Recent Advancement in Palladium Catalysed C-C bond Activation of Strained Ring Systems: Three and four-membered carbocycles as prominent C3/C4 building blocks

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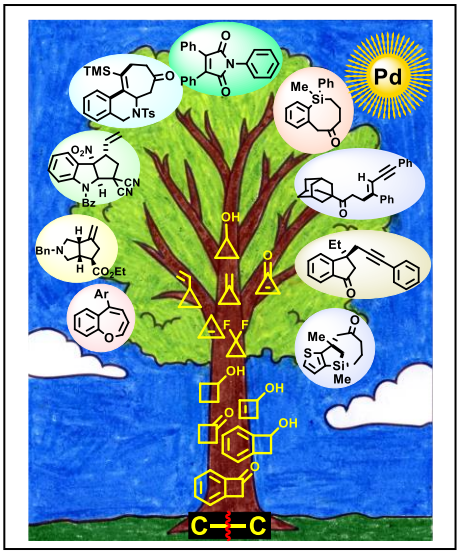
ABSTRACT: In recent years, transition metal catalysed strong C-C bond activation has significantly attracted the attention of synthetic chemists. This enables simultaneous and direct functionalization of two different M-C bonds. Among different types of C-C bond activation strategies, strain-driven C-C bond activation has resulted in a variety of transformations, which is otherwise impossible. In this context, palladium catalyst has been extensively used and studied due to its robust nature in terms of its reactivity and selectivity. Herein, we have provided a brief discussion about palladium catalysed C-C bond activation of three and four-membered cycloalkane derivatives.



1. INTRODUCTION

Carbon-carbon bonds are considered as the basic backbone of organic molecules. Thus, cleavage and formation of these C-C bonds are extremely significant in organic synthesis. The C-C bond-forming reactions are useful to make a variety of man-made substances, including medicines, pesticides, fertilizers, plastics etc.[1] However, selective C-C bond cleavage reactions are usually regarded very difficult, due to its high thermodynamic stability.[2]

C-C bond cleavage process are particularly prevalent in carbohydrate metabolism and cracking of hydrocarbons in the crude oil refineries. Furthermore, one of the world's pressing problems is to develop effective solutions to alleviate the energy crisis and pollution. The C-C bond cleavage procedures are extremely useful for the modification of waste generated in oil industry and breakdown of plastic objects that may cause environmental pollution. Therefore, the development of new approaches in the field of C-C bond cleavage is urgent.

Synthetic organic chemists who are involved in synthesizing a wide range of organic compounds, including simple to complex molecules such as natural products, have paid close attention to the cleavage of strong carbon-carbon bonds.

In this context, transition metal catalysed C-C bond activation has been considered as the powerful technique.[3] This C-C bond activation strategy typically proceed through different pathways.[4] One typical tactic is to use small rings (three- and four-membered) having high strain energy that offers a substantial driving force for the cleavage of C-C bond, are great candidates for transition-metal-catalyzed C-C bond cleavage procedures (figure 1).

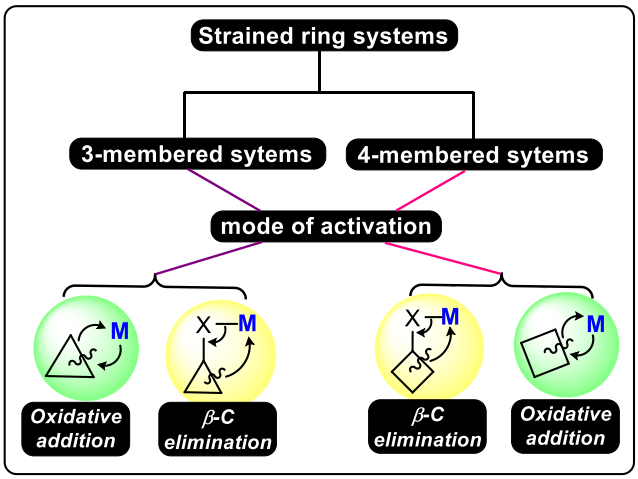


Figure 1. Modes of C-C bond activation in 3 and 4-membered strained system.

In this case, the cleavage event is associated with strain-release energy which serves as a key driving factor. Activation

of C-C bond, or the addition of C-C bonds to the metal (oxidative addition), can be accomplished in two ways, that is undirected or directed pathways. The directed path can frequently improve reaction rates and provide enhanced regiocontrol. Further, the C-C bond activation process occurs in two pathways (i) oxidative addition of C-C bonds to the transition metal and (ii) β -carbon elimination. This review focuses on both the reactive pathways of C-C bond activation that enables three and four membered strained system as C3/C4 building blocks.

Palladium as a catalyst has been extensively used by scientific community for the synthesis of various drugs, natural products, and bio-active scaffolds.[5] Its practical utility as a catalyst has been exploited in various C-X bond activation strategy. Among them, usage of simple palladium catalyst in C-C bond activation of strained cycloalkanes is now a booming area. As compared to C-H bond activation reaction, C-C bond activation reactions have not been extensively explored.[6] But this trend is now changing very fast, as many groups are now actively getting involved in C-C bond activation of three and four membered ring systems.

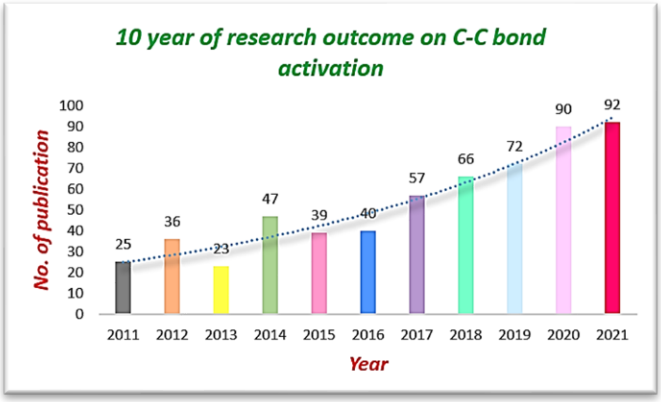


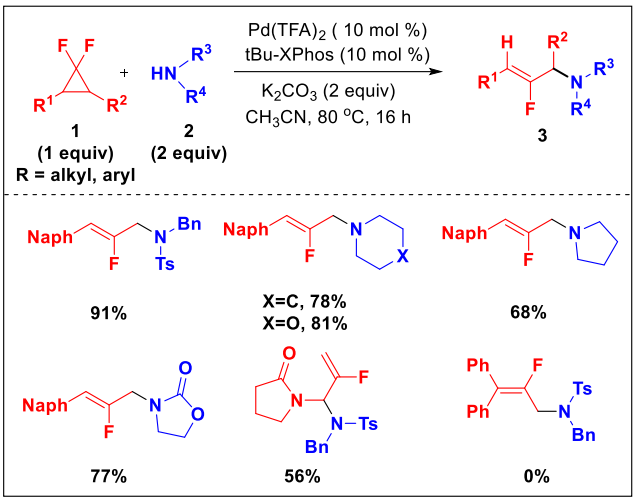
Figure 2. 10 Year of research outcome on transition metal catalysed C-C bond activation (Scifinder keyword search: C-C bond activation, refined by years)

This is reflected from the rise in the number of publications since last ten years (figure 2).

Three and four membered ring systems are ideal 3C and 4C synthons for the synthesis of useful compounds through C-C bond activation. In this context palladium catalyzed C-C bond activation reactions are constantly on the rise, therefore a detailed account on this topic is both timely and useful to scientific community to explore its vast potential. The goal of this study is to highlight some of the main palladium catalysed C-C bond activation reaction that have been established with cyclopropane and cyclobutane derivatives. This review focuses on key synthetic advances reported from mid-2011 to early-2022.

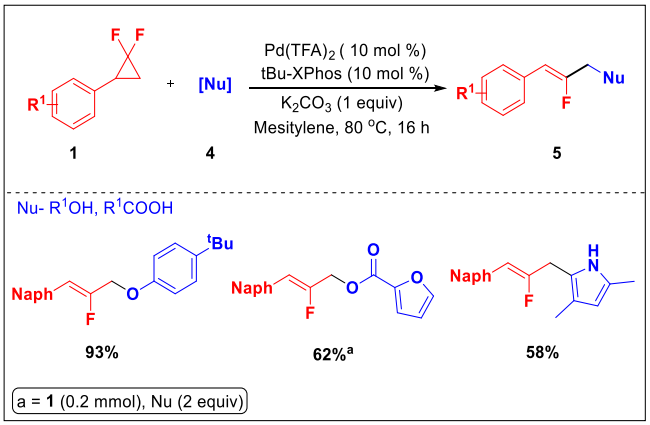
Cyclopropane:

The first report on Pd-catalysed regioselective activation of gem-difluorinated cyclopropanes has been unravelled by Fu and co-workers in 2015.[7] The C-C bond cleavage followed by simultaneous β-F elimination process of gem difluorinated cyclopropanes **1** and coupling with wide range of nucleophiles **2**/**4** delivered 2-fluoroallylic amines **3**, ethers, esters, and alkylation products **5** with high *Z*-selectivity (Scheme 1.1a and b). This procedure is operationally simple and utilizes easily available substrates compared to the earlier methods[7b] providing the product in good yields with high *Z*-selectivity.



Scheme 1.1a Pd-catalysed regioselective activation of gem-difluorinated cyclopropanes.

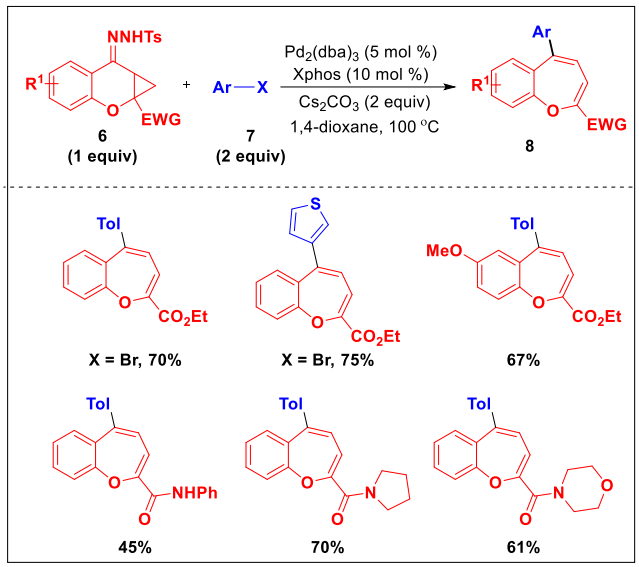
The N, C, O, nucleophiles used in the reaction provide a distinct and important synthetic protocol for the synthesis of a range of 2-fluorinated allylic products. The N-nucleophiles (protected benzylamines, protected aromatic amines, secondary amines) employed, mostly gave a linear major product with high Z-selectivity. When 1-(2,2-difluorocyclopropyl)pyrrolidin-2-one was used as a substrate, it resulted in branched product with a moderate yield. Substrate with terminal substituents did not yield the product even at higher temperatures. With some modification in the reaction condition other nucleophiles such as phenols, alcohols, carboxylate salts delivered the corresponding 2-fluoro allylic ether, ester and alkylation product in excellent to moderate yields. This reaction can also be done in a gram scale which gives a promising hope for its future use in industrial application.



Scheme 1.1b Pd-catalysed regioselective activation of gem-difluorinated cyclopropanes.

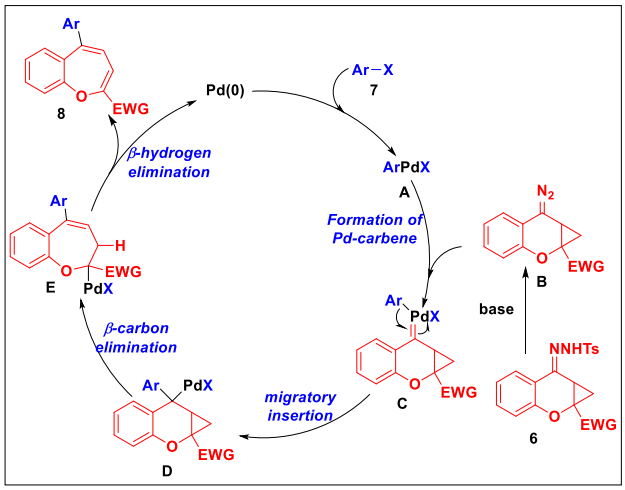
Benzoxepines occur in biological system and in a variety of natural products.[8] Its derivatives exhibit wide range of pharmacological properties.[9] Therefore, synthesis of benzoxepines has attracted a significant attention. In 2016,

Zhao and co-workers demonstrated Pd-catalysed synthesis of benzoxepines **8** from the ring opening protocol of cyclopropane derivatives of *N*-tosyl hydrazones **6** and aryl halide **7**, in good yield (Scheme 1.2). The reaction is facilitated by the presence of a strong base Cs_2CO_3 and non-polar solvent 1,4-dioxane.



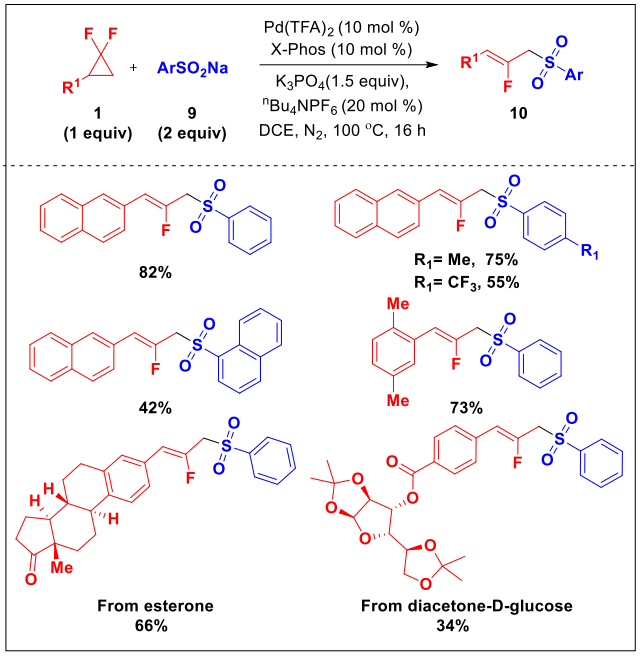
Scheme 1.2 Pd-catalysed regiospecific synthesis of benzoxepines.

Further, the generality of the optimized condition has been tested. Variation in yield was observed by varying substituent pattern on the aromatic ring of *N*-tosyl hydrazones. By changing the electron withdrawing group from ester to amide, there is no significant variation in the product yield.



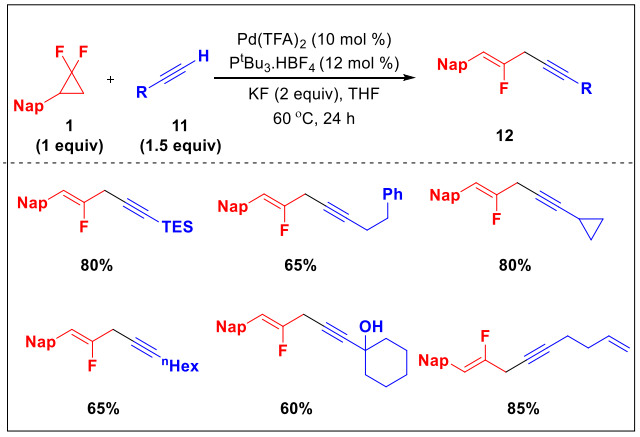
Scheme 1.3 Plausible mechanism.

The authors proposed a plausible mechanism for this transformation (scheme 1.3). Pd(II) complex **A** is formed by the oxidative addition of the aryl halide to Pd(0). Then, *N*-tosylhydrazone in the presence of the base forms a diazo compound **B** which in the presence of Pd(II) complex forms a carbene intermediate **C**. The migratory insertion of aryl group into the Pd carbene occurs prior to the regiospecific C-C bond cleavage through *β*-carbon elimination. The intermediate **E** further undergoes *β*-H elimination delivering the



Scheme 1.4 Palladium-catalyzed ring-opening coupling of gem difluorocyclopropanes for the construction of 2-fluoroallylic sulfones.

benzoxepine **8** with the regeneration of active Pd(0) catalyst. Ring opening reactions of gem-difluorocyclopropanes have been reported using different metal catalyst such as Ni, and Ag. However, palldium catalysed selective allylic sulfonylation of gem-difluorocyclopropanes has not been studied until 2019.[10]

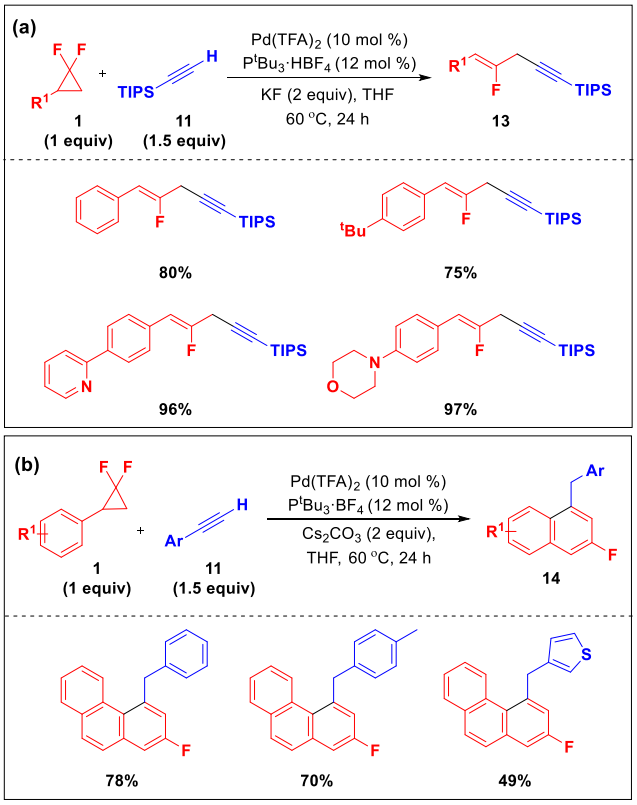


Scheme 1.5 Scope of alkynes in palladium-catalysed ring-opening alkynylation of gem-difluorinated cyclopropanes.

Due to its importance for the synthesis of drugs and agrochemical materials, Zhang and co-workers disclosed a new method through ring opening coupling of gem-difluorocyclopropanes **1** with sodium arylsulfinates **9** in the presence of 10 mol % $Pd(TFA)_2$, 10 mol % X-phos, 1.5 equiv K_3PO_4, and 20 mol % of n-Bu_4NPF_6 in dichloroethane (DCE) solvent at 100 °C (Scheme 1.4). The reaction proceeded through C-C bond cleavage, *β*-F elimination and allylic coupling to form corresponding 2-fluoroallylic sulfones **10** efficiently with *Z*-selectivity. This reaction has been used in versatile ways to produce pharmaceutically useful products by taking vari-

ous biomolecular derivatives of estrone, diacetone-D-glucose etc. Extensive research has been done for the synthesis of skipped enynes due to their importance as a useful synthetic precursor. Skipped enynes are also found in many bio-active molecules. Many methods are used for their synthesis including Wittig-reaction, transition metal catalysed allyl-alkynyl coupling reaction etc. However, there are only very few methods reported for the synthesis of fluorinated skipped enyne.

Fu and co-workers in 2020 reported Pd-catalysed alkynylation of gem-difluorinated cyclopropane via C-C activation/ C-F elimination followed by C(sp^3)-C(sp) bond formation.[11] The reaction does not take place in the absence of palladium catalyst. The cross-coupling between gem-difluorinated cyclopropane **1** and alkyne **11** occurs in the presence of 10 mol % of $Pd(TFA)_2$ to deliver *Z*-selective fluorinated skipped enyne **12** product with minor *E*-isomer (Scheme 1.5). The variation in the alkyne substrate containing silyl, cyclopropyl, and n-hexyl groups gave the product in moderate to good yield. Different aryl substituted gem-difluorinated cyclopropanes underwent ring opening alkynylation and afforded the product in good to excellent yield (Scheme 1.6a).



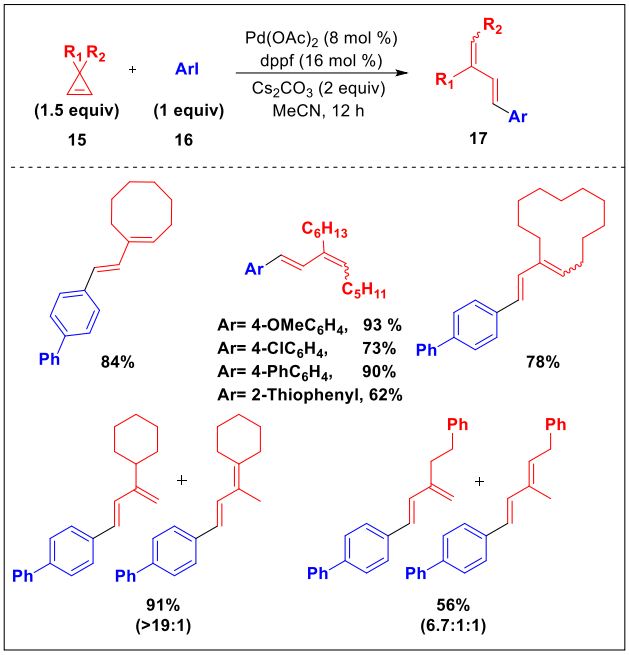
Scheme 1.6 (a) Scope of arenes in palladium-catalysed ring-opening alkynylation of gem-difluorinated cyclopropanes. (b) Synthesis of aromatic arenes.

With the small modification in the optimized reaction conditions, a wide range of aromatic arenes has been synthesized *via* an additional cyclization step in moderate to good yield (Scheme 1.6b).

1.1 Cyclopropene:

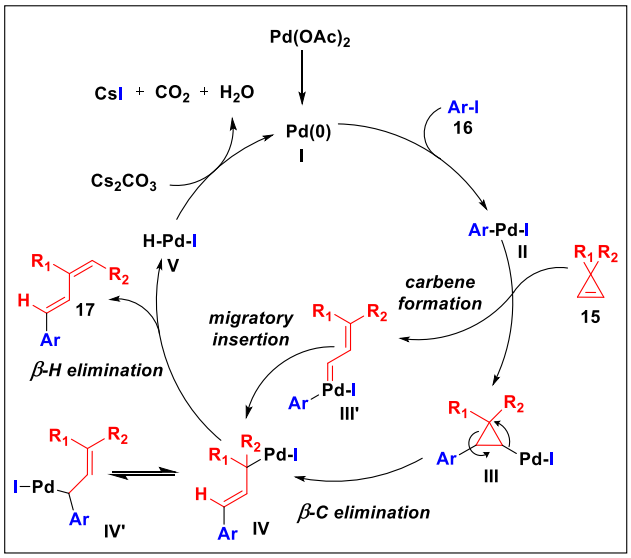
Cyclopropene is another class of three-membered strained system that has been used widely as a 3C synthon and an active coupling partner in different value-added transformations. Under catalytic condition the double bond of cyclopropene interact with metal to undergo various efficient transformations.

In 2014, Wang and co-workers developed stereoselective Pd(0) catalyzed ring opening cross coupling of cyclopropene **15** with aryl iodides **16** that delivered 1,3-butadiene derivatives **17** (Scheme 1.7).[12] The generality of the reaction condition has been tested by varying substituents on cyclopropene as well as aryl iodide (Scheme 1.7). As observed, electron donating substituent on aryl iodides gave better yield at lower temperature than the electron withdrawing group. Aryl iodides with two aliphatic chains resulted in the mixture of *E* and *Z*-isomers. Cyclopropene and 4-iodobiphenyls produced regioisomers due to the presence of two different substituents on the cyclopropene ring which can undergo *β*-H elimination.



Scheme 1.7 Pd-catalyzed ring-opening cross-coupling of cyclopropenes with aryl iodides.

They have proposed a plausible catalytic cycle for the above transformation (Scheme 1.8). The cyclopropene is activated by the Pd(II) aryl iodide intermediate in two different pathways. In one pathway, insertion of the C-C bond of cyclopropane **15** in the metal alkyl bond **II** afforded cyclopropyl palladium species **III**, which on *β*-carbon elimination leads to the opening of the strained ring to give the intermediate **IV**. Subsequent *β*-H elimination from intermediate **IV** afforded 1,3-diene product **17**. However, in other pathway, it may also proceed via formation of palladium carbene species **III'** followed by the migration of the aryl group to deliver the intermediate **IV**. This on the subsequent *β*-H elimination delivered the desired product **17**, with the generation of active palladium (II) species. The active Pd(0) species regenerate

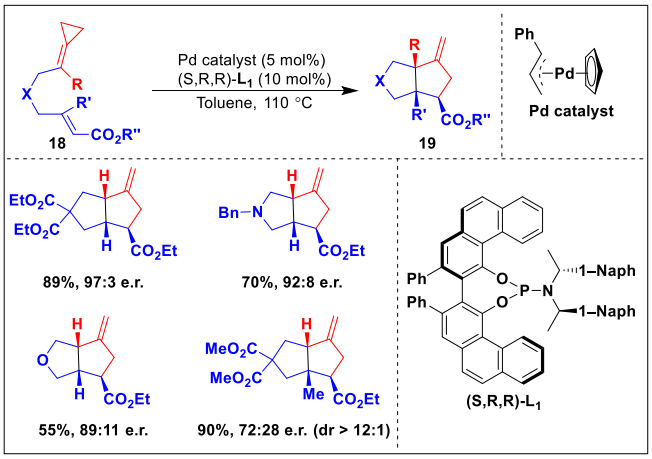


Scheme 1.8 Plausible mechanism.

from intermediate **V** in the presence of Cs_2CO_3 for the next catalytic cycle.

1.3 Alkylidene cyclopropane (ACP):

Alkylidene cyclopropane (ACPs) are a class of three-membered strained system that has been heavily exploited in the palladium catalysed C-C bond activation.[13] ACPs are mostly used as active 3C synthons in the cycloaddition reaction to synthesize various value-added products.

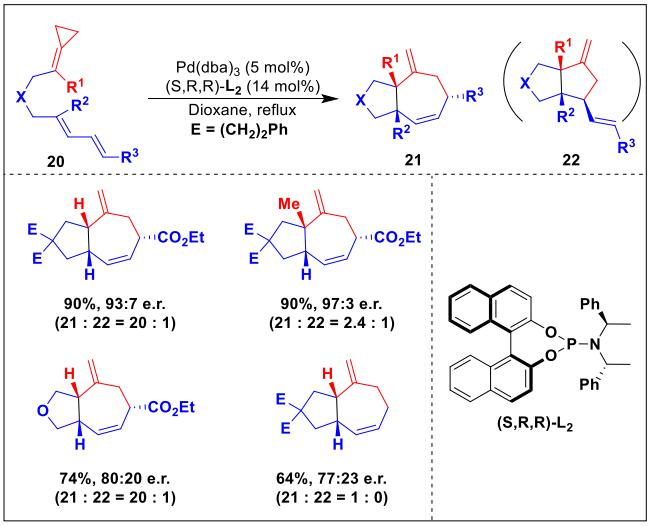


Scheme 1.9 Scope of the Pd-Catalyzed [3C + 2C] Cycloaddition.

Cycloaddition reactions are one of the most appealing techniques for assembling complex polycyclic skeletons, because they are atom-economic and able increase the complexity in the final product in just one step.

Classical cycloadditions reactions are confined to substrates that are electronically compatible. In this setting, transition-metal catalysis is a particularly effective way to induce annulations of normally nonreactive, nonactivated precursors. Furthermore, by adding chiral ligands at the metal centre, enantioselective variations can be created, allowing for the construction of enantio-rich cyclic scaffolds.

In 2018, Lopez and co-workers discovered that alkylidenecyclopropanes (ACPs) **18** and alkenes can undergo a highly enantioselective [3C + 2C] intramolecular cycloaddition (Scheme 1.9).[14] The best result came when chiral phosphoramidite ligands $\mathbf{L_1}$ were used in the reaction. Furthermore, they showed that when dienes **22** (in place of alkenes), are used as reaction partners, extremely efficient [4C + 3C] cycloadditions can be done with the help of analogous but less bulky phosphoramidites $\mathbf{L_2}$ (Scheme 2.0). These reactions offer a practical, straightforward, and selective route to optically active and synthetically attractive 5,5- and 5,7-bicyclic complexes.



Scheme 2.0 Scope of the Enantioselective Pd-Catalyzed [4 + 3] Cycloaddition

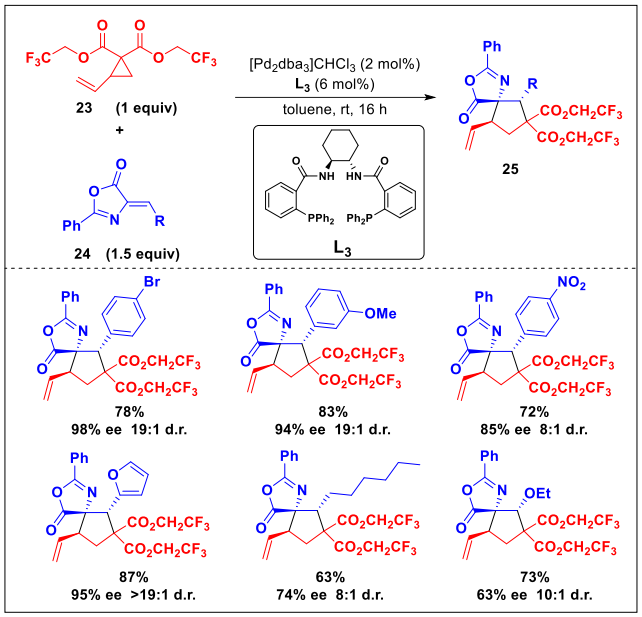
1.4 Vinyl Cyclopropane (VCP):

Lately, Vinyl cyclopropanes (VCPs) containing electron-withdrawing group have gained a lot of attention as a new group of "three-carbon-atom" precursors for asymmetric cycloaddition reactions.[15] They can generate 1,3-dipolar equivalents in the presence of Pd(0) catalysts, and then trap a dipolarophile to form diverse substituted five-membered rings.[15,16]

In both organic and medicinal chemistry, the discovery of new enantioselective procedures for the creation of cyclopentane rings with numerous stereocenters is critical. In the presence of palladium(0) catalysts, vinyl epoxides, aziridines, and cyclopropanes containing electron-withdrawing groups are known to open into 1,3- dipoles. The resulting Pd(II) complexes add across olefins, isocyanates, carbodiimides, and aldehydes to afford five-membered rings.

In 2011, Trost and co-workers discovered a novel palladium-catalyzed enantioselective formal [3+2] cycloaddition between vinyl cyclopropanes **23** and prochiral Michael acceptors **24** (Scheme 2.1).[17] Very good yields and selectivities were obtained when bis(2,2,2-trifluoroethyl)malonate vinylcyclopropanes are used. They anticipated that cyclopentanes can be synthesized using 1,3-dipoles generated from vinyl cyclopropanes as a novel three carbon fragment with the help of palladium catalysis. They used alkylidene azalactones as the acceptor for this reaction which re-

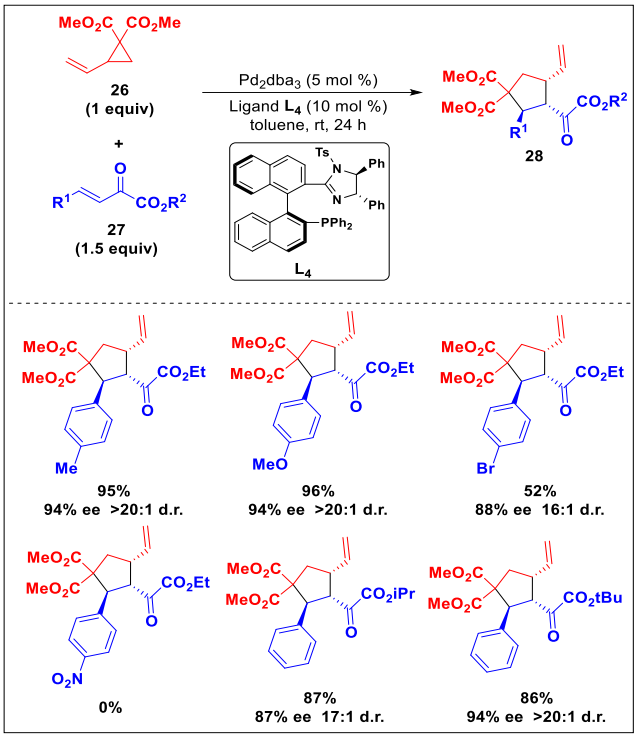
sulted in highly functionalized chiral amino acid derivatives, a technique that simultaneously sets three stereogenic centres in excellent enantio- and diastereoselectivities. This is the first-time racemic vinyl cyclopropanes have been employed in a formal [3+2] cycloaddition to generate carbocycles in an asymmetric fashion, as well as the first time this family of chiral ligands has been used to induce asymmetry in conjugate addition processes.



Scheme 2.1 Formal [3+2]-cycloaddition of vinyl cyclopropanes and alkylidene azlactones.

Cyclopentanes containing multiple stereocenter have long been employed as important building blocks in medicinal and agrochemical materials.[18] In the presence of chiral imidazolinephosphine ligand (aS,S,S)-**L4**, an efficient diastereo- and enantioselective palladium-catalysed formal [3+2] cycloaddition reaction has been developed by Shi and co-workers.[19] The reaction between vinyl cyclopropanes **26** and β,γ-unsaturated α-keto esters **27**, yielded multiple stereocenters containing cyclopropane motif **28** (Scheme 2.2). The optimum ligand for this reaction is the axially chiral imidazolinephosphine ligand **L4**. This is a newly developed chiral ligand and is crucial for this reaction. Since, the chiral imidazoline-phosphine-palladium (II) complexes are excellent catalysts for asymmetric allylic alkylation reactions, these new ligands developed are widely used in these types of reactions.

The reaction performed in toluene provided high diastereoselectivity and good enantiomeric excess, according to the solvent effects analysis. The axial chirality (ligands) was discovered to determine the absolute configuration of product. When an electron-rich aromatic ring is present as R^1, the reactions proceeded smoothly, giving good yields of cyclopentanes with excellent distereoselectivities and ee values. However, when an electron deficient substituent such as bromo group present in aromatic ring, the corresponding products were formed in modest yields and lower ee values, despite excellent diastereoselectivities. No desired product was observed when a very electron deficient group, such as



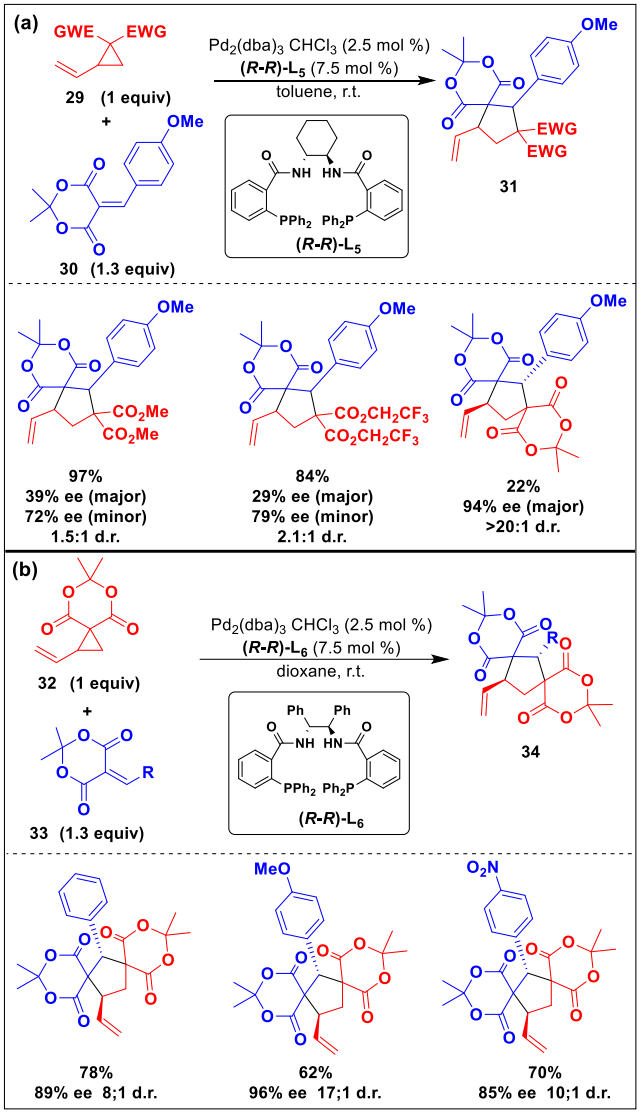
Scheme 2.2 Palladium-catalyzed asymmetric formal [3+2] cycloaddition of vinyl cyclopropanes and ß, γ -unsaturated a-keto esters.

para-NO_2 substituent was present in the substrate. Since the release of strain energy provides a thermodynamic driving force for producing dipoles, substituted cyclopropanes have been routinely used as dipole precursors. These cyclopropanes are considered as "donor-acceptor" because the dipole formed is generally stabilized by the substitution of cyclopropane with an electron donating group and an electron withdrawing group which are capable of stabilizing the cation and anion respectively. Moreover, the interaction of these dipoles with an olefin, results in a formal [3 + 2]- cycloaddition process, which in turn results in the formation of two new C-C bonds and up to four stereocenters.

In 2012, Trost and co-workers presented [3 + 2]-cycloaddition between substituted vinylcyclopropanes **29**, **32** and electron-deficient olefins in the form of Meldrum's acid alkylidenes **30** and **33** to generate highly substituted cyclopentane products, which is catalyzed by 2.5 mol % of palladium (Scheme 2.3).[20] Moreover, these formal cycloaddition reactions are diastereo- and enantioselective.

A range of vinylcyclopropanes substituted with electron-withdrawing groups was reacted with Meldrum's acid adduct. Dimethylmalonyl substrate and di(trifluoroethyl) ester analogue was found to undergo the cycloaddition process forming the product in high yield with a slightly improved diastereocontrol observed in later case. But, in both cases enantioselectivity was good for minor diastereomer and poor for major diastereomer. Finally, a Meldrum's acid derivative of vinyl cyclopropane **32** gave the product with excellent diastereo- and enantiocontrol but with a lower yield.

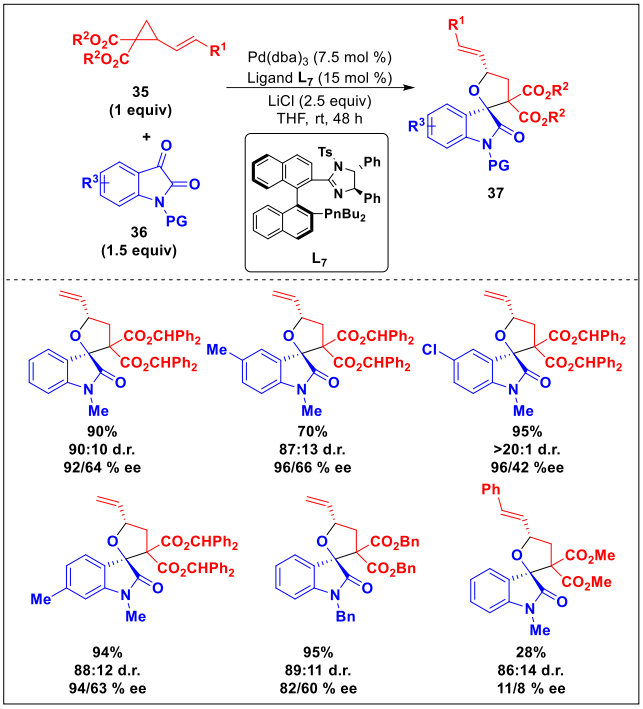
Inspired from the final result, cycloaddition of Meldrum's acid-substituted vinylcyclopropane with a variety of Meldrum's acid alkylidenes was performed and substituted cyclopentane products were obtained in good yield and outstanding stereoselectivity (Scheme 2.3b). Here, Meldrum's acid alkylidenes was employed as the suitable class of substrates due to high electron withdrawing nature of the substituents. Furthermore, the chiral di-phosphine ligands used in the reaction helped in creating sufficient chiral space for the highly enantioselective addition.



Scheme 2.3 Palladium-catalyzed diastereo- and enantioselective formal [3 + 2]-cycloadditions of substituted vinylcyclopropanes.

Synthesis of spirooxindoles is one of the most popular and appealing subjects among the scientific community, lately. Several effective techniques are developed for their synthesis as they are omnipresent structural moiety in many clinical pharmaceuticals and natural products.[21] Among the several forms of spirooxindoles, the oxindole-fused spirotetrahydrofuran is a truly interesting scaffold, since it exhibits a wide-range of bioactivities, including antibacterial, anticancer, and growth inhibitory properties.[22]

In 2013, Shi and co-workers further extended the palladium catalysed C-C bond activation of vinyl cyclopropane for the synthesis of spirotetrahydrofuran oxindole motif. Under mild reaction conditions, palladium (0)-catalysed efficient asymmetric formal [3+2] cycloaddition between vinylcyclopropanes **35** and isatins **36** was developed, which gave rise to functionalized spirotetrahydrofuran oxindoles **37** in high yields with very good enantio- and diastereoselectivities (Scheme 2.4).[23]



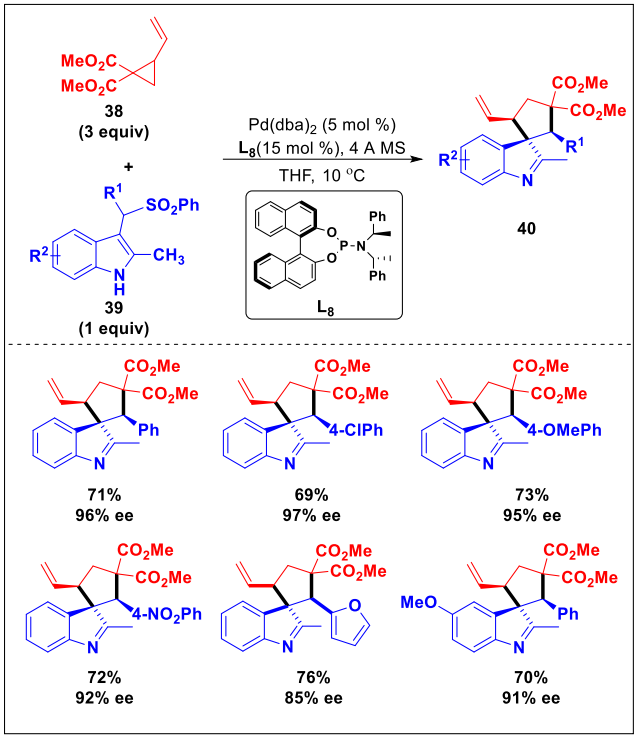
Scheme 2.4 Diastereo- and enantioselective construction of oxindole-fused spiro tetrahydrofuran scaffolds.

The diversification of the reaction scope has been shown, where a wide range of electronically and sterically biased substrate were found compatible delivering the desired product with good yields with high enantio- and diastereomeric ratio.

The spiroindolenine and spiroindoline units are found in a wide range of biologically active compounds and natural products, including pharmaceuticals.[24] In 2014, Liu and coworkers developed a strategy that disclosed palladium catalysed [3 + 2] cycloaddition between vinyl cyclopropane **38** and α,β-unsaturated imines **39** (generated in situ from aryl sulfonyl indoles) (Scheme 2.5).[25] The reaction resulted in high distereoselectivity, delivering the spiroindolenine **40** with three contiguous stero-centers that are optically enriched. The product formed has an all-carbon quaternary centre and two tertiary stereocenters. The complex (zwitterionic π-allylpalladium) formed from vinylcyclopropane derivatives acted as a base for the deprotonation of arene sulfonyl indoles, resulting in conjugate imines.

In every example, the reaction showed excellent diastereoselectivity, with just a single stereoisomer being isolated. Moreover, protic solvent like water and ethanol almost had no influence on the reaction. The temperature had a little influence on the reaction; lower temperature resulted in better selectivity but a significantly slower reaction. The enantioselectivity decreased when the temperature was

raised. Sulfonyl indole's steric hindrance had a significant role on enantioselectivities and yield. Regardless of the electronics of the substituents, substrates having substituents on the meta- or para- position of the phenyl ring attached to the carbon connected to the sulfonyl group are tolerated, however ortho-substituted substrates produced poor yields.

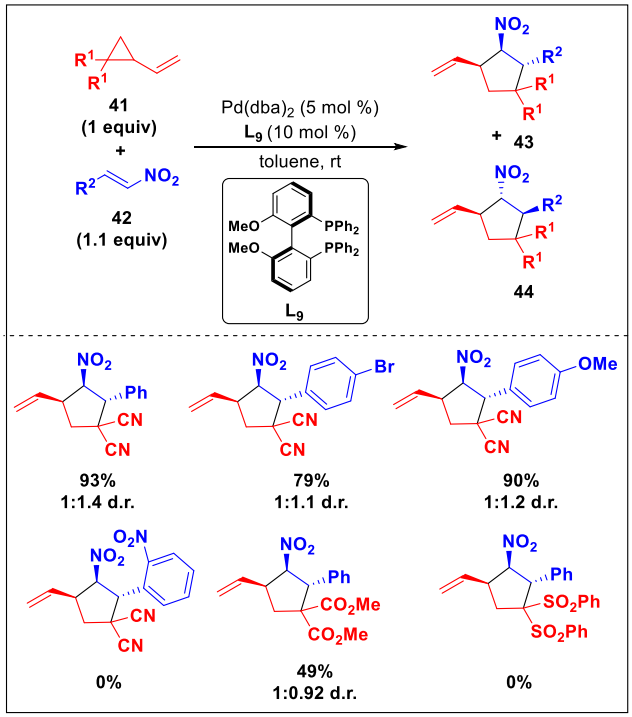


Scheme 2.5 Palladium-catalysed asymmetric cycloadditions of vinylcyclopropanes and in situ formed unsaturated imines.

Nitroolefins are flexible dipolarophiles that produce useful nitrogen-containing products in (3+2)-cycloadditions, which may be smoothly transformed into synthetically and medicinally important chemicals *via* reduction, Nef reaction and other transformations.[26]

The formation of nitro-cyclopentanes which are optically active and a precursor of cyclopentyl amines, would be possible through the cycloaddition (enantioselective) between vinyl cyclopropane derivatives and nitroolefins. In 2015, Liu and co-workers demonstrated the C-C bond activation of vinylcyclopropane di-carbonitriles **41** and nitro-olefins **42**, resulting in optically enriched nitro-cyclopentane derivatives **43** and **44** having three consecutives chiral stereocenters in up to 92% ee and 96% yield (Scheme 2.6).[27]

The diastereomeric ratio is just modest (1:1.4), however the two diastereomeric isomers are easily separated using simple chromatography technique, making the current technique appealing in the field of chemical synthesis. Both diastereoisomers can be prepared in optically enriched form using this approach. The diastereoselectivity in chlorinated solvents was poor. However, diastereomeric ratio was better in aprotic polar solvents like acetonitrile and DMSO. It may be because of the interaction of nitro functionality of nitroolefin with the polar solvent.



Scheme 2.6 Enantioselective cycloadditions of vinyl cyclopropanes and nitroolefins.

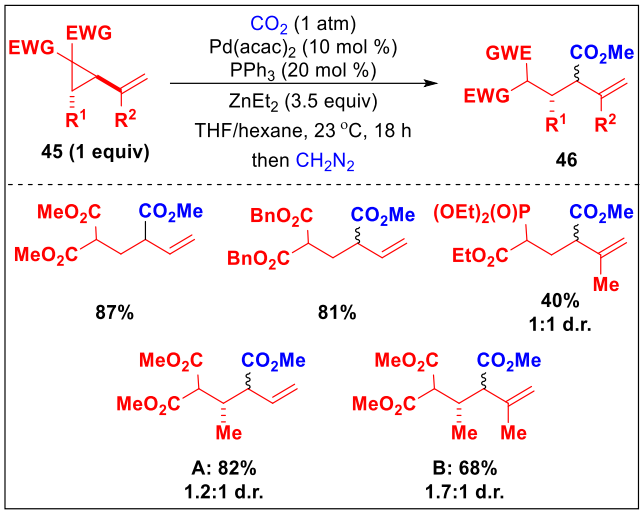
The electronic character of substituents connected to the nitroolefin's aromatic ring had a big impact on yield and enantioselectivity. Aromatic ring with electron donating and halo-substrate delivered the desired nitro cyclopentane in good to excellent yield. Whereas, substrate with a high electron-withdrawing nature, failed to give any product. Instead of di-carbonitrile substituent, another electron withdrawing substituent like ester also delivered the product albeit lower yield. However, sulphonyl substituent on the cyclopropane ring resulted in no reaction.

Further in 2016, Sato and co-workers has taken advantage of activated vinyl cyclopropane containing two electron withdrawing group at the gem carbon. Here, the carboxylation of activated vinylcyclopropanes **45** by cleaving the C-C bond and then forming new the C-C bond with the help of palladium catalysis has been established. Under a CO_2 environment (1 atm), activated vinylcyclopropanes are effectively transformed into β, γ-unsaturated carboxylic acids **46** using 10 mol % of palladium catalyst, and 3.5 equivalent of $ZnEt_2$ (Scheme 2.7).[28]

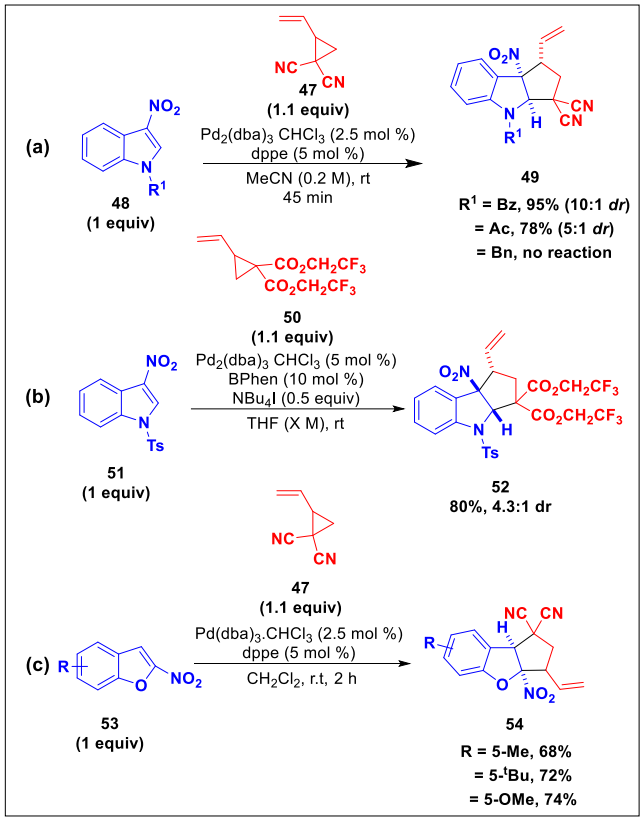
The η^1- allylethylpalladium species (nucleophilic), which would be formed from $ZnEt_2$ and π-allylpalladium, is thought to be the intermediate in this reaction.

Since, CO_2 is a cheap, plentiful, and generally harmless C1 source, CO_2 is catalytically incorporated into simple organic molecules, which is a hot topic in current organic chemistry research. To produce β,γ-unsaturated carboxylic acids, C-C bond cleavage and formation with CO_2 would occur concurrently.

The structure of phosphine ligands has a significant impact on carboxylation, according to catalyst modification experiments.



Scheme 2.7 Palladium-catalysed carboxylation of activated vinylcyclopropanes with CO_2.



Scheme 2.8 Palladium(0)-catalysed dearomatization cyclization through formal (3+2) cycloadditions with electron deficient vinylcyclopropanes.

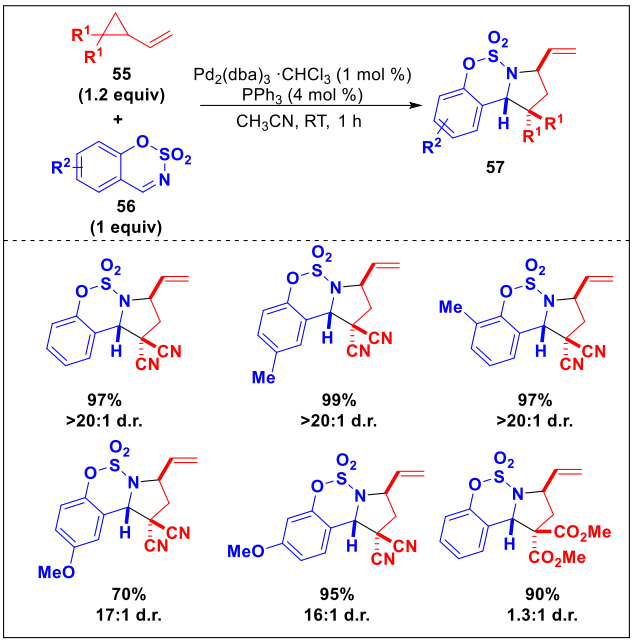
Vinylcyclopropanes containing diethyl, dimethyl, dibenzyl, and di-tert-butyl malonate when subjected to the standard reaction condition, delivered the carboxylation product with ease, giving high yields of corresponding β,γ-unsaturated carboxylic acids. A C2-methyl substituted vinyl cyclopropane also produce **A** and **B** in excellent yields with diastereomeric ratio ranging from 1.2:1 to 1.7:1.

Dearomatization reactions are effective methods used to generate high molecular diversity and complexity from simple materials like heteroarenes and arenes. In this context, Vitale and Hyland individually demonstrated the dearomative cyclization of heteroarenes with electron deficient vinyl cyclopropanes. Vitale and co-workers focused on the (3+2) dearomative cyclization of 3-nitro indoles **48** with electron deficient vinyl cyclopropanes **47** that resulted in functionalized indolines **49** with good yields and diastereoselectivities (Scheme 2.8a).[29] In this protocol nitrogen substituted with electron withdrawing substituent is working better, however alkyl substituent resulted in no reaction. In this methodology the cis-relationship between nitro group and the allyl group has been established. In contrast to this observation, when Hyland and co-worker change the electron withdrawing substituent on vinyl cyclopropane from cyano to ester, trans relationship between nitro and allyl functionality was observed in the product **52** (Scheme 2.8b).[30] The reversible addition of the VCP-derived zwitterionic dipole to the 3-nitroindole is expected to have a role in determining the reaction's ultimate diastereoselectivity. It was postulated that π-σ-π interconversion between the two diastereomeric zwitterionic-allylpalladium complexes formed from the addition of vinylcyclopropane **50** to the 3-nitroindole **51** could be a key control element in controlling the reaction's diastereomeric ratio. Furthermore, the reaction conditions were applied to an N-tosyl indole with a trifluoroketone at C3 instead of a nitro group, but no conversion was detected, suggesting that the presence of a nitro group at C3 is required for reactivity.

In 2018, Vitale and co-workers extended this concept of dearomative cyclization, and coupled a wide range of 2-nitro furan **53** with vinyl cyclopropane di-carbonitrile **47** that successfully delivered the cyclopenta[b]benzofuran **54** in the presence of 2.5 mol % of palldium catalyst, 5 mol% of dppe in DCM solvent (Scheme 2.8c).[31] A wide range of cyclopenta[b]benzofuran derivatives with average to exceptional yields can be prepared by using this novel and atom-economical methodology.

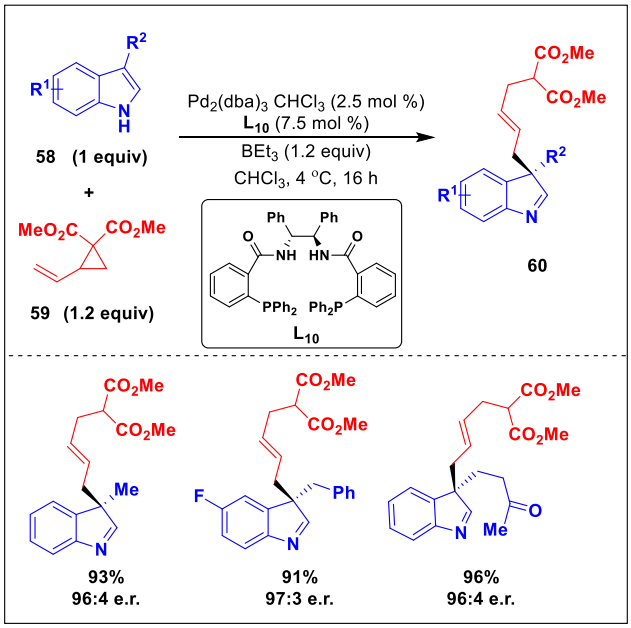
Sulfamate-functionalized heterocycles with varying ring systems and ring sizes have been extensively used in the designing of various drugs and pharmacological compounds due to their specific biological activities.[32] Furthermore, pyrrolidines are a kind of heterocycle found in many natural products, medicinal compounds, and synthetic intermediates.[33] As a result, discovering innovative techniques for the synthesis of heterocycles with both pyrrolidine and sulfamate parts is significant.

In 2018, Guo and co-workers devloped a palladium-catalysed [3 + 2] cycloaddition of vinyl cyclopropanes **55** with cyclic imines (sulfamate-derived) **56**, which provides a better accessibility to pyrrolidine derivatives fused with sulfamate moieties **57** (Scheme 2.9).[34] In high to exceptional yields, this process provided functionalized and biologically significant derivatives such as 2,3-dihydrobenzo[e]pyrrolo[1,2-c][1,2,3]oxathiazine 5,5-dioxide.



Scheme 2.9 Pd-Catalysed diastereoselective [3 + 2] cycloaddition of vinylcyclopropanes with sulfamate-derived cyclic imines

Moreover, the reaction was extremely efficient under mild conditions. The transformation is working efficiently in gram scale and can tolerate a wide range of substrates, which indicates that the process is a practical and can be used to make biologically active heterocycles.

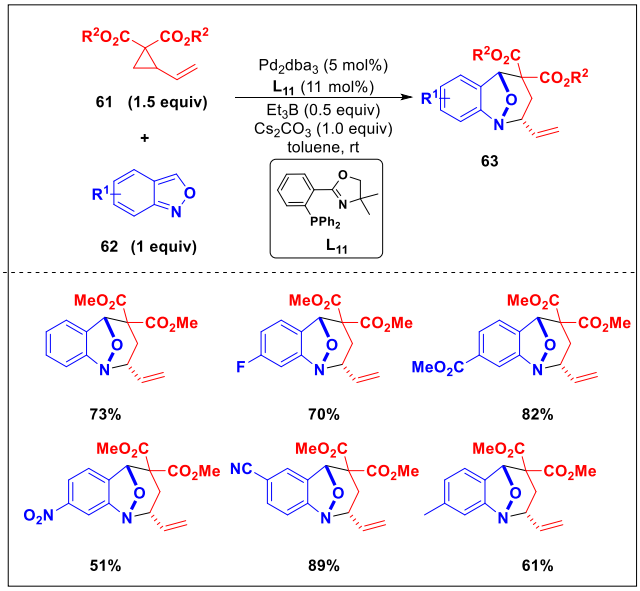


Scheme 3.0 Palladium-catalyzed asymmetric allylic alkylation of 3-substituted 1H-indoles.

Indole alkaloids, are widely prevalent in nature, and have a wide spectrum of anticancer, antibacterial, and antifungal properties.[35] Their indoline cores merge with other hetero- or carbocyclic backbones, resulting in incredible structural complexity and variety.

In 2018, Trost and co-workers developed a new asymmetric allylic alkylation method with strong chemo-, regio-, and enantioselectivity and full atom economy employing VCPs **59** as electrophiles to functionalize 3-substituted 1H-indoles **58** (Scheme 3.0).[36] They wondered whether the transition metal-catalyzed asymmetric allylic alkylation of 3-substituted indoles can be used to reverse the reactivity of other reaction partners (nucleophile) to electrophiles, allowing them to access indolenine/indoline compounds with functionalized C3-allylic motifs. This is the first time VCPs have been used in a Pd-catalyzed asymmetric allylic alkylation to atom economically functionalize 3-substituted 1H-indoles and tryptophan derivatives.

With the optimized condition, a variety of 3-substituted 1H-indoles were employed to explore the scope of this C3-allylation reaction and excellent yields were obtained in all cases. In another reaction they went on to substrates with a pendant nucleophile that might intercept produced imines under reaction conditions, resulting in a variety of tricyclic skeletons. Scope of this tandem C3-allylation/cyclization reaction was also tested by using variety of 3-substituted 1H-Indoles. Here also high yields were observed. Stilbene-derived Trost ligand $\mathbf{L_{10}}$, was found to be the optimal ligand for the transformation. Moreover, this reaction can be carried out on a gram scale.



Scheme 3.1 Pd-catalyzed dearomatization of anthranils with vinylcyclopropanes by [4+3] cyclization reaction.

Chemical feedstocks for the production of medicines and functional compounds include anthranil and its derivatives.[37] These aromatic compounds have a high coordinating proclivity and a weak N-O bond, which makes ring opening under transition-metal catalysis simple. The transformation of planar aromatic compounds into enantio-enriched chiral cyclic molecules can be accomplished by catalytic asymmetric dearomatization (CADA) processes. Under Pd catalysis, dearomatization reactions of anthranils with vinylcyclopropanes (VCPs) could lead to the synthesis of new bridging heterocycles.

In 2019, You and co-workers developed Pd-catalyzed dearomative [4+3] cyclization reactions of anthranils **62** with VCPs **61** (Scheme 3.1).[38] They discovered that triethylborane is an effective anthranil activator, and that dearomative [4+3] cyclization of anthranils with VCPs can be accomplished using Pd-catalysis. At room temperature, the reaction performed with good yield and excellent diastereoselectivity using a widely accessible Pd catalyst and catalytic quantity of borane as an activator. The reactions were carried out with high enantioselectivity after the addition of a chiral PHOX ligand **L11**. The newly developed approach made it simple to access a variety of bridged cyclic molecules, which were shown to undergo a variety of transformations. Borane is important for this transformation, most likely because it forms a borane–anthranil complex, which has been validated by NMR experiments. In ^{1}H NMR, the chemical shift of anthranil downshifted when Et_3B was added, demonstrating Et_3B coordination with anthranil.

The electron-withdrawing groups in the substrates, such as ester, trifluoromethyl, cyanide, and even nitro, reacted with VCP to provide the bridging cyclic products in high to excellent yields. Moreover, in this reaction, the electron-donating methyl group was also compatible, as product was produced in 61% yield.

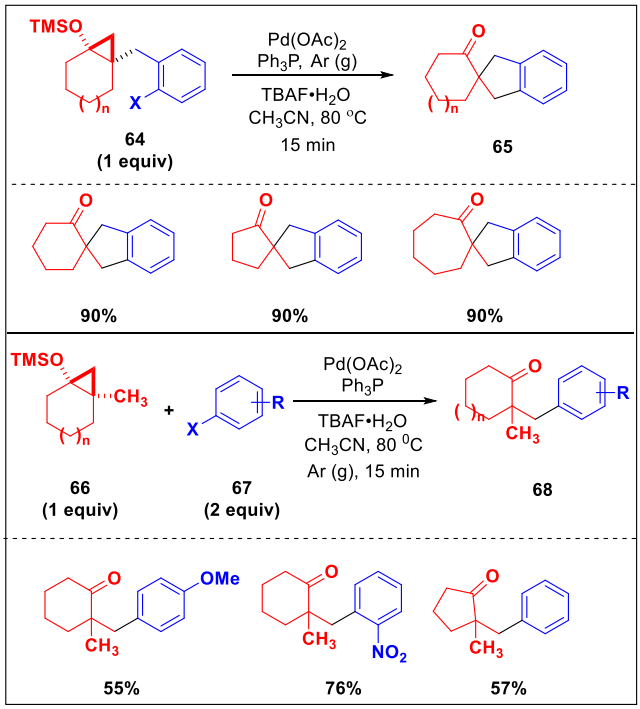
1.5 Cyclopropanol:

Cyclopropanols are the smallest cyclic alcohols, first studied by Cottle and co-workers in 1942 as a three-carbon synthetic precursor.[39] Recently, there is a surge of popularity in the use of cyclopropanols because of its facile synthetic procedure namely Kulinkovich's reaction and unique reactivity.[40] Out of several pathway through which ring opening of cyclopropanol is possible, C-C bond activation pathway catalysed by transition metal is recently gaining immense attention. In presence of a metal catalyst cyclopropanol ring opens mostly through β-carbon elimination pathway rather than oxidative addition of C-C bond to the metal.

The chemistry of cyclopropanol has been extensively explored by Orellana group as three carbon synthons for the synthesis of different molecular architecture. In 2011, Arturo and co-workers successfully unravelled the intra and Inter-molecular cross coupling of cyclopropanol-derived palladium homo-enolates with aryl halides **67** to synthesize spiro lactones **65** and ketones **68** in excellent yield under simple and mild catalytic condition (Scheme 3.2).[41]

There was no effect on the product yield when aryl bromide was used in place of aryl iodides. Aryl halide bearing electron withdrawing substituents resulted in higher yield than that of electron rich substituents. Excellent yield was obtained in the case of intramolecular reaction and moderate to good yield was observed for intermolecular reaction.

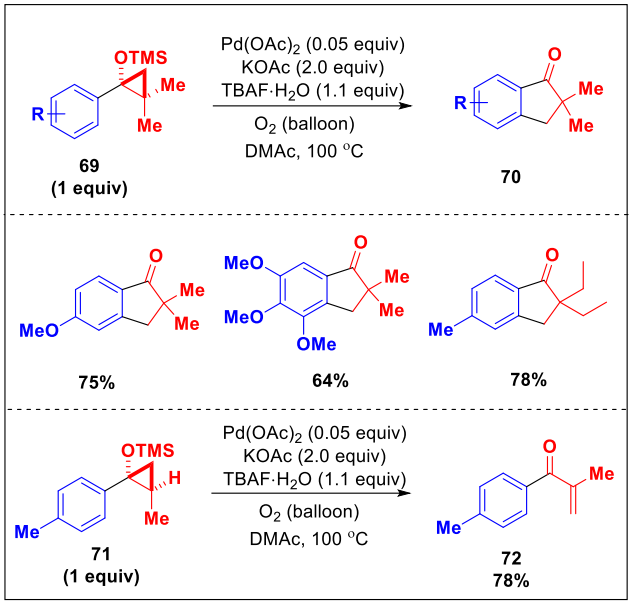
Further, in the 2012 Orellana and co-workers extended the palladium catalysed C-C bond activation strategy for the synthesis of 2,2- disubstituted alpha-indanones **70**.[42] The reaction proceeded through in-situ formation of cyclopropanol **69** and further rearrangement and direct arylation in the presence of 5 mol % of $Pd(OAc)_2$ as catalyst, and 2 equivalent KOAc as base (Scheme 3.3). 1-indanones are important moiety present in natural products and pharmaceutical agents with significant biological activity. Many methods are used for their synthesis including Nazarov-type cyclization, Friedel-crafts acylation and variety of palladium catalysed reactions. Here the reaction proceeds through palladium homoenolates, formed due to the ring strain of cyclopropanols. Comparatively milder conditions are enough for the ring opening of unprotected cyclopropanols, but the formation of homoenolates from silyloxy cyclopropanes and cyclopropane acetals are more difficult. A base is required for the reaction and its nature is also critical. Because the base used must be strong enough to deprotonate cyclopropanol and facilitate the arylation. Moreover, it should be mild to prevent base-catalysed rearrangement of cyclopropanol to ketone, which is an undesired rearrangement. KOAc was found to be the best base. Requirement of an acetate base suggested that the arylation step goes through a concerted metallation-deprotonation pathway. A higher product yield was obtained when the cyclopropanol was generated by in situ deprotonation of the TMS ether instead of using unprotected cyclopropanol.



Scheme 3.2 Palladium-catalysed cross-coupling of cyclopropanols with aryl halides.

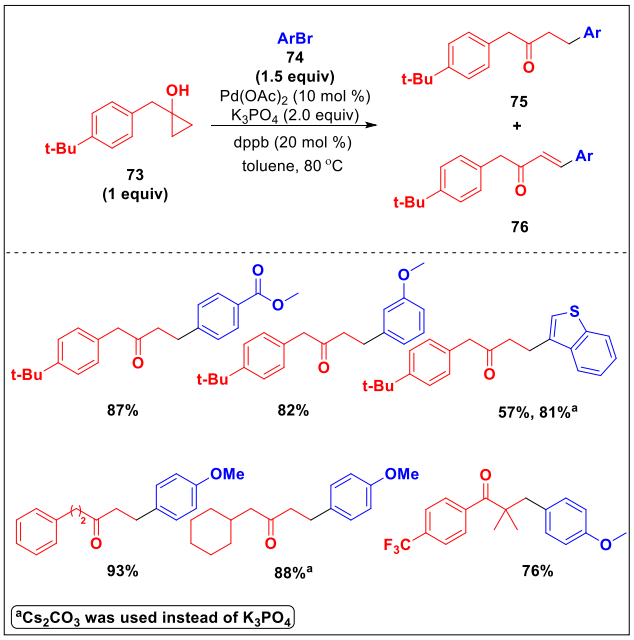
In contrary to the previous observation, Orellana and co-workers have shown that the cross-coupling reaction between cyclopropanol derived homo-enolates having *β*-hydrogen **73** with aryl and heteroaryl bromide **74** (Scheme 3.4).[43] Homo-enolates are important umpolung synthons which have a charge affinity pattern equivalent to that of enolate anions. Generation of homo-enolates catalytically from *α, β*-unsaturated aldehydes was enabled with the help of *N*-heterocyclic carbenes. However, these reactions were not manageable to form C-C bonds between aryl electrophiles and homo-enolates. In this case, palladium homoenolates formed, will not undergo *β*-hydride elimination to deliver *α, β*-unsaturated ketones. A wide range of functional groups were tolerated under the demonstrated protocol.

This reaction is limited to 2,2-disubstituted *α*-indanones as the presence of *β*-hydrogen in the homo-enolate leads to direct intramolecular arylation results in the formation of α, β-unsaturated ketone.



Scheme 3.3 Synthesis of α-indanones *via* intramolecular direct arylation.

The choice of base and catalyst system plays an important role on the product distribution, because the reaction condition should not facilitate the chance of cyclopropanol rings to undergo ring opening (base mediated) to form ketone and avoid palladium homoenolate's tendency to undergo *β*- hydride elimination to form α, β-unsaturated ketone **76**.

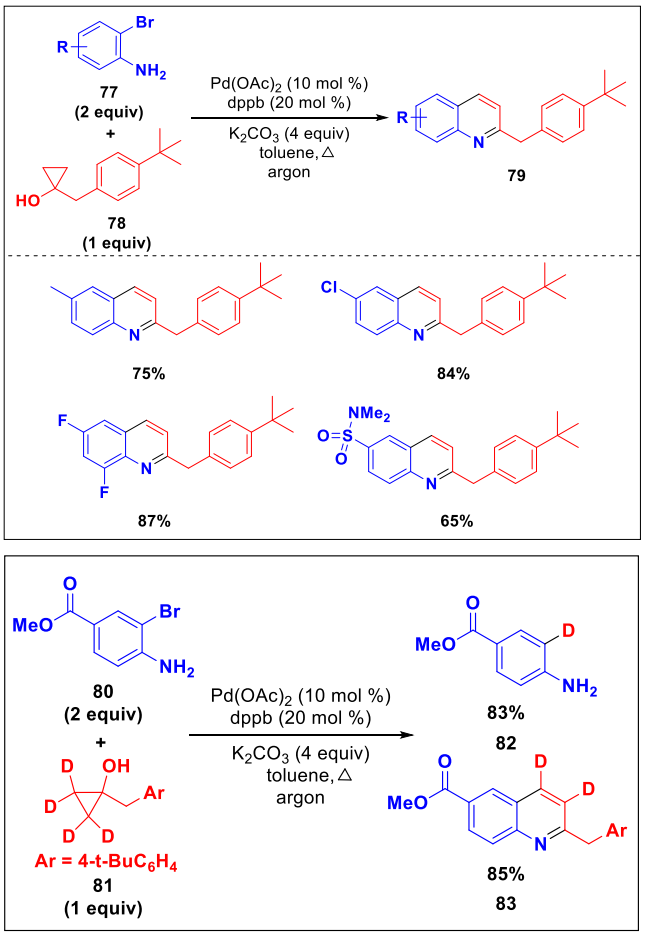


Scheme 3.4 Palladium-catalysed cross-coupling of cyclopropanol-derived ketone homo-enolates with aryl bromides.

It is worthy to mention that, product yield is influenced by the different ligands used and enhanced when Buchwald ligands (monodentate bi-aryl phosphine ligands) were used. Good yield of coupled products **75** and **76** was obtained when aryl halides having electron donating and electron withdrawing functional groups were used. An aryl halide substituted at both ortho positions, provided moderate product yield. When Cs_2CO_3 was used in place of K_3PO_4 the yield of the coupled product improved. Monocyclic cyclopropanols bearing alkyl, allyl, benzyl, aryl substituents at 1-position showed effective coupling and monocyclic 1,2 - distributed cyclopropanols showed selective coupling. In addition, monocyclic 1,2-distributed cyclopropanols gives the product by the breaking of the least substituted bond of cyclopropane.

Quinolines are heterocyclic aromatic organic compounds with important pharmaceutical properties.[44] In the process of exploring the cyclopropanol chemistry, Orellana and coworkers provided a direct one-pot synthetic sequence for the synthesis of quinoline derivatives **79**. The cross-coupling reaction between unprotected ortho-bromoanilines **77** and cyclopropanols **78** proceeded in a single operation via intermolecular condensation and oxidation using 10 mol% of $Pd(OAc)_2$, 20 mol % of dppb, 4 equiv of K_2CO_3 in toluene at 80 °C (Scheme 3.5). [45]

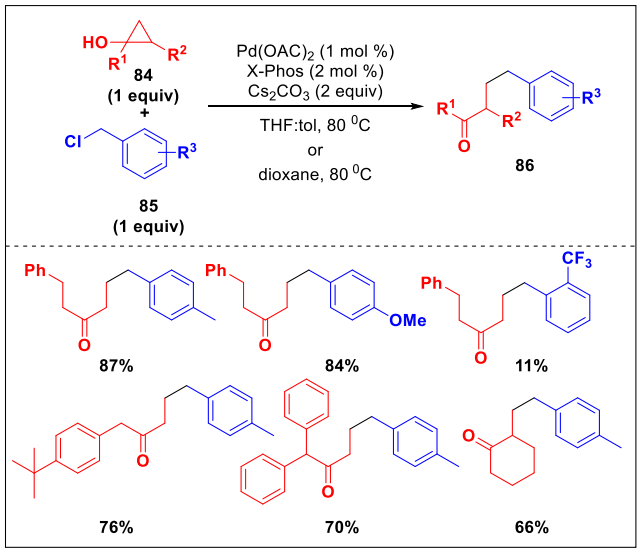
When *ortho*-bromoaniline **80** is cross coupled with a monosubstituted tertiary cyclopropanol **81**, the quinoline product **83** and aniline **82** was formed in a nearly 1:1 ratio.



Scheme 3.5 One-step synthesis of quinolines via palladium-catalysed cross-coupling of cyclopropanols.

This formation of aniline suggested that the *o*-bromoaniline act as an oxidant. Thus, increasing the equivalence of *o*-bromoaniline enhanced the product yield. *O*-iodo aniline also provided the expected quinoline in a moderate yield. Cyclopropanols which have only one substitution provided good yields of the quinoline, irrespective of the substituent on cyclopropanol. Quinolines having a substituent at the 3-position was obtained when easily accessible cyclopropanols having substitution at the 2-position was used. Tricyclic quinolines were obtained in moderate yield when bicyclic cyclopropanols was used. Reactions are conducted under conditions (argon atmosphere and phosphine ligand used with the palladium catalyst) where oxidation of dihydroquinoline is not expected.

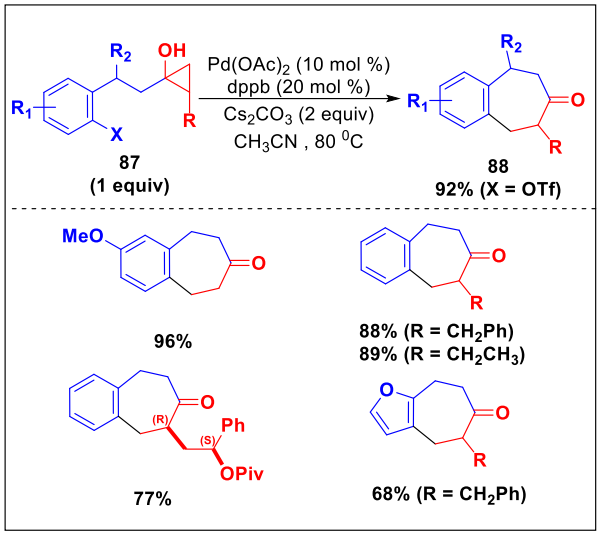
To provide evidence for the hypothesis, that the orthobromo aniline act as terminal oxidant, a deuterium labelling experiment was conducted. In this experiment, deuterated cyclopropanol is prepared from perdeuterated ethyl bromide following the Kulinkovich protocol and is then cross-coupled with bromoaniline. The reaction provided deuterated quinoline at the 3- and 4- position and ortho-deuterated aniline as products, which proved that *ortho*-bromo aniline act as terminal oxidant.



Scheme 3.6 Palladium-catalysed cross-coupling of benzyl chlorides with cyclopropanol-derived ketone homoenolates.

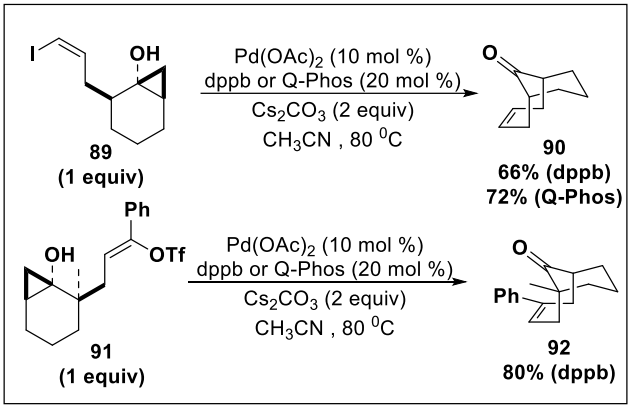
In 2014, Orellana and co-workers have demonstrated the palladium-catalysed cross-coupling reaction of cyclopropanols **84** with benzylic halides **85** (Scheme 3.6).[46] Reaction gives higher yield when electron neutral and electron rich benzyl chloride are used. Reaction can be conducted with low catalyst loadings (1 % palladium) and on a gram scale with no reduction in yield. Yield was reduced when electron poor benzyl halides were used and the reason for this is unclear to the author. A base is required to consume the acid generated during the ligand exchange step

Here, X-phos, a bulky, electron rich monodentate phosphine is used as the ligand that favoured reductive elimination rather than *β*- hydride elimination to yield the desired product. Cs_2CO_3 is chosen as the base because it does not promote base catalysed ring opening of cyclopropanol to the corresponding ketone even at elevated temperatures. Solubility of the base plays an important role in the success of the reaction and so switching the solvent to THF provided good yields of product.



Scheme 3.7 Construction of seven-membered carbocycles via ring opening of cyclopropanols.

An intramolecular cross-coupling between cyclopropanols and alkenyl or aryl halides or triflates **87** has been developed by Cha and co-workers to deliver a large variety of seven-membered carbocycles **88** (Scheme 3.7).[47] Both bridged and fused bicyclic compounds are easily accessible by this cyclization reaction. Till the discovery by Cha group, no example showed the use of synthetically more versatile pseudohalides or alkenyl halides instead of aryl derivatives, because alkenyl halides or pseudohalides can allow β-hydride elimination.

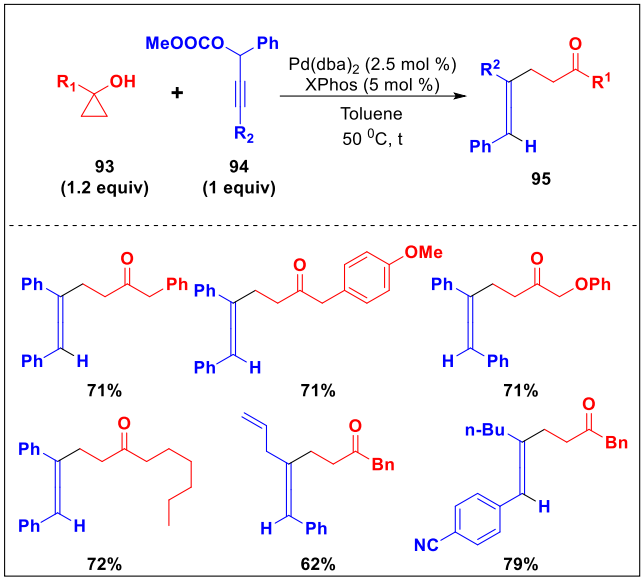


Scheme 3.8 Construction of bridged bicyclo[4.3.1] ketones.

The cyclization method is also applied to cyclopropanols for the construction of bridged bicyclo[4.3.1] ketones **90** and **92** (Scheme 3.8). Moreover, this method offered an effective and new alternative to the difficult enantioselective [4+3] cycloaddition of oxy-allyls. This intramolecular cross-coupling reaction offered new access to bridged and fused seven-membered ring compounds.

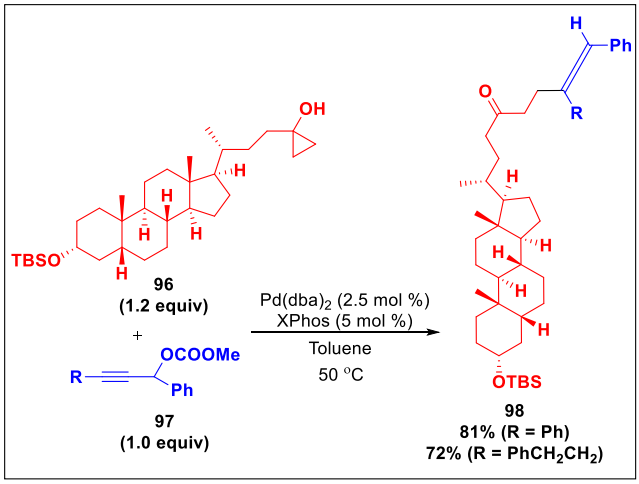
In 2017 Ma and co-workers developed a palladium-catalysed highly selective and efficient synthesis of allenyl ketones **95** via the ring opening- coupling reaction of cyclopropanols **93** with propargylic carbonates **94** (scheme

3.9).[48] This reaction allows the efficient introduction of the allene unit into useful organic skeletons including steroidal skeletons. Since some allene bearing steroidal skeleton shows pharmacological activities, this result will be useful.



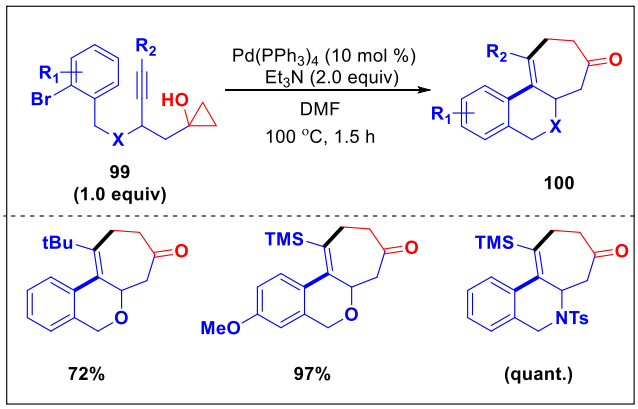
Scheme 3.9 Matched coupling of propargylic carbonates with cyclopropanols.

Moreover, the reaction goes smoothly in mild conditions with Pd(0)/XPhos catalysis in the absence of external base. Using XPhos as ligand provided product in high yield and formation of by-products can also be decreased to a very low level. Aiming to introduce the allene unit into the steroidal skeleton, steroid unit bearing cyclopropanol **96** is subjected to the standard conditions and the reaction with propargylic carbonates **97** worked smoothly to provide the corresponding allene products **98** in high yields (Scheme 4.0). This reaction has a greater potential because the allene product formed can be subjected to various transformations, such as 1,2-addition of the ketone group with EtMgBr, reduction of the ketone group with $NaBH_4$ to form the secondary alcohol or alkynyl lithium reagent to generate the tertiary alcohol and reductive amination, which yields allenyl amine.



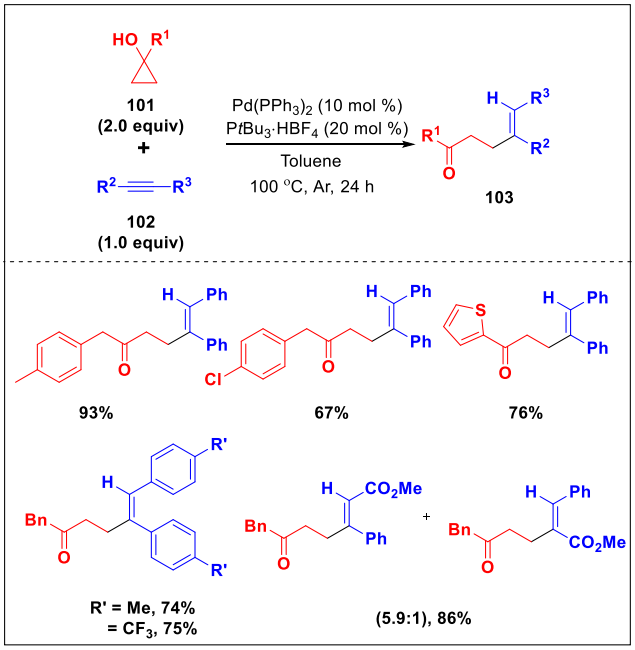
Scheme 4.0 Reaction of steroid bearing cyclopropanol with alkyne.

Cyclopropane units and carbon-carbon triple bonds and are two simplest organic moieties with high energy. Heat is produced during the conversion of a triple bond into a double bond by a formal addition reaction. Moreover, the ring opening of cyclopropane is also exothermic because the Baeyer and Pitzer strains are released during the process. So, these two moieties are widely used in many transformations (synthetic). In 2018, Werz and co-workers unravelled the formation of tetra substituted double bonds embedded in oligo cyclic systems **100** through a cascade reaction (intramolecular) consisting of a formal anti-carbopalladation, which is terminated by a cyclopropanol **99** ring opening. (Scheme 4.1).[49]



Scheme 4.1 Intramolecular trans-carbocarbonation of internal alkynes.

Moreover, a variety of silyl-masked alkynes, decorated arene rings, and chain lengths were converted to seven-membered ketone derivatives by this demonstrated protocol. The generated olefin unit has carbonyl functionality in γ-position.

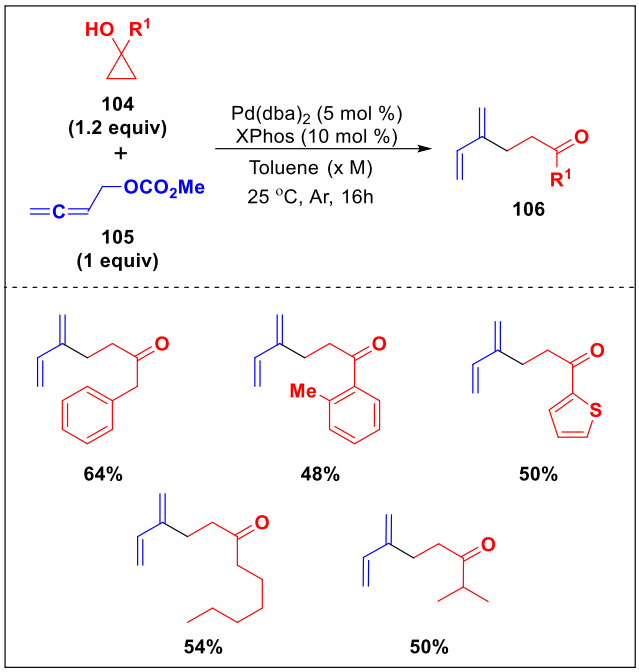


Scheme 4.2 Palladium-catalyzed hydroalkylation of alkynes with cyclopropanols.

Polar aprotic solvents are required for the formal anti-carbopalladation reaction. Silyl groups are used to mask terminal alkynes, because they can be easily cleaved by acid or TBAF and can be converted into other functionalities.

In the same year, Yao and co-workers demonstrated the palldium catalysed hydroalkylation of alkynes via C-C bond activation of cyclopropanol (Scheme 4.2).[50] As discussed above, ring opening coupling of cyclopropanol with aryl/alkyl halides, and acyl halides have been well studied by various pioneering group. However, hydroalkylation of alkyne **102** by ring opening of cyclopropanol **101** was first realized by Yao group that deliver γ,δ-unsaturated ketones **103**. The product configuration has been assigned as *Z*-isomer that was confirmed from Nuclear Overhauser Effect (NOE) experiment.

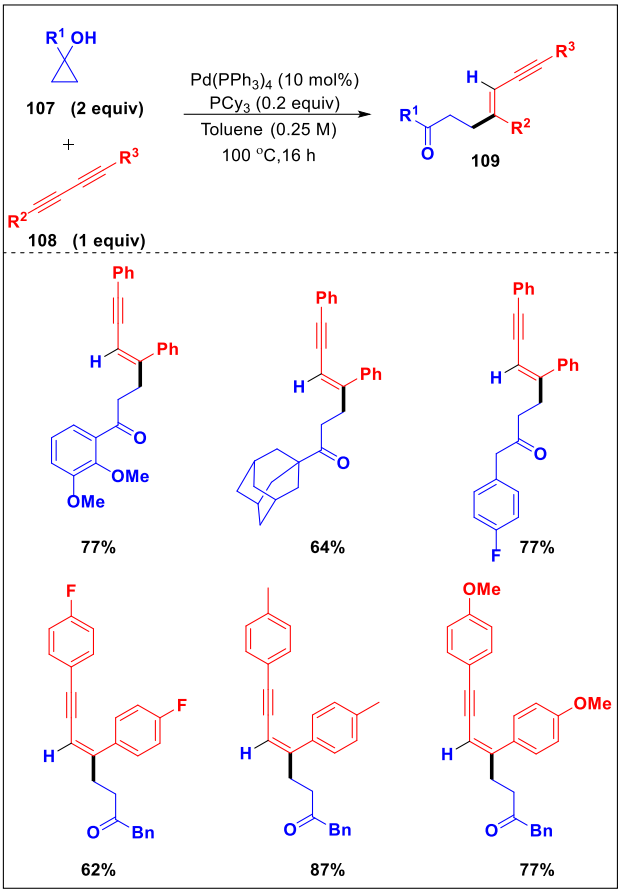
The use of cyclopropanol as metal homo-enolate surrogate has been heavily exploited by various pioneering group that made cyclopropanol as a successful 3C synthon. In 2019, Ma and co-workers developed the coupling reaction of cyclopropanols **104** with 2,3-allenylic carbonates **105**, which provides synthetically useful 1,3-diene products **106** efficiently (Scheme 4.3).[51] Moreover, the reaction worked at room temperature under very mild reaction conditions tolerating various different functional groups.



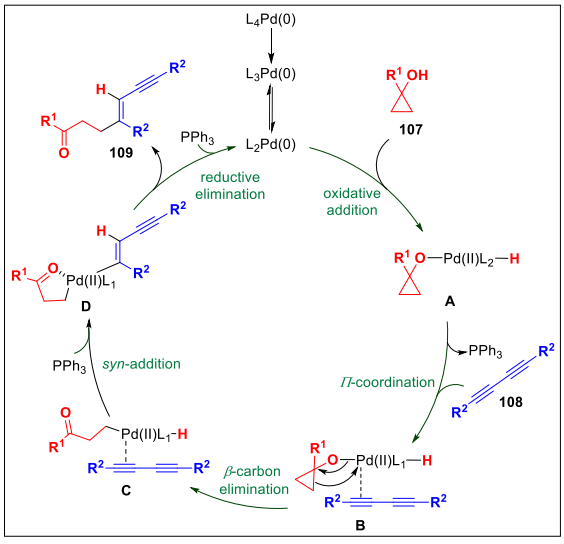
Scheme 4.3 A Pd-catalysed ring opening coupling reaction of 2,3-allenylic carbonates with cyclopropanols

The final diene product can undergo different transformations such as the Suzuki coupling reaction and Diels-Alder reaction, which shows the utility of this reaction. Moreover, steroid containing 2,3-disubstituted diene can be synthesized by this reaction, which prove its wide scope. X-Phos was found to be the optimal ligand and $Pd(dba)_2$, optimal catalyst for the reaction. The control experiments showed that NaOMe and Pd(ll) facilitates the protonolysis resulting in the ring opening of cyclopropanol.

With the growing interest in the field of cyclopropanol as 3C synthon, its utility has been further expanded recently by Ravikumar and co-workers. 1,3-enynes are very important skeleton because of its usefulness in material and pharmaceutical chemistry.[52] With the target of providing one-step synthetic protocol for the synthesis of 1,3-enynes **109**, Ravikumar and co-workers has demonstrated the palladium catalysed stereoselective alkenylation between cyclopropanol **107**, and 1,3-diynes **108** (Scheme 4.4).[53] Thus, 10 mol % of $Pd(PPh_3)_4$, 20 mol % of PCy_3, in toluene solvent at 100 °C was found to be the optimal condition for the desired transformation.



Scheme 4.4 Palladium-catalyzed selective C–C bond cleavage and stereoselective alkenylation between cyclopropanol and 1,3-diyne.



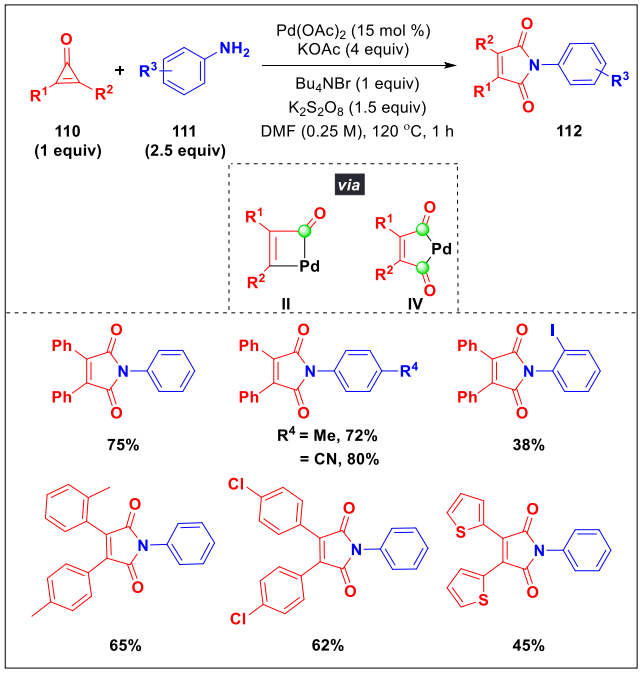
Scheme 4.5 Plausible catalytic cycle.

Various cyclopropanol and 1,3-dialkyne derivatives were found to be compatible under the optimized reaction condition and delivered a wide range of 1,3-enyne product successfully. After performing various mechanistic studies, they have proposed a plausible catalytic cycle (Scheme 4.5). Palladium (0) undergoes oxidative addition between the O-H bond of cyclopropanol leads to the formation of intermediate **A**. Further, release of PPh_3 and π-coordination with 1,3-diyne gave intermediate **B**. Next, β-carbon elimination afford intermediate **C**, that on consecutive syn-addition with hydrogen atom transfer to furnish the homo-enolate intermediate **D**. Finally the regeneration of Pd(0) catalyst through reductive elimination tend to deliver the desired product. The proposed catalytic cycle has been further supported by theoretical calculation (DFT calculation).

1.6 Cyclopropenone:

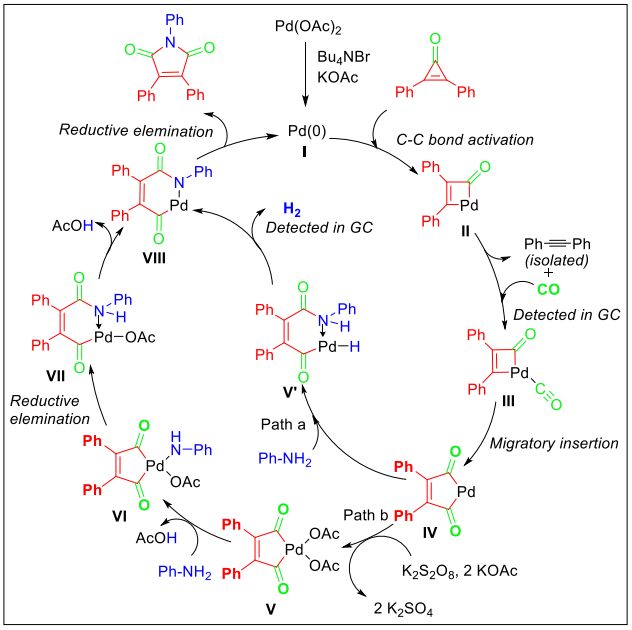
Cyclopropenone as the smallest aromatic system has been used as 3C synthon in various valuable transformations. The inherent ring strain was the driving force, that helps cyclopropenone ring to open up under various base and transition metal catalysed condition. Cyclopropenone was first synthesized by Breslow and Volpin in 1959, and after that its chemistry has grown into several branches.[54]

Cyclopropenone as 3C synthon has been well explored in cycloaddition, base catalysed ring opening, and in C-H functionalisation reactions.[55] However, transition-metal catalysed C-C bond activation of smallest aromatic ring has not been studied until Ravikumar and co-workers in 2020, disclosed palladium catalysed amination and concomitant carbon monoxide recapture to get highly functionalized maleimide derivatives **112** (Scheme 4.6).[56] For the first time cyclopropenone was recognized as a carbon monoxide source. The four membered pallada-cyclobutenone **II** was found to be the key intermediate that release and recapture carbon monoxide to produce palladacyclopentendione **IV**.



Scheme 4.6 Palladium-catalysed cascade C-C bond activation of cyclopropenone and carbonylative amination.

A diverse range of electron donating and withdrawing anilines has been found compatible delivering good to very good yield. Similarly, cyclopropenone scope also has been shown to diversify the synthetic methodology. From detailed mechanistic study and control experiment they have concluded the formation of 4-membered palladacyclobutenone **II** that leads to diphenyl acetylene and carbon monoxide (detected through gas chromatography) in a side reaction pathway.

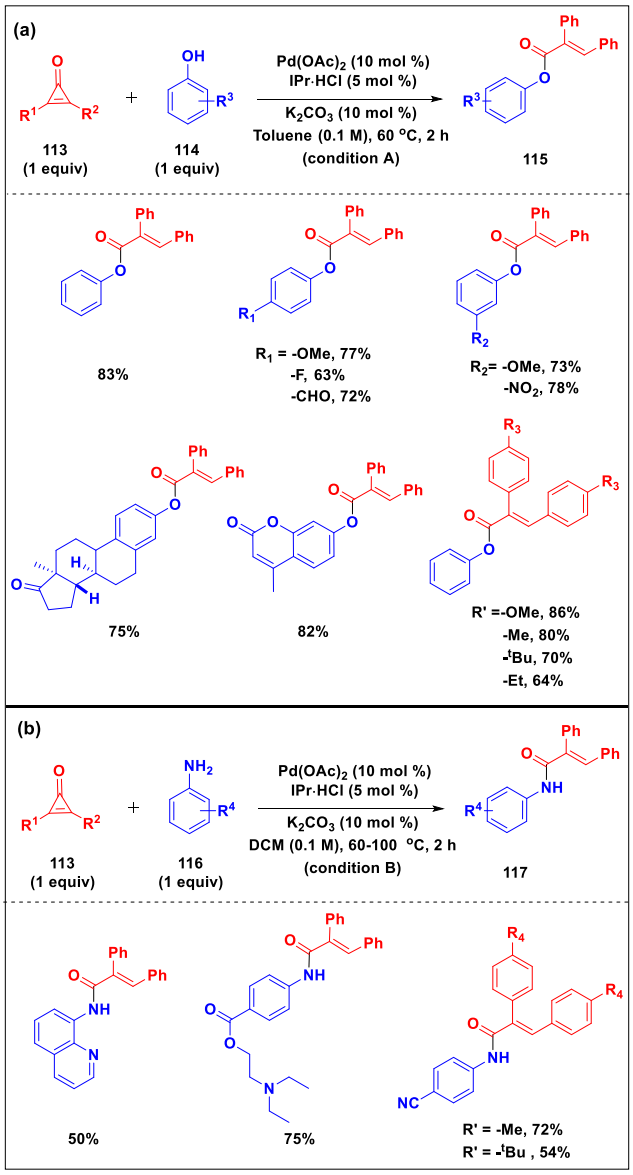


Scheme 4.7 Plausible mechanism.

They have proposed a plausible catalytic cycle (Scheme 4.7). Pd(0) was formed *in situ* in the presence of tetrabutyl ammonium bromide and potassium acetate. C-C bond of cyclopropenone oxidatively insert in to Pd(0) forming four-membered palladacycle **II**, that tends to release carbon monoxide and diphenylacetylene. The concomitant recapture and migratory insertion lead to the formation of five-membered palladacycle **IV**. Then, in path a, aniline undergoes addition to the C-Pd bond and gave intermediate **V'**. Release of the hydrogen gas followed by reductive elimination gave the desired product. In path b, Pd(II) underwent oxidation to Pd(IV) in presence of $K_2S_2O_8$ and gave intermediate **V**, which upon ligand exchange and reductive elimination gave intermiediate **VII**. Then, removal of acetic acid followed by reductive elimination deliver the desired product and regenerate the active catalyst.

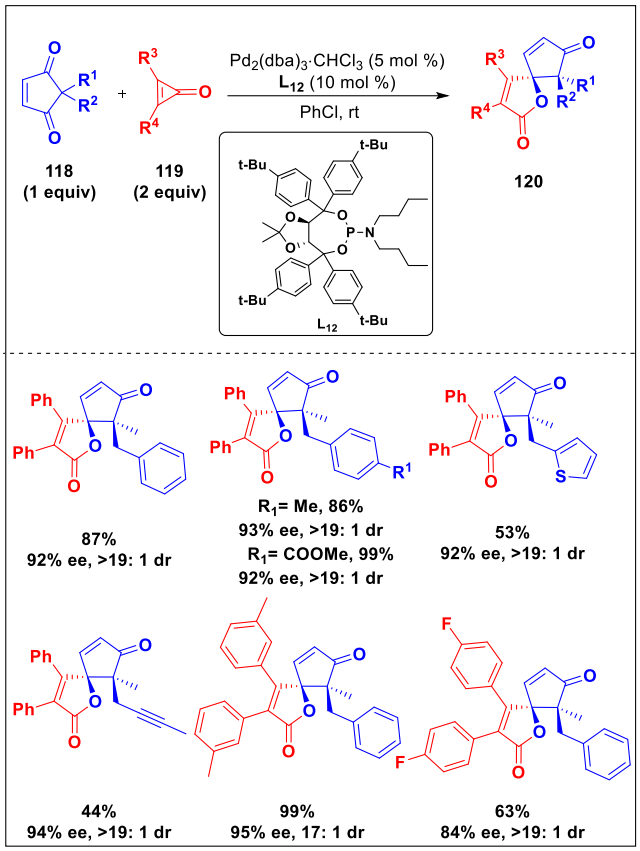
After the above mentioned successful approach, Ravikumar and co-worker extended the C-C bond activation strategy of cyclopropenone to synthesize a wide array of *α,β*-unsaturated esters and amides. α,β-Unsaturated carbonyl compounds presumes biological significance.[57] In this context, an operationally simple and non-tedious method has been developed by Ravikumar and co-workers, wherein aryl/alkyl cyclopropenone **113** was coupled with phenol/aniline **114/116** in the presence of 10 mol % of $Pd(OAc)_2$, 5 mol % of IPr·HCl, 10 mol % of K_2CO_3 in 0.1 M toluene/DCM (Scheme 4.8).[58] The reaction has commenced in very short time at 60 °C. *N*-heterocyclic ligands found to plays a very

critical role as it helps in generating Pd(0) *in situ* in the presence of base. By using this methodology, natural products and drug molecules has been converted to its respective *α,β*-unsaturated products.



Scheme 4.8 C-C bond activation of cyclopropenone to synthesize a wide array of *α,β*-unsaturated esters and amides.

Though, initial approach in the field of palladium catalysed C-C bond activation of cyclopropenone has been made by Ravikumar group; enantioselective transformation based on this topic is still underexplored. In 2021, Xu and co-workers devised a methodology based on the synthesis of oxaspiro **120** product (Scheme 4.9).[59] This protocol consists of C(sp_2)-C(sp_2) bond activation of cyclopropenone **119** through palladium catalysed (3+2) annulation with cyclic 1,3-diketone **118** merged with click desymmetrization to form synthetically valuable product. TADDOL derived bulky P-ligand **L12** was found to control the product enantioselectivity and diastereoselectivity. The condition developed was found viable with a broad range of substrate having sensitive functional group. Both electron donating and withdrawing substrates worked well and delivered the product

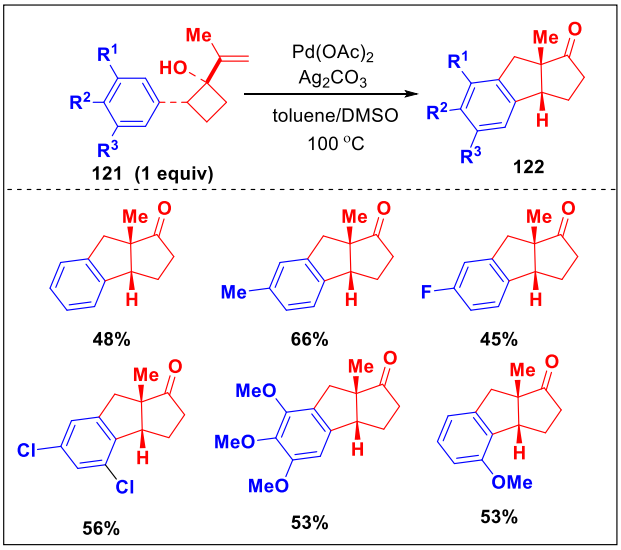


Scheme 4.9 C-C bond activation of cyclopropenone to synthesize a wide array of *α,β*-unsaturated esters and amides.

in high enantiomeric and diastereomeric excess. Substituted cyclopropenone also furnished the product in good yield with high ee value.

1.7 Cyclobutanol:

In 2010, an efficient palladium catalyzed semipinacol rearrangement and direct arylation was described for the synthesis of benzodiquinanes **122** by Orellena and co-workers.

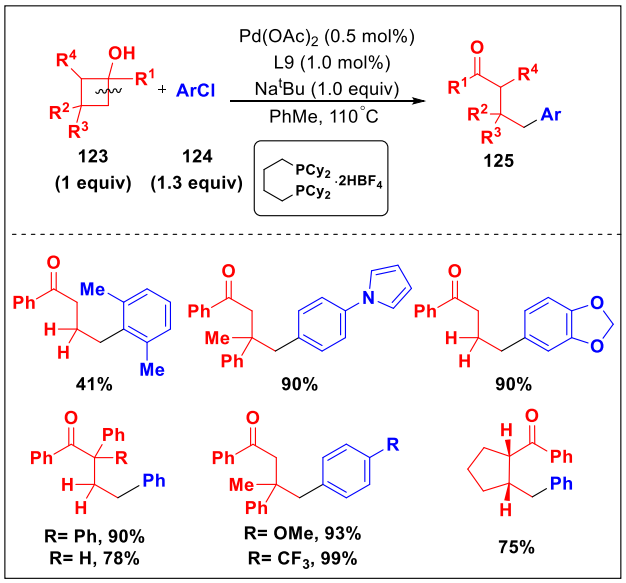


Scheme 5.0 Synthesis of benzodiquinanes.

They provided a cascade reaction, including the coordination of the cyclobutanol **121** with the electrophillic palladium intermediate, generation of the palladium homoenolate and intramolecular arylation (Scheme 5.0).[60]

A multitude of substrates bearing methyl, halogen, and alkoxy group gave moderate to good yield. They suggested that the moderate yield observed was due to the possibility of another pathway for the undesired product.

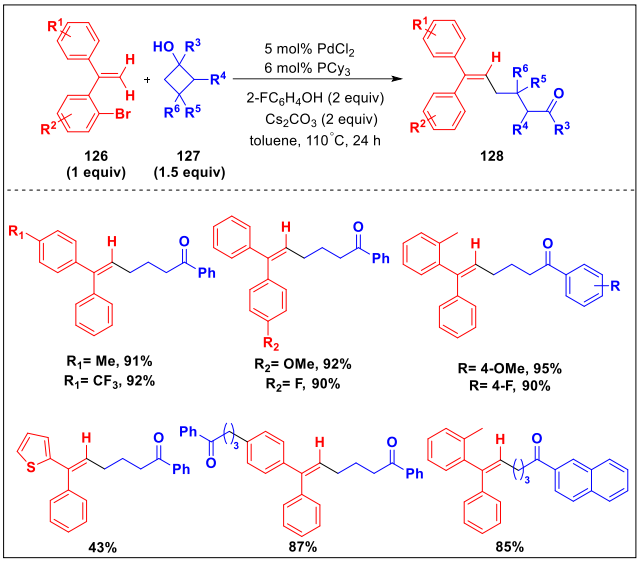
Zaidi and Martin in 2012, described an efficient method for the synthesis of γ- arylated ketones **125**. The reaction proceeded by Pd-catalyzed C-C bond cleavage of four-membered cyclobutanol **123** and coupling with aryl halide **124** to deliver the γ- arylated ketones **125** system (Scheme 5.1).[61] In this protocol they have used bulky and electron rich ligand which was important for stabilizing the monoligated L1Pd(0) species which aided to have a faster oxidative addition process. The demonstrated protocol endowed to have a broad substrate scope and a very good functional group compatibility.



Scheme 5.1 Pd-catalyzed ketone γ-arylation via c-c cleavage with aryl chlorides.

In the year 2019, Yu and co-workers disclosed the C-H alkylation of gem disubstituted ethylenes **126** through aryl to vinyl 1,4-palladium migration. The alkenylation via ring opening coupling of cyclobutanols **127** provided highly regioselective tri-substituted alkenes **128** (Scheme 5.2).[62] 5 Mol% of $PdCl_2$, 6 mol % of PCy_3, 2 equiv. of 2-fluoro phenol, 2 equiv. of Cs_2CO_3 in toluene solvent at 110 °C was found to be the optimal condition for the aforementioned transformation.

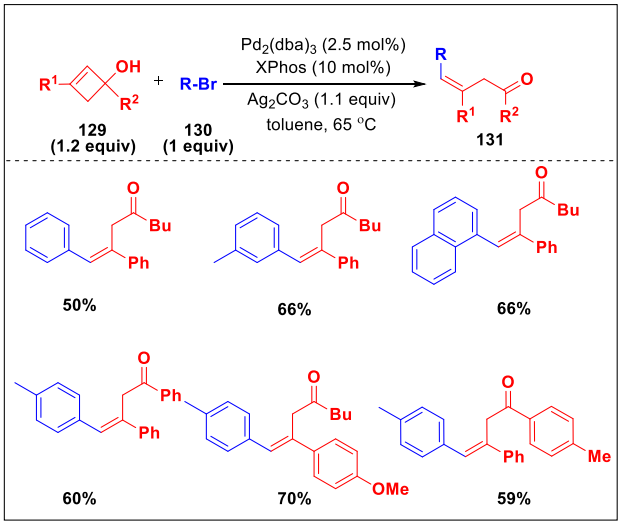
The reaction was screened with a variety of terminal alkenes, which gave the target aryl to vinyl 1,4-Pd migration products. Both electron donating and withdrawing substitution on the phenyl rings did not affect the efficiency of the reaction. However, when excess of 1-phenylcyclobutanol was used it gave a double alkylated product. A variety of cyclobutanols were also screened and gave good to excellent



Scheme 5.2 C–H alkylation of alkenes through an aryl to vinyl 1,4-palladium migration/C–C cleavage cascade.

yield. The 2-fluoro phenol assist the 1,4-Pd migration, that has been confirmed from DFT study.

1.8 Cyclobutenol:



Scheme 5.3 Palladium-catalyzed ring-opening coupling of cyclobutenols with aryl halides.

In the year 2017, Matsuda and co-workers developed the synthesis of γ-arylated β, γ-unsaturated ketones **131** through ring opening cross-coupling of tert-cyclobutenols **129** with the aryl halides **130** (Scheme 5.3).[63] The reaction was achieved via the oxidative addition of the substrate to Pd (0) followed by ring opening by the β-carbon elimination and selective C(sp^2)-C(sp^3) bond cleavage. And finally reductive elimination afforded the γ-arylated β, γ-unsaturated ketone. The reaction proceeded only with 2.5 mol % of catalyst loading that shows the efficacy of the transformation.

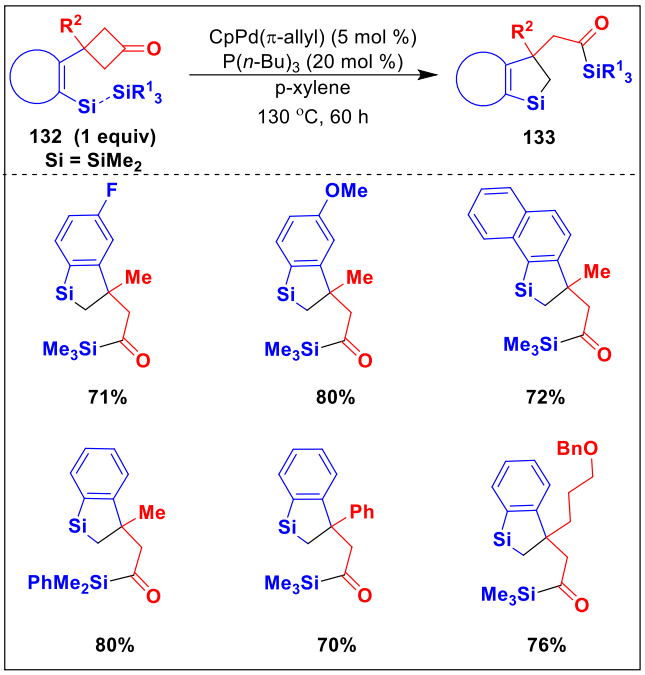
The scope of cyclobutanol and aryl halide has been screened under optimized reaction condition and found compatible delivering the products in moderate to good yields. Moreover, the product formed was further converted to bicyclic

aromatic compound through intramolecular condensation reaction.

1.9 Cyclobutanone:

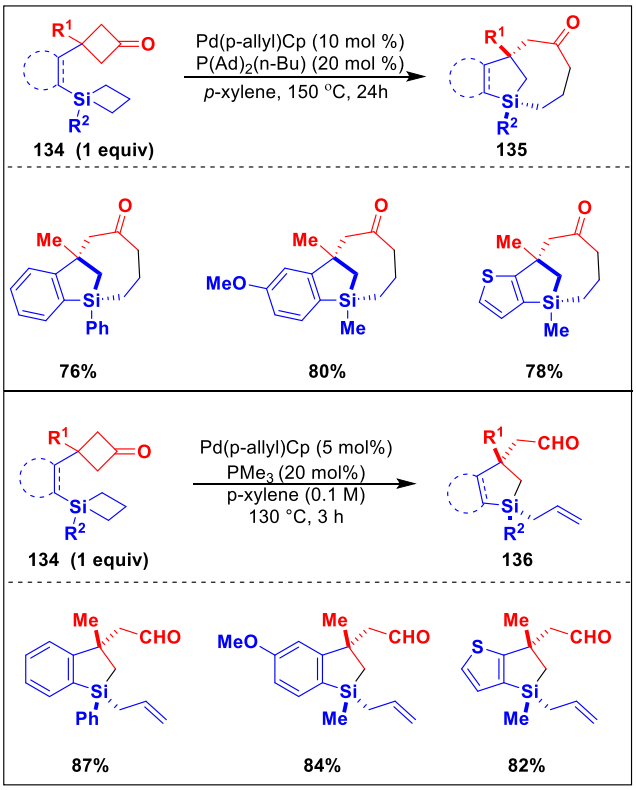
Among various four-membered strain ring system, cyclobutanone has been explored extensively due to its high synthetic accessibility. In the presence of palladium catalyst, two type of ring opening of cyclobutanone is possible that is (i) oxidative addition of C-C σ-bond to the metal, and (ii) β-carbon elimination.

Based on oxidative addition process, in 2012, Murakami and co-workers developed a intramolecular σ-bond metathesis between C-C bond of cyclobutanone **132** and Si-Si bond of disilane. The sigma bond swapping occurs between the cyclobtanone C-C bond and disilane Si-Si bond connected through a phenylene linker in the presence of Pd(0) catalyst to give silaindane skeleton **133** along with acyl silane functionality (Scheme 5.4).[64] The reaction commenced under 5 mol % of CpPd(π-allyl) as catalyst, 20 mol % of P(*n*-Bu)$_3$ as ligand in *p*-xylene solvent at 130 °C for 60 h. A variety of functionalities found compatible and smoothly converted to the desired product in good to very good yield.



Scheme 5.4 Intramolecular σ-bond metathesis between carbon-carbon and silicon-silicon bonds.

We know that, cleavage of nonpolar σ-bonds is difficult and majority of organic compounds' reactivities are attributed to their π-bonds and polar σ-bonds. These bonds have orbitals which are significantly more accessible for interaction with the orbitals of reagents or catalysts both in terms of energy and space than nonpolar σ-bonds like C-C and C-H single bonds. However, cleaving nonpolar σ-bonds and immediately subjecting them to fresh bond formation and/or functionalization would greatly simplify the process for constructing organic skeletons. But nonpolar σ-bonds are far more difficult to change without the involvement of π-bonds. As a result, nonpolar σ-bond cleavage and subsequent exchange processes was confined to biphenylenes and alkylidenecyclopropane substrates.

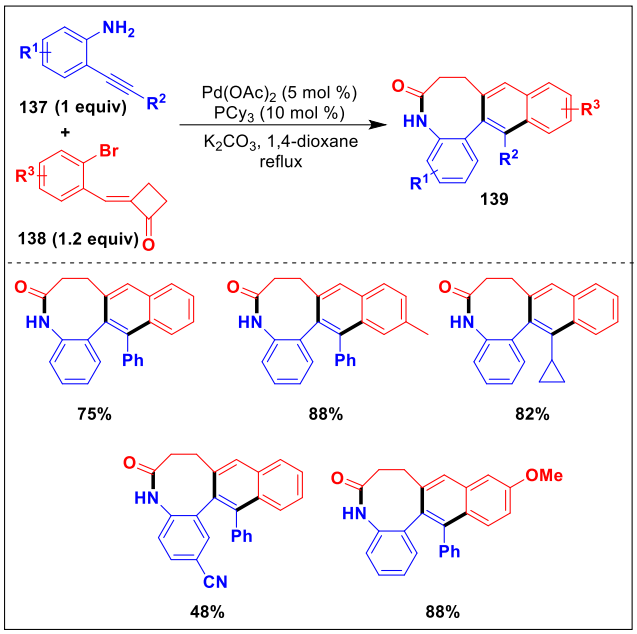


Scheme 5.5 Cleavage of C–C and C–Si σ-bonds and their intramolecular exchange.

In 2014, Murakami and co-workers developed an intramolecular σ-bond exchange process in which a cyclobutanone's C-C single bond and a silacyclobutane's C-Si single bond are cleaved and swapped to form a diastereoselective silabicyclo[5.2.1]-decane skeleton **135** in the presence of palladium catalyst (Scheme 5.5).[65] They assumed that the C-Si and C-C bonds are oxidatively added to palladium at the same time, and that the bonds are swapped by reductive elimination.

A unique ligand-based product dichotomy was also observed. When the ligand is sterically bulky P(Ad)$_2$(n-Bu) (Ad = 1- adamantyl), a silabicyclo[5.2.1]decane skeleton is formed. The usage of sterically less bulky PMe$_3$ on the other hand preferentially provided the ring-opened aldehydes **136**. The difference in steric bulkiness between the two phosphine ligands is thought to be the cause of the observed dichotomy. PMe$_3$ is sterically less bulky, it facilitates an agostic interaction between the β-hydrogen and the palladium centre, resulting in β-hydride elimination and the formation of ring opened aldehydes in addition to silacycle. The sterically larger P(Ad)$_2$(n-Bu) on the other hand, will not facilitate the agostic interaction. Rather, it promotes reductive elimination, alleviating steric congestion around the palladium core and leads to the formation of silabicyclo[5.2.1]decane skeleton.

A variety of substrates were employed to explore the scope of the transformation. Corresponding silabicyclo[5.2.1]decane skeleton products and ring-opened aldehyde products were formed in good yield depending on the ligand used.



Scheme 5.6 Synthesis of Benzo[b]naphtho[2,3-d]azocin-6(5H)-ones.

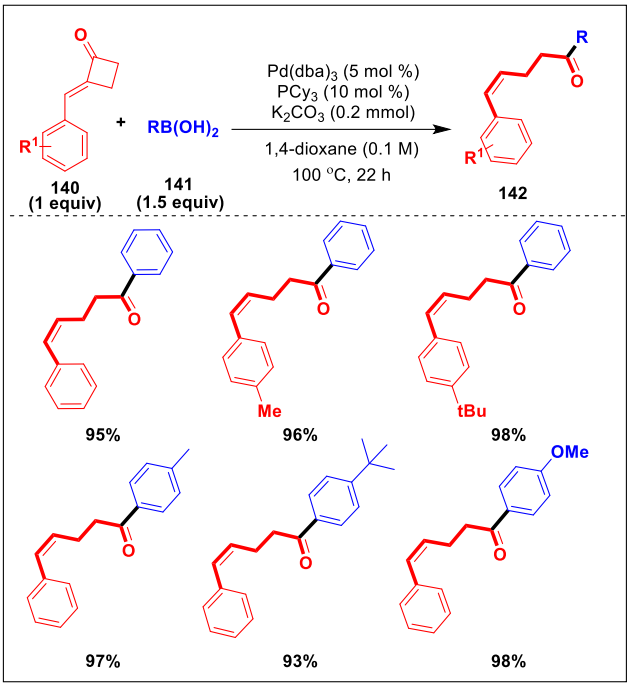
Because of their applicability as medicinal agents and research tools in biology, small molecules having natural product scaffolds have recently become key aspects of investigations. Tandem reactions have been shown to be ideal procedure for the creation of such molecules among other available procedures. Moreover, substrates having several reactive sites would be a good candidate for reaction development in a tandem process.

Wu and co-workers in 2016 described a palladium-catalyzed tandem reaction of 2-alkynylanilines **137** with 2-(2-bromobenzylidene)cyclobutanones **138** as an effective approach to 7,8-dihydrobenzo[b]naphtho[2,3-d]azocin-6(5H)-ones **139** (Scheme 5.6).[66] Double carbometalation occurs during the reaction, resulting in good selectivity and the production of three new bonds. This method is appealing because it allows for easy incorporation of molecular variety and complexity.

Screening of different reaction conditions revealed 1,4-dioxane (solvent), tricyclohexylphosphine (Cy_3P) (ligand), potassium carbonate (base) and palladium acetate (catalyst) as the optimum reaction condition. With the optimised reaction condition in hand, a variety of substrates were employed to explore the scope of the reaction. All of the processes went well and yielded 7,8-dihydrobenzo[b]naphtho[2,3- d]azocin-6(5H)-ones in moderate to excellent yields. Under standard conditions, the reaction was compatible with a wide spectrum of functional groups. Nitrile, halide, aryl, alkyl, trimethylsilyl, and thienyl groups were among them. It was shown both electron-rich and electron-poor substituents linked to the aromatic ring of 2-alkynylanilines were well tolerated.

Likewise, ring opening coupling reaction of cyclopropanol, cyclobutanol, cyclobutanone also undergoes ring-opening arylation with organo-boron reagents. In 2016, Song and co-workers disclosed the ring opening arylation of cyclobutanone **140** via an unusual palladium catalysed 1,2-addition of aryl boronic acids **141** to give γ,δ-unsaturated ketones **142** (Scheme 5.7).[67] Generally, boronic acid known to undergo 1,4 addition, however in this case the unusual palladium catalysed 1,2-addition makes the methodology very novel. Moreover, *Z*-alkenes are highly valuable owing to their presence in various bioactive materials, flavours and natural products. Thus, synthesizing (*Z*)-alkenes in selective manner will be highly desirable.

The reaction is facilitated by the ligand, confirmed from the control experiment where without ligand no product was detected. The product yield and selectivity are influenced by the base used; however, the selective formation of thermodynamically less stable *Z*-isomer is still unclear. The electronic bias in the substrate has no influence in the product yield and selectivity delivering the desired product in excellent yields.



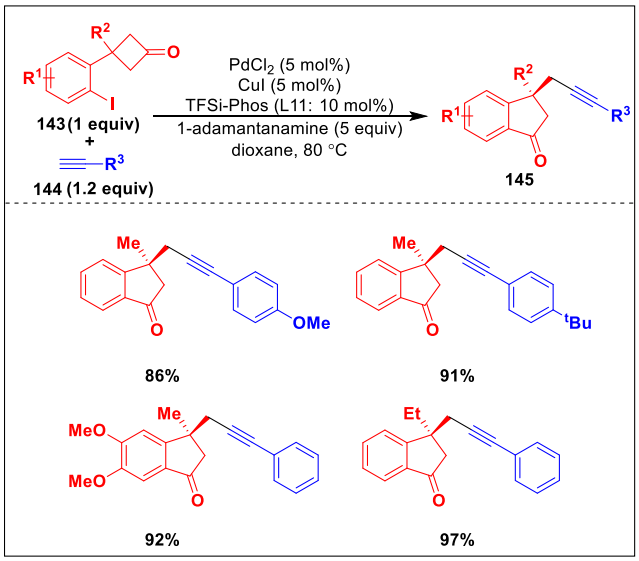
Scheme 5.7 *Z*-Selective synthesis of γ,δ-unsaturated ketones.

The C–C triple bond is one of the most important functionalities and a fundamental synthon in organic chemistry, with a wide range of reactivity. Alkynes are involved in a number of significant and useful synthetic transformations for the creation of functional molecules. The direct metalation of terminal alkynes is one of the most straightforward methods for incorporating alkynyl moieties into organic substrates. Classical Sonogashira type alkynylation reactions employ this method.

In 2019, Xu and co-workers disclosed a novel palladium/copper catalysed enantioselective alkynylation of cyclobutanones **143** with terminal alkynes **144** via sequential

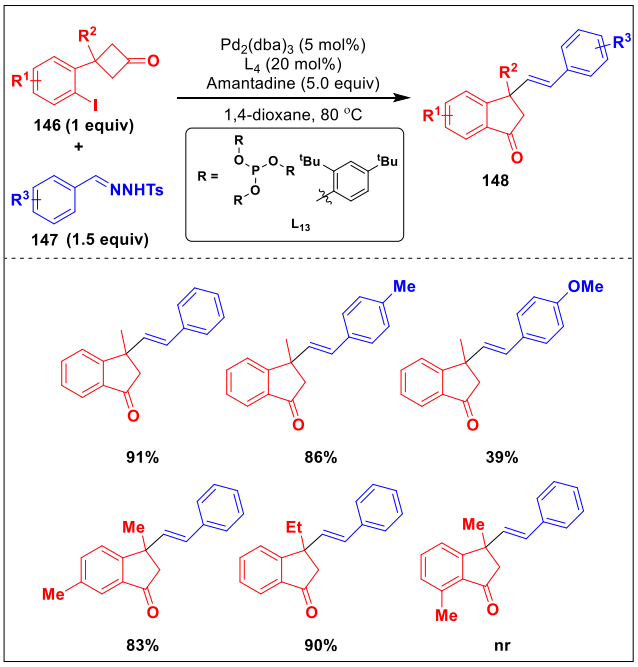
C–C bond activation/Sonogashira-type cross coupling reaction (Scheme 5.8).[68] This method provided access to a wide range of chiral alkynylated indanones **145** having all carbon quaternary stereocenter and an alkyne moiety with up to 97.5:2.5 er. A newly designed chiral TFSi-Phos ligand is used in this reaction.

This ligand was observed to be effective for both the breakage of C(sp^2)-C(sp^3) bonds and the creation of new C(sp^3)–C(sp) bonds. This transition was influenced significantly by the structure of ligands. Bulky monodentate phosphine ligands produced greater yields than bidentate ligands. Under standard reaction condition, many substrates were employed to explore the scope of the reaction. Arylacetylene with a variety of phenyl ring substituents, such as -OMe, -^{t}Bu, -Me, -CF_3, -F, and -Cl, interacted effectively to produce the desired products in high yields. Heteroaromatic groups like 2-thiophenyl were also well tolerated. The scope was also looked at in terms of cyclobutanones. Cyclobutanones having phenyl moiety containing -Me, -OMe, -F, -Cl, and -Br, were all responsive to this transition, giving plenty of potential for additional functionalization. A gram scale experiment was also carried out to establish the feasibility of the reaction, and the product was formed in 90% yield with 95: 5 er.



Scheme 5.8 *Z*-Selective synthesis of γ,δ-unsaturated ketones.

In 2021, Shang and co-workers discovered that the palladium catalysed C–C bond activation of cyclobutanones may be used to make alkenyl and carbonylated indanones. They performed the C–C bond activation of 3-(2-iodophenyl)-3-methylcyclobutan-1-ones **146** with *N*-tosylhydrazones **147**, which react with the alkyl palladium intermediate, to produce alkenylated indanones **148** (Scheme5.9).[69]



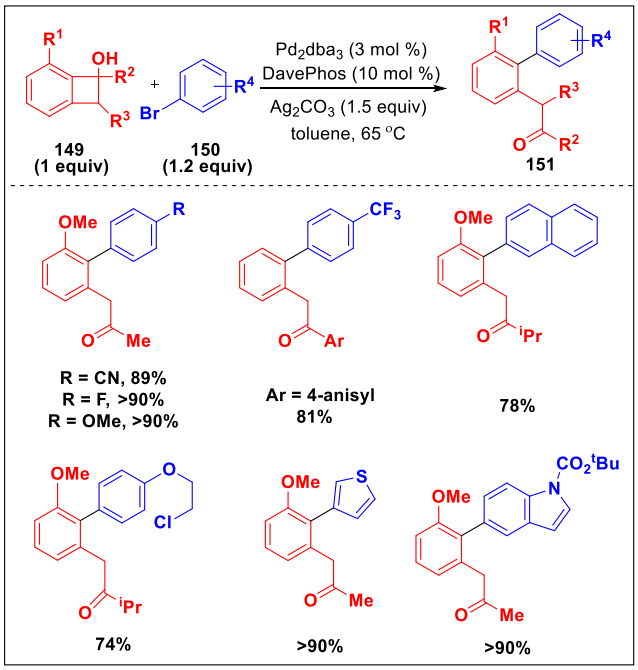
Scheme 5.9 *Z*-Selective synthesis of γ,δ-unsaturated ketones.

Under standard condition, a variety of substrates were employed to explore the scope of the reaction. Both electron-donating and electron-withdrawing groups on N-tosylhydrazones were well tolerated, resulting in good to outstanding yields of alkenylated indanones. It was observed that this alkenylative C–C bond cleavage reaction did not work with aliphatic hydrazone. The investigation was also done with different 3-(2- iodophenyl)-3-methylcyclobutan-1-ones. Among which -Me, -OMe, -F, and -Br functional groups were well tolerated, and the corresponding products were produced in high yields. 3-ethyl substituted indanone was obtained in 90% yield. All these reactions were performed under mild conditions and showed excellent functional group tolerance.

2.0 Benzocyclobutenol:

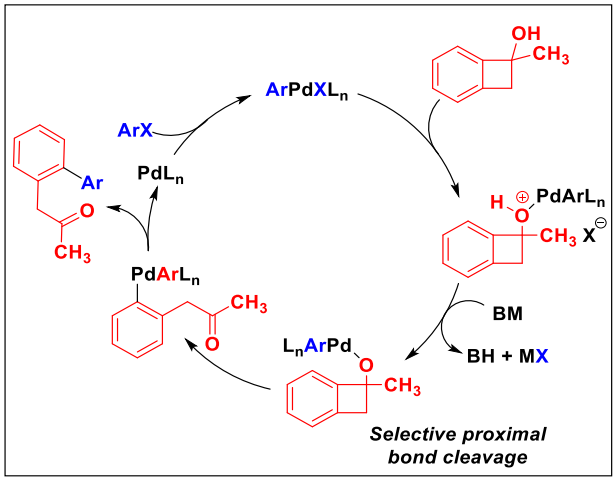
In 2011, Orellana and co-workers have demonstrated the selective carbo-elimination of benzocyclobutenol **149** followed by cross-coupling with aryl bromides **150** in the presence of palladium catalyst (Scheme 6.0).[70]

They have proposed a mechanistic pathway (Scheme 6.1) which generated an aryl palladium (II) intermediate on oxidative addition of aryl halide to Pd(0)L_n, that further engages in ligand exchange with the benzocyclobutenol. Selective deprotonation of the Pd-bound benzocyclobutenol can be done to avoid uncontrolled ring opening. Further, it can lead to proximal bond cleavage of the cyclobutenol ring, followed by the reductive elimination leading to the formation of the desired product. In the initial stage with the usage of simple catalyst and electron-neutral aryl bromide gave a moderate yield but the efficiency of the catalytic system was not good as the reaction



Scheme 6.0 *Z*-Selective synthesis of γ,δ-unsaturated ketones.

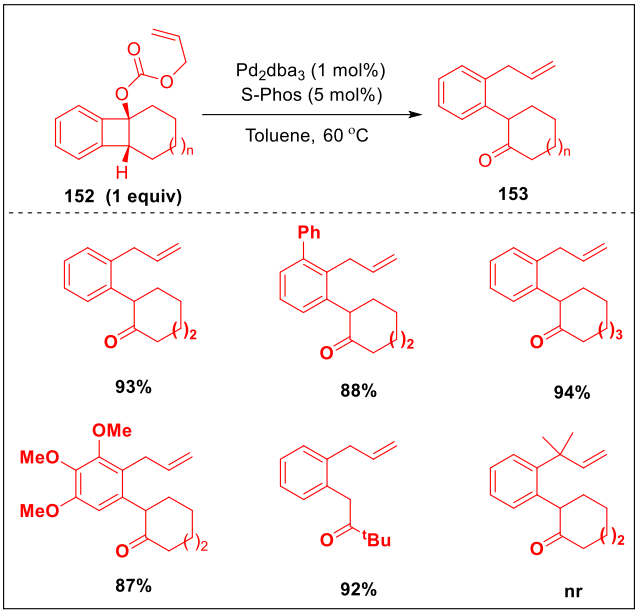
took longer time for completion. However, with the use of DavePhos as the ligand and Pd_2dba_3 as catalyst with Ag_2CO_3, yield of the desired product increased with a lesser reaction time. Basically, the role of Ag(I) is to promote the generation of cationic palladium intermediates by abstraction of halide ion that led to the enhancement in the yield of the product.



Scheme 6.1 Plausible catalytic cycle.

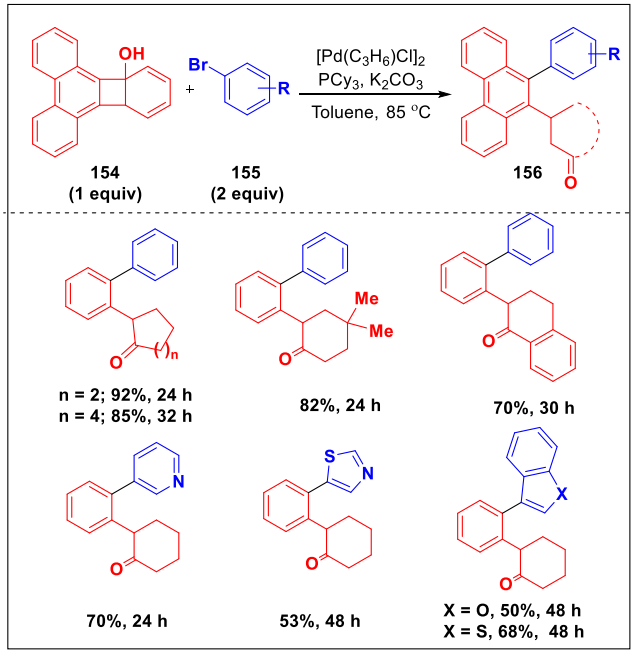
Electron rich, electron neutral as well as electron deficient substrates were screened and gave excellent yields of the desired product. Primary alkyl chloride bearing substrate showed diminished yield, possibly due to the presence of the electron rich phosphine ligand. Heteroaryl bromide substrate gave good yield. But di-substituted aryl bromides failed to give the cross-coupled product.

Further, the work has been extended by the same group in 2012, where they have used allylated benzocyclobutenyl carbonates **152** as substrate which undergo decarboxylative allylation and fragmentation to give *ortho* allyl α-arylated ketones **153** (Scheme 6.2).[71] The mechanism suggested by them inolved the ionization of allyl benzocyclobutenyl carbonates by the Pd (0) catalyst which leads to the generation of a pair consisting of a cationic allyl palladium intermediate and an alkoxide anion due to decarboxylation. Further Pd coordinates with the alkoxide oxygen followed by selective β-carboelimination and reductive elimination to give the desired product.



Scheme 6.2 *ortho* allyl α-arylated ketones.

The substrate had to be synthesized and isolated to carry out the palladium catalysed C-C bond activation process.



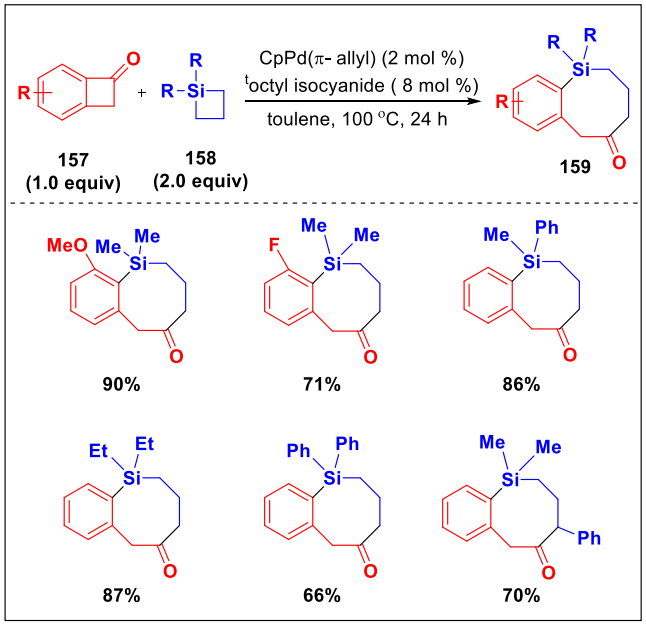
Scheme 6.3 C–C Bond hetero-arylation of ring-fused benzocyclobutenols .

Therefore, benzocyclobutenol were isolated first and then allyl carbonate functionalization was introduced in a separate reaction. A range of biarylphosphine (Buchwald ligands) were screened and Pd_2dba_3, with S-Phos giving excellent yield of the desired product. Substrates having an allyl carbonate functional group and a fused cycloheptane ring produced excellent amount of the coupled products. 1,1-dimethylallyl and crotyl carbonate functional group bearing substrate, did not give the desired product.

Due to the use of costly DavePhos ligand and stochiometric amount of Ag_2CO_3 by the Orellana group (Scheme 6.0),[70] in 2017 Zhu and co-workers brought in place a more practical and efficient method to synthesize ketone derivatives (Scheme 6.3).[72] They developed an alternative way for the C-C heteroarylation of ring-fused benzocyclobutenols (RBCBs). Thus, benzocyclobutenols **154** underwent ring opening coupling with aryl halide **155** to deliver the ketone derivatives **156** in the presence of palladium catalyst, PCy_3 and K_2CO_3. Five to eight membered rings fused BCBs gave the phenylated product in good to excellent yields. Varying the substitution on the ring did not affect the yield of the desired product concluding that substrate electronics has no effect in the reaction. Polycyclic compound was also synthesised by increasing the rings on the RBCBs. Both electron donating and withdrawing groups gave good yield. Moreover, various heteroaryls like pyrimidyl, quinolyl, thiazolyl, and benzofuryl were found compatible under reaction condition.

2.1 Benzocyclobutenone:

After successfully reporting Pd-catalysed intramolecular σ-bond exchange between C-C and C-Si bond (Scheme 5.4) in substrate containing cyclobutanone and silacyclobutane, Murakami and co-workers in 2017 extended their work to benzocyclobutenone.



Scheme 6.4 Palladium-catalyzed intermolecular exchange between C–C and C–Si σ-bonds.

They have reported a palladium-isocyanide complex catalysed cleavage of the C(aryl)-C(carbonyl) bond of benzocyclobutenone **157** and a C(sp^3)-Si bond in silacyclobutanes **158** forming an eight membered silacycle **159** (Scheme 6.4).[73] The C-C bond of benzocyclobutenone get oxidatively added to the palladium-isocyanide complex exclusively.

A variety of benzocyclobutanone and silacyclobutanes were screened to show the generality of the developed condition. Alkoxy and fluoro substitued benzocyclobutanone gave the corresponding eight membered silacycle in excellent to good yield. Silacyclobutanes with phenyl substitution also gave the product in good yield. However, in the case of nonsymmetric 2-phenylsilacyclobutanes, the C(benzylic)-Si with sterically less hindered site will cleaved selectively rather than the sterically crowded C(methelyene)-Si bond to give the product. Thus, benzocyclobutenone, a four-membered strained system has been employed as 4C synthon for the synthesis of 8-membered silacycle.

Summary and outlook

Herein, we have discussed about palladium catalysed C-C bond activation of three-membered and four membered carbocycles that serves as a valuable C3 and C4 building blocks towards the synthesis of various bioactive drugs and natural products. Palladium has been known for its robustness, reactivity and wide application in various synthetic methodologies. Reaction those are not feasible with other transition-metal were found successful when palladium was employed as catalyst.

In the other hand, strain rings are known to open up in the presence of reactive transition metal. Thus, combined effect of metal inherent energy and strain energy of three and four-membered cycloalkane led to various value-added transformation. In this process strained systems were evolved as very important and useful skeleton to synthesized complex scaffold and the reactivity of the palladium played a very crucial role.

Though significant progress has been made in the palladium catalysed C-C bond activation of strained system, there is immense potential to expand this field. In this context, there are numerous aspects that needs further modification such as (a) designing of other strained system that can enable intramolecular cascade cyclization, (b) generation of chiral centre in the product, (c) synthesizing the molecules in enantioselective manner, (d) wider use of cheaper palladium salt than complicated and costly ones, (e) more exploration towards the C-C bond activation of cyclopropenone, as there are very limited reports, and (f) expansion of its utility towards the synthesis of drug, natural product and bioactive molecule This provides a unique opportunity to the synthetic chemist to explore the underexplored chemical space.

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Authors Contribution

†T.N and M.F contributed equally.

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