CHAPTER 1

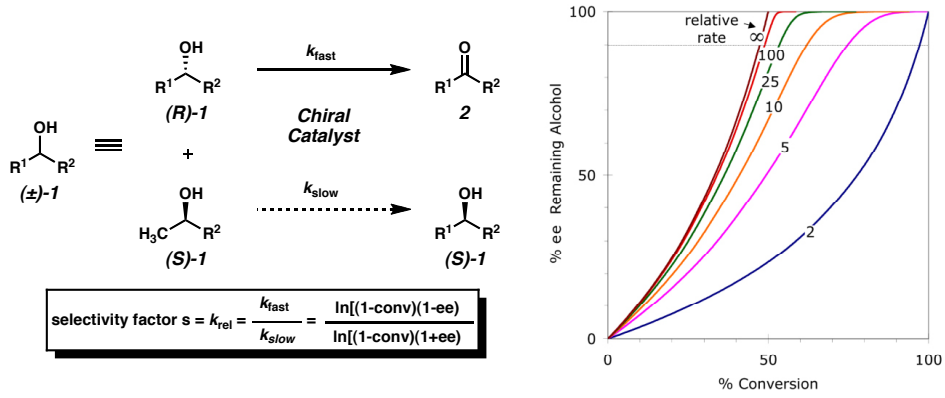
1.1 An Introduction to Oxidative Kinetic Resolution

1.1.1 Introduction

Enantiopure secondary alcohols are invaluable in organic synthesis as they are found in natural products and medicinal drugs. Furthermore, enantiopure secondary alcohols can also lead to carbon-carbon bond formation while transferring the chirality (e.g., allylic alkylation) to afford various types of complex products. One method to access enantioenriched secondary alcohols is via a kinetic resolution, which allows for the isolation of one enantioenriched alcohol from a racemic mixture via a chemical transformation, not the separation of both enantiomers.[1] In an oxidative kinetic resolution of secondary alcohols, one enantiomer (e.g., (*R*)-**1**) reacts faster with the enantiopure catalyst, at a rate of k_{fast}, to provide oxidized product **2**, while the other enantiomer (e.g., (*S*)-**1**) reacts much more slowly (k_{slow}) than its counterpart (Figure 1.1.1). Ideally, the reaction is terminated when all or most of the faster-reacting

enantiomer has been converted to product **2**. The remaining enantioenriched alcohol ((*S*)-**1**) and ketone **2** can then be separated by standard techniques. In an efficient oxidative kinetic resolution, the selectivity factor (s), which is determined by measuring the relative rate (k_{rel}) of reaction of the two enantiomers ($k_{rel} = k_{fast} / k_{slow}$), will be high (s > 15). In practice, the selectivity factor is usually determined by measuring the total conversion of starting material to product and the enantiomeric excess of the recovered starting material.[2] To achieve optimum selectivity, the chiral reagent or catalyst should maintain the same relative enantiomeric preference throughout the reaction; hence, the selectivity factor remains constant. The enantiomeric excess of the starting material will always increase with increasing conversion for any kinetic resolution with a selectivity factor greater than 1 (Figure 1.1.1). Thus, kinetic resolutions have the capacity to provide compounds with high enantioenrichment for even modestly selective processes at higher levels of conversion.

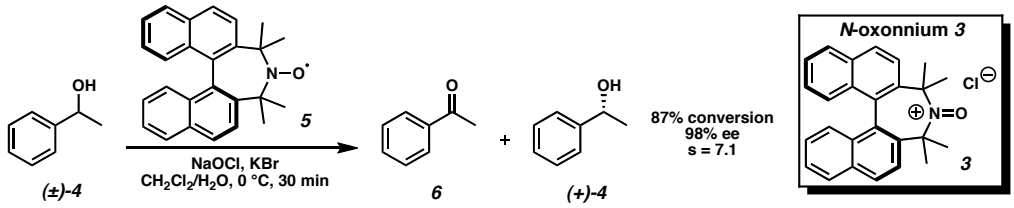
Figure 1.1.1 Kinetic Resolution Overview.



1.1.2 Nitroxyl Radicals in an Oxidative Kinetic Resolution of Secondary Alcohols

The first approach toward a kinetic resolution via alcohol oxidation involved the catalytic use of a nitroxyl radical, which formed an active *N*-oxoammonium species (**3**) under the reaction conditions. Rychnovsky reported the oxidative kinetic resolution of secondary alcohol **4** using chiral nitroxyl radical **5** and sodium hypochlorite as the oxidizing agent (Scheme 1.1.1).[3] Although modest selectivities were achieved (s = 1.5–7.1), this system represented the first example of a nonenzymatic catalytic enantioselective oxidation of secondary alcohols.

Scheme 1.1.1



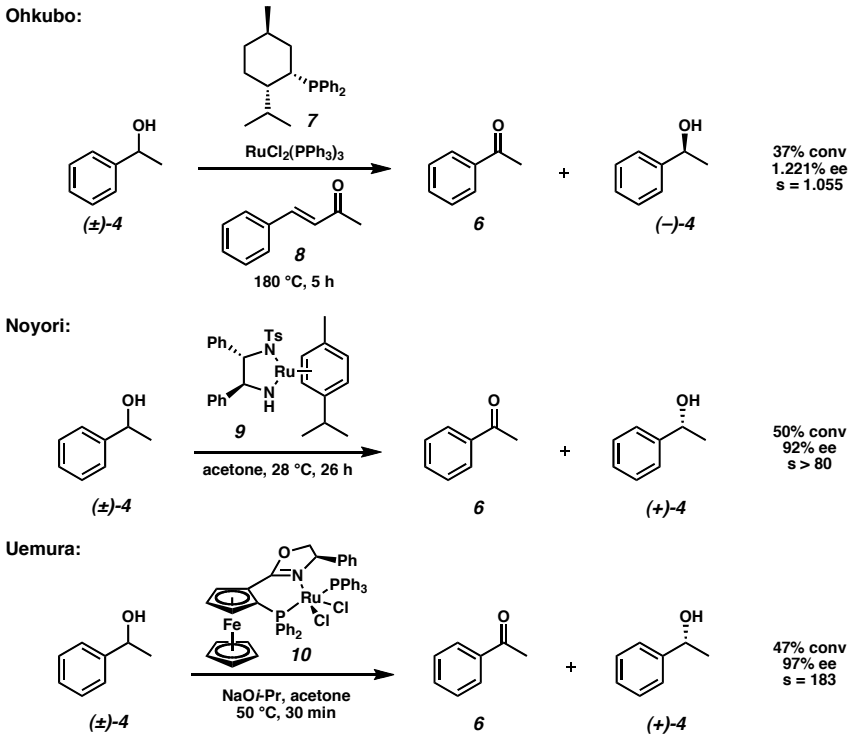
Even though improvements in enantioselectivity using this approach have been realized,[4] this methodology has not been used in the context of total synthesis.

1.1.3 Transition Metals in Oxidative Kinetic Resolutions of Secondary Alcohols

The other general approach to the oxidative kinetic resolution of secondary alcohols employs transition metal catalysis. The first report by Ohkubo et al.[5] validated the catalytic use of a transition metal in an oxidative kinetic resolution. The reaction proceeded by transfer hydrogenation using a menthol-derived phosphine (**7**) ligand to

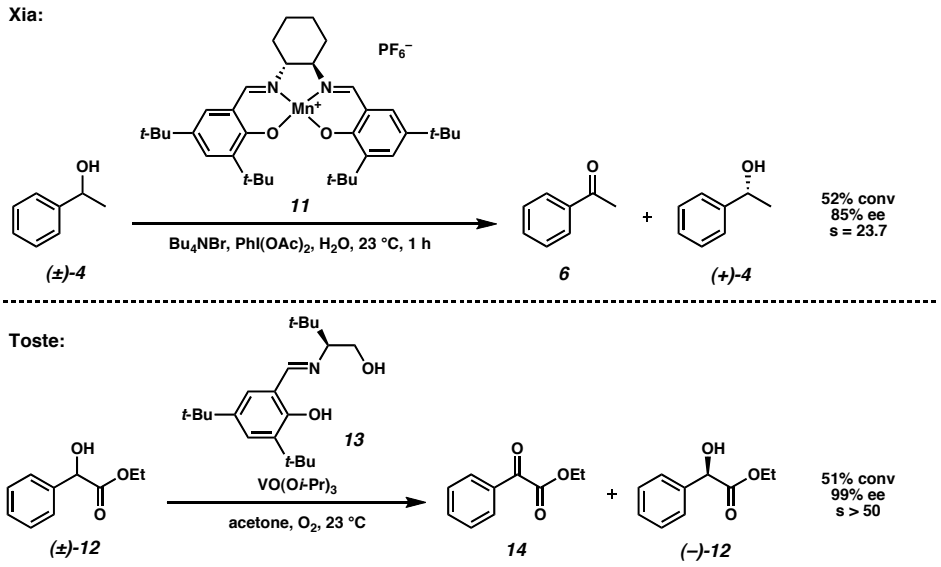
provide *sec*-phenethyl alcohol in 1.2% ee, and a selectivity factor (s) of 1.055 (Scheme 1.1.2). Since then, Noyori and Uemura have developed highly enantioselective variants of a ruthenium-catalyzed kinetic resolution of secondary alcohols. Noyori demonstrated the use of ruthenium-diamine catalyst **9** to resolve secondary alcohols with acetone as the hydrogen acceptor.[6] Uemura later reported a similar system using a ruthenium-ferrocenyloxazoline complex (**10**).[7] In both of these cases, a plethora of benzylic secondary alcohols were resolved to high enantiopurity with very high selectivity (s > 100). Furthermore, Ikariya has shown that iridium and rhodium are viable metal catalysts for the oxidative kinetic resolution of secondary alcohols. Using O_2 as the stoichiometric oxidant and Noyori's diamine ligand motif, Ikariya was able to access highly enantioenriched secondary benzylic alcohols with good selectivity factors (s > 10).[8]

Scheme 1.1.2



More recently, Xia initially reported an oxidative kinetic resolution of benzylic alcohols using a manganese-salen catalyst (**11**) and iodobenzene diacetate as the stoichiometric oxidant (Scheme 1.1.3).[9] It was later reported by Xia that changes in solvent and catalyst allowed for better selectivities for some substrates.[7b] In addition, Toste has described a vanadium catalyst using chiral salicylaldimine ligand **13** for the asymmetric oxidation of α-hydroxy esters.[10,11] High selectivities for an array of α-hydroxy esters were realized, although less-activated alcohols, such as benzylic alcohols, reacted poorly when exposed to this system.[12]

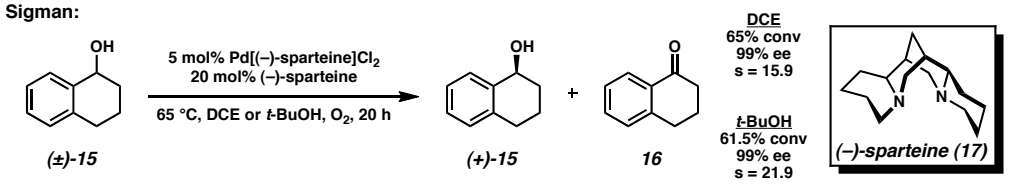
Scheme 1.1.3



In addition, Sigman published a system using (–)-sparteine (**17**) as the chiral ligand with $Pd(OAc)_2$ or $PdCl_2$,[13] and O_2 as the stoichiometric oxidant (Scheme 1.1.4). This system was optimized to use either dichloroethane (DCE) or *t*-butanol (*t*-BuOH) as solvent to obtain modest selectivities (generally s = 5–15) for a wide range of secondary alcohols.[14] Sigman has also shown that at lower catalyst loadings of (–)-sparteine (**17**), the rate-determining step is deprotonation of the alcohol. However, when 20 mol% of

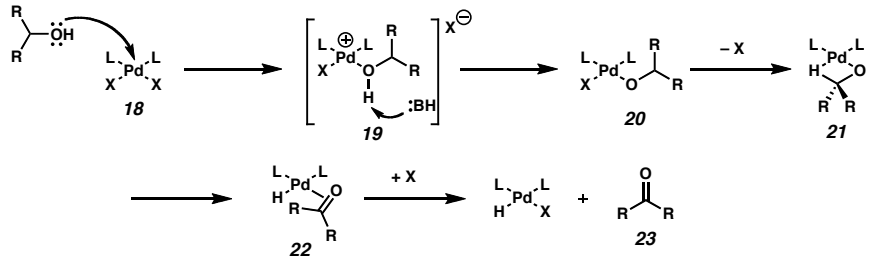
(–)-sparteine is used in the optimized conditions (Scheme 1.1.4), the rate-determining step is β-hydride elimination.[9c] Since β-hydride elimination is directly involved in enantioselectivity, slowing this step enhances the selectivity.

Scheme 1.1.4



In general, the oxidation of secondary alcohols to ketones by palladium(II) most likely involves associative alcohol substitution at the palladium(II) center (**18**), followed by deprotonation of the resulting palladium alcohol complex (**19**) by base to form palladium alkoxide **20** (Figure 1.1.2). At this stage, β-hydride elimination (**20**→**22**) and subsequent dissociation from palladium provides product **23**.

Figure 1.1.2 Proposed Mechanism for Alcohol Oxidation by Palladium.

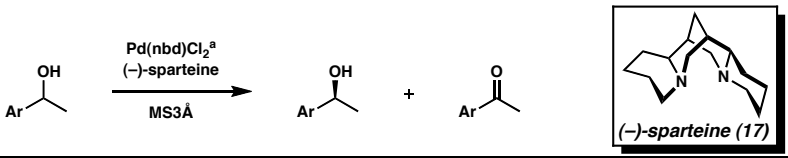


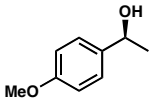
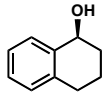
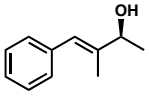
1.1.4 A Pd(II)-catalyzed Oxidative Kinetic Resolution Developed by the Stoltz Laboratory

In 2001, based on early work by Uemura,[15] the Stoltz laboratory developed a palladium(II)-catalyzed oxidative kinetic resolution utilizing (–)-sparteine as the chiral ligand and O_2 as the stoichiometric oxidant.

Since the initial development of the palladium(II)-catalyzed oxidative kinetic resolution of secondary alcohols using (–)-sparteine (**17**),[16] several improvements and further optimization to the catalytic system were accomplished. The palladium(II)-catalyzed oxidative kinetic resolutions can now be performed on a number of activated secondary alcohols to efficiently provide optically enriched secondary alcohols (Table 1.1.1).

Table 1.1.1 Oxidative Kinetic Resolution of Secondary Alcohols.



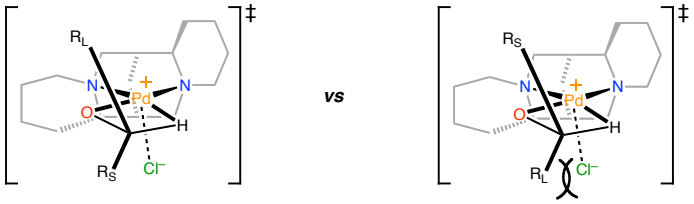
	Original [b] O_2, PhMe 80 °C	*Rate Accelerated* [c] O_2, PhMe, 60 °C Cs_2CO_3, *t*-BuOH	*Chloroform/O_2* [d] O_2, $CHCl_3$, 23 °C Cs_2CO_3	*Chloroform/Air* [e] Air, $CHCl_3$, 23 °C Cs_2CO_3
 *24*	96 h 67% conv 98% ee s = 12	9.5 h 67% conv 99.5% ee s = 15	48 h 63% conv 99.9% ee s = 27	24 h 62% conv 99.8% ee s = 25
 *25*	40 h 69% conv 98% ee s = 16	12 h 62% conv 99% ee s = 21	24 h 58% conv 98% ee s = 28	16 h 60% conv 99.6% ee s = 28
 *26*	120 h 70% conv 92% ee s = 6.6	12 h 65% conv 88% ee s = 7.5	48 h 63% conv 98.7% ee s = 18	44 h 65% conv 98.9% ee s = 16

[a] nbd = norbornadiene, s = selectivity factor, 500 mg, 3ÅMS/mmol substrate were used for all four sets of conditions. [b] 5 mol% palladium catalyst, 0.20 equiv (–)-sparteine (**17**), 0.10 M in PhMe. [c] 5 mol% palladium catalyst, 0.20 equiv (–)-sparteine (**17**), 0.50 equiv Cs_2CO_3, 1.5 equiv *t*-BuOH, 0.25 M in PhMe. [d] 5 mol% palladium catalyst, 0.12 equiv (–)-sparteine (**17**), 0.40 equiv Cs_2CO_3, 0.25 M in $CHCl_3$. Reactions were run open to air through a short drying tube of Drierite.

A model for selectivity in the palladium(II)-catalyzed oxidative kinetic resolution of secondary alcohols was developed by Dr. Raissa Trend, in collaboration with the Goddard laboratory, and is thoroughly discussed within her thesis.[17] The key conclusions from Trend's results are that (–)-sparteine is not behaving as a pseudo C_2 symmetric ligand; rather, it acts as a C_1 ligand allowing for selective displacement of a single

chloride from palladium. Furthermore, her results show that the displaced chloride ion, which has been calculated to be closely associated with palladium in an apical position under the square plane,[18] affects selectivity by clashing with one of the enantiomers of the substrate bound to palladium (Figure 1.1.3). It is thought that this is the main interaction that inhibits β-hydride elimination of one of the enantiomers.

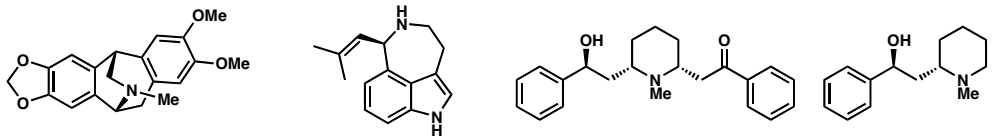
Figure 1.1.3 Proposed β-Hydride Elimination Transition State for Each Enantiomer.



fast-reacting enantiomer ***slow-reacting enantiomer***

To demonstrate the utility of this methodology, the Stoltz laboratory has completed the syntheses of (–)-amurensinine (**27**), (–)-aurantioclavine (**28**), (–)-lobeline (**29**), and (–)-sedamine (**30**) (Figure 1.1.4).[19] Each synthesis relied upon a palladium(II)-catalyzed oxidative kinetic resolution to establish a benzylic stereocenter in high enantioselectivity.

Figure 1.1.4 Natural Products Synthesized via Palladium(II)-catalyzed OKR.

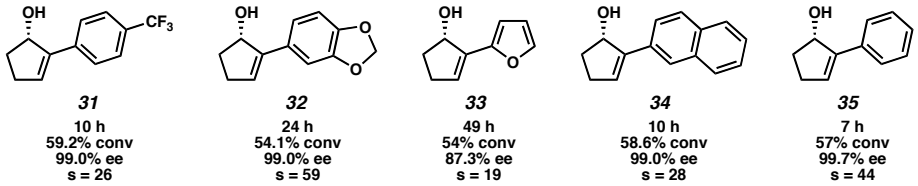


(+)-amurensinine (27) ***(–)-aurantioclavine (28)*** ***(–)-lobeline (29)*** ***(–)-sedamine (30)***

The scope of secondary alcohols used in the palladium(II)-catalyzed oxidative kinetic resolution currently includes activated alcohols bearing benzylic, allylic, or cyclopropyl substituents. One class of exceptional substrates for the palladium(II)-catalyzed oxidative kinetic resolution are 2-aryl cyclopentenols (Figure 1.1.5). Exposure

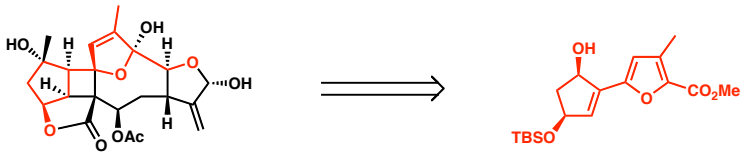
of these racemic alcohols to the original conditions (cf. Table 1.1.1) in the palladium(II)-catalyzed oxidative kinetic resolution provides cyclopentenols **31**–**35** with excellent enantioselectivity and selectivity factors (s).[20]

Figure 1.1.5 Enantioenriched 2-Aryl Cyclopentenols using the Original Conditions.



These substrates led us to examine several natural products bearing an allylic secondary alcohol for the application of this methodology toward further total syntheses. One such molecule was bielschowskysin (**36**) (Figure 1.1.6). We envisioned using the palladium(II)-catalyzed oxidative kinetic resolution to access a key alcohol intermediate (**37**) in high enantioselectivity.

Figure 1.1.6 Substrate for the Palladium(II)-catalyzed Ox. Kinetic Resolution.

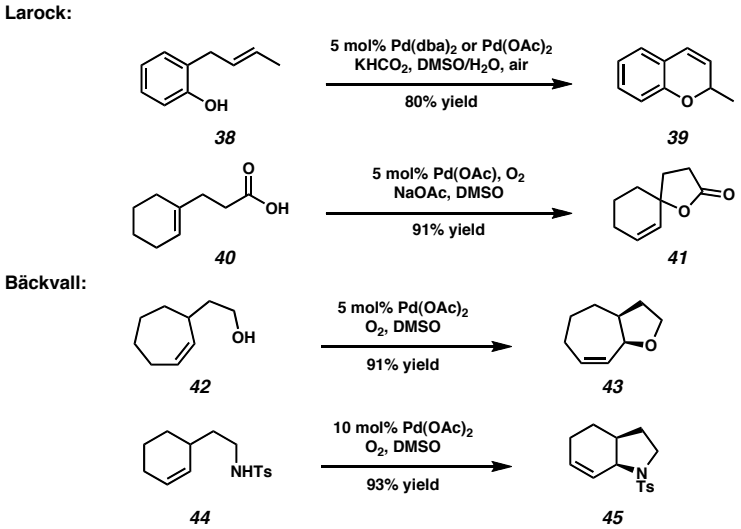


1.2 Introduction to Palladium(II)-Catalyzed Oxidative Heterocyclizations

1.2.1 Racemic and Enantioselective Pd(II)-catalyzed Oxidative Heterocyclizations

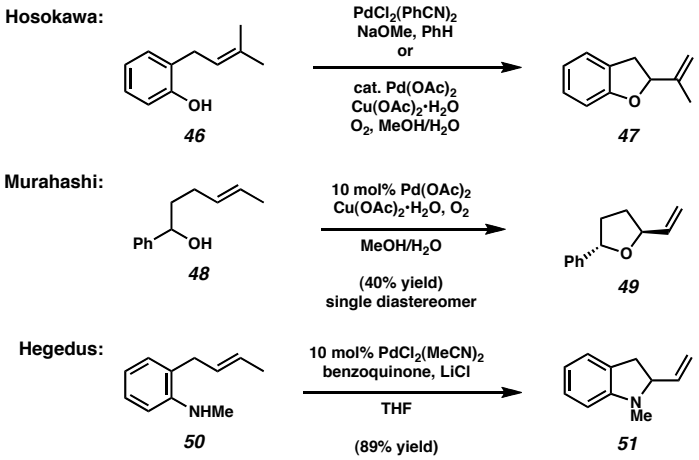
In the well-known Wacker process, $PdCl_2$ in the presence of O_2 and a copper cocatalyst oxidizes ethylene to acetaldehyde.[21] Although the Wacker process has been studied extensively, various aspects of its mechanism, such as the role of the chloride ion, are still disputed.[22] For over several decades now, it has been known that using palladium(II) complexes along with a variety of oxidants can catalyze simple Wacker-type cyclizations to provide racemic mixtures of products. Larock, Bäckvall, and others have demonstrated that palladium(II)-catalyzed oxidative heterocyclizations of olefin-appended nucleophiles provided racemic products using O_2 as the stoichiometric oxidant and DMSO as the solvent (Scheme 1.2.1).[23]

Scheme 1.2.1



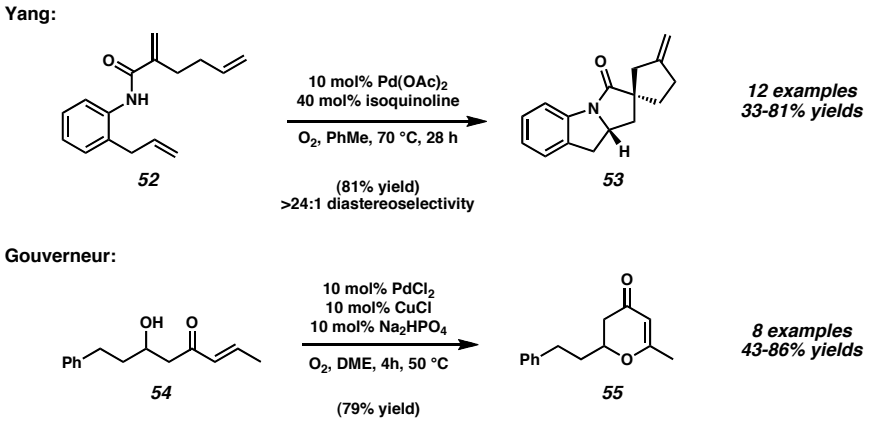
Furthermore, palladium(II)-catalyzed cyclizations have also been developed that use copper/O_2 and benzoquinone as the stoichiometric oxidants. In an early example, Hosokawa showed that stoichiometric palladium(II) could be used to cyclize olefin-appended phenols (Scheme 1.2.2), and that this methodology could be made catalytic in the presence of copper and O_2.[24] Other substrates, such as alcohols and amides, have been cyclized under similar conditions as demonstrated by Murahashi, Hegedus, and others.[25]

Scheme 1.2.2



More recent examples by Yang and Gouverneur highlight recent advances in palladium(II)-catalyzed oxidative heterocyclizations. Yang has reported an oxidative cascade cyclization using *N*-acyl anilines (**52**) to afford spirocycles (**53**) in high diastereoselectivity and good yield (Scheme 1.2.3).[26] In addition, Gouverneur has developed a palladium(II)-catalyzed oxidative cyclization of secondary alcohols (**54**) onto α,β-unsaturated olefins to provide 2,3-dihydro-4*H*-pyran-4-ones (**55**) in good yield.[27]

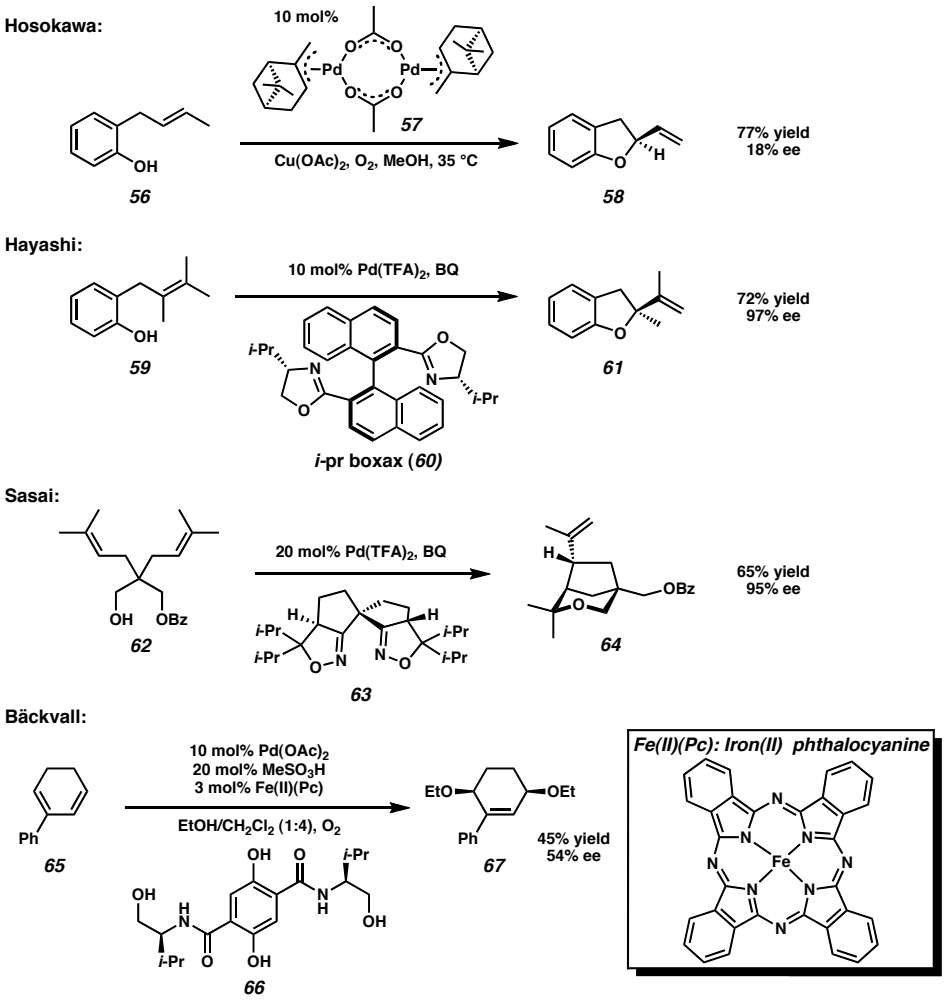
Scheme 1.2.3



Although all of these examples constitute significant advances in palladium(II)-catalyzed oxidative cyclization reactions, the conditions vary for different substrate types, and many do not meet the ideal conditions for asymmetric reactions. For example, the use of additives and co-oxidants such as $Cu(OAc)_2$ can create complex reaction conditions making optimization difficult. Furthermore, the use of highly coordinating solvents such as DMSO inhibits coordination of chiral ligands and thereby prevents the formation of any chiral palladium species necessary for an asymmetric process.

Despite these obstacles, several examples of asymmetric palladium(II)-catalyzed oxidative heterocyclizations have been reported (Scheme 1.2.4). In 1981, Hosokawa described an asymmetric oxidative cyclization with a pinene-derived palladium(II) complex (**57**).[28] More recently, Hayashi and Sasai have employed novel ligand frameworks (ligands **60** and **63**, respectively) and benzoquinone (BQ) as an oxidant to obtain cyclized products with high enantioselectivity.[29,30] In a proof-of-principle experiment by Bäckvall, a chiral benzoquinone generated in situ from arene **66** acted as a ligand in the enantioselective dialkoxylation of diene **65**.[31]

Scheme 1.2.4



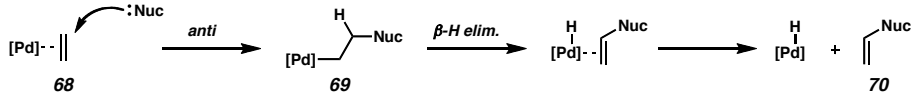
These examples established the potential for enantioselective palladium(II)-catalyzed oxidative heterocyclizations and dialkoxylations using benzoquinone oxidation systems. While these examples are limited in substrate scope, the examples by Sasai and Hayashi represent significant advances toward a general palladium(II)-catalyzed oxidative heterocyclization system.

1.2.2 Possible Mechanisms for the Pd(II)-catalyzed Oxidative Heterocyclization

Palladium(II)-catalyzed nucleophilic attack onto an olefin by a heteroatom can proceed by a variety of mechanisms. One key distinction to be made among them is whether attack occurs with the metal and nucleophile on the same face (syn, internal), or on opposite faces (anti, external) of the olefin. Another subtlety is whether π-allyl palladium(II) species are involved. This section will discuss some of the evidence that has been obtained for each mechanism.

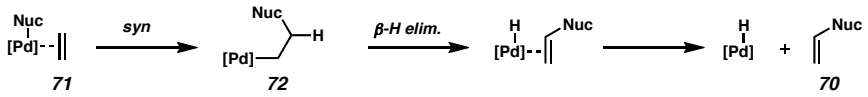
A commonly employed mechanism for palladium(II)-catalyzed oxidative heterocyclization initiates with activation of olefin **68** by palladium, followed by anti-nucleophilic attack (e.g., anti oxypalladation, Figure 1.2.1). The resulting palladium(II) alkyl intermediate (**69**) then undergoes β-hydride elimination to provide product **70**.

Figure 1.2.1 A Generic Heteroatom anti Palladation.



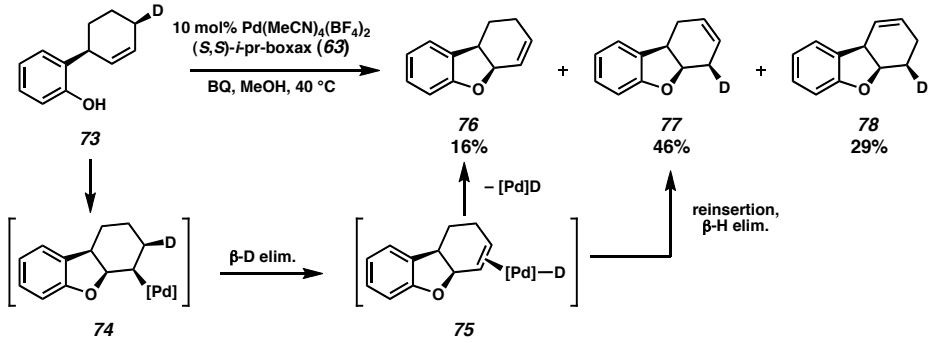
A second possible mechanism is heteroatom syn palladation (e.g., syn oxypalladation), which initially involves a nucleophile bound directly to palladium (**71**, Figure 1.2.2). The bond formed between nucleophile and olefin occurs internally via a migratory insertion, as well as on the same olefin face as the newly formed alkyl-palladium bond (**72**). At this stage, β-hydride elimination and ligand dissociation provides product **70**.

Figure 1.2.2 A Generic Heteroatom syn Palladation.



For evidence of syn oxypalladation, Hayashi and coworkers described the reaction of a stereospecifically deuterium-labeled phenol substrate (**73**) under their enantioselective conditions.[32] As shown in Scheme 1.2.5, after the oxypalladation step, the newly formed C-O bond, palladium, and deuterium are all syn to each other (**74**). Subsequent syn β-deuterium elimination (**74**→**75**) led to the initial product **76**. Compound **77** and olefin isomer **78** are also formed in the reaction as a result of olefin isomerization of product **76**. Nevertheless, all three products are consistent with syn oxypalladation. Interestingly, in the presence of excess chloride ion, anti oxypalladation predominated, which suggests that subtle changes in reaction conditions can have dramatic effects on the mechanism.

Scheme 1.2.5

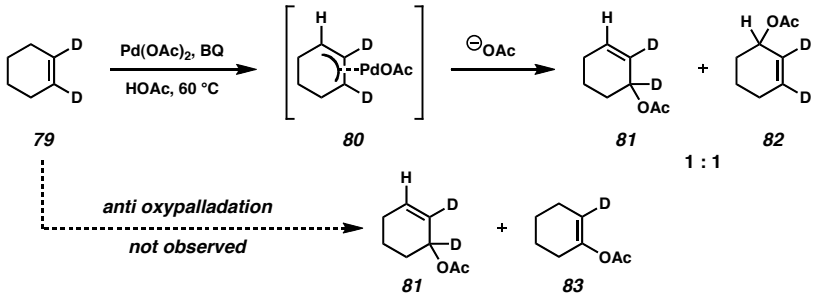


Further evidence of syn oxypalladation by Wolfe and coworkers shows that both oxygen and nitrogen nucleophiles can operate under this mechanism.[33]

Another potential reaction pathway for palladium-olefin cyclizations entails allylic C–H activation by palladium(II) to form an intermediate π-allyl species that would

then undergo reductive elimination with a heteroatom nucleophile. Trost has shown that $Pd(TFA)_2$ will form π-allyl complexes by C-H activation of olefins in acetone.[34] Experimental evidence for this pathway was shown in an intermolecular oxidative acetylation reaction of deuterium-labeled cyclohexene **79** (Scheme 1.2.6).[35] Bäckvall reported that the reaction yielded a 1:1 mixture of products **81** and **82**. This supports the intermediacy of π-allyl complex **80**, whereas anti oxypalladation would produce compound **81** and **83**.

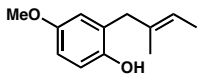
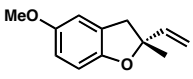
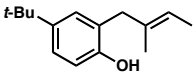
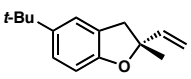
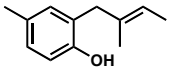
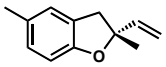
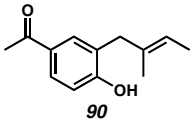
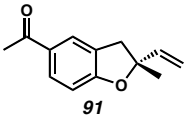
Scheme 1.2.6



1.2.3 A Pd(II)-catalyzed Oxidative Heterocyclization Developed by the Stoltz Laboratory

The Stoltz laboratory has developed an enantioselective palladium(II)-catalyzed oxidative phenol cyclization using palladium(II) catalysis with (–)-sparteine as the chiral ligand, to provide electron-rich dihydrobenzofurans in modest yield and good enantioselectivity (Table 1.2.1).[17c] Unfortunately, other substrates examined such as amines, anilines, and acids cyclize with only moderate enantioselectivity.

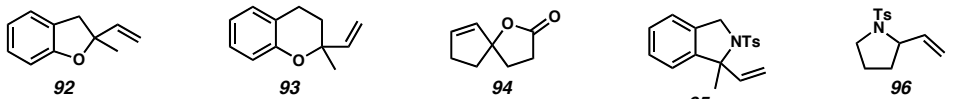
Table 1.2.1 Enantioselective Cyclization of Olefin-Appended Phenols.[a]

entry	substrate	product	time	yield[b]	ee[c]
1.	 **84**	 **85**	24 h 60 h @ 55 °C	64% 57%	88% 90%
2.	 **86**	 **87**	36 h	47%	83%
3.	 **88**	 **89**	36 h	47%	86%
4.	 **90**	 **91**	24 h	60%	20%

[a] 10 mol% (sp)Pd(TFA)$_2$, 100 mol% (–)-sparteine (**17**), 2.0 equiv Ca(OH)$_2$, 500 mg 3ÅMS/mmol substrate, 1 atm O_2, PhMe (0.10 M), 80 °C. [b] Isolated yield. [c] Measured by GC.

Accordingly, using a Pd(TFA)$_2$/pyridine/O_2 catalyst system, 3ÅMS in toluene at 80 °C, along with an exogenous base such as Na_2CO_3, a variety of heteroatom substrates cyclize to provide the desired products (**92**-**96**) in good yield (Figure 1.2.3). For some substrates, it was found that omitting Na_2CO_3 allowed for better conversion, probably due to variations of substrate pKa.

Figure 1.2.3 Heterocycles Accessed via a Pd(II)-catalyzed Oxidative Heterocyclization.



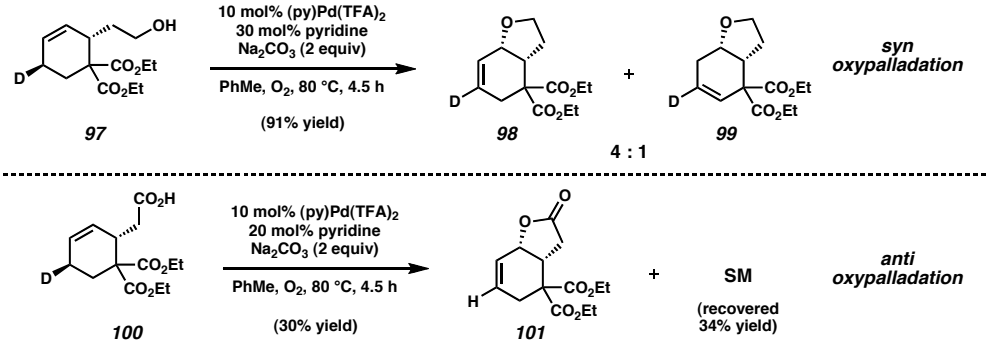
92 95% yield[a] **93** 85% yield[a] **94** 62% yield[c] **95** 88% yield[b] **96** 90% yield[b]

[a] mol% Pd(TFA)$_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C. [b] 5 mol% Pd(TFA)$_2$, 20 mol% pyridine, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C. [c] 10 mol% Pd(TFA)$_2$, 40 mol% pyridine, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C.

In addition, further studies found that the mechanism for the palladium(II)-catalyzed oxidative heterocyclization changes between syn and anti heteroatom palladation depending on the substrate. Using deuterium-labeled substrates, it was found

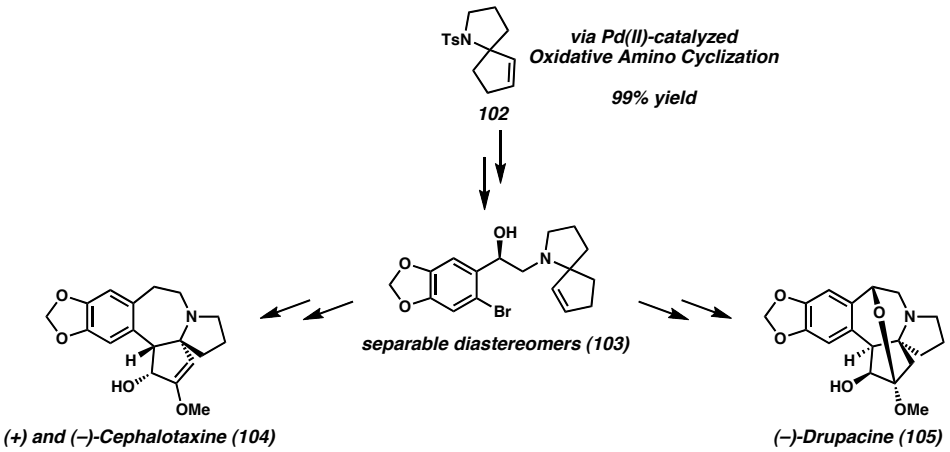
that alcohol **97** reacted via syn oxypalladation to provide tetrahydrofurans **98** and **99** in a 4:1 ratio, whereas acid **100** cyclized via anti oxypalladation to provide γ-lactone **101** (Scheme 1.2.7).[36] These changes in mechanism might be attributed to differences in the pKa of the two substrates (**97** and **100**); however, the exact reasons for the switch in mechanism has not been fully elucidated.[37]

Scheme 1.2.7



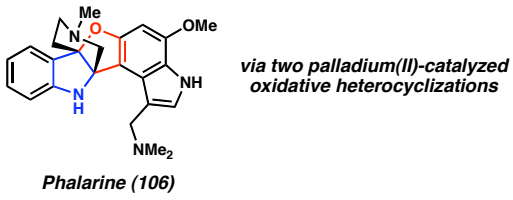
To demonstrate the application of this methodology in natural product synthesis, the Stoltz laboratory has completed the formal total synthesis of both enantiomers of cephalotaxine (**104**), as well as the asymmetric total synthesis of (–)-drupacine (**105**). All three were derived from intermediate **103**, which was accessed in excellent yield via a palladium(II)-catalyzed oxidative heterocyclization to form the spirocyclic amine moiety in intermediate **102** (Figure 1.2.4).[38]

Figure 1.2.4 Natural Products Synthesized via a Pd(II)-catalyzed Oxidative Heterocyclization.



The Stoltz laboratory is always searching for biologically active natural products that could be efficiently synthesized using developed group methodologies. For one such molecule, phalarine (**106**), we envisioned using two palladium(II)-catalyzed oxidative heterocyclizations to form the dihydrofuran (red) and dihydropyrrole (blue) rings respectively (Figure 1.2.5).

Figure 1.2.5 Structure of (–)-Phalarine.



This thesis will describe efforts toward an enantioselective total synthesis of bielschowskysin using a palladium(II)-catalyzed oxidative kinetic resolution to provide an enantioenriched early intermediate. Moreover, attempts toward the synthesis of phalarine using two palladium(II)-catalyzed oxidative heterocyclizations to construct the core of the natural product will also be discussed.

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