The Synthesis of 3-Vinylindolines by the Palladium-Catalyzed Intramolecular Allylic Alkylation of Cinnamyl Acetates and the Synthesis of Polyphenolic 4-Aryl-3,4-dihydrocoumarins by Domino Friedel-Crafts Reactions

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Historically, the alkylation of allylic acetates with non-stabilized C(sp^3) nucleophiles has been challenging. The metal-catalyzed alkylation of allylic acetates and carbonates with organotin and organoboron reagents has significantly increased the scope of nucleophiles available to participate in such reactions; however, the generation of C(sp^3)-C(sp^3) bonds in this manner remains difficult.

We therefore designed a substrate in order to explore the intramolecular transition metal-catalyzed alkylation of an allylic acetate with a C(sp^3) organotin nucleophile. From this substrate we were able to successfully synthesize a number of 3-vinylindolines in modest to good yields in as little as seven steps through the palladium-catalyzed intramolecular allylic alkylation of cinnamyl acetates with tethered organotin nucleophiles. To the best of our knowledge this represents the first example of such a transformation, resulting in the formation of novel C(sp^3)-C(sp^3) bonds.

It has been shown that polyphenolic procyandins, members of the flavonoid class of compounds, possess moderate affinity for a synthetic model of a proline rich region of the microtubule associated protein tau. The phosphorylation of this region of tau is thought to be correlated with the development of intraneuronal protein deposits, a hallmark of Alzheimer's disease physiopathology. In the second part of this thesis, we set out to utilize the domino Friedel-Crafts alkylation/acylation of benzylidene Meldrum's acids with phenols previously developed in our group for the synthesis of a number of polyphenolic 4-aryl-3,4-dihydrocoumarins, members of the neoflavonoid class of compounds. By synthesizing a library of polyphenolic neoflavonoids in this manner, which possessed variation in the number and position of hydroxyl groups about the

aromatic rings, a systematic survey of the structure-activity relationship was to be conducted. This would allow us gain a better understanding of potential therapeutic agents that may be able to attenuate the formation of these intraneuronal protein deposits in the treatment of Alzheimer's disease.

Acknowledgments

When I first arrived in Waterloo to begin my graduate studies I had no idea what to expect. Coming from a small university in northern Ontario the size of the campus, the number of buildings and the vast expanse of knowledge and expertise contained within the halls of this institution was overwhelming. Professor Eric Fillion made me feel welcome on my very first day and I will never forget the guidance and patience he showed towards me over the last two years. Our regular talks about the events of the day, the state of politics in the world, and the quirks of life in a small town were always a joy, a cause for laughter, and the occasional mutual sighs of exasperation. He has made me realize that a life in the sciences is where I truly belong and provided me with invaluable experience, life lessons, and opportunity that I could have never anticipated. For this and so much more, I cannot thank you enough.

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Å	angstrom
Ac	acetyl
AD	Alzheimer's disease
AIBN	azobis*iso*butyronitrile
Bn	benzyl
Bu	butyl
Boc	*tert*-butoxycarbonyl
brs	broad singlet
C	catalyst
COD	cyclooctadiene
d	doublet
Da	Dalton
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
dec	decomposition
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
ee	enantiomeric excess
equiv.	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
ex.	example
h	hour
Hi-vac	high vacuum
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	*iso*-propyl
J	spin coupling constant
L	litre or ligand
lit.	literature
m	multiplet
M	molarity or metal
m.p.	melting point
*m*CPBA	*meta*-chloroperbenzoic acid

Me	methyl
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
mmol	millimole
mL	millilitre
mol	mole
m/z	mass/charge
Ms	methanesulfonyl
MS	molecular sieves
NFT	neurofibrillary tangle
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
OMOM	methoxymethyl ether
ORTEP	Oak Ridge thermal-ellipsoid plot
OTf	trifluoromethansulfonate
o-tol	*ortho*-toluyl
pin	pinacol
q	quartet
rt	room temperature
s	singlet
stannatrane	1-aza-5-stannabicyclo[3.3.3]undecane
t	triplet
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
Teoc	(2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THAB	tetra-*n*-hexylammonium bromide
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-tolylsulfonyl
U.V.	ultraviolet
wt	weight

Chapter 1: Introduction

1.1: Introduction and Background

The development of new methodologies for the synthesis of small molecules is one of the key aims of synthetic organic chemists. This is exemplified by the fact that up to 90% of orally active drug candidates that reached phase II clinical trials had a molecular weights of less than 550 Da.[1] Specifically, heterocyclic compounds represent one of the greatest subsets of biologically active small molecules owing to the diverse biochemical interactions that they may partake in and their ubiquitous nature in biological systems.[2] Among this subset of biologically active chemical species two scaffolds stand out as strong candidates for development of therapeutically beneficial drugs, namely the coumarin and indole skeletons and the saturated derivatives thereof (Figure 1.1).[2,3] Derivatives of molecules belonging to these classes of compounds possess antibacterial,

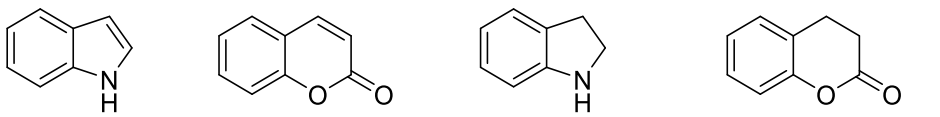


Figure 1.1 Structure of Indole, Coumarin, Indoline, and 3,4-Dihydrocoumarin

antifungal, antitumor, vasoconstrictive, antiviral, psychoactive, and anticoagulant properties, among many others. [2-11] Some of the more commonly recognized indole and coumarin derivatives are tryptophan, serotonin, psilocybin, warfarin, and scopoletin, though this is an extremely small sampling of these classes of heterocycles (Figure 1.2).[2,10,11]

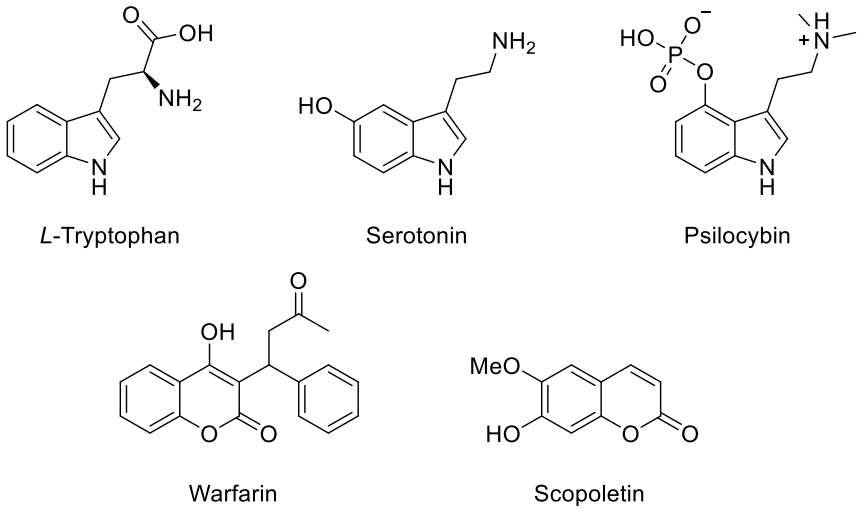


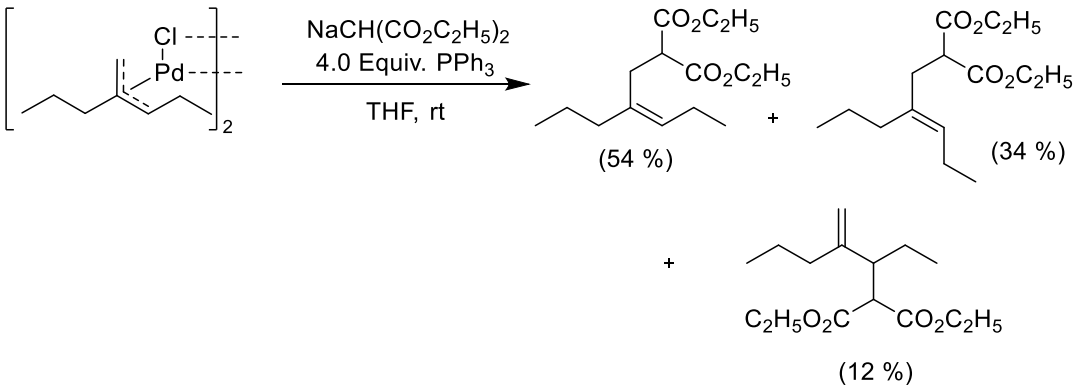
Figure 1.2 Commonly Encountered Indoles and Coumarins

Owing to their rich biological activity and therapeutic utility, considerable effort has been placed into the development of new methods of accessing heterocyclic skeletons of this nature. Among the most common means of functionalizing aryl and heteroaryl groups are transition metal catalyzed cross-coupling reactions, Friedel-Crafts reactions and more recently direct C-H functionalization.[12] Enhanced selectivity, functional group tolerance, yields and practicality are all hallmarks of a strong synthetic methodology. Two reactions that have historically demonstrated the potential to meet these qualities are transition metal-catalyzed allylic alkylation reactions and the Lewis acid-catalyzed Friedel-Crafts reactions.[13,14]

1.2: Allylic Alkylation (Tsuji-Trost) Reactions

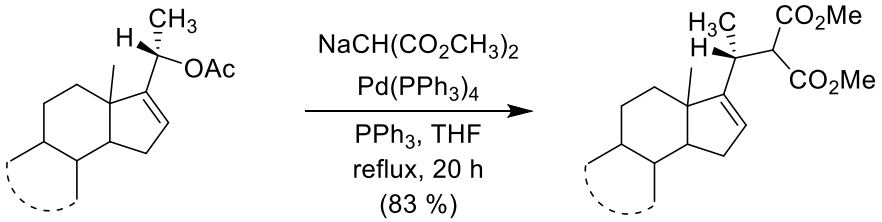
The first example of an allylic alkylation utilizing a carbon nucleophile was reported by Jiro Tsuji in 1965, wherein stoichiometric quantities of a π-allylpalladium complex were reacted with stabilized carbanions to form new carbon-carbon bonds in high yields.[15] This methodology was then greatly expanded upon over the following years, particularly by the Trost group who first introduced the use of phosphine ligands to these reactions. These initial forays into allylic

alkylation reactions were limited: requiring stoichiometric amounts of preformed π-allylpalladium complexes, four equivalents of phosphine, and were lacking in both scope and selectivity (Scheme 1.1).[16] Trost reported that in the absence of the phosphine ligands no alkylation product was obtained and suggested that coordination of the phosphine ligand to palladium was required for the formation of a cationic π-allylpalladium complex.[16] Later that same year Trost and Dietsche reported an asymmetric variant of the reaction utilizing (-)-sparteine and chiral phosphines to promote the reaction obtaining optically active alkylated products, though this approach still faced the same limitations as the initial report.[17]



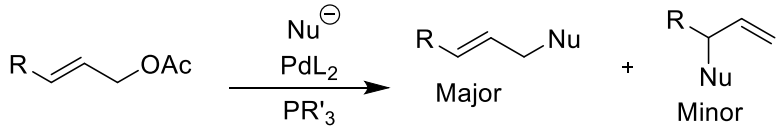
Scheme 1.1 The First Phosphine-Mediated Allylic Alkylation

The first allylic alkylation catalytic in palladium was reported by Trost and Verhoeven in 1976 when they showed the alkylation of an allylic acetate with the sodium salt of dimethyl malonate. Using as little as 0.1 mol % of tetrakis(triphenylphosphine)palladium, the alkylated products were obtained in excellent yields proceeding with complete retention of the stereochemistry (Scheme 1.2).[18] This was a significant advancement in this methodology since it allowed for the *in situ* generation of the π-allylpalladium complex and the regeneration of the catalyst system. Then, the following year, an asymmetric variant of the allylic alkylation reaction catalytic in palladium facilitated by chiral phosphine ligands was disclosed by Trost.[19]



Scheme 1.2 Alkylation of Allylic Acetates Catalyzed by Palladium

Generally, this reaction proceeds with the less substituted terminus being the most favoured site of C-C bond formation though there are exceptions. The selectivity of these reactions may depend upon both the substrate and catalyst system, and often a mixture of regioisomers are obtained (Scheme 1.3).[20]



Scheme 1.3 Regioselectivity in Allylic Alkylation Reactions

In the years since these discoveries there have been considerable advancements in the application of the allylic alkylation reaction, expanding its utility beyond palladium catalysts and allylic acetate or halide substrates.[21,22] Additionally, the scope of nucleophile has been expanded increasing the type of carbon-carbon bonds that can be formed and allowing for the generation of carbon-heteroatom bonds.[22] One of the greatest areas of research has been on the application of this reaction in asymmetric synthesis and in the generation of quaternary centres.[13,21–25] The mechanism of allylic alkylation reactions can be dependent upon many factors; however, the generally accepted mechanism for the palladium catalyzed coupling of allylic acetates with soft nucleophiles is depicted in Figure 1.3.[23]

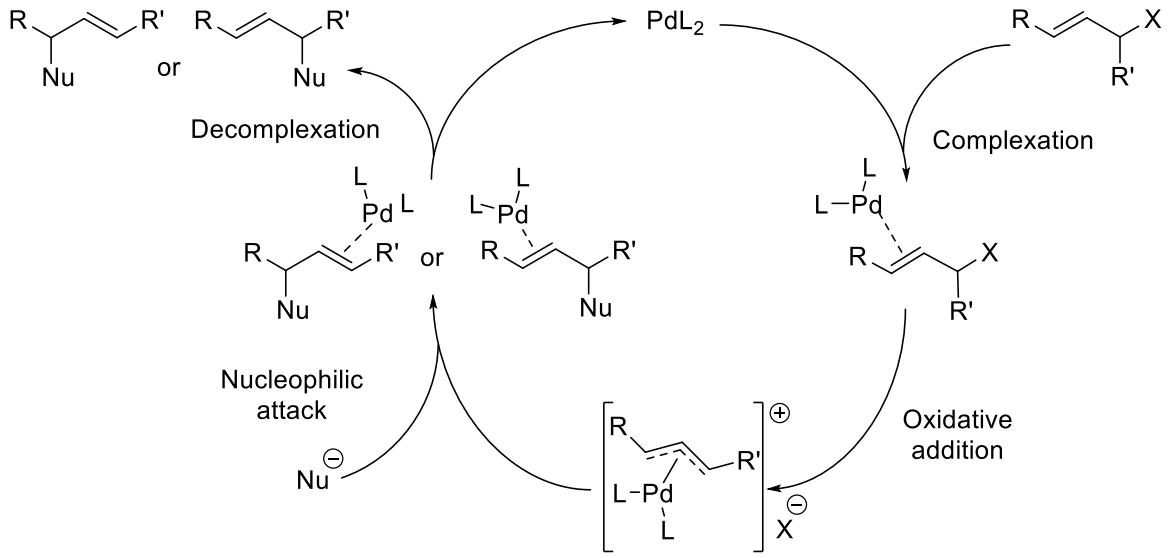
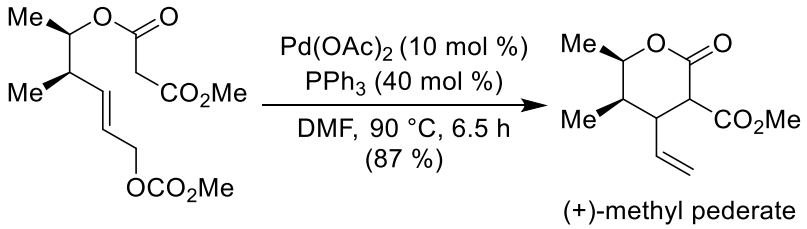


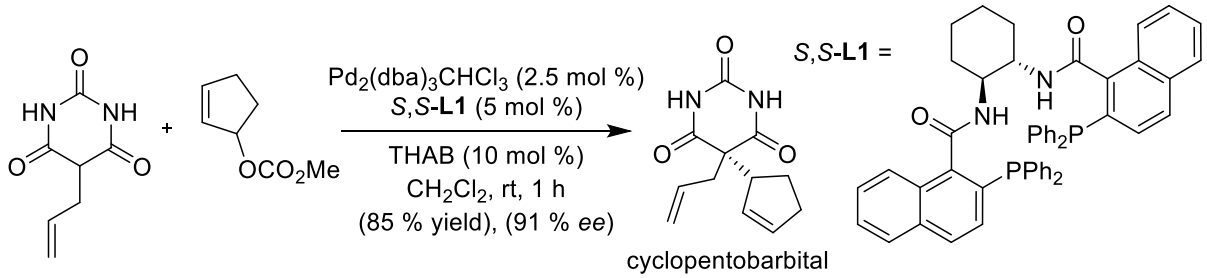
Figure 1.3 Mechanism of the Palladium-Catalyzed Tsuji-Trost Reaction

This mechanism proceeds with complete retention of stereochemistry due to two inversion events, the first being the oxidative addition step and the second being the attack of the nucleophile on the face opposite the π-allylpalladium complex.[23] This has allowed for stereochemical control in the synthesis of natural products and pharmaceutically active compounds from enantioenriched substrates, for which this reaction has been used extensively.[22,23,25-28] Intramolecular allylic alkylation was utilized by the Toyota group in the synthesis of (+)-methyl pederate, a potential intermediate in the total syntheses of a number of myclamides, a class of compounds with potent antiviral and antitumor activities (Scheme 1.4).[26]



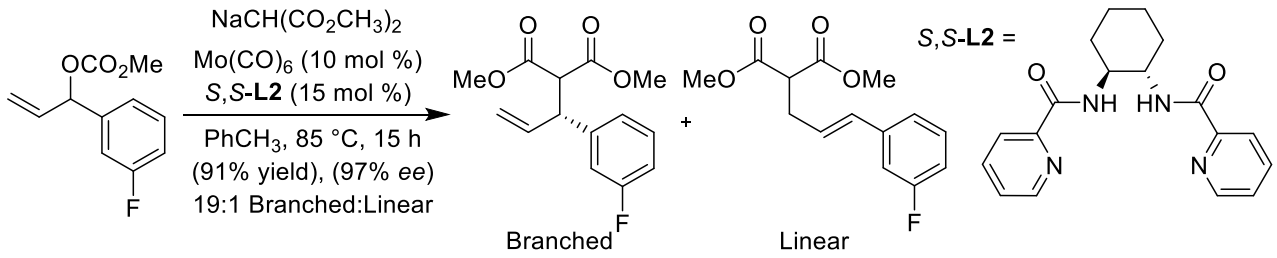
Scheme 1.4 Synthesis of Methyl Pederate by Intramolecular Allylic Alkylation

Trost also showed the first catalytic asymmetric synthesis of 5,5-disbustituted barbituric acid derivatives through the palladium-catalyzed alkylation of allylic carbonates with 5-substituted barbituric acids to yield enantioenriched products.[27] Through the application of this methodology the highly enantioselective synthesis of cyclopentobarbital, a sedative and hypnotic pharmaceutical was achieved in high yields (Scheme 1.5).[27]



Scheme 1.5 Asymmetric Synthesis of Cylopentobarbital via Allylic Alkylation

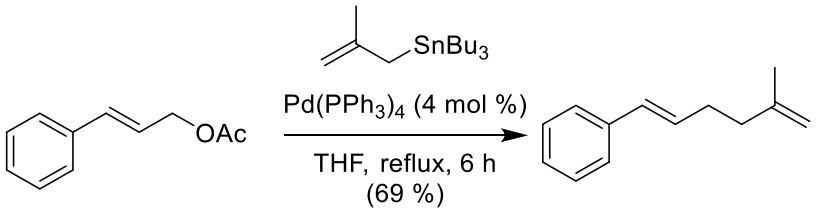
Researchers at Merck laboratories reported the molybdenum catalyzed asymmetric allylic alkylation of an allylic carbonate yielding the irregular, branched alkylation product in excellent yields with high enantiomeric excess (Scheme 1.6).[28] This was one of two key steps which set the stereochemistry in the synthesis of an undisclosed potential therapeutic agent.



Scheme 1.6 Molybdenum-Catalyzed Allylic Alkylation

1.3: Allylic Alkylation via Transmetalation

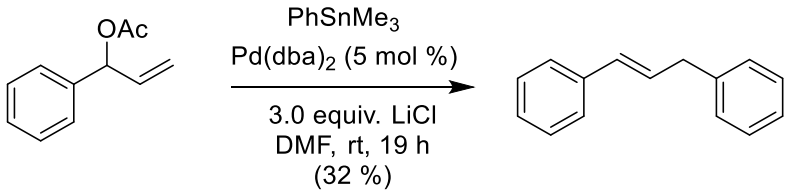
The implementation of transmetallating agents such as organostannanes expanded the scope of potential nucleophiles for use in allylic alkylation type reactions. Since the Tsuji-Trost reaction was historically restricted to stabilized carbanions (ex. the salts of compounds which possess an α-carbonyl group, either preformed or generated *in situ*), this adaptation has facilitated the formation of new carbon-carbon bonds not possible otherwise.[29] While this methodology has found some use in the synthesis of some target molecules, the utility and limitations of this reaction remain largely unexplored. The first example of the coupling between cinnamyl acetates and tetraalkyltin reagents was disclosed by Trost and Keinan in 1980.[29] In this seminal work they showed the efficient palladium catalyzed coupling utilizing a number of allyl stannanes as nucleophiles (Scheme 1.7).[29] In this work the scope of allylic acetates appeared to be limited to allyl acetate and cinnamyl acetate though this greatly increased the scope of nucleophiles that were available to partake in these reactions.[29]



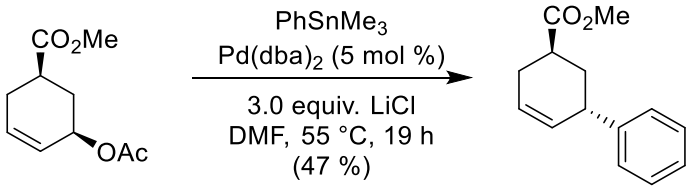
Scheme 1.7 Palladium-Catalyzed Coupling Between Allyl Stannanes and Cinnamyl Acetate

This methodology was expanded upon a decade later by the Hegedus group who showed the "ligandless" palladium catalyzed allylic alkylation of vinyl and phenyl stannanes in the presence of lithium chloride.[30] This work greatly expanded the scope of allylic acetates that were available to partake in these reactions. They were able to show the favoured formation of the linear alkylation product, even starting from the more substituted allylic acetate (Scheme 1.8), as well as

the complete inversion of stereochemistry at the site of alkylation (Scheme 1.9).[30] Under these conditions the application of ligands such as triphenylphosphine was observed to be detrimental to the reactivity of this system. This was proposed to be due to the suppression of the transmetalation of the organotin nucleophile to the cationic π-allylpalladium complex, owing to the electron donating effects of the ligands, which decreases the electrophilicity of the palladium catalyst.[30]

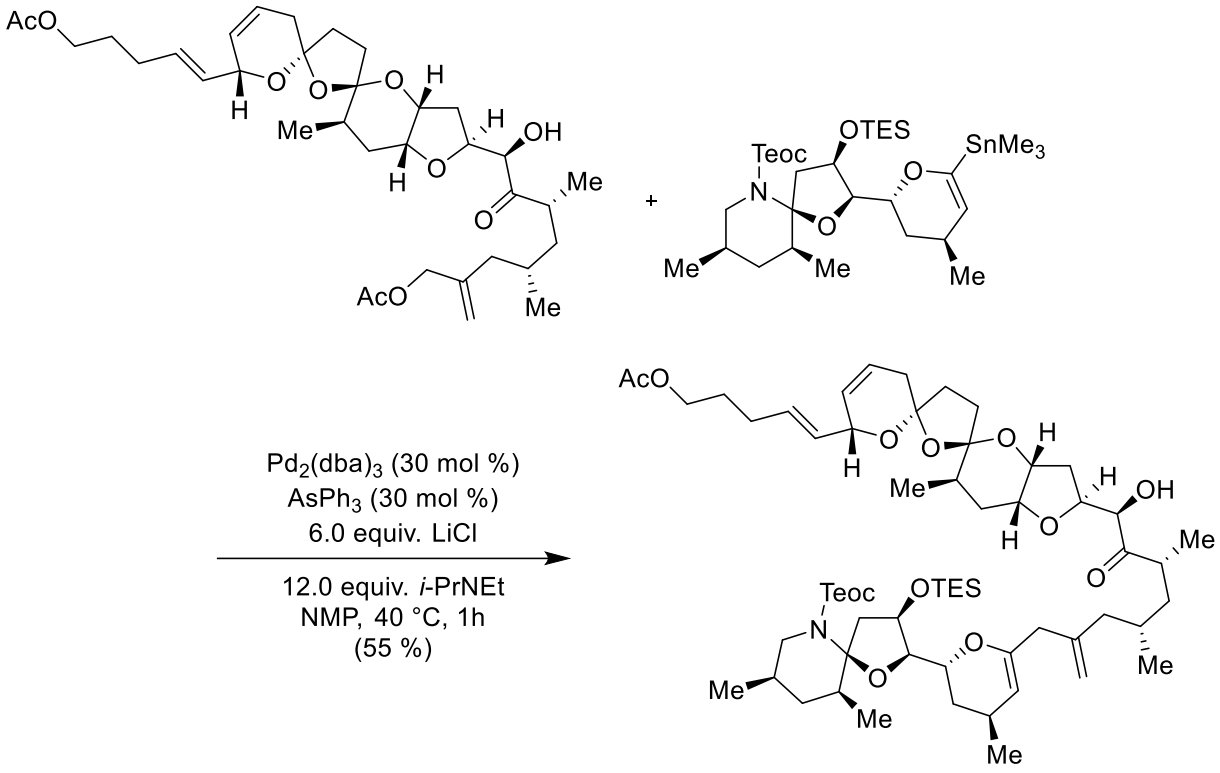


Scheme 1.8 Favoured Formation of Linear Alkylation Products in Allylic Alkylation via Transmetalation Reactions



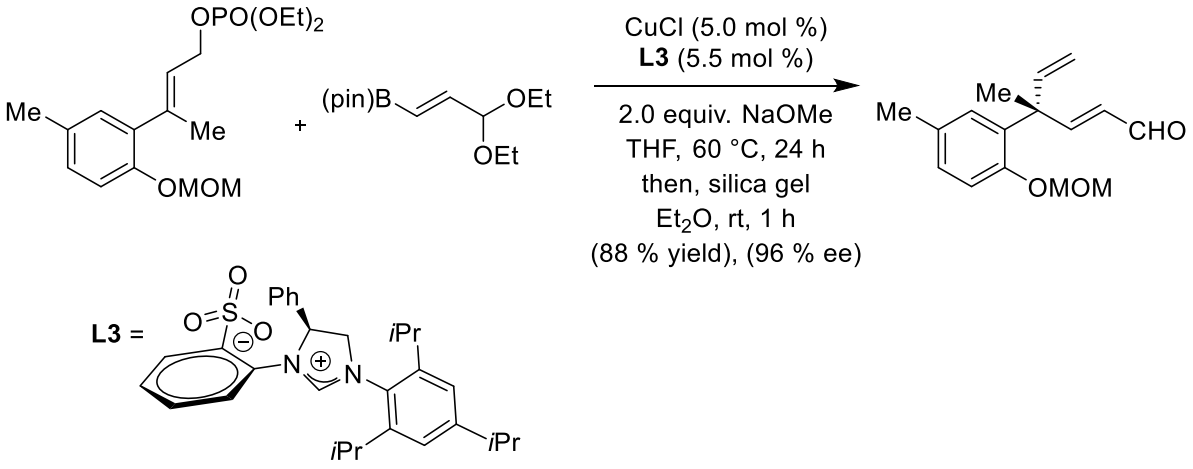
Scheme 1.9 Inversion of Stereochemistry at the Site of Nucleophilic Attack in Allylic Alkylation via Transmetalation Reactions

The alkylation of allylic substrates by transmetalation has found some utility in the synthesis of natural products. A notable example of this reaction was utilized by Nicolaou and co-workers in a key step towards the total synthesis of azaspiracid-1 (Scheme 1.10).[31]



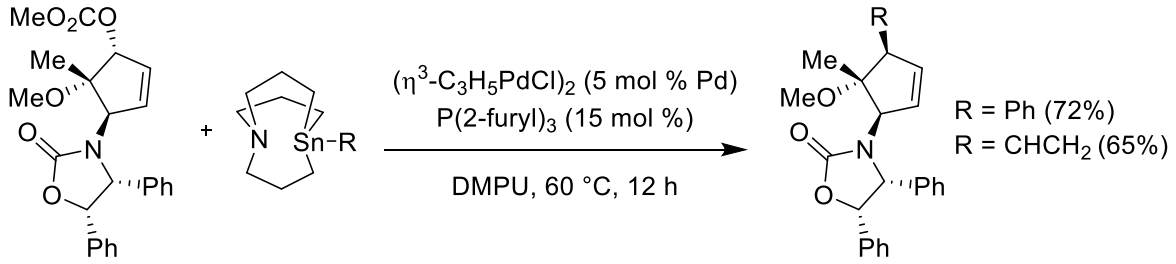
Scheme 1.10 Allylic Alkylation via Transmetalation as a Key Step Towards the Total Synthesis of Azaspiracid-1

Additionally, the use of organoboron reagents as nucleophiles has also been implemented in allylic alkylation reactions with some success. Hoveyda's group showed the copper catalyzed asymmetric allylic alkylation of allylic phosphates with vinylboron reagents which proceeded with high yields and excellent enantiomeric excess. They utilized this methodology in the enantioselective synthesis of a precursor to two diastereomers of Pummerer ketone, an intermediate in the biosynthetic route to morphine (Scheme 1.11).[32]



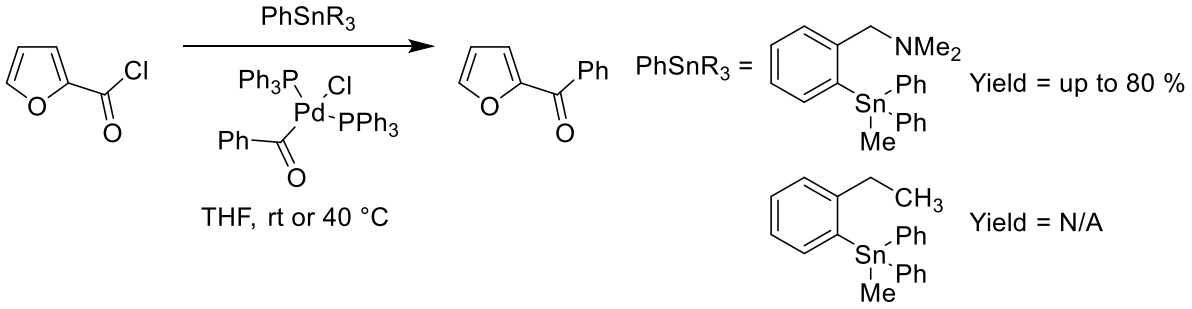
Scheme 1.11 Copper-Catalyzed Asymmetric Allylic Alkylation with Organoboron Nucleophiles

Finally, the group of Hegedus reported the successful alkylation of highly functionalized, sterically hindered allylic carbonates with C(sp^2)-stannatranes in good yields where a number of alternative strategies failed – including the use of tributyl- and trimethyl tin species, as well as organozinc and organoboron nucleophiles (Scheme 1.12).[33] Stannatranes are known to have internal coordination of the apical nitrogen atom to the tin centre, which results in an increased exocyclic bond length and enhanced reactivity in Stille couplings.[34] From the results of this synthesis, it appears that this intramolecular activation also extends to allylic alkylation reactions. It is worth noting that while C(sp^2) stannatranes coupled effectively, the transfer of a C(sp^3) alkyl group did not result in the alkylation of the allylic carbonate. Hegedus attributed this lack of reactivity to the slow transmetalation of the alkyl stannatrane which resulted in decomposition of the π-allylpalladium complex.[33]



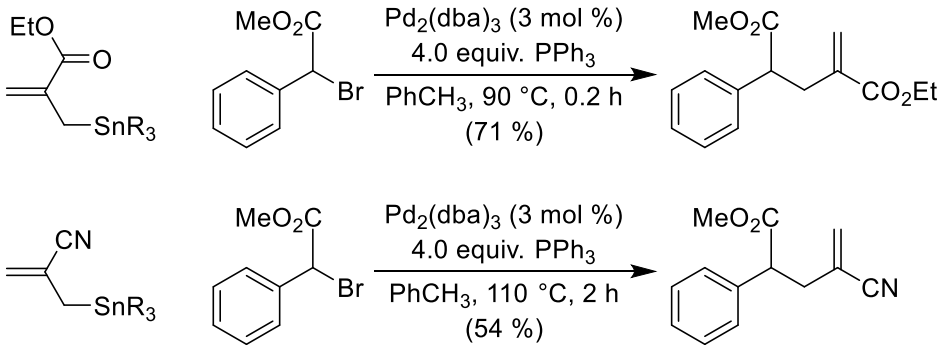
Scheme 1.12 Alkylation of Allylic Carbonates with Alkyl Stannatranes

The slow transmetalation of stannanes to palladium may be facilitated by the presence of an intramolecular Lewis basic site capable of coordinating with the tin centre in a manner analogous to the internal coordination of stannatranes. Brown showed that the presence of a neighboring tertiary nitrogen had a hundred-fold increase the reactivity of C(sp^2) stannanes in coupling reactions, demonstrated by increased reactivity in the cross-coupling of furoyl chloride with Lewis basic-activated organostannanes and a lack of reactivity in analogous non-activated organostannanes (Scheme 1.13).[35] Furthermore, Koten's group showed the internal coordination of nitrogen to the tin centre through both X-ray diffraction and increased reactivity of 8-(dimethylamino)-1-naphthyl-trimethylstannane in redistribution reactions with trimethyltin chloride.[36]



Scheme 1.13 Coordination of Internal Nitrogen Promotes Cross-coupling

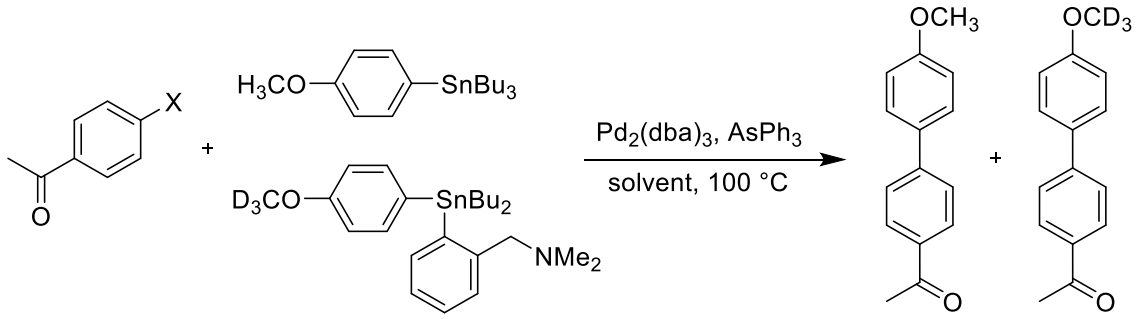
Additionally, Fouquet and co-workers were able to show that the intramolecular coordination of an ester carbonyl group to the tin centre resulted in a significant increase in the reactivity of monoallyltin nucleophiles in Stille couplings with benzyl bromide derivatives (Scheme 1.14).[37] Analogous substrates which did not possess a Lewis basic site capable of intramolecularly coordinating to the tin required more forcing conditions and extended reaction times in order to obtain the cross-coupled products.[37]



Scheme 1.14 Intramolecular Coordination of Carbonyl Oxygen Promotes Stille Couplings

Contrary to the experimental results obtained by Brown and Koten regarding the intramolecular activation of organotin nucleophiles with suitably oriented amine functionalities to facilitate Stille coupling reactions, Farina found that there was no appreciable increase in reactivity within these systems.[38,39] A study on the effect of substituents upon the aryl group in Stille coupling reactions between aryl(tributyl)stannanes and unsaturated triflates revealed no significant increase in reaction rates for substrates that contained Lewis basic sites that may coordinate to the tin centre casting doubt upon the generality of the observations made by Vedejs, Brown, and Koten.[38] Competition experiments in Stille coupling reactions using an aryl stannane and a deuterium labelled, intramolecularly activated aryl stannane in various solvents revealed no appreciable difference in reactivity between the two organometallic nucleophiles (Table 1.1).[39]

Table 1.1 Competition Experiments of Aryl Stannanes in Stille Couplings



Entry #	X	Solvent	Ratio OCH_3/OCD_3
1	I	$PhCH_3$	1.2
2	I	Dioxane	0.94
3	I	NMP	0.91
4	OTf	NMP	1.5

Negishi proposed that the transmetalation of organometallic species with palladium (II) intermediates is the rate determining step in the palladium-catalyzed cross-coupling of organozinc reagents with aryl and alkenyl halides.[40] The application of halide salts, particularly lithium chloride, has been long known to promote Stille cross-coupling reactions and the role of this additive has been proposed to be the facilitation of the transmetalation step in the catalytic cycle.[41,42] There are two generally accepted mechanisms for the transmetalation of transition metal catalysts with organometallic nucleophiles, which are the cyclic mechanism and the open mechanism, demonstrated by the depicted potential transition states for the Stille coupling of aryl bromides with methylstannatrane (Figure 1.4).[39]

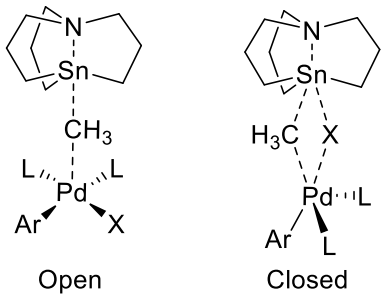


Figure 1.4 Open and Closed Transition States During Transmetalation

The use of highly polar, aprotic solvents such as DMF, DMSO, DMPU or HMPA also have significant impacts on increasing the rate of reaction and efficiency of Stille cross-couplings.[42] These solvents possess Lewis basic functionalities that may stabilize the electrophilic organometallic species formed during the reaction and are also capable of solubilizing additives such as lithium chloride.[42] Finally, the Farina group demonstrated the utility of electron-deficient ligands in promoting palladium catalyzed Stille cross-couplings.[43,44] Tri(2-furyl)phosphine and triphenylarsine were found to be the most effective ligand systems in the Suzuki coupling of tributyl(1-propenyl)tin with a C(sp^2) triflate and C(sp^3) alkyl chloride in the synthesis of C-3 substituted cephems.[43] "Soft ligands" such as these are less strongly donating to the palladium centre, increasing the electrophilicity of the palladium (II) species. This has the effect of facilitating the nucleophilic attack of the organotin species to the palladium catalyst, accelerating the rate of transmetalation and therefore increasing the rate and efficiency of Stille couplings.[43,44]

The mechanism of allylic alkylation via transmetalation proposed by Hegedus is shown in Figure 1.5. As was originally shown by Hegedus, there is inversion of stereochemistry at the site of nucleophilic attack due to the inversion of stereochemistry during oxidative addition and the retention of bond geometry during the transmetalation and reductive elimination steps.[45] The

inversion of stereochemistry allows for stereochemical control in the methodological approach for the synthesis of natural products or enantioenriched compounds.

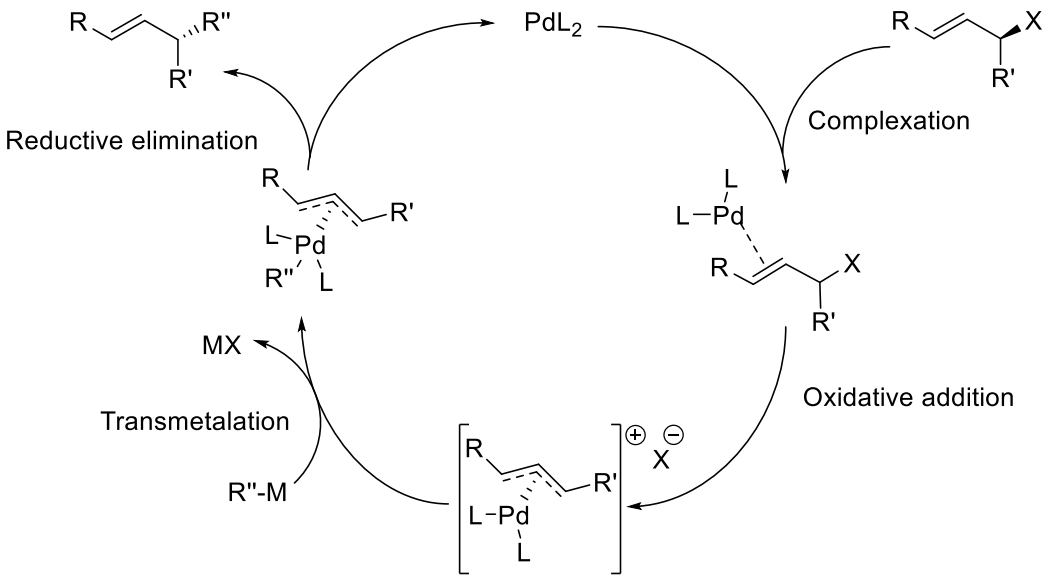


Figure 1.5 Mechanism of Allylic Alkylation via Transmetalation

1.4: Friedel-Crafts Alkylation/Acylation Reactions

The Friedel-Crafts alkylation and acylation of organic compounds are among the most important carbon-carbon bond forming reactions in organic chemistry.[46,47] Friedel-Crafts alkylation was first discovered more than 130 years ago and in the intervening years, these two reactions have undergone considerable advancement.[14] The Friedel-Crafts reactions were initially limited to arenes, which would be coupled with alkyl halides or acyl halides, generally promoted by stoichiometric quantities of Lewis acids such as $AlCl_3$.[14,46] This meant that there were significant drawbacks to the utility of these reactions owing to the large quantity of aluminum salt and corrosive by-products formed in the course of the reaction, which make workup and waste disposal tedious.[46] This is particularly true for Friedel-Crafts acylation reactions where $AlCl_3$ forms a stable complex with the ketone formed in the reaction.[46]

Additionally, the mechanism of the Friedel-Crafts alkylation from primary alkyl halides results in the generation of a primary carbocation which will often undergo rearrangement to a more stable secondary or tertiary carbocation, leading to a mixture of alkylation products (Figure 1.6).[48,49] The mechanism of Friedel-Crafts acylation reactions is analogous to that of Friedel-Crafts alkylation, proceeding through the formation of an acylium ion, though typically only the carbonylation product is observed.[49]

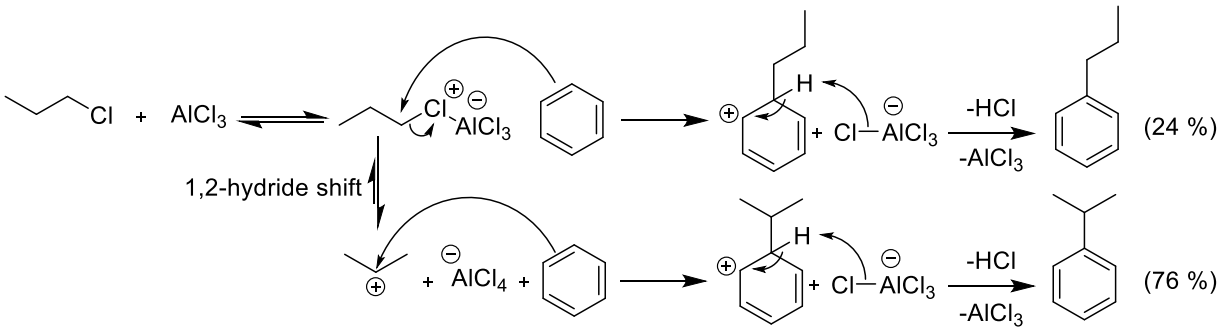
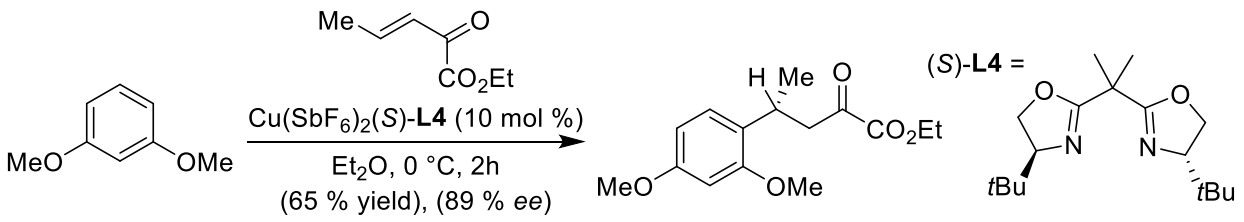


Figure 1.6 Mechanism of Friedel-Crafts Alkylation Reactions

The development of methods that use catalytic amounts of Lewis acids, such as the lanthanide triflates, have dramatically increased the synthetic utility of these reactions.[46,50,51] The application of electrophiles such as anhydrides, carboxylic acids, α,β-unsaturated carbonyls, alkenes, and alcohols has also been a significant advancement in expanding the scope of carbon-carbon bonds that can be formed in these reactions. [14,51,52] These substrates also have the benefit of decreasing the quantity of halogenated side products produced in the course of these reactions, though they generally require more forcing conditions.[51,52] The arylation of electron-deficient olefins by Friedel-Crafts alkylation represents a powerful tool for the functionalization of aromatic species.[53] To this end, Jensen and co-workers developed a method for the copper-catalyzed enantioselective Friedel-Crafts alkylation between arenes and β,γ-unsaturated α-ketoesters under mild conditions (Scheme 1.15).[53] While considerable progress has been made in developing

catalyst systems for such transformations, the explorations into novel electrophiles which possess suitable reactivity, stability, generality, and ease of synthesis are scarce.[46,47,50-56]



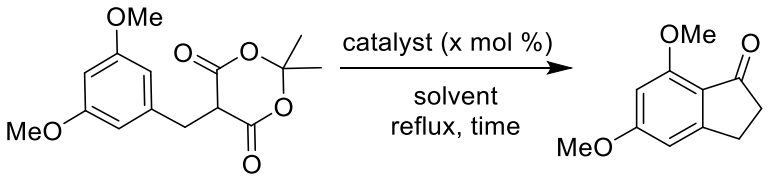
Scheme 1.15 Friedel-Crafts Alkylation Between Electron-Deficient Alkenes and Arenes

1.5: Friedel-Crafts Reactions Utilizing Meldrum's Acid Derivatives

Intramolecular variants of Friedel-Crafts acylation reactions are potent means of accessing the benzocyclic ketone skeletons; however, most of the first developed procedures suffered from many of the limitations described above.[51,55] Therefore, the Fillion group began to explore the use of new electrophilic coupling partners tethered to an arene in order to develop a novel, milder approach to intramolecular Friedel-Crafts acylation with easily synthesized and purified substrates, greater functional group tolerance, and decreased catalyst loading.[55]

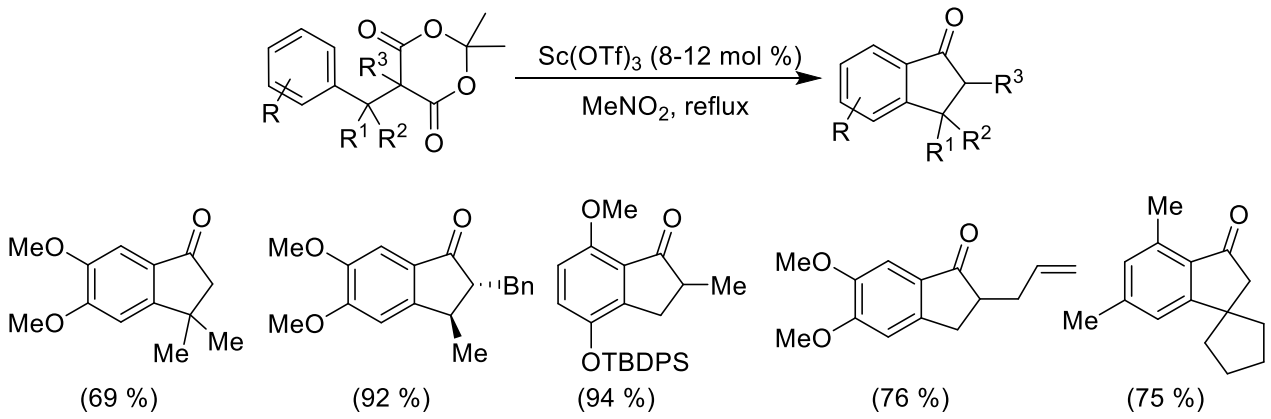
In 2003, the intramolecular acylation of highly functionalized benzyl Meldrum's acids, catalyzed by a number of Lewis and Brønsted acids, was reported by our group (Table 1.2).[55] While at that time there were a small number of intermolecular Friedel-Crafts acylation reaction conditions catalyzed by rare-earth metal triflates in the literature, intramolecular examples were largely unknown.[57,58] The metal triflate found to have superior catalytic activity in the intramolecular Friedel-Crafts acylation of 5-benzyl Meldrum's acids was $Sc(OTf)_3$. However, even in the absence of a catalyst, the model substrate 3,5-dimethoxybenzyl Meldrum's acid was found to give the cyclized product in refluxing nitromethane in a moderate yield (Table 1.2).[55]

Table 1.2 Friedel-Crafts Acylation of 5-(3,5-Dimethoxybenzyl) Meldrum's acid



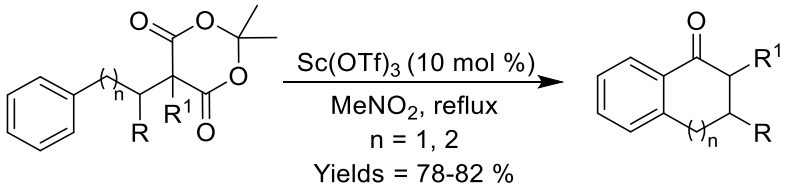
Entry	Catalyst	Solvent	Time (h)	% Yield
1	None	CH_3NO_2	3	52
2	$Dy(OTf)_3$ (12 mol %)	CH_3NO_2	1	56
3	$Yb(OTf)_3$ (12 mol %)	CH_3NO_2	1	67
4	$Sc(OTf)_3$ (12 mol %)	CH_3NO_2	1	73
5	TfOH (20 mol %)	$ClCH_2CH_2Cl$	2.75	38
6	TFA (20 mol %)	$ClCH_2CH_2Cl$	17	37
7	TMSOTf (20 mol %)	$ClCH_2CH_2Cl$	3	60

This work showed good functional group tolerance, allowing for the synthesis of diversely functionalized benzocyclic ketones in good to excellent yields. This was demonstrated by the synthesis of a large number of highly functionalized 1-indanones, of which a representative sampling is depicted in Scheme 1.16.[58]



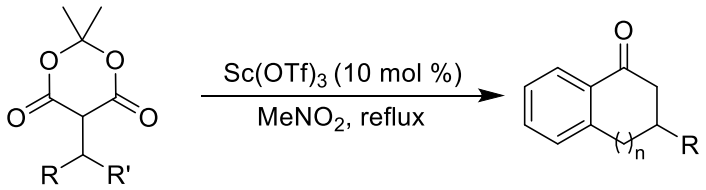
Scheme 1.16 Synthesis of Functionalized 1-Indanones from Benzyl Meldrum's Acids

Our group was also able to show the synthesis of 1-tetralones and 1-benzosuberones by increasing the length of the alkyl tether (Scheme 1.17).[58] In competition experiments, the results of which were amended by Douglas and co-workers, it was observed that 1-tetralones were preferentially formed over the corresponding indanones and benzosubarones, and that 1-indanones were favoured over benzosubarones (Table 1.3).[58,59]



Scheme 1.17 Synthesis of 1-Tetralones and 1-Benzosubarones from 5-Alkyl Meldrum's Acids

Table 1.3 Competition Experiments of 5-Alkyl Meldrum's Acids

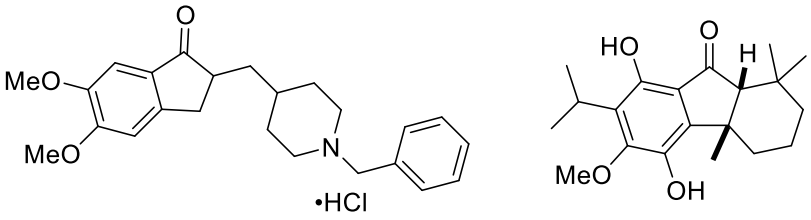


	Substrate[A]		Product		
Entry #	**R**	**R'**	**n**	**R**	**% Yield**
1	Ph	CH_2Ph	1	Ph	51
2	Ph	$(CH_2)_2Ph$	0	$(CH_2)_2Ph$	42
3	CH_2Ph	$(CH_2)_2Ph$	1	$(CH_2)_2Ph$	59

A: Substrate added by syringe pump over approximately 8 h followed by 1 h at reflux

The by-products of these cyclization reactions are acetone and carbon dioxide, both of which are highly volatile which represents an additional advantage to this methodology.[55] There

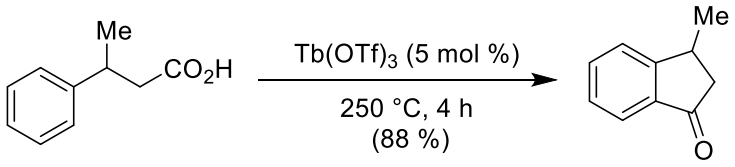
were some limitations to the generality of the reaction conditions, the presence of a basic nitrogen inhibited catalysis by Lewis acids; however, this was overcome by the application of an excess of Lewis or Brønsted acid.[58] The reactivity of substituted Meldrum's acids in intramolecular Friedel-Crafts acylation reactions would be exploited in our lab in order to conduct the total synthesis of donepezil hydrochloride and (±)-taiwaniaquinol B (Figure 1.7).[58,60]



Donepezil hydrochloride (±)-Taiwaniaquinol B

Figure 1.7 Structure of Donepezil Hydrochloride and (±)-Taiwaniaquinol B

In contrast to the methodology developed in the Fillion lab, Shimada's group reported the $Tb(OTf)_3$ catalyzed Friedel-Crafts acylation of 3-arylpropionic acids in 2008. They utilized this approach to synthesize several 1-indanones; however, these conditions required high temperatures, longer reaction times, and only displayed moderate functional group tolerance (Scheme 1.18).[56]



Scheme 1.18 Intramolecular Friedel-Crafts Acylation of a Tethered Carboxylic Acid

The forcing conditions required for the Lewis acid-catalyzed cyclization of 3-arylpropionic acids illustrates the synthetic utility and electrophilic acylating potential of Meldrum's acids derivatives. In 1987 Nair reported the one-pot synthesis of 4-aryl-3,4-dihydrocoumarins from Meldrum's acid, benzaldehyde and phloroglucinol.[61] The scope and limitations of this procedure

were not well defined, but Nair proposed that this reaction proceeded through the formation of a benzylidene Meldrum's acid intermediate.[61] Since our group had previously shown that Meldrum's acid derivatives were powerful acylating reagents when catalyzed by Lewis acids, and inspired by Nair's report, our group began to explore the Lewis acid-catalyzed reactions of alkylidene Meldrum's acid derivatives with phenols. It was reasoned that the electron-deficient nature of the alkene in alkylidene Meldrum's acids would make this substrate ideal for Lewis acid promoted nucleophilic attack by arenes.[62,63] Using this strategy, the Fillion group was able to demonstrate the efficient synthesis of coumarins or chromen-2-ones, 3,4-dihydrocoumarins or chroman-2-ones, chromones, and chromanones in this manner.[62,63] The heterocycle formed was predictable and dependent upon the substitution of the Meldrum's acid derivatives (Figure 1.8).[62]

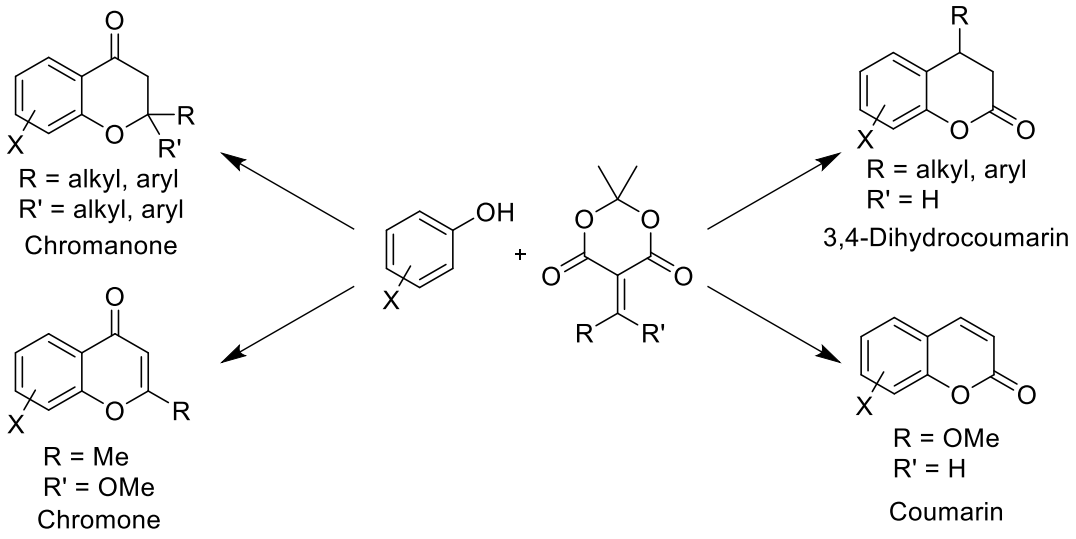
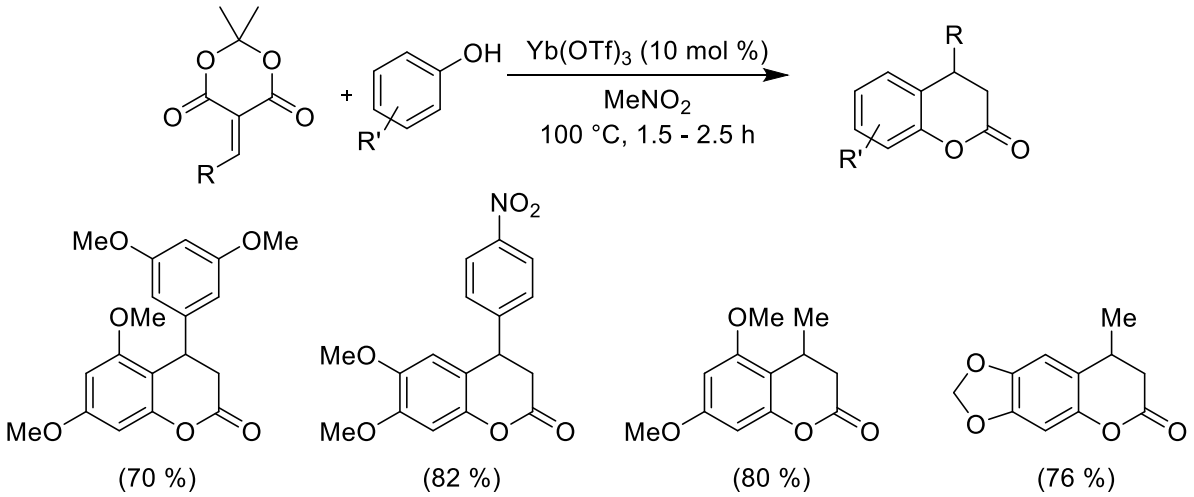


Figure 1.8 Lewis Acid-Catalyzed Reactions of Alkylidene Meldrum's Acids with Phenols

The unsaturated coumarins and chromones are likely formed via a domino Lewis acid-catalyzed Friedel-Crafts alkylation/acylation followed by the elimination of methanol.[62] Coumarins and 3,4-dihydrocoumarins are the product of Friedel-Crafts *C*-alkylation/*O*-acylation, while the chromone and chromanones are the product of *O*-alkylation/*C*-acylation.[62] These

reactions proceeded efficiently when catalyzed by $Yb(OTf)_3$ moderate functional group tolerance was demonstrated for each of these transformations, and the short reaction times and generally high yields make these synthetic approaches very attractive.[62,63] Of the most consequence to this research project is the synthesis of 3,4-dihydrocoumarin derivatives from functionalized alkylidene Meldrum's acids. A representative sample of 3,4-dihydrocoumarins synthesized in this manner by our group is depicted in Scheme 1.19.[62]

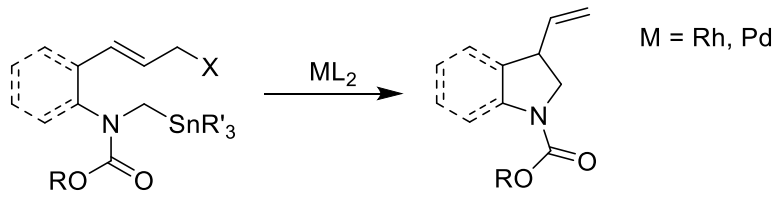


Scheme 1.19 Synthesis of 3,4-Dihydrocoumarins from Alkylidene Meldrum's Acids

1.6: Summary and Thesis Objectives

The continued development of methodologies for the formation of new carbon-carbon bonds in an efficient and synthetically useful manner is of special importance to organic chemists. The alkylation of allylic acetates in the presence of transition metal catalysts represents a powerful tool in the synthetic chemist's arsenal to facilitate such transformations. Furthermore, intramolecular allylic alkylation reactions are useful methods for the synthesis of carbo- and heterocycles. To this end we set out to develop a substrate which under the correct conditions

would allow for the transition metal-catalyzed intramolecular alkylation of an allylic acetate via the transmetallation of a tethered C(sp^3) stannane or stannatrane (Scheme 1.20).



Scheme 1.20 Proposed Substrate Design for the Palladium-Catalyzed Intramolecular Allylic Alkylation by Transmetallation of C(sp^3) Stannanes

The development of asymmetric variants of such a transformation would have the potential to greatly expedite the synthesis of enantioenriched heterocycles. To our knowledge, if this transformation is realized this would represent the first intramolecular transition metal-catalyzed alkylation of allylic acetates utilizing C(sp^3) organotin nucleophilic partners in allylic alkylation reactions, the results of which will be discussed in Chapter 2.

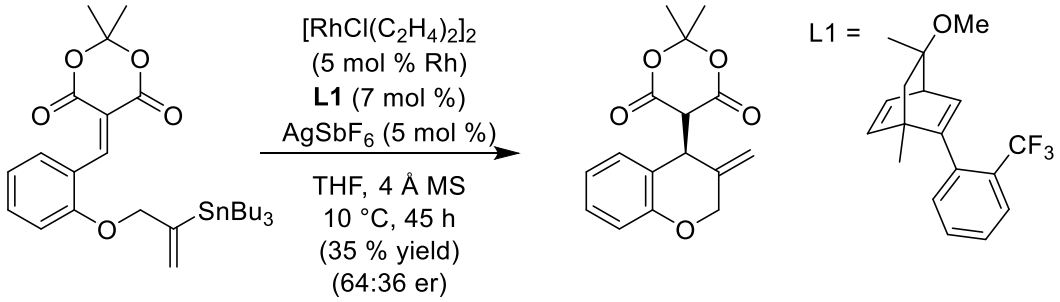
Additionally, as a separate project we proposed the application of the domino Friedel-Crafts alkylation/acylation reaction between benzylidene Meldrum's acids and phenols that had been previously developed in the Fillion lab for the synthesis of a number of highly functionalized 4-aryl-3,4-dihydrocoumarins. This skeleton represents a subclass of the neoflavonoid family of compounds; polyphenolic flavonoids have been shown to have affinity for consequential regions of the microtubule associated protein tau which has been implicated in the development and progression of Alzheimer's disease. We therefore set out to synthesize a number of polyphenolic derivatives of the 4-aryl-3,4-dihydrocoumarin skeleton using this methodology in order to assess the affinity of these compounds for a synthetic model of tau. The synthesis of these compounds is covered in Chapter 3, and the biological assessment of these compounds remains to be realized.

Chapter 2: Synthesis of 3-Vinylindolin-1-carboxylic Acid Esters

2.1: Introduction and Background

As discussed in Chapter 1, transition metal-catalyzed allylic alkylation reactions represent a powerful tool to facilitate the formation of new carbon-carbon bonds. The application of organotin nucleophiles in palladium-catalyzed reactions has broadened the scope of coupling partners to which this methodology may be applied; however, there are still limitations. The transfer of C(sp^3) carbons in this manner are rare, due to the slow transmetalation of these nucleophiles to palladium which may lead to the decomposition of the cationic π-allylpalladium complex.[33] Studies have shown that compounds which possess intramolecular coordination of a Lewis basic site to the tin centre display increased reactivity in Stille couplings which has been attributed to an increased rate of transmetalation.[34-36]

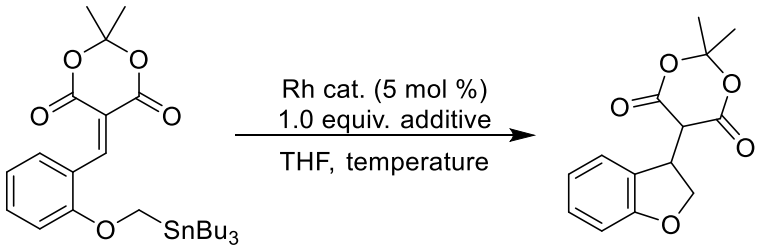
In the past, our group has made considerable effort towards exploring the reactivity of organometallic nucleophiles in conjugate addition reactions with electron-deficient alkenes.[64-66] For example, in 2009 our group reported a number of intermolecular asymmetric conjugate additions between benzylidene Meldrum's acids and alkenyl stannanes.[64] In this same report it was found that alkenyl stannanes which contained a geminal olefin were unreactive in intermolecular couplings under the developed conditions; however, our group was able to show the intramolecular conjugate addition of a geminal alkenyl stannane to yield the cyclized product with moderate yield and enantioselectivity suggesting increased reactivity and rate of reaction in intramolecular conjugate addition reactions (Scheme 2.1).[64]



Scheme 2.1 Rhodium-Catalyzed Intramolecular Conjugate Addition of a Geminal Alkenyl Stannane

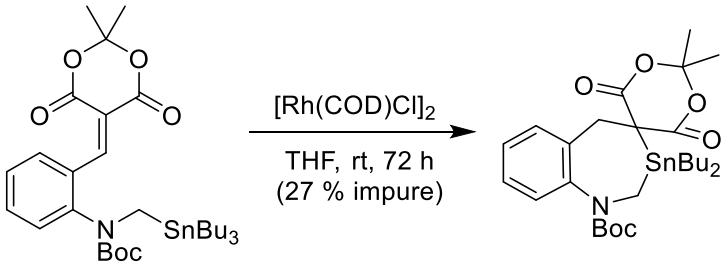
David Moon, a member of our research group, synthesized a benzylidene Meldrum's acid derivative which contained a C(sp^3) stannane bound to an α-oxygen which was expected to both stabilize the growing negative charge on the methylene carbon, as well as prevent β-hydride elimination from occurring.[67] Moon was able to show the intramolecular conjugate addition of this substrate though the activity of the rhodium catalysts employed appeared to be negligible, and rather the reactions seemed to be promoted by the presence of TBAB (Table 2.1).[67]

Table 2.1 Intramolecular Conjugate Addition of a C(sp^3) Stannane with an Electron-Deficient Alkene



Entry	Catalyst	Temp (°C)	Additive	% Yield
1	$[Rh(COD)(MeCN)_2]BF_4$	80	H_2O	0
2	$[Rh(COD)(MeCN)_2]BF_4$	50	H_2O, TBAB	23
3	None	50	H_2O, TBAB	29

A similar approach was employed by Siawash Ahmar in our group who successfully synthesized a benzylidene Meldrum's acid which contained a C(sp^3) stannane bound to a *tert*-butyl carbamate in the *ortho* position of the aromatic ring (Scheme 2.2).[68] The carbamate was expected to promote the transmetalation of the C(sp^3) stannane to the rhodium catalyst by acting as an intramolecular directing group and further stabilize the rhodium centre via intramolecular coordination. This substrate was subjected to a number of rhodium-catalyzed conjugate addition conditions but none of the expected 3-substituted indoline product was obtained. Siawash proposed that the carbonyl oxygen of the carbamate promoted the transmetallation of an *n*-butyl group to the rhodium catalyst which subsequently underwent β-hydride elimination. This was followed by reduction of the alkylidene by hydrorhodiation, and the subsequent nucleophilic attack of the Meldrum's acid enolate to the tin centre gave rise to the metallacycle depicted in Scheme 2.2, though the tin centre acting as an electrophile in this manner is suspect.[68]



Scheme 2.2 Attempted Rhodium-Catalyzed Conjugate Addition of an Intramolecularly Activated C(sp^3) Stannane to an Electron-Deficient Alkene

While our group had shown that rhodium-catalyzed conjugate additions to electron deficient alkenes were an efficient way of developing new sp^2-sp^3 carbon-carbon bonds, attempts at developing methods for intramolecular variants that would facilitate the formation of new C(sp^3)-C(sp^3) bonds suffered from poor selectivity and yields.[64,67,68] We therefore decided to change the nature of the olefinic electrophile involved in the reactions from a benzylidene

Meldrum's acid to a cinnamyl acetate. Accordingly, we designed a substrate (**1**) which contained a carbamate functionality bound to a C(sp^3) stannane which was tethered to a cinnamyl acetate that we believed would facilitate the synthesis of 3-vinylindoline derivatives under rhodium catalysis. In this system we first anticipated that the transmetalation of the rhodium catalyst with the C(sp^3) organotin centre would yield the active C(sp^3) organorhodium species (Figure 2.1).[69,70] Subsequent carborhodation of the allylic acetate would yield a η^1-rhodium complex and then β-elimination of the acetate functionality could yield the S_N2' nucleophilic substitution product, a 3-vinylindoline derivative, and regenerate the rhodium (I) catalyst (Figure 2.1).[71,72,73]

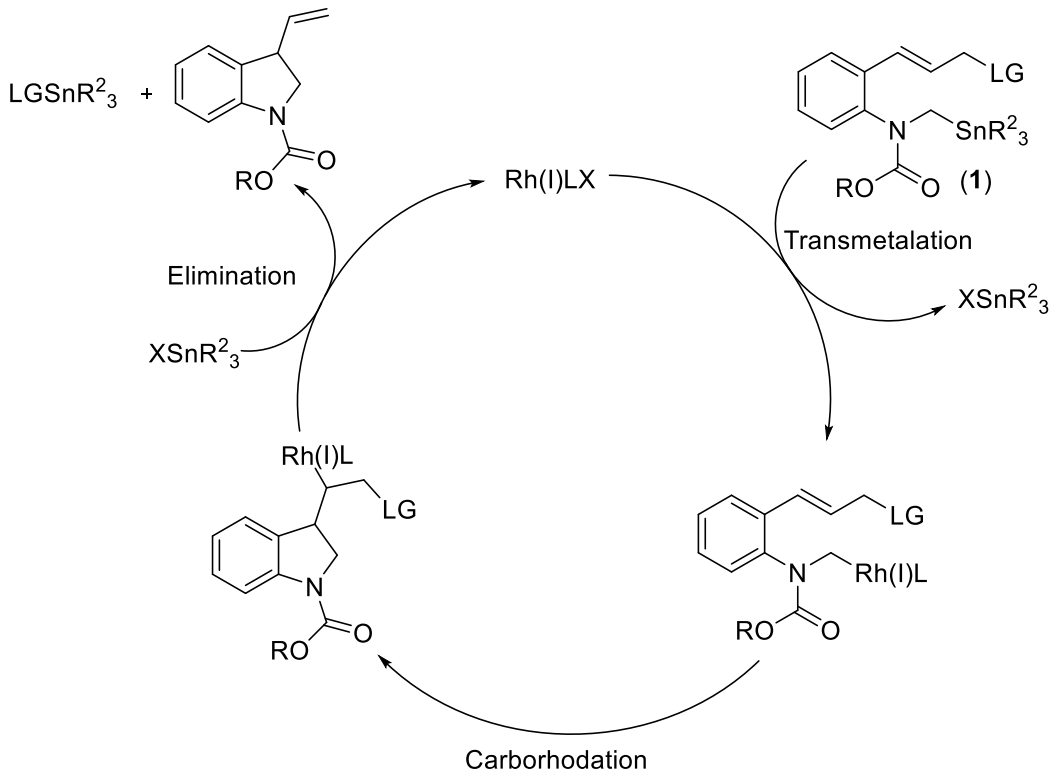
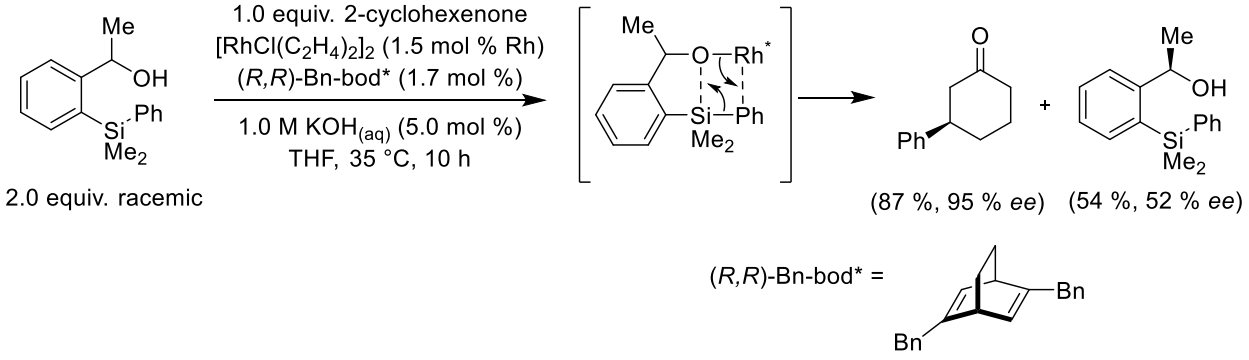


Figure 2.1 Proposed Mechanism for the Intramolecular Rhodium-catalyzed Nucleophilic Substitution of Allylic Acetates

Furthermore, we anticipated that the carbamate functionality adjacent to the methylene carbon would be suitably oriented to act as a directing group for the rhodium catalyst, promoting

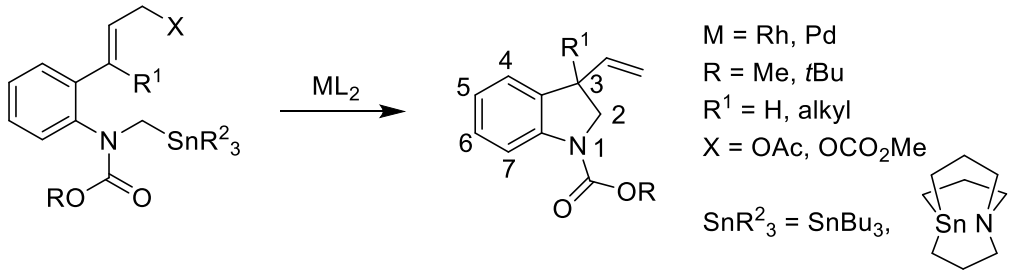
transmetalation with the C(sp^3) stannane to form an active organorhodium species. Promotion of transmetalation of rhodium catalysts with organosilanes through the Lewis basic activation of an adjacent benzylic alcohol was demonstrated by the Hyashi group in enantioselective 1,4-conjugate addition processes.[74] Hyashi proposed that the alcohol functionality assisted the transmetalation by the formation of a rhodium alkoxide intermediate which would direct the catalyst to the organometallic nucleophile to form the active organorhodium species (Scheme 2.3). This was supported by the observation of enantioenrichment in the unreacted aryltriorganosilane when two equivalents of this reagent were employed with a chiral rhodium catalyst system (Scheme 2.3).[74] We anticipated that the carbonyl group present in the carbamate functionality may be able to play a similar role in directing the rhodium catalyst promoting transmetalation with the C(sp^3) stannane.



Scheme 2.3 Intramolecular Promotion of Transmetalation in Conjugate Addition Reactions

This same substrate when complexed with a palladium catalyst, would form an electrophilic, cationic π-allylpalladium complex. Similarly, we reasoned that if the palladium-catalyzed reaction was successful we could anticipate the synthesis of 3-vinylindolines through the formation of the C2-C3 carbon-carbon bond (indole numbering). These approaches were advantageous as it would also be possible to generate an all carbon quaternary centres in this manner through substitution on the allylic acetate group (Scheme 2.4). As far as we are aware, this

would also represent the first intramolecular alkylation of allylic acetates utilizing a C(sp^3) stannane in transition metal-catalyzed allylic alkylation reactions.



Scheme 2.4 Proposed Substrate Design for the Intramolecular Allylic Alkylation via the Transmetalation of a Tethered C(sp^3) Stannane

While the development of new methods of carbon-carbon bond formation is one of the key areas of research in synthetic organic chemistry, the efficient synthesis of heterocycles is in and of itself a desirable goal. The indole skeleton represents one of the most ubiquitous motifs in natural products and pharmacologically active chemical species.[2,75] The biological activity of indoles and indolines (2,3-dihydroindole) includes, but is not limited to, analgesic, anticancer, antioxidant, antibacterial, antiprotozoan, anti-inflammatory, insecticidal, antiviral and antifungal properties.[75-78] Examples of biologically active indole derivatives include pericine, an opioid agonist and anti-cancer agent; bizelesin, a pyrroloindole dimer which contains two indoline and four indole moieties which has pronounced anti-tumor and cytotoxic effects, and the 2,3-cyclized-indoline physostigmine an acetylcholinesterase inhibitor which had seen trials for the treatment of Alzheimer's disease but was abandoned due to pronounced side effects (Figure 2.2).[79-82] Owing to such diverse biological activity there has been considerable effort placed in the development of new synthetic methods to access these bicyclic heterocycles.

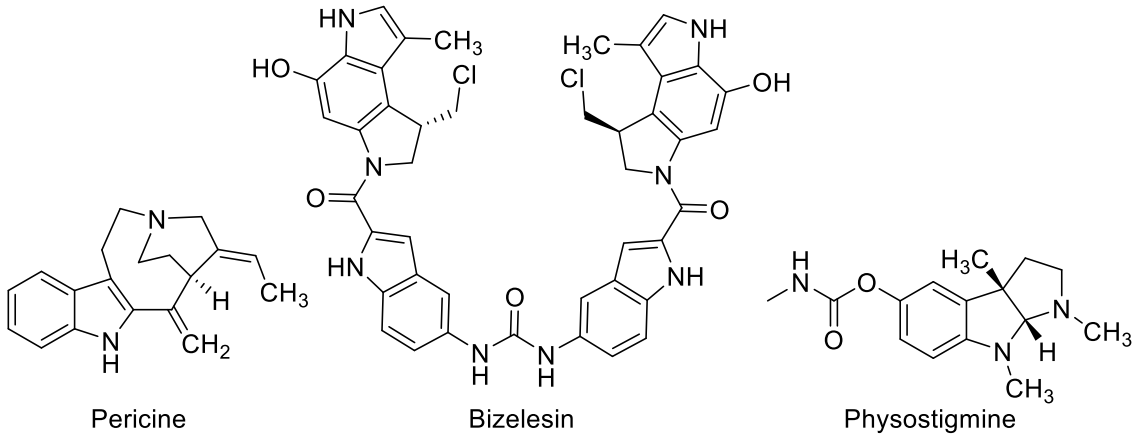


Figure 2.2 Biologically Active Indole and Indoline Derivatives

When considering possible disconnections in the synthesis of indoline heterocycles there are in essence four approaches that may be taken. In a review of the literature it was noted that three of these synthetic approaches have used relatively extensively: 1,2 C-N bond formation, 1,5 C-N bond formation, and 3,4 C-C bond formation while one remains largely unexplored: 2,3 C-C bond formation (Figure 2.3).[83-92]

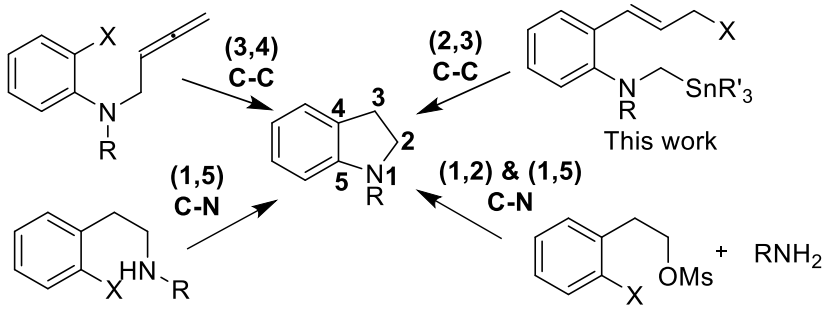
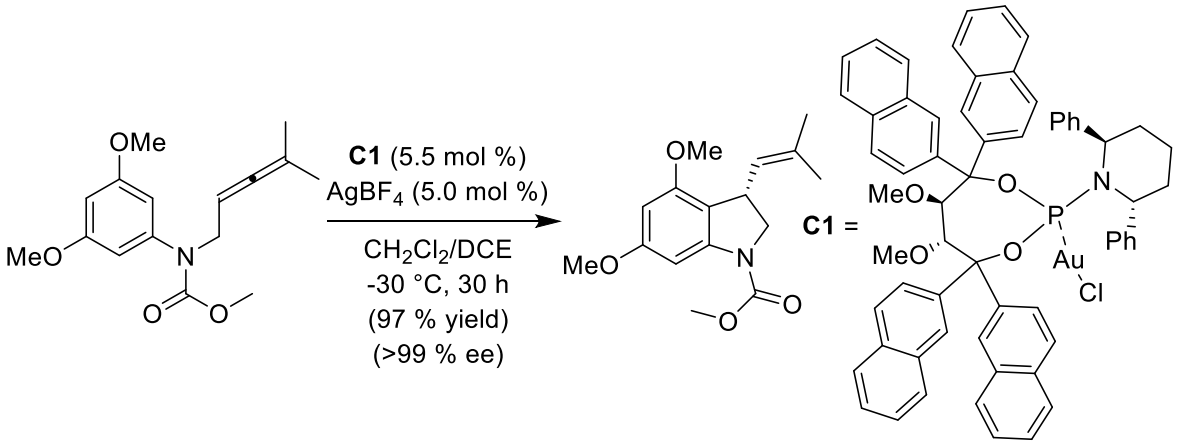


Figure 2.3 Representative Synthetic Approaches in the Synthesis of Indolines

In the course of this research project we will show an effective means of promoting the transmetalation of a C(sp^3)-tin moiety to a transition metal catalyst in intramolecular allylic alkylation reactions in order to facilitate the synthesis of new carbon-carbon bonds and simultaneously provide a new means of accessing the indoline skeleton. As far as we are aware,

this is the first example of indoline synthesis wherein the ring closure of the pyrrolidine moiety is undertaken by the formation of the C2-C3 carbon-carbon bond (Figure 2.3).[90]

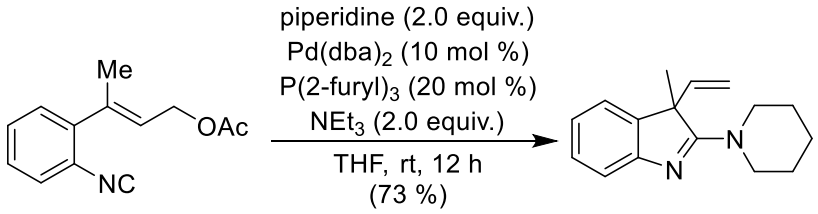
One of the many benefits of palladium catalysis is the ability to develop enantioenriched products through the application of chiral ligands.[21, 23, 25] As shown in Scheme 2.3, the anticipated product formed in the proposed intramolecular allylic alkylation reaction is a 3-vinylindoline derivative. To date the only groups who have reported the synthesis of 3-vinylindolines have utilized radical based cyclization reactions to generate the pyrrolidine ring which yield racemic mixtures.[93-96] In contrast to these approaches, Fürstner and co-workers showed the gold catalyzed, asymmetric intramolecular hydroarylation of tethered allenes in the synthesis of methyl 3-(2-methylpropenyl)indoline-1-carboxylate (Scheme 2.5).[97] This procedure was only applicable to



Scheme 2.5 Gold-Catalyzed Asymmetric Synthesis of 3-Alkenylindolines

electron-rich aromatic substrates, but proceeded in moderate to excellent yields to furnish the corresponding 3-alkenylindolines, and upon recrystallization optically pure materials could be obtained. Therefore, the development of a more general method to access enantioenriched 3-alkenylindolines would be of great synthetic utility.

The Takemoto group utilized an intramolecular palladium-catalyzed allylic amidination reaction in the synthesis of 3,3-disubstituted 2-aminoindolenines which possessed a terminal alkene at the C3 position of the indolenine ring (Scheme 2.6).[98] This reaction utilized an isocyanate functional group as a C(sp^2) nucleophile to facilitate the formation of the C2-C3 carbon-carbon bond in the indolenine core and featured the concomitant introduction of the 2-amino functionality. The application of a chiral amine such as *L*-proline methyl ester induced moderate diastereoselectivity in the product indicating that the steric bulk of the amine influences stereochemistry at the C3 position of the heterocyclic ring.[98] To the best of our knowledge a truly asymmetric variation of this reaction through the use of racemic starting materials and chiral ligands has not been reported. The results of this synthesis suggest that intramolecular allylic alkylation reactions may represent valuable means of synthesizing 3-substituted indole derivatives that possess all carbon quaternary centres at the C-3 position.

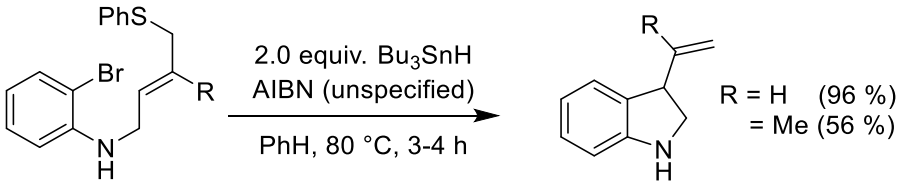


Scheme 2.6 Intramolecular Allylic Amidination in the Synthesis of 3,3-Disubstituted 2-Piperidinylindolenine

2.2: Previous Methods of Accessing 3-Vinylindolines

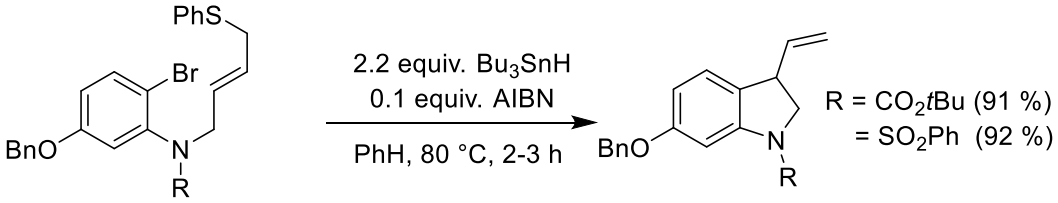
To date three methods have been reported for the synthesis of 3-substituted indoline derivatives which contain a terminal alkene. The first such example was published in 1982 by the Ueno group though a radical cyclization of *N*-(4-phenylthio-2-butenyl)-2-bromoanilines (Scheme

2.7).[88] This reaction was induced by tributyltin hydride and the radical initiator AIBN (azobisisobutyronitrile) to give the corresponding 3-alkenyl indolines.



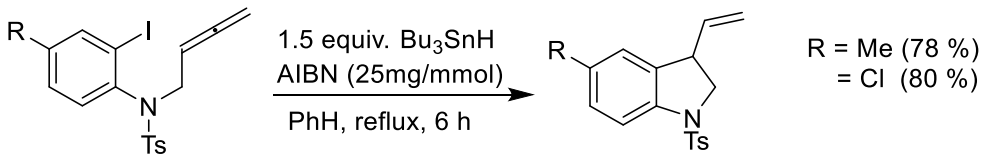
Scheme 2.7 Tributyltin Hydride-Mediated Synthesis of 3-Alkenylindolines

This methodology would be employed by Boger and co-workers in the synthesis of the left-hand subunit of CC-1065, an anti-tumor/anti-biotic indole alkaloid first isolated from cultures of *Streptomyces zelensis*. In this report, the indoline motif of the left-hand subunit was synthesized by the cyclization of 5-benzyloxy-2-bromo-*N*-(3-(phenylthio)allyl)aniline promoted by tributyltin hydride and AIBN as was first shown by Ueno (Scheme 2.8).[89]



Scheme 2.8 Tributyltin Hydride-Mediated Cyclization in the Partial Synthesis of CC-1065

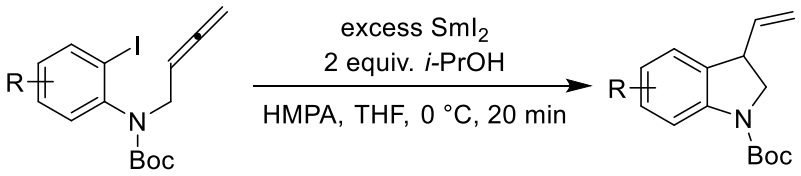
Balasubramanian's group reported the radical cyclization of *o*-haloaryl allenylmethyl amines and ethers furnishing *N*-tosyl-3-vinylindolines and 3-vinyl-2,3-dihydrobenzofurans in moderate to excellent yields promoted by tributyltin hydride and AIBN (Scheme 2.9).[90]



Scheme 2.9 Tributyltin Hydride-Mediated Radical Cyclization of Allenes

Finally, Yamashita's group developed the intramolecular cyclization of tethered allenes with aryl iodides promoted by samarium iodide (Table 2.2). This allowed for the synthesis of a number of 3-vinylindoline derivatives generally proceeding in excellent yields.[91]

Table 2.2 Samarium Diiodide-Mediated Cyclization of *N*-Tethered Allenes



Entry	R	% Yield	Entry	R	% Yield
1	H	97	**5**	4-Cl	62
2	4-OMe	89	**6**	3-OMe	90
3	4-Me	81	**7**	5-OMe	85
4	4-CO_2Me	48	**8**	6-OMe	88

From this review of methods to access 3-alkenylindolines possessing terminal alkenes, it is evident that there is considerable room for improvement in terms of functional group tolerance, efficiency, and selectivity. The results of our exploration into developing a palladium catalyzed allylic alkylation via the transmetalation of an intramolecularly activated tethered C(sp^3) organotin reagent will be discussed in the following section.

2.3: Proposal

When considering a model compound to explore the reactivity of a C(sp^3) stannane under rhodium and palladium catalysis, we envisaged the synthesis of derivatives of substrate **1** (Figure 2.4). Complexation with palladium would form a cationic η^3-palladium complex which could undergo transmetalation with the tethered C(sp^3) organotin nucleophile to form the desired C-C bond. We anticipated that the treatment of this substrate with rhodium (I) catalysts would first undergo transmetalation to form an organorhodium intermediate which could undergo nucleophilic substitution with the allylic acetate functionality to form the desired C-C bond.

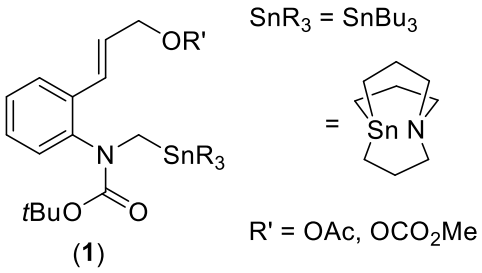
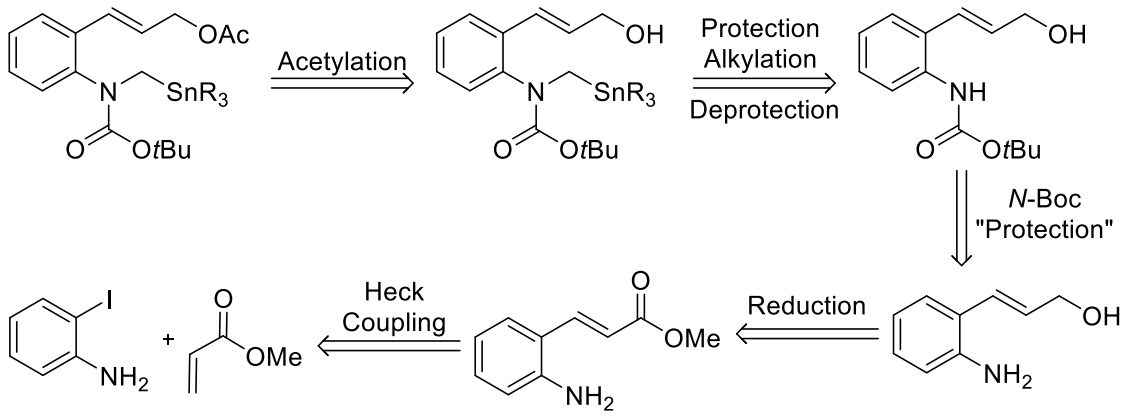


Figure 2.4 Design of Model Substrates for Intramolecular Allylic Alkylation Reactions

A retrosynthetic analysis suggested that derivatives of **1** could likely be accessed from commercially available 2-iodoaniline derivatives in a moderate number of steps (Scheme 2.10). The synthetic approach involved the Heck coupling of 2-iodoanilines with methyl acrylate to yield methyl 2-aminocinnamates which, upon reduction of the methyl ester, could furnish 2-aminocinnamyl alcohols. It was expected that carbonylation of the aniline with di-*tert*-butyl dicarbonate, *N*-alkylation with iodomethylstannatrane or tributyl(iodomethyl)stannane in the presence of a base, and then treatment of the *N*-alkylated product with acetic anhydride or methyl chloroformate could yield derivatives of substrate (**1**). From this approach we expected a good

degree of functional group tolerance with generally high yields owing to the relatively simple transformations that are required throughout most stages of the synthesis.



Scheme 2.10 Retrosynthetic Analysis of the Model Substrate 1

We also considered whether protection of the cinnamyl alcohol functionality would be required in order to conduct the nucleophilic substitution with the halomethylorgano stannanes owing to the potential nucleophilic competition between the carbamate and alcohol functional groups. We therefore began to explore the conditions that may allow us to synthesize derivatives of the model substrate starting from the commercially available 2-iodoaniline and methyl acrylate.

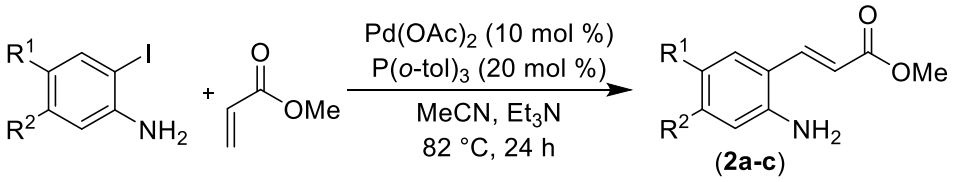
2.4: Results and Discussion

2.5: Synthesis of 2-Aminocinnamyl Alcohols

Following a modified procedure developed by Alabugin for the Heck coupling of 2-iodoaniline with ethyl acrylate, and its subsequent reduction to 2-aminocinnamyl alcohol. We were able to successfully conduct a number of Heck couplings between 2-iodoaniline derivatives and methyl acrylate in excellent yields (Table 2.3).[99] The subsequent reduction of the methyl esters

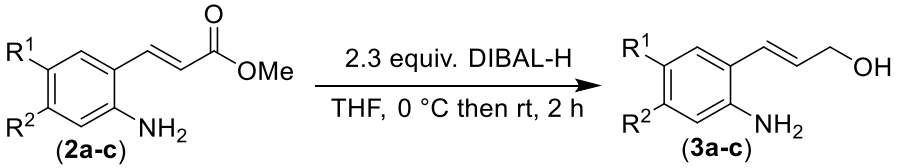
obtained from the Heck coupling by DIBAL-H was also successful albeit in modest to good yields to provide 2-aminocinnamyl alcohol derivatives **3a-c** (Table 2.4).[99]

Table 2.3 Heck Coupling of 2-Iodoaniline Derivatives



Entry #	R_1	R_2	% Yield
1	H	H	97 (**2a**)
2	H	Cl	90 (**2b**)
3	Cl	H	94 (**2c**)

Table 2.4 DIBAL-H Reduction of Methyl Esters



Entry #	R_1	R_2	% Yield
1	H	H	57 (**3a**)
2	H	Cl	67 (**3b**)
3	Cl	H	48 (**3c**)

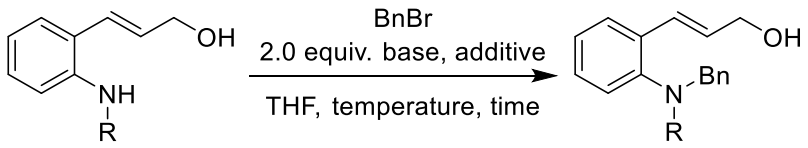
2.6: *N*-Alkylation with an ICH_2SnR_3 Motif

As discussed previously, alkyl stannatranes generally have increased reactivity in Stille couplings when compared with typical coupling agents owing to an increased exocyclic C(sp^3)-Sn

bond length which is attributed to the internal coordination of the tin centre with the nitrogen atom within the stannatrane cage.[34] Alkyl stannatranes offer an additional advantage in that there is selectivity in the alkyl transfer step, for when typical reagents are utilized such as $RSnBu_3$ where R is a primary alkyl group, a lack of selectivity in the alkyl group transferred may be observed.[34,100,101]

Understanding the difficulty in the transmetalation of $C(sp^3)$ carbon-tin bonds to transition metal catalysts, we thought it would be beneficial to utilize the more reactive stannatrane reagent in the intramolecular alkylation of a cinnamyl acetate with a $C(sp^3)$-tin group. We intended to introduce this motif through a nucleophilic substitution reaction between 2-aminocinnamyl alcohol (**3a**) and iodomethylstannatrane (**4b**). Since there are two nucleophilic sites on compound **3a** we first set out to determine the chemoselectivity of nucleophilic substitution before attempting to introduce the stannatrane group. Owing to the cost and synthetic steps associated with the synthesis of halomethylorgano stannanes (*vide infra*), benzyl bromide was selected as a representative $C(sp^3)$ alkyl halide and it was subsequently reacted with 2-aminocinnamyl alcohol (**3a**) and its *tert*-butyl carbamate derivative under various conditions (Table 2.5). Upon the addition of *n*-BuLi (2.5 M in hexanes) to a solution of 2-aminocinnamyl alcohol derivatives in THF a bright red precipitate formed which prevented stirring. Therefore, the addition of TMEDA was made to solubilize the resultant dianion by chelating the lithium ion formed upon treatment with *n*-BuLi, which resulted in the formation of a homogeneous mixture. From the results of this screening it was observed that the aniline anion generated by treatment with *n*-BuLi was more nucleophilic than that of the oxygen since only the *N*-alkylated product was obtained (Table 2.5, entries 2 and 5). We therefore thought that protection of the alcohol group may not be necessary and began attempting to install the $C(sp^3)$ stannatrane and tributyl stannane motifs.

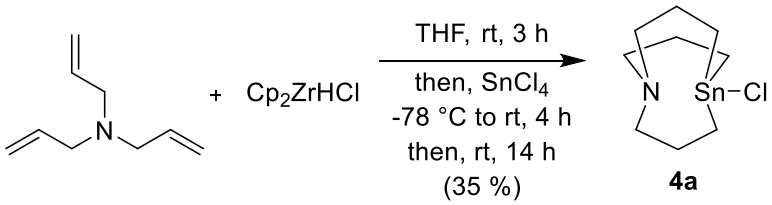
Table 2.5 Alkylation of 2-Aminocinnamyl Alcohols with Benzyl Bromide



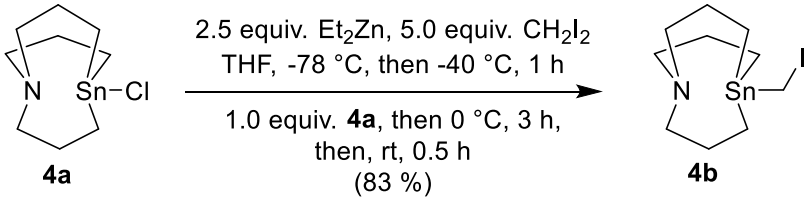
Entry #	R	Base	Additive	Temp	Time	% Yield[A]
1	CO_2tBu	*n*-BuLi	N/A	-78 °C to rt	23 h	N/D
2	CO_2tBu	*n*-BuLi	N/A	-78 °C to rt	3 h	8
3[B]	CO_2tBu	K_2CO_3	N/A	rt to 56 °C	6 h	N/D
4	CO_2tBu	*n*-BuLi	TMEDA	-78 °C to rt	26h	N/D
5	H	*n*-BuLi	TMEDA	-78 °C to rt	5h	30

A: Isolated yields, B: Acetone used as solvent, excess K_2CO_3

Stannatrane chloride (**4a**) was synthesized in the manner developed by the Vedejs group via the hydrozirconation of triallylamine followed by metal exchange with tin tetrachloride (Scheme 2.11).[34] The synthesis of iodomethylstannatrane (**4b**) was conducted from stanntrane chloride using the method reported by Jensen (Scheme 2.12).[102]

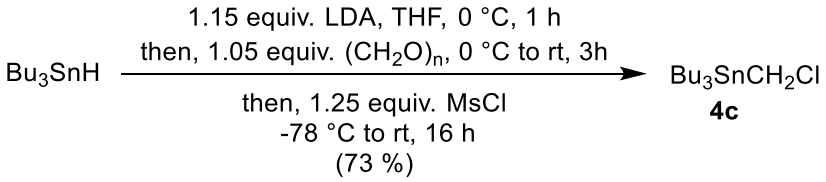


Scheme 2.11 Synthesis of Stannatrane Chloride

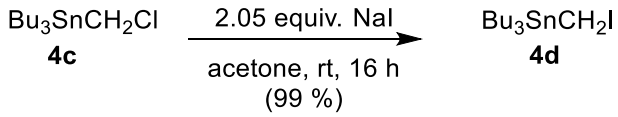


Scheme 2.12 Synthesis of Iodomethylstannatrane

All attempts at carrying out the alkylation with stannatrane **4b** utilizing varying amounts of *n*-BuLi and TMEDA, at different temperatures, with and without an *N*-*tert*-butoxycarbonyl group failed to produce the *N*-alkylated product. The application of the method employed by Jensen (K_2CO_3/DMF) at various temperatures and reaction times also failed to produce the desired *N*-alkylated products.[102] In light of the repeated failure to obtain the alkylation product we decided to use the less sterically hindered tributyl(iodomethyl)stannane as the electrophile. For this reagent there was also a greater literature precedent for the alkylation of *N*-*tert*-butoxycarbonyl amines as was shown by the Bode group in the synthesis of piperazines and morpholines.[103,104] Following the procedure reported by Bode, tributyl(iodomethyl)stannane was readily synthesized in good yields from commercially available tributyltin hydride in two steps (Schemes 2.13, 2.14).[103]



Scheme 2.13 Synthesis of Tributyl(chloromethyl)stannane

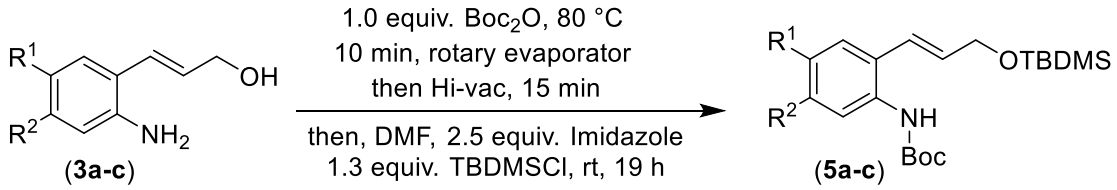


Scheme 2.14 Synthesis of Tributyl(iodomethyl)stannane

With the synthesis of the alkylating agents **4b** and **4d** complete, the suitable conditions for the *N*-alkylation of 2-aminocinnamyl alcohol was finally realized by the conversion of the amine functionality to a *tert*-butyl carbamate and protection of the alcohol with *tert*-butyldimethylsilyl chloride. Carbonylation of the aniline motif was achieved following the procedure developed by

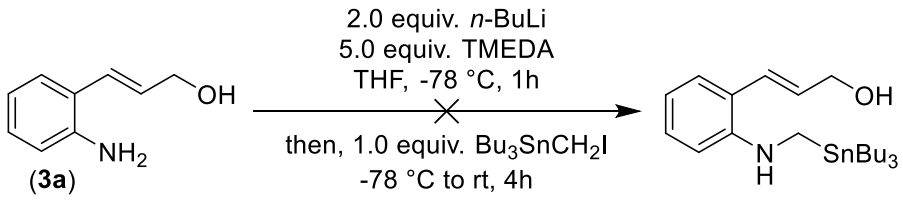
Singh, and upon treatment of the crude material with standard silylation conditions carbonylated 2-aminocinnamyl ethers **5a-c** were obtained (Table 2.6).[105,106]

Table 2.6 Silylation and Carbonylation of 2-Aminocinnamyl Alcohols



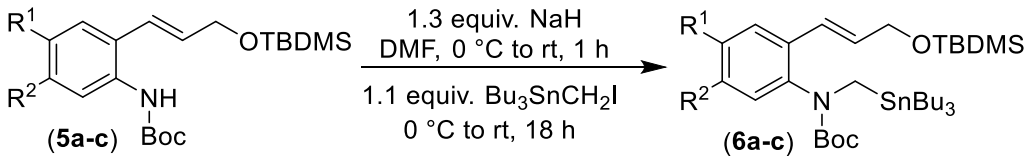
Entry #	R_1	R_2	% Yield
1	H	H	69 (**5a**)
2	H	Cl	60 (**5b**)
3	Cl	H	69 (**5c**)

When 2-aminocinnamyl alcohol **3a** was subjected to the reaction conditions outlined in Table 2.5 (entry 5) utilizing stannane **4d** as an alkylating agent none of the expected *N*-alkylated cinnamyl alcohol was obtained (Scheme 2.15). However, treatment of the protected carbamate **5a** with sodium hydride and stannane **4d** in DMF, in a manner analogous to that utilized by Bode was ultimately successful in the formation of the desired C-N bond furnishing compounds **6a-c** in moderate to good yields (Table 2.7).[104]



Scheme 2.15 Alkylation of 2-Aminocinnamyl Alcohol with Tributyl(iodomethyl)stannane

Table 2.7 *N*-Alkylation of TBDMS Protected Cinnamyl Carbamates

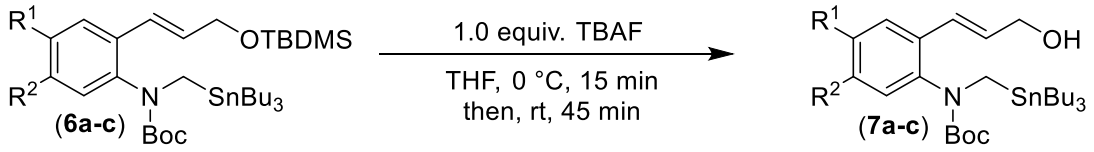


Entry #	R_1	R_2	% Yield
1	H	H	69 (**6a**)
2	H	Cl	58 (**6b**)
3	Cl	H	79 (**6c**)

2.7: Synthesis of Cinnamyl Acetates

All that remained to complete the synthesis for the model substrate for the cyclization via allylic alkylation was the cleavage of the silyl ether and the installation of an appropriate leaving group. The deprotection was achieved by treating compounds **6a-c** with tetrabutylammonium fluoride furnishing the corresponding alcohols in excellent yields within one hour (Table 2.8).[107]

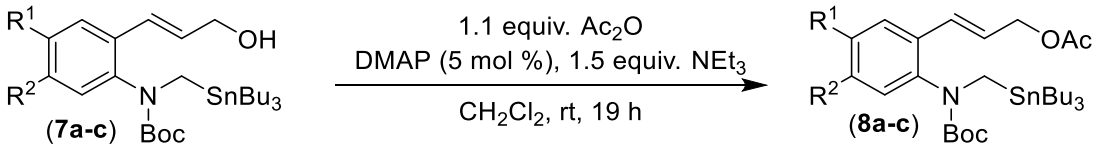
Table 2.8 Tetrabutylammonium Fluoride-Mediated Deprotection of Cinnamyl Ethers



Entry #	R_1	R_2	% Yield
1	H	H	92 (**7a**)
2	H	Cl	89 (**7b**)
3	Cl	H	87 (**7c**)

Finally, in order to complete the synthesis of the model substrate shown in Figure 2.3 the acetylation of the cinnamyl alcohols was required. This transformation was achieved by treating cinnamyl alcohols **7a-c** with acetic anhydride under conditions previously employed by our group (Table 2.9).[65]

Table 2.9 Acetylation of Cinnamyl Alcohols

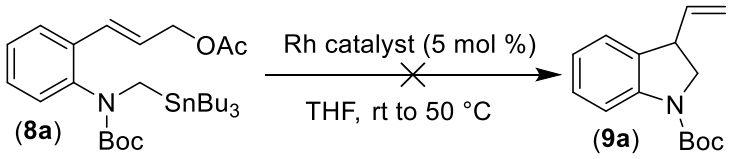


Entry #	R_1	R_2	% Yield
1	H	H	97 (**8a**)
2	H	Cl	92 (**8b**)
3	Cl	H	87 (**8c**)

2.8: Allylic Alkylation of Cinnamyl Acetates via Transmetalation

With cinnamyl acetate **8a** in hand we began to explore conditions that may be applicable in the alkylation of allylic acetates with the tethered C(sp^3) stannane. Three rhodium catalysts were selected to examine whether the cyclized product could be formed under these conditions (Table 2.10); however, none of these catalyst systems proved successful in furnishing the anticipated alkylation product. In all cases significant quantities of unreacted starting material were recovered, and a small amount of an unidentified substrate that only displayed singlet signals by ^{1}H NMR analysis was obtained.

Table 2.10 Attempted Rhodium-Catalyzed Alkylation of Cinnamyl Acetate 8a



Entry #	Catalyst	Temperature	Time
1	$[Rh(COD)_2]BF_4$	rt then 50 °C	20 h then 48 h
2	$[Rh(COD)(MeCN)_2]BF_4$	50 °C	18 h
3	$[Rh(COD)(OH)]_2$	50 °C	20 h
4[A]	$[Rh(COD)_2]BF_4$	112 °C	20 h

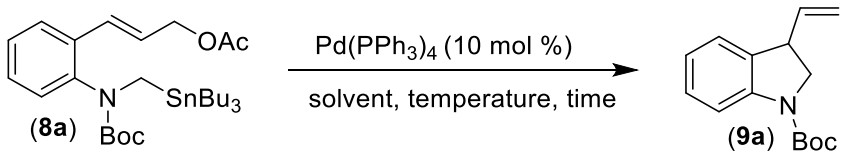
A: Reaction conducted in toluene

It is not clear whether the transmetalation of the rhodium catalyst with the organotin motif was unsuccessful which resulted in the failure to obtain the anticipated product or if the transmetalation was successful and it was the carborhodation and subsequent elimination of acetate that failed to take place. The latter would result in the sequestering of the rhodium catalyst leading to a lack of reactivity. Even after twenty hours in refluxing toluene there was no sign of the anticipated indoline product in the crude ^{1}H NMR. Further investigations into this system are required in order to gain insights into why we were unable to obtain the cyclized products. An examination of additives such as phosphine ligands and further investigations into solvent systems, reaction times and temperatures may prove fruitful. Additionally, applying stoichiometric quantities of rhodium catalyst may allow us to determine whether it was the transmetalation step that failed to take place or whether the S_N2' nucleophilic substitution prevented the reaction from progressing.

We then thought to attempt the application of palladium catalysts which are the traditional catalysts used in allylic alkylation type reactions.[29, 30, 33] We therefore began a series of test

reactions in which cinnamyl acetate **8a** was treated with $Pd(PPh_3)_4$ in THF or toluene at various temperatures (Table 2.11). Analysis of the reaction mixture by TLC showed complete consumption of the starting material (Table 2.11, entries 2 and 3) and we subsequently observed the formation of what we have determined to be *N*-*tert*-butoxycarbonyl-3-vinylindoline **9a**.

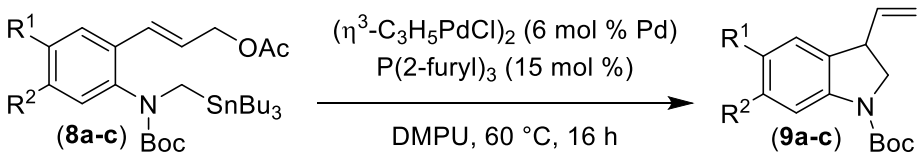
Table 2.11 Palladium-Catalyzed Allylic Alkylation of Cinnamyl Acetate 8a



Entry #	Solvent	Temperature	Time	% Yield
1	THF	rt to 50 °C	3.5 h then 18 h	Trace
2	Toluene	112 °C	4.5 h	10
3	Toluene	112 °C	24 h	50

We then set out to optimize the reaction conditions by examining different catalyst and solvent systems. It was shown by Hegedus' group that both vinyl and phenylstannatrane could be efficiently coupled with allylic carbonates that had proved unreactive to more typical conditions through the application of the palladium catalyst $(\eta^3\text{-}C_3H_5PdCl)_2$ and ligand P(2-furyl)$_3$ in *N*,*N*'-dimethylpropyleneurea (DMPU).[33] On our first attempt at optimizing the palladium catalyst system we subjected cinnamyl acetate **8a** to the conditions employed by Hegedus and were pleased to obtain indoline **9a** in an 86% yield. These reaction conditions were subsequently applied to various substrates to obtain a number of 3-vinylindoline derivatives (Table 2.12).

Table 2.12 Synthesis of *N*-Boc-3-vinylindolines from Cinnamyl Acetates



Entry #	R_1	R_2	% Yield
1	H	H	86 (**9a**)
2	H	Cl	47 (**9b**)
3	Cl	H	34 (**9c**)

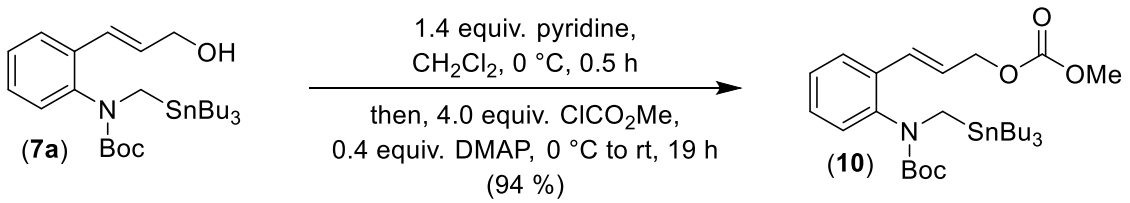
When undertaking the purification of indolines **9a-c** there was significant contamination of the products with a tributylstannane by-product, likely tributyltin acetate. This side-product was not detectable by TLC analysis even with the use of a variety of stains, and could not be successfully removed from the indoline species by distillation or extraction into *n*-pentane. Tin is a fluorophilic element, and so the washing of the organic layers with a saturated aqueous KF solution significantly reduced the quantity of the by-product but was insufficient to completely remove it from the organic phase.[108] Some success was found in running an excess of hexanes through the column during purification before increasing the polarity of the mobile phase and isolating the products formed in the reaction but this method was unreliable. A more consistent approach was found in which 10% wt/wt of finely-ground, dried KF in silica gel was utilized as the stationary phase during the purification which was sufficient to remove the tributyltin impurity by ^{1}H NMR analysis.[109]

When cinnamyl acetates which contained chlorine substituents upon the aromatic ring were subjected to these conditions the yields were significantly decreased when compared to the

unsubstituted analogue (Table 2.12). It is not immediately clear why this is the case; it may be due to competitive oxidative addition of the palladium catalyst across the aryl chloride bond, which has been documented through the development of Stille coupling reactions of aryl chlorides with aryl(tributyl)stannanes and allyl(tributyl)stannanes.[110,111] If there is a competitive oxidative addition pathway then decomposition of the palladium catalyst may occur resulting in decreased turnover rates for the catalyst system and lower yields of the desired products. Detailed analysis of the crude ^{1}H NMR spectra obtained from these reactions was difficult due to significant quantities of residual DMPU and tributyltin by-products present, even when using hexanes as the workup solvent. However, when purifying these reaction mixtures the only products observed were the anticipated 3-vinylindoline derivatives and no products that could be attributed to intermolecular or intramolecular Stille coupling reactions were obtained. Aromatic halides draw electron density from the aromatic ring due to the electronegativity of these substituents; however, they are also capable of donating electron density through resonance.[112,113] These effects may have an influence on electron density at both the allylic acetate and the C(sp^3) organotin nucleophile thereby altering the reactivity of the system leading to decreased yields. However, no general trend in reactivity can be drawn as only two examples have been synthesized to date which both resulted in significant decreases in the obtained yields (Table 2.12). This result, combined with the position of the chloride substitutions relative to the allylic acetate (*para*- in **8b** and *meta*- in **8c**) does not fit into a readily explained model of reactivity. To further probe these results the synthesis of cinnamyl acetate derivatives which contain more strongly electron donating or withdrawing groups that will not undergo oxidative addition with palladium catalysts will be conducted. This would allow us to gain a better understanding of the effect that both electron density about the aromatic ring and potential oxidative addition pathways have on the reactivity in this system.

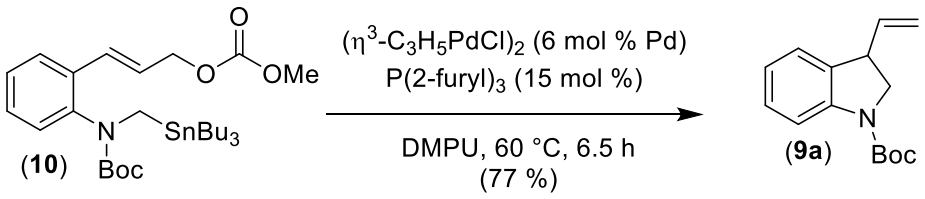
2.9: Synthesis and Allylic Alkylation of a Cinnamyl Carbonate

We set out to synthesize a cinnamyl carbonate derivative in order to determine whether increased yields may be obtained through the use of this leaving group since allylic carbonates have been shown to possess increased reactivity when compared to their allylic acetate analogues.[114] Therefore, cinnamyl alcohol **7a** was carbonylated with methyl chloroformate. These reaction conditions were well tolerated and the resultant cinnamyl carbonate **10** was obtained in an excellent yield (Scheme 2.16).[33]



Scheme 2.16 Acylation of Cinnamyl Alcohol 7a with Methyl Chloroformate

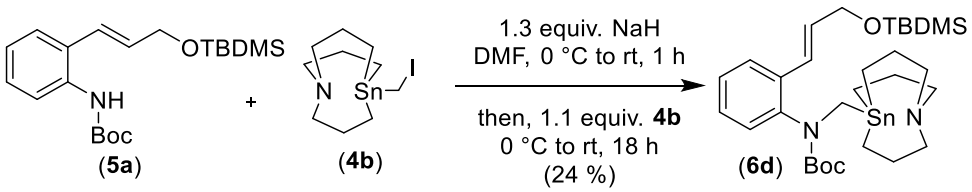
Cinnamyl carbonate **10** was then subjected to the reaction conditions described above for the intramolecular alkylation of allylic acetates. The reaction proceeded cleanly furnishing 3-vinylindoline **9a** in a slightly reduced yield, but the reaction was observed to have gone to completion by TLC analysis within 6.5 hours in comparison to the 16 hours required for the reaction employing the analogous cinnamyl acetate to complete (Scheme 2.17). There was no further optimization of the reaction conditions employed for the allylic alkylation of this substrate; however, it may be that exploring alternative conditions such as altering the temperature and length of reaction could facilitate increased yields of the 3-vinylindoline derivative **9a** through the use of this leaving group.



Scheme 2.17 Synthesis of *N*-Boc-3-vinylindoline from Cinnamyl Carbonate 10

2.10: The Synthesis and Allylic Alkylation of a Stannatrane Derivative

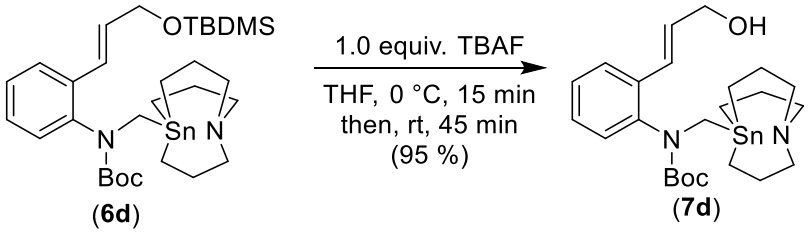
Once the conditions for the N-alkylation of TBDMS protected cinnamyl carbamate **5a** with stannane **4d** were obtained (Table 2.7) we returned to attempting to synthesize an *N*-methylstannatrane carbamate from stannatrane **4b**. Upon reacting carbamate **5a** with iodomethylstannatrane under the same conditions, TLC analysis showed near complete consumption of the starting material and ^{1}H NMR of the crude material showed evidence for the formation of the desired C-N bond. However, upon attempting to purify the reaction mixture through flash chromatography as was used in the purification of the tributylstannane derivative **6a**, none of the stannatrane analogue was obtained and protodestannylation was observed. By introducing 1% NEt_3 to the mobile phase during the purification the *N*-alkylated stannatrane derivative **6d** was obtained in a modest yield (Scheme 2.18).



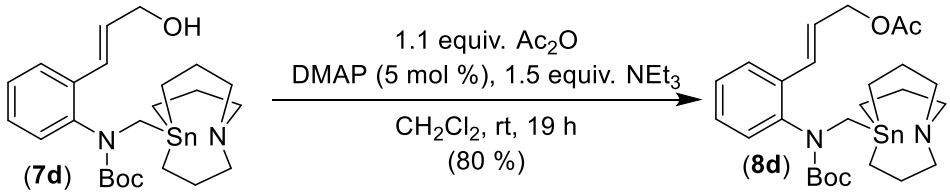
Scheme 2.18 *N*-Alkylation of Cinnamyl Carbamate 5a with Iodomethylstannatrane

Cleavage of the silyl ether in **6d** by tetrabutylammonium fluoride as described in Table 2.8 proceeded efficiently to furnish cinnamyl alcohol **7d** in an excellent yield (Scheme 2.19).

Subsequent acetylation of **7d** with acetic anhydride under conditions analogous to those employed in Table 2.9 proceeded cleanly furnishing cinnamyl acetate **8d** in very good yields (Scheme 2.20).

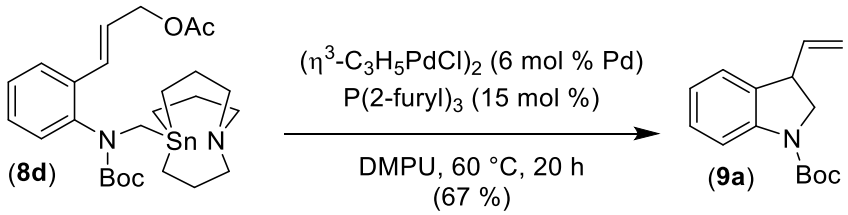


Scheme 2.19 TBAF-Mediated Deprotection of Stannatrane 6d



Scheme 2.20 Acetylation of Stannatrane Derivative 7d

When **8d** was subjected to the conditions employed for the cyclization of allylic acetates with a tributylstannane handle (Table 2.10) the anticipated indoline **9a** was obtained in a good yield (Scheme 2.21). This nucleophile is advantageous in that there is no tributyltin by-product which pervades most fractions under typical purification techniques. Therefore, this approach does not require the use of KF doped silica gel which is a distinct advantage over the analogous tributylstannane derivative.

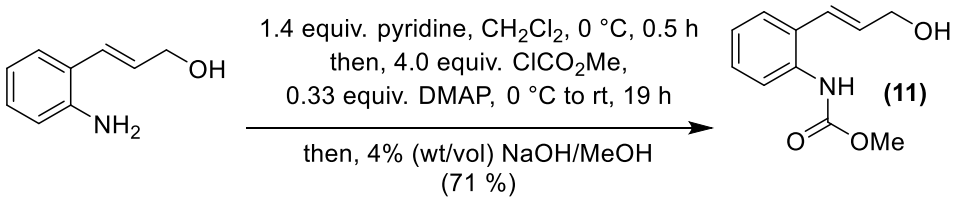


Scheme 2.21 Allylic Alkylation by Transmetalation of Stannatrane Derivative 8d

The yield obtained from this reaction was considerably lower than that obtained from the tributylstannane analogue (Scheme 2.21). This result was unexpected since organostannatranes have been shown to possess notable reactivity in Stille coupling reactions, conjugate addition reactions and intermolecular allylic alkylation reactions.[33,34,100] At this stage of the research project limited optimization of the reaction conditions for this substrate were conducted, something our group is currently continuing to explore.

2.11: Synthesis of *N*-Methoxycarbonyl-3-vinylindoline

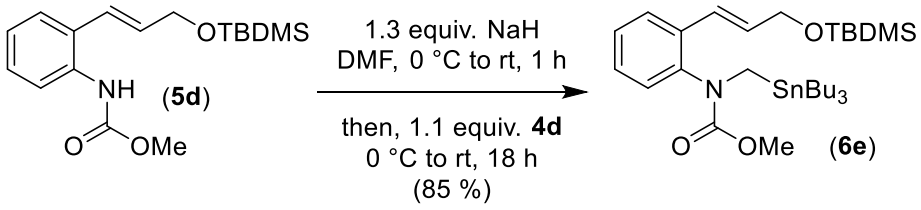
We also set about synthesizing a 3-vinylindoline which contained an *N*-methylcarbamate functionality in order to fully resolve the structure of the obtained product from the intramolecular allylic alkylation reactions. There was some ambiguity in the spectral data obtained from indoline **9a** due to the presence of a particularly broad, poorly defined peak within the aromatic region of the ^{1}H NMR spectrum. While this is not uncommon for indole derivatives containing a carbamate motif upon the nitrogen atom, we wanted to unambiguously asign the structure of the product formed in these reactions.[115] We reasoned that the synthesis of a methyl carbamate, for use in the intramolecular allylic alkylation reaction, may provide greater insight in to the structure of the product formed. As such, we treated 2-aminocinnamyl alcohol **3a** with methyl chloroformate and the subsequent basic hydrolysis of the carbonate furnished methyl carbamate **11** in good yields (Scheme 2.22).[33,116] Silylation of the cinnamyl alcohol under the developed conditions proceeded cleanly and efficiently to produce the cinnamyl ether **5d** in excellent yield (Scheme 2.23).



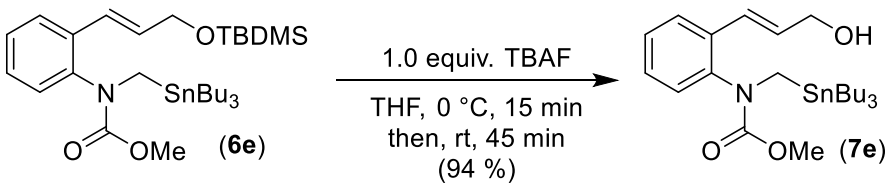
Scheme 2.22 Synthesis of Methyl Carbamate 11

Scheme 2.23 Silylation of Cinnamyl Alcohol 11 with TBDMSCl

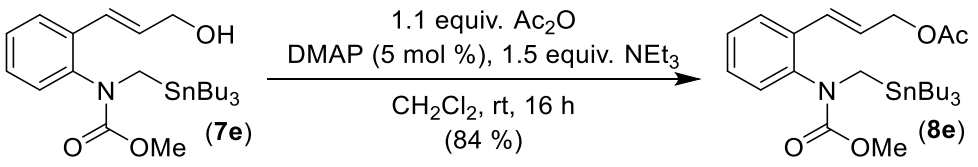
Alkylation of cinnamyl ether **5d** with Bu_3SnCH_2I furnished the *N*-alkylated product **6e** in a high yield (Scheme 2.24). Deprotection of the *N*-alkylated product proceeded in the typical fashion to yield the corresponding cinnamyl alcohol **7e** in an excellent yield (Scheme 2.25). The subsequent acetylation of cinnamyl alcohol **7e** with acetic anhydride under the developed conditions provided cinnamyl acetate **8e** in a very good yield (Scheme 2.26).



Scheme 2.24 *N*-Alkylation of Carbamate 5d with Iodomethyl(tributyl)stannane

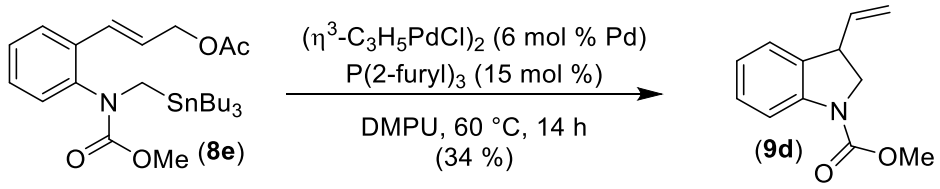


Scheme 2.25 Silyl Ether Cleavage of 6e with Tetrabutylammonium Fluoride



Scheme 2.26 Acetylation of Cinnamyl Alcohol 7e with Acetic Anhydride

Finally, with the cinnamyl acetate **8e** in hand the intramolecular allylic alkylation could be undertaken in order to synthesize *N*-methoxycarbonyl-3-vinylindoline. Upon subjecting cinnamyl acetate **8e** to the conditions described in Table 2.12 the anticipated indoline **9d** was obtained in a modest yield as a pale-yellow solid (Scheme 2.27).



Scheme 2.27 Synthesis of *N*-Methoxycarbonyl-3-vinylindoline via Allylic Alkylation

The drastic decrease in the obtained yield of *N*-methoxycarbonyl-3-vinylindoline **9d** compared to indoline **9a** cannot be readily explained owing to the high degree of similarity between substrates **8a** and **8e**. The conditions employed in the alkylation of cinnamyl acetate **8e** were not optimized for this substrate in any meaningful way. This reaction was conducted twice, and unreacted starting material was observed by TLC analysis in both cases after the reaction time had elapsed. It is possible that an increase in catalyst loading or more forcing conditions could provide higher yields of the indoline derivative **9d**, something that our group is currently exploring.

In the analysis of the ^{1}H NMR spectrum of **9d** there was a similarly broad, poorly defined peak within the aromatic region. However, there was sufficient peak intensity to obtain an HMQC correlation between the broad peak in the ^{1}H NMR spectrum and a signal in the ^{13}C NMR spectrum

corresponding to the C-7 position of the indoline ring. This provided verification that the product formed in this reaction was the expected *N*-methoxycarbonyl-3-vinylindoline. By extending this observation and analyzing the chemical shifts of the ^{1}H NMR, ^{13}C NMR, and DEPT spectra of indolines **9a-c** we were able to confidently determine that the products formed in the allylic alkylation reactions were in fact the expected *N-tert*-butoxycarbonyl-3-vinylindoline derivatives. Additionally, the spectral data obtained from **9a** correlates well with what was previously reported in the literature.[96] A suitable crystal of *N*-methoxycarbonyl-3-vinylindoline was acquired by evaporative recrystallization from pentane/Et_2O which allowed for an X-ray crystal structure to be obtained which confirmed the observations from the HMQC analysis (Figure 2.5).

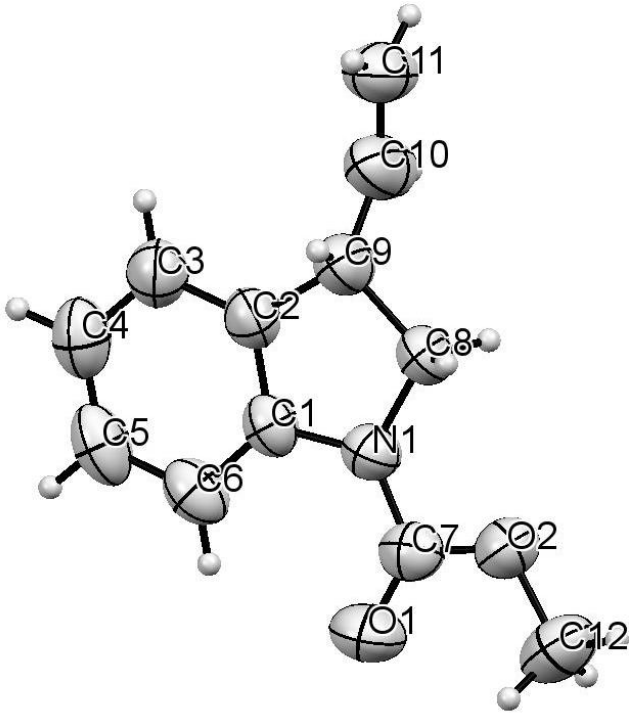


Figure 2.5 ORTEP Diagram of *N*-Methoxycarbonyl-3-vinylindoline 9d

2.12: Summary of Chapter 2

We have shown for the first time that 3-vinylindolines may be obtained from the palladium-catalyzed alkylation of cinnamyl acetates via the transmetallation of *ortho*-tethered intramolecularly activated C(sp^3) stannanes and stannatranes. Further, we have shown that allylic carbonates are suitable substrates for such transformations and that chlorine substitutions upon the aromatic ring are well tolerated throughout much of the synthetic methodology, though these substitutions appeared to be detrimental in the allylic alkylation reactions. We are further exploring the generality of these reaction conditions, examining the applicability of various functional groups including nitriles, ethers, tertiary amines, and alkyl substituents. To the best of our knowledge this represents the first example of a palladium-catalyzed synthesis of 3-vinylindolines and the first example of an intramolecular allylic alkylation utilizing a C(sp^3) stannane or stannatrane transmetalating reagent. The methodology presented herein represents a significant advancement in the synthesis of the indoline skeleton which may find utility in the synthesis of natural products or drug targets.

2.13: Experimental Section

General Methods: Unless otherwise noted, all reactions were carried out in flame-dried glassware under a nitrogen atmosphere. N_2 was passed over KOH and $CaSO_4$ before entering the Schlenk line. Allylic alkylation reactions were conducted in a resealable Schlenk tube utilizing standard Schlenk techniques. All solvent concentrations are relative to the limiting reagent. DMPU, pyridine, Et_3N and CH_2Cl_2 were distilled over CaH_2, DMPU was distilled under aspirator vacuum. Toluene and THF were distilled over Na/benzophenone. DMF was dried by stirring for 24 h with activated 4 Å molecular sieves and was stored over freshly activated 4 Å molecular sieves under

N_2. The methanol used was 99.9% HPLC grade and used as received. Anhydrous acetonitrile was used as obtained from Caledon Chemical Laboratories. Hexanes utilized in workup procedures was ≥98.5 % HPLC grade hexanes used as purchased from Aldrich. Acetone used in halogen exchange was ≥99.9 % HPLC grade acetone from Aldrich. All other chemicals were purchased from Aldrich and used as obtained. KF was flame dried under reduced pressure before preparing the 10% wt/wt KF/silica mixture.

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Avance-300 spectrometers. Residual ^{1}H shift in $CDCl_3$ (7.26 ppm) was used as the internal reference for ^{1}H NMR. Residual ^{13}C shift in $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR. Chemical shifts reported in ppm and coupling constants are reported in Hz. Abbreviations used for the description of ^{1}H NMR multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and brs = broad singlet. The proton signals arising from methylene carbons bound to trialkyltin species appeared and are reported as AB quartets with $^{117/119}Sn$-H satellites appearing as shoulders upon the peaks. For ^{13}C NMR, $^{117/119}Sn$-C constants are reported where the satellites were clearly discernable, a non-reported coupling is not meant to imply that no coupling is present.

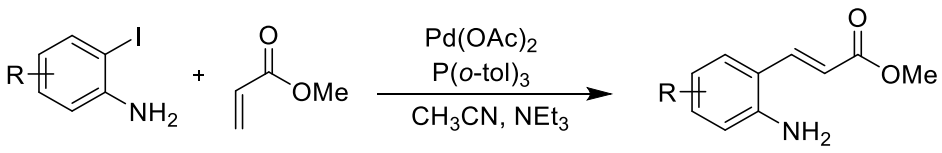
HRMS data was collected on a Thermo Scientific Q-Exactive Orbitrap HRMS utilizing electrospray ionization (ESI) and 50:50:0.1 MeCN/H_2O/formic acid, 50:50:0.1 MeOH/H_2O/formic acid, or 1:1 MeCN/H_2O treated with 10 μL of dilute $LiOAc_{(aq)}$. The ^{116}Sn isotope was selected in HRMS analysis of compounds containing tin in order to exclude interference from heavier isotopes of other elements present in the analyzed compounds.

Reactions were monitored by thin-layer chromatography (TLC) on glass or aluminum backed pre-coated plates with a thickness of 250 μm, a particle size of 60Å, and with a F-254 indicator

purchased from Silicycle. Developed plates were visualized through U.V. illumination, or by staining with I_2/silica or $KMnO_4$ solution. Flash chromatography was conducted utilizing 230-400 mesh silica gel purchased from Silicycle.

Stannatranes **4a** and **4b** were synthesized according to the literature procedure; spectral data was consistent with that reported in the literature.[34,102] Stannanes **4c** and **4d** were synthesized according to the literature procedure; spectral data was consistent with that reported in the literature.[103]

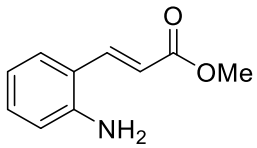
General Procedure A: Heck Coupling of 2-Iodoanilines with Methyl Acrylate



The Heck coupling of methyl acrylate with 2-iodoaniline derivatives was based upon a procedure developed by Alabugin in which ethyl acrylate was used as the substrate.[99] In a typical experiment a flame-dried round-bottomed flask equipped with a stir bar and reflux condenser was charged with a 2-iodoaniline derivative (5.00 g, 22.8 mmol, 1.00 equiv.), $Pd(OAc)_2$ (480 mg, 2.28 mmol, 0.10 equiv.), and P(*o*-tol)$_3$ (1.40 g, 4.56 mmol, 0.20 equiv.). The solids were dissolved in anhydrous MeCN and Et_3N (2:1) such that the solution was 1.0 M relative to 2-iodoaniline. To this stirred solution methyl acrylate (8.27 mL, 91.3 mmol, 4.00 equiv.) was added dropwise and the solution was allowed to reflux for 24 hours. Upon completion of the reaction time, the reaction was quenched by the addition of 100 mL of H_2O and 100 mL of EtOAc. The suspension was filtered through filter paper (Buchner funnel) to remove palladium precipitates, washing with EtOAc and the phases were separated. The aqueous phase was extracted an additional two times with 100 mL of EtOAc and the combined organic phases were washed with 150 mL of brine. The mixture was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The

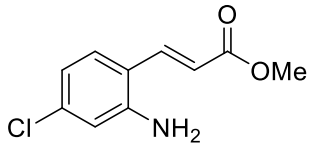
residue was purified via flash chromatography on silica gel to yield the corresponding methyl esters.

Methyl (*E*)-3-(2-Aminophenyl)acrylate (2a)



Synthesized according to General Procedure A from 2-iodoaniline (5.00 g, 22.8 mmol), $Pd(OAc)_2$ (480 mg, 2.28 mmol), P(*o*-tol)$_3$ (1.40 g, 4.56 mmol), and methyl acrylate (8.27 mL, 91.3 mmol). The reaction was allowed to reflux for 24 hours. Purification via flash chromatography using (1:9 EtOAc:hexanes to 3:7 EtOAc:hexanes) yielded ester **2a** as a yellow solid (3.92 g, 97 % yield). Melting point = 59-62 °C (m.p. lit. = 64-66 °C).[117] Spectral data is consistent with that reported in the literature.[117] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 15.8 Hz), 7.37 (1H, d, *J* = 7.7 Hz), 7.17 (1H, t, *J* = 7.5 Hz), 6.76 (1H, t, *J* = 7.5 Hz), 6.70 (1H, d, *J* = 8.1 Hz), 6.36 (1H, d, *J* = 15.8 Hz), 3.98 (2H, brs), 3.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 145.6, 140.3, 131.3, 128.0, 119.8, 118.9, 117.6, 116.7, 51.6. HRMS(ESI) *m/z* calculated for $C_{10}H_2NO_2$ [$(M+H)^+$]: 178.0863. Found: 178.0864.

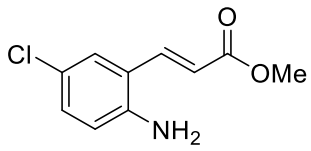
Methyl (*E*)-3-(2-Amino-4-chlorophenyl)acrylate (2b)



Synthesized according to General Procedure A from 5-chloro-2-iodoaniline (3.04 g, 12.0 mmol), $Pd(OAc)_2$ (253 mg, 1.20 mmol), P(*o*-tol)$_3$ (738 mg, 2.40 mmol), and methyl acrylate (4.35 mL, 48.0 mmol). The reaction was allowed to reflux for 24 hours. Purification via flash chromatography using (1:9 EtOAc:hexanes to 3:7 EtOAc:hexanes) yielded ester 2**b** as a yellow solid (2.29 g, 90 % yield). Melting point = 113-116 °C (m.p. lit. = 124-125 °C).[118] Spectral data is consistent with that reported in the literature.[118] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 15.8 Hz), 7.29 (1H, d, *J* = 8.3 Hz), 6.73 (1H, d, *J* = 10.0 Hz), 6.71 (1H, s), 6.33 (1H, d, *J* = 15.8 Hz), 4.02 (2H, brs), 3.80 (3H, s). ^{13}C NMR (75 MHz,

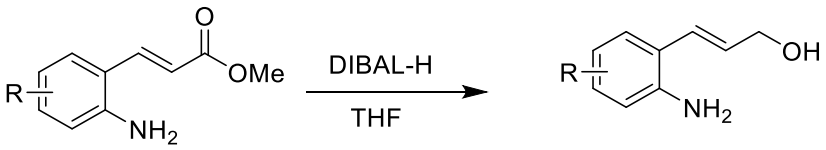
$CDCl_3$) δ 167.5, 146.4, 139.1, 136.8, 129.2, 119.1, 118.2, 118.0, 116.2, 51.7. HRMS(ESI) *m/z* calculated for $C_{10}H_{11}{}^{35}ClNO_2$ [$(M+H)^+$]: 212.0473. Found: 212.0473.

Methyl (*E*)-3-(2-Amino-5-chlorophenyl)acrylate (2c)



Synthesized according to General Procedure A from 4-chloro-2-iodoaniline (3.04 g, 12.0 mmol), $Pd(OAc)_2$ (253 mg, 1.20 mmol), P(*o*-tol)$_3$ (738 mg, 2.40 mmol), and methyl acrylate (4.35 mL, 48.0 mmol). The reaction was allowed to reflux for 24 hours. Purification via flash chromatography using (1:9 EtOAc:hexanes to 3:7 EtOAc:hexanes) yielded ester **2c** as a yellow solid (2.38 g, 94 % yield). Melting point = 89-90 °C (m.p. lit. = 92-94 °C)[117]. Spectral data is consistent with that reported in the literature.[117] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* = 15.8 Hz), 7.34 (1H, d, *J* = 2.3 Hz), 7.12 (1H, dd, *J* = 8.5, 2.4 Hz), 6.64 (1H, d, *J* = 8.6 Hz), 6.35 (1H, d, *J* = 15.8 Hz), 3.94 (2H, brs), 3.81 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 144.0, 138.8, 130.9, 127.2, 123.5, 120.9, 118.8, 117.9, 51.7. HRMS(ESI) *m/z* calculated for $C_{10}H_{11}{}^{35}ClNO_2$ [$(M+H)^+$]: 212.0473. Found: 212.0473.

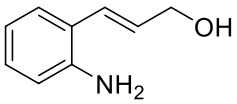
General Procedure B: DIBAL-H-Mediated Reduction of Esters



The reduction of methyl ester derivatives **2a-c** was conducted according to the procedure reported by Alabugin who utilized this methodology in the reduction of ethyl esters.[99] In a typical reaction a flame dried two-neck round bottomed flask equipped with a stir bar and dropping funnel under N_2 was charged with the ester derivative (3.50 g, 19.8 mmol, 1.00 equiv.) which was

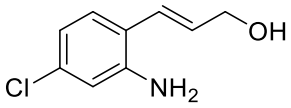
dissolved in dry THF (0.8 M). To the dropping funnel, a solution of DIBAL-H (45.4 mL, 45.4 mmol, 2.30 equiv., 1.0 M in $PhCH_3$) was added. The solution was cooled to 0 °C with stirring and DIBAL-H was added dropwise over 15 minutes. After the addition, the reaction was allowed to warm to room temperature and was stirred for 2 hours. The solution was then cooled to 0 °C and with vigorous stirring, 10 mL of MeOH was carefully added dropwise followed by 10 mL of H_2O, also dropwise. This slurry was allowed to stir for two hours before being filtered through a fritted funnel, washing with EtOAc and H_2O. Then 100 mL of EtOAc and 100 mL of H_2O were added, the phases were partitioned, and the aqueous phase was extracted an additional two times with 100 mL of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via flash chromatography yielded the corresponding 2-aminocinnamyl alcohol derivatives.

2-Aminocinnamyl Alcohol (3a)



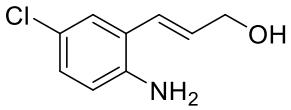
Synthesized according to General Procedure B from ester derivative **2a** (3.50 g, 19.8 mmol), DIBAL-H (45.4 mL, 45.4 mmol, 1.0 M in $PhCH_3$). Upon purification via flash chromatography using (3:7 EtOAc:hexanes to 1:1 EtOAc:hexanes), 2-aminocinnamyl alcohol **3a** was obtained as a dark-yellow waxy solid (1.68 g, 57 % yield). Melting point = 41-44 °C (m.p. lit = 54-55 °C).[119] Spectral data is consistent with that reported in the literature.[99, 119] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, d, *J* = 7.2 Hz), 7.08 (1H, t, *J* = 7.9 Hz), 6.76 (1H, t, *J* = 7.4 Hz), 6.68 (1H, d, *J* = 8.1 Hz), 6.67 (1H, d, *J* = 15.5 Hz), 6.23 (1H, dt, *J* = 15.7, 5.5 Hz), 4.32 (2H, d, *J* = 5.4 Hz), 3.67 (2H, brs), 1.92 (1H, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 130.3, 128.6, 127.5, 126.6, 123.0, 119.0, 116.1, 63.8. HRMS(ESI) *m/z* calculated for $C_9H_{12}NO$ [$(M+H)^+$]: 150.0913. Found: 150.0916.

2-Amino-4-chlorocinnamyl Alcohol (3b)



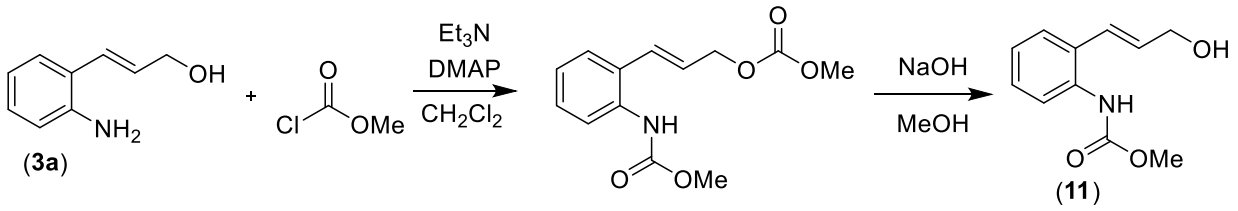
Synthesized according to General Procedure B from ester derivative **2b** (2.19 g, 10.3 mmol), DIBAL-H (23.7 mL, 23.7 mmol, 1.0 M in $PhCH_3$). Upon purification via flash chromatography using (3:7 EtOAc:hexanes to 1:1 EtOAc:hexanes), cinnamyl alcohol **3b** was obtained as a yellow solid (1.27 g, 67 % yield). Melting point = 69-74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 8.2 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 6.68 (1H, s), 6.59 (1H, d, *J* = 15.8 Hz), 6.22 (1H, dt, *J* = 15.7, 5.5 Hz), 4.34 (2H, d, *J* = 5.4 Hz), 3.67 (2H, brs), 1.74 (1H, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 133.8, 130.7, 128.5, 125.4, 121.4, 118.9, 115.6, 63.6. HRMS(ESI) *m/z* calculated for $C_9H_{11}{}^{35}ClNO$ [$(M+H)^+$]: 184.0524. Found: 184.0524.

2-Amino-5-chlorocinnamyl Alcohol (3c)



Synthesized according to General Procedure B from ester derivative **2c** (2.30 g, 10.9 mmol), DIBAL-H (25.1 mL, 25.1 mmol, 1.0 M in $PhCH_3$). Upon purification via flash chromatography using (3:7 EtOAc:hexanes to 1:1 EtOAc:hexanes), cinnamyl alcohol **3c** was obtained as a brown solid (977 mg, 48 % yield). Melting point = 71-73 °C. Spectral data is consistent with that reported in the literature.[120] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 2.2 Hz), 7.02 (1H, dd, *J* = 8.4, 2.2 Hz), 6.75-6.66 (2H, m), 6.24 (1H, dt, *J* = 15.7, 5.3 Hz), 4.34 (2H, d, *J* = 5.2 Hz), 3.74 (2H, brs), 1.63 (1H, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 131.6, 128.3, 127.0, 125.0, 124.6, 123.7, 117.4, 36.4. HRMS(ESI) *m/z* calculated for $C_9H_{11}{}^{35}ClNO$ [$(M+H)^+$]: 184.0524. Found: 184.0524.

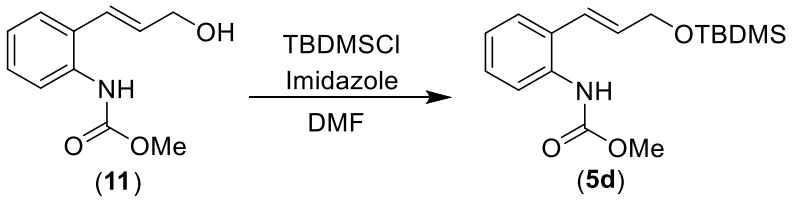
Procedure for the Synthesis of Methyl (*E*)-(2-(3-Hydroxyprop-1-en-1-yl)phenyl)carbamate (11)



The procedure for the carbonylation of 2-aminocinnamyl alcohol with methyl chloroformate was based on the methodology reported by Hegedus and the chemoselective basic hydrolysis of the carbonate functionality was derived from a similar transformation reported by Corey.[33,116] The conditions for the synthesis of cinnamyl carbonate **11** are as follows: to a flame-dried round-bottomed flask equipped with a stir bar cinnamyl alcohol **3a** (50 mg, 0.34 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (0.07 M). This solution was cooled to 0 °C with stirring and dry pyridine (38 μL, 0.469 mmol, 1.40 equiv.) was added dropwise. The solution was let stir at 0 °C for 30 minutes, then methyl chloroformate (104 μL, 1.34 mmol, 4.00 equiv.) was added dropwise with stirring and then *N*,*N*-dimethylaminopyridine (14 mg, 0.111 mmol, 0.330 equiv.) was added in one portion. The mixture was allowed to warm to room temperature and was let stir for 18 hours. After the reaction time, it was diluted with 5 mL of CH_2Cl_2 and quenched with 10 mL of H_2O. The layers were separated and the aqueous phase was extracted with an additional 3x 10 mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then treated with 25 mL of a 4% wt/vol methanolic sodium hydroxide solution and allowed to stir at room temperature for two hours. When complete by TLC analysis, 50 mL of H_2O and 50 mL of CH_2Cl_2 were added to the solution and the phases were separated. The aqueous phase was extracted with an additional 2x50 mL of CH_2Cl_2 and the combined organic phases were washed with 50 mL of brine, dried over

$MgSO_4$, filtered and concentrated under reduced pressure. Purification via flash chromatography using (1:4 EtOAc:hexanes to 1:1 EtOAc:hexanes) yielded the title product as a white solid (49 mg, 71 % yield). Melting point = 96-101 °C (m.p. lit. = 100-102 °C).[121] Spectral data is consistent with that reported in the literature.[121] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.65 (1H, m), 7.35 (1H, d, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 7.3 Hz), 7.09 (1H, t, *J* = 7.5 Hz), 6.77 (1H, brs), 6.70 (1H, d, *J* = 15.8 Hz), 6.23 (1H, dt, *J* = 15.8, 5.2 Hz), 4.31 (2H, d, *J* = 4.9 Hz), 3.76 (3H, s), 2.35 (1H, brs). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 134.5, 132.5, 129.0, 128.3, 127.0, 125.3, 124.6, 122.4, 63.3, 52.4. HRMS(ESI) *m/z* calculated for $C_{11}H_{13}NNaO_3$ [$(M+Na)^+$]: 230.0788. Found: 230.0787.

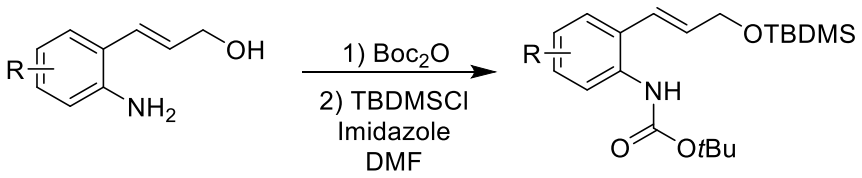
Procedure for the Synthesis of Cinnamyl Ether 5d



The procedure for the silylation of cinnamyl carbamate **5d** was adopted from the procedure reported by Coelho with modification to the equivalents of TBDMSCl and purification.[105] The reaction conditions were as follows: to a flame-dried round-bottomed flask equipped with a stir bar under N_2 cinnamyl carbamate **11** (300 mg, 1.45 mmol, 1.00 equiv.) was dissolved in dry DMF (2.0 M) and to this solution imidazole (246 mg, 3.62 mmol, 2.50 equiv.) was added and upon complete dissolution, the addition of TBDMSCl (316 mg, 2.10 mmol, 1.45 equiv.) was made. The mixture was allowed to stir at room temperature for 21 hours and was then treated with 50 mL of H_2O and 50 mL of EtOAc. The phases were separated and the aqueous layer was extracted an additional two times with 50 mL of EtOAc. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silyl ether **12**

was purified by dissolving in 5 mL of MeOH and placing in a freezer for 20 minutes. Upon removing from the freezer an unidentified white precipitate had formed which was filtered out through a pad of celite washing with ice-cold methanol. The filtered solution was then dried under reduced pressure to yield the pure compound **5d** as an oil. (434 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.73 (1H, m), 7.35 (1H, d, *J* = 7.8 Hz), 7.29-7.21 (2H, m), 7.09 (1H, t, *J* = 7.4 Hz), 6.68 (1H, d, *J* = 15.7 Hz), 6.55 (1H, brs), 6.18 (1H, dt, *J* = 15.6, 4.6 Hz), 4.36 (2H, d, *J* = 4.7 Hz), 3.77 (3H, s), 0.95 (9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 135.0, 134.4, 133.3, 129.1, 128.0, 127.0, 124.4, 123.8, 121.9, 63.5, 52.3, 25.8, 18.3. HRMS(ESI) *m/z* calculated for $C_{17}H_{27}KNO_3Si$ [$(M+K)^+$]: 360.1392. Found: 360.1392.

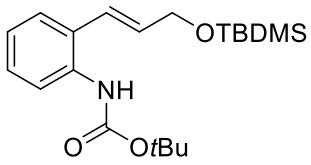
General Procedure C: *O*-Silylation and *N*-Carbonylation of 2-Aminocinnamyl Alcohols



The procedure for the *O*-silylation and *N*-carbonylation is a modification of the procedures developed by Singh and Coelho for the formation of the *N*-*tert*-butylcarbamates and *tert*-butyldimethylsilyl ethers respectively.[105,106] In a typical experiment a flame-dried round-bottomed flask equipped with a stir bar was charged with cinnamyl alcohol (149 mg, 1.00 mmol, 1.00 equiv.) and di-*tert*-butyl dicarbonate (218 mg, 1.00 mmol, 1.00 equiv.). The flask was then placed on a rotary evaporator and under an aspirator vacuum was placed into a pre-heated water bath at 80 °C for 10 minutes or until bubbling stopped with vigorous rotation. The flask was then allowed to cool to room temperature and placed under high-vacuum for 15 minutes or until bubbling subsided. The resultant thick oil was then dissolved in DMF (2.0 M) and to this resulting solution was added imidazole (170 mg, 2.50 mmol, 2.50 equiv.). Once the imidazole was fully dissolved, TBDMSCl

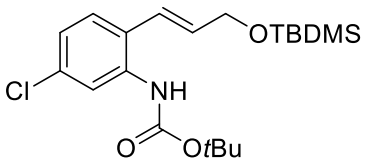
(196 mg, 1.30 mmol, 1.30 equiv.) was added in one portion and the mixture was let stir at room temperature for 19 hours. When the reaction time had elapsed, the workup was conducted in one of two ways. The crude material was either partitioned between 30 mL of EtOAc and 10 mL of brine, the aqueous phase was extracted an additional two times with EtOAc. The combined organic phases were washed with 30 mL of H_2O, then 30 mL of brine and dried over $MgSO_4$. Alternatively, the crude mixture was partitioned between 30 mL of hexanes and 10 mL of brine. The organic layer was washed with 10 mL of brine, then 20 mL of H_2O and dried over $MgSO_4$. Filtration and purification via column chromatography on silica yielded the *N*-carbonylated, *O*-silylated cinnamyl ether derivatives.

***tert*-Butyl (*E*)-(2-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)carbamate (5a)**



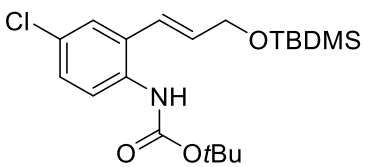
Synthesized according to General Procedure C from cinnamyl alcohol **3a** (149 mg, 1.00 mmol), di-*tert*-butyl dicarbonate (218 mg, 1.00 mmol), imidazole (170 mg, 2.50 mmol), and *tert*-butyldimethylsilyl chloride (196 mg, 1.30 mmol). Upon purification via flash chromatography using (1:19 EtOAc:hexanes), carbamate **5a** was obtained as an off-white solid (249 mg, 69 % yield). Melting point = 55-56 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 7.7 Hz), 7.23 (1H, t, *J* = 7.9 Hz), 7.04 (1H, t, *J* = 7.5 Hz), 6.71 (1H, d, *J* = 15.6 Hz), 6.45 (1H, brs), 6.17 (1H, dt, *J* = 15.6, 4.4 Hz), 4.38 (2H, d, *J* = 4.3 Hz), 1.52 (9H, s), 0.97 (9H, s), 0.14 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 135.0, 133.0, 128.4, 128.0, 126.9, 123.8, 123.7, 121.4, 80.3, 63.5, 28.3, 25.9, 18.3, -5.2. HRMS(ESI) *m/z* calculated for $C_{20}H_{33}NNaO_3Si$ [$(M+Na)^+$]: 386.2122. Found: 386.2122.

***tert*-Butyl (*E*)-(2-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-5-chlorophenyl)carbamate (5b)**



Synthesized according to General Procedure C from cinnamyl alcohol **3b** (1.15 g, 6.26 mmol), di-*tert*-butyl dicarbonate (1.37 g, 6.26 mmol), imidazole (1.07 g, 15.7 mmol), and *tert*-butyldimethylsilyl chloride (1.23 g, 8.14 mmol). Upon purification via flash chromatography using (3:97 EtOAc:hexanes to 1:19 EtOAc:hexanes), carbamate 5**b** was obtained as a pale-yellow solid (1.49 g, 60 % yield). Melting point = 54-57 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, s), 7.22 (1H, d, *J* = 8.3 Hz), 7.00 (1H, dd, *J* = 8.3, 1.9 Hz), 6.62 (1H, d, *J* = 15.6 Hz), 6.45 (1H, brs), 6.15 (1H, dt, *J* = 15.6, 4.2 Hz), 4.36 (2H, dd, *J* = 4.2, 1.9 Hz), 1.52 (9H, s), 0.96 (9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 136.0, 133.9, 133.6, 128.0, 126.1, 123.5, 122.7, 120.5, 80.9, 63.3, 28.2, 25.9, 18.4, -5.2. HRMS(ESI) *m/z* calculated for $C_{20}H_{32}{}^{35}ClNNaO_3Si$ [$(M+Na)^+$]: 420.1732. Found: 420.1733.

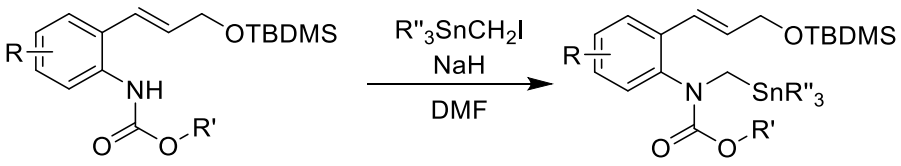
***tert*-Butyl (E)-(2-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-4-chlorophenyl)carbamate (5c)**



Synthesized according to General Procedure C from cinnamyl alcohol **3c** (612 mg, 3.33 mmol), di-*tert*-butyl dicarbonate (728 mg, 3.33 mmol), imidazole (567 mg, 8.33 mmol), and *tert*-butyldimethylsilyl chloride (653 mg, 4.33 mmol). Upon purification via flash chromatography using (3:97 EtOAc:hexanes to 1:19 EtOAc:hexanes), carbamate **5c** was obtained as a pale-yellow solid (919 mg, 69 % yield). Melting point = 62-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 2.1 Hz), 7.18 (1H, dd, *J* = 8.7, 2.3 Hz), 6.64 (1H, d, *J* = 15.6 Hz), 6.38 (1H, brs), 6.18 (1H, dt, *J* = 15.5, 4.2 Hz), 4.37 (2H, dd, *J* = 2.1, 1.9 Hz), 1.51 (9H, s), 0.96

(9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 134.6, 133.8, 130.1, 129.0, 127.9, 126.9, 122.8, 122.7, 80.9, 63.4, 28.4, 26.1, 18.5, -5.1. HRMS(ESI) *m/z* calculated for $C_{20}H_{32}{}^{35}ClKNO_3Si$ [$(M+K)^+$]: 436.1472. Found: 436.1271.

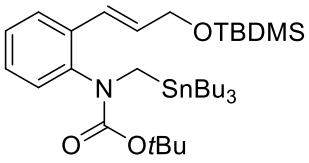
General Procedure D: *N*-Alkylation of Cinnamyl Carbamates with Tributyl(iodomethyl)stannane and Iodomethylstannatrane



The general procedure for the alkylation of cinnamyl carbamates with tributyl(iodomethyl)stannane followed the methodology reported by Bode.[103] In a typical experiment a flame dried round bottomed flask equipped with a stir bar under N_2 was charged with sodium hydride (13 mg, 0.325 mmol, 1.30 equiv., 60 wt% in mineral oil) which was washed with 3x 0.5 mL pentane. The resultant grey powder was allowed to dry under a flow of N_2 for 15 minutes and then DMF was added (0.2 M) and the suspension was cooled to 0 °C followed by the addition of the cinnamyl carbamate (91 mg, 0.250 mmol, 1.00 equiv.) in DMF (0.625 M) dropwise. The mixture was allowed to warm to room temperature and let stir for one hour before being cooled again to 0 °C. Bu_3SnCH_2I (119 mg, 0.275 mmol, 1.10 equiv.) was added dropwise via tared syringe and the solution was allowed to warm to room temperature and was stirred for 18 hours. The solution was then cooled to 0 °C and 5 mL of saturated aqueous NH_4Cl was added slowly. The mixture was extracted with 4x 7 mL of EtOAc, the combined organic layers were washed with 2x 5 mL of H_2O and then 5 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The procedure for alkylation with stannatrane **3b** was a modification of the above procedure in which the solid stannatrane was added in one portion (1.00 equiv.). Purification via

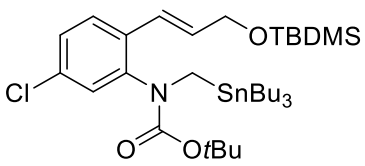
flash chromatography yielded the corresponding alkyl tributylstannyl(methyl)amino carbamates as well as the *tert*-butyl 1-aza-5-stannabicyclo[3.3.3]undecan-5-yl(methyl) amino carbamate as oils.

tert-Butyl (_E_)-(2-(3-((_tert_-Butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)((tributylstannyl)methyl)carbamate (6a)



Synthesized according to General Procedure D from cinnamyl carbamate **5a** (91 mg, 0.250 mmol), NaH (13 mg, 0.325 mmol, 60 wt% in mineral oil), and stannane **4d** (119 mg, 0.275 mmol). Upon purification via flash chromatography using (1:99 EtOAc:hexanes) compound **6a** was isolated as a pale-yellow oil (115 mg, 69 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.50 (1H, m), 7.23-7.17 (2H, m), 7.05-6.99 (1H, m), 6.57 (1H, d, J = 15.7 Hz), 6.26 (1H, dt, J = 15.9, 5.0 Hz), 4.35 (2H, d, J = 5.0 Hz), 3.07 (2H, ABq, $\Delta\nu_{AB}$ = 108.7 Hz, J_{AB} = 12.8 Hz), 1.50-1.39 (9H, m), 1.34-1.21 (15H, m), 0.93 (9H, s), 0.90-0.80 (15H, m), 0.10 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 142.9, 134.0, 130.6, 127.8, 127.6, 126.7, 126.0, 125.5, 79.3, 64.2, 36.9, 29.1(J_{Sn-C} = 9.0 Hz), 28.2, 27.4 (J_{Sn-C} = 28.4 Hz), 25.9, 18.4, 13.7, 10.7, -5.2. HRMS(ESI) *m/z* calculated for $C_{33}H_{62}NO_3Si^{116}Sn$ [$(M+H)^+$]: 664.3511. Found: 664.3514.

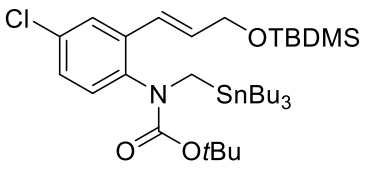
tert-Butyl (_E_)-(2-(3-((t_ert_-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-5-chlorophenyl)((tributylstannyl)methyl)carbamate (6b)



Synthesized according to General Procedure D from cinnamyl carbamate 5**b** (1.40 g, 3.52 mmol), NaH (183 mg, 4.57 mmol, 60 wt% in mineral oil), and stannane **4d** (1.67 g, 3.87 mmol). Purification via flash chromatography on silica gel using (1:99 EtOAc:hexanes to 1:49

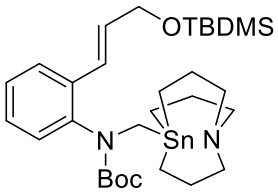
EtOAc:hexanes) yielded compound **6b** as a pale-yellow oil (1.43 g, 58 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 8.4 Hz), 7.17 (1H, d, *J* = 8.5 Hz), 7.03 (1H, s), 6.50 (1H, d, *J* = 16.0 Hz), 6.24 (1H, dt, *J* = 15.8, 5.1 Hz), 4.33 (2H, d, *J* = 3.9 Hz), 3.03 (2H, ABq, $\Delta\nu_{AB}$ = 98.4 Hz, J_{AB} = 13.0 Hz), 1.53-1.39 (6H, m), 1.35-1.22 (15H, m), 0.93 (9H, s), 0.91-0.81 (15H, m), 0.09 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 143.8, 132.8, 132.7, 131.2, 127.8, 127.1, 126.9, 124.5, 79.8, 64.0, 36.8, 29.1 ($J_{Sn\text{-}C}$ = 9.9 Hz), 28.1, 27.4 ($J_{Sn\text{-}C}$ = 28.7 Hz), 25.9, 18.4, 13.7, 10.8, -5.2 HRMS(ESI) *m/z* calculated for $C_{33}H_{61}{}^{35}ClNO_3Si^{116}Sn$ [$(M+H)^+$]: 698.3121. Found: 698.3119.

tert-Butyl (*E*)-(2-(3-((_tert_-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-4-chlorophenyl)((tributylstannyl)methyl)carbamate (6c)



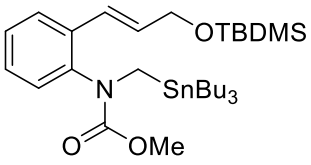
Synthesized according to General Procedure D from cinnamyl carbamate **5c** (1.20 g, 3.01 mmol), NaH (157 mg, 3.92 mmol, 60 wt% in mineral oil), and stannane **4d** (1.43 g, 3.32 mmol). Purification via flash chromatography using (1:99 EtOAc:hexanes to 1:49 EtOAc:hexanes) yielded the title product **6c** as a pale-yellow oil (1.67 g, 79 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (1H, s), 7.16 (1H, d, *J* = 8.4 Hz), 6.95 (1H, d, *J* = 8.5 Hz), 6.50 (1H, d, *J* = 15.9 Hz), 6.26 (1H, dt, *J* = 15.9, 4.9 Hz), 4.34 (2H, d, *J* = 4.8 Hz), 3.01 (2H, ABq, $\Delta\nu_{AB}$ = 112.0 Hz, J_{AB} = 12.7 Hz), 1.60-1.37 (6H, m), 1.35-1.16 (15H, m), 0.93 (9H, s), 0.89-0.77 (15H, m), 0.10 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 141.4, 135.8, 132.2, 132.0, 128.9, 127.8, 126.0, 124.3, 79.7, 63.8, 36.9, 29.1 ($J_{Sn\text{-}C}$ = 8.7 Hz), 28.2, 27.4 ($J_{Sn\text{-}C}$ = 28.3 Hz), 25.9, 18.4, 13.7, 10.7, -5.2. HRMS(ESI) *m/z* calculated for $C_{33}H_{61}{}^{35}ClNO_3Si^{116}Sn$ [$(M+H)^+$]: 698.3121. Found: 698.3122.

***tert*-Butyl (*E*)-((1-aza-5-Stannabicyclo[3.3.3]undecan-5-yl)methyl)(2-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)carbamate (6d)**



Synthesized following a modified version of General Procedure D from cinnamyl carbamate 5**a** (91 mg, 0.250 mmol), NaH (13 mg, 0.330 mmol, 60 wt% in mineral oil), and stannatrane **4b** (100 mg, 0.250 mmol), which was added in one portion. Purification via flash chromatography using (5:95:1 EtOAc:hexanes:NEt_3) yielded the title product as a thick pale-yellow oil (38 mg, 24 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 5.9 Hz), 7.22-7.14 (2H, m), 7.05-6.98 (1H, m), 6.59 (1H, d, J = 15.8 Hz), 6.23 (1H, dt, J = 15.9, 5.4 Hz), 4.34 (2H, dd, J = 5.4, 1.3 Hz), 2.79 (2H, ABq, $\Delta\nu_{AB}$ = 110.9 Hz, J_{AB} = 12.8 Hz), 2.35 (6H, t, J = 5.6 Hz), 1.69-1.58 (6H, m), 1.28 (9H, s), 0.93 (9H, s), 0.77-0.55 (6H, m), 0.10 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 143.5, 133.9, 130.0, 127.7, 127.6, 126.2, 125.8, 78.6, 64.4, 54.9 (J_{Sn-C} = 13.6 Hz), 43.7, 28.3, 26.0, 23.4 (J_{Sn-C} = 12.9 Hz), 18.4, 7.9, -5.1. HRMS(ESI) *m/z* calculated for $C_{30}H_{52}N_2NaO_3Si^{116}Sn$ [$(M+Na)^+$]: 655.2657. Found:655.2658.

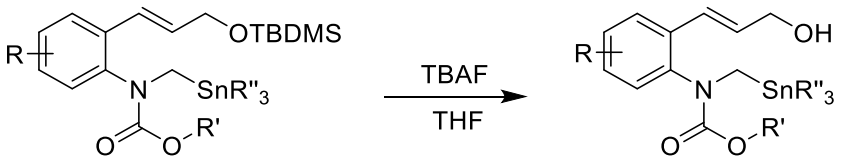
Methyl (*E*)-(2-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)((tributylstannyl)methyl)carbamate (6e)



Synthesized according to General Procedure D from cinnamyl carbamate **5d** (364 mg, 1.13 mmol), NaH (59 mg, 1.47 mmol, 60 wt% in mineral oil), and stannane **4d** (537 mg, 1.25 mmol). Purification via flash chromatography (1:49 EtOAc:hexanes to 1:19 EtOAc:hexanes) furnished the title product **6d** as a pale-yellow oil (600 mg, 85 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.54 (1H, m), 7.28-7.22 (2H, m), 7.10-7.02 (1H, m), 6.56 (1H, d, J = 16.0), 6.29 (1H, dt, J = 15.8, 5.0 Hz), 4.35 (2H, d, J = 5.0 Hz), 3.58 (3H, s), 3.11 (2H, ABq, $\Delta\nu_{AB}$ = 120.8 Hz, J_{AB} = 12.9 Hz), 1.57-1.40 (6H, m),

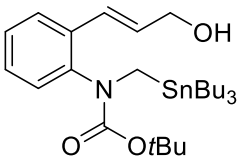
1.37-1.22 (6H, m), 0.94 (9H, s), 0.92-0.84 (15H, m), 0.10 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 142.1, 134.2, 131.4, 128.2, 127.7, 127.4, 126.4, 124.7, 64.1, 53.1, 37.8, 29.0 (J_{Sn-C} = 9.8 Hz), 27.4 (J_{Sn-C} = 28.5 Hz), 25.9, 18.4, 13.7, 10.6, -5.2. HRMS(ESI) *m/z* calculated for $C_{30}H_{55}KNO_3Si^{116}Sn$ [$(M+K)^+$]: 660.2600. Found: 660.2600.

General Procedure E: Deprotection of Cinnamyl Silyl Ethers



The procedure for the tetrabutylammonium fluoride mediated silyl ether cleavage was derived from the methodology reported by Corey and Venkateswarlu.[107] The general reaction conditions were as follows: to a flame-dried round-bottomed flask equipped with a stir bar under N_2 was added cinnamyl ether derivative (52 mg, 0.078 mmol, 1.00 equiv.) and THF such that the solution was 0.3 M. This stirred solution was cooled to 0 °C and a solution of tetrabutylammonium fluoride (78 μL, 0.078 mmol, 1.00 equiv., 1.0 M in THF) was added dropwise. The mixture was allowed to stir at this temperature for 15 minutes and was then allowed to warm to room temperature and stir for another 45 minutes. The reaction was then treated with 0.5 mL of H_2O and the solvent was removed under reduced pressure. Purification via flash chromatography yielded the corresponding cinnamyl alcohols in excellent yields.

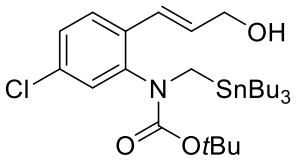
***tert*-Butyl (*E*)-(2-(3-Hydroxyprop-1-en-1-yl)phenyl)((tributylstannyl)methyl)carbamate (7a)**



Synthesized according to General Procedure E from cinnamyl ether **5a** (52 mg, 0.078 mmol) and TBAF (78 μL, 0.078 mmol, 1.0 M in THF). Purification via flash chromatography on silica gel (1:19 EtOAc:hexanes to 1:9

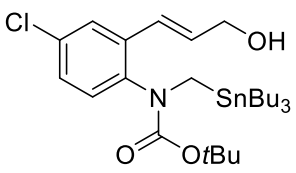
EtOAc:hexanes) yielded cinnamyl alcohol **7a** as a pale-yellow oil (40 mg, 92 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, J = 5.3 Hz), 7.25-7.17 (2H, m), 7.08-7.01 (1H, m), 6.61 (1H, d, J = 15.9 Hz), 6.34 (1H, dt, J = 16.0, 5.4 Hz), 4.39-4.29 (2H, m), 3.06 (2H, ABq, $\Delta\nu_{AB}$ = 72.7 Hz, J_{AB} = 12.9 Hz), 1.51-1.38 (7H, m), 1.35-1.19 (15H, m), 0.94-0.77 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 143.1, 133.6, 129.8, 128.2, 127.5, 127.1, 126.8, 126.1, 79.4, 64.0, 37.0, 29.1 (J_{Sn-C} = 8.5 Hz), 28.2, 27.4 (J_{Sn-C} = 28.5 Hz), 13.7, 10.7. HRMS(ESI) *m/z* calculated for $C_{27}H_{47}NNaO_3{}^{116}Sn$ [$(M+Na)^+$]: 572.2466. Found: 542.2466.

***tert*-Butyl (*E*)-(5-Chloro-2-(3-hydroxyprop-1-en-1-yl)phenyl)((tributylstannyl)methyl) carbamate (7b)**



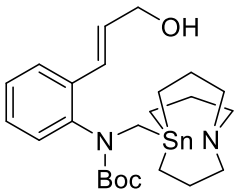
Synthesized according to General Procedure E from cinnamyl ether **6b** (1.24 g, 1.77 mmol) and TBAF (1.77 mL, 1.77 mmol, 1.0 M in THF). Purification via flash column chromatography (1:9 EtOAc:hexanes to 15:85 EtOAc:hexanes) yielded cinnamyl alcohol **7b** as a pale-yellow oil (924 mg, 89 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 8.4 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.06 (1H, s), 6.53 (1H, d, J = 16.0 Hz), 6.31 (1H, dt, J = 15.9, 5.6 Hz), 4.31 (2H, t, J = 5.0 Hz), 3.03 (2H, ABq, $\Delta\nu_{AB}$ = 61.8 Hz, J_{AB} = 12.7 Hz), 1.75 (1H, brs), 1.59-1.38 (6H, m), 1.36-1.21 (15H, m), 0.99-0.74 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 143.9, 133.1, 132.4, 130.5, 127.7, 127.1, 127.0, 125.9, 79.9, 63.7, 36.9, 29.0 (J_{Sn-C} = 9.9 Hz), 28.1, 27.4 (J_{Sn-C} = 28.5 Hz), 13.6, 10.8. HRMS(ESI) *m/z* calculated for $C_{27}H_{47}{}^{35}ClNO_3{}^{116}Sn$ [$(M+H)^+$]: 584.2256. Found: 584.2258.

***tert*-Butyl (*E*)-(4-Chloro-2-(3-hydroxyprop-1-en-1-yl)phenyl)((tributylstannyl)methyl) carbamate (7c)**



Synthesized according to General Procedure E from cinnamyl ether **6c** (1.67 g, 2.38 mmol) and TBAF (2.38 mL, 2.38 mmol, 1.0 M in THF). Purification via flash column chromatography (1:9 EtOAc:hexanes to 15:85 EtOAc:hexanes) yielded cinnamyl alcohol **7c** as a pale-yellow oil (1.21 g, 87 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, s), 7.19 (1H, d, J = 8.3 Hz), 6.98 (1H, d, J = 8.3 Hz), 6.53 (1H, d, J = 16.0 Hz), 6.33 (1H, dt, J = 15.9, 5.3 Hz), 4.32 (2H, d, J = 5.2 Hz), 3.00 (2H, ABq, $\Delta\nu_{AB}$ = 71.4 Hz, J_{AB} = 12.8 Hz), 1.73 (1H, brs), 1.59-1.37 (6H, m), 1.35-1.19 (15H, m), 0.99-0.73 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 141.6, 135.4, 132.3, 131.4, 128.9, 128.1, 126.1, 125.7, 79.8, 63.6, 37.0, 29.0 (J_{Sn-C} = 9.8 Hz), 28.2, 27.4 (J_{Sn-C} = 28.6 Hz), 13.7, 10.8. HRMS(ESI) *m/z* calculated for $C_{27}H_{47}{}^{35}ClNO_3{}^{116}Sn$ [$(M+H)^+$]: 584.2257. Found: 584.2257.

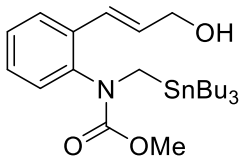
***tert*-Butyl (*E*)-((1-aza-5-Stannabicyclo[3.3.3]undecan-5-yl)methyl)(2-(3-hydroxyprop-1-en-1-yl)phenyl)carbamate (7d)**



Synthesized according to General Procedure E from cinnamyl ether **6d** (38 mg, 0.060 mmol) and TBAF (60μL, 0.060 mmol, 1.0 M in THF). Purification via flash chromatography on silica gel (10:90:1 EtOAc:hexanes:NEt_3 to 20:80:1 EtOAc:hexanes:NEt_3) furnished the cinnamyl alcohol **7d** as a thick pale-yellow oil (29 mg, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 6.0 Hz), 7.22-7.14 (2H, m), 7.03 (1H, d, J = 7.2 Hz), 6.63 (1H, d, J = 15.9 Hz), 6.32 (1H, dt, J = 15.8 Hz, 6.6 Hz), 4.32 (2H, t, J = 5.4 Hz), 2.79 (2H, ABq, $\Delta\nu_{AB}$ = 92.3 Hz, J_{AB} = 12.4 Hz), 2.36 (6H, t, J = 5.0 Hz), 1.69-1.57 (6H, m), 1.55 (1H, brs), 1.38 (9H, s), 0.78-0.56 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 143.6,

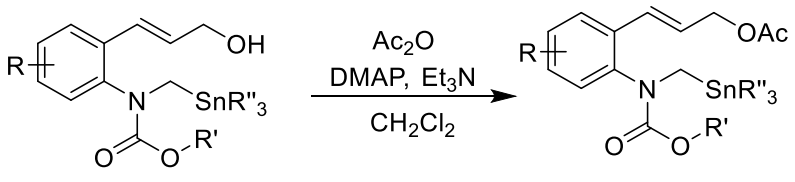
133.6, 129.3, 127.9, 127.7, 126.3, 125.8, 78.7, 64.1, 54.9 (J_{Sn-C} = 13.4 Hz), 43.9, 28.3, 23.3, 13.6, 7.9.

Methyl (*E*)-(2-(3-Hydroxyprop-1-en-1-yl)phenyl)((tributylstannyl)methyl)carbamate (7e)



Synthesized following General Procedure E from cinnamyl ether **6e** (562 mg, 0.900 mmol) and TBAF (9.00 mL, 0.900 mmol, 1.0 M in THF). Purification via flash chromatography (15:85 EtOAc:hexanes) yielded cinnamyl alcohol **7e** as a pale-yellow oil (433mg, 94 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, t, *J* = 5.2 Hz), 7.32-7.19 (2H, m), 7.12-7.01 (1H, m), 6.59 (1H, d, *J* = 15.7 Hz), 6.36 (1H, dt, *J* = 15.9, 5.6 Hz), 4.33 (2H, t, *J* = 5.7 Hz), 3.59 (3H, s), 3.09 (2H, ABq, $\Delta\nu_{AB}$ = 89.0 Hz, J_{AB} = 12.9 Hz), 1.55-1.37 (7H, m), 1.36-1.20 (6H, m), 0.99-0.76 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 142.3, 133.7, 130.7, 128.6, 127.7, 127.5, 126.5, 126.3, 63.9, 53.2, 37.8, 29.1 (J_{Sn-C} = 10.4 Hz), 27.4 (J_{Sn-C} = 28.5 Hz), 13.7, 10.6. HRMS(ESI) *m/z* calculated for $C_{24}H_{41}KNO_3{}^{116}Sn$ [$(M+K)^+$]: 546.1736. Found: 546.1735.

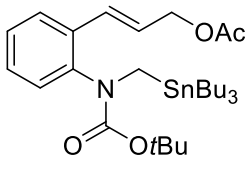
General Procedure F: Acetylation of Cinnamyl Alcohol Derivatives



The procedure employed for the acetylation of cinnamyl alcohol derivatives was followed according to the procedure reported by Fillion.[62] In a typical experiment a flame-dried round-bottomed flask equipped with a stir bar under N_2 was charged with cinnamyl alcohol derivative (552 mg, 1.00 mmol, 1.00 equiv.) which was dissolved in dry CH_2Cl_2 such that the concentration was 0.1 M. To this stirred solution was added *N*,*N*-(dimethylamino)pyridine (DMAP) (6 mg, 0.050

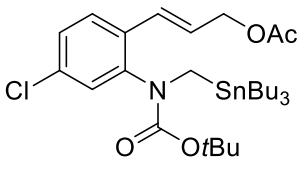
mmol, 0.050 equiv.), triethylamine (209 μL, 1.50 mmol, 1.50 equiv.), and finally acetic anhydride (Ac_2O) (104 μL, 1.10 mmol, 1.10 equiv.) dropwise. This mixture was allowed to stir at room temperature for 17 hours. The reaction mixture was then diluted with 50 mL of EtOAc and the reaction was quenched by the addition of 50 mL saturated aqueous NH_4Cl. The phases were partitioned and the aqueous phase was extracted an additional two times with 50 mL of EtOAc. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via flash chromatography yielded the corresponding cinnamyl acetates as oils.

(*E*)-3-(2-((*tert*-Butoxycarbonyl)((tributylstannyl)methyl)amino)phenyl)allyl acetate (8a)



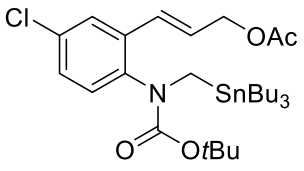
Synthesized according to General Procedure F from cinnamyl alcohol 7**a** (552 mg, 1.00 mmol), DMAP (6 mg, 0.05 mmol), Et_3N (209 μL, 1.50 mmol), and Ac_2O (104 μL, 1.10 mmol). Purification via flash chromatography using (1:19 EtOAc:hexanes) yielded the cinnamyl acetate **8a** as a pale-yellow oil (575 mg, 97 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 7.0 Hz), 7.27-7.15 (2H, m), 7.06 (1H, d, J = 7.0 Hz), 6.64 (1H, d, J = 15.9 Hz), 6.26 (1H, dt, J = 16.0, 6.3 Hz), 4.72 (2H, d, J = 6.2 Hz), 3.06 (2H, ABq, $\Delta\nu_{AB}$ = 56.6 Hz, J_{AB} = 12.8 Hz), 2.09 (3H, s), 1.57-1.37 (6H, m), 1.36-1.16 (15H, m), 0.98-0.71 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.2, 143.3, 133.2, 130.0, 128.6, 127.5, 126.7, 126.1, 124.4, 79.5, 65.2, 37.0, 29.1 (J_{Sn-C} = 9.8 Hz), 28.1, 27.4 (J_{Sn-C} = 28.4 Hz), 20.9, 13.7, 10.8. HRMS(ESI) *m/z* calculated for $C_{29}H_{50}NO_4Sn^{116}$ [$(M+H)^+$]: 592.2752. Found: 592.2753.

(*E*)-3-(2-((*tert*-Butoxycarbonyl)((tributylstannyl)methyl)amino)-4-chlorophenyl)allyl acetate (8b)



Synthesized according to General Procedure F from cinnamyl alcohol **7b** (757 mg, 1.29 mmol), DMAP (8 mg, 0.065 mmol), Et_3N (270 μL, 1.93 mmol), and Ac_2O (134 μL, 1.42 mmol). Purification via flash chromatography using (1:19 EtOAc:hexanes) yielded the cinnamyl acetate **8b** as a pale-yellow oil (744 mg, 92 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 8.4 Hz), 7.18 (1H, d, J = 8.5 Hz), 7.08 (1H, s), 6.56 (1H, d, J = 15.9 Hz), 6.24 (1H, dt, J = 16.0, 6.3 Hz), 4.71 (2H, d, J = 6.3 Hz), 3.02 (2H, ABq, $\Delta\nu_{AB}$ = 42.1 Hz, J_{AB} = 11.9 Hz), 2.09 (3H, s), 1.53-1.39 (6H, m), 1.37-1.21 (15H, m), 0.99-0.77 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.8, 144.1, 133.5, 131.9, 128.8, 127.6, 127.1, 127.0, 125.0, 80.0, 64.9, 36.9, 29.0 ($J_{Sn\text{-}C}$ = 9.9 Hz), 28.1, 27.4 ($J_{Sn\text{-}C}$ = 28.5 Hz), 20.9, 13.7, 10.8. HRMS(ESI) *m/z* calculated for $C_{29}H_{49}{}^{35}ClNO_4{}^{116}Sn$ [$(M+H)^+$]: 626.2362. Found: 626.2362.

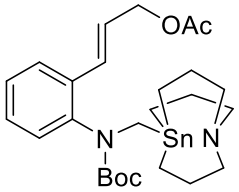
(*E*)-3-(2-((*tert*-Butoxycarbonyl)((tributylstannyl)methyl)amino)-5-chlorophenyl)allyl acetate (8c)



Synthesized according to General Procedure F from cinnamyl alcohol **7c** (1.00 g, 2.06 mmol), DMAP (10 mg, 0.103 mmol), Et_3N (356 μL, 3.09 mmol), and Ac_2O (177 μL, 2.26 mmol). Purification via flash chromatography using (1:19 EtOAc:hexanes) yielded the cinnamyl acetate **8c** as a pale-yellow oil (937 mg, 87 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, s), 7.21 (1H, d, J = 8.4 Hz), 7.00 (1H, d, J = 8.4 Hz), 6.56 (1H, d, J = 15.9 Hz), 6.26 (1H, dt, J = 16.0, 6.2 Hz), 4.72 (2H, d, J = 6.2 Hz), 3.00 (2H, ABq, $\Delta\nu_{AB}$ = 52.2 Hz, J_{AB} = 13.0 Hz), 2.09 (3H, s), 1.53-1.39 (6H, m), 1.35-1.21 (15H, m), 0.98-0.74 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.1, 142.0, 135.1, 132.5,

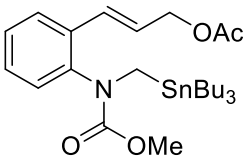
128.9, 128.7 (2), 126.2, 126.1, 80.0, 64.9, 37.2, 29.2 (J_{Sn-C} = 10.0 Hz), 28.2, 27.5 (J_{Sn-C} = 28.7 Hz), 21.0, 13.8, 11.0. HRMS(ESI) *m/z* calculated for $C_{29}H_{49}{}^{35}ClNO_4{}^{116}Sn$ [$(M+H)^+$]: 626.2362. Found: 626.2360.

(*E*)-3-(2-(((1-aza-5-Stannabicyclo[3.3.3]undecan-5-yl)methyl)(*tert*-butoxycarbonyl)amino)phenyl)allyl acetate (8d)



Synthesized according to General Procedure F from cinnamyl alcohol **7d** (137 mg, 0.260 mmol), DMAP (2 mg, 0.013 mmol), Et_3N (55 μL, 0.390 mmol), and Ac_2O (27 μL, 0.29 mmol). Purification via flash chromatography using (5:95:1 EtOAc:hexanes:NEt_3) yielded the cinnamyl acetate **8d** as a pale-yellow oil (118 mg, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 7.0 Hz), 7.24-7.13 (2H, m), 7.05 (1H, d, *J* = 6.5 Hz), 6.68 (1H, d, *J* = 15.9 Hz), 6.24 (1H, dt, *J* = 15.9, 6.3 Hz), 4.72 (2H, d, *J* = 6.2 Hz), 2.79 (2H, ABq, $\Delta\nu_{AB}$ = 61.0 Hz, J_{AB} = 12.7 Hz), 2.36 (6H, t, *J* = 5.2 Hz), 2.09 (3H, s), 1.70-1.59 (6H, m), 1.36-1.21 (9H, s), 0.80-0.54 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.6, 143.7, 133.0, 130.3, 128.3, 127.4, 126.2, 125.7, 123.6, 78.7, 65.2, 54.8 (J_{Sn-C} = 13.5 Hz), 43.8, 28.1, 23.2 (J_{Sn-C} = 12.3 Hz), 20.8, 7.8 HRMS(ESI) *m/z* calculated for $C_{26}H_{41}N_2O_4{}^{116}Sn$ [$(M+H)^+$]: 561.20783. Found: 561.20780.

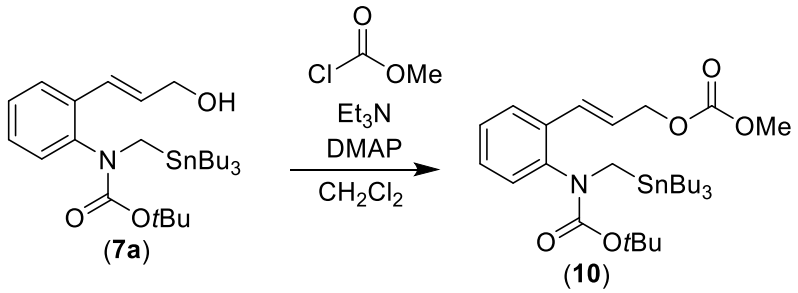
(*E*)-3-(2-((Methoxycarbonyl)((tributylstannyl)methyl)amino)phenyl)allyl acetate (8e)



Synthesized according to General Procedure F starting from alcohol 7e (426 mg, 0.835 mmol), DMAP (5 mg, 0.042 mmol), Et_3N (175 μL, 1.25 mmol), and Ac_2O (87 μL, 0.918 mmol). Purification via flash chromatography using (1:19 EtOAc:hexanes) yielded the cinnamyl acetate **8e** as a colourless oil (386 mg, 84 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 6.3 Hz), 7.30-7.26 (2H, m), 7.08 (1H, d, *J* = 7.4

Hz), 6.62 (1H, d, J = 16.0 Hz), 6.28 (1H, dt, J = 15.9, 6.4 Hz), 4.72 (2H, d, J = 6.2 Hz), 3.59 (3H, s), 3.09 (2H, ABq, $\Delta\nu_{AB}$ = 78.5 Hz, J_{AB} = 13.0 Hz), 2.10 (3H, s), 1.53-1.39 (6H, m), 1.36-1.22 (6H, m), 0.95-0.82 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 156.7, 142.5, 133.3, 129.1, 128.9, 127.6, 127.4, 126.5, 125.4, 65.0, 53.1, 37.8, 29.0 (J_{Sn-C} = 9.8 Hz), 27.4 (J_{Sn-C} = 28.6 Hz), 20.9, 13.7, 10.6. HRMS(ESI) *m/z* calculated for $C_{26}H_{43}KNO_4{}^{116}Sn$ [$(M+K)^+$]: 588.1841. Found: 588.1840.

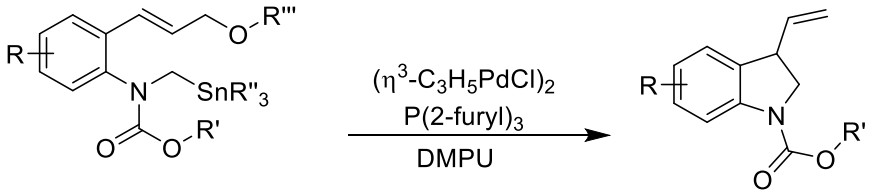
Procedure for the Synthesis of Cinnamyl Carbonate 10



The procedure for the acylation of cinnamyl alcohol **7a** with methyl chloroformate was based upon a procedure reported by Hegedus.[33] The general reaction conditions are as follows: to a flame-dried round-bottomed flask equipped with a stir bar under N_2 cinnamyl alcohol **7a** (50 mg, 0.091 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 such that the concentration was 0.07 M. This stirred solution was cooled to 0 °C and dry pyridine (10 μL, 0.127 mmol, 1.40 equiv.) was added and the solution was let stir at this temperature for 30 minutes. Then methyl chloroformate (28 μL, 0.362 mmol, 4.00 equiv.) was added dropwise at 0 °C followed by the addition of DMAP (4 mg, 0.030 mmol, 0.033 equiv.). The solution was let stir warming naturally to room temperature for 19 hours. The reaction mixture was diluted with 5 mL of CH_2Cl_2 and treated with 10 mL of H_2O. The layers were separated and the aqueous phase was extracted with an additional 3x 10 mL of CH_2Cl_2. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$,

filtered and concentrated under reduced pressure. Purification via flash chromatography (1:19 EtOAc:hexanes) yielded the cinnamyl carbonate **10** as a pale-yellow oil (52 mg, 94 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 7.2 Hz), 7.30-7.23 (2H, m), 7.05 (1H, d, *J* = 7.1 Hz), 6.68 (1H, d, *J* = 15.9 Hz), 6.28 (1H, dt, *J* = 15.8, 6.5 Hz), 4.78 (2H, d, *J* = 6.5 Hz), 3.80 (3H, s), 3.05 (2H, ABq, $\Delta\nu_{AB}$ = 66.5 Hz, J_{AB} = 12.4 Hz), 1.53-1.39 (6H, m), 1.36-1.22 (15H, m), 1.00-0.77 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 155.2, 143.4, 133.2, 130.7, 128.8, 127.5, 126.8, 126.2, 123.8, 79.6, 68.6, 54.8, 37.1, 29.1 (J_{Sn-C} = 9.8 Hz), 28.1, 27.4 (J_{Sn-C} = 28.4 Hz), 13.7, 10.7. HRMS(ESI) *m/z* calculated for $C_{29}H_{49}NNaO_5{}^{116}Sn$ [$(M+Na)^+$]: 630.2520. Found: 630.2520.

General Procedure G: Palladium-catalyzed Intramolecular Allylic Alkylation via Transmetallation of N-C(sp^3)-Tributylstannanes and N-C(sp^3)-Tricarbastannatranes



The procedure for the intramolecular allylic alkylations of cinnamyl acetates and carbonates was adopted from the report by Hegedus and was modified for use in Schlenk tubes.[33] Two methods were employed to achieve this transformation: general procedure G_1 and general procedure G_2.

General Procedure G$_1$

A typical experiment was conducted as follows: inside the glove-box a flame dried Schlenk tube equipped with a stir bar, Teflon stopper and rubber septum was charged with $(Pd(\eta^3\text{-}C_3H_5)Cl)_2$ (1 mg, 2.5 μM, 3 mol %). Outside the box, $P(2\text{-furyl})_3$ (3 mg, 0.013 mmol, 15 mol %) was added to the tube followed by DMPU (0.2 M) and this solution was allowed to stir at room temperature

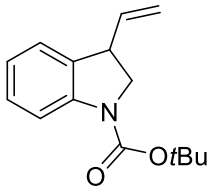
for 15 minutes. Then, in a flame dried vial cinnamyl acetate derivative (50 mg, 0.084 mmol, 1.00 equiv.) was dissolved in DMPU (0.4 M) and was transferred to the Schlenk tube via cannula under a flow of N_2. The vial and cannula were rinsed with an additional aliquot of DMPU (0.4 M) adding it to the solution as well. Thus, the final concentration of the solution was 0.1 M, the tube was sealed and placed in a pre-heated oil bath at 60 °C for 16 hours. The reaction was then allowed to cool to room temperature and was treated with 10 mL H_2O and extracted with 10 mL EtOAc. The aqueous layer was extracted an additional two times with 10 mL EtOAc and the combined organic layers were washed with 10 mL brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified via flash chromatography to yield the corresponding 3-vinylindolines. Alternatively, the extractive workup may be conducted with hexanes in order to exclude the bulk of the DMPU from the organic phase.

General Procedure G_2

In a typical experiment, a flame dried vial was charged with cinnamyl acetate derivative (220 mg, 0.350 mmol, 1.00 equiv.) and the vial was taken into the glove-box for the addition of DMPU (0.4 M). Inside the glove-box a separate flame dried vial equipped with a stir bar was loaded with $(Pd(\eta^3\text{-}C_3H_5)Cl)_2$ (4 mg, 10.5 μM, 3 mol %), $P(2\text{-furyl})_3$ (12 mg, 52.5 μM, 15 mol %), and DMPU (0.4 M). The solution was stirred for 15 minutes and then transferred to a flame dried Schlenk tube equipped with a stir bar and Teflon stopper via pipette rinsing the vial with an additional portion of DMPU. This was followed by the addition of the solution of cinnamyl acetate derivative via pipette rinsing the vial with an additional portion of DMPU. The Schlenk tube was sealed, then taken outside the box and placed in a pre-heated oil bath at 60 °C and stirred for 15 hours or until complete by TLC. The mixture was allowed to cool to room temperature and was then poured over 50 mL of H_2O. The mixture was extracted with 3x 50 mL of hexanes and the

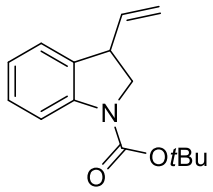
combined organic layers were then washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via flash chromatography furnished the 3-vinylindoline derivatives.

***N-tert*-Butoxycarbonyl-3-vinylindoline (9a)**



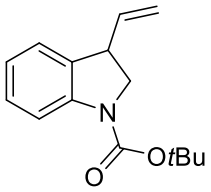
Synthesized according to General Procedure G_1 from cinnamyl acetate **8a** (50 mg, 0.084 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (1 mg, 2.5 μM) and P(2-furyl)$_3$ (3 mg, 0.013 mmol). Purified via flash chromatography on silica gel using (hexanes to 1:49 Et_2O:hexanes) to furnish the title product **9a** as a pale-yellow oil (18 mg, 86 % yield). Spectral data is consistent with that reported in the literature.[95] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.39 (1H, brs), 7.19 (1H, t, *J* = 7.6 Hz), 7.08 (1H, d, *J* = 7.3 Hz), 6.95 (1H, t, *J* = 7.4 Hz), 5.90-5.78 (1H, m), 5.23-5.13 (2H, m), 4.20 (1H, t, *J* = 10.5 Hz), 3.95 (1H, q, *J* = 8.7 Hz), 3.69 (1H, dd, *J* = 10.5, 7.5 Hz), 1.57 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 138.0, 133.7, 131.3, 125.4, 122.2, 116.7, 115.1, 113.9, 81.2, 54.0, 43.9, 28.3 HRMS(ESI) *m/z* calculated for $C_{15}H_{19}LiNO_2$ $[(M+Li)^+]$: 252.1570. Found: 252.1569.

***N-tert*-Butoxycarbonyl-3-vinylindoline (9a)**



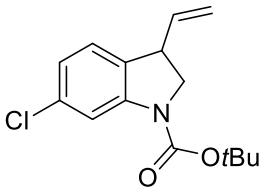
Synthesized according to General Procedure G_1 from cinnamyl carbonate **10** (52 mg, 0.085 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (1 mg, 2.6 μM) and P(2-furyl)$_3$ (3 mg, 0.013 mmol). Purified via flash chromatography on silica gel using (hexanes to 1:49 Et_2O:hexanes) to furnish the title product **9a** as a pale-yellow oil (16 mg, 77 % yield). Spectral data matches that reported above.

***N-tert*-Butoxycarbonyl-3-vinylindoline (9a)**



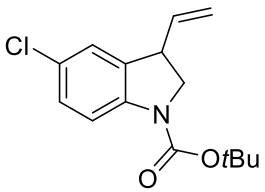
Synthesized according to General Procedure G_1 from cinnamyl acetate **8d** (50 mg, 0.089 mmol), $(Pd(\eta^3\text{-}C_3H_5)Cl)_2$ (1 mg, 2.7 μM) and P(2-furyl)$_3$ (3 mg, 0.013 mmol). Purified via flash chromatography on silica gel using (hexanes to 1:49 Et_2O:hexanes) to furnish the title product **9a** as a pale-yellow oil (15 mg, 67 % yield). Spectral data matches that reported above.

***N-tert*-Butoxycarbonyl-6-chloro-3-vinylindoline (9b)**



Synthesized according to General Procedure G_2 from cinnamyl acetate **8b** (220 mg, 0.350 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (4 mg, 10.5 μM) and P(2-furyl)$_3$ (12 mg, 0.052 mmol). Purified via flash chromatography on 1:9 KF:silica gel using (1:99 Et_2O:hexanes) to furnish the title product **9b** as a pale-yellow oil (46 mg, 47 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, brs), 6.97 (1H, d, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 7.9 Hz), 5.86-5.75 (1H, m), 5.30-5.14 (2H, m), 4.20 (1H, t, *J* = 10.4 Hz), 3.91 (1H, q, *J* = 8.6 Hz), 3.70 (1H, dd, *J* = 10.4, 7.7 Hz), 1.56 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 143.5, 138.0, 133.7, 131.3, 125.3, 122.2, 116.7, 115.1, 81.1, 54.0, 43.9, 28.3. HRMS(ESI) *m/z* calculated for $C_{15}H_{18}{}^{35}ClKNO_2$ [$(M+K)^+$]: 318.0658. Found: 318.0661.

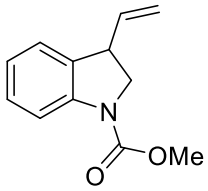
***N-tert*-Butoxycarbonyl-5-chloro-3-vinylindoline (9c)**



Synthesized according to General Procedure G_1 from cinnamyl acetate **8c** (50 mg, 0.089 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (1 mg, 2.7 μM) and P(2-furyl)$_3$ (3 mg, 0.013 mmol). Purified via flash chromatography on silica gel (hexanes to 1:49 Et_2O:hexanes) to furnish the title product **9c** as an off-white solid (15 mg, 67 % yield). Spectral is consistent with that reported in the literature (note: Yamashita reported obtaining this

product as a colourless oil).[95] Melting point = 39-43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (1H, brs), 7.14 (1H, d, *J* = 8.6 Hz), 7.03 (1H, s), 5.86-5.75 (1H, m), 5.24-5.16 (2H, m), 4.20 (1H, t, *J* = 10.5 Hz), 3.93 (1H, q, *J* = 8.7 Hz), 3.69 (1H, dd, *J* = 10.4, 7.8 Hz), 1.55 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 141.2, 137.7, 134.8, 128.9, 127.2, 124.9, 117.0, 115.6, 81.0, 53.8, 44.3, 28.4. HRMS(ESI) *m/z* calculated for $C_{15}H_{18}{}^{35}ClKNO_2$ [$(M+K)^+$]: 318.0658. Found: 318.0661.

***N*-Methoxycarbonyl-3-vinylindoline (9d)**

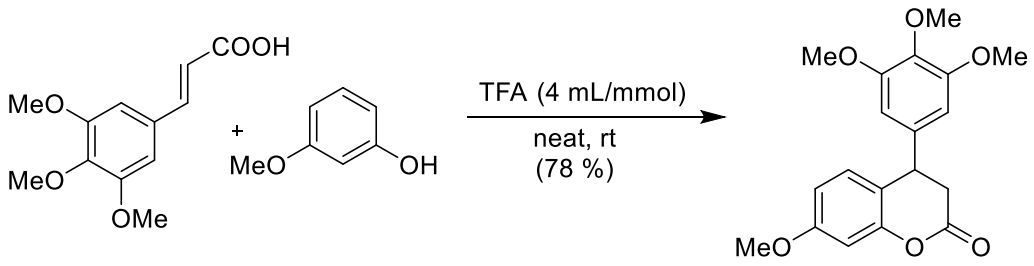


Synthesized according to General Procedure G_1 from cinnamyl acetate **8e** (253 mg, 0.458 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (5 mg, 0.014 mM) and $P(2\text{-furyl})_3$ (16 mg, 0.069 mmol). Purified via flash chromatography on 1:9 KF:silica gel (hexanes to 1:49 Et_2O:hexanes) to furnish the title product **9d** as an off-white solid (32 mg, 34 % yield). Melting point = 56-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, brs), 7.22 (1H, t, *J* = 7.6 Hz), 7.10 (1H, d, *J* = 7.3 Hz), 6.99 (1H, t, *J* = 7.4 Hz), 5.90-5.78 (1H, m), 5.23-5.14 (2H, m), 4.23 (1H, t, *J* = 10.4 Hz), 3.99 (1H, q, *J* = 8.5 Hz), 3.84 (3H, s), 3.74 (1H, dd, *J* = 10.1, 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 142.2, 138.3, 132.7, 128.1, 124.7, 122.7, 116.4, 114.7, 53.4, 52.5, 44.5. HRMS(ESI) *m/z* calculated for $C_{12}H_{14}NO_2$ [$(M+H)^+$]: 204.1019. Found: 204.1020.

Chapter 3: Polyphenolic 4-Aryl-3,4-dihydrocoumarin Synthesis

3.1: Synthesis and Biological Activity of 3,4-Dihydrocoumarins

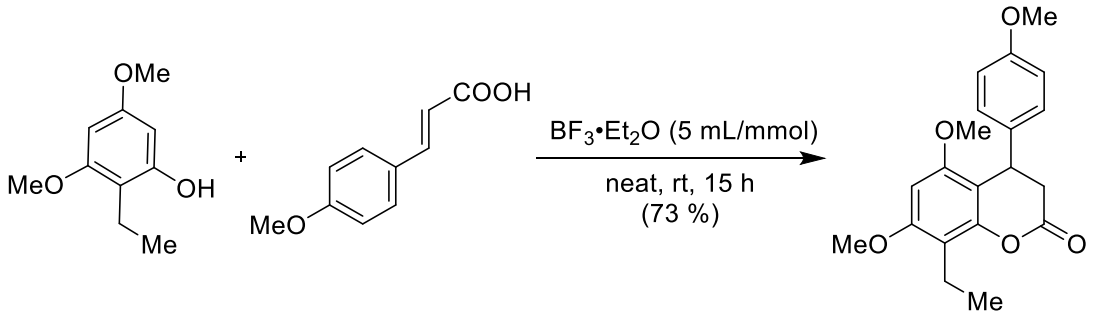
As was briefly discussed in Chapter 1, the rich biological activity of coumarins and their derivatives, such as 4-aryl-3,4-dihydrocoumarins has resulted in considerable interest being placed in the development of methods to facilitate the synthesis of these classes of compounds.[3,122] The 4-aryl-3,4-dihydrocoumarins can be classified as neoflavonoids as they are structural isomers of the flavonoid class of compounds, and have been demonstrated to possess antibacterial, anti-inflammatory, antioxidant, antifungal, esterogenic, and insecticidal activities.[3] Among the more common methods of accessing the 4-aryl-3,4-dihydrocoumarin skeleton is the Pechmann condensation in which cinnamic acids or esters are reacted with phenols in the presence of an excess of strong Brønsted acids.[122-124] Approaches that utilize more mild conditions have been developed to promote these transformations, an example of this is the trifluoroacetic acid (TFA) mediated cyclization of electron rich cinnamic acids with phenols developed by Merlini (Scheme 3.1).[125]



Scheme 3.1 TFA-Promoted Synthesis of 4-Aryl-3,4-dihydrocoumarins

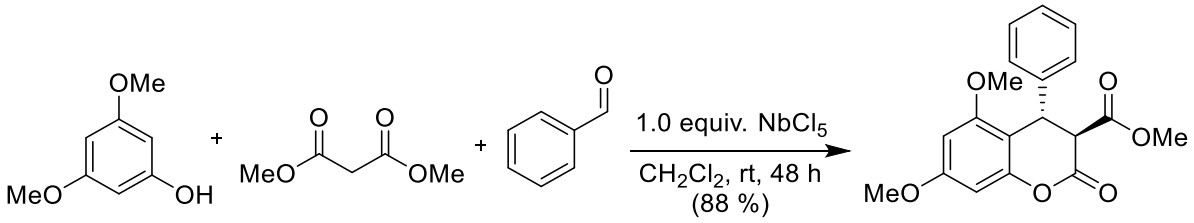
More recently, approaches that involve the use of Lewis acids as promoters in these reactions have attracted the attention of synthetic chemists. These conditions have found use in the

synthesis of a number of 4-aryl-3,4-dihydrocoumarins, such as the BF_3•Et_2O mediated cyclization reported by Keukeleire in the synthesis of a number of 8-alkyl-4-aryl-3,4-dihydrocoumarins (Scheme 3.2).[126]



Scheme 3.2 Lewis Acid-Promoted Synthesis of 4-Aryl-3,4-dihydrocoumarins

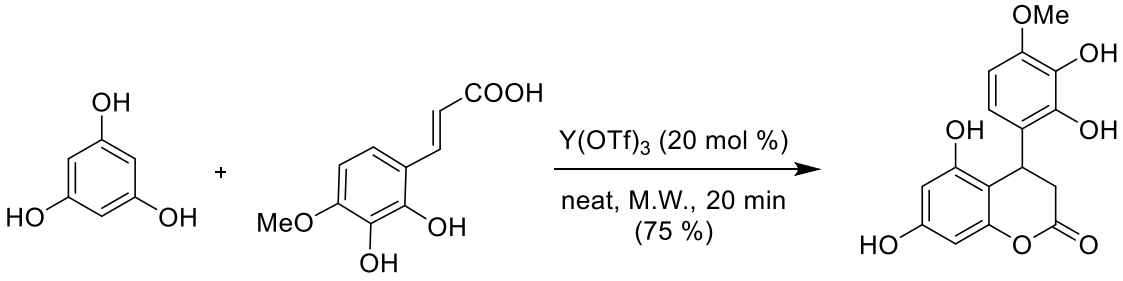
Dos Santos and Silva-Filho utilized stoichiometric amounts of the Lewis acid niobium pentachloride in the diastereoselective synthesis of methyl 5,7-dimethoxy-4-arylchroman-2-one-3-carboxylate from 3,5-dimethoxyphenol, benzaldehyde derivatives and dimethyl malonate (Scheme 3.3).[127]



Scheme 3.3 $NbCl_5$-Promoted Synthesis of 4-Aryl-3,4-dihydrocoumarins

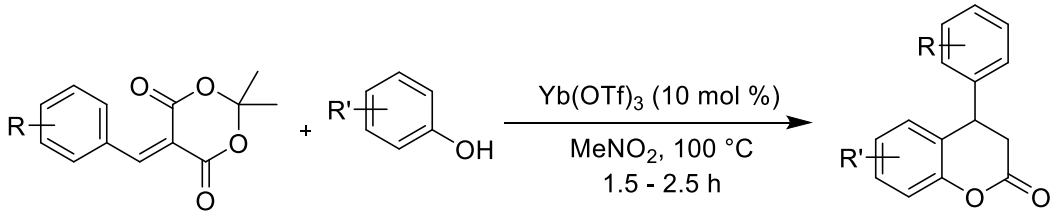
Catalytic Lewis acid catalyzed approaches to the synthesis of these heterocycles have been developed in recent years. A good example of this is the microwave assisted yttrium triflate-catalyzed condensation of phenols with cinnamic acid derivatives (Scheme 3.4).[128] This approach is attractive due to the relatively low catalyst loading required, solvent free conditions and low

reaction time required using a domestic microwave oven, though these conditions were only applied to the phenols resorcinol and phloroglucinol.



Scheme 3.4 Microwave Assisted Synthesis of 4-Aryl-3,4-dihydrocoumarins

From this brief review of the methods utilized for the synthesis of 4-aryl-3,4-dihydrocoumarins it can be seen that there still remains much to be explored in the synthesis of coumarins and their derivatives. As discussed in Chapter 1, the synthesis of a number of heterocycles was reported in 2006 by Aaron Dumas of the Fillion group through domino Friedel-Crafts reactions between phenols and benzylidene Meldrum's acids catalyzed by ytterbium triflate (Scheme 3.5).[62] Enhanced functional group tolerance, decreased catalyst loading, milder reaction conditions, and the general accessibility of the methodology made the synthetic approach developed by our group appealing for the synthesis of highly functionalized 4-aryl-3,4-dihydrocoumarins.[62]



Scheme 3.5 $Yb(OTf)_3$-Catalyzed Synthesis of 4-Aryl-3,4-dihydrocoumarins

3.2: Polyphenols in the Treatment of Tauopathy

The hyperphosphorylation of microtubule associated protein tau is linked to the abnormal polymerization of tau into neurofibrillary tangles (NFT) in Alzheimer's disease (AD) physiopathology.[129] The phosphorylation of tau is regulated by tau kinase and tau phosphatase activities, and extensive NFT formation leads to loss of neuronal function, degradation and consequently cell death, a condition referred to as tauopathy.[130] It was shown by Guéroux that procyandins, a class of polyphenolic flavonoids, formed hydrogen bonds with threonine residues T205 and T212 upon a synthetic proline-rich region of tau (P2 region) known to be correlated with microtubule association and abnormal phosphorylation (figure 3.1).[129] It is thought that the affinity of these polyphenols for this consequential region of tau may be sufficient to inhibit the phosphorylation activity of tau kinases, particularly at residue Ser214, a site known to be readily

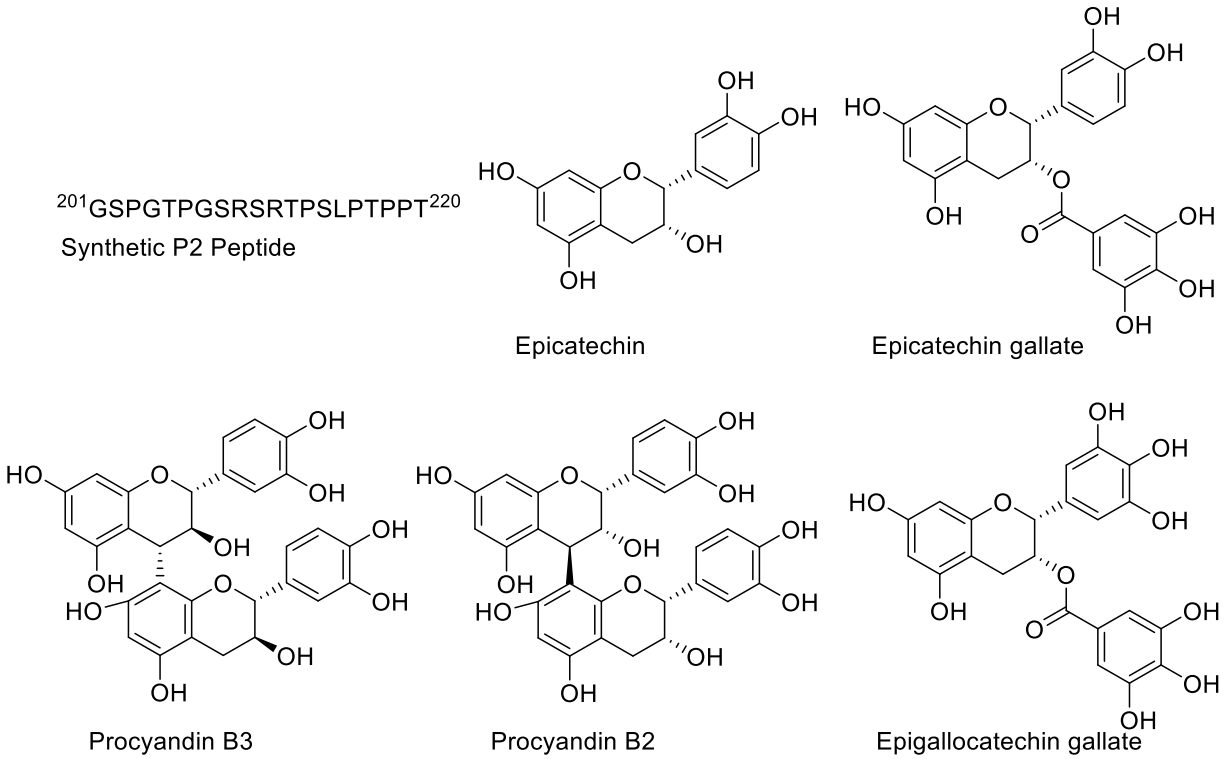


Figure 3.1 Synthetic Tau Peptide Model and Structure of Phenolic Procyandins

phosphorylated and to play a key role in the aggregation of tau.[129,131] Additionally, in mouse models of AD it has been shown that a diet rich in grapeseed-derived polyphenols has the ability to attenuate AD pathologies and tau aggregation.[132] This suggests that at least some polyphenolic compounds contained within grapeseed extract may be capable of crossing the blood brain barrier, and provides some evidence to show a reduction in the abnormal aggregation of tau by the activity of these polyphenolic flavonoids.[129,132]

3.3: Proposal

It is therefore proposed that the synthesis of a number of polyphenolic 4-aryl-3,4-dihydrocoumarins, containing structural variations of the hydroxyl functional groups, be conducted in order to assess the affinity that these neoflavonoids possess for a synthetic model of the tau peptide (Figure 3.2). These compounds were selected owing to their structural relation to the procyandins evaluated for their affinity to a synthetic model of tau by Fouquet and co-workers. Furthermore, the systematic variation of both the number and position of the hydroxyl groups would allow us to gain insights into the structural motifs of potential hydrogen bonding sites that may hold increased affinity for this consequential region of tau. This would allow for the creation of a systematic structure – activity relationship model through the analytical techniques developed by our collaborators in the Fouquet group.[129] The results of this biological assessment could be utilized in order to facilitate the development of more potent competitive inhibitors of tau kinases that may be able to both attenuate the extent of abnormal tau phosphorylation and aggregation into neurofibrillary tangles, as well as cross the blood brain barrier, a requirement to have efficacy *in vivo*.[129]

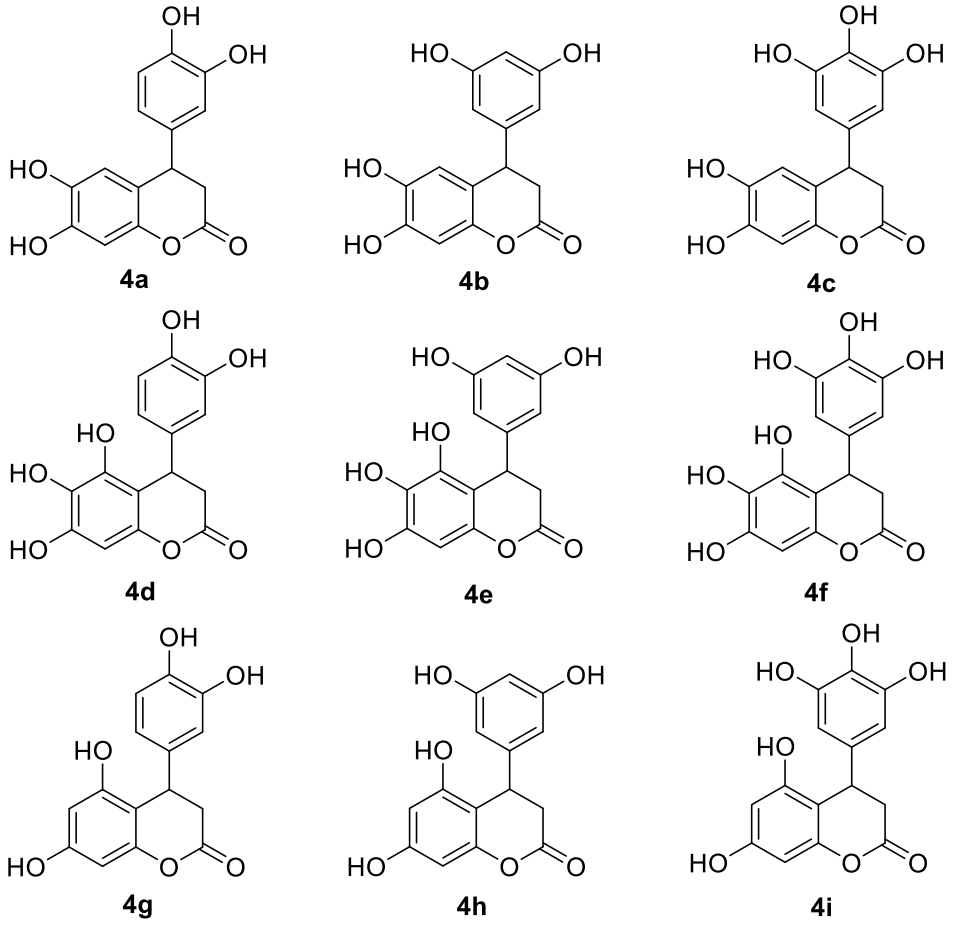
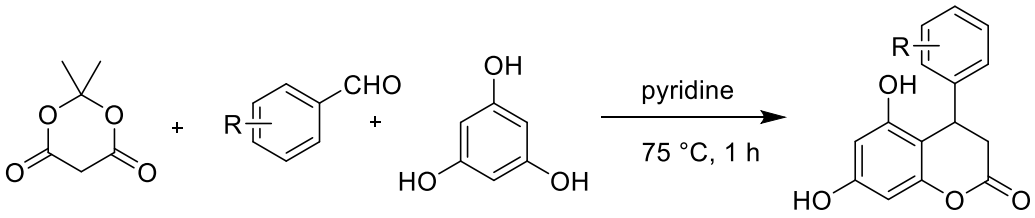


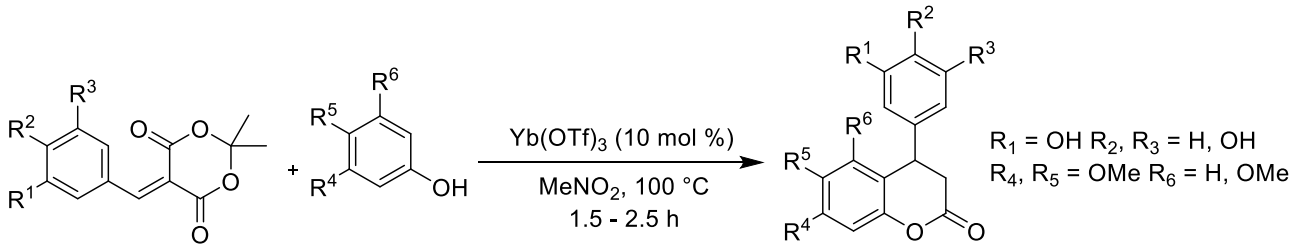
Figure 3.2 Structure of Polyphenolic 4-Aryl-3,4-dihydrocoumarins

In 1987 it was reported by Nair that 5,7-dihydroxy-4-aryl-3,4-dihydrocoumarins could be synthesized in a one-pot manner through the reaction of phloroglucinol, Meldrum's acid and benzaldehyde derivatives.[61] The high yields and readily available starting materials required for this reaction made it appealing for the synthesis of polyphenolic 4-aryl-3,4-dihydrocoumarins containing hydroxyl substitutions at the 5 and 7 positions of the coumarin skeleton (Scheme 3.6).



Scheme 3.6 One-Pot Synthesis of 5,7-Dihydroxy-3,4-dihydrocoumarins

The synthesis of 4-aryl-3,4-dihydrocoumarins from phenols and benzylidene Meldrum's acids developed in the Fillion group is well suited to electron rich substrates (Scheme 3.7).[62] Furthermore, the ease with which benzylidene Meldrum's acids and phenols may be accessed (*vide infra*) made this approach particularly attractive. The synthetic strategy to access these compounds involved the reaction of hydroxy-substituted benzylidene Meldrum's acids with methoxy-substituted phenols (Scheme 3.7) which, upon demethylation, would yield the target polyphenolic 4-aryl-3,4-dihydrocoumarins. By varying the substitution about 3 positions on each of the reactants a systematic evaluation of the structure-activity relationships may be built to evaluate the affinity for tau and the potential these compounds hold for tau kinase inhibition and the potential attenuation of tauopathy (Figure 3.2).



Scheme 3.7 Proposed Synthesis of 4-Aryl-3,4-dihydrocoumarins by Friedel-Crafts Reactions

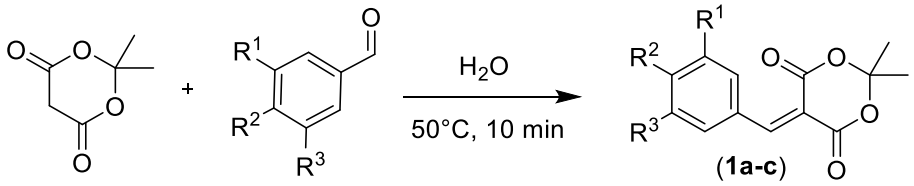
3.4: Results and Discussion

3.5: Synthesis of Benzylidene Meldrum's Acids and Methoxy Phenols

The planned synthetic route to varying the pattern of substitution of the polyphenolic 4-aryl-3,4-dihydrocoumarins (Figure 3.2) requires the synthesis of 3,5-dihydroxy-, 3,4-dihydroxy-, and 3,4,5-trihydroxybenzylidene Meldrum's acids (Scheme 3.7). Following the protocol reported

by Bigi, the synthesis of these three benzylidene Meldrum's acids proceeded efficiently and cleanly at a reduced temperature and time in comparison to the literature (Table 3.1).[133]

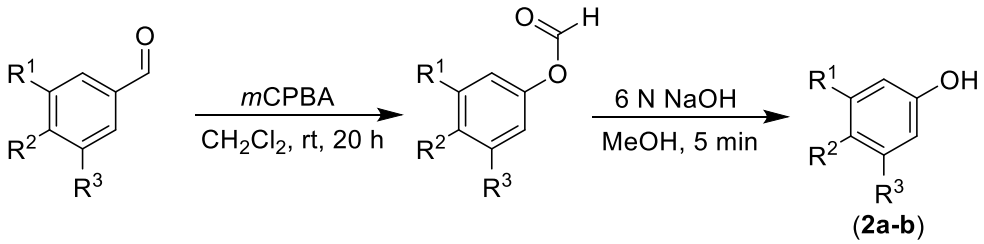
Table 3.1 Synthesis of Benzylidene Meldrum's Acids in Water



Entry #	R_1	R_2	R_3	% Yield
1	OH	OH	H	99 (**1a**)
2	OH	H	OH	99 (**1b**)
3	OH	OH	OH	87 (**1c**)

The other required substrate for the synthesis of 4-aryl-3,4-dihydrocoumarins as developed by A. Dumas and co-workers were functionalized phenols as shown in Scheme 3.7.[62] While the two phenols are commercially available, the cost was prohibitive and thus these substrates were accessed from the corresponding 3,4-dimethoxy and 3,4,5-trimethoxybenzaldehydes. This transformation was conducted via Baeyer-Villiger oxidation of the aldehyde followed by basic hydrolysis of the resultant formate ester which gave the desired compounds 3,4-dimethoxyphenol **2a** and 3,4,5-trimethoxyphenol **2b** in excellent and modest yields respectively (Table 3.2).[134] It is not clear why such a significant difference in yields was obtained between the two aldehydes but the disparity was consistent across multiple attempts.

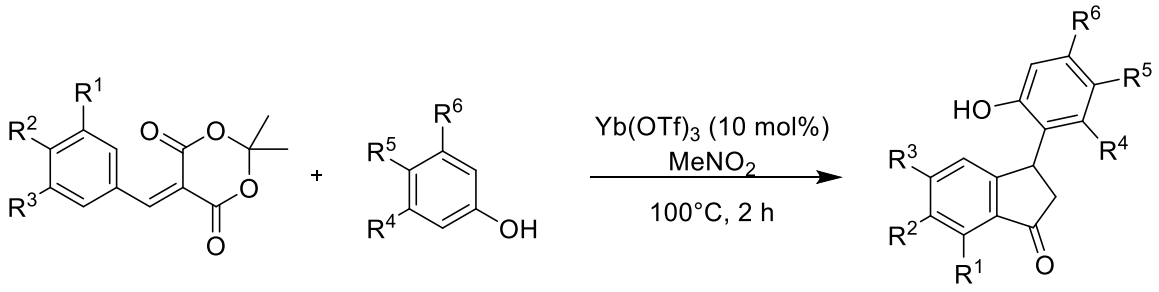
Table 3.2 Synthesis of Methoxyphenols from Benzaldehydes



Entry #	R_1	R_2	R_3	% Yield
1	OMe	OMe	H	82 (**2a**)
2	OMe	OMe	OMe	30 (**2b**)

3.6: 4-Aryl-3,4-dihydrocoumarins from Benzylidene Meldrum's Acids

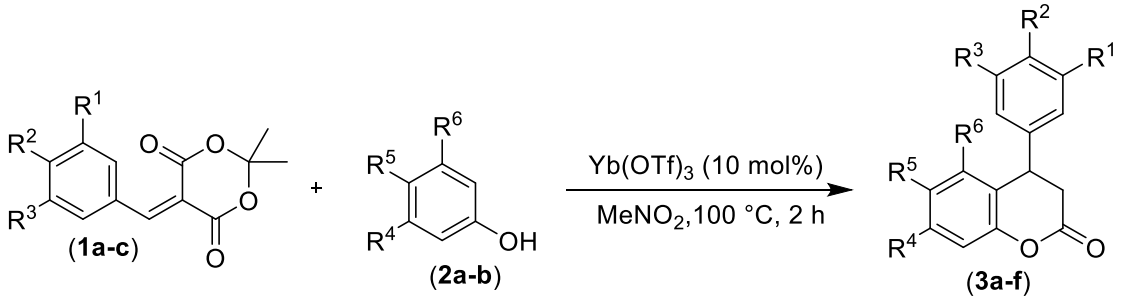
With the required benzylidene Meldrum's acids and methoxy substituted phenols in hand, the synthesis of the desired 4-aryl-3,4-dihydrocoumarin skeleton was undertaken. When Meldrum's acid **1a** was reacted with the phenols **2a** and **2b** the reaction proceeded cleanly with no observed side reactions and the desired coumarins **3a** and **3d** were obtained in good yields (Table 3.3, entries 1 and 4). However, in the cases involving the reaction of Meldrum's acids **1b** and **1c** there was some difficulty in obtaining sufficiently pure quantities of the desired coumarin products and poor yields were obtained as a result (Table 3.3, entries 2, 3, 5, and 6). We hypothesized that a competitive side reaction was occurring in which a Friedel-Crafts acylation reaction takes place upon the aromatic ring of the benzylidene Meldrum's acid derivatives **1b** and **1c** due to the *ortho-*/*para-* activating effect of the hydroxyl substitutions. This would result in the formation of a 3-aryl-1-indanone species which was supported by the preliminary analysis of the crude ^{1}H NMR spectrum though the isolation and complete characterization of this compound was never achieved as the two products were largely inseparable (Scheme 3.8).



Scheme 3.8 Proposed Structure of 3-Aryl-1-Indanone By-Product

The side reaction proved problematic as it was difficult to separate the two species by flash chromatographic techniques. Ultimately, the tedious purification of the products formed in these reactions was successful in yielding the desired 4-aryl-3,4-dihydrocoumarins **3b**, **3c**, **3e**, and **3f** in moderate yields (Table 3.3, entries 2-3, 5-6).

Table 3.3 Friedel-Crafts Reactions in the Synthesis of 3,4-Dihydrocoumarins

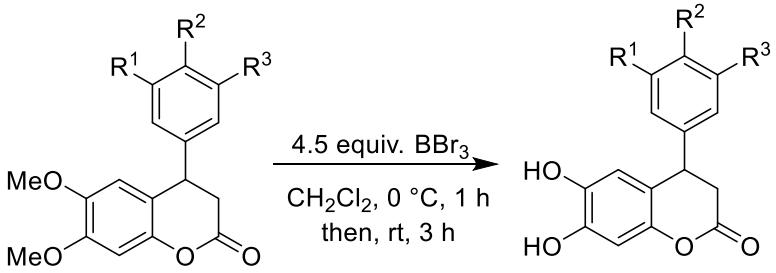


Entry #	R_1	R_2	R_3	R_4	R_5	R_6	% Yield
1	OH	OH	H	OMe	OMe	H	61 (**3a**)
2	OH	H	OH	OMe	OMe	H	35 (**3b**)
3	OH	OH	OH	OMe	OMe	H	27 (**3c**)
4	OH	OH	H	OMe	OMe	OMe	45 (**3d**)
5	OH	H	OH	OMe	OMe	OMe	26 (**3e**)
6	OH	OH	OH	OMe	OMe	OMe	22 (**3f**)

3.7: Demethylation of 4-Aryl-3,4-dihydrocoumarins

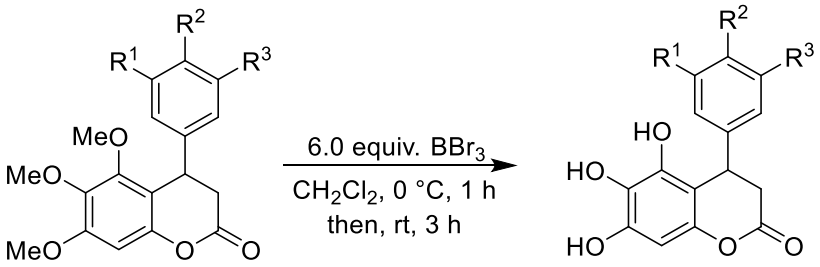
The only step remaining in the synthesis of the polyphenolic 4-aryl-3,4-dihydrocoumarins was cleavage of the methyl ethers. This transformation was achieved utilizing the demethylating agent boron tribromide.[135] After some optimization of reaction conditions, the desired polyphenolic 4-aryl-3,4-dihydrocoumarins were obtained in good to excellent yields in a modification of the procedure employed by Keukeleire (Table 3.4, Table 3.5).[126]

Table 3.4 Methyl Ether Cleavage of 6,7-Dimethoxy-4-aryl-3,4-dihydrocoumarins



Entry #	R_1	R_2	R_3	% Yield
1	OH	OH	H	68 (**4a**)
2	OH	H	OH	74 (**4b**)
3	OH	OH	OH	95 (**4c**)

Table 3.5 Methyl Ether Cleavage of 5,6,7-Trimethoxy-4-aryl-3,4-dihydrocoumarins

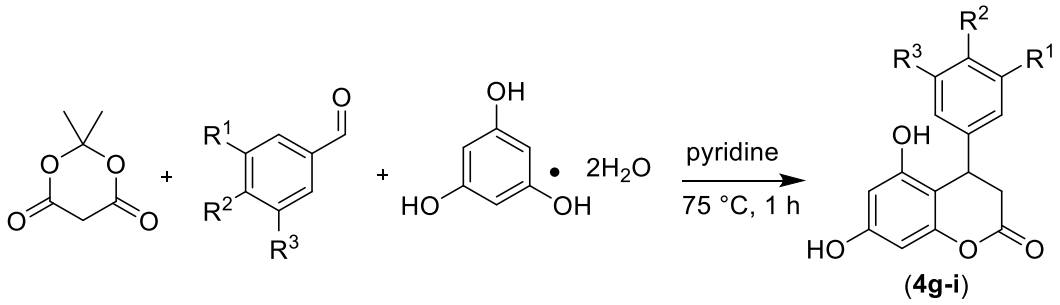


Entry #	R_1	R_2	R_3	% Yield
1	OH	OH	H	69 (**4d**)
2	OH	H	OH	92 (**4e**)
3	OH	OH	OH	69 (**4f**)

3.8: One-Pot Synthesis of 5,7-Dihydroxy-4-aryl-3,4-dihydrocoumarins

The one-pot protocol developed by Nair was successful in the synthesis of 4-phenolic 5,7-dihydroxy-chroman-2-ones albeit in modest yields for two of the three examples (entries 1 and 3, Table 3.6). Nair reported obtaining the mono pyridinium salts upon recrystallization of the crude material from DCM/heptane; however, the obtained crude materials were non-soluble even in boiling dichloromethane.[61] Recrystallization from methanol was also unsuccessful. Upon treatment of the crude material with 3 M HCl, workup, and purification via flash chromatography the desired 4-phenolic-5,7-dihydroxychroman-2-ones **4g**, **4h**, and **4i** were obtained (Table 3.6). Unfortunately, this reaction appeared to be only applicable to the electron rich phenol phloroglucinol as, for example, when 3,4-dimethoxyphenol **2a** was submitted to these conditions none of the corresponding 3,4-dihydrocoumarin was observed. Purification of the products obtained from these reactions proved tedious and increased yields may be observed if reverse phase chromatographic techniques are developed, particularly substrates **4g** and **4i** (Table 3.6).

Table 3.6 One-Pot Synthesis of 4-Aryl-3,4-dihydrocoumarins



Entry #	R_1	R_2	R_3	% Yield
1	OH	OH	H	7 (**4g**)
2	OH	H	OH	68 (**4h**)
3	OH	OH	OH	14 (**4i**)

3.9: Summary of Chapter 3

The initial series of nine polyphenolic 4-aryl-3,4-dihydrocoumarins (Figure 3.2) that had been intended for use in studies examining the affinity of these compounds for a synthetic model of tau were successfully synthesized. Three of the desired substrates were accessed in a one-pot manner from benzaldehyde derivatives, Meldrum's acid and phloroglucinol to provide the 5,7-dihydroxy-4-aryl-3,4-dihydrocoumarins **4g**, **4h**, and **4i**.[61] The remaining six were synthesized utilizing the synthetic methodology that was developed in the Fillion lab starting from functionalized benzaldehydes, Meldrum's acid and methoxy substituted phenols.[62] This synthetic approach only required three steps starting from functionalized benzaldehydes. For these six examples the yields of the final polyphenolic 4-aryl-3,4-dihydrocoumarins over the synthesis ranged between 5% and 34% relative to the methoxy substituted benzaldehyde starting materials. The synthesis of these polyphenolic neoflavonoids represents a good example of the utility of the

synthetic methodology developed in the Fillion lab furnishing highly functionalized heterocycles in moderate to high yields from readily available and easily purified precursors. There are significant improvements that may be made regarding the purification of the products formed in the domino Friedel-Crafts reactions and one-pot syntheses in order to obtain greater yields of the desired 4-aryl-3,4-dihydrocoumarins.

3.10: Experimental Section

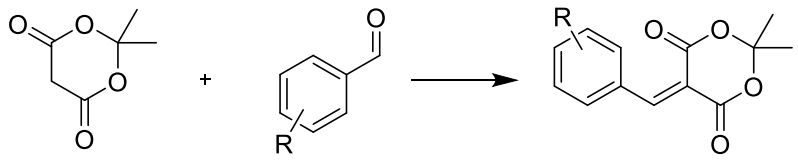
General Methods: Unless otherwise noted, all reactions were carried out in flame-dried glassware under a nitrogen atmosphere. N_2 was passed over KOH and $CaSO_4$ before entering the Schlenk line. Friedel Crafts alkylation/acylation reactions were conducted in a resealable Schlenk tube utilizing standard Schlenk techniques. $MeNO_2$ and CH_2Cl_2 were distilled over CaH_2. The methanol used was 99.9% HPLC grade and used as received. Pyridine was used as received from Caledon Laboratories Ltd., and Meldrum's acid was purchased from Oakwood Chemical and used as received. All other chemicals were purchased from Aldrich and used as received. Deionized water was used in the Knoevenagel condensation of benzaldehyde derivatives with Meldrum's acid.

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker Avance-300 spectrometers. Residual ^1H shift in DMSO-d_6 (2.49 ppm) was used as the internal reference for ^1H NMR. The ^{13}C shift in DMSO-d_6 (39.5 ppm) was used as the internal reference for ^{13}C NMR. Chemical shifts are reported in ppm and coupling constants are reported in Hz. Abbreviations used for the description of ^1H NMR multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and brs = broad singlet.

HRMS data was collected on a Thermo Scientific Q-Exactive Orbitrap HRMS utilizing electrospray ionization (ESI) and 50:50:0.1 MeCN/H_2O/formic acid, 50:50:0.1 MeOH/H_2O/formic acid, or 1:1 MeOH/H_2O.

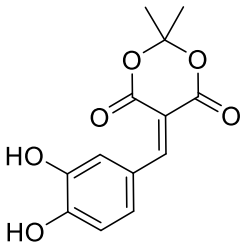
Reactions were monitored by thin-layer chromatography (TLC) on glass or aluminum backed pre-coated plates with a thickness of 250 μm, a particle size of 60Å, and with an F-254 indicator purchased from Silicycle. Developed plates were visualized through U.V. illumination, or by staining with I_2/silica or $KMNO_4$ solution. Flash chromatography was conducted utilizing 230-400 mesh silica gel purchased from Silicycle.

General Procedure A: Synthesis of 5-Benzylidene-Meldrum's Acids



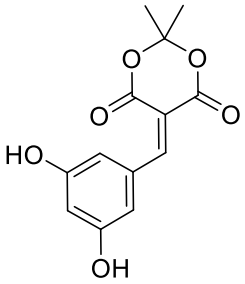
The methodology employed was a modification of the procedure developed by F. Bigi in which the temperature and length of the reaction have both been decreased.[133] In a typical experiment benzaldehyde derivative (691 mg, 5.00 mmol, 1.0 equiv.) and Meldrum's acid (793 mg, 5.50 mmol, 1.1 equiv.) were added to a round-bottomed flask and dissolved in deionized H_2O such that the concentration was 0.5 M. The solution was heated with stirring at 50 °C for 5-10 minutes or until a bright yellow precipitate formed which prevented further stirring of the mixture. Upon cooling to room temperature, the mixture was filtered by suction filtration, and the collected precipitate was washed with ice cold deionized H_2O. The obtained yellow solid was dried under reduced pressure to yield the corresponding benzylidene Meldrum's acid which was generally of sufficient purity for use in the following step without further purification. If necessary residual benzaldehyde may be removed by recrystallization from MeOH or H_2O.

5-(3,4-Dihydroxybenzylidene)-Meldrum's Acid (1a)



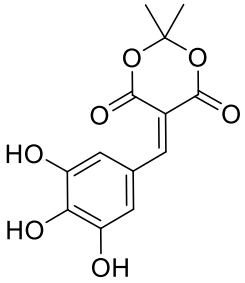
Prepared according to General Procedure A starting from 3,4-dihydroxybenzaldehyde (691 mg, 5.00 mmol) and Meldrum's acid (793 mg, 5.50 mmol) to yield **1a** as a bright yellow solid (1.30 g, 99% yield). Melting point (dec) = 161 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.54 (1H, brs), 9.55 (1H, brs), 8.13 (1H, s), 7.91 (1H, s), 7.53 (1H, d, *J* = 8.0 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 1.70 (6H, s). HRMS(ESI) *m/z* calculated for $C_{13}H_{11}O_6$ [(M-H)$^-$]: 263.0550. Found: 263.0561.

5-(3,5-Dihydroxybenzylidene)-Meldrum's Acid (1b)



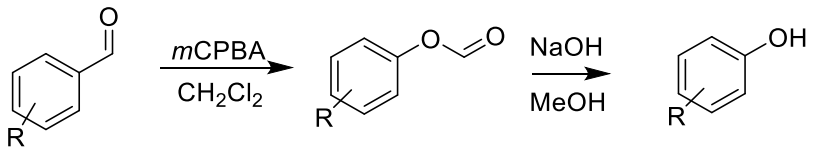
Procedure was as followed according to General Procedure A starting from 3,5-dihydroxybenzaldehyde (5.00 mmol, 691 mg) and Meldrum's acid (5.50 mmol, 793 mg) obtaining **1b** as a yellow solid (1.38 g, 99% yield). Melting point (dec) = 186°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (2H, brs), 8.10 (1H s), 6.87 (2H, s), 6.44 (1H, s), 1.73 (6H, s). HRMS(ESI) *m/z* calculated for $C_{13}H_{11}O_6$ [(M-H)$^-$]: 263.0550 Found: 263.0561.

5-(3,4,5-Trihydroxybenzylidene)-Meldrum's Acid (1c)



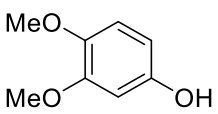
Procedure followed according to General Procedure A starting from 3,4,5-trihydroxybenzaldehyde monohydrate (5.00 mmol, 861 mg) and Meldrum's acid (5.50 mmol, 793 mg) to yield **1c** as a yellow solid (1.31 g, 87% yield). Melting point (dec) = 189 °C. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.84 (1H, brs), 9.50 (2H, brs), 8.01 (1H, s), 7.33 (2H, s), 1.70 (6H, s). HRMS(ESI) *m/z* calculated for $C_{13}H_{11}O_7$ [(M-H)$^-$]: 279.0499. Found: 279.0511.

General Procedure B: Synthesis of Methoxyphenols



In a typical experiment, a flame-dried round-bottomed flask under N_2 was charged with a benzaldehyde derivative (5.00 g, 30.1 mmol, 1.0 equiv.) which was dissolved in CH_2Cl_2 such that the solution was 0.05 M. To this stirred solution *meta*-chloroperbenzoic acid (*m*CPBA) (8.65 g, 30.1 mmol, 1.0 equiv., 60 wt% in *meta*-chlorobenzoic acid) was added portion-wise and the solution was allowed to stir at room temperature for 24 hours or until complete by TLC. The solution was then washed with 3x100 mL of saturated $NaHCO_3$ and then 100 mL of saturated Na_2CO_3. The organic phase was washed with 100 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was dissolved in 75 mL MeOH and treated with 5 mL of 6 N NaOH dropwise with stirring. The resulting solution was allowed to stir for 5 minutes, it was then diluted with 50 mL of EtOAc and with 50 mL of water. The layers were separated and the aqueous phase was extracted with an additional 50 mL of EtOAc. The combined organic layers were then washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification via flash chromatography the corresponding phenols were obtained.[134]

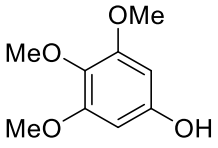
3,4-Dimethoxyphenol (2a)



Synthesized according to General Procedure B starting from 3,4-dimethoxybenzaldehyde (5.00 g, 30.1 mmol), and *m*CPBA (8.65 g, 30.1 mmol, 60 wt%). Following purification via flash chromatography using 1%MeOH:99%DCM the title product **2a** was obtained as a light brown solid (3.93 g, 82% yield). Melting point = 68 °C (m.p.

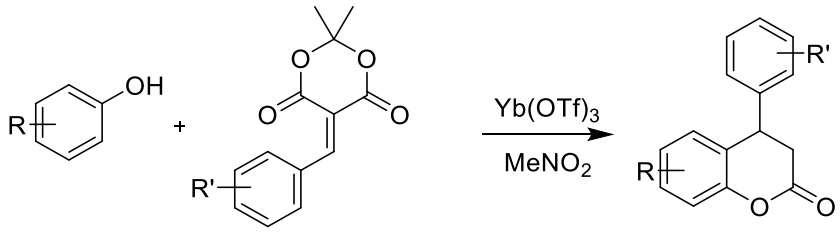
lit = 80-81 °C).[136] Spectral data is consistent with that reported in the literature.[136] ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (1H, brs), 6.72 (1H, d, *J* = 8.6 Hz), 6.39 (1H, d, *J* = 2.3 Hz), 6.24 (1H, dd, *J* = 8.6, 2.3 Hz) 3.68 (3H, s), 3.63 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 149.8, 141.8, 113.7, 105.6, 100.8, 56.4, 55.3.

3,4,5-Trimethoxyphenol (2b)



Synthesized according to General Procedure B starting from 3,4,5-trimethoxybenzaldehyde (5.91 g, 30.1 mmol) and *m*CPBA (8.65 g, 30.1 mmol, 60 wt%). Purified via flash chromatography (1:99 MeOH:CH_2Cl_2) to furnish **2b** as an orange powder (1.67 g, 30% yield). Melting point = 127 °C (m.p. lit. = 147-148 °C).[137] Spectral data is consistent with that reported in the literature.[137] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (1H, brs), 6.03 (2H, s), 3.68 (6H, s), 3.53 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.9, 153.4, 130.4, 92.9, 60.1, 55.5.

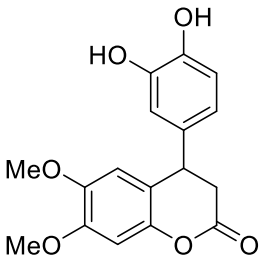
General Procedure C: Yb(OTf)$_3$ Catalyzed 4-Aryl-3,4-dihydrocoumarin Synthesis



The following procedure is a modification of the method developed by Aaron Dumas from the Fillion group.[62] In a typical experiment a flame-dried Schlenk tube equipped with a stir bar under N_2 was charged with methoxyphenol derivative (771 mg, 5.0 mmol, 1.0 equiv.), benzylidene Meldrum's acid derivative (1.45 g, 5.5 mmol, 1.1 equiv.), and Yb(OTf)$_3$ (310 mg, 0.5 mmol, 0.1 equiv.). To the tube was added dry $MeNO_2$ such that the solution was 0.4 M relative to phenol.

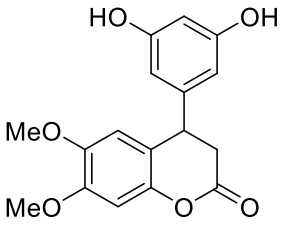
The tube was then sealed and placed in a pre-heated oil bath at 100 °C for 3-5 hours, monitoring by TLC. When judged to be complete the reaction was cooled to room temperature and the contents of the tube were washed into a separatory funnel with EtOAc and H_2O. Reaction mixture was treated with 50 mL H_2O and extracted 3x with 50 mL EtOAc. Combined organic phases were washed with 50 mL brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Upon purification via flash chromatography the corresponding methoxy substituted 4-aryl-3,4-dihydrocoumarins were obtained.

6,7-Dimethoxy-4-(3,4-dihydroxyphenyl)-3,4-dihydrocoumarin (3a)



Synthesized according to General Procedure C from 3,4-dimethoxyphenol (771 mg, 5.00 mmol), benzylidene Meldrum's acid **1a** (1.45 g, 5.50 mmol) and $Yb(OTf)_3$ (310 mg, 0.10 mmol) at 100 °C for 5 h. Purification via flash chromatography (1:99 MeOH:CH_2Cl_2) gave the coumarin **3a** as an off-white powder (958 mg, 61% yield). Melting point = 222 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (2H, brs), 6.81 (1H, s), 6.72 (1H, s), 6.65 (1H, d, *J* = 8.1 Hz), 6.45 (1H, d, *J* = 1.8 Hz), 6.38 (1H, dd, *J* = 8.0, 1.8 Hz), 4.19 (1H, dd, *J* = 5.3, 5.3 Hz), 3.76 (3H, s), 3.66 (3H, s), 3.10 (1H, dd, *J* = 15.9, 6.4 Hz), 2.83 (1H, dd, *J* = 15.9, 4.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.9, 148.6, 145.4, 145.0, 144.3, 132.7, 117.8, 116.9, 115.7, 114.3, 111.4, 101.3, 55.9, 55.86, 38.5, 37.2. HRMS(ESI) *m/z* calculated for $C_{17}H_{17}O_6$ [$(M+H)^+$]: 317.1020. Found: 317.1020.

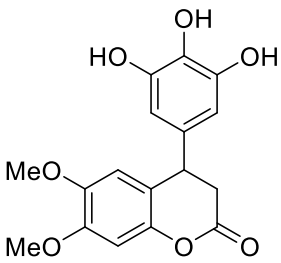
6,7-Dimethoxy-4-(3,5-dihydroxyphenyl)-3,4-dihydrocoumarin (3b)



Synthesized following General Procedure C from 3,4-dimethoxyphenol (154 mg, 1.00 mmol), benzylidene Meldrum's acid **1b** (291 mg, 1.10 mmol) and $Yb(OTf)_3$ (62 mg, 0.10 mmol) at 100 °C for 4 h. Purification

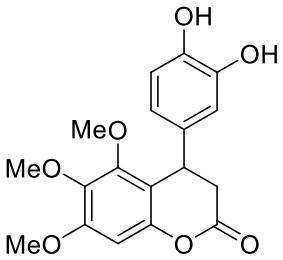
via flash chromatography (1:99 MeOH:CH_2Cl_2) yielded the desired coumarin **3b** as an off-white powder (113 mg, 35% yield). Melting point = 120 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (2H, brs), 6.82 (1H, s), 6.76 (1H, s), 6.05 (1H, s), 5.94 (2H, s), 4.16 (1H, dd, *J* = 5.7, 3.3 Hz), 3.76 (3H, s), 3.67 (3H, s), 3.14 (1H, dd, *J* = 16.0, 6.7 Hz). 2.80 (1H, dd, *J* = 16.0, 3.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.8, 158.7, 148.8, 145.4, 145.1, 144.1, 116.3, 111.5, 105.1, 101.4, 101.2, 56.0, 55.9, 39.2, 36.9. HRMS(ESI) *m/z* calculated for $C_{17}H_{17}O_6$ [$(M+H)^+$]: 317.1020. Found: 317.1020.

6,7-Dimethoxy-4-(3,4,5-trihydroxyphenyl)-3,4-dihydrocoumarin (3c)



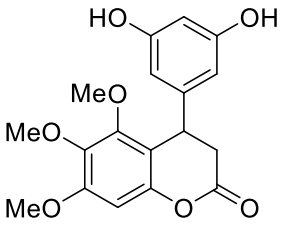
Synthesized following General Procedure C from 3,4-dimethoxyphenol (771 mg, 5.00 mmol), benzylidene Meldrum's acid **1c** (1.54 g, 5.50 mmol) and ytterbium triflate (310 mg, 0.50 mmol) at 100 °C for 4 h. Purification via flash chromatography (1:49 MeOH:CH_2Cl_2) yielded the desired coumarin **3c** as a white powder (449 mg, 27% yield). Melting point = 250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (2H, brs), 8.02 (1H, brs), 6.81 (1H, s), 6.74 (1H, s), 6.00 (2H, s), 4.10 (1H, dd, *J* = 5.0, 5.0 Hz), 3.76 (3H, s), 3.67 (3H, s), 3.09 (1H, dd, *J* = 15.7, 6.5 Hz), 2.78 (1H, dd, *J* = 15.9, 3.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.9, 148.6, 146.2, 145.4, 145.0, 132.1, 131.9, 116.9, 111.5, 105.7, 101.3, 56.0, 55.9, 38.8, 37.3. HRMS(ESI) *m/z* calculated for $C_{17}H_{17}O_7$ [$(M+H)^+$]: 333.0969. Found: 333.0969.

5,6,7-Trimethoxy-4-(3,4-dihydroxyphenyl)-3,4-dihydrocoumarin (3d)



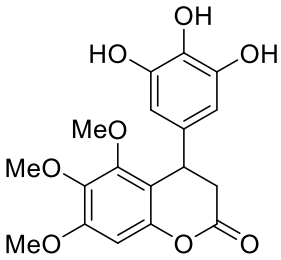
Synthesized according to General Procedure C starting from 3,4,5-trimethoxyphenol (921 mg, 5.00 mmol), benzylidene Meldrum's acid **1a** (1.45 g, 5.50 mmol) and $Yb(OTf)_3$ (310 mg, 0.50 mmol) at 100 °C for 4 h. Purified via flash chromatography (1:99 MeOH:CH_2Cl_2) to yield the desired coumarin **3d** as a beige solid (764 mg, 45% yield). Melting point = 66 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (1H, brs), 8.80 (1H, brs), 6.70 (1H, s), 6.62 (1H, d, *J* = 7.9 Hz), 6.40 (1H, s), 6.33 (1H, d, *J* = 7.7 Hz), 4.34 (1H, d, *J* = 5.8 Hz), 3.81 (3H, s), 3.70 (3H, s), 3.60 (3H, s), 3.17 (1H, dd, *J* = 15.7, 6.6 Hz), 2.74 (1H, d, *J* = 15.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 153.1, 150.0, 147.3, 145.3, 144.2, 138.4, 132.9, 117.3, 115.8, 113.9, 111.5, 97.1, 60.9, 60.5, 56.1, 37.3, 34.0. HRMS(ESI) *m/z* calculated for $C_{18}H_{19}O_7$ [$(M+H)^+$]: 347.11253. Found: 347.11249.

5,6,7-Trimethoxy-4-(3,5-dihydroxyphenyl)-3,4-dihydrocoumarin (3e)



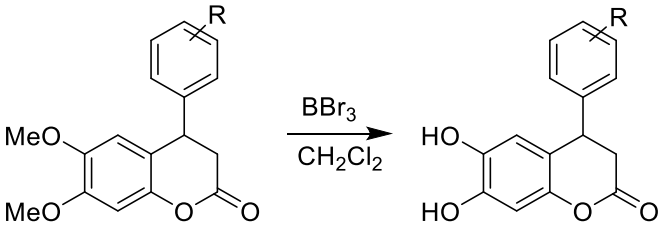
Synthesized according to the General Procedure C from 3,4,5-trimethoxyphenol (553 mg, 3.00 mmol), benzylidene Meldrum's acid **1b** (872 mg, 3.30 mmol) and $Yb(OTf)_3$ (186 mg, 0.30 mmol) at 100 °C for 3 h. Purified via flash chromatography (1:99 MeOH:CH_2Cl_2) to yield the desired coumarin **3e** as a beige solid (267 mg, 26% yield). Melting point = 199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (2H, brs), 6.70 (1H, s), 6.03 (1H, s), 5.91 (2H, s), 4.31 (1H, d, *J* = 5.5 Hz), 3.81 (3H, s), 3.71 (3H, s), 3.63 (3H, s), 3.18 (1H, dd, *J*= 15.7, 6.7 Hz), 2.73 (1H, d, *J* = 15.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 158.6, 153.2, 150.0, 147.4, 144.2, 138.4, 111.0, 104.6, 101.2, 97.1, 60.9, 60.5, 56.1, 36.9, 34.6. HRMS(ESI) *m/z* calculated for $C_{18}H_{19}O_7$ [$(M+H)^+$]: 347.11253. Found: 347.11249.

5,6,7-Trimethoxy-4-(3,4,5-trihydroxyphenyl)-3,4-dihydrocoumarin (3f)



Synthesized according to the General Procedure C from 3,4,5-trimethoxyphenol (921 mg, 5.00 mmol), benzylidene Meldrum's acid **1c** (1.54 g, 5.50 mmol) and $Yb(OTf)_3$ (310 mg, 0.50 mmol) at 100 °C for 3 h. Purified via flash chromatography (1:49 MeOH:CH_2Cl_2) to yield the desired coumarin **3f** as a brown solid (475 mg, 26% yield). Melting point = 171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (2H, brs), 8.00 (1H, brs), 6.69 (1H, s), 5.97 (2H, s), 4.26 (1H, d, *J* = 6.3 Hz), 3.81 (3H, s), 3.70 (3H, s), 3.61 (3H, s), 3.13 (1H, dd, *J* = 15.9, 6.9 Hz), 2.70 (1H, d, *J* = 15.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.7, 153.1, 150.1, 147.4, 146.2, 138.5, 132.3, 131.9, 111.6, 105.4, 97.2, 61.0, 60.6, 56.2, 37.4, 34.3. HRMS(ESI) *m/z* calculated for $C_{18}H_{19}O_8$ [$(M+H)^+$]: 363.10744. Found: 363.10741.

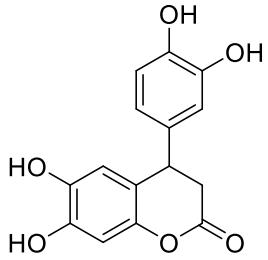
General Procedure D: BBr_3-Mediated Demethylation of 6,7-Dimethoxy-4-aryl-3,4-dihydrocoumarins



A modification of the procedure employed by Keukeleire was used in the demethylation of 6,7-dimethoxy-4-aryl-3,4-dihydrocoumarins.[125] In a flame-dried round-bottomed flask equipped with a stir bar under N_2, the methoxy substituted coumarin (200 mg, 0.632 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 such that the concentration was 0.1 M. The suspension was

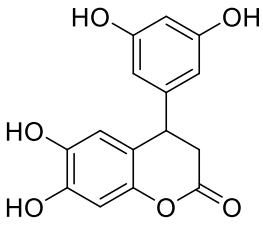
cooled to 0 °C with stirring and neat BBr_3 (270 μL, 2.85 mmol, 4.5 equiv.) was added dropwise via gas-tight syringe. The solution was allowed to stir at 0 °C for 1 h then warmed to rt and allowed to stir for 3 h. After stirring for 3 h at rt, the reaction mixture was slowly poured over 50 mL of ice-water and extracted with 3x 50 mL of EtOAc. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via flash chromatography yielded the corresponding 6,7-dihydroxy-4-aryl-3,4-dihydrocoumarins **4a-c**.

6,7-Dihydroxy-4-(3,4-dihydroxyphenyl)-3,4-dihydrocoumarin (4a)



Synthesized according to General Procedure D from coumarin **3a** (200 mg, 0.632 mmol) and neat BBr_3 (270 μL, 2.85 mmol). The reaction was allowed to proceed for 1 h at 0 °C and 3 h at rt. After purification via flash chromatography (1:9 MeOH:$CHCl_3$) the desired coumarin **4a** was obtained as a brown solid (124 mg, 68% yield). Melting point = 198 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (4H, brs), 6.65 (1H, d, *J* = 8.0 Hz), 6.49 (1H, s), 6.46 (1H, s), 6.41-6.36 (3H, m), 4.06 (1H, dd, *J* = 5.8, 5.8 Hz), 2.96 (1H, dd, *J* = 15.8, 6.0 Hz), 2.81 (1H, dd, *J* = 15.9, 6.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.2, 145.3, 145.0, 144.2, 143.6, 141.9, 132.7, 118.0, 116.3, 115.7, 114.6, 114.3, 103.9, 38.4, 37.1. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_6$ [$(M+H)^+$]: 289.0707. Found: 289.0706.

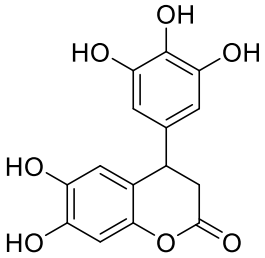
6,7-Dihydroxy-4-(3,5-dihydroxyphenyl)-3,4-dihydrocoumarin (4b)



Synthesized according to General Procedure D starting from coumarin **3b** (85 mg, 0.267 mmol) and neat BBr_3 (114 μL, 1.20 mmol). The reaction was allowed to proceed for 1 h at 0 °C and for 3 h at rt. Purification via flash

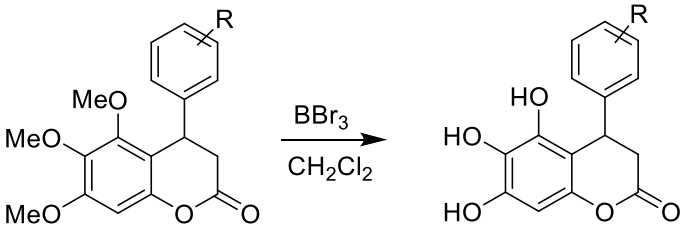
chromatography (1:9 MeOH:$CHCl_3$) yielded the desired coumarin **4b** as a light-brown solid (57 mg, 74% yield). Melting point = 266 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (3H, brs), 8.90 (1H, brs), 6.49 (1H, s), 6.41 (1H, s), 6.06 (1H, s), 5.96 (2H, s), 4.04 (1H, dd, *J* = 5.7, 5.7 Hz), 3.00 (1H, dd, *J* = 15.9, 6.3 Hz), 2.79 (1H, dd, *J* = 15.9, 5.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 158.6, 145.1, 144.1, 143.7, 142.0, 115.6, 114.4, 105.2, 103.9, 101.1, 39.0, 36.8. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_6$ [$(M+H)^+$]: 289.07066. Found: 289.07052.

6,7-Dihydroxy-4-(3,4,5-trihydroxyphenyl)-3,4-dihydrocoumarin (4c)



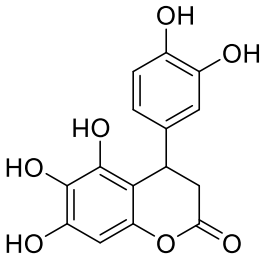
Synthesized according to General Procedure D starting from coumarin **3c** (100 mg, 0.30 mmol) and BBr_3 (129 μL, 1.35 mmol). The reaction was allowed to proceed for 1 h at 0 °C and 3 h at rt. Purification via flash chromatography (1:9 MeOH:$CHCl_3$) yielded the desired coumarin **4c** as a brown solid (87 mg, 95% yield). Melting point = 243 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.15 (1H, brs), 8.88 (1H, brs), 8.78 (2H, brs), 8.02 (1H, brs), 6.48 (1H, s), 6.39 (1H, s), 6.01 (2H, s), 3.97 (1H, dd, *J* = 5.9 Hz, 5.7 Hz), 2.96 (1H, dd, *J* = 15.7 Hz, 6.1 Hz), 2.75 (1H, dd, *J* = 15.8 Hz, 5.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3, 146.2, 145.0, 143.7, 141.9, 132.1, 131.9, 116.2, 114.5, 106.0, 103.9, 38.6, 37.2. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_7$ [$(M+H)^+$]: 305.0656. Found: 305.0655.

General Procedure E: BBr_3-Mediated Demethylation of 5,6,7-Trimethoxy-4-aryl-3,4-dihydrocoumarins



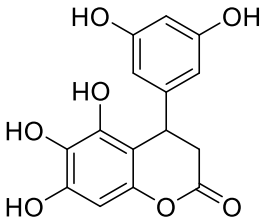
The demethylation of 5,6,7-trimethoxy-4-aryl-3,4-dihydrocoumarins was conducted in a modification of the procedure developed by Keukeleire.[125] In a flame-dried round-bottomed flask equipped with a stir bar under N_2, the trimethoxy substituted coumarin (100 mg, 0.289 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 such that the concentration was 0.1 M. The suspension was cooled to 0 °C with stirring and neat BBr_3 (164 μL, 1.73 mmol, 6.0 equiv.) was added dropwise via gas-tight syringe. The solution was allowed to stir at 0 °C for 1 h then warmed to rt and allowed to stir for 3 h monitoring by TLC. After stirring for 3 h at rt the reaction mixture was slowly poured over 25 mL of ice-water and extracted with 3x 25 mL of EtOAc. The combined organic phases were washed with 25 mL of brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via flash chromatography yielded the corresponding 5,6,7-trihydroxy-4-aryl-3,4-dihydrocoumarins **4d-f**.

5,6,7-Trihydroxy-4-(3,4-dihydroxyphenyl)-3,4-dihydrocoumarin (4d)



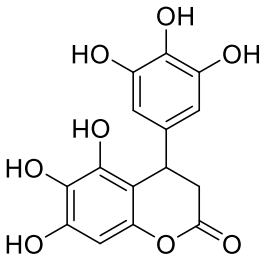
Synthesized according to General Procedure E starting from coumarin **3d** (509 mg, 1.47 mmol) and neat BBr_3 (837 μL, 8.82 mmol). The reaction was allowed to proceed at 0 °C for 1 h and at rt for 4 h. Purification via flash chromatography (1:19 to 1:9 MeOH:$CHCl_3$) yielded the desired coumarin **4d** as an orange powder (308 mg, 69% yield). Melting point = 200-204 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (1H, brs), 8.77, (1H, brs), 8.72 (1H, brs), 8.68 (1H, brs), 8.21 (1H, brs), 6.59 (1H, d, *J* = 8.0 Hz), 6.40 (1H, s), 6.33 (1H, d, *J* = 7.3 Hz), 6.10 (1H, s), 4.27 (1H, d, *J* = 6.0 Hz), 3.04 (1H, dd, *J* = 15.7, 6.6 Hz), 2.69 (1H, d, *J* = 15.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3, 145.6, 145.1, 144.3, 143.9, 143.5, 133.3, 129.7, 117.5, 115.6, 114.2, 104.6, 94.8, 37.6, 33.6. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_7$ [$(M+H)^+$]: 305.0656. Found: 305.0655.

5,6,7-Trihydroxy-4-(3,5-dihydroxyphenyl)-3,4-dihydrocoumarin (4e)



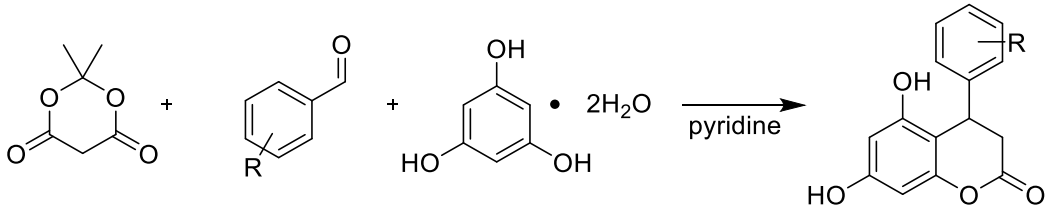
Synthesized according to General Procedure E starting from coumarin **3e** (100 mg, 0.289 mmol) and neat BBr_3 (164 μL, 1.73 mmol). The reaction was allowed to proceed at 0 °C for 1 h and at rt for 4.5 h. Purification via flash chromatography (1:9 MeOH:$CHCl_3$) yielded the desired coumarin **4e** as a brown solid (81 mg, 92% yield). Melting point = 141 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (1H, brs), 9.11 (2H, brs), 8.75 (1H, brs), 8.21 (1H, brs), 6.10 (s, 1H), 6.00 (1H, s), 5.91 (2H, s), 4.23 (1H, d, *J* = 6.5 Hz), 3.06 (1H, dd, *J* = 16.0 Hz, 7.3 Hz), 2.67 (1H, d, *J* = 15.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 158.4, 145.6, 144.6, 144.3, 143.5, 129.6, 104.8, 104.0, 100.9, 94.7, 37.2, 34.3. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_7$ [$(M+H)^+$]: 305.0656. Found: 305.0655.

5,6,7-Trihydroxy-4-(3,4,5-trihydroxyphenyl)-3,4-dihydrocoumarin (4f)



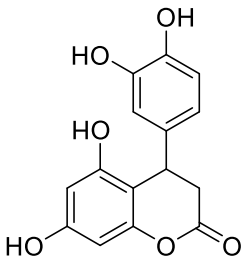
Synthesized according to General Procedure E starting from coumarin **4f** (100 mg, 0.276 mmol) and neat BBr_3 (157 μL, 1.66 mmol). The reaction was allowed to proceed at 0°C for 1 h and at rt for 3 h. Purification via flash chromatography (1:9 MeOH:$CHCl_3$) yielded the desired coumarin **4f** as a brown solid (69 mg, 69% yield). Melting point = 60-74 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.36 (1H, brs), 8.70 (3H, brs), 8.22 (1H, brs), 7.91 (1H, brs), 6.10 (1H, s), 5.97 (2H, s), 4.19 (1H, d, *J* = 5.8 Hz), 3.02 (1H, dd, *J* = 15.6 Hz, 6.6 Hz), 2.66 (1H, d, *J* = 15.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3, 145.9, 145.5, 144.3, 143.5, 132.5, 131.7, 129.6, 105.5, 104.5, 97.8, 37.6, 33.8. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_8$ [$(M+H)^+$]: 321.0605. Found: 321.0604.

General Procedure F: The Synthesis of 5,7-Dihydroxy-4-aryl-3,4-dihydrocoumarins



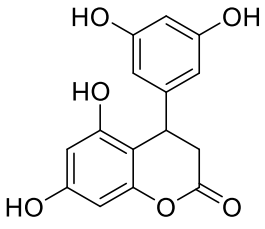
The procedure for the synthesis of 5,7-dihydroxy-4-aryl-3,4-dihydrocoumarins was based upon the procedure developed by Nair with modifications.[61] The typical conditions employed are as follows: in a round-bottomed flask equipped with a stir bar, Meldrum's acid (432 mg, 3.0 mmol. 1.0 equiv.) and phloroglucinol dihydrate (486 mg, 3.0 mmol, 1.0 equiv.) were dissolved in pyridine such that the mixture was 0.4 M relative to Meldrum's acid. A flow of nitrogen gas was bubbled through the stirring solution for 10 minutes. Then, hydroxy substituted benzaldehyde (456 mg, 3.3 mmol, 1.1 equiv.) was added in one portion and the mixture was heated to 75 °C for 1.25 h, monitoring by TLC. When complete by TLC, the reaction was cooled to room temperature and then poured over 50 mL of ice-water. The crude mixture was extracted twice with 50 mL of EtOAc. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, and filtered. Concentration under reduced pressure at 35 °C afforded a white/pink solid. The crude product was acidified with ~10 mL of 3 M HCl with stirring for 5 minutes and was extracted twice with 50 mL of EtOAc. The combined organic phases were washed with 50 mL of brine and dried over $MgSO_4$. The suspension was filtered, then concentrated under reduced pressure and purified via flash column chromatography on silica gel to yield the corresponding 5,7-dihydroxy-4-aryl-3,4-dihydrocoumarins **4g-i**.

5,7-Dihydroxy-4-(3,4-dihydroxyphenyl)-3,4-dihydrocoumarin (4g)



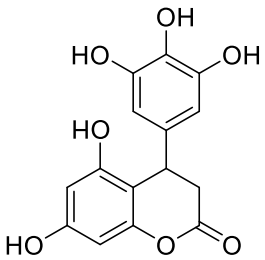
Synthesized according to General Procedure F from Meldrum's acid (432 mg, 3.0 mmol), phloroglucinol dihydrate (486 mg, 3.0 mmol), and 3,4-dihydroxybenzaldehyde (456 mg, 3.3 mmol). Purified via flash chromatography (1:19 to 1:9 MeOH:$CHCl_3$) to afford the title product **4g** as a light-brown solid (62 mg, 7% yield). Melting point = 216 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (1H, brs), 9.50 (1H, brs), 8.78 (1H, brs), 8.69 (1H, brs), 6.59 (1H, d, *J* = 7.5 Hz), 6.40 (1H, s), 6.33 (1H, d, *J* = 6.9 Hz), 6.14 (1H, s), 5.99 (1H, s), 4.24 (1H, d, *J* = 4.9 Hz), 3.08 (1H, dd, *J* = 15.9, 6.7 Hz), 2.70 (1H, d, *J* = 15.6 Hz). ^{13}C NMR (75 MHz, DMSO) δ 168.0, 157.6, 155.3, 152.9, 145.1, 143.9, 133.3, 117.4, 115.6, 114.0, 103.7, 98.7, 94.6, 37.5, 33.1. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_6$ [$(M+H)^+$]: 289.0707. Found: 289.0704.

5,7-Dihydroxy-4-(3,5-dihydroxyphenyl)-3,4-dihydrocoumarin (4h)



Synthesized according to General Procedure F starting from Meldrum's acid (288 mg, 2.0 mmol), phloroglucinol dihydrate (324 mg, 2.0 mmol), and 3,5-dihydroxybenzaldehyde (304mg, 2.2 mmol). Purified via flash chromatography (1:19 to 1:9 MeOH:$CHCl_3$) to yield **4h** as an off-white powder (392 mg, 68% yield). Melting point = 134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (1H, brs), 9.52 (1H, brs), 9.12 (2H, brs), 6.14 (1H, s), 5.99 (2H, s), 5.91 (2H, s), 4.20 (1H, d, *J* = 6.6 Hz), 3.11 (1H, dd, *J* = 15.7, 7.8 Hz), 2.96 (1H, d, *J* = 15.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.9, 158.4, 157.7, 155.4, 153.0, 144.6, 104.7, 103.2, 100.9, 98.6, 94.6, 37.2, 33.8. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_6$ [$(M+H)^+$]: 289.0707. Found: 289.0707.

5,7-Dihydroxy-4-(3,4,5-trihydroxyphenyl)-3,4-dihydrocoumarin (4i)



Synthesized according to General Procedure F from Meldrum's acid (216 mg, 1.50 mmol), phloroglucinol dihydrate (243 mg, 1.50 mmol) and 3,4,5-trihydroxybenzaldehyde monohydrate (284 mg, 1.65 mmol). Purified via flash chromatography (1:19 to 1:9 MeOH:$CHCl_3$) to yield **4i** as an orange solid (62 mg, 14% yield). Melting point = 138 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (1H, brs), 9.50 (1H, brs), 8.71 (2H, brs), 7.92 (1H, brs), 6.14 (1H, d, *J* = 1.7 Hz), 5.98 (1H, d, *J* = 1.8 Hz), 5.96 (2H, s), 4.15 (1H, d, *J* = 6.4 Hz), 3.06 (1H, dd, *J* = 16.0, 6.7 Hz), 2.66 (1H, d, *J* = 15.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.0, 167.6, 165.4, 162.9, 155.9, 142.5, 141.6, 115.4, 113.6, 108.7, 104.6, 47.6, 43.3. HRMS(ESI) *m/z* calculated for $C_{15}H_{13}O_7$ [$(M+H)^+$]: 305.0656. Found: 305.0655.

Chapter 4: Summary, Conclusions and Future Work

4.1: Summary of Intramolecular Allylic Alkylation via Transmetalation

In Chapter 2 the alkylation of cinnamyl acetates and carbonates by the transmetallation of tethered C(sp^3) stannanes and stannatranes was disclosed. This is a continuation of our research group's efforts on developing novel methods for the metal-promoted formation of novel carbon-carbon bonds.[62-68, 138] To the best of our knowledge this represents the first example of a palladium-catalyzed intramolecular alkylation of an allylic acetate utilizing the C(sp^3) stannane and stannatrane motifs as nucleophiles. Four 3-vinylindoline derivatives were synthesized in this manner in moderate to good yields and we were able to confirm the structure of these heterocycles by obtaining an X-ray crystal structure of *N*-methoxycarbonyl-3-vinyldinoline.

We have undertaken the early stages of exploring the generality of these reaction conditions, showing that chlorine substituents upon the aromatic ring are well tolerated throughout much of the synthesis (Chapter 2, products **9b** and **9c**). The synthesis, starting from commercially available 2-iodoaniline derivatives, was conducted in seven steps and most steps generally proceeded in good to excellent yields with simple experimental protocols. This synthesis demonstrates the utility of stannanes and stannatranes as nucleophiles in palladium-catalyzed intramolecular coupling reactions.

4.2: Summary of the Synthesis of Polyphenolic 4-Aryl-3,4-dihydrocoumarins

Chapter 3 focused on the synthesis of nine polyphenolic 4-aryl-3,4-dihydrocoumarins containing a systematic variation of both the number and position of hydroxyl groups around the aromatic rings (Figure 4.1).

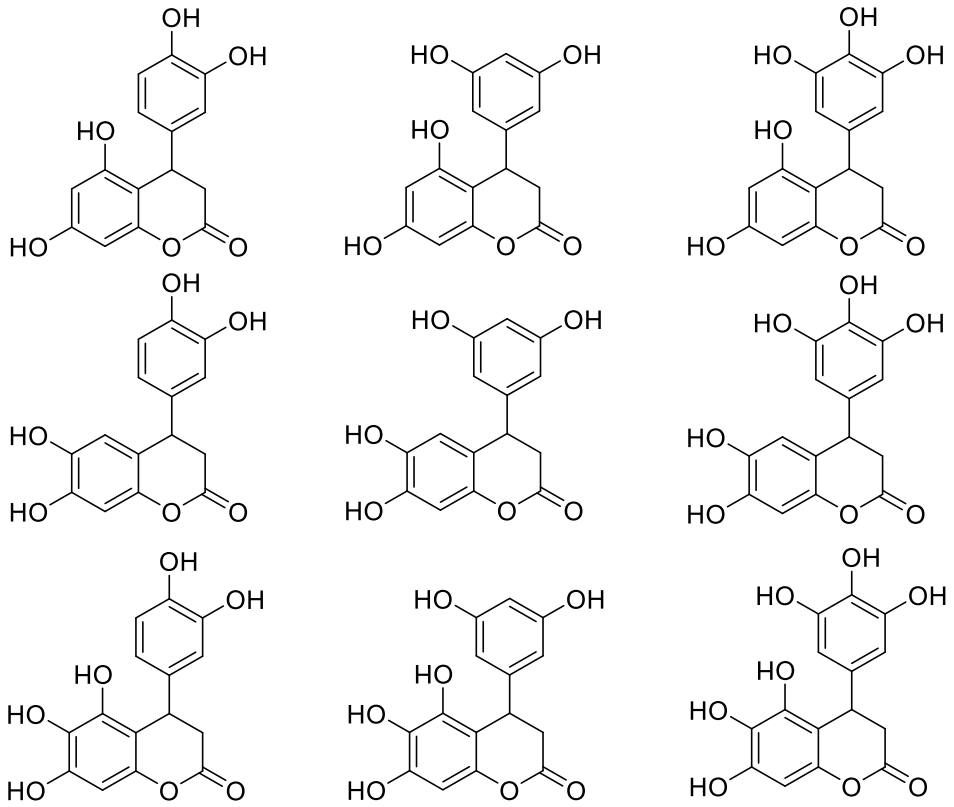
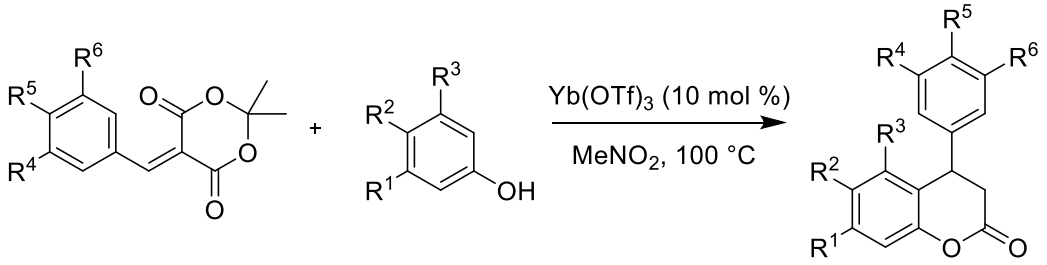


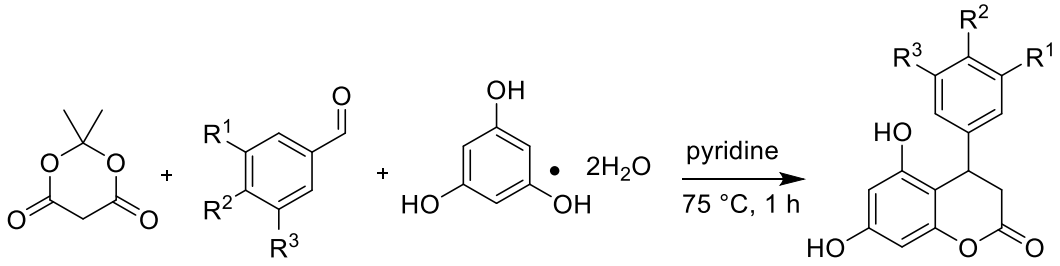
Figure 4.1 Polyphenolic 4-Aryl-3,4-dihydrocoumarins

The synthesis of six of these compounds was achieved by the application of the domino Friedel-Crafts alkylation/acylation of methoxy substituted phenols with functionalized benzylidene Meldrum's acids which was developed in the Fillion lab, and then the subsequent cleavage of the resultant methyl ethers (Scheme 4.1).[62]



Scheme 4.1 Synthesis of 4-Aryl-3,4-dihydrocoumarins from Benzylidene Meldrum's Acids and Phenols

This synthesis represents a good example of the synthetic utility of the methodology that has been developed in the Fillion lab for the synthesis of these highly functionalized heterocycles.[62] The additional three polyphenolic 4-aryl-3,4-dihydrocoumarins were obtained in a one-pot manner from Meldrum's acid, benzaldehyde derivatives, and phloroglucinol. (Scheme 4.2).[61]



Scheme 4.2 One-Pot Synthesis of 5,7-Dihydroxy-4-aryl-3,4-dihydrocoumarins

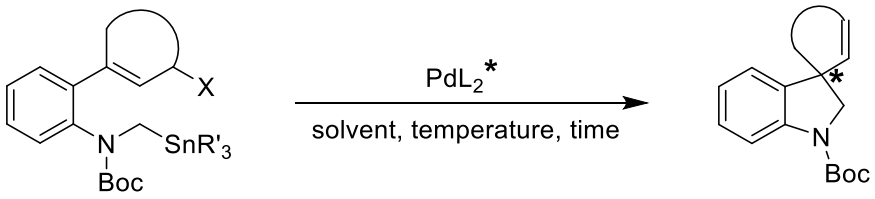
The synthesis of benzylidene Meldrum's acid precursors proceeded in excellent yields, and generally, the Friedel-Crafts reactions proceeded with modest to good yields and upon deprotection the corresponding polyphenolic 4-aryl-3,4-dihydrocoumarins were obtained in only three steps.

4.3: Future Work

In regards to the intramolecular allylic alkylation of cinnamyl acetates we are continuing to explore the functional group tolerance of the applied synthetic methodology. We anticipate good functional group tolerance throughout much of the methodology which would make this synthetic approach appealing for use in the synthesis of highly functionalized indoline and indole products.

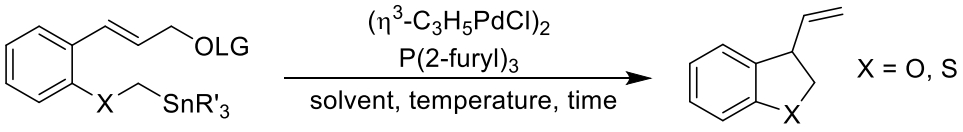
Our group has begun the development of an asymmetric variant of the intramolecular allylic alkylation through the application of chiral phosphine and BINOL ligands, though the results thus far have been limited. Additionally, if a substitution is made at the benzylic position

of the cinnamyl acetate the synthesis of an all-carbon quaternary centre at the C-3 position of the indoline ring could be conducted (Scheme 4.3). Furthermore, it may also be possible to synthesize spirocyclic indoline derivatives in this manner (Scheme 4.3). If sufficient enantiomeric excess is achieved this would represent a significant advancement in the synthesis of the indoline motif with stereocenters at the C-3 position.



Scheme 4.3 Asymmetric Allylic Alkylation to Generate All-Carbon Quaternary Centres

The intramolecular alkylation of cinnamyl acetates may also be able to facilitate the synthesis of 2,3-dihydrobenzofurans and 2,3-dihydrobenzothiophenes by altering the heteroatom *ortho* to the cinnamyl acetate functionality (Scheme 4.4).



Scheme 4.4 Plausible Synthesis of Additional Bicyclic Heterocycles

Our group will also continue to explore the potential for intramolecular rhodium-catalyzed alkylation reactions through the formation of organorhodium species followed by S_N2' nucleophilic substitution mechanisms. The application of additives such as phosphine ligands has yet to be explored, and we have yet to explore the reactivity of alternative organometallic handles to promote the transmetalation of the rhodium catalyst such as boronic acids and organosilanes.

In the second half of this research project nine polyphenolic 4-aryl-3,4-dihydrocoumarins (Figure 4.1) were prepared in order to assess their affinity for a synthetic model of the p2 region of the microtubule associated protein tau. This region has been identified as a consequential site of phosphorylation and implicated in the polymerization of tau into neurofibrillary tangles (NFT), a hallmark of Alzheimer's physiopathology.[120,121] If a therapeutic substrate is able to competitively inhibit the phosphorylation of residues in this region this may have an attenuating impact on the extent of tau aggregation. This aspect of the research project remains to be carried out, but the development of a structure-activity relationship for this library of compounds could hold valuable information regarding the development of therapeutic agents to attenuate the formation of NFTs. If this assay is realized and yields positive results, the development of secondary and tertiary libraries of polyphenolic compounds based on the methodologies developed in the Fillion lab for the synthesis of chromones, chromanones and coumarins could be conducted for assessment. This would allow for a better understanding of which motifs within these polyphenols hold the greatest affinity for tau and could potentially lead to the development of novel therapeutic agents for the treatment of Alzheimer's disease and dementia.

There is room for improvement in the synthetic approach, particularly in regards to the purification of the polyphenols, which could result in increased yields and purity of the obtained products. Early explorations were made into the application of reverse phase preparative HPLC purification which held promising results. The polyphenolic 4-aryl-3,4-dihydrocoumarins were subsequently obtained by the careful implementation of standard chromatographic techniques and were obtained in moderate to good yields.

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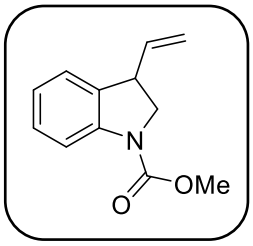
Appendix A: Crystallographic Data for 9d



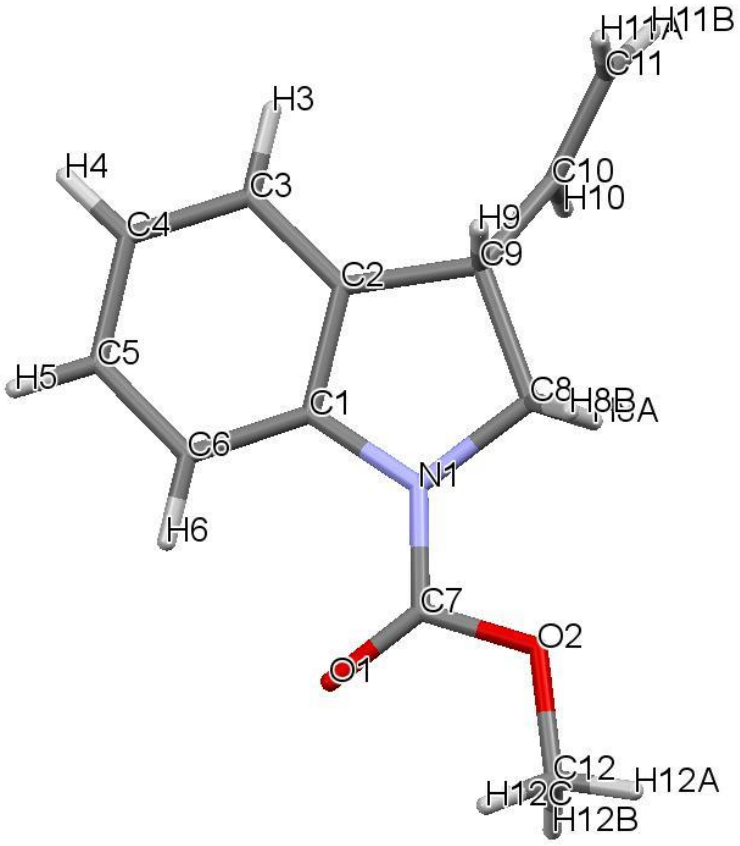


Table S1. Crystal data and structure refinement for 9d.

Identification code	EF27_0m	
Empirical formula	$C_{12}H_{13}NO_2$	
Formula weight	203.23	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 7.8606(3) Å	α= 90°.
	b = 18.4587(8) Å	β= 112.2918(12)°.
	c = 8.1274(4) Å	γ = 90°.
Volume	1091.12(8) $Å^3$	
Z	4	
Density (calculated)	1.237 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	432	
Crystal size	0.460 x 0.150 x 0.040 mm^3	
Theta range for data collection	2.207 to 25.998°.	
Index ranges	-9<=h<=9, -22<=k<=22, -10<=l<=9	
Reflections collected	17068	
Independent reflections	2129 [R(int) = 0.0272]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7460 and 0.7044	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2129 / 0 / 139	
Goodness-of-fit on F^2	1.155	
Final R indices [I>2sigma(I)]	R1 = 0.0759, wR2 = 0.1420	
R indices (all data)	R1 = 0.0998, wR2 = 0.1561	
Extinction coefficient	0.0040(10)	
Largest diff. peak and hole	0.763 and -0.492 $e.Å^{-3}$	

Table S2. Atomic coordinates and equivalent isotropic displacement parameters for 9d.

	x	y	z	U(eq)
O(1)	496(4)	5886(1)	2884(3)	89(1)
O(2)	1723(3)	6257(1)	5737(3)	71(1)
N(1)	2301(3)	5145(1)	5089(3)	61(1)
C(1)	2347(4)	4523(2)	4094(4)	56(1)
C(2)	3557(4)	4025(2)	5190(4)	60(1)
C(3)	3868(5)	3377(2)	4507(5)	72(1)
C(4)	2947(5)	3232(2)	2715(5)	81(1)
C(5)	1744(5)	3732(2)	1649(5)	80(1)
C(6)	1403(4)	4385(2)	2300(4)	69(1)
C(7)	1416(4)	5771(2)	4428(4)	63(1)
C(8)	3482(4)	5038(2)	6980(4)	64(1)
C(9)	4465(6)	4316(2)	7077(4)	80(1)
C(10)	4638(7)	3857(2)	8472(5)	106(2)
C(11)	6050(6)	3587(2)	9736(5)	90(1)
C(12)	868(5)	6953(2)	5218(6)	93(1)
H(3)	4687	3040	5242	87
H(4)	3145	2797	2237	97
H(5)	1135	3629	447	96
H(6)	575	4719	1564	83
H(8A)	2746	5023	7704	77
H(8B)	4367	5429	7400	77
H(9)	5724	4442	7219	96
H(10)	3520	3713	8510	127
H(11A)	7230	3700	9810	108
H(11B)	5886	3281	10572	108
H(12A)	1399	7291	6173	139
H(12B)	-427	6911	4952	139
H(12C)	1060	7120	4184	139

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table S3. Bond lengths [Å] and angles [°] for 9d.

O(1)-C(7)	1.206(4)
O(2)-C(7)	1.342(4)
O(2)-C(12)	1.436(4)
N(1)-C(7)	1.350(4)
N(1)-C(1)	1.412(4)
N(1)-C(8)	1.477(4)
C(1)-C(2)	1.378(4)
C(1)-C(6)	1.386(4)
C(2)-C(3)	1.381(4)
C(2)-C(9)	1.523(4)
C(3)-C(4)	1.385(5)
C(3)-H(3)	0.9300
C(4)-C(5)	1.370(5)
C(4)-H(4)	0.9300
C(5)-C(6)	1.384(5)
C(5)-H(5)	0.9300
C(6)-H(6)	0.9300
C(8)-C(9)	1.527(4)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-C(10)	1.380(5)
C(9)-H(9)	0.9800
C(10)-C(11)	1.292(5)
C(10)-H(10)	0.9300
C(11)-H(11A)	0.9300
C(11)-H(11B)	0.9300
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600

C(7)-O(2)-C(12)	116.2(3)
C(7)-N(1)-C(1)	126.1(3)
C(7)-N(1)-C(8)	123.7(3)
C(1)-N(1)-C(8)	110.1(2)

C(2)-C(1)-C(6)	121.3(3)
C(2)-C(1)-N(1)	109.5(2)
C(6)-C(1)-N(1)	129.2(3)
C(1)-C(2)-C(3)	120.2(3)
C(1)-C(2)-C(9)	111.1(3)
C(3)-C(2)-C(9)	128.6(3)
C(2)-C(3)-C(4)	119.3(3)
C(2)-C(3)-H(3)	120.4
C(4)-C(3)-H(3)	120.4
C(5)-C(4)-C(3)	119.7(3)
C(5)-C(4)-H(4)	120.2
C(3)-C(4)-H(4)	120.2
C(4)-C(5)-C(6)	122.2(3)
C(4)-C(5)-H(5)	118.9
C(6)-C(5)-H(5)	118.9
C(5)-C(6)-C(1)	117.3(3)
C(5)-C(6)-H(6)	121.3
C(1)-C(6)-H(6)	121.3
O(1)-C(7)-O(2)	124.3(3)
O(1)-C(7)-N(1)	125.4(3)
O(2)-C(7)-N(1)	110.3(3)
N(1)-C(8)-C(9)	106.1(2)
N(1)-C(8)-H(8A)	110.5
C(9)-C(8)-H(8A)	110.5
N(1)-C(8)-H(8B)	110.5
C(9)-C(8)-H(8B)	110.5
H(8A)-C(8)-H(8B)	108.7
C(10)-C(9)-C(2)	118.2(3)
C(10)-C(9)-C(8)	118.0(3)
C(2)-C(9)-C(8)	102.8(3)
C(10)-C(9)-H(9)	105.5
C(2)-C(9)-H(9)	105.5
C(8)-C(9)-H(9)	105.5
C(11)-C(10)-C(9)	132.6(5)
C(11)-C(10)-H(10)	113.7
C(9)-C(10)-H(10)	113.7

C(10)-C(11)-H(11A)	120.0
C(10)-C(11)-H(11B)	120.0
H(11A)-C(11)-H(11B)	120.0
O(2)-C(12)-H(12A)	109.5
O(2)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(2)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Table S4. Anisotropic displacement parameters for 9d.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	89(2)	95(2)	67(2)	16(1)	13(1)	18(1)
O(2)	74(2)	62(1)	77(2)	4(1)	29(1)	10(1)
N(1)	65(2)	61(2)	51(1)	2(1)	16(1)	5(1)
C(1)	55(2)	64(2)	53(2)	-4(1)	24(1)	-10(1)
C(2)	68(2)	61(2)	54(2)	-2(1)	27(2)	-3(2)
C(3)	83(2)	67(2)	73(2)	-4(2)	37(2)	-1(2)
C(4)	96(3)	78(2)	79(2)	-23(2)	44(2)	-15(2)
C(5)	84(2)	100(3)	60(2)	-23(2)	31(2)	-28(2)
C(6)	62(2)	86(2)	55(2)	-2(2)	18(2)	-14(2)
C(7)	54(2)	69(2)	66(2)	9(2)	23(2)	1(2)
C(8)	72(2)	65(2)	50(2)	-2(1)	18(2)	6(2)
C(9)	104(3)	71(2)	56(2)	-2(2)	21(2)	17(2)
C(10)	154(4)	77(3)	64(2)	-4(2)	16(3)	21(3)
C(11)	105(3)	73(2)	71(2)	6(2)	11(2)	13(2)
C(12)	96(3)	64(2)	120(3)	13(2)	43(3)	16(2)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$