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Mild Hydrofunctionalizations of Olefins Using More Cost-Effective Metal Catalysts

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MILD HYDROFUNCTIONALIZATIONS OF OLEFINS USING MORE COST-EFFECTIVE METAL CATALYSTS

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I would like to thank my parents for their unending support during my academic pursuits. Thank you, Mom and Dad, for everything. This dissertation would not be possible without my family and friends. Thank you, Lisa, for listening to my practice talks and keeping me upbeat whenever things got tough.

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ABSTRACT

The focus of this dissertation is the study of alkene hydroaylation reactions. In the first chapter, a review of the relevant literature concerning zinc- and iron-catalyzed hydroarylation of unsaturated bonds is presented. In chapter two, the development of a zinc-catalyzed hydroarylation of alkenes is presented, which is quickly followed by a detailed investigation into the probable mechanism. Chapter three discusses the development of an iron/silver-catalyzed arene prenylation reaction, followed by the development of an iron/zinc-catalyzed arene prenylation reaction. The final section of chapter three discusses the adaptation of the iron/zinc-catalyzed arene prenylation into an undergraduate organic teaching laboratory.

LIST OF ABBREVIATIONS

HCl	hydrochloric acid
FC	Friedel-Crafts
$ZnCl_2$	zinc (II) chloride
$FeCl_3$	iron (III) chloride
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
NOE	Nuclear Overhauser Effect
COSY	Correlation Spectroscopy

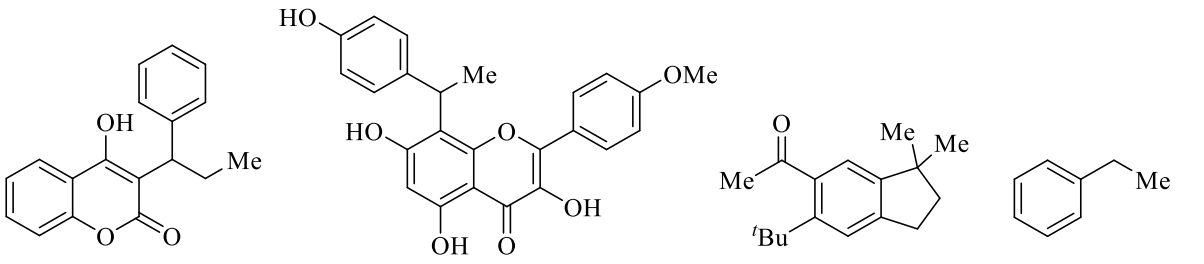
CHAPTER ONE

RECENT ADVANCES IN THE HYDROARYLATION OF UNSATURATED CARBON-CARBON BONDS USING ZINC OR IRON-BASED CATALYSTS

Introduction

Alkyl-arenes are important organic motifs that have a variety of applications in industrially relevant fields such as drug development,[1–3] natural product total synthesis,[4–8] the fragrance industry,[9–11] and petroleum chemical synthesis.[12–15] Some examples of important alkyl-arenes are represented in Figure 1. However, the development of techniques that access

Figure 1. Examples of industrially important alkyl-arenes



phenprocoumon *anticoagulant* | haplopappin *plant extract* | celestolide *musk fragrance* | ethylbenzene *precursor to styrene*

these important molecules is a challenge in synthetic chemistry. Catalysis remains the most powerful method for the synthesis of alkyl arenes, the two most widely practiced techniques being arene alkyl cross-coupling reactions[1,16–25] and Friedel-Crafts alkylations.[5,6,26,27] Recent examples of cross-coupling reactions by Buchwald,[24] Fu,[17] Tang,[25] and others have demonstrated the versatility of this technology, yet these examples are catalyzed by expensive precious metals, typically palladium[17,18,20–24] and produce a stoichiometric amount of halide by-products. In

contrast, the Friedel-Crafts alkylation of aromatic rings with unsaturated carbon-carbon bonds (a.k.a.hydroarylation) is an efficient method for aryl-alkane synthesis that relies on readily available acid catalysts and petroleum-derived aromatics. Since this method is a type of addition reaction, it avoids the generation of wasteful by-products. In addition, unsaturated carbon-carbon bond containing molecules are readily available making the hydroarylation method ideal for commercial exploitation.[14,28–31]

In addition to being an effective strategy for alkyl-arene synthesis, the hydroarylation of unsaturated carbon-carbon bonds has been successfully applied to natural product synthesis, pharmaceutical production, and other industrial products. Hydroarylation served as an effective strategy for the synthesis of natural products including rotenone,[32] diazonamide A,[33] and (±)-dihydroisosubamol.[34] Additionally, the drugs phenprocoumon,[35] an anti-coagulant, and L-tolterodine,[36] a bladder relaxant, have been synthesized using hydroarylation protocols. Furthermore, the industrial production of ethylbenzene, a precursor to styrene, the monomer of Styrofoa, relies on the hydroarylation reaction. Millions of kilotons of ethylbenzene are produced annually through the hydroarylation of ethylene with benzene.[31,37,38] Together, the synthesis of these highly valuable products was successfully realized by the use of a wide variety of catalysts.

Of the many catalysts studied, Lewis acids based on gold,[39] platinum,[40] palladium,[41] iridium,[42] and metal triflates[43] offer diverse reactivity, yet these catalysts are expensive and their presence as residual impurities in drugs can be problematic and is therefore tightly regulated,[44] making them less attractive for applications in pharmaceuticals. Catalysts based on bismuth have emerged as effective promoters of hydroarylation reactions, yet bismuth and its chloride

salt are not readily available with the metal being the 83rd most abundant element[45] in the Earth's crust, and the chloride salt costing $558/mol.[46] Alternative catalysts based on naturally abundant and inexpensive metals that offer complementary reactivity would be desirable. Lewis acids based on iron and zinc are promising candidates for hydroarylation reactions due to their high abundance, higher tolerance in drugs as trace impurities, and low cost.[44,47,48] For example, iron is the 4th most abundant element in the Earth's crust,[45] is considered an essential micronutrient, and iron halides such as iron chloride only cost $4/mol.[49] Zinc is the 24th most abundant metal in the Earth's crust,[45] is an essential nutrient in the human diet,[50,51] and zinc chloride costs $16/mol.[52] In contrast, palladium is the 74th most abundant metal in the Earth's crust, its presence in drugs is tightly regulated, and palladium chloride costs $4469/mol.[53] Therefore, the development of hydroarylation methods using iron or zinc halides would offer a much more cost-effective catalyst design than utilization of expensive late transition metals.

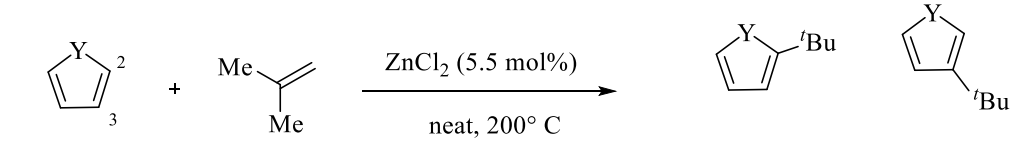
The overall goal of this review (Chapter 1) is to highlight the application of iron and zinc halides towards the hydroarylation of unsaturated carbon-carbon bonds and the role of these methods in important industrial and synthetic processes. These earth-abundant metal catalysts, when used as promoters in the hydroarylation of olefins, provide efficient access to biologically and industrially important compounds at much lower cost than late transition metals and metal triflates. A survey of the advances in hydroarylation of unsaturated carbon-carbon bonds concerning these metals is lacking, thus a review showcasing their utility is essential to draw attention to their synthetic potential. Following this review, reports from our work addressing the zinc-catalyzed hydroarylation of simple olefins and an in-depth mechanistic analysis are highlighted (Chapter 2). Finally, our work concerning iron-catalyzed arene prenylation reactions

are highlighted and their recent application toward the teaching of an undergraduate organic labratory are discussed (Chapter 3).

Zinc-Catalyzed Hydroarylation

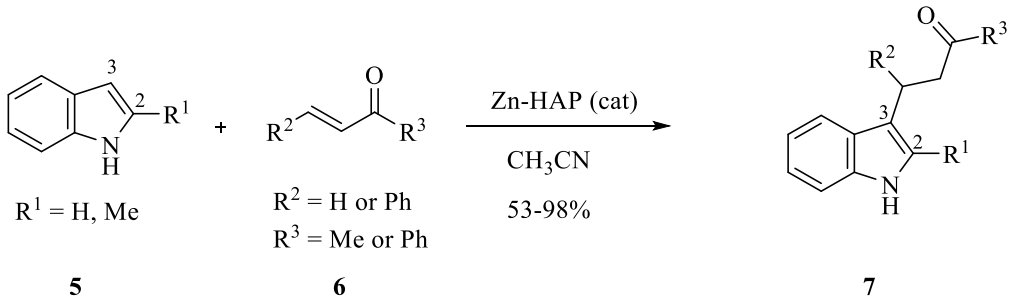
Zinc halides are considered to be weak Lewis acids[54,55] yet there are many reports of zinc salts being used as effective catalysts for the hydroarylation of various olefins with polymerizable arenes. For example, the hydroarylation of α-olefins using heteroaromatics such as pyrrole, furan, and thiophene is a difficult reaction to accomplish effectively since these molecules tend to polymerize under strongly acidic conditions.[56,57] In order to address this challenge, Petrovskaya and co-workers employed mild zinc halide catalysts for the hydroarylation of isobutylene **2** with *N*-methylpyrroles and thiophenes **1** (Scheme 1).[58] A moderate isolated yield (42%) of *tert*-butylated *N*-heterocycles was observed when zinc chloride was employed at elevated temperatures (200 °C). A mixture of two regioisomers **3** and **4** was observed and the regioselectivity depended greatly on the identity of the heterocycle; thiophene was selectively alkylated in the 2-position while *N*-methylpyrrole was selectively alkylated in the 3-position. While this zinc-catalyzed hydroheteroarylation method provided access to useful butylated heterocycles, the scope of this method was not significantly developed.

Scheme 1. Zinc-catalyzed hydroarylation of isobutene with pyrrole and thiophene[58]



Tahir and co-workers demonstrated that the hydroarylation of unsaturated carbon-carbon bonds could be extended to α,β-unsaturated ketones (Scheme 2).[59] Using a zinc bromide catalyst

Scheme 2. Tahir's zinc-catalyzed hydroarylation of conjugated ketones[59]

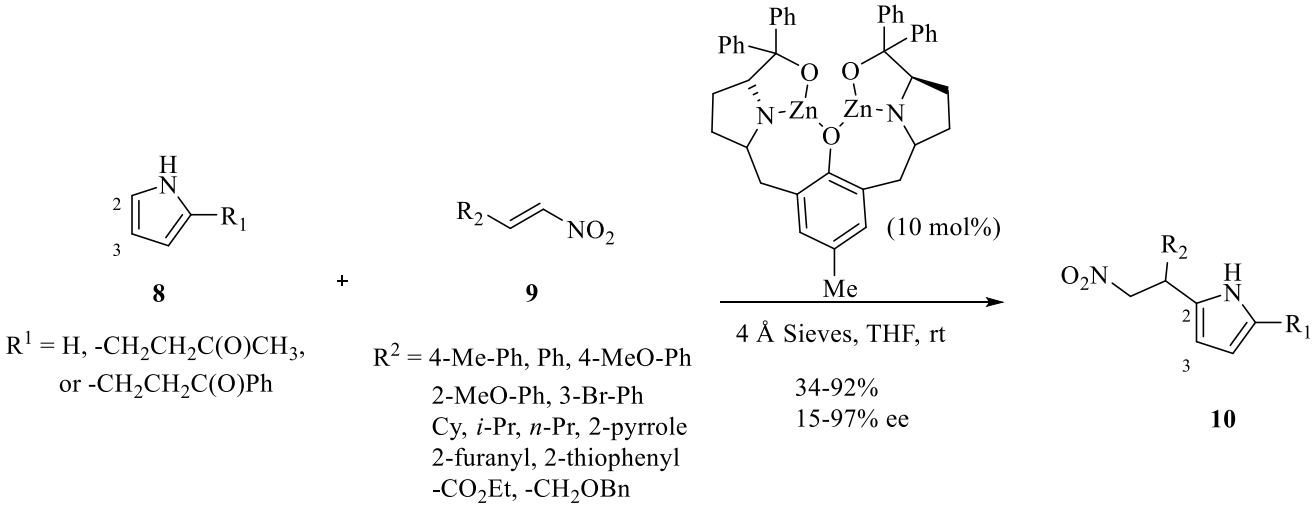


mounted on hydroxyapatite (HAP), the 1,4-conjugate addition of indole nucleophiles **5** to ketones **6** provided the desired indole-ketones **7**. HAP is an inexpensive heterogenous support system that allowed for the efficient recycling of the zinc-catalyst after the hydroarylation. The regioselectivity of the reaction was exclusive to the 3-position of the heterocycle providing the desired indole-ketone **7** in good to excellent isolated yields (53-98%). The indoles were exclusively alkylated in the 3-position of the heterocycle and good isolated yields (69-98%) of the β-arylated ketones were observed.

Zinc-catalyzed stereoselective hydroarylation of olefins has recently been explored by Trost and co-workers.[60] Using a zinc-bisProPhenol complex as catalyst, the 1,4-conjugate addition of a variety of pyrroles **8** onto nitro-olefins **9** was successfully demonstrated. Alkylation was exclusive to the 2-position of the unprotected pyrrole and moderate to excellent yields were observed using a variety of aryl- and alkyl-substituted nitroalkenes (34-92%). The enantiopurity of the final alkylated pyrrole **3** was excellent in most cases (>90% ee) but diminished enantiopurity was observed when a ketone-substituted pyrrole was tested (56% ee). This method was an effective demonstration of a zinc-catalyzed, stereoselective hydroarylation

reaction, and the final nitro-alkane products are versatile building blocks for further synthesis.[61,62] It should be noted that the synthesis of the zinc-bisProPhenol requires access to relatively inexpensive diethyl zinc ($185/mol)[63] and commercially available but expensive bis-ProPhenol ligand ($18,206/mol).[64]

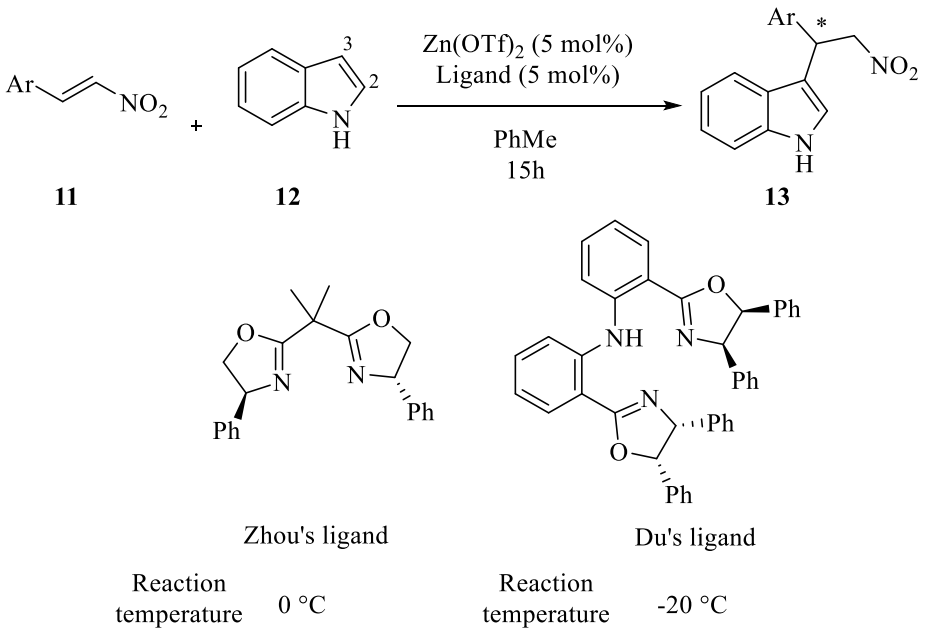
Scheme 3. Trost's zinc-catalyzed enantioselective hydroarylation of nitroalkenes[60]



Further development of zinc-catalyzed stereoselective hydroarylation reactions involving heterocycles have recently been reported by a number of groups. For example, Zhou and co-workers developed a zinc complex based on a commercially available bis-oxazole ligand scaffold ($95,051/mol)[65] that was active for the stereoselective hydroarylation of nitro-olefins **11** (Scheme 4).[66] Indoles **12** were exclusively alkylated in the 3-position of the heterocycle and provided moderate to excellent isolated yields (57-98%) of the desired nitro-alkanes **13**. Very mild reaction conditions allowed moderate to good enantioselective hydroarylation of unprotected indoles in 61-90% ee. Interestingly, extension of the procedure to *N*- or arene-substituted indoles led to an erosion in the observed enantiopurities of the final product (21-80% ee). Du and co-workers were able later to address this limitation with the development of a

different bis-oxazole-zinc complex.[67] Unfortunately, both Du's and Zhou's catalyst systems rely on the expensive triflate salts ($1410/mol)[68] as the zinc source which contradicts the economic practicality of using zinc catalysts in hydroarylation protocols.

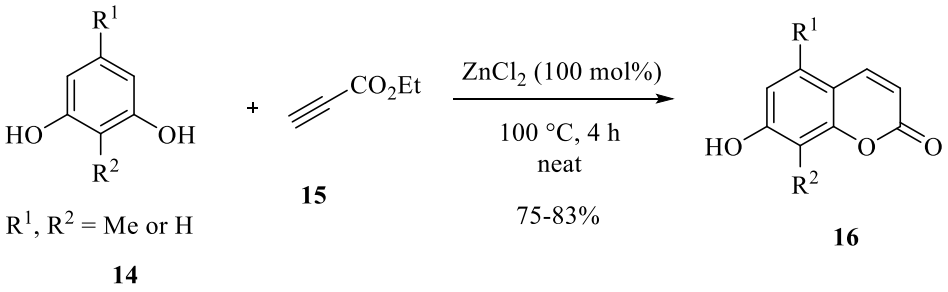
Scheme 4. Zhou's and Du's zinc-catalyzed stereoselective hydroarylation of nitro-olefins[66,53]



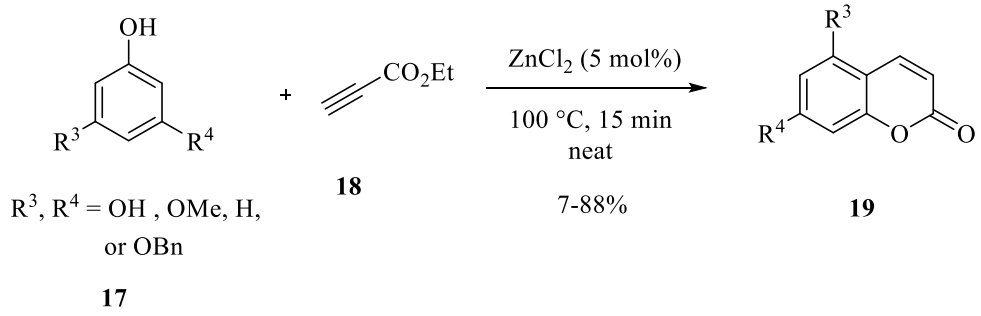
Zinc-catalyzed intramolecular hydroarylation reactions are powerful methods for the synthesis of privileged[69,70] ring systems. In particular, the efficient synthesis of privileged heterocycles such as coumarins is of significant interest to drug development.[71,72] For example, in 1965, Kaufman and Kelly discovered that zinc chloride promoted the tandem hydroarylation-transesterification of alkynyl esters which provided hydroxycoumarins in good yields.[73] Utilizing one equivalent of zinc chloride, electron-rich phenols **14** reacted with ethyl propynylate (**15**) which were cleanly converted to 5,7-dihydroxycoumarin **16** in 83% yield (Scheme 5). Further development of this protocol by Costa and co-workers led to a reduction in the amount of zinc chloride from 100 mol% to 5 mol% with little effect on the overall yield (Scheme 5).[74]

Scheme 5. Zinc catalyzed synthesis of coumarins using hydroarylation of alkynes[73,74]

Kaufman et al:



Costa et al:

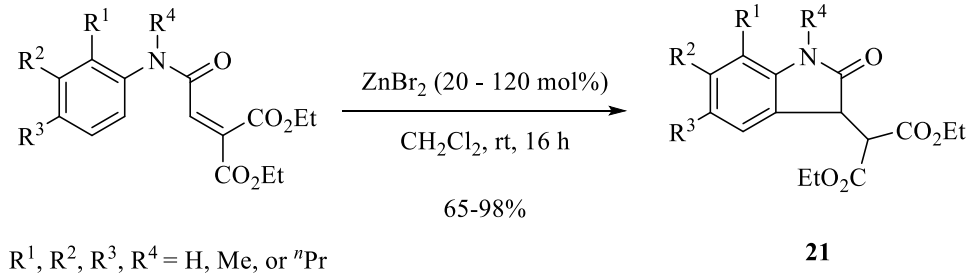


This catalytic method was effective for the synthesis of a wide variety of mono- and di-substituted coumarins **19** in poor to good isolated yields (7-88%). Interestingly, this zinc-promoted tandem hydroarylation-transesterification of alkynyl esters has been recently utilized for the total synthesis of natural products such as wedelolactones,[75] prandiol,[76] decursinol angelate,[77] and decursin[77] in yield ranging from 5-85% depending on the starting phenol. Clearly, the zinc-promoted hydroarylation of alkynyl esters is an effective method for heterocycle formation, but further method development is needed to address the unpredictable yields for different substrates.

Other heterocycles such as oxindole derivatives can be effectively synthesized utilizing zinc-catalyzed intramolecular hydroarylation methods. For example, Yamazaki and co-workers described in a report from 2004 that zinc halides effectively promoted the synthesis of oxindoles

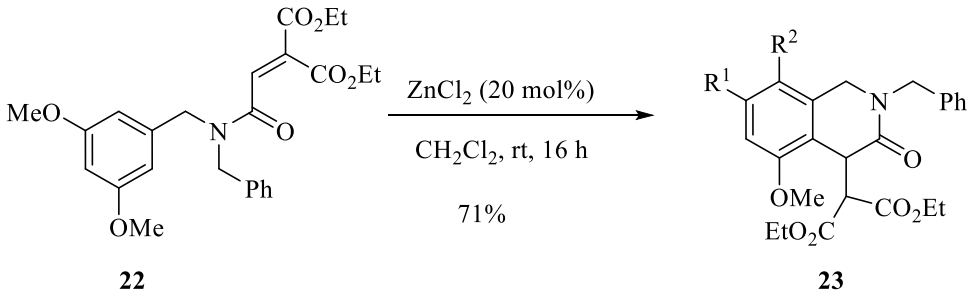
from alkylidene malonic ester-amides **20** (Scheme 6).[78] Formally, this hydroarylation reaction is another example of a 1,4-conjugate addition, but this example involves a ring-closing event which makes it distinct from the previous intermolecular examples. Good to excellent isolated

Scheme 6. Yamazaki's zinc-mediated hydroarylation of alkylidene malonic esters[78]



yields of the desired oxindoles **21** were reported (65-98%). This zinc-catalyzed hydroarylation method effectively constructed an important heterocycle under mild conditions with consistently high isolated yields. Yamazaki and co-workers recently extended this method towards the synthesis of six-membered nitrogen heterocycles such as **23** in 71% isolated yield (Scheme 7).[79]

Scheme 7. Yamazaki's zinc-catalyzed syntheis of tetrahydro-oxo-isoquinolines[79]

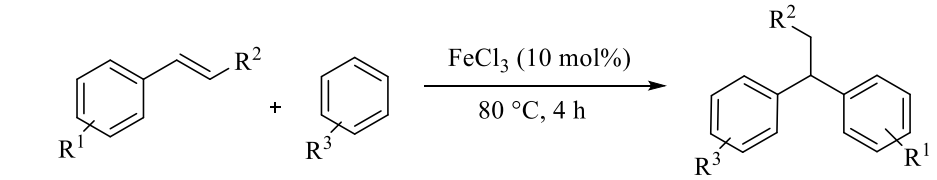


Iron-Catalyzed Hydroarylation

Ferric salts are considered to be strong Friedel-Crafts alkylation catalysts,[28] but their use in hydroarylation chemistry has only been developed recently with many of the discoveries occurring within the last two decades.[80–82] In 2006, Beller and co-workers discovered that

styrenes were effective alkylating reagents in the iron-catalyzed benzylation of arenes.[83] Iron chloride (hydrate or anhydrous) catalyzed the intermolecular hydroarylation reaction between substituted styrenes **24** and electron-rich arenes **25** (Scheme 8). Alkyl-, alkoxy-, and phenoxy-substituted arenes were well tolerated and the diarylmethines **26**were isolated in were reported in good to excellent (>90%) GC yields. Heteroaromatics like thiophene were isolated in moderate GC yields (36-51%) but with a high degree of regioselectivity. A large excess (>100 equivalents in all cases) of the nucleophile was employed.

Scheme 8. Beller's hydroarylation of styrenes catalyzed by iron chloride[83]

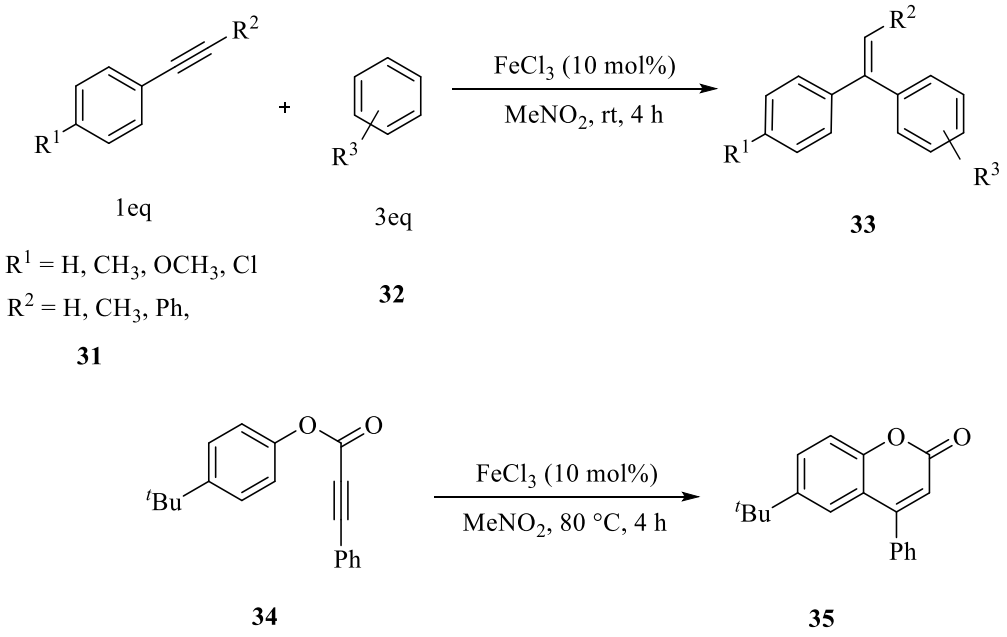


R^1 = H, CH_3, CF_3
R^2 = H, CH_3, Ph
R^3 = CH_3, OH, OCH_3

24 **25** **26**

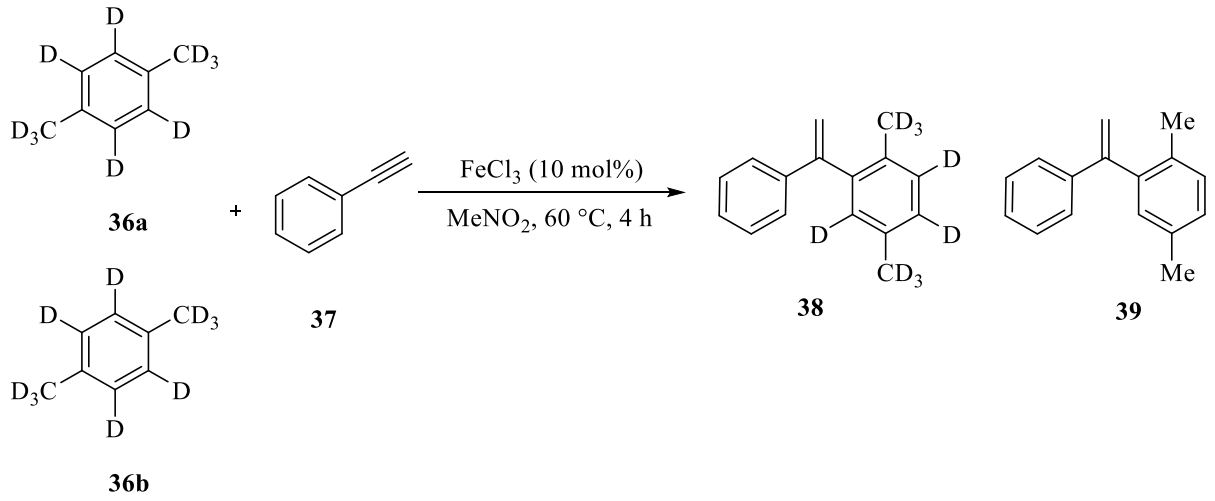
Alkynes are readily available unsaturated molecules[84] that can also act as very effective hydroarylation reagents which is consistent with their greater reactivity. Wenjun Lu and co-workers proved that room temperature intermolecular hydroarylation of phenyl-acetylenes could be catalyzed by $FeCl_3$ (Scheme 9).[85] Employing nitromethane as the solvent significantly enhanced the activity of the catalyst system provided the highest isolated yields among all the solvents tested. Poor to good isolated yields (11-86%) were observed for the hydroarylation of

Scheme 9. Lu's iron chloride-catalyzed hydroarylation of phenylacetylenes[85]



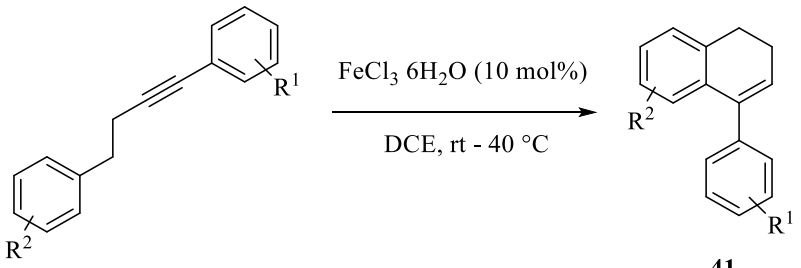
phenylacetylenes **31** with electron rich arenes **32**. The hydroarylation of *p*-methoxy and *p*-chloro-substituted phenylacetylenes **31** provided acceptable yields (87% and 69%, respectively) with exclusive alkylation in the α-position of the alkyne. Attempts at reacting β-alkyl substituted acetylenes provided a complex mixture of *E*/*Z* isomers, likely due to acid-catalyzed isomerization. Additionally, one example of an intramolecular hydroarylation provided the desired substituted coumarin in 53% isolated yield in a single step starting from readily available materials. In order to determine a working mechanism, the authors took mixtures of the iron catalyst, nitromethane, water, and **36a** and observed no H-D exchange which is ruled out mechanisms that involved C-H activation. Furthermore, employing deuterium labelled xylene **36a** alongside undeuterated **36b** as the nucleophilic arenes, the authors report isolating **38** and **39** in a 1:1 ratio which is consistent with an electrophilic aromatic substitution mechanism.[86]

Scheme 10. Lu's mechanistic investigation of iron-catalyzed hydroarylations[85]



Iron-catalyzed intramolecular hydroarylation reactions have proven to be powerful methods for the construction of a variety of privileged ring systems. Dihydronaphthalenes are important all-carbon fused bicycles that have been used in the scaffold of many effective pharmaceuticals.[87–89] Efficient access to dihydronaphthalenes was realized by Campagne and co-workers through an intramolecular hydroarylation of 1,4-diaryl-substituted propynes (Scheme 11).[90] Efficient cyclization was observed when the reaction temperature was between room temperature and 40 °C to minimize the presence of undesired side products such as transfer hydrogenations. Various electron-releasing substituents such as methyl groups and methoxy groups were well tolerated, and the desired dihydronaphthalenes **41** were isolated in good yields (68-86%).

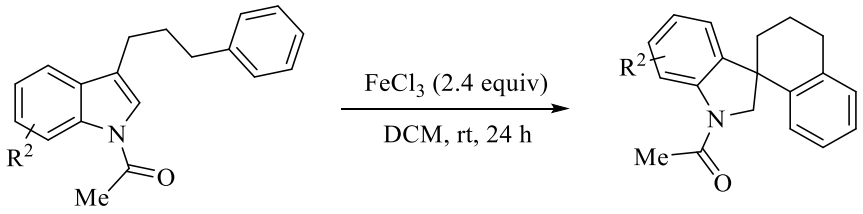
Scheme 11. Campagne's iron-catalyzed intramolecular hydroarylation of 1,4-diaryl pentynes[90]



40 **41**

A rather unusual intramolecular hydroarylation of indoles with electron-rich benzene derivatives was discovered by Vincent and co-workers.[91] In their report, 3,3-spiroindolines were effectively synthesized using iron chloride as the promoter (Scheme 12). The generality of this reaction was explored using a variety of 1-aryl-3-indole-substituted propanes **42**. The resulting spirocyclic tetrahydronaphthalenes **43** were efficiently synthesized in 38-79% isolated yields. It was recently suggested through DFT calculations that the high concentration of iron chloride promoter allows a positive charge on C-3 of the indole to develop by coordination to the *N*-acetyl group which helps facilitate this unusual hydroarylation reaction.[92]

Scheme 12. Vincent's iron-promoted spiro-cyclization of indoles

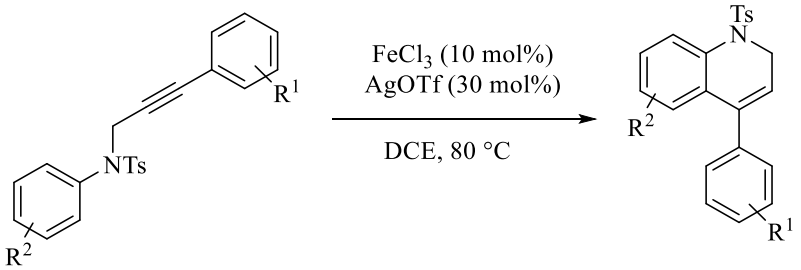


42 **43**

Other important heterocycles like quinolines and dihydroquinolines have been effectively synthesized through intramolecular hydroarylation strategies. A powerful method for producing dihydroquinolines was reported by Takaki and co-workers (Scheme 13) through the

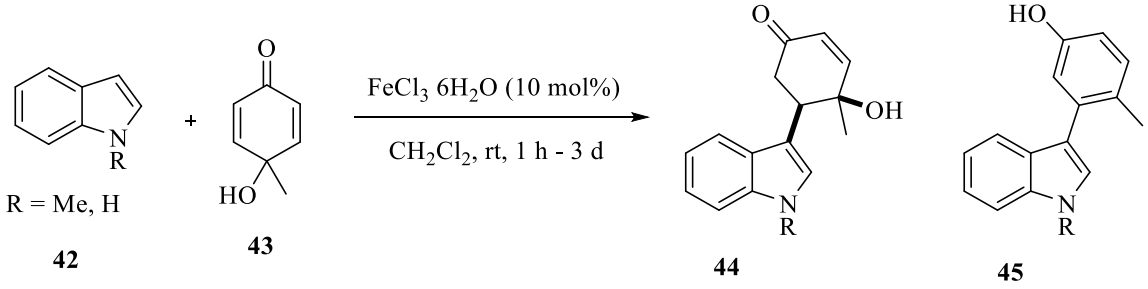
intramolecular iron-catalyzed hydroarylation of propargylic amines **44**.[93] The reaction requires the use of electron-donating groups on the alkyne; the employment of any electon-withdrawing substituents did not lead to appreciable amounts of cyclized products. The isolated dihydroquinolines **45** were isolated in moderate yields. More recently, Kim and co-workers were to be able extend the method towards the synthesis of vinyl sulfide substituted dihydroquinolines.[94] These examples of intramolecular hydroarylation provide efficient one-step protocols to pharmaceutically important heterocycles.

Scheme 13. Takaki's iron-catalyzed cyclization of propargylic amines[93]



Iron-catalyzed diastereoselective hydroarylations are rarely reported, however Carreno and co-workers described an iron-catalyzed intermolecular hydroarylation reaction between indoles **42** and *p*-quinols **43** (Scheme 14).[95] Formally, the hydroarylation is a 1,4- conjugate

Scheme 14. Carreno's hydroarylation of *p*-quinols with indoles[95]



addition reaction into an α, β-unsaturated ketone, however the introduction of the alcohol into the substrate allowed for the development of a diastereoselective alkylation reaction. The approach

of the indole nucleophiles occurs exclusively on the face as the hydroxyl group providing high stereoselectivity for the *syn*-ketone **44** product. Ester-, furan-, and halo- substituted indoles were well-tolerated in this unique mode of alkylation. The isolated yields (51-91%) of the aryl-substituted keto-ols were moderate to excellent and the method was later developed into an asymmetric alkylation process using chiral phosphoric acids.

Conclusion

Zinc and iron catalyzed hydroarylations of unsaturated bonds are exceptionally useful reactions that have proven useful for the synthesis of coumarin, oxindoles, and many other important heterocycles. In many cases, the isolated material is obtained in good regio- and stereoselectivity which increases the value of these important reactions. However, limited mechanistic evidence exists on the hydroarylation of unsaturated carbon-carbon bonds, and this is an area that requires more attention. A lack of mechanistic understanding makes it increasingly difficult to rationally design new catalysts systems. Recent efforts by our group[96] to address this issue are provided in Chapter Two, which includes a mechanistic model for the hydroarylation of olefins using a zinc catalyst. In addition, Chapter Three addresses the use of bimetallic catalysts to promote arene prenylation, which is another important powerful example of a hydroarylation reaction.

CHAPTER TWO

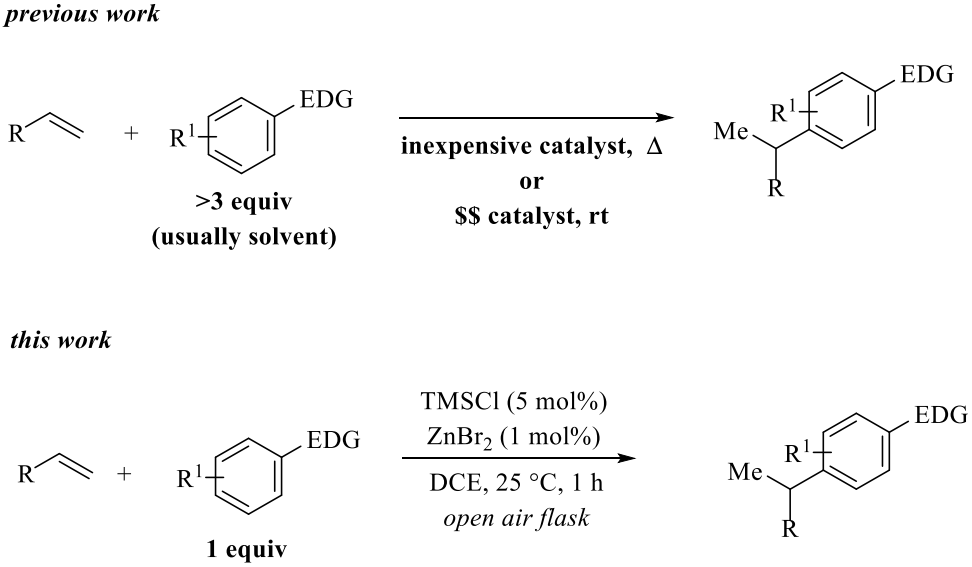
INVESTIGATIONS INTO THE MILD HYDRORYLATIONS OF OLEFINS

Introduction

Alkyl arenes are an important structural motif in various materials, pharmaceuticals, and fine chemicals.[31,97] In particular, diarylmethines represent privileged scaffolds in therapeutic development.[97–99] Traditional methods to access diarylmethines include olefin hydrogenation[100] and Friedel−Crafts alkylation using alkyl halide electrophiles.[26] Hydroarylation of olefins represents an atom-efficient Friedel−Crafts alkylation reaction that employs simple organic building blocks. Currently, two synthetic tactics are known to achieve the hydroarylation of olefins: Friedel−Crafts alkylation and transition metal catalysis.[27] The Friedel−Crafts method has been realized with $AlCl_3$,[97] $FeCl_3$,[83] bismuth reagents,[101,102] gold complexes,[103,104] and graphene oxide (Scheme 15, eq 1).[105] In addition, Brønsted acids,[106,107] including acidic resins,[108] and zeolites,[109,110] are capable of achieving the hydroarylation of olefins. Major drawbacks of these procedures include high temperatures,[60,77,81–88,90] polyalkylation,[31] stoichiometric amounts of Lewis acid,[31] and requirement of the arene to be used in excess (commonly as solvent).[60,77,81–88,90] A room temperature hydroarylation was achieved by Niggemann and co-workers[111] using $Ca(NTf_2)_2$ with Bu_4NPF_6; however, this reagent combination is expensive and also requires excess arene. Stephan and co-workers reported an elegant advance in this area; however, the phosphonium cation catalyst requires multiple steps to

produce.[112] The alternative tactic using transition metal catalysts such as Ru,[113–115] Ir,[42] Pt,[40,116] and Pd/Cu[117] provides hydroarylated products with a high degree of regio- and chemoselectivity; however, these methods require expensive, toxic metals and generally harsh reaction conditions. Our laboratory's interest in atom-efficient functionalizations of π-systems[118] prompted us to explore a strategy to generate diarylmethines through the hydroarylation of styrene derivatives. To address the shortcomings of previous reports, we sought a low-cost, mild method for the hydroarylation of styrene derivatives. We were primarily interested in developing a Lewis acid system that could perform the hydroarylation at ambient temperature while using equivalent stoichiometries of styrene and arene. Based on previous success in carbon−carbon bond-forming reactions,[119–121] we focused our attention on the use of silicon halides along with an additive. Herein, we report a TMSCl/$ZnBr_2$ cocatalyst system for the mild hydroarylation of styrene (Scheme 15, eq 2). To the best of our knowledge, there are currently no known reports of olefin functionalization using this catalyst system.

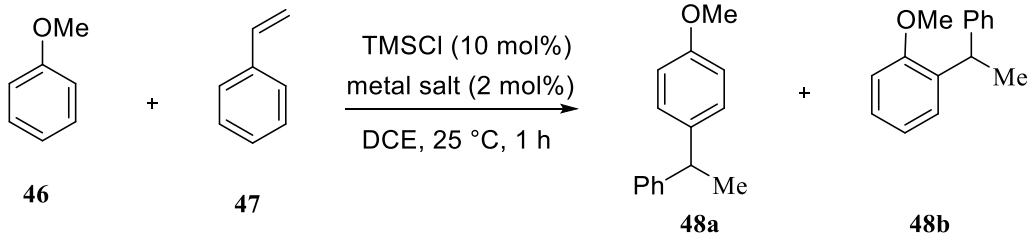
Scheme 15. Mild conditions for the hydroarylation of olefins.



Development of a Zinc-Catalyzed Hydroarylation of Olefins

We first explored the hydroarylation of styrene (**47**) with anisole (**46**) using trimethylsilyl chloride (TMSCl) in combination with various metal salts (Table 1). We observed that zinc salts afforded the highest conversion and yields of hydroarylation products. The employment of zinc dust provided the highest yield of hydroarylation product **48a** (entry 10). Zinc chloride and zinc bromide provided similar yield and conversion to the hydroarylation products (entries 11 and 12). After surveying multiple reactions using Zn, $ZnCl_2$, and $ZnBr_2$ in parallel, we observed that

Table 1. Metal salt screening.[a]



46 **47** **48a** **48b**

Entry	Metal Salt	Yield (%)[a]		Selectivity (*p*- / *o*-)[a]
		48a	**48b**	
1	$AgSbF_6$	68	16	4:1
2	$AgBF_4$	65	15	4:1
3	$AgPF_6$	68	18	4:1
4	$CoCl_2$	46	8	6:1
5	$SnCl_2$	65	13	5:1
6	$FeBr_2$	61	13	5:1
7	$MnCl_2$	51	15	3:1
8	$TiCl_4$	62	19	3:1
9	$AlCl_3$	62	11	6:1
10	Zn	77	13	6:1
11	$ZnCl_2$	72	14	5:1
12	$ZnBr_2$	79	12	7:1

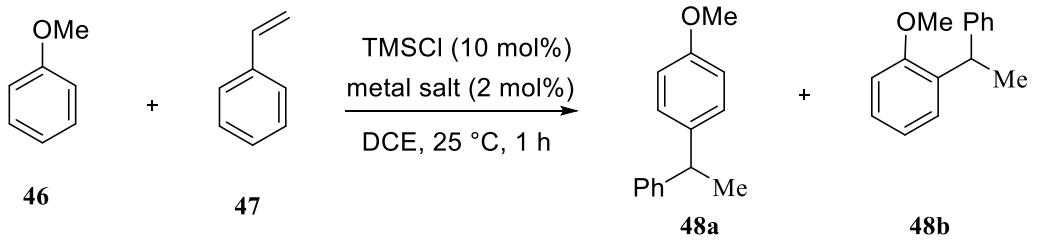
[a] Yield and selectivity was determined by GC/MS of crude reaction mixutre.

Zn and $ZnCl_2$ produced inconsistent results. Therefore, we chose $ZnBr_2$ as our optimal cocatalyst for further screening.

Through examining the stoichiometry and catalyst loading, we determined that TMSCl/$ZnBr_2$ is optimal at a 5:1 ratio based on entries 1 and 2 (Table 2). Removal of either TMSCl or $ZnBr_2$ provided no reaction, which demonstrates the necessity for each reagent in the hydroarylation (entries 3 and 4). Finally, we screened various halosilanes (entries 5-7) and chose TMSCl as the optimal catalyst due to lower cost and ease of use.

With the optimized reaction conditions, we investigated the scope of the hydroarylation

Table 2. Silyl halide screening[a]



46 **47** **48a** **48b**

Entry	$ZnBr_2$ (mol%)	Silyl halide (mol %)	Yield (%)[a]	
			48a	**48b**
1	2	TMSCl (10)	75	16
2	1	TMSCl (5)	76	15
3	-	TMSCl (10)	0	0
4	1	-	0	0
5	2	DMSCl (10)	75	17
6	2	TIPSCl	67	15
7	2	TMSI (10)	68	15

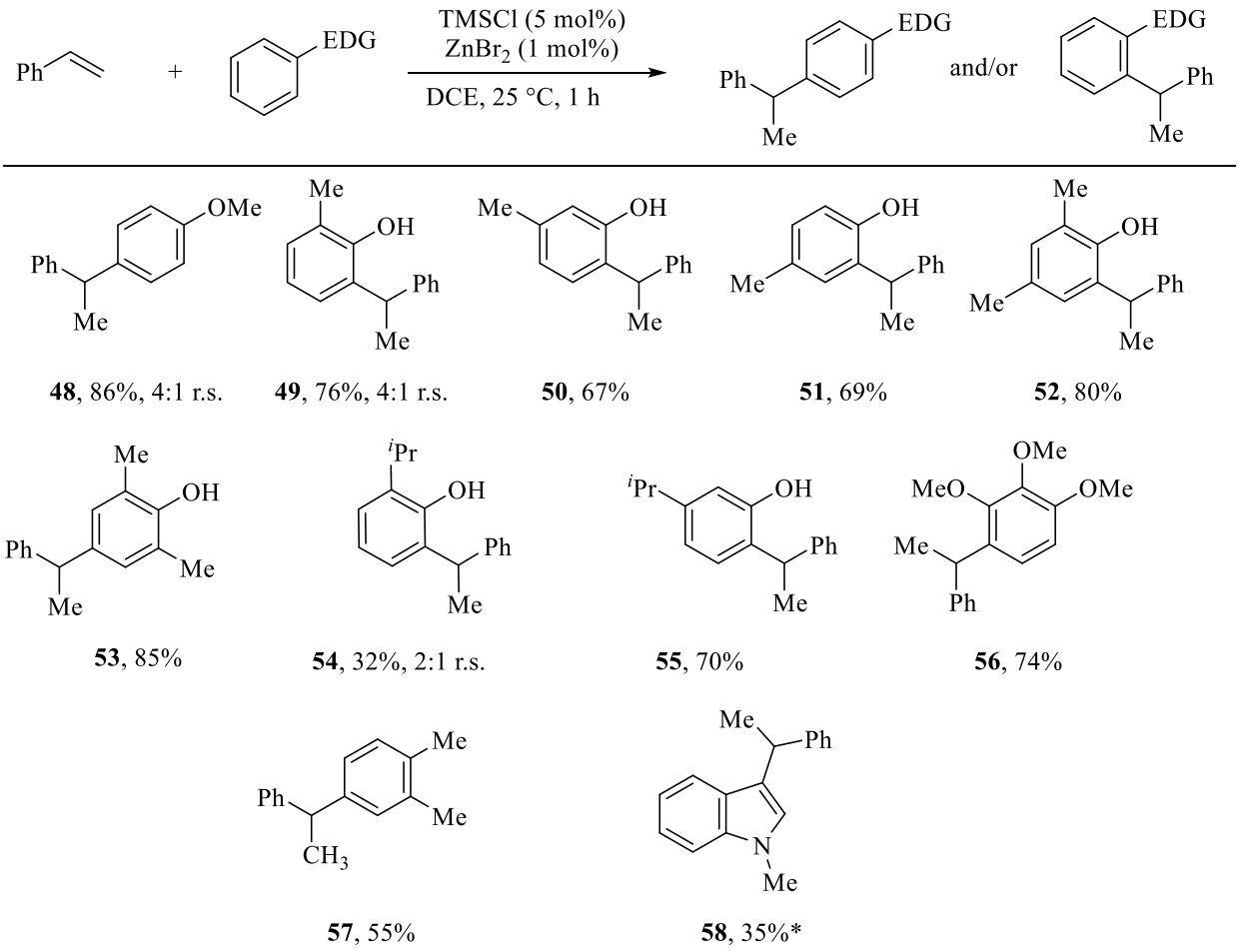
[a] Yield was determined by GC/MS of crude reaction mixutre. TMSCl = chlorotrimethylsilane; TIPSCl = chlorotriisopropylsilane; DMSCl = chlorodimethylsilane; TMSI = iodotrimethylsilane

of styrene with electron-rich arenes (Scheme 16). Methylated phenols with different substitution patterns were capable of producing hydroarylation products **48-55** in good to excellent yields. Phenols with 2-isopropyl or 3- isopropyl groups proceeded to give 73% of **54** and 70% of **55**, respectively. A good yield was observed using 1,2,3-trimethoxybenzene, affording 74% of **56** as a single regioisomer. Interestingly, o-xylene was efficient at producing the hydroarylation

product **57** in 55% yield under our optimized conditions at 1:1 stoichiometry of o-xylene/styrene. Xylene substrates are less nucleophilic and often require the xylene to be used in large excess for efficient reactivity.[83,101,102] Notably, complete regioselectivity was observed in the production of **50-53** and **55-58**. Mixtures of regioisomers were obtained with products **48**, **49**, and **54**, which is consistent with other Friedel–Crafts systems.[77,81–88,90]

Alkylation of indoles using a hydroarylation strategy has observed significant advances[104] in recent years as alkylated indoles are a common structural motif in biorelevant compounds.[122,123] Unfortunately, we did not observe the hydroarylation product of indole under our standard conditions. A brief screen of modified conditions revealed that

Scheme 16. Substrate scope of various arene with styrene[a]

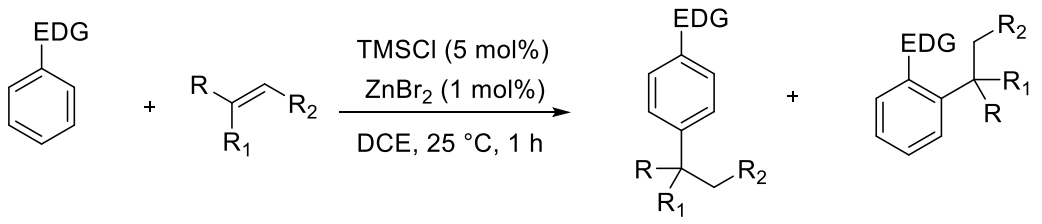


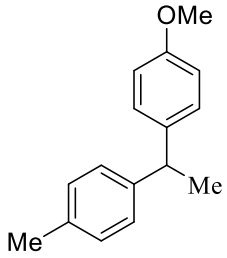
[a]Isolated yields are reported as an average of two 0.9 mmol scale reactions. Regioselectivity (r.s.) was determined by ^{1}H NMR analysis of the isolated material.

2-methyltetrahydrofuran as the solvent at an increased temperature provides the hydroarylation product of styrene with *N*-methylindole in a 35% yield (product **58**).

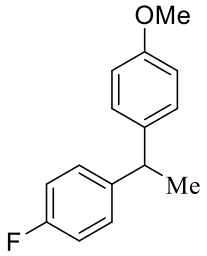
To expand the scope of this hydroarylation strategy, we also surveyed the hydroarylation of other olefins with anisole under the optimized conditions (Scheme 17). Substitution on the phenyl ring of styrene was well-tolerated and provided the hydroarylation products in good yields and regioselectivities (**59** and **60**). Both α- and β-substituted styrenes provided good to

Scheme 17. Scope of reaction using substituted olefins[a]

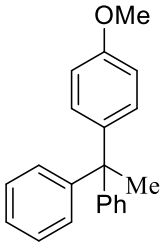




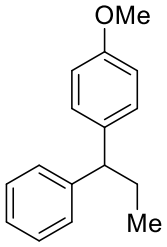
59, 96%, 10:1 r.s.



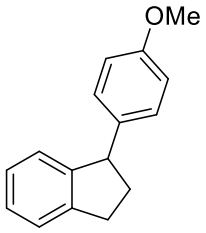
60, 82%, 8:1 r.s.



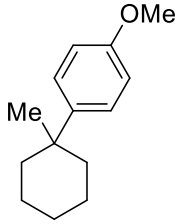
61, 95%, >20:1 r.s.



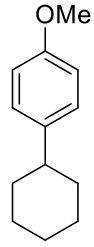
62, 51%, >20:1 r.s.



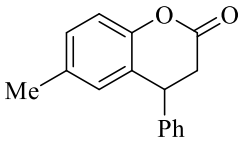
63, 63%, 15:1 r.s.



64, 70%, >20:1 r.s.[b]



65, 11%, 1:1 r.s[b,c]



66, 98%[d]

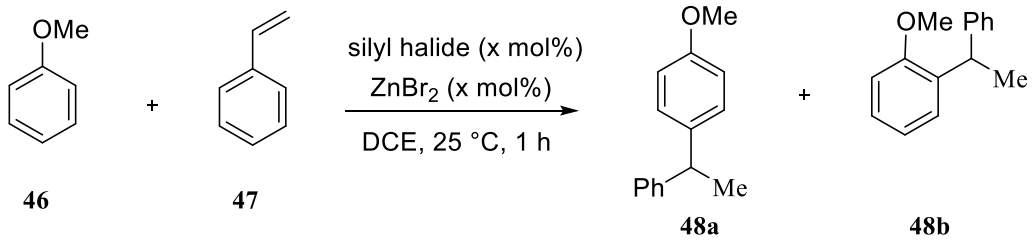
[a]Isolated yields are reported as an average of two 0.9 mmol scale reactions. Regioselectivity (r.s.) was determined by ^{1}H NMR analysis of the isolated material. [b]Reaction performed with 5 equiv of anisole. [c]Yield reported is based on GC analysis relative to an internal standard. [d]Reaction performed with *p*-cresol (1 mmol) and ethyl cinnamate (1 mmol) with 2 equiv of $SiCl_4$, 1 mol% $ZnBr_2$ solvent-less for 48 h in a sealed vessel.

excellent isolated yields and high regioselectivity (**61**, **62**, and **63**). Non-styrenyl substrates are rarely reported for the hydroarylation process, with the exception of reports by Bergman,[106] Doye,[107] Niggemann,[111] and Stephan.[112] Employing an equivalent stoichiometry of anisole and alkyl olefin unfortunately provided the hydroarylated products in low yield. Increasing the amount of anisole provided a more efficient reaction, with trisubstituted olefins giving a 70% yield of **64**. Hydroarylation of cyclohexene provided a low yield of the product **65**. Extension of this protocol towards α,β-unsaturated ester ethyl cinnamate led to the isolation of dihydrocoumarin **66** in excellent yield. The isolated yield of **66** using our protocol offers complementary results to recently reported protocols that also utilize cinnamic acid derivatives

as starting materials in 58-94% yields.[124–129] This heterocyclic product has been used as a key intermediate in the synthesis of tolterodine (Detrol)[36,99,130,131], a phenylethylamine with bladder-relaxant properties.[132,133]

Industrial applications of hydroarylation of olefins typically involves zeolite catalysts that can recycled for decades without any significant loss in reactivity.[31,134] While catalysts mounted on silicates have been reported as effective and recyclable promoters for the hydroarylation of styrene derivatives,[135,136] more common metal halides often are not recyclable.[27] We were interested in determining if the zinc bromide in our catalyst system is recyclable without any chemical modifications to the original reaction conditions. The results from these experiments are presented in Table 3. Surprisingly, the zinc bromide catalyst could be reused up to three

Table 3. Recyclability of zinc bromide catalyst[a]



46 **47** **48a** **48b**

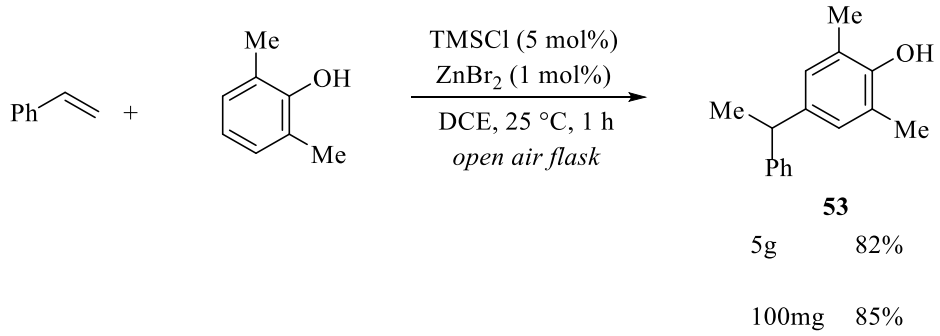
Run	Acid source (mol %)	$ZnBr_2$ (mol %)	Yield (%)[a]	
			48a	**48b**
1	TMSCl (5)	1	76	15
2[b]	TMSCl (5)	1	76	15
3[c]	TMSCl (5)	1	76	15
4[d]	TMSCl (5)	1	76	15

[a] Yield was determined by GC/MS of crude reaction mixture; after 1 h, the reaction was centrifuged, supernatunant was removed, and the catalyst kept in the falcon tube for the next run. [b]Reaction performed with zinc catalyst from run 1. [c]Reaction performed with zinc catalyst from run 2. [d]Reaction performed with zinc catalyst from run 3.

additional times after the initial reaction without loss of reactivity which implies that the Lewis acid does not experience any significant catalyst decomposition after the transformation takes place. In addition, no change in the selectivity the catalyst was observed during these

experiments. The ability of the zinc bromide to be recycled many times without loss of reactivity or selectivity makes this hydroarylation reaction attractive for industrial applications. In addition, this reaction could be performed on a 5 g scale, as demonstrated by the hydroarylation of styrene with 2,6-dimethylphenol gave product **53** in 82% yield (Scheme 18). When this yield is compared to the small scale hydroarylation of xylenol (85%), it demonstrates that our reaction conditions are scalable to gram-scale synthesis of diarylmethines without a significant impact on the isolated yield.

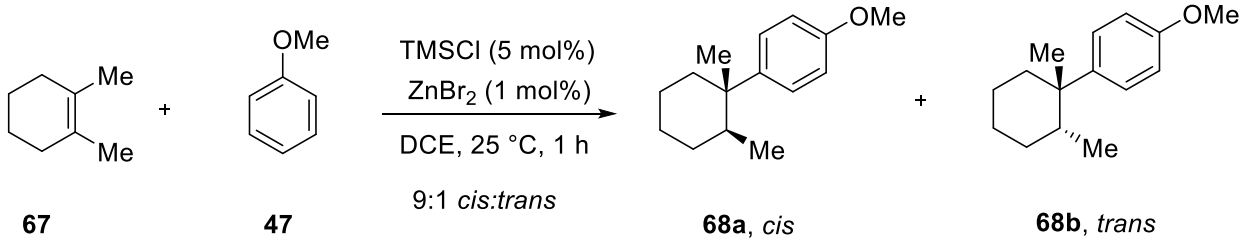
Scheme 18. The hydroarylation of styrene with xylenol on different scales



Finally, we wanted to investigate whether the hydroarylation of olefins could provide stereoenriched aryl-alkanes. This subject is an area of consideration since the stereoselective synthesis of aryl-cycloalkanes has been of great interest to the synthetic community for many years.[137–139] However, there is only one report of stereoselective hydroarylation being utilized for the synthesis of aryl-cycloalkanes.[95] Due to our interest in developing useful hydroarylation chemistry, we synthesized a 1,2-disubsituted olefin which could provide access to a mixture of diastereomers. Specifically, we investigated the hydroarylation of 1,2-dimethylcyclohexene which could provide two distinct diastereomers **68a** and **68b** (Scheme 19). Under standard conditions, the hydroarylation took place and a 32% yield of alkylated product

was isolated and 9:1 ratio of two diastereomers, which was observed by 1D ^{1}H NMR spectroscopy.

Scheme 19. Diastereoselective hydroarylation of 1,2-dimethylcyclohexene

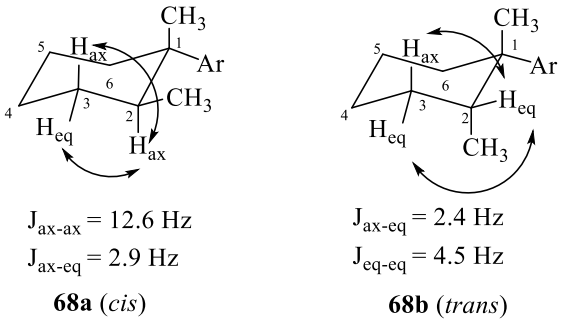


67 **47** **68a**, *cis* **68b**, *trans*

In order to determine the structure of each of the diastereomers, further NMR experiments were conducted. The preferred chair conformations of each of the observed diastereomers is drawn in Figure 1. Due to the high $A^{1,3}$ strain for aryl substituted cyclohexanes,[140] the preferred conformational isomers force the aryl ring to be oriented in an equatorial position. Next, a 2D COSY NMR (Appendix B) was taken of the mixture which indicated that the major diastereomer had a doublet centered at 0.60 ppm which was coupled to the proton centered at 1.95 ppm. The likely assignment of the 0.60 ppm peak is the methyl substituent attached to C2 (Figure 1). The only proton capable of 3-bond coupling with this substituent is the proton attached to C2. Further experimentation is need to analyze the spectral difference between diastereomers **68a** and **68b**. After modeling the two isomers in Spartan '16, it became apparent that diastereomer **68a** and **68b** can be differentiated by the coupling constant from the interaction between the C2 proton the two protons on C3.[141] For example, the expected coupling constant for **68a** C2-H_{ax} with C3-H_{ax} is about 8-13 Hz while the predicted coupling constant for C2-H_{ax} with C3-H_{eq} is expected to be about 1-6 Hz.[141] Using DFT calculations and NMR prediction, the estimated expected coupling constants for each isomer were obtained and is presented in Figure 2.

In order to isolate the coupling between the proton on C2 and the protons on C3, a 1D

Figure 2. Most stable conformers of **68a** and **68b** with coupling constants calculated from DFT calculations noted



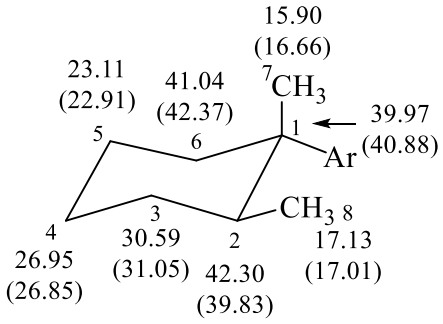
$J_{ax\text{-}ax}$ = 12.6 Hz
$J_{ax\text{-}eq}$ = 2.9 Hz
68a (*cis*)

$J_{ax\text{-}eq}$ = 2.4 Hz
$J_{eq\text{-}eq}$ = 4.5 Hz
68b (*trans*)

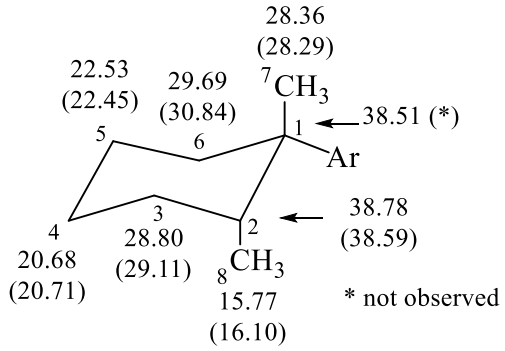
NOE experiment was performed. Irradiation of the signal centered at 0.60 ppm effectively decouples the C2-methyl group in the major isomer from any vicinal proton signals (C2-H) leaving a simplified 1D proton NMR in its place. The result of this decoupling experiment provided a doublet of doublets centered at 1.95 ppm where J_{large} is 11.1 Hz and J_{small} is 3.7 Hz (Appendix B). This evidence supports **68a** being the major diastereomer in the mixture.

Support for the minor isomer's structure is provided by the correlation the calculated ^{13}C signals with the observed signals from the 500 MHz instrument (Figure 3). Despite low the abundance of the minor isomer, the majority ^{13}C signals were accurately correlated within 0.40 (±0.41) ppm with the ^{13}C NMR calculated using Spartan '16 at the Density Function level of theory. Based on the good agreement between the NMR shift values of the minor isomer from the DFT calculations and the actual chemical shift values observed, we are confident that the minor isomer from the hydroarylation experiment is the *trans*-dimethyl molecule **68b**.

Figure 3. DFT-calculated ^{13}C NMR shifts in ppm with observed shifts in parentheses



68a (*cis*)



68b (*trans*)

We were then able to determine that the diastereomeric ratio is 88:12 *cis*:*trans*-1,2-dimethyl-1-phenylcyclohexane from an integration of the proton spectrum. With the diastereomeric ratio determined, we can conclude that the hydroarylation of rigid 1,2-disubsituted cycloalkenes such as 1,2-dimethylcyclohexene can provide aryl-cycloalkane products with good diastereoselectivity which could provide useful chemistry for drug development.

Mechanistic Investigation Concerning the Hydroarylation of Olefins Using a Zinc Catalyst

After developing an efficient protocol for the hydroarylation of olefins using zinc catalysts, we were interested in developing an understanding of the reaction mechanism. The motivation for this interest is two-fold: one, the study of hydroarylation from a mechanistic point of view has largely been unexplored in the literature, and two, a better understanding of the mechanism could lead to further developments and improvements of the catalyst system. While Olah and co-workers have studied the use of conventional Lewis acids for the hydroarylation of styrene,[28] there are no reports of weak Lewis acids such as zinc halides being studied mechanistically. In order to address this gap in the literature, we have collaborated with the

Devery laboratory to provide a more detailed mechanistic analysis of our previously reported[96] hydroarylation of olefins using zinc halide and silyl chlorides.

To initiate our mechanistic studies, anisole **46** and styrene **47** were mixed together with the addition of TMSCl (5 mol%) and $ZnBr_2$ (1 mol%) under optimized conditions (Table 4, entry 1). The addition of 2,6-di-*tert*-butylpyridine has been used to test for the possibility of a Lewis acid acting as a hidden Bronsted acid.[142–144] The cavity around the nitrogen in 2,6-di-*tert*-butylpyridine is only large enough for the approach of protons, thus the addition of this base into our reaction set up was meant to explore the importance of protic acids during the catalysis.[145] The presence of this base in the reaction (entry 2) completely inhibited the formation of the final products **48a** and **48b**. In fact, the use of other bases such as potassium carbonate (entry 3) or pyridine (entry 4) also completely inhibited the formation of the diarylmethines **48a** and **48b** and only the starting materials **46** and **47** were observed by GC-MS. We believe that these results when considered together are consistent with the conclusion that a Brønsted acid plays a pivotal

Table 4. Analysis of hydroarylation reactions with added base.

46 **47** **48a** **48b**

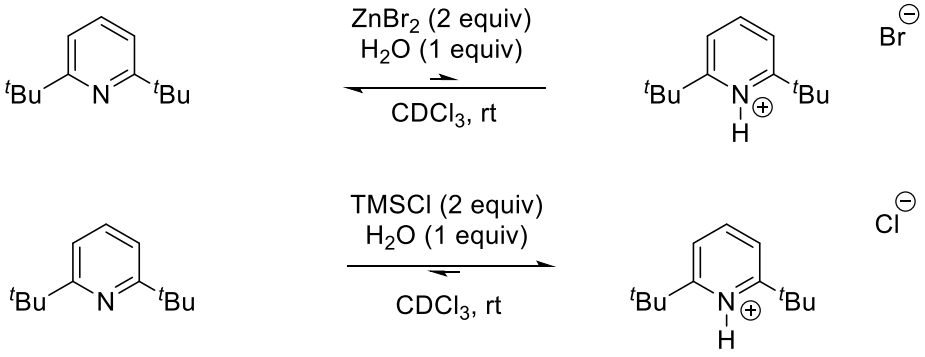
Entry	Acid source (mol %)	Base (mol %)	Yield (%)[a]	
			48a	**48b**
1	TMSCl (5)	-	80	12
2[b]	TMSCl (5)	2,6-di-*tert*-butylpyridine (5)	0	0
3[c]	TMSCl (5)	K_2CO_3 (100)	0	0
4[d]	TMSCl (5)	pyridine (10)	0	0

[a] Yield was determined by GC/MS of crude reaction mixture.

role in the reaction mechanism. We then pursued identifying the source of the protic acid.

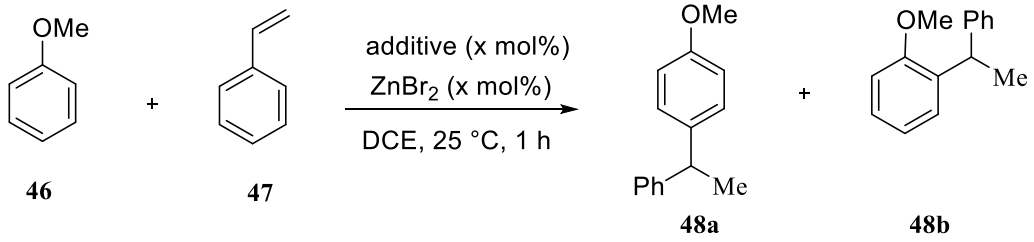
Of the possible sources of protic acid, the most likely is from the Lewis acids $ZnBr_2$ or TMSCl, both of which generate hydrohalic acid upon hydrolysis.[146,147] Inspired by the report from Spencer and co-workers, a stoichiometric reaction between the Lewis acids, water, and 2,6-di-*tert*-butylpyridine was monitored by 1D proton NMR.[144] The NMR in this experiment can be used to measure the extent of hydrolysis of differently added Lewis acids since the 2,6-di-*tert*-butylpyridine will immediately capture any dissolved protic acids such as HCl or HBr. The conjugate acid of the pyridine derivative is a pyridinium salt that is soluble in $CDCl_3$, and its aromatic protons are shifted significantly downfield in comparison to the free base. The results of these experiments are summarized in Scheme 20. The extent of the hydrolysis of the zinc Lewis acid was neglible and no pyridinium salt formation was visible by NMR. On the other hand, trimethylsilyl chloride in the presence of one equivalent of water and pyridine base completely hydrolyzed and produced the pyridinium salt. No unreacted di-*tert*-butylpyridine was observed in the NMR. The results of this experiment suggest that trimethylsilyl chloride will completely hydrolyze in the presence of water to provide the protic acid hydrogen chloride.

Scheme 20. Measuring the extent of hydrolysis through NMR monitored proton capture.



In order to provide further evidence that HCl is a pivotal component in the hydroarylation of alkenes using our $ZnBr_2$/TMSCl catalyst system, we tested the replacement of TMSCl with HCl(*g*) directly (Table 4, entry 1), and the diarylmethine products **48a** and **48b** were observed in excellent GC yield. In order to test whether or HCl alone could promote the hydroarylation reaction, the zinc catalyst was removed, but this led to the recovery of the starting materials unchanged (entry 2). These results are consistent with the conclusion that both a Brønsted acid such as HCl and a Lewis acid such as zinc bromide are both necessary for the successful hydroarylation reaction.

Table 5. Hydroarylation of styrene with anisole in the presence of different additives.



46 **47** **48a** **48b**

Entry	Additives (mol %)	$ZnBr_2$ (mol %)	Yield (%)[a]	
			48a	**48b**
1	HCl (*g*) (excess)	1	80	12
2	HCl (*g*) (excess)	-	0	0
3	benzyl chloride (5)	1	79	11
4	1-phenethylchloride (5)	1	79	11
5	benzyl chloride (5)	-	0	0
6	1-phenethylchloride (5)	-	0	0

[a] Yield was determined by GC/MS of the crude reaction mixutre.

Benzyl chloride readily reacts with electron-rich arenes via a Friedel-Crafts alkylation mechanism pathway and produce a mole of acid for every benzyl halide consumed.[28, 148–150] In fact, alkyl halides are common additives in alkene polymerization reactions.[28,151–153] In an effort to introduce a catalytic amount of HCl into the reaction, various alkyl halides were added in catalytic amounts to a mixture of zinc bromide, styrene, and anisole (entries 3 and 4). The

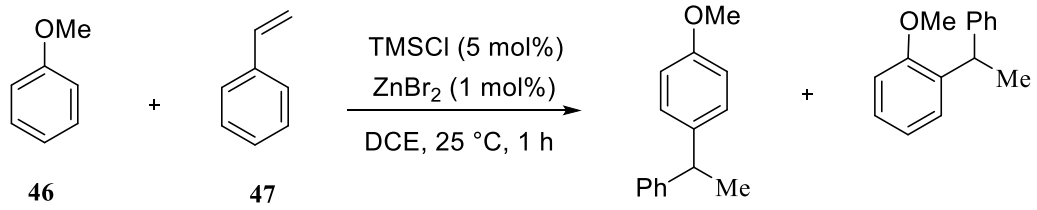
desired diarylmethines **48a** and **48b** were observed in good GC yield (90%) in a 5:1 ratio. No diarylmethane products were observed when the zinc catalyst was removed (entries 5 and 6) which suggests that the arene substitution must be Lewis acid catalyzed. These results are consistent with the conclusion that catalytic amounts of Brønsted acid (HCl) and Lewis acid ($ZnBr_2$) promote the hydroarylation reaction synergistically. Dual Lewis acid/ Brønsted acid mechanisms are a type of cooperative catalysis that been reported in a variety of recent reports.[2,154,155]

Adventitious water has been implicated as important component in a number of reported reactions involving alkenes and Lewis acids.[111,116,151,156–159] More specifically, the presence of small amounts water has been a concern for Lewis acid-catalyzed polymerization[156,157] and metal-catalyzed hydroarylation.[111,116,159] In order to determine the importance of adventitious water on the mechanism being studied, we examined two reactions in parallel: one reaction was performed with rigorously dried reagents while the other employed reagent-grade materials with no further purification (Scheme 21). It was found that rigorously dried reagents did not allow for the production of substation amounts of diarylmethine **48a** or **48b**. The use of reagent-grade solvents and reagents (i.e. undried) leads to the isolation of the desired diarylmethines in good yields. Thus, we believe that water from the reagent-grade materials is most likely responsible for the direct hydrolysis of the silyl halide.

Next, we examined the role of HCl on each of the substrates separately (Scheme 22). Anisole was left unchanged, but styrene was converted to the hydrochlorinated product **69** in 25% conversion as confirmed by NMR. Hydrochlorination is a common addition reaction that has

been studied under a variety of reaction conditions.[160–162] Normally, the addition reaction does not require any catalyst for a successful transformation, however the employment of Lewis

Scheme 21. Comparing, in parallel, rigorously dried reagents with undried reagents for the hydroarylation of styrene with anisole.



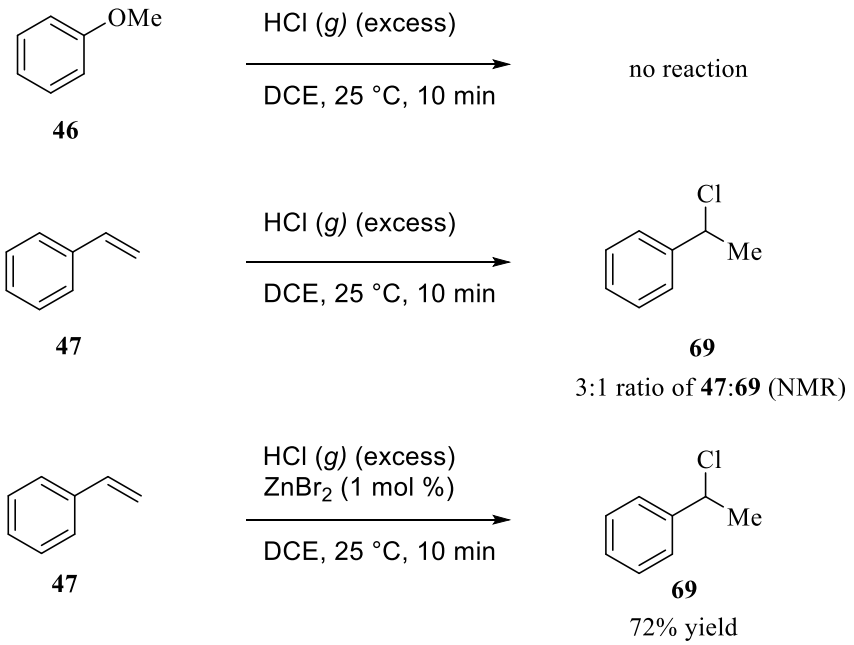
46 **47** **48a** **48b**

dried reagents	0%
undried reagents	81% yield (5:1 r.s.)

acids could allow for a faster and more efficient reaction.[163,164] Upon the addition of zinc halide into the reaction medium, the observed benzyl halide was isolated in a 72% yield with a reaction time of only ten minutes.

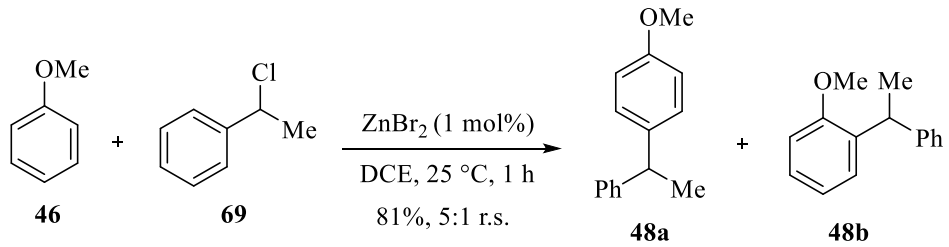
Finally, we tested 1-phenethylchloride **69** in a Friedel-Crafts-type reaction. If this molecule is produced within the catalytic cycle, then the diarylmethine product should be observed when α-phenethyl chloride **69** is used as the alkylating reagent. Traditionally, zinc salts are often poor catalysts for this type of reaction,[28,54] but in our hands, the diarylmethines **48a** and **48b** were isolated in a combined 81% yield (Scheme 23) when chloride **69** was used as the alkylating reagent, which is identical to the isolated yield and regioselectivity reported for the zinc bromide-TMSCl catalyzed hydroarylation (Scheme 21, undried). It may be concluded from this evidence that phenethyl chloride **69** is a probable intermediate in the catalytic cycle.

Scheme 22. The effect of HCl (*g*) on the reaction of anisole or styrene.



Based on the evidence provided above, we propose the following mechanism for the zinc bromide/TMSCl-catalyzed hydroarylation of styrenes (Scheme 24). Initiation of the mechanism begins with the hydrolysis of TMSCl with adventitious water, which produces two moles of HCl per mole of water. Next, styrene undergoes a hydrochlorination reaction, whose mechanism has

Scheme 23. Testing the Friedel-Crafts alkylation of anisole using chloride **69** as the alkylating reagent

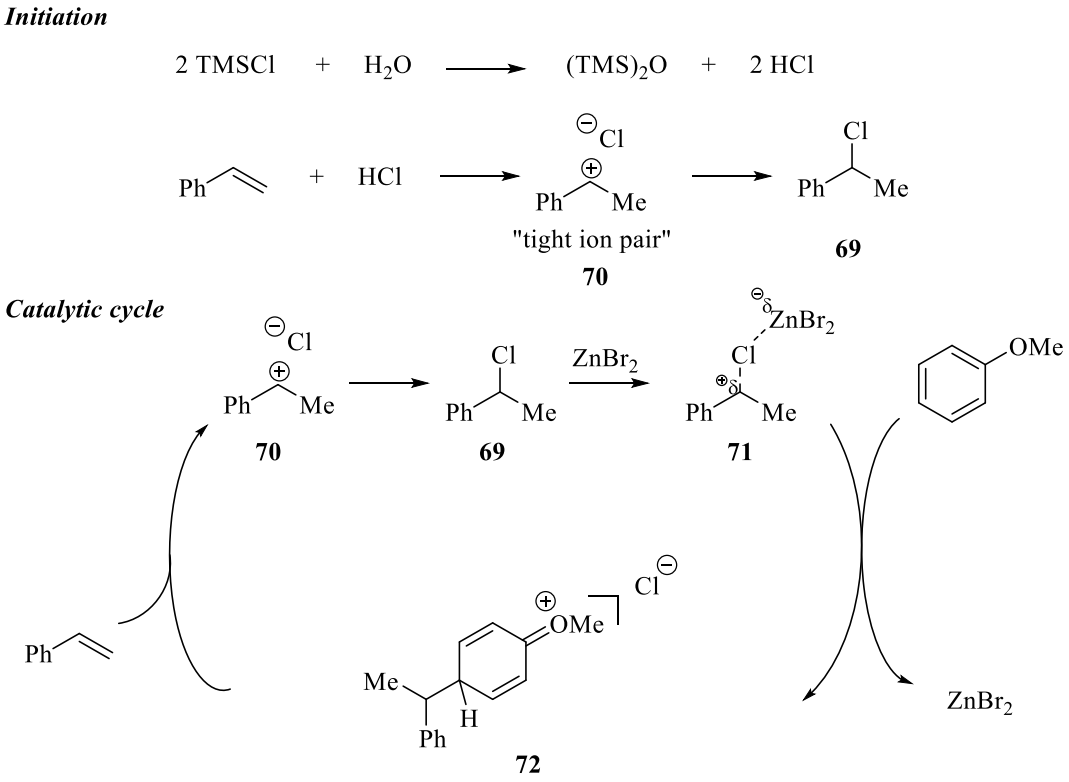


per mole of water. Next, styrene undergoes a hydrochlorination reaction, whose mechanism has been described previously as going through a two-step AdE_2-type addition.[161,165] The tight ion pair **70** is a short-lived intermediate during hydrochlorination and quickly collapses into the

stable benzyl chloride **69**. Alkyl chloride **69** is activated by the Lewis acidic $ZnBr_2$ to create a σ-complex **71**.[28,166] The chlorine-carbon bond in **71** is significantly weakened by the coordinated Lewis acid. Nucleophilic attack of the arene onto **71** creates the unstable Wheland complex **72**.[54,149] Proton abstraction from **72** by a molecule of styrene reproduces the tight ion pair **70** which re-enters the catalytic cycle when it collapses back into the stable alkyl chloride **69**.

In conclusion, we have developed a low-cost, mild, and scalable catalyst system for the efficient hydroarylation of olefins. Our method provides valuable diarylmethine products in good to excellent yields while avoiding harsh conditions and wasteful use of reagents. Our current understanding of the reaction mechanism is that HCl, a product of TMSCl hydrolysis, adds to styrene to create a benzyl chloride intermediate which acts as the actual alkylating reagent via a Friedel-Crafts alkylation mechanism. Both HCl and the zinc bromide can be used catalytically since HCl is produced after the Friedel-Crafts alkylation event. Current investigations into the kinetics of this reaction are ongoing in the Devery laboratory, which should provide additional information into the rate-limiting step. An improved understanding of the mechanism of this reaction will enable further progress in expanding its general utility.

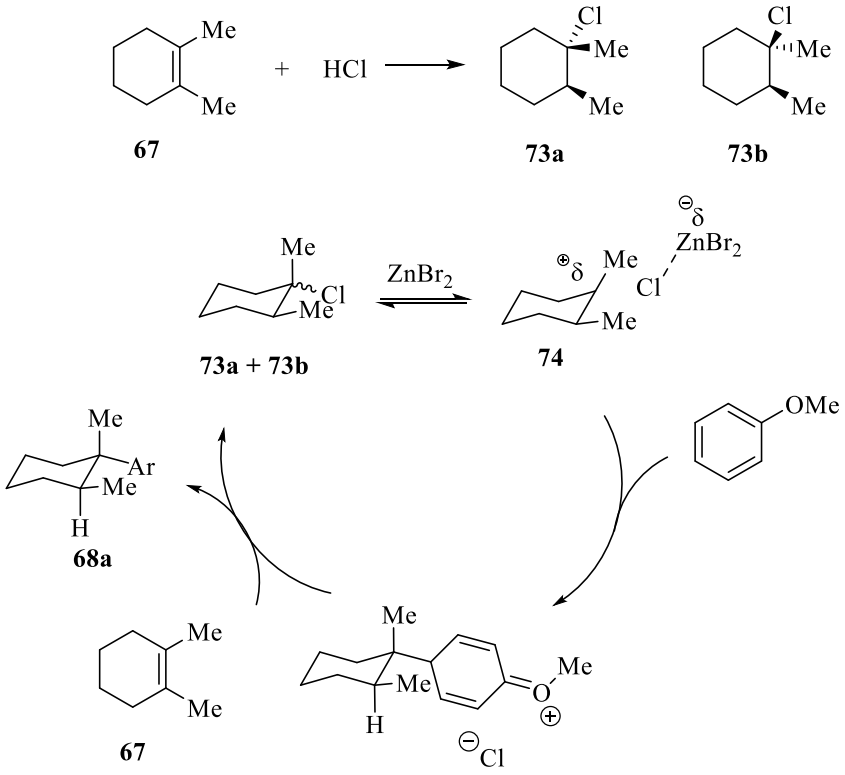
Scheme 24. Proposed catalytic cycle



In light of this proposed mechanism, the diastereoselective hydroarylation of 1,2-dimethylcyclohexene can be explained through the mechanism provided in Scheme 25. Hydrochlorination of alkene **67** produces a mixture of hydrochlorination products **73a** and **73b**.[161,167,168] Rapid conversion of this intermediate into the ionized complex **74** provides the active electrophile for aromatic substitution. The state of ionization of this intermediate is a unclear, however it is generally agreed that halide abstraction from a tertiary halide by a Lewis acid creates a powerful alkylating complex **74**. Due to the steric effects of the neighboring methyl group, the preferred approach of the incoming arene to the alkylating complex **74** would be from the equatorial side. The result of this bond-forming event would be the formation of the Wheland complex **75** which can transfer a proton and a chloride ion to re-

create a mixture of hydrochlorination products **73a** and **73b**. The stereochemistry of this particular reaction is likely influenced by sterics, thus substituents that are larger than methyl should improve the ratio of the *cis* products.

Scheme 25. Proposed mechanistic rationale for conversion of **67** into **68a**.



75

Conclusion

In conclusion, we have developed an efficient, zinc-catalyzed hydroarylation reaction employing readily available olefins. The reaction provides access to biologically relevant diarylmethines in a one-step method with easy-to-handle reagents. A mechanistic investigation, revealed an interesting tandem hydrochlorination-alkylation pathway. This new mechanistic information can be used to develop an enantioselective hydroarylation reaction protocol.

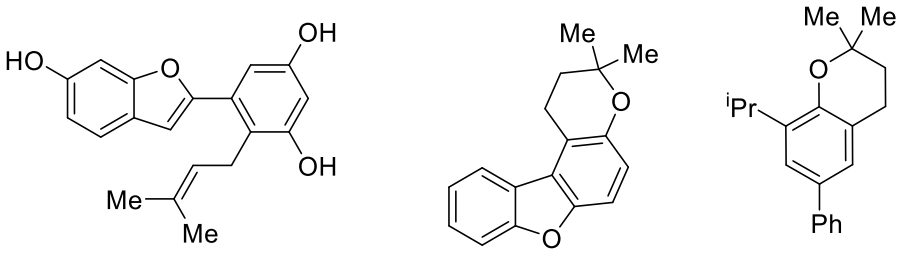
CHAPTER THREE

IRON-CATALYZED SYNTHESIS OF CHROMANS, INDANES, AND LINEAR PRNEYL ARENES

Introduction

Prenylated arenes and the related 2,2-dimethylchroman moiety represent useful scaffolds in therapeutic development. Naturally occurring[169,170] and synthetic prenylated arenes[171–173] display a range of biological activity (Figure 4). Additionally, the incorporation of an isoprene unit into bioactive molecules increases lipophilicity, which is shown to increase potency in many cases.[174–177] The importance of accessing these structures has driven the development of many methods to incorporate prenyl groups into substituted arenes.[178,179] Catalytic installation of the isoprene unit represents the most utilized method for arene prenylation, where the catalysts include precious metals[18] and Lewis acids.[180,181] Additionally,the isoprene unit is often derived from prenyl surrogates such as prenyl halides[180] andorganometallic reagents.[18,181] The most efficient and atom economic route to prenylated arenes and 2,2-dimethylchromans is the direct implementation of isoprene. This strategy is rare but can be realized using catalytic amounts of metal triflates[182–185] or zeolites;[142] however, inherent complications exist using this approach. First, the reaction often produces a mixture of mono- and poly-prenylated product. Second, for non-phenolic substrates, it is challenging to isolate the acyclic prenylated arene without subsequent cyclization to an indane product.[185] The development of a complementary catalytic

Figure 4. Structures of biologically active prenylated arenes.



dimethylmoracin I
aromatase inhibitor

benzofurochroman
antimycobacterial

CSIC-E379
UCP inhibitor

method to access prenylated arenes or 2,2-dimethylchromans would be a valuable addition to the synthetic chemist's toolbox for the synthesis of biorelevant prenylated arenes. First, the reaction often produces a mixture of mono- and poly-prenylated product. Second, for non-phenolic substrates, it is challenging to isolate the acyclic prenylated arene without subsequent cyclization to an indane product.[185] The development of a complementary catalytic method to access prenylated arenes or 2,2-dimethylchromans would be a valuable addition to the synthetic chemist's toolbox for the synthesis of biorelevant prenylated arenes.

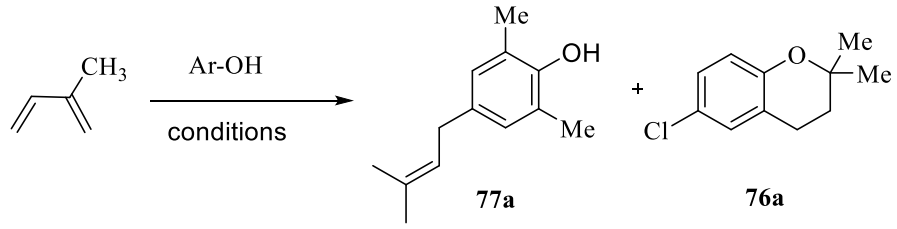
Isoprene activation using iron is known in the context of hydrovinylations,[186] and polymerizations;[187] however, these processes are presumed to operate under a low valent iron center during catalysis. To the best of our knowledge, isoprene functionalization using a high valent, or cationic, iron species has not been reported. Iron-catalyzed processes are becoming more sophisticated as new methods unveil novel reactivity patterns.[188–190] These recent advances and our interest in atom economic processes led us to investigate the Lewis acidic properties of iron as a catalyst for this Friedel-Crafts (FC) type reaction.[83,191–193] An intrinsic issue with FC chemistry is the employment of organohalides and/or an excess of metal salts, which limits FC-type reactions on an industrial scale.[26,194] A recent surge in methods to circumvent these issues

have been reported through the use of catalytic, low toxicity metals,[184,185,193] and activated alcohols[191,193] or π-components[184,185,193] in lieu of organohalides. The method described herein utilizes an iron/silver co-catalyst system to promote the efficient and selective prenylation of activated arenes.

Development of the First Reported Iron(III)-Catalyzed Arene Prenylation Method

We began our investigations by studying various iron sources as catalysts for the prenylation of 2,6-dimethylphenol and 4-chlorophenol (Table 1). A thorough screening of iron sources and additives (not shown) determined that iron(II) or iron(III) halides in combination with silver salts aimed at producing the desired prenylated arene or 2,2-dimethylchromans in high yields while minimizing isoprene oligomer byproduct formation. Ferrous bromide (1 mol %) and $AgBF_4$ (2 mol %) were effective in the production of prenylated product 1a (entry 1); however, ferric chloride proved to be a more active catalyst, allowing for higher conversion to 1a (entry 2). Lowering the catalyst loading or removing the iron source did not provide beneficial results (entries 3 and 4). Reducing the $AgBF_4$ loading to 1 mol % did not diminish reactivity (entry 5), and increasing the amount of isoprene to 2 equivalents afforded higher conversion to **73a** (entry 6). Finally, removing the silver resulted in suppressed activity (entry 7). Applying the same best conditions to 4-chlorophenol provided low conversion to 2,2-dimethylchroman product **74a** (entry 8). Ultimately, increasing the temperature of the reaction to 60 °C offered the highest conversion to the product (entry 9), which we then employed as our standard conditions. Performing the reaction in the presence of 2,6-di-tert-butylpyridine (DTBP) or potassium

Table 6. Optimization of reaction conditions.



Entry[a]	Phenol	Fe source (mol %)	$AgBF_4$ (mol %)	GC conversion
1	2,6-dimethyl	$FeBr_2$ (1)	2	22
2	2,6-dimethyl	$FeCl_3$ (1)	2	51
3	2,6-dimethyl	$FeCl_3$ (0.5)	1	25
4	2,6-dimethyl	-	1	<5
5	2,6-dimethyl	$FeCl_3$ (1)	1	53
6[c]	2,6-dimethyl	$FeCl_3$ (1)	1	53
7[c]	4-chloro	$FeCl_3$ (1)	1	71
8[c]	4-chloro	$FeCl_3$ (1)	1	39
9[c,d]	4-chloro	$FeCl_3$ (1)	1	80
10[c,d,e]	4-chloro	$FeCl_3$ (1)	1	72
11[c,d,f]	4-chloro	$FeCl_3$ (1)	1	53
12[c,d,g]	4-chloro	-	-	52

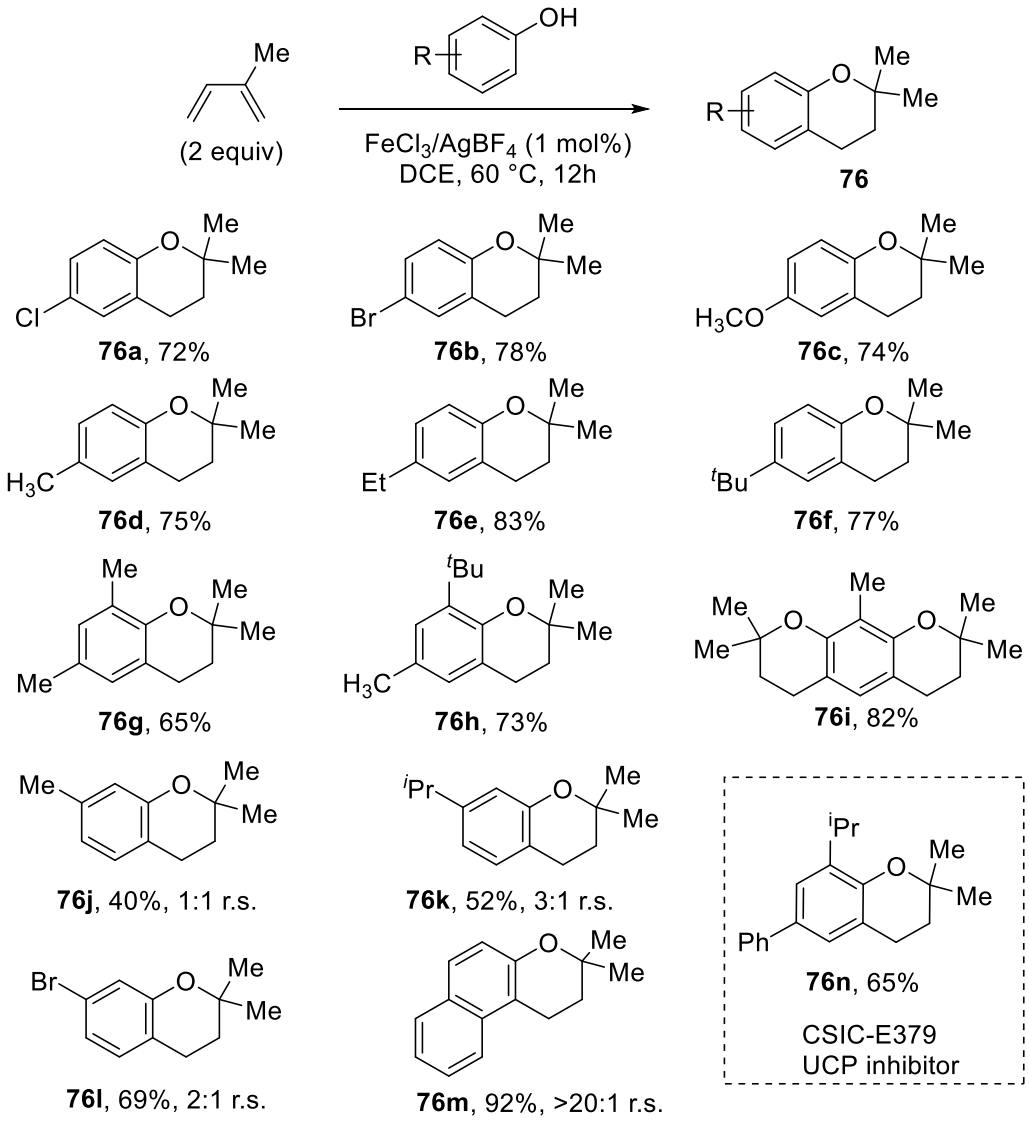
[a] Reactions performed with isoprene/Ar-OH (1:1) in 1,2-dichloroethane (1 M) at 23 °C for 12 h. [b]GC conversion based on crude integration of product and starting Ar-OH. [c]Reaction performed with isoprene/Ar-OH (2:1). [d]Reaction performed with 2 mol% of 2,6-di-*tert*-butylpyridine. [f]Reaction performed with 1 equiv of K_2CO_3. [g]Reaction performed with 1 mol% of HBF_4-H_2O.

carbonate resulted in reduced reactivity (entries 10 and 11).[143,195–197] Because we still observe moderate conversion to the chroman product in the presence of these Brønsted bases, we hypothesize that a combination of Brønsted acid activation and Lewis acid activation is operative.[143,195] The phenolic proton and/or adventitious water are likely sources for the acidic media. To support this hypothesis, we performed the reaction with 1 mol% HBF4•Et2O in place of the Fe/Ag system and achieved 52% yield of the chroman (entry 12). This result shows that

the $FeCl_3/AgBF_4$ combination is a more effective catalyst through slow generation of the protic acid, which is optimal for this reaction.[143]

The substrate scope of this method for the synthesis of 2,2-dimethylchroman products is summarized in Scheme 26. Phenols containing para-substitution afforded the chroman product

Scheme 26. Reaction scope for 2,2-dimethylchroman products.[a]



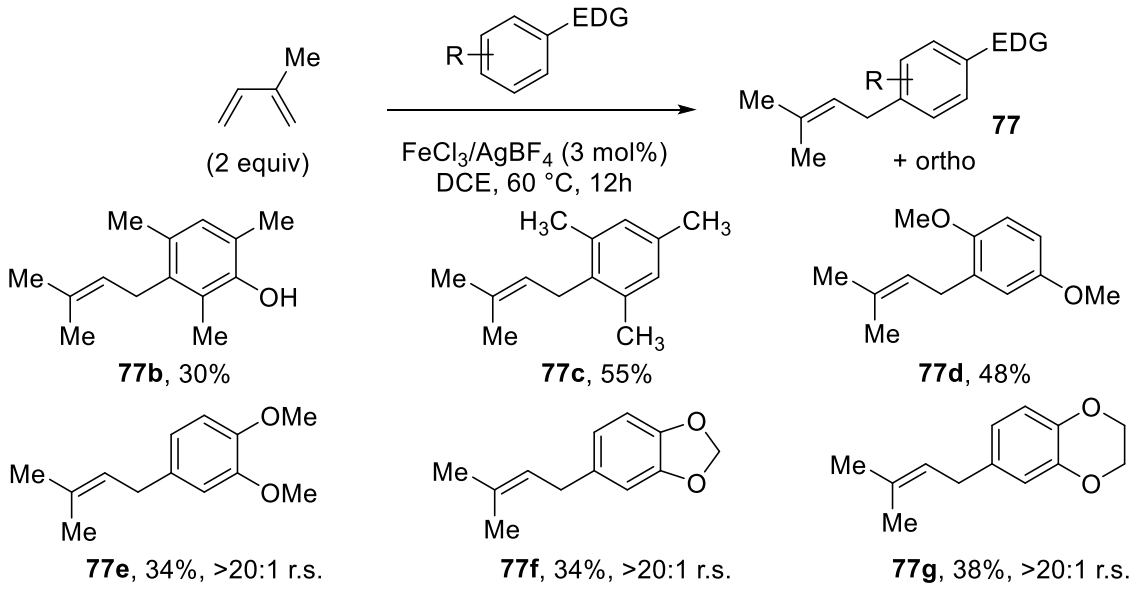
[a] Isolated yields are an average of two reactions on a 1 mmol scale. Products **1j**-**1m** isolated as a mixture of regioisomers where the regioselectivity (r.s.) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

in high yields with a range of electron donation ability (**76a**-**76h**). Interestingly, reaction of 2-methylresorcinol proceeded to give bis-chroman product **76i** in high yield. To probe the regioselectivity of the process, we subjected 3-substituted phenols to our reaction conditions. As expected, increasing the size of the substituent resulted in an increase in regioselectivity (1:1 to 3:1) of chroman products **76j**-**76k**. 2-Naphthol provided the best result where a >20:1 regioselectivity was observed in 92% yield (**76m**). The incorporation of Lewis basic sites on the substrates, such as 4-hydroxybenzamide, resulted in an unproductive reaction, which is a common problem for these types of reactions.[193] Fortunately, products **76a**, **76b**, and **76l** allow further functionalization through cross-coupling chemistry such as Ullmann[198] or Buchwald-Hartwig aminations.[199–202] Additionally, increasing catalyst loading for low-yielding substrates did not result in higher yields, but rather increased formation of diprenylated products and isoprene oligomers. Finally, we were interested in the application of this method to the synthesis of known UCP inhibitor CSIC-E379 (**76n**).[172] This method afforded the desired product in 65% yield, demonstrating the utility of the method in the synthesis of bioactive molecules.

The linear prenylation of selected arenes is depicted in Scheme 27. Using slightly more catalyst (3 mol %), substituted phenols were capable of providing prenylated arenes **77b** in moderate yield. Prenylmesitylene **77c** was synthesized in 55% yield. Additionally, dimethoxybenzenes were effective as substrates in the production of compounds **77d** and **77e**. We then examined 1,3-benzodioxole and benzo-1,4-dioxane for the synthesis of prenyl products **77f** and **77g**. Each substrate produced the desired product albeit in low yield. However, excellent regioselectivity was observed. It is important to note that when employing $Bi(OTf)_3$ as a catalyst

for this reaction, complete cyclization to an indane product is observed.[185] The ability to truncate the reaction at the linear prenylated arene under our conditions demonstrates the unique reactivity of the $FeCl_3/AgBF_4$ catalyst system. Additionally, the low to moderate yields for this process is comparable to other systems, which underscores the challenge of this reaction.[184]

Scheme 27. Reaction scope for prenylated arene production.[a]

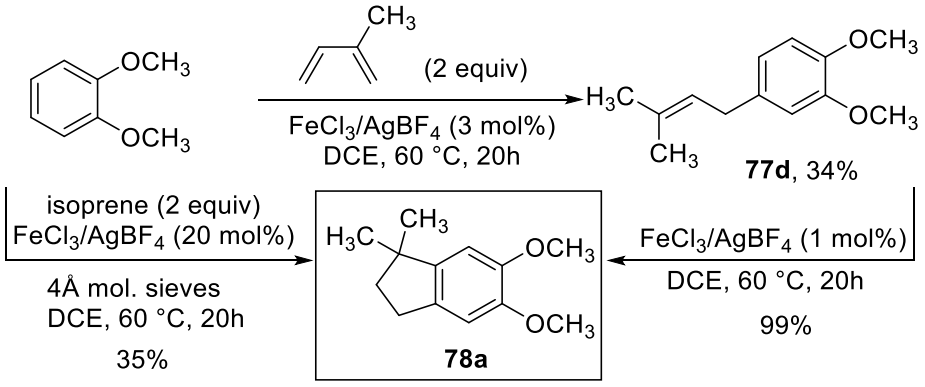


[a] Isolated yields are an average of two reactions on a 1 mmol scale. Regioselectivity (r.s.) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

During our examination of veratrole we observed the formation of small quantities of indane product **78a**. We explored the selective formation of these potentially useful products using a modified $FeCl_3/AgBF_4$ catalyst system (Scheme 28). Subjecting **77d** to our original prenylation conditions afforded indane product **78a** in 99% yield. Direct conversion to the indane was possible through increasing the catalyst loading to 20 mol % $FeCl_3$ and $AgBF_4$. Using this direct prenylation/cyclization protocol, a 35% yield of **78a** was obtained. These results demonstrate the unique ability of the $FeCl_3/AgBF_4$ system to stop the reaction at

prenylated arene product **77e**, and its ability to produce indane products under modified conditions.

Scheme 28. Selective formation of indane products.

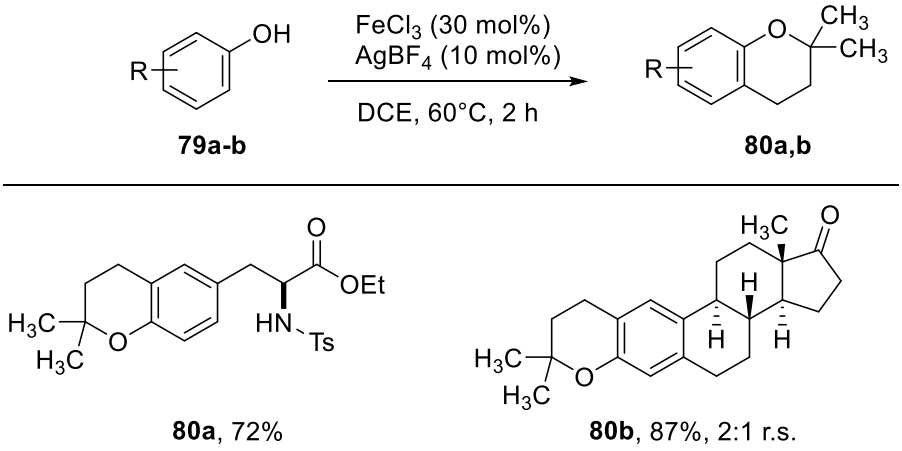


[a] Isolated yields are an average of two reactions on a 1 mmol scale. Regioselectivity (r.s.) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

To explore the application of the iron-catalyzed process to the prenylation of privileged scaffolds, we pursued the prenylation of protected tyrosine **79a** and estrone **79b** (Scheme 29). The direct prenylation of these molecules has potential applications in medicinal chemistry and chemical biology arenas. Upon reacting protected tyrosine **79a** under our optimized conditions, low reactivity was observed presumably due to the presence of Lewis basic functional groups. Increasing the loading to 30 mol % $FeCl_3$ and 5 mol % $AgBF_4$, we were pleased to observe the formation of tyrosine derivative **80a** in a 72% yield. To the best of our knowledge, this chroman-functionalized tyrosine has not been explored as an amino acid derivative in chemical biology, and this new product represents an interesting scaffold in peptide and peptidomimetic syntheses. This procedure was also effective in the prenylation of estrone **80b** to obtain 87% yield of **80b** in a 2:1 regioisomeric ratio. These reactions exhibit the applicability of the iron-catalyzed prenylation process for natural product diversification.

In summary, we report a mild and selective iron catalyst system for the production of a

Scheme 29. Prenylation of L-tyrosine and estrone.



[a] Regioselectivity (r.s.) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

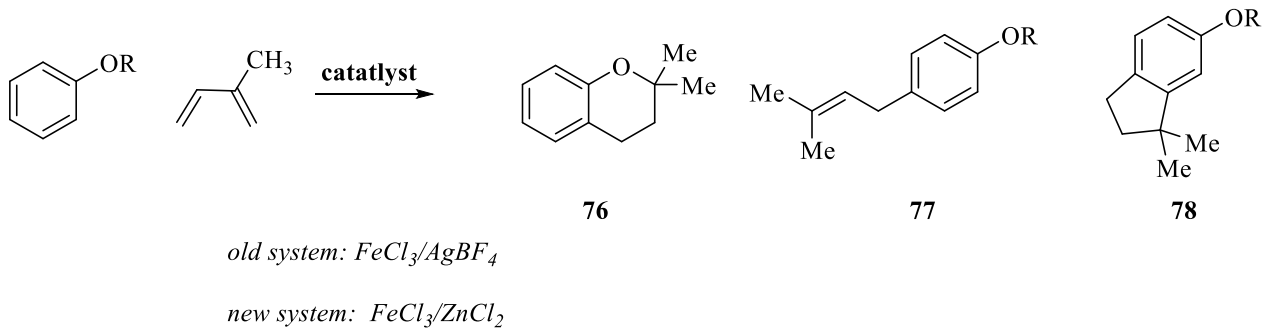
variety of highly useful 2,2-dimethylchroman and prenylated arene products. This method avoids the use of stoichiometric Lewis/Brønsted acids and employs isoprene directly, which makes the process 100% atom economic. We applied the method to the synthesis of a known UCP inhibitor and to the functionalization of a new tyrosine derivative that has potential utility in peptidomimetic synthesis. Efforts to employ this catalyst system to additional Friedel-Crafts and other atom economic processes are ongoing in our laboratory.

Synthesis of Chromans Using a Modified Iron(III) Catalyst System

Prenylated arenes such as 2,2-dimethylchromans and 1,1-dimethylindanes are frequently encountered in many useful natural products and fragrances.[203–208] Furthermore, natural prenylated arenes such cromakalim and osthole have been reported as having powerful vasodilator[209] and antiviral properties,[210] respectively. The 1,1-dimethylindane structure is display in a number of musk reagents such as celestolide and have been used extensively in the perfume industry.[9–11,211]

The most direct method of introducing the prenyl side group onto an aromatic ring is the hydroarylation of isoprene.[178,179] When phenols are employed as the arene, typically 2,2-dimethylchromans are isolated.[129,142,182–184] A number of catalysts have reported to catalyze this type of reaction including metal triflates,[182–184] zeolites, and Bronsted acids.[212] When methoxy-arenes such as veratrole are used as the arene, the result can either be linear prenylated products **77** or 1,1-dimethylindanes **78** which can both be accessed using metal triflates as the catalyst (Scheme 30).[185] We envisioned using inexpensive, readily available metal halides as the

Scheme 30. Development of an iron- and zinc-catalyzed arene prenylation reaction.



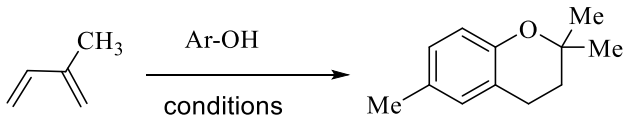
catalysts in arene prenylation. For example, iron chloride is relatively inexpensive and has been reported as an attractive catalyst for a number of alkene hydrofunctionalizations.[213,214] The development of a complementary catalyst system based on iron chloride that can access 2,2-dimethylchromans and 1,1-dimethylindanes efficiently would be a valuable method for the synthesis of biorelevant prenylated arenes.

Recently, our group reported the prenylation of arenes catalyzed by catalytic iron salts but with a silver additive.[118] Due to the high cost of silver reagents, we were interested in

developing a cheaper alternative catalyst system that does not rely on silver. We have developed a more cost-effective catalyst system for arene prenylation which is described herein.

We initialized our study by examining the coupling of *p*-cresol and isoprene in the presence of iron salts and metal co-catalysts (Table 7). Iron (III) chloride provided the desired 2,2-dimethylchroman in moderate yield (entry 1). Ferrous salts did not provide any improvement (entries 2 and 3). Based on our previous results in activating isoprene with Lewis acids, we attempted reaction conditions that employed a second Lewis acid which could help abstract the halide of iron chloride for arene prenylation which is described herein. Fortunately,

Table 7. Optimization for 2,2-dimethylchroman synthesis using iron salts.



81b

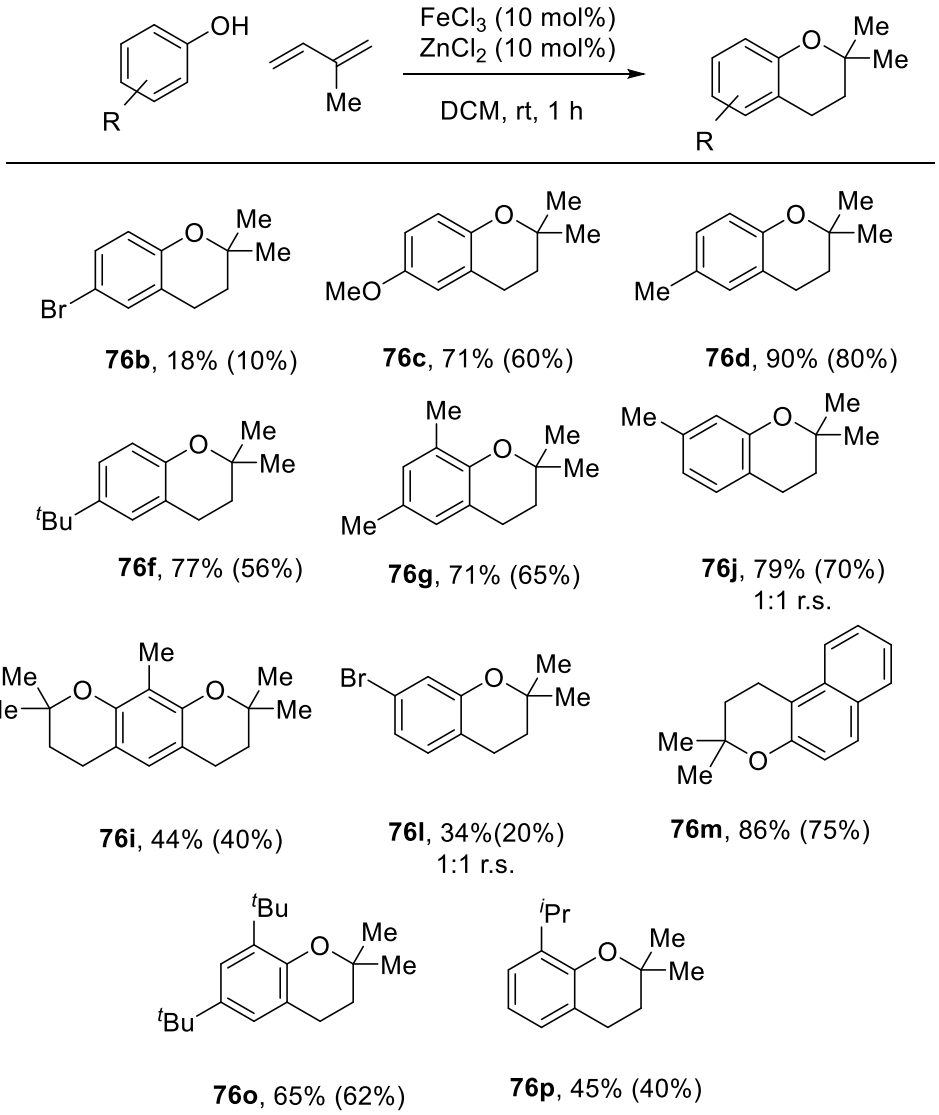
Entry[a]	Fe source (mol %)	Additive (mol %)	GC yield
1	$FeCl_3$ (10)	-	43
2	$FeBr_2$ (10)	-	<5
3	$FeCl_2$ (10)	-	<5
4	$FeCl_3$ (10)	$ZnCl_2$ (10)	90
5	$FeCl_3$ (10)	4 Å Sieves	17
6[c]	$FeCl_3$ (10)	$ZnCl_2$ (10)	69
7[d]	$FeCl_3$ (10)	$ZnCl_2$ (10)	0
8[e]	$FeCl_3$ (10)	$ZnCl_2$ (10)	14
9[f]	$FeCl_3$ (10)	$ZnCl_2$ (10)	73
10	-	$ZnCl_2$ (10)	<5
11	$FeCl_3$ (1)	$ZnCl_2$ (1)	29

[a] Reactions performed with isoprene/Ar-OH (2:1) in methylene chloride (1 M) at 23 °C for 1 h. [b]GC conversion based on crude integration of product and starting Ar-OH. [c]Reaction performed in chloroform. [d]Reaction performed in hexane. [e]Reaction performed in ether. [f]Reaction performed with isoprene/Ar-OH (1:1) in methylene chloride for 1 h.

the addition of zinc chloride provided the desired 2,2-dimethylchroman with 90% GC yield. A brief solvent screen (entries 6-9) revealed methylene chloride as the best solvent for chroman synthesis. Removal of iron (III) chloride (entry 10) or lowering the catalyst loading (entry 11) led to diminished GC yields. Therefore, the optimized reaction condition was 10 mol% iron (III) chloride with 10 mol% zinc chloride (entry 4).

With the optimized the optimized reaction conditions in hand, we next investigated the general scope when applied to various substituted phenols (Scheme 31). We were pleased to

Scheme 31. Arene scope for 2,2-dimethylchroman synthesis.



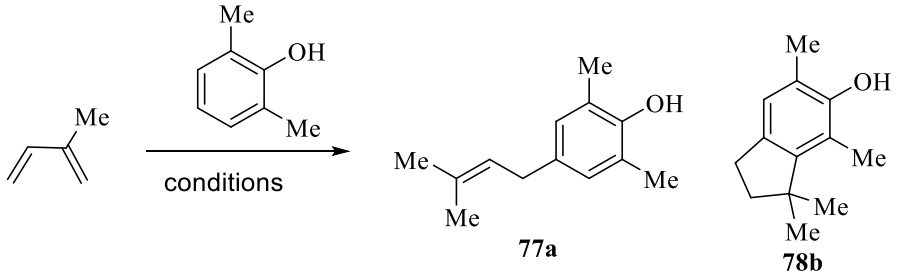
[a] Reactions performed with isoprene/Ar-OH (2:1) in methylene chloride (1 M) at 23 °C for 1 h. [b]GC conversion reported, isolated yields in parenthesizes.

find that the reaction tolerated a variety of *para*-substituted mono-alkyl- and mono-ether-substituted phenols generated the desired chromans **76c**, **76d**, and **76f** in good yields. Using dialkylated phenols as the starting arenes provided **76g** or **76o** moderate yields. Substitution in the *meta* position led a statistical mixture of regioisomers (entry **72j**). Halogenated 2,2-dimethylchromans **76b** and **76l** were isolated in poor yields likely due to the decrease in the

nucleophilicity in the aromatic ring. The 2,2-dimethylchroman of 2-naphthol **76m** was isolated as a single regioisomer in excellent yield. The regioselectivity of this substrate is consistent with our previous report. Interestingly, bis-chroman **76i** was isolated in moderate yield.

Applying this catalyst system to the synthesis of 1,1-dimethylindanes was then tested. In a representative reaction, 2,6-dimethylphenol was reacted with isoprene at room temperature. A mixture of linear **77a** and indane **78a** was isolated and observed by NMR. Attempts to increase the selectivity of this reaction led us to choose nitromethane as a solvent for the reaction (Scheme 32). The selectivity of the reaction was greatly enhanced by using nitromethane as solvent as no **77a** was detected by NMR under those conditions. Performing the reaction in a pressure vessel led to further improvement in the isolated yield of the final product.

Scheme 32. Indane synthesis optimization.



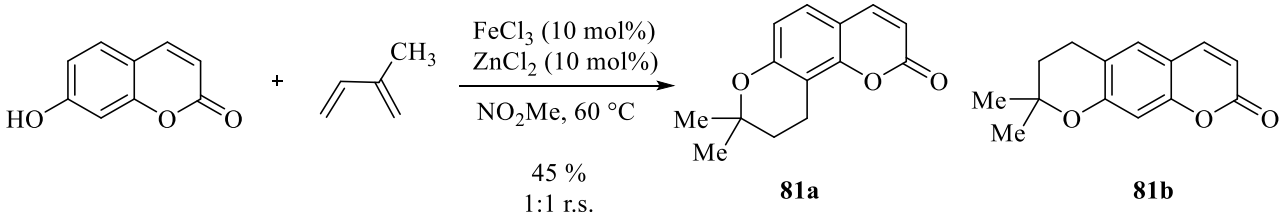
Entry[a]	Solvent	**4a**:**4b**	Yield[b]
1	DCM	1:1	-
2[c]	DCM	1:1	-
3[c]	NO_2Me	0:1	52%

[a] Reactions performed with isoprene/Ar-OH (2:1) in methylene chloride (1 M) at 23 °C for 1 h. [b] Isolated yield after chromatography. [c] Reaction performed at 60 °C.

Finally, applying this iron chloride/zinc chloride catalyzed prenylation toward biologically relevant heterocycles including 7-hydroxycoumarin led to the isolation of two

regioisomers **81a** and **81b** in moderate yield in 1:1 ratio (Scheme 33). Both of these isolated prenylated coumarins has been investigated for acetylcholinesterase inhibition studies.[215] Notably, this reported synthesis of both **81a** and **81b** represents the first example of using isoprene as effective starting material for these important 2,2-dimethychromans.

Scheme 33. Direct prenylation of 7-hydroxycoumarin using isoprene.



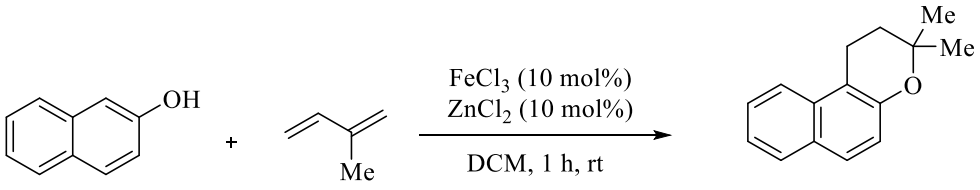
In conclusion, we have demonstrated the ability of a newly developed catalyst system for the synthesis of biologically relevant 2,2-dimethylchromans and 1,1-dimethylindanes. This catalyst system benefits frmom using cheap, readily available iron and zinc chlorides as effective promoters of arene prenylation using isoprene as the alkylating reagent.

Adaptation to an Organic Teaching Laboratory

The Friedel-Crafts alkylation of benzene derivatives catalyzed by Lewis acids is a popular experiment for organic chemistry courses.[216–224] Recent examples of organic laboratory experiments have emphasized the use of more environmentally friendly features for the reaction such as replacing the traditional $AlCl_3$ catalyst with graphite[224] or using alcohols as alkylating reagents.[218,220] These later examples show that development and implementation of a procedure that avoids the production of noxious HCl(*g*) would be beneficial for students in an organic chemistry course. The hydroarylation of olefins is a special type of Friedel-Crafts alkylation that does not produce stoichiometric amounts of HCl(*g*) during the reaction. In fact, olefins such as

isoprene are cheap and effective alkylating reagents, yet there are relatively few reports that describe the use of alkenes in a teaching laboratory setting.[217] We have developed a relatively inexpensive iron chloride/zinc bromide catalyst system that can effectively promote the prenylation of phenols using isoprene as the alkylating reagent. The final product, a 2,2-dimethylchroman, is an example of an important sub-class of the terpenoid family. As an example for the prenylation of phenols using olefins, we report the synthesis of the 2,2-dimethylchroman of 2-naphthol (Scheme 34).

Scheme 34. Synthesis of 2,2-dimethylchroman of 2-naphthol.



76m

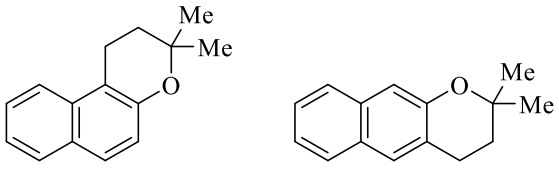
The laboratory was effectively timed to fit in a typical 3 h second-semester organic chemistry laboratory session and was led by two instructors with 36 students in two sections. Prior to the experiment, the students were required to answer a 5-question, multiple choice quiz that covered important safety topics in the laboratory. During the laboratory, a short lecture was presented that included proper handling of silica, waste disposal, and an explanation of the techniques (GC, silica gel chromatography, NMR) that would be utilized during the experiment.

All reagents of this reaction are easily handled in an organic chemistry teaching laboratory. For example, reagent-grade isoprene is a liquid under standard temperature and pressure and can be stored safely for years in a chemical refrigerator without decomposition. The experiment set-up is simple, making implementation of this procedure amenable to a limited

budget. The reaction takes place in a 20 mL scintillation vial. Dry ingredients (iron chloride, zinc chloride, 2-naphthol) are added to the vial along with a Teflon-coated stir bar. The reaction is diluted with methylene chloride and placed on an ice bath. To the reaction mixture is added two equivalents of isoprene. After the addition is complete, the reaction is stirred at room temperature for one hour at which point stirring is discontinued. The reaction is filtered through a small plug of silica gel and the desired product is obtained by evaporation of the solvent on a watch glass in a hood. Characterization of the final product is performed using GC and NMR. Examples of student-prepared spectra are presented in Appendix E.

The students are then asked to write a short write-up of the experiment based on the results from their GC data and the NMR data from one sample taken on a 300 MHz instrument. Based on the splitting patterns from the data provided in the 1D proton NMR, the students are asked to assign which isomer from Figure 3 was isolated. In addition, they are asked to calculate the percentage conversion of their reaction based on a GC plot taken from a sample of their reaction compared to a GC plot of the starting material.

Figure 5. The two possible regioisomers from the alkylation experiment.



76m **76q**

After running the experiment for two sections of 36 students each, we accessed how the students performed. The results of this assessment is summarized in Table 8. There was only one pair of students that did not have any detectable amounts of amounts, but the other 36 groups

were able to detect the formation of the product. Many of the students, who worked in pairs during this experiment, successfully demonstrated that they were able to form the desired chroman with moderate conversion (Table 8).

Table 8. Average conversion from each class where n is the number of groups participating.

	Class 1	Class 2	Total
n	18	19	37
Average Conversion	73 (±29)	89 (±16)	85 (±19)

In conclusion, this procedure is an effective method for developing a student's skills in Friedel-Crafts coupling reactions. The students gain experience handling common Lewis acids while at the same time synthesizing interesting tricyclic oxygen-containing heterocycles. Further, the students are asked to interpret complex structural data which is important for helping develop critical analytical skills.

Conclusion

In conclusion, we have developed two complementary iron-catalyzed arene prenylation protocols which can be used to effectively synthesize chromans, indanes, and other biologically relevant scaffolds. Both catalyst systems were applied to the prenylation of biologically important molecules such as estrone, L-tyrosine, and 7-hydroxycoumarin. In addition, a method for arene prenylation was successfully adapted to the teaching organic chemistry laboratory where students were able to handle common Lewis acids catalysts and use them for the synthesis of biologically relevant terpenoids.

APPENDIX A

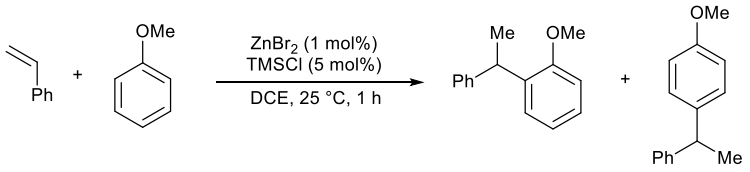
EXPERIMENTAL INFORMATION

FOR CHAPTER TWO

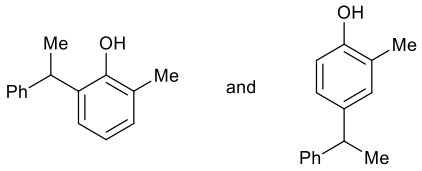
General Information

All hydroarylation reactions were conducted in oven- or flame-dried glassware with magnetic stirring. 1,2-Dichloroethane (DCE), tetrahydrofuran (THF) and anisole were distilled prior to use. Styrene was purified by passing through an alumina column. Other reagents were used as purchased unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on Merck Silica Gel 60-F plates and visualized with UV light. Flash column chromatography was carried out using silica gel 60 (230-400 mesh). 1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian INOVA 500 MHz spectrometer. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard (0 ppm). Data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, b = broad. Coupling constant(s) are measured in Hz. Decoupled 13C NMR spectra were recorded at 75 MHz on Varian INOVA 300 MHz spectrometer with CDCl3 as the internal standard (77.15 ppm). GC-MS spectra were obtained on Agilent 6890N with a Hewlett-Packard 5973 quadrupole mass spectrometer (EI). High Resolution Mass Spectrometry were recorded by the Mass Spectrometry & Proteomics Facility at the University of Notre Dame on a Bruker micrOTOF II.

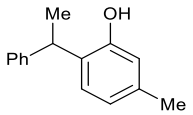
General Procedure for the Hydroarylation of Styrene



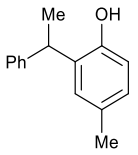
1-Methoxy-2-(1-phenylethyl)benzene (**48a**) and 1-methoxy-4-(1-phenylethyl)benzene (**48b**) (mixture of approximately 1 : 4 *ortho* and *para* isomers): To a 4 mL screw-capped vial with $ZnBr_2$ (2 mg, 8.9×10^{-3} mmol) open to air, 1,2-dichloroethane (800 μL) and chlorotrimethylsilane (6 μL, 0.047 mmol) were added. Anisole (95 μL, 0.874 mmol) was then added followed by styrene (100 μL, 0.872 mmol). The reaction mixture was stirred at room temperature for 1 hour. A 10 μL aliquot of this solution was removed for GC-MS analysis. The rest of the solution was filtered through a pad of celite (1 cm, DCM wash) and the solvent was evaporated to dryness. The crude reaction mixture was purified by column chromatography (hexane:EtOAc = 9:1) to obtain the 159 mg (86 % combined yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 1a) 7.32 - 7.10 (m, 7 H), 6.84-6.82 (m, 2 H), 4.14 (q, *J* = 7.5 Hz, 1 H), 3.80 (s, 3 H), 1.64 (d, *J* = 7.5 Hz, 3 H); (minor isomer, 1b) 7.32 - 7.00 (m, 7 H), 6.87-6.84 (m, 2 H), 4.62 (q, *J* = 7.5 Hz, 1 H), 3.80 (s, 3 H), 1.61 (d, *J* = 7.5 Hz, 3 H); LRMS (ESI): m/z calcd for both isomers for $C_{15}H_{16}O$ $[M]^+$: 212.1; found: 212.1



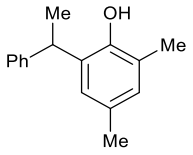
2-Methyl-6-(1-phenylethyl)phenol (**49a**) and 2-methyl-4-(1-phenylethyl)phenol (**49b**) (mixture of approximately 4 : 1 *ortho* and *para* isomers): Following the general procedures using *o*-cresol (95 mg, 0.878 mmol) and purified by column chromatography to afford 141 mg (76 % combined yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[226]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer) 7.31 - 7.10 (m, 6 H), 6.73 - 6.66 (m, 2 H), 4.55 (bs, 1 H), 4.31 (q, *J* = 7.2 Hz), 2.19 (s, 3 H), 1.64 (d, *J* = 7.2 Hz, 3 H) ; (minor isomer) 7.31 - 7.10 (m, 6 H) 6.83 - 6.80 (m, 2 H), 4.50 (bs, 1 H), 4.04 (q, *J* = 7.2 Hz, 1 H), 2.20 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 1 H); LRMS (ESI): m/z calcd for both isomers for $C_{15}H_{16}O$ $[M]^+$: 212.1; found: 212.1



5-Methyl-2-(1-phenylethyl)phenol (**50**): Following the general procedures using *m*-cresol (95 mg, 0.878 mmol) and purified by column chromatography to afford 124 mg (67 % yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[226]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.28 - 7.12 (m, 6 H), 6.68-6.62 (m, 2 H), 4.50 (bs, 1 H), 4.24 (q, , *J* = 7.2 Hz, 1 H), 2.17 (s, 3 H), 1.57 (d, *J* = 7.2 Hz, 3 H) ; LRMS (ESI): m/z calcd for $C_{15}H_{16}O$ $[M]^+$: 212.1; found: 212.1

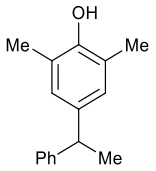


4-Methyl-2-(1-phenylethyl)phenol (**51**): Following the general procedures using *p*-cresol (95 mg, 0.878 mmol) and purified by column chromatography to afford 127 mg (69 % yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[226]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.29 - 7.13 (m, 5 H), 7.03 (d, *J* = 7.2 Hz, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H) 6.65 (d, *J* = 7.8 Hz, 1 H), 4.42 (bs, 1 H), 4.33 (q, *J* = 7.2 Hz, 1H), 2.27 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3 H); LRMS (ESI): m/z calcd for $C_{15}H_{16}O$ $[M]^+$: 212.1; found: 212.1

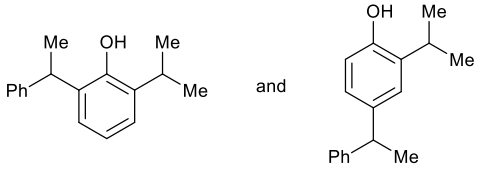


2,4-Dimethyl-6-(1-phenylethyl)phenol (**52**): Following the general procedures using 2,4-dimethylphenol (107 mg, 0.876 mmol) and purified by column chromatography to afford 158 mg

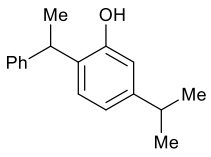
(80 % yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[227]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.26 - 7.10 (m, 5 H), 6.90 (s, 1 H) 6.81 (s, 1H), 4.38 (bs, 1 H), 4.24 (q, *J* = 7.2 Hz, 1H), 2.24 (s, 3 H), 2.12 (s, 3 H), 1.59 (d, , *J* = 7.2 Hz, 3 H); LRMS (ESI): m/z calcd for $C_{16}H_{18}O$ $[M]^+$: 226.1; found: 226.1



2,6-Dimethyl-4-(1-phenylethyl)phenol (**53**): Following the general procedures using 2,6-dimethylphenol (107 mg, 0.876 mmol) and purified by column chromatography to afford 168 mg (85 % yield) of a pale yellow oil. The analytical data for this compound matched with the previously reported compound[105]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31 - 7.10 (m, 5 H), 6.82 (s, 2H), 4.44 (bs, 1 H), 4.02 (q, *J* = 7.2 Hz, 1H), 2.20 (s, 6 H), 1.59 (d, *J* = 7.2 Hz, 3 H); LRMS (ESI): m/z calcd for $C_{16}H_{18}O$ $[M]^+$: 226.1; found: 226.1

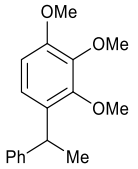


2-(1-Phenethyl)-6-(propan-2-yl)phenol (**54a**) and 4-(1-phenethyl)-2-(propan-2-yl)phenol (**54b**): (mixture of approximately 2 : 1 *ortho* and *para* isomers): Following the general procedures using 2-isopropylphenol (119 mg, 0.874 mmol) and purified by column chromatography to afford 158 mg (73 % combined yield) of a colorless oil. Analytical data: ^{1}H NMR (500 MHz; $CDCl_3$): □ (major isomer, 7a) 7.30 - 7.11 (m, 7 H), 6.97 - 6.94 (d, *J*=8 Hz, 1 H), 4.60 (bs, 1 H), 4.28 (q, *J*=7.2 Hz, 1 H), 3.14 (sept, *J* = 8 Hz, 1 H), 1.63 (d, *J*=7.1 Hz, 3 H), 1.21 (dd, *J* = 7.1 Hz, 6 H); (minor isomer, 7b) 7.33 - 7.11 (m, 7 H), 6.65 (d, *J*=7.5 Hz, 1 H), 4.50 (bs, 1 H), 4.08 (q, *J* = 7.2 Hz, 1 H), 3.14 (sept, *J* = 7.1 Hz, 1 H), 1.60 (d, *J*=7.2 Hz, 3 H), 1.24 (d, *J* = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ major isomer (**11a**): 150.8, 145.2, 135.0, 131.3, 129.0, 127.6, 126.8, 125.2, 124.4, 120.6, 39.7, 27.1, 23.1, 22.8, 21.7; minor isomer (**11b**): 152.7, 149.0, 134.2, 128.3, 127.5, 126.7, 126.5, 125.9, 121.1, 115.3, 44.8, 27.4, 22.6, 22.6, 21.6; IR (thin film neat, cm^{-1}): 3537, 2964, 2876, 1502, 1450, 1253, 821, 750, 700; HRMS (ESI): m/z calcd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1593; found 241.1630

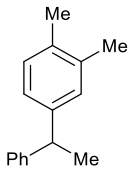


5-(1-Methylethyl)-2-(1-phenylethyl)phenol (**55**): Following the general procedures using 3-isopropylphenol (119 mg, 0.874 mmol) and purified by column chromatography to afford 147 mg (70 % yield) of a colorless oil. Analytical data: ^{1}H NMR (500 MHz; $CDCl_3$): □ 7.31 - 7.28

(m, 3 H), 7.26 - 7.25 (m, 1 H), 7.21 - 7.20 (m, 1 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 6.81 (d, *J*=7.8 Hz, 1 H), 6.63 (s, 1 H), 4.51 (bs, 1 H), 4.31 (q, *J*=7.3 Hz, 1 H), 2.83 (sept, *J*=6.8 Hz, 1 H), 1.62 (d, *J*=7.3 Hz, 3 H), 1.22 (d, *J*=6.8 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 148.7, 145.6, 129.1, 128.7, 127.7, 127.6, 126.4, 119.0, 114.2, 38.8, 33.8, 24.1, 21.3; IR (thin film neat, cm^{-1}): 3455, 2924, 2852, 1575, 1446, 1292, 1251, 958, 84, 752, 709; HRMS (ESI): m/z calcd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1593; found 241.1620.

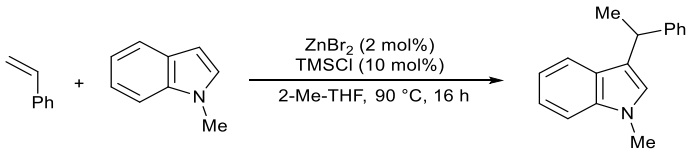


1,2,3-Trimethoxy-4-(1-phenylethyl)-benzene (**55**): Following the general procedures using 1,2,3-trimethoxybenzene (147 mg, 0.874 mmol) and purified by column chromatography to afford 176 mg (74 % yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[228]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.29 – 7.15 (m, 5 H), 6.89 (d, *J* =8 .7 Hz, 1 H), 6.64 (d, *J* = 8.7 Hz, 1 H), 4.45 (q, *J* = 7.2 Hz, 1 H), 3.81 – 3.85 (m, 9 H), 1.56 (d, *J* =7.2 Hz, 1 H); LRMS (ESI): m/z calcd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1; found: 272.1



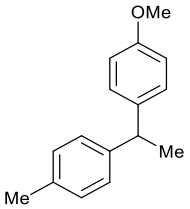
1,2-Dimethyl-4-(1-phenylethyl)-benzene (**56**): Following the general procedures using *o*-xylene (93 mg, 0.876 mmol) and purified by column chromatography to afford 101 mg (55 % yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.27 – 6.90 (m, 8 H), 4.30 (q, *J* =7.2 Hz, 1 H), 2.37 – 2.20 (m, 6H), 1.60 (d, *J* =7.2 Hz, 3 H); LRMS (ESI): m/z calcd for $C_{16}H_{18}$ $[M]^+$: 210.1; found: 210.1

Procedure for the Hydroarylation of Styrene with 1-Methylindole

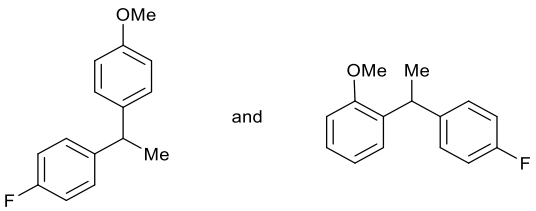


1-Methyl-3-(1-phenylethyl)-1*H*-Indole (**57**): To a 4 mL screw-capped vial with $ZnBr_2$ (4 mg, 0.018 mmol) open to air, 2-methyltetrahydrofuran (800 μL) and chlorotrimethylsilane (12 μL, 0.095 mmol) were added. 1-Methylindole (109 μL, 0.873 mmol) was then added followed by styrene (100 μL, 0.872 mmol). The reaction mixture was stirred at 90 ºC for 16 hours. A 10 μL aliquot of this solution was removed for GC-MS analysis. The rest of the solution was filtered through a pad of celite (1 cm, DCM wash) and the solvent was evaporated to dryness. The crude reaction mixture was purified by column chromatography (hexane:EtOAc = 9:1) to obtain the 72

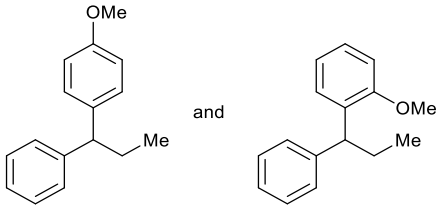
mg (35 % yield) of a pale yellow oil. The analytical data for this compound matched with the previously reported compound[229]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38 (d, *J* = 8.2 Hz, 1 H), 7.31 – 7.19 (m, 7H), 7.09 (t, *J* = 7.0 Hz, 1 H), 6.85 (s, 1 H), 4.38 (q, *J* = 7.2 Hz, 1 H), 3.77 (s, 3 H), 1.71 (d, *J* = 7.2 Hz, 3 H) ; LRMS (ESI): m/z calcd for $C_{17}H_{17}N$ $[M]^+$: 235.1; found: 235.1



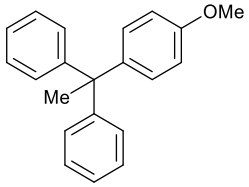
1-Methoxy-4-[1-(4-methylphenyl)ethyl]benzene (**58**): Following the general procedure of styrene with anisole using 4-methylstyrene (95 μL, 0.896 mmol) and purified by column chromatography to afford 193 mg (95% combined yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.26 – 7.11 (m, 6 H), 6.84 (d, *J* = 2.1 Hz, 2 H), 4.11 (q, *J* = 6.3 Hz, 1 H), 3.79 (s, 3 H), 2.33 (s, 3 H), 1.58 (d, *J* = 6.3 Hz, 3 H); LRMS (ESI): m/z calcd for $C_{16}H_{18}O$ $[M]^+$: 226.1; found: 226.1



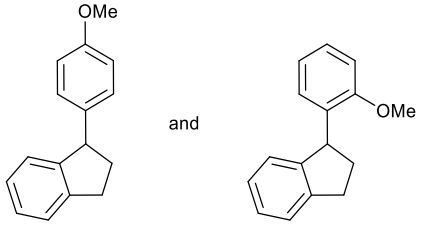
1-Methoxy-4-[1-(4-fluorophenyl)ethyl]benzene (**59a**) and 1-methoxy-2-[1-(4-fluorophenyl)ethyl]benzene (**59b**) (mixture of approximately 8 : 1 *para* and *ortho* isomers): Following the general procedure of styrene with anisole using 4-fluorostyrene (107 μL, 0.898 mmol) and purified by column chromatography to afford 172 mg (83% combined yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 13a) 7.22 – 7.09 (m, 4 H), 6.97 – 6.94 (m, 2 H), 6.82 (d, *J* = 6.5 Hz, 2 H), 4.11 (q, *J* = 5.4 Hz, 1 H), 3.80 (s, 3 H), 1.61 (d, *J* = 5.4 Hz, 3 H); (minor isomer, 13b) 7.22 – 7.09 (m, 4H), 6.95 – 6.92 (m, 2 H), 6.80 (d, *J* = 6.5 Hz, 2 H), 4.56 (q, *J* = 5.4 Hz, 1 H), 3.79 (s, 3 H), 1.58 (d, *J* = 5.4 Hz, 3 H); LRMS (ESI): m/z calcd for both isomers $C_{15}H_{15}FO$ $[M]^+$: 230.1; found: 230.1



1-Methoxy-4-(1-phenylpropyl)benzene (**60a**) and 1-methoxy-2-(1-phenylpropyl)benzene (**60b**) (mixture of approximately 10:1 *para* and *ortho* isomers: Following the general procedure of styrene with anisole using β-methylstyrene (97 μL, 0.901 mmol) and purified by column chromatography to afford 104 mg (51% yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 14a) 7.26 – 7.12 (m, 7 H), 6.83 (d, *J* = 6.4 Hz, 2 H), 3.72 – 3.74 (m, 4 H), 2.04 (m, 2 H), 0.88 (m, 3 H); (minor isomer, 14b) 7.26 – 7.12 (m, 7 H), 6.80 (d, *J* = 6.2 Hz, 2 H), 4.28 (t, *J* = 7.2 Hz, 1 H), 3.72 – 3.70 (m, 3H), 2.00 (m 2 H), 0.87 (3 H);LRMS (ESI): m/z calcd for both isomers $C_{16}H_{18}O$ $[M]^+$: 226.1; found: 226.1

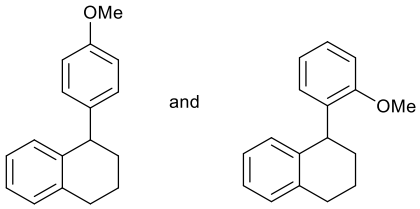


1-(1,1-Diphenylethyl)-4-methoxybenzene (**61**): Following the general procedure of styrene with anisole using diphenylethylene (166 μL, 0.902 mmol) and purified by column chromatography to afford 246 mg (95% yield) of a colorless oil which crystallized upon standing. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 (td, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 4 H), 7.34 (dd, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 2 H), 7.20 (dd, J_1 = 5.5 Hz, *J* = 1.5 Hz, 4 H), 7.10 (dd, *J* = 5.5 Hz, *J* = 1.5 Hz, 2 H), 6.88 (dd, *J* = 5.5 Hz, *J* = 1.5 Hz, 2 H), 3.86 (s, 3 H), 2.26 (s, 3 H); LRMS (ESI): m/z calcd for $C_{21}H_{20}O$ $[M]^+$: 288.1; found: 288.1



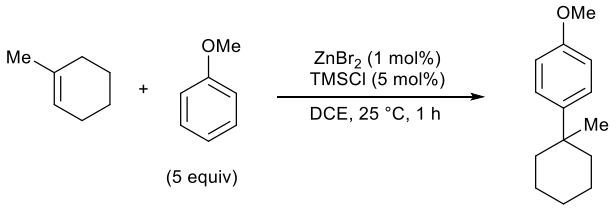
1-(4-Methoxyphenyl)-2,3-dihydro-1*H*-indene (**62a**) and 1-(2-methoxyphenyl)-2,3-dihydro-1*H*-indene (**62b**) (mixture of approximately 15 : 1 *para* and *ortho* isomers): Following the general procedure of styrene with anisole using indene (104 μL, 0.899 mmol) and purified by column chromatography to afford 127 mg (63% combined yield) of a pale yellow oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 16a) 7.29 (d, *J* = 6.2 Hz, 1 H), 7.20 – 7.11 (m, 4 H), 6.97 (d, *J* = 6.2 Hz, 1 H), 6.87 (d, *J* = 6.2 Hz, 2 H), 4.32 (t, *J* = 6 Hz, 1 H), 3.74 (s, 3 H), 3.02 – 2.89 (m, 2 H),

2.58 – 2.55 (m, 1 H), 2.05 - 2.00 (m, 1 H); (minor isomer, 16b) 7.30 (d, d, *J* = 6.2 Hz, 1 H) 7.20 - 7.11 (m, 4 H), 6.96 (d, *J* = 6.2 Hz), 6.86 (d, *J* = 6.2 Hz, 2 H), 4.70 (t, *J* = 6 Hz, 1 H), 3.02 – 2.89 (m, 2 H), 2.58 – 2.55 (m, 1 H), 2.05 - 2.00 (m, 1 H); LRMS (ESI): m/z calcd for $C_{16}H_{16}O$ $[M]^+$: 224.1; found: 224.1



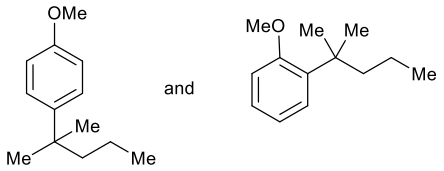
1-(4-Methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (**63a**) and 1-(2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (**63b**) (mixture of approximately 15 : 1 *para* and *ortho* isomers): Following the general procedure using 1,2-dihydronaphthalene (117 μL, 0.901 mmol) and purified by column chromatography to afford 126 mg (59 % combined yield) of a pale yellow oil. The analytical data for this compound matched with the previously reported compound[225]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 17a) 7.12 – 7.02 (m, 6 H), 6.86 – 6.83 (m, 3 H), 4.06 (t, *J* = 6 Hz), 3.80 (s, 3 H), 2.91 – 2.79 (m, 2 H), 2.12 – 1.76 (m, 4 H); (minor isomer, 17b) 7.12 – 7.02 (m, 6 H), 6.89 – 6.78 (m, 2 H), 4.61 (t, *J* = 6 Hz), 2.91 – 2.79 (m, 2 H), 2.12 – 1.76 (m, 4 H); LRMS (ESI): m/z calcd for $C_{17}H_{18}O$ $[M]^+$: 238.1 ; found: 238.1

General Procedure for the Hydroarylation of Alkyl Olefins with Anisole

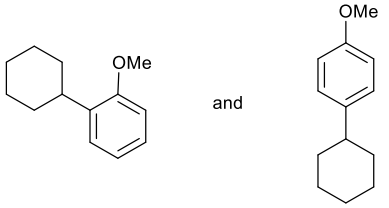


1-Methoxy-4-(1-methylcyclohexyl)-benzene (**64**): To a 4 mL screw-capped vial with $ZnBr_2$ (2 mg, 8.9×10^{-3} mmol) open to air, 1,2-dichloroethane (420 μL) and chlorotrimethylsilane (6 μL, 0.047 mmol) were added. Anisole (475 μL, 4.37 mmol) was then added followed by 1-methyl-1-cyclohexene (103 μL, 0.869 mmol). The reaction mixture was stirred at room temperature for 1 hour. A 10 μL aliquot of this solution was removed for GC-MS analysis. The rest of the solution was filtered through a pad of celite (1 cm, DCM wash) and the solvent was evaporated to dryness. The crude reaction mixture was purified by column chromatography (Hexane:EtOAc = 9:1) to obtain the 125 mg (70 % yield) of a pale yellow oil. The analytical data for this compound matched with the previously reported compound[230]: ^{1}H NMR (500 MHz; $CDCl_3$): δ

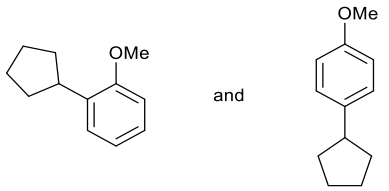
7.29 (d, *J* = 8 Hz, 2 H), 6.87 (d, *J* = 8 Hz, 1 H), 3.81 (s, 3 H), 1.99 - 1.94 (m, 2 H), 1.58 – 1.45 (m, 8 H), 1.17 (s, 3 H); LRMS (ESI): m/z calcd for $C_{14}H_{20}O$ $[M]^+$: 204.1; found: 204.1



1-Methoxy-4-(2-methylpetan-2-yl)benzene (**65a**) and 1-methoxy-2-(2-methylpentan-2-yl)benzene (**65b**) (mixture of approximately 1.5:1 *para* and *ortho* isomers): Following the general procedure using 2-methyl-1-pentene (108 μL, 0.875 mmol) and purified by column chromatography to afford 116 mg (69 % yield) of a colorless oil. Analytical data: ^{1}H NMR (500 MHz, $CDCl_3$) □ major isomer: 7.24 (d, *J*=8.8 Hz, 2 H), 6.84 (d, *J*=8.8 Hz, 2 H), 3.79 (s, 3 H), 1.56 - 1.53 (m, 2 H), 1.27 (s, 6 H), 1.10 – 0.95 (m, 2 H), 0.81 (t, *J*=7.3 Hz, 3 H); minor isomer: 7.21 – 7.16 (m, 2 H), 6.90 – 6.86 (m, 2 H), 3.81 (s, 3H), 1.79 – 1.75 (m, 2 H), 1.34 (s, 6 H), 1.10 – 0.95 (m, 2 H), 0.81 (t, *J*=7.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer: 157.2, 142.0, 126.8, 113.4, 55.3, 47.4, 37.3, 29.3, 18.2, 15.0; minor isomer: 158.6, 137.0, 127.7, 127.0, 120.3, 111.6, 55.2, 43.7, 38.4, 28.6, 18.7, 15.1; IR (thin film neat, cm-^{1}): 2957, 1612, 1514, 1249, 1238, 1037, 829, 748; HRMS (ESI): m/z calcd for $C_{13}H_{20}O$ $[M]^+$: 192.1513; found 192.1515.



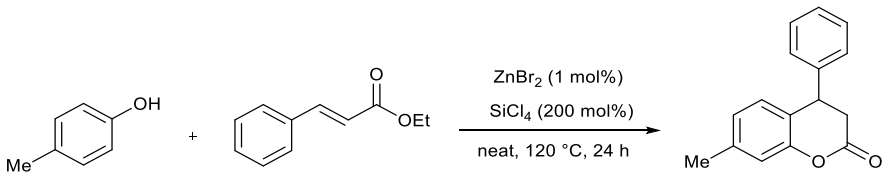
1-Cyclohexyl-2-methoxybenzene (**66a**) and 1-cyclohexyl-4-methoxybenzene (**66b**) (mixture of approximately 1 : 1 *para* and *ortho* isomers): Following the general procedure using cyclohexene (88 μL, 0.869 mmol) and purified by column chromatography to afford 18 mg (11 % combined yield) of a colorless oil. The analytical data for this compound matched with the previously reported compound[231]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer, 20a) 7.12 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 8 Hz, 2 H), 3.80 (s, 3 H), 2.50 – 2.37 (m, 1 H), 1.85 – 1.17 (m, 10H); (minor isomer, 20b) 7.12 (d, *J* = 8.0 Hz), 6.84 (d, *J* = 8.0 Hz), 3.83 (s, 3 H), 3.01 – 2.90 (m, 1 H), 1.85 – 1.17 (m, 10H); LRMS (ESI): m/z calcd for $C_{13}H_{18}O$ $[M]^+$: 190.1; found: 190.1



1-Cyclopentyl-2-methoxybenzene (**67a**) and 1-cyclopentyl-4-methoxybenzene (**25b**) (mixture of approximately 1 : 1 *para* and *ortho* isomers): Following the general procedures using cyclopentene (80 μL, 0.874 mmol) and purified by column chromatography to afford 14 mg (9 % combined yield) of a colorless oil. The analytical data for this compound matched with the

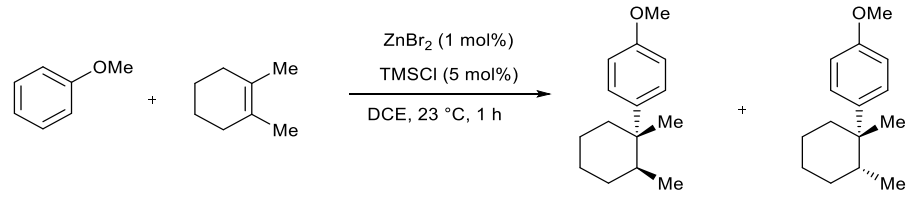
previously reported compound[232]: ^{1}H NMR (500 MHz; $CDCl_3$): δ (major isomer) 7.16 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 3.79 (s, 3 H), 2.97 – 2.92 (m, 1 H), 2.03 – 1.55 (m, 8 H); (minor isomer) 7.25 – 7.16 (m, 2 H), 6.95 – 6.94 (m, 1 H), 6.87 (d, *J* = 8.0 Hz), 3.83 (s, 3 H), 3.37 – 3.35 (m, 1 H), 2.03 – 1.55, 8 H); LRMS (ESI): m/z calcd for $C_{12}H_{16}O$ $[M]^+$: 176.1; found: 176.1

General Procedure for the Hydroarylation of Ethylcinnamate

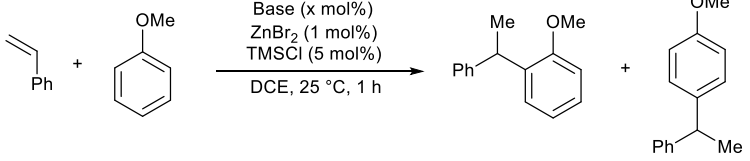


7-**methyl-4-phenylchroman-2-one** (**68**): To a 150mL screw-capped pressure vessel with $ZnBr_2$ (2.2 mg, 0.01 mmol) open to air, tetrachlorosilane (229 μL, 2.0 mmol) was added. Ethyl cinnamate (176.2 mg) and *p*-cresol (108.1 mg, 1.0 mmol) were then added, followed by water (18 μL, 1.0 mol). The reaction was stirred at 120 C for 24 hours. After cooling the reaction to room temperature, the reaction was filtered through a pad silica. Removal the solvent from the eluent provided the desired product (279 mg, 98% yield). The analytical date for this compound matched with the previously reported compound:[125] **^{1}H NMR** (500 MHz; $CDCl_3$): δ 2.28 (s, 3H), 2.99-3.11 (m, 2H), 4.32 (t, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 8.0 Hz), 7.15 (d, *J* = 6.8 Hz), 7.18 (d, *J* = 7.2 Hz, 2H), 7.29-7.40 (m, 3H); **^{13}C NMR** (125 MHz) δ 21.1, 37.2, 40.4, 117.5, 122.7, 125.5, 127.6, 127.6, 128.1, 129.1, 139.2, 140.6, 151.6, 167.9

General Procedure for the Hydroarylation of 1,2-Dimethylcyclohexene



***cis*-1,2-dimethyl-1-(4-methoxyphenyl)-cyclohexane (68a) and *trans*-1,2-dimethyl-1-(4-methoxyphenyl)-cyclohexane (68b)** (88:12 *cis*:*trans)*: To a 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mmol) open to air, 1,2-dichloroethane (420 μL) and chlorotrimethylsilane (6 μL, 0.047 mmol) were added. Anisole (108 μL, 1.02 mmol) was then added, followed by 1,2-dimethylcyclohexene (110 mg, 1.0 mmol), which was synthesized by known procedures. Filtration of the reaction through a pad of silica, eluting with DCM, and removal of solvent *in vacuo* provided the desired product in 70.0 mg (32% yield): (major isomer): **^{1}H NMR** (500 MHz; $CDCl_3$): δ 7.34 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 1.98 – 1.90 (m, 1H), 1.79 (m, 1H), 1.69 (td, J = 12.8, 12.4, 4.4 Hz, 1H), 1.61 – 1.46 (m, 2H), 1.42 – 1.31 (m, 1H), 1.24 (d, J = 0.7 Hz, 2H), 0.64 (d,

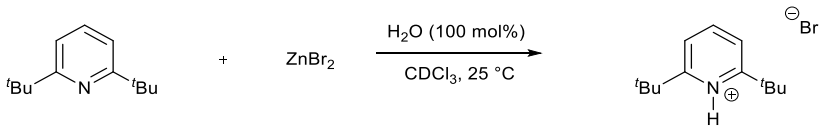


J = 7.1 Hz, 6H), 0.60 (d, J = 6.8 Hz, 2H); **^{13}C NMR** (125 MHz) δ 157.40, 143.32, 127.11, 113.46, 55.40, 42.37, 40.88, 39.82, 31.05, 26.85, 17.01, 16.66.

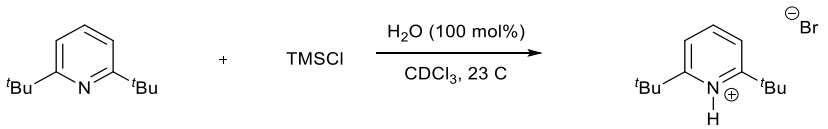
General Procedure for Base Inhibition of Hydroarylation

A 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mg) open to air, 1,2-dichloroethane (420 μL), anisole (110 μL, 1.0 mmol), and styrene (95 μL, 1.0 mmoL) was added. An appropriate amount (x mol%) of the base being tested was then added to the mixture, followed quickly by chlorotrimethylsilane (6 μL, 0.047 mmol). A Teflon-coated stir bar was then added and the reaction was stirred at room temperature for 1 hour. An aliquot (about 10 μL) was removed for GC-MS analysis. The reaction was then quenched with water (1.0 mL), extracted with EtOAc (about 2 mL), and dried with sodium sulfate. The solvent was removed *in vacuo* and the resulting oil was analyzed by NMR.

General Procedure for the Determination of the Extent of Acid Hydrolysis Using NMR

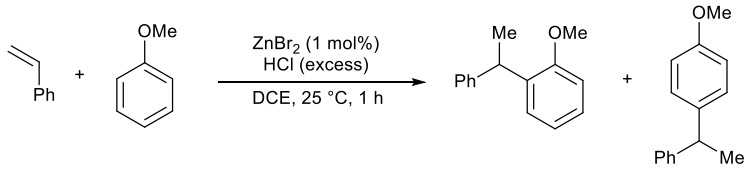


A 4-mL screw-capped vial with 2,6-di-*tert*-butylpyridine (19.1 mg, 0.1 mmol) was dissolved in 0.5 mL of $CDCl_3$. This solution was transferred to a 4-mL that contained $ZnBr_2$ (45.0 mg, 0.2 mmol) and water (1.8 mg, 0.1 mmol). A Teflon-coated stir-bar was added and the reaction was stirred for ten minutes at room temperature. During this time, the zinc halide did not dissolve. The reaction was decanted into an NMR tube so as not to transfer any of the undissolved zinc salt. Proton NMR of the reaction mixture was recorded, which revealed that the pyridine derivative was left unreacted:[144] ^{1}H NMR (500 MHz): 7.51 (t, *J* = 8 Hz, 1 H), 7.08 (d, *J* = 8 Hz, 2 H), 1.25 ppm (s, 18 H).



Hydrolysis of trimethylsilyl chloride: Following the general procedure from above, trimethyl silyl chloride (22.1 mg, 0.20 mmol) was use. A precipitate was observed immediately after the solution containing the pyridine derivative was added to the TMSCl/water mixture. Proton NMR of the reaction mixture was measured, and all of the pyridine derivative appears to have reacted and provided the pyridinium salt:[144] ^{1}H NMR (500 MHz): 8.51 (t, *J* = 8 Hz, 1 H), 7.94 (d, *J* = Hz, 2 H), 1.57 ppm (s, 18 H).

General Procedure for the Hydroarylation of Styrene Using HCl(*g*)

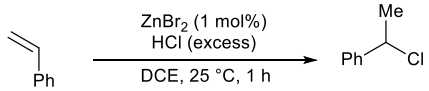


To a 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mmol) open to air, 1,2-dichloroethane (800 µL) was added. Anisole (105 µL, 1.0 mmol) was then added followed by styrene (110 µL, 1.0 mmol). Gaseous HCl was produced by dropping H_2SO_4 over sodium chloride in a Schlenk-flask. Rubber tubing was attached to one end of the Schlenk flask and plastic syringe was inserted into the tubing, provided a tight fit. A metal needle was attached to the syringe and the tip was submerged into the reaction mixture. The rate of bubbling was controlled by carefully opening the stop-cock on the Schlenk flask. The bubbling was continued for the duration of the experiment (one hour) after which the reaction was filtered through a pad Celite, eluting with DCM. The eluent was concentrated *in vacuo* and a small sample of the crude product mixture was analyzed by NMR.

General Procedure for the Hydroarylation of Styrene Using Benzyl Halides

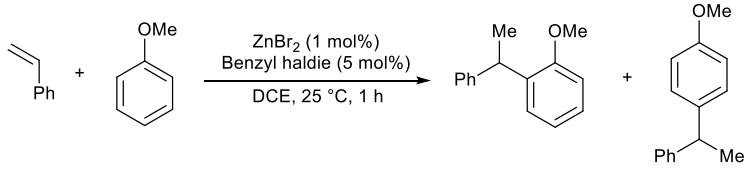
To a 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mmol) and a Teflon-coated stir-bar open to air, 1,2-dichloroethane (800 µL) was added. Anisole (105 µL, 1.0 mmol) was then added followed by styrene (110 µL, 1.0 mmol). The reaction was initiated when the benzyl halide (0.05 mmol) was added, and the reaction mixture was stirred for one hour at room temperature. The reaction was filtered through a pad Celite, eluting with DCM. The eluent was concentrated *in vacuo* and a small sample of the crude product mixture was analyzed by NMR.

General Procedure for the Hydrochlorination of Styrene Using HCl(*g*)



To a 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mmol) and a Teflon-coated stir-bar open to air, 1,2-dichloroethane (800 µL) was added. Styrene (110 µL, 1.0 mL) was then added. Bubbling of HCl gas commenced using the set-up described in "General Procedure for the Hydroarylation of Styrene Using HCl(g)." After ten minutes of bubbling and stirring the reaction mixture, the crude mixture was filtered, concentrated, and small sample of the isolated material was examined by NMR. The final yield of the phenylethyl chloride was 104.0 mg (72% yield).

General Procedure for the Friedel-Crafts Alkylation of Anisole Using $ZnBr_2$ and α-phenethylchloride



To a 4 mL screw-capped vial with $ZnBr_2$ (2.2 mg, 0.01 mmol) and a Teflon-coated stir-bar open

to air, 1,2-dichloroethane (800 μL) was added. Anisole (105 μL, 1.0 mmol) was then added followed by styrene (110 μL, 1.0 mmol). The reaction was initiated when the benzyl halide (144.0 mg, 1.0 mmol) was added, and the reaction mixture was stirred for one hour at room temperature. The reaction was filtered through a pad Celite, eluting with DCM. The eluent was concentrated *in vacuo* and a small sample of the crude product mixture was analyzed by NMR. The final product was isolated after purification via column chromatography (1% EtOAc:hexanes) to provide 174 mg of a colorless oil (80% yield). The analytical data of the final product matched with the previous reported compound.[225]

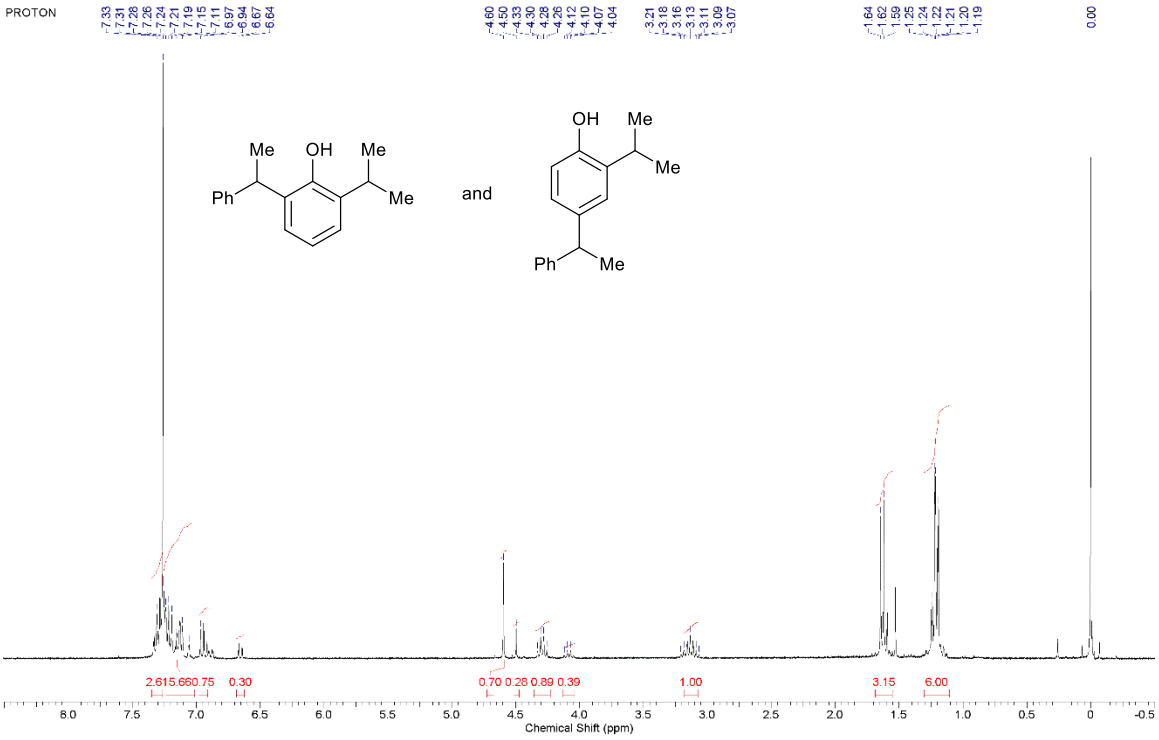
APPENDIX B

NMR SPECTRA

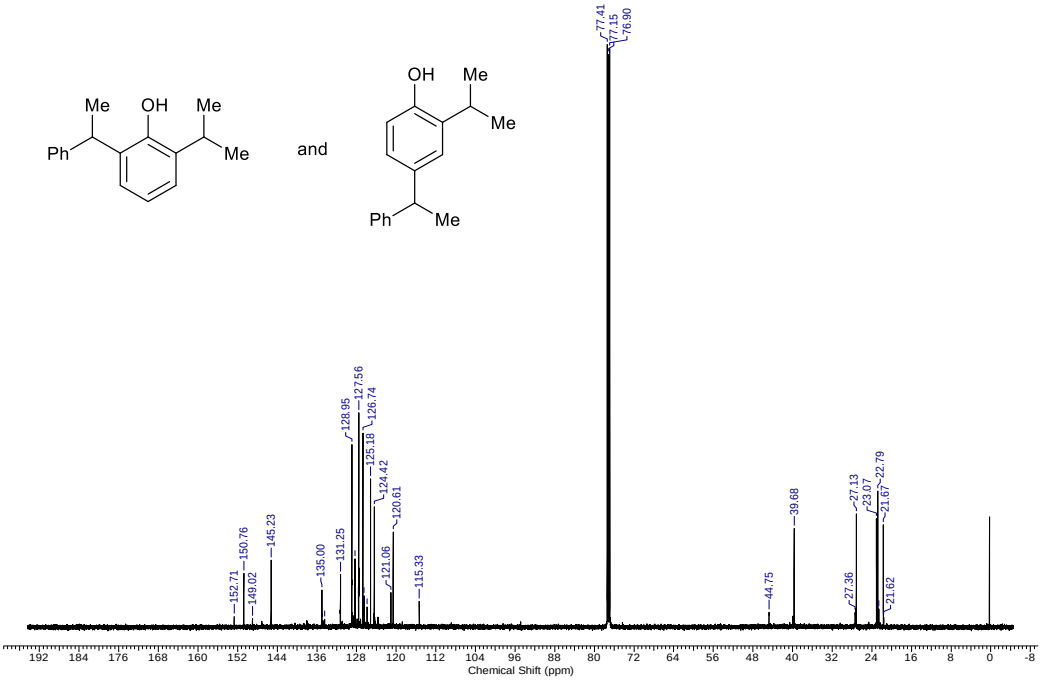
FOR CHAPTER TWO

NMR Spectra of New Compounds

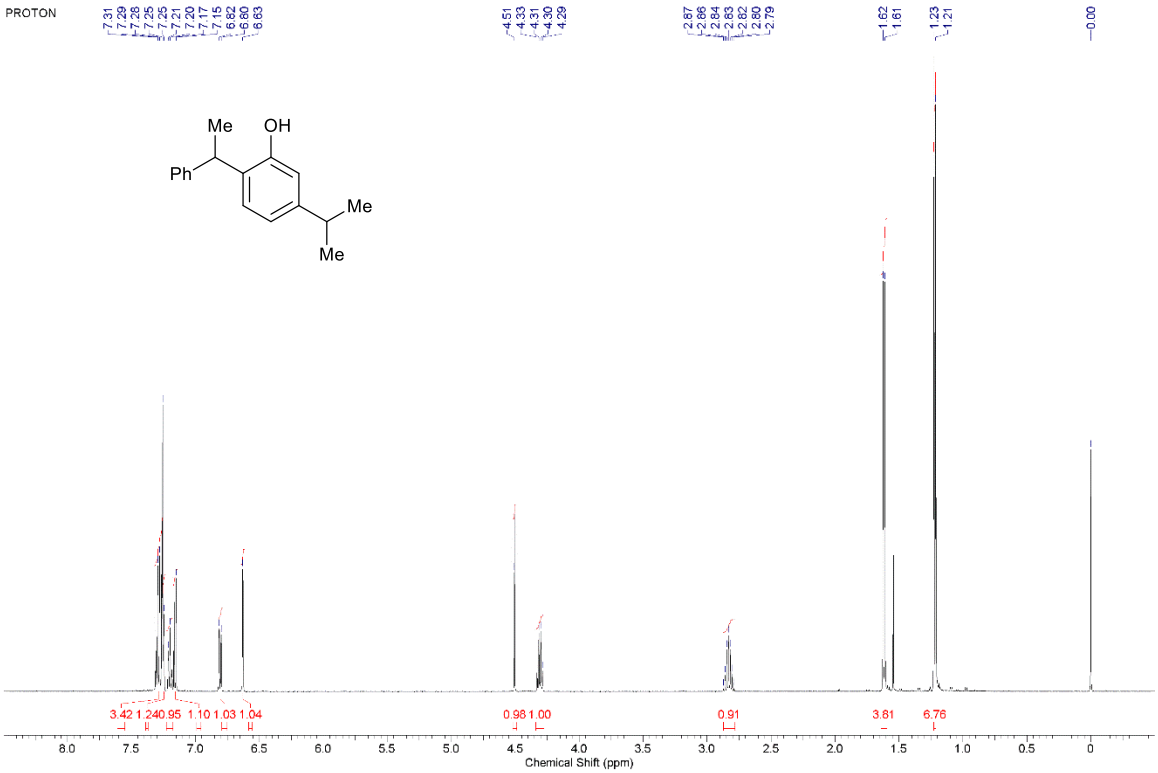
^{1}H NMR for 2-(1-Methylethyl)-6-(1-phenylethyl)phenol and 2-(1-Methylethyl)-4-(1-phenylethyl)phenol (54a and 54b)



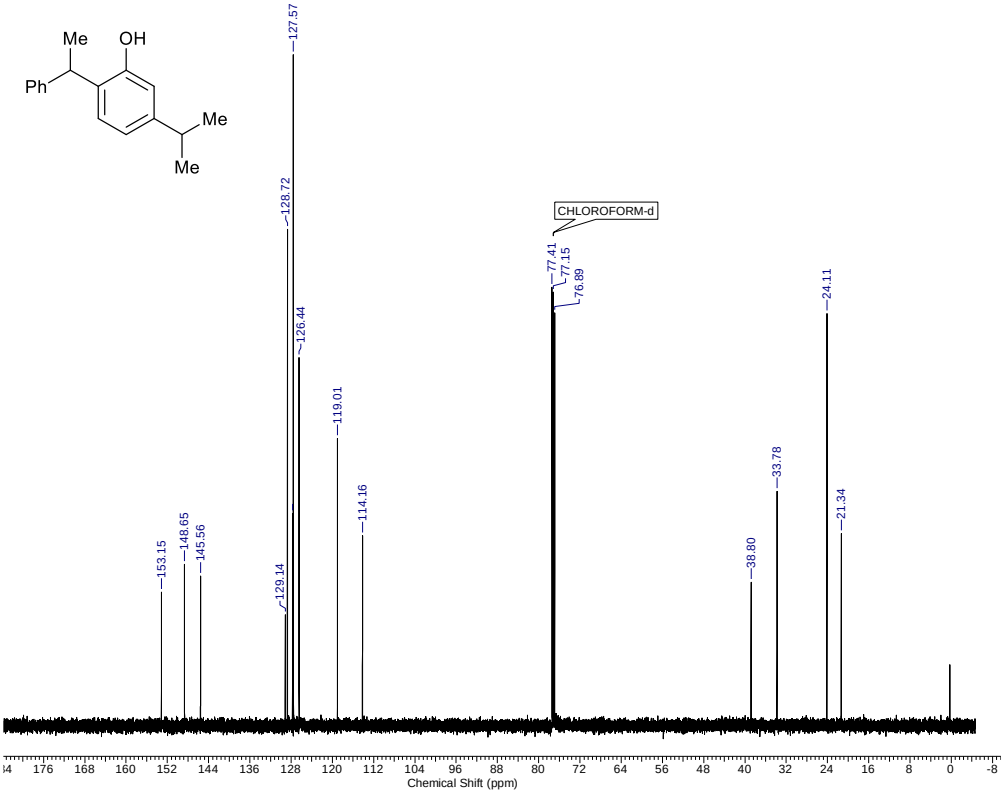
^{13}C NMR for 2-(1-Methylethyl)-6-(1-phenylethyl)phenol and 2-(1-Methylethyl)-4-(1-phenylethyl)phenol (54a and 54b)



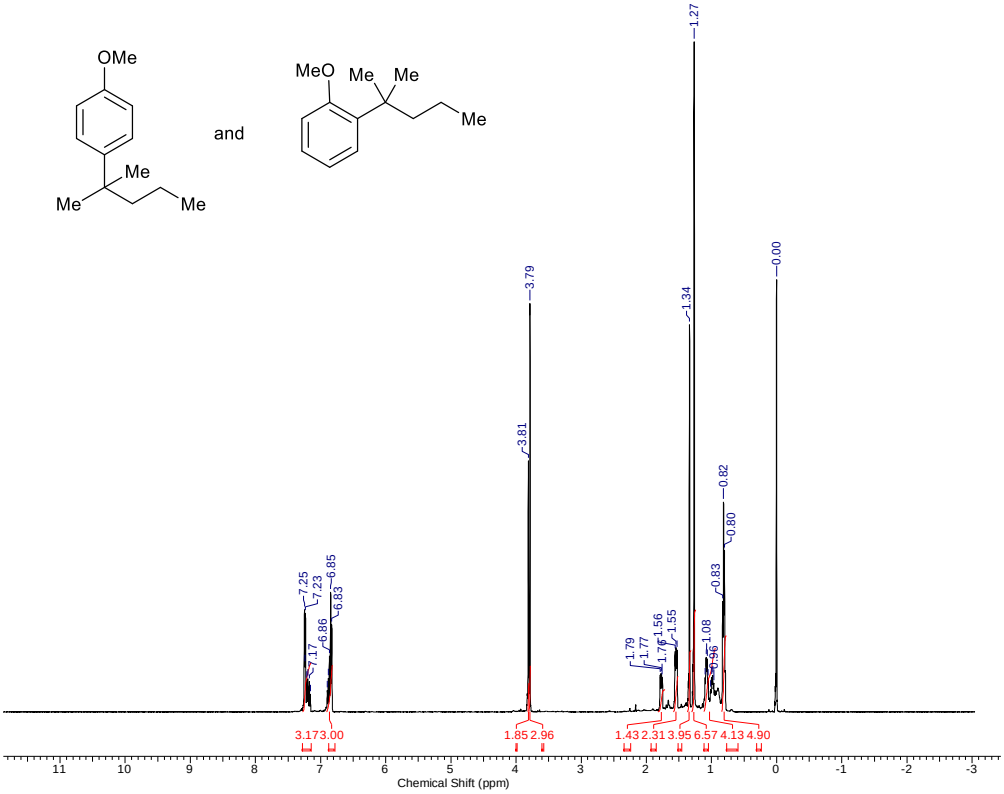
^{1}H NMR for 5-(1-Methylethyl)-2-(1-phenylethyl)phenol (55)



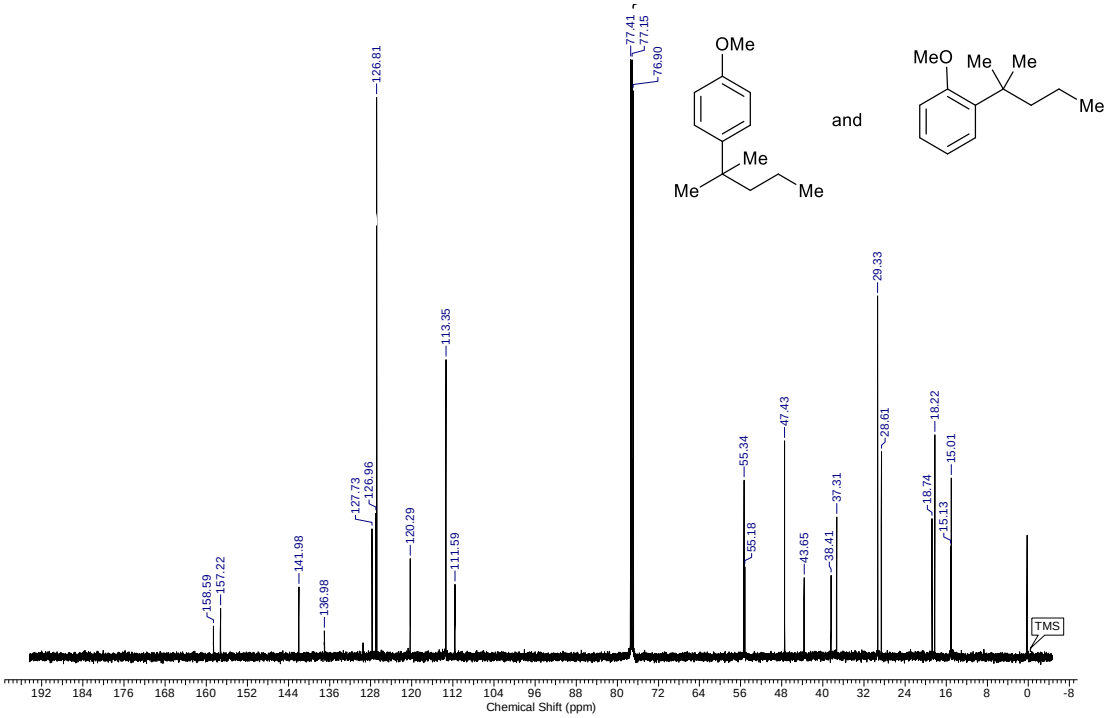
^{13}C NMR for 5-(1-Methylethyl)-2-(1-phenylethyl)phenol (55)



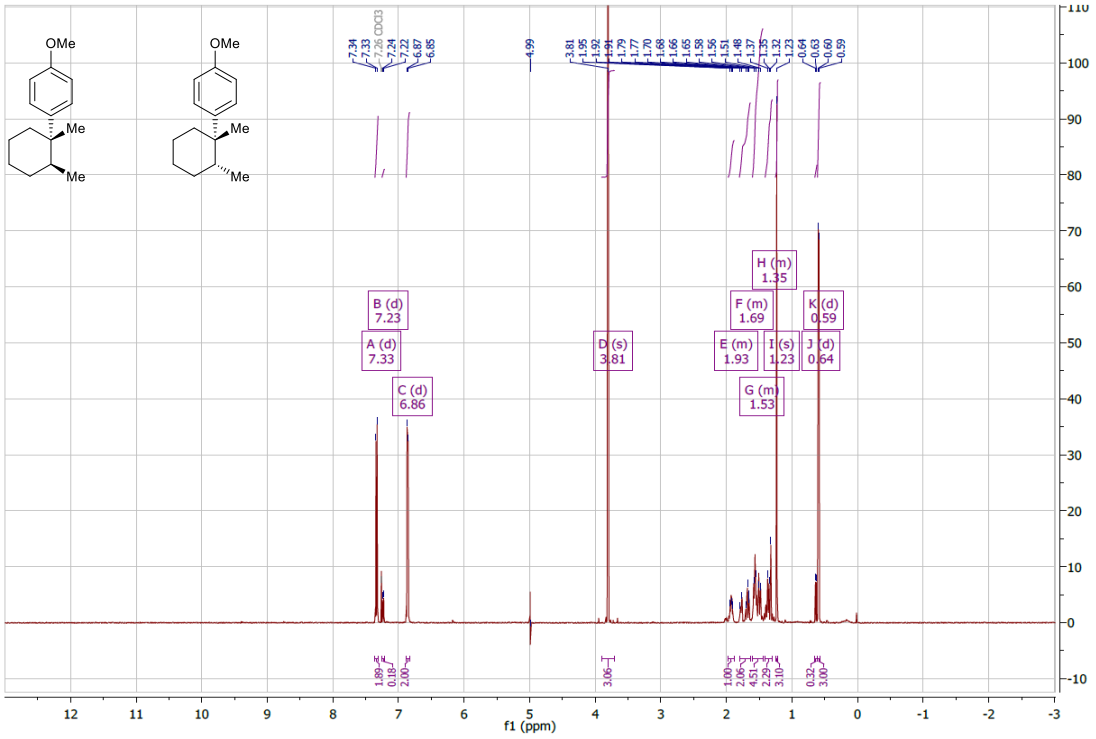
^{1}H NMR for 1-(1,1-Dimethylbutyl)-4-methoxybenzene (65)



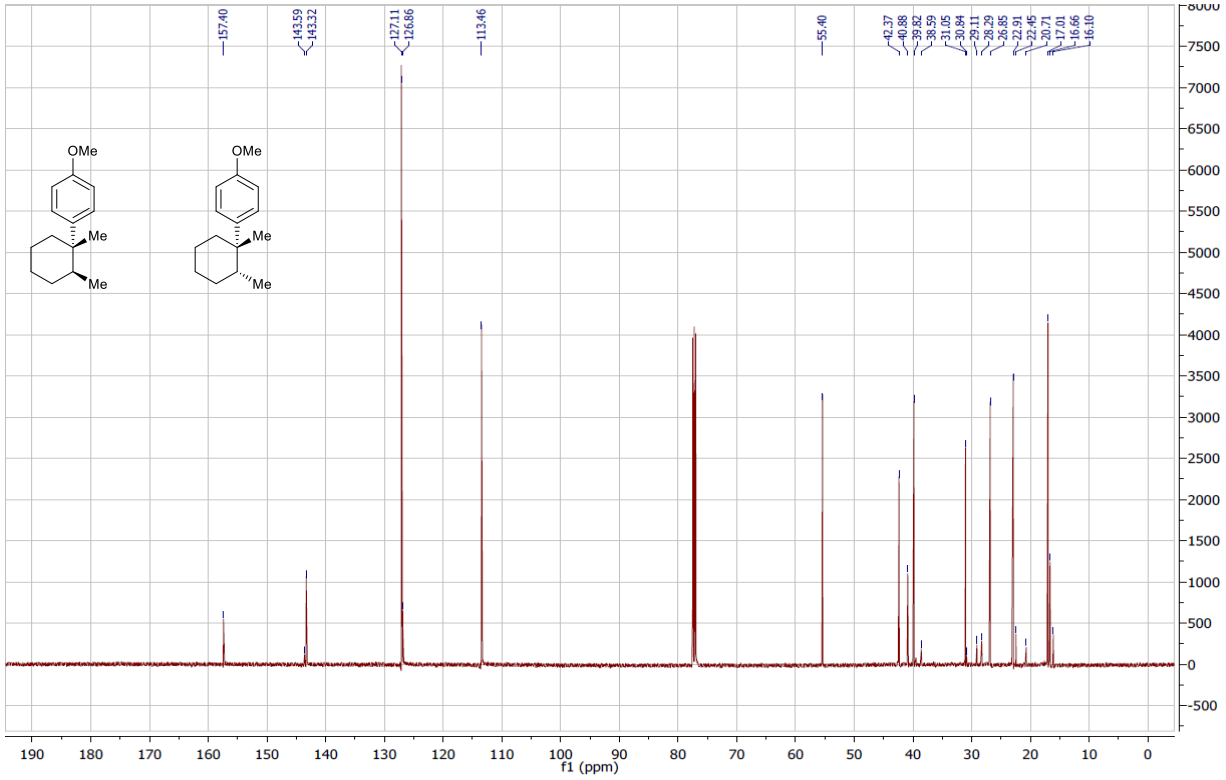
^{13}C NMR for 1-(1,1-Dimethylbutyl)-4-methoxybenzene (65)



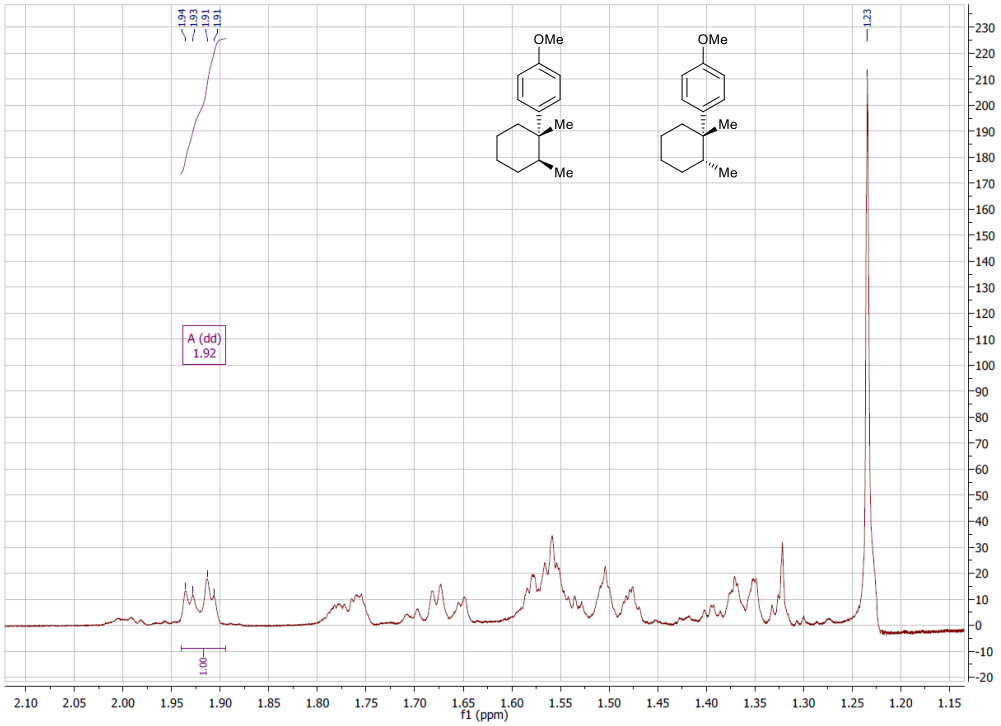
^{1}H NMR for 1-(4-methoxyphenyl)-1,2-*trans*-dimethylcyclohexane (68a) and 1-(4-methoxyphenyl)-1,2-cis-dimethylcyclohexane (68b)



^{13}C NMR for 1-(4-methoxyphenyl)-1,2-*cis*-dimethylcyclohexane (68a) and 1-(4-methoxyphenyl)-1,2-*trans*-dimethylcyclohexane (68b)

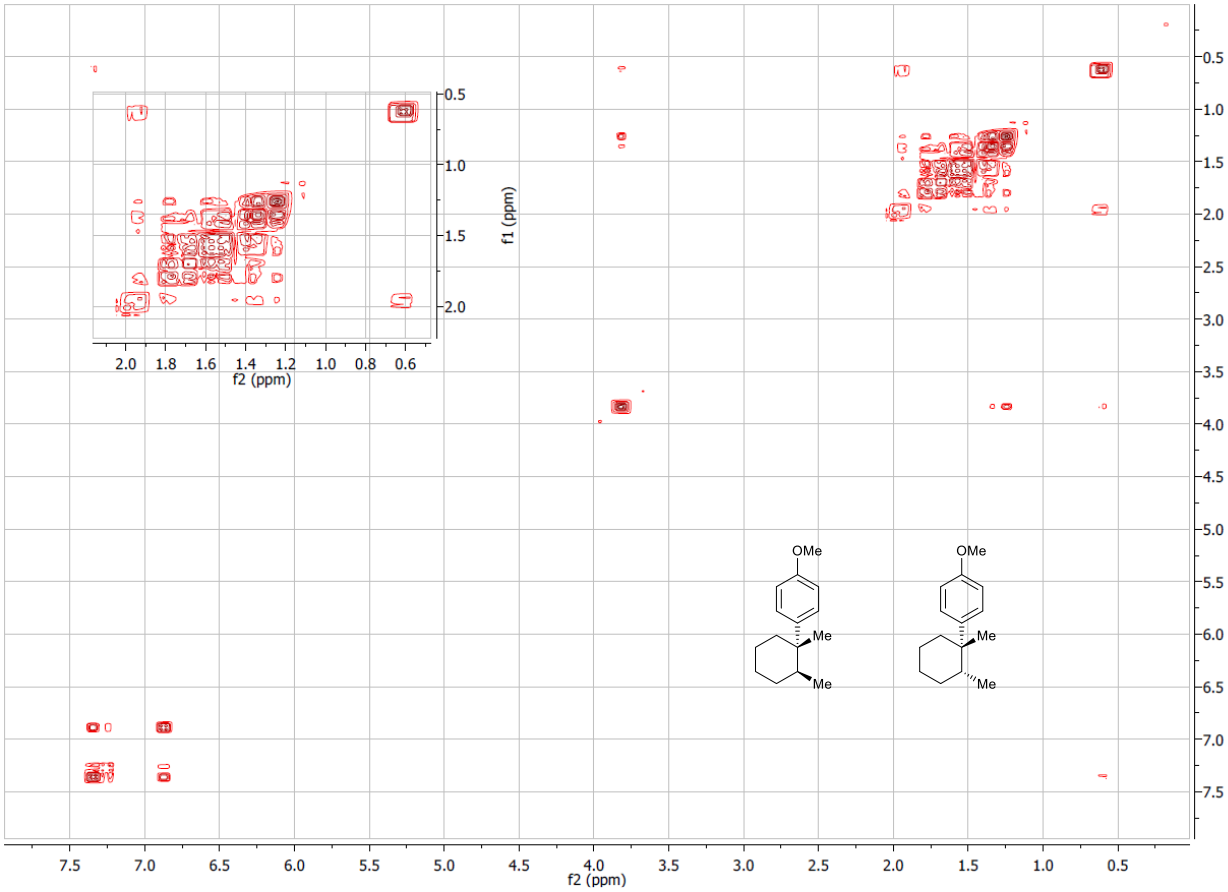


1D NOE ^{1}H NMR of 68a and 68b, irradiating at 0.6 ppm

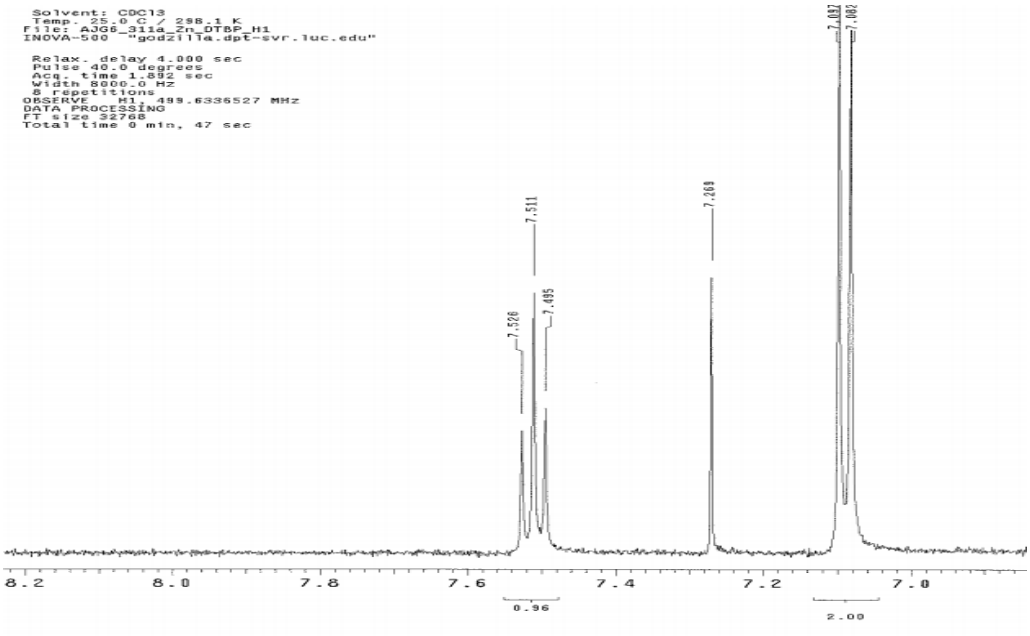


1H NMR (500 MHz, Chloroform-d) δ 1.92 (dd, J = 11.1, 3.7 Hz, 1H)

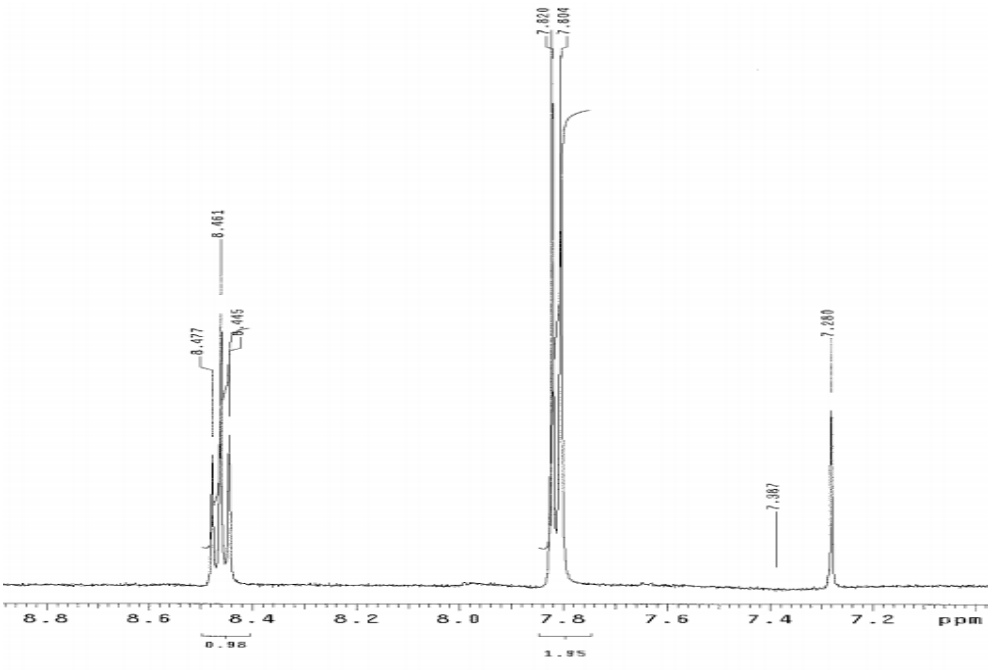
2D COSY NMR of 68a and 68b



^{1}H NMR of Unreacted 2,6-di-*tert*-butylpyridine from the $ZnBr_2$ hydrolysis experiment



^{1}H NMR of 2,6-di-*tert*-butylpyridine from the hydrolysis of TMSCl experiment



APPENDIX C

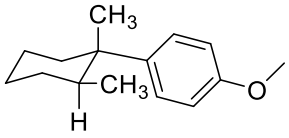
SPARTAN ’16 CALCULATIONS

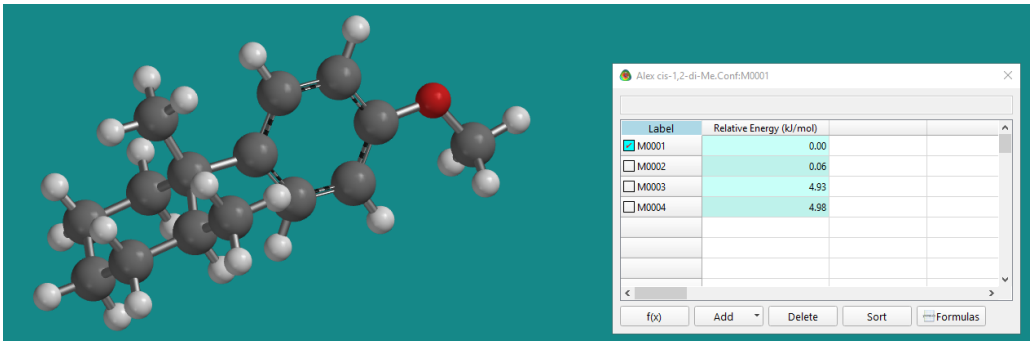
FOR CHAPTER TWO

General Information about Spartan Calculations

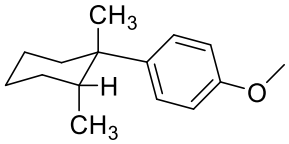
Models of the cyclohexane molecules **68a** and **68b** were drawn using Spartan '16 and energy minimization calculations were performed using DF EDF2/6-31G*. Four stable conformations were found for each of the conformers were found for each diastereomer, the most stable ones being listed here:

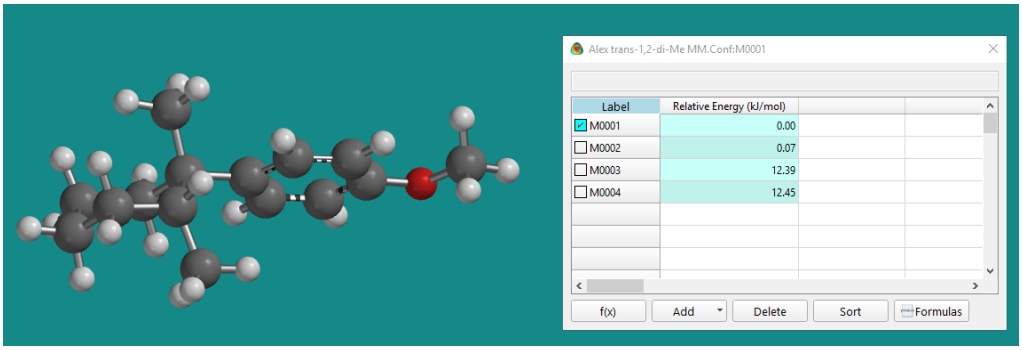
1-(Methoxyphenyl)-1,2-*cis*-dimethylcyclohexane (**68a**):





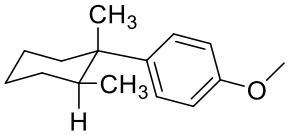
1-(Methoxyphenyl)-1,2-*trans*-dimethylcyclohexane (**68b**):





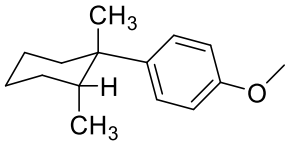
NMR spectra for the most stable conformers of **68a** and **68b** were calculated using density functional theory (DFT) at the EDF2/6-31G* level of theory. Key proton and carbon resonances could be assigned by *in silico* calculated chemical shift values. The key chemical shift resonances and calculated coupling constants are presented here:

1-(Methoxyphenyl)-1,2-*cis*-dimethylcyclohexane (**68a**):



		Uncorrected	Corrected	
11	H2	2.04	1.82	^3J = 2.9 6.4(x3) 12.6

1-(Methoxyphenyl)-1,2-*trans*-dimethylcyclohexane (**68b**):



		Uncorrected	Corrected	
34	H23	2.20	2.03	^3J = 2.2 4.5 6.5(x3)

APPENDIX D

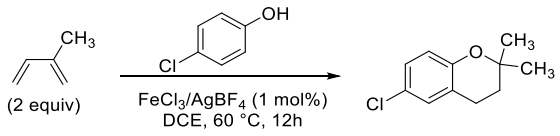
EXPERIMENTAL DETAILS

FOR CHAPTER THREE

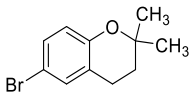
General Information

All reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego. 1,2-Dichloroethane (DCE) and isoprene were freshly distilled from CaH_2 prior to use. Purification of reaction products was carried out by using bulb-to-bulb distillation. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and vanillin or potassium permanganate stain followed by heating. Infrared spectra were recorded on Shimadzu IRAffinity-1S with NaCl salt plates. ^{1}H NMR spectra were recorded on a Varian Inova NMR (300 or 500 MHz) spectrometer and are reported in ppm using residual protiated solvent as an internal standard ($CHCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = apparent triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Inova 300 or 500 MHz (75 or 125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). GC-MS data were obtained on a HP 6890N GC equipped with a 5973 MS quad detector (ESI). HRMS data were obtained on a Shimadzu IT-TOF quad detector (ESI).

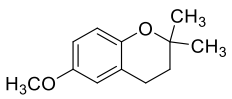
Representative Procedure for Synthesis of Chromans Using Iron Chloride and Silver Tetrafluoroborate



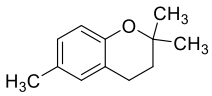
6-Chloro-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76a): In an oven-dried 1 dram vial was added $FeCl_3$ (1.6 mg, 0.01 eq), $AgBF_4$ (2.0 mg, 0.01 eq), and 4-chlorophenol (135.0 mg, 1.0 mmol). The flask was purged with N_2 and diluted with freshly distilled 1,2-DCE (1.0 mL). Isoprene (200 µL, 2.0 mmol) was added dropwise to the stirring reaction over the course of one minute. Completion of the reaction was determined by GC-MS after which the reaction was placed in a separatory funnel, diluted with ethyl acetate, and washed with a saturated brine solution. The organic layer was then washed with 1M NaOH and again with brine solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then subjected to bulb-to-bulb distillation *in vacuo* to afford 149 mg of product as a colorless oil (74% yield). NMR spectra were identical to those in the literature.



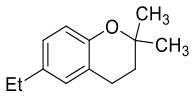
6-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76b): Prepared according to the general procedure using 173.0 mg (1.0 mmol) of 4-bromophenol. Purified by bulb-to-bulb distillation to yield 190 mg of product as a colorless oil (79% yield). NMR spectra were identical to those in the literature.



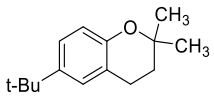
3,4-Dihydro-6-methoxy-2,2-dimethyl-2*H*-benzopyran (76c): Prepared according to the general procedure using 124.0 mg (1.0 mmol) of *p*-methoxyphenol. Purified by bulb-to-bulb distillation to yield 142 mg of product as a colorless oil (74% yield). NMR spectra were identical to those in the literature.[3]



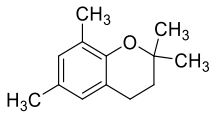
2,6,6-Trimethyl-3,4-dihydro-2*H*-1-benzopyran (76d): Prepared according to the general procedure using 108.0 mg (1.0 mmol) of *p*-cresol. Purified by bulb-to-bulb distillation to yield 135 mg of product as a colorless oil (77% yield). NMR spectra were identical to those in the literature.[3]



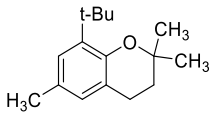
2,2-Dimethyl-6-ethyl-3,4-dihydro-2*H*-1-benzopyran (76e): Prepared according to the general procedure using 122.0 mg (1.0 mmol) of 4-ethylphenol. Purified by bulb-to-bulb distillation to yield 160 mg of product as a pale yellow oil (84% yield). NMR spectra were identical to those in the literature.[3]



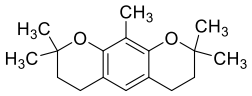
2,2-Dimethyl-6-*tert*-butyl-3,4-dihydro-2*H*-1-benzopyran (76f): Prepared according to the general procedure 150.0 mg (1.0 mmol) of 4-*tert*-butylphenol Purified by bulb-to-bulb distillation to yield 170 mg of product as a colorless oil (78% yield). NMR spectra were identical to those in the literature.[4]



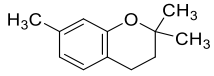
2,2,6,8-Tetramethyl-3,4-dihydro-2*H*-1-benzopyran (76g): Prepared according to the general procedure using 122.0 mg (1.0 mmol) of 2,4-dimethylphenol. Purified by bulb-to-bulb distillation to yield 125 mg of product as a pale yellow oil (66% yield). NMR spectra were identical to those in the literature.[4]

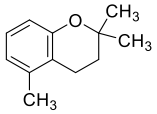


2,2,6-Trimethyl-8-*tert*-butyl-3,4-dihydro-2*H*-1-benzopyran (76h): Prepared according to the general procedure using 164.0 mg (1.0 mmol) of 4-methyl-2-*tert*-butylphenol. The reaction was performed at 20 h to increase conversion. Purified by bulb-to-bulb distillation to yield 170 mg of product as a pale yellow oil (73% yield). Analytical data: **^{1}H NMR (300 MHz, $CDCl_3$):** d = 6.91 (s, 1H), 6.74 (s, 1H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 1.76 (t, *J* = 6.8 Hz, 2H), 1.32-1.37 (15H); **^{13}C NMR (75 MHz, $CDCl_3$):** d 150.2, 137.4, 127.8, 127.4, 125.2, 120.4, 73.4, 34.6, 32.6, , 29.8, 26.8, 23.0, 20.8; **HRMS (ESI):** calcd for $C_{16}H_{24}O$ $[M]^+$: 232.1827; found 232.1834; **IR (thin film in $CDCl_3$, cm^{-1}):** 2970, 2951, 2866, 1470, 1443, 1369, 1250, 1219, 1157, 1122, 941.

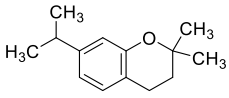


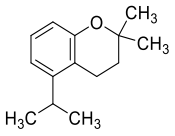
2,2,8,8,10-Pentamethyl-3,4,6,7-tetrahydro-2*H*,8*H*-benzo<1,2b:5,4-b'>dipyran (76i): Prepared according to the general procedure using 124.0 mg (1.0 mmol) of 2-methylrescorcinol. Purified by bulb-to-bulb distillation to yield 215 mg of product as a colorless oil (83% yield). NMR spectra were identical to those in the literature.[5]





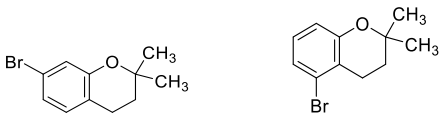
3,4-Dihydro-2,2,7-trimethyl-2*H*-1-benzopyran and 3,4-Dihydro-2,2,5-trimethyl-2*H*-1-benzopyran (76j): Prepared according to the general procedure using 108.0 mg (1.0 mmol) of m-cresol. Purified by bulb-to-bulb distillation to yield 72 mg of a 1:1 ratio of product as a pale yellow oil (41% yield). NMR spectra were identical to those in the literature.[6]



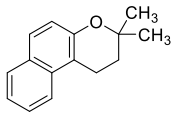


3,4-Dihydro-2,2-dimethyl-7-(1-methylethyl)-2*H*-1-benzopyran and 3,4-Dihydro-2,2-dimethyl-5-(1-methylethyl)-2*H*-1-benzopyran (76k): Prepared according to the general procedure using 136.0 mg (1.0 mmol) of 3-isopropylphenol. Purified by bulb-to-bulb distillation to yield 110 mg of a 3:1 ratio of product as a colorless oil (54% yield). Analytical data: **^{1}H NMR (300MHz ,$CDCl_3$):** (major) = d 6.97 (d, *J* = 7.6 Hz, 1 H), 6.78 - 6.61 (m, 2 H), 2.64-2.82 (m, 3H), 1.78 (t, *J* = 6.8 Hz, 2H), 1.33 (s, 6 H), 1.22 (d, *J* = 6.9 Hz, 6 H) ; minor: 7.11 (t, *J* = 8.2 Hz, 1H), 6.81 (m, 1H), 6.64 (m, 1H), 2.74-2.89 (m, 3H), 1.79-1.85 (m, 2H), 1.35 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6 H); **^{13}C NMR (75 MHz, $CDCl_3$):** (minor) = d

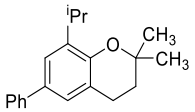
153.74, 148.35, 129.17, 118.09, 118.04, 114.81, 74.03, 33.73, 32.90, 26.92, 23.94, 22.11; **HRMS (ESI):** calcd for $C_{14}H_{20}O$ $[M]^{+\cdot}$ 204.1514; found: 204.1519; **IR (thin film in $CDCl_3$, cm^{-1}):** 2963, 2932, 2870, 2245, 1732, 1570, 1501, 1454, 1423, 1385, 1369, 1308, 1296, 1269, 1250, 1219, 1177, 1157, 1122, 975, 914, 902, 887, 748, 721, 648.



7-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran and 5-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76l): Prepared according to the general procedure using 173.0 mg (1.0 mmol) of 3-bromophenol. Purified by bulb-to-bulb distillation to yield 166 mg of a 2:1 ratio of product as a pale yellow foam (69% yield). Analytical data: **^{1}H NMR (300 MHz; $CDCl_3$), major isomer:** δ 6.91-6.95 (m, 3H), 2.70 (t, J = 6.8 Hz, 2H), 1.78 (t, J = 6.8 Hz, 2H), 1.31(s, 6H); **^{1}H NMR (300 MHz; $CDCl_3$), minor isomer:** δ 7.09 (m, 1H), 6.98 (m, 1H), 6.74 (m, 1H), 2.74 (t, J = 6.8 Hz, 2H), 1.82 (t, J = 6.8 Hz, 2H), 1.32 (s, 6H); **^{13}C NMR (75 MHz; $CDCl_3$), major isomer:** δ 154.8, 130.6, 127.9, 122.6, 120.2, 116.5, 74.7, 32.4, 26.5, 22.0; **^{13}C NMR (75 MHz; $CDCl_3$), minor isomer:** δ 155.1, 125.2, 123.6, 121.3, 119.9, 119.8, 74.3, 32.8, 26.5, 23.5; **HRMS (ESI):** calcd for $C_{11}H_{13}OBr$ $[M+H]^+$: 241.0185, found 241.0207; **IR (thin film in $CDCl_3$):** 2978, 2932, 1732, 1597, 1570, 1481, 1450, 1408, 1369, 1296, 1238, 1211, 1157, 1123, 953.

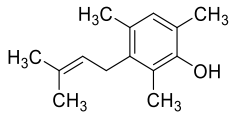


2,3-Dihydro-3,3-Dimethyl-1*H*-benzo[f]chromene (76m): Prepared according to the general procedure using 144.0 mg (1.0 mmol) of 2-naphthol. Purified by bulb-to-bulb distillation to yield 200 mg of product as a pale yellow foam (94% yield). NMR spectra were identical to those in the literature.[5]

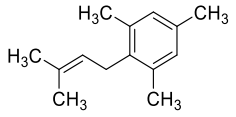


4-Phenyl-2-isopropylchroman (76n): Prepared according to the general procedure using 21 mg (0.1 mmol) of 2-isopropyl-4-phenylphenol. Purified via bulb-to-bulb distillation to yield 18 mg of product as a pale yellow oil (65% yield). NMR spectra were identical to those in the literature.[7]

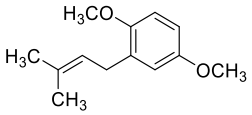
Representative Procedure for Synthesis of Prenyl Arenes



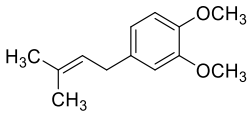
2,4,6-Trimethyl-3-(3-methyl-2-buten-1-yl)-phenol (77b): In an oven-dried 1 dram vial was added $FeCl_3$ (5.0 mg, 0.03 eq), $AgBF_4$ (6.0 mg, 0.03 eq), and 2,3,5-trimethylphenol (136.0 mg, 1.0 mmol). The flask was purged with N_2 and diluted with freshly distilled 1,2-DCE (1.0 mL). Isoprene (200 μL, 2.0 mmol) was added dropwise to the stirring reaction over the course of one minute. Completion of the reaction was determined by GC-MS after which the reaction was placed in a separatory funnel, diluted with ethyl acetate, and washed with a saturated brine solution. The organic layer was then washed with 1M NaOH and again with brine solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then subjected to bulb-to-bulb distillation to yield 65 mg of a pale yellow oil (32% yield). NMR spectra were identical to those in the literature.[8]



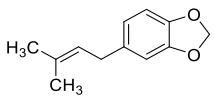
1,3,5-Trimethyl-2-(3-methyl-2-buten-1-yl)-benzene (77c): Prepared according to the general procedure using 120.0 mg (1.0 mmol) of mesitylene. Purified by bulb-to-bulb distillation to yield 107 mg of product as a pale yellow oil (56% yield). NMR spectra were identical to those in the literature.[8]



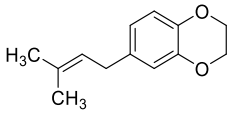
5-(3-Methyl-2-buten-1-yl)-1,4-dimethoxybenzene (77d): Prepared according to the general procedure using 124.0 mg (1.0 mmol) of 1,4-dimethoxybenzene. Purified by bulb-to-bulb distillation to yield 98 mg of product as a pale yellow oil (48% yield). NMR spectra were identical to those in the literature.[8]



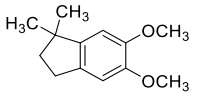
2,3-Dimethoxy-5-(3-methyl-buten-1-yl)-benzene (77e): Prepared according to the general procedure using 124.0 mg (1.0 mmol) of veratrole. Purified by bulb-to-bulb distillation to yield 72 mg of product a pale yellow oil (35% yield). NMR spectra were identical to those in the literature.[8]



5-(3-Methyl-2-buten-1-yl)-1,3-benzodioxole (77f): Prepared according to the general procedure using 122.0 mg (1.0 mmol) of 1,3-benzodioxole. Purified by bulb-to-bulb distillation to yield 70 mg of product as a pale yellow oil (36% yield). NMR spectra were identical to those in the literature.[8]

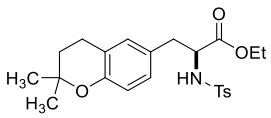


5-(3-Methyl-2-buten-1-yl)-1,4-benzodioxane (77g): Prepared according to the general procedure using 136.0 mg (1.0 mmol) of 1,4-benzodioxane. Purified by bulb-to-bulb distillation to yield 80 mg of product as a pale yellow oil (38% yield). Analytical data: **^{1}H NMR (300 MHz):** 6.63-6.76 (m, 3H), 5.28 (m, 1H), 4.22 (m, 4H), 3.22 (d, J = 7.1 Hz), 1.73 (s, 3H), 1.69 (s, 3H) ; **^{13}C NMR (75 MHz):** 143.3, 141.5, 135.1, 132.3, 123.3, 121.1, 117.0, 116.8, 64.4, 64.3, 33.5, 25.7, 17.7; **HRMS (ESI):** calcd for $C_{13}H_{16}O_2$ $[M+H]^+$: 204.1150; found 204.1153; **IR (thin film in $CDCl_3$, cm^{-1}):** 2985, 2967, 2932, 2920, 2880, 1591, 1490, 1468, 1450, 1305, 1275, 1253, 1120, 1065, 840, 740.



2,3-Dihydro-5,6-dimethoxy-1,1-dimethyl-1*H*-indene (78a): In an oven-dried 1 dram vial was added $FeCl_3$ (32.0 mg, 0.20 eq), $AgBF_4$ (40.0 mg, 0.20 eq), veratrole (124.0 mg, 1.0 mmol), and 4 Å molecular sieves (100.0 mg). The flask was purged with N_2 and diluted with freshly distilled 1,2-DCE (1.0 mL). Isoprene (200 µL, 2.0 mmol) was added dropwise to the stirring reaction over the course of one minute. Completion of the reaction was determined by GC-MS after which the reaction was placed in a separatory funnel, diluted with ethyl acetate, and washed with a saturated brine solution. The organic layer was then washed with 1M NaOH and again with brine solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was then subjected to bulb-to-bulb distillation to yield 72 mg of product as a pale yellow oil (35% yield). NMR spectra were identical to those in the literature.[9]

Preparation of **3** was also achieved by taking 20 mg of **2e** (0.1 mmol) in an oven-dried 1 dram vial followed by $FeCl_3$ (0.16 mg, 0.01 eq) and $AgBF_4$ (0.20 mg, 0.01 eq). The flask was purged with N_2 and diluted with freshly distilled 1,2-DCE (1.0 mL). The reaction was heated to 60°C for 1 h. Completion of the reaction was determined by GC-MS after which the reaction was filtered through a short silica plug (1cm) to remove the catalyst and eluted with hexanes. The solvent was removed under reduced pressure to yield 20 mg of product as a pale yellow oil (99% yield). NMR spectra were identical to those in the literature.[9]

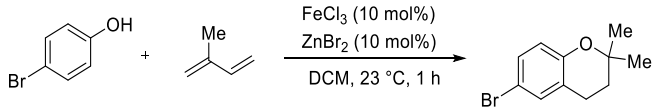


Ethyl (2*S*)-3-(2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-2-(4-methylbenzene-sulfonamido) propanoate (80a): In an argon glove box, to an oven-dried 1 dram vial was added $FeCl_3$ (4.8 mg, 0.30 equiv), $AgBF_4$ (1.0 mg, 0.05 equiv), *N*-tosyl-ethtylester L-tyrosine[10] (23.0 mg, 0.10 mmol) and an internal standard *tert*-butylbenzene (0.1 mmol). The vial was removed from the glove box, purged with N_2 and DCE (1.0 mL) was added. Isoprene (50 μL, 5 equiv) was added dropwise to the reaction over the course of one minute, then reaction was stirred at 60 °C for 20 h. Completion of the reaction was determined by GC-MS. The starting tyrosine was completely consumed providing a 72% GC yield (averaged over two runs). The crude mixture was subjected to column chromatography (1-10% MeOH/DCM) to give an inseparable mixture of a yellow oil. Final purification was achieved by preparative HPLC through Northwestern's ChemCore facility. Analytical data: **^{1}H NMR (500 MHz):** 7.65 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.73-6.77 (m, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 5.00 (d, J = 9.3 Hz, 1H), 4.11 (m, 1H), 3.91 (q, *J* = 6.8 Hz, 2H), 2.93 (m, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.40 (s, 3H), 1.77 (t, *J* = 6.6 Hz, 2H), 1.31 (s, 6H), 1.07 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (125 MHz):** 171.7, 154.2, 144.3, 131.2, 130.3, 129.0, 128.0, 121.6, 118.0, 75.0, 62.3, 57.5, 39.4, 33.5, 27.6, 27.6, 23.2, 22.3, 14.7; **HRMS (ESI):** calcd for $C_{23}H_{29}NO_5S$ $[M+H]^+$: 431.1766; found 431.1745; IR (thin film in $CDCl_3$, cm^{-1}): 2978, 2927, 1736, 1496, 1369, 1342, 1257, 1207, 1161, 1122, 1092, 910, 895, 741, 648.

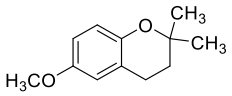
(3a*S*,3b*R*,11b*S*,13a*S*)-8,8,13a-trimethyl-3,3a,3b,4,5,8,9,10,11b,12,13,13a-dodeca-hydrocyclopenta[5,6]naphtho[1,2-g]chromen-1(2*H*)-one and (6b*S*,8a*S*,11a*S*,11b*R*)-3,3,8a-trimethyl-2,3,6b,7,8,8a,10,11,11a,11b,12,13-dodecahydrocyclopenta[5,6]-naphtho[2,1-f]chromen-9(1*H*)-one (80b): In an argon glove box, to an oven-dried 1 dram vial was added $FeCl_3$ (0.30 equiv), $AgBF_4$ (0.05 equiv), estrone (0.1 mmol), and an internal standard *tert*-butylbenzene (0.1 mmol). The reaction was diluted with DCE (1.0 mL) and isoprene (5 equiv), then stirred at 60° C for 20 hours. Completion of the reaction was determined by GC-MS. The starting estrone was completely consumed providing an 87% GC yield of product as a 2:1 ratio of regioisomers (averaged over two reactions). Isolation of the products was achieved by column chromatography of the crude reaction (11% EtOAc/hexanes) to give an inseparable mixture of white powders. Final purification was achieved by preparative HPLC through Northwestern's ChemCore facility. Analytical data: (3a*S*,3b*R*,11b*S*,13a*S*)-8,8,13a-trimethyl-3,3a,3b,4,5,8,9,10,11b,12,13,13a-dodecahydrocyclopenta[5,6]naphtho [1,2-g]chromen-1(2*H*)-one: **^{1}H NMR (300 MHz):** δ 6.98 (s, 1H), 6.54 (s, 1H), 1.73-2.84 (m, 11H), 1.24-1.72 (m, 14H), 0.90 (s, 3H); **^{13}C NMR (75 MHz):** δ 221.1, 151.8, 135.6, 131.0, 126.1, 118.2, 116.8, 74.0, 50.4, 48.0, 43.9, 38.4, 35.9, 33.0, 31.6, 29.1, 27.0, 26.7, 26.6, 25.9, 22.3, 21.6, 13.6; **HRMS (ESI):** calcd for $C_{23}H_{30}O_2$ $[M]^+$: 338.2246; found 338.2341; **IR (thin film in $CDCl_3$, cm^{-1}):** 2928, 2866, 2241, 1732, 1474, 1454, 1373, 1261, 1057, 1034.

(6b*S*,8a*S*,11a*S*,11b*R*)-3,3,8a-trimethyl-2,3,6b,7,8,8a,10,11,11a,11b,12,13-dodecahydro-cyclopenta[5,6]-naphtho [2,1-f]chromen-9(1*H*)-one: **^{1}H NMR (300 MHz):** δ 7.10 (d, *J* = 8.6 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 1.76-2.85 (m, 11H), 1.23-1.75 (m, 14H), 0.90 (s, 3H); **^{13}C NMR (75 MHz):** δ 221.2, 151.8, 135.2, 130.9, 124.1, 119.0, 114.8, 73.0, 50.4, 47.9, 44.2, 37.7, 44.2, 37.7, 35.9, 32.8, 31.6, 29.7, 27.4, 26.6, 26.0, 25.8, 21.5, 20.1, 13.8; **HRMS (ESI):** calcd for $C_{16}H_{24}O$ $[M+H]^+$: 338.2246; found 338.2231; **IR (thin film in $CDCl_3$):** 2932, 2866, 1732, 1493, 1454, 1373, 1258, 1157, 1123.

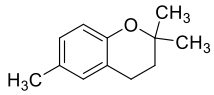
Representative Procedure for Synthesis of Chromans Using Iron Chloride and Zinc Chloride



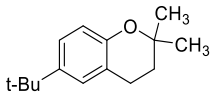
6-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76b): To a 4 mL vial was added 4-bromophenol (173.0 mg, 1.0 mmol), iron chloride (16.2 mg, 0.01 mmol), and zinc chloride (13.6 mg, 0.01 mmol). To this mixture was added a Teflon-coated stir bar, 1.0 mL of methylchloride (DCM), and finally isoprene (200 L, 2.0 mmol). The reation was stirred for one hour, after which the reaction was filtered through a small pad of silica (eluting with DCM). The eluent was concentrated *in vacuo* and subjected to vacuum distillation to yield a light tan oil (24.0 mg, 10%). NMR spectra were identical to those reported in the literature (REF).



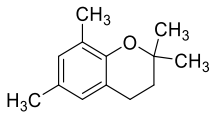
3,4-Dihydro-6-methoxy-2,2-dimethyl-2*H*-benzopyran (76c): Prepared according to the general procedure using 124.1 mg (1.0 mmol) of *p*-methoxyphenol. Purified by vacuum distillation to yield 115.4 mg of product as a colorless oil (60% yield). NMR spectra were identical to those in the literature (REF).



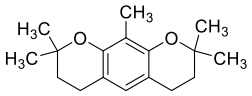
2,6,6-Trimethyl-3,4-dihydro-2*H*-1-benzopyran (76d): Prepared according to the general procedure using 108.0 mg (1.0 mmol) of *p*-cresol. Purified by vacuum distillation to yield 141.0 mg of product as a colorless oil (80% yield). NMR spectra were identical to those in the literature.



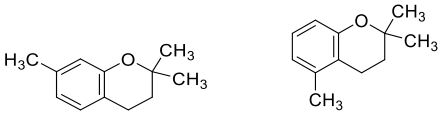
2,2-Dimethyl-6-*tert*-butyl-3,4-dihydro-2*H*-1-benzopyran (76f): Prepared according to the general procedure 150.0 mg (1.0 mmol) of 4-*tert*-butylphenol. Purified by vacuum distillation to yield 122.0 mg of product as a colorless oil (56% yield). NMR spectra were identical to those in the literature.



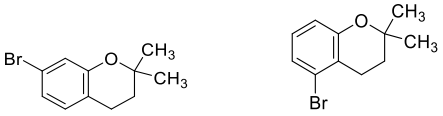
2,2,6,8-Tetramethyl-3,4-dihydro-2*H*-1-benzopyran (76g): Prepared according to the general procedure using 122.0 mg (1.0 mmol) of 2,4-dimethylphenol. Purified by bulb-to-bulb distillation to yield 124.0 mg of product as a pale yellow oil (65% yield). NMR spectra were identical to those in the literature.



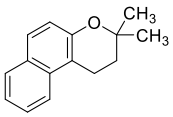
2,2,8,8,10-Pentamethyl-3,4,6,7-tetrahydro-2*H*,8*H*-benzo<1,2b:5,4-b'>dipyran (76i): Prepared according to the general procedure using 124.0 mg (1.0 mmol) of 2-methylrescorcinol. Purified by vacuum distillation to yield 104.0 mg of product as a colorless oil (40% yield). NMR spectra were identical to those in the literature.



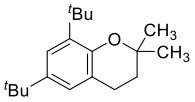
3,4-Dihydro-2,2,7-trimethyl-2*H*-1-benzopyran and 3,4-Dihydro-2,2,5-trimethyl-2*H*-1-benzopyran (76j): Prepared according to the general procedure using 108.0 mg (1.0 mmol) of m-cresol. Purified by bulb-to-bulb distillation to yield 123.3 mg of a 1:1 ratio of product as a pale yellow oil (70% yield). NMR spectra were identical to those in the literature.



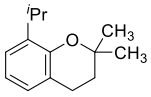
7-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran and 5-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76l): Prepared according to the general procedure using 173.0 mg (1.0 mmol) of 3-bromophenol. Purified by bulb-to-bulb distillation to yield 48.2 mg of a 1:1 ratio of product as a pale yellow foam (20% yield). NMR spectra were identical to those in the literature.[118]



2,3-Dihydro-3,3-Dimethyl-1*H*-benzo[f]chromene (76m): Prepared according to the general procedure using 144.0 mg (1.0 mmol) of 2-naphthol. Purified by vacuum distillation to yield 159.2 mg of product as a pale yellow foam (75% yield). NMR spectra were identical to those in the literature.

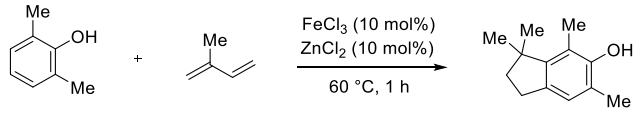


6,8-di-*tert*-butyl-2,2-dimethylchromane (76o): Prepared according to the general procedure using 208.0 mg (1.0 mmol) of 2,4-di-*tert*-butylphenol. Purified by vacuum distillation to yield 170.2 mg of product as a colorless oil (62% yield). Analytical data: **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.17 (d, J = 1.0 Hz, 0H), 6.94 (d, J = 1.1 Hz, 0H), 2.81 (t, J = 6.8 Hz, 1H), 1.81 (t, J = 7.3 Hz, 1H), 1.42 – 1.31 (m, 6H); **^{13}C NMR** (126 MHz, CDCl3) δ 150.13, 140.81, 136.78, 124.00, 121.63, 119.71, 77.26, 77.00, 76.75, 73.67, 34.99, 34.11, 32.88, 31.68, 29.84, 27.10, 23.36.



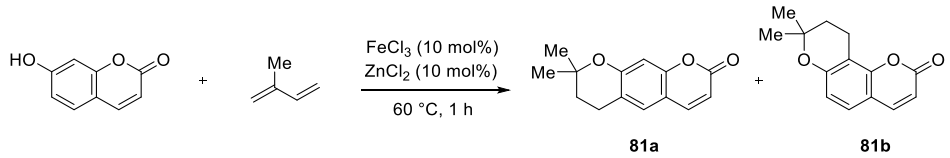
8-isopropyl-2,2-dimethylchromane (76p): Prepared according to the general procedure using 124. 0 mg (1.0 mmol) of 2-isopropylphenol. Purified by vacuum distillation to yield 81.7 mg of product as a colorless oil (40% yield). Analytical data: ^{1}H NMR (500 MHz, Chloroform-d) δ 7.06 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 3.30 (dt, J = 13.9, 7.0 Hz, 1H), 2.81 (t, J = 6.8 Hz, 2H), 1.82 (t, J = 6.8 Hz, 2H), 1.39 – 1.34 (m, 6H), 1.24 (d, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 151.40, 136.79, 127.04, 123.92, 120.60, 119.32, 73.96, 33.03, 31.92, 30.08, 27.28, 22.71.

General Procedure for Synthesis of Indane 78b



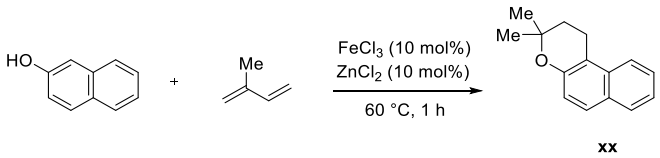
3,3,4,6-tetramethyl-2,3-dihydro-1H-inden-5-ol (78b): To a vacuum flask (60 mL), was added 120.0 mg of xylenol (1.0 mmol), iron chloride 22.6 mg (0.10 mmol), 22.6 mg of zinc bromide (0.10 mmol) and 1.0 mL nitromethane. The mixture was stirred in an ice bath for about 10 minutes after which 200 mcL of isoprene was added. The reaction vesse was sealed with a Teflon-coated screw-cap fitted with an O-ring. The reaction was warmed to 60 °C where it was left to stir for one hour. The reaction was then cooled, transferred to a 25 mL round-bottom flask, and the solvent was removed *in vacuo*. The RBF containing the crude mixture was then attached to a U-bend for vacuum fractional distillation. The lower boiling fraction was identified by NMR as unreacted xylenol and the higher boiling fraction (bp > 200 C) was collected and identified as the desired product by NMR. The total amount of higher boiling fraction collected was xx mg (xx yield). Analytical data: ^{1}H NMR (500 MHz, Chloroform-d) δ 6.85 (s, 1H), 4.52 (s, 1H), 2.78 (t, J = 7.2 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 1.93 (t, J = 7.3 Hz, 2H), 1.39 (s, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 151.18, 148.37, 135.20, 124.07, 121.22, 119.55, 77.52, 77.27, 77.01, 45.74, 43.89, 29.45, 27.83, 16.40, 11.61.

General Procedure for Synthesis of Chromans 81a and 81b



8,8-dimethyl-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-one (81a) and 8,8-dimethyl-9,10-dihydro-2H,8H-pyrano[2,3-f]chromen-2-one (81b) (1:1 mixture): Following the general procedure outlined for indane **78b** using 136.0 mg (1.0 mmol) of 7-hydroxycoumarin. Purified by column chromatography using a mixture of 1-5% methanol in DCM to yield a mixture of **81a** and **81b** as a light orange oil, 92.0 mg (45% yield). NMR of the mixture was identical to those found in the literature.

General Procedure for Prenylation of 2-Napthol in an Undergraduate Laboraotory



The hydrogroscopic iron chloride (xx mg, xx mmol) and zinc chloride (xx mg, xx mmol) were placed placed in separate individual vials, sealed with plastic snap-caps, and stored a dessicator prior to the experiment.

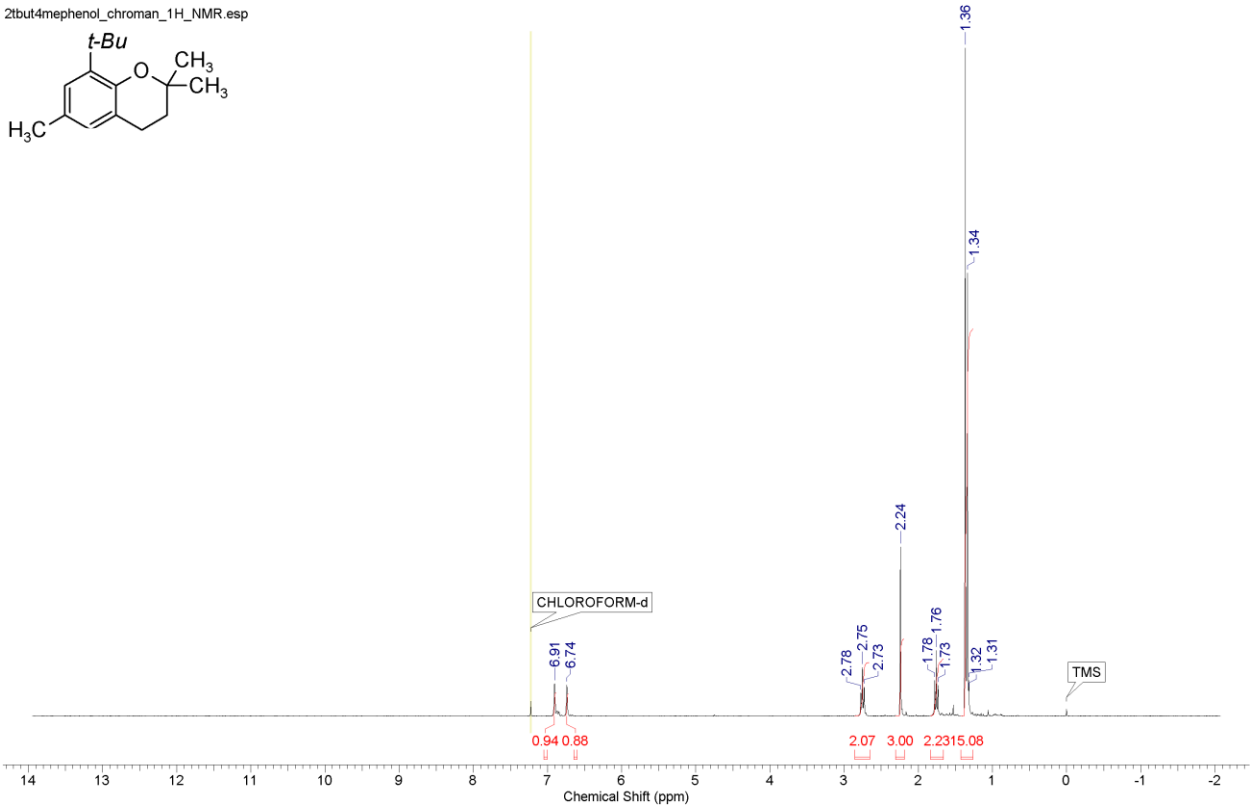
APPENDIX E

NMR SPECTRA

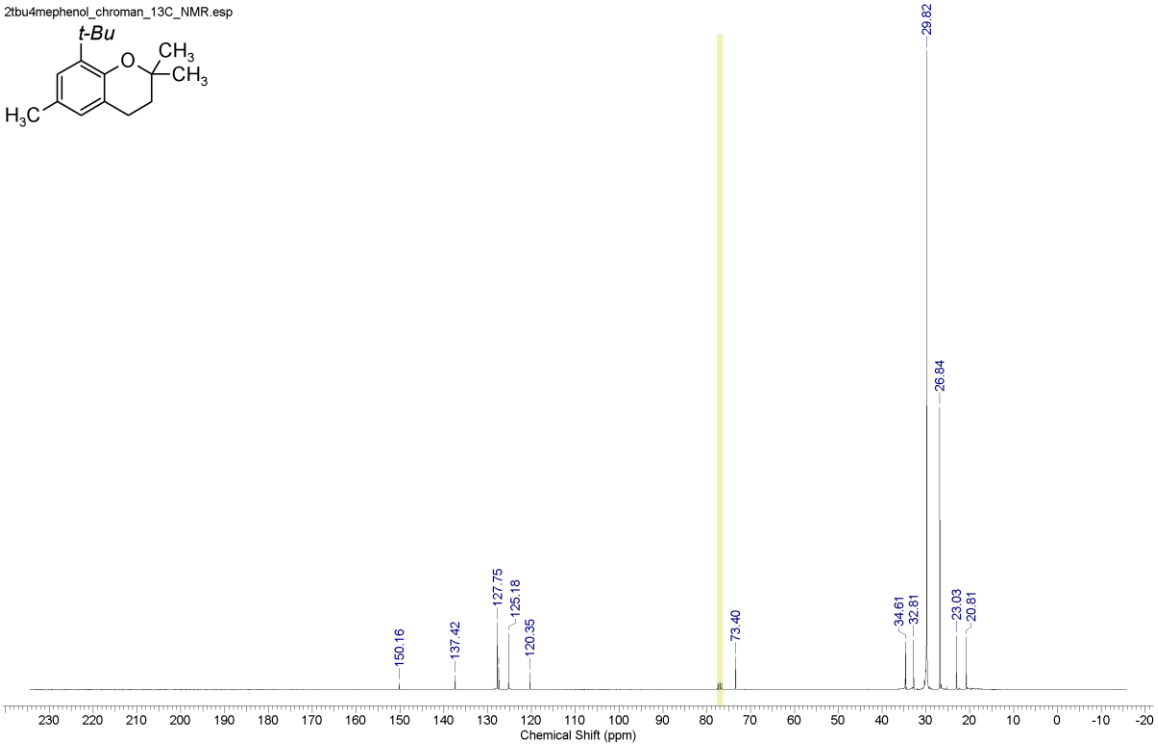
FOR CHAPTER THREE

Selected NMR Spectra for New Compounds

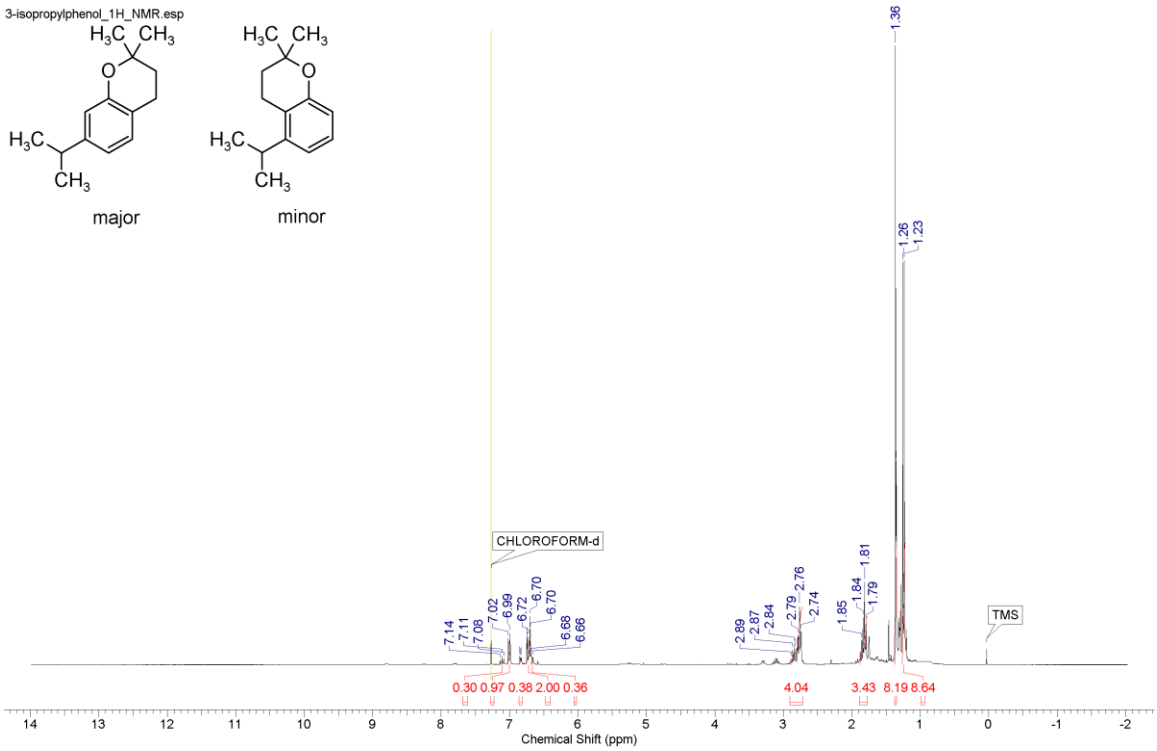
2,2,6-Trimethyl-8-*tert*-butyl-3,4-dihydro-2*H*-1-benzopyran (76h) ^{1}H NMR



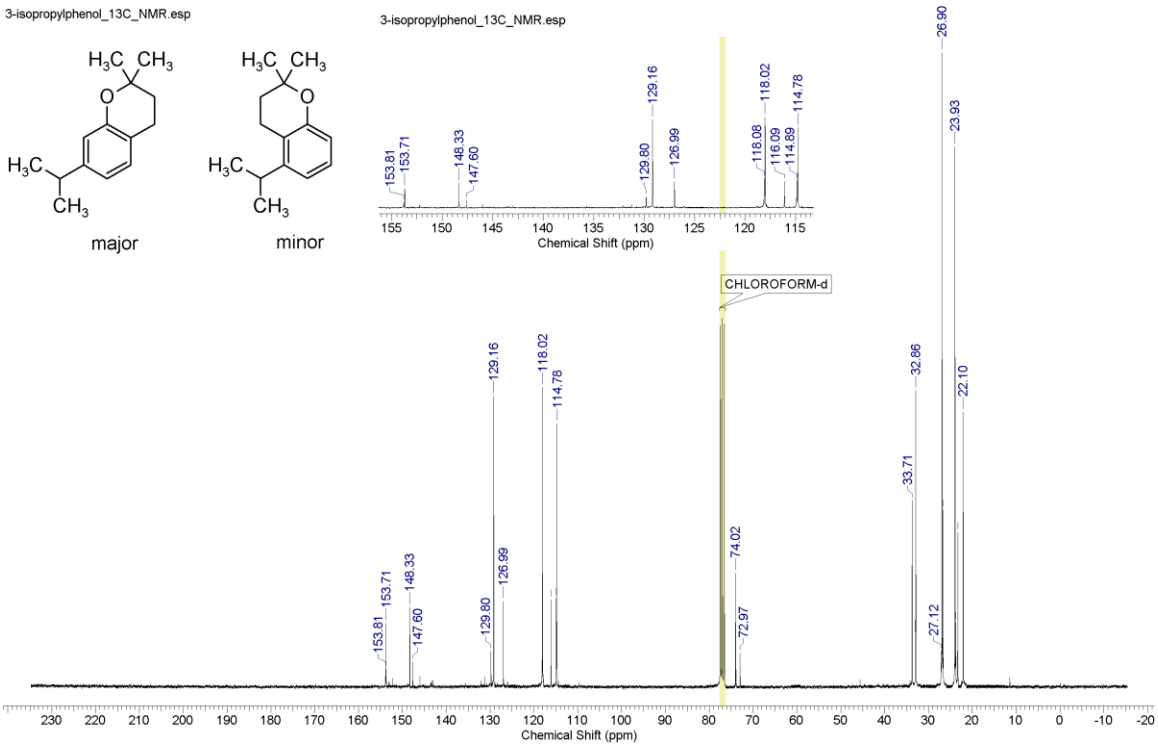
2,2,6-Trimethyl-8-*tert*-butyl-3,4-dihydro-2*H*-1-benzopyran (76h) ^{13}C NMR



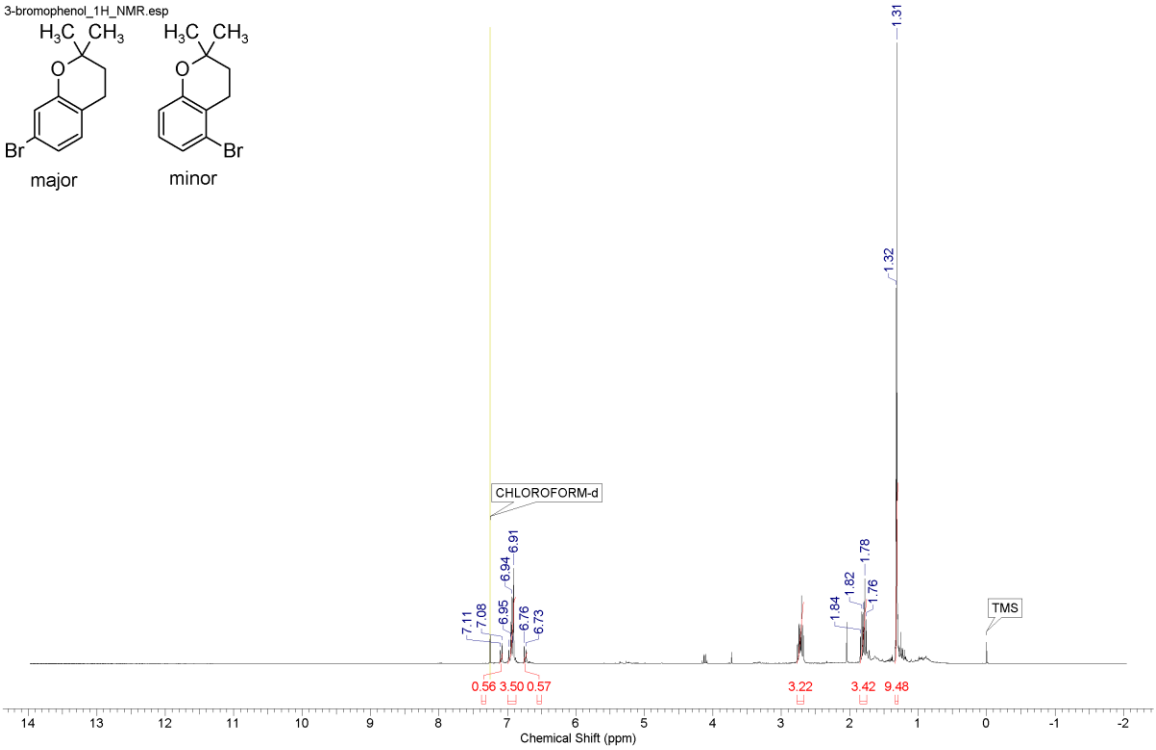
3,4-Dihydro-2,2-dimethyl-7-(1-methylethyl)-2*H*-1-benzopyran and 3,4-Dihydro-2,2-dimethyl-5-(1-methylethyl)-2*H*-1-benzopyran benzopyran (76k) ^{1}H NMR



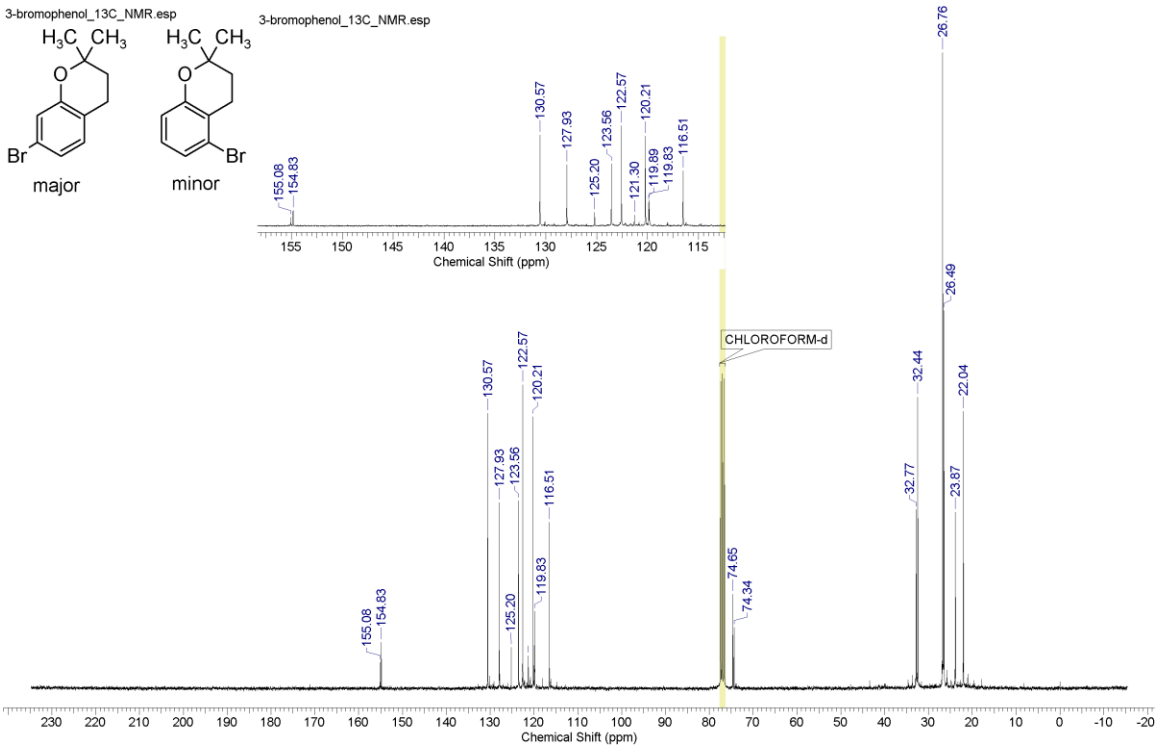
3,4-Dihydro-2,2-dimethyl-7-(1-methylethyl)-2*H*-1-benzopyran and 3,4-Dihydro-2,2-dimethyl-5-(1-methylethyl)-2*H*-1-benzopyran (76k) ^{13}C NMR



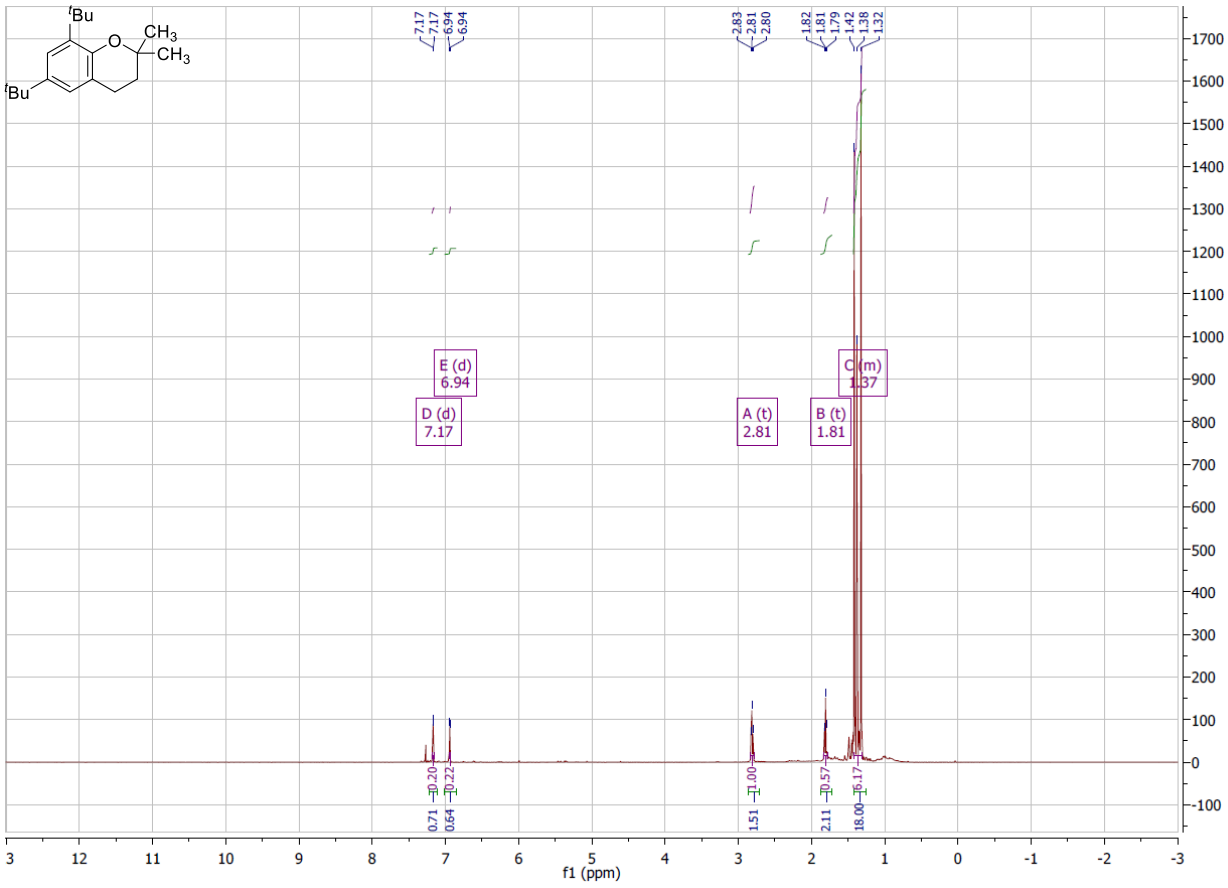
7- Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran and 5-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76l), ^{1}H NMR



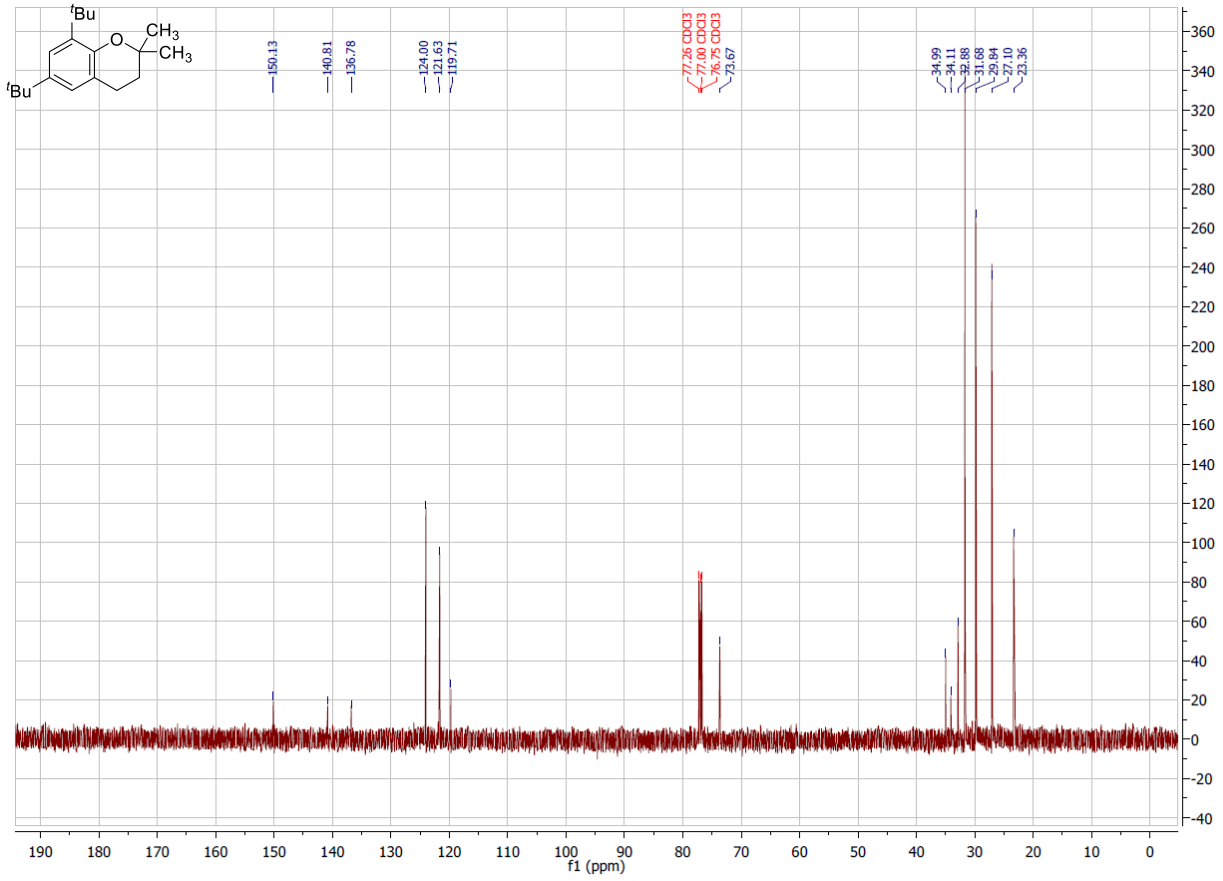
7-Bromo-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran and 5- Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran (76l), ^{13}C NMR



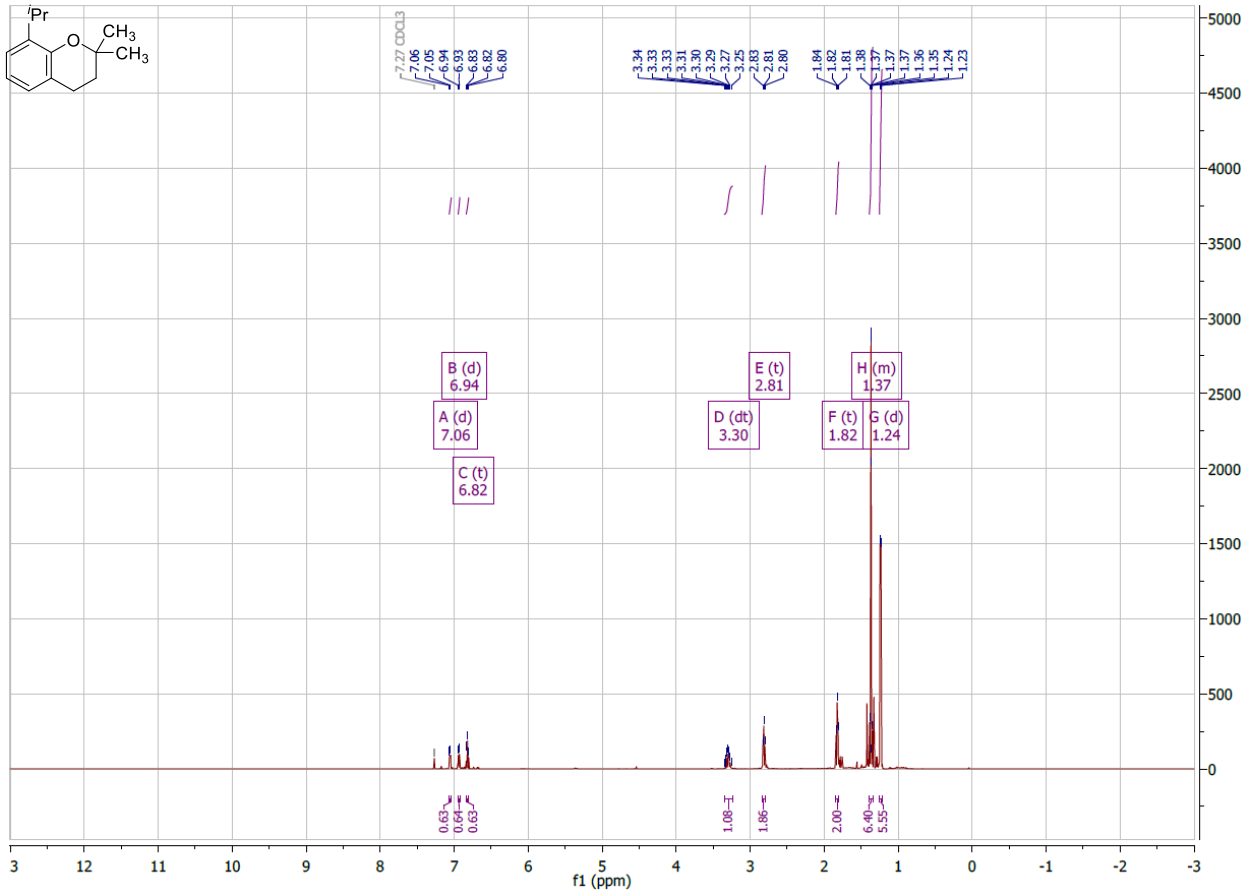
6,8-di-*tert*-butyl-2,2-dimethylchromane (76o), ^{1}H NMR:



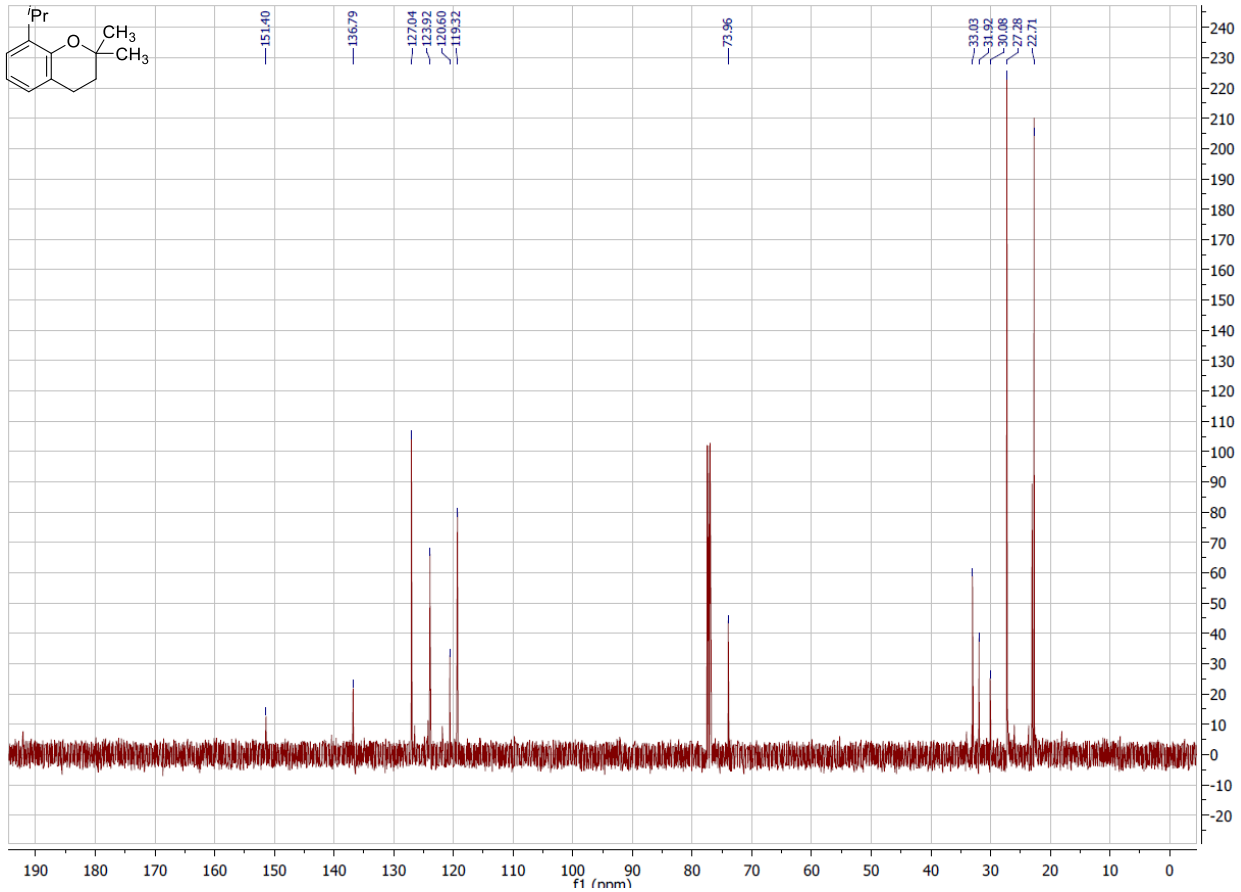
6,8-di-*tert*-butyl-2,2-dimethylchromane (76o), ^{13}C NMR:



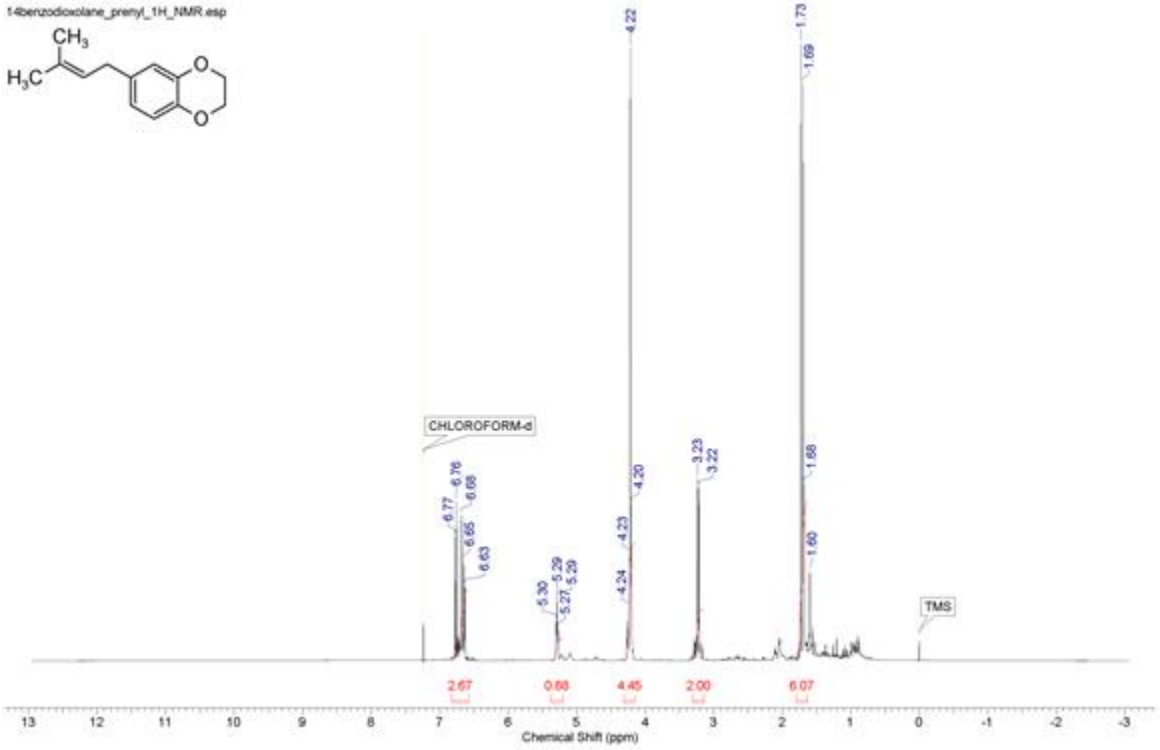
8-isopropyl-2,2-dimethylchromane (76p), ^{1}H NMR



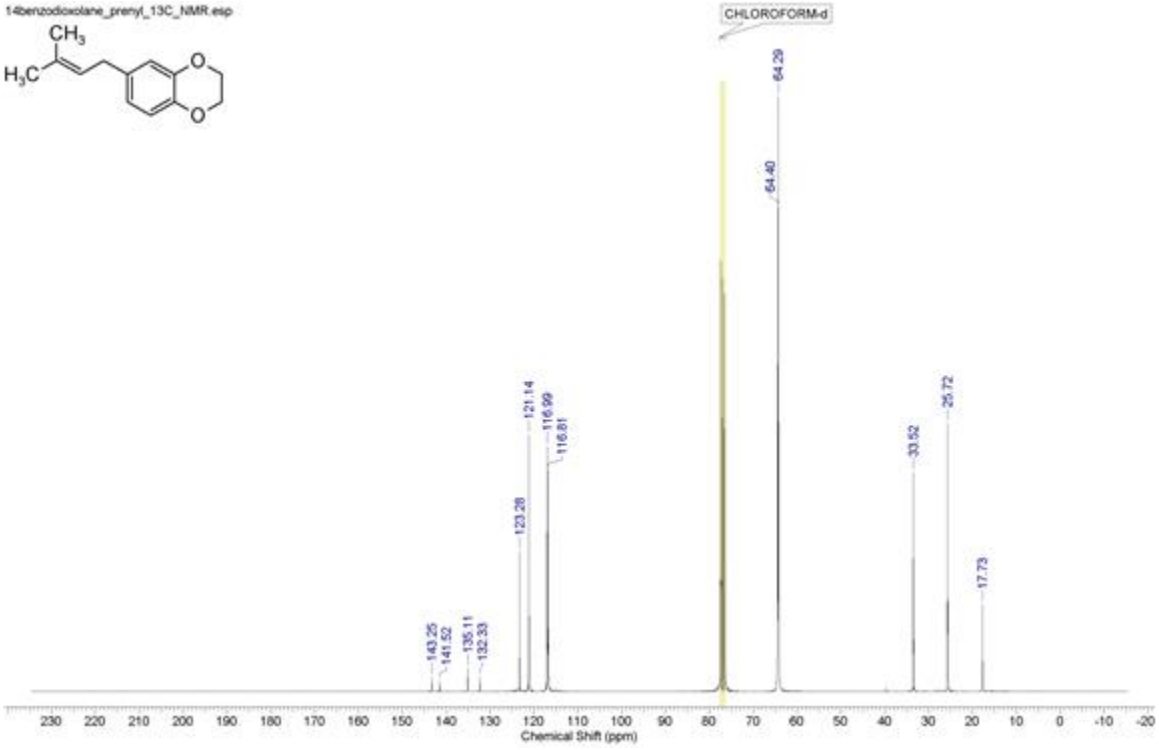
8-isopropyl-2,2-dimethylchromane (76p), ^{13}C NMR



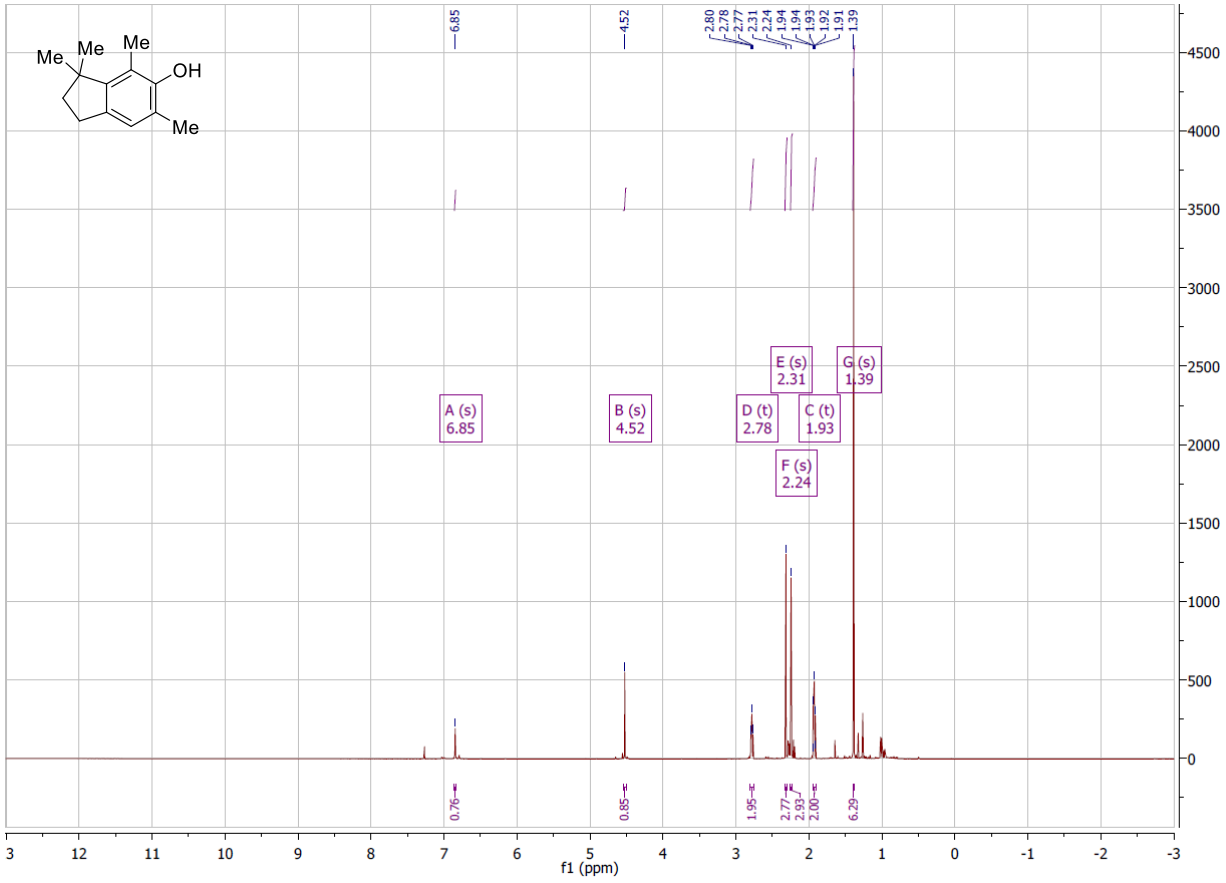
5-(3-Methyl-2-buten-1-yl)-1,4-benzodioxane (77f) ^{1}H NMR



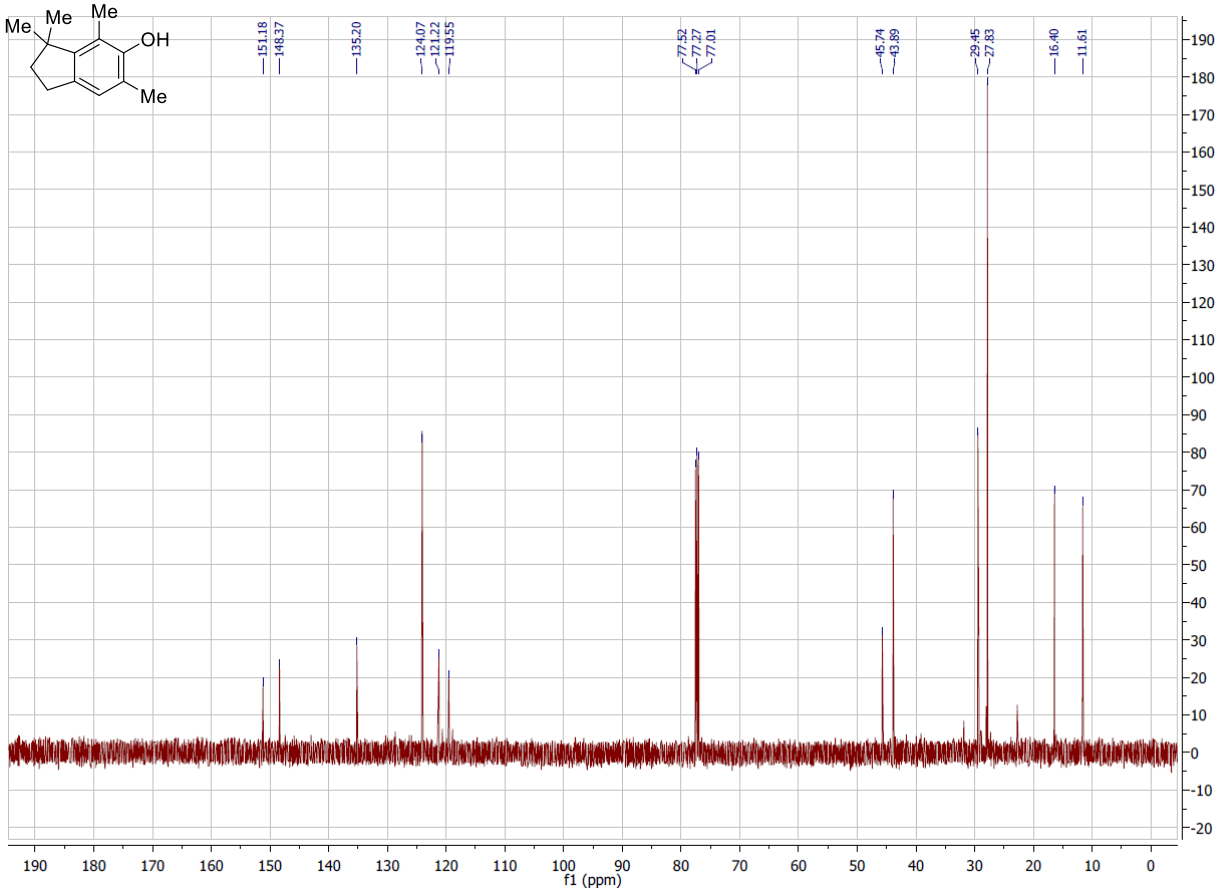
5-(3-Methyl-2-buten-1-yl)-1,4-benzodioxane (77f) ^{13}C NMR


14benzodioxolane_prenyl_13C_NMR.esp
CHLOROFORM-d
64.29
64.40
143.25
141.52
135.11
132.33
123.28
121.14
116.99
116.81
33.52
25.72
17.73
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
Chemical Shift (ppm)

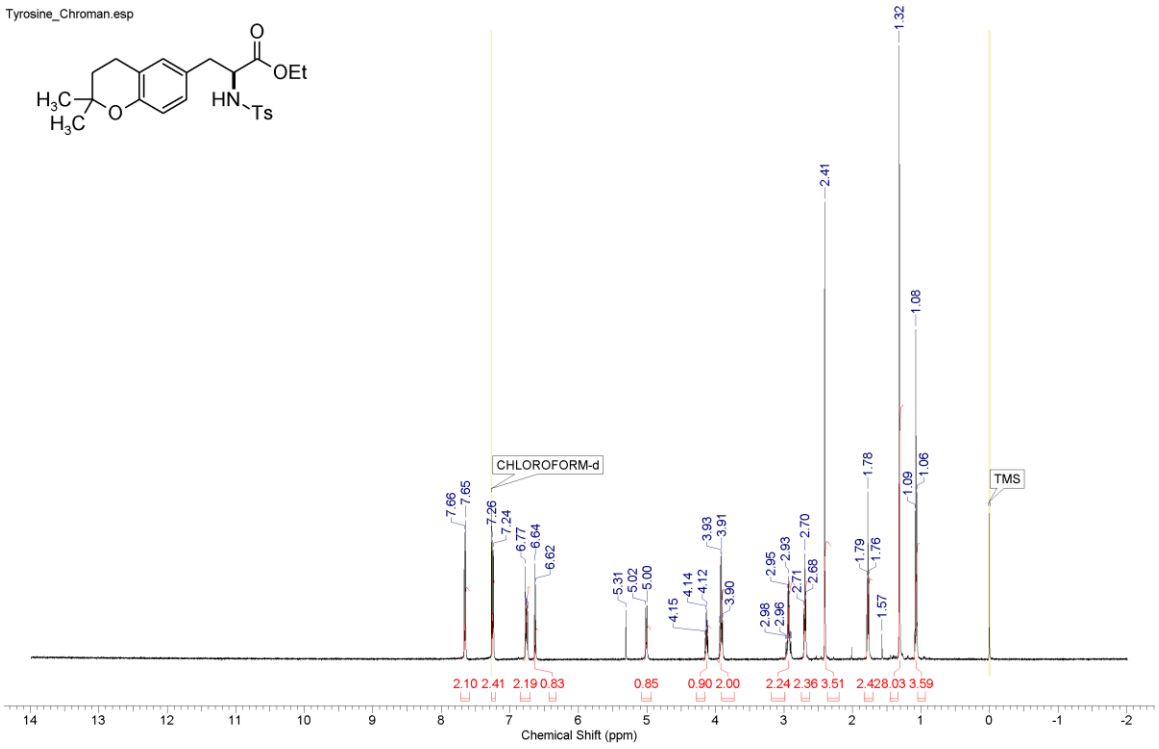
3,3,4,6-tetramethyl-2,3-dihydro-1H-inden-5-ol (78b), 1H NMR



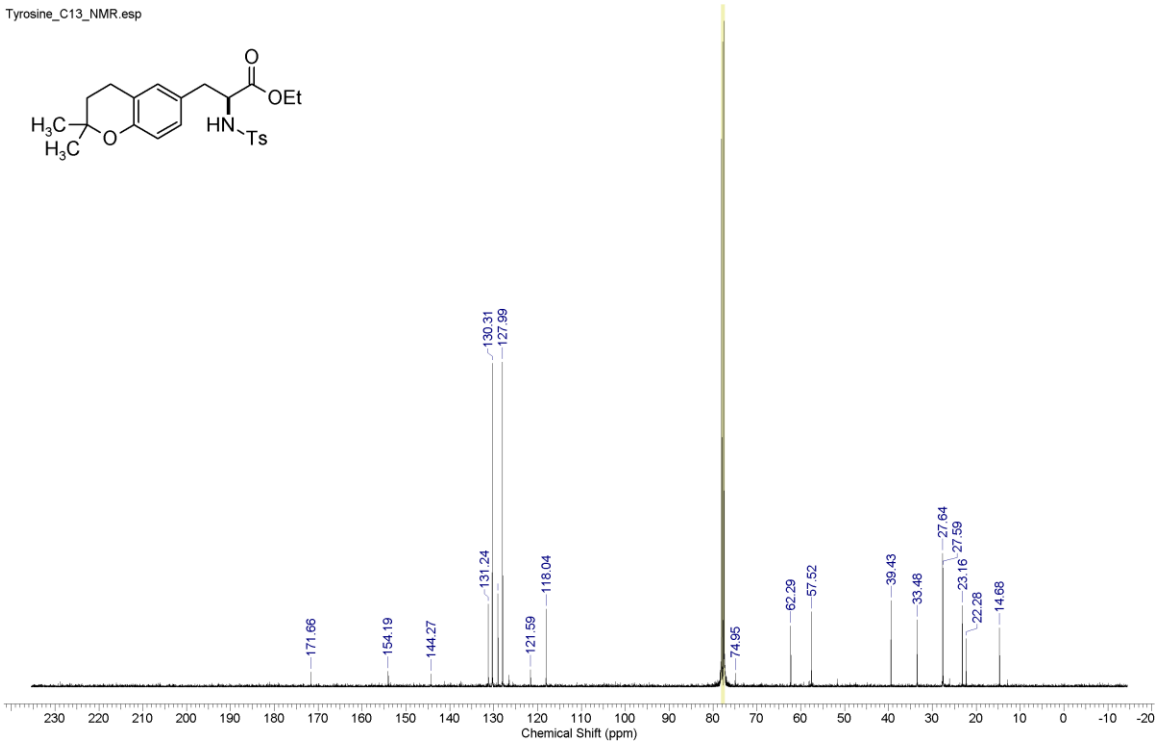
3,3,4,6-tetramethyl-2,3-dihydro-1H-inden-5-ol (78b), ^{13}C NMR



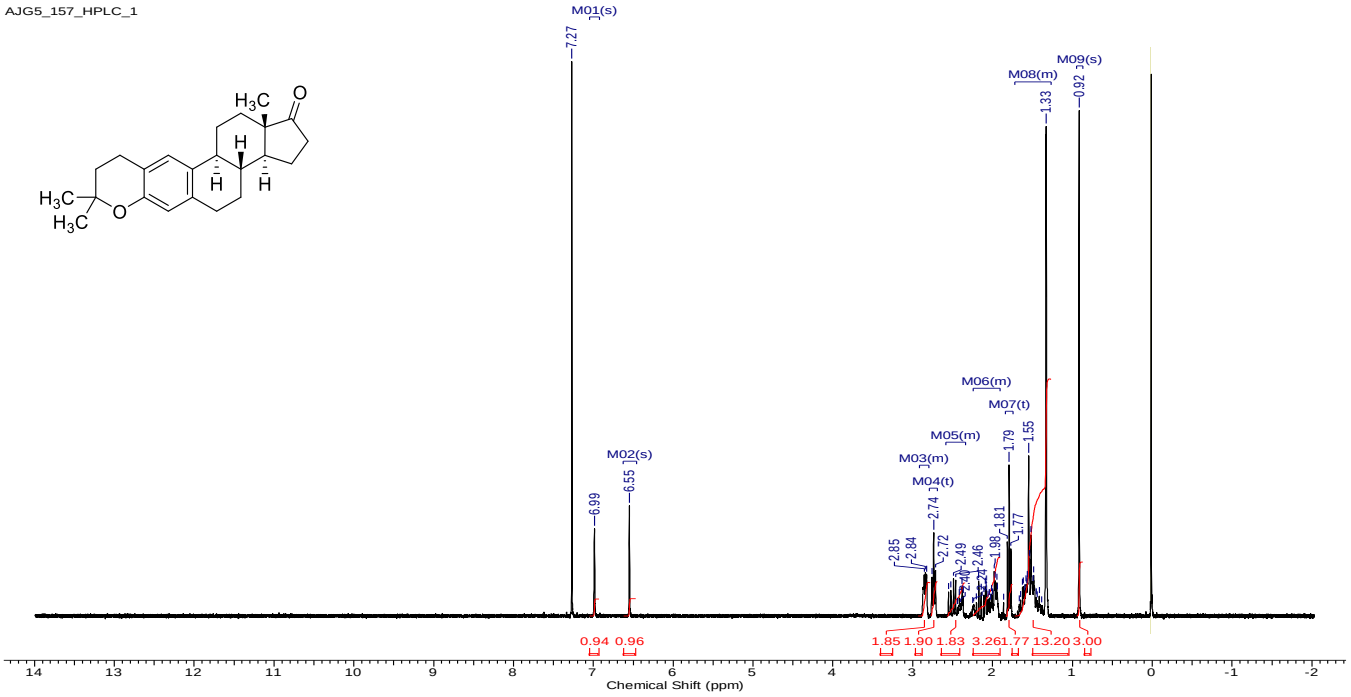
Ethyl (2S)-3-(2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-2-(4-methylbenzenesulfonamido)propanoate (80a) ^{1}H NMR



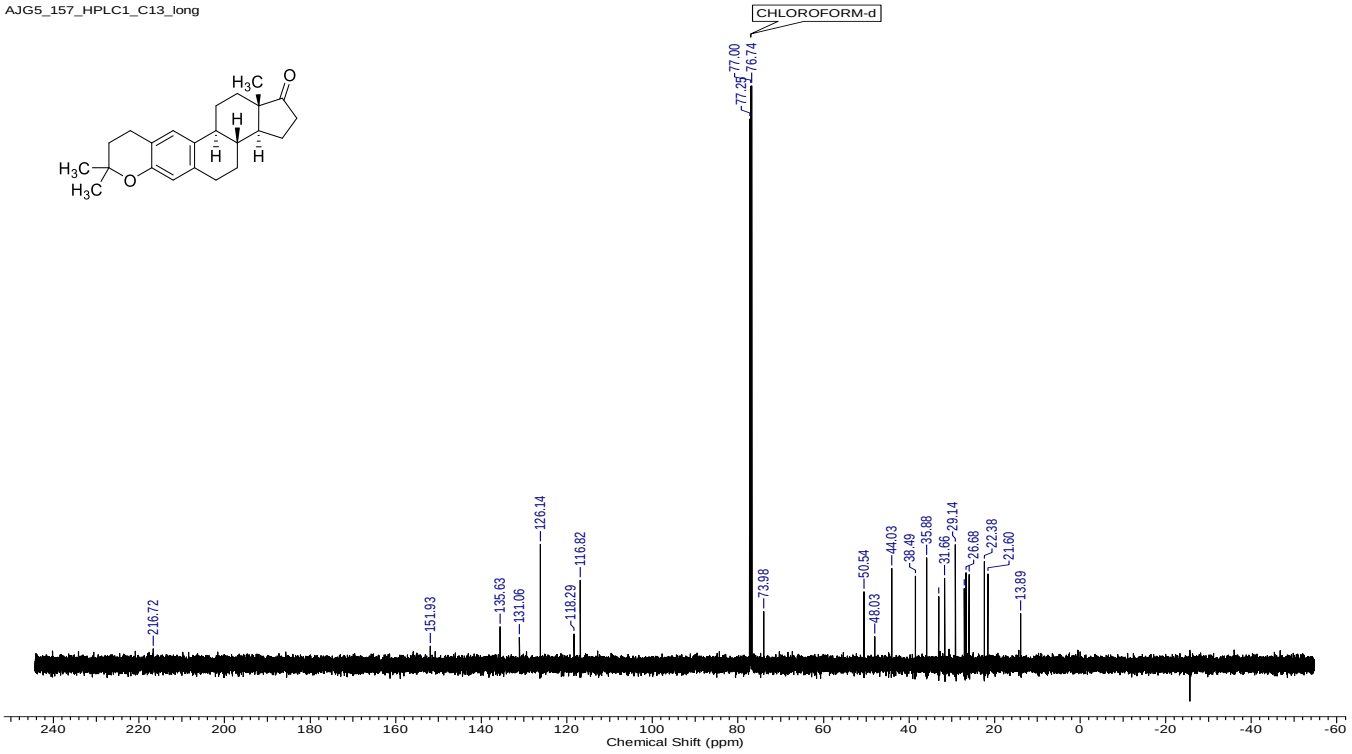
Ethyl (2S)-3-(2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-2-(4-methylbenzenesulfonamido)propanoate (80a) ^{13}C NMR



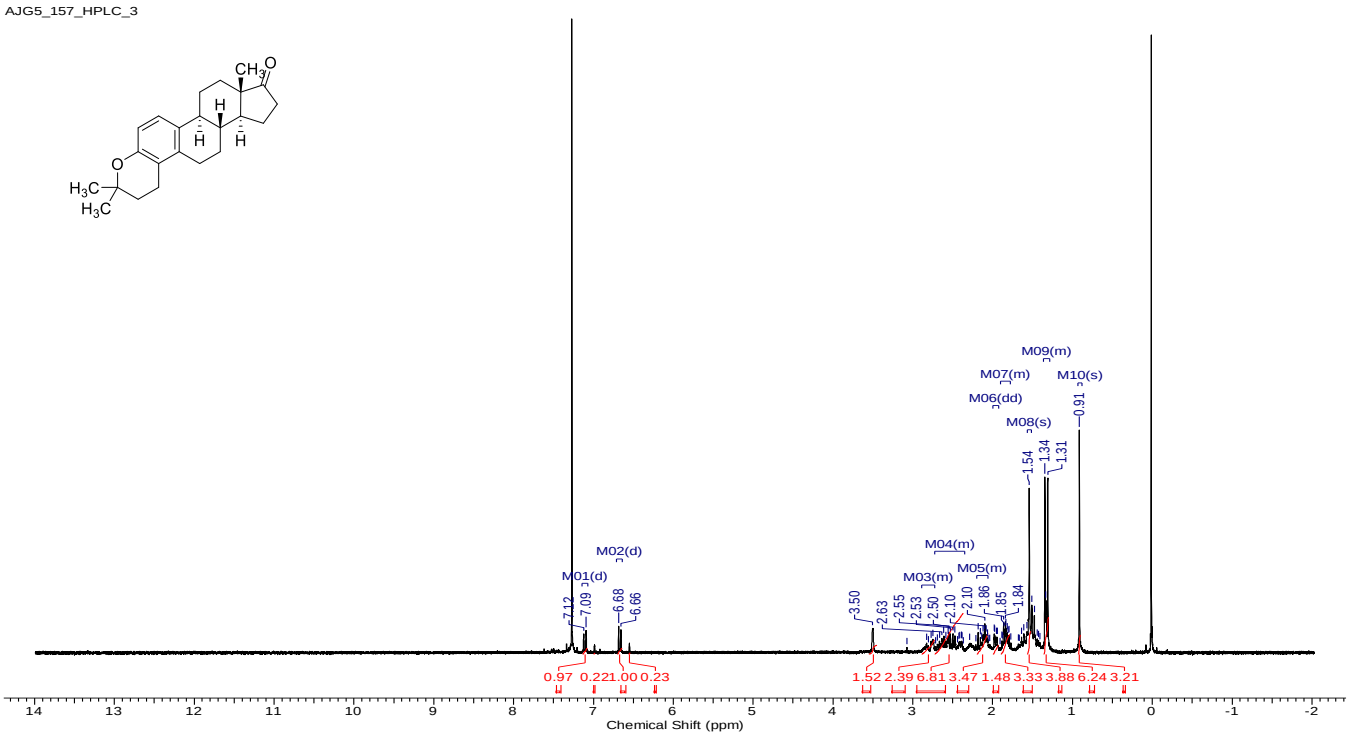
(3aS,3bR,11bS,13aS)-8,8,13a-trimethyl-3,3a,3b,4,5,8,9,10,11b,12,13,13a-dodeca-hydrocyclopenta[5,6]naphtho[1,2-g]chromen-1(2H)-one, (80b) ^{1}H NMR



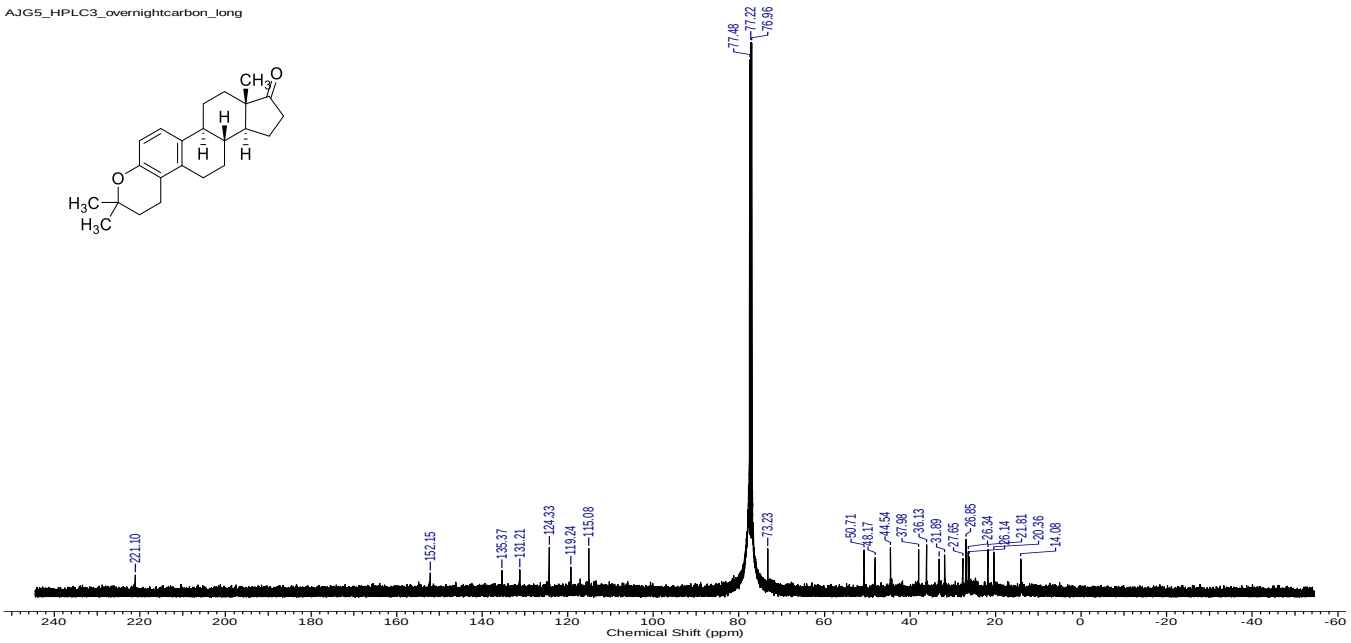
(3a*S*,3b*R*,11b*S*,13a*S*)-8,8,13a-trimethyl-3,3a,3b,4,5,8,9,10,11b,12,13,13a-dodecahydrocyclopenta[5,6]naphtho[1,2-g]chromen-1(2*H*)-one, (80b) ^{13}C NMR



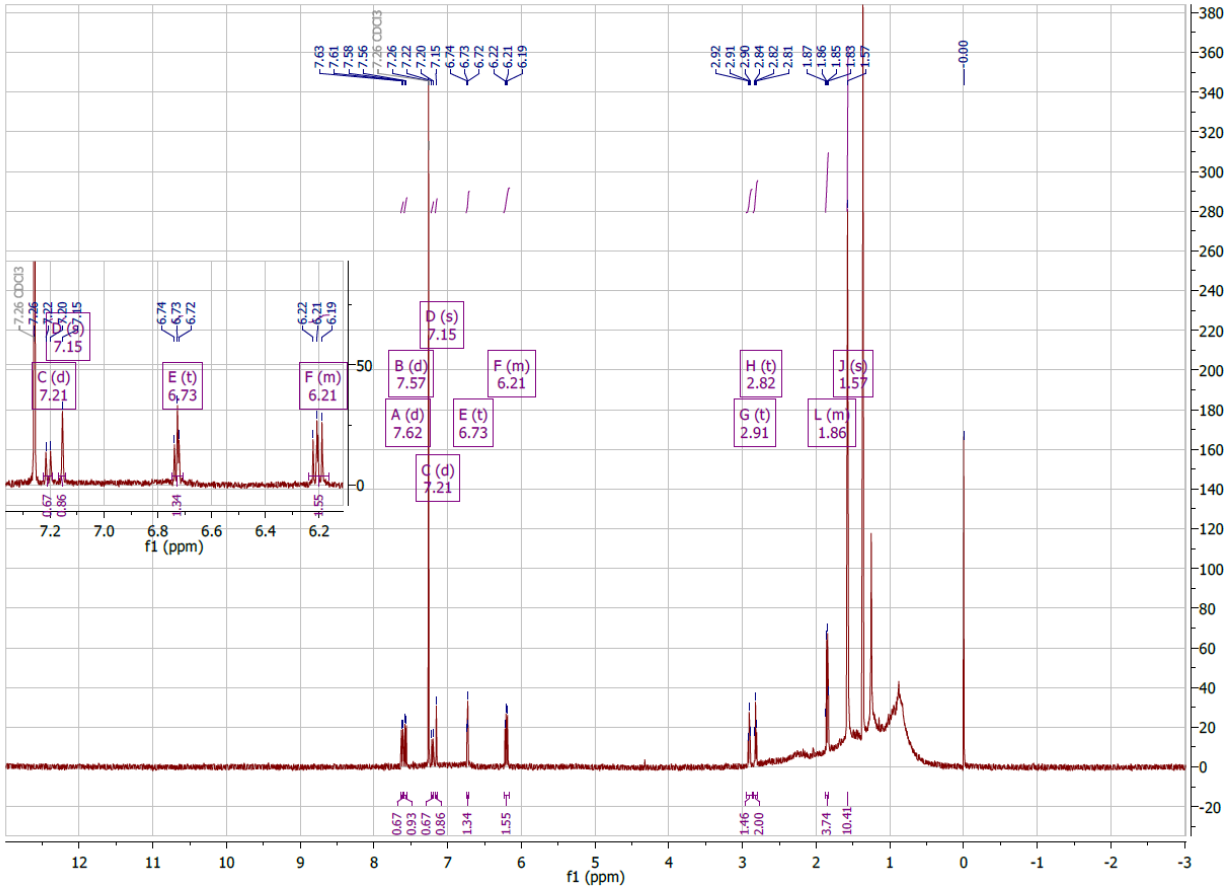
(6b*S*,8a*S*,11a*S*,11b*R*)-3,3,8a-trimethyl-2,3,6b,7,8,8a,10,11,11a,11b,12,13-dodecahydrocyclopenta[5,6]-naphtho[2,1-f]chromen-9(1*H*)-one, (80b) ^{1}H NMR



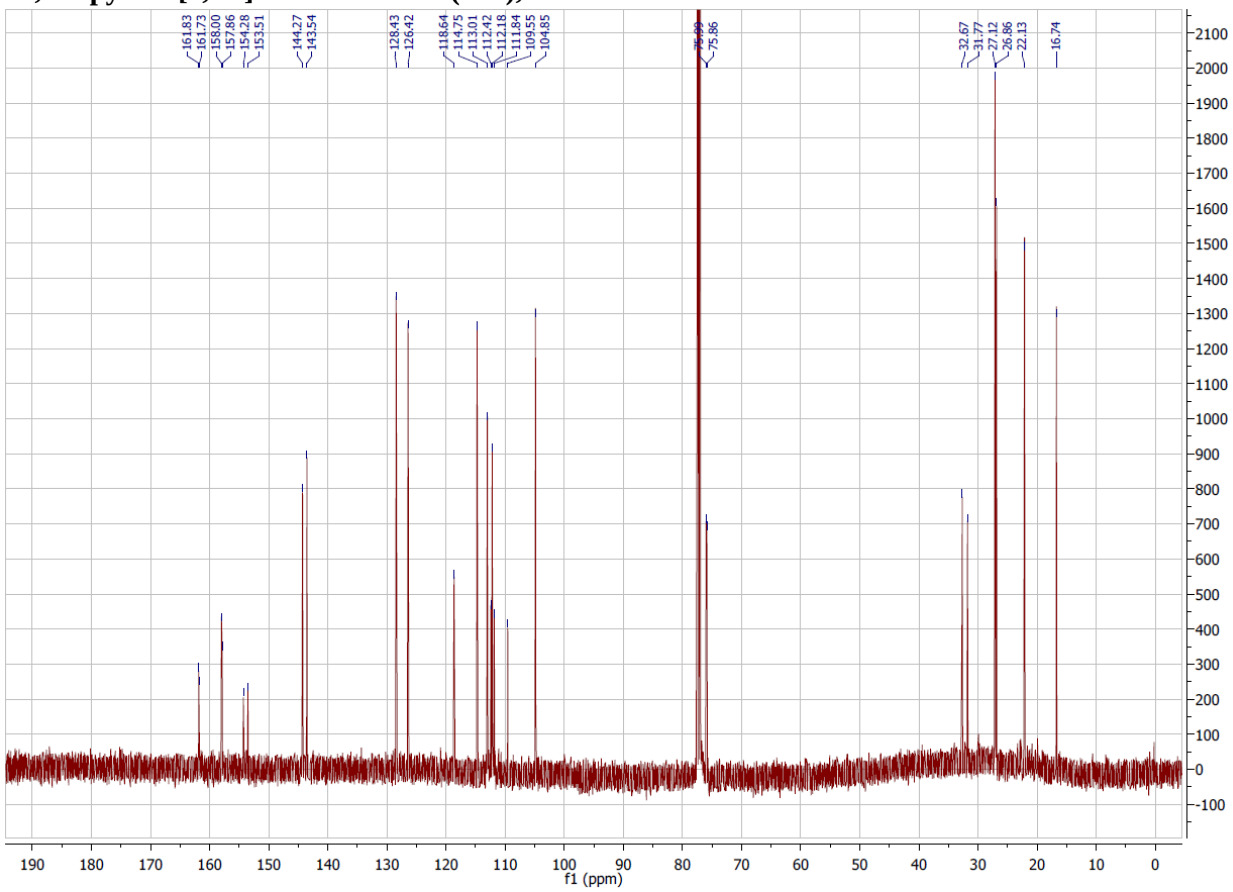
(6b*S*,8a*S*,11a*S*,11b*R*)-3,3,8a-trimethyl-2,3,6b,7,8,8a,10,11,11a,11b,12,13-dodecahydrocyclopenta[5,6]-naphtho[2,1-f]chromen-9(1*H*)-one, (80b), ^{13}C NMR



8,8-dimethyl-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-one (81a) and 8,8-dimethyl-9,10-dihydro-2H,8H-pyrano[2,3-f]chromen-2-one (81b), ^{1}H NMR



8,8-dimethyl-7,8-dihydro-2H,6H-pyrano[3,2-g]chromen-2-one (81a) and 8,8-dimethyl-9,10-dihydro-2H,8H-pyrano[2,3-f]chromen-2-one (81b), ^{13}C NMR

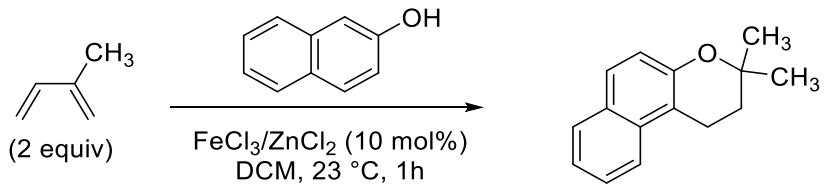


APPENDIX F

EXPERIMENAL FROM

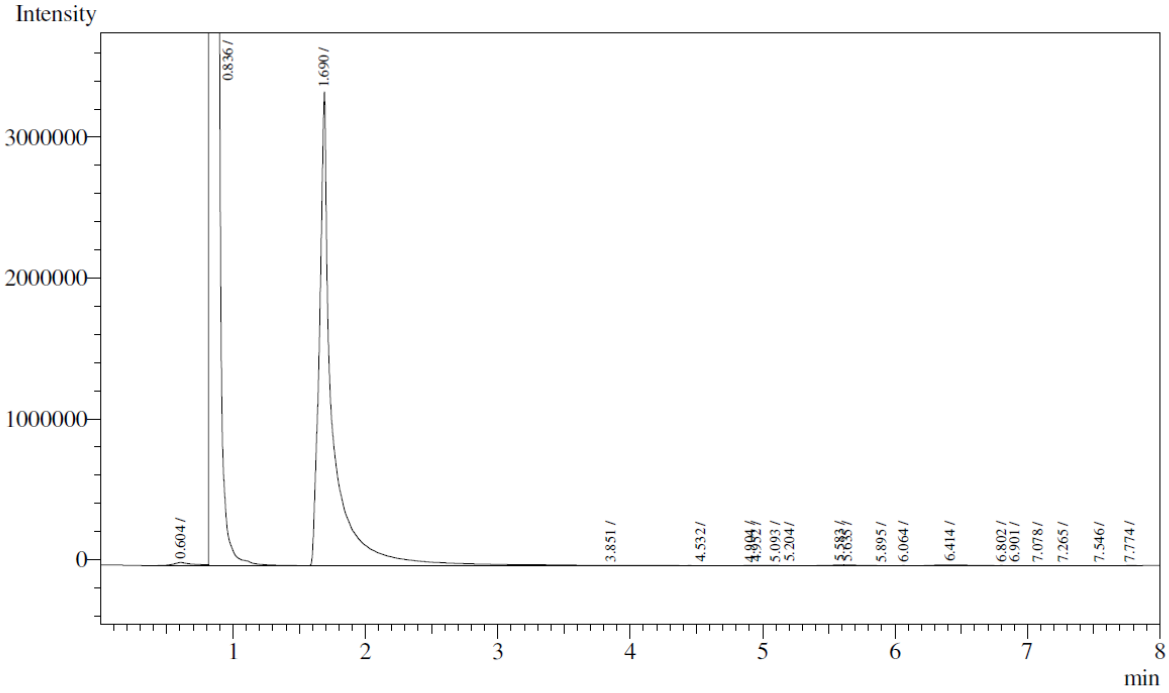
UNDERGRADUATE PRENYLATION LAB

General Procedure for the Prenylation of 2-Naphthol in an Undergraduate Teaching Organic Laboratory



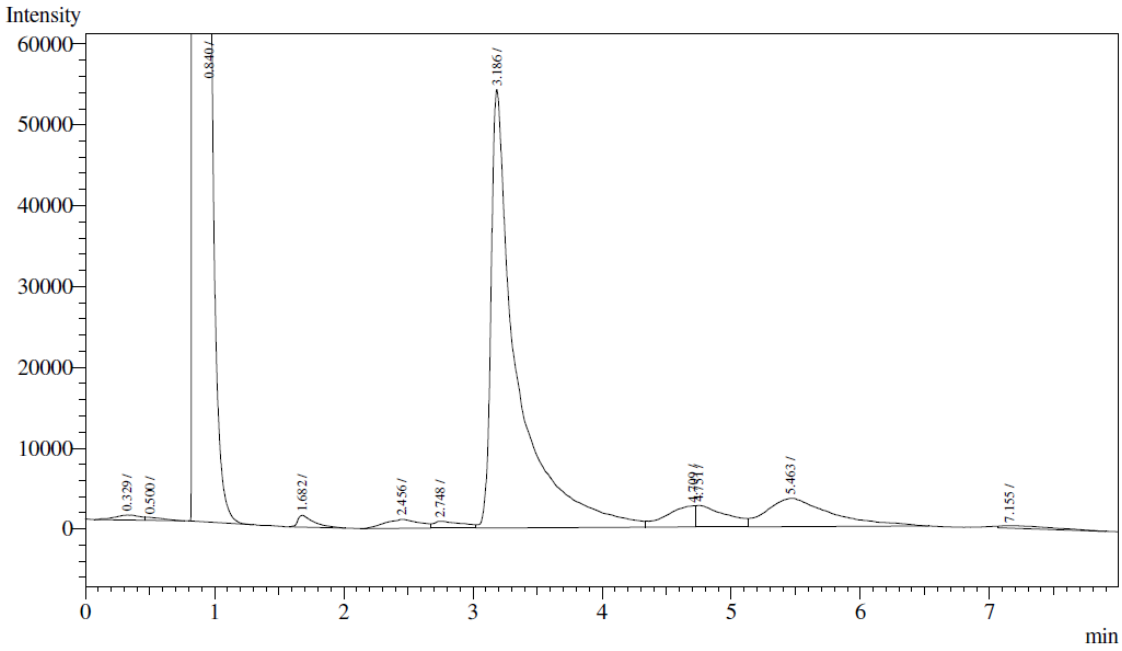
Weigh out 0.72 g of 2-naphthol. Transfer the solid into a 25-mL scintillation vial. Carefully Transfer the iron chloride (81.1 mg, 0.5 mmol) and zinc chloride (68.2 mg, 0.5 mmol) which has been pre-measured by the Teaching Assistants and stored in smaller 1-mL scintillation vials prior to the experiment. Place a Teflon-coated stir-bar in the bottom of the vial, and then transfer 6.0 mL of DCM to the vial. Allow the mixture to stir at room temperature while an ice bath is prepared. After the 2-naphthol has mostly dissolved, place the vial in the ice bath and cool the mixture. Once the reaction is cool, transfer 1.0 mL of isoprene to the vial and remove the vial from the ice bath. Stir the reaction at room temperature for one hour. After an hour of stirring, remove the vial and prepare a pad of silica gel on a Buckner funnel using 15-25 g of silica and 15-25 mL of DCM. Filter the reaction through the pad silica gel, collecting the liquid. A gentle, brief (1-2 seconds) of suction using the vacuum line can be used to collect more liquid. Use 4-5 drops of this liquid to prepare your GC sample and dilute with DCM (your TA can assist with this step). The remaining liquid is transferred to a tared watch glass and left in the back of the hood to help evaporate the remaining DCM. The weight of the final product is recorded and the final yield is calculated. Two samples from each class are taken for NMR analysis to validate the correct regioisomer was obtained. All data is posted online after the class in order to complete a lab write-up.

GC Plot of 2-naphthol:



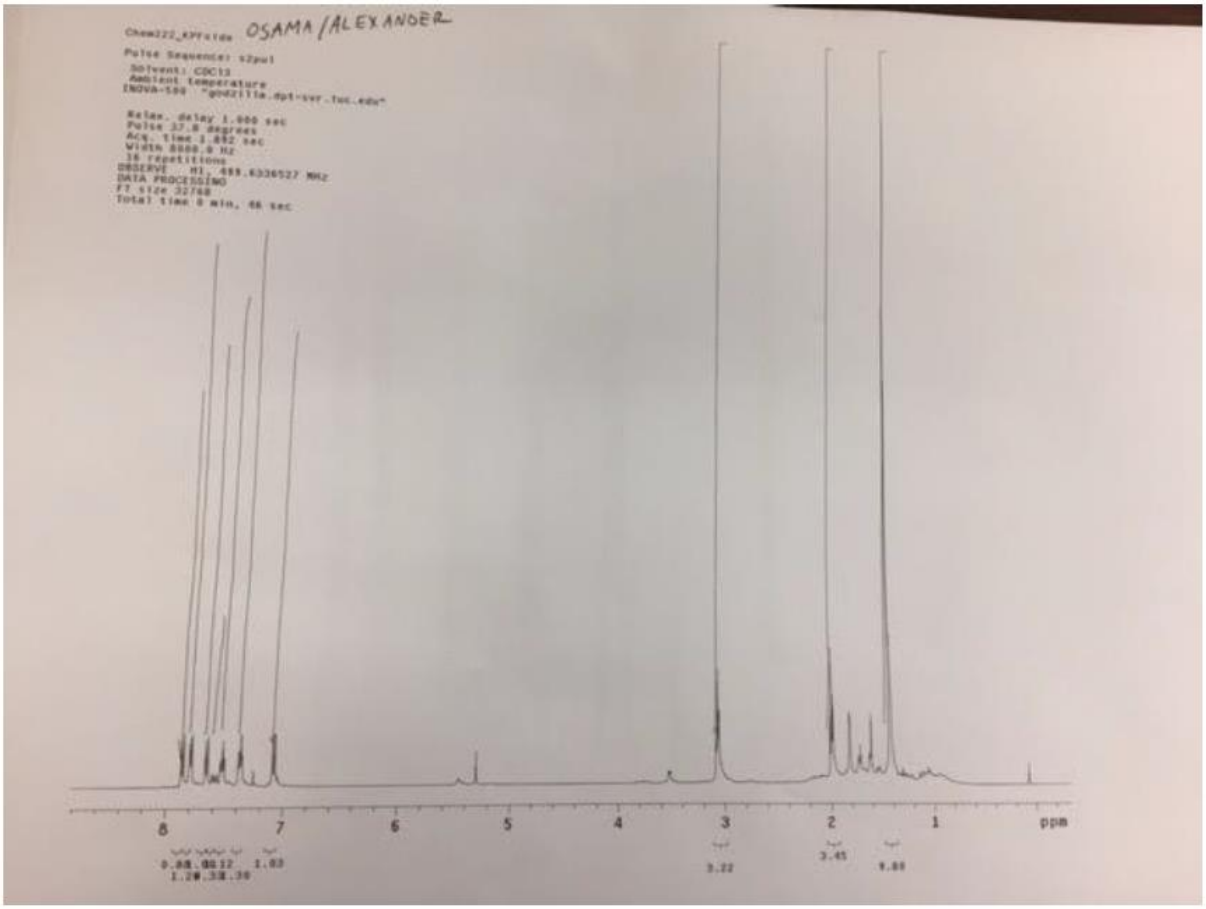
Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	0.604	226748	21863	0.000				
2	0.836	415506814	178737595	0.000		V		
3	1.690	23120124	3330773	0.000		SV		
4	3.851	2441	483	0.000		T		
5	4.532	1039	295	0.000		TV		
6	4.904	8819	1586	0.000				
7	4.952	8905	1538	0.000		V		
8	5.093	7206	1256	0.000		V		
9	5.204	2725	517	0.000		V		
10	5.583	38127	4013	0.000		V		
11	5.635	40904	3939	0.000		V		
12	5.895	4225	983	0.000		V		
13	6.064	6633	1083	0.000		V		
14	6.414	105897	5392	0.000		V		
15	6.802	5140	1178	0.000		V		
16	6.901	1498	511	0.000		V		
17	7.078	1144	319	0.000				
18	7.265	1212	300	0.000		V		
19	7.546	1974	507	0.000				
20	7.774	2916	632	0.000				
Total		439094491	182114763					

GC plot of student-prepared reaction sample:

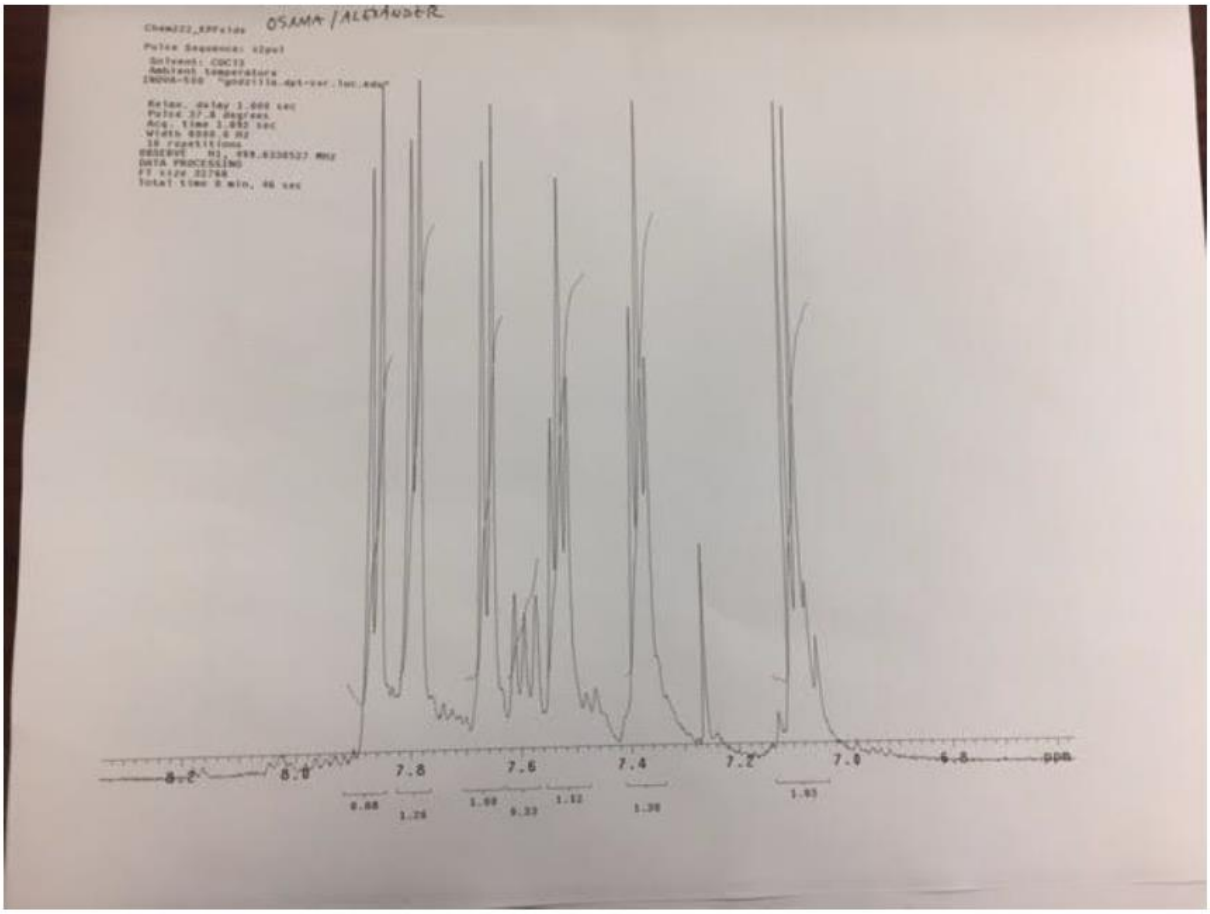


Peak#	Ret.Time	Area	Height	Conc.	Unit	Mark	ID#	Cmpd Name
1	0.329	8405	605	0.000				
2	0.500	3689	379	0.000		V		
3	0.840	125839579	47662524	0.000				
4	1.682	12654	1455	0.000				
5	2.456	20660	1127	0.000				
6	2.748	13198	846	0.000		V		
7	3.186	754976	54211	0.000		V		
8	4.709	40080	2621	0.000		V		
9	4.751	42860	2669	0.000		V		
10	5.463	120522	3515	0.000		V		
11	7.155	9551	312	0.000		V		
Total		126866174	47730264					

^{1}H NMR of student-prepared final product (full spectrum):



^{1}H NMR of student-prepared final product (spectral zoomed in on aromatic region):



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