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Part I. Approaches Toward the Total Synthesis of Tyloindicine F

Part II. Palladium-Catalyzed C−H Functionalization of β-Enaminones

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Part I. Approaches Toward the Total Synthesis of Tyloindicine F

Part II. Palladium-Catalyzed C−H Functionalization of β-Enaminones

By

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Submitted to the Department of Medicinal Chemistry and the Faculty of the
Graduate School of the University of Kansas
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

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Chairperson

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Date Defended:_____

To my parents

Acknowledgement

The impact of this period of my life would be profound, technically and beyond. Many people need to be credited herein.

Most of all, I am fully indebted to my parents. Their support and endurance is greatly appreciated.

I would like to thank Dr. Gunda I. Georg as my academic advisor, for the freedom of personal exploration and continued support. Interaction with a diverse assembly of people in the group, both scientifically and culturally, provided me with opportunities to think from different perspectives.

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Part I. Approaches Toward the Total Synthesis of Tyloindicine F
Part II. Palladium-Catalyzed C−H Functionalization of β-Enaminones

By

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Abstract

Tyloindicine F is a potent anticancer natural product first isolated from the Himalaya region of India. It demonstrated a unique profile in the NCI60 human tumor cell line anticancer drug screen. Due to its scarcity from natural sources, a total synthesis of tyloindicine F is desirable. Two attempts at the synthesis of this natural product have been conducted and are discussed.

β-Enaminones are a group of push-pull olefins whereas C–H functionalization/C–C coupling is a highly efficient method of constructing new carbon-carbon bonds. β-Enaminones are highly polarized and their β position is suitable for C–H functionalization by means of electropalladation. A novel methodology for the oxidative Hiyama coupling of β-enaminones has been developed and two new bifunctional activators/reoxidants have been found. Furthermore, a non-oxidative version for β-enaminone C–H functionalization and the decarboxylative coupling of β-enaminones were also investigated.

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List of Abbreviations

5-FU – 5-fluorouracil

Ac – acetate

Ar – aryl

Bn – benzyl

br – broad

Boc – *tert*-butoxycarbonyl

CAN – ammonium cerium (IV) nitrate

d – doublet

de – diastereomeric excess

DDQ – 2,3-dichloro-5,6-dicyanobenzoquinone

DIBAL-H – diisobutylaluminum hydride

DMAP – 4-*N*,*N*-dimethylaminopryidine

DMF – *N*,*N*-dimethylformamide

DMFDMA – *N*,*N*-dimethylformamide dimethyl acetal

DMSO – dimethyl sulfoxide

E – energy

EDCI – 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ee – enantiomeric excess

EDG – electron donating group

EI – electron impact

ESI – electrospray ionization

Et – ethyl

EWG – electron withdrawing group

FAB – fast atom bombardment

FDA – Food and Drug Administration

HOMO – highest occupied molecular orbital

HPLC – high performance liquid chromatography

IR – infrared

LiHMDS – lithium bis(trimethylsilyl)amide

LUMO – lowest unoccupied molecular orbital

m – multiplet

Me – methyl

MHz – millionhertz

mg – milligram

mL – milliliter

mmol – millimole

mp – melting point

MS – mass spectrometry

NBS – *N*-bromosuccinimide

NCI – National Cancer Institute

nM – nanomolar

NMR – nuclear magnetic resonance

NOE – Nuclear Overhauser Effect

NR – no reaction

ppm – parts per million

Ph – phenyl

Rf – retention factor

RNA – ribonucleic acid

RT – room temperature

s – singlet

t – triplet

TBAF – tetrabutylammonium fluoride

Tf – trifluoromethanesulfonyl

TMS – trimethylsilyl

t-Bu – *tert*-butyl

TEA – triethylamine

TFA – trifluoroacetic acid

TLC – thin layer chromatography

TMS – trimethylsilyl

THF – tetrahydrofuran

Ts – p-toluenesulfonyl

q – quartet

Part I

Approaches toward the Total Synthesis of Tyloindicine F

Chapter 1. Discovery of Tyloindicine F

1.1. Impact of Natural Products on Drug Discovery[1-5]

History has seen the use of natural products from different sources for preventive and curative medicinal purposes for thousands of years. Prior to the modern era, medicines worldwide were solely based on natural products, mainly from herbal sources. Historically, botanical extracts were prepared and used in human subjects, and then the results were collected and examined. These informal human clinical trials were conducted unaware of the active component(s) and the underlying mechanism(s) of action. The successful cases were then recorded in *materia medicas* around the globe.[a]

Today, nearly eighty percent of the world's population continues to utilize herbal remedies for their primary or alternative health care.[b] Meanwhile, most contemporary drug discovery is based largely on the concept of one molecule targeting one protein.[c] A multidisciplinary approach is typically needed when searching for that *one* active compound for a particular indication. In addition to efficacy, more importantly, a drug candidate must be safe in order to pass the strict requirements of the US Food and Drug Administration (FDA) and other governing bodies.

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[a] Virtually every ancient civilization had experience with herbal remedies. To name a few, Artemisia (artemisinin) for malaria treatment in China; Opium poppy (morphine) as sedatives in Egypt; coca bush (cocaine) for stimulants in the Aztec and Mayan cultures.
[b] In practice, The Pharmacopoeia of the People's Republic of China consists of two volumes. Volume 1 covers the Traditional Chinese Materia Medica, including Traditional Chinese Patent Medicines, while Volume 2 is dedicated to conventional pharmaceuticals.
[c] Other drug targets include carbohydrates, lipids and nucleic acids.

Various approaches can lead to finding bioactive chemical structures. Despite the recent popularity of combinatorial chemistry in the pharmaceutical industry over half of the therapeutic agents approved by the FDA from 1981 to 2006 were of natural product origin.[6] Regarded as outliers of Lipinski's "rule of five",[7] natural products possess distinctive chemical properties with respect to their molecular weight, elemental composition, and structural arrangement when compared with small molecule synthetic libraries.[8] Since natural products resemble marketed drugs more than the synthetic combinatorial molecules,[9] natural products have been and continue to be a primary source of inspiration for new drug leads and the resurgence in their importance can be no surprise.[10-12]

1.2. Anti-Cancer Chemotherapy from Herbal Sources[13-17]

After heart disease, cancer is the second leading cause of death in the US.[18] According to the American Cancer Society,[19] "Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death." "Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. Ten or more years often pass between exposure to external factors and detectable cancer." "Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy."

Natural products are ready-made drug leads. After millions of years of structural evolution, natural products have been optimized by nature for antimicrobial, antiproliferative and immunoregulating activities. In fact, natural products and related compounds make up seventy-four percent of oncology drugs.[20] Many are obtained from higher plants with various mechanisms of action (Table 1.1), although this is only a small fraction of the estimated 200,000 compounds available in nature.[2]

Table 1.1. Selected Plant-Derived Anti-Cancer Natural Products[1, 14]

Natural product	Plant source	Target/Mechanism
vinca alkaloids	*Vinca rosea*	tubulin underpolymerization
taxanes	*Taxus brevifolia*	tubulin overpolymerization
epipodophyllotoxins	*Podophyllum peltatum*	topoisomerase II inhibition
camptothecins	*Campotheca acuminata*	topoisomerase I inhibition
homoharringtonine	*Cephalotaxus harringtonia*	unknown
elliptinium	Apocynaceae family	unknown

1.3. Phenanthroindolizidine Alkaloids[21-26] from *Tylophora indica*

Alkaloids are a group of structurally diverse nitrogen-containing natural products. More than seven thousand in number, they form the largest group of secondary metabolites.[2] Most alkaloids are from plants. In general, structurally complex and unique alkaloids are found within a narrow range of species and genera, often located in specific parts of the plant.[27, 28]

The indolizidine ring system, derived biosynthetically derived from lysine, is a common structural motif among alkaloids.[2] However, only a few such alkaloids also contain a phenanthrene nucleus in the same molecule (Figure 1.1). They have all been isolated from the Asclepiadaceae family, including *Tylophora, Cynanchum,* and *Vincentoxicum*. One exception, from the Moracea family, is *Ficus septica*.
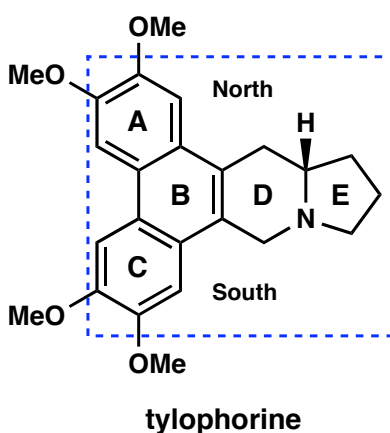
tylophorine

Figure 1.1. Tylophorine, a representative phenanthroindolizidine alkaloid (the phenanthroindolizidine ring system is in the box)

Tylophora indica Merrill, indigenous to India and Malaya, is a climbing perennial plant with long fleshy roots and small ovate leaves that possesses laxative, expectorant, diaphoretic (sweating), and purgative (vomiting) properties. It is traditionally used as a folk remedy in certain regions of India for the treatment of asthma, inflammation, bronchitis, allergies, rheumatism, and dermatitis. Numerous alkaloids have been found throughout the years from all parts of this specific plant.[29-]

[31] Among them, three have been shown to possess antineoplastic activity (Figure 1.2).[2]
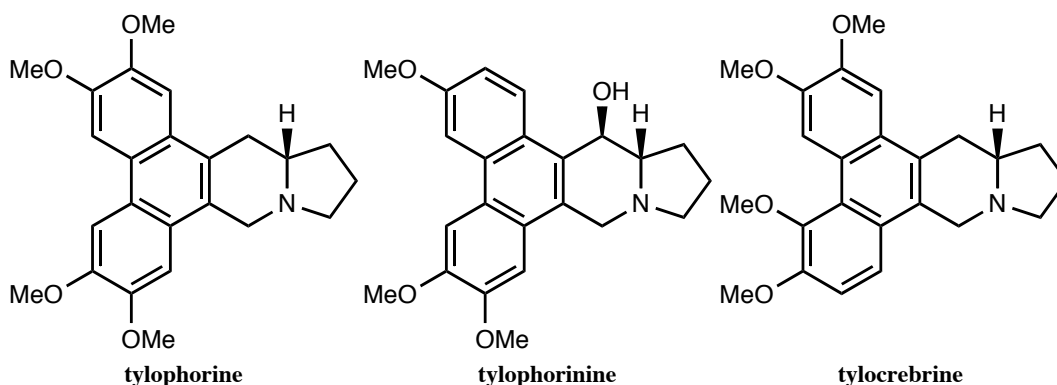
Figure 1.2. Structures of three well-known phenanthroindolizidine alkaloids

1.4. Phenanthroindolizidines and Their Seco Derivatives with Novel Structures

In 1991, the discoverers of tyloindicines A-E[30] reported the isolation of another group of phenanthroindolizidine alkaloids, namely tyloindicines F, G, H, and I (Figure 1.3).[31] This group of compounds contains unique features which are different from those of any previously known phenanthroindolizidines (Figure 1.3). The double bond in ring D, which is typically part of the phenanthrene core, appears at the exo position (C7 and C8, *vide infra*) rather than at the regular endo position (C6 and C7, i.e. in tylophorine). This double bond is a common structural pattern in this newly found group of compounds. Other features include the angular tertiary hemiaminal seen in tyloindicines F and G, and an unusual diene system in tyloindicine I.

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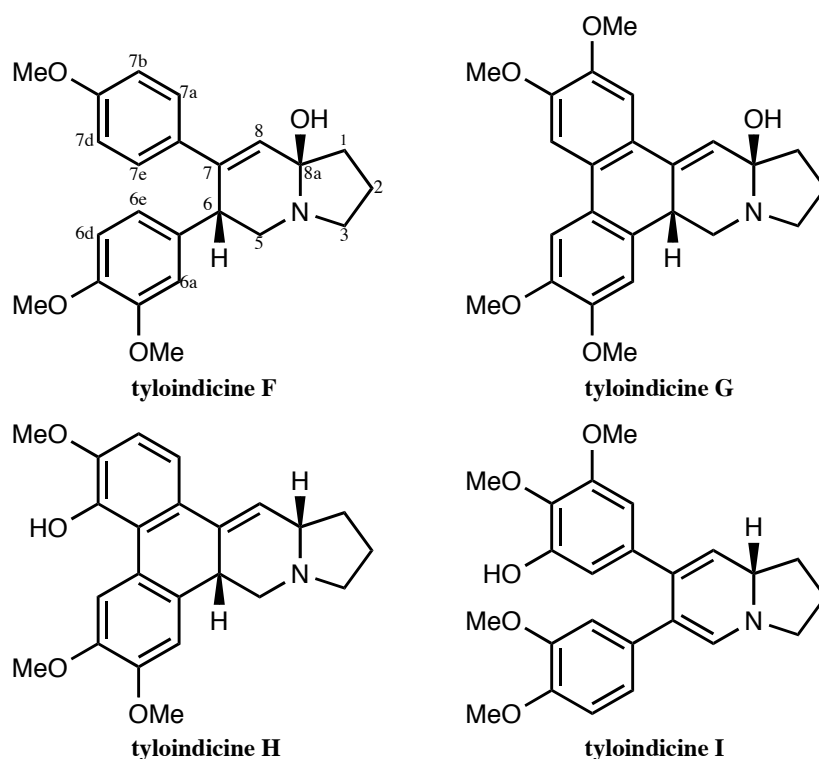
Figure 1.3. Structures of tyloindicines F, G, H, and I

1.5. Tyloindicine F – Biological Activity and Chemical Structure Validation

After their discovery,[31] the indolizidine alkaloids tyloindicines F, G, H, and I were sent to the National Cancer Institute (NCI) for testing in an *in vitro* primary disease oriented anti-tumor screen. The tests were performed according to the standard protocol for the NCI60 human tumor cell line anticancer drug screen.[32] The alkaloid samples were tested at five different concentrations. Tyloindicine F demonstrated remarkable cytotoxicity against lung cancer (non-small cell and small cell) and melanoma cell lines in the nanomolar to subnanomolar range.[33]

Furthermore, the differential sensitivity of tyloindicine F (as revealed by COMPARE analysis) against the cell lines from different major human tumors indicated that this compound has specific anti-cancer activity and is not a general toxin. The COMPARE pattern analysis of the mean graph profile from the NCI60 has developed into a convenient and powerful tool to correlate mechanisms of action across different anticancer agents.[34] In this analysis, two or more compounds showing similar inhibitory profiles in the NCI60 screen are presumed to function through the same mode of action. Tyloindicine F did not show a COMPARE pattern comparable to any known anticancer agent, thus suggesting that it acts either through a unique mechanism or a combination of several mechanisms. A new mode of action is of significant interest in anticancer drug development since cancer cells often acquire resistance against currently used chemotherapeutic agents. Undoubtedly, it is both scientifically and clinically important to understand both the structure-activity relationship and pharmacology of the tyloindicines. In order to achieve this goal, the availability of tyloindicine F is necessary.

In natural product discovery, the proposed structure of the isolated natural product can be incorrect due to errors in structure determination or through chemical reactions that occur during the isolation or characterization of the natural product. Due to the uniqueness and potential chemical instability of the structures of this group of compounds, a discussion about their discovery and structural assignment[31] is necessary and worthwhile.

Tyloindicines F, G, H, and I were isolated from the aerial parts of *Tylophora indica* in the western Himalayan region.[31] The air-dried crude sample was extracted thoroughly by a high-temperature percolation with methanol. After further treatment, a crude extract was obtained that was then triturated with dry ethyl acetate. The insoluble tyloindane part (impurity) was filtered off and the solution was concentrated *in vacuo.* The concentrated extract was eluted over basic alumina with mixtures of benzene, ethyl acetate and methanol of increasing polarities. Tyloindicine F was obtained from the benzene-ethyl acetate elution (1:1) in 0.004% yield. Elution with benzene-ethyl acetate (1:3) furnished tyloindicine G (0.001%) and tyloindicine H (0.0013%). Elution with pure ethyl acetate afforded tyloindicine I in 0.0013% yield. The structure of tyloindicine F was determined via chemical tests and through spectroscopic characterization (Table 1.2).

Table 1.2. Structure Determination of Tyloindicine F

tyloindicine F
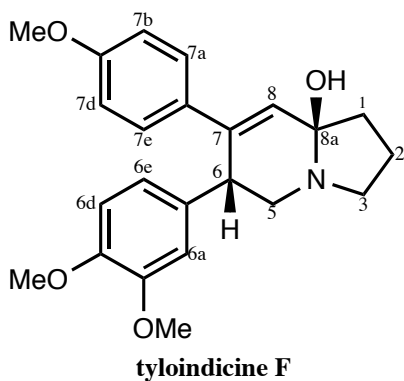
Test/Spectrum	Result/Signal	Structural deduction
FeCl$_3$	No Reaction	phenol-absent
CH$_2$N$_2$	No Reaction	phenol-absent
Ac$_2$O/Pyridine	No Reaction	3° hydroxyl
MP	245-247 ^{o}C	
IR	3350 cm^{-1}	hydroxyl-present
UV	No shift with NaOH addition	phenol-absent
MS	[M]$^+$ 381	C$_{23}$H$_{27}$NO$_4$
MS	[M-H$_2$O]$^+$ 363	hydroxyl-present
MS	296	loss of hydroxypyrrolidine
^{1}H-NMR	7.70 ppm	7a
^{1}H-NMR	7.10 ppm	7b
^{1}H-NMR	8.00 ppm	7d
^{1}H-NMR	7.10 ppm	7e
^{1}H-NMR	7.70 ppm	6d
^{1}H-NMR	6.96 ppm	6e
^{1}H-NMR	6.73 ppm	6a
^{1}H-NMR	2.83 ppm	6
^{1}H-NMR	5.60 ppm	8
^{1}H-NMR	3.73 ppm	methoxy groups at 6b, 6c
^{1}H-NMR	3.66 ppm	methoxy group at 7c
^{1}H-NMR	5.00 ppm	hydroxy

The most informative data was from NMR spectroscopy even though no ^{13}C NMR data were provided. Only a table of the proton NMR peak assignments was available from the original literature. *However, it was acquired on a 60 MHz Varian T-60 spectrometer using TFA as the solvent.* The graphical spectrum itself, though, could not be obtained from the supporting material or through direct contact with the authors. It was reported that there were three methoxy group signals in the tyloindicine F proton NMR spectrum. The substitution patterns on the southern and northern rings were undetermined and therefore assigned arbitrarily since their chemical shifts were not in accordance with other structurally related alkaloids like septicine[29] and tylohirsuticine.[35] Unlike the structural identification of similar phenanthroindolizidine alkaloids,[36] no NOE experiments were carried out for tyloindicine F, and therefore the exact structure remained unsolved. Additionally, the specific optical rotation of tyloindincine F was reported as -0.5 ($c = 0.05$, acetic acid), which suggested the possibility that the compound may have been isolated as a racemic mixture.

Because of these concerns, further work toward the elucidation of the structure of tyloindicine F was undertaken. Attempts by our research group to obtain samples from the authors were unsuccessful. Next, a sample of the plant *Tylophora indica* from a commercial source was obtained. However, tyloindicines F-I, as described in the original publication, could not be found in the extract of the commercial sample. Since this group of alkaloids had been screened by the NCI, samples were obtained from the NCI. These samples turned out to be significantly

decomposed, showing eighteen peaks upon HPLC analysis, and therefore no further structural characterization could be carried out. Efforts to purify the samples were not successful. Hence, a total synthesis approach was needed to verify the proposed structure of tyloindicine F.

In summary, tyloindicine F exhibited impressive anti-cancer activity and selectivity, but it has limited availability from natural sources. Hence, a total synthesis was undertaken to increase the supply of this natural product for both biological and structural studies.

In 2003, Baker *et al.* filed a patent claiming the synthesis of tyloindicines F-I.[37] However, the synthetic procedures in this patent were vague and little supporting data was presented. The same group subsequently published several journal articles describing the synthesis and evaluation of novel cytotoxic tylophorine analogues,[38, 39] but they did not report the syntheses of tyloindicines F-I.

Chapter 2. Studies Toward the Synthesis of Tyloindicine F

2.1. Overview

The main goal of our efforts toward the total synthesis of tyloindicine F was to provide sufficient material for its pharmacological evaluation and to confirm its structure. In addition, we planned to carry out structure-activity studies, which require chemical approaches that allow for facile structural variations. The phenanthroindolizidine core has been prepared numerous times and many different synthetic strategies have been used to prepare tylophorine, antofine, septicine, cryptopleurine and julandine. Previous approaches, racemic or asymmetric, utilized classical transformations such as a) intramolecular aldol reactions,[40-43] b) [3+2] cycloadditions,[44, 45] c) double Michael additions,[46, 47] d) enamine addition,[48] e) Friedel-Crafts acylation,[49] f) Pictet-Spengler reactions,[50, 51] g) Bischler-Napieralski reactions,[52, 53] h) click chemistry,[54] i) directed lithiation followed by addition into a pyrrole aldehyde[55] and j) pyridinium reduction.[56] In addition, transition metal-catalyzed reactions have been employed to prepare phenanthroindolizidine alkaloids.[57-59]

The challenge of synthesizing tyloindicine F, 6-(3',4'-dimethoxyphenyl)-7-(4'-methoxyphenyl)-2,3,5,6-tetrahydro-1*H*-indolizin-8a-ol, is a result of its unique structural features that include a) an exo double bond between C7 and C8, b) a highly acidic proton at C6 and c) an angular hemiaminal at C8a. Notably, features *a* and/or *b* were only found in the tyloindicines F-I described by Ali *et al.*[31] As for the tertiary hemiaminal at the angular position, indolizomycin[60-62] and mitomycins[63-67] possess

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this structural feature (Figure 2.1). The Ali group also reported the isolation of 13a-

hydroxytylophorine, a closely related phenanthroindolizidine alkaloid containing such

a moiety.[68] For hemiaminal-containing indolizidine structures, a monocyclic nine-

membered ring (open form) was reported, although in all cases the indolizidine
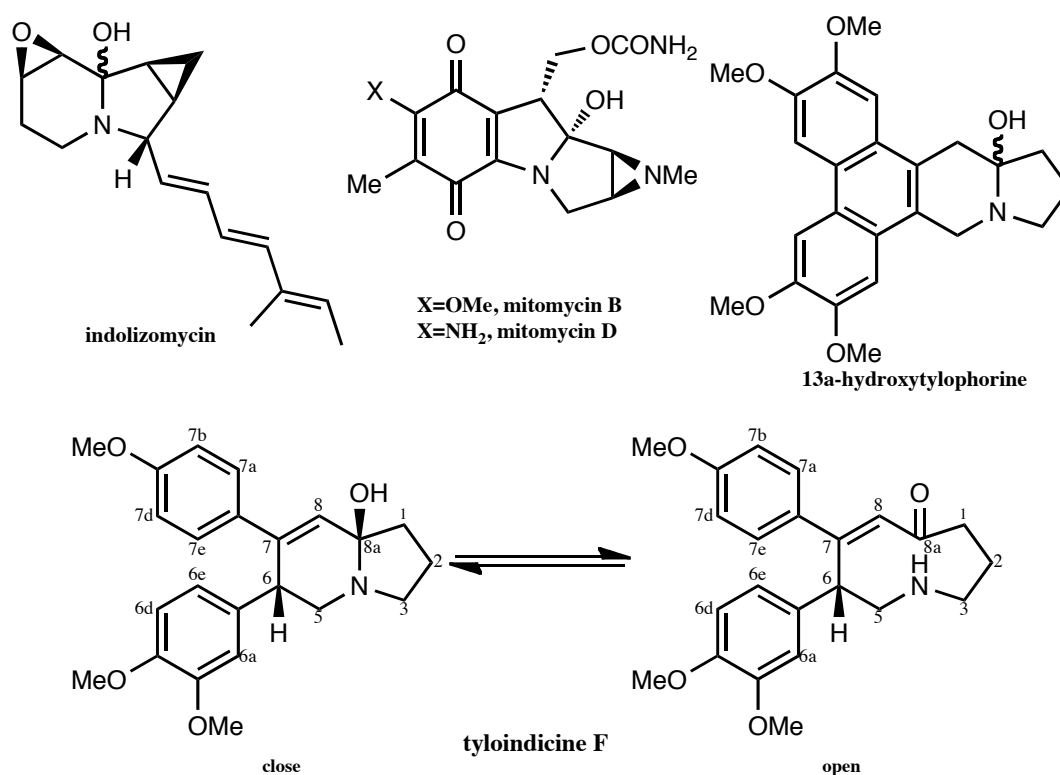
nitrogen atom was either alkylated or acylated.[69-72]

Figure 2.1. Selected natural products containing an angular hemiaminal moiety

2.2. Intramolecular Imino Diels-Alder Route

2.2.1. Retrosynthetic Analysis

When we planned a route toward the synthesis of tyloindicine F that allows the construction of the C7-C8 double bond, an approach used by the Weinreb group was considered.[73-79] The Weinreb group had used an intramolecular imino Diels-Alder reaction to assemble the two core rings of indolizidine and quinolizidine alkaloids in a single step (Scheme 2.1).[73, 75]

Scheme 2.1

tylophorine
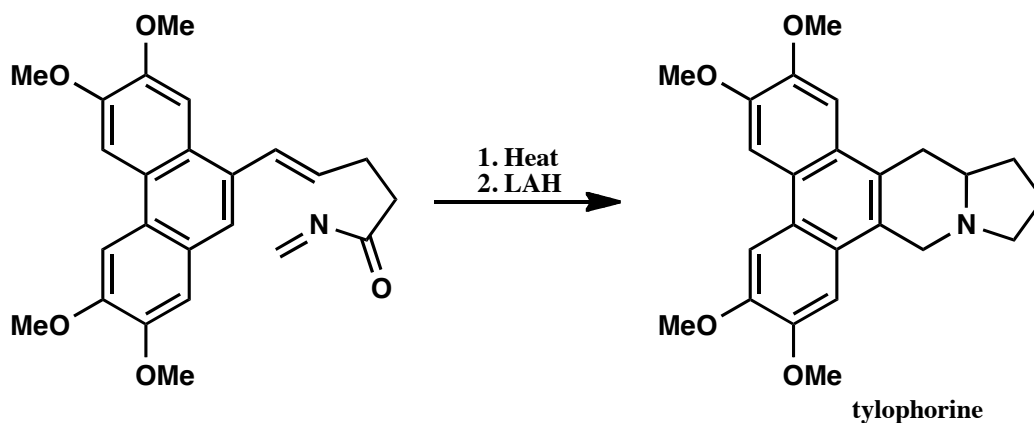
Previously, this chemistry had been used in our research group towards the synthesis of tyloindicine H. Given both the convenience of this approach, and the earlier experience in our research group, an imino-Diels-Alder route toward tyloindicine F was devised (Scheme 2.2). Another advantage of this route was that the installation of the anticipated labile tertiary hemiaminal structure would be carried out at the very end of the synthesis through oxidation of 8a-deoxy tyloindicine F (**II**).

Scheme 2.2

tyloindicine F, (I)   (II)   (III)

(IV)

(V)

NH$_3$

HCHO

(VI)
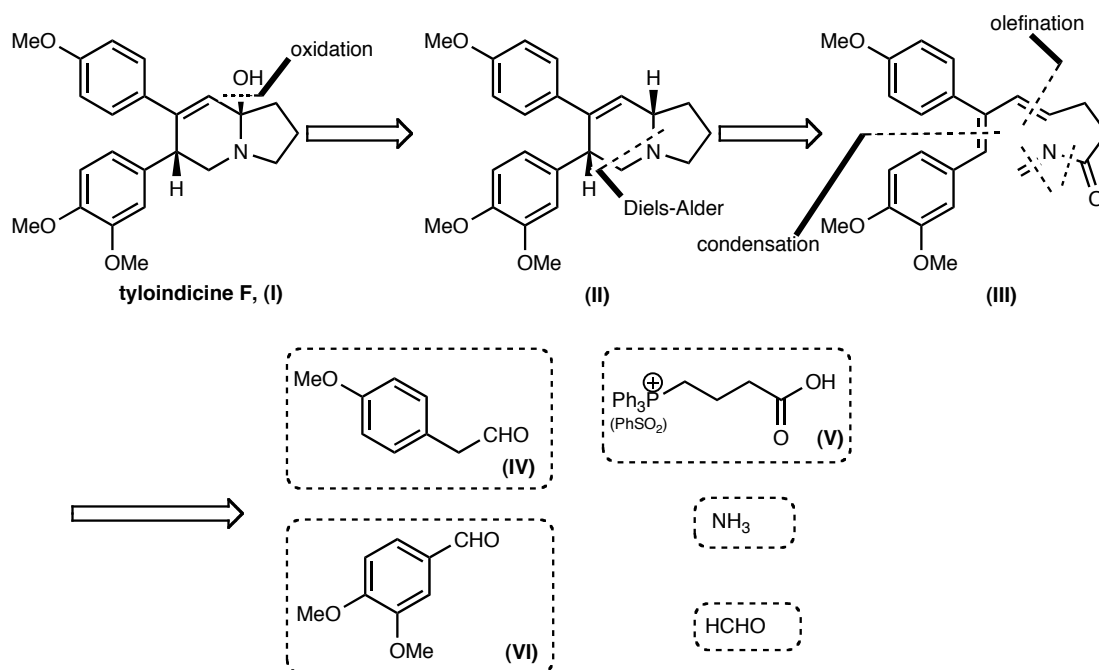
Retrosynthetically, tyloindicine F (**I**) was to be prepared by adding water to

the angular iminium ion generated through the oxidation of 8a-deoxy tyloindicine F

(**II**). A few examples of similar transformations had been reported before.[80, 81] The

bicyclic indolizidine ring structure in **II** could be set up by an intramolecular imino

Diels-Alder reaction from **III** followed by amide reduction. Precursor **III** can be

constructed from three major parts — aldehyde **IV**, carboxylic acid **V**, and aldehyde

VI. Intermediates **IV** and **VI** could be joined by an aldol or Perkin condensation

whereas the Perkin condensation product and **V** can be used for a Wittig or Julia

olefination. In addition, ammonium and formaldehyde surrogates were required for

the formation of the acyl imine used in the Diels-Alder reaction.

2.2.2. Synthetic Studies

2.2.2.1. Synthesis of the Cinnamic Aldehyde Derivative

The synthesis of tyloindicine F started with the preparation of the biaryl aldehyde **I-04**. A direct aldol condensation, followed by dehydration, between the two aldehydes **IV** and **VI** was considered as a straightforward approach to this structure. However, one of the reactants, 4-methoxyphenylacetaldehyde (**IV**) was not commercially available from major vendors. Despite the easy access of this compound from the hydroboration-oxidation of 4-methoxystyrene, 4-methoxyphenylacetic acid was used instead in the Perkin reaction after comparing the prices of starting materials and reviewing literature examples (Scheme 2.3).[82]

Scheme 2.3
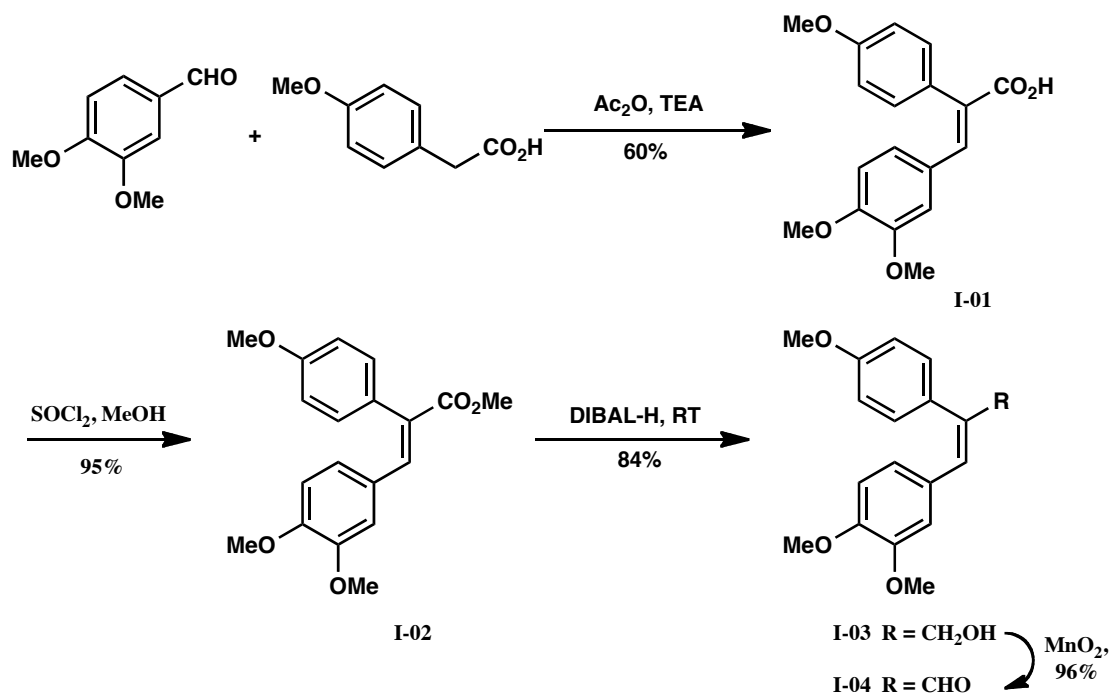
The Perkin condensation between 3,4-dimethoxybenzaldehyde and 4-methoxyphenylacetic acid, both commercially available, took place smoothly with a satisfactory yield via a mixed acid anhydride. Acetic anhydride was used as the solvent and triethylamine as the base. To convert the resulting carboxylic acid into an aldehyde, an esterification-reduction protocol was required. When the substituted cinnamic acid **I-01** was subjected to a Fisher esterification using a catalytic amount of concentrated sulfuric acid the reaction did not go to completion. Replacing concentrated sulfuric acid with one equivalent of thionyl chloride provided a high yield of the corresponding methyl ester **I-02**.

A low temperature DIBAL-H reduction of **I-02** was expected to afford the desired aldehyde **I-04**. However, the excess of DIBAL-H needed to drive this reaction to completion produced a mixture of aldehyde **I-04** and the over-reduced alcohol **I-03** in almost equal ratio. Hence, a two-step process was used. Methyl ester **I-02** was reduced at room temperature by DIBAL-H, providing a fast and complete conversion to alcohol **I-03**. Allylic oxidation with activated manganese dioxide provided the aldehyde **I-04**. This second step took two days, but the operation was simple and the isolation of the desired product was easy. A simple Celite pad filtration of the greenish crude reaction mixture was usually sufficient to obtain aldehyde **I-04**. Flash column chromatography was employed as needed for additional purification.

In another approach, carboxylic acid **I-01** was reacted with *N,O*-dimethylhydroxylamine to form the corresponding Weinreb amide, which was subsequently reduced with DIBAL-H to furnish aldehyde **I-04** (Scheme 2.4). Unexpectedly, over-reduction still occurred along with the desired aldehyde.

Scheme 2.4
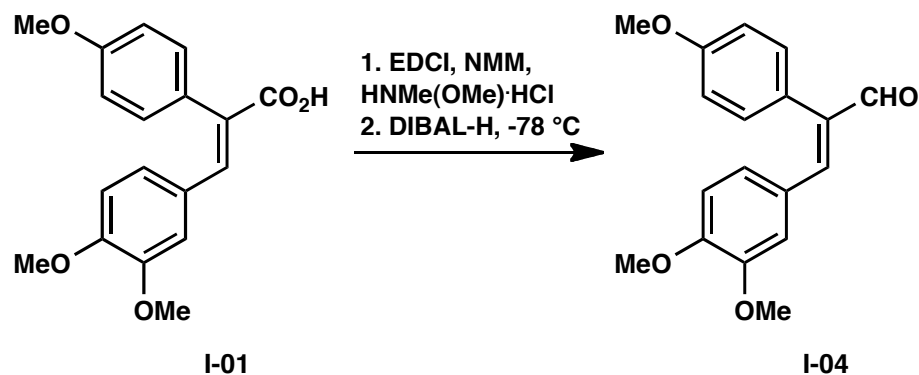
2.2.2.2. Determination of the *cis* Conformation of the Perkin Product

Several grams of aldehyde **I-04** were prepared using the protocol described above. However, there remained one question – the stereochemical relationship between the two aromatic rings, i.e. whether they were cis or trans to each other across the double bond connecting them. The trans product was deemed the favored isomer in which the two rings are on opposite sides of the double bond, thereby avoiding potentially unfavorable steric interactions between the two aryl rings.

Although it is known that Perkin reaction typically yields the cis products,[82] experimental proof was needed to verify the structure of aldehyde **I-04**. A proton NOE experiment conducted on aldehyde **I-04** showed a positive NOE signal between the aldehyde hydrogen and the vinyl hydrogen, suggesting their proximity in space. This can only happen when the two aromatic rings are cis to each other.

In addition, a single crystal of alcohol **I-03** was submitted for X-ray diffraction. The resulting structure verified the cis relationship between the southern and northern rings (Figure 2.2).

Since the two aromatic rings are connected by a double bond, they could be conjugated and oriented nearly in the same plane. Interstingly, the X-ray showed that the two ring planes are twisted, and almost orthogonal to each other. This observation is noteworthy because in phenanthrenes, a bond between C5 and C11 locks these two rings into a common plane, thereby forming an extensive π-system. Since the X-ray revealed that seco derivatives are structurally and electronically distinctive from the corresponding phenanthrenes, they should also possess different biological activities.
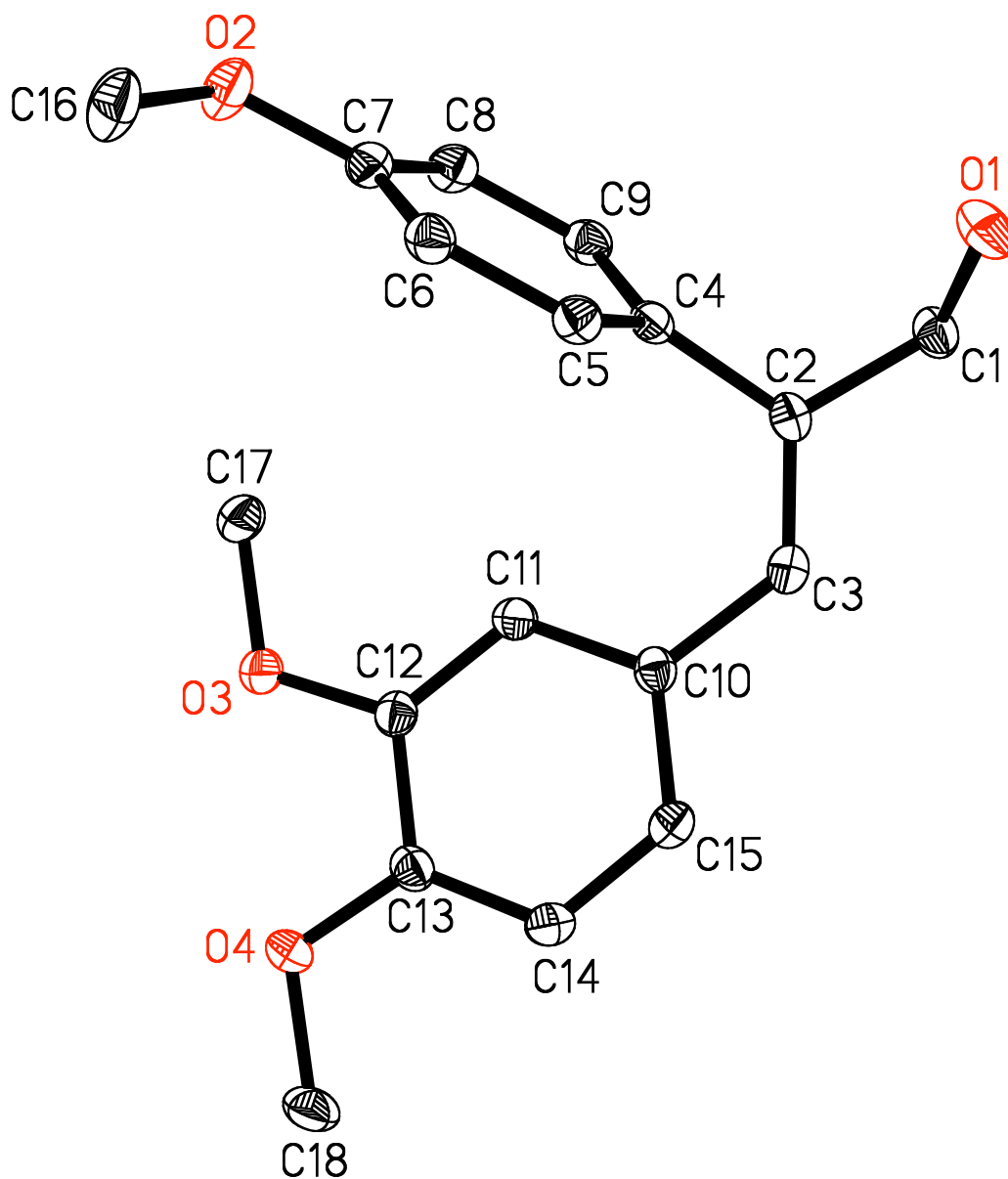
Figure 2.2. X-ray structure of alcohol **I-03**

2.2.2.3. Synthesis of the Imino Diels-Alder Reaction Precursor

The next step in our route toward the synthesis of tyloindicine F was the

reaction between aldehyde **I-04** and fragment **V** through an olefination reaction

(Scheme 2.2, *vide supra*), setting up the diene system for the intramolecular imino

Diels-Alder reaction. The formation of two stereoisomers, (E) or (Z), could be the

outcome of this reaction, whereas only the (E) product was desired for the subsequent

Diels-Alder reaction (Figure 2.3). Among various options, a Wittig olefination was

chosen for its convenience and because the starting Wittig salt (4-

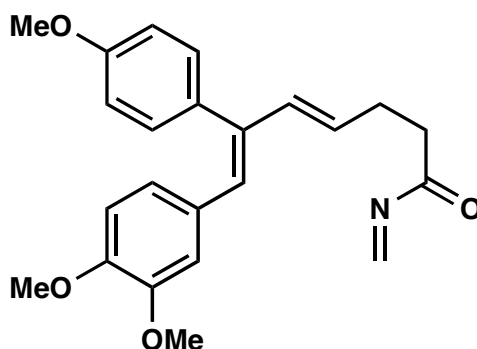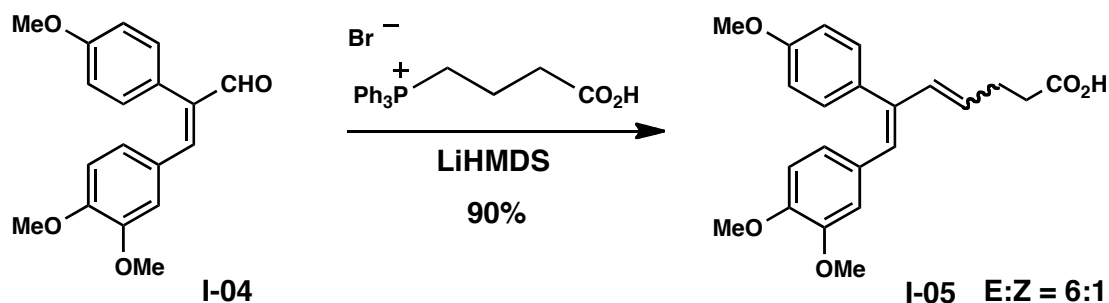carboxypropyl)triphenylphosphonium bromide (Scheme 2.5) is commercially

available.

Figure 2.3. Structure of the Diels-Alder reaction precursor

Scheme 2.5

Although a freshly prepared batch of this phosphonium salt was previously used in our research group for this reaction, it was found that the commercial salt purchased from Sigma-Aldrich worked just as well after being heated under reduced pressure before each reaction. Highly concentrated reaction conditions were employed. Thus, a 1.0 M solution of lithium bis(trimethylsilyl) amide in THF was added directly into a round-bottom flask containing the phosphonium salt powder under argon. The deep reddish/orange ylide was usually ready within one hour at room temperature. At this time, a THF solution of aldehyde **I-04** was added to the reaction mixture with a syringe.

The stereochemistry of the newly established double bond was of utmost concern. Although an unstabilized phosphorus ylide was used, the E/Z ratio in the product was 6 to 1 (monitored by NMR), satisfactory enough to be used in the next step without further purification.

In addition, a Julia olefination was carried out (Scheme 2.6). However, due to the comparable acidity between the protons α to the sulfone group and to the ester

group, multiple compounds were found after the reaction and therefore this reaction was not pursued any further.

Scheme 2.6
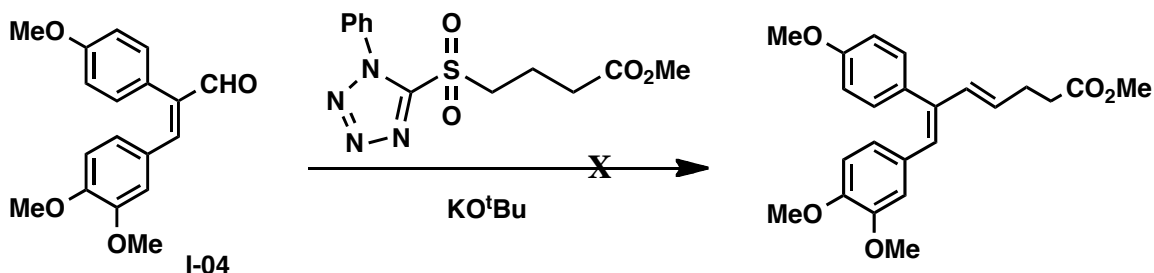
Next, the carboxylic acid **I-05** must be converted into the corresponding *N*-methyleneamide, shown in Figure 2.3, which can be generated *in situ* from amidomethylacetate **I-07** (Scheme 2.7). Transformation of acid **I-05** to amide **I-06** was achieved by mixed anhydride activation, followed by ammonia addition (solid ammonium bicarbonate for ease of handling). The resulting diene amide **I-06** was reacted with formaldehyde (solid paraformaldehyde for ease of use) in the presence of cesium carbonate and then quenched with acetic anhydride. *N*-Acetoxymethylamide **I-07** was quite stable. It survived silica gel flash column chromatography and could be stored in pure form as a yellowish powder for at least a few weeks.

Scheme 2.7
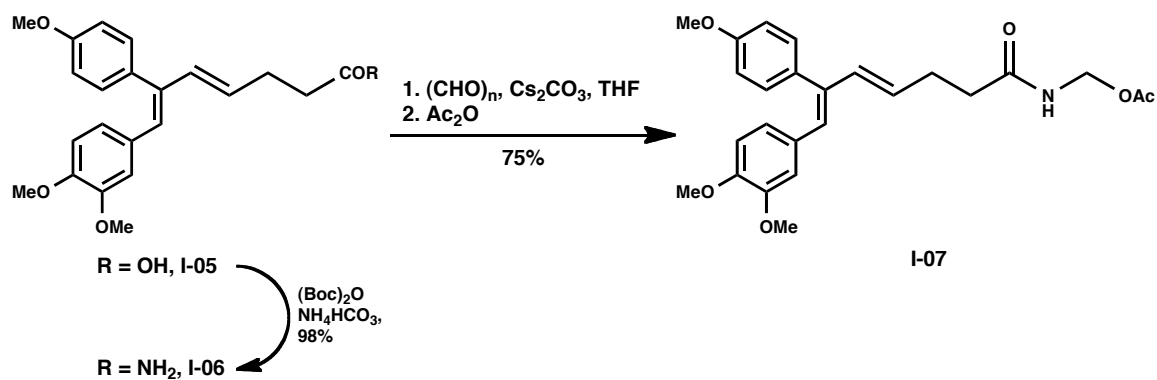
2.2.2.4. Intramolecular Imino Diels-Alder Reaction

The key step in this approach towards tyloindicine F was the intramolecular imino Diels-Alder reaction. In this transformation, the indolizidine core, a [6,5] bicyclic ring system was to be constructed in a single step. This chemistry, which has been primarily explored by Weinreb[73-79] and Grieco,[83-86] has been reviewed extensively. Numerous indolizidine and quinolizidine alkaloids have been prepared in this way, including phenanthroindolizidines such as tylophorine.[73] According to previous studies, substituents have an influence on the reactivity and stereoselectivity of the reaction as in all Diels-Alder reactions. Overall, two strategies that differed in the dienophile portion of the precursor molecule were considered.

Scheme 2.8
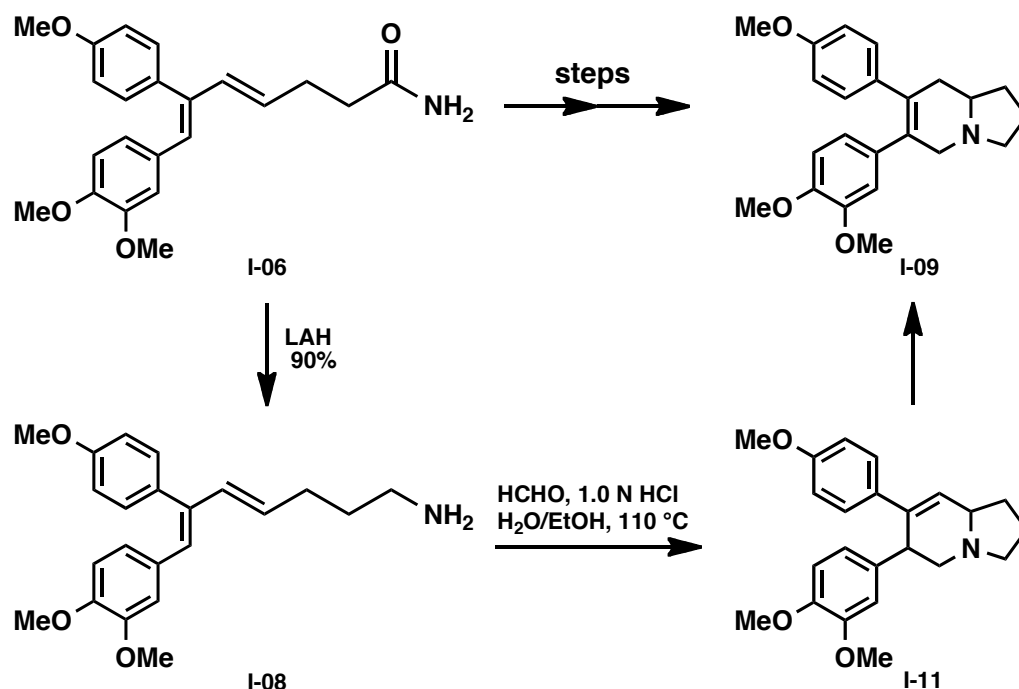
Imines are good dienophiles and can be prepared by direct condensation between a terminal amine (e.g. **I-08**) and formaldehyde.[87] Thus, reaction of **I-08** with formaldehyde furnished the corresponding imine, which participated in the intramolecular Diels-Alder reaction at 110 °C in a sealed tube under acidic conditions (Scheme 2.8).[84-86] The reaction proceeded smoothly and a product was isolated in moderate yield. The product was, however, not the expected "exo" product **I-11** but the conjugated "endo" product **I-09**, which is formed by isomerization of the double bond after the intramolecular imino Diels-Alder reaction. This isomerization had previously been described by Grieco.[84]

A solution to this problem was provided by the Weinreb variation of the intramolecular imino Diels-Alder reaction (Scheme 2.9). In the Weinreb version, the imine dienophile (*vide supra*) was prepared *in situ* from precursor **I-07**. This approach had been used in several previous phenanthroindolizidine alkaloid syntheses including efforts made by our research group toward the synthesis of tyloindicine H.[88] Thermal decomposition of **I-07** generated the intermediate imine, without the use of proton or Lewis acids that are thought to promote the undesired double bond isomerization.

Scheme 2.9
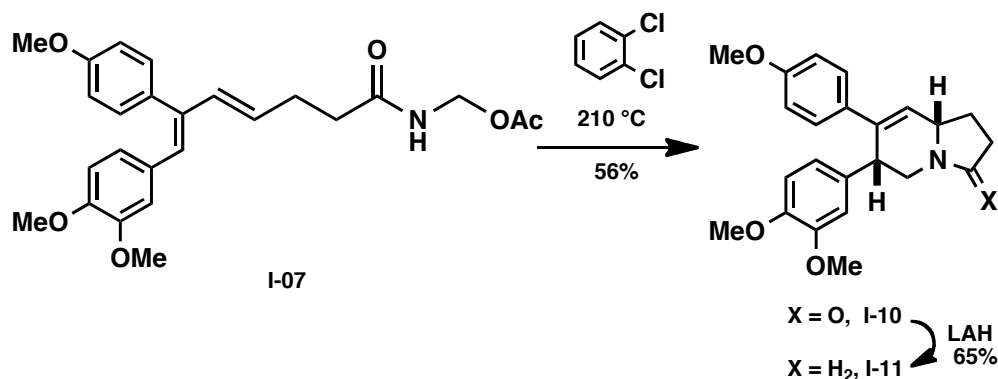
N-Acetoxymethylamide **I-07** was heated at 210 °C in a sealed tube for four hours, affording the desired product in an acceptable yield. This reaction had to be carefully monitored since short reaction times led to an incomplete Diels-Alder reaction, but long reaction times resulted in lower product yield. The desired Diels-Alder product was more polar than the starting material. The most indicative evidence

for the formation of this compound was the presence of an olefinic proton singlet at δ

6.2 ppm (solvent $CDCl_3$, internal standard TMS) in the ^{1}H-NMR spectrum, which is

characteristic for the "exo" double bond. This signal peak had also been reported in

the earlier synthetic studies of tyloindicine H conducted in our research group.[88] This

signal peak was missing in the ^{1}H-NMR spectrum of compound **I-09**.

Mechanistically, this transformation could be categorized as a type I, internally

activated, aza intramolecular Diels-Alder reaction (Figure 2.4).[89] It is thought to take

place in a HOMO/diene controlled fashion. Both the northern and southern rings are

electron-rich and conjugated with the diene while the acyl group activates the imine

dienophile. There are a few points worth making. First of all, this reaction presumably

goes through an asynchronous transition state in which the two new chemical bonds

in the product, N1-C6 and C2-C3, are formed not concurrently despite the fact that

this is a concerted, non-stepwise reaction.[87] Secondly, theoretical calculations

determined that the the *s*-cis form is the most stable N-acylimine conformer, which is

energetically favored over the *s*-trans form by 3 kcal/mol and the orthogonal nonpolar

form by 4 kcal/mol, respectively.[78] And last, in intramolecular imino Diels-Alder

reactions, activating acyl groups strongly prefer the *endo* orientation.[87] This, however,

has no influence on the diastereoselectivity of the product since the free angular

nitrogen in the indolizidine structure is not a stereogenic center.
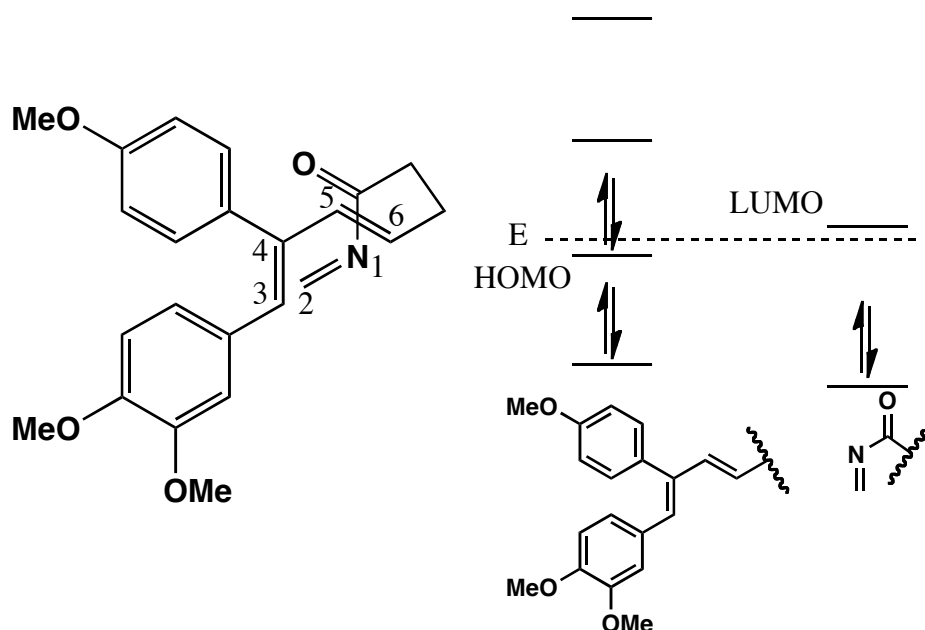
Figure 2.4. Process of the intramolecular imino Diels-Alder reaction

The Diels-Alder product **I-10** was then treated with lithium aluminum

hydride, resulting in the formation of 8a-deoxy-tyloindicine F (**I-11**). This reduction

was facile but was achieved only in modest yield. **I-11** showed an IR band at 2776

cm^{-1}, which is absent in that of **I-10**, and is indicative of the basic nitrogen in the

indolizidine core. This band reflected the presence of the diaxial C−H bonds, relative

to the free lone pair of electrons of the indolizidine angular nitrogen atom.[90] In

bridgehead nitrogen bicyclic systems, this band is unique to trans fused cores, and

was therefore termed a *trans* or T band (Figure 2.5). It also is referred to as the

Bohlmann band.
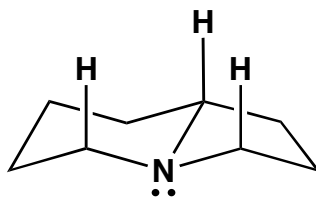
Figure 2.5. Origin of T-band in the IR of the indolizidine core

2.2.2.5. Installation of the Hemiaminal Moiety

With 8a-deoxy tyloindicine F (**II**) in hand the final step, the oxidative installation of the hydroxyl group at the *8a* position was investigated. Finding the right oxidant would be the key to the success of this transformation.

Our first attempt was made with mercuric acetate following examples reported in the 1950s.[80, 81, 91-97] In the case of antofine, a related phenanthroindolizidine alkaloid, the initial oxidation product was presumably an iminium ion that was then further oxidized into a pyridinium species. In the presence of cyanide, addition to the iminium ion took place (Scheme 2.10) to furnish the corresponding cyano derivative. In the case of 13a-hydroxysepticine treatment with a Lewis acid resulted in dehydration (Scheme 2.10),[68] which could also be a side reaction in the acid catalyzed mercuric acid oxidation.

Scheme 2.10

antofine

13a-hydroxysepticine
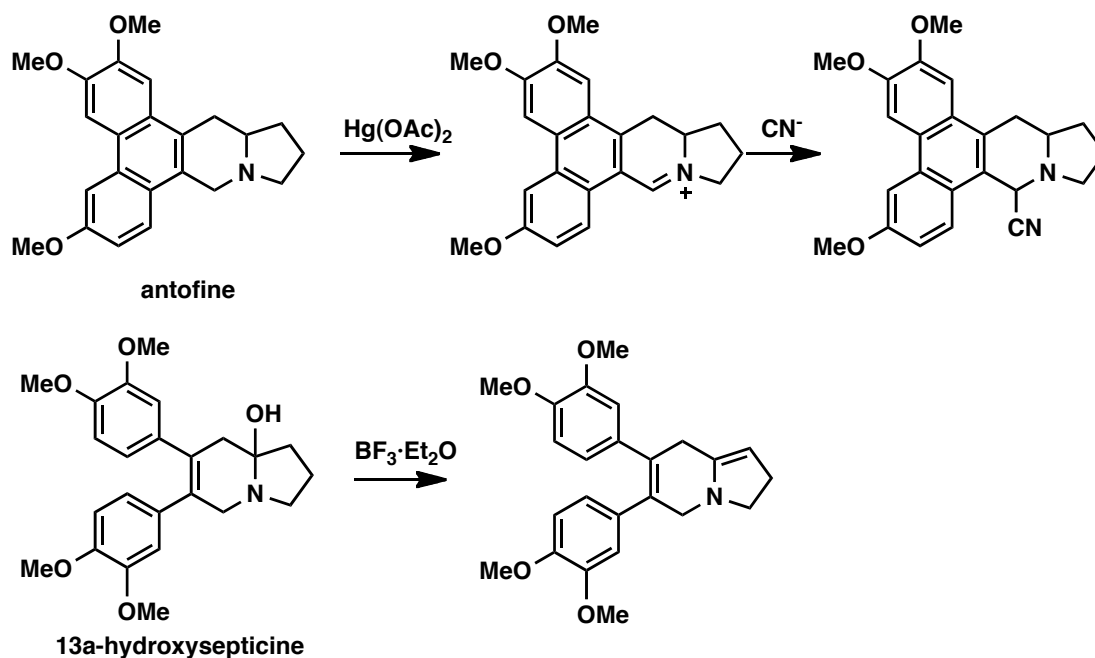
Despite the concerns mentioned above, mercuric oxidation was attempted at room temperature. The reaction went smoothly, and an exceedingly polar major product formed, which was purified by flash column chromatography over basic alumina, and eluted with chloroform and methanol. Upon NMR and IR studies, this product turned out to be the pyridinium derivative. Given the electron-rich nature of this system (one methoxy group at the northern ring and two methoxy groups at the southern ring), this result was not surprising. Next, other oxidations were examined. Among them, allylic oxidation methods were considered a suitable alternative. Selenium dioxide is well known for this transformation. However, there are two allylic positions for the "exo" double bond. The unwanted position C6 happens to be

a benzylic position while C8a is next to the electronegative nitrogen and less hindered. Hence, selectivity was a concern. Despite this uncertainty, *8a*-deoxytyloindicine F (**I-11**) was reacted with a catalytic amount of selenium dioxide and a stoichiometric amount of *tert*-butyl hydroperoxide as co-oxidant following the Sharpless protocol.[98] No reaction was observed under these conditions. When the amount of selenium dioxide was increased to 1.5 equivalents without a co-oxidant, the same pyridinium species as observed in the mercuric oxidation was obtained.

Table 2.1. Oxidation of 8a-Deoxytyloindicine F

Conditions	Results	Oxidation class
$Hg(OAc)_2$, HOAc	pyridinium	two-electron
SeO_2	pyridinium	allylic
NBS, CCl_4	no reaction	free radical
NBS, BnOOH, CCl_4	pyridinium	free radical
CAN, H_2O/CH_3CN	pyridinium	free radical
DDQ, MeOH, -78^oC	pyridinium	free radical

Another choice for the desired synthetic transformation was a radical-mediated oxidation. Commonly used reagents for such reactions include *N*-bromosuccinimide (NBS), ceric ammonium nitrate (CAN) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). All these reagents were examined but led to the same pyridinium product. When a stoichiometric amount of NBS was used,[99] no reaction took place (Table 2.1).

A last attempt at this transformation was made by performing a Polonovski reaction. In our system, *N*-oxidation was not observed and the same pyridinium product formed that had been observed previously, accompanied by other decomposition products.

While the α hydroxylation of tertiary nitrogens has been proposed in biotransformation,[100] its utilization in chemical reactions has been met with limited success. In certain recent cases, this chemistry was successful using unusual reagents[101-103] or rearrangements,[104] but it cannot be regarded as a general reaction. Given the propensity of 8a-deoxytyloindicine F to form the corresponding pyridinium ion under oxidative conditions, no further attempts were made to convert it into tyloindicine F.

2.3. Dual Cyclization Route

2.3.1. Retrosynthetic Analysis

The Diels-Alder route had provided a convenient way for the construction of the phenanthroindolizidine core (*vide supra*). Nonetheless, the final oxidation step could not be accomplished. Therefore, another route for the synthesis of tyloindicine F was devised and examined (Scheme 2.11).

Scheme 2.11

tyloindicine F   VII

VIII   IX   X
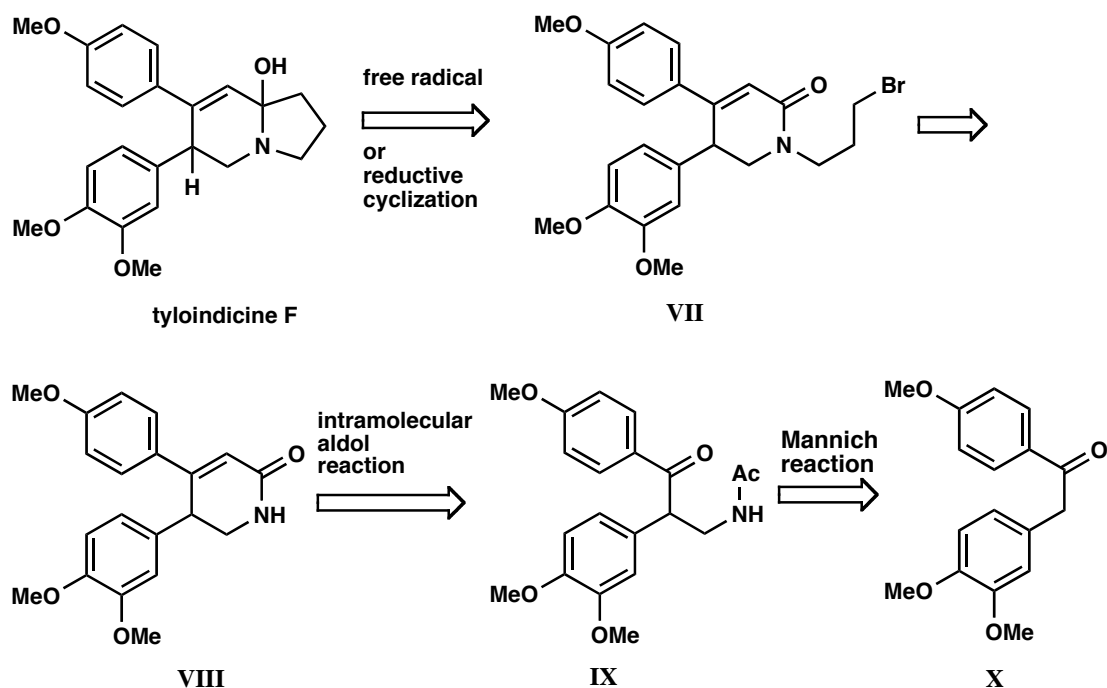
In this revised synthetic plan, the introduction of the hemiaminal moiety was to be carried out as the very last step of the reaction sequence, as had been the case in the Diels-Alder route. However, instead of preparing the [6,5] bicyclic system

concurrently, we planned to construct the two rings in a stepwise fashion. The angular aminal group and the five-membered ring would be the products of a cyclization reaction, either a reductive Barbier/Nozaki-Hiyama-Kishi (NHK) reaction or a free radical reaction. The six-membered ring could be obtained from an intramolecular aldol reaction (reminiscent of the Robinson annulation). The precursor of this aldol reaction, in turn, could be formed from a diaryl ketone via a Mannich reaction. All reactions involved in this approach are classical organic chemistry transformations with ample precedent.

2.3.2. Synthetic Studies

2.3.2.1. Synthesis of (3,4-Dimethoxy)benzyl-3-methoxyphenylketone

The dual cyclization route started from the non-commercially-available diarylketone **I-13**. To synthesize this compound, a Buchner-Curtius-Schlotterbeck reaction was carried out since the previous application of this reaction in the attempted tyloindicine H synthesis had been successful (Scheme 2.12).[88]

3,4-Dimethoxybenzaldehyde was reacted with tosylhydrazine, resulting in the corresponding hydrazone, in yellowish powder form. This hydrazone was stable and could be stored for more than a year without noticeable decomposition. After treating the hydrazone with a solution of sodium hydroxide in ethanol, a deep red color developed within minutes. This color clearly indicated the formation of the resultant diazo compound. Next, 4-methoxybenzaldehyde was added to this solution in

portions. The desired diaryl ketone **I-13** was obtained through this formal carbene

insertion reaction, albeit in poor yield.

Scheme 2.12
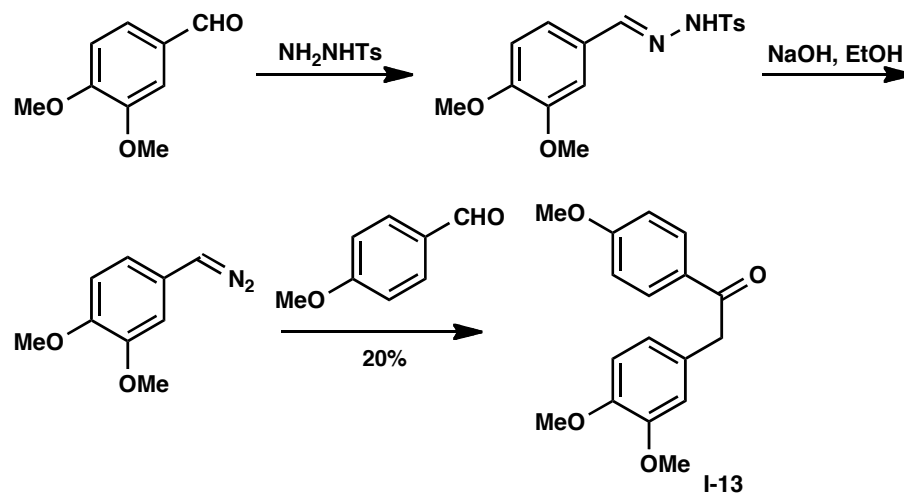
The reaction pathway is thought to involve the addition of the diazo

compound to the aldehyde, followed by a [1,2] hydride shift and simultaneous

nitrogen gas ejection (Figure 2.6). Various side-reactions are possible and they

account for the low yield of this transformation. In addition, it proved difficult to

isolate the desired product in pure form.
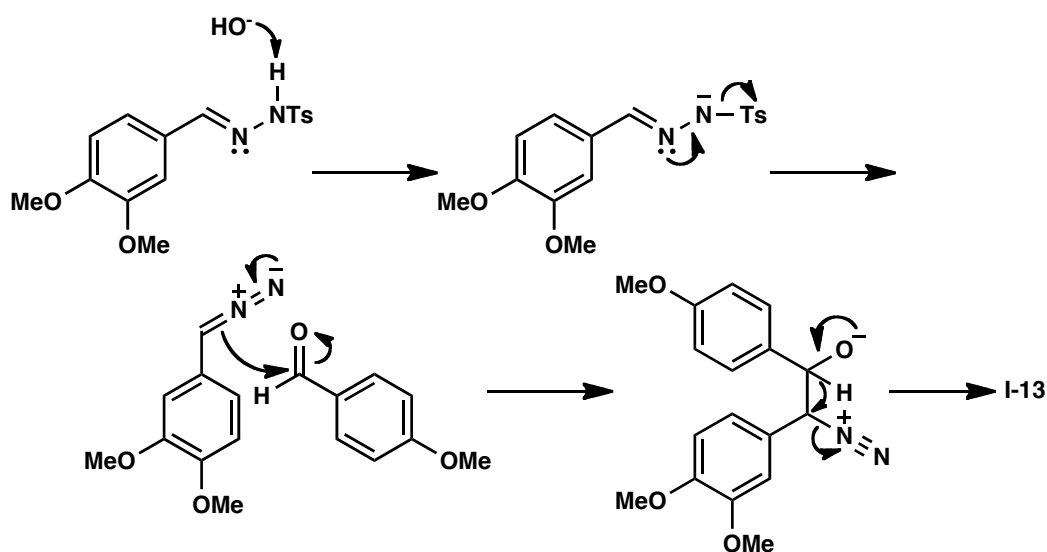
Figure 2.6. Mechanism of the Buchner-Curtis-Schlotterbeck reaction

Therefore, another route involving a Friedel-Crafts reaction, was used to prepare ketone I-**13** (Scheme 2.13). In this sequence, 3,4-dimethoxyphenylacetic acid was first transformed into its acid chloride. Then, upon treatment with a Lewis acid, a reactive acylium intermediate was generated and reacted with the electron-rich anisole via electrophilic aromatic substitution, producing ketone **I-13** in moderate yield. Separation of the reaction product was easily achieved and gram quantities of ketone **I-13** were prepared at low cost.

Scheme 2.13
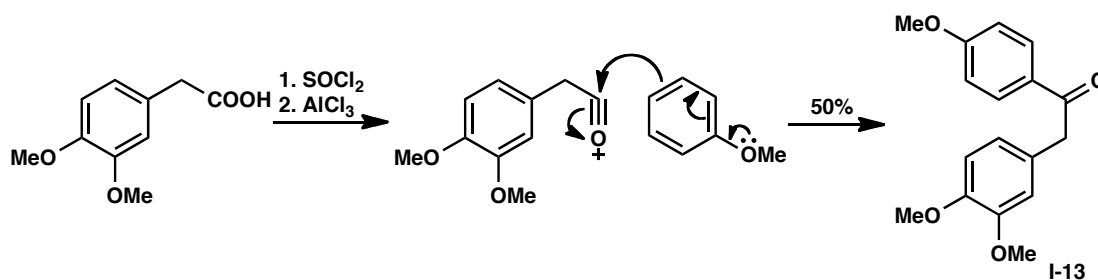
2.3.2.2. Synthetic Studies on the Mannich Reaction

Since the acylated Mannich base **IX** (Scheme 2.11) was proposed as an intermediate to prepare the six-membered ring, efforts towards its synthesis were made. Diarylketone **I-13** was dissolved in ethanol before being mixed with 1-pentamine and a 37% formaldehyde solution. This mixture was then made acidic by adding 2N hydrochloric acid and refluxed overnight (Scheme 2.14). However, under these reaction conditions, a Hoffman elimination reaction took place, giving an α,β unsaturated ketone as the isolated product. In retrospect, it was not surprising that this reaction occurred given that the structure of this ketone is highly stabilized through conjugation. Accordingly, a protecting group was considered as a way to stabilize the intermediate Mannich base.

Scheme 2.14
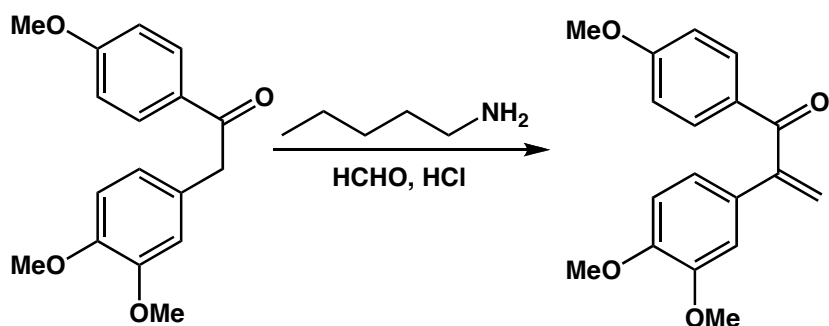
The Boc-protected amine **I-15** (*vide supra*) derived from ketone **I-13** was therefore targeted (Scheme 2.15). An acid-catalyzed reaction was again employed using *tert*-butyl carbamate (Boc-NH$_2$) instead of an unprotected amine. However, because of the acid lability of the Boc group, neither acid nor heat was suitable for this reaction. When a weaker acid – formic acid and lower temperatures were employed, no reaction took place.

In order to form the desired Boc-protected amine **I-15**, a N-Boc imine surrogate *tert*-butyl tosylmethylcarbamate (**I-14**) was chosen and the reaction to form **I-15** was attempted in a basic environment. *tert*-Butyl tosylmethylcarbamate (**I-14**) was prepared by reacting *tert*-butyl carbamate and sodium tosylate with an aqueous formaldehyde solution in the presence of formic acid. This solution was stirred for 48 hours. *tert*-Butyl tosylmethylcarbamate (**I-14**) precipitated as colorless needles that were easily separated.

The Mannich reaction between ketone **I-13** and N-Boc imine surrogate **I-14** was subsequently carried out under basic conditions, rather than the classical acidic

conditions. Gratifyingly, the expected transformation occurred (Scheme 2.15). The Boc protected Mannich base was isolated in moderate yield and its structure was verified by NMR.

Scheme 2.15
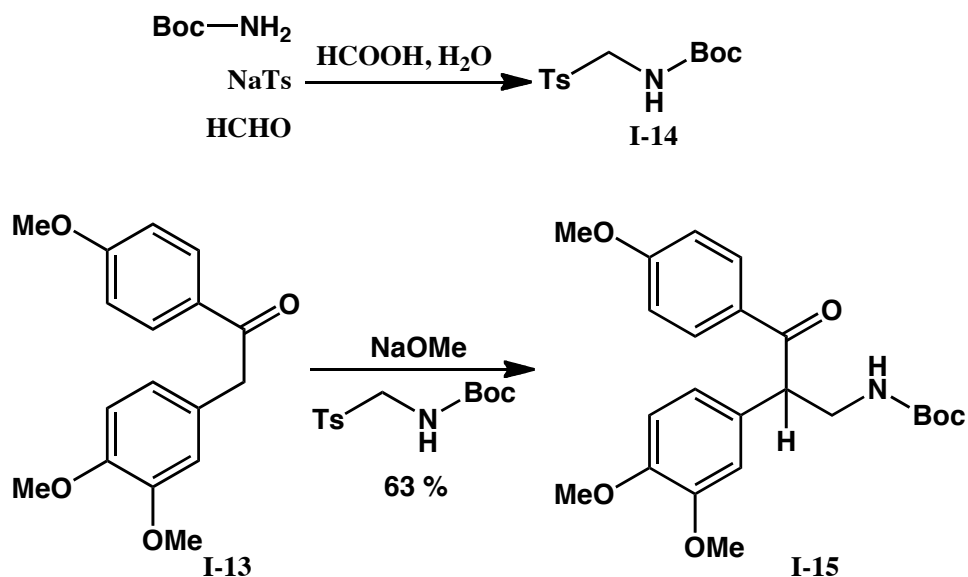
In the subsequent reaction between ketone **I-13** and **I-14** self-condensation of the starting ketone **I-13** turned out to be a significant side reaction. In addition, it was observed that prolonged reaction times lowered the reaction yield. The color of the reaction mixture also became dark brown. Hence, the stability of the isolated product **I-15** was tested by exposing it to the base used in this reaction (sodium hydride). Almost immediately, the clear solution turned to the previously seen dark brown color and TLC showed that **I-15** had vanished completely and a very polar spot had

formed at the baseline. Apparently, **I-15** is base labile. After numerous trials, a

reaction protocol was developed to reduce the side reactions and product

decomposition. In this protocol, only one equivalent of base was used and the

progress of the reaction was carefully monitored by TLC.[d]

Acetamide was also tried as a substrate for the Mannich reaction (Scheme

2.16).[105-107] It was anticipated that a tandem intramolecular aldol reaction might occur

in a one-pot fashion. Despite extended reaction times and strong acidic conditions, no

reaction was observed. An asymmetric version of the Mannich reaction was also

explored, using Ellman's sulfinamide,[108, 109] which is known to provide reaction

products with high stereoselectivity. Another advantage of this reagent is the fact that

the protecting group can be removed easily. This transformation was briefly explored

but was unsuccessful despite multiple tries (Scheme 2.16).

Scheme 2.16

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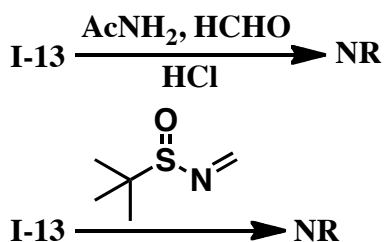
[d] This protocol can be found in the experimental part.

2.3.2.3 Attempted Nucleophilic Addition to the N-Boc Mannich Base

With the *N*-Boc Mannich base **I-15** in hand it was explored whether an acetate

carbanion or its synthetic equivalent could undergo nucleophilic addition into the

carbonyl group of compound **I-15** (Scheme 2.17). If that reaction was successful,

removal of the Boc group, followed by a transamidation reaction should provide 5,6-

dihydropyridine-2(1*H*)-one **VIII**.

Scheme 2.17
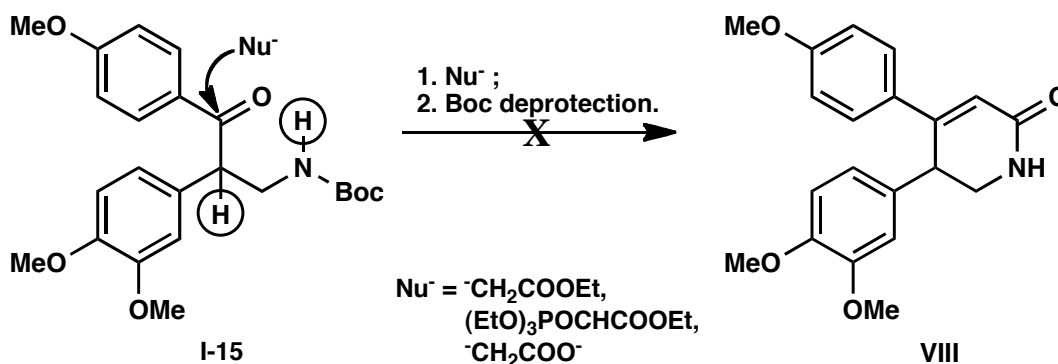
However, somewhat to our surprise, neither the aldol reaction nor Horner -

Wadsworth-Emmons or Wittig reactions successfully led to the desired product. Not

even the strongly nucleophilic acetate dianion (Ivanov reagent) reacted with the

ketone. Only starting material was recovered from this reaction. This outcome could

be a result of the deprotonation of the two highly acidic protons in **I-15** (circled),

which prevented nucleophilic addition. The only nucleophile that reacted with **I-15**

was Tebbe reagent (μ-chloro-μ-methylene-bis(cyclopentadienyl)

titaniumdimethylaluminum) (Scheme 2.18).[110, 111]

Scheme 2.18
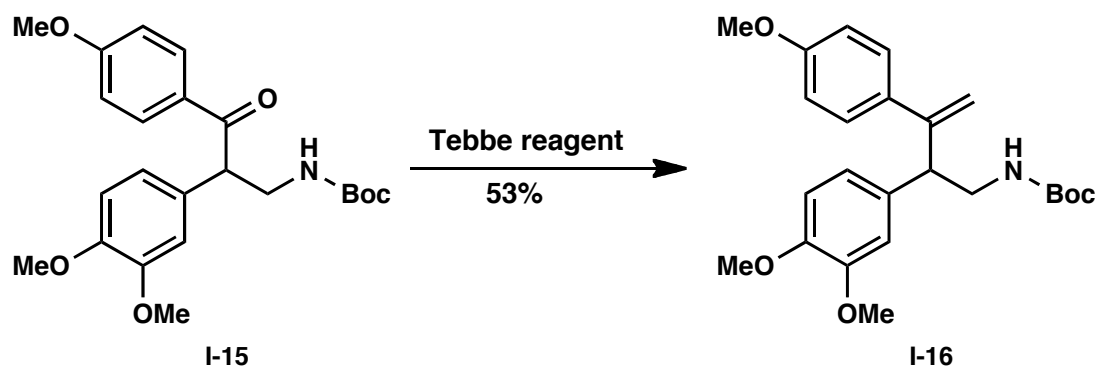
These unexpected difficulties required a revision of the original synthetic plan

show in Scheme 2.17. In the new approach the reaction sequence starting from ketone

I-15 to structure **VIII** was reversed. The Boc group would be first deprotected, then

the free amino group would be acylated, and subsequently subjected to an

intramolecular aldol reaction. Accordingly, compound **I-15** was treated with

trifluroacetic acid (TFA) to effect Boc group removal. Gratifyingly, the possible

Hoffman elimination product (Scheme 2.14) was not found.

A wide variety of acylation conditions (EDCI coupling, acyl chlorides, acyl

anhydrides) were then attempted. None of these standard conditions led to the

desired product. However, reaction of the amine with an excess of acetic anhydride

(>10 equivalents) yielded the diacylated (not the monoacylated) product **I-17**

(Scheme 2.19) as determined by NMR and verified by X-ray crystallography.

Scheme 2.19

I-15 → 1. TFA, 2. Et$_3$N, DMAP, Ac$_2$O, 60% → I-17
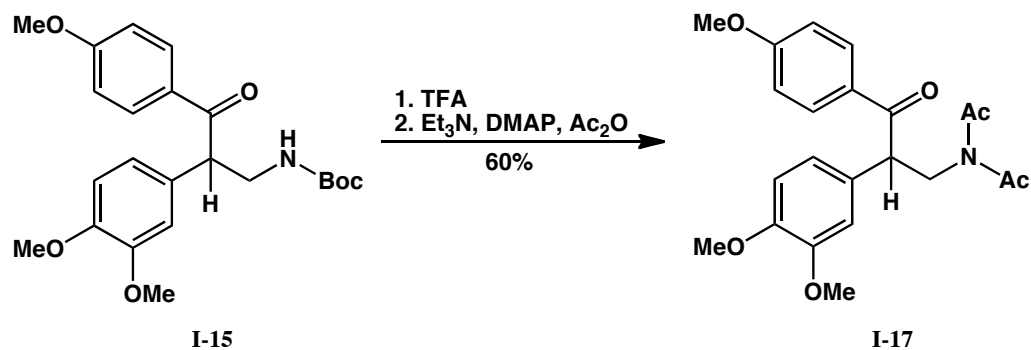
With compound **I-17** in hand, cyclization was explored to form the desired

5,6-dihydropyridine-2(1*H*)-one (Table 2.2).[112, 113] However, an aldol reaction was not

observed under either acidic or basic conditions.

Table 2.2. Attempted Intramolecular Aldol Reactions

Conditions	Results
K$_2$CO$_3$, DMF, RT	unidentified products
HCl, EtOH, reflux	unidentified products
NaH (excess), Br(CH$_2$)$_3$Br, THF, reflux	deacylation

A silylative version of the aldol reaction caught our attention and the reported protocol was followed (Scheme 2.20).[114] Gratifyingly, this reaction occurred to give a product in quantitative yield. The product was identified as compound **I-18** through NMR examination, although it was somewhat surprising that the labile TMS group was retained on the tertiary alcohol moiety.

Scheme 2.20
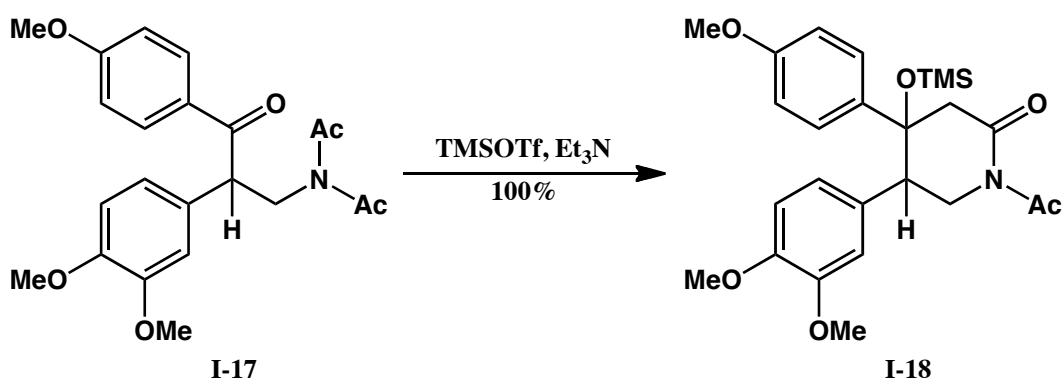
With intermediate **I-18** in hand, future synthetic steps towards the tyloindicine F total synthesis include de-acetylation, cyclization, TMS deprotection and dehydration.

In summary, intensive efforts towards the total synthesis of tyloindicine F have been made.[e] Two synthetic routes were proposed and explored. Advanced intermediates were synthesized in both routes. Further studies on the total synthesis of tyloindicine F are ongoing in our research group.

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[e] The author also attempted other synthetic routes that are not covered in this dissertation.

Part II

Palladium-Catalyzed C−H Functionalization of β-Enaminones

Chapter 3. Oxidative Hiyama Coupling Reactions of β-Enaminones

3.1. β-Enaminone – A Push-Pull Olefin

3.1.1. Electronic Property

Olefins are among the most common functional groups in organic molecules. Thus, their chemical properties have been thoroughly studied.[115, 116]

The chemical reactivity of olefins is a result of the π bonding interactions between 2p-orbitals of carbon atoms. π Bonds, by themselves, are moderately susceptible to electrophiles (Figure 3.1, A). The carbon-carbon double bond is unpolarized if the carbon atoms at both ends are identical. This character is best reflected in the IR spectrum – no symmetrical vibration pattern of a carbon-carbon double bond is seen for symmetrical olefins (Figure 3.1, B). When this physical phenomenon is translated into chemical reactivity, little regioselectivity is observed for electrophilic addition reactions of simple aliphatic olefins[115] (Figure 3.1, C).
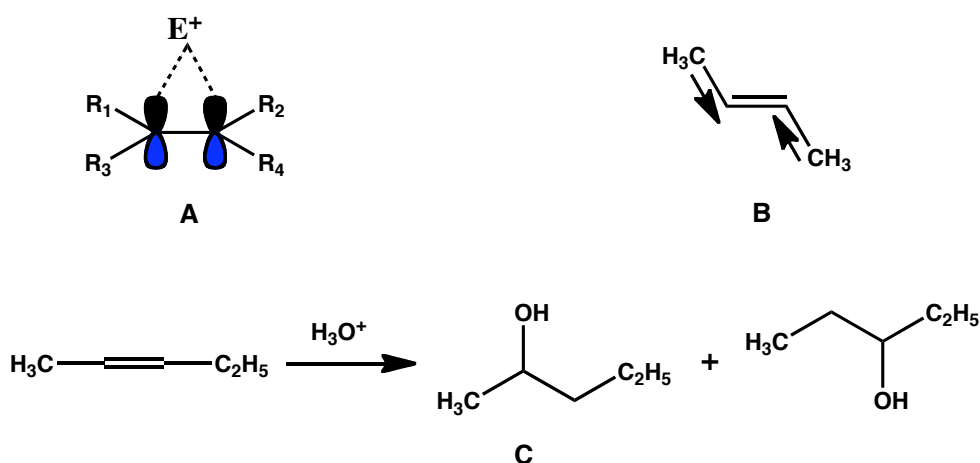
Figure 3.1. Properties of an olefinic bond

The regioselectivity of electrophilic addition to alkenes can be altered by the presence of certain functional groups, which polarize the double bond. As a result, the electronic distribution of the π bond is no longer equal between the two participating carbon atoms.

A carbon-carbon double bond may be connected to either an electron-withdrawing/pulling group (EWG) or an electron-donating/pushing group (EDG). Typically, an electron-withdrawing group exerts its influence through an *inductive effect*[117] or *conjugation*[118] whereas an electron-donating group works primarily via *conjugation*.[119, 120] Therefore, a substituted olefin can act as either a nucleophile or an electrophile (Figure 3.2).

A. Nucleophilic olefins   **B. Electrophilic olefins**
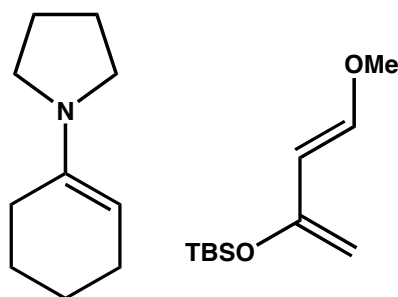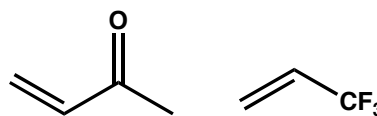
Figure 3.2. Electronic attributes of different categories of olefins

There can be a maximum of four groups linked to a given carbon-carbon double bond. Any of these groups could be electron donating or withdrawing.

Depending on how the EWG(s)/EDG(s) and the olefin part are connected, the net electronic outcome of a multi-substituted olefin varies from highly electrophilic to highly nucleophilic (Figure 3.3).
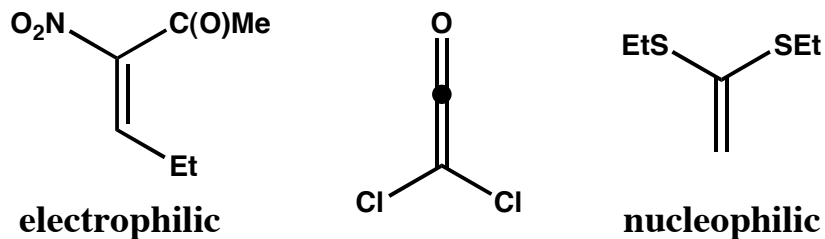
Figure 3.3. Examples of multi-substituted olefins

EWGs and EDGs function in opposite ways. When placed at the same side of a carbon-carbon double bond, they tend to cancel out the electronic influence of each other. In contrast, when positioned at the opposite end of a carbon-carbon double bond, they reinforce each other electronically (Table 3.1).

Table 3.1. Interaction of Multiple Electronic Groups
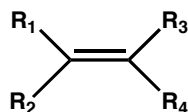
	EWG_g	EWG_v	EDG_g	EDG_v
EWG	+	-	-	+
EDG	-	+	+	-

EWG, electron-withdrawing group; EDG, electron-donating group; g, germinal (1,1-) position; v, vicinal (1,2-) position; +, synergistic; -, antagonistic. R$_1$, R$_2$, R$_3$ and R$_4$ can be either electron-withdrawing or electron-donating.

In particular, groups of the same electronic attributes (EWG/EWG or EDG/EDG) at the same carbon (geminal) and groups of opposing electronic characteristics (EWG/EDG) at the neighboring carbons (vicinal) both have additive effects. The latter, because of its electronic distribution pattern, is termed as a *push-pull olefin*. The olefinic bond inside a *push-pull olefin* is highly polarized.

β-Enaminones[121] (also called β-ketoenamines or γ-oxoenamines) fall into this push-pull category. An electron-donating amino group pushes the olefin at one end while an electron-withdrawing carbonyl group pulls it at the other end. β-Enaminones may be viewed as the monoenamines of 1,3-dicarbonyl compounds or as vinylogous amides. Thus, with regard to their structure and reactivity, β-enaminones possess the general aspects of both enamines and enones. Typically, the enamine moiety is regarded as the parental chemical group from which β-enaminones are derived and the carbon numbering of α or β is based on the enamine part rather than the enone part (Figure 3.4).
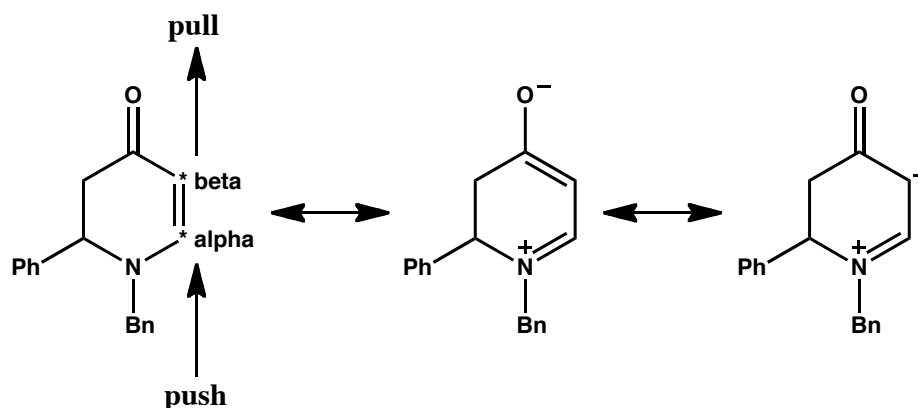
Figure 3.4. β-Enaminone, a push-pull olefin

3.1.2. Structure[122]

The β-carbonyl group endows the enamine with unique features. All three functional groups in an β-enaminone molecule – the amino group (non-bonding orbital), the olefin (π-bonding orbital) and the carbonyl group (π-bonding orbital) are in conjugation (*mesomeric effect*). Hence, for a tertiary β-ketoenamine/β-enaminone, the n-π interaction demands co-planarity of all the eight atoms involved – one N, one O, and six Cs. This has been shown by X-ray structural determination in a related case.[123] This configuration is different from a typical enamine, in which the nitrogen atom adopts a pyramidal configuration.[122, 124]

This electron delocalization also alters other characteristics of β-enaminones. The order of the double bond is decreased (< 2) while the bond length is increased. At the same time, the rotational barrier is lowered significantly ($\Delta G^{\neq} = 50 - 70$ kJ/mol) compared with that of an average alkene ($\Delta G^{\neq} = 260 - 270$ kJ/mol).[125] In addition, the

C_{olefin}-C=O bond and C_{olefin}-N bond, both possess double bond characteristics; that is, shorter bond length and a significant rotational barrier.

Since all three bonds in an β-enaminone structure have rotational barriers, each of them could adopt an E or Z configuration. Dynamic NMR is the primary tool to determine the major conformers,[125] as movement over the rotational barriers can be observed on the NMR time scale.[126, 127] There are up to eight major conformers possible for this molecule.[125] Primary or secondary acyclic β-enaminones, can form a six-membered pseudo-ring in aprotic solvents as a result of intramolecular hydrogen bonding. Tertiary enamine derivatives adopt the E configuration at the olefinic double bond. For cyclic β-enaminones, either endocyclic or exocyclic, all bond configurations are determined by the ring system (Figure 3.5).[121]
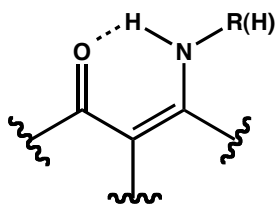
1°, 2° beta-enaminone   **endocyclic beta-enaminone**
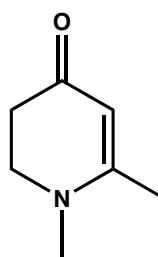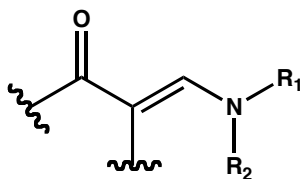
3° beta-enaminone   **exocyclic beta-enaminone**
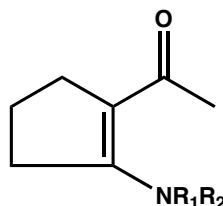
Figure 3.5. Configurations of different β-enaminones

3.1.3. Reactivity

3.1.3.1. Physical Organic Chemistry

In terms of π electron delocalization, push-pull olefins are analogous to di-substituted phenyl rings with push-pull electronic pairs at the para positions (Figure 3.6).
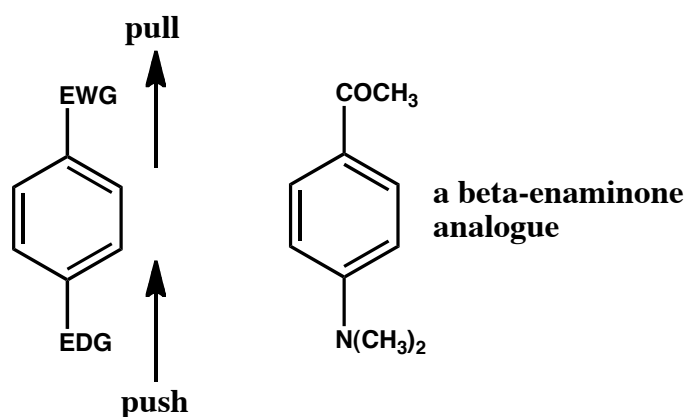
Figure 3.6. Example of a push-pull aromatic system

The Hammett equation,[128] developed in the 1930's, provides a quantitative description regarding the electronic influence of a variety of substituents on the reaction rates of benzene derivatives with electrophiles and nucleophiles. It describes a linear free-energy relationship concerning equilibrium constants and reaction rates in aromatic systems. It has been used widely for correlating the thermodynamic or kinetic behavior of EWGs/EDGs in different reactions.[129]

There are two factors in the Hammett equation — the substituent constant (σ) and the reaction constant (ρ). Since the value of the substituent constant σ illustrates the electron withdrawing/donating capability of a certain functional group, the difference between the σ values of EWG(s) and EDG(s) ($\Delta\sigma$) can be established as a marker of the polarity of a push-pull olefin.

As far as β-enaminones are concerned, the amino group and carbonyl group are conjugated. As a consequence, this synergic effect prompts the use of σ^+ value for the carbonyl group and σ^- value for the amino group, rather than their regular σ values ($\sigma_{CH3CO} = 0.47$, $\sigma_{NH2} = -0.30$). Therefore, the $\Delta\sigma$ value of β-enaminones is calculated as [σ^-_{CH3CO} (0.82) - σ^+_{NH2} (-1.30)], equal to 2.12. Numerically, the value of σ^-_{CH3CO} is among the largest of electron withdrawing groups whereas that of σ^+_{NH2} is almost at the top of all electron-donating groups. As a result, the remarkably large $\Delta\sigma$ value of β-enaminones reflects the unusually high polarity of their π-electron system and accounts for their fairly high chemical reactivity (*vide infra*).

As for the reaction constant ρ, it is theoretically applicable to push-pull olefins as well, where nucleophilic reactions and electrophilic reactions carry opposite signs and their values can be determined experimentally. Overall, the linear free energy relationship has not been extensively studied in non-aromatic systems, with only few exceptions.[130, 131]

3.1.3.2. Common Reactions[122, 124, 132-134]

The highly polarized nature of β-enaminones makes them reactive toward both electrophiles and nucleophiles (Figure 3.7).
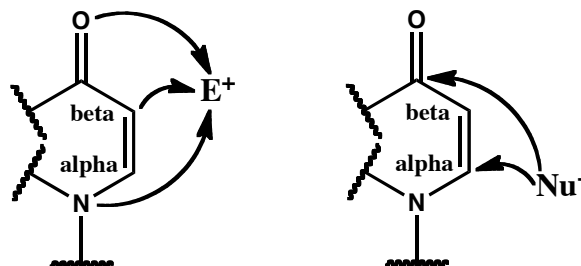
Figure 3.7. Potential reaction sites of β-enaminones

In an β-enaminone molecule, there are three possible sites of electrophilic reactions – the carbonyl oxygen atom, the β-carbon atom, and the nitrogen atom. Reactions at each of these positions have been described.[121, 125] The regiochemistry of the reaction depends on the nature of the electrophile and the solvent. Electrophiles that have been used include alkyl halides, acyl halides,[f] ketones, iminium ions, or isocyanates (Figure 3.8). Additionally, if the α carbon in an β-enaminone is unsubstituted, a reaction with an electrophile can also take place at the so-called β' position.[135]

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[f] These are essentially the non-aromatic versions of the Friedel-Crafts reaction.

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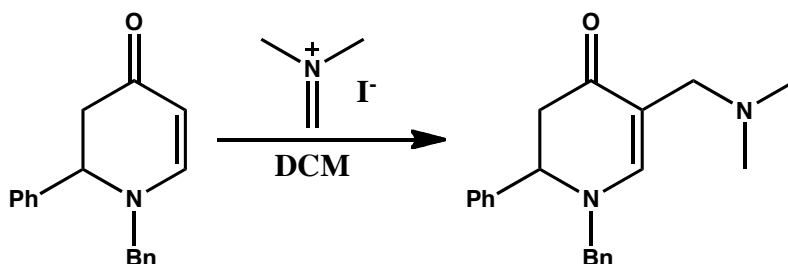
Figure 3.8. Reaction of an β-enaminone with an iminium electrophile

β-Enaminones are subject to 1,4-nucleophilic attack with nucleophiles such as Grignard reagents and hydrides.[121, 132] The resulting enolate can be trapped, for example, with Comins reagent.[136] In addition, β-enaminones can undergo radical,[137] photochemical,[138] and cycloaddition reactions.[139] Last but not the least, β-enaminones are prone to acidic decomposition in the presence of most mineral and organic acids.[140]

3.1.4. Preparation[133, 134]

β-Enaminones can be prepared in many ways.[121, 132, 134] The most straightforward method is to react 1,3-dicarbonyl compounds with 1° or 2° amines.[141] Other routes involve condensation between C−H acidic compounds and *N,N*-dimethylformamide dimethyl acetal (DMFDMA)[142] or enamine acylations.[143] 1,2-Oxazole ring opening can also lead to β-enaminone formation.[144]

For our intended studies, various β-enaminones were required. Two approaches different from the ones described above were used to meet this goal. They

are discussed below.

The Comins group developed an excellent protocol for the assembly of endocyclic β-enaminones[145] that we employed for the preparation of our starting materials (Scheme 3.1). Accordingly, *N*-benzyl-4-pyridone was prepared by alkylation of 4-methyoxypyridine followed by hydrolysis, pyridone silylation and reaction with phenylmagnesium bromide. After a weakly acidic work-up, the *N*-substituted tertiary enaminone was obtained.

Scheme 3.1. Comins Synthesis of 1-Benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one
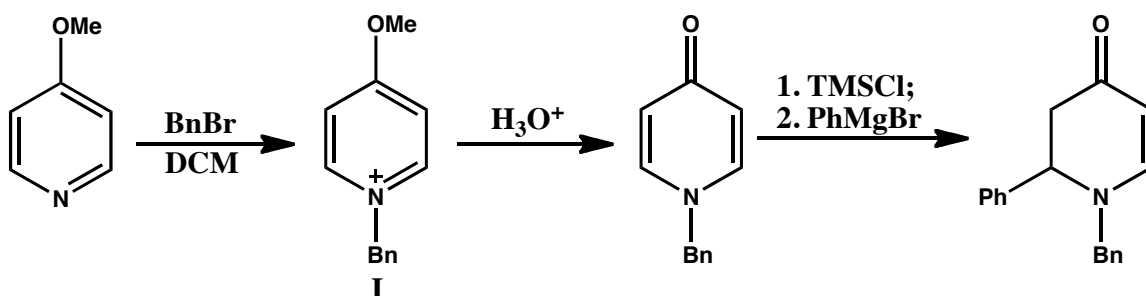
Several observations were made when carrying out this reaction sequence that are worth mentioning. We hypothesized that a direct Grignard addition to pyridinium **I** (without hydrolysis and silylation) could potentially provide the same dihydropyridinone product after acidic workup. This hypothesis, however, turned out to be wrong. Despite several attempts at this reaction, only decomposed reaction products were found.[146] Also, due to the instability of β-enaminones to acids, extra caution must be taken to avoid over-acidification during the work-up.

Previously an β-enaminone synthesis protocol using β-amino acids was developed in our research group,[147] which was used in the present work to synthesize a bicyclic β-enaminone (Scheme 3.2).

Scheme 3.2. Georg Synthesis of 7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one
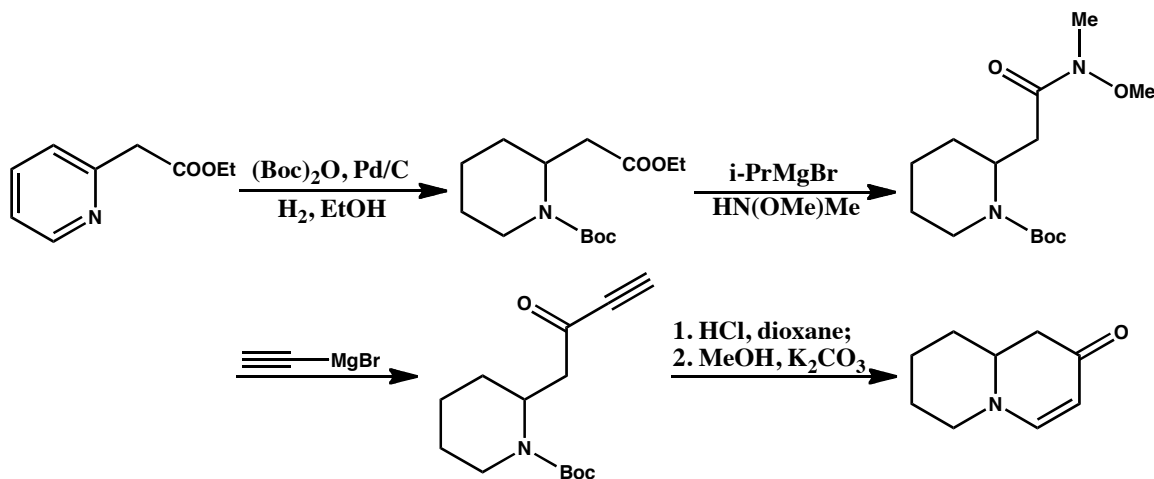
Commercially available ethyl 3-pyridinylacetate was hydrogenated in the presence of Boc anhydride to furnish the Boc-protected β-amino acid ester, which was converted to the Weinreb amide. After Boc deprotection, the amino group underwent a formal conjugated addition reaction to the ynone moiety,[g] to form the cyclic β-enaminone.[147]

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[g] The actual cyclization process was proposed as follows. The chloride adds into the ynone first, forming a β-chloro α,β unsaturated ketone (enone). Then the free amino group reacts with this intermediate via a sequential Michael addition – retro Michael addition, yielding the enaminone. For a detailed account, refer to the reference cited in this paragraph.

3.2. Carbon-Hydrogen Bond Functionalization

3.2.1. Introduction

In synthetic organic chemistry, the discovery of new carbon-carbon bond forming reactions is one of the most important research areas. The armory of classical reactions includes transformations such as the aldol condensation, Diels-Alder reaction, and free radical cyclizations, to name only a few.

These reactions proceed through various reaction mechanisms and have been used for the synthesis of many different types of organic molecules. They have in common that a nearby polarizable functional group is essential for reactivity. These could be a carbonyl group, an unsaturated bond, or a halogen atom. Another common feature for all these examples is that all of them could take place without participation of transition metals.

3.2.2. Transition Metal-Catalyzed Cross Coupling

3.2.2.1. Background

In general, the term coupling reaction refers to the joining of two hydrocarbon fragments, predominantly under the catalysis of a metal. Examples of facile homocoupling reactions include the McMurry coupling, the Wurtz reaction, and the Ullman reaction.

Since their beginnings in the mid 1970s, cross coupling reactions have had a very significant impact on the field of organic synthesis, because novel carbon-carbon bond-forming strategies could be developed. Certain difficult reactions in classical

syntheses, e.g. the formation of a new chemical bond between unsaturated carbon

centers, can be carried out easily using novel cross-coupling reactions. A general

scheme of a transition metal-catalyzed cross coupling reaction is presented (Figure

3.9).

X = Cl, Br,
    I, OTf, ...

M = Li, Mg, Zn,
    Sn, B, Si, ...
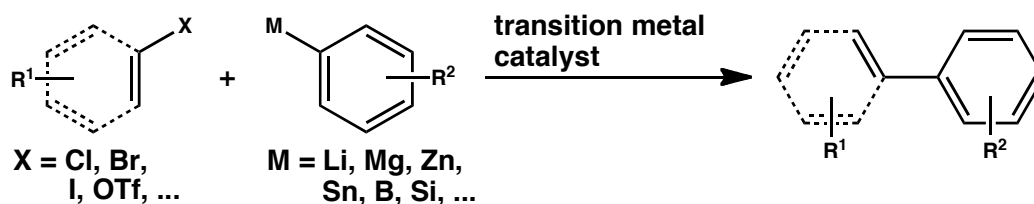
Figure 3.9. A cross coupling reaction

A typical cross-coupling reaction takes place between an organometallic

reagent and a vinyl or aromatic halide, promoted by a late transition metal. Although

seemingly proceeding via nucleophilic substitution, it has a distinctive reaction

pathway (Figure 3.10). A transition metal (M_t, palladium for example) with an

oxidation number i has to possess two empty d orbitals in order to initiate a cross

coupling reaction. Usually this is realized in a dissociative fashion. A cross coupling

catalytic cycle consists of four sequential steps. In step one, the transition metal

inserts in between the aromatic group Ar_1 and the halide X while breaking the bond

connecting them. Since the oxidation number of transition metal M_t is i+2, this step is

referred to as *oxidative addition*. The intermediate *A* from this step then goes through

transmetallation, where a ligand exchange takes place with the aromatic group Ar_2

replacing the halide X. A byproduct, salt MX, is produced in step two. Next, given a

characteristic square planar configuration of M_t (*B*), a *trans-cis isomerization* step

must occur (formation of *C*) to permit the following step – *reductive elimination*.

During this last step, the final cross coupling product Ar_1-Ar_2 (*D*) is released and the

transition metal catalyst M_t is regenerated with the oxidation number i therefore

reduced and ready for the next catalytic cycle.
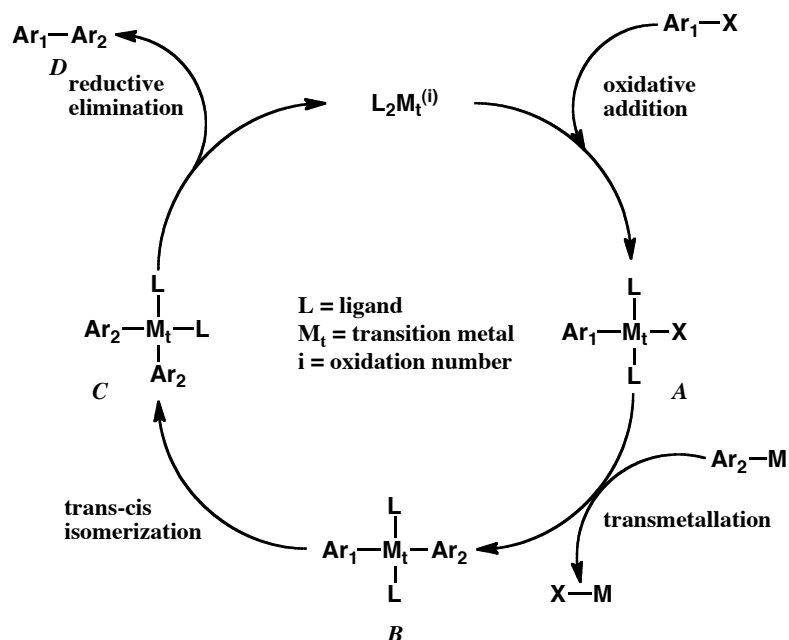
Figure 3.10. Mechanism of a cross coupling reaction

Due to the importance of these reactions nearly every main group metal

element has been investigated for its potential in cross-coupling reactions. Reagents

that were explored early on are organolithium reagents, organomagnesium (Grignard)

reagents (Kumada coupling), and organozinc reagents (Negishi coupling). Usually,

the coupling proceeds well in spite of numerous potential side-reactions. However, functional group compatibility is always a concern when one plans to apply a coupling reaction to the synthesis of a complex molecule. The organometallic reagents mentioned here are nucleophilic and therefore incompatible with a carbonyl group and similar functional groups. In addition, the preparation and storage of these reagents is problematic, due to their instability in the presence of air and moisture.

Accordingly, attention has been directed to more stable organometallic reagents and even some non-metal reagents. With larger electronegativity of the non-carbon part, these reagents are stable and able to co-exist with sensitive functional groups. In this regard, organotin reagents (Stille), organoboron reagents (Suzuki-Miyaura) and organosilicon reagents (Hiyama) stand out as preferred coupling partners, which is a result of intensive studies during the past two decades.

As the organic halide component of the cross-coupling reaction, most often bromide, iodide, and common halogen-like or pseudo-halide groups including trifluoromethanesulfonate (triflate) are employed, whereas chloride and phosphate are used less frequently. As far as catalysts are concerned, palladium is often the catalyst of choice. The examination of other transition metals (nickel, iron, etc.) as catalysts is still under way. The choice of matching ligand(s) is pivotal in determining the success of a particular catalytic system.

3.2.2.2. Cross Hiyama Coupling[148-151]

Every class of organometallic reagents has its pros and cons. Silicon, the second most abundant element on earth, has long been used in the semi-conductor industry. It serves an indispensable role in electronics and information technology.[h] Nevertheless, as a coupling partner in cross coupling reactions, organosilanes are intrinsically inert. In comparison to other organometallic elements, silicon is more electronegative and therefore the carbon-silicon bond is less polarized and harder to break. To enable silicon to perform the transmetallation step (*vide infra*), it is crucial that a pentavalent silicate is formed. Efforts made by many groups showed that certain silane derivatives are effective coupling partners in the Hiyama coupling reaction (Figure 3.11).
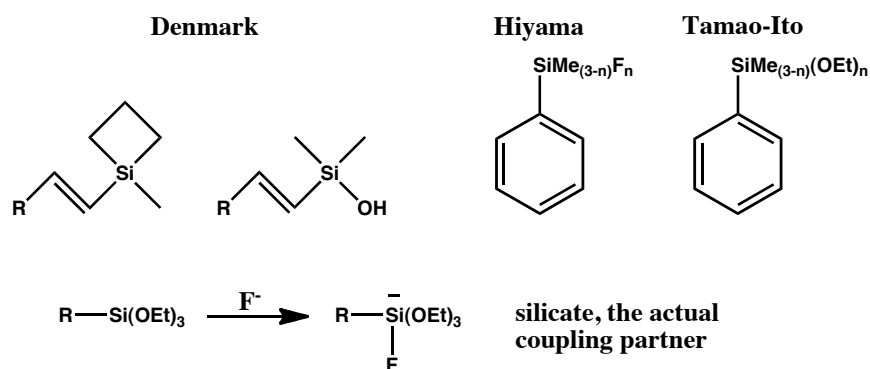
Figure 3.11. Different Hiyama coupling partners

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[h] This is what "silicon valley" refers to.

The typical Hiyama coupling proceeds in accordance with the general cross coupling pathway – oxidative addition, transmetallation, cis/trans isomerization, and reductive elimination (Figure 3.10). To generate the required pentavalent species, an external activator is needed. Fluorides, and sometimes oxygen-based activators, are used because the new F-Si/O-Si bond is among the strongest chemical bonds known, promoting the coupling reaction thermodynamically.

As a relatively new type of cross coupling reaction (1990's), the Hiyama reaction has a unique substrate scope and its own advantages. Organosilicon compounds are ultimately environmentally benign as their final oxidation product is silica gel. The aforementioned electronics industry has boosted the availability of organosilicon reagents. The silicon moiety can be carried through multi-step syntheses. Rarely discussed but also important, is that silicon provides a stereo center (in contrast to boron) that can be used to direct asymmetric syntheses.

3.2.3. Carbon-Hydrogen Bond (C−H) Functionalization

3.2.3.1. Background

Technically, C−H functionalization refers to any reaction where a carbon-hydrogen bond is replaced with a new chemical bond, such as a carbon-carbon, carbon-oxygen, or carbon-nitrogen bond.

Carbon-hydrogen bonds are among the most common chemical bonds in organic molecules. However, in classical chemical reactions, the carbon-hydrogen bond is not regarded as a functional group. Hydrogen is more electronegative than

most other elements in the periodic table, including some non-metals, with a Pauling electronegativity value of 2.20. The short length of a C−H bond implies a large bond energy. This fact is consistent with the observation that saturated hydrocarbons are essentially inert in traditional chemical reactions. Furthermore, carbon-hydrogen bonds are ubiquitous in the organic world. Even if they are made reactive under certain circumstances, how to differentiate among the various C-H bonds in a molecule remains a major problem in developing C−H functionalization reactions. Pragmatically, there is very little space to maneuver in terms of chemoselectivity and regioselectivity, given that the difference among various C−H bonds in alkanes is extremely small. To satisfy these two requirements, highly reactive species including free radicals[152, 153] and carbene/nitrene[154-157] have been used in a controlled manner.

3.2.3.2. C−H Functionalization on Aromatic Carbon Centers

Both free radicals[158, 159] and carbenes[154, 160] have been well studied in classical organic chemistry and new research continues to broaden their usage. When it comes to C−H functionalization, unsaturated hydrocarbons are far more reactive than saturated carbons, considering that sp^2 carbons are more electronegative than sp^3 carbons and better able to accommodate a negative charge. In classical organic chemistry, at least two classes of carbon-carbon bond-forming reactions, the Friedel-Crafts reaction and the heteroatom-directed α metallation, could be considered as the prototype of C−H functionalization reactions.

As of this writing, the field of cross-coupling reactions is progressing rapidly.[i]

New catalyst/ligand systems are reported frequently and rarely is the total synthesis of

a complex organic molecule executed without the use of a cross-coupling reaction.

New directions including the development of environmentally-friendly reactions,

simple operations, and highly efficient transformations. Based on the notion of C−H

functionalization, *direct-coupling reactions* have been developed (Figure 3.12).
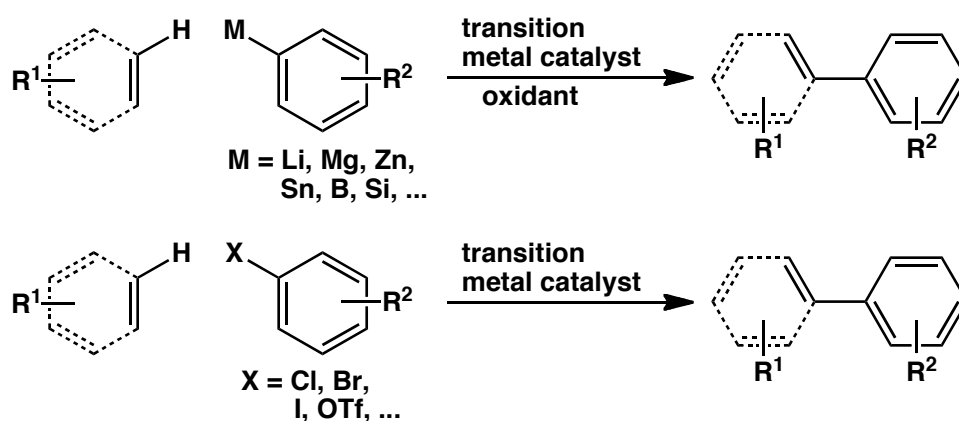
Figure 3.12. Direct C−H functionalization/coupling reactions

In a conventional cross-coupling reaction, both coupling partners are pre-

functionalized, one in the form of an organometalloid and the other one in the form of

a (pseudo)halide. As such, the polarity of the coupling partners is matched and a self-

sustaining catalytic cycle is realized. In this process, the final coupling product is

generated, along with a metal halide as by-product. In terms of atom efficiency,

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[i] A Scifinder search with "cross coupling" returned over 28,000 results. An obvious trend of the increasing number of annual publications on this key word can be found since the 1970's. The number is given here for the past five years: Year 2005, 1853; Year 2006, 2012; Year 2007, 2251; Year 2008, 2398; Year 2009, 2469.

however, this is not the best option, since it can take multiple steps for the preparation

of both starting materials. Both the metal and the halide need to be placed at the

desired positions of their respective unsaturated systems. This could be difficult to

achieve and therefore such processes could be inefficient or impractical, especially

for industrial applications. When the coupling reaction is finished, though, these pre-

functional groups are no longer present in the final product. At the same time, a new

by-product that is potentially hazardous is produced. Altogether, the net result of a

multi-step operation is the substitution of an alkyl or aryl group at the position of a

particular hydrogen atom. Thus, for an arylation reaction, a more straightforward

approach would involve the reaction of an unfunctionalized arene with a metalloid or

halide, yielding the same coupling product (Figure 3.13).
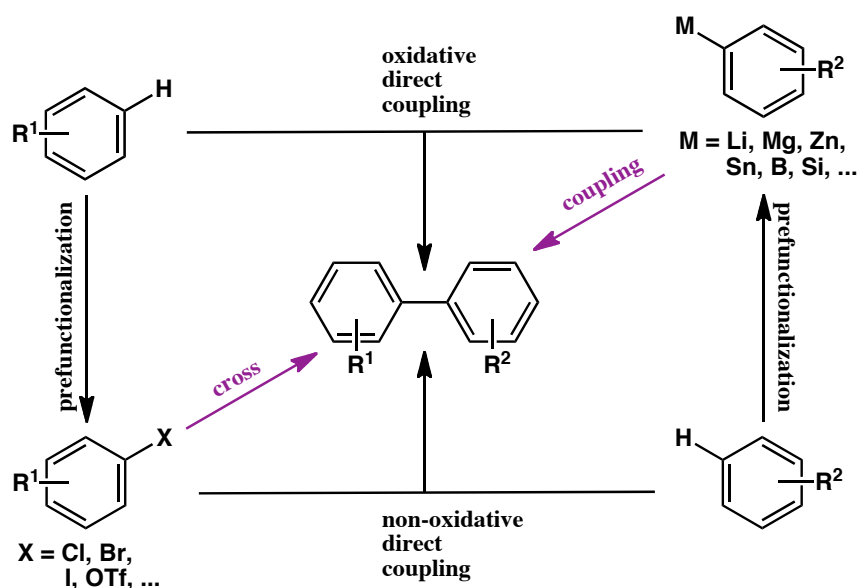
Figure 3.13. Direct coupling vs cross-coupling

Atom economy (or efficiency)[161] is defined as (molecular weight of the desired product)/(molecular weight of all products) x 100%. As shown in Figure 3.14, a direct Hiyama coupling reaction has a significantly higher atom economy (53%) than the corresponding Hiyama cross coupling reaction (39%).
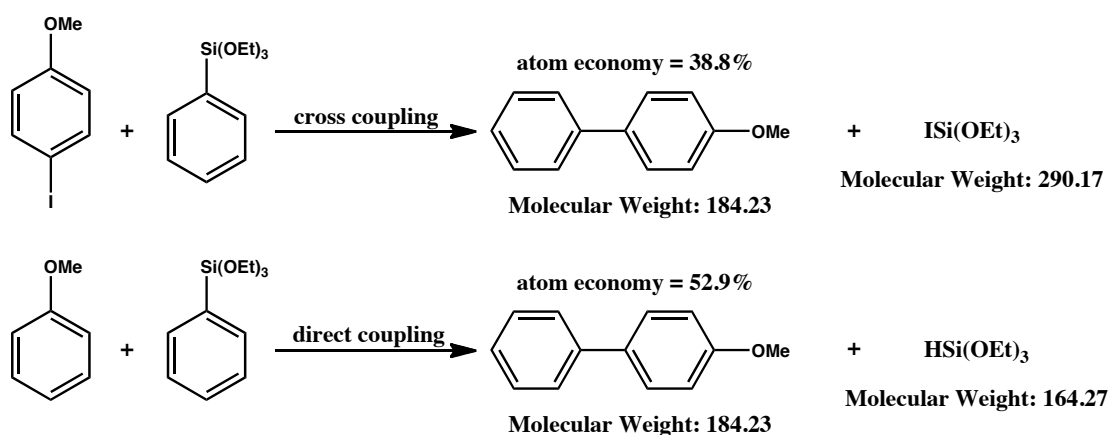
Figure 3.14. Comparison of atom economy between direct- and cross-coupling

This direct transformation fits the definition of a C−H functionalization. Significant progress has been made in the past decade in this field. Protocols for both undirected and directed C−H functionalization/coupling reactions have been developed and some examples are shown (Figure 3.15).

A. Undirected, electron-rich heteroarene

0.5 mol% Pd(OAc)$_2$
5 mol% benzoquinone
1.3 equiv THBP
Ac$_2$O/AcOH, 50 °C

B. Undirected, electron-poor arene

Pd(OAc)$_2$ (5 mol%)
P^{t}Bu$_2$Me-HBF$_4$ (10 mol%)
K$_2$CO$_3$ (1.1 equiv)
DMA, 120 °C

C. Directed

5 mol% Pd(OAc)$_2$
Ph$_2$IBF$_4$ (1.1 equiv)
AcOH
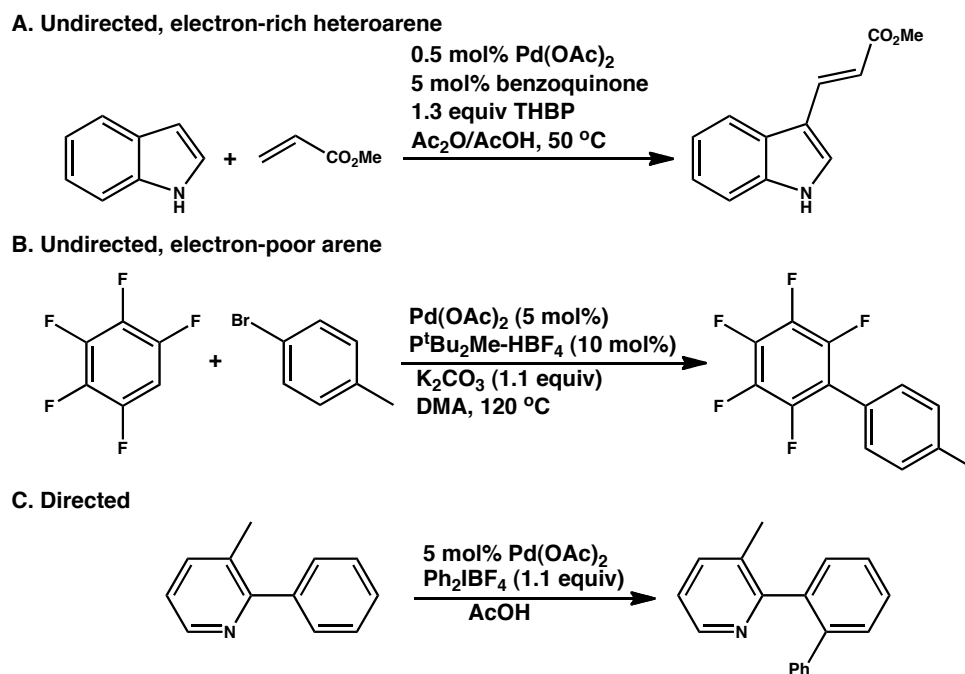
Figure 3.15. C−H functionalization without and with a directing group

The π electrons of arenes and heteroarenes can occupy the empty d-orbitals of a transition metal and therefore serve as good ligands of transition metals (Figure 3.15, A).[162] For electron-rich π systems, an electrophilic metallation process would take place; while for electron-poor aromatic systems, a deprotonation step might be involved. (Figure 3.15, B).[163] As for directing groups, the formation of a five or six-membered metallocycle is required (Figure 3.15, C).[164]

In contrast to cross coupling reactions, these processes do not involve a typical oxidative addition-transmetallation-reductive elimination catalytic cycle. Therefore, the oxidative addition of a transition metal into a carbon-hydrogen bond is

termed "C−H activation" in order to stress the uniqueness of this chemistry (Figure 3.16).[165, 166]
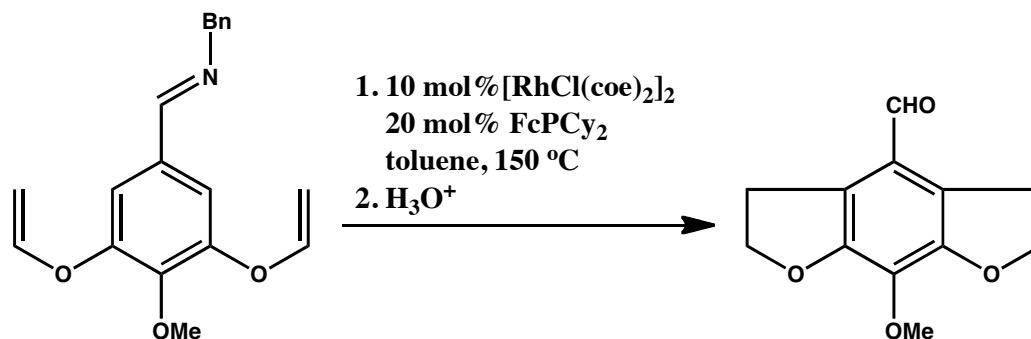
Figure 3.16. C−H activation reaction

3.2.3.3. Direct Hiyama Coupling

Taking into consideration the many benefits of organosilicon reagents over other organometalloids, the direct Hiyama coupling is an important reaction and thus worth studying. Most recently, two cases have been reported (Figure 3.17).[167, 168]
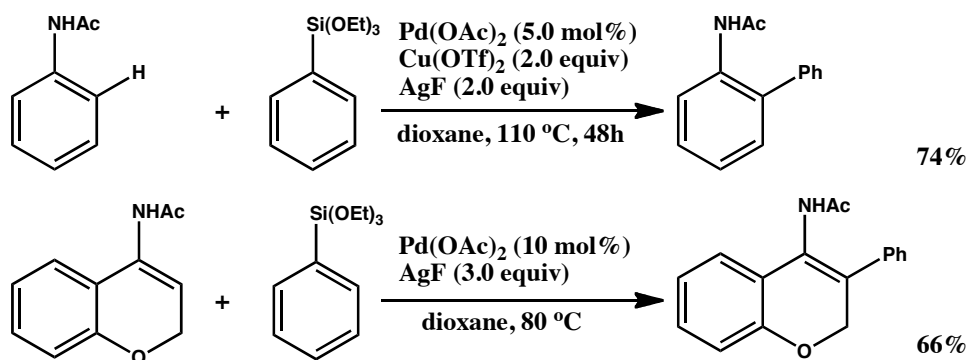
Figure 3.17. Examples of direct Hiyama coupling reactions

In a direct Hiyama coupling reaction (Figure 3.18), electrophilic metallation takes place, resulting in the same intermediate (*A*) obtained from oxidative addition in cross coupling reactions. This intermediate then enters the catalytic cycle, furnishing the coupling product and the regenerated catalyst. If an organometalloid is utilized as the coupling partner, an oxidant is then required to convert the transition metal catalyst back to its starting oxidation state. Most of the time, the use of a base is redundant since no deprotonation is required in the catalytic cycle although occasionally, for electron-deficient arenes,[163] a deprotonation procedure cannot be avoided.
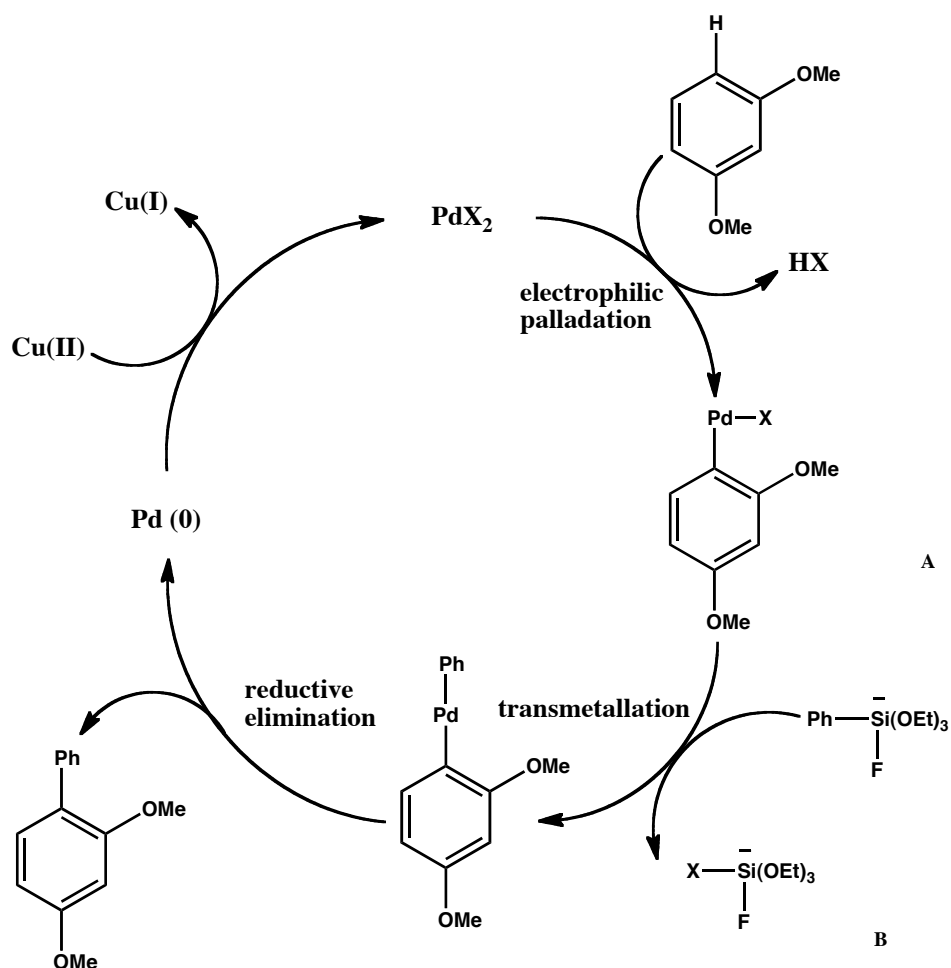
Figure 3.18. Mechanism of the direct Hiyama coupling

3.3. Oxidative Hiyama Coupling of β-Enaminones

As push-pull olefins, β-enaminones can react with nucleophiles (alkylation) and electrophiles (acylation). The electrophilic reactions proceed at the β position of the β-enaminones in a "Friedel-Crafts like" manner. Recently, a direct Suzuki coupling on the β position of β-enaminones was discovered in our group.[169] We therefore decided to investigate whether a direct Hiyama coupling of β-enaminones

could also be achieved, despite the fact that the direct Hiyama coupling has never

been realized in a non-aromatic system in a non-directed fashion.

Another well-known organic reaction, the Wacker oxidation, provides

directions for developing such a transformation.[170, 171] The Wacker oxidation refers to

the palladium (II) oxidation of olefins, primarily terminal olefins, to their

corresponding ketones with a copper (II) salt as the co-oxidant in open air and water

(Figure 3.19). The fact that the Wacker oxidation was the first organometallic

reaction applied on an industrial scale can be attributed to many factors including the

facile conversion, the ease of operation, and the mild reaction conditions.

Figure 3.19. Examples for Wacker oxidations

In a Wacker-type reaction, the alkene binds to the Pd (II) species reversibly as

a mono-dentate ligand. The interaction is between the π electrons of the alkene and

one of the empty d orbitals of palladium (II). It can be seen as a Lewis acid-base

complex as well. After this activation step, the olefin becomes electro-deficient,[j]

ready for the attack by nucleophiles. A nucleophile, for instance water, approaches

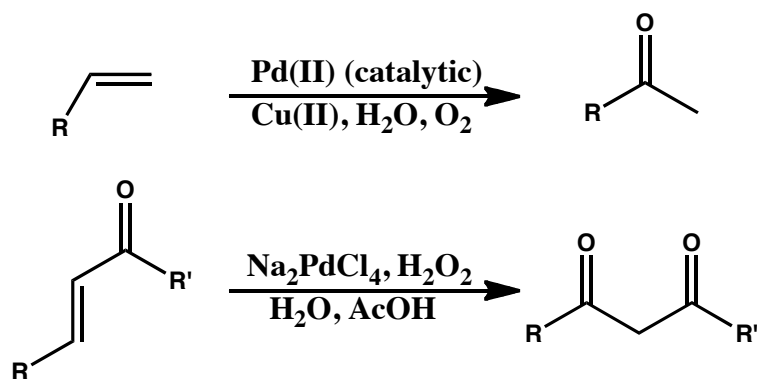the olefin from the opposite side of the palladium (II) ion in a trans-addition mode on

the more substituted carbon. Upon the completion of the nucleophilic addition, a new

carbon-palladium σ bond has formed and this σ complex is the diversification point

for a series of different possible reaction pathways. Most of the time, a syn β hydride

elimination takes place, leaving a more substituted olefin compared with the starting

material. After reductive elimination, palladium (0) is generated. Since palladium is

an expensive heavy metal, the utilization of a catalytic amount is desired due to

economic and environmental concerns, especially if this chemistry will be used in an

industrial process. Therefore, a re-oxidant system needs to be in place in order to

close the catalytic cycle. Besides the $CuCl_2/O_2$ procedure often used in industry, other

oxidative reagents have been employed, including benzoquinone and *tert*-butyl

hydroperoxide (t-BuOOH). The choice of the re-oxidant is determined by its

compatibility with the olefin, the nucleophile, and the reaction product. Because of its

operational simplicity, air oxidation would be the first choice in almost every case.

The Wacker process provides some precedence for the transition metal-

mediated direct coupling of β-enaminones (Figure 3.20). In order for this type of

coupling to ensue, initial electrophilic metallation followed by the formation of a σ-

complex has to take place. However, in the Wacker oxidation, only terminal alkenes

are effective substrates. Except for few specialized cases, internal and geminal di-

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[j] This is an Umpolung reaction, since the electron property of the olefin has been reversed.

substituted olefins react so slowly that they are considered inert substrates. The olefin moiety in an β-enaminone is by nature internal since at one end it is connected to a carbonyl group while an amino group flanks the other end.

Nevertheless, β-enaminones are doubly activated, highly nucleophilic alkenes (*vide supra)*, a property that could counterbalance the disadvantages of an internal olefin and increase the low electrophilic metallation rate suffered by other internal olefins. In addition, structurally different β-enaminones, (cis vs trans, endocyclic vs exocyclic, etc.) are expected to possess different reactivities. Last but not the least, various substituents on the β-enaminones could also influence their reactivity.
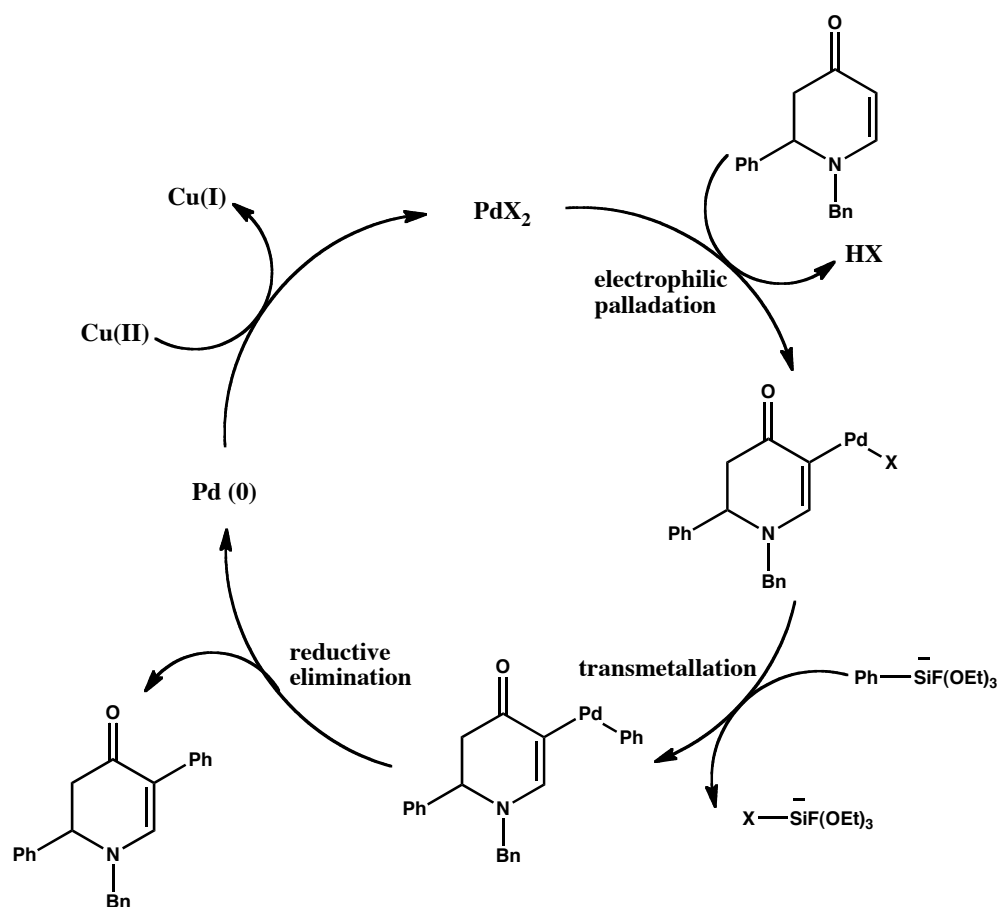
Figure 3.20. Proposed mechanism for the oxidative Hiyama coupling of β-enaminones

We decided to explore the substrate scope of both β-enaminones and organosilanes and to carry out experiments to optimize the reaction conditions of this novel transformation. As a "standard" β-enaminone we selected 1-benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one. Since the β-enaminone moiety itself is not strongly UV active, for operational ease a phenyl and a benzyl group were included in the structure. The palladium (II) catalyst – copper (II) reoxidant system that is used in the

industrial Wacker oxidation process had been tested in arene oxidative Hiyama

coupling reactions (Figure 3.17) and was therefore selected for our studies. As for the

other components, those of the classical Hiyama coupling were explored –

dichloro(methyl)phenylsilane as the coupling partner, tetrabutylammonium fluoride

(TBAF) as the activator, and tetrahydrofuran (THF) as the solvent. The reaction

temperature was initially set to 60 °C arbitrarily (Scheme 3.3).

Scheme 3.3
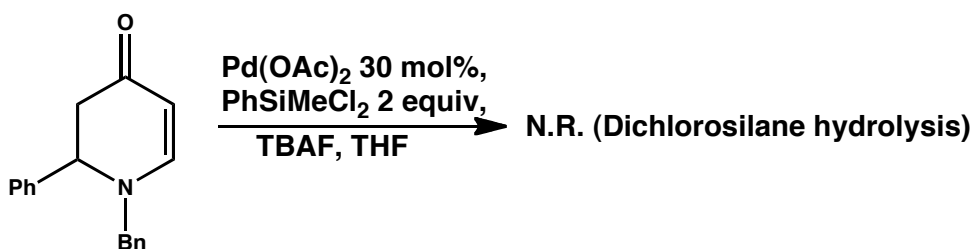
The initial attempt at this chemistry did not yield promising results. Large

amounts of the starting β-enaminone remained unreacted, and the dichlorosilane

coupling partner had completely disappeared. The hydrolytic product of the

dichlorosilane was identified, but no coupling product was observed.

Next, trialkoxysilanes were used, which are more resistant to hydrolysis and

highly activated as well. Gratifyingly, the majority of the β-enaminone and all of the

triethoxyphenylsilane were consumed and two new products were seen on the TLC

plate. They were then isolated by silica gel flash chromatography and characterized

using NMR. The lower spot proved to be the direct coupling product, albeit in a

rather poor yield. Nevertheless this result confirmed our earlier hypothesis and indicated that β-enaminones can be substrates for the oxidative Hiyama coupling. The other spot on the TLC plate with a larger R_f value was found to be biphenyl, arising from the dimerization reaction of triethoxyphenylsilane, facilitated by the palladium (II) salt (*vide infra*). This side reaction has been observed repeatedly in palladium (II)-catalyzed reactions as it lowers the effective concentration of the silicon coupling partner.

Now that the viability of this transformation was confirmed, an improved reaction protocol was sought. All reaction components were examined in this regard, including the transition metal catalyst, the re-oxidant, the activator, the solvent, and reaction temperature and time.

First, tetrahydrofuran was replaced with dioxane to allow for possibly higher reaction temperatures. Then different fluoride salts and copper (II) salts were investigated (Table 3.2).

Table 3.2. Screening of Activator/Reoxidant

Pd source	Activator	Reoxidant	T	Solvent	Result
$Pd(OAc)_2$	TBAF	$Cu(OAc)_2$	60 °C	THF	Trace
$Pd(OAc)_2$	KF	$Cu(OAc)_2$	60 °C	dioxane	Trace
$Pd(OAc)_2$	AgF	$Cu(OTf)_2$	60 °C	dioxane	Decom
$Pd(OAc)_2$	AgF	$Cu(OAc)_2$	60 °C	dioxane	30%
$Pd(OAc)_2$	CuF_2	CuF_2	60 °C	dioxane	NR

As seen in the Table 3.2, the most common fluoride sources, tetrabutylammonium fluoride (TBAF) and potassium fluoride (KF) provided product, but only in trace amounts. The use of silver fluoride did increase the yield of the coupling product, possibly due to the oxidative effect of silver (I) (Figure 3.17). Nonetheless, its oxidative efficiency was not as good as reported in the original account.[167] When cupric triflate, known for its capability to suppress triethoxyphenylsilane dimerization,[167] was investigated, the β-enaminone starting material was consumed but no coupling product was observed. We then realized that cupric triflate is a strong Lewis acid that caused the decomposition of the β-enaminone when heated for a prolonged time.

Given the fact that the fluoride ion serves as an activator (in the Hiyama coupling) while the cupric salt functions as a re-oxidant (in the Wacker oxidation), a compound containing both of them would be desirable. Cupric fluoride was then examined but no reaction took place, to our surprise. Since copper, silver and gold are all in the same group in the periodic table, their chemical properties resemble one another. The elements analogous to copper (II) would be silver (II) or gold (II). Gold (II) does not exist in nature but silver (II) could be used as a substitute for copper (II). Two compounds with a silver (II) oxidation state in their formula – AgO and AgF_2 are commercially available. Silver (II) fluoride (AgF_2) was then tested under the reaction conditions shown in Scheme 3.4. It was found that the oxidative Hiyama coupling reaction with β-enaminones succeeded in a short time and with an increased

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yield. This led to the selection of AgF$_2$ as the activator/re-oxidant for the further development of this methodology.

Scheme 3.4
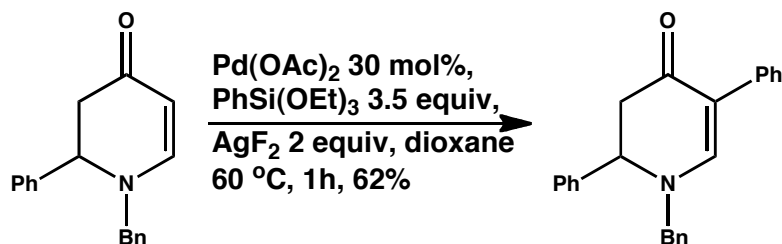
Unlike AgO, which is a 1:1 mixture of Ag(I) oxide and Ag(III) oxide,[172] AgF$_2$ truly consists of Ag(II) and fluoride. Structurally, it is isomorphous with Cu(II) fluoride[173] but different from AgF.[174] In the field of chemical physics, it has been considered as a component of potential superconductors.[175] However, it has not found many applications in synthetic chemistry due to its high oxidation state that results in strongly oxidizing properties. Recently though, AgF$_2$ was utilized in an asymmetric Mukaiyama aldol type reaction between enolsilanes and α-ketoesters.[176] Given this precedence, this reagent may find new uses in the future.

High reactivity of the catalyst is the most important factor for the success of direct coupling reactions. For Hiyama coupling reactions, palladium catalysts have been the dominant catalytic source although nickel catalysts are the favorite of some research groups.[177-179] We therefore screened a number of palladium (II) and nickel (II) catalysts (Table 3.3).

Table 3.3. Screening of Catalyst

Catalyst	Yield
Pd(OAc)$_2$	50%
Pd(TFA)$_2$	48%
PdCl$_2$	trace
PdI$_2$	N/R
White catalyst	40%
Pd(CH$_3$CN)$_2$Cl$_2$	trace
NiF$_2$	trace
NiBr$_2$	N/R

Conditions: PhSi(OEt)$_3$ (2 equiv), AgF$_2$, 60 °C, dioxane.

As shown in Table 3.3, several commercially available palladium (II) salts were examined. Among them, palladium acetate and palladium trifluoroacetate gave the best results (approximately 50% yield). Palladium halides, however, were found ineffective in promoting this transformation. Neither palladium iodide nor the standard catalyst for the Wacker oxidation, palladium chloride, was effective and only trace amounts of the coupling product were formed. This observation was somewhat unexpected in that the original idea for the direct β-enaminone coupling was inspired by the Wacker process.

Other catalysts included stable palladium (II) complexes containing organic ligands, and the nickel (II) salts NiF$_2$ and NiBr$_2$. Metal ligands have an impact on the initial electrophilic palladation step since π-acceptors like acetonitrile enhance the

eletrophilicity of the palladium. When palladium diacetonitrile chloride and the "White catalyst"[180] (1,2-bis(phenylsulfinyl)ethane palladium(II) acetate) were tested, we found no significant differences in comparison with the corresponding non-liganded palladium catalyst. Furthermore, two nickel (II) salts, nickel fluoride and nickel bromide were shown to be ineffective to mediate the direct coupling of β-enaminones.

Considering all results, palladium acetate was selected as the optimal catalyst, based on its stability to air and moisture, ready availability and low price. The solvent was to be optimized next. Since cyclic ethers such as tetrahydrofuran and dioxane are generally used in Hiyama coupling reactions, we conducted our initial studies in dioxane. In order to investigate the influence of solvents on reactivity, we also carried out reactions in polar, nonprotic solvents (dimethyl sulfoxide (DMSO) and acetonitrile). Of special interest was a DMSO/O_2 combination, which had been applied in other studies as the re-oxidative system.[181] Nevertheless, reactions carried out in either DMSO or acetonitrile led to incomplete conversion and a much lower yield. Polar protic solvents proved to be superior to nonpolar solvents. *tert*-Butyl alcohol was selected as a protic solvent, because of its resistance to oxidation and high boiling point. Under these conditions, the coupling product was obtained in 70% yield. The strongly polar, ionic solvate presumably formed under these conditions stabilized the charge-separated resonance structure of the β-enaminone and its σ-complex with palladium (II) (Figure 3.4).

On the other hand, protons could attach to palladium (II) in a general acid catalysis mode, increasing its electrophilicity towards the β-enaminone and thus accelerating the pivotal electropalladation process. It is well known that acids can greatly enhance reaction rates in Pd(II) catalyzed reaction.[182] β-Enaminones are acid-labile (*vide supra*) and strong acids will degrade them rapidly. Therefore, only weak acids were realistic choices as reaction promoters. Acetic acid was then added to *tert*-butyl alcohol as the co-solvent. To our surprise, there was no pronounced increase in yield when using acetic acid as the co-solvent. However, in the case of palladium iodide reaction only took place in the presence of acetic acid. When a mixture of *tert*-butanol and acetic acid at a ratio of 4:1 was used, the coupling product could be seen on TLC together with unconsumed starting material. This is probably a result of ligand exchange at palladium. In comparison to a halide, coordination between Pd(II) and an oxygen-containing acid anion possesses higher electrophilicity.

The 4:1 *tert*-butyl alcohol/acetic acid mixture was subsequently adopted as the standard solvent for another practical reason. At room temperature, *tert*-butyl alcohol is a solid and has to be measured and transferred quickly to avoid refreezing. However, with acetic acid present, the mixture is in liquid form, and easy to handle.

Now that all reaction components had been studied and a good coupling yield had been achieved for the model reaction, there was still one issue left. The coupling partner, trialkoxysilane, is vulnerable to oxidation by AgF_2. For this reason, a large excess (>3 equivalents) of trialkoxysilane was needed to obtain the desired yield. The milder oxidant CuF_2 was reinvestigated using this *tert*-butyl alcohol-acetic acid
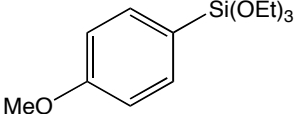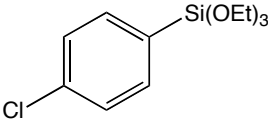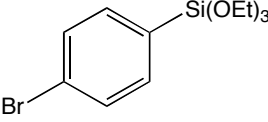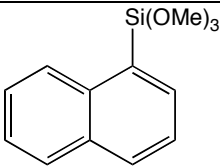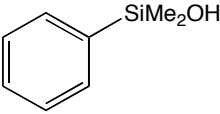
mixture instead of dioxane as the solvent. This time, a clean oxidative Hiyama

coupling reaction was achieved and the yield was even better than that obtained with

AgF$_2$ in pure t-BuOH.

The quantitative variables still needed to be determined. Numerous runs were

performed to decide the catalyst loading, the amount of trialkoxysilane, as well as the

reaction temperature and time. Also, as for any general methodology, the substrate

scope was an important issue to explore. Different triethoxysilanes (and sometimes

trimethoxysilane) were employed. The results are listed in Table 3.4.

Table 3.4. Direct Coupling with Siloxanes
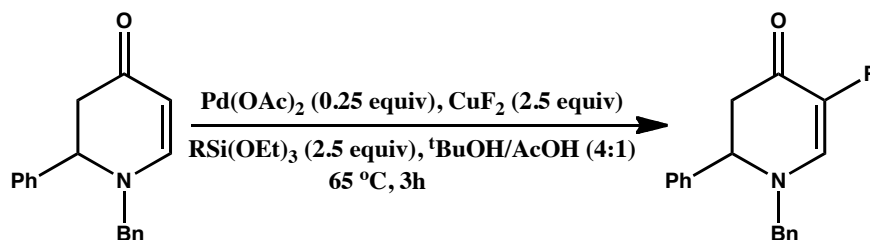
Entry	Siloxane	R (product)	Yield (%)
1		Phenyl **II-01**	82
2		p-Me-C$_6$H$_4$ **II-02**	85
3		p-CF$_3$-C$_6$H$_4$ **II-03**	73

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4	Si(OEt)$_3$, MeO	p-OMe-C$_6$H$_4$ **II-04**	50
5	Si(OEt)$_3$, Cl	p-Cl-C$_6$H$_4$ **II-05**	65
6	Si(OEt)$_3$, Br	p-Br-C$_6$H$_4$ **II-06**	61
7	Si(OMe)$_3$	α-Naphthyl **II-07**	43
8[k]	SiMe$_2$OH	Phenyl **II-01**	80

As shown in Table 3.4, the oxidative Hiyama coupling reactions of β-enaminones worked well with substituted phenyltriethoxysilanes that carry electron-donating groups, electron-withdrawing groups, halogens, or an alkyl group. α-Naphthyltrimethoxysilane was also a suitable coupling partner. Dimethylphenylsilanol, introduced by Denmark,[183-185] was tested as well (entry 8, Table 3.4). The clean, complete conversion clearly demonstrated its utility as an alternative coupling partner. However, substituted phenylsilanols are not commercially available and this limited their use.

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[k] See the experimental part.

Several other triethoxysilanes were explored (Figure 3.21) but did not react. Different reasons accounted for their incompatibility. Specifically, five-membered heteroaromatics were prone to oxidation, not withstanding the mildly oxidative environment. Unprotected triethoxysilyl anilines did not react either.

Various β-enaminones were used in the coupling reaction and these findings are shown in Table 3.5.
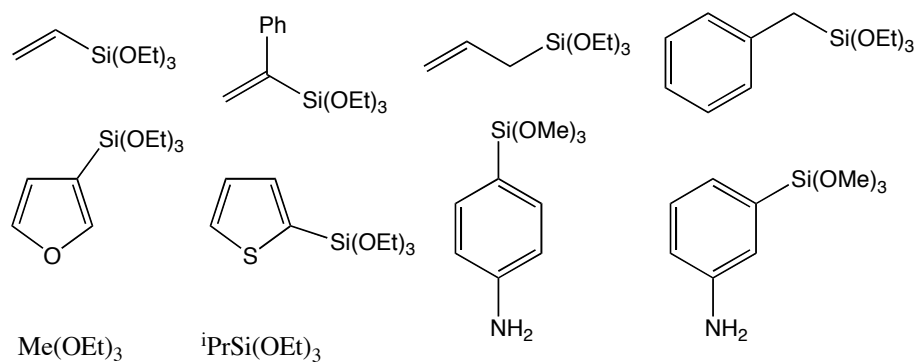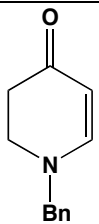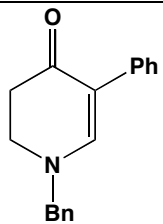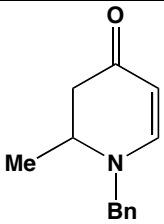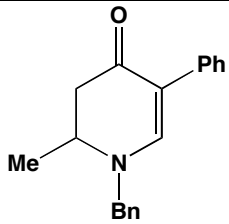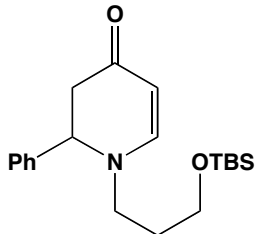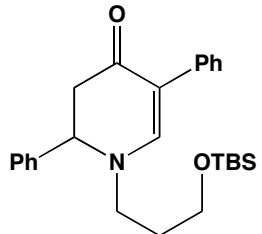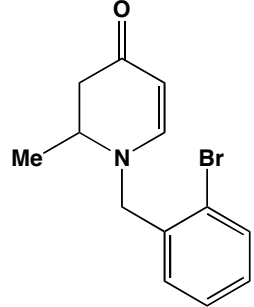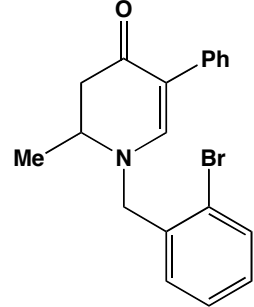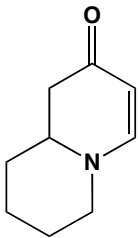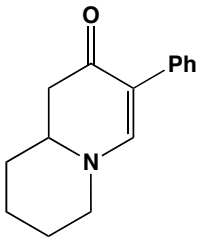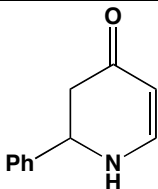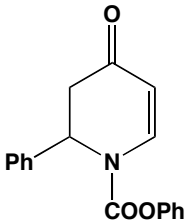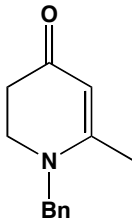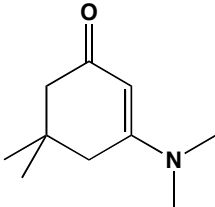
Figure 3.21. Incompatible siloxanes

Table 3.5. Direct Coupling with Different β-Enaminones

Entry	β-Enaminone	Product	Yield (%)
1		**II-08**	62
2		**II-09**	81
3		**II-10**	75
4			68

		II-11	
5		**II-12**	72
6		not observed	0
7		not observed	0
8		not observed	0
9		not observed	0

As seen in Table 3.5, the general trend for β-enaminone behavior in the oxidative Hiyama coupling reaction can be summarized as follows. Endocyclic tertiary N-alkyl β-enaminones, either monocyclic or bicyclic, were sufficiently active in the oxidative direct coupling. However, some simple variations in the β-enaminone structure prevented reactions. It can be broken down to two aspects – electronics and sterics. For secondary β-enaminones (Table 3.5, entry 6), the lone-pair electrons of nitrogen coordinate to palladium (II), rendering it unreactive, which is similar to the poisoning[1] of palladium catalysts by triethylamine. The N-acyl β-enaminone (Table 3.5, entry 7) did not react because the nitrogen lone-pair electrons were in conjugation with the acyl group, thus lowering the nucleophilicity at the β-carbon, and therefore preventing electropalladation.

For α-substituted endocyclic β-enaminones and exocyclic β-enaminones (Table 3.5, entries 8 and 9), the olefin is trisubstituted. Both of them proved incompatible with oxidative direct coupling, likely because of steric hindrance. This is a similar result as that observed for the Wacker oxidation. Neither internal olefins nor 1,1-disubstituted olefins showed any noticeable reactivity. Even though the reactivity of β-enaminones is reinforced by dual activation from both the carbonyl group and the amino group, three substituting groups were too large a hurdle for adequate electropalladation.

Uracil, one of the four bases used in nucleosides and ribonucleic acids (RNA) is of biological significance. Antimetabolites, such as 5-FU, are part of anti-cancer

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[1] From experimental results. Triethylamine is believed to work as a σ-donor.

chemotherapeutic regimens.[186] Chemically, an β-enaminone motif is concealed in the

pyrimidine structure of uracil. Accordingly, it became a candidate for the oxidative

Hiyama coupling. A test run was then conducted and the result was something of an

anomaly.

The standard reaction conditions were applied to dimethyluracil and the

reaction went smoothly. Initially, the reaction product I-13 was believed to be the

oxidative direct coupling product. A thorough study of the NMR spectra of the

product revealed that a coupling reaction did take place, but not at the expected C5

position of dimethyluracil. Instead, reaction took place at the neighboring C6 position

(Scheme 3.5).

Scheme 3.5
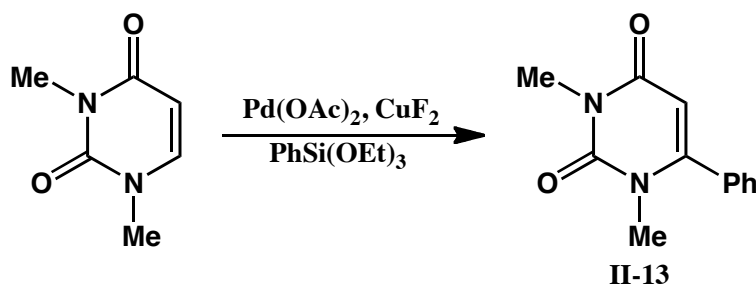
Once more, precedence could be found in the Wacker oxidation. Unlike other

internal olefins, α,β unsaturated ketones are subject to Wacker oxidation under

specific conditions, resulting in a 1,3-diketone (Figure 3.19). Dimethyluracil can be

divided into two parts – a dimethylurea portion and an α,β unsaturated ketone

portion. The conjugation system of the β-enaminone is disrupted in dimethyluracil.

As a result, a silico-Heck reaction occured (Figure 3.22).
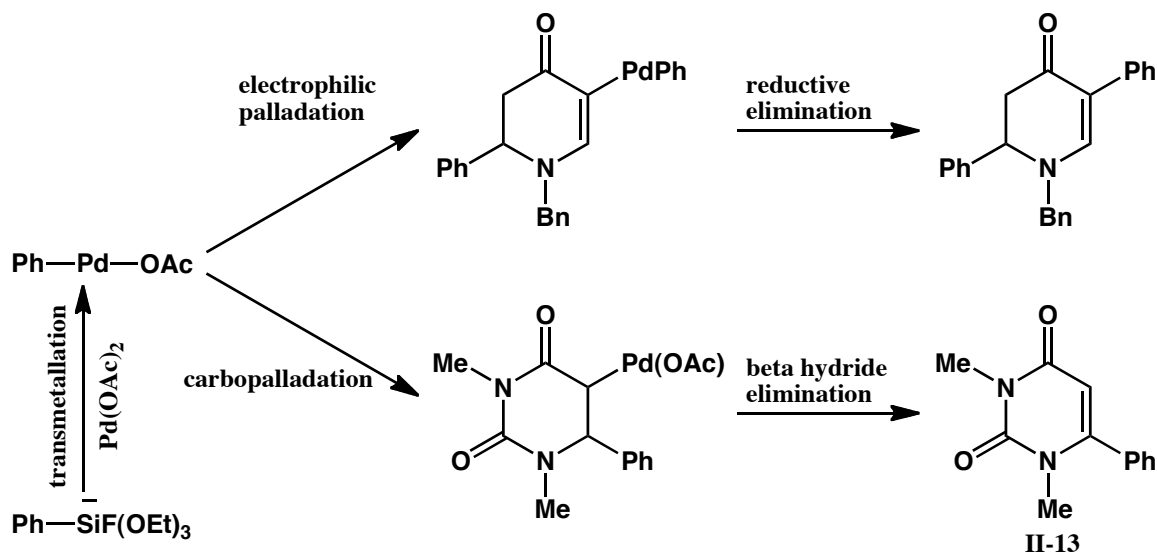
Figure 3.22. Mechanisms of the direct Hiyama coupling and the silico Heck reaction

In a normal Heck reaction, the very first step is the oxidative addition of a

palladium (0) species into an organic halide, generating a palladium (II) intermediate.

In a silico-Heck reaction, this palladium (II) intermediate is generated via

transmetallation between the palladium (II) catalyst and the organosilicon species.

This intermediate then enters the catalytic cycle. After carbopalladation and β-

hydride elimination the Heck coupling product is released, and the palladium (0)

species generated in this process is re-oxidized back to its original palladium (II)

oxidation state.

In summary, we have developed a method for the oxidative Hiyama coupling of β-enaminones. The reaction takes place in open air and is not sensitive to moisture. To our knowledge, this is the first direct Hiyama coupling reaction operated on a non-aromatic system in a non-directed fashion. AgF_2 and CuF_2 were employed for the first time as bifunctional activator/re-oxidants. The reaction conditions are compatible with silyl protecting groups, thus it can be expected that this chemistry can be applied in multi-step organic syntheses.

Chapter 4. Other Palladium-Catalyzed Coupling Reactions of β-Enaminones

4.1. Introduction

As a general C−H functionalization method, the oxidative Hiyama coupling of β-enaminones has numerous merits (*vide supra*). There is, however, room for improvement, e.g. a lower catalyst loading, avoiding the need for an oxidant, and operation at ambient temperature. In order to address these issues, other options were explored.

The σ-complex (**I**) that is generated after electrophilic palladation of the β-enaminone is the active species that leads to the direct coupling of the β-enaminone (Figure 4.1). In oxidative Hiyama coupling reactions, the intermediate **I** is generated from the transmetallation between a palladium (II) catalyst and an organosilane. That raises the possibility that other methods could be used to prepare this reactive intermediate. In this chapter, three additional strategies are presented towards this goal and the initial results are briefly discussed.
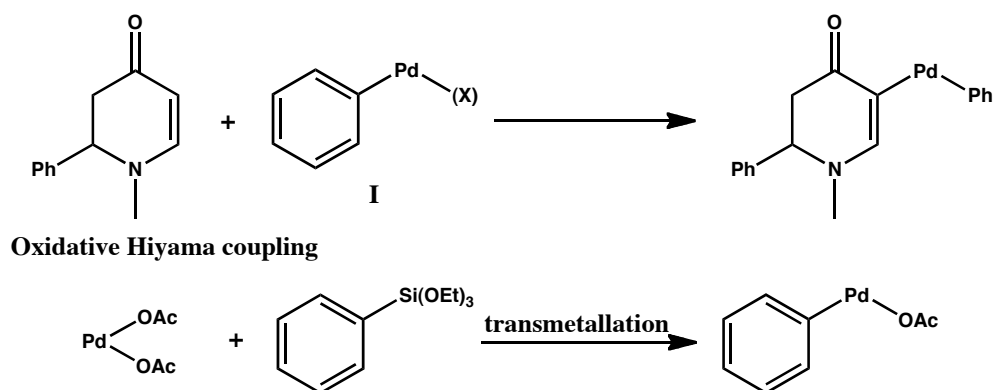
Figure 4.1. Mechanisms for the formation of Pd σ-complexes

4.2. Non-Oxidative Direct Coupling

In oxidative Hiyama coupling reactions, a palladium (II) catalyst is employed and regenerated through oxidation after each round of the catalytic cycle. For this purpose, heavy metal salts like copper (II) are needed. To alleviate the environmental impact and potential safety issues, a catalytic direct coupling cycle that does not require re-oxidation was sought. This also lowers the cost of the starting materials and would allow the use of this chemistry for oxidation-sensitive substrates. In this context, palladium (0) catalysts were considered.

4.2.1. Coupling With Aryl Halides

In C−H functionalization/direct coupling reactions (Figure 3.12), one of the cross coupling partners is unfunctionalized, whereas the other reactant, can be either a nucleophilic organometalloid or an electrophilic organohalide.

Organohalides, especially iodides, have been explored extensively in direct Pd-catalyzed coupling reactions; and in fact, they are more commonly utilized than organometalloids. Various organohalides are readily available from commercial sources. In addition, the transition metal catalyst is regenerated in its starting oxidation state, and a re-oxidant is not needed in these reactions. In aromatic systems, reactions of this kind have been explored broadly.[187, 188] Direct coupling reactions with organohalides proceed predominantly in a directing group-controlled fashion (Figure 4.2).[187, 189]

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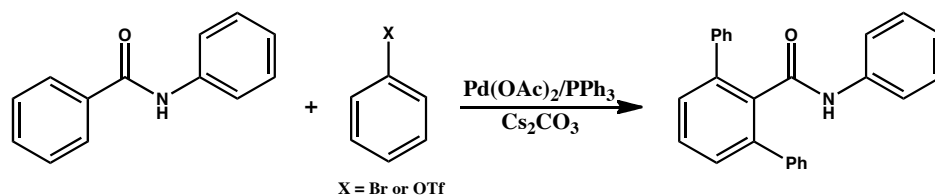
Figure 4.2. Example of a non-oxidative direct coupling reaction

Given the many examples of direct coupling reactions between organohalides and aromatic systems, we decided to explore this type of chemistry with β-enaminones. A test reaction was carried out with phenyliodide in a reaction, catalyzed by tetrakis(triphenylphosphine) palladium(0) (Scheme 4.1), but no reaction was observed.

Scheme 4.1
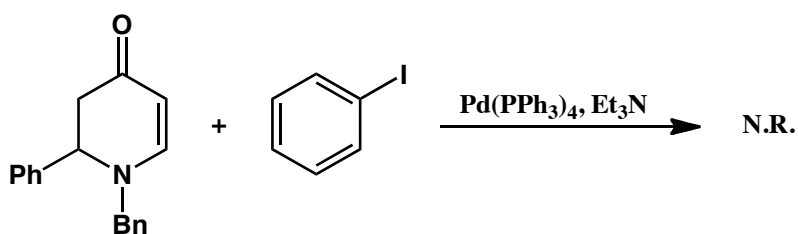
To understand this result, details of the reaction mechanisms of cross coupling and direct coupling (Figure 4.3) needed to be considered.
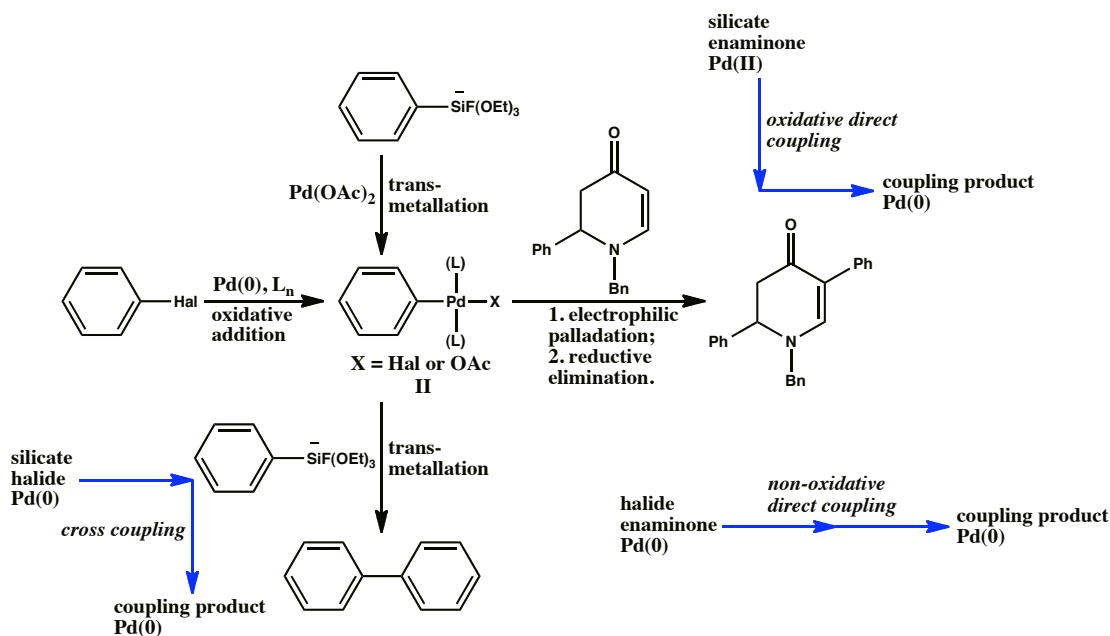
Figure 4.3 Various transition metal-catalyzed coupling pathways

In Pd(0)-catalyzed cross coupling reactions, oxidative addition is the rate-limiting step. This suggests that electron-rich ligands should be utilized to increase the nucleophilicity of the palladium catalyst. Triaryl or trialkylphosphines are among the common ligands for this purpose. After the oxidative addition step, a palladium (II) species (intermediate **II**) is generated, bound with a carbon ligand, a halogen ligand and two phosphine ligands.

Yet in an oxidative direct coupling reaction (Chapter 3), transmetallation is the key step when a palladium (II) catalyst is employed. The counter ion of that palladium (II) salt serves as its anionic ligand. If palladium acetate is used, then the anionic ligand is an acetate ion (OAc⁻).

In a non-oxidative direct coupling reaction with organohalides, exactly the same oxidative addition step as in a cross coupling reaction takes place and the same palladium (II) intermediate (intermediate **II**) is obtained. Nevertheless, the subsequent electrophilic palladation step is different from the transmetallation step in a cross coupling reaction. For this step to happen, the electrophilicity of the common palladium (II) species (intermediate **II**) is vital. In general, the higher leaving tendency an anionic ligand has, the more electrophilic that palladium (II) species (intermediate **II**) is. As anionic ligands, halogen ions have a higher affinitive to the palladium (II) cation than carboxyl groups, e.g. acetate or triflate. In reference to the β-enaminone oxidative Hiyama coupling reaction (Chapter 3, Table 3.3), palladium iodide was not an ideal catalyst for that transformation. At the same time, the electron-donating phosphine ligands suitable for oxidative addition would hamper the next step in the electrophilic palladation process.[190] Therefore, a fine balance between the nucleophilicity of palladium (0) and the electrophilicity of palladium (II) would have to be maintained in order to promote a non-oxidative direct coupling reaction between an β-enaminone and an organohalide.

In Heck reactions, the Jeffery conditions are ligand-free and work well even for some difficult coupling cases.[191] Without electron rich ligands, the palladium (II) intermediate generated from the oxidative addition step is more electrophilic. Moreover, the inorganic base present helps displace the halide from the palladium (II) species, further facilitating the electrophilic palladation step.[192] Hence, a Jeffery condition protocol was selected for our studies.[193] The result was rewarding – the

114

expected non-oxidative direct coupling reaction proceeded in 83% yield (Scheme 4.2). This discovery provided strong support for the original hypothesis, although a possible Pd(II)/Pd(IV) catalytic cycle could not be ruled out.[188] Further investigation is needed to fully establish this methodology.

Scheme 4.2
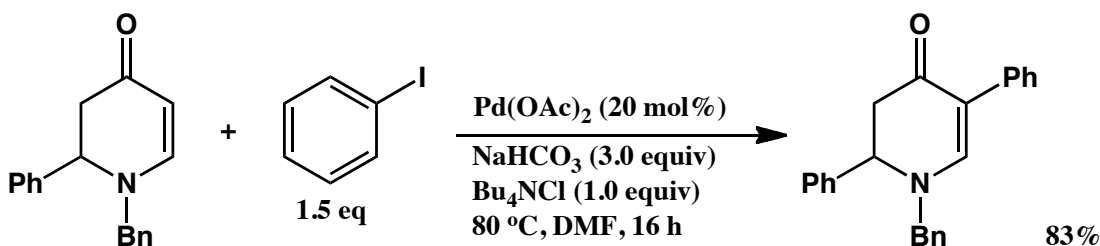
4.2.2. Coupling with an Aryl Diazonium Salt

Diazonium salts are prepared from primary amines via diazotization.[194] Aliphatic diazonium compounds are extremely unstable even at low temperatures while their aromatic counterparts have a much longer life span at temperatures below 0 °C in aqueous solutions. The instability of diazonium compounds can be traced to the leaving group ($-N_2^+$), which is expelled in the form of nitrogen gas.

Aryl diazonium salts have been used in cross-coupling reactions for a long time.[195] They are substitutes for organic halides and pseudohalides as electrophilic coupling partners in cross-coupling reactions. Moreover, as the surrogate of halides, aryl diazonium compounds only require mild reaction conditions at room temperature

and a short reaction time, due to the excellent leaving group properties of the

diazonium group (Figure 4.4).[196-198]
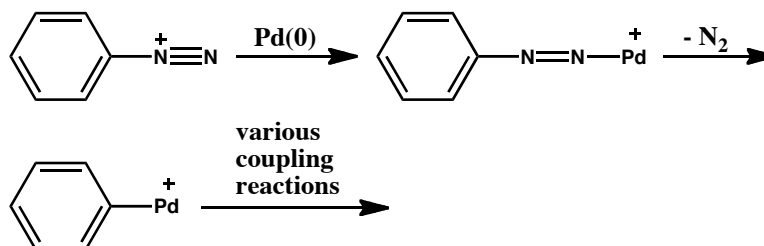
Figure 4.4. Aromatic diazonium compound as the coupling partner

After the initial nucleophilic addition of palladium (0), the collapse of the

cationic palladium intermediate leaves an aryl palladium cation that is highly

electrophilic, compared with the regular product from the palladium oxidative

addition of an organic halide.

In our experiments we reacted the β-enaminone with the phenyl diazonium

salt, using palladium tetrakis(triphenylphosphine) and palladium acetate as catalysts.

It is known that diazonium salts are able to oxidize triphenylphosphine. For the latter

reaction, multiple spots were observed by TLC. The major product did come from a

reaction between the β-enaminone and phenyldiazonium tetrafluoroborate.

Nevertheless, it was not the product expected. Instead, an azo compound was formed,

through the well-known azo coupling reaction, which does not require transition

metal catalysis (Scheme 4.3).

Scheme 4.3
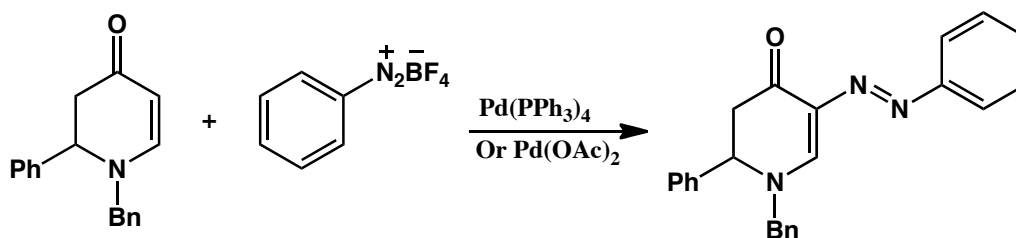
4.3. Decarboxylative Direct Coupling

We also explored the direct decaboxylative direct coupling reaction with β-enaminones. Decarboxylation is the loss of carboxylate in the form of carbon dioxide. The release of carbon dioxide is an irreversible process, providing the extra help in the entropy that a reaction needs. In organic chemistry, decarboxylations have found many applications. Since decarboxylation leaves a negative charge at the α position of the carboxylate group, any factor stabilizing this carbanion will facilitate this process. Some good decarboxylation substrates include trichloroacetic acid, 2,4,6-trinitrobenzoic acid, ethyl malonates, cyanoacetates, and ethyl acetoacetates.

With regard to transition metal-catalyzed coupling reactions, organic carboxylates are surrogates of organometalloids. After the carbon dioxide extrusion, the corresponding organometallic species is formed and can participate in coupling reactions. The decarboxylation process can be carried out using only a catalytic amount of the metal salt (Figure 4.5).
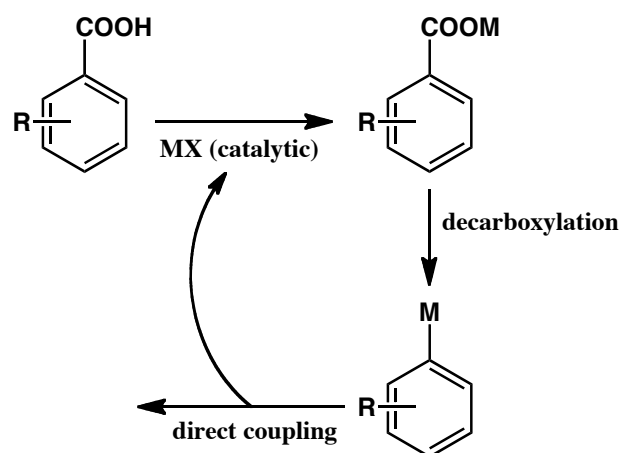
Figure 4.5. Catalytic decarboxylation in direct coupling

Decarboxylation is a clean process producing only carbon dioxide. Furthermore, since the organometallic species is generated in situ, the storage and transfer of organometalloids, which can be troublesome, is avoided. A large variety of different carboxylates are readily available commercially at low prices and can be handled with ease. Astonishingly, this field has been relatively under-explored despite some excellent work reported by a few groups (Figure 4.6).[199-204]

Stoltz

Pd$_2$(dba)$_3$
(S)-*t*-Bu-PHOX

97%, 92% ee

Tunge

Pd(PPh$_3$)$_4$

Ph

Ph

77%

Goossen

R

—COOH + Ar—Br

(1.5 equiv)
R = NO$_2$, OMe, F, ...

Pd(acac)$_2$ (1 mol%)
CuI (3 mol%),
1,10-phenanthroline
(5 mol%)

K$_2$CO$_3$, 3Å MS,
NMP, 160 ºC

R

—Ar

Myers

MeO   COOH

+

OMe

Pd(TFA)$_2$ (0.2 equiv)
Ag$_2$CO$_3$ (3 equiv)
5% DMSO-DMF
80 ºC

MeO

OMe
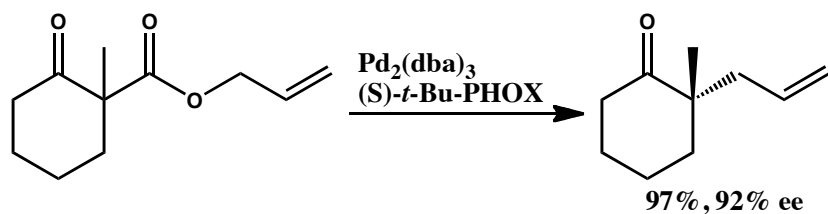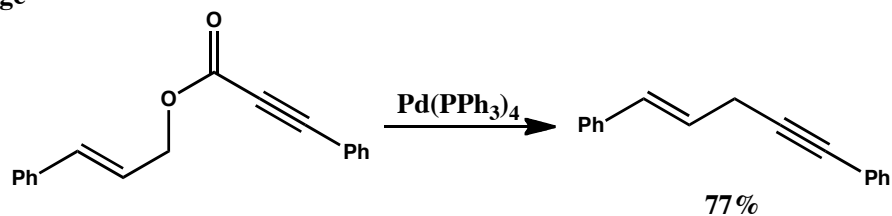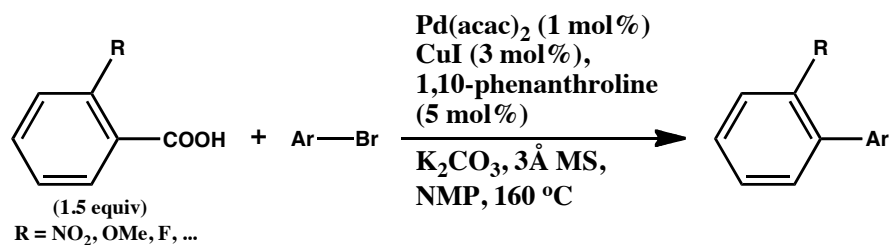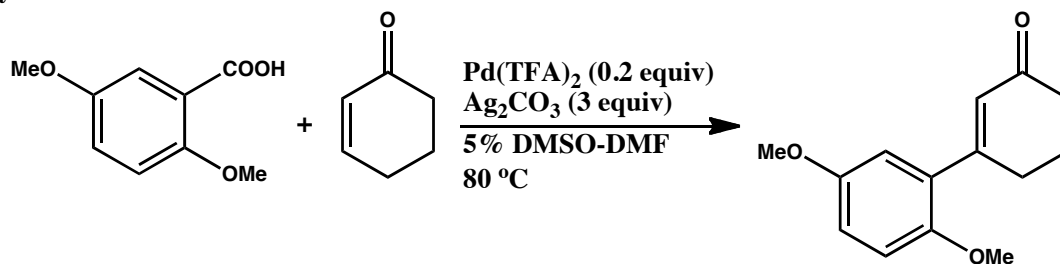
Figure 4.6. Some decarboxylative coupling reactions

The decarboxylative Tsuji-Trost type reactions rely on facile β-keto acid
decarboxylations (Figure 4.6, A). Biaryl synthesis through decarboxylative cross
coupling has been realized as well (Figure 4.6, C). In this case, a catalytic amount of
CuI, the decarboxylation catalyst, is required and the coupling catalyst loading is very

low. Nevertheless, decarboxylation is an endothermic process and for example benzoic acid decarboxylation requires a rather high temperature and extensive heating. This limitation in part accounts for the relative unpopularity of decarboxylative cross coupling reactions. The palladium-catalyzed decarboxylative coupling between heteroaromatic carboxylic acids and aryl bromides has also been reported although the proposed mechanism involves a rare decarboxylative palladium migration.[203]

The Myers group reported a decarboxylative Heck coupling reaction with α,β-unsaturated ketones using palladium trifluoroacetate as the single catalyst.[193, 205, 206] Most importantly, this reaction took place at 80 °C, a much lower temperature than that of a regular benzoic acid decarboxylation. In addition, a similar protodecarboxylation reaction was reported independently from another group.[207]

A simple test run was tried with mixed results, using the Myers conditions. The major product was the symmetrical biphenyl derived from the decarboxylative homodimerization of 3,4-dimethoxyl benzoic acid (Scheme 4.4). Thus, the decarboxylation did occur, but the β-enaminone did not react. Further studies need to be carried out to elucidate this reaction.

Scheme 4.4
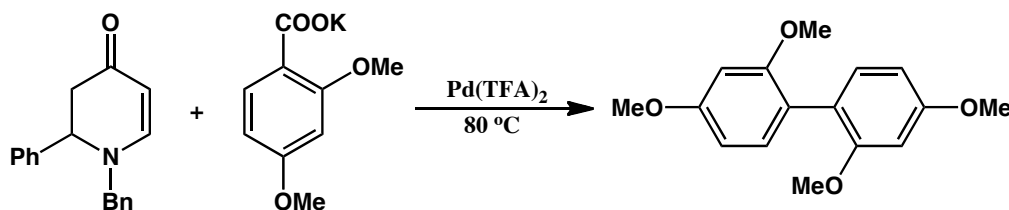
<p style="text-align: center;">Chapter 5. Experimental Data</p>

5.1 Approaches toward the Total Synthesis of Tyloindicine F (Part I)

5.1.1 Materials and Methods

All commercially available reagents and solvents were used without further purification unless otherwise noted. Proton and carbon nuclear magnetic resonance spectra were recorded using a Bruker 400 MHz spectrometer. All chemical shifts were recorded as parts per million (ppm), and all samples were dissolved in $CDCl_3$ using residual solvent peak as internal standard unless otherwise noted. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. Mass spectra were obtained from a ZAB HS mass spectrometer equipped with a 11/250 data system. Fast-atom bombardment mass spectrometry (FAB-MS) experiments were performed with a Xenon gun operated at 8 Kev energy and 0.8 mA emission at the MS laboratory at the University of Kansas. A Nicolet 6700 Fourier Transform infrared spectrophotometer was used to record infrared spectra. Melting points are uncorrected. All moisture-sensitive reactions were performed using either oven or flame dried glassware under a positive pressure of argon or nitrogen unless otherwise noted.

Solvents and reagents that are commercially available were used without further purification unless otherwise noted. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under argon. Methylene chloride was distilled freshly from calcium hydride under argon. Silica gel (230-400 mesh)

was used for flash column chromatography. All compounds were concentrated using a rotary evaporator and reduced pressure.

5.1.2 Experimental Procedures
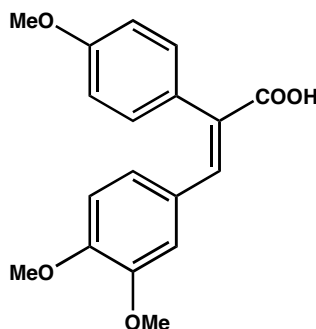
(*E*)-3-(3',4'-Dimethoxyphenyl)-2-(4'-methoxyphenyl)acrylic Acid (I-01). 4-Methoxyphenylacetic acid (33.2 g, 200 mmol) and 3,4-dimethoxybenzaldehyde (33.2 g, 200 mmol) were dissolved in acetic anhydride (500 mL) and triethylamine (25 mL). The mixture was stirred overnight at 120 °C. The mixture was then cooled to room temperature and water (25 mL) was added slowly to hydrolyze the excess acetic anhydride with careful monitoring to ensure the reaction temperature did not exceed 100 °C. The mixture was then cooled in an ice bath and stirred for an additional 2 h during which the product precipitated. The precipitate was filtered and washed with water. Drying over sodium sulfate followed by recrystallization in ethyl alcohol provided 37.7 g (60%) of a white solid. Mp 215.0 -216.0 °C; ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 12.43 (s, 1H), 7.66 (s, 1H), 7.09 (dd, J = 6.7 Hz, 2.0 Hz, 2H), 6.96 (dd, J = 6.8 Hz, 2.1 Hz, 2H), 6.83 (d, J = 6.7 Hz, 1H), 6.79 (d, J = 6.8 Hz, 1H), 6.52 (s, 1H),

3.76 (s, 3H), 3.70 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.7, 158.6, 149.6, 147.8, 138.9, 130.8 (2C), 130.4, 128.7, 127.1, 124.5, 114.1 (2C), 112.7, 111.2, 55.3, 55.1, 54.6; MS (EI) *m/e* calc'd for $C_{18}H_{18}O_5$: 314.1154, found 314.1158.
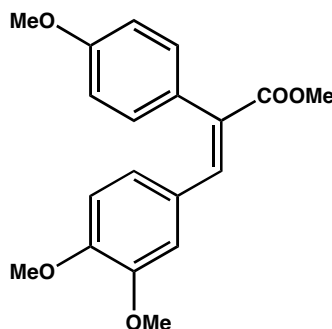
(**E**)-**Methyl 3-(3',4'-Dimethoxyphenyl)-2-(4'-methoxyphenyl)acrylate (I-02).** To a solution of acid **I-01** (314 mg, 1.00 mmol) in dry methanol (20 mL) under nitrogen at room temperature was added thionyl chloride (0.2 mL, 3.0 mL). The resulting mixture was stirred at 60 °C for 2 h and then quenched by dropwise addition of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3X) and the organic layers were combined, dried over sodium sulfate and the solvent was removed *in vacuo* to afford the title compound (310 mg, 95%) as a white solid. Mp 92.0 – 93.0 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.13 (dd, *J* = 6.7 Hz, 2.0 Hz, 2H), 6.90 (d, *J* = 6.7 Hz, 2.0 Hz, 2H), 6.78 (d, *J* = 6.7 Hz, 1H), 6.66 (d, *J* = 6.7 Hz, 1H), 6.44 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.5, 159.2, 149.9, 148.1, 140.2, 131.2 (2C), 129.6, 128.5, 127.5, 125.3, 114.2 (2C), 112.4, 110.5, 55.7, 55.2, 55.1, 52.1; MS (EI) *m/e* calc'd for $C_{19}H_{20}O_5$: 328.1311, found 328.1317.
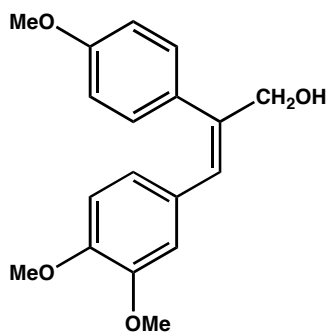
(*E*)-3-(3',4'-Dimethoxyphenyl)-2-(4'-methoxyphenyl)-prop-2-en-1-ol (I-03). To a

solution of ester **I-02** (5.50 g, 16.9 mmol) in toluene (55 mL) at 0 °C was added a

solution of diisobutylaluminum hydride (70.0 mL, 1.0 M in toluene) over 15 min. The

reaction mixture was stirred for an additional 30 min at 0 °C and then quenched by

the careful addition of methanol (20 mL) at 0 °C. The resulting gel was diluted with

methanol and filtered over Celite. The filtrate was concentrated under reduced

pressure, leaving a yellow oil. The crude residue was purified by silica gel flash

chromatography (hexanes/ethyl acetate 6:1) and 4.3 g of the alcohol was obtained as

colorless crystals. The calculated yield was 84%. Mp 91.2 – 92.8 °C; ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.18 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.67 (s, 2H), 6.58

(s, 1H), 6,50 (s, 1H), 4.41 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.50 (s, 3H), 1.75 (bs,

1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.0, 148.0, 147.9, 139.4, 131.0, 130.1 (2C),

129.4, 126.1, 122.3, 114.3 (2C), 111.8, 110.6, 68.7, 55.7, 55.3, 55.2; MS (EI) *m/e*

calc'd for C$_{18}$H$_{20}$O$_4$: 300.1362, found 300.1368.
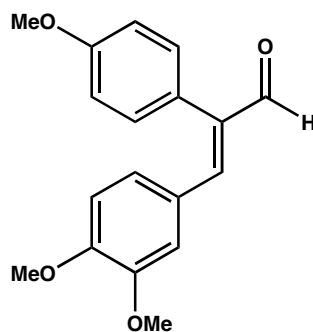
(*2E*)-3-(3',4'-Dimethoxyphenyl)-2-(4'-methoxyphenyl)-propenal (I-04). To a solution of alcohol **I-03** (9.08 g, 30.0 mmol), in benzene (180 mL) and chloroform (20 mL) was added activated manganese dioxide (36.0 g, 41.4 mmol). After 48 h of stirring at room temperature, the black suspension was filtered through Celite and washed with chloroform. The filtrate was concentrated *in vacuo*, leaving 8.61 g (96%) of the aldehyde as colorless crystals. Mp 95.2 – 96.7 °C; IR (neat) 2837 cm^{-1}, 2712 cm^{-1}, 1678 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.72 (s, 1H), 7.29 (s, 1H), 7.16 (dd, *J* = 6.6 Hz, 2.0 Hz, 2H), 6.99 (s, 1H), 6.97 (dd, *J* = 6.5 Hz, 1.9 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.71(s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.1, 159.5, 150.9, 150.1, 148.4, 139.6, 130.8 (2C), 127.1, 125.9, 125.7, 114.5 (2C), 112.5, 110.7, 55.9, 55.3, 55.2; MS (EI) *m/e* calc'd for C$_{18}$H$_{18}$O$_4$: 298.1205, found 298.1203.
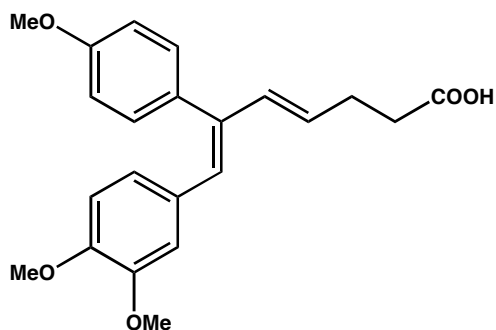
7-(3',4'-Dimethoxyphenyl)-6-(4'-methoxyphenyl)-hepta-4_E_,6_Z_-dienoic acid (I-05). 3-(Carboxypropyl)triphenylphosponium bromide (2.2 g, 5.0 mmol) was taken into a dry round bottom flask under nitrogen to which lithium bis(trimethylsilyl)amide (10 mL, 1.0 M solution in THF) was added slowly at room temperature. This mixture was stirred for 30 min until a clear deep red solution resulted. Aldehyde **I-04** (0.31 g, 1.0 mmol) was then added in one portion. The mixture was stirred at room temperature for 4 h before it was quenched at 0 °C with water (2 mL), followed by titration with HCl (4N) to pH 2. The product was then isolated by extraction with ethyl acetate. The combined organic layer were dried over sodium sulfate, filtered and concentrated to yield a yellow oil. Silica gel flash chromatography (hexanes/ethyl acetate 3:1) afforded 331 mg (90%) of the diene acid as an off-white solid. Mp 149.2 – 150.2 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.11 (d, _J_ = 8.4 Hz, 2H), 6.95 (d, _J_ = 8.3 Hz, 2H), 6.69 (d, _J_ = 8.4 Hz, 1H), 6.63 (m, 1H), 6.48 (d, _J_ = 15.7 Hz, 1H), 6.45 (m, 1H), 6.34 (s, 1H), 5.31 (m, _J_ = 15.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.46 (s, 3H), 2.50 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 179.6, 159.2, 148.4, 139.5, 137.2, 131.3 (2C), 130.8, 130.3, 130.2, 129.1, 129.0, 123.2,

114.8 (2C), 111.9, 110.9, 56.1, 55.7, 55.5, 34.2, 28.2; MS (FAB+) *m/e* calc'd for

$C_{22}H_{25}O_5$: 369.1702, found 369.1688.
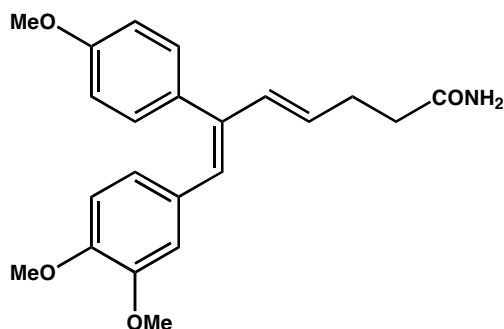
7-(3',4'-Dimethoxyphenyl)-6-(4'-methoxyphenyl)-hepta-4*E*,6*Z*-dienamide (I-06).

To a solution of the acid **I-05** (110 mg, 0.293 mmol) in tetrahydrofuran (3 mL) was

added di-*tert*-butyl dicarbonate (87 mg, 0.38 mmol) and ammonium bicarbonate (120

mg, 1.52 mmol). The mixture was stirred overnight before and then quenched with

water (1 mL). The product was isolated by extraction with ethyl acetate. The

combined organic layer was dried over sodium sulfate, filtered and concentrated to

yield a yellow oil. Silica gel flash chromatography (hexanes/ethyl acetate 2:1)

afforded 108 mg (98%) of the diene amide as an off-white solid. Mp 118.9 – 120.1

°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H),

6.67 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.46 (s, 1H), 6,44 (m, 1H), 6.32 (s,

1H), 5.45 (bd, 2H), 5.30 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.43 (s, 3H), 2.48 (m,

2H), 2.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.5, 158.8, 148.0, 147.9, 139.0,

137.0, 131.0, 130.9 (2C), 130.3, 130.0, 129.9, 122.8, 114.4 (2C), 111.5, 110.5, 55.7,

55.3, 55.1, 35.5, 28.6; MS (EI) *m/e* calc'd for $C_{22}H_{25}NO_4$: 367.1784, found 367.1790.
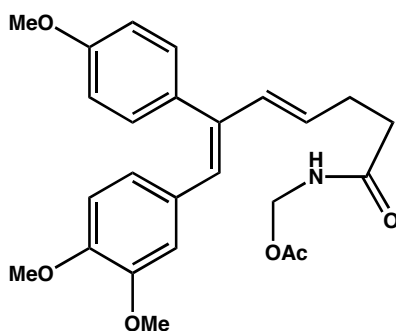
[7-(3',4'-Dimethoxyphenyl)-6-(4'-methoxyphenyl)-hepta-4*E*,6*Z*-dienoyl amino]methyl Acetate (I-07). To a solution of amide **I-06** (104 mg, 0.283 mmol) in tetrahydrofuran (2 mL) at room temperature was added paraformaldehyde (9 mg, 0.3 mmol) along with cesium carbonate (185 mg, 0.560 mmol). The mixture was stirred for 3 h and subsequently treated with excess acetic anhydride (1 mL). The mixture was stirred for an additional 0.5 h. The solvent was removed *in vacuo* and silica gel chromatography afforded (hexanes/ethyl acetate 3:1) 124 mg (75%) of **I-07** as an oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.45 (s, 1H) 6.42 (m, 1H), 6.31 (s, 1H), 5.25 (m, 2H), 5.22 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.45 (s, 3H), 2.48 (m, 2H), 2.27 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.9, 172.2, 159.0, 148.1, 148.0, 139.2, 137.2, 131.1, 131.0 (2C), 130.1, 130.1, 130.0, 123.0, 114.6 (2C), 111.6, 110.7, 64.3, 55.9, 55.5, 55.3, 36.2, 28.5, 21.1; MS (EI) *m/e* calc'd for C$_{25}$H$_{29}$NO$_6$: 439.1995, found 439.1988.
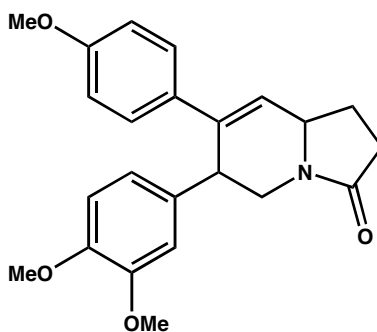
6-(3',4'-Dimethoxyphenyl)-7-(4'-methoxyphenyl)-1,5,6,8a-tetrahydro-*2H*-indolizin-3-one (I-10). Compound **I-07** (16 mg, 0.036 mmol) was dissolved in 1,2-dichlorobenzene (2 mL) under nitrogen and heated to 210 °C in a sealed tube for 4 h. The reaction mixture was cooled to room temperature and the mixture was subjected to silica gel chromatography (pure hexanes, then pure ethyl acetate) directly to afford 9 mg (56%) of **I-10** as a yellowish oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.76 (m, 3H), 6.23 (s, 1H), 4.42 (m, 1H), 4.22 (m, 1H), 3.94 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.32 (m, 1H), 3.47 (m, 3H), 1.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.0, 159.1, 148.9, 147.8, 136.6, 134.0, 132.3, 127.1 (2C), 124.0, 119.8, 114.0 (2C), 111.2, 110.9, 55.5, 55.3, 55.1, 44.8, 43.3, 32.0, 30.6, 27.1; MS (FAB+) *m/e* calc'd for C$_{23}$H$_{26}$NO$_4$: 380.1862, found 380.1852.
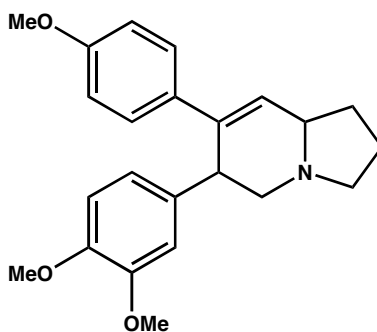
6-(3',4'-Dimethoxyphenyl)-7-(4'-methoxyphenyl)-1,2,3,5,6,8a-

hexahydroindolizine (I-11). To a solution of **I-10** (180 mg, 0.475 mmol) in

tetrahydrofuran (11 mL) at 0 °C was added lithium aluminum hydride (109 mg, 2.87

mmol) in portions carefully over 15 min. The mixture was allowed to stir for 4 h,

warming to room temperature over the course of the reaction. The mixture was

subsequently cooled to 0 °C, diluted with ethyl acetate and quenched by dropwise

addition of saturated aqueous sodium sulfate. The mixture was then filtered to remove

the aluminum salts and washed with ethyl acetate. After concentration in vacuo, the

crude product was purified by silica gel column chromatography (5%

methanol/dichloromethane) to afforded 112 mg (65%) of **I-11**. IR (neat) 2781 cm^{-1} (*T*

band); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.68 (m, 5H), 6.18 (s,

1H), 4.05 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.67 (m, 1H), 3.10 (m, 1H),

2.95 (m, 1H), 2.83 (m, 1H), 2.78 (m, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H),

1.69 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.6, 147.6, 146.4, 136.5, 134.0,

131.6, 126.1 (2C), 123.9, 119.6, 112.5 (2C), 110.9, 109.9, 59.7, 54.7, 54.6, 54.2, 54.1,

51.9, 41.9, 29.6, 21.7; MS (FAB+) *m/e* calc'd for C$_{23}$H$_{28}$NO$_3$: 366.2069, found

366.2078.
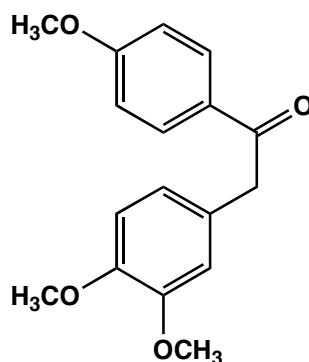
2-(3',4'-Dimethoxyphenyl)-1-(4'-methoxyphenyl)ethanone (I-13). Method A. To a

solution of (3,4-dimethoxy)benzaldehyde tosylhydrazone (1.28 g, 4.00 mmol) in

ethanol (20 mL) was added a solution of sodium hydroxide (2M, 20 mL). The

resulting solution was protected from light. *p*-Anisaldehyde (0.27g, 2.0 mmol) was

added, and the reaction mixture was heated at 70 °C for 10 h, until the light red color

of the solution had disappeared. The solvent was removed *in vacuo*. The residue was

diluted was water (100 mL) and dichloromethane (50 mL). The aqueous layer was

extracted with dichloromethane (2 x 50 mL) and the combined organic layer was

dried over sodium sulfate and concentrated. The crude product was purified by silica

gel flash chromatography (hexanes/ethyl acetate 4:1) to afford 0.12 g (21%) of the

title compound as white powder. **Method B**. To a cooled (0 °C) solution of (3,4-

dimethoxy)benzoic acid (364 mg, 2.00 mmol) in dry toluene (20 mL) was slowly

added thionyl chloride (0.28 mL, 4.1 mmol). The mixture was stirred for 15 min at 0

°C and refluxed for 3 h. The volatiles were removed *in vacuo* and the resulting oil

was dissolved in dry dichloromethane (15 mL). The resulting solution was added

dropwise to a stirred suspension of aluminum chloride (582 mg, 4.10 mmol) and

anisole (217 mg, 2.00 mmol) in dry dichloromethane (25 mL) at 0 °C. The reaction

was stirred at this temperature for 2 h and quenched with 4M HCl (10 mL). The

mixture was extracted with dichloromethane (3 x 25 mL). The combined organic

layer was dried over sodium sulfate and concentrated. The crude product was purified

by silica gel flash chromatography (hexanes/ethyl acetate 4:1) to afford 288 mg

(50%) of the title compound as white powder. Mp 136.0 – 137.0 °C ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.70 (m, 3H), 4.07

(s, 2H), 3.75 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.4, 162.5, 147.6, 146.9, 130.1

(2C), 129.6, 128.5, 126.6, 120.5, 113.0 (2C), 111.6, 110.5, 54.8, 54.7, 43.8; MS

(FAB+) m/e calc'd for C$_{17}$H$_{18}$O$_4$: 287.1283, found 287.1285.
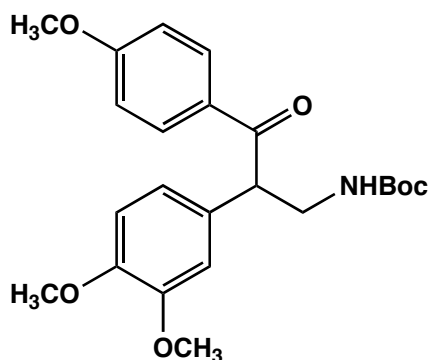
tert-Butyl (2-(3',4'-Dimethoxyphenyl)-3-(4'-methoxyphenyl)-3-

oxopropyl)carbamate (I-15). A solution of sodium methoxide (0.69g, 7.2 mmol) and

N-Boc-α-aminomethyl-p-tolyl sulfone **I-14** (1.4 g, 4.8 mmol) in THF (25 mL) were

stirred at room temperature for 20 min. Ketone **I-13** (0.44 g, 1.5 mmol) was then

added in portions over a period of 30 min. The resulting mixture was allowed to stir

for another 30 min before being quenched by adding saturated aqueous ammonium

chloride solution (10 mL). The aqueous layer was extracted with dichloromethane (3

x 15 mL) and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica gel flash chromatography (hexanes/ethyl acetate 3:1) to afford 392 mg (63%) of the title compound as a semi-oil. Mp 41.2 – 43.9; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.82 (m, 3H), 5.00 (s, 1H), 4.78 (s, 1H), 3.86 (s, 3H), 3.83 (s, 6H), 3.62 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.4, 163.9, 156.4, 149.7, 148.7, 131.6 (2C), 130.2, 129.7, 121.0, 114.1 (2C), 112.0, 111.4, 79.7, 56.3, 56.2, 55.8, 53.6, 44.3, 28.8 (3C); MS (FAB+) m/e calc'd for C$_{23}$H$_{30}$NO$_6$: 416.2094, found 416.2073.
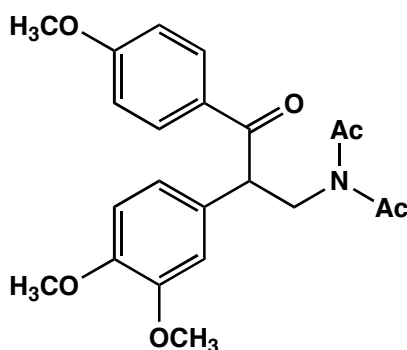
N-Acetyl-N-(2-(3',4'-dimethoxyphenyl)-3-(4'-methoxyphenyl)-3-oxopropyl)acetamide (I-16). To a solution of ketone **I-15** (416 mg, 1.00 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (3 mL) at room temperature. The reaction mixture was stirred for 40 min at room temperature. The volatiles were removed *in vacuo* and the residue was dissolved in dry dichloromethane (5 mL). To this solution was added triethylamine (0.42 mL, 3.0 mmol), 4-dimethylaminopyridine

(122 mg, 1.00 mmol) and acetic anhydride (1.13 mL, 12.0 mmol). The reaction

mixture was stirred at room temperature for 16 h. The volatiles were removed *in*

vacuo. The crude product was purified by silica gel flash chromatography

(hexanes/ethyl acetate 3:1) to afford 241 mg (60%) of the title compound as colorless

crystals. Mp 94.5 – 96.8 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 8.7 Hz, 2H),

6.75 (d, J = 8.7 Hz, 2H), 6.70 (m, 3H), 4.94 (m, 1H), 4.22 (m, 1H), 3.93 (m, 1H), 3.77

(s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.3,

174.0 (2C), 163.6, 149.5, 148.7, 131.1 (2C), 129.4, 129.1, 120.8, 113.8 (2C), 111.7,

111.3, 56.0, 55.8, 55.4, 51.0, 48.9, 26.2 (2C); MS (FAB+) *m/e* calc'd for C$_{22}$H$_{26}$NO$_6$:

400.1760, found 400.1771.
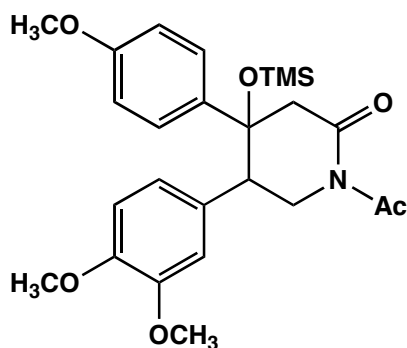
N-Acetyl-3-(4'-methoxybenzyl)-3-(trimethylsilylhydroxyl)-4-(3',4'-

dimethoxybenzyl)cyclohexamide (I-17). To a solution of ketone **I-16** (110 mg,

0.270 mmol) in dichloromethane (2 mL) was added triethylamine (0.20 mL, 1.4

mmol) and trimethylsilyltrifluoromethanesulfonate (0.20 mL, 1.1 mmol) under

nitrogen. The resulting solution was stirred at room temperature for 90 min. The

volatiles were removed *in vacuo*. The crude product was purified by silica gel flash

chromatography (hexanes/ethyl acetate 3:1) to afford 134 mg (100%) of the title

compound as an oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.89 (d, J = 8.9 Hz, 2H), 6.66 (d,

J = 1.7 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.3 Hz, 1H), 6.41 (dd, J = 8.2

Hz, 1.8 Hz, 1H), 3.99 (m, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.45 (d, J =

17.6 Hz, 1H), 2.96 (m, 2H), 2.57 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

173.9, 171.8, 158.5, 148.1, 148.1, 135.5, 130.0, 126.7 (2C), 121.8, 113.0 (2C), 112.2,

110.4, 77.6, 55.7, 55.7, 55.1, 52.2, 47.9, 46.9, 28.0, 2.0 (3C); MS (FAB+) m/e calc'd

for C$_{25}$H$_{34}$NO$_6$Si: 472.2155, found 472.2143.

5.2 Palladium-Catalyzed C−H Functionalization of β-Enaminones (Part II)

5.2.1 Materials and Methods

Palladium (II) acetate was purchased from Strem Chemicals, Inc. All other chemicals and solvents were purchased from Acros Organics and Sigma-Aldrich. Flash column chromatography was carried out on silica gel. TLC was conducted on silica gel 250 micron, F254 plates. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. Chemical shifts are reported in ppm with TMS as an internal standard (TMS: 0.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Bruker 100 MHz NMR spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 77.2 ppm). High-resolution mass spectrometry was performed by the University of Minnesota Mass Spectroscopy Facility.

5.2.2 Experimental Procedure

General Procedures of Palladium (II)-Catalyzed Oxidative Hiyama Coupling of β-Enaminones. All reactions were run at the 0.2 mmol (β-enaminone) scale. The suspension of the corresponding β-enaminone (0.2 mmol) and palladium acetate (12 mg, 0.050 mmol) in a mixture of *tert*-butyl alcohol and acetic acid (4:1, 1 mL) were stirred at 65 °C for 30 min. The suspension of the corresponding siloxane (0.5 mmol) and cupric fluoride (252 mg, 0.5 mmol) in a mixture of *tert*-butyl alcohol and acetic

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acid (4:1, 1 mL) were stirred at room temperature for 30 min. The two suspensions then were mixed and allowed to stir for another 3 h. The reaction mixture was cooled down and filtered though a silica gel pad, washed with ethyl acetate. The volatiles were removed *in vacuo*. The crude product was purified by silica gel flash chromatography (hexanes/ethyl acetate) to afford the corresponding title compound.
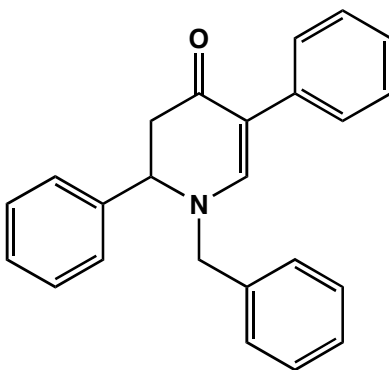
N-**Benzyl-2,5-diphenyl-2,3-dihydropyridin-4(1*H*)-one (II-01)**. **Method A**, refer to the general procedure. *N*-Benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (53 mg, 0.20 mmol) was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 56 mg of the title compound was obtained as an oil. The calculated yield was 82%. **Method B**, refer to the general procedure. *N*-Benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (53 mg, 0.20 mmol) was reacted with dimethylphenylsilanol (76 mg, 0.50 mmol) and 54 mg of the title compound was obtained as an oil. The calculated yield was 80%. **Method C**, a mixture of *N*-benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (100 mg, 0.380 mmol), phenyl iodide (0.064 mL, 0.570 mmol), palladium (II) acetate (18 mg, 0.080 mmol), sodium bicarbonate (96 mg, 1.1 mmol), and tetrabutylammonium chloride (106 mg, 0.380 mmol) in DMF (2 mL) was heated at 80 °C under nitrogen.

After 16 h, the reaction mixture was allowed to cool, and the cooled solution was diluted with ethyl acetate (20 mL). The resulting dark suspension was filtered through a silica gel pad. The filtrate was washed with water (3 x 5 mL). The product solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. Purification of the residue by silica gel flash chromatography (hexanes/ethyl acetate 3:1) afforded 107 mg of the title compound as an oil. The calculated yield was 83%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (s, 1H), 7.33 (d, $J =$ 8.2 Hz, 2H), 7.24 (m, 13H), 4.46 (t, $J =$ 7.4 Hz, 1H), 4.32 (d, $J =$ 15.1 Hz, 1H), 4.06 (d, $J =$ 14.8 Hz, 1H), 2.89 (dd, $J =$ 16.3 Hz, 7.0 Hz, 1H), 2.74 (dd, $J =$ 16.1 Hz, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.6, 153.3, 138.4, 136.1, 135.9, 129.1 (2C), 129.0 (2C), 128.5(2C), 128.3, 128.2 (2C), 127.8 (2C), 127.7 (2C), 127.1, 125.8, 111.3, 60.8, 57.7, 44.3; MS (ESI) m/e calc'd for C$_{24}$H$_{22}$NO: 340.1701, found 340.1685.
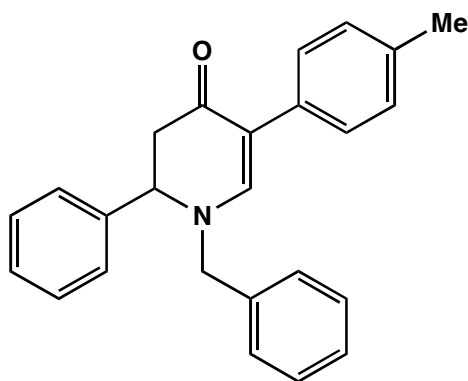
_N_-Benzyl-2-phenyl-5-(4'-tolyl)-2,3-dihydropyridin-4(1_H_)-one (II-02). Refer to the general procedure. _N_-Benzyl-2-phenyl-2,3-dihydropyridin-4(1_H_)-one (53 mg, 0.20

mmol) was reacted with triethoxy(4-tolyl)silane (127 mg, 0.500 mmol) and 60 mg of

the title compound was obtained as an oil. The calculated yield was 85%. ^{1}H NMR

(400 MHz, CDCl$_3$) δ 7.47 (s, 1H), 7.28 (m, 11H), 7.12 (m, 3H), 4.48 (t, 7.6 Hz), 4.34

(d, J = 15.1 Hz, 1H), 4.12 (d, J = 15.1 Hz, 1H), 2.91 (dd, J = 16.2 Hz, 6.9 Hz, 1H),

2.75 (dd, J = 16.3 Hz, 8.0 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

187.8, 153.0, 138.5, 135.9, 135.4, 133.0, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.4,

128.3 (2C), 127.8 (2C), 127.7 (2C), 127.1, 111.4, 60.9, 57.6, 44.3, 21.1; MS (ESI)

m/e calc'd for C$_{25}$H$_{24}$NO: 354.1858, found 354.1872.

_N_-Benzyl-2-phenyl-5-(4'-(trifluoromethyl)phenyl)-2,3-dihydropyridin-4(1_H_)-one

(II-03). Refer to the general procedure. _N_-Benzyl-2-phenyl-2,3-dihydropyridin-

4(1_H_)-one (53 mg, 0.20 mmol) was reacted with triethoxy(4-

(trifluoromethyl)phenyl)silane (154 mg, 0.500 mmol) and 59 mg of the title

compound was obtained as an oil. The calculated yield was 73%. ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.63 (s, 1H), 7.56 (m, 4H), 7.36 (m, 6H), 7.25 (d, J = 8.3 Hz, 2H),

7.20 (d, J = 8.2 Hz, 2H), 4.59 (t, J = 7.2 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.25 (d, J

= 15.1 Hz, 1H), 3.02 (dd, J = 16.3 Hz, 7.2 Hz, 1H), 2.83 (dd, J = 16.3 Hz, 7.2 Hz,

1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.3, 153.4, 139.7, 138.0, 135.4, 129.2 (2C),

129.1 (2C), 128.6 (2C), 128.5, 127.8 (2C), 127.4 (2C), 126.9 (2C), 125.1, 125.1,

125.0, 109.7, 60.6, 57.9, 44.0; MS (ESI) m/e calc'd for C$_{25}$H$_{21}$F$_3$NO: 408.1575, found
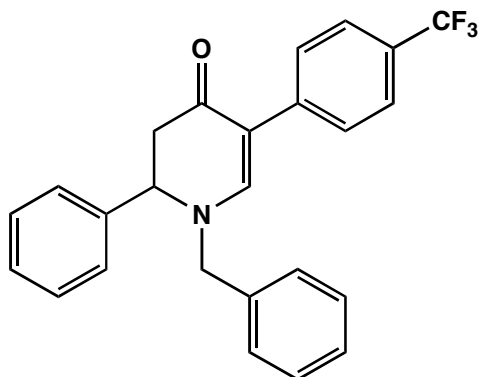
408.1558.
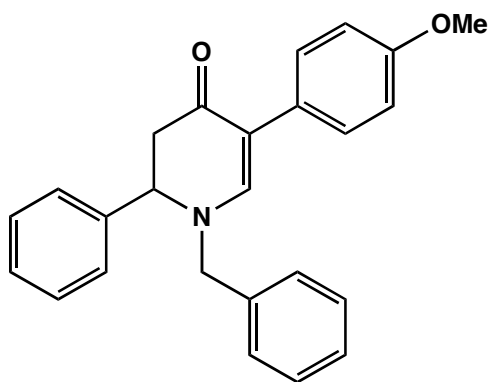
N-Benzyl-5-(4'-methoxyphenyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (II-04).

Refer to the general procedure. N-Benzyl-2-phenyl-2,3-dihydropyridin-4(1H)-one (53

mg, 0.20 mmol) was reacted with triethoxy(4-methoxyphenyl)silane (135 mg, 0.500

mmol) and 37 mg of the title compound was obtained as an oil. The calculated yield

was 50%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (s, 1H), 7.35 (m, 7H), 7.27 (m, 3H),

7.16 (d, J = 7.7 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.55 (t, J = 7.6 Hz, 1H), 4.42 (d, J

= 15.1 Hz, 1H), 4.19 (d, J = 15.1 Hz, 1H), 3.80 (s, 3H), 2.98 (dd, J = 16.3 Hz, 6.9 Hz,

1H), 2.83 (dd, J = 16.3 Hz, 8.2 Hz, 1H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.9, 157.9,

152.8, 138.5, 135.9, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.5, 128.4, 128.3, 127.7

(2C), 127.1 (2C), 113.7 (2C), 111.2, 60.9, 57.5, 55.3, 44.3; MS (EI) *m/e* calc'd for

$C_{25}H_{24}NO_2$: 370.1807, found 370.1788.
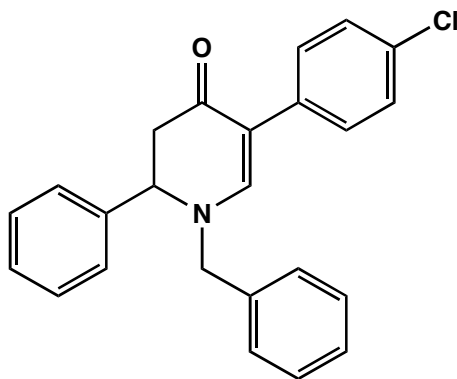
N-Benzyl-5-(4'-chlorophenyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (II-05).

Refer to the general procedure. *N*-Benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (53

mg, 0.20 mmol) was reacted with triethoxy(4-chlorophenyl)silane (137 mg, 0.500

mmol) and 49 mg of the title compound was obtained as an oil. The calculated yield

was 65%. ^{1}H NMR (400 MHz, CDCl₃) δ 7.55 (s, 1H), 7.36 (m, 8H), 7.27 (m, 4H),

7.16 (d, *J* = 7.7 Hz, 2H), 4.56 (t, *J* = 7.3 Hz, 1H), 4.44 (d, *J* = 15.1 Hz, 2H), 4.22 (d, *J*

= 15.1 Hz, 1H), 2.99 (dd, *J* = 16.3 Hz, 7.1 Hz, 1H), 2.81 (dd, *J* = 16.3 Hz, 7.6 Hz,

1H); ^{13}C NMR (100 MHz, CDCl₃) δ 187.5, 153.1, 138.2, 135.6, 134.5, 131.3 (2C),

129.2 (2C), 129.1 (2C), 128.8, 128.5, 128.4, 128.3 (2C), 127.7 (2C), 127.0 (2C),

110.1, 60.7, 57.8, 44.1; MS (ESI) *m/e* calc'd for $C_{24}H_{21}ClNO$: 374.1312, found

374.1337.

N-Benzyl-5-(4'-bromophenyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (II-06).

Refer to the general procedure. N-Benzyl-2-phenyl-2,3-dihydropyridin-4(1H)-one (53

mg, 0.20 mmol) was reacted with triethoxy(4-bromophenyl)silane (159 mg, 0.500

mmol) and 51 mg of the title compound was obtained as an oil. The calculated yield

was 61%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.42 (dd, J = 6.5 Hz, 1.9 Hz,

2H), 7.35 (m, 8H), 7.16 (dd, J = 7.7 Hz, 2.0 Hz, 2H), 4.56 (t, J = 7.3 Hz, 1H), 4.44 (d,

J = 15.1 Hz, 1H), 4.22 (d, J = 15.1 Hz, 1H), 2.99 (dd, J = 16.3 Hz, 7.0 Hz, 1H), 2.81

(dd, J = 16.3 Hz, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.5, 153.0, 138.1,

135.6, 134.9, 131.2 (2C), 129.1 (2C), 129.1 (2C), 129.0, 128.5, 128.4 (2C), 127.7

(2C), 127.0 (2C), 119.3, 110.0, 60.7, 57.7, 44.1; MS (ESI) *m/e* calc'd for

C$_{24}$H$_{21}$BrNO: 418.0807, found 418. 0782.

_N_-Benzyl-5-(1'-naphthyl)-2-phenyl-2,3-dihydropyridin-4(1_H_)-one (II-07). Refer
to the general procedure. _N_-Benzyl-2-phenyl-2,3-dihydropyridin-4(1_H_)-one (53 mg,
0.20 mmol) was reacted with trimethoxy(1-naphthyl)silane (124 mg, 0.500 mmol)
and 34 mg of the title compound was obtained as an oil. The calculated yield was
43%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (m, 3H), 7.34 (m, 13H), 7.16 (d, _J_ = 7.6 Hz,
2H), 4.68 (t, _J_ = 7.5 Hz, 1H), 4.37 (d, _J_ = 14.8 Hz, 1H), 4.20 (d, _J_ = 15.1 Hz, 1H),
3.08 (dd, _J_ = 16.4 Hz, 7.1 Hz, 1H), 2.94 (dd, _J_ = 16.3 Hz, 8.0 Hz, 1H); ^{13}C NMR (100
MHz, CDCl$_3$) δ 187.9, 135.9, 134.1, 133.9, 129.2 (2C), 129.1 (2C), 129.0, 128.5,
128.4, 128.3 (2C), 127.9, 127.8, 127.7(2C), 127.2, 127.1, 126.2, 125.8, 125.7, 125.6,
125.5 (2C), 61.0, 57.6, 44.2; MS (ESI) _m/e_ calc'd for C$_{28}$H$_{24}$NO: 390.1858, found
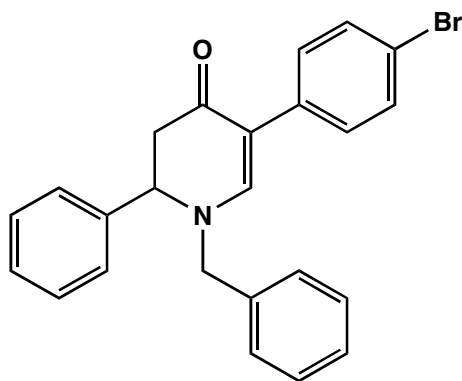390.1872.

N-Benzyl-5-phenyl-2,3-dihydropyridin-4(1*H*)-one (II-08). Refer to the general procedure. *N*-Benzyl-2,3-dihydropyridin-4(1*H*)-one (37 mg, 0.20 mmol) was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 33 mg of the title compound was obtained as an oil. The calculated yield was 62%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (m, 4H), 7.32 (m, 5H), 7.17 (t, *J* = 7.3 Hz, 2H), 4.43 (s, 2H), 3.44 (t, *J* = 7.7 Hz, 2H), 2.60 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.6, 153.2, 136.3 (2C), 135.7, 129.1 (2C), 128.4 (2C), 128.2, 127.8, 127.7 (2C), 125.7, 111.2, 60.2, 46.8, 36.3; MS (ESI) *m/e* calc'd for C$_{18}$H$_{18}$NO: 264.1388, found 264.1370.
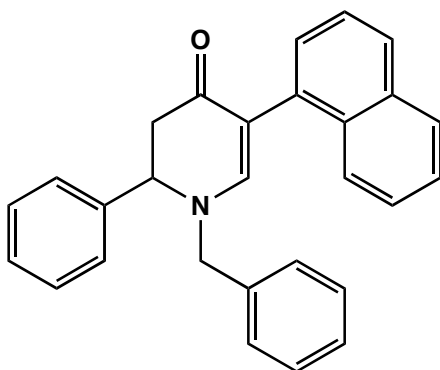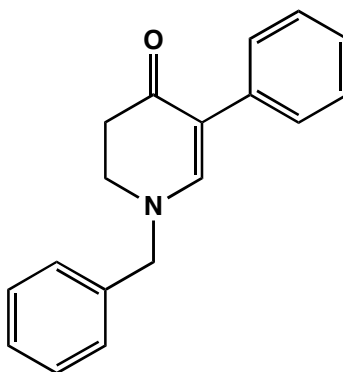

N-Benzyl-2-methyl-5-phenyl-2,3-dihydropyridin-4(1*H*)-one (II-09). Refer to the general procedure. *N*-Benzyl-2-methyl-2,3-dihydropyridin-4(1*H*)-one (40 mg, 0.20

mmol) was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 45 mg of

the title compound was obtained as an oil. The calculated yield was 81%. ^{1}H NMR

(400 MHz, CDCl$_3$) δ 7.34 (m, 4H), 7.25 (m, 6H), 7.07 (t, J = 7.4 Hz, 1H), 4.37 (dd, J

= 25.8 Hz, 15.3 Hz, 2H), 3.55 (m, 1H), 2.76 (dd, J = 16.1 Hz, 6.5 Hz, 1H), 2.28 (dd, J

= 16.0 Hz, 4.8 Hz, 1H), 1.18 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ

187.0, 150.6, 135.3, 128.0 (2C), 127.3, 127.1 (2C), 126.5, 126.4 (2C), 126.3 (2C),

124.5, 108.8, 56.5, 50.9, 42.1, 14.3; MS (ESI) m/e calc'd for C$_{19}$H$_{20}$NO: 278.1545,

found 278.1561.
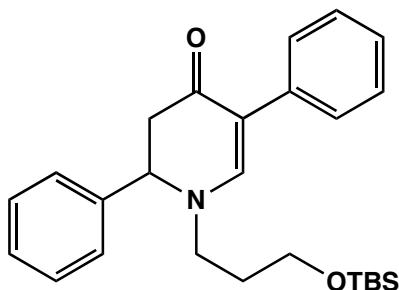
N-(3'-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,5-diphenyl-2,3-dihydropyridin-4(1*H*)-one (II-10). Refer to the general procedure. N-(3'-((*tert*-Butyldimethylsilyl)oxy)propyl)-2-phenyl-2,3-dihydropyridin-4(1*H*)-one (69 mg, 0.20

mmol) was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 63 mg of

the title compound was obtained as an oil. The calculated yield was 75%. ^{1}H NMR

(400 MHz, CDCl$_3$) δ 7.45 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.31 (m, 7H), 7.15 (dd, J

= 13.4 Hz, 7.4 Hz, 1H), 4.67 (t, J = 7.4 Hz, 1H), 3.63 (t, J = 5.5 Hz, 1H), 3.38 (m,

1H), 3.24 (m, 1H), 3.02 (dd, J = 16.2 Hz, 6.9 Hz, 1H), 2.82 (dd, J = 16.2 Hz, 7.8 Hz,

1H), 0.84 (s, 9H), -0.01 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.3,

153.7, 138.6, 136.2, 129.1(2C), 128.3, 128.2 (2C), 127.5(2C), 126.9 (2C), 125.6, 110.7, 61.2, 59.2, 50.5, 44.3, 31.5, 25.8 (3C), 18.2, -5.4 (2C); MS (ESI) *m/e* calc'd for $C_{26}H_{35}NO_2Si$: 422.2515, found 422.2501.

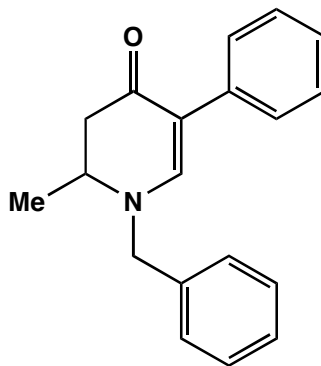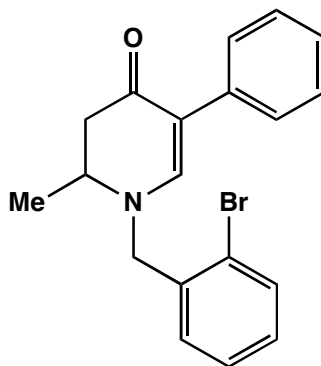**N-(2'-Bromobenzyl)-2-methyl-5-phenyl-2,3-dihydropyridin-4(1H)-one (II-11)**.

Refer to the general procedure. *N*-(2'-Bromo)benzyl-2-methyl-2,3-dihydropyridin-4(1*H*)-one (56 mg, 0.20 mmol) was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 48 mg of the title compound was obtained as an oil. The calculated yield was 68%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (m, 4H), 7.31 (m, 4H), 7.20 (m, 1H), 4.53 (dd, *J* = 37.6 Hz, 15.5 Hz, 2H), 3.66 (m, 1H), 2.91 (dd, *J* = 16.1 Hz, 6.6 Hz, 1H), 2.37 (dd, *J* = 16.0 Hz, 3.8 Hz, 1H), 1.27 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.0, 151.6, 136.2, 135.3, 133.6, 130.0, 129.6, 128.2 (2C), 128.0, 127.6 (2C), 125.6, 123.9, 110.2, 57.5, 52.5, 43.0, 15.3; MS (ESI) *m/e* calc'd for $C_{19}H_{19}BrNO$: 356.0650, found 356.0636.
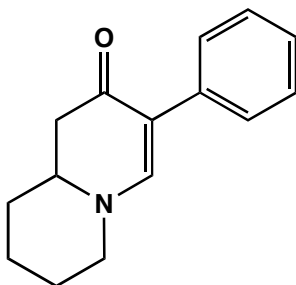
3-Phenyl-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (II-12). Refer to the

general procedure. 7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one (30 mg, 0.20 mmol)

was reacted with triethoxyphenylsilane (120 mg, 0.500 mmol) and 33 mg of the title

compound was obtained as an oil. The calculated yield was 72%. ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.30 (d, 2H, J = 8.8 Hz), 7.05 (s, 1H), 6.85 (m, 3H), 3.41 (m, 1H),

3.36 (m, 1H), 3.01 (dt, 1H, J = 2.6, 6.3 Hz), 2.58 (m, 1H), 2.51 (m, 1H), 1.80 (m,

3H), 1.52 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.2, 156.5, 152.9, 128.9 (2C),

128.1, 127.7 (2C), 105.4, 54.9, 51.7, 41.4, 29.8, 23.8, 20.8; MS (ESI) *m/e* calc'd for

C$_{15}$H$_{18}$NO: 228.1388, found 228.1400.
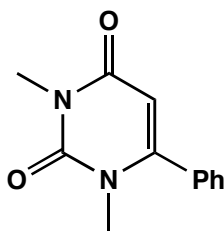
***N,N*-Dimethyl-6-phenyl-uracil (II-13)**. Refer to the general procedure. *N,N*-

Dimethyl-6-phenyl-uracil (28 mg, 0.20 mmol) was reacted with triethoxyphenylsilane

(120 mg, 0.500 mmol) and 22 mg of the title compound was obtained as an oil. The

calculated yield was 51%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (dd, J = 4.4 Hz, 1.6

Hz, 2H), 7.31 (m, 3H), 5.69 (s, 1H), 3.39 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz,

CDCl$_3$) δ 162.5, 154.6, 133.3, 130.2, 129.0 (2C), 128.4, 127.7 (2C), 102.4, 34.6, 28.0;

MS (ESI) *m/e* calc'd for C$_{12}$H$_{13}$N$_2$O$_2$: 217.0977, found 217.1002.

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Epilogue

"An unexamined life is not worth living." (Socrates) I have been on the scientific track likely since the time of reading the popular science works of *Isaac Asimov* and *Ye, Yonglie*, among other writers. Also, I was in *the Chemistry Olympic School* system during the high school years.

This graduate school experience certainly has influenced me in a profound way. The majority of my research has been summarized herein. Moreover, some personal flashbacks outside the labs are well worth being mentioned: in Kansas, the July 4th firework watched from the top of Mount Oread; the Red dog's dog days and the Lawrence Soccer League; a tenet from a campus building, "Whoso findeth wisdom findeth life." in Minnesota, the Center for Outdoor Adventure and group fitness classes; late nights waiting for a bus outside in the winter. And much more that can only be looked back.

During the preparation of this dissertation, the corresponding author of Reference 163, Dr. Keith Fagnou, passed away untimely in Nov 2009 from complications caused by the H1N1 flu. His group was a major contributor of transition metal-catalyzed C–H functionalization reactions and had developed numerous high-profile methodologies. I have gained many inspirational insights from their papers and reviews. This is certainly a loss to science, particularly this field. It is, at the same time, also a reminder to me that what I have been doing does serve a purpose despite the current chaos in the health care policy debate and the pharmaceutical industry.