Lewis and Brønsted acid-catalyzed reactions of alcohol pro-electrophiles as novel synthetic strategies for C-X (X = C, N, O, S) bond formation

Zhang, Xiaoxiang

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**LEWIS AND BRØNSTED ACID-CATALYZED
REACTIONS OF ALCOHOL PRO-ELECTROPHILES AS
NOVEL SYNTHETIC STRATEGIES FOR C-X (X = C, N, O,
S) BOND FORMATION**

ZHANG XIAOXIANG

School of Physical and Mathematical Sciences

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ABSTRACT

The work in this thesis was undertaken at the Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University from August 2007 to June 2011 under the supervision of Asst. Prof. Philip Wai Hong Chan.

The work of this thesis has been directed toward establishing new Lewis and Brønsted acid-catalyzed reactions of alcohol pro-electrophiles as novel synthetic strategies for C–X (X = C, N, O, S) bond formation. This thesis is divided into three parts:

- Part I consists of Chapter I, which gives an introduction of Lewis and Brønsted acid catalyzed reactions of alcohol pro-electrophiles, particularly those containing a pendant activated alcohols such as allylic, propargylic, benzylic and cyclopropylmethyl functional group.
- Part II describes the new strategies developed for C–X (X = C, N, O, S) bond formation employing alcohols as pro-electrophiles. Chapter II reports iron(III) chloride catalyzed direct nucleophilic α -substitution of Morita-Baylis-Hillman alcohols with alcohols, arenes, 1,3-dicarbonyl compounds, and thiols. In Chapter III, a new method to indenols that relied on ytterbium(III) triflate catalyzed tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols is described. Chapter IV detailed the synthesis of highly substituted indene derivatives *via* Brønsted acid catalyzed intramolecular Friedel-Crafts cyclization of homoallylic alcohols. In Chapter V, a novel strategy to di- and trisubstituted thiazoles *via* Brønsted acid catalyzed cyclization of propargylic alcohols with thioamides was described. Chapter VI

disclosed an efficient method for the preparation of di- and trisubstituted 2-aryloxazoles *via* ytterbium(III) triflate catalyzed cyclization of tertiary propargylic alcohols with aryl amides.

- Part III contains the experimental section (Chapter VII) and references section (Chapter VIII) pertaining to this thesis.

PUBLICATIONS

1. “Efficient Synthesis of Di- and Trisubstituted 2-Aryloxazoles *via* Ytterbium(III) Triflate Catalyzed Cyclization of Tertiary Propargylic Alcohols with Aryl Amides”, **Zhang, X.**; Teo, W. T.; Chan, P. W. H. *J. Organomet. Chem.* **2011**, 696, 331 (*highlighted in SYNFACTS, Synfacts* **2011**, 3, 250).
2. “Brønsted Acid-Catalyzed Cyclization of Propargylic Alcohols with Thioamides. Facile Synthesis of Di- and Trisubstituted Thiazoles”, **Zhang, X.**; Teo, W. T.; Sally; Chan, P. W. H. *J. Org. Chem.* **2010**, 75, 6290 (*highlighted in SYNFACTS, Synfacts* **2010**, 12, 1345).
3. “Ytterbium(III) Triflate-Catalyzed Tandem Friedel-Crafts Arylation/Hydroarylation of Propargylic Alcohols with Phenols as an Expedient Route to Indenols”, **Zhang, X.**; Teo, W. T.; Chan, P. W. H. *Org. Lett.* **2009**, 11, 4990.
4. “Iron(III) Chloride-Catalysed Direct Nucleophilic α -Substitution of Morita-Baylis-Hillman Alcohols with Alcohols, Arenes, 1,3-Dicarbonyl Compounds, and Thiols”, **Zhang, X.**; Rao, W.; Sally; Chan, P. W. H. *Org. Biomol. Chem.* **2009**, 7, 4186 (*featured as the inside front cover by invitation from the editor and reviewers*).
5. “Iodine-Catalyzed Allylic Alkylation of Thiols with Allylic Alcohols”, **Zhang, X.**; Rao, W.; Chan, P. W. H. *Synlett* **2008**, *Special Issue*, 2204 (*issue dedicated to Prof. Sir J. E. Baldwin’s 70th birthday*).
6. “Ytterbium(III) Triflate-Catalyzed Amination of 1-Cyclopropylprop-2-yn-1-ols as an Expedient Route to Conjugated Enynes”, Rao, W.; **Zhang, X.**; Sze, E. M. L.; Chan, P. W. H. *J. Org. Chem.* **2009**, 74, 1740.

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7. “Gold-and Silver-Catalyzed allylic alkylation of 1,3-dicarbonyl compounds with allylic alcohols” Kothandaraman, P.; Rao, W.; **Zhang, X.**; Chan, P. W. H. *Tetrahedron* **2009**, 65, 1833 (*invited paper for the Symposia-In-Print series on “Catalysis using Gold Complexes*).

ABBREVIATIONS

ACS	American Chemical Society
Ar	aryl
BINAPHANE	1,2-bis[(<i>R</i>)-4,5-dihydro-3 <i>H</i> -binaphtho (1,2- <i>c</i> :2',1'- <i>e</i>)phosphino]benzene
Bu	butyl
Bn	benzyl
DBSA	dodecylbenzenesulfonic acid
DCE	1,2-dichloroethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNBSA	2,4-dinitrobenzenesulfonic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EWG	electron withdrawing group
Et	ethyl
h	hour
HMPA	hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
<i>i</i> Pr	isopropyl
LDA	lithium diisopropylamide
MBH	Morita-Baylis-Hillman
Me	methyl
m.p.	melting point

NMR	nuclear magnetic resonance
Nu	nucleophile
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
OE _t	ethoxyl
OMe	methoxyl
OTf	trifluoromethanesulfonate
PG	protecting group
Ph	phenyl
<i>p</i> -TsOH·H ₂ O	<i>p</i> -toluenesulfonic acid monohydrate
r.t.	room temperature
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
α	alpha
β	beta
γ	gamma
δ	delta

Chapter I. Alcohol Pro-electrophiles in Lewis and Brønsted Acid Catalysis

1.1 Introduction

Lewis and Brønsted acids are among one of the most widely used catalysts in organic synthesis.¹⁻⁶ Indeed, this is reflected by their use in a myriad of C–X (X = C, N, O, S) bond forming and breaking reactions, such as functional group protections/deprotections, alkylations, isomerizations and acylations.² Within this field of chemistry, a synthetic strategy that has attracted an increasing amount of attention has been reactions of alcohol pro-electrophiles in combination with ecologically friendly Lewis and Brønsted catalysts such as Au, Ag, Cu, Fe, *p*-TsOH·H₂O and TfOH at low catalyst loadings.³ In 2005, this new concept of C–OH bond activation was considered as one key approach in the integration of green chemistry into the pharmaceutical industry by the ACS Green Chemistry Institute and global pharmaceutical corporations.⁴ The advantages of this synthetic approach were noted to the wide availability of the alcohol substrate and its ease of preparation that provided the possibility to introduce a wide range of substitution patterns. Added to this is the formation of a quaternary carbon centre by utilizing tertiary alcohols and formation of H₂O as the only side product.⁵ Although this type of electrophilic activation is extremely attractive, the methodology still suffers from drawbacks such as poor reactivity at low temperatures or in the absence of additives due to the poor leaving-group of the hydroxy group.⁶ Currently, one solution to these problems has been to employ activated alcohols whose structure contain a π -system or “sp² equivalent” adjacent to the hydroxy group. Typically, this has been in the form of allylic, propargylic, benzylic and cyclopropylmethyl functional groups that can stabilize the putative carbon cationic species formed in these reactions and thus subsequent transformations possible.⁶ The focus of this introduction is on recent

developments in this field of catalytic C–X (X = C, N, O, S) bond formation that employs unsaturated alcohols in the presence of ecologically friendly Lewis and Brønsted acids as the catalyst.

1.2 Allylic alcohols

One of the most powerful and efficient methods to introduce a C₃ unit is the allylic alkylation reaction.⁸ The advantage of this synthetic approach is the retention of the C=C bond in the product that can act as a handle for further functional group transformations. First described in 1965, one synthetic strategy that has been often relied upon to introduce this functional group is the Tsuji-Trost reaction (Scheme 1.1).⁹ However, a drawback of this C–C bond formation is the generation of waste products resulting from displacement of the leaving group on treating with a catalyst and/or nucleophile.¹⁰ Typically, the identity of this byproduct is the hydrogen halide, carboxylate, carbonate, triflate or phosphate. Given the highly acidic and thus corrosive nature of these Brønsted acid waste products, recent attention has been focused on developing Tsuji-Trost-type allylic allylations that make use of ecologically benign and atom economical allylic alcohols as the electrophile.⁶ Although this concept is not new⁷, it is still attractive.

Scheme 1.1 Tsuji-Trost allylic alkylations.

As early as 1997, Fukuzawa and co-workers described Sc(OTf)₃ catalyzed Friedel-Crafts alkylation reaction of allylic alcohols **2** with benzene **1** (Table 1.1, entry 1).¹¹ The corresponding allylbenzene derivatives **3** and/or **4** were obtained in

48-95% yield with minimal side products detected in these reactions. The less-substituted allylic carbon was always attacked by the benzene nucleophile. However, only a few aliphatic allylic alcohols were examined and benzene was used as both the nucleophile and solvent at 115-120 °C. In this work, it was reported that there was no desired product when cyclic allylic alcohols were employed as the substrate under the reported conditions.

Table 1.1 Lewis and Brønsted acid catalyzed intermolecular allylic alkylations.

Entry	Catalyst	Yield (%)	Ref
1	Sc(OTf) ₃	48-95	11
2	AlCl ₃	50-90	12
3	AuCl ₃	50-99	13
4	(Ph ₃ P)AuNTf ₂	33-91	14
5	C ₆ F ₅ B(OH) ₂	0-99	15
6	Ca(NTf ₂) ₂	0-88	16
7	<i>p</i> -TsOH·H ₂ O	55-84	18
8	TfOH	55-95	19
9	calix[<i>n</i>]arene sulfonic acid	60-94	20

Following this pioneer work, a number of Lewis and Brønsted acid catalysts were shown to catalyze this type of Friedel-Crafts alkylation with allylic alcohols. In 2008, Liu and co-workers reported AlCl₃ mediated C–C bond forming reactions of

α -hydroxyketene-*S,S*-acetals with various arenes (Table 1.1, entry 2).¹² In this work, Morita-Baylis-Hillman (MBH) alcohols with an electron-withdrawing group on the C=C bond were regarded as a special type of allylic alcohol as they could undergo further intramolecular cyclization after Friedel-Crafts alkylation to provide a series of bioactive and pharmacologically important compounds such as the dihydrocoumarins.

Recently, gold complexes have come under increasing scrutiny as efficient catalysts for Friedel-Crafts allylic alkylations. In 2008, Chan and co-workers disclosed AuCl₃ catalyzed allylic alkylation of aromatic and heteroaromatic compounds with allylic alcohols (Table 1.1, entry 3).¹³ In this work, the reaction was found to proceed well in the presence of AuCl₃ as the catalyst, affording the corresponding products in up to 99% yield and with good to excellent regioselectivity at room temperature. One year later, Liu developed a domino method for the preparation of arylated (*Z*)-enones and -enals from enynols and furans in the presence of the Gagosz catalyst (Ph₃P)AuNTf₂ (Table 1.1, entry 4).¹⁴ In this work, the gold complex was regarded as an efficient catalyst for both the Friedel-Crafts alkylation and furan/alkyne cyclization steps, providing the corresponding adducts in 33-91% yield.

In 2010, Cubbin and co-workers reported a C₆F₅B(OH)₂ catalyzed Friedel-Crafts reaction of allylic alcohols with electron-rich arenes and heteroarenes (Table 1.1, entry 5).¹⁵ The desired products were obtained in up to 99% yield in the presence of 10 mol% of the catalyst. The advantage of this method was the ability of C₆F₅B(OH)₂ to efficiently complex with sterically hindered alcohols. The boron catalyst was also shown to be soluble in a variety of organic solvents, stable to air and moisture, and easily recovered from complex mixtures *via* a simple basic extraction.

In the same year, Niggemann and co-workers reported $\text{Ca}(\text{NTf}_2)_2$ catalyzed alkylation of electron-rich arenes using allylic alcohols at room temperature, providing the corresponding adducts in up to 88% yield (Table 1.1, entry 6).¹⁶ In this work, the transformation of allylic alcohols could not proceed without the presence of Bu_4NPF_6 as an additive. Notably, allylic alcohols not activated by an additional aryl substituent at the α -position to the hydroxy group, were shown to efficiently undergo intermolecular Friedel-Crafts allylic alkylation reactions, which was rarely seen in previous methods catalyzed by other Lewis acid catalysts.¹⁷

Not only Lewis acids but also Brønsted acids have been recently shown to be efficient catalysts in the Friedel-Crafts allylic alkylation reaction. In 2006, Sanz and co-workers reported $p\text{-TsOH}\cdot\text{H}_2\text{O}$ catalyzed direct Friedel-Crafts allylic alkylation of various arenes and indoles with high selectivity and yields (Table 1.1, entry 7).¹⁸ The reactions could be carried out without the need of an inert atmosphere in an open flask using analytical grade solvents. This metal-free method provided an environmentally friendly, clean and low cost replacement for metal catalysts, which made large scale reactions a possibility. One year later, Bras and co-workers expanded this reaction by employing various electron-rich arenes in the presence of TfOH (Table 1.1, entry 8).¹⁹ This reaction performed well in the absence of a solvent, and afforded the corresponding products in up to 95% yield.

Friedel-Crafts alkylations with allylic alcohols in water has also been explored as another approach to advancing this area of green chemistry. In 2008, Wang and co-workers described Friedel-Crafts allylic alkylation of allylic alcohols in water using calix[*n*]arene sulfonic acid bearing pendant aliphatic chains as recyclable surfactant-type Brønsted acid as an efficient catalyst (Table 1.1, entry 9).²⁰ Using this synthetic method, a variety of allylated aromatic and heteroaromatic products were

obtained in 60-94% yield. A highlight of this work was the ability to recover the Brønsted acid surfactant from water up to seven times and its reuse without significant decrease of catalytic ability.

In 2006, Baba and co-workers reported direct allylic allylation of indoles **6** with allylic alcohols **5** catalyzed by InCl_3 (Table 1.2, entry 1).²¹ The C-3 alkylated products **7** and/or **8** were obtained in 64-78% yield and with high regioselectivity. In this work, the regioisomers obtained through 2-alkylation or allylic amination were not observed. However, the scope of this approach was not extensively explored as only two examples were investigated.

Yadav and co-workers subsequently showed that the generality of indole allylic allylation reaction with allylic alcohols could be expanded by employing InBr_3 as catalyst (Table 1.2, entry 2).²² At about the same time, FeCl_3 was also described by Jana and co-workers to be efficient catalyst in the regioselective C-3 allylic alkylation of indoles, furnishing the product in 56-98% yield (Table 1.2, entry 3).²³

Table 1.2 Lewis acid catalyzed Friedel-Crafts alkylation with allylic alcohols **5**.

Entry	Catalyst	Yield (%)	Ref
1	InCl_3	64-78	21
2	InBr_3	85-93	22
3	FeCl_3	56-98	23

The intramolecular Friedel-Crafts allylic alkylation was shown by Li and co-workers to be an efficient strategy for the construction of indene derivatives (Table 1.3, entry 1).²⁴ By employing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the catalyst, the cyclization of a variety of allylic alcohols of the type **9** was reported to give the corresponding 3-iodo-1*H*-indene derivatives **11** ($\text{R}^2 = \text{I}$) in 55-90% yield under mild conditions, which are valuable compounds for constructing multi-aryl substituted indene derivatives through further Suzuki coupling reactions.

Table 1.3 Lewis and Brønsted acid catalyzed intramolecular Friedel-Crafts allylic alkylation.

Entry	Catalyst	Yield (%)	Ref
1	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	55-90	24
2	$\text{TsOH} \cdot \text{H}_2\text{O}$	80-97	25
3	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	56-93	26

In the same year, Liu and co-workers described the preparation of highly substituted indenenes and spiroindenenes *via* intramolecular cyclization of arylated allylic alcohols **9** in the presence of $\text{TsOH} \cdot \text{H}_2\text{O}$ (Table 1.3, entry 2).²⁵ Following this work, Zhou and co-workers reported a convenient and efficient method for the synthesis of substituted indene derivatives from aryl substituted allylic alcohols **10** (Table 1.3,

entry 3).²⁶ This reaction was demonstrated to perform well in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst, providing a variety of substituted indene derivatives in up to 93% yield.

The intramolecular Friedel-Crafts 6-*exo-trig* cyclization of allylic alcohols was also reported by two groups (Table 1.3). In 2008, Nishizawa and co-workers described 6-*exo-trig* arylene cyclization of allylic alcohols **12** catalyzed by $\text{Hg}(\text{OTf})_2$ at a low catalyst loading of 0.5 mol% (Table 1.3, entry 1).²⁷ The cyclized 6-membered ring products **15** were obtained with catalytic turnovers of up to 200 times. The reaction was shown to proceed *via* Friedel-Crafts cyclization of **12** to form an organomercuric intermediate **13** followed by activation of the allylic hydroxyl group by *in situ* formed TfOH to form a cationic species **14**. After that, demercuration regenerated the catalyst smoothly and afforded the products **15**. Although product yields up to 99% could be obtained, a drawback of the reaction was the toxic nature of the mercury salt even at a catalyst loading of 0.5 mol%.

Table 1.4 Lewis acid catalyzed intramolecular Friedel-Crafts 6-*exo-trig* cyclization of allylic alcohols.

Entry	[M]	X	Yield (%)	Ref
1	$\text{Hg}(\text{OTf})_2$	CH_2	30-99	27
2	AgOTf	CH_2 , NHTs, $\text{C}(\text{COOEt})_2$	53-90	28

A year later, the AgOTf catalyzed version of this reaction was developed by the group of Bandini and co-workers (Table 1.3, entry 2).²⁸ The reaction was shown not only to benefit from a less toxic Lewis acid catalyst but also without the need of a ligand. At a slightly higher catalyst loading of 10 mol%, the functionalized 1-vinyl-1,2,3,4-tetrahydronaphthalenes and a 4-vinyl-1,2,3,4-tetrahydroisoquinoline was obtained in up to 90% yield and with high levels of regiochemistry. The mechanism was proposed to be similar to that reported for the Hg(OTf)₂ catalyzed reactions.

In 2009, Bandini and co-workers showed allylic alcohols of the type **16** could undergo asymmetric intramolecular Friedel-Crafts 6-*exo-trig* cyclization (Scheme 1.2).²⁹ The polycyclic indolyl-containing products **17** were obtained in 52-87% yield and with up to 96% ee by using an efficient chiral gold catalyst, which was generated *in situ* from reaction of AuCl·Me₂S with the chiral ligand **18**. This is the first example of employing alcohols in the direct catalytic asymmetric Friedel-Crafts allylic alkylation reaction.

Scheme 1.2 Gold catalyzed enantioselective Friedel-Crafts allylic alkylation of substituted indoles.

In 2010, the Bandini group expanded this enantioselective gold catalyzed transformation to the synthesis of functionalized 2-vinyl-morpholines **20** via intramolecular alkyloxylation of allylic alcohols **19** in the presence of a chiral gold

complex generated *in situ* from the reaction of $\text{Au}_2\text{Cl}_2(\text{dppf})$ and AgNTf_2 (Scheme 1.3).³⁰ The corresponding products were obtained in 41-94% yield and with up to 95% ee.

Scheme 1.3 Gold catalyzed enantioselective synthesis of substituted 2-vinyl-morpholines **20** from allylic alcohols **19**.

In addition to aromatic compounds, 1,3-dicarbonyl compounds were reported to be efficient nucleophiles in allylic alkylation reactions (Table 1.5). In 2006, Baba and co-workers reported the direct allylic allylation of 1,3-dicarbonyl compounds with allylic alcohols in the presence of InCl_3 as catalyst (Table 1.5, entry 1).³¹ The allylic alkylation products **20** and/or **21** were obtained in 79-95% yield under mild reaction conditions. Subsequent works demonstrated other Lewis acidic catalysts such as $\text{Bi}(\text{OTf})_3$ ³², $\text{Yb}(\text{OTf})_3$ ³⁴, FeCl_3 ³⁵ and the lanthanum triflates $\text{Ln}(\text{OTf})_n$ ($\text{Ln} = \text{Yb}, \text{La}, \text{Hf}; n = 3, 4$)³³ could also efficiently mediated this C–C bond formation reaction (Table 1.5, entry 2-5).

Following these works, Chan and co-workers demonstrated I_2 catalyzed allylic alkylation of 1,3-dicarbonyl compounds **21** with allylic alcohols **5** could be achieved (Table 1.5, entry 6).³⁶ The corresponding allylic adducts were afforded in 51-99% yield in the presence of the low cost, air and moisture tolerance molecular iodine catalyst.

Table 1.5 Lewis and Brønsted acid catalyzed intermolecular allylic alkylation of 1,3-dicarbonyl compounds **21** with allylic alcohols **5**.

Entry	Catalyst	Yield (%)	Ref
1	InCl ₃	75-95	31
2	Bi(OTf) ₃	62-73	32
3	Ln(OTf) _n	51-92	33
4	Yb(OTf) ₃	72-93	34
5	FeCl ₃	72-82	35
6	I ₂	51-99	36
7	<i>p</i> -TsOH·H ₂ O	80-72	18

Allylic alkylation of 1,3-dicarbonyl compounds **21** with allylic alcohols **5** catalyzed by a polymer-bound *p*-toluenesulfonic acid catalyst was subsequently reported by Sanz and co-workers (Table 1.5, entry 7).¹⁸ This solid acid catalyst was shown to be applicable to large-scale reactions and recovery required only a simple filtration. In this study, one example of allylic amination of allylic alcohol **5** with 4-nitrobenzenamine **27** employing the solid acid as catalyst was demonstrated, providing the corresponding aminated product in 86% yield was also reported (Table 1.6, entry 1).¹⁸

This direct allylic amination approach was further explored by Shibasaki and co-workers who reported Bi(OTf)₃ catalyzed substitution of allylic alcohols with

Table 1.6 Lewis and Brønsted acid catalyzed intermolecular allylic amination with allylic alcohols **5**.

Entry	Catalyst	NH ₂ R ³	Yield (%)	Ref
1	<i>p</i> -TsOH·H ₂ O	27	86	18
2	Bi(OTf) ₃	28	55-99	37
		29 30		
3	AuCl ₃	28 31	58-96	38
4	I ₂	28 29	61-96	39
5	32 /AgSbF ₆	33	85-100	40

sulfonamides **28**, carboxamides **29** and carbamates **30** (Table 1.6, entry 2).³⁷ The reaction was shown to be significantly promoted in the presence of KPF₆, providing the corresponding allylic amination adducts **25** and/or **26** in 55-99% yield. At about the same time, Liu and co-workers found that not only sulfonamides **28** but also substituted anilines **31** could be used as efficient nucleophiles in intermolecular allylic amination of allylic alcohols by employing AuCl₃ as catalyst (Table 1.6, entry 3).³⁸ The desired allylic amination products were obtained in 58-96% yield at room temperature. One year later, Chan and co-workers reported molecular iodine to be an efficient catalyst in the allylic amination of sulfonamides and carbamates with allylic alcohols at room temperature, providing the substituted allylic products in good to excellent yields (Table 1.6, entry 4).³⁹ More recently, Widenhoefer and co-workers demonstrated gold catalyzed direct amination of allylic alcohols with cyclic ureas **33** (Table 1.6, entry 5).⁴⁰ In the presence of a 1:1 mixture of [P(*t*-Bu)₂(*o*-biphenyl)]AuCl and AgSbF₆ as catalyst, the intermolecular allylic aminated adducts were obtained in 85-100% yield and with high regioselectivity.

In 2008, Liang and co-workers reported the efficient synthesis of highly substituted pyrroles **36** through tandem intermolecular allylic amination/intramolecular hydroamination of allylic alcohols **34** with sulfonamides **28** catalyzed by H₂AuCl₄·H₂O (Scheme 1.4).⁴¹ The pyrrole derivatives **36** were obtained in up to 83% yield *via* the allylic sulfonamide intermediate **35**. This reaction was shown to be effective only for cyclohexanol substrates **34** and required 15 equiv of TsNH₂ and a high catalyst loading of the gold salt.

Scheme 1.4 Gold catalyzed tandem allylic amination/hydroamination of **34**.

Liu and co-workers demonstrated a similar method for the synthesis of highly substituted pyrroles *via* Au/Ag catalyzed amination/intramolecular hydroamination of allylic alcohols **37** with 4-nitroaniline **27** or TsNH₂ (Scheme 1.5).⁴² The reaction was shown to proceed by first forming the allylic aminated intermediate **38** followed by hydroamination to give desired products in 40-48% yield in the presence of (*p*-MeOC₆H₄)₃PAuCl under milder reaction condition at room temperature.

Scheme 1.5 Gold catalyzed tandem allylic amination/hydroamination of **37**.

In 2008, Nishizawa and co-workers reported Hg(OTf)₂ catalyzed intramolecular allylic amination of *N*-tosylanilinoallylic alcohols **40** at room temperature (Scheme 1.6).⁴³ The corresponding 5-7-membered nitrogen-containing heterocycles **41** were afforded in 41-99% yield. Two years later, the combination of the chiral ligand of (*R*)-BINAPHANE **42** and Hg(OTf)₂ was found to be an efficient catalytic system for developing an enantioselective version of this reaction (Scheme 1.6).⁴⁴ The desired

2-vinyl indoline derivatives were obtained in 91-99% yield and with up to 99% ee employing a catalyst loading as low as 1 mol%.

Scheme 1.6 Hg(OTf)_2 catalyzed cyclization of anilino sulfonamide allyl alcohol **40**.

In 2010, Cossy and co-workers reported the highly diastereoselective synthesis of substituted *cis*-2,6-piperidines and *cis*-2,6-tetrahydropyrans **44** from allylic alcohols **43** catalyzed by $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (Scheme 1.7).⁴⁵ The corresponding thermodynamically stable *cis*-isomers were obtained in 51-100% yield at room temperature.

Scheme 1.7 Iron catalyzed intermolecular cyclization of allyl alcohols **43**.

More recently, the intramolecular amination of allylic alcohols involving 1,3-chirality transfer was reported by Widenhoefer and co-workers. In this work, the intramolecular allylic amination of (*R,Z*)-**45** (96% ee) in the presence of 1:1 mixture of $[\text{P}(t\text{-Bu})_2o\text{-biphenyl}]\text{AuCl}$ as catalyst and AgSbF_6 as co-catalyst, provided (*R,E*)-**46** in 99% yield and with 96% ee, which was consistent with the net syn addition of the amine nucleophile relative to the departing hydroxyl group (Scheme 1.8).⁴⁶

Scheme 1.8 Gold catalyzed intermolecular amination of enantioenriched allylic alcohols **45**.

At about the same time, Kawai and co-workers described the chiral preparation of substituted tetrahydroisoquinoline derivatives **48** from chiral amino allyl alcohols **47** (Scheme 1.9).⁴⁷ This reaction proceeded with 1,3-chirality transfer in the presence of $\text{Bi}(\text{OTf})_3$ as catalyst, affording the corresponding aminated products in good yields with high stereoselectivity. In this work, it was highlighted that the stereochemistry of the products generated proceeded *via* a syn $\text{S}_{\text{N}}2'$ process that was significantly influenced by the substituent on the benzene ring.

Scheme 1.9 Bismuth catalyzed intermolecular amination of allyl alcohol **47**.

In addition to 6-*exo-trig* cyclization, the 6-*endo-trig* amination of amino allylic alcohols was reported by Chan and co-workers in 2009 (Scheme 1.20).⁴⁸ The reaction was conducted in toluene in the presence of catalytic amount of AuCl_3 and AgSbF_6 at room temperature, providing the corresponding cyclized products **50** in 40-91% yield.

The utility of this methodology was expanded by its application to the synthesis of the bioactive natural product ($\pm$) angustureine **51**.

Scheme 1.20 Gold catalyzed intramolecular amination of allyl alcohol **49**.

The reactions of alcohols as both the nucleophiles and electrophiles in monoallylic diols was first explored by Aponick and co-workers in $\text{Ph}_3\text{PAuCl}/\text{AgOTf}$ catalyzed synthesis of *cis*-tetrahydropyrans and *cis*-tetrahydrofurans **53** from allylic alcohols **52** (Scheme 1.21).⁴⁹ At reaction temperature as low as -78°C with catalyst loadings as low as 0.1 mol%, the cyclized products were afforded in 79-99% yield with dr values up to $> 25 : 1$.

Scheme 1.21 Gold catalyzed intermolecular alkyloxylation of allyl alcohol **52**.

Two years later, an approach involving 6-*endo-trig* cyclization of *o*-(1-hydroxyallyl)-phenols **54** was reported by the same group (Scheme 1.22).⁵⁰ The reaction was conducted in THF with $[\text{P}(t\text{-Bu})_2(o\text{-biphenyl})]\text{AuCl}/\text{AgOTf}$ as the catalyst combination, providing the desired chromenes **55** in up to 91% yield.

Scheme 1.22 Gold catalyzed intermolecular alkoxylation of allyl alcohol **54**.

In 2011, Aponick and co-workers disclosed 1,3-chirality transfer in the formation of tetrahydropyrans **57** employing chiral monoallylic diols **56** catalyzed by $\text{Ph}_3\text{PAuCl}/\text{AgOTf}$ (Scheme 1.23).⁵¹ In this reaction, it was found that the stereochemistry of the product **57** was influenced by the olefin geometry of **56**.

Scheme 1.23 Gold catalyzed chirality transfer reactions of monoallyl diols **56**.

More recently, Rueping and co-workers reported enantioselective intramolecular alkyloxylation of allylic alcohols employing highly acidic *N*-triflylphosphoramidate **60** as an efficient chiral Brønsted acid catalyst (Scheme 1.24).⁵² In this manner, the substituted chromenes **59** were afforded in 61-95% yield and with up to 96% ee. The mode of enantioselective induction was proposed to involve the formation of a chiral ion pair generated between the chiral Brønsted acid and the allylic alcohol **58**.

Scheme 1.24 Chiral Brønsted acid catalyzed asymmetric allylic substitution of **58**.

1.3 Propargylic Alcohols

Traditionally, the nucleophilic substitution of propargylic compounds has relied upon the Nicholas reaction. While shown to be highly efficient, drawbacks to this reaction included the need for multi steps and stoichiometric amount of $[\text{Co}_2(\text{CO})_8]$. Added to this is the generation of excess amount of byproducts, which limited its synthetic application in organic synthesis (Scheme 1.25).⁵³ Hence, much attention has been paid to developing catalytic versions of this reaction in the view of atom economy.

Scheme 1.25 Nicholas reactions of propargylic compounds.

In 2005, Campagne and co-workers reported the direct nucleophilic substitution of propargylic alcohols with various nucleophiles, such as arenes **63**, allyltrimethylsilane **64**, alcohols **65** and thiols **66**, catalyzed by $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ without the need for multi steps and high catalyst loading (Table 1.7, entry 1).⁵⁴ The desired substituted propargylic adducts **62** were obtained in 33-97% yield. Mechanistically, the reaction was thought to proceed *via* a carbocationic intermediate based on observations that a

racemic substituted product was obtained from an enantiomerically propargylic alcohol (96% ee) under the described reaction conditions. Following this work, Zhan and co-workers described BiCl_3 catalyzed propargylic substitution reaction of propargylic alcohols with C-, O-, S-, and N-centered nucleophiles provided the corresponding substituted products in 10-94% yield with complete regioselective control under mild conditions (Table 1.7, entry 2).⁵⁵ In this work, not only internal but also terminal propargylic alcohols could be employed as the starting materials. At about the same time, the same group disclosed that this reaction could be also accomplished with FeCl_3 as catalyst, providing the substituted products in up to 95% yield (Table 1.7, entry 3).⁵⁶

Subsequently, this nucleophilic substitution reaction was further examined in the presence of a catalytic amount of $p\text{-TsOH}\cdot\text{H}_2\text{O}$ by Sanz and co-workers. The direct propargylation of 1,3-dicarbonyl compound derivatives **21** with the Brønsted acid catalyst was shown to proceed well in air and non-anhydrous solvent, affording the desired propargylic adducts in 43-93% yield. (Table 1.7, entry 4).⁵⁷ In this work, the Meyer-Schuster rearrangement was detected as a competing reaction when tertiary propargylic alcohols were employed, leading to the formation of α,β -unsaturated carbonyl derivatives followed by aldol-type condensation with 1,3-dicarbonyl compounds to give corresponding conjugated diene-diones.

In 2008, Yoshimatsu and co-workers examined nucleophilic substitutions of phenylsulfanyl and selenyl propargylic alcohols in the presence of $\text{Sc}(\text{OTf})_3$ as catalyst, providing the desired product in 65-100% yield with high regioselectivity (Table 1.7, entry 5).⁵⁸ In this work, the presence of the sulfur and selenium functional

Table 1.7 Lewis and Brønsted acid catalyzed direct nucleophilic substitution of propargylic alcohols **61**.

Entry	Catalyst	NuH	Yield (%)	Ref
1	NaAuCl ₄ ·2H ₂ O	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>63</p> </div> <div style="text-align: center;"> <p>64</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <p>R¹OH</p> <p>65</p> </div> <div style="text-align: center;"> <p>R¹SH</p> <p>66</p> </div> </div>	33-97	54
2	BiCl ₃	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>63</p> </div> <div style="text-align: center;"> <p>64</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <p>R¹OH</p> <p>65</p> </div> <div style="text-align: center;"> <p>R¹SH</p> <p>66</p> </div> <div style="text-align: center;"> <p>R¹SO₂NH₂</p> <p>28</p> </div> </div>	10-94	55
3	FeCl ₃	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>63</p> </div> <div style="text-align: center;"> <p>64</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <p>R¹OH</p> <p>65</p> </div> <div style="text-align: center;"> <p>R¹SH</p> <p>66</p> </div> <div style="text-align: center;"> <p>R¹SO₂NH₂</p> <p>28</p> </div> </div>	38-95	56
4	<i>p</i> -TsOH·H ₂ O	<p>21</p>	43-93	57
5	Sc(OTf) ₃	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>63</p> </div> <div style="text-align: center;"> <p>64</p> </div> </div>	65-100	58

groups on the propargylic alcohol was summarized to be important to stabilize the putative carbocationic species formed on activation of the substrate by the metal catalyst.

In the same year, Zhou and co-workers reported a tandem reaction for the preparation of spirocarbocycles *via* $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed intramolecular Friedel-Crafts annulation and hydroarylation sequence of aryl substituted propargylic alcohols **67** (Scheme 1.26).⁵⁹ Mechanistically, the reaction was proposed to proceed *via in situ* allene intermediate **68** and intramolecular hydroarylation of this adduct afforded the corresponding spirocarbocycles **69** in 68-91% yield under mild reaction conditions.

Scheme 1.26 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed synthesis of spirocyclic compounds **69** from propargylic alcohols **67**.

Following this work, Aponick and co-workers reported an interesting synthesis of olefin-containing spiroketal **71** catalyzed by a cationic gold (I) complex generated from $[\text{P}(t\text{-Bu})_2(o\text{-biphenyl})]\text{AuCl}$ and AgOTf *via* intramolecular cyclization of substituted monopropargylic triols **70** (Scheme 1.27).⁶⁰ The desired substituted 5- and 6-membered ring spiroketals were obtained in 75-99% yield employing only 2 mol% of $[\text{P}(t\text{-Bu})_2(o\text{-biphenyl})]\text{AuCl}$ as catalyst in THF at 0 °C.

Scheme 1.27 Gold catalyzed cyclization of monopropargylic triols **70**.

At about the same time, Lu and co-workers reported $\text{Yb}(\text{OTf})_3$ catalyzed tandem reactions of substituted aziridines **73** and aryl substituted tertiary propargylic alcohols **72**, providing the desired functionalized indenenes **74** in 41-79% yield (Scheme 1.28).⁶¹ Further transformation of the indene to indenone, powerful therapeutic candidates for the treatment of diabetes, was successfully carried out with molecular iodine as the oxidant under basic conditions.

Scheme 1.28 $\text{Yb}(\text{OTf})_3$ catalyzed synthesis of functionalized indenenes **74**.

In 2006, Knight and co-workers first reported AgNO_3 catalyzed intramolecular tandem reaction of propargylic alcohols **76** for the construction of a variety of aromatic heterocycles **77** (Table 1.8, entry 1).⁶² The desired pyrrole, furan and thiophene products were obtained in 70-99% yield. A limitation of this approach, however, was that terminal propargylic starting alcohols were found to be ineffective under the AgNO_3 catalyzed conditions.

Table 1.8 Metal catalyzed synthesis of substituted heterocycles **77** from propargylic alcohols **76**.

Entry	Catalyst	Yield (%)	Ref
1	AgNO ₃	70-99	62
2	[P(<i>t</i> -Bu) ₂ (<i>o</i> -biphenyl)]AuCl / AgOTf	87-99	63
3	(Ph ₃ P)AuCl/AgNTf ₂	85-98	64

Subsequently, a [P(*t*-Bu)₂(*o*-biphenyl)]AuCl catalyzed version of this reaction was reported by Aponic and co-workers (Table 1.8, entry 2).⁶³ In the presence of [P(*t*-Bu)₂(*o*-biphenyl)]AuCl as catalyst and AgOTf as a co-catalyst, a variety of secondary and tertiary propargylic alcohols were shown to afford the corresponding heterocycles **77** in up to 99% yield at catalyst loading as low as 0.05 mol% under mild conditions.

At about the same time, Akai and co-workers reported a similar approach (Table 1.8, entry 3).⁶⁴ The synthetic procedure was demonstrated not only to be applicable to secondary and tertiary propargylic alcohols but also terminal ones in the presence of (Ph₃P)AuCl/AgNTf₂ as catalyst at room temperature. Under these conditions, the desired furans and pyrroles were provided in up to 98% yield.

In 2010, Chan and co-workers disclosed an intramolecular tandem cycloisomerization/Friedel-Crafts alkylation of 2-tosylaminophenylprop-1-yn-3-ols **78** employing a AuCl/AgOTf catalytic system (Scheme 1.29).⁶⁵ This afforded the

indenyl-fused and 2,3-disubstituted indole derivatives in up to 94% yield. However, this reaction was shown to proceed well in only the presence of 20 mol% HMPA and CaSO_4 .

Scheme 1.29 Au catalyzed tandem reactions of propargylic alcohols **78**.

At about the same time, Zhan and co-workers reported an efficient AgOTf catalyzed method for the preparation of *N*-fused indole derivatives **83** from propargylic alcohols **61** and substituted 1*H*-indoles **81** (Scheme 1.30).⁶⁶ The desired adducts were obtained in up to 95% yield and was proposed to proceed *via* formation of the **82** that involved a Friedel-Crafts reaction/*N*-C bond formation process. When $\text{R}^2 = \text{H}$, the desired products **84** were reported to be obtained in 48-85% yield after further isomerization of **83**.

Scheme 1.30 AgOTf catalyzed tandem synthesis of *N*-fused heterocycles **83**.

In 2010, Liang and co-workers reported an efficient method for the preparation of substituted 3,4-diiodoheterocyclics **86** from but-2-yne-1,4-diol and 4-aminobut-2-yn-1-ol derivatives **85** promoted by I_2 at room temperature (Scheme 1.31).⁶⁷ In this work, it was reported that a trace amount of water was necessary for the generation of an iodine ion pair that was thought to effect the reaction. After attacking the iodinated allene intermediate by the heteroatom, the substituted 3,4-diiodoheterocyclic compounds **86** were obtained in 70-99% yield.

Scheme 1.31 I_2 promoted synthesis of 3,4-diiodoheterocyclics **86**.

Based on this approach, Liang and co-workers showed that replacing the heteroatom in **85** with a substituted aromatic ring as in **87**, the diiodinated carbocycles **88** and heterocycles **90** could be afforded (Scheme 1.32).⁶⁸ A trace amount of water was again shown to be necessary for the intramolecular ring forming process to efficiently proceed, and afford the dihalogenated products **88** and **90** in up to 79% yield.

Scheme 1.32 I₂ promoted synthesis of 2,3-diiodoheterocyclics **88** and **90**.

In the same year, the synthesis of *N*-(2-iodo/bromoinden-1-yl)arenesulfonamides **91** from reaction of propargylic alcohols **61** with arylsulfonamides **28** and NXS (X = Br, I) promoted by BF₃·Et₂O was reported by Wang and co-workers (Scheme 1.33).⁶⁹ The corresponding monohalogenated indene adducts were afforded in 40-77% yield under mild reaction conditions. However, a limitation of this reaction was that it was only applicable to tertiary propargylic alcohols.

Scheme 1.33 BF₃·Et₂O promoted tandem synthesis of 2-haloindenamines **91**.

More recently, Wang and co-workers reported the preparation of 1,4-naphthoquinone methides **94** from TFA catalyzed tandem cyclization of

benzannulated enediynyl alcohols **92** at room temperature (Scheme 1.34).⁷⁰ The transformation was shown to undergo an unusual two carbon ring expansion route to give the corresponding cyclized adducts **94** in up to 92% yield. It was realized high product yields were obtained due to the presence of a methoxyl group at R² providing further stabilization to the putative cabocationic species formed. In this work, it was also found that the indene derivative could be afforded in the absence of the two methyl groups adjacent to hydroxyl group in **92**.

Scheme 1.34 TFA catalyzed tandem synthesis of 1,4-naphthoquinone methides **92**.

1.4 Benzylic Alcohols

The direct nucleophilic substitution of benzylic alcohols is one of the most important methods for introducing benzyl function group. In 2005, Beller and co-workers reported the arylation of benzylic alcohols **95** in the presence of FeCl₃ provided the corresponding diarylmethanes and arylheteroarylmethanes in 37-99% yield with high regioselectivity (Table 1.9, entry 1).⁷¹ However, only the reaction of *o*-xylene **98** was examined which was used as both the nucleophile and solvent with different substituted primary and secondary benzylic alcohols under mild conditions. Following this pioneering study, the scope of these reactions was expanded to include a variety of different nucleophiles by employing a variety of Lewis and Brønsted

acids. In 2006, Rueping and co-workers described $\text{Bi}(\text{OTf})_3$ as an efficient catalyst in Friedel-Crafts-type benzylation of arenes and heteroarenes with benzylic alcohols (Table 1.9, entry 2).⁷² The benzylated products were obtained in 35-99% yield with a catalyst loading as low as 0.5 mol%. In addition to intermolecular benzylation, two intramolecular benzylation reactions were also realized, providing a useful method for the synthesis of substituted fluorenes.

In the same year, Campagne demonstrated the direct amination of benzylic alcohols with *N*-nucleophiles such as 4-nitroaniline **27**, tosylamine **28** and trimethylsilyl azide **99** catalyzed by NaAuCl_4 (Table 1.9, entry 3).⁷³ In this work, the formation of the aminated products was successfully achieved by employing the above *N*- nucleophiles. With the exception of primary alcohols, which were reported to be ineffective, secondary benzylic alcohols showed good reactivity to afford up to quantitative product yields.

Later works showed NaAuCl_4 to be an efficient catalyst for the synthesis of unsymmetrical ethers from benzylic alcohols **95** and alkyl alcohols **65** (Table 1.9, entry 6).⁷⁶ The desired ethers were obtained in 47-96% under mild conditions with a catalyst loading as low as 2 mol%. In this work, Asensio and co-workers reported that the symmetrical ether byproduct was not detected in the etherification process. Mechanistically, the furnishing of the racemic ether from a chiral benzylic was provided as evidence for a reaction pathway involving a carbocationic intermediate.

In 2007, Liu and co-workers reported the nucleophilic substitution of benzylic alcohols with α -EWG ketene-(*S,S*)-acetals **100** (EWG = CN, COR, CONH_2) (Table 1.9, entry 4).⁷⁴ This C–C coupling reaction was shown to proceed well in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temperature, providing the corresponding benzylated adducts **97** in 65-95% yield.

Table 1.9 Lewis and Brønsted acid catalyzed direct nucleophilic substitution of benzylic alcohols **95**.

Entry	Catalyst	NuH	Yield (%)	Ref
1	FeCl ₃	98	37-99	71
2	Bi(OTf) ₃	63	35-99	72
3	NaAuCl ₄	R^1NH_2 TMSN_3 24 99	63-100	73
4	BF ₃ ·Et ₂ O	100	65-95	74
5	DBSA	63 21 R^1SH R^1NH_2 66 24	62-96	75
6	NaAuCl ₄	R^1OH 65	47-96	76
7	InBr ₃	TMSCN 101	56-99	77
8	Ga(OTf) ₃	102 103 104 105	52-94	78

The dehydration of benzylic alcohols is known to proceed better in organic solvents than in water which is a more environmentally attractive media. In 2007, Kobayashi and co-workers successfully carried out the direct dehydrative nucleophilic substitution of benzylic alcohols with a variety of nucleophiles in water in the presence of the surfactant-type Brønsted acid DBSA (dodecylbenzenesulfonic acid) as catalyst (Table 1.9, entry 5).⁷⁵ The corresponding C-, S- and N-centered benzylated adducts were obtained in up to 96% yield. In this work, it was found that the substitution reaction was significantly affected by both the surfactant property and strong acidity of DBSA.

About one year later, Ding and co-workers reported the direct cyanation of benzylic alcohols with TMSCN **101** for the synthesis of α -aryl nitriles (Table 1.9, entry 7).⁷⁷ This reaction performed well in the presence of a catalytic amount of InBr₃, affording the desired products in moderate to excellent yield in a short reaction time. This method provided a convenient synthesis of nitrile precursors, which could be further applied in the preparation of clinically important compounds **106-109** (Fig 1.1).

Fig 1.1 Verapamil and α -aryl nitrile derivatives.

Following this work, Wu and co-workers reported the formation of thiol compounds from benzylic alcohols and sulfur nucleophiles *via* Ga(OTf)₃ catalyzed

direct nucleophilic substitution, which was much more convenient compared to the traditional Mitsunobu reaction (Table 1.9, entry 8).⁷⁸ In this work, phosphorothioic acid **102**, phenyltetrazole **103**, and other heteroaromatic thiols **104** and **105** were shown to be as efficient nucleophiles that afforded the corresponding sulfides products in up to 94% yield, which were very useful due to their application in the preparation of sulfones and Julia olefination reactions.

In 2008, Wang and co-workers reported that FeCl_3 and ZnCl_2 were efficient co-catalysts in the domino intermolecular benzylation/annulation/oxidation of α -amino substituted 2-amino benzylic alcohols **110** with β -ketoesters **21** (Scheme 1.35).⁷⁹ The desired 3-quinolinecarboxylic ester products **111** were obtained in up to 94% yield. In this work, it was shown that the activity of the catalytic system was decreased significantly by employing either FeCl_3 or ZnCl_2 as the sole catalyst, respectively.

Scheme 1.35 $\text{FeCl}_3/\text{ZnCl}_2$ catalyzed tandem reactions of 2-amino benzylic alcohols.

At about the same time, Jana and co-workers described a tandem reaction between terminal aryl acetylenes **112** and benzylic alcohols **113** catalyzed by FeCl_3 (Scheme 1.36).⁸⁰ This reaction was reported to proceed *via* the benzylic carbon cation of **113**, which was attacked by aryl acetylene **112** to generate the vinyl carbon cation **114**. Subsequent trapping by the hydroxide ion afforded the corresponding aryl ketone **115** in up to 80% yield.

Scheme 1.36 FeCl_3 catalyzed synthesis of aryl ketones **115**.

One year later, it was found that the chloro or bromo anion of the iron (III) salt in this reaction could act as an efficient nucleophile trap for the *in situ* formed vinyl carbon cation species. At room temperature, this provided the trisubstituted substituted vinylic halides **116** in moderate to good yields (Scheme 1.37).⁸¹

Scheme 1.37 FeCl_3 catalyzed synthesis of vinylic halides **116**.

In addition to metal catalysts, Brønsted acid have been shown to catalyze in the tandem reactions of benzylic alcohols. In 2007, Sanz and co-workers reported the Brønsted acid DNBSA (2,4-dinitrobenzenesulfonic acid) could catalyze amidation of secondary benzylic alcohols (Scheme 1.38).⁸² The desired *N*-benzylacetamide products **118** were obtained in up to 91% yield after employing water to trap the nitrilium cation **117** generated from reaction of benzylic alcohol **113** and acetonitrile. It was reported that this version of the Ritter reaction represented a more cleaner and environmentally friendly approach than previously described literature methods.

Scheme 1.38 DNBSA catalyzed synthesis of *N*-benzylacetamides **116**.

In 2010, Liu and co-workers reported CuBr_2 catalyzed one-pot preparation of dihydrocoumarins **120** from 2-hydroxy benzilic alcohols **119** and ketene dithioacetals **100** (Scheme 1.39).⁸³ The desired products were obtained in 67-98% yield although a higher catalyst of 30 mol% was required.

Scheme 1.39 CuBr_2 catalyzed synthesis of dihydrocoumarins **120**.

At about the same time, Chan and co-workers reported $\text{Cu}(\text{OTf})_2$ catalyzed intramolecular hydroamination of homoallylic or α -amino benzylic alcohols (Scheme 1.40).⁸⁴ This reaction proceeded well without the need for exclusion of air or moisture, affording the nitrogen-containing heterocycles of *trans*-2,5-dihydro-1*H*-pyrroles **122** with efficient transfer of chirality and 1,2-dihydroquinolines **124** in up to 98% yield under mild condition in the presence of $\text{Cu}(\text{OTf})_2$ as catalyst. Mechanistically, the diene compound generated by simple dehydration of **121** or **123** was considered as key intermediate in this reaction.

Scheme 1.40 $\text{Cu}(\text{OTf})_2$ catalyzed intramolecular hydroamination of homoallylic amino alcohols **121** and **122**.

In 2011, Liu and co-workers reported a stereospecific $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed olefin synthesis *via* direct coupling of alcohols **125** with benzylic alcohols **126** (Scheme 1.41).⁸⁵ In this work, only substituted (*E*)-alkene **127** were obtained in up to 99% yield in the presence of 10 mol% of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and 1 equiv of TsOH. While the scope of this reaction limited was to R¹ and R³ = H, the scaled up of the reaction could be achieved.

Scheme 1.41 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed cross-coupling reactions of alcohols **125** and benzylic alcohols **126**.

1.5 α -Cyclopropylmethyl Alcohols

Recently, much attention has been paid to Lewis and Brønsted acid-catalyzed ring-opening and/or rearrangement of α -cyclopropylmethyl alcohols for the construction of complex compounds.⁸⁶

In 2001, Doris and co-workers reported $\text{BF}_3 \cdot \text{Et}_2\text{O}$ mediated rearrangement of secondary benzylic alcohols (Scheme 1.42).⁸⁷ The substituent on the three-membered ring was shown to be important in controlling product selectively through stabilizing the carbocationic species generated in these reactions. The polycyclic cyclobutanes **132** were obtained in 91-97% after intramolecular alkoxylation of a cyclobutyl cation **131** generated by ring expansion of the initially formed cyclopropylcarbinyl cation **129**. When R^2 was changed from H to Ph, the oxygen-containing seven-membered ring **133** was afforded as the sole example in 47% yield after intramolecular alkoxylation of the benzylic cation **130** that was produced by ring fission of cyclopropylcarbinyl cation **129**.

Scheme 1.42 $\text{BF}_3 \cdot \text{OEt}_2$ -mediated rearrangement of cyclopropylmethyl carbinols **126**.

In 2009, Chan and co-workers reported the synthesis of conjugated enynes **135** from $\text{Yb}(\text{OTf})_3$ catalyzed ring opening substituted 1-cyclopropyl-2-propyn-1-ols **134**

with arylsulfonamides (Scheme 1.43).⁸⁸ The desired products were obtained in up to 75% yield with high regioselectivity. In this work, other *N*-containing nucleophiles such as anilines, *tert*-butyl carbamate, and *N*-aminophthalimide were shown to give either very low yields or the propargylation adduct **136**.

Scheme 1.43 Yb(OTf)₃ catalyzed amination of cyclopropylmethyl alcohols **134** with arylsulfonic amides.

A TfOH catalyzed version of this transformation with alcohols as both the nucleophile and solvent was subsequently reported by Chan and co-workers (Scheme 1.44).⁸⁹ The desired tri- and tetrasubstituted conjugated enynes were afforded in 44-100% yield and with up to 10,000 turnovers. However, a drawback of the alkoxylation reaction was that it was limited to tertiary propargylic alcohols of the type **137**.

Scheme 1.44 TfOH catalyzed alkoxylation of cyclopropylmethyl alcohols **137** with alcohols **65**.

In an effort to expand the synthetic versatility of cyclopropyl substituted benzylic alcohols, Chan and co-workers showed an intermolecular tandem amination/ring expansion of benzylic alcohols with sulfonamides (Scheme 1.45).⁹⁰ The corresponding pyrrolidine derivatives **140** were obtained in 30-91% yield in the presence of AuCl/AgOTf as catalyst. If both R¹ and R² were aliphatic groups, the yield of the desired pyrrolidines was significantly decreased. In this work, the possibility of TfOH generated *in situ* as the true catalyst was ruled out due to the low product yields obtained and need for higher catalyst loadings of the Brønsted acid.

Scheme 1.45 Au catalyzed tandem reactions of cyclopropylmethyl alcohols **139**.

More recently, Chan and co-workers reported a TfOH-catalyzed one-pot, two-step synthetic method for the preparation of 3-halohydrofurans **142** from cyclopropylmethyl alcohols **139** (Scheme 1.46).⁹¹ The reaction was shown to be efficient for a variety of cyclopropyl alcohols in the presence of TfOH at a low catalyst loading of 1 mol%. After hydroxylation, halocyclization of the resultant homoallylic alcohols **141** formed *in situ* with NIS gave the desired substituted 3-iodofurans **142** were obtained in up to 98% yield and with complete *cis* selectivity.

Scheme 1.46 TfOH catalyzed tandem reactions of cyclopropylmethyl alcohols **139**.

1.6 Proposed Work

The work of this thesis has been directed toward providing new synthetic methodologies for the delivery of potential applicable compounds in an efficient and selective manner. This will be accomplished by exploring the reactions involving various ecologically benign Lewis and Brønsted acid catalysts and inexpensive and readily available alcohol pro-electrophiles with a variety of nucleophiles under operationally straightforward and mild conditions.

Thus, the purpose of this project has been to establish new Lewis and Brønsted acid-catalyzed protocols for the efficient and selective formation of substituted cyclic MBH compounds, indenols, thiazoles, 2-aryloxazoles, and indenenes from their respective alcohol substrates (Figure 1.2). It was envisioned that the direct nucleophilic α -substituted MBH products can be developed in an efficient and complete regioselective manner from the reaction of the MBH alcohols with alcohols, arenes, 1,3-dicarbonyl compounds, and thiols. Changing the MBH alcohols to propargylic alcohols, 6-hydroxyindenenes can be prepared *via* tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols by using ytterbium(III) triflate as catalyst. Alternatively, we reasoned that the indene work frame could be prepared *via* intramolecular tandem cyclization reactions of homoallylic alcohols in

the presence of a Brønsted acid by replacing the propargylic moiety of the propargylic alcohol substrate with a homoallylic group. Finally, we summarized that on the activity of di- and tri-substituted thiazoles and 2-aryloxazoles could be accessed by the reactions of propargylic alcohols with respective thioamids and aryl amides.

Figure 1.2 Lewis and Brønsted acid catalyzed strategies for C–X (X = C, N, O, S) bond formation from activated alcohols.

Chapter II. Iron(III) Chloride Catalyzed Direct Nucleophilic α -Substitution of Morita-Baylis-Hillman Alcohols with Alcohols, Arenes, 1,3-Dicarbonyl Compounds and Thiols

2.1 Introduction

Nucleophilic substitution of MBH adducts has received an increasing amount of attention in recent years due to their versatility as building blocks in organic synthesis.⁹²⁻⁹⁴ Generally, the MBH acetate is used as the substrate in this type of reaction presumably due to the perceived poor leaving group ability and low reactivity of the hydroxy group in the alcohol precursor.^{92,93} Although shown to be highly efficient, a drawback of this approach is the need to perform the acylation step. Added to this is the possibility of competitive side reactions mediated by the acetic acid byproduct formed during the course of the reaction. For this reason, the establishing of strategies for the direct nucleophilic substitution of MBH alcohols has been actively pursued since the only potential byproduct produced in such reactions would be H₂O.⁹⁴⁻¹⁰² As part of an ongoing program examining the utility of alcohols as pro-electrophiles,⁹⁹ we recently reported that the direct α -arylation of a cyclic MBH alcohol with 2,6-dimethylphenol could be accomplished in near quantitative yield using gold catalysis.¹³ The efficiency of the catalysis led us to explore the scope of these substitutions due to their frequent use as intermediates in numerous synthetic routes to heterocycles and compounds of biological interest.⁹²⁻⁹⁴ We envisioned the method would also greatly benefit from the use of cheaper and commercially available catalysts, such as iron complexes. Recently, iron-mediated substitutions of alcohol pro-electrophiles with a variety of nucleophiles as the basis for efficient and selective C–X (X = C, N, O, S, halide) have been reported.^{96, 103} While the majority of

these works have focused on the reactions of allylic, benzylic and propargylic alcohols, this has also hitherto included three reports on regioselective substitutions of acyclic and cyclic MBH alcohols. Das and co-workers described an efficient iron-catalyzed γ -chlorination of acyclic MBH alcohols that gave the corresponding γ -allylic chlorides in good yields.¹⁰⁰ Following this work, Jia and co-workers reported a similar iron-mediated approach for the γ -alkoxylation of acyclic MBH alcohols.¹⁰¹ At about the same time, Kim and co-workers also showed nucleophilic substitution of cyclic MBH alcohols with sulfonamides that proceeded with complete α -regioselectivity in excellent yields.¹⁰² To our knowledge, however, the analogous iron catalyzed α -substitution reactions of cyclic MBH alcohols with C-, O- and S-centered nucleophiles are not known. Herein, we report the use of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ for the α -substitution of cyclic MBH alcohols with a wide variety of carbon- and heteroatom centered nucleophiles that include alcohols, arenes, 1,3-dicarbonyl compounds, and thiols (Scheme 2.1). The substituted cyclic MBH products were afforded in good to excellent yields with exclusive α -regioselectivity and without the need for inert and moisture-free conditions.

Scheme 2.1 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed direct nucleophilic α -substitution of MBH alcohols **143**.

2.2 Results and Discussion

At the outset of this study, we chose 2-(hydroxy(phenyl)-methyl)cyclohex-2-enone **143a** and 1,3-diphenylpropane-1,3-dione **21a** as the model substrates to establish the reaction conditions (Table 2.1). This revealed that treating an open round flask containing **143a** and **21a** in CH₂Cl₂ with 10 mol% of FeCl₃·6H₂O at 40 °C for 4 h gave the best result (entry 1). Under these conditions, 2-((6-oxocyclohex-1-enyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione **145a** was afforded in 90% yield. No side-products that could be attributed to competitive substitution at the γ -carbon or elimination of the hydroxyl group of **143a** could be detected by ¹H NMR analysis of the crude reaction mixture.¹⁰⁴ The α -substituted MBH product was confirmed by ¹H NMR analysis and X-ray crystal structure determination of two closely related products (see later). At room temperature, a longer reaction time of 23 h was required to obtain a comparable product yield (entry 2). Under these latter conditions at room temperature, repeating the reaction with a catalyst loading of 5 or 10 mol% and 1,2-dichloroethane as the solvent was also found to give **145a** in similar yields of 89 and 77%, respectively (entries 3-4). In contrast, performing the reaction in other solvents at room temperature was found to be markedly less effective (entries 5-8). When either toluene, MeCN or MeNO₂ were employed as the solvent, low product yields of 26-40% were obtained (entries 5-7). On the other hand, TLC and ¹H NMR analysis of the crude mixture of the reaction conducted in THF detected only the starting alcohol and 1,3-dicarbonyl compound (entry 8). Inspection of entries 9-12 in Table 2.1 also revealed the reaction proceeded less well with other common and commercially available Lewis acid catalysts. In these latter reactions, the use of either CuOTf or InCl₃ resulted in the formation of **145a** in markedly lower yields of 29 and 25%, respectively (entries 11-12). However,

switching the catalyst to Yb(OTf)₃ or AgOTf was found to lead to no reaction on the basis of TLC and ¹H NMR analysis (entries 9-10).

Table 2.1 Optimization of reaction conditions.^a

<div style="display: flex; justify-content: space-around; margin-top: 10px;"> <div style="text-align: center;"> <chem>O=C1C=CC(Cc2ccccc2)CC1</chem> 143a </div> <div style="text-align: center;"> <chem>O=C(Cc1ccccc1)CC(=O)c2ccccc2</chem> 21a </div> <div style="text-align: center;"> <chem>O=C1C=CC(Cc2ccccc2)C(C(=O)c3ccccc3)C1C(=O)c4ccccc4</chem> 145a </div> </div>			
Entry	Catalyst	Solvent	Yield (%)
1 ^b	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	90
2	FeCl ₃ ·6H ₂ O	CH ₂ Cl ₂	92
3	FeCl ₃ ·6H ₂ O	CH ₂ ClCH ₂ Cl	89
4 ^c	FeCl ₃ ·6H ₂ O	CH ₂ ClCH ₂ Cl	77
5	FeCl ₃ ·6H ₂ O	PhMe	37
6	FeCl ₃ ·6H ₂ O	MeCN	26
7	FeCl ₃ ·6H ₂ O	MeNO ₂	40
8	FeCl ₃ ·6H ₂ O	THF	- ^d
9	Yb(OTf) ₃	CH ₂ Cl ₂	- ^d
10	AgOTf	CH ₂ Cl ₂	- ^d
11	CuOTf	CH ₂ Cl ₂	29
12	InCl ₃	CH ₂ Cl ₂	25

^a All reactions were performed at room temperature for 23 h with a catalyst:**143a**:**21a** ratio of 1:10:20. ^b Reaction conducted at 40 °C for 4 h. ^c Reaction conducted with a catalyst loading of 5 mol%. ^d No reaction detected based on TLC and ¹H NMR analysis.

Applying the conditions shown in entry 1 of Table 2.1, a variety of substituted cyclic MBH alcohols and 1,3-dicarbonyl compounds were examined to determine the substrate scope of the present procedure (Table 2.2). As shown in entries 1-3, substitution of **143a** with a variety of substituted 1,3-dicarbonyl compounds gave the

Table 2.2 FeCl₃·6H₂O catalyzed α -substitution of **143a-l** with **21a-d**.^a

Entry	Substrates	Product	Yield (%)
1	143a + 21b	145b , R ¹ = R ² = Me	90
2	143a + 21c	 145c , R ¹ = Ph, R ² = Me	92
3	143a + 21d	145d , R ¹ = Ph, R ² = OEt	97 ^b
4 ^c	143b + 21a	145e , R = NO ₂	80
5	143c + 21a	145f , R = F	99
6	143d + 21a	145g , R = Cl	95
7	143e + 21a	145h , R = Br	91
8	143f + 21a	145i , R = Me	66
9	143g + 21a	145j , R = OEt	40

Table 2.2 (continued)

Entry	Substrates	Product	Yield (%)	
10	143h + 21a		145k , R = NO ₂	- ^d
11	143i + 21a		145l , R = Cl	88
12	143j + 21a		145m	84
13	143k + 21a		145n	61
14	143l + 21a		- ^e	

^a All reactions were performed at 40 °C with a catalyst:**143**:**21** ratio of 1:10:20. ^b Obtained as a 5:1 mixture of diastereomers separable by flash column chromatography. ^c Reaction conducted with 50 mol% of FeCl₃·6H₂O. ^d No reaction based on TLC and ¹H NMR analysis. ^e Only starting material was recovered.

corresponding α -substituted cyclic MBH products **145b-d** in excellent yields. Notably, this included α -substitution of **143a** with the less acidic β -ketoester **21d**, which gave **145d** as a separable 5:1 mixture of diastereomers in near quantitative yield (entry 3). The present procedure was also shown to work well for reactions of **21a** with cyclic MBH alcohols with a pendant electron-withdrawing aryl group on the carbinol carbon centre, affording **145e-h** in excellent yields (entries 4-7). In our hands, reaction of **143b** with **21a** was the only example where a low product yield of 27% was obtained under the standard conditions but could be increased to 80% yield on repeating with a

catalyst loading of 50 mol% (entry 4). On the other hand, moderate to good product yields were afforded for reactions of **143f** and **143g** bearing an electron donating aryl group on the carbinol carbon centre (entries 8-9). Mixtures of side-products were also afforded in both reactions that could not be identified by ^1H NMR analysis. Stereoelectronic effects of the cyclic MBH alcohol may also play a role since a substrate containing the strongly coordinating *o*-nitrophenyl group on the carbinol carbon resulted in no reaction (entry 10). A similar outcome was found on repeating this reaction with a stoichiometric amount of catalyst. In contrast, α -substitution of **143i**, which contains a bulky *o*-chlorophenyl group on the carbinol carbon, with **21a** was found to give **145l** in 88% yield (entry 11). Reactions of starting alcohols containing an α,β -unsaturated cyclopentanone or 2,3-dihydropyran-4-one ring moiety with **21a** were also shown to provide **145m** and **145n** in good to excellent yields (entries 12-13). However, only starting material was recovered when aryl group of MBH alcohol changed to alkyl group (entry 14).

In this work, the $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed direct α -substitution of **21a** with a variety of different carbon, oxygen and sulfur-centered nucleophiles was also examined (Table 2.3) Under the standard conditions, Friedel-Crafts arylation of **143a** with arenes **144a** and **144b** afforded the α -substituted MBH products **145o** and **145p** in 62 and 88% yield (entries 1-2). Inspection of entries 3-8 revealed that the present procedure also proceeds well on switching C-centered nucleophiles to O- and S-centered nucleophiles. When EtOH **65a** was employed as the nucleophile, the reaction was found to give **145q** in 94% yield (entry 3). We were also pleased to find comparable high product yields of 95 and 85% could be furnished for the analogous $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed α -substitutions of **143a** with **65b** and **65c**, respectively (entries 4-5). Similarly, when **143a** was treated with ethanethiol **66a** under the standard

conditions, the corresponding MBH thioether adduct **145t** was afforded in 96% yield (entry 6). In our hands, the arylthiols **66b** and **66c**, which contain either a *para*-substituted electron-withdrawing or electron-donating aryl group, respectively, were also found to be good sulfur sources (entries 7-8).

Table 2.3 FeCl₃·6H₂O catalyzed α -substitution of **143a** with **144a-b**, **65a-c** and **66a-c**.^a

<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;"> <p>144a, R = H 144b, R = Me</p> </div> <div style="text-align: center;"> <p>65a, R = Me 65b, R = Ph 65c, R = CH₂CH=CH₂</p> </div> <div style="text-align: center;"> <p>EtSH</p> <p>66a</p> </div> <div style="text-align: center;"> <p>66b, R = Cl 66c, R = Me</p> </div> </div>				
Entry	NuH	Product		Yield (%)
1 ^b	144a		145o , R = H	62
2 ^b	144b		145p , R = Me	88
3 ^c	65a		145q , R = Et	94
4 ^c	65b		145r , R = Bn	95
5 ^b	65c		145s	85
6 ^d	66a		145t	96
7 ^d	66b		145u , R = Cl	87
8 ^d	66c		145v , R = Me	83

^a All reactions were performed at 40 °C with a catalyst: **143a** : **144** or **65** or **66** ratio of 1:10:20. ^b Reaction time = 2 h. ^c Reaction time = 3 h. ^d Reaction time = 4 h.

In these reactions, the corresponding α -substituted cyclic MBH thioethers **145u** and **145v** were furnished in yields of 83-87%. Consistent with our earlier findings for the substitution of **143a** with **21a**, in all the above reactions no side-products resulting from competitive γ -substitution or elimination of the hydroxyl group of the MBH alcohol could be detected by ^1H NMR and TLC analysis. Without exception, the α -substituted MBH adduct was obtained as the sole product in every case. This was further confirmed by X-ray crystal structure determination of **145m** and **145p**, as shown in Fig. 2.1.¹⁰⁵

Fig. 2.1 ORTEP drawings of (a) **145m** and (b) **145p** with thermal ellipsoids at 50% probability levels.

Although a mechanistic discussion would be highly speculative at this juncture, we tentatively propose one possible pathway in Scheme 2.2 for the present $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed α -substitution reaction. This could involve activation of the alcohol substrate through coordination of the iron catalyst with the hydroxyl and carbonyl groups. This delivers an iron(III) coordinated intermediate **146** which can undergo elimination to give a putative carbocation species **147**. It is possible that the newly

formed cationic species subsequently undergoes nucleophilic attack by NuH and protodemetalation of [Fe]-OH to deliver the α -substituted cyclic MBH product **145** and metal catalyst.

Scheme 2.2 Tentative mechanism for $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed direct nucleophilic α -substitution of MBH alcohols.

The role of the iron catalyst in facilitating dehydroxylation of the cyclic MBH alcohol would account for our earlier findings showing the need for a catalyst loading of 50 mol% and no product formation for the respective reactions of **143b** and **143h** with **21a** (entries 4 and 10 in Table 2.2). It would not be inconceivable that such interactions are weakened due to the introduction of a strongly coordinating nitro moiety on the alcohol substrate. It is possible that the α -regioselectivities obtained could also be attributed to such interactions since coordination of the metal catalyst to the carbonyl oxygen would give a stable six-membered ring coordinate in **146**, as shown in Scheme 2.2. The gradual decrease in product yields with increasing

electron-donating ability of the substituent on the carbinol on going from **143a** → **143f** → **143g** shown in entry 1 in Table 2.1 and entries 8-9 in Table 2.2 would be consistent with the formation of the resultant carbocation species. It might be expected that this is a result of decreasing reactivity as inductive and resonance stabilization of the cation species increases with increasing electron-donating ability of the substituent. The involvement of a carbocation intermediate would also account for our results on the reaction of enantioenriched **143a** with **21a**. Under our experimental conditions, the α -substituted cyclic MBH product **145a** was obtained as a racemic mixture in 80% yield, as shown in Scheme 2.3.

Scheme 2.3 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ catalyzed direct nucleophilic α -substitution of enantioriched **143a** with **21a**.

2.3 Conclusion

In summary, a general and efficient iron-catalyzed method for the direct nucleophilic α -substitution of MBH alcohols with a structurally diverse set of nucleophiles that include alcohols, 1,3-dicarbonyl compounds and thiols, has been reported. These results show the reaction to proceed with complete α -regioselectivity and provide the corresponding α -substituted MBH products in good to excellent yields. The reaction was also demonstrated to be practical and operationally straightforward since inert and moisture-free conditions were not required. Moreover,

the present method offers a highly atom economical synthetic route to important building blocks from simple alcohol substrates that can be accessed in one step from low cost starting materials and an iron catalyst that is also inexpensive. Efforts to apply the method to the preparation of heterocycles and natural products synthesis are currently underway and will be reported in due course.

**Chapter III. Ytterbium(III) Triflate Catalyzed Tandem Friedel-Crafts
Arylation/Hydroarylation of Propargylic Alcohols with Phenols as an Expedient
Route to Indenols**

3.1 Introduction

Indenes are important core structures in organic chemistry as a substructure in many natural products and role as privileged scaffolds in bioactive pharmaceutical compounds.¹⁰⁶ They are also versatile building blocks for functional materials¹⁰⁷ and are utilized as ligands in metallocene-based olefin polymerization catalysts.¹⁰⁸ While this has led to many synthetic methods,¹⁰⁹ those that describe the construction of 6-hydroxyindenes have remained sparse. The 6-hydroxyindenes, the only member of the indene family compounds, also exhibit potential estrogenic bioactivity, their synthesis has been reported to need several steps and often harsh conditions.¹¹⁰ Hence, mild and efficient approaches to this class of carbocycles from commercially available substrates or ones that can be accessed in one step are desirable. Recent reports have demonstrated the use of propargylic compounds as efficient substrates in several Lewis and Brønsted acid catalyzed carbon-carbon and carbon-heteroatom bond formation strategies.¹¹¹⁻¹¹⁹ For instance, we recently reported Yb(OTf)₃ to be an efficient catalyst for the regioselective formation of conjugated enynes based on nucleophilic ring opening of unactivated 1-cyclopropyl-2-propyn-1-ols with aryl sulfonamides.¹¹² On the basis of these earlier studies we reasoned that a strategy that made use of propargylic alcohols¹¹³ and phenols in the presence of a rare earth metal Lewis acid catalyst¹¹⁴ would hold promise as a new method for indenol synthesis. To our knowledge, approaches to indenes that explore combining ecologically benign Lewis acid catalysts¹¹⁵ with propargylic alcohols have thus far been limited to three recent reports describing the synthesis of 3-phenyl-1*H*-indenes,¹¹⁶ spiroindenes,¹¹⁷ and

indenyl sulfonamides.¹¹⁸ In addition, those that involve the use of phenols have been previously reported to typically give the propargylation, benzofuran, and benzopyran products.^{111i,119} As part of an ongoing program examining the utility of alcohols in organic synthesis,^{112,120} we report herein the use of Yb(OTf)₃ for tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols (Scheme 3.1). The reactions were found to proceed to give 6-indenols in good to excellent yields up to 99% and with complete regioselectivity for a wide variety of substrates under mild conditions.

Scheme 3.1 Yb(OTf)₃ catalyzed formation of 6-indenols from propargylic alcohols.

3.2 Results and Discussion

Initially, we chose to focus our attention on the reaction of 1,1,3-triphenylprop-2-yn-1-ol **61a** and 2,6-dimethylphenol **144b** by a variety of Lewis acid catalysts to establish the reaction conditions (Table 3.1). This revealed treating a solution of reaction containing **61a** (1 equiv) and **144b** (2 equiv) with 10 mol% Yb(OTf)₃ at 80 °C for 24 h gave the best result (entry 1). Under these conditions, 5,7-dimethyl-1,1,3-triphenyl-1*H*-inden-6-ol **148a** was afforded in 90% yield. The indenol product was confirmed by ¹H NMR analysis and an X-ray crystal structure determination of a closely related product (see below). On the other hand, a slightly lower product yield was observed when the reaction was performed in MeCN and 1,2-dichloroethane in place of MeNO₂ as solvent (entries 2 and 3). Similar product

Table 3.1 Optimization of reaction conditions.^a

Entry	Catalyst	Solvent	Yield (%) ^b
1	Yb(OTf) ₃	MeNO ₂	90
2	Yb(OTf) ₃	MeCN	77
3	Yb(OTf) ₃	(CH ₂ Cl) ₂	86
4	Cu(OTf) ₂	MeNO ₂	46
5	InCl ₃	MeNO ₂	47
6	FeCl ₃ ·6H ₂ O	MeNO ₂	- ^c
7	AlCl ₃	MeNO ₂	26
8	AuBr ₃	MeNO ₂	85
9	PtCl ₂	MeNO ₂	82
10	TfOH	MeNO ₂	64
11	TfOH	MeNO ₂	72 ^d

^a All reactions were performed at 80 °C for 24 h with catalyst/**61a**/**144b** ratio = 1:10:20. ^b Isolated yield. ^c Mixture of unknown side products afforded based on ¹H NMR analysis of the crude mixture. ^d Reaction conducted with TfOH catalyst loading of 20 mol%.

yields were also obtained when the reaction was repeated with AuBr₃ and PtCl₂ as catalyst (entries 8 and 9). In contrast, while the use of Cu(OTf)₂, InCl₃ and AlCl₃ as the catalyst provided **148a** in markedly lower yields of 26-47%, the expected indenol product was not obtained employing FeCl₃·6H₂O (entries 4-7). In this latter case, the

reaction was found to result in the formation of a mixture of side products that could not be identified by ^1H NMR analysis (entry 6). Additional control experiments with TfOH at catalyst loadings of 10 and 20 mol% led to lower catalytic activities, providing evidence that the cationic Yb(III) complex is the active species (entries 10 and 11).¹²¹

To define the scope of the present procedure, we next turned our attention to the reactions of a variety of propargylic alcohols with **144** (Table 3.2). Reactions of propargylic alcohols with a pendant electron-withdrawing or electron-donating group on the carbinol or alkyne carbon with **144b** gave the desired indenols in moderate to excellent yields (entries 1-13). We also tested the effect of an aliphatic substituent and found that, for substrates where R^1 or $\text{R}^3 = \text{alkyl}$, lower yields were obtained for **148o** (56% and requiring reflux conditions and a longer reaction time of 48 h; entry 14), **148p** (44%; entry 15), **148q** (34%; entry 17), respectively. In contrast, in the case of starting alcohols where R^1 and $\text{R}^2 = \text{alkyl}$ or $\text{R}^2 = \text{H}$, the corresponding propargylation adducts **149a** and **149b** were preferentially furnished in yields of 61% and 83%, respectively (entries 16 and 18). A propargylic alcohol containing a terminal alkyne moiety was also examined under the standard conditions but was found to give a mixture of decomposition products that could not be identified by ^1H NMR analysis of the crude mixture (entry 19). On the other hand, reactions of starting alcohols with **144a** were found to proceed well and provide the corresponding indenols in excellent yields (entries 20-23). Under the standard conditions, reactions of **61l** with the less electron-rich or extremely sterically bulky phenols **144c** and **144d**

Table 3.2 Yb(OTf)₃ catalyzed synthesis of 6-indenols **148b-u**.^a

Entry	Alcohol	Product	Yield (%) ^b
1		148b , R ¹ = 4-FC ₆ H ₄	92
2	<p>61b-f</p>	<p>148c, R¹ = 4-ClC₆H₄</p>	87
3		<p>148d, R¹ = 4-BrC₆H₄</p>	82
4		<p>148e, R¹ = 4-CNC₆H₄</p>	99
5		148f , R ¹ = 4-MeC ₆ H ₄	84
6	<p>61g-j</p>	148g , R ¹ = R ² = 4-FC ₆ H ₄	94
7		148h , R ¹ = R ² = 4-ClC ₆ H ₄	91
8		148i , R ¹ = R ² = 4-BrC ₆ H ₄	98
9		148j , R ¹ = R ² = 4-MeC ₆ H ₄	72
10	<p>61k-n</p>	148k , R ³ = 4-FC ₆ H ₄	89
11		148l , R ³ = 4-ClC ₆ H ₄	76
12		148m , R ³ = 4-MeC ₆ H ₄	80
13		148n , R ³ = 4-MeOC ₆ H ₄	50
14	<p>61o-p</p>	148o , R ¹ = <i>i</i> Pr	56 ^c
15		148p , R ¹ = Me	44

Table 3.2 (continued)

Entry	Alcohol	Product	Yield (%) ^b
16	<p>61q</p>	<p>149a</p>	61
17	<p>61r</p>	<p>148q</p>	34
18	<p>61s</p>	<p>149b</p>	83
19	<p>61t</p>		- ^d
20		148r , R ¹ = R ² = Ph	83
21	<p>61a, 61c, 61e, 61h</p>	<p>148s, R¹ = 4-ClC₆H₄, R² = Ph</p>	80
22		148t , R ¹ = Ph, R ² = 4-CNC ₆ H ₄	89
23		148u , R ¹ = R ² = 4-ClC ₆ H ₄	77

Table 3.2 (*continued*)

Entry	Alcohol	Product	Yield (%) ^b
24	61I	150a , R ⁴ = R ⁵ = H	53
25	61I	150b , R ⁴ = R ⁵ = <i>i</i> Pr	40

^a All reactions were performed at 80 °C for 24 h with Yb(OTf)₃/**61**/**144** ratio = 1:10:20. ^b Isolated yield. ^c Reaction conducted at reflux for 48 h. ^d Mixture of unknown side-products afforded based on ¹H NMR analysis of the crude mixture.

were the only instances where the corresponding 4-(1*H*-inden-1-yl)phenols were preferentially obtained in moderate yields (entries 24 and 25).

We tentatively propose the present Yb(OTf)₃ catalyzed indenol-forming reaction to proceed by the mechanism outlined in Scheme 3.2, although it is highly speculative. This could involve activation of the alcohol substrate through coordination of the metal catalyst with the hydroxyl functional group. This delivers the Yb(III)-coordinated intermediate **A**, which undergoes elimination to give the alkynyl cation species **B** and its allenic resonance form **C**. Friedel-Crafts reaction at the acetylenic carbon center in **B** or allenic carbocation center in **C** with **144** followed by subsequent Yb(III)-mediated intramolecular hydroarylation and re-aromatization would provide the indenyl-ytterbium complex **E**. A final protodemetalation step would then deliver the indenol product **148**. The product regioselectivities obtained could be due to trapping at the sterically less hindered carbon center of the presumed ionized species **B** or **C** when R¹ and R² = aryl.¹²² In this manner, any unfavorable

steric interactions between these substituents of the cationic intermediate and the incoming nucleophile would be limited. The possibility of such steric interactions on the regioselectivities obtained would account for our earlier findings showing the exclusive formation of the propargylation product in cases where less sterically demanding secondary and 1,1-dimethylsubstituted alcohols were examined (entries 16 and 18 in Table 3.2).¹²² Indeed, this is further supported by the fact that when a MeNO₂ solution containing **61a** and **144b** was treated with 10 mol% of Yb(OTf)₃ at room temperature under the conditions shown in Scheme 3.3, the allene adduct **151** was obtained as the sole product in 90% yield. On retreating compound **151** to the standard conditions of 10 mol% of Yb(OTf)₃ in MeNO₂ at 80 °C for 12 h, the expected indenol **148o** was obtained in 64% yield, which is comparable to that

Scheme 3.2 Tentative mechanism for Yb(OTf)₃ catalyzed tandem Friedel-Crafts arylation/hydroarylation of **61** with **144**.

furnished from **61o** shown in entry 14 in Table 3.2. The origin of the indene products **150a** and **150b** could be due to competitive cyclization between one of the Ph groups and the phenolic moiety on the respective allene intermediates **D** presumably formed in these reactions. In the former case, it is possible that the proximity of a geminal electron-withdrawing group ($R^3 = p\text{-ClC}_6\text{H}_4$) to that of the phenol moiety (R^4 and $R^5 = \text{H}$) makes hydroarylation via the slightly more electron-rich Ph group in **D** more favorable. In the latter case with steric factors coming to the fore, cyclization of phenol unit (R^4 and $R^5 = i\text{Pr}$) onto the allene functional group in **D** is now sterically unfavorable.

Scheme 3.3 Synthesis of **149** and its conversion to **146o**.

In this work, the conversion of indenols to their indendione derivatives was also examined (Scheme 3.4). Subjecting a CHCl_3 solution containing **148a** to an atmosphere of oxygen for 2.5 days was found to give **152a** in 96% yield.¹²³ The

Scheme 3.4 Oxidation of **148a**, **148c**, and **148f** to **152a-c**.

structure of **152a** was established by X-ray crystallographic analysis (Fig. 3.1).¹²⁴ Under similar conditions, the oxidation of **148c** and **148f** gave the corresponding indendiones **152b** and **152c** in 73% and 64% yield, respectively. In view of the reported potential antifungal, antibiotic, antimalarial, and antitumor activities exhibited by a myriad of compounds with an indendione moiety,¹²⁵ the present method also provides a new route to this important class of carbocycles.

Fig. 3.1 ORTEP drawings of **152a** with thermal ellipsoids at 50% probability levels.

3.3 Conclusion

In summary, an efficient ytterbium catalyzed synthetic route to 6-indenols based on the tandem reaction of propargylic alcohols with phenols has been reported. These results show that the reaction tolerates a structurally diverse set of alcohol substrates that can be accessed in one step from commercially available and low-cost starting materials. Our studies show that while TfOH can also mediate the tandem Friedel-Crafts arylation/hydroarylation process, the lower yields obtained with TfOH and the milder conditions of ytterbium catalysis provides an attractive alternative synthetic route to 6-indenols. The utility of the present method to this class of

carbocycles was also shown by the conversion of three adducts obtained to their indendione derivatives, which are also bioactive compounds of current interest. Efforts are currently underway to apply the method to natural product synthesis and will be reported in due course.

Chapter IV. Synthesis of Highly Substituted Indene Derivatives *via* Brønsted

Acid Catalyzed Nazarov Cyclization of Homoallylic Alcohols

4.1 Introduction

In the previous chapter, we reported $\text{Yb}(\text{OTf})_3$ catalyzed tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols as a synthetic method to 6-indenols.¹²⁶ Drawbacks to this approach was the need for excess amount of phenol nucleophile compound with a substrate scope limited to tertiary propargylic alcohols, in which one of the substitutes must be an aryl group. In this regard, we queried whether an intramolecular approach could be developed that would address such issues. The establishing of a new synthetic method based on Brønsted acid catalysts would also be attractive in view of its low cost, high tolerance to air and moisture and applicability for scale up reactions. While Brønsted acid catalyzed reactions of alcohols pro-electrophile with allylic and benzylic alcohols are known,¹²⁷ to our knowledge, the intramolecular formation of indene derivatives from homoallylic alcohols has not been explored. Herein, we report $p\text{-TsOH}\cdot\text{H}_2\text{O}$ to be an efficient catalyst in Nazarov cyclization of intramolecular homoallylic alcohols in the formation of highly substituted indene derivatives in good to excellent yields (Scheme 4.1).

Scheme 4.1 Synthesis of indenenes **154** from homoallylic alcohols **153**.

4.2 Results and Discussion

We began by choosing 2-methyl-1,1-diphenylbut-3-en-1-ol **153a** as model substrate to establish the reaction conditions (Table 4.1). This revealed that subjecting

Table 4.1 Optimization of the reaction conditions.^a

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> <p>153a</p> </div> <div style="margin: 0 20px; text-align: center;"> $\xrightarrow[\text{Solvent}]{\text{Catalyst}}$ </div> <div style="text-align: center;"> <p>154a</p> </div> </div>				
Entry	Catalyst	Solvent	Time(h)	Yield(%)
1	<i>p</i> -TsOH·H ₂ O	(CH ₂ Cl) ₂	0.5	99
2	<i>p</i> -TsOH·H ₂ O	(CH ₂ Cl) ₂	0.5	99 ^b
3	<i>p</i> -TsOH·H ₂ O	(CH ₂ Cl) ₂	20	62 ^c
4	<i>p</i> -TsOH·H ₂ O	PhMe	15	94
5	<i>p</i> -TsOH·H ₂ O	CH ₃ CN	15	79
6	<i>p</i> -TsOH·H ₂ O	CH ₃ NO ₂	15	68
7	<i>p</i> -TsOH·H ₂ O	1,4-dioxane	15	- ^d
8	Tf ₂ NH	(CH ₂ Cl) ₂	15	trace
9	TfOH	(CH ₂ Cl) ₂	0.5	trace
10	TFA	(CH ₂ Cl) ₂	15	- ^d
11	H ₃ PO ₄ ^e	(CH ₂ Cl) ₂	15	- ^d

^a Unless stated otherwise, all reactions were performed at 80 °C with a catalyst/**153a** ratio of 1:10. ^b Reaction conducted with 5 mol% of *p*-TsOH·H₂O. ^c Reaction conducted at room temperature. ^d No reaction based on TLC and ¹H NMR. ^e Used as a 80% solution in H₂O.

0.3 mmol **153a** in the presence of 10 mol% of *p*-TsOH·H₂O in 1,2-dichloro methane at 80 °C for 0.5 h gave the best yield (Table 4.1, entry 1). Under this conditions, 1,2-dimethyl-3-phenyl-1*H*-indene **154a** was obtained in 99% yield. Similarly, a near quantitative yield was afforded on decreasing the catalyst loading from 10 to 5 mol% (Table 4.1, entry 2). A lower yield was obtained when the reaction was repeated at room temperature, even under prolonged reaction time to 20 h (Table 4.1, entry 3). Similarly, lower product yields were obtained when the reaction solvent was changed from (CH₂Cl)₂ to PhMe, CH₃CN or CH₃NO₂ (Table 4.1, entry 4-6). In our hands, no reaction was observed when 1,4-dioxane was employed as the solvent (Table 4.1, entry 7). However, only trace amount of product was observed when the reaction was performed by using more stronger acid Tf₂NH or TfOH as catalyst (Table 4.1, entries 8-9). There was no reaction in the presence of relative weaker acid such as TFA and H₃PO₄ (Table 4.1, entries 10-11).

Under the optimized catalytic conditions, we explored the scope of the present reaction by examining a series of homoallylic alcohols **153b-s** (Table 4.2). Reactions of homoallylic alcohols **153** bearing an electron-withdrawing group on both of the two phenyl rings gave the corresponding substituted indenenes in good to excellent yields (Table 4.2, entries 1-3). Similarly, the analogous reactions of **153** where the two phenyl rings contained a pendant electron-donating group afforded the corresponding substituted indenenes in good to excellent yields (Table 4.2, entries 4-5). However, when R¹ contained an *ortho*-substituted aromatic group at the carbinol carbon as in **153g**, only unknown products were obtained that could not be identified by ¹H NMR (Table 4.2, entry 6). Cyclization of starting alcohols bearing an electron-withdrawing or electron-donating group on the *para*-position of phenyl ring where the identity of R¹ was methyl group were also found to afford **154g-k** in 58-79

% yield (Table 4.2, entries 7-11). On the other hand, the desired indene product could not be obtained on introducing an indole group at carbinol carbon in place of a phenyl ring (Table 4.2, entry 12). Under the standard conditions, the 1,4-diene compound **155** was obtained in 83% yield. The position of the methyl formed C=C is unusual as the conjugated diene might have been expected to be the thermodynamically favored product. Product yields of 73-76% were obtained when we examined the substitution at R³ (Table 4.2, entries 13-14). In contrast, internal homoallylic alcohols were also examined. The desired product **154n** was obtained in 72% yield. In this case, the cyclization of 1,3-diene to desired product **154n** *via* Michael addition process could be also possible. However, only the intermediate 1,3-diene compound **156** was obtained in 88% yield when **153q** was used as starting alcohol. The ratio of *E/Z* for **156** was 4:1. The conformation of **156** was confirmed by comparison with literature data.¹²⁸ The reason for the no further cyclization of **156** might be the major *E*-isomer was activated by acid catalyst much faster, whose conformation was not suitable for cyclization,¹²⁹ and depletion of acid catalyst for the *Z*-isomer. We also examined secondary homoallylic alcohols, but found no reaction and recovery of only the starting material (Table 4.2, entry 17). When R³ was replaced by proton, the reaction was observed to give a complex mixture of unknown products based on TLC and ¹H NMR analysis of the crude reaction mixture (Table 4.2, entry 18).

Table 4.2 *p*-TsOH·H₂O catalyzed synthesis of substituted indenenes **154b-o**.^a

	153		154	
Entry	Alcohol	Product		Yield (%)
1			154b R = F	98
2			154c R = Cl	88
3			154d R = Br	88
4			154e R = Me	90
5			154f R = OMe	82
6				- ^b
7			154g R = Cl	64
8			154h R = Br	58
9			154i R = H	60
10			154j R = Me	79
11			154k R = OMe	77

Table 4.2 (continued)

Entry	Alcohol	Product	Yield (%)
12	153m	155	83
13	153n-o	154l R= Br	73
14		154m R= H	76
15	151p	154n	72
16	153q	156	88 ^c
17	153r (dr = 1 : 0.8)		- ^d
18	153s		- ^e

^a All reactions were performed at 80 °C in (CH₂Cl)₂ with a *p*-TsOH·H₂O :

153a ratio of 1:20. ^b Mixture of unknown compounds. ^c *E/Z* = 4:1. ^d Only

starting material was recovered. ^e Unknown products based on TLC and ¹H

NMR analysis of the crude reaction mixture.

We tentatively propose a mechanism of the present reaction to proceed as depicted in Scheme 4.2. This could involve activation of homoallylic alcohol **153** in the presence of p -TsOH·H₂O to give **157**, followed by dehydration to deliver the homoallylic carbocation **158**. The intermediate 1,3-diene **159** was formed by deprotonation of **158**. After protonation of **159**, the resultant resonance stabilized allylic carboncation intermediate **160** was formed. Then Nazarov cyclization of **160** to give an indanyl cation, followed by deprotonation to give desired product indene **154**.

Scheme 4.2 Proposed mechanism for the synthesis of indenenes from homoallylic alcohols.

We found that the desired product could not be obtained by introducing an indole group instead of phenyl group in the homoallylic alcohol, due to the formation of 1,4-diene, which is a very special case in indole chemistry.¹³⁰ Here, we propose that the reason for the deprotonation of **153m** with p -TsOH·H₂O at methyl group might be due to the steric hindrance of indole group. The possible mechanism is shown in Scheme 4.3.

Scheme 4.3 Synthesis of 1-methyl-2-(3-methylpenta-1,4-dien-2-yl)-1*H*-indole **155** from **153m**.

4.3 Conclusion

In summary, we have developed a Brønsted acid catalyzed method for the Nazarov cyclization of homoallylic alcohols as an efficient approach to highly substituted indenenes under mild conditions. The reaction was shown to be applicable to a broad substrate scope. This is notable given the demand for more rapid and direct atom economical chemical processes that can make use of low cost and readily available reagents and catalysts.

Chapter V. Brønsted Acid Catalyzed Cyclization of Propargylic Alcohols with Thioamides. Facile Synthesis of Di- and Trisubstituted Thiazoles

5.1 Introduction

Thiazoles are important structural moieties found in many natural products and compounds of current biological and material interest as well as versatile building blocks in organic synthesis.¹³¹⁻¹³⁴ Among the myriad reactions devoted to the construction of this aromatic heterocycle,¹³¹⁻¹³⁴ the most often relied upon synthetic method is the Hantzsch thiazole synthesis,³ which makes use of α -halo ketones and thioamides as the substrates. While recent efforts have led to a number of advances made in the development of this reaction,^{131,134} the establishment of more versatile and flexible methodologies to functionalized thiazoles with selective control of substitution patterns are still needed. This is all the more so if it can be accomplished with low cost and readily available starting materials and catalysts that follow the principles of atom economy.¹³⁵ One such synthetic strategy has been to replace the electrophile in these reactions with a propargylic alcohol in the presence of a Lewis acid catalyst.^{134,136} According to the seminal reports by the groups of Zhan^{134a} and Yoshimatsu,^{134b} these catalytic systems are thought to proceed via either an allenic or propargylic cationic species that underwent the [3 + 2] cycloaddition process. Although shown to be efficient, producing H₂O as potentially the only byproduct, this was countered by the likelihood of forming metal impurities that lessened the potential of this approach for scale-up applications. Added to this is a substrate scope that is limited to ones containing functional groups that cannot take part in strong metal coordination. In this regard, we reasoned that these drawbacks could be readdressed by developing a Brønsted acid catalyzed version of this regioselective

thiazole forming reaction. An inexpensive and commercially available reagent class that has a high tolerance to air and moisture, Brønsted acids have been shown to mediate a wide variety of organic transformations in an efficient and selective manner.¹³⁷⁻¹³⁹ Recently, this has included stereoselective C–X (X = C, N, O, S) bond formation strategies that combine the use of Brønsted acid catalysis with alcohol pro-electrophiles such as allylic, benzylic, and propargylic alcohols.^{138,139} For example, we recently reported TfOH to be a highly efficient catalyst for the regioselective formation of conjugated enynes based on nucleophilic ring-opening of 1-cyclopropyl-2-propyn-1-ols with alcohols.^{138b} As part of an ongoing program exploring the utility of alcohol pro-electrophiles in organic synthesis,^{138b,139} we report herein *p*-TsOH·H₂O catalyzed cyclization of trisubstituted propargylic alcohols with thioamides that did not require air- and moisture-free conditions (Scheme 5.1).

Scheme 5.1 *p*-TsOH·H₂O catalyzed formation of 2,4-di and trisubstituted thiazoles **164** from propargylic alcohols **61** and thioamides **163**.

The 2,4-di- and trisubstituted thiazole products were obtained as a single regioisomer in moderate to excellent yields comparable to those noted for the closely related metal promoted approaches to this aromatic heterocycle.¹³⁴ To our knowledge, a synthetic approach to thiazoles from trisubstituted propargylic alcohols catalyzed by a Brønsted acid is not known.

5.2 Results and Discussion

We began by choosing 1,1,3-triphenylprop-2-yn-1-ol **61a** and thioacetamide **163a** as the model substrates to establish the reaction conditions (Table 5.1). This initially revealed that subjecting 1 equiv of **61a** and 2 equiv of **163a** to 10 mol% of *p*-TsOH·H₂O in 1,2-dichloroethane at 100 °C for 5 h gave the highest yield (entry 1). Under these conditions, 4-benzhydryl-2-methyl-5-phenylthiazole **164a** was afforded in 90% yield, comparable to those obtained for the closely related Sc- and Ag catalyzed reactions.¹³⁴ The structure and regiochemistry of the thiazole product were determined on the basis of ¹H NMR measurements and X-ray crystallographic analysis (Fig 5.1).¹⁴⁰ A slightly lower product yield of 86% was obtained on decreasing the catalyst loading from 10 to 5 mol% (entry 2). In contrast, lower product yields were found when the reaction was repeated with 10 mol% of *p*-TsOH·H₂O at room temperature or on changing the solvent from 1,2-dichloroethane to MeNO₂, MeCN, 1,4-dioxane, or toluene (entries 3-7). A similar outcome was found when stronger Brønsted acid catalysts in place of *p*-TsOH·H₂O were examined (entries 8-10). In these latter reactions, the use of 10 mol% of TfOH, TFA, and H₃PO₄ in MeNO₂ gave **164a** in lower yields of 59-73%. On the basis of these studies, reaction of **61a** with **163a** in the presence of 5 mol% of *p*-TsOH·H₂O in 1,2-dichloroethane at 100 °C for 5 h was deemed to provide the optimal conditions. By applying these conditions, we were pleased to find that a product yield of 927 mg (77%) could be afforded when the reaction was repeated on a large scale with 1 g (3.52 mmol) of **61a** and 0.53 g (7.04 mmol) of **163a**.

Table 5.1 Optimization of the reaction conditions.^a

<div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <chem>c1ccccc1C(O)C#Cc2ccccc2</chem> 61a </div> <div style="text-align: center;"> <chem>CC(=S)N</chem> 163a </div> <div style="text-align: center;"> $\xrightarrow[\text{solvent, air, 100 } ^\circ\text{C}]{\text{catalyst (5 mol\%)}}$ </div> <div style="text-align: center;"> <chem>Cc1nc(Cc2ccccc2)c(Cc3ccccc3)s1</chem> 164a </div> </div>			
Entry	Catalyst	Solvent	Yield (%)
1	<i>p</i> -TsOH·H ₂ O	(CH ₂ Cl) ₂	90
2	<i>p</i> -TsOH·H ₂ O ^b	(CH ₂ Cl) ₂	86
3 ^c	<i>p</i> -TsOH·H ₂ O	(CH ₂ Cl) ₂	39
4	<i>p</i> -TsOH·H ₂ O	MeNO ₂	81
5	<i>p</i> -TsOH·H ₂ O	MeCN	87
6	<i>p</i> -TsOH·H ₂ O	1,4-dioxane	25
7	<i>p</i> -TsOH·H ₂ O	PhMe	86
8	TfOH	MeNO ₂	73
9	TFA	MeNO ₂	70
10	H ₃ PO ₄ ^d	MeNO ₂	59

^a Unless stated otherwise, all reactions were performed at 100 °C for 5 h with a catalyst/**61a**/**163a** ratio of 1:10:20. ^b Reaction conducted with 5 mol% of *p*-TsOH·H₂O. ^c Reaction conducted at room temperature. ^d Used as a 80% solution in H₂O.

Fig. 5.1 ORTEP drawings of **164a** with thermal ellipsoids at 50% probability levels.

To define the generality of the present procedure, we next examined a series of propargylic alcohols **61b-x** and thioamides **163a-h** (Table 4.2 and 4.3). Reactions of propargylic alcohols bearing either an electron-withdrawing or electron-donating group on the carbinol or alkyne carbon with **163a** gave the corresponding thiazoles in good to excellent yields (entries 1-13). Similarly, the analogous cyclizations with starting alcohols containing either an alkyl functional group at R¹ or R³ or a terminal alkyne moiety afforded **164o-q** in 54-79% yield, albeit requiring a catalyst loading of 30 mol% (entries 14, 15, and 17). In contrast, recovery of both the propargylic alcohol and thioamide was found when both substituents on the carbinol carbon of the alcohol substrate were an alkyl functional group as in **61q** (entry 16). A propargylic alcohol containing an acid-sensitive acetylenic ketone moiety was also examined under the standard conditions but was found to give a mixture of decomposition products that could not be identified by ¹H NMR analysis of the crude mixture (entry 22). On the other hand, propargylic alcohols bearing a nitrile, thiophene, or carboxamide moiety were found to proceed well under the present conditions and give the corresponding thiazoles **164e**, **164r**, and **164s** (at a catalyst loading of 30 mol%) in excellent yields (entries 4, 18, and 19). Additionally, reactions of starting alcohols **61a** and **61c** with

Table 5.2 Synthesis of substituted thiazoles **164b-s** catalyzed by *p*-TsOH·H₂O.^a

	61	163	164 or 165
Entry	Alcohol	Product	Yield (%)
1		164b , R ¹ = 4-FC ₆ H ₄	96
2		164c , R ¹ = 4-ClC ₆ H ₄	98
3		164d , R ¹ = 4-BrC ₆ H ₄	93
4		164e , R ¹ = 4-CNC ₆ H ₄	98
5		164f , R ¹ = 4-MeC ₆ H ₄	79
6		164g , R ¹ = R ² = 4-FC ₆ H ₄	94
7		164h , R ¹ = R ² = 4-ClC ₆ H ₄	85
8		164i , R ¹ = R ² = 4-BrC ₆ H ₄	88
9		164j , R ¹ = R ² = 4-MeC ₆ H ₄	74
10		164k , R ³ = 4-FC ₆ H ₄	86
11		164l , R ³ = 4-ClC ₆ H ₄	87
12		164m , R ³ = 4-MeC ₆ H ₄	89
13		164n , R ³ = 4-MeOC ₆ H ₄	69
14 ^b		164o	76

Table 5.2 (continued)

Entry	Alcohol	Product	Yield (%)
15 ^b	61r	164p	79
16	61q		- ^c
17 ^b	61t	164q	54
18	61u	164r	96
19 ^b	61v	164s	78
20	61s, 61w	165a, 165b, R ¹ = R ³ = Ph	75
21			72
22	61x		- ^d

^a All reactions were performed at 100 °C for 1.5-24 h with *p*-TsOH·H₂O/**61**/**163** ratio = 1:20:40. ^b Reaction conducted at 30 mol% catalyst loading. ^c No reaction. ^d Mixture of side products obtained that could not be identified.

Table 5.3 Synthesis of substituted thiazoles **164t-z** catalyzed by *p*-TsOH·H₂O.^a

Entry	Thioamide	Product	Yield (%)	
1	163b		164t , R ¹ = Ph	30
2	163c		164u , R ¹ = 4-ClC ₆ H ₄ , R ⁴ = Ph	91
3	163d		164v , R ¹ = 4-ClC ₆ H ₄ , R ⁴ = 4-FC ₆ H ₄	92
4	163e		164w , R ¹ = R ⁴ = 4-ClC ₆ H ₄	90
5	163f		164x , R ¹ = 4-ClC ₆ H ₄ , R ⁴ = 2-ClC ₆ H ₄	93
6	163g		164y , R ¹ = 4-ClC ₆ H ₄ , R ⁴ = 4-BrC ₆ H ₄	93
7	161h		164z , R ¹ = 4-ClC ₆ H ₄ , R ⁴ = 4-MeOC ₆ H ₄	97

^a All reactions were performed at 100 °C for 1.5-24 h with *p*-TsOH·H₂O/**61**/**163** ratio = 1:20:40.

other thioamide nucleophiles were found to give the corresponding thiazoles in moderate to excellent yields (Table 5.3, entries 1-7).

This included one example of a cyclic thioamide (**163b**) that gave **164t** and the structure of which was confirmed by X-ray crystallography (Fig 5.2).¹⁴⁰ In our hands, reactions of secondary alcohols **61u** and **61v** were the only instances where the

corresponding *N*-propargylation products **165a** and **165b** were preferentially obtained as the sole product in 75 and 72% yield, respectively (Table 5.2, entries 20-21). This contrasts markedly to a recent work reporting *p*-TsOH·H₂O to catalyze the reaction of a closely related secondary propargylic alcohol and thioamide in chlorobenzene giving the corresponding thiazole in 12% yield.^{134a}

Fig. 5.2 ORTEP drawings of **164t** with thermal ellipsoids at 50% probability levels.

We tentatively propose the mechanism of the present reaction to proceed in a manner similar to that described for the analogous metal-catalyzed cyclizations of di- and trisubstituted propargylic alcohols with thioamides.¹³⁴ As depicted in Scheme 4.2, this could involve Brønsted acid mediated dehydration of **61** to deliver alkynyl cation species **B** and its allenic resonance form **C**. Subsequent attack by the thioamide at the sterically less hindered acetylenic carbon center of **B** or allenic carbocation center **C** when followed by 5-*exo-trig* cyclization of the newly formed intermediate **G** would then provide the thiazole product. It might be anticipated that trapping at the sterically less hindered carbon center of **B** or **C** when R¹ and/or R² = aryl would limit any unfavorable steric interactions between the incoming nucleophile and these substituents of the cationic species.¹⁴¹ Indeed, our earlier findings showing the

exclusive formation of the *N*-propargylation adduct in cases where less sterically demanding secondary alcohols were examined would be consistent with the influence of such steric interactions on the regioselectivities found (entries 20 and 21 in Table 4.2). We surmise the origin of the chloro-substituted thiazole **164t** could be due to ring-opening of the iminium cation **G'** by a chloride anion generated in situ from the 1,2-dichloroethane solvent under the acidic conditions.

Scheme 5.2 Tentative mechanism for $p\text{-TsOH}\cdot\text{H}_2\text{O}$ catalyzed cyclization of **61** with **163**.

5.3 Conclusion

In summary, we have developed a Brønsted acid catalyzed method for the cyclization of tertiary propargylic alcohols with thioamides as an efficient approach to

2,4-di- and trisubstituted thiazoles under conditions that did not require the exclusion of air and moisture. The reaction was shown to be applicable to a broad substrate scope that compliments the metal-mediated versions of this transformation.¹³³ Moreover, the possibility of the present operationally simplistic method as a potential regioselective scale-up strategy for thiazole synthesis was exemplified by the large-scale preparation of one example in excellent yield. This is notable given the recent demand for more rapid and direct atom economical chemical processes that can make use of low cost and readily available reagents and catalysts.

**Chapter VI. Efficient Synthesis of Di- and Trisubstituted 2-Aryloxazoles via
Ytterbium(III) Triflate Catalyzed Cyclization of Tertiary Propargylic Alcohols
with Aryl Amides**

6.1 Introduction

Oxazoles constitute an immensely important member of the aromatic heterocycle family due to their presence in a myriad of bioactive natural products, role as privileged pharmacophores and ability to serve as versatile building blocks in organic synthesis.¹⁴² Accordingly, this has led to numerous synthetic methods for constructing this aromatic heterocycle and the continued pursuit of ever more efficient and flexible approaches.¹⁴² Recently, this has hitherto included works describing oxazole synthesis via cyclization of propargylic alcohols as pro-electrophiles¹⁴³ with amides.¹⁴² First reported by Uemura and co-workers, oxazole formation from reaction of these substrates was found to be possible by employing a dual diruthenium(II,III) and gold(III) catalytic system.^{142j} Following this work, Liu and Kumar demonstrated a dual ruthenium(III) and zinc(II) catalyst combination could also mediate the cyclization of propargylic alcohols with amides that afforded the oxazole product in excellent yields.^{142k} More recently, Zhan and co-workers described a Brønsted acid mediated version of this ring forming reaction could be achieved in the presence of a stoichiometric amount of *p*-TsOH·H₂O.^{142l} Although shown to be highly efficient, generating H₂O as potentially the only byproduct, a drawback in these respective synthetic approaches was the need for two metal catalysts, one to achieve alkyne propargylation and another for subsequent cyclization of the resulting propargylated intermediate, or a stoichiometric amount of the Brønsted acid. Added to this is the cost of the catalysts and a substrate scope limited to terminal propargylic alcohols in reactions catalyzed by the dual metal systems. In this regard, we envisioned

ytterbium(III) triflate would hold promise as a catalyst for cyclization of tertiary propargylic alcohols with aryl amides. A low cost and commercially available metal salt that has a high tolerance to air and moisture, $\text{Yb}(\text{OTf})_3$ is one prominent member of the family of lanthanide salts that has been shown to be versatile in mediating a wide variety of organic transformations that make use of alcohol pro-electrophiles in excellent yields and with high selectivity.^{126,88,143b-h} For example, we recently reported $\text{Yb}(\text{OTf})_3$ to be an efficient catalyst for the regioselective formation of indenols based on tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols.¹²⁶ As part of an ongoing program examining the utility of alcohol pro-electrophiles in organic synthesis,^{126, 88-90, 48, 120a, 99a-b, 39, 13, 36, 143i-j} we report herein the use of $\text{Yb}(\text{OTf})_3$ for tandem allenation/cycloisomerization of tertiary propargylic alcohols with aryl amides (Scheme 6.1). The di- and trisubstituted 2-aryloxazole products were obtained in moderate to excellent yields and as a single isomer with regiochemistry opposite to those reported for the closely related dual metal and Brønsted acid promoted synthetic methods.¹⁴²

Scheme 6.1 Synthesis of di- and tri substituted 2-aryloxazoles **167** based on $\text{Yb}(\text{OTf})_3$ catalyzed cyclization of tertiary propargylic alcohols **61** with aryl amides **166**.

6.2 Results and Discussion

At the start of the study, we chose to examine the cyclization of 1,1,3-triphenylprop-2-yn-1-ol **61a** with benzamide **166a** by a variety of Lewis acids to establish the reaction conditions (Table 6.1). This revealed subjecting 1 equiv of **61a** with 2 equiv of **166a** in the presence of 5 mol% of Yb(OTf)₃ in toluene at 100 °C for 24 h gave the best result (entry 1). Under these conditions, 4-benzhydryl-2,5-diphenyloxazole **167a** was furnished in 88% yield (Table 6.1, entry 1), comparable to those obtained for the closely related dual metal and Brønsted acid mediated reactions.¹⁴² The structure and regiochemistry of the oxazole product was determined on the basis of ¹H NMR measurements and X-ray crystallographic analysis (Fig. 6.1)¹⁴⁴. A comparable product yield was afforded on replacing toluene with 1,2-dichloroethane as the solvent or decreasing the amount of **166a** from 2 to 1.2 equiv (Table 6.1, entries 2, 3). In contrast, markedly lower product yields were obtained when the reaction was repeated in MeCN or MeNO₂ in place of toluene as solvent (Table 6.1, entries 4, 5). Low product yields were also found on switching the Lewis acidic catalyst from Yb(OTf)₃ to either AgOTf, CuBr or FeCl₃·6H₂O (Table 6.1, entries 6-8). Moreover, a low product yield of 54% furnished from a control experiment with TfOH as the catalyst provided evidence that, in the presence of potential TfOH formed in situ, the cationic Yb(III) complex is the catalytically active species (Table 6.1, entry 9).

Table 6.1 Optimization of reaction conditions.^a

entry	catalyst	solvent	yield (%) ^b
1	Yb(OTf) ₃	PhMe	88
2 ^c	Yb(OTf) ₃	PhMe	86
3 ^d	Yb(OTf) ₃	(CH ₂ Cl) ₂	85
4 ^d	Yb(OTf) ₃	MeCN	53
5	Yb(OTf) ₃	MeNO ₂	76
6	AgOTf	MeNO ₂	60
7	CuBr	MeNO ₂	56
8	FeCl ₃ ·6H ₂ O	MeNO ₂	40
9	TfOH	MeNO ₂	54

^a All reactions were performed at 100 °C for 24 h with catalyst/**61**/**166a** ratio = 1:20:40. ^b Isolated yield. ^c Reaction conducted with 1.2 equiv of **166a**. ^d Reaction conducted at reflux temperature

Fig. 6.1 ORTEP drawing of 2-aryloxazole **167a** with thermal ellipsoids at 50% probability levels.

With the optimum conditions established, we next explored the scope of the present reaction by examining a series of propargylic alcohols **61b-t** and amides **166a-l** (Table 6.2 and 5.3). This showed that reactions of **166a** with propargylic alcohols bearing an electronwithdrawing group on the carbinol or alkyne carbon gave the corresponding 2-aryloxazoles in good to excellent yields (Table 6.2, entries 1-7). Similarly, the analogous reactions of **166a** with propargylic alcohols where the carbinol or alkyne carbon contained a pendant electron-donating group afforded the corresponding 2-aryloxazoles in good to excellent yields (Table 6.2, entries 8-10). Cyclizations of **166a** with starting alcohols where the identity of R^3 was either an alkyl or heterocycle functional group or a terminal alkyne moiety were also found to proceed well and afford **167l-n** in 51-88% yield (Table 6.2, entries 11-13). In contrast, reactions of **166a** with propargylic alcohols where either or both R^1 and R^2 was a methyl functional group, as in **61p** and **61q**, gave either a mixture of side products that could not be identified by ^1H NMR analysis or near quantitative recovery of the substrates (Table 6.2, entries 14, 15). Similarly, reaction of **166a** with the secondary alcohol **61s** led to the preferential formation of the corresponding *N*-propargylation adduct **168** in 31% yield in addition to recovery of the substrate in 31% yield (entry 16).

Table 6.2 Yb(OTf)₃ catalyzed synthesis of substituted oxazoles **167b-n**.^a

Entry	Alcohol	Product	Yield (%) ^b
1			167b , R ¹ = R ² = 4-FC ₆ H ₄ 80
2	61g-h		167c , R ¹ = R ² = 4-ClC ₆ H ₄ 73
3			167d , R ¹ = 4-FC ₆ H ₄ 91
4			167e , R ¹ = 4-ClC ₆ H ₄ 88
5			167f , R ¹ = 4-BrC ₆ H ₄ 84
6			167g , R ³ = 4-FC ₆ H ₄ 65
7			167h , R ³ = 4-ClC ₆ H ₄ 75
8			167i , R ¹ = R ² = 4-MeC ₆ H ₄ 70
9			167j , R ¹ = 4-MeC ₆ H ₄ , R ² = Ph 88
10			167k , R ³ = 4-MeC ₆ H ₄ 81
11			167l , R ³ = H 51
12			167m , R ³ = <i>n</i> -Bu 73
13			167n 88
	61u		

Tabel 6.2 (continued)

Entry	Alcohol	Product	Yield (%) ^b
14			$R^1 = \text{Me}, R^2 = \text{Ph}$ - ^c
15			$R^1 = R^2 = \text{Me}$ - ^d
16			168 , $R^1 = \text{H}, R^2 = \text{Ph}$ 31 ^e

^a All reactions were performed at 100 °C with Yb(OTf)₃/**61**/**166a** ratio = 1:20:40. ^b Isolated yield. ^c No reaction detected based on TLC and ¹H NMR analysis and near quantitative recovery of the starting materials. ^d Mixture of unknown side products detected based on TLC and ¹H NMR analysis. ^e Starting alcohol was recovered in 31% yield.

An examination of reactions of **61a** with different aryl amides, on the other hand, gave the corresponding 2-aryloxazole adducts **167o-t** in moderate to excellent yields (Table 6.3, entries 1-11). Under the standard conditions, reactions of **61a** with the alkyl amides **166i-k** and urea **166l** were the only instances that resulted in the recovery of the starting alcohol in near quantitative yields, which might due to the strong coordination between the nucleophile and catalyst (Table 6.3, entries 8-11). Later, this hypothesis was confirmed by conducting an experiment in the presence of 2.5 equivalent of Yb(OTf)₃, which only provided the Meyer-Schuster rearrangement product **170** in 99% yield (Scheme 6.2). In addition, treating **61a** with the cyclic amide **166h** was found to afford the ketoamide **169**, structure of which was confirmed by X-ray crystallography (Fig. 6.2),¹⁴⁴ as the sole product in 69% yield

Table 6.3 Yb(OTf)₃ catalyzed synthesis of substituted oxazoles **167o-t**.^a

Entry	Amide	Product	Yield (%) ^b
1		167o , R ⁴ = 2-MeC ₆ H ₄	70
2		167p , R ⁴ = 3-MeC ₆ H ₄	60
3	 166b-g	 167q , R ⁴ = 4-MeC ₆ H ₄	57
4		 167r , R ⁴ = 4-MeOC ₆ H ₄	64
5		167s , R ⁴ = 4-BrC ₆ H ₄	79
6		167t , R ⁴ = 2-ClC ₆ H ₄	66
7	 166h	 169	69
8	 166i		– ^c
9	 166j		– ^c
10	 166k		– ^c
11	 166l		– ^c

^a All reactions were performed at 100 °C with Yb(OTf)₃/**61a**/**166** ratio = 1:20:40. ^bIsolated yield. ^c No reaction detected based on TLC and ¹H NMR analysis and near quantitative recovery of the starting materials.

(Table 6.3, entry 7). A similar outcome in product chemoselectivity leading to preferential formation of the ketoamide adduct from reaction of a secondary propargylic alcohol with cyclic amide **166h** has also been reported for the analogous *p*-TsOH·H₂O mediated approach.^{142k}

Fig. 6.2 ORTEP drawing of ketoamide **169** with thermal ellipsoids at 50% probability levels.

Although highly speculative, we tentatively propose the present Yb(OTf)₃ catalyzed oxazole forming reaction to proceed by the mechanism outlined in Scheme 6.3. In a manner similar to that proposed for the Yb(OTf)₃ mediated tandem Friedel-Crafts arylation/hydroarylation of propargylic alcohols with phenols, this could involve initial activation of the propargylic alcohol resulting from coordination of the Lewis acid to the hydroxy group.¹²⁶ This provides the Yb(III)-coordinated complex **A** which can undergo elimination to furnish the alkynyl and allenic cation species **B** and **C** as well as [Yb]-OH, which releases the metal catalyst upon protodemetalation. Attack by the aryl amide at the sterically less hindered carbon center of **B** or **C** followed by 5-*exo-trig* cyclization of the newly formed allene intermediate **H** would then deliver the oxazole product. The regioselective outcome of the reaction could be due to nucleophilic attack at the sterically less hindered carbon

center of **B** or **C** when R^1 and $R^2 = \text{aryl}$.^{126,143b, d, k-p} In this manner, any unfavorable steric interactions between the incoming nucleophile and the substituents of the cationic species would be limited. Our earlier findings showing preferential formation of the *N*-propargylation product **168** with the less sterically demanding secondary alcohol **61q** would be consistent with the influence of such steric interactions on the regioselectivities obtained (entry 16 in Table 6.2). In addition, if the cationic species that is involved in the nucleophilic addition step is closer to intermediate **C** in character, a further consequence would be attack of the aryl amide through the less nucleophilic oxygen atom. We surmise that the formation of the ketoamide **169** could be due to facile ring opening of the iminium cation **I** by H_2O generated *in situ* from

Scheme 6.2 Tentative mechanism for $\text{Yb}(\text{OTf})_3$ catalyzed cyclization of **61** with **166** and formation of **169**.

elimination of the OH functional group of the propargylic substrate or the presence of trace amounts of H₂O in the toluene solvent, as shown in Scheme 6.2. A similar rationale for the formation of the ketoamide adduct in the analogous *p*-TsOH·H₂O mediated reaction of a secondary propargylic alcohol with cyclic amide **166h** was also put forward by Zhan and co-workers.^{142l}

Scheme 6.3 Experiment conducted to elucidate the mechanism.

6.3 Conclusion

In summary, we have developed an approach for di- and tri substituted 2-aryloxazole synthesis that relies on the cyclization of tertiary propargylic alcohols and aryl amides in the presence of Yb(OTf)₃ as the catalyst. The reactions were shown to proceed in moderate to excellent product yields and be applicable to a broad substrate scope that compliments the analogous dual metal and Brønsted acid mediated versions of this ring forming process.¹⁴² The regiochemistry of 2-aryloxazole products obtained were also found to be the opposite of those furnished for the dual metal and Brønsted acid mediated reactions. With the recent shift in emphasis in green chemistry for more rapid and direct atom economical chemical processes that can make use of ecologically benign, low cost and readily available reagents and catalysts, the present Yb(OTf)₃ strategy thus offers one such method to this class of synthetically useful aromatic heterocycles.

Chapter VII. Experimental Section

7.1 General Remarks

All reactions were performed open to the atmosphere. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. All cyclic MBH alcohol substrates reported in this work were prepared following literature procedures.¹⁴⁵ Solvents were purified following standard literature procedures; CH₂Cl₂ was purified prior to use by passing through a PURESOLV(tm) Solvent Purification System. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Unless otherwise stated, ¹H and ¹³C NMR spectra were measured on Bruker Avance 400 MHz spectrometer. Unless otherwise stated, chemical shifts (ppm) were recorded with respect to TMS in CDCl₃. Multiplicities were given as: s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet, doublet) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Infrared spectra were recorded on Shimadzu IR Prestige-21 FTIR Spectrometer. High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP LC/HRMS. Mass spectral data were reported in units of mass to charge (*m/z*). Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Daicel Chirapak AD-H or OJ-H column.

7.2 Iron(III) Chloride Catalyzed Direct Nucleophilic α -Substitution of Morita-Baylis-Hillman Alcohols with Alcohols, Arenes, 1,3-Dicarbonyl Compounds and Thiols

General Procedure for Optimizing the Lewis Acid-Catalyzed α -Substitution of **143a** with **21a**

To a solution of CH_2Cl_2 (3 mL) contained in a round bottom flask open to air at room temperature was successively added **143a** (0.25 mmol), **21a** (0.5 mmol) and 10 mol% of the Lewis acid. The reaction mixture was stirred at room temperature or 40 °C and monitored by TLC analysis. On completion, the solvent was removed under reduced pressure and the resultant residue obtained was directly purified by flash column chromatography (EtOAc/*n*-hexane) to afford the product **145a**.

General Procedure for Iron(III) Chloride Catalyzed α -Substitution of Cyclic MBH Alcohols **143** with **21b-d**, **142a-b**, **65a-c**, **66a-c**

To a solution of CH_2Cl_2 (3 mL) contained in a round bottom flask open to air at room temperature was successively added **143** (0.25 mmol), **21b-d** or **142a-b** or **65a-c**

or **66a-c** (0.5 mmol) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.025 mmol). The reaction mixture was stirred at 40 °C and monitored by TLC analysis. On cooling to room temperature, the solvent was removed under reduced pressure and the resultant residue obtained was purified by flash column chromatography (EtOAc/*n*-hexane) to afford the product **145**.

2-((6-Oxocyclohex-1-enyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione 145a

White solid; yield: 92%; m.p. 177-178 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.56-1.65 (m, 1H), 1.72-1.79 (m, 1H), 2.05-2.25 (m, 4H), 4.87 (d, $J = 11.4$ Hz, 1H), 6.73 (d, $J = 11.4$ Hz, 1H), 6.95 (t, $J = 4.1$ Hz, 1H), 7.03-7.54 (m, 11H), 7.86 (d, $J = 7.4$ Hz, 2H), 8.00 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.3, 26.2, 39.0, 50.0, 59.2, 126.6, 128.2, 128.5, 128.6, 128.7, 128.8, 129.0, 133.2, 133.5, 136.8, 137.0, 139.4, 140.4, 148.7, 194.4, 195.1, 199.2; IR (neat): 3019, 1697, 1670, 1215, 756, 667, 513 cm^{-1} ; MS (ESI) m/z 409 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{25}\text{O}_3$: 409.1804, found: 409.1811.

3-((6-Oxocyclohex-1-enyl)(phenyl)methyl)pentane-2,4-dione 145b

White solid; yield: 90%; m.p. 110-111 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.89-1.90 (m, 5H), 2.14 (s, 3H), 2.33-2.38 (m, 4H), 4.68 (d, $J = 12.5$ Hz, 1H), 4.78 (d, $J = 12.5$ Hz, 1H), 6.90 (t, $J = 3.8$ Hz, 1H), 7.17-7.27 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.5, 26.2, 28.5, 30.7, 38.6, 44.5, 72.8, 127.0, 128.1, 128.6, 139.5, 140.0, 146.3, 197.9,

202.9, 203.1; IR (neat): 3019, 1730, 1697, 1674, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 285 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{O}_3$: 285.1491, found: 285.1490.

2-((6-Oxocyclohex-1-enyl)(phenyl)methyl)-1-phenylbutane-1,3-dione 145c

Pale yellow solid; yield: 92%; m.p. 120-121 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 1.68-1.77 (m, 2H), 1.91-1.94 (m, 2H), 1.99 (s, 3H), 2.12 (s, 3H), 2.21-2.22 (m, 4H), 2.38-2.41 (m, 4H), 4.86 (d, $J = 12.0$ Hz, 1H), 5.05 (d, $J = 12.1$ Hz, 1H), 5.58 (d, $J = 12.1$ Hz, 1H), 5.78 (d, $J = 12.0$ Hz, 1H), 6.84 (t, $J = 4.0$ Hz, 1H), 7.02-7.89 (m, 17H), 7.88 (d, $J = 7.6$, 2H), 8.05 (d, $J = 7.6$, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.3, 22.5, 26.1, 26.3, 27.5, 28.6, 38.7, 38.8, 45.1, 46.9, 66.3, 67.2, 126.7, 127.0, 128.1, 128.4, 128.4, 128.6, 128.7, 128.7, 128.9, 128.9, 133.6, 133.7, 136.9, 137.0, 139.5, 139.7, 140.1, 140.4, 146.6, 147.8, 194.5, 194.7, 198.2, 198.4, 202.9, 203.5; IR (neat): 3024, 2926, 1722, 1676, 1595, 1236, 756, 665 cm^{-1} ; MS (ESI) m/z 347 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{23}\text{O}_3$: 347.1647, found: 347.1648.

Ethyl 2-benzoyl-3-(6-oxocyclohex-1-enyl)-3-phenylpropanoate 145d

Yield: 97%; Major isomer: white solid; m.p. 166-167 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 0.91 (t, $J = 7.1$ Hz, 3H), 1.72-1.79 (m, 2H), 2.15-2.28 (m, 4H), 3.86-3.89 (m, 2H), 4.76 (d, $J = 11.8$ Hz, 1H), 5.57 (d, $J = 11.8$ Hz, 1H), 6.84 (t, $J = 4.0$ Hz, 1H), 7.18-7.58 (m, 8H), 8.07 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 13.7,

22.3, 26.1, 38.8, 47.1, 57.4, 61.4, 126.8, 128.3, 128.5, 128.7, 128.9, 133.6, 136.6, 139.6, 140.4, 146.5, 168.0, 193.7, 198.3; IR (neat): 3019, 1733, 1682, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 377 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{25}\text{O}_4$: 377.1753, found: 377.1735. Minor isomer: white solid; m.p. 120-121 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 1.14 (t, $J = 7.0$ Hz, 3H), 1.90-1.94 (m, 2H), 2.36-2.40 (m, 4H), 4.02-4.13 (m, 2H), 4.82 (d, $J = 11.8$ Hz, 1H), 5.58 (d, $J = 11.8$ Hz, 1H), 7.02-7.54 (m, 9H), 7.95 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.1, 22.6, 26.3, 38.9, 46.7, 56.8, 61.5, 126.5, 128.2, 128.2, 128.6, 128.7, 133.4, 136.7, 140.0, 140.3, 147.0, 168.3, 193.2, 198.1; IR (neat): 3019, 1734, 1682, 1215, 754, 665 cm^{-1} ; MS (ESI) m/z 377 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{25}\text{O}_4$: 377.1753, found: 377.1744.

2-((4-Nitrophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione

145e

Pale yellow solid; yield: 80% m.p. 174-175 $^{\circ}\text{C}$; ^1H NMR(CDCl_3 , 400 MHz): δ 1.53-1.56 (m, 1H), 1.73-1.76 (m, 1H), 2.00-2.27 (m, 4 H), 4.89 (d, $J = 11.3$ Hz, 1H), 6.77 (d, $J = 11.3$ Hz, 1H), 7.00 (t, $J = 4.1$ Hz, 1H), 7.34-7.60 (m, 8 H), 7.89 (d, $J = 7.2$ Hz, 2H), 8.00-8.03 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.1, 26.2, 38.8, 50.3, 58.0, 123.4, 128.6, 128.8, 129.0, 129.0, 129.3, 133.7, 133.9, 136.5, 138.1, 146.5, 148.2, 150.3, 193.5, 194.7, 199.2; IR (neat): 3019, 1694, 1668, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 454 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{24}\text{NO}_5$: 454.1654, found: 454.1646.

2-((4-Fluorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione
e 145f

White solid; yield: 99%; m.p. 160-162 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.61-1.77 (m, 2H), 2.05-2.12 (m, 1H), 2.19-2.26 (m, 3H), 4.85 (d, $J = 11.4$ Hz, 1H), 6.69 (d, $J = 11.4$ Hz, 1H), 6.79-6.83 (m, 2H), 6.94 (t, $J = 8.3$ Hz, 1H), 7.27-7.54 (m, 8H), 7.86 (d, $J = 7.6$ Hz, 2H), 8.00 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.3, 26.2, 39.0, 49.4, 59.2, 114.9, 115.1, 128.6, 128.8, 128.9, 130.0, 130.1, 133.3, 133.5, 136.1, 136.8, 136.9, 139.2, 148.8, 160.2, 162.7, 194.2, 194.9, 199.3; IR (neat): 3017, 2928, 1694, 1670, 1595, 1223, 754, 687 cm^{-1} ; MS (ESI) m/z 427 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{24}\text{FO}_4$: 427.1709, found: 427.1703.

2-((4-Chlorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione
e 145g

White solid; yield: 95%; m.p. 178-179 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.62-1.63 (m, 1H), 1.74-1.79 (m, 1H), 2.03-2.10 (m, 1H), 2.17-2.27 (m, 3H), 4.82 (d, $J = 11.4$ Hz, 1H), 6.70 (d, $J = 11.4$ Hz, 1H), 6.94 (t, $J = 8.1$ Hz, 1H), 7.09-7.56 (m, 10H), 7.87 (d, $J = 7.6$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.2,

26.2, 39.0, 49.7, 58.9, 128.3, 128.3, 128.6, 128.7, 128.8, 129.0, 129.9, 132.3, 133.4, 133.6, 136.7, 136.9, 139.0, 149.1, 194.0, 194.9, 199.2; IR (neat): 3019, 1695, 1653, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 443 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{24}\text{ClO}_3$: 443.1414, found: 443.1416.

2-((4-Bromophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione 145h

White solid; yield: 91%; m.p. 190-191 $^{\circ}\text{C}$; ^1H NMR(CDCl_3 , 400 MHz): δ 1.57-1.60 (m, 1H), 1.62-1.78 (m, 1H), 2.05-2.09 (m, 1H), 2.16-2.26 (m, 3H), 4.81 (d, $J = 11.4$ Hz, 1H), 6.70 (d, $J = 11.4$ Hz, 1H), 6.94 (t, $J = 4.2$ Hz 1H), 7.20-8.00 (m, 14H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.2, 26.2, 38.9, 49.7, 58.8, 120.5, 128.6, 128.7, 128.8, 129.0, 130.2, 131.3, 133.4, 133.6, 136.7, 136.8, 138.9, 139.5, 149.2, 194.0, 194.9, 199.2; IR (neat): 3019, 1695, 1653, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 487 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{24}\text{BrO}_3$: 487.0909, found: 487.0912.

2-((6-Oxocyclohex-1-enyl)(*p*-tolyl)methyl)-1,3-diphenylpropane-1,3-dione 145i

Pale brown solid; yield: 66%; m.p. 204-205 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ

1.58-1.61 (m, 1H), 1.70-1.75 (m, 1H), 2.04-2.09 (m, 2H), 2.18 (s, 3H), 2.21-2.22 (m, 2H), 4.86 (d, $J = 11.4$ Hz, 1H), 6.72 (d, $J = 11.4$ Hz, 1H), 7.20-7.22 (m, 3H), 7.26-7.52 (m, 8H), 7.87 (d, $J = 7.6$ Hz, 2H), 8.01 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR(CDCl_3 , 100 MHz): δ 20.9, 22.3, 26.2, 39.0, 49.6, 59.4, 128.3, 128.5, 128.7, 128.7, 129.0, 129.0, 133.1, 133.4, 136.0, 136.9, 137.1, 137.4, 139.5, 148.5, 194.3, 195.2, 199.2; IR (neat): 3019, 1690, 1667, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 445 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{26}\text{O}_3\text{Na}$: 445.1780, found: 445.1768.

2-((4-Ethoxyphenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenyl propane-1,3-dione 145j

White solid; yield: 40%; m.p. 215-216 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 1.31 (t, $J = 7.0$ Hz, 3H), 1.63-1.79 (m, 2H), 2.04-2.26 (m, 4H), 3.88 (q, $J = 7.2$ Hz, 2H), 4.83 (d, $J = 11.4$ Hz, 1H), 6.64-6.69 (m, 3H), 6.92 (t, $J = 3.9$ Hz, 1H), 7.21-7.53 (m, 8H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.8, 22.3, 26.2, 39.0, 49.2, 59.7, 63.2, 114.2, 128.5, 128.7, 128.7, 129.0, 129.5, 132.3, 133.1, 133.4, 136.9, 137.1, 139.6, 148.3, 157.5, 194.5, 195.1, 199.3; IR (neat): 3019, 1692, 1674, 1661, 1215, 756, 667 cm^{-1} ; MS(ESI) m/z 475 $[\text{M} + \text{Na}]^+$; HRMS(ESI) calcd for $\text{C}_{30}\text{H}_{28}\text{O}_4\text{Na}$: 475.1885, found: 475.1881.

2-((2-Chlorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione 145l

White solid; yield: 88%; m.p. 169-170 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.43-1.48 (m, 1H), 1.68-1.70 (m, 1H), 1.96-2.24 (m, 4H), 5.20 (d, $J = 11.2$ Hz, 1H), 6.92 (d, $J = 11.2$ Hz, 1H), 6.99-7.08 (m, 3H), 7.22-7.68 (m, 8H), 7.89 (d, $J = 7.2$ Hz, 2H), 8.04 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR(CDCl_3 , 100 MHz): δ 22.1, 26.2, 39.1, 47.2, 57.7, 126.3, 127.7, 128.5, 128.6, 128.8, 129.0, 129.9, 133.3, 133.6, 133.6, 134.5, 136.3, 136.9, 136.9, 137.2, 152.1, 193.5, 195.5, 199.7; IR (neat): 3019, 1697, 1670, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 443 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{24}\text{ClO}_3$: 443.1414, found: 443.1408.

2-((4-Chlorophenyl)(5-oxocyclopent-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione 145m

White solid; yield: 84%; m.p. 195-196 °C; ^1H NMR(CDCl_3 , 400 MHz): δ 2.17-2.33 (m, 2H), 2.46-2.47 (m, 2H), 4.97 (d, $J = 11.2$, 1H), 6.75 (d, $J = 11.2$ Hz, 1H), 7.08-7.10 (m, 2 H), 7.31-7.52 (m, 9H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.97 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 26.7, 35.3, 45.1, 58.9, 128.6, 128.6, 128.7, 128.8,

128.9, 130.1, 132.8, 133.4, 133.6, 136.6, 136.7, 138.3, 145.3, 161.7, 194.2, 194.3, 209.4; IR (neat): 3393, 1686, 1659, 756 cm^{-1} ; MS (ESI) m/z 429 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{22}\text{ClO}_3$: 429.1257, found: 429.1260.

2-((4-Chlorophenyl)(4-oxo-4H-chromen-3-yl)methyl)-1,3-diphenylpropane-1,3-dione 145n

Pale yellow solid; yield: 61%; m.p. 213-214 $^{\circ}\text{C}$; ^1H NMR(CDCl_3 , 400 MHz): δ 4.93 (d, $J = 10.9$ Hz, 1H), 7.09-7.12 (m, 2H), 7.31-7.60 (m, 12H), 7.93-8.12 (m, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 47.4, 57.4, 118.1, 123.6, 124.3, 125.2, 125.7, 128.5, 128.7, 128.7, 128.9, 128.9, 130.2, 132.8, 133.5, 133.7, 136.7, 136.7, 138.5, 155.1, 155.9, 178.0, 194.2, 194.7; IR (neat): 3019, 1690, 1634, 1466, 1263, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 493 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{22}\text{ClO}_4$: 493.1207, found: 493.1214.

2-((4-Hydroxy-3-methylphenyl)(phenyl)methyl)cyclohex-2-enone 145o

Colorless oil; yield: 62%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.99-2.02 (m, 2H), 2.15 (s, 1H), 2.37-2.38 (m, 2H), 2.44-2.47 (m, 2H), 5.36 (s, 1H), 5.39 (s, 1H), 6.42 (s, 1H),

6.58-6.60 (m, 2H), 6.71-6.74 (m, 1H), 6.83 (s, 1H), 7.06-7.08 (m, 2H), 7.15-7.18 (m, 1H), 7.23-7.27 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.0, 22.9, 26.2, 38.7, 48.6, 114.7, 123.8, 126.2, 127.4, 128.3, 129.0, 131.6, 134.1, 142.8, 143.0, 148.2, 152.5, 198.7; IR (neat) 1662, 1505, 1269, 910, 730 cm^{-1} ; MS (ESI) m/z 293 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_2$: 293.1542, found: 293.1542.

2-({4-Hydroxy-3,5-dimethylphenyl}(phenyl)methyl)cyclohex-2-enone 145p

White solid; yield: 88%; m.p. 174-176 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 1.98-2.04 (m, 2H), 2.17 (s, 6H), 2.37-2.47 (m, 4H), 4.60 (s, 1H), 5.36 (s, 1H), 6.41 (t, 1H, J = 4.0 Hz), 6.68 (s, 2H), 7.07-7.27 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 16.1, 22.9, 26.2, 38.7, 48.6, 122.8, 126.1, 128.2, 129.0, 129.1, 133.8, 142.8, 143.1, 147.8, 150.7, 198.2; IR (neat) 1670, 1489, 1263, 908, 738 cm^{-1} ; HRMS (ESI) calcd. For $\text{C}_{21}\text{H}_{22}\text{O}_2\text{Na}$: 329.1517, found: 329.1977.

2-(Ethoxy(phenyl)methyl)cyclohex-2-enone 145q

Colorless oil; yield: 94%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.20 (t, J = 7.0 Hz, 3H), 1.92-2.00 (m, 2H), 2.32-2.45 (m, 4H), 3.44 (q, J = 7.2 Hz, 2H), 5.38 (s, 1H), 7.02 (t, J = 4.8 Hz, 1H), 7.20-7.36 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 15.3, 22.6, 25.8, 38.4, 64.6, 76.3, 127.1, 127.3, 128.2, 140.9, 142.2, 145.7, 197.9; IR (neat): 2926,

1672, 1454, 1377, 1169, 1086, 698 cm^{-1} ; MS (ESI) m/z 185 $[\text{M} - \text{OC}_2\text{H}_5]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966, found: 185.0958.

2-(Benzyloxy(phenyl)methyl)cyclohex-2-enone 145r

Pale yellow oil; yield: 95%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.90-2.00 (m, 2H), 2.34-2.43 (m, 4H), 4.42-4.48 (m, 2H), 5.48 (s, 1H), 7.10 (t, $J = 4.0$ Hz 1H), 7.23-7.40 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.6, 25.8, 38.5, 71.0, 76.4, 127.3, 127.5, 127.6, 127.8, 128.3, 128.3, 138.4, 140.7, 140.8, 145.9, 197.8; IR (neat): 3391, 2922, 1663, 1452, 1375, 1169, 734, 696 cm^{-1} ; MS (ESI) m/z 293 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{O}_2$: 293.1542, found: 293.1536.

2-((But-3-enyloxy)(phenyl)methyl)cyclohex-2-enone 145s

Pale yellow oil; yield: 85%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.90-2.00 (m, 2H), 2.31-2.43 (m, 6H), 3.41-3.46 (m, 2H), 4.99-5.07 (m, 2H), 5.36 (s, 1H), 5.74-5.85 (m, 1H), 7.23 (t, $J = 7.2$ Hz, 1H), 7.25-7.35 (m, 5 H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.6, 25.8, 34.3, 38.4, 68.5, 76.5, 116.3, 127.1, 127.4, 128.2, 135.3, 140.8, 141.1, 145.8, 197.9; IR (neat): 2926, 1674, 1641, 1454, 1375, 1086, 1074, 914, 700, 525 cm^{-1} ; MS (ESI) m/z 185 $[\text{M} - \text{OC}_4\text{H}_6]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966, found: 185.0961.

2-((Ethylthio)(phenyl)methyl)cyclohex-2-enone 145t

White solid; yield: 96%; m.p. 41-42 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.17-1.21 (m, 3H), 1.92-2.00 (m, 2H), 2.35-2.5 (m, 6H), 5.25 (s, 1H), 7.12 (t, $J = 3.8$, 1H), 7.18-7.40 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.2, 22.7, 26.2, 26.4, 38.4, 45.2, 127.0, 128.3, 128.4, 140.0, 141.0, 147.3, 197.2; IR (neat): 3017, 1670, 1454, 1373, 1215, 756, 667 cm^{-1} ; MS (ESI) m/z 185 $[\text{M} - \text{SC}_2\text{H}_5]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966, found: 185.0959.

2-((4-Chlorophenylthio)(phenyl)methyl)cyclohex-2-enone 145u

Colorless oil; yield: 87%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.94-1.97 (m, 2H), 2.39-2.46 (m, 4H), 5.63 (s, 1H), 7.12-7.35 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.6, 26.2, 38.3, 49.0, 127.4, 128.3, 128.5, 128.9, 131.5, 132.6, 134.5, 139.0, 139.7, 148.2, 197.1; IR (neat): 2947, 2926, 1672, 1476, 1452, 1371, 1246, 1167, 1094, 1011, 812, 723, 696, 507 cm^{-1} ; MS (ESI) m/z 185 $[\text{M} - \text{SClC}_6\text{H}_4]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966, found: 185.0961.

2-(Phenyl(*p*-tolylthio)methyl)cyclohex-2-enone 145v

Colorless oil; yield: 83%; ^1H NMR (CDCl_3 , 400 MHz): δ 1.92-1.97 (m, 2H), 2.26 (s, 3H), 2.38-2.47 (m, 4H), 5.60 (s, 1H), 6.98-7.00 (m, 2H), 7.13-7.27 (m, 4H), 7.35-7.37 (m, 2H), 7.97 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.1, 22.6, 26.2, 38.4, 49.4, 127.1, 128.3, 128.4, 129.6, 130.9, 132.2, 136.7, 139.3, 140.3, 148.0, 197.2; IR (neat): 3026, 2945, 2866, 1672, 1634, 1597, 1492, 1452, 1371, 1246, 1167, 1130, 1090, 979, 802, 721, 698, 525 cm^{-1} ; MS (ESI) m/z 185 $[\text{M} - \text{SC}_7\text{H}_7]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966, found: 185.0960.

7.3 Ytterbium(III) Triflate Catalyzed Tandem Friedel-Crafts Arylation/Hydroarylation of Propargylic Alcohols with Phenols as an Expedient Route to Indenols

Representative Experimental Procedure for the Preparation of Propargylic Alcohols 61

To a solution of alkyne (3 mmol, 1.0 equiv.) in THF was added LDA (2.0 M in THF, 2.25 mL, 1.5 equiv.) at -78 $^\circ\text{C}$. The resulting solution was stirred for a further 1 h at -78 $^\circ\text{C}$ prior to slow addition of the ketone or aldehyde (3 mmol, 1.0 equiv.) in THF (2 mL). The resulting reaction mixture was warmed up to room temperature and

stirred for a further 10 h. On completion, the reaction mixture was quenched by addition of saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Mg_2SO_4 , concentrated under reduced pressure, and purified by flash column chromatography on silica gel (eluent: *n*-hexane: ethyl acetate = 9: 1) to give the title compound.

Experimental Procedure for the Preparation of 1,1-Diphenylprop-2-yn-1-ol **61t**¹⁴⁶

To a solution of benzophenone (0.55 g, 3.0 mmol, 1.0 equiv.) in THF was added Ethynylmagnesium bromide (0.5 M in THF, 9.0 mL, 1.5 equiv.) at $-78\text{ }^\circ\text{C}$. The resulting solution was stirred for 1 h at $-78\text{ }^\circ\text{C}$ further 10 h at room temperature. The reaction mixture was quenched by addition of saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine, dried over Mg_2SO_4 then the solvent was removed under reduced pressure and isolated via column chromatography on silica gel to give the desired product.

Representative Experimental Procedure for $\text{Yb}(\text{OTf})_3$ Catalyzed Preparation of Indenols **148**

To a 5 mL round-bottom flask were successively added **61** (0.25 mmol), **142** (0.5 mmol), $\text{Yb}(\text{OTf})_3$ (0.025 mmol) and CH_3NO_2 (3 mL). The resultant reaction mixture

was heated to 80 °C and stirred at this temperature for 24 h. On cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (EtOAc/*n*-hexane: 1/20→1/15; CH₂Cl₂/*n*-hexane for **148q**: 1/1 v/v) to give the title compound.

Experimental Procedure for the Two Step Synthesis of 1-Isopropyl-5,7-dimethyl-1,3-diphenyl-1*H*-inden-6-ol **148o**

To a 5 mL round-bottom flask were successively added **61o** (0.25 mmol), **142a** (0.5 mmol), Yb(OTf)₃ (0.025 mmol) and CH₃NO₂ (3 mL). The resultant reaction mixture was stirred at room temperature for 12 h. On completion, the reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (EtOAc/*n*-hexane: 1/20→1/15) gave allene **149** in 90% yield. Further dissolution of **149** in CH₃NO₂ (3 mL) and addition of Yb(OTf)₃ (0.025 mmol), the resultant reaction mixture was heated to 80 °C and stirred at this temperature for 12 h. On cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (EtOAc/*n*-hexane: 1/20→1/15) to afford **148o** in 64% yield.

Representative Experimental Procedure for the Synthesis of Indendiones 152

To a 5 mL round-bottom flask containing **148** (0.25mmol) in CHCl_3 (3 mL) at room temperature was purged with an oxygen balloon. The reaction mixture maintained under an atmosphere of oxygen and monitored by TLC analysis until completion. The reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (EtOAc/*n*-hexane: 1/20→1/15) to give the title compound.

1,1,3-Triphenylprop-2-yn-1-ol 61a^{147a-b}

^1H NMR (CDCl_3 , 400 MHz): δ 2.89 (s, 1H), 7.22-7.38 (m, 9H), 7.52-7.54 (m, 2H), 7.69-7.70 (d, $J = 7.8$ Hz, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 74.9, 87.3, 91.7, 122.4, 126.1, 127.8, 128.3, 128.7, 131.8, 145.0.

1-(4-Fluorophenyl)-1,3-diphenylprop-2-yn-1-ol 61b

Yellow solid; m.p. 61-62 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.95 (s, 1H), 6.99-7.03 (m, 2H), 7.28-7.37 (m, 6H), 7.50-7.51 (m, 2H), 7.62-7.66 (m, 4H); ^{13}C NMR (CDCl_3 ,

100 MHz): δ 74.4, 87.5, 91.4, 115.1 (1C, d, $J_{C-F} = 21.5$ Hz), 122.3, 126.0, 127.9, 128.0, 128.4, 128.8, 131.8, 140.9, 144.9, 162.3 (1C, d, $J_{C-F} = 244.9$ Hz). IR (neat): 3588, 2120, 1601, 1450, 1231, 838 cm^{-1} ; MS (ESI) m/z 285 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{14}\text{F}$: 285.1080, found: 285.1078.

1-(4-Chlorophenyl)-1,3-diphenylprop-2-yn-1-ol 61c¹⁴⁸

^1H NMR (CDCl_3 , 500 MHz): δ 2.87 (s, 1H), 7.30-7.36 (m, 8H), 7.50-7.52 (m, 2H), 7.60-7.67 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 74.4, 87.6, 91.1, 122.2, 126.0, 127.6, 128.0, 128.4, 128.5, 128.5, 128.9, 131.8, 133.6, 143.6, 144.7.

1-(4-Bromophenyl)-1,3-diphenylprop-2-yn-1-ol 61d

Yellow solid; m.p. 97-98 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz): δ 2.94 (s, 1H), 7.31-7.38 (m, 8H), 7.47-7.57 (m, 4H), 7.66-7.67 (d, $J = 8$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 74.4, 87.6, 91.1, 121.9, 122.2, 126.0, 127.9, 128.0, 128.4, 128.5, 128.9, 131.4, 131.8, 144.2, 144.6. IR (neat): 3597, 2110, 1443, 1217, 894 cm^{-1} ; MS (ESI) m/z 345 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{14}\text{Br}$: 345.0279, found: 345.0274.

4-(1-Hydroxy-1,3-diphenylprop-2-ynyl)benzonitrile 61e

Yellow solid; m.p. 140-141 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 3.03 (s, 1H), 7.30-7.39 (m, 6H), 7.50-7.52 (m, 2H), 7.62-7.66 (m, 4H), 7.78-7.80 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 74.4, 88.2, 90.5, 111.4, 118.8, 121.9, 126.0, 126.8, 128.4, 128.5, 128.7, 129.1, 131.8, 132.2, 144.1, 150.2. IR (neat): 3413, 3021, 2232, 1607, 1490, 1215, 739 cm^{-1} ; MS (ESI) m/z 292 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{14}\text{N}$: 292.1126, found: 292.1112.

1,3-Diphenyl-1-*p*-tolylprop-2-yn-1-ol 61f¹⁴⁹

^1H NMR (CDCl_3 , 500 MHz): δ 2.36 (s, 3H), 2.90 (s, 1H), 7.18-7.39 (m, 8H), 7.53-7.67 (m, 4H), 7.71-7.72 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 21.1, 74.8, 87.1, 91.9, 122.5, 126.1, 126.1, 127.7, 128.3, 128.4, 128.7, 129.0, 131.8, 137.5, 142.3, 145.2.

1,1-Bis(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol 61g¹⁴⁹

¹H NMR (CDCl₃, 500 MHz): δ 2.93 (s, 1H), 7.02-7.05 (m, 4H), 7.36-7.51 (m, 5H), 7.61-7.63 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 74.0, 87.7, 91.1, 115.2 (1C, d, J_{C-F} = 21.5 Hz), 122.0, 127.9 (1C, d, J_{C-F} = 8.2 Hz), 128.4, 129.0, 131.8, 140.7, 162.3 (1C, d, J_{C-F} = 245.4 Hz).

1,1-Bis(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol 61h^{147a, 149}

¹H NMR (CDCl₃, 500 MHz): δ 3.02 (s, 1H), 7.32-7.37 (m, 7H), 7.50-7.60 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 74.0, 87.9, 90.6, 121.9, 127.5, 128.5, 128.6, 129.1, 131.8, 133.9, 143.2.

1,1-Bis(4-Bromophenyl)-3-phenylprop-2-yn-1-ol 61i

White solid; m.p. 173-174 °C; ¹H NMR (CDCl₃, 500 MHz): δ 2.92 (s, 1H), 7.35-7.36 (m, 3H), 7.47-7.53 (m, 10H); ¹³C NMR (CDCl₃, 125 MHz): δ 74.1, 88.0, 90.4, 121.9, 122.1, 127.8, 128.5, 129.1, 131.5, 131.8, 143.7. IR (neat): 3404, 3026, 2230, 1482,

1214, 691 cm^{-1} ; MS (ESI) m/z 423 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{13}\text{Br}_2$: 422.9384, found: 422.9380.

3-Phenyl-1,1-di-*p*-tolylprop-2-yn-1-ol 61j¹⁴⁹

^1H NMR (CDCl_3 , 500 MHz): δ 2.37 (s, 6H), 2.89 (s, 1H), 7.18-7.19 (m, 4H), 7.36-7.60 (m, 9H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 74.7, 86.9, 92.1, 122.6, 126.0, 128.4, 128.6, 129.0, 131.8, 137.4, 142.4.

3-(4-Fluorophenyl)-1,1-diphenylprop-2-yn-1-ol 61k

Yellow solid; m.p. 51-52 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 2.94 (s, 1H), 7.02-7.06 (m, 2H), 7.30-7.32 (d, $J = 7.2$ Hz, 2H), 7.35-7.39 (m, 4H), 7.49-7.52 (m, 2H), 7.68-7.70 (d, $J = 8.0$ Hz, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 74.9, 86.2, 91.5, 115.7 (1C, d, $J_{\text{C-F}} = 22.0$ Hz), 118.5 (1C, d, $J_{\text{C-F}} = 3.5$ Hz), 126.1, 127.8, 128.4, 133.7 (1C, d, $J_{\text{C-F}} = 8.5$ Hz), 144.9, 162.8 (1C, d, $J_{\text{C-F}} = 248.4$ Hz). IR (neat): 3578, 3060, 2232, 1450, 1411, 1232, 775 cm^{-1} ; MS (ESI) m/z 285 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{14}\text{F}$: 285.1080, found: 285.1072.

3-(4-Chlorophenyl)-1,1-diphenylprop-2-yn-1-ol 61l¹⁵⁰

¹H NMR (CDCl₃, 500 MHz): δ 2.96 (s, 1H), 7.24-7.40 (m, 10H), 7.63-7.64 (m, 4H);

¹³C NMR (CDCl₃, 125 MHz): δ 74.9, 86.2, 92.8, 120.9, 126.1, 127.9, 128.4, 128.8, 133.1, 134.8, 144.9.

1,1-Diphenyl-3-p-tolylprop-2-yn-1-ol 61m^{147a}

¹H NMR (CDCl₃, 500 MHz): δ 2.33 (s, 3H), 2.91(s, 1H), 7.10-7.40 (m, 10H), 7.66-7.67 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 75.0, 87.5, 91.1, 119.4, 126.1,

127.7, 128.4, 129.2, 131.8, 138.9, 145.2.

3-(4-Methoxyphenyl)-1,1-diphenylprop-2-yn-1-ol 61n^{147a, 150}

¹H NMR (CDCl₃, 400 MHz): δ 3.04 (s, 1H), 3.82(s, 3H), 6.87-6.89 (d, J = 8.8 Hz, 2H), 7.30-7.39 (m, 6H), 7.46-7.48 (d, J = 8.4 Hz, 2H), 7.71-7.73 (d, J = 7.2 Hz, 4H);

¹³C NMR (CDCl₃, 100 MHz): δ 55.4, 74.9, 87.3, 90.5, 114.0, 114.6, 126.1, 127.7, 128.3, 133.3, 145.3, 159.9.

4-Methyl-1,3-diphenylpent-1-yn-3-ol 61o¹⁵¹

¹H NMR (CDCl₃, 400 MHz): δ 0.89-0.91 (d, J = 6.8 Hz, 3H), 1.15-1.16 (d, J = 6.8 Hz, 3H), 2.15-2.24 (m, 1H), 2.46 (s, 1H), 7.29-7.40 (m, 6H), 7.51-7.52 (m, 2H), 7.68-7.70 (d, J = 7.6 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 17.6, 18.1, 40.6, 86.9, 90.3, 122.8, 126.2, 127.7, 128.0, 128.4, 128.5, 131.8, 144.0.

2,4-Diphenylbut-3-yn-2-ol 61p¹⁵²

¹H NMR (CDCl₃, 300 MHz): δ 1.91 (s, 3H), 2.78 (s, 1H), 7.33-7.44 (m, 6H), 7.50-7.53 (m, 2H), 7.77-7.79 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 33.4, 70.5, 85.0, 92.6, 122.6, 125.1, 127.8, 128.4, 128.4, 128.6, 131.8, 145.7.

2-Methyl-4-phenylbut-3-yn-2-ol 61q¹⁵²

¹H NMR (CDCl₃, 400 MHz): δ 1.61 (s, 6H), 2.19 (s, 1H), 7.27-7.28 (m, 3H), 7.40-7.41 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 31.5, 65.6, 82.1, 93.9, 122.8, 128.2, 128.3, 131.7.

1,1-Diphenylhept-2-yn-1-ol 61r¹⁵³

¹H NMR (CDCl₃, 400 MHz): δ 0.96-0.99 (t, J = 7.6 Hz, 3H), 1.45-1.54 (m, 2H), 1.58-1.66 (m, 2H), 2.36-2.40 (t, J = 7.2 Hz, 2H), 2.81 (s, 1H), 7.28-7.37 (m, 6H), 7.64-7.66 (d, J = 7.2 Hz, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ 13.7, 18.7, 22.1, 30.7, 74.5, 83.1, 88.3, 126.1, 127.5, 128.2, 145.6.

1,3-Diphenylprop-2-yn-1-ol 61s^{154,147b}

¹H NMR (CDCl₃, 400 MHz): δ 2.78 (bs, 1H), 5.71 (s, 1H), 7.31-7.37 (m, 4H), 7.39-7.49 (m, 2H), 7.50-7.52 (d, J = 5.5 Hz, 2H), 7.63-7.65 (d, J = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 65.1, 86.7, 88.9, 122.5, 126.8, 128.4, 128.5, 128.7, 131.8, 140.7.

1,1-Diphenylprop-2-yn-1-ol 61t¹⁴⁶

¹H NMR (CDCl₃, 300 MHz): δ 2.80 (s, 1H), 2.98 (s, 1H), 7.20-7.31 (m, 6H), 7.56-7.59 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz): δ 74.4, 75.7, 86.5, 126.1, 127.9, 128.4, 144.5.

5,7-Dimethyl-1,1,3-triphenyl-1*H*-inden-6-ol 146a

Yellow solid; m.p. 218-219 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.91 (s, 3H), 2.30 (s, 3H), 4.58 (s, 1H), 6.56 (s, 1H), 7.21-7.39 (m, 12H), 7.41-7.43 (d, $J = 7.4$ Hz, 2H), 7.58-7.59 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.8, 16.6, 65.9, 121.0, 121.5, 121.8, 126.5, 127.7, 127.8, 128.1, 128.5, 128.8, 135.4, 135.6, 140.2, 141.0, 142.3, 149.6, 151.0; IR (neat): 3684, 3019, 1216, 756 cm^{-1} ; MS (ESI) m/z 389 [$\text{M} + \text{H}$] $^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{25}\text{O}$: 389.1905, found: 389.1906.

1-(4-Fluorophenyl)-5,7-dimethyl-1,3-diphenyl-1*H*-inden-6-ol 148b

Yellow solid; m.p. 222-223 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 1.90 (s, 3H), 2.29 (s, 3H), 4.60 (s, 1H), 6.52 (s, 1H), 6.91-6.95 (m, 2H), 7.21-7.28 (m, 8H), 7.34-7.35 (d, $J = 7.2$ Hz, 1H), 7.39-7.42 (m, 2H), 7.56-7.58 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 12.8, 16.6, 65.3, 114.9 (1C, d, $J_{\text{C-F}} = 21.0$ Hz), 121.1, 121.5, 122.0, 126.7, 127.8, 127.8, 128.2, 128.6, 128.7, 130.3, 130.4, 135.3, 135.5, 136.0, 140.0, 141.1, 142.1, 149.4, 151.1, 161.6 (1C, d, $J_{\text{C-F}} = 243.6$ Hz); IR (neat): 3569, 1598, 1504, 1360, 1228, 769 cm^{-1} ; MS (ESI) m/z 407 [$\text{M} + \text{H}$] $^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{OF}$: 407.1811, found: 407.1808.

1-(4-Chlorophenyl)-5,7-dimethyl-1,3-diphenyl-1H-inden-6-ol 148c

Yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 1.90 (s, 3H), 2.29 (s, 3H), 4.62 (s, 1H), 6.50 (s, 1H), 7.22-7.23 (m, 6H), 7.25-7.26 (m, 4H), 7.34-7.36 (d, $J = 7.2$ Hz, 1H), 7.39-7.43 (m, 2H), 7.56-7.58 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.8, 16.6, 65.4, 121.2, 121.5, 122.0, 126.7, 127.8, 127.8, 128.2, 128.3, 128.6, 128.7, 130.2, 132.3, 135.3, 135.4, 139.0, 139.7, 141.4, 141.8, 149.2, 151.2; IR (neat): 3613, 3019, 1490, 1216, 769 cm^{-1} ; MS (ESI) m/z 423 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{OCl}$: 423.1516, found: 423.1512.

1-(4-Bromophenyl)-5,7-dimethyl-1,3-diphenyl-1H-inden-6-ol 148d

Yellow solid; m.p. 107-108 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz): δ 1.89 (s, 3H), 2.28 (s, 3H), 4.59 (s, 1H), 6.49 (s, 1H), 7.15-7.17 (d, $J = 8.5$ Hz, 2H), 7.20-7.25 (m, 6H), 7.32-7.36 (m, 3H), 7.38-7.41 (m, 2H), 7.55-7.57 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 12.9, 16.6, 65.4, 120.5, 121.2, 121.5, 122.1, 126.8, 127.8, 127.9, 128.3, 128.6, 128.7, 130.6, 131.2, 135.3, 135.4, 139.7, 141.4, 141.7, 149.1, 151.2; IR (neat): 3606, 3019, 1599, 1491, 1216, 1011, 908, 770 cm^{-1} ; MS (ESI) m/z 467 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{OBr}$: 467.1011, found: 467.1009.

4-(6-Hydroxy-5,7-dimethyl-1,3-diphenyl-1*H*-inden-1-yl)benzonitrile 148e

Yellow solid; m.p. 248-249 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.88 (s, 3H), 2.31 (s, 3H), 4.65 (s, 1H), 6.49 (s, 1H), 7.23-7.31 (m, 5H), 7.37-7.45 (m, 5H), 7.53 (s, 1H), 7.55-7.58 (m, 3); ^{13}C NMR (CDCl_3 , 125 MHz): δ 13.0, 16.6, 65.9, 110.2, 119.0, 121.4, 121.6, 122.5, 127.0, 127.8, 128.1, 128.5, 128.7, 129.5, 132.0, 135.1, 135.2, 138.8, 140.9, 142.2, 146.9, 148.6, 151.4; IR (neat): 3613, 3019, 2400, 2229, 1603, 1215, 772 cm^{-1} ; MS (ESI) m/z 414 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{24}\text{ON}$: 414.1858, found: 414.1844.

5,7-Dimethyl-1,3-diphenyl-1-*p*-tolyl-1*H*-inden-6-ol 148f

Yellow solid; m.p. 91-92 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.92 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 4.59 (s, 1H), 6.55 (s, 1H), 7.06-7.08 (d, $J = 8.0$ Hz, 2H), 7.18-7.22 (m, 5H), 7.24 (s, 1H), 7.29-7.31 (d, $J = 7.4$ Hz, 2H), 7.33-7.34 (d, $J = 7.3$ Hz, 1H), 7.38-7.40 (m, 2H), 7.57-7.59 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 12.8, 16.6, 21.1, 65.6, 121.0, 121.5, 121.8, 126.5, 127.7, 127.8, 128.1, 128.5, 128.7, 128.9, 135.5, 135.7, 136.1, 137.0, 140.5, 140.8, 142.5, 149.7, 151.1; IR (neat): 3581, 3020, 1598, 1217, 759 cm^{-1} ; MS (ESI) m/z 403 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{27}\text{O}$: 403.2062, found: 403.2048.

1,1-Bis(4-fluorophenyl)-5,7-dimethyl-3-phenyl-1H-inden-6-ol 148g

Yellow solid; m.p. 225-226 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.89 (s, 3H), 2.29 (s, 3H), 4.61 (s, 1H), 6.49 (s, 1H), 6.92-6.96 (m, 4H), 7.21-7.24 (m, 5H), 7.34-7.36 (d, $J = 7.0$ Hz, 1H), 7.40-7.43 (m, 2H), 7.55-7.57 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.7, 16.5, 64.6, 115.0 (1C, d, $J_{\text{C-F}} = 21.1$ Hz), 121.2, 121.4, 122.1, 127.8 (1C, d, $J_{\text{C-F}} = 13.7$ Hz), 128.6, 130.2, 130.3, 135.1, 135.3, 135.8, 141.2, 141.9, 149.3, 151.2, 161.6 (1C, d, $J_{\text{C-F}} = 244.2$ Hz); IR (neat): 3594, 3019, 1602, 1507, 1215, 1157, 765 cm^{-1} ; MS (ESI) m/z 425 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{OF}_2$: 425.1717, found: 425.1715.

1,1-Bis(4-chlorophenyl)-5,7-dimethyl-3-phenyl-1H-inden-6-ol 148h

Yellow oil; ^1H NMR (CDCl_3 , 500 MHz): δ 1.88 (s, 3H), 2.27 (s, 3H), 4.64 (s, 1H), 6.44 (s, 1H), 7.17-7.22 (m, 9H), 7.34-7.35 (d, $J = 7.2$ Hz, 1H), 7.39-7.42 (m, 2H), 7.54-7.56 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 12.9, 16.6, 64.9, 121.3, 121.5, 122.3, 127.8, 128.0, 128.4, 128.7, 130.1, 132.5, 135.2, 138.5, 141.3, 141.7, 148.8, 151.3; IR (neat): 3590, 3019, 1595, 1487, 1216, 1095, 759 cm^{-1} ; MS (ESI) m/z

457 $[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{23}OCl_2$: 457.1126, found: 457.1132.

1,1-Bis(4-bromophenyl)-5,7-dimethyl-3-phenyl-1*H*-inden-6-ol 148i

Yellow solid; m.p. 98-99 °C; 1H NMR ($CDCl_3$, 400 MHz): δ 1.91 (s, 3H), 2.31 (s, 3H), 4.63 (s, 1H), 6.45 (s, 1H), 7.14-7.16 (d, J = 8.8 Hz, 4H), 7.23 (s, 1H), 7.36-7.46 (m, 7H), 7.56-7.58 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 12.8, 16.5, 64.9, 120.6, 121.3, 121.4, 122.2, 127.7, 128.0, 128.6, 130.4, 131.3, 135.1, 139.0, 141.1, 141.8, 148.6, 151.3; IR (neat): 3467, 3019, 1215, 759 cm^{-1} ; MS (ESI) m/z 545 $[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{23}OBr_2$: 545.0116, found: 545.0109.

5,7-Dimethyl-3-phenyl-1,1-dip-tolyl-1*H*-inden-6-ol 148j

Yellow oil; 1H NMR ($CDCl_3$, 300 MHz): δ 1.91 (s, 3H), 2.28 (s, 3H), 2.30 (s, 6H), 4.56 (s, 1H), 6.52 (s, 1H), 7.04-7.06 (d, J = 7.8 Hz, 4H), 7.16-7.20 (m, 5H), 7.31-7.34 (d, J = 6.9 Hz, 1H), 7.39-7.41 (m, 2H), 7.56-7.58 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.8, 16.6, 21.0, 65.3, 120.9, 121.4, 121.7, 127.6, 127.8, 128.5, 128.7, 128.8, 135.5, 135.8, 136.0, 137.3, 140.6, 142.6, 149.8, 151.0; IR (neat): 3581,

3021, 2245, 1209, 758 cm^{-1} ; MS (ESI) m/z 417 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{29}\text{O}$: 417.2218, found: 417.2214.

3-(4-Fluorophenyl)-5,7-dimethyl-1,1-diphenyl-1H-inden-6-ol 148k

Yellow solid; m.p. 203-204 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz): δ 1.91 (s, 3H), 2.29 (s, 3H), 4.59 (s, 1H), 6.52 (s, 1H), 7.08-7.11 (m, 2H), 7.15 (s, 1H), 7.21-7.29 (m, 10H), 7.53-7.55 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 12.8, 16.6, 65.9, 115.4 (1C, d, $J_{\text{C-F}} = 21.3$ Hz), 120.8, 121.6, 121.9, 126.6, 128.2, 128.8, 129.4, 129.5, 131.6, 135.3, 140.0, (1C, d, $J_{\text{C-F}} = 10.1$ Hz), 142.2, 149.5, 151.1, 162.4 (1C, d, $J_{\text{C-F}} = 245.2$ Hz); IR (neat): 3559, 3019, 1587, 1216, 756 cm^{-1} ; MS (ESI) m/z 407 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{OF}$: 407.1811, found: 407.1801.

3-(4-Chlorophenyl)-5,7-dimethyl-1,1-diphenyl-1H-inden-6-ol 148l

Yellow solid; m.p. 221-222 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz): δ 90 (s, 3H), 2.28 (s, 3H), 4.59 (s, 1H), 6.54 (s, 1H), 7.14 (s, 1H), 7.18-7.26 (m, 10H), 7.35-7.37 (d, $J = 8.3$ Hz, 2H), 7.48-7.51 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.8, 16.6, 65.9, 120.8, 121.7, 121.9, 126.6, 128.2, 128.7, 128.8, 129.1, 133.5, 134.1, 135.0, 140.0, 142.6, 149.5, 151.2; IR (neat): 3556, 3019, 1487, 1216, 769 cm^{-1} ; MS (ESI) m/z 423

$[M + H]^+$; HRMS (ESI) calcd for $C_{29}H_{24}OCl$: 423.1516, found: 423.1505.

5,7-Dimethyl-1,1-diphenyl-3-p-tolyl-1*H*-inden-6-ol 148m

Yellow solid; m.p. 229-230 °C; 1H NMR ($CDCl_3$, 400 MHz): δ 1.91 (s, 3H), 2.28 (s, 3H), 2.38 (s, 3H), 4.56 (s, 1H), 6.52 (s, 1H), 7.21-7.30 (m, 13H), 7.47-7.49 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.8, 16.6, 21.3, 65.8, 121.0, 121.5, 121.8, 126.5, 127.7, 128.1, 128.8, 129.2, 132.7, 135.6, 137.5, 140.4, 140.9, 141.9, 149.6, 151.0; IR (neat): 3561, 3022, 1584, 1215, 756 cm^{-1} ; MS (ESI) m/z 403 $[M + H]^+$; HRMS (ESI) calcd for $C_{30}H_{27}O$: 403.2062, found: 403.2049.

3-(4-Methoxyphenyl)-5,7-dimethyl-1,1-diphenyl-1*H*-inden-6-ol 148n

Yellow oil; 1H NMR ($CDCl_3$, 500 MHz): δ 1.91 (s, 3H), 2.29 (s, 3H), 3.83 (s, 3H), 4.60 (s, 1H), 6.49 (s, 1H), 6.94-6.96 (d, $J = 8.5$ Hz, 2H), 7.20-7.30 (m, 11H), 7.51-7.53 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.8, 16.6, 55.4, 65.8, 113.9, 120.9, 121.5, 121.8, 126.4, 128.1, 128.8, 129.0, 135.7, 140.4, 141.4, 149.6, 151.0, 159.3; IR (neat): 3612, 3018, 1599, 1509, 1216, 1028, 756 cm^{-1} ; MS (ESI) m/z 419 $[M + H]^+$; HRMS (ESI) calcd for $C_{30}H_{27}O_2$: 419.2011, found: 419.2008.

1-Isopropyl-5,7-dimethyl-1,3-diphenyl-1H-inden-6-ol 148o

Yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 0.65-0.67 (d, $J = 6.8$ Hz, 3H), 1.34-1.36 (d, $J = 6.4$ Hz, 3H), 2.04 (s, 3H), 2.29 (s, 3H), 3.29-3.36 (m, 1H), 4.52 (s, 1H), 6.43 (s, 1H), 7.20 (s, 1H), 7.22-7.26 (m, 1H), 7.28-7.30 (m, 2H), 7.35-7.37 (m, 2H), 7.42-7.46 (m, 1H), 7.50-7.54 (m, 2H), 7.69-7.71 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 10.9, 16.5, 17.6, 21.3, 28.7, 64.3, 119.9, 120.0, 120.7, 126.0, 127.6, 127.8, 127.9, 128.1, 128.6, 135.3, 136.2, 137.3, 140.0, 144.7, 150.6, 151.9; IR (neat): 3612, 3019, 1598, 1493, 1215, 760 cm^{-1} ; MS (ESI) m/z 355 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{27}\text{O}$: 355.2062, found: 355.2067.

1,5,7-Trimethyl-1,3-diphenyl-1H-inden-6-ol 148p

Yellow solid; m.p. 62-63 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz): δ 1.77 (s, 3H), 1.91 (s, 3H), 2.24 (s, 3H), 4.50 (s, 1H), 6.20 (s, 1H), 7.12-7.18 (m, 6H), 7.28-7.30 (d, $J = 7.2$ Hz, 1H), 7.34-7.39 (m, 2H), 7.51-7.53 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 11.6, 16.5, 20.1, 55.9, 119.9, 120.3, 121.2, 126.2, 126.3, 127.5, 127.7, 128.4, 128.5, 135.4, 135.9, 140.3, 142.2, 143.2, 151.0, 151.5; IR (neat): 3452, 3019, 1642, 1215, 755 cm^{-1} ; MS (ESI) m/z 327 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{O}$: 327.1749, found: 327.1756.

3-Butyl-5,7-dimethyl-1,1-diphenyl-1*H*-inden-6-ol 148q

Yellow solid; m.p. 120-123 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.91-0.95 (t, J = 14.4 Hz, 3H), 1.37-1.45 (m, 2H), 1.59-1.69 (m, 2H), 1.86 (s, 3H), 2.30 (s, 3H), 2.42-2.47 (m, 2H), 4.49 (s, 1H), 6.19 (s, 1H), 6.97 (s, 1H), 7.18-7.24 (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 2.7, 14.0, 16.5, 22.8, 27.1, 30.0, 65.7, 119.5, 121.0, 121.6, 126.2, 128.0, 137.4, 139.7, 140.7, 141.0, 149.2, 150.7; IR (neat): 3613, 3019, 1215, 759 cm^{-1} ; MS (EI) m/z 312 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{O}$: 312.2218, found: 312.2228.

5-Methyl-1,1,3-triphenyl-1*H*-inden-6-ol 148r

Yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 2.56 (s, 3H), 4.70 (s, 1H), 6.67 (s, 1H), 6.81 (s, 1H), 7.20-7.29 (m, 11H), 7.35-7.37 (d, J = 7.3 Hz, 1H), 7.41-7.45 (m, 2H), 7.61-7.63 (d, J = 7.2 Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.1, 65.3, 113.1, 122.2, 123.6, 126.7, 127.7, 127.9, 128.4, 128.6, 135.3, 135.6, 139.7, 142.2, 144.1, 150.8, 152.3; IR (neat): 3552, 3019, 1597, 1490, 1444, 1216, 758 cm^{-1} ; MS (ESI) m/z 375 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{23}\text{O}$: 375.1749, found: 375.1748.

1-(4-Chlorophenyl)-5-methyl-1,3-diphenyl-1*H*-inden-6-ol 148s

Yellow solid; m.p. 85-86 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.24 (s, 3H), 4.89 (s, 1H), 6.60 (s, 1H), 6.77 (s, 1H), 7.18-7.25 (m, 9H), 7.29 (s, 1H), 7.33-7.37 (m, 1H), 7.40-7.44 (m, 2H), 7.59-7.61 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.1, 64.8, 113.0, 122.6, 123.8, 126.9, 127.7, 127.8, 128.0, 128.5, 128.5, 128.7, 129.3, 132.5, 135.1, 135.4, 139.1, 142.6, 142.8, 143.6, 150.4, 152.5; IR (neat): 3611, 3019, 1490, 1215, 758, 668 cm^{-1} ; MS (ESI) m/z 409 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{ClO}$: 409.1359, found: 409.1366.

4-(6-Hydroxy-5-methyl-1,3-diphenyl-1*H*-inden-1-yl)benzonitrile 148t

Yellow solid; m.p. 232-233 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.21 (s, 3H), 5.09 (s, 1H), 6.53 (s, 1H), 6.74 (s, 1H), 7.18-7.19 (m, 6H), 7.29-7.34 (m, 3H), 7.37-7.41 (m, 2H), 7.43-7.45 (d, $J = 8.4$ Hz, 2H), 7.54-7.56 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.1, 65.3, 110.3, 112.9, 119.0, 123.0, 124.0, 127.7, 127.7, 127.8, 128.2, 128.6, 128.7, 132.2, 135.0, 135.1, 138.0, 142.7, 143.4, 149.6, 150.3, 152.9; IR (neat): 3539, 3019, 2224, 1599, 1490, 1215, 753 cm^{-1} ; MS (ESI) m/z 400 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{22}\text{ON}$: 400.1701, found: 400.1690.

1,1-Bis(4-Chlorophenyl)-5-methyl-3-phenyl-1H-inden-6-ol 148u

Yellow liquid; ^1H NMR (CDCl_3 , 400 MHz): δ 2.26 (s, 3H), 4.87 (s, 1H), 6.55 (s, 1H), 6.75 (s, 1H), 7.15-7.23 (m, 8 H), 7.30 (s, 1H), 7.37-7.39 (d, $J = 7.2$ Hz, 1H), 7.42-7.46 (m, 2H), 7.59-7.60 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.1, 64.2, 112.8, 122.7, 123.9, 127.7, 128.1, 128.6, 128.7, 129.1, 132.7, 135.0, 135.2, 138.5, 142.2, 142.9, 150.1, 152.6; IR (neat): 3597, 3018, 1596, 1489, 1216, 758 cm^{-1} ; MS (ESI) m/z 443 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{Cl}_2\text{O}$: 443.0969, found: 443.0972.

2,6-Dimethyl-4-(2-methyl-4-phenylbut-3-yn-2-yl)phenol 148a

Yellow oil. ^1H NMR (CDCl_3 , 400 MHz): δ 1.64 (s, 6H), 2.26 (s, 6H), 4.55 (s, 1H), 7.21 (s, 2H), 7.28-7.29 (m, 3H), 7.44-7.46 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.2, 31.9, 35.6, 81.7, 97.1, 122.7, 124.0, 125.9, 127.6, 128.2, 131.7, 138.7, 150.7; IR (neat): 3473, 2973, 1598, 1489, 1184, 755 cm^{-1} ; MS (EI) m/z 265 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{O}$: 265.1592, found: 265.1592.

4-(1,3-Diphenylprop-2-ynyl)-2,6-dimethylphenol 148b

Yellow solid; m.p. 100-101 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 2.20 (s, 6H), 4.53 (s, 1H), 5.08 (s, 1H), 7.02 (s, 2H), 7.22-7.33 (m, 6H), 7.43-7.48 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 16.1, 43.0, 84.6, 90.8, 123.2, 123.7, 126.8, 127.8, 127.9, 128.1, 128.3, 128.6, 131.7, 133.4, 142.3, 151.2 ; IR (neat): 3618, 3019, 1490, 1215, 759 cm^{-1} ; MS (ESI) m/z 313 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{O}$: 313.1592, found: 313.1596.

4-(1-(4-Chlorophenyl)-3-phenyl-1H-inden-1-yl)phenol 150a

Yellow solid; m.p. 113-114 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 4.82 (s, 1H), 6.70 (s, 1H), 6.71-6.73 (d, $J = 9.0$ Hz, 2H), 7.12-7.13 (d, $J = 7.7$ Hz, 2H), 7.20 (bs, 4H), 7.24 (s, 1H), 7.29-7.31 (m, 2H), 7.38-7.39 (d, $J = 6.9$ Hz, 1H), 7.43-7.46 (m, 2H), 7.55-7.56 (d, $J = 7.3$ Hz, 1H), 7.61-7.63 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 64.4, 115.3, 121.5, 125.5, 126.1, 127.2, 127.8, 128.1, 128.5, 128.7, 129.1, 129.2, 132.6, 135.1, 135.3, 141.3, 142.3, 142.6, 142.61, 151.1, 154.5; IR (neat): 3459, 3019, 1645, 1215, 765 cm^{-1} ; MS (ESI) m/z 395 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{20}\text{OCl}$: 395.1203, found: 395.1206.

4-(1-(4-Chlorophenyl)-3-phenyl-1*H*-inden-1-yl)-2,6-diisopropylphenol 150b

Yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 1.16-1.18 (d, $J = 6.8$ Hz, 12H), 3.05-3.11 (m, 2H), 4.70 (s, 1H), 6.76 (s, 1H), 6.95 (s, 2H), 7.18-7.24 (m, 5H), 7.28-7.30 (d, $J = 6$ Hz, 1H), 7.32-7.34 (d, $J = 7.6$ Hz, 1H), 7.38-7.40 (d, $J = 7.6$ Hz, 1H), 7.43-7.47 (m, 2H), 7.54-7.56 (d, $J = 7.6$ Hz, 1H), 7.63-7.65 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 22.6, 22.8, 27.5, 64.9, 121.4, 123.2, 125.4, 125.9, 127.0, 127.8, 128.0, 128.3, 128.6, 129.2, 132.3, 133.4, 134.4, 135.4, 141.7, 142.3, 142.4, 143.2, 149.0, 151.5; IR (neat): 3449, 3019, 2965, 2400, 1647, 1488, 1216, 1014, 765 cm^{-1} ; MS (ESI) m/z 479 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{32}\text{OCl}$: 479.2142, found: 479.2143.

2,6-Dimethyl-4-(4-methyl-1,3-diphenylpenta-1,2-dienyl)phenol 151

Yellow oil. ^1H NMR (CDCl_3 , 300 MHz): δ 1.24 (d, $J = 6.6$ Hz, 6H), 2.21 (s, 6H), 2.96-3.05 (m, 1H), 4.65 (s, 1H), 7.00 (s, 2H), 7.20-7.25 (m, 2H), 7.27-7.34 (m, 4H), 7.38-7.40 (d, $J = 6.9$ Hz, 2H), 7.46-7.48 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 16.0, 22.5, 22.6, 29.0, 113.4, 115.8, 123.0, 126.6, 126.8, 127.0, 128.2, 128.4, 128.4, 128.5, 128.6, 136.4, 137.5, 151.6, 205.3; IR (neat): 3434, 2966, 2401, 1597, 1488, 1445, 1216, 1196, 1131, 769, 667 cm^{-1} ; MS (ESI) m/z 355 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{27}\text{O}$: 355.2062, found: 355.2067.

5,7-Dimethyl-1,1,3-triphenyl-1*H*-indene-2,6-dione 152a

Orange solid; m.p. 231-232 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.67 (s, 3H), 2.19 (s, 3H), 7.29-7.35 (m, 10H), 7.46-7.51 (m, 3H), 7.58-7.60 (m, 2H), 7.62 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.7, 17.5, 63.8, 127.5, 128.2, 128.4, 128.7, 129.2, 129.7, 130.1, 130.4, 132.6, 138.5, 142.5, 143.3, 149.8, 150.0, 187.3, 203.1; IR (neat): 3029, 1704, 1616, 1492, 1441, 1308, 1129, 889, 768, 732, 696 cm^{-1} ; MS (ESI) m/z 403 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{O}_2$: 403.1698, found: 403.1683.

3-(4-Chlorophenyl)-4,6-dimethyl-1,3-diphenyl-3*H*-indene-2,5-dione 152b

Orange solid; m.p. 192-193 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.68 (s, 3H), 2.20 (s, 3H), 7.29-7.34 (m, 9H), 7.50-7.51 (m, 3H), 7.58-7.59 (m, 2H), 7.63 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.8, 17.5, 63.2, 127.7, 128.2, 128.6, 128.6, 128.8, 129.0, 129.6, 130.2, 130.4, 130.6, 132.7, 133.6, 136.9, 138.2, 142.4, 143.5, 149.3, 150.0, 187.1, 202.8; IR (neat): 3019, 1707, 1617, 1491, 1310, 1216, 891, 768, 698 cm^{-1} ; MS (ESI) m/z 437 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{22}\text{ClO}_2$: 437.1308, found: 437.1300.

4,6-Dimethyl-1,3-diphenyl-3-*p*-tolyl-3*H*-indene-2,5-dione 152c

Orange solid; m.p. 185-186 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.67 (s, 3H), 2.18 (s, 3H), 2.33 (s, 3H), 7.12-7.14 (d, J = 8.0 Hz, 2 H), 7.22-7.33 (m, 7 H), 7.45-7.50 (m, 3H), 7.57-7.59 (d, J = 7.6 Hz, 2H), 7.61 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.8, 17.5, 21.1, 63.5, 127.4, 128.2, 128.4, 128.7, 129.1, 129.2, 129.2, 129.8, 130.1, 130.5, 132.5, 135.3, 137.3, 138.8, 142.5, 143.3, 149.9, 150.0, 187.3, 203.3; IR (neat): 3022, 1710, 1622, 1492, 1307, 1216, 890, 768, 696 cm^{-1} ; MS (ESI) m/z 417 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{25}\text{O}_2$: 417.1855, found: 417.1852.

7.4 Synthesis of Highly Substituted Indene Derivatives *via* Brønsted Acid Catalyzed Intramolecular Nazarov Cyclization of Homoallylic Alcohols

Representative Experimental Procedure for Preparation of Homoallylic Alcohols

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To a solution of benzophenone (2 mmol, 1.0 equiv.) in THF was added 1-methyl-2-propenylmagnesium chloride (0.5 M in THF, 8 mL, 2.0 equiv.) at room temperature. The resulting solution was stirred overnight. Then the reaction mixture was quenched by addition of saturated NH_4Cl (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Mg_2SO_4 , concentrated under reduced pressure, and purified by flash

column chromatography on silica gel (eluent: *n*-hexane: ethyl acetate = 9: 1) to give the **153a** as a white solid.

Synthesis of Internal Homoallylic Alcohols (E)-Methyl 5-hydroxy-4-methyl-5,5-diphenylpent-2-enoate 153p

To round bottom flask equipped with a reflux condenser was charged Grubbs second generation catalyst (34 mg, 7 mol%) and copper iodide (11 mg, 10 mol%). A solution of 2-Methyl-1,1-diphenylbut-3-en-1-ol (134 mg, 0.56 mmol, 1.0 eq) in freshly distilled CH_2Cl_2 was added followed by methyl acrylate (0.1 ml, 2.0 eq). The flask was immersed in an oil bath preheated to 40 °C for 20 h. Solvent was evaporated in vacuo and the crude product was purified by column chromatography on silica gel (eluent: *n*-hexane: ethyl acetate = 8: 1) to give the **153p** as a white solid.

Synthesis of 1-(1-Methyl-1*H*-indol-2-yl)ethanol 153ma

To a solution of 1-methyl-1*H*-indole-2-carbaldehyde (6 mmol, 1.0 equiv.) in THF was added Methylmagnesium bromide (3M in THF, 4 mL, 2.0 equiv.) at room temperature. After stirring at room temperature for 3h, the reaction mixture was

quenched by addition of saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Mg_2SO_4 , concentrated under reduced pressure, and purified by flash column chromatography on silica gel to give the **153ma** as a brown liquid.

Synthesis of 1-(1-Methyl-1*H*-indol-2-yl)ethanone **153mb**

IBX (837 mg, 6mmol) was added to a solution of alcohol **153ma** (525 mg, 3 mmol) in DMSO (15 mL), and the reaction was stirred at room temperature. After 5h, the reaction was diluted with CH_2Cl_2 (10 mL). The precipitate was removed by filtration, washed with CH_2Cl_2 , and the combined filtrate was subsequently diluted with aqueous saturated NaHCO_3 . The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 . The combined organic phases were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica to afford **153mb** as a brown liquid.

Representative Experimental Procedure for PTSA Catalyzed Preparation of Indenes 154

To a 5 mL round-bottom flask **153a** (0.3 mmol), PTSA (5 mol%) were successively added to (CH₂Cl)₂ (3 mL). The resultant reaction mixture was heated to 100 °C and stirred at 100 °C, checked by TLC. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (eluent: n-hexane: EtOAc = 10: 1) to give the title compound **154a**.

2-Methyl-1,1-diphenylbut-3-en-1-ol **153a**¹⁵⁵

¹H NMR (CDCl₃, 300 MHz): δ 0.99 (d, J = 6.8 Hz, 3H), 2.27 (s, 1H), 3.51-3.56 (m, 1H), 5.11-5.20 (m, 2H), 5.81-5.93 (m, 1 H), 7.14-7.19 (m, 2 H), 7.24-7.31 (m, 4 H), 7.49-7.55 (m, 4 H); ¹³C NMR (CDCl₃, 75 MHz): δ 13.6, 44.4, 79.4, 117.4, 125.8, 126.0, 126.6, 126.7, 128.3, 128.3, 139.4, 145.9, 146.9.

1,1-Bis(4-fluorophenyl)-2-methylbut-3-en-1-ol **153b**

White solid; m.p. 61-62 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.03 (d, $J = 6.8$ Hz, 3H), 2.42 (s, 1H), 3.46-3.53 (m, 1H), 5.17-5.25 (m, 2H), 5.83-5.95 (m, 1 H), 6.99-7.05 (m, 4 H), 7.47-7.56 (m, 4 H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.4, 44.5, 78.7, 114.8, 114.9, 115.1, 115.2, 117.7, 127.4, 127.5, 127.6, 127.7, 138.8, 141.4, 141.4, 142.4, 142.4, 161.5 (1C, d, $J_{\text{C-F}} = 243.8$ Hz), 161.6 (1C, d, $J_{\text{C-F}} = 243.8$ Hz). IR (neat): 3555, 3015, 2978, 1602, 1512, 1091, 775, 570 cm^{-1} MS (ESI) m/z 257 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{F}_2$: 257.1142, found: 257.1147.

1,1-Bis(4-chlorophenyl)-2-methylbut-3-en-1-ol 153c

White solid; m.p. 93-94 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.97 (d, $J = 6.8$ Hz, 3H), 2.28 (s, 1H), 3.40-3.49 (m, 1H), 5.14-5.21 (m, 2H), 5.75-5.87 (m, 1 H), 7.24-7.27 (m, 4 H), 7.7.39-7.46 (m, 4 H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.2, 44.1, 78.7, 118.0, 127.1, 127.3, 128.4, 128.5, 132.5, 132.7, 138.4, 143.9, 144.9. IR (neat): 3556, 3017, 2978, 1600, 1512, 1091, 775, 571 cm^{-1} MS (ESI) m/z 289 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Cl}_2$: 289.0551, found: 289.0548.

1,1-Bis(4-bromophenyl)-2-methylbut-3-en-1-ol 153d

White solid; m.p. 113-114 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.95 (d, $J = 6.8$ Hz, 3H),

2.28 (s, 1H), 3.38-3.47 (m, 1H), 5.12-5.23 (m, 2H), 5.73-5.84 (m, 1 H), 7.29-7.41 (m, 8 H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.3, 44.0, 78.8, 118.1, 120.8, 120.9, 127.6, 127.7, 131.4, 131.5, 138.4, 144.4, 145.4. IR (neat): 3554, 3011, 2974, 1610, 1512, 1091, 775, 573 cm^{-1} MS (ESI) m/z 378 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Br}_2$: 378.9520, found: 378.9530.

2-Methyl-1,1-di-*p*-tolylbut-3-en-1-ol 153e

White solid; m.p. 76-77 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.98 (d, J = 6.8 Hz, 3H), 2.21 (s, 1H), 2.28 (s, 6H), 3.44-3.51 (m, 1H), 5.10-5.20 (m, 2H), 5.82-5.93 (m, 1 H), 7.08 (d, J = 8.0 Hz, 4H), 7.35-7.42 (m, 4 H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.7, 21.1, 44.5, 79.3, 117.2, 125.8, 126.0, 129.0, 129.0, 135.9, 136.1, 139.8, 143.3, 144.2. IR (neat): 3559, 3017, 2978, 1612, 1510, 1215, 769 cm^{-1} MS (ESI) m/z 249 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}$: 249.1643, found: 249.1633.

1,1-Bis(4-methoxyphenyl)-2-methylbut-3-en-1-ol 153f

White solid; m.p. 92-93 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.98 (d, J = 6.9 Hz, 3H), 2.20 (s, 1H), 3.39-3.47 (m, 1H), 3.76 (s, 6H), 5.10-5.19 (m, 2H), 5.81-5.92 (m, 1 H), 6.82 (d, J = 8.4 Hz, 4H), 7.35-7.44 (m, 4 H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.6, 44.6,

55.2, 78.8, 113.4, 113.4, 117.0, 126.9, 127.1, 138.3, 139.2, 139.6, 158.0, 158.1. IR (neat): 3552, 3001, 2965, 1608, 1582, 1506, 1246, 1033, 752 cm^{-1} MS (ESI) m/z 281 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2$: 281.1542, found: 281.1547.

1-(2-Chlorophenyl)-2-methyl-1-phenylbut-3-en-1-ol 153g

Colorless liquid; dr = 1:2; ^1H NMR (CDCl_3 , 300 MHz): δ 0.96-1.00 (m, 3H), 3.17 (s, 1H, A or B diastereomer), 3.35 (s, 1H, A or B diastereomer), 3.59-3.68 (m, 1H, A or B diastereomer), 3.80-3.84 (m, 1H, A or B diastereomer), 5.03-5.19 (m, 2H), 5.92-6.01 (m, 1H), 7.19-7.34 (m, 8H), 7.90-7.93 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 15.2, 15.7, 42.9, 43.9, 79.8, 78.0, 115.7, 116.6, 126.4, 126.5, 126.7, 127.0, 127.4, 127.5, 127.6, 128.4, 128.5, 128.7, 129.1, 131.6, 131.6, 132.7, 139.9, 140.4, 142.7, 143.0, 144.4, 144.8. IR (neat): 3570, 3061, 2976, 1635, 1598, 1446, 914, 752 cm^{-1} MS (ESI) m/z 193 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{Cl}$: 193.0784 found: 193.0784.

2-(4-Chlorophenyl)-3-methylpent-4-en-2-ol 153h

Colorless liquid; dr = 1:1.1; ^1H NMR (CDCl_3 , 400 MHz): δ 0.83 (d, J = 6.9 Hz, 3H, A or B diastereomer), 0.93 (d, J = 6.9 Hz, 3H, A or B diastereomer), 1.48 (s, 3H), 2.08 (s, 1H, A or B diastereomer), 2.17 (s, 1H, A or B diastereomer), 2.44-2.54 (m, 1H), 5.05-5.11 (m, 2H), 5.61-5.67 (m, 1H, A or B diastereomer), 5.68-5.82 (m, 1H, A or B

diastereomer), 7.25-7.34 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.2, 14.7, 26.0, 28.4, 48.9, 48.9, 75.5, 75.6, 116.6, 116.9, 126.9, 127.1, 128.0, 128.0, 132.2, 132.4, 139.5, 139.6, 145.5, 145.6. IR (neat): 3466, 3074, 2976, 1680, 1637, 1490, 1093, 1012, 835 cm^{-1} MS (ESI) m/z 193 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{Cl}$: 193.0784, found: 193.0793.

2-(4-Bromophenyl)-3-methylpent-4-en-2-ol 153i

Colorless liquid; dr = 1:1.1; ^1H NMR (CDCl_3 , 400 MHz): δ 0.84 (d, J = 5.5 Hz, 3H, A or B diastereomer), 0.94 (d, J = 5.5 Hz, 3H, A or B diastereomer), 1.48 (s, 3H), 2.02 (s, 1H, A or B diastereomer), 2.12 (s, 1H, A or B diastereomer), 2.46-2.55 (m, 1H), 5.06-5.12 (m, 2H), 5.62-5.67 (m, 1H, A or B diastereomer), 5.68-5.81 (m, 1H, A or B diastereomer), 7.27-7.42 (m, 2H), 7.42-7.44 (m, 2H,); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.1, 14.7, 26.0, 28.4, 48.8, 75.5, 75.6, 116.7, 117.0, 120.4, 120.6, 127.2, 127.5, 129.9, 130.9, 131.9, 139.5, 139.6, 146.1, 146.1. IR (neat): 3469, 3076, 2974, 1680, 1635, 1589, 1485, 1394, 1078, 1008, 918 cm^{-1} MS (ESI) m/z 237 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{Br}$: 237.0279, found: 237.0289.

3-Methyl-2-phenylpent-4-en-2-ol 153j

Yellow liquid; dr = 1:2; ^1H NMR (CDCl_3 , 300 MHz): δ 0.84 (d, J = 6.9 Hz, 3H, A or B diastereomer), 0.94 (d, J = 6.9 Hz, 3H, A or B diastereomer), 1.49 (s, 3H), 1.98 (s, 1H, A or B diastereomer), 2.06 (s, 1H, A or B diastereomer), 2.46-2.61 (m, 1H),

5.04-5.09 (m, 2H), 5.63-5.86 (m, 1H), 7.17-7.21 (m, 1H), 7.22-7.32 (m, 2H), 7.37-7.42 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.2, 14.8, 26.0, 28.5, 48.8, 49.0, 75.8, 75.8, 116.3, 116.6, 125.3, 125.6, 126.5, 126.6, 127.9, 140.0, 140.1, 147.1. IR (neat): 3469, 3061, 2974, 1635, 1601, 1494, 1446, 1371, 914, 762, 702, 572 cm^{-1} MS (ESI) m/z 159 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}$: 159.1174, found: 159.1175.

3-Methyl-2-*p*-tolylpent-4-en-2-ol 153k

Colorless liquid; dr = 1:1.9; ^1H NMR (CDCl_3 , 400 MHz): δ 0.85 (d, $J = 6.9$ Hz, 3H, A or B diastereomer), 0.93 (d, $J = 6.9$ Hz, 3H, A or B diastereomer), 1.48 (s, 3H), 2.03 (s, 1H, A or B diastereomer), 2.10 (s, 1H, A or B diastereomer), 2.31 (s, 3H, A or B diastereomer) 2.46-2.57 (m, 1H), 4.88-5.09 (m, 2H), 5.66-5.83 (m, 1H), 7.10-7.12 (m, 2H), 7.25-7.30 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.3, 14.9, 21.0, 26.0, 28.5, 48.9, 49.1, 75.7, 75.8, 116.1, 116.4, 125.3, 125.6, 128.7, 135.9, 136.1, 140.2, 140.2, 144.2, 144.2. IR (neat): 3469, 3022, 2974, 1676, 1635, 1512, 1454, 1371, 1078, 912, 815 cm^{-1} MS (ESI) m/z 213 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{ONa}$: 213.1255, found: 213.1261.

2-(4-Methoxyphenyl)-3-methylpent-4-en-2-ol 153l

Yellow liquid; dr = 1:2; ^1H NMR (CDCl_3 , 400 MHz): δ 0.88 (d, $J = 6.8$ Hz, 3H, A or B diastereomer), 0.94 (d, $J = 6.8$ Hz, 3H, A or B diastereomer), 1.51 (s, 3H), 1.92 (s,

1H, A or B diastereomer), 2.00 (s, 1H, A or B diastereomer), 2.48-2.58 (m, 1H), 3.80 (s, 3H), 4.89-5.28 (m, 2H), 5.69-5.84 (m, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.30-7.36 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.3, 14.8, 25.8, 28.3, 49.1, 55.2, 75.5, 75.5, 113.2, 116.2, 116.5, 126.4, 126.7, 139.2, 140.1, 140.2, 158.1, 159.3. IR (neat): 3478, 3072, 2974, 1635, 1610, 1581, 1510, 1298, 1249, 1033, 914, 833 cm^{-1} MS (ESI) m/z 189 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{O}$: 189.1279, found: 189.1272.

1-(1-Methyl-1*H*-indol-2-yl)ethanol 153ma

Brown liquid. ^1H NMR (CDCl_3 , 500 MHz): δ 1.65 (d, $J = 6.6$ Hz, 3H), 3.74 (s, 3H), 4.98 (q, $J = 6.5$ Hz, 1H), 6.41 (s, 1 H), 7.06-7.10 (m, 1 H), 7.19-7.20 (m, 1H), 7.21-7.29 (m, 1H), 7.56 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 22.4, 30.0, 63.1, 98.4, 109.1, 119.6, 120.8, 121.8, 127.1, 138.0, 142.7. IR (neat): 3371, 3053, 2976, 1469, 1371, 1076, 908, 732 cm^{-1} MS (ESI) m/z 158 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{N}$: 158.0970, found: 158.0973.

1-(1-Methyl-1*H*-indol-2-yl)ethanone 153mb

Brown liquid. ^1H NMR (CDCl_3 , 400 MHz): δ 2.62 (s, 3H), 4.08 (s, 3H), 7.15-7.19 (m, 1H), 7.29 (s, 1 H), 7.38-7.39 (m, 2 H), 7.70 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 28.0, 32.2, 110.4, 112.0, 120.7, 122.9, 125.8, 125.9, 134.9, 140.1, 191.7. IR (neat): 3018, 2953, 1651, 1514, 1217, 962, 752, 584 cm^{-1} MS (ESI) m/z 174 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}$: 174.0919, found: 174.0927.

3-Methyl-2-(1-methyl-1*H*-indol-2-yl)pent-4-en-2-ol 153m

Brown liquid; dr = 1:1; ^1H NMR (CDCl_3 , 400 MHz): δ 0.83 (d, $J = 5.6$ Hz, 3H, A or B diastereomer), 1.13 (d, $J = 5.4$ Hz, 3H, A or B diastereomer), 1.53 (s, 3H), 1.93 (s, 1H, A or B diastereomer), 2.14 (s, 1H, A or B diastereomer), 2.86-2.89 (m, 1H), 3.91 (s, 3H, A or B diastereomer), 3.93 (s, 3H, A or B diastereomer), 4.90-4.96 (m, 2H, A or B diastereomer), 5.19-5.23 (m, 2H, A or B diastereomer), 5.57-5.64 (m, 1H, A or B diastereomer), 5.92-5.99 (m, 1H, A or B diastereomer), 6.31 (s, 1H, A or B diastereomer), 6.35 (s, 1H, A or B diastereomer), 7.05-7.18 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 14.1, 15.6, 23.9, 25.1, 32.4, 32.4, 46.2, 46.4, 74.6, 74.7, 100.7, 101.5, 109.3, 109.4, 115.6, 117.5, 119.7, 120.6, 121.7, 121.8, 127.1, 138.9, 139.0, 139.6, 139.8, 143.3, 144.2. IR (neat): 3550, 3215, 2999, 1633, 1608, 1529, 1215, 912, 790, 667 cm^{-1} . MS (ESI) m/z 212 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}$: 212.1439, found:212.1445.

2-(4-Bromophenyl)-3-phenylpent-4-en-2-ol 153n¹⁵⁶

dr > 99; ^1H NMR (CDCl_3 , 400 MHz): δ 1.40 (s, 3H), 2.07 (s, 1H), 3.55 (d, $J = 8.8$ Hz, 1H), 4.93 (d, $J = 17.1$ Hz, 1H), 5.05 (d, $J = 10.3$ Hz, 1H), 6.05-6.14 (m, 1H), 7.10 (d, $J = 6.7$ Hz, 2H), 7.17-7.25 (m, 6H), 7.40 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 28.4, 61.8, 76.1, 118.4, 120.6, 127.0, 127.6, 128.3, 129.6, 130.9, 137.1, 139.9, 145.6.

2,3-Diphenylpent-4-en-2-ol 153o¹⁵⁷

dr > 99; ¹H NMR (CDCl₃, 400 MHz): δ 1.40 (s, 3H), 2.54 (s, 1H), 3.62 (d, *J* = 8.6 Hz, 1H), 4.90 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 5.97-6.30 (m, 1H), 7.11-7.28 (m, 10H); ¹³C NMR (CDCl₃, 100 MHz): δ 28.6, 62.0, 76.4, 118.1, 125.6, 126.7, 126.9, 127.9, 128.2, 129.8, 137.5, 140.3, 146.6.

(E)-methyl 5-hydroxy-4-methyl-5,5-diphenylpent-2-enoate 153p

White solid; m.p. 100-101 °C; ¹H NMR (CDCl₃, 400 MHz): δ 1.03 (d, *J* = 6.8 Hz, 3H), 2.54 (s, 1H), 3.55-3.58 (m, 1H), 3.60 (s, 3H), 5.83 (d, *J* = 15.9 Hz, 1H), 7.03 (dd, *J* = 15.9, 7.4 Hz, 1H), 7.13-7.19 (m, 2 H), 7.23-7.30 (m, 4 H), 7.43-7.47 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ 14.5, 44.4, 51.5, 79.7, 122.4, 125.8, 125.9, 126.8, 126.9, 128.3, 128.3, 145.5, 145.7, 150.3, 166.8. IR (neat): 3581, 3018, 2951, 1709, 1651, 1448, 1215, 756 cm⁻¹ MS (ESI) *m/z* 279 [M - OH]⁺; HRMS (ESI) calcd for C₁₉H₁₉O₂: 279.1385, found: 279.1391.

(E)-ethyl 5-hydroxy-5-phenylhex-2-enoate 153q¹⁵⁶

¹H NMR (CDCl₃, 300 MHz): δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.58 (s, 3H), 2.10 (s, 1H), 2.61-2.78 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.84 (d, *J* = 15.6 Hz, 1H), 6.79-6.89 (m, 1H), 7.23-7.27 (m, 1H), 7.27-7.37 (m, 2H), 7.44-7.45 (m, 2H); ¹³C NMR (CDCl₃, 75

MHz): δ 14.2, 29.8, 46.8, 60.3, 74.1, 124.6, 124.8, 127.0, 128.4, 144.0, 147.1, 166.2.

2-Methyl-1-phenylbut-3-en-1-ol 153r¹⁵⁷

dr = 1:1.3; ¹H NMR (CDCl₃, 500 MHz): δ 0.85 (d, J = 6.9 Hz, 3H, A or B diastereomer), 0.99 (d, J = 6.9 Hz, 3H, A or B diastereomer), 2.11 (d, J = 3.7 Hz, A or B diastereomer), 2.26 (d, J = 2.7 Hz, A or B diastereomer), 2.44-2.49 (m, 1H, A or B diastereomer), 2.54-2.57 (m, 1H, A or B diastereomer), 4.32-4.34 (m, 2 H, A or B diastereomer), 5.15-5.19 (m, 1H, A or B diastereomer), 5.70-5.81 (m, 2H), 5.83-7.33 (m, 10 H); ¹³C NMR (CDCl₃, 125 MHz): δ 14.1, 16.5, 44.7, 46.3, 77.4, 77.9, 115.5, 116.8, 126.6, 126.9, 127.4, 127.7, 128.1, 128.3, 140.4, 140.7, 142.5, 142.6.

1,1-Diphenylbut-3-en-1-ol 153s¹⁵⁷

¹H NMR (CDCl₃, 300 MHz): δ 2.55 (s, 1H), 3.07 (d, J = 7.2 Hz, 2H), 5.15-5.27 (m, 2H), 5.59-5.73 (m, 1H), 7.19-7.23 (m, 6 H), 7.30-7.46 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz): δ 46.7, 120.5, 126.1, 126.8, 126.9, 128.2, 128.2, 133.5, 146.5.

1,2-Dimethyl-3-phenyl-1*H*-indene 154a

Yellow solid; m.p. 51-52 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.38 (d, $J = 7.6$ Hz, 3H), 2.05 (s, 3H), 3.6 (q, $J = 7.5$ Hz, 1H), 7.14-7.22 (m, 3H), 7.31-7.48 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.2, 16.1, 47.7, 119.6, 122.8, 124.5, 126.7, 127.2, 128.7, 129.5, 135.8, 137.5, 145.2, 145.8, 148.5. IR (neat): 3043, 2966, 1589, 1508, 1157, 829, 735 cm^{-1} MS (ESI) m/z 221 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}$: 221.1330, found: 221.1327.

6-Fluoro-3-(4-fluorophenyl)-1,2-dimethyl-1*H*-indene 154b

Yellow liquid; ^1H NMR (CDCl_3 , 300 MHz): δ 1.35 (d, $J = 7.6$ Hz, 3H), 2.00 (s, 3H), 3.32 (q, $J = 7.5$ Hz, 1H), 6.86-6.98 (m, 1H), 7.02-7.16 (m, 4H), 7.22-7.35 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.9, 15.8, 47.3, 110.4 (1C, d, $J_{\text{C-F}} = 22.5$ Hz), 112.9 (1C, d, $J_{\text{C-F}} = 22.5$ Hz), 115.3, 115.6, 119.5, 119.6, 130.7, 130.8, 131.2, 131.2, 135.6, 140.7, 145.2, 145.3, 150.2, 150.3 162.0 (1C, d, $J_{\text{C-F}} = 240.8$ Hz), 162.0 (1C, d, $J_{\text{C-F}} = 244.5$ Hz). IR (neat): 3017, 2968, 1571, 1489, 1463, 1215, 1091, 827 cm^{-1} MS (ESI) m/z 257 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{F}_2$: 257.1142, found: 257.1142.

6-Chloro-3-(4-chlorophenyl)-1,2-dimethyl-1H-indene 154c

Yellow solid; m.p. 93-94 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.37 (d, $J = 7.6$ Hz, 3H), 2.03 (s, 3H), 3.36 (q, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 8.1$ Hz, 1H), 7.18-7.21 (m, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.38-7.45 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.9, 15.6, 119.8, 123.2, 126.6, 128.8, 130.4, 130.4, 133.0, 133.5, 143.0, 146.6, 149.9. IR (neat): 3014, 2966, 1566, 1485, 1215, 1008, 758 cm^{-1} MS (ESI) m/z 289 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Cl}_2$: 289.0551, found: 289.0555.

6-Bromo-3-(4-bromophenyl)-1,2-dimethyl-1H-indene 154d

Yellow solid; m.p. 93-94 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.37 (d, $J = 7.6$ Hz, 3H), 2.03 (s, 3H), 3.34 (q, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 8.1$ Hz, 1H), 7.22-7.40 (m, 4H), 7.52-7.60 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.9, 15.6, 47.5, 118.5, 120.3, 121.2, 126.0, 129.4, 130.8, 131.2, 131.7, 133.9, 135.7, 143.4, 146.6, 150.2. IR (neat): 3015, 2936, 1546, 1435, 1215, 756 cm^{-1} MS (ESI) m/z 377 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{Br}_2$: 376.9540, found: 376.9535.

1,2,6-Trimethyl-3-*p*-tolyl-1*H*-indene 154e

White solid; m.p. 48-49 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.37 (d, $J = 7.6$ Hz, 3H), 2.03 (s, 3H), 2.40 (s, 3H), 2.41 (s, 3H), 3.32 (q, $J = 7.5$ Hz, 1H), 7.02-7.12 (m, 2H), 7.21-7.32 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.9, 16.0, 21.3, 21.5, 47.2, 119.0, 123.5, 127.0, 129.1, 132.8, 133.7, 136.5, 136.8, 142.5, 144.2, 148.6. IR (neat): 3014, 2966, 1510, 1215, 756 cm^{-1} MS (ESI) m/z 249 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}$: 249.1643, found: 249.1654.

6-Methoxy-3-(4-methoxyphenyl)-1,2-dimethyl-1*H*-indene 154f

Yellow solid; m.p. 58-59 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 1.35 (d, $J = 7.5$ Hz, 3H), 2.00 (s, 3H), 3.30 (q, $J = 7.5$ Hz, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 6.74-6.78 (m, 1H), 6.97-7.00 (m, 3H), 7.09 (d, $J = 8.1$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.9, 16.1, 47.3, 55.3, 55.6, 109.7, 111.3, 113.8, 119.5, 128.1, 130.0, 136.1, 138.4, 14.7, 150.1, 157.6, 158.5. IR (neat): 3008, 2906, 1604, 1514, 1217, 1035, 827, 756 cm^{-1} MS (ESI) m/z 281 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for

$C_{19}H_{21}O_2$: 281.1542, found: 281.1533.

6-Chloro-1,2,3-trimethyl-1*H*-indene 154g

Colorless liquid; 1H NMR ($CDCl_3$, 500 MHz): δ 1.26 (d, $J = 7.6$ Hz, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 3.18 (q, $J = 7.3$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.22-7.24 (m, 1H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.2, 12.1, 15.6, 46.8, 118.7, 122.7, 126.3, 129.8, 130.5, 143.7, 144.7, 150.0. IR (neat): 2966, 1571, 1460, 1074, 817 cm^{-1} . MS (ESI) m/z 193 $[M + H]^+$; HRMS (ESI) calcd for $C_{12}H_{14}Cl$: 193.0784, found: 193.0782.

6-Bromo-1,2,3-trimethyl-1*H*-indene 154h

Colorless liquid; 1H NMR ($CDCl_3$, 500 MHz): δ 1.26 (d, $J = 7.6$ Hz, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 3.17 (q, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 7.37-7.43 (m, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.2, 12.1, 15.6, 46.9, 117.8, 119.2, 125.5, 129.2, 130.6, 143.8, 145.1, 150.3. IR (neat): 3076, 2964, 1463, 1066, 816 cm^{-1} . MS (ESI) m/z 259 $[M + Na]^+$; HRMS (ESI) calcd for $C_{12}H_{13}BrNa$: 259.0066, found: 259.0061.

1,2,3-Trimethyl-1*H*-indene 154i¹⁵⁸

¹H NMR (CDCl₃, 300 MHz): δ 1.28 (d, J = 7.5 Hz, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 3.19 (q, J = 7.3 Hz, 1H), 7.12-7.29 (m, 3H), 7.35 (d, J = 7.3 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 10.2, 12.0, 15.7, 46.9, 117.9, 122.1, 123.8, 126.3, 131.0, 143.2, 146.2, 148.2.

1,2,3,6-Tetramethyl-1*H*-indene 154j

Yellow liquid; ¹H NMR (CDCl₃, 500 MHz): δ 1.24 (d, J = 7.6 Hz, 3H), 1.94 (s, 3H), 1.99 (s, 3H), 2.37 (s, 3H), 3.13 (q, J = 7.2 Hz, 1H), 7.04-7.08 (m, 2H), 7.15 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 10.3, 12.0, 15.9, 21.5, 46.7, 117.6, 123.2, 126.9, 130.8, 133.3, 142.1, 143.6, 148.5. IR (neat): 3005, 2962, 1481, 812, 597 cm⁻¹. MS (ESI) m/z 173 [M + H]⁺; HRMS (ESI) calcd for C₁₃H₁₇: 173.1330, found: 173.1337.

6-Methoxy-1,2,3-trimethyl-1*H*-indene 154k

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz): δ 1.28 (d, J = 7.5 Hz, 3H), 1.97 (s, 3H), 2.02 (s, 3H), 3.18 (q, J = 7.2 Hz, 1H), 3.85 (s, 3H), 6.81-6.84 (m, 1H), 6.98 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 10.3, 12.0, 16.0, 46.8, 55.6,

109.5, 111.1, 118.1, 130.4, 139.4, 140.9, 150.0, 157.4. IR (neat): 2960, 1608, 1583, 1475, 1286, 1031 cm^{-1} MS (ESI) m/z 189 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{O}$: 189.1279, found: 189.1283.

1-Methyl-2-(3-methylpenta-1,4-dien-2-yl)-1*H*-indole¹⁵⁵

Brown liquid; ^1H NMR (CDCl_3 , 500 MHz): δ 1.22 (d, $J = 7.0$ Hz, 3H), 3.25-3.31 (m, 1H), 3.68 (s, 3H), 5.01-5.09 (m, 2H), 5.15 (s, 1H), 5.41 (s, 1H), 5.86-5.93 (m, 1H), 6.41 (s, 1H), 7.08-7.11 (m, 1H), 7.7.19-7.21 (m, 1H), 7.29 (d, $J = 8.2$ Hz, 1H), 7.57 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.0, 31.0, 44.1, 100.8, 109.5, 114.2, 116.2, 119.7, 120.5, 121.5, 127.7, 138.0, 141.5, 141.6, 144.6. IR (neat): 3055, 2966, 1635, 1521, 1463, 1311, 912, 732 cm^{-1} MS (ESI) m/z 212 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}$: 212.1439, found: 212.1443.

6-Bromo-1,3-dimethyl-2-phenyl-1*H*-indene ^{154l}

Yellow solid; m.p. 82-83 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz): δ 1.21 (d, $J = 7.6$ Hz, 3H), 2.24 (s, 3H), 3.88 (q, $J = 7.4$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.32-7.39 (m, 3H), 7.44-7.59 (m, 3H), 7.59 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 11.6, 16.3, 45.8, 119.0, 120.4, 126.0, 127.0, 128.4, 129.0, 132.7, 136.1, 144.8, 147.2, 150.4. IR (neat): 3014, 2968, 1597, 1568, 1215, 1076, 956, 756, 547 cm^{-1} MS (ESI) m/z 299 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{Br}$: 299.0435, found: 299.0435.

1,3-Dimethyl-2-phenyl-1*H*-indene 154m

Yellow solid; m.p. 74-75 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 1.27 (d, $J = 7.5$ Hz, 3H), 2.31 (s, 3H), 3.93 (q, $J = 7.3$ Hz, 1H), 7.29-7.52 (m, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 11.7, 16.4, 45.8, 119.2, 122.6, 125.0, 126.7, 126.7, 128.4, 129.1, 133.3, 136.6, 145.9, 146.8, 148.4. IR (neat): 3014, 2966, 1598, 1492, 1215, 756 cm^{-1} MS (ESI) m/z 221 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}$: 221.1330, found: 221.1321.

Methyl 2-(2-methyl-3-phenyl-1*H*-inden-1-yl)acetate 154n

Yellow liquid; ^1H NMR (CDCl_3 , 300 MHz): δ 2.03 (s, 1H), 2.49-2.57 (m, 1H), 2.79-2.86 (m, 1H), 3.76 (s, 1H), 3.86 (t, $J = 7.4$ Hz, 1H), 7.13-7.23 (m, 3H), 7.33-7.48 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.1, 35.8, 48.6, 51.8, 119.6, 122.9, 124.5, 126.9, 127.2, 128.5, 129.2, 135.1, 138.8, 142.5, 145.1, 145.7. IR (neat): 3014, 2966, 1598, 1492, 1215, 756 cm^{-1} MS (ESI) m/z 279 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{O}_2$: 279.1385, found: 279.1395.

(E)-ethyl 5-phenylhexa-2,4-dienoate 156¹²⁸

Known compound. Yellow liquid; *E:Z* = 4:1. ¹H NMR (CDCl₃, 500 MHz): δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.32 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 6.01 (d, *J* = 15.1 Hz, 1H), 6.59 (d, *J* = 11.7 Hz, 1H), 7.34-7.41 (m, 3H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.78 (q, *J* = 12.0, 15.0 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.4, 16.6, 60.3, 121.4, 124.7, 126.0, 128.3, 128.5, 140.7, 142.0, 145.4, 167.4. IR (neat): 3055, 2980, 1707, 1618, 1444, 1139, 1035, 977, 761, 696 cm⁻¹. MS (ESI) *m/z* 217 [M + H]⁺; HRMS (ESI) calcd for C₁₄H₁₇O₂: 217.1229, found: 217.1221.

7.5 Brønsted Acid Catalyzed Cyclization of Propargylic Alcohols with Thioamides. Facile Synthesis of Di- and Trisubstituted Thiazoles

Representative Procedure for *p*-TsOH·H₂O Catalyzed Synthesis of 2,4-Di- and Trisubstituted Thiazoles 164.

To a 5 mL round bottom flask containing 1,2-dichloroethane (3mL) were successively added **61a** (0.25mmol), **163a** (0.5mmol) and *p*-TsOH·H₂O (12.5μmol). The resultant reaction mixture was heated to 100 °C and stirred for 5 h. On cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue obtained was directly purified by flash column chromatography on silica

gel (eluent: *n*-hexane/EtOAc=8:1) to give the title compound.

Experimental Procedure for Synthesis of Pyrrolidine-2-thione **163b**

Lawesson's reagent (1.2 equiv) was added to a THF solution (5 mL/mmol) of pyrrolidin-2-one (1 equiv). The stirred mixture was then brought to reflux and stirred at this temperature overnight. After cooling to room temperature and evaporation of the solvent under reduced pressure, the resulting mixture was subjected to flash column chromatography on silica gel (eluent: *n*-hexane : EtOAc = 1:1) to give the product **163b** in 70% yield.

1,1-Bis(4-chlorophenyl)-3-(thiophen-3-yl)prop-2-yn-1-ol **61s**

Yellow solid; m.p. 188-189 °C; ¹H NMR (CDCl₃, 400 MHz): δ 2.90 (s, 1H), 7.15-7.16 (m, 1H), 7.31-7.33 (m, 5H), 7.53-7.57 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 74.0, 83.1, 90.2, 120.9, 125.7, 127.5, 128.6, 129.8, 129.8, 133.9, 143.2. IR (neat): 3414, 3020, 2229, 1909, 1672, 1643, 1579, 1519, 1487, 1396, 1215, 1089, 1056, 999, 902, 866, 769, 698, 667, 624 cm⁻¹. MS (ESI) *m/z* 340 [M - OH]⁺; HRMS (ESI) calcd for C₁₉H₁₁Cl₂S: 340.9959, found: 340.9957.

6-Hydroxy-N,6,6-triphenylhex-4-ynamide 61t

White solid; m.p. 144-145 °C; ^1H NMR (DMSO, 400 MHz): δ 2.61-2.83 (m, 4H), 6.61 (s, 1H), 7.04-7.07 (m, 1H), 7.12-7.20 (m, 6H), 7.30-7.34 (m, 2H), 7.51-7.53 (d, J = 6.8 Hz, 4H), 7.66-7.68 (d, J = 7.6 Hz, 2H), 10.08 (s, 1H); ^{13}C NMR (DMSO, 100 MHz): δ 15.2, 35.9, 73.2, 85.0, 85.7, 119.5, 123.6, 126.1, 127.2, 128.2, 129.2, 139.7, 147.3, 170.0. IR (neat): 3273, 3020, 2231, 1953, 1886, 1813, 1643, 1591, 1487, 1444, 1311, 1263, 1215, 1076, 1029, 1006, 916, 893, 752, 667 cm^{-1} . MS (ESI) m/z 338 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{20}\text{NO}$: 338.1545, found: 338.1536.

1-(4-Bromophenyl)-3-(4-fluorophenyl)prop-2-yn-1-ol 61v

^1H NMR (CDCl_3 , 300 MHz): δ 2.46 (s, 1H), 5.62 (s, 1H), 6.98-7.04 (m, 2H), 7.40-7.53 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 64.4, 85.9, 87.9, 115.7 (1C, d, $J_{\text{C-F}}$ = 22.0 Hz), 118.2, 118.2, 122.5, 128.4, 131.8, 133.7, 133.8, 139.5, 162.8 (1C, d, $J_{\text{C-F}}$ = 248.8 Hz). IR (neat): 3309, 3017, 2399, 2231, 2029, 1894, 1647, 1600, 1506, 1402, 1215, 1155, 1091, 1070, 1010, 837 cm^{-1} . MS (ESI) m/z 287 $[\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_9\text{BrF}$: 286.9872, found: 286.9875.

6-Hydroxy-1,6,6-triphenylhexa-1,4-diyne-3-one 61w

Yellow solid; m.p. 107-108 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 3.38 (s, 1H), 7.31-7.42 (m, 8H), 7.48-7.52 (m, 1H), 7.61-7.63 (d, $J = 7.5$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 74.6, 86.4, 89.3, 92.7, 93.8, 119.2, 126.1, 128.4, 128.6, 128.8, 131.5, 133.5, 143.1, 160.5. IR (neat): 3420, 3019, 2201, 1631, 1215, 765 cm^{-1} MS (ESI) m/z 319 [$\text{M} - \text{OH}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{15}\text{O}$: 319.1123, found: 319.1128.

Pyrrolidine-2-thione 163b ¹⁵⁹

^1H NMR (CDCl_3 , 300 MHz): δ 2.17-2.28 (m, 2H), 2.89-2.95 (t, $J = 7.9$ Hz, 2H), 3.65-3.70 (t, $J = 7.2$ Hz, 2H), 8.68 (bs, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 22.9, 43.3, 49.8, 205.7.

4-Benzhydryl-2-methyl-5-phenylthiazole 164a

White solid; m.p. 163-164 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 (s, 3H), 5.51 (s, 1H), 7.17-7.19 (m, 2H), 7.20-7.27 (m, 8H), 7.36-7.37 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 50.0, 126.4, 128.1, 128.3, 128.7, 129.2, 129.9, 132.0, 133.3, 143.4, 151.6, 163.9. IR (neat): 3019, 1599, 1533, 1493, 1215, 1074, 1030, 669, 634, 617,

584, 507 cm^{-1} ; MS (ESI) m/z 342 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{NS}$: 342.1316, found: 342.1316.

4-((4-Fluorophenyl)(phenyl)methyl)-2-methyl-5-phenylthiazole 164b

White solid; m.p. 130-131 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 (s, 3H), 5.48 (s, 1H), 6.92-6.96 (m, 2H), 7.19-7.29 (m, 7H), 7.33-7.39 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 49.2, 115.1 (1C, d, $J_{\text{C-F}} = 21.1$ Hz), 126.5; 128.2, 128.4, 128.8, 129.1, 129.8, 130.7, 130.8, 131.9, 133.4, 139.1, 139.2, 143.3, 151.5, 161.5 (1C, d, $J_{\text{C-F}} = 243.0$ Hz), 164.1. IR (neat): 3019, 1601, 1539, 1056, 1217, 1074, 1016, 700, 613, 507 cm^{-1} ; MS (ESI) m/z 360 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{FNS}$: 360.1222, found: 360.1223.

4-((4-Chlorophenyl)(phenyl)methyl)-2-methyl-5-phenylthiazole 164c

Yellow solid; m.p. 124-125 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 500 MHz): δ 2.66 (s, 3H), 5.46 (s, 1H), 7.18-7.27 (m, 9H), 7.32-7.37 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.5, 49.4, 126.6, 128.3, 128.4, 128.5, 128.8, 129.1, 129.8, 130.6, 131.8, 132.2, 133.6, 142.0, 143.0, 151.1, 164.1. IR (neat): 3017, 1599, 1537, 1489, 1215, 1088, 1015, 669, 605, 519 cm^{-1} ; MS (ESI) m/z 376 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{ClNS}$: 376.0927, found: 376.0911.

4-((4-Bromophenyl)(phenyl)methyl)-2-methyl-5-phenylthiazole 164d

White solid; m.p. 135-136 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 (s, 3H), 5.44 (s, 1H), 7.12-7.18 (m, 2H), 7.19-7.25 (m, 5H), 7.27-7.38 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 49.4, 120.4, 126.6, 128.3, 128.5, 128.8, 129.1, 129.8, 131.0, 131.4, 131.8, 133.6, 142.5, 142.9, 151.0, 164.1. IR (neat): 3057, 3024, 1906, 1599, 1531, 1485, 1215, 1069, 1009, 853, 714, 698, 513 cm^{-1} ; MS (ESI) m/z 420 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{BrNS}$: 420.0422, found: 420.0416.

4-((2-Methyl-5-phenylthiazol-4-yl)methyl)benzonitrile 164e

White solid; m.p. 134-135 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.67 (s, 3H), 5.51 (s, 1H), 7.23-7.25 (m, 3H), 7.26-7.32 (m, 6H), 7.34-7.40 (m, 3H), 7.52-7.54 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 50.0, 110.2, 119.1, 126.9, 128.4, 128.6, 128.9, 129.1, 129.7, 130.0, 131.5, 132.1, 134.1, 142.0, 149.0, 150.1, 164.4. IR (neat): 3020, 2228, 1599, 1493, 1215, 1184, 968, 756, 698, 550, 507 cm^{-1} ; MS (ESI) m/z 367 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{S}$: 367.1269, found: 367.1273.

2-Methyl-5-phenyl-4-(phenyl(p-tolyl)methyl)thiazole 164f

White solid; m.p. 120-121 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.29 (s, 3H), 2.65 (s, 3H), 5.49 (s, 1H), 7.07-7.09 (d, J = 8.0 Hz, 2H), 7.15-7.19 (m, 3H), 7.25-7.26 (m, 4H), 7.35-7.37 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.6, 21.1, 49.6, 126.3, 128.1, 128.3, 128.7, 129.0, 129.1, 129.2, 129.9, 132.1, 133.2, 135.9, 140.5, 143.7, 151.2, 163.9. IR (neat): 3022, 1599, 1531, 1510, 1493, 1215, 1076, 1030, 754, 667, 613, 505 cm^{-1} ; MS (ESI) m/z 356 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{22}\text{NS}$: 356.1473, found: 356.1461.

4-(Bis(4-fluorophenyl)methyl)-2-methyl-5-phenylthiazole 164g

White solid; m.p 127-128 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 2.66 (s, 3H), 5.45 (s, 1H), 6.94-6.97 (m, 4H), 7.18-7.22 (m, 4H), 7.31-7.33 (d, J = 7.0 Hz, 2H), 7.33-7.40 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.5, 48.5, 115.1 (1C, d, $J_{\text{C-F}}$ = 20.9 Hz), 128.3, 128.8, 129.7, 130.5, 130.6, 131.8, 133.5, 138.9, 139.0, 151.2, 161.5 (1C, d, $J_{\text{C-F}}$ = 243.3 Hz), 164.3. IR (neat): 3017, 1603, 1506, 1217, 1157, 770, 700, 669, 571, 534, 509 cm^{-1} ; MS (ESI) m/z 378 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{18}\text{F}_2\text{NS}$: 378.1128, found: 378.1131.

4-(Bis(4-chlorophenyl)methyl)-2-methyl-5-phenylthiazole 164h

Yellow solid; m.p. 140-141 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.65 (s, 3H), 5.41 (s, 1H), 7.14-7.17 (m, 4H), 7.22 (s, 3H), 7.24-7.32 (m, 3H), 7.36-7.39 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.5, 48.8, 128.4, 128.5, 128.8, 129.7, 130.5, 131.6, 132.4, 133.8, 141.5, 150.6, 164.3. IR (neat): 3019, 1599, 1537, 1489, 1215, 1090, 1015, 756, 700, 567, 521 cm^{-1} ; MS (ESI) m/z 410 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{18}\text{Cl}_2\text{NS}$: 410.0537, found: 410.0533.

4-(Bis(4-bromophenyl)methyl)-2-methyl-5-phenylthiazole 164i

White solid; m.p. 192-193 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 2.68 (s, 3H), 5.39 (s, 1H), 7.11-7.13 (d, $J = 8.2$ Hz, 4H), 7.31-7.33 (d, $J = 7.6$ Hz, 2H), 7.40-7.41 (m, 7H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.5, 48.9, 120.6, 128.4, 128.8, 129.7, 130.9, 131.5, 131.6, 133.8, 141.9, 150.4, 164.4. IR (neat): 3019, 2399, 1599, 1535, 1487, 1215, 1184, 1072, 1011, 756, 700, 699, 561, 513 cm^{-1} ; MS (ESI) m/z 498 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{18}\text{Br}_2\text{NS}$: 497.9527, found: 497.9522.

2-Methyl-5-phenyl-4-(di-*p*-tolylmethyl)thiazole 164j

Yellow solid. m.p. 127-128 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.29 (s, 6H), 2.65 (s, 3H), 5.44 (s, 1H), 7.06-7.08 (d, $J = 7.7$ Hz, 4H), 7.14-7.35 (m, 9H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.6, 21.1, 49.3, 128.1, 128.7, 129.0, 129.1, 129.9, 132.1, 133.0, 135.8, 140.7, 152.1, 163.8. IR (neat): 3017, 1902, 1601, 1520, 1443, 1215, 1179, 1022, 968, 769, 698, 667, 573, 536 cm^{-1} ; MS (ESI) m/z 370 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{NS}$: 370.1629, found: 370.1628.

4-Benzhydryl-5-(4-fluorophenyl)-2-methylthiazole 164k

White solid; m.p. 143-144 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 2.65 (s, 3H), 5.44 (s, 1H), 7.05-7.08 (m, $J = 8.5$ Hz, 2H), 7.17-7.20 (m, 2H), 7.24-7.31 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.5, 50.0, 115.7, 115.8 (1C, d, $J_{\text{C-F}} = 21.6$ Hz), 126.5, 128.4, 129.2, 131.6, 131.7, 132.1, 143.3, 151.9, 161.7 (1C, d, $J_{\text{C-F}} = 247.0$ Hz), 164.0. IR (neat): 3026, 1894, 1651, 1601, 1452, 1342, 1215, 1030, 968, 912, 837, 627, 550 cm^{-1} ; MS (ESI) m/z 360 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{FNS}$: 360.1222, found: 360.1212.

4-Benzhydryl-5-(4-chlorophenyl)-2-methylthiazole 164l

White solid; m.p. 129-130 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.65 (s, 3H), 5.44 (s, 1H), 7.17-7.21 (m, 2H), 7.23-7.28 (m, 10H), 7.34-7.36 (d, J = 8.4 Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 50.1, 126.5, 128.4, 129.0, 129.2, 130.5, 131.1, 132.0, 134.3, 143.2, 152.1, 164.2. IR (neat): 3024, 1902, 1599, 1531, 1489, 1215, 1180, 1094, 968, 831, 704, 667, 633, 584, 513 cm^{-1} ; MS (ESI) m/z 376 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{ClNS}$: 376.0927, found: 376.0922.

4-Benzhydryl-2-methyl-5-*p*-tolylthiazole 164m

White solid; m.p. 141-142 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.36 (s, 3H), 2.63 (s, 3H), 5.51 (s, 1H), 7.17-7.18 (d, J = 6.3 Hz, 4H), 7.23-7.26 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 21.3, 50.0, 126.4, 128.3, 129.0, 129.3, 129.5, 129.8, 133.4, 138.1, 143.6, 151.5, 163.6. IR (neat): 3021, 1908, 1601, 1537, 1447, 1215, 1175, 1111, 1030, 820, 756, 633, 584 cm^{-1} ; MS (ESI) m/z 356 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{22}\text{NS}$: 356.1473, found: 356.1468.

4-Benzhydryl-5-(4-methoxyphenyl)-2-methylthiazole 164n

White solid; m.p. 145-146 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.63 (s, 3H), 3.79 (s, 3H), 5.49 (s, 1H), 6.89-6.91 (d, $J = 8.6$ Hz, 2H), 7.16-7.19 (m, 2H), 7.23-7.27 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 19.5, 50.0, 55.4, 114.2, 124.2, 126.4, 128.3, 129.2, 131.1, 133.2, 143.6, 151.3, 159.6, 163.4. IR (neat): 3078, 2893, 1954, 1599, 1537, 1344, 1111, 920, 772, 667, 635, 563, 530 cm^{-1} ; MS (ESI) m/z 372 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{22}\text{NOS}$: 372.1422, found: 372.1427.

2-Methyl-4-(2-methyl-1-phenylpropyl)-5-phenylthiazole 164o

Yellow solid; m.p. 101-102 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.64-0.66 (d, $J = 6.6$ Hz, 3H), 0.71-0.73 (d, $J = 6.5$ Hz, 3H), 2.51-2.59 (m, 1H), 2.66 (s, 3H), 3.41-3.44 (d, $J = 10.6$ Hz, 1H), 7.10-7.45 (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.4, 21.3, 21.6, 33.9, 53.2, 126.1, 127.8, 128.2, 128.5, 128.7, 130.2, 132.1, 132.3, 143.8, 153.3, 163.4. IR (neat): 3061, 3020, 2967, 2868, 2399, 1699, 1599, 1539, 1489, 1466, 1383, 1217, 1180, 1072, 1030, 966, 912, 756, 698, 667, 521 cm^{-1} ; MS (ESI) m/z 308 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{NS}$: 308.1473, found: 308.1468.

4-Benzhydryl-5-(4-butylphenyl)-2-methylthiazole 164p

Yellow solid; m.p. 53-54 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.83-0.88 (s, 3H), 1.26-1.33 (m, 2H), 1.46-1.56 (m, 2H), 2.58 (s, 3H), 2.69-2.74 (t, $J = 7.7$ Hz, 2H), 5.50 (s, 1H), 7.16-7.29 (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.8, 19.4, 22.3, 26.1, 34.2, 50.3, 126.3, 128.3, 129.2, 133.9, 143.2, 151.4, 161.8. IR (neat): 2959, 2930, 1495, 1215, 1182, 1032, 756, 700, 667, 633 cm^{-1} ; MS (ESI) m/z 322 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{NS}$: 322.1629, found: 322.1622.

4-Benzhydryl-2-methylthiazole 164q

White solid; m.p. 62-63 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.68 (s, 3H), 5.64 (s, 1H), 6.50 (s, 1H), 7.15-7.29 (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.3, 53.8, 115.8, 126.6, 128.4, 129.1, 142.7, 158.8, 165.8. IR (neat): 3018, 1598, 1535, 1490, 1205, 720 cm^{-1} ; MS (ESI) m/z 266 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{NS}$: 266.1003, found: 266.0991.

4-(Bis(4-chlorophenyl)methyl)-2-methyl-5-(thiophen-3-yl)thiazole 164r

White solid; m.p. 62-63 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.56 (s, 3H), 5.40 (s, 1H), 6.96-6.98 (m, 1H), 7.06-7.09 (m, 5H), 7.15-7.17 (m, 4H), 7.27-7.29 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.5, 49.1, 124.0, 126.5, 128.4, 128.6, 128.6, 130.1, 131.5, 132.5, 141.3, 151.0, 163.9. IR (neat): 3019, 1923, 1668, 1576, 1489, 1408, 1364, 1304, 1285, 1215, 1179, 1088, 1016, 853, 696, 567, 517 cm^{-1} ; MS (ESI) m/z 416 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{NS}_2$: 416.0101, found: 416.0081.

3-(4-Benzhydryl-2-methylthiazol-5-yl)-*N*-phenylpropanamide 164s

Brown liquid; ^1H NMR (CDCl_3 , 300 MHz): δ 2.30-2.35 (t, $J = 7.6$ Hz, 2H), 2.53 (s, 3H), 3.11-3.15 (t, $J = 7.3$ Hz, 2H), 5.58 (s, 1H), 7.04-7.09 (m, 1H), 7.15-7.27 (m, 12H), 7.36-7.38 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 19.3, 22.2, 38.9, 50.3, 120.0, 124.4, 126.5, 128.4, 129.0, 129.2, 131.3, 137.7, 142.9, 152.4, 162.7, 169.4. IR (neat): 3296, 3059, 2245, 1948, 1880, 1807, 1693, 1599, 1487, 1444, 1371, 1310, 1250, 1184, 1078, 1031, 1002, 908, 729, 584 cm^{-1} ; MS (ESI) m/z 413 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{OS}$: 413.1688, found: 413.1684.

4-Benzhydryl-2-(3-chloropropyl)-5-phenylthiazole 164t

Yellow solid; m.p. 154-155 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.25-2.31 (m, 2H), 3.13-3.17 (t, $J = 7.2$ Hz, 2H), 3.61-3.64 (t, $J = 6.4$ Hz, 2H), 5.52 (s, 1H), 7.20-7.23 (m, 2H), 7.29-7.30 (m, 8H), 7.38-7.42 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 30.4, 32.1, 44.0, 50.0, 126.3, 128.2, 128.3, 128.7, 129.8, 131.8, 133.2, 143.4, 151.6, 166.7. IR (neat): 3020, 2466, 1597, 1556, 1531, 1487, 1469, 1446, 1303, 1271, 1217, 1182, 1111, 1074, 1029, 771 cm^{-1} ; MS (ESI) m/z 404 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{ClNS}$: 404.1240, found: 404.1242.

4-((4-Chlorophenyl)(phenyl)methyl)-2,5-diphenylthiazole 164u

Yellow solid; m.p. 142-143 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 5.59 (s, 1H), 7.28-7.52 (m, 17H), 7.99-8.01 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 49.7, 126.4, 126.6, 128.4, 128.4, 128.5, 128.9, 128.9, 129.1, 129.8, 129.9, 130.7, 131.6, 132.2, 133.8, 134.1, 142.1, 143.1, 152.3, 165.7. IR (neat): 3019, 2399, 1597, 1531, 1489, 1458, 1408, 1312, 1215, 1090, 1032, 1013, 756, 669, 610, 507 cm^{-1} ; MS (ESI) m/z 438 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{ClNS}$: 438.1083, found: 438.1064.

4-((4-Chlorophenyl)(phenyl)methyl)-2-(4-fluorophenyl)-5-phenylthiazole 164v

Yellow solid; m.p. 132-133 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 5.51 (s, 1H), 7.06-7.10 (m, 2H), 7.19-7.34 (m, 9H), 7.39-7.44 (m, 5H), 7.88-7.91 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 49.7, 115.9 (1C, d, $J_{\text{C-F}} = 22.0$ Hz), 126.6, 128.3, 128.4, 128.4, 128.4, 128.5, 128.9, 129.1, 129.7, 130.2, 130.2, 130.6, 131.4, 132.2, 134.1, 142.0, 143.0, 152.4, 162.6, 164.5, 165.1. IR (neat): 3019, 2399, 1956, 1896, 1597, 1514, 1487, 1454, 1408, 1296, 1231, 1155, 1090, 1015, 947, 839, 770, 667, 611, 584 cm^{-1} ; MS (ESI) m/z 456 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{20}\text{ClFNS}$: 456.0989, found: 456.0968.

2-(4-Chlorophenyl)-4-((4-chlorophenyl)(phenyl)methyl)-5-phenylthiazole 164w

Yellow solid; m.p. 167-168 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 5.52 (s, 1H), 7.21-7.40 (m, 16H), 7.83-7.85 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 49.7, 126.6, 127.6, 128.4, 128.5, 128.6, 128.9, 129.1, 129.1, 129.8, 130.6, 131.4, 132.3, 132.3,

134.5, 135.8, 142.0, 143.0, 152.6, 164.4. IR (neat): 3019, 2399, 1908, 1597, 1522, 1489, 1450, 1396, 1215, 1089, 1010, 833, 767, 669, 609 cm^{-1} ; MS (ESI) m/z 472 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{20}\text{Cl}_2\text{NS}$: 472.0694, found: 472.0689.

2-(2-Chlorophenyl)-4-((4-chlorophenyl)(phenyl)methyl)-5-phenylthiazole 164x

Yellow solid; m.p. 138-139 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz): δ 5.56 (s, 1H), 7.22-7.41 (m, 17H), 8.23-8.25 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 49.6, 126.6, 127.1, 128.4, 128.4, 128.5, 128.9, 129.2, 129.8, 130.2, 130.7, 130.8, 131.4, 131.8, 132.1, 132.2, 136.0, 142.2, 143.1, 151.2, 161.0. IR (neat): 3020, 2926, 1953, 1898, 1599, 1564, 1525, 1487, 1433, 1271, 1215, 1089, 1064, 1039, 1015, 950, 918, 852, 756, 696, 669, 611 cm^{-1} ; MS (ESI) m/z 472 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{20}\text{Cl}_2\text{NS}$: 472.0694, found: 472.0679.

2-(4-Bromophenyl)-4-((4-chlorophenyl)(phenyl)methyl)-5-phenylthiazole 164y

White solid; m.p. 187-188 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 5.51 (s, 1H), 7.19-7.33

(m, 9 H), 7.40-7.45 (m, 5 H), 7.51-7.53 (d, $J = 8.4$ Hz, 2 H), 7.77-7.79 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 49.7, 124.1, 126.6, 127.8, 128.4, 128.4, 128.6, 128.9, 129.1, 129.7, 130.6, 131.3, 132.0, 132.3, 132.7, 134.5, 141.9, 142.9, 152.6, 164.4. IR (neat): 3019, 2399, 1597, 1520, 1489, 1450, 1391, 1215, 1088, 1006, 771, 609 cm^{-1} ; MS (ESI) m/z 516 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{20}\text{ClBrNS}$: 516.0188, found: 516.0192.

4-((4-Chlorophenyl)(phenyl)methyl)-2-(4-methoxyphenyl)-5-phenylthiazole 164z

Yellow solid; m.p. 181-182 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): δ 3.83 (s, 3H), 5.50 (s, 1H), 6.91-6.93 (d, $J = 8.8$ Hz, 2H), 7.20-7.41 (m, 14 H), 7.85-7.87 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 49.7, 55.4, 114.2, 126.5, 126.9, 127.9, 128.3, 128.3, 128.4, 128.8, 129.2, 129.7, 130.7, 131.7, 132.1, 133.1, 142.2, 143.2, 151.9, 161.1, 165.5. IR (neat): 3019, 2837, 2555, 2399, 2048, 1957, 1894, 1820, 1761, 1645, 1602, 1517, 1487, 1454, 1408, 1300, 1170, 1093, 1014, 941, 875, 831, 669, 630, 590 cm^{-1} ; MS (ESI) m/z 468 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{ClNOS}$: 468.1189, found: 468.1166.

***N*-(1,3-Diphenylprop-2-ynyl)ethanethioamide 165a**

Brown liquid; ^1H NMR (CDCl_3 , 400 MHz): δ 2.37 (s, 3H), 5.80 (s, 1H), 7.29-7.39 (m, 6 H), 7.47-7.50 (m, 2H), 7.57-7.59 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 30.0, 38.3, 85.3, 86.6, 122.7, 127.7, 128.0, 128.3, 128.5, 128.8, 131.8, 138.6, 193.6. IR (neat): 3019, 2399, 1685, 1598, 1442, 1354, 1215, 1130, 1028, 952, 754, 667, 630 cm^{-1} ; MS (ESI) m/z 266 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{NS}$: 266.1003, found: 266.1000.

***N*-(1-(4-Bromophenyl)-3-(4-fluorophenyl)prop-2-ynyl)ethanethioamide 165b**

Brown liquid; ^1H NMR (CDCl_3 , 300 MHz): δ 2.37 (s, 3H), 5.72 (s, 1H), 6.98-7.04 (m, 2 H), 7.41-7.49 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 30.0, 37.7, 84.5, 85.6, 115.6 (1C, d, $J_{\text{C-F}} = 22.0$ Hz), 118.4, 118.5, 122.0, 129.4, 131.9, 133.7, 133.8, 137.7, 162.7 (1C, d, $J_{\text{C-F}} = 248.6$ Hz), 193.3. IR (neat): 3019, 2958, 2922, 2881, 2250, 1886, 1693, 1600, 1504, 1487, 1404, 1354, 1294, 1232, 1155, 1072, 1010, 954, 908, 835, 759, 624, 530 cm^{-1} ; MS (ESI) m/z 362 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{ClBrNS}$: 362.0014, found: 362.9993.

7.6 Efficient Synthesis of Di- and Trisubstituted 2-Aryloxazoles via Ytterbium(III) Triflate Catalyzed Cyclization of Tertiary Propargylic Alcohols with Aryl Amides

Representative Experimental Procedure for the Synthesis of 2-Aryloxazoles **167**

To a solution of **61** (0.25 mmol) and **166** (0.3 mmol) in toluene (3mL) was added Yb(OTf)₃ (12.5 mmol) and heated at 100 °C for 24 h. Upon completion, the reaction mixture was cooled to room temperature, concentrated under reduced pressure and the resulting residue was further purified by flash column chromatography on silica gel (n-hexane/EtOAc: 20/1/15/1) to give the title compound.

4-Benzhydryl-2,5-diphenyloxazole **167a**

Pale yellow solid; m.p. 167-168 °C; ¹H NMR (CDCl₃, 300 MHz): δ 5.65 (s, 1H), 7.19-7.23 (m, 2H), 7.24-7.36 (m, 5H), 7.38-7.47 (m, 9H), 7.62-7.64 (m, 2H), 8.07-8.10 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 48.2, 126.5, 126.6, 127.8, 128.3, 128.4, 128.7, 128.8, 128.9, 129.2, 130.2, 138.4, 142.7, 146.6, 160.0. IR (neat): 3021, 1595, 1549, 1493, 1449, 1215, 1069, 924, 756, 669 cm⁻¹; MS (ESI) m/z 388 [M + H]⁺;

HRMS (ESI) calcd for $C_{28}H_{22}NO$: 388.1701, found: 388.1720.

4-(Bis(4-fluorophenyl)methyl)-2,5-diphenyloxazole 167b

White solid; m.p. 175-176 °C; 1H NMR ($CDCl_3$, 300 MHz): δ 5.59 (s, 1H), 6.96-7.02 (m, 4H), 7.33-7.41 (m, 10H), 7.42-7.61 (m, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.7, 115.3 (1C, d, $J_{C-F} = 21.5$ Hz), 126.5, 126.6, 127.6, 128.5, 128.6, 128.7, 129.0, 130.3, 130.6, 130.7, 138.0, 138.2, 146.6, 160.1, 162.0 (1C, d, $J_{C-F} = 240.0$ Hz). IR (neat): 3019, 1601; 1551, 1506, 1447, 1217, 1157, 1094, 762, 670 cm^{-1} ; MS (ESI) m/z 424 $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{20}F_2NO$: 424.1513, found: 424.1504.

4-(Bis(4-chlorophenyl)methyl)-2,5-diphenyloxazole 167c

White solid; m.p. 180-181 °C; 1H NMR ($CDCl_3$, 300 MHz): δ 5.56 (s, 1H), 7.25-7.41 (m, 8H), 7.41-7.47 (m, 6H), 7.57-7.59 (m, 2H), 8.05-8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.0, 126.5, 126.6, 127.5, 128.4, 128.6, 128.7, 129.0, 130.4, 130.5, 132.7, 137.4, 140.7, 146.7, 160.3. IR (neat): 3018; 1653, 1591, 1489, 1215, 1090, 1015, 773,

670 cm^{-1} ; MS (ESI) m/z 457 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{20}\text{Cl}_2\text{NO}$: 456.092, found: 46.0910.

4-((4-Fluorophenyl)(phenyl)methyl)-2,5-diphenyloxazole 167d

White solid; m.p. 192-193 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz): δ 2.30 (s, 6H), 5.58 (s, 1H), 7.10 (d, $J = 8.1$ Hz, 4H), 7.20-7.36 (m, 5H), 7.39-7.45 (m, 5H), 7.63 (d, $J = 7.2$ Hz, 2H), 8.07-8.10 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.1, 47.5, 126.6, 127.8, 128.2, 128.6, 128.9, 129.0, 129.1, 130.1, 136.0, 138.8, 139.9, 146.4, 160.0. IR (neat): 3019, 1647, 1510, 1447, 1215, 1026, 772, 670 cm^{-1} ; MS (ESI) m/z 416 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{26}\text{NO}$: 416.2014, found: 416.2011.

4-((4-Chlorophenyl)(phenyl)methyl)-2,5-diphenyloxazole 167e

White solid; m.p. 93-94 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz): δ 5.62 (s, 1H), 6.95-7.00 (m, 2H), 7.19-7.28 (m, 1H), 7.30-7.45 (m, 12H), 7.61 (d, $J = 7.3$ Hz, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 47.5, 126.6, 126.8, 127.7, 128.4, 128.5, 128.7, 129.0, 129.1, 130.3, 130.7, 130.8, 138.2, 138.4, 138.5, 142.5, 146.6, 160.1, 163.3. IR (neat): 3019, 1638, 1056, 1449, 1215, 752, 670 cm^{-1} ; MS (ESI) m/z 406 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{FNO}$: 406.1607, found: 406.1613.

4-((4-Bromophenyl)(phenyl)methyl)-2,5-diphenyloxazole 167f

White solid; m.p. 119-120 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.60 (s, 1H), 7.20-7.31 (m, 4H), 7.33-7.38 (m, 4H), 7.41-7.46 (m, 7H), 7.60 (d, $J = 7.2$ Hz, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 47.6, 126.6, 126.8, 127.6, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 130.3, 130.7, 132.5, 137.9, 141.2, 142.2, 146.7, 160.2. IR (neat): 3019, 1643, 1638, 1489, 1449, 1215, 752, 670 cm^{-1} ; MS (ESI) m/z 422 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{ClNO}$: 422.1312, found: 422.1308.

4-Benzhydryl-5-(4-fluorophenyl)-2-phenyloxazole 167g

White solid; m.p. 121-122 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.58 (s, 1H), 7.14-7.46 (m, 17H), 7.61 (d, $J = 8.4$ Hz, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 47.7, 120.6, 126.6, 126.9, 127.6, 128.3, 128.5, 128.6, 128.7, 129.0, 129.1, 130.3, 131.1, 131.5, 137.8, 141.8, 142.1, 146.7, 160.2. IR (neat): 3019, 1630, 1485, 1450, 1215, 752, 669 cm^{-1} ; MS (ESI) m/z 466 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{BrNO}$: 466.0807, found: 466.0801.

4-Benzhydryl-5-(4-chlorophenyl)-2-phenyloxazole 167h

White solid; m.p. 109-110 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.30 (s, 3H), 5.62 (s, 1H), 7.09-7.29 (m, 3H), 7.30-7.39 (m, 5H), 7.40-7.44 (m, 7H), 7.61-7.64 (m, 2H), 8.08-8.07 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.2, 47.9, 126.5, 126.6, 127.8, 128.3, 128.4, 128.7, 128.9, 129.2, 129.3, 130.2, 136.2, 138.7, 139.7, 142.9, 146.5, 160.0. IR (neat): 3019, 1651, 1553, 1485, 1449, 1215, 756, 669 cm^{-1} ; MS (ESI) m/z 402 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1858, found: 402.1846.

2,5-Diphenyl-4-(di-*p*-tolylmethyl)oxazole 167i

White solid; m.p. 161-162 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.57 (s, 1H), 7.10-7.16 (m, 2H), 7.22-7.26 (m, 2H), 7.28-7.33 (m, 4H), 7.40 (d, $J = 7.4$ Hz, 7H), 7.55-7.60 (m, 2H), 8.06-8.09 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 48.2, 115.8(1C, d, $J_{\text{C-F}} = 21.7$ Hz), 125.0, 126.5, 126.6, 127.6, 128.3, 128.4, 128.5, 128.6, 129.2, 130.2, 138.2, 142.5, 145.7, 160.0. IR (neat): 3019, 1643, 1601, 1504, 1495, 1449, 1215, 1159, 1074, 768, 669 cm^{-1} ; MS (ESI) m/z 406 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{22}\text{FNO}$: 406.1607, found: 406.1601.

2,5-Diphenyl-4-(phenyl(*p*-tolyl)methyl)oxazole 167j

Pale yellow solid; m.p. 178-179 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.58 (s, 1H), 7.22-7.25 (m, 2H), 7.28-7.33 (m, 4H), 7.38-7.43 (m, 9H), 7.52-7.55 (m, 2H), 8.05-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 48.3, 126.6, 126.7, 127.2, 127.5, 127.7, 128.4, 128.7, 129.2, 130.3, 134.2, 138.9, 142.3, 145.5, 160.2. IR (neat): 3019, 1489, 1449, 1217, 1094, 772 cm^{-1} ; MS (ESI) m/z 422 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{ClNO}$: 422.1312, found: 422.1300.

4-Benzhydryl-2-phenyl-5-*p*-tolylloxazole 167k

White solid; m.p. 151-152 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.38 (s, 3H), 5.63 (s, 1H), 7.18-7.32 (m, 8H), 7.38-7.43 (m, 7H), 7.51 (d, $J = 8.1$ Hz, 2H), 8.05-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.4, 48.2, 126.0, 126.6, 127.9, 128.4, 128.6, 129.2, 130.0, 137.9, 138.3, 142.8, 146.8, 159.8, 160.0. IR (neat): 3021, 1638, 1508, 1485, 1449, 1215, 752, 667 cm^{-1} ; MS (ESI) m/z 402 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1858, found: 402.1841.

4-Benzhydryl-2-phenyloxazole 167l

Yellow solid; m.p. 102-103 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.43 (s, 1H), 7.15 (s, 1H), 7.15-7.33 (m, 10H), 7.40-7.42 (m, 3H), 8.00-8.03 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 49.6, 126.5, 126.8, 127.6, 128.5, 128.7, 128.9, 130.3, 136.7, 142.1, 145.0, 162.0. IR (neat): 3061, 3021, 1599, 1585, 1557, 1450, 1348, 1215, 754, 669 cm^{-1} ; MS (ESI) m/z 312 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{NO}$: 312.1388, found: 312.1390.

4-Benzhydryl-5-butyl-2-phenyloxazole 167m

Yellow solid; m.p. 56-57 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.22-1.29 (m, 2H), 1.48-1.55 (m, 2H), 2.46 (t, $J = 7.8$ Hz, 2H), 5.39 (s, 1H), 7.18-7.22 (m, 2H), 7.25-7.38 (m, 11H), 7.98-8.01 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 13.8, 22.4, 24.8, 30.7, 48.4, 126.2, 126.5, 128.1, 128.3, 128.4, 128.6, 129.2, 129.7, 137.3, 142.7, 149.0, 159.4. IR (neat): 3019, 2959, 1655, 1601, 1557, 1493, 1449, 1215, 772, 700 cm^{-1} ; MS (ESI) m/z 368 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{NO}$: 368.2014, found: 368.2010.

4-(Bis(4-chlorophenyl)methyl)-2-phenyl-5-(thiophen-3-yl)oxazole 167n

Orange solid; m.p. 150-151 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.54 (s, 1H), 7.25-7.27 (m, 8H), 7.29-7.35 (m, 1H), 7.38-7.43 (m, 5H), 8.03-8.06 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 47.1, 122.3, 125.7, 126.5, 126.9, 127.4, 128.7, 128.8, 129.1, 130.4, 130.5, 132.8, 136.8, 140.5, 143.6, 159.8. IR (neat): 3019, 1647, 1489, 1449, 1215, 1092, 752, 710, 669 cm^{-1} ; MS (ESI) m/z 462 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{18}\text{NOSC}_2$: 462.0486, found: 462.0480.

4-Benzhydryl-5-phenyl-2-o-tolyloxazole 167o

Yellow solid; m.p. 121-122 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.7 (s, 3H), 5.65 (s, 1H), 7.18-7.35 (m, 10H), 7.40-7.46 (m, 6H), 7.62-7.65 (m, 2H), 8.03-8.06 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 22.4, 48.4, 125.9, 126.5, 126.6, 128.3, 128.4, 128.7, 128.9, 129.0, 129.2, 129.8, 131.7, 137.7, 138.0, 142.9, 146.0, 160.3. IR (neat): 3053, 3019, 1595, 1537, 1487, 1445, 1215, 845, 754, 694 cm^{-1} ; MS (ESI) m/z 402 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1858, found: 402.1850.

4-Benzhydryl-5-phenyl-2-*m*-tolylloxazole 167p

White solid; m.p. 169-170 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.39 (s, 3H), 5.65 (s, 1H), 7.19-7.24 (m, 3H), 7.28- 7.34 (m, 6H), 7.37-7.46 (m, 6H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.88 (d, $J = 9.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.4, 48.2, 123.7, 126.6, 127.1, 127.7, 128.3, 128.4, 128.6, 128.9, 129.3, 131.0, 138.4, 142.7, 146.5, 160.2. IR (neat): 3019, 1638, 1551, 1493, 1447, 1215, 752, 698 cm^{-1} ; MS (ESI) m/z 402 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1858, found: 402.1866.

4-Benzhydryl-5-phenyl-2-*p*-tolylloxazole 167q

White solid; m.p. 184-185 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 2.38 (s, 3H), 5.64 (s, 1H), 7.19-7.23 (m, 4H), 7.27-7.32 (m, 5H), 7.36-7.43 (m, 6H), 7.62 (d, $J = 8.1$ Hz, 2H), 7.97 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.6, 48.2, 125.1, 126.5, 128.2, 128.4, 128.8, 129.2, 129.3, 138.3, 140.4, 142.7, 146.3, 160.2. IR (neat): 3019, 1638, 1497, 1215, 756, 669 cm^{-1} ; MS (ESI) m/z 402 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1858, found: 402.1870.

4-Benzhydryl-2-(4-methoxyphenyl)-5-phenyloxazole 167r

White solid; m.p. 191-192 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 3.84 (s, 3H), 5.63 (s, 1H), 6.94 (d, $J = 8.9$ Hz, 2H), 7.19-7.27 (m, 1H), 7.30-7.32 (m, 5H), 7.32-7.36 (m, 7H), 7.40-7.63 (m, 2H), 8.02 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 48.2, 55.4, 114.0, 120.7, 126.4, 126.5, 128.1, 128.2, 128.4, 128.8, 128.9, 129.2, 138.2, 142.7, 146.0, 160.1, 161.2. IR (neat): 3019, 1638, 1612, 1497, 1254, 1215, 1273, 1024, 756, 698 cm^{-1} ; MS (ESI) m/z 418 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}_2$: 418.1807, found: 418.1816.

4-Benzhydryl-2-(4-bromophenyl)-5-phenyloxazole 167s

White solid; m.p. 176-177 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.64 (s, 1H), 7.19-7.27 (m, 2H), 7.30-7.41 (m, 4H), 7.41-7.45 (m, 7H), 7.54 (d, $J = 8.7$ Hz, 2H), 7.60-7.62 (m, 2H), 7.93 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 48.2, 124.6, 126.6, 126.7, 128.0, 128.4, 128.5, 128.6, 129.0, 131.9, 138.6, 142.5, 146.9, 159.2. IR (neat): 3019, 1599, 1492, 1479, 1447, 1396, 1310, 1215, 1011, 837, 770 cm^{-1} ; MS (ESI) m/z 466 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{NOBr}$: 466.0807, found: 466.0802.

4-Benzhydryl-2-(4-chlorophenyl)-5-phenyloxazole 167t

White solid; m.p. 175-176 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 5.64 (s, 1H), 7.19-7.27 (m, 2H), 7.30-7.35 (m, 4H), 7.37-7.46 (m, 9H), 7.61 (d, $J = 7.2$ Hz, 2H), 8.00 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 48.2, 126.3, 126.6, 127.8, 128.4, 128.6, 128.9, 129.2, 136.2, 138.6, 142.5, 146.9, 159.1. IR (neat): 3021, 1638, 1481, 1404, 1215, 1094, 837, 752, 669 cm^{-1} ; MS (ESI) m/z 423 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{NOCl}$: 422.1312, found: 422.1305.

***N*-(1,3-diphenylprop-2-ynyl)benzamide 168¹⁶⁰**

^1H NMR (400 MHz, CDCl_3): δ 6.49 (d, $J = 8.4$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 7.33-7.51 (m, 11H), 7.66 (d, $J = 7.5$ Hz, 2H), 7.83 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): 45.6, 85.4, 87.0, 122.4, 127.1, 127.2, 128.2, 128.3, 128.7, 128.8, 131.9, 133.8, 139.0, 166.2.

1-(1-Oxo-1,3,3-triphenylpropan-2-yl)pyrrolidin-2-one169

White solid; m.p. 178-179 °C; ^1H MNR (CDCl_3 , 300 MHz): δ 1.49-1.53 (m, 1H), 1.67-1.71 (m, 1H), 1.92-2.03 (m, 1H), 2.09-2.17 (m, 1H), 3.12-3.28 (m, 2H), 4.88 (d, $J = 11.7$ Hz, 1H), 6.60 (d, $J = 11.7$ Hz, 1H), 7.01 (m, 1H), 7.10-7.19 (m, 3H), 7.21-7.40 (m, 4H), 7.42-8.08 (m, 5H), 8.10 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 18.1, 30.7, 43.3, 50.1, 55.7, 126.8, 127.0, 128.1, 128.2, 128.6, 128.7, 128.9, 129.2, 133.7, 135.6, 140.3, 140.7, 174.8, 195.5. IR (neat): 3019, 1674, 1597, 1495, 1265, 1215, 752, 669 cm^{-1} ; MS (ESI) m/z 370 $[\text{M} + \text{H}]^+$; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_2$: 370.1807, found: 370.1806.

Chapter VIII. References

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171 **172**

105. CCDC 711037 and 729201 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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