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Development of Fragment Coupling Methodologies and the Application to Natural Product Synthesis

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ABSTRACT

Development of Fragment Coupling Methodologies and the Application to Natural Product Synthesis

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Small molecules such as indanes, chromanes, tetralins and their derivatives play a significant role in drug discovery due to their potent biological activity. This research herein presents a facile Brønsted acid-catalyzed allylsilane annulation methodology to generate fused ring systems such as indanes. The reaction goes through a homoallylic intermediate which then readily cyclizes to form the desired product. Different types of fused ring systems such as chromanes and lignan natural products can be accessed in a similar fashion using differently substituted allylsilanes and benzyl alcohol species. Structural complexity was rapidly built from simple precursors.

The second part of the research focuses on developing a "traceless" variant of the Petasis Borono-Mannich reaction. A one-pot synthesis of allylic alcohols by the sulfonylhydrazide-mediated coupling of aldehydes with alkenyl trifluoroborates was achieved. The process involves *in situ* generation of a hydrazone species and subsequent loss of N_2. Further development of the methodology is still underway.

Thesis advisor: Professor Regan J. Thomson

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I would like to thank my parents for their unconditional love and trust in all the decisions I made. I will continue to make you guys proud.

List of Abbreviations

Ac	acetyl
AcO	acetate
Ac_2O	acetic anhydride
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
BP	1,1’-biphenyl
bpy	2,2’-bipyridine
Bu or *n*Bu	butyl
BuLi	*n*-butyl lithium
Bz	benzoyl
Cbz	carboxybenzyl
Cp	cyclopentadienyl
Cy	cyclohexane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine

DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
DTBP	2,6-di-*tert*-butylpyridine
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
Et	ethyl
EtCN	propionitrile
EtOAc	ethyl acetate
equiv.	equivalents
FT	Fourier transform
GC	gas chromatography
HMPA	hexamethylphosphoramide
$HNTf_2$	trifluoromethanesulfonimide
HRMS	high resolution mass spectrometry
HPLC	high pressure liquid chromatography
IBX	2-iodoxybenzoic acid

iPr or i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesitylene
MOM	methoxymethyl
Ms	methanesulfonyl
Nap	napthyl
NBS	*N*-bromosuccinimide
NBSH	2-nitrobenzenesulfonyl hydrazine
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance spectrometry
NOE	nuclear Overhauser effect
PBQ	*p*-benzoquinone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

Ph	phenyl
Pr or *n*Pr	propyl
pTsOH or TsOH	toluenesulfonic acid
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl
Tf	(trifluoromethyl)sulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl

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Chapter 1

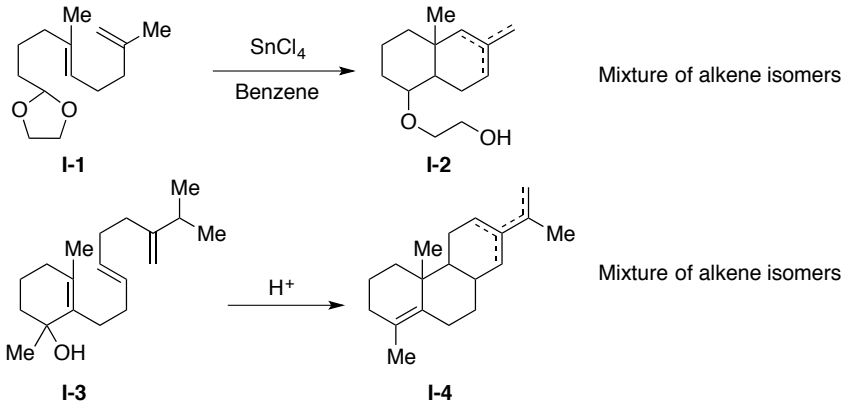
Previously Reported Allylsilane Annulation Methodologies

1 Chapter 1

1.1 Introduction

The construction of carbocyclic and heterocyclic structures has long been a vital task in organic synthesis. One of the main cyclization strategies is the nucleophilic addition into carbonium ions using alkene terminators, which has been extensively investigated and successfully applied to numerous natural product total syntheses. For instance, the polyene cyclization represents a powerful method to rapidly construct the polycyclic core of natural products in a biomimetic fashion.[1-4] The use of alkene terminators, however, sometimes leads to a mixture of regioisomers due to the uncontrollable nature of the cyclization, therefore alkene isomerization is often observed (Scheme 1.1).[5] This drawback limits the scope of its synthetic utility.

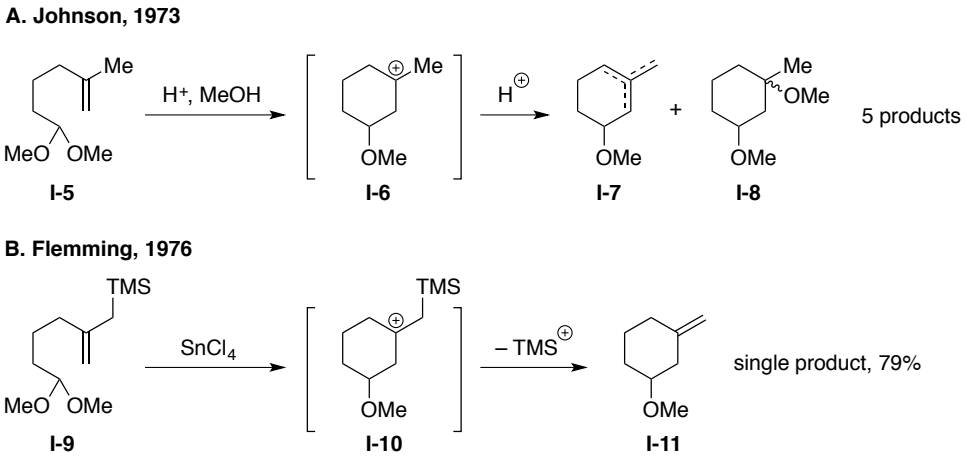
Scheme 1.1 Alkene-terminated cyclization



In 1976, Flemming and coworkers addressed this issue and proposed a solution to control the regioselectivity of the carbonium ion cyclization using an allylsilane terminator.[6] They found out that by strategically placing the trimethylsilyl group on the appropriate carbon atom in the starting material, a single product can be made from the carbocation intermediate. This was demonstrated in comparison to the work of Johnson *et al*.,[7] in which the carbonium ion formed from the initial

acetal **I-5** gave rise to a mixture of five products upon treatment of acid (Scheme 1.2A). On the contrary, the same acetal with an allylsilane functionality **I-9** afforded only one product followed by the loss of the TMS group (Scheme 1.2B).

Scheme 1.2 A. Johnson's original reaction and B. Flemming's cyclization using an allylsilane terminator

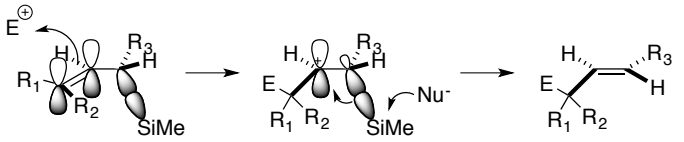


The unique properties of silicon allows for the development of rich and diverse organosilane chemistry. In addition, they are relatively air-stable, nontoxic and easily prepared, rendering organosilanes one of the most frequently employed building blocks in organic chemistry. For instance, they have been widely adopted as protecting groups, reducing reagents and cross-coupling components. Of particular interest here is the use of allylsilanes as carbon nucleophiles to participate in nucleophilic addition.[8]

In 1982, Kumada and coworkers prepared optically active allylsilanes and unambiguously determined that their reactions with electrophiles proceed through an *anti*-S_E' pathway (Scheme 1.3).[9] A carbocation β to the silicon atom is formed upon the electrophilic addition, followed by elimination of the silicon group to generate a new double bond. This phenomenon has been widely

observed and explained by the β-silicon effect.[10] The β-silyl carbocation is stabilized by σ–π conjugation via overlap between the Si-C σ bond and the adjacent vacant p orbital. This strong hyperconjucation originates from the polarizability of the Si-C bond.

Scheme 1.3 Electrophilic addition of allylsilanes and the β-silicon effect



In the past 40 years, numerous methodologies featuring allylsilanes to generate carbocycles and heterocycles have been reported. Selected examples with different participating electrophiles will be addressed in the following sections.

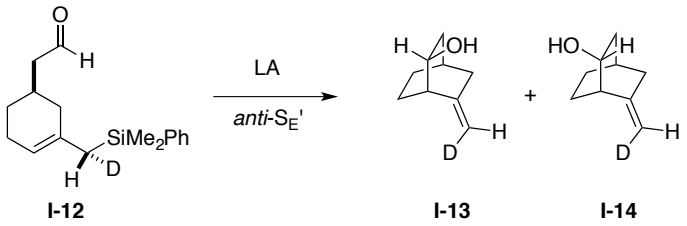
1.2 Cyclization with Activated C=O Bond

One common type of electrophile for allylsilane addition is the activated C=O bond. For instance, a famous example is the Hosomi–Sakurai reaction of aldehydes and ketones, developed by Hosomi and Sakurai in 1976.[11] Strong Lewis acids are required to activate the carbon electrophiles. Allylsilanes can also undergo nucleophilic addition with esters, generating multi-allylated products under Lewis acid catalysis.[12] When such reactions are carried out in an intramolecular fashion, cyclic compounds can be afforded rapidly.

1.2.1 Nucleophilic Addition into Aldehydes

The mechanism of Lewis acid-promoted allylsilane additions into aldehydes have been extensively studied by chemists over the past 30 years.[13] In 1994, Denmark reported the intramolecular variant of these reactions and found that cyclization proceeded with a strong preference for the *anti*-S_E' pathway (Scheme 1.4).[14]

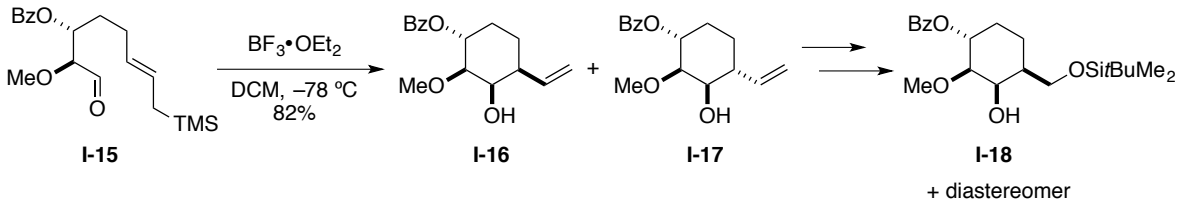
Scheme 1.4 Intramolecular addition of an allylsilane into aldehyde



I-12 **I-13** **I-14**

Synthesis of the cyclohexyl fragment (**I-18**) of FK-506, an immunosuppressive natural product, was also carried out featuring an BF_3•OEt_2-mediated intramolecular allylsilane addition into aldehyde **I-15** by Maier and coworkers (Scheme 1.5).[15]

Scheme 1.5 Synthesis of the cyclohexyl fragment of FK-506

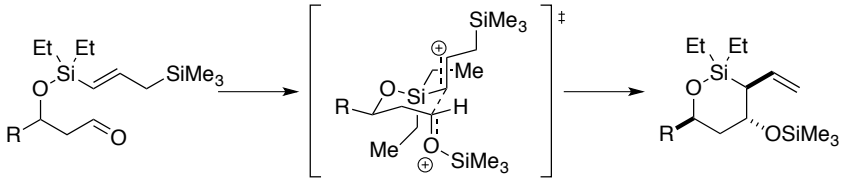


I-15 **I-16** **I-17** **I-18**

+ diastereomer

In 2003, Beignet and coworkers reported an intramolecular addition between an allylsilane and an aldehyde using a silyl ether tether (Scheme 1.6).[16] A Lewis acid such as TMSOTf was needed to activate the aldehyde species. Locating the silyl ether tether at the γ position of the allylsilane allows the reaction to proceed through a better defined cyclic transition state **I-20**, which has been shown to give better stereochemical control.[17] The allylsilane group would be exocyclic in the transition state and resemble the corresponding intermolecular reaction. High diastereoselectivity was achieved for the cyclic products. The tether can be later cleaved for further synthetic elaboration.

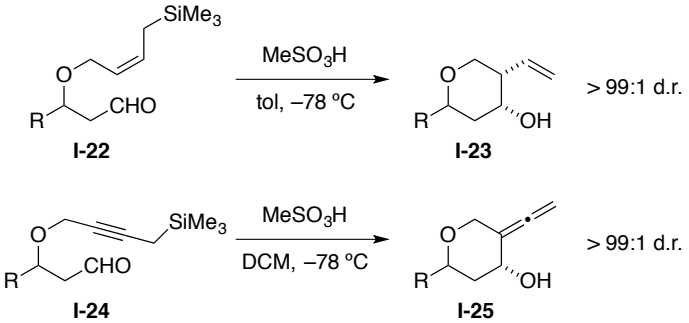
Scheme 1.6 Addition into aldehydes with silyl ether tether



I-19 **I-20** **I-21**

In 2006, Cox and coworkers substituted the diethylsilyl ether tether for a methylene group, which would generate substituted tetrahydropyrans as the cyclic products (Scheme 1.7).[18] Due to the robustness of the methylene bridge, Brønsted acid activators could be investigated. Switching from TMSOTf to $MeSO_3H$ led to a dramatic increase in stereoselectivity. In addition to allylsilanes, propargyl silanes **I-24** also cyclized to form allene-containing tetrahydropyrans, proving the versality of this methodology.

Scheme 1.7 Addition into aldehydes without the tether

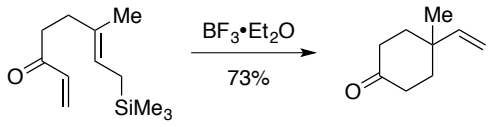


I-22 **I-23** **I-24** **I-25**

1.2.2 Nucleophilic Addition into Ketones

The first intramolecular Sakurai reaction was published in 1982 by Wilson and coworkers. During their study, they built a model system and generated cyclohexanone **I-27** through 1,4-addition of allylsilanes into α,β-unsaturated ketones in the presence of BF_3•OEt_2. The cyclization proceeded smoothly to give the product in 73% yield (Scheme 1.8).[19]

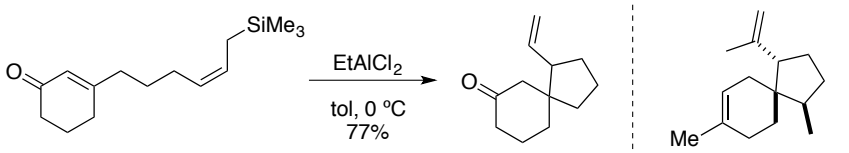
Scheme 1.8 Synthesis of cyclohexanone by intramolecular allylsilane addition into ketone



I-26 **I-27**

Fused ring systems and spirocyclic systems can also be formed using this method, depending on where the allylsilane side chain is placed. In 1984, Schinzer and coworkers developed a stereoselective route to generate spiro[4,5]decanone **I-29** (Scheme 1.9). The mild Lewis acid ethylaluminum dichloride proved to be the optimal promotor for this reaction. When 1.1 equivalents of $EtAlCl_2$ was used, undesirable protodesilylation side reactions were inhibited and good yields were achieved.[20] The major diastereomers formed represent core skeletons of some spirocyclic natural products such as lubimine and α-acoradiene (**I-30**).

Scheme 1.9 Formation of spirocyclic structure

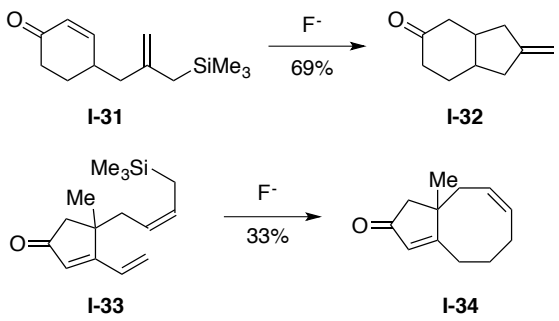


I-28 **I-29** α-acoradiene **(I-30)**

In addition to Lewis acid catalysts, Lewis base activators were also used to promote such reactions. Majetich and coworkers generated fused ring structures using fluoride ion as the activator, while Lewis acids such as $TiCl_4$ and BF_3•OEt_2 failed to give the desired compound with the presence of desilylation product. The results suggested that Lewis acid-catalyzed allylsilane cyclizations are substrate dependent.[21] Fluoride ion-mediated formation of eight-membered rings were also investigated. Intramolecular Sakurai reactions take place via 1,6-addition into conjugated dienones

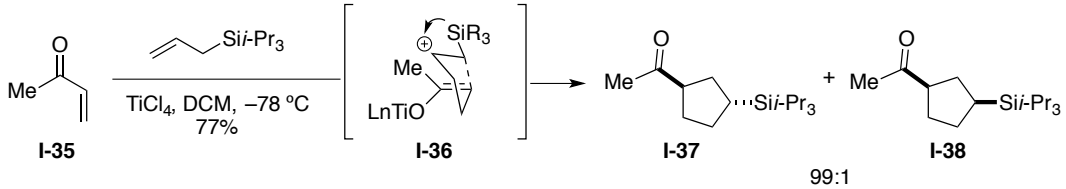
I-33 (Scheme 1.10).[22] The methodology was later applied to two total syntheses of epi-widdrol using ethylaluminum dichloride as catalyst.[23]

Scheme 1.10 Formation of fused ring structure using a Lewis base activator



Danheiser and coworkers developed a novel [3+2] annulation strategy using allylsilanes as three-carbon components for the synthesis of five-membered carbocycles.[24] Propargyl silanes and trimethylsilyl allenes have also been successfully employed in such transformations to generate a diverse range of five-membered ring compounds such as dihydropyrrolines,[25, 26] dihydrofurans,[26] isoxazoles,[25] azulenes[25, 27] and furans.[28] The reactions appear to proceed through stepwise mechanisms of 1,2-silyl shift and cyclization via the rearranged carbocation after the initial electrophilic addition to the organosilane (Scheme 1.11). Many of them also proceed with high level of stereoselectivity.[24]

Scheme 1.11 Danheiser's [3+2] annulation strategy using allylsilanes

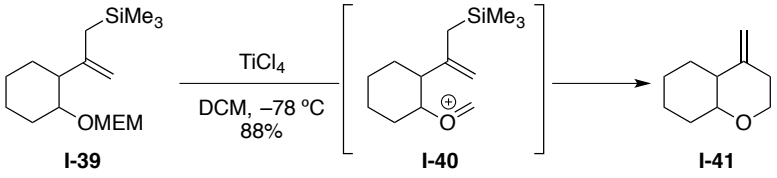


1.2.3 Nucleophilic Addition into Oxonium Ions

A frequently employed electrophile for allylsilane addition is the oxonium ion species, which is usually generated as reaction intermediates. When they are tethered to allylsilanes, intramolecular cyclization takes place, usually with high level of regiocontrol because of the β-silicon stabilization effect.

One of the common methods to generate oxonium ions is through the ionization of acetals. In 1982, Nishiyama and coworkers developed regioselective cleavage of unsymmetrical acetals in the presence of allylsilanes and $TiCl_4$ to give homoallylic ethers or five- and six-membered oxacyclic rings.[29] The 2-methoxyethoxy methyl (MEM) ether was selected as the protecting group, which formed bidentate coordination with titanium tetrachloride to facilitate the elimination of the 2-methoxyethoxy group and led to nucleophilic attack of the allylsilane (Scheme 1.12).

Scheme 1.12 Formation of an oxacyclic ring through oxonium ion-allylsilane cyclization

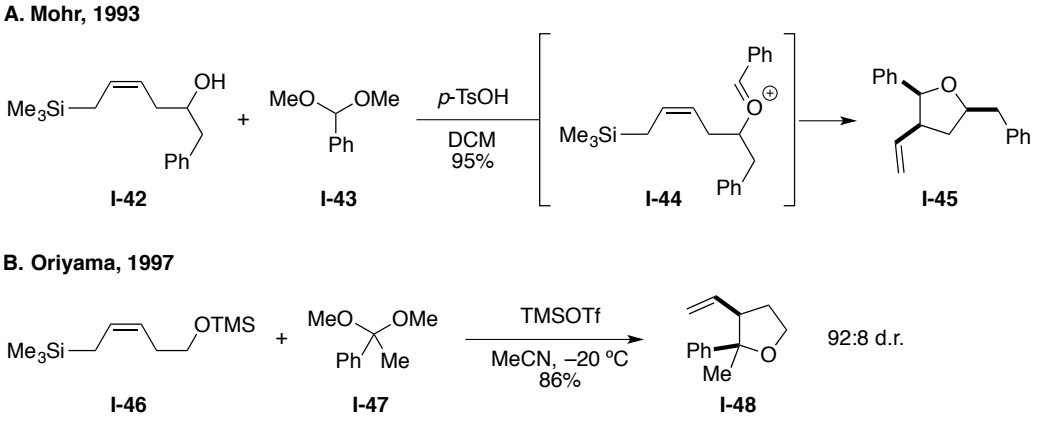


I-39 **I-40** **I-41**

Intermolecular additions between allylsilanes and acetals have also been carried out smoothly. In these reactions, an oxocarbenium ion is formed *in situ* by transacetalization followed by acid-catalyzed ionization. Nucleophilic addition of the allylsilane into the oxocarbenium ion could furnish the formation of the cyclic products. Mohr published the synthesis of differently substituted furans and tetrahydrofurans using allyl silyl alcohol **I-42** and acetal **I-43** as coupling partners (Scheme 1.13A).[30] On the other hand, Oriyama and coworkers utilized allyl silyl TMS ether **I-46**

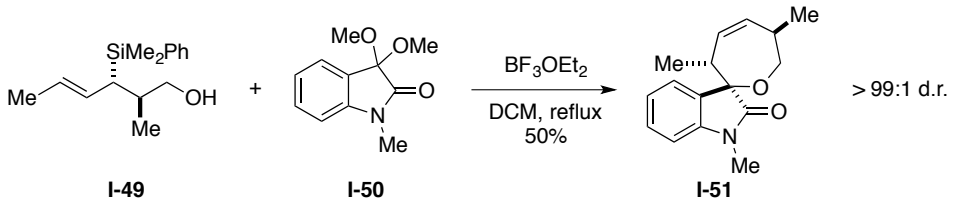
as the dianion equivalent of 4-atom unit to generate functionalized tetrahydrofuran and 4-methylenetetrahydropyran species (Scheme 1.13B).[31-33]

Scheme 1.13 A. Mohr's methodology using allyl silyl alcohols and B. Oriyama's work using allyl silyl TMS ether



Medium sized rings can also be generated in a similar fashion. In 2009, Panek and coworkers developed a Lewis acid promoted [5+2] annulation using chiral silyl alcohols to afford spirooxindoles with great stereoselectivity (Scheme 1.14). Highly functionalized compounds can be generated under mild reaction conditions, which can be applied towards library synthesis in preparation for subsequent biological evaluation.[34]

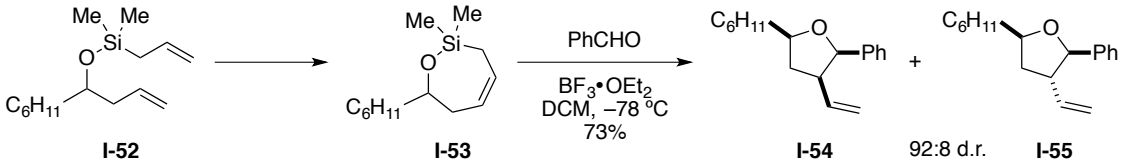
Scheme 1.14 [5+2] annulation to synthesize spirooxindoles from allylsilane and acetal



Another frequently investigated method featuring allylsilane addition into oxonium ions to generate heterocyclic compounds is the silyl-Prins cyclization.[35] This type of reactions usually involves acid-catalyzed addition into an aldehyde for the synthesis of five- to seven-membered

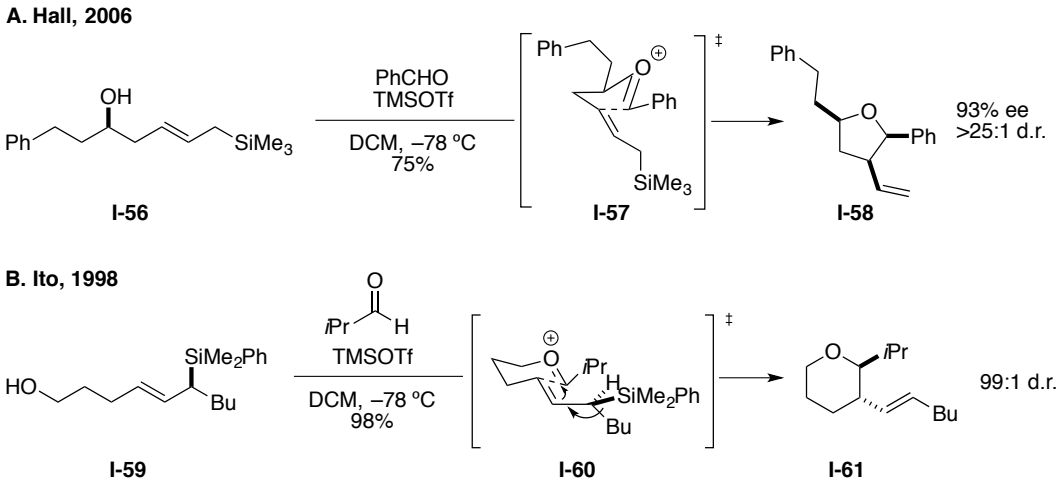
oxacycles. Tetrahydrofurans have been successfully synthesized in this fashion, even though 5-*endo-trig* cyclizations are unfavorable according to Baldwin's rules. In 1997, Cassidy and coworkers developed an allylsilane metathesis/nucleophilic addition sequence to generate substituted tetrahydrofurans in high yields (Scheme 1.15).[36] Functionalized cyclic allylsilanes were prepared as precursors for condensation with the aldehyde.

Scheme 1.15 Allylsilane metathesis/nucleophilic addition sequence



In 2006, Hall and coworkers reported the stereoselective synthesis of highly substituted tetrahydrofurans through acid-catalyzed addition of allyl silyl alcohols into aldehydes.[37] The pseudo-diequatorial arrangement of substituents in the chair-like transition state (**I-57**) gave rise to the high diastereoselectivity (Scheme 1.16A).

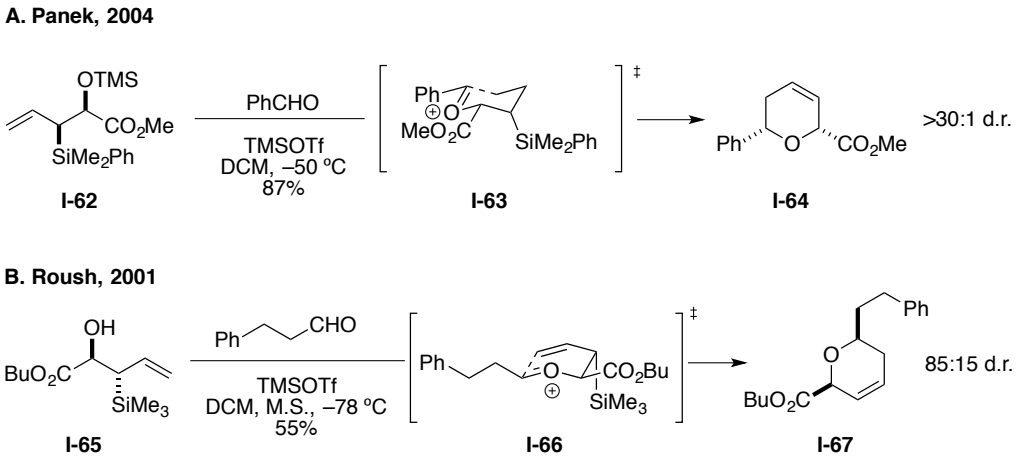
Scheme 1.16 Synthesis of A. tetrahydrofurans and B. tetrahydropyrans



Similar results were achieved by Ito and coworkers, who used TMSOTf as promotors to generate disubstituted tetrahydropyrans in high yields with high selectivity.[38] A chair-like transition state (**I-60**) was again proposed (Scheme 1.16B).

The synthesis of functionalized pyrans have also been well studied. Panek and coworkers developed an acid-catalyzed [4+2] annulation for the synthesis of *cis*-2,6-disubstituted[39] and *cis*-2,6-*trans*-5,6-trisubstituted[40, 41] dihydropyrans. Research suggested that a chair-like transition state **I-63** was favored during the cyclization, giving rise to high diastereoselectivity (Scheme 1.17A). The methodology was also applied to various total syntheses of natural products, which will be addressed later. Similarly, Roush and coworkers used β-hydroxy allylsilanes **I-65** to condense with aldehydes in the presence of TMSOTf and generated cis-2,6-dihydropyrans through silyl-Prins cyclization.[42] In this case, the boat-like transition state **I-66** was favored (Scheme 1.17B).

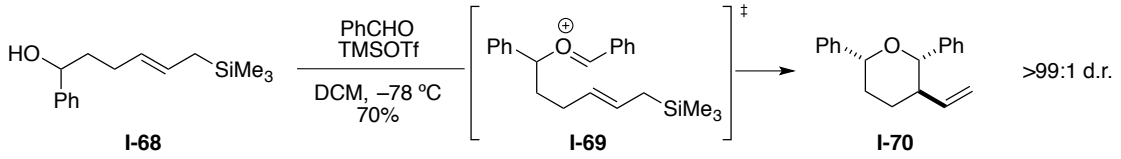
Scheme 1.17 Stereoselective synthesis of polysubstituted dihydropyrans through A. chair-like and B. boat-like transition states



Allylsilanes with a terminal silyl group (**I-68**) were also employed for the silyl-Prins type cyclization. In 2002, Szabó and coworkers synthesized tetrahydropyran and octahydrochromene

derivatives under Lewis-acid catalysis (Scheme 1.18).[43] According to DFT calculations, the high stereoselectivity arises from steric and hyperconjugation interactions taking place in the reaction intermediates. A chair-like transition state was proposed, which served to minimize the steric strain between the substituents.

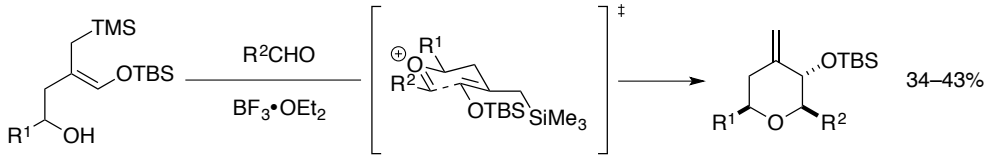
Scheme 1.18 Synthesis of tetrahydropyran using allylsilanes with a terminal silyl group



I-68 **I-69** **I-70**

Polysubstituted methylenetetrahydropyrans have been major targets for the silyl-Prins transformation. Markó and coworkers performed a series of studies on the Lewis acid catalyzed intramolecular cyclization between allylsilanes and aldehyde.[44-49] The preferred pseudo-equatorial arrangement of substituents during the chair-like transition state (**I-72**) ensured the high diastereoselectivity of this transformation (Scheme 1.19).

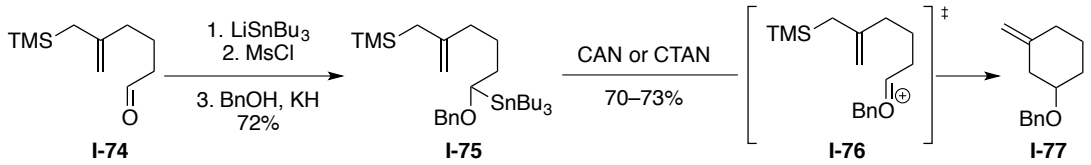
Scheme 1.19 Markó's synthesis of polysubstituted methylenetetrahydropyrans



I-71 **I-72** **I-73**

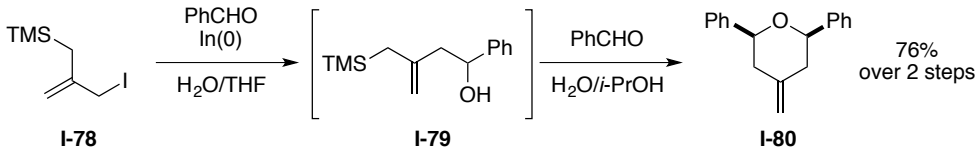
Mariano and coworkers developed a oxidative Prins cyclization methodology which tolerates Lewis acid sensitive functionality.[50] The α-stannyl ether species **I-75** was first generated from the allyl silyl aldehyde, which can be readily transformed to oxonium ion **I-76** by metal-based oxidizing agents, setting the stage for the final cyclization (Scheme 1.20).

Scheme 1.20 An oxidative Prins cyclization methodology



Minehan and coworkers published a tandem allylation/Prins sequence, during which the homoallylic alcohol **I-79** was generated *in situ* before the silyl-Prins cyclization to afford the tetrahydropyran (Scheme 1.21).[51] The methodology was applied to a short total synthesis of centrolobine. This protocol takes place in environmentally benign conditions and tolerates acid sensitive alcohol protecting groups. Similar approach was investigated by Markó and coworkers, who developed a tandem ene reaction/silyl-Prins sequence to generate polysubstituted tetrahydrapyrans via *in situ* formation of the homoallylic alcohol intermediate.[48]

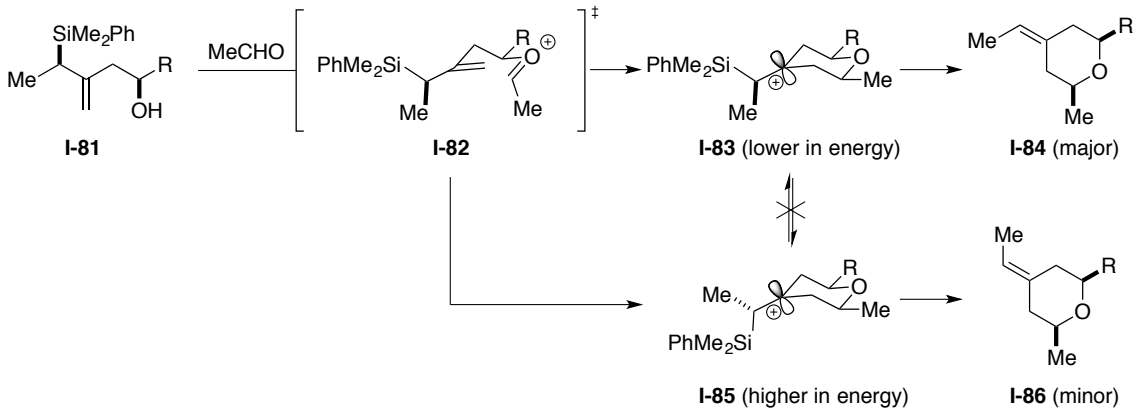
Scheme 1.21 Tandem allylation/Prins protocol to synthesize tetrahydropyran



In 2013, Wender and coworkers performed mechanistic and computational studies of exocyclic stereocontrol of the silyl-Prins cyclization.[52] The selectivity was rationalized using the chair-like transition state, in which the substituents adopt equatorial positions to minimize the steric strain. Two possible cyclization modes give rise to intermediates **I-83** and **I-85**. Interconversion between these two is not allowed because it'll go through a transition state for which β-silyl stabilization is lost. The stereoselectivity of the Prins cyclization is determined by the energy difference between the intermediates. The more stable **I-83** gives rise to the major diastereomer **I-84**. The combined

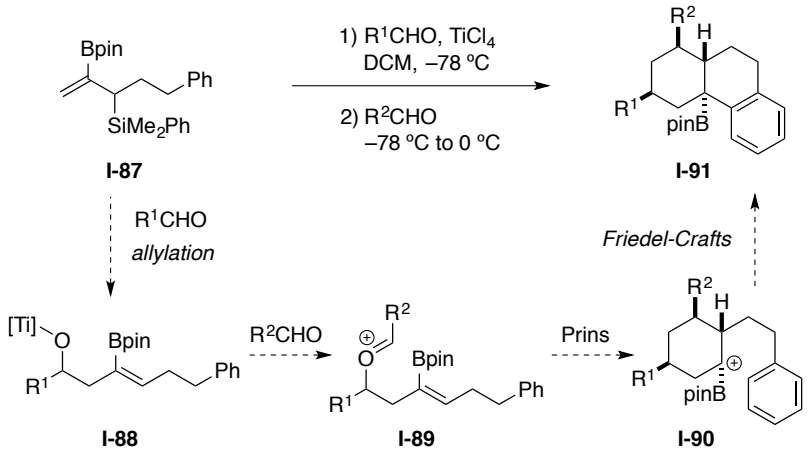
steric and electronic effects give rise to excellent stereoselectivity (Scheme 1.22). The situation applies to both *syn*- and *anti*-β-hydroxy allylsilanes.

Scheme 1.22 Stereocontrol of the silyl-Prins cyclization



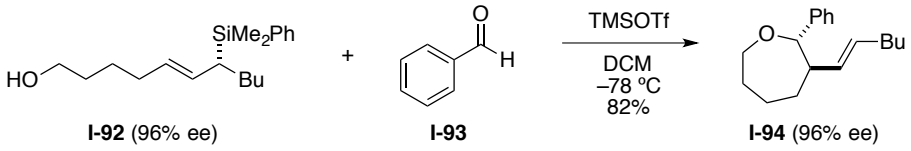
Sometimes the silyl-Prins cyclization can be combined with other reactions to generate tetrahydropyrans through a cascade reaction sequence. In 2003, Ito and coworkers developed an allylation/Prins/Friedel–Crafts sequence for the synthesis of tricyclic scaffolds.[53] The allylation step was much faster than the acetal formation in the presence of $TiCl_4$ (Scheme 1.23). Two different aldehydes can be employed in the protocol, which allow for the synthesis of a variety of tricyclic compounds. Boryl-substituted allylsilanes (**I-87**) were used, which were essential for the high diastereoselectivity in the cyclization. Similarly, a stereoselective Sakurai-Hosomi/Prins/Friedel–Crafts sequence utilizing allylsilanes and aldehyde electrophiles to generate trisubstituted tetrahydropyrans was reported by Reddy and coworkers in 2009.[54]

Scheme 1.23 Synthesis of substituted tetrahydropyrans through cascade reaction sequence



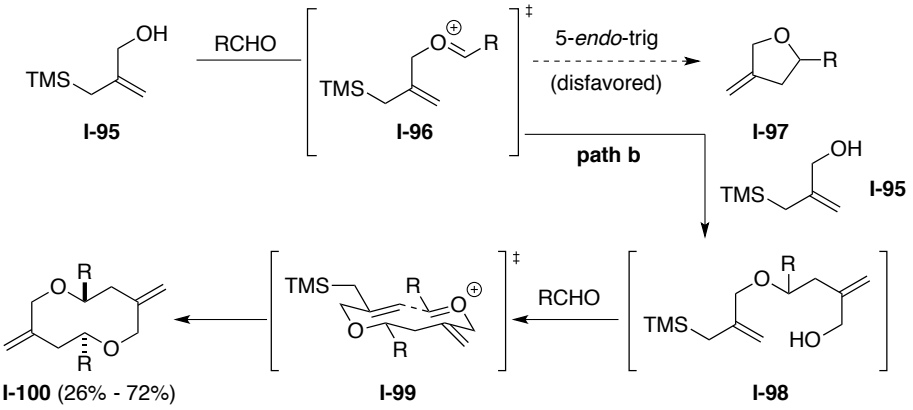
Other than five- and six-membered rings, medium-sized ring compounds can also be accessed through the silyl-Prins protocol. In 1999, Suginome and coworkers reported the stereoselective synthesis of oxepanes via acetalization-cyclization of an enantioenriched functionalized allylsilane with aldehydes (Scheme 1.24).[55] High levels of chirality transfer were achieved.

Scheme 1.24 Synthesis of oxepanes



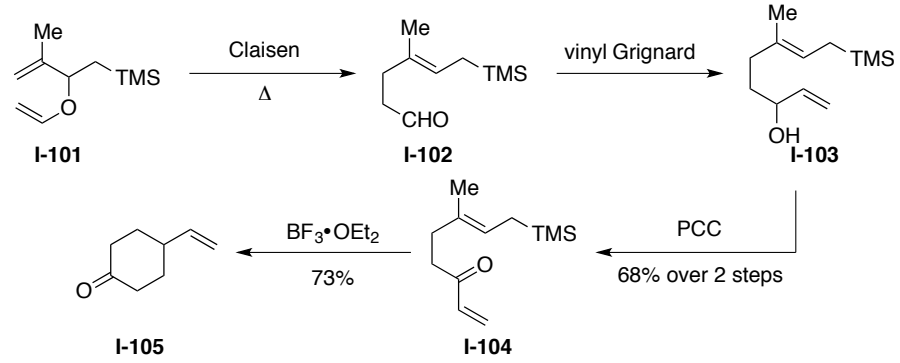
Cho and coworkers developed a double Prins-type cyclization of (allenylmethyl)silane or allylsilane with aromatic aldehydes to generate 1,6-dioxecanes.[56] This was the first example to employ inter- and intramolecular Prins reactions in a single process to generate entropically unfavorable medium-sized rings. The second condensation with allylsilane took place because the alternative 5-endo-trig cyclization was kinetically unfavorable according to Baldwin's rules (Scheme 1.25).

Scheme 1.25 Synthesis of 1,6-dioxecane through double Prins-type cyclization



Last but not the least, allylsilane cyclization can be combined with Cope or Claisen rearrangement reactions to generate functionalized cyclic compounds efficiently. In 1982, Wilson and coworkers developed a silicon-mediated Claisen rearrangement.[19] After the silyl vinyl ether rearrangement, further substrate elaboration followed by allylsilane cyclization led to vinylcyclohexanone **I-105** (Scheme 1.26). The highly ordered transition state in the Claisen rearrangement gave rise to high stereoselectivity.

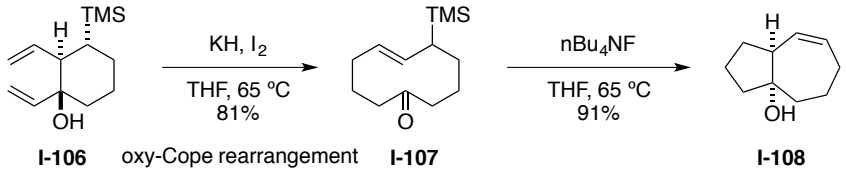
Scheme 1.26 Allylsilane cyclization coupled to Claisen rearrangement



Similarly, White and coworkers developed an oxy-Cope rearrangement/allylsilane cyclization sequence to produce 1,2-divinylcyclohexanols (Scheme 1.27).[57] The resulting hydroazulenols moiety **I-108** with *cis* ring fusion can be found in many natural products of biological interest.

Speckamp and coworkers also investigated the silyl-mediated oxy-Cope rearrangement using vinyl and allylsilanes.[58]

Scheme 1.27 Allylsilane cyclization coupled to oxy-Cope rearrangement

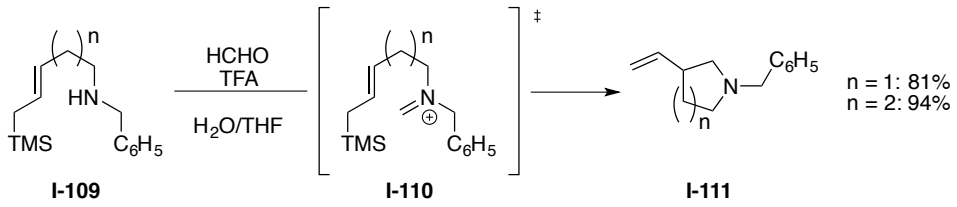


1.3 Cyclization with Activated C=N Bonds

1.3.1 Allylsilane Addition into Iminium Ions

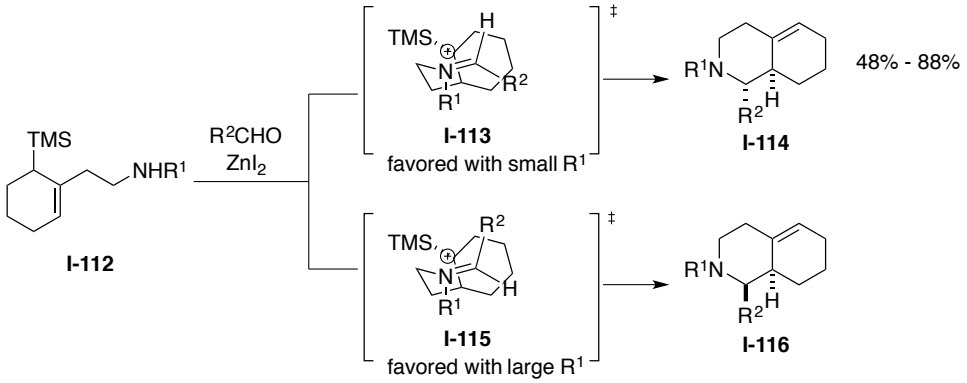
A classic method to generate iminium ions *in situ* is through adopting the Mannich-type conditions. Greico and coworkers developed a novel aminomethano desilylation-cyclization process in the presence of formaldehyde under acidic conditions (Scheme 1.28).[59, 60] Five-, six-, seven- and eight-membered rings containing nitrogen have been successfully generated under Mannich-like conditions.

Scheme 1.28 Allylsilane addition into iminium ions under Mannich-type conditions



In 1993, Overman and coworkers developed a stereocontrolled Mannich-type reaction using allylsilane amines and aldehydes (Scheme 1.29).[61] The stereochemical outcome of the iminium ion cyclization can be modified by tuning the geometry of substituents on nitrogen. This method could be applied towards the synthesis of the widely occurring reduced isoquinoline rings in natural alkaloids.

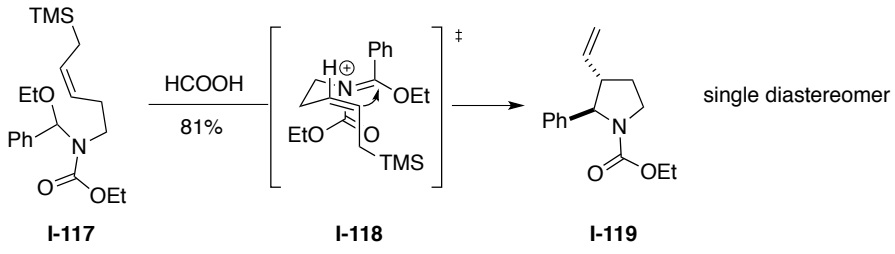
Scheme 1.29 Overman's stereocontrolled Mannich-type allylsilane addition



1.3.2 Allylsilane Addition into N-Acyliminium Ions

Allylsilane additions into N-acyliminium ions derived from lactams have been heavily investigated. The N-acyliminium ions are generally formed *in situ* from a lactam species and readily cyclize upon allylsilane addition. In the 1980s, Speckamp and coworkers published one of the early examples. Induced by protic or Lewis acids, 3-vinylpyrrolidines (**I-119**) or 3-vinylpiperidines can be synthesized in high yields (Scheme 1.30).[62] A chair-like transition state (**I-118**) was proposed,[63] as well as a preferred planar S-*cis* conformation of the N-acyliminium structure and the E geometry of the iminium structure. A combination of these effects led to high stereoselectivity.

Scheme 1.30 Synthesis of 3-vinylpyrrolidine

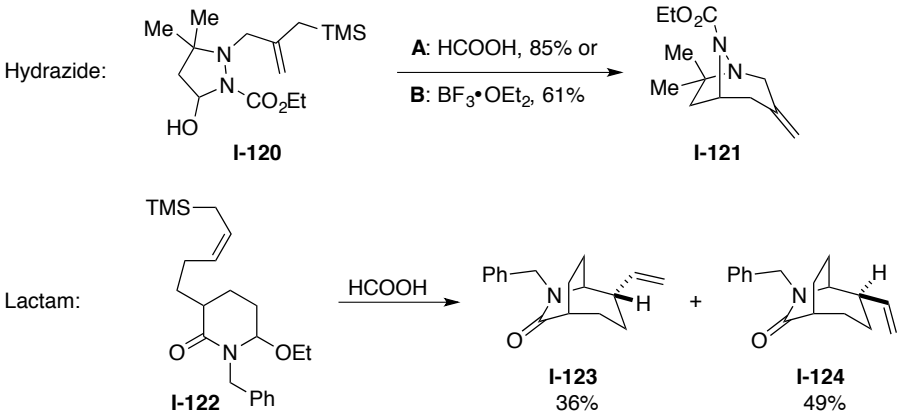


Judd and coworkers also investigated cyclization between allylsilanes and N-acyliminium ions.[64] They discovered that a strategically positioned benzyloxy group on the chiral allylsilane species

could control the diastereoselectivity of the reactions. It was proposed that products were formed under thermodynamic control.

Bridged bicyclic structures can also be generated in a similar fashion. Hiemstra and Speckamp published the synthesis of bridged azabicycles such as hydrazides (**I-121)**[65] and medium-sized ring lactams (**I-123** and **I-124**) (Scheme 1.31).[66] Brønsted and Lewis acids have been employed, while the chair-like transition state was again proposed for the reaction intermediates. Propargyl silanes have also been subjected to the same reaction conditions to afford allenes.

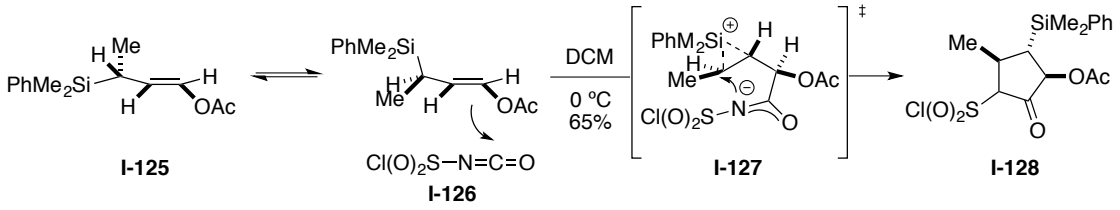
Scheme 1.31 Synthesis of bridged azabicycles



1.3.3 Allylsilane Addition with Other Nitrogenous Initiator

In 1999, Isaka and coworkers developed a novel uncatalyzed [3+2] cycloaddition using allylsilane **I-125** and N-chlorosulfonyl isocyanate **I-126**.[67] The reactions proceed through an initial formation of a zwitterionic intermediate **I-127**, followed by a 1,2-migration of the silyl group to give the unusual [3+2] cyclization rather than the conventional [2+2] cycloaddition observed with olefins (Scheme 1.32). This method offered an additional strategy of making γ-lactams and γ-amino acid derivatives.

Scheme 1.32 [3+2] cycloaddition between allylsilane and N-chlorosulfonyl isocyanate

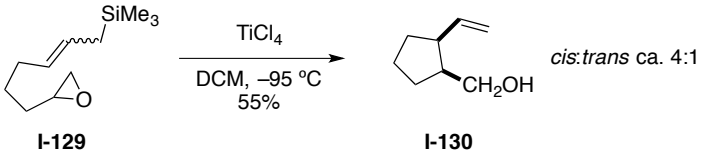


1.4 Cyclization with Other Electrophiles

1.4.1 Allylsilane Addition with Epoxides

It has been observed that Lewis acid-activated nucleophilic ring-opening of the epoxides gives rise to a stable carbocation.[68, 69] When the substrate is tethered to an allylsilane moiety, intramolecular cyclization can take place to afford cyclic products with high efficiency. In 1984, Tan and coworkers reported a $TiCl_4$-mediated epoxy-allylsilane cyclization (Scheme 1.33).[70] The main product (**I-130**) isolated was the *cis*-isomer. It was noteworthy that such reactions are substrate-dependent, since previous attempt to cyclize epoxy-allylsilanes by Parsons and coworkers only resulted in rearrangement products.[71]

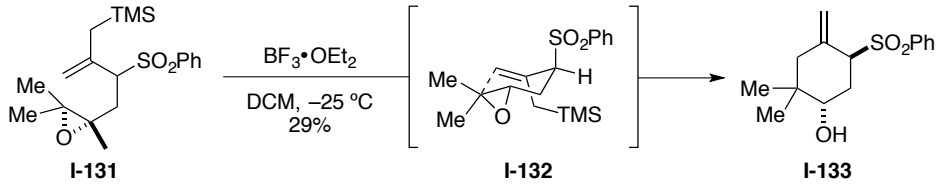
Scheme 1.33 Tan's epoxy-allylsilane cyclization



In 1988, Xiao and coworkers developed sulfone-directed diastereoselective cyclization of epoxy-allylsilanes.[72] The bulky phenyl sulfonyl group restricted the orientation of the C–TMS bond during the chair-like transition state (**I-132**). Since the σ orbital of the C–Si bond also needed to overlap with the π-orbital of the double bond, only one diastereomer of the cyclization substrate

would cyclize, affording a single product **I-133** (Scheme 1.34). The other diastereomer would undergo rearrangement through hydride migration to afford a ketone.

Scheme 1.34 Sulfone-directed diastereoselective cyclization of epoxy-allylsilane

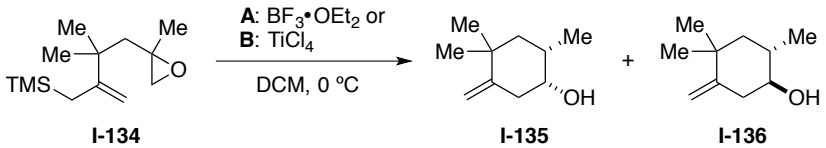


I-131 **I-132** **I-133**

Frejd and coworker looked further into the Lewis acid-catalyzed cyclization of epoxy-allylsilanes, especially the factors determining whether rearrangement or cyclization would take place.[73] It was observed that both the protecting groups on the substrates and the stereochemistry of the system played vital roles in which transformation took place.

In 2010, Pulido and coworkers synthesized 3-methylenecyclohexan-1-ols by the Lewis acid catalyzed cyclization of epoxy-allylsilanes.[74] They found out that cyclization showed two different behaviors depending on which Lewis acid was used. For instance, *syn*-cyclohexanol **I-135** was obtained with a smaller Lewis acid (e.g., BF_3OEt_2), indicating a synclinal transition state, while the cyclization went through an antiperiplanar transition state with larger Lewis acids such as $TiCl_4$ to afford *anti*-cyclohexanol **I-136** (Scheme 1.35).

Scheme 1.35 Stereoselective synthesis of 3-methylenecyclohexan-1-ols



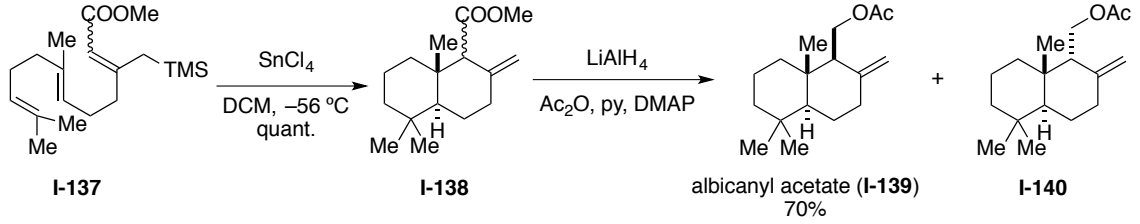
I-134 **I-135** **I-136**

A 2:1, 87%
B 1:10, 80%

1.4.2 Allylsilane Addition with Unsaturated C–C Bonds

Although less reactive than the C=O and C=N bonds, unsaturated carbon–carbon bonds can sometimes serve as good electrophiles for allylsilane addition. In 1982, Armstrong and coworkers discovered that allylsilanes could activate conjugated esters in a polyene cyclization to selectively produce exocyclic alkenes.[75] The transformation was initiated by protons or mercury trifluoroacetate. Synthesis of (±)-albicanyl acetate (**I-139**) and its C-9 epimer **I-140** was achieved using this method (Scheme 1.36).

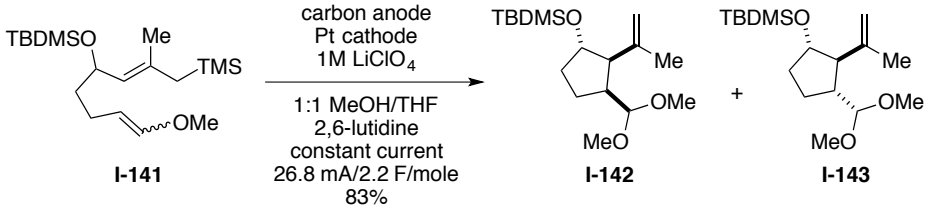
Scheme 1.36 Synthesis of (±)-albicanyl acetate



I-137 **I-138** albicanyl acetate (**I-139**) 70% **I-140**

On the other hand, Frey and coworkers studied the intramolecular anodic olefin coupling reactions between allylsilanes and allylic alkoxy groups.[76] Five-membered carbocycle structure was synthesized under constant current electrolysis conditions (Scheme 1.37). Only two (**I-142** and **I-143)** of the four possible diastereomers were obtained.

Scheme 1.37 Anodic olefin coupling between allylsilane and allylic alkoxy group

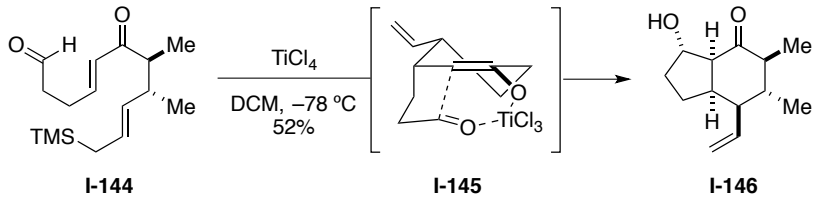


I-141 **I-142** **I-143**

Allylsilanes have also been employed in tandem Sakurai-Aldol addition. Nelson and coworkers prepared a series of chiral allylsilane precursors through an olefin isomerization-Claisen

rearrangement. Upon treatment with $TiCl_4$, highly stereoselective conjugate addition afforded a trichlorotitanium enolate intermediate **I-145**, which readily cyclized to provide polysubstituted cyclohexanone derivatives (Scheme 1.38).[77] Structural complexity and new stereocenters can be rapidly generated from simple starting materials, which is expected to be useful in both diversity- and target-oriented syntheses.

Scheme 1.38 Tandem Sakurai-Aldol addition using allylsilanes

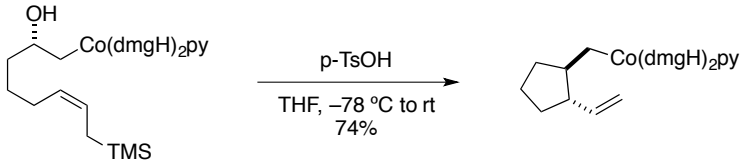


I-144 **I-145** **I-146**

1.4.3 Allylsilane Addition with Carbocations

Allylsilanes can undergo nucleophilic addition into carbocations generated *in situ*. In 1998, Pattenden and coworkers carried out the cationic carbocyclization by treating the allyl silyl alcohol **I-147** with catalytic amount of *p*-TsOH (Scheme 1.39).[78] Overall retention of configuration due to double inversion via the corresponding cobalt-π-cation was achieved as expected.

Scheme 1.39 Enantiospecific cobaloxime π-cation initiated carbocyclization

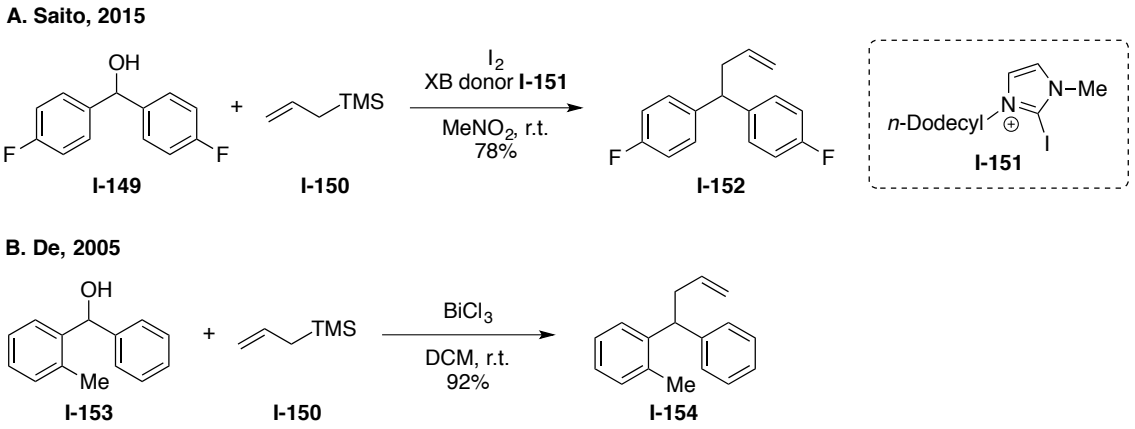


I-147 **I-148**

Benzylic alcohols also readily ionize under catalytic conditions to generate carbocations *in situ*. Many research groups have reported fragment coupling reactions between allylsilanes and benzhydrols using Lewis[79-84] and Brønsted acid[85] catalysts. For instance, Saito and coworkers developed a cocatalyst system using a halogen bond donor and TMS-halide, which effectively

facilitated coupling reactions between alcohol **I-149** and allyltrimethylsilane (Scheme 1.40A).[79] De and coworkers also reported a bismuth-catalyzed deoxygenative allylation of substituted benzylic alcohols with allyl-TMS. Reactions were completed in 0.5–3 hours in excellent yields (Scheme 1.40B).[80]

Scheme 1.40 Fragment coupling between benzylic alcohol and allylsilane



1.5 Application to Natural Product Total Syntheses

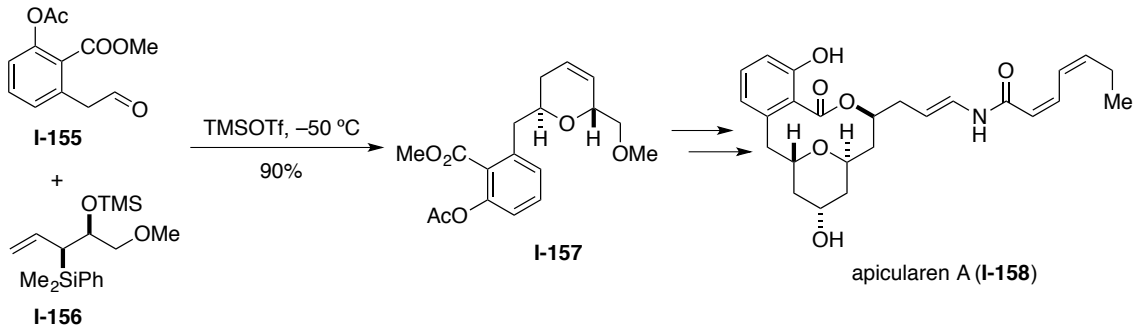
Many natural product total syntheses have employed the allylsilane cyclization strategy to build structural complexity. The syntheses can be achieved through a simple nucleophilic attack or silane-terminated polyene cyclization cascade sequence. Recent advances in this filed are herein discussed.

1.5.1 Total Synthesis of (–)-Apicularen A

In 2003, Su and Panek reported the total synthesis of (–)-apicularen A (**I-158**), a powerful inhibitor of human cancer cells.[39] The core of the natural product was assembled through a highly enantio- and diastereoselective [4+2] dihydropyran annulation between a chiral allylsilane (**I-156**) and an aldehyde (**I-155**) (Scheme 1.41). The stereochemical outcome was determined by the relative stereochemical arrangement of the silicon and the adjacent silyl ether of the crotysilane. This

method provided a promising and novel approach for the synthesis of other pyran-containing natural products.

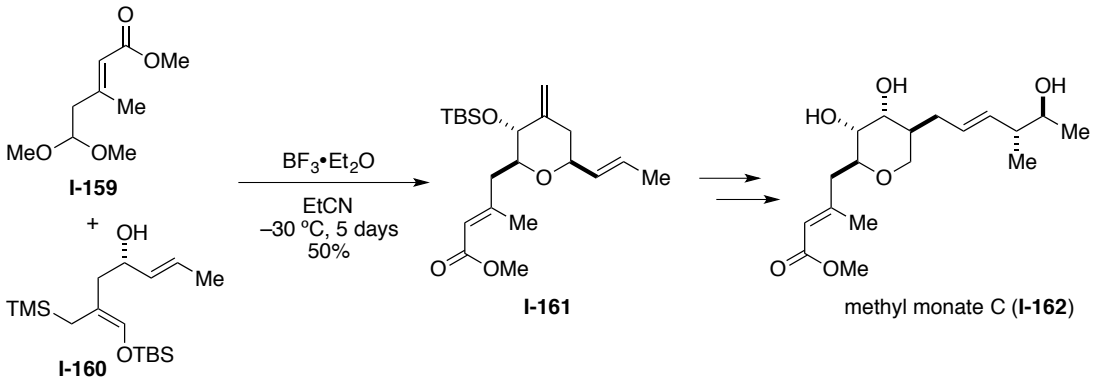
Scheme 1.41 Total synthesis of (–)-apicularen A



1.5.2 Total Synthesis of Methyl Monate C

Pseudomonic acid C is a potent antibiotic produced by a strain of *Pseudomonas fluorescens*, acting as an effective antimicrobial agent against Gram-positive bacteria. Markó and coworkers reported an asymmetric total synthesis of methyl monate C (**I-162**), the methyl ester derivative of pseodomonic acid A.[49] The synthesis featured an ene-intramolecular modified Sakurai cyclization to prepare the tetrahydropyran core **I-161**. Single diastereomer was obtained upon treatment with BF_3•OEt_2 through a chair-like transition state. Subsequent allylic alkylation and cross-metathesis enabled the insertion of the right-hand side chain (Scheme 1.42).

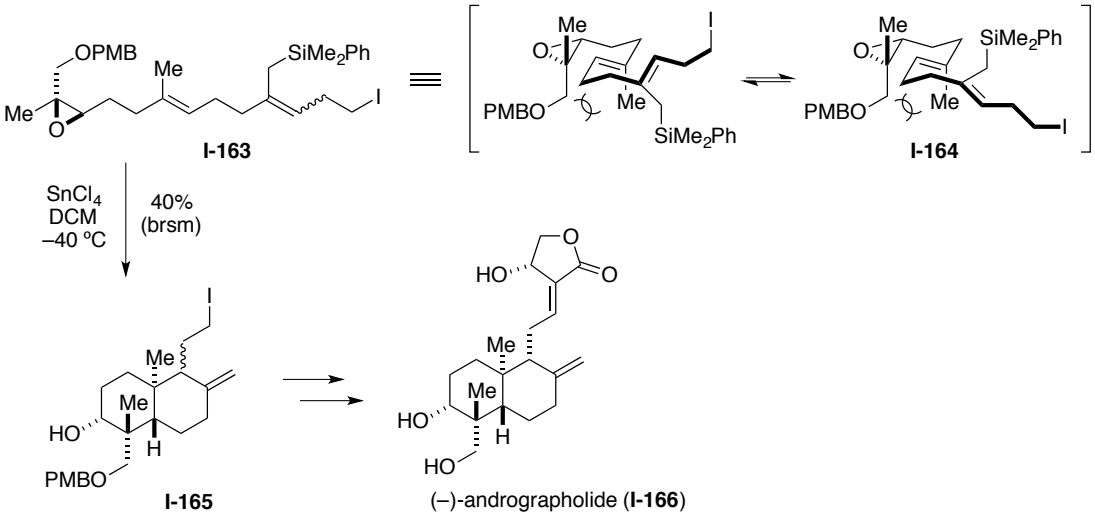
Scheme 1.42 Total synthesis of methyl monate C



1.5.3 Total Synthesis of (–)-Andrographolide and (+)-Rostratone

(–)-Andrographolide (**I-166**) is the main ingredient of the Asian medicinal herb Acanthaceae, which has been widely used in Chinese traditional treatments for inflammation. Recent studies confirmed its wide range of pharmacological properties including anti-inflammatory, antipyretic, immunostimulatory and antitumor.

Scheme 1.43 Total synthesis of (–)-andrographolide

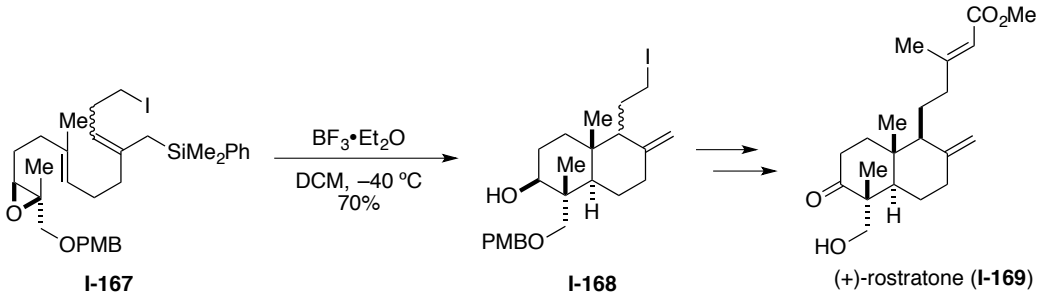


In 2014, Li and coworkers published the first asymmetric total synthesis of (–)-andrographolide via the biomimetic cyclization of an epoxy-allylsilane precursor **I-163** (Scheme 1.43).[86] The

reaction proceeded smoothly upon treatment with $SnCl_4$ despite substantial steric repulsion between substituents. Further elaboration of the substrate led to (–)-andrographolide.

Asymmetric total synthesis of the antipodal labdanoid (+)-rostratone (**I-169**) was synthesized using a similar strategy (Scheme 1.44).[86] The epoxy-allylsilane precursor **I-167** was synthesized and underwent BF_3•OEt_2-catalyzed cyclization to afford the bicyclic iodide product **I-168** in good yields. It was then advanced to (+)-rostratone in a biomimetic fashion through an oxidation/olefination sequence and protecting group manipulation.

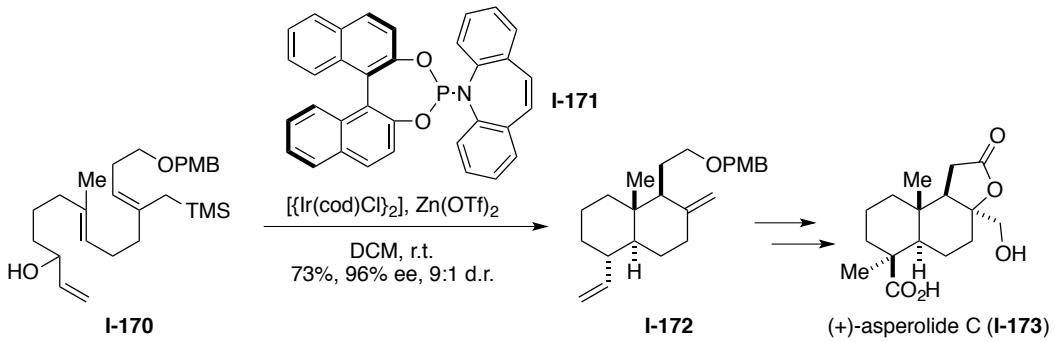
Scheme 1.44 Total synthesis of (+)-rostratone



1.5.4 Total Synthesis of (+)-Asperolide C

Asperolide C is a tetranorlabdane diterpenoid isolated from *Aspergillus wentii* EN-48. The labdane diterpenoids are widely distributed in terrestrial and marine organisms, while many of their natural product components exhibit important biological properties such as anti-inflammatory, antibacterial and antimutagenic.[87] In 2013, Carreira and coworkers published the first total synthesis of (+)-Asperolide C (**I-173**).[88] The strategy features a unique asymmetric catalytic polyene cyclization cascade terminated by the allylsilane group to afford the *trans*-decalin core **I-172** (Scheme 1.45). Iridium and chiral binaphthyl ligand **I-171** were selected as the optimal catalyst system, allowing for excellent enantioselectivity and good yield.

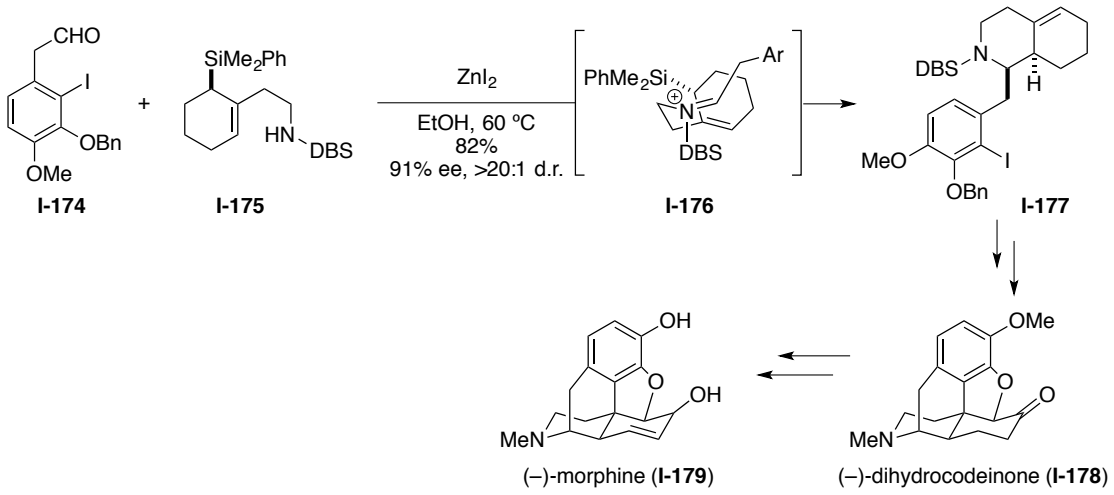
Scheme 1.45 Total synthesis of (+)-asperolide C



1.5.5 Total Synthesis of (–)-Morphine and (–)-Dihydrocodeinone

Polycyclic alkaloids containing nitrogen can also be synthesized through allylsilane-terminated cyclization. One of the great examples is Overman's total synthesis of both enantiomers of the natural opium alkaloids (–)-morphine (**I-179**) and (–)-dihydrocodeinone (**I-178**) (Scheme 1.46).[89] The key step involved a zinc-catalyzed allylsilane cyclization onto the iminium ion **I-176**. Bulky DBS amine protecting group was used to facilitate the preferential formation of the *trans* structure present in the natural products, leading to high diastereoselectivity. Subsequent Heck reaction and further substrate elaboration gave rise to the target compounds.

Scheme 1.46 Total synthesis of (–)-morphine and (–)-dihydrocodeinone



1.6 Summary

In summary, allylsilane reagents play a pivotal role in fragment coupling reactions to form new carbocycles. Their unique properties and ease of preparation allow for the development of many new methodologies over the past 40 years. With new complex natural products being discovered each year, synthetic need for more powerful allylsilane annulation methods will continue to grow.

Chapter 2

An Allylsilane Annulation Methodology for the Synthesis of Indanes, Tetralins and Chromanes

Portions of this chapter appear in the following publication:

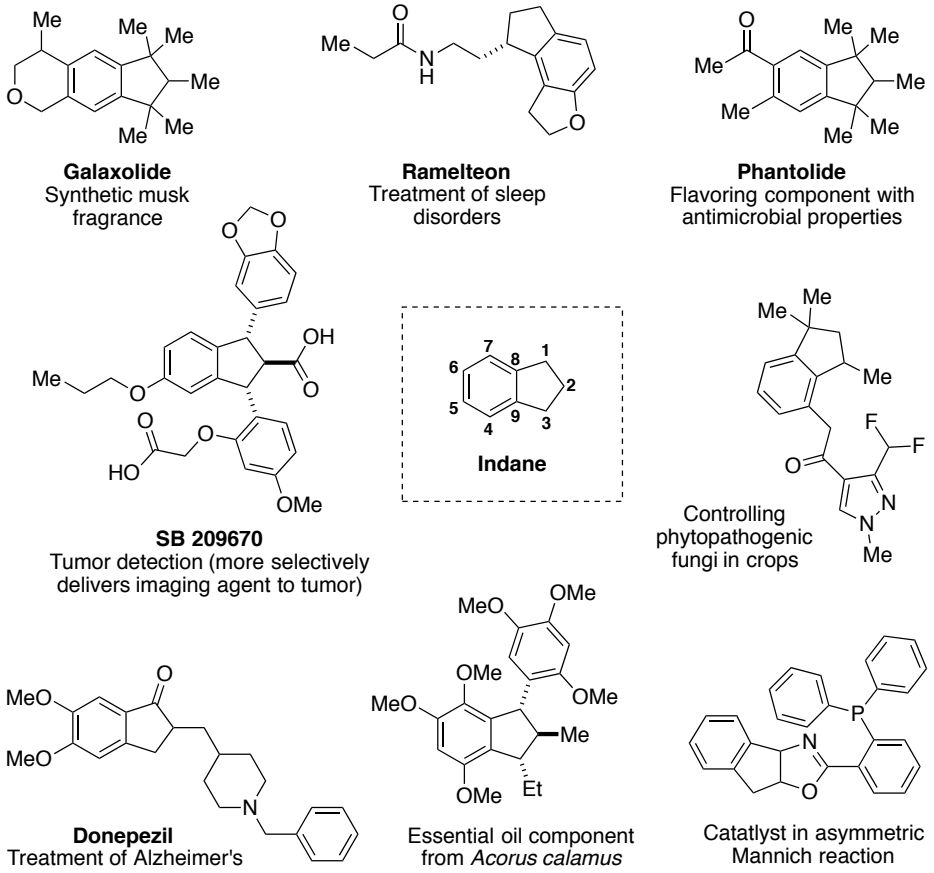
Reddel, J. C. T.; Wang, W.; Koukounas, K.; Thomson, R. J., Triflimide-Catalyzed Allylsilane Annulations of Benzylic Alcohols for the Divergent Synthesis of Indanes and Tetralins. *Chem. Sci.* **2017**, 8, 2156–2160.

2 Chapter 2

2.1 Introduction

Indane is a hydrocarbon compound characterized as a fused benzene and cyclopentane ring system (Figure 2.1). It is related to indene, an important organometallic ligand. The indanyl core is present in numerous natural products and synthetic compounds with desirable properties, while also serving as an essential motif in ligands for many chiral catalysts. Therefore, the indane chemotype has been extensively used in the pharmaceutical and fragrance industries.[90, 91]

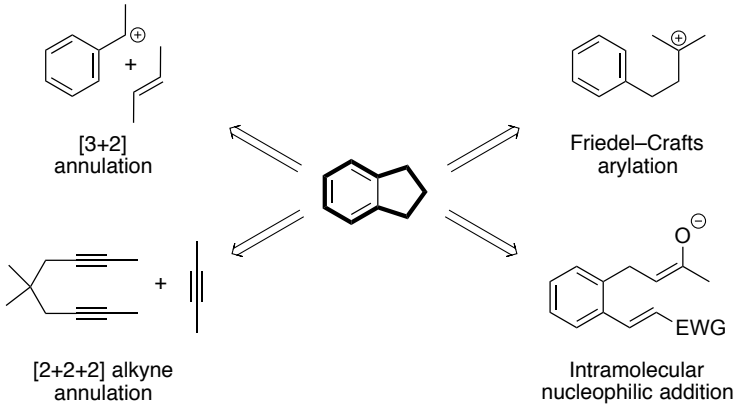
Figure 2.1 Selected examples of active compounds containing an indane core



Due to the ubiquity and importunate of the indane moiety, it is not surprising that many methods for its synthesis have been reported. Numerous types of disconnections have been investigated in

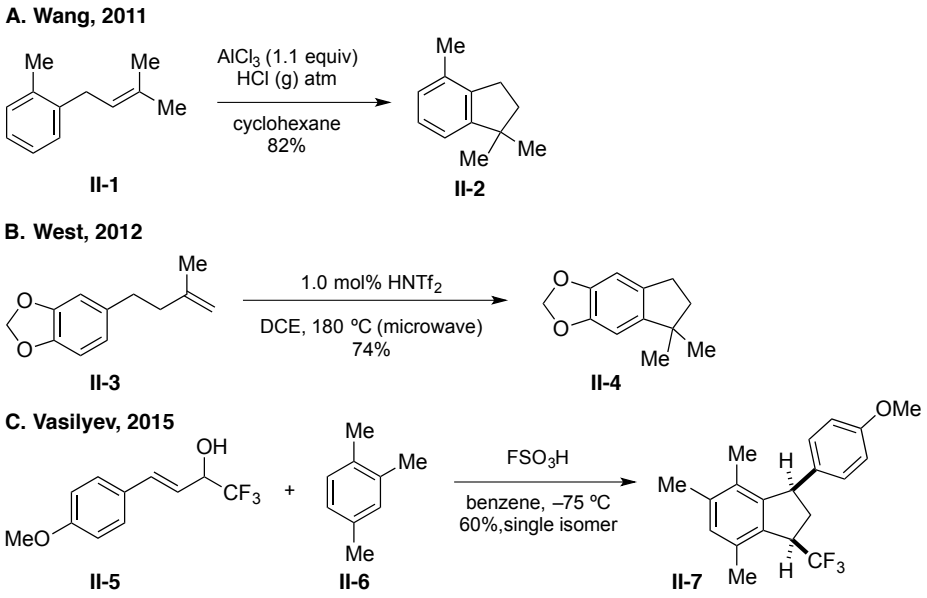
the retrosynthetic analysis of the basic indane ring system. Some of the most common methods chemists have employed to generate the indane core are the Friedel–Crafts arylation, intramolecular nucleophilic addition, [3+2] annulation and [2+2+2] alkyne annulation (Figure 2.2).

Figure 2.2 Some of the most frequently employed indane methodologies



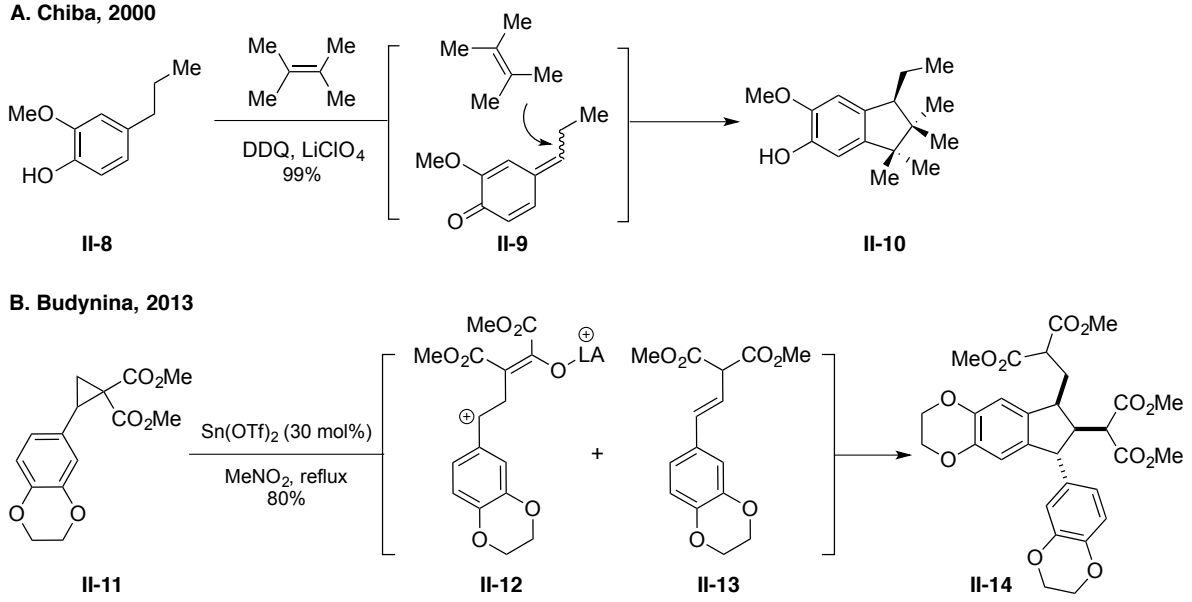
One straightforward method to synthesize indanes is the Friedel–Crafts arylation. In 2011, Wang and coworkers treated the branched alkene **II-1** with strongly acidic conditions, generating a carbocation which readily cyclized to afford the indane product (Scheme 2.1A).[92] West and coworkers developed a similar acid-catalyzed route also using unactivated alkenes such as **II-3**. Short reaction times and good yields were achieved under reflux or microwave heating (Scheme 2.1B).[93] In 2015, Vasilyev and coworkers reported a diastereoselective synthesis of CF_3-indanes,[94] with the *cis*-conformer being the preferred isomer (Scheme 2.1C). Anhydrous $FeCl_3$ and FSO_3H proved to be the most efficient activators, leading to short reaction times, good yields and simplicity of the reaction procedure.

Scheme 2.1 Selected examples of indane syntheses through Friedel–Crafts arylation



Another common approach is the [3+2] cycloaddition between aromatic rings and alkenes or epoxides to generate the bicyclic system (Scheme 2.2). This annulation can be realized under oxidative and acid-catalyzed conditions.

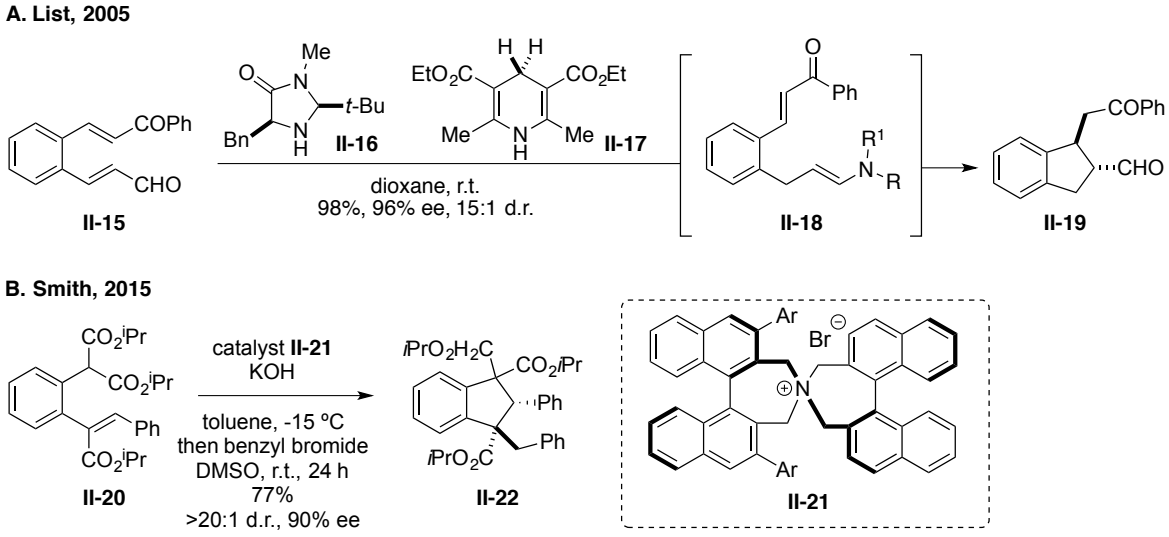
Scheme 2.2 Selected examples of indane syntheses through [3+2] cycloaddition



In 2000, Chiba and coworkers reported intermolecular [3+2] cycloaddition between alkene **II-8** and *in situ* generated *p*-quinomethane **II-9** (Scheme 2.2A).[95] Oxidative medium lithium perchlorate greatly facilitated the reaction by stabilizing the *in situ* generated zwitterion. In 2013, Budynina and coworkers developed a novel route to indanes using two cyclopropane units as cross-coupling partners.[96] The reaction involved Lewis-acid catalyzed cyclopropane opening to afford enonate **II-12** and styrylmalonate **II-13**, which underwent cyclodimerization to generate polysubstituted indanes (Scheme 2.2B). The products were found to be non-toxic to normal cells while showing significant toxicity against tumor cell lines, rendering this methodology promising towards anticancer studies.

Some other strategies rely on an intramolecular nucleophilic addition to forge the carbocycle (Scheme 2.3).

Scheme 2.3 Selected examples of indane syntheses through intramolecular Michael addition

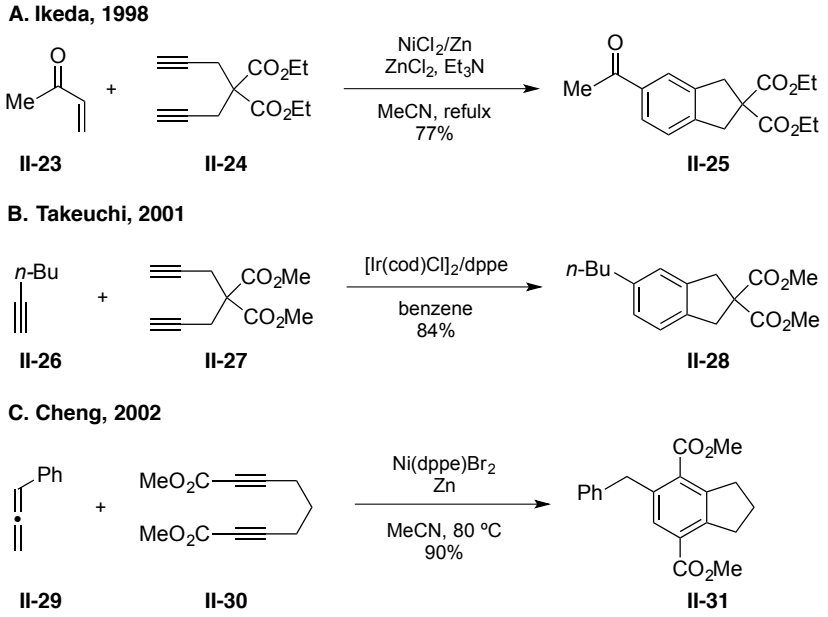


In 2005, List and coworkers developed an enantioselective reductive Michael cyclization.[97] The reaction proceeds through an *in situ* iminium catalytic conjugate reduction, followed by an

asymmetric enamine catalytic intramolecular Michael reaction. High chemo-, regio-, diastereo- and enantioselectivity was achieved (Scheme 2.3A). On the other hand, Smith and coworkers reported a kinetically unfavorable 5-*endo*-*trig* cyclization Michael reaction to generate complex indanes.[98] A chiral cation facilitated the highly enantio- and diastereoselective transformation (Scheme 2.3B).

A less frequently encountered method is the [2+2+2] alkyne annulation. Such reactions are often catalyzed by transition metals (Scheme 2.4).

Scheme 2.4 Selected examples of indane syntheses through [2+2+2] annulation



Ikeda and coworkers developed a binary metal-mediated cycloaddition between terminal diynes (**II-24**) and enones (**II-23**) (Scheme 2.4A).[99] Takeuchi and coworkers applied similar terminal alkynes (**II-27**) in the iridium-catalyzed cycloaddition with monoalkynes (**II-26**) to give indane derivatives in good yields (Scheme 2.4B).[100] On the other hand, Cheng and coworkers reported a highly regio- and chemoselective [2+2+2] cycloaddition between internal diynes (**II-30**) and

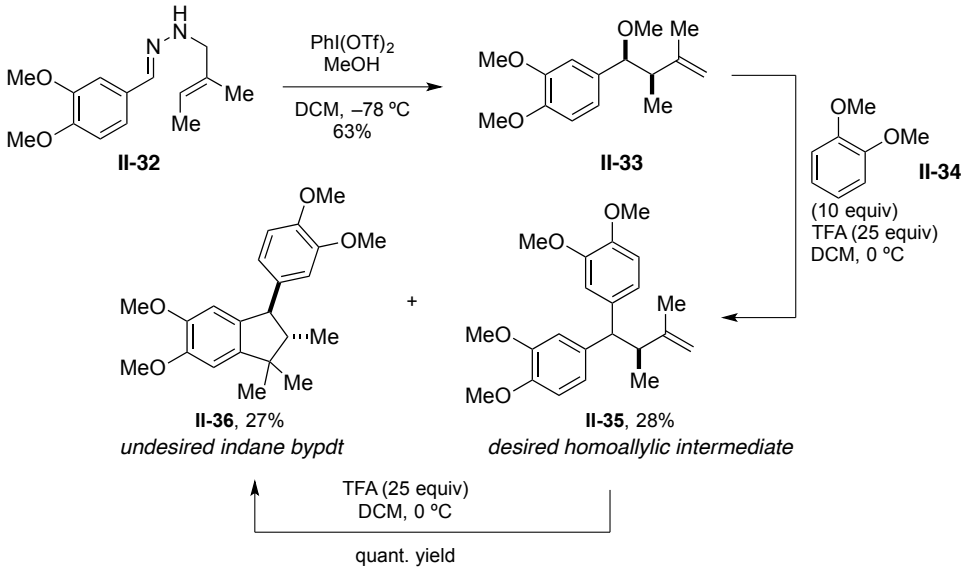
allenes (**II-29**) catalyzed by nickel complexes (Scheme 2.4C).[101] In their example, allenes were used as a synthetic equivalent to terminal alkynes.

Most of the previously reported methods, however, suffer from one or more of the following limitations: the use of harsh or toxic reaction conditions, precious metal catalysts, complicated starting materials and limited substrate scope. Development of facile and mild indane methodologies is therefore of great interest to synthetic chemists.

2.2 Initial Attempt Using Homoallylic Ether Substrate

We aimed to devise a versatile and facile Lewis/Brønsted acid-catalyzed synthesis that allows for the rapid formation of indanes under mild conditions. The initial inspiration stemmed from the Thomson group's early efforts to synthesize lignan natural products, wherein an unexpected indane derivative was observed as the cyclization byproduct (Scheme 2.5).

Scheme 2.5 Formation of an indane byproduct

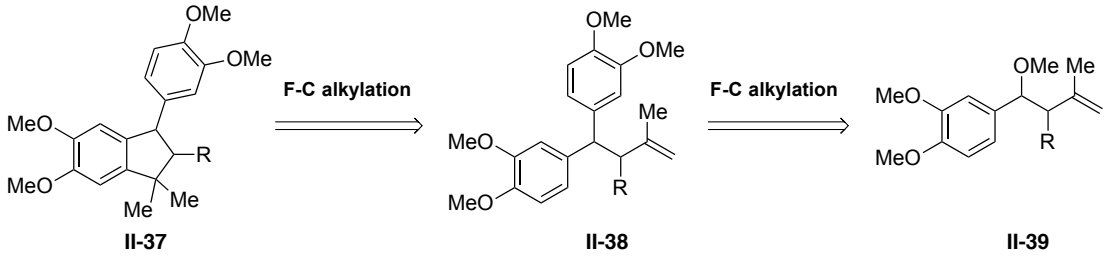


The *N*-allylhydrazone **II-32** underwent [3,3]-sigmatropic rearrangement to afford the homoallylic ether **II-33**. Upon treatment with excess TFA and 1,2-dimethoxybenzene, an unexpected indane

byproduct **II-36** was formed in addition to the desired benzhydryl **II-35**. When the benzhydryl species was treated with TFA, full conversion to indane **II-36** can be achieved.

This intriguing discovery represents a potential methodology to synthesize indanes and inspired our initial retrosynthetic analysis using a convergent strategy (Scheme 2.6). We decided to target the homoallylic benzhydryl species **II-38**, which can undergo a Friedel–Crafts arylation to afford indanes. The benzhydryl intermediate would be derived from homoallylic ether **II-39** through two-component coupling with an aryl species.

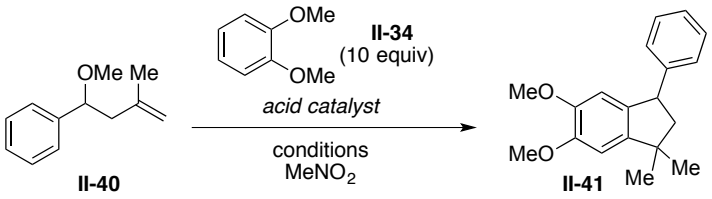
Scheme 2.6 Initial retrosynthetic analysis of indanes



II-37 **II-38** **II-39**

The optimization studies were performed using a simplified homoallylic ether substrate **II-40**, which was easily prepared through either a Grignard addition or Hosomi–Sakurai reaction, followed by methylation of the resulting alcohol. A variety of reaction conditions were examined to optimize the system, which commenced with a screen of acid catalysts. Treatment with excess TFA was investigated first to mimic the original transformation that generated the indane byproduct, however the yields were not satisfactory (Table 2.1, Entry 1–3). Triflimide ($HNTf_2$)-catalyzed reactions gave rise to higher yields with lower catalyst loading (Table 2.1, Entry 5–6). On the other hand, *p*-TsOH also gave improved yield comparing to the TFA-catalyzed reactions, but stoichiometric amounts of acid were required (Table 2.1, Entry 6).

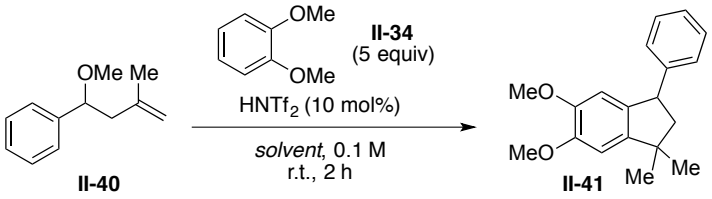
Table 2.1 Acid catalyst screen with the homoallylic ether starting material



Entry	Acid Catalyst	Conditions	Yield %
1	TFA (25 equiv)	0 ºC to r.t., 13 h	29
2	TFA (5 equiv)	0 ºC to r.t., 42 h	31
3	TFA (2.5 equiv)	0 ºC to r.t., 22 h	3
4	*p*-TsOH (1 equiv)	0 ºC to r.t., 24 h	52
5	$HNTf_2$ (20 mol%)	0 ºC, 2.5 h	44
6	$HNTf_2$ (20 mol%)	r.t., 15 min	50

We sought to further optimize the reaction by exploring the potential of different solvents to achieve higher yields (Table 2.2).

Table 2.2 Solvent screen with the homoallylic ether starting material

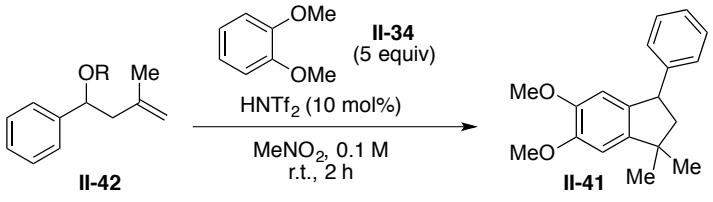


Entry	Solvent	Yield %
1	Toluene (dry)	9
2	DCM (dry)	12
3	Trifluoro-toluene	5
4	MeCN (dry)	No rxn
5	THF (dry)	No rxn
6	$MeNO_2$	52

We hypothesized that a more polar solvent would better stabilize the positive charge generated by ionization of the ether starting material **II-40**, thereby enhancing desired reaction rates and minimizing byproducts derived from elimination. As expected, $MeNO_2$ gave the best yield (Table 2.2, Entry 6), while the remaining candidates produced no reaction or only a small amount of the desired prodcut. We therefore selected $MeNO_2$ (0.1 M) and $HNTf_2$ (10 mol%) as our optimal reaction conditions. Similar solvent effects were observed by Rueping and coworkers during their benzylation of arenes.[102]

At this point we were unable to improve the yield further, and hypothesized that this was due to the poor ionizability of the methyl ether group. Different ionizable groups were therefore installed, and to our delight improved yields were observed in all cases (Table 2.3). When the readily ionizable trifluoacetate was used, excellent yields can be achieved (Table 2.3, Entry 4).

Table 2.3 Ionizable group screen with the homoallylic ether starting material



Entry	R	Yield %
1	OMe	52
2	H	56
3	Ac	87
4	$COCF_3$	94

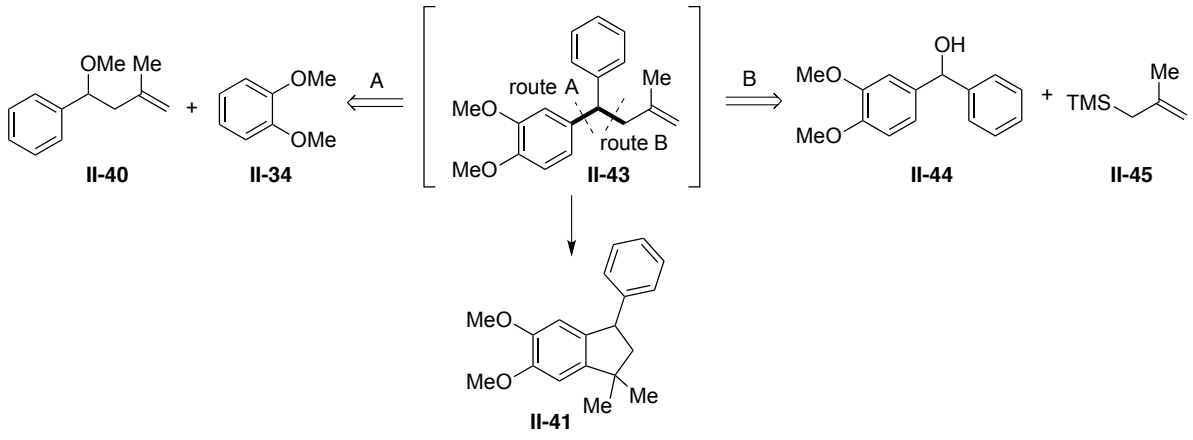
There were two major drawbacks, however, associated with this approach. Firstly, an extra step was required to install the ionizable group, complicating the synthetic route. Secondly, the substrate scope was relatively limited, as we were not able to incorporate any electron-deficient

substituents on the aryl group of the alcohol starting material. Electron-rich aromatic rings were necessary to facilitate the Friedel–Crafts arylation and stabilize the positive charge generated from ionization. We opted to explore an alternative approach despite the promising results.

2.3 Alternative Benzhydryl Approach

Due to the limitations of the methyl ether approach, we took a step back and re-examined our retrosynthetic analysis. We decided to access the same homoallylic intermediate **II-43** through an alternative benzhydryl approach (Scheme 2.7, Route B). We envisioned that intermediate **II-43** can be generated from the benzhydryl starting material **II-44**, in which the second aryl group was pre-installed onto the substrate. This new route would allow us to 1) realize more efficient ionization with the alcohol ionizable group; 2) incorporate electron-deficient groups into the system, leading to a wider substrate scope.

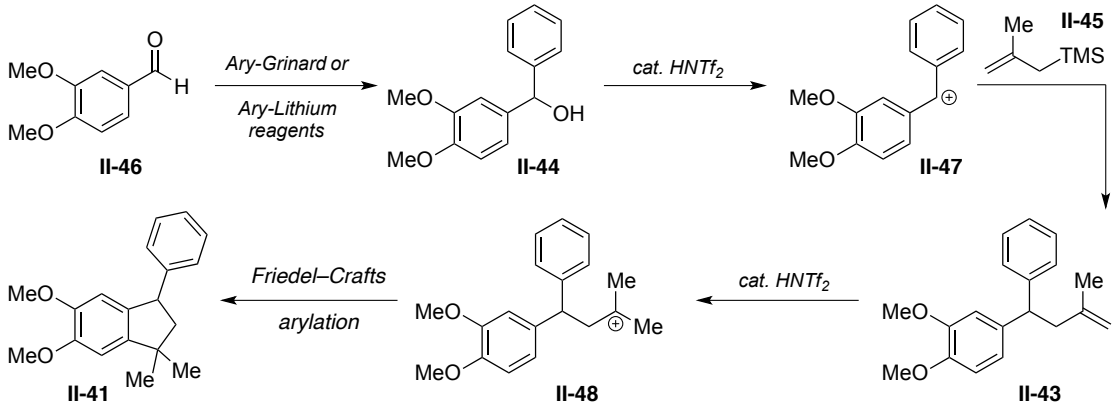
Scheme 2.7 Alternative approach to access the homoallylic intermediate



In our proposed mechanism (Scheme 2.8), the benzhydryl alcohol **II-44** can be readily synthesized through the addition of either an aryl-Grignard or aryl-lithium reagent to aldehyde **II-46**. The alcohol would ionize under acidic conditions to generate the benzhydryl cation **II-47**, which undergoes fragment coupling with allylsilane **II-45** to give the targeted homoallylic intermediate

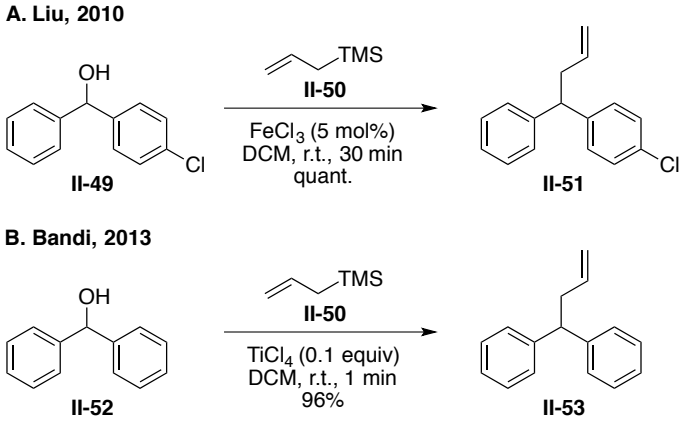
II-43. Protonation of the terminal alkene would give rise to the tertiary carbocation **II-48**, followed by an intramolecular Friedel–Crafts arylation to afford indane **II-41**.

Scheme 2.8 Proposed mechanism for indane synthesis



Fragment coupling reactions between benzhydryl alcohols and allylsilanes have been well studied in the previous literature (Section 1.4.3). Various Lewis and Brønsted acids such as BF_3,[82] $InCl_3$,[81] $BiCl_3$,[80] $FeCl_3$,[83] $TiCl_4$[84] and HBF_4•OEt_2[85] have shown superb catalytic activity for such reactions.

Scheme 2.9 Fragment coupling between benzhydryl alcohol and allylsilane



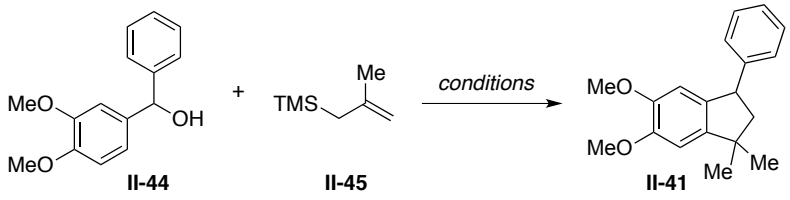
For instance, Liu and coworkers utilized $FeCl_3$ to promote a highly-efficient allylsilane addition to benzhydryl alcohol **II-49** (Scheme 2.9A).[83] Bandi and coworkers reported a similar allylation

reaction using $TiCl_4$ as catalyst, completing the reaction in one minute with excellent yield under mild reaction conditions (Scheme 2.9B).[84]

2.3.1 Reaction Condition Optimization

We selected commercially available methallyltrimethyl silane **II-45** and the electron-rich benzhydryl alcohol **II-44** for our optimization studies. A brief catalyst and solvent screen was performed to confirm that $MeNO_2$ and $HNTf_2$ were still the optimal candidates. To our delight, this combination gave us the highest yield of **II-41** (Table 2.4 Entry 7). Increasing or decreasing the temperature did not afford an increase in yield (Table 2.4, Entry 5–6).

Table 2.4 Solvent and catalyst screen for benzhydryl alcohol substrate



II-44 **II-45** **II-41**

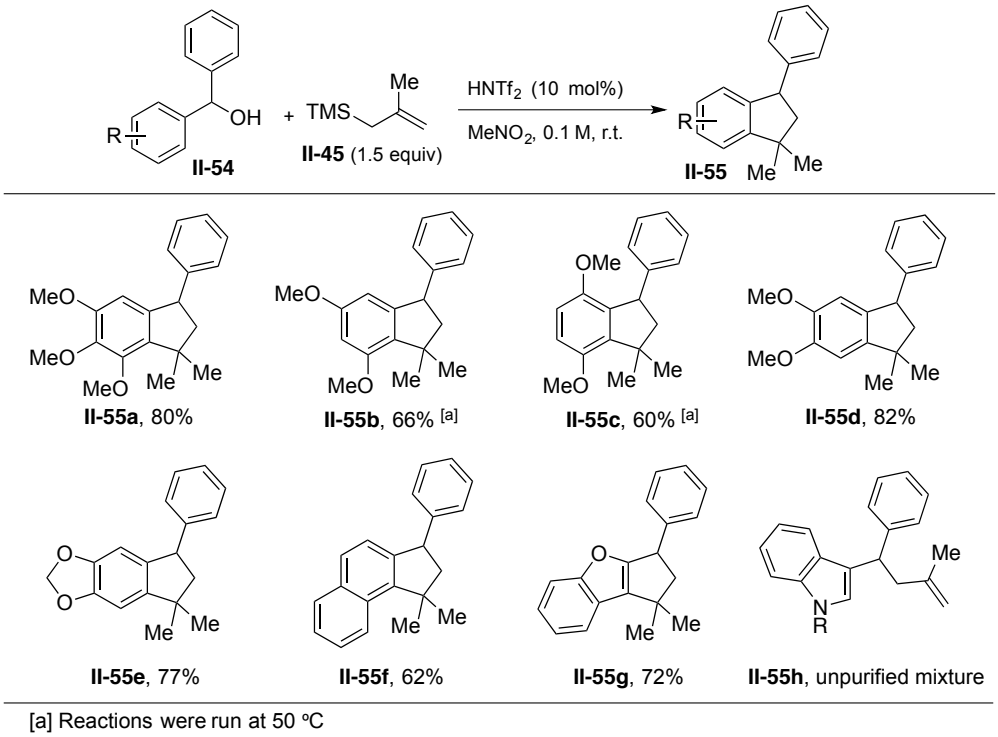
Entry	Solvent	Catalyst	Temperature	Yield %
1	DCM	$HNTf_2$ (10 mol%)	r.t.	41
2	DCE	$HNTf_2$ (10 mol%)	r.t.	22
3	$MeNO_2$	TFA (50 mol%)	r.t.	No rxn
4	$MeNO_2$	TMSOTf (20 mol%)	r.t.	54
5	$MeNO_2$	$HNTf_2$ (10 mol%)	0 ºC	67
6	$MeNO_2$	$HNTf_2$ (10 mol%)	80 ºC	19
7	$MeNO_2$	$HNTf_2$ (10 mol%)	r.t.	74

2.3.2 Exploration of Substrate Scope

To examine the substrate scope of our proposed transformation, the optimized conditions were applied to a variety of benzhydryl alcohols (Table 2.5). We were pleased to find that the system was mild and versatile enough to accommodate a wide range of substrates. The results were

grouped into several categories based on which ring the cyclization took place. We first investigated benzhydrols with an electron-rich aryl ring and an electron-neutral phenyl ring. The Friedel–Crafts arylation was anticipated to occur exclusively at the former ring. Indanes **II-55a**, **II-55d** and **II-55e** were obtained in clean reactions with high yields. In some cases, such as compound **II-55b** and **II-55c**, elevated temperature was required to most likely overcome the steric strain of cyclization due to the *ortho* substituents. In these two cases, a substantial increase in yield (~50%) was observed when the temperature was raised from 20 °C to 50 °C. We were able to obtain **II-55f** as a single isomer with cyclization occurring at the electron-rich position on naphthalene. Benzofuran also proved to be electron-rich enough to undergo the Friedel–Crafts alkylation, yielding product **II-55g**. While not an indane, the benzofuran chemotype is present in many bioactive compounds.[103]

Table 2.5 Benzhydrol substrates with phenyl and electron-rich aryl rings

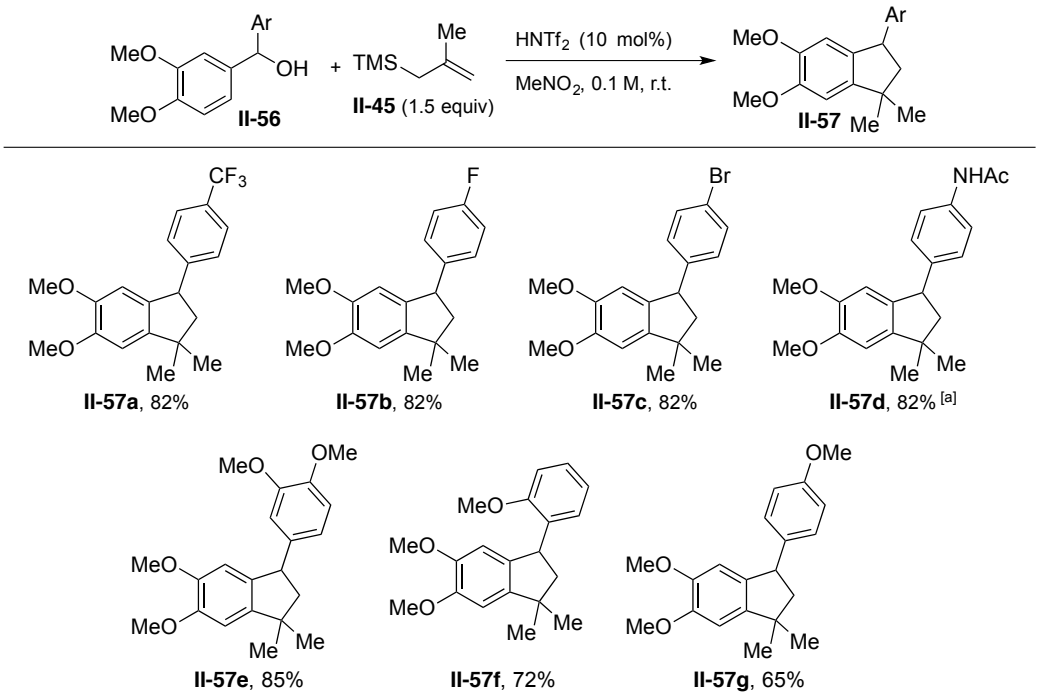


[a] Reactions were run at 50 °C

Thiophene and furan-derived starting materials showed signs of minor decomposition even when the reaction was run at 0 °C. Indole and methylindole containing substrates only yielded the uncyclized homoallylic products **II-55h**, possibly due to the side reaction between the indole and triflimide. The reduced electron density in the methylindole ring system might also be problematic. Non-substituted and mono-methoxy substituted phenyl rings failed to provide the desired indane products, which was not surprising due to the lack of electron-rich rings required for the cyclization.

We also examined benzhydryl alcohol substrates with electron-rich dimethoxybenzene rings, where the cyclization was expected to occur (Table 2.6). Electron-deficient and electron-rich substituents can be effectively incorporated, giving single product with satisfying yields. To our delight, the aniline-containing substrate afforded a protected indane **II-57d** when heated to 80 ºC.

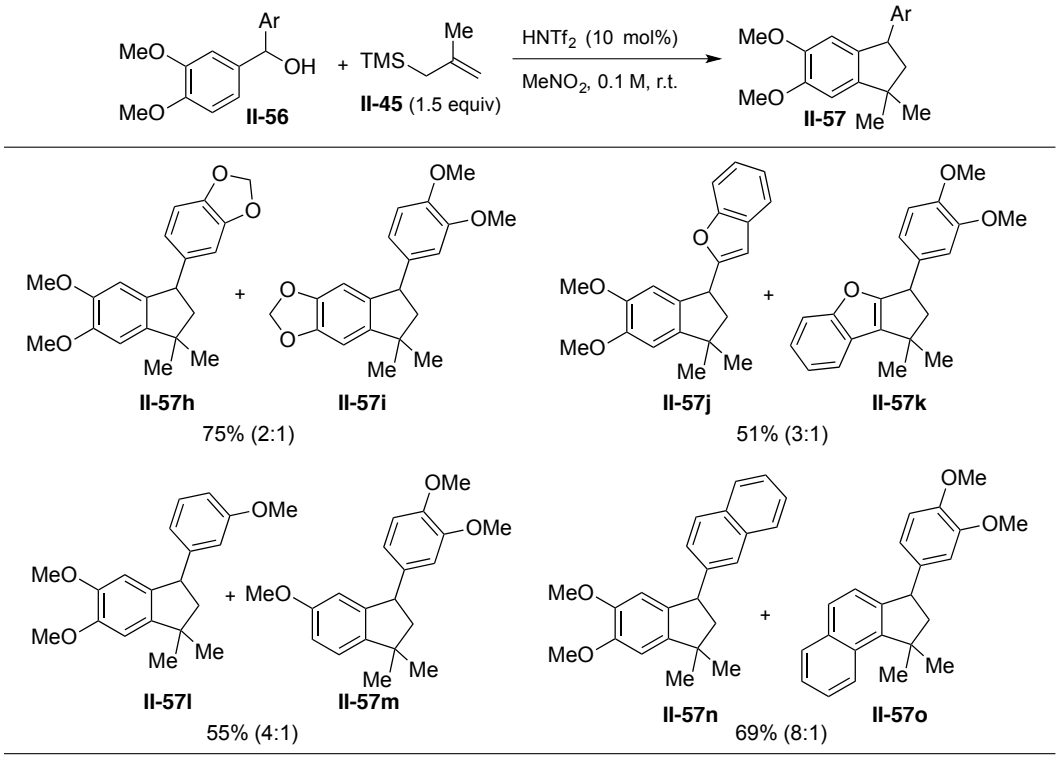
Table 2.6 Benzhydrol substrates with one dimethoxybenzene ring



[a] Reaction was run at 80 ºC

As the electron density of the second ring increases, however, a mixture of cyclization regioisomers were obtained (Table 2.7). Selectivity improves as the difference in electron density between the two rings increases, indicating cyclization was governed by electronic effects in this case.

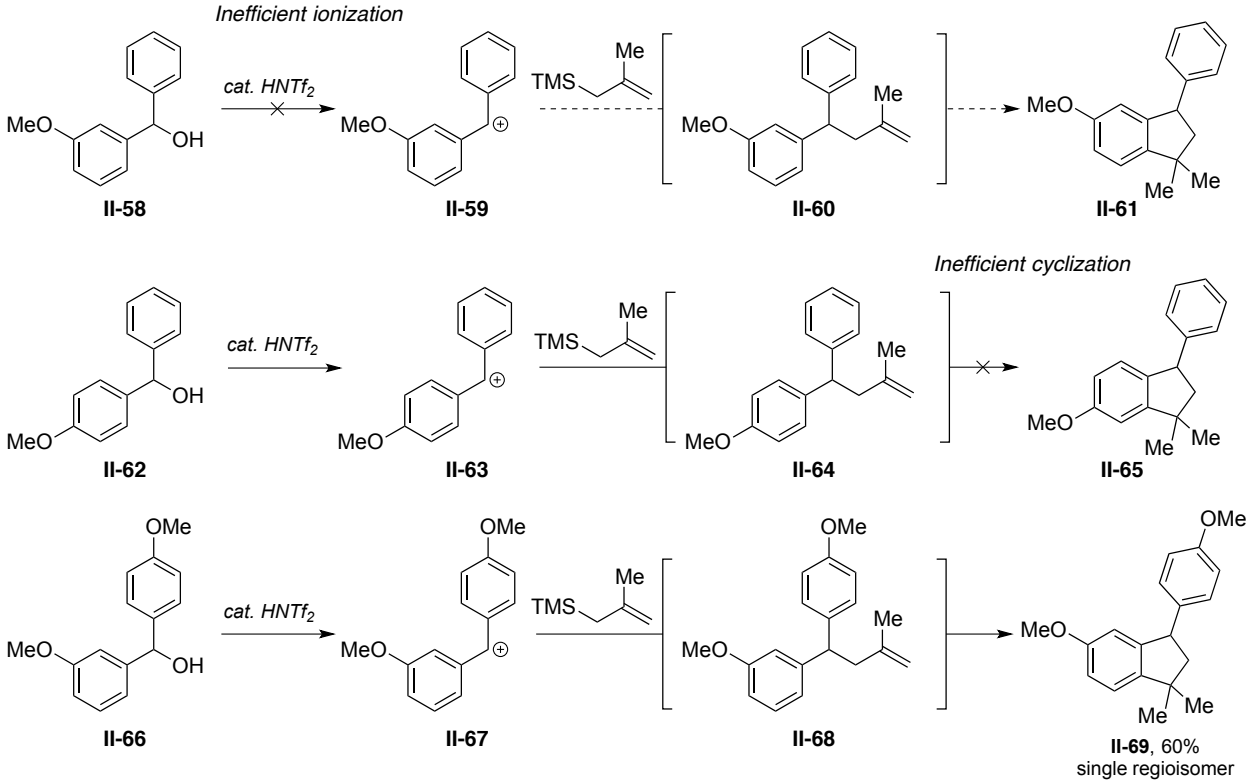
Table 2.7 Benzhydrol substrates with two electron-rich aryl rings



Of particular interest are the benzhydrol substrates with mono-methoxy substitution. According to our previous studies, the mono-methoxy substituted benzhydrols all failed to yield the indane structure (Scheme 2.10). For *meta*-methoxy substituted benzhydrol **II-58**, the ionization was not efficient due to the lack of electron-donating group *para* to the ionization site. For *para*-methoxy substituted benzhydrol **II-62**, the cyclization was not efficient due to the lack of electron-donating group *para* to the cyclization site. When we switched out the phenyl group for an electron-rich

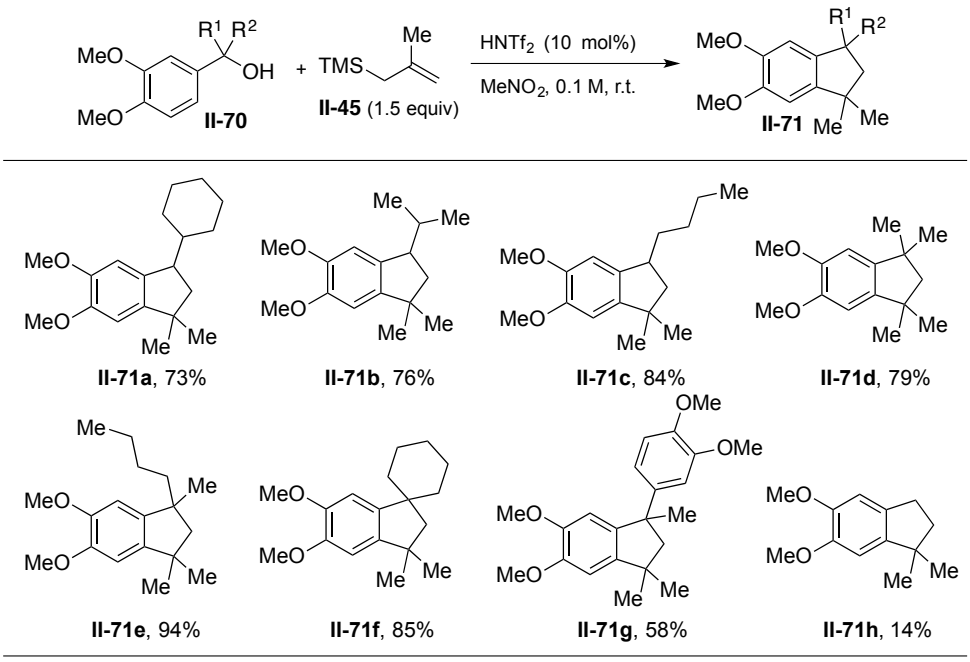
dimethoxy benzene, however, we started observing indane products in both cases (**II-57g**, **II-57l** and **II-57m**). Inspired by this outcome, we introduced the benzhydrol species with *meta*-methoxy substituent on one ring, and *para*-methoxy substituent on the other ring. A single regioisomer **II-69** was obtained with 60% yield. The combined results here again confirmed that this transformation was predominantly governed by electronic effects.

Scheme 2.10 Benzhydrol substrates with mono-methoxy substitution



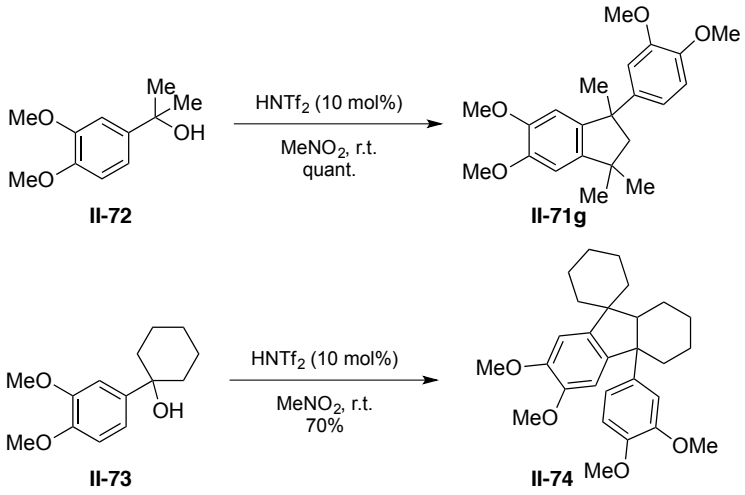
In addition to aromatic rings, alkyl substituents were also successfully introduced into the products (Table 2.8). The spirocycle system in **II-71f** can be found in many natural products and bioactive compounds.[104, 105] As the ionization site became too hindered, however, the yield was slightly compromised (**II-71g**). A primary benzylic alcohol was also employed, though we were not able to achieve a satisfying yield likely due to the poor ionizability of the substrate (**II-71h**).

Table 2.8 Benzhydrol substrates with alkyl substituents



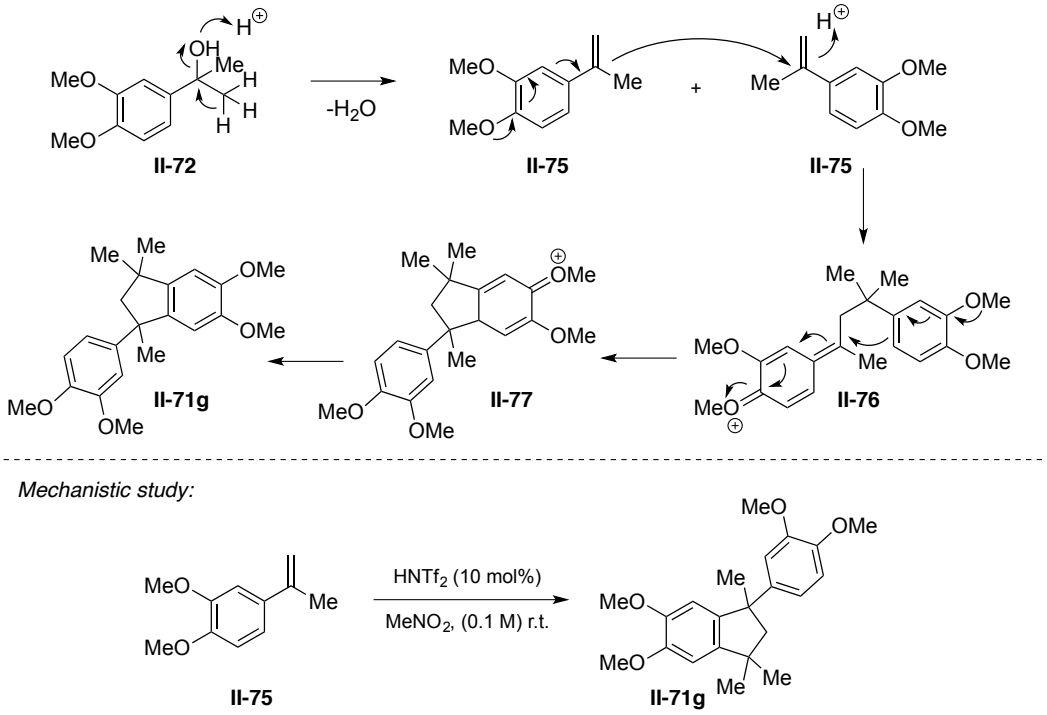
It was noteworthy that although **II-71g** was synthesized in mediocre yield, it can be otherwise accessed through a silane free method (Scheme 2.11). In the absence of the allylsilane, electron-rich benzhydryl alcohols with a quaternary center can undergo acid-promoted dimerization to yield indane products rather efficiently. Complicated fused ring structure **II-74** can also be generated.

Scheme 2.11 Silane-free synthesis of indanes



According to our proposed mechanism of this intriguing transformation, an olefin species **II-75** was generated upon ionization of alcohol **II-72**. Olefin **II-75** then dimerized under acidic conditions and underwent Friedel–Crafts arylation to generate the dimeric indane **II-71g** (Scheme 2.12). In order to prove the feasibility of the proposed mechanism, a benzylic olefin species **II-75** was prepared. Upon treatment with $HNTf_2$, the olefin gave rise to the dimerization product with full conversion. This result confirmed olefin **II-75** as the reaction intermediate.

Scheme 2.12 Proposed mechanism for the formation of dimer indane

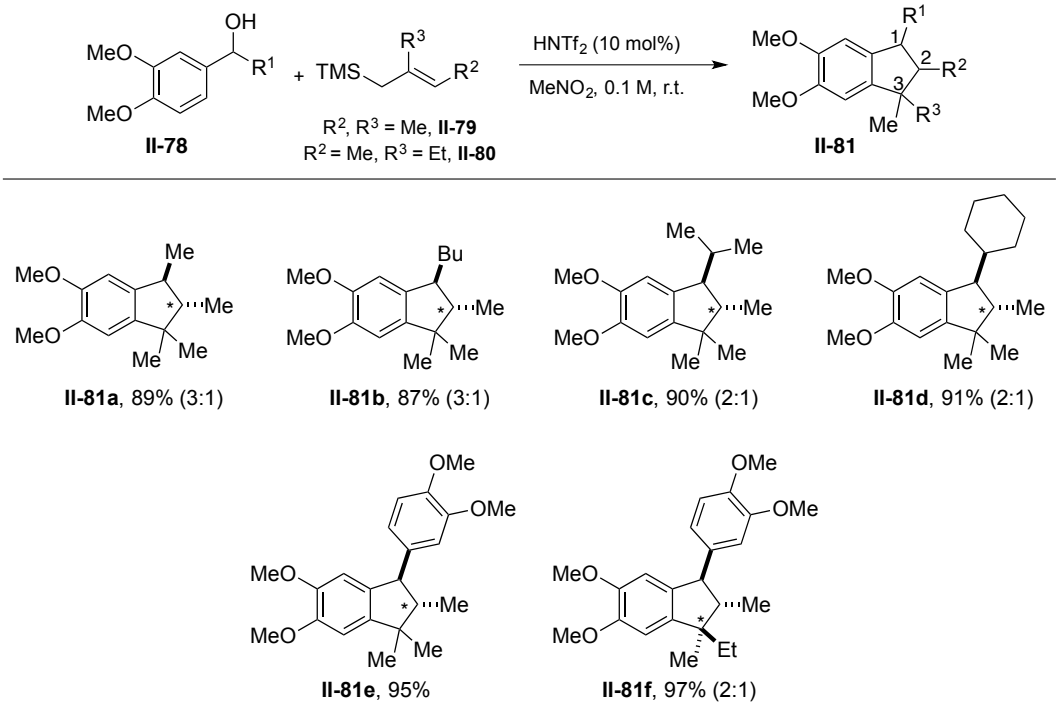


2.3.3 Synthesis of Indanes with Additional Substitution

In addition to the commercially available methallyltrimethyl silane, we also explored allylsilanes with additional substituents, which would generate indanes with substitution at the 2 position. These silane reagents have been well studied and applied to fragment coupling reactions by many research groups, including the Yamamoto group.[106] A previous graduate researcher, Dr. Jordan

Reddel, prepared allylsilane **II-79** and **II-80** and showed they can be used to smoothly afford indanes with two or more stereocenters (Table 2.9). She noticed that when a mixture of *syn* and *anti* diastereomers were formed (**II-81a**–**f**), the difference in A-values between the aryl and R^1 group affects the diastereoselectivity.

Table 2.9 Substrate scope for indanes with additional substitution



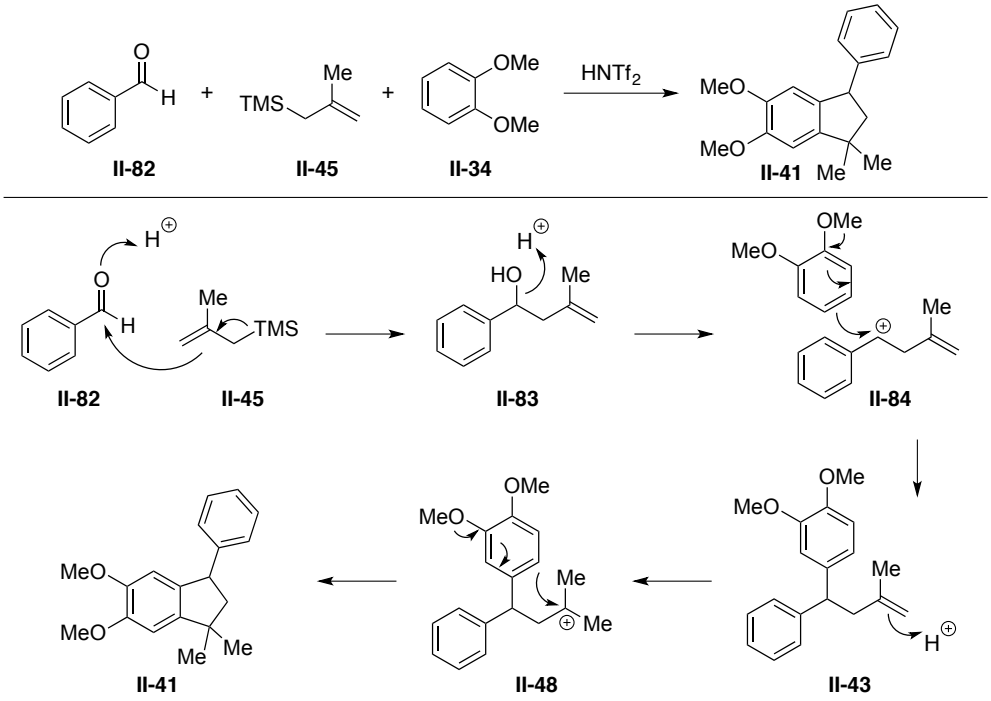
Only major diastereomers are shown

2.3.4 One-Pot synthesis of Indanes

Encouraged by the development of this methodology, we wondered if the synthesis of indanes can be rendered into a one pot process. Such a reaction would allow us to join three molecules, form three bonds, one ring and potentially three contiguous stereocenters in one step. My investigation commenced with the use of commercially available benzaldehyde, 1,2-dimethoxybenzene and methallyltrimethyl silane as starting materials. In the proposed mechanism, the reaction first

proceeds through a Brønsted acid-catalyzed addition of allylsilane into benzaldehyde. The resulting benzylic alcohol **II-83** would subsequently ionize under acidic conditions, trapping the electron-rich aryl ring, giving rise to the homoallylic intermediate **II-43**. A late-stage ionization of the olefin followed by an intramolecular Friedel–Crafts arylation would lead to the desired indane product as demonstrated previously (Scheme 2.13).

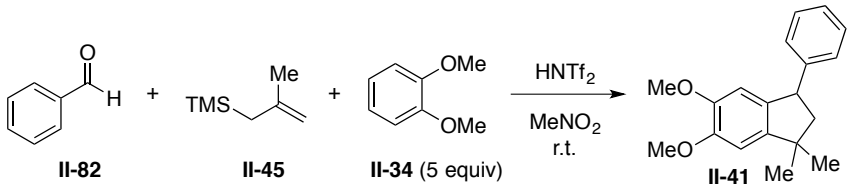
Scheme 2.13 Proposed mechanism for the one-pot synthesis of indanes



A variety of reaction conditions were screened. Nitromethane and $HNTf_2$ gave the highest yield again as they did in the benzhydrol approach. It was noticed that as more equivalents of the reagents were used, a higher yield was achieved. A slightly more concentrated solution also facilitated the intermolecular reaction. Eventually, two equivalents of the allylsilane and 20 mol% catalyst loading were selected as the standard conditions (Table 2.10, Entry 7), in an attempt to maintain atom efficiency. The best yield obtained (61%) was not as great as our previous results

from the two-component coupling indane methodology. We hypothesized that the low yield was partially due to an inefficient allylation step, since the reaction gave only trace amount of product **II-83** when it was ran individually in $MeNO_2$.

Table 2.10 Reaction condition screen for one-pot synthesis of indane

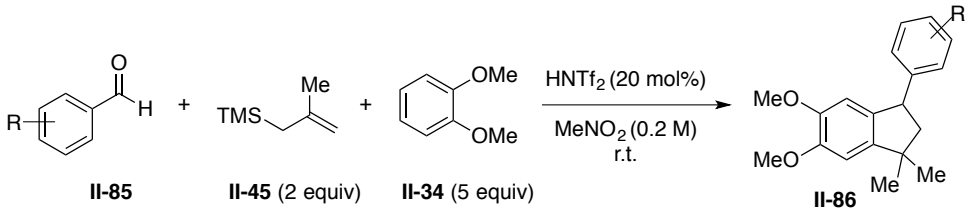


II-82 **II-45** **II-34** (5 equiv) **II-41**

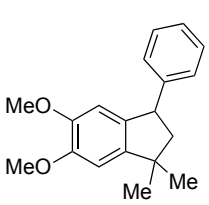
Entry	Silane Equiv.	Catalyst Loading	Conc.	Yield %
1	1.5	10 mol%	0.1 M	30
2	1.5	10 mol%	0.2 M	44
3	1.5	15 mol%	0.2 M	49
4	1.5	20 mol%	0.1 M	32
5	1.5	20 mol%	0.2 M	52
6	1.5	20 mol%	0.5 M	49
7	2	20 mol%	0.2 M	61

The optimized reaction conditions were applied to some of the selected substrates. Preliminary data proved that indanes could be successfully synthesized in a one-pot fashion. The system tolerates electron-neutral, electron-rich and electron-poor aryl substituents. Two regioisomers were again observed for the double-electron-rich ring systems, as we had expected (Table 2.11). We wish to further optimize this one-pot system in the future. It represents a powerful method to build structural complexity from simple building blocks, and can be potentially applied to the syntheses of natural products and bioactive compounds.

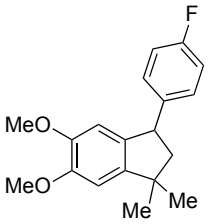
Table 2.11 Substrate table for one-pot synthesis of indanes



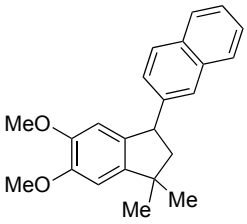
II-85 **II-45** (2 equiv) **II-34** (5 equiv) **II-86**



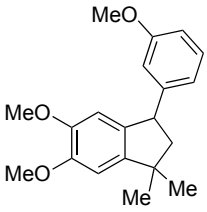
II-55d, 45%



II-57b, 44%



II-57n, 52% [a]



II-57l, 44% [a]

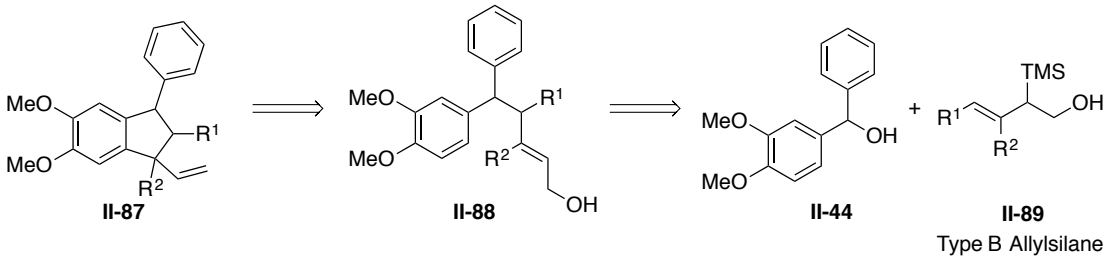
[a] Only the major regioisomer was shown

2.4 Development and Application of Type-B Allylsilanes

So far methallyltrimethyl silane and its derivatives have been explored, which yield indane products with a gem-dialkyl group. We decided to label them as Type A allylsilanes. However, we hoped to expand our substrate scope by utilizing differently substituted allylsilanes, which would allow us to introduce more structural variance and render our methodology more practical.

We envisioned that the cyclization of the new substrates would proceed through a S_N2' type displacement instead of a tertiary carbocation, therefore indanes without a quaternary center could be generated. According to our retrosynthetic analysis, allylic alcohol **II-88** would ionize under acidic conditions, followed by cyclization to generate indane **II-87** with an exocyclic olefin. Synthesis of the key intermediate **II-88** can be realized through fragment coupling between the previously reported benzhydryl alcohol **II-44** and allylsilane **II-89**, which we referred to as Type B allylsilanes (Scheme 2.14).

Scheme 2.14 Retrosynthetic analysis with Type B allylsilanes

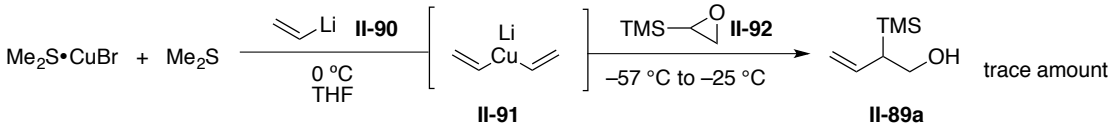


2.4.1 Synthesis of Type B Allylsilanes

A few syntheses of allylsilanes with a similar substitution pattern have been reported in the literature,[107-110] but synthetic methods for our desired Type B allylsilanes were much less well developed. We sought to devise a facile and general protocol to access these reagents through epoxide opening.

According to some previously reported examples of regioselective addition of epoxides, cuprate reagents give rise to the most promising results.[111-113] The initial attempt was to generate vinyl cuprate **II-91** through addition of vinyl lithium to copper bromide facilitated by dimethyl sulfide ligand.[112] The cuprate reagent formed *in situ* would readily open epoxide **II-92** in a regioselective fashion, affording Type B allylsilane **II-89a** (Scheme 2.15).

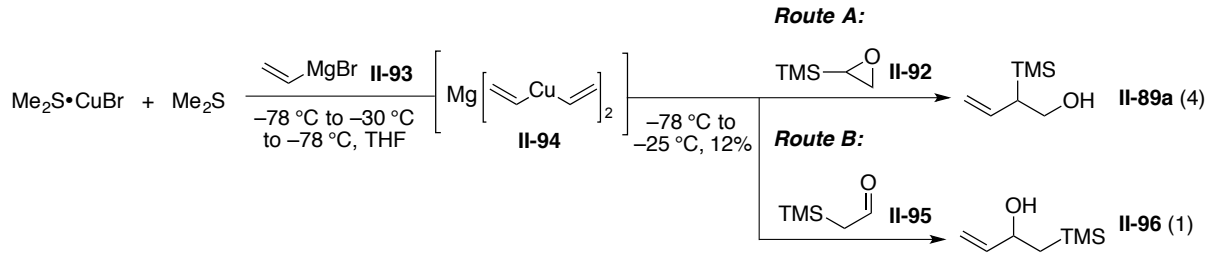
Scheme 2.15 Initial attempt using vinyl lithium reagents



The vinyl lithium route, however, was less than satisfactory since only trace amount of product was obtained after reaction optimization. This protocol was also not ideal for large scale synthesis because hazardous *t*-BuLi was required to prepare the vinyl lithium reagent.[114]

We then turned our attention to Grignard reagents, which are more easily prepared and suitable for scaling-up. Freshly made vinyl magnesium bromide **II-93** was subjected to copper bromide at low temperature to afford cuprate **II-94** *in situ*,[115] which subsequently underwent epoxide opening in one pot (Scheme 2.16, Route A).

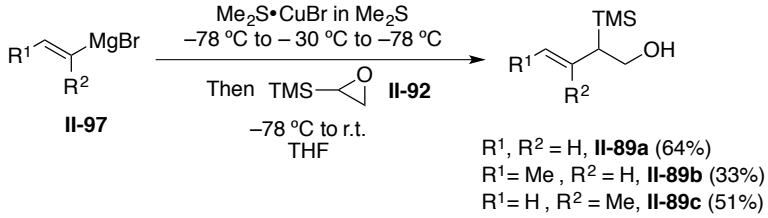
Scheme 2.16 Preliminary results using Grignard reagents



Unfortunately, a mixture of regioisomers were obtained with our desired isomer being the major product (**II-89a**). We hypothesized that the formation of byproduct **II-96** may have arisen from rearrangement of epoxysilane **II-92** to aldehyde **II-95**, followed by 1,2-addition of the vinyl cuprate (Scheme 2.16, Route B).

After screening a variety of conditions, it was found that rapidly warming the reaction to room temperature at the final stage, instead of slowly warming to –25 ºC, gave our desired allylsilane **II-89a** as a single regioisomer in 64% yield. One possible explanation for this seemingly counterintuitive phenomenon is that route A proceeded at a much faster rate under room temperature than route B did. Predominant formation of allylsilane **II-89a** was therefore achieved under kinetic control. Applying this method to two more vinyl Grignard substrates allowed us to access a total of three differently substituted Type B allylsilanes as single regioisomer (Scheme 2.17).

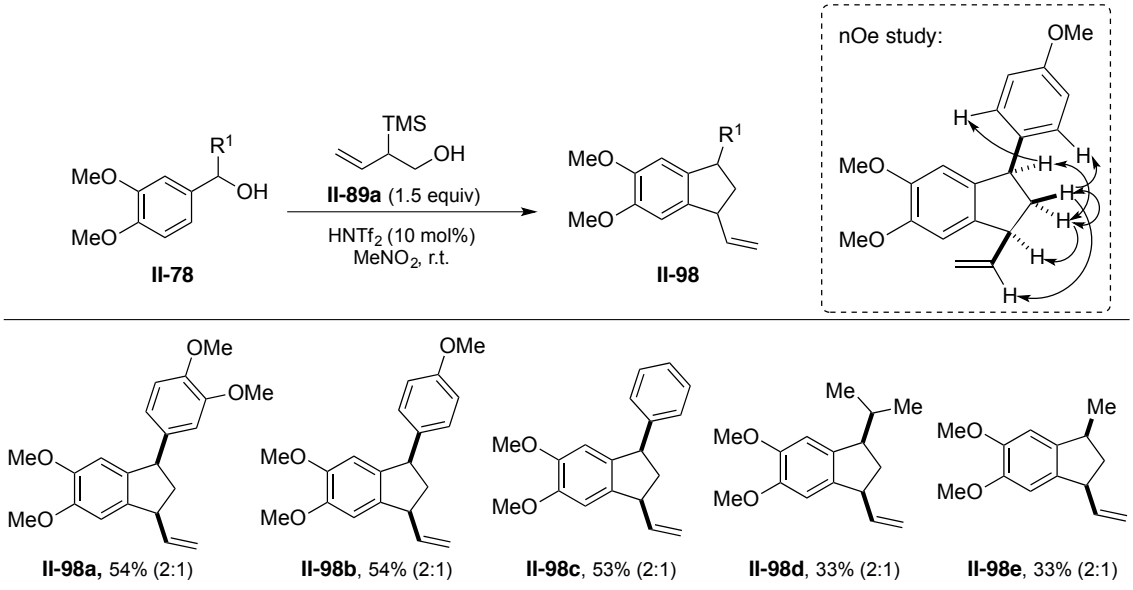
Scheme 2.17 Synthesis of Type B allylsilanes



2.4.2 Indane Substrate Scope with Type B Allylsilanes

With the new silane reagents in hand, we applied them to our indane methodology. We first explored the substrate scope using the most simplified Type B allylsilane **II-89a**. Highest yields were achieved when electron-rich benzhydrol starting materials were used (Table 2.11, **II-98a–c**). A mix of diastereomers were isolated in all cases with the major products being the *syn*-isomers, which was determined through nOe studies.

Table 2.12 Synthesis of indanes using simplified Type B allylsilane



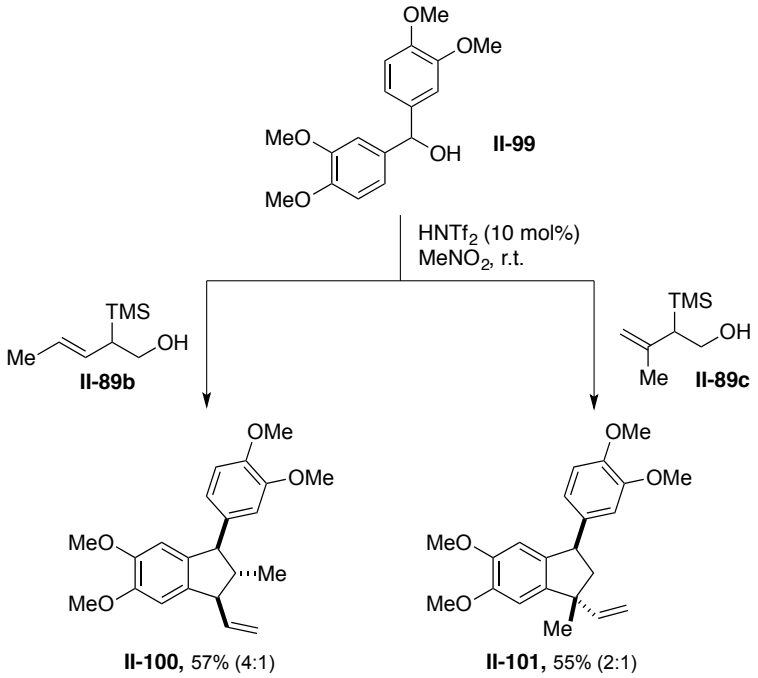
Only major diastereomers were shown

This stereochemical outcome might be due to the preferred pseudoequatorial position taken by the substituents during the cyclization transition state. Yields were not as high as our previous

examples with Type A allylsilane, possibly due to the less efficient S_N2' cyclization pathway since unreacted homoallylic benzhydryl intermediates were observed. Future optimization might involve exploration of harsher reaction conditions and better leaving groups.

Similarly, with an extra methyl substituent on the allylsilane, **II-89b** and **II-89c** reacted promptly with benzhydrols to afford indanes with up to three contiguous stereocenters. Electron-rich symmetrical benzhydrol **II-99** gave the highest yields (Scheme 2.18). We were able to achieve better stereoselectivity for **II-100** because of the increased steric strain on the indane backbone. Uncyclized intermediates, however, were again observed in both cases.

Scheme 2.18 Synthesis of indanes using Type B allylsilane **II-89b** and **II-89c**

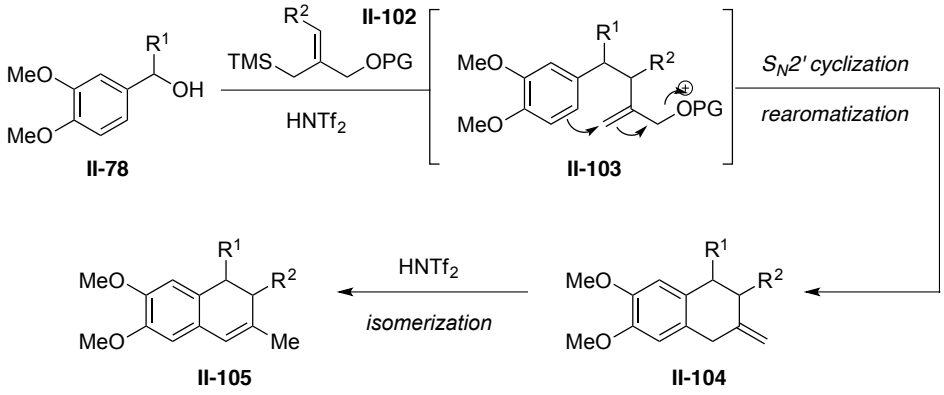


2.5 Synthesis of Tetralins Using Type C Allylsilanes

Encouraged by the development of Type B allylsilanes, we sought alternative silane reagents that would expand our substrate scope beyond the indane chemotype. Trost and coworkers previously synthesized a series of allylsilanes with a silyl ether leaving group and applied them to palladium-

catalyzed cycloaddition to generate carbocycles.[116, 117] We were particularly interested in these compounds, since the silyl ether functionality might serve as a suitable leaving group during fragment coupling to generate six-membered ring products. We labeled them Type C allylsilanes, which were anticipated to afford the homoallylic benzhydryl intermediate **II-103** upon coupling with the benzyl alcohol. The intermediate **II-103** would then undergo acid-catalyzed S_N2' displacement to afford tetralin **II-104** with an exocyclic olefin. We envisioned that an acid-catalyzed olefin isomerization would readily occur to generate the more stable, conjugated internal alkene **II-105** (Scheme 2.19).

Scheme 2.19 Formation of tetralin from Type C allylsilane

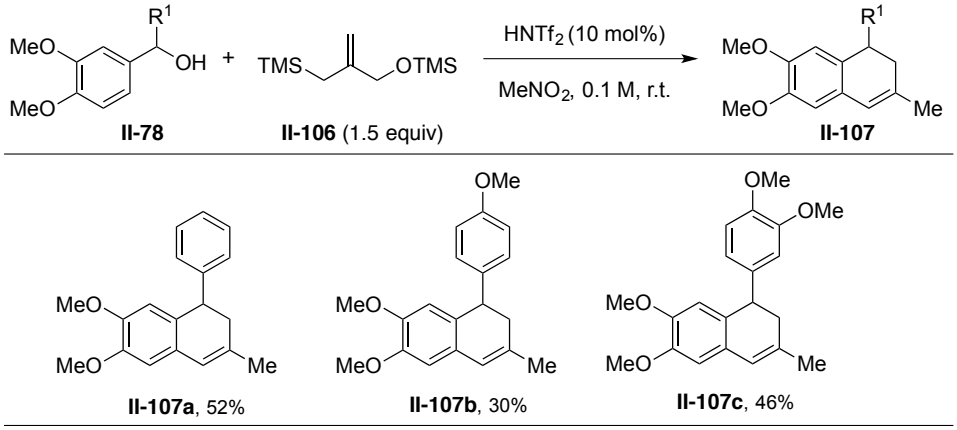


2.5.1 Preliminary Studies Using a Simple Type C Allylsilanes

Silane reagent **II-106** was prepared according to Trost's protocol and subjected to our standard reaction conditions. Tetralin products were obtained with electron-rich benzhydryol substrates (Table 2.13). The modest yields were primarily due to inefficient cyclization, since uncyclized reaction intermediates were observed, similar to what we saw with Type B allylsilanes. This limitation can be partially overcome by using higher catalyst loading, but efforts in reaction optimization to significantly improve yields proved to be fruitless. Substrates containing only

electron-neutral phenyl rings and/or alkyl chains, as well as heterocycles (e.g. benzofuran) failed to afford cyclization products.

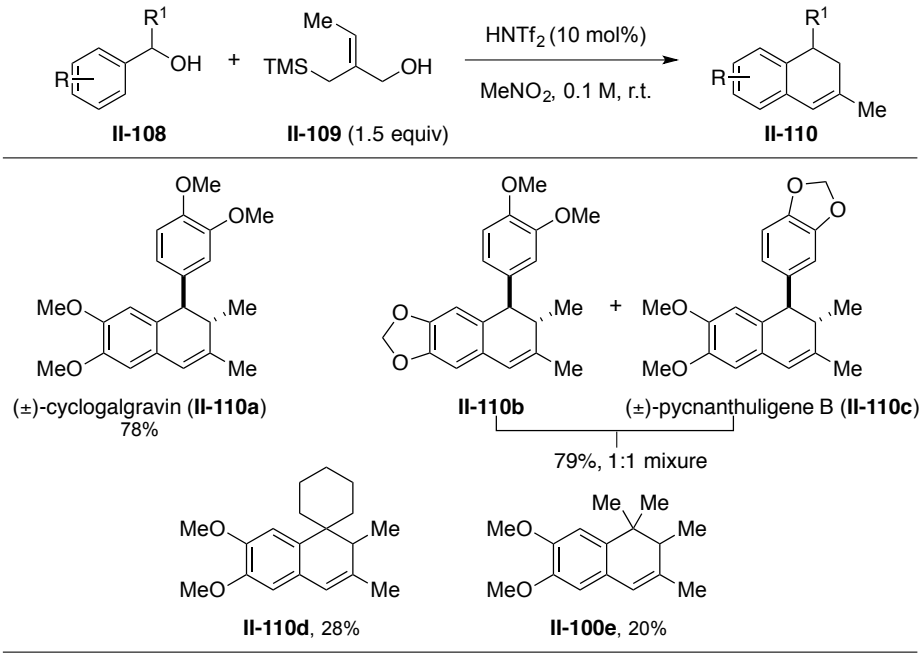
Table 2.13 Synthesis of tetralins with Type C allylsilane **II-106**



2.5.2 Synthesis of Lignan Natural Products

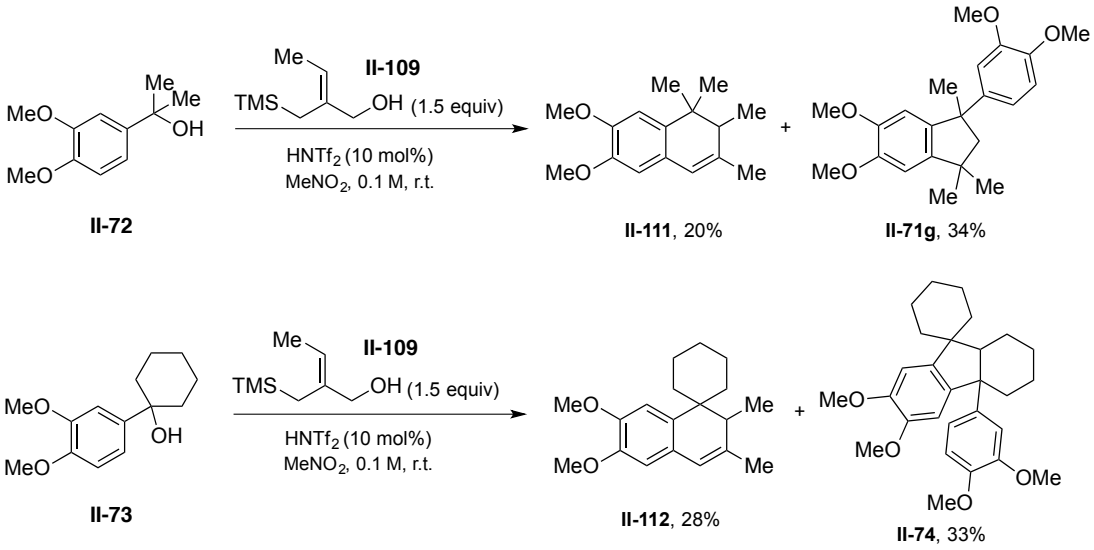
The preliminary results, however, showed great potential in applying this method to the synthesis of tetralins and tetralin-related natural products. The structure of **II-107c** closely resembles the lignan natural product cyclogalgravin, with the difference of a single methyl group. We envisioned a differently-substituted Type C allylsilane would allow us to access the natural product. We therefore turned our attention to allylsilane **II-109**, a known reagent synthesized by Trost and coworkers from a propargyl alcohol.[117] To our delight, subjecting it to our standard reaction conditions gave rise to cyclogalgravin (**II-110a**) in 78% yield. It represents a mild and highly-efficient three-step total synthesis (two step longest linear sequence) of the natural product. Pycnanthuligene B (**II-110c**) was also synthesized in a similar fashion, isolated as an inseparable 1:1 mixture of cyclization regioisomers. A preferred *anti* geometry was observed in both cases, as we had seen previously with Type A allylsilanes (Table 2.9). Benzhydryol substrates with alkyl substituents afforded tetralin products with lower yields (Table 2.14).

Table 2.14 Synthesis of tetralins and lignan natural products



As we were examining the mass balance of these reactions, two types of byproducts were observed, which would explain the low-efficiency of these transformation (Scheme 2.20).

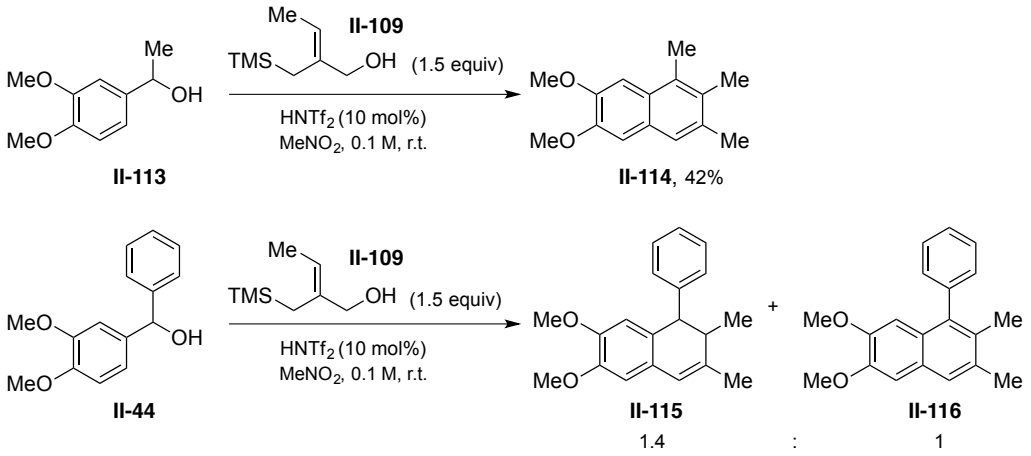
Scheme 2.20 Formation of dimerization byproducts



The acid-catalyzed dimerization side reaction afforded indanes in roughly 1:1 ratio to our desired tetralins, similar to what we had observed with Type A allysilanes (Scheme 2.11). The undesired products were extremely difficult to suppress for electron-rich benzhydrols containing a quaternary center.

On the other hand, unanticipated oxidation occurred during almost all of the reactions, giving rise to fully-conjugated naphthalene byproducts (Scheme 2.21). In some of the cases, naphthalene was even isolated as the major product (**II-114**). Optimizing reaction conditions, such as degassing the solvent and using air-tight vessels, did not suppress the side reaction.

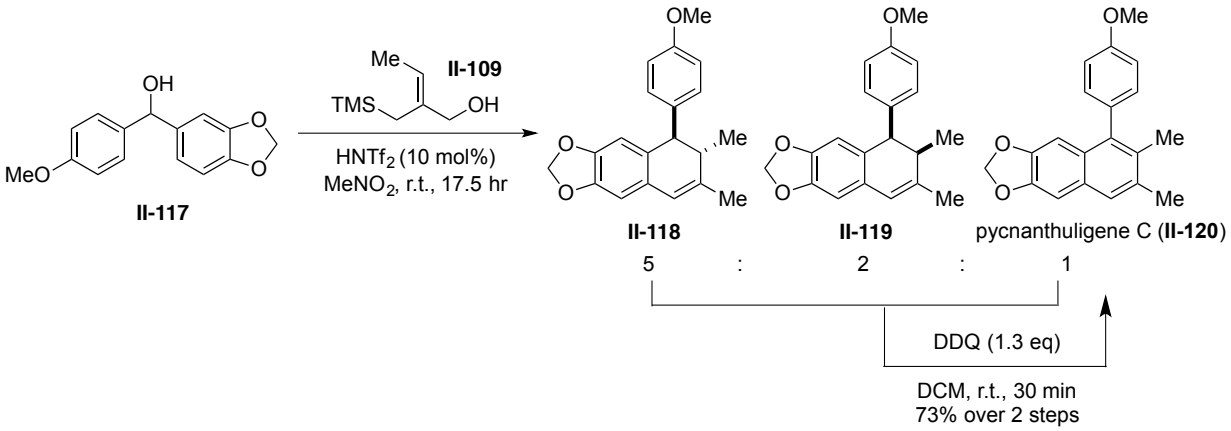
Scheme 2.21 Formation of oxidation byproducts



2.5.3 Oxidation Byproducts and Naphthalene-Type Lignans

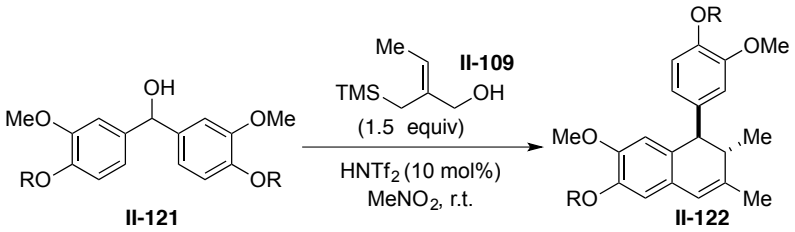
Despite the limitation of byproducts, we saw the oxidation side reaction as an opportunity to further expand our substrate scope and access naphthalene-type natural products. When benzhydrol **II-117** underwent fragment coupling with Type C allylsilane, pycnanthuligene C (**II-120**) was originally obtained as a minor oxidation byproduct in addition to the tetralins. Treating the reaction mixture with DDQ yielded the natural product in 73% yield over two steps (Scheme 2.22).

Scheme 2.22 Synthesis of pycnanthuligene C



Inspired by this result, we next targeted free alcohol-containing naphthalene lignans, such as cinnamophilin A and sacidumlignan A. The corresponding benzhydrol substrates bearing a free alcohol substituent, however, failed to undergo fragment coupling with only starting materials recovered (Table 2.15, Entry 1). We hypothesized that the phenol may have been protonated by triflimide, consuming the acid catalyst before the desired transformation could occur. Various phenol protecting groups were therefore screened with benzhydrol **II-121** (Table 2.15).

Table 2.15 Examination of phenol protecting groups

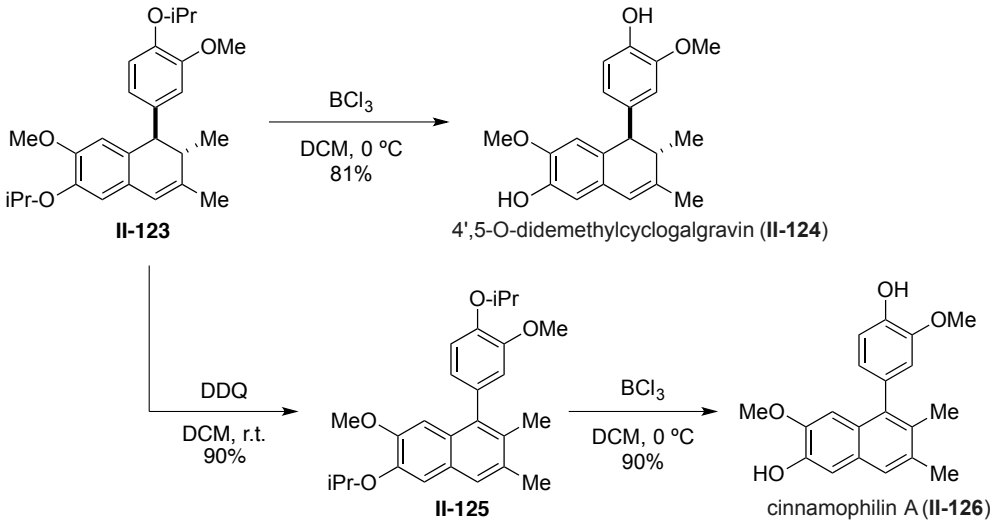


Entry	R (Protecting Group)	Result
1	H	No rxn
2	Bn	No rxn
3	Piv	No rxn
4	TIPS	Mono deprotection
5	*i*Pr	49%

Unfortunately, both benzyl- and pivaloyl-protected benzhydrols failed to give the desired tetralin product (Table 2.15, Entry 2–3), while the TIPS-protected substrate only yielded the mono-deprotected benzhydrol **II-121** (Table 2.15, Entry 4). However, the isopropyl protecting group allowed for successful formation of tetralin **II-122** in 49% yield (Table 2.15, Entry 5). The yield was compromised possibly due to ionization of the isopropyl ether under acidic conditions, which might have also happened with the benzyl-protected substrate.

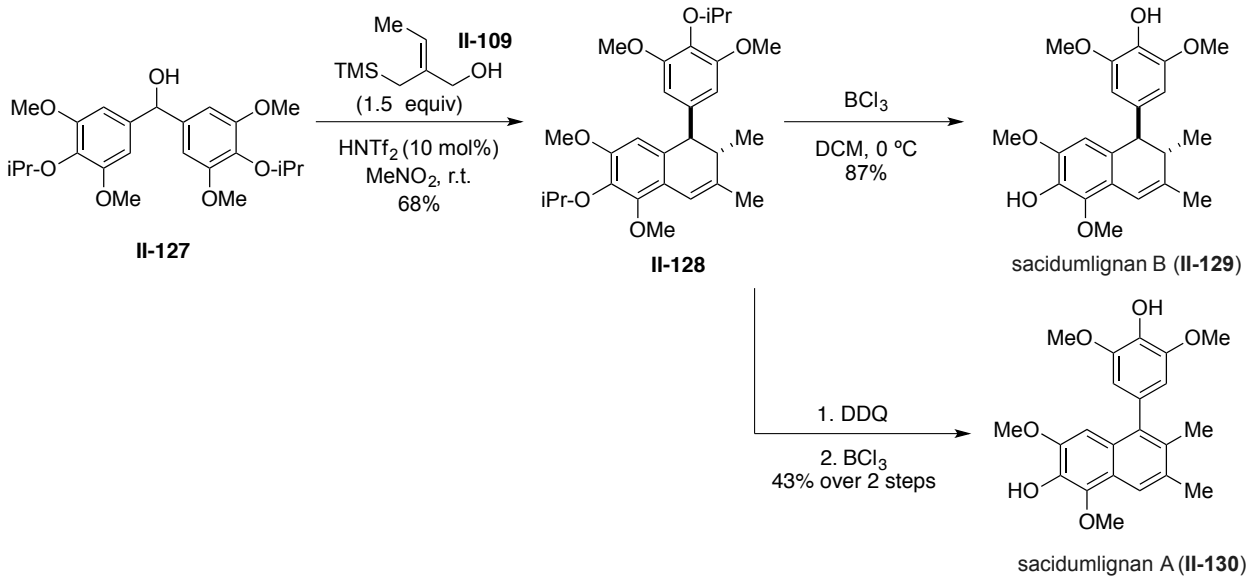
With the isopropyl-protected tetralin intermediate **II-123** in hand, we sought proper deprotection conditions to unveil the phenol in the presence of methyl ethers. Initial attempts with $AlCl_3$ only led to decomposition. After literature search, we discovered that treatment with BCl_3 selectively cleaved the isopropyl group while leaving the methyl ethers intact.[118] Thus, synthesis of the natural product 4',5-O-didemethylcyclogalgravin (**II-124**) was achieved in 81% yield. On the other hand, subjecting **II-123** to DDQ oxidation conditions led to isopropyl-protected naphthalene intermediate **II-125**, which afforded cinnamophilin A (**II-126**) after BCl_3 promoted deprotection (Scheme 2.23).

Scheme 2.23 Synthesis of 4',5-O-didemethylcyclogalgravin and cinnamophilin A



Following the same cyclization-(oxidation)-deprotection sequence, highly-substituted natural products sacidumlignan B and sacidumlignan A were synthesized with satisfying yields (Scheme 2.24).

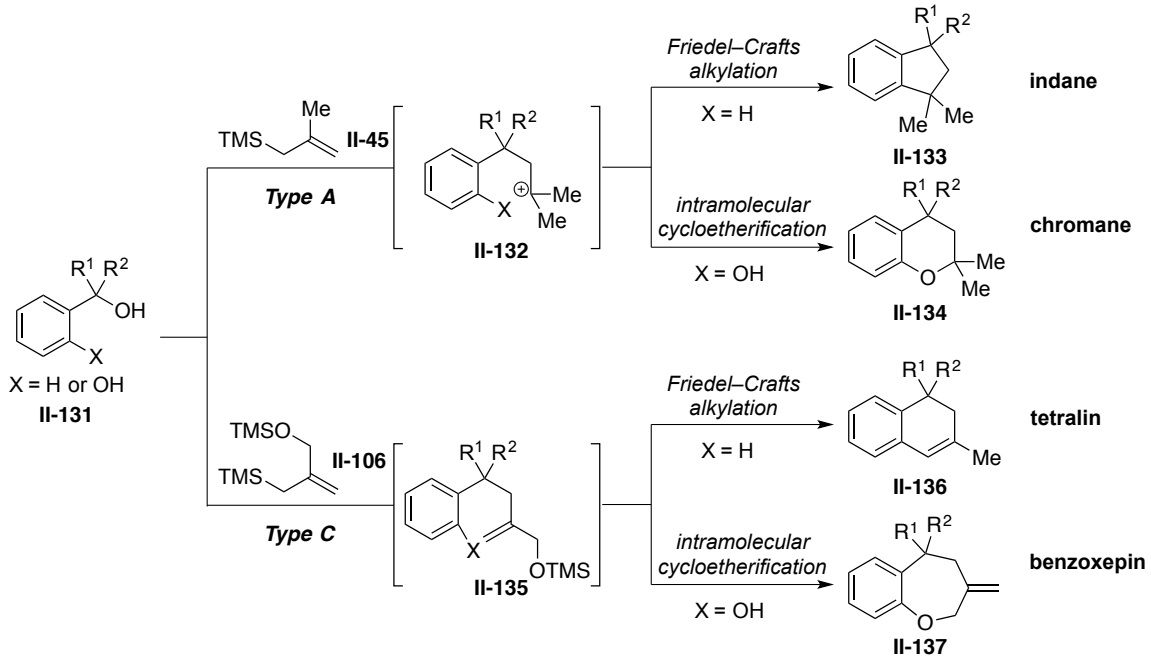
Scheme 2.24 Synthesis of sacidumlignan B and sacidumlignan A



2.5.4 Potential Application to the Synthesis of Heterocycles

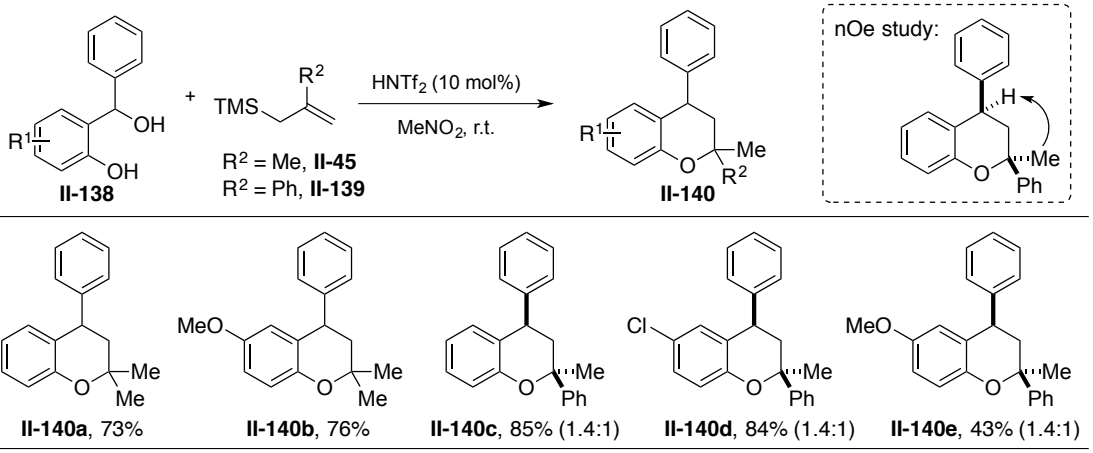
We saw potential in applying this methodology to the synthesis of heterocycles such as chromanes and benzoxepins (Scheme 2.25). Benzhydrols with an *ortho*-alcohol substituent (**II-131**) would undergo fragment coupling with Type A allylsilanes to afford intermediate **II-132**, which yields chromane **II-134** through intramolecular cycloetherification. Similarly, fragment coupling with Type C allylsilanes would give rise to benzoxepin **II-137** through an S_N2' pathway. Their H-substituted counterparts generated indanes and tetralins smoothly as reported in the previous sections.

Scheme 2.25 Expansion of methodology to access heterocycles



Our preliminary results suggested that heterocycles can be indeed synthesized in this fashion. Chromane compounds with a gem-dialkyl group were synthesized in modest to good yields using Type A allylsilanes (Table 2.16).

Table 2.16 Preliminary results of chromane synthesis



Only major diastereomers are shown

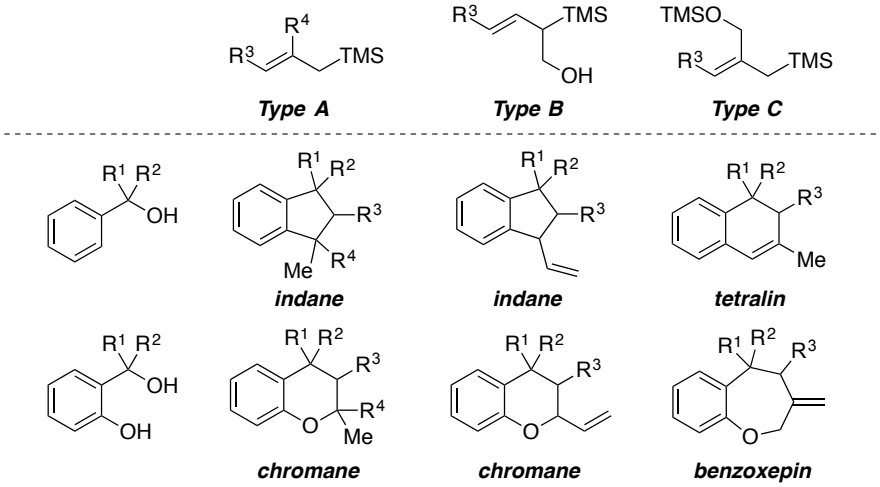
The methodology tolerates electron-rich and electron-poor aryl substituents. A mixture of inseparable diastereomers was obtained when phenyl-substituted allylsilane **II-139** was used. The *syn* isomer was preferred according to nOe studies, similar to the selectivity we observed with Type B allylsilanes (Section 2.4.2). Benzhydryl alcohol starting materials containing a quaternary center failed to give the desired chromane, only elimination of the benzylic alcohol was observed. Type B allylsilanes were also subjected to the same starting materials (**II-138**). However, significant difficulty was met during cyclization with a large amount of uncyclized reaction intermediates recovered. Poor leaving group and steric strain during cyclization might be the main causes of the inefficiency.

Future studies involve optimization of reaction conditions, such as investigating better leaving groups and exploring the substrate scope. We also see potential for enantioselective chromane synthesis through chiral counterion catalysis using chiral Brønsted acid catalysts.[119, 120] In addition to the chromane chemotype, we envisioned benzoxepins can be formed using Type C allylsilanes. expanding our methodology to the synthesis of medium-sized rings.

2.5.5 Summary and Outlook

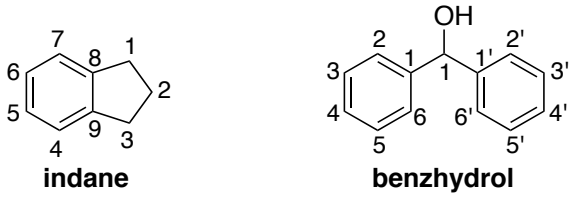
In summary, a highly efficient allylsilane fragment coupling methodology was developed. The mild reaction conditions allow for facile synthesis of various cyclic compounds, such as indanes and tetralins (Figure 2.3). A wide range of substituents can be tolerated, leading to excellent substrate diversity. The synthetic utility of this method was demonstrated through the total synthesis of seven lignan natural products and successful formation of chromanes.

Figure 2.3 Application of the allylsilane fragment coupling methodology



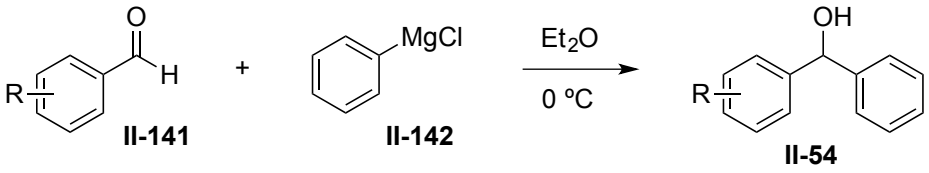
2.6 Experimental Section

Figure 2.4 Indane and benzhydrol numbering systems



2.6.1 Indane Starting Material Experimental Procedure and Characterization Data

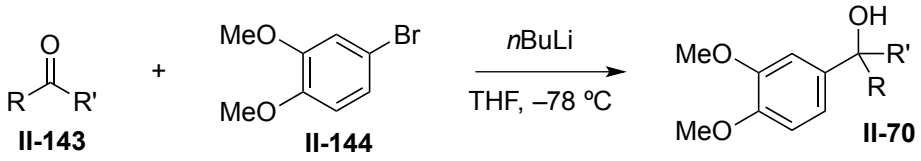
Scheme 2.26 General method A for synthesis of starting materials through a Grignard reaction



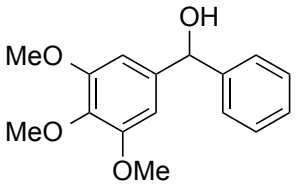
General Method A: Aryl aldehyde **II-141** (1 equiv) was dissolved in dry Et_2O (0.33 M soln), cooled to 0 ºC and allowed to stir under N_2 atmosphere. Phenylmagnesium chloride (1.8 equiv) was then added dropwise to the stirred solution. The reaction mixture was allowed to stir at 0 ºC until all starting material was consumed as determined by TLC. The reaction was quenched with

sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with EtOAc in hexanes solvent systems.

Scheme 2.27 General method B for synthesis of starting materials through a lithium-halogen exchange reaction

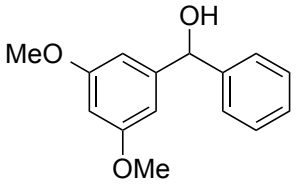


General Method B: 4-Bromoveratrol (1.6 equiv) was dissolved in dry THF (0.33 M soln) and cooled to –78 ºC. A solution of *n*BuLi in hexanes (1.5 equiv) was added dropwise and the solution was allowed to stir at –78 ºC under N_2 atmosphere for two hours. Aryl aldehyde or ketone **II-143** (1 equiv) was dissolved in dry THF (1 mL/ mmol **II-143**) and added dropwise via cannula to the stirred solution (1 mL/ mmol **II-143** rinse). The solution was allowed to come to room temperature and stir for 1 hour. At this time, all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with EtOAc in hexanes solvent systems.

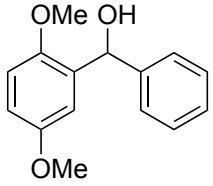


3,4,5-Trimethoxybenzhydrol (SII-55a): Synthesized from 3,4,5-trimethoxy benzaldehyde (4.74 mmol) via General Method A (1.15 g, 88% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.24 (m, 5H), 6.61 (s,

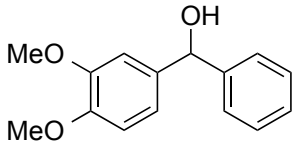
2H), 5.78 (d, *J* = 3.1 Hz, 1H), 3.83 (s, 9H), 2.27 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 143.7, 139.6, 137.4, 128.7, 127.9, 126.6, 103.6, 76.5, 61.0, 56.2. All spectroscopic data for this compound agrees with previously reported values.[121, 122]



3,5-Dimethoxybenzhydrol (SII-55b): Synthesized from 3,5-dimethoxy benzaldehyde (1.84 mmol) via General Method A (440 mg, 98% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.79 (d, *J* = 3.5 Hz, 1H), 3.79 (s, 6H), 2.25 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 146.4, 143.6, 128.7, 127.8, 126.7, 104.7, 99.6, 76.4, 55.5. All spectroscopic data for this compound agrees with previously reported values.[123]

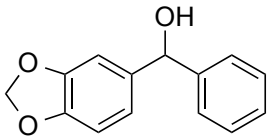


2,5-Dimethoxybenzhydrol (SII-55c): Synthesized from 2,5-dimethoxybenzaldehyde (5.06 mmol) via General Method A (1.2 g, 97% yield): IR (Germanium ATR): 3418, 2934, 1591, 1492, 1213, 1038, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H), 6.83 (d, *J* = 3.0 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.04 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 151.1, 143.2, 133.2, 128.3, 127.4, 126.6, 114.2, 112.9, 112.0, 72.4, 56.1, 55.8; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}O_3$ $[M+Na]^+$, 267.0992. Found 267.1000.

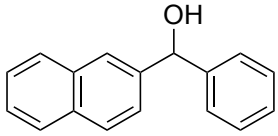


3,4-Dimethoxybenzhydrol (II-44): Synthesized from veratraldehyde (5.11 mmol) via General Method A (1.2 g, 99% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 5H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.81 (d, *J* = 3.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.18 (d, *J* = 3.5 Hz, 1H);

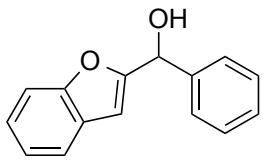
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.6, 144.0, 136.7, 128.6, 127.7, 126.6, 119.1, 111.1, 109.9, 76.2, 56.1, 56.0. All spectroscopic data for this compound agrees with previously reported values.[124]



3,4-Methylenedioxybenzhydrol (SII-55e): Synthesized from piperonal (2.18 mmol) via General Method A (497 mg, 99% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 6.91 – 6.85 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.95 (q, *J* = 1.4 Hz, 2H), 5.79 (d, *J* = 3.4 Hz, 1H), 2.20 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 147.2, 143.9, 138.1, 128.6, 127.7, 126.5, 120.2, 108.2, 107.3, 101.2, 76.2. All spectroscopic data for this compound agrees with previously reported values.

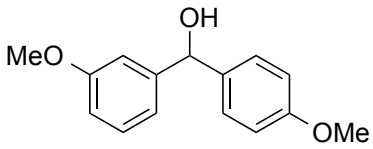


2-Naphthyl(phenyl)methanol (SII-55f): Synthesized from 2-naphthaldehyde (4.95 mmol) via General Method A (1.2 g, 99% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.87 – 7.78 (m, 3H), 7.51 – 7.45 (m, 2H), 7.45 – 7.40 (m, 3H), 7.38 – 7.32 (m, 2H), 7.31 – 7.26 (m, 1H), 6.01 (d, *J* = 3.5 Hz, 1H), 2.32 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 141.3, 133.4, 133.0, 128.7, 128.5, 128.2, 127.8, 127.8, 126.9, 126.3, 126.1, 125.2, 124.9, 76.5. All spectroscopic data for this compound agrees with previously reported values.[125]

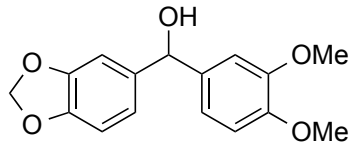


2-(1-Hydroxyphenylmethyl)benzofuran (SII-55g): Synthesized from 2-benzofurancarboxaldehyde (4.0 mmol) via General Method A (870 mg, 97% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 3H), 7.45 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.26 (td, *J* = 7.7, 1.4 Hz, 1H), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H), 6.53 (s, 1H), 5.96 (d, *J* = 4.5 Hz, 1H), 2.49 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 158.6, 155.2, 140.4, 128.8, 128.6, 128.2, 126.9, 124.5, 123.0, 121.3, 111.5, 104.2, 70.9. All spectroscopic data for this compound agrees with previously reported values.[125]

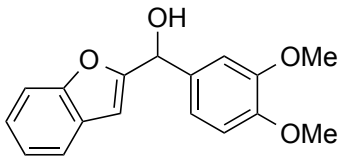


3,4'-Dimethoxybenzhydrol (II-66): 4-bromoanisole (8 mmol) was dissolved in dry THF (15 mL) and cooled to –78 ºC. A solution of *n*BuLi in hexanes (7.5 mmol) was added dropwise and the solution was allowed to stir at –78 ºC under N_2 atmosphere for two hours. 3-anisaldehyde (5 mmol) was dissolved in dry THF (5 mL) and added dropwise via cannula to the stirred solution (5 mL rinse). The solution was allowed to come to room temperature and stir for 1 hour. At this time, all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (1.2 g, 98% yield): melting point: 33.5–35.8 ºC; IR (Germanium ATR): 3415, 3001, 2835, 1609, 1510, 1244, 1029, 833, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 3H), 6.98 – 6.91 (m, 2H), 6.89 – 6.84 (m, 2H), 6.80 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 5.77 (d, J = 3.5 Hz, 1H), 3.79 (s, 6H), 2.17 (d, J = 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 159.2, 145.8, 136.2, 129.6, 128.0, 118.9, 114.0, 113.0, 112.1, 75.9, 55.4, 55.4; HRMS (ESI): Exact mass calcd for $C_{15}H_{16}O_3$ $[M+Na]^+$, 267.0992. Found 267.0998.

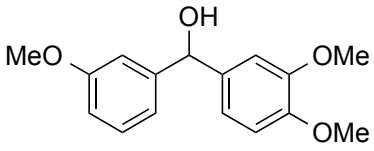


3,4-Methylenedioxy-3',4'-dimethoxybenzhydrol (SII-57h): Synthesized from piperonal (1.0 mmol) via General Method B (242 mg, 84% yield): melting point: 101.5–103.5 ºC; IR (Germanium ATR): 3338, 2992, 2837, 1594, 1505, 1235, 1140, 1021, 874, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 1.8 Hz, 1H), 6.88 (dd, J = 8.3, 1.8 Hz, 2H), 6.86 – 6.84 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.4 Hz,

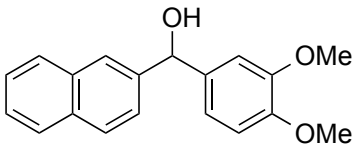
1H), 5.94 (s, 2H), 5.72 (d, J = 3.3 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 2.14 (d, J = 3.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.6, 147.9, 147.1, 138.2, 136.6, 120.0, 118.8, 111.1, 109.7, 108.2, 107.3, 101.2, 75.9, 56.1, 56.0; HRMS (ESI): Exact mass calcd for $C_{16}H_{16}O_5$ $[M+Na]^+$, 311.0890. Found 311.0899.



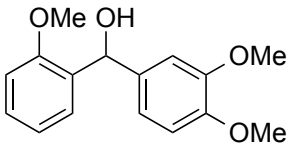
Benzo[b]furan-2-yl-(3,4-dimethoxyphenyl)carbinol (SII-57j): Synthesized from 2-benzofurancarboxaldehyde (2.0 mmol) via General Method B (475 mg, 83% yield): IR (Germanium ATR): 3453, 3002, 2836, 1512, 1453, 1254, 1136, 1024, 809, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.26 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.21 (ddd, J = 7.5, 7.2, 0.9 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.01 (ddd, J = 8.3, 2.0, 0.4 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.54 (t, J = 0.9 Hz, 1H), 5.91 (d, J = 4.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.51 (d, J = 4.3 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 155.2, 149.3, 149.3, 133.0, 128.2, 124.4, 123.0, 121.3, 119.4, 111.5, 111.1, 110.0, 104.0, 70.7, 56.1, 56.1; HRMS (ESI): Exact mass calcd for $C_{17}H_{16}O_4$ $[M+Na]^+$, 307.0941. Found 307.0951.



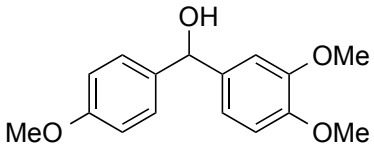
3,3',4-Trimethoxybenzhydrol (SII-57l): Synthesized from 3-anisaldehyde (5.0 mmol) via General Method B (1.0 g, 74% yield): melting point: 113.5–115.2 ºC; IR (Germanium ATR): 3392, 3089, 2841, 1520, 1261, 1134, 1025, 798, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 6.98 – 6.92 (m, 3H), 6.89 (dd, J = 8.2, 2.0 Hz, 1H), 6.85 – 6.79 (m, 2H), 5.77 (d, J = 3.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 2.18 (d, J = 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 149.2, 148.7, 145.7, 136.5, 129.6, 119.1, 118.9, 113.0, 112.2, 111.1, 109.9, 76.1, 56.1, 56.0, 55.4; HRMS (ESI): Exact mass calcd for $C_{16}H_{18}O_4$ $[M+Na]^+$, 297.1097. Found 297.1107.



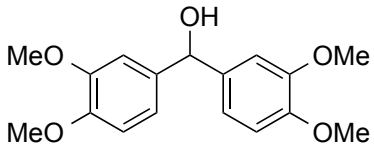
(3,4-Dimethoxyphenyl)(2-naphthyl)methanol (SII-57n): Synthesized from 2-naphthaldehyde (3.0 mmol) via General Method B (608 mg, 69% yield): melting point: 84.9–86.1 ºC; IR (Germanium ATR): 3334, 3053, 2837, 1591, 1511, 1232, 1135, 1021, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.87 – 7.81 (m, 2H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.43 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.93 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.95 (d, *J* = 3.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.36 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.7, 141.3, 136.5, 133.4, 133.0, 128.4, 128.2, 127.8, 126.3, 126.1, 125.0, 124.9, 119.3, 111.1, 110.0, 76.2, 56.0, 56.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{18}O_3$ $[M+Na]^+$, 317.1148. Found 317.1158.



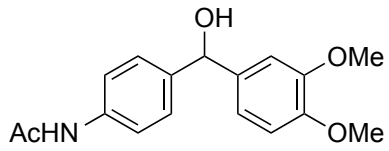
2,3',4'-Trimethoxybenzhydrol (SII-57f): Synthesized from 2-anisaldehyde (1.0 mmol) via General Method B (274 mg, 99% yield): melting point: 60.5–68.1 ºC; IR (Germanium ATR): 3198, 3009, 2835, 1504, 1243, 1153, 1020, 802, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (td, *J* = 8.2, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.02 (d, *J* = 5.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.02 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 148.9, 148.3, 135.9, 132.2, 128.9, 127.9, 121.0, 119.0, 110.9, 110.9, 110.1, 72.2, 56.0, 56.0, 55.6; HRMS (ESI): Exact mass calcd for $C_{16}H_{18}O_4$ $[M+H]^+$, 275.1278. Found 275.1285.



3,4,4'-Trimethoxybenzhydrol (SII-57g): Synthesized from 4-anisaldehyde (5.0 mmol) via General Method B (961 mg, 70% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.89 – 6.85 (m, 3H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.76 (d, *J* = 3.1 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 2.18 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.13, 149.13, 148.49, 136.87, 136.34, 127.91, 118.89, 113.96, 111.03, 109.77, 75.68, 56.05, 55.98, 55.41. All spectroscopic data for this compound agrees with previously reported values.[126]

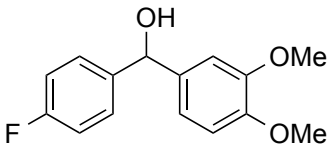


3,3',4,4'-Tetramethoxybenzhydrol (II-99): Synthesized from veratraldehyde (5.0 mmol) via General Method B (1.46 g, 96% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, *J* = 1.9 Hz, 2H), 6.88 (dd, *J* = 8.2, 1.9 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 5.75 (d, *J* = 3.5 Hz, 1H), 3.87 (s, 6H), 3.85 (s, 6H), 2.19 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.6, 136.7, 119.0, 111.0, 109.8, 75.9, 56.1, 56.0. All spectroscopic data for this compound agrees with previously reported values.[127]

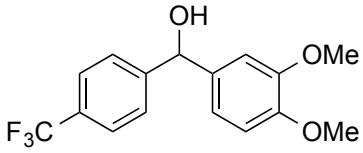


4-(*N*-Acetamide)-3',4'-dimethoxybenzhydrol (SII-57d): *N*-(4-bromophenyl)acetamide (8 mmol) was dissolved in dry THF (15 mL) and cooled to –78 ºC. A solution of *n*BuLi in hexanes (15 mmol) was added dropwise and the solution was allowed to stir at –78 ºC under N_2 atmosphere for 20 min. Veratraldehyde (5 mmol) was dissolved in dry THF (5 mL) and added dropwise via cannula to the stirred solution (5 mL rinse). The solution was allowed to come to room temperature and stir for 30 min. At this time, all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash

column chromatography on silica gel with a 30% to 50% EtOAc in hexanes gradient solvent system (393 mg, 27% yield): IR (Germanium ATR): 3333, 3197, 3066, 2959, 2935, 1602, 1512, 1232, 1137 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.20 (s, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 8.2, 2.0 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.77 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.22 (s, 1H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 149.2, 148.6, 140.0, 137.3, 136.6, 127.3, 120.0, 119.1, 111.1, 109.8, 75.7, 56.1, 56.0, 24.8; HRMS (ESI): Exact mass calcd for $C_{17}H_{19}NO_4$ $[M+H]^+$, 302.1387. Found 302.1399.

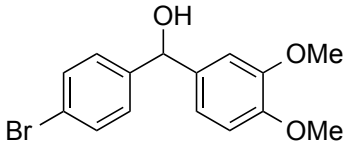


4-fluoro-3',4'-dimethoxybenzhydrol (SII-57b): Synthesized from 4-fluoro benzaldehyde (6.18 mmol) via General Method A (1.4 g, 86% yield): IR (Germanium ATR): 3464, 3005, 1603, 1507, 1464, 1419, 1260, 1223, 1138, 1030, 841, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.05 – 6.99 (m, 2H), 6.90 – 6.81 (m, 3H), 5.78 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.22 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 245.7 Hz), 149.3, 148.7, 139.7 (d, J = 3.1 Hz), 136.5, 128.2 (d, J = 8.0 Hz), 119.0, 115.4 (d, J = 21.4 Hz), 111.1, 109.8, 75.5, 56.1, 56.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{15}FO_3$ $[M+Na]^+$, 285.0884. Found 285.0899.

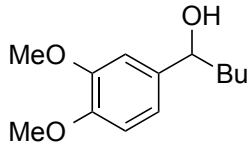


4-Trifluoromethyl-3',4'-dimethoxybenzhydrol (SII-57a): Synthesized from 4-trifluoromethylbenzaldehyde (5.0 mmol) via General Method A (1.0 g, 66% yield): melting point: 77.6–81.3 ºC; IR (Germanium ATR): 3549, 3187, 3003, 2842, 1517, 1328, 1103, 1068, 1016, 812 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 6.90 – 6.85 (m, 2H), 6.85 – 6.82 (m, 1H), 5.84 (d, J = 3.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.26 (d, J = 3.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ149.4, 149.0, 147.7, 136.0, 129.7 (q, J_{CF} = 32.3 Hz), 126.7 (2C), 125.5

(q, J_{CF} = 3.9 Hz, 2C), 124.3 (q, J_{CF} = 272.0 Hz), 119.3, 111.2, 109.8, 75.7, 56.1, 56.0; HRMS (ESI): Exact mass calcd for $C_{16}H_{15}F_3O_3$ $[M+Na]^+$, 335.0866. Found 335.0877.

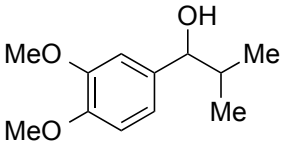


4-Bromo-3',4'-dimethoxybenzhydrol (SII-57c): Synthesized from 4-bromo benzaldehyde (5.0 mmol) via General Method A (1.0 g, 62% yield): IR (Germanium ATR): 3456, 3000, 2834, 1592, 1511, 1256, 1136, 1008, 800, 600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 6.90 – 6.86 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 5.77 (d, J = 3.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.22 (d, J = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 148.9, 142.9, 136.2, 131.6, 128.3, 121.5, 119.1, 111.1, 109.8, 75.6, 56.1, 56.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{15}BrO_3$ $[M+Na]^+$, 345.0097. Found 345.0107.

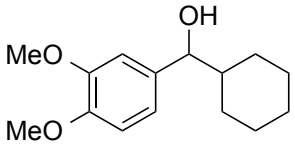


1-(3,4-Dimethoxyphenyl)pentan-1-ol (SII-71c): Veratraldehyde (3 mmol) was dissolved in dry Et_2O (6 mL) and cooled to –78 ºC under N_2 atmosphere. A solution of *n*BuLi in hexanes (3.0 mmol) was added dropwise. The solution was slowly allowed to warm to room temperature and stir for 12 hours. At this time, all starting material was consumed as determined by TLC and the solution was cooled to 0 ºC. The reaction was then quenched with sat. NH_4Cl solution and extracted with Et_2O (3 x 6 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (673 mg, 67% yield): IR (Germanium ATR): 3403, 3003, 2932, 1516, 1463, 1259, 1138, 1027, 808 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 1.9 Hz, 1H), 6.86 (dd, J = 8.2, 1.9 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 4.61 (dd, J = 7.4, 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.85 – 1.76 (m, 2H), 1.73 – 1.64 (m, 1H), 1.44 – 1.31 (m, 3H), 1.31 – 1.17 (m,

2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.5, 137.8, 118.3, 111.0, 109.1, 74.7, 56.1, 56.0, 38.9, 28.2, 22.8, 14.2; HRMS (ESI): Exact mass calcd for $C_{13}H_{20}O_3$ $[M+Na]^+$, 247.1305. Found 247.1315.

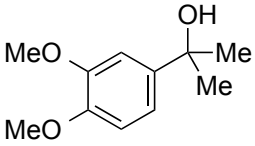


1-(3,4-Dimethoxyphenyl)-2-methyl-1-propanol (SII-71b): Veratraldehyde (2 mmol) was dissolved in dry Et_2O (9 mL), cooled to 0 ºC and allowed to stir under N_2 atmosphere. A solution of isopropylmagnesium chloride (3 mmol) was then added dropwise to the stirred solution. The reaction mixture was allowed to stir at 0 ºC for 30 min, at which point all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (383 mg, 91% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.83 (s, 2H), 4.29 (d, J = 7.2 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.00 – 1.87 (m, 1H), 1.78 (s, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.5, 136.5, 119.1, 110.8, 109.6, 80.2, 56.1, 56.0, 35.5, 19.2, 18.7. All spectroscopic data for this compound agrees with previously reported values.[128]

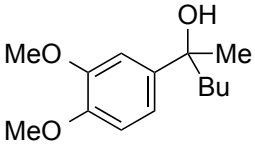


1-Cyclohexyl-1-(3,4-dimethoxyphenyl)methanol (SII-71a): Synthesized from cyclohexanecarboxaldehyde (1.0 mmol) via General Method B (186 mg, 74% yield): melting point: 91.7–93.2 ºC; IR (Germanium ATR): 3497, 3002, 2922, 2850, 1593, 1258, 1138, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, J = 1.4 Hz, 1H), 6.85 – 6.78 (m, 2H), 4.29 (d, J = 7.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.01 (dtd, J = 12.9, 4.5, 4.1, 2.3 Hz, 1H), 1.85 – 1.73 (m, 2H), 1.70 – 1.53 (m, 3H), 1.36 (ddq, J = 12.6, 3.8, 2.0 Hz, 1H),

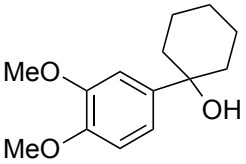
1.30 – 1.10 (m, 3H), 1.04 (tdd, *J* = 12.7, 11.3, 3.5 Hz, 1H), 0.90 (qd, *J* = 12.4, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.5, 136.5, 119.1, 110.8, 109.7, 79.5, 56.1, 56.0, 45.1, 29.5, 29.3, 26.6, 26.2, 26.2; HRMS (ESI): Exact mass calcd for $C_{15}H_{22}O_3$ $[M+Na]^+$, 273.1461. Found 273.1473.



3,4-Dimethoxy-(1'-hydroxy-1'-methylethyl)benzene (II-72): Synthesized from acetone (5.0 mmol) via General Method B (721 mg, 73% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.70 (s, 1H), 1.58 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.9, 142.1, 116.5, 110.9, 108.4, 72.5, 56.1, 56.0, 32.0. All spectroscopic data for this compound agrees with previously reported values.[129]

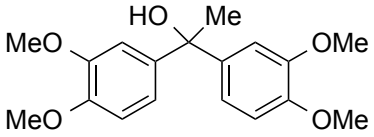


2-(3,4-Dimethoxyphenyl)haxan-2-ol (SII-71e): Synthesized from 2-hexanone (5.0 mmol) via General Method B (1.0 g, 85% yield): IR (Germanium ATR): 3499, 2933, 1591, 1509, 1463, 1255, 1140, 1026, 806 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 2.2 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.84 – 1.72 (m, 2H), 1.54 (s, 3H), 1.31 – 1.09 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 147.7, 141.1, 117.0, 110.8, 108.7, 74.7, 56.0, 56.0, 44.1, 30.2, 26.4, 23.2, 14.2; HRMS (ESI): Exact mass calcd for $C_{14}H_{22}O_3$ $[M+Na]^+$, 261.1461. Found 261.1474.



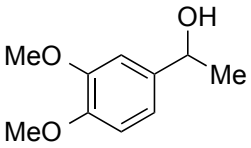
1-(3,4-Dimethoxyphenyl)cyclohexanol (II-73): Synthesized from cyclohexanone (5.0 mmol) via General Method B (1.2 g, 85% yield): melting point: 92.1–94.0 ºC; IR (Germanium ATR): 3518, 2997, 2928, 2833, 1583,

1515, 1463, 1256, 1143, 1026, 975, 799, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 2.2 Hz, 1H), 7.00 (dd, J = 8.4, 2.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.87 – 1.70 (m, 7H), 1.67 – 1.61 (m, 2H), 1.55 (s, 1H), 1.37 – 1.22 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.9, 142.5, 116.7, 110.9, 108.6, 73.1, 56.1, 56.0, 39.1, 25.7, 22.4; HRMS (ESI): Exact mass calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$, 259.1305. Found 259.1314.

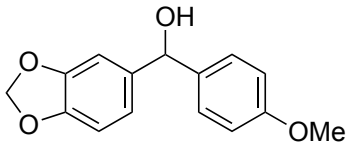


3,3',4,4'-Tetramethoxy-7-methylbenzhydrol (SII-71g): 3,3',4,4'-tetramethoxybenzhydrol **(II-99)** (0.617 mmol) was dissolved in dry THF (3 mL) at room temperature. Manganese (IV) oxide (4.01 mmol) was then added portionwise. Starting material was consumed after 36 h, as determined by TLC. The solution was filtered through a pad of Celite and concentrated. A portion of the resulting benzhydryl ketone (0.474 mmol) was dissolved in dry THF (5 mL), cooled to 0 ºC and allowed to stir under N_2 atmosphere. A solution of methylmagnesium bromide (0.947 mmol) was then added dropwise to the stirred solution. The reaction mixture was allowed to stir at 0 ºC for 1 hour, at which point all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 50% EtOAc in hexanes solvent system (139 mg, 92% yield over two steps): melting point: 129.3–130.3 ºC; IR (Germanium ATR): 3513, 3001, 2934, 1596, 1511, 1462, 1253, 1138, 1024, 811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, J = 2.2 Hz, 2H), 6.90 (dd, J = 8.4, 2.2 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 3.87 (s, 6H), 3.83 (s, 6H), 2.11 (s, 1H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 148.1, 141.0, 118.2, 110.6, 109.7, 76.2,

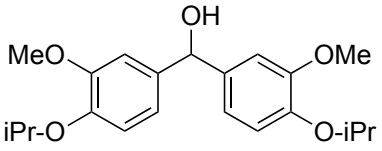
56.0, 56.0, 31.5; HRMS (ESI): Exact mass calcd for $C_{18}H_{22}O_5$ $[M+Na]^+$, 341.1359. Found 341.1372.



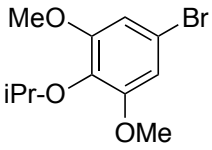
1-(3,4-Dimethoxyphenyl)ethanol (II-113): Veratraldehyde (5 mmol) was dissolved in dry Et_2O (15 mL), cooled to 0 ºC and allowed to stir under N_2 atmosphere. A solution of methylmagnesium bromide (7.5 mmol) was then added dropwise to the stirred solution. The reaction mixture was allowed to stir at 0 ºC for 15 min, at which point all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (659 mg, 72% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.9 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.86 (q, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.76 (bs, 1H), 1.49 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.5, 138.7, 117.7, 111.1, 108.8, 70.4, 56.1, 56.0, 25.2. All spectroscopic data for this compound agrees with previously reported values.[130]



3,4-Methylenedioxy-4'-methoxybenzhydrol (II-117): Synthesized from piperonal (8.2 mmol) with 4-bromoanisole (9.6 mmol) rather than 4-bromoveratrol via General Method B (2.34 g, 99% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 6.90 – 6.82 (m, 4H), 6.78 – 6.74 (m, 1H), 5.93 (s, 2H), 5.72 (d, *J* = 3.4 Hz, 1H), 3.79 (s, 3H), 2.14 (d, *J* = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 147.9, 147.0, 138.4, 136.3, 127.8, 120.0, 114.0, 108.2, 107.2, 101.2, 77.2, 75.7, 55.4. All spectroscopic data for this compound agrees with previously reported values.[131]

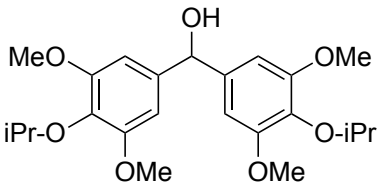


4,4'-Diisopropoxy-3,3'-dimethoxybenzhydrol (SII-123): 4-bromo-1-isopropoxy-2-methoxy-benzene (10.0 mmol) was dissolved in dry THF (20 mL) and cooled to –78 ºC. A solution of nBuLi in hexanes (10.0 mmol) was added dropwise and the solution was allowed to stir at –78 ºC under N_2 atmosphere for one hour. Freshly distilled ethyl formate (5.0 mmol) was added dropwise to the stirred solution. The solution was allowed to come to room temperature and stir for 5 hours. At this time, all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (1.21 g, 67% yield): IR (Germanium ATR): 3511, 2981, 1605, 1506, 1465, 1419, 1260, 1225, 1136, 1036, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 1.2 Hz, 2H), 6.87 – 6.84 (m, 4H), 5.74 (d, J = 2.9 Hz, 1H), 4.50 (hept, J = 6.1 Hz, 2H), 3.82 (s, 6H), 2.15 (d, J = 3.4 Hz, 1H), 1.36 (d, J = 6.1 Hz, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5, 146.9, 137.0, 119.1, 115.6, 110.7, 76.0, 71.6, 56.1, 22.3; HRMS (ESI): Exact mass calcd for $C_{21}H_{28}O_5$ $[M+Na]^+$, 383.1829. Found 383.1832.



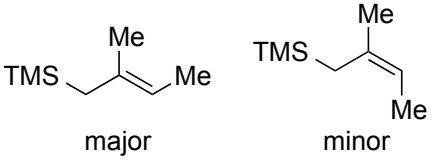
5-bromo-1,3-dimethoxy-2-isopropoxybenzene: 4-bromo-2,6-dimethoxyphenol (17.16 mmol) was dissolved in dry DMF (20 mL) followed by the addition of 2-bromopropane (34.32 mmol) and K_2CO_3 (25.74 mmol). The solution was heated to 90 ºC and allowed to stir under N_2 atmosphere for 6 hours. The reaction was then cooled down to room temperature and allowed to stir overnight. Starting material was still present as determined by TLC, therefore more 2-bromopropane (34.32 mmol) was added and the reaction

was stirred overnight. At this time, all starting material was consumed and the reaction was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with HCl (0.5 M, 100 mL) and H_2O (100 mL), then dried over Na_2SO_4 and concentrated under reduced pressure to afford the product (4.63 g, 98% yield). IR (Germanium ATR): 2972, 2933, 1585, 1491, 1404, 1303, 1224, 1124, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 2H), 4.31 (hept, J = 6.2 Hz, 1H), 3.80 (s, 6H), 1.27 (d, J = 6.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 135.5, 115.8, 109.0, 75.5, 56.4, 22.5; HRMS (ESI): Exact mass calcd for $C_{11}H_{15}BrO_3$ $[M+Na]^+$, 297.0097. Found 297.0097.

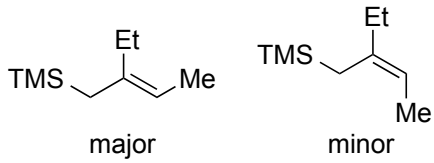


4,4'-Diisopropoxy-3,3'-dimethoxy-5,5'-dimethoxybenzhydrol (II-127): 5-bromo-1,3-dimethoxy-2-isopropoxybenzene (2.49 mmol) was dissolved in dry THF (4 mL) and cooled to –78 ºC. A solution of *n*BuLi in hexanes (2.49 mmol) was added dropwise and the solution was allowed to stir at –78 ºC under N_2 atmosphere for one hour. Freshly distilled ethyl formate (1.24 mmol) was added dropwise to the stirred solution. The solution was allowed to come to room temperature and stir overnight. At this time, all starting material was consumed as determined by TLC. The reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting material was purified by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system (210.7 mg, 40% yield): IR (Germanium ATR): 3449, 2974, 2935, 1593, 1462, 1418, 1325, 1228, 1123, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 4H), 5.71 (d, J = 3.3 Hz, 1H), 4.34 (hept, J = 6.3 Hz, 2H), 3.80 (s, 12H), 2.21 (d, J = 3.6 Hz, 1H), 1.29 (d, J = 6.2 Hz, 12H); ^{13}C NMR

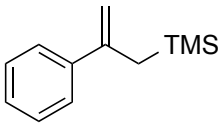
(126 MHz, $CDCl_3$) δ 154.0, 138.8, 135.7, 104.0, 76.6, 75.4, 56.3, 22.6; HRMS (ESI): Exact mass calcd for $C_{23}H_{32}O_7$ $[M+Na]^+$, 443.204. Found 443.2054.



1-(Trimethylsilyl)-2-methyl-2-butene (II-79): Followed same procedure as Yamamoto and coworkers[132] (185 mmol scale, 11.7 g, 44% yield after distillation, 3.3:1 d.r.): Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (qq, J = 6.6, 1.2 Hz, 1H), 1.59 (q, J = 1.1 Hz, 3H), 1.56 (dq, J = 6.7, 1.1 Hz, 3H), 1.46 (t, J = 1.1 Hz, 2H), -0.01 (s, 9H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5, 116.9, 30.0, 18.5, 13.7, -1.1; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 5.12 – 5.06 (m, 1H), 1.67 (p, J = 1.5 Hz, 3H), 1.52 – 1.49 (m, 5H), 0.03 (s, 9H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1, 115.9, 26.4, 23.0, 14.1, -0.5. All spectroscopic data for this compound agrees with previously reported values.[132]



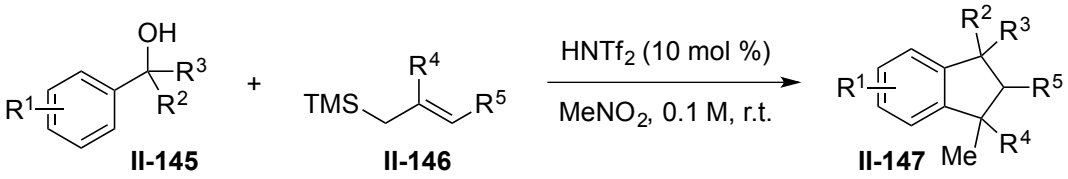
1-(Trimethylsilyl)-2-ethyl-2-butene (II-80): Followed same procedure as Yamamoto and coworkers[132] (46 mmol scale, 10.22 g, 33% yield after distillation, 4:1 d.r.): Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (q, J = 6.7 Hz, 1H), 1.97 (q, J = 7.7 Hz, 2H), 1.57 (d, J = 6.7 Hz, 3H), 1.45 (s, 2H), 0.95 (t, J = 7.6 Hz, 3H), -0.01 (s, 9H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 115.8, 26.5, 25.0, 13.3, 12.8, -1.0; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (q, J = 6.9 Hz, 1H), 1.94 (q, J = 6.0 Hz, 2H), 1.55 – 1.50 (m, 5H), 0.98 (t, J = 7.4 Hz, 3H), 0.02 (s, 9H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 113.9, 32.0, 21.2, 14.1, 13.0, -0.5. All spectroscopic data for this compound agrees with previously reported values.[132]



2-Phenyl-3-(trimethylsilyl)-1-propene (II-139): Followed same procedure as Ferraris and coworkers[132] (40 mmol scale, 2.47 g, 31% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.30 (tt, *J* = 6.7, 0.9 Hz, 2H), 7.26 – 7.22 (m, 1H), 5.13 (d, *J* = 1.7 Hz, 1H), 4.87 (dd, *J* = 1.2 Hz, 1H), 2.03 (d, *J* = 1.1 Hz, 2H), -0.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 142.9, 128.2, 127.3, 126.5, 110.2, 26.3, -1.3. All spectroscopic data for this compound agrees with previously reported values.[133]

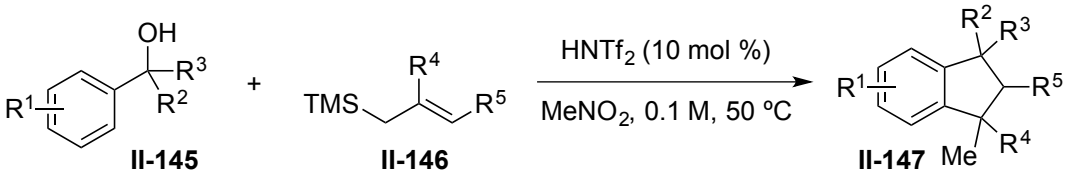
2.6.2 Indane Experimental Procedures and Characterization Data

Scheme 2.28 General method C for synthesis of indanes

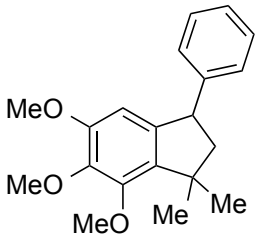


General Method C (standard indane reaction): Benzhydryl or benzyl alcohol **II-145** (1 equiv) was dissolved in $MeNO_2$ (0.1 M soln) and allowed to stir under N_2 atmosphere. Alkyl silane **II-146** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at room temperature for 2 hours before being quenched with sat. $NaHCO_3$ solution. The biphasic solution was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired indane.

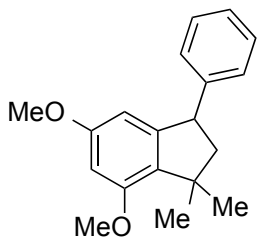
Scheme 2.29 General method D for synthesis of indanes at elevated temperature



General Method D (indane reaction at elevated temperature): Benzhydryl or benzyl alcohol **II-145** (1 equiv) was dissolved in $MeNO_2$ (0.1 M soln) and allowed to stir while warming to 50 ºC under N_2 atmosphere. Alkyl silane **II-146** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at 50 ºC for 2 hours before being quenched with sat. $NaHCO_3$ solution. The biphasic solution was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired indane.

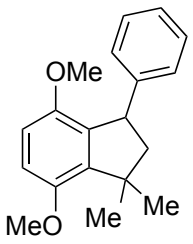


5,6,7-Trimethoxy-1,1-dimethyl-3-phenylindane (II-55a): Synthesized from 3,4,5-trimethoxybenzhydrol (**SII-55a**, 0.200 mmol) and silane **II-45** via General Method C (50 mg, 80% yield): IR (Germanium ATR): (Germanium ATR): 2937, 1605, 1479, 1411, 1327, 1226, 1201, 1104, 1029, 933 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.26 – 7.22 (m, 3H), 6.16 (d, J = 1.0 Hz, 1H), 4.29 (ddd, J = 10.3, 7.8, 1.1 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 2.31 (dd, J = 12.5, 7.7 Hz, 1H), 1.94 (dd, J = 12.5, 10.2 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 150.4, 145.2, 141.4, 141.2, 136.4, 128.6, 128.5, 126.5, 103.9, 61.0, 60.8, 56.3, 53.9, 49.8, 44.1, 29.1, 27.7; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}O_3$ $[M+H]^+$, 313.1798. Found 313.1811.

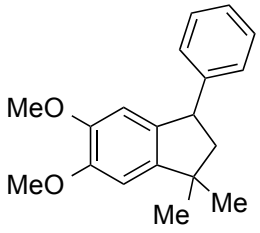


5,7-Dimethoxy-1,1-dimethyl-3-phenylindane (II-55b): Synthesized from 3,5-dimethoxybenzhydrol (**SII-55b**, 0.308 mmol) and silane **II-45** via General Method D (58 mg, 66% yield): IR (Germanium ATR): 2999, 2834, 1597, 1486, 1454, 1300, 1203, 1155, 1074, 1045, 933, 752, 717 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 6.32 (dd, *J* = 2.2, 0.8 Hz, 1H), 5.99 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.33 – 4.28 (m, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 2.34 (dd, *J* = 12.6, 7.9 Hz, 1H), 1.95 (dd, *J* = 12.6, 10.0 Hz, 1H), 1.48 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 157.3, 148.1, 145.4, 131.6, 128.6, 126.4, 101.0, 97.7, 55.6, 55.2, 53.8, 50.0, 43.6, 28.8, 26.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}O_2$ $[M+H]^+$, 283.1693. Found 283.1701.

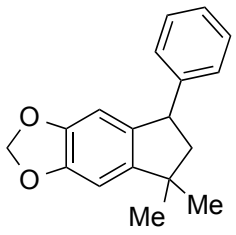


4,7-Dimethoxy-1,1-dimethyl-3-phenylindane (II-55c): Synthesized from 2,5-dimethoxybenzhydrol (**SII-55c**, 0.620 mmol) and silane **II-45** via General Method D (105 mg, 60% yield): IR (Germanium ATR): 3029, 1601, 1491, 1462, 1358, 1255, 1215, 1064, 842, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 7.17 – 7.12 (m, 1H), 7.11 – 7.06 (m, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 4.46 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 2.46 (dd, *J* = 13.0, 9.2 Hz, 1H), 1.92 (dd, *J* = 13.0, 5.9 Hz, 1H), 1.36 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 150.9, 146.8, 141.4, 133.9, 128.1, 127.5, 125.6, 110.5, 110.0, 55.9, 55.7, 53.0, 47.2, 45.1, 28.5, 28.3; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}O_2$ $[M+H]^+$, 283.1693. Found 283.1678.

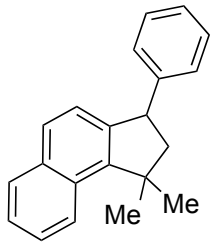


5,6-Dimethoxy-1,1-dimethyl-3-phenylindane (II-55d): Synthesized from 3,4-dimethoxybenzhydrol (**II-44**, 0.368 mmol) and silane **II-45** via General Method C (86 mg, 82% yield): IR (Germanium ATR): 2951, 2859, 1605, 1500, 1464, 1453, 1291, 1212, 1069, 1029, 995, 855, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.26 – 7.20 (m, 3H), 6.72 (s, 1H), 6.41 (s, 1H), 4.38 – 4.32 (m, 1H), 3.91 (s, 3H), 3.72 (s, 3H), 2.40 (dd, *J* = 12.4, 7.5 Hz, 1H), 1.93 (dd, *J* = 12.4, 9.8 Hz, 1H), 1.39 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 148.4, 145.7, 144.9, 136.7,

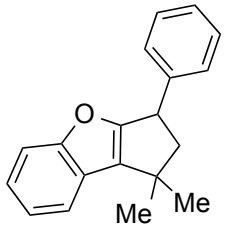
128.6, 128.4, 126.4, 108.1, 105.1, 56.2, 56.2, 53.5, 49.1, 43.3, 29.3, 29.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}O_2$ $[M+H]^+$, 283.1693. Found 283.1702.



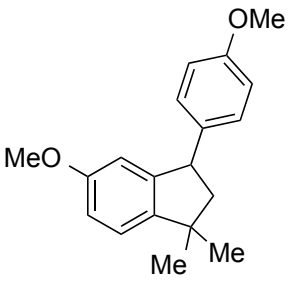
5,6-Methylenedioxy-1,1-dimethyl-3-phenylindane (II-55e): Synthesized from 3,4-methylenedioxybenzhydrol (**SII-55e**, 0.189 mmol) and silane **II-45** via General Method C (39 mg, 77% yield): IR (Germanium ATR): 2954, 1603, 1495, 1476, 1357, 1268, 1234, 1072, 1042, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 6.67 (s, 1H), 6.32 (s, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.89 (d, *J* = 1.4 Hz, 1H), 4.29 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.39 (dd, *J* = 12.5, 7.5 Hz, 1H), 1.96 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.36 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 146.7, 146.2, 145.4, 138.2, 128.6, 128.4, 126.5, 105.6, 102.6, 101.1, 53.2, 48.9, 43.1, 29.2, 29.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{18}O_2$ $[M+H]^+$, 267.138. Found 267.1369.



1,1-Dimethyl-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (II-55f): Synthesized from 2-naphthyl(phenyl)methanol (**SII-55f**, 0.560 mmol) silane **II-45** via General Method C (95 mg, 62% yield): IR (Germanium ATR): 3052, 3025, 2958, 2863, 1601, 1513, 1495, 1363, 1029, 817, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.51 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.30 – 7.23 (m, 3H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.49 (t, *J* = 8.9 Hz, 1H), 2.57 (dd, *J* = 12.7, 8.1 Hz, 1H), 2.15 (dd, *J* = 12.7, 9.7 Hz, 1H), 1.78 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 145.8, 142.9, 134.0, 130.0, 129.4, 128.6, 128.6, 128.0, 126.5, 125.7, 124.8, 124.1, 123.8, 54.6, 49.4, 45.4, 30.3, 27.8; HRMS (ESI): Exact mass calcd for $C_{21}H_{20}$ $[M+H]^+$, 273.1638. Found 273.1644.

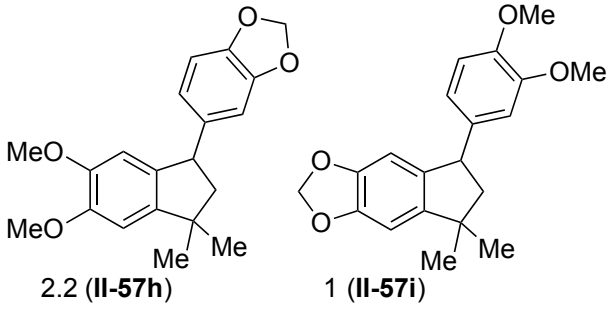


1,1-Dimethyl-3-phenyl-2,3-dihydro-1*H*-cyclopenta[*b*]benzofuran (II-55g): Synthesized from 2-(1-Hydroxyphenylmethyl)benzofuran (**SII-55g**, 0.259 mmol) and silane **II-45** via General Method C (49 mg, 72% yield): IR (Germanium ATR): 3061, 3028, 2955, 2864, 1630, 1604, 1497, 1444, 1363, 1205, 1054, 1009, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 1H), 7.47 – 7.41 (m, 1H), 7.37 – 7.31 (m, 2H), 7.26 (m, 5H), 4.52 (dd, *J* = 8.5, 6.6 Hz, 1H), 2.88 (dd, *J* = 13.0, 8.5 Hz, 1H), 2.32 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 160.5, 143.0, 130.8, 128.8, 127.6, 126.9, 125.6, 123.1, 122.6, 118.9, 112.3, 56.0, 44.0, 37.9, 29.7, 28.9; HRMS (ESI): Exact mass calcd for $C_{19}H_{18}O$ $[M+H]^+$, 263.143. Found 263.1424.



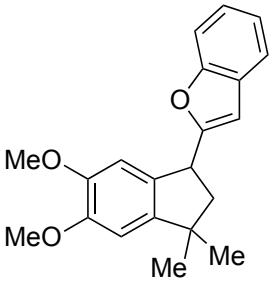
5-Methoxy-3-(4-methoxyphenyl)-1,1-dimethylindane (II-69): Synthesized from 3,4'-dimethoxybenzhydrol (**SII-69**, 0.650 mmol) and silane **II-45** via General Method C (111 mg, 60% yield): IR (Germanium ATR): 2997, 2952, 2861, 1609, 1584, 1512, 1487, 1249, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.77 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 6.40 (dd, *J* = 2.5, 1.1 Hz, 1H), 4.31 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 2.36 (dd, *J* = 12.4, 7.5 Hz, 1H), 1.93 (dd, *J* = 12.4, 10.3 Hz, 1H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 158.3, 147.3, 145.1, 137.1, 129.5, 122.6, 114.0, 113.1, 110.1, 55.6, 55.4, 53.4, 48.4, 42.5, 29.3, 29.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}O_2$ $[M+H]^+$, 283.1693. Found 283.1712.

5,6-Dimethoxy-3-(3,4-methylenedioxyphenyl)-1,1-dimethylindane (II-57h) and **5,6-Methylenedioxy-3-(3,4-dimethoxyphenyl)-1,1-dimethylindane (II-57i)**: Synthesized from 3,4-methylenedioxy-3',4'-dimethoxy benzhydrol (**SII-57h**, 0.507 mmol) and silane **II-45** via General Method C (124 mg, 2.2:1 cyclization isomer ratio, 75% yield): IR (Germanium ATR): 2999, 2862, 1605, 1501, 1487, 1440, 1294, 1231, 1140, 1069, 1038 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.72 – 6.69 (m, 2H), 6.66 (s, 1H), 6.41 (s, 1H), 5.94 (dd, *J* = 5.5, 1.3 Hz, 2H), 4.27 (dd, *J* = 9.6, 7.4 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 2.36 (dd, *J* = 12.5, 7.5 Hz, 1H), 1.87 (dd, *J* = 12.4, 9.8 Hz, 1H), 1.38 (s, 3H), 1.22 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 148.4, 147.9, 146.1, 144.8, 139.6, 136.7, 121.5, 108.6, 108.2, 108.0, 105.1, 101.0, 56.2, 56.2, 53.5, 48.8, 43.2, 29.3, 29.1; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.72 – 6.69 (m, 1H), 6.66 (s, 1H), 6.34 (s, 1H), 5.90 (dd, *J* = 15.7, 1.5 Hz, 2H), 4.23 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.36 (dd, *J* = 12.5, 7.5 Hz, 1H), 1.93 (dd, *J* = 12.5, 10.2 Hz, 1H), 1.36 (s, 3H), 1.21 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 147.7, 147.1, 146.7, 146.1, 138.3, 137.8, 120.4, 111.5, 111.3, 105.5, 102.6, 101.1, 56.1, 56.1, 53.3, 48.6, 43.0, 29.1, 29.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}O_4$ $[M+Na]^+$, 349.141. Found 349.142.

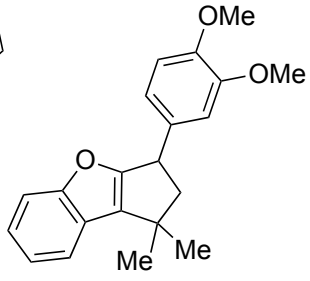


2.2 (**II-57h**) 1 (**II-57i**)

2-(5,6-Dimethoxy-3,3-dimethylindan-1-yl)benzofuran (II-57j) and 3-(3,4-Dimethoxyphenyl)-1,1-dimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]benzofuran (II-57k): Synthesized from benzo[b]furan-2-yl-(3,4-dimethoxyphenyl) carbinol **(SII-57j**, 0.30 mmol) and silane **II-45** via General Method C (50 mg, 3.3:1 cyclization isomer ratio, 51% yield): IR (Germanium ATR): 3059, 2996, 2862, 1605, 1502, 1454, 1295, 1254, 1214, 1070, 1028, 855, 755 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 1H), 7.46 – 7.42 (m, 1H), 7.25 – 7.17 (m, 2H), 6.73 (s, 1H), 6.71 (d, *J* = 0.9 Hz, 1H), 6.47 (d, *J* = 0.9 Hz, 1H), 4.56 (t, *J* = 8.1 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 2.41 (dd, *J* = 12.5, 7.9 Hz, 1H), 2.28 (dd, *J* = 12.5, 8.5 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H); Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 1H), 7.46 – 7.41 (m, 1H), 7.26 – 7.16 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.80 – 6.76 (m, 2H), 4.46 (dd, *J* = 8.4, 6.7 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.85 (dd, *J* = 12.9, 8.5 Hz, 1H), 2.32 – 2.27 (m, 1H), 1.52 (s, 3H), 1.42 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 155.1, 149.3, 148.5, 144.4, 133.2, 128.9, 123.5, 122.6, 120.6, 111.2, 107.8, 105.5, 102.5, 56.3, 56.2, 48.3, 43.5, 42.5, 29.4, 29.4; Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 160.6, 149.3, 148.0, 135.5, 130.6, 125.6, 123.1, 122.7, 119.5, 118.9, 112.4, 111.5, 110.8, 56.1, 56.1, 56.0, 43.7, 37.8, 29.8, 28.8; HRMS (ESI): Exact mass calcd for $C_{21}H_{22}O_3$ $[M+H]^+$, 323.1462. Found 323.1653.

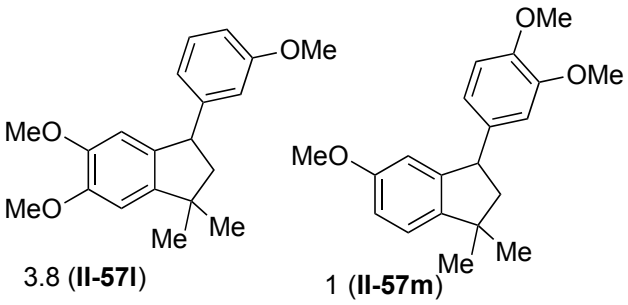


3.3 (**II-57j**)



1 (**II-57k**)

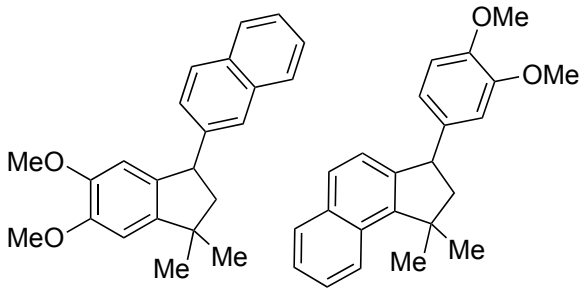
5,6-Dimethoxy-3-(3-methoxyphenyl)-1,1-dimethylindane (II-57l) and **5-Methoxy-3-(3,4-dimethoxy phenyl)-1,1-dimethylindane (II-57m):**



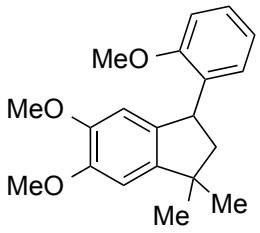
3.8 (**II-57l**) 1 (**II-57m**)

Synthesized from 3,3',4-trimethoxybenzhydrol (**SII-57l**, 0.322 mmol) and silane **II-45** via General Method C (56 mg, 3.8:1 cyclization isomer ratio, 55% yield): IR (Germanium ATR): 2998, 2950, 2860, 2832, 1607, 1500, 1464, 1314, 1236, 1212, 1139, 1069, 1030, 996, 855, 767 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (td, *J* = 7.7, 0.8 Hz, 1H), 6.83 – 6.76 (m, 3H), 6.71 (s, 1H), 6.43 (d, *J* = 1.0 Hz, 1H), 4.32 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 2.39 (dd, *J* = 12.4, 7.5 Hz, 1H), 1.93 (dd, *J* = 12.4, 9.7 Hz, 1H), 1.38 (s, 3H), 1.23 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 148.8, 148.4, 147.4, 144.9, 136.5, 129.5, 120.9, 114.2, 111.6, 108.1, 105.1, 56.2 (2C), 55.3, 53.3, 49.1, 43.3, 29.3, 29.1; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 1H), 6.86 – 6.76 (m, 3H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.44 (s, 1H), 4.35 – 4.28 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H), 2.44 – 2.33 (m, 1H), 1.99 – 1.89 (m, 1H), 1.40 (s, 3H), 1.23 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 149.1, 147.7, 147.1, 145.1, 137.5, 122.6, 120.6, 113.2, 111.6, 111.3, 110.1, 56.1, 56.1, 55.6, 53.3, 48.9, 42.5, 29.2, 29.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}O_3$ $[M+H]^+$, 313.1798. Found 313.1805.

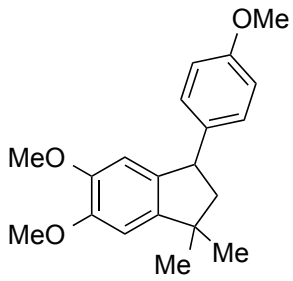
2-(5,6-Dimethoxy-3,3-dimethylindan-1-yl)naphthalene (II-57n) and **3-(3,4-Dimethoxyphenyl)-1,1-dimethyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (II-57o):** Synthesized from (3,4-dimethoxyphenyl)(2-naphthyl)methanol (**SII-57n**, 0.418 mmol) and silane **II-45** via General Method C (96 mg, 8.3:1 cyclization isomer ratio, 69% yield): IR (Germanium ATR): 2999, 2955, 2859, 2829, 1603, 1500, 1463, 1236, 1213, 1139, 1029, 889, 819, 754 cm^{-1}; Major Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 3H), 7.72 (s, 1H), 7.54 – 7.41 (m, 2H), 7.31 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.76 (s, 1H), 6.41 (s, 1H), 4.52 (dd, *J* = 9.6, 7.7 Hz, 1H), 3.93 (s, 3H), 3.68 (s, 3H), 2.46 (dd, *J* = 12.5, 7.5 Hz, 1H), 2.04 (dd, *J* = 12.5, 9.8 Hz, 1H), 1.43 (s, 3H), 1.28 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 148.5, 144.9, 143.0, 136.7, 133.7, 132.5, 128.3, 127.8, 127.7, 126.9 (2C), 126.1, 125.5, 108.1, 105.2, 56.2, 56.7, 53.3, 49.3, 43.4, 29.4, 29.2; Minor Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 4.42 (dd, *J* = 9.8, 8.0 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 2.53 (dd, *J* = 12.6, 7.9 Hz, 1H), 2.11 (dd, *J* = 12.6, 9.9 Hz, 1H), 1.77 (s, 3H), 1.54 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 147.7, 146.1, 143.0, 138.3, 134.0, 130.0, 129.4, 128.0, 125.7, 124.8, 124.1, 123.8, 120.6, 111.6, 111.3, 56.1, 56.0, 54.7, 49.0, 45.3, 30.3, 27.7; HRMS (ESI): Exact mass calcd for $C_{23}H_{24}O_2$ $[M+H]^+$, 333.1849. Found 333.1855.



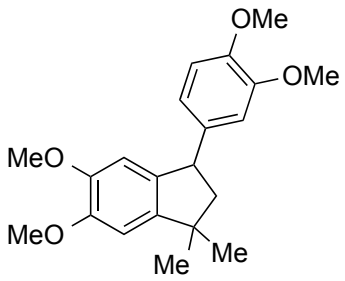
8.3 (**II-57n**) 1 (**II-57o**)



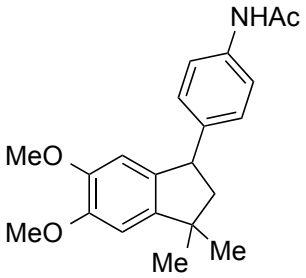
5,6-Dimethoxy-3-(2-methoxyphenyl)-1,1-dimethylindane (II-57f): Synthesized from 2,3',4'-trimethoxybenzhydrol (**SII-57f**, 0.187 mmol) and silane **II-45** via General Method C (42 mg, 72% yield): IR (Germanium ATR): 2950, 1599, 1491, 1238, 1211, 1068, 1029, 855, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.92 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H), 6.72 (s, 1H), 6.48 (s, 1H), 4.80 (t, *J* = 8.8, 7.9 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H), 2.43 (dd, *J* = 12.4, 7.9 Hz, 1H), 1.84 (dd, *J* = 12.4, 8.8 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 148.6, 148.3, 145.1, 136.3, 134.3, 128.4, 127.2, 120.8, 110.5, 108.3, 105.3, 56.2, 56.2, 55.6, 51.4, 43.3, 41.4, 29.6, 29.6; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}O_3$ $[M+H]^+$, 313.1798. Found 313.1806.



5,6-Dimethoxy-3-(4-methoxyphenyl)-1,1-dimethylindane (II-57g): Synthesized from 3,4,4'-trimethoxybenzhydrol (**SII-57g**, 0.295 mmol) and silane **II-45** via General Method C (60 mg, 65% yield): IR (Germanium ATR): 3005, 2948, 2833, 1604, 1499, 1462, 1178, 1038, 997, 870, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 6.39 (s, 1H), 4.29 (ddd, *J* = 9.8, 7.5, 1.0 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H), 2.37 (dd, *J* = 12.4, 7.5 Hz, 1H), 1.89 (dd, *J* = 12.4, 9.8 Hz, 1H), 1.38 (s, 17H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 148.7, 148.4, 144.7, 137.6, 137.0, 129.3, 114.0, 108.1, 105.1, 56.2, 56.2, 55.4, 53.6, 48.2, 43.2, 29.2, 29.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}O_3$ $[M+H]^+$, 313.1798. Found 313.1803.

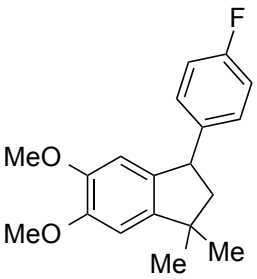


5,6-Dimethoxy-3-(3,4-dimethoxyphenyl)-1,1-dimethylindane (II-57e): Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.302 mmol) and silane **II-45** via General Method C (88 mg, 85% yield): IR (Germanium ATR): 2996, 2950, 2860, 1500, 1211, 1138, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.1 Hz, 1H), 6.78 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.72 (m, 2H), 6.42 (s, 1H), 4.29 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 2.38 (dd, *J* = 12.4, 7.4 Hz, 1H), 1.90 (dd, *J* = 12.4, 9.8 Hz, 1H), 1.39 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.7, 148.4, 147.6, 144.7, 138.1, 136.8, 120.4, 111.4, 111.3, 108.0, 105.1, 56.2, 56.2, 56.0, 56.0, 53.5, 48.7, 43.1, 29.1, 29.1; HRMS (ESI): Exact mass calcd for $C_{21}H_{26}O_4$ $[M+H]^+$, 343.1904. Found 343.1904.

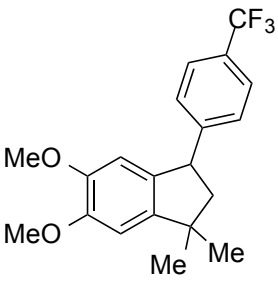


***N*-(4-(5,6-Dimethoxy-3,3-dimethylindan-1-yl)phenyl)acetamide (II-57d):** 4-(*N*-acetamide)-3',4'-dimethoxybenzhydrol **(SII-57d**, 0.201 mmol) was dissolved in $MeNO_2$ (0.1 M soln) and allowed to stir while warming to 80 ºC under N_2 atmosphere. Silane **II-45** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at 80 ºC for 2 hours before being quenched with sat. $NaHCO_3$ solution. The biphasic solution was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired indane (64 mg, 95% yield): IR (Germanium ATR): 3310, 3000, 2953, 1666, 1602, 1513, 1500, 1210, 1068, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.19 – 7.15 (m, 2H), 6.71 (s, 1H), 6.37 (d, *J* = 0.9 Hz, 1H), 4.31 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 2.37 (dd, *J* = 12.4, 7.5 Hz, 1H), 2.18 (s, 3H), 1.89 (dd, *J* =

12.5, 9.8 Hz, 1H), 1.71 – 1.62 (m, 1H), 1.37 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 148.8, 148.4, 144.8, 141.8, 136.7, 136.1, 129.0, 120.3, 108.0, 105.2, 56.2, 56.2, 53.4, 48.5, 43.3, 29.2, 29.1, 24.7; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}NO_3$ $[M+H]^+$, 340.1907. Found 340.1919.

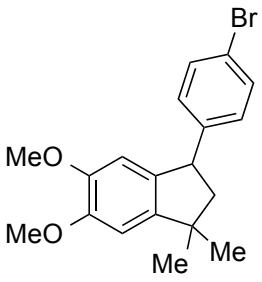


3-(4-Fluorophenyl)-5,6-dimethoxy-1,1-dimethylindane (II-57b): Synthesized from 4-fluoro-3',4'-dimethoxybenzhydrol (**SII-57b**, 0.320 mmol) and silane **II-45** via General Method C (65 mg, 67% yield): IR (Germanium ATR): 2952, 2861, 1604, 1502, 1290, 1212, 1068, 856, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 7.03 – 6.97 (m, 2H), 6.71 (s, 1H), 6.36 (s, 1H), 4.32 (dd, J = 9.8, 7.5 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.39 (dd, J = 12.5, 7.5 Hz, 1H), 1.88 (dd, J = 12.5, 9.8 Hz, 1H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, J_{CF} = 243.9 Hz), 148.9, 148.5, 144.8, 141.3 (d, J_{CF} = 3.1 Hz), 136.6, 129.8 (d, J_{CF} = 7.8 Hz, 2C), 115.4 (d, J_{CF} = 21.1 Hz, 2C), 108.0, 105.2, 56.2, 56.2, 53.6, 48.3, 43.3, 29.2, 29.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}FO_2$ $[M+Na]^+$, 323.1418. Found 323.1422.

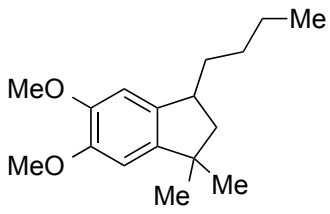


5,6-Dimethoxy-1,1-dimethyl-3-(4-(trifluoromethyl)phenyl)-indane (II-57a): Synthesized from 4-trifluoromethyl-3',4'-dimethoxybenzhydrol (**SII-57a**, 0.570 mmol) and silane **II-45** via General Method C (164 mg, 82% yield): IR (Germanium ATR): 2953, 2863, 1618, 1500, 1461, 1322, 1128, 1068, 858, 840 cm cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.72 (s, 1H), 6.36 (s, 1H), 4.40 (dd, J = 9.6, 7.6 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 2.42 (dd, J = 12.5, 7.6 Hz, 1H), 1.90 (dd, J = 12.5, 9.6 Hz, 1H), 1.39 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 149.0, 148.6, 145.0, 135.7, 128.7 (2C), 128.7 (q, J_{CF} = 32.3 Hz),

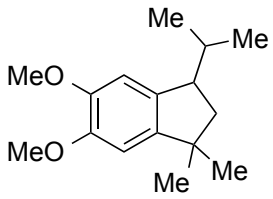
125.6 (q, J_{CF} = 3.9 Hz, 2C), 124.5 (q, J_{CF} = 272.1 Hz), 107.9, 105.2, 56.2 (2C), 53.4, 49.0, 43.5, 29.3, 29.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{21}F_3O_2$ $[M+H]^+$, 351.1566. Found 351.1572.



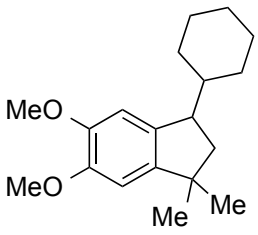
3-(4-Bromophenyl)-5,6-dimethoxy-1,1-dimethylindane (II-57c): Synthesized from 4-bromo-3',4'-dimethoxybenzhydrol (**SII-57c**, 0.400 mmol) and silane **II-45** via General Method C (119 mg, 82% yield): IR (Germanium ATR): 3019, 2952, 1604, 1500, 1292, 1211, 1069, 1009, 855, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.71 (s, 1H), 6.36 (s, 1H), 4.30 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.39 (dd, *J* = 12.5, 7.5 Hz, 1H), 1.87 (dd, *J* = 12.5, 9.7 Hz, 1H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 148.5, 144.9, 144.8, 136.1, 131.7, 130.2, 120.1, 107.9, 105.2, 56.2, 56.2, 53.4, 48.6, 43.4, 29.2, 29.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}BrO_2$ $[M+Na]^+$, 383.0617. Found 383.0617.



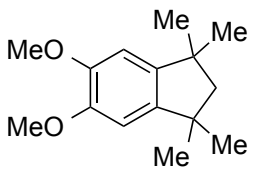
3-Butyl-5,6-dimethoxy-1,1-dimethylindane (II-71c): Synthesized from 1-(3,4-dimethoxyphenyl)pentan-1-ol (**SII-71c**, 0.156 mmol) and silane **II-45** via General Method C (33 mg, 84% yield): IR (Germanium ATR): 2952, 2856, 1606, 1499, 1464, 1212, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.66 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.14 – 3.02 (m, 1H), 2.14 (dd, *J* = 12.2, 7.3 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.52 (dd, *J* = 12.3, 8.9 Hz, 1H), 1.46 – 1.34 (m, 5H), 1.33 (s, 3H), 1.15 (s, 3H), 0.98 – 0.92 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.2, 144.3, 138.0, 106.8, 105.5, 56.2, 56.2, 49.1, 42.9, 42.0, 35.3, 30.2, 29.7, 29.5, 23.1, 14.3; HRMS (ESI): Exact mass calcd for $C_{17}H_{26}O_2$ $[M+Na]^+$, 285.1825. Found 285.1842.



3-Isopropyl-5,6-dimethoxy-1,1-dimethylindane (II-71b): Synthesized from 1-(3,4-dimethoxyphenyl)-2-methyl-1-propanol (**SII-71b**, 0.209 mmol) and silane **II-45** via General Method C (39 mg, 76% yield): IR (Germanium ATR): 2951, 1605, 1499, 1463, 1289, 1211, 1073, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (d, *J* = 1.1 Hz, 1H), 6.64 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.16 (dddd, *J* = 9.1, 7.7, 4.6, 1.1 Hz, 1H), 2.21 (pd, *J* = 6.9, 4.6 Hz, 1H), 1.87 (dd, *J* = 12.5, 7.7 Hz, 1H), 1.66 (dd, *J* = 12.5, 9.1 Hz, 1H), 1.32 (s, 3H), 1.15 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 148.1, 145.0, 136.5, 107.3, 105.4, 56.3, 56.1, 48.0, 42.5, 42.3, 30.1, 29.4, 29.4, 21.6, 17.2; HRMS (ESI): Exact mass calcd for $C_{16}H_{24}O_2$ $[M+Na]^+$, 271.1669. Found 271.1683.

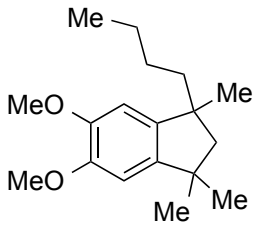


3-Cyclohexyl-5,6-dimethoxy-1,1-dimethylindane (II-71a): Synthesized from 1-cyclohexyl-1-(3,4-dimethoxyphenyl)methanol **(SII-71a**, 0.408 mmol) and silane **II-45** via General Method C (86 mg, 73% yield): IR (Germanium ATR): 2993, 2922, 2849, 1605, 1500, 1448, 1317, 1288, 1212, 1070, 993 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.63 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.11 (td, *J* = 8.4, 4.6 Hz, 1H), 1.88 (dd, *J* = 12.5, 7.8 Hz, 1H), 1.84 – 1.66 (m, 6H), 1.50 – 1.42 (m, 1H), 1.38 – 1.08 (m, 10H), 1.02 – 0.88 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.0, 145.0, 136.1, 107.5, 105.5, 56.4, 56.1, 47.6, 43.5, 42.6, 40.3, 32.3, 30.1, 29.5, 27.8, 27.2, 26.9, 26.8; HRMS (ESI): Exact mass calcd for $C_{19}H_{28}O_2$ $[M+Na]^+$, 311.1982. Found 311.1996.

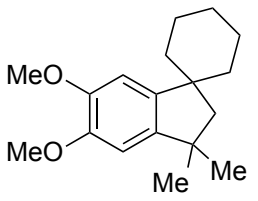


5,6-Dimethoxy-1,1,3,3-tetramethylindane (II-71d): Synthesized from 3,4-dimethoxy-(1'-hydroxy-1'-methylethyl)benzene (**II-72**, 0.400 mmol) and silane **II-45** via General Method C (75 mg, 79% yield): IR (Germanium

ATR): 3008, 2860, 1602, 1502, 1464, 1290, 1213, 1059, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 2H), 3.88 (s, 6H), 1.91 (s, 2H), 1.29 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 142.8, 105.6, 57.1, 56.2, 42.6, 31.7; HRMS (ESI): Exact mass calcd for $C_{15}H_{22}O_2$ $[M+Na]^+$, 257.1512. Found 257.1532.

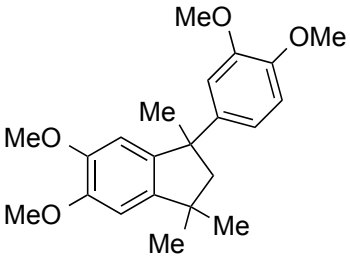


1-Butyl-5,6-dimethoxy-1,3,3-trimethylindane (II-71e): Synthesized from 2-(3,4-dimethoxyphenyl)haxan-2-ol (**SII-71e**, 0.600 mmol) and silane **II-45** via General Method C (157 mg, 94% yield): IR (Germanium ATR): 2952, 2859, 1605, 1502, 1464, 1288, 1212, 1149, 1057, 852 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.58 (s, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 2.01 (d, J = 13.2 Hz, 1H), 1.76 (d, J = 13.2 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.55 – 1.45 (m, 1H), 1.35 – 1.27 (m, 3H), 1.29 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.21 – 1.12 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 148.4, 143.1, 142.3, 105.9, 105.5, 56.2, 56.1, 53.8, 45.9, 43.3, 42.5, 32.3, 31.5, 29.8, 27.5, 23.6, 14.2; HRMS (ESI): Exact mass calcd for $C_{18}H_{28}O_2$ $[M+NH_4]^+$, 294.2428. Found 294.2441.

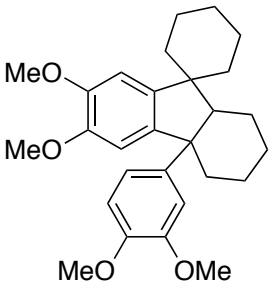


5',6'-Dimethoxy-3',3'-dimethylspiro[cyclohexane-1,1'-indane] (II-71f): Synthesized from 1-(3,4-dimethoxyphenyl)cyclohexanol (**II-73**, 0.301 mmol) and silane **II-45** via General Method C (62 mg, 85% yield): IR (Germanium ATR): 2952, 2852, 1604, 1503, 1464, 1289, 1214, 1032, 974, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.63 (s, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 1.95 (s, 2H), 1.76 – 1.66 (m, 3H), 1.61 – 1.53 (m, 4H), 1.51 – 1.40 (m, 2H), 1.29 (s, 6H), 1.33 – 1.22 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 148.5, 143.0, 143.0, 105.8, 105.6, 56.1, 56.1, 51.6, 46.9, 42.7, 40.2,

32.2, 26.1, 23.6; HRMS (ESI): Exact mass calcd for $C_{18}H_{26}O_2$ $[M+NH_4]^+$, 292.2271. Found 292.2273.

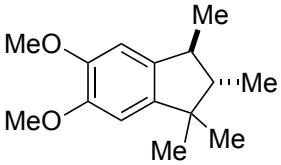


1-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1,3,3-trimethylindane (II-71g): Synthesized from 3,3',4,4'-tetramethoxy-7-methylbenzhydrol (**SII-71g**, 0.102 mmol) and silane **II-45** via General Method C (21 mg, 58% yield): IR (Germanium ATR): 2995, 2953, 1604, 1502, 1463, 1253, 1145, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.70 – 6.66 (m, 2H), 6.60 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.34 (d, J = 12.9 Hz, 1H), 2.17 (d, J = 12.9 Hz, 1H), 1.66 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.5, 148.5, 147.0, 144.2, 144.1, 140.4, 118.8, 110.6, 110.6, 107.6, 105.3, 59.9, 56.3, 56.1, 56.0, 55.9, 50.5, 42.9, 31.0, 31.0, 30.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{28}O_4$ $[M+NH_4]^+$, 374.2326. Found 374.2336.

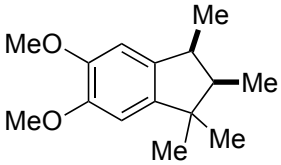


II-74: 1-(3,4-Dimethoxyphenyl)cyclohexanol (**II-73**, 0.205 mmol) was dissolved in $MeNO_2$ (0.1 M) followed by the addition of a solution of $HNTf_2$ in DCM (10 mol%). The reaction was allowed to stir at room temperature under N_2 atmosphere for before being quenched with saturated aqueous $NaHCO_3$ solution. Same workup protocol as General Method C was followed to afford II-X (32 mg, 70% yield). IR (Germanium ATR): 2996, 2930, 1603, 1498, 1464, 1251, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.78 (d, J = 2.2 Hz, 1H), 6.70 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.58 (dd, J = 8.4, 2.2 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 2.90 (dd, J = 11.0, 5.6 Hz, 1H), 2.24 – 2.13 (m, 1H), 1.95 – 0.71 (m, 17H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 148.5, 147.8, 146.7, 145.9, 144.3, 137.0, 118.8, 110.6, 110.4, 108.6, 107.1, 56.6, 56.1,

56.0, 55.9, 54.3, 50.2, 49.7, 39.6, 37.4, 32.6, 26.2, 25.3, 24.2, 23.7, 23.4. HRMS (ESI): Exact mass calcd for $C_{28}H_{36}O_4$ $[M+Na]^+$, 459.2506. Found 459.2512.



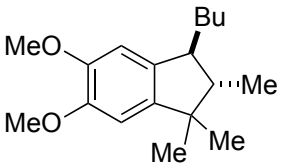
3.2 **(II-81a major)**



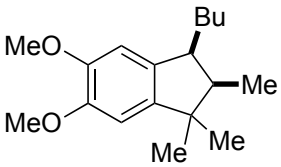
1 **(II-81a minor)**

***anti*-5,6-Dimethoxy-1,1,2,3-tetramethylindane (II-81a major)** and ***syn*-5,6-Dimethoxy-1,1,2,3-tetramethylindane (II-81a minor):** Synthesized from 1-(3,4-dimethoxyphenyl)ethanol (**II-113**, 0.268 mmol) and silane **II-79** via General Method C (56 mg, 3.2:1 d.r., 89% yield): IR (Germanium ATR): 2954, 2867, 1608, 1501, 1464, 1405, 1288, 1212, 1049, 853, 766 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.64 (ddt, *J* = 10.1, 7.4, 6.2 Hz, 1H), 1.63 – 1.52 (m, 1H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.26 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 148.2, 144.7, 138.1, 106.5, 105.7, 56.3, 56.2, 54.6, 44.7, 43.2, 26.9, 23.7, 17.3, 11.9; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.65 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.14 (p, *J* = 7.5 Hz, 1H), 2.20 (p, *J* = 7.5 Hz, 1H), 1.20 (s, 3H), 1.12 (d, *J* = 7.4 Hz, 3H), 1.08 (s, 3H), 0.92 (d, *J* = 7.5 Hz, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.2, 143.8, 138.9, 107.3, 105.9, 56.2, 56.2, 47.7, 45.6, 41.2, 28.9, 26.3, 17.1, 10.6; HRMS (ESI): Exact mass calcd for $C_{15}H_{22}O_2$ $[M+Na]^+$, 257.1512. Found 257.1512.

***anti*-3-Butyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81b major)** and ***syn*-3-Butyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81b minor):** Synthesized from 1-(3,4-dimethoxyphenyl)pentan-1-ol (**SII-71c**, 0.143 mmol) and silane **II-79** via General Method C



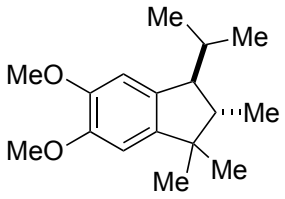
2.8 (**II-81b major**)



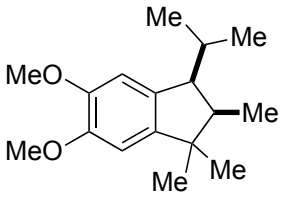
1 (**XX II-81b minor**)

(34 mg, 2.9:1 d.r., 87% yield): IR (Germanium ATR): 2953, 2927, 2858, 1606, 1498, 1209, 1058, 982 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.68 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.72 – 2.57 (m, 1H), 1.82 – 1.65 (m, 2H), 1.62 – 1.33 (m, 5H), 1.26 (s, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.97 – 0.94 (m, 3H), 0.93 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 148.0, 144.9, 137.0, 107.0, 105.6, 56.3, 56.2, 51.0, 48.4, 44.7, 31.8, 29.3, 27.2, 23.9, 23.5, 14.3, 12.8; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.68 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.02 (q, J = 7.3 Hz, 1H), 2.23 (p, J = 7.3 Hz, 1H), 1.82 – 1.65 (m, 1H), 1.62 – 1.33 (m, 5H), 1.20 (s, 3H), 1.14 (s, 3H), 0.97 – 0.94 (m, 3H), 0.90 (d, J = 7.3 Hz, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.7, 144.0, 137.5, 108.1, 106.0, 56.2, 56.2, 48.0, 46.3, 45.3, 30.9, 30.3, 28.8, 25.5, 23.3, 14.3, 10.6; HRMS (ESI): Exact mass calcd for $C_{18}H_{28}O_2$ $[M+Na]^+$, 299.1982. Found 299.1991.

***anti*-3-Isopropyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81c major)** and ***syn*-3-Isopropyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81c minor):** Synthesized from 1-(3,4-dimethoxyphenyl)-2-methyl-1-propanol (**SII-71b**, 0.216 mmol) and silane **II-79** via General Method C (51 mg, 2.2:1 d.r., 90% yield): IR (Germanium ATR): 2954, 2870, 1605, 1499, 1464, 1211, 1060, 987, 851, 773 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, J = 0.9 Hz, 1H), 6.65 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.91 (ddd, J = 7.3, 7.3, 0.8 Hz, 1H), 2.27 (dq, J = 7.4, 7.4 Hz, 1H), 2.05 – 1.91 (m, 1H), 1.19 (s, 3H), 1.12 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.3, 144.8, 135.9, 109.5, 105.8, 56.3, 56.1, 53.0, 48.7, 45.2, 29.0, 28.1, 25.1, 24.1, 22.1, 11.3; Minor



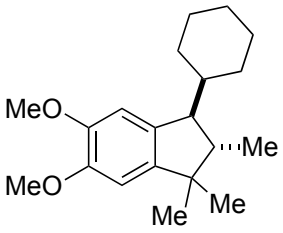
2.2 (**II-81c major**)



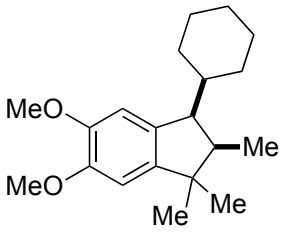
1 (**II-81c minor**)

Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 1.1 Hz, 1H), 6.65 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.68 (ddd, *J* = 9.6, 2.9, 1.0 Hz, 1H), 2.20 (pd, *J* = 7.0, 2.9 Hz, 1H), 1.86 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.25 (s, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.8, 145.3, 135.3, 107.6, 105.5, 56.3, 56.1, 54.9, 47.0, 44.8, 29.0, 27.5, 24.4, 20.3, 20.1, 14.4; HRMS (ESI): Exact mass calcd for $C_{17}H_{26}O_2$ $[M+H]^+$, 263.2006. Found 263.2008.

***anti*-3-Cyclohexyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81d major)** and ***syn*-3-Cyclohexyl-5,6-dimethoxy-1,1,2-trimethylindene (II-81d minor):** Synthesized from 1-cyclohexyl-1-(3,4-dimethoxyphenyl)-methanol (**SII-71a**, 0.197 mmol) and silane **II-79** via General Method C (54 mg, 1.8:1 d.r., 91% yield): IR (Germanium ATR): 2924, 2851, 1606, 1501, 1464, 1211, 1064, 842, 768 cm^{-1}; Major Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.65 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.85 (t, *J* = 7.2 Hz, 1H), 2.28 (p, *J* = 7.4 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.82 – 1.46 (m, 6H), 1.33 – 1.12 (m, 4H), 1.19 (s, 3H), 1.08 (s, 3H), 1.01 (d, *J* = 7.3 Hz, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.2, 144.9, 135.8, 109.9, 105.7, 56.3, 56.1, 52.3, 48.6, 45.4, 38.4, 35.3, 32.4, 28.9, 27.2, 27.1, 26.8, 25.5, 11.1; Minor Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.64 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.62 (dd, *J* = 9.5, 2.9 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.82 – 1.46 (m, 6H), 1.33 – 1.12 (m, 5H), 1.24 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.8, 145.4, 135.3, 107.8, 105.5, 56.4, 56.1, 54.8, 47.2, 44.8, 40.3, 31.3, 30.8, 27.7, 27.5, 27.5, 27.2, 24.5, 14.6; HRMS (ESI): Exact mass calcd for $C_{20}H_{30}O_2$ $[M+NH_4]^+$, 320.2584. Found 320.2593.

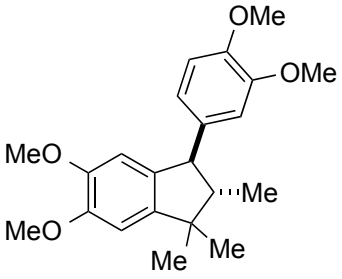


1.8 (**II-81d major**)



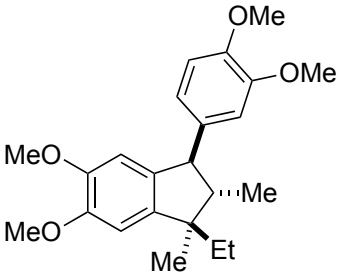
1 (**II-81d minor**)

***anti*-3-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1,1,2-trimethylindane (II-81e):** Synthesized



from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.204 mmol) and silane **II-79** via General Method C (69 mg, 95% yield): IR (Germanium ATR): 2999, 2955, 2869, 2831, 1605, 1514, 1499, 1463, 1247, 1208, 1030, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 8.2, 2.0 Hz, 1H), 6.75 (s, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.39 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.69 (d, J = 10.6 Hz, 1H), 1.97 (dq, J = 10.6, 6.9 Hz, 1H), 1.34 (s, 3H), 1.02 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.6, 148.2, 147.8, 145.1, 136.5, 136.4, 121.2, 111.6, 111.1, 108.0, 105.3, 56.6, 56.2 (3C), 56.1, 56.0, 44.7, 26.8, 23.6, 11.7; HRMS (ESI): Exact mass calcd for $C_{22}H_{28}O_4$ $[M+H]^+$, 357.206. Found 357.2059.

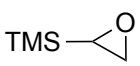
(1*R*,2*S*,3*R*)-3-(3,4-Dimethoxyphenyl)-1-ethyl-5,6-dimethoxy-1,2-dimethylindane (II-81f):



Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.174 mmol) and silane **II-80** via General Method C (71 mg, 1.8:1 d.r., 97% yield): IR (Germanium ATR): 2995, 2956, 2831, 1605, 1512, 1503, 1464, 1249, 1205, 1069, 1030, 853, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, J = 8.2 Hz, 1H), 6.78 (dd, J = 8.1, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.66 (s, 1H), 6.38 (s, 1H), 3.90 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.68 (d, J = 10.2 Hz, 1H), 2.15 (dq, J = 10.3, 6.8 Hz, 1H), 1.78 (dq, J = 14.9, 7.5 Hz, 1H), 1.68 (dq, J = 14.6, 7.4 Hz, 1H), 1.02 (s, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.6, 148.2, 147.8, 143.3, 137.1, 137.1, 121.1, 111.7, 111.2,

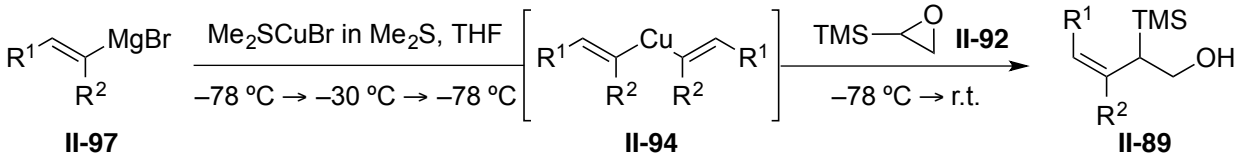
107.9, 105.7, 56.4, 56.3, 56.1, 56.0, 56.0, 51.0, 48.3, 31.0, 23.6, 12.4, 9.3; HRMS (ESI): Exact mass calcd for $C_{23}H_{30}O_4$ $[M+Na]^+$, 393.2036. Found 393.2045.

2.6.3 Type B Allylsilane Experimental Procedures and Characterization Data



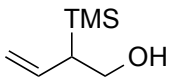
(Trimethylsilyl)ethylene oxide (II-92): A modified version of Croudace's procedure was used[134]: A solution of *m*CPBA (77%, 50.3 g, 224 mmol) in chloroform (370 mL) was added dropwise to a solution of vinyltrimethylsilane (15 g, 150 mmol) in chloroform (40 mL) at 0 ºC. The mixture was then gradually warmed to room temperature and allowed to stir overnight. The cloudy white reaction was neutralized by careful treatment with 5% aqueous $NaHCO_3$ at 0 ºC. The organic layer was washed repetitively with 5% $NaHCO_3$ (2 L) until *m*CPBA was no longer present as monitored by TLC. The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure. The crude material was distilled at atmospheric pressure and 110 ºC to afford the title compound as a clear oil (74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.91 (dd, J = 5.8, 5.6 Hz, 1H), 2.56 (dd, J = 5.8, 4.1 Hz, 1H), 2.20 (dd, J = 5.5, 4.1 Hz, 1H), 0.06 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.8, 44.3, -3.7. All spectroscopic data for this compound agrees with previously reported values.[135]

Scheme 2.30 General method for synthesis of Type B allylsilanes

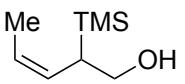


General Method E: A solution of copper(I) bromide dimethyl sulfide complex (1 equiv) in dimethyl sulfide (0.5 M soln) was charged in a round bottom flask with dry THF (0.1 M total solution volume) and cooled to –78 ºC under N_2 atmosphere. A solution of vinyl bromide Grignard

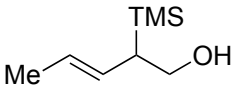
in THF (0.5 M, 2 equiv) was added dropwise to the suspension. The mixture was slowly warmed up to –30 ºC and stirred for 10 min, then cooled back to –78 ºC. (Trimethylsilyl)ethylene oxide (1 equiv) was added dropwise to the reaction. The mixture was then warmed up to room temperature and allowed to stir overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl soln and stirred for 20 min before being filtered through Celite. The organic layer was washed with additional NH_4Cl soln. The aqueous layer was extracted with diethyl ether, dried over magnesium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel with 30% ether/pentanes solvent system to afford the desired allylsilane.



2-(Trimethylsilyl)but-3-en-1-ol (II-89a): Synthesized from vinyl cuprate via General Method E (10.5 mmol scale, 64% yield): IR (Germanium ATR): 3379, 3077, 2953, 1628, 1248, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.1, 10.3, 9.6 Hz, 1H), 5.07 (ddd, *J* = 10.4, 1.8, 0.6 Hz, 1H), 5.01 (ddd, *J* = 17.2, 1.9, 1.0 Hz, 1H), 3.80 – 3.74 (m, 1H), 3.74 – 3.68 (m, 1H), 1.92 (ddd, *J* = 10.7, 9.7, 4.2 Hz, 1H), 1.48 – 1.43 (m, 1H), 0.02 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 115.2, 62.4, 40.2, -2.9; HRMS (ESI): Exact mass calcd for $C_7H_{16}OSi$ $[M+Na]^+$, 167.0863. Found 167.0869.



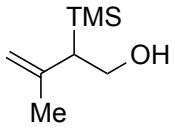
1.7 (**II-89b major**)



1 (**II-89b minor**)

2-(Trimethylsilyl)pent-3-en-1-ol (II-89b): Synthesized from 1-propenyl cuprate via General Method E (15.0 mmol scale, 1.7:1 *Z*:*E* ratio, 73% yield): IR (Germanium ATR): 3354, 3008, 2954, 1648, 1251, 1095, 1049, 965, 861, 833, 749 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (dqd, *J* = 10.8, 6.8, 0.9 Hz, 1H), 5.32 – 5.21 (m, 1H), 3.77 (ddd, *J* = 10.6, 8.1, 3.9 Hz, 1H), 3.65 – 3.57 (m, 1H), 2.27 (tdd, *J* = 11.2, 4.0, 0.9 Hz, 1H), 1.62 (dd, *J* = 6.8,

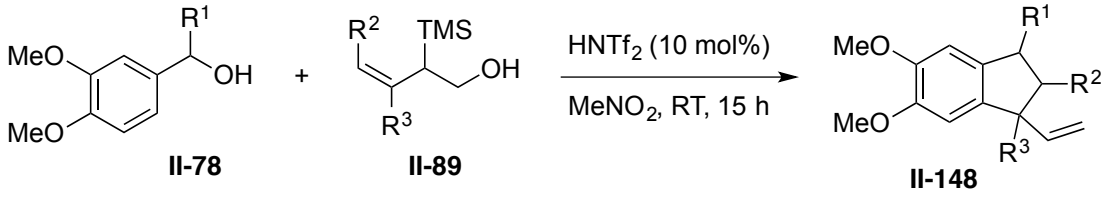
1.8 Hz, 3H), 1.38 (d, *J* = 8.2 Hz, 1H), 0.00 (s, 9H); Major Isomer ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.0, 125.8, 63.5, 33.7, 13.5, -2.7; Minor Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (dqd, *J* = 15.2, 6.3, 0.7 Hz, 1H), 5.32 – 5.21 (m, 1H), 3.71 (ddd, *J* = 10.7, 8.2, 4.0 Hz, 1H), 3.65 – 3.57 (m, 1H), 1.81 (td, *J* = 10.4, 4.1 Hz, 1H), 1.71 (dd, *J* = 6.3, 1.5 Hz, 3H), 1.48 (d, *J* = 8.3 Hz, 1H), -0.01 (s, 9H); Minor Isomer ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.1, 126.6, 62.7, 38.6, 18.4, -2.8; HRMS (ESI): Exact mass calcd for $C_8H_{18}OSi$ $[M+Na]^+$, 181.1019. Found 181.102.



3-methyl-2-(Trimethylsilyl)but-3-en-1-ol (II-89c): Synthesized from isopropenyl cuprate via General Method E (5.0 mmol scale, 51% yield): IR (Germanium ATR): 3329, 3008, 2955, 2880, 1437, 1248, 1095, 1049, 862, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, *J* = 1.5 Hz, 1H), 4.66 (d, *J* = 1.5 Hz, 1H), 3.84 (td, *J* = 11.3, 2.2 Hz, 1H), 3.72 (ddd, *J* = 11.4, 8.0, 4.4 Hz, 1H), 1.94 (dd, *J* = 11.8, 4.4 Hz, 1H), 1.75 (s, 3H), 1.60 – 1.59 (m, 1H), 0.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 110.2, 61.8, 43.0, 23.8, -2.2; HRMS (ESI): Exact mass calcd for $C_8H_{18}OSi$ $[M+Na]^+$, 181.1019. Found 181.1022.

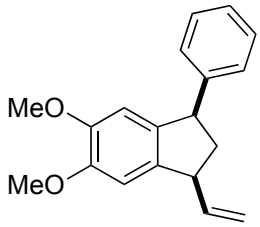
2.6.4 Type B Indane Experimental Procedures and Characterization Data

Scheme 2.31 General method for synthesis of indanes with Type B allylsilanes

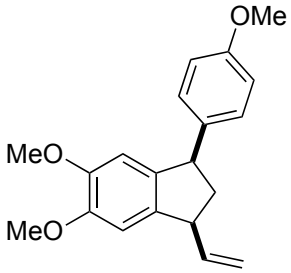


General Method F: Benzhydrol **II-78** (1 equiv) was dissolved in $MeNO_2$ (0.1 M) and allowed to stir under N_2 atmosphere. Alkyl silane **II-89** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at room temperature for 15 hours before being quenched with saturated aqueous $NaHCO_3$ solution. The biphasic solution was

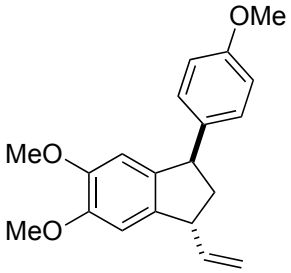
extracted with DCM and the combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired indane.



***syn*-1-Phenyl-5,6-dimethoxy-3-vinylindane (II-98c):** Synthesized from 3,4-dimethoxybenzhydrol (**II-44**, 0.138 mmol) and 2-(trimethylsilyl)but-3-en-1-ol **(II-89a)** via General Method F (21 mg, 2:1 d.r., 53% yield): IR (Germanium ATR): 2999, 2853, 2830, 1619, 1500, 1463, 1453, 1290, 1213, 1185, 1082, 1029, 913, 855, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.26 – 7.23 (m, 3H), 6.71 (s, 1H), 6.43 (s, 1H), 5.88 (ddd, *J* = 17.1, 10.0, 8.6 Hz, 1H), 5.25 (ddd, *J* = 17.0, 1.9, 0.9 Hz, 1H), 5.15 (dd, *J* = 9.9, 1.9 Hz, 1H), 4.24 (dd, *J* = 10.4, 7.3 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.72 – 3.70 (m, 1H), 2.74 (dt, *J* = 12.6, 7.2 Hz, 1H), 1.84 (dt, *J* = 12.6, 10.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 148.6, 145.1, 141.3, 138.3, 137.9, 128.7, 128.5, 126.6, 115.7, 108.0, 107.1, 56.3, 56.2, 50.8, 49.2, 45.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}O_2$ $[M+H]^+$, 281.1536. Found 281.1542.



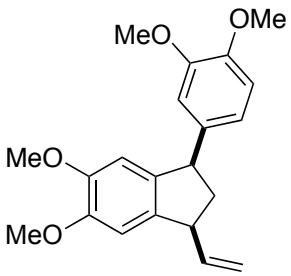
II-98b major



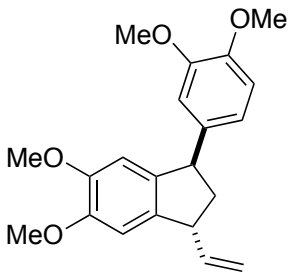
II-98b minor

***syn*-5,6-Dimethoxy-1-(4-methoxyphenyl)-3-vinylindane (II-98b major)** and ***anti*-5,6-Dimethoxy-1-(4-methoxyphenyl)-3-vinylindane (II-98b minor):** Synthesized from 3,4,4'-trimethoxybenzhydrol (**SII-57g**, 0.203 mmol) and 2-(trimethylsilyl)but-3-en-1-ol **(II-89a)** via General Method F (34 mg, 2:1 d.r., 54% yield): IR (Germanium ATR): 3066, 2996, 2832, 1610, 1515, 1463, 1290, 1247, 1213, 1175, 1081, 1034, 915, 857, 816 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H), 6.90

– 6.86 (m, 2H), 6.71 (s, 1H), 6.42 (s, 1H), 5.87 (ddd, *J* = 16.9, 10.0, 8.6 Hz, 1H), 5.24 (ddd, *J* = 17.0, 1.9, 0.9 Hz, 1H), 5.15 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.18 (dd, *J* = 10.5, 7.2 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.72 – 3.69 (m, 1H), 2.71 (dt, *J* = 12.5, 7.1 Hz, 1H), 1.79 (dt, *J* = 12.5, 10.3 Hz, 1H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 148.7, 148.5, 141.3, 138.7, 137.8, 137.1, 129.4, 115.7, 114.1, 108.0, 107.1, 56.2, 56.2, 55.4, 50.0, 49.1, 45.4; Minor Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 – 7.00 (m, 2H), 6.85 – 6.81 (m, 2H), 6.73 (s, 1H), 6.56 (s, 1H), 5.89 (ddd, *J* = 17.0, 10.0, 8.1 Hz, 1H), 5.09 (ddd, *J* = 17.0, 1.9, 1.0 Hz, 1H), 5.05 (ddd, *J* = 10.0, 1.9, 0.8 Hz, 1H), 4.34 (dd, *J* = 8.2, 5.5 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72 – 3.69 (m, 1H), 2.38 (ddd, *J* = 12.7, 8.2, 6.0 Hz, 1H), 2.27 (ddd, *J* = 13.0, 7.9, 5.6 Hz, 1H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 148.8, 148.6, 141.5, 138.2, 138.0, 137.5, 128.8, 114.5, 114.0, 108.1, 107.5, 56.2, 56.1, 55.4, 49.2, 48.4, 44.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}O_3$ $[M+Na]^+$, 333.1461. Found 333.1473.



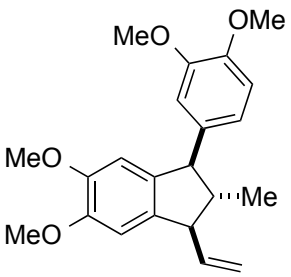
II-98a major



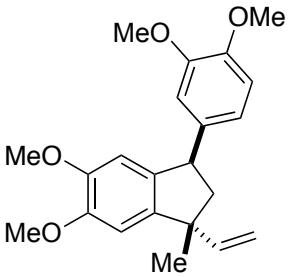
II-98a minor

***syn*-1-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-3-vinylindane (II-98a major)** and ***anti*-1-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-3-vinylindane (II-98a minor):** Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.291 mmol) and 2-(trimethylsilyl)but-3-en-1-ol **(II-89a)** via General Method F (54 mg, 2:1 d.r., 54% yield): IR (Germanium ATR): 3072, 2950, 1639, 1604, 1501, 1463, 1211, 1028, 915, 855 cm^{-1}; Major Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.82 (d, J = 1.9 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.72 (s, 1H), 6.45 (s, 1H), 5.97 – 5.83 (m, 1H), 5.25 (dd, J = 16.7, 1.6 Hz, 1H), 5.16 (dd, J = 10.0, 1.9 Hz, 1H), 4.18 (dd, J = 10.5, 7.1 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 3.74 (s, 3H), 3.73

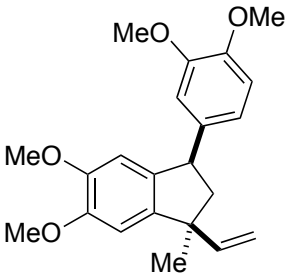
– 3.68 (m, 1H), 2.72 (dt, J = 12.5, 7.1 Hz, 1H), 1.81 (dt, J = 12.4, 10.2 Hz, 1H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.7, 148.6, 147.8, 141.2, 138.5, 137.8, 137.5, 120.6, 115.7, 111.4, 111.3, 108.0, 107.1, 56.3, 56.2, 56.1, 56.1, 50.5, 49.0, 45.3; Minor Isomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.74 (s, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.57 (s, 1H), 5.97 – 5.83 (m, 1H), 5.09 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.05 (dd, *J* = 9.9, 1.9 Hz, 1H), 4.34 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.89 (s, 6H), 3.81 (s, 3H), 3.78 (s, 3H), 3.73 – 3.68 (m, 1H), 2.39 (ddd, *J* = 12.7, 8.1, 5.6 Hz, 1H), 2.29 (ddd, *J* = 12.8, 7.9, 5.9 Hz, 1H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.8, 148.7, 147.6, 141.4, 138.4, 138.0, 137.5, 119.8, 114.5, 111.3, 111.1, 108.1, 107.5, 56.3, 56.2, 56.1, 56.0, 49.6, 48.4, 44.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}O_4$ $[M+Na]^+$, 363.1567. Found 363.158.



1-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-2-methyl-3-vinylindane (II-100): Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.197 mmol) and (*E*)-2-(trimethylsilyl)pent-3-en-1-ol **(II-89b)** via General Method F (40 mg, 4:1 d.r., 57% yield): IR (Germanium ATR): 3016, 2953, 1639, 1503, 1463, 1212, 1027, 913 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 8.2 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 1.0 Hz, 1H), 6.42 (d, *J* = 1.0 Hz, 1H), 5.81 (ddd, *J* = 17.0, 10.0, 9.0 Hz, 1H), 5.30 – 5.21 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 3.68 (d, *J* = 10.1 Hz, 1H), 3.25 (t, *J* = 9.3 Hz, 1H), 2.03 (tq, *J* = 10.0, 6.6 Hz, 1H), 1.12 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (126 MHz, $CDCl_3$) δ 149.2, 148.7, 148.5, 147.9, 140.1, 138.0, 137.4, 136.2, 121.2, 117.2, 111.5, 111.2, 108.0, 107.1, 58.3, 56.9, 56.3, 56.2, 56.1, 56.0, 53.7, 15.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}O_4$ $[M+NH_4]^+$, 372.2169. Found 372.2179.



II-101 major

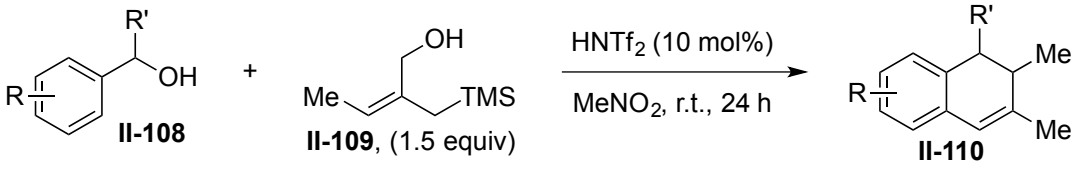


II-101 minor

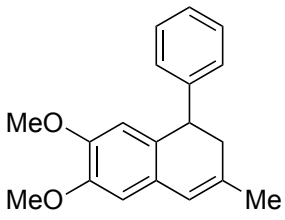
***anti*-3-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1-methyl-1-vinylindane (II-101 major)** and ***syn*-3-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1-methyl-1-vinylindane (II-101 minor):** Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**SII-57e**, 0.184 mmol) and 3-methyl-2-(trimethylsilyl)but-3-en-1-ol **(II-89c)** via General Method F (42 mg, 2:1 d.r., 55% yield): IR (Germanium ATR): 2997, 2953, 1634, 1499, 1463, 1208, 1027, 911 cm^{-1}; Major Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.81 – 6.77 (m, 1H), 6.73 – 6.71 (m, 1H), 6.69 (s, 1H), 6.44 (s, 1H), 6.00 (dd, *J* = 17.2, 10.4 Hz, 1H), 4.91 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.70 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.19 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 2.52 (dd, *J* = 12.4, 7.1 Hz, 1H), 1.94 (dd, *J* = 12.4, 10.3 Hz, 1H), 1.47 (s, 3H); Major Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.7, 147.7, 146.9, 145.9, 140.9, 138.1, 137.5, 120.5, 111.5, 111.3, 111.1, 108.0, 106.4, 56.2, 56.2, 56.1, 56.1, 52.4, 49.6, 49.1, 26.3; Minor Isomer ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.81 – 6.77 (m, 1H), 6.73 – 6.71 (m, 1H), 6.63 (s, 1H), 6.44 (s, 1H), 6.09 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.17 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.11 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.34 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.88 (s, 6H), 3.82 (s, 3H), 3.74 (s, 3H), 2.38 (dd, *J* = 12.6, 7.4 Hz, 1H), 2.08 (dd, *J* = 12.6, 9.8 Hz, 1H), 1.34 (s, 3H); Minor Isomer ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 148.7, 148.7, 148.6, 145.9, 142.4, 137.7, 137.1, 120.5, 112.0, 111.5, 111.3, 108.0, 106.2, 56.2, 45.2, 56.1, 56.1, 52.3, 49.5, 48.5, 24.9; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}O_4$ $[M+NH_4]^+$, 372.2169. Found 372.2175.

2.6.5 Type C Allylsilanes Experimental Procedures and Characterization Data

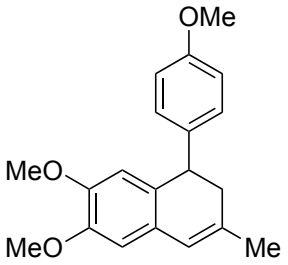
Scheme 2.32 General method for synthesis of tetralins with Type C allylsilanes



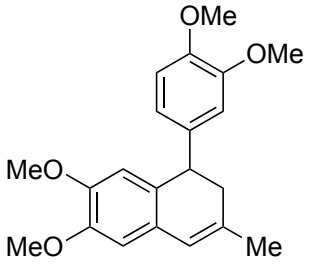
General Method G: Benzhydrol **II-108** (1 equiv) was dissolved in $MeNO_2$ (0.1 M) and allowed to stir under N_2 atmosphere. Alkyl silane **II-109** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at room temperature for 24 hours before being quenched with saturated aqueous $NaHCO_3$ solution. The biphasic solution was extracted with DCM and the combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired tetralin.



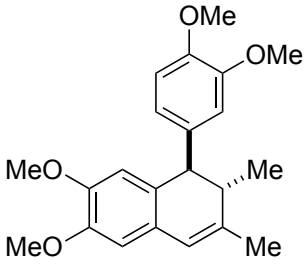
4-Phenyl-3,4-dihydro-6,7-dimethoxy-2-methylnaphthalene (II-107a): Synthesized from 3,4-dimethoxybenzhydrol (**II-44**, 0.148 mmol) and 2-trimethylsilylmethyl-3-trimethylsiloxy-l-propene **(II-106)** via General Method G (22 mg, 52% yield): IR (Germanium ATR): 2998, 2956, 2829, 1605, 1510, 1464, 1452, 1401, 1309, 1270, 1232, 1112, 1030, 866, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 6.62 (s, 1H), 6.40 (s, 1H), 6.20 (q, J = 1.5 Hz, 1H), 4.07 (t, J = 8.3 Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 2.58 (ddt, J = 16.7, 7.5, 1.2 Hz, 1H), 2.46 (ddt, J = 16.7, 9.1, 1.2 Hz, 1H), 1.85 (d, J = 1.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 147.4, 145.2, 134.6, 128.8, 128.6, 128.3, 128.3, 126.5, 122.4, 111.9, 109.2, 56.1, 56.1, 44.3, 37.9, 23.5; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}O_2$ $[M+H]^+$, 281.1536. Found 281.1545.



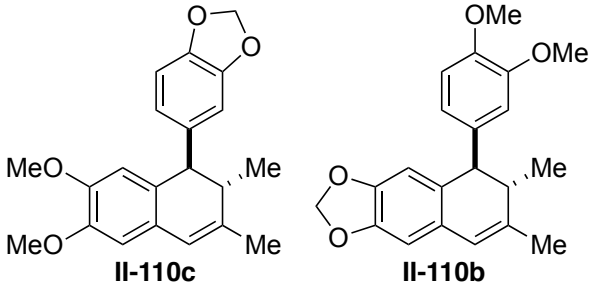
4-(4-Methoxyphenyl)-3,4-dihydro-6,7-dimethoxy-2-methylnaphthalene (II-107b): Synthesized from 3,4,4'-trimethoxybenzhydrol (**SII-57g**, 0.155 mmol) and 2-trimethylsilylmethyl-3-trimethylsiloxy-l-propene **(II-106)** via General Method G (15 mg, 30% yield): IR (Germanium ATR): 2999, 2955, 2831, 1609, 1512, 1464, 1401, 1305, 1248, 1232, 1112, 1035, 990, 866 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2H), 6.87 – 6.81 (m, 2H), 6.61 (s, 1H), 6.40 (s, 1H), 6.19 (d, *J* = 1.6 Hz, 1H), 4.02 (dd, *J* = 9.2, 7.5 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 2.54 (ddt, *J* = 16.7, 7.5, 1.2 Hz, 1H), 2.42 (ddt, *J* = 16.7, 9.3, 1.3 Hz, 1H), 1.85 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 147.7, 147.4, 137.2, 134.8, 129.3, 129.2, 128.2, 122.3, 113.9, 111.8, 111.8, 109.3, 109.2, 56.1, 56.1, 55.4, 43.5, 38.1, 23.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}O_3$ $[M+H]^+$, 311.1642. Found 311.1648.



4-(3,4-Dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-2-methyl naphthalene (II-107c): Synthesized from 3,3',4,4'-tetramethoxybenzhydrol (**II-99**, 0.251 mmol) and 2-trimethylsilylmethyl-3-trimethylsiloxy-l-propene **(II-106)** via General Method G (40 mg, 46% yield): IR (Germanium ATR): 2998, 2956, 2831, 1603, 1512, 1463, 1260, 1231, 1111, 1028, 994, 864, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.62 (s, 1H), 6.40 (s, 1H), 6.20 (d, *J* = 1.5 Hz, 1H), 4.01 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 2.56 – 2.41 (m, 2H), 1.87 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 147.7, 147.7, 147.4, 137.6, 134.9, 129.2, 128.2, 122.3, 120.5, 111.7, 111.4, 111.2, 109.2, 56.1 (2C), 56.0, 56.0, 44.1, 38.1, 23.5; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}O_4$ $[M+H]^+$, 341.1747. Found 341.1751.



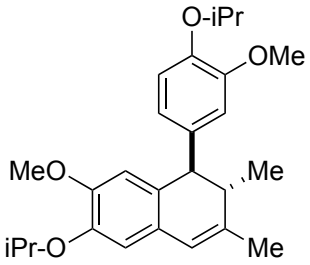
(±)-Cyclogalgravin (II-108a): Synthesized from 3,3',4,4'-tetramethoxy benzhydrol (**SII-57e**, 0.259 mmol) and (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol **(II-109)** via General Method G (72 mg, 78% yield): IR (Germanium ATR): 2956, 1604, 1508, 1463, 1226, 1140, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.62 (s, 1H), 6.55 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.55 (s, 1H), 6.14 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.68 (d, *J* = 3.2 Hz, 1H), 2.39 (qd, *J* = 7.0, 3.0 Hz, 1H), 1.80 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.7, 147.6, 147.4, 139.0, 138.3, 127.4, 127.2, 121.2, 119.7, 113.0, 111.1, 111.0, 109.0, 56.1 (2C), 55.9, 55.9, 51.0, 42.1, 22.3, 18.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}O_4$ $[M+H]^+$, 355.1904. Found 355.1913. All spectroscopic data for this compound agrees with previously reported values.[136, 137]



II-110c **II-110b**

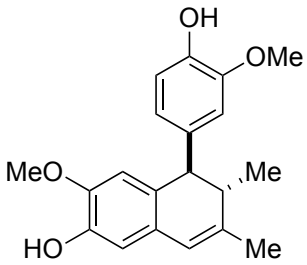
(±)-Pycnanthulignene B (II-110c) and **(7'*R*,8'*S*)-7'-(3',4'-Dimethoxyphenyl)-8,8'-dimethyl-7',8'-dihydronaphtho [4,5-*d*][1,3]dioxole (II-110b):** Synthesized from 3,4-methylenedioxy-3',4'-dimethoxybenzhydrol **(SII-57h**, 0.215 mmol) and (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol **(II-109)** via General Method G (57 mg, 1:1 regioisomer, 79% yield): IR (Germanium ATR): 3000, 2958, 2902, 1605, 1512, 1483, 1452, 1230, 1124, 1038, 941, 871 cm^{-1}; Pycnanthulignene B ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 6.55 – 6.51 (m, 3H), 6.13 (s, 1H), 5.90 – 5.85 (m, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.66 (d, *J* = 2.8 Hz, 1H); 2.46 – 2.30 (m, 1H), 1.80 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H); Pycnanthulignene B ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 147.7, 147.6, 145.9, 139.8,

138.7, 127.2, 127.1, 121.3, 120.6, 113.0, 109.1, 108.2, 108.1, 100.9, 56.1, 56.1, 51.0, 42.4, 22.2, 19.0; (7'*R*,8'*S*)-7'-(3',4'-Dimethoxyphenyl)-8,8'-dimethyl-7',8'-dihydronaphtho [4,5-*d*][1,3]dioxole ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 2.1 Hz, 1H), 6.57 (s, 1H); 6.57 (dd, *J* = 8.3, 2.1 Hz, 1H); 6.50 (s, 1H), 6.10 (s, 1H), 5.90 – 5.85 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.64 (d, *J* = 3.7 Hz, 1H); 2.46 – 2.30 (m, 1H), 1.79 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H) (7'*R*,8'*S*)-7'-(3',4'-Dimethoxyphenyl)-8,8'-dimethyl-7',8'-dihydronaphtho [4,5-*d*][1,3]dioxole ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.5, 146.3, 146.1, 139.0, 138.1, 129.0, 128.3, 121.6, 119.7, 111.1, 111.0, 110.0, 106.1, 100.8, 56.0, 55.9, 51.4, 41.7, 22.4, 18.7; HRMS (ESI): Exact mass calcd for $C_{21}H_{22}O_4$ $[M+Na]^+$, 361.141. Found 361.1419. All spectroscopic data for this compound agrees with previously reported values.[137, 138]

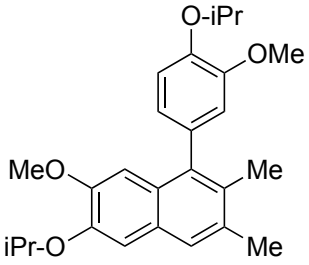


***trans*-4-(4-Isopropoxy-3-methoxyphenyl)-3,4-dihydro-7-isopropoxy-6-methoxy-2,3-dimethylnaphthalene (II-123):** Synthesized from 4,4'-diisopropoxy-3,3'-dimethoxybenzhydrol **(SII-123**, 0.112 mmol) and (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol **(II-109)** via General Method G (23 mg, 49% yield): IR (Germanium ATR): 2973, 2928, 1603, 1508, 1465, 1264, 1224, 1138, 1112, 1036, 941, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.2 Hz, 1H), 6.64 (s, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.53 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.50 (p, *J* = 6.1 Hz, 1H), 4.44 (p, *J* = 6.1 Hz, 1H), 3.74 (d, *J* = 0.9 Hz, 6H), 3.66 (d, *J* = 3.5 Hz, 1H), 2.39 (qd, *J* = 7.0, 3.5 Hz, 1H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.36 (dd, *J* = 6.1, 3.5 Hz, 6H), 1.33 (dd, *J* = 6.1, 1.8 Hz, 6H), 1.08 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 149.2, 145.9, 145.7, 138.7, 138.7, 128.2, 127.3, 121.3, 119.8, 115.5, 113.8, 113.7, 111.9, 71.7,

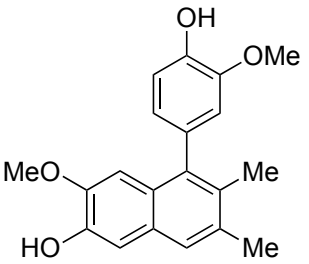
71.4, 56.2, 56.0, 51.1, 42.0, 22.4, 22.4, 22.3, 18.8; HRMS (ESI): Exact mass calcd for $C_{26}H_{34}O_4$ $[M+H]^+$, 411.253. Found 411.2536.



(±)-4',5-*O*-Didemethylcyclogalgravin (II-124): 4-(4-Isopropoxy-3-methoxy phenyl)-3,4-dihydro-7-isopropoxy-6-methoxy-2,3-dimethyl-naphthalene **(II-123**, 0.151 mmol) was dissolved in DCM (12 mL) and cooled to 0 ºC. BCl_3 (1.0 M in DCM, 0.453 mmol, 0.453 μL) was added and the reaction was allowed to stir for 50 min before being quenched with MeOH. The solution was washed with brine, and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system afforded the desired product (40 mg, 81% yield): IR (Germanium ATR): 3511, 2962, 2841, 1611, 1507, 1463, 1449, 1357, 1265, 1219, 1092, 1031, 879 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, J = 8.1 Hz, 1H), 6.67 (s, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.56 (dd, J = 8.1, 2.0 Hz, 1H), 6.52 (s, 1H), 6.11 (d, J = 1.7 Hz, 1H), 5.45 (s, 1H), 5.43 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.65 (d, J = 3.3 Hz, 1H), 2.35 (qd, J = 7.0, 3.2 Hz, 1H), 1.78 (d, J = 1.6 Hz, 3H), 1.07 (d, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 145.2, 144.3, 144.0, 139.0, 137.9, 127.9, 127.0, 121.2, 120.5, 114.1, 112.2, 111.8, 110.2, 56.1, 55.9, 51.2, 42.3, 22.3, 18.9; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}O_4$ $[M+Na]^+$, 349.141. Found 349.1428. All spectroscopic data for this compound agrees with previously reported values.[139]

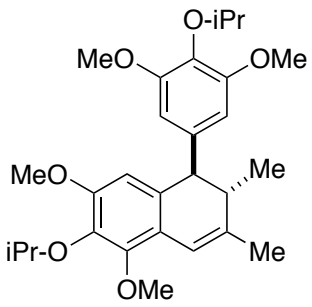


4-(4-Isopropoxy-3-methoxyphenyl)-7-isopropoxy-6-methoxy-2,3-dimethylnaphthalene (II-125): *trans*-4-(4-Isopropoxy-3-methoxyphenyl)-3,4-dihydro-7-isopropoxy-6-methoxy-2,3-dimethyl-naphthalene **(II-123**, 0.083 mmol**)** was dissolved in dry DCM (6 mL) and DDQ (0.08 mmol, 18.1 mg) was added in one portion. The reaction was allowed to stir at room temperature for 30 min before being quenched with H_2O (10 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system afforded the title compound (31 mg, 90% yield): IR (Germanium ATR): 2975, 2934, 1604, 1503, 1466, 1248, 1109, 1038, 955, 877 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.09 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.79 – 6.76 (m, 2H), 6.69 (s, 1H), 4.72 – 4.59 (m, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 2.44 (s, 3H), 2.13 (s, 3H), 1.48 – 1.40 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 149.8, 147.0, 146.1, 137.2, 133.8, 133.5, 131.5, 127.7, 127.6, 125.8, 122.4, 115.8, 114.1, 109.4, 106.1, 71.5, 71.0, 56.1, 55.8, 22.4, 22.3, 22.1, 21.2, 17.6; HRMS (ESI): Exact mass calcd for $C_{26}H_{32}O_4$ $[M+H]^+$, 409.2373. Found 409.238.

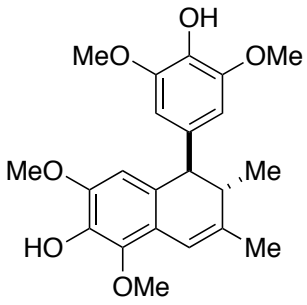


Cinnamophilin A (II-126): 4-(4-Isopropoxy-3-methoxyphenyl)-7-isopropoxy-6-methoxy-2,3-dimethylnaphthalene **(II-125**, 0.054 mmol) was dissolved in DCM (5 mL) and cooled to 0 ºC. BCl_3 (1.0 M in DCM, 0.162 mmol, 162 μL) was added and the reaction was allowed to stir for 1 hour before being quenched with MeOH. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system afforded the desired product (16 mg, 90% yield): IR (Germanium ATR): 3419, 2923, 1609, 1050, 1457,

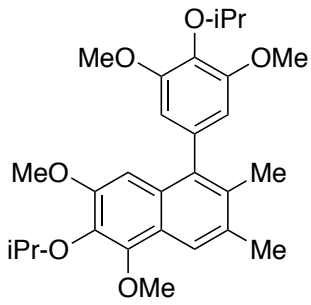
1417, 1249, 1201, 1033, 880 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.18 (s, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 7.8, 1.9 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.66 (s, 1H), 5.78 (s, 1H), 5.66 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 2.43 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7, 146.6, 145.0, 144.5, 137.3, 133.9, 133.0, 131.4, 128.2, 127.5, 125.9, 123.2, 114.5, 112.8, 108.7, 104.9, 56.2, 55.8, 21.2, 17.6; HRMS (ESI): Exact mass calcd for $C_{20}H_{20}O_4$ $[M+Na]^+$, 347.1254. Found 347.1263. All spectroscopic data for this compound agrees with previously reported values.[140]



***trans*-4-(4-Isopropoxy-2,3-dimethoxyphenyl)-7-isopropoxy-6,8-dimethoxy-2,3-dimethylnaphthalene (II-128):** Synthesized from 4,4'-diisopropoxy-3,3'-dimethoxy-5,5'-dimethoxybenzhydrol **(II-127**, 0.197 mmol) and (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol **(II-109)** via General Method G (63 mg, 68% yield): IR (Germanium ATR): 2971, 2933, 1635, 1589, 1487, 1464, 1415, 1334, 1232, 1127, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 1.7 Hz, 1H), 6.34 (s, 1H), 6.27 (s, 2H), 4.40 (hept, *J* = 6.2 Hz, 1H), 4.28 (hept, *J* = 6.2 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.71 (s, 6H), 3.63 (d, *J* = 3.8 Hz, 1H), 2.41 (qd, *J* = 7.0, 3.8 Hz, 1H), 1.82 (d, *J* = 1.5 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 6H), 1.26 (d, *J* = 6.2 Hz, 6H), 1.08 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 152.5, 149.5, 140.5, 138.8, 138.6, 134.5, 130.9, 121.2, 115.3, 109.0, 105.0, 75.5, 75.2, 61.2, 56.0, 56.0, 52.3, 41.7, 22.7, 22.7, 22.6, 18.8; HRMS (ESI): Exact mass calcd for $C_{28}H_{38}O_6$ $[M+H]^+$, 471.2741. Found 471.2751.

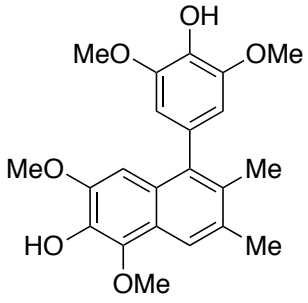


(±)-Sacidumlignan B (II-129): *trans*-4-(4-Isopropoxy-2,3-dimethoxyphenyl)-7-isopropoxy-6,8-dimethoxy-2,3-dimethyl-naphthalene **(II-128**, 0.066 mmol) was dissolved in DCM (4 mL) and cooled to 0 ºC. BCl_3 (1.0 M in DCM, 0.199 mmol, 199 μL) was added and the reaction was allowed to stir for 1 hour before being quenched with MeOH. The solution was washed with brine, and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system afforded the desired product (22 mg, 87% yield): IR (Germanium ATR): 3439, 2958, 2934, 2839, 1612, 1517, 1456, 1320, 1215, 1114, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1H), 6.35 (s, 1H), 6.30 (s, 2H), 5.43 (s, 1H), 5.34 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.78 (s, 6H), 3.60 (d, J = 3.5 Hz, 1H), 2.37 (qd, J = 7.1, 3.5 Hz, 1H), 1.82 (d, J = 1.5 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 146.0, 142.5, 139.3, 137.2, 136.7, 133.1, 126.9, 121.0, 115.0, 108.2, 104.5, 61.4, 56.3 (3C), 51.9, 42.1, 22.7, 18.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}O_6$ $[M+Na]^+$, 409.1622. Found 409.1629. All spectroscopic data for this compound agrees with previously reported values.[141]



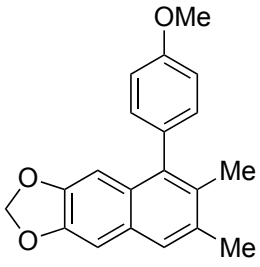
4-(4-Isopropoxy-2,3-dimethoxyphenyl)-7-isopropoxy-6,8-dimethoxy-2,3-dimethylnaphthalene: *trans*-4-(4-Isopropoxy-2,3-dimethoxyphenyl)-7-isopropoxy-6,8-dimethoxy-2,3-dimethyl-naphthalene **(II-128**, 0.029 mmol**)** was dissolved in dry DCM (4 mL) and the reaction was cooled to 0 ºC. DDQ (0.028 mmol, 6.3 mg) was added in one portion. The reaction was allowed to stir at 0 ºC for 30 min before being quenched

with H_2O (10 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 15% EtOAc in hexanes solvent system afforded the title compound (6 mg, 44% yield): IR (Germanium ATR): 2972, 2033, 1577, 1462, 1399, 1336, 1257, 1236, 1124, 1089, 981, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 6.48 (s, 3H), 4.50 (hept, J = 6.2 Hz, 1H), 4.49 (hept, J = 6.2 Hz, 1H), 4.04 (s, 3H), 3.80 (s, 6H), 3.63 (s, 3H), 2.48 (s, 3H), 2.16 (s, 3H), 1.37 (d, J = 6.2 Hz, 6H), 1.33 (d, J = 6.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 152.8, 148.0, 138.2, 137.5, 136.1, 134.8, 133.3, 132.9, 129.0, 122.9, 120.8, 107.2, 101.5, 75.9, 75.2, 61.2, 56.3, 55.6, 29.9, 22.7, 22.6, 21.4, 17.8; HRMS (ESI): Exact mass calcd for $C_{28}H_{36}O_6$ $[M+Na]^+$, 491.2404. Found 491.2411.



Sacidumlignan A (II-130): 4-(4-Isopropoxy-2,3-dimethoxyphenyl)-7-isopropoxy-6,8-dimethoxy-2,3-dimethylnaphthalene (0.011 mmol) was dissolved in DCM (2 mL) and cooled to 0 ºC. BCl_3 (1.0 M in DCM, 0.011 mmol, 11 μL) was added and the reaction was allowed to stir for 30 min before being quenched with MeOH. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 30% EtOAc in hexanes solvent system afforded the desired product (4 mg, 98% yield): IR (Germanium ATR): 3490, 3437, 3001, 2935, 1609, 1518, 1463, 1414, 1336, 1286, 1209, 1114, 1083, 913, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.50 (s, 1H), 6.48 (s, 2H), 5.73 (s, 1H), 5.59 (s, 1H), 4.04 (s, 3H), 3.86 (s, 6H), 3.75 (s, 3H), 2.48 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 147.3, 139.5, 137.7, 136.5, 133.8, 133.5, 132.0, 132.0, 126.8, 122.8, 120.2, 106.8, 101.0, 61.2, 56.5, 56.1, 21.5, 17.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{24}O_6$ $[M+Na]^+$, 407.1465.

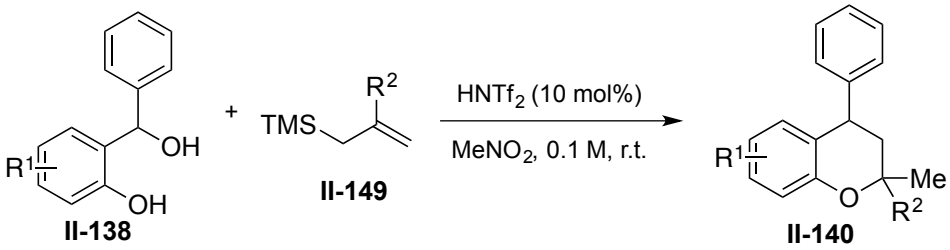
Found 407.1471. All spectroscopic data for this compound agrees with previously reported values.[141]



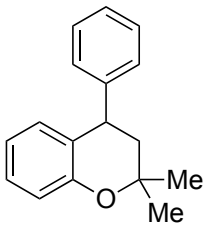
Pycnanthuligene C (II-120): A mixture of *cis*- and *trans*-dihydronaphthalene isomers were synthesized from 3,4-methylenedioxy-4'-methoxybenzhydrol **(II-117**, 0.173 mmol) and (*Z*)-2-trimethylsilylmethyl-2-buten-1-ol **(II-109)** via General Method G. The crude reaction mixture was then re-dissolved in dry DCM (10 mL) and DDQ (0.200 mmol, 45 mg) was added in one portion. The reaction was allowed to stir at room temperature for 30 min before being quenched with H_2O (10 mL). The organic layer was separated and dried over Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with a 10% EtOAc in hexanes solvent system afforded the title compound (34 mg, 73% yield over two steps): IR (Germanium ATR): 2994, 2898, 1610, 1515, 1497, 1461, 1285, 1236, 1175, 1039, 1039, 900 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.15 – 7.12 (m, 2H), 7.06 – 7.01 (m, 3H), 6.64 (s, 1H), 5.94 (s, 2H), 3.90 (s, 3H), 2.43 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 146.9, 146.7, 137.7, 133.8, 133.1, 132.0, 131.3, 129.0, 128.9, 126.6, 114.0, 103.2, 103.2, 100.9, 55.5, 21.1, 17.6; HRMS (ESI): Exact mass calcd for $C_{20}H_{18}O_3$ $[M+H]^+$, 307.1329. Found 307.133. All spectroscopic data for this compound agrees with previously reported values.[138]

2.6.6 Chromane Experimental Procedures and Characterization Data

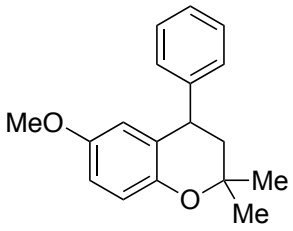
Scheme 2.33 General method H for synthesis of chromanes



General Method H: Benzyl alcohol **II-138** (1 equiv) was dissolved in $MeNO_2$ (0.1 M soln) and allowed to stir under N_2 atmosphere. Alkyl silane **II-149** (1.5 equiv) was added, followed by a solution of triflimide in DCM (10 mol%). The reaction was allowed to stir at room temperature for 2 hours before being quenched with sat. $NaHCO_3$ solution. The biphasic solution was extracted with DCM and the combined organic layers were dried over Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with EtOAc in hexanes solvent systems afforded the desired chromane.



2,2-dimethyl-4-phenylchroman (II-140a): Synthesized from 2-(hydroxyphenylmethyl)phenol (0.184 mmol) and silane **II-45** via General Method H (31 mg, 70% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 6H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.76 – 6.71 (m, 2H), 4.09 (dd, *J* = 12.0, 6.6 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 145.2, 129.9, 128.9, 128.7, 127.9, 126.7, 124.7, 120.0, 117.4, 74.7, 43.7, 40.1, 30.1, 24.4. All spectroscopic data for this compound agrees with previously reported values.[142]



6-Methoxy-2,2,-dimethyl-4-phenylchroman (II-140b): Synthesized from 2-(hydroxyphenylmethyl)-4-methoxyphenol (0.166 mmol) and silane **II-45** via General Method H (34 mg, 76% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 5H), 6.77 (d, J = 8.8 Hz, 1H), 6.70 (ddd, J = 8.9, 3.0, 0.9 Hz, 1H), 6.29 (dd, J = 3.1, 1.0 Hz, 1H), 4.06 (dd, J = 12.0, 6.6 Hz, 1H), 3.60 (s, 3H), 2.05 – 1.93 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 148.3, 145.0, 128.9, 128.7, 126.8, 125.3, 117.9, 114.7, 113.9, 74.4, 55.8, 43.8, 40.5, 30.1, 24.2. All spectroscopic data for this compound agrees with previously reported values.[142]

Chapter 3

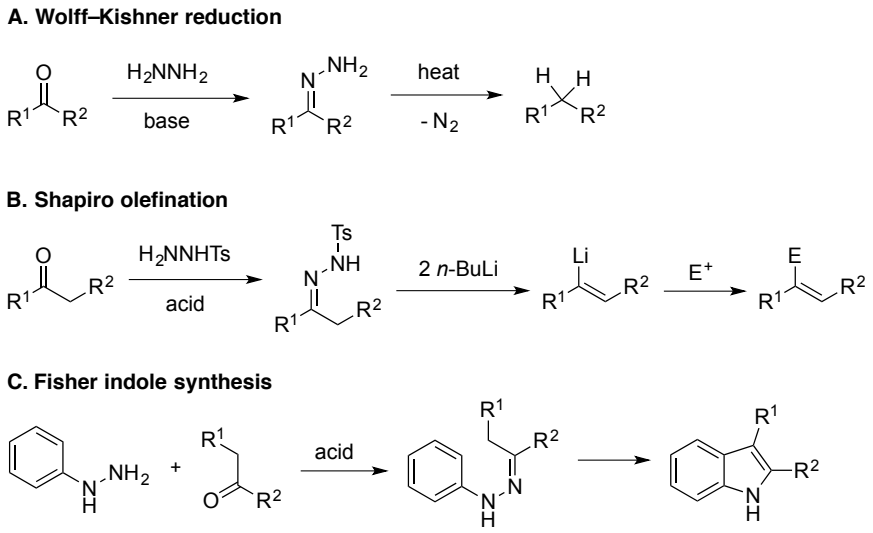
Development of a “Traceless” Petasis reaction for the Synthesis of Allylic Alcohols

3 Chapter 3

3.1 Introduction

The Thomson group has a long-standing interest in the development of highly-efficient fragment coupling reactions. One particular area that has inspired us in forming new carbon–carbon bonds is the chemistry of hydrazones. Hydrazones are usually generated through condensation between a hydrazine and a carbonyl species. These compounds contain a highly potent α-hydrogen, a lone pair of electrons conjugated with the C=N bond and a carbon atom that is both electrophilic and nucleophilic. Their unique chemical character, as well as their diverse biological and pharmacological properties have made hydrazones important building blocks for the synthesis of heterocyclic compounds in the past several decades.[143] We were more drawn to the synthetic utility of hydrazones as reaction intermediates, however, which has also been heavily investigated in the previous literatures.

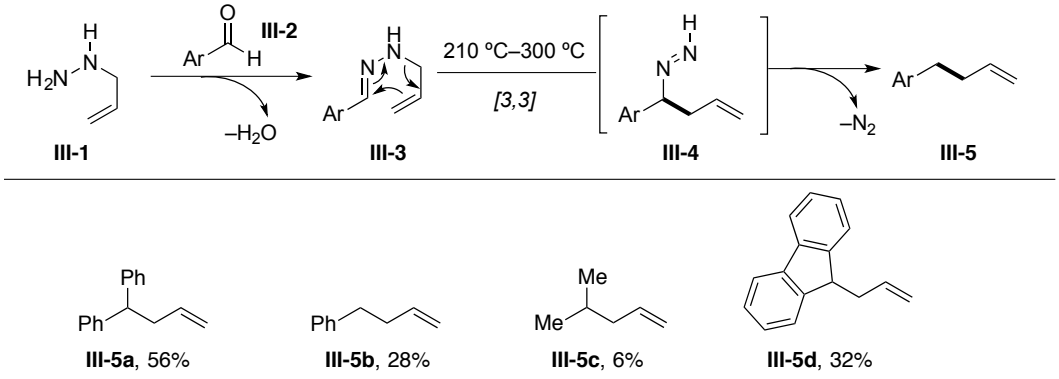
Scheme 3.1 Hydrazones as important reaction intermediates



Some of the extremely useful reactions involving hydrazone intermediates are the Wolff–Kishner reduction, Shapiro olefination and Fisher indole synthesis (Scheme 3.1). The first two examples take advantage of the readily-fragmented nature of the hydrazone species to achieve rapid construction of a new carbon–carbon bond.

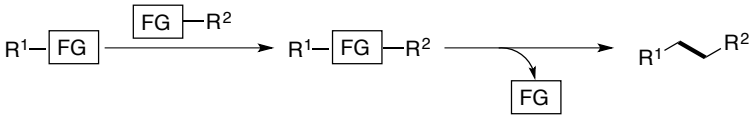
The Thomson group was especially intrigued by the work of Stevens and coworkers on [3,3]-sigmatropic rearrangement of *N*-allylhydrazones.[144] Differently-substituted aldehydes were condensed with allylhydrazines to afford hydrazone **III-3**, which underwent thermally-induced sigmatropic rearrangement to afford the diazine intermediate **III-4**. Fragmentation of the intermediate through nitrogen gas loss gave rise to a series of allylated hydrocarbon products (Scheme 3.2).

Scheme 3.2 Stevens' [3,3]-sigmatropic rearrangement of *N*-allylhydrazones



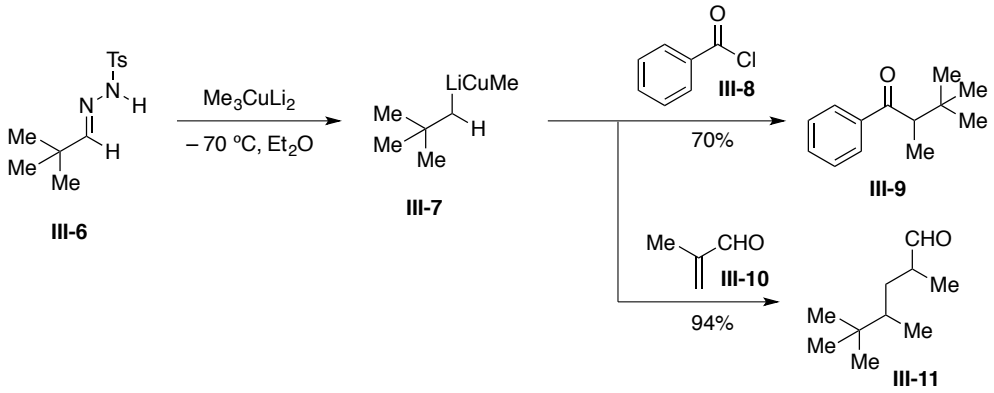
Even though the yields were not high possibly due to the harsh reaction conditions, this interesting transformation inspired us to look into "traceless" bond formation enabled by hydrazone intermediates (Scheme 3.3). During "traceless" fragment coupling reactions, the original functional groups that enable the transformation to occur are no longer present in the final product, which allows for non-obvious disconnections during retrosynthetic analysis.

Scheme 3.3 "Traceless" fragment coupling reaction



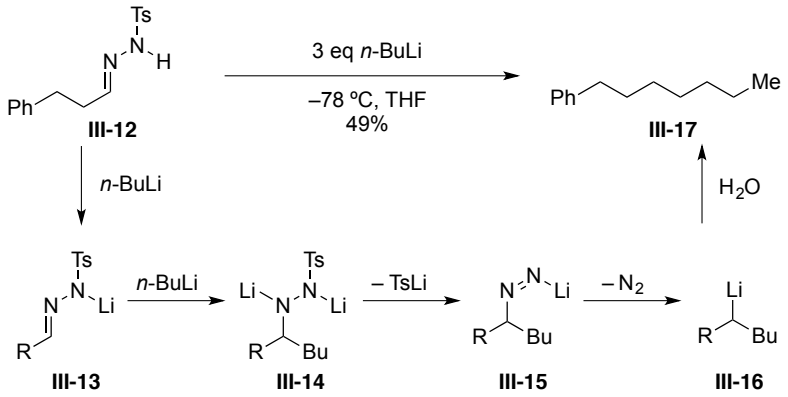
Several literature precedents have demonstrated the synthetic utility of traceless bond formation. In 1980, Bertz reported a novel reaction to generate hindered cuprate reagents from aldehyde tosylhydrazones **III-6**, which can be subjected to alkylation conditions to afford branched hydrocarbons in excellent yields (Scheme 3.4).[145] This was the first method to prepare such highly hindered cuprate reagents at that time.

Scheme 3.4 Preparation of cuprate reagent from tosylhydrazone



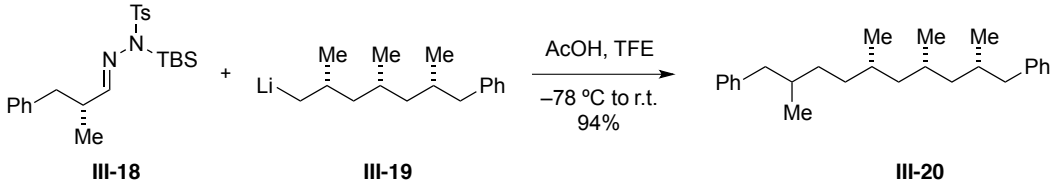
In 1977, Vedejs and coworkers published the first example of reductive alkylation of aldehyde-derived tosylhydrazone **III-12**.[146] Organolithium reagents readily underwent addition to afford a variety of alkylation products at low temperature (Scheme 3.5). However, the yields were modest as side reactions with the mono-lithiated tosylhydrazone intermediate could not be eliminated. The byproduct was converted into a nitrile and a lithium salt of *p*-toluenesulfonamide under basic conditions.

Scheme 3.5 Reductive alkylation of tosylhydrazones



In 1990, Myers and coworkers modified Vedejs's procedure to afford a more efficient process. They transformed aldehyde tosylhydrazones into stable *N*-*tert*-butyldimethylsilyl derivatives **III-18**, which underwent smooth 1,2-addition with organolithium reagents in much higher yields (Scheme 3.6).[147] They also demonstrated that nitrogen extrusion could occur in a free-radical pathway with saturated alkyllithium reagents, which distinguished their methodology apart from the precedents of Vedejs and Bertz.[148]

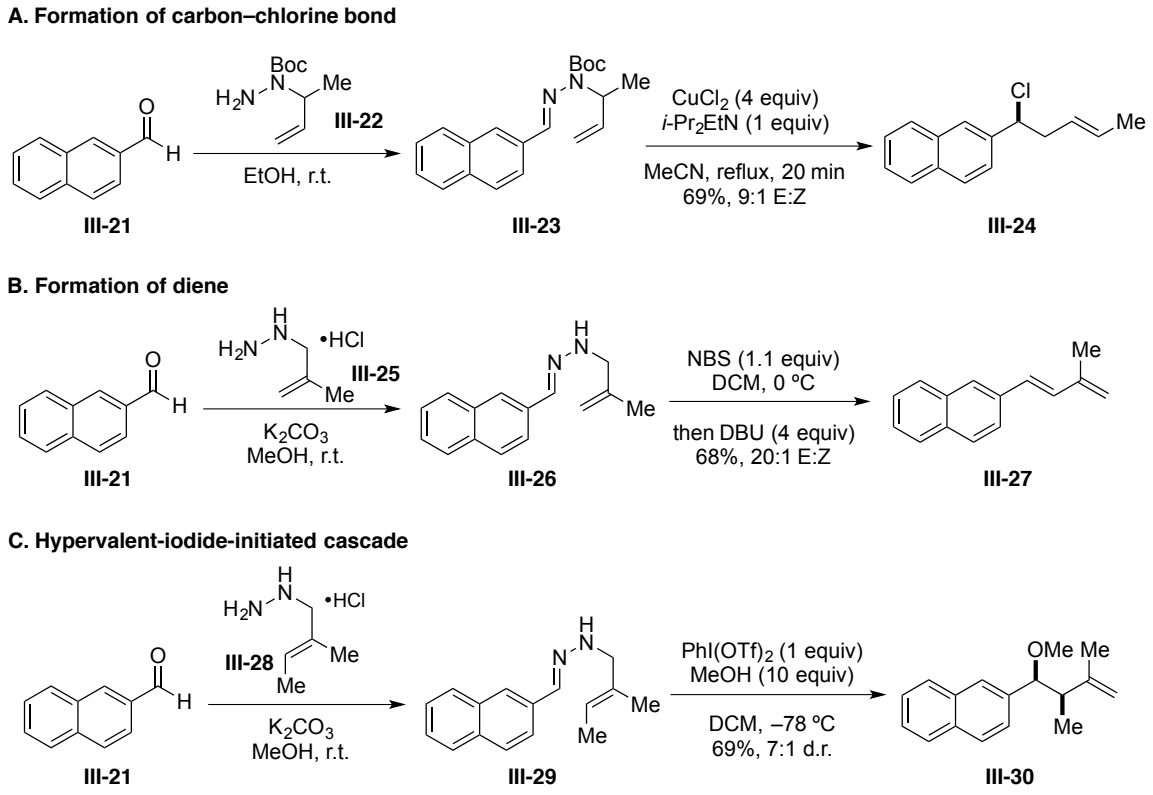
Scheme 3.6 Myer's modification



The Thomson group has been investigating "traceless" [3,3]-sigmatropic rearrangement of hydrazones for over 10 years. A series of methodologies that form new carbon–carbon bonds under various catalytic conditions were developed. For instance, they reported a $CuCl_2$-promoted system that generates both a carbon–carbon bond and a carbon–chlorine bond. A concerted mechanism was proposed after isotopic labeling experiments while (*E*)-alkenes were selectively synthesized

(Scheme 3.7A).[149] Shortly after, they expanded the methodology to the synthesis of dienes through stereoselective elimination of the halogen atom, which could be achieved by using NBS as the halogen source (Scheme 3.7B). An ionic mechanism was proposed as the reaction proceeded in the dark.[150] In 2011, they reported a novel hypervalent-iodide-initiated cascade of aldehydes and allylic hydrazides. The hydrazone intermediate **III-29** was formed which then underwent oxidative rearrangement to afford various substituted alkenes (Scheme 3.7C).[151] This methodology achieved a high degree of chirality transfer and was later applied to the total synthesis of multiple lignan natural products.[152]

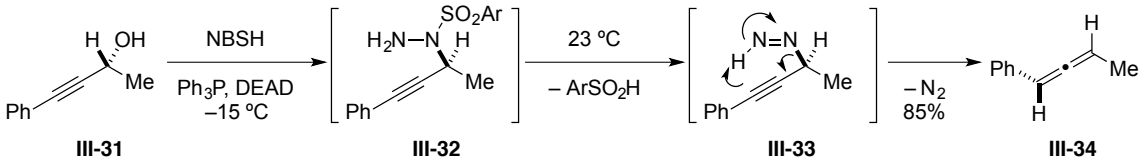
Scheme 3.7 Selected "traceless" hydrazone methodologies from the Thomson group



Aside from alkenes, allenes can also be synthesized in a similar fashion. In 1996, Myers developed a high-yielding and stereospecific synthesis of allenes using propargyl alcohols. The alcohol

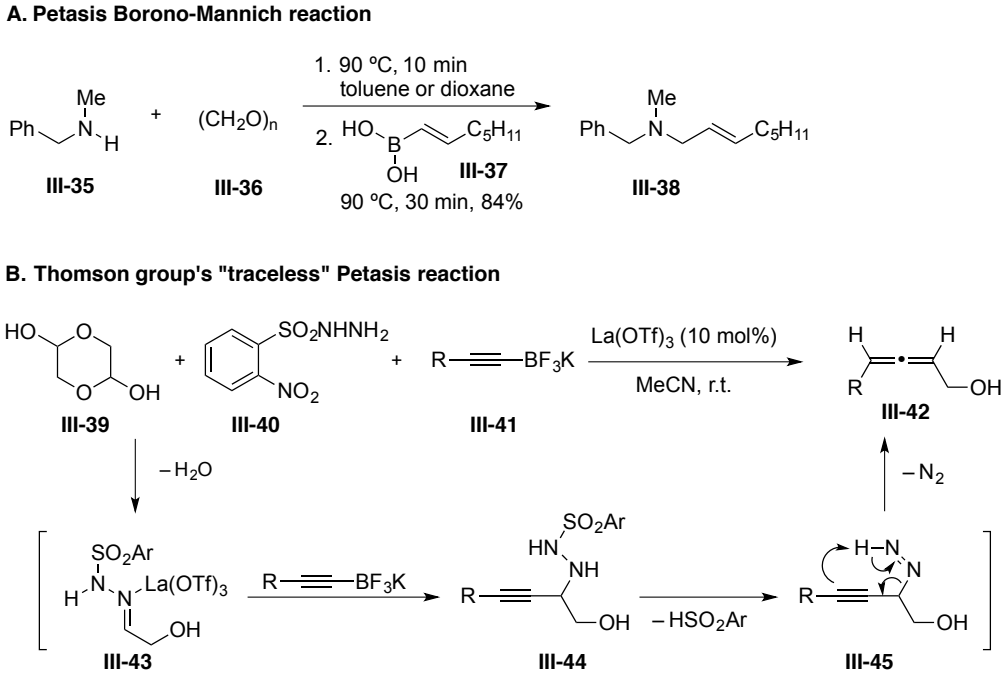
starting materials underwent Mitsunobu displacement with NBSH to afford **III-32**, which readily fragmented into **III-33**, followed by a retro-ene decomposition to afford allenes (Scheme 3.8).[153] The relative rates of Mitsunobu inversion, fragmentation and formation of diazene allowed for the success of the reaction cascade.

Scheme 3.8 Myer's allene synthesis



Inspired by Myer's work, our group looked into combining the allene synthesis protocol with Petasis reaction, a three-component fragment coupling developed by Nicos Petasis between an aldehyde, an amine and a boronic acid species (Scheme 3.9A).[154]

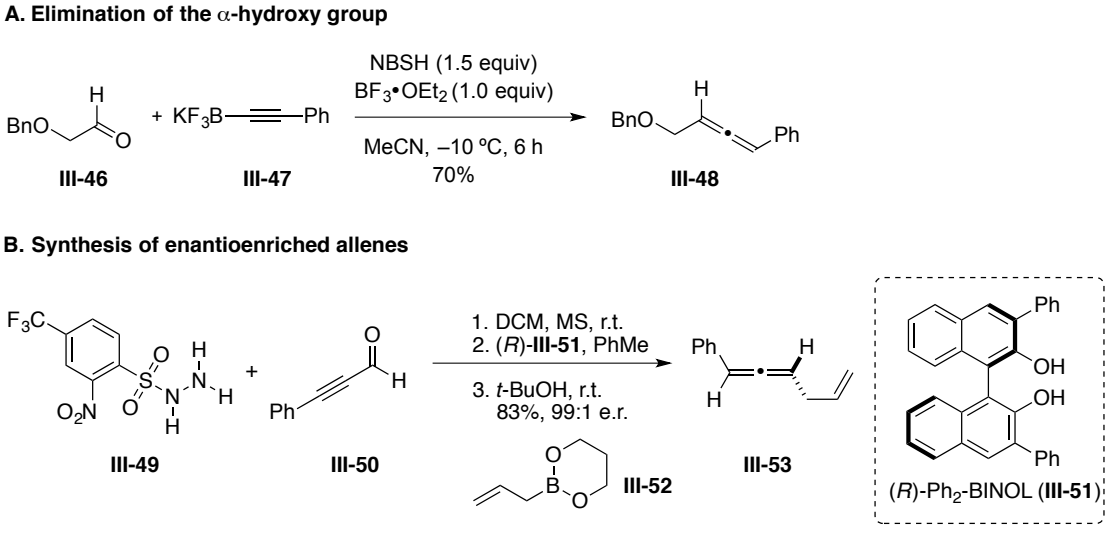
Scheme 3.9 Combination of Petasis reaction and Myer's allene synthesis



Former group member Dr. Mundal modified the procedure by using a hydrazine (**III-40**) and propargyl trifluoroborate salt (**III-41**) instead, which formed diazene **III-44** *in situ* before going through retro-ene to afford the desired allene product (Scheme 3.9B).[155] A hydroxy group on the α position of the aldehyde was necessary to direct the boronic species addition.

Later, Dr. Diagne and coworkers expanded the substrate scope of the "traceless" Petasis reaction to substrates lacking α-hydroxy substituents.[156] A reaction condition screen was carried out with the aid of high-throughput optimization, while BF_3•OEt_2 proved to be the most effective promotor (Scheme 3.10A). In subsequent work with the Schaus lab at Boston University, they were also able to render the transformation enantioselective using chiral BINOL-based catalysts. This methodology was one of the few strategies to directly synthesize enantioenriched chiral allenes from achiral precursors (Scheme 3.10B).[157]

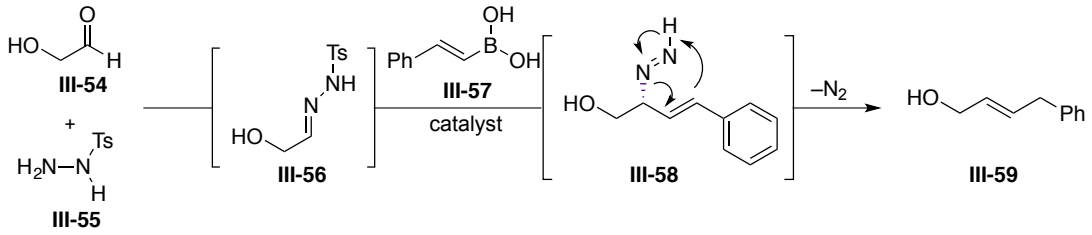
Scheme 3.10 Expansion of the substrate scope of allene synthesis



3.2 Expansion of the Methodology to Allylic Alcohols

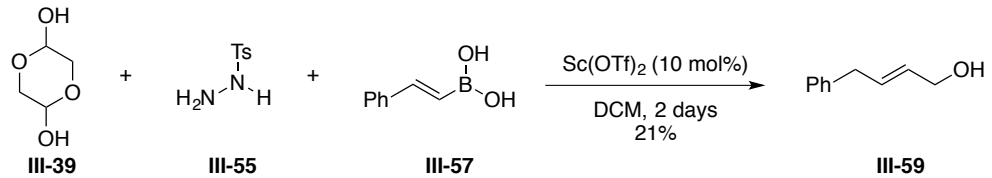
Encouraged by the previous development of the allene synthesis, we were interested in expanding the methodology to the synthesis of allylic alcohols. We envisioned this could be achieved by using alkenyl boronic reagents (**III-57**) instead of the alkynyl ones. Based on our proposed mechanism, the Petasis reaction would generate the allylic diazene intermediate **III-58**, which undergoes rearrangement and extrusion of nitrogen to afford allylic alcohol products (Scheme 3.11). We expected this transformation would be more challenging to achieve than allene synthesis, however, due to the less nucleophilic nature of the alkenyl boronic reagents.

Scheme 3.11 Proposed mechanism for the synthesis of allylic alcohols



Our previous group member Dr. Mundal briefly investigated this transformation using vinylboronic acid **III-57** and tosylhydrazone **III-55**. According to his preliminary results, allylic alcohol **III-59** could be indeed generated in this fashion. However, the yield of alcohol was only 21% (Scheme 3.12).

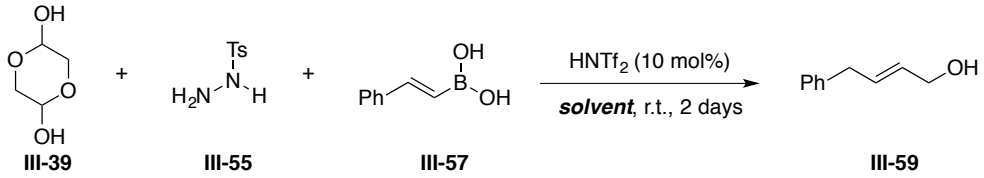
Scheme 3.12 Dr. Mundal's preliminary results



3.2.1 Preliminary Reaction Condition Optimization

Our initial reaction condition screen commenced with the use of $HNTf_2$ as catalyst. Commercially available glycolaldehyde dimer and tosyl hydrazide were pre-mixed before the addition of phenyl vinylboronic acid. A variety of solvents were investigated (Table 3.1). Most of them yielded little or no desired product except dichloromethane, which gave 28% yield (Table 3.1, Entry 6). The transformation was not very efficient and took a long time to complete as expected. Heating the reaction failed to expedite the process, while mostly decomposition of the reaction intermediates was observed.

Table 3.1 Solvent screen with $HNTf_2$ as catalyst

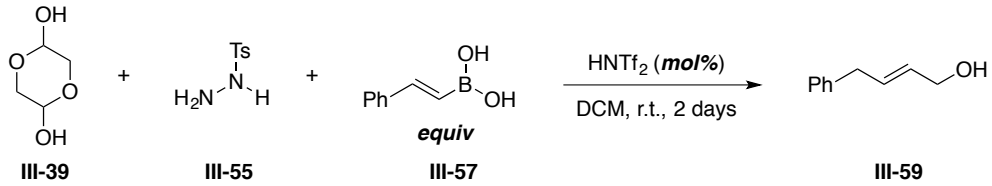


III-39 **III-55** **III-57** **III-59**

Entry	Solvent	Yields %
1	DMSO	no pdt
2	$MeNO_2$	no pdt
3	toluene	trace amount
4	MeCN	messy mixture with little pdt
5	CH_3Cl	messy mixture with little pdt
6	DCM	28

We also briefly examined the effect of boronic acid equivalents and catalyst loading. Increasing the amount of acid catalyst might have led to slightly better yields, but not as significant as we had hoped (Table 3.2, Entry 1). On the other hand, the amount of boronic acid used did not seem to affect the reaction outcome substantially.

Table 3.2 The effect of reagent equivalents

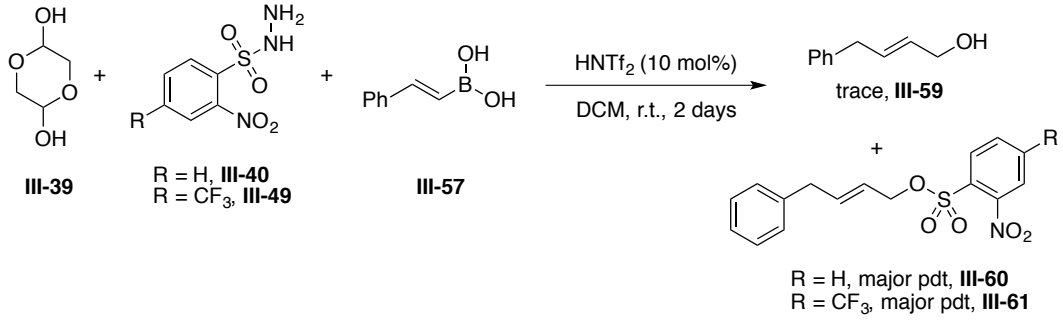


III-39 III-55 III-57 III-59

Entry	Boronic acid equiv	Catalyst loading	Yields % (by NMR)
1	1	20 mol%	35
2	1	50 mol%	27
3	2	10 mol%	13
4	3	10 mol%	12

Different hydrazide candidates (**III-40** and **III-49**) have also been subjected to the reaction condition, while only trace amount of the desired product was obtained. As we were examining the mass balance of the reaction mixture, an olefin species was recovered as the major product (Scheme 3.13). According to NMR and mass spectrometry studies, the byproduct most likely resulted from sulfonylation of our desired allylic alcohol product.

Scheme 3.13 Isolation of a major byproduct



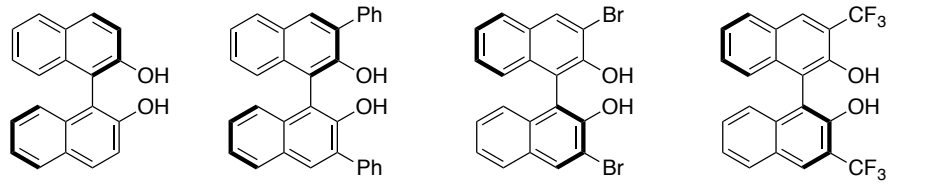
III-39 R = H, **III-40** R = CF_3, **III-49** III-57

R = H, major pdt, **III-60**
R = CF_3, major pdt, **III-61**

As an attempt to suppress the byproduct formation, the reaction temperature was lowered to 0 ºC. We were delighted to achieve a higher yield up to 51%, but even longer time (four days) was required to accomplish the reaction.

We recognized that the strong Brønsted acid triflimide might not be the best catalyst option. Considering our goal to eventually render this methodology enantioselective, we turned our attention to the chiral BINOL-based catalysts, which have shown superb activity during the previous synthesis of allenes.[157]

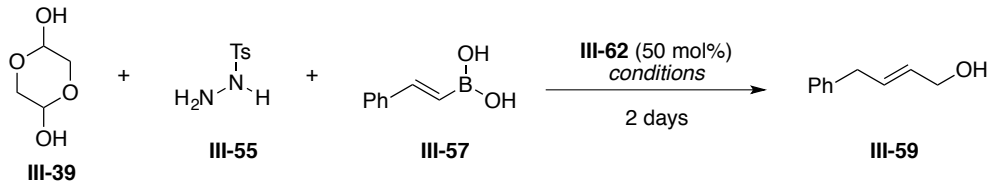
Figure 3.1 Chiral BINOL-based catalysts



(*R*)-BINOL (**III-62**) (*R*)-Ph_2-BINOL (**III-51**) (*S*)-Br_2-BINOL (**III-63**) (*S*)-$(CF_3)_2$-BINOL (**III-64**)

A series of chiral BINOL-based catalysts were prepared following previously reported procedure (Figure 3.1).[157] Reaction conditions were investigated again, with a focus on temperature and additive effects. Commercially available (*R*)-BINOL (**III-62**) was first subjected to the screen. It was discovered that addition of dry molecular sieves improved the yields in both DCM and chloroform (Table 3.3, Entry 3 and Entry 5). Heating the reaction mixture to ~45 ºC also significantly increased the efficiency of the desired transformation. However, a long reaction time was still required in order to reach full conversion, as monitored by TLC. Reaction in chloroform gave similar yield than its DCM counterpart, unfortunately it was much messier with inseparable byproduct isolated along with the allylic alcohol product.

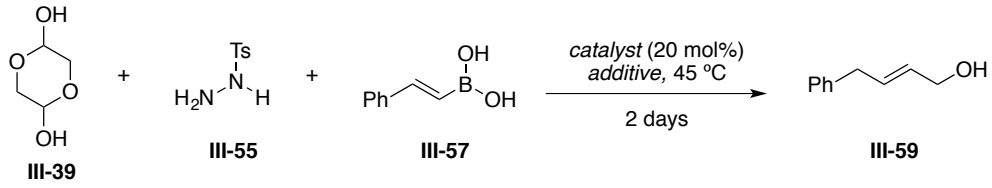
Table 3.3 Temperature and additive effect



Entry	Solvent	Temperature	Additives	Yields %
1	DCM	r.t.	none	no pdt
2	DCM	45 ºC	none	20
3	DCM	45 ºC	M.S.	32
4	Chloroform	45 ºC	none	no pdt
5	Chloroform	45 ºC	M.S.	40 (minor impurity)

The Br_2- (**III-63**) and CF_3-substituted (**III-64**) chiral BINOL catalysts were also examined (Table 3.4). Both displayed superior reactivity at lower catalyst loading (20 mol%) comparing to BINOL (50 mol%).

Table 3.4 Examination of substituted BINOL catalysts



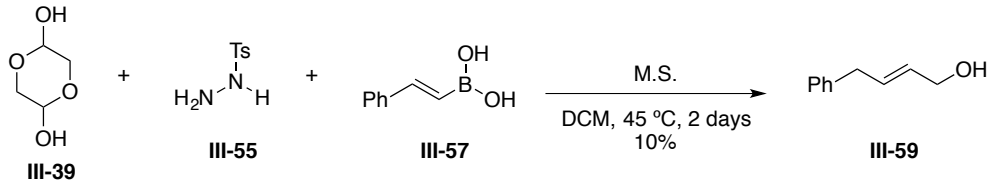
Entry	Catalyst	Solvent	Additives	Yields %*
1	**III-64**	DCM	none	30
2	**III-64**	DCM	M.S.	50
3	**III-64**	Chloroform	M.S.	38
4	**III-63**	DCM	none	37
5	**III-63**	DCM	M.S.	53
6	**III-63**	Chloroform	M.S.	28

* Yields were approximated, due to minor impurities in the products

Similar trends were observed, with higher yields obtained in the presence of molecular sieves. The (*S*)-Br_2-BINOL gave slightly better results (Table 3.4, Entry 5). Considering its relatively shorter synthetic preparation than **III-64**, it was selected as the standard catalyst in subsequent studies.

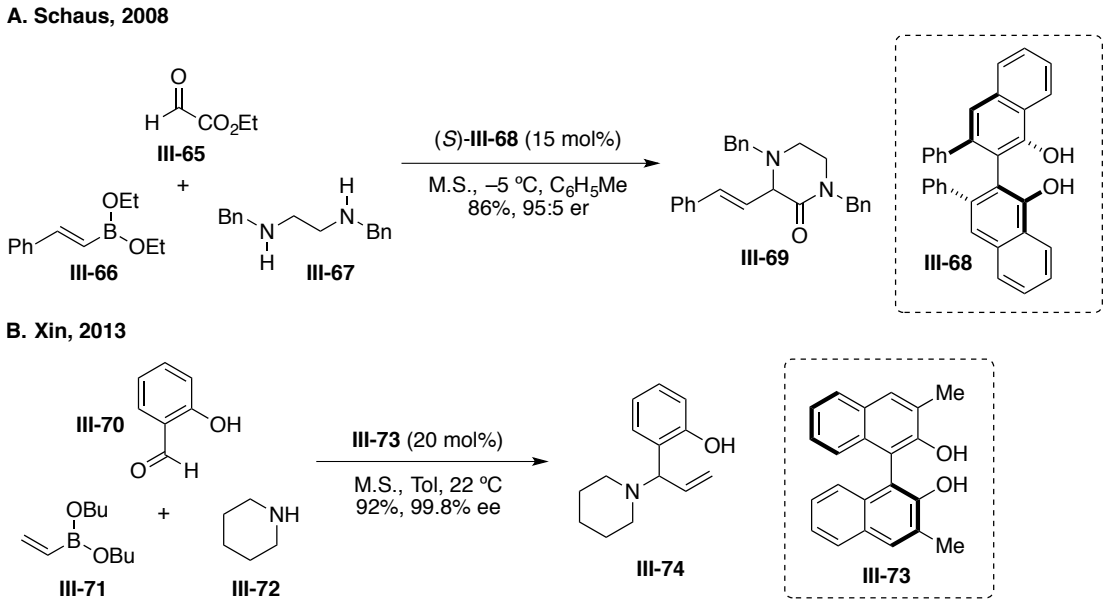
We also noticed the presence of a background reaction based on our catalyst-free trial. Allylic alcohol **III-59** was isolated in ~10% yield in the absence of BINOL catalysts (Scheme 3.14), which is something to be concerned about if we wish to develop an enantioselective route using chiral catalysts in the future.

Scheme 3.14 Background reaction



In addition to phenyl vinyl boronic acid, we explored additional boronic reagents. Our collaborator Prof. Scott Schaus at Boston University reported a series of asymmetric Petasis reactions catalyzed by chiral biphenols. Various styrylboronic acid derivatives were examined while the boronates gave rise to enhanced yields and stereoselectivity in many cases, especially diethyl styrylboronate **III-66** (Scheme 3.15A).[158, 159] In 2013, Xin and coworkers also developed a catalytic asymmetric Petasis reaction between vinylboronates, salicylaldehyde and secondary amines. High yields and enantioselectivity using BINOL-based catalysts (Scheme 3.15B).[160]

Scheme 3.15 Previously reported asymmetric Petasis reactions using vinyl boronates



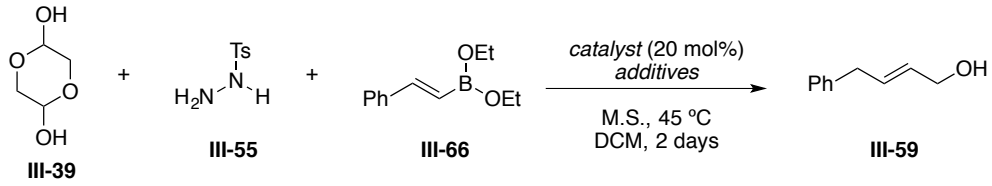
We decided to synthesize styrylboronate ester **III-66**, which showed superior reactivity in Schaus's asymmetric Petasis reactions. Esterification of boronic acid **III-57** afforded the desired boronate ester smoothly following previously reported protocol, no further purification was carried out. When subjected to the standard reaction conditions, no significant difference in yield was observed (Table 3.5, Entry 1).

Hoping to further optimize the reaction, we also sought additional additives that might help facilitate the transformation. In 2015, Szabó and coworkers published an asymmetric allyboration of ketones catalyzed by similar chiral BINOL-derivatives.[161] They discovered that catalytic amount of *t*BuOH promoted the reaction whereas MeOH and *i*PrOH failed to give the same results. It was believed that tertiary alcohols such as *t*BuOH might have helped regenerate the BINOL catalyst. In the asymmetric "traceless" Petasis methodology previously published by the Thomson group, three equivalents of *t*BuOH were also utilized as promotor.[157] When we applied the same condition to our reaction, an increase in yield was indeed observed (Table 3.5, Entry 2). However,

the discrepancy was not significant enough to conclude that *t*BuOH served as an active species in enhancing the efficiency of this transformation.

In the meantime, (*R*)-Ph_2-BINOL (**III-51**) was prepared according to literature procedure and examined with boronate ester **III-66**. Unfortunately, a much messier reaction mixture was obtained and no isolated yield could be obtained (Table 3.5, Entry 3).

Table 3.5 Further optimization with boronate ester



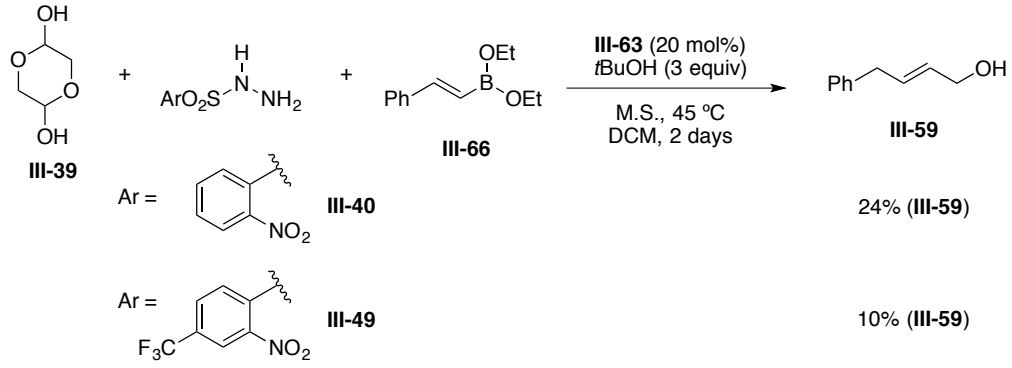
Entry	Catalyst	Additives	Yields %
1	**III-63**	none	51
2	**III-63**	*t*BuOH	60
3	**III-51**	*t*BuOH	NA (messy)

Our final effort to optimize this reaction with boronate ester **III-66** was to experiment a variety of hydrazide species. Based on the Thomson group's previous studies of the "traceless" Petasis methodologies, the reaction outcome was partially determined by electronic effects. The electron density of the substituents on the hydrazides needs to be fine-tuned in order to facilitate both the initial nucleophilic addition into the aldehyde and the late-stage fragmentation of the diazene intermediate.

Following previously reported procedures,[156] differently substituted hydrazides were synthesized from the corresponding sulfonyl chloride precursors. When subjected to the standard reaction conditions, none of the hydrazides led to enhanced yields (Scheme 3.16). A significant amount of byproduct was isolated when hydrazide **III-40** was used. Although its exact structure could not be

confirmed yet due to difficulties in purification, it was likely the diazene intermediate or a derivative of the diazene based on NMR and GC/MS studies of the crude reaction mixture.

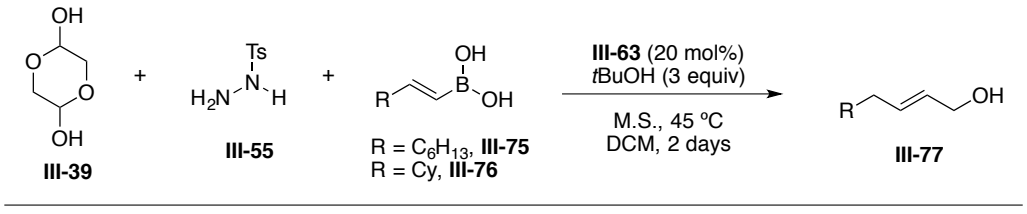
Scheme 3.16 Exploration of alternative hydrazide species



3.2.2 Expansion of the Substrate Scope

Having established a preliminary system for the "traceless" Petasis reaction, we looked into expanding the substrate scope beyond aromatic compounds. To our delight, alkyl chains and rings could be incorporated into the product in addition to the phenyl moiety (Table 3.6), simply by using commercially available vinyl boronic acids **III-75** and **III-76**.

Table 3.6 Incorporating alkyl groups into the product

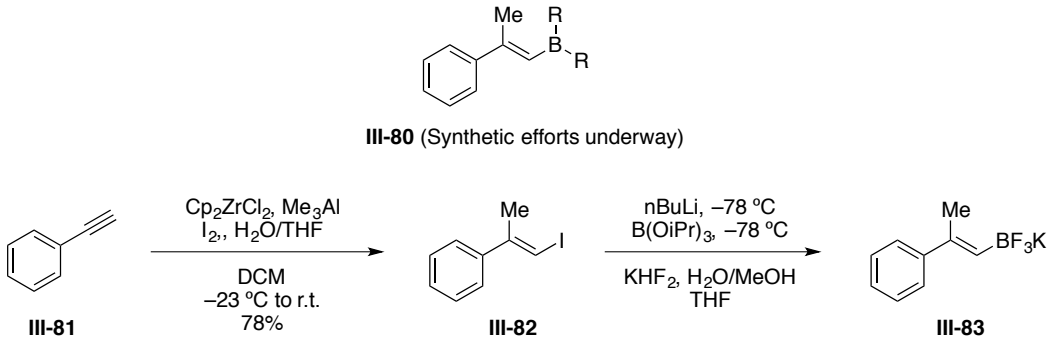


* Yields were approximated, due to minor impurities in the products

Considering our goal to eventually render this reaction enantioselective, we aimed to install a stereogenic center in the product. The most simplified boron reagent that would allow us to achieve

this is 2-phenylpropene-1-boronic ester **III-80**. While efforts to access these reagents are still underway due to synthetic difficulties, we successfully prepared the trifluoroborate salt derivative **III-83** based on Dr. Mundal's unpublished results. Phenyl acetylene was converted to vinyl iodide **III-82** using Schwartz's reagent, followed by installation of the trifluoroborate group (Scheme 3.17). Crude product was applied directly to the Petasis reactions.

Scheme 3.17 Synthesis of 2-phenylpropene-1-trifluoroborate salt

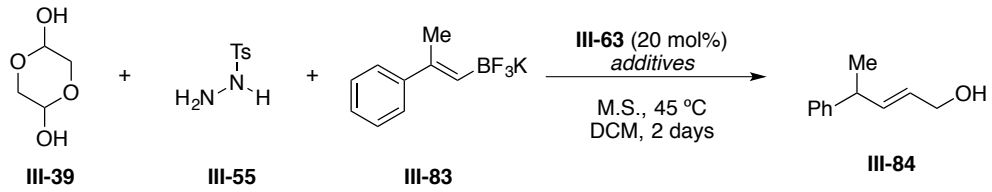


With the methyl-substituted vinyl boronic reagent **III-83** in hand, we promptly subjected it to the previously optimized reaction conditions. We were encouraged to achieve a 60% yield of the branched allylic alcohol **III-84** (Table 3.7, Entry 1), and wondered if the system could be further optimized with the new trifluoroborate salt.

An additive screen was first performed. We were inspired by the work of May and coworkers, who developed a series of asymmetric addition of aryl trifluoroborates and vinyl boronic acids to conjugated ketones.[162, 163] They reported the use of Mg(O*t*Bu)$_2$ or *t*BuOH to accelerate the reaction. These additives were postulated to be acting as proton transfer agents during the transformation. When we adopted Mg(O*t*Bu)$_2$ in the Petasis reactions, good yields were achieved, comparable to the results obtained with *t*BuOH promotor (Table 3.7, Entry 2). Lithium bromide has also been employed to facilitate trifluoroborate addition into conjugated ketone in the previous literature.[162]

However, it only led to unsatisfying yields in our reaction (Table 3.7, Entry 3). Similarly, known fluoride scavenger silyl chloride gave rise to a very messy/inseparable reaction mixture (Table 3.7, Entry 4).

Table 3.7 Additive screen with trifluoroborate salt

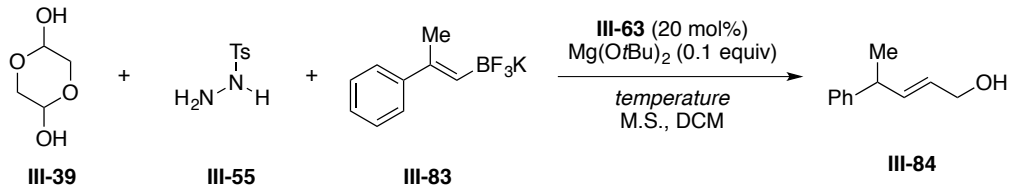


III-39 III-55 III-83 III-84

Entry	Additive	Yields %
1	*t*BuOH (3 equiv)	60
2	$Mg(OtBu)_2$ (0.1 equiv)	60
3	LiBr (1 equiv)	10
4	TBSCl (1 equiv)	messy, mixed pdts
5	nBu_4NCl (0.1 equiv)	messy, mixed pdts

Temperature of the system was also examined. Attempts to simplify the reaction setup by running it at room temperature led to significantly reduced yields and increased amount of byproducts, indicating that vinyl boronic reagents are much less reactive than their alkynyl counterparts (Table 3.8, Entry 2). Due to the low boiling point of dichloromethane, carrying out the reaction at higher temperature was challenging. We solved the problem by using the microwave. Unfortunately, no improved yield was observed at 70 ºC aside from higher level of decomposition, even though the reaction was terminated after only 2 hours (Table 3.8, Entry 3). Similar result was obtained with running the reaction at 45 ºC in the microwave (Table 3.8, Entry 4).

Table 3.8 Temperature screen with trifluoroborate salt

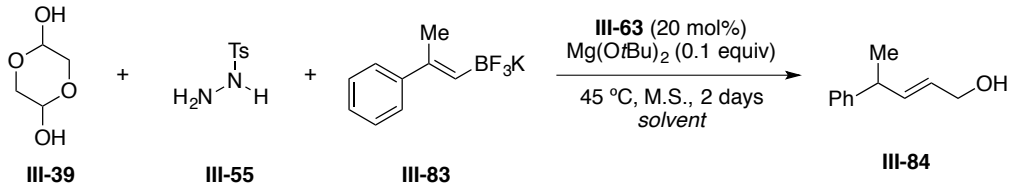


III-39 **III-55** **III-83** **III-84**

Entry	Temperature	Yields %
1	45 ºC (heating, 2 days)	60
2	r.t.	10
3	70 ºC (mw, 2 hrs)	messy, mixed pdts
4	45 ºC (mw, 12 hrs)	messy, mixed pdts

A brief solvent screen was performed to confirm that dichloromethane was indeed the optimal choice. Both dichloroethane and trifluorotoluene afforded a much messier reaction mixture with higher byproduct to product ratio (Table 3.9).

Table 3.9 Solvent screen with trifluoroborate salt

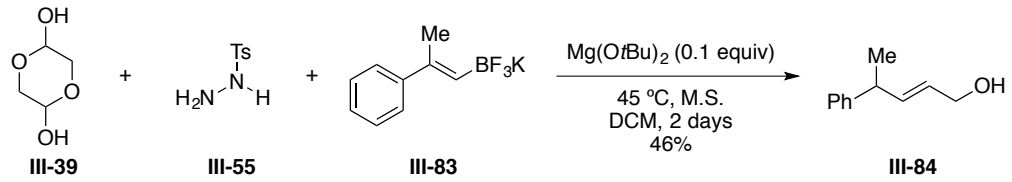


III-39 **III-55** **III-83** **III-84**

Entry	Solvent	Yields %
1	DCM	60
2	DCE	messy, mixed pdts
3	trifluorotoluene	messy, mixed pdts

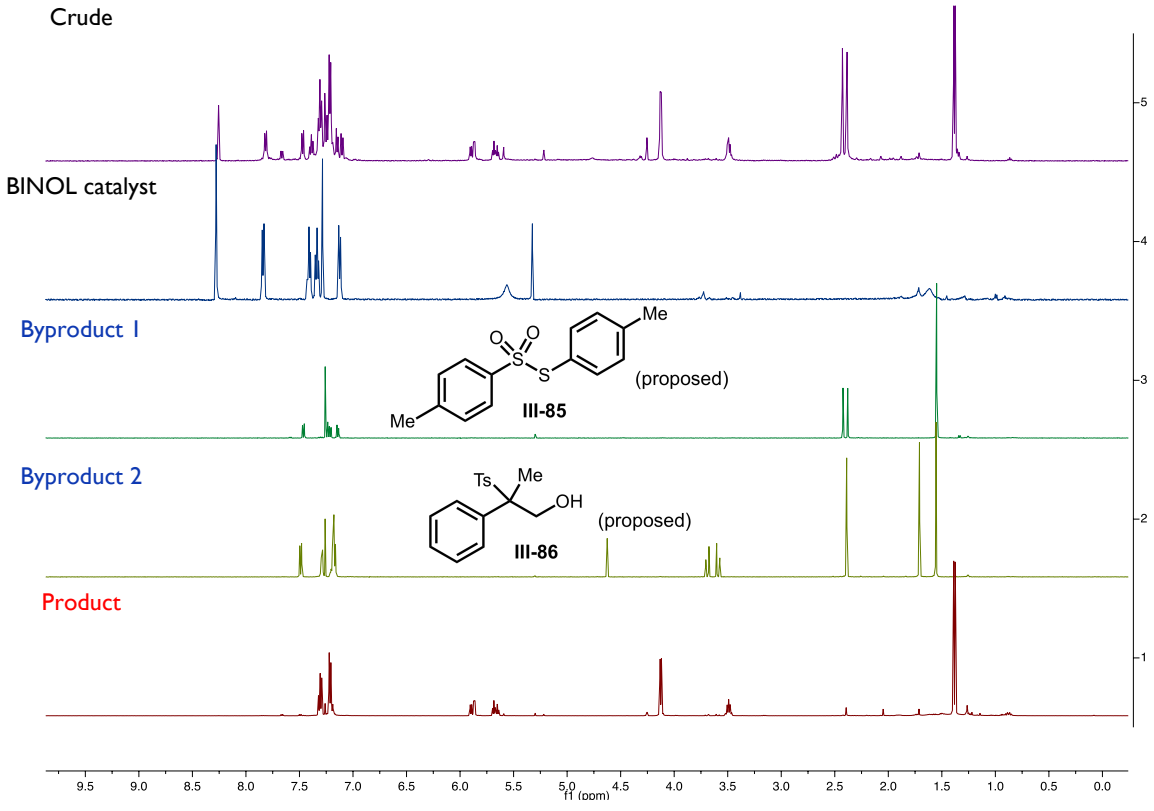
It was noteworthy that a background reaction was again observed with the trifluoroborate salt **III-83**. Allylic alcohol **III-84** could be synthesized in up to 46% yield in the absence of BINOL catalysts with optimized reaction conditions (Scheme 3.18).

Scheme 3.18 Background reaction with trifluoroborate salt



While examining the mass balance of the "traceless" Petasis reaction, two major byproducts **III-85** and **III-86** were isolated in addition to the recovered catalyst (Figure 3.2). According to NMR and GC/MS studies, they were likely derived from the interaction between the hydrazide and trifluoroborate salt. Elucidation of their exact structure and mechanism of formation is still underway.

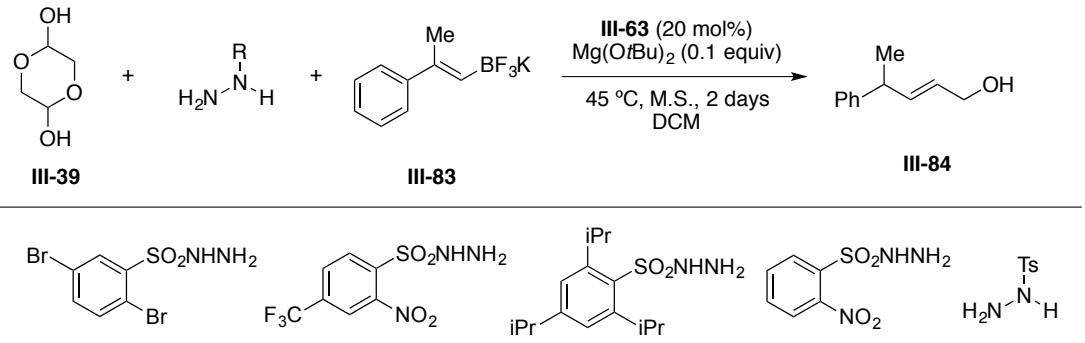
Figure 3.2 Mass balance study of the "traceless" Petasis reaction



We hypothesized that some of the byproducts were formed due to oxidation of the reagents. However, efforts to suppress byproduct formation by utilizing deoxygenated solvent proved to be fruitless.

We also tested a series of hydrazide species. Arene-*N*-sulfonyl hydrazides with electron-donating and electron-withdrawing substituents were synthesized based on previously reported protocol. Those containing electron-deficient arenes afforded lower yields comparing to hydrazides with *i*Pr and Me substituents (Table 3.10). Reasons for this trend are still under investigation. The boc-protected hydrazide was also subjected to the Petasis reaction. However, no desired product was obtained.

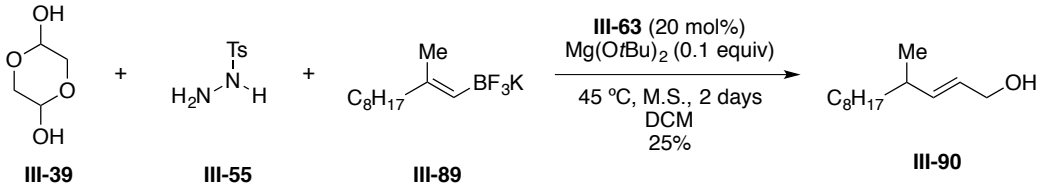
Table 3.10 Hydrazide screen with trifluoroborate salt



Yield of III-84:	24%	15%	41%	10%	60%

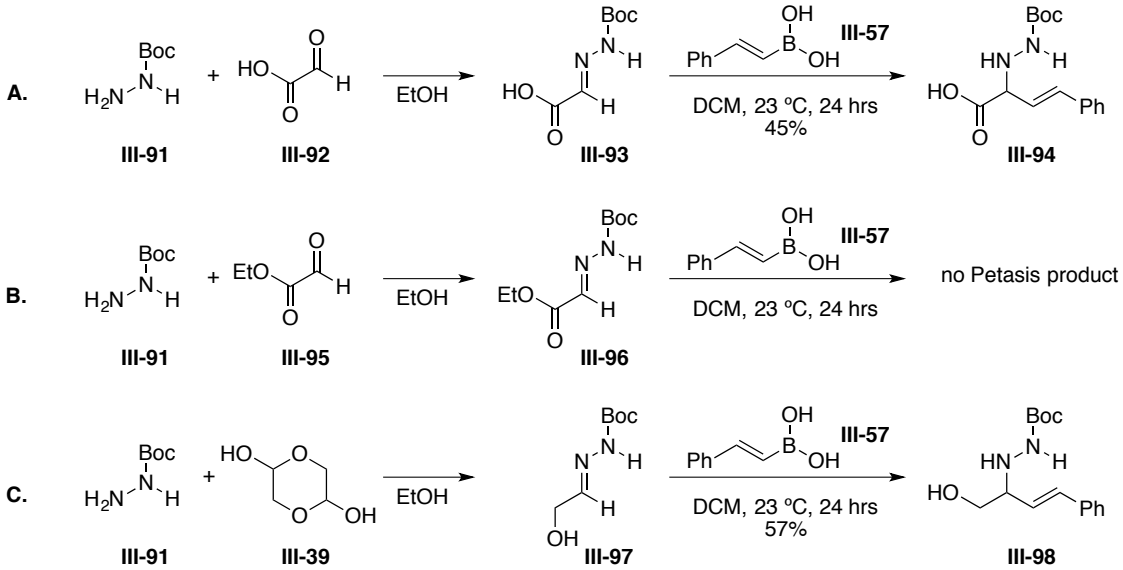
Encouraged by the preliminary results with 2-phenylpropene-1-trifluoroborate **III-83**, we prepared the trifluoroborate salt **III-89** containing an alkyl substituent from alkyne following a similar method. Allylic alcohol **III-90** was achieved in 25% yield (Scheme 3.19). We hypothesized that lower nucleophilicity of the alkyl-substituted trifluoroborate reagent led to decreased yield comparing to its aromatic counterpart.

Scheme 3.19 Investigation of alkyl-substituted trifluoroborate salt



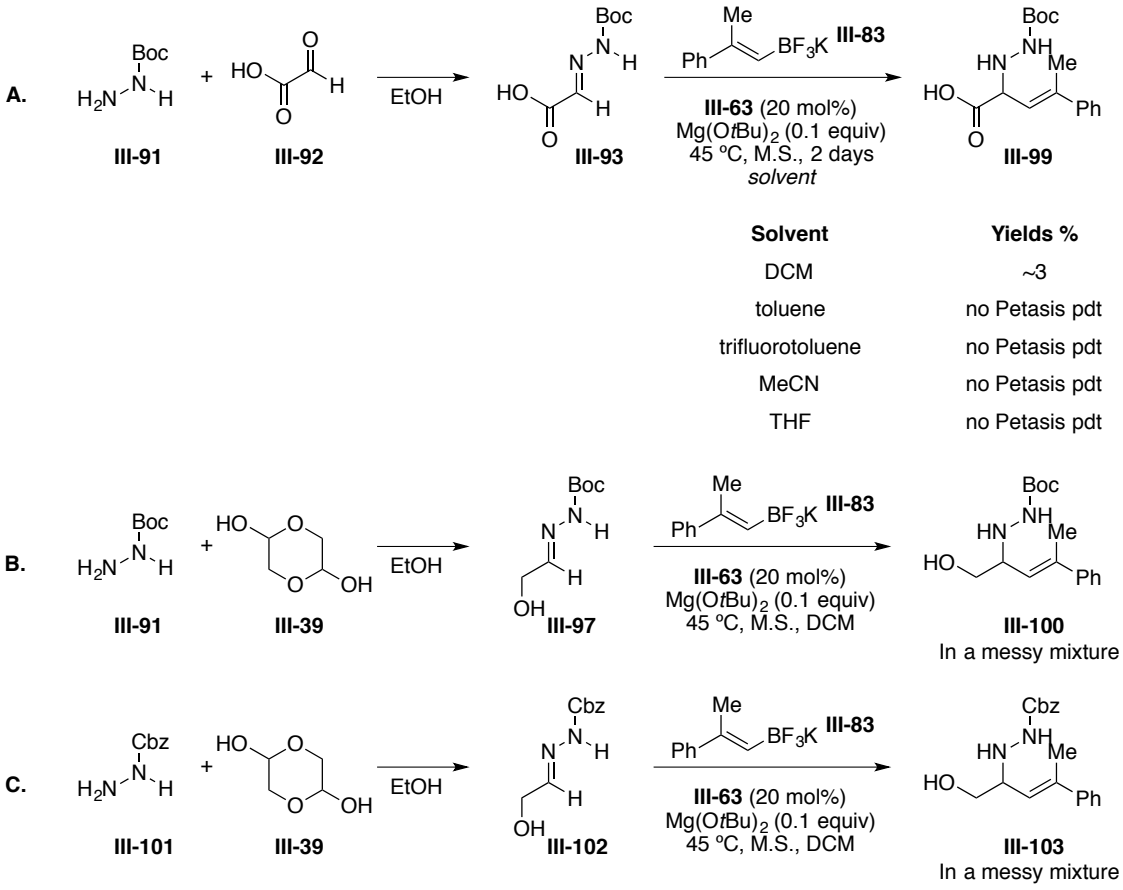
As optimization of the three-component coupling reaction hit a bottleneck, we looked into the possibility of further increasing the overall yield through a two-step sequence. This alternative route might help eliminate some of the byproducts and give us more flexibility in terms of solvent selection. During Dr. Mundal's preliminary studies of "traceless" Petasis reaction using styrylboronic acid **III-57**, Boc-protected hydrazide **III-91** underwent condensation with a few carbonyl compounds smoothly to afford hydrazone products (Scheme 3.20). Although further fragmentation of the resulting hydrazones were not investigated extensively, we were hopeful that our optimized system could afford the desired product in this fashion.

Scheme 3.20 Addition of vinyl boronic acids to Boc hydrazides by Dr. Mundal



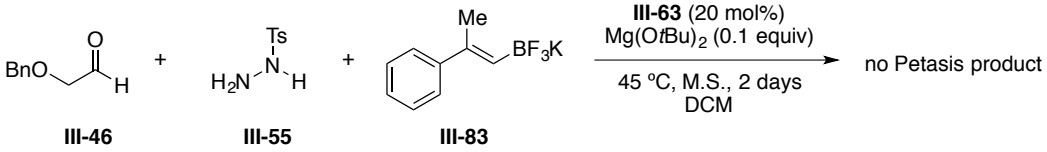
Condensation between Boc-hydrazide and glyoxylic acid afforded the desired hydrazone **III-93** with no further purification needed. Subsequent Petasis reaction with trifluoroborate salt afforded a mixture of products which were hard to isolate. However, NMR spectra indicated the presence of hydrazide **III-99** in the crude reaction mixture, although further fragmentation and alkene walk turned out to be problematic. Attempts were made to improve the reaction efficiency by screening different solvents, while dichloromethane turned out to be the best candidate for trifluoroborate addition again (Scheme 3.21A). Similar results were obtained when glycolaldehyde (Scheme 3.21B) and Cbz-hydrazide **III-101** (Scheme 3.21C) were utilized.

Scheme 3.21 Stepwise analysis of the three-component coupling



Similar to the previously reported allene methodology using alkynyl trifluoroborate,[155] aldehydes containing an α-hydroxy directing group were necessary to facilitate the intermolecular addition with the boron species. When we subjected the Bn-protected aldehyde **III-46** to our standard conditions, no desired Petasis product was obtained (Scheme 3.22)

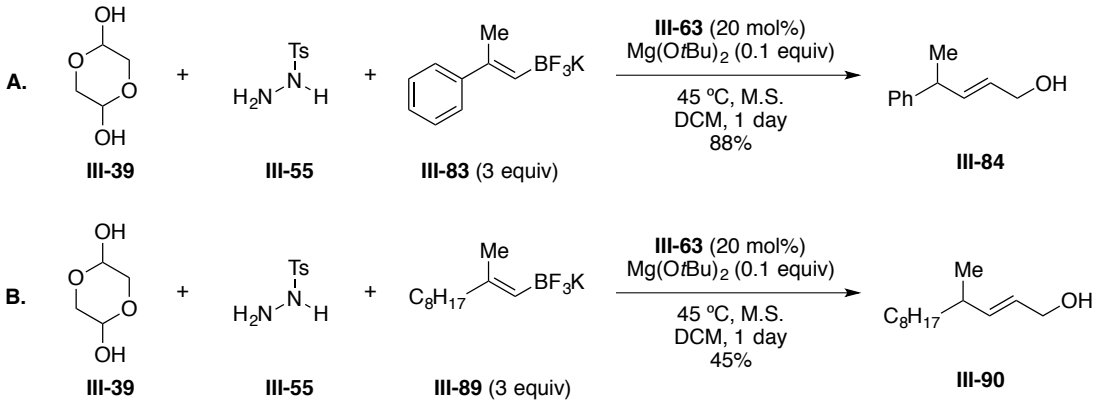
Scheme 3.22 The importance of α-hydroxy directing group



3.2.3 Final Optimization Using Excess Amount of Trifluoroborate Salt

For a long time we were unable to improve the yield beyond 60%, which eventually prompted us to examine the equivalents of reagents used. Increasing the amount of aldehyde or hydrazide did not have any significant effect on the reaction outcome. When three equivalents of the trifluoroborate salt **III-83** was used, however, we were delighted to achieve 88% yield of the allylic alcohol product (Scheme 3.23A). Reaction time could also be shortened to 24 hours in order to prevent decomposition.

Scheme 3.23 Higher equivalence of trifluoroborate salt

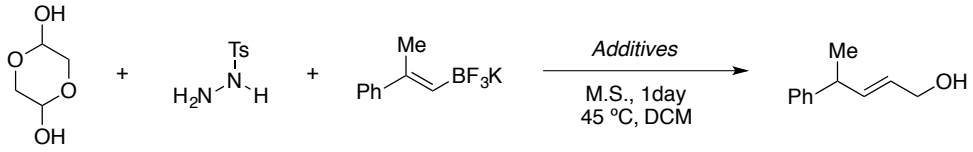


Encouraged by this result, excess amount of alkyl-substituted vinyl trifluoroborate **III-89** was employed, which also gave rise to improved yield (25% to 45%, Scheme 3.23B) with minor impurities in the product.

Due to solubility issue of the trifluoroborate salt in dichloromethane, we wondered if a more polar solvent would better assist the Petasis reaction. However, switching to MeCN failed to improve the yield, affording only 53% of the desired alcohol **III-84**.

With the new reaction conditions in hand, we decided to perform another comprehensive additive/catalyst screen. Lewis acid $Sc(OTf)_3$ did not outperform the substituted chiral BINOL-based catalysts (Table 3.11, Entry 3), while *t*BuOH and phenol gave surprisingly high yields (Table 3.11, Entry 6–7).

Table 3.11 Additive/catalyst screen with excess amount of trifluoroborate salt



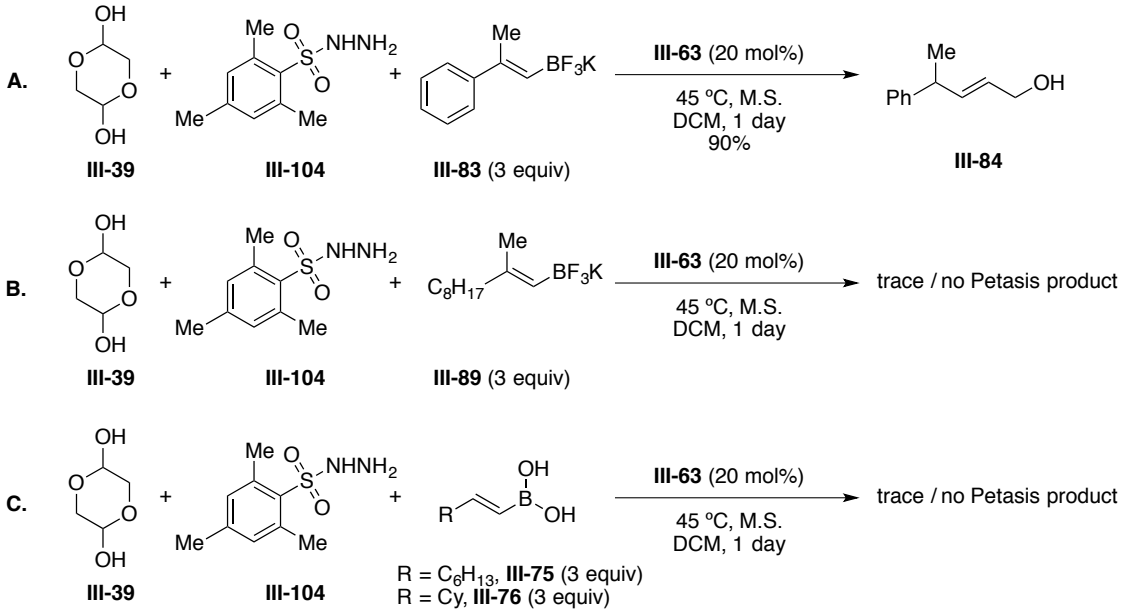
III-39 **III-55** **III-83** (3 equiv) **III-84**

Entry	Additive 1	Catalyst/Additive 2	Yields %
1	-	**III-63** (20 mol%)	81
2	$Mg(OtBu)_2$ (0.1 equiv)	-	60
3	$Mg(OtBu)_2$ (0.1 equiv)	$Sc(OTf)_3$ (20 mol%)	52
4	$Mg(OtBu)_2$ (0.1 equiv)	**III-63** (20 mol%)	88
5	$Mg(OtBu)_2$ (0.1 equiv)	(*S*)-BINOL (20 mol%)	20
6	$Mg(OtBu)_2$ (0.1 equiv)	*t*BuOH (3 equiv)	80
7	$Mg(OtBu)_2$ (0.1 equiv)	Phenol (20 mol%)	67
8	$Mg(OtBu)_2$ (0.1 equiv)	$BF_3 \bullet OEt_2$ (1 equiv, distilled)	20
9	$Mg(OtBu)_2$ (0.1 equiv)	**III-64** (20 mol%)	64
10	KHF_2 (0.1 equiv)	**III-63** (20 mol%)	60

With excess amount of trifluoroborate salt, it was discovered that the effect of $Mg(OtBu)_2$ additive was almost negligible under the catalysis of (*S*)-Br_2-BINOL (Entry 1). Efficiency of the catalyst-free background reaction also increased (46% to 60%, Entry 2). May and coworkers proposed a fluoride dissociation pathway of the trifluoroborate reagent, which was confirmed by adding exogenous fluoride – all reactivity was eliminated.[162] Such evidence was not observed with our methodology (Table 3.11, Entry 10).

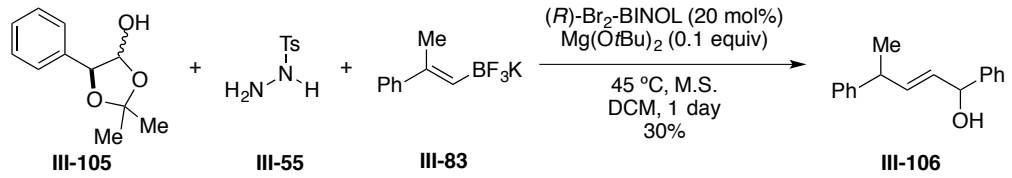
One final attempt to re-optimize the methodology was to examine new arene-sulfonyl hydrazides. According to our previous studies, electron-rich hydrazides both gave rise to higher yields (Table 3.10). We therefore prepared trimethyl-substituted phenyl sulfonyl hydrazide **III-104**. It worked extremely well as we had expected without any additives, affording the product in 90% yield (Scheme 3.24A). Interestingly, this hydrazide failed to yield Petasis reaction with alkyl-substituted trifluoroborate salt or boronic acids, giving rise to little to no desired product (Scheme 3.24B/C).

Scheme 3.24 Exploration using trimethyl-substituted phenyl sulfonyl hydrazide



Although aldehyde starting materials lacking an α-hydroxy directing group failed to yield the desired Petasis product (benzaldehyde, decanal, etc.), we were interested in exploring alternative substrates bearing an α-hydroxy group. Summer undergraduate student researcher Rebekah Reynolds prepared optically enriched protected aldehyde **III-105** with a phenyl substitution. It underwent "traceless" Petasis reaction to afford allylic alcohol **III-106** in 30% yield with minor impurities (Scheme 3.25).

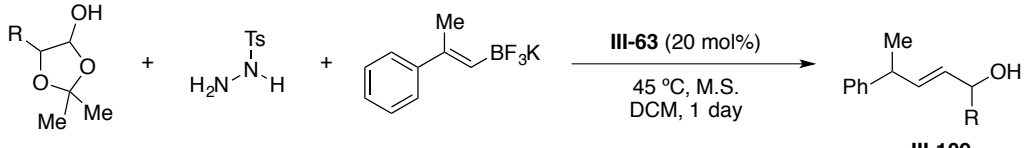
Scheme 3.25 Reynolds' preliminary result with alternative aldehyde substrate



III-105 **III-55** **III-83** **III-106**

We synthesized a few dimethoxypropane-protected aldehyde substrates based on previously reported procedure[157] and subjected them to our optimized reaction conditions. Differently-substituted allylic alcohol products were obtained, albeit in lower yields (Table 3.12). Preparation and exploration of more aldehyde substrates are underway.

Table 3.12 Exploration of alternative aldehyde substrates



R = *i*Pr, **III-107**
R = -CH_2Ph, **III-108**

III-55

III-83 (3 equiv)

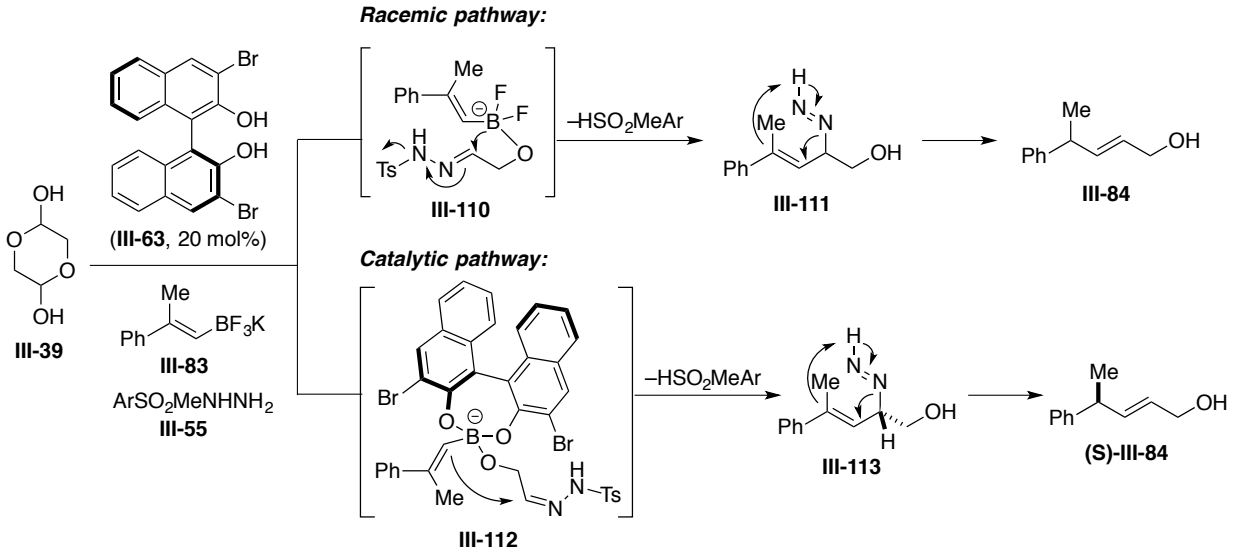
III-109

III-109a, 20% **III-109b**, 45%

*Yields were approximated due to difficulties in separation

A mechanism was proposed for the Petasis reaction with two possible reaction pathways based on preliminary data (Scheme 3.26). The presence of background reactions (Scheme 3.18) suggested that a racemic pathway was possible, during which the trifluoroborate salt underwent α hydroxy-directed addition without catalyst exchange, affording racemic allylic alcohol products. However, the intermediate could also potentially go through a catalytic pathway, during which the boron species undergoes catalyst exchange with the BINOL group before the addition (**III-112**), generating enantioenriched intermediate **III-113**. Hydrazone rearrangement/decomposition through the conformer with minimized allylic 1,3-strain would give rise to **(*S*)-III-84**. Unfortunately, preliminary product analysis using chiral HPLC showed little or no enantioselectivity so far under current reaction conditions, indicating the dominant pathway was likely the racemic one, or that the diol catalyst used provided no selectivity. Exploration of other catalysts will be needed for future work.

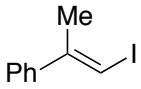
Scheme 3.26 Proposed reaction pathways for the "traceless" Petasis reaction



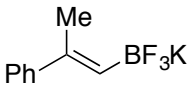
3.3 Summary

In summary, we developed a novel "traceless" Petasis reaction to synthesize differently-substituted allylic alcohols. This multi-component coupling methodology potentially enables rapid access to complicated molecules from simple precursors. Future studies involve further expansion of the substrate scope by exploring different carbonyl substrates and boron reagents. Efforts to render this transformation enantioselective are also underway.

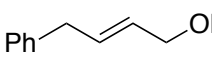
3.4 Experimental Section



1-iodo-2-phenylpropene (III-82): A solution of trimethylaluminum in hexanes (2.0 M, 50 mL) was added to Cp_2ZrCl_2 (10 mmol, 2.92 g) in dry DCM (50 mL) at –23 ºC under N_2 atmosphere. Then water (30 mmol, 540 μL) was carefully added. After 5 min, phenylacetylene in dry DCM (25 mL) was added dropwise using cannula. The mixture was stirred for 15 min before a solution of iodine (37.5 mmol, 9.52 g) in dry THF (40 mL) was added dropwise. Reaction was then warmed up and stirred at room temperature for 2 hours. The light yellow solution was cooled to –78 ºC and carefully quenched with water (20 mL). It was then warmed up to room temperature, diluted with diethyl ether (100 mL) and filtered through celite. The filtrate was washed with 0.5 M sodium thiosulfate solution (100 mL), dried over sodium sulfate and concentrated under reduced pressure. Flash column chromatography on silica gel using hexanes afforded a light yellow oil (3.8 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 5H), 6.45 – 6.43 (m, 1H), 2.21 (d, J = 1.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 141.6, 128.6, 128.0, 126.2, 79.3, 24.5. All spectroscopic data for this compound agrees with previously reported values.[164]

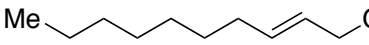


(2-phenylprop-1-en-1-yl)trifluoroborate (III-83): A solution of *n*BuLi (4.82 mmol) in hexanes was added dropwise to 1-iodo-2-phenylpropene (**III-82**, 4.02 mmol) in dry THF (14 mL) at –78 ºC under N_2 atmosphere. After 15 min, B(O*i*Pr)$_3$ (6.03 mmol) was added via syringe. The reaction was allowed to warm up to room temperature and stir for 2 hours. The mixture turned from light yellow to cloudy white. Methanol (4 mL) was added at 0 ºC, then KHF_2 (24 mmol) in water (5 mL) was added through addition funnel at 0 ºC dropwise. Reaction turned clear and was stirred at 0 ºC for 1 hour. Concentration under reduced pressure afforded white solids, which were dried overnight. Acetone (10 mL) was added to the mixture, which was stirred at 45 ºC for 30 min before filtered through celite and washed with acetone. The filtrate was concentrated in vacuum, redissolved in acetone (3 mL), followed by addition of diethyl ether (20 mL). White solids crashed out, which were collected through filtration (746 mg, 83% yield). The product was subjected to Petasis reaction without further purification.

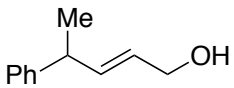


4-phenylbut-2-en-1-ol (III-59): Glycolaldehyde dimer (0.1 mmol) and tosyl hydrazide (**III-55**, 0.2 mmol) were dissolved in dry dichloromethane with 4Å molecular sieves (100 mg). The mixture was stirred at room temperature for 1 hour under N_2 atmosphere before the addition of *trans*-2-phenylvinylboronic ester (1.0 M solution in toluene, 0.2 mL), (*S*)-Br$_2$-BINOL (**III-63**, 20 mol%) and *t*BuOH (0.6 mmol). A condenser was attached and the reaction was stirred at 45 ºC for 48 hours under N_2 atmosphere. Concentration under reduced pressure followed by flash column chromatography on silica gel with 25% EtOAc in hexanes solvent system afforded the desired alcohol (19 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.23 – 7.17 (m, 3H), 5.92 – 5.83 (m, 1H), 5.76 – 5.66 (m, 1H), 4.13 (d, *J* = 5.8 Hz, 2H), 3.39

(d, J = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 131.8, 130.4, 128.7, 128.6, 126.3, 63.7, 38.8. All spectroscopic data for this compound agrees with previously reported values.[165]

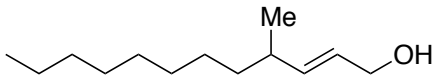


2-decen-1-ol (III-78): Glycolaldehyde dimer (0.1 mmol) and tosyl hydrazide (**III-55**, 0.2 mmol) were dissolved in dry dichloromethane with 4Å molecular sieves (100 mg). The mixture was stirred at room temperature for 1 hour under N_2 atmosphere before the addition of *trans*-1-octen-1-ylboronic acid (0.2 mmol), (*S*)-Br_2-BINOL (**III-63**, 20 mol%) and *t*BuOH (0.6 mmol). A condenser was attached and the reaction was stirred at 45 ºC for 48 hours under N_2 atmosphere. Concentration under reduced pressure followed by flash column chromatography on silica gel with 20% EtOAc in hexanes solvent system afforded the desired alcohol (19 mg, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 – 5.58 (m, 2H), 4.08 (d, J = 4.3 Hz, 2H), 2.09 – 1.97 (m, 2H), 1.41 – 1.16 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8, 128.9, 64.1, 32.4, 32.0, 29.3, 29.3, 22.8, 14.3. All spectroscopic data for this compound agrees with previously reported values.[166]



4-Phenylpent-2-en-1-ol (III-84): Glycolaldehyde dimer (0.1 mmol) and tosyl hydrazide (**III-55**, 0.2 mmol) were dissolved in dry dichloromethane with 4Å molecular sieves (100 mg). The mixture was stirred at room temperature for 1 hour under N_2 atmosphere before the addition of potassium (2-phenylprop-1-en-1-yl)trifluoroborate (**III-83,** 0.6 mmol), (*S*)-Br_2-BINOL (**III-63**, 20 mol%) and $Mg(OtBu)_2$ (0.02 mmol). A condenser was attached and the reaction was stirred at 45 ºC for 24 hours under N_2 atmosphere. Concentration under reduced pressure followed by flash column chromatography on silica gel with 20% EtOAc in hexanes solvent system afforded the desired alcohol (28 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.27 – 7.23 (m, 3H), 5.92 (ddt, J = 15.4, 6.7, 1.4 Hz, 1H), 5.70 (dtd,

J = 15.4, 5.9, 1.4 Hz, 1H), 4.16 (dt, *J* = 5.9, 1.2 Hz, 2H), 3.53 (p, *J* = 7.0 Hz, 1H), 1.53 (brs, 1H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 137.6, 128.6, 127.9, 127.3, 126.3, 63.8, 42.1, 21.2. All spectroscopic data for this compound agrees with previously reported values.[167]



III-90: Glycolaldehyde dimer (0.1 mmol) and tosyl hydrazide (**III-55**, 0.2 mmol) were dissolved in dry dichloromethane with 4Å molecular sieves (100 mg). The mixture was stirred at room temperature for 1 hour under N_2 atmosphere before the addition of trifluoroborate **III-89** (0.6 mmol), (*S*)-Br_2-BINOL (**III-63**, 20 mol%) and $Mg(O\textit{t}Bu)_2$ (0.02 mmol). A condenser was attached and the reaction was stirred at 45 ºC for 24 hours under N_2 atmosphere. Concentration under reduced pressure followed by flash column chromatography on silica gel with 15% EtOAc in hexanes solvent system afforded the desired alcohol (24 mg, 45% yield). IR (Germanium ATR): 3328, 2955, 2923, 2853 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 5.60 – 5.56 (m, 2H), 4.09 (d, *J* = 4.3 Hz, 2H), 2.16 – 2.08 (m, 1H), 1.36 – 1.21 (m, 15H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 127.1, 64.1, 37.0, 36.5, 32.1, 29.9, 29.8, 29.5, 27.4, 22.8, 20.5, 14.3. HRMS (ESI): Exact mass calcd for $C_{13}H_{26}O$ $[M+Na]^+$, 221.1876. Found 221.1877.

References

1. Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, 90, 2994–2996.

2. Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, 99, 8341–8343.

3. Yoder, R. A.; Johnston, J. N. *Chem. Rev. (Washington, DC, U. S.)* **2005**, 105, 4730–4756.

4. Barrett, T. N.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2014**, 136, 17013–17015.

5. Johnson, W. S.; van der Gen, A.; Swoboda, J. J. *J. Am. Chem. Soc.* **1967**, 89, 170–172.

6. Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182–183.

7. Van der Gen, A.; Wiedhaup, K.; Swoboda, J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, 95, 2656–2663.

8. Masse, C. E.; Panek, J. S. *Chem. Rev. (Washington, DC, U. S.)* **1995**, 95, 1293–1316.

9. Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, 104, 4962–4963.

10. Hosomi, A. *Acc. Chem. Res.* **1988**, 21, 200–206.

11. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 17, 1295–1298.

12. Bandi Chenna Kesava, R.; Belostotskii, A.; Hassner, A. *Adv. Synth. Catal.* **2014**, 356, 2661–2670.

13. Schinzer, D. *Synthesis* **1988**, 1988, 263–273.

14. Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, 59, 5130–5132.

15. Maier, M. E.; Schöffling, B. *Tetrahedron Lett.* **1990**, 31, 3007–3010.

16. Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, 5, 4231–4234.

17. Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, 44, 3889–3898.

18. Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Org. Lett.* **2006**, 8, 4649–4652.

19. Wilson, S. R.; Price, M. F. *J. Am. Chem. Soc.* **1982**, 104, 1124–1126.

20. Schinzer, D. *Angewandte Chemie International Edition in English* **1984**, 23, 308–309.

21. Majetich, G.; Desmond, R.; Casares, A. M. *Tetrahedron Lett.* **1983**, 24, 1913–1916.

22. Majetich, G.; Hull, K.; Desmond, R. *Tetrahedron Lett.* **1985**, 26, 2751–2754.

23. Majetich, G.; Hull, K. *Tetrahedron* **1987**, 43, 5621–5635.

24. Danheiser, R. L.; Takahashi, T.; Bertók, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, 34, 3845–3848.

25. Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, 57, 6094–6097.

26. Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y. M. *J. Am. Chem. Soc.* **1985**, 107, 7233–7235.

27. Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, 111, 389–391.

28. Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, 111, 4407–4413.

29. Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, 47, 2496–2498.

30. Mohr, P. *Tetrahedron Lett.* **1993**, 34, 6251–6254.

31. Oriyama, T.; Ishiwata, A.; Sano, T.; Matsuda, T.; Takahashi, M.; Koga, G. *Tetrahedron Lett.* **1995**, 36, 5581–5584.

32. Sano, T.; Oriyama, T. *Synlett* **1997**, 1997, 716–718.

33. Oriyama, T.; Ishiwata, A.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **2001**, 74, 569–570.

34. Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, 11, 3366–3369.

35. Díez‐Poza, C.; Barbero, A. *Eur. J. Org. Chem.* **2017**, 2017, 4651–4665.

36. Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 12, 1411–1413.

37. Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, 129, 3070–3071.

38. Suginome, M.; Iwanami, T.; Ito, Y. *J. Org. Chem.* **1998**, 63, 6096–6097.

39. Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, 126, 2425–2430.

40. Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, 122, 9836–9837.

41. Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, 7, 3231–3234.

42. Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 2001, 0955–0959.

43. Kjellgren, J.; Szabó, K. J. *Tetrahedron Lett.* **2002**, 43, 1123–1126.

44. Markó, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1992**, 33, 1799–1802.

45. Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, 50, 7141–7156.

46. Markó, I. E.; Leroy, B. *Tetrahedron Lett.* **2000**, 41, 7225–7230.

47. Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, 42, 8685–8688.

48. Leroy, B.; Markó, I. E. *J. Org. Chem.* **2002**, 67, 8744–8752.

49. van Innis, L.; Plancher, J. M.; Markó, I. E. *Org. Lett.* **2006**, 8, 6111–6114.

50. Chen, C.; Mariano, P. S. *J. Org. Chem.* **2000**, 65, 3252–3254.

51. Pham, M.; Allatabakhsh, A.; Minehan, T. G. *J. Org. Chem.* **2008**, 73, 741–744.

52. Ogawa, Y.; Painter, P. P.; Tantillo, D. J.; Wender, P. A. *J. Org. Chem.* **2013**, 78, 104–115.

53. Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, 680, 43–50.

54. Reddy Udagandla, C.; Bondalapati, S.; Saikia Anil, K. *Eur. J. Org. Chem.* **2009**, 2009, 1625–1629.

55. Suginome, M.; Iwanami, T.; Ito, Y. *Chem. Commun. (Cambridge, U. K.)* **1999**, 2537–2538.

56. Ullapu, P. R.; Min, S. J.; Chavre Satish , N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Chang, M. H.; Cho, Y. S. *Angew. Chem. Int. Ed.* **2009**, 48, 2196–2200.

57. Li, J.; Gallardo, T.; White, J. B. *J. Org. Chem.* **1990**, 55, 5426–5428.

58. Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, 50, 7129–7140.

59. Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, 27, 5067–5070.

60. Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, 108, 3512–3513.

61. Heerding, D. A.; Hong, C. Y.; Kado, N.; Look, G. C.; Overman, L. E. *J. Org. Chem.* **1993**, 58, 6947–6948.

62. Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, 26, 3155–3158.

63. Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, 44, 6729–6738.

64. Judd, W. R.; Ban, S.; Aubé, J. *J. Am. Chem. Soc.* **2006**, 128, 13736–13741.

65. Pirrung, F. O. H.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, 31, 5365–5368.

66. Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *J. Org. Chem.* **1984**, 49, 1149–1151.

67. Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, 72, 2115–2116.

68. Procter, G.; Russell, A. T.; Murphy, P. J.; Tan, T. S.; Mather, A. N. *Tetrahedron* **1988**, 44, 3953–3973.

69. Overman, L. E.; Renhowe, P. A. *J. Org. Chem.* **1994**, 59, 4138–4142.

70. Tan, T. S.; Mather, A. N.; Procter, G.; Davidson, A. H. *J. Chem. Soc., Chem. Commun.* **1984**, 585–586.

71. Cutting, I.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1435–1436.

72. Xiao, X. Y.; Park, S. K.; Prestwich, G. D. *J. Org. Chem.* **1988**, 53, 4869–4872.

73. Pettersson, L.; Frejd, T. *J. Chem. Soc., PerkinTrans. 1* **2001**, 789–800.

74. Pulido Francisco, J.; Barbero, A.; Castreño, P. *Eur. J. Org. Chem.* **2010**, 2010, 1307–1313.

75. Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1982**, 60, 673–675.

76. Frey, D. A.; Krishna Reddy, S. H.; Moeller, K. D. *J. Org. Chem.* **1999**, 64, 2805–2813.

77. Stevens, B. D.; Nelson, S. G. *J. Org. Chem.* **2005**, 70, 4375–4379.

78. Kettschau, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, 39, 2027–2028.

79. Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Org. Lett.* **2015**, 17, 3000–3003.

80. De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, 46, 8345–8350.

81. Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* **2004**, 43, 1414–1416.

82. Cella, J. A. *J. Org. Chem.* **1982**, 47, 2125–2130.

83. Han, J.; Cui, Z.; Wang, J.; Liu, Z. *Synth. Commun.* **2010**, 40, 2042–2046.

84. Hassner, A.; Bandi, C. R. *Synlett* **2013**, 24, 1275–1279.

85. Orizu, I.; Bolshan, Y. *Tetrahedron Lett.* **2016**, 57, 5798–5800.

86. Gao, H.-T.; Wang, B.-L.; Li, W.-D. Z. *Tetrahedron* **2014**, 70, 9436–9448.

87. Barrero, A. F.; Herrador, M. M.; Arteaga, P.; Arteaga, J. F.; Arteaga, A. F. *Molecules* **2012**, 17, 1448–1467.

88. Jeker Oliver, F.; Kravina Alberto, G.; Carreira Erick, M. *Angew. Chem. Int. Ed.* **2013**, 52, 12166–12169.

89. Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, 115, 11028–11029.

90. Fráter, G.; Müller, U.; Kraft, P. *Helv. Chim. Acta* **1999**, 82, 1656–1665.

91. Steele, L. S.; Glazier, R. H. *Canadian Family Physician* **1999**, 45, 917–919.

92. Wang, J.; Zhou, P.; Wang, Y. *Eur. J. Org. Chem.* **2011**, 2011, 264–270.

93. Bonderoff, S. A.; West, F. G.; Tremblay, M. *Tetrahedron Lett.* **2012**, 53, 4600–4603.

94. Kazakova, A. N.; Iakovenko, R. O.; Boyarskaya, I. A.; Nenajdenko, V. G.; Vasilyev, A. V. *J. Org. Chem.* **2015**.

95. Kim, S.; Kitano, Y.; Tada, M.; Chiba, K. *Tetrahedron Lett.* **2000**, 41, 7079–7083.

96. Ivanova, O. A.; Budynina, E. M.; Skvortsov, D. A.; Limoge, M.; Bakin, A. V.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y. *Chem. Commun. (Cambridge, U. K.)* **2013**, 49, 11482–11484.

97. Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, 127, 15036–15037.

98. Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton, R. S.; Smith, M. D. *Nat. Chem.* **2015**, 7, 171–177.

99. Ikeda, S.-i.; Watanabe, H.; Sato, Y. *J. Org. Chem.* **1998**, 63, 7026–7029.

100. Takeuchi, R.; Tanaka, S.; Nakaya, Y. *Tetrahedron Lett.* **2001**, 42, 2991–2994.

101. Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* **2002**, 67, 7724–7729.

102. Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, 348, 1033–1037.

103. Santana, L.; González-Díaz, H.; Quezada, E.; Uriarte, E.; Yáñez, M.; Viña, D.; Orallo, F. *J. Med. Chem.* **2008**, 51, 6740–6751.

104. Radwan, M. M.; ElSohly, M. A.; Slade, D.; Ahmed, S. A.; Wilson, L.; El-Alfy, A. T.; Khan, I. A.; Ross, S. A. *Phytochemistry* **2008**, 69, 2627–2633.

105. Fox, B. M.; Sugimoto, K.; Iio, K.; Yoshida, A.; Zhang, J.; Li, K.; Hao, X.; Labelle, M.; Smith, M.-L.; Rubenstein, S. M.; Ye, G.; McMinn, D.; Jackson, S.; Choi, R.; Shan, B.; Ma, J.; Miao, S.; Matsui, T.; Ogawa, N.; Suzuki, M.; Kobayashi, A.; Ozeki, H.; Okuma, C.; Ishii, Y.; Tomimoto, D.; Furakawa, N.; Tanaka, M.; Matsushita, M.; Takahashi, M.; Inaba, T.; Sagawa, S.; Kayser, F. *J. Med. Chem.* **2014**, 57, 3464–3483.

106. Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, 115, 11490–11495.

107. Fujii, K.; Hara, O.; Sakagami, Y. *Biosci. Biotechnol. Biochem.* **1997**, 61, 1394–1396.

108. Schlosser, M.; Franzini, L. *Synthesis* **1998**, 1998, 707–709.

109. H. Dussault, P.; T. Eary, C.; J. Lee, R.; R. Zope, U. *J. Chem. Soc., PerkinTrans. 1* **1999**, 2189–2204.

110. Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* **2001**, 2001, 1042–1045.

111. Wagner, M.; Dziadek, S.; Kunz, H. *Chem. Eur. J.* **2003**, 9, 6018–6030.

112. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, 40, 1460–1469.

113. Hayakawa, F.; Watanabe, S.-i.; Shimizu, N.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1993**, 66, 153–157.

114. Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, 62, 6928–6951.

115. Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. *Tetrahedron* **2012**, 68, 9624–9637.

116. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, 105, 2315–2325.

117. Trost, B. M.; Matelich, M. C. *Synthesis* **1992**, 1992, 151–156.

118. Yu, H.-Y.; Chen, Z.-Y.; Sun, B.; Liu, J.; Meng, F.-Y.; Liu, Y.; Tian, T.; Jin, A.; Ruan, H.-L. *J. Nat. Prod.* **2014**, 77, 1311–1320.

119. Akiyama, T.; Mori, K. *Chem. Rev. (Washington, DC, U. S.)* **2015**, 115, 9277–9306.

120. Monaco, M. R.; Pupo, G.; List, B. *Synlett* **2016**, 27, 1027–1040.

121. Krasovskiy, A.; Straub Bernd, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, 45, 159–162.

122. Tanpure, R. P.; Harkrider, A. R.; Strecker, T. E.; Hamel, E.; Trawick, M. L.; Pinney, K. G. *Bioorg. Med. Chem.* **2009**, 17, 6993–7001.

123. Muller, G. W.; Payvandi, F.; Zhang, L. H.; Robarge, M. J.; Chen, R.; Man, H.-W. (Celgene Corp). US2005107339 A1, **2005**

124. Lantaño, B.; Aguirre, J. M.; Finkielsztein, L.; Alesso, E. N.; Brunet, E.; Moltrasio, G. Y. *Synth. Commun.* **2004**, 34, 625–641.

125. Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Onomura, O. *Tetrahedron* **2010**, 66, 6814–6819.

126. Kumar, A. S.; Ghosh, S.; Bhima, K.; Mehta, G. N. *J. Chem. Res.* **2009**, 2009, 482–484.

127. Peng, Y.; Luo, Z.-B.; Zhang, J.-J.; Luo, L.; Wang, Y.-W. *Org. Biomol. Chem.* **2013**, 11, 7574–7586.

128. Zacchino, S. A.; López, S. N.; Pezzenati, G. D.; Furlán, R. L.; Santecchia, C. B.; Muñoz, L.; Giannini, F. A.; Rodríguez, A. M.; Enriz, R. D. *J. Nat. Prod.* **1999**, 62, 1353–1357.

129. Lambertucci, C.; Sundukova, M.; Kachare, D. D.; Panmand, D. S.; Dal Ben, D.; Buccioni, M.; Marucci, G.; Marchenkova, A.; Thomas, A.; Nistri, A.; Cristalli, G.; Volpini, R. *Eur. J. Med. Chem.* **2013**, 65, 41–50.

130. Zhu, K.; Shaver Michael, P.; Thomas Stephen, P. *Eur. J. Org. Chem.* **2015**, 2015, 2119–2123.

131. Qin, C.; Wu, H.; Cheng, J.; Chen, X. a.; Liu, M.; Zhang, W.; Su, W.; Ding, J. *J. Org. Chem.* **2007**, 72, 4102–4107.

132. Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, 124, 67–77.

133. Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem. Int. Ed.* **2013**, 52, 2529–2533.

134. Croudace, M. C.; Schore, N. E. *J. Org. Chem.* **1981**, 46, 5357–5363.

135. Jankowski, P.; Masnyk, M.; Wicha, J. *Synth. Commun.* **1989**, 19, 873–880.

136. Fonseca, S. F.; Nielsen, L. T.; Rúveda, E. A. *Phytochemistry* **1979**, 18, 1703–1708.

137. Reddel, J. C. T.; Lutz, K. E.; Diagne, A. B.; Thomson, R. J. *Angew. Chem. Int. Ed.* **2014**, 53, 1395–1398.

138. Nono, E. C. N.; Mkounga, P.; Kuete, V.; Marat, K.; Hultin, P. G.; Nkengfack, A. E. *J. Nat. Prod.* **2010**, 73, 213–216.

139. Messiano, G. B.; Wijeratne, E. M. K.; Lopes, L. M. X.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2010**, 73, 1933–1937.

140. Rangkaew, N.; Suttisri, R.; Moriyasu, M.; Kawanishi, K. *Fitoterapia* **2009**, 80, 377–379.

141. Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, 77, 1566–1571.

142. Aoyama, T.; Furukawa, T.; Hayakawa, M.; Takido, T.; Kodomari, M. *Synlett* **2015**, 26, 1875–1879.

143. Verma, G.; Marella, A.; Shaquiquzzaman, M.; Akhtar, M.; Ali, M. R.; Alam, M. M. *Journal of Pharmacy & Bioallied Sciences* **2014**, 6, 69–80.

144. Stevens, R. V.; McEntire, E. E.; Barnett, W. E.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1973**, 662–663.

145. Bertz, S. H. *Tetrahedron Lett.* **1980**, 21, 3151–3154.

146. Vedejs, E.; Stolle, W. T. *Tetrahedron Lett.* **1977**, 18, 135–138.

147. Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, 112, 8208–8210.

148. Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, 120, 8891–8892.

149. Mundal, D. A.; Lee, J. J.; Thomson, R. J. *J. Am. Chem. Soc.* **2008**, 130, 1148–1149.

150. Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, 11, 465–468.

151. Lutz Kelly, E.; Thomson Regan, J. *Angew. Chem. Int. Ed.* **2011**, 50, 4437–4440.

152. Reddel Jordan, C. T.; Lutz Kelly, E.; Diagne Abdallah, B.; Thomson Regan, J. *Angew. Chem. Int. Ed.* **2013**, 53, 1395–1398.

153. Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, 118, 4492–4493.

154. Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, 34, 583–586.

155. Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2012**, 134, 5782–5785.

156. Diagne, A. B.; Li, S.; Perkowski, G. A.; Mrksich, M.; Thomson, R. J. *ACS Combinatorial Science* **2015**, 17, 658–662.

157. Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E. *J. Am. Chem. Soc.* **2017**, 139, 1998–2005.

158. Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, 130, 6922–6923.

159. Muncipinto, G.; Moquist Philip, N.; Schreiber Stuart, L.; Schaus Scott, E. *Angew. Chem. Int. Ed.* **2011**, 50, 8172–8175.

160. Shi, X.; Kiesman, W. F.; Levina, A.; Xin, Z. *J. Org. Chem.* **2013**, 78, 9415–9423.

161. Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc.* **2015**, 137, 11262–11265.

162. Shih, J.-L.; Nguyen Thien, S.; May Jeremy, A. *Angew. Chem. Int. Ed.* **2015**, 54, 9931–9935.

163. Le, P. Q.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2012**, 14, 6104–6107.

164. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, 107, 6639–6647.

165. Mao, Y.; Zhai, X.; Khan, A.; Cheng, J.; Wu, X.; Zhang, Y. J. *Tetrahedron Lett.* **2016**, 57, 3268–3271.

166. Brodl, E.; Ivkovic, J.; Tabib, C. R.; Breinbauer, R.; Macheroux, P. *Bioorg. Med. Chem.* **2017**, 25, 1487–1495.

167. Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, 13, 70–73.