

CHAPTER ONE

Palladium in Organic Synthesis

1.1 Background

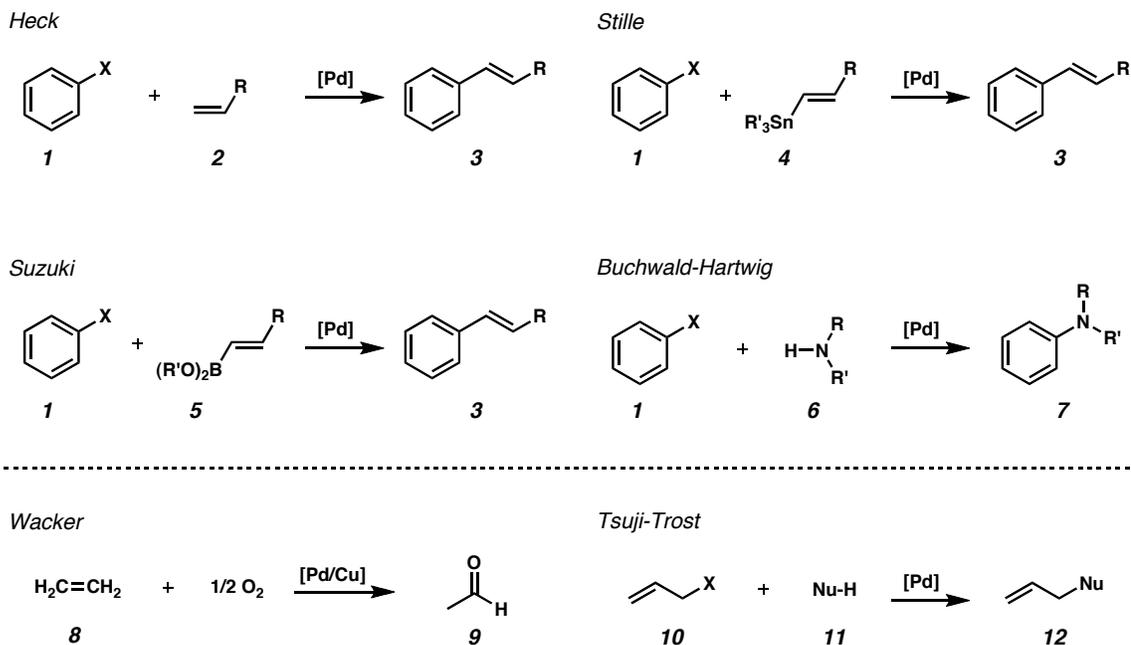
1.1.1 Introduction

Palladium (Pd), named after the asteroid Pallas, is arguably the most versatile and ubiquitous metal in modern organic synthesis.^{1,2} Palladium-mediated processes have become essential tools, spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals. In part, this far-reaching scope is due to palladium's ability to participate in catalytic transformations, as well as its high functional group tolerance. Nearly every area of organic synthesis has been impacted by this versatile transition metal, which has fundamentally changed the way retrosynthetic analysis is approached.

Palladium can be used to conduct myriad transformations with organic molecules. In fact, there are a number of well-known name reactions that feature this metal, including the Heck, Suzuki, Stille, and Buchwald-Hartwig cross-couplings; the Wacker process;³ and the Tsuji-Trost allylation (Scheme 1.1.1).^{1,2} In addition, Pd also enables hydrogenation; hydrogenolysis; carbonylation; the formation of C–C, C–O, C–N, and C–S bonds; cycloisomerization; and even pericyclic reactions.^{1,2} Palladium-based methods often proceed under mild conditions affording high yields, with excellent levels of stereo-, regio-, and chemoselectivity. Domino catalysis, where multiple Pd-catalyzed

transformations are carried out in a single operation, is also a powerful extension of this chemistry.^{1u}

Scheme 1.1.1



1.2 Palladium(0) and Palladium(II)

1.2.1 Oxidation States of Palladium

Although palladium can exist in a number of different oxidation states, useful organic methods are dominated by the use of Pd(0) and Pd(II),^{1,2} although the utility of Pd(IV)⁴ has been steadily emerging in its own right. The remaining oxidation states have not, as of yet, found practical applications, and their observation remains rare.⁵ The increased stability of the even-numbered oxidation states (e.g., 0, +2, +4) can be rationalized by the low tendency of palladium to undergo one-electron or radical processes; conversely, it readily participates in two-electron oxidation or reduction.^{2a}

Palladium's ability to undergo facile and reversible two-electron operations has contributed to its widespread use as a catalyst, since each oxidation state can yield different chemistry (see Figure 1.2.1 for examples of reaction classes). Reactions such as cross-couplings and olefin hydrogenation are common to the Pd(0) platform, while transformations such as alcohol oxidation and cycloisomerization can be achieved using Pd(II).

Figure 1.2.1

Types of Transformations

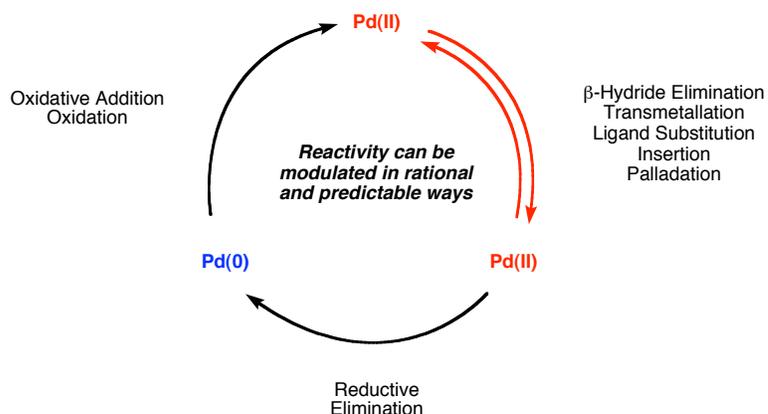
Pd ⁰	Pd ^{II}
Cross-couplings	Wacker Process
Allylic Alkylation	Cycloisomerization
Hydrogenation	Alcohol Oxidation
Hydrogenolysis	Allylic Oxidation
Carbonylation	Allylic Rearrangements

1.2.2 General Reactivity

The bulk of the organopalladium literature is centered on the use of Pd(0) and Pd(II). Although many reports do not clearly delineate the active catalyst (e.g., Pd(II) precatalysts can be used to generate Pd(0) in situ), in general, palladium-catalyzed reactions proceed through the simplified cycle presented in Figure 1.2.2. Pd(0) can undergo either oxidation or oxidative addition, which affords a Pd(II) complex. Pd(II) complexes can generate new Pd(II) complexes via processes such as β -hydride elimination, transmetallation, ligand substitution, insertion, or palladation. Finally, reductive elimination converts the Pd(II) complex back to Pd(0). This mechanistic understanding, combined with the ability of ligands and reaction parameters to modulate

the reactivity of palladium, has allowed for a substantial amount of rational design in this field.

Figure 1.2.2



1.2.3 Palladium(0) Reactivity

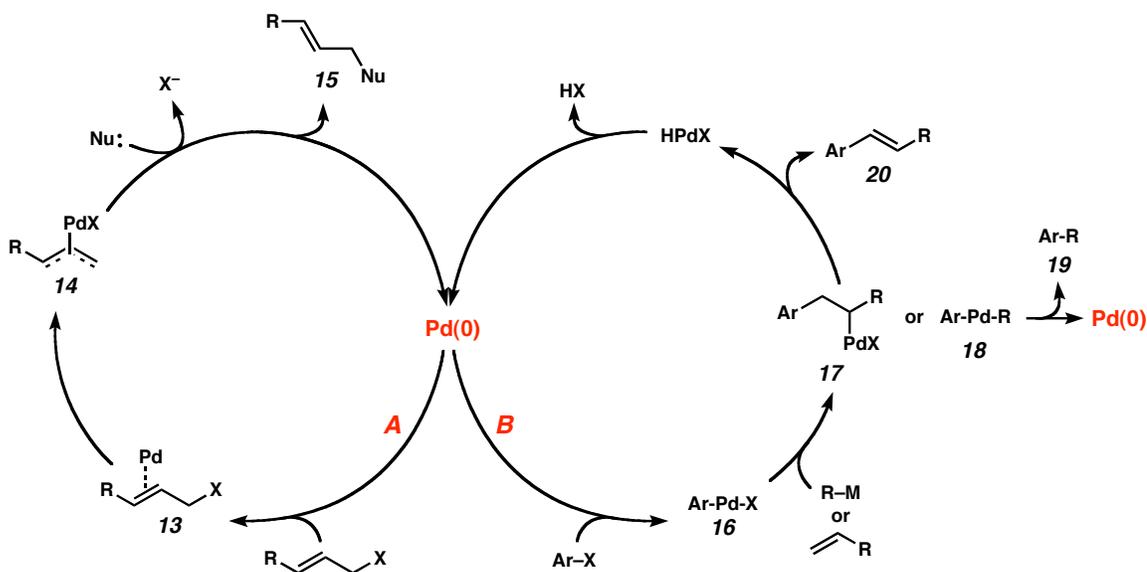
Palladium(0) catalysis has been the focal point of palladium research over the past several decades. A popular method of preparing Pd(0) complexes is via an in situ reduction of a Pd(II) species by reagents such as alkenes, alcohols, amines, phosphines, or metal hydrides. Considered to be nucleophilic, Pd(0) complexes contain a d^{10} palladium, and they are easily oxidized to the Pd(II) state; thus most of the catalytic processes using Pd(0) generally begin with oxidative addition. In general, increasing the electron density on palladium promotes oxidative addition.

One frequent mode of reactivity characteristic of Pd(0) involves the complexation of an olefin with an allylic leaving group, and subsequent oxidative addition (e.g., Pd(0) \rightarrow **13** \rightarrow **14**) to generate a Pd(II) π -allyl complex (**14**, Path A, Scheme 1.2.1). Subsequent

nucleophilic attack, which occurs predominately at the less-hindered carbon of the palladium π -allyl complex, affords the product (**15**) and regenerates the Pd(0) catalyst.

Another common reaction pathway for Pd(0) is regularly observed in cross-coupling chemistry. Specifically, oxidative addition to a molecular bond (e.g., Ar-X) forms an electrophilic Pd(II) complex (e.g., **16**, Path B). At this juncture, any number of Pd(II) reactions can take place, such as olefin insertion (**16** \rightarrow **17**) or transmetalation (**16** \rightarrow **18**). Pd(0) is eventually regenerated by a reductive elimination sequence; β -hydride elimination of **17** produces **20** and HPdX, which becomes Pd(0) and HX upon reductive elimination. Similarly, reductive elimination of **18** affords the product (**19**) and Pd(0) directly.

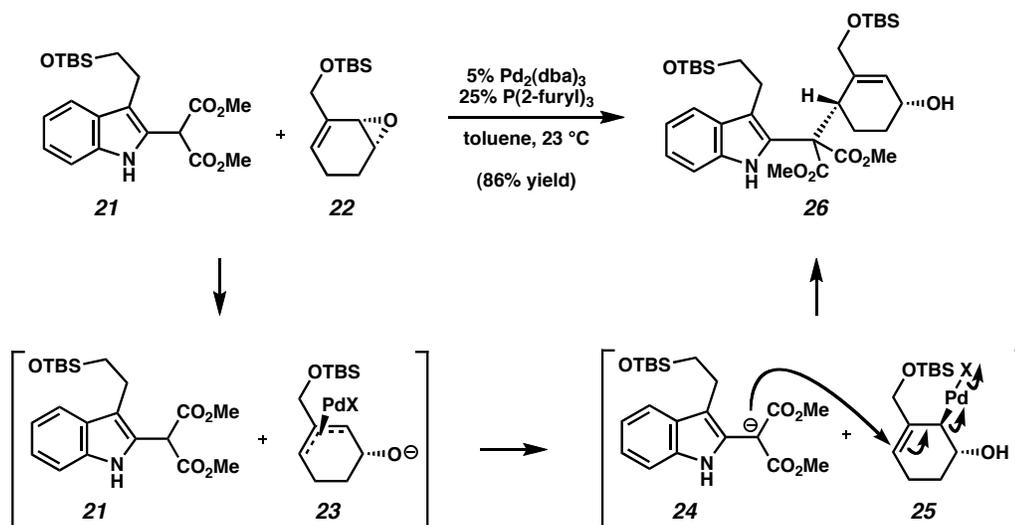
Scheme 1.2.1



Fukuyama recently carried out a relevant example of Pd(0) catalysis in the early steps of his total synthesis of (-)-strychnine.⁶ Indole malonate **21** and vinyl epoxide **22**

were treated with Pd(0) at room temperature (Scheme 1.2.2). Initial oxidative addition to the vinyl epoxide produced Pd(II) π -allyl complex **23**, and the resulting alkoxide was quenched by malonate **21** to form **24**. The malonate anion (**24**) then attacked the electrophilic palladium(II) complex (**25**) in a stereo- and regioselective manner to yield the product (**26**). This product is an intermediate in the synthesis of (-)-strychnine, and was subsequently carried forward to complete the total synthesis.

Scheme 1.2.2



1.2.4 Palladium(II) Reactivity

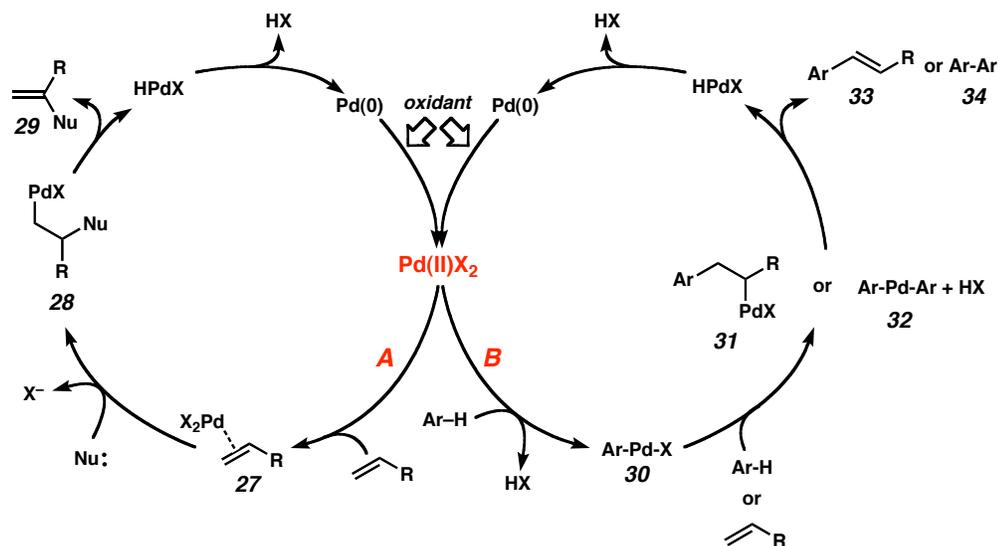
Palladium(II) catalysis, in contrast to palladium(0), has received significantly less attention from the synthetic community in the past, although there has been a revitalized interest within the last several years.^{1i-k} Pd(II) complexes are typically electrophilic and air stable, and thus usually interact with electron-rich functionalities such as olefins, alkynes, and arenes. The lack of Pd(II) research may initially seem surprising, considering that Pd(II) also promotes useful modes of reactivity (see Figure 1.2.1).

However, one of the main complications that has been problematic in the development of Pd(II) methodology is the difficulty of reoxidizing Pd(0) \rightarrow Pd(II). Completion of the catalytic cycle to regenerate Pd(II) requires the presence of a stoichiometric oxidant, such as CuCl₂, Cu(OAc)₂, benzoquinone, *tert*-butyl hydroperoxide (TBHP), MnO₂, HNO₃, and most recently O₂. Not unexpectedly, the addition of these oxidants to a reaction has often interfered with the catalyst/ligand system (or the substrates themselves), and has led to complications in maintaining chemo- or stereoselective processes.

A typical reaction with electrophilic Pd(II) commences with the complexation of an olefin by Pd(II) (**27**, Path A, Scheme 1.2.3). An intermolecular or intramolecular nucleophilic attack on the resulting olefin complex can then occur, generally at the more substituted position of the olefin (**28**, Path A—Wacker-type mechanism). Although any number of Pd(II) processes can occur at this stage (see Figure 1.2.2), the final product typically results from β -hydride elimination (e.g., **28** \rightarrow **29**). The resultant palladium hydride, HPdX, then undergoes a reductive elimination–oxidation sequence to regenerate the active Pd(II) catalyst.⁷

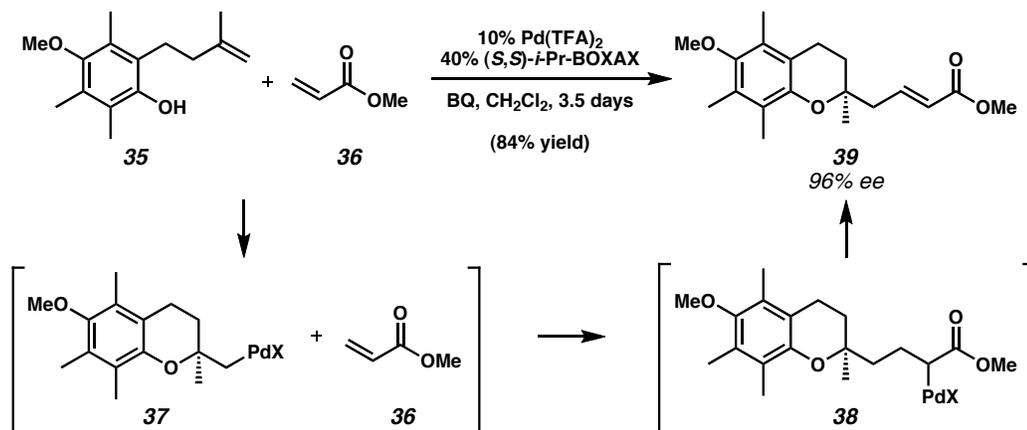
Alternatively, a pathway involving direct attack of the Pd(II)X₂ complex by a nucleophile (e.g, an arene) is also possible (**30**, Path B—Friedel-Crafts-type mechanism).⁸ In a similar fashion, this complex (**30**) can then participate in traditional Pd(II) pathways such as a successive Friedel-Crafts type attack to form **31**, or olefin insertion to form **32**. Although different processes may be observed, β -hydride elimination and reductive elimination sequences are likely to be the final steps in the cycle prior to reoxidation of palladium.

Scheme 1.2.3



A recent report disclosed by Tietze pertaining to the synthesis of vitamin E highlights the synthetic utility of Pd(II).⁹ Tietze's synthetic route relied upon a critical cyclization event, in which phenol **35** and methyl acrylate (**36**) were exposed to a chiral Pd(II) salt where (*S,S*)-*i*-Pr-BOXAX served as the ligand (Scheme 1.2.4). Enantiofacial coordination of the palladium to the olefin of phenol **35**, followed by oxypalladation, results in the formation of the key tertiary stereogenic center, which then leaves palladium(II) intermediate **37** without an accessible β-hydride. Without a competing β-hydride elimination pathway, intermediate **37** is able to react further, and underwent a Heck coupling with methyl acrylate (**36**) to afford Pd(II) complex **38**. Restoration of the enoate through β-hydride elimination then generated the product (**39**), as well as a Pd(II) hydride, X-Pd-H. Reductive elimination to liberate HX then afforded a Pd(0) species, which could be reoxidized to Pd(II) using benzoquinone. The chroman product (**39**) obtained by Tietze was later elaborated to furnish vitamin E.

Scheme 1.2.4



1.3 Conclusion

In summary, both Pd(0) and Pd(II) have had, and continue to have, far-reaching impacts on organic synthesis. The versatile nature of palladium, in conjunction with the mechanistic understanding and predictive models that have been elucidated, has permitted a wealth of exploration into the seemingly endless potential of this metal. Additionally, deficiencies in the Pd(II) and Pd(IV) literature are likely to be remedied as greater control over the oxidation of palladium(0) is achieved.

1.4 Notes and References

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