IV.8 Synthesis of Natural Products via Carbopalladation

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A. INTRODUCTION

From a purely chemical perspective, the total synthesis of natural products presents a challenging proving ground for synthetic methodology. Chemists widely employ reactions that efficiently promote fragment coupling, annelate, close a variety of ring sizes (small, medium, or large), or introduce stereocenters with high diastereoselectivity or enantioselectivity. When the substrates for the transformation are either readily available or easily prepared, the reaction is particularly useful. Transformations that are insensitive to steric factors and tolerant of an array of potentially sensitive functionality are also desirable. Unique in the preparative chemist's arsenal are reactions that perform several of these tasks. Carbopalladation methodology fulfills all of these criteria and has been widely utilized in natural product and other complex molecule syntheses.

Carbopalladation is the reaction of a σ-bonded organopalladium complex **1** with an unsaturated molecule (such as an alkene **2**) to yield the migratory insertion product **3** (**Scheme 1**).[1] The reaction is tremendously flexible, allowing for a wide variety of structural types for both reactants **1** and **2**. The precursors of palladium complexes **1** are commonly alkenyl or aryl halides or triflates (**8** and **9**, respectively), the reaction of which is more commonly termed the Heck reaction.[2],[3] Allylic systems **10**, which react to provide π-allylpalladium complexes, can participate in the reaction as can benzylic precursors **11**. Acylpalladium complexes **12** also react and are commonly generated in the same reaction vessel by Pd-catalyzed carbonylation. Their unsaturated reaction partners include alkenes **2**, alkynes **4**, dienes **6**, allenes, and arenes, all of which can be electron rich or poor. Carbopalladation occurs in a *syn* fashion allowing the installation of stereocenters (**2**→**3**) or control of alkene geometry (**4**→**5**).

Carbopalladation reactions yield another carbon-bound palladium complex **13**, which can undergo a variety of reactions (**Scheme 2**). The most common pathway yields an alkene **14** via a *syn*-β-hydride elimination. Two other useful reactions are carbonylation (**13**→**15**) and anion capture (**13**→**16**), which provide opportunities for further functionalization.[4] Additionally, carbopalladation products can be induced to undergo another carbopalladation reaction, creating the opportunity to forge multiple carbon–carbon bonds.[5] Simple combinations of palladium complex precursors and reactions quickly

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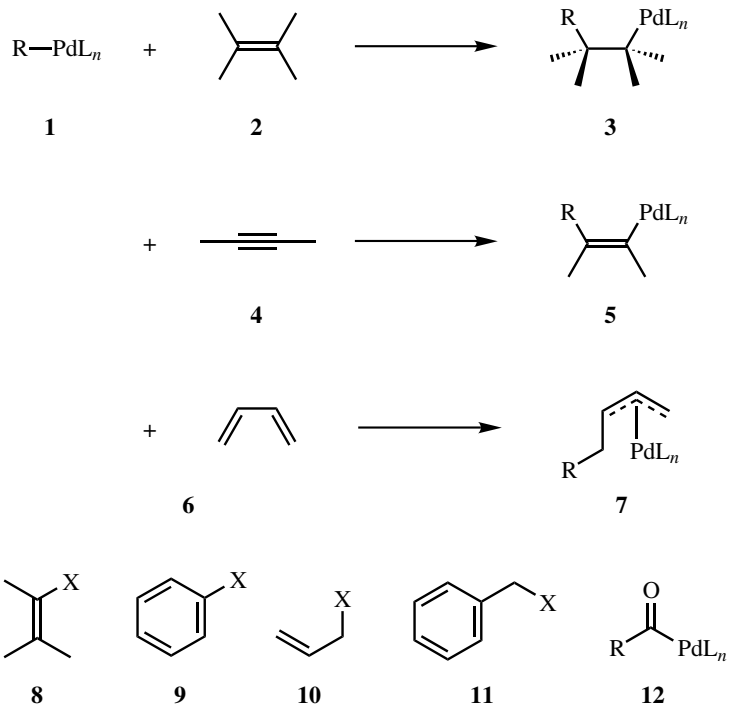
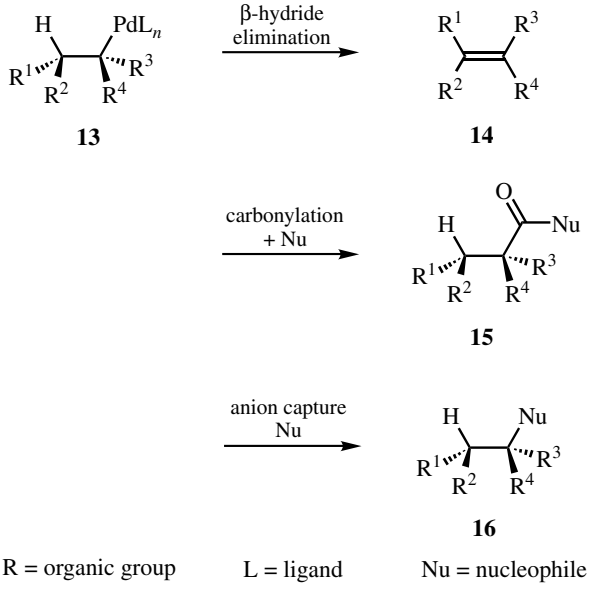


X = halogen, triflate, etc. L = ligand R = organic group

Scheme 1

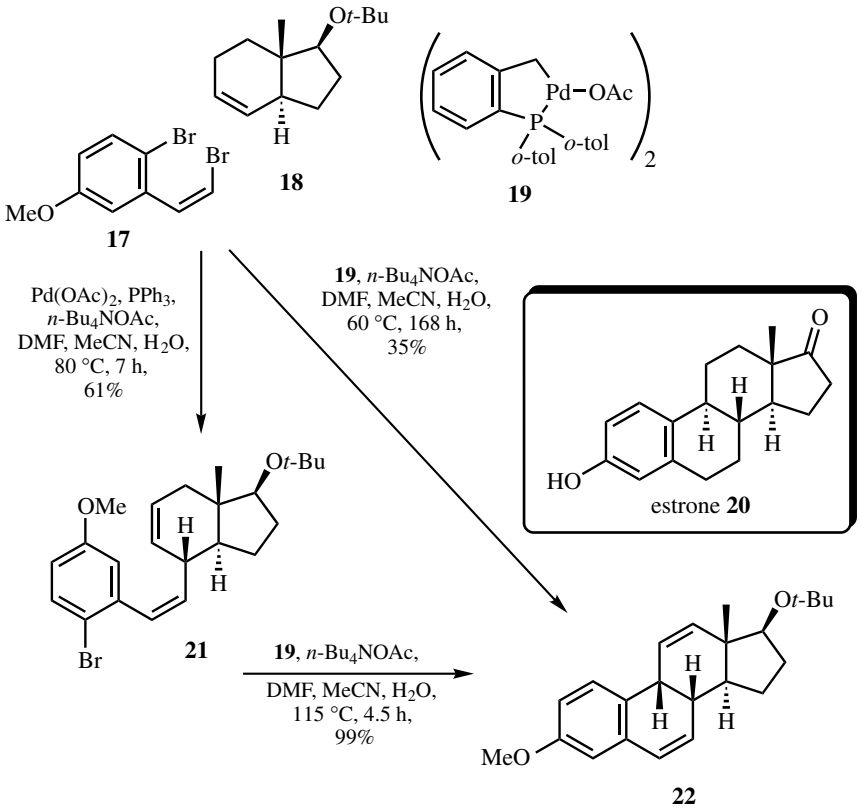


R = organic group L = ligand Nu = nucleophile

Scheme 2

lead to complex products of diverse structure, making carbopalladation a useful reaction for the preparation of a variety of complex targets.

One illustrative example of the synthetic potential of carbopalladation in natural product synthesis (**Scheme 3**) is a concise preparation of estrone **20**.[6],[7] Exposure of dibromide **17** to an appropriate catalyst in the presence of alkene **18** yields the intermolecular Heck product **21**. Stereoselectivity in this transformation is driven by the steric influence of the angular methyl group of **18**, which forces the reaction to take place on the opposite face. The reaction is also regioselective, and **21** is the only product isolated. Treatment of aryl bromide **21** with palladacycle **19**[8] efficiently induces a 6-*exo* intramolecular Heck reaction to construct the *cis*-fused decalin ring system embedded within tetracycle **22**. Both the inter- and intramolecular carbopalladation can be triggered in the same reaction by treating **17** and **18** with palladacycle **19** to directly provide tetracycle **22** in modest yield. The transformation highlights the potential for carbopalladation to simplify the construction of complex targets. In this sequence, the reaction accomplishes the key fragment coupling, regioselectively forms two carbon–carbon bonds, closes a six-membered ring, and diastereoselectively sets two ring junction stereocenters. The reaction also highlights the potential impact of new catalysts on these transformations. Palladacycle **19** catalyzes the intramolecular step for which normal catalyst systems fail.



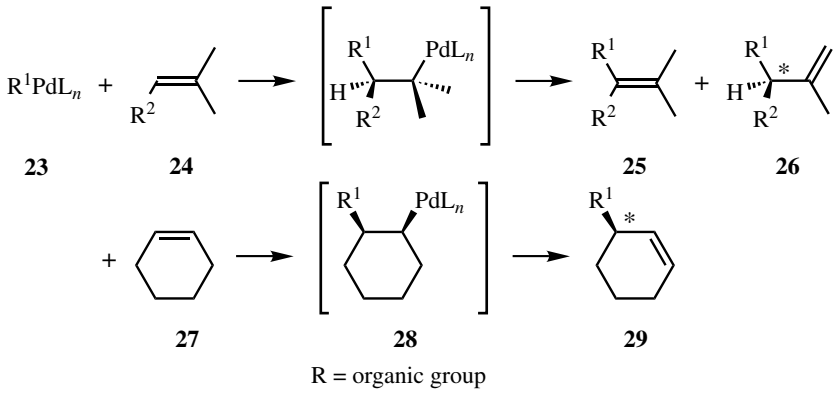
Scheme 3

The remainder of this section will focus on the different ways carbopalladation has been used to construct natural products.[9] First, **Sect. B** will consider intermolecular cases. Then, **Sect. C** will discuss intramolecular carbopalladation showing the potential of the reaction to create small, medium, or large rings. Finally, domino reactions, cycloisomerizations of enynes, and asymmetric reactions will be highlighted.

B. INTERMOLECULAR CARBOPALLADATION

B.i. Overview

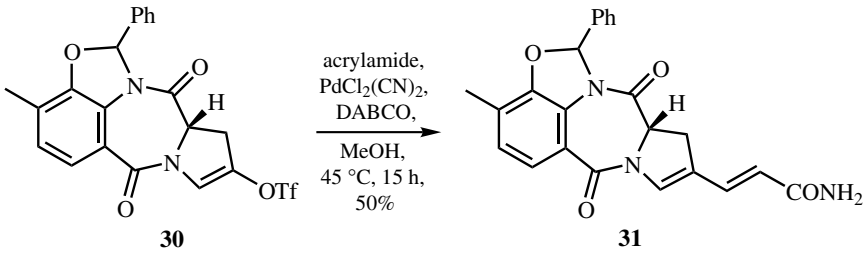
Intermolecular carbopalladation has been utilized in natural product synthesis for a variety of purposes. Strategic uses include side chain introduction, chain coupling followed by ring closure to effect a net annelation, diene synthesis, and fragment coupling. Carbopalladation between a generic palladium complex **23** and an alkene **24** can yield two different types of products after β-hydride elimination (**Scheme 4**). Alkene **25** is called the vinylic substitution product due to its relationship with the starting alkene **24**. The result of β-hydride elimination toward the formerly allylic carbon is alkene **26**, which is important due to the creation of a new stereocenter. Cyclic alkenes like cyclohexene **27** constitute a special case of the carbopalladation reaction. The *cis*-carbopalladation intermediate **28** is unable to undergo *syn*-β-hydride elimination to the substitution product. Rather, β-hydride elimination occurs to provide substituted cyclohexene **29** and results in the formation of a new stereocenter.

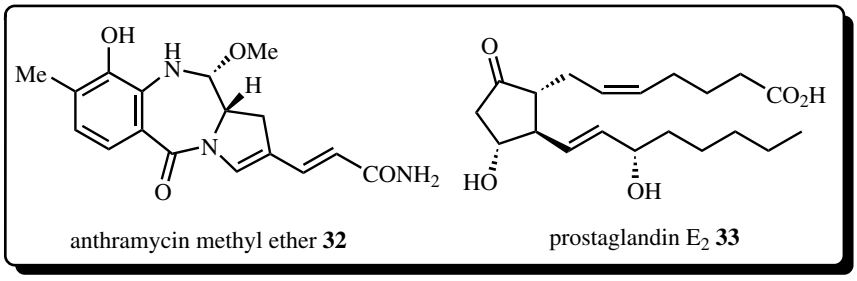


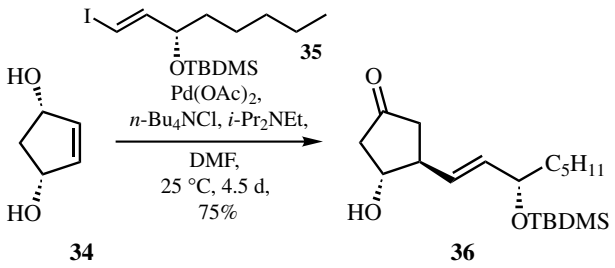
Scheme 4

B.ii. Vinylic Substitution

Side chain introduction by carbopalladation has been utilized in a total synthesis of anthramycin methyl ether (**32**) (**Scheme 5**).[10] Heck reaction of the alkenyl triflate **30** with acrylamide installs the necessary three-carbon chain in moderate yield. The desired alkene geometry and oxidation state are observed in the dienamide **31** with no need for protection of the primary amide. The organopalladium precursor can also be part of the side chain being introduced as illustrated in a synthesis of prostaglandin E_2 **33**.[11]





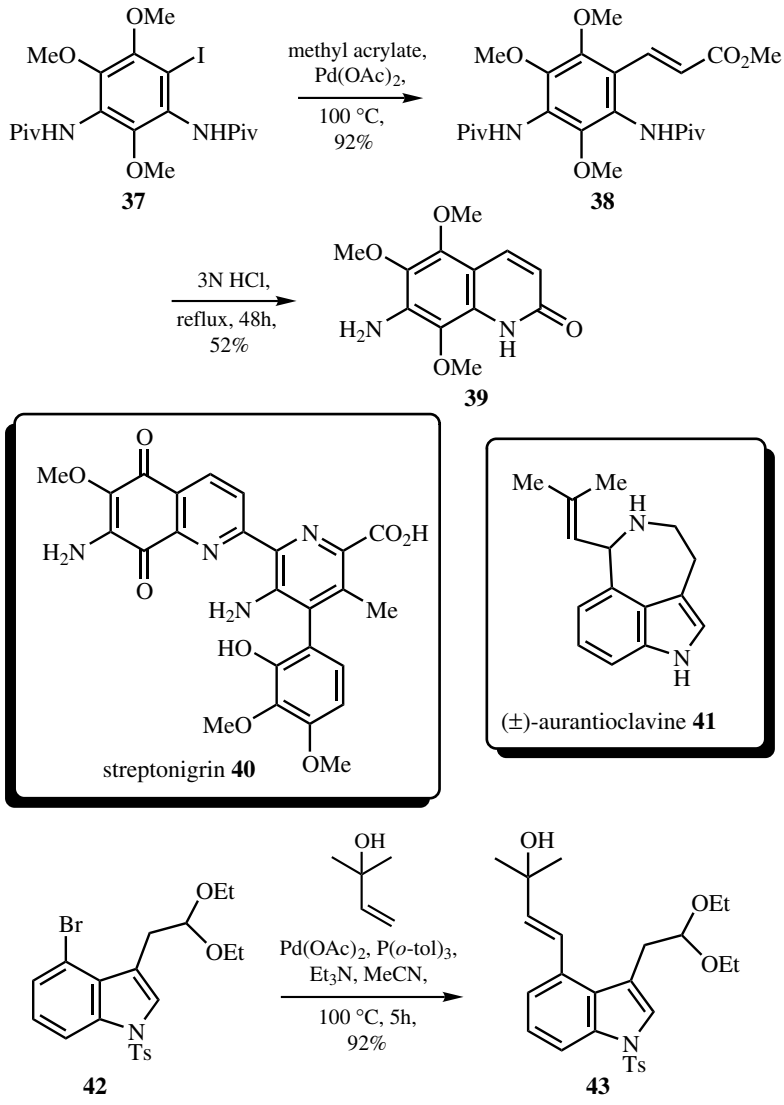


Scheme 5

Enantiopure alkenyl iodide **35** reacts with the unprotected diol **34** in the presence of palladium acetate to provide cyclopentanone **36** plus a diastereomer in 75% yield.

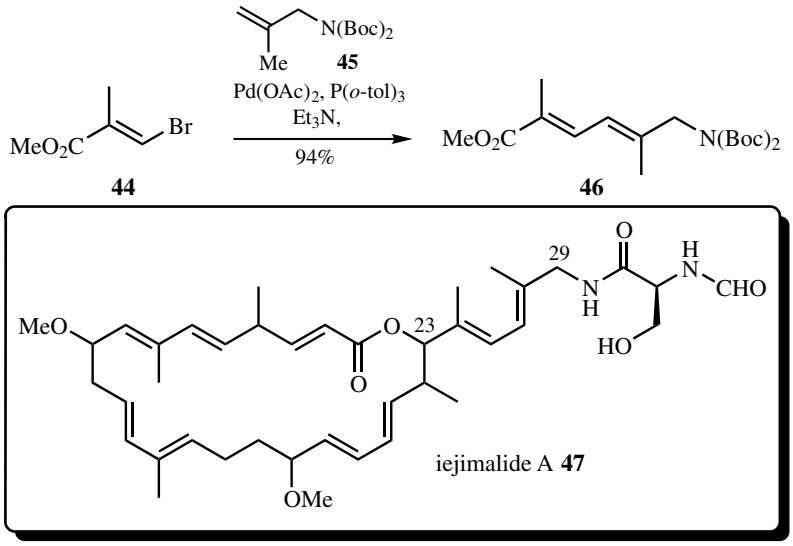
Another common use of carbopalladation is to effect a net annelation by side chain installation followed by cyclization. One example from the synthesis of a protected form of the 2-quinolone portion of streptonigrin **40** begins with iodide **37** (**Scheme 6**).[12] Heck reaction of this electron-rich fully substituted aryl iodide **37** with methyl acrylate provides the substitution product **38**. Extended reflux of **38** under acidic conditions promotes double deprotection, isomerization, and cyclization reaction yielding enamide **39**. Another example from the synthesis of (±)-aurantioclavine **41** involves coupling of aryl bromide **42**.[13] Standard Heck conditions provide the substitution product **43** in excellent yield at the appropriate oxidation state for cyclization to form the azepine ring *en route* to the natural product.

Vinylic substitution carbopalladation can also be employed to synthesize dienes (**Scheme 7**). Bromide **44** and the protected allylic amine **45** efficiently couple to yield diene **46** stereoselectively.[14] Diene **46** has been used to build a C_{23}–C_{29} fragment of the cytotoxic macrocycle iejimalide A (**47**). Diels–Alder reactions of dienes generated by similar reactions can also be envisioned to be useful in complex molecule synthesis.



Scheme 6

One pivotal application of intermolecular carbopalladation is fragment coupling (**Scheme 8**). The reaction has been chosen for this purpose due to its efficiency and mild reaction conditions. In principle, the reaction has an advantage over other cross-coupling protocols, such as the Stille reaction, in that no special group (like a trialkylstannane) needs to be installed on one of the coupling partners. Furthermore, stoichiometric quantities of toxic tin salts are not reaction by-products simplifying product isolation and waste disposal. One interesting example comes from a synthesis of the pigments G-2N **51** and G-2A **52**.[15] Treatment of iodoaryltriflate **49** and alkenyl triflate **48** with an unusual catalyst cocktail efficiently yields the pentacyclic alkene **50**. The unusual catalyst derived from palladium bistrifluoroacetate and tri(pentafluorophenyl)phosphine promotes coupling of an aryl iodide in



Scheme 7

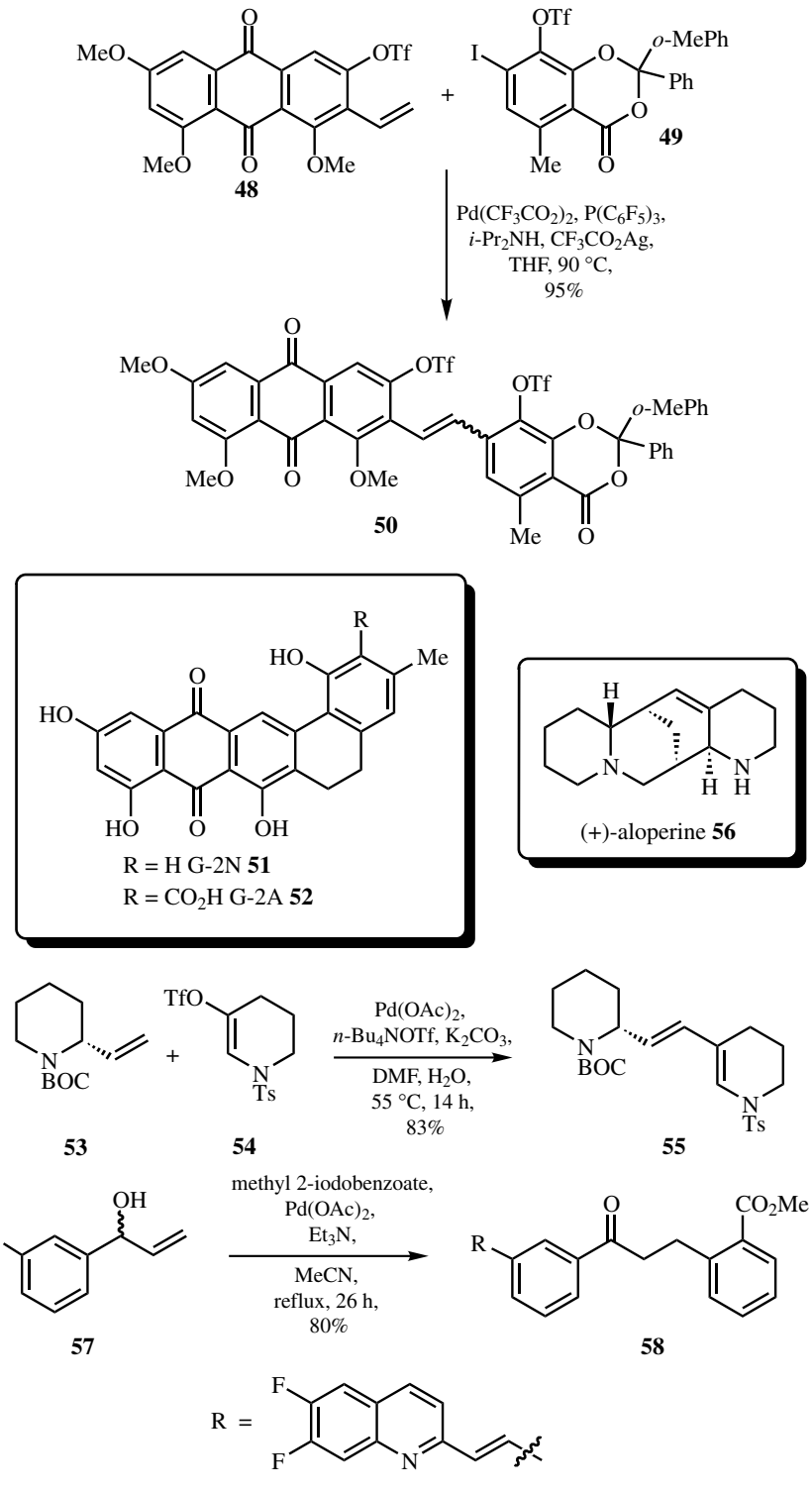
the presence of two potentially reactive aryl triflates. Another example of effective fragment coupling comes from a synthesis of (+)-aloperine **56**.[16] Heck reaction of triflate **54** with alkene **53** yields the *trans*-alkene **55**. Notably, the reaction occurs without racemization of the allylic stereocenter of enantiopure **53**. One hallmark of reaction practicality is its utilization by industrial process chemists. Fragment coupling via the Heck reaction has been used in the synthesis of the LTD_4 antagonist L-708738.[17] Coupling of methyl 2-iodobenzoate with allylic alcohol **57** on a 1.92 mole scale yielded 0.728 kg of ketone **58** in 80% yield. Selectivity in the reaction of the terminal alkene over the disubstituted alkene was observed.

B.iii. Carbopalladation with Double Bond Migration

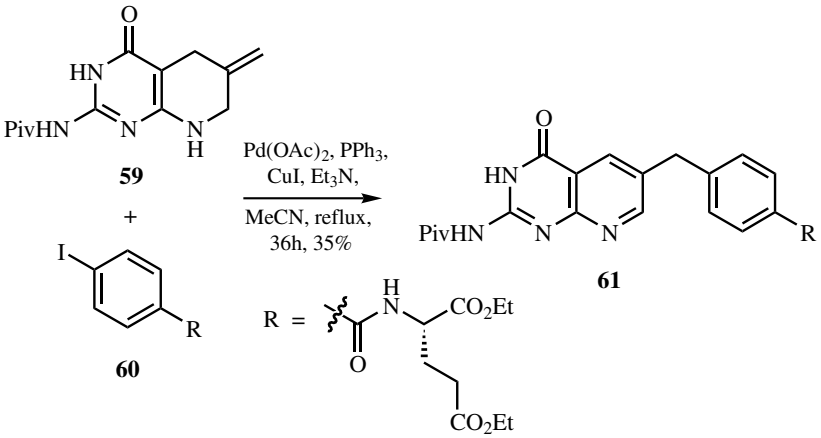
Carbopalladation with double bond migration has been utilized to couple fragments. An example from the synthesis of potential anticancer agents is shown in **Scheme 9**.[18] Aryl iodide **60** couples with *exo*-alkene **59** to give **61** after Heck coupling and oxidation/aromatization in modest yield. The reaction is unusual in that the carbopalladation intermediate contains a relatively unstable tertiary alkyl–palladium bond.

B.iv. Mechanism of the Asymmetric Intermolecular Heck Reaction

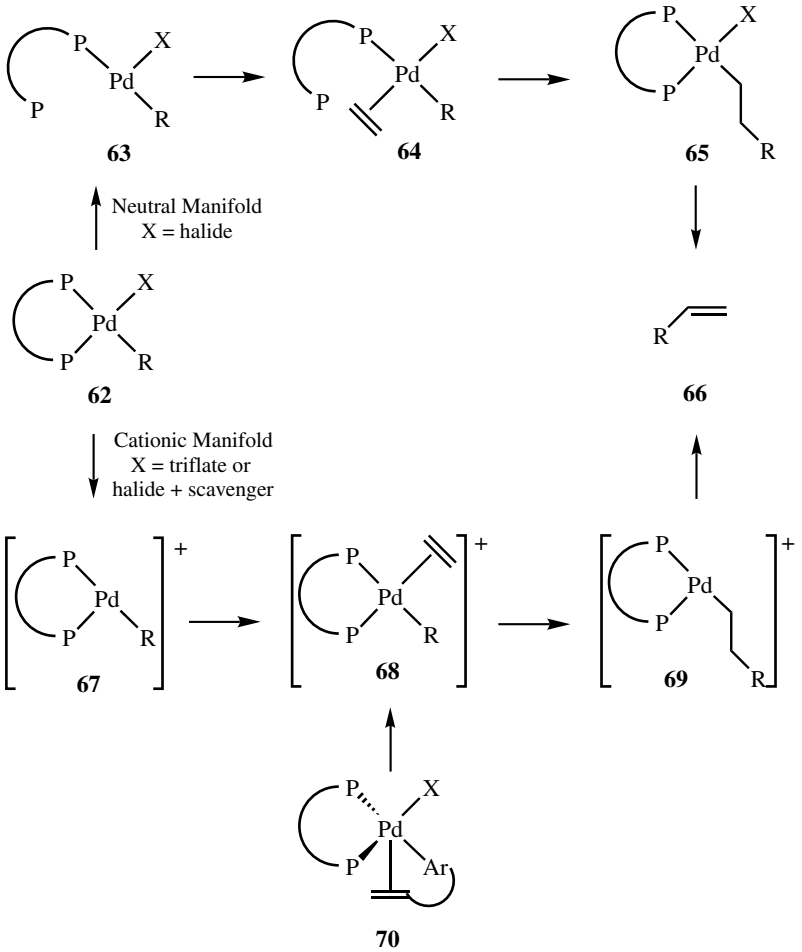
The asymmetric reaction is an area of great potential impact for carbopalladation chemistry (see **Sect. IV.2.3**). To date, most research has been devoted to the Heck reaction and an understanding of the reaction is evolving.[19]–[21] Several reaction manifolds are potentially accessible and are illustrated in **Scheme 10**. Oxidative addition of a palladium bisphosphine complex to RX provides complex **62**. When X is a halide, the reaction commonly proceeds via the neutral manifold of the carbopalladation mechanism. Along this pathway, one of the phosphines dissociates to yield **63**, providing an opportunity for the reacting alkene to coordinate the metal yielding **64**. After migratory insertion generates complex **65**, β-hydride elimination provides the alkene **66** and stoichiometric base


MeO
OTf
MeO
O
OMe
48
+
OTf
I
o-MePh
Ph
Me
49
Pd(CF3CO2)2, P(C6F5)3,
i-Pr2NH, CF3CO2Ag,
THF, 90 °C,
95%
50
R = H G-2N 51
R = CO2H G-2A 52
(+)-aloperine 56
TfO
BOC
Ts
Pd(OAc)2,
n-Bu4NOTf, K2CO3,
DMF, H2O,
55 °C, 14 h,
83%
53
54
55
OH
methyl 2-iodobenzoate,
Pd(OAc)2,
Et3N,
MeCN,
reflux, 26 h,
80%
CO2Me
57
58
R =

Scheme 8



Scheme 9



Scheme 10

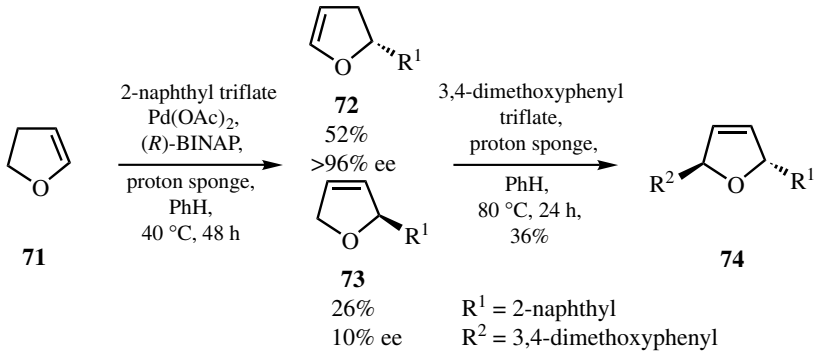
transforms the resultant hydridopalladium species back into the catalytically active intermediate. Experimentally it has been determined that asymmetric Heck reactions give high enantioselectivities with bidentate ligands, and BINAP is frequently the premier phosphine. Typically, when reactions proceed via the neutral pathway, enantioselectivity is poor (although there are some notable exceptions[22]).

When the substrate is a triflate, or when a halide is subjected to appropriate reaction conditions in the presence of a halide scavenger (such as silver or thallium salts), the reaction proceeds via the cationic manifold. After oxidative addition, dissociation of X yields cationic intermediate **67**. Alkene coordination provides **68** and migratory insertion delivers **69**. β-Hydride elimination then yields the desired product **66**. Of importance in the pathway **62→67→68→69→66** is that both phosphines maintain contact with the metal throughout the process. This is ostensibly the factor responsible for the high enantioselectivities observed for reactions that are thought to proceed along this pathway. This contrasts with the course of events in the neutral pathway, where phosphine dissociation is thought to be responsible for low enantioselectivities.

Research into the mechanism of the Heck reaction continues and the understanding of the reaction is increasing. Recent research has revealed that in some intramolecular cases another mechanism is observed.[23] Cationic intermediate **68** can be accessed by associative displacement via the pentacoordinate intermediate **70**, leading to high enantioselectivity from a reaction that might be thought to proceed via a neutral pathway. Other studies have also identified key roles for pentacoordinate intermediates as well as anionic complexes.[21]

B.v. Asymmetric Intermolecular Carbopalladation

An example of the use of an intermolecular carbopalladation in complex molecule synthesis is the preparation of a PAF (platelet activating factor) antagonist (**Scheme 11**).[24] In the key step, an intermolecular Heck reaction of 2-naphthyl triflate with 2,3-dihydrofuran **71** yields 2-naphthyl-2,3-dihydrofuran **72** in 52% yield with excellent enantioselectivity. The reaction presumably occurs via the cationic manifold and the alkene is isomerized by a hydropalladation/dehydropalladation reaction. The minor product 2,5-dihydrofuran **73** is obtained in 26% yield with modest enantioselectivity favoring the opposite absolute configuration at the key center. Critical to the reaction is the use of the sterically demanding and highly basic proton sponge [1,8-bis(dimethylamino)naphthalene] as the base. It is



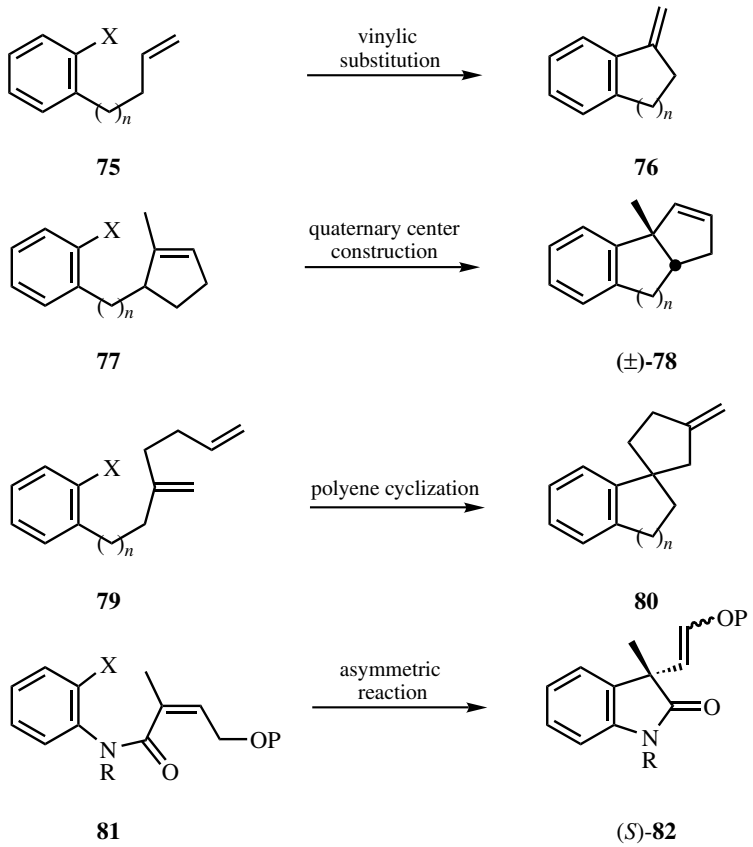
Scheme 11

postulated that one key factor in the high enantioselectivity for the formation of **72** is a kinetic resolution hydropalladation/dehydropalladation reaction of **73** in which the base plays a fundamental role. Without isolation a second Heck reaction with 3,4-dimethoxyphenyltriflate provides a 36% yield (based on 2-naphthyl triflate) of optically pure diaryldihydrofuran **74**. Hydrogenation of the alkene yields the desired PAF antagonist.

C. INTRAMOLECULAR CARBOPALLADATION

C.i. Overview

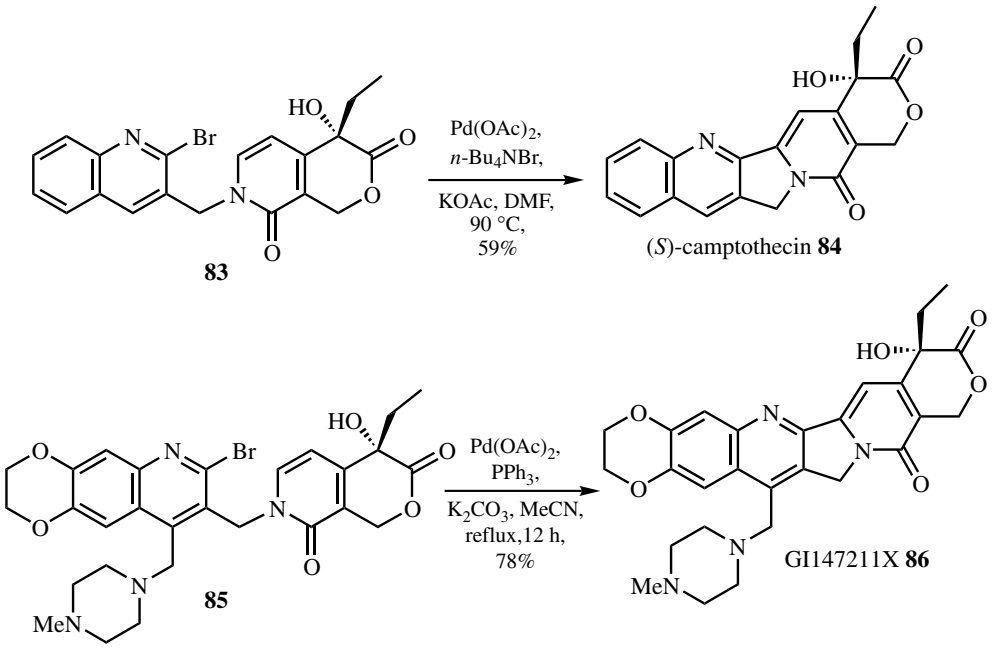
Intramolecular carbopalladation has widely been used to assemble the polycyclic frameworks of natural products. The majority of these carbopalladations are intramolecular Heck reactions and examples of 5-*exo*, 6-*exo*, 7-*exo*, 8-*exo*, 6-*endo*, 8-*endo*, and macrocyclic ring closures will be presented (**Scheme 12**). Examples fall into two basic categories: vinylic substitution (**75**→**76**) and quaternary center construction (**77**→**78**). Investigation of domino reactions like polyene cyclizations (**79**→**80**) and asymmetric Heck reactions (**81**→**82**) has been fruitful.



Scheme 12

C.ii. 5-*exo* Intramolecular Carbopalladation

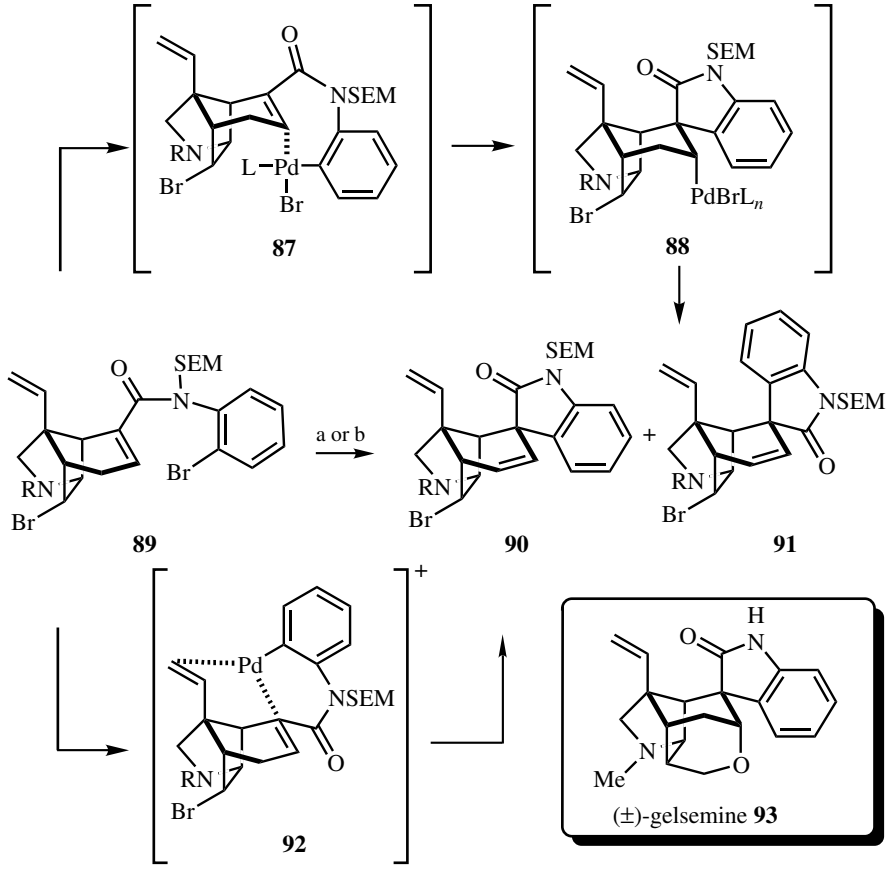
The intramolecular Heck reaction is an excellent method for closing five-membered rings due to the facility of 5-*exo* carbopalladation (**Scheme 13**). Comins and co-workers have employed a 5-*exo* intramolecular Heck substitution reaction in a concise synthesis of (*S*)-camptothecin **84**.[25] The reaction plays a key strategic role in this synthesis due to the ease of preparing the substrate. Reaction precursor **83** is convergently assembled by *N*-alkylation of a pyridone with a halomethyl-bromoquinoline. Cyclization of the aryl bromide **83** to the natural product **84** occurs under Jeffery's reaction conditions.[26] The reaction has one unusual mechanistic feature. After insertion and carbopalladation the intermediate could be categorized as a π-allylpalladium complex or a vinylogous palladium amide enolate. Thus, elimination may be base-initiated rather than a β-hydride elimination. The potential of (*S*)-camptothecin **84** as an anticancer agent has stimulated analog syntheses, some of which have been based on Comins's approach. One such analog, for which a related salt is undergoing clinical evaluation, is GI147211X **86**.[27] The reaction of bromide **85** has been scaled up to provide quantities of **86** in 125 g batches.



Scheme 13

The 5-*exo* carbopalladative construction of oxindoles has been widely investigated. One intriguing example comes from an approach toward gelsemine **93** (**Scheme 14**).[28] Cyclization of aryl bromide **89** produces diastereomeric oxindoles **90** and **91**. Conditions were developed that favor the synthesis of either isomer. Exposure of **89** to the palladium catalyst $Pd_2(dba)_3$ under "ligandless" conditions provides spirocyclic oxindole **90** as the major product in good yield. In this reaction, insertion of the transition metal into the carbon–bromine bond and complexation to the eneamide alkene leads to complex **87**. Migratory insertion then gives intermediate **88**, which after β-hydride elimination provides **90**.

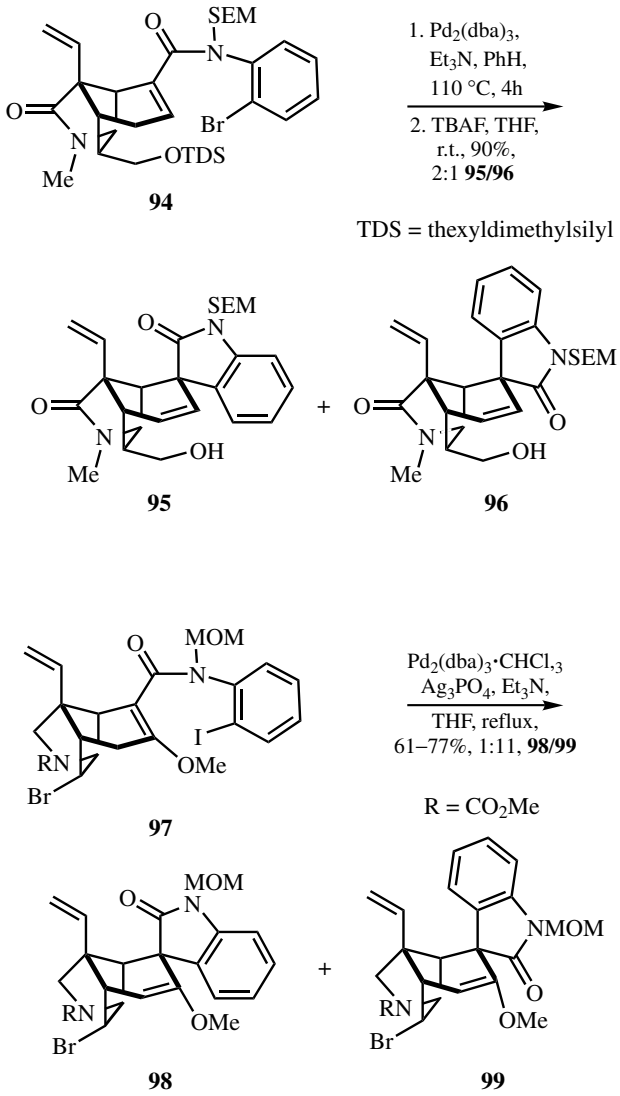
One particularly remarkable feature of this reaction is that it occurs on the *endo* face of **89** and builds a quaternary center in the congested environment of the proximal two-carbon bridge. The diastereoselectivity of the reaction could be reversed by switching solvents and adding Ag_3PO_4 to the reaction mixture. Under these conditions the silver salt is thought to remove the bromine from the coordination sphere of the palladium intermediate leading to the proposal of cationic intermediate **92**. Additional coordination to the vinyl group is invoked to explain the selectivity of the reaction. Experimental support for this idea comes from the cyclization of the corresponding saturated intermediate. Its cyclization under similar conditions provides a 1:1 mixture of stereoisomeric oxindoles.



R = CO_2Me (a) $Pd_2(dba)_3$, Et_3N, tol, 110 °C, 80–95%, 89:11, **90/91**.
L = ligand (b) $Pd_2(dba)_3$, Ag_3PO_4, THF, 66 °C, 77%, 3:97, **90/91**.

Scheme 14

These reaction conditions have been employed in two total syntheses of (±)-gelsemine **93** on similar intermediates (**Scheme 15**). In one synthesis the key reaction (**94→95**) is heavily sterically biased due to the presence of the bulky CH_2OTDS group.[29] In spite of this obstacle, a 2:1(**95/96**) ratio of oxindoles favoring spirocycle **95** is produced. The reaction will also tolerate a tetrasubstituted alkene. Heck cyclization of vinylogous carbamate **97** under cationic conditions stereoselectively delivers oxindole **99** *en route* to

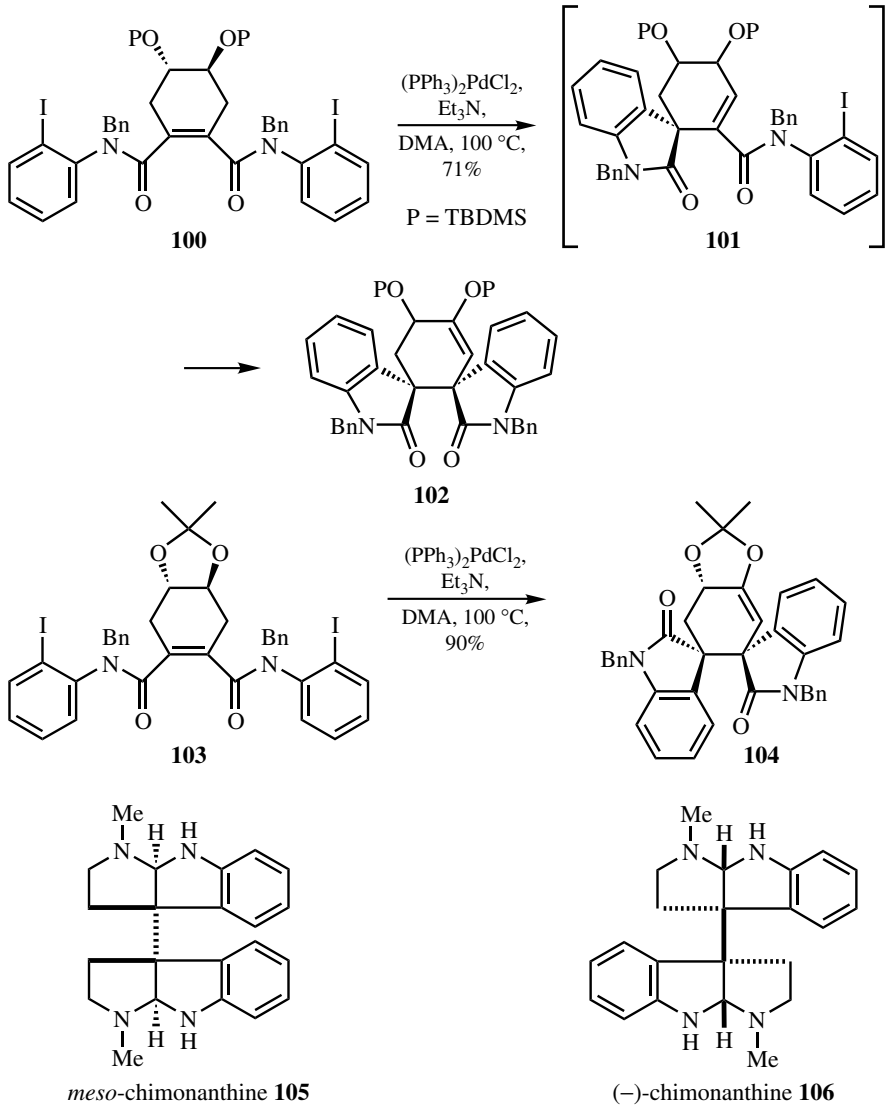


Scheme 15

(±)-gelsemine **93**.[30] It is interesting to note that either stereochemical result can tactically be utilized to reach the natural product.

The 5-*exo* intramolecular Heck reaction has been employed to construct both *meso*-chimonanthine **105** and (−)-chimonanthine **106** (**Scheme 16**).[31] The synthetically most challenging structural features of these bispyrroloindoline alkaloids are their vicinal quaternary centers. The synthetic plan relies on two sequential 5-*exo* carbopalladations to stereoselectively produce pentacycles **102** and **104** from closely related intermediates. Heck cyclization of **100** requires a challenging tetrasubstituted alkene insertion to provide **101**. A second 5-*exo* carbopalladation reaction adjacent to the newly formed quaternary center installs the second quaternary center and oxindole unit. The tartrate-derived ene-diamide **100** underwent bis-5-*exo* carbopalladation when

heated with $(PPh_3)_2PdCl_2$ to provide a single bisoxindole **102** in 71% yield. Pentacycle **102** has a *meso* relationship between the two oxindole units. The remote TBDMS-protected alcohols influence the reaction toward the product **102**, which is converted to *meso*-chimonanthine **105**. An additional challenge was to alter the stereoselectivity of the transformation either by manipulating the substrate or tuning the catalyst with the goal of producing either antipode in addition to the *meso* alkaloid. Changing the alcohol-protecting group to an acetonide altered the stereoselectivity of the double cyclization. Exposure of diiodide **103** to similar reaction conditions stereoselectively provided hexacycle **104** in excellent yield. In this case, conversion of the bisoxindole **104** to a bispyrroloindoline yielded (−)-chimonanthine **106**.



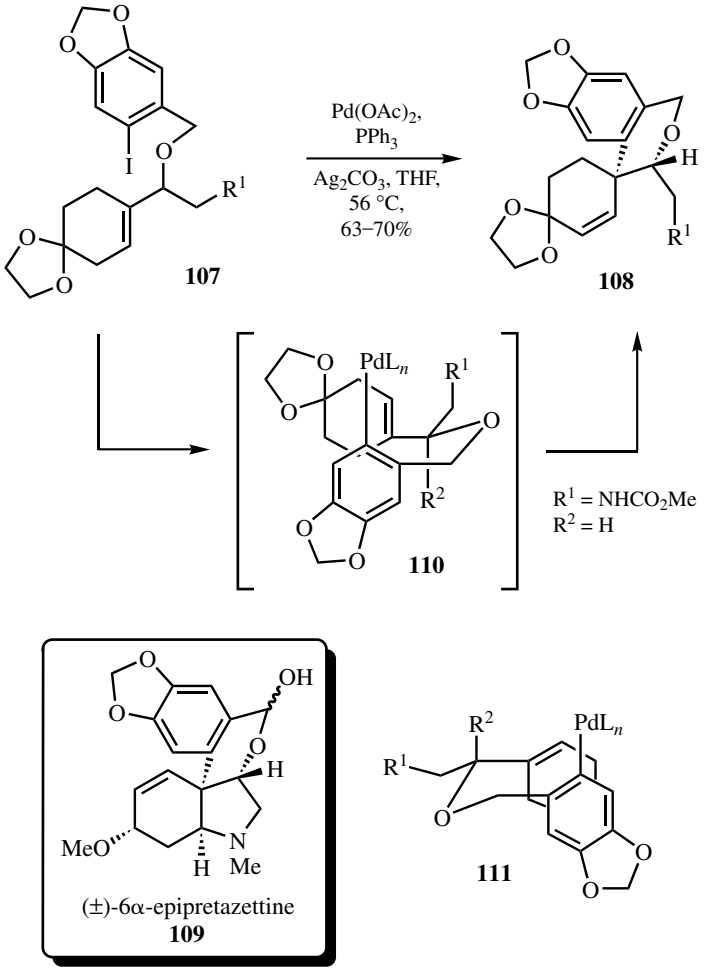
100 **101** **102** **103** **104**

meso-chimonanthine **105** (−)-chimonanthine **106**

Scheme 16

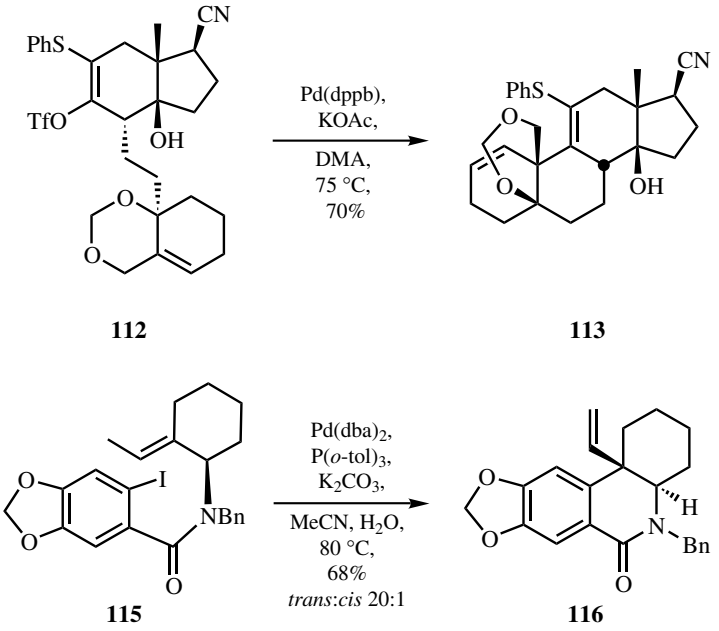
C.iii. 6-*exo* Intramolecular Carbopalladation

Carbopalladation has also been employed in the construction of six-membered rings. Most examples are 6-*exo* cyclizations as is the pyran ring synthesis (**107→108**) used in the construction of (±)-6α-epipretazettine **109** and (±)-tazettine (**Scheme 17**).[32] The Heck cyclization formed a quaternary center with a diastereoselectivity in excess of 20:1. The selectivity of the reaction is of particular interest in this case as it provides information about the orientation of the carbon–palladium σ bond and the reacting alkene in the carbopalladation transition state. Two limiting transition state geometries for the closure are intermediate **110**, which leads to the observed product, and intermediate **111**, which would lead to a diastereomer. In the preferred transition state **110**, the carbon–palladium σ bond and alkene are eclipsed, which is a lower energy state than the corresponding twisted orientation **111**.



Scheme 17

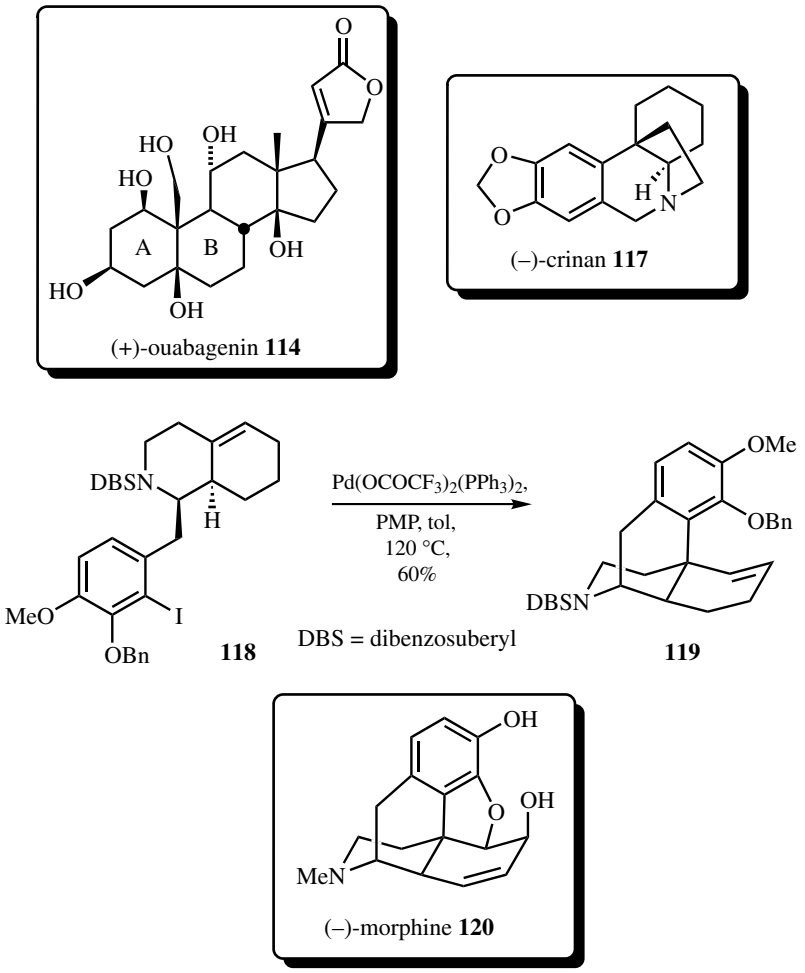
One common target of intramolecular 6-*exo* carbopalladations are *cis*-fused decalins. Of the numerous examples from natural product syntheses, one of the most interesting cases arises from complex steroid synthesis (**Scheme 18**). In pursuit of enantiopure cardenolides like (+)-ouabagenin **114** an intramolecular Heck approach to form the *cis*-fused AB ring system has been reported.[33] Treatment of tetrasubstituted α-sulfenyl enol triflate **112** with Pd(dppb) in the presence of KOAc gave the pentacyclic nitrile **113** in 70% yield. Protection of the tertiary alcohol during the transformation is not required and the integrity of the potentially labile dioxolane is maintained. The *cis* A/B ring juncture is observed in the only isolated product. As with most trends there are exceptions. An example of the formation of a *trans* ring juncture from an intramolecular carbopalladation comes from a synthesis of (−)-crinan **117**.[34] Cyclization of aryl iodide **115** under standard conditions provides a 20:1 mixture of the *trans*-fused tetracycle **116** and the *cis*-fused isomer in 68% yield. In addition to establishing the stereochemistry of the ring juncture, the reaction also constructs a quaternary center with moderate efficiency. Another example of the potential of the reaction comes from a total synthesis of (−)-morphine **120**.[35] Cyclization of the electron-rich aryl iodide **118** under forcing reaction conditions provides the alkene **119**. In the reaction, the aromatic substituent must assume an axial orientation and swing over the octahydroisoquinoline core to forge the critical quaternary center and complete the synthesis of the carbon skeleton. The newly formed alkene is ideally situated to form the final furan ring and install the functionality needed to complete the synthesis. Historically, this bond was created under cationic cyclization conditions for which an electron-rich aryl ring was necessary to form the critical bond. One notable advantage of intramolecular carbopalladation is that either electron-rich or electron-poor aryl rings can be employed. This capacity has been exploited to prepare several electron-poor pyridinyl morphine analogs.[36]



112 **113**

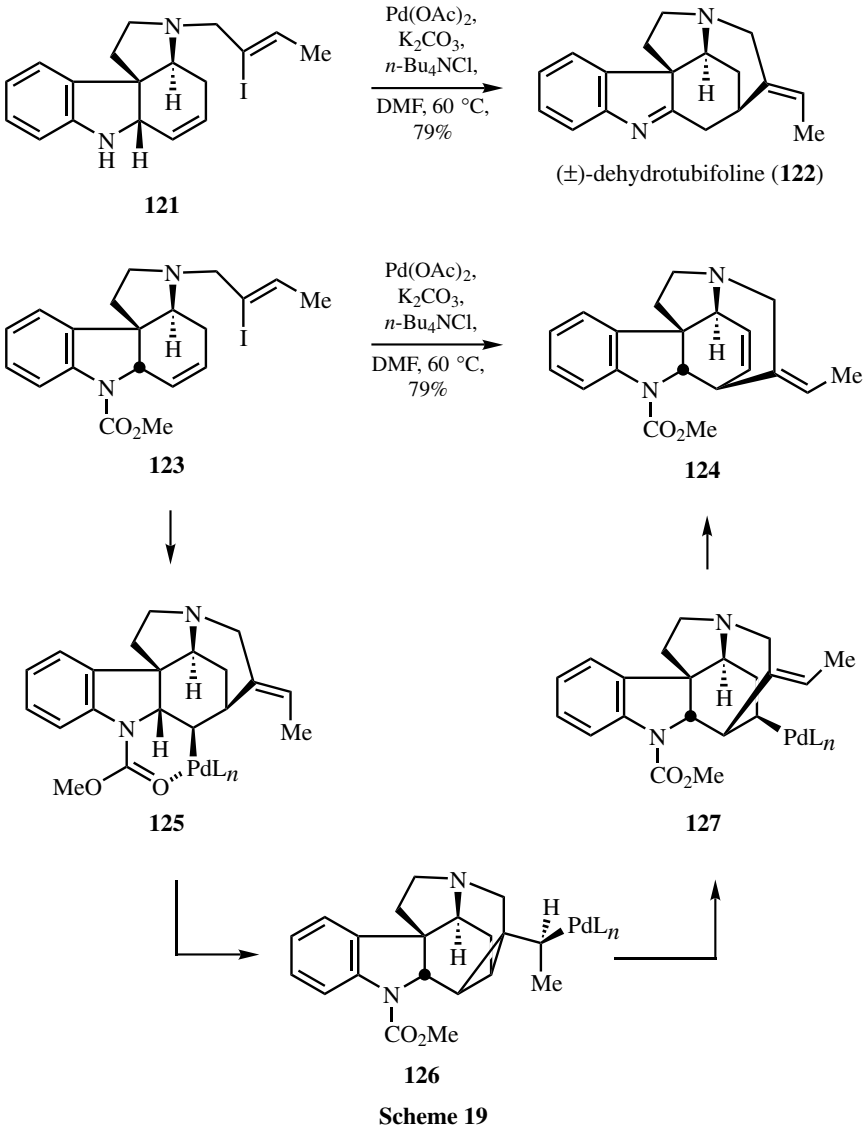
115 **116**

Scheme 18 (*Continued*)



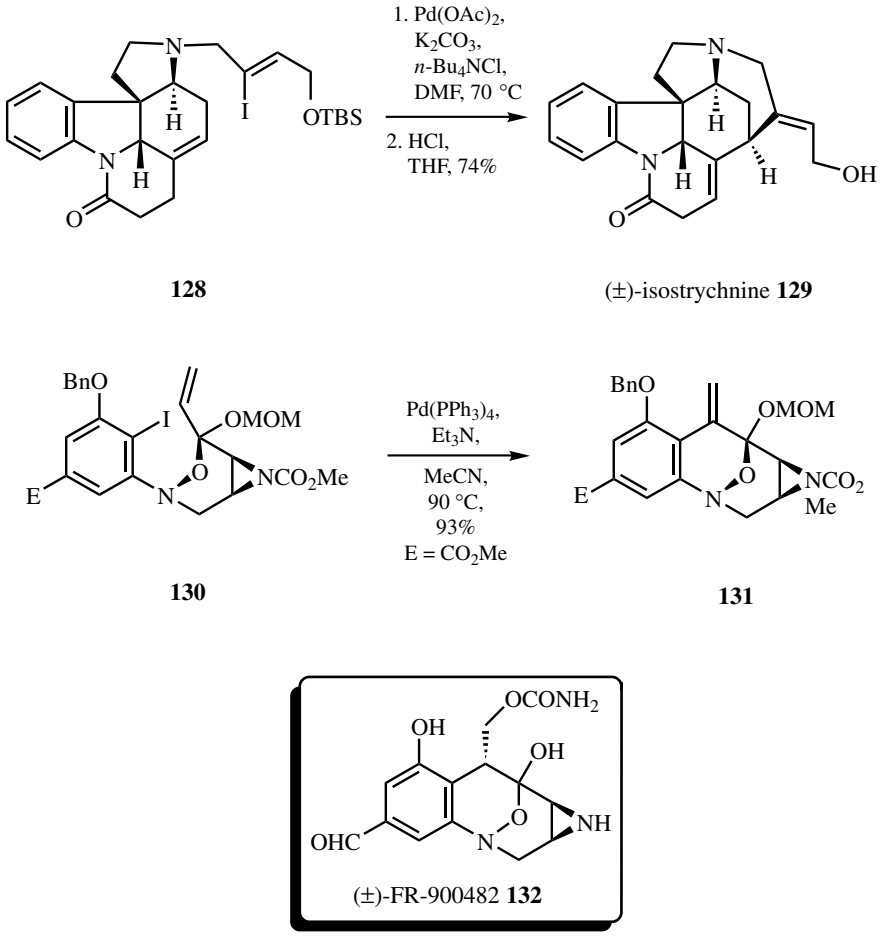
Scheme 18

The *Strychnos* alkaloids have received extensive attention from synthetic chemists due to their complex structures and physiological activities. One challenge in their synthesis is control of exocyclic alkene geometry. The intramolecular Heck reaction has been selected to assemble these polycyclic structures because it preserves alkene geometry and efficiently closes rings. An example is the conversion of iodide **121** into (±)-dehydrotubifolene **122** (**Scheme 19**).[37] 6-*exo* Cyclization under Jeffery's conditions, β-hydride elimination, and enamine–imine tautomerization lead to the desired product when the indoline nitrogen is unprotected. One unexpected finding in this system was that reaction of the corresponding carbamate **123** provides the 7-*endo* product **124** with inversion of alkene geometry.[38] The mechanistic rationale invokes 6-*exo* cyclization to provide palladium complex **125**, which is stabilized by carbamate complexation, preventing β-hydride elimination. A second carbopalladation creates the cyclopropylmethyl palladium complex **126**, which rapidly undergoes cyclopropylmethyl to homoallyl rearrangement to give **127**. β-Hydride elimination then ensues to provide the observed product. Similar reactions are precedented in simpler systems.[39]



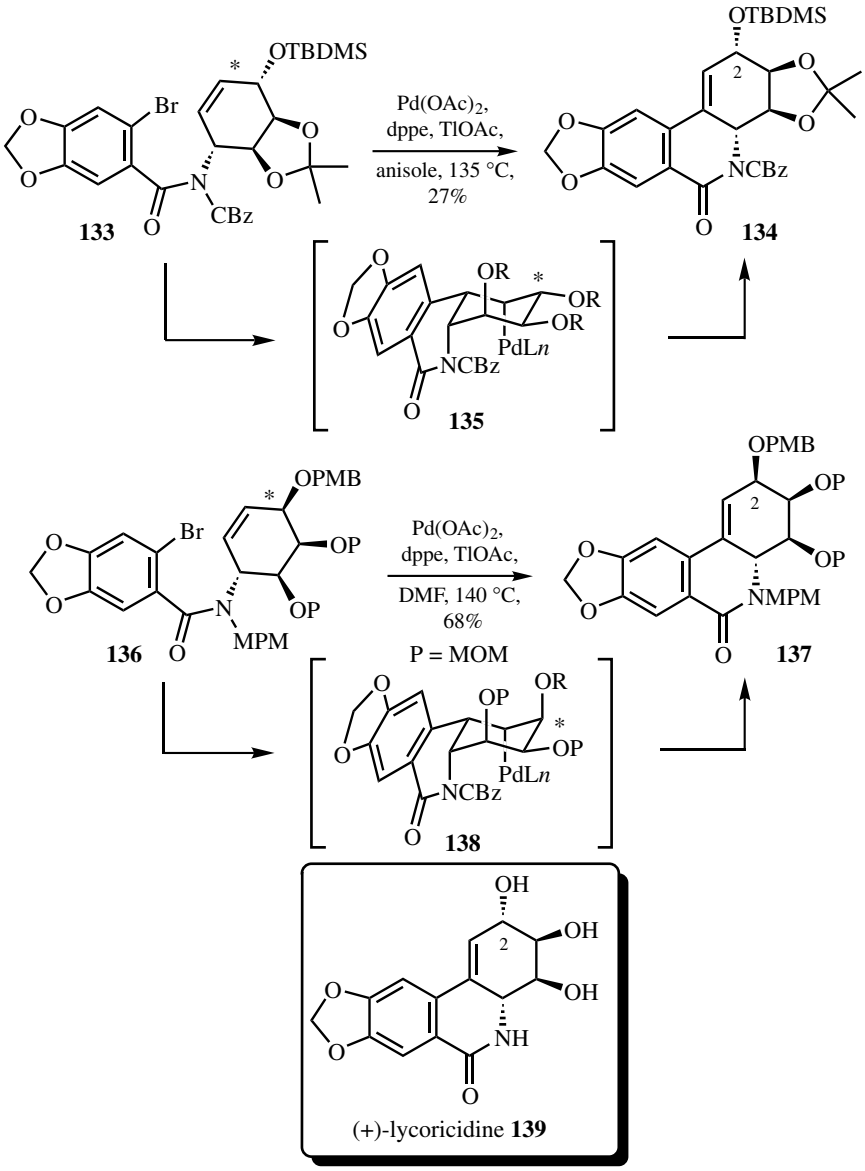
Scheme 19

The reaction has also been employed in a short sythesis of (±)-strychnine (**Scheme 20**).[40] Intramolecular Heck reaction of alkenyl iodide **128** yields (±)-isostrychnine (**129**) after deprotection. The reaction is notable since the intermediate generated during the 6-*exo* closure contains a normally unstable tertiary alkyl–palladium bond. It is remarkable that the reaction overcame this hurdle to deliver (±)-isostrychnine **129** so efficiently. In a program that resulted in the synthesis of (±)-FR-900482 **132**, a 6-*exo* intramolecular Heck reaction closes the central ring.[41] In the key reaction, tetrakis(triphenylphosphine)palladium catalyzes the cyclization of aryl iodide **130** to the vinylic substitution product **131** in 93% yield. The reaction shows the exquisite functional group tolerance of carbopalladations as both the aziridine and allylic ketal are unaffected by the conditions for this conversion.



Scheme 20

Several groups have undertaken syntheses of (+)-lycoricidine **139** due to its structural similarity to the potential anticancer agent pancratistatin. Intramolecular carbopalladation has been a popular approach (**Scheme 21**). Prior to experimentation, the configuration of the C^2 stereocenter was considered important due to the potential of the hydrogen to be involved in β-hydride elimination. In one example, aryl bromide **133** undergoes Heck cyclization to yield the substitution product **134**.[42],[43] In this case, *syn*-β-hydride elimination from the insertion product **135** is impossible and the substitution product **134** is isolated. Therefore, **134** is the result of an *anti*-β-hydride elimination. Remarkably, cyclization of **136** also yields the substitution product **137**.[44],[45] The result is surprising as carbopalladation would initially provide intermediate **138**. β-Hydride elimination of the neighboring *syn*-proton on C^2 was the next expected step to yield an enol ether. This reaction may be driven by the thallium salt, coupled with the acidity of the benzylic hydrogen.

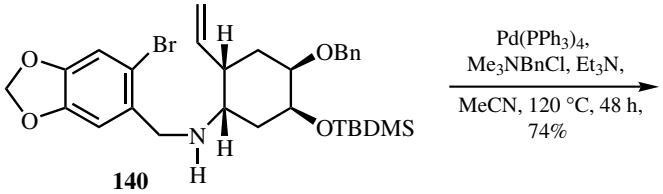


Scheme 21

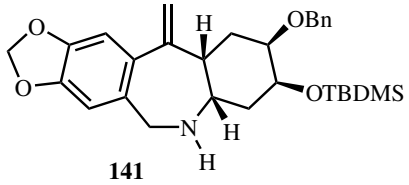
C.iv. 7 or 8-*exo* Intramolecular Carbopalladation

Medium sized rings can also be efficiently assembled by carbopalladation reactions. An example from natural product synthesis is the construction of several Amaryllidacae alkaloids including (−)-pancracine **142**.[46],[47] Treatment of aryl bromide **140** with tetrakis(triphenylphosphine)palladium in the presence of Me_3NBnCl gave the substitution product, the exocyclic alkene **141** in good yield (**Scheme 22**). An efficient synthesis of (±)-cephalotaxine **143** has also relied on a Heck reaction to close a

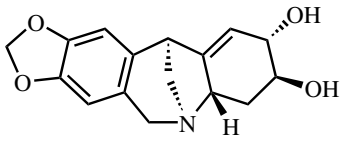
seven-membered ring.[48] Electron-rich aryl bromide **145** undergoes Heck cyclization in the presence of *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) to provide pentacycle **146** in 80% yield. It should be noted that the palladacycle effectively catalyzed the reaction when typical Heck conditions were unproductive. The newly formed carbon–carbon bond closes a seven-membered ring and sets the stereocenter at the ring junction. Recent efforts toward the synthesis of CP-263,114 **144** illustrate another potential application of 7-*exo* carbopalladation.[49] Furyl iodide **147** undergoes intramolecular Heck reaction to provide furan-annelated bicyclo[4.3.1]undecenone **148** in good yield. This key step establishes the basic carbon skeleton of the natural product.



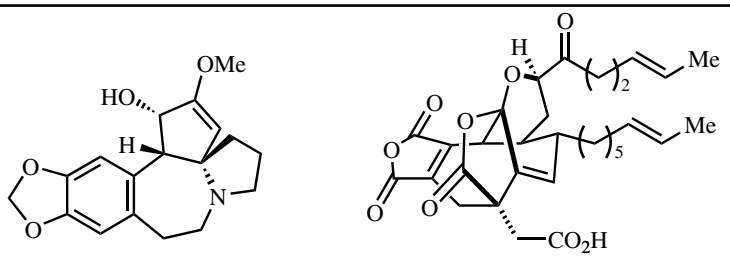
140



141



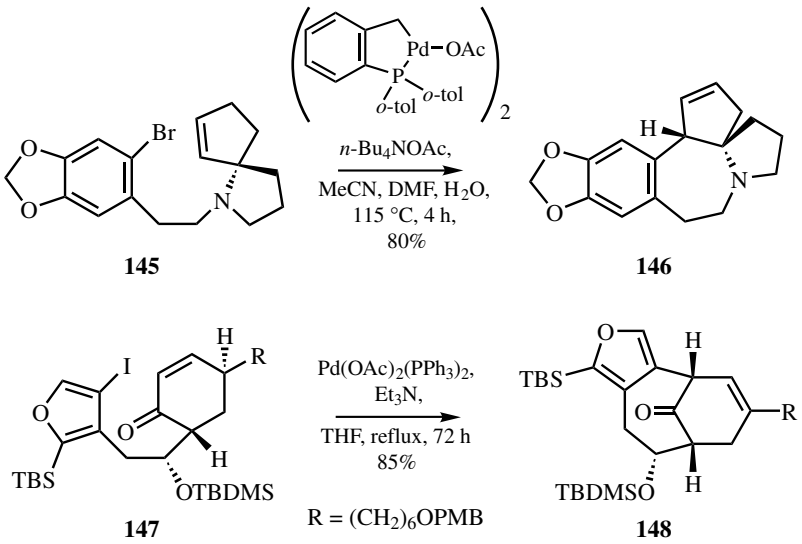
(–)-pancracine **142**



(±)-cephalotaxine **143**

CP-263,114 **144**

Scheme 22

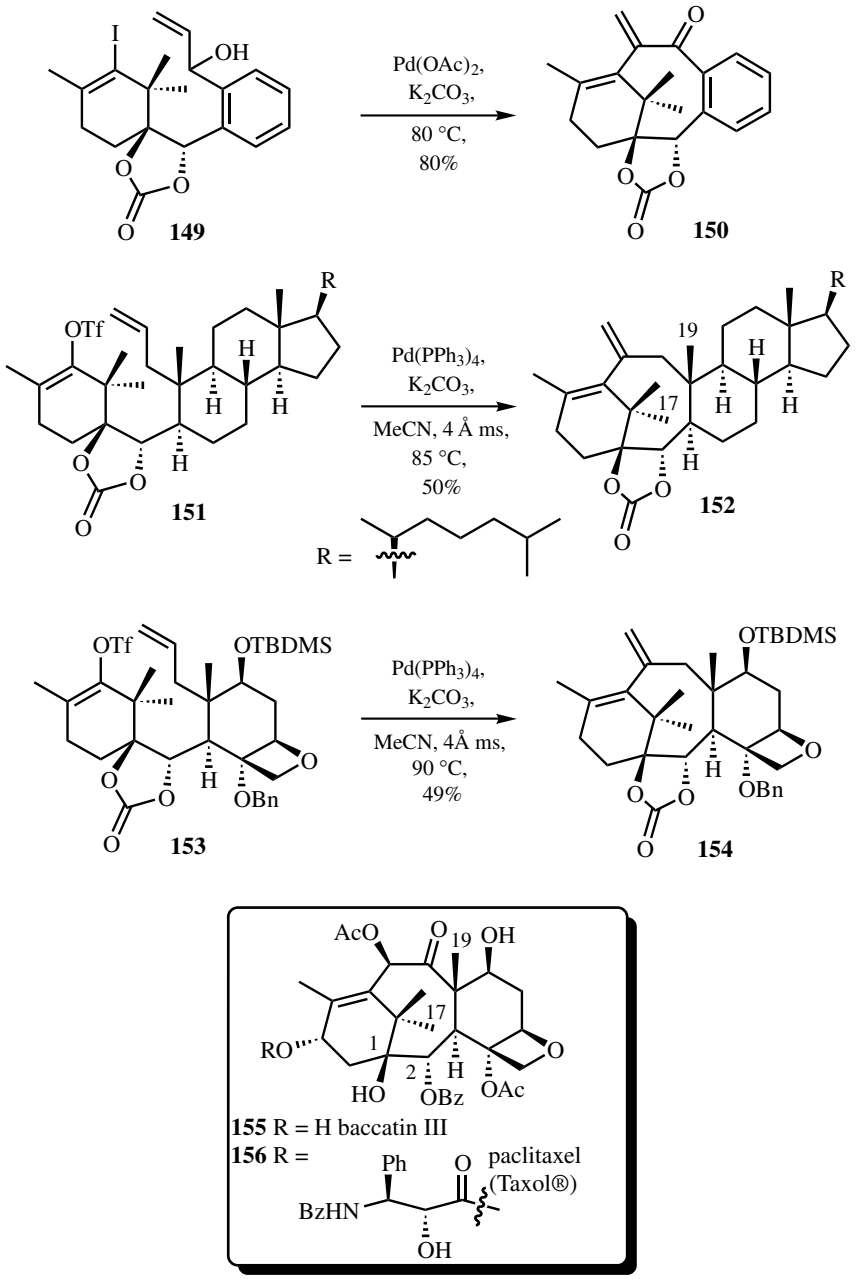


Scheme 22 (*Continued*)

Taxol® **156** and its relative baccatin III **155** have stimulated an enormous amount of interest from the synthetic community. These efforts have highlighted the challenge of assembling eight-membered rings. The eight-membered ring of Taxol® **156** poses a particularly challenging synthetic problem due to the dense functionality, bridgehead double bond (which is *exo* to the eight-membered ring), and the steric hurdles that must be surmounted in any cyclization approach. One steric interaction that must successfully be overcome is the C^{17}–C^{19} methyl–methyl interaction. The application of an 8-*exo* carbopalladation to this system has been successful (**Scheme 23**). Early cyclization candidates contained an aromatic C ring.[50] The potential closure of such intermediates is simplified since the C^{17}–C^{19} interaction is not present. The C^1 and C^2 alcohols are protected as a cyclic carbonate, which rigidifies the system, aiding cyclization by removing degrees of freedom in the substrate. Treatment of iodide **149** with palladium acetate closes the eight-membered ring, effectively coupling a tetrasubstituted alkene. Concomitant oxidation of the secondary alcohol was observed and an 80% yield of **150** was realized. Steroidal hybrid **151** provides a more relevant system since cyclization must overcome the C^{17}–C^{19} methyl–methyl interaction.[51] In this case, alkenyl triflate **151** cyclized to provide diene **152** in moderate yield. The reaction also successfully cyclized triflate **153** to pentacyclic diene **154** *en route* to a total synthesis of baccatin III **155**.[52],[53] Stoichiometric amounts of catalyst were required to promote the ring closure of all three substrates. An advantage of this type of cyclization in this system is the tolerance of the oxetane to the reaction conditions. Other cyclizations (e.g., McMurry reaction) may pose a threat to the oxetane, leading to less convergent approaches.

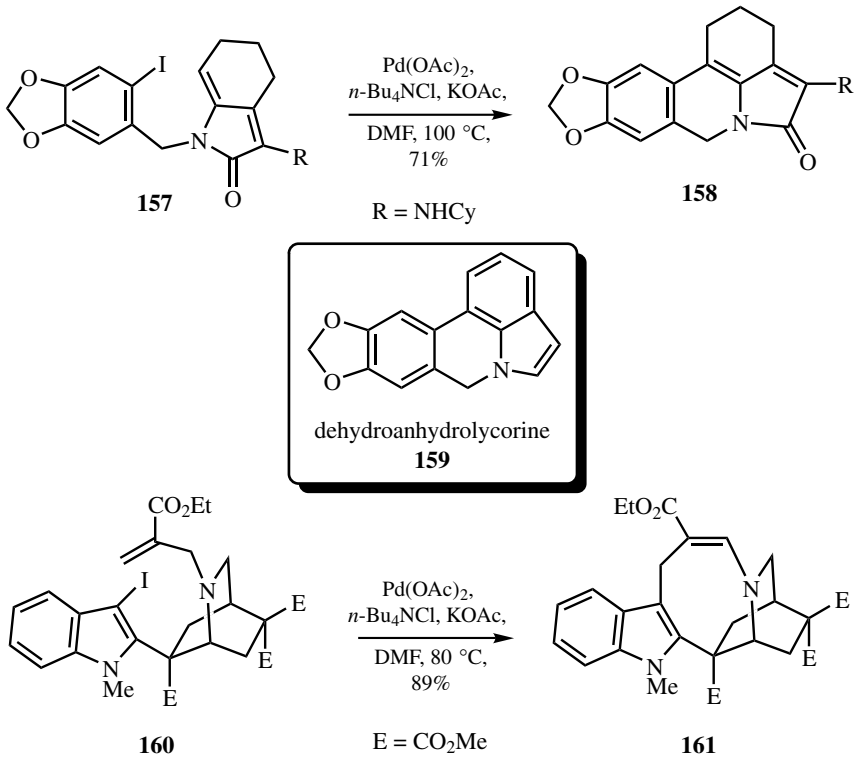
C.v. *Endo* Intramolecular Carbopalladation

Although the majority of intramolecular carbopalladations yield *exo* products, there are numerous examples of *endo* cyclizations. Dehydroanhydrolycorine **159** was constructed



Scheme 23

relying on a 6-*endo* intramolecular Heck reaction (**Scheme 24**).[54] Cyclization of aryl iodide **157** under Jeffery's reaction conditions gives pentacycle **158** in 71% yield. An example of an 8-*endo* carbopalladation was reported in the preparation of analogs of the *Iboga* alkaloids.[55] In the transformation, indole iodide **160** closes to provide the unsaturated ester **161** in good yield.



157 **158** **159** **160** **161**

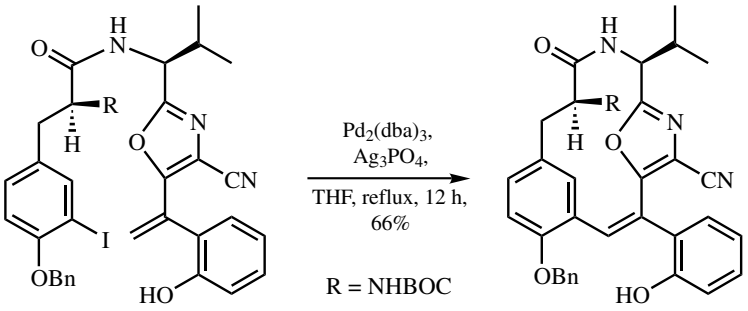
Scheme 24

C.vi. Macrocycling Intramolecular Carbopalladation

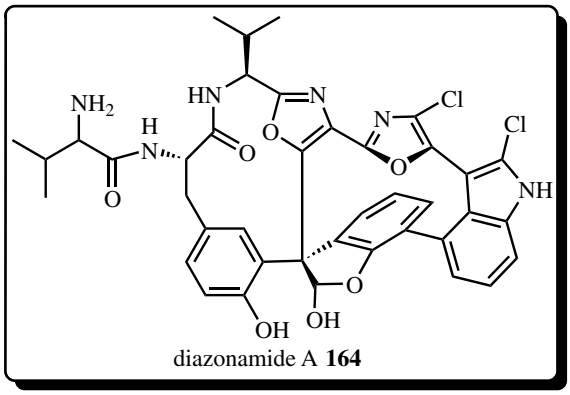
Carbopalladation reactions have been shown to be effective in closing macrocyclic rings both in solution and on substrates attached to a solid support.[56] In an effort directed toward the synthesis of the cytotoxic natural product diazonamide A **164** a 13-membered ring was assembled (**Scheme 25**).[57] Palladium-mediated 13-*endo* macrocyclization of alkenyl iodide **162** yields macrocycle **163** in moderate yield. The free phenol plays a critical role in the reaction. Substrates with a proton or methoxy substituent at this position cyclize much less efficiently ($<10\%$), hinting at the possibility of substrate preorganization.

C.vii. Domino Reactions

Carbopalladation products can be induced to undergo other reactions than β-hydride elimination. For instance, carbopalladation products can undergo a second carbopalladation to form a second carbon–carbon bond. Such reactions have been termed polyene cyclizations and have been exploited to construct the carbon skeletons of the scopadulcic acids (**Scheme 26**).[58] Treatment of alkenyl iodide **165** under typical carbopalladation conditions induces a 6-*exo* carbopalladation onto the *exo* double bond. The resulting neopentylpalladium intermediate then undergoes a second 5-*exo* carbopalladation reaction followed by β-hydride elimination delivering tetracycle **166**. Conversion of allylic alcohol **166** to (−)-scopadulcic acid A **167** as well as analogous conversions in the enantiomeric series have lead to an enantiodivergent synthesis of both antipodes of the natural product.



162 **163**



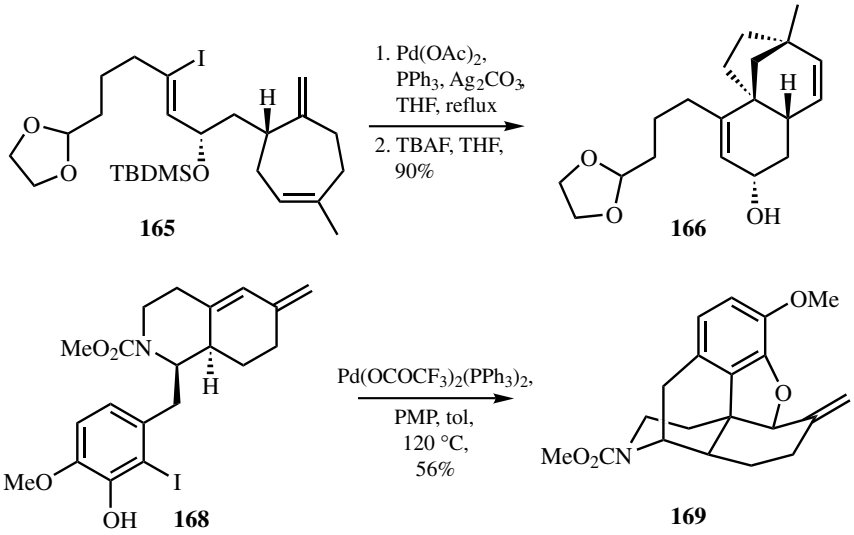
diazonamide A **164**

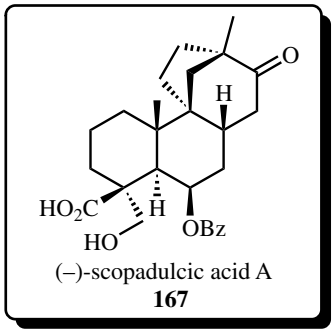
Note: The structure of this natural product has recently been revised.[57a]

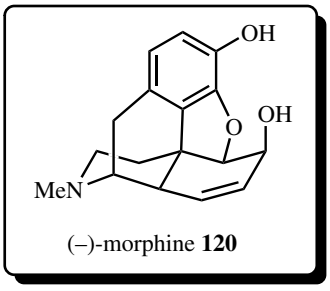
Scheme 25

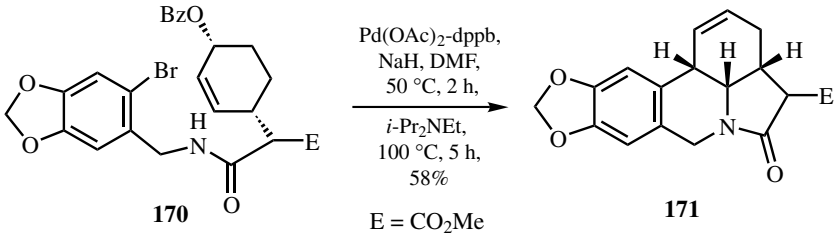
Carbopalladation of dienes yields π-allylpalladium intermediates capable of capturing nucleophiles. An example of this type of reaction in natural product synthesis is the conversion of the aryl iodide **168** into pentacycle **169**.[59] After 6-*exo* carbopalladation the free phenol is captured by the resultant π-allylpalladium intermediate to yield allylic ether **169** *en route* to (−)-morphine **120**. The domino reaction closes a six-membered ring, forges a quaternary center, and forms a five-membered furan ring. The reaction sequence has also been effectively reversed in a construction of (+)-γ-lycorane **172**.[60] Treatment of allylic benzoate **170** with a palladium catalyst in the presence of sodium hydride triggers π-allylpalladium formation and intramolecular amide capture. π-Allylpalladium formation occurs with inversion, as does reaction with the pendant amide, resulting in a net retentive 1,3-transposition of stereochemical information. Subsequent addition of base and thermolysis induces 6-*exo* intramolecular carbopalladation to yield alkene **171**.

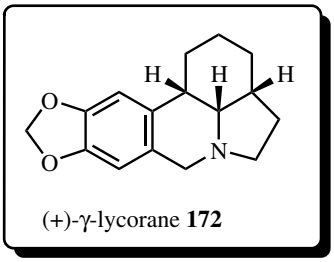
Several other types of domino reactions have been employed in the synthesis of natural products. Diastereoselective conversion of allylic carbonate **173** into enone **174** was one key transformation in a total synthesis of (+)-3-isorauniticine **175** (**Scheme 27**).[61] Treatment of allylic sulfonamide **173** with a palladium catalyst regioselectively forms a π-allylpalladium intermediate by carbonate displacement. Carbopalladation of the pendant alkene, carbonylation, a second intramolecular alkene insertion, and β-hydride elimination delivers a 67:22:11 mixture of stereoisomers of which enone **174** is the major product (isolated in 45–53% yield). Carbopalladation products can also undergo anion capture reactions. For instance, during the synthesis


1. Pd(OAc)2,
PPh3, Ag2CO3,
THF, reflux
2. TBAF, THF,
90%
TBDMSO
165
166
MeO2CN
MeO
OH
168
Pd(OCOCF3)2(PPh3)2,
PMP, tol,
120 °C,
56%
OMe
MeO2CN
169

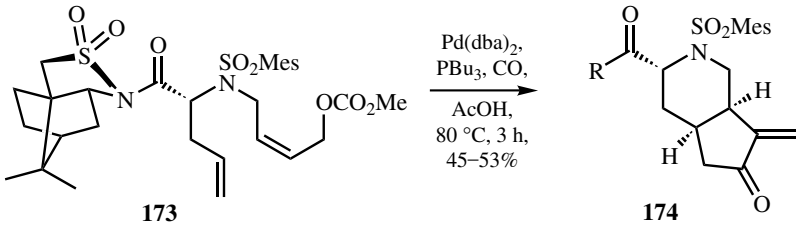

HO2C
HO
OBz
(–)-scopadulcic acid A
167


OH
OH
MeN
(–)-morphine 120

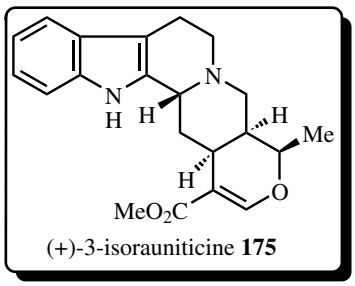

BzO
Br
170
Pd(OAc)2-dppb,
NaH, DMF,
50 °C, 2 h,
i-Pr2NEt,
100 °C, 5 h,
58%
E = CO2Me
171


(+)-γ-lycorane 172

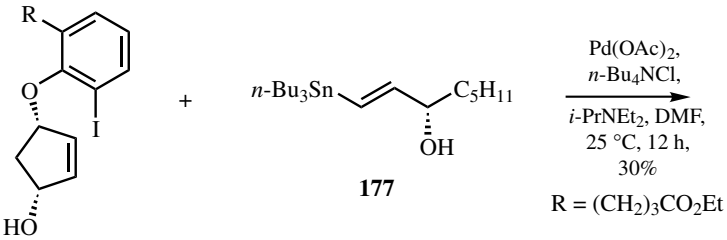
Scheme 26



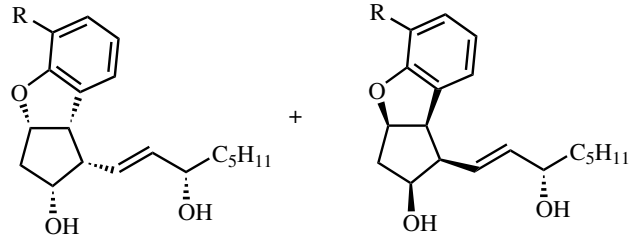
173 **174**



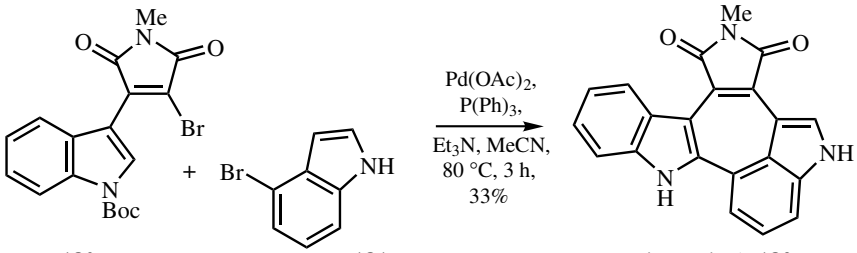
(+)-3-isorauniticine **175**



(±)-**176** **177**



178 **179**



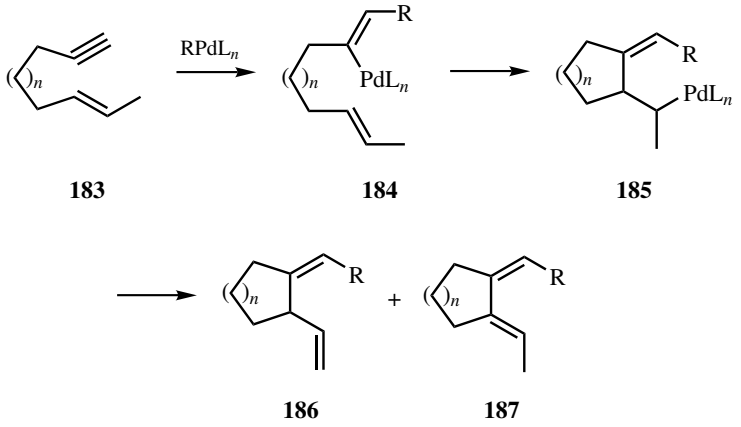
180 **181** arcyriacyanin A **182**

Scheme 27

of benzoprostacyclins like **178** (stable prostacyclin analogs) treatment of racemic iodide **176** with palladium acetate in the presence of enantiopure alkenylstannane **177** provides a 1:1 mixture of tricycles **178** and **179** in 30% yield.[62] *cis*-5-*exo* Carbopalladation followed by coupling with the alkenylstannane accounts for the stereochemical result. Aromatic rings can also participate in carbopalladation reactions. The slime mold alkaloid arcyriacyanin A **182** has rapidly been assembled using such an approach.[63] Treatment of the bromides **180** and **181** with palladium acetate in the presence of triphenylphosphine gives the hexacyclic natural product **182** by a sequence of an intra- and an intermolecular carbopalladation.

C.viii. Cycloisomerization of Enynes

Cycloisomerization of enynes has been employed to construct an array of natural products.[64] Although the precise mechanistic details of the reaction have not been elucidated, and may vary from case to case, one potential mechanism is shown in **Scheme 28**. Generation of an alkyl- or hydridopalladium complex in the presence of enyne **183** may lead to carbo- or hydridopalladation to give an alkenyl palladium intermediate **184**. Intramolecular cyclization (**184**→**185**) then follows to form five-, six-, or seven-membered rings followed by β-hydride elimination to yield 1,4-diene **186** and/or 1,3-diene **187**. There are also examples of yne–yne cyclizations in natural product synthesis.[65]



183 **184** **185**

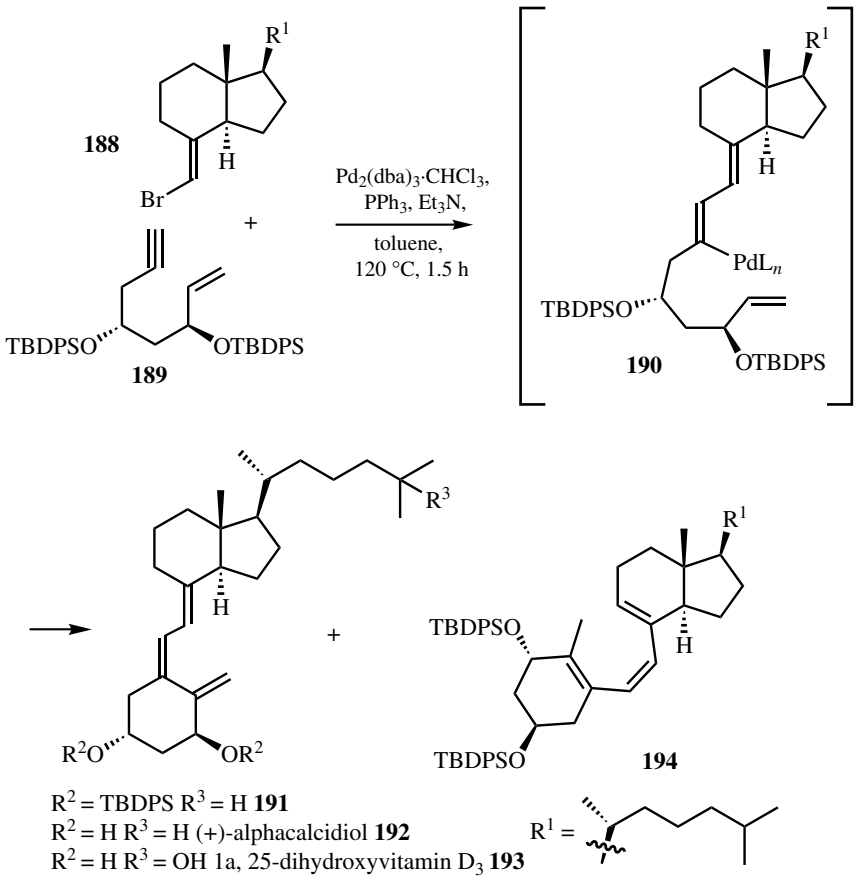
186 **187**

R = H, organic Group

Scheme 28

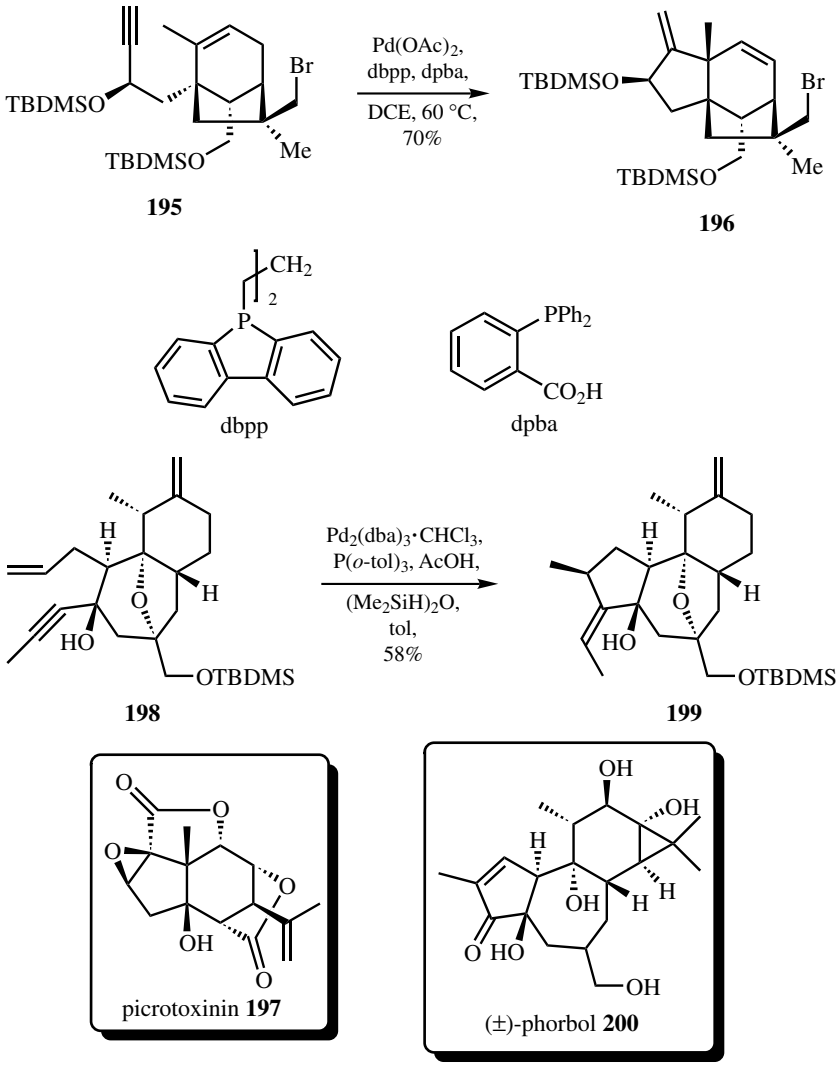
There has been broad scientific interest in the synthesis of analogs of 1α,25-dihydroxyvitamin D_3 **193** due their potential clinical applications. A concise entry into the triene-containing tricyclic core structure from simple precursors is available using an enyne cycloisomerization. The precursors of the central cascade reaction are the alkenyl bromide **188** and enyne **189**, which are easily obtained in enantiomerically pure form (**Scheme 29**).[66],[67] In the key reaction, alkenyl bromide **188** and enyne **189** are converted into a 10:1 mixture of triene **191** and the thermally rearranged product **194**. After recycling of **194** to **191**, a yield of 76% was realized. Alkenyl bromide **188** undergoes regiospecific intramolecular carbopalladation of enyne **189** to provide the dienylpalladium complex **190**.

Intramolecular carbopalladation of the pendant alkene then provides triene **191** as well as the thermally rearranged product **194** via a [1,7]-hydrogen shift. In this one-pot transformation two carbon–carbon bonds are formed. One couples the two key fragments and the other closes a six-membered ring in a controlled manner generating a single triene isomer *en route* to (+)-alphacalcidiol **192**.



Scheme 29

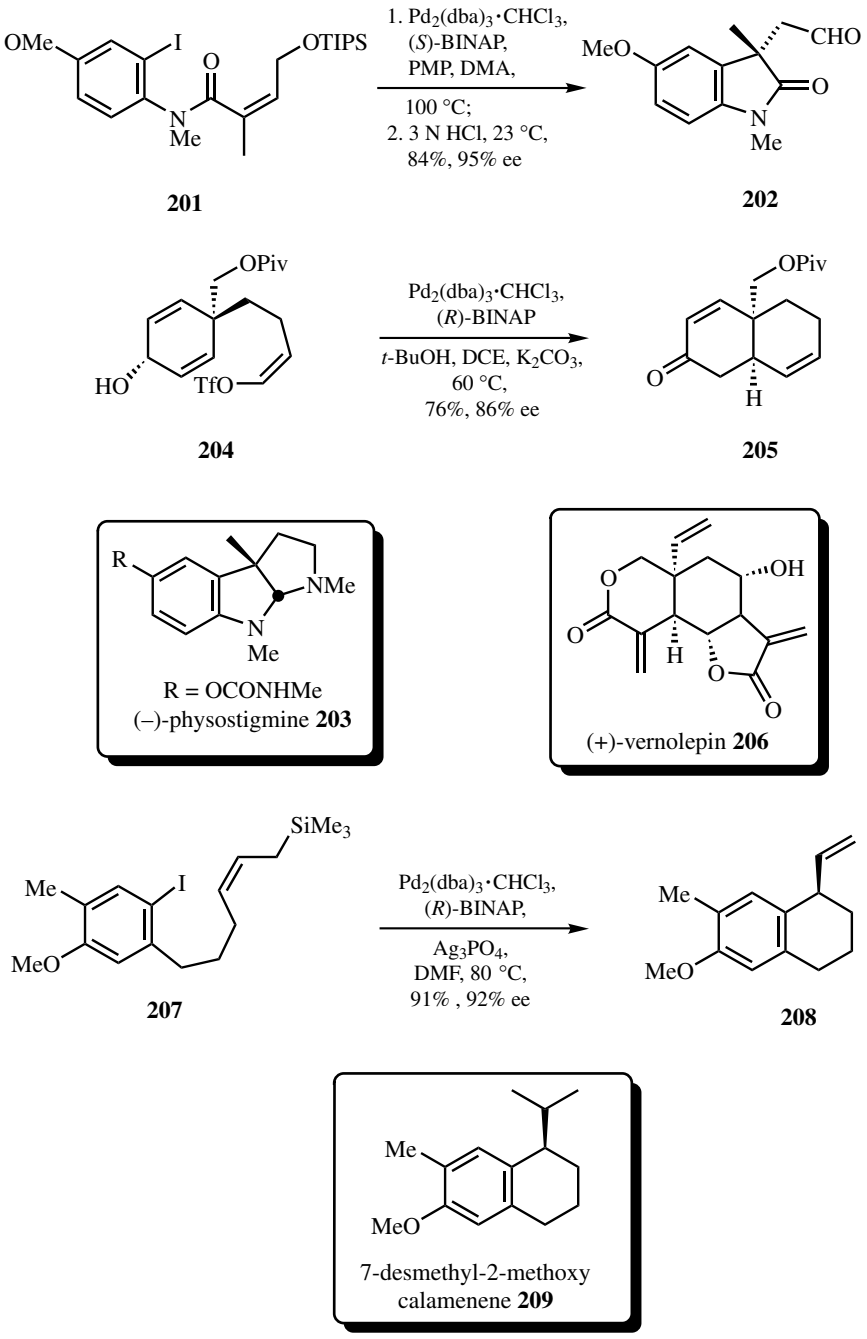
Hydridopalladative entry into the reaction cycle is also practical. In a total synthesis of picrotoxinin **197**, enyne **195** was converted into tricycle **196** in the presence of palladium acetate, dbpp, and dpba (**Scheme 30**).[68],[69] The unusual catalyst system was necessary to catalyze the reaction in the hindered environment present on the *endo* face of the bicycle **195**. Utilization of dbpp (which is sterically less demanding than dppe) and dpba[70] in the presence of palladium acetate catalyzed the transformation. Of note is the survival of the neopentyl bromide under the reaction conditions. Other avenues for terminating the reaction sequence exist. In a formal synthesis of (±)-phorbol (**200**) a hydridopalladation-initiated reaction takes place, which is not terminated by a β-hydride elimination.[71] Rather, a reductive cyclization is observed in the presence of $(Me_2SiH)_2O$, which stereoselectively yields the heavily substituted cyclopentanol **199**.



Scheme 30

C.ix. Asymmetric Intramolecular Carbopalladation

Asymmetric intramolecular carbopalladation is an effective reaction for producing enantioenriched polycycles. Most examples are intramolecular Heck reactions. One seminal example from natural product synthesis is the 5-*exo* carbopalladation of eneamide **201** to oxindole **202** (after acid treatment) from a total synthesis of (−)-physostigmine **203** (**Scheme 31**).[72],[73] The reaction occurs in 84% yield with 95% ee, which is remarkably efficient for the construction of a quaternary center. Reaction conditions that favor the neutral manifold of the Heck reaction are employed. Examination of the scope of the oxindole synthesis and mechanistic analysis have appeared.[74] Group selective reactions are also powerful reactions in carbopalladation asymmetric synthesis.[75]–[77] From a synthesis of (+)-vernolepin **206**, alkenyl triflate **204** is

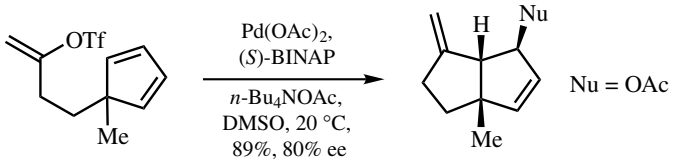


Scheme 31

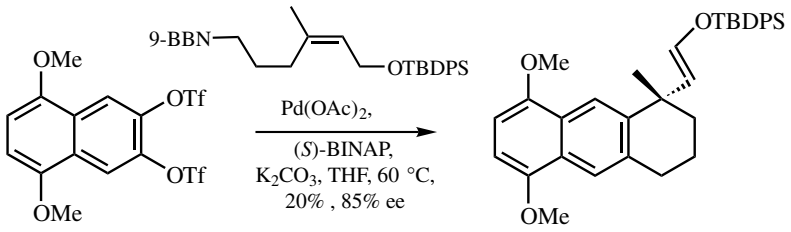
efficiently cyclized to bicycle **205**.[78] Intramolecular 6-*exo* group selective carbopalladation followed by β-hydride elimination under reaction conditions that presumably favor the cationic manifold gave an 86% ee. Asymmetric Heck reactions are frequently utilized to construct quaternary centers. However, tertiary centers have been more

challenging due to the potential for β-hydride elimination to destroy the newly formed center. A solution is to control the regiochemistry of elimination by employing allyltrimethylsilanes such as **207**.[79] Intramolecular carbopalladation under conditions to favor the cationic manifold provides bicycle **208** in 91% yield with 92% ee *en route* to 7-desmethyl-2-methoxycalamenene **209**.[80],[81]

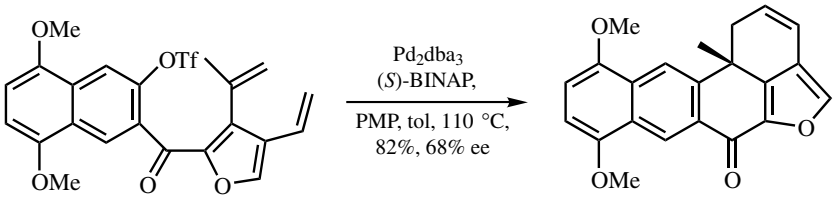
Asymmetric carbopalladation can also be combined with other reactions to give domino asymmetric processes. A group selective example from a synthesis of (−)-$\Delta^{9(12)}$-capnellene **216** features the cyclization of the alkenyl triflate **210** (**Scheme 32**).[82] The resultant π-allylpalladium intermediate has effectively been captured with a variety of nucleophiles including acetate anion for the synthesis. A domino Suzuki coupling/intramolecular Heck reaction converts ditriflate **212** into tricycle **213** in modest yield with 85% ee.[83]–[85] The transformation accomplises an annnelation, two carbon–carbon bond formations, and enantioselectively establishes a quaternary center in a synthesis of halenaquinol **217**. An example of an asymmetric polyene cyclization from a synthesis of (+)-xestoquinone **218** features cyclization of furan **214** into pentacycle **215**.[86] The reaction (as do the previous two examples) occurs under conditions that favor the cationic manifold and give the product in 82% yield with 68% ee. The first step in the cyclization is 6-*exo* and the second is 6-*endo*.



210 **211**

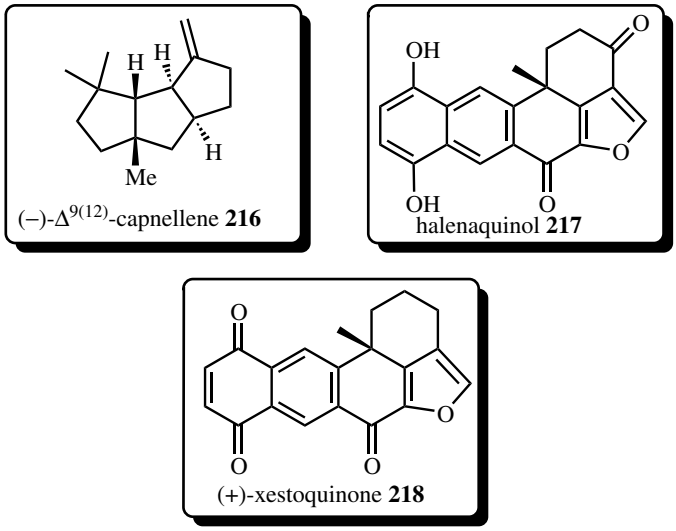


212 **213**



214 **215**

Scheme 32 (*Continued*)



Scheme 32

D. SUMMARY

Carbopalladation methodology has gained widespread acceptance within the synthetic community due to its capacity to fashion carbon–carbon bonds. It is widely employed in the synthesis of natural products, and other complex molecules, due to its wide scope, efficiency, functional group compatibility, ease of precursor preparation, tolerance of steric impediments, and operational simplicity. Tactically, it is useful for side chain addition, annelation, fragment coupling, ring closure (small, medium, and large), and stereocenter introduction. Furthermore, domino reactions allow for the formation of several bonds in a single operation, and asymmetric carbopalladations provide highly enantioselective transformations. The methodology has successfully been applied to complex small scale syntheses, process scale problems, and solid support reactions. Future discoveries promise to add to an already solid methodology, which will continue to expedite complex molecule synthesis.

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