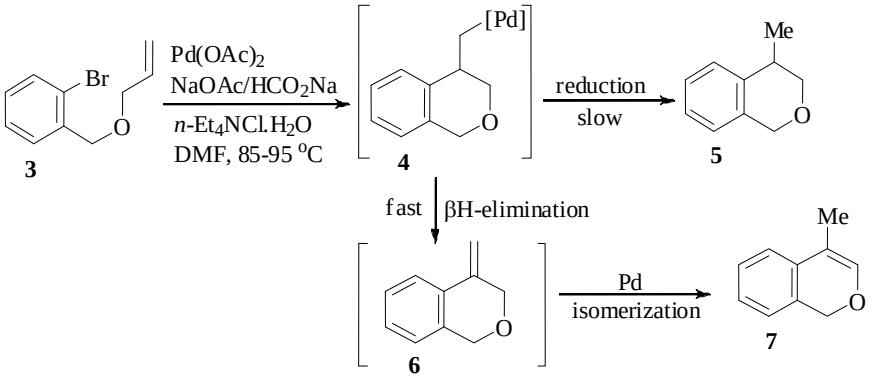
In palladium-catalyzed Heck reaction, aryl iodide has been found to be the most commonly used halide source.[13] However, the use of aryl bromide or aryl chloride for the construction of heterocycles would be very much interesting from the synthetic point of view.[14] In an investigation, Liu et al. reported the use of aryl bromide **1** for the synthesis of 2,3-dihydrobenzofurans **2** under ligand free $Pd(OAc)_2$–catalyzed reductive Heck[15] cyclization (**Scheme 1**).[16] However, an excellent improvement in the yield of **2** (87%) was observed under the Buchwald condition.[17] 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,[18] a 70% yield of **2** was obtained.



Scheme 1

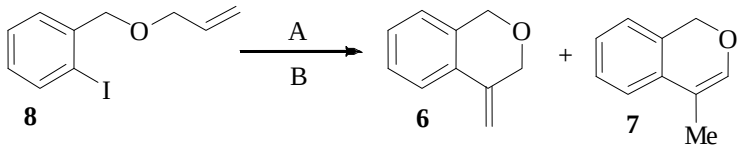
The efficiency of the methodology was explored by the synthesis of chromans and isochromans in excellent yields. Quite interestingly, the greater propensity of formation of normal Heck product **7** instead of reductive cyclization product **5** from the ether **3**, under reductive Heck condition, clearly indicated

faster *β*-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

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.*[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.

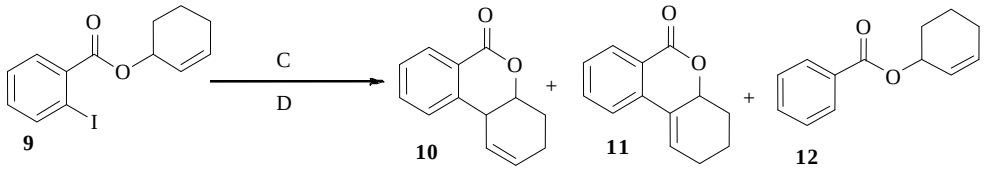


Conditions A: $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Et_3N (2 equiv.) $AgNO_3$ (1 equiv.), MeCN, 80 °C

Conditions B: Styrene (3 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Et_3N (2 equiv.), $AgNO_3$ (1 equiv.), MeCN, 80 °C

Scheme 3

In contrast to ether, the intramolecular Heck reaction[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**).



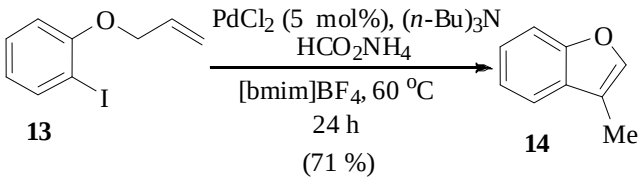
	9 + 11	**12**
Condition C:	13%	14%
Condition D:	34%	0%

Condition C: $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Et_3N (2 equiv), MeCN, 80 °C

Condition D: $Pd(OAc)_2$ (10 mol%), KOAc (2 equiv.), *n*-Bu_4NBr (1 equiv.), 4 Å MS, DMF, 80 °C

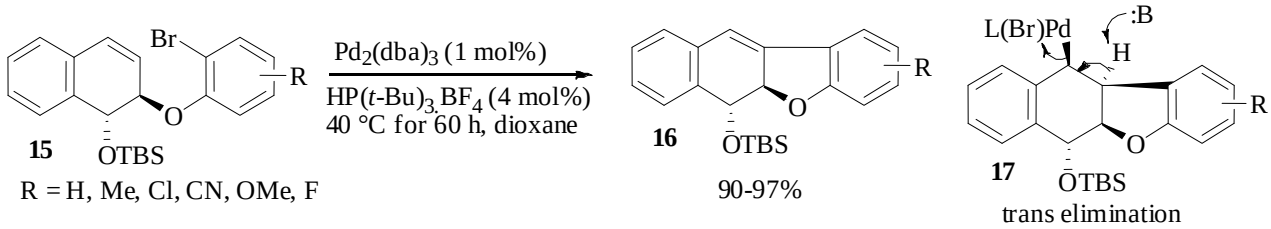
Scheme 4

The use of ionic liquids[21] in $PdCl_2$-catalyzed intramolecular Heck reaction for the synthesis of benzofuran derivative **14** was demonstrated by She *et al.*[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**).



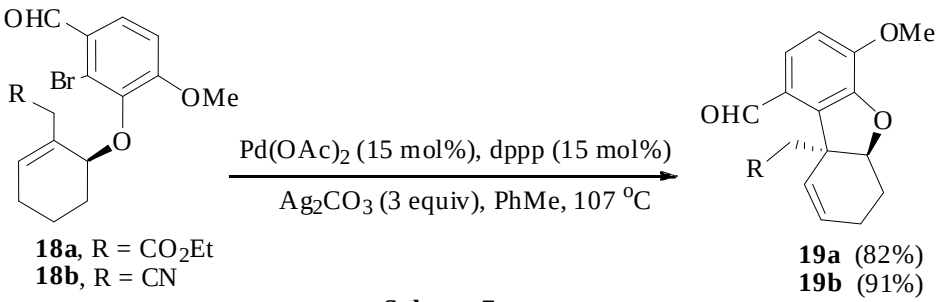
Scheme 5

Lautens and Fang reported[23] 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 *anti*-hydride elimination[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[25] (**Scheme 6**).



Scheme 6

The $Pd(OAc)_2$-catalyzed asymmetric allylic alkylation of chiral *o*-bromoarylcyclohexenyl ethers **18a**,**b** for the construction of tricyclic benzofuran moieties **19a**,**b** was described.[26] Utilizing Jeffery condition[27] and also in the presence of monodentate ligand P(*o*-tol)$_3$, 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 *o*-bromoarylcyclohexenyl ethers **18a**,**b** give correspong Heck product **19a**,**b** in excellent yield (**Scheme 7**).

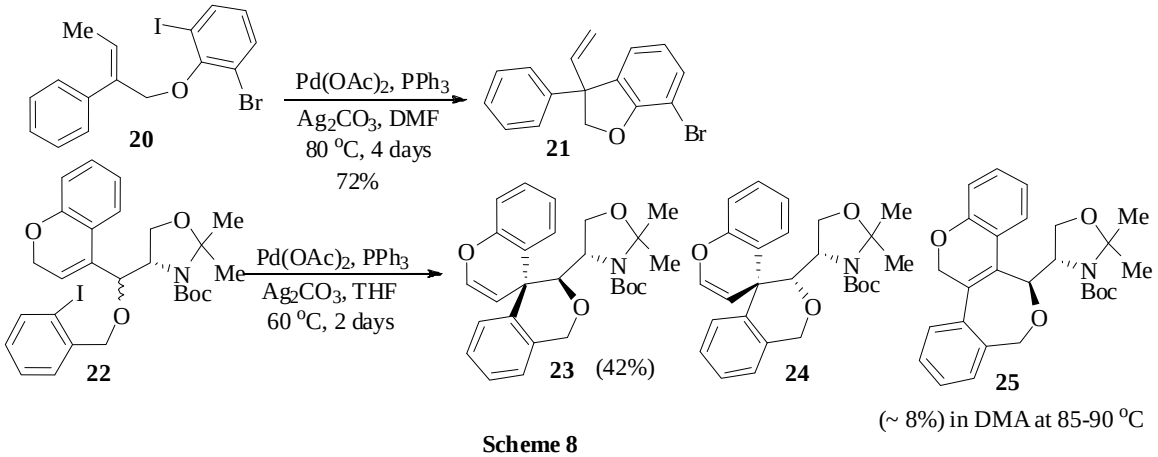


Scheme 7

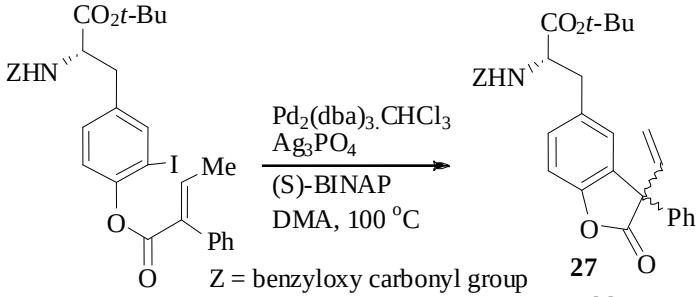
Pattenden and co-workers in an investigation towards the formation of quarternary stereocenter and heterocyclic core of diazonide A, reported that iodoalkene **20**, as a 3:1 mixture of *Z*- and *E*-isomers, when subjected to $Pd(OAc)_2$ in DMF in the presence of Ag_2CO_3 and PPh_3 for 4 days underwent 5-*exo*-*trig* cyclization to afford benzodihydrofuran **21** in 72% yield (**Scheme 8**).[28] The same catalytic combination in THF when applied to the mixture of *syn* and *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 $Pd_2(dba)_3.CHCl_3$ as catalyst, (*S*)-BINAP as ligand and Ag_3PO_4 as additive afforded the cyclized product **27** as a 3:2 mixture of diastereomers **(Scheme 9)**.

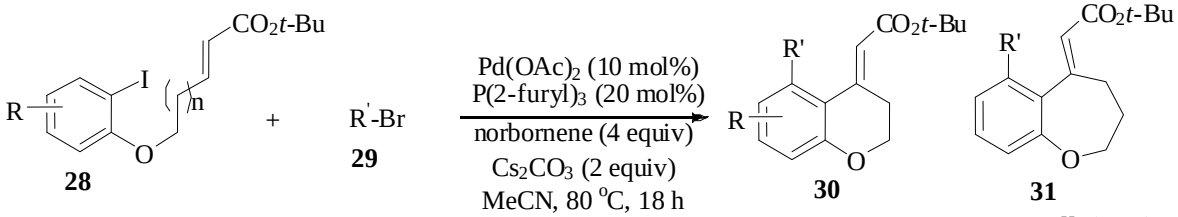


Scheme 8



Scheme 9

Norbornene-mediated $Pd(OAc)_2$-catalyzed reaction of *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 *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.



n = 1; **a**, R = 4-OMe; **b**, R = 5-NO_2; **c**, R = 4-Cl
n = 2; **d**, R = H

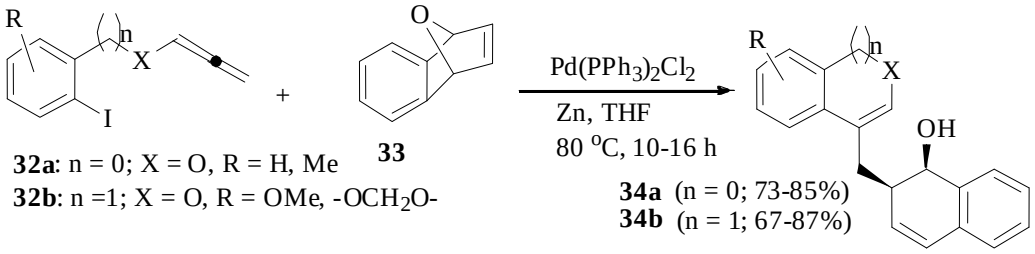
a, R' = $Ph(CH_2)_3$-
b, R' = $Cl(CH_2)_3$ -
c, R' = $EtO_2C(CH_2)_3$-
d, R' = $Ph(CH_2)_3$-

30aa (55%)
30ba (74%)
30ca (77%)

31db (47%)
31dc (45%)
31dd (45%)

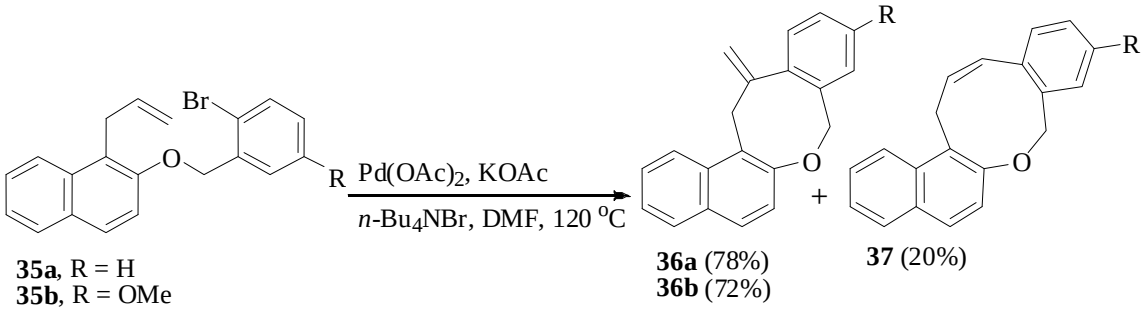
Scheme 10

Methyl-1,2-dihydro-1-napthalenol substituted benzofuran and 1*H*-isochromene derivative **34** were prepared[31] by a palladium-catalyzed cascade ring closure/ring opening reaction. By using $Pd(PPh_3)_2Cl_2$ 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]



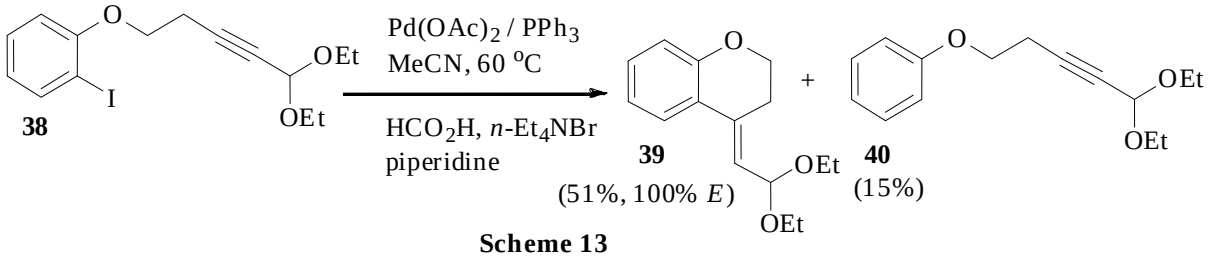
Scheme 11

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

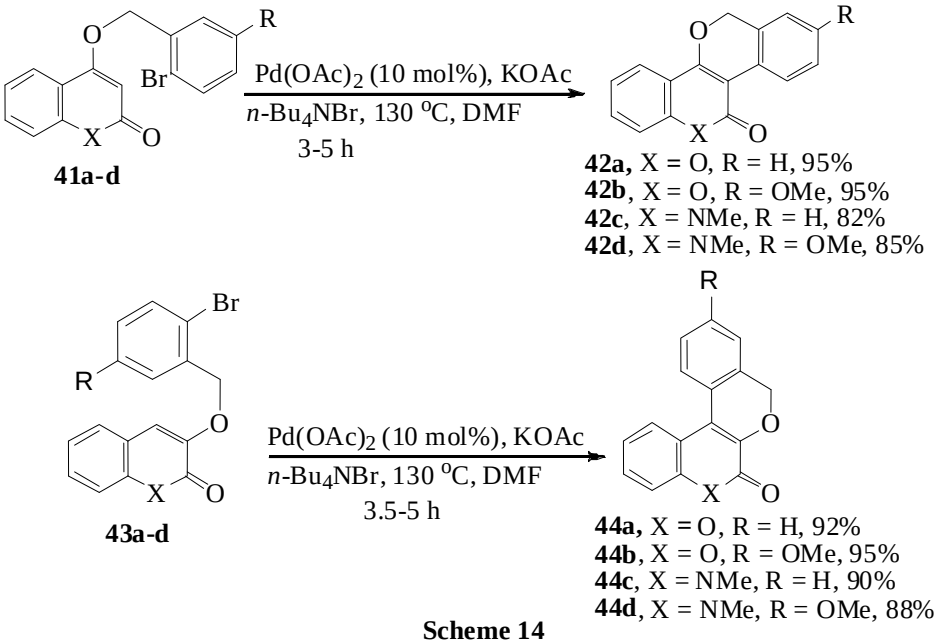
Intramolecular hydroarylation reaction of the homopropargyl ether **38** with $Pd(OAc)_2$ catalyst was reported to afford the chromene **39** along with inseparable alkyne byproduct **40** (**Scheme 13**).[33]



Scheme 13

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

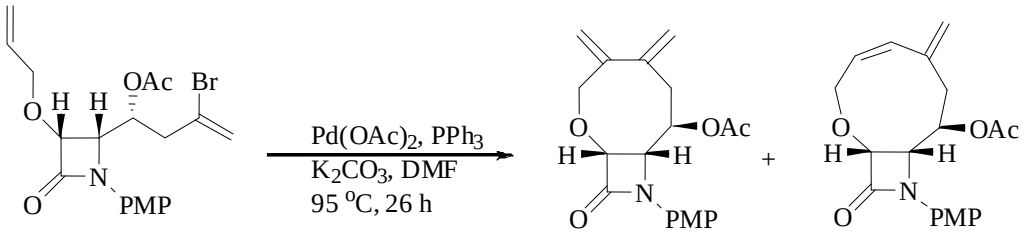
that for quinolone moiety the reaction yield is slight lower than that for corresponding coumarin moiety. By using $Pd(OAc)_2$ as catalyst, KOAc as base, and *n*-Bu_4NBr as additive in DMF a series of coumarin and quinolone derivatives **42a-d** and **44a-d** were synthesized.



Scheme 14

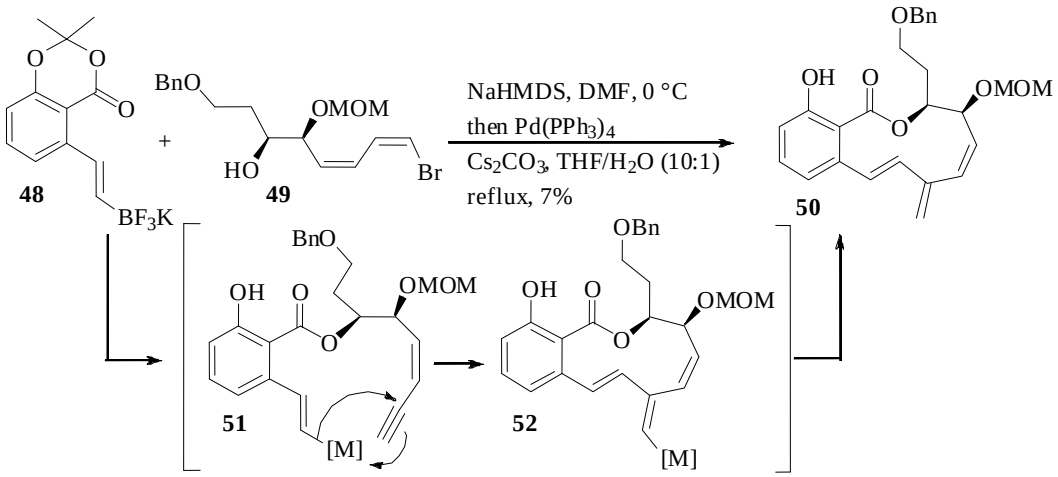
2.2 REACTIONS OF VINYL HALIDES

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**).



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**.

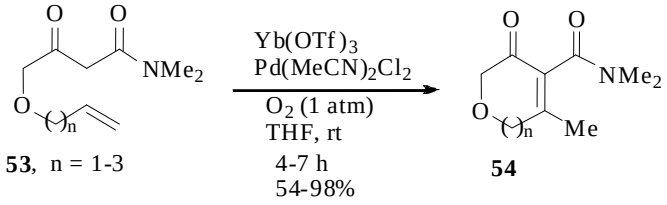


Scheme 16

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.[38] Thus the intramolecular coupling reaction of tethered vinyl or aryl halides and ketone enolates provides a useful route to a wide variety of heterocycles.[11]

The enolate generated from the *γ*-heteroalkenyl *β*-keto amides **53** underwent oxidative coupling[39] with the tethered alkene when subjected to $Pd(MeCN)_2Cl_2$ and $Yb(OTf)_3$ in dry THF under 1 atm O_2 as terminal oxidant.[40,41] A variety of six-, seven- and eight-membered oxygen heterocycles **54** were synthesized regioselectively from the heteroalkenyl *β*-ketoamides **53** 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.[41]



53, n = 1-3 **54**

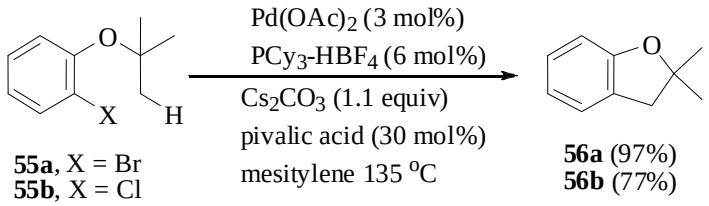
Scheme 17

3. CYCLIZATION VIA C-H BOND FUNCTIONALIZATION

Palladium-catalyzed functionalization of C-H bond[42] has undergone a rapid development over the past decade.[43] The potentiality of this excellent protocol has proven to be extremely useful for the synthesis of a wide variery of N- and O-heterocycles under mild conditions.[44] 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.[45] However, with unactivated alkanes, the functionalization reaction depends on less clearly defined substrate catalyst interactions.[46] Both intra- and intermolecular versions of this reaction are discussed in the following section.

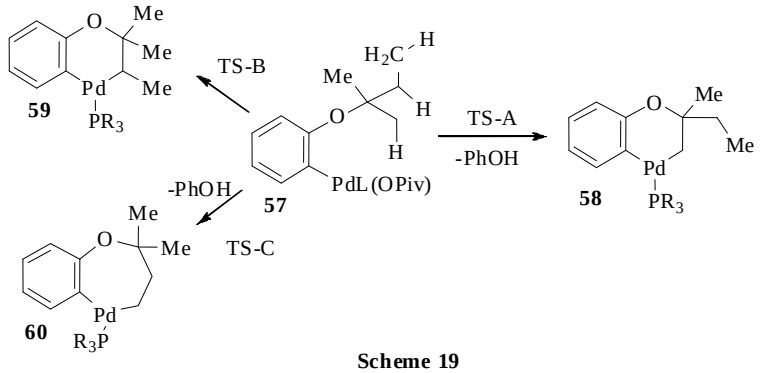
3.1 FUNCTIONALIZATION OF ALKANE C-H BONDS

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 realatively 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 $Pd(OAc)_2/PCy_3.HBF_4/Cs_2CO_3$/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 = Br and 77 %, X = Cl (**Scheme 18**).

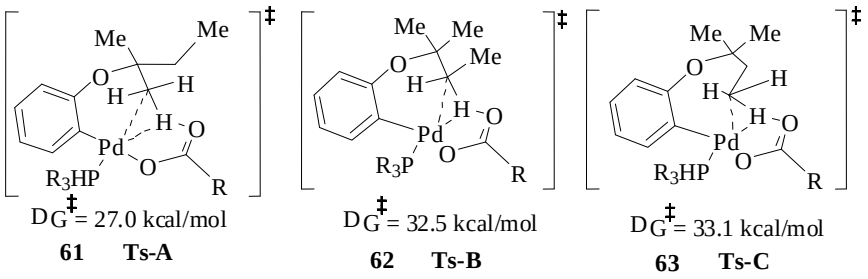


Scheme 18

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**).



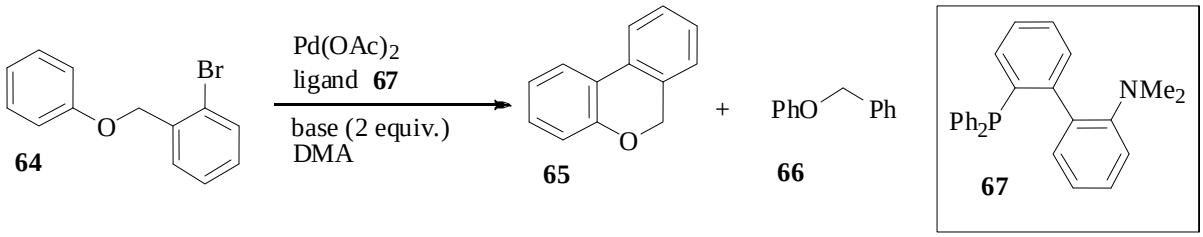
Scheme 19



3.2 FUNCTIONALIZATION OF AROMATIC C-H BONDS

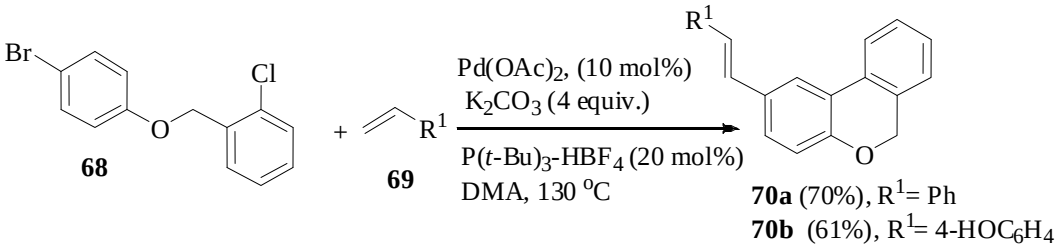
3.2.1 DIRECT FUNCTINALIZATION REACTIONS

The palladium-catalyzed direct functionalization of aromatic or heteroaromatic C-H bond[51] via C-H activation is a versatile way to generate a wide variety of O-heterocycles under mild conditions.[52] 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**[53] with low catalyst loading.[54] 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**).



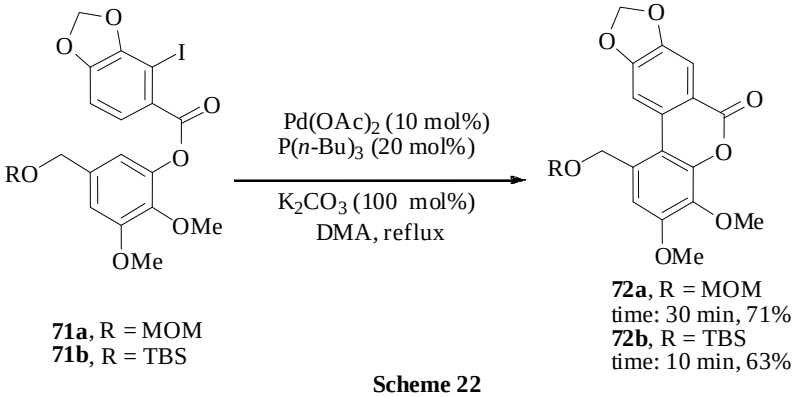
Scheme 20

Fagnou *et al*. reported that by employing a single catalytic system $Pd(OAc)_2/P(t\text{-}Bu)_3\text{-}HBF_4/K_2CO_3$ in the presence of styrene, compound **68** underwent domino intramolecular Heck reaction and direct arylation reaction to give the products **70a** in one pot[55] (**Scheme 21**). A *p*-acetoxy group on the styrenyl component becomes cleaved under the reaction conditions.



Scheme 21

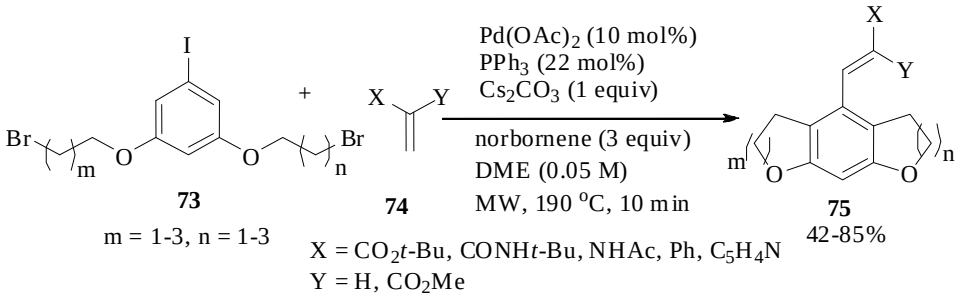
Palladium-catalyzed intramolecular biaryl coupling of phenyl benzoate derivatives **71a**,**b** was investigated.[56] The reactions of **71a**,**b** in the presence of $Pd(OAc)_2$, $P(n\text{-}Bu)_3$ and K_2CO_3 in DMA under refluxing condition proceeded smoothly to give benzo[*c*]chromen-6-ones **72a**,**b** (**Scheme 22**).



Scheme 22

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

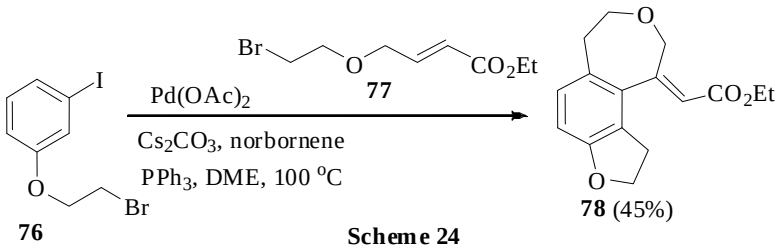
developed.[57,58] The interesting feature of this reaction is that two alkyl-aryl bonds and one alkenyl-aryl bond were formed in one-pot. Using various olefins as Heck acceptor and lengthening the bromoalkyl chain of the aryl iodide **73**, the syntheses of [5,6,5] ring, symmetrical [6,6,6]- and unsymmetrical [5,6,6; 7,6,7] systems **75** 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

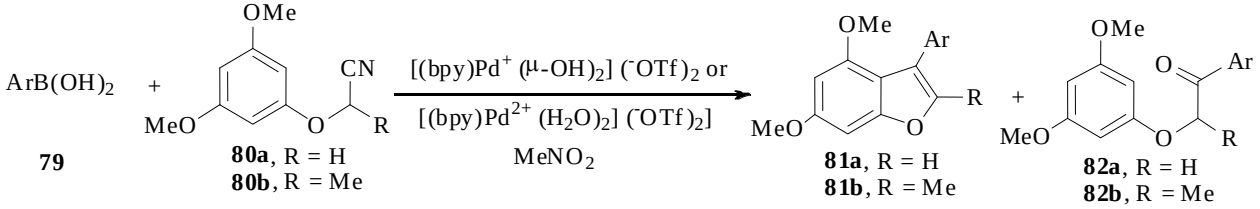
For the synthesis of sulfur and nitrogen heterocycles, slight modification of the reaction conditions (increased the catalyst loading to 20 mol%) was required to obtain a modest yield of the cyclized products[58,59]

An extensive work on the palladium-catalyzed domino three C-H functionalization for the synthesis of polycyclic heterocycles has recently been reported.[60] The norbornene-mediated and $Pd(OAc)_2$-catalyzed reaction of **77** and **76** afforded tricylic 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 $[(bpy)Pd^{+}(\mu\text{-}OH)_2](^{-}OTf)_2$ (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**).[61]



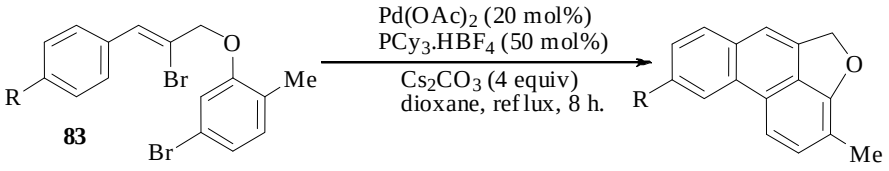
79, Ar = Ph, 4-Me-C_6H_4,4-MeO-C_6H_4,1-naphthyl, 2-naphthyl, 4-F-C_6H_4, 3-NO_2-C_6H_4, 4-$CF_3C_6H_4$ 3,5-diFC_6H_3, 3-MeO-C_6H_4, 2-MeO-C_6H_4, 2-Cl-c_6H_4

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

Scheme 25

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"[62] 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_2CO_3 in dioxane afforded[63] 5*H*-phenanthro[1,10-*bc*]furan derivative **84** (**Scheme 26**).

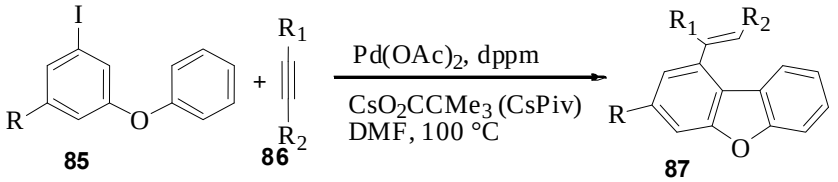


Scheme 26

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.[43] 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.

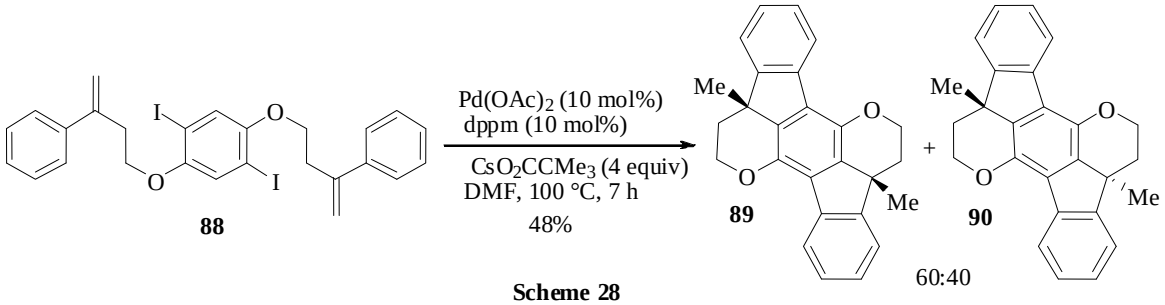
Recently, Larock *et al*. have applied their vinylic to aryl palladium migration strategy for the synthesis of substituted dibenzofurans,[64] although Pd-O coordination would be expected to be much weaker than Pd-N coordination. A series of 3-iodophenyl phenyl ether **85** reacted with various internal alkynes under the reaction conditions $Pd(OAc)_2$, bis(diphenylphosphino)methane (dppm) and CsO_2CCMe_3 (CsPiv) in DMF at 100 °C to afford two isomeric dibenzofurans **87a** and **87b** in moderate to excellent yield.[65] 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**).



R	R_1	R_2	yield	**87a: 87b**
H	Et	Ph	30	8:1
PhO	Et	Ph	75	9:1
MeO	Et	Ph	80	9:1
MeO	Me	Ph	78	9:1

Scheme 27

A novel methodology based on C-H activation via 1,4-palladium alkyl to aryl migration[64] followed by intramolecular arylation providing an expedient route to fused ring systems has been reported. Under the optimized reaction conditions aryl halides **88** afforded the compounds **89** and **90** (**Scheme 28**).[66]



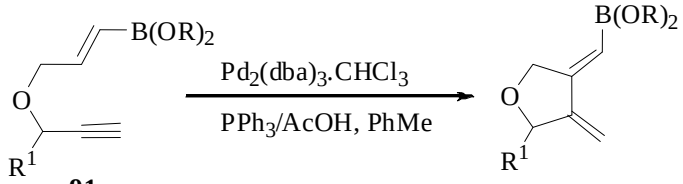
Scheme 28

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.[67] The reactions are broadly classified into two major categories: (a) cycloisomerization reaction[68] and (b) cascade addition-cyclization[69] reaction. The cyclization reaction usually proceeds through the generation of vinyl or alkyl palladium species either via hydro metallation pathway[70] (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.

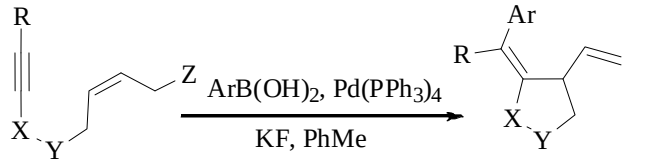
4.1 CYCLOISOMERIZATION REACTIONS

Palladium-catalyzed cycloisomerization reaction has proven as one of the versatile process to construct cyclic compounds from the acyclic 1,*n*-unsaturated precursors.[71] In general, 1,6-unsaturated system affords five-membered cyclic product. The cycloisomerization of enyne **91** in the presence of palladium source $Pd_2(dba)_3.CHCl_3/PPh_3$/AcOH afforded five-membered heterocycles **92** (**Scheme 29**).[72] By utilizing this protocol, a number of five-membered oxygen heterocycles were synthesized.



Scheme 29

Zhang and collaborators extensively investigated the palladium-catalyzed domino cycloisomerization/Suzuki coupling of 1,6-enynes.[73] 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**).

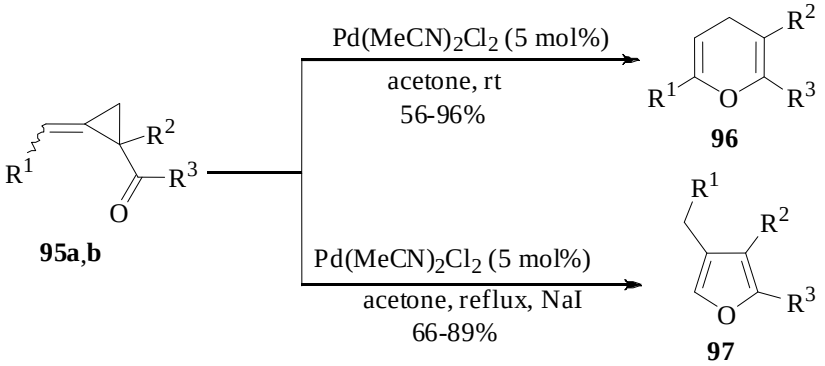


93a, X = CH_2; Y = O,
Z = Cl, Br, OCO_2Et
R = H, Me, CH_3OCH_2, Bu, Ph
93b, X = CO; Y = O, Z = Cl
R = Me, Bu, Ph

94a (21-90%)
94b (45-82%)

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**).[74] Interestingly, the reaction of the cyclopropyl ketones **95b** in the presence of NaI with the same catalyst afforded substituted furan derivatives **97**.



95a,**b**

96

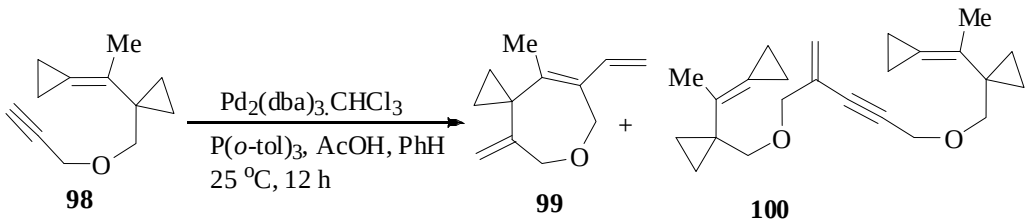
R^1 = C_7H_{15}, *n*-Bu, Bn, C_8H_{17}, $TBSO(CH_2)_3$
R^2 = CO_2Et, COMe, SO_2Ph, H
R^3 = Me, Ph

97

R^1 = C_7H_{15}, *n*-Bu, Bn, $TBSO(CH_2)_3$, H
R^2 = CO_2Et, SO_2Ph, H
R^3 = Me, Ph, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4, 1-naphthyl, 2-furyl

Scheme 31

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**).[75]



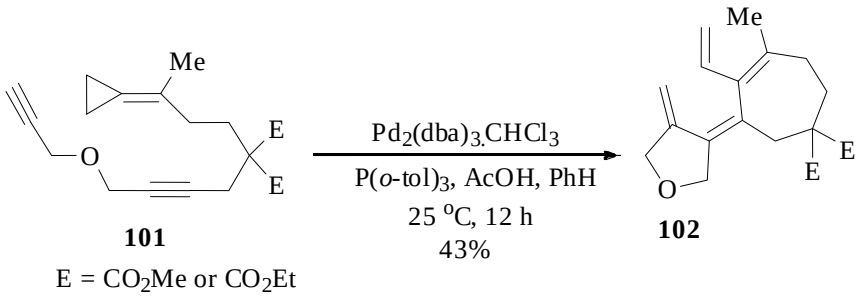
98

99

100

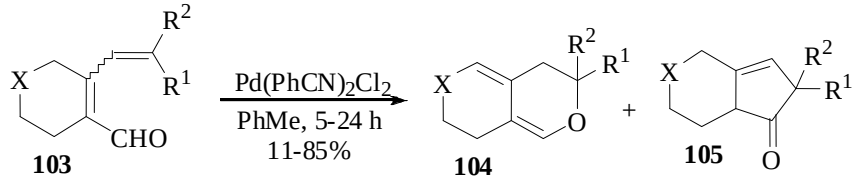
Scheme 32

The oligounsaturated open chain compounds **101** also underwent palladium-catalyzed oligocyclization for the construction of an elegant and efficient assembly of oligocyclic systems.[76] 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**).



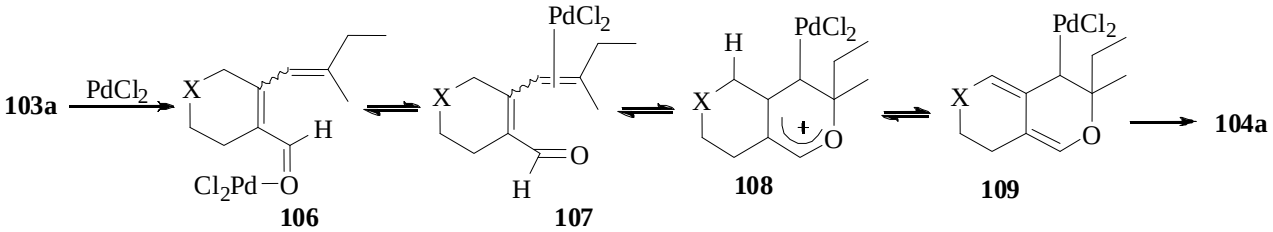
Scheme 33

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*.[77] The reaction was carried out in the presence of $Pd(PhCN)_2Cl_2$ in PhMe efficient for efficient construction of 2*H*-pyranderivatives **104** except only for three substrates [(i) R^1 = Me, R^2 = Et; (ii) R^1 = Me, R^2 = *i*-Pr; (iii) R^1 = R^2 = -{CH_2}$_4$-] 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**).



Scheme 34

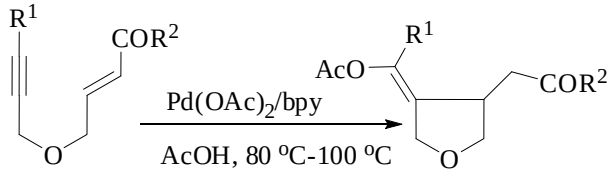
Mechanistically the *cis*-2,4-dien-als **103a** were expected to follow the pathway **106→107→108→109**. The added 2,6-lutidine accelerated the deprotonation reaction of intermediate **108** and preferably gave 2*H*-pyrans **104a** with the change of chemoselectivity (**Scheme 35**).



Scheme 35

4.2 CASCADE ADDITION-CYCLIZATION REACTIONS

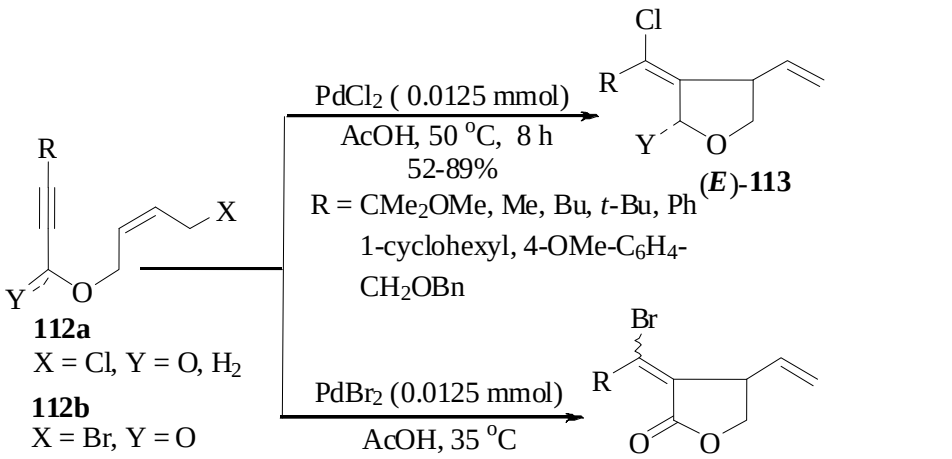
The divalent palladium-catalyzed intramolecular enyne coupling reaction initiated by acetoxypalladation[78] and halopalladation of alkyne was developed for the construction of a wide variety of five-membered oxygen and nitrogen heterocycles.[79] An assays of oxygen- tethered enynes **110** on treatment 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**).[80] The reactions were highly stereoselective as all the products contained *Z*-configured double bonds.



110 **111**

Scheme 36

An expedient route to the synthesis of stereo-defined α-halomethylene-γ-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**).



112a
X = Cl, Y = O, H_2

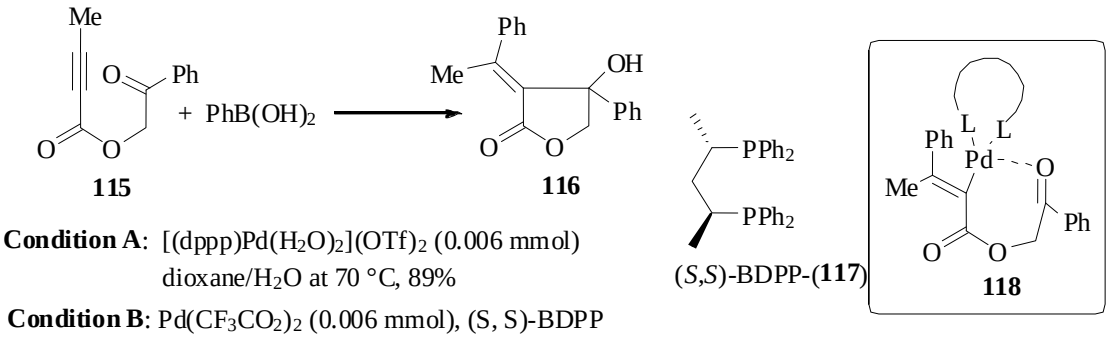
112b
X = Br, Y = O

(***E***)-**113**

114a, 73%, *E*/*Z*: 94/6, R = Me
114b, 82%, *E*/*Z*: 91/9, R = Ph

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)-$Pd(H_2O)_2$]$(OTf)_2$[84] as catalyst the reaction between **115** and arylboronic acids afforded α-alkylidene-β-hydroxy-γ-lactones **116** in excellent yields with *E*-configured exocyclic double bond. The asymmetric version of this reaction was conducted using $Pd(CF_3CO_2)_2$/(*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]



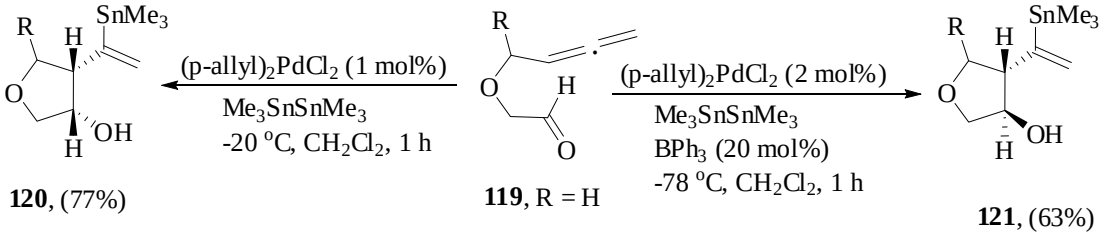
115 **116** (*S*,*S*)-BDPP-(**117**) **118**

Condition A: $[(dppp)Pd(H_2O)_2](OTf)_2$ (0.006 mmol) dioxane/H_2O at 70 °C, 89%

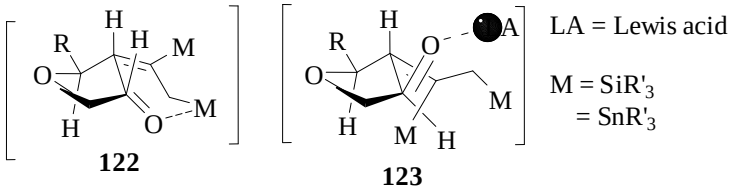
Condition B: $Pd(CF_3CO_2)_2$ (0.006 mmol), (S, S)-BDPP (0.0066 mmol), CH_2ClCH_2Cl/H_2O, 70 °C 87%, 82% *ee*

Scheme 38

Lewis acid additive showed high influence on the diastereoselectivity of the intramolecular allyl transfer reaction of allenic aldehydes **119** with hexamethylditin catalyzed by (π-allyl)$_2$PdCl$_2$ (**Scheme 39**).[86] Moderate-to-good yields of *trans*-products **121** were obtained by using $B(C_6F_5)_3$ 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 π-facial selectivity to yield *trans*-**121** may proceed via **123**.



120, (77%) **119**, R = H **121**, (63%)



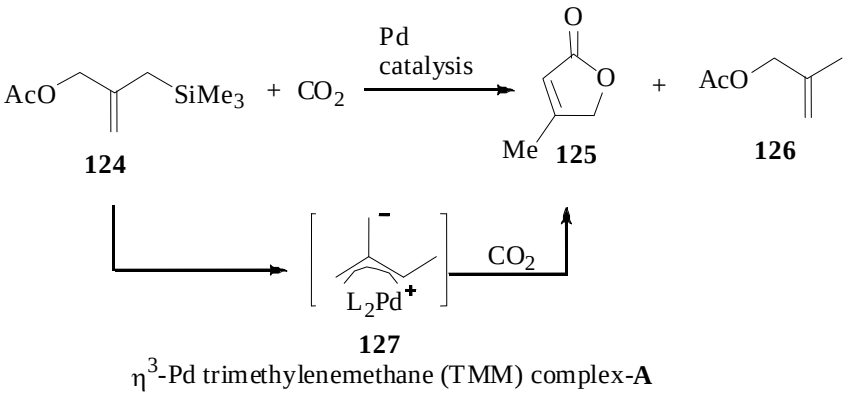
122 **123**

Scheme 39

5. CYCLOADDITION REACTIONS

5.1. [3+2] CYCLOADDITION REACTIONS

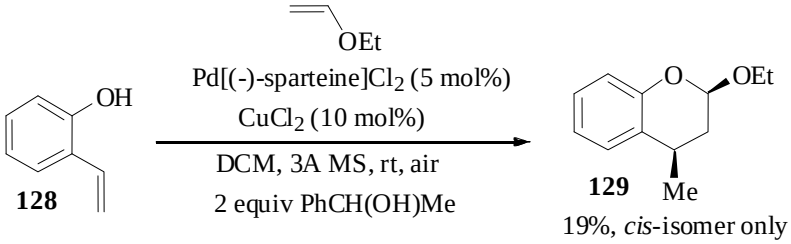
Palladium-catalyzed [3+2] cycloaddition[87] reaction is an efficient method to prepare five-membered heterocycles. A number of oxazolidine[88] and imidazolidine[89] derivatives were synthesized by [3+2] cycloaddition between oxiranes and aziridines with heterocumulenes. An extensive investigation on 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 η^3-Pd trimethylenemethane (TMM) complex-(**A**), the three atom partner, which underwent [3+2] cycloaddition with carbon dioxide to afford γ-butyro lacone **125** as the major product along with acetylated compound **126** (**Scheme 40**).



Scheme 40

5.2 [4+2] CYCLOADDITION (DIELS-ALDER REACTION)

A palladium-catalyzed *endo*-cycloaddition reaction has recently ben 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 (**Schem 41**).[91] The yield of the product **129** could be increased to 30% when 10% Et_3N was added to the reaction. The formation of the compound **129** is assumed to proceed via in situ generation of *o*-quinone methide[13] which undergoes cycloaddition with ethyl vinyl ether in an *endo* manner.

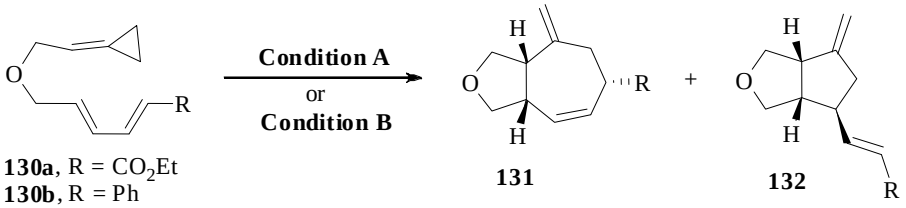


Scheme 41

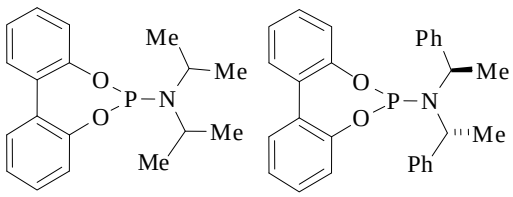
5.3. [4+3] CYCLOADDITION REACTIONS

First example of palladium-catalyzed [4+3] intramolecular cycloaddition of alkylidenecyclopropanes and dienes has recently been reported.[92] 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_2Et 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**).

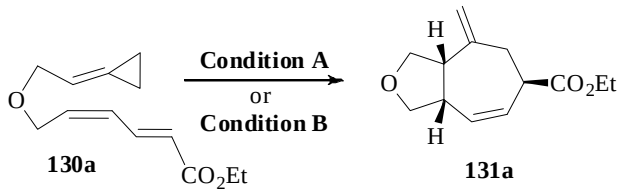


entry	R	131/132 ratio	yield (%), 131
1	CO_2Et	A: 10:1	70%
		B :10:1	74%
2	Ph	A: > 8:1	40%



Conditions A: dioxane, 101°C (50 mM), for 2-3 h, $Pd_2(dba)_3$ (6 mol%) and phosphoramidite **133** (24%)
Conditions B: dioxane, 101 °C (50 mM), for 2-3 h, $Pd_2(dba)_3$ (6 mol%) and phosphoramidite **134** (24%)

Scheme 42

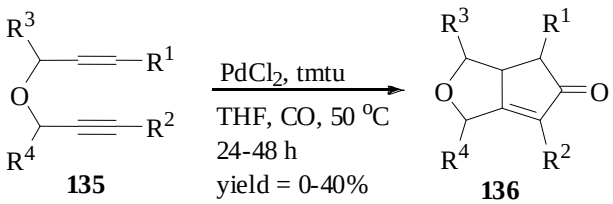


131a/132/ ratio	yield (%) of 131a
A : 1.4:1	32
B : 2.1:1	56

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 group.[93] 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[94] 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.[95] Different allylpropargyl ethers when subjected to Pauson-Khand reaction utilizing $PdCl_2$ as catalyst and tetramethyl thiourea (tmtu)[96] **135** as additive in the presence of CO using THF as solvent at 50 °C produced the desired cycloadducts **136** in moderate yields (**Scheme 44**). In absence of tmtu the Pd(II)-catalyst was precipitated immediately. The yield of the reaction was poor for allylpropergyl ethers compared to allylpropergyl amines.



Scheme 44

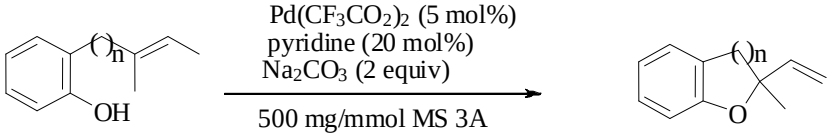
6. HETEROCYCLIZATION REACTIONS: CYCLIZATION VIA CARBON-HETEROATOM BOND FORMATION

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.[1,2] 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 reactons 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 formtion of π-complex through the coordination of nucleophile to the C-C unsaturated bond followed by intramolecular nucleophilic addion to the electron deficient unsaturated bond.

6.1.1. ADDITION TO ALKENE

Alkene appended heteroatom nucleophiles have been found to undergo palladiun(II)-catalyzed heterocyclization to produce a variety of heterocyclic compounds.[97] Both activated and unactivated double bonds can react with the nucleophiles. The synthesis of a number of five- and six-membered oxygen heterocycles **138** has been reported via oxidative cyclization of a variety of nucleophiles such as phenol onto unactivated double bonds catalyzed by $Pd(CF_3CO_2)_2$ and pyridine in the presence of molecular oxygen as the sole stoichiometric oxidant in a nonpolar solvent (PhMe) (**Scheme 45**).[98]

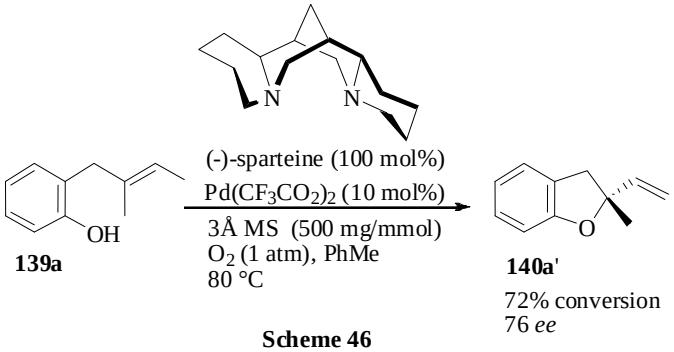


137a, n = 1
137b, n = 2

138a (95%)
138b (85%)

Scheme 45

The asymmetric version of this reaction was successfully carried out by using pre-synthesized $Pd(CF_3CO_2)_2$ 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**).



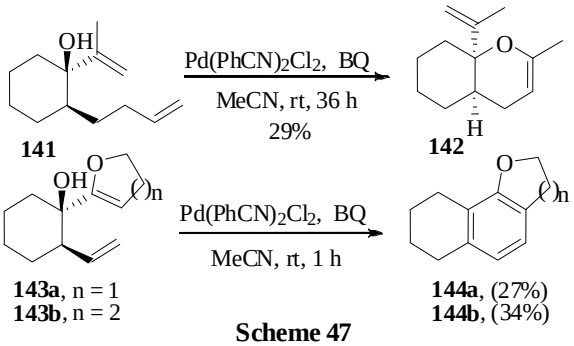
139a

140a'
72% conversion
76 *ee*

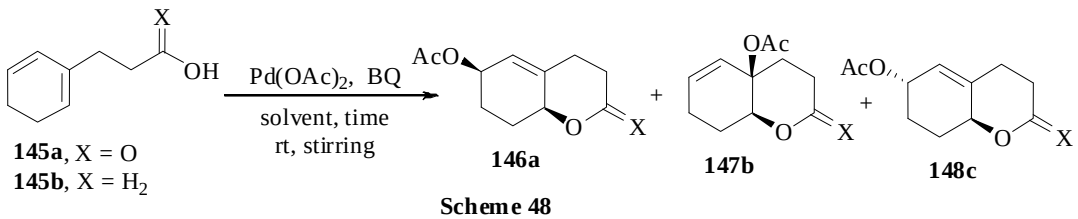
Scheme 46

Quite similarly, 1,7-dien-3-ol **141** on treatment with $Pd(PhCN)_2Cl_2$ and BQ as oxidant underwent 6-*exo* Wacker-type oxidative[99] cyclization, followed by alkene migration to the more highly substituted position to afford hexahydrochromene derivative **142** (**Scheme 47**).[100] 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[101] (AcOH/acetone) (**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 absene of LiCl and LiOAc the *cis*-isomer was formed exclusively in 53% yield. 1,4-Oxidation of alocohol when performed in AcOH without the addition of MnO_2 also followed the same pathway.

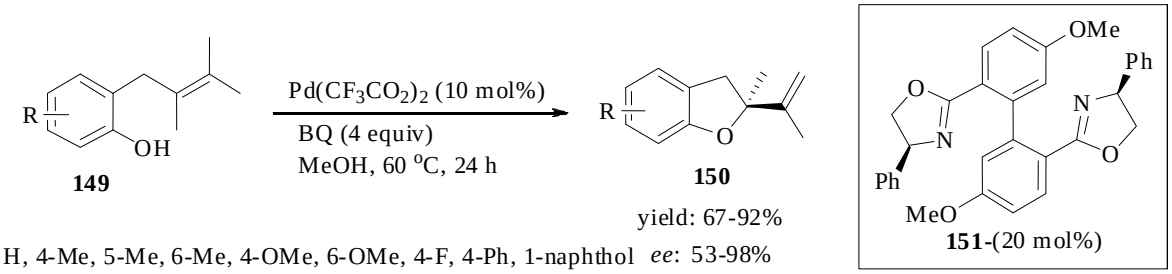


Scheme 47



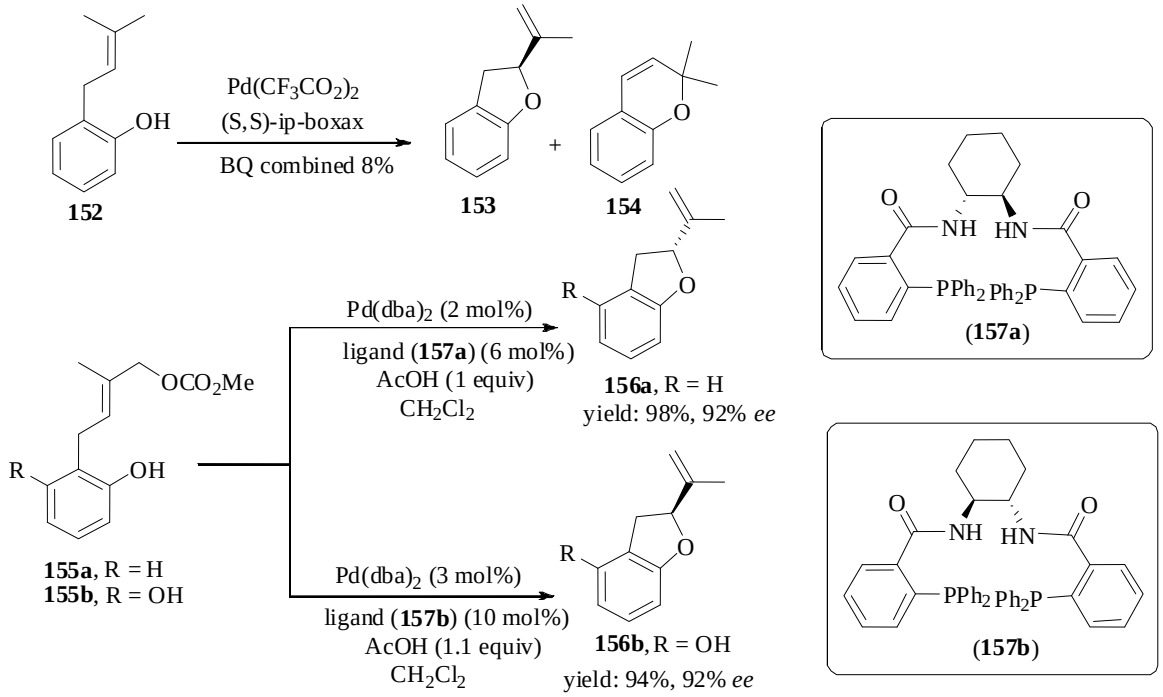
Scheme 48

The use of chiral bisoxazoline ligands based on binaphthyl[102] and biphenyl backbone[103] in the Pd(II)-catalyzed enantioselective Wacker-type cyclization of *o*-allylphenols has been well documented. In a related study, C_2-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 $Pd(CF_3CO_2)_2$ with bisoxazoline-**151** (Pd/ligand 1:2) and BQ to afford the corresponding chiral 2,3-dihydrobenzofuran **150** with excellent enantioselectivity (90-98% *ee*).[104]



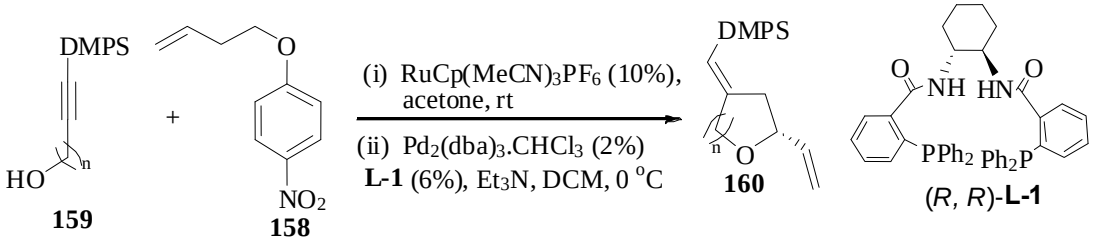
Scheme 49

Asymmetric cyclization of 2-(3-methylbut-2-enyl)phenol **152** with a chiral ligand and catalytic palladium afforded[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**)[106] and catalytic $Pd(dba)_2$ furnished the required volatile 2-isopropenyl-2,3-dihydrobenzofuran **156a**[107] from the alcohol **155a**. The opposite enantiomer of **156b** was also synthesized by similar treatment of **155b** with $Pd(dba)_2$ using the opposite Trost chiral ligand (**157b**).



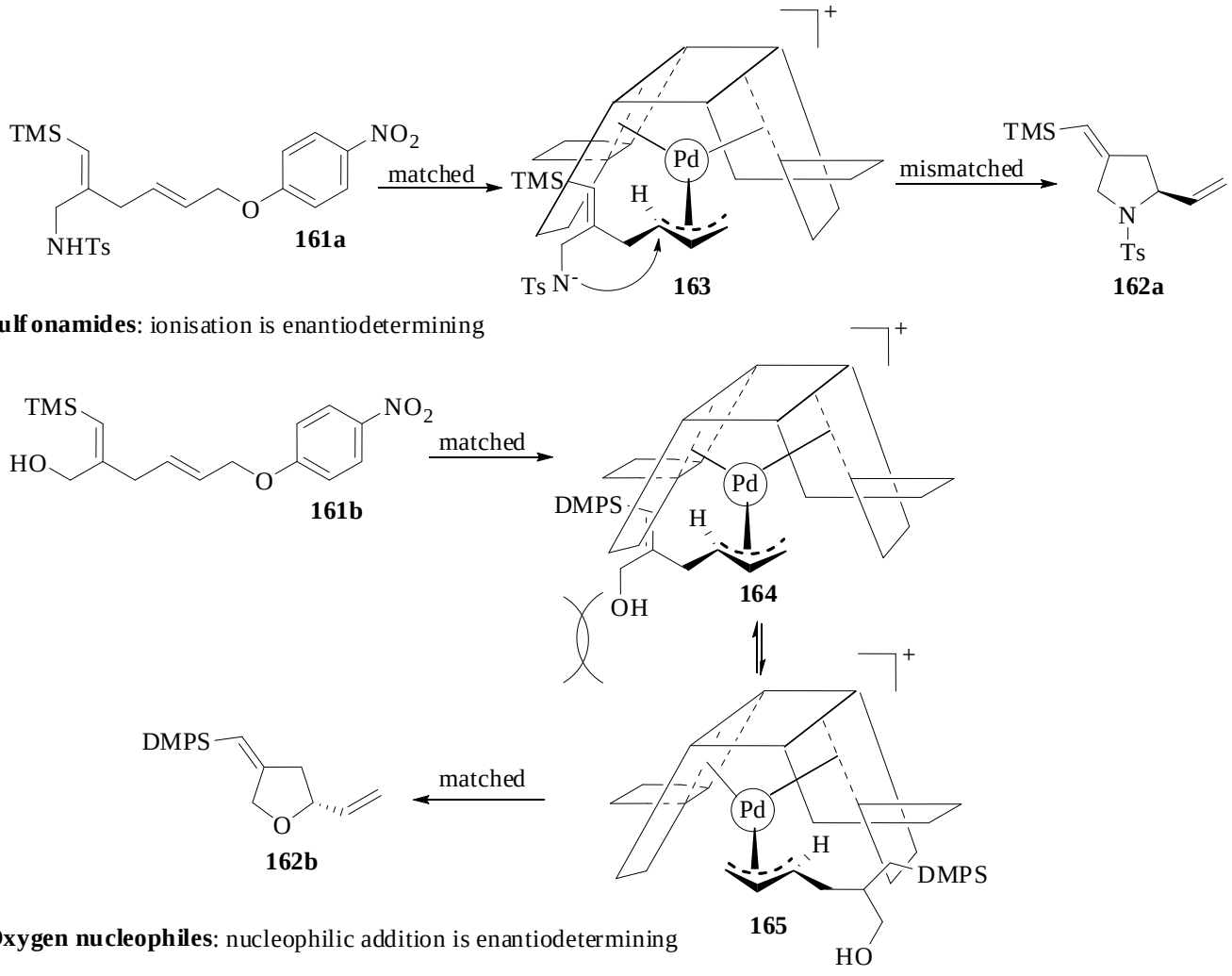
Scheme 50

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[108] to 1,4-diene followed by (ii) intramolecular nucleophilic trapping of π-alkylpalladium species, in a one-pot reaction sequence for the synthesis of enantio- and diastereo pure *O*-heterocycles.[109] A different catalytic combination $Pd_2(dba)_3.CHCl_3$, and **L-1** were employed for the enantioselective O-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**).



Scheme 51

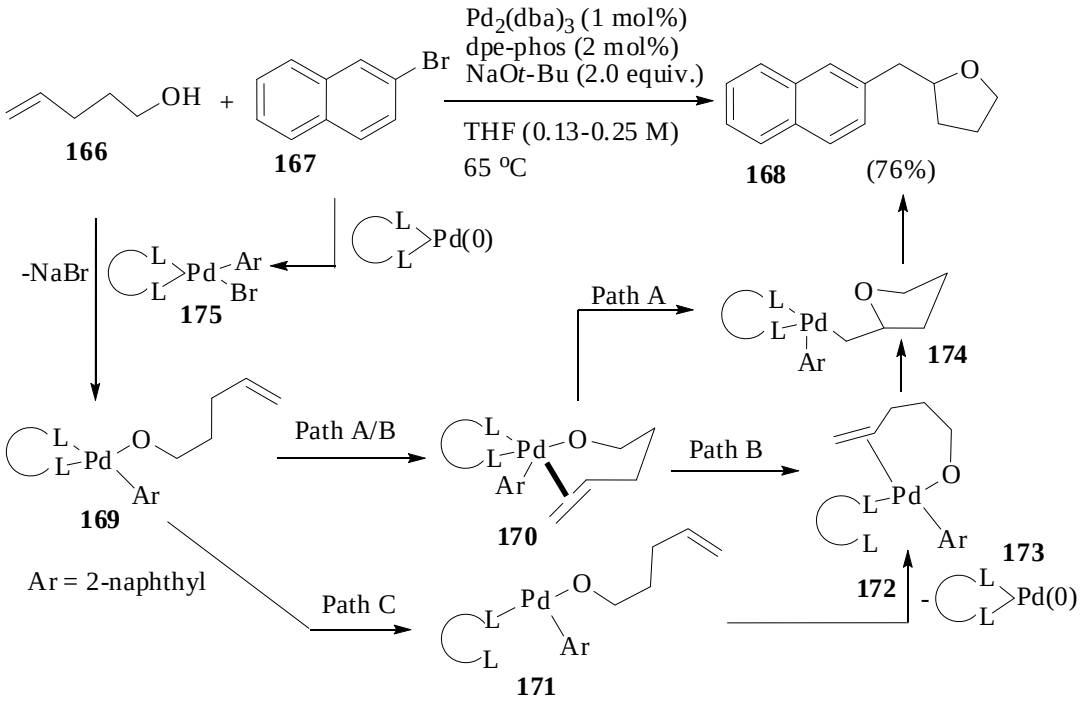
It is worthwhile to note that oxygen and nitrogen nucleophiles showed opposite selectivity in the enantioselective heterocyclization reaction. In case of sulfonamide substrates, the enantiodetermining[110] matched ionisation[111] was followed by fast intramolecular mismatched nucleophilic addition. As 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 equlibration of the palladium-allyl diastereomer, the nucleophlic 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**).



Scheme 52

Wolfe et al. reported that the reaction between 4-penten-1-ol **166** and 2-naphthylbromide **167** employing a combination of $Pd_2(dba)_3$/dpe-phos/NaO*t*-Bu catalysts presumably proceeded via palladium(aryl)(alkoxide) intermediate[112] **169** which underwent intramolecular insertion of the alkene into the Pd-O bond[113] followed by reductive elimination to afford the 2-naphthyltetrahydrofuran **168** (**Scheme 53**).[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)[113a] or insertion through four-coordinated intermediate **172**, formed by an associative ligand substitution process that too proceeds through the five-coordinated complex **170**.[115]

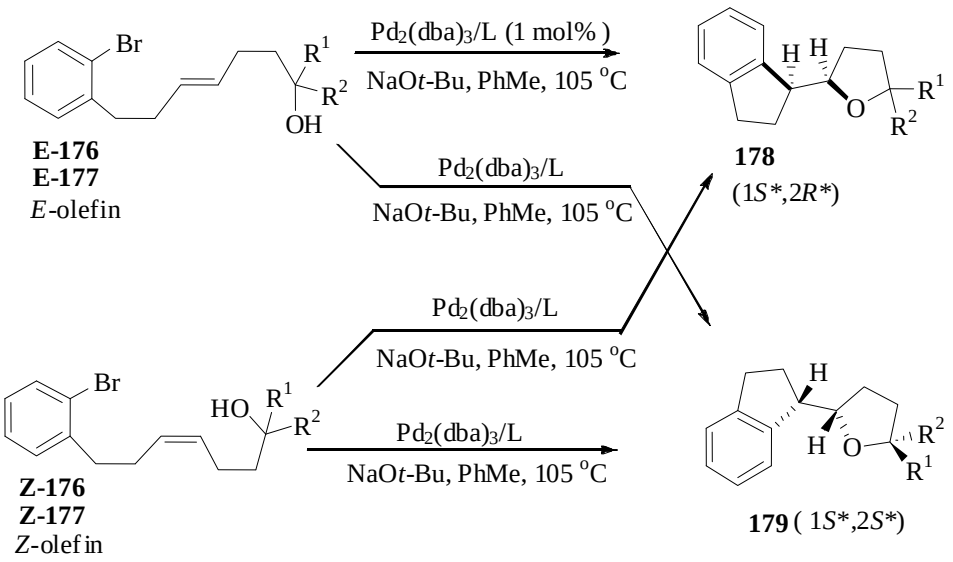


Scheme 53

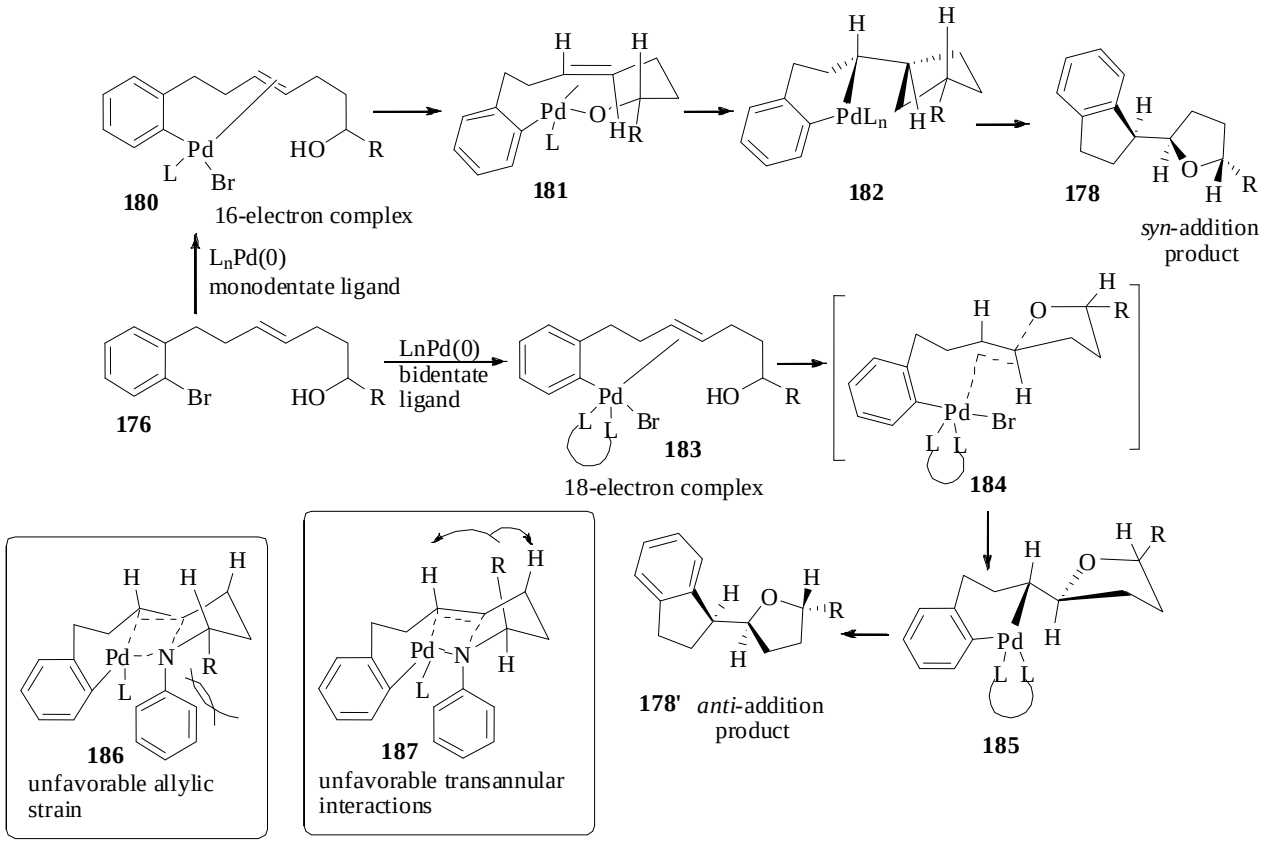
The stereochemical outcome of the carboetherification and carboamination[116] reactions of γ-hydroxy **176** and **177** with tethered aryl bromides are highly influenced by the nature of the heteroatom and added ligand. Phosphine ligand controls the *syn*- versus *anti*-addition pathways in the catalytic cycle, which allows for stereoselective construction of either of the two possible product diastereomers from a given substrate. For example, the (1*S**,2*R**)-2-indan-1-yl tetrahydrofuran **178** (51%, *syn* addition product) was synthesized in 51% and 60% yields from both *E*- and *Z*-alkene alcohols (**176** and **177**) via the $Pd_2(dba)_3/PCy_3.HBF_4$ and $Pd_2(dba)_3$/(±)-BINAP-catalyzed *syn*- and *anti*-additions respectively (**Scheme 54**).[117] Similarly, both the *syn*- and *anti*-additions are observed during the preparation of (1*S**,2*S**)-isomer **179** from both the alkenes (**176** and **177**) by changing from chelating dppb to monodentate P[(*p*-MeO)C_6H_4]$_3$ 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,[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**).

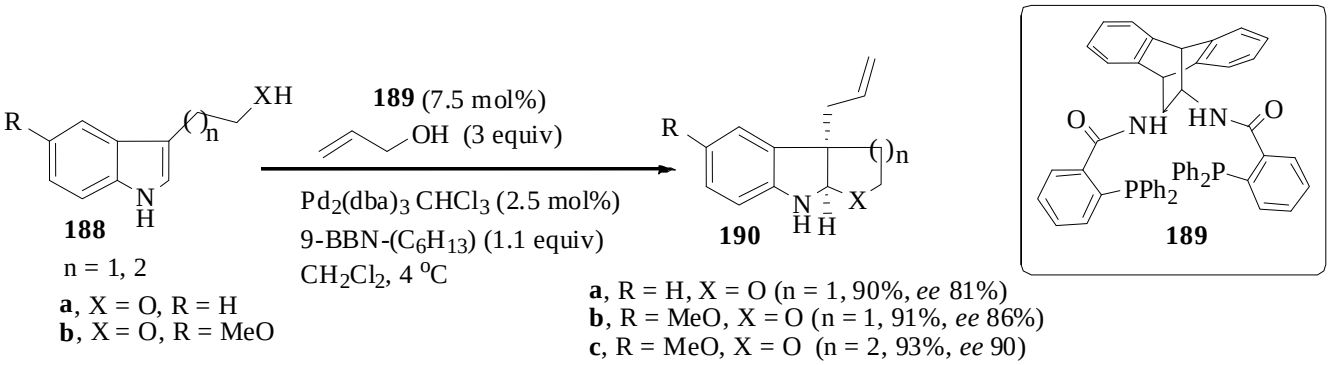


Scheme 54



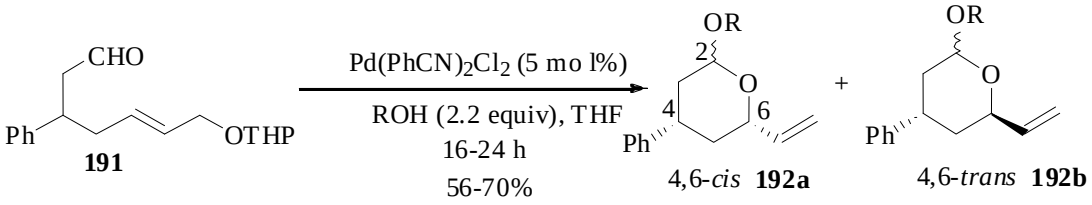
Scheme 55

Palladium-catalyzed enantioselective C-3 allylation of 3-substituted-1*H*-indoles using trialkylboranes was developed by Trost *et al*.[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_6H_{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,[120] 9-BBN-(C_6H_{13}) is directly involved in the enantiodiscriminating step (**Scheme 56**).



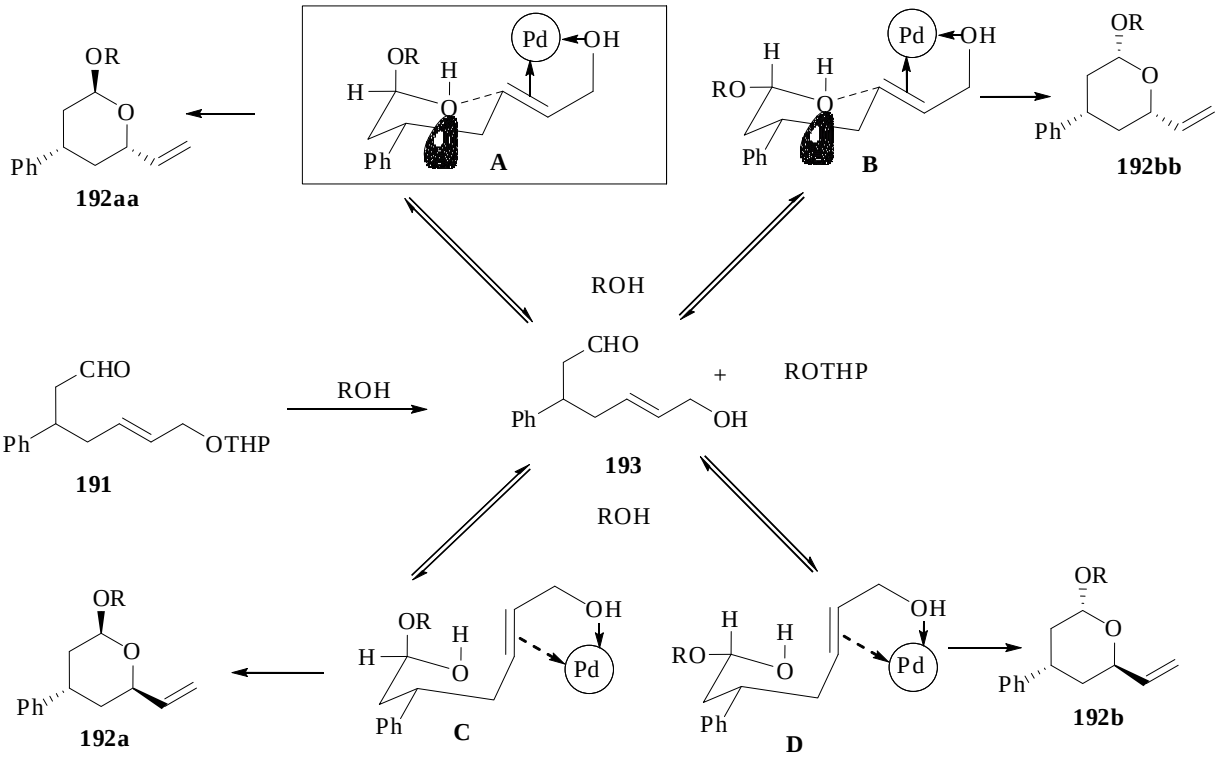
Scheme 56

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.[121] The cyclization was carried out employing different alcohol using $Pd(PhCN)_2Cl_2$ as catalyst. In the case of *2α* and *2β* products, major products were 2*β* isomer and the stereoselectivity (2*β*:2*α*) was almost 3:1-2:1 (**Scheme 57**).



Scheme 57

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 *2β*-isomer **192aa** (**Scheme 58**).



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.[122] 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.[123]

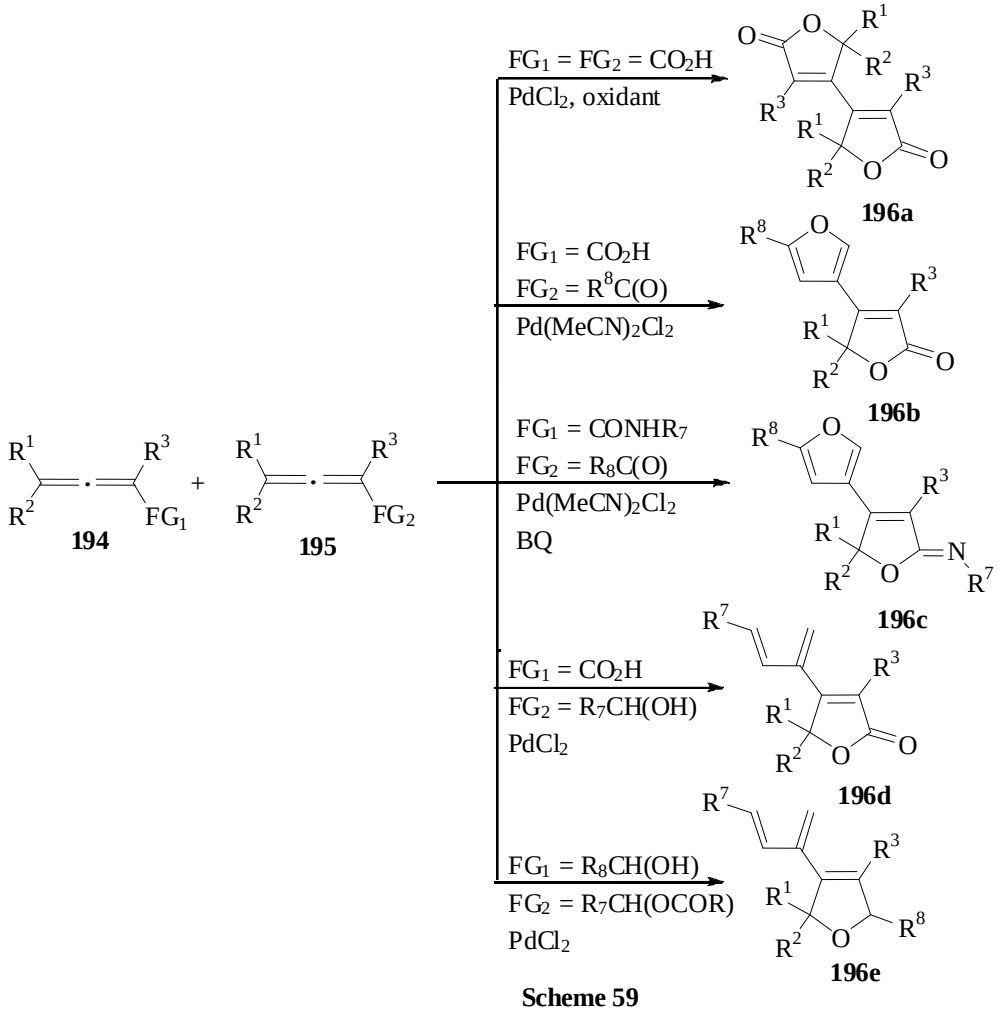
In particular, the reaction between two same or differently functionalized allenes, i.e, homodimerization reaction of functionalized allenes **194** and **195** is of considerable interest. Hasmi *et al*. reported the homodimerization reaction of allenyl ketone.[124] The intermolecular dimerization of 2,3-allenoic acids using $PdCl_2$ as catalyst afforded bicyclic butenolide.[125] 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.[126] An interesting *β*-hydroxy elimination to dienyl unit was observed during the palladium-catalyzed cyclization of 2,3-allenoic acids in the presence of 2,3-allenols.[127] Alcaide and co-workers also reported similar cross-coupling cyclization reactions of R-allenols in the presence of 2,3-allenyl carboxylates (**Scheme 59**).[128]

Intermolecular cross couplig reaction between 2,3-allenoic acids **194** and simple allenes **197** by $Pd(OAc)_2$ and BQ afforded highly substituted furan-2(5*H*)-ones *Z*-**198** (**Scheme 60**).[129]

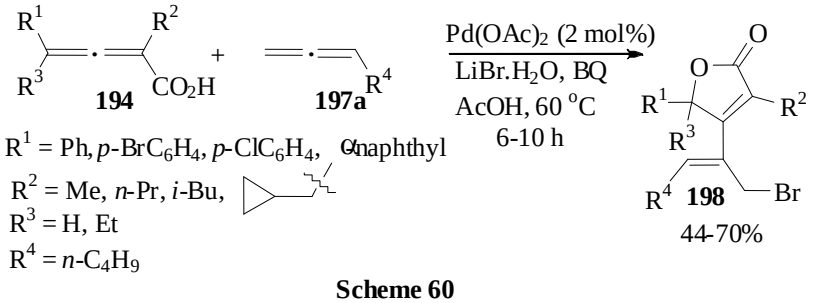
The catalytic cycle that leads to furan-2(5*H*)-ones is suggested to proceed via initial cyclic oxypalladation of 2,3-allenoic acids with Pd(II) to generate furanonyl palladium intermediates **199** which is trapped by the simple allenes to afford *π*-allylic intermediates (**Scheme 61**).

The synthesis of sterically congested bicyclic tetrahydrofurans **201a**,**b** from allenyltetrahydroxyfurans **200a**,**b** by palladium-catalyzed sequential cyclization-coupling reactions has recently been reported.[130]

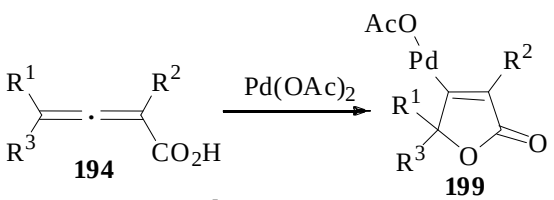
The $PdCl_2$-$CuCl_2$-catalyzed reaction showed excellent results for the construction of bicyclic tetrahydrofurans **201a** (98%) (**Scheme 62**).



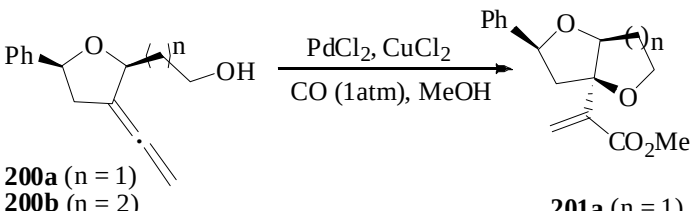
Scheme 59



Scheme 60



Scheme 61

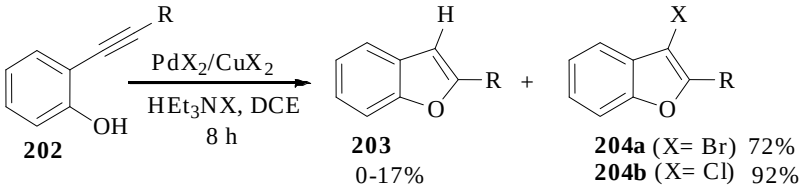


Scheme 62

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 π-palladium alkyne complex, which is generated in situ by the coordination of Pd(II) to carbon-carbon triple bond.[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-alkylphenols for the synthesis of 2-substituted 3-halobenzo[*b*]furans **204a**,**b**[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_3NX, employed in the reaction, may labilize the palladium-carbon σ-bond, thereby converting palladium into a good leaving group.[132]

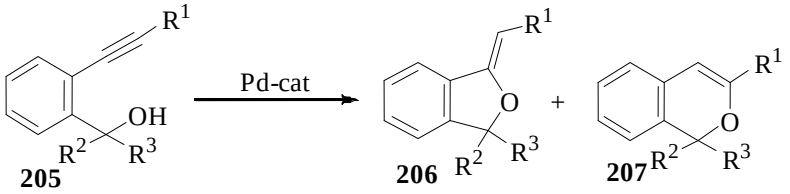


202 **203** 0-17% **204a** (X= Br) 72% **204b** (X= Cl) 92%

Condition A: (0.3 mmol), $PdCl_2$ (5 mol%), $CuCl_2$ (3 equiv) HEt_3NI (0.2 equiv), DCE (5 ml), rt
Condition B: (0.3 mmol), $PdBr_2$ (5 mol%), $CuBr_2$ (3 equiv) HEt_3NI (0.2 equiv), DCE (5mL), rt

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-*exo-dig* or 6-*endo-dig* cyclization of 2-alkynylbenzyl alcohols **205** (**Scheme 64**).[133]

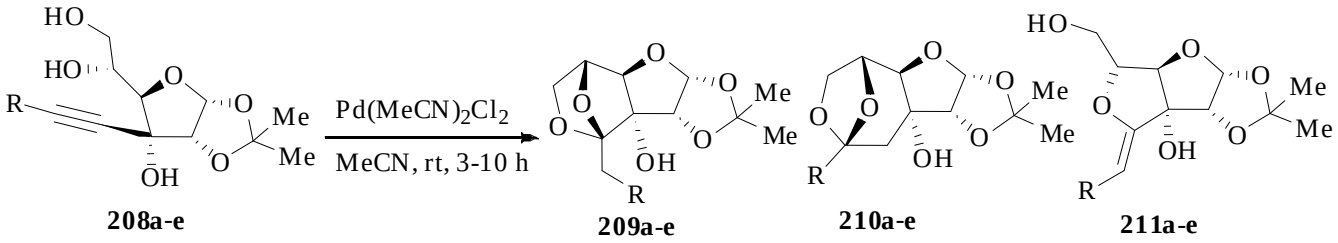


205 **206** **207**

Scheme 64

Electronic factors show high impact on the regioselectivity of the palladium-catalyzed hydroalkoxylation of alkynols by controlling the mode of cyclization i.e. 5-*exo-dig* versus 6-*endo-dig*.[134] This is in contrast to the base promoted cyclization where the cyclization proceeds through 5-*exo-dig* mode exclusively.[135] In the $Pd(MeCN)_2Cl_2$ mediated cycloisomerization of sugar acetylenic derivatives **208a-e** both 5-*exo-dig* and 6-*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.[136] It is interesting to note that electron-donating group attached to the aromatic ring favors a 6-*endo-dig* while electron attracting group

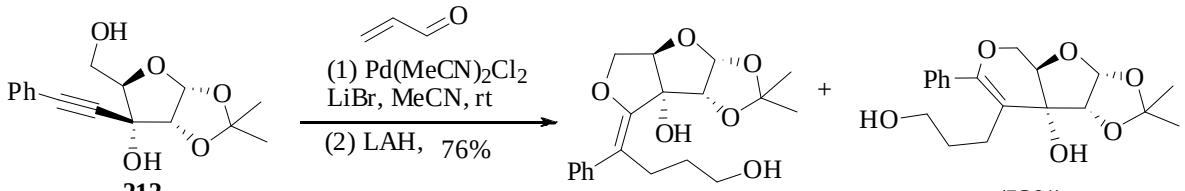
favors a 5-*exo-dig* mode of cyclization. The formation of ketals **209a**, **210b** and **210e** occur due to further cyclization of the free hydroxyl group at C_6 (**Scheme 65**).



208a-e **209a-e** **210a-e** **211a-e**

Scheme 65

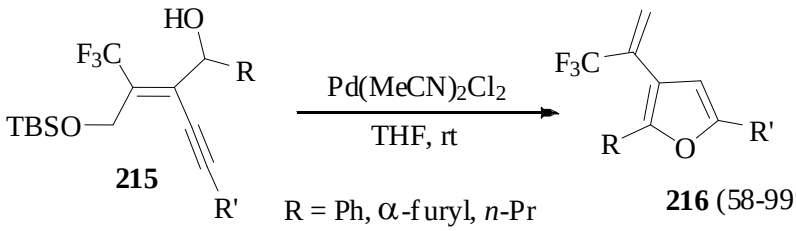
Palladium-catalyzed cyclization and subsequent conjugate addition of the carbopalladium intermediates have been achieved by successive hydroalkoxylation of **212** with $Pd(MeCN)_2Cl_2$, conjugate addition with acrolein and LAH reduction in one-pot to give a mixture of compounds **213** and **214** (**Scheme 66**).



212 **213** (23%) **214** (53%)

Scheme 66

3,3,3-Trifluoroprop-1-en-2-yl substituted furans **215** were efficiently synthesized by $Pd(MeCN)_2Cl_2$-catalyzed cyclization-isomerization of 1,1,1-trifluoro-2-[*t*-butyldimethylsilyloxy)-methyl]-3-alkynylbut-2-en-1-ols (**Scheme 67**).[137] The catalysts like $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $Pd(PPh_3)_2Cl_2$ 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.

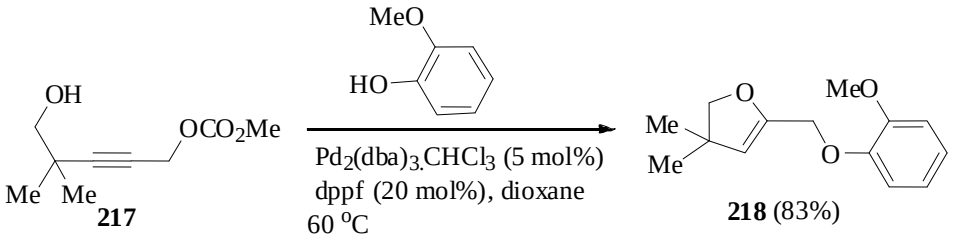


215 R = Ph, α-furyl, *n*-Pr **216** (58-99%)

R' = Ph, *p*-$MeOC_6H_4$, *p*-$MeO_2CC_6H_4$, *n*-pentyl

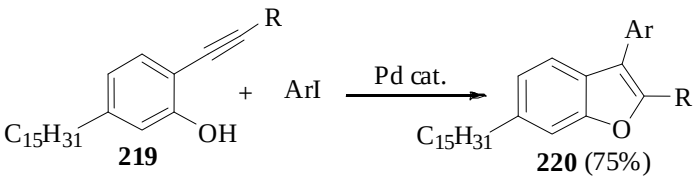
Scheme 67

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**).[138] The reaction was carried out using $Pd_2(dba)_3.CHCl_3$-dppf catalytic system in dioxane.



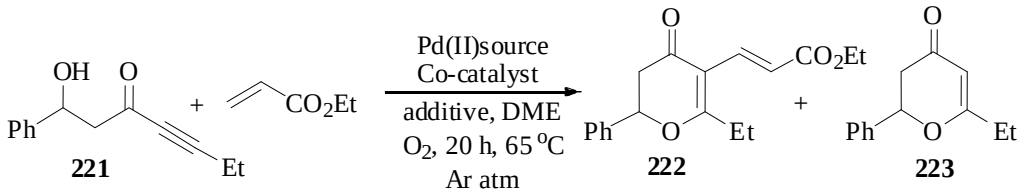
Scheme 68

The hydroxypalladation-reductive elimination reaction between *o*-alkynylcardanol **219** and iodobenzene utilizing $Pd_2(dba)_3$, 2,2'-bipyridyl (bpy) and K_2CO_3 in acetonitrile at 50 °C afforded 2,3-disubstituted benzo[*b*]furan derivative **220** (**Scheme 69**).[139]



Scheme 69

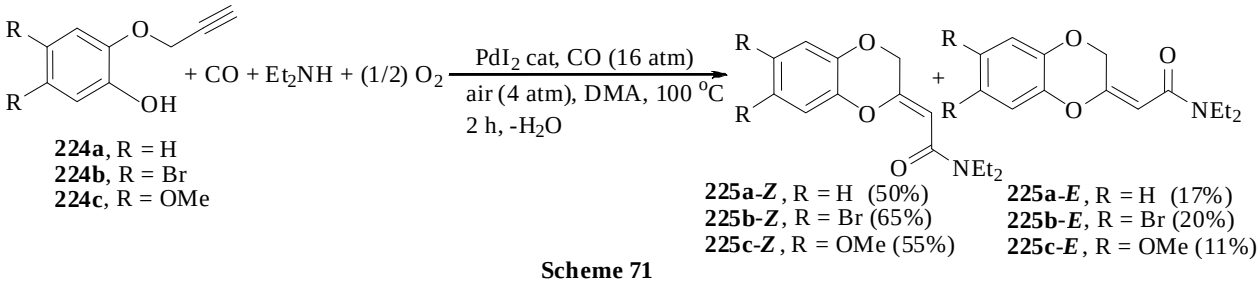
Gouverneur et al. devised a palladium(II)-catalyzed Wacker-Heck reaction involving the union of structurally diversed hydroxy-ynones **221** and ethyl acrylate, two electron deficient species. The reaction, generally, proceeds through intramolecular hydroxylation to generate the σ-alkenyl palladium intermediate 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 $Pd(MeCN)_4(BF_4)_2$, K_2CO_3, PPh_3, $Cu(OAc)_2$-H_2O or in 10 mol% of $Pd(MeCN)_4(BF_4)_2$, K_2CO_3 respectively, the desired product was obtained exclusively along with side product **223** due to the protonolysis of the σ-alkenyl palladium intermediate. Interstingly, 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 $Pd(MeCN)_2Cl_2$, $Cu(OAc)_2$, PPh_3 and 20 mol% of LiBr in DME at 65 °C under an atmospheric pressure of oxygen (**Scheme 70**).



Scheme 70

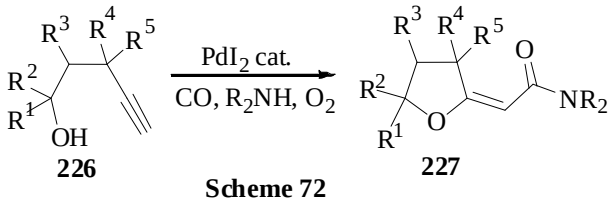
Gabriele *et al*. recently developed a PdI_2-catalyzed new, selective and atom economical methodology for the synthesis of 2-[(dialkylcarbamoyl)methylene]-2,3-dihydrobenzo[1,4]dioxine **225** starting from 2-prop-2-ynyloxyphenols **224** as a mixture of *E*- and *Z*-isomers of which *Z*-isomer was produced

predominantly.[141] The methodology was also extended to other secondary amines such as morpholine where also *Z*-isomers were formed as the major products (**Scheme 71**).



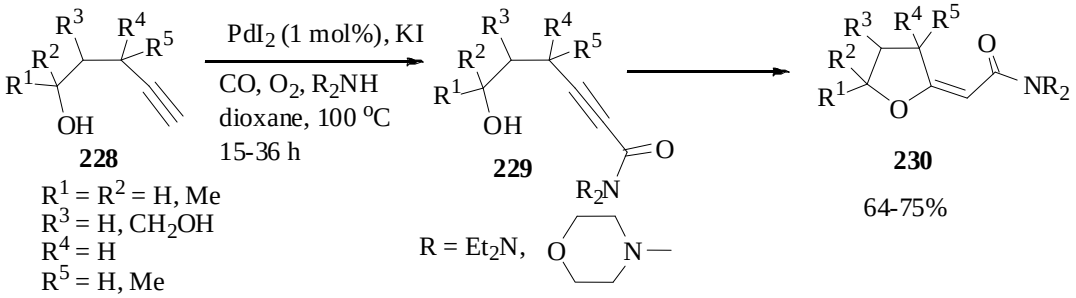
Scheme 71

A similar sequential oxidative aminocarbonylation-intramolecular conjugate addition-cyclization was observed during the synthesis of 2-[(dialkylcarbamoyl)methylene]tetrahydrofuran derivatives[142] **227** starting from pent-4-yn-1-ols **226**, under the aforesaid reaction conditions (**Scheme 72**).



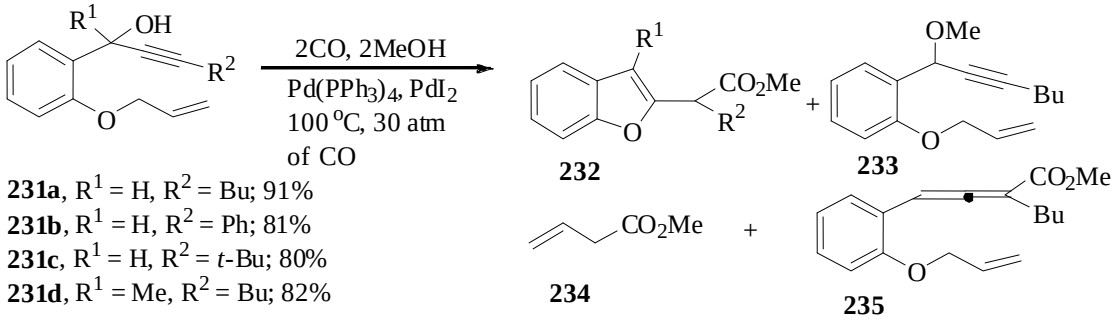
Scheme 72

Gabriele *et al*. recently reported palladium-catalyzed oxidative aminocarbonylation[143] of various substituted alkynols for the construction of different heterocyclic skeletons. The product fromation depends on the position of the OH group with respect to the triple bond. The alkynols **228** were reacted with PdI_2, 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, followd by a 5-*exo-dig* cyclization leading to the formation of dihydrofuran derivatives **230** (**Scheme 73**).[144]



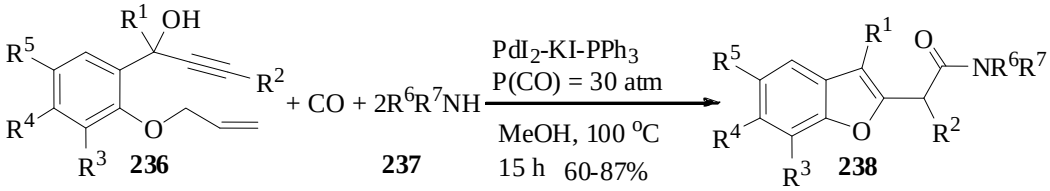
Scheme 73

Bioactive benzofurans **232** were synthesized by sequential homobimetallic[145,146] from precursors **231** using $Pd(PPh_3)_4$ and PdI_2 (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**).



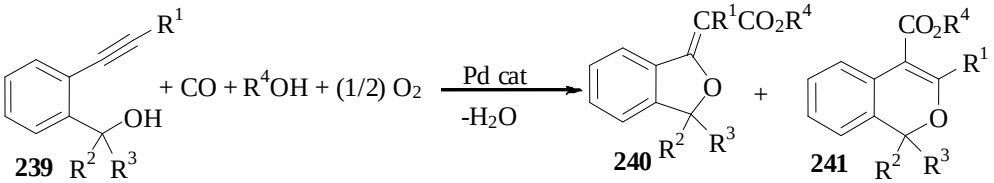
Scheme 74

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 PdI_2-PPh_3-KI has been developed utilizing sequential homobimtallic concept (**Scheme 75**).



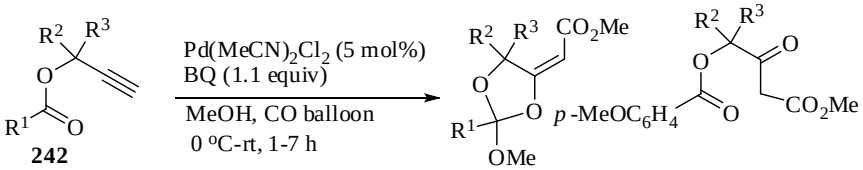
Scheme 75

The scope of the oxidative carbonylation-cyclization protocol was further extended[148] by synthesizing benzofurans **240** and benzopyran **241** derivatives (**Scheme 76**).



Scheme 76

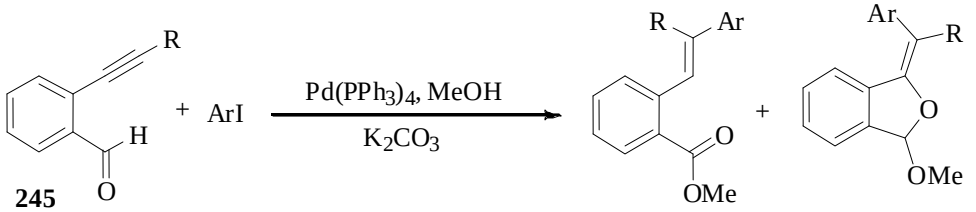
Propargylic esters **242** in the presence of $Pd(MeCN)_2Cl_2$/BQ underwent oxidative cyclization-carbonylation reaction to afford methoxycarbonylated orthoester **243** (**Scheme 77**).[149] The uncyclized product **244** was obtained only when R^1 is *p*-methoxyphenyl. Very poor yield of the compound **244** was observed only with the benzoate having electron-attracting group attached to the *para*-position of the aromatic ring.



R^1 = Me, Ph, *p*-OMePh, *p*-$NO_2C_6H_4$
R^2 = Me
R^3 = -$(CH_2)_6$-, -$(CH_2)_5$-, -$(CH_2)_2NBoc(CH_2)_2$-, -CH_2CH_2Ph

Scheme 77

Wu *et al*. reported Pd(0)-catalyzed cascade addition-oxidation reaction of 2-alkynylbenzaldehyde **245** with aryliodides in methanol.[150] The one-step reaction afforded the regio- and stereoselective synthesis of stereoisomeric methyl-2-(2,2-disubstituted-vinyl) benzoates **247** along with the addition product **246**. The exclusive formation of the products **247** 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**).



245

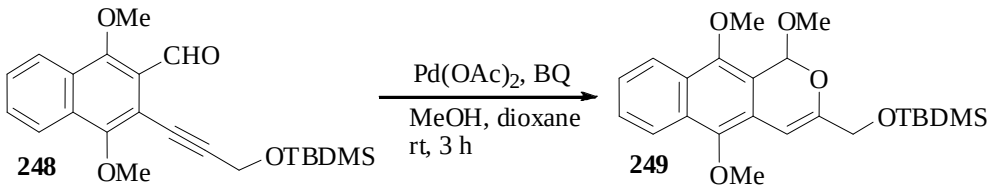
R = Ph, *p*-$MeOC_6H_4$, *n*-C_4H_9, *p*-$CF_3C_6H_4$

Ar = *p*-MeC_6H_4, C_6H_4, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$ *p*-$CF_3C_6H_4$ and *o*-pyridinyl.

246 (35-74%) **247** (3-100%)

Scheme 78

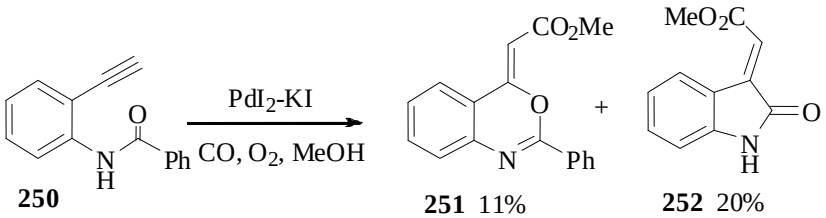
The reaction of alkenyl aldehydes with methanol in the presence of Pd(II) catalyst to afforded a mixture of five- and six-membered alkenyl ethers.[151] However with alkynyl benzaldehyde **248**, the cyclization in the presence of $Pd(OAc)_2$, BQ and MeOH gave exclusively six-membered product **249** 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**).



248 **249**

Scheme 79

Oxidative carbonylation of the substrate **250** was carried out with PdI_2 catalyst with KI leading to complete conversion of the substrate with the formation of products **251** and the benzoxazine derivative **252**. The product **251** is formed by a 6-*exo-dig* mode of cyclization (**Scheme 80**).[152] The dihydroindolone derivative **252** is formed due to in situ formation of 2-ethynylaniline by cleavage of the amide bond.



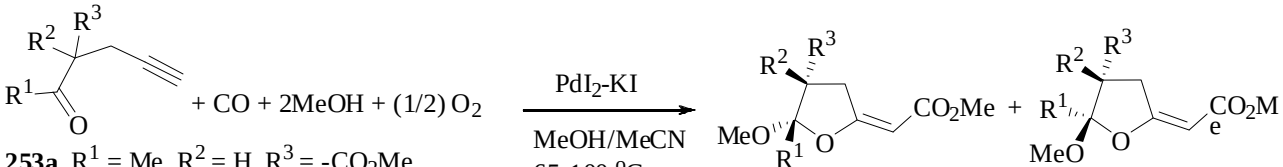
250

251 11% **252** 20%

Scheme 80

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**).

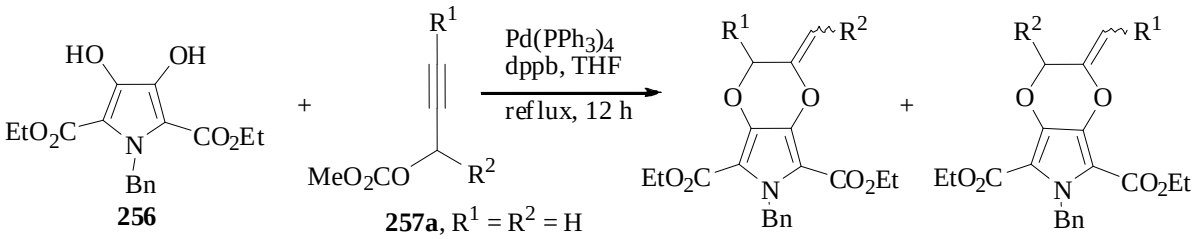
Palladium-catalyzed cyclization of the dihydroxy pyrrole **256** with propargylic carbonate **257** afforded 2-alkylidenepyrrolo[*c*]-1,4-dioxane derivatives **258** and **259** with around 85:15 regioselectivity (**Scheme 82**).[154] The reactions of alkynes **257a**,**c**,**d** were conducted using $Pd(PPh_3)_4$ 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**.



253a, R^1 = Me, R^2 = H, R^3 = -CO_2Me
253b, R^1 = Me, R^2 = Et, R^3 = -CO_2Me
253c, R^1 = Me, R^2 = Bn, R^3 = -CO_2Me
253d, R^1 = Me, R^2 = Et, R^3 = -COMe
253e, R^1 = R^2 = -$(CH_2)_4$-, R^3 = -CO_2Et
253f, R^1 = Ph, R^2 = R^3 = H
253g, R^1 = Ph, R^2 = Me, R^3 = CO_2Me

254a-g (33-89%) **255a-g** (0-30%)

Scheme 81



256

257a, R^1 = R^2 = H
257b, R^1 = H; R^2 = Me
257c, R^1 = Me; R^2 = H
257d, R^1 = Et; R^2 = H
257e, R^1 = H; R^2 = Et

258a (85%)
258b (traces)
258c (95%)
258d (95%)
258e (traces)

259a (traces)
259b (98%)
259c (traces)
259d (traces)
259e (96%)

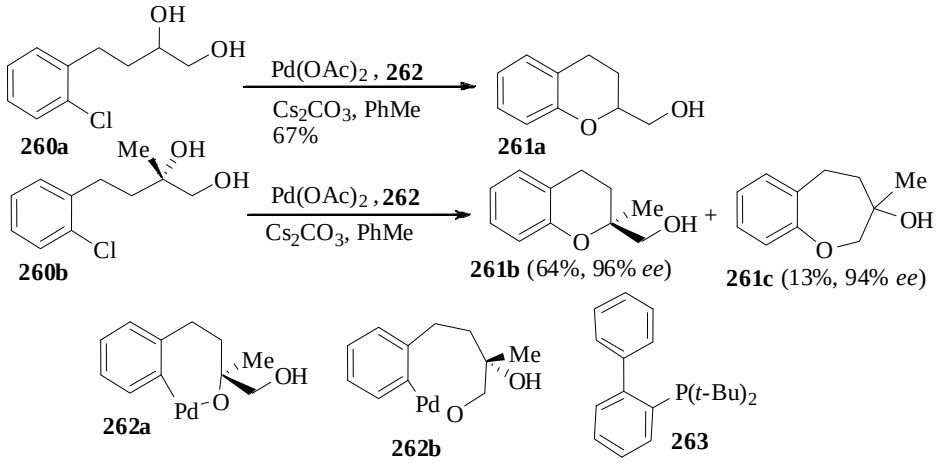
Scheme 82

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]

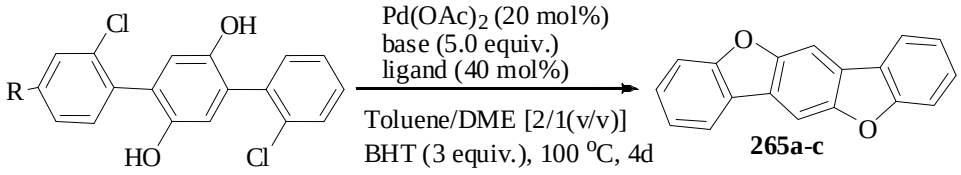
A palladium-catalyzed highly efficient enantioselective synthesis of chiral substituted 2-methylchromans was developed.[155] The product distribution in this reaction is controlled by the steric environment adjacent to the alcohol. Thus from the substrate having both primary and secondary alcohol at 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[156] by $Pd(OAc)_2$-catalyzed intramolecular *O*-arylation of **264a-c** using 2-di-*tert*-butylphosphino-2'-methylbiphenyl (**L_1**) 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**).



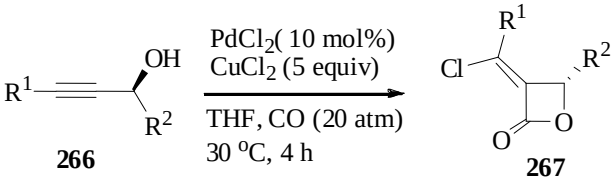
product	base	solvent	yield
265a	KOAc	PhMe/DME[2:1(v/v)]	70%
265b	K_3PO_4	PhMe/DME[2:1(v/v)]	48%
265c	K_3PO_4	DME	31%

Scheme 84

6.3. CYCLOCARBONYLATION AND CYCLOCARBOXYLATION REACTIONS

The palladium-mediated carbonylation[157] and carboxylation[158] 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.[159] In the presence of $PdCl_2$-$CuCl_2$ catalytic system and carbon monoxide optically

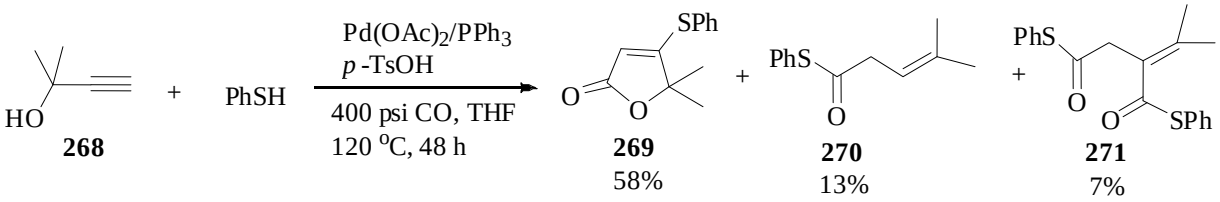
active propargylic alcohols **266** allowed a convenient synthesis of the corresponding (*Z*)-*α*-chloroalkylidene-*β*-lactones **267** with high ee values (**Scheme 85**).



266 **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]

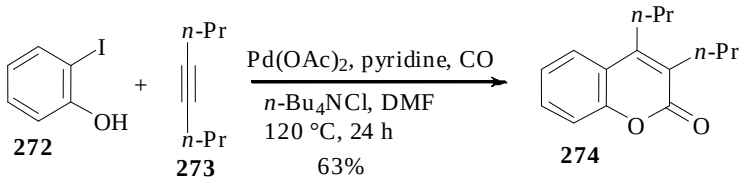


268 **269** **270** **271**

Scheme 86

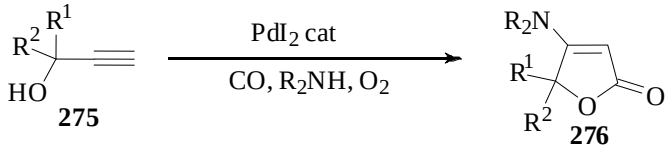
Palladium-catalyzed annulation of internal alkynes by *o*-iodophenol in the presence of CO employing $Pd(OAc)_2$, pyridine, and *n*-Bu_4NCl afforded coumarin derivative **274**[161] (**Scheme 87**).

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.



272 **273** **274**

Scheme 87

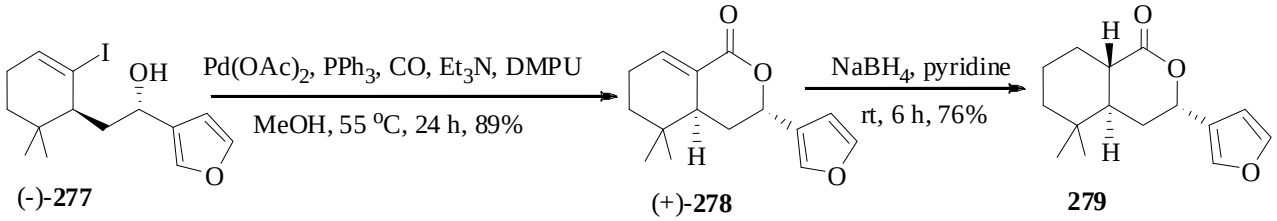


275 **276**

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 (+)-**278** was constructed via intramolecular carbonyl insertion of the alcohol (-)-**277** in the presence $Pd(OAc)_2$ and

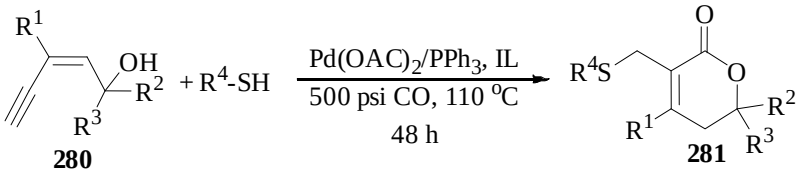
triphenylphosphine. Reduction of compound **278** with sodium borohydride resulted in the formation of (+)-ricciocarpin **279** (**Scheme 89**).



(-)-**277** (+)-**278** **279**

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.[164] 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_2N], exhibited excellent chemoselectivity and resulted in the formation of the monocarbonylated product **281** (**Scheme 90**).[165]



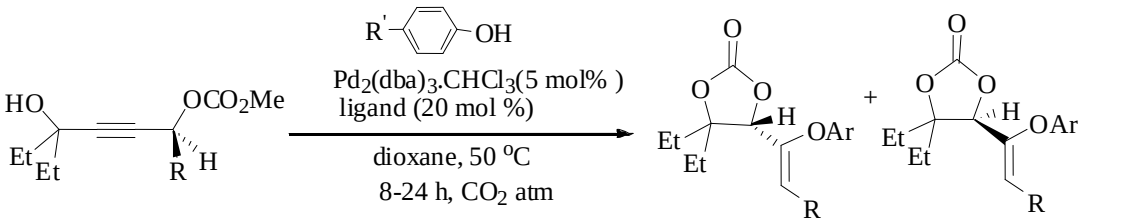
280 **281**

R^1 = H, Ph, *p*-MeC_6H_4, *p*-EtC_6H_4, *m*-$MeOC_6H_4$ *p*-$CF_3C_6H_4$
$R^2 = R^3$ = H, -$(CH_2)_5$-
R^4 = Ph, -OC_6H_4, *p*-FC_6H_4, 2-naphthyl, C_6H_{17}, *i*-Pr

IL	Yield (%)
[bmim]PF_6	17-91
[bmim][Tf_2N]	34-90

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**).[166]



(*S*)-**282a**, R = Me
(*S*)-**282b**, R = pentyl

(*Z*,*S*)-**283aa**-**283ae**
R = Me
(*Z*,*S*)-**283ba**
R = pentyl

(*E*,*R*)-**283aa**-**283ae**
R = Me
(*E*,*R*)-**283ba**
R = pentyl

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**.

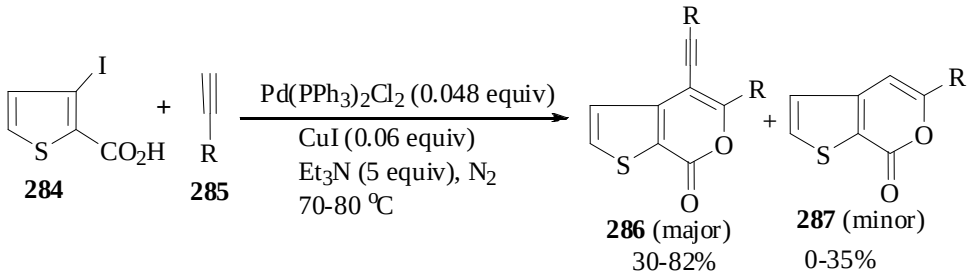
7. CYCLIZATION VIA CASCADE CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION: HETEROCYCLIZATION REACTIONS

7.1 HETEROCYCLIZATION REATIONS WITH ALKYNES

Palladium-catalyzed intermolecular heterocyclization of alkynes has emerged as an accomplished route to the synthesis of large varieties of heterocycles.[167] 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 cylization approach afford the heterocycles.[168] 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.[169]

7.1.1. REACTIONS WITH TERMINAL ALKYNES: SONOGASHIRA COUPLING-CYCLIZATION REACTIONS

3-Iodothiophene-2-carboxylic acid **284** reacted smoothly with terminal alkynes **285** in the presence of $Pd(PPh_3)_2Cl_2$-Et_3N-CuI affording predominantly 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones **286** in good yields along with a minor amount of 5-substituted thieno[2,3-*c*]pyran-7-ones **287**.[170] The reaction showed high regioselectivity as no isomeric thieno[2,3-*c*]furan-6-one resulting from 5-*exo*-*dig* cyclization was detected. Among the different solvents used for the reaction of $Pd(PPh_3)_2Cl_2$ catalysts, DMF was found to give better results (**Scheme 92**).

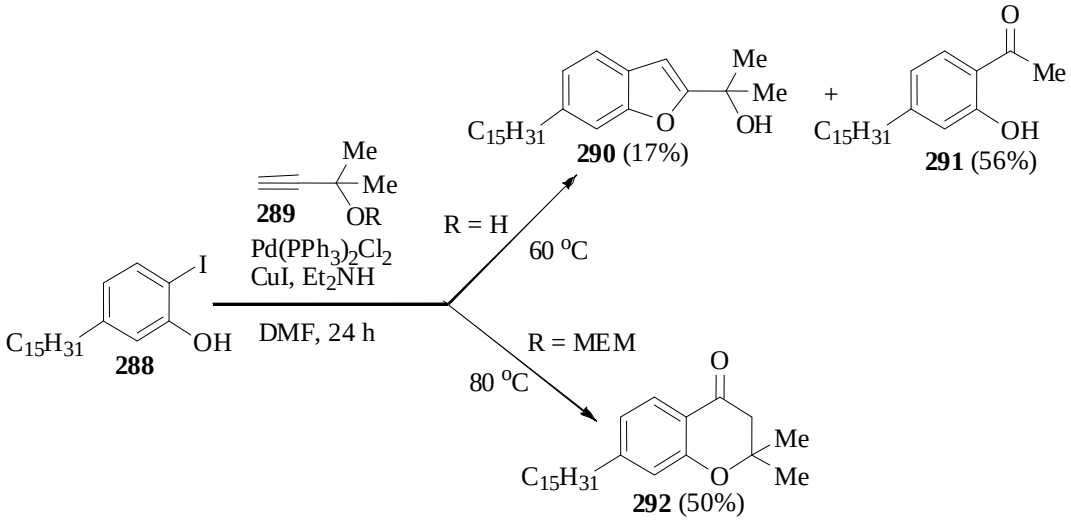


R = CMe_2OH, $CH(OH)Me$, $(CH_2)_3Me$, $(CH_2)_5Me$, Ph, *p*-MeC_6H_4, *p*-$C_5H_{11}C_6H_4$, $CH_2OC_6H_4$

Scheme 92

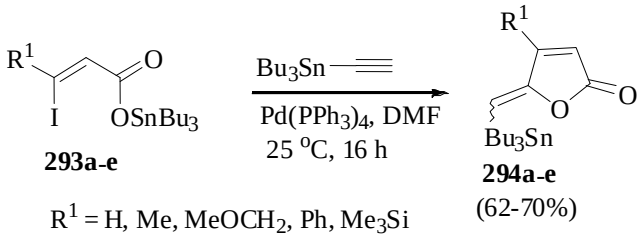
An interesting substituent effect on the mode of cyclization during palladium-catalyzed domino Sonograshira cross coupling cyclization of *o*-iodocardanol **288** was reported. Substituent effect was found to be very effective for the synthesis of lipophilic benzo[*b*]furans **290** from terminal alkynes and *o*-iodophenols.[139,171] 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

intermediate, addition of water to carbon-carbon triple bond, an eliminition step and conjugate addition of the phenolic oxygen to the resultant *α,β*-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**. Apprarently, 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 $Pd(PPh_3)_2Cl_2$ (0.02 equiv), CuI (0.04 equiv), Et_2NH (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.



Scheme 93

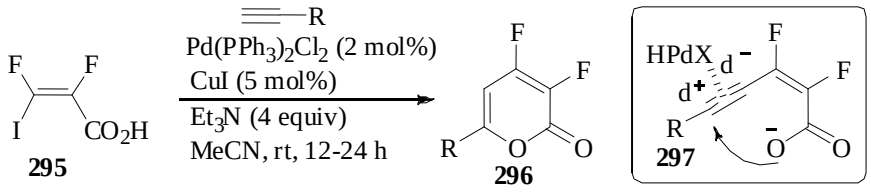
Regio- and stereocontrolled synthesis of stannylated butenolides was achieved through palladium-catalyzed domino cross-coupling/cyclization reaction of tributylstannyl (*Z*)-3-substituted iodopropenoate with tributylstannylacetylene.[172] $Pd(PPh_3)_4$ is an efficient catalyst for the preparation of (*E*)-5-tributylstannylmethylidene-5*H*-furan-2-ones **294a-e** (**Scheme 94**).



R^1 = H, Me, $MeOCH_2$, Ph, Me_3Si

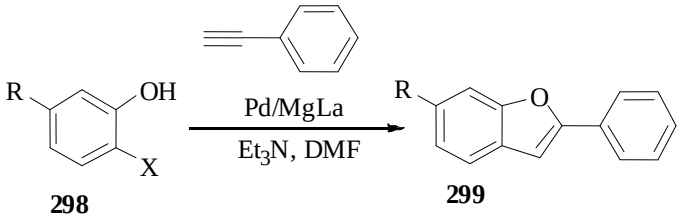
Scheme 94

(2*E*)-2,3-Difluoro-3-iodoacrylic acid **295** underwent coupling-cyclization with terminal alkyne under co-catalysis of $Pd(PPh_3)_2Cl_2$ (2 mol%) and 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 R = Ph) was assumed to involve in situ generation of ynenoic 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**).



Scheme 95

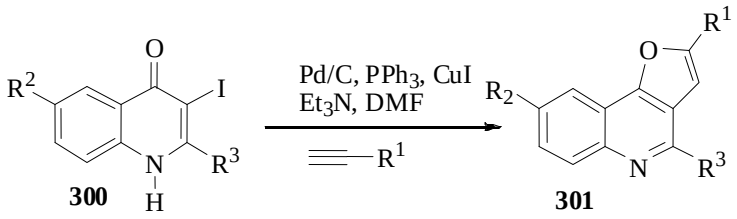
Heterogenous catalyst, Pd/MgLa mixed metal oxide has been utilized to conduct the copper free Sonogashira coupling between *o*-halogenated phenols and phenylacetylene.[174] The reaction is efficient only in the case of 2-iodophenol giving the 2-arylbenzofuran derivative **299** while with bromo- and chloro-compounds due to low reactivity afforded the desired benzofuran derivative in low yield (**Scheme 96**).



Entry	R	X	Yield (%)
1	H	I	61
2	Me	Br	<10
3	H	Cl	<10

Scheme 96

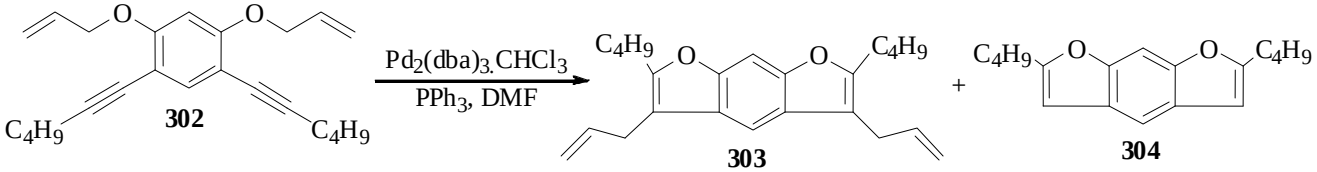
One pot synthesis of diverse 2-substituted furo[3,2-*c*]quinoline derivatives[175] based on domino coupling-cyclization[176] between 3-iodoquinoline-4-ones **300** and terminal acetylenes afforded the compounds **301** in excellent yields (**Scheme 97**).



Scheme 97

7.1.2. REACTIONS WITH INTERNAL ALKYNES

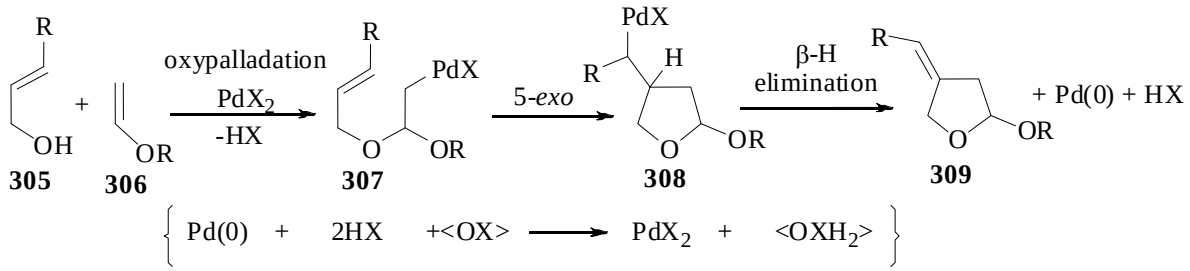
Double annulation of bis(allyloxy)bis(alkynyl)benzene **302** in the presence of $Pd_2(dba)_3.CHCl_3$ catalyst and PPh_3 as ligand afforded the tetrasubstituted benzodifuran **303** in 71% yield along with a trace amount of **304**[177] (**Scheme 98**).



Scheme 98

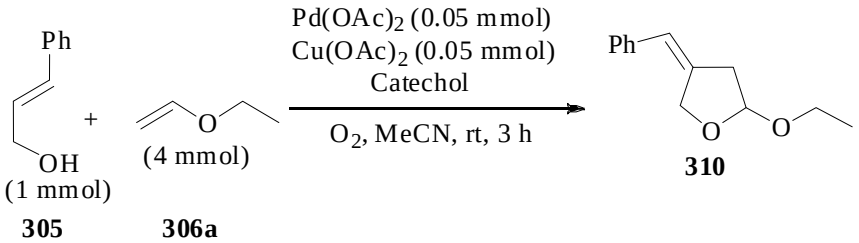
7.2 HETEROCYCLIZATION REACTIONS WITH ALKENES

Pd(II)-catalyzed oxidative annulation of alkenes with oxygen nucleophiles, commonly known as Oshima Utimoto reaction,[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.[178] Mechanistically, the reaction proceeds via oxypalladation followed by 5-*exo* cyclization and *β*-hydrogen elimination to give the cyclic ether **309** (**Scheme 99**).



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**).[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-*exo* cyclization of the oxypalladium intermediate **307** rather than 6-*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.



Pd:Cu:	GC yield (%)
1:1:-	48
1:1:1	82
1:1:2	84(82)[a]
1:1:4	79

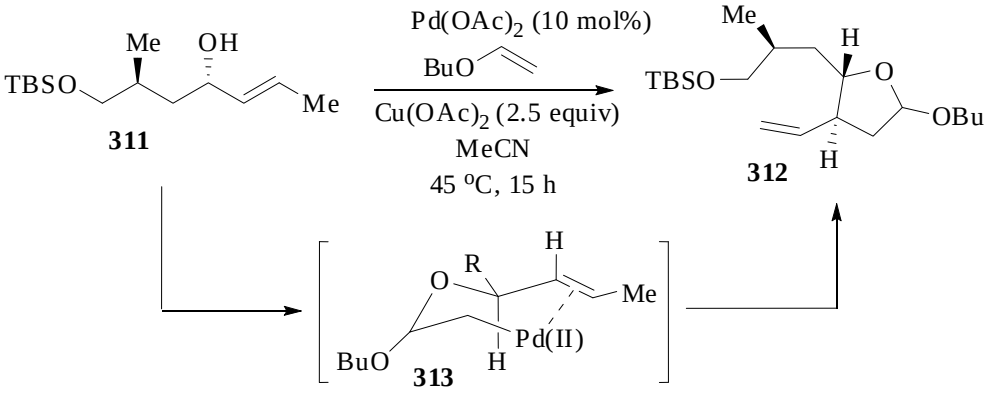
[a] Isolated yield

Scheme 100

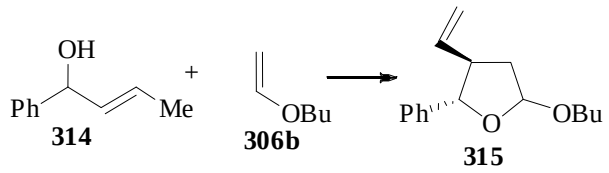
Palladium-catalyzed stereoselective Oshima-Utimoto reaction was successfully achieved for the construction of five-membered oxacycle **312** employed for the preparation of lactone ring in the asymmetric synthesis of (-)-11*R*,1,3-dihydroxanthatin.[180] The allylic alcohol **311** on treatment with $Pd(OAc)_2/Cu(OAc)_2$ catalytic system in acetonitrile afforded the tetrhydrofuran derivative in 68% yield and with >12:1 1,2-stereoinduction (**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 ^oC for 15 h afforded the furan derivative **315** in 69% yield with >15:1 1,2 diastereoinduction (**Scheme 102**).[181]

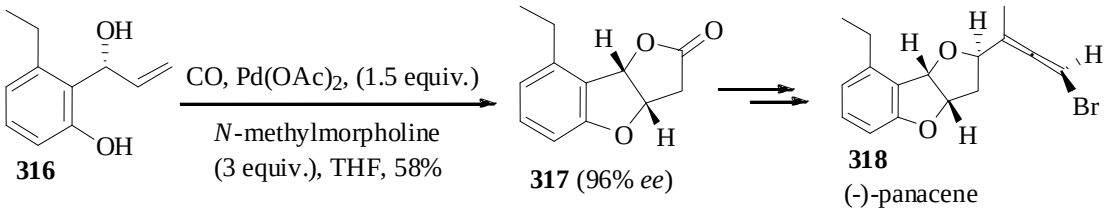


Scheme 101



Scheme 102

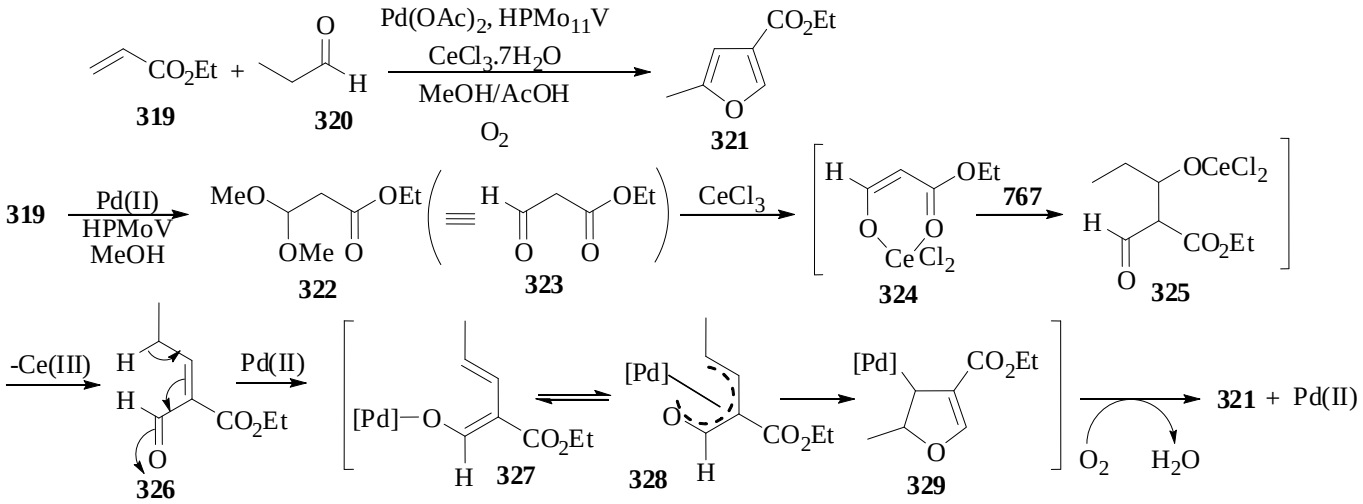
Stereocontrolled synthesis of tricyclic core *cis*-lactone **317** of the natural product (-)-panacene **765** via intramolecular alkoxycarbonylation-lactonization protocol was achieved[182] by $Pd(OAc)_2$-catalyzed domino cyclization of the phenol **316**. The natural (-)-panacene **318** was then synthesized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



Scheme 103

Catalytic amounts of Pd(II), $H_4PMo_{11}VO_{40}.28H_2O$ ($HPMo_{11}V$), and Lewis acid-like $CeCl_3$[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**.[184] The reaction was conducted in the presence of 1 atmosphere of oxygen

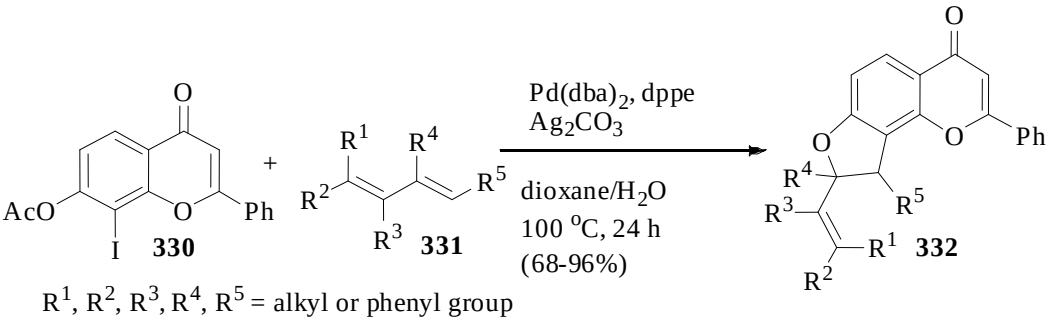
using solvent mixture (MeOH-AcOH). It is proposed that the acrylate initially formed acetal **322** or its synthetic equivalent **323** may undergo aldol type condensation with **320** by $CeCl_3$ to give an *α,β*-unsaturated carbonyl condensate **326** which on subsequent enolization by Pd(II) followed 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 $HPMo_{11}V/O_2$ reoxidation system (**Scheme 104**).[185]



Scheme 104

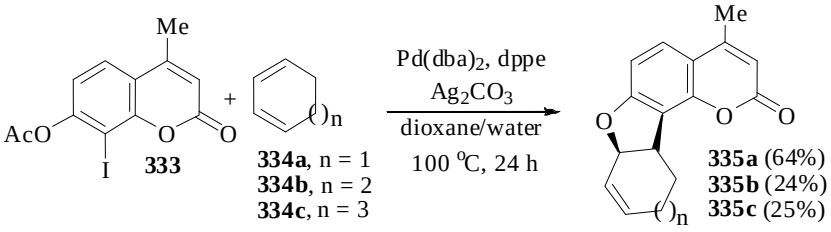
7.3. HETEROCYCLIZATION REACTIONS WITH DIENES

Larock et al. reported an efficient approach to biologically interesting dihydrofuroflavonoids **332** via palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids **330**.[186] The regioselective reaction was accomplished by employing catalyst $Pd(dba)_2$/dppe and base Ag_2CO_3 in dioxane/H_2O as solvent (4:1) to afford compound **332** (**Scheme 105**).



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**).[187]



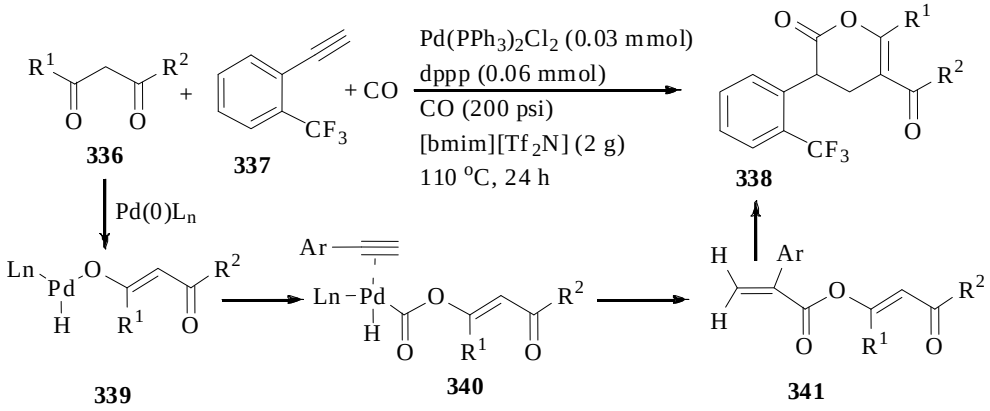
Scheme 106

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 tolerence of functional groups.

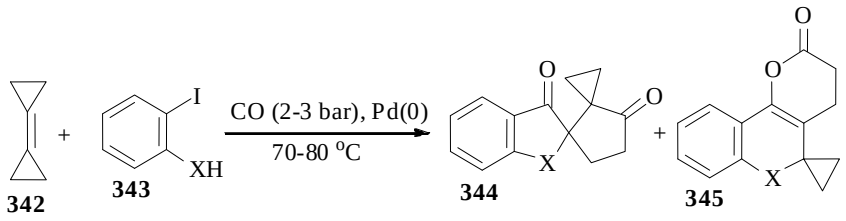
8.1. PALLADIUM-CATALYZED THREE-COMPONENT REACTION

Three-component reaction between 1,3-diketone with terminal alkyne in the presence of carbon monoxide was effected in the presence of $Pd(PPh_3)_2Cl_2$ as catalyst and dppp as ligand in ionic liquid [bmim][Tf_2N] 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**.



Scheme 107

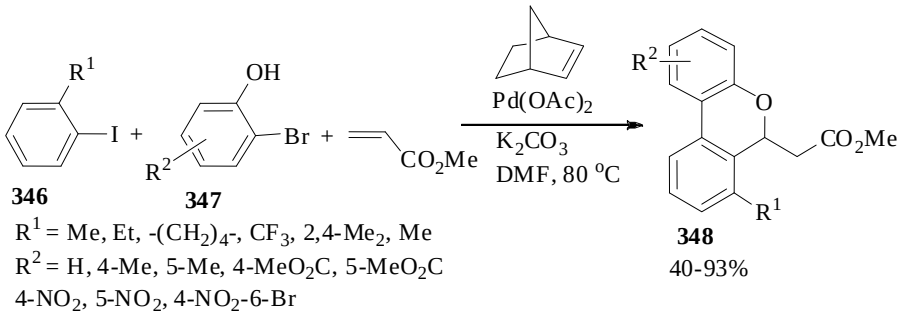
Meijere *et al*. developed a Pd(0)-catalyzed novel multicomponents queuing cascade reaction for the construction of spiro-annulated five- and six-membered heterocycles.[192] The three-component cross coupling reactions of bicyclopropylidene **342** with *with o*-iodophenols were investigated using various catalytic conditions. However for *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.



Reaction conditions: A: [$Pd(OAc)_2$] (10 mol%), PPh_3 (20 mol%) *n*-Bu_4NBr (100 mol%), CO (2- 3 bar), DMF. **B**: [$Pd(PPh_3)_4$] (4 mol%) MeCN. **C**: K_2CO_3, *n*-Bu_4NBr (150 mol%). **D**: [$Pd_2(dba)_3$] (3 mol%), PPh_3 (12 mol%). **E**: as in **D**, *n*-Bu_4NBr (150mol%)

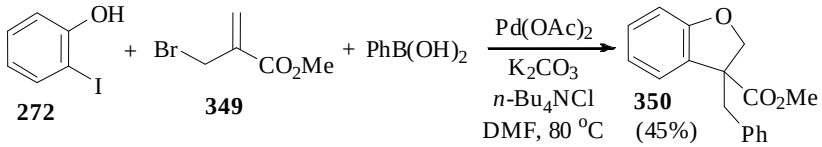
Scheme 108

A palladium-catalyzed one-pot three-component reaction was developed for the synthesis of 6*H*-dibenzopyran derivatives.[193] The reaction of aryl iodide, *o*-bromophenol and methyl acrylate in the presence of $Pd(OAc)_2$, and norbornene as catalyst and K_2CO_3 as a base in DMF at 80 °C for 24 h under nitrogen afforded the compounds **348** (**Scheme 109**).



Scheme 109

Recently, a novel three-component reaction affording new dihydrobenzofurans has been developed.[194] The domino reaction of 2-iodophenol, methyl bromomethylacrylate and phenylboronic acid in the presence of $Pd(OAc)_2$, K_2CO_3 and *n*-Bu_4NCl in DMF provided 3,3-disubstituted 2,3-dihydro benzofuran **350**. By employing a single catalytic system this reaction proceeded through allylic alkylation of 2-iodophenol followed by *exo-trig* cyclization via carbopalladation of the acrylate and then Suzuki cross coupling of the resulting alkylpalladium species (**Scheme 110**).

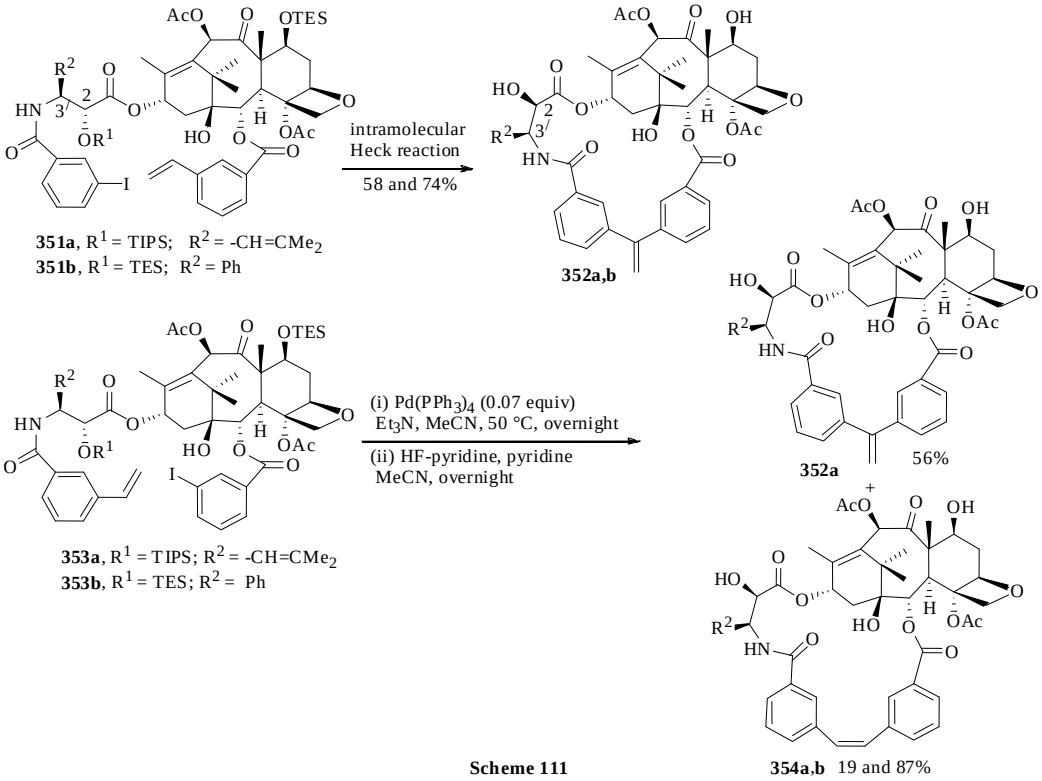


Scheme 110

9. MISCELLANEOUS

9.1 INTRAMOLECULAR HECK REACTION

The syntheses of the macrocyclic taxoids[195] **352a** and **352b** from **351a** and **351b** were achieved by using the catalysts $Pd(PPh_3)_4$ and $Pd_2(dba)_3/AsPh_3$ respectively by an exclusive *exo*-cyclization mode (**Scheme 111**). Likewise, the macrocycles **354** were also obtained in good yields.



351a, R^1 = TIPS; R^2 = -CH=CMe_2
351b, R^1 = TES; R^2 = Ph

352a,b

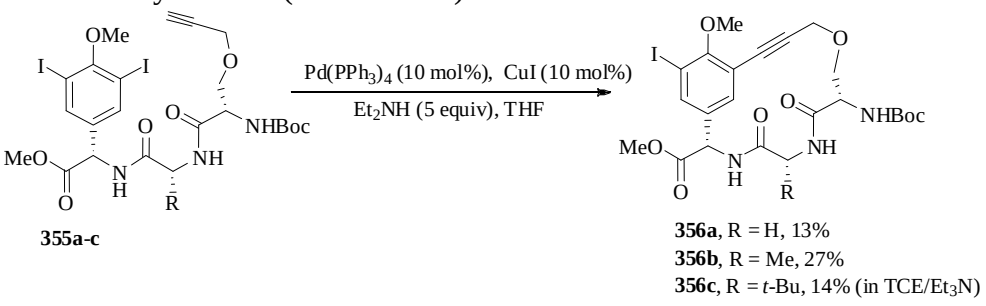
353a, R^1 = TIPS; R^2 = -CH=CMe_2
353b, R^1 = TES; R^2 = Ph

352a

354a,b

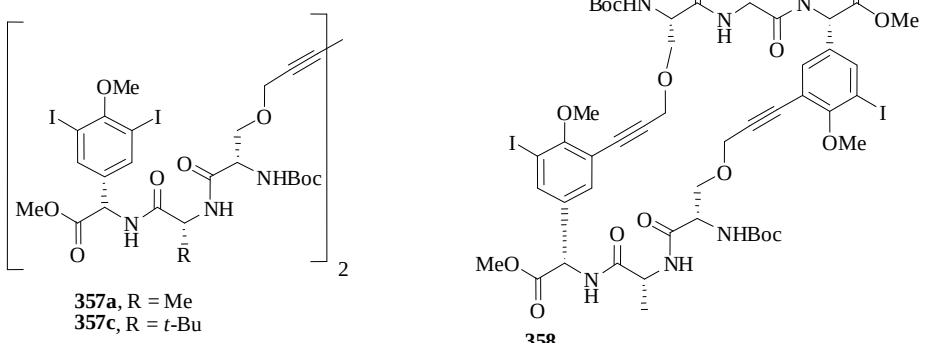
Scheme 111

Synthesis of a range of highly constrained cyclic tripeptides, a mimic of vancomycine's carboxylate-binding pocket, via intramolecular Sonogashira coupling as the ring-closing reaction was reported by Liskamp and co-workers.[196] The linear precursors **355a-c** when subjected to $Pd(PPh_3)_4$, CuI and Et_2NH 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**).



355a-c

356a, R = H, 13%
356b, R = Me, 27%
356c, R = *t*-Bu, 14% (in TCE/Et_3N)



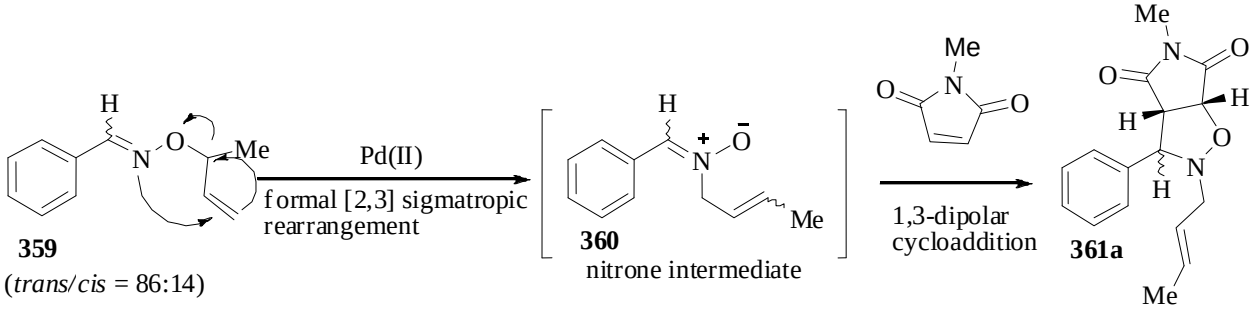
357a, R = Me
357c, R = *t*-Bu

358

Scheme 112

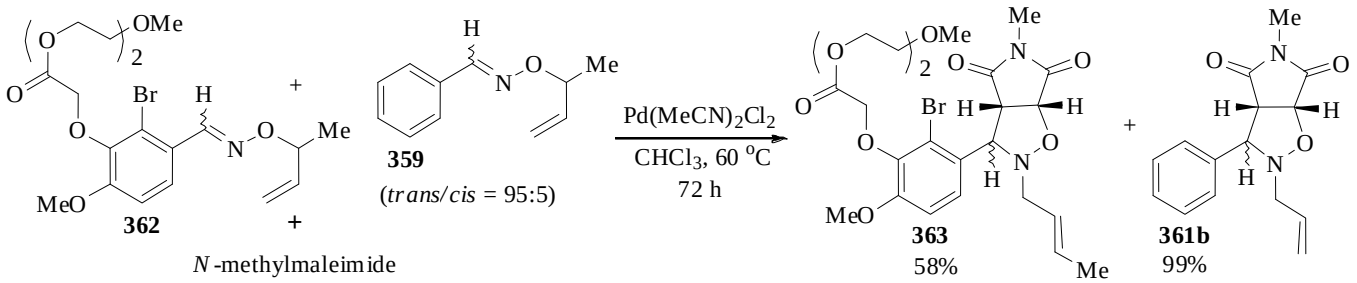
9.2. CYCLOADDITION REACTIONS

The behavior of oxime ether in the presence of palladium catalyst is quite interesting. It has been observed that the oxime O-allylether **359** in the presence of $Pd(MeCN)_2Cl_2$ as catalyst in $CHCl_3$ 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**).[197] This reaction is nonselective as diastereomeric mixture is obtained.



Scheme 113

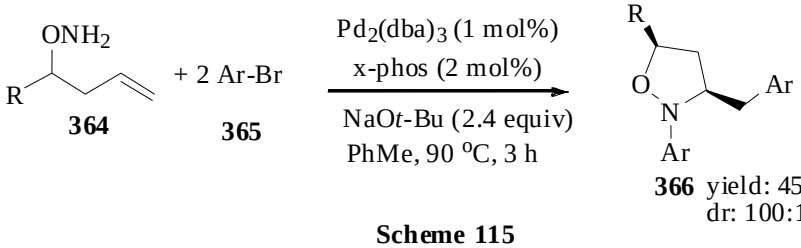
To test the intramolecular nature of the nitrone formation, a cross over experiment was set to allow scrambling of the partners (**Scheme 114**). However, after 72 h the formation of products **361b** and **363** clearly indicate that the nitrone formation proceeds completely in an intramolecular fashion.



Scheme 114

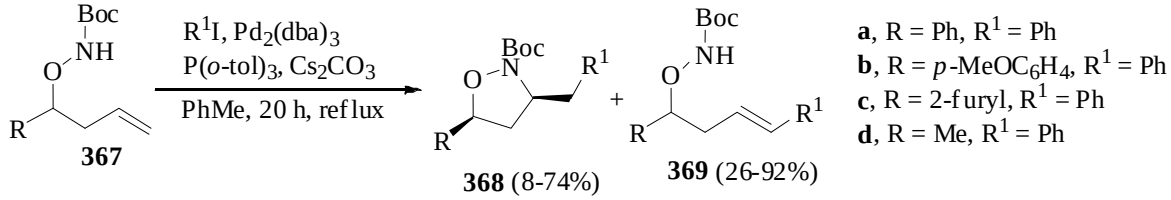
9.3. INTRAMOLECULAR ADDITION OF N-H BONDS ACROSS ALKENE

Domino *N*-arylation/cyclization/C-arylation of *O*-homoallylhydroxylamines **364** with aryl bromides in the presence of $Pd_2(dba)_3$, x-phos and NaO*t*-Bu afforded *cis*-disubstituted isoxazolidine derivatives **366** (**Scheme 115**).[198]



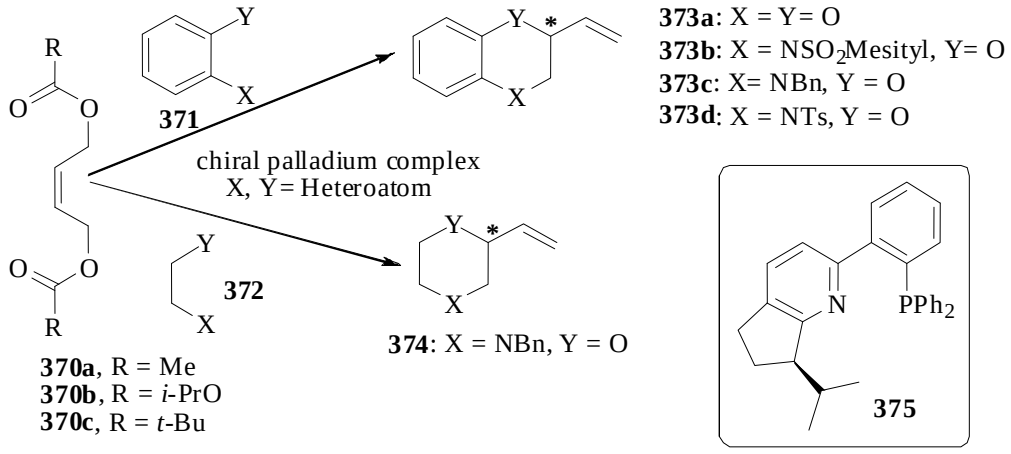
Scheme 115

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**.[199] 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_2CO_3 in refluxing PhMe for 20 h to afford the isoxazolidine derivatives **368** together with normal Heck coupling adducts **369** (**Scheme 116**).



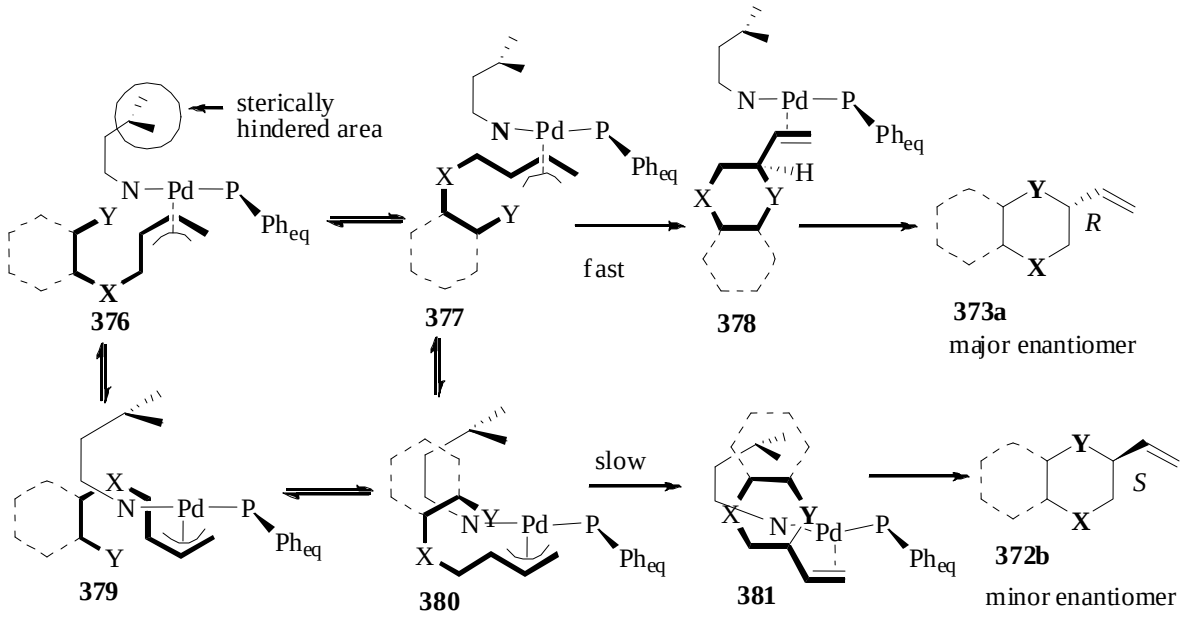
Scheme 116

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**)[200] as chiral ligand have been reported.[201] All the reactions were carried out using [Pd(C_3H_5)Cl] as catalyst in CH_2Cl_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_2CO_3 as the base with good enantioselectivity. In all the cases the products **373** and **374** were formed with *R*-configuration (**Scheme 117**).



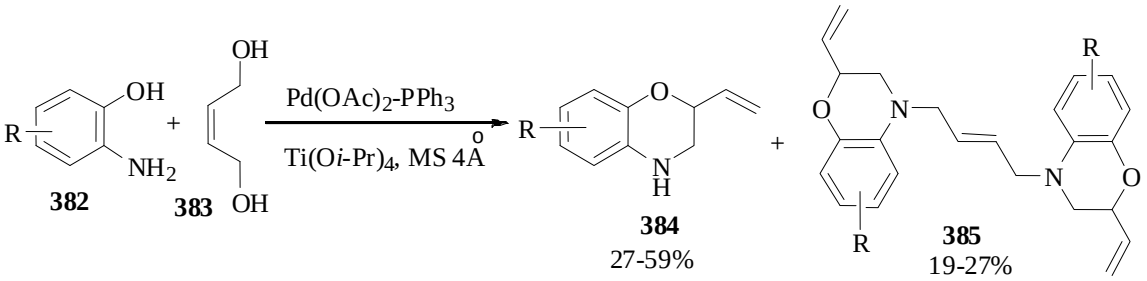
Scheme 117

Formation of the products **373** and **374** proceeds via π-allylpalladium complexes. The possible diastereomeic 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**).



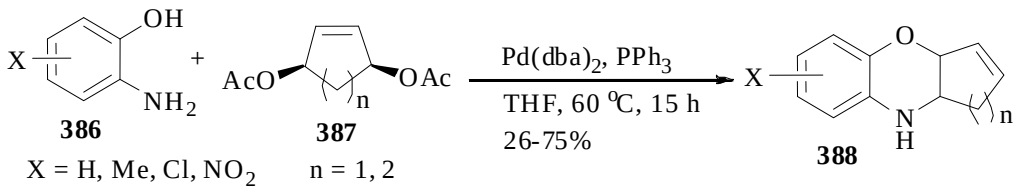
Scheme 118

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.[202] 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.[203]



Scheme 119

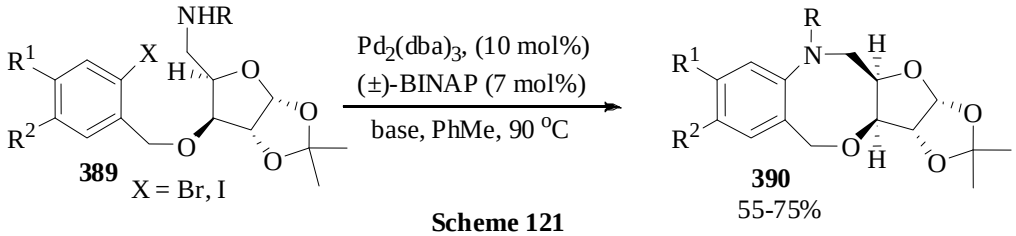
The reaction of 2-aminophenols with cyclic *meso*-allylic diacetates **387** catalyzed by $Pd(dba)_2/PPh_3$ gave phenoxazines **388** (**Scheme 120**).[204] Based on well-known π-allylpalladium chemistry it is assumed that the relative stereochemistry of the morpholine ring and cyclopentene and / or the cyclohexene ring should be *cis*.



Scheme 120

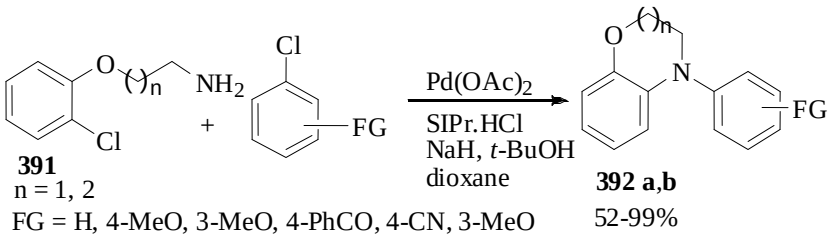
9.4. INTRAMOLECULAR COUPLING OF NH AND OH WITH ARYL HALIDE

The Pd-catalyzed intramolecular arylamination and aryl etherification on carbohydrate derived substrates by using bulky biarylphosphine ligands has been reported.[205] A variety of highly functionalized *cis*-fused tricyclic furobenzoxazocines **390** were prepared from D-glucose-derived substrates **389** utilizing $Pd_2(dba)_3$ as catalyst and (±)-BINAP as ligand. KO*t*-Bu + K_2CO_3 was found to give excellent results for the bromo substrates **389** while the iodo substrate afforded better result with Cs_2CO_3 (**Scheme 121**).



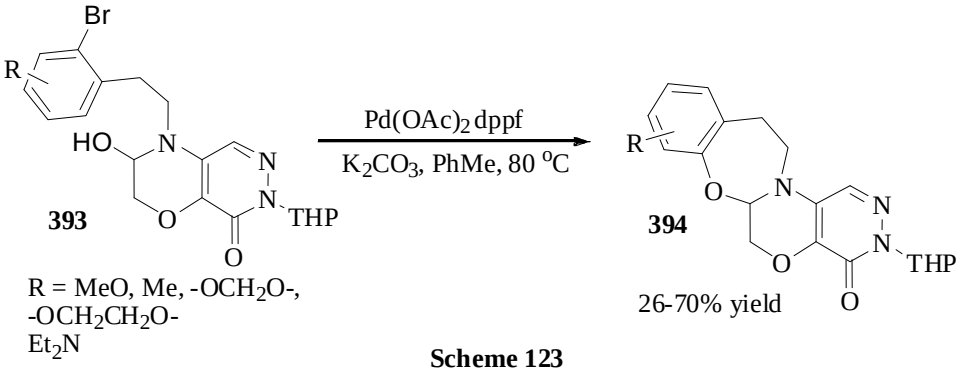
Scheme 121

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.[206] 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, NaO*t*-Bu and $Pd(OAc)_2$ was found to be effective. This diarylation protocol was also applied to the synthesis of benzoxazines **392a** and benzoxazepines **392b** from **391** by employing the same conditions (**Scheme 122**).



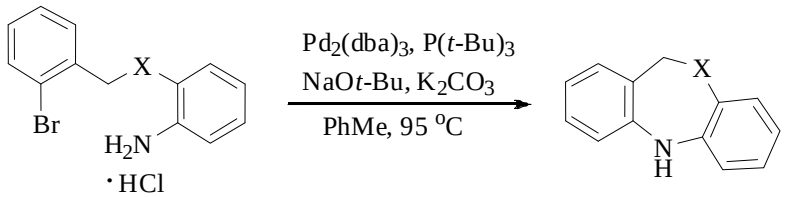
Scheme 122

Ma *et al*. reported the synthesis of oxazepine ring **394** containing pyridazinone moiety via palladium catalyzed intramolecular coupling of an aryl bromide with an alcohol **393**.[207] The pyridazinone when treated with $Pd(OAc)_2$ and (dppf) afforded the product **394**. The reaction is assumed to proceed via palladium oxapalladacycle followed by C-O bond forming reductive elimination (**Scheme 123**).



Scheme 123

Palladium-catalyzed intramolecular cycloamination strategy for the synthesis of an assembly of oxazepine **396a** and thiazepine ring **396b** systems[208] were carried out using $Pd_2(dba)_3$, P(*t*-Bu)$_3$ and NaO*t*-Bu or with K_2CO_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**).



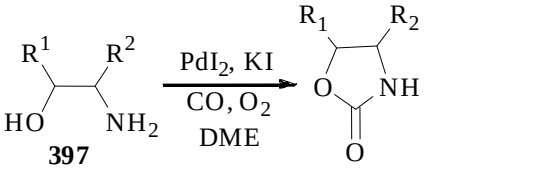
395a, X= O
395b, X = S

396a, (87%)
396b, (67%)

Scheme 124

9.5. CYCLOCARBONYLATION AND CYCLOCARBOXYLATION REACTIONS

Gabriele *et al*. reported[209,210] that a combination of PdI_2 and KI in DME exhibited excellent catalytic efficieny in the oxidative cyclocarbonylation reaction of *β*-amino alcohols and 2-aminophenol (**Scheme 125**)



397

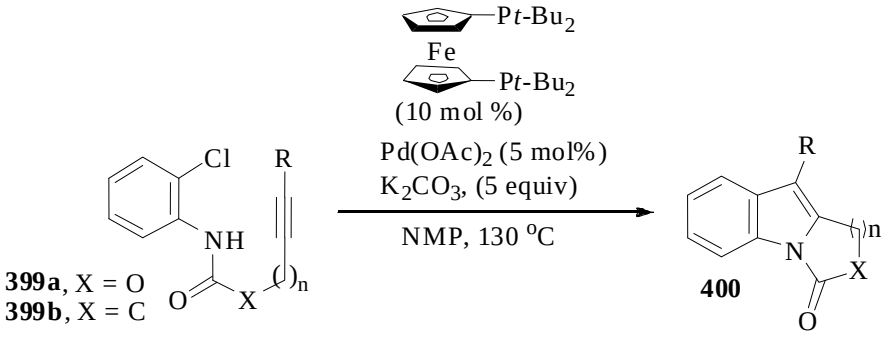
398 (83-100%)

R^1 = H, Me, Ph
R^2 = H, Me, Ph, *i*-Pr, Bn

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[211] by using D*t*-BPF as ligand, K_2CO_3 as base and NMP as solvent at 130 °C (**Scheme 126**). The reaction is also applicable when X = nitrogen affording corresponding nitrogen heterocycles.



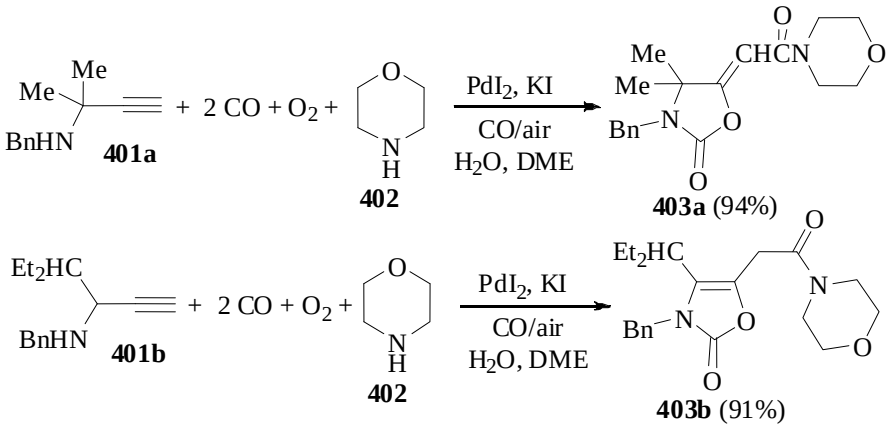
399a, X = O
399b, X = C

400

Scheme 126

9.7. PALLADIUM-CATALYZED FOUR-COMPONENT REACTION

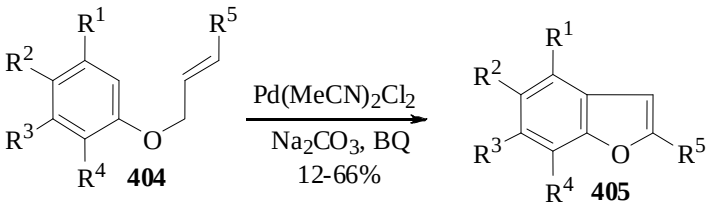
Gabriele *et al*. reported an efficient concatenation of aminocarbonylation and cyclocarbonylation for the synthesis of 2-oxazolidinones 403a,b.[212] The one-pot method consists of the reaction of *α,α*-disubstituted 2-ynylamines with CO, O_2, and morpholine in the presence of catalytic amounts of PdI_2 in conjunction with KI and H_2O (PdI_2/KI/1/2/H_2O molar ratio1:10:100:500: 500), in DME as the solvent at 100 ^oC 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 *α*-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 3*H*-oxazol-2-one derivative 403b (Scheme 127).



Scheme 127

9.8. CLAISEN REARRANGEMENT

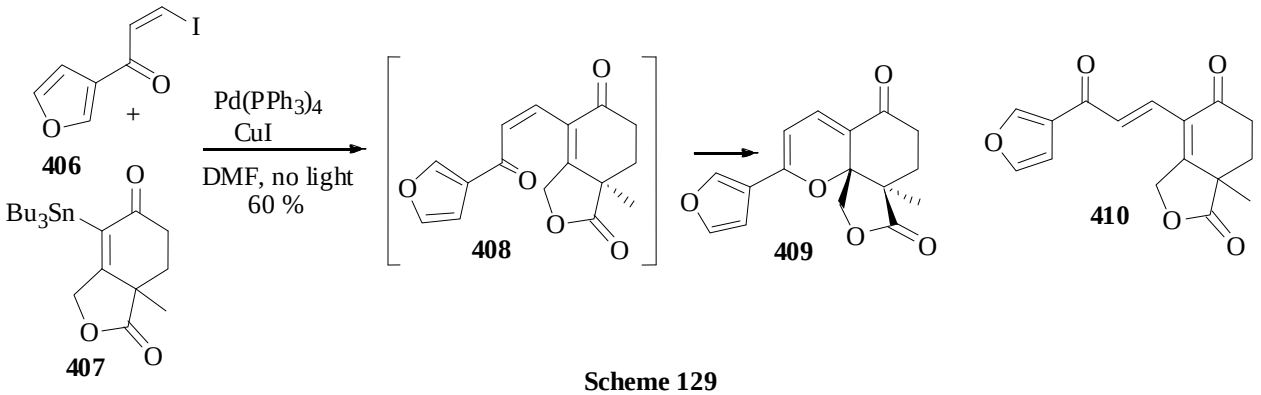
Pd-catalyzed domino Claisen rearrangement[213]/oxidative cyclization of allyl aryl ethers **404** into benzofurans **405** was investigated by Youn *et al*.[214] The scope of this sequential process was tested with different allyl aryl ethers in the presence of $Pd(MeCN)_2Cl_2$ as catalyst, Na_2CO_3 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**).



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**).



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.

11. ACKNOWLEDGEMENTS

We thank the DST (New Delhi) for financial assistance. Two of us (B. C. and S. S.) are grateful to the CSIR (New Delhi) for a senior research fellowship.

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