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CATALYTIC PALLADIUM-MEDIATED CARBOCYCLIZATIONS: BISDIENE TO TRIENE CYCLOISOMERIZATIONS

by

Francis Clement

A DISSERTATION

Presented to the Faculty of

The Graduate College at the University of Nebraska-Lincoln

In Partial Fulfillment of Requirements

For the Degree of Doctor of Philosophy

Major: Chemistry

Under the supervision of Professor James M. Takacs

Lincoln, Nebraska

August 1996

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DISSERTATION TITLE

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SUPERVISORY COMMITTEE:

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GRADUATE COLLEGE
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CATALYTIC PALLADIUM-MEDIATED CARBOCYCLIZATIONS: BISDIENE TO TRIENE CYCLOISOMERIZATIONS

Francis Clement, Ph.D.

University of Nebraska-Lincoln, 1996

Advisor: James M. Takacs

One of the areas of focus in the Takacs laboratories is the development of synthetic methodology using catalytic palladium for the formation of five- and six-membered carbocyclic ring systems. The palladium-mediated bisdiene to triene cycloisomerizations leading to five and six-membered rings in the absence of a trapping agent is described in this dissertation. The methodology has been successfully extended to electron rich dienes affording cyclized trienes in high yields and high diastereoselectivity. In the five-membered ring system where the cyclized triene is a mixture of double bond isomers, alkyl substitution, based on a literature precedent, has afforded the cyclized product stereoselectively and in excellent chemical yield. The mechanism of palladium-catalyzed cyloisomerizations and also palladium-mediated elimination of allylic acetates using isotopic labeling studies has been investigated. Preliminary results obtained from the mechanistic study argue against the commonly accepted β-hydride elimination mechanism.

Dedicated to my loving parents

Mary and Joseph Clement

ACKNOWLEDGEMENTS

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CHAPTER ONE

LITERATURE REVIEW

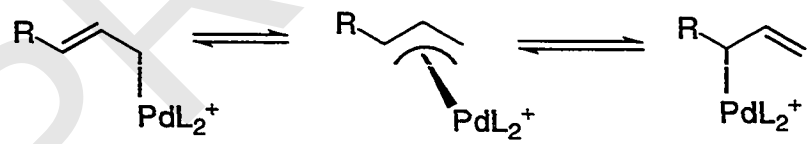
In 1990 Seebach[1] had predicted that, "the discovery of truly *new* reactions is likely to be limited to the realm of transition-metal organic chemistry which will almost certainly provide us with additional 'miracle reagents' in the years to come". No area of classical synthetic chemistry today still offers such innovative possibilities as metal-mediated processes.

Organotransition metal chemistry is concerned with compounds that have an organic group bonded to a transition metal *via* a direct metal-carbon bond.[2] This is an exciting interdisciplinary area that blends organic and inorganic chemistry for the benefit of state-of-the art organic synthesis. Homogeneous catalysis, where the transition metal is a soluble metal complex, is an intensively studied area with diverse potential industrial applications. One can often observe a combination of mild conditions, favorable rates and high selectivity. Transition metal-catalyzed reactions are becoming increasingly significant, not only for industrially important intermediates but also for the synthesis of complex building blocks.[3] One of the notable examples of an important application of homogenous catalysis is with the production of "L-Dopa" by Monsanto for the treatment of Parkinson's disease.[4]

Among the transition metal series, palladium is one of the most important metals for organic chemistry. Its derivatives have been used very effectively in new synthetic methodology as well as in the total synthesis of organic compounds. One of the main

reasons for its use in organic synthesis is a consequence of the relative ease of forming derivatives from unsaturated organic compounds. For any synthetic methodology to be widely accepted by the synthetic community one of the prime requirements is that the transformation should be accomplished in the presence of other sensitive functional and/or protecting groups. This indeed is the case for palladium-catalyzed reactions as many of the examples below will amply demonstrate. For many reactions, organopalladium intermediates are formed *in situ* from palladium(II) salts such as $Pd(OAc)_2$, but in some cases, zerovalent palladium compounds such as $Pd(PPh)_4$ or $Pd_2(dba)_3$ are employed. Elemental palladium has been found not to be an effective catalyst except in hydrogenations and isomerizations.[5]

An η^3- or π-allyl palladium species is easily formed from organic substrates containing at least one double bond. The π-allyl palladium complex is in equilibrium with the two isomeric σ-allyl palladium complexes as depicted in Scheme 1.

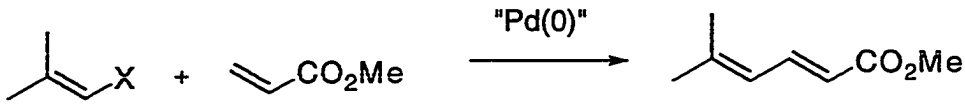


Scheme 1

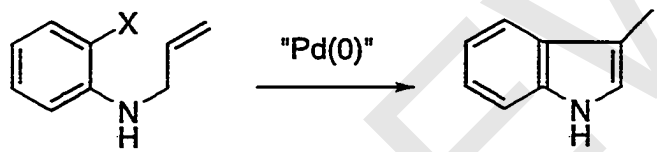
The π-allyl and the σ-allyl complexes are often in dynamic equilibrium and either one can be the reactive species. In general, the π-allyl palladium complexes are more stable than the σ-allyl complexes due to the π-electron system bonding to two coordination positions of the metal. The π-allyl palladium species can be attacked by a variety of carbon and heteroatom nucleophiles. If the reaction is rendered intramolecular, this nucleophilic addition can be a powerful and versatile tool for the construction of carbocyclic or heterocyclic ring systems. The chemistry of other σ-bonded palladium compounds, especially aryl- and vinyl-palladium, is also well developed and exceptionally useful.

More than two decades ago Mizoroki[6] and Heck[7] independently discovered the palladium-catalyzed arylation and vinylation of olefins. This methodology has become known as the Heck reaction (Scheme 2) and is synthetically useful due to its high chemoselectivity, mild reaction conditions and the low cost of reagents.[8] The Heck reaction is regio- as well as stereoselective, and therefore in both its inter- and intramolecular versions, it is now widely used as an important method for effecting carbon-carbon bond formation. The intramolecular Heck reaction has been applied to the construction of a variety of carbocycles and heterocycles in the total syntheses of natural products with complex architecture.

Intermolecular Heck Reaction



Intramolecular Heck Reaction



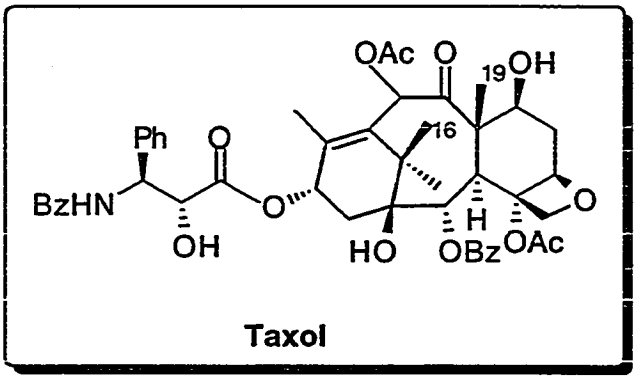
X = I, Br, OTf

Scheme 2

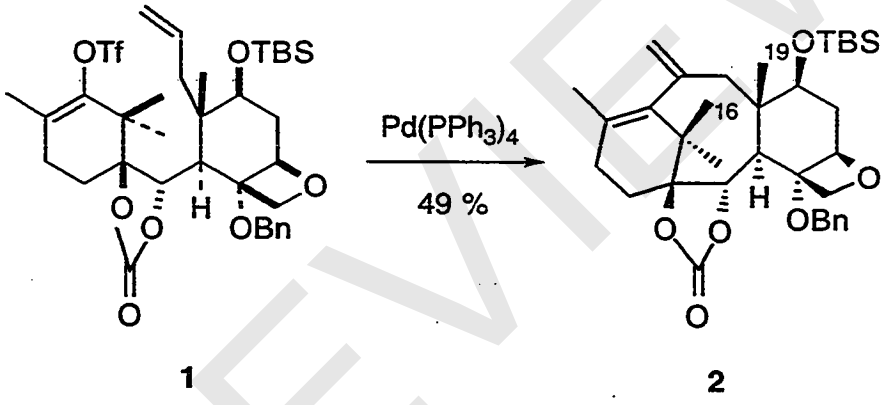
The initial goal of this dissertation research was the synthesis of a steroid using a key palladium-mediated cyclization. The remainder of this chapter is devoted to a brief account of the applications of palladium-catalyzed chemistry to the total syntheses of natural products. A few of the notable examples in literature include taxol (Danishefsky[9]), (±)-dehydrotubifoline (Rawal[10]), scopadulcic acid B (Overman[11]), (+)-morphine (Overman[12]), (±)-tazettine (Overman[13]), (+)-lycoricidine (Ogawa[14]), (±)-duocarmycin SA (Natsume[15]), CC-1065 (Tietze[16]), (*S*)-camptothecin (Comins[17]), (+)-vernelopin (Shibasaki[18]), (-)-physostigimine(Overman[19]), (-)-eptazocine (Shibasaki[20]), pentalenolactone E methyl ester (Oppolzer[21]), (±)-hirsutene (Oppolzer[22]), (±)-dynemicin A (Danishefsky[23]) and *allo*-pumiliotoxin 339 B (Trost[24]). Owing to the

versatility of palladium, a recent issue of *Angewandte Chemie International Edition in English* (September 1, 1995) depicted Pd(0) on its cover page to highlight its use in the landmark syntheses of taxol[9] and (±)-dynemicin A[23] from the Danishefsky research group. In the crucial ring forming steps palladium-catalyzed reactions were used with great success.

In the synthesis of taxol, Danishefsky and co-workers[9] made use of the palladium-catalyzed intramolecular Heck ring closure (Scheme 3) to assemble the highly functionalized core tetracyclic ring system in **2**. Modeling studies for **1** had shown that ring closure would be difficult owing to the strong repulsion between the C(16) and C(19) methyl groups. Inspite of this, the ring closure was effected in a remarkable yield of 49 % using palladium catalysis.



Taxol

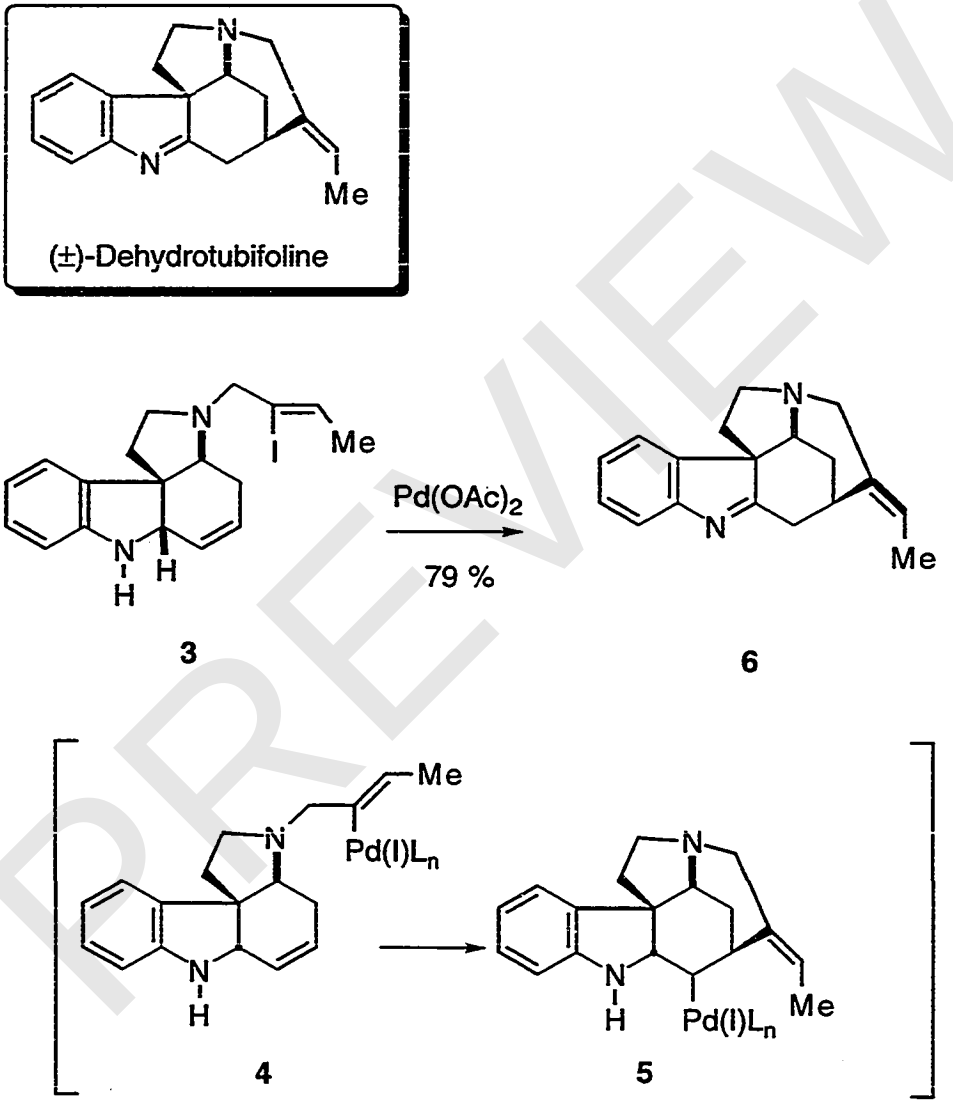


1 2

Scheme 3

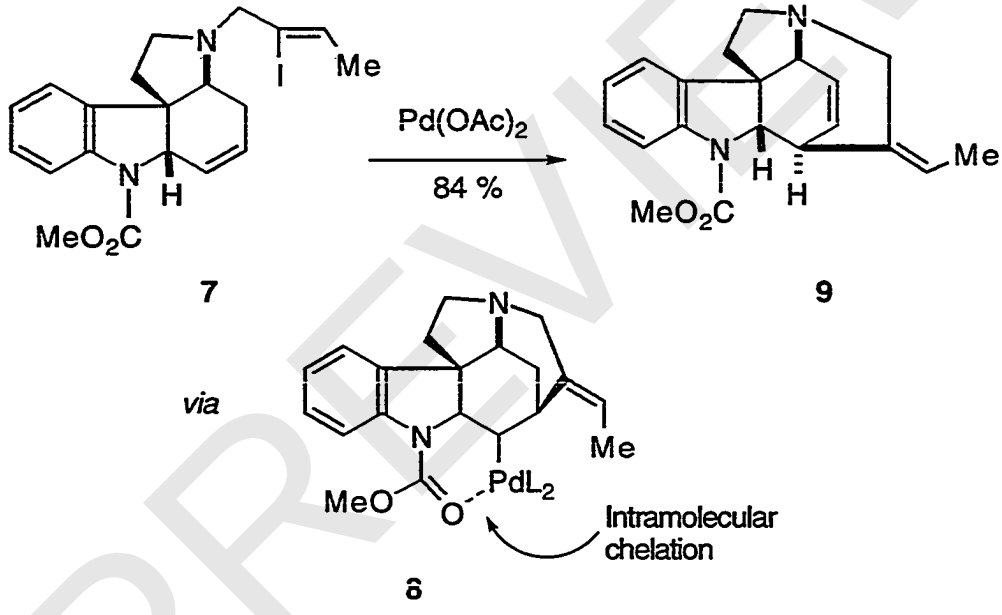
Rawal and co-workers applied the intramolecular Heck reaction to the concise synthesis of (±)-dehydrotubifoline.[25] Starting from vinyl iodide **3** the crucial ring closure in **6** (Scheme 4) was effected by using 5 mol % of $Pd(OAc)_2$ in a yield of 79 %. The first step is called as 'oxidative addition' because the metal is formally oxidized from Pd(0) to Pd(II) and the oxidizing agent, RX adds to the metal.[26] Therefore, oxidative addition of the carbon-iodine bond in **3** affords the vinylpalladium species **4**, which then allows for a ligand insertion leading to a new carbon-palladium σ-bond in **5**. Finally β-

hydride elimination affords the pentacycle **6**. It was noted by the authors that the axially oriented pyrrolidine nitrogen greatly facilitated the reaction.



Scheme 4

In an unusual Heck reaction, Rawal[10] found that the normal exo-cyclization was not followed by β-hydride elimination (Scheme 5). Rather it goes through the sequence: cyclopropane formation; rearrangement; and finally, elimination. In assembling the *Strychnos* alkaloid ring systems, it was observed that the presence of a carbamate moiety in **7** dramatically alters the course of palladium-catalyzed cyclizations. Owing to an apparent intramolecular carbamate chelation in intermediate **8**, the 7-endo cyclization product **9** was obtained in 84 % yield.



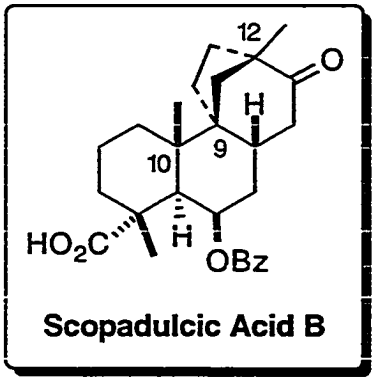
Scheme 5

In the first step, the σ-alkyl palladium species **8** is stabilized by intramolecular chelation. The next step would usually be the β-hydride elimination of the syn β-hydrogen, but chelation prevents this elimination due to improper alignment of the syn-β-H and the C-Pd σ-bond. Instead, the next step is cyclopropane formation followed by

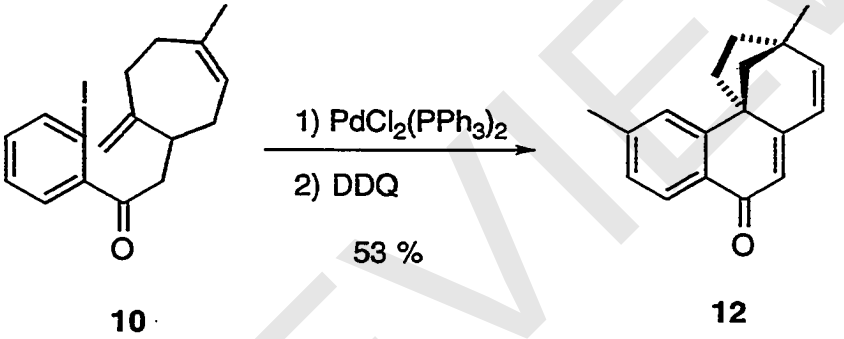
rearrangement, and finally elimination affords **9**. This shows that by the judicious placement of coordinating groups, it is possible to intercept the σ-Pd intermediate to dramatically alter the course of the reaction.

Overman and co-workers[11] used the palladium-catalyzed Heck reaction as a key step in the first total synthesis of scopadulcic acid B, an active component of a plant used in Paraguayan folk medicine (Scheme 6). Apart from the total synthesis of an unusual diterpene, this cyclization illustrates the power of palladium-catalyzed polyene cyclizations for the formation of bridged polycyclics. The intramolecular Heck reaction constructs the congested quarternary carbon centers at C(9) and C(12) of the bicyclooctane substructure in a single step. The key bis-cyclization of dienyl iodide **10** was accomplished in a scale as large as 14 g to yield a mixture of enones, which was oxidized by DDQ to yield a single enone **12** in an overall yield of 53 %.

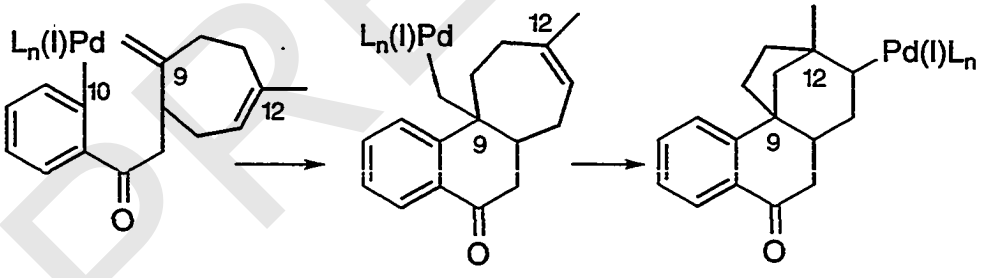
The bond construction is shown in Scheme 6. The first step most likely is the formation of the vinylpalladium species **11**, which undergoes ligand insertion to close the second ring (e.g. **11a**). Subsequent insertion would then afford **11b**, and finally, β-hydride elimination would afford enone **12**.



Scopadulcic Acid B



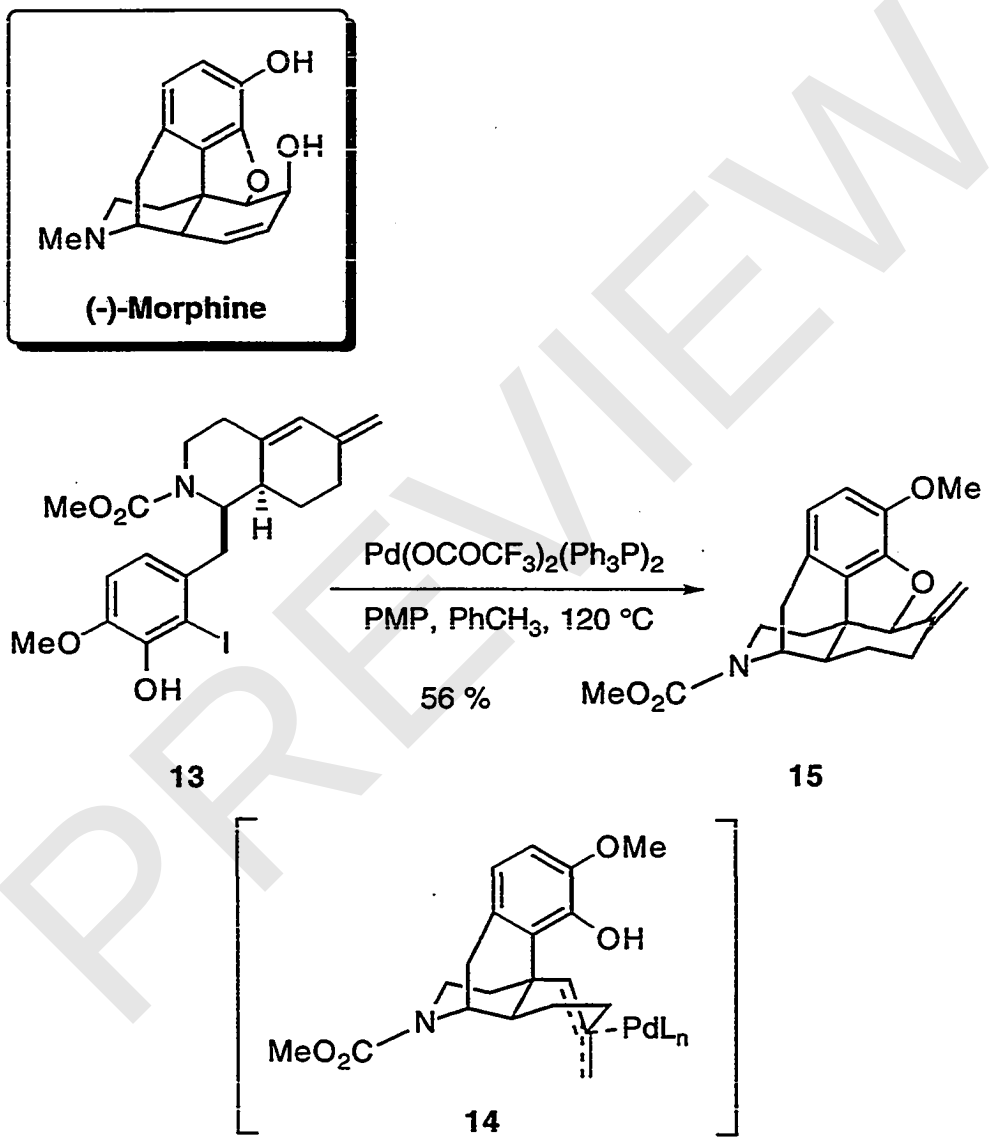
10 **12**



11 **11a** **11b**

Scheme 6

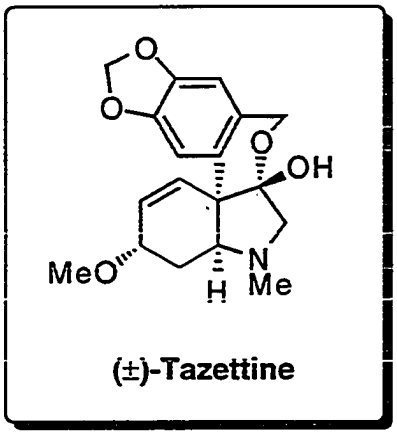
In the total synthesis of the opium alkaloid morphine (Scheme 7), Overman's approach [12] successfully exploits a palladium-catalyzed bis-cyclization for the tandem intramolecular Heck insertion/heterocyclization of a trisubstituted 1,3-diene. The Heck



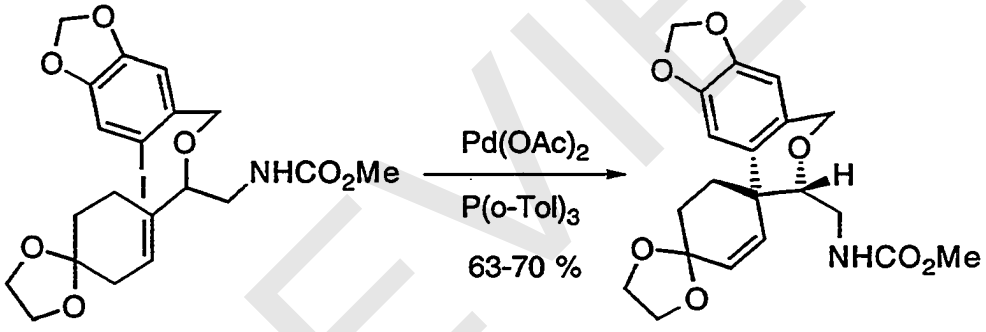
Scheme 7

reaction was the key in forging the critical quaternary center in **14**. Cyclization of the hydroisoqinoline diene **13** was effected using 20 mol % of the palladium catalyst $Pd(OCOCF_3)_2(Ph_3P)_2$ in the presence of the base, pentamethylpiperidine (PMP), to afford **15** in a yield of 56 %.

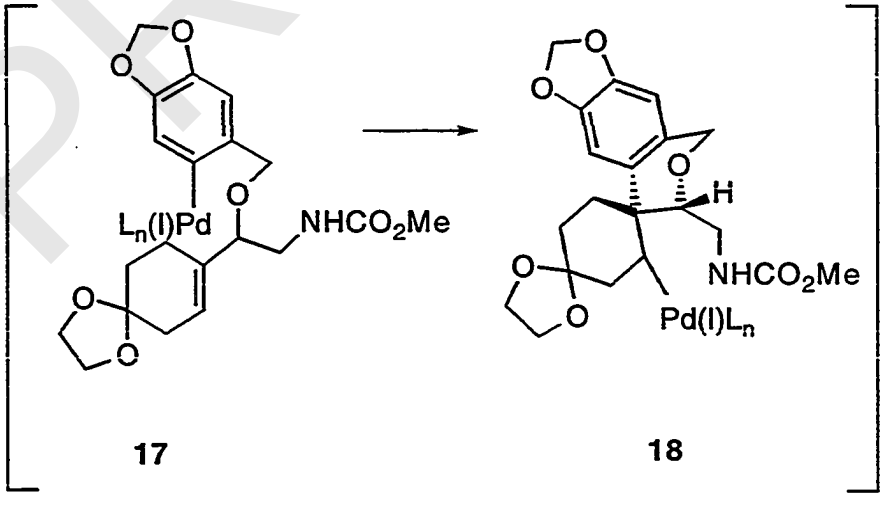
In the study of Amaryllidacea alkaloids, Overman[13] found that the key A and C rings can be joined by a palladium-catalyzed intramolecular insertion with greater efficiency than obtained *via* a biomimetic protocol. This strategy was implemented for the synthesis of (±)-tazettine (Scheme 8). The alkenyl aryl iodide **16** efficiently cyclized to give the pentacycle **19** in 63-70 % yield and with a high stereoinduction (>20:1). The formation of vinylpalladium species **17** is presumably the first step followed by ligand insertion to afford **18** which undergoes a β-hydride elimination to afford the pentacycle **19**.



(±)-Tazettine



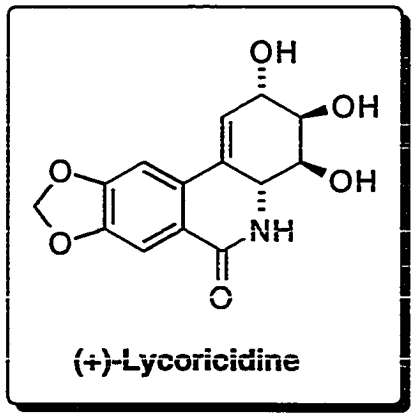
16 19



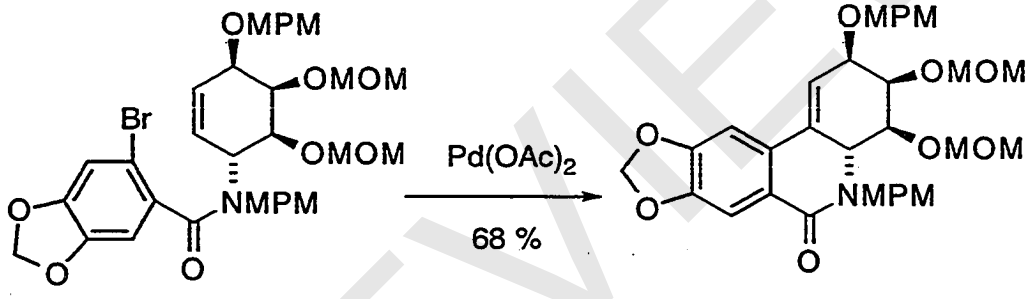
17 18

Scheme 8

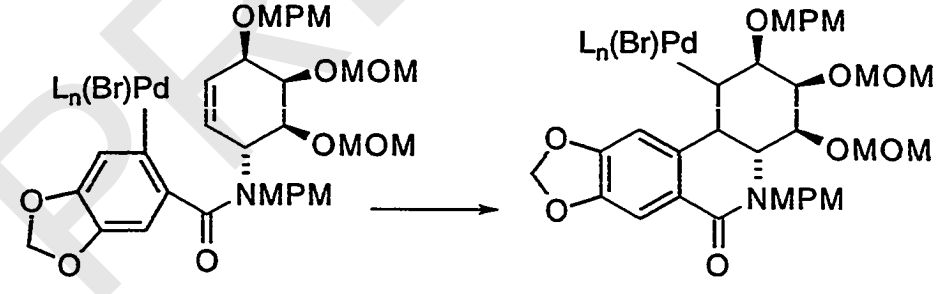
(+)-Lycoricidine, a member of the phenanthridone alkaloid family has attracted attention due to its powerful antimitotic and cytoxic properties. In a stereoselective total synthesis of (+)-lycoricidine (Scheme 9) starting from D-glucose, Ogawa and co-workers[14] used a palladium-catalyzed intramolecular Heck reaction to build the phenanthridone skeleton. The tetracycle **21** was obtained from the bromo-olefin **20** in a yield of 68 % as a single diastereomer. Oxidative addition of the carbon-bromine bond in **20** affords the vinylpalladium species **20a**, which then allows for a ligand insertion leading to a new carbon-palladium σ-bond in **20b**. Finally, β-hydride elimination affords the product **21**.



(+)-Lycoricidine



20 21



20a 20b

Scheme 9