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REVIEW

Recent Advances in Palladium-Catalyzed [4 + *n*] Cycloaddition of Lactones, Benzoxazinanones, Allylic Carbonates, and Vinyloxetanes

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Abstract

Palladium-catalyzed allylation cyclization reaction has recently emerged as an efficient and powerful synthetic platform for the construction of diverse and valuable carbo- and heterocycles. Thus the development of new allylic motifs for achieving this type of transformations in high reactivity and selectivity is of great importance. Generally, these substrates have been utilized as 1,3-, 1,4-, 1,5-, 1,6-dipoles in many reactions, which are applied to prepare highly functionalized products with complete control of chemo-, regio-, diastereo-, and enantioselectivity. In this review, we focus our attention on the development of palladium-catalyzed [4 + *n*] cycloaddition of allylic motifs and describe a comprehensive and impressive advances in this area. Meanwhile, the related mechanism and the application of these annulation strategies in natural product total synthesis will be highlighted in detail.

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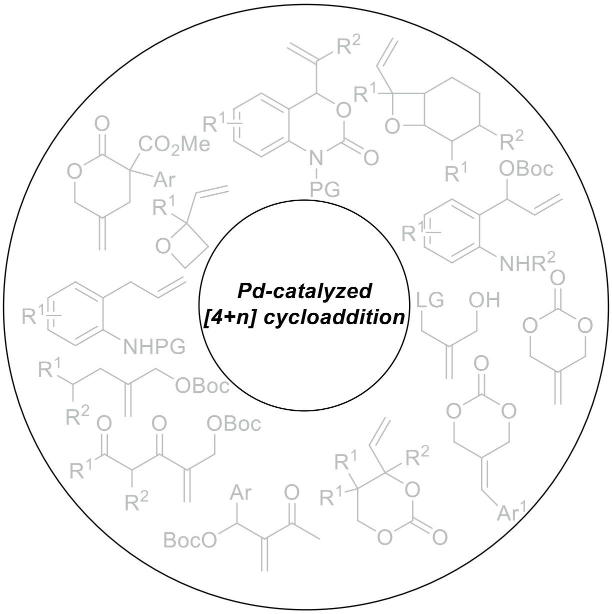
Graphical Abstract

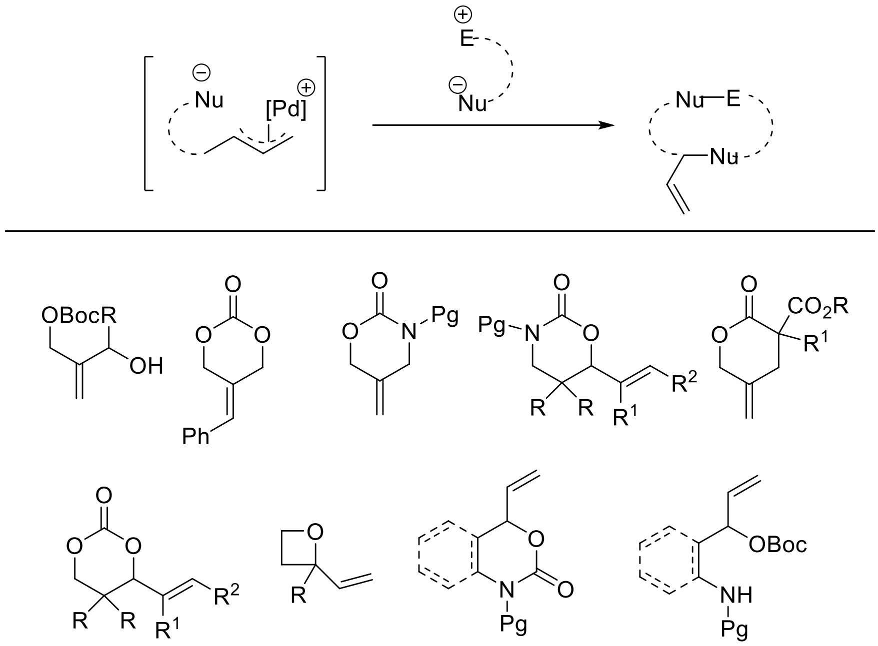


Keywords Palladium catalysis · [4 + *n*] cycloaddition · Allylation

1 Introduction

[4 + *n*] cycloadditions have evolved into a powerful tool for the construction of cyclic molecules, which are applied in the preparation of a wide range of natural products, pharmaceuticals, and agrochemicals [1, 2]. In particular, Diels–Alder reaction, which has been widely utilized in organic synthesis, is probably the most well-known and important [4 + *n*] cycloaddition reaction [3, 4]. Notably, organocatalysis and metal catalysis have pushed this kind of cycloaddition to the state of the art in recent decades, and a large number of unprecedented [4 + *n*] cycloaddition reactions have been developed in laboratories worldwide. Although important progress has been made, the growing demand in the field urges organic chemists to develop novel, practical strategies to complement the existing methods. Thus a new review involving [4 + *n*] cycloaddition will provide organic chemists with a systematically picture of this research field, leading to further development in this new reaction modes.

Palladium-catalyzed allylation cyclization reaction, pioneered by Trost group in the early 1980s, [5] has grown rapidly in the past decades. Different allylic substrates have been developed and applied as 1,3-, 1,4-, 1,5-, 1,6-dipoles in [3 + *n*], [4 + *n*], [5 + *n*], and [6 + *n*] cyclizations with various electrophiles, preparing a wide range of highly functionalized products in a chemo-, diastereo-, and

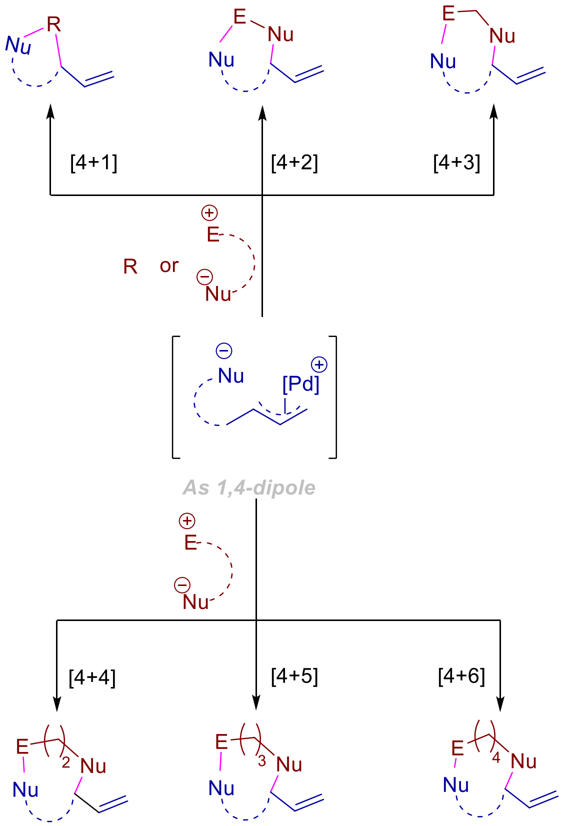


Scheme 1 Different allylic 1,4-dipole synthons

enantioselective manner [6]. Among the existing reactions, palladium-catalyzed [4 + *n*] cycloaddition has emerged as an efficient source of four-carbon building blocks for producing both carbocycles and heterocycles. Consequently, the development of reliable methods to access cyclic compounds through [4 + *n*] cycloaddition is of great interest. As shown in Scheme 1, chemists have designed many types of allylic motifs involving four-carbon synthons to explore some unexpected reaction pathways and solve the challenging in classic palladium-catalyzed allylation cycloadditions, such as the problems of the reactivity and selectivity with different acceptors.

Scheme 2 summarizes the major achievements in the area of these palladium-catalyzed [4 + *n*] cycloaddition from our laboratory and others. In these reaction, highly active and short-lived zwitterionic intermediate was first stabilized by palladium catalyst to form the π-allylpalladium intermediate, which could serve as a 1, 4-dipole, in [4 + 1], [4 + 2], [4 + 3], [4 + 4], [4 + 5], and [4 + 6] cyclizations with various electrophiles. Given the importance of this topic, several reviews involving palladium-catalyzed cycloaddition have been reported until now [7–11]. For example, in 2022, Yuan and coworkers reported recent advance involving palladium-catalyzed decarboxylative cycloadditions [7]. While these reviews have covered partial aspects of [4 + *n*] cycloadditions, to the best of our knowledge, there still has not been a comprehensive review involving palladium-catalyzed [4 + *n*] cycloaddition. In this review, we will summarize and classify the related research works, and hope that the comprehensive summary in stage will inspire chemists to explore and discover more types of reactions for palladium-catalyzed allylation cyclization.

Scheme 2 The latest overview of the Pd-catalyzed [4 + *n*] cycloaddition

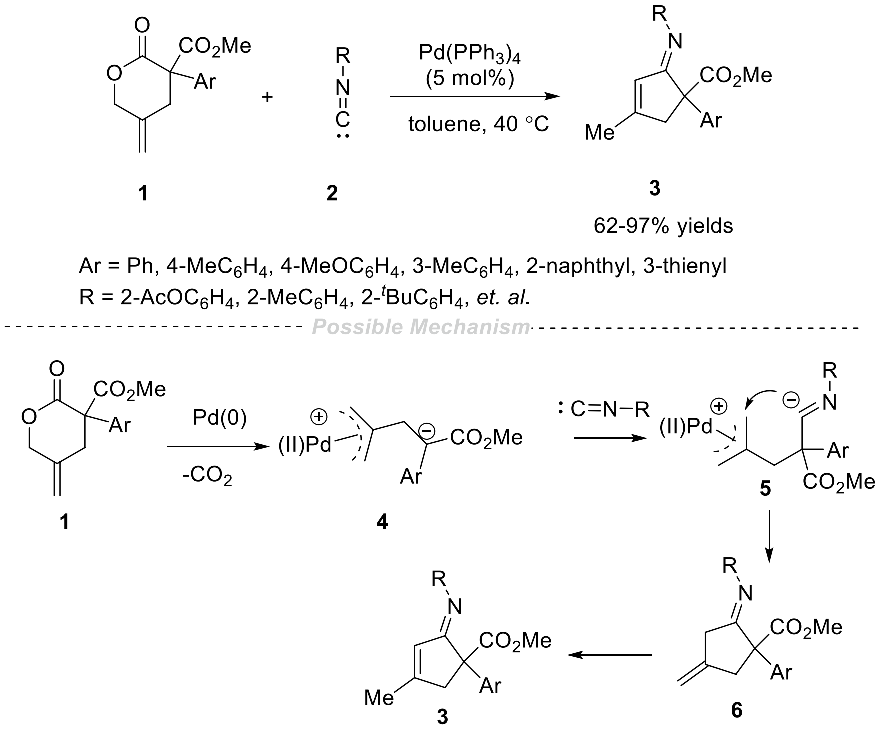


2 Allylic Motifs as "1,4-Dipole" in [4 + 1] Annulations

Five-membered carbo- and heterocyclic skeletons represent privileged scaffolds in many biologically active compounds, pharmaceutical molecules, and natural products. In the past decades, a wide range of cycloadditions, including intramolecular cyclization, [3 + 2] cyclization, and [4 + 1] cyclization [12–14], were successfully developed to construct such skeletally related molecules. In this section, we will summarize the development of palladium-catalyzed [4 + 1] cycloadditions in detail.

2.1 γ-Methylidene-δ-Valerolactones as "1,4-Dipole" in [4 + 1] Annulations

In 2009, Hayashi and coworkers reported a palladium-catalyzed decarboxylative [4 + 1] cyclization of γ-methylidene-δ-valerolactones with isocyanides, producing the desired cyclopentenimines in moderate to high yields [15]. The authors found that the solvents had certain influence on the yield of products, and the best result was obtained using toluene as the solvent. In addition, the use of lactone **1** having



Scheme 3 Palladium-catalyzed [4 + 1] cyclization of γ-methylidene-δ-valerolactones with isocyanides

a methyl group at the δ-position could react with **2**, selectively giving ethylcyclopentenimine **3** at the less substituted carbon atom. Then a possible mechanism was proposed. Firstly, 1,4-zwitterionic species **4** was obtained by palladium-catalyzed decarboxylation, which then attacked the carbon atom of **2** to give intermediate **5**. Subsequently, a ring-closure process led to the formation of five-membered carbocycle **6** and regenerated palladium catalyst. Finally, more stable conjugated cyclopentenimine **3** was obtained by an *exo*-methylene readily isomerization (Scheme 3).

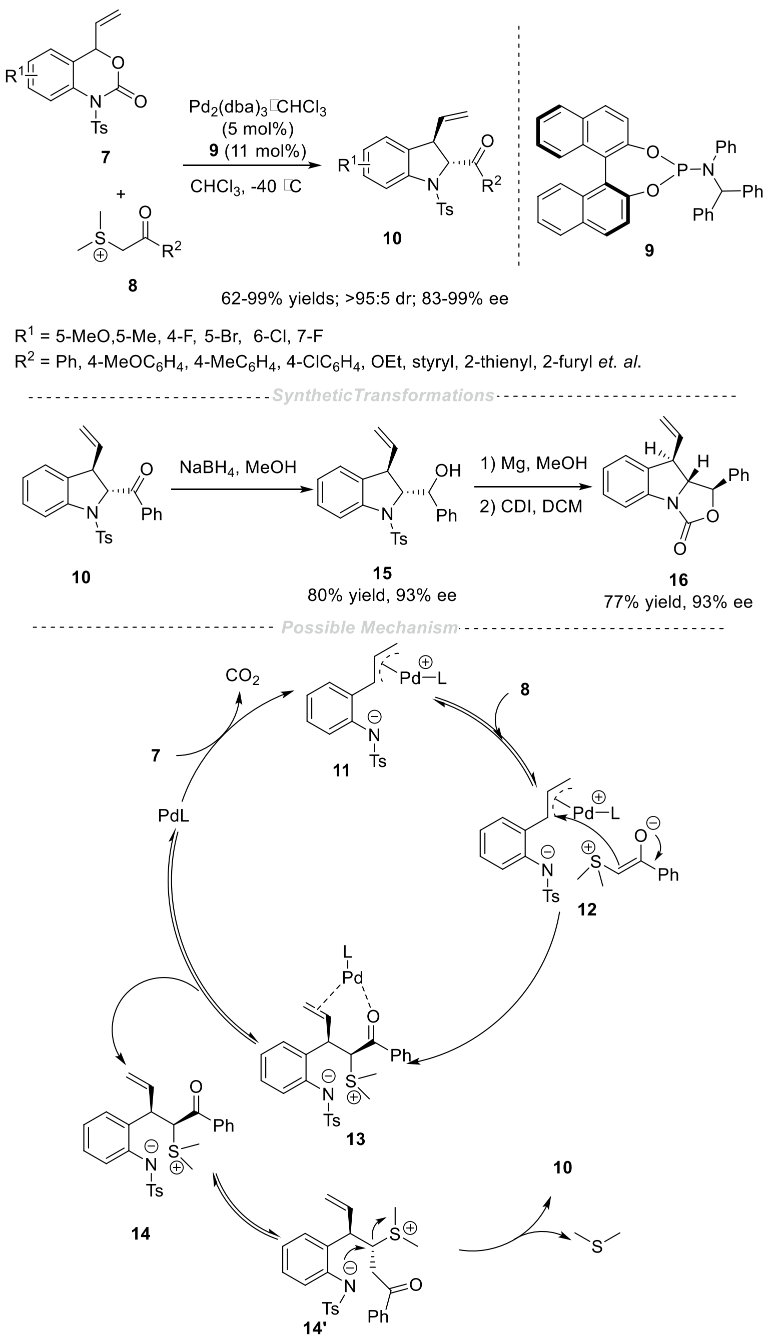
2.2 Benzoxazinanones as "1,4-Dipole" in [4 + 1] Annulations

Vinyl benzoxazinones has emerged as promising substrates for Pd-catalyzed decarboxylative [4 + 1] cyclization. In 2014, Xiao and coworkers disclosed a palladium-catalyzed decarboxylation [4 + 1] cycloaddition of vinyl benzoxazinones with sulfur ylides [16]. Notably, the reaction could proceed smoothly by using palladium complex with You's chiral ligand **9** as catalyst in chloroform at −40 °C, affording a wide range of 3-vinyl indoline products **10** in good yields (62–99% yields), diastereoselectivity (up to > 95:5 *dr*), and enantioselectivity (up to 99% *ee*). In addition, the obtained product **10** could be converted into the desired product **16** with an oxazolo[3, 4-a]indol-3-one core by three steps, which was not only a new class of potent antibacterial agents but also an important intermediate in the synthesis of natural indoline alkaloids. Finally, a possible and reasonable mechanism was proposed for this transformation. Initially, the intermediate **11** was obtained by palladium-catalyzed decarboxylation, which reacted with sulfur ylide **8** to form Pd complex **12** through electronic interaction. Next, a new C–C bond was formed irreversibly via an intramolecular asymmetric allylation reaction, generating the new intermediate **13** in good regioselectivity and stereoselectivity. Subsequently, the zwitterionic species **14** was formed by decomposition of intermediate **13** and regenerated the chiral Pd(0) catalyst. Finally, a bond rotation and *N*-alkylation occurred to give the desired chiral indoline products **10**. According to the authors' viewpoint, the electrostatic interaction between the positive sulfonium ion and negative sulfamide anion was believed to play a pivotal role in the complete branched regioselectivity and good enantioselectivity (Scheme 4). Later, the authors devised a similarly decarboxylative [4 + 1] cycloaddition process by using iron catalyst [17].

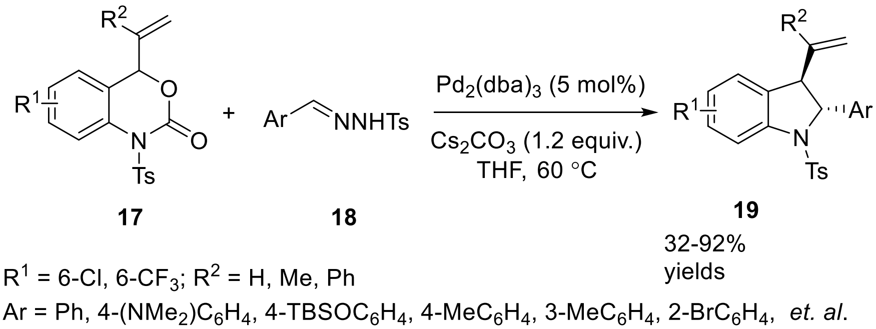
Diazo compounds as C1-synthons have been well studied in different reactions by in situ formation of carbene in the presence of metal catalysts (such as Rh and Pd) [18–21]. In 2020, Ashfeld and coworkers reported a palladium-catalyzed [4 + 1] cycloaddition of vinyl benzoxazinones with the diazo compound generated in situ from *N*-sulfonyl hydrazones **18**, producing the desired cycloadducts in moderate to good yields [22]. Notably, 1,1-dimethyl substitution and 1,2-substitution of the alkenes were not tolerated under the optimized reaction conditions. Control experiment indicated the viability of a π-allyl Pd(II) carbene intermediate followed by sequential C–C and C–N bond formation to construct the indoline core framework (Scheme 5).

In 2018, Shibata and coworkers developed a palladium-catalyzed interceptive decarboxylative benzylic [4 + 1] cycloaddition reaction using trifluoromethyl benzoxazinanones and sulfur ylides as reactive substrates, providing a series of CF_3-substituted indolines **21** in high to excellent yields with high diastereoselectivity [23]. Notably, a CF_3 substitution at the benzylic position of benzoxazinanone **20** played an important role in the transformation, and the Me-substituted benzoxazinanone **20** gave a lower yield (Scheme 6). Later, the authors reported a [4 + 1] cycloaddition of trifluoromethyl benzoxazinones and sulfur ylides in a transition-metal-free manner, affording the desired CF_3-substituted indolines **21** in moderate to good yields [24].

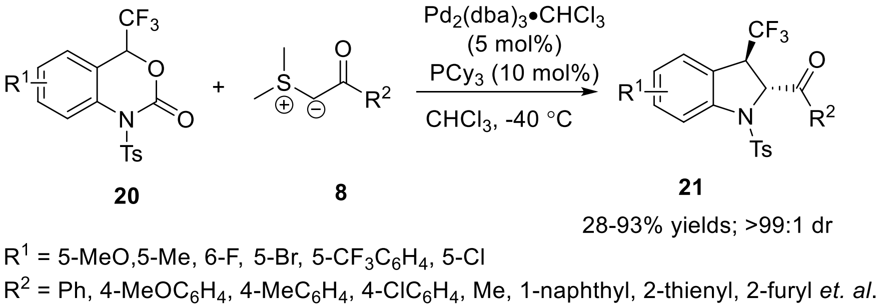
Metal-polarized aza-*ortho*-quinone methides (aza-*o*-QMs) are a unique and efficient handle for aza-heterocycle synthesis. In 2023, Lu and coworkers reported a palladium-catalyzed [4 + 1] cycloaddition reaction of benzoxazinones with aza-sulfur ylides [25]. Mechanistical studies showed these unprecedented reaction first underwent a dearomatization aziridination process to obtain the dearomatized spiroaziridine intermediates **30**, which then underwent rearomatization reaction to give the desired products. The reactions showed good substrate tolerance. The authors used three types of benzoxazinones in this reaction, and three sequential dearomatization–rearomatization reactions of benzimidazolines with aza-sulfur ylides were accomplished, affording benzimidazolines and dibenzodiazepines with high yields (Scheme 7).



Scheme 4 Palladium-catalyzed decarboxylation [4 + 1] cycloaddition of vinyl benzoxazinones with sulfur ylides



Scheme 5 Palladium-catalyzed [4 + 1] cycloaddition of vinyl benzoxazinones with the diazo compound

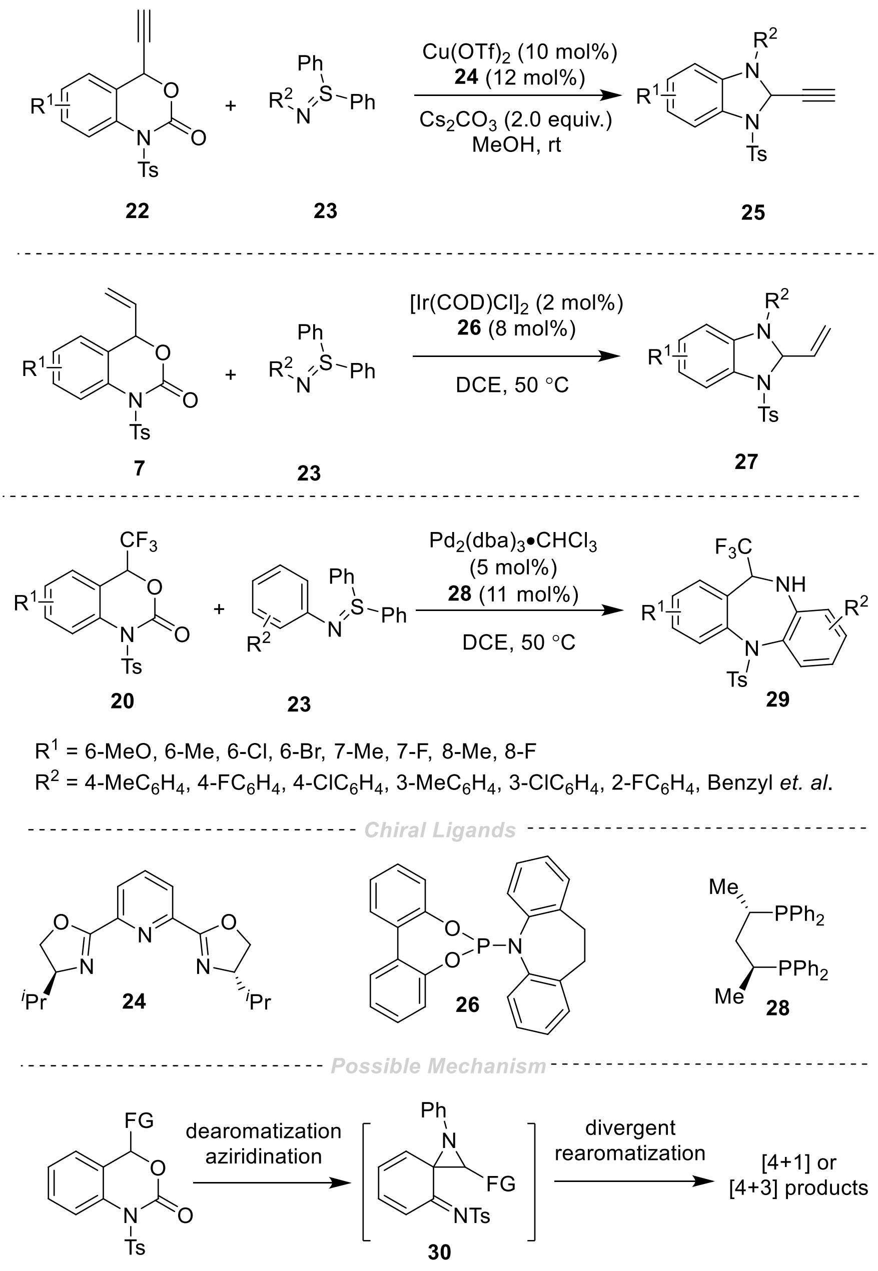


Scheme 6 Palladium-catalyzed interceptive benzylic [4 + 1] cycloaddition reaction of trifluoromethyl benzoxazinanones

2.3 Allyl Carbonate as "1,4-Dipole" in [4 + 1] Annulations

Spirooxindoles represent privileged scaffolds in the field of pharmaceutical discovery and natural chemistry. Thus, the development of an efficient strategy to synthesize these molecules is still highly desired. In 2021, Fu and coworkers developed a palladium-catalyzed [4 + 1] cycloaddition reaction using 2-methylidenetrimethylene carbonate and diphenyl 1-methyl-2-oxoindolin-3-yl phosphate as reactive substrates [26]. A large variety of structurally useful spirooxindole derivatives were formed in good yields. Furthermore, the reaction could proceed smoothly to obtain the desired product in 80% yield using 1-methylindoline-2,3-dione **34**, diphenyl phosphonate **35**, and **32** as the starting materials by a one-pot two-step method. In addition, the obtained products could be further converted different compounds under suitable catalytic conditions, which showed the valuable synthetic utility of the products (Scheme 8).

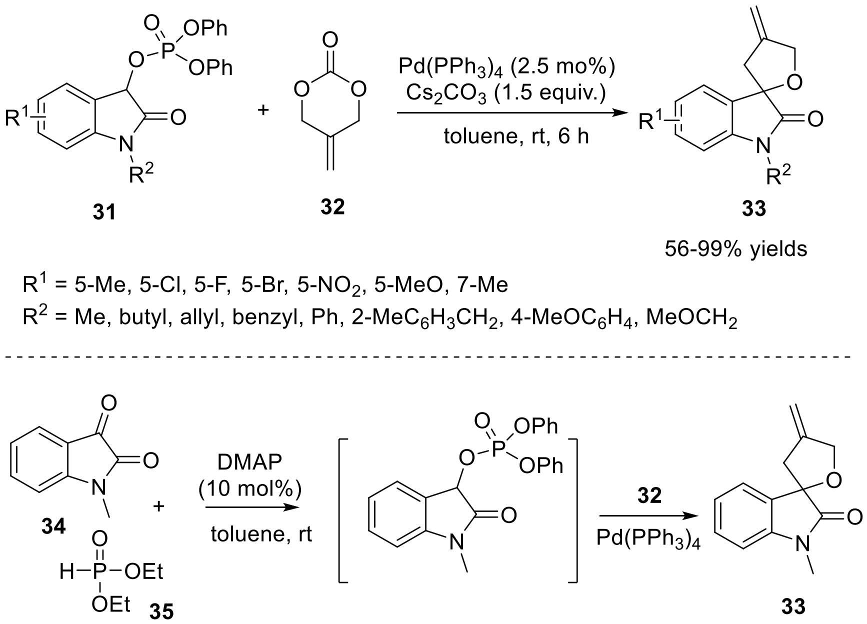
The Kukhtin–Ramirez adducts, pioneered by Kukhtin and Ramirez, constitute a class of C1 synthons generated in situ from 1,2-dicarbonyl compounds and trivalent phosphorus reagents, which have been well studied as reactive intermediates in organic synthesis in recent years [27, 28]. In 2022, Li and coworkers



R^1 = 6-MeO, 6-Me, 6-Cl, 6-Br, 7-Me, 7-F, 8-Me, 8-F
R^2 = 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-MeC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-FC$_6$H$_4$, Benzyl *et. al.*

Scheme 7 Metal-catalyzed dearomatization–rearomatization reactions of benzoxazinones with azasulfur ylides

disclosed a cooperative system that combined P(NEt$_2$)$_3$-promoted umpolung addition of isatin derivatives with palladium-catalyzed allylation of (2-(hydroxymethyl)allyl) carbonates, affording the desired 3,3′-spirooxindoles with excellent



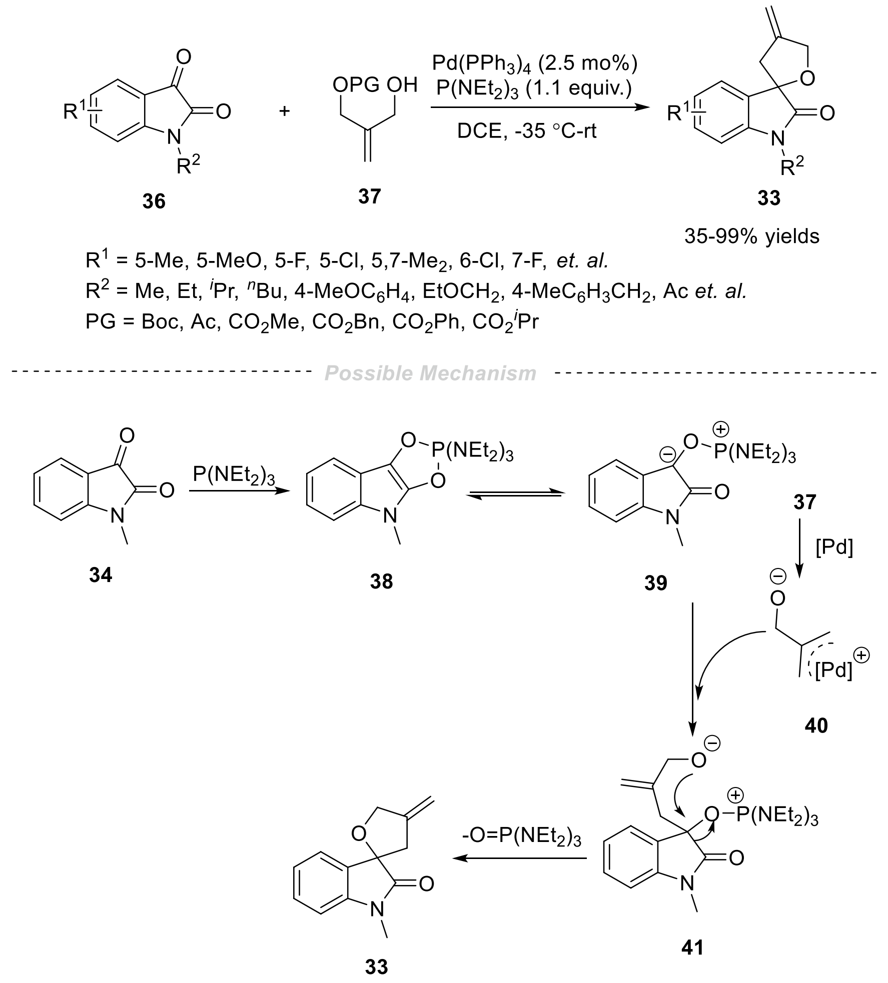
Scheme 8 Palladium-catalyzed [4+1] cycloaddition reaction of diphenyl 1-methyl-2-oxoindolin-3-yl phosphate

yields and chemoselectivity [29]. The authors proposed a plausible mechanism for this transformation. Initially, the Kukhtin–Ramirez adducts **38/39** were in situ generated from isatin **34** and $P(NEt_2)_3$. Simultaneously, substrate **37** coordinated with $Pd(PPh_3)_4$ to form the π-allylpalladium complex **40**. Next, an allylic alkylation of the π-allylpalladium complex **40** with the Kukhtin–Ramirez adduct give intermediate **41** and regenerated Pd catalyst. Finally, intramolecular nucleophilic attack of the oxygen anion at C-3 afforded the target product **33** with the release of phosphoric triamide byproduct (Scheme 9).

3 Allylic Motifs as a "1,4-Dipole" in [4+2] Annulations

3.1 γ-Methylidene-δ-Valerolactones as a "1,4-Dipole" in [4+2] Annulations

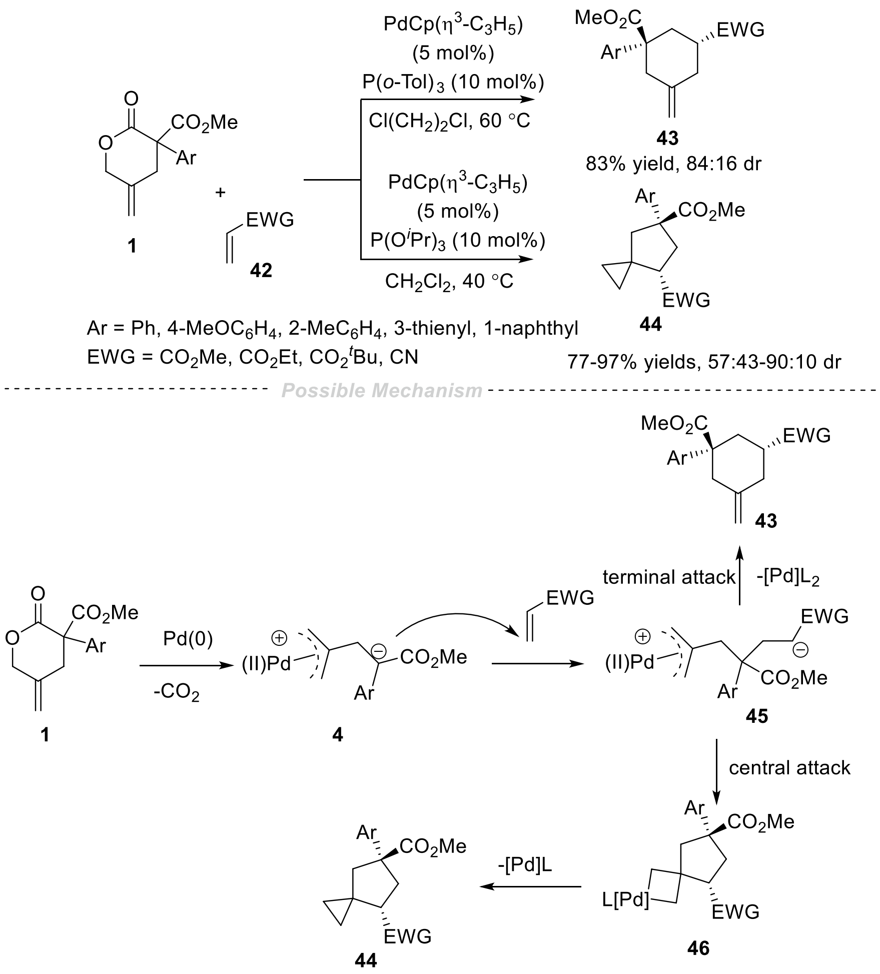
Six-membered carbo- and heterocycles have been commonly prepared by catalytic cycloadditions, including [4+2], [3+3] and [5+1] cycloadditions. Among them, [4+2] cycloadditions have been well studied for the construction of six-membered cycles, and various 1,4-dipoles have been designed in these reactions. In 2007, Hayashi and coworkers developed a new 1,4-dipole, which was named γ-methylidene-δ-valerolactone, and performed palladium-catalyzed [4+2] cycloaddition reactions with methyl acrylate [30]. The experiment showed that the size of ligands had a great effect on regioselectivity. The use of relatively small phosphine (PPh_3), bisphosphine ligand (BINAP), and phosphite ligands ($P(OMe)_3$, $P(O^iPr)_3$)



Scheme 9 Cooperative palladium-catalyzed $P(NEt_2)_3$-mediated [4 + 1] annulation of isatins

tended to give spiro[2. 4]heptanes **44**, while the use of bulky phosphine ligands preferentially afforded [4 + 2] cycloadducts **43**. The authors proposed a possible mechanism, which is outlined in Scheme 10. Initially, 1,4-zwitterionic species **4** was formed by palladium-catalyzed decarboxylation. Then the intermediate attacked the electron-deficient olefin **42** to give intermediate **45**. The two paths are shown below. When dual-ligand coordinated Pd(π-allyl)L_2 species was used as catalyst, the ring closure through a nucleophilic attack to the central carbon of the π-allylpalladium moiety gave palladacyclobutane **46**. When mono-ligand coordinated Pd(π-allyl) L species was used, [4 + 2] cycloadducts were obtained by the terminal attack (Scheme 10).

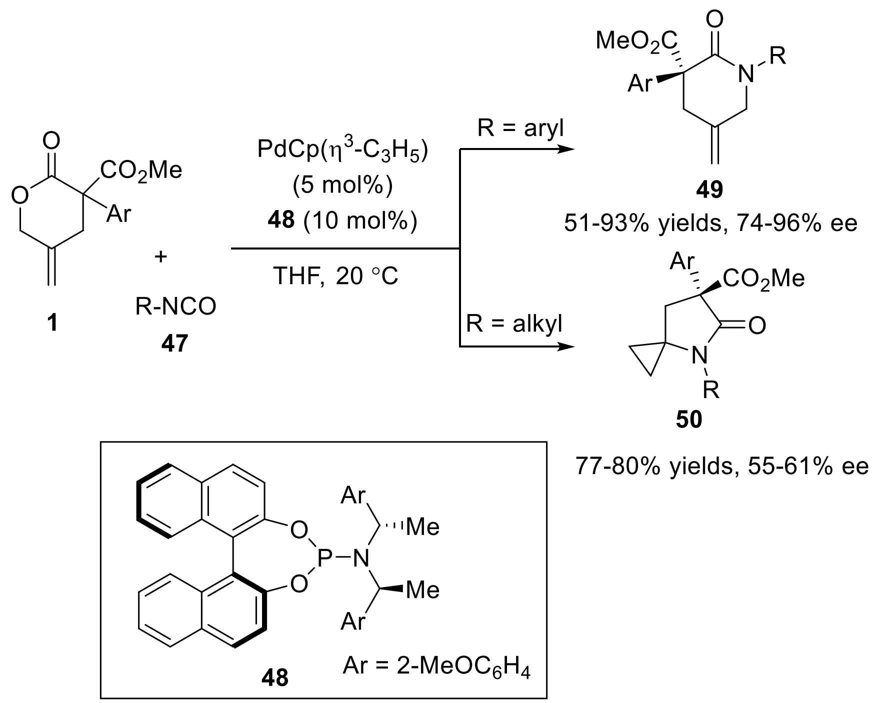
In 2008, Hayashi and coworkers used chiral phosphoramidites as ligands, disclosing an efficient palladium-catalyzed asymmetric [4 + 2] cycloaddition of



Scheme 10 Palladium-catalyzed [4 + 2] cycloaddition reactions with methyl acrylate

γ-methylidene-δ-valerolactones with isocyanate [31]. After extensive condition screening, The corresponding products **49** were obtained in good yields with high enantioselectivity. Interestingly, the use of alkyl isocyanates selectively led to the formation of azaspiro[2. 4]heptanones **50**. Later, the authors explained the mechanism by some control experiments (Scheme 11) [32].

In 2009, the same group reported a palladium-catalyzed decarboxylative [4 + 2] cycloaddition of γ-methylidene-δ-valerolactones with isatins, By using a newly prepared phosphoramidite ligand, the desired spirooxindoles were obtained in good yields with excellent diastereoselectivity [33]. For exploring the development of asymmetric variant of this catalytic process, the authors employed chiral phosphoramidite **51** as a ligand. Notably, the reaction proceeded smoothly at 0 °C to give the corresponding spirooxindoles **52** with promising yields (70–98%). Interestingly, the



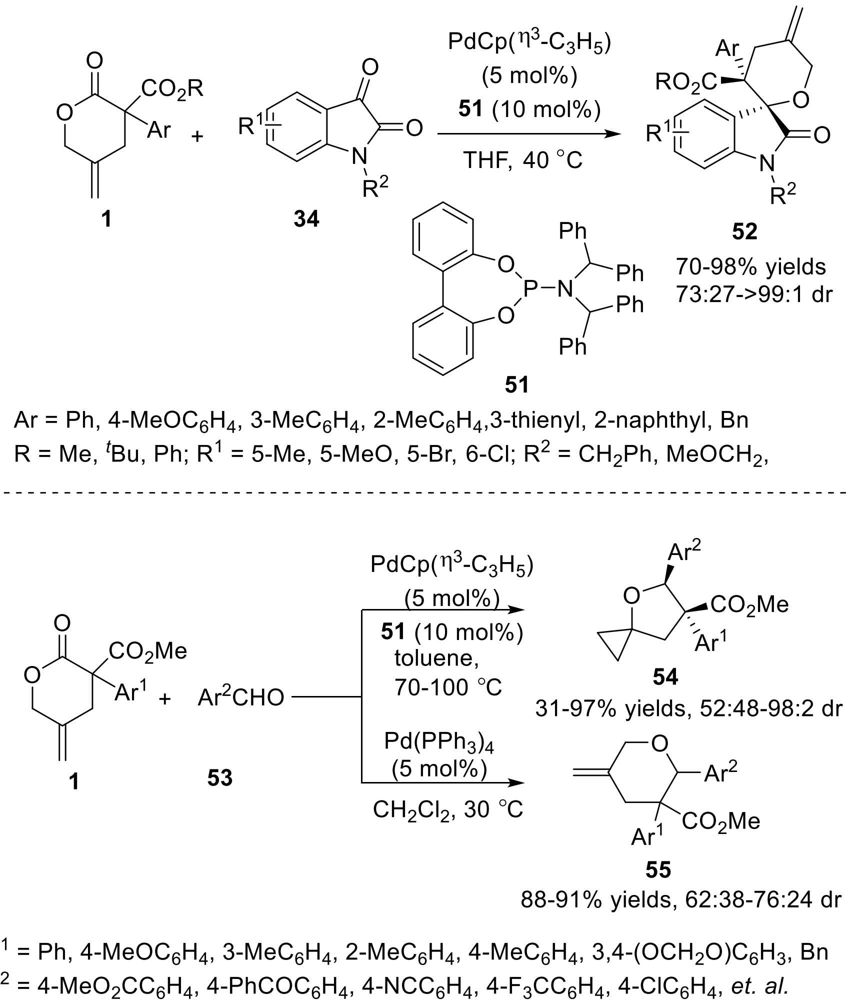
Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,3-thienyl, 3-furyl, 2-naphthyl, Bn
R = 4-MeOC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-ClC$_6$H$_4$, 3,5-(MeO)$_2$C$_6$H$_3$, Bn, ^{n}Bu

Scheme 11 Palladium-catalyzed asymmetric [4+2] cycloaddition of γ-methylidene-δ-valerolactones with isocyanate

4-oxaspiro[2. 4]-heptanes **54** were obtained using γ-methylidene-δ-valerolactones with aromatic aldehydes as reactive substrates in toluene in the presence of phosphoramidite ligand. However, the [4+2] cycloaddition occurred by using Pd(PPh$_3$)$_4$ as catalyst in CH$_2$Cl$_2$, affording the methylene-tetrahydropyrans in good yields with moderate diastereoselectivity (Scheme 12) [34].

In 2012, Hayashi and coworkers described a palladium-catalyzed decarboxylative [4+2] cycloaddition of γ-methylidene-δ-valerolactones with imines, leading to biologically and synthetically valuable piperidine derivatives in good yields with high diastereoselectivity [35]. It was worth noting that bulky *N*-diphenylphosphinoyl imines played the key role in the control of diastereoselectivity (91:9 *dr*). The relatively small *N*-tosyl species resulted in low diastereoselectivity (58:42 *dr*). Notably, α-alkyl lactones, a heteroaryl or an alkenyl imine could also give the corresponding products in high yields, albeit with lower diastereoselectivity (Scheme 13).

Pyridinium zwitterion is an important functional skeleton in organic synthesis that can be easily transformed into a series of useful heterocycles. In 2018, Yoo, Baik, and coworkers reported a palladium-catalyzed [4+2] cycloaddition

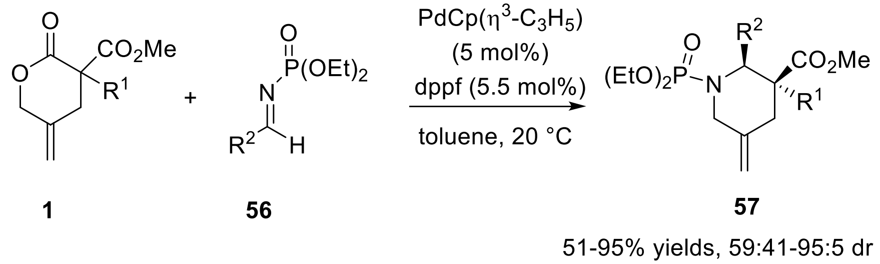


Ar = Ph, 4-$MeOC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4,3-thienyl, 2-naphthyl, Bn
R = Me, ^{t}Bu, Ph; R^1 = 5-Me, 5-MeO, 5-Br, 6-Cl; R^2 = CH_2Ph, $MeOCH_2$,

Ar^1 = Ph, 4-$MeOC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 3,4-(OCH_2O)C_6H_3, Bn
Ar^2 = 4-$MeO_2CC_6H_4$, 4-$PhCOC_6H_4$, 4-NCC_6H_4, 4-$F_3CC_6H_4$, 4-ClC_6H_4, *et. al.*

Scheme 12 Palladium-catalyzed decarboxylative [4 + 2] cycloaddition of isatins or aromatic aldehydes

reaction of γ-methylidene-δ-valerolactones **1** with pyridinium zwitterions **58**, affording a series of fused *N*-heterocyclic compounds **59** in high yields [36]. The authors proposed a plausible mechanism, as shown in Scheme 14, the generation of the Pd(II)-1,4-zwitterionic complex (**4**) first attacked C4 of the pyridinium zwitterion (**58**), giving intermediate **60**. Next, intramolecular cyclization of **60** gave the six-membered ring **61**. Finally, the desired product **59** was obtained by a second intramolecular cyclization of **61** and regenerated the Pd(0) catalyst (Scheme 14).



R^1 = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-naphthyl, 3-thienyl, Bn

R^2 = 4-MeOC_6H_4, 4-BrC_6H_4, 3-MeOC_6H_4, 3-ClC_6H_4, 2-MeC_6H_4, 3-thienyl, styryl

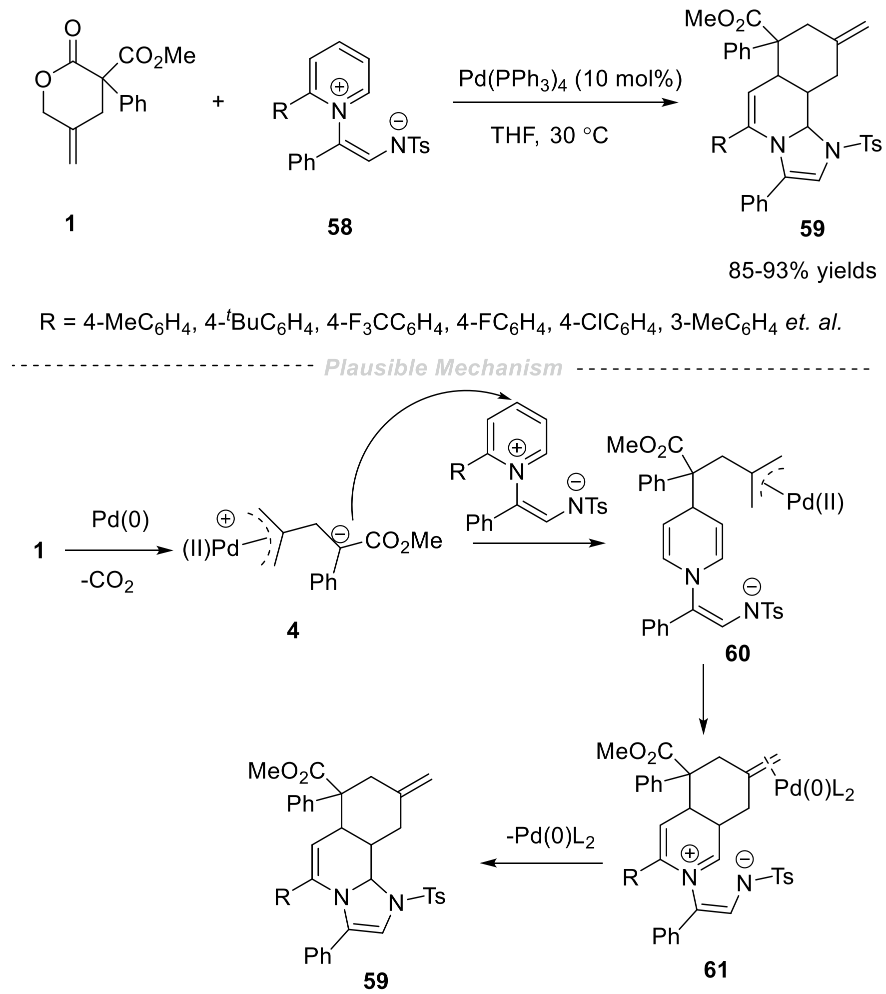
Scheme 13 Palladium-catalyzed [4 + 2] cycloaddition of imines

3.2 Benzoxazinanones as "1,4-Dipole" in [4 + 2] Annulations

In 2008, Tunge and coworkers reported a palladium-catalyzed [4 + 2] cycloaddition reaction by using vinyl benzoxazinanones and arylidene malononitriles as reactive substrates [37]. Condition optimization suggested that the reactions proceeded smoothly in CH_2Cl_2 at room temperature in the presence of Pd/Trost's ligand complex, producing the highly substituted dihydroquinolines **64** with high diastereoselectivity and enantioselectivity. It was noteworthy that the reaction selectivity was largely unaffected by the increased reaction temperature (Scheme 15).

Compared with the use of ligands containing phosphine and nitrogen, chiral sulfide-containing ligands are undeveloped, and only limited success is achieved. In 2016, Xiao and coworkers designed a chiral hybrid P,S ligand by combining chiral sulfides and phosphoramidites, which showed good stereocontrol in palladium-catalyzed [4 + 2] cycloaddition reaction of vinyl benzoxazinanones with nitroacrylates [38]. Screening of ligands showed that the β-amino sulfide backbone might play a vital role in the stereoinduction process, and a large variety of structurally useful tetrahydroquinolines were obtained in good yields with excellent enantioselectivity by using chiral P,S ligand **66**. Furthermore, the obtained products could be further converted to quinoline analogs, which exhibited widespread synthetic utility (Scheme 16).

Since the proof of concept was reported in 2001, the combination of transition metal with organocatalysis has undergone a tremendous development [39–46]. And a large number of unprecedented cycloaddition reactions involving transition metal with organocatalyst dual catalysis have been developed in laboratories worldwide. In 2016, Jørgensen and coworkers used a palladium/diphenylprolinol silyl ether synergistic catalysis, developing a [4 + 2] cycloaddition of vinyl benzoxazinanones and α,β-unsaturated aldehydes [47]. The influence of *N*-protecting groups in the vinyl benzoxazinanone was also tested under optimized reaction conditions; when *N*-protecting groups (Ts) were used, no desired product was obtained. The authors thought that this result was due to the poor nucleophilic character of the nitrogen atom in vinyl benzoxazinanone. In addition, the presence of acid was found to be crucial for

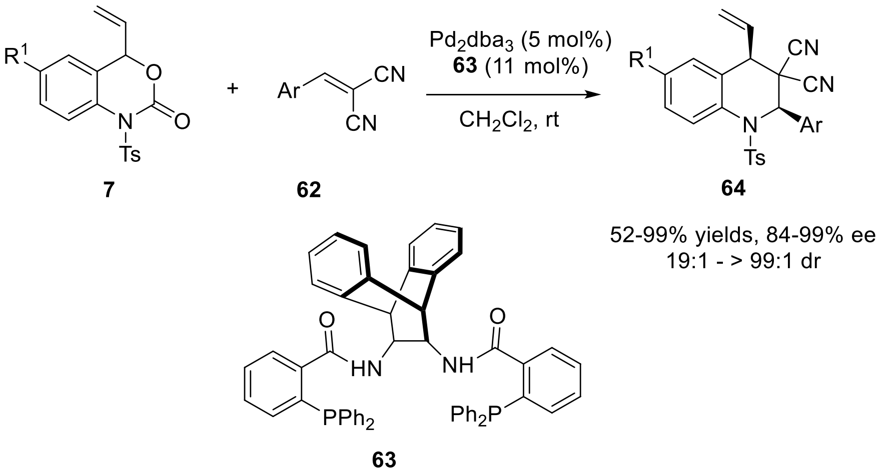


R = 4-MeC$_6$H$_4$, 4-^{t}BuC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-MeC$_6$H$_4$ *et. al.*

Scheme 14 Palladium-catalyzed [4 + 2] cycloaddition reaction of pyridinium zwitterion

the reaction to occur, which had a dual role: (1) acid could promote the condensation between the diphenylprolinol silyl ether catalyst and the aldehyde; (2) acid was crucial for the decarboxylation of 4-vinyl benzoxazinanones (Scheme 17).

A plausible mechanism was proposed involving the combination of palladium-catalyzed decarboxylation of vinyl benzoxazinanone with iminium-ion activated α,β-unsaturated aldehydes. As outlined in Scheme 18. Initially, vinyl benzoxazinanone reacted with palladium to produce intermediate **72** in a reversible oxidative addition, which subsequently underwent irreversible decarboxylation to form the π-allylpalladium complex **73** in the presence of acid. Simultaneously, intermediate **74** was obtained by the iminium-ion activated α,β-unsaturated aldehyde. Next, an enantioselective nucleophilic 1, 4-addition of intermediate **73** to intermediate

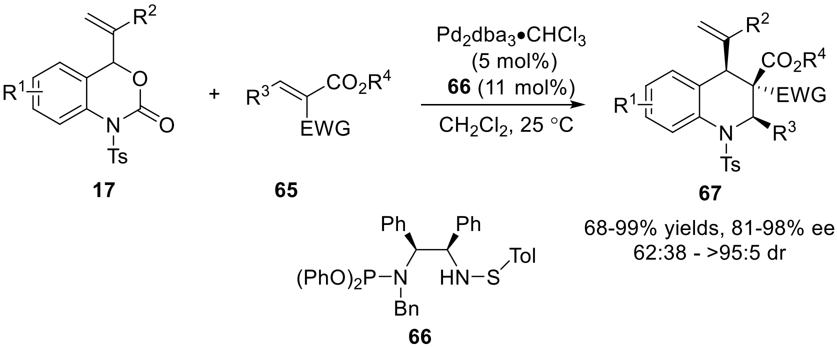


52-99% yields, 84-99% ee
19:1 - > 99:1 dr

R^1 = Me, MeO, H, F;

Ar = 4-$NO_2C_6H_4$, 2-$F_3CC_6H_4$, 4-$MeO_2CC_6H_4$, Ph, 4-$F_3CC_6H_4$, 4-$AcOC_6H_4$

Scheme 15 Palladium-catalyzed [4+2] cycloaddition reaction of arylidene malononitriles



68-99% yields, 81-98% ee
62:38 - >95:5 dr

R^1 = 6-Me, 6-MeO, H, 8-F, 7-Cl, 7-CF_3; R^2 = H, Me;

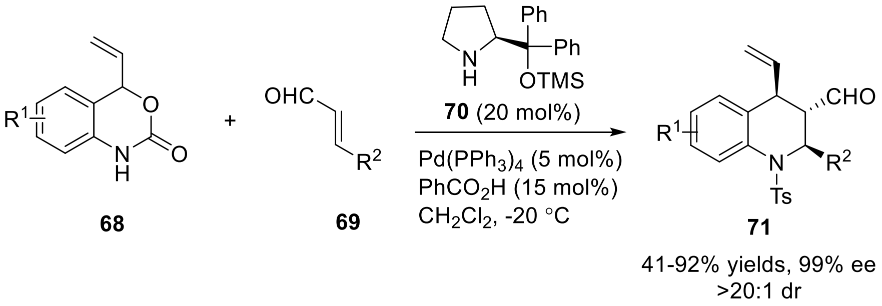
R^3 = 3-$MeOC_6H_4$, 2-MeC_6H_4, 4-MeC_6H_4, Ph, 3,4-$(OCH_2O)C_6H_3$, 2-naphthyl, 3-thienyl *et. al.*

R^4 = Me, ^{t}Bu; EWG = NO_2, CN

Scheme 16 Palladium-catalyzed [4+2] cycloaddition reaction of nitroacrylates

74 formed intermediate **75**. Finally, an enamine-catalyzed ring-closure reaction occurred to form of the vinyl tetrahydroquinoline **71** and release of the catalyst (Scheme 18).

Methyleneindolinones have emerged as versatile reactants for the construction of spirooxindole scaffolds in organic synthesis. In 2017, Shi and coworkers reported a palladium-catalyzed [4+2] cycloaddition of vinyl benzoxazinanones **7** with methyleneindolinones **76**, providing a series of chiral 3, 3′-spirooxindoles in high yields and with excellent diastereo- and enantioselectivity [48]. The experiment result suggested that raising the reaction temperature could improve the yield and the

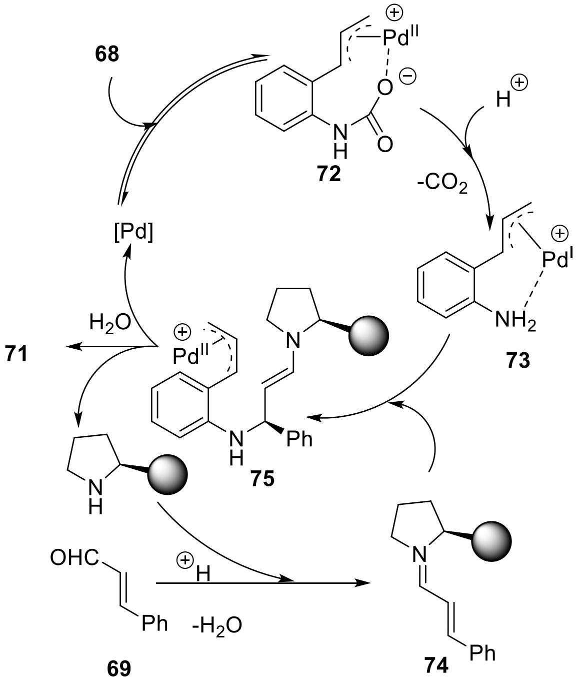


R^1 = 8-MeO, 7-MeO, H, 6-Me, 6-Cl, 7-CF_3

R^2 = 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, Ph, 2-$NO_2C_6H_3$, 2-naphthyl, ^{n}Bu *et. al.*

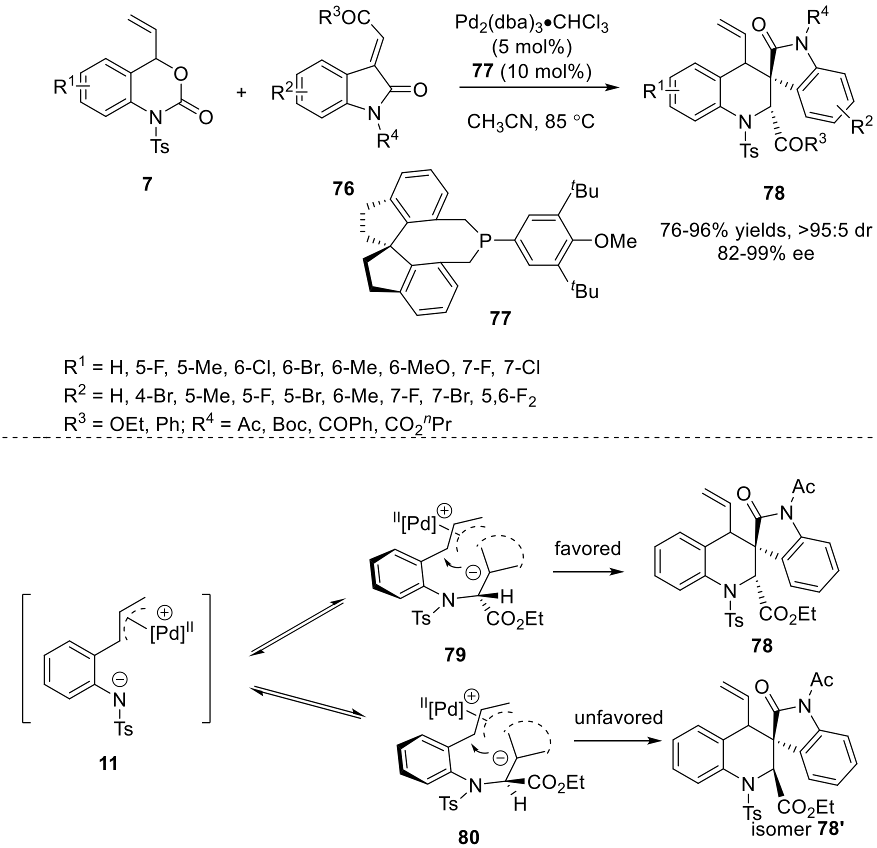
Scheme 17 Decarboxylative [4 + 2] cycloaddition by synergistic palladium and organocatalysis

Scheme 18 A plausible mechanism for decarboxylative [4 + 2] cycloaddition by synergistic palladium and organocatalysis



enantioselectivity. The authors thought that two new zwitterionic intermediates **79** and **80** might be produced by a reversible Michael addition of reactive intermediate **11** to methyleneindolinone **76**. Thus, raising the reaction temperature might play dual roles: (1) accelerating the intramolecular cyclization of the favorable **79**; (2) helpful for the unfavorable **80** to transform into the favorable **79** by the reversible Michael addition (Scheme 19).

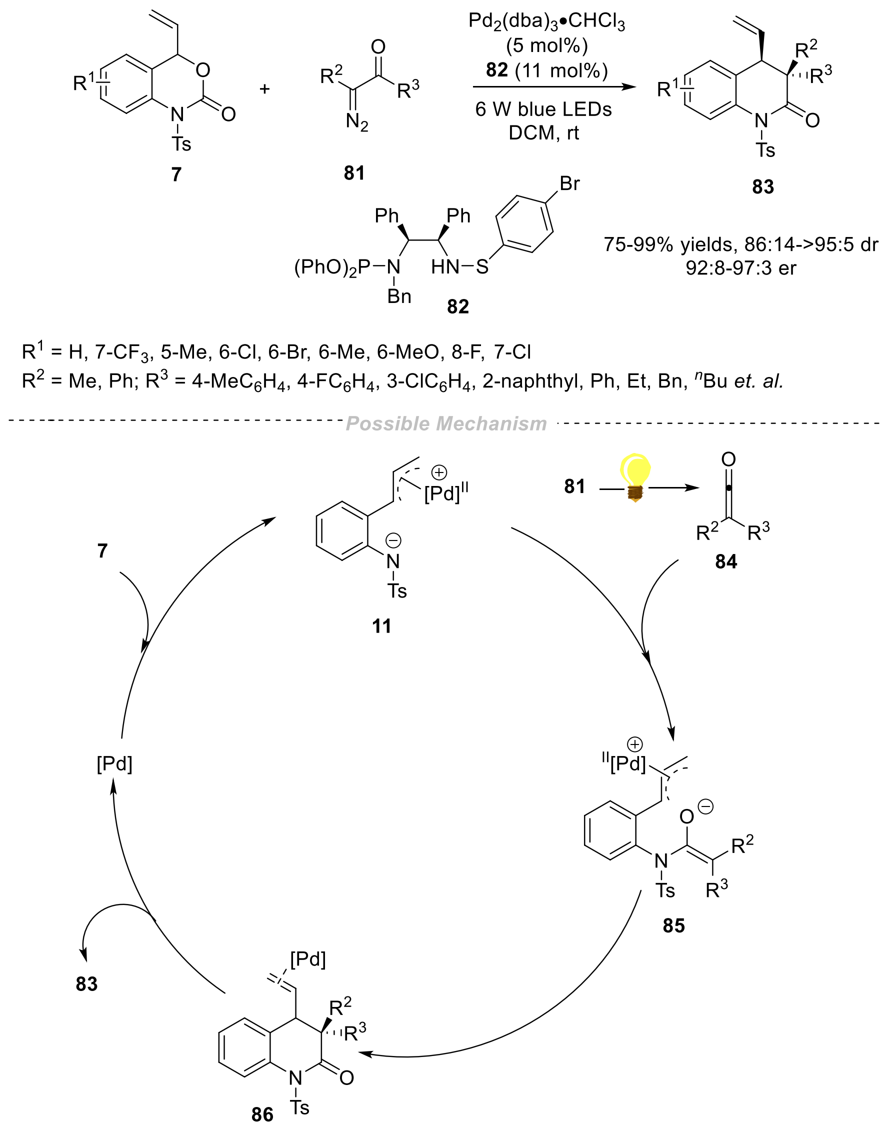
Visible-light photoactivation has demonstrated a powerful and promising method for the construction of valuable cyclic compounds in organic synthesis.



R^1 = H, 5-F, 5-Me, 6-Cl, 6-Br, 6-Me, 6-MeO, 7-F, 7-Cl
R^2 = H, 4-Br, 5-Me, 5-F, 5-Br, 6-Me, 7-F, 7-Br, 5,6-F$_2$
R^3 = OEt, Ph; R^4 = Ac, Boc, COPh, CO$_2{}^n$Pr

Scheme 19 Palladium-catalyzed [4 + 2] cycloaddition of methyleneindolinones

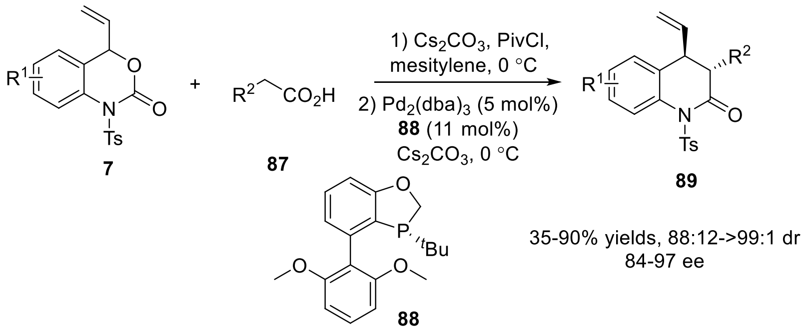
In 2017, Xiao and coworkers used visible-light photoactivation and palladium catalyst synergistic system, realizing a palladium-catalyzed [4 + 2] cycloaddition reaction of reactive ketene intermediates [49]. Under the optimized conditions, the authors examined the scope and limitation of the substrates. Notably, these reactions proceeded well, giving the corresponding products in excellent yields with high levels of asymmetric induction. The authors also explained why this photochemical approach to transiently generate ketenes in situ usually gave quinolinone products in higher yields than the direct use of prepared ketenes: although ketenes might decompose in the presence of Pd catalysts,it was much slower than the photolysis process and the Pd-catalyzed cycloaddition. Plausible mechanisms were proposed for this transformation. Initially, the Pd-containing 1,4-dipolar intermediate **11** was generated by palladium-catalyzed oxidative addition/decarboxylation processes. Simultaneously, ketene **84** was obtained by Wolff rearrangement of diazo compound under the visible-light-driven photocatalysis. Next, a nucleophilic addition of tosyl amide anion to ketene **84** would form a new zwitterionic intermediate **85**. Finally, the chiral quinolinone **83** was obtained



Scheme 20 Palladium-catalyzed [4 + 2] cycloaddition reaction of reactive ketene intermediates

by an intramolecular Pd-catalyzed AAA reaction of the enolate component and regenerated the palladium catalyst (Scheme 20).

In 2018, Deng, Tang, and coworkers accomplished a palladium-catalyzed [4 + 2] cycloaddition of 4-vinyl benzoxazinanones with carboxylic acids [50]. Under the optimized conditions, a broad range of vinyl benzoxazinanones and carboxylic acids were tested, and the reaction proceeded smoothly, affording diverse 3, 4-dihydroquinolin-2-ones in moderate to good yields with good to



R^1 = H, 6-Cl, 6-F, 6-Me, 6-MeO, 7-CF_3, 7-Cl, 7-Me
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-MeC_6H_4, 1-naphthyl, 2-naphthyl, 3-thienyl *et. al.*

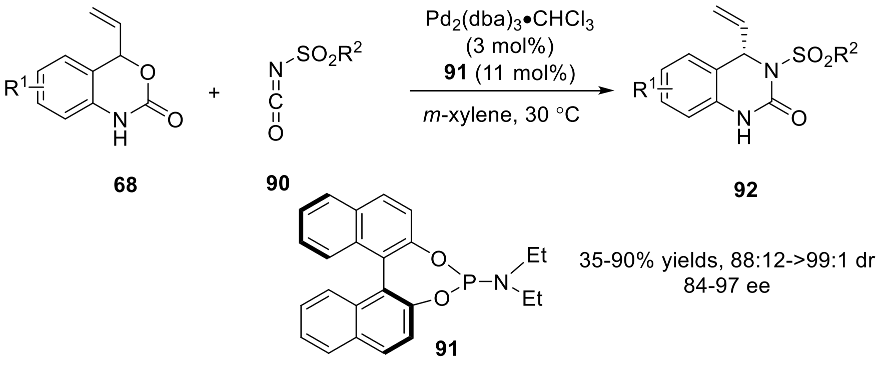
Scheme 21 Palladium-catalyzed [4 + 2] cycloaddition of carboxylic acids

excellent stereoselectivity. The authors found that the phenylacetic acids with electron-donating groups resulted in higher stereoselectivity than the phenylacetic acids with electron-withdrawing group. Mechanism studies suggested that 3, 4-dihydroquinolin-2-ones **89** with electron-withdrawing groups on the phenyl group could more easily undergo epimerization via keto−enol tautomerization in the presence of base, giving decreased *dr* and *ee* values (Scheme 21).

In 2018, Shi and coworkers reported the reaction of vinyl benzoxazinanones with sulfonyl isocyanates by using $Pd_2(dba)_3.CHCl_3$/ chiral ligand as catalyst and *m*-xylene as the solvent [51]. It is worth mentioning that various substituted substrates could participate in the reaction very well and exhibited good reactivity and stereoselectivity. In addition, the N–H group of vinyl benzoxazinanones **68** played an important role in controlling stereoselectivity of the reaction, and *N*-Ts-protected vinyl benzoxazinanone was used, only a moderate enantioselectivity (71:29 *er*) was obtained under the optimal reaction conditions (Scheme 22).

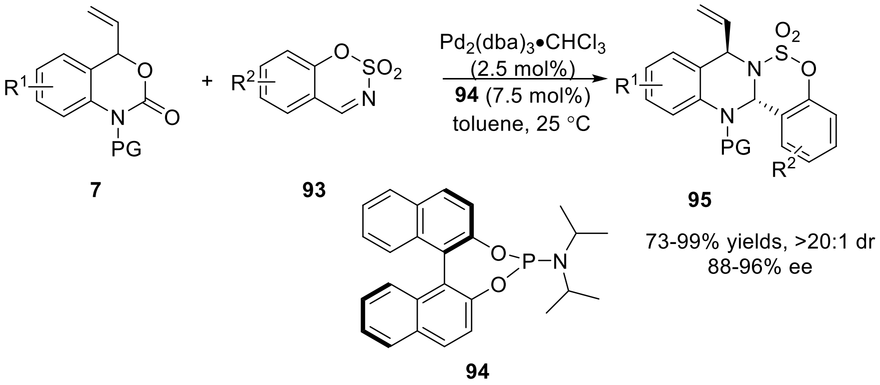
Shortly thereafter, Guo and coworkers disclosed a palladium-catalyzed [4 + 2] cycloaddition of vinyl benzoxazinones with sulfamate-derived cyclic imines. Using $Pd_2(dba)_3·CHCl_3$ as palladium source, various chiral ligands were evaluated, the use of $Pd_2(dba)_3·CHCl_3$ (2.5 mol%) and chiral ligand **94** (7.5 mol%) as the catalyst in toluene at room temperature was optimal, and provided the tetrahydroquinazolines in good to excellent yields with good to excellent diastereo- and enantioselectivity [52]. In 2019, Kim and coworkers reported a similar result using the same reaction condition (Scheme 23) [53].

Following this, Zhao and coworkers disclosed a method for the synthesis of enantioenriched barbiturate-fused spirotetrahydroquinolines, which constituted a class of structurally diverse and complex nitrogen-containing spiroheterocyclic scaffolds [54]. Under the indicated reaction conditions, a series of vinyl benzoxazinanones and barbiturate-based olefins were tested, and the reaction showed good tolerance, providing the desired products in up to 90% yield with up to > 99:1 *dr* and 97% *ee* (Scheme 24).



R^1 = H, 5-Cl, 5-F, 5-Me, 6-MeO, 6-Cl, 6-Me, 6-Br, 7-Me, 7-MeO *et. al.*
R^2 = 4-MeC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 2-MeC_6H_4,

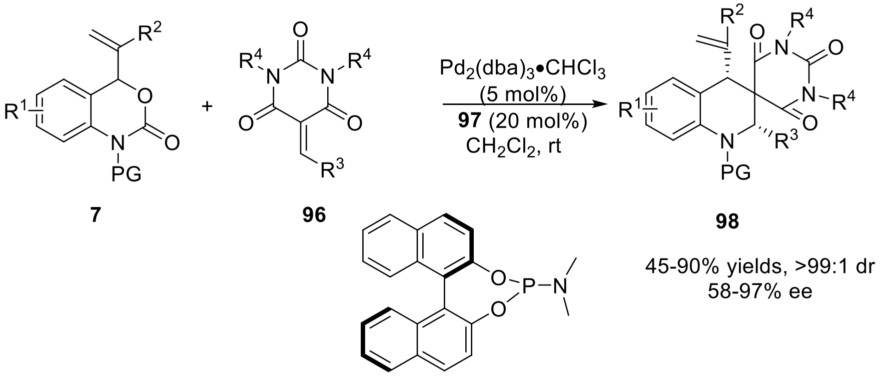
Scheme 22 Palladium-catalyzed [4 + 2] cycloaddition of sulfonyl isocyanates



R^1 = H, 6-Me, 7-Me, 6-F, 7-F, 6-MeO; PG = Ts, SO_2Ph
R^2 = 6-Me, 7-Me, 7-^{i}Pr, 7-^{t}Bu, 6-^{t}Bu, 7-OMe, 8-F, 6-Cl *et. al.*

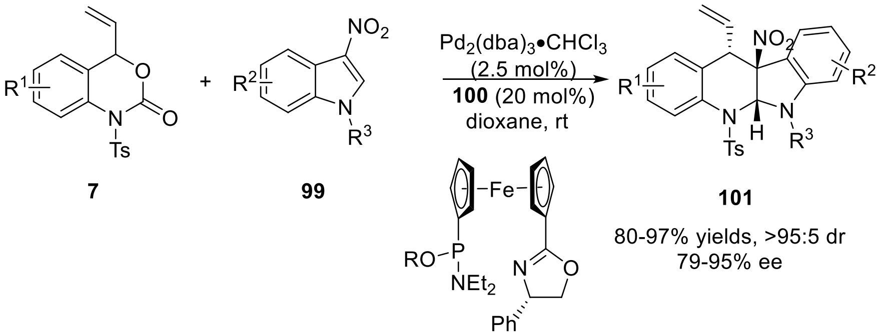
Scheme 23 Palladium-catalyzed [4 + 2] cycloaddition of sulfamate-derived cyclic imines

3-Nitroindoles are considered as 1, 2-synthons in organic synthesis and have been successfully used in the Pd-catalyzed cycloadditions through the dearomatization approach [55]. In 2019, Hou, Ding, and coworkers established a palladium-catalyzed asymmetric [4 + 2] cycloaddition of 3-nitroindoles and vinyl benzoxazinanones [56]. Using Pd/SIOCPhox ligands **100** as catalyst, the reaction proceeded smoothly in dioxane at room temperature, affording the corresponding products **101** with uniformly excellent diastereoselectivity and enantioselectivity. It was worth noted that the *N*-protecting group on the vinyl benzoxazinanone had certain influence on reactivity, no adducts were obtained when tosyl (Ts) group on the **99** were replaced with proton, nosyl, or acetyl (Scheme 25).



R^1 = H, 6-Me, 6-Br, 6-Cl, 7-F,7-Me, 7-Cl; PG = Ts, H, Bn; R^2 = H, Me
R^3 = Ph, 2-MeOC$_6$H$_4$, 2-BrC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-furyl, 2-naphthyl, ^{i}Pr *et. al.*
R^4 = Me, H

Scheme 24 Palladium-catalyzed [4 + 2] cycloaddition of barbiturate-based olefins

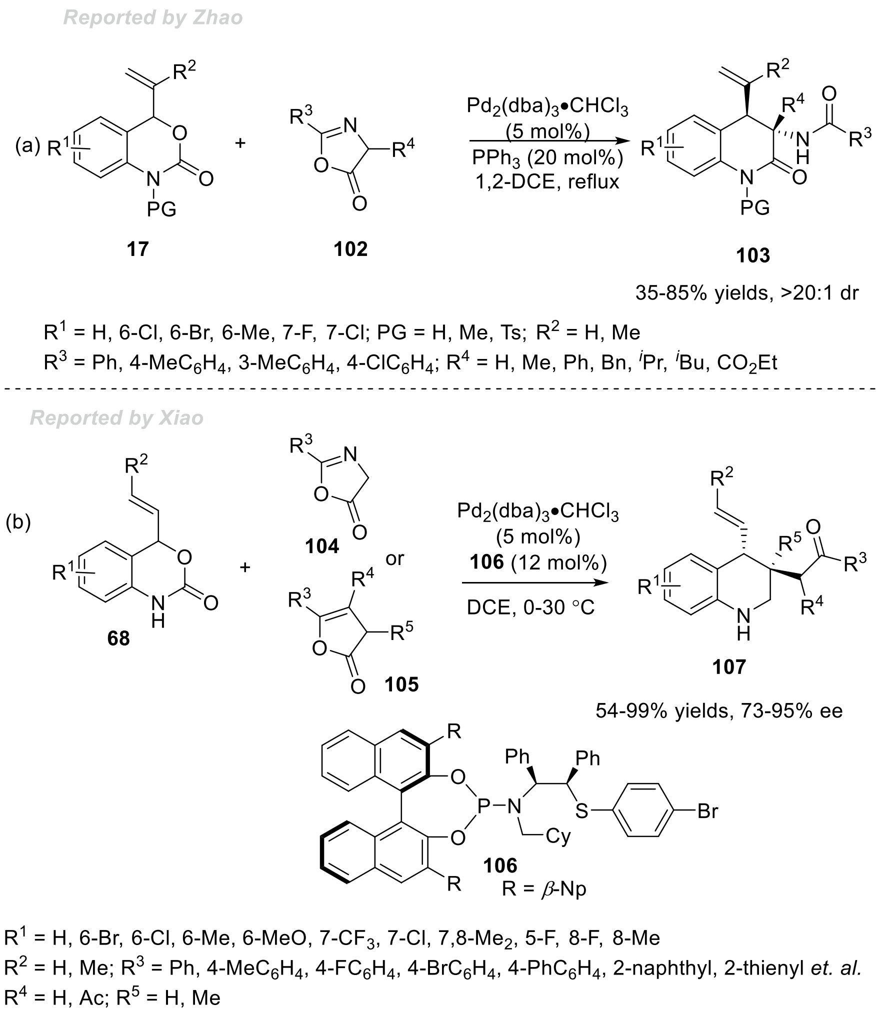


R = (*R*)-2′-hydroxy-1,1′-binaphthyl-2-yl
100

R^1 = H, 6-Me, 6-Br, 6-MeO, 7-Br, 8-Me
R^2 = 4-F, 4-Cl, 5-Br, 5-CO$_2$Me, 6-Cl, 6-Me, 7-CO$_2$Me, 6-CN; R^3 = Ts, CO$_2$Me, Boc

Scheme 25 Palladium-catalyzed asymmetric [4 + 2] cycloaddition of 3-nitroindoles

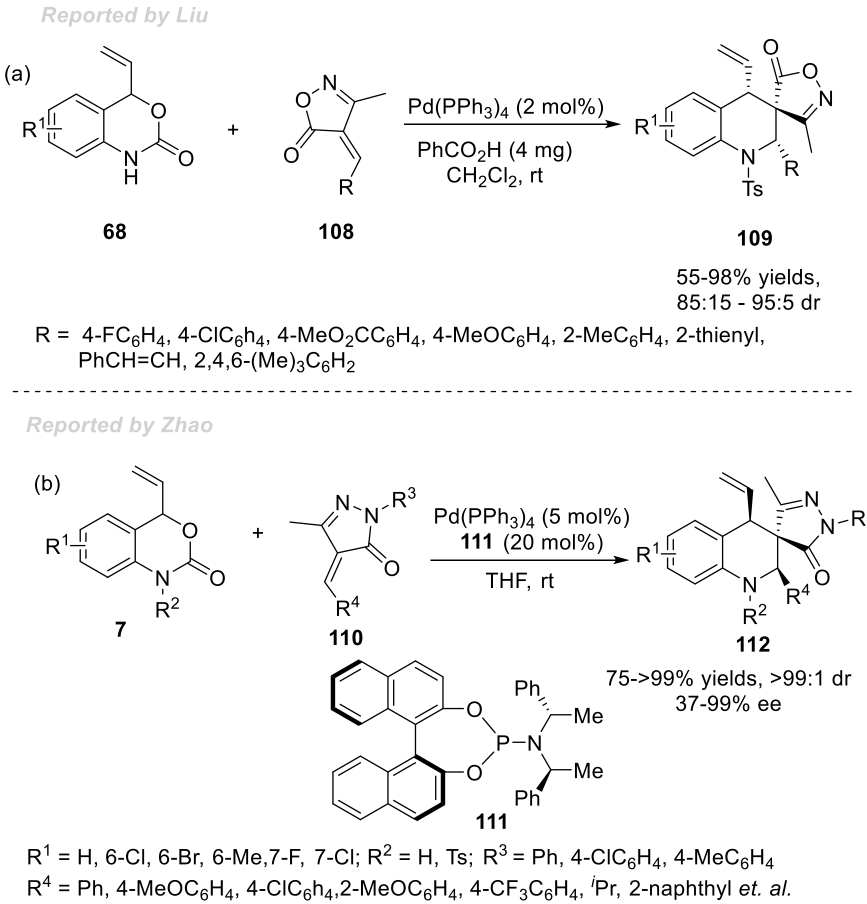
In the same year, Zhao and coworkers designed a palladium-catalyzed [4 + 2] cycloaddition of vinyl benzoxazinones with oxazol-5-(4*H*)-ones, furnishing a wide range of 3,4-disubstituted dihydro-2(1*H*)-quinolinones in the reasonable yields with excellent diastereoselectivity [57]. Notably, highest yield was obtained when the additive (PhCOOH) was used in 1,2-DCE at reflux in the presence of Pd$_2$(dba)$_3$·CHCl$_3$/PPh$_3$ catalyst (Scheme 26, a). Almost simultaneously, Xiao and coworkers used their hybrid P,S ligands, performing a palladium-catalyzed asymmetric [4 + 2] cycloaddition of vinyl benzoxazi-nones **68** with azlactones **104** and butenolides **105** [58]. A broad range of optically active 3,4-dihydroquinolin-2(1*H*)-ones



Scheme 26 Palladium-catalyzed [4 + 2] cycloaddition of oxazol-5-(4*H*)-ones

107 were produced in high yields and enantioselectivity (54% to > 99% yields, 73–95% *ee*) with excellent diastereoselectivity (> 95:5 *dr*). In addition, the DFT calculations were performed to illustrate the observed high level of enantio- and diastereocontrol (Scheme 26, b).

In 2020, Liu and coworkers developed a palladium-catalyzed [4 + 2] cycloaddition of arylidene-isoxazol-5-ones with vinyl benzoxazinanones, giving the desired compounds in high yields (Scheme 27, a) [59]. Later, Zhao and coworkers used arylidene pyrazolones and vinyl benzoxazinanones as reactive substrates, finishing a palladium-catalyzed [4 + 2] cycloaddition [60]. In this transformation, the reaction showed good tolerance, a wide variety of spiropyrazolones were obtained in excellent yields in THF at room temperature under $Pd(PPh_3)_4$/**111** complex catalysis. In

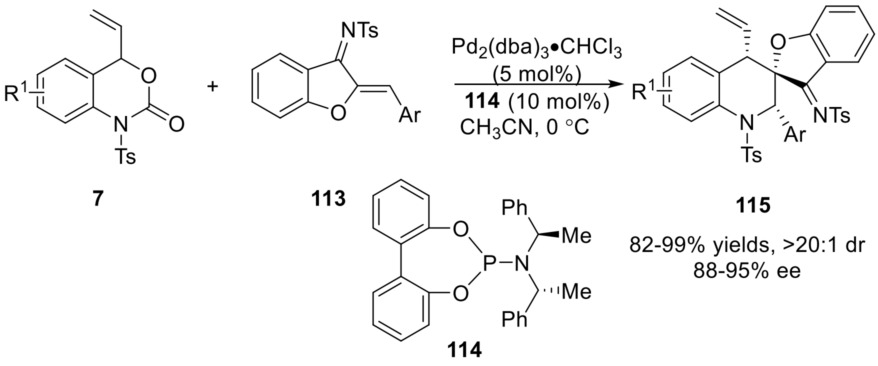


Scheme 27 Palladium-catalyzed [4+2] cycloaddition of arylidene-isoxazol-5-ones and arylidene pyrazolones

addition, the experiment showed that the excellent enantioselectivity and the lower yield were obtained by using $Pd_2(dba)_3$/**111** complex catalyst. The authors thought that a Pd(II)-π-allyl complex bearing one molecule of **111** and one molecule of PPh_3 might be produced in the presence of $Pd(PPh_3)_4$/**111** complex, which exhibited a higher reactivity in this reaction (Scheme 27, b).

Benzofuran-derived azadienes have be well used to serve as a four-atom synthon in various [4+*n*] annulation reactions. However, rare examples of **113** serving as two-atom synthons was used in the cycloaddition. In 2021, Zhao and coworkers illustrated a palladium-catalyzed [4+2] cycloaddition of vinyl benzoxazinanones with azadienes, generating an array of the desired spirotetrahydroquinolines **115** as a single diastereomer in high enantioselectivity (Scheme 28) [61].

Cooperative bimetallic catalysis has emerged as a powerful strategy for asymmetric catalysis and synthesis. In 2021, Lu and coworkers disclosed a Pd/Co



7 **113** **114** **115**

R^1 = H, 6-F, 6-Br, 6-Me,6-MeO, 7-F, 7-Cl, 7-Me

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-naphthyl *et. al.*

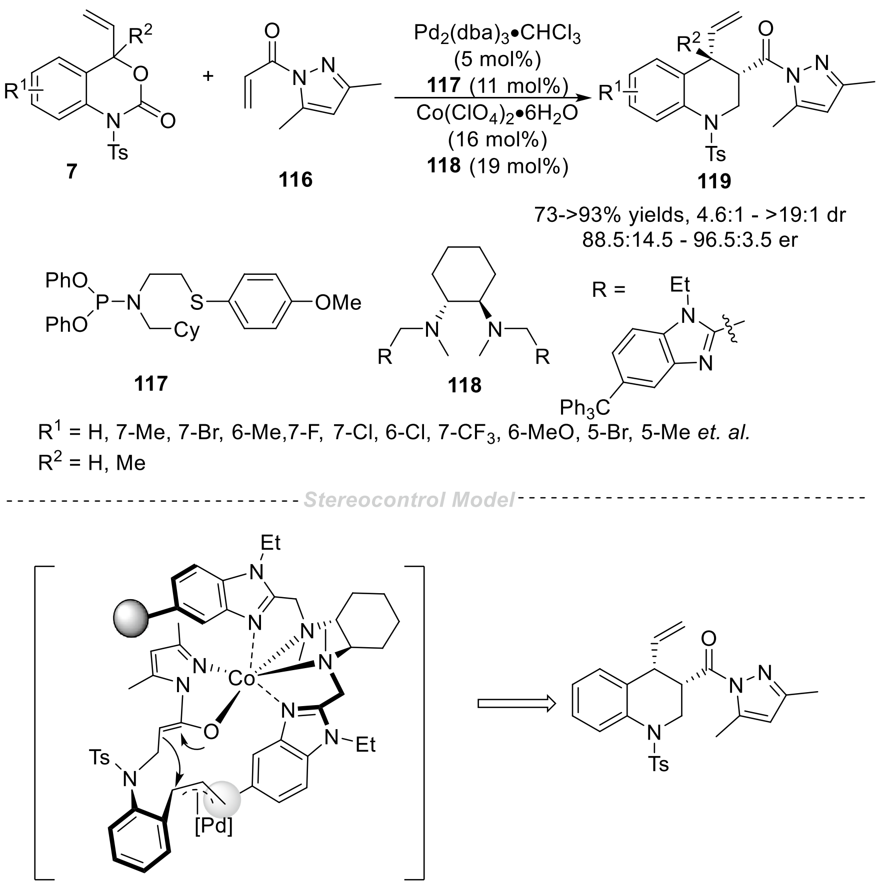
Scheme 28 Palladium-catalyzed [4 + 2] cycloaddition of azadienes

cooperative bimetallic catalysis system. The use of nonchiral Pd complexes and chiral Co complexes, an enantioselective [4 + 2] cycloaddition of vinyl benzoxazinones and *N*-acylpyrazoles was successfully realized [62]. The reaction applied to a variety of vinyl benzoxazinones and bearing various substituents on the different positions of the benzene ring could be well tolerated. In addition, the authors proposed a stereoinduction model to rationalize the stereochemical outcome (Scheme 29).

In 2022, Li, Liu, and coworkers used a Pd(0)/Cu(I) bimetallic catalytic system, achieving an asymmetric [4 + 2] cycloaddition of 3-cyanocoumarins with vinyl benzoxazinones [63]. The reaction proceeded smoothly, producing the coumarin-derived condensed rings **123** in high yields with excellent diastereoselectivity and enantioselectivity. While the substituents of vinyl benzoxazinones **7** in the benzene ring played the key role in reaction activity and enantioselectivity, when the authors evaluated the scope of vinyl benzoxazinones, only *N*-CO_2Et showed good enantioselectivity. In addition, The mechanistic studies revealed that the chiral Cu(I) and chiral Pd(0) complex were indispensable, in which the Cu(I)-Box complex as an available Lewis acid catalyst activated 3-cyanocoumarin, and chiral Pd(0) complex activated benzoxazinone by the formation of π-allyl-palladium intermediate (Scheme 30).

The reaction of vinyl benzoxazinanones with ketones usually suffered from low reactivity and selectivity. To solve this challenge, Huang, Yang, and coworkers used pyrazolone 4,5-diones with vinyl benzoxazinanones as reactive substrates, achieving a palladium-catalyzed asymmetric [4 + 2] annulation [64]. The reaction has a broad substrate scope, in most cases, affording the corresponding adducts in moderate to good yield with high enantioselectivity (Scheme 31).

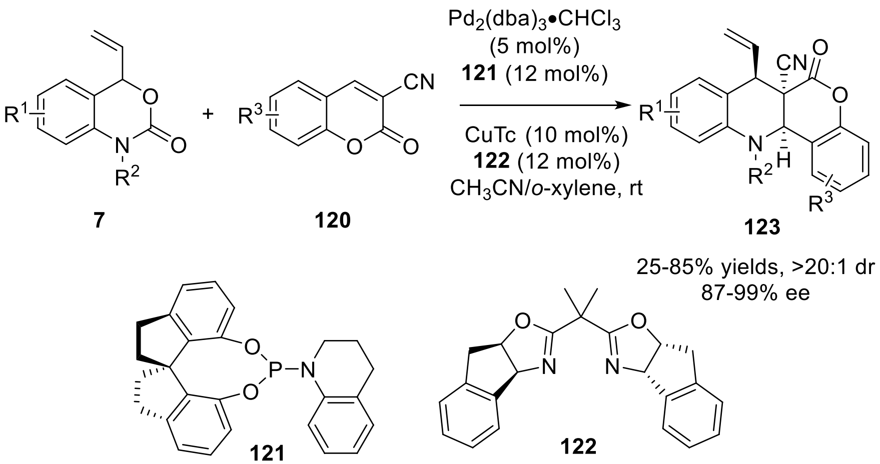
In 2023, Huang and coworkers developed a highly efficient palladium-catalyzed stereodivergent [4 + 2] annulation reaction of vinyl benzoxazinaones and seven-membered cyclic *N*-sulfonyl aldimines [65]. Under the optimized conditions, a broad range of tetrahydroquinoxalines containing [6.7]-fused *N*-heterocycles **129** and **130** were obtained in good yield and excellent diastereodivergency. Interestingly, the



Scheme 29 Pd/Co cooperative catalyzed [4 + 2] cycloaddition of *N*-acylpyrazoles

experiment result suggested that the selective formation of *anti*- and *syn*-diastereoisomers was easily achieved by the simple variation of solvents. In addition, all four stereoisomers of the [6.7]-fused *N*-heterocycle products could be prepared with a simple switch of the configuration of chiral ligand **128** using different solvents (Scheme 32).

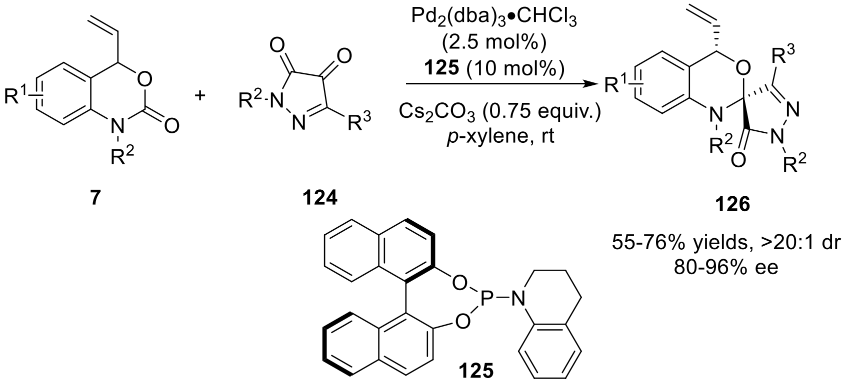
ortho-Allyl anilines could undergo allylic C–H oxidation to act as vinyl benzoxazinanones, which achieved the desired 1,4-dipoles, In 2021, Li, Liu, and coworkers reported palladium-catalyzed asymmetric [4 + 2] cycloadditions of *ortho*-allyl anilines and electron-deficient alkenes [66]. In this transformation, various aromatic and heteroaromatic amines were well tolerated, and a wide range of hydroquinolines were obtained in moderate to high yields, diastereoselectivity, and enantioselectivity. Notably, *meta*-chloride, *meta*-trifluoromethyl, and bulky substituent (^{i}Pr) at the *para*-position of *ortho*-allyl anilines gave unsatisfactory yields. In addition, the authors proposed a plausible reaction mechanism. Initially, an allylic C–H oxidation of 2, 5-DMBQ to *ortho*-allyl anilines and subsequent coordinated with Pd(0)



R^1 = H, 6-F, 6-Br, 5-Me,6-MeO, 7-Me, 6-Cl, 5-Me, 7-Cl, 7-Br

R^2 = Troc, CO$_2$Et; R^3 = H, 6-Me, 6-MeO, 6-F, 6-Cl, 7-Me, 7-MeO, 8-Meo, 8-F *et. al.*

Scheme 30 Pd(0)/Cu(I) synergistic catalyzed asymmetric [4+2] cycloaddition of 3-cyanocoumarins with vinyl benzoxazinones

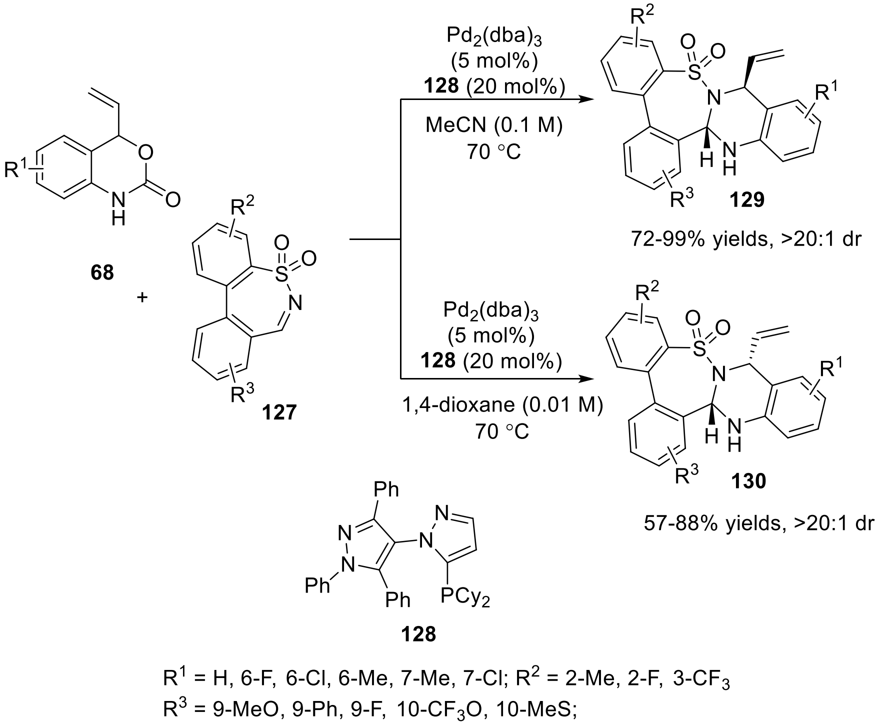


R^1 = H, 6-F, 6-Cl, 6-Me, 7-Me, 7-F, 7-Cl, 7-Br

R^2 = 3-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-BrC$_6$H$_4$ *et. al.*; R^3 = Me

Scheme 31 Palladium-catalyzed asymmetric [4+2] annulation of vinyl benzoxazinanones with pyrazolone 4, 5-diones

complex generated π-allyl-palladium intermediate **134**. Next, a pair of zwitterionic intermediates **135** and **135’** might be obtained by a reversible aza-Michael addition of **134** to electron-deficient olefin **62**. Finally, the intramolecular allylic alkylation provided the sterically more favored product **133** and regenerated the palladium catalyst (Scheme 33).

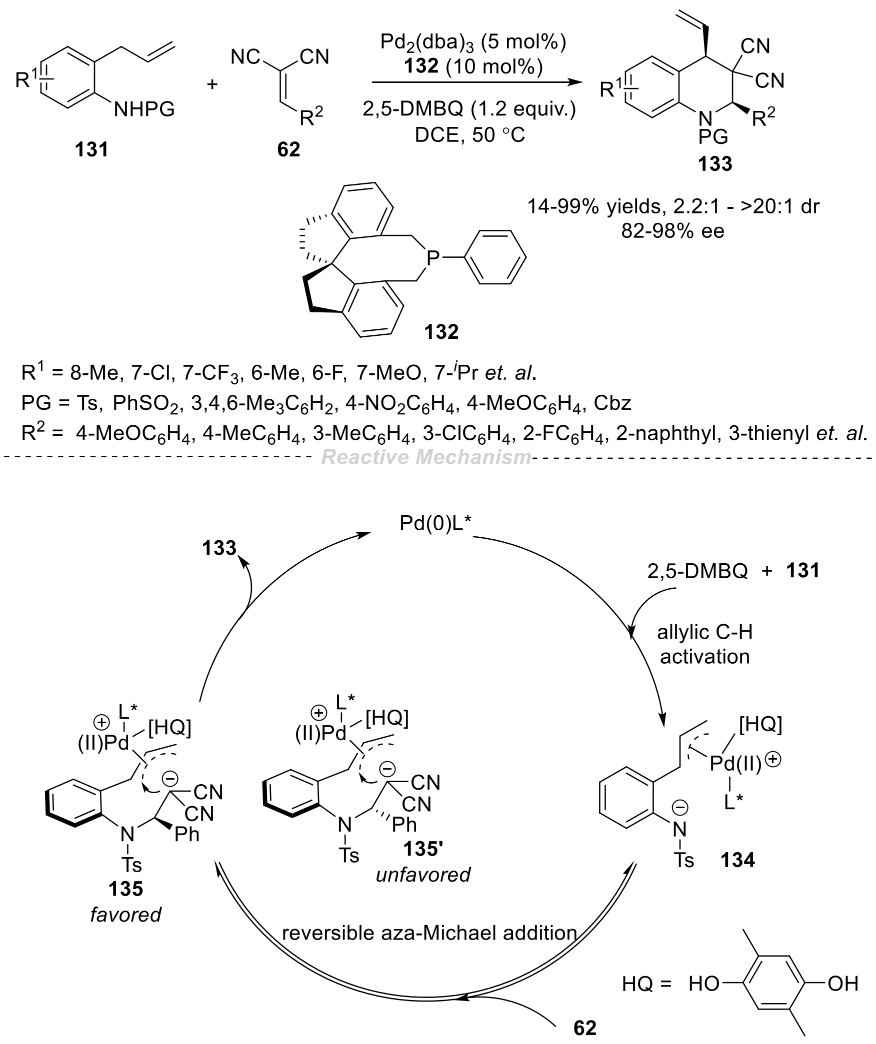


Scheme 32 Palladium-catalyzed stereodivergent [4+2] annulation reaction of vinyl benzoxazinaones and seven-membered cyclic *N*-sulfonyl aldimines

More recently, Li and coworkers developed new kinds of *P*-chiral ligands. The novel *P*-chiral ligands showed good stereocontrol ability in palladium-catalyzed asymmetric cycloaddition reaction of vinyl benzoxazinanone with α-arylidene succinimides [67]. The authors found that diastereoselectivity could be changed by switching appropriate ligands. When the *P*-chiral ligands were used in this reaction, the desired adducts (*S*, *R*, *S*)-**137** were obtained in good yields with diastereoselectivity and enantioselectivity. Using the Pd/**111** complex as the catalyst, the reaction proceeded smoothly to produce the diastereoisomers (*R*, *R*, *R*)-**137**. Obviously, these reported methodologies showed a bright prospect to the stereodivergent synthesis of spiro compounds from the same set of starting materials, which are important molecular skeletons that widely occur in natural molecules, pharmaceuticals, and functional materials (Scheme 34).

3.3 Allyl Carbonates as a "1,4-Dipole" in [4+2] Annulations

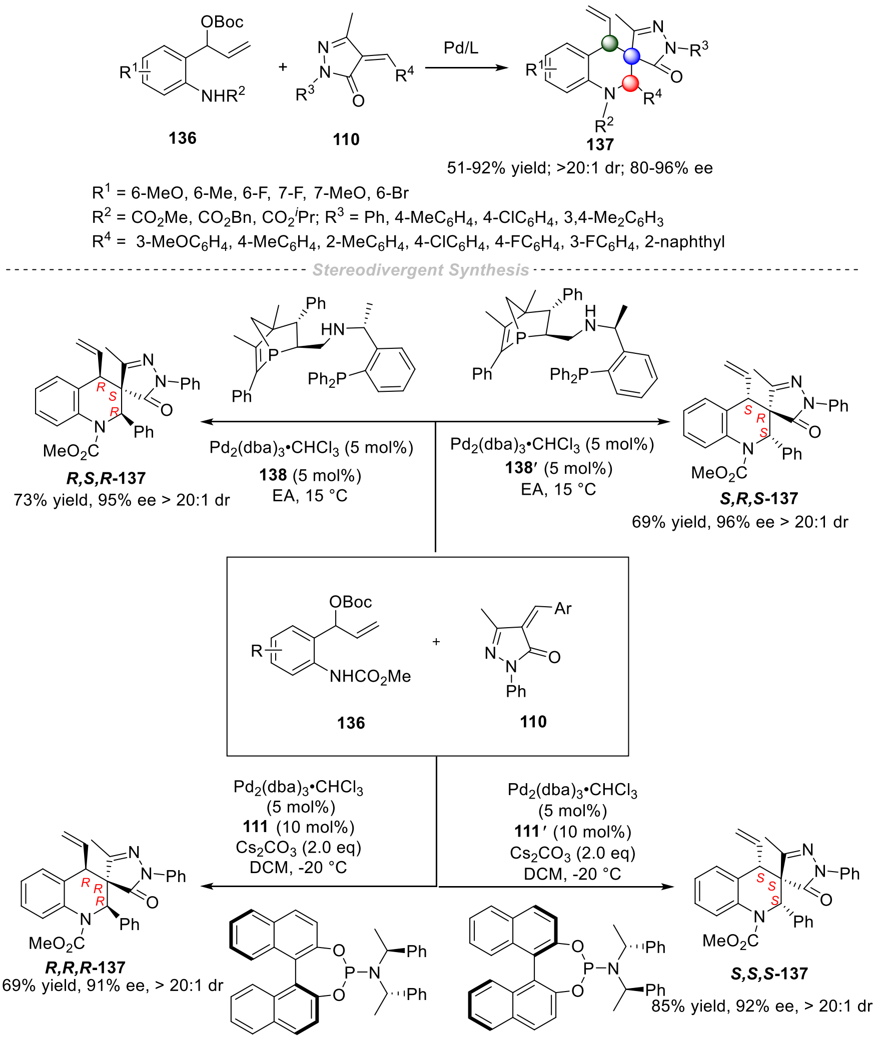
In 2006, Tunge and coworkers developed a new 6-vinyl oxazinanones as 1,4-dipole synthon, firstly achieving a palladium-catalyzed [4+2] cycloaddition of arylidene malononitriles [68]. In 2017, Yao, Lin, and coworkers described a



Scheme 33 Palladium-catalyzed asymmetric [4 + 2] cycloadditions of *ortho*-allyl anilines

palladium-catalyzed [4 + 2] cycloaddition of *para*-quinone methides with allyl carbonates, affording the desired 2-oxaspiro-cyclohexadienones in moderate to good yields and diastereoselectivity [69]. Notably, the carbonate ester was crucial for reactivity of this reaction, only -$OCO_2{}^tBu$ group resulted in the highest reactivity (94% yield). In addition, an asymmetric [4 + 2] annulation reaction was also examined by using chiral ligands, unfortunately, only moderate enantioselectivity was obtained after screening considerable reaction conditions (Scheme 35).

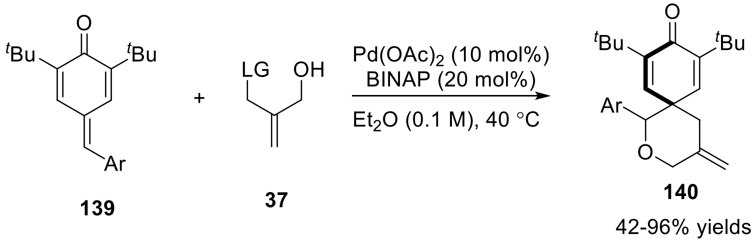
In 2020, Ni, Song, and coworkers reported a palladium-catalyzed [4 + 2] cycloaddition of 2-alkenylbenzothiazoles with allyl carbonates [70]. A variety of 2-alkenylbenzothiazoles bearing either electron-withdrawing or electron-donating groups



Scheme 34 Palladium-catalyzed asymmetric [4 + 2] cycloaddition reaction of α-arylidene succinimides

on the aromatic group were tested; in most cases, the corresponding cycloadducts were obtained with good to excellent yields and excellent diastereoselectivity. Regrettably, only moderate enantioselectivity (37% *ee*) was obtained by an extensive screening of chiral bidentate ligands. In addition, further synthetic transformation demonstrated the potential utility of 3-methylenetetrahydropyrans (Scheme 36).

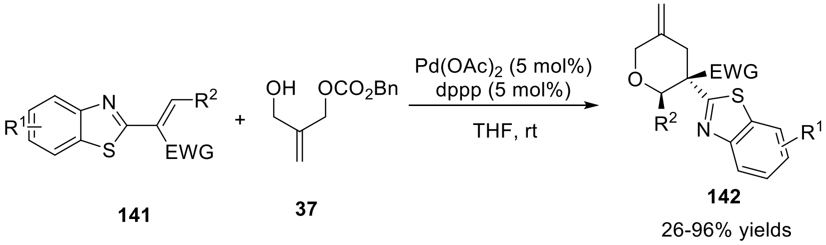
In 2022, Guo and coworkers applied a type of new hydroxy-tethered allyl carbonates as valuable precursors for the formation of 1,4-*C*,*O*-dipole allylpalladium intermediates, developing a palladium-catalyzed [4 + 2] cycloaddition of various electron-deficient alkenes [71]. The transformation showed good tolerance, the authors used five types of electron-deficient alkenes as reactive substrates, in



Ar = Ph, 3-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 2-naphthyl, 2-thienyl *et. al.*

Entry	Leaving group	Yield (%)
1	OCO$_2$Me	64
2	OCO$_2$Et	70
3	OCO$_2$^{i}Pr	92
4	OCO$_2$^{t}Bu	94
5	OCO$_2$Bn	88
6	OAc	nr
7	OPO(OPh)$_2$	nr

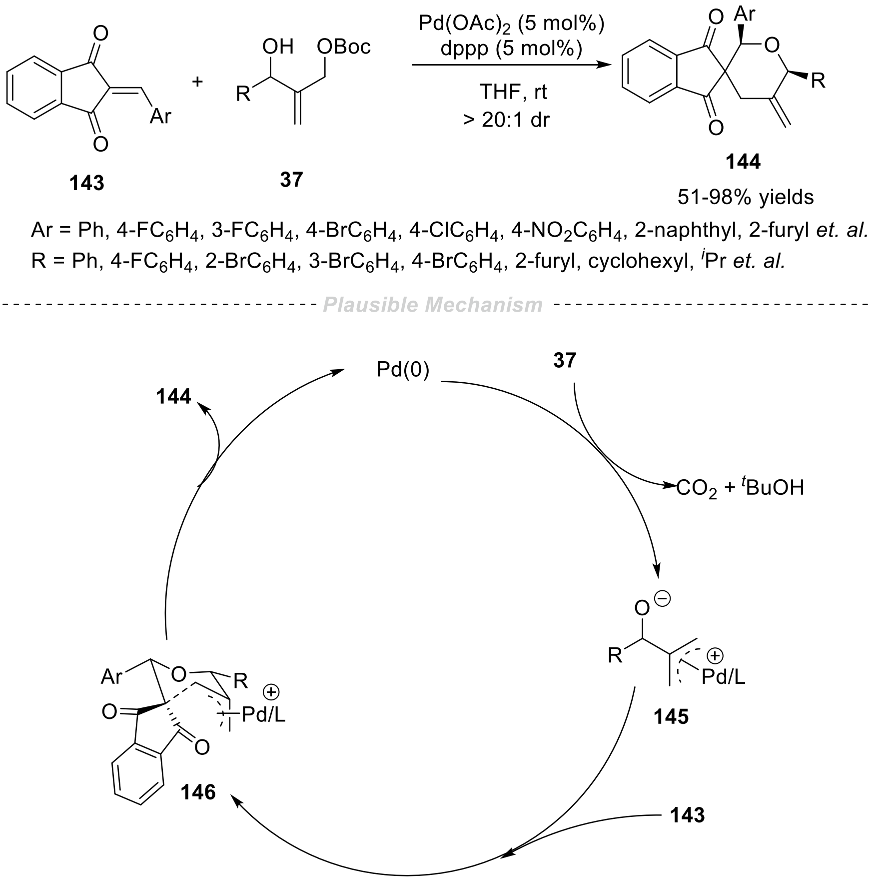
Scheme 35 Palladium-catalyzed [4 + 2] cycloaddition of *para*-quinone methides with allyl carbonates



R^1 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-naphthyl, 2-thienyl *et. al.*
R^2 = H, 5-Cl; EWG = CN, CO$_2$Et

Scheme 36 Palladium-catalyzed [4 + 2] cycloaddition of 2-alkenylbenzothiazoles

most cases, the desired tetrahydropyrans could be produced in moderate to high yields with excellent *dr* values. Despite all this, the substituents of indandione-based alkenes had remarkably negative effect on the reaction, strong electron-withdrawing (2-NO$_2$ and 4-NO$_2$) and 1-naphthyl-substituted alkenes failed to form the cycloadducts. In addition, the authors proposed a plausible mechanism. Initially, π-allylpalladium intermediate **145** was produced through palladium-catalyzed decarboxylation/deprotonation by the release of CO$_2$ and ^{t}BuOH. Subsequently, the treatment of intermediate **146** to 2-arylideneindane-1, 3-dione **143**



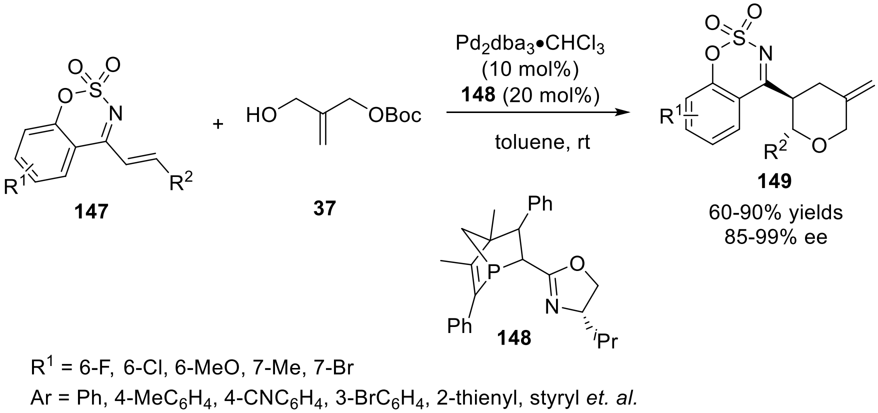
Ar = Ph, 4-FC_6H_4, 3-FC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-naphthyl, 2-furyl *et. al.*
R = Ph, 4-FC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-furyl, cyclohexyl, ^{i}Pr *et. al.*

Scheme 37 Palladium-catalyzed [4+2] cycloaddition of allyl carbonates with various electron-deficient alkenes

gave the intermediate **146**, which finally underwent an intramolecular cyclization to produce the product **144** and regenerated the palladium catalyst (Scheme 37).

Sulfamate-derived cyclic imines are generally identified in natural products and pharmaceuticals. They are also widely used as chiral auxiliaries and important synthetic reagents in various catalytic asymmetric strategies. In 2022, Li and coworkers designed a novel P-chiral ligands, which was called Mengphos. The authors realized an asymmetric [4+2] cycloaddition of sulfamate-derived cyclic imines with allyl carbonates under the catalysis of Pd/Mengphos complex [72]. In this reaction, the Mengphos ligands demonstrated excellent performance in site selectivity and enantioselectivity, affording the desired tetrahydropyrans **149** in high yields and up to 99% *ee*. In addition, further DFT study were performed to afford the energy profile of the Michael addition step and ring formation step (Scheme 38).

2-Alkylidene-trimethylene carbonates that were first synthesized by Tsuji and coworkers in 1984 [73], acted as a new type of 1,4-dipole synthon by Hayashi and

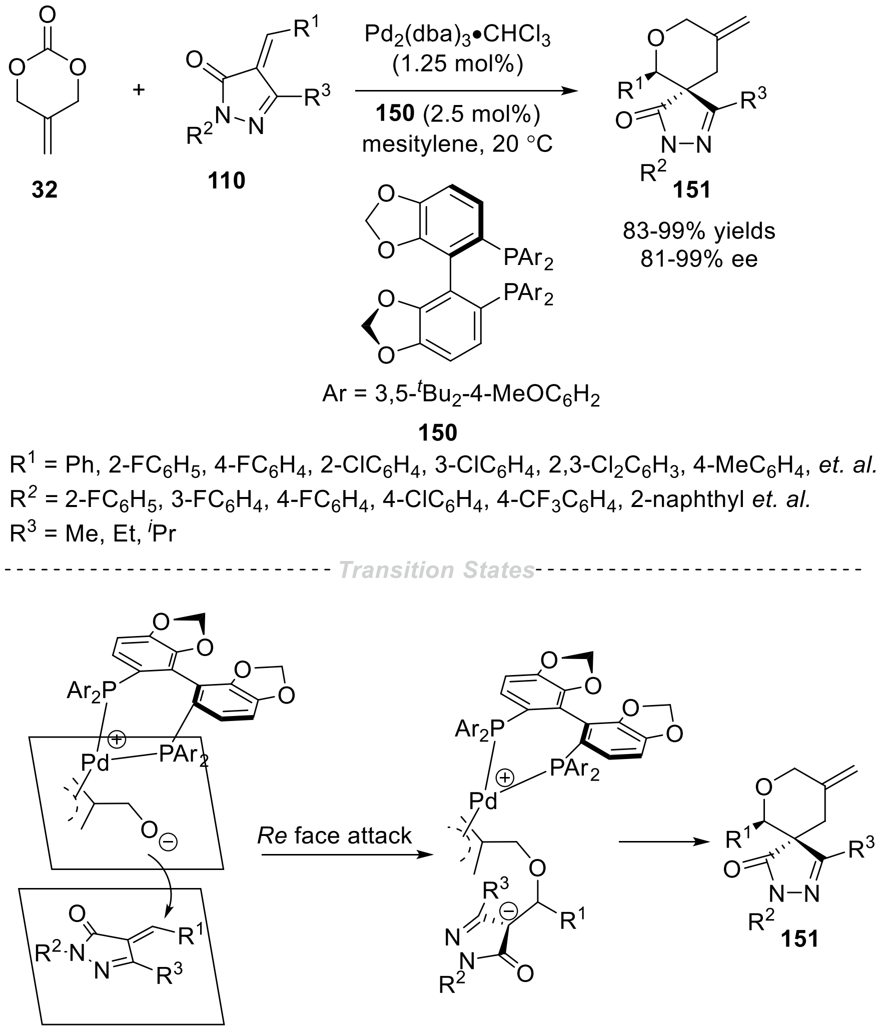


Scheme 38 Palladium-catalyzed [4+2] annulations of sulfamate-derived cyclic imines

coworkers in 2011 and applied it in palladium-catalyzed nonasymmetric decarboxylative cyclopropanation or [4+2] cycloaddition with alkylisocyanates [74]. Encouraged by this result, Guo and coworkers reported a palladium-catalyzed asymmetric [4+2] cycloaddition of 2-methylidenetrimethylene carbonate with unsaturated pyrazolones [75]. The reaction showed good tolerance, three types of electron-deficient alkenes (including unsaturated pyrazolones, indandione-derived alkenes, and barbiturate-derived alkenes) were used, the reaction proceeded smoothly to afford corresponding products in good to excellent yields with excellent enantioselectivity. It was noted that 2-thienyl-substituted alkene was not suitable substrate. The authors thought that the electron-rich thienyl group might decrease the reactivity of olefinic bond or the catalytic activity of the palladium catalyst through coordination. In addition, a plausible transition state model was proposed to reveal the enantioselectivity of reaction (Scheme 39). In 2022, the authors finished a palladium-catalyzed [4+2] cycloaddition of 5-methylene-1,3-oxazinan-2-ones with 4-arylidene-2,4-dihydro-3*H*-pyrazol-3-ones, generating the desired spiropyrazolones in high yields with excellent diastereoselectivity by employing $Pd_2(dba)_3 \cdot CHCl_3$ /PPh_3 as the catalyst [76].

In 2021, Lu and coworkers applied photo/palladium cooperative system, carrying out asymmetric [4+2] cycloadditions of 2-alkylidenetrimethylene carbonates with ketenes [77]. With 6 W blue LEDs as the light source, Pd/chiral P, olefin ligand complex as catalyst, a variety of ketenes in situ generated from α-diazoketones and 2-alkylidenetrimethylene carbonates could participate in this cycloaddition well, and diverse chiral lactones were delivered in generally good yields and selectivity. Unfortunately, as alkyl-substituted 2-alkylidenetrimethylene carbonates were applied under the standard conditions, the desired lactone products were not obtained. In addition, two selected transformations were performed to illustrate the utility of this methodology (Scheme 40).

In 2022, Yuan and coworkers reported a palladium-catalyzed [4+2] cycloaddition of 2-alkylidenetrimethylene carbonates with 3-nitroindoles, affording a wide range of indoline-fused tetrahydropyrans in good yields [78]. This reaction featured

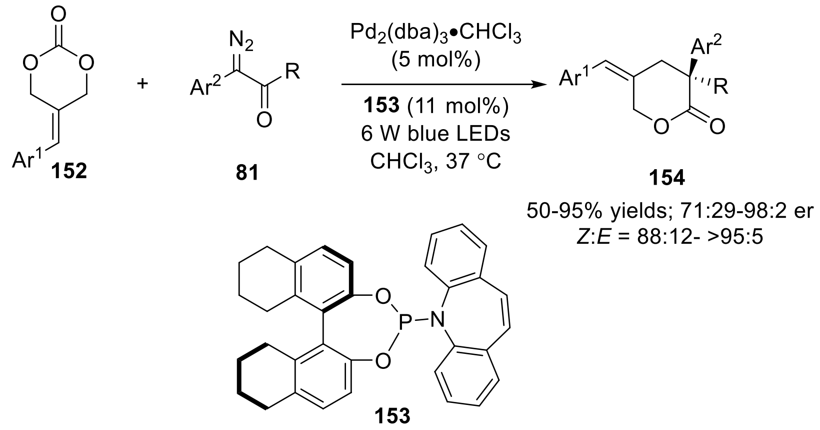


R^1 = Ph, 2-FC_6H_5, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 2,3-$Cl_2C_6H_3$, 4-MeC_6H_4, *et. al.*
R^2 = 2-FC_6H_5, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 2-naphthyl *et. al.*
R^3 = Me, Et, ^{i}Pr

Scheme 39 Palladium-catalyzed asymmetric [4 + 2] cycloaddition of unsaturated pyrazolones

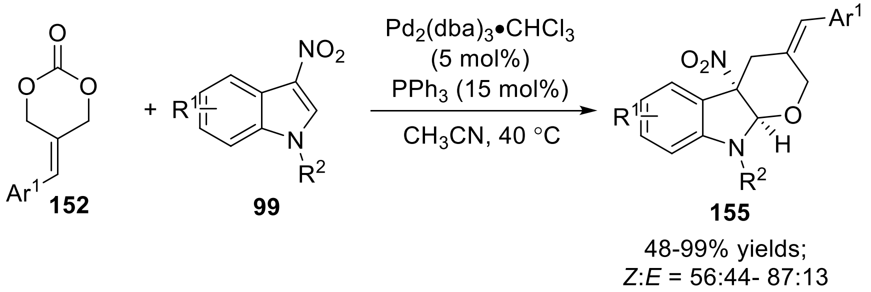
a wide substrate scope and mild condition. Moreover, an asymmetric version of this cycloaddition reaction was also screened using several commercialized chiral phosphine ligands, and only moderate enantioselectivity was obtained (Scheme 41).

The construction of *gem*-difluoroalkyl moiety has gained much attention due to its unique property in organic synthesis and medicinal chemistry. Thus, developing effective transformations for their construction are highly important. Recently, Shibata and coworkers applied substituted-2-alkylidenetrimethylene carbonates as reactive substrates, reporting a palladium-catalyzed [4 + 2] cycloaddition of *gem*-difluoroalkyl ketones [79]. The reaction was well tolerated, and cyclic or acyclic *gem*-difluoroalkyl ketones could react with substituted-2-alkylidenetri-methylene



Ar^1 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-MeC$_6$H$_4$
Ar^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-naphthyl
R = Et, ^{n}Bu, ^{i}Bu, Bn, butenyl, pentylenyl, BnO(CH$_2$)$_3$

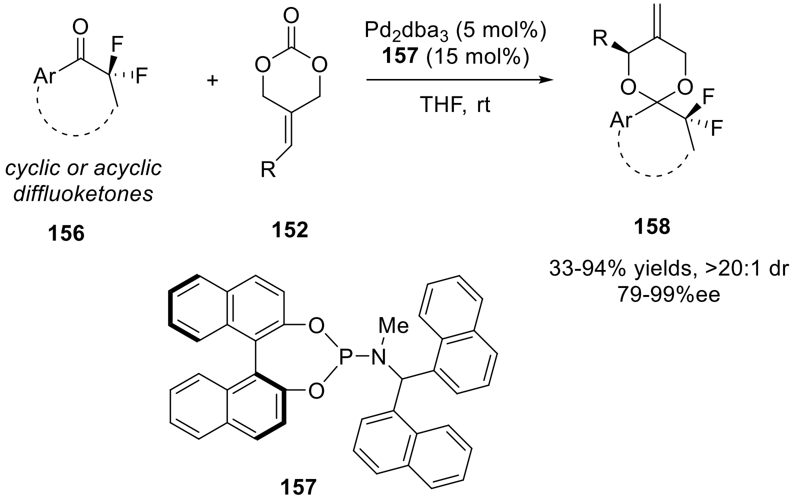
Scheme 40 Palladium-stabilized oxo-1,4-dipoles with photochemically generated ketenes



Ar^1 = Ph, 2-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 3-MeOC$_6$H$_4$;
R^1 = 5-Br, 5-CN, 5-Me, 6-Me, 7-F, 7-Cl, 5-F, 5-Cl, 6-F, 6-Br, 6-Me, 7-Br, 7-Me
R^2 = Ts, Bs, Ac, CO$_2$Me, CO$_2$Bn, CO$_2$^{t}Bu

Scheme 41 Palladium-catalyzed [4 + 2] cycloaddition of 3-nitroindoles

carbonates, affording the functionalized difluoromethylene compounds in high yield with excellent regio- and enantioselectivity. It should be noted here that the amine substitution of the BINOL-phosphoramidite ligands has a dramatic effect on the reactivity and regioselectivity. Newly designed bulkier 1,1-dinaphthylmethanamino-substituted ligand **134** afforded **135a** with 97% *ee* and complete diastereoselectivity in the presence of Pd$_2$(dba)$_3$. Further study suggested that monofluorinated ketones could not react with 2-alkylidenetrimethylene carbonate. The authors thought that the electronegativity of the difluoro-substitution pattern enhanced the electrophilicity of the ketones to stabilize the hemiketal intermediate sufficiently (Scheme 42) [80].



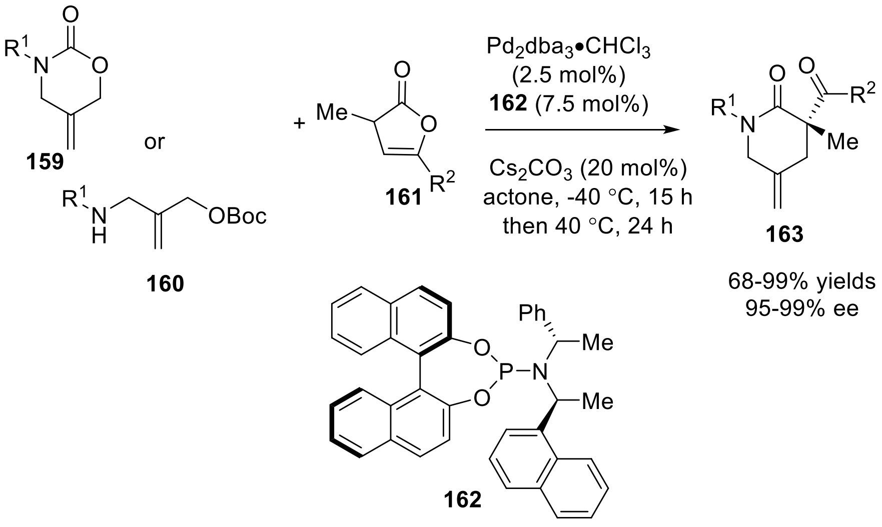
R = Ph, 4-MeC_6H_4, 4-FC_6H_4, 3-$CF_3C_6H_4$, 3-BrC_6H_4, 2-MeC_6H_4, 2-naphthyl, 2-furyl, Cy *et. al.*

Scheme 42 Palladium-catalyzed [4 + 2] cycloaddition of *gem-* difluoroalkyl ketones

In the same year, Yuan, Zhou, and coworkers reported a palladium-catalyzed enantioselective [4 + 2] cycloaddition of deconjugated butenolides with cyclic carbamates or amide-substituted acyclic carbonates [81]. Under optimal conditions, the reactions showed high activity and excellent stereocontrol. In most cases, the desired products were obtained in good yields with excellent enantioselectivities except for *N*-Boc protected cyclic carbamates. The authors thought that the steric hindrance of the Boc group made the corresponding intramolecular aminolysis difficult. Investigation of the reaction process suggested that the reaction underwent successive α-allylation of deconjugated butenolides and intramolecular aminolysis process to give optically pure 2-piperidones (Scheme 43).

In 2020, Ding and coworkers synthesized a new type of benzylic substituted chiral *P*,*N*-ligand and applied it in a palladium-catalyzed asymmetric [4 + 2] cycloaddition of 4-vinyl-1,3-dioxan-2-ones with α,β-disubstituted nitroalkenes [82]. Under the optimized conditions, a range of disubstituted nitroalkenes reacted with vinyldioxanones smoothly in the presence of Pd(dba)$_2$ and ligand **166**, the desired tetrahydropyrans were obtained in high yields with high diastereo- and enantioselectivity. The authors thought that the chiral center on the oxazoline ring of the ligand might controll the enantioselectivity of products **167**, while the yield and the diastereoselectivity of the reaction were mainly affected by the chiral center on the benzylic position (Scheme 44).

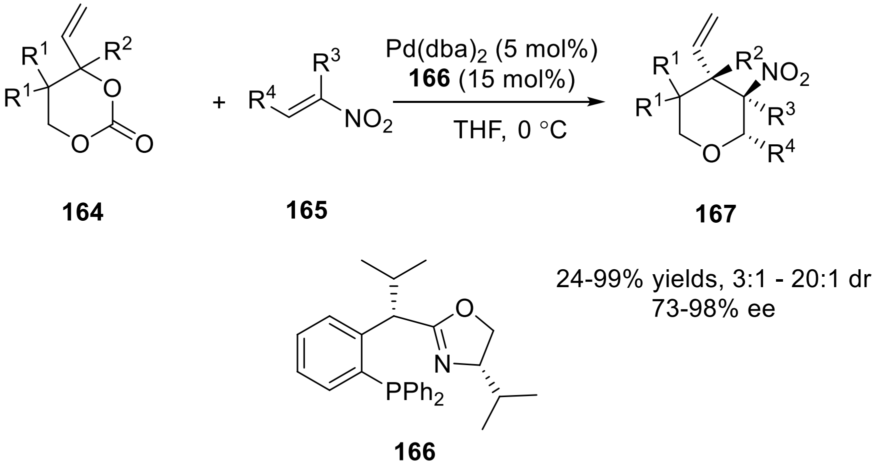
Pioneered by Trost, palladium-catalyzed trimethyl-enemethane (TMM) cycloaddition have been well developed in organic synthesis. These reactions have been widely used in the generation of odd-numbered and, in particular, five-membered rings. Despite the significant progress in this field, developing novel 1, *n*-dipole intermediates (where $n = 4$) is very important due to the ubiquity



R^1 = Ts, Ns, Boc, Bs, Ms

R^2 = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-naphthyl, Me, Et, ^{i}Pr *et. al.*

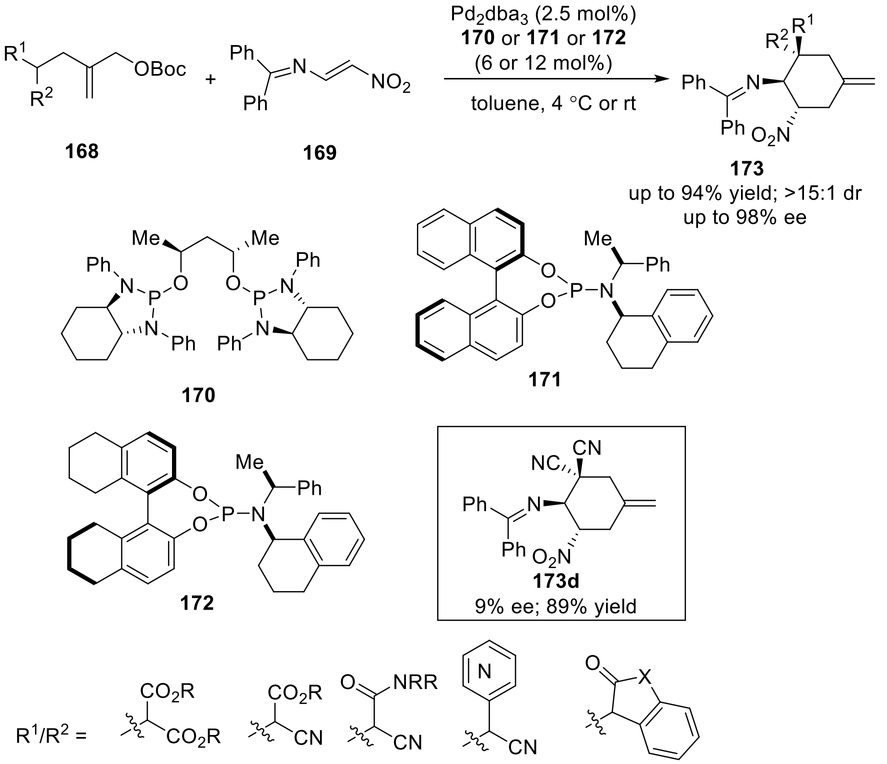
Scheme 43 Palladium-catalyzed [4+2] cycloaddition of butenolides with cyclic carbamates and amide-substituted acyclic carbonates



R^1 = H, Me; R^2 = H, -$(CH_2)_5$-; R^3 = Me, Et, Ph, ^{i}Pr

R^4 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4, 2-MeC_6H_4, 2-ClC_6H_4, 1-naphthyl, 2-furyl, 3-pyridyl

Scheme 44 Palladium-catalyzed asymmetric [4+2] cycloaddition of 4-vinyl-1,3-dioxan-2-ones with α,β-disubstituted nitroalkenes

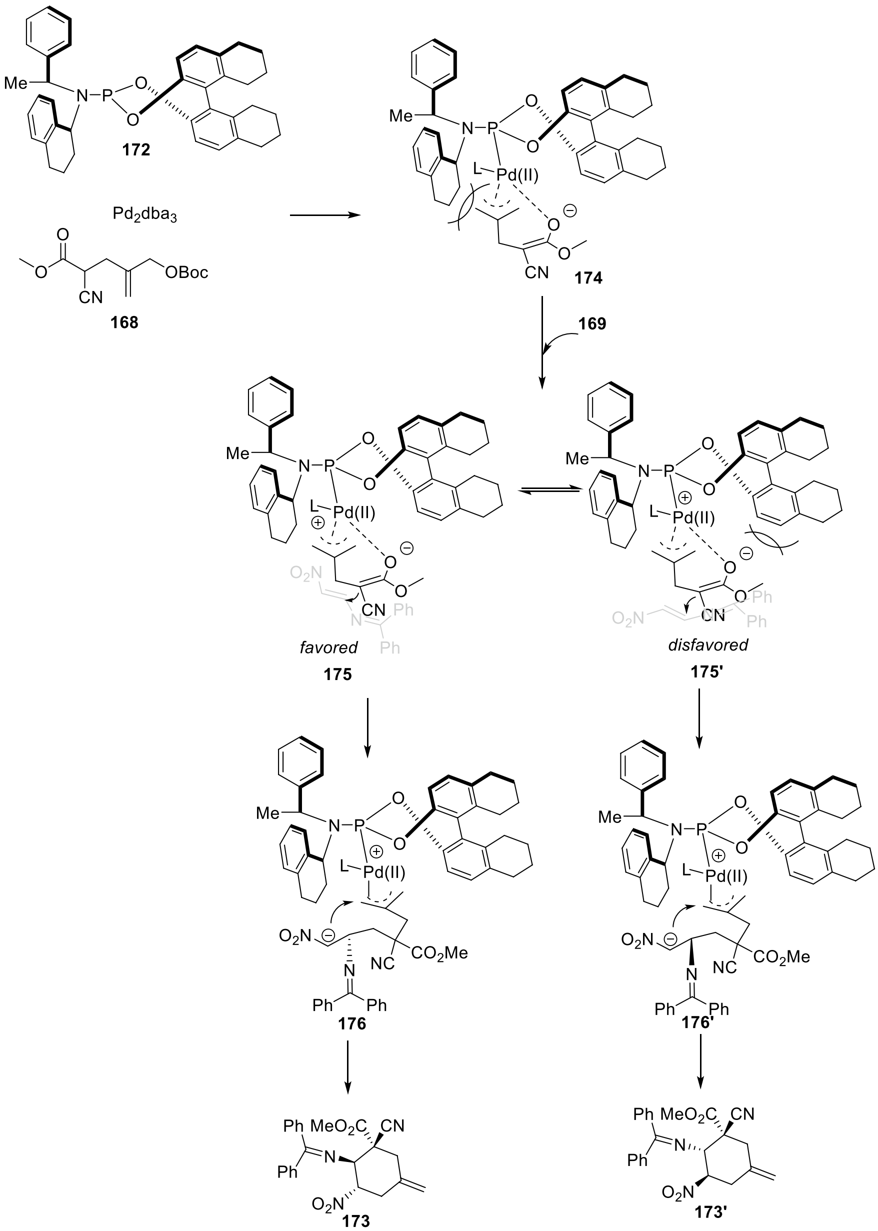


Scheme 45 Palladium-catalyzed [4+2] cycloaddition with C=C acceptors

of stereochemically diverse six-membered cycles. In 2020, Trost and coworkers designed a new palladium-stabilized 1,4-dipole intermediate by introducing an additional carbon linker to the conventional Pd-TMM donors and finished a palladium-catalyzed [4+2] cycloaddition with C=C acceptors [83]. Notably, the reaction tolerated a variety of enolate precursors and was not limited to substrates with rigidified cyclic frameworks. In most cases, the enantioenriched all-carbon six-membered rings were obtained with high yields and selectivity (Scheme 45).

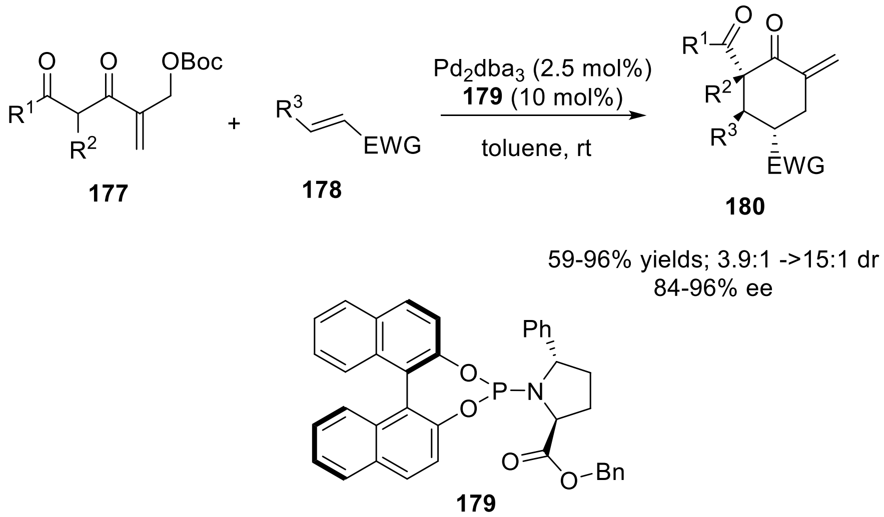
The authors proposed a possible mechanism. The treatment of palladium catalyst with dipole precursors generated the key intermediate **174**. For explaining good selectivity and the special example of **173d**, the authors thought that the enolate oxygen was likely binding to the palladium cation center, producing a six-membered ring system and geometry confirmed enolate. Next, the acceptor **168** attacked the **174** from the *Re* face due to the *Si* face of the ring presumably hindered by the phosphoramidite ligand, giving the **175**. A final intramolecular cyclization afforded **176** as the major product and regenerated the palladium catalyst (Scheme 46).

After that, the same group used electron-deficient allylic carbonates as new 1,4-dipole synthon, developing a palladium-catalyzed [4+2] cycloaddition [84].



Scheme 46 A possible mechanism for palladium-catalyzed [4 + 2] cycloaddition with C=C acceptors

By using C_2-unsymmetric phosphoramidite ligand **179**, the cycloaddition reactions with various electron-deficient acceptors could produce the desired chiral cyclohexanones in good to excellent results. It was worth noted that the acidity of the active C–H bond of **177** might play a crucial role in the reaction process, the

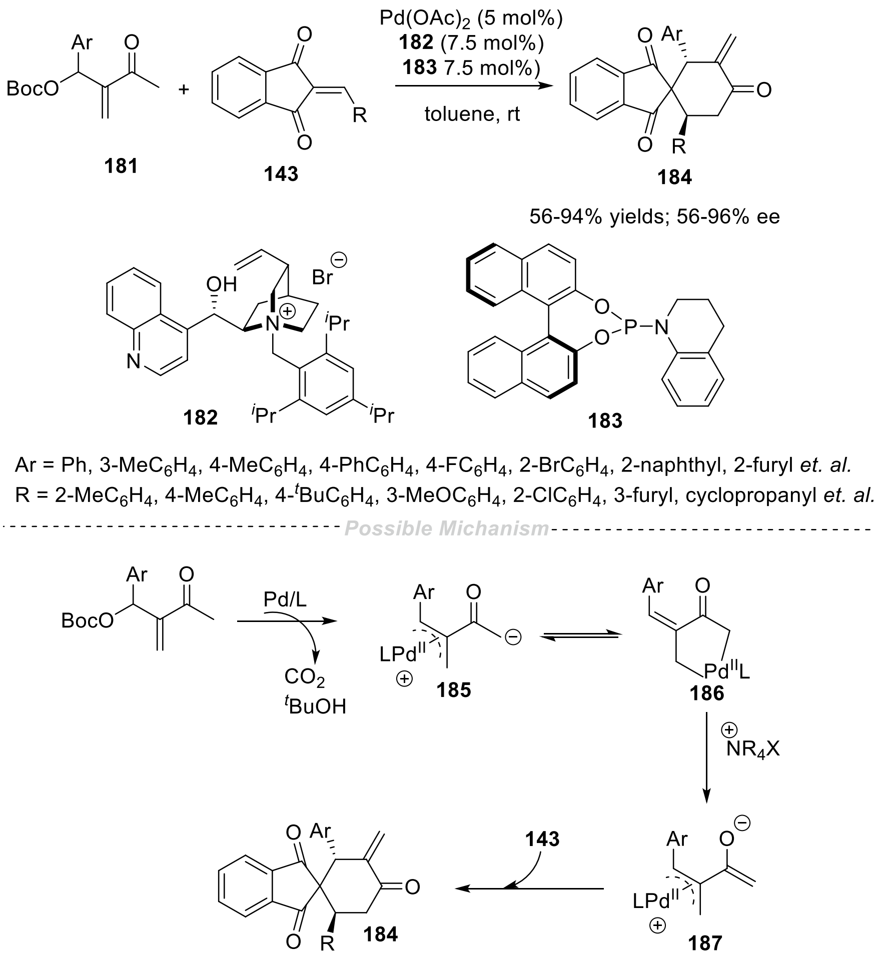


Scheme 47 Palladium-catalyzed [4 + 2] cycloaddition of electron-deficient allylic carbonates

weak acidic methyl ketone resulted in low reactivity. From the scope of the investigated substrates, the reaction was widely tolerated, the desired products were obtained in good yields with high enantioselectivity. Screening of the R^2 group indicated that the carbonyl group on the ester or amide might also act another role as a directing group (Scheme 47).

According to Trost's report, methyl vinyl ketone was not a suitable substrate in palladium-catalyzed 1, 4-dipole cycloaddition. Chen thought that the corresponding intermediates, either 1,4-carbodipoles **157** or Pd-ligated five-membered species **158** after the oxidative addition/deprotonation process, resulted in low stability or poor reactivity. Thus Chen and coworkers used ammonium halide salts **182** as ion-pair catalysts (IPCs), which could form ion-pairing intermediates **187** from unstable 1,4-carbodipole species **185** and realizing the palladium-catalyzed [4 + 2] cycloaddition of methyl vinyl ketones with diverse activated alkenes or isatins [85]. Using palladium complex and ammonium halide cooperative system, the reaction enabled the synthesis of a wide range of functionalized spirocyclic compounds in moderate to good yields with excellent stereoselectivity. In addition, diastereodivergent [4 + 2] annulations between MBH carbonates and 3-olefinic oxindoles were also carried out by modifying the flexible assembly of the palladium complex and ion-pairing agent (Scheme 48).

More recently, Guo and coworkers used amido-tethered allylic carbonates with oxazol-5-(4*H*)-ones as reactive substrates, describing a palladium-catalyzed [4 + 2] cycloaddition [86]. The reaction proceeded smoothly under mild reaction conditions, affording various piperidine derivatives in moderate to excellent yields. In this reaction, the authors performed some transformations of the products to further demonstrate the potential application of the [4 + 2] cycloaddition (Scheme 49).



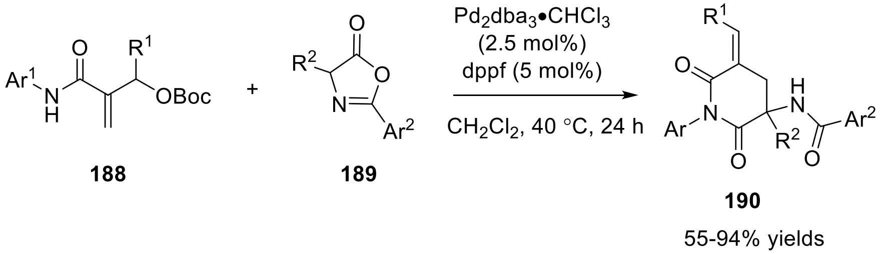
Ar = Ph, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-FC$_6$H$_4$, 2-BrC$_6$H$_4$, 2-naphthyl, 2-furyl *et. al.*
R = 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-^{t}BuC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-furyl, cyclopropanyl *et. al.*

Scheme 48 Palladium-catalyzed [4 + 2] cycloaddition of methyl vinyl ketones

3.4 Vinyloxetanes as "1,4-Dipole" in [4 + 2] Annulations

2-Vinyloxetanes is another 1,4-dipole synthons and can be used for [4 + 2] cycloaddition to prepare six-member cyclic compounds. In 1999, Alper and coworkers first achieved a palladium-catalyzed [4 + 2] cycloaddition of 2-vinyloxetanes with heterocumulenes in THF at room temperature, giving the desired 4-vinyl-1, 3-oxazin-2-imines and 4-vinyl-1, 3-oxazin-2-ones in moderate to good yields [87]. In addition, The reaction of the bicyclic vinyloxetanes with heterocumulenes were also tested. In most cases, the desired bicyclic *cis*-oxazin-2-imines were produced in good yields (Scheme 50).

In 2019, Zhang and coworkers described a palladium-catalyzed [4 + 2] cycloaddition reaction of vinyloxetanes with formaldehyde. Screening reaction condition suggested the reaction in diethyl ether showed the best results in the presence of



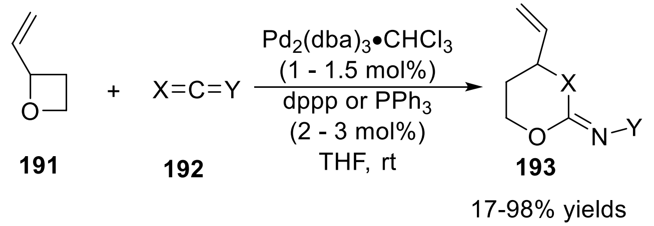
R^1 = Ph, H, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 3-MeC_6H_4 *et. al.*

R^2 = ^{t}Bu, Me, Et, ^{i}Pr, Ph, H

Ar^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4 *et. al.*

Ar^2 = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3,5-$Cl_2C_6H_3$, 2-MeC_6H_4, 3-MeC_6H_4 *et. al.*

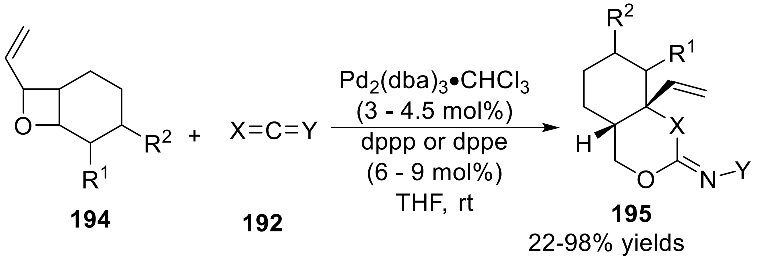
Scheme 49 Palladium-catalyzed [4+2] cycloaddition of amido-tethered allylic carbonates with oxazol-5-(4*H*)-ones



R^1 = Me, H;

X = PhN, 4-ClC_6H_4N, 4-MeC_6H_4N, 4-$MeOC_6H_4N$, 2-MeC_6H_4N, 4-BrC_6H_4N

Y = O, PhN, 4-ClC_6H_4N, 4-MeC_6H_4N, 4-$MeOC_6H_4N$, 2-MeC_6H_4N, 4-BrC_6H_4N

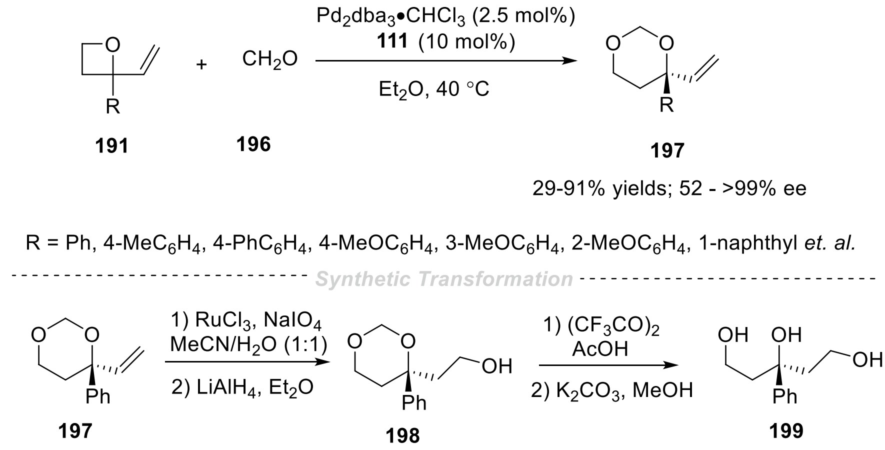


R^1 = Me, H; R^2 = H, Me

X = PhN, 4-ClC_6H_4N, 4-MeC_6H_4N, 4-$MeOC_6H_4N$, 2-MeC_6H_4N, 4-BrC_6H_4N

Y = O, PhN, 4-ClC_6H_4N, 4-MeC_6H_4N, 4-$MeOC_6H_4N$, 2-MeC_6H_4N, 4-BrC_6H_4N

Scheme 50 Palladium-catalyzed [4+2] cycloaddition of 2-vinyloxetanes with heterocumulenes



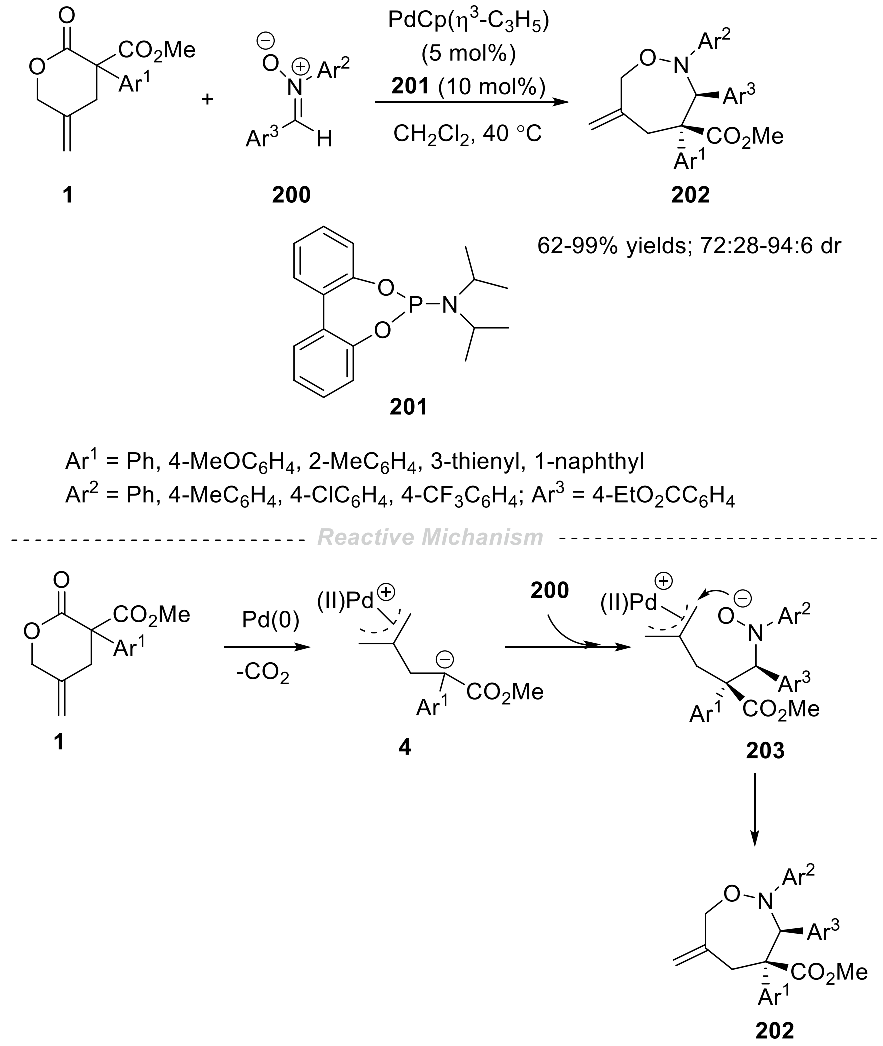
Scheme 51 Palladium-catalyzed [4+2] cycloaddition reaction of vinyloxetanes with formaldehyde

Pd_2dba_3•$CHCl_3$/phosphoramidite ligand **111** complex [88]. Notably, the reaction was well tolerated, a wide range of 1, 3-dioxanes were obtained in moderate to high yields with good to high enantioselectivity. However, the aliphatic-substituted vinyloxetane was not suitable substrate; only poor yield and enantioselectivity were observed. In addition, the triol **199** could be obtained in 86% yield without a significant loss of enantioselectivity by simple two-step synthesis, which demonstrated synthetic potentiality of this transformation (Scheme 51).

4 Allylic Motifs as "1,4-Dipole" in [4+3] Annulations

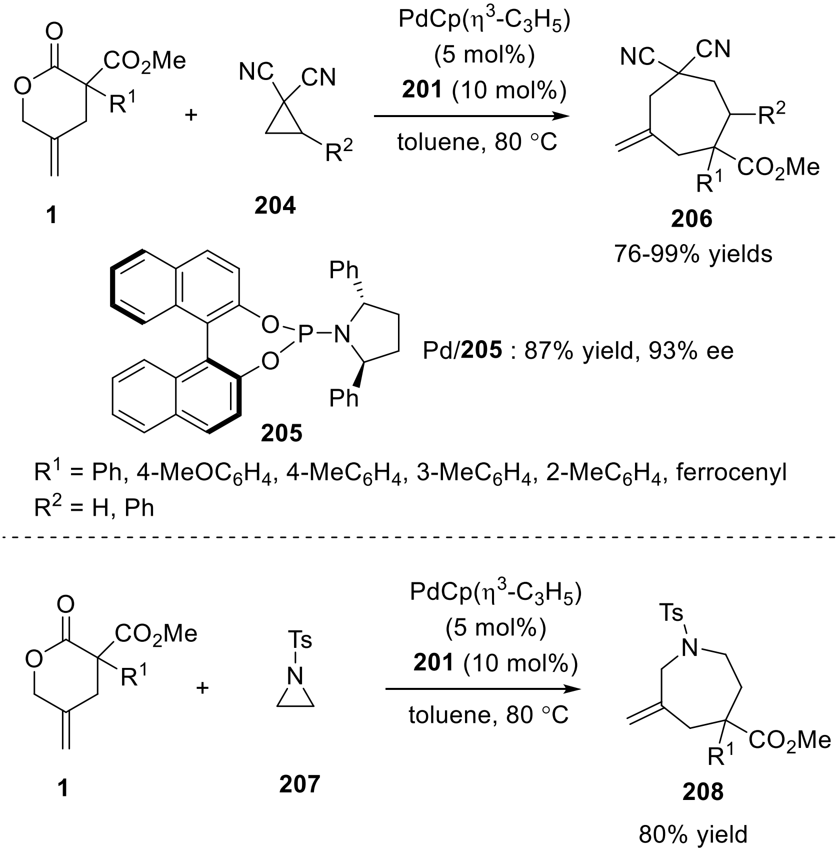
4.1 γ-Methylidene-δ-valerolactones as "1,4-Dipole" in [4+3] Annulations

The [4+3] cycloadditions have emerged as powerful strategies for constructing seven-membered cyclic compounds. Thus considerable efforts have been made for the development of efficient synthetic methods. In 2007, Hayashi and coworkers applied γ-methylidene-δ-valerolactones as 1, 4-dipole synthon, developing a palladium-catalyzed [4+3] cycloaddition reaction. The reaction of γ-methylidene-δ-valerolactones with nitrones resulted in the highly functionalized 1,2-oxazepines in good yields and high diastereoselectivity under PdCp(η^3-C_3H_5)/phosphoramidite complex catalysis [89]. The authors proposed a possible mechanism. Initially, the 1,4-zwitterionic species **4** was obtained by an oxidative addition of **1** to palladium(0) and subsequent decarboxylation. Then the nucleophilic attack of species **4** to the electrophilic carbon of **200** gave intermediate **203**. Finally, an intramolecular ring closure afforded the desired 1,2-oxazepine **202** and regenerated palladium(0) catalyst. Later, the authors demonstrated their utility in the context of stereoselective [4+3] cycloaddition with nitrones (Scheme 52) [90].



Scheme 52 Palladium-catalyzed [4 + 3] cycloaddition reaction of nitrones

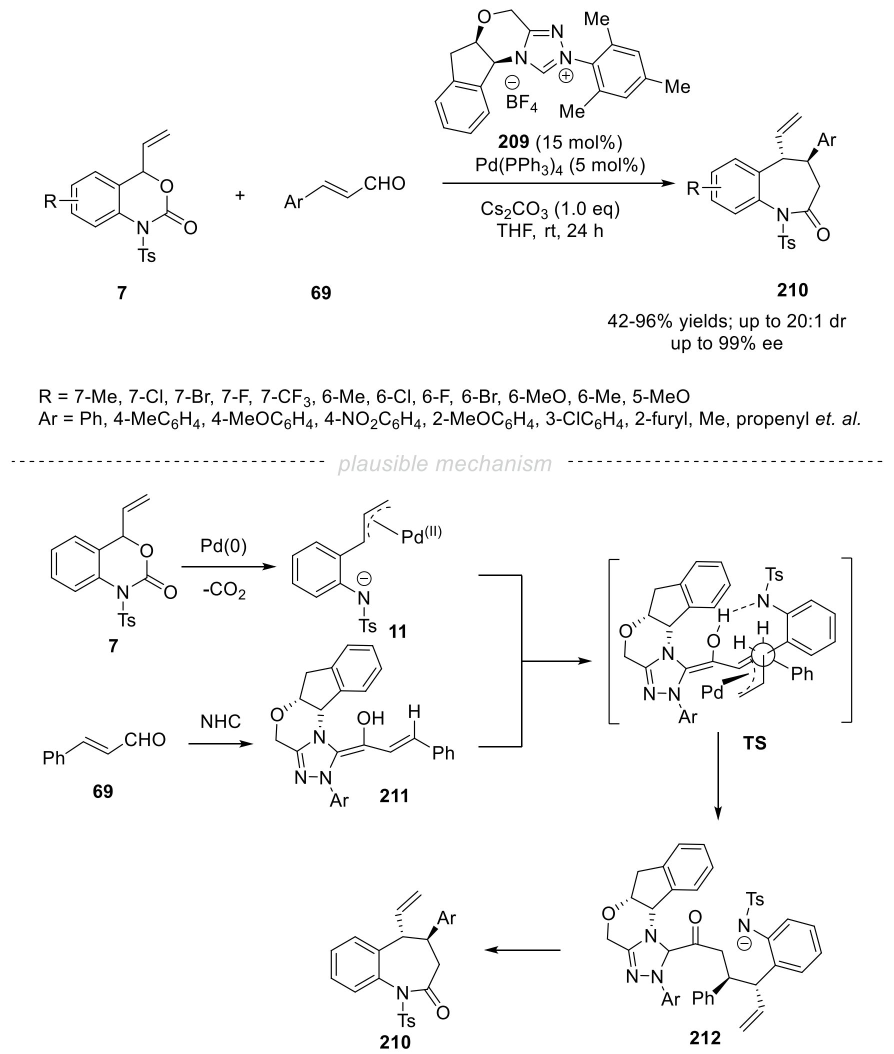
In 2009, the same group used the 1,1-dicyano-cyclopropanes as electrophilic receptor, realizing a palladium-catalyzed [4 + 3] cycloaddition of γ-methylidene-δ-valerolactones [91]. Under the optimized conditions, the reactions were well tolerated, and different 1,1-dicyanocyclopropanes including 2-phenyl-1, 1-dicyanocyclopropane and aziridines were suitable substrates in the transformations. Diverse cycloheptanes and azepanes were obtained in good yields. In addition, when chiral phosphoramidite **205** was used, the desired cycloadducts were obtained in up to 93% *ee* (Scheme 53).



Scheme 53 Palladium-catalyzed [4 + 3] cycloaddition of 1,1-dicyano-cyclopropanes

4.2 Benzoxazinanones as "1,4-Dipole" in [4 + 3] Annulations

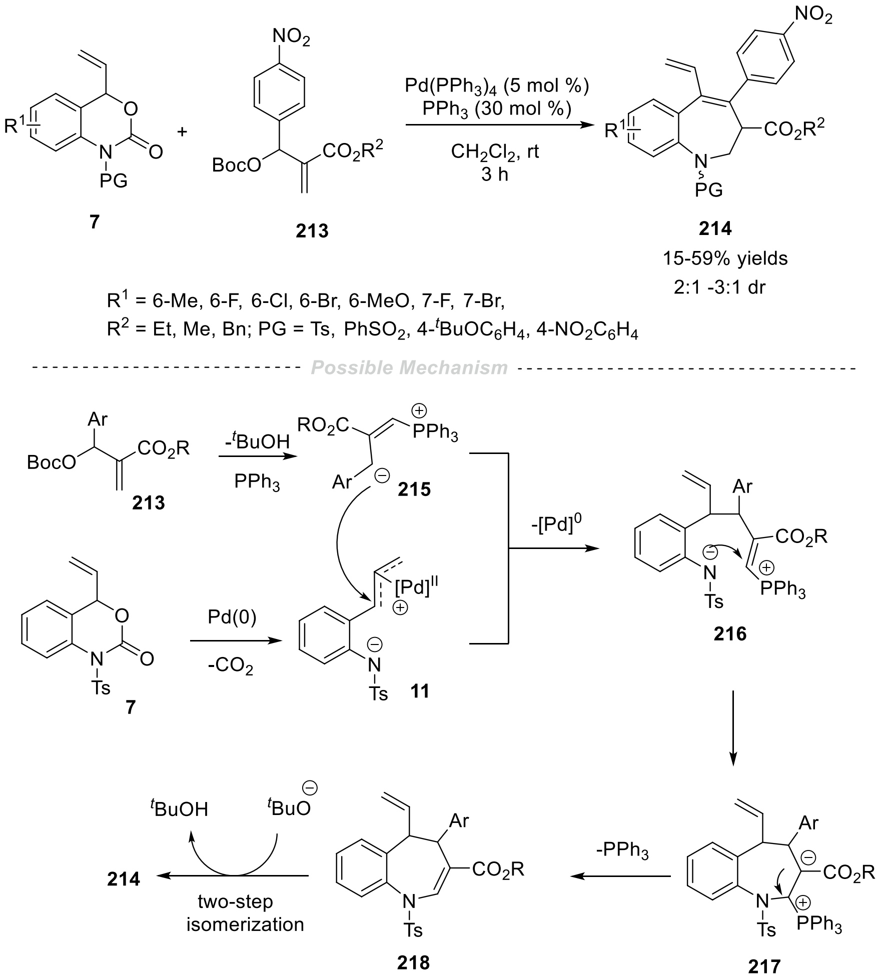
N-heterocyclic carbene (NHC) catalysis is recognized as a powerful tool for the construction of complex organic frameworks from simple and readily available starting materials [92–98]. However, NHC catalysis is typically limited to established substrate classes and reaction molds. Thus cooperative combination of transition-metal catalysis and NHC catalysis could dramatically expand the scope of NHC catalysis and providing access to currently inaccessible reaction pathways [99]. In 2016, Glorius and coworkers developed an asymmetric cooperative system for the intermolecular [4 + 3] cycloaddition reaction that combines transition-metal / NHC organocatalysis system [100]. This asymmetric process demonstrated the compatibility of these two important catalytic modes and efficiently afforded annulated 1-benzazepine products with excellent regio- and enantioselectivity. A plausible "cooperative activation" concept was proposed in this paper: Firstly, the coordination of vinyl benzoxazinanone **7** to the palladium



R = 7-Me, 7-Cl, 7-Br, 7-F, 7-CF$_3$, 6-Me, 6-Cl, 6-F, 6-Br, 6-MeO, 6-Me, 5-MeO
Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-furyl, Me, propenyl *et. al.*

Scheme 54 The intermolecular [4 + 3] cycloaddition reaction that combines Pd/NHC cooperative system and plausible mechanism

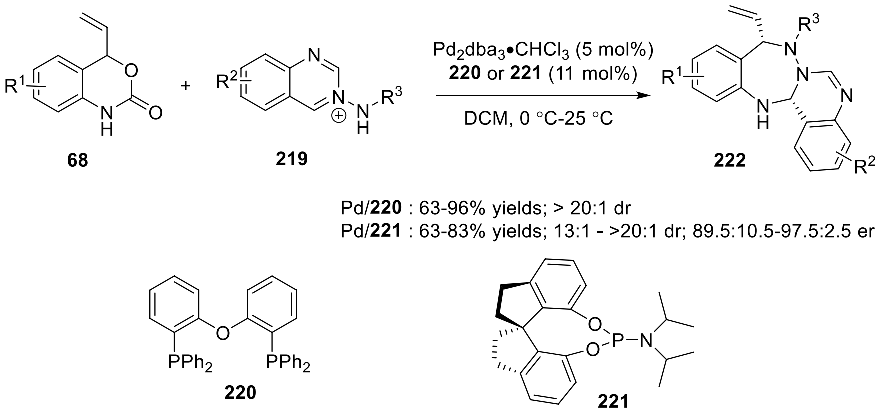
catalyst formed an electrophilic allyl-palladium(II) complex **11** upon decarboxylation, and, simultaneously, the nucleophilic addition of NHC organocatalyst to the enal **69** gave rise to the NHC-homoenolate **211**. Then, the NHC-homoenolate **211** underwent conjugate addition to the allyl-palladium(II) complex, affording the acyl azolium **212** and released the palladium catalyst. Finally, this species underwent *N*-acylation cyclization to furnish the final product **210** and regenerate the NHC organocatalyst **209** (Scheme 54). Later, Glorius and coworkers reported the detailed mechanistic studies involving a palladium catalyst and an NHC organocatalyst dual catalytic systems. This result revealed that the NHC, besides



Scheme 55 Palladium/phosphine cooperative catalytic [4 + 3] annulation reaction of Morita-Baylis–Hillman carbonates

its role as an organocatalyst, also fortuitously acts as a ligand on the active metal catalyst [101].

Tertiary phosphines are not only applied as ligands that coordinate with the metal center, but also can be directly used as organocatalyst to catalyze the chemical reaction [102–107]. That is to say, in the dual catalytic system, tertiary phosphine can coordinate with the transition metal involved, which will result in the inactivation of catalytic system, thereby diminishing or even preventing the individual reactivity of each substrate. Thus, rare examples have been reported involving transition metal/phosphine dual catalytic system [108–110]. In 2019, Li and co-workers used Morita-Baylis–Hillman carbonates and vinyl benzoxazinanones as reactive substrates, developing a phosphine/palladium cooperative catalytic [4 + 3] annulation



Pd/**220** : 63-96% yields; > 20:1 dr
Pd/**221** : 63-83% yields; 13:1 - >20:1 dr; 89.5:10.5-97.5:2.5 er

R^1 = H, 6-Me, 6-MeO, 6-Cl, 6-F, 7-Me, 7-Br, 7-MeO, 5-F, 5-Cl, 5-Br, 5-Me
R^2 = 8-F, 8-Cl, 7-F, 7-Cl, 6-Cl, 6-F, 5-F, 5-Cl, 6,7-MeO$_2$, 7-MeO, 6-Me, 6-MeO, 5-Me, 8-Me, 6,7-OCH$_2$O; R^3 = Ts, $SO_2C_6H_5$

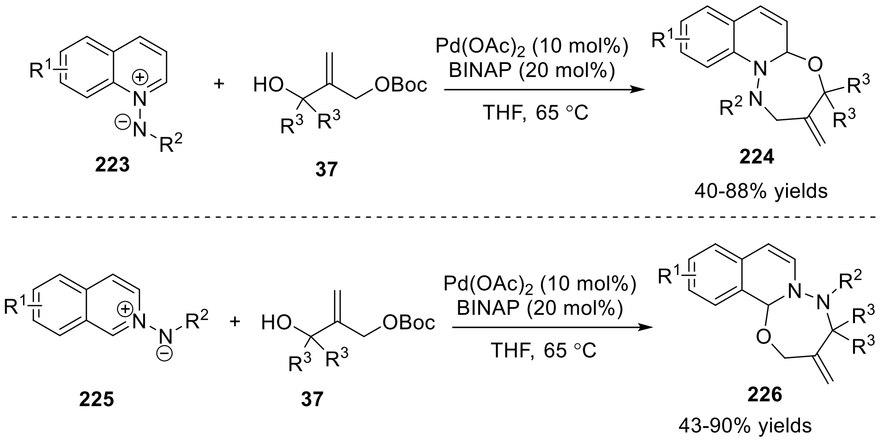
Scheme 56 Palladium-catalyzed [4+3] cycloaddition of azomethine imines

reaction. The reaction showed good substrate tolerance, providing a range of vinyl 2,3-dihydro-1*H*-benzo[*b*]azepine derivatives in moderate to good yields and diastereoselectivity [111]. The authors proposed a plausible mechanism. As outlined in Scheme 55. The reaction was first triggered by nucleophilic attack of PPh_3 on MBH carbonates **213** to yield zwitterion **215**, Simultaneously, **7** and $Pd(PPh_3)_4$ produced the π-allylpalladium complex **11**. Next, the γ-regioselective addition of the zwitterionic intermediate **215** to the π-allylpalladium complex **11** gave the intermediate **216** and regenerate Pd(0) catalyst. An intramolecular Michael addition occurred to produce the intermediate **217**. Then the electron-transfer process and subsequent β-elimination of PPh_3 afforded the corresponding intermediate **218**. Finally, two-step isomerization of C=C bond produces the observed adducts **214** in the presence of base (Scheme 55).

Azomethine imines have been used as stable and readily accessible 1,3-dipoles for efficient synthesis of dinitro-fused heterocycles. In 2020, Miao and coworkers reported a palladium-catalyzed [4+3] cycloaddition of vinyl benzoxazinanones **68** with azomethine imines **219**.[112] In this transformation, the authors first investigated the scope of the reaction by using $Pd_2(dba)_3·CHCl_3$ as the catalyst and **220** as the ligand in DCM at 25 °C. A range of structurally diverse 1,2,4-benzotriazepines **222** were obtained in good yields with excellent diastereoselectivity. In addition, an asymmetric version of the reaction was examined by using Pd/chiral phosphoramidites **221** complex at 0 °C in DCM. In most cases, the desired compounds were obtained in good yields and diastereo- and enantioselectivity (Scheme 56).

4.3 Allyl Carbonates as "1,4-Dipole" in [4+3] Annulations

In 2020, Liu, Chen, and coworkers disclose a palladium-catalyzed [4+3] cycloaddition of *N*-iminoquinolinium ylides and 2-(hydroxymethyl)allyl *t*-butyl carbonates



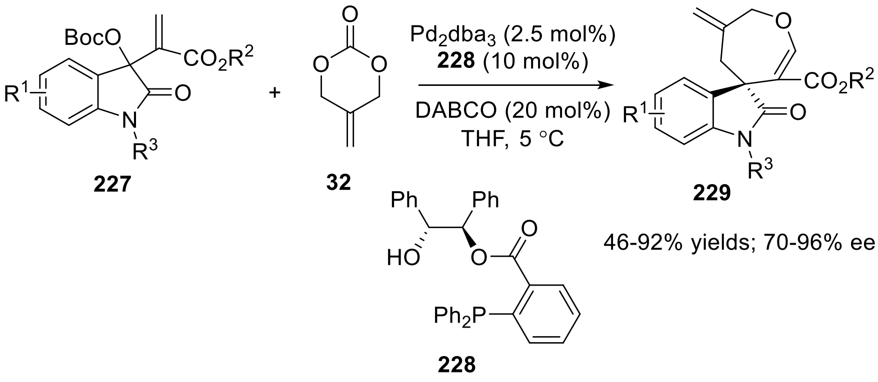
R^1 = H, 6-Me, 6-MeO, 6-Cl, 6-F, 7-Me, 7-Br, 5-MeO, 5-Cl
R^2 = Ts, 4-$MeOC_6H_4SO_2$, 4-$ClC_6H_4SO_2$, 4-$BrC_6H_4SO_2$, 4-$^tBuC_6H_4SO_2$, Ac, CH_3CH_2CO,
R^3 = H, Me

Scheme 57 Palladium-catalyzed [4 + 3] cycloaddition of *N*-iminoquinolinium ylides or *N*-iminoisoquinolinium ylides

[113]. With the optimal reaction conditions, the reaction performed well, affording the desired products in high yields. Notably, *N*-iminoisoquinolinium ylides also performed well in this reaction, the corresponding products were obtained in moderate to good yields. In addition, gram-scale preparation and diversification of the synthesized seven-membered ring demonstrated the synthetic utility and versatile applicability of this method (Scheme 57).

In 2021, Chen and coworkers used 2-methylidene-trimethylene carbonate as 1,4-dipole synthon, developing a palladium-catalyzed [4 + 3] cycloaddition of MBH carbonates [114]. Applying Pd/DABCO cooperative catalytic strategy, the reaction performed well, and a range of oxepanes were produced in moderate to good yields with moderate to high enantioselectivity. Screening of chiral ligands showed that the hydrogen bonding interaction played the key role in improving reactivity and enantiocontrol. In addition, apparently diminished enantiocontrol was observed for the MBH carbonates **227** possessing diverse electron-withdrawing groups (Cl, Br, F) or other *N*-protecting groups (allyl, MOM, Bn) (Scheme 58). In 2023, Cui, Chen, and coworkers reported a palladium-catalyzed sequential [4 + 3] cyclization/[1, 3]-rearrangement reaction of Morita-Baylis–Hillman Expansion (MBH) carbonates and *tert*-butyl 2-(hydroxymethyl)allyl carbonates [115].

More recently, Li and coworkers first reported a palladium-catalyzed asymmetric (4 + 3) cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines with 2-methylidenetrimethylene carbonate [116]. The reaction performed well in stereocontrol, and a wide array of trifluoromethylated spirooxindoles **232** were obtained in moderate yields and good to excellent *ee* values. In mechanism, the authors thought that the oxygen anion of the π-allylpalladium intermediate **233** first acted as a Brønsted base to abstract the proton of substrate **230**, affording intermediate **234**, which



R^1 = H, 5-Me, 5-MeO, 6-MeO, 7-Me, 5,7-Me$_2$, 5-Cl, 5-Br, 5-F, 7-Br
R^2 = Me, Et; R^3 = Me, allyl, MOM, Bn

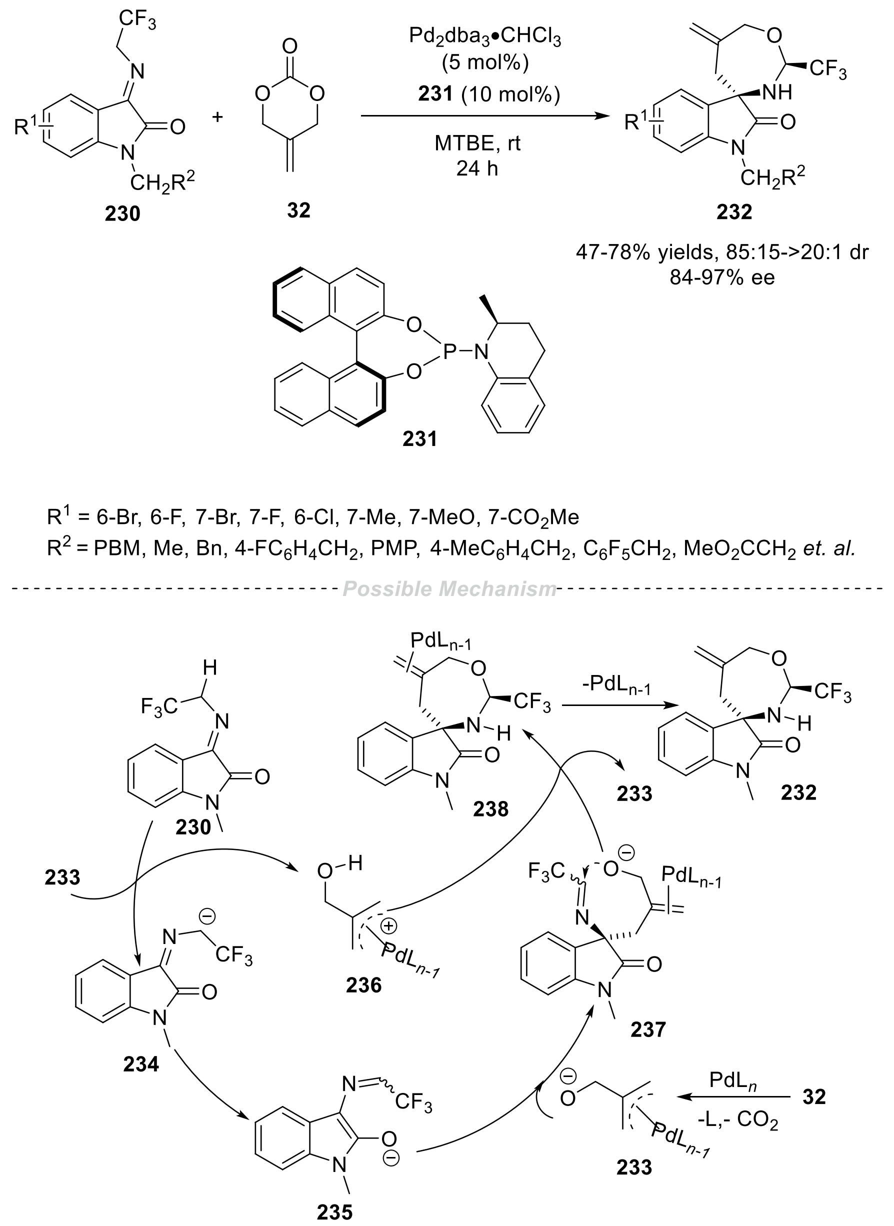
Scheme 58 Palladium/DABCO cooperative catalytic [4 + 3] cycloaddition of MBH carbonates

readily resonated into its enolate **235**. Subsequently, intermediate **235** attacked another intermediate **233**, to generate intermediate **237**. Finally, intermediate **237** intramolecularly cyclized and accepted one proton (e.g., from intermediate **236**) to afford the desired product **232** and released the palladium catalyst (Scheme 59).

5 Allylic Motifs as "1,4-Dipole" in [4 + 4] Annulations

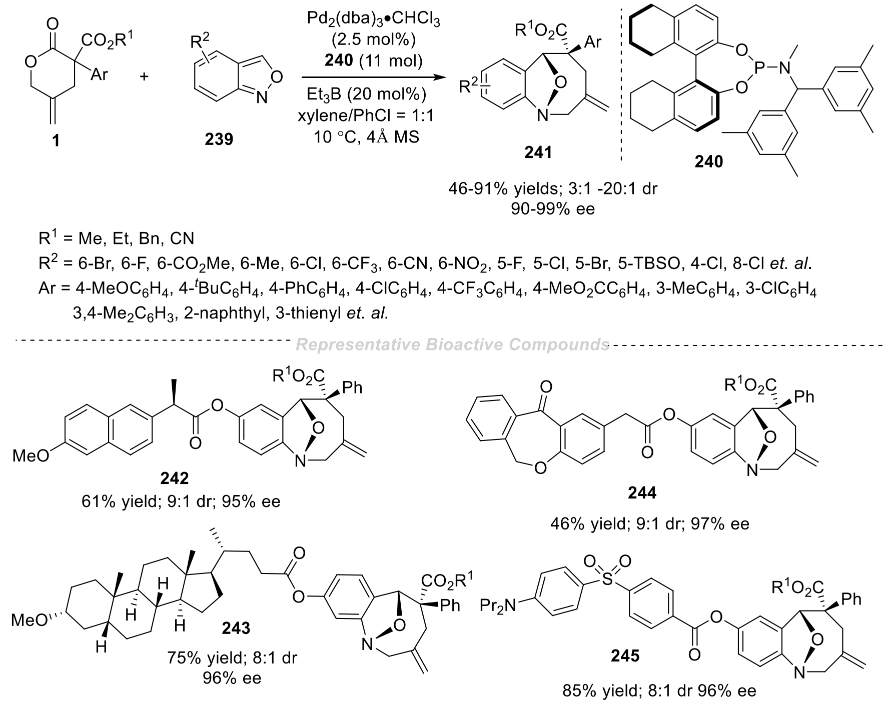
5.1 γ-Methylidene-δ-Valerolactones as "1,4-Dipole" in [4 + 4] Annulations

Eight-membered cyclic ethers are widely present in bioactive natural products and pharmaceuticals. Thus, the development of efficient methods for constructing these molecules is highly desired. In 2021, Li and coworkers reported a palladium-catalyzed asymmetric [4 + 4] cycloaddition of γ-methylidene-δ-valerolactones with anthranils. Under Pd$_2$(dba)$_3$·CHCl$_3$/phosphoramidites **240** complex catalysis, the transformation performed fairly broad functional group tolerance, affording the desired eight-membered tetrahydro-benzo[*b*]azocine **241** in good to excellent yields, diastereoselectivity, and enantioselectivity [117]. However, The reaction of γ-methylidene-δ-valerolactones **1** and α,β-unsaturated imine did not result in the desired product under the optimized reaction conditions. It is worth noting that the authors applied this strategy to the functionalization of bioactive natural products and drug-like molecules. A series of further transformations (such as cross-coupling reactions, oxidation, and hydrogenation) were performed, which demonstrated the potential synthetic utility of this protocol. The control experiment suggested that Et$_3$B played the key role in this reaction, which underwent a coordination with anthranils to form new species under reaction conditions, thus promoting this catalytic transformation (Scheme 60).



Scheme 59 Palladium-catalyzed asymmetric [4+3] cycloaddition of *N*-2,2,2- trifluoroethylisatin ketimines

The authors proposed a plausible reaction mechanism. As outlined in Scheme 61, the 1,4-dipolar intermediate **4** was firstly produced by palladium-catalyzed decarbonylation. Simultaneously, the coordination of Et$_3$B with anthranils gave the more electrophilic intermediate **246**. Then the complex **247** was obtained by a



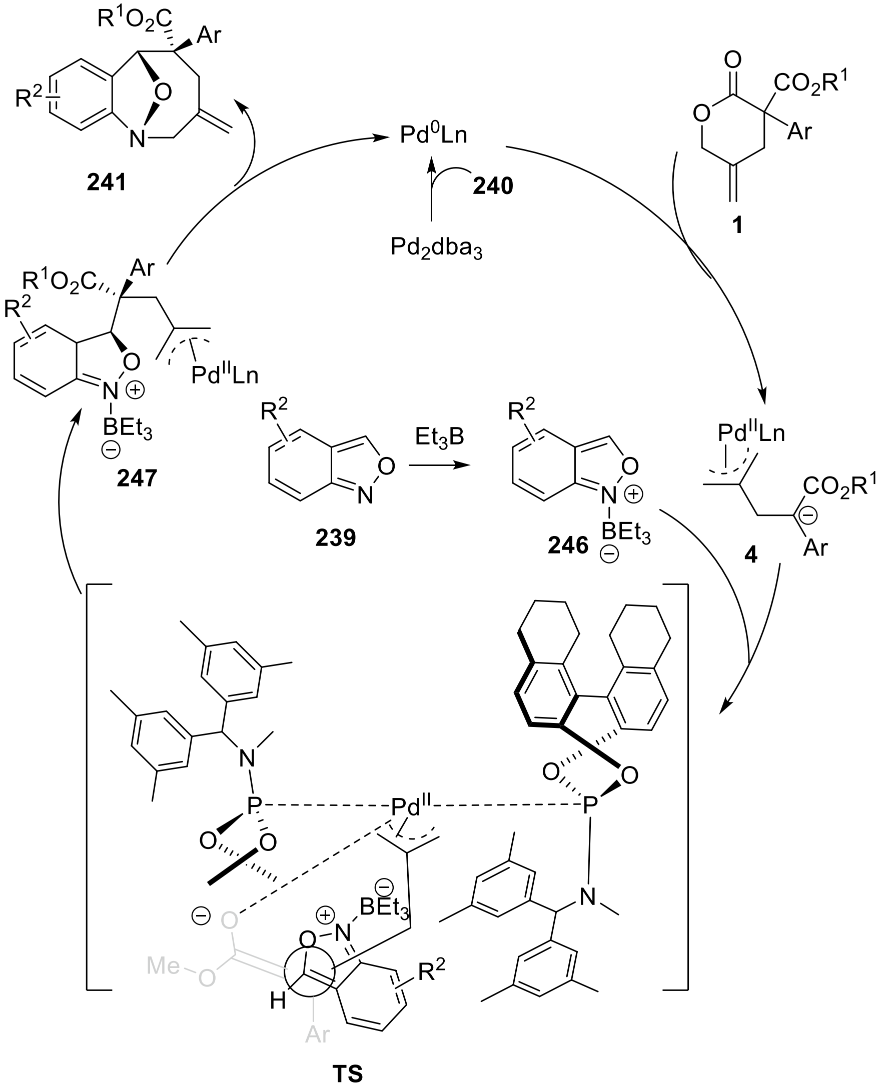
Scheme 60 Palladium-catalyzed asymmetric [4+4] cycloaddition of anthranils

nucleophilic attack of intermediate **4** to substrate **246**. Finally, the intramolecular cyclization afforded the desired product **241** and regenerated Pd(0) and Et_3B. The authors proposed that the *Si* face of 1,4-dipolar species **4** underwent enantioselective addition to anthranil **239** more favorably because of the backbone of chiral phosphoramidite ligand (Scheme 61).

In 2022, the same group used *ortho*-quinone methides as reactive substrates, describing a new palladium-catalyzed [4+4] cycloaddition of γ-methylidene-δ-valerolactones [118]. Employing phosphoramidites **240** as ligands, the reactions could be well achieved, providing the corresponding products in good yields with high stereoselectivity. The experiment result showed the electronic character of the aryl substituents of γ-methylidene-δ-valerolactones played predominantly in the control of diastereoselectivity, and γ-methylidene-δ-valerolactones bearing electron-withdrawing substituents gave much higher diastereoselectivity (Scheme 62).

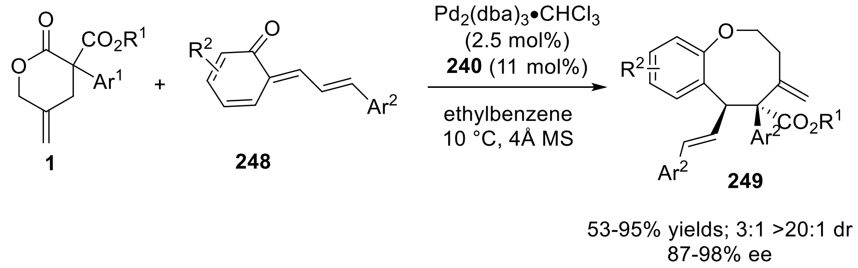
5.2 Allyl Carbonate as "1,4-Dipole" in [4+4] Annulations

Divergent synthesis of two or more stereoisomers from the same starting materials is a long-standing goal of organic synthesis chemistry. In 2021, Lin, Yao, and coworkers reported a ligand-control, palladium-catalyzed asymmetric [4+4] and [2+4] cycloaddition reactions of benzofuran-derived azadienes with *tert*-butyl



Scheme 61 A possible mechanism for palladium-catalyzed asymmetric [4+4] cycloaddition of anthranils

[2-(hydroxymethyl)allyl] carbonate [119]. Interestingly, the inherent steric and electronic effects of chiral ligands resulted in different regioselectivity of reaction process. When Pd(dba)$_2$/chiral P,N-ligands complex **250** was used as catalyst, the [4+4] cycloaddition reaction occurred to afford the desired benzofuro[2, 3-*c*][1, 5] oxazocines in good yields with excellent enantioselectivity. While using Pd(PPh$_3$)$_4$/(*S*)-Cl-MeO-BIPHEP complex catalysis, the tetrahydropyran-fused spirocyclic products were generated in good yields with moderate to good enantioselectivity (Scheme 63).

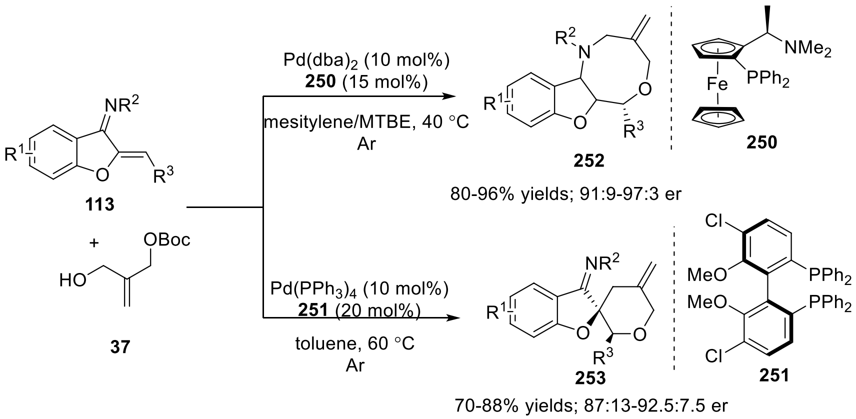


R^1 = Me, Et, Bn; R^2 = 3,4-OCH$_2$O, 3,4-MeO

Ar^1 = Ph, 4-ClC$_6$H$_4$, 4-CNC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-MeO$_2$CC$_6$H$_4$, 3,4-F$_2$C$_6$H$_3$, 3,5-Br$_2$C$_6$H$_3$, 3-F-4-BrC$_6$H$_3$ *et. al.*

Ar^2 = 4-MeC$_6$H$_4$, 4-MeOc$_6$H$_4$, 4-BrC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 1-naphthyl, 2-thienyl *et. al.*

Scheme 62 Palladium-catalyzed [4 + 4] cycloaddition of *ortho*-quinone methides



R^1 = H, 6-F, 5-Br, 5-MeO, 5-Me; R^2 = Ts, CF$_3$C$_6$H$_4$SO$_2$

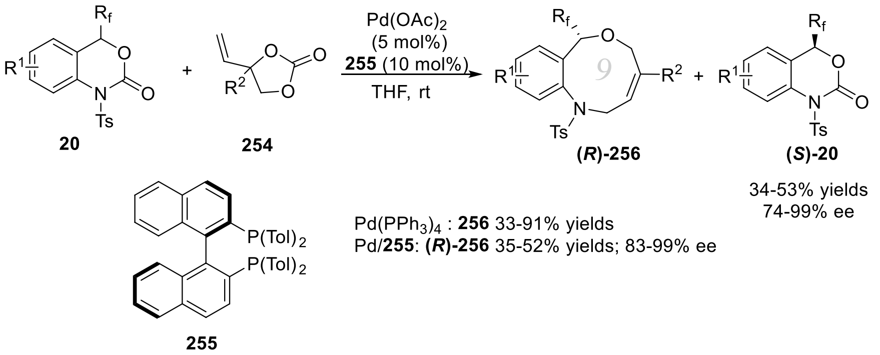
R^3 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeO$_2$CC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-naphthyl, 2-thienyl, ^{t}Bu *et.al.*

Scheme 63 Ligand-control, palladium-catalyzed asymmetric [4 + 4] and [2 + 4] cycloaddition reactions of benzofuran-derived azadienes

6 Allylic Motifs as "1,4-Dipole" in [4 + 5] Annulations

6.1 Benzoxazinanones as "1,4-Dipole" in [4 + 5] Annulations

In 2018, Shibata and coworkers disclosed a palladium-catalyzed [4 + 5] cycloaddition of benzoxazinanones with vinylethylene carbonates, affording the nine-membered trifluoromethyl benzo[*c*][1, 5]oxazonines with good yields [120]. Notably, the reaction temperature affected reactivity dramatically, the highest yield was observed when the temperature was increased to 80 °C. The experiment result showed that trifluoromethyl substituent at the C-4 position of benzoxazinanones played an important role in this transformation, no desired nine-membered cyclized product was



R^1 = 9-Me, 10-F, 9-Cl, 9-Br

R^2 = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-FC_6H_4, 2-MeOC_6H_4, 2-furyl, 2-thienyl cyclohexyl, 2-naphthyl *et. al.*

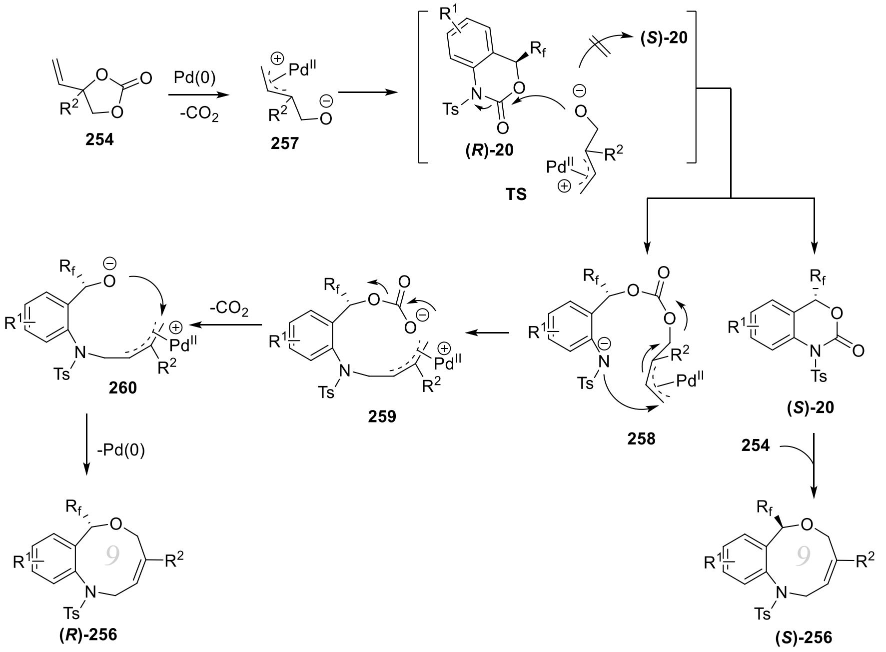
Scheme 64 Palladium-catalyzed [4+5] cycloaddition of benzoxazinanones with vinylethylene carbonates

obtained by using various vinyl-substituted benzoxazinanones. In 2020, the authors used Pd(OAc)$_2$/(*R*)-Tol-BINAP complex as catalyst, demonstrating the enantioselective synthesis of optically active CF$_3$-benzo[*c*][1, 5]oxazinones [121]. Interestingly, the authors found a kinetic resolution process of **20** with vinyl ethylene carbonates, that is, **(R)-256** could first be obtained with high enantiopurity in the presence of Pd(OAc)$_2$/(*R*)-Tol-BINAP complex. Then, the nonreactive enantiomer **(S)-20** reacted with vinylethylene carbonates to give the desired enantiomers **(S)-256** with high enantiopurity, the catalyst Pd(PPh$_3$)$_4$ without any chiral auxiliary was used as catalyst in this process (Scheme 64).

The authors proposed a plausible reaction mechanism. Firstly, the oxidative addition of Pd(0) with **254** followed by decarboxylation generates the π-allyl-Pd(II) complex **257**. Then, oxygen anion of **257** attacked the carbonyl carbon of (*R*)-**20**, followed by a ring-opening reaction to generate the chiral zwitterion **258**. (*S*)-**20** should be sterically mismatched with **257** and thus prevent the reaction (kinetic resolution). The nitrogen atom of chiral zwitterion **258** then attacked the terminal *sp*^{2}-hybridized carbon atom of the π-allyl-Pd moiety to provide the chiral zwitterion **260** by decarboxylation of the chiral zwitterion **259**. Finally, the species **260** underwent an intramolecular nucleophilic attack of the oxygen atom to the terminal position of the π-allyl-Pd moiety generated the [4+5] cycloaddition product **(R)-256** and regenerated the palladium catalyst. In addition, under achiral P(PPh$_3$)$_4$ catalysis, the reaction of **(S)-20** with **254** afforded **(S)-256** in a similar fashion with retention of the stereochemistry of **(S)-20** (Scheme 65).

6.2 Allyl Carbonate as "1,4-Dipole" in [4+5] Annulations

In 2020, Shibata and coworkers applied a C–N bond-cleaving ring-expansion strategy, developing a palladium-catalyzed [*n*+5] cycloaddition (*n*=4, 5, 6) for the synthesis of highly functionalized, medium-sized *gem*-difluoromethylene heterocyclic



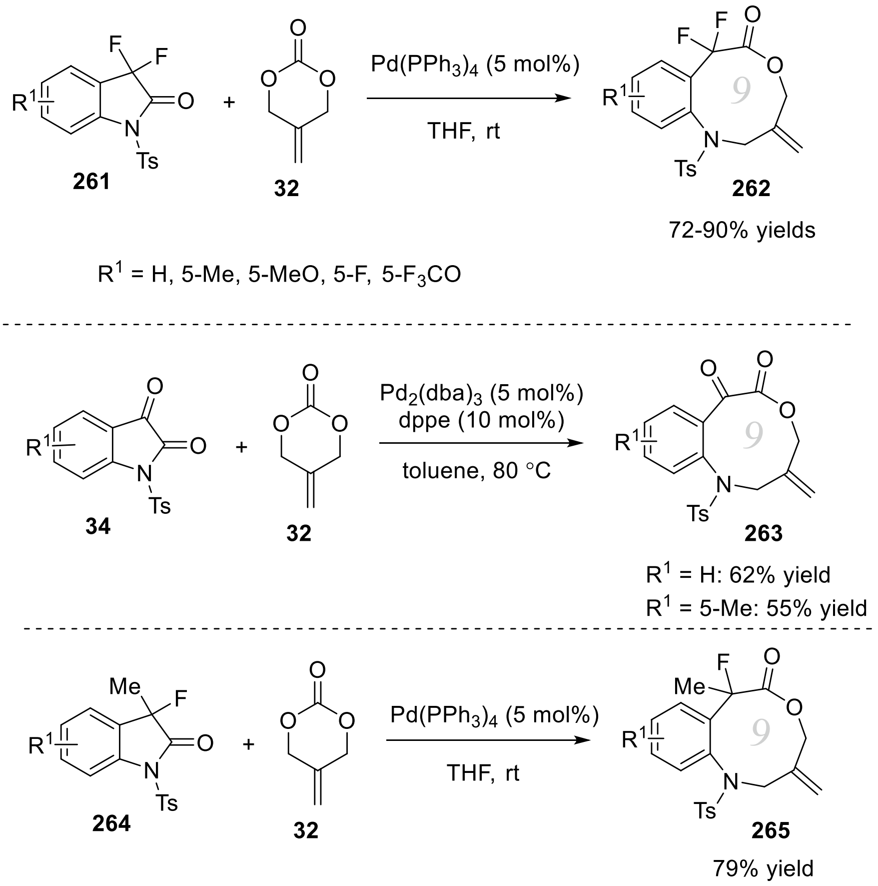
Scheme 65 A possible mechanism for palladium-catalyzed [4 + 5] cycloaddition of benzoxazinanones with vinylethylene carbonates

lactones [122]. Notably, when the authors used the 2-methylidenetrimethylene carbonates **32** as zwitterion precursors, the [4 + 5] cycloaddition reaction proceeded smoothly under Pd(PPh$_3$)$_4$ in THF at room temperature, producing the nine-membered *gem*-difluoromethylene lactones in good yields. It was noteworthy that a strong electron-withdrawing tosyl group of difluoro-oxindoles is essential for this ring expansion. No reaction occurred by changing *N*-protecting groups to *N*-benzyl or *N*-benzoyl group. In addition, methyl-substituted isatin **34** or 3-methyl-oxindoles **264** with a fluorine substituent could also react with 2-methylidenetrimethylene carbonates, affording the nine-membered *N*-heterocyclic lactones in moderate to good yields (Scheme 66).

7 Allylic Motifs as "1, 4-Dipole" in [4 + 6] Annulations

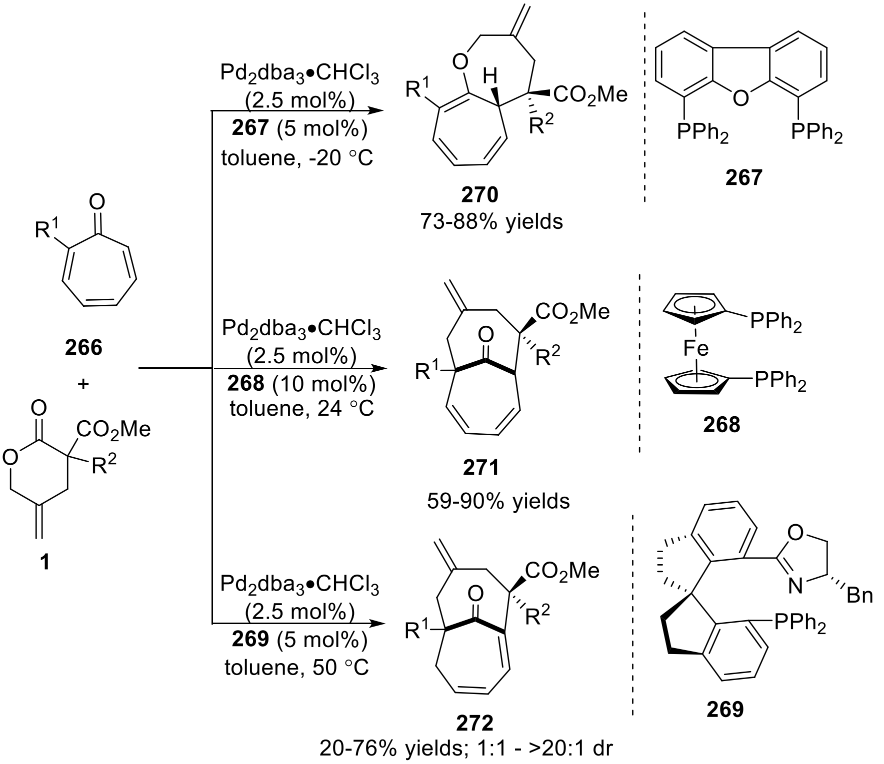
7.1 γ-Methylidene-δ-Valerolactones as a "1,4-Dipole" in [4 + 6] Annulations

Troponean including seven-membered cyclic ketone has served as reliable substrate for the preparation of bridged or fused bicyclic compounds. In 2020, Zhao and coworkers reported a palladium-catalyzed [4 + 6] cycloaddition of tropones with



Scheme 66 Palladium-catalyzed [4 + 5] cycloaddition reaction of 2-methylidenetrimethylene carbonates

γ-methylidene-δ-valerolactone [123]. In this transformation, three medium-sized bicyclic products could be selectively obtained by switching the reaction condition. When DBFphos (**267**) was used as ligand, the reaction displayed the highest selectivity for the formation of **270**, while the desired bicyclo[4. 4. 1]-undecadienes **271** were obtained in the presence of [Pd]/dppf complex. Notably, the use of bulky ligand **269** with gentle heating resulted in the synthesis of bridgehead alkene-containing bicyclo[4. 4. 1]-undecadienes **272**. It is worth noting that all three products could be selectively formed in good yields with high diastereoselectivity. Detailed mechanistic studies and DFT calculations were carried out to provide intriguing insight for the origin of the divergent reactivity of the intermediate formed in this catalytic system. In addition, derivatization of these medium-sized bicyclic compounds to a range of medium-sized bicyclic and polycyclic compounds was performed to demonstrate the potential utility of this transformations (Scheme 67).



Scheme 67 Palladium-catalyzed [4 + 6] cycloaddition of tropones with γ-methylidene-δ-valerolactone

8 Conclusions

Palladium-catalyzed 1,4-dipole cycloaddition represents a very promising strategy to construct the highly functionalized cyclic compounds from simple starting materials and has attracted interest from a large number of research groups since the proof of concept was reported. As described in this review, we have summarized the recent advances on palladium-catalyzed [4 + *n*] cycloadditions by using many kinds of precursors, including γ-methylidene-δ-valerolactones, benzoxazinanones, allyl carbonate, and vinyloxetane. With these excellent methods, various biologically active and synthetically useful cyclic compounds ranging from five-membered to ten-membered ring are able to be expediently synthesized by [4 + 1], [4 + 2], [4 + 3], [4 + 4], [4 + 5], and [4 + 6] cycloaddition process. Obviously, these reported methodologies show a bright prospect to further design and discover newly unprecedented dipolar cycloaddition modes and realize challenging chemical transformations. Therefore, palladium-catalyzed dipole cycloadditions are showing a great vitality and useful perspective in synthetic chemistry.

Although great progress has been achieved, palladium-catalyzed 1, 4-dipole cycloadditions are still an emerging research area, and there are still many challenges to be addressed: (a) a general, efficient method for chemical synthesis of medium-sized rings, especially chiral medium-sized rings, is still lacking; (b) only three types of π-allyl palladiums bearing *C*-, *N*-, *O*-nucleophilic site were well studied, while π-allyl palladiums bearing *S*- or *P*-nucleophilic site have still not been exploited; (c) the concept of green chemistry and sustainable development will prompt chemists to develop new avenues to lowering catalyst loading. Therefore, the growing demand for three-dimensional cyclic motifs in the field of pharmaceutical research urges the chemists to develop novel, practical active zwitterionic π-allyl palladium species. Thus we hope that new advances in palladium-catalyzed 1, 4-dipole cycloadditions will appear to promote the development of practical organic synthesis in the future.

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Data availability The data supporting this study's findings are openly available on the internet, as in the reference stated below. The authors also confirm that the data and materials supporting the findings of this study are available within the article.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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