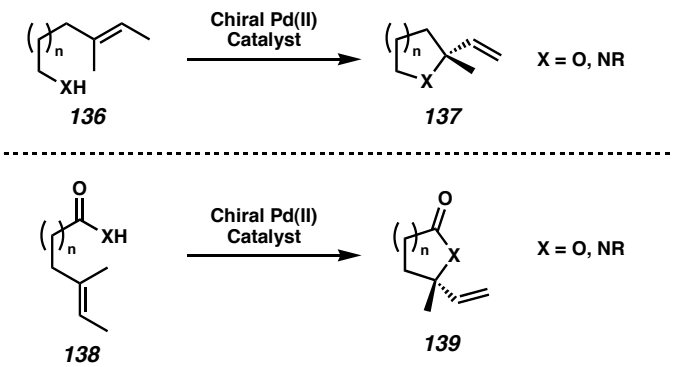
CHAPTER THREE

Palladium-Catalyzed Aerobic Wacker Cyclizations and the Formal Total Synthesis of Cephalotaxine

3.1 Introduction

The design of palladium-catalyzed dehydrogenative transformations is an important area of research for our laboratory.[1] The initial studies led to the development of an oxidative kinetic resolution of secondary alcohols using molecular oxygen as the sole stoichiometric oxidant.[2] The kinetic resolution, however, was just one example of the array of non-heteroatom transfer oxidations we were intent on developing. Oxidative heterocyclizations (Scheme 3.1.1) are another fundamental class of transformations that were of interest. These reactions involve the cyclization of a heteroatom nucleophile onto an olefin to afford a heterocycle. This process is in essence an intramolecular variant of a Wacker oxidation, where an olefin is activated by palladium(II) for subsequent nucleophilic attack.[3] Most of the systems developed for Wacker oxidations, however, are simply not amenable to asymmetric catalysis. Prompted by our studies of a palladium(II) oxidation system that clearly was amenable to enantioselective catalysis, we sought to apply this system toward oxidative heterocyclizations.[4]

Scheme 3.1.1



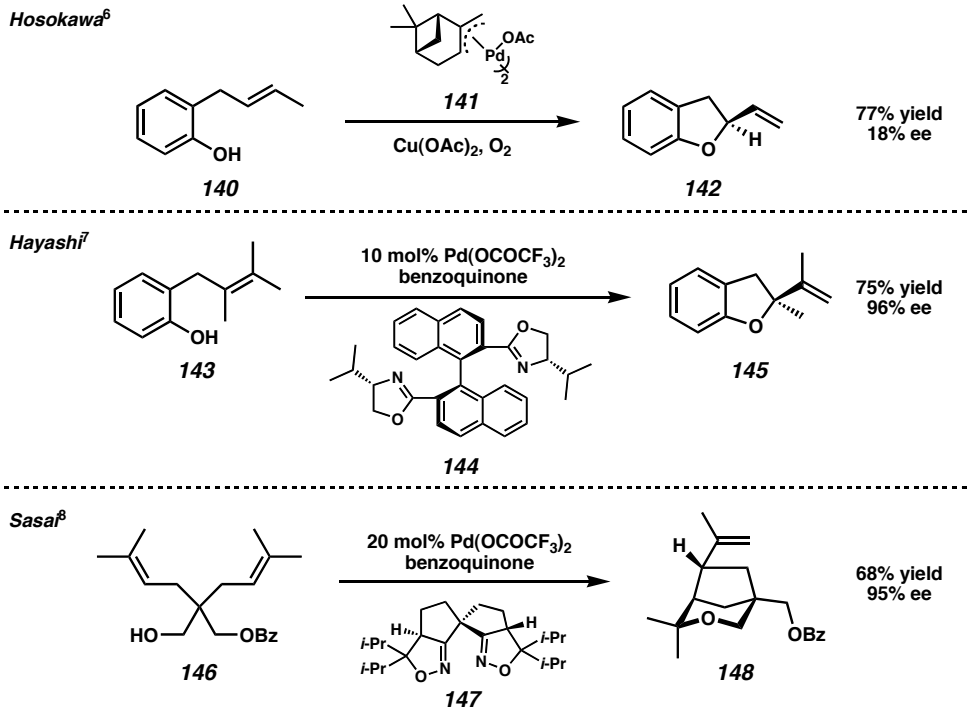
3.2 Background

Racemic intramolecular Wacker cyclizations to form heterocycles, variants of those depicted in Scheme 3.1.1, have been studied extensively.[5] A range of heteroatom nucleophiles have been investigated, including phenols, alcohols, amines, tosylamides, carboxylic acids, and amides. Palladium(II) catalysis, a general method for this process, provides heterocycles in typically excellent yields. Most of the reactions reported, however, utilize cooxidants such as copper(II) salts or benzoquinone to effect the reoxidation from palladium(0) to electrophilic palladium(II). These cooxidants would likely be problematic in the development of asymmetric heterocyclizations employing chiral palladium(II) complexes. Chiral ligands could preferentially bind to copper instead of palladium; benzoquinone and hydroquinone could act as competitive ligands to the palladium center.

Despite these complicating factors, works by Hosokawa,[6] Hayashi,[7] and Sasai[8] have demonstrated the possibility of enantioselective oxidative heterocyclizations via palladium catalysis (Scheme 3.2.1). Hosokawa and Murahashi reported the first case of an asymmetric heterocyclization using an isopinocampheyl-palladium acetate dimer (**141**), affording dihydrobenzofuran **142** in 18% ee.[6] Over fifteen years later, Hayashi disclosed the first highly enantioselective Wacker cyclization on a similar substrate using a binaphthyl-bisoxazoline ligand (BOXAX, **144**) with $Pd(OCOCF_3)_2$ and benzoquinone as the stoichiometric reoxidant.[7] With this system, dihydrobenzofurans such as **143** are obtained in >90% ee. More recently, Sasai described an asymmetric Wacker transformation of a non-phenolic substrate (**146**), which underwent a double cyclization

in the presence of a palladium-SPRIX (**147**) catalyst to afford bicycle **148** in good yield and high ee.[8] Analogous to Hayashi's system, benzoquinone was used as the stoichiometric cooxidant. The reports by Hayashi and Sasai were the only examples of highly enantioselective palladium-catalyzed Wacker cyclizations.

Scheme 3.2.1



Based on our successes in the palladium-catalyzed oxidative kinetic resolution of secondary alcohols,[2a] we speculated that a similar oxidation system could be utilized toward the development of asymmetric intramolecular Wacker reactions. Specifically, the alcohol oxidation system described by Uemura ($Pd(OAc)_2$, pyridine, O_2)[9] was used as a starting point for the discovery of the kinetic resolution ($Pd(nbd)Cl_2$, (–)-sparteine, O_2). We anticipated that an oxidation system similar to that of Uemura could catalyze oxidative heterocyclizations. The success of this strategy could facilitate the extension to

asymmetric variants in an analogous fashion to our kinetic resolution work. Described herein are our efforts to apply the palladium(II) aerobic oxidation system we had been studying toward intramolecular Wacker cyclizations to form heterocycles.

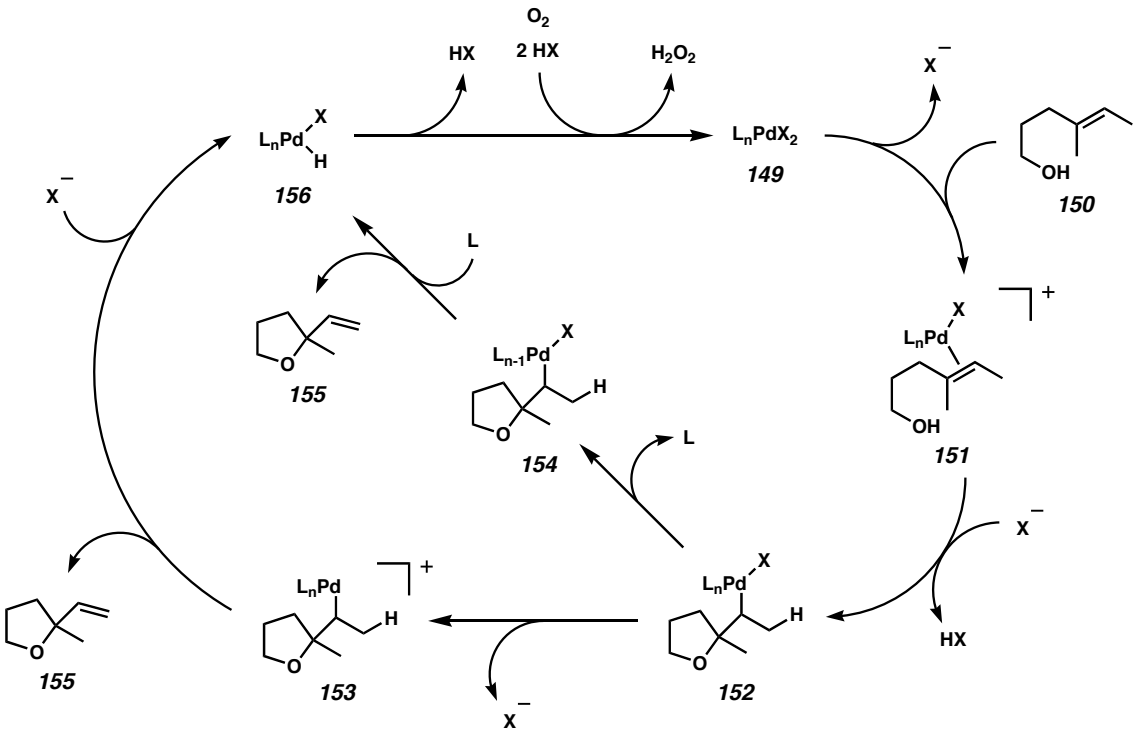
3.3 The Development of Palladium-Catalyzed Aerobic Heterocyclizations

3.3.1 Oxidative Cyclizations with Molecular Oxygen

Palladium-catalyzed heterocyclizations that use molecular oxygen as the sole stoichiometric oxidant are rare. The only aerobic system reported involves catalytic $Pd(OAc)_2$ in DMSO, pioneered by the investigations of Larock and Bäckvall.[10] The development of asymmetric variants based on these works would certainly be hindered by the ligating ability of DMSO to palladium, interfering with a palladium-chiral ligand catalyst. The system of Uemura, which uses toluene as the solvent, was considerably more attractive in this light.

The mechanism that was envisioned for the aerobic oxidative heterocyclization is depicted in Scheme 3.3.1. Ligated palladium(II) catalyst **149** dissociates an X-type ligand and binds an olefin to give cationic intermediate **151**. The olefin is activated for intramolecular nucleophilic attack with concomitant deprotonation by X^-, which leads to palladium-alkyl intermediate **152**. At this stage, an open site on the palladium center is likely necessary for β-hydride elimination; this occurs via dissociation of either an X-type ligand to cationic intermediate **153** or an L-type ligand to neutral intermediate **154**. The palladium hydride (**156**) generated from the elimination and dissociation of **155** is converted back to palladium(II) species **149** through an oxidation pathway involving molecular oxygen.[11]

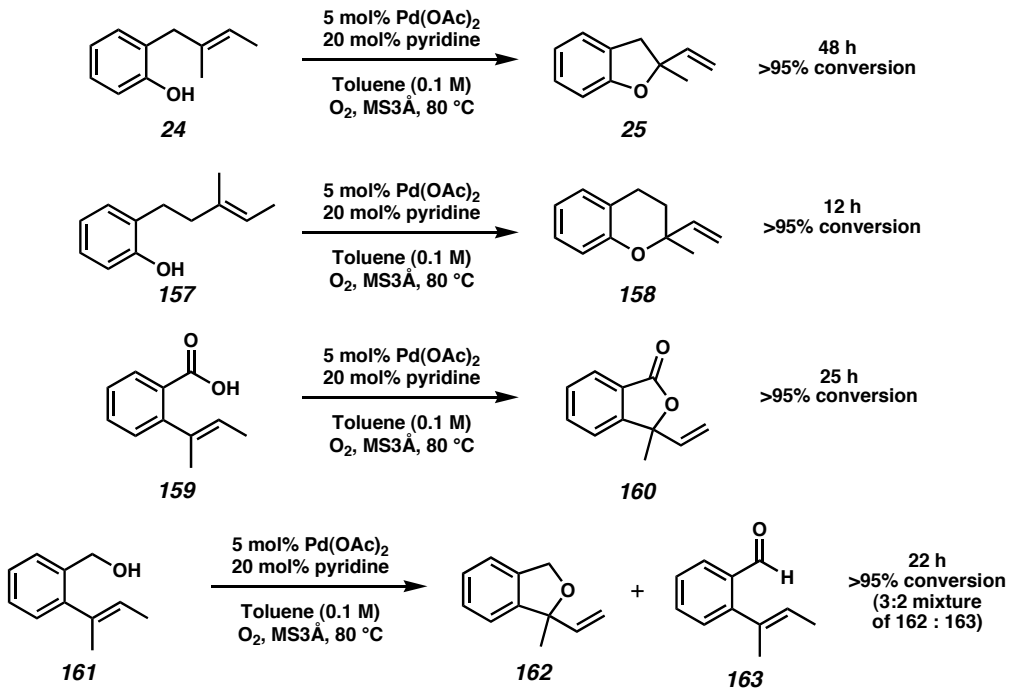
Scheme 3.3.1



3.3.2 Initial Experiments

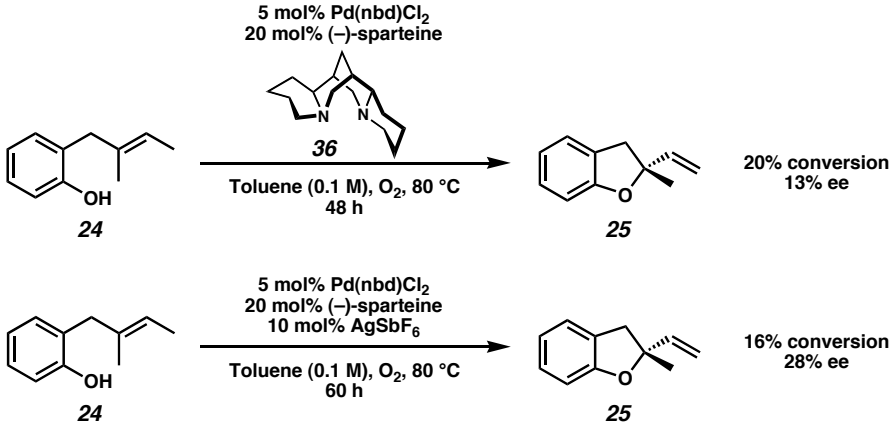
To test the feasibility of these cyclizations under the aerobic oxidation system described by Uemura,[9] a number of olefin substrates were synthesized and subjected to the standard conditions ($Pd(OAc)_2$, pyridine, O_2, toluene, 80 °C). As shown in Scheme 3.3.2, cyclizations proceeded to complete conversion for a variety of heteroatom nucleophiles. Phenols **24** and **157** cyclized to produce dihydrobenzofuran **25** and dihydrobenzopyran **158**, respectively. A carboxylic acid was also a competent nucleophile, cyclizing to afford lactone **160**. In the case of benzylic alcohol **161**, both dihydrofuran **162**, arising from oxidative cyclization, and aldehyde **163**, arising from alcohol oxidation, were observed.

Scheme 3.3.2



With the success of cyclization under the desired conditions, we then probed the possibility of asymmetric variants of these heterocyclizations. As a test experiment, the optimized conditions from the palladium-catalyzed kinetic resolution ($Pd(nbd)Cl_2$, (–)-sparteine, O_2, toluene, 80 °C, see Scheme 3.3.3) were employed. Although the reaction was extremely sluggish (20% conversion after 48 h), there was some observed enantioinduction (13% ee). Furthermore, when 10 mol% $AgSbF_6$ was added to the reaction mixture, the enantioselectivity increased measurably.[12] Although the selectivities were modest, these encouraging results demonstrated the viability of extending the simple palladium/ligand/oxygen/toluene system to enantioselective variants.

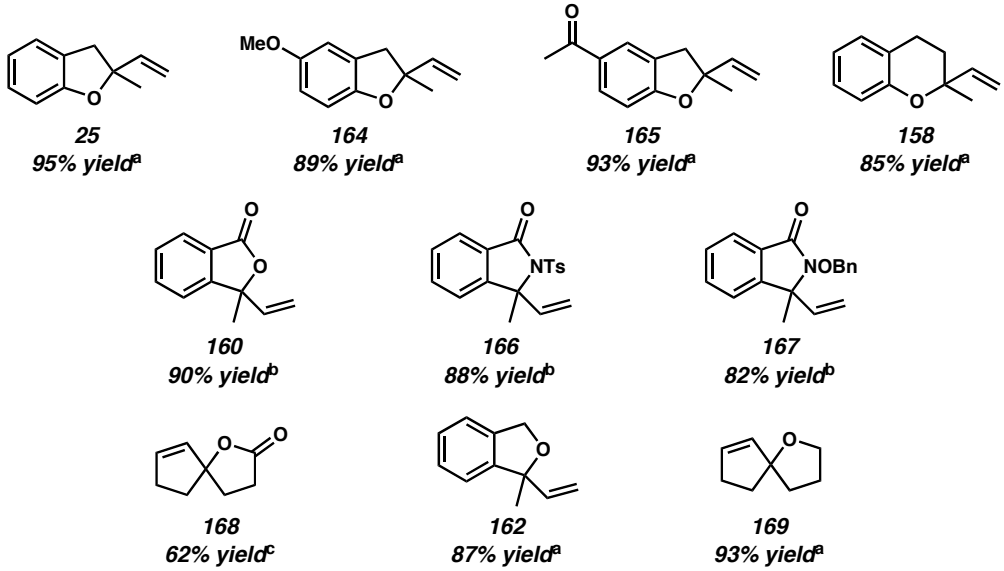
Scheme 3.3.3



3.3.3 Reaction Development

At this point, this project was carried to completion by Raissa Trend, a graduate student in the Stoltz laboratory, and Dr. Yeeman Ramtohul, a postdoctoral scholar in the same laboratory. After considerable investigation and optimization, an array of heterocycles could be synthesized in excellent yields by this oxidative system (Figure 3.3.1).[4,13] Analogous to the kinetic resolution chemistry, a significant counterion effect was observed during these studies. $Pd(OCOCF_3)_2$ was an especially effective palladium precursor for catalyzing these oxidative transformations.[14] Heterocycles including dihydrobenzofurans, dihydrobenzopyrans, lactones, and lactams were obtained using this palladium-catalyzed aerobic intramolecular Wacker cyclization. Interestingly, furans **162** and **169** could be accessed exclusively via these oxidative transformations; aldehyde products were not observed.

Figure 3.3.1 Heterocycles accessed via the palladium-catalyzed aerobic oxidative Wacker cyclization.



25 ***95% yield[a]*** ***164*** ***89% yield[a]*** ***165*** ***93% yield[a]*** ***158*** ***85% yield[a]***

160 ***90% yield[b]*** ***166*** ***88% yield[b]*** ***167*** ***82% yield[b]***

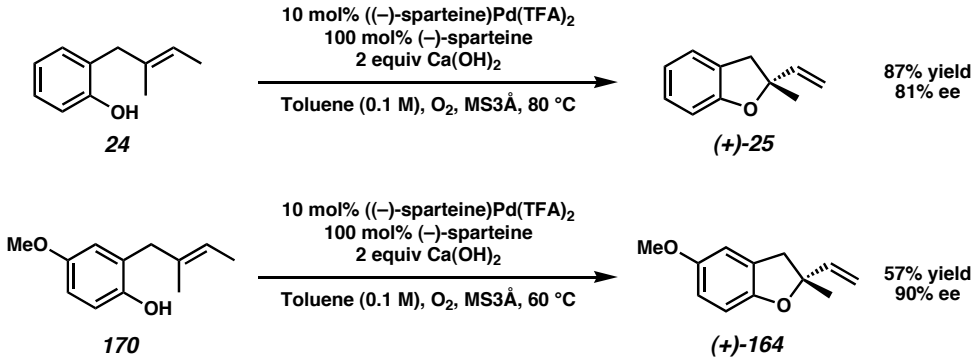
168 ***62% yield[c]*** ***162*** ***87% yield[a]*** ***169*** ***93% yield[a]***

[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C. [b] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C. [c] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C.

Importantly, highly enantioselective variants of these oxidative heterocyclizations could be realized under similar systems (Scheme 3.3.4).[4] Again, using (–)-sparteine as the chiral ligand, the cyclization of phenols **24** and **170** proceeded with high enantioinduction to afford dihydrobenzofurans **25** (81% ee) and **164** (90% ee), respectively. These results represented the first examples of palladium-catalyzed asymmetric heterocyclizations using molecular oxygen as the sole stoichiometric oxidant. They also demonstrate a critical proof of concept: the simple palladium/ligand/oxygen/toluene oxidative system provided a straightforward entry toward the discovery of highly selective asymmetric variants. Not only was this viable in the alcohol oxidation chemistry, but now it was possible in oxidative Wacker cyclizations as well. This versatile palladium(II) system clearly had wide potential in oxidative

transformations, and further extensions of this chemistry to novel asymmetric cyclizations is a promising future direction.

Scheme 3.3.4



3.4 The Formal Total Synthesis of Cephalotaxine

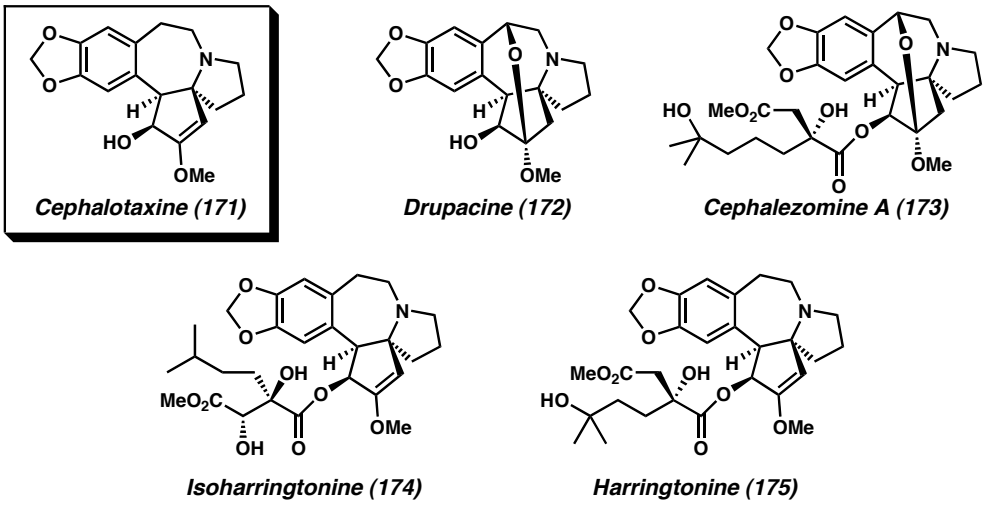
3.4.1 Introduction and Background

While the heterocyclization investigations were ongoing, we desired to demonstrate the utility of these palladium(II) oxidative transformations in natural product synthesis. To this end, we pursued the total synthesis of the *Cephalotaxus* alkaloids.[15] In the synthetic design, we wanted to exploit the potential of palladium(II) dehydrogenative reactions to build molecular architectures in a rapid, efficient fashion.

The *Cephalotaxus* alkaloids (Figure 3.4.1), first isolated in 1974,[16] are an interesting class of biologically active natural products. Although the parent compound, cephalotaxine (**171**), has shown no biological activity, esters of the C-3 hydroxyl have shown potent antileukemic activity. Additionally, cancer patients who have become resistant to other forms of chemotherapy responded positively to cephalotaxine esters, indicative of possible multiple drug resistance reversing activity.[17] With the clear

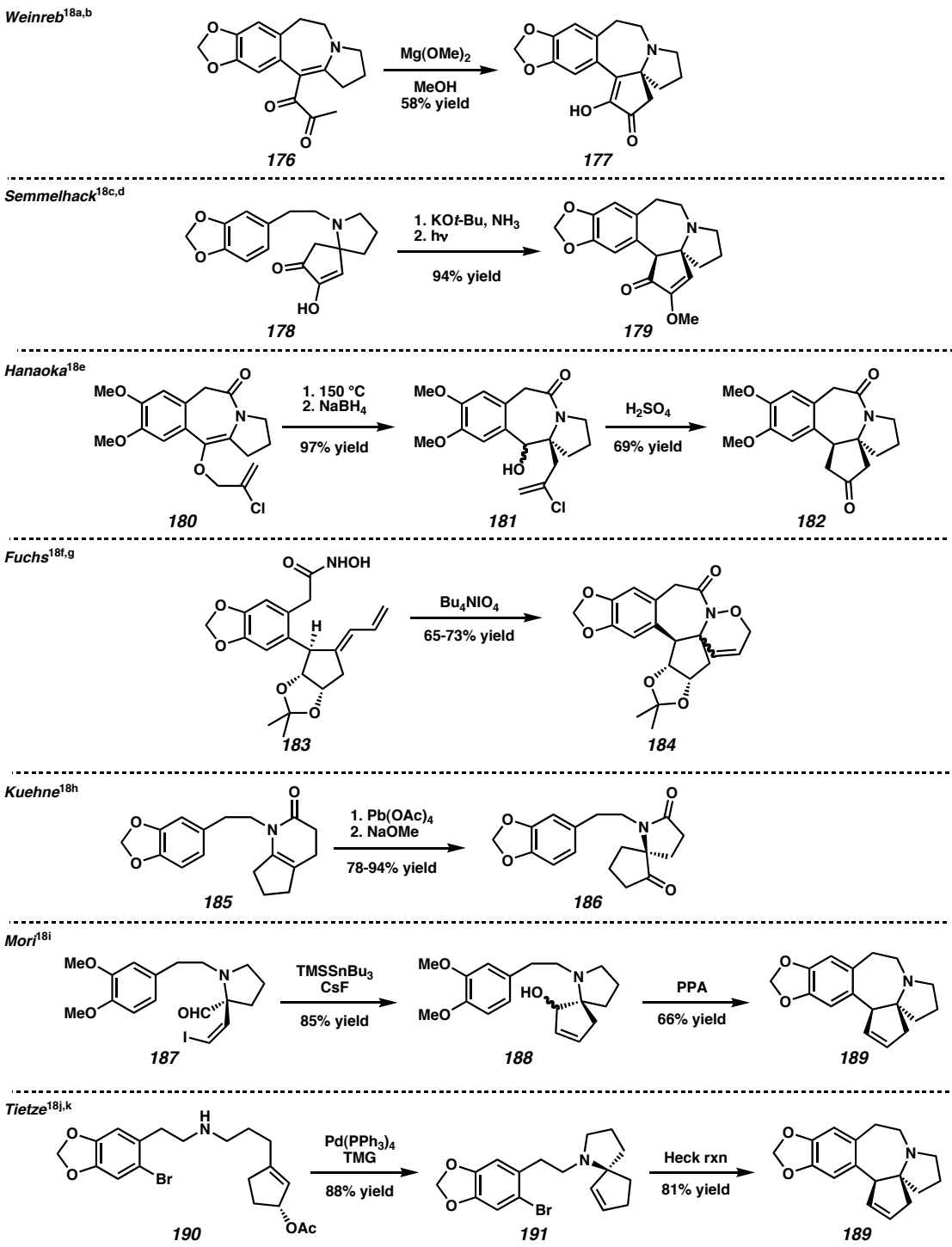
biological importance of these compounds, an efficient synthesis of the alkaloids is highly desirable.

Figure 3.4.1 Representative examples of the *Cephalotaxus* alkaloids.



The total synthesis of cephalotaxine has been pursued by several laboratories. Since the report of the first total synthesis by Weinreb in 1972, a number of syntheses have been reported in the literature.[18,19] The key transformation that was utilized in each individual synthesis is outlined in Scheme 3.4.1. Although the synthesis of cephalotaxine has been extensively investigated, we envisioned that the synthesis of this molecule would serve to illustrate the utility of the palladium(II) oxidative chemistry we had studied thus far.

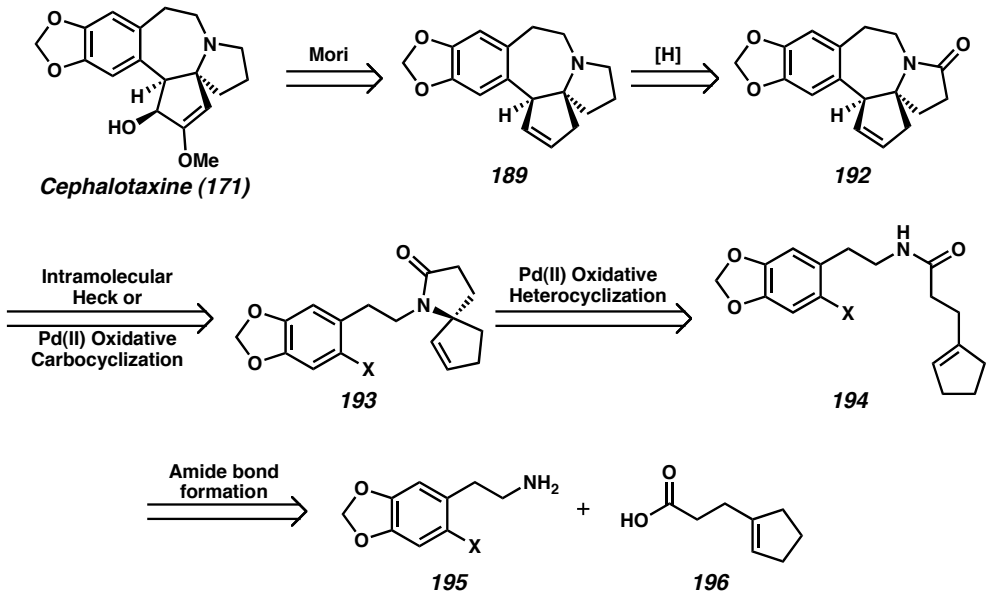
Scheme 3.4.1


Weinreb[18a,b]
Mg(OMe)2
MeOH
58% yield
176
177
Semmelhack[18c,d]
1. KOt-Bu, NH3
2. hν
94% yield
178
179
Hanaoka[18e]
1. 150 °C
2. NaBH4
97% yield
H2SO4
69% yield
180
181
182
Fuchs[18f,g]
Bu4NIO4
65-73% yield
183
184
Kuehne[18h]
1. Pb(OAc)4
2. NaOMe
78-94% yield
185
186
Mori[18i]
TMSSnBu3
CsF
85% yield
PPA
66% yield
187
188
189
Tietze[18j,k]
Pd(PPh3)4
TMG
88% yield
Heck rxn
81% yield
190
191
189

3.4.2 Retrosynthetic Plan

Outlined in Scheme 3.4.2 is our retrosynthetic plan. We first targeted the known olefin intermediate **189**, which has been converted to the natural product in enantiopure form by Mori.[18i] The amine could arise from a reduction of lactam **192**. This lactam could be formed from spirolactam **193** via a diastereoselective intramolecular Heck reaction (X = halogen). Another possibility is to use palladium(II) chemistry to form the seven-membered ring. If X = H, then under palladium(II) catalysis, arene palladation and subsequent diastereoselective olefin insertion and β-hydride elimination could occur, leading to the identical product arising from the Heck reaction (**192**).[20] The spirolactam could be formed from amide **194** by a palladium(II)-catalyzed intramolecular heterocyclization. Amide **194** could be synthesized from amine **195** and acid **196** through straightforward coupling chemistry.

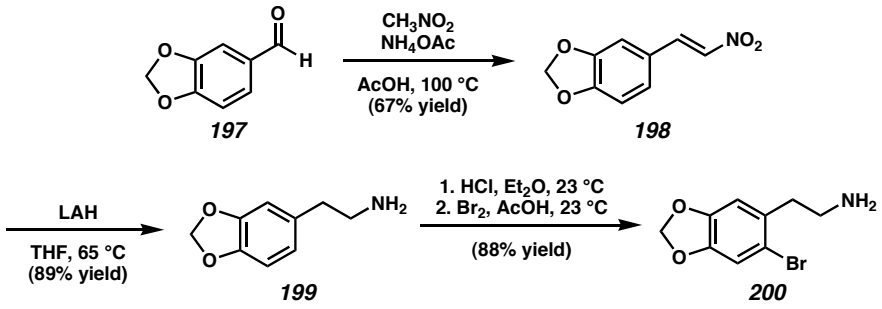
Scheme 3.4.2



3.4.3 Formal Total Synthesis of (±)-Cephalotaxine

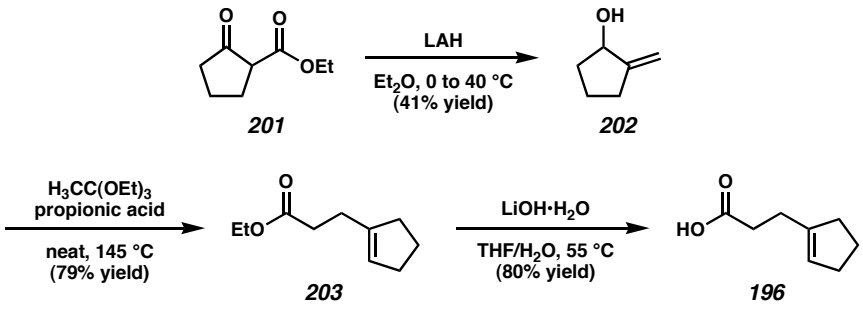
For our first approach, we decided to pursue the route involving the intramolecular Heck reaction since it was more precedented at the onset of this study. Amine **200** can be synthesized in three steps according to the procedures of Marsden and MacLean,[21] and of Tietze and Schirok (Scheme 3.4.3).[18k] Piperonal (**197**) is treated with nitromethane under Henry conditions[22] to afford β-nitrostyrene derivative **198**. Lithium aluminum hydride reduction to the amine followed by arene bromination provides amine **200** in excellent yield.

Scheme 3.4.3



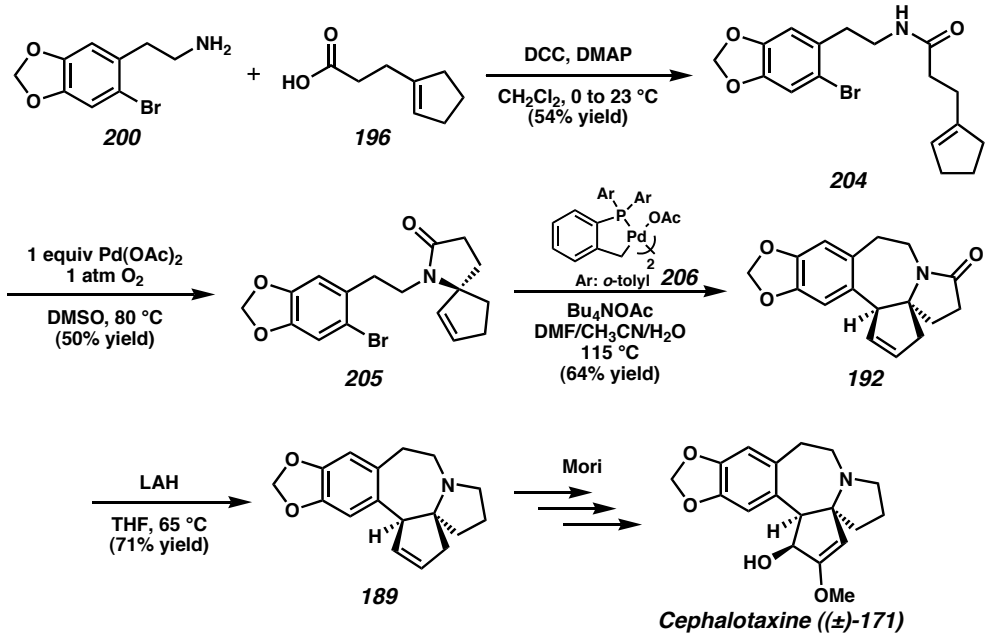
Carboxylic acid **196**[4] was readily synthesized from commercially available β-ketoester **201** (Scheme 3.4.4). The ketoester is reduced to allylic alcohol **202** by lithium aluminum hydride.[23] The allylic alcohol is treated with triethyl orthoacetate under Johnson orthoester Claisen conditions[24] to afford ethyl ester **203**,[25] which is subsequently saponified by base to produce acid **196**.

Scheme 3.4.4



The completion of the formal total synthesis of (±)-cephalotaxine is outlined in Scheme 3.4.5. DCC-mediated amide bond formation provided **204** in 54% yield. Unfortunately, the oxidative heterocyclization of **204** under catalytic palladium(II) conditions did not proceed efficiently. To our delight, however, spirolactam **205** was produced in 50% yield using 1 equiv $Pd(OAc)_2$ in DMSO at 80 °C. Notably, the aryl bromide did not react under these conditions. The intramolecular Heck reaction[26] proceeded cleanly and diastereoselectively to afford lactam **192**.[18h] LAH reduction of amide **192** afforded amine **189**, which Mori has shown can be converted to cephalotaxine in four steps.[18i]

Scheme 3.4.5

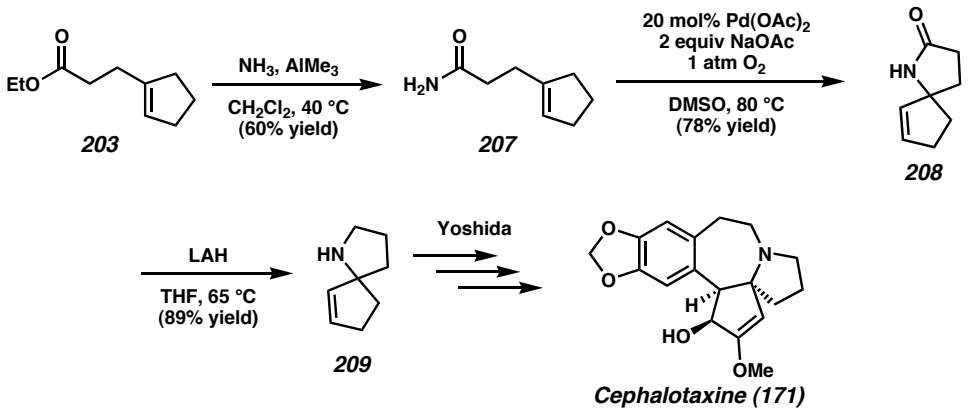


There are a number of aspects that warrant discussion with this synthesis. Currently, the spirolactam formation (**204** → **205**) requires stoichiometric quantities of palladium. The design of improved oxidative systems will be necessary in order to achieve catalyst turnover. Importantly, the synthesis can be carried out with complete diastereoselectivity based on the stereocenter formed in the palladium-mediated heterocyclization step. Therefore, in the event of the development of an asymmetric heterocyclization, it can readily be applied to an enantioselective total synthesis of (–)-cephalotaxine. Finally, as mentioned in the retrosynthetic plan, the seven-membered ring could alternatively be formed by a palladium(II)-mediated carbocyclization on a non-brominated arene. The development of similar reactions to form carbocycles will be discussed in Chapter 4 of this thesis.

3.4.4 A Second Formal Total Synthesis of (±)-Cephalotaxine

Regarding the first of these issues, we have investigated heterocyclizations that can proceed under catalytic conditions and can be applied to the synthesis of cephalotaxine (Scheme 3.4.6). Ethyl ester **203** was converted to amide **207** by treatment with NH_3 and trimethylaluminum.[27] In contrast to the more substituted system, the oxidative heterocyclization of **207** proceeded under catalytic conditions to afford spirolactam **208** in good yield.[28,29] Reduction of the lactam afforded pyrrolidine **209**, which Yoshida has shown is an intermediate in his recently reported total synthesis of cephalotaxine.[19d] This constituted a second formal total synthesis of (±)-cephalotaxine, with the advantage of using direct dioxygen-coupled palladium catalysis.

Scheme 3.4.6

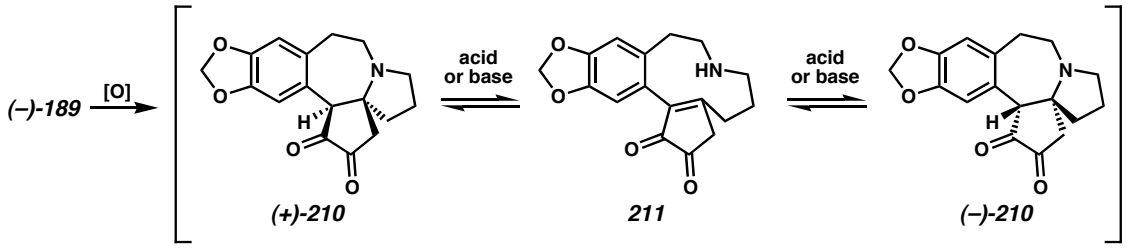


3.5 A Proposed Total Synthesis of Drupacine

Particularly noteworthy among the synthetic efforts toward cephalotaxine was the first asymmetric synthesis reported by Mori.[18i] In this report, diketone intermediate **210**, arising from olefin **189** via a two-step oxidation sequence, was shown to be susceptible to racemization under acidic or basic conditions (Scheme 3.5.1). Under carefully optimized

acidic conditions, this racemization event could be avoided, and (–)-cephalotaxine was thereby accessed. We anticipated that we could utilize the known racemization of this compound as a key transformation in the enantioselective total synthesis of (–)-drupacine (**172**), another member of the *Cephalotaxus* alkaloids.[30]

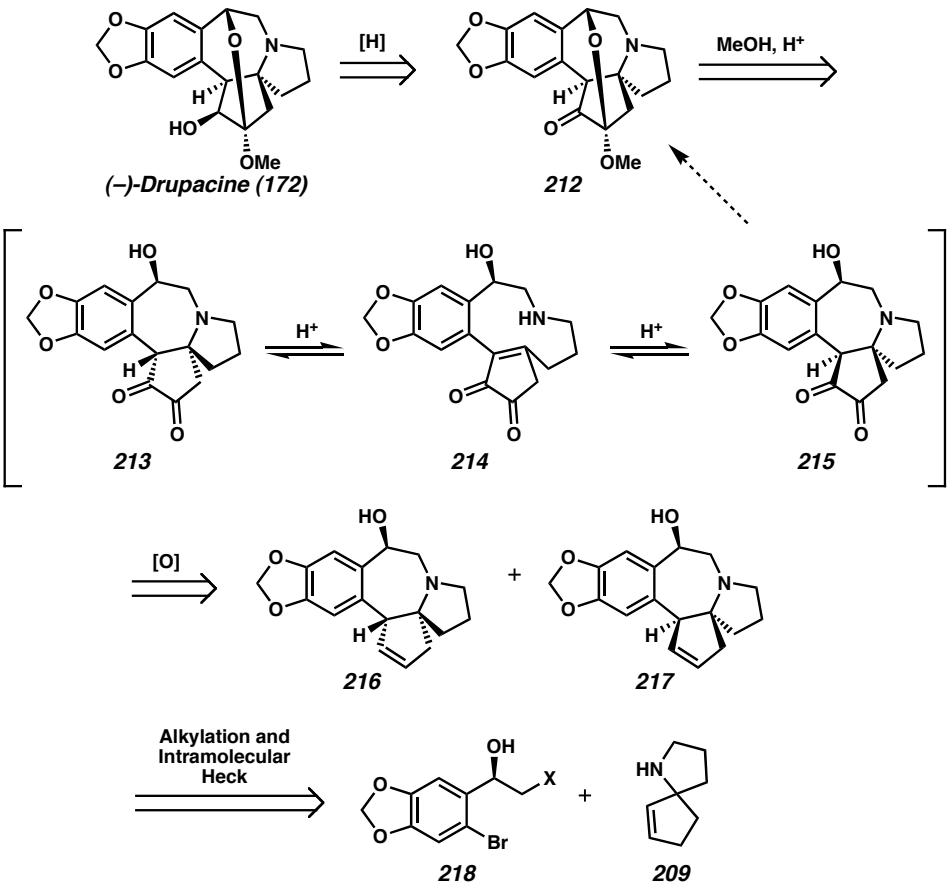
Scheme 3.5.1



A proposed retrosynthetic plan for the synthesis of (–)-drupacine is outlined in Scheme 3.5.2. The natural product is expected to arise from a ketone reduction of **212**. It is believed that this acetal can be derived from an equilibrating mixture of diketone diastereomers (**213** and **215**). The equilibration is expected to occur via an analogous racemization pathway to that described by Mori for the similar diketones **(+)-210** and **(–)-210** (see Scheme 3.5.1). The diketone moiety in diastereomer **215** is positioned in close proximity to the benzylic alcohol, thus allowing the formation of the acetal under acidic conditions. The same acetal cannot form in diastereomer **213** because the alcohol is too far away from the diketone moiety—it therefore undergoes the racemization step. This dynamic diastereomeric resolution is expected to eventually funnel all of the material to acetal **212**. These diketones (**213** and **215**) can be derived from diastereomeric olefins **216** and **217** through a straightforward oxidation sequence. These olefins are expected to arise from alcohol **218** and pyrrolidine **209** via an alkylation and subsequent intramolecular Heck reaction. We anticipate that enantiopure alcohol **218** can be

accessed from the palladium-catalyzed oxidative kinetic resolution, while we have already demonstrated that pyrrolidine **209** can be formed from the palladium(II)-catalyzed heterocyclization chemistry (*vide supra*). This synthesis would be highly illustrative of the synthetic utility of the aerobic palladium(II) transformations we have developed thus far.

Scheme 3.5.2



3.6 Conclusion

Following the discovery of the oxidative kinetic resolution of alcohols, we desired to extend this aerobic oxidation method to other transformations. Our efforts toward this goal resulted in the demonstration that similar catalytic systems can be used for

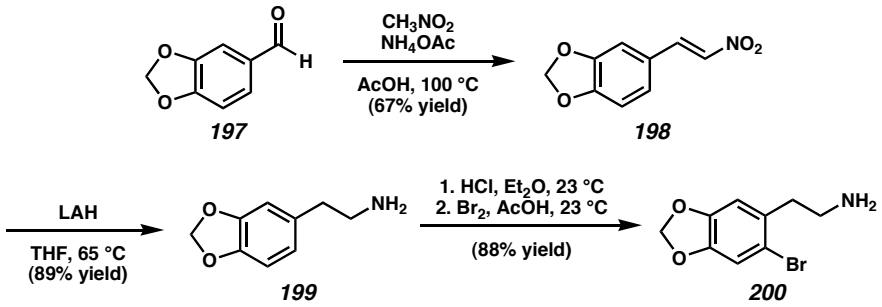
intramolecular Wacker cyclizations to form heterocycles. The reactions are remarkably simple, employing a palladium-pyridine catalyst and molecular oxygen as the sole stoichiometric oxidant. Furans, lactones, lactams, and pyrans can all be accessed in high yields via this method. Importantly, the developed system allowed for entry into asymmetric variants, which ultimately led to the highly enantioselective synthesis of dihydrobenzofurans using a palladium-sparteine catalyst. We have also begun to apply some of these reactions toward the synthesis of the *Cephalotaxus* alkaloids, completing two formal syntheses of (±)-cephalotaxine. In hopes of further developing palladium(II)-catalyzed dehyrogenative reactions, there were two key directions we believed were in need of substantial investigation. The first involved the development of novel enantioselective heterocyclizations to make chiral heterocycles beyond dihydrobenzofurans. Approaches to this goal will be discussed in Chapter 5. The other direction we wanted to pursue was the use of this palladium(II) oxidative system toward carbon-carbon bond forming reactions. Our efforts in this area will be described in the next chapter.

3.7 Experimental Section

3.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(OAc)_2$ was purchased from Strem Chemicals, Inc., Newburyport, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

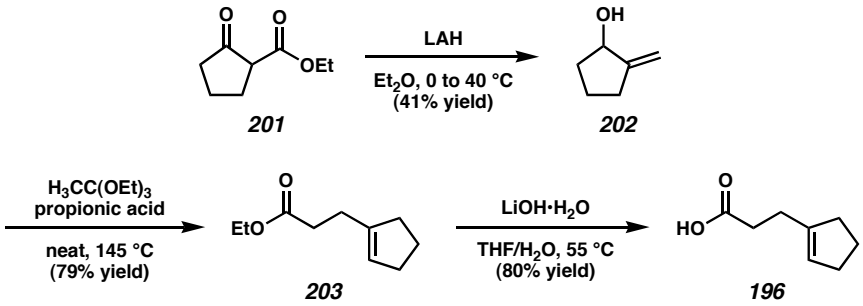
3.7.2 Preparative Procedures



Amine 200. Amine **199** was synthesized according to the procedure of Marsden and MacLean.[21] To a solution of piperonal (5.00 g, 33.3 mmol) in 49.7 mL acetic acid was added nitromethane (3.07 mL, 56.6 mmol), then NH_4OAc (6.68 g, 86.6 mmol). The reaction mixture was heated to 100 °C and stirred for 6 h. The mixture was then cooled to room temperature and poured over ice (200 mL). After 1 h, the yellow precipitate that formed was collected by filtration. The crude material was recrystallized from hot ethanol to afford β-nitrostyrene derivative **198** (4.31 g, 67% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as yellow needlelike crystals.

To a stirring suspension of LAH (1.18 g, 31.2 mmol) in 62.3 mL THF at 65 °C was added a solution of **198** (2.00 g, 10.4 mmol) in 41.7 mL THF dropwise via an addition funnel over 20 min. The resulting mixture was stirred at 65 °C for 15 h, then cooled to 0 °C and quenched slowly with 1.18 mL H_2O, 1.18 mL 15% aq. NaOH, and 3.54 mL H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred vigorously. Once a white precipitate had formed, the mixture was filtered, and the filtrate was concentrated in vacuo. Amine **199**[21] (1.53 g, 89% yield, R_F = 0.00 in 4:1 hexanes/EtOAc) was sufficiently pure to be carried to the subsequent reaction.

Bromination of amine **199** was performed according to the procedure of Tietze and Schirok.[18k] HCl (g) was bubbled through a solution of the crude amine (9.27 mmol) in Et_2O at 23 °C for 5 min. The solution was then concentrated to a solid, which was then suspended in 10.3 mL AcOH at 23 °C. Bromine (951 μl, 18.5 mmol) was added dropwise, and the mixture was stirred at 23 °C for 10 h. The reaction was then quenched with 5% aq. Na_2SO_3 until the color dissipated, then basified with 20% aq. NaOH until pH >13. The mixture was extracted with CH_2Cl_2 (4 x 75 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated to an oil. Amine **200** (2.00 g, 88% yield, R_F = 0.00 in 4:1 hexanes/EtOAc) was carried on without further purification.

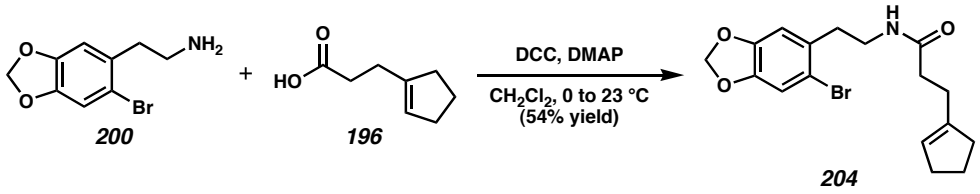


Carboxylic acid 196. Allylic alcohol **202** was synthesized according to the procedure of Dreiding and Hartman.[23a] To a stirring suspension of lithium aluminum hydride (13.6 g, 359 mmol) in Et_2O (120 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (**201**, 25.0 mL, 169 mmol) in Et_2O (50 mL) dropwise via an addition funnel. The reaction mixture was heated to 40 °C and stirred 30 min. The mixture was then cooled to 0 °C and quenched by the slow addition of water. The resulting mixture was diluted with Et_2O (500 mL) and stirred vigorously with 20% aqueous solution of sodium potassium tartrate (150 mL) for 1 h. The phases were then separated, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$

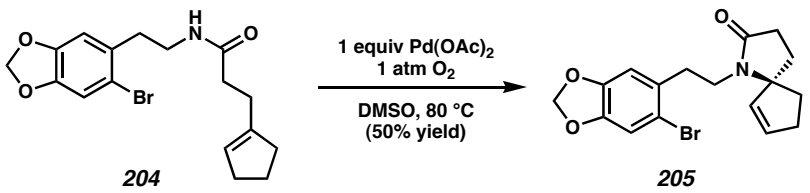
and concentrated to a yellow oil. Fractional distillation of the oil (bp 92 °C at 68 torr) provided allylic alcohol **202**[31] (6.83 g, 41% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

The allylic alcohol (2.50 mL, 24.3 mmol) was dissolved in triethylorthoacetate (35.6 mL, 194 mmol), and the solution was treated with propionic acid (660 μl, 8.31 mmol). The reaction was heated to 145 °C with distillative removal of ethanol. After distillation was complete, the reaction was stirred at 145 °C for an additional 60 min, then cooled to 23 °C and diluted with Et_2O (300 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (300 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided ester **203** (3.22 g, 79% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

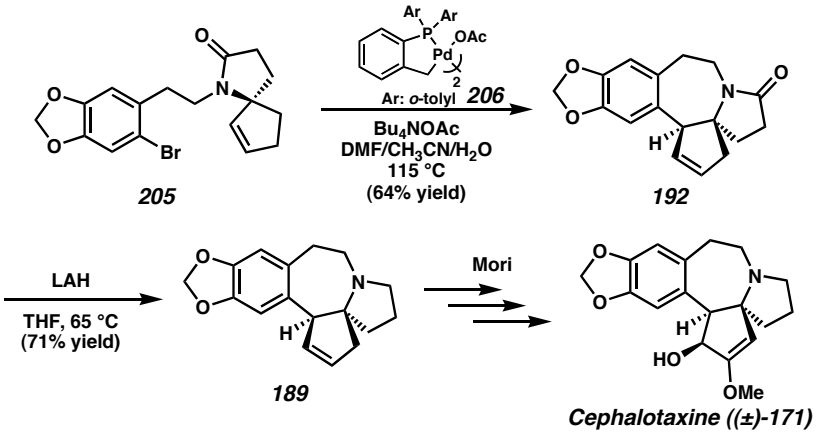
To a solution of ethyl ester **203** (2.99 g, 17.8 mmol) in THF/H_2O (89 mL, 1:1) at 23 °C was added LiOH•H_2O (3.73 g, 89.0 mmol). The mixture was heated to 50 °C and stirred overnight (12 h). The mixture was cooled to room temperature, and the volatile solvent was removed by rotary evaporation. The aqueous residue was cooled to 0 °C, acidified with 3.0 N HCl, then extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to an oil. The residue was purified by flash chromatography (100% CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH eluent) to afford carboxylic acid **196**[4] (2.00 g, 80% yield, R_F = 0.35 in 4:1 hexanes/EtOAc) as a white solid.



Amide 204. To a solution of acid **196** (119 mg, 0.848 mmol) in 2.54 mL CH_2Cl_2 at 0 °C was added DCC (177 mg, 0.856 mmol), DMAP (5.2 mg, 0.0424 mmol), and a solution of amine **200** (207 mg, 0.848 mmol) in 1.70 mL CH_2Cl_2, sequentially. The mixture was stirred at 0 °C for 15 min, then allowed to warm to 23 °C and stirred 90 min. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and filtered through a plug of celite to remove the white precipitates. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford amide **204** (167 mg, 54% yield, R_F = 0.43 in 15:1 CH_2Cl_2/MeOH) as a yellow semisolid. **Amide 204**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.70 (s, 1H), 5.96 (s, 2H), 5.56 (br s, 1H), 5.33 (br s, 1H), 3.47 (app.q, *J* = 6.9 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.40-2.20 (comp m, 6H), 2.36 (t, 2H), 1.84 (app.quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 147.7, 147.4, 143.5, 131.5, 124.3, 114.8, 113.0, 110.6, 101.9, 39.6, 35.9, 35.3, 35.2, 32.6, 27.2, 23.6; IR (film) 1641, 1502, 1477, 1230 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{20}NO_3Br]^+$: 365.0627, found 365.0631.



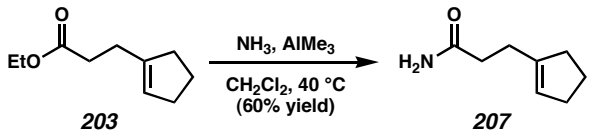
Spirolactam 205. To a solution of amide **204** (225 mg, 0.614 mmol) in 6.14 mL DMSO at 23 °C was added $Pd(OAc)_2$ (138 mg, 0.614 mmol). The mixture was cooled to 0 °C, evacuated and backfilled with O_2 three times, and then heated to 80 °C and stirred. After 90 min, the reaction was cooled to room temperature, diluted with EtOAc (100 mL), and washed with H_2O (2 x 75 mL). The aqueous phases were extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provided spirolactam **205** (113 mg, 50% yield, R_F = 0.19 in 1:1 hexanes/EtOAc) as a yellow oil. **Spirolactam 205**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.77 (s, 1H), 5.94 (s, 2H), 5.92-5.90 (m, 1H), 5.27-5.25 (m, 1H), 3.35-3.25 (m, 1H), 3.10-3.01 (m, 1H), 2.98-2.86 (comp m, 2H), 2.54-2.29 (comp m, 4H), 1.96 (app.t, *J* = 7.8 Hz, 2H), 1.94 (comp m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 147.6, 147.2, 134.8, 134.2, 132.1, 114.8, 112.8, 111.0, 101.8, 76.4, 40.5, 35.3, 34.5, 33.2, 31.5, 30.5; IR (film) 1681, 1477, 1406, 1230 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{18}NO_3Br]^+$: 363.0470, found 363.0455.



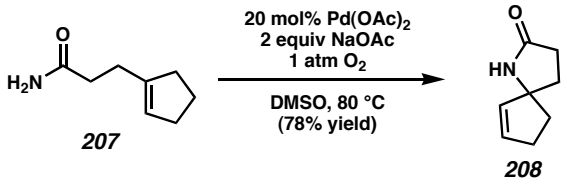
Amine 189. The intramolecular Heck reaction was performed according to a modified procedure of Tietze and Schirok.[18k] To a solution of spirolactam **205** (113 mg, 0.310 mmol) in DMF (3.1 mL), CH_3CN (3.1 mL), and H_2O (620 μl) under argon at 23 °C was added palladium-phosphine dimer **206**[32] (32.8 mg, 0.0310 mmol), then Bu_4NOAc (187 mg, 0.620 mmol). The reaction mixture was heated to 115 °C. After 19 h, the mixture was cooled to room temperature, and the volatile solvents were removed by rotary evaporation. The residue was partitioned between 75 mL EtOAc and 30 mL H_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford amide **192**[18h] (56.2 mg, 64% yield, R_F = 0.27 in 3:1 EtOAc/hexanes) as a yellow solid.

To a stirring suspension of LAH (15.2 mg, 0.400 mmol) in 800 μl THF at 23 °C was added a solution of amide **192** (28.3 mg, 0.100 mmol) in 200 μl THF dropwise over 1 min. The mixture was heated to 65 °C and stirred for 1 h. It was then cooled to 0 °C, diluted with 4 mL Et_2O, and quenched with 15.2 μl H_2O, 15.2 μl 15% aq. NaOH, and 45.6 μl H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred until a white precipitate formed. The precipitate was removed by filtration through a plug of celite (THF eluent), and the filtrate was concentrated in vacuo. Amine

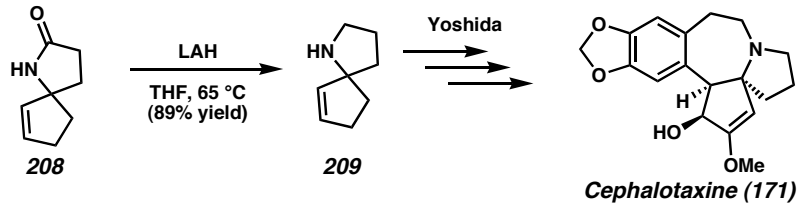
189[18i] (19.1 mg, 71% yield, R_F = 0.17 in 5:1 EtOAc/MeOH w/ 1% Et_3N) was isolated as a pale yellow oil.



Amide 207. 35.0 mL CH_2Cl_2 was saturated with NH_3 by bubbling ammonia gas for 3 min at 0 °C. The solution was warmed to 23 °C, and trimethylaluminum (12.2 mL, 2.5 M in hexanes, 30.6 mmol) was added dropwise over 10 min. The mixture was stirred for 15 min, then a solution of ethyl ester **203** (2.57 g, 15. 3 mmol) in 3.3 mL CH_2Cl_2 was added dropwise. The reaction mixture was heated to 40 °C and stirred for 46 h. The mixture was then cooled to 0 °C, quenched by slow addition of 1.0 N HCl, and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (100% EtOAc eluent) provided amide **207** (1.28 g, 60% yield, R_F = 0.39 in 100% EtOAc) as a white solid. **Amide 207**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 5.58 (br s, 1H), 2.38 (br s, 1H), 2.39 (app.s, 4H), 2.32-2.22 (comp m, 4H), 1.86 (app.quintet, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 143.3, 124.5, 35.3, 34.4, 32.6, 27.0, 23.6; IR (film) 3382, 3183, 1657, 1632, 1416 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{13}NO]^+$: 139.0997, found 139.0996.



Spirolactam 208. To a solution of amide **207** (209 mg, 1.50 mmol) in 15.0 mL DMSO at 23 °C was added $Pd(OAc)_2$ (67.3 mg, 0.300 mmol). The mixture was cooled to 0 °C, evacuated and backfilled with O_2 three times, and then heated to 80 °C and stirred. After 48 h, the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (100% EtOAc eluent) to provided spirolactam **208** (161 mg, 78% yield, R_F = 0.25 in 100% EtOAc) as a yellow solid. **Spirolactam 208**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (br s, 1H), 5.81-5.78 (m, 1H), 5.59-5.56 (m, 1H), 2.46-2.23 (comp m, 4H), 2.07-1.85 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 135.2, 133.2, 71.4, 37.9, 33.9, 30.9; IR (film) 3191, 1690, 1366, 753 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{11}NO]^+$: 137.0841, found 137.0835.



Amine 209. To a suspension of LAH (417 mg, 11.0 mmol) in 10.4 mL THF at 0 °C was added a solution of spirolactam **208** (504 mg, 3.68 mmol) in 8.0 mL THF dropwise over 2 min. The reaction mixture was heated to 65 °C and stirred. After 16 h, the mixture was cooled to 0 °C and quenched with 417 μl H_2O, 417 μL 15% aq. NaOH, and 1.25 μL H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred vigorously until a white precipitate had formed. The mixture was then suction filtered,

and the filtrate was concentrated in vacuo to provide amine **209**[19d] (402 mg, 89% yield, R_F = 0.00 in 100% EtOAc) as a yellow oil.

3.8 Notes and References

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(10) For leading references on the Pd(II)/DMSO oxidative system for heterocyclizations, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem*. **1993**, *58*, 5298-5300. (b) Rönn, M.; Bäckvall, J. -E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 7749-7752. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem*. **1996**, *61*, 3584-3585.

(11) This mechanistic pathway was simply a proposed hypothesis based on similar literature examples. Another pathway involving O-H bond insertion to a palladium alkoxide intermediate followed by olefin insertion was not ruled out as operative. Mechanistic aspects of these heterocyclizations will be briefly discussed as part of Chapter 5 of this thesis.

(12) The silver salt is believed to at least partially abstract the chloride counterion(s) from the palladium center. This contributed to the notion that the palladium counterion would have an effect on the selectivity and reactivity of the reaction, as we had seen in the kinetic resolution chemistry.

(13) While this research was underway, a similar cyclization of tosylamides was reported. See: Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed*. **2002**, *41*, 164-166.

(14) The efficacy of $Pd(OCOCF_3)_2$ is attributed to its electron-deficient nature compared to $Pd(OAc)_2$ or $PdCl_2$, making it more reactive toward reactions involving electrophilic activation pathways.

(15) For reviews on the *Cephalotaxus* alkaloids, see: (a) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. Cephalotaxus alkaloids. In *The Alkaloids*; Academic Press: New York,

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(28) The catalyst loading could be reduced to 5 mol% on small scale reactions (ca. 100 mg substrate). When larger scale reactions were conducted, the catalyst loading needed to be increased.

(29) The oxidative heterocyclization of **207** was also investigated using the palladium/pyridine/toluene system. The reaction proceeded to completion with stoichiometric palladium, and modest turnover was observed under catalytic conditions. For the purposes of accessing large quantities of material, however, the palladium/DMSO conditions were more effective.

(30) There has been only one total synthesis of (±)-drupacine reported. See reference 18g.

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