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. The initial studies led to the development of an oxidative kinetic resolution of secondary alcohols using molecular oxygen as the sole stoichiometric oxidant. 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. 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.

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. 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, Hayashi, and Sasai 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. 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(OCOCF₃)₂ and benzoquinone as the stoichiometric reoxidant. 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. 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, 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, O₂) was used as a starting point for the discovery of the kinetic resolution (Pd(nbd)Cl₂, (-)-sparteine, O₂). 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}$
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, O2, 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.
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)Cl₂, (−)-sparteine, O₂, 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% AgSbF₆ 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.
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).\textsuperscript{4,13} Analogous to the kinetic resolution chemistry, a significant counterion effect was observed during these studies. Pd(OCOCF\textsubscript{3})\textsubscript{2} was an especially effective palladium precursor for catalyzing these oxidative transformations.\textsuperscript{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.

![Heterocycle Structures](image)

Importantly, highly enantioselective variants of these oxidative heterocyclizations could be realized under similar systems (Scheme 3.3.4). 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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. 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**

\[ \text{Weinreb}^{18a,b} \]

![Diagram](image1)

176 \[ \xrightarrow{\text{Mg(OMe)\textsubscript{2}, MeOH}} \] 177

58\% yield

**Semmelhack**

\[ \text{Semmelhack}^{18c,d} \]

![Diagram](image2)

178 \[ \xrightarrow{1. \text{KOAc}, Bu,N, 2. \text{hv}} \] 179

94\% yield

**Hanaoka**

\[ \text{Hanaoka}^{18e} \]

![Diagram](image3)

180 \[ \xrightarrow{1. \text{150}^\circ\text{C, 2. NaBH\textsubscript{4}}} \] 181

97\% yield

181 \[ \xrightarrow{\text{H\textsubscript{2}SO\textsubscript{4}}} \] 182

69\% yield

**Fuchs**

\[ \text{Fuchs}^{18f,g} \]

![Diagram](image4)

183 \[ \xrightarrow{\text{Bu\textsubscript{4}NIO\textsubscript{4}}} \] 184

65\%-73\% yield

**Kuehne**

\[ \text{Kuehne}^{18h} \]

![Diagram](image5)

185 \[ \xrightarrow{1. \text{Pb(OAc)}\textsubscript{2}, 2. \text{NaOMe}} \] 186

78\%-94\% yield

**Mor**

\[ \text{Mor}^{18i} \]

![Diagram](image6)

187 \[ \xrightarrow{\text{TMSSnBu\textsubscript{3}, CsF}} \] 188

85\% yield

188 \[ \xrightarrow{\text{PPA}} \] 189

66\% yield

**Tietze**

\[ \text{Tietze}^{18j,k} \]

![Diagram](image7)

190 \[ \xrightarrow{\text{Pd(PPh\textsubscript{3})\textsubscript{4}, TMG}} \] 191

88\% yield

191 \[ \xrightarrow{\text{Heck rxn}} \] 189

81\% yield
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.\textsuperscript{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).\textsuperscript{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 preceded at the onset of this study. Amine 200 can be synthesized in three steps according to the procedures of Marsden and MacLean, and of Tietze and Schirok (Scheme 3.4.3). Piperonal (197) is treated with nitromethane under Henry conditions 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 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. The allylic alcohol is treated with triethyl orthoacetate under Johnson orthoester Claisen conditions to afford ethyl ester 203, which is subsequently saponified by base to produce acid 196.
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.$^{18i}$
There are a number of aspects that warrant discussion with this synthesis. Currently, the spirolactam formation \((204 \rightarrow 205)\) 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 NH₃ and trimethylaluminum. In contrast to the more substituted system, the oxidative heterocyclization of 207 proceeded under catalytic conditions to afford spirolactam 208 in good yield. Reduction of the lactam afforded pyrrolidine 209, which Yoshida has shown is an intermediate in his recently reported total synthesis of cephalotaxine. 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. 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.\(^3\)

*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 dehydrogenative 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$_4$Si ($\delta$ 0.0). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ 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$_4$Si ($\delta$ 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.\textsuperscript{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$_4$OAc (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$_2$O, 1.18 mL 15% aq. NaOH, and 3.54 mL H$_2$O, 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\textsuperscript{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. HCl (g) was bubbled through a solution of the crude amine (9.27 mmol) in Et₂O 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. Na₂SO₃ until the color dissipated, then basified with 20% aq. NaOH until pH >13. The mixture was extracted with CH₂Cl₂ (4 x 75 mL), and the combined organic phases were dried over Na₂SO₄ and concentrated to an oil. Amine 200 (2.00 g, 88% yield, R₆ = 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. To a stirring suspension of lithium aluminum hydride (13.6 g, 359 mmol) in Et₂O (120 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (201, 25.0 mL, 169 mmol) in Et₂O (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 Et₂O (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 Et₂O (2 x 100 mL). The combined organic layers were dried over MgSO₄.
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 Et₂O (300 mL). The solution was stirred with 1.0 M aq. KHSO₄ (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 NaHCO₃, dried over MgSO₄, and concentrated in vacuo. Purification of the residue by flash chromatography (30:1 hexanes/Et₂O eluent) provided ester 203 (3.22 g, 79% yield, \(R_F = 0.62\) in 4:1 hexanes/Et₂O) as a clear oil.

To a solution of ethyl ester 203 (2.99 g, 17.8 mmol) in THF/H₂O (89 mL, 1:1) at 23 °C was added LiOH•H₂O (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 Na₂SO₄ and concentrated to an oil. The residue was purified by flash chromatography (100% CH₂Cl₂ → 9:1 CH₂Cl₂/MeOH eluent) to afford carboxylic acid 196\(^{d}\) (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$_2$Cl$_2$ 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$_2$Cl$_2$, 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$_2$Cl$_2$ (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$_2$Cl$_2$/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$_3$Br]$^+$: 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$_2$O (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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$Br]$^+$: 363.0470, found 363.0455.
Amine 189. The intramolecular Heck reaction was performed according to a modified procedure of Tietze and Schirok.\textsuperscript{18k} To a solution of spirolactam 205 (113 mg, 0.310 mmol) in DMF (3.1 mL), CH\textsubscript{3}CN (3.1 mL), and H\textsubscript{2}O (620 µl) under argon at 23 °C was added palladium-phosphine dimer 206\textsuperscript{32} (32.8 mg, 0.0310 mmol), then Bu\textsubscript{4}NOAc (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\textsubscript{2}O. The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford amide 192\textsuperscript{18h} (56.2 mg, 64% yield, R\textsubscript{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\textsubscript{2}O, and quenched with 15.2 µl H\textsubscript{2}O, 15.2 µl 15% aq. NaOH, and 45.6 µl H\textsubscript{2}O, 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\textsuperscript{18i} (19.1 mg, 71% yield, R\textsubscript{F} = 0.17 in 5:1 EtOAc/MeOH w/ 1% Et\textsubscript{3}N) was isolated as a pale yellow oil.

Amide 207. 35.0 mL CH\textsubscript{2}Cl\textsubscript{2} was saturated with NH\textsubscript{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\textsubscript{2}Cl\textsubscript{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\textsubscript{2}Cl\textsubscript{2} (3 x 75 mL). The combined organic phases were dried over MgSO\textsubscript{4} and concentrated in vacuo. Purification of the residue by flash chromatography (100% EtOAc eluent) provided amide 207 (1.28 g, 60% yield, R\textsubscript{F} = 0.39 in 100% EtOAc) as a white solid. Amide 207: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{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\textsuperscript{-1}; HRMS (EI\textsuperscript{+}) m/z calc'd for [C\textsubscript{8}H\textsubscript{13}NO]\textsuperscript{+}: 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$_8$H$_{11}$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$_2$O, 417 µL 15% aq. NaOH, and 1.25 µL H$_2$O, 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 \textbf{209}^{19d} (402 mg, 89% yield, 
$R_F = 0.00$ in 100% EtOAc) as a yellow oil.
3.8 Notes and References


(4) Portions of this research have been described in a communication: Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. Angew. Chem., Int. Ed. 2003, 42, 2892-2895.


(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,


(20) We also considered a palladium(II)-catalyzed mechanistic pathway involving olefin activation followed by nucleophilic attack by the electron-rich aromatic system, much like a Wacker mechanism. The elucidation of the mechanism in similar reactions will be discussed as part of Chapter 4 of this thesis.


(26) The conditions for the intramolecular Heck reaction were derived from the work of Tietze on a similar compound. See reference 18k.


(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.
