Ruthenium Pincer Catalyzed Organic Transformations

By

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List of Publications arising from the thesis

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1. Thiyagarajan, S.‡; **Sankar, R. V.‡**; Gunanathan, C. Ruthenium Catalyzed α-Alkylation of Ketones Using Secondary Alcohols. *Org. Lett*. **2020**, *22*, 7879-7884. (‡**Authors with Equal Contributions**)
2. Thiyagarajan, S.‡; **Sankar, R. V**.‡; Anjakrishna, P, K.; Suresh, C, H. Gunanathan, C. Catalytic Formal Conjugate Addition: Direct Synthesis of δ-Hydroxynitriles from Nitriles and Allylic Alcohols. *ACS Catal*. **2022**, *12*, 2191-2204. (‡**Authors with Equal Contributions**)
3. **Sankar, R. V**.; Manikpuri, D.; Gunanathan, C. Ruthenium Catalyzed α-Prenylation of Ketones Using Prenol. *Org. Biomol. Chem.* **2023**, *21*, 273-278.
4. **Sankar, R. V.;** Mathew, A.; Pradhan, S.; Kuniyil, R.; Gunanathan, C. Ruthenium-Catalyzed Selective α-Alkylation of β-Naphthols using Primary Alcohols: Elucidating the Influence of Base and Water. *Chem. Eur. J.* **2023**, *29*, e2023021.
5. **Sankar, R. V**.; Gunanathan, C. Synthesis of Functionalized Benzo[*f*]chromanes and Hydroxyalkyl Naphthols: Catalytic Coupling of Naphthols and Allylic Alcohols. *Adv. Synth. Catal*. **2024**, 10.1002/adsc.202401243.

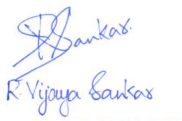
Publications not included in the thesis

1. Pradhan, S.; **Sankar, R. V.;** Gunanathan, C. A Boron-Nitrogen Double Transborylation Strategy for Borane-Catalyzed Hydroboration of Nitriles. *J. Org. Chem.* **2022***, 87, 12386-12396.*
2. Kumar, N.‡; **Sankar, R. V.‡;** Gunanathan, C. Ruthenium- Catalyzed Self-Coupling of Secondary Alcohols. *J. Org. Chem.* **2023**, *88*, 17155-17163. (‡**Authors with Equal Contributions**)
3. Manikpuri, D.; **Sankar, R. V**.; Gunanathan, C. Direct Synthesis of Aldoximes: Ruthenium-Catalyzed Coupling of Alcohols and Hydroxylamine Hydrochloride. *Chem. Asian J.* **2023**, *18*, e202300678.
4. Maharana, P.; **Sankar, R. V.;** Sankaralingam, M.; Gunanathan, C. Synthesis of Functionalized Lactones: Catalytic Cross-Coupling of 1,2 Diols and Allylic Alcohols (*Manuscript Under Preparation*).
5. Tiwari, D.; **Sankar, R. V.;** Gunanathan, C. Selective C-3 Alkylation of Indenes Using Alcohols (*Manuscript Under Preparation*).

Conferences

1. **Poster Presentation:** Modern Trends in Inorganic Chemistry (MTIC XIX), at Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, during 15 to 17 December, 2022, Title: Catalytic Formal Conjugate Addition: Direct Synthesis of δ-Hydroxynitriles from nitriles and Allylic Alcohols.
2. **Oral Presentation:** JNOST Conference (JNOST-23) for Young Researchers at IISER Pune, 10-12 October, 2023, Title: Ruthenium Catalyzed C-C Bond Formation Using Alcohols and Allylic Alcohols.

3. **Poster Presentation:** Emerging trends in Organometallic Chemistry (ETOMC-24) at Department of Chemical Science, IISER Kolkata, Kolkata, during 12-13 July, 2024, Title: Ruthenium Catalyzed Selective α-alkylation of β-naphthols Using Primary Alcohols: Elucidating the Influence of Base and Water. Awarded 'Best Poster' of the Conference.



R. Vijaya Sankar

It is Important to be a Successful Person
It is even more Important to be a Good Person

Inspired from the words of
Prof. C. Gunanathan

Dedicated to

‘‘Late Mr. E. Sundaram’’

My Parents & Prof. C. Gunanathan

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First and foremost, I thank God, for providing me good health and wealth in making my journey smooth and successful. It would be grossly unfair, if I didn't acknowledge ''Late Mr. E. Sundaram'' who stood beside me in achieving this dream, he will be forever in my heart. I would therefore like to offer my sincere thanks and prayers to him. I am very much delightful in thanking my thesis supervisor Prof. C. Gunanathan for his constant guidance, support, sincere advice and valuable moral support to improve my quality and personality both in profession and personal life. I pay my sincere respect and thanks for all his valuable time, stimulating ideas and funding to make my project experience interesting and productive. Also, I would like to express my gratitude to him for providing me the opportunity to work on this exciting and inventive project. My sincere gratitude goes to Prof. Hirendra Nath Ghosh, Director (NISER), Prof. Sudhakar Panda, former Director (NISER) and Prof. T. K. Chandrasekar, founder-Director (NISER). I would like to thank my doctoral committee members, Dr. Chandra Shekar Purohit, Dr. Nagendra Kumar Sharma, Dr. Bharghava B.L and Dr. Akhilesh Kumar Singh for their kind support and suggestions. I am also privileged by the immense help of all faculty members of School of Chemical Sciences. I would like to recognize Mr. Sanjaya Mishra for his kind help in recording NMR and Mr. Deepak Kumar Behra for his kind help in X-ray analysis and Mr. Amit Sankar Sahu and Mr. Prakash Chandra Behra for their kind help in ESI-MS analysis. This journey would not be possible without the continuous and unconditional support from my lab mates Dr. S. Thiyagarajan, Dr. Sandip Pattanaik , Dr. Biplap K Pandia, Dr. Arunachalam, Dr. S. Muthumari, Manas Kumar Sahu, Deepsagar Manikpuri, Deepak Kumar Sahoo, Hariharan, Nirmal Chandra Sahoo, Shubham Jaiswal, Amlan, Subham Pradhan, Anurag, Nitin, Premananda, Arijit, Priyanka, Sahil, Kumaresh, Debashis, Nivetha, Devendra Tiwari . My sincere thanks to them in kind cooperation in lab, which helped me to plan and execute the experiments meticulously. I would like to thank

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....R. Vijaya Sankar

SYNOPSIS

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3. **Enrolment No.** : CHEM11201904007
4. **Title of the Thesis** : Ruthenium Pincer Catalyzed Organic Transformations
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SYNOPSIS

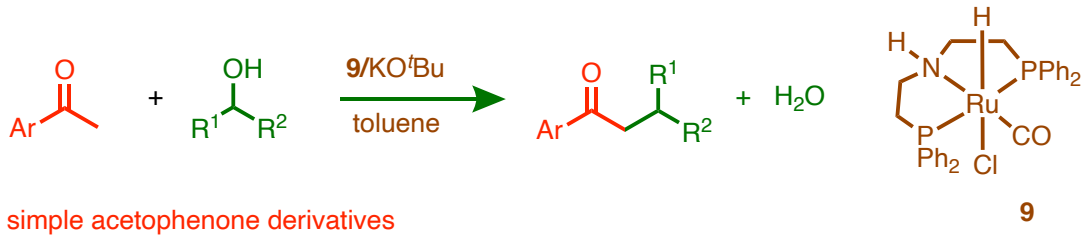
Contents:

Chapter 1: Introduction: Ruthenium Pincer Complexes and their Catalytic Applications in C-C Bond Formation Reactions Using Alcohols as Alkylating Reagents

Transition metal organometallic complexes have displayed widespread catalytic applications in diverse organic transformations. Simple metal salts, widely used Grubbs catalysts, phosphine ligated and other bidentate ligated organometallic complexes have been extensively used in various catalytic reactions. While the simple metal precursors have multiple vacant sites available for substrate coordination often leading to loss of reaction selectivity, metal complexes having mono and bidentate ligands suffer from thermal instability as such complexes on exposure to higher temperature lose their integrity. Hence, such complexes cannot be useful catalysts for thermodynamically challenging reactions. Pincer complexes are composed of pincer ligands, which are tridentate in nature. These ligands upon complexation with metal precursors in general enforce meridional geometry on the metal center, which gives a rigid strength of coordination and a unique balance of stability *vs* reactivity to the pincer complexes.[1-2] Some of the complexes with flexible ligand framework are found to show facial geometry. A unique mode of bond activation process was observed by Milstein and coworkers in pincer complexes, known as metal-ligand cooperation (MLC) in activating inert chemical bonds.[3] A number of ruthenium pincer complexes have been reported in the literature for a wide range of catalytic applications. Particularly, ruthenium pincer complexes are used in various carbon-carbon bond formation reactions using alcohols as green alkylating agents. In this thesis, I describe the development of different C-C bond formation reactions resulting in alkylation and formal conjugate addition reactions, using a Ru-Macho catalyst and alcohols as alkylating reagents. Chapter 1 provides a summary of ruthenium complexes reported so far in the literature, which have been classified on the basis of the donor ligands employed for complexation, and also a summary of C-C bond formation reactions reported for some of these complexes.

Chapter 2: Ruthenium Catalyzed α-Alkylation of Ketones Using Secondary Alcohols to Generate β-Disubstituted Ketones

In this chapter, ruthenium catalyzed α-alkylation of ketones using secondary alcohols leading to the synthesis of β-disubstituted ketones is discussed. Previously reported catalytic methods rely on the use of stochiometric amounts of base and with the limitation of only sterically hindered ketones employed for alkylation reactions. We have developed a simple and efficient strategy where a catalytic amount of base and catalyst **9** (Scheme 1) is used for the alkylation of ketones using secondary alcohols via the borrowing hydrogen (BH) strategy. An assortment of ketones, including challenging simple acetophenones and their derivatives, were successfully coupled with a variety of secondary alcohols, where the liberated water molecule is found to be the only byproduct.[4]

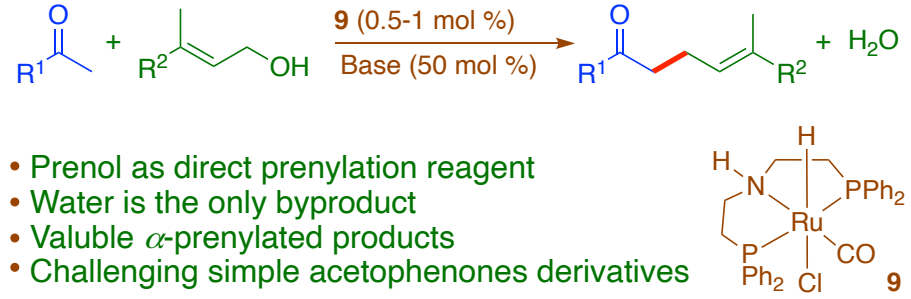


Scheme 1: Ruthenium Catalyzed α-Alkylation of Ketones Using Secondary Alcohols

Chapter 3: Ruthenium Catalyzed α-Prenylation of Ketones Using Prenols

In this chapter, a simple and efficient method for catalytic α-prenylation of ketones using prenols is reported. In reported catalytic methods, ketones react with either prenol or prenol derivatives such as corresponding acetates and carbamates, which act as better leaving groups. These methods also require the use of multiple ligands and additives to achieve the α-prenylated ketones or homoallylic ketones via a Tsuji-Trost allylation reaction condition. Thus, a direct method of employing prenol as an alternative alkylating agent was developed in which

an assortment of ketones, including simple challenging acetophenones and their derivatives, were successfully prenylated following the borrowing hydrogen methodology, and delivering water as the only byproduct. The synthesized prenylated compounds were transformed into valuable products via simple synthetic methods. Mechanistic studies revealed the role of catalyst in O-H bond activation and the amine-amide metal-ligand cooperative effect in catalyst **9** (Scheme 2).[5]

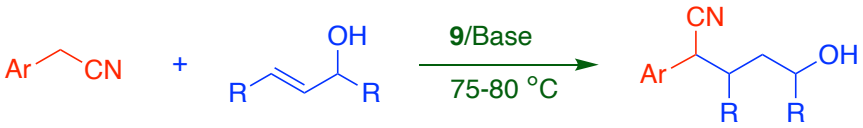


Scheme 2: Ruthenium Catalyzed α-Prenylation of Ketones Using Prenols

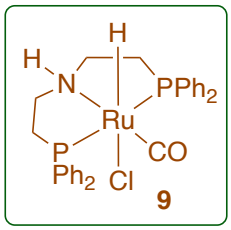
Chapter 4: Catalytic Formal Conjugate Addition: Direct Synthesis of δ-Hydroxynitriles from Nitriles and Allylic Alcohols

Alcohol and nitrile functionalities have widespread applications in biochemical and chemical synthesis. A simple and selective method for coupling of nitriles with allylic alcohols catalyzed by the ruthenium pincer complex **9** is described (Scheme 3). Alcohols with different functional groups, such as carbamate, sulfonate, olefin, cyano, and trifluoromethyl, underwent reactions with diverse arylmethyl nitriles, delivering the δ-hydroxynitrile products. Mechanistic studies indicated that the allylic alcohols initially undergo selective oxidation by the catalyst to α,β-unsaturated carbonyl compounds, followed by 1,4-conjugate addition of benzyl nitriles catalyzed by a base, and subsequent catalytic reduction of the carbonyl functionality, leading to the formation of δ-hydroxynitrile products. The proposed catalytic cycle of this tandem process was investigated by density functional theory calculations. Remarkably, the drug anipamil was successfully synthesized using this catalytic protocol. The utility of the δ-

hydroxynitrile products in the synthesis of biologically active molecules, and their further functionalization, are also demonstrated.[6]



Advantages:
(i) allylic alcohols: cheap industrial feedstock
(ii) broad substrate scope
(iii) no stoichiometric base required
(iv) exclusive anti-Markovnikov selectivity
(v) atom economical & mild reaction conditions
(vi) functionalization of complex molecules
(vii) synthesis of natural products and drugs

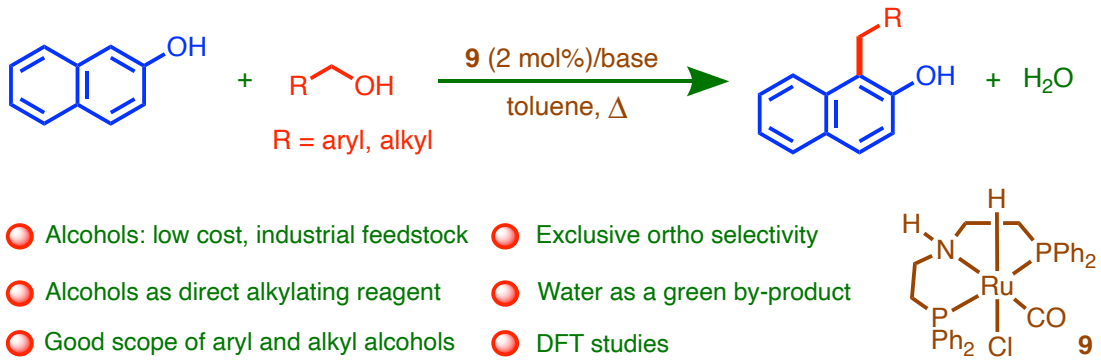


Scheme 3: Catalytic Formal Conjugate Addition: Direct Synthesis of δ-Hydroxynitriles from Nitriles and Allylic Alcohols

Chapter 5: Ruthenium-Catalyzed Selective α-Alkylation of β-Naphthols using Primary Alcohols: Elucidating the Influence of Base and Water

Substituted naphthols are an important class of chemical compounds and have diverse applications in chemical synthesis and material chemistry. Selective functionalization of arenols is a topic of prime interest. In this report, a ruthenium pincer catalyzed direct α-alkylation of β-naphthol using primary alcohols as alkylating reagents is described. Notably, aryl and heteroaryl methanols, and linear and branched aliphatic alcohols, underwent selective alkylation reactions, in which water is the only byproduct. The catalytically derived α-alkyl-β-naphthol products displayed high absorbance, emissive properties, and quantum yields (up to 93.2%). Dearomative bromination on α-alkyl-β-naphthol is demonstrated as a synthetic application. Mechanistic studies indicate that α-alkylation of β-naphthol involves an aldehyde intermediate. DFT studies support this finding and further reveal that a stoichiometric amount of base is required to enable the aldol condensation, as well as elementary steps required for

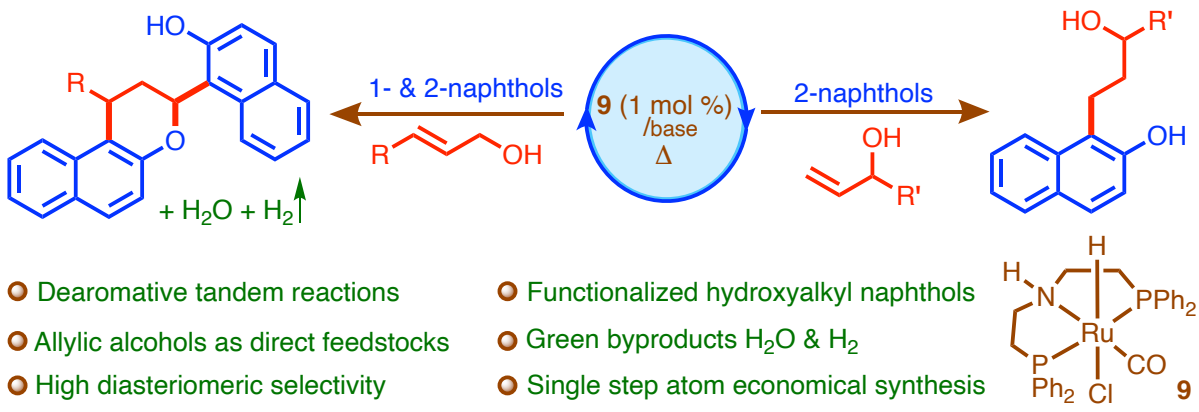
regeneration of the catalytically active species. The in situ-generated water molecules from the aldol condensation reaction play an important role in the regeneration of the active catalyst.[7]



Scheme 4: Ruthenium-Catalyzed Selective α-Alkylation of β-Naphthols using Primary Alcohols

Chapter 6: Synthesis of Benzo(*f*)Chromanes and Hydroxyalkyl Naphthol: Catalytic Coupling of Naphthols and Allylic Alcohols

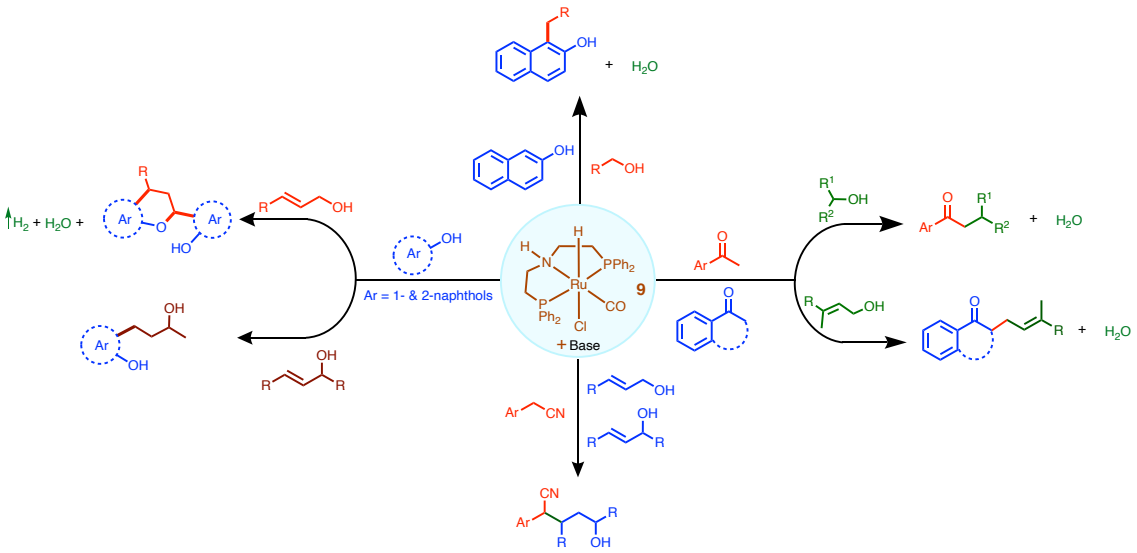
A simple and efficient strategy for coupling naphthols with allylic alcohols is reported. A single Ru(II) pincer catalyzed coupling of naphthols with primary allylic alcohols led to the formation of benzo(f)chromanes, whereas the use of secondary alcohols delivered the hydroxyalkyl naphthols. Broad substrate scope and good functional group tolerance are demonstrated. Notably, a high diastereoselectivity is attained on chromanes. Hydroxyalkyl naphthols are synthetically transformed into spiroethers, and dearomative bromination is achieved on chromanes. Mechanistic studies revealed the involvement of tandem reactions. A formal O-H bond activation of allylic alcohols by an active catalyst, via amine-amide metal-ligand cooperation, provided α,β-unsaturated carbonyl intermediates, which further underwent 1,4-conjugate addition with dearomatized naphthols. One of the crucial intermediates, a naphthyl radical, is elucidated by EPR studies and trapped using a radical scavenger. Liberated hydrogen and water molecules are the only byproducts in these transformations.[8]



Scheme 5: Catalytic Coupling of Naphthols and Allylic Alcohols

Chapter 7: Conclusions

In summary, using ruthenium pincer complex **9**, carbon-carbon bond formation reactions via the borrowing hydrogen methodology are reported (Scheme 6). Carbon-carbon bond formation on the sp^3 α-carbon of ketones, using alcohols and prenols as alkylating reagents, provided β-disubstituted ketones and α-prenylated ketones, respectively. An unprecedented formal conjugate addition of nitriles, with allylic alcohols as alkylating agents, was developed for the direct synthesis of δ-hydroxynitriles. Also employing arenols, such as naphthols, with alcohols and allylic alcohols, carbon-carbon bond formation reactions on challenging sp^2 carbons were also developed. Notably, the above developed strategies generate either water, molecular hydrogen, or no byproducts at all, which make them environmentally benign and atom economical. Amine-amide metal-ligand cooperation was found to be operative in these catalytic transformations, which maintains the oxidation state of the metal as +2 during the whole catalytic process.



Scheme 6: Catalytic Transformations Using Ruthenium Pincer Complex 9

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List of Schemes **Page No**

List of Figures **Page No**

List of Tables **Page No**

List of Abbreviations Used

Å	Angstrom
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
bp	Boiling Point
br	Broad
°C	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
conv	Conversion
d	Doublet, Days
DCM	Dichloromethane
dd	Doublet of a Doublet
DMF	N,N-Dimethyl Formamide
eq	Equation
equiv	Equivalent
Et	Ethyl
g	Grams
h	Hours
HRMS	High-resolution Mass Spectrometry
IR	Infrared
K	Kelvin
kcal	Kilo calories

lit	Liter
m	Multiplet
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
MHz	Mega Hertz
Min	Minutes
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Mass Spectra
N	Normal
NMR	Nuclear Magnetic Resonance
ppm	Parts per Million
rt	Room Temperature
s	Singlet, Seconds
XRD	X-Ray Diffraction

Table of Contents

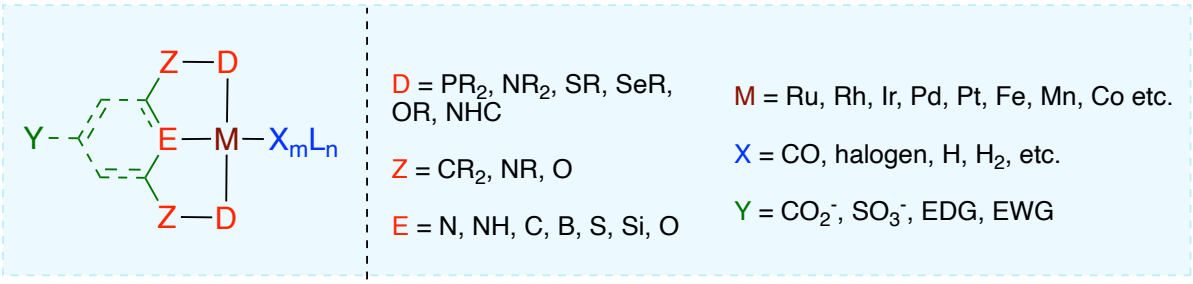
CHAPTER 1

Introduction: Ruthenium Pincer Complexes and their Catalytic Applications in C-C Bond Formation Reactions Using Alcohols as Alkylating Reagents

Fossil fuels are a major energy source, but they are finite, and their extensive use has significant environmental impact. As we face the reality of their depletion and the urgent need to address climate change, transitioning to renewable energy sources is crucial. Catalysis in modern chemistry and industry has made a significant impact.[1] By providing a more efficient and sustainable approach to chemical reactions, catalysts help to accelerate the rate of reactions, increase selectivity, and reduce the need for excessive energy or harsh conditions. This not only makes the synthesis of industrial feedstocks and fine chemicals more cost-effective but also minimizes their environmental footprint.[2] Catalysis by organometallic complexes containing transition metals are well explored and many organic transformations have been developed in the past few decades. The key issue associated with transition metal-containing organometallic complexes in catalysis is that they indeed offer a broad range of reactivity due to their multiple reactive sites at the metal center, which can facilitate different transformations. However, such multifarious reactivity can also lead to selectivity challenges, as the metal center might interact with multiple substrates or intermediates, making it difficult to control the reaction outcome precisely. Additionally, stability of the catalysts is crucial for sustained reactivity. Many organometallic complexes show instability at elevated temperatures. When exposed to higher temperatures, these complexes can decompose or undergo undesirable side reactions, thus limiting their utility in thermodynamically demanding reactions. This instability often results from the loss of ligands, oxidation or reduction of the metal center, or changes in the electronic environment of the metal. Pincer complexes have garnered significant interest in recent years due to their versatility and efficiency in various industrially-relevant processes. These

complexes typically consist of tridentate ligands coordinated to a metal center, which typically enforces a meridional geometry upon complexation with metal precursors.[3,] There are also a few examples where a facial geometry is achieved, due to their flexible nature of the pincer ligands . The unique structure of pincer complexes offers a beneficial balance between stability and reactivity.[4] A schematic representation of pincer complexes illustrates that the central ligand core can be formed from an aryl or heterocyclic unit, such as phenyl, pyridine, or pyrazole, or acyclic systems containing appropriate heteroatoms or a carbon atom (**Figure 1.1**).[5] The central ring features substitutions at the two ortho positions, along with two chelating arms that contain donor atom substituents. These flanking arms and the central core create either symmetric or asymmetric metallacycles, usually enforcing the complex to attain either a facial or meridional configuration The three donor sites of a pincer ligand lie in the same plane, while the ligands from the metal precursors are positioned in a perpendicular plane, resulting in the formation of pincer complexes. Recent advancements in pincer chemistry have also introduced complexes with aliphatic backbones.

Figure 1.1: Schematic Representation of Transition Metal Based Pincer Complexes



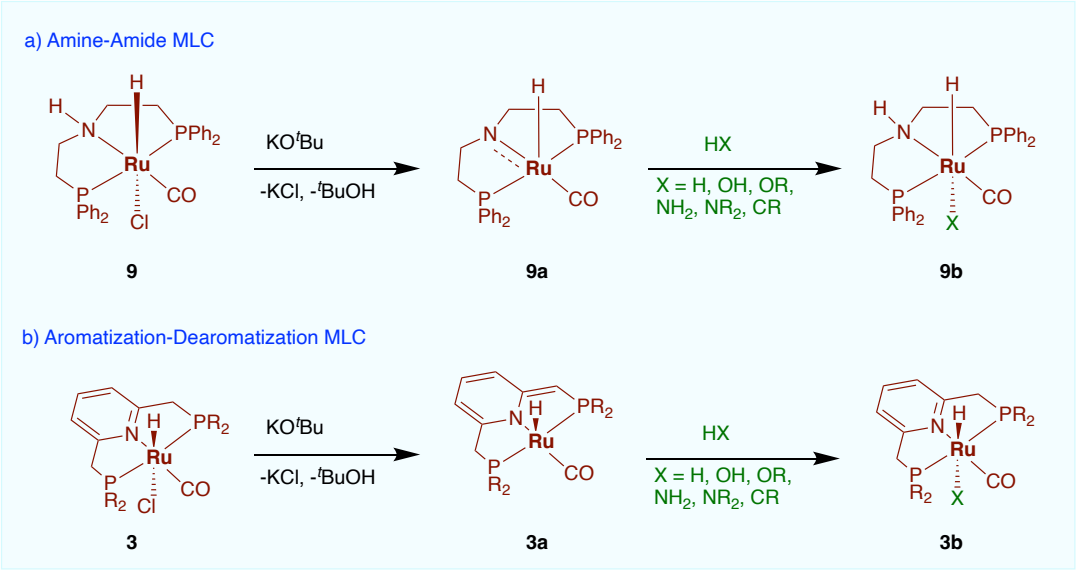
In nature, the metal-ligand cooperative effect is essential in various biological systems, especially in metalloproteins and metalloenzymes.[6] This effect describes how metal ions and ligands interact synergistically in oxygen transport, nitrogen fixation and catalytic reactions of small molecules in biological systems. For example, in hemoglobin, iron interacts with heme to facilitate efficient oxygen binding and release. Similarly, in enzymes like hydrogenase particularly [Fe-Fe]-hydrogenase and [Ni-Fe], metal ions can stabilize reaction intermediates

and lower activation energy that is crucial for catalytic activity. Overall, this cooperative interaction is vital for many biological processes, enabling organisms to carry out complex functions effectively. It is intriguing how these interactions contribute to the complexity and efficiency of biochemical processes. Chemists have developed such cooperative effects in transition metal complexes, which are also termed bifunctional catalysts. For example, Noyori-type catalysts contain a diamine ligand coordinated to the metal center, which acts as proton donor or acceptor, and together with the metal center facilitates chemical transformations.[7]

In 2005, Milstein and his group observed a novel reactivity mode in pincer complexes,[8] highlighting the metal-ligand cooperation (MLC) effect in bifunctional catalytic systems. There are two common modes of MLC observed in pincer complexes (Scheme 1.1), namely, amine-amide MLC and dearomatization-rearomatization MLC. Complex **9** (Scheme 1.1), which is coordinatively saturated, undergoes a facile dehydrohalogenation upon reaction with base, resulting in the coordinatively unsaturated intermediate **9a**. The amine-type ligand in complex **9**, on reaction with base, turns into an amide-type ligand that is nucleophilic, and can accept a proton during bond activation in small molecules like H_2, H_2O, ROH, NH_3, H−NR_2, and C−H, in cooperation with the metal center, to provide coordinatively saturated complex **9b** (Scheme 1.1a). Similarly, complex **3**, with an aromatic pyridine backbone, upon reaction with base undergoes deprotonation of an acidic proton from the CH_2 group on its arm and turns into the dearomatized complex **3a**. Further reaction with inert chemical bonds of small molecules leads to bond activation, and regenerates the aromatized coordinatively-saturated ruthenium complex **3b** (Scheme 1.1b). Transition metals, play a pivotal role in catalysis, driving key reactions in industries such as pharmaceuticals, petrochemicals, and materials science. Among them, ruthenium is one of the most widely used metals, which can show a variety of oxidation states, from 0 to +8, and -2. The most common oxidation states are +2, +3 and +4. Due to the remarkable variety of oxidation states shown by this metal, it exhibits unique properties in

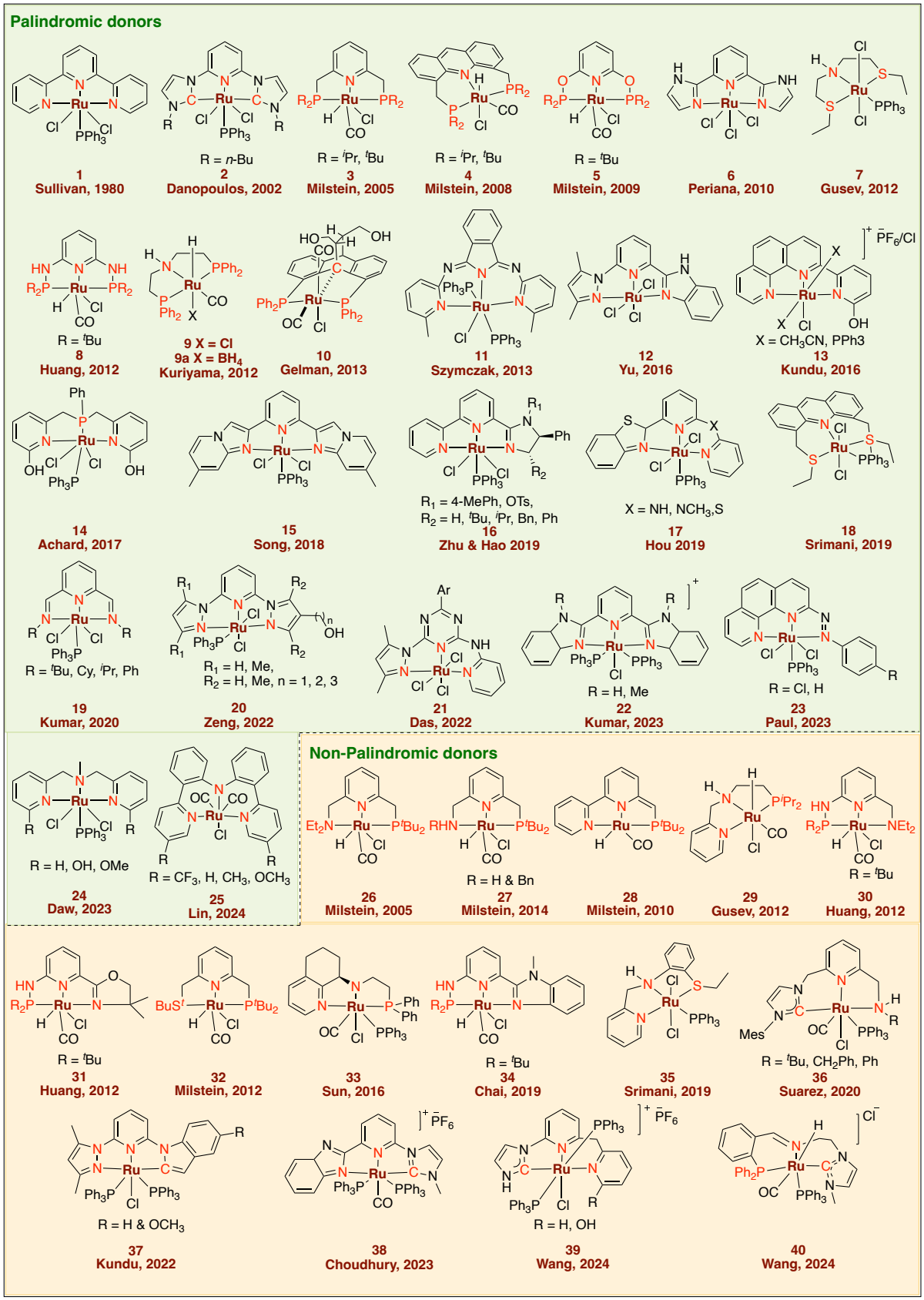
redox reactions. In this thesis, I focus on catalysis by ruthenium pincer complex **9**, which has shown remarkable efficiency in a wide range of catalytic transformations. Ruthenium's catalytic versatility and high performance in several critical reactions make it a valuable choice for overcoming challenges that other metals can't offer. Ruthenium's unique electronic properties allow it to efficiently break bonds that are typically resistant to activation, opening up new avenues for the synthesis of compounds that are otherwise difficult to obtain. Furthermore, ruthenium-based catalysis has the potential to streamline processes that are essential for the sustainable production of chemicals and pharmaceuticals. By enabling reactions that are both efficient and selective, ruthenium can contribute to more cost-effective and environmentally friendly synthetic methodologies, particularly in large-scale industrial applications. Its ability to facilitate C-H activation, hydrogenation, carbon-carbon bond formation, and other critical transformations has proven indispensable in both academic and industrial settings. Through this research, I aim to explore the potential of ruthenium in tackling challenging reactions in modern catalysis, further demonstrating its importance in advancing green chemistry.

Scheme 1.1: Modes of MLC: (a) MLC Based on Amine-Amide (b) MLC based on Aromatization-Dearomatization



There are several ruthenium pincer complexes reported by various groups which involve MLC for activation of small molecules. Some of the pincer complexes are listed in Figure 1.2, classified according to their donor system. They can be divided into two groups, i.e., palindromic donors and non-palindromic donors.[9] Palindromic donors are those where the tridentate ligands with the symmetrical donor atoms, whereas non-palindromic donors have the unsymmetrical tridentate ligands. The donor atoms can be, for example, phosphorous, nitrogen, sulphur and carbon. While metal-ligand cooperation at both types of complexes **3** and **9** can be operative either at the N-H proton for **9** (Scheme1.1a) or CH_2 methylene arm for **3** (Scheme 1.1b) of the tridentate ligands which involves amine-amide or aromatization-dearomatization MLC, respectively. Complexes with aliphatic backbones, such as **7** and **9**, exhibit amine-amide MLC involving the central donor atom bearing an N-H functionality. The complexes listed below (**Figure 1.2**) exhibit different tridentate ligands synthesized via traditional organic synthesis methods, which have a basic nitrogen-containing heterocyclic unit in them. They also have donor atoms on flanking arms, which can form a five- and six- membered metallacycles upon complexation with a metal center. Moreover, one can attain cationic complexes, depending upon the ligand motifs and precursors. There are several organic transformations reported using these complexes as catalysts. Selected examples will be discussed briefly below.

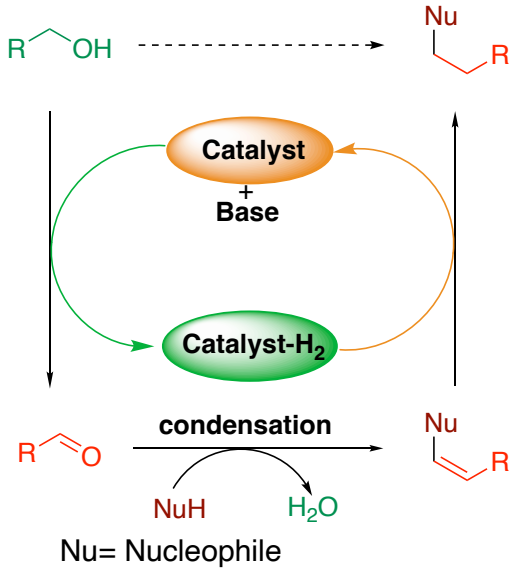
Figure 1.2: List of Reported Ruthenium Pincer Complexes



In the past few decades, the increasing interest in ruthenium pincer complexes for bond activation, particularly in C-C bond formation reactions, reflects a significant shift toward more sustainable and efficient catalytic methods. These pincer complexes, characterized by their ability to stabilize metal centers and facilitate various transformations, have become central to a variety of green chemistry strategies, particularly in the context of C-C bond construction.

One of the most innovative and environmentally friendly approaches that has gained prominence in recent years is the borrowing hydrogen concept, particularly in the use of alcohols as alkylating agents (Figure 1.2a). This method is part of a broader trend toward more atom-efficient and sustainable catalytic processes.

Figure 1.2a: General Description of Borrowing Hydrogen Strategy



The borrowing hydrogen concept leverages the ability of alcohols to undergo dehydrogenation and rehydrogenation steps in the presence of a catalyst, typically a ruthenium pincer complex, to form C-C bonds without requiring stoichiometric amounts of external reagents or bases. In traditional methods of C-C bond formation, the use of stoichiometric amounts of reagents, such as Grignard reagents, or the need for external bases, often leads to the generation of waste and reduced atom economy. Moreover, these processes may require harsh reaction conditions,

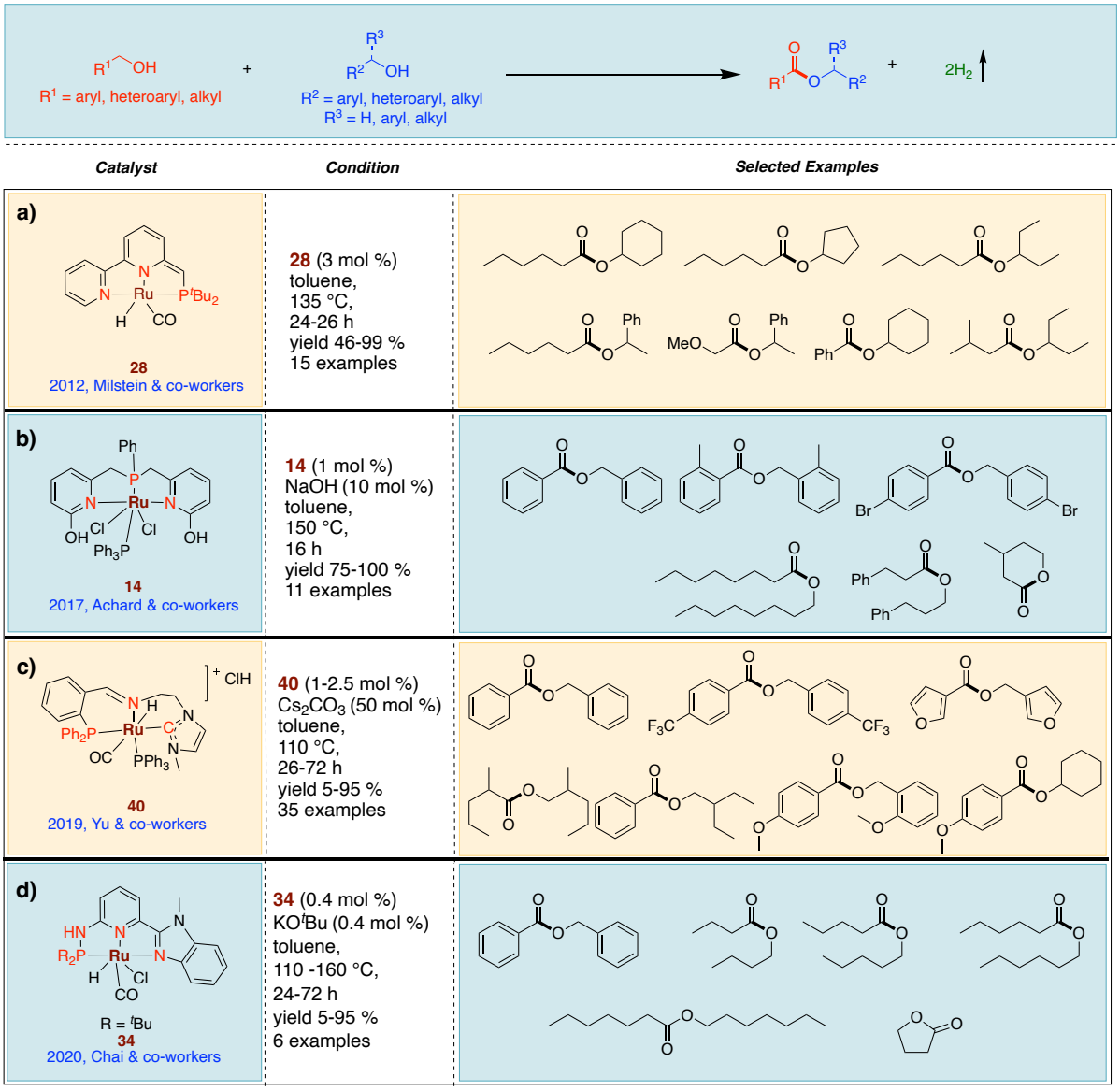
limiting their practical applications and environmental sustainability. The following sections outline various C-C bond formation reactions involving different organic functionalities, such as ketones, alcohols, nitriles, and arenols, via the borrowing hydrogen methodology. In these reactions, alcohols are employed as alkylating agents, offering a sustainable and efficient alternative to traditional methods. This approach has garnered significant attention due to its ability to minimize waste and enhance atom economy, making it a valuable tool in modern synthetic chemistry.

1.1 Dehydrogenative Self- and Cross-Coupling of Alcohols:

Esters play a vital role across various industries due to their desirable properties and appealing fragrances.[10a] They are commonly utilized in the production of solvents, plasticizers, fragrances, and food flavourings. Recent advancements have highlighted catalytic methods that leverage the self-coupling of primary alcohols, promoting a sustainable approach by using alcohols as green alkylating agents and producing hydrogen as a benign byproduct. In 2012, Milstein and coworkers[10b] utilized an activated NNP catalyst **28** and reported the synthesis of esters by cross-coupling of primary and secondary alcohols (Scheme 1.2 a). Following this, Achard and coworkers[10c] reported a bifunctional catalyst **14** to facilitate dehydrogenative coupling of primary alcohols to esters. They have also attained intramolecular dehydrogenative coupling of diols, which resulted in formation of lactones (Scheme 1.2b). In 2019, Yu and coworkers[10d] advanced the catalytic ester synthesis further by employing a carbene-ligated catalyst, **40**, and successfully demonstrated dehydrogenative self and cross-coupling of alcohols to esters (Scheme 1.2 c). Recently, Chai and coworkers reported an NNP type catalyst, **34**, and reported ester synthesis where both intra- and intermolecular esters were obtained (Scheme 1.2 d). These developments reflect a growing trend towards more sustainable and efficient catalytic processes in ester synthesis.

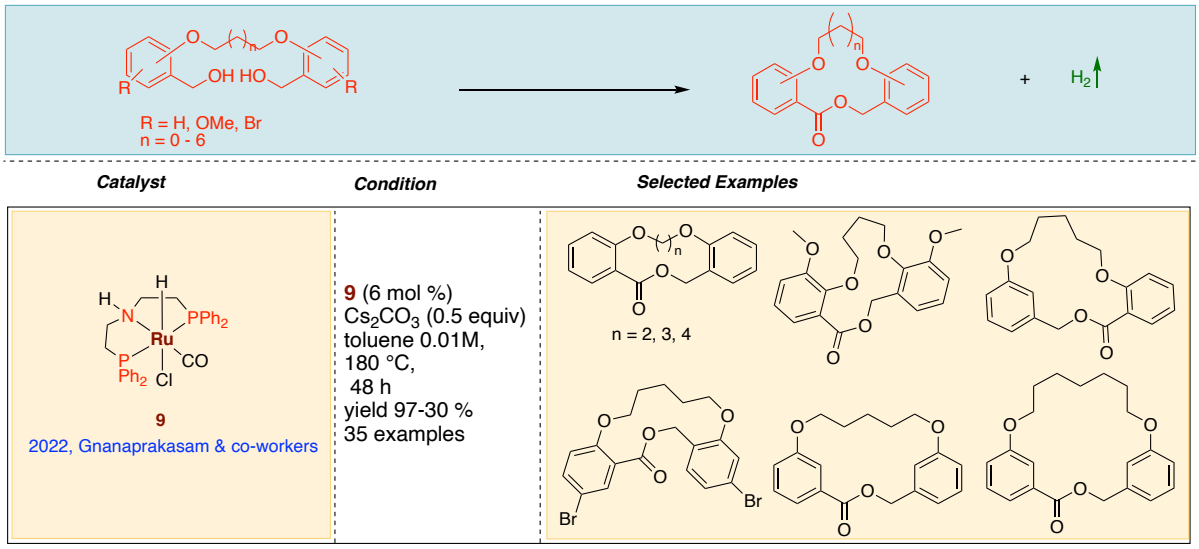
Macrolactones are a class of cyclic esters with widespread applications in pharmaceuticals, perfumes, and biologically active compounds.[11a] Following the successful development of dehydrogenative coupling methods for ester synthesis by various research groups, Gnanaprakasam and coworkers recently extended this strategy for the synthesis of macrolactones (Scheme 1.3).[11b] They introduced an atom-economical and sustainable synthesis of macrolactones following both inter- and intramolecular approaches.

Scheme 1.2: Dehydrogenative Coupling of Alcohols Leading to Ester Synthesis.



This method utilizes the ruthenium pincer complex **9** and cesium carbonate (Cs_2CO_3) as a base, operating at elevated temperatures without the need for external oxidants or additives. As a result, a diverse range of alcohols underwent dehydrogenative coupling, and delivered the corresponding macrolactones efficiently where the liberated molecule of hydrogen is found to be the only byproduct.

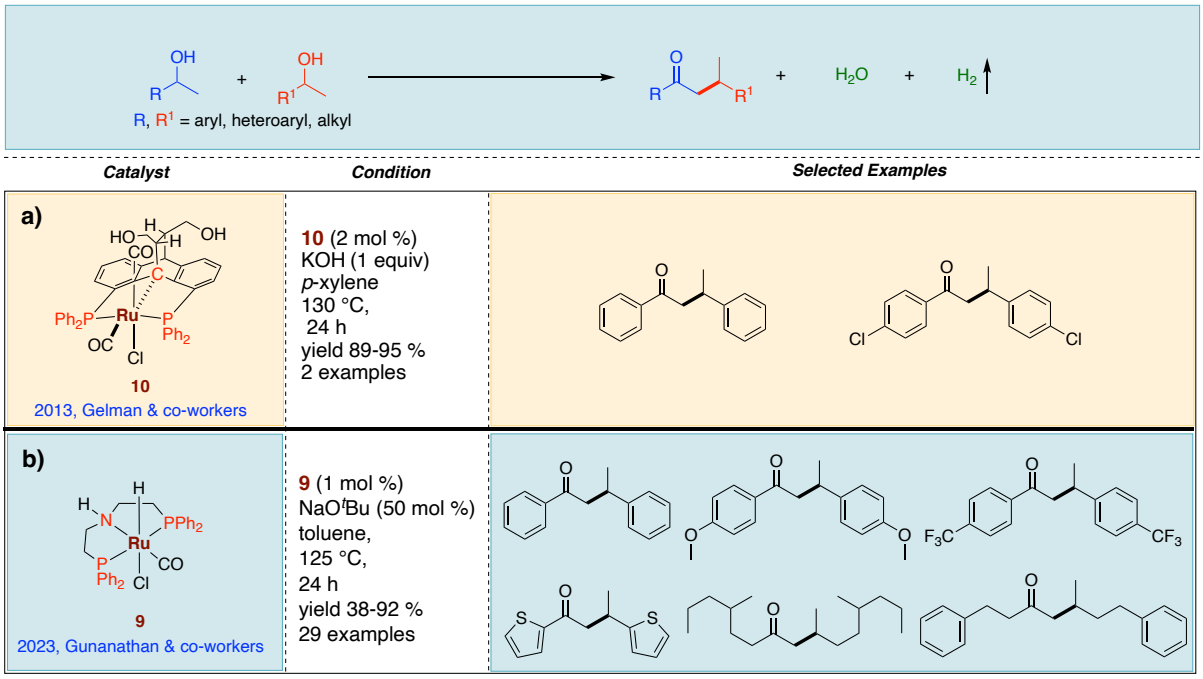
Scheme 1.3: Dehydrogenative Intramolecular Self Coupling of Alcohols Leading to Macrocyclization



The dehydrogenative self-coupling of secondary alcohols to obtain β-disubstituted ketones is a significant reaction in synthetic organic chemistry, especially given its relevance in pharmaceuticals and agrochemicals. The ability to convert alcohols directly into valuable keto compounds while producing only water and hydrogen as byproducts is a clear advantage, which makes this process both efficient and environmentally friendly. In 2013, Gelman and coworkers[12a] demonstrated the use of a pincer catalyst, **10**, with stoichiometric KOH to facilitate this self-coupling reaction (Scheme 1.4a). However, their work revealed limitations in substrate scope, which restricted the versatility of the reaction. More recently, Gunanathan and coworkers[12b] made strides in expanding the scope of this reaction by utilizing the catalyst **9** and sodium *tert*-butoxide as a base (Scheme 1.4b). Notably, they have successfully achieved

the self-coupling of various heteroaryl phenylethanols and challenging linear aliphatic alcohols, resulting in good to excellent yields of the desired β-disubstituted ketones. This advancement not only broadens the range of substrates that can be used but also enhances the practical application of this method in synthetic chemistry. The progress made in this area highlights the importance of catalyst design and choice of base in optimizing reaction conditions for effective dehydrogenative coupling, opening up new avenues for the development of useful chemical intermediates.

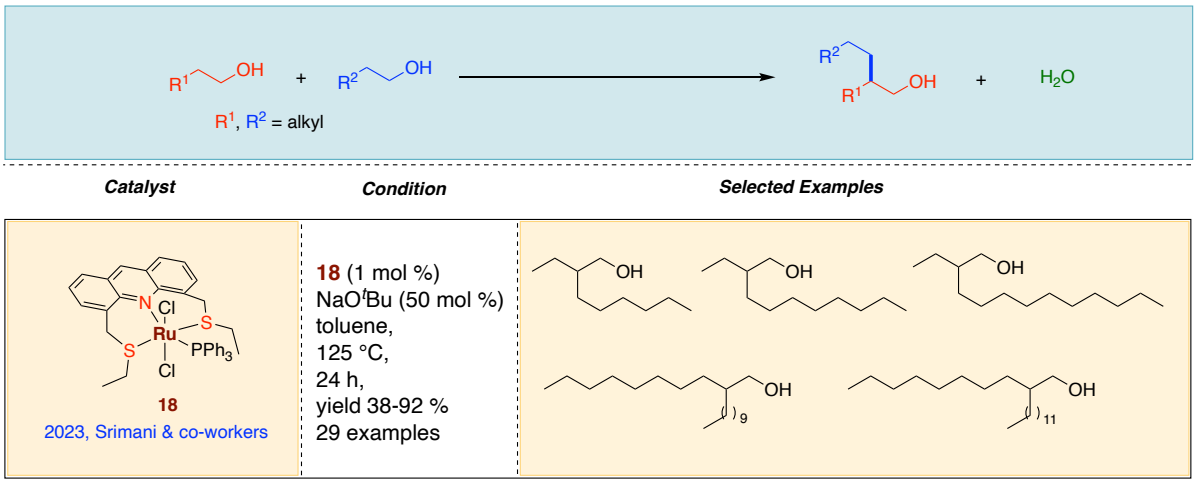
Scheme 1.4: Dehydrogenative Self Coupling of Secondary Alcohols Leading to β-Disubstituted Ketones



The Guerbet reaction is a valuable method for carbon chain elongation, allowing for the transformation of primary alcohols into higher alcohols through a homocoupling process. In 2023, Srimani and coworkers[13] reported a ruthenium catalyzed coupling of primary alcohols into branched alcohols via Guerbet reactions. They used the catalyst **18** for homocoupling of primary alcohols, from C5 to C10, into their higher homologues (Scheme 1.5). The success of this transformation relies on the direct use of alcohols in building longer carbon chain alcohols

and liberating water molecules as the only byproduct.

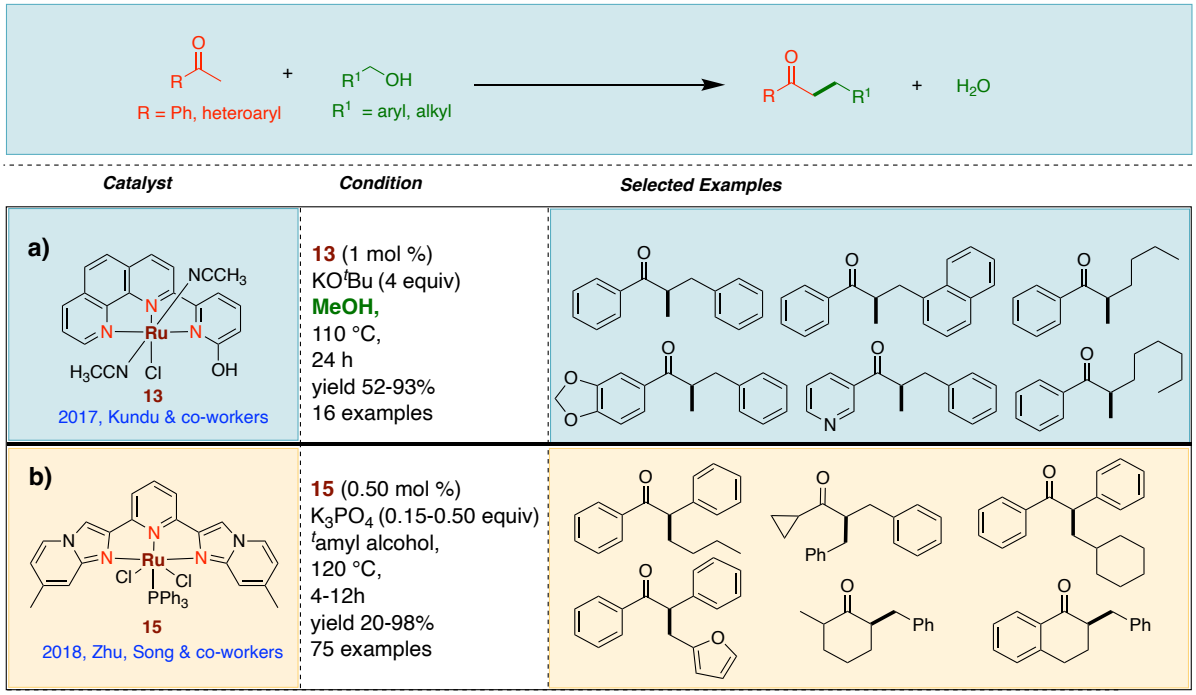
Scheme 1.5: Dehydrogenative Homocoupling of Primary Alcohols Leading to Higher Alcohols



1.2 α-Alkylation of Ketones Using Alcohols

Carbon-carbon bond formation is a fundamental reaction in organic chemistry, essential for synthesizing complex molecules. A noteworthy advancement is the borrowing hydrogen concept[14a], which utilizes alcohols as green alkylating agents. This approach is particularly attractive because it not only minimizes waste by generating water as a byproduct but also enhances atom economy, making it environmentally benign. Recently, it has garnered increased attention due to the versatility of the resulting products, which are highly valuable in pharmaceuticals and various industries. Several transformations have been reported in recent times with various carbon nucleophiles[14b,c] which react directly with alcohols, resulting in the formation of new C-C bonds. In 2017, Kundu and coworkers[14d] introduced an efficient method for the alkylation of ketones using primary alcohols, employing the pincer complex **13** as catalyst. They also showcased a multicomponent reaction pathway that included methanol as a C1 source, resulting in the formation of α-methylated ketones (Scheme 1.6a).

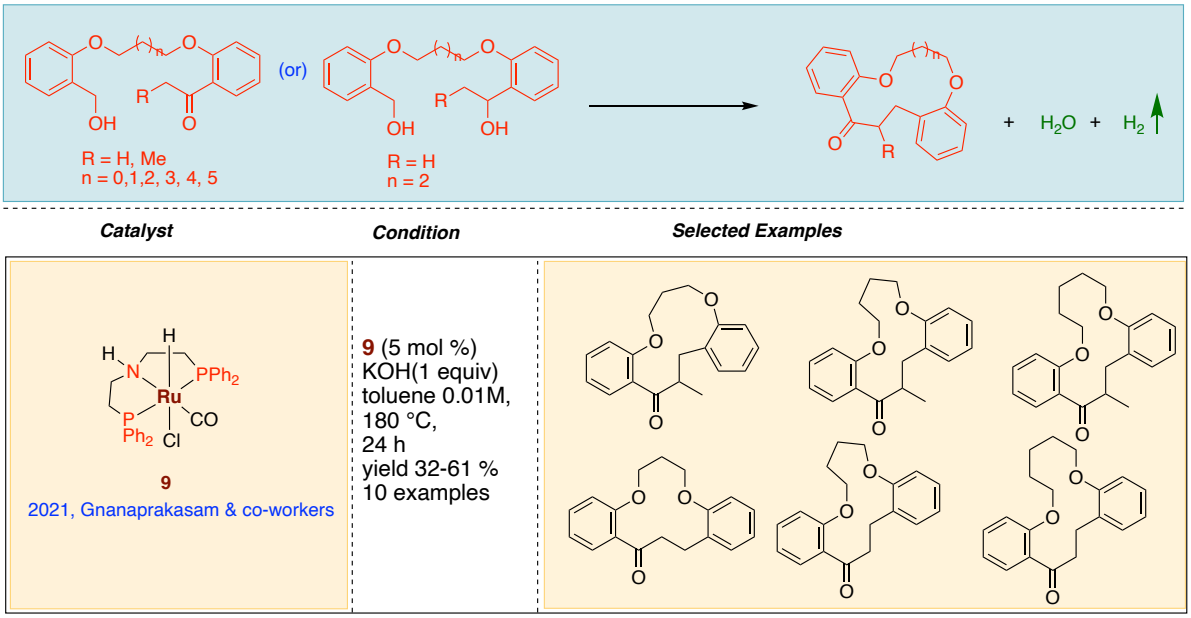
Scheme 1.6: α-Alkylation of Ketones with Primary Alcohols Leading to α-substituted Ketones



Subsequently, Song and coworkers[14e] used the catalyst **15** to carry out alkylation reactions on ketones with primary alcohols. They explored a wide variety of ketones, including cyclic, acyclic, and methylene-substituted types, successfully alkylating them with different aliphatic and aryl methanols, which yielded α-alkylated ketones (Scheme 1.6b).

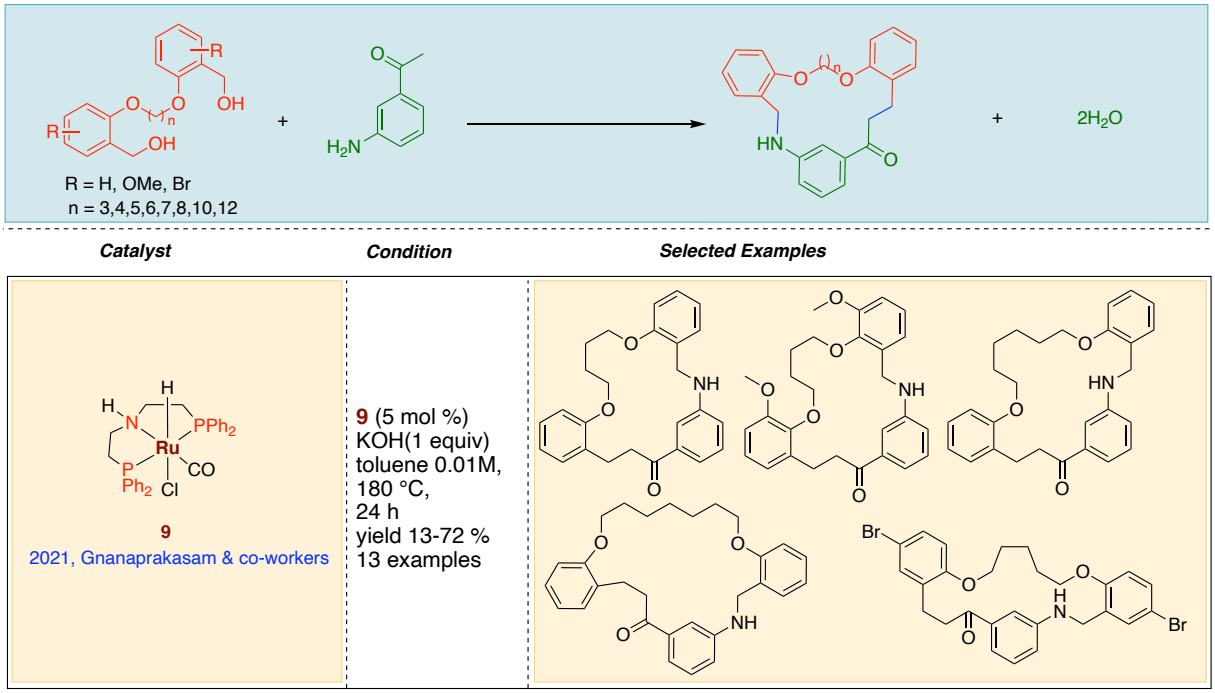
Macrocyclic ketones are a class of chemical compounds that have a wide range of applications in pharmaceuticals, materials science, and supramolecular chemistry. Recently, Gnanaprakasam and coworkers[15] developed a strategy to expand the alkylation of ketones using linear long-chain spacers, with one end attached to ketones and the other end tethered to primary alcohols, or both ends as alcohols. They employed the catalyst **9** with a stoichiometric amount of KOH in a toluene solution. Various spacers, ranging from n = 0 to 5, were utilized in the intramolecular alkylation reaction, which provided macrocyclic ketones via alkylation reaction in moderate to good yields (Scheme 1.7).

Scheme 1.7: Intramolecular α-Alkylation of ketones with Primary Alcohol leading to Macrocyclization.



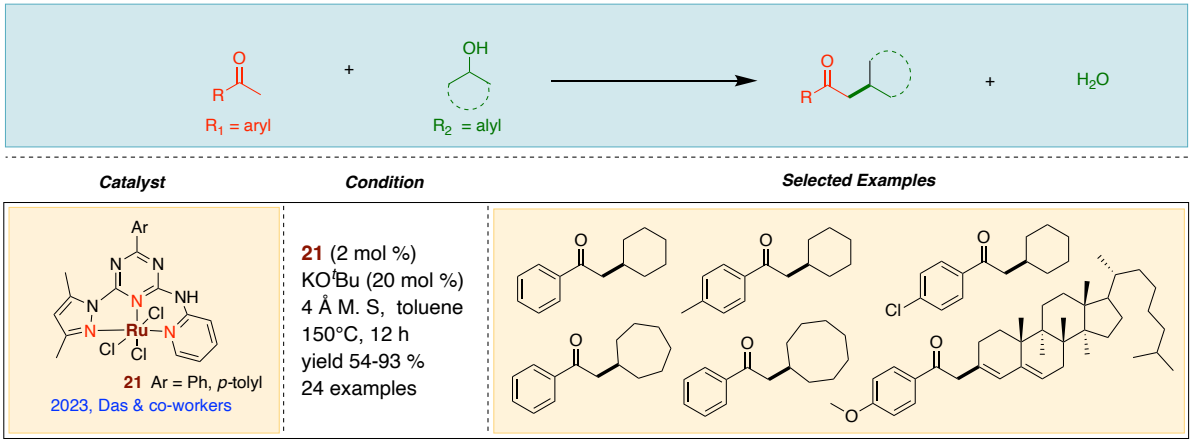
In the same report, Gnanaprakasam and coworkers[15] utilized the catalyst **9** under identical optimal conditions also to demonstrate macrocyclization via an intermolecular alkylation reaction. They employed a phenyl ring bearing a methyl ketone at one end and an amino group at the meta position. Macrocyclization via both C- and N-alkylation, with aryl methanol spacers ranging in length from n = 3 to 12, resulted in inter- and intramolecular alkylation reactions that produced macrocycles with amine and keto functionalities in moderate to good yields (Scheme 1.8).

Scheme 1.8: Intermolecular α-Alkylation of Ketones and Amines with Primary Alcohols Leading to Macrocyclization.



Alkylation of ketones with secondary alcohols presents significant challenges due to the propensity of the ketones to undergo various side reactions, leading to unwanted aldol products. Several studies[16] have shown that using highly substituted acetophenones can minimize these undesired aldol reactions, resulting in the formation of β-disubstituted ketones. However, these methods typically require a stoichiometric amount of base (2-3 equivalents) to achieve the desired results. Recently, our group published a report[17a] demonstrating ketone alkylation using secondary alcohols with the PNP-type catalyst **9**and a catalytic amount of base (1 mol % **9** and 5 mol % KO^{t}Bu), allowing us to successfully synthesize β-disubstituted ketones. Notably, this marks the first instance where a catalytic amount of base has been employed alongside simple acetophenones and their derivatives. Following our work, Das and coworkers reported[17b] in 2023 the same reaction, utilizing an NNN-type complex, **21**, which also effectively facilitated the alkylation of simple acetophenones and their derivatives with secondary alcohols, leading to the formation of β-disubstituted ketones (Scheme 1.9).

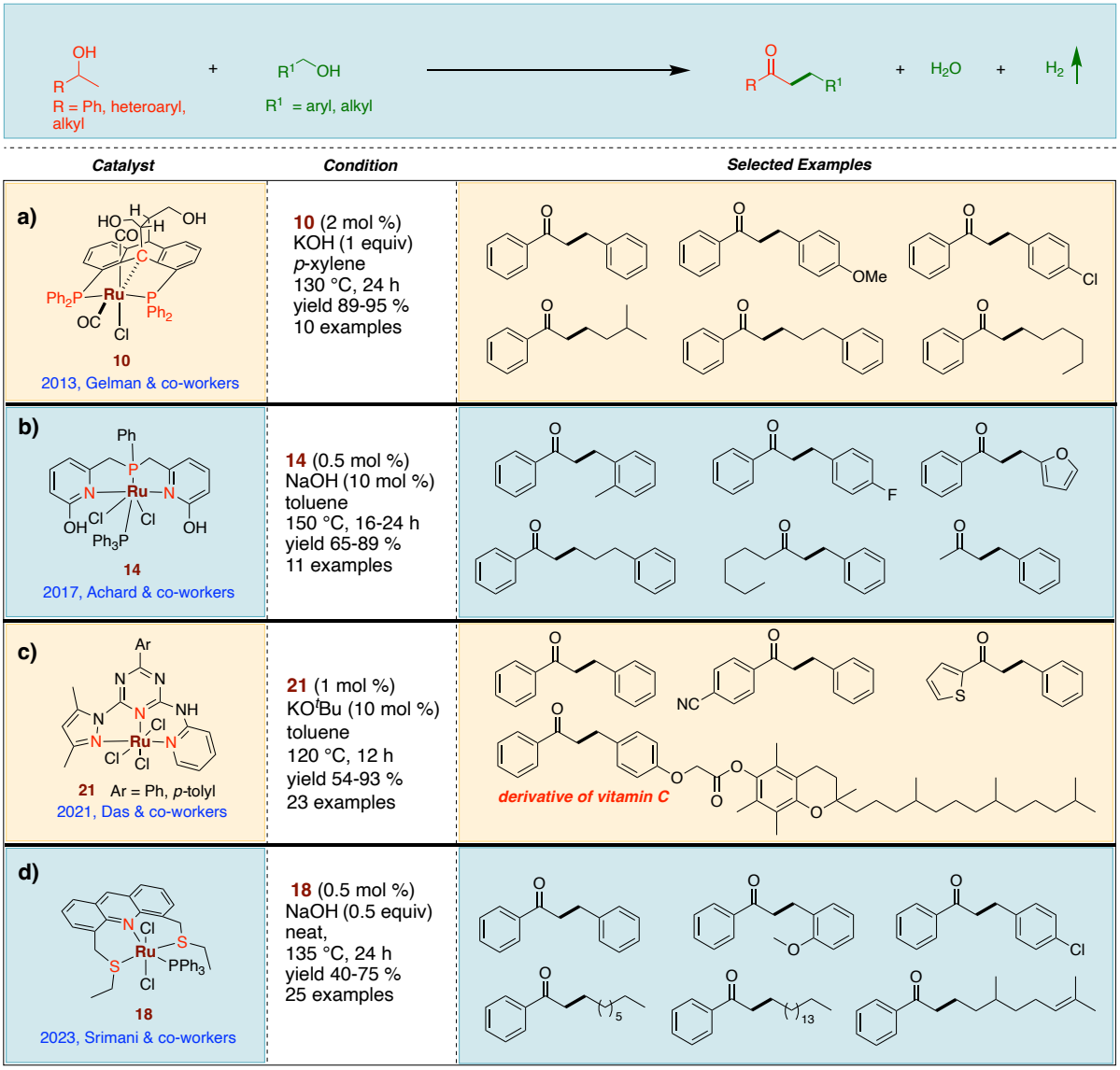
Scheme 1.9: α-Alkylation of Ketones Using Secondary Alcohols.



1.2.1 Dehydrogenative β-Alkylation of Secondary Alcohols using Primary Alcohols to Afford α-Substituted Ketones

The cross-coupling of two different alcohols to yield α-alkylated ketones via a borrowing hydrogen strategy has garnered significant attention due to its direct use of alcohols as starting materials, which are readily available industrial feedstocks, thereby enhancing atom economy. In 2013, Gelman and coworkers[18a] reported the β-alkylation of secondary alcohols with primary alcohols using the pincer complex **10** as catalyst in conjunction with KOH as a base, attained good to excellent yields of α-substituted ketones (Scheme 1.10a). Achard and coworkers[18b] introduced a bifunctional NPN complex, **14**, which catalyzed the same transformation with a catalytic amount of base (Scheme 1.10b). In 2021, Das and coworkers[18c] presented the NNN-type catalyst **21**, which features an NH moiety in the methylene arm that facilitates metal-ligand cooperation for alcohol activation, successfully enabling the synthesis of α-substituted ketones in the presence of a catalytic amount of base.

Scheme 1.10: β-Alkylation of Secondary Alcohols Using Primary Alcohols to α-Substituted Ketones



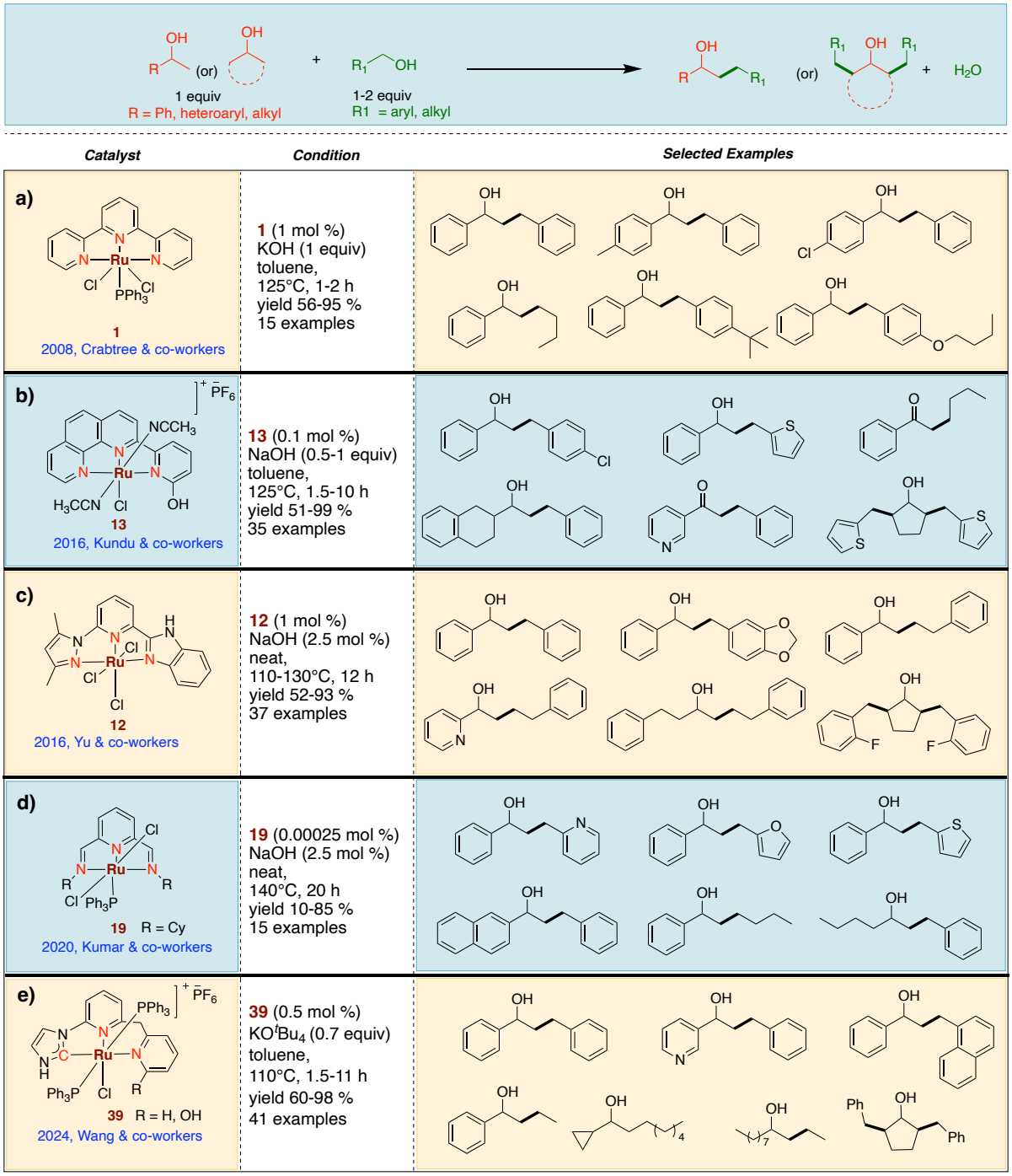
Notably, they synthesized a Vitamin C derivative, thereby expanding the applicability of this alkylation method (Scheme 1.10c). Srimani and coworkers[18d] utilized an acridine-based SNS-type catalyst, **18**, to achieve the β-alkylation of secondary alcohols, employing a substoichiometric amount of NaOH base, resulting in moderate to good yields of alkylated ketones (Scheme 1.10d)

1.2.2 Dehydrogenative β-alkylation of Secondary Alcohols Using Primary alcohols to Afford β-Substituted Alcohols

While the β-alkylation of secondary alcohols for synthesizing α-substituted ketones has been extensively studied, there are limited reports on catalytic systems that, after the alkylation reaction using the borrowing hydrogen strategy, further hydrogenate the ketone to yield β-alkylated alcohols. This approach extends the Guerbet reaction, allowing for the direct transformation of simple alcohols into their higher homologues.

In 2008, Crabtree and coworkers reported[19a] a terpyridinyl-based NNN-ligated pincer catalyst, **1**, that effectively catalyzed the β-alkylation of secondary alcohols, demonstrating a broad scope and functional group tolerance (Scheme 1.11a). In 2016, Kundu and coworkers[19b] introduced a bifunctional NNN-type pincer catalyst, **13** (Scheme 1.11b), while Yu and coworkers[19c] presented another NNN-type complex, **12** (Scheme 1.11c). Both groups demonstrated the alkylation of various alcohols, with cyclic aliphatic secondary alcohols undergoing successful dialkylation at both alpha positions, yielding dialkylated alcohols in excellent yields. More recently, Kumar and coworkers[19d] utilized the catalyst **19** to achieve β-alkylation with minimal catalyst and base loading (0.00025 and 2.5 mol %, respectively) under solvent-free conditions, obtaining moderate to good yields of the alkylated products (Scheme 1.11d). Additionally, Yu and coworkers[19e] employed a CNN-type catalyst, **39**, featuring an abnormal carbene ligand, and demonstrated an alkylation reaction that included a variety of secondary alcohols, including cyclic secondary alcohols, which underwent both mono- and dialkylation at the alpha positions, and delivered the alkylated products in good to excellent yields (Scheme 1.11e).

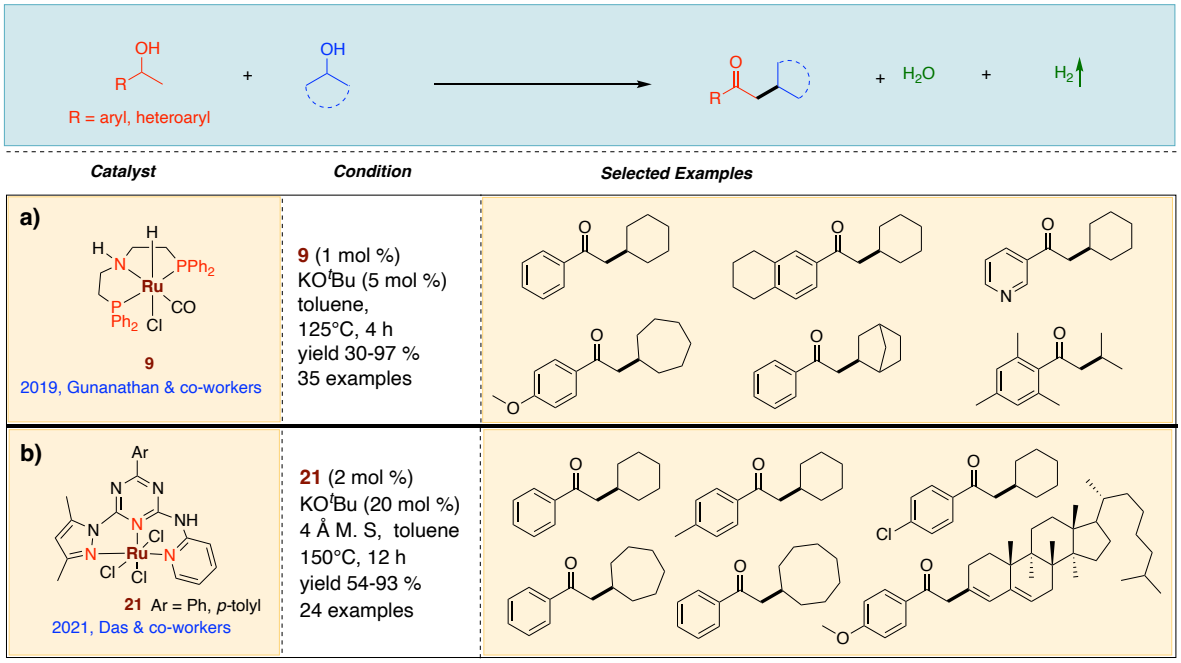
Scheme 1.11: β-Alkylation of Secondary Alcohols Using Primary Alcohols to β-Substituted alcohols



In 2019, Gunanathan and coworkers reported[20a], for the first time, a reaction involving the cross-coupling of two different secondary alcohols to produce β-disubstituted ketones. They utilized the PNP-type pincer catalyst **9** (1 mol %) along with KO^{t}Bu (5 mol %) in toluene as

the solvent (Scheme 1.12a). This approach demonstrated successful cross-coupling using a variety of both aryl and aliphatic alcohols, which provided β-disubstituted ketones in moderate to excellent yields. Later, Das and colleagues[20b] reported the NNN-type pincer catalyst **21**, used together with KO^{t}Bu (20 mol%) at slightly elevated temperatures to successfully alkylate simple ketones to provide β-disubstituted ketones in good to excellent yields (Scheme 1.12b). These strategies represent a new method for the synthesis of β-disubstituted ketones, and minimize the use of base. Water and hydrogen are the only byproducts obtained in these reactions.

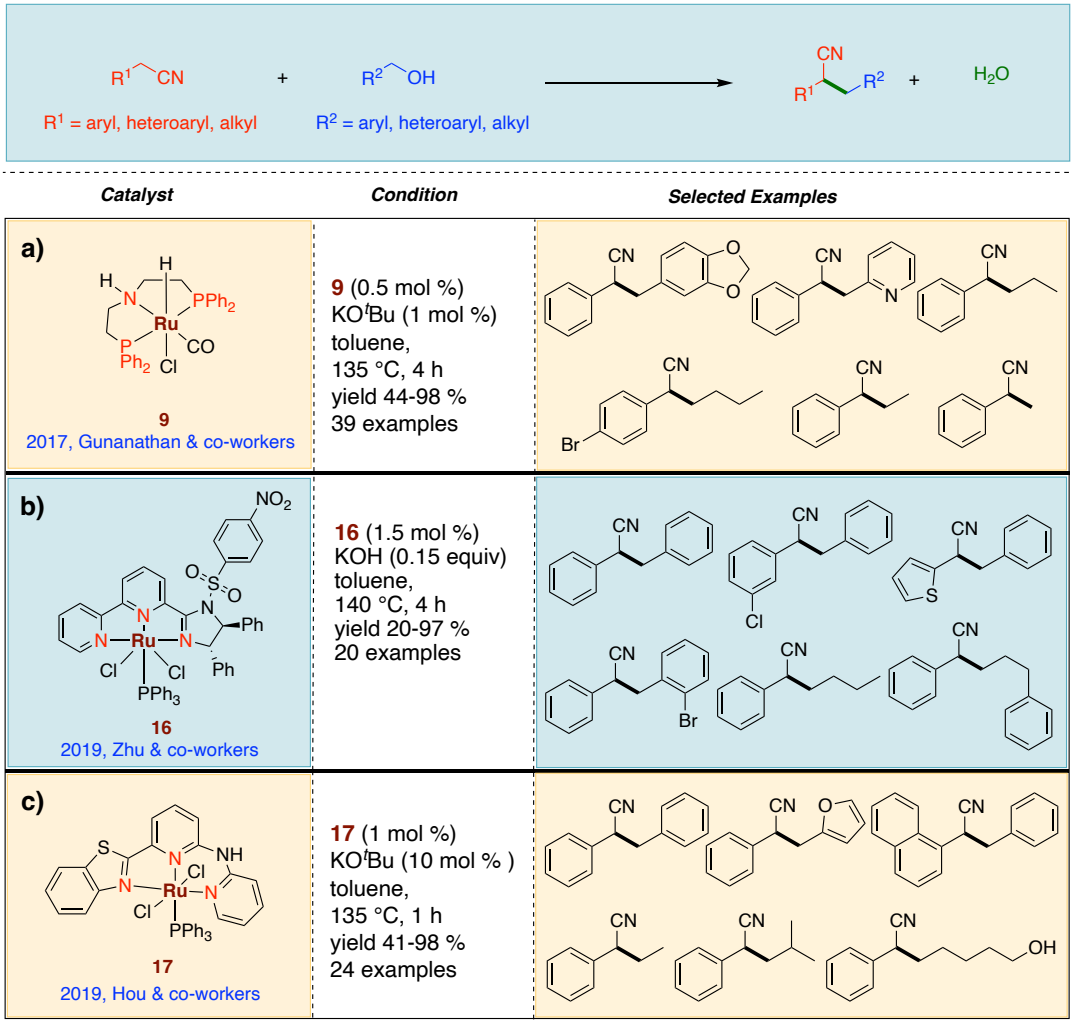
Scheme 1.12: Catalytic Cross-Coupling of Secondary Alcohols



Alkylation reactions utilizing the borrowing hydrogen strategy have gained significant attention, for the alkylation of aryl methyl nitriles using alcohols as alkylating agents, which are valuable precursors for various biologically active compounds. In 2017, Thiyagarajan and Gunanathan[21a] introduced a catalytic method for this alkylation using primary alcohols. A catalytic amount of the pincer complex **9** (0.5 mol%) was used, together with KO^{t}Bu as base (5 mol%), to successfully alkylate a range of aryl methyl nitriles with both aliphatic and aryl

methanols, achieving good to excellent yields. Notably, they demonstrated the methylation and ethylation at the α-position of aryl methyl nitriles using challenging substrates like methanol and ethanol (Scheme 1.13a). Following this pioneering report, Zhu and coworkers reported[21b] in 2019 the alkylation of aryl methyl nitriles using an NNN-type catalyst with a chiral diamine backbone, **16**, which resulted in moderate to excellent yields (Scheme 1.13b). That same year, Hou and colleagues[21c] used an NNN-type pincer catalyst featuring an NH arm, **17**, which facilitated the alkylation of aryl methyl nitriles with a catalytic amount of base within a short reaction time of one hour, and provided moderate to excellent yields (Scheme 1.13c). Importantly, all of these catalytic processes generate water as the sole byproduct.

Scheme 1.13: α-Alkylation of Nitriles Using Primary Alcohols

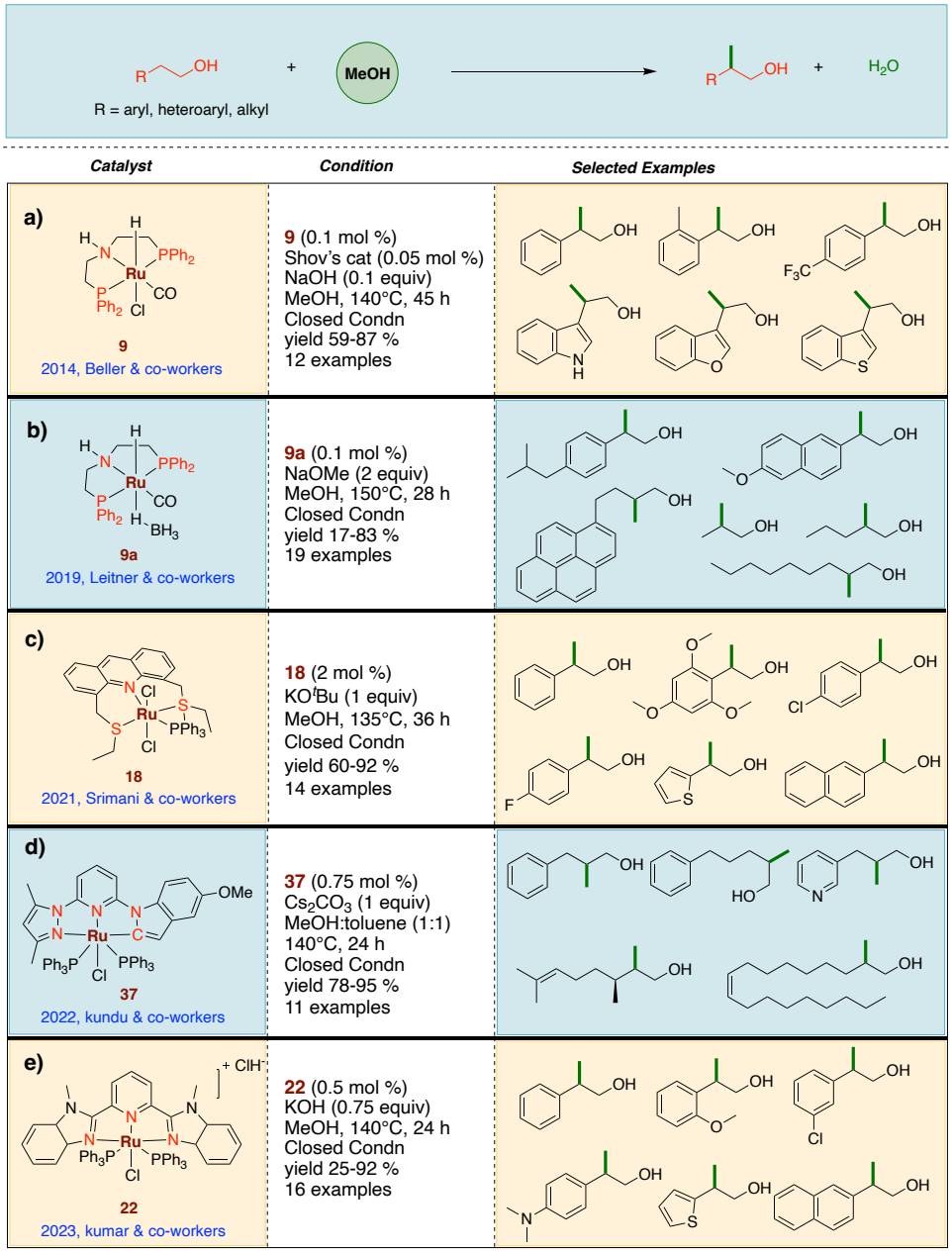


1.3 Dehydrogenative Methylation Reactions Using Methanol as a C1 Source

Methylation reactions are crucial and challenging, as they are often present in many biologically active compounds and play a significant role in modulating pharmaceutical properties. Recently, chemists have adopted the borrowing hydrogen strategy, using methanol as a C1 source for methylation at various nucleophilic centers. Several notable transformations have been reported.

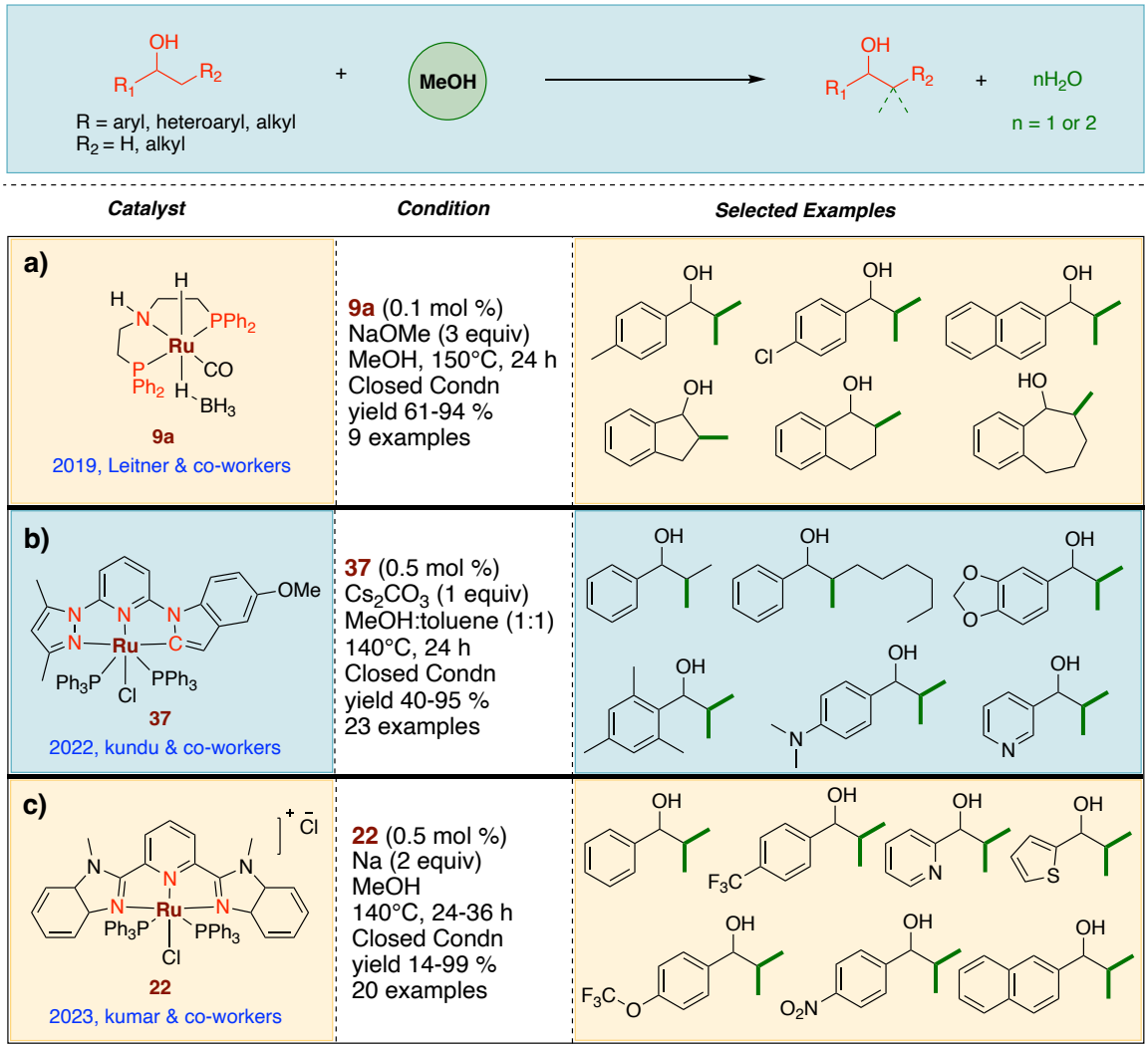
In 2014, Beller and coworkers[22a] demonstrated the β-methylation of primary alcohols using the PNP-type pincer catalyst **9**, successfully methylating a range of simple aryl and heteroaryl ethanol derivatives (Scheme 1.14a). In 2019, Leitner and coworkers[22b] utilized the similar PNP-bearing **a** borane complex **9a**, known as Ru-MACHO-BH_3, and achieved β-methylation of primary alcohols with moderate to good yields (Scheme 1.14b). In 2021, Srimani and coworkers[22c] employed an acridine-based SNS-type pincer catalyst, **18**, for the methylation of primary alcohols, yielding products in good to excellent yields (Scheme 1.14c). Kundu and coworkers[22d] reported a similar methylation approach using an NNC-type catalyst featuring an abnormal carbene ligand, **37**, which also resulted β-methylated primary alcohols in good to excellent yields. Notably, the citronellol molecule was successfully methylated to its β-methylated product in good yield (Scheme 1.14d). In 2023, Kumar and coworkers[22e] used an NNN-type pincer catalyst, **22**, for the β-methylation of diverse primary alcohols (Scheme 1.14e).

Scheme 1.14: β-Methylation of Primary Alcohols using Methanol as a C1 Source



Secondary alcohols, in addition to primary alcohols, have been utilized for β-methylation reactions using methanol as the carbon source. In 2019, Leitner and coworkers[23a] reported methylation at the β-position of both acyclic and cyclic secondary alcohols with the pincer catalyst **9a**.

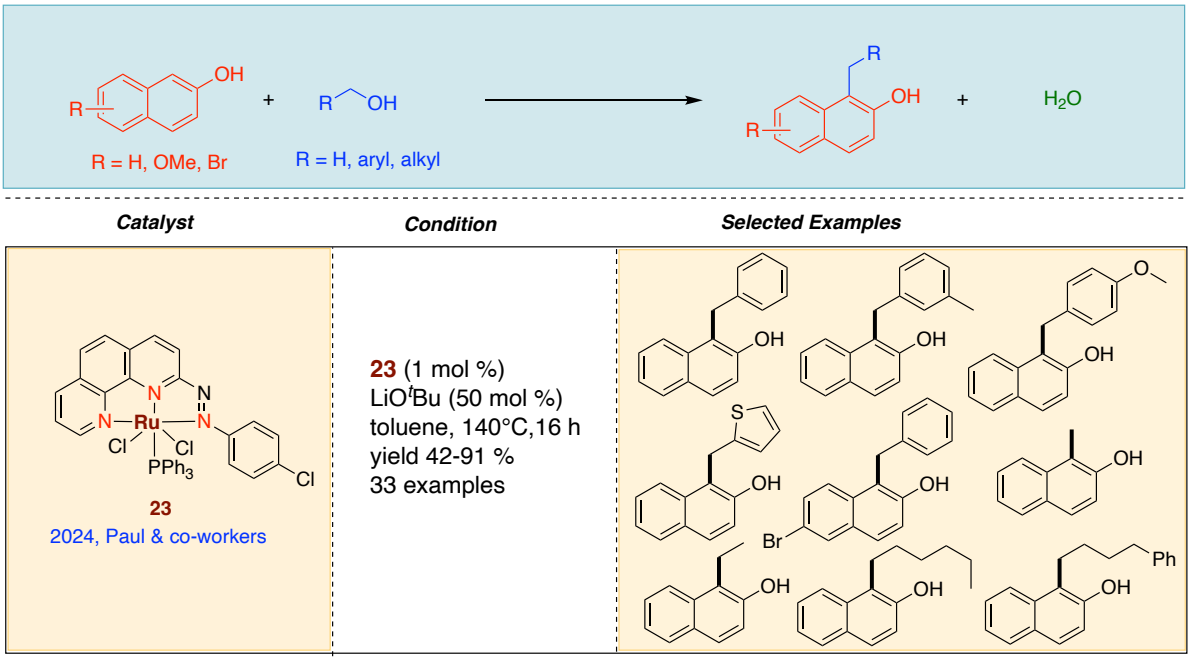
Scheme 1.15: β-Methylation of Secondary Alcohols using Methanol as a C1 Source



Notably, simple arylethanols underwent dimethylation, resulting in β-disubstituted alcohols (Scheme 1.15a). Subsequently, Kundu and coworkers[23b] achieved similar β-methylation of secondary alcohols using the abnormal NNC-ligated pincer catalyst **37**, demonstrating both mono- and dimethylation in cyclic and acyclic secondary alcohols, with yields ranging from moderate to excellent (Scheme 1.15b). More recently, Kumar and coworkers[23c] described a dimethylation process for arylethanols utilizing the pincer catalyst **22** together with sodium metal and methanol, which generated sodium methoxide in situ as a base, thereby facilitating the β-methylation reaction (Scheme 1.15c). Their protocol employs methanol as a source for both carbon and the in situ generated base.

The formation of C-C bonds between sp^3 carbon centers using a borrowing hydrogen strategy, which employs alcohols as alkylation agents with various carbon nucleophiles, has seen significant advancements. However, achieving C-C bond formation at sp^2 carbon centers remains challenging, particularly in the selective alkylation of arenols. Recently, our group reported[24a] the selective alkylation of β-naphthols using primary alcohols via the borrowing hydrogen strategy, marking the first application of a pincer complex in this context. After our report, in 2024, Paul and coworkers[24b] introduced a simple, air-stable NNN-type pincer catalyst, **23**, and demonstrated the selective alkylation of β-naphthols with various primary alcohols. Notably, they successfully performed challenging methylation and ethylation reactions (Scheme 1.16).

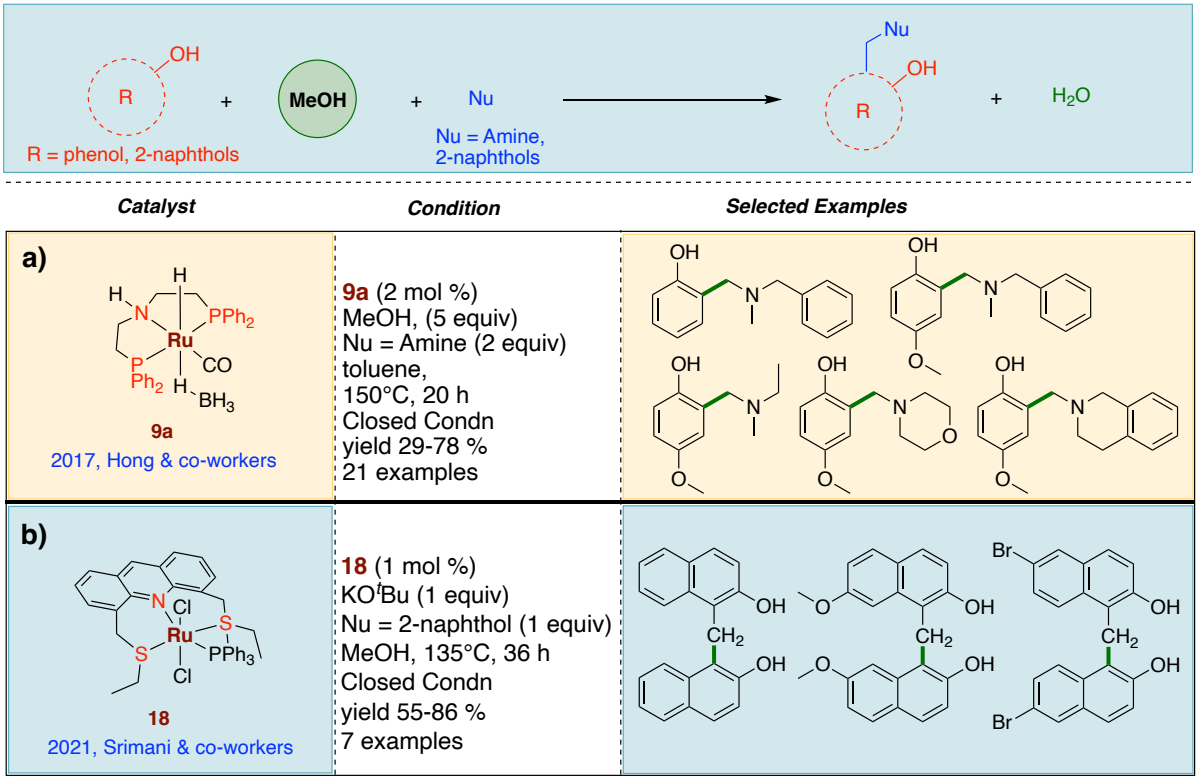
Scheme 1.16: Dearomative α-Alkylation of β-Naphthols Using Primary Alcohols



Methylation reactions at sp^3 carbon centers using methanol as a C1 source have been extensively studied. Recently, researchers have turned their attention to methylation reactions on challenging sp^2 carbon centers. Upon dearomatization of β-naphthol, the α-position undergoes nucleophilic attack with the in situ generated formaldehyde from the catalytic

oxidation of methanol. Subsequent dehydration reaction provides the unsaturated enone intermediate. This intermediate either gets hydrogenated by the catalyst and forms methylated product or the used specific nucleophile undergoes Michael addition reaction resulting in formation of a new C-C or C-N bond. In 2017, Hong and coworkers[25a] reported a dearomative aminomethylation reaction utilizing the pincer catalyst **9a** with amines as nucleophiles. They allowed various phenols to react with methanol as the C1 source, leading to formation of aminomethylated phenols in good to excellent yields (Scheme 1.17a). Subsequently, Srimani and coworkers[25b] used complex **18** and carried out similar methylation reactions using methanol, where naphthols were employed as nucleophiles. This approach also led to the formation of methylene dinaphthol products in good yields via Michael addition (Scheme 1.17b).

Scheme 1.17: Dearomative *ortho*-Functionalization of Arenols using Methanol as a C1 Source



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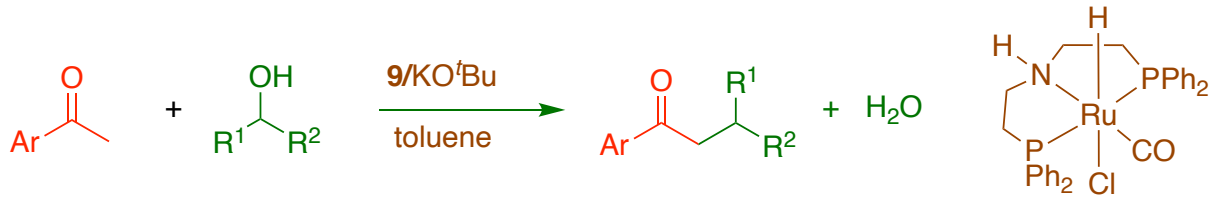
CHAPTER-2

Ruthenium-Catalyzed α-Alkylation of Ketones Using Secondary Alcohols to Generate β-Disubstituted Ketones

2.1 ABSTRACT



simple acetophenone derivatives **9**

An assortment of aromatic ketones were successfully functionalized with a variety of unactivated secondary alcohols that serve as alkylating agents, providing β-disubstituted ketone products in good to excellent yields. Challenging substrates, such as simple acetophenone derivatives, are effectively alkylated by this ruthenium-based catalytic system. Substituted cyclohexanol compounds displayed product-induced diastereoselectivity. Mechanistic studies indicate the involvement of a borrowing hydrogen pathway in these alkylation reactions. Notably, this selective catalytic C−C bond-forming reaction requires only a minimal loading of catalyst and base, and produces H_2O as the only byproduct, making this protocol attractive and environmentally benign.

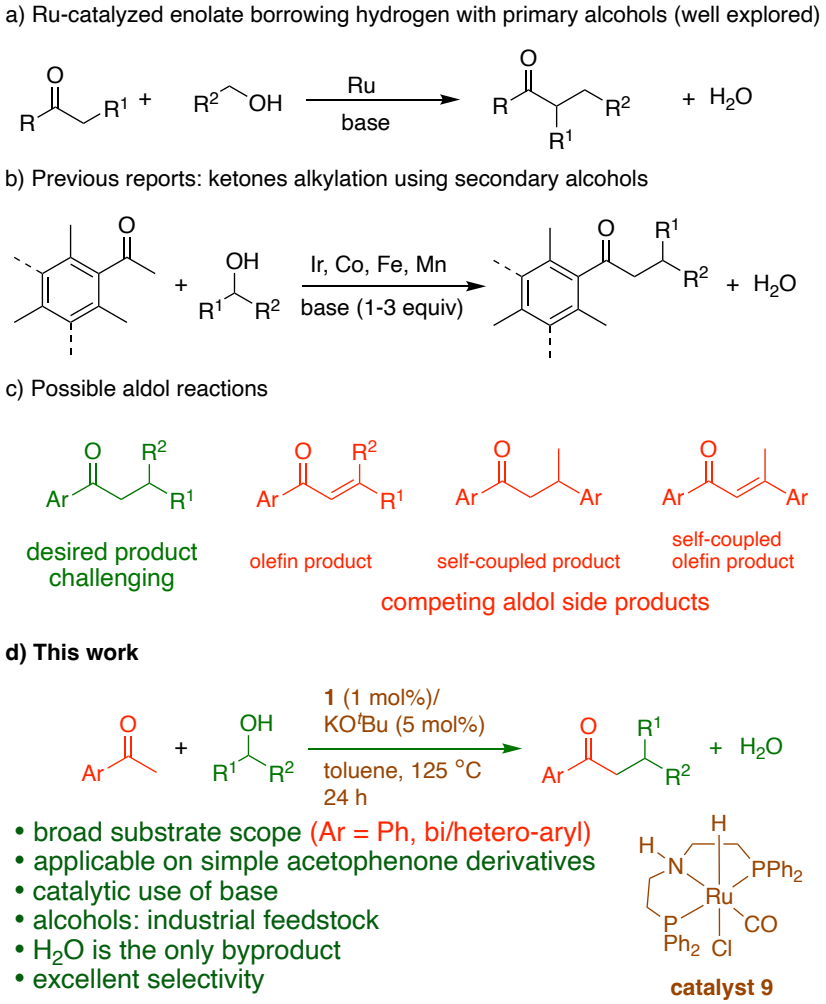
2.2 INTRODUCTION

The borrowing hydrogen strategy is an attractive method for C−C and C−N bond formation, which are transformations of fundamental importance in chemical synthesis.[1] This strategy has become acceptable and well-recognized, since it represents low-waste transformations. In these processes, the catalyst "borrows" hydrogen from alcohols via oxidation reactions to provide the corresponding carbonyl compounds and further concomitant condensation, with

nucleophilic enolates forming unsaturated carbonyl compound. Finally, the hydrogen "borrowed" by the catalyst is added to the (C=C bond) of the unsaturated carbonyl compound to deliver the hydrogenated product. Ketones are of great importance in biology and industries, where they are produced on a large scale as solvents, polymer precursors, and pharmaceuticals.[5] Conventionally, α-alkylated ketones are prepared by the reaction of base-generated ketone enolate species with alkyl halides.[2] Therefore, the development of simple, selective, and atom-economical alkylation reactions for ketones is highly desired. This can be realized by applying the hydrogen-borrowing methodology, using alcohols as alkylating agents. Alcohols are cheap, readily available, and can be produced from lignocellulosic biomass,[3] and their use as alkylating agents produces water as the only byproduct.[1,4] The use of primary alcohols for α-alkylation of ketones and β-alkylation of secondary alcohols is well established, and generates linear or branched ketones.[1,4,6] A ruthenium-catalyzed hydrogen borrowing strategy, which uses primary alcohols with ketone enolates, is well known (**Scheme 2.1a**).[1,4] However, the use of secondary alcohols for alkylation reactions is poorly documented. In contrast to α-branched ketones, formation of β-disubstituted products is more challenging and relatively underdeveloped. In 2017, the Donohoe group reported the synthesis of β-branched ketones via α-alkylation of ketones using secondary alcohols.[7] Very recently Co-,[8] Fe-,[9] and Mn-catalyzed[10] α-alkylation of ketones using secondary alcohols has been reported (**Scheme 2.1b**). Also, there are some possibility of various competing aldol side products which can decrease the atom economy of the reaction (**Scheme 2.1c**). All of these enticing developments can be summarized as follows: (i) Stoichiometric excess of base is required, which results in aldol side reactions; (ii) To avoid base-promoted self-condensation, highly hindered aryl ketones are employed, and, in general, these methods work only for pentamethylphenyl (Ph*) ketones or trisubstituted aryl ketones; (iii) Unsubstituted or other aryl ketones are less appropriate for such synthetic strategies and, thus, suffer from a limited

substrate scope. Importantly, the Ph* group, which prevents ketone self-condensation reactions, can also be detached to prepare a range of carbonyl derivatives, such as esters and amides, through a retro-Friedel-Crafts acylation reaction.[7–10] To circumvent the above drawbacks, and ensure the success of this process and its broad application, an efficient catalytic system is essential that can preclude the self-condensation of non-substituted ketone substrates. Recently, selective cross-coupling of secondary alcohols to β-disubstituted ketones was reported by our group.[11] However, as far as we know, there is no general method for the α-alkylation of ketones, especially for acetophenone with few or no substituents, using secondary alcohols. Thus, a simple catalytic method with a broad substrate scope is required. Modern transition metal catalysis is focused on the development of sustainable, one-step, and atom-economical strategies for the preparation of valuable building blocks from readily available starting materials. In this regard, we have developed ruthenium-pincer-catalyzed selective hydrogenation of epoxides,[12] ketazine synthesis,[13] α-alkylation, and α-olefination of nitriles and N,N-dialkylation of acylhydrazides using alcohols.[14] In continuation, herein we report the simple method which employs a catalytic amount of base for the α-alkylation of ketones using secondary alcohols to generate β-disubstituted ketones (**Scheme 2.1d**). Remarkably, H_2 and H_2O are the only byproducts of these green catalytic processes.

Scheme 2.1. Selective Catalytic α-Alkylation of Ketones Using Primary and Secondary Alcohols

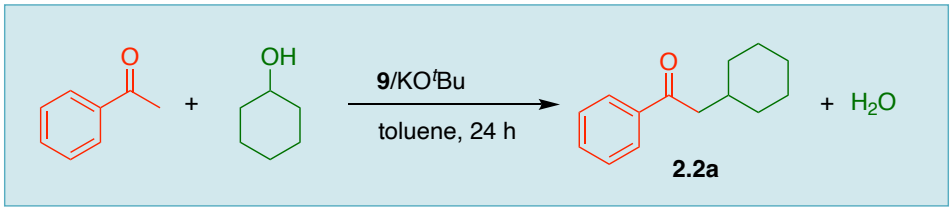


2.3 RESULTS AND DISCUSSION

Initially, the reaction of acetophenone (0.5 mmol) and cyclohexanol (1 mmol) was investigated as a model system in the presence of the ruthenium pincer catalyst **9** (1 mol %, Ru-MACHO) and 2 equiv of a base (KO^{t}Bu) in toluene at 135 °C. Surprisingly, catalyst **9** was found to exhibit distinctively high activity in forming the alkylated product **2.2a** along with a trace amount of aldol side products. The undesired aldol side products (**Scheme 2.1c**) were inseparable by column chromatography, and thus we were unable to isolate and identify them. The complete conversion of acetophenone was observed in 24 h, and the desired α-alkylated product 2.2a was isolated in 59% yield (entry 1, **Table 2.1**). When the temperature or the amount of KO^{t}Bu

and secondary alcohol were decreased, product formation slightly increased (entries 2 and 3).

Table 2.1. Optimization for the α-Alkylation of Ketones Using Secondary Alcohols Catalyzed by 9[a]



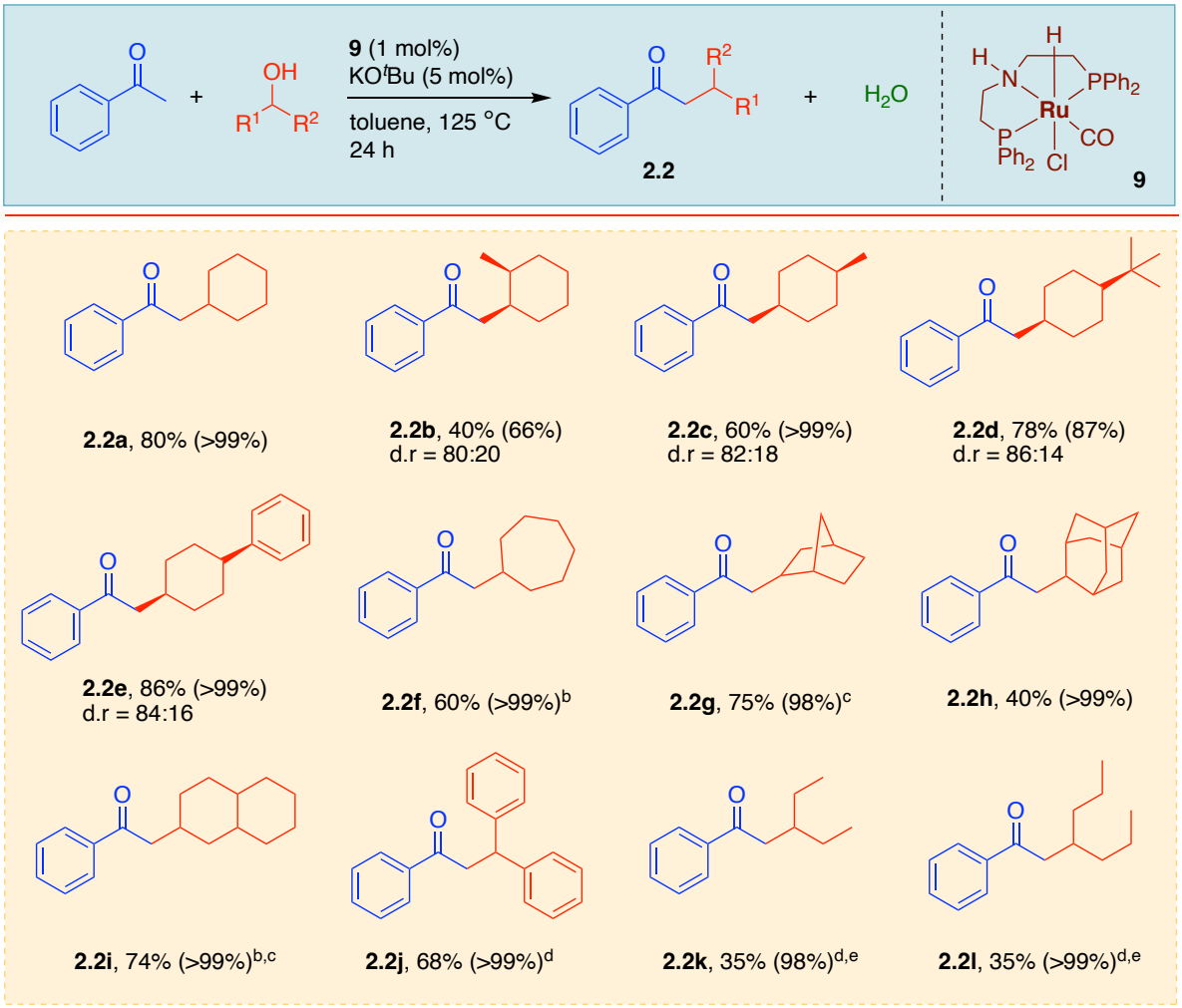
entry	cat. (mol%)	base (mol%)	alcohol (equiv)	temp. (°C)	conv. (%)[b]	yield (%)[c]
1	1	200	2	135	>99	59
2	1	200	2	125	>99	68
3	1	100	1.2	125	>99	70
4	1	20	1.2	125	>99	73
5	1	5	1.2	125	>99	80
6	1	2	1.2	125	40	35
7	1	5	1.5	125	>99	79
8	1	5	1.2	120	97	74
9	1	5	1.2	100	5	-
10	0.5	2.5	1.2	125	95	75
11[d]	1	5	1.2	125	85	65
12[e]	1	5	1.2	125	5	-
13[f]	1	5	1.2	125	>99	79
14[g]	-	5	1.2	125	55	-
15[g]	-	-	1.2	125	-	-
16[h]	1	5	1.2	125	>99	75

[a]Reaction conditions: acetophenone (0.5 mmol), cyclohexanol (0.6 mmol), catalyst **9**, KO^{t}Bu and toluene (1.5 mL) were heated at 125°C in an open flask under argon flow. [b]Conversion of

acetophenone was determined by GC using mesitylene as an internal standard. [c]Isolated yields after column chromatography. [d]1,4-Dioxane used as a solvent. [e]5 mol% of Cs_2CO_3 used as base. [f]5 mol% of NaO^{t}Bu used as base. [g]Reaction performed twice. [h]Reaction performed at 1 mmol scale.

Using the optimal catalytic conditions, the reactivity of acetophenone toward different secondary alcohols was explored (**Scheme 2.2**). Substituted cyclohexanol derivatives afforded the corresponding alkylated products **2.2b-e** in good to moderate yields**.** Substitution on the cyclohexyl ring resulted in products that are mixtures of diastereomers, and the diastereomeric ratios were obtained from ^{1}H NMR analyses of the crude reaction mixtures. Reaction of cycloheptanol and *exo*-norborneol with acetophenone afforded the α-alkylated products **2.2f** and **2.2g** in 60 and 75% yield, respectively. Highly hindered 2-adamantanol provided product **2.2h** in 40% yield. Decahydronaphthalen-2-ol is well tolerated in this catalytic protocol and converted into the α-alkylated product **2.2i** in 74% yield. Diphenylmethanol provided the product **2.2j** in 68% yield. Finally, 5 equivalents of 3-pentanol and 4-heptanol reacted with acetophenone, using an increased loading of catalyst (5 mol%) and KO^{t}Bu (10 mol%), and the corresponding alkylated products **2.2k** and **2.2l** were isolated in moderate yields.

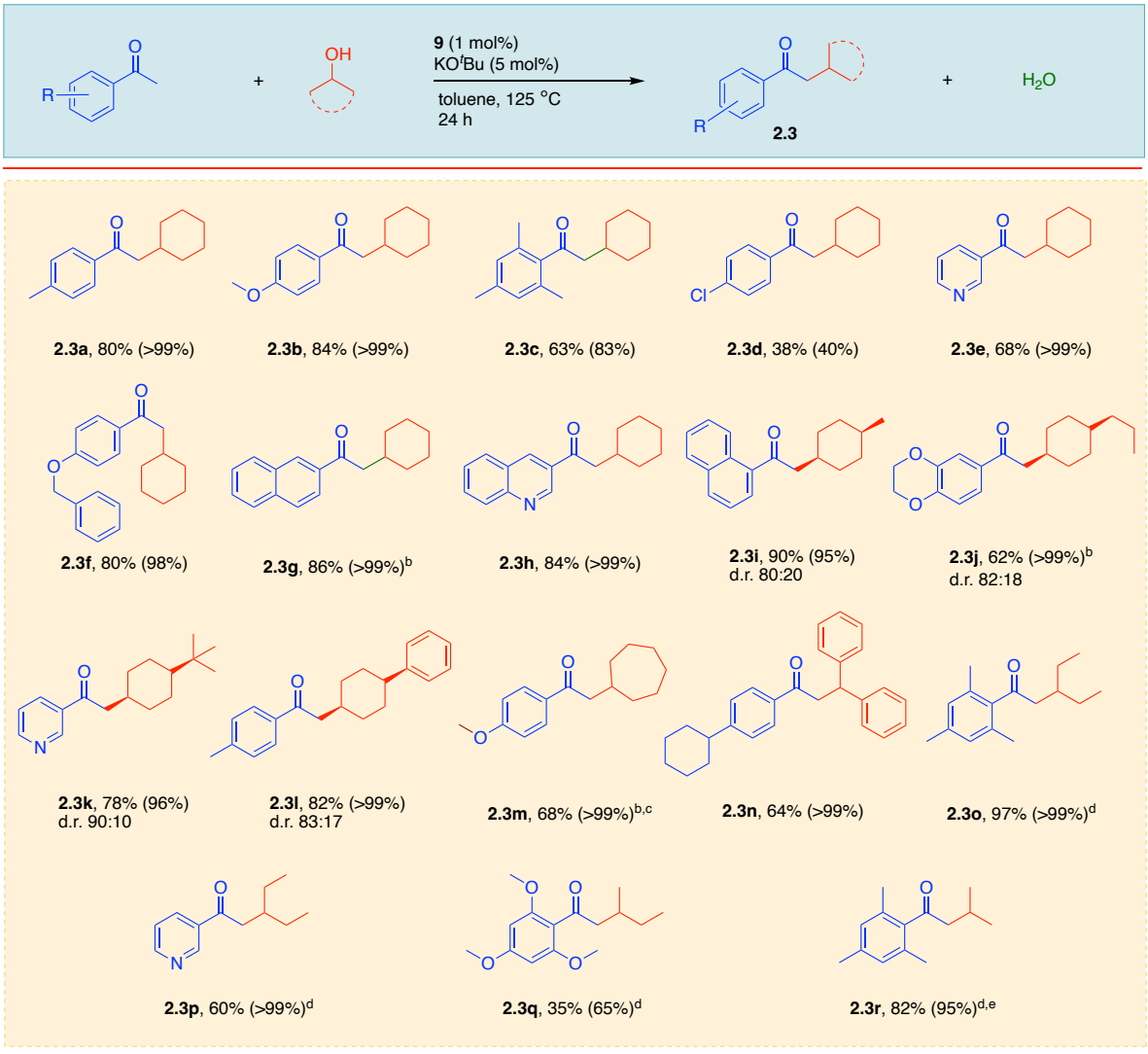
Scheme 2.2: Ruthenium-Catalyzed α-Alkylation of Acetophenone Using Secondary Alcohol[a]



[a]Reaction conditions: Acetophenone (0.5 mmol), secondary alcohol (0.6 mmol), toluene (1.5 mL), catalyst **9** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C in an open flask under nitrogen flow. Conversion of acetophenone was determined by GC analysis using mesitylene as an internal standard and is shown in parentheses. Diastereomeric ratios (d.r) were determined by ^{1}H NMR analysis of the crude reaction mixture. Yields refer to isolated pure products after column chromatography. [b]3 mol% of catalyst **9** and 10 mol% of base were used. [c]diastereomeric mixture, d.r ratio not determined. [d]Reaction performed using 5 mol% of catalyst **9** and 10 mol% of base. [e]5 equiv of alcohol were used.

The application of the α-alkylation reaction was subsequently extended to diverse ketones with different secondary alcohols, delivering the β-branched ketone products in good to excellent yields (**Scheme 2.3**). Both electron-donating and electron-withdrawing groups on the aryl ketones were well tolerated in this catalytic protocol. Reaction of cyclohexanol with a variety

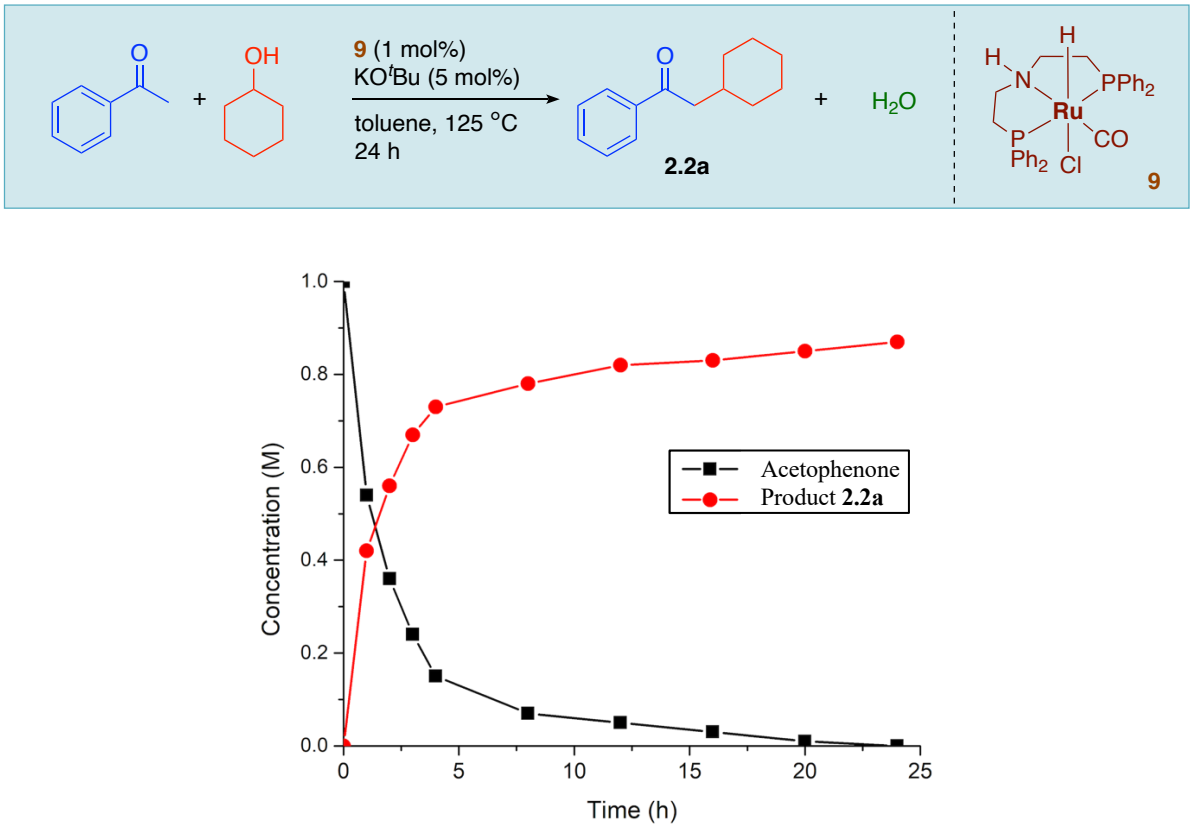
Scheme 2.3: Ruthenium-Catalyzed α-Alkylation of Ketones Using Secondary Alcohols[a]



[a]Reaction conditions: same as in **Scheme 2.2**, but instead of acetophenone, other ketones (0.5 mmol) were used. [b]3 mol% of catalyst **9** and 15 mol% of KO^{t}Bu were used. [c]3 equiv of cycloheptanol were used. [d]Reaction performed using 5 equiv of alcohol, 5 mol% of catalyst **9** and 20 mol% of base. [e]10 equiv of isopropanol were used.

of ketones provided the α-alkylated ketone products **2.3a-h** in moderate to good yields (38-86%). 4-methyl-, 4-propyl-, 4-tert-butyl-, and 4-phenyl-substituted cyclohexanol derivatives provided the products **2.3i-l** in good yields (62-90%) and also as mixtures of diastereomers, and the diastereomeric ratios were obtained from the ^{1}H NMR spectra of the crude reaction mixtures. Cycloheptanol reacted with 4-methoxyacetophenone to give product **2.3m** (68% yield). Diphenylmethanol reacted with 4-cyclohexylacetophenone and the desired ketone product **2.3n** was isolated in 64% yield. Interestingly, unactivated acyclic secondary alcohols were also tolerated, enabling the synthesis of β-disubstituted ketones **2.3o-r** in very good yields. Remarkably, *N*-heteroarene-containing ketones successfully participated in α-alkylation with secondary alcohols to afford the products **2.3e, 2.3h, 2.3k** and **2.3p** in moderate to good yields. However, the reactions of cyclohexanol with other heteroaromatic ketones, namely, 2-acetylpyridine, 2-acetylfuran and 2-acetylthiophene, did not provide the desired α-alkylated products. Catalytic alkylation of aliphatic ketones, such as cyclopropyl methyl ketone and 2-heptanone, were also performed using cyclohexanol, but resulted in incomplete reactions and provided complex mixtures, indicating the importance of having an aryl group in the ketone. Experiments designed to understand the reaction pathways and enable kinetic analysis were carried out. Under standard conditions, reaction of acetophenone and cyclohexanol catalyzed by **9** was monitored using gas chromatography (GC), indicating that the reaction follows first order kinetics with respect to the consumption of acetophenone (**Figure 2.1**).

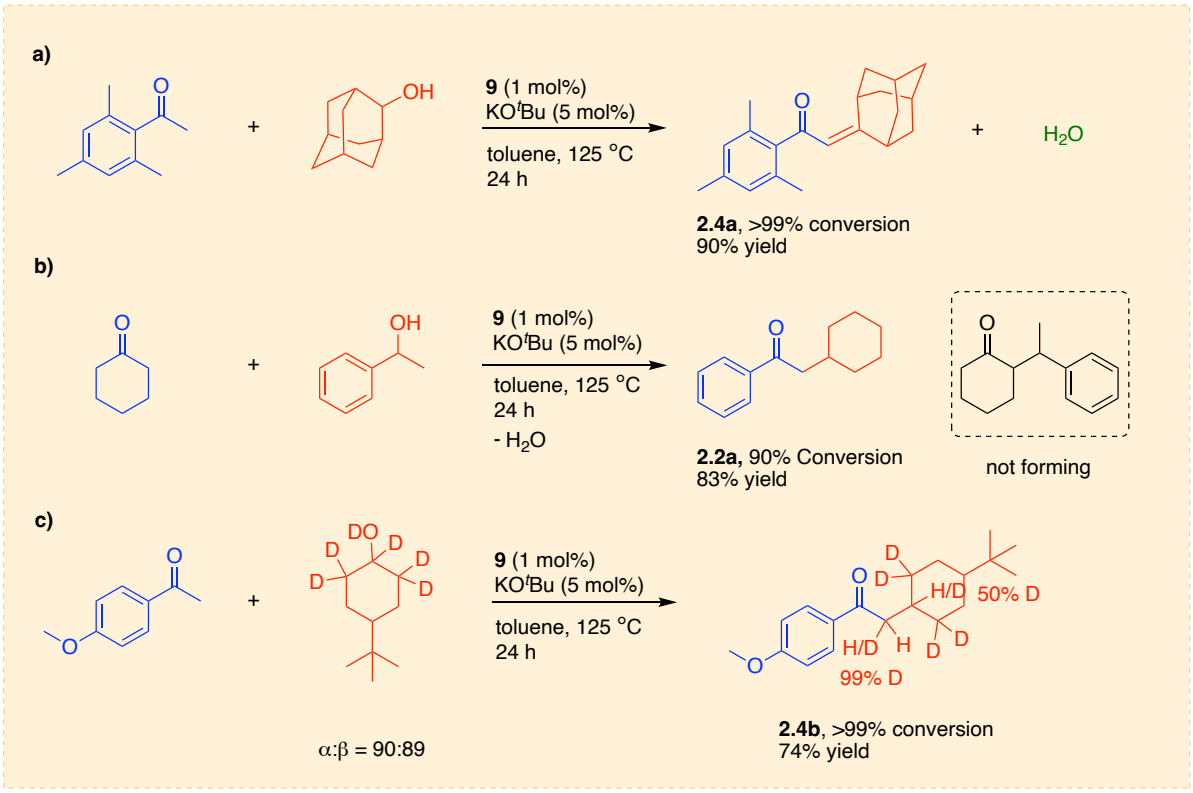
Figure 2.1: GC Monitoring of the Reaction Between Acetophenone and Cyclohexanol to Afford Product 2.2a Catalyzed by Complex 9



Reaction of 1-mesitylethan-1-one with 2-adamantanol was carried out under standard reaction conditions, leading to selective formation of α,β-unsaturated ketone product **2.4a**, isolated in 90% yield (**Scheme 2.4a**). Due to the high steric hindrance at enone **2.4a**, further hydrogenation by the catalyst was prevented, and this observation confirms the involvement of enone intermediates in the reaction. Cyclohexanone reacted with 1-phenylethanol to afford the α-alkylated ketone product **2.2a** in 83% yield (**Scheme 2.4b**). Notably, cyclohexanone did not undergo α-alkylation with 1-phenylethanol, clearly indicating that aryl ketones undergo faster α-alkylation than aliphatic ketones in the presence of a catalytic amount of base. A deuterium-labeling experiment was performed with 4-methoxyacetophenone and deuterated 4-tert-butylcyclohexanol, and the outcome revealed that the reaction proceeds through a borrowing hydrogen pathway. The product **2.4b** was isolated in 74% yield, and exhibited 99 and 50%

deuterium incorporation at the α- and β-positions, respectively (**Scheme 2.4c**). The H/D scrambling at the β-position may be the result of H/D exchange between an in situ formed Ru-D intermediate and H_2O. The preferential deuteration at the α-position is perhaps due to the selective reaction of the catalyst with the α,β-unsaturated intermediate through the borrowing hydrogen pathway.

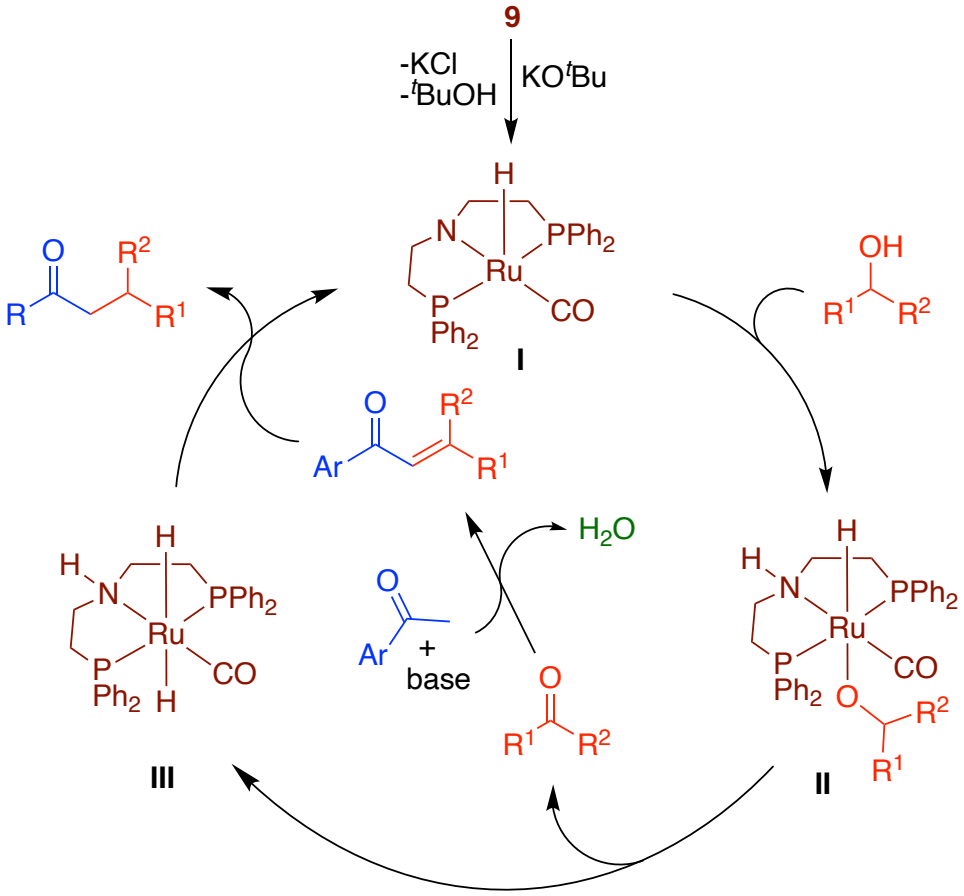
Scheme 2.4: Mechanistic Studies of the α-Alkylation of Ketones Using Secondary Alcohols Catalyzed by Complex 9



A plausible mechanism for the α-alkylation of ketones using secondary alcohols, catalyzed by **9**, is delineated in **Scheme 2.5**. Catalyst **9** was found to activate O–H, N–H and sp–C–H bonds under facile conditions.[11-15] Catalyst **9** reacts with base to generate an unsaturated reactive intermediate **I**,[15b,16] which further reacts with a secondary alcohol to provide an alkoxy-ligand-containing intermediate **II**.[15d] At this point, O-H activation takes place via β-hydride

elimination, which releases a ketone and generates a ruthenium dihydride intermediate **III**. The in situ formed ketone undergoes condensation with an aromatic ketone under basic conditions, leading to the formation of an α,β-unsaturated carbonyl compound. Finally, the α,β-unsaturated carbonyl intermediate is hydrogenated by complex **III**, resulting in the alkylated product and regenerating the catalytically active intermediate **I**. The amine-amide metal-ligand cooperation is operative in the catalytic cycle in which the intermediates maintain the same +2 oxidation state of the metal center.

Scheme 2.5. Proposed Reaction Mechanism for the Ruthenium-Catalyzed *α*-Alkylation of Ketones Using Secondary Alcohols



2.4 CONCLUSIONS

In conclusion, an efficient and convenient method for the synthesis of β-branched ketones was developed, based on the ruthenium-pincer-catalyzed α-alkylation of ketones using secondary alcohols as alkylating agents. Contrary to previously reported procedures, this strategy can make use of unsubstituted and non-hindered acetophenone derivatives as coupling partners for a variety of secondary alcohols. Importantly, this methodology is highly atom economical and environmentally friendly, with the formation of water as the only byproduct.

2.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under the nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed under nitrogen in an MBRAUN glovebox. The compound Ru-MACHO [Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl) ethyl]amino}ethyl]amino}ruthenium(II)] (complex **9**) was purchased from Sigma-Aldrich and stored inside the glovebox. Ketones and secondary alcohols were purchased from Acros, Sigma-Aldrich, Alfa-Aesar and Himedia Chemicals, and used without further purification. Solvents were dried according to standard procedures. Infrared (IR) spectra were recorded on Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF-Q II spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ions $[M+Na]^+$, $[M+H]^+$ or $[M]^+$. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on Bruker AV-700 (^1H at 700 MHz, ^{13}C at 175 MHz) and Bruker AV-400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) spectrometers at 25 °C. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS; δ 0.00 ppm). ^1H NMR chemical shifts are referenced to the ^1H resonance of TMS present in solution, and ^{13}C NMR chemical shifts are referenced to the ^{13}C resonance of $CDCl_3$ (δ 77.160 ppm). Coupling

constants are reported in Hertz (Hz). Abbreviations used in the description of NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartet of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of the ^{13}C NMR peaks was done based on a one-dimensional dept-135 NMR experiment.

GC Method: GC data were obtained using a gas chromatograph equipped with an SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320°C; 320°C, 7 min. The response factor for all of the necessary compounds was calculated from the average of three independent GC runs, using mesitylene as an internal standard.

General Optimization Procedure for the α-Alkylation of Acetophenone Using Cyclohexanol: A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01-0.005 mmol), base (2-0.02 mmol), acetophenone (0.5 mmol), cyclohexanol (1-0.6 mmol) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was heated to 125 °C (oil bath temperature), and stirred at this temperature for 24 h in an open system under a gentle flow of argon. The completion of the reaction was determined by GC analysis. After cooling the reaction mixture to room temperature, 0.5 mmol of mesitylene (internal standard) was added and the conversion of acetophenone was calculated, based on GC analysis. Subsequently, the solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography over silica gel (100-200 mesh), using an ethyl acetate/hexane mixture (2:98) as the eluent. Yields were calculated for isolated pure products.

Procedure for 1 mmol Scale α-Alkylation of Acetophenone Using Cyclohexanol:

A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01 mmol), base (0.05 mmol), acetophenone (1 mmol), cyclohexanol (1.2 mmol) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was heated to 125 °C (oil bath temperature), and stirred at this temperature for 24 h in an open system under a gentle flow of argon. The completion of the reaction was determined by GC analysis. After cooling the reaction mixture to room temperature, 1 mmol of mesitylene (internal standard) was added and the conversion of acetophenone was calculated, based on GC analysis. Subsequently, the solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography over silica gel (100-200 mesh), using an ethyl acetate/hexane mixture (2:98) as the eluent. This procedure provided product **2.2a** in 75 % yield (151 mg).

General Procedure for the α-Alkylation of Acetophenone Using Secondary Alcohols:

A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01 mmol), KO^{t}Bu (0.05 mmol), acetophenone (0.5 mmol), secondary alcohol (0.6 mmol) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was heated to 125 °C (oil bath temperature), and stirred at this temperature for 24 h in an open system under a gentle flow of argon. The completion of the reaction was determined by GC analysis. After cooling the reaction mixture to room temperature, 0.5 mmol of mesitylene (internal standard) was added, and the conversion of acetophenone was calculated, based on GC analysis. Subsequently, the solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography over silica gel (100-200 mesh), using an ethyl acetate/hexane mixture (2 : 9 8) as the eluent. Yields were calculated for isolated pure products.

General Procedure for the α-Alkylation of Ketones Using Secondary Alcohols:

A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01 mmol), base (0.05 mmol), ketone (0.5 mmol), secondary alcohol (0.6 mmol) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was refluxed (oil bath temperature at 125 °C) with stirring for 24 h in an open system under a gentle flow of argon. The completion of the reaction was determined by GC analysis. After cooling the reaction mixture to room temperature, 0.5 mmol of mesitylene (internal standard) was added and the conversion of the ketone was calculated, based on GC analysis. Subsequently, the solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography over silica gel (100-200 mesh), using an ethyl acetate/hexane mixture (2 : 9 8) as the eluent. Yields were calculated for isolated pure products. Product-induced diastereoselectivity was observed, and the diastereomeric ratios (d.r) of the products were determined by ^{1}H NMR analysis of the crude reaction mixture. Upon isolation, the α-alkylated products were obtained as a mixture of diastereomers and the diastereomeric signals in the ^{1}H and ^{13}C NMR spectra were assigned on the basis of previous reports.[1]

Procedure for the Kinetic Analysis of the α-Alkylation of Acetophenone Using Cyclohexanol:

A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01 mmol), base (0.05 mmol), acetophenone (0.5 mmol), cyclohexanol (0.6 mmol), mesitylene (0.5 mmol, internal standard) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was heated to 125 °C (oil bath temperature), and stirred at this temperature in an open system under a gentle flow of argon. The composition of the reaction mixture was analyzed by GC every 1 h for the first 4 h, and then every 4 h for remaining 20 h of the catalytic reaction time. The consumption

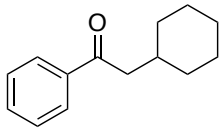
of acetophenone was corroborated by the increasing concentration of the α-alkylated product **2.2a**. The kinetic data obtained in this experiment indicate that the reaction follows a first-order rate law with respect to acetophenone consumption. The first order rate law is calculated using equation 1.

$\ln[A] = -kt + \ln[A_0]$…….equation (1).

[A] = concentration of product **2.2a**, [A_0] = concentration of acetophenone

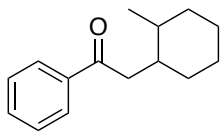
Experimental Data for the α-Alkylated Products:

2-Cyclohexyl-1-phenylethanone (2.2a):[11] Purified by silica gel column chromatography



using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 87 mg, 80% (for 0.5 mmol scale) and 151 mg, 75% (for 1 mmol scale). IR (DCM; cm^{-1}): 3052, 2987, 2853, 1672, 1447, 1267, 1047, 895, 747. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H, ArC*H*), 7.46 (tt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArC*H*), 7.37 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H, ArC*H*), 2.73 (d, J = 6.8 Hz, 2H, COCH_2), 1.85-1.94 (m, 1H, C*H*), 1.56 -1.70 (m, 5H, CH_2), 1.19 (qt, J_1 = 12.8 Hz, J_2 = 2.8 Hz, 2H, CH_2), 1.02-1.10 (m, 1H, CH_2), 0.92 (qd, J_1 = 12.8 Hz, J_2 = 2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.3, 137.6, 132.9, 128.6, 128.2, 46.3, 34.6, 33.5, 26.3, 26.2. HRMS (ESI): m/z calcd for $C_{14}H_{19}O$ $(M+H)^+$: 203.1430, found: 203.1429.

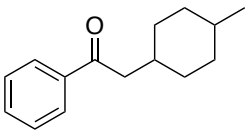
2-(2-Methylcyclohexyl)-1-phenylethan-1-one (2.2b): Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 43 mg, 40%. ^1H NMR analysis of the crude mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.76 (d, J =7.2 Hz, 2H, COCH_2, major product), 2.55 (d, J = 6.5 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3054, 2923, 2853, 1686, 1597, 1461, 1283, 739, 690. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 -7.89 (m, 2H, ArC*H*), 7.47 (d, J = 7.4

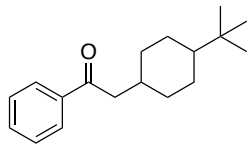
Hz, 1H, ArC*H*), 7.38 (t, *J* = 7.6 Hz, 2H, ArC*H*), 2.66 (ddd, J_1 = 24.4 Hz, J_2 = 12.5 Hz, J_3 = 7.3 Hz, 2H, COCH_2), 2.20 (ddd, J_1 = 8.1 Hz , J_2 = 6.1 Hz, J_3 = 3.4 Hz, 1H, C*H*), 1.11-1.66 (m, 9H, CH_2), 0.84 (d, *J* = 7.1 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.8, 136.6, 131.9, 127.6, 127.2, 42.8, 39.7, 36.8, 35.5, 31.9, 31.3, 27.2, 25.4, 23.5, 21.4, 19.6, 14.1. HRMS (ESI): m/z calcd for $C_{15}H_{20}ONa$ $(M+Na)^+$: 239.1406, found: 239.1398.

2-(4-Methylcyclohexyl)-1-phenylethan-1-one (2.2c): Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 64 mg, 60%. ^1H NMR analysis of the crude mixture showed a d.r. of 82:18, as determined by comparison of the following signals: δ 2.85 (d, *J* =7.2 Hz, 2H, COCH_2, major product), 2.75 (d, *J* =6.5 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3058, 2920, 2850, 1681, 1597, 1447, 1284, 739, 690. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 -7.91 (m, 2H, ArC*H*), 7.48 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.39 (t, *J* = 7.6 Hz, 2H, ArC*H*), 2.80 (dd, J_1= 41.8 Hz, J_2 = 6.9 Hz, 2H, COCH_2), 2.14 (ddd, J_1 = 10.8, J_2 = 7.1 Hz , J_3 = 3.9 Hz, 1H, C*H*), 1.15 -1.64 (m, 9H, C*H*&CH_2), 0.78 - 0.88 (m, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.6, 137.6, 132.9, 128.6, 128.2, 46.3, 43.4, 35.1, 34.5, 33.5, 32.6, 32.0, 30.8, 30.0, 29.0, 22.7, 20.3. HRMS (ESI): m/z calcd for $C_{15}H_{20}ONa$ $(M+Na)^+$: 239.1406, found: 239.1410.

2-(4-(*tert*-Butyl)cyclohexyl)-1-phenylethanone (2.2d):[11] Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 100 mg, 78%. ^1H NMR analysis of the crude mixture showed a d.r. of 86:14, as determined by comparison of the following signals: δ 2.91 (d, *J* = 7.2 Hz, 2H, COCH_2, major product), 2.73 (d, *J* = 6.5 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3052, 2984, 2863, 1674, 1419, 1262, 895, 749. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87-7.90 (m,

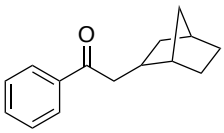
2H, ArC*H*), 7.45-7.49 (m, 1H, ArC*H*), 7.36-7.40 (m, 2H, ArC*H*), 2.91 (d, *J* = 7.2 Hz, 2H, COCH_2, major product), 2.73 (d, *J* = 6.5 Hz, 2H, COCH_2, minor product), 2.35-2.38 (m, 1H, C*H*), 1.58-1.61 (m, 2H, CH_2), 1.42-1.51 (m, 4H, CH_2), 1.05-1.15 (m, 2H, CH_2), 0.88-0.94 (m, 1H, C*H*), 0.78 (s, 9H, 3×CH_3, major product), 0.75 (s, 9H, 3×CH_3, minor product). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.7, 137.5, 132.9, 128.6, 128.2, 48.4, 47.9, 46.2, 40.4, 34.8, 33.9, 32.6, 32.5, 30.8, 29.2, 27.6, 27.6, 27.2, 22.0. HRMS (ESI): m/z calcd for $C_{18}H_{27}O$ $(M+H)^+$: 259.2056, found: 259.2074.

1-Phenyl-2-(4-phenylcyclohexyl)ethan-1-one (2.2e): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield 119 mg, 86%. ^1H NMR analysis of the crude mixture showed a d.r. of 84:16, as determined by comparison of the following signals: δ 2.82 (d, *J* =7.2 Hz, 2H, COCH_2, major product), 2.54 (d, *J* =6.5 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3058, 3025, 2923, 2852, 1685, 1448, 1265, 1012, 954, 750. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.49 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.40 (t, *J* = 7.6 Hz, 2H, ArC*H*), 7.16-7.29 (m, 4H, ArC*H*), 7.12 (t, *J* = 7.0 Hz, 1H, ArC*H*), 2.91 (d, *J* = 7.06 Hz, 6.9 Hz, 2H, COCH_2), 2.51-2.60 1H, C*H*), 2.42 (dt, J_1 = 16.9 Hz, J_2 = 8.3 Hz, 1H, C*H*), 1.59-1.74 (m, 7H, CH_2), 1.40-1.55 (m, 1H, CH_2). ^{13}C $\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.4, 146.5, 146.1, 136.5, 132.0, 127.7, 127.4, 127.2, 126.0, 124.9, 45.1, 43.3, 42.1, 40.3, 33.2, 33.1, 32.7, 29.3, 28.7, 28.8, 28.1. HRMS (ESI): m/z calcd for $C_{20}H_{22}ONa$ $(M+Na)^+$: 301.1563, found: 301.1553.

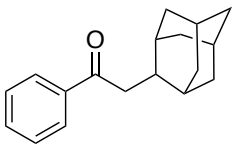
2-Cycloheptyl-1-phenylethanone (2.2f):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 64.8 mg, 60%. IR (DCM; cm^{-1}): 3057, 2923, 2852, 1682, 1460, 1264, 799, 739. ^1H NMR (400

MHz, $CDCl_3$): δ 7.86 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H, ArC*H*), 7.46 (tt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArC*H*), 7.37 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H, ArC*H*), 2.73 (d, J = 6.8 Hz, 2H, COCH_2), 2.14 (m, 1H, C*H*), 1.68 (dd, J_1 = 9.6 Hz, J_2 = 5.8 Hz, 2H, CH_2), 1.60 (m, 4H, CH_2), 1.41 (dd, J_1 = 15.4 Hz, J_2 = 17.0 Hz, 4H, CH_2), 1.20 (dd, J_1 = 21.7 Hz, J_2 = 9.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.5, 136.6, 131.9, 127.6, 127.2, 45.9, 35.1, 34.0, 27.4, 25.4. HRMS (ESI): m/z calcd for $C_{15}H_{20}ONa$ $(M+Na)^+$: 239.1406, found: 239.1409.

2-(Bicyclo[2.2.1]heptan-2-yl)-1-phenylethan-1-one (2.2g):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 80 mg, 75%. IR (DCM; cm^{-1}): 3026, 2950, 2869, 1684, 1597, 1265, 1001, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87-7.89 (m, 2H, ArC*H*), 7.47 (t, J = 7.3 Hz, 1H, ArC*H*), 7.38 (t, J = 7.5 Hz, 2H, ArC*H*), 2.92 (ddd, J_1 = 24.6 Hz, J_2 = 16.4 Hz, J_3 = 7.3 Hz, 2H, COCH_2), 2.31-2.33 (m, 1H, C*H*), 2.13 (d, J = 13.1 Hz, 2H, CH_2), 1.79-1.87 (m, 1H, C*H*), 1.41-1.50 (m, 2H, CH_2), 1.29-1.33 (m, 2H, CH_2), 1.22 (dd, J_1 = 9.4 Hz, J_2 = 1.8 Hz, 1H, C*H*), 1.06 (ddd, J_1 = 11.4 Hz, J_2 = 6.7 Hz, J_3 = 2.4 Hz, 1H, CH_2), 0.62 (ddd, J_1 = 12.3 Hz, J_2 = 5.2 Hz, J_3 = 2.3 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.6, 137.4, 132.9, 128.6, 128.1, 42.0, 40.4, 39.9, 37.2, 37.1, 35.9, 30.2, 23.0. HRMS (ESI): m/z calcd for $C_{15}H_{19}O$ $(M+H)^+$: 215.1436, found: 215.1440.

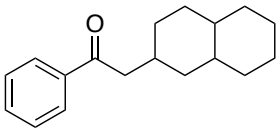


2-(Adamantan-2-yl)1-phenylethan-1-one (2.2h): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 51 mg, 40%. IR (DCM; cm^{-1}): 3054, 2907, 2851, 1686, 1447, 1264, 739, 690. ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.94 (m, 2H, Ar*CH*), 7.44-7.50 (m, 1H, Ar*CH*), 7.38 (dd, J = 8.3 Hz, 6.9 Hz, 2H, Ar*CH*), 3.01 (d, J = 7.0 Hz, 2H, COCH_2),

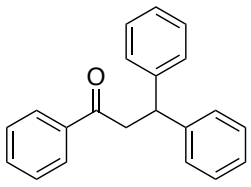


2.36 (t, *J* = 7.3 Hz, 1H, C*H*), 1.87 (d, *J* = 13.0 Hz, 2H, CH_2 &C*H*), 1.71-1.83 (m, 6H, CH_2&C*H*), 1.67 (t, *J* = 3.2 Hz, 4H, CH_2&C*H*), 1.47-1.56 (m, 2H, CH_2&C*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 200.6, 137.7, 132.9, 128.7, 128.2, 42.1, 40.8, 39.2, 38.4, 32.3, 32.0, 28.1, 28.1. HRMS (ESI): m/z calcd for $C_{18}H_{22}ONa$ $(M+Na)^+$: 277.1563, found: 277.1559.

2-(Decahydronaphthalen-2-yl)-1-phenylethan-1-one (2.2i): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 95 mg, 74%. IR (DCM; cm^{-1}): 3056, 2919, 2852, 1685, 1597, 1448, 1376, 1264, 1215, 1179, 739, 690. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 11.9, 6.4 Hz, 2H, Ar*CH*), 7.48 (t, *J* = 7.3 Hz, 1H, Ar*CH*), 7.38 (t, *J* = 7.3 Hz, 2H, Ar*CH*), 2.68-3.03 (m, 2H, COCH_2), 1.87-2.14 (m, 1H, C*H*), 1.01-1.75 (m, 16H, CH_2&C*H*). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 200.5, 200.3, 200.3, 137.5, 137.5, 132.9, 132.8, 128.5, 128.2, 128.1, 46.4, 43.7, 41.1, 38.0, 37.7, 35.9, 35.9, 35.5, 35.3, 34.2, 34.0, 32.7, 32.3, 32.2, 30.2, 29.9, 29.1, 28.8, 27.8, 27.0, 26.7, 26.7, 25.8, 25.7, 20.9. HRMS (ESI): m/z calcd for $C_{18}H_{24}ONa$ $(M+Na)^+$: 257.1900, found: 257.1898.

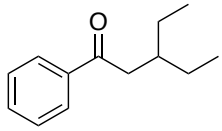


1,3,3-Triphenylpropan-1-one (2.2j):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 97 mg, 68%. IR (DCM; cm^{-1}): 3058, 3028, 2926, 1687, 1597, 1494, 1449, 1363, 1264, 1205, 983, 737. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, J_1 = 7.8 Hz, J_2 = 0.5 Hz, 2H, ArC*H*), 7.44 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.33 (t, *J* = 7.6 Hz, 2H, ArC*H*), 7.18 (d, *J* = 4.4 Hz, 8H, ArC*H*), 7.08 (dd, J_1 = 8.5 Hz, J_2 = 4.3 Hz, 2H, ArC*H*), 4.74 (t, *J* = 7.3 Hz, 1H, *C*H), 3.65 (d, *J* = 7.3 Hz, 2H, COCH_2). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 198.1, 144.2, 137.1, 133.1, 128.7, 128.6, 128.1, 127.9, 126.4, 46.0, 44.8. HRMS (ESI): m/z calcd for $C_{21}H_{18}ONa$

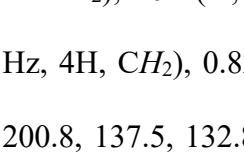


$(M+Na)^+$: 309.1250, found: 309.1226.

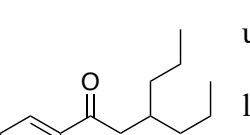
3-Ethyl-1-phenylpentan-1-one (2.2k): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 33 mg, 35%. IR (DCM; cm^{-1}): 2961, 2925, 2875, 1683, 1447, 1267, 747, 690. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.9 Hz, 2H, ArC*H*), 7.48 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.38 (t, *J* = 7.5 Hz, 2H, ArC*H*), 2.80 (d, *J* = 6.7 Hz, 2H, COCH_2), 1.92 (dt, J_1 = 12.8 Hz, J_2 = 6.4 Hz, 1H, C*H*), 1.31 (dq, J_1 = 14.4 Hz, J_2 = 7.1 Hz, 4H, CH_2), 0.82 (t, *J* = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.8, 137.5, 132.8, 128.5, 128,1, 42.6, 37.2, 26.0, 10.9. HRMS (ESI): m/z calcd for $C_{13}H_{18}ONa$ $(M+Na)^+$: 213.1250, found: 213.1254.



1-Phenyl-3-propylhexan-1-one (2.2l): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 38 mg, 35%. IR(DCM; cm^{-1}): 2956, 2926, 2871, 1686, 1681, 1448, 1266, 741, 690. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.4 Hz, 2H, Ar*CH*), 7.48 (t, *J* = 7.3 Hz, 1H, Ar*CH*), 7.38 (t, *J* = 7.5 Hz, 2H, Ar*CH*), 2.80 (d, *J* = 6.6 Hz, 2H, COCH_2), 2.07 (d, *J* = 18.4 Hz, 1H, C*H*), 1.13-1.32 (m, 8H, CH_2), 0.81 (t, *J* = 6.5 Hz, 6H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 199.9, 136.6, 131.9, 127.6, 127.2, 42.6, 35.6, 33.0, 18.9, 13.5. HRMS (ESI): m/z calcd for $C_{15}H_{22}ONa$ $(M+Na)^+$: 241.1563, found: 241.1563

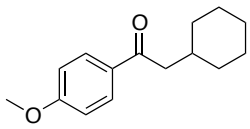


2-Cyclohexyl-1-(*p*-tolyl)ethanone (2.3a):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 92 mg, 80%. IR (DCM; cm^{-1}): 3051, 2923, 2851, 1675, 1605, 1447, 1264, 1005, 908, 736. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 2H, ArC*H*), 7.17 (d, *J* = 8 Hz, 2H, ArC*H*), 2.71 (d, *J* = 6.8 Hz, 2H, COCH_2), 2.33 (s, 3H, CH_3), 1.86-1.91 (m, 1H, C*H*), 1.56-1.69 (m, 5H, CH_2), 1.15-1.26



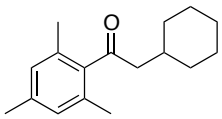
(m, 2H, CH_2), 1.02-1.11 (m, 1H, CH_2), 0.95 (qd, J_1 = 12.4 Hz, J_2 = 2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.1, 143.7, 135.1, 129.3, 128.4, 46.2, 34.8, 33.5, 26.3, 26.2, 21.7. HRMS (ESI): m/z calcd for $C_{15}H_{21}O$ $(M+H)^+$: 217.1587, found: 217.1579.

2-Cyclohexyl-1-(4-methoxyphenyl)ethanone (2.3b):[11] Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 101 mg, 84%. IR (DCM; cm^{-1}): 3052, 2985, 2851, 1667, 1427, 1264, 895, 704. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.84 (d, *J* = 8.8 Hz, 2H, ArC*H*), 3.78 (s, 3H, OCH_3), 2.68 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.84-1.92 (m, 1H, C*H*), 1.55-1.69 (m, 5H, CH_2), 1.06-1.25 (m, 3H, CH_2), 0.92 (qd, J_1 = 12.4 Hz, J_2 = 1.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.0, 163.4, 130.7, 130.5, 113.7, 55.5, 46.0, 34.9, 33.5, 26.3, 26.2. HRMS (ESI): m/z calcd for $C_{15}H_{21}O_2$ $(M+H)^+$: 233.1536, found: 233.1538.

2-Cyclohexyl-1-mesitylethanone (2.3c):[11] Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 73 mg, 63%. IR (DCM; cm^{-1}): 3052, 2924, 2852, 1696, 1609, 1447, 1265, 1034, 908, 736. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 2H, ArC*H*), 2.51 (d, *J* = 6.4 Hz, 2H, COCH_2), 2.19 (s, 3H, CH_3), 2.11 (s, 6H, CH_3), 1.92-2.00 (m, 1H, C*H*), 1.74 (d, *J* = 12 Hz, 2H, CH_2), 1.58-1.64 (m, 3H, CH_2), 1.18-1.34 (m, 3H, CH_2), 0.90 (qd, J_1 = 12 Hz, J_2 = 2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 210.2, 140.0, 138.2, 132.5, 128.6, 52.6, 33.4, 32.8, 26.4, 26.2, 21.1, 19.1. HRMS (ESI): m/z calcd for $C_{17}H_{24}ONa$ $(M+Na)^+$: 267.1719, found: 267.1708.

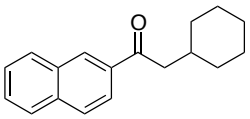
1-(4-Chlorophenyl)-2-cyclohexylethanone (2.3d):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 56 mg, 38%. IR (DCM; cm^{-1}): 3052, 2987, 2859, 1680, 1430, 1264, 1062, 897, 740, 707. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 13.3 Hz, 2H, ArC*H*), 7.35 (d, *J* = 13.3 Hz, 2H, ArC*H*), 2.71 (d, *J* = 11.9 Hz, 2H, COCH_2), 1.81-1.94 (m, 1H, C*H*), 1.53-1.69 (m, 5H, CH_2), 1.07-1.26 (m, 3H, CH_2), 0.93 (q, *J* = 21 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.1, 139.4, 135.9, 129.7, 128.9, 46.3, 34.6, 33.5, 26.3, 26.2. HRMS (ESI): m/z calcd for $C_{14}H_{18}ClO$ $(M+H)^+$: 237.1041, found: 237.1053.

2-Cyclohexyl-1-(pyridin-3-yl)ethanone (2.3e):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 73 mg, 68%. IR (DCM; cm^{-1}): 3051, 2984, 2851, 1686, 1445, 1265, 895, 704. ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (dd, J_1 = 2.4 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 8.69 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 1H, ArC*H*), 8.14 (dt, J_1 = 8 Hz, J_2 =2 Hz, 1H, ArC*H*), 7.34 (ddd, J_1 = 5.2 Hz, J_2 = 2.8 Hz, J_3 = 0.8 Hz, 1H, ArC*H*), 2.77 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.86-1.97 (m, 1H, C*H*), 1.57-1.72 (m, 5H, CH_2), 1.18-1.27 (m, 2H, CH_2), 1.07-1.15 (m, 1H, CH_2), 0.96 (qd, J_1 = 11.6 Hz, J_2 = 2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.1, 153.4, 149.8, 135.5, 132.7, 123.7, 46.6, 34.5, 33.5, 26.3, 26.2. HRMS (ESI): m/z calcd for $C_{13}H_{18}NO$ $(M+H)^+$: 204.1383, found: 204.1359.

1-(4-(Benzyloxy)phenyl)-2-cyclohexylethan-1-one (2.3f):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 120 mg, 80%. IR (DCM; cm^{-1}): 3056, 2983, 2929, 2853, 1733, 1669, 1599, 1241, 1046, 747. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.87 (m, 2H, ArC*H*), 7.26-7.36 (m, 5H,

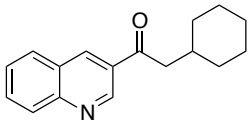
ArC*H*), 6.91-6.94 (m, 2H, ArC*H*), 5.05 (s, 2H, OCH_2), 2.68 (d, J = 6.8 Hz, 2H, COCH_2), 1.85-1.89 (m, 1H, C*H*), 1.51-1.68 (m, 5H, CH_2), 1.06-1.22 (m, 3H, CH_2), 0.92 (dd, J_1 = 23.8 Hz, J_2 = 11.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.0, 162.5, 136.3, 130.9, 130.5, 128.8, 128.3, 127.6, 114.6, 70.2, 46.0, 34.9, 33.6, 26.4, 26.3. HRMS (ESI): m/z calcd for $C_{21}H_{25}O_2$ $(M+H)^+$: 309.1849, found: 309.1845.

2-Cyclohexyl-1-(naphthalen-2-yl)ethanone (2.3g):[11] Purified by silica gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 108 mg, 86%. IR (DCM; cm^{-1}): 3062, 2925, 2853, 1676, 1627, 1468, 1265, 1003, 739. ^1H NMR (700 MHz, $CDCl_3$): δ 8.37 (s, 1H, ArC*H*), 7.94 (dd, J_1 = 9.1 Hz, J_2 = 1.4 Hz, 1H, ArC*H*), 7.88 (d, J = 8.4 Hz, 1H, ArC*H*), 7.79 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 2H, ArC*H*), 7.50 (td, J_1 = 8.4 Hz, J_2 = 0.7 Hz, 1H, ArC*H*), 7.46 (td, J_1 = 8.4 Hz, J_2 = 0.7 Hz, 1H, ArC*H*), 2.86 (d, J = 6.3 Hz, 2H, COCH_2), 1.94-1.98 (m, 1H, C*H*), 1.72 (d, J = 12.6 Hz, 2H, CH_2), 1.57-1.63 (m, 3H, CH_2), 1.21 (qt, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 2H, CH_2), 1.09 (qt, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 1H, CH_2), 0.98 (qd, J_1 = 11.9 Hz, J_2 = 3.5 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 200.4, 135.6, 134.9, 132.6, 129.8, 129.6, 128.4, 128.4, 127.8, 126.8, 124.1, 46.4, 34.8, 33.6, 26.4, 26.3. HRMS (ESI): m/z calcd for $C_{18}H_{21}O$ $(M+H)^+$: 253.1587, found: 253.1591.

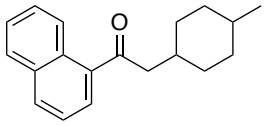
2-Cyclohexyl-1-(quinolin-3-yl)ethanone (2.3h):[11] Purified by silica gel column



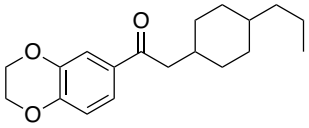
chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 104 mg, 84%. IR (DCM; cm^{-1}): 3053, 2926, 2853, 1684, 1618, 1420, 1265, 1027, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H, ArC*H*), 8.64 (s, 1H, ArC*H*), 8.10 (d, J = 8.4 Hz, 1H, ArC*H*), 7.89 (d, J = 8 Hz, 1H, ArC*H*), 7.77 (t, J = 8.4 Hz, 1H, ArC*H*), 7.56 (t, J = 7.2 Hz, 1H, ArC*H*), 2.88 (d, J = 6.8 Hz, 2H, COCH_2), 1.90-2.02 (m, 1H, C*H*), 1.59-1.75 (m, 5H, CH_2), 1.09-1.28 (m,

3H, CH_2), 1.00 (q, J = 12 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.1, 149.8, 149.4, 137.1, 132.0, 129.7, 129.5, 129.4, 127.6, 127.0, 46.6, 34.6, 33.5, 26.3, 26.2. HRMS (ESI): m/z calcd for $C_{17}H_{20}NO$ $(M+H)^+$: 254.1539, found: 254.1542.

2-(4-Methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (2.3i):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 119 mg, 90%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.92 (d, J = 7.1 Hz, 2H, COCH_2, major product), 2.82 (d, J = 6.9 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3052, 2985, 2851, 1684, 1435, 1264, 895, 729, 703. ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J = 8.3 Hz, 1H, ArCH), 7.86 (d, J = 8.2 Hz, 1H, ArCH), 7.71-7.78 (m, 2H, ArCH), 7.37-7.50 (m, 3H, ArCH), 2.92 (d, J = 7.1 Hz, 2H, COCH_2, major product), 2.82 (d, J = 6.9 Hz, 2H, COCH_2, minor product), 2.14-2.20 (m, 1H, CH), 1.39-1.53 (m, 7H, CH&CH_2), 1.13-1.25 (m, 2H, CH_2), 0.83 (d, J = 6.8 Hz, 3H, CH_3, major product), 0.77 (d, J = 6.5 Hz, 3H, CH_3, minor product). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): (Mixture of diastereomers) δ 205.1, 137.0, 134.1, 132.3, 130.2, 128.5, 127.8, 127.2, 126.5, 125.8, 124.4, 50.0, 47.1, 35.1, 34.8, 33.4, 32.6, 32.3, 30.8, 30.0, 29.0, 22.7, 20.3. HRMS (ESI): m/z calcd for $C_{19}H_{23}O$ $(M+H)^+$: 267.1743, found: 267.1724.

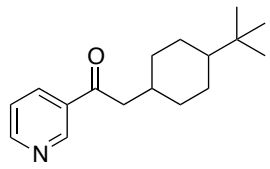


1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-(4-propylcyclohexyl)ethan-1-one (2.3j): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield 93 mg, 62%. ^1H NMR analysis of the crude mixture showed a d.r. of 82:18, as determined by comparison of the following signals: δ 2.74 (d, J =7.2 Hz, 2H, COCH_2, major product), 2.64 (d, J =6.5 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 2955, 2923, 2852, 1674, 1605, 1581, 1505, 1428, 1319, 1291, 1258,



1067, 896, 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 2H, Ar*CH*), 6.82 (d, *J* = 9.0 Hz, 1H, Ar*CH*), 4.19-4.24 (m, 4H, CH_2), 2.69 (dd, J_1 = 38.7 Hz, J_2 = 6.9 Hz, 2H, COCH_2), 1.75-2.16 (m, 1H, *CH*), 0.86-1.48 (m, 13H, CH_2&CH_3), 0.81 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): (Mixture of diastereomers) δ 199.0, 147.9, 143.3, 131.4, 122.3, 117.7, 117.2, 64.7, 64.2, 46.0, 43.1, 39.7, 37.2, 36.6, 35.1, 34.8, 33.4, 33.0, 32.5, 29.1, 28.9, 20.4, 20.0, 14.4. HRMS (ESI): m/z calcd for $C_{19}H_{27}O_3$ $(M+H)^+$: 303.1955, found: 303.1948.

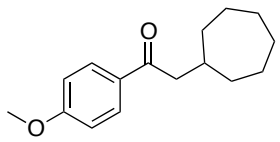
2-(4-(*tert*-Butyl)cyclohexyl)-1-(pyridin-3-yl)ethanone (2.3k):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (10:90) mixture as the eluent. Colorless liquid. Yield: 116 mg, 78%. ^{1}H NMR analysis of the crude mixture showed a d.r. of 90:10, as determined by comparison of the following signals: δ 2.94 (d, *J* = 7.1 Hz, 2H, COCH_2, major product), 2.76 (d, *J* = 6.4 Hz, 2H, COCH_2, minor product). IR (DCM; cm^{-1}): 3052, 2942, 2865, 1684, 1419, 1264, 1003, 895, 737. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H, ArC*H*), 8.70 (d, *J* = 4.2 Hz, 1H, ArC*H*), 8.16 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.34-7.37 (m, 1H, ArC*H*), 2.94 (d, *J* = 7.1 Hz, 2H, COCH_2, major product), 2.76 (d, *J* = 6.4 Hz, 2H, COCH_2, minor product), 2.31-2.44 (m, 1H, C*H*), 1.69-1.78 (m, 1H, C*H*), 1.45-1.62 (m, 6H, CH_2), 1.04-1.14 (m, 2H, CH_2), 0.90-0.99 (m, 2H, CH_2), 0.79 (s, 9H, 3×CH_3, major product), 0.77 (s, 9H, 3×CH_3, minor product). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): (Mixture of diastereomers) δ 199.4, 153.4, 149.8, 135.5, 132.6, 123.7, 48.3, 47.3, 46.5, 40.8, 36.2, 34.6, 33.9, 32.6, 30.8, 29.1, 27.7, 27.6, 25.7, 22.0. HRMS (ESI): m/z calcd for $C_{17}H_{26}NO$ $(M+H)^+$: 260.2009, found: 260.1996



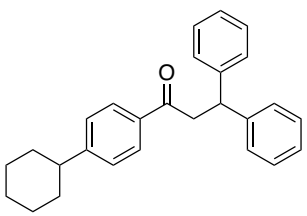
2-(4-Phenylcyclohexyl)-1-(*p*-tolyl)ethanone (2.3l):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 120 mg, 82%. ^{1}H NMR analysis of the crude mixture showed a d.r. of

83:17, as determined by comparison of the following signals: δ 2.95 (d, *J* = 7.1 Hz, 2H, COC*H*$_2$, major product), 2.78 (d, *J* = 6.7 Hz, 2H, COC*H*$_2$, minor product). IR (DCM; cm^{-1}): 3052, 2984, 2855, 1680, 1436, 1264, 1045, 895, 753. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H, ArC*H*), 7.16-7.22 (m, 5H, ArC*H*), 7.09-7.12 (m, 2H, ArC*H*), 2.95 (d, *J* = 7.1 Hz, 2H, COC*H*$_2$, major product), 2.78 (d, *J* = 6.7 Hz, 2H, COC*H*$_2$, minor product), 2.49-2.57 (m, 1H, C*H*$_2$), 2.37-2.44 (m, 1H, C*H*), 2.33 (s, 3H, C*H*$_3$), 1.80-1.86 (m, 1H, C*H*), 1.66-1.71 (m, 4H, C*H*$_2$), 1.59-1.64 (m, 3H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): (Mixture of diastereomers) δ 200.0, 147.1, 143.7, 135.1, 129.4, 128.4, 128.4, 127.0, 125.9, 46.0, 44.3, 43.1, 41.2, 34.4, 34.1, 33.7, 30.3, 29.9, 29.8, 29.1, 21.7. HRMS (ESI): m/z calcd for $C_{21}H_{25}O$ $(M+H)^+$: 293.1900, found: 293.1906.

2-Cycloheptyl-1-(4-methoxyphenyl)ethanone (2.3m):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 83 mg, 68%. IR (DCM; cm^{-1}): 3051, 2983, 2964, 1675, 1455, 1257, 1028, 895, 733. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.85 (d, *J* = 8.8 Hz, 2H, ArC*H*), 3.79 (s, 3H, OC*H*$_3$), 2.74 (d, *J* = 6.9 Hz, 2H, COC*H*$_2$), 2.10-2.17 (m, 1H, C*H*), 1.65-1.69 (m, 2H, C*H*$_2$), 1.52-1.61 (m, 4H, C*H*$_2$), 1.37-1.46 (m, 4H, C*H*$_2$), 1.15-1.23 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 199.1, 163.4, 130.7, 130.5, 113.7, 55.5, 46.6, 36.4, 35.0, 28.4, 26.4. HRMS (ESI): m/z calcd for $C_{16}H_{23}O_2$ $(M+H)^+$: 247.1693, found: 247.1696.

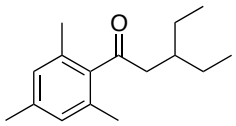


1-(4-Cyclohexylphenyl)-3,3-diphenylpropan-1-one (2.3n): Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield 118 mg, 64% IR (DCM; cm^{-1}): 3083, 3053, 3025, 3001, 2923, 2850, 1676, 1604, 1493, 1448, 1319, 1264, 1053, 1002, 826, 738, 695. ^{1}H

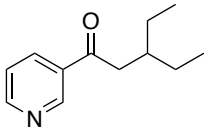


NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H, Ar*CH*), 7.17 (d, *J* = 4.8 Hz, 10H, Ar*CH*), 7.07 (dd, J_1 = 4.6 Hz, J_2 = 2.8 Hz, 2H, Ar*CH*), 4.75 (t, *J* = 7.3 Hz, 1H, C*H*), 3.63 (d, *J* = 7.3 Hz, 2H COCH_2), 2.46 (dd, J_1 = 11.1 Hz, J_2 = 8.7 Hz, 1H C*H*), 1.77 (m, 4H, CH_2), 1.18-1.35 (m, 6H, CH_2) $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 197.6, 153.8, 144.4, 135.0, 128.6, 128.4, 127.9, 127.1, 126.4, 45.9, 44.7, 44.7, 34.2, 26.8, 26.1. HRMS (ESI): m/z calcd for $C_{27}H_{28}ONa$ $(M+Na)^+$: 391.2032, found: 391.2016.

3-Ethyl-1-mesitylpentan-1-one (2.3o):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 112 mg, 97%. IR (DCM; cm^{-1}): 2962, 2921, 2875, 1700, 1611, 1458, 1400, 1378, 1003, 850. ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H, ArC*H*), 2.56 (d, *J* = 6.3 Hz, 2H, COCH_2), 2.20 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 1.88-1.92 (m, 1H, C*H*), 1.27-1.39 (m, 4H, CH_2), 0.81 (t, *J* = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 210.5, 140.1, 138.2, 132.5, 128.6, 49.0, 35.5, 25.7, 21.1, 19.2, 10.9. HRMS (ESI): m/z calcd for $C_{16}H_{25}O$ $(M+H)^+$: 233.1905, found: 233.1909.



3-Ethyl-1-(pyridin-3-yl)pentan-1-one (2.3p):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 57 mg, 60%. IR (DCM; cm^{-1}): 2963, 2932, 2875, 1733, 1457, 1265, 1045, 739. ^1H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H, ArC*H*), 8.70 (d, *J* = 4.5 Hz, 1H, ArC*H*), 8.16 (dd, J_1 = 8.0 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 7.35 (dd, J_1 =7.9 Hz, J_2 = 4.8 Hz, 1H, ArC*H*), 2.82 (d, *J* = 6.7 Hz, 2H, COCH_2), 1.89-1.96 (m, 1H, C*H*), 1.27-1.35 (m, 4H, CH_2), 0.83 (t, *J* = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.6, 153.3, 149.7, 135.6, 132.7, 123.8, 43.1, 37.2, 26.1, 11.0. HRMS (ESI): m/z calcd for $C_{12}H_{18}NO$ $(M+H)^+$: 192.1383, found: 192.1381.



3-Methyl-1-(2,4,6-trimethoxyphenyl)pentan-1-one (2.3q):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (20:80) mixture as the eluent. Pale yellow liquid. Yield: 47 mg, 35%. IR (DCM; cm^{-1}): 2960, 2839, 1697, 1605, 1461, 1438, 1414, 1335, 1226, 115, 813, 735. ^1H NMR (400 MHz, $CDCl_3$): δ 6.02 (s, 2H, ArC*H*), 3.74 (s, 3H, OCH_3), 3.70 (s, 6H, OCH_3), 2.67 (dd, J_1 =16.3 Hz, J_2 = 5.6 Hz, 1H, COCH_2), 2.46 (dd, J_1 = 16.3 Hz, J_2 = 8.1 Hz, 1H, COCH_2), 1.87-1.94 (m, 1H, C*H*), 1.14-1.31 (m, 2H, CH_2), 0.78-0.86 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 204.7, 162.1, 158.2, 114.1, 90.7, 55.8, 55.5, 52.2, 31.7, 31.0, 29.6, 19.5, 11.4. HRMS (ESI): m/z calcd for $C_{15}H_{22}O_4Na$ $(M+Na)^+$: 289.1410, found: 289.1392.

1-Mesityl-3-methylbutan-1-one (2.3r):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (20:80) mixture as the eluent. Colorless liquid. Yield: 83 mg, 82%. IR (DCM; cm^{-1}): 2958, 2926, 2871, 1696, 1610, 1467, 1265, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 2H, ArC*H*), 2.52 (d, *J* = 6.6 Hz, 2H, COCH_2), 2.19-2.29 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 0.93 (d, *J* = 6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 210.2, 139.9, 138.2, 132.6, 128.6, 53.8, 23.7, 22.8, 21.1, 19.2. HRMS (ESI): m/z calcd for $C_{14}H_{21}O$ $(M+H)^+$: 205.1592, found: 205.1602.

2-(Adamantan-2-ylidene)-1-mesitylethan-1-one (2.4a):[11] Purified by silica gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless solid. Yield: 90%. IR (DCM; cm^{-1}): 3049, 2982, 2851, 1662, 1435, 1264, 1047, 895, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 2H, ArC*H*), 6.04 (s, 1H, olefinic-C*H*), 3.46-3.57 (m, 1H, C*H*), 2.30-2.37 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.14 (s, 6H, ArCH_3), 1.69-1.93 (m, 14H, C*H*&CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 200.7, 171.3, 140.7, 137.9, 133.1, 128.5, 120.1, 41.9, 40.4, 39.5,

36.9, 33.3, 28.0, 21.1, 19.3. HRMS (ESI): m/z calcd for $C_{21}H_{27}O$ $(M+H)^+$: 295.2056, found: 295.2061.

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Figure 2.2 ^{1}H NMR Spectrum of **2.4a**

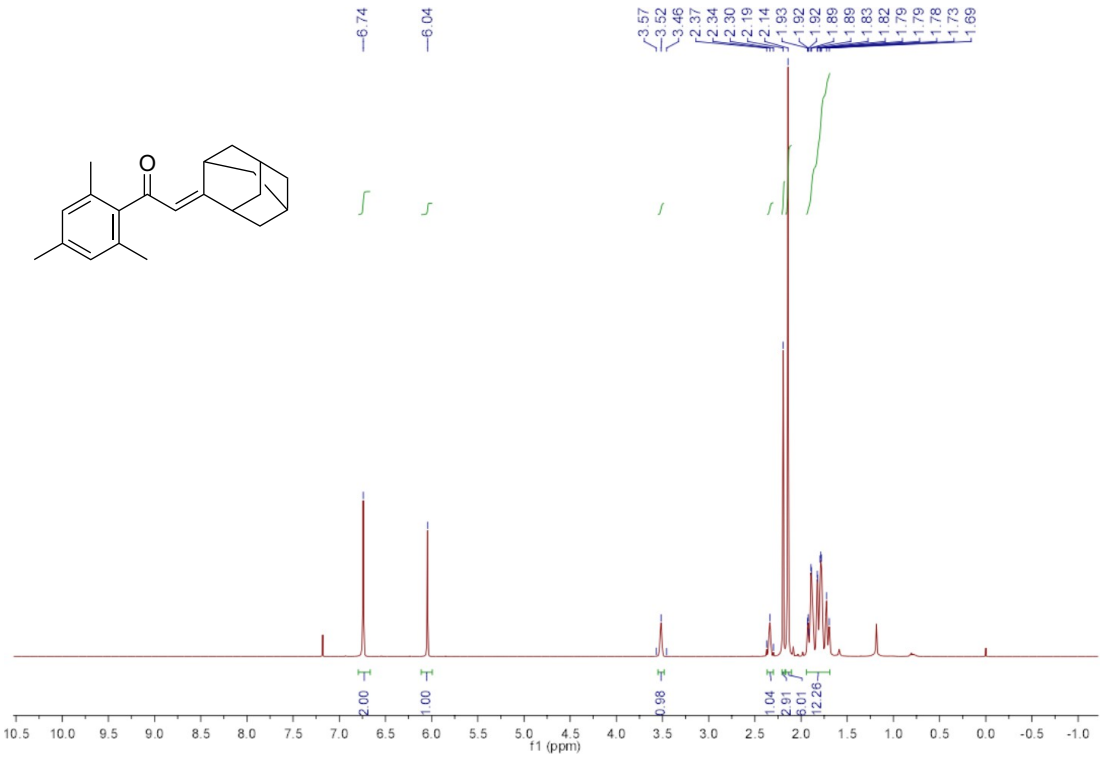
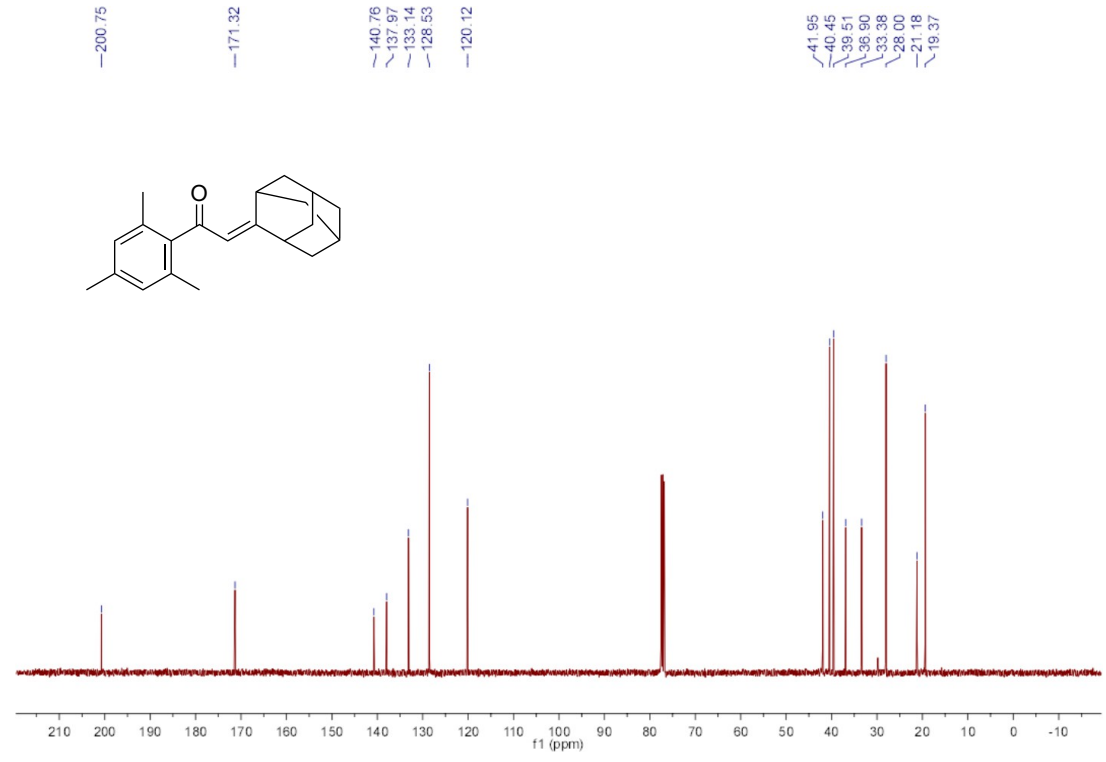


Figure 2.3 ^{13}C{^{1}H} NMR Spectrum of **2.4a**



Procedure for Deuterium Labeling in the Mechanistic Study of the α-Alkylation of Ketones Using Secondary Alcohols:

A Schlenk flask (25 mL) was loaded with a magnetic stirring bar, catalyst **9** (0.01 mmol), base (0.05 mmol), 4-methoxyacetophenone (0.5 mmol, 1 equiv), α,β-deuterated 4-*tert*-butylcyclohexanol (0.6 mmol, 1.2 equiv) and toluene (1.5 mL) under a nitrogen atmosphere in a glovebox. The flask was then taken out of the glovebox, equipped with a condenser, and the solution was heated to 125 °C (oil bath temperature), and stirred at this temperature for 24 h in an open system under a gentle flow of argon. The completion of the reaction was determined by GC analysis. After cooling the reaction mixture to room temperature, 0.5 mmol of mesitylene (internal standard) was added and the conversion of 4-methoxyacetophenone was calculated, based on GC analysis. Subsequently, the solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography over silica gel (100-200 mesh) using an ethyl acetate/petroleum ether mixture (2:98) as the eluent. The deuterated product **2.4b** was isolated in 74% yield.

Figure 2.4 ^{1}H NMR Spectrum of **2.4b**

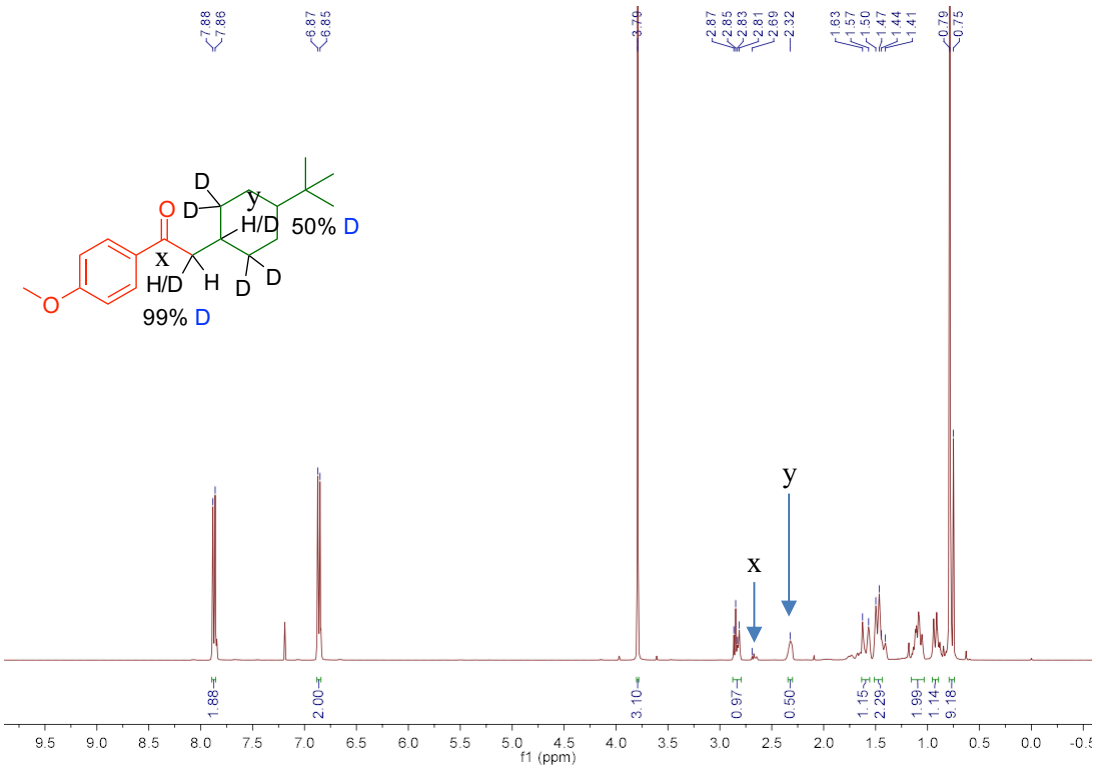


Figure 2.5 ^{13}C{^{1}H} NMR Spectrum of **2.4b**

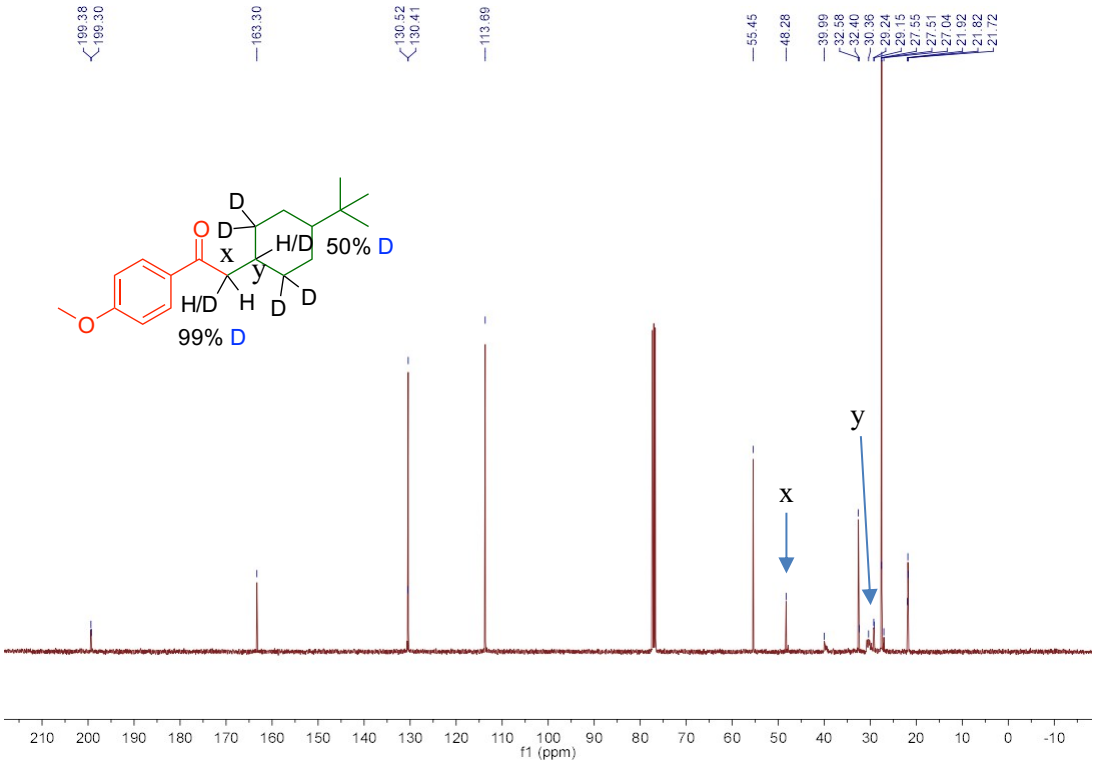


Figure 2.6 ^{2}H NMR Spectrum of **2.4b:**

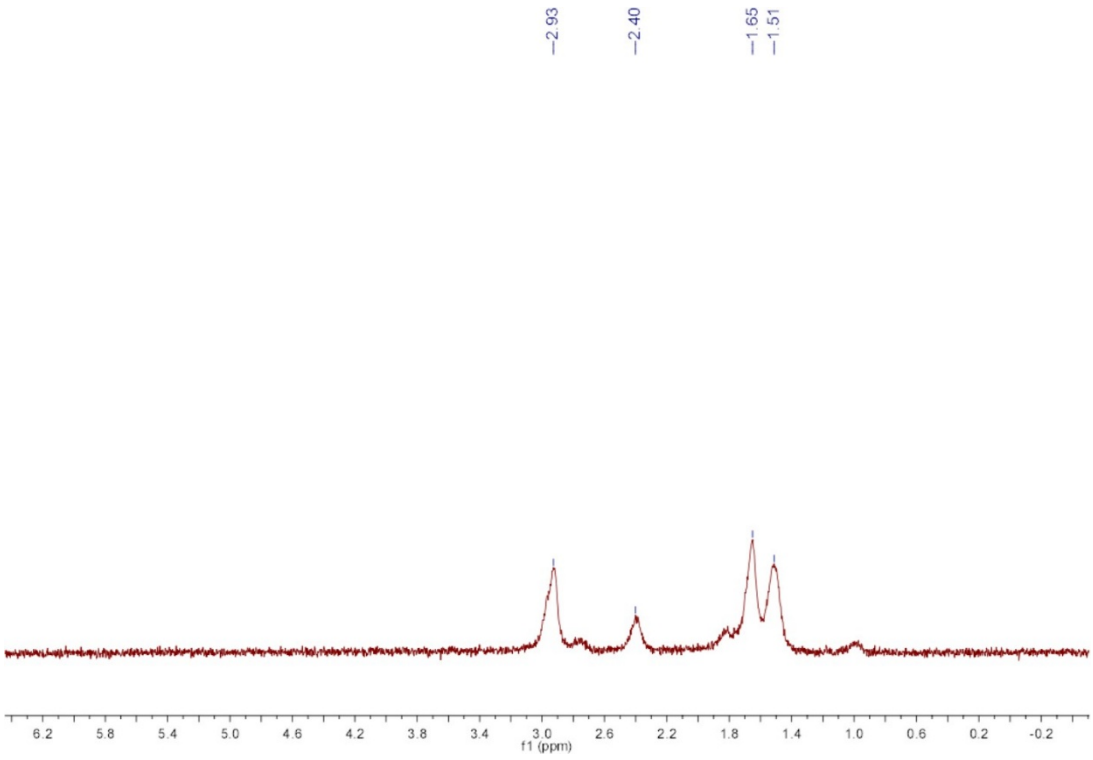


Figure 2.7 ^{1}H NMR spectrum of 2-cyclohexyl-1-phenylethanone **2.2a**:

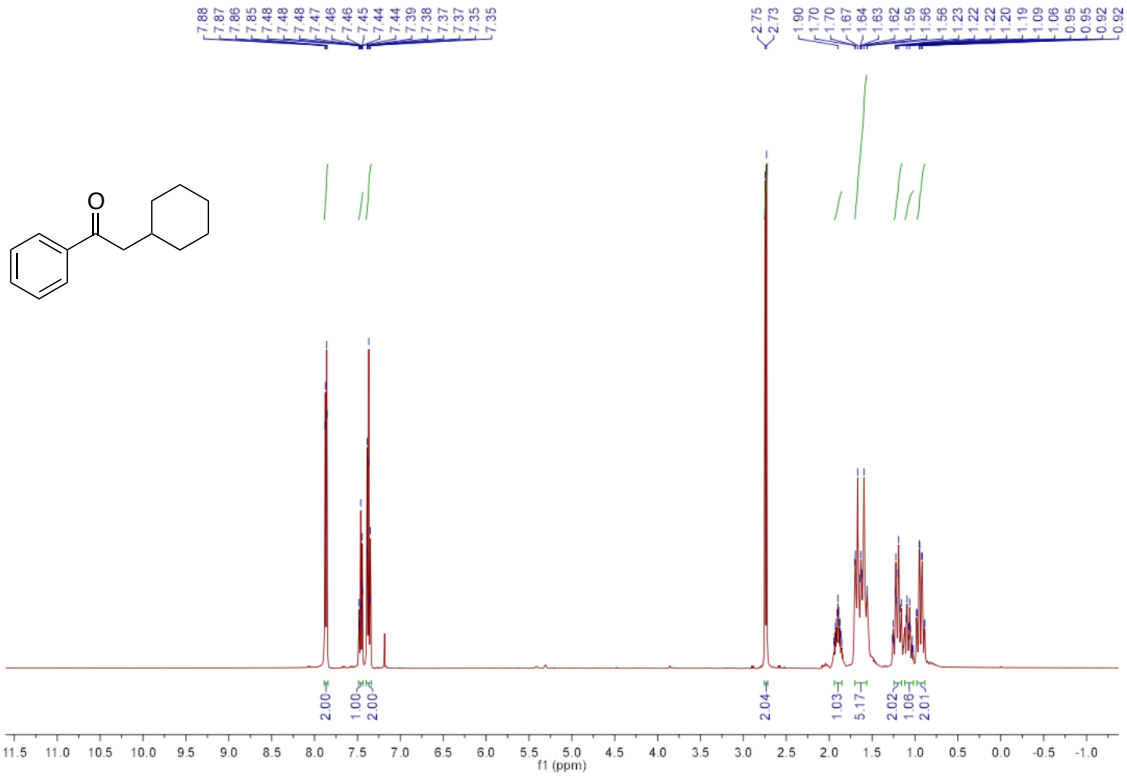


Figure 2.8 ^{13}C{^{1}H} NMR spectrum of 2-cyclohexyl-1-phenylethanone **2.2a**:

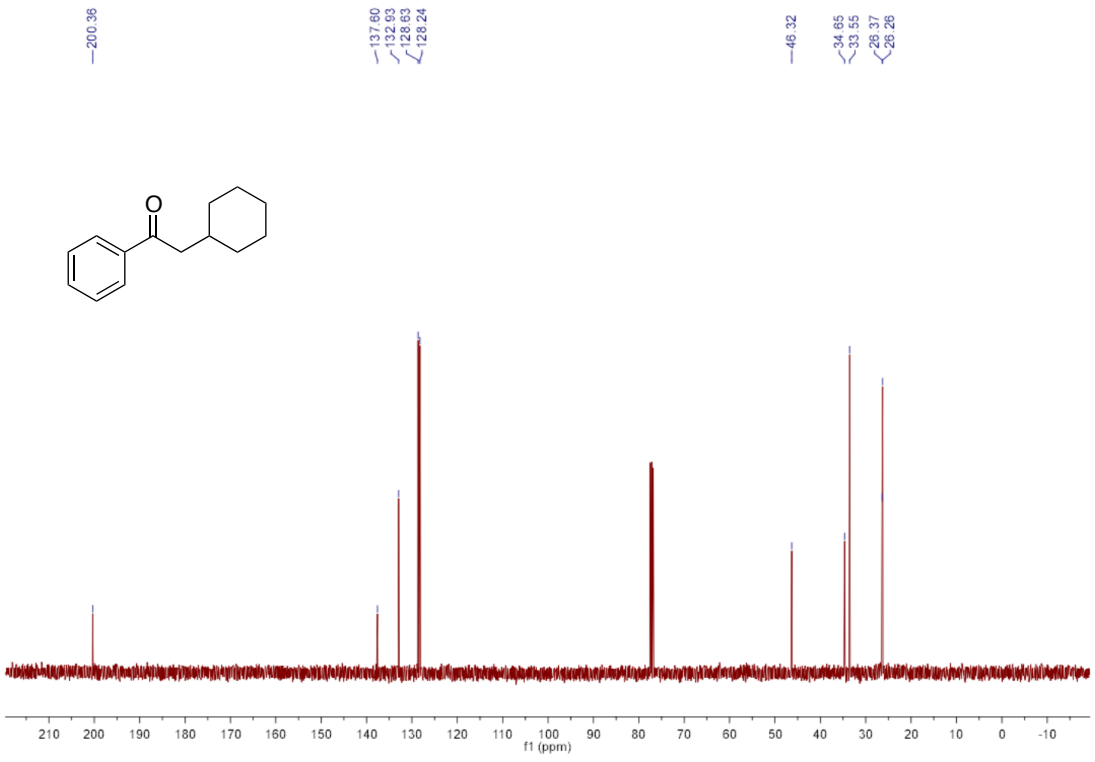


Figure 2.9 ^{1}H NMR spectrum of 2-cyclohexyl-1-(pyridin-3-yl)ethanone **2.3k**:

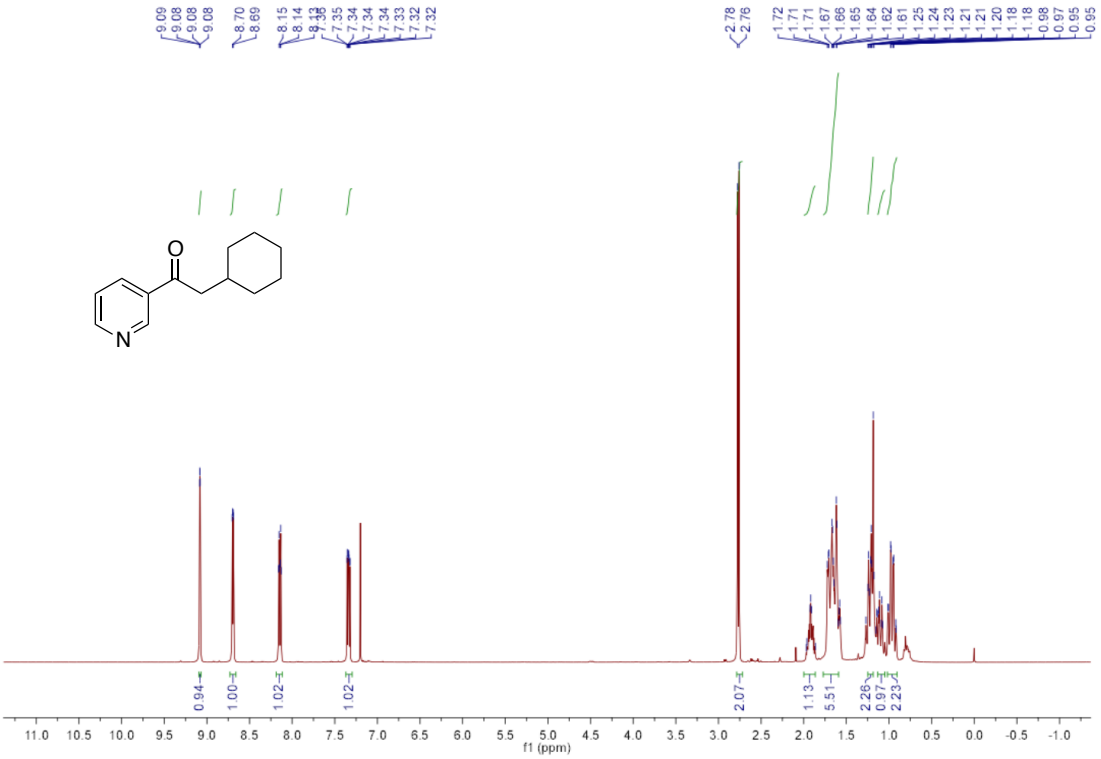
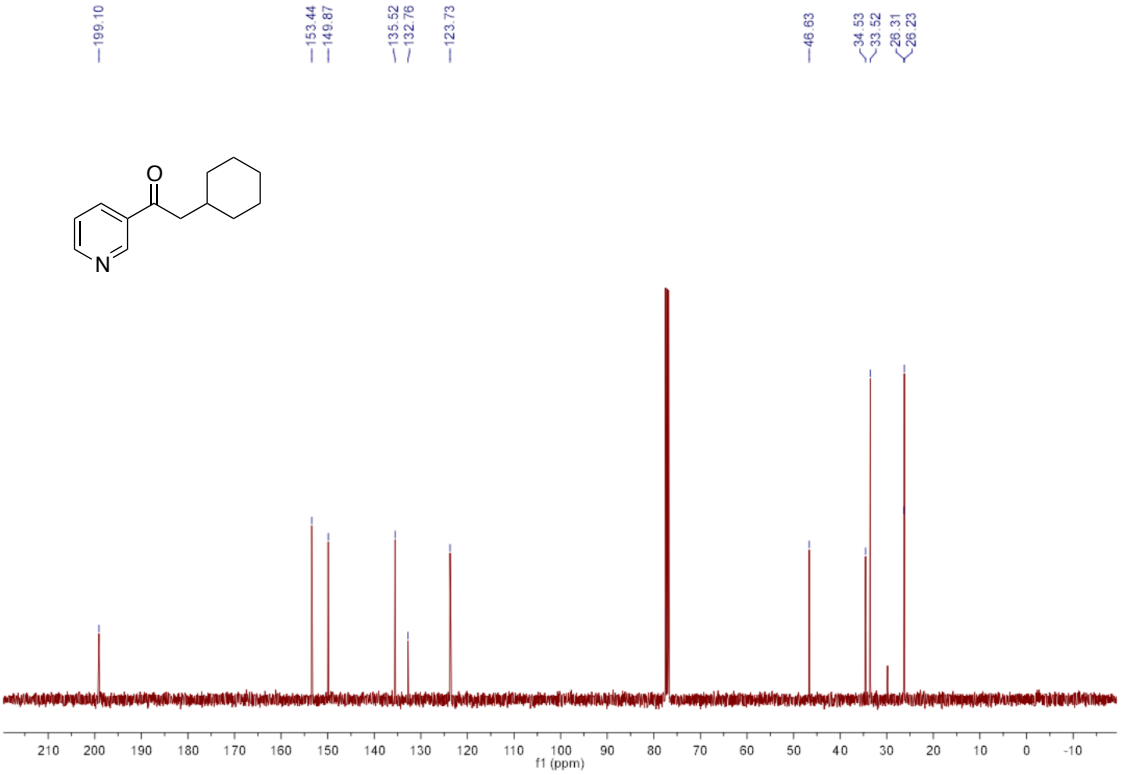


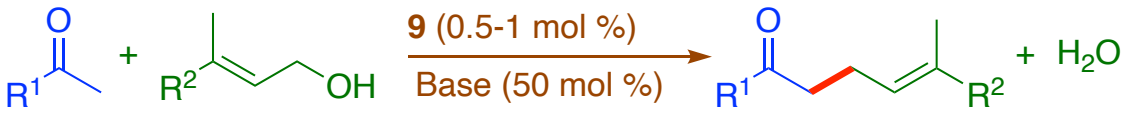
Figure 2.10 ^{13}C{^{1}H} NMR spectrum of 2-cyclohexyl-1-(pyridin-3-yl)ethanone **2.3k**:



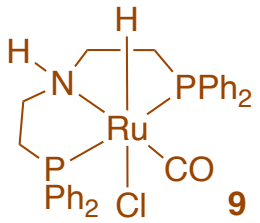
CHAPTER-3

Ruthenium-Catalyzed α-Prenylation of Ketones Using Prenol

3.1 ABSTRACT



- Prenol as direct prenylation reagent
- Water is the only co-product
- Valuble a-prenylated products
- Challenging simple acetophenones derivatives



Prenols and isoprenoids are common structural motifs found biological systems and possess diverse applications. Known catalytic allylation methods suffer from requirement of either prenol derivatives or multiple catalysts, additives, salts and stoichiometric excess base. In this report, a simple catalytic method for the direct prenylation of ketones is developed. Catalytic direct prenylation is an unknown reaction. An assortment of cyclic ketones, and notably, challenging substrates of simple and functionalized acetophenone derivatives, heteroarylmethyl ketones and polyaryl methyl ketones are selectively α-prenylated using prenols as direct allylation partner. Representatively, resulted α-prenylated ketones are transformed to diverse functionalized products. Remarkably, this C-C bond formation reaction requires only a ruthenium pincer catalyst and a base, and H¬2O is the only coproduct, which makes the strategy greener and environmentally benign. Dual role of catalyst and base was observed, and a catalytic cycle incorporating amine-amide metal-ligand cooperation is proposed.

3.2 INTRODUCTION

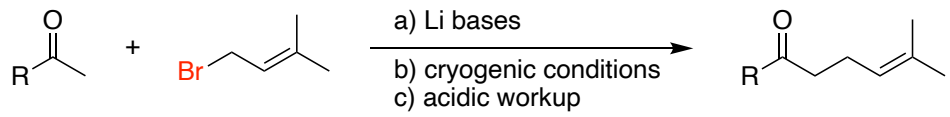
Isoprenoids are an important class of organic compounds containing consecutive unsaturated carbon skeleton with repeating prene units, which are prevalently present in enzymes (e.g., coenzyme Q and dolichyl phosphate), animals (geranyl-, farnesyl- and squalene-pyrophosphates, fat-soluble vitamins and Juvenile hormone), plants (isopentenyl pyrophosphate, geranyl diphosphate, farnesyl diphosphate, geranylgeranyl diphosphate, bornyl diphosphate, limonene, and carotenoids, etc) and possess widespread applications such as drugs (taxol and artimisinin), rubber (latex), and perfumes (geraniol).[1,2] Homoallylic ketones are γ,δ-unsaturated ketones, which are vital constituents in diverse functional molecules,[3] and such ketones are key intermediates in the synthesis of carbocycles and heterocycles such as pyrroles, pyridines, bromopyranes, trioxanes, natural products, and peptidomimetics.[4] Borrowing hydrogen strategy has become a prominent approach for C-C bond formation in organic chemistry.[5,6] Based on this strategy, various alkylation of carbonyl compounds are developed in which both primary and secondary alcohols have been used as alkylation reagents.[7] Notably, such direct use of alcohols has many advantages as they are biorenewable, and provide atom-economical and environmentally benign reactions.[8] Using alcohols, diverse chemical transformations have been developed in recent years. Allylic alcohols have also attracted attention in recent years and are used as an alternative synthon for allyl triflates and acryl aldehydes and allylic ketones in chemical reactions.[9] Prenol is the simplest isoprenoid, a naturally occurring alcohol, and an important structural motif, and possesses significant industrial and biological relevance.[1,2] Incorporation of a prenol unit was found to have resourceful advantages both in organic chemistry and biochemistry.[10] Particularly, *a*-prenylated ketones are highly useful intermediates in the synthesis of functional products.[11] Conventionally, the *a*-prenylated ketones are prepared using corresponding allyl halides, strong stoichiometric base, and under cryogenic conditions, which suffer from the generation of

copious environmental waste and poor atom economy (**Scheme 3.1a**).[12] Few catalytic methods are also developed. Palladium-catalysed Tsuji-Trost allylation,[13] use of acetates and carbonate derivatives of allyl alcohols, and direct use of allyl alcohols[14] were reported to provide the homoallylic ketones (**Scheme 3.1b**).[15] Stochiometric addition of vinyl Grignard reagents with carboxylic esters[16] and gold-catalysed tandem reaction of alkynes and allyl alcohols[17] resulted in homoallylic ketones.

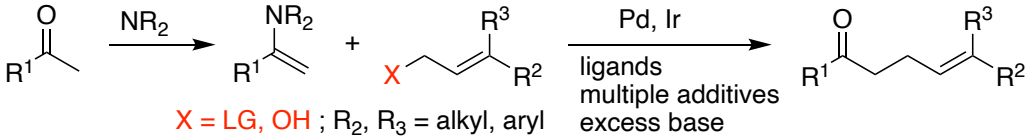
Recently, palladium-catalysed redox-divergent coupling of terpenol derivatives with ketones was also reported to produce diverse products at variable experimental conditions using different amine cocatalysts.[18] In addition, the first catalytic prenylation and reverse prenylation for installing the isoprene units were achieved using coupling of allenes and dienes with alcohols/aldheydes[18b] and enantioselective coupling of allenes and alcohol/aldehydes.[18c] A C-H prenylation strategy was reported using an iridium catalyzed coupling of allenes with aromatic and unsaturated carboxamides.[18d] Ruthenium catalyzed regioselective coupling of oxindoles with isoprene units leading to the prenylation and gernylation was attained.[18e] Our group developed the catalytic cross-coupling of two different secondary alcohols leading to β-disubstituted ketones, α-alkylation and olefination of nitriles, ketazine synthesis using secondary alcohols, N,N-dialkylation of acyl hydrazides using alcohols, and α-alkylation of ketones using secondary alcohols.[19] Recently, a formal conjugate addition of nitriles with allyl alcohol was established, leading to the direct synthesis of δ-hydroxynitriles (**Scheme 3.1c**).[20] Herein, we report the alpha prenylation of ketones directly from prenol (**Scheme 3.1d**). Notably, water is the only byproduct in the reaction.

Scheme 3.1. Advances in α-prenylation: conventional vs catalytic approaches and Ru-catalysed cross-coupling of alcohols with carbon compounds.

a) Traditional method for a-prenylation of ketones



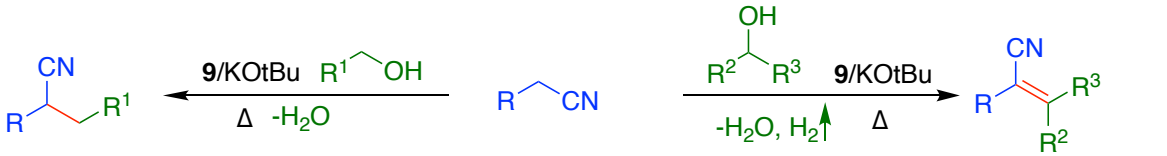
b) Known catalytic methods for a-prenylation/allylation of ketones



X = LG, OH ; R_2, R_3 = alkyl, aryl

c) Our previous reports

i) Catalytic alkylation and akenylation of arylmethyl nitriles using alcohols

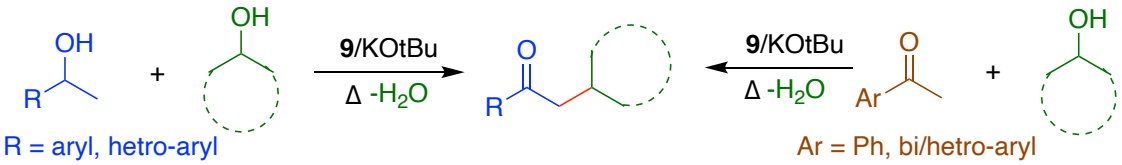


R1 = H, Me, alkyl, aryl

R = aryl, alkyl, hetroaryl

R2, R3 = alkyl, aryl

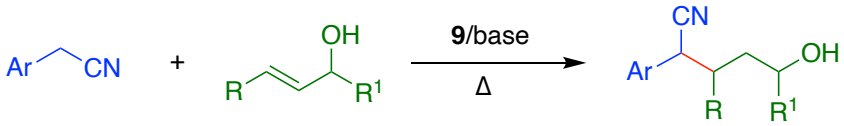
ii) Cross-coupling of secondary alcohols and alkylation of ketones using secondary alcohols



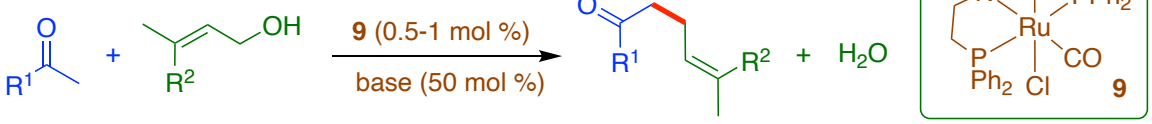
R = aryl, hetro-aryl

Ar = Ph, bi/hetro-aryl

iii) Catalytic formal conjugate addition of nitriles using allylic alcohols



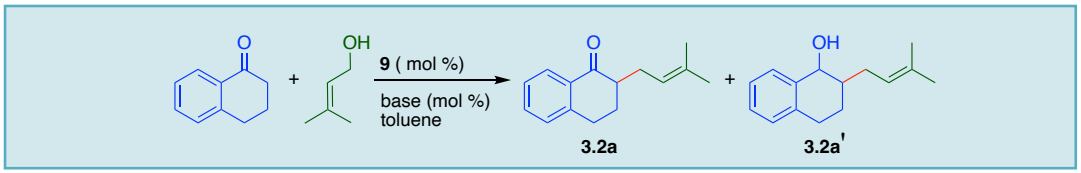
d) This work: catalytic direct a-prenylation of ketones



3.3 RESULTS AND DISCUSSION

Initial investigation for catalytic prenylation was tested using tetralone (0.5 mmol) with prenol (3-methyl 2-buten-1-ol, 1 mmol), catalyst **9** (1 mol %), and KO^{t}Bu (20 mol %) in toluene and the reaction mixture heated at 80 °C for 16 h under nitrogen atmosphere, which resulted in the

Table 3.1. Optimization of reaction condition for *α* -Prenylation of tetralone[a]



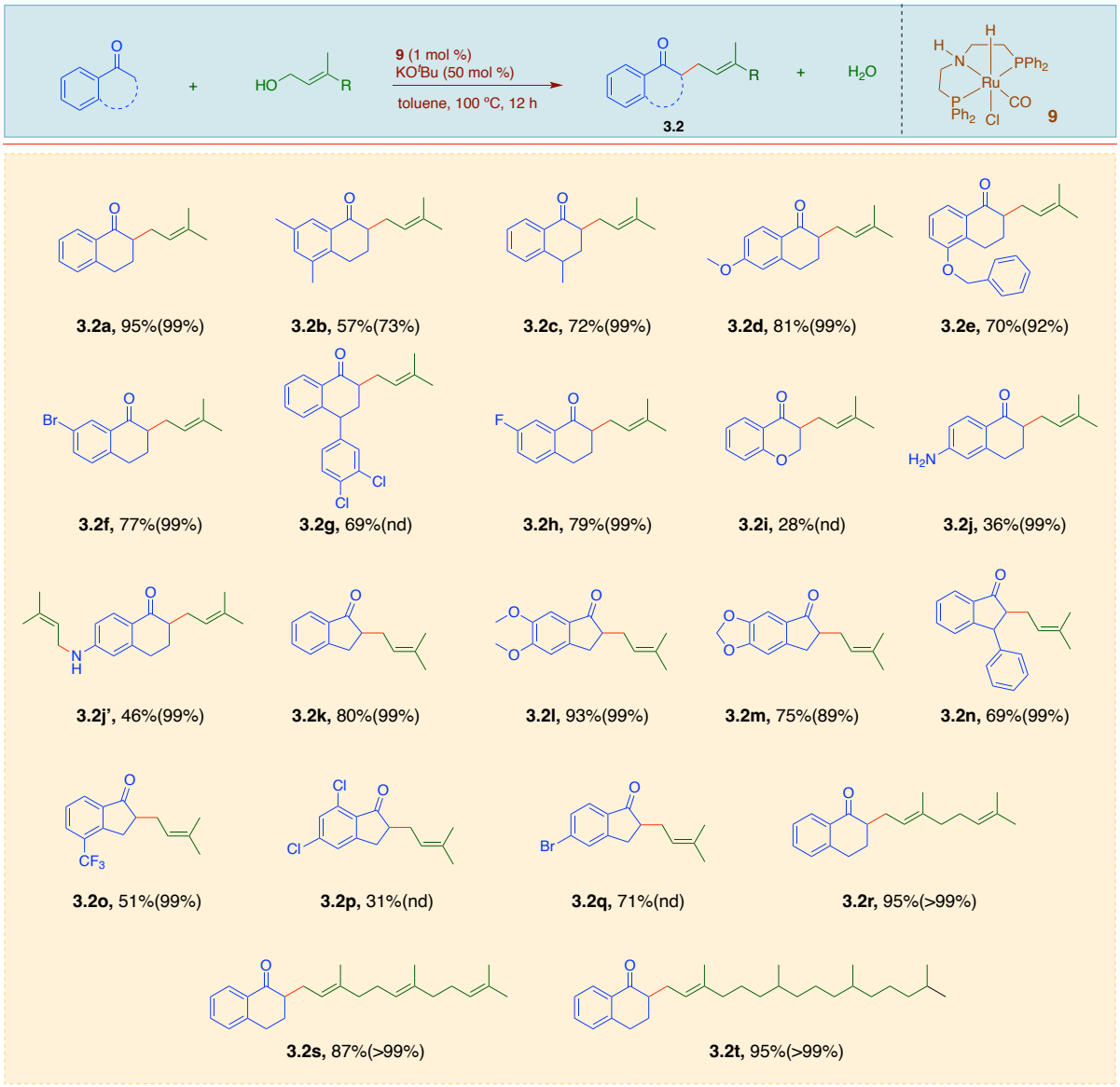
entry	base (mol %)	temp (°C)	time (h)	**3.2a** (%)[b]	**3.2a'** (%)[b]
1	KO^{t}Bu (20)	80	16	37	10
2	KO^{t}Bu (30)	80	16	54	10
3	KO^{t}Bu (50)	80	12	79	12
4	**KO^{t}Bu (50)**	**100**	12	**95**	**3**
5	KO^{t}Bu (30)	100	12	88	6
6[c]	KO^{t}Bu (30)	100	12	72	16
7	Cs_2CO_3 (30)	100	12	-	-
8	K_2CO_3 (50)	100	12	-	-
9	KO^{t}Bu (50)	100	12	-	-

[a]Reaction conditions: tetralone (0.5 mmol, 1 equiv), prenol (1 mmol, 2 equiv), toluene (2 mL), catalyst **9**, and base were heated at an indicated temperature under nitrogen flow. [b]Yields were calculated for pure isolated products after column chromatography. [c]Prenol (0.75 mmol, 1.5 equiv) was used.

formation of the desired prenylated ketone product **3.2a** in 37% and a homoallylic alcohol **3.2a'** in 10% yield (entry 1, **Table 3.1**). Reaction performed with increased base KO^{t}Bu (30 mol %) provided the product **3.2a** in 54% yield (entry 2, **Table 3.1**). When the reaction was performed using 50 mol % base for 12 h, an increase in the formation of product **3.2a** (79%) was observed (entry 3, **Table 3.1**). Next, increasing the reaction temperature to 100 °C resulted in optimal conditions from which 95% yield of **2a** with a minor amount (3%) of **2a'** was obtained. From this condition, further experiments using decreased amounts of base (30 mol %) and prenol (1.5 equiv.) delivered the products in diminished yields (entries 5,6, **Table 3.1**). Employing the milder bases such as K_2CO_3 and Cs_2CO_3 failed to provide the desired reaction (entry 7,8, **Table 3.1**). Control experiment carried out without using a catalyst and base KO^{t}Bu (50 mol %) alone resulted in an unidentified complex reaction mixture (entry 9, **Table 3.1**).

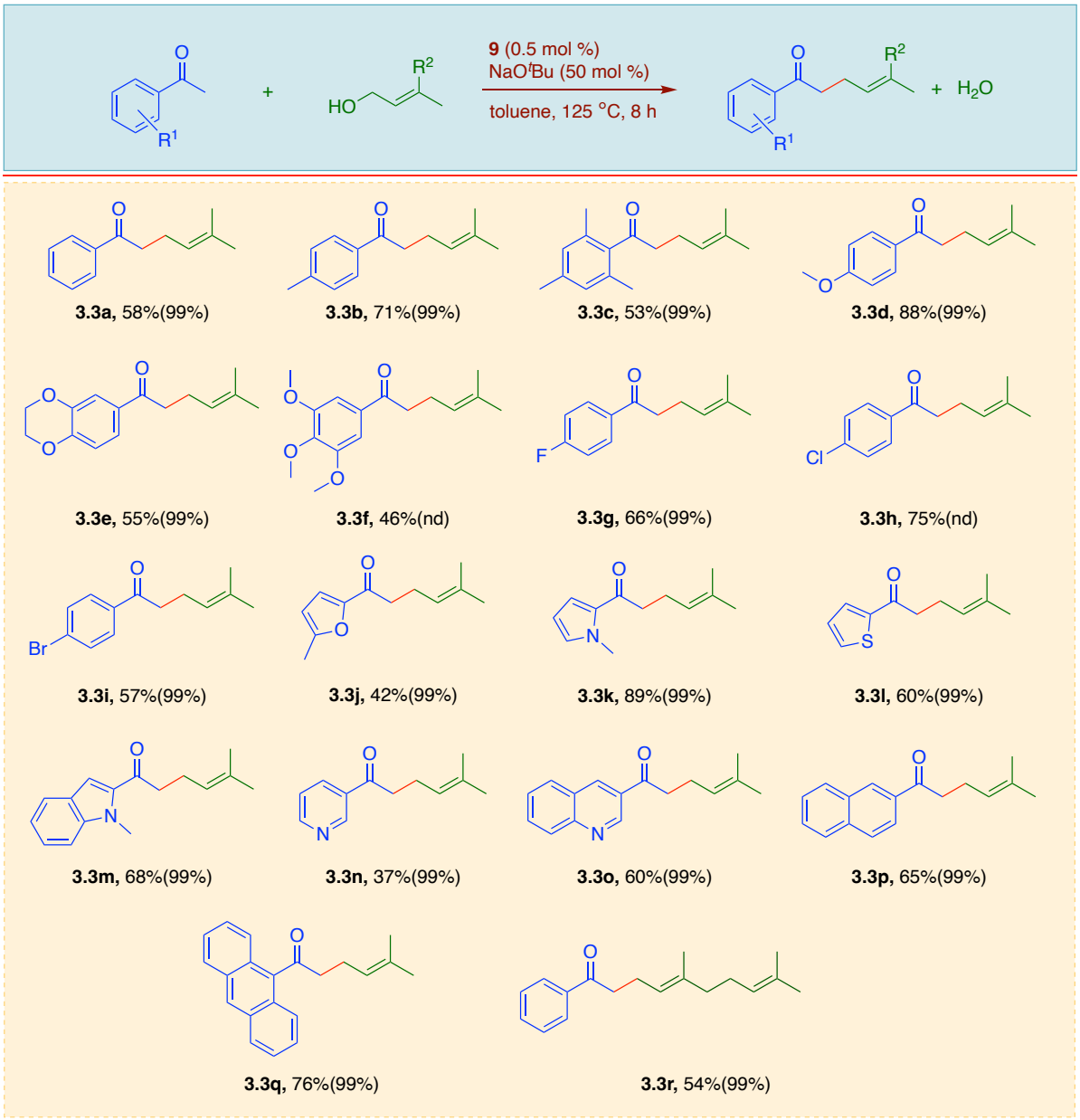
With the optimized conditions in hand, we explored the substrate scope of various substituted cyclic ketones (**Scheme 3.2**). Tetralones bearing methyl, methoxy, and benzyloxy-substituted tetralone delivered the corresponding products **3.2b-3.2e** in good yields. Tetralone bearing electron-withdrawing substituents such as 7-bromo, 4-(3,4-dichlorophenyl), and 7-fluoro functionalities provided the corresponding prenylation products **3.2f-3.2h** in moderate to good yields. Interestingly, chromanones are biologically important and ubiquitous among natural products, and are also prenylated and result in product **3.2i**. Upon reaction with 6-aminotetralone, prenylation occurred at α-carbon and nitrogen centers leading to the formation of mono- and diprenylated products **3.2j** and **3.2j′**, respectively, in moderate yields. Next, indanones having different substitutions on aryl and aliphatic rings were subjected to the reac tion, which provided the corresponding prenylated products **3.2k**-**3.2q**. Furthermore, terpenol derivatives bearing multiple isoprene units such as geraniol, phytol, and farnesol also underwent successful prenylation with tetralone leading to the corresponding prenylated compounds **3.2r-3.2t** in excellent yields.

Scheme 3.2. α-Prenylation of Cyclic Ketones Using Prenols.



Reaction conditions: cyclic ketone (0.5 mmol), prenol (1 mmol), catalyst 9 (1 mol%), KO^{t}Bu (50 mol%), and toluene (2 mL) were heated at 100 °C under a nitrogen flow. Conversions were calculated by GC using mesitylene as an internal standard. The reported yields correspond to pure isolated products after column chromatography. Values in parentheses correspond to the conversion of cyclic ketones. nd = not detected.

Scheme 3.3. Catalytic α-Prenylation of Simple Ketones Using Prenols



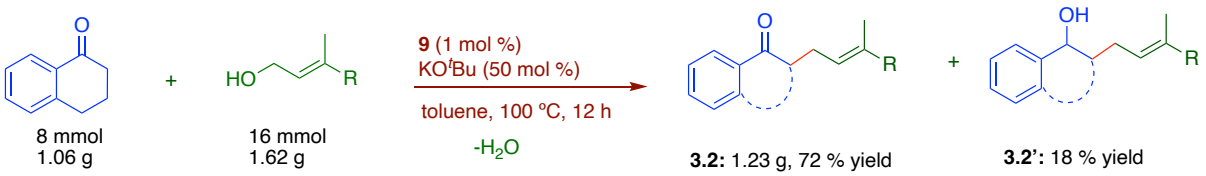
Reaction conditions: acetophenone (0.5 mmol), prenol (1 mmol), catalyst **9** (0.5 mol%), NaO^{t}Bu (50 mol%), and toluene (2 mL) were refluxed at 125 °C under a nitrogen flow. Conversions were calculated by GC using mesitylene as an internal standard. The reported yields correspond to isolated products after column chromatography. Values in parentheses correspond to the conversion of arylmethyl ketone derivatives. nd = not detected.

Linear substitution at the α-position of simple ketones such as acetophenones leading to the formation of α-alkylated products is one of the challenging transformations as their conventional synthesis requires stoichiometrically excess strong bases and involves deleterious side reactions such as aldol self-condensation, resulting in diminished atom economy. Hence, several catalytic protocols using both primary and secondary alcohols leading to α-alkylated ketones were recently developed.[21] Moreover, α-prenylated acetophenone derivatives are present in many natural products, especially used as a synthetic intermediate in total synthesis and as common precursors of flavonoids and isoflavonoids.[22] Notably, there is no catalytic method reported for the direct prenylation of acyclic ketones. Thus, having successfully established the prenylation of cyclic ketones, next, we envisaged the direct catalytic prenylation of simple ketones (**Scheme 3.3**). Employing the optimized conditions for cyclic ketones, catalytic prenylation of acetophenone was carried out, which provided incomplete conversion and a complex mixture with the desired prenylated product **3.3a** (isolated in 36% yield), over the reduced corresponding homoallylic alcohol, and prenyl unit hydrogenated ketone. Hence, different experimental conditions suitable for the prenylation of simple ketones were tested. The use of a low loading of catalyst **9**(0.5 mol%), a base NaO^{t}Bu (50 mol%), and elevated temperature (125 °C) delivered the desired results in which prenylated acetophenone product 3a was isolated in 58% yield. Under these experimental conditions, acetophenones having electron-donating (**3.3b-f**) and electron-withdrawing (**3.3g-i**) substituents were successfully α-prenylated. Next, heteroaryl ketones such as furan, pyrrole, and thiophene were tested, and the corresponding α-prenylated compounds **3.3j-l** were obtained. Furthermore, N-methyl-2-acetylindole, 3-acetylpyridine, and 3-acetylquinoline were catalytically prenylated to provide the corresponding products (**3.3m-o**) in good yields. Direct prenylated products are also obtained from polyaryl ketones such as 2-acetyl naphthalene and 9-acetyl anthracene (**3.3p** and **3.3q**). The reaction of geraniol with acetophenone delivered **3.3r** with double isoprenoid units

remaining intact in the product. Notably, a minor amount of the product with over hydrogenation on the alkene functionality was observed in all experiments

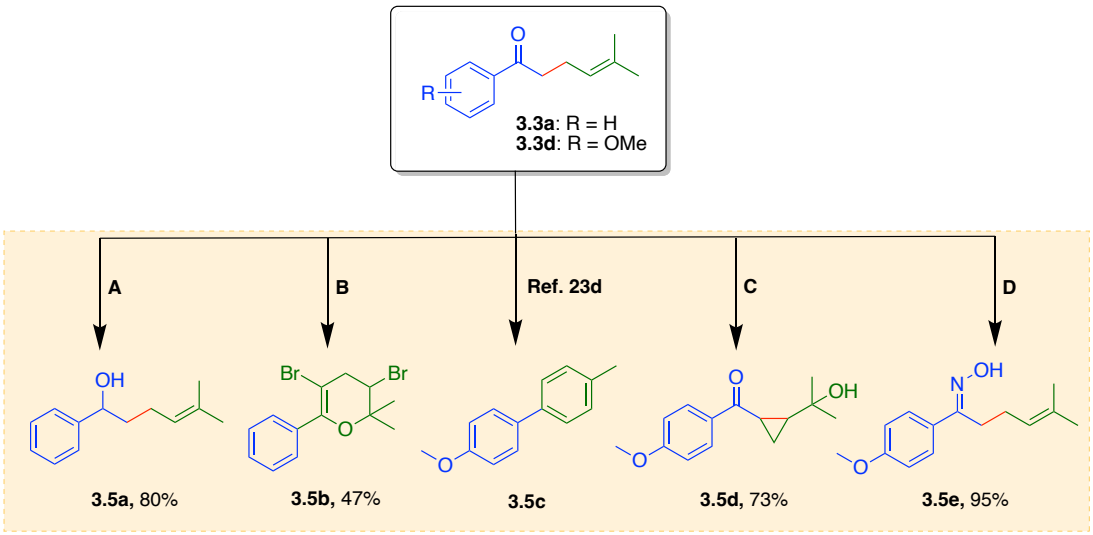
In order to demonstrate the practicality of this method, a gram-scale synthesis was performed which delivered the prenylated product **3.2a** in 72% isolated yield together with a minor amount of hydroxyl compound **3.2a′** (**Scheme 4.4**). The synthetic utilities of the prenylated products were examined by further transformations using prenylated acetophenone products **3.3a** and **3.3d** (**Scheme 3.5**). The prenylated acetophenone **3.3a** on treatment with $NaBH_4$ resulted in a reduction of the carbonyl motif and leads to the formation of the corresponding homoallylic alcohol **3.5a** in 80% yield.

Scheme 3.4. Catalytic Prenylation of Tetralone on a Gram Scale.



The reaction of **3.3a** with NBS at room temperature afforded the 3,5-dibromodihydropyran derivative **3.5b**.[23a] The product **3.3d** underwent a reaction with aqueous NBS and a base (KOH) to provide highly functionalized cyclopropane **3.5d**.[23b] Upon reaction with the N-hydroxylamine hydrochloride salt, prenylated ketone **3.3d** afforded the corresponding oxime product **3.5e** in an excellent yield.[23c] These demonstrated representative applications reveal the importance of prenylated products and their potential use in diverse chemical transformations.

Scheme 3.5. Synthetic Applications of α-Prenylated Acetophenones

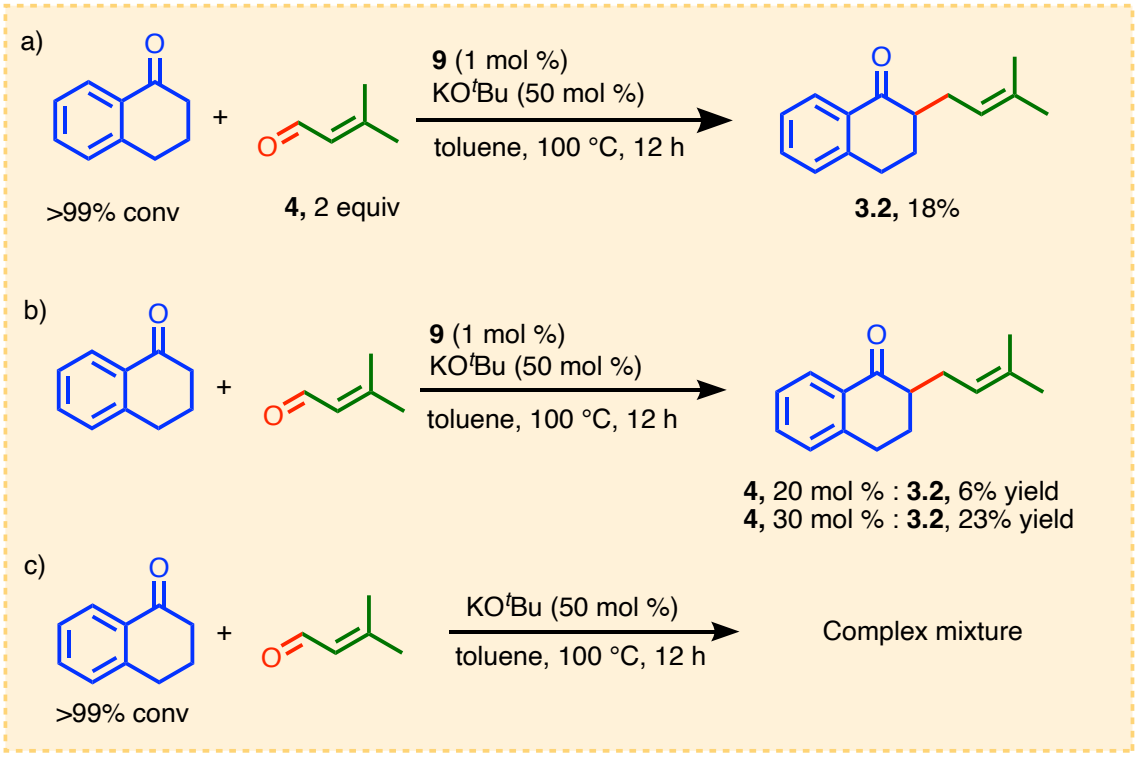


Reaction conditions: Conditions A: **3.3a** (0.3 mmol, 1 equiv.), $NaBH_4$ (0.6 mmol, 2 equiv.), MeOH, 0 °C. Conditions B: **3.3a** (0.3 mmol, 1 equiv.), NBS (0.6 mmol, 2 equiv.), DCM, r.t., 1 min. Conditions C: **3.3d** (0.3 mmol, 1 equiv.), NBS (0.33 mmol, 1.1 equiv.), KOH (1.5 mmol, 5 equiv.), DMSO (1% H2O), 0 °C, r.t., 12 h. Conditions D: **3.3d** (0.5 mmol, 1 equiv.), hydroxyl amine hydrochloride (2 mmol, 4 equiv.), pyridine (2 mmol, 4 equiv.), EtOH, r.t. addition, followed by reflux, 2 h.

To gain mechanistic insight into this α-prenylation of ketones, reactions were performed between tetralone and 3-methyl-2-butenal (**4**) under the standard conditions. Although the involvement of the corresponding aldehyde intermediate from prenol was found while monitoring the reaction progress through ^{1}H NMR analysis, the direct use of 3-methyl2-butenal (**4**) provided a poor yield of α-prenylated product **3.2a** (18%, Scheme **3.6a**). The diminished yield can be attributed to the strong coordination of aldehyde to the catalyst leading to the retardation of the reactivity of the catalyst.[24] In order to understand this phenomenon, further experiments were per formed using 3-methyl-2-butenal (**4**) at lower concentrations (20 and 30 mol%, **Scheme 3.6b**) in which the formation of product **3.2a** in 6 and 23% yield, respectively,

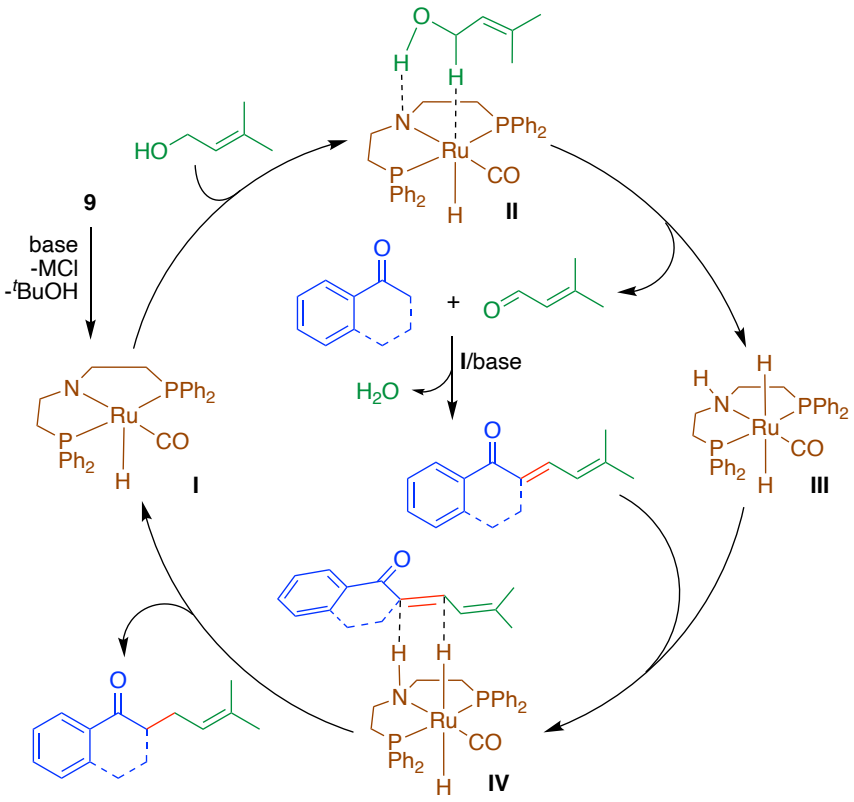
was achieved, indicating that effective inhibition of catalyst reactivity occurs when aldehyde is available at high concentrations. The reaction of tetralone and a base (KO^t Bu, 50 mol%) without using catalyst **9** led to the formation of a complex mixture (**Scheme 3.6c**). These above experiments reveal that in situ formed 3-methyl-2-butenal from the oxidation of prenol by catalyst **9** is concomitantly reacted with ketone, the direct use of prenol is advantageous, and the catalyst is necessary to attain the desired α-prenylation of ketones and selectivity.

Scheme 3.6 Mechanistic Studies



Based on experimental observations and our previous studies using catalyst **9**, a plausible mechanism is proposed for the direct prenylation of ketones using prenol in (**Scheme 3.7**). Upon reaction with a base, **9** undergoes dehydrohalogenation to generate the active catalyst I, which is a coordinatively unsaturated intermediate. The reaction of **I** with prenol involves amine-amide metal-ligand cooperation leading to O-H activation via intermediate **II**,

Scheme 3.7 Plausible Mechanism of the Catalytic α-Prenylation of Ketones using Prenol.



which generates 3-methyl 2-butenal, and forms a ruthenium dihydride complex **III**. [20,25] In situ generated 3-methyl-2-butenal undergoes a base and metal mediated concomitant condensation reaction with the ketone and delivers an α,β-unsaturated chalcone in which the enone functionality is hydrogenated by ruthenium dihydride intermediate **III** involving a cyclic transition state **IV**.[20] This selective hydrogenation of electron-deficient conjugated alkene releases the prenylated product and regenerates the active catalyst **I** to complete the catalytic cycle.

3.4 CONCLUSIONS

In conclusion, a ruthenium pincer catalysed α-prenylation of ketones was established, leading to the formation of α-prenylated ketones. Cyclic ketones such as tetralone, chromanone, and indanones were selectively α-prenylated. In addition to prenol, extended isoprenoid derivatives

such as geraniol, phytol, and farnesol also successfully participated in the catalytic α-prenylation of ketones. Remarkably, challenging substrates of simple acetophenone derivatives, functionalized arylmethyl ketones, heteroarylmethyl ketones and polyaryl methyl ketones also afforded α-prenylated products in moderate to excellent yields. The desirable uses of the catalytically derived α-prenylated compounds in different fundamental chemical transformations, which delivered interesting functionalized products, are demonstrated. The mechanistic studies indicate that in situ formed 3-methyl-2-butenal from the oxidation of by catalyst **9** is the intermediate involved and is concomitantly consumed in the reaction. Interestingly, the catalyst performed the oxidation of prenol and further proposed to undergo the hydrogenation of the in situ formed α,β-unsaturated ketone intermediate via a ruthenium dihydride intermediate involving amine-amide metal-ligand cooperation. Remarkably, H_2O is the only byproduct in this protocol, which makes this catalytic method both atom economical and environmentally benign.

3.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-Macho [Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}ruthenium(II)] (**9**) was purchased from Sigma-Aldrich and stored inside glove box. Chemicals (ketones and Prenol) were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were

recorded at Bruker AV-700 (^{1}H at 700 MHz, ^{13}C at 175 MHz) and Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1} H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS, δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz).^{1} H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (dept-135) NMR techniques.

GC Method: GC data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard mesitylene was calculated from the average of three independent GC runs.

General optimization procedure for α-prenylation of cyclic ketones using prenols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol), base (0.20-0.25 mmol) tetralone (0.5 mmol), prenol (0.75-1 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 100 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 12 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (mesitylene) was added into the reaction mixture and the conversion of tetralone was calculated using GC analysis. Further the solvent was evaporated, and the reaction was quenched using water (0.5 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried

over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (1:99) mixture as the eluent. Yields were calculated for isolated pure products.

General procedure for the α-prenylation of cyclic ketones using prenol:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 1 mol %), KO^{t}Bu (0.25 mmol, 50 mol %), tetralone (0.5 mmol), prenol (1 mmol), and toluene (1.5 mL) were added under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 100 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 12 h. The completion of the reaction was monitored using GC analysis. Upon completion, reaction mixture was cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added into the reaction mixture and the conversion of cyclic ketones was calculated using GC analysis. Further, the solvent was evaporated the reaction was quenched using water (0.5 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (1:99) mixture as the eluent. Yields were calculated for isolated pure products.

General procedure for α-prenylation of simple acetophenone derivatives using prenol:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.0025 mmol, 0.5 mol %), NaO^{t}Bu (0.25 mmol, 50 mol %), acetophenone derivatives (0.5 mmol), prenol (1 mmol), and toluene (1.5 mL) were added under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed at 125 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 8 h. The completion of the reaction was monitored using GC analysis. Upon completion, reaction mixture was cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added

into the reaction mixture and the conversion of acetophenone was calculated using GC analysis. Further, the solvent was evaporated and the reaction was quenched by water (0.5 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (1:99) mixture as the eluent. Yields were calculated for isolated pure products.

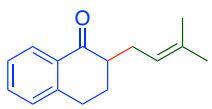
Mechanistic studies

General procedure for control experiment of tetralone with 3-methyl-2-butanal:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 1 mol %), KO^{t}Bu (0.25 mmol, 50 mol %), Tetralone (0.5 mmol), 3-methyl-2-butanal (1 mmol) and toluene (1.5 mL) were added under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 100 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 12 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (mesitylene) was added into the reaction mixture and the conversion of tetralone was calculated using GC analysis. Further, the solvent was evaporated the reaction was quenched with water (0.5 mL) and extracted with dichloromethane (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography over silica gel (100–200 mesh) with hexane/ethyl acetate (1:99) mixture as the eluent. Yields were calculated for isolated pure products.

Spectral data of the α-prenylated products:

2-(3-Methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2a): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 102 mg, 95%. IR (DCM; cm^{-1}): 2927, 1688, 1600, 1455, 1220, 1156, 933, 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.8 Hz, 1H,



ArC*H*), 7.47 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.33-7.24 (m, 2H, ArC*H*), 5.20 (t, *J* = 6.7 Hz, 1H, Olefinic C*H*), 3.00 (t, *J* = 5.9 Hz, 2H, CH_2), 2.69-2.64 (m, 1H, CH_2), 2.51 (ddd, J_1 = 11.4 Hz, J_2 = 7.9 Hz, J_3 = 4.0 Hz, 1H, CH_2), 2.30-2.19 (m, 2H, CH_2), 1.93-1.85 (m, 1H, C*H*), 1.74 (s, 3H, CH_3), 1.66 (s, 3H, CH_3). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 200.0, 144.1, 133.5, 133.1, 132.6, 128.7, 127.4, 126.5, 121.8, 48.1, 28.7, 28.1, 28.0, 25.9, 17.9. HRMS (ESI) m/z calcd for $C_{17}H_{22}O$ $(M+H)^+$: 215.1436, found: 215.1480.

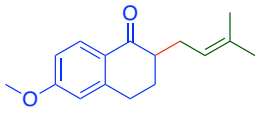
5,7-Dimethyl-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2b):

Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 69 mg, 57%. IR(DCM; cm^{-1}): 2924, 1683, 1611, 1451, 1377, 1287, 1157, 871. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H, ArC*H*), 7.16 (s, 1H, ArC*H*), 5.18 (t, *J* = 6.8 Hz, 1H, Olefinic C*H*), 2.89 (dt, J_1 = 17.2 Hz, J_2 = 4.4 Hz, 1H, CH_2), 2.73 (ddd, J_1 = 16.5 Hz, J_2 = 10.8 Hz, J_3 = 5.0 Hz, 1H, CH_2), 2.63-2.59 (m, 1H, CH_2), 2.45 (ddd, J_1 = 11.7 Hz, J_2 = 8.1 Hz, J_3 = 4.0 Hz, 1H, CH_2), 2.29 (s, *J* = 23.8 Hz, (2*3= 6H), ArCH_3), 2.20 (qd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 2H, CH_2), 1.87-1.78 (m, 1H, C*H*), 1.72 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 200.8, 139.6, 136.2, 135.7, 135.7, 133.5, 132.7, 125.4, 122.0, 47.5, 28.1, 27.5, 26.0, 25.3, 21.0, 19.4, 18.0. HRMS (ESI) m/z calcd for $C_{17}H_{22}O$ $(M+H)^+$: 265.1568, found: 265.1572.

4-Methyl-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2c): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 81 mg, 72%. IR(DCM; cm^{-1}): 2963, 2855, 1683, 1600, 1470, 1377, 1265, 894, 780. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.93 (m, 1H, ArC*H*), 7.41 (qd, J_1 = 7.4 Hz, J_2=1.4 Hz, 1H, ArC*H*), 7.26-7.19 (m, 2H, ArC*H*), 5.13-5.07 (m, 1H, Olefinic C*H*), 3.12-2.97 (m, 1H), 2.69-2.41 (m, 2H), 2.21-1.88 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.48 (d, *J* = 12.2 Hz, 1H), 1.33 (dd, J_1 = 14.2 Hz, J_2 =7.0 Hz, 3H). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 200.1, 148.8, 148.2, 133.5, 133.4, 133.3, 131.6, 128.1, 127.5,

127.4, 126.5, 126.4, 126.3, 121.9, 121.8, 48.4, 43.2, 37.7, 34.6, 33.1, 31.5, 28.4, 28.1, 25.9, 21.6, 20.3, 17.9. HRMS (ESI) m/z calcd for $C_{16}H_{20}O$ $(M+H)^+$: 251.1389, found: 251.1406.

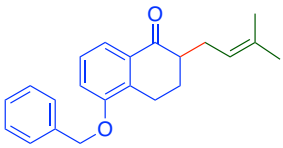
6-Methoxy-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2d): Purified



by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 99 mg, 81% IR(DCM; cm^{-1}): 2927, 16767, 1600, 1495, 1352, 1251, 1154, 1029, 856, 830. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.7 Hz, 1H, ArC*H*), 6.72 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, ArC*H*), 6.59 (s, *J* = 2.0 Hz, 1H, ArC*H*), 5.11-5.07 (m, 1H, Olefinic C*H*), 3.75 (s, 3H), 2.86-2.83 (m, 2H), 2.59-2.52 (m, 1H), 2.39-2.31 (m, 1H), 2.17-2.06 (m, 2H), 1.79-1.69 (m, 1H), 1.63 (s, 3H), 1.55 (s, 3H). ^{13}C {^1H} NMR (100.6 MHz, $CDCl_3$): δ 198.8, 163.4, 146.6, 133.4, 129.9, 126.2, 122.0, 113.1, 112.4, 55.4, 47.7, 29.0, 28.2, 28.0, 25.9, 17.9. HRMS (ESI) m/z calcd for $C_{16}H_{20}O$ $(M+H)^+$: 251.1389, found: 251.1406.

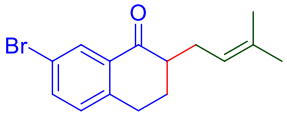
5-(Benzyloxy)-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2e):

Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as



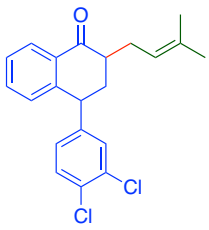
the eluent. Colorless liquid. Yield: 112 mg, 70%. IR (DCM; cm^{-1}): 2926, 1684, 1582, 1454, 1377, 1265, 1189, 1041, 905, 795. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.8 Hz, 1H, ArC*H*), 7.45-7.32 (m, 5H, ArC*H*), 7.24 (t, *J* = 7.9 Hz, 1H, ArC*H*), 7.06 (d, *J* = 8.0 Hz, 1H, ArC*H*), 5.20-5.16 (m, 1H, Olefinic C*H*), 5.10 (s, 2H), 3.18-3.11 (m, 1H), 2.84-2.75 (m, 1H), 2.64-2.45 (m, 2H), 2.25-2.18 (m, 2H), 1.87-1.80 (m, 1H), 1.72 (s, 3H), 1.63 (s, 3H). ^{13}C {^1H} NMR (100.6 MHz, $CDCl_3$): δ 200.4, 156.0, 137.0, 133.9, 133.6, 128.7, 128.1, 127.3, 126.9, 121.9, 119.5, 115.5, 70.4, 47.7, 28.1, 27.3, 26.0, 22.3, 18.0. HRMS (ESI) m/z calcd for $C_{22}H_{25}O_2$ $(M+H)^+$:321.1855, found: 321.1859.

7-Bromo-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2f): Purified by



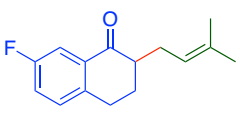
silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 113 mg, 77%. IR (DCM; cm^{-1}):2927, 1687, 1589, 1473, 1404, 1212, 850, 772. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 2.3 Hz, 1H, ArC*H*), 7.47 (dd, J_1 = 8.2 Hz, J_2 = 2.2 Hz, 1H, ArC*H*), 7.04 (d, *J* = 8.2 Hz, 1H, ArC*H*), 5.10-5.05 (m, 1H, Olefinic C*H*), 2.88-2.81 (m, 2H), 2.58-2.53 (m, 1H), 2.43-2.36 (m, 1H), 2.17-2.10 (m, 2H), 1.80-1.72 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 142.9, 135.9, 134.2, 133.9, 130.6, 130.3, 121.5, 120.6, 47.9, 28.2, 28.0, 27.7, 25.9, 18. HRMS (ESI) m/z calcd for $C_{15}H_{17}OBr$ $(M+H)^+$:315.0368, found: 315.0355.

4-(3,4-Dichlorophenyl)-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99)



mixture as the eluent. Colorless liquid. Yield: 124 mg, 69%. IR(DCM; cm^{-1}): 2927, 1700, 1491, 1437, 1271, 1159, 892. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J_1 = 11.7, J_2 = 7.9 Hz, 1H, ArC*H*), 7.51-7.14 (m, 4H, ArC*H*), 7.06-7.04 (m, 1H, ArC*H*), 6.88-6.78 (m, 1H, ArC*H*), 5.18-5.03 (m, 1H, Olefinic C*H*), 4.38-4.19 (m, 1H), 2.80-2.48 (m, 2H), 2.38-2.20 (m, 2H), 1.96 (q, *J* = 13.2 Hz, 1H), 1.70-1.62 (m, 6H). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 199.4, 199.0, 145.8, 145.1, 144.3, 143.9, 134.1, 134.1, 133.9, 133.4, 133.0, 132.9, 132.8, 132.8, 131.2, 130.9, 130.9, 130.9, 130.6, 130.5, 129.7, 129.0, 128.3, 128.0, 127.9, 127.8, 127.6, 127.3, 121.5, 121.1, 48.4, 46.0, 43.4, 42.5, 38.2, 35.9, 28.2, 28.0, 26.0, 26.0, 18.1, 18.0. HRMS (ESI) m/z calcd for $C_{21}H_{20}Cl_2O$ $(M+H)^+$: 381.0789, found: 381.0803.

7-Fluoro-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2h): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as eluent. Colorless liquid. Yield: 92 mg, 79% . IR(DCM; cm^{-1}): 2928, 1687, 1588, 1435, 1352, 1271, 1160, 892, 734. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd,

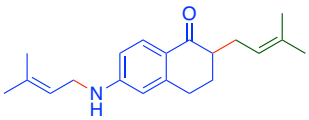
J_1 = 9.3 Hz, J_2 = 2.6 Hz, 1H, ArC*H*), 7.11 (ddd, J_1 = 19.7 Hz, J_2 = 8.2 Hz, J_3 = 4.0 Hz, 2H, ArC*H*), 5.10-5.07 (m, 1H, Olefinic C*H*), 2.87 (dd, J_1 = 9.7 Hz, J_2 = 4.5 Hz, 2H), 2.58-2.53 (m, 1H), 2.43-2.38 (m, 1H), 2.19-2.11 (m, 2H), 1.82-1.71 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 199.1, 199.1, 162.8, 160.3, 139.9, 139.9, 134.2, 134.2, 133.8, 130.6, 130.5, 121.6, 120.6, 120.4, 113.4, 113.2, 47.8, 28.1, 28.0, 25.9, 18.0. HRMS (ESI) m/z calcd for $C_{15}H_{17}FO$ $(M+H)^+$: 233.1348, found: 233.1336.

3-(3-Methylbut-2-en-1-yl)chroman-4-one (3.2i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 30 mg, 28%. IR(DCM; cm^{-1}): 2924, 1695, 1605, 1479, 1269, 1125, 1014, 827, 780. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1H, ArC*H*), 7.42 (td, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H, ArC*H*), 6.99-6.90 (m, 2H, ArC*H*), 5.11 (td, J_1 = 7.4 Hz, J_2 = 1.1 Hz, 1H, Olefinic C*H*), 4.43 (dd, J_1 = 11.4 Hz, J_2 = 4.5 Hz, 1H, CH_2), 4.21 (dd, J_1 = 11.4 Hz, J_2 = 8.7 Hz, 1H, CH_2), 2.63 (tt, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H, CH_2), 2.51-2.45 (m, 1H, CH_2), 2.23 (dt, J_1 = 14.8 Hz, J_2 = 8.9 Hz, 1H, C*H*), 1.68 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.4, 161.7, 135.8, 135.1, 127.5, 121.4, 120.7, 120.2, 117.8, 70.1, 46.4, 25.9, 25.1, 17.9. HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2$ $(M+H)^+$: 239.1058, found: 239.1043.

6-Amino-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Colorless liquid. Yield: 42 mg, 36%. IR(DCM; cm^{-1}): 3350, 3232, 2923, 2855, 1633,1582, 1362, 1274, 893. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, J_1 = 8.4 Hz, J_2 = 3.4 Hz, 1H, ArC*H*), 6.48 (dd, J_1 = 8.4 Hz, J_2 = 2.3 Hz, 1H, ArC*H*), 6.35 (d, J = 2.1 Hz, 1H, ArC*H*), 5.11 (td, J_1 = 7.4 Hz, J_2 = 1.4 Hz, 1H, Olefinic C*H*), 4.06 (s, 2H, NH_2), 2.78 (dd, J_1 = 7.4 Hz, J_2 = 4.9 Hz, 2H, CH_2), 2.58 (dt, J_1 = 13.2 Hz, J_2 = 6.1 Hz, 1H, CH_2), 2.35 (ddt, J_1 = 10.9 Hz, J_2 = 8.8 Hz, J_3 = 4.4 Hz, 1H, CH_2), 2.19-2.05 (m, 2H, CH_2),

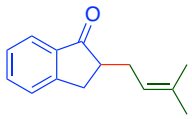
1.79-1.71 (m, 1H, C*H*), 1.66 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 151.2, 146.8, 133.3, 130.1, 124.0, 122.3, 113.3, 112.5, 47.7, 28.9, 28.4, 28.0, 26.0, 18.0. HRMS (ESI) m/z calcd for $C_{15}H_{19}NO$ $(M+H)^+$: 252.1364, found: 252.1375.

2-(3-Methylbut-2-en-1-yl)-6-((3-methylbut-2-en-1-yl)amino)-3,4-dihydronaphthalen-1(2H)-one (3.2j'): Purified by silica-gel column chromatography using an ethyl acetate/hexane



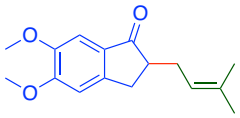
(2:98) mixture as the eluent. Colorless liquid. Yield: 64 mg, 46%. IR(DCM; cm^{-1}): 3438, 2924, 1652, 1597, 1354, 1273, 1229, 1126, 759. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.7 Hz, 1H, ArC*H*), 6.43-6.41 (m, 1H, ArC*H*), 6.24 (s, 1H, ArC*H*), 5.26-5.23 (m, 1H, Olefinic C*H*), 5.14-5.10 (m, 1H, Olefinic C*H*), 4.26 (s, 1H, N*H*), 3.68 (d, *J* = 6.8 Hz, 2H, CH_2), 2.80 (t, *J* = 6.1 Hz, 2H, CH_2), 2.60-2.55 (m, 1H, CH_2), 2.35 (dt, J_1 = 9.9 Hz, J_2 = 4.9 Hz, 1H, C*H*), 2.19-2.06 (m, 2H, CH_2), 1.76-1.73 (m, 1H, C*H*), 1.67 (d, *J* = 17.0 Hz, 9H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.4, 152.0, 146.7, 136.8, 133.2, 129.8, 122.9, 122.4, 120.5, 111.7, 109.7, 47.5, 41.4, 29.1, 28.4, 28.0, 26.0, 25.8, 18.1, 18.0. HRMS (ESI) m/z calcd for $C_{20}H_{27N}O$ $(M+H)^+$: 320.1990, found: 320.2000.

2-(3-Methylbut-2-en-1-yl)-2,3-dihydro-1H-inden-1-one (3.2k): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the



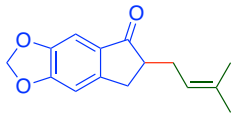
eluent. Colorless liquid. Yield: 80 mg, 80%. IR(DCM; cm^{-1}): 2926, 1699, 1608, 1436, 1267, 1092, 739. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 1H, ArC*H*), 7.60 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.47 (d, *J* = 7.6 Hz, 1H, ArC*H*), 7.38 (t, *J* = 7.4 Hz, 1H, ArC*H*), 5.14 (t, *J* = 6.7 Hz, 1H, Olefinic C*H*), 3.28 (dd, J_1 = 17.3 Hz, J_2 = 7.7 Hz, 1H), 2.85-2.61 (m, 3H, CH_2 & C*H*), 2.27 (dt, J_1 = 14.9 Hz, J_2 = 7.7 Hz, 1H, C*H*), 1.68 (d, *J* = 19.2 Hz, 6H, CH_3). ^{13}C {^{1}H} NMR (100.6 MHz, $CDCl_3$): 208.8, 154.0, 136.9, 134.8, 134.7, 134.0, 127.4, 126.7, 124.0, 121.1, 47.7, 32.3, 29.7, 25.9, 18.1. HRMS (ESI) m/z calcd for $C_{14}H_{16}O$ $(M+H)^+$: 223.1098, found: 223.1103

5,6-Dimethoxy-2-(3-methylbut-2-en-1-yl)-2,3-dihydro-1H-inden-1-one (3.2l):



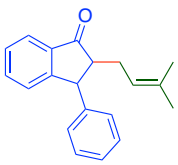
Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 120 mg, 93%. IR(DCM; cm^{-1}): 3438, 1700, 1576, 1507, 1456, 1387, 1312, 778. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H, ArC*H*), 6.90 (s, 1H, ArC*H*), 5.13 (t, *J* = 6.7 Hz, 1H, Olefinic C*H*), 3.96 (d, *J* = 22.3 Hz, 6H, CH_2), 3.19 (dd, J_1 = 17.6 Hz, J_2 = 8.1 Hz, 1H, CH_2), 2.76-2.73 (m, 2H, CH_2), 2.62 (t, *J* = 7.1 Hz, 1H, CH_2), 2.27 (dd, J_1 = 14.8 Hz, J_2 = 7.6 Hz, 1H, C*H*), 1.69 (d, *J* = 18.1 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 155.4, 149.3, 149.2, 133.7, 129.5, 121.1, 107.4, 104.2, 56.2, 56.0, 47.7, 31.9, 29.8, 25.8, 17.9. HRMS (ESI) m/z calcd for $C_{16}H_{20}O_3$ $(M+H)^+$: 260.1412, found: 260.1430.

6-(3-Methylbut-2-en-1-yl)-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-one (3.2m):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 91 mg, 75%. IR(DCM; cm^{-1}): 2913, 1699, 1471, 1383, 1037, 940, 869, 735.^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H, ArC*H*), 6.75 (s, 1H, ArC*H*), 6.01 (s, 2H, ArC*H*), 5.04 (t, *J* = 7.3 Hz, 1H, Olefinic C*H*), 3.11-3.05 (m, 1H, CH_2), 2.69-2.60 (m, 2H, CH_2), 2.52 (dt, J_1 = 13.6, J_2 = 6.3 Hz, 1H, CH_2), 2.16 (dt, J_1 = 15.1 Hz, J_2 = 7.8 Hz, 1H, C*H*), 1.63 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7, 154.3, 151.5, 148.3, 134.0, 131.4, 121.1, 105.8, 102.5, 102.2, 48.1, 32.2, 29.9, 25.9, 18.0. HRMS (ESI) m/z calcd for $C_{15}H_{16}O_3$ $(M+H)^+$: 267.1018, found: 267.0992.

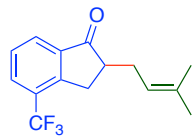
2-(3-Methylbut-2-en-1-yl)-3-phenyl-2,3-dihydro-1H-inden-1-one (3.2n): Purified by silica-



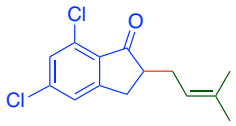
gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 95 mg, 69%. IR(DCM; cm^{-1}): 3478, 2926, 2811, 1735, 1694, 1472, 1376, 1286, 1094, 744. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.6 Hz, 1H, ArC*H*), 7.49-7.45 (m, 1H, ArC*H*), 7.33 (t, *J* = 7.4 Hz, 1H, ArC*H*),

7.24-7.21 (m, 2H, ArC*H*), 7.18-7.15 (m, 1H, ArC*H*), 7.11 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.03-7.00 (m, 2H, ArC*H*), 4.99 (t, *J* = 7.4 Hz, 1H, Olefinic C*H*), 4.11 (d, *J* = 4.5 Hz, 1H, C*H*), 2.66 (dt, J_1 = 7.5 Hz, J_1 = 4.6 Hz, 1H, CH_2), 2.48 (ddt, J_1 = 30.3 Hz, J_2 = 14.8 Hz, J_3 = 7.4 Hz, 2H, C*H*), 1.60 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 156.7, 143.3, 136.2, 134.8, 133.8, 128.5, 127.9, 127.6, 126.6, 126.5, 123.1, 120.5, 58.0, 50.1, 28.0, 25.5, 17.8. HRMS (ESI) m/z calcd for $C_{20}H_{20}O$ $(M+H)^+$: 299.1411, found: 299.1420.

2-(3-Methylbut-2-en-1-yl)-4-(trifluoromethyl)-2,3-dihydro-1H-inden-1-one (3.2o): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 68 mg, 51%. IR(DCM; cm^{-1}): 3445, 2973, 17212, 1699, 1486, 1377, 1163, 1059, 811, 708. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.83 (d, *J* = 7.6 Hz, 1H, ArC*H*), 7.51-7.47 (m, 1H, ArC*H*), 5.09 (t, *J* = 7.3 Hz, 1H, Olefinic C*H*), 3.44 (dd, J_1 = 18.1 Hz, J_2 = 8.1 Hz, 1H, CH_2), 2.94 (dd, J_1 = 18.1 Hz, J_2 = 3.6 Hz, 1H, CH_2), 2.76 (tt, J_1 = 8.5 Hz, J_2 = 4.2 Hz, 1H, CH_2), 2.64-2.57 (m, 1H, CH_2), 2.26 (dt, J_1 = 15.0 Hz, J_2 = 7.7 Hz, 1H, C*H*), 1.67 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 151.3, 138.4, 134.7, 131.3, 131.3, 127.8, 127.5, 120.4, 47.3, 31.0, 29.6, 25.9, 18.0. HRMS (ESI) m/z calcd for $C_{15}H_{15}F_3O$ $(M+H)^+$: 291.0987, found: 291.0967.



5,7-Dichloro-2-(3-methylbut-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-one (3.2p): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 41 mg, 31%. IR(DCM; cm^{-1}): 2942, 1654, 1635, 1457, 1036, 875, 737. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.25 (m, 2H, ArC*H*), 5.04- 4.99 (m, 1H, Olefinic C*H*), 3.16 -3.09 (m, 1H, CH_2), 2.55 -2.48 (m, 2H, CH_2), 2.24 -2.16 (m, 1H, C*H*), 1.62 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.1, 157.2, 141.0, 134.6, 132.8, 131.5, 129.3, 125.4, 120.5, 48.4, 31.5, 29.7, 25.9, 18.0. HRMS (ESI) m/z calcd for $C_{14}H_{14}Cl_2O$ $(M+H)^+$: 269.0500, found: 269.0521.



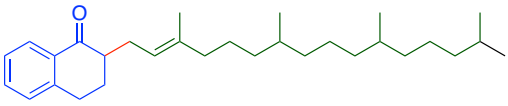
5-Bromo-2-(3-methylbut-2-en-1-yl)-2,3-dihydro-1H-inden-1-one (3.2q): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 99 mg, 71%. IR(DCM; cm^{-1}): 2923, 1716, 1699, 1575, 1432, 1316, 1199,1057, 868. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 11.9 Hz, 2H, ArC*H*), 7.46-7.44 (m, 1H, ArC*H*), 5.03 (t, *J* = 7.1 Hz, 1H, Olefinic C*H*), 3.19 (dd, J_1 = 17.3 Hz, J_2 = 7.8 Hz, 1H, CH_2), 2.77-2.64 (m, 2H, CH_2), 2.56-2.50 (m, 1H, CH_2), 2.24-2.16 (m, 1H, C*H*), 1.63 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.5, 155.6, 135.8, 134.4, 131.0, 130.1, 130.0, 125.23, 120.6, 47.7, 31.9, 29.6, 25.9, 18.1. HRMS (ESI) m/z calcd for $C_{14}H_{15}BrO$ $(M+H)^+$: 301.0212, found: 301.0198.

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2r): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 134 mg, 95%. IR (DCM; cm^{-1}): 2925, 1682, 1456, 1282, 1220, 74. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J_1 = 7.8 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 7.38 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H, ArC*H*), 7.25-7.15 (m, 2H, ArC*H*), 5.14-4.99 (m, 2H, Olefinic C*H*), 2.91 (dd, J_1 = 7.5 Hz, J_2 = 4.7 Hz, 2H, CH_2), 2.63-2.58 (m, 1H, CH_2), 2.46-2.40 (m, 1H, CH_2), 2.22-2.13 (m, 2H, CH_2), 2.03-1.94 (m, 4H, CH_2), 1.78 (ddt, J_1 = 13.3 Hz, J_2 = 11.5 Hz, J_3 = 7.6 Hz, 1H, C*H*), 1.60-1.53 (m, 9H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.1, 144.2, 144.2, 137.3, 137.2, 133.2, 132.7, 131.7, 131.4, 128.8, 128.7, 127.5, 126.6, 124.4, 124.3, 122.6, 121.9, 48.2, 48.1, 39.9, 32.1, 29.8, 28.8, 28.2, 28.0, 28.0, 27.9, 26.7, 26.6, 25.8, 23.6, 17.8, 16.2. HRMS (ESI) m/z calcd for $C_{20}H_{26}O$ $(M+H)^+$: 283.2058, found: 283.2056.

2-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.2s): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 152 mg, 87%. IR (DCM; cm^{-1}): 2925, 1700, 1600, 1454, 1375, 1220,

739. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.8 Hz, 1H, ArC*H*), 7.37 (td, J_1 = 7.4 Hz, J_2 = 1.3 Hz, 1H, ArC*H*), 7.22 (t, J = 7.5 Hz, 1H, ArC*H*), 7.15 (d, J = 7.7 Hz, 1H, ArC*H*), 5.13-5.00 (m, 3H, Olefinic C*H*), 2.90 (dd, J_1 = 7.2 Hz, J_2 = 4.5 Hz, 2H, CH_2), 2.59 (td, J_1 = 9.9 Hz, J_2 = 4.5 Hz, 1H, CH_2), 2.44-2.40 (m, 1H, CH_2), 2.20-2.12 (m, 2H, CH_2), 2.04-1.94 (m, 7H, CH_2), 1.89 (q, J = 7.5 Hz, 1H, CH_2), 1.81-1.76 (m, 1H, C*H*), 1.61-1.52 (m, 12H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 144.2, 137.2, 137.2, 135.1, 133.2, 132.7, 131.6, 131.3, 128.7, 127.5, 126.6, 125.1, 124.4, 124.2, 121.9, 121.8, 48.1, 40.2, 39.9, 39.8, 32.1, 28.8, 28.7, 28.0, 28.0, 28.0, 26.8, 26.7, 26.6, 26.5, 25.8, 25.8, 23.6, 23.5, 17.8, 17.7, 16.3, 16.2, 16.1.HRMS (ESI) m/z calcd for $C_{25}H_{35}O$ $(M+H)^+$:351.2688, found: 351.2709.

(*E*)-2-(3,7,11,15-Tetramethylhexadec-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one(3.2t):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 202 mg, 95%. IR (DCM; cm^{-1}): 2925, 1686.92, 1455, 1282, 1219, 742. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.8 Hz, 1H, ArC*H*), 7.38 (t, J = 7.4 Hz, 1H, ArC*H*), 7.21 (q, J = 6.9 Hz, 1H, ArC*H*), 7.16 (d, J = 7.6 Hz, 1H, ArC*H*), 5.12 (t, J = 7.2 Hz, 1H, Olefinic C*H*), 2.91 (dd, J_1 = 7.5 Hz, J_2 = 4.7 Hz, 2H, CH_2), 2.60 (dt, J_1 = 14.3 Hz, J_2 = 5.4 Hz, 1H, CH_2), 2.43 (ddd, J_1 = 11.8 Hz, J_2 = 8.3 Hz, J_3 = 3.9 Hz, 1H, CH_2), 2.17 (ddd, J_1 = 19.9 Hz, J_2 = 11.2 Hz, J_3 = 5.7 Hz, 2H, CH_2), 1.91 (t, J = 7.4 Hz, 2H, CH_2), 1.82-1.76 (m, 1H, CH_2), 1.56 (s, 3H, CH_2), 1.46 (dt, J_1 = 13.2 Hz, J_2 = 6.6 Hz, 1H, CH_2), 1.33-1.25 (m, 4H, CH_2), 1.20 (ddd, J_1 = 13.1 Hz, J_2 = 9.8 Hz, J_3 = 4.2 Hz, 7H, CH_2), 1.10-1.06 (m, 2H, CH_2), 1.02-0.95 (m, 4H, CH_2), 0.79 (d, J = 14.1 Hz, 13H, C*H* & CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 144.1, 137.6, 133.1, 132.6, 128.7, 128.7, 127.5, 126.6, 122.2, 121.5, 48.1, 40.2, 39.4, 37.5, 37.5, 37.4, 36.7, 34.7, 32.9, 32.8, 32.8, 32.7, 31.7, 28.8, 28.7, 28.1, 28.1, 28.0, 27.8, 27.0, 25.57, 25.4, 24.9, 24.6, 23.6, 22.8, 22.7, 19.8, 16.2. HRMS (ESI) m/z calcd for $C_{30}H_{49}O$ $(M+H)^+$:425.3783, found: 425.3783.

5-Methyl-1-phenylhex-4-en-1-one (3.3a):[1] Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 54 mg, 58% . IR (DCM; cm^{-1}): 1697, 1458, 1435, 1185, 735. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.9 Hz, 2H, ArC*H*), 7.56 (d, *J* = 7.4 Hz, 1H, ArC*H*), 7.48 (t, *J* = 7.6 Hz, 2H, ArC*H*), 5.20 (td, J_1 = 7.1 Hz, J_2 = 0.8 Hz, 1H, Olefinic C*H*), 3.02 (t, *J* = 7.5 Hz, 2H, CH_2), 2.44 (q, *J* = 7.4 Hz, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.66 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 137.1, 133.0, 132.9, 128.7, 128.2, 123.0, 38.9, 25.8, 23.0, 17.8.HRMS (ESI) m/z calcd for $C_{15}H_{19}O$ $(M+H)^+$: 215.1436, found: 215.1480.

5-Methyl-1-(p-tolyl)hex-4-en-1-one (3.3b):[1] Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 70 mg, 71%. IR (DCM; cm^{-1}): 1695, 1456, 1436, 1180, 831, 735. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.1 Hz, 2H, ArC*H*), 7.19 (d, *J* = 8.1 Hz, 2H, ArC*H*), 5.13-5.09 (m, 1H, Olefinic C*H*), 2.90 (t, *J* = 7.5 Hz, 2H, CH_2), 2.37-2.32 (m, 5H, CH_2 & ArCH_3), 1.63 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.9, 143.7, 134.6, 132.8, 129.3, 128.3, 123.1, 38.7, 25.8, 23.1, 21.7, 17.8. HRMS (ESI) m/z calcd for $C_{14}H_{18}O$ $(M+H)^+$: 225.1255, found: 225.1259.

1-Mesityl-5-methylhex-4-en-1-one (3.3c):[1] Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 61 mg, 53% . IR (DCM; cm^{-1}): 3443, 1696, 1558, 1457, 1434, 850, 702. ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H, ArC*H*), 5.06 (t, *J* = 7.3 Hz, 1H, Olefinic C*H*), 2.64 (t, *J* = 7.4 Hz, 2H, CH_2), 2.31 (d, *J* = 7.3 Hz, 2H, CH_2), 2.19 (s, 3H, ArCH_3), 2.10 (s, 6H, ArCH_3), 1.60 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.7, 139.8, 138.3, 133.0, 132.6, 128.5, 122.8, 44.9, 25.8, 22.2, 21.1, 19.2, 17.8. HRMS (ESI) m/z calcd for $C_{16}H_{22}O$ $(M+H)^+$: 253.1535, found: 253.1563.

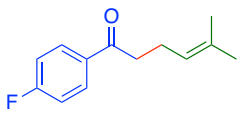
1-(4-Methoxyphenyl)-5-methylhex-4-en-1-one (3.3d): [1] Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 95 mg, 88%. IR (DCM; cm^{-1}): 2925, 1678, 1511, 1258, 1171, 1031, 97, 841. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.95 (d, *J* = 8.8 Hz, 2H, ArC*H*), 5.19 (td, J_1 = 7.2, *J* = 1.0 Hz, 1H, Olefinic C*H*), 3.88 (s, 3H, ArOCH_3), 2.96 (t, *J* = 7.5 Hz, 2H, CH_2), 2.43 (q, *J* = 7.4 Hz, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.65 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 163.3, 132.6, 130.3, 130.1, 123.1, 113.6, 55.4, 38.4, 25.7, 23.1, 17.6. HRMS (ESI) m/z calcd for $C_{14}H_{18}O_2$ $(M+H)^+$: 241.1208, found: 241.1199.

1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-methylhex-4-en-1-one (3.3e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 68 mg, 55%. IR (DCM; cm^{-1}): 3445, 1683, 1582, 1457, 1319, 1260, 1066, 893, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H, ArC*H*), 6.83 (d, *J* = 8.9 Hz, 1H, ArC*H*), 5.09 (t, *J* = 7.2 Hz, 1H, Olefinic C*H*), 4.25-4.20 (m, 4H, CH_2), 2.84 (t, *J* = 7.5 Hz, 2H, CH_2), 2.32 (q, *J* = 7.4 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 147.9, 143.3, 132.7, 131.0, 123.17, 122.2, 117.6, 117.2, 64.7, 64.2, 38.5, 25.8, 23.2, 17.8. HRMS (ESI) m/z calcd for $C_{15}H_{18}O_3$ $(M+H)^+$: 269.1153, found: 269.1157.

5-Methyl-1-(3,4,5-trimethoxyphenyl)hex-4-en-1-one (3.3f) : Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 64 mg, 46% . IR (DCM; cm^{-1}): 2928, 1700, 1585, 1456, 1322, 1231, 1154, 1004, 895, 835. ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 2H, ArC*H*), 5.12-5.09 (m, 1H, Olefinic C*H*), 3.84 (s, 9H, ArOCH_3), 2.89 (t, *J* = 7.5 Hz, 2H, CH_2), 2.34 (q, *J* = 7.4 Hz, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 153.1, 142.5, 132.9, 132.4, 123.0, 105.6, 61.0, 56.3, 38.6,

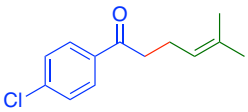
25.8, 23.2, 17.8. HRMS (ESI) m/z calcd for $C_{16}H_{22}O_4$ $(M+H)^+$: 301.1404, found: 301.1410.

1-(4-Fluorophenyl)-5-methylhex-4-en-1-one (3.3g): Purified by silica-gel column



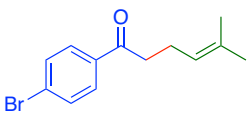
chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 68 mg, 66% . IR (DCM; cm^{-1}): 3438, 1696, 1558, 1457, 1407, 850, 807, 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J_1 = 8.1 Hz, J_2 = 5.8 Hz, 2H, ArC*H*), 7.05 (t, J = 8.5 Hz, 2H, ArC*H*), 5.09 (td, J_1 = 7.2 Hz, J_2 = 1.0 Hz, 1H, Olefinic C*H*), 2.90 (t, J = 7.5 Hz, 2H, CH_2), 2.34 (d, J = 7.3 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.5, 167.0, 164.4, 133.5, 133.5, 133.0, 130.8, 130.7, 122.9, 115.8, 115.6, 38.7, 25.8, 23.0, 17.8. HRMS (ESI) m/z calcd for $C_{13}H_{25}OF$ $(M+H)^+$: 229.1000, found: 229.0999.

1-(4-Chlorophenyl)-5-methylhex-4-en-1-one (3.3h):[1] Purified by silica-gel column



chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 83 mg, 75% . IR (DCM; cm^{-1}): 3438, 1684, 1635, 1362, 1093, 912, 734.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.6 Hz, 2H, ArC*H*), 7.36 (d, J = 8.6 Hz, 2H, ArC*H*), 5.10-5.06 (m, 1H, Olefinic C*H*), 2.91-2.87 (m, 2H, CH_2), 2.34 (q, J = 7.2 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 139.4, 135.4, 133.1, 129.6, 129.0, 122.8, 38.8, 25.8, 23.0, 17.8. HRMS (ESI) m/z calcd for $C_{13}H_{16}ClO$ $(M+H)^+$: 223.0890, found: 223.0900.

1-(4-Bromophenyl)-5-methylhex-4-en-1-one (3.3i): [1] Purified by silica-gel column



chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colorless liquid. Yield: 76 mg, 57% . IR (DCM; cm^{-1}): 3446, 2925, 1683, 1585, 1483, 1259, 1070, 978, 789. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 2H, ArC*H*), 7.54-7.50 (m, 2H, ArC*H*), 5.10-5.05 (m, 1H, Olefinic C*H*), 2.90-2.86 (m, 2H, CH_2), 2.36-2.30 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.1, 135.8, 133.1, 131.9, 129.9, 129.7, 128.1, 122.8, 38.8, 25.8, 22.9, 17.8. HRMS

(ESI) m/z calcd for $C_{13}H_{15}BrO$ $(M+H)^+$: 289.0203, found: 289.0201.

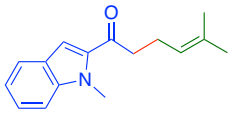
5-Methyl-1-(5-methylfuran-2-yl)hex-4-en-1-one (3.3j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 39 mg, 42% . IR (DCM; cm^{-1}): 2924, 1674, 1516, 1456, 1375, 1026, 796. ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 3.4 Hz, 1H, ArC*H*), 6.15-6.14 (m, 1H, ArC*H*), 5.17-5.13 (m, 1H, Olefinic C*H*), 2.78 (t, *J* = 7.6 Hz, 2H, CH_2), 2.42-2.37 (m, 5H, CH_2 & ArCH_3), 1.69 (s, 3H, CH_3), 1.64 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.7, 157.7, 151.6, 132.9, 122.9, 119.1, 108.9, 38.4, 25.8, 23.4, 17.8, 14.2. HRMS (ESI) m/z calcd for $C_{12}H_{16}O_2$ $(M+H)^+$: 215.1048, found: 215.1054.

5-Methyl-1-(1-methyl-1H-pyrrol-2-yl)hex-4-en-1-one (3.3k): Purified by silica-gel column chromatography using an ethyl acetate/hexane (3:97) mixture as the eluent. Colorless liquid. Yield: 84 mg, 89% . IR (DCM; cm^{-1}): 3446, 1700, 1683, 1558, 1456, 1418, 1274, 764, 749.^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (dd, J_1 = 4.1 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 6.71 (d, *J* = 2.1 Hz, 1H, ArC*H*), 6.04 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H, ArC*H*), 5.12-5.06 (m, 1H, olefinic C*H*), 3.86 (s, 3H, N-CH_3), 2.71 (d, *J* = 7.9 Hz, 2H, CH_2), 2.33-2.27 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.2, 132.5, 130.8, 123.3, 119.0, 107.8, 39.2, 37.7, 25.7, 23.8, 17.7. HRMS (ESI) m/z calcd for $C_{12}H_{17}NO$ $(M+H)^+$: 214.1207, found: 214.1213.

5-Methyl-1-(thiophen-2-yl)hex-4-en-1-one (3.3l): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 58 mg, 60% . IR (DCM; cm^{-1}): 2925, 1661, 1519, 1416, 1354, 1233, 1062, 854. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J_1 = 3.7 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 7.54 (dd, J_1 = 4.9 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 7.05 (dd, J_1 = 4.8 Hz, J_2 = 3.9 Hz, 1H, ArC*H*), 5.11-5.07 (m, 1H, Olefinic C*H*), 2.85 (t, *J* = 7.5 Hz, 2H, CH_2), 2.35 (q, *J* = 7.4 Hz, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1,

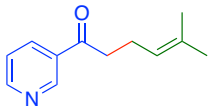
144.5, 133.4, 133.1, 131.8, 128.1, 122.8, 39.6, 25.8, 23.4, 17.8. HRMS (ESI) m/z calcd for $C_{11}H_{14}OS(M+H)^+$: 217.0648, found: 217.0658.

5-Methyl-1-(1-methyl-1H-indol-2-yl)hex-4-en-1-one (3.3m): Purified by silica-gel column



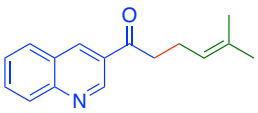
chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Colorless liquid. Yield: 82 mg, 68% . IR (DCM; cm^{-1}): 3442, 1695, 1576, 1456, 1539, 1506, 1456, 776.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34-8.31 (m, 1H, ArC*H*), 7.64 (s, 1H, ArC*H*), 7.27-7.22 (m, 3H, ArC*H*), 5.15 (t, J = 7.2 Hz, 1H, Olefinic C*H*), 3.76 (s, 3H, N-CH_3), 2.80 (dd, J_1 = 8.5 Hz, J_2 = 6.8 Hz, 2H, CH_2), 2.41 (t, J = 7.6 Hz, 2H, CH_2), 1.64-1.59 (m, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.4, 135.3, 126.4, 123.5, 123.3, 122.7, 122.6, 116.6, 109.6, 40.0, 33.5, 25.8, 23.7, 17.8. HRMS (ESI) m/z calcd for $C_{16}H_{19}NO$ $(M+H)^+$: 264.1364, found: 264.1375.

5-Methyl-1-(pyridin-3-yl)hex-4-en-1-one (3.3n): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 35 mg, 37%. IR (DCM; cm^{-1}): 3442, 1695, 1576, 1456, 1539, 1506, 1456, 776. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (d, J = 2.2 Hz, 1H, ArC*H*), 8.70 (dd, J_1 = 4.7 Hz, J_2 =1.6 Hz, 1H, ArC*H*), 8.16 (d, J = 7.9 Hz, 1H, ArC*H*), 7.34 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, ArC*H*), 5.15-4.95 (m, 1H, Olefinic C*H*), 2.94 (t, J = 7.4 Hz, 2H, CH_2), 2.37 (d, J = 7.4 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 153.4, 149.7, 135.4, 123.7, 122.5, 39.1, 29.8, 25.8, 22.7, 17.8, 14.2. HRMS (ESI) m/z calcd for $C_{12}H_{15}NO$ $(M+H)^+$: 190.1237, found: 190.1226.

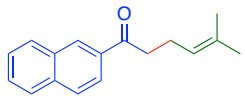
5-Methyl-1-(quinolin-3-yl)hex-4-en-1-one (3.3o): Purified by silica-gel column



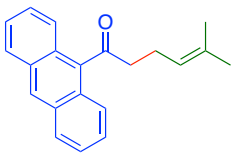
chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Colorless liquid. Yield: 72 mg, 60%. IR (DCM; cm^{-1}): 3446, 2923, 1683, 1616, 1436, 1375, 1126, 949, 751. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (s, 1H, ArC*H*), 8.72 (s, 1H, ArC*H*), 8.17 (d, J = 8.4 Hz, 1H, ArC*H*), 7.95 (d, J = 8.2 Hz, 1H, ArC*H*),

7.85 (t, *J* = 7.7 Hz, 1H, ArC*H*), 7.64 (t, *J* = 7.5 Hz, 1H, ArC*H*), 5.24-5.20 (m, 1H, Olefinic C*H*), 3.14 (t, *J* = 7.4 Hz, 2H, CH_2), 2.51 (q, *J* = 7.3 Hz, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.67 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 149.9, 149.3, 137.1, 133.4, 132.0, 129.6, 129.4, 129.3, 127.6, 127.0, 122.6, 39.2, 25.8, 22.9, 17.9. HRMS (ESI) m/z calcd for $C_{16}H_{17n}O$ $(M+H)^+$: 240.1388, found: 240.1399.

5-Methyl-1-(naphthalen-2-yl)hex-4-en-1-one (3.3p):[26] Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid. Yield: 77 mg, 65%. IR (DCM; cm^{-1}): 2966, 1700, 1456, 1374, 1181, 1123, 862, 747. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H, ArC*H*), 7.99-7.94 (m, 1H, ArC*H*), 7.89-7.87 (m, 1H, ArC*H*), 7.83-7.79 (m, 2H, ArC*H*), 7.54-7.45 (m, 2H, ArC*H*), 5.19-5.11 (m, 1H, olefinic C*H*), 3.06 (t, 2H, CH_2), 2.41 (q, *J* = 7.4 Hz, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.58 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.1, 135.6, 134.4, 132.9, 132.6, 129.7, 129.6, 128.4, 128.4, 127.8, 126.8, 124.0, 123.0, 38.9, 25.8, 23.1, 17.8. HRMS (ESI) m/z calcd for $C_{17}H_{18}O$ $(M+H)^+$: 261.1255, found: 261.1264.



1-(4a,10-Dihydroanthracen-9-yl)-5-methylhex-4-en-1-one (3.3q): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colorless liquid. Yield: 109 mg, 76% . IR (DCM; cm^{-1}): 2926, 1699, 1674, 1331, 1269, 1109, 936, 889, 735. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.94-7.90 (m, 2H, ArC*H*), 7.73-7.71 (m, 2H, ArC*H*), 7.42-7.38 (m, 4H, ArC*H*), 5.15-5.14 (m, 1H, Olefinic C*H*), 3.01 (q, J_1 = 8.6 Hz, J_2 = 8.0 Hz, 2H, CH_2), 2.50 (q, *J* = 7.4 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.57 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.4, 136.8, 133.3, 131.2, 128.9, 128.2, 127.1, 126.7, 125.5, 124.5, 122.7, 46.5, 25.8, 22.5, 17.9. HRMS (ESI) m/z calcd for $C_{21}H_{20}O$ $(M+H)^+$: 311.1411, found: 311.1425.



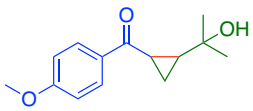
(*E*)-5,9-Dimethyl-1-phenyldeca-4,8-dien-1-one (3.3r): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. Colourless liquid. Yield: 69 mg, 54% . IR (DCM; cm^{-1}): 2976,1716, 1581, 1377, 1265, 1025, 896.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.9 Hz, 2H, ArC*H*), 7.50-7.46 (m, 1H, ArC*H*), 7.38 (t, *J* = 7.7 Hz, 2H, ArC*H*), 5.12 (t, *J* = 7.2 Hz, 1H, Olefinic C*H*), 5.03-4.99 (m, 1H, Olefinic C*H*), 2.93 (t, *J* = 7.5 Hz, 2H, CH_2), 2.37 (q, *J* = 7.4 Hz, 2H, CH_2), 1.95 (td, J_1 = 18.1 Hz, J_2 = 10.4 Hz, 4H, CH_2), 1.56 (t, *J* = 14.8 Hz, 9H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.1, 137.1, 136.5, 133.0, 131.4, 128.6, 128.1, 124.3, 122.8, 39.8, 38.8, 26.7, 25.7, 23.0, 17.8, 16.1. HRMS (ESI) m/z calcd for $C_{20}H_{16}O(M+H)^+$: 283.2058, found: 283.2090.

Spectral Data of Functionalized Compounds Prepared from α-Prenylated Ketones:

5-Methyl-1-phenylhex-4-en-1-ol (3.5a): Purified by silica-gel column chromatography using ethyl acetate/hexane (2:98) mixture as the eluent. Colourless liquid. Yield: 76 mg, 80% . ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, *J* = 6.2 Hz, 4H, ArC*H*), 7.20 (dd, J_1 = 8.6 Hz, J_2 = 4.3 Hz, 1H, ArC*H*), 5.08-5.05 (m, 1H, Olefinic C*H*), 4.59 (t, *J* = 6.6 Hz, 1H, C*H*), 1.98 (t, *J* = 7.2 Hz, 2H, CH_2), 1.81-1.65 (m, 3H, CH_2 & *OH*), 1.62 (s, 3H, CH_3), 1.51 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.8, 132.4, 128.5, 127.5, 126.0, 123.9, 74.3, 39.1, 25.8, 24.6, 17.8.

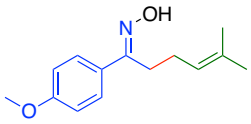
3,5-Dibromo-2,2-dimethyl-6-phenyl-3,4-dihydro-2H-pyran (3.5 b):[27] Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Colorless liquid. Yield: 81 mg, 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.38 (m, 2H, ArC*H*), 7.34-7.22 (m, 3H, ArC*H*), 4.13 (dd, J_1 = 9.1 Hz, J_2 = 6.0 Hz, 1H, C*H*), 3.06 (s, 1H, CH_2), 2.94 (dd, J_1 = 17.5 Hz, J_2 = 9.0 Hz, 1H, CH_2), 1.43 (d, *J* = 11.9 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.59, 135.28, 129.17, 129.09, 127.99, 92.51, 77.96, 51.89, 40.95, 26.88, 20.66.

(2-(2-Hydroxypropan-2-yl)cyclopropyl)(4-methoxyphenyl)methanone (3.5d):[28] Purified



by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Colorless liquid. Yield: 84 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.6 Hz, 2H, ArC*H*), 6.88 (d, J = 8.6 Hz, 2H, ArC*H*), 3.81 (s, 3H, ArOCH_3), 2.68 (dt, J_1 = 8.4 Hz, J_2 = 4.3 Hz, 1H, C*H*), 1.70-1.65 (m, 1H, CH_2), 1.44-1.41 (m, 1H, O*H*), 1.30 (dt, J_1 = 8.8 Hz, J_2 = 4.3 Hz, 1H, CH_2), 1.25 (d, J = 4.0 Hz, 6H, CH_3), 1.11-1.07 (m, 1H, C*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 163.5, 131.0, 130.4, 113.8, 68.9, 55.6, 36.4, 29.9, 29.6, 20.7, 14.1.

(E)-1-(4-Methoxyphenyl)-5-methylhex-4-en-1-one oxime (3.5e):[29] Purified by silica-gel



column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 110 mg, 95% . ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H, O*H*), 7.49 (d, J = 8.7 Hz, 2H, ArC*H*), 6.84 (d, J = 8.7 Hz, 2H, ArC*H*), 5.12 (t, J = 6.8 Hz, 1H, ArC*H*), 3.76 (s, 3H, ArOCH_3), 2.74 (t, J = 8.0 Hz, 2H, CH_2), 2.20 (q, J = 7.8 Hz, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.51 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 158.1, 131.8, 127.5, 126.8, 126.8, 122.5, 113.2, 113.1, 54.5, 25.7, 24.8, 24.1, 16.9.

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^{1}H and ^{13}C NMR spectra of *α*-prenylated products:

Figure 3.1 ^{1}H NMR spectrum of 2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1-one **3.2a**:

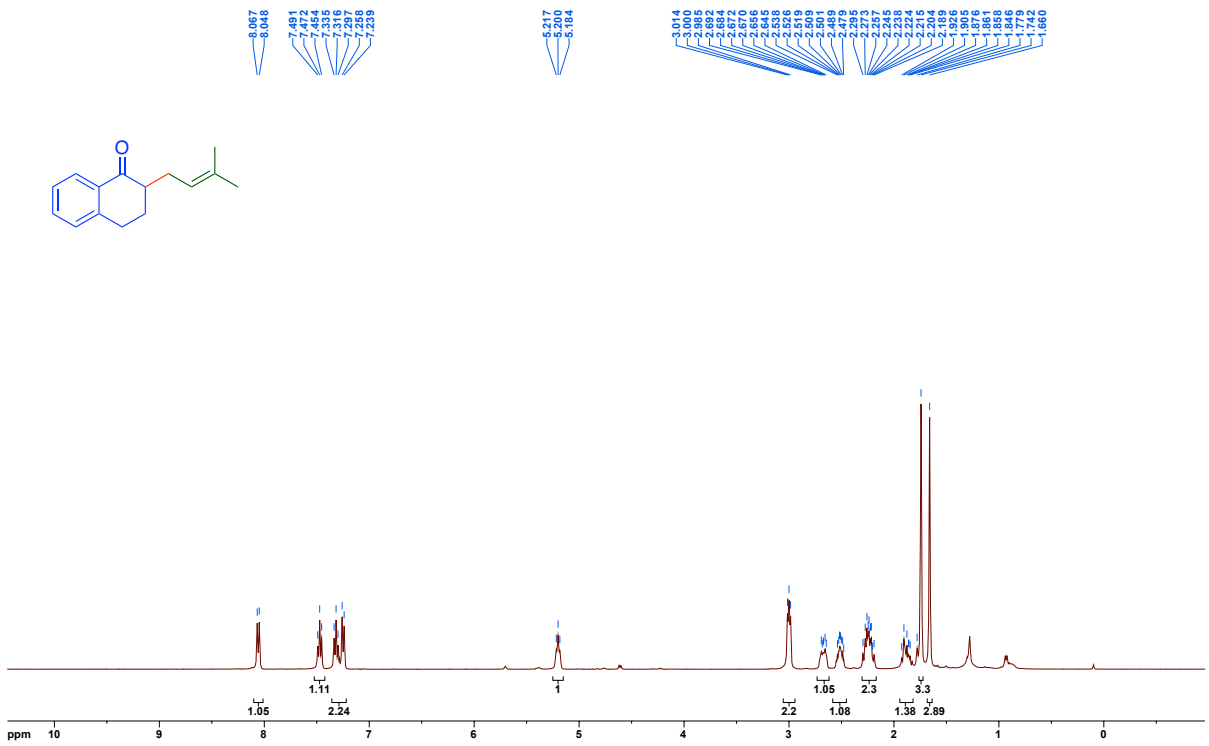


Figure 3.2 ^{13}C NMR spectrum of 2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1-one **3.2a:**

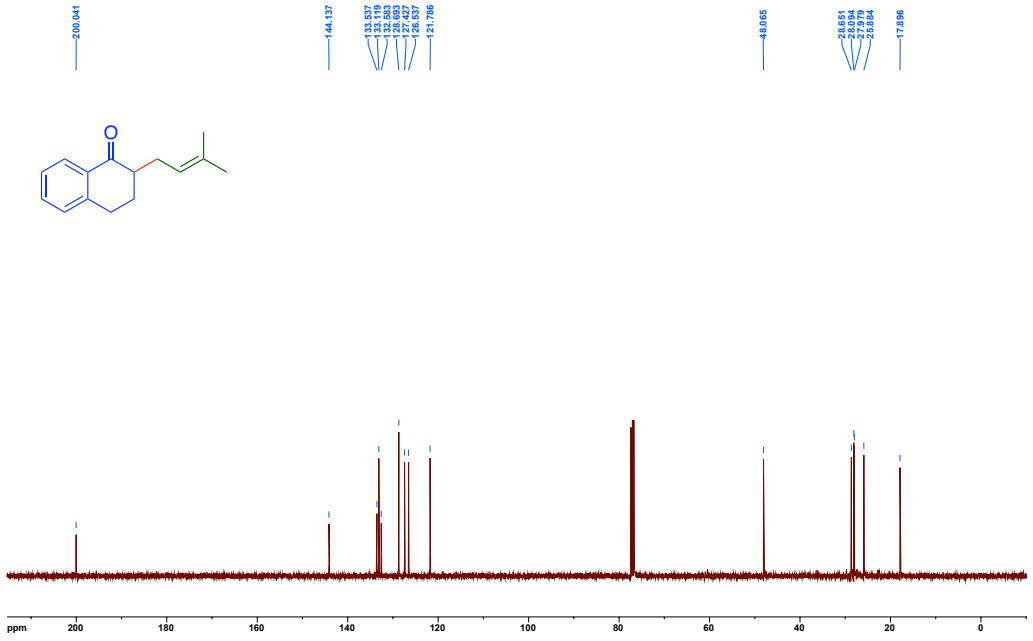


Figure 3.3 ^{1}H NMR spectrum of 7-bromo-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one **3.2f:**

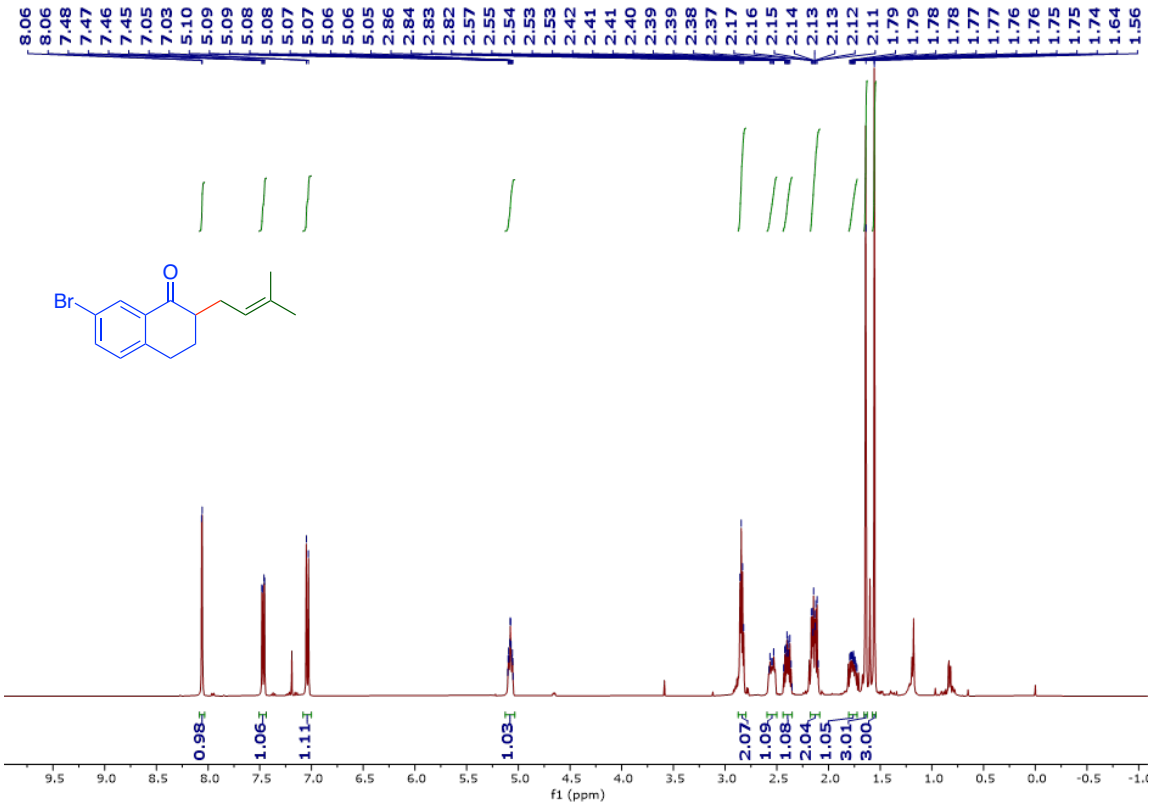


Figure 3.4 ^{13}C NMR spectrum of 7-bromo-2-(3-methylbut-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one **3.2f:**

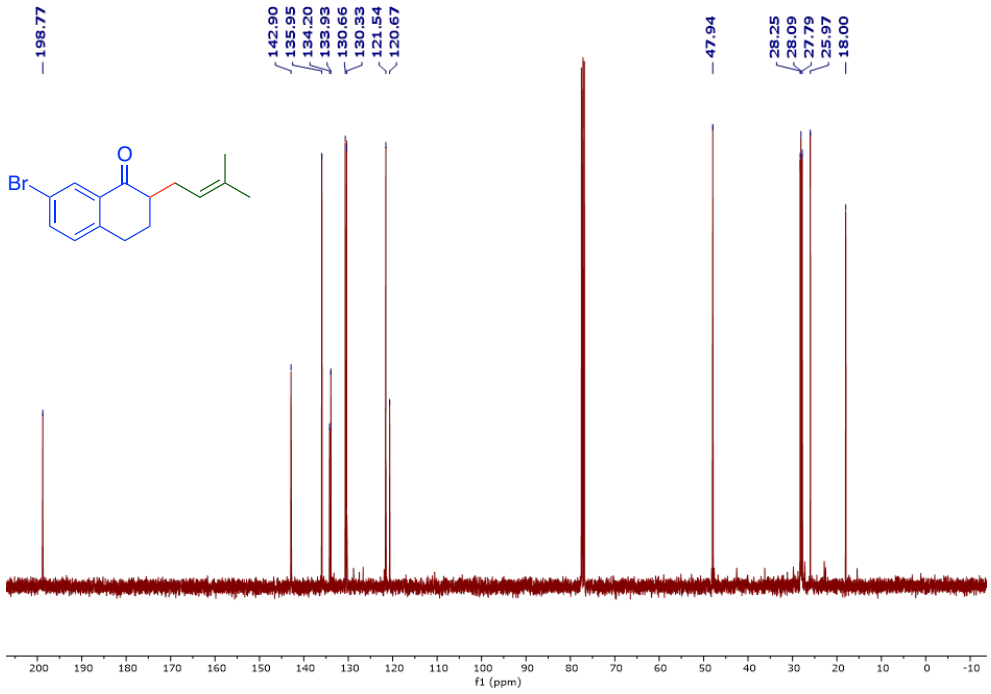


Figure 3.5 ^{1}H NMR spectrum of 5-methyl-1-phenylhex-4-en-1-one **3.3a:**

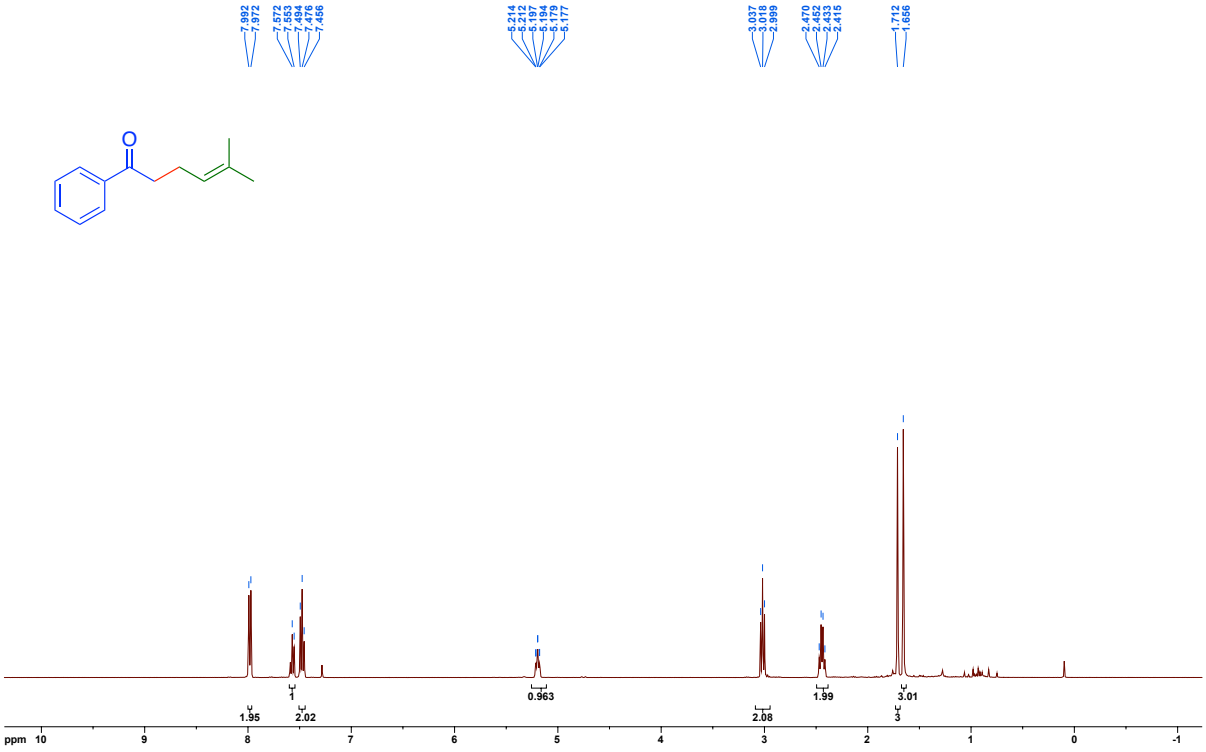


Figure 3.6 ^{13}C NMR spectrum of 5-methyl-1-phenylhex-4-en-1-one **3.3a:**

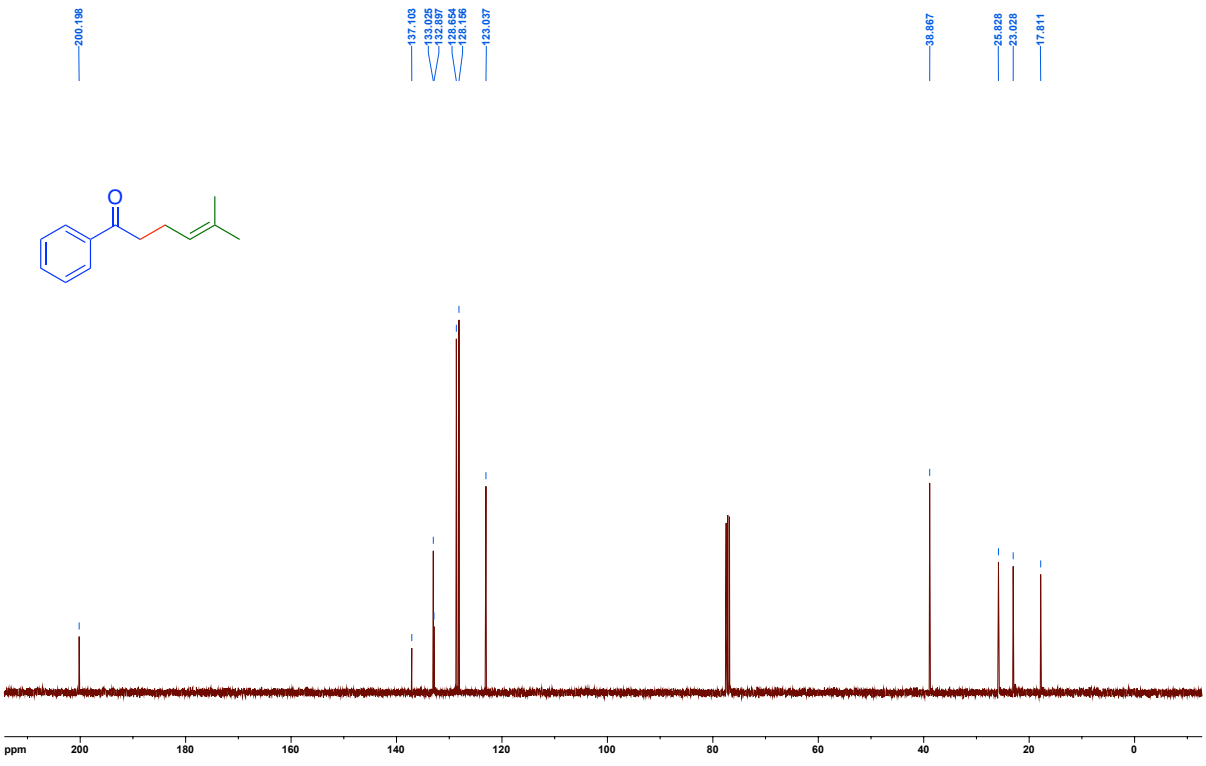


Figure 3.7 ^{1}H NMR spectrum of (2-(2-hydroxypropan-2-yl)cyclopropyl)(4-methoxyphenyl)methanone **3.5d:**

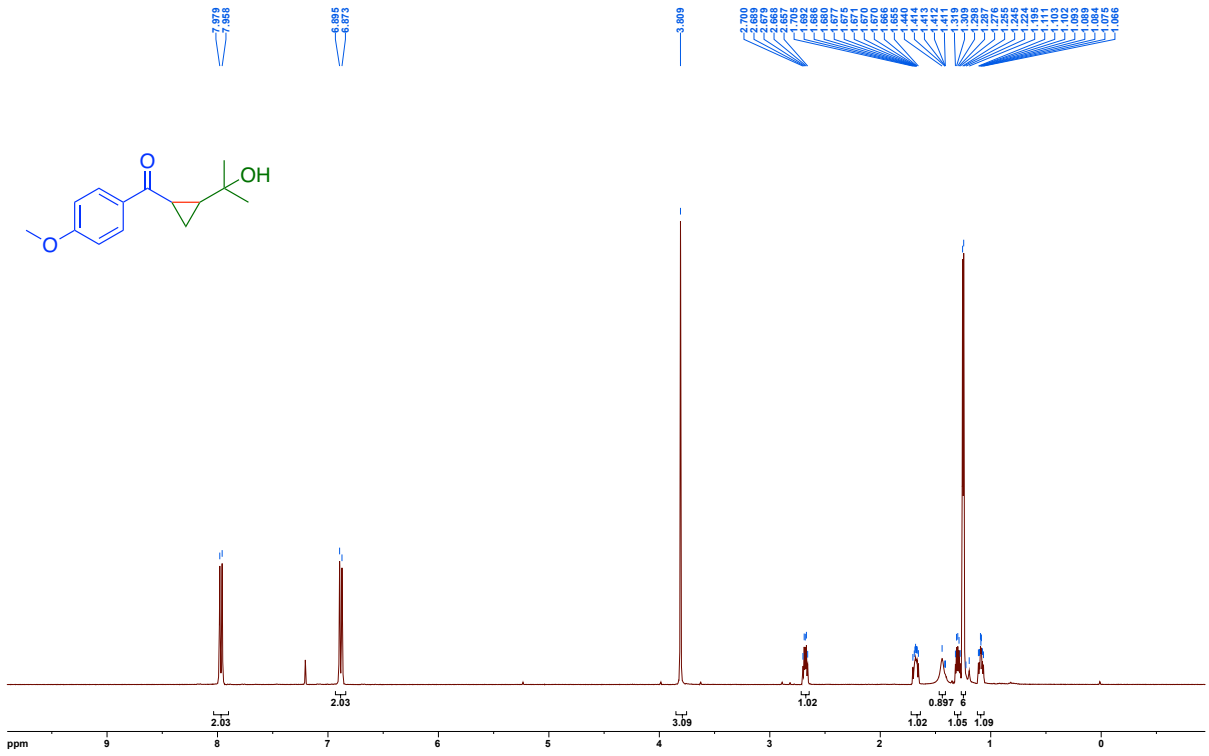
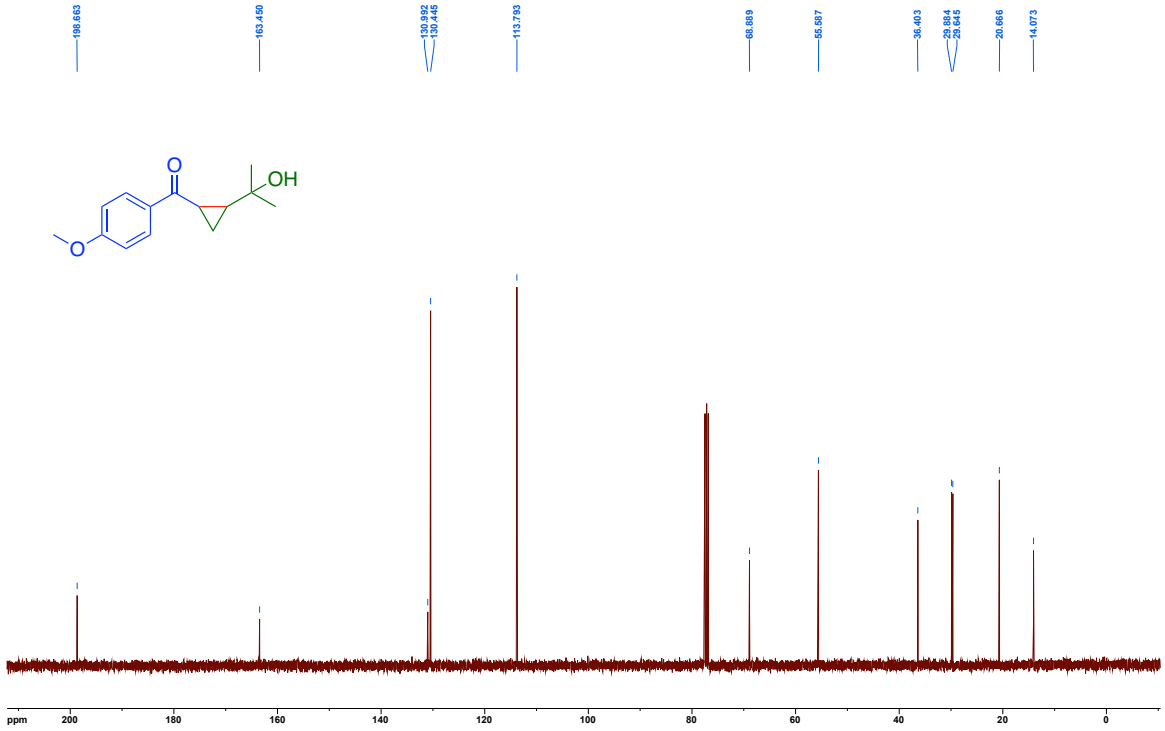


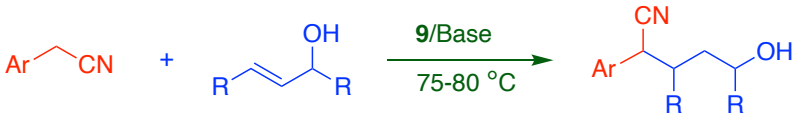
Figure 3.8 ^{13}C NMR spectrum of (2-(2-hydroxypropan-2-yl)cyclopropyl)(4-methoxyphenyl)methanone **3.5d:**



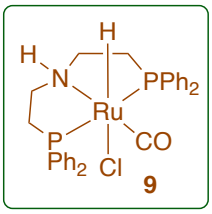
CHAPTER-4

Catalytic Formal Conjugate Addition: Direct Synthesis of δ-Hydroxynitriles from Nitriles and Allylic Alcohols

4.1 ABSTRACT



Advantages:
(i) allylic alcohols: cheap industrial feedstock
(ii) broad substrate scope
(iii) no stoichiometric base required
(iv) exclusive anti-Markovnikov selectivity
(v) atom economical & mild reaction conditions
(vi) functionalization of complex molecules
(vii) synthesis of natural products and drugs



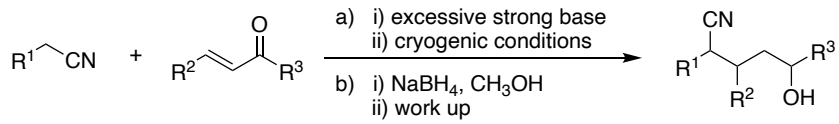
Alcohols and nitrile functionalities have widespread applications in biochemical and chemical synthesis. Catalytic transformations involving C−C bond formation relying on unsaturated coupling partners create important pathway for processes in synthetic, material, and medicinal chemistry. The discovery of a simple and selective coupling of nitriles with allylic alcohols catalyzed by a ruthenium pincer complex is described, which tolerates reactive functional groups such as carbamate, sulfonate, olefin, cyano, trifluoromethyl substituted benzyl nitriles. Homo allylic alcohols also provided 1,4-addition products following isomerization of double bonds. Mechanistic studies supported that the allylic alcohols initially undergo selective oxidation by the catalyst to α,β-unsaturated carbonyl compounds followed by 1,4-conjugate addition of benzyl nitriles-catalyzed by base, and subsequent catalytic reduction of carbonyl functionality leading to the formation of δ-hydroxynitrile products. Catalytic cycle of this tandem process is established by DFT studies. Remarkably, anipamil drug is successfully synthesized using this catalytic protocol. The utility of the δ-hydroxynitrile products in the synthesis of biologically active molecules and their further functionalization are also demonstrated

4.2 INTRODUCTION

From environmental and economic points of view, toxic byproducts-free and waste-free catalytic carbon-carbon (C–C) bond formation reactions are highly attractive, sustainable, and fundamentally important in synthetic chemistry. In this regard, the conjugate addition reactions are among the most important chemical transformations for C–C bond formation.[1] In the past two decades, great efforts have been made in conjugate addition reactions. As a testament to this, the Michael addition reaction remains the foremost method for the construction of a new C–C bond.[2-4] Till date, several elegant methods have been developed for the formation of new C–C bonds from α,β-unsaturated carbonyl compounds with carbon nucleophiles.[5-8] Although the base-mediated conjugate addition reactions are the powerful synthetic method, the conditions are often incompatible with reactive functional groups and lead to side reactions. Milstein and coworkers have reported a base free conjugate addition of nitriles with α,β-unsaturated carbonyl compounds using Re and Mn pincer catalyst systems.[9,10] Formal conjugate addition of allylic alcohols is a burgeoning strategy; the reaction of heteroatom (O, NH) nucleophiles has been reported for the synthesis of functionalized alcohols. A pioneering report by Oe and coworkers demonstrated the formal anti-Markovnikov hydroamination of allylic alcohols using a ruthenium catalyst.[11] Wang and coworkers reported iron-catalyzed conjugate addition of amines and amides with allylic alcohols.[12] Very recently, ruthenium and manganese catalyzed anti-Markovnikov hydroamination of allylic alcohols for the synthesis of chiral γ-amino alcohols has been reported.[13-16] The formal anti-Markovnikov hydroalkoxylation of allylic alcohols has been described.[17] Despite these enticing developments using heteroatom nucleophiles with allylic alcohols, the carbon nucleophiles are poorly documented in the formal conjugate addition reactions.[18-21]

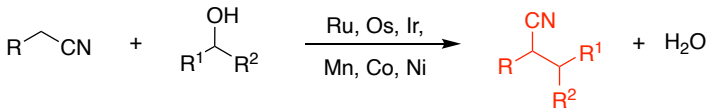
Scheme 4.1 State of the Art of Nitriles in BH, ADC Reactions Using Alcohols as Alkylating Agents and Envisaged Strategy for Conjugate Addition Reactions with Allyl Alcohols

a) Conventional method: 1,4-conjugate addition of α,β-unsaturated carbonyl compounds and further reduction

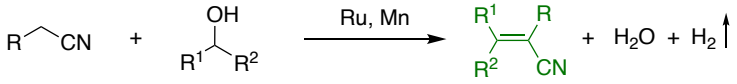


Drawbacks:
(i) high risk & safety issues
(ii) side reactions
(iii) multi step procedure
(iv) copious waste

b) α-Alkylation and α-olefination of nitriles using primary and secondary alcohols



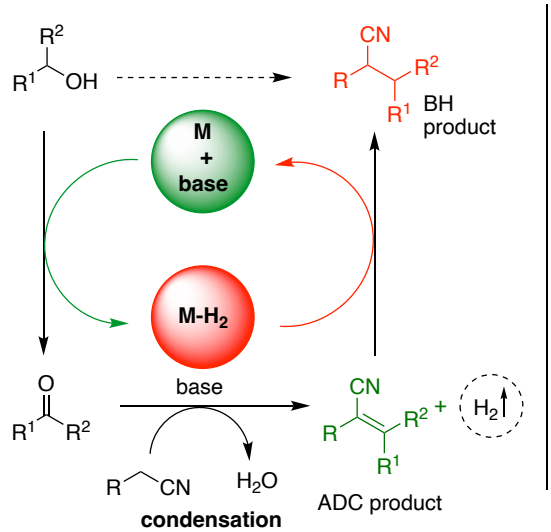
via borrowing hydrogen (BH) strategy



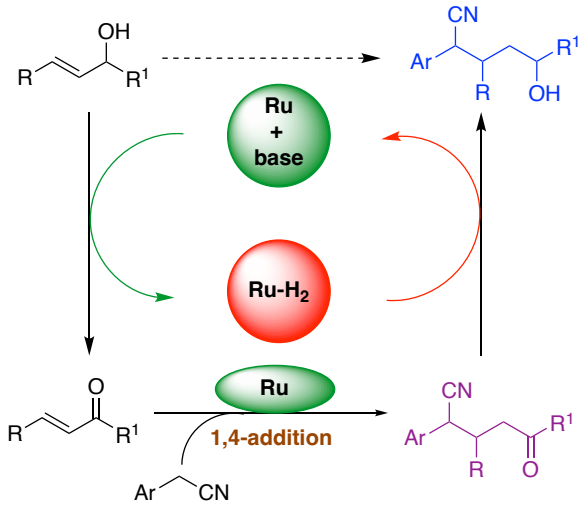
via accetorless dehydrogenative coupling (ADC) strategy

R = aryl, alkyl; R^1 = H, aryl, alkyl; R^2 = aryl, alkyl

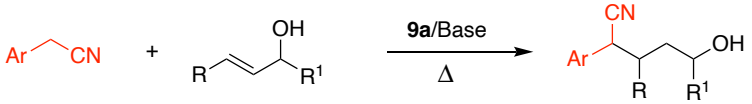
c) General pathways for BH and ADC reactions

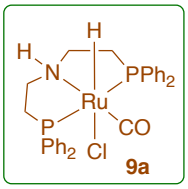


d) Envisaged strategy: catalytic formal conjugate addition of nitriles to allylic alcohols



e) This work: formal conjugate addition of nitriles with allylic alcohols





Advantages:
(i) allylic alcohols: cheap industrial feedstock
(ii) broad substrate scope
(iii) excellent selectivity
(iv) no stoichiometric base required
(v) exclusive anti-Markovnikov selectivity
(vi) atom economical & mild reaction conditions
(vii) drug synthesis and further functionalizations

Nitrile is a fundamental structural motif in pharmaceuticals and natural product synthesis.[22,23] δ-Hydroxynitriles are frequently used as starting materials and intermediates for the synthesis of diols, lactones, lactams, amino alcohols, and cyclic amine derivatives.[24-28] Furthermore, 5-hydroxy-2,3-diphenylpentanonitrile derivatives were used as herbicides and plant growth regulators.[29] Synthesis of δ-hydroxynitrile compounds from conventional processes requires multistep procedures and tedious experimental conditions (**Scheme. 4.1a**).[30,31] Direct formal conjugate addition of allylic alcohols with nitriles is one of the most atom economical and environmentally benign methods for constructing new C–C bonds (**Scheme 4.1d-e**). However, the catalytic formal conjugate addition of nitriles with allylic alcohols to directly synthesize δ-hydroxynitriles remains unknown in the literature. The major challenge in formal conjugate addition reactions is the deleterious side reactions involving in situ formed α,β-unsaturated carbonyl compounds, which undergo self-coupling via aldol reactions and generates undesired byproducts and hence, diminishes the atom economy of the overall transformation. Thus, it is desirable to develop a new catalytic strategy for the synthesis of δ-hydroxynitriles directly from nitriles and allylic alcohols (**Scheme 4.1e**).

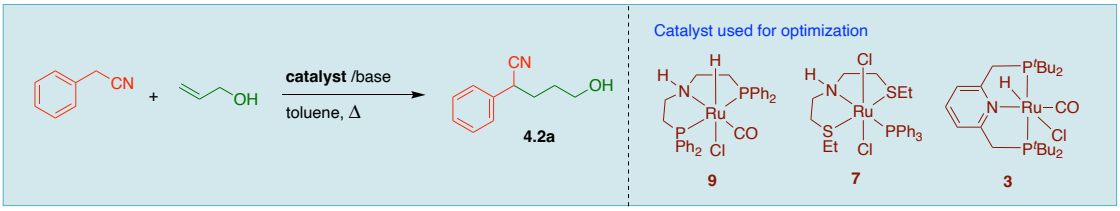
Our group demonstrated Ru-macho (**9**) catalyzed selective α-alkylation and α-olefination of nitrile compounds by primary and secondary alcohols in which the reactions proceeded through borrowing hydrogen and acceptorless dehydrogenative coupling pathways, respectively (**Scheme 4.1b-c**).[32,33] Notably, various transition metal catalysts are also reported by other research groups for the α-alkylation[34-41] and α-olefination[42] of nitriles using alcohols (**Scheme 4.1b-c**). Selective cross-coupling of secondary alcohols to β-disubstituted ketones,[43,44] α-alkylation of ketones,[45] ketazines synthesis[46] using secondary alcohols, N,N-dialkylation of acylhydrazides using both primary and secondary alcohols[47] and regioselective hydrogenation of epoxides to secondary alcohols catalyzed by **9** have been reported by us.[48] In continuation, we envisioned the formal conjugate addition of allylic alcohols with nitriles as carbon

nucleophiles and regeneration of hydroxyl functionality through hydrogenation of in situ formed carbonyl motif (**Scheme. 4.1d**). Accordingly, herein we report the catalytic synthesis of δ-hydroxynitrile compounds with diverse functionalities through a formal 1,4-addition of nitriles to primary and secondary allylic alcohols (**Scheme 4.1e**). Notably, this catalytic method does not require stoichiometric oxidants; it requires only a catalyst, a catalytic amount of base, and proceeds under mild reaction conditions.

4.3 RESULTS AND DISCUSSION

At the outset of investigations, the reaction of selected model substrates phenyl acetonitrile (0. 5 mmol, 1 equiv) and allyl alcohol (1 mmol, 2 equiv) using catalyst **9** (0.5 mol%) and base (KO^tBu, 1 mol%) at 80 °C (entry 1, **Table 4.1**) was performed. Complete conversion of phenyl acetonitrile was observed, and the anticipated conjugate addition product **4.2a** was isolated in 61% yield (entry 1, **Table 4.1**). In contrast to our previous report using primary alcohols, α-alkylation product was not detected in this catalysis.[32] Notably, a minor amount of undesired O-addition product (11%) along with other unpredictable mixture of oligomer products were observed. Further, by varying the temperature under similar conditions, no improvement in yield was observed (entries 2-3, **Table 4.1**). When the catalyst (**9**) loading increased to 1 mol % and amount of base to 2 mol %, the product yield slightly increased to 66% (entry 4, **Table 4.1**). Lowering catalyst loading and base, varying stoichiometry of allyl alcohol, and use of 1,4-dioxane and isopropyl alcohol together with toluene as mixture of solvents, the target product **4.2a** was drastically decreased (entries 5-9, **Table 4.1**). Furthermore, reducing the temperature to 75 °C improved the product formation to 75% isolated yield (entry 10, **Table 4.1**). Indeed, the yield of product **4.2a** was improved by using mild bases (entries 11-13, **Table 4.1**). Interestingly, with the use of catalyst **9** (1 mol %) and K_2CO_3 base (2 mol %), the yield of product **4.2a** was obtained in 85% (entry 14, **Table 4.1**).

Table 4.1 Optimization Reaction Conditions[a]



entry	cat. (mol%)	base (mol%)	alcohol (equiv.)	temp (°C)	time (min)	conv (%)[b]	yield (%)[c]
1	9 (0.5)	KO^{t}Bu (1 mol %)	2	80	20	>99	61
2	9 (0.5)	KO^{t}Bu (1 mol %)	2	65	120	85	48
3	9 (0.5)	KO^{t}Bu (1 mol %)	2	90	20	>99	65
4	9 (1)	KO^{t}Bu (2 mol %)	2	80	20	>99	66
5	9 (0.2)	KO^{t}Bu (0.5mol %)	2	80	120	50	30
6	9 (0.5)	KO^{t}Bu (1 mol %)	3	80	20	>99	59
7	9 (0.5)	KO^{t}Bu (0.5 mol %)	2	80	30	75	50
8[d]	9 (0.5)	KO^{t}Bu (1 mol %)	2	80	240	>99	48
9[e]	9 (0.5)	KO^{t}Bu (1 mol %)	2	80	240	77	10
10	9 (0.5)	KO^{t}Bu (1 mol %)	2	75	120	>99	75
11	9 (0.5)	LiO^{t}Bu (1 mol %)	2	80	240	>99	76
12	9 (0.5)	K_2CO_3 (1 mol %)	2	80	30	>99	77
13	9 (0.5)	K_2CO_3 (1 mol %)	1.5	75	120	>99	82
14	9 (1)	K_2CO_3 (2 mol %)	1.5	75	120	>99	85
15	9 (0.5)	K_2CO_3 (1 mol %)	1.3	75	240	90	66
16	9 (0.5)	Cs_2CO_3 (1 mol %)	1.5	75	240	94	70

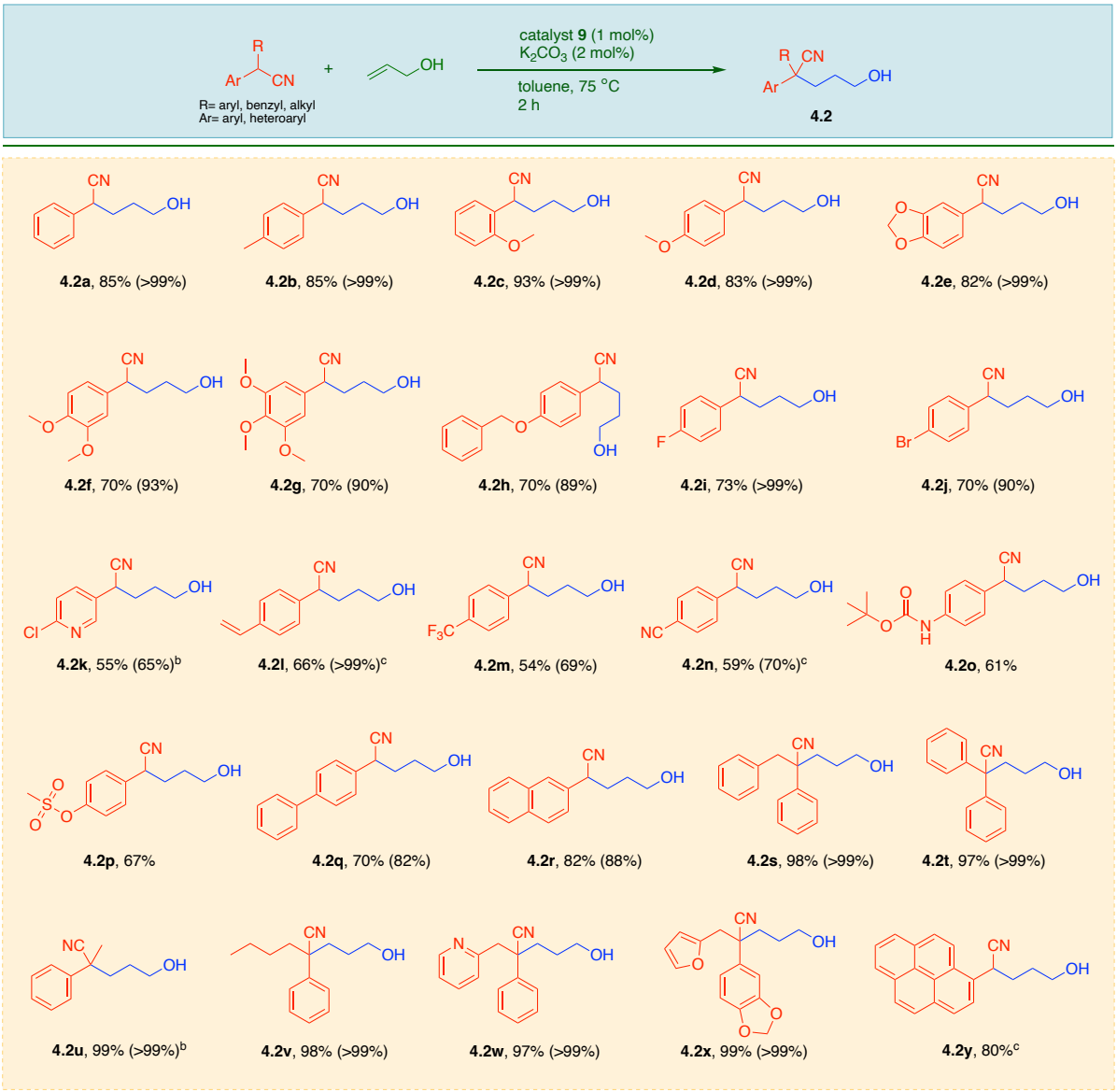
17[f]	9 (1)	K_2CO_3 (2 mol %)	1.5	75	120	60	54
18[g]	9 (1)	K_2CO_3 (2 mol %)	1.5	75	120	>99	61
19	7 (1)	K_2CO_3 (2 mol %)	1.5	75	120	-	-
20	3 (1)	K_2CO_3 (2 mol %)	1.5	75	120	10	-
21[h]	-	K_2CO_3 (1 mol %)	1.5	75	240	5	-
22[h]	-	-	1.5	75	240	-	-

[a]Reaction conditions: phenyl acetonitrile (0.5 mmol, 1 equiv), allyl alcohol, toluene (1.5 mL), catalyst **9, 7, 3** and base were heated at an indicated temperature under nitrogen flow. [b]Conversion of phenyl acetonitrile was determined by GC analysis using mesitylene as an internal standard. [c]Yields were calculated for pure isolated products after column chromatography. [d]1:1 ratio of toluene and 1,4-dioxane was used as a solvent. [e]1:1 ratio of toluene and isopropyl alcohol was used as a solvent. [f]Benzene was used as a solvent. [g]THF was used as a solvent. [h]Reaction was performed up to 24 h.

Further, reducing catalyst loading, amount of base, and stoichiometry allyl alcohol, and changing to milder base Cs_2CO_3 resulted in comparatively lower yields of **4.2a** (entries 15-16, **Table 4.1**). Moreover, reactions performed in benzene and tetrahydrofuran (THF) solvents afforded the product **4.2a** in diminished yields (entries 17,18, **Table 4.1**). Next, applicability of other catalysts such as Gusev catalyst (**7**), and Milstein PNP pincer catalyst (**3**) on this formal conjugate addition was tested, which failed to provide the product **4.2a** (entries 19,20, **Table 4.1**). Finally, control experiments were performed, in the absence ofcatalyst and in the absence of both catalyst and base provided no product formation indicating the importance of catalyst and base for the success of this catalytic reaction (entries 21,22, **Table 4.1**).

With the optimized reaction conditions established, the scope of the conjugate addition reactions was investigated. Using allyl alcohol as a standard substrate, a reaction with different substituted nitriles was tested in this protocol (Scheme 4.2). Simple substituents like methyl, methoxy, methylenedioxy, trimethoxy and benzyloxy-phenyl acetonitrile derivatives were well tolerated and provided the products **4.2b**-**4.2h** in good yields. A broad range of functional groups such as halides, heteroarene, olefin, trifluoromethyl, cyano, carbamate, sulfonates and biaryl substituted arylmethyl nitriles were well tolerated in this transformation and ensued the corresponding products **4.2i**-**4.2r** in moderate to very good yields. Tri-substituted phenyl acetonitrile derivatives resulted in complete conversion with excellent yields of the products **4.2s**-**4.2x**. The reaction of 2-(pyren-1-yl) acetonitrile with allyl alcohol afforded the product **4.2y** in 80% yield [upon the use of increased catalyst loading (3 mol %) and base (6 mol %)].

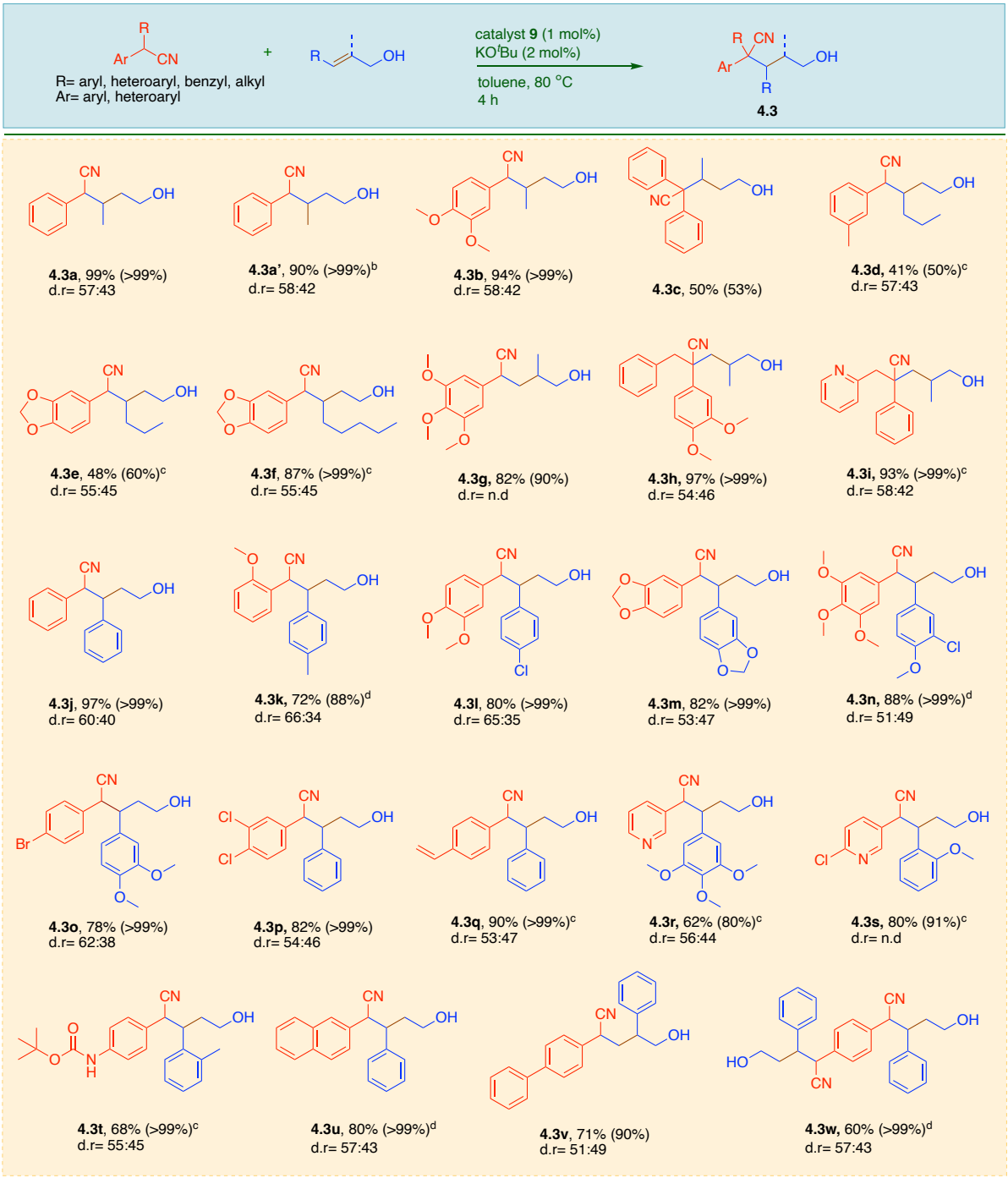
Scheme 4.2. Ruthenium-Catalyzed Selective Formal Conjugate Addition of Nitriles with Allyl Alcohol[a]



Reaction conditions: [a]Nitrile (0.5 mmol, 1 equiv), allyl alcohol (0.75 mmol, 1.5 equiv), toluene (1.5 mL), catalyst **9** (1 mol %), and K_2CO_3 (2 mol %) were heated at 75 °C under nitrogen flow for 2 h. Conversion of nitrile was determined by GC analysis using mesitylene as an internal standard is given within parentheses. Reported yields were calculated for pure isolated products after column chromatography. [b]2 mol % of catalyst **9** and 4 mol % of K_2CO_3 were used. [c]Reaction was performed using 3 mol % of catalyst **9** and 6 mol % of K_2CO_3 base.

The applicability of various allylic alcohols in reaction with different arylmethyl nitriles was explored next. However, use of K_2CO_3 as a base in conjugate addition with substituted allylic alcohol was found to be ineffective. Thus, upon the use of KO^{t}Bu as a base, similar catalytic reactivity as in the case of allyl alcohol was observed, the reactions proceeded facile with substituted allylic alcohol derivatives, and the results are summarized in **Scheme 4.3**. The reaction of crotyl alcohol with phenyl acetonitrile afforded the product **4.3a** in quantitative yield. Notably, the products were isolated as diastereomers, and the diastereomeric ratios were determined from ^{1}H NMR analyses of the crude reaction mixtures. Interestingly, the reaction of 1-buten-4-ol with phenyl acetonitrile also provided the anticipated product **4.3a'** in 90% yield in which catalytic conjugate addition occurred after isomerization of the double bond. Different primary allylic alcohols were investigated, and the products **4.3b-4.3i** were obtained in good to excellent yields. Further, cinnamyl alcohol bearing a variety of substituents (methyl, chloro, methylenedioxy, dimethoxy) on the arene ring with different nitriles compounds were converted to the corresponding products **4.3j-4.3p** in moderate to very good yields. The reaction of 4-vinyl phenyl acetonitrile with cinnamyl alcohol given the product **4.3q** in quantitative conversion and high yield (90%) in which the vinyl functionality is retained. Similarly, 2-(pyridin-3-yl)acetonitrile derivatives are also well-tolerated and afforded the products **4.3r**, and **4.3s**. 4-*N*-Boc-phenyl acetonitrile and 2-napthylacetonitrile were reacted with substituted cinnamyl alcohols, and the corresponding products **4.3t** and **4.3u** were obtained in good yields. When 4-biphenylacetonitrile reacted with 2-phenylprop-2-en-1-ol, the corresponding product **4.3v** was isolated in 71% yield. Remarkably, a reaction of 1,4-phenylendiacetonitrile with cinnamyl alcohol was tested, which afforded **4.3w** in 60% yield.

Scheme 4.3 Ruthenium-Catalyzed Selective Formal Conjugate Addition of Nitriles with Allylic Alcohols[a]

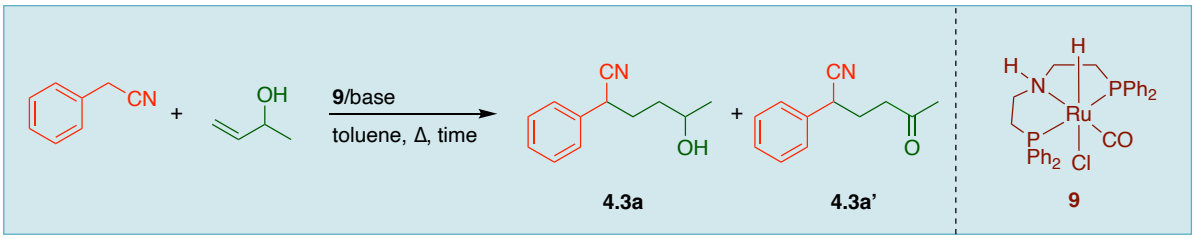


Reaction conditions: [a]Nitrile (0.5 mmol, 1 equiv), allylic alcohol (0.75 mmol, 1.5 equiv), toluene (1.5 mL), catalyst **9** (1 mol %) and KO^{t}Bu (2 mol %) heated at 80 °C under nitrogen flow for 4 h. Conversion of nitrile is given within parentheses and determined by GC analysis using mesitylene as an internal standard. Reported yields were calculated for pure isolated

products after column chromatography. [b]5 mol % of KO^{t}Bu was used. [c]3 mol % of catalyst **9** and 6 mol % of KO^{t}Bu base were used. [d]Reaction was performed using 2 mol % of catalyst **9** and 4 mol% of KO^{t}Bu base. n.d = not determined.

After exploring the substrate scope of primary allylic alcohols, we turned our attention to secondary allylic alcohols. Using 3-buten-2-ol as standard substrate, initial experiments with potassium carbonate (K_2CO_3) as a base provided a mixture of δ-hydroxynitrile and δ-ketonitrile products (**4.4a** and **4.4a'**, entries 1-4, **Table 4.2**). The catalytic reaction using KO^{t}Bu as a base and excess of 3-buten-2-ol (3 equiv) also provided **4.4a** and **4.4a'** in almost 1:1 ratio (entry 5, **Table 4.2**). This observation can be attributed to relatively challenging hydrogenation of in situ formed keto functionality in comparison with aldehydes (**Schemes 4.2,4.3**).

Table 4.2 Optimization Table for the Ruthenium-Catalyzed Selective Formal Conjugate Addition of Phenyl Acetonitrile with 3-Buten-1-ol[a]



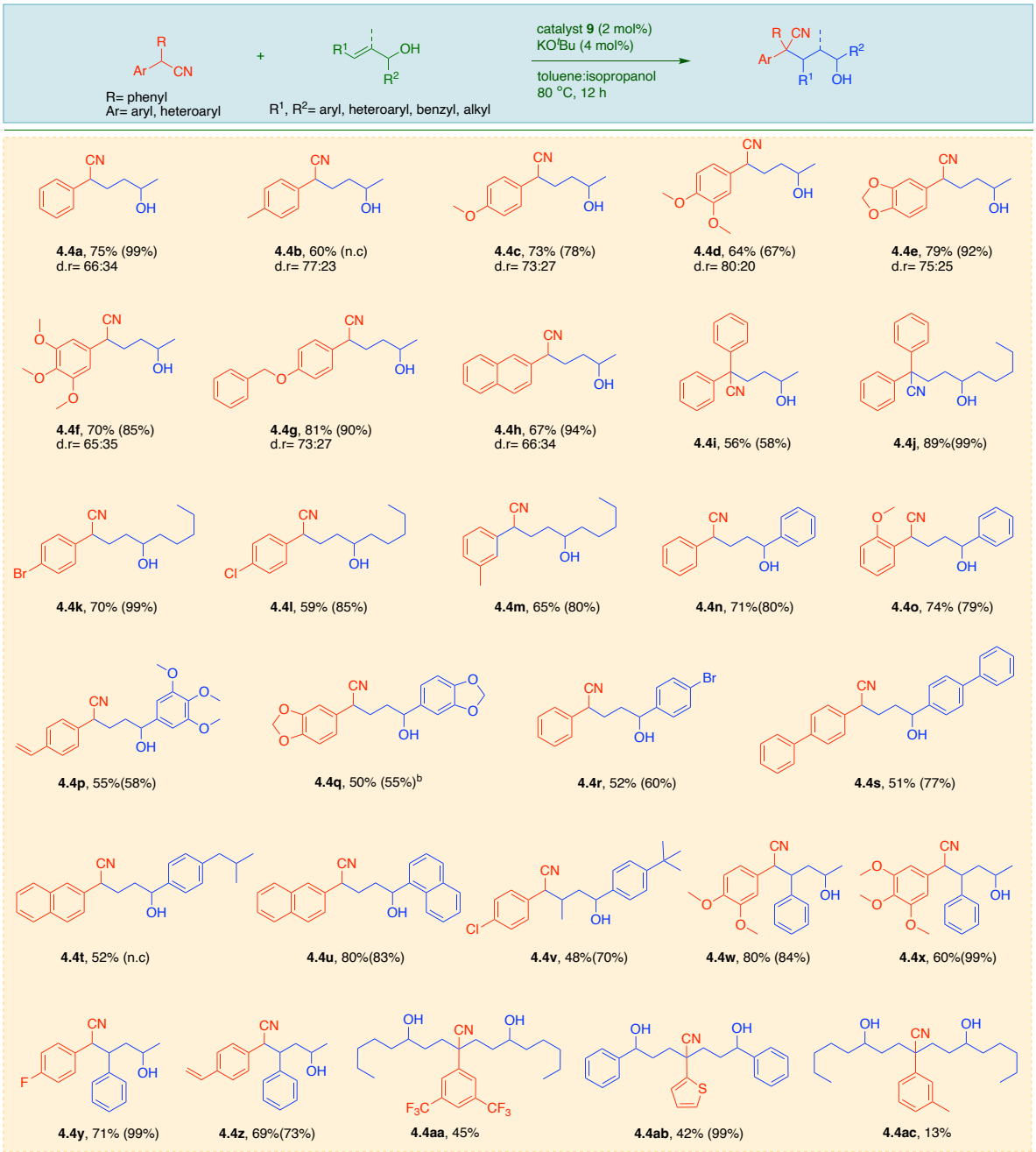
entry	cat. **9** (mol%)	base (mol %)	alcohol (equiv.)	temp. (°C)	time (h)	solvent	yield (%)[b]	
							4.3a	4.3a'
1	1	K_2CO_3(2 mol %)	2	75	12	toluene	48	29
2	1	K_2CO_3(2 mol %)	1	75	4	toluene	30	-
3	2	K_2CO_3 (4 mol %)	2	80	4	toluene	38	22
4[c]	2	K_2CO_3 (4 mol %)	2	80	4	toluene + IPA	49	16
5	1	KO^{t}Bu (2 mol %)	3	80	4	toluene	35	36
6[d]	2	KO^{t}Bu (4 mol %)	2	80	12	toluene + IPA	75	10
7[d]	2	KO^{t}Bu (4 mol %)	2	80	16	toluene + IPA	60	-
8[d]	-	KO^{t}Bu (4 mol %)	2	80	24	toluene + IPA	-	-
9[d]	-	-	2	80	24	toluene + IPA	-	-

[a]Reaction conditions: phenyl acetonitrile (0.5 mmol, 1 equiv), 3-buten-2-ol, toluene (1.5 mL), catalyst **9** and base were heated at indicated temperature under nitrogen flow. [b]Yields were calculated for pure isolated products after column chromatography. [c]200 μL of isopropyl alcohol (IPA) was used. [d]Toluene and isopropyl alcohol (IPA) were used 3:1 ratio.

In order to solve this selectivity issue, the addition of IPA was envisaged as it can assist the hydrogenation of ketone through the transfer hydrogenation process. Upon use of 3:1 mixture of toluene and IPAas a solvent, predominant formation of δ-hydroxynitrile **4.4** (75%) was obtained (entry 6, **Table 4.2**). Notably, the reaction was performed for longer time 16 h and the exclusive formation of product **4.4** was observed in 60% yield (entry 7, **Table 4.2**). No product formation was observed on control experiments performed with and without base and catalyst (entries 8,9, **Table 4.2**).

Following the optimized conditions shown in **Scheme 4.4**, an assortment of substituted phenyl acetonitrile derivatives reacted with 3-buten-2-ol and delivered the corresponding δ-hydroxylnitrile products **4.4b**-**4.4i** in moderate to good efficiency. Likewise, the reaction of 1-octen-3-ol with different nitriles provided the products **4.4j**-**4.4m** in good yields. Furthermore, a variety of aryl-substituted allylic alcohols was amenable to formal conjugate addition and produced the δ-hydroxylnitrile products **4.4n**-**4.4z** in high yields. Interestingly, the reaction of electron-deficient arylacetonitrile with secondary allylic alcohol such as 1-octene-3-ol delivered exclusive double conjugate addition product **4.4aa** in 45% yield. Moreover, the similar double conjugate addition products **4.4ab** and **4.4ac** were isolated in good to moderate yields (Scheme 4). Notably, the formation of δ-ketonitrile compound (**4.4a'**) remained pertain to the reaction of benzylnitrile and 3-buten-2-ol and such δ-ketonitrile was not observed in any other reactions (**4.4b**-**4.4aa**).

Scheme 4.4 Ruthenium-Catalyzed Selective Formal Conjugate Addition of Nitriles with Secondary Allylic Alcohols[a]

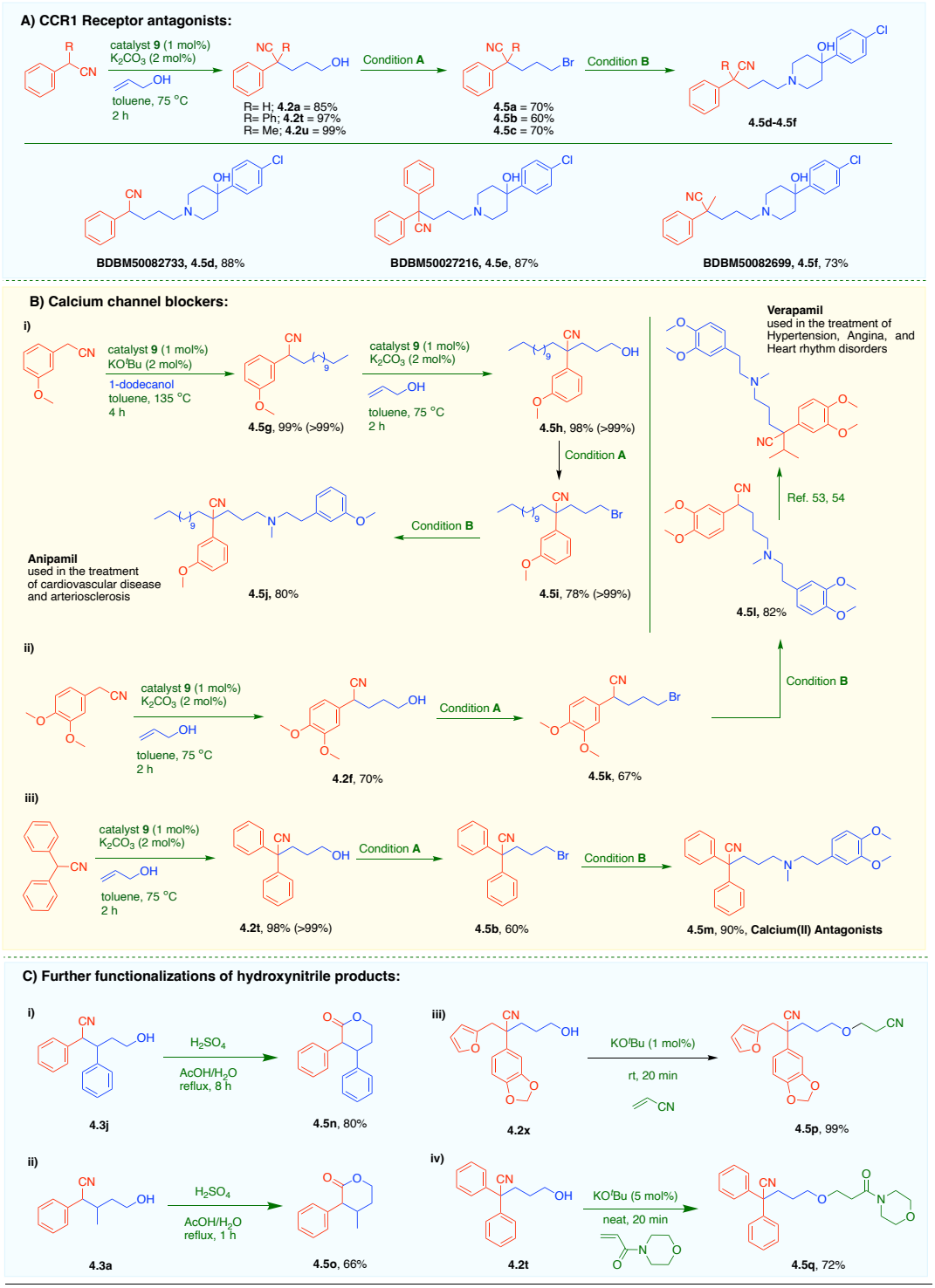


[a]Reaction conditions: Nitrile (0.5 mmol, 1 equiv), allylic secondary alcohol (1 mmol, 2 equiv), mixture of toluene and isopropyl alcohol (3:1 ratio, 2 mL), catalyst **9** (2 mol %), KO^{t}Bu base (4 mol%) were heated at 80 °C under nitrogen flow. Conversion of nitrile was determined by ^{1}H NMR analyses of the crude reaction mixture using benzyl benzoate as an internal standard is given within parentheses. Yields were calculated for pure isolated products after column

chromatography. [b]3 mol % of catalyst **9** and 6 mol % of KO^{t}Bu base were used. n.c = not calculated.

Synthetic Applications. To demonstrate the utility of the δ-hydroxynitrile products, synthesis towards various drugs and pharmaceutically important molecules was conducted (**Scheme 4.5**). Products **4.2a**, **4.2t,** and **4.2u** were converted to the corresponding bromo compounds **4.5a**, **4.5b,** and **4.5c** in 60, 70, and 60% yield, respectively. Then, the reaction of 4-(4-chlorophenyl) piperidin-4-ol with **4.5a-4.5c**, delivered the CCR1 receptor antagonists (**4.5d-4.5f**) in very good yields, which are used for the treatment of chronic inflammatory diseases (**Scheme 4.5A**).[49,50] Next, the applicability of this catalytic process for the synthesis of drug molecules was examined. Alkylation of 3-methoxy phenylacetonitrile with 1-dodecanol catalyzed by **9** provided the product **4.5g** in quantitative yield,[32] which further reacted with allyl alcohol under standard reaction conditions and resulted in the product **4.5h** in 98% yield. Then, the resulting alcohol **4.5h** is subjected to bromination to obtain **4.5i**, followed by N-alkylation reaction with (3-methoxy)-*N*-methyl phenethylamine to result in anipamil drug **4.5j** in 80% yield (**Scheme 4.5Bi**). Notably, this is the first catalytic synthesis of anipamil drug.[51,52] Besides, formal synthesis of verapamil drug is also demonstrated. Product **4.2f** is converted into the brominated compound **4.5k** in 67% isolated yield and then N-alkylation with (3,4-dimethoxy)-*N*-methyl phenethylamine afforded product **4.5l** in 82% yield (**Scheme 4.5Bii**). Introducing an isopropyl unit at benzylic nitrile carbon on **4.5l** following the reported procedure can result in verapamil.[53,54] Then, under a similar procedure, verapamil-like drug **4.5m was** also synthesized, which is used for treating cardiovascular diseases (**Scheme 4.5Biii**). Notably, these new catalytic syntheses have many advantages in terms of synthetic brevity and atom economy compared to conventional synthesis involving strong bases, stoichiometrically excess reagents, and elongated synthetic steps. Furthermore, functionalization of the δ-hydroxynitrile products is conducted.

Scheme 4.5 Application of Catalytic Formal Conjugate Addition Reactions in Synthesis of Biologically Active Molecules, Drugs and Further Functionalization

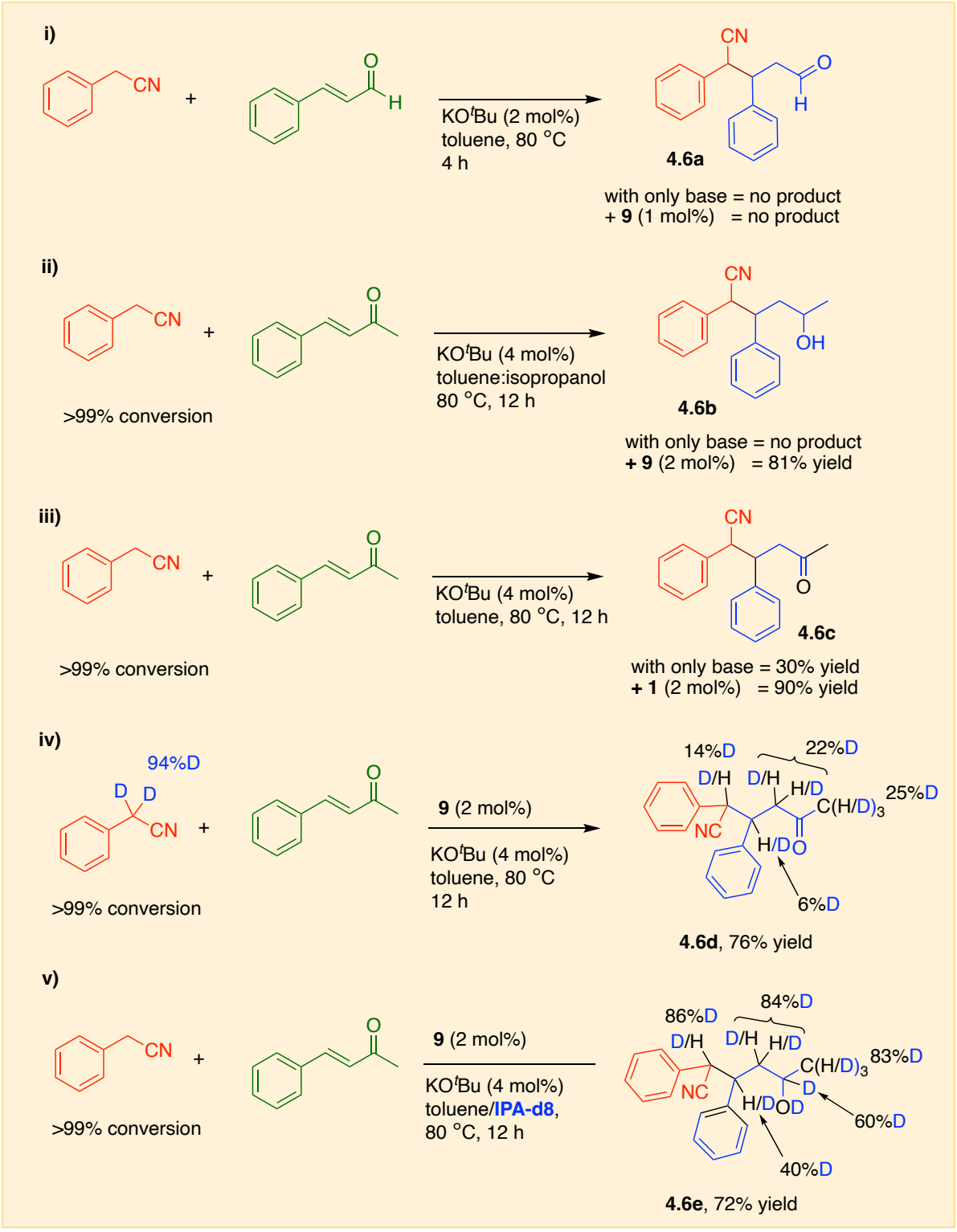


Reaction conditions: Condition **A**: *δ*-Hydoxynitrile derivative (0.5 mmol, 1 equiv), PBr_3 (0.6 mmol, 1.1 equiv), toluene, 100 °C, 2 h. Condition **B:** Aliphatic bromide (0.3 mmol, 1 equiv), amine derivative (0.3 mmol, 1 equiv), Na_2CO_3 (0.9 mmol, 3 equiv), CH_3CN, 80 °C, 6 h.

Products **4.3j** and **4.3a** are transformed to the corresponding lactone products **4.5n** and **4.5o** in 80%, 66% yield respectively (**Scheme 4.5Ci and 5Cii**). In addition, *δ*-hydroxynitriles **4.2x** and **4.2t** are underwent the Michael addition reaction to provide products **4.5p** and **4.5q** in very good yields (**Scheme 4.5Ciii** and **4.5Civ**).[55]

Mechanistic Studies: Further experiments were performed to investigate the reaction mechanism of this new C−C bond formation and tandem transformation. The reaction of phenyl acetonitrile and trans-cinnamaldehyde with base (KO^{t}Bu, 2 mol %) alone or under the standard condition with catalyst **9** failed to provide the 1,4-conjugateaddition product **4.6a** (**Scheme 4.6i**). Perhaps this failure can be attributed to the strong binding of the aldehyde functionality to the metal center and ligand backbone, leading to the deactivation of the active catalytic intermediate.[56,57] However, the reaction of 4-phenylbut-3-en-2-one with phenyl acetonitrile under standard reaction conditions afforded the product **4.6b** in 81% isolated yield. A similar reaction performed without catalyst resulted in no product formation (**Scheme 4.6ii**), and this observation confirms the role of the catalyst in the C−C bond formation. An experiment was performed using toluene alone as a solvent (excluding IPA), which provided the ketone product **4.6c** in 90% yield (**Scheme 4.6iii**). Besides, 30% of product **4.6d** was isolated upon using only base (4 mol %). These results suggest the role of IPA in the transfer hydrogenation of in situ formed ketone functionality. When α-deuterated benzyl nitrile (94% D) was reacted with 4-phenylbut-3-en-2-one under standard reaction condition, the corresponding deuterium-incorporated product **4.6d** was obtained in 76% yield (**Scheme 4.6iv**). Notably, the observed deuterium scrambling in product **4.6d** indicates that acidic C−H protons readily undergo H/D exchange by catalyst **9**.[58] Similarly, a reaction was conducted using a mixture of toluene and isopropanol-d_8 as the solvent, in which efficient deuteration at all the acidic protons of the product (**4.6e**) was observed, which also supported the role of catalyst **9** in the oxidation, C−C bond formation reaction, and further hydrogenation reactions (**Scheme 4.6v**).

Scheme 4.6 Mechanistic Studies



In general, carbonyl compounds such as aldehydes and ketones undergo condensation reaction with carbon nucleophiles under basic conditions. However, allylic alcohols used in the catalytic formal conjugate addition reactions are in situ transformed to α, β-unsaturated carbonyl compounds, in which β-carbon is more electrophilic and hence tend to follow 1,4-conjugate addition over condensation pathway. In addition, the condensation reaction of aldehydes and ketones with arylmethyl nitriles occurs at higher temperature (135°C) [32,33] compared to the conjugate addition, which takes place at 75−80 °C. Furthermore, the energies associated with condensation and 1,4-conjugate addition of phenyl acetonitrile with acrylaldehyde were calculated, which revealed that condensation reaction takes place with a small barrier of 4.0kcal/mol, whereas the 1,4-conjugate addition was nearly barrierless.

DFT Studies: To decipher the reaction mechanism further, density functional theory (DFT) calculations[59,60] were performed for the ruthenium-catalyzed selective formal conjugate addition of nitriles with allylic alcohols at the M06L+SMD/BS2//M06L/BS1 level[61-63]. The complete catalytic cycle obtained on the basis of the DFT results is presented in **Figure 4.1a**. The entire reaction can be described in seven steps. Step I involved the formation of the active catalyst "**a**". Step II shows the simultaneous occurrence of O-H deprotonation and C-H activation (toward hydride generation) of allylic alcohol in the coordination sphere of "**a**," leading to the formation of adduct "**c**". The adduct "**c**" exhibits anagostic C-H interaction, which promotes the C-H bond activation in the ruthenium PNP pincer complex.[64-66] The formation of ruthenium dihydride "**f**" by the elimination of acrylaldehyde "**e**" is elucidated in Step III. At this stage, the acrylaldehyde undergoes catalytic 1,4-conjugate addition with aryl acetonitrile "**k**." This step of the reaction (**IV**) can be regarded as a supporting side reaction, which generates the intermediate 5-oxo-2-arylpentanenitrile "**g**." The "**g**" forms an adduct "**h**" with the Ru-dihydride through the N-H···O hydrogen bond and "Ru-H···C(O)HR" interactions. Step V describes the hydride transfer from the ruthenium to the carbonyl carbon

of "**g**." Step VI shows N-H deprotonation, which delivers the final product 5-hydroxyarylpentanenitrile "**4.2a**" as an adduct "**j**" with the active form of the catalyst. By the dissociation of "**4.2a**" from "**j**," the active form of the catalyst is regenerated to execute the next catalytic cycle.

Figure 4.1a Catalytic Cycle for ruthenium-catalyzed oxidation of allylic alcohol, subsequent addition, and reduction reactions

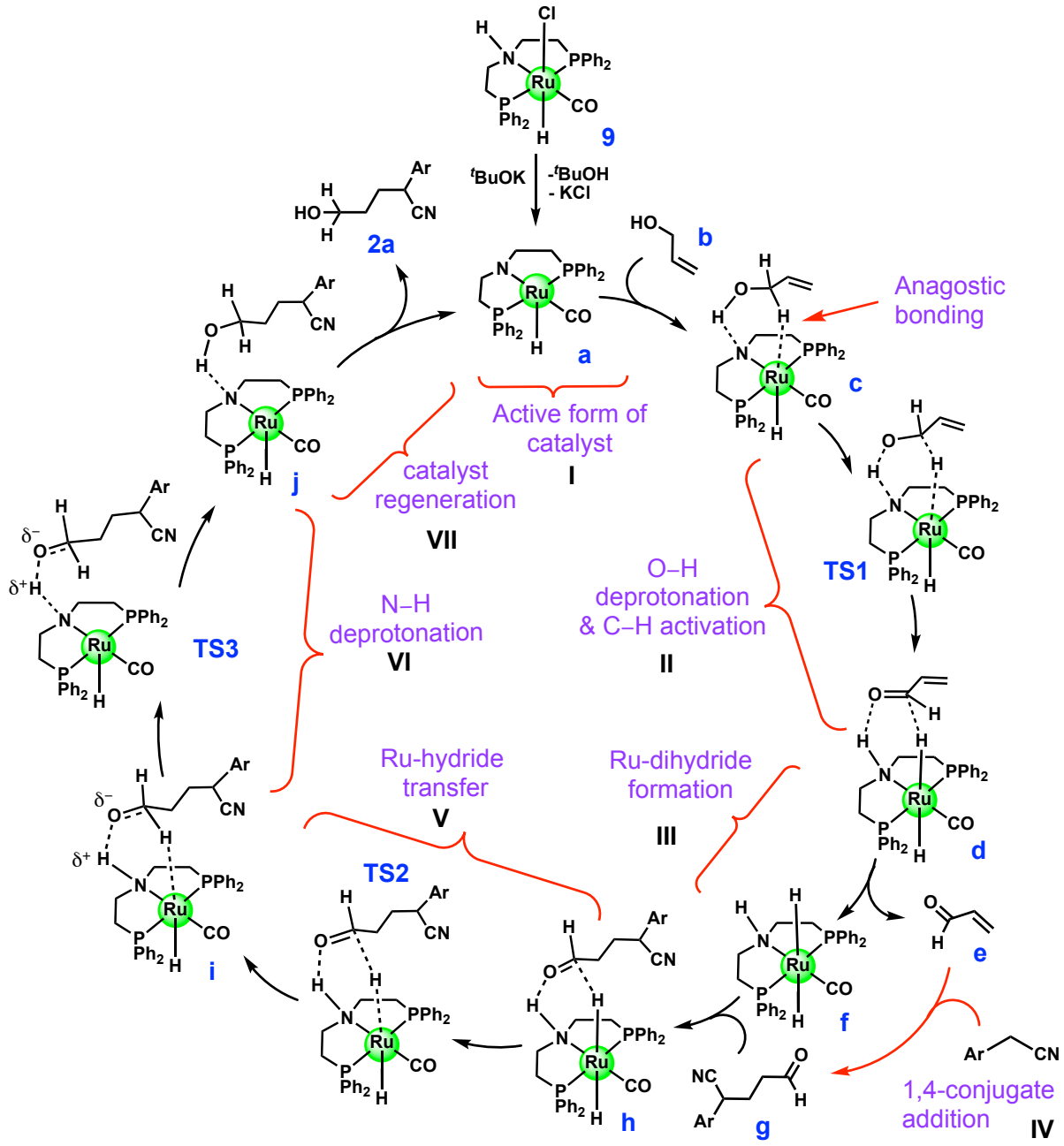
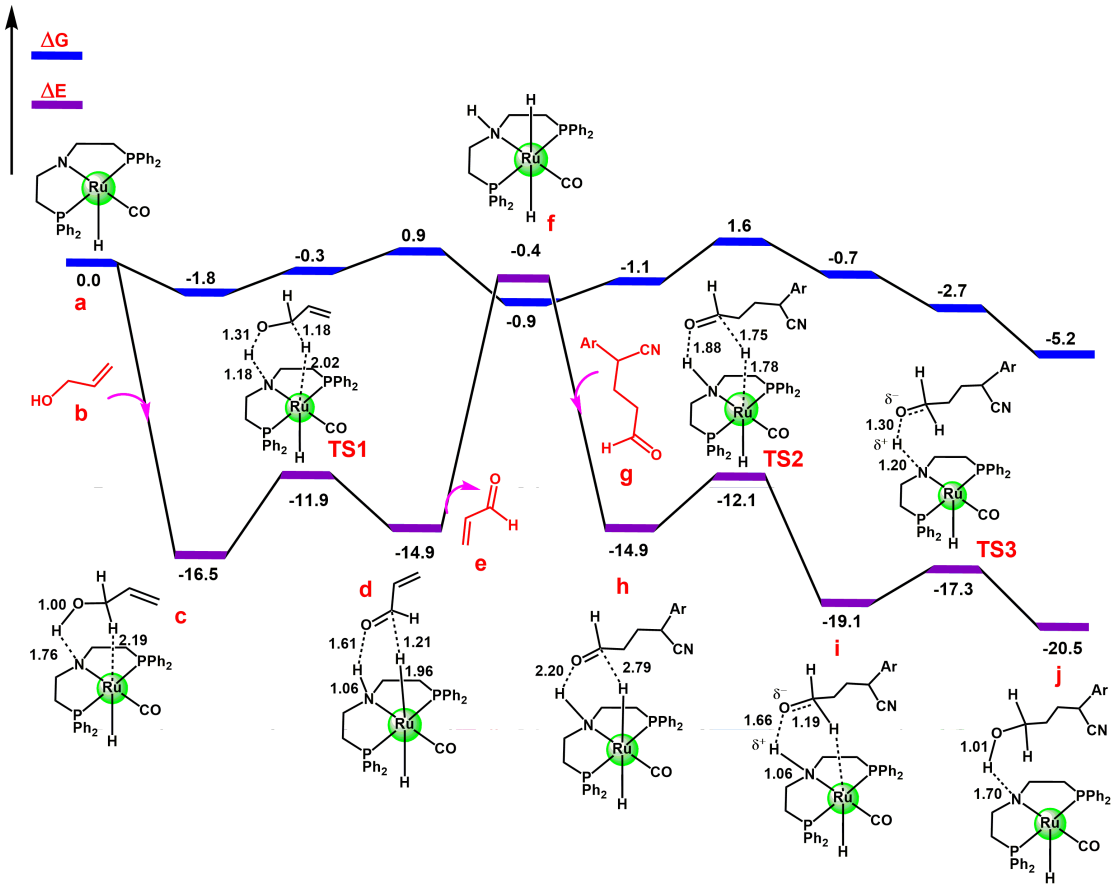


Figure 4.1b Energy profile for the reaction. The energetics are described using the solvation energy corrected free energy (G) changes.

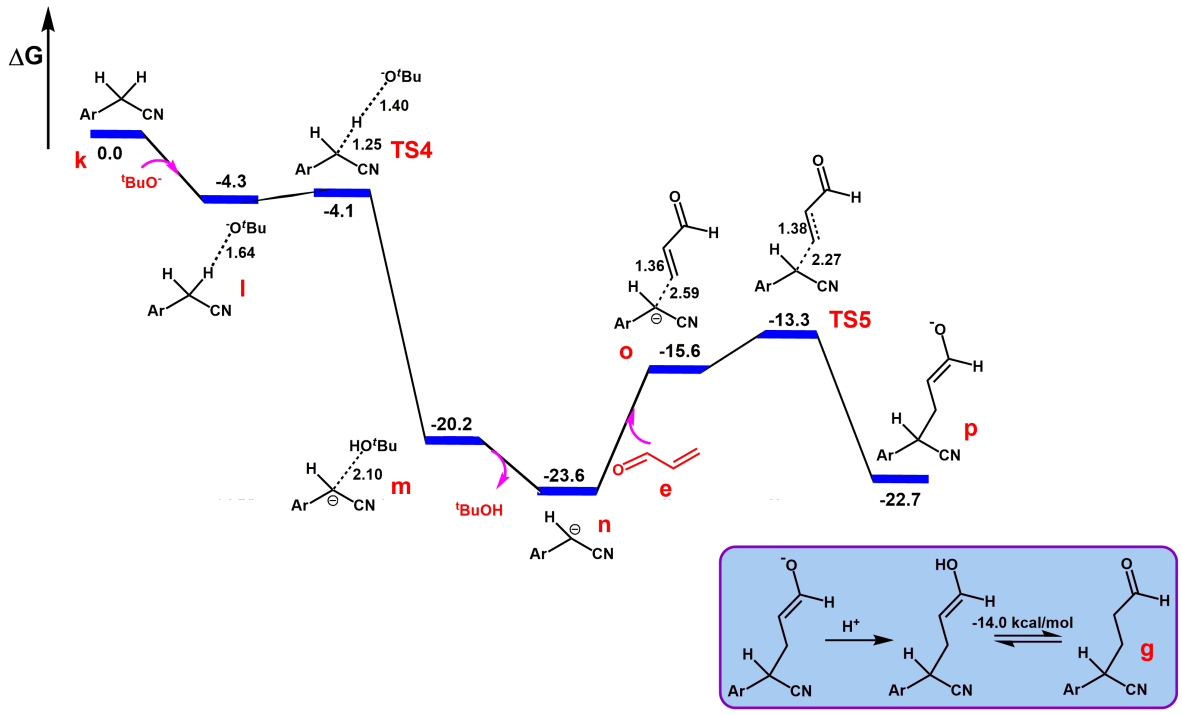


The total energy and Gibbs free-energy profiles of the entire catalytic cycle are depicted in **Figure 4.1b**. The formation of active catalyst "**a**" involves two steps; initially, the N-H deprotonation of catalyst "**9**" takes place in the presence of a strong base KO^{t}Bu with a very small barrier of 0.2 kcal/mol to cross, and subsequently, the chloride ion dissociation generates "**a**." The formation of "**a**" is found to be exergonic by 12.5 kcal/mol. The transition state TS1 located for stage II of the reaction shows substantial activation of the sp^3 C-H bond of the allylic alcohol toward the metal center along with the elongation of O-H bond toward the amide nitrogen, leading to the simultaneous formation of Ru-H and N-H bonds. Though two strong bonds are cleaved during this process, the observed activation barrier (E_{act}) is only 4.6 kcal/mol. For the hydride transfer described in stage V, TS2 is located, wherein "Ru−H···C(O)HR"

distance 1.75 Å indicates the corresponding C-H bond formation, whereas the RHCO···HN distance 1.88 Å indicates a stabilizing hydrogen bond formation in the transition state. The RHCO···HN hydrogen bond leads to further activation of the H−N bond through the formation of TS3, wherein the O···H distance 1.30 Å suggests the proton transfer from N to carbonyl O to deliver the final product 5-hydroxyarylpentanenitrile "**4.2a**" with E_{act} of 1.8 kcal/mol. The energy profile, as shown in Figure 1b, shows that the elimination of acrylaldehyde (step III) is an endothermic process by 14.5 kcal/mol, whereas due to the positive entropy factor, its free-energy profile shows an exergonic character by 0.9 kcal/mol. Overall, on the free-energy profile, the entire catalytic cycle appears nearly barrierless and exergonic, where in the highest activation free energy (G_{act}) is 2.7 kcal/mol for the C-H bond formation through TS2. Also, the TS1 cannot be clearly defined on the free-energy profile as it shows lower free energy than the related intermediate (technically, it disappears). The anagostic bonding[67,68] observed in "**c**" and the positive entropy factor associated with the acrylaldehyde elimination are driving this stage of the reaction toward a near barrierless pathway. Furthermore, the catalytic dehydrogenation of ethanol and 2-buten-1-ol to acetaldehyde and 2-butenal, respectively, was calculated, and the obtained energy barriers indicate both reactions follow the same mechanistic pathway as observed in allyl alcohol. The barrier associated with the dehydrogenation of alcohol is observed to be very small in all these cases, indicating the feasibility of the suggested mechanism over the other reaction pathways. In addition, key steps in our mechanism (Ru-hydride transfer and N−H deprotonation) and the catalytic cycle are in good agreement with the same proposed by Dub and Gordon.[69]A possible mechanism for the formation of 5-oxo-2-arylpentanenitrile (1,4-conjugate addition, step IV) is also derived (Figure 4.2). Interaction of ^{t}BuO− with the −CH_2 proton of the aryl acetonitrile "**k**" is most likely the first step of the reaction, which provides complex "**l**." The coordination free energy for this step is −4.3 kcal/mol. The abstraction of CH_2 proton of "**k**" by ^{t}BuO- is found to be

very easy, proceeds via TS4 with G_{act} of 0.2 kcal/mol to form complex "**m**," which easily dissociates to generate the anion "n" and ^{t}BuOH. This dissociation is exergonic by 3.4 kcal/mol. In the next step, the carbanion interacts with the allylic α-carbon of acrylaldehyde "**e**" to form the intermediate "**o**." The intermediate "**o**" passes through TS5 to provide the enolate ion "**p**." The final product 5-oxo-2-arylpentanenitrile is formed as a result of the protonation of the enolate followed by the tautomerization of the enol to the keto form, which is exergonic by 14.0 kcal/mol.

Figure 4.2 Free Energy Profile for the 1,4-Conjugate Michael Addition Reaction. Inset shows the protonation of enolate anion and subsequent enol-keto tautomerization.



4.4 CONCLUSIONS

In summary, we have developed an unprecedented ruthenium pincer-catalyzed efficient and convenient method for the formal conjugate addition of nitriles with allylic alcohols to δ-hydroxynitriles. On contrary to the conventional procedures, this new strategy explored the formal conjugate addition reaction of diverse arylmethyl nitriles with a range of both primary

and secondary allylic alcohols. Potential applications of this catalytic protocol are demonstrated by the successful synthesis of drug molecules and transformation of products to important functionalized compounds. Mechanistic studies indicate that the entire reaction mechanism proceeds through ruthenium pincer catalyst **9**. This catalytic protocol allows the efficient C−C bond formation, and the reaction is highly atom economical, proceeds under mild conditions, and is environmentally friendly. The complete catalytic cycle of the reaction is established through DFT studies, which shows a nearly barrierless exergonic pathway for oxidation of allylic alcohol to acrylaldehyde catalyzed by the ruthenium monohydride intermediate. 1,4-Conjugate addition between in situ formed α,β-unsaturated carbonyl compounds and arylmethyl nitriles and reduction of δ-oxonitrile to δ-hydroxynitrile reactions are catalyzed by ruthenium dihydride intermediates. Furthermore, the mechanism of the reaction confirms a very facile tandem catalytic process, in which, interestingly, both the catalyst and the base play dual roles. The base activates the catalyst and catalyzes the conjugate addition reaction together with the catalyst, whereas the catalyst performs both oxidation of allylic alcohols and hydrogenation of intermediate carbonyl compounds. This catalytic protocol could have widespread impact in sustainable chemical synthesis and allow efficient synthesis of materials, pharmaceuticals, functional, and bioactive compounds.

4.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under an nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO [Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}ruthenium(II)] (**9**) was purchased from Sigma-Aldrich and stored inside glove box. Chemicals (Nitriles and Allylic alcohols) were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared

(IR) spectra were recorded in Perkin-Elmer FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded at Bruker AV-700 (^1H at 700 MHz, ^{13}C at 175 MHz) and Bruker AV-400 (^1H at 400 MHz, ^{13}C at 100.6 MHz) spectrometers. ^1H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethylsilane (TMS, δ 0.00 ppm) and ^{13}C $\{^1H\}$ NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^1H NMR spectroscopy abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (dept-135) NMR techniques.

GC Method: GC data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard mesitylene was calculated from the average of three independent GC runs.

Experimental Procedure for the Synthesis of Starting Materials:

a) General Procedure for the Synthesis of Nitrile Derivatives:

Arylmethyl nitriles required for the conjugate addition products **4.2o, 4.2p, 4.2s, 4.2v, 4.2w,** and **4.2x** were synthesized by the following procedure. To a stirred solution of arymethyl chloride (or) bromide (5 mmol, 1 equiv) in DMF was added NaCN (10 mmol, 2 equiv) at 0 °C under N_2 atmosphere. Further, the reaction mixture was allowed to stir at room temperature

overnight. Then, cold water was added slowly (for quenching) to the reaction mixture, and the resulted aqueous solution was extracted using ethyl acetate (10 mL × 3). The collected organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure using a rotavapor. The resulted residue was purified through silica gel column chromatography using 10% ethyl acetate/hexane mixture as an eluent, which provided the corresponding nitrile derivatives.

b) General Procedure for the Synthesis of Cinnamyl Alcohols Derivatives:

To a stirred solution of cinnamic acid derivatives (5 mmol, 1 equiv) in THF was added NEt_3 (1 mmol, 1 equiv) under N_2 atmosphere. The mixture cooled to -7 °C, and $ClCO_2Et$ (1 mmol, 1 equiv) was slowly added. The resulted reaction mixture was stirred for 1 h at -7 °C and brought to room temperature. Further, the mixture was filtered, and the filtrate was taken in an oven-dried round bottom flask, $NaBH_4$ (3 mmol, 3 equiv) in MeOH (10 mL) added drop by drop at 0 °C. The mixture was further stirred at r.t for 12 h, and the solvent was removed under reduced pressure. The resulted residue was dissolved in water (10 mL) and extracted using ethyl acetate (10 mL × 3). The collected organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure using a rotavapor. The residue obtained was purified by silica-gel column chromatography using an ethyl acetate/hexane (20:80) as an eluent, which provided the corresponding cinnamyl alcohol derivatives.[70,71]

b) General Procedure for the Synthesis of Secondary Allylic Alcohols Derivatives:

In a round bottom flask, aldehyde (1 mmol, 1 equiv) was taken with freshly prepared anhydrous THF and allowed to stir at 0 °C for 5 min under nitrogen atmosphere. Vinyl magnesium bromide in 1M THF solution (1 mmol, 1 mL, 1 equiv) was added dropwise and allowed to stir for 4 h. Aqueous NH_4Cl solution was added to the reaction mixture (for quenching) and extracted using ethyl acetate (10 mL × 3). The collected organic layer was washed with brine

and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure using a rotavapor. The residue obtained was purified by silica-gel column chromatography using an ethyl acetate/hexane (10:90) as an eluent, which provided the corresponding allylic secondary alcohol derivatives.[72]

General Optimization Procedure for the Formal Conjugate Addition of Phenylacetonitrile with Allyl Alcohol:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.02-0.001 mmol), base (0.05-0.002 mmol), phenyl acetonitrile (0.5 mmol), allyl alcohol (0.75-1 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution was heated at 75 °C (oil bath temperature) with stirring in an open system under a flow of argon for 2 h. The completion of the reaction was monitored using GC analysis. Upon completion, the reaction mixture cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added and the conversion of phenyl acetonitrile was calculated using GC analysis. Further, the solvent was evaporated and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (35:65)mixture as the eluent. Yields were calculated for pure isolated products.

General Procedure for the Formal Conjugate Addition of Nitriles with Allyl Alcohol:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.001 mmol), K_2CO_3 (0.002 mmol), arylmethyl nitrile (0.5 mmol), allyl alcohol (0.75 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution was heated at 75 °C (oil bath temperature) with stirring in an open system under a flow of argon for 2 h. The completion of the reaction was monitored using GC analysis. Upon completion, the reaction mixture cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added, and the conversion of arylmethyl nitrile was

calculated using GC analysis. Further, the solvent was evaporated and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Yields were calculated for pure isolated products.

General Procedure for the Formal Conjugate Addition of Nitriles with Other Allylic Primary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.001 mmol), KO^{t}Bu (0.002 mmol), arylmethyl nitrile (0.5 mmol), allylic primary alcohol (1 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution was heated at 80 °C (oil bath temperature) with stirring in an open system under a flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. Upon completion, the reaction mixture cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added, and the conversion of arylmethyl nitrile calculated using GC analysis. Further, the solvent was evaporated, and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Yields were calculated for pure isolated products.

General Optimization Procedure for the Formal Conjugate Addition of Phenylacetonitrile with 3-Buten-2-ol:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9**(0.001-0.002 mmol), base (0.002-0.004 mmol), phenyl acetonitrile (0.5 mmol), buten-2-ol (1-3 mmol), toluene (1.5 mL), and isopropyl alcohol (IPA, 0.5 ml) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution was heated at 80 °C (oil bath temperature) with stirring in an open system under a flow of argon for 12 h. Upon completion, the reaction mixture was cooled to room temperature, 0.5 mmol of internal standard (benzyl benzoate) was added, and the conversion of phenyl acetonitrile was calculated using ^{1}H NMR analysis of crude reaction mixture. Further, the solvent was evaporated, and the

resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (30:70)mixture as the eluent. Yields were calculated for pure isolated products.

General Procedure for the Formal Conjugate Addition of Nitriles with Other Allylic Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9**(0.002 mmol), base (0.004 mmol), arylmethyl nitrile (0.5 mmol), secondary allylic alcohol (1 mmol), toluene (1.5 mL), and IPA (0.5 ml) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution heated at 80 °C (oil bath temperature) with stirring in an open system under a flow of argon for 12 h. Upon completion, the reaction mixture was cooled to room temperature, 0.5 mmol of internal standard (benzyl benzoate) was added, and the conversion of arylmethyl nitrile was calculated using ^{1}H NMR analysis of crude reaction mixture. Further, the solvent evaporated, and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (30:70)mixture as the eluent. Yields were calculated for pure isolated products.

Synthesis of Biologically Active Molecules

General Procedure for the Synthesis of Aliphatic Bromides (4.5a, 4.5b, 4.5c):

The δ-hydroxynitrile compound (0.5 mmol, 1 equiv) was taken in toluene under nitrogen atmosphere, cooled to -5 °C, and PBr3 (0.6 mmol, 1.1 equiv) added very slowly, and the reaction mixture stirred for 30 minutes. Then the reaction mixture was allowed to warm to room temperature and heated at 100 °C for 2 h. Upon cooling, the reaction mixture was poured into ice, and the aqueous layer was extracted using diethyl ether (2 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na2SO4. The solvent was removed under reduced pressure using a rotavapor, and the resulted residue was purified by silica gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent.

Yields were calculated for pure isolated products.[74]

General Procedure for the Synthesis of CCR1 Receptor Antagonists (4.5d, 4.5e, 4.5f):

Products **4.5a**, **4.5e**, and **4.5f** were synthesized following the slightly modified literature method.5 Aliphatic bromides (**4.5a**, **4.5b**, and **4.5c**, 0.3 mmol, 1 equiv) and 4-(4-chlorophenyl)piperidin-4-ol (0.3 mmol, 1 equiv) were taken in acetonitrile (1 mL), and freshly grouded anhydrous Na_2CO_3 (0.9 mmol, 3 equiv) was added as one portion, and the solution was heated at 80 °C for 6 h. After completion of the reaction, the solvent was removed under reduced pressure using a rotavapor, and the resulted residue was dissolved in water (2 mL). The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the resulted residue was purified by silica gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. Yields were calculated for pure isolated products.[75]

General Procedure for the Synthesis of Calcium Channel Blocker:

Synthesis of Anipamil (4.5j):

Experimental Procedure for Synthesis of 2-(3-Methoxyphenyl)tetradecanenitrile (4.5g):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.1 mmol), KO^{t}Bu (0.002 mmol), 3-methoxy phenyl acetonitrile (1 mmol), 1-dodecanol (2 mmol), and toluene (1.5 mL)-added in sequence under nitrogen atmosphere in the glove box. The flask was taken out of the glove box and fitted with a condenser, and the reaction mixture refluxed (oil bath temperature 135 °C) with stirring under the flow of nitrogen for 4 h. Upon completion, the solvent was evaporated, and the crude reaction mixture was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. The conversion of 3-methoxyphenyl acetonitrile was calculated using GC, and yield was determined for the pure isolated product (**4.5g**).[76]

Experimental Procedure for Synthesis of 2-(3-Hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (4.5h):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.001 mmol), K2CO3 (0.002 mmol), 2-(3-methoxyphenyl)tetradecanenitrile (**4.5g**, 0.5 mmol), allyl alcohol (0.75 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser, and the solution was heated at 75 °C (oil bath temperature) with stirring in an open system under a flow of argon for 2 h. The completion of the reaction was monitored using GC analysis. Upon completion, the reaction mixture cooled to room temperature, 0.5 mmol of internal standard (mesitylene) was added, and the conversion of nitrile was calculated using GC analysis. Further, the solvent was evaporated, and the resulted residue was purified by silica-gel (100-200 mesh) column chromatography using an ethyl acetate/hexane (20:80) mixture as the eluent. Yield was calculated for the pure isolated product (**4.5h**).

Experimental Procedure for Synthesis of 2-(3-Bromopropyl)-2-(3-methoxyphenyl)hexanenitrile (4.5i):

To a round bottom flask, a magnetic stir bar, 2-(3-hydroxypropyl)-2-(3-methoxyphenyl) tetradecanenitrile (**4.5h**, 0.5 mmol, 1 equiv) and toluene (1 mL) were added under nitrogen atmosphere and cooled to -5 °C. To this solution, PBr_3 (0.6 mmol, 1.1 equiv) was added dropwise and stirred for 30 minutes. The reaction mixture was allowed to warm to room temperature and then heated at 100 °C for 2 h. Upon completion, reaction mixture was cooled to room temperature, poured into ice, and the resulted aqueous solution was extracted using diethyl ether (2 × 10mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure using a rotavapor, and the residue obtained was purified by silica gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Yield calculated for the pure isolated product(**4.5i**).

Experimental Procedure for Synthesis of 2-(3-((3-Methoxyphenethyl)(methyl)amino)propyl)-2- (3-methoxyphenyl)tetradecanenitrile (4.5j): 2-(3-Bromopropyl)-2-(3-methoxyphenyl)tetradecanenitrile (87, 0.3 mmol, 1 equiv), 2-(3- methoxyphenyl)-N-methylethan-1-amine (0.3 mmol, 1 equiv) and acetonitrile (1 mL) were charged in a round bottom flask. Freshly ground anhydrous Na_2CO_3 (0.9 mmol, 3 equiv) was added as one portion, and the solution was heated at 80 °C for 6 h. Upon completion of the reaction, the solvent was removed under reduced pressure using a rotavapor, and the residue obtained was dissolved in water (2 mL). The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over unhydrous Na_2SO_4. The solvent was removed, and resulted residue purified by silica gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. Yields were calculated for pure isolated products. The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous Na2SO4. The solvent was removed, and the resulted residue was purified by silica gel column chromatography using DCM/MeOH (90:10) mixture as the eluent. Yield was calculated for the pure isolated product (**4.5j**)

Synthesis of Verapamil Precursor (4.5q):

Experimental Procedure for synthesis of 5-((3,4-dimethoxyphenethyl)(methyl)amino)-2-(3,4- dimethoxyphenyl)pentanenitrile(90):

A magnetic stir bar, 2-(3-bromopropyl)-2-(3,4 -dimethoxyphenyl)hexanenitrile (**4.5k**, 0.3 mmol, 1 equiv), 2-(3,4 -dimethoxyphenyl)-N-methylethan-1-amine (0.3 mmol, 1 equiv) and acetonitrile (1 mL) were were charged in a round bottom flask. Freshly ground anhydrous Na_2CO_3 (0.9 mmol, 3 equiv) was added as one portion, and the solution was heated at 80 °C for 6 h. Upon completion of the reaction, the solvent was removed under reduced pressure using a rotavapor. The residue obtained was dissolved in water (2 mL), extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous

Na2SO4. The solvent was removed, and the resulted residue was purified by silica gel column chromatography using DCM/MeOH (80:20) mixture as the eluent. Yield was calculated for the pure isolated product (**4.5l**).

Experimental Procedure for Synthesis of 5-((3,4-dimethoxyphenethyl)(methyl)amino)-2,2- diphenylpentanenitrile (4.5m):

To a round bottom flask aliphatic bromide, 5-bromo-2,2-diphenylpentane nitrile (**4.5b**, 0.3 mmol, 1 equiv) and 2-(3,4 -dimethoxyphenyl)-N-methylethan-1-amine (0.3 mmol, 1 equiv) in acetonitrile (1 mL) and freshly ground anhydrous Na2CO3 (0.9 mmol, 3 equiv) was added as one portion, and the solution was heated at 80 °C for 6 h. Upon completion of the reaction, the solvent was removed under reduced pressure using a rotavapor, and the residue obtained was dissolved in water (2 mL). The aqueous solution was extracted using ethyl acetate (3 × 10 mL), the combined organic layer washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the resulted residue was purified by silica gel column chromatography using DCM/MeOH (90:10) mixture as the eluent. Yield was calculated for the pure isolated product (**4.5m**).

Experimental Procedure for Synthesis of Products **4.5n** and **4.5o**:

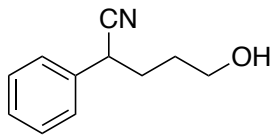
Products **4.5n** and **4.5o** were synthesized following the reported literature method.[77]

Experimental Procedure for Synthesis of Products **4.5p** and **4.5q**:

Products **4.5p** and **4.5q** were synthesized following the reported literature method.[78]

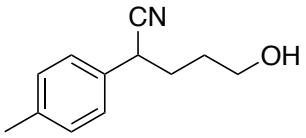
Spectral Data of the δ-Hydroxynitrile Products:

5-Hydroxy-2-phenylpentanenitrile (4.2a):[79] Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless oil. Yield: 74 mg, 85%. IR (DCM; cm^{-1}): 3451, 3076, 2844, 2389, 2221, 1756, 1493, 1459, 1266, 917, 738, 520. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.31 (m, 5H, ArC*H*), 3.78 (t, *J* = 7.4 Hz, 1H, O*H*), 3.53-3.59 (m, 2H, CH_2), 2.17 (s, 1H, C*H*), 1.87-1.94



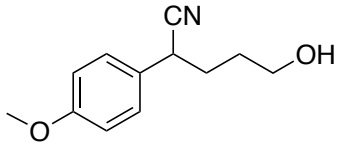
(m, 2H, CH_2), 1.56-1.69 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 135.7, 129.1, 128.1, 127.3, 120.9, 61.6, 37.1, 32.4, 29. HRMS (ESI) m/z calcd for $C_{11}H_{13}NONa$ $(M+Na)^+$: 198.0899 found: 198.0900.

5-Hydroxy-2-(p-tolyl)pentanenitrile (4.2b): [79] Purified by silica-gel column chromatography



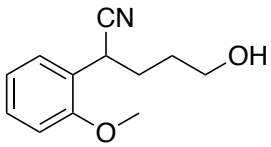
using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 80 mg, 85%. IR (DCM; cm^{-1}): 3608, 3466, 3053, 2927, 2869, 2305, 2240, 1514, 1265, 1060, 1021, 939, 895, 815, 738, 580. ^1H NMR (400 MHz, $CDCl_3$): δ 7.08-7.14 (m, 4H, ArCH), 3.73 (t, J = 7.4 Hz, 1H, CH), 3.56 (tt, J_1 = 6.3 Hz, J_2 = 3.2 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.18 (s, 1H, OH), 1.87-1.93 (m, 2H, CH_2), 1.56-1.66 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 137.9, 132.7, 127.2, 121.1, 61.7, 36.8, 32.4, 29.9, 21.1. HRMS (ESI) m/z calcd for $C_{12}H_{15}NONa$ $(M+Na)^+$: 212.1046 found: 212.1036.

5-Hydroxy-2-(4-methoxyphenyl)pentanenitrile (**4.2c**):[79] Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 85 mg, 83%. IR (DCM; cm^{-1}): 3610, 3497, 3054, 2936, 2839, 2305, 2240, 1612, 1513, 1265, 1180, 1033, 832, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J = 8.7 Hz, 2H, ArCH), 6.84 (d, J = 8.6 Hz, 2H, ArCH), 3.73-3.77 (m, 4H, OCH_3 & CH), 3.59-3.62 (m, 2H, CH_2), 2.00 (d, J = 28.8 Hz, 1H, OH), 1.89-1.95 (m, 2H, CH_2), 1.60-1.69 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 159.4, 128.4, 127.7, 121.2, 114.5, 61.8, 55.4, 36.4, 32.5, 29.9. HRMS (ESI) m/z calcd for $C_{12}H_{16}NO_2$ $(M+H)^+$: 206.1176 found: 206.1173.

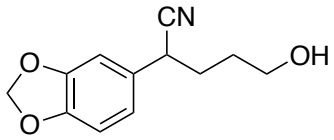
5-Hydroxy-2-(2-methoxyphenyl)pentanenitrile (4.2d): Purified by silica-gel column



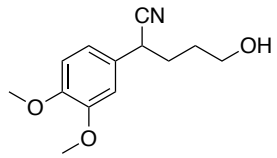
chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 95 mg, 93%. IR (DCM; cm^{-1}): 3606, 3458, 3054, 2879, 2842, 2306, 2241, 1598, 1164, 1113, 940, 897, 581, 431. ^1H NMR (400

MHz, $CDCl_3$): δ 7.30 (dd, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1H, ArC*H*), 7.21 (td, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H, ArC*H*), 6.87-6.91 (m, 1H, ArC*H*), 6.81 (d, *J* = 8.3 Hz, 1H, ArC*H*), 4.14 (t, *J* = 7.2 Hz, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 2.08 (s, 1H), 1.82-1.90 (m, 2H), 1.56-1.70 (m, 2H). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): *δ* 156.1, 129.4, 128.3, 124.0, 121.2, 120.9, 110.9, 61.8, 55.5, 31.2, 30.2, 30.1. HRMS (ESI) m/z calcd for $C_{12}H_{16}NO_2$ $(M+H)^+$: 206.1176 found: 206.1173.

2-(Benzo[d][1,3]dioxol-5-yl)-5-hydroxypentanenitrile (4.2e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 90 mg, 82%. IR (DCM; cm^{-1}): 3608, 3502, 3053, 2866, 2240, 1560, 1505, 1490, 1265, 1249, 1039, 738, 703. ^1H NMR (400 MHz, $CDCl_3$): δ 6.79- 6.81 (m, 3H, ArC*H*), 5.97 (s, 2H, CH_2), 3.78 (dd, J_1 = 7.9 Hz, J_2 =7.0 Hz, 1H, C*H*), 3.66 (td, J_1 = 6.1 Hz, J_2 =1.3 Hz, 2H, CH_2), 2.20 (s, 1H, O*H*), 1.92-2.01 (m, 2H, CH_2), 1.65-1.76 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 148.3, 147.5, 129.4, 121.0, 120.8, 108.6, 107.7, 101.5, 61.7, 36.8, 32.5, 29.8. HRMS (ESI) m/z calcd for $C_{12}H_{14}NO_3$ $(M+H)^+$: 220.0968 found: 220.0965.

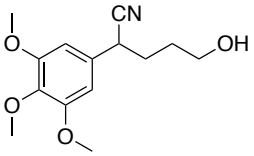


2-(3,4-Dimethoxyphenyl)-5-hydroxypentanenitrile (4.2f): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 90 mg, 82%. IR (DCM; cm^{-1}): 3610, 3517, 3055, 2940, 2839, 2306, 2240, 1597, 1518, 1460, 1421, 1264, 1147, 1027, 896, 808, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 6.82-6.76 (m, 3H, ArC*H*), 3.81 (dd, J_1 = 7.9 Hz, J_2 = 2.5 Hz, 6H, ArOCH_3), 3.74 (t, *J* = 7.4 Hz, 1H, C*H*), 3.60 (td, J_1 = 6.1 Hz, J_2 = 1.9 Hz, 2H, CH_2), 1.98-1.86 (m, 3H, CH_2 *&* O*H*), 1.71-1.60 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.4, 148.8, 128.2, 128.1, 121.1, 119.6, 111.5, 110.3, 61.7, 56.0, 56.0, 36.7, 32.4, 29.9. HRMS (ESI) m/z calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$: 236.1281 found: 236.1279.

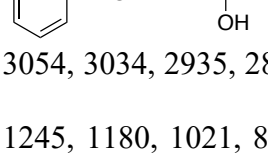


5-Hydroxy-2-(3,4,5-trimethoxyphenyl)pentanenitrile (4.2g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid.

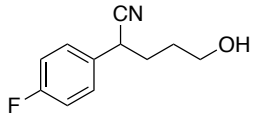
Yield 93 mg, 70%. IR (DCM; cm^{-1}): 3522, 3055, 2939, 2841, 2240, 1594, 1506, 1464, 1456, 1419, 1338, 1265, 1129, 1003, 895, 828, 737, 703. ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (s, 2H, ArC*H*), 3.81 (s, 6H, ArOC*H*$_3$), 3.77 (s, 3H, ArOC*H*$_3$), 3.64 (td, J_1 = 6.1 Hz, J_2 = 2.5 Hz, 2H, C*H*$_2$), 1.91-1.99 (m, 2H, C*H*$_2$), 1.82 (s, 1H, O*H*), 1.62-1.77 (m, 2H, C*H*$_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 153.7, 137.7, 131.4, 120.9, 104.4, 61.8, 61.0, 56.3, 37.5, 32.5, 30.0. HRMS (ESI) m/z calcd for $C_{14}H_{19}NO_4Na$ $(M+Na)^+$: 288.1206 found: 288.1203.



2-(4-(Benzyloxy)phenyl)-5-hydroxypentanenitrile (4.2h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 98 mg, 70%. IR (DCM; cm^{-1}): 3516, 3054, 3034, 2935, 2875, 2305, 2240, 1958, 1885, 1732, 1610, 1511, 1455, 1382, 1300, 1265, 1245, 1180, 1021, 834, 738, 697, 533. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25-7.37 (m, 5H, ArC*H*), 7.18 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.90 (d, *J* = 8.7 Hz, 2H, ArC*H*), 4.99 (s, 2H, C*H*$_2$), 3.74 (t, *J* = 7.4 Hz, 1H, C*H*), 3.61 (t, *J* = 6.0 Hz, 2H, C*H*$_2$), 1.85-1.98 (m, 2H, C*H*$_2$), 1.58-1.71 (m, 2H, C*H*$_2$), 1.54-1.42 (m, 1H, O*H*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.6, 136.8, 128.8, 128.5, 128.2, 128.1, 127.6, 121.1, 115.5, 70.2, 62.0, 36.5, 32.5, 29.9. HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_2Na$ $(M+Na)^+$: 304.1308 found: 304.1322.

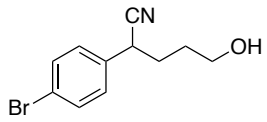


2-(4-Fluorophenyl)-5-hydroxypentanenitrile (4.2i):[79] Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 70 mg, 73%. IR (DCM; cm^{-1}): 3613, 3481, 3054, 2986, 2953, 2881, 2305, 2242, 1604, 1510, 1452, 1420, 1265, 1234, 1059, 938, 895, 835, 736, 578, 528. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.27 (m, 2H, ArC*H*), 6.98-7.03 (m, 2H, ArC*H*), 3.80 (t, J = 7.4 Hz, 1H, C*H*), 3.59-3.68 (m, 2H, C*H*$_2$), 1.89-1.97 (m, 2H, C*H*$_2$), 1.62-1.72 (m, 2H, C*H*$_2$), 1.51 (s, 1H, O*H*). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 163.6, 161.2, 131.6, 131.6, 129.1, 129.0, 120.8, 116.2, 116.0, 61.7, 36.5, 32.5, 29.8. HRMS (ESI) m/z calcd



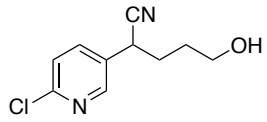
for $C_{11}H_{12}FNONa$ $(M+Na)^+$: 216.0795 found: 216.0792.

2-(4-Bromophenyl)-5-hydroxypentanenitrile (4.2j):[79] Purified by silica-gel column



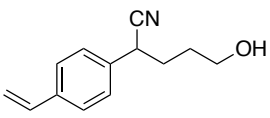
chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless solid. Yield: 89 mg, 70%. IR (DCM; cm^{-1}): 3416, 3062, 3031, 2933, 2868, 2240, 1600, 1494, 1455, 1266, 1059, 738, 699. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.14 (d, *J* = 8.5 Hz, 2H, ArC*H*), 3.77 (t, *J* = 7.4 Hz, 1H, C*H*), 3.54-3.63 (m, 2H, CH_2), 2.16 (s, 1H, O*H*), 1.86-1.96 (m, 2H, CH_2), 1.56-1.69 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 134.8, 132.3, 129.0, 122.2, 120.4, 61.7, 36.7, 32.3, 29.7. HRMS (ESI) m/z calcd for $C_{11}H_{12}BrNONa$ $(M+Na)^+$: 275.9994 found: 276.0015.

2-(6-Chloropyridin-3-yl)-5-hydroxypentanenitrile (4.2k): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (40:60) mixture as the eluent. Colorless liquid. Yield: 58 mg, 55%. IR (DCM; cm^{-1}): 3390, 3054, 2928, 2243, 2189, 1732, 1716, 1699, 1695, 1588, 1568, 1463, 1455, 1436, 1418, 1390, 1266, 1143, 1109, 1061, 1023, 836, 739, 702. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 0.2 Hz, 1H, ArC*H*), 7.63-7.65 (m, 1H, ArC*H*), 7.33 (d, *J* = 8.3 Hz, 1H, ArC*H*), 3.91-3.88 (m, 1H, C*H*), 3.69-3.66 (m, 2H, CH_2), 1.95-2.03 (m, 2H, CH_2), 1.81 (s, 1H, O*H*), 1.66-1.73 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 151.6, 148.6, 137.7, 130.9, 124.9, 119.5, 61.6, 34.3, 32.5, 29.6. HRMS (ESI) m/z calcd for $C_{10}H_{12}ClN_2O$ $(M+H)^+$: 211.0633 found: 211.0612.

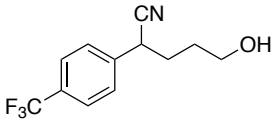
5-Hydroxy-2-(4-vinylphenyl)pentanenitrile (4.2l): Purified by silica-gel column



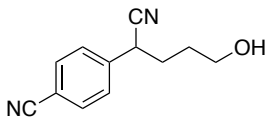
chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless solid. Yield: 66 mg, 66%. IR (DCM; cm^{-1}): 3627, 3565, 2936, 2872, 2240, 1699, 1694, 1683, 1511, 1506, 1456, 1418, 1267, 1061, 840, 763, 748, 702. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.2 Hz, 2H, ArC*H*), 7.21 (d, *J* = 8.2 Hz, 2H, ArC*H*), 6.62 (dd, J_1 = 17.6 Hz, J_2 = 10.9 Hz, 1H, olefin C*H*), 5.69 (d, *J* = 17.6 Hz, 1H, olefin C*H*), 5.21 (d, *J* = 10.9 Hz, 1H, olefin C*H*), 3.78 (t, *J* = 7.4 Hz, 1H, C*H*), 3.54-3.63 (m, 2H,

C*H*$_2$), 1.88-1.95 (m, 2H, C*H*$_2$), 1.78 (s, 1H, O*H*), 1.64 (tq, J_1 = 14.1 Hz, J_2 = 7.0 Hz, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 137.6, 136.0, 135.1, 127.5, 126.9, 120.8, 114.8, 61.8, 36.9, 32.4, 29.8. HRMS (ESI) m/z calcd for $C_{13}H_{15}NONa$ $(M+Na)^+$: 224.1046 found: 224.1034.

5-Hydroxy-2-(4-(trifluoromethyl)phenyl)pentanenitrile (4.2m):[79] Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 65 mg, 54%. IR (DCM; cm^{-1}): 3446, 3055, 2938, 2878, 2308, 2243, 1619, 1419, 1327, 1266, 1168, 1128, 1068, 1019, 839, 739, 704, 606. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.2 Hz, 2H, ArC*H*), 7.41 (d, J = 8.2 Hz, 2H, ArC*H*), 3.91 (t, J = 7.4 Hz, 1H, C*H*), 3.59-3.68 (m, 2H, C*H*$_2$), 1.97 (q, J = 7.8 Hz, 2H, C*H*$_2$), 1.82 (d, J = 22.2 Hz, 1H, O*H*), 1.61-1.73 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 139.8, 131.1, 130.8, 130.5, 130.1, 127.9, 126.3, 126.3, 126.2, 126.2, 125.2, 122.5, 120.2, 119.8, 61.7, 37.1, 32.5, 29.7. HRMS (ESI) m/z calcd for $C_{12}H_{13}F_3NONa$ $(M+H)^+$: 224.0944 found: 224.0926.



4-(1-Cyano-4-hydroxybutyl)benzonitrile (4.2n): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 59 mg, 59%. IR (DCM; cm^{-1}): 3051, 2931, 2231, 1694, 1609, 1505, 1415, 1266, 1056, 837, 736, 702, 553. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.2 Hz, 2H, ArC*H*), 7.45 (d, J = 8.2 Hz, 2H, ArC*H*), 3.95 (t, J = 7.4 Hz, 1H, C*H*), 3.62-3.71 (m, 2H, C*H*$_2$), 2.00 (q, J = 7.7 Hz, 2H, C*H*$_2$), 1.80 (s, 1H, O*H*), 1.63-1.76 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 141.1, 133.0, 128.3, 119.7, 118.2, 112.3, 61.6, 37.3, 32.4, 29.6. HRMS (ESI) m/z calcd for $C_{12}H_{13}N_2O$ $(M+H)^+$: 201.1022 found: 201.1016.



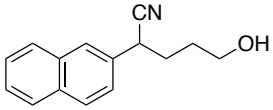
***tert*-Butyl (4-(1-cyano-4-hydroxybutyl)phenyl)carbamate (4.2o):** Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 88 mg, 61%. IR (DCM; cm^{-1}): 3647, 3423, 3335, 3055, 2979, 2934, 2240, 1716, 1596, 1522, 1414, 1368, 1318, 1265, 1238, 1159, 1054, 835, 774, 737, 703. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.1 Hz, 2H, ArC*H*), 7.18 (t, *J* = 9.5 Hz, 2H, ArC*H*), 6.62 (s, 1H, N*H*), 3.75 (t, *J* = 7.3 Hz, 1H, C*H*), 3.60 (t, *J* = 5.9 Hz, 2H, CH_2), 1.91 (q, *J* = 7.2 Hz, 2H, CH_2), 1.74 (s, 1H, O*H*), 1.64 (dt, J_1 = 13.8 Hz, J_2 = 6.9 Hz, 2H, CH_2), 1.45 (s, 9H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 152.8, 138.4, 130.1, 128.0, 121.0, 119.1, 80.9, 61.9, 36.6, 32.4, 29.8, 28.4. HRMS (ESI) m/z calcd for $C_{16}H_{22}N_2O_3Na$ $(M+Na)^+$: 313.1523 found:313.1536.

4-(1-Cyano-4-hydroxybutyl)phenyl methanesulfonate (4.2p): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 90 mg, 70%. IR (DCM; cm^{-1}): 3425, 3029, 2928, 2305, 2242, 1907, 1720, 1600, 1502, 1450, 1416, 1365, 1267, 1200, 1176, 1060, 870, 735, 527. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.2 Hz, 2H, ArC*H*), 7.23-7.26 (m, 2H, ArC*H*), 3.87 (t, *J* = 7.3 Hz, 1H, ArC*H*), 3.62 (t, *J* = 5.9 Hz, 2H, CH_2), 3.11 (s, 3H, SO_2CH_3), 1.94 (t, *J* = 7.6 Hz, 3H, CH_2 *&* O*H*), 1.67 (dq, J_1 = 13.7 Hz, J_2 = 6.9 Hz, 2H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 148.8, 135.2, 129.1, 122.8, 120.4, 61.6, 37.6, 36.6, 32.4, 29.7. HRMS (ESI) m/z calcd for $C_{12}H_{16}NO_4S$ $(M+H)^+$: 270.0795 found: 270.0788.

2-([1,1'-Biphenyl]-4-yl)-5-hydroxypentanenitrile (4.2q):[79] Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 88 mg, 70%. IR (DCM; cm^{-1}): 3443, 3053, 2931, 2874, 2241, 1676, 1601, 1563, 1486, 1447, 1410, 1189, 1060, 838, 701, 509. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, *J* = 8.2 Hz, 4H, ArC*H*), 7.33 (ddt, J_1 = 19.7 Hz, J_2 = 13.3 Hz, J_3 = 6.9 Hz, 5H, ArC*H*), 3.84 (t, *J* = 7.3 Hz, 1H, C*H*), 3.62 (t, *J* = 5.8 Hz, 2H, CH_2), 1.97

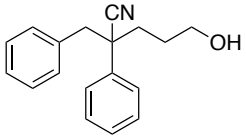
(q, J = 7.6 Hz, 2H, CH_2), 1.69 (ddd, J_1 = 21.4 Hz, J_2 = 14.3 Hz, J_3 = 7.0 Hz, 3H, CH_2 & OH). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 141.2, 140.3, 134.7, 129.0, 127.9, 127.8, 127.7, 127.2, 120.9, 61.9, 36.9, 32.5, 29.9. HRMS (ESI) m/z calcd for $C_{17}H_{17}NONa$ $(M+Na)^+$: 274.1202 found: 274.1205.

5-Hydroxy-2-(naphthalen-2-yl)pentanenitrile (4.2r): Purified by silica-gel column



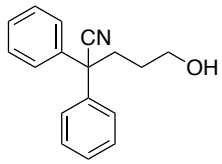
chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 92 mg, 82%. IR (DCM; cm^{-1}): 3438, 3054, 2936, 2870, 2305, 2240, 1600, 1508, 1452, 1370, 1265, 1060, 858, 818, 735, 703, 478. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77-7.82 (m, 4H, ArCH), 7.43-7.48 (m, 2H, ArCH), 7.35 (dd, J_1 = 8.5 Hz, J_2 =1.8 Hz, 1H, ArCH), 3.96- 4.00 (m, 1H, CH), 3.60-3.69 (m, 2H, CH_2), 2.02-2.08 (m, 2H, CH_2), 1.65-1.75 (m, 2H, CH_2), 1.48 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 133.4, 133.0, 132.9, 129.2, 128.0, 127.8, 126.9, 126.6, 126.5, 124.9, 120.9, 61.9, 37.4, 32.4, 29.9. HRMS (ESI) m/z calcd for $C_{15}H_{16}NO$ $(M+H)^+$: 226.1226 found: 226.1230.

2-Benzyl-5-hydroxy-2-phenylpentanenitrile (4.2s): Purified by silica-gel column



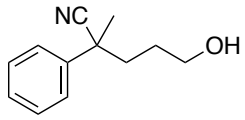
chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 130 mg, 98%. IR (DCM; cm^{-1}): 3608, 3446, 3055, 3031, 2953, 2876, 2304, 2236, 1496, 1454, 1448, 1265, 1048, 1031, 769, 737, 701, 517. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17-7.28 (m, 5H, ArCH), 7.08-7.12 (m, 3H, ArCH), 6.90 (dd, J_1 = 7.1 Hz, J_2 = 2.1 Hz, 2H, ArCH), 3.49 (t, J = 6.2 Hz, 2H, CH_2), 3.09 (q, J = 13.6 Hz, 2H, CH_2), 2.01-2.15 (m, 2H, CH_2), 1.86 (s, 1H, OH), 1.61 (tq, J_1 = 12.4 Hz, J_2 = 6.1 Hz, 1H, CH_2), 1.32 (tq, J_1 = 12.5 Hz, J_2 = 6.2 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 137.6, 134.9, 130.4, 128.9, 128.1, 127.9, 127.3, 126.4, 122.0, 62.0, 49.5, 48.0, 35.8, 28.6. HRMS (ESI) m/z calcd for $C_{18}H_{19}NONa$ $(M+Na)^+$: 288.1359 found: 288.1359.

5-Hydroxy-2,2-diphenylpentanenitrile (4.2t): Purified by silica-gel column chromatography



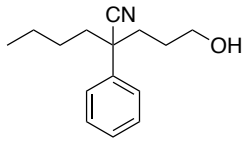
using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 122 mg, 97%. IR (DCM; cm^{-1}): 3309, 3060, 2941, 2875, 2236, 1699, 1597, 1493, 1446, 1265, 1063, 1001, 964, 751, 738, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.35 (m, 10H, ArC*H*), 3.64 (t, *J* = 6.1 Hz, 2H, ArC*H*), 2.43-2.47 (m, 2H, CH_2), 1.60-1.67 (m, 2H, CH_2), 1.48 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 140.2, 129.0, 128.0, 127.0, 122.5, 62.2, 51.6, 36.2, 29.0. HRMS (ESI) m/z calcd for $C_{17}H_{17}NONa$ $(M+Na)^+$: 274.1202 found: 274.1202.

5-Hydroxy-2-methyl-2-phenylpentanenitrile (4.2u): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 188 mg, 99%. IR (DCM; cm^{-1}): 3441, 3056, 2944, 2875, 2307, 2238, 1723, 1602, 1493, 1450, 1384, 1266, 1059, 917, 738, 521. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.47 (m, 5H, ArC*H*), 3.62 (t, *J* = 6.1 Hz, 2H, CH_2), 2.00-2.06 (m, 2H, CH_2), 1.68-1.89 (m, 5H, CH_2 & CH_3), 1.45-1.52 (m, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 139.9, 129.0, 127.8, 125.4, 123.4, 62.0, 42.4, 38.5, 28.7, 27.9. HRMS (ESI) m/z calcd for $C_{12}H_{15}NONa$ $(M+Na)^+$: 212.1046 found: 212.1044.

2-(3-Hydroxypropyl)-2-phenylhexanenitrile (4.2v):[80] Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 113 mg, 98%. IR (DCM; cm^{-1}): 3441, 3059, 2956, 2872, 2235, 1494, 1467, 1456, 1448, 1436, 1380, 1265, 1062, 766, 738, 700, 519. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.34 (m, 5H, ArC*H*), 3.50 (t, *J* = 6.2 Hz, 2H, CH_2), 1.79-2.06 (m, 5H, CH_2), 1.57-1.67 (m, 1H, CH_2), 1.14-1.43 (m, 4H, CH_2 & O*H*), 0.97- 1.08 (m, 1H, CH_2), 0.78 (t, *J* = 7.3 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 138.4, 129.0, 127.7, 125.9, 122.6, 62.1, 48.1, 41.0, 37.5, 28.5, 27.4, 22.6, 13.8. HRMS (ESI) m/z calcd for $C_{15}H_{21}NONa$ $(M+Na)^+$: 254.1515 found: 254.1512.

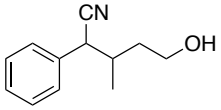
5-Hydroxy-2-phenyl-2-(pyridin-2-ylmethyl)pentanenitrile (4.2w): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 129 mg, 97%. IR (DCM; cm^{-1}): 3377, 2934, 2871, 2251, 2237, 1593, 1495, 1455, 1435, 1051, 786, 750, 700, 516. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 4.4 Hz, 1H, ArC*H*), 7.51 (t, *J* = 7.6 Hz, 1H, ArC*H*), 7.21-7.36 (m, 5H, ArC*H*), 7.12 (t, *J* = 6.2 Hz, 1H, ArC*H*), 7.01 (d, *J* = 7.8 Hz, 1H, ArC*H*), 3.57 (t, *J* = 6.1 Hz, 2H, CH_2), 3.37 (q, *J* = 19.8 Hz, 2H, CH_2), 2.28 (s, 1H, O*H*), 2.10-2.22 (m, 2H, CH_2), 1.62-1.70 (m, 1H, CH_2), 1.37-1.45 (m, 1H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 155.4, 149.0, 137.8, 136.7, 129.0, 128.1, 126.3, 125.0, 122.5, 122.0, 62.1, 48.8, 48.3, 35.4, 28.6. HRMS (ESI) m/z calcd for $C_{17}H_{19}N_2O$ $(M+H)^+$: 267.1492 found: 267.1504.

2-(Benzo[d][1,3]dioxol-5-yl)-2-(furan-2-ylmethyl)-5-hydroxypentanenitrile (4.2x): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 148 mg, 99%. IR (DCM; cm^{-1}): 3417, 3119, 3056, 2951, 2599, 2307, 2238, 1842, 1730, 1611, 1504, 1489, 1440, 1243, 1147, 1039, 1015, 933, 813, 732, 702, 599. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1H, ArC*H*), 6.76-6.81 (m, 2H, ArC*H*), 6.69 (d, *J* = 8.1 Hz, 1H, ArC*H*), 6.18 (s, 1H, ArC*H*), 5.99 (t, *J* = 0.8 Hz, 1H, ArC*H*), 5.90 (s, 2H, CH_2), 3.52 (t, *J* = 5.7 Hz, 2H, CH_2), 3.14 (q, *J* = 12.3 Hz, 2H, CH_2), 1.99 (t, *J* = 8.2 Hz, 2H, CH_2), 1.78-1.86 (m, 1H, O*H*), 1.32-1.63 (m, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 149.6, 148.3, 147.3, 142.1, 131.4, 122.0, 119.9, 110.5, 109.1, 108.3, 106.3, 101.5, 62.0, 48.0, 40.2, 35.9, 28.5. HRMS (ESI) m/z calcd for $C_{17}H_{17}NO_4Na$ $(M+Na)^+$:322.1050 found: 322.1061.

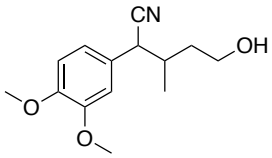
5-Hydroxy-2-(pyren-1-yl)pentanenitrile (4.2y): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 119 mg, 80%. IR (DCM; cm^{-1}): 3434, 3049, 2926, 2858, 2240, 1727, 1666, 1596, 1452, 1383, 1265, 1183, 1061, 897, 846, 737,

622, 508. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-8.04 (m, 9H, ArC*H*), 4.73 (t, *J* = 7.3 Hz, 1H, C*H*), 3.55 (qt, J_1 = 9.4 Hz, J_2 = 6.7 Hz, 2H, CH_2), 2.07 (q, *J* = 7.8 Hz, 2H, CH_2), 1.67-1.76 (m, 3H, CH_2 & O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 131.3, 131.2, 130.5, 128.8, 128.7, 127.9, 127.6, 127.3, 126.3, 125.8, 125.5, 125.2, 125.2, 125.0, 124.6, 121.5, 121.3, 61.9, 34.4, 32.3, 30.1. HRMS (ESI) m/z calcd for $C_{21}H_{18}NO$ $(M+nH)^+$: 300.1383 found: 300.1368.

5-Hydroxy-3-methyl-2-phenylpentanenitrile (4.3a): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 93 mg, 99%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 57:43, as determined by comparison of the following signals: δ 0.93 (d, *J* =6.8 Hz, 3H, CH_3)-major product, 1.02 (d, *J* =6.8 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3381, 3063, 3031, 2934, 2239, 1601, 1495, 1457, 1455, 1053, 742, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.34 (m, 5H, ArC*H*), 3.52-3.92 (m, 3H, CH_2 & C*H*), 1.69-2.20 (m, 2H, CH_2), 1.38-1.60 (m, 3H, C*H* & O*H*), 0.97 (dd, J_1 = 35.6 Hz, J_2 = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 134.7, 134.3, 129.0, 128.9, 128.2, 128.1, 128.0, 127.9, 120.2, 119.6, 60.1, 44.3, 43.4, 37.5, 35.4, 35.4, 35.1, 17.6, 15.6. HRMS (ESI) m/z calcd for $C_{12}H_{16}NO$ $(M+H)^+$: 190.1226 found: 190.1230.

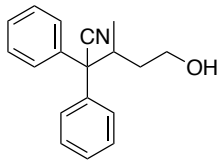


2-(3,4-Dimethoxyphenyl)-5-hydroxy-3-methylpentanenitrile (4.3b): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 117 mg, 94%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 58:42, as determined by comparison of the following signals: δ 0.94 (d, *J* =6.7 Hz, 3H, CH_3)-major product, 1.00 (d, *J* =6.7 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3531, 2962, 2935, 2837, 2238, 1517, 1266, 1145, 1026, 736. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73-6.83 (m, 3H, ArC*H*), 3.83 (t, *J* = 5.4 Hz, 6H, OCH_3), 3.74 (ddd, J_1 = 14.8 Hz, J_2 = 9.4 Hz, J_3 = 4.5 Hz, 1H, CH_2 & C*H*), 3.54-3.69 (m, 2H, CH_2), 2.08-2.17 (m, 1H, C*H*), 1.69-1.78 (m, 1H, C*H*), 1.54 (ddt, J_1 = 14.0 Hz, J_2 = 6.4 Hz, J_3 = 3.5 Hz,



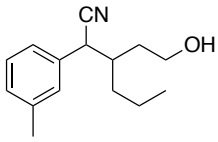
1H, C*H*), 1.45 (s, 1H, O*H*), 0.97 (dd, J_1 = 24.9 Hz, J_2 = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 149.2, 149.2, 148.8, 148.7, 127.1, 126.7, 120.5, 120.3, 120.2, 119.8, 111.2, 110.9, 110.8, 60.2, 56.1, 56.0, 43.9, 43.1, 37.4, 35.5, 35.3, 35.1, 17.5, 15.7. HRMS (ESI) m/z calcd for $C_{14}H_{19}NO_3$ $(M+Na)^+$: 272.1257 found: 272.1247.

5-Hydroxy-3-methyl-2,2-diphenylpentanenitrile (4.3c): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 66 mg, 50%. IR (DCM; cm^{-1}): 3435, 3060, 2949, 2879, 2237, 1708, 1596, 1439, 1450, 1384, 1265. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J_1 = 23.0 Hz, J_2 = 7.9 Hz, 4H, ArC*H*), 7.25-7.31 (m, 4H, ArC*H*), 7.18-7.20 (m, 2H, ArC*H*), 3.61-3.75 (m, 2H, CH_2), 2.95-2.99 (m, 1H, C*H*), 1.80-1.72 (m, 1H, CH_2), 1.47-1.52 (m, 1H, CH_2), 1.43 (s, 1H, O*H*), 1.00 (d, *J* = 6.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 139.9, 139.6, 129.2, 129.1, 129.0, 128.4, 127.8, 127.7, 127.0, 126.7, 121.1, 60.5, 58.9, 35.9, 35.7, 15.8. HRMS (ESI) m/z calcd for $C_{18}H_{19}NO$ $(M+Na)^+$: 288.1359 found: 288.1368.

3-(2-Hydroxyethyl)-2-(m-tolyl)hexanenitrile (4.3d): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 47 mg, 41%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 57:43, as determined by a comparison of the following signals: δ 3.99 (d, *J* =5.2 Hz, 1H, CH)-major product, 3.94 (d, *J* =4.9 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3508, 3052, 2928, 2855, 2304, 1714, 1592, 1421, 1264, 1128, 1065, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (dd, J_1 = 9.6 Hz, J_2 = 5.4 Hz, 1H, ArC*H*), 7.04 (d, *J* = 8.7 Hz, 3H, ArC*H*), 3.96 (dd, J_1 = 22.0 Hz, J_2 = 5.1 Hz, 1H, C*H*), 3.73-3.43 (m, 2H, CH_2 & C*H)*, 2.28 (s, 3H, ArCH_3), 1.97-1.94 (m, 1H, C*H*), 1.72-1.48 (m, 3H, CH_2), 1.43-1.37 (m, 1H, CH_2), 1.33-1.25 (m, 2H, CH_2 & O*H*), 1.17-1.03 (m, 1H, CH_2), 0.88-0.72 (m, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 138.9, 138.8, 138.7, 138.7, 134.7, 134.7, 134.6, 134.6, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 125.1, 125.1, 125.0, 124.9, 120.1,

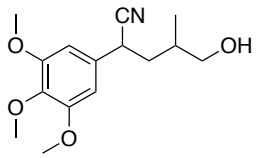
119.8, 60.6, 60.6, 60.4, 60.3, 41.4, 41.4, 41.3, 41.2, 40.0, 40.0, 39.9, 39.9, 34.2, 34.2, 34.1, 34.1, 33.3, 33.2, 32.4, 32.4, 21.5, 20.1, 20.1, 19.9, 19.9, 14.2, 14.2, 14.2. HRMS (ESI) m/z calcd for $C_{15}H_{22}NO$ $(M+H)^+$: 232.1696 found: 232.1692.

2-(Benzo[d][1,3]dioxol-5-yl)-3-(2-hydroxyethyl)hexanenitrile (4.3e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 63 mg, 48%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 55:45, as determined by a comparison of the following signals: δ 3.93 (d, *J* =5.5 Hz, 1H, CH)-major, 3.87 (d, *J* =5.4 Hz, 1H, CH)-minor. IR (DCM; cm^{-1}): 3462, 3055, 2957, 2931, 2239, 1726, 1614, 1491, 1444, 1371, 1245, 1191, 1039, 933, 862, 736, 704, 572. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72-6.74 (m, 3H, ArC*H*), 5.91 (s, 2H, CH_2), 3.91 (dd, J_1= 26.7 Hz, J_2 = 5.5 Hz, 1H, C*H*), 3.47-3.73 (m, 2H, C*H* &CH_2), 1.89-1.95 (m, 1H, C*H*), 1.49-1.70 (m, 4H, CH_2), 1.28-1.39 (m, 3H, CH_2 *&* O*H*), 1.07-1.13 (m, 1H, CH_2), 0.75-0.88 (m, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 148.3, 148.2, 147.4, 147.4, 128.5, 128.3, 121.4, 121.4, 120.1, 119.9, 108.6, 108.5, 108.3, 108.3, 101.5, 101.5, 60.5, 60.3, 41.2, 41.1, 40.1, 40.0, 34.1, 33.9, 33.2, 32.4, 20.0, 19.9, 14.2. HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_3Na$ $(M+Na)^+$: 284.1257 found: 284.1261.

2-(Benzo[d][1,3]dioxol-5-yl)-3-(2-hydroxyethyl)octanenitrile (4.3f): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 126 mg, 87%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 55:45, as determined by a comparison of the following signals: δ 3.89 (d, *J* =5.3 Hz, 1H, CH)-major, 3.94 (d, *J* =5.5 Hz, 1H, CH)-minor. IR (DCM; cm^{-1}): 3585, 3502, 3055, 2931, 2859, 2239, 1504, 1490, 1444, 1265, 1252, 1040, 934, 739, 704. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (s, 3H, ArC*H*), 5.91 (s, 2H, CH_2), 3.91 (dd, J_1 = 20.8 Hz, J_2 = 5.4 Hz, 1H, C*H*), 3.47-3.70 (m, 2H, C*H* & CH_2), 1.90 (t, *J* = 5.7 Hz, 1H, C*H*), 1.57-1.67 (m, 4H, CH_2), 1.09-1.39 (m, 8H, CH_2*&* O*H*), 0.80 (dt, J_1 = 20.4

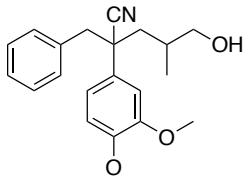
Hz, J_2 = 6.6 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 148.2, 148.2, 147.4, 147.3, 128.5, 128.3, 121.4, 121.4, 120.1, 119.9, 108.6, 108.5, 108.3, 108.2, 101.5, 101.5, 77.5, 77.2, 76.8, 60.5, 60.3, 41.1, 41.0, 40.3, 40.3, 34.0, 33.2, 31.9, 31.9, 31.6, 30.1, 26.5, 26.3, 22.6, 22.6, 14.1, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{24}NO_3$ $(M+H)^+$: 290.1751 found: 290.1739.

5-Hydroxy-4-methyl-2-(3,4,5-trimethoxyphenyl)pentanenitrile (4.3g): Purified by silica-



gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 114 mg, 82%. IR (DCM; cm^{-1}): 3627, 3505, 3055, 2940, 2839, 2239, 1592, 1506, 1464, 1456, 1418, 1334, 1265, 1243, 1129, 1003, 737, 703. ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, J = 2.5 Hz, 2H, ArCH), 3.85-3.98 (m, 1H, CH), 3.79 (d, J = 15.8 Hz, 9H, OCH_3), 3.42-3.62 (m, 2H, CH_2), 1.75-1.93 (m, 3H, CH & OH), 0.95 (dd, J_1 = 13.1 Hz, J_2 = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 153.7, 137.7, 131.9, 131.9, 131.9, 121.4, 120.9, 104.4, 67.8, 61.0, 56.4, 56.3, 40.3, 40.2, 39.9, 39.8, 35.9, 35.7, 33.9, 33.9, 33.6, 17.1, 16.1. HRMS (ESI) m/z calcd for $C_{15}H_{13}NO_4$ $(M+H)^+$: 280.1543 found: 280.1539.

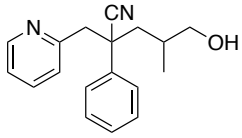
2-Benzyl-2-(3,4-dimethoxyphenyl)-5-hydroxy-4-methylpentanenitrile (4.3h): Purified by



silica- gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 165 mg, 97%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 54:46, as determined from a comparison of the following signals: δ 0.76 (d, J =6.7 Hz, 3H, CH_3)-major, 1.06 (d, J =6.7 Hz, 3H, CH_3)-minor. IR (DCM; cm^{-1}): 3515, 3061, 3030, 2933, 2873, 2837, 2236, 1732, 1604, 1591, 1518, 1454, 1415, 1253, 1149, 1026, 854, 809, 733, 702. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 5.3 Hz, 3H, ArCH), 6.75-6.98 (m, 5H, ArCH), 3.86 (d, J = 29.6 Hz, 6H, OCH_3), 3.49-3.61 (m, 1H, CH), 3.08-3.29 (m, 3H, CH_2), 2.37 (ddd, J_1 = 44.0 Hz, J_2 = 14.3 Hz, J_3 = 4.3 Hz, 1H, CH_2), 1.67-1.97 (m, 3H, CH_2 & OH), 0.91 (dd, J_1 = 117.9 Hz, J_2 = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 148.9, 148.8, 148.5, 148.5,

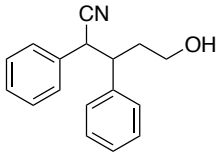
134.9, 130.5, 130.4, 129.9, 129.8, 128.0, 127.3, 122.7, 122.6, 119.0, 118.9, 111.0, 110.0, 67.8, 67.2, 56.0, 55.9, 49.5, 49.0, 48.6, 47.9, 42.5, 42.2, 33.4, 33.1, 18.4, 17.5. HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3$ $(M+Na)^+$: 362.1727 found: 362.1756.

5-Hydroxy-4-methyl-2-phenyl-2-(pyridin-2-ylmethyl)pentanenitrile (4.3i): Purified by



silica- gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 130 mg, 93%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 58:42, as determined from a comparison of the following signals: δ 0.88 (d, *J* =6.8 Hz, 3H, CH_3)-major product, 0.71 (d, *J* =6.8 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3364, 3055, 2928, 2237, 1718, 1593, 1472, 1441, 1378, 1266, 1152, 1091, 1042, 895, 702, 515. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (t, *J* = 6.9 Hz, 1H, ArC*H*), 7.37-7.55 (m, 1H, ArC*H*), 7.29-7.32 (m, 1H, ArC*H*), 7.19-7.25 (m, 4H, ArC*H*), 7.05-7.13 (m, 1H, ArC*H*), 6.70 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1H, ArC*H*), 3.18-3.60 (m, 5H, CH_2 & O*H*), 2.39 (ddd, J_1 = 12.4 Hz, J_2 = 8.3 Hz, J_3 = 4.3 Hz, 1H, C*H*), 1.75-1.91 (m, 2H, CH_2), 0.78 (t, *J* = 6.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 155.58, 155.17, 148.93, 148.76, 138.48, 137.93, 136.73, 136.50, 128.97, 128.78, 128.09, 128.03, 126.54, 126.38, 125.35, 125.27, 122.56, 122.53, 122.47, 122.42, 67.87, 67.59, 48.86, 48.35, 47.28, 47.05, 42.21, 40.80, 33.79, 32.94, 18.81, 17.86. HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O$ $(M+H)^+$: 281.1648 found: 281.1644.

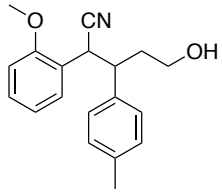
5-Hydroxy-2,3-diphenylpentanenitrile (4.3j): Purified by silica-gel column chromatography



using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 122 mg, 97%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 60:40, as determined from a comparison of the following signals: δ 3.91 (d, *J* =7.0 Hz, 1H, CH)-major product, 4.02 (d, *J* =6.8 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3627, 3564, 3445, 3063, 3029, 2943, 2239, 1495, 1455, 1044, 758,

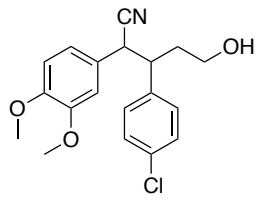
737, 700. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dt, J_1 = 17.5 Hz, J_2 = 3.7 Hz, 6H, ArC*H*), 6.98-7.07 (m, 4H, ArC*H*), 3.97 (dd, J_1 = 46.3 Hz, J_2 =6.9 Hz, 1H, C*H*), 3.45 (ddt, J_1 = 19.2 Hz, J_2 = 11.0 Hz, J_3 = 5.5 Hz, 1H, C*H*), 3.14-3.34 (m, 2H, CH_2), 1.93-2.16 (m, 2H, CH_2), 1.72 (s, 1H, O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 139.2, 134.3, 134.3, 128.7, 128.5, 128.5, 128.2, 128.1, 128.1, 127.7, 127.6, 120.1, 119.8, 60.0, 47.3, 47.1, 44.8, 44.3, 35.7, 34.4. HRMS (ESI) m/z calcd for $C_{17}H_{18}NO$ $(M+H)^+$: 252.1383 found: 252.1384.

5-Hydroxy-2,3-diphenylpentanenitrile (4.3k): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 106 mg, 72%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 66:34, as determined from a comparison of the following signals: δ 4.31 (d, *J* =5.7 Hz, 1H, CH)-major product, 4.44 (d, *J* =7.0 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3479, 3052, 2939, 2240, 1730, 1600, 1514, 1494, 1464, 1438, 1290, 1265, 1249, 1163, 1111, 1050, 1028, 737, 703. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.5 Hz, 1H, ArC*H*), 7.16 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.96-7.01 (m, 2H), 6.78-6.90 (m, 3H, ArC*H*), 6.70-6.75 (m, 1H, ArC*H*), 4.37 (dd, J_1 = 54.2 Hz, J_2 = 6.3 Hz, 1H, C*H*), 3.73 (d, *J* = 22.8 Hz, 3H, OCH_3), 3.11-3.47 (m, 3H, CH_2 & C*H*), 2.21 (s, 3H, ArCH_3), 1.88-2.05 (m, 2H, CH_2), 1.84 (s, 1H, O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 156.1, 156.0, 137.2, 137.1, 137.0, 136.2, 129.5, 129.4, 129.4, 129.3, 129.1, 128.3, 127.8, 123.0, 122.8, 120.7, 120.7, 120.2, 110.8, 110.6, 60.4, 60.3, 55.6, 55.5, 44.6, 44.1, 39.3, 38.1, 35.7, 35.7, 33.5, 21.1, 21.0. HRMS (ESI) m/z calcd for $C_{19}H_{22}NO_2$ $(M+H)^+$: 296.1645 found: 296.1642.

3-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-5-hydroxypentanenitrile (4.3l): Purified by

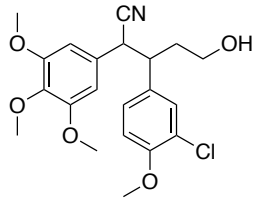


silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 138 mg, 80%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 65:35, as

determined from a comparison of the following signals: δ 3.83 (d, *J* =7.3 Hz, 1H, CH)-major product, 4.01 (d, *J* =7.2 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3051, 3058, 3003, 2936, 2837, 2239, 1716, 1594, 1516, 1238, 1144, 1026, 828, 732, 702, 519. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, *J* = 9.8 Hz, 2H, ArC*H*), 6.95 (d, *J* = 7.7 Hz, 2H, ArC*H*), 6.66-6.69 (m, 1H, ArC*H*), 6.59 (dd, J_1 = 16.7 Hz, J_2 = 8.2 Hz, 1H, ArC*H*), 6.39 (d, *J* = 29.2 Hz, 1H , ArC*H*), 3.92 (dd, J_1 = 69.6 Hz, J_2 = 6.8 Hz, 1H, C*H*), 3.73-3.78 (m, 3H, OCH_3), 3.66 (d, *J* = 13.3 Hz, 3H, OCH_3), 3.49-3.58 (m, 1H, C*H*), 3.39-3.14 (m, 2H, CH_2), 1.91-2.20 (m, 2H, CH_2), 1.71 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 148.9, 148.8, 148.8, 137.6, 137.1, 133.5, 133.4, 130.0, 129.8, 128.8, 128.7, 126.2, 126.0, 120.6, 120.5, 120.1, 111.1, 111.0, 110.9, 59.9, 55.9, 55.8, 46.7, 46.6, 44.1, 43.7, 35.5, 34.7. HRMS (ESI) m/z calcd for $C_{19}H_{20}ClNO_3Na$ $(M+Na)^+$: 368.1024 found: 368.1018.

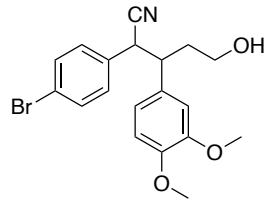
2,3-Bis(benzo[d][1,3]dioxol-5-yl)-5-hydroxypentanenitrile (4.3m): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 139 mg, 82%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 57:43, as determined from a comparison of the following signals: δ 3.95 (d, *J* =7.3 Hz, 1H, CH)-major product, 3.88 (d, *J* =7.2 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3444, 2897, 2239, 1716, 1609, 1504, 1489, 1444, 1396, 1247, 1102, 1038, 813, 733, 651. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (dd, J_1 = 15.2 Hz, J_2 = 7.5 Hz, 3H, ArC*H*), 6.56-6.47 (m, 3H, ArC*H*), 5.88 (d, *J* = 5.1 Hz, 4H, CH_2), 3.83 (dd, J_1 = 29.6 Hz, J_2 = 7.2 Hz, 1H, C*H*), 3.51 (dq, J_1 = 10.3 Hz, J_2 = 5.1 Hz, 1H, C*H*), 3.37-3.26 (m, 1H, CH_2), 3.09-3.03 (m, 1H, CH_2), 2.14-1.81 (m, 2H, CH_2), 1.63 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 148.1, 148.0, 148.0, 147.9, 147.5, 147.5, 147.1, 147.0, 132.9, 132.5, 127.9, 127.9, 122.1, 121.8, 121.8, 121.7, 120.1, 119.9, 108.5, 108.5, 108.4, 108.4, 108.3, 108.1, 101.5, 101.2, 60.1, 47.2, 47.0, 44.6, 44.2, 35.8, 34.7. HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_5Na$ $(M+H)^+$: 340.1179 found: 340.1157.

3-(3-Chloro-4-methoxyphenyl)-5-hydroxy-2-(3,4,5-trimethoxyphenyl)pentanenitrile



(4.3n): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 178 mg, 88%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 51:49, as determined from a comparison of the following signals: δ 3.96 (d, *J* =7.2 Hz, 1H, CH)-major product, 4.04 (d, *J* =5.8 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3500, 3055, 2940, 2840, 2305, 2240, 1593, 1504, 1463, 1423, 1265, 1129, 1065, 895, 736, 703 . ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 14.5 Hz, 1H, ArC*H*), 6.90 (dd, J_1 = 13.7 Hz, J_2 = 9.2 Hz, 1H, ArC*H*), 6.75 (dd, J_1 = 13.0, J_2 = 9.0 Hz, 1H, ArC*H*), 6.19-6.22 (m, 2H, ArC*H*), 3.88 (dd, J_1 = 55.5 Hz, J_2 = 7.0 Hz, 1H, C*H*), 3.77 (d, *J* = 4.6 Hz, 3H, OCH_3), 3.72-3.73 (m, 3H, OCH_3), 3.66 (s, 6H, OCH_3), 3.50 (dd, J_1 = 10.1 Hz, J_2 = 3.7 Hz, 1H, C*H*), 3.13-3.37 (m, 2H, CH_2), 1.95-2.15 (m, 3H, CH_2 & O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 154.4, 154.3, 153.2, 153.1, 137.7, 137.7, 132.0, 131.7, 130.1, 129.7, 129.6, 129.2, 128.0, 127.9, 122.3, 122.2, 119.9, 119.6, 112.0, 111.9, 105.4, 105.3, 60.9, 60.8, 59.7, 56.1, 46.1, 45.9, 44.7, 44.3, 35.4, 34.6. HRMS (ESI) m/z calcd for $C_{21}H_{25}ClNO_5$ $(M+H)^+$: 406.1416 found: 406.1400.

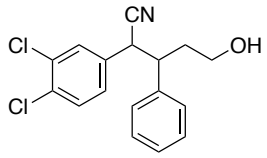
2-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)-5-hydroxypentanenitrile (4.3o): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 152 mg, 78%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 62:38, as determined from a comparison of the following signals: δ 4.05 (d, *J* =5.8 Hz, 1H, CH)-major product, 3.87 (d, *J* =7.0 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3612, 3524, 3054, 2985, 2938, 2837, 2305, 2241, 1606, 1591, 1517, 1488, 1464, 1421, 1264, 1143, 1074, 1027, 895, 812, 736, 703, 525. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, J_1 = 7.4 Hz, J_2 = 5.8 Hz, 2H, ArC*H*), 7.02 (d, *J* = 8.0 Hz, 1H, ArC*H*), 6.93 (d, *J* = 8.1 Hz, 1H, ArC*H*), 6.77 (dd, J_1 = 10.5 Hz, J_2 = 5.6 Hz, 1H, ArC*H*), 6.64 (dd, J_1 = 22.0 Hz, J_2 = 8.2 Hz, 1H, ArC*H*), 6.53 (d, *J* = 22.1

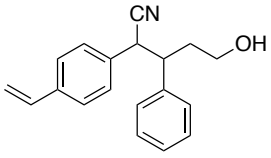
Hz, 1H, ArC*H*), 4.04 (dd, J_1 = 71.0 Hz, J_2 = 6.4 Hz, 1H, C*H*), 3.83-3.89 (m, 3H, ArOCH_3), 3.77 (d, *J* = 14.6 Hz, 3H, ArOCH_3), 3.37-3.72 (m, 2H, CH_2), 3.20 (dt, J_1 = 13.8 Hz, J_2 = 6.7 Hz, 1H, C*H*), 2.02-2.25 (m, 2H, CH_2), 1.67 (s, 1H, O*H*). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 149.0, 148.8, 148.6, 148.5, 133.5, 133.4, 131.9, 131.8, 131.1, 130.2, 129.9, 129.9, 122.3, 122.2, 120.8, 120.4, 119.8, 119.4, 111.7, 111.3, 111.1, 60.1, 60.1, 56.0, 55.9, 55.9, 47.0, 46.8, 44.4, 43.9, 35.8, 34.6. HRMS (ESI) m/z calcd for $C_{19}H_{21}BrNO_3$ $(M+H)^+$: 390.0699 found: 390.0701.

2-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)-5-hydroxypentanenitrile (4.3p): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 131 mg, 82%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 54:46, as determined from a comparison of the following signals: δ 4.17 (d, *J* =6.3 Hz, 1H, CH)-major product, 3.97 (d, *J* =7.7 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3439, 3056, 2929, 2305, 2242, 1896, 1719, 1599, 1562, 1470, 1398, 1265, 1193, 1136, 1034, 886, 821, 704, 623, 593, 525, 440. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.25 (m, 1H, ArC*H*), 7.16-7.21 (m, 3H, ArC*H*), 7.12 (dd, J_1 = 23.0 Hz, J_2 = 2.1 Hz, 1H, ArC*H*), 6.97-7.02 (m, 2H, ArC*H*), 6.83 (ddd, J_1 = 26.4 Hz, J_2 = 8.3 Hz, J_3 = 2.2 Hz, 1H, ArC*H*), 4.00 (dd, J_1 = 77.3 Hz, J_2 = 7.0 Hz, 1H, C*H*), 3.45-3.58 (m, 1H, C*H*), 3.14 -3.39 (m, 2H, CH_2), 2.34 (s, 1H, O*H*), 1.96-2.19 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 138.3, 137.7, 134.5, 134.4, 132.9, 132.8, 132.5, 132.4, 130.6, 130.1, 128.9, 128.7, 128.5, 128.1, 128.0, 127.9, 127.5, 127.5, 119.4, 118.9, 59.6, 59.6, 47.2, 46.9, 43.8, 43.2, 35.5, 34.7. HRMS (ESI) m/z calcd for $C17H15Cl_2NONa$ $(M+Na)^+$: 342.0423 found: 342.0412.

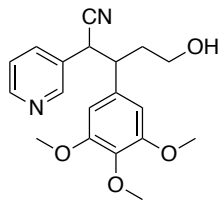
5-Hydroxy-3-phenyl-2-(4-vinylphenyl) pentanenitrile (4.3q): Purified by silica- gel column



chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 125 mg, 90%. ^1H NMR analysis of the

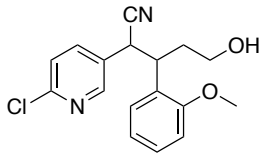
crude reaction mixture showed a d.r. of 53:47, as determined from a comparison of the following signals: δ 4.02 (d, *J* = 6.7 Hz, 1H, CH)-major product, 3.92 (d, *J* =6.9 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3608, 3480, 3053, 2983, 2937, 2304, 2240, 1511, 1454, 1408, 1265, 1042, 915, 842, 737, 702. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.24 (m, 5H, ArC*H*), 7.01 (td, J_1 = 18.2 Hz, J_2 = 7.6 Hz, 4H, ArC*H*), 6.58 (ddd, J_1 = 17.1 Hz, J_2 = 11.3 Hz, J_3 = 5.4 Hz, 1H, olefin C*H*), 5.63-5.68 (m, 1H, olefin C*H*), 5.18 (d, *J* = 10.9 Hz, 1H, olefin C*H*), 3.97 (dd, *J* = 41.1 Hz, J_2 = 6.8 Hz, 1H, C*H*), 3.49 (ddt, *J* = 19.8 Hz, J_2 = 10.5 Hz, J_3 = 5.1 Hz, 1H, C*H*), 3.15-3.36 (m, 2H, CH_2), 1.93-2.18 (m, 2H, CH_2), 1.52 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 139.2, 138.5, 137.4, 137.4, 136.1, 136.0, 133.7, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 126.6, 120.0, 119.8, 114.8, 114.7, 60.1, 60.1, 47.3, 47.1, 44.6, 44.1, 35.7, 34.4. HRMS (ESI) m/z calcd for $C_{19}H_{20}NO$ $(M+H)^+$: 278.1539 found: 278.1544.

5-Hydroxy-2-(pyridin-3-yl)-3-(3,4,5-trimethoxyphenyl) pentanenitrile (4.3r): Purified by



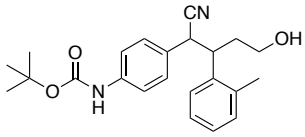
silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 106 mg, 63%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 56:44, as determined from a comparison of the following signals: δ 4.07 (d, *J* =7.0 Hz, 1H, CH)-major product, 4.29 (d, *J* =5.6 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3376, 3054, 2938, 2841, 2241, 1956, 1718, 1590, 1507, 1426, 1355, 1243, 1126, 1052, 1004, 832, 7355, 626, 529. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 39.3 Hz, 2H, ArC*H*), 7.11-7.45 (m, 2H, ArC*H*), 6.19 (d, *J* = 24.2 Hz, 1H), 4.12 (dd, J_1 = 87.7 Hz, J_2 = 6.3 Hz, 1H, C*H*), 3.65-3.74 (m, 9H, OCH_3), 3.46-3.62 (m, 1H, C*H*), 3.14-3.39 (m, 2H, CH_2), 2.43 (s, 1H, O*H*), 1.96-2.16 (m, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 153.5, 153.2, 149.3, 149.2, 149.1, 137.7, 136.0, 136.0, 134.0, 133.1, 118.9, 105.7, 105.3, 61.0, 59.8, 59.8, 56.3, 56.2, 47.5, 47.4, 42.2, 41.6, 35.8, 34.6. HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O_4$ $(M+H)^+$: 343.1652 found: 343.1660.

2-(6-Chloropyridin-3-yl)-5-hydroxy-3-(2-methoxyphenyl)pentanenitrile (4.3s): Purified



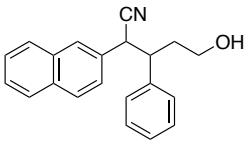
by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 106 mg, 63%. IR (DCM; cm^{-1}): 3598, 3053, 2985, 2304, 1586, 1492, 1459, 1388, 1265, 1109, 1025, 908, 737, 704. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-8.07 (m, 1H, ArC*H*), 6.96-7.51 (m, 4H, ArC*H*), 6.60-6.93 (m, 2H, ArC*H*), 4.17-4.28 (m, 1H, C*H*), 3.27-3.78 (m, 6H, OCH_3), 1.98-2.19 (m, 2H, CH_2), 1.62 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 157.1, 157.1, 151.1, 151.0, 150.0, 149.4, 149.0, 148.9, 139.3, 138.4, 138.1, 137.8, 130.2, 129.2, 128.8, 128.8, 128.8, 128.8, 128.6, 128.5, 125.8, 125.6, 124.2, 123.8, 123.8, 121.2, 121.1, 121.1, 119.1, 118.9, 111.0, 110.7, 60.1, 60.1, 55.4, 55.2, 39.9, 39.7, 34.4, 33.4, 29.8, 29.4. HRMS (ESI) m/z calcd for C17H18ClNO $(M+H)^+$: 317.1051 found: 317.1047.

***tert*-Butyl(4-(1-cyano-4-hydroxy-2-(o-tolyl)butyl) phenyl)carbamate (4.3t):** Purified by

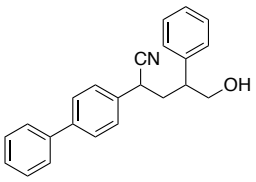


silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 129 mg, 68%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 55:45, as determined from a comparison of the following signals: δ 3.92 (d, *J* =7.2 Hz, 1H, CH)-major product, 3.82 (d, *J* =7.6 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3331, 3113, 3053, 2974, 2932, 2241, 1708, 1601, 1529, 1414, 1318, 1240, 1161, 1054, 836, 735, 540, 457. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-7.30 (m, 8H, ArC*H*), 6.56 (s, 1H, N*H*), 3.87 (dd, J_1 = 39.0 Hz, J_2 = 7.4 Hz, 1H, C*H*), 3.44-3.55 (m, 2H, CH_2), 3.21-3.26 (m, 1H, C*H*), 1.91-2.02 (m, 5H, CH_3 & CH_2), 1.43 (d, *J* = 3.3 Hz, 11H, O*H* & CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; CDCl3): δ 152.7, 138.5, 138.3, 137.8, 137.6, 137.4, 137.1, 130.8, 130.6, 129.0, 128.7, 128.6, 127.3, 127.2, 126.6, 126.5, 120.2, 118.5, 118.5, 80.9, 80.9, 60.1, 60.1, 43.9, 43.7, 36.1, 34.9, 28.4, 19.8, 19.7. HRMS (ESI) m/z calcd for $C_{23}H_{28}N_2O_3Na$ $(M+H)^+$: 403.1992 found:403.2014.

5-hydroxy-2-(naphthalen-2-yl)-3-phenylpentanenitrile (4.3u): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 120 mg, 80%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 57:43, as determined from a comparison of the following signals: δ 4.10 (d, *J* =6.7 Hz, 1H, CH)-major product, 4.19 (d, *J* =6.9 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3605, 3463, 3055, 2934, 2305, 2241, 1721, 1601, 1500, 1450, 1422, 1265, 1043, 895, 818, 737, 705, 478. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.74 (m, 3H, ArC*H*), 7.54 (dd, J_1 = 49.4 Hz, J_2 = 1.0 Hz, 1H, ArC*H*), 7.38-7.42 (m, 2H, ArC*H*), 7.09-7.21 (m, 5H, ArC*H*), 7.01-7.05 (m, 1H, ArC*H*), 4.15 (dd, J_1 = 36.0 Hz, J_2 = 6.8 Hz, 1H, C*H*), 3.45-3.56 (m, 1H, C*H*), 3.24-3.39 (m, 2H, CH_2), 1.19-2.99 (m, 2H, CH_2), 1.35 (s, 1H, O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 139.3, 139.3, 138.6, 138.5, 133.1, 132.9, 132.8, 132.8, 131.7, 131.6, 128.9, 128.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 128.2, 128.2, 128.0, 128.0, 127.8, 127.8, 127.8, 127.8, 127.6, 127.5, 127.4, 126.7, 126.7, 126.6, 126.6, 125.6, 125.6, 125.5, 125.5, 120.0, 120.0, 119.9, 60.2, 60.2, 47.2, 47.1, 45.1, 44.6, 35.8, 35.8, 34.2. HRMS (ESI) m/z calcd for $C_{12}H_{20}NO$ $(M+H)^+$: 302.1539 found: 302.1554.



2-([1,1'-Biphenyl]-4-yl)-5-hydroxy-4-phenylpentanenitrile (4.3v): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 116 mg, 71%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 51:49, as determined from a comparison of the following signals: δ 3.11 (d, *J* =6.8 Hz, 1H, CH)-major product, 2.67 (d, *J* =6.8 Hz, 1H, CH)-minor product. IR (DCM; cm^{-1}): 3052, 2924, 2852, 1696, 1609, 1447, 1265, 1034, 908, 736. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.51 (m, 14H, ArC*H*), 3.43-3.73 (m, 3H, CH_2 & C*H*), 2.65-3.16 (m, 1H, C*H*), 1.99-2.38 (m, 2H, CH_2), 1.68 (s, 1H, O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 141.4, 141.2, 140.3, 140.0, 139.9, 135.0, 134.2, 129.3, 129.1, 128.9, 128.2, 128.2, 128.1, 127.9, 127.9, 127.7, 127.7, 127.7, 127.6, 127.5, 127.2, 127.1,



121.3, 120.4, 67.1, 67.1, 47.0, 45.3, 38.8, 37.8, 35.3, 34.4. HRMS (ESI) m/z calcd for $C_{23}H_{22}NO$ $(M+H)^+$: 328.1696 found: 328.1700.

2,2'-(1,4-Phenylene) bis(5-hydroxy-3-phenylpentanenitrile (4.3w): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 127 mg, 60%. IR (DCM; cm^{-1}): 3052, 2924, 2852, 1696, 1609, 1447, 1265, 1034, 908, 736. ^1H NMR (400 MHz, $CDCl_3$): 7.20 (d, *J* = 5.8 Hz, 6H, ArC*H*), 6.89-7.02 (m, 8H, ArC*H*), 4.03-4.08 (m, 1H, C*H*), 3.88-3.92 (m, 1H, C*H*), 3.47-3.59 (m, 2H, CH_2), 3.34-3.40 (m, 1H, CH_2), 3.12-3.30 (m, 3H, C*H* & CH_2), 1.93-2.18 (m, 4H, CH_2), 1.69 (s, 2H, O*H*). $^{13}C\{^1H\}$ NMR (100.6 MHz; CDCl3): δ 138.9, 138.9, 138.2, 138.1, 134.4, 134.3, 134.3, 129.1, 129.0, 129.0, 128.9, 128.9, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.3, 128.2, 128.2, 127.9, 127.9, 127.8, 127.8, 119.9, 119.5, 119.4, 60.1, 60.0, 60.0, 47.5, 47.4, 47.1, 47.0, 44.4, 44.3, 43.9, 43.8, 35.7, 35.7, 35.6, 34.8, 34.8. HRMS (ESI) m/z calcd for C28H28N2O2Na $(M+Na)^+$: 447.2043 found: 447.2025.

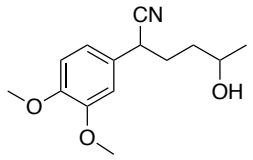
5-Hydroxy-2-phenylhexanenitrile (4.4a):[7] Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Yellow oil. Yield: 71 mg, 75%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 66:34, as determined from a comparison of the following signals: δ 1.21 (d, *J* = 6.2 Hz, 3H, CH_3)-major product, 1.15 (d, *J* = 6.2 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3688, 3053, 2985, 2304, 1421, 1265, 909, 740, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23-7.33 (m, 5H, ArC*H*), 3.73-3.81 (m, 2H, C*H*), 1.87-2.02 (m, 2H, CH_2), 1.50-1.57 (m, 2H, CH_2), 1.48 (s, 1H, O*H*), 1.14 (dd, J_1 = 6.2 Hz, J_2 = 2.6 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 136.0, 135.9, 129.3, 128.3, 127.5, 127.4, 121.1, 121.0, 67.8, 67.4, 37.6, 37.3, 36.5, 36.2, 32.7, 32.2, 24.1, 24.0. HRMS (ESI) m/z calcd for $C_{12}H_{15}NONa$ $(M+Na)^+$: 212.1046 found: 212.1051.

5-Hydroxy-2-(p-tolyl)hexanenitrile (4.4b): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless oil. Yield: 61 mg, 60%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 77:23, as determined from a comparison of the following signals: δ 1.01 (d, *J* =6.8 Hz, 3H, CH_3)-major product, 0.96 (d, *J* =5.4 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3461, 3054, 3022, 2953, 2925, 2866, 2240, 2188, 1634, 1508, 1464, 1456, 1382, 1365, 1065, 1019, 856, 817, 748, 477. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (q, *J* = 8.0 Hz, 4H, ArC*H*), 3.74 (td, J_1 = 12.0 Hz, J_2 = 6.2 Hz, 2*1 = 2H, C*H*), 2.27 (s, 3H, CH_3), 1.80-2.02 (m, 3H, CH_2 *&* O*H*), 1.46-1.60 (m, 2H, CH_2), 1.12 (d, *J* = 6.0 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): *δ* 138.0, 132.8, 132.8, 129.8, 127.2, 127.2, 121.2, 121.1, 67.6, 67.2, 37.1, 36.8, 36.3, 36.0, 32.5, 32.0, 23.9, 23.8, 21.2.

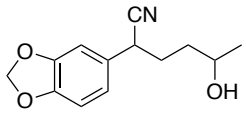
HRMS (ESI) m/z calcd for C13H17NONa $(M+Na)^+$: 226.1202 found: 226.1186.

5-Hydroxy-2-(4-methoxyphenyl) hexanenitrile (4.4c): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Yellow oil. Yield: 80 mg, 73%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 73:27, as determined from a comparison of the following signals: δ 1.14 (dd, J_1 = 6.2 Hz, J_2 = 2.4 Hz, 3H, CH_3)-major product, 1.13 (d, *J* = 2.4 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3421, 2964, 2931, 2239, 1612, 1513, 1455, 1304, 1251, 1180, 1130, 1032, 831, 749. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.19 (m, 2H, ArC*H*), 6.84 (d, *J* = 8.6 Hz, 2H, ArC*H*), 3.71-3.80 (m, 5H, OCH_3 & 2 C*H*), 1.83-2.03 (m, 2H, CH_2), 1.47-1.61 (m, 3H, CH_2 & O*H*), 1.14 (dd, J_1 = 6.2 Hz, J_2 = 2.4 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; CDCl3): δ 159.4, 128.5, 128.5, 127.9, 127.8, 121.3, 121.2, 114.5, 67.7, 67.3, 55.5, 36.7, 36.4, 36.4, 36.0, 32.6, 32.1, 24.0, 23.9. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO_2Na$ $(M+Na)^+$: 242.1151 found: 242.1151.

2-(3,4-Dimethoxyphenyl)-5-hydroxyhexanenitrile (4.4d): Purified by silica-gel column chromatography using an ethyl acetate/hexane (40:60) mixture as the eluent. Yellow liquid. Yield: 80 mg, 64%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 80:20, as determined from a comparison of the following signals: δ 1.16 (d, *J* = 1.9 Hz, 3H, CH_3)-major product, 1.15 (d, *J* = 2.0 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3508, 2963, 2932, 2838, 2239, 1593, 1519, 1463, 1455, 1418, 1262, 1240, 1144, 1026, 852, 764, 735, 641. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77-6.83 (m, 3H, ArC*H*), 3.83 (d, *J* = 7.7 Hz, 6H, OC*H*$_3$), 3.72-3.81 (m, 2*1 = 2H, C*H*), 2.06-1.84 (m, 2H, C*H*$_2$), 1.47-1.65 (m, 3H, C*H*$_2$ *&* O*H*), 1.16 (dd, J_1 = 6.1 Hz, J_2 = 1.9 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 149.4, 148.9, 128.3, 128.2, 121.2, 121.1, 119.7, 119.6, 111.5, 110.3, 110.2, 67.7, 67.2, 56.1, 56.1, 37.1, 36.8, 36.4, 36.1, 32.6, 32.1, 24.0, 23.9. HRMS (ESI) m/z calcd for $C_{14}H_{19}NO_3Na$ $(M+Na)^+$: 272.1257 found: 272.1257.



2-(Benzo[d][1,3]dioxol-5-yl)-5-hydroxyhexanenitrile (4.4e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (40:60) mixture as the eluent. Colorless oil. Yield: 92 mg, 79%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 75:25, as determined from a comparison of the following signals: δ 1.10 (d, *J* = 6.0 Hz, 3H, CH_3)-major product, 1.05 (d, *J* = 6.2 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3445, 2967, 2928, 2240, 1610, 1504, 1488, 1444, 1373, 1249, 1125, 1039, 935, 811, 738, 702. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 9.0 Hz, 3H, ArC*H*), 5.90 (s, 2H, C*H*$_2$), 3.66-3.79 (m, 2H, C*H*), 1.80-2.01(m, 2H, C*H*$_2$), 1.63 (s, 1H, O*H*), 1.45-1.58 (m, 2H, C*H*$_2$), 1.12-1.13 (m, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 148.3, 147.5, 129.5, 129.4, 121.1, 121.0, 120.8, 120.8, 108.7, 107.7, 107.7, 101.5, 67.6, 67.2, 37.1, 36.8, 36.2, 35.9, 32.5, 32.1, 23.9, 23.8. HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_3Na$ $(M+Na)^+$: 256.0944 found: 256.0934.



5-Hydroxy-2-(3,4,5-trimethoxyphenyl)hexanenitrile (4.4f): Purified by silica-gel column chromatography using an ethyl acetate/hexane (50:50) mixture as the eluent. Yellow liquid. Yield: 98 mg, 70%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 65:35, as determined from a comparison of the following signals: δ 1.17 (d, *J* = 0.3 Hz, 3H, CH_3)-major product, 1.16 (d, *J* = 0.7 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3508, 3055, 2966, 2938, 2840, 2240, 1652, 1593, 1509, 1463, 1422, 1337, 1265, 1245, 1184, 11130, 1004, 829, 738, 703, 657. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (s, 2H, ArC*H*), 3.69-3.81 (m, 11H, C*H* & OCH_3), 1.86-2.06 (m, 2H, CH_2), 1.50-1.64 (m, 3H, ArCH_2 & O*H*), 1.16 (dd, J_1 = 5.5 Hz, J_2 = 0.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 153.5, 137.6, 137.5, 131.5, 131.5, 131.4, 120.9, 120.9, 120.8, 104.3, 104.3, 67.4, 67.4, 67.0, 66.9, 60.8, 56.2, 56.2, 37.6, 37.6, 37.3, 36.3, 36.3, 36.0, 36.0, 32.4, 32.4, 31.9, 31.9, 23.8, 23.8, 23.0. HRMS (ESI) m/z calcd for $C_{15}H_{21}NO_4Na$ $(M+Na)^+$: 302.1363 found: 302.1362.

2-(4-(Benzyloxy)phenyl)-5-hydroxyhexanenitrile (4.4g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless oil. Yield: 120 mg, 81%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 73:27, as determined from a comparison of the following signals: δ 1.12 (d, *J* = 2.1 Hz, 3H CH_3)-major product, 1.10 (d, *J* = 2.3 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3446, 3052, 2930, 2869, 2240, 1884, 1699, 1609, 1511, 1453, 1265, 1245, 1179, 1022, 830, 737, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.35 (m, 5H, ArC*H*), 7.16 (d, *J* = 8.4 Hz, 2H, ArC*H*), 6.88 (d, *J* = 8.4 Hz, 2H, ArC*H*), 4.97 (s, 2H, CH_2), 3.72 (dq, J_1 = 17.6 Hz, J_2 = 6.3 Hz, 2H, CH_2), 1.80-2.00 (m, 2H, C*H*), 1.51 (tt, J_1 = 13.8 Hz, J_2 = 6.7 Hz, 3H, CH_2 & O*H*), 1.11 (dd, J_1 = 6.1 Hz, J_2 = 2.2 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 158.6, 136.7, 128.7, 128.5, 128.5, 128.2, 128.1, 128.1, 127.6, 121.2, 121.1, 115.4, 70.2, 67.6, 67.2, 36.7, 36.4, 36.3, 36.0, 32.5, 32.1, 23.9, 23.8. HRMS (ESI) m/z calcd

for $C_{19}H_{21}NO_2Na$ $(M+Na)^+$: 318.1465 found: 318.1450.

5-Hydroxy-2-(naphthalen-2-yl) hexanenitrile (4.4h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless oil. Yield: 80 mg, 67%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 66:34, as determined by a comparison of the following signals: δ 1.06 (d, *J* = 5.4 Hz, 3H, CH_3)-major product, 0.98 (d, *J* = 5.4 Hz, 3H, CH_3)-minor product. IR (DCM; cm^{-1}): 3054, 2970, 2304, 2241, 1599, 1508, 1422, 1375, 1265, 1124, 895, 858, 818, 738, 478. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, J_1 = 11.9 Hz, J_2 = 6.7 Hz, 4H, ArC*H*), 7.44 (t, *J* = 4.0 Hz, 2H, ArC*H*), 7.34 (d, *J* = 8.4 Hz, 1H, ArC*H*), 3.93-3.97 (m, 1H, C*H*), 3.81-3.73 (m, 1H, C*H*), 1.94-2.13 (m, 2H, ArCH_2), 1.82 (s, 1H, O*H*), 1.48-1.66 (m, 2H, CH_2), 1.13 (dd, J_1 = 6.0 Hz, J_2 = 3.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 133.3, 133.1, 133.0, 132.9, 129.2, 127.9, 127.8, 126.8, 126.6, 126.4, 126.4, 124.8, 124.8, 120.9, 120.9, 67.7, 67.2, 37.6, 37.3, 36.3, 36.0, 32.4, 31.9, 24.0, 23.8. HRMS (ESI) m/z calcd for $C_{16}H_{17}NONa$ $(M+Na)^+$: 262.1202 found: 262.1196.

5-Hydroxy-2,2-diphenylhexanenitrile (4.4i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (25:75) mixture as the eluent. Colorless liquid. Yield: 74 mg, 56%. IR (DCM; cm^{-1}): 3404, 3060, 2965, 2931, 2871, 2235, 1598, 1493, 1449, 1375, 1131, 1032, 1003, 983, 752, 640, 542. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.34 (m, 10H, ArC*H*), 3.75 (ddd, J_1 = 7.8 Hz, J_2 = 6.2 Hz, J_3 = 4.4 Hz, 1H, C*H*), 2.57 (ddd, J_1 = 13.5 Hz, J_2 = 12.1 Hz, J_3 = 4.6 Hz, 1H, CH_2), 2.30 (ddd, J_1 = 13.5, 12.0 Hz, J_2 = 4.6 Hz, 1H, CH_2), 1.63 (s, 1H, O*H*), 1.43-1.56 (m, 2H, CH_2), 1.10 (d, *J* = 6.2 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 140.3, 139.9, 128.9, 127.9, 126.9, 126.8, 122.4, 67.6, 51.6, 35.9, 35.1, 23.8. HRMS (ESI) m/z calcd for $C_{18}H_{19}NONa$ $(M+Na)^+$: 288.1359 found: 288.1373.

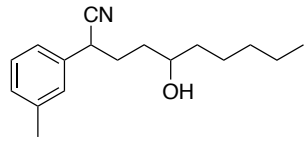
5-Hydroxy-2,2-diphenyldecanenitrile (4.4j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (25:75) mixture as the eluent. Colorless liquid. Yield: 143 mg, 89%. IR (DCM; cm^{-1}): 3602, 3482, 3055, 2860, 2305, 2237, 1598, 1493, 1450, 1127, 1031, 897, 540. ^1H NMR (400 MHz, $CDCl_3$): δ 7.16-7.32 (m, 10H, ArC*H*), 3.53 (tt, J_1 = 7.7 Hz, J_2 = 3.9 Hz, 1H, C*H*), 2.28-2.61 (m, 2H, CH_2), 1.65 (dd, J_1 = 30.6 Hz, J_2 =13.1 Hz, 1H,), 1.58-1.53 (m, 1H), 1.43-1.38 (m, 1H), 1.34-1.26 (m, 3H), 1.21-1.14 (m, 5H), 0.78 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 140.5, 140.0, 128.9, 128.9, 127.9, 127.0, 126.9, 122.5, 71.6, 51.6, 37.6, 35.9, 33.4, 31.8, 25.3, 22.6, 14.1. HRMS (ESI) m/z calcd for $C_{18}H_{19}NONa$ $(M+Na)^+$: 288.1359 found: 288.1373.

2-(4-Bromophenyl)-5-hydroxydecanenitrile (4.4k): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 113 mg, 70%. IR (DCM; cm^{-1}): 3475, 3052, 2929, 2857, 2304, 2242, 1714, 1592, 1488, 1455, 1406, 1377, 1264, 1185, 1125, 1073, 1101, 823, 738, 521. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.8 Hz, 2H, ArC*H*), 7.25 (t, J = 11.8 Hz, 2H, ArC*H*), 3. 86 (q, J = 7.4 Hz, 1H, C*H*), 3.62-3.65 (m, 1H, ArC*H*), 2.14-1.94 (m, 2H, CH_2), 1.27-1.69 (m, 11H, CH_2 & O*H*), 0.90 (q, J = 7.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 134.9, 134.8, 132.2, 129.0, 128.9, 122.1, 120.4, 120.3, 71.5, 70.9, 37.8, 37.7, 37.0, 36.6, 34.4, 34.0, 32.4, 31.8, 31.8, 25.3, 25.2, 22.6, 14.0. HRMS (ESI) m/z calcd for $C_{17}H_{23}BrNO$ $(M+H)^+$: 324.0958 found: 324.0945.

2-(4-Chlorophenyl)-5-hydroxydecanenitrile (4.4l): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 82 mg, 59%. IR (DCM; cm^{-1}): 3458, 3053, 2930, 2861, 2242, 1710, 1598, 1492, 1457, 1409, 1265, 1093, 1015, 827, 738, 509. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 3.80 (q, J = 7.3 Hz, 1H), 3.57-3.54 (m, 1H), 2.08-1.84 (m, 2H), 1.62-1.47 (m, 3H), 1.37-1.22 (m, 8H), 0.83 (t,

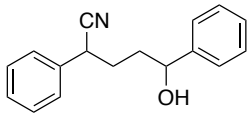
J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 134.5, 134.4, 134.1, 129.4, 129.4, 128.7, 128.7, 120.6, 120.5, 71.5, 71.0, 37.8, 37.7, 37.0, 36.6, 34.5, 34.1, 32.5, 31.9, 31.8, 25.4, 25.3, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{16}H_{23}ClNO$ $(M+H)^+$: 280.1463 found: 280.1475.

5-Hydroxy-2-(m-tolyl)decanenitrile (4.4m): Purified by silica-gel column chromatography



using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 84 mg, 65%. IR (DCM; cm^{-1}): 3664, 3605, 3474, 3053, 2929, 2861, 2306, 2241, 1711, 1603, 1455, 1380, 1265, 1125, 1059, 896, 840, 736, 431. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 7.0 Hz, 3H), 3.49-3.80 (m, 2H), 2.27 (s, 3H), 1.93 (dddt, J_1 = 55.5 Hz, J_2 = 14.0 Hz, J_3 = 9.6 Hz, J_4 = 4.7 Hz, 2H), 1.19-1.61 (m, 12H), 0.80 (t, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 139.0, 135.9, 135.8, 129.0, 128.9, 128.9, 128.0, 128.0, 124.4, 124.4, 121.2, 121.0, 71.6, 71.1, 37.8, 37.7, 37.5, 37.2, 34.7, 34.4, 32.5, 32.0, 31.9, 25.4, 25.3, 22.7, 21.5, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{25}NONa$ $(M+Na)^+$: 282.1828 found: 282.1834.

5-Hydroxy-2,5-diphenylpentanenitrile (4.4n): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 89 mg, 71%. IR (DCM; cm^{-1}): 3439, 3061, 3030, 2925, 2865, 2241, 1493, 1453, 1397, 1266, 1200, 1062, 1002, 945, 914, 758, 737, 699, 549. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20-7.29 (m, 10H, ArC*H*), 4.59 (dt, J_1 = 11.3 Hz, J_2 = 5.5 Hz, 1H, C*H*), 3.71 (q, J = 6.5 Hz, 1H, C*H*), 2.11 (s, 1H, O*H*), 1.91-2.01 (m, 1H, CH_2), 1.73-1.86 (m, 3H, ACH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 144.0, 144.0, 135.7, 135.6, 129.1, 128.7, 128.7, 128.1, 127.9, 127.9, 127.4, 127.3, 125.8, 120.9, 120.8, 73.8, 73.5, 37.3, 37.0, 36.2, 35.9, 32.3, 31.9. HRMS (ESI) m/z calcd for $C_{17}H_{17}NONa$ $(M+Na)^+$: 274.1202 found: 274.1219.

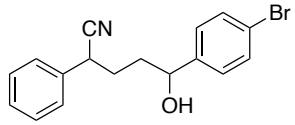
5-Hydroxy-2-(2-methoxyphenyl)-5-phenylpentanenitrile (4.4o): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 104 mg, 74%. IR (DCM; cm^{-1}): 3444, 3028, 2937, 2838, 2240, 1600, 1588, 1494, 1463, 1454, 1438, 1250, 1051, 1026, 755, 701, 553. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.29 (m, 7H, ArC*H*), 6.79-6.91 (m, 2H, ArC*H*), 4.61 (q, *J* = 6.6 Hz, 1H, C*H*), 4.13 (t, *J* = 6.5 Hz, 1H, C*H*), 3.74 (s, 3H, OCH_3), 1.75-2.03 (m, 5H, CH_2 & O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 156.1, 144.1, 144.0, 129.4, 128.6, 128.6, 128.4, 128.4, 127.8, 127.8, 125.9, 124.0, 123.9, 121.3, 121.2, 121.0, 121.0, 110.9, 73.9, 73.7, 55.5, 36.3, 36.1, 31.3, 31.2, 30.2, 29.7. HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_2Na$ $(M+Na)^+$: 304.1308 found: 304.1326.

5-Hydroxy-5-(3,4,5-trimethoxyphenyl)-2-(4-vinylphenyl)pentanenitrile (4.4p): Purified by silica-gel column chromatography using an ethyl acetate/hexane (50:50) mixture as the eluent. Colorless liquid. Yield: 101 mg, 55%. IR (DCM; cm^{-1}): 3482, 2937, 2838, 2240, 1694, 1629, 1592, 1508, 1462, 1420, 1328, 1235, 1127, 1005, 915, 842, 735, 699, 527. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (dd, J_1 = 58.4 Hz, J_2 = 8.0 Hz, 4H, ArC*H*), 6.63 (dd, J_1 = 17.5 Hz, J_2 = 10.9 Hz, 1H, ArC*H*), 6.46 (d, *J* = 32.6 Hz, 2H, olefin C*H*), 5.69 (d, *J* = 17.6 Hz, 1H, olefin C*H*), 5.22 (d, *J* = 10.9 Hz, 1H, olefin C*H*), 4.54 (s, 1H, O*H*), 3.78 (d, *J* = 4.0 Hz, 2H, C*H*), 3.75 (s, 9H, OCH_3), 1.74-2.02 (m, 4H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 153.3, 140.0, 140.0, 137.5, 137.5, 137.1, 137.1, 136.8, 135.9, 135.0, 135.0, 127.5, 127.5, 126.9, 120.8, 120.7, 114.8, 103.7, 102.5, 74.0, 73.6, 65.4, 60.9, 56.1, 56.1, 37.0, 36.7, 36.1, 35.8, 32.2, 31.8. HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_4Na$ $(M+Na)^+$: 390.1676 found: 390.1688.

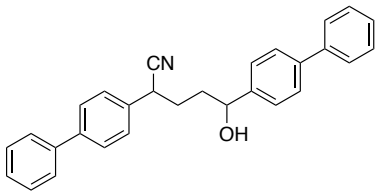
2,5-Bis(benzo[d][1,3]dioxol-5-yl)-5-hydroxypentanenitrile (4.4q): Purified by silica-gel column chromatography using an ethyl acetate/hexane (50:50) mixture as the eluent. Colorless liquid. Yield: 85 mg, 50%. IR

(DCM; cm^{-1}): 3464, 3057, 2898, 2779, 2240, 2186, 1850, 1722, 1609, 1503, 1487, 1443, 1368, 1247, 1123, 1038, 932, 863, 811, 736, 702, 639, 569, 503. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63-6.72 (m, 6H, ArC*H*), 5.85-5.88 (m, 4H, CH_2), 4.48-4.58 (m, 1H, C*H*), 3.63 (dt, J_1 = 8.0 Hz, J_2 = 5.3 Hz, 1H, C*H*), 2.06 (s, O*H*), 1.63-1.97 (m, 4H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 148.3, 148.0, 148.0, 147.5, 147.2, 147.2, 138.1, 138.1, 129.4, 129.3, 120.9, 120.9, 120.8, 120.8, 119.2, 108.7, 108.2, 107.7, 107.7, 106.3, 101.5, 101.2, 73.7, 73.5, 37.0, 36.7, 36.1, 35.8, 32.4, 32.0. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_5Na$ $(M+Na)^+$: 362.0999 found: 362.1110.

5-(4-Bromophenyl)-5-hydroxy-2-phenylpentanenitrile (4.4r): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 86 mg, 52%. IR (DCM; cm^{-1}): 3450, 3051, 3015, 2945, 2870, 2230, 1537, 1480, 1424, 920, 762, 723, 680, 520. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.2 Hz, 2H, ArC*H*), 7.27 (dq, J_1 = 29.3 Hz, J_2 = 7.1 Hz, 5H, ArC*H*), 7.12 (d, J = 8.2 Hz, 2H, ArC*H*), 4.62 (dt, J_1 = 11.1 Hz, J_2 = 5.5 Hz, 1H, C*H*), 3.77 (q, J = 6.9 Hz, 1H, C*H*), 2.15 (s, 1H, O*H*), 2.00 (q, J = 8.6 Hz, 1H, CH_2), 1.82 (qt, J_1 = 13.5 Hz, J_2 = 7.0 Hz, 3H, CH_2). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 143.0, 143.0, 135.6, 135.5, 131.8, 131.8, 129.2, 128.3, 127.6, 127.3, 127.3, 121.7, 121.6, 120.8, 120.8, 73.2, 72.9, 37.3, 37.1, 36.2, 35.9, 32.1, 31.8. HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNONa$ $(M+Na)^+$: 352.0307 found: 352.0286.

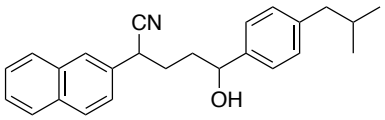


2,5-Di([1,1'-biphenyl]-4-yl)-5-hydroxypentanenitrile (4.4s): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. White Solid. Yield: 103 mg, 51%. IR (DCM; cm^{-1}): 3054, 2927, 2305, 2246, 1485, 1451, 1412, 1264, 1067, 1026, 943, 897, 840, 735, 506. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 5.8 Hz, 8H, ArC*H*), 7.27-7.38 (m, 10H, ArC*H*), 4.69-4.74 (m, 1H, C*H*), 3.80-3.85 (m, 1H, C*H*), 2.08 (dq, J_1 = 12.5 Hz, J_2 = 6.6 Hz, 1H, CH_2), 1.83-1.97 (m, 3H, CH_2), 1.52 (s, 1H, O*H*). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 143.0, 143.0, 141.3, 141.0, 141.0, 140.8, 140.4, 134.7, 129.0, 128.9, 127.9,



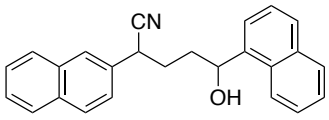
127.9, 127.8, 127.7, 127.5, 127.5, 127.2, 126.3, 120.9, 120.8, 73.9, 73.6, 37.1, 36.9, 36.2, 35.9, 32.4, 32.0. HRMS (ESI) m/z calcd for C29H25NONa $(M+Na)^+$: 426.1828 found: 426.1825.

5-Hydroxy-5-(4-isobutylphenyl)-2-(naphthalen-2-yl)pentanenitrile (4.4t): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Yellow oil. Yield: 93 mg, 52%. IR (DCM; cm^{-1}): 3454, 3054, 3023, 2924, 2866, 2239, 2188, 1683, 1634, 1600, 1575, 1508, 1465, 1418, 1365, 1311, 1125, 1065, 944, 893, 817, 748, 557, 477. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.80 (m, 4H, ArC*H*), 7.40-7.43 (m, 2H, ArC*H*), 7.28 (d, J = 8.5 Hz, 1H, ArC*H*), 7.00-7.16 (m, 4H, ArC*H*), 4.59 (dt, J_1 = 11.2 Hz, J_2 =5.9 Hz, 1H, C*H*), 3.89 (dt, J_1 = 8.6 Hz, J_2 = 4.4 Hz, 1H, C*H*), 2.37 (dd, J_1 = 7.2 Hz, J_2 = 3.0 Hz, 2H, CH_2), 2.05-2.10 (m, 1H, C*H*), 1.72-1.95 (m, 5H, CH_2 & O*H*), 0.81 (dd, J_1 = 6.6 Hz, J_2 = 2.5 Hz, 2 x 3 = 6H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 153.4, 153.1, 152.9, 139.7, 139.7, 134.2, 134.1, 134.1, 129.3, 128.6, 120.3, 120.3, 102.4, 74.1, 73.7, 60.9, 56.2, 56.2, 56.1, 56.1, 36.8, 36.4, 36.0, 35.7, 32.3, 31.8. HRMS (ESI) m/z calcd for $C_{25}H_{27}NONa$ $(M+Na)^+$: 380.1985 found: 380.1989.

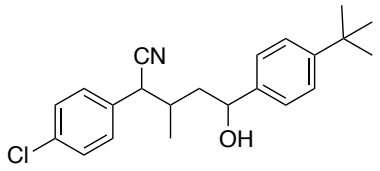
5-Hydroxy-5-(naphthalen-1-yl)-2-(naphthalen-2-yl)pentanenitrile (4.4u): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Yellow liquid. Yield: 140 mg, 80%. IR (DCM; cm^{-1}): 3590, 3476, 3053, 2928, 2304, 2241, 1729, 1599, 1509, 1421, 1394, 1264, 1060, 1019, 894, 818, 737, 703, 478. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (t, J = 9.1 Hz, 1H, ArC*H*), 7.68-7.81 (m, 6H, ArC*H*), 7.54 (d, J_1 = 7.1 Hz, 1H, ArC*H*), 7.41 (ddd, J_1 = 14.6, Hz, J_2 = 11.4 Hz, J_3 = 7.4 Hz, 5H, ArC*H*), 7.30 (t, J = 7.4 Hz, 1H, ArC*H*), 5.42-5.47 (m, 1H, C*H*), 3.93 (t, J = 6.8 Hz, 1H, ArC*H*), 1.98-2.20 (m, 4H, CH_2), 1.88 (s, 1H, O*H*). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 139.5, 139.4, 133.8, 133.3, 133.2, 132.9, 132.8, 132.8, 132.8, 130.1, 129.1, 129.1, 129.0, 128.3, 127.9, 127.7, 126.7, 126.7, 126.5, 126.5, 126.5, 126.4, 126.3, 125.7, 125.4, 124.8, 122.9, 122.8, 122.8, 120.9, 120.8, 70.6, 70.3, 37.4, 37.1, 35.1, 34.7, 32.3, 31.9.

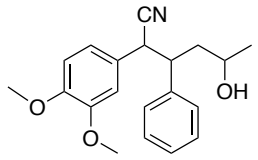
HRMS (ESI) m/z calcd for $C_{25}H_{21}NONa$ $(M+Na)^+$: 374.1515 found: 374.1515.

5-(4-(*tert*-Butyl)phenyl)-2-(4-chlorophenyl)-5-hydroxy-3-methylpentanenitrile (4.4v):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid. Yield: 85 mg, 48%. IR (DCM; cm^{-1}): 3682, 3593, 3054, 2964, 2870, 2684, 2305, 2241, 1605, 1492, 1418, 1094, 1016, 895, 835, 738, 580, 515. ^1H NMR (400 MHz, $CDCl_3$): δ 7.13-7.33 (m, 8H, ArC*H*), 4.71-4.78 (m, 1H, C*H*), 3.99 (dd, J_1 = 18.1 Hz, J_2 = 4.9 Hz, 1H, C*H*), 2.05-1.94 (m, 1H, CH_2), 1.82 (t, J = 6.9 Hz, 1H, CH_2), 1.23-1.26 (s, 9H, CH_3), 1.19 (s, 1H, O*H*), 0.93 (dd, J_1 = 14.1 Hz, J_2 = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 151.3, 151.2, 141.6, 140.9, 134.0, 134.0, 133.6, 133.5, 129.3, 129.2, 129.2, 129.1, 129.1, 125.8, 125.8, 125.7, 125.5, 119.1, 119.1, 72.3, 71.9, 44.3, 43.5, 43.3, 41.8, 36.0, 35.3, 34.7, 31.5, 29.8, 16.5, 15.3. HRMS (ESI) m/z calcd for $C_{22}H_{26}ClNONa$ $(M+Na)^+$: 378.1595 found: 378.1578.

2-(3,4-Dimethoxyphenyl)-5-hydroxy-3-phenylhexanenitrile (4.4w): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 130 mg, 80%. IR (DCM; cm^{-1}): 3507, 3060, 3003, 2963, 2837, 2238, 1726, 1594, 1517, 1454, 1420, 1374, 1343, 1265, 1186, 1144, 1067, 1026, 939, 810, 736, 702, 647, 562, 447. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.28 (m, 3H, ArC*H*), 7.08-7.13 (m, 2H, ArC*H*), 6.65-6.77 (m, 2H, ArC*H*), 6.37-6.51 (m, 1H, ArC*H*), 3.92-4.16 (m, 1H, C*H*), 3.81-3.88 (m, 3H, OCH_3), 3.72 (dd, J_1 = 24.3 Hz, J_2 = 13.1 Hz, 3H, ArOCH_3), 3.10-3.63 (m, 2H, C*H*), 1.83-2.09 (m, 2H, CH_2), 1.71 (s, 1H, O*H*), 1.16 (td, J_1 = 11.6 Hz, J_2 = 6.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 139.0, 138.6, 134.4, 134.3, 128.9, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.2, 128.2, 128.1, 127.8, 127.7, 120.0, 119.7, 65.9, 65.5, 47.5, 47.5, 44.8, 43.8, 42.5, 42.1, 24.7, 23.6. HRMS (ESI) m/z calcd for $C_{20}H_{23}NO_3Na$ $(M+Na)^+$: 348.1570 found: 348.1555.



2-(3,4,5-Trimethoxyphenyl)-5-hydroxy-3-phenylhexanenitrile (4.4x): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 106 mg, 60%. IR (DCM; cm^{-1}): 3495, 3055, 2468, 2937, 2840, 2306, 2241, 1712, 1593, 1507, 1460, 1424, 1333, 1264, 1128, 1004, 896, 831, 737, 528. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.28 (m, 3H, ArC*H*), 7.10 (dt, J_1 = 6.3 Hz, J_2 = 3.1 Hz, 2H, ArC*H*), 6.18-6.28 (m, 2H, ArC*H*), 3.89-4.15 (m, 1H, C*H*), 3.79-3.80 (m, 3H, ArOCH_3), 3.72 (d, J = 6.0 Hz, 6H, ArOCH_3), 3.16 -3.38 (m, 1H, C*H*), 1.86-2.10 (m, 2H, CH_2), 1.17 (ddd, J_1 = 14.1 Hz, J_2 = 10.9 Hz, J_3 = 6.1 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 153.0, 139.4, 139.1, 138.8, 138.4, 137.5, 137.4, 129.7, 129.6, 129.2, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 127.5, 127.5, 127.4, 119.7, 119.5, 105.3, 105.2, 105.2, 66.0, 66.0, 65.5, 65.5, 65.3, 64.9, 60.8, 56.0, 56.0, 56.0, 55.8, 48.2, 47.3, 47.2, 47.1, 44.8, 44.7, 44.7, 43.5, 42.2, 41.8, 41.4, 41.1, 24.6, 24.5, 23.4, 22.8. HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_4Na(M+Na)^+$: 378.1676 found: 378.1685.

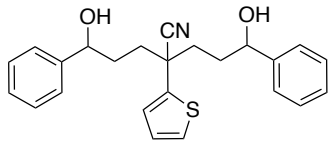
2-(4-Fluorophenyl)-5-hydroxy-3-phenylhexanenitrile (4.4y): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 100 mg, 71%. IR (DCM; cm^{-1}): 3602, 3477, 3054, 2968, 2930, 2305, 2241, 1710, 1603, 1510, 1420, 1376, 1265, 1233, 1101, 895, 835, 737, 571, 523. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 6.3 Hz, 3H, ArC*H*), 7.02-7.10 (m, 4H, ArC*H*), 6.96 (t, J = 8.4 Hz, 2H, ArC*H*), 3.98-4.25 (m, 1H, C*H*), 3.54-3.89 (m, 1H, C*H*), 3.08-3.39 (m, 1H, C*H*), 1.85-2.26 (m, 2H, CH_2), 1.59 (s, 1H, O*H*), 1.18 (td, J_1 = 15.0 Hz, J_2 = 6.1 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 163.7, 163.6, 161.2, 139.1, 138.7, 138.3, 130.3, 130.3, 130.2, 130.2, 130.0, 129.9, 129.9, 129.9, 129.9, 129.8, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.2, 127.9, 127.8, 120.0, 119.8, 119.5, 115.9, 115.9, 115.7, 115.6, 66.3, 65.8, 65.5, 48.6, 47.6, 47.5, 44.2, 44.0, 42.8, 42.4, 42.0, 41.6, 24.8, 23.7, 23.1. HRMS (ESI) m/z calcd for $C_{18}H_{19}FNO$ $(M+H)^+$: 284.1445 found: 284.1450.

5-Hydroxy-3-phenyl-2-(4-vinylphenyl)hexanenitrile (4.4z): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 100 mg, 69%. IR (DCM; cm^{-1}): 3459, 3054, 2969, 2930, 2241, 1604, 2241, 1604, 1509, 1452, 1409, 1265, 1124, 1029, 992, 914, 842, 738, 703, 485. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-6.92 (m, 9H, ArC*H*), 6.53-6.61 (m, 1H, olefin C*H*), 5.50-5.66 (m, 1H, olefin C*H*), 5.11 (dd, J_1 = 50.0 Hz, J_2 = 11.0 Hz, 1H, olefin C*H*), 3.88-4.10 (m, 1H, C*H*), 3.00-3.72 (m, 2H, C*H*), 1.68-1.96 (m, 2H, CH_2), 1.62 (s, 1H, O*H*), 0.98-1.18 (m, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 139.6, 139.4, 139.0, 138.6, 137.4, 137.4, 137.3, 137.3, 136.1, 136.1, 136.1, 133.8, 133.7, 133.5, 128.8, 128.8, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 126.5, 126.5, 120.0, 119.9, 119.6, 114.7, 114.7, 114.6, 66.2, 65.7, 65.4, 65.0, 64.9, 48.2, 47.3, 47.2, 44.6, 44.5, 44.5, 44.4, 43.4, 42.4, 42.4, 42.1, 41.2, 40.8, 24.6, 24.6, 23.5, 22.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}NONa$ $(M+Na)^+$: 314.1515 found: 314.1520.

2-(3,5-Bis(trifluoromethyl)phenyl)-5-hydroxy-2-(3-hydroxyoctyl)decanenitrile (4.4aa): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 114 mg, 45%. IR (DCM; cm^{-1}): 3344, 2931, 2859, 2238, 1715, 1622, 1459, 1372, 1278, 1171, 1339, 899, 845, 740, 707, 682, 527. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 3H, ArC*H*), 3.46-3.55 (m, 2H, C*H*), 2.28 (s, 1H, CH_2), 2.17 (dd, J_1 = 12.7 Hz, J_2 = 3.9 Hz, 1H, CH_2), 2.05-2.08 (m, 1H, CH_2), 1.91 (dt, J_1 = 0.6 Hz, J_2 = 0.3 Hz, 1H, CH_2), 1.76 (t, J = 0.2 Hz, 2H, O*H*), 1.53-1.62 (m, 2H, CH_2), 1.33 (s, 6H, CH_2), 1.22 (dd, J_1 = 15.5 Hz, J_2 = 6.0 Hz, 11H, CH_2), 1.08 (t, J = 6.2 Hz, 1H, CH_2), 0.81 (t, J = 6.5 Hz, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz; $CDCl_3$): δ 141.9, 141.7, 141.7, 141.5, 133.1, 132.8, 132.7, 132.4, 132.1, 126.4, 126.4, 126.4, 124.4, 122.3, 122.3, 122.2, 122.2, 122.2, 121.7, 121.3, 121.2, 121.1, 71.2, 71.2, 48.1, 48.1, 48.0, 37.5, 37.5, 37.4, 37.1, 37.0, 36.7, 36.5, 32.8, 32.7, 31.7, 25.3, 25.2, 22.6, 14.0. HRMS (ESI) m/z calcd for

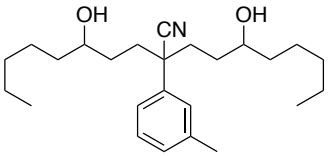
$C_{26}H_{37}F_6NO_2Na$ $(M+Na)^+$: 532.2621 found:532.2637.

5-Hydroxy-2-(3-hydroxy-3-phenylpropyl)-5-phenyl-2-(thiophen-2-yl)pentanenitrile



(4.4ab): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 82 mg, 42%. IR (DCM; cm^{-1}): 3417, 3061, 3029, 2924, 2858, 2238, 1716, 1672, 1602, 1493, 1453, 1266, 1238, 1201, 1058, 1027, 916, 845, 763, 738, 700, 625, 547, 511 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.84-7.28 (m, 13H, ArC*H*), 4.52-4.61 (m, 2H, C*H*), 1.59-2.16 (m, 10H, CH_2 & O*H*). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 143.8, 143.7, 128.6, 127.8, 127.8, 126.7, 126.2, 125.8, 125.7, 125.3, 125.3, 125.3, 121.4, 121.4, 121.3, 73.8, 73.7, 44.8, 44.8, 38.5, 38.3, 38.3, 34.4, 34.3, 34.3. HRMS (ESI) m/z calcd for $C_{24}H_{25}NO_2SNa$ $(M+Na)^+$: 414.1498 found:414.1480.

5-Hydroxy-2-(3-hydroxyoctyl)-2-(m-tolyl)decanenitrile (4.4ac): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 25 mg, 42%. IR (DCM; cm^{-1}): 3676, 3564, 3405, 3374, 3043, 2939, 2761, 2206, 1811, 1703, 1555, 1280, 1165, 959, 887, 860, 766. ^1H NMR (400 MHz, $CDCl_3$): δ 7.03-7.21 (m, 4H, ArC*H*), 3.38-3.51 (m, 2H, C*H*), 2.30 (s, 3H, ArCH_3), 1.80-2.20 (m, 4H, CH_2), 1.57 (dd, J_1 = 8.0 Hz, J_2 = 4.1 Hz, 4H, CH_2 & O*H*), 1.12-1.32 (m, 18H, CH_2), 0.79 (t, J = 6.9 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz; $CDCl_3$): δ 138.8, 138.5, 138.3, 128.9, 128.6, 126.9, 123.0, 122.9, 122.9, 122.7, 122.6, 71.7, 71.6, 47.9, 37.6, 37.5, 37.5, 37.1, 37.0, 33.1, 33.0, 31.9, 25.4, 25.3, 22.7, 21.7, 14.1. HRMS (ESI) m/z calcd for $C_{25}H_{15}NO_2$ $(M+H)^+$: 388.3210 found: 388.3238.



Spectral Data of Synthesized Biologically Active Molecules

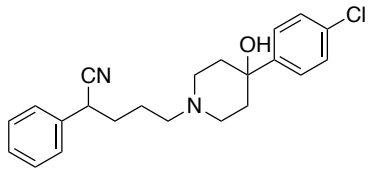
A) CCR1 Receptor Antagonists

5-Bromo-2-phenylpentanenitrile (4.5a):[75] Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Yellow oil. Yield: 83 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.33 (m, 5H, Ar*CH*), 3.76 (t, *J* = 6.7 Hz, 1H, *CH*), 3.33 (t, *J* = 5.7 Hz, 2H, CH_2), 1.91-1.99 (m, 4H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 135.2, 129.2, 128.3, 127.2, 120.4, 36.6, 34.2, 32.3, 29.7.

5-Bromo-2,2-diphenylpentanenitrile (4.5b):[75] Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Yellow oil. Yield: 94 mg, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.33 (m, 10H, Ar*CH*), 3.34 (t, *J* = 6.2 Hz, 2H, CH_2), 2.46-2.50 (m, 2H, CH_2), 1.92 (dq, J_1 = 10.4 Hz, J_2 = 5.6 Hz, 2H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 139.8, 129.1, 128.2, 126.9, 122.2, 51.3, 38.4, 33.0, 28.8.

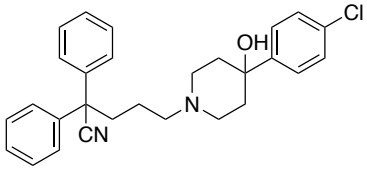
5-Bromo-2-methyl-2-phenylpentanenitrile (4.5c):[75] Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as the eluent. Yellow oil. Yield: 88 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.48 (m, 5H, Ar*CH*), 3.38 (t, *J* = 6.1 Hz, 2H, CH_2), 2.08 (dq, J_1 = 29.7 Hz , J_2 = 7.5 Hz, 3H, CH_3), 1.76 (s, 4H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 139.5, 129.1, 128.0, 125.4, 123.1, 42.1, 40.5, 32.8, 28.6, 28.1.

5-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-2-phenylpentanenitrile (4.5d):[75]



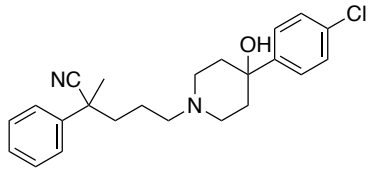
Purified by silica-gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. White solid. Yield: 97 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (ddd, J_1 = 33.6 Hz, J_2 = 16.1 Hz, J_3 = 7.5 Hz, 9H, Ar*CH*), 3.74 (t, *J* = 7.1 Hz, 1H, *CH*), 2.64-2.63 (m, 3H, CH_2 & O*H*), 2.32 (t, *J* = 11.0 Hz, 4H, CH_2), 1.99-1.93 (m, 2H, CH_2), 1.87-1.76 (m, 2H, CH_2), 1.59 (d, *J* = 12.9 Hz, 4H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 147.0, 135.7, 132.6, 129.1, 128.3, 128.1, 127.2, 126.2, 120.8, 70.8, 57.6, 49.3, 38.2, 37.2, 33.8, 24.2.

5-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-2,2-diphenylpentanenitrile (4.5e):[75]



Purified by silica-gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. White solid. Yield: 116 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.35 (m, 14H, Ar*CH*), 2.61 (d, *J* = 11.3 Hz, 2H, CH_2), 2.24-2.37 (m, 6H, CH_2), 1.98 (dt, J_1 = 12.6 Hz, J_2 = 6.3 Hz, 2H, CH_2), 1.83 (s, 1H, O*H*), 1.53-1.60 (m, 4H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 147.1, 140.3, 132.8, 129.0, 128.5, 128.0, 127.0, 126.2, 122.5, 71.1, 58.0, 51.8, 49.5, 38.5, 37.6, 23.3.

5-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-2-methyl-2-phenylpentanenitrile (4.5f):[75]

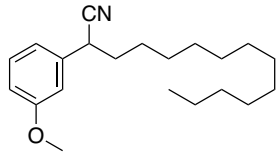


Purified by silica-gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. White solid. Yield: 84 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.41 (m, 9H, Ar*CH*), 2.65 -2.72 (m, 2H, CH_2), 2.30-2.39 (m, 4H, CH_2), 2.23-2.27 (m, 1H, CH_2), 1.99-2.09 (m, 2H, CH_2), 1.89-1.96 (m, 2H, CH_2), 1.63-1.68 (m, 6H, ArCH_3 & CH_2 & O*H*), 1.37 -1.44 (m, 1H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 146.9,

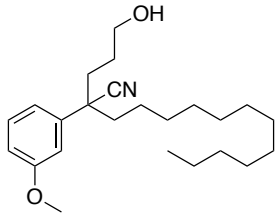
140.1, 132.9, 129.1, 128.5, 127.9, 126.2, 125.5, 123.5, 71.0, 57.9, 49.5, 49.2, 42.6, 39.9, 38.3, 28.0, 23.0

B) Calcium Channel Blockers:

2-(3-Methoxyphenyl)tetradecanenitrile (4.5g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent. Colorless liquid . Yield: 312 mg, 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (td, J_1 = 8.2 Hz, J_2 = 0.9 Hz, 1H, Ar*CH*), 6.76-6.83 (m, 3H, Ar*CH*), 3.74 (s, 3H, ArOCH_3), 3.66 (dd, J_1 = 8.5 Hz, J_2 = 6.3 Hz, 1H, *CH*), 1.74 -1.86 (m, 2H, CH_2), 1.34-1.45 (m, 2H, CH_2), 1.18-1.24 (m, 18H, CH_2), 0.80 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 160.1, 137.7, 130.2, 121.0, 119.6, 113.4, 113.2, 55.4, 37.5, 35.9, 32.0, 29.7, 29.7, 29.6, 29.5, 29.4, 29.1, 27.2, 22.8, 14.2.



2-(3-Hydroxypropyl)-2-(3-methoxyphenyl)tetradecanenitrile (4.5h): Purified by silica-gel column hromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid . Yield: 183 mg, 98%. IR (DCM; cm^{-1}): 3612, 3054, 2927, 2855, 2305, 1603, 1490, 1427, 1264, 1155, 1047, 895, 738 . ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.32 (m, 1H, Ar*CH*), 6.95-6.99 (m, 2H, Ar*CH*), 6.83-6.88 (m, 1H, Ar*CH*), 3.83 (s, 3H, ArOCH_3), 3.58 (t, *J* = 6.2 Hz, 2H, CH_2), 1.83-2.12 (m, 6H, CH_2), 1.66-1.74 (m, 1H, CH_2), 1.34-1.49 (m, 2H, CH_2), 1.11-1.32 (m, 20H, CH_2 & O*H*), 0.89 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 160.0, 140.1, 130.0, 122.6, 118.2, 112.5, 112.4, 62.1, 55.3, 48.2, 41.3, 37.5, 32.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 28.6, 25.3, 22.8, 14.2. HRMS (ESI) m/z calcd for $C_{24}H_{40}NO_2$ $(M+H)^+$: 374.3054 found:374.3033.



2-(3-Bromopropyl)-2-(3-methoxyphenyl)tetradecanenitrile (4.5i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as the eluent. Colorless liquid . Yield: 170 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.35 (m, 1H), 6.95-7.00 (m, 2H), 6.87 (dd, J_1 = 8.2 Hz, J_2 = 0.6 Hz, 1H), 3.85 (s, 3H), 3.36 (t, J = 5.7 Hz, 2H), 1.88-2.14 (m, 5H), 1.70-1.62 (m, 2H), 1.46-1.50 (m, 1H), 1.18-1.31 (m, 20H), 1.11-1.17 (m, 1H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 160.1, 139.7, 130.2, 122.4, 118.2, 112.8, 112.3, 55.5, 47.9, 41.5, 39.6, 33.2, 32.0, 29.7, 29.7, 29.6, 29.5, 29.5, 29.5, 29.4, 28.5, 25.3, 22.8, 14.3. HRMS (ESI) m/z calcd for $C_{24}H_{39}BrNO$ $(M+H)^+$: 436.2210 found:436.2195.

2-(3-((3-Methoxyphenethyl)(methyl)amino)propyl)-2-(3-methoxyphenyl)hexanenitrile(4.5j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (70:30) mixture as the eluent. Viscous yellow Oil. Yield: 125 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.1 Hz, 1H, Ar*CH*), 7.21 (s, 1H, Ar*CH*), 6.97 (d, J = 9.2 Hz, 2H, Ar*CH*), 6.85 (d, J = 8.1 Hz, 1H, Ar*CH*), 6.74-6.78 (m, 3H, Ar*CH*), 3.83 (d, J = 10.7 Hz, 6H, ArO*CH*$_3$), 2.71 (t, J = 7.9 Hz, 2H, *CH*$_2$), 2.54 (t, J = 7.8 Hz, 2H, *CH*$_2$), 2.36 (d, J = 7.0 Hz, 2H, *CH*$_2$), 2.22 (s, 3H, N-*CH*$_3$), 1.84-1.98 (m, 4H, *CH*$_2$), 1.43-1.67 (m, 2H, *CH*$_2$), 1.23-1.27 (m, 21H, *CH*$_2$), 0.90 (t, J = 6.5 Hz, 3H, *CH*$_3$). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 160.0, 159.7, 142.2, 140.4, 130.0, 129.4, 122.7, 121.2, 118.3, 114.6, 112.5, 112.4, 111.3, 59.3, 56.9, 55.4, 55.2, 48.4, 42.1, 41.3, 38.8, 33.8, 32.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 25.4, 23.2, 22.8, 14.3. HRMS (ESI) m/z calcd for C34H53N2O2 (M+H)+ : 521.4102 found: 521.4105.

5-Bromo-2-(3,4-dimethoxyphenyl)pentanenitrile (4.5k): Purified by silica-gelcolumn chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. Yellow oil. Yield: 100 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$):

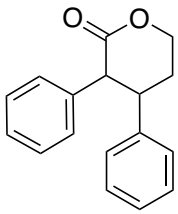
δ 6.82-6.75 (m, 3H), 3.84 (dd, J_1 = 15.9 Hz, J_2 = 9.5 Hz, 6H), 3.72 (dd, J_1 = 9.3 Hz, J_2 = 4.9 Hz, 1H), 3.37-3.35 (m, 2H), 2.03-1.92 (m, 5H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.6, 149.1, 127.6, 119.7, 111.6, 110.2, 56.1, 36.3, 34.3, 32.4. HRMS (ESI) m/z calcd for $C_{13}H_{16}BrNO_2Na$ $(M+Na)^+$: 320.0257 found: 320.0253.

5-((3,4-Dimethoxyphenethyl)(methyl)amino)-2-(3,4-dimethoxyphenyl)pentanenitrile (4.5l):[82] Purified by silica-gel column chromatography using DCM/MeOH (95:5) mixture as the eluent. Viscous yellow oil. Yield: 101 mg, 82%. ^1H NMR (400 MHz, $CDCl_3$): δ 6.72-6.83 (m, 6H, Ar*CH*), 3.74-3.89 (m, 13H, ArO*CH₃* & C*H*), 2.63 (dt, J_1 = 53.4 Hz, J_2 = 7.7 Hz, 4H, *CH₂*), 2.42 (t, *J* = 6.9 Hz, 2H, *CH₂*), 2.27 (s, 3H, N-*CH₃*), 1.92-1.61 (m, 4H, *CH₂*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.3, 148.8, 148.7, 147.3, 132.9, 128.2, 121.1, 120.5, 119.6, 111.9, 111.3, 111.2, 110.1, 59.7, 56.6, 56.0, 55.9, 55.9, 55.8, 42.1, 36.8, 33.8, 33.4, 24.6.

5-(3,4-Dimethoxyphenethyl)(methyl)amino)-2,2-diphenylpentanenitrile (4.5m):[74] Purified by silica-gel column chromatography using DCM/MeOH (95:5) mixture as elutent. Colorless viscous oil. Yield 116 mg, 90%. H NMR (400 MHz, $CDCl_3$): δ 7.19-7.31 (m, 10H, Ar*CH*), 6.68 (dd, *J* = 23.9 Hz, J_2 = 7.5 Hz, 3H, Ar*CH*), 3.77 (d, *J* = 4.7 Hz, 6H, ArO*CH₃*), 2.62 (t, *J* = 7.7 Hz, 2H, *CH₂*), 2.47 (t, *J* = 7.7 Hz, 2H, *CH₂*), 2.34 (ddd, J_1 = 18.3 Hz, J_2 = 10.0 Hz, J_3 = 4.5 Hz, 4H, *CH₂*), 2.16 (s, 3H, N-*CH₃*), 1.53 (dt, J_1 = 15.2 Hz, J_2 = 7.4 Hz, 2H, *CH₂*). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 148.9, 147.3, 140.3, 133.1, 128.9, 127.9, 126.9, 122.5, 120.6, 112.1, 111.3, 59.5, 56.9, 56.0, 55.9, 51.7, 42.1, 37.4, 33.3, 23.6.

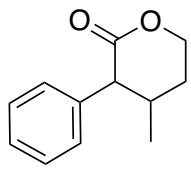
Spectral Data of the Functionalized δ-Hydroxynitrile Products:

3,4-Diphenyltetrahydro-2H-pyran-2-one (4.5n):[83] Purified by silica-gel column chromatography using ethyl acetate/hexane (10:90) mixture as the eluent. White solid . Yield: 101 mg, 80%. ^1H-NMR (400 MHz, $CDCl_3$): δ 6.90-7.20 (m, 10H, ArC*H*), 4.48 (tdd, J_1 = 11.0

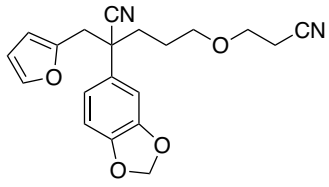


Hz, J_2 = 8.9 Hz, J_3 = 6.7 Hz, 2H, CH_2), 3.77 (d, J = 10.8 Hz, 1H, CH), 3.22 (td, J_1 = 10.3 Hz, J_2 = 5.2 Hz, 1H, CH), 2.17 (dddq, J_1 = 22.9 Hz, J_2 = 13.9 Hz, J_3 = 9.2 Hz, J_4 =4.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 172.2, 141.9, 137.9, 128.8, 128.7, 128.5, 127.2, 127.1, 127.1, 68.7, 55.3, 46.6, 30.7.

4-Methyl-3-phenyltetrahydro-2H-pyran-2-one (4.5o):[84] Purified by silica-gel column chromatography using ethyl acetate/hexane (10:90) mixture as the eluent. Colorless Liquid. Yield: 63 mg, 66%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10-7.29 (m, 5H, ArCH), 4.32-4.45 (m, 2H, CH_2), 3.18 (d, J = 10.7 Hz, 1H, CH), 1.97-2.18 (m, 2H, CH_2), 1.68 (td, J_1 = 9.4 Hz, J_2 = 4.7 Hz, 1H, CH), 0.88 (d, J = 6.5 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 172.4, 138.0, 128.8, 128.6, 127.3, 68.1, 55.9, 34.4, 30.9, 20.4.



2-(Benzo[d][1,3]dioxol-5-yl)-5-(2-cyanoethoxy)-2-(furan-2-ylmethyl)pentanenitrile



(4.5p): Purified by silica-gel column chromatography using ethyl acetate/hexane (10:90) mixture as the eluent. Yellow oil. Yield: 86 mg, 99%. IR (DCM; cm^{-1}): 3952, 3655, 3536, 3162, 3059, 2938, 2624, 2410, 2292, 2251, 2064, 1847, 1815, 1373, 932, 851, 814, 599, 442.^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1H, ArCH), 6.76-6.81 (m, 2H, ArCH), 6.70 (d, J = 8.0 Hz, 1H, ArCH), 6.18 (s, 1H), 5.99 (s, 1H, ArCH), 5.90 (s, 2H, CH_2), 3.64-3.67 (m, 1H, CH_2), 3.49 (t, J = 5.8 Hz, 2H, CH_2), 3.37 (t, J = 5.7 Hz, 2H, CH_2), 3.13 (q, J = 12.8 Hz, 2H, CH_2), 2.55-2.58 (m, 1H, CH_2), 2.50 (d, J = 5.8 Hz, 1H, CH_2), 2.00 (t, J = 8.0 Hz, 2H, CH_2), 1.37-1.65 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.5, 148.2, 147.2, 142.0, 131.2, 121.9, 119.8, 118.0, 117.6, 110.4, 109.0, 108.3, 106.3, 101.4, 70.2, 65.8, 65.1, 47.8, 40.1, 35.9, 25.4, 18.8, 18.8. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_2O_4Na$ $(M+Na)^+$: 375.1315 found: 375.1331.

5-(3-Morpholino-3-oxopropoxy)-2,2-diphenylpentanenitrile (4.5q): Purified by silica-gel column chromatography using ethyl acetate/hexane (10:90) mixture as the eluent. Viscous colorless oil. Yield: 71 mg, 72%. IR (DCM; cm^{-1}): 3943, 3669, 3471, 3054, 2925, 2861, 2306, 2236, 1540, 1445, 1363, 1114, 1030, 847, 572, 540. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.28 (m, 10H, ArC*H*), 3.73 (t, *J* = 6.4 Hz, 2H, CH_2), 3.65 (dd, J_1 = 9.1 Hz, J_2 = 4.3 Hz, 5H, CH_2), 3.50 (t, *J* = 5.4 Hz, 3H, CH_2), 2.60 (t, *J* = 6.5 Hz, 2H, CH_2), 2.47 (dt, J_1 = 7.7 Hz, J_2 = 4.1 Hz, 2H, CH_2), 1.67-1.74 (m, 4H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 169.7, 140.1, 128.9, 127.9, 126.8, 122.3, 70.3, 66.9, 66.8, 66.7, 51.5, 46.1, 41.9, 36.5, 33.4, 26.0. HRMS (ESI) m/z calcd for $C_{24}H_{28}N_2O_3Na$ $(M+Na)^+$: 415.1992 found: 415.2009.

Mechanistic Studies: Spectral Data:

5-Hydroxy-2,3-diphenylhexanenitrile (4.5b): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 25 mg, 80%. IR (DCM; cm^{-1}): 3655, 3536, 3162, 3059, 2938, 2282, 2251, 1615, 1494, 1440, 1373, 1245, 1117, 1038, 932, 861, 814, 736, 599, 442. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02-7.27 (m, 10H, ArC*H*), 3.92-4.14 (m, 1H, C*H*), 3.42-3.77 (m, 1H, C*H*), 3.06-3.35 (m, 1H, C*H*), 1.72-2.03 (m, 2H, CH_2), 1.42 (s, 1H, O*H*), 1.03-1.12 (m, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 139.0, 138.6, 134.4, 134.3, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 120.0, 119.7, 65.9, 65.5, 47.5, 47.5, 44.8, 43.8, 42.5, 42.1, 24.7, 23.6. HRMS (ESI) m/z calcd for $C_{18}H_{19}NONa$ $(M+Na)^+$: 288.1359 found:288.1350.

5-Oxo-2,3-diphenylhexanenitrile (4.5c): Purified by silica-gel column chromatography using an ethyl acetate/hexane (35:65) mixture as the eluent. Colorless liquid. Yield: 25 mg, 80%. IR (DCM; cm^{-1}): 3054, 2985, 2305, 1717,

1494, 1421, 1362, 1265, 1160, 895, 737 . ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92-7.24 (m, 10H, ArC*H*), 4.14 (dd, J_1 = 101.5 Hz, J_2 = 6.0 Hz, 1H, C*H*), 3.51-3.66 (m, 1H, C*H*), 3.07 (dt, J_1 = 17.6 Hz, J_2 = 8.8 Hz, 1H, CH_2), 2.86 (ddd, J_1 = 29.7 Hz, J_2 = 17.6 Hz, J_3 = 5.3 Hz, 1H, CH_2), 2.01 (d, J = 39.4 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz; $CDCl_3$): δ 206.3, 206.3, 205.6, 139.5, 139.5, 138.2, 134.1, 133.7, 129.0, 128.8, 128.8, 128.6, 128.5, 128.2, 128.2, 128.0, 127.8, 119.6, 119.4, 46.6, 45.5, 45.2, 45.0, 44.1, 43.1, 30.8, 30.7. HRMS (ESI) m/z calcd for $C_{18}H_{17}NONa$ $(M+Na)^+$: 286.1202 found:286.1188.

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^{1}H and ^{13}C Spectra for δ-Hydroxynitrile Products

Figure 4.3 ^{1}H NMR spectrum of 5-hydroxy-2-phenylpentanenitrile **4.2a**:

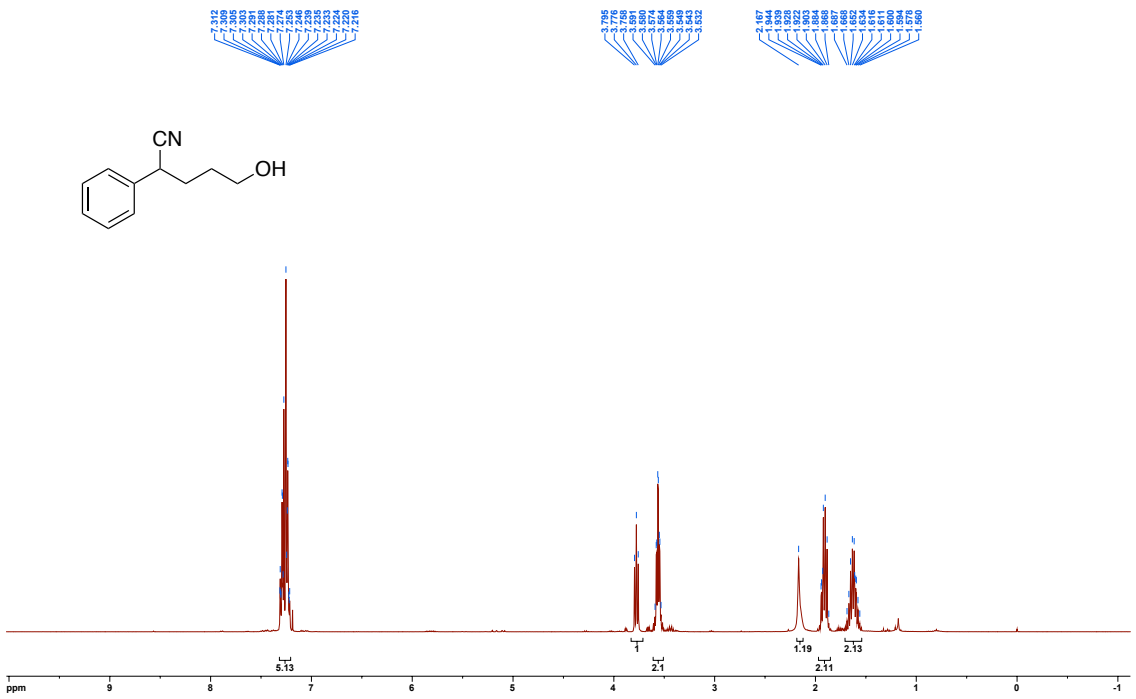


Figure 4.4 ^{13}C NMR spectrum of 5-hydroxy-2-phenylpentanenitrile **4.2a:**

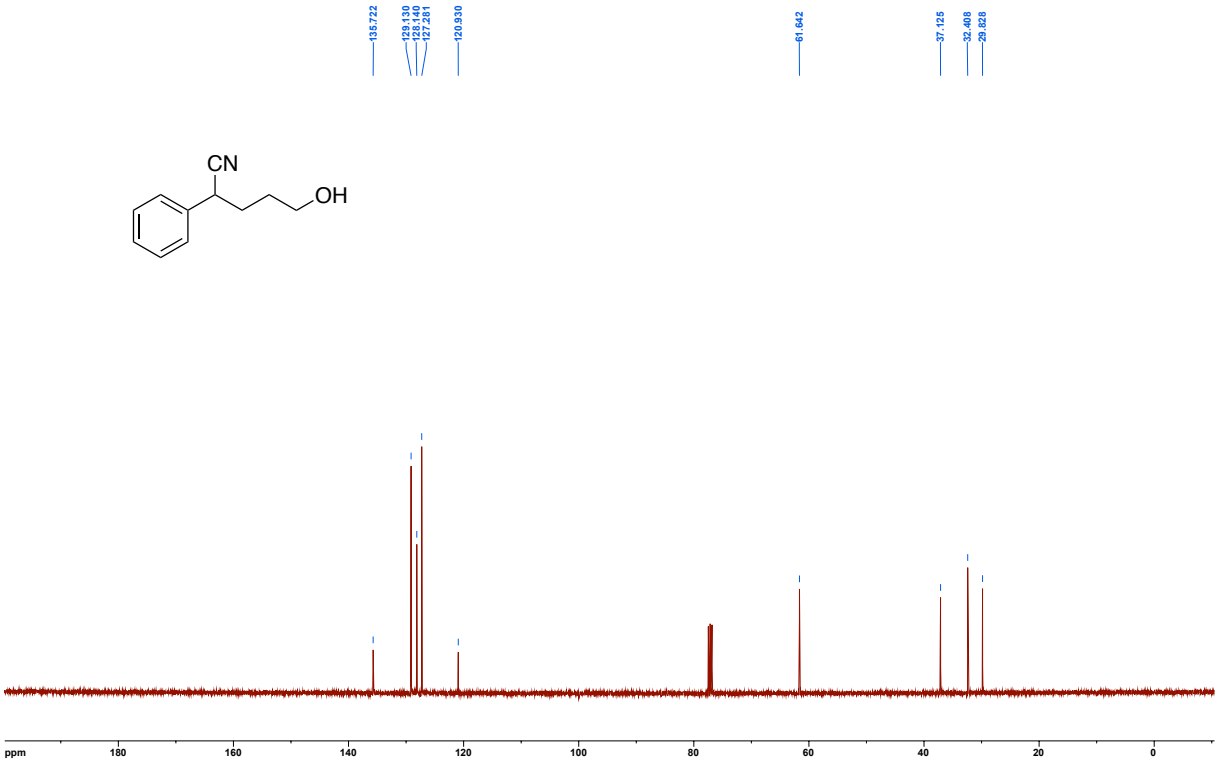


Figure 4.5 ^{1}H NMR spectrum of 5-hydroxy-2-phenyl-2-(pyridin-2-ylmethyl)pentanenitrile **4.2w:**

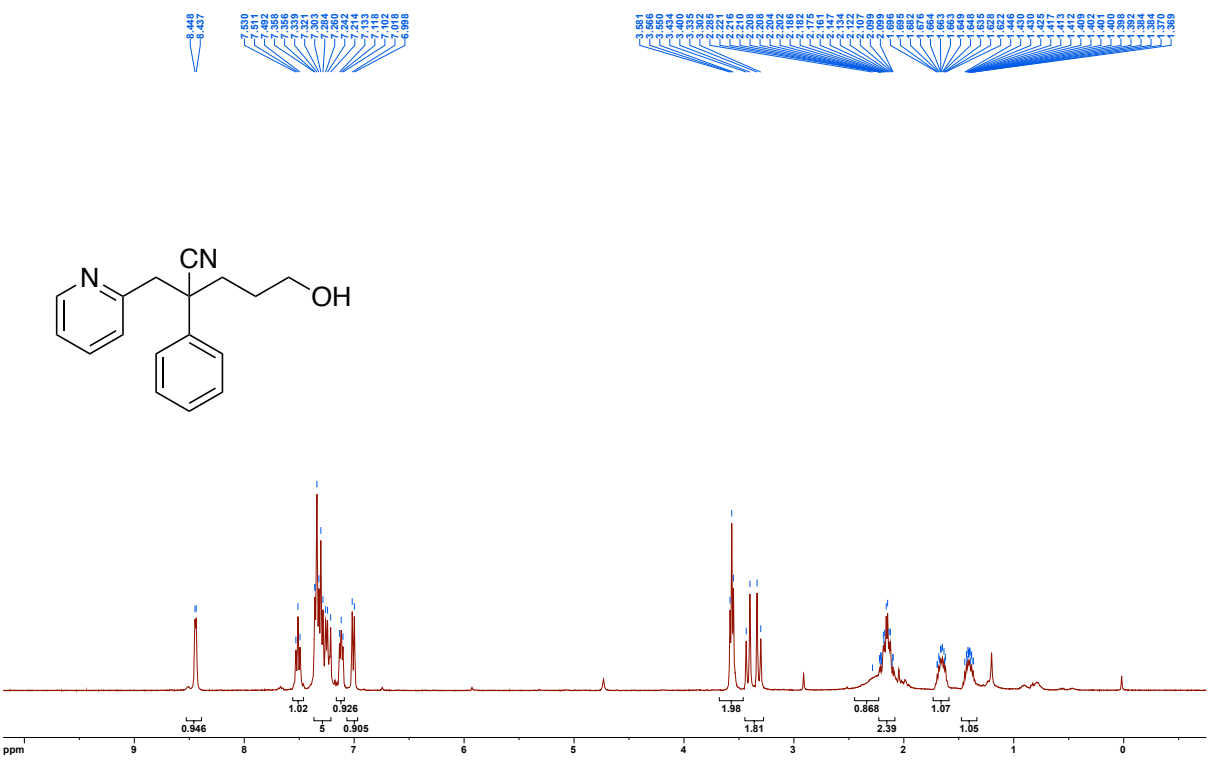


Figure 4.6 ^{13}C NMR spectrum of 5-hydroxy-2-phenyl-2-(pyridin-2-ylmethyl)pentanenitrile **4.2w:**

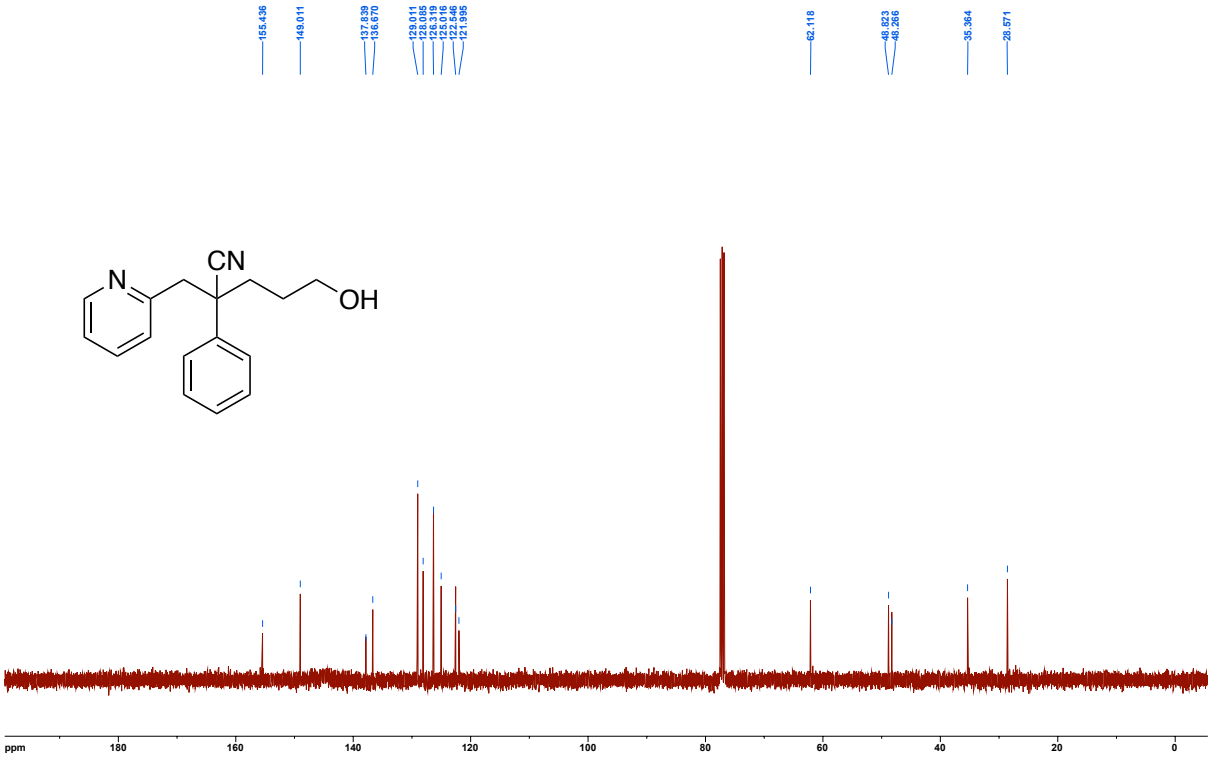


Figure 4.7 ^{1}H NMR spectrum of 5-hydroxy-3-methyl-2-phenylpentanenitrile **4.3a:**

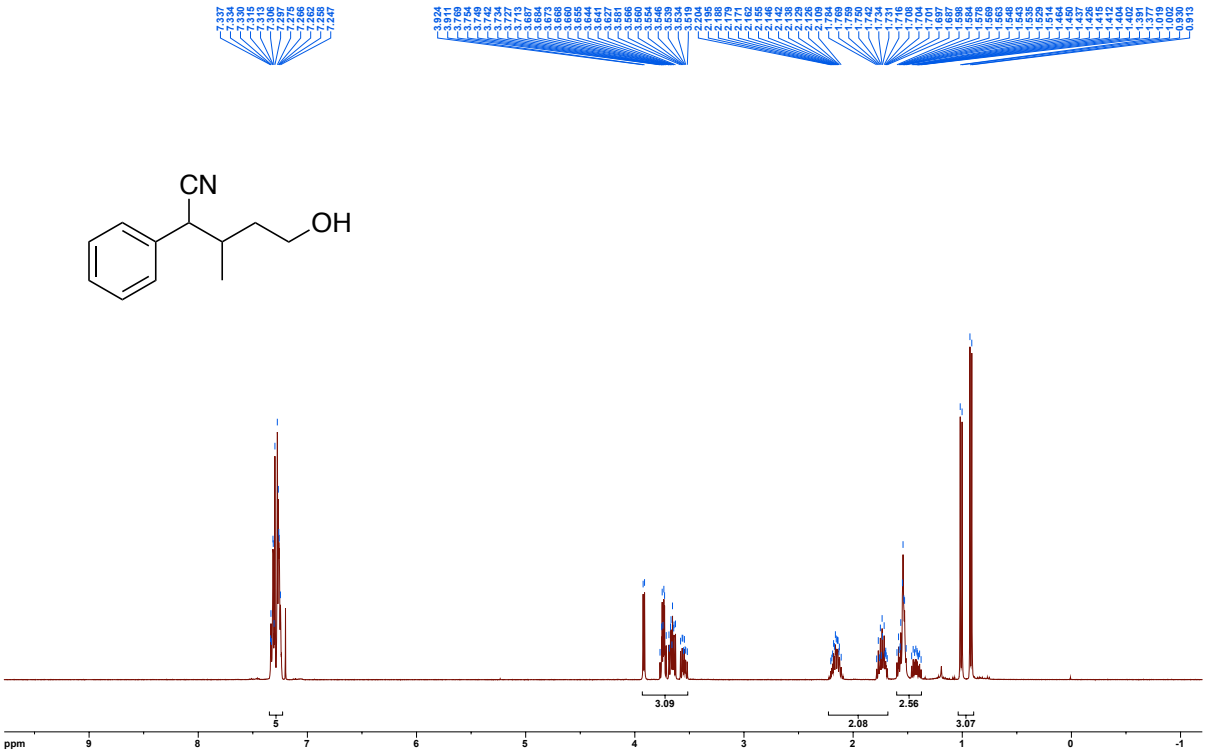


Figure 4.8 ^{13}C NMR spectrum of 5-hydroxy-3-methyl-2-phenylpentanenitrile **4.3a:**

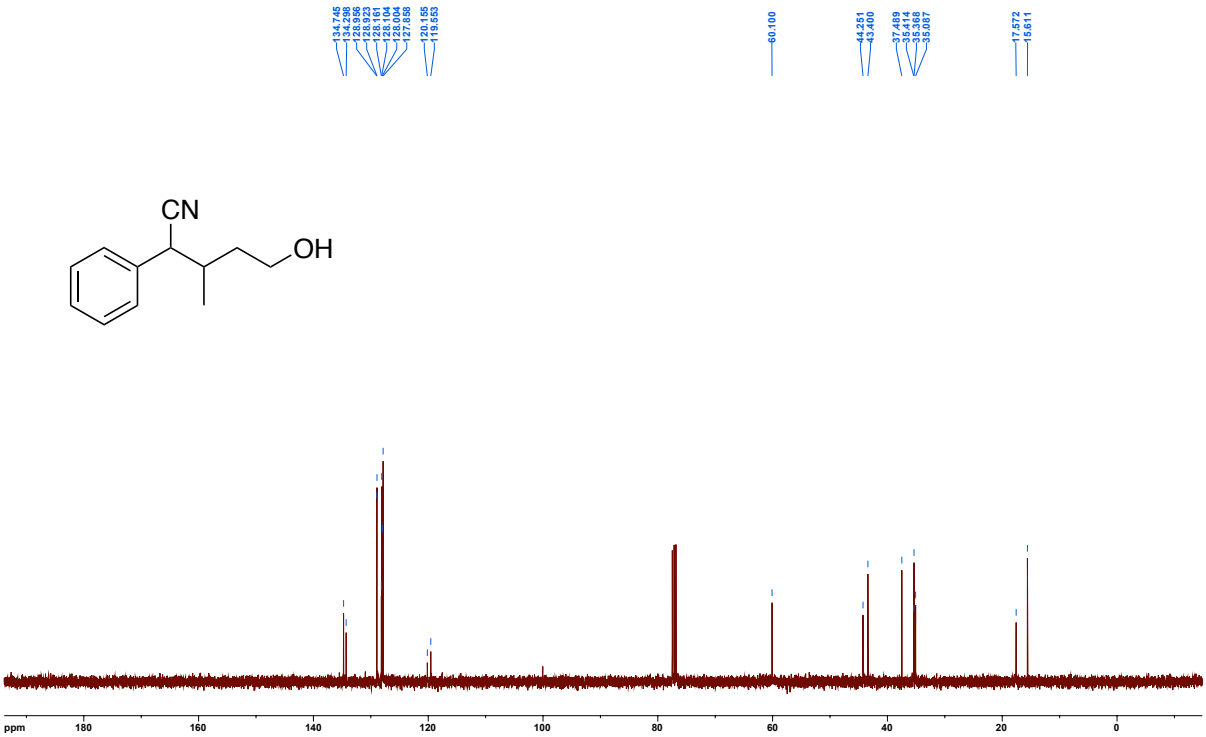


Figure 4.9 ^{1}H NMR spectrum of 5-hydroxy-2-phenylhexanenitrile **4.4a:**

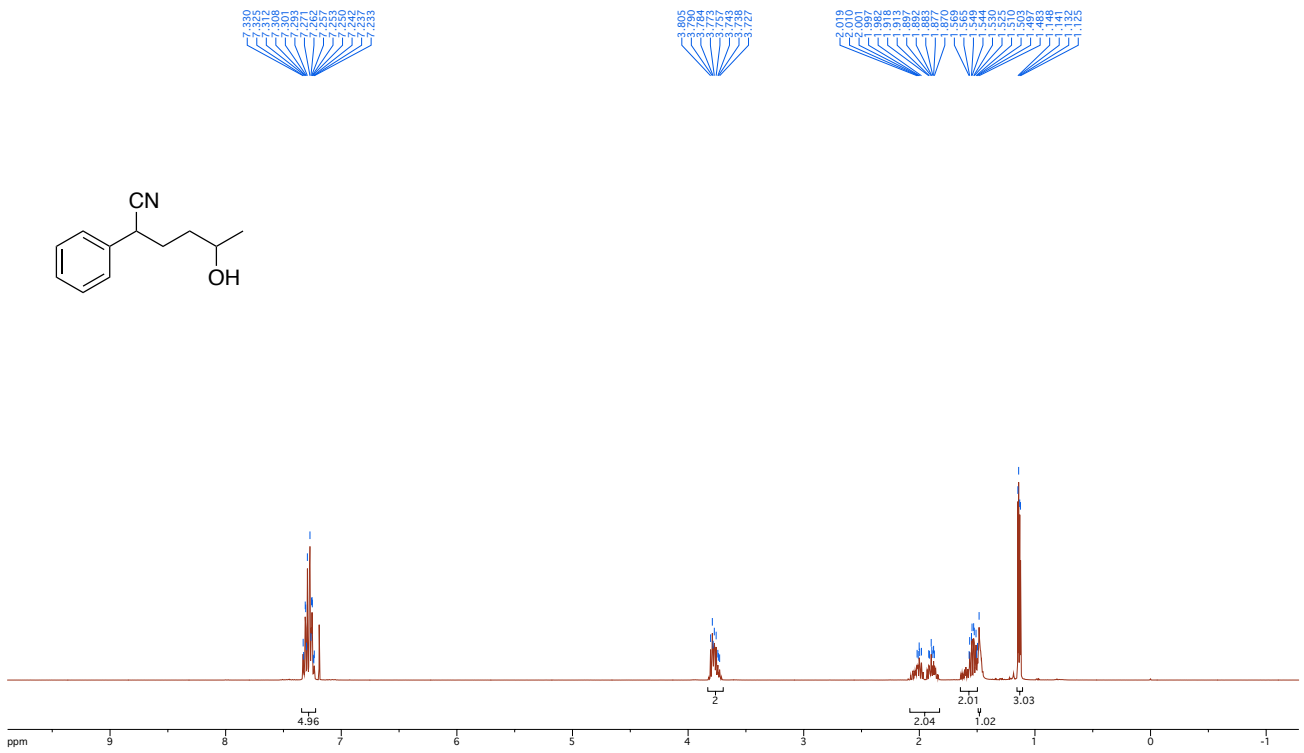


Figure 4.10 ^{13}C NMR spectrum of 5-hydroxy-2-phenylhexanenitrile **4.4a:**

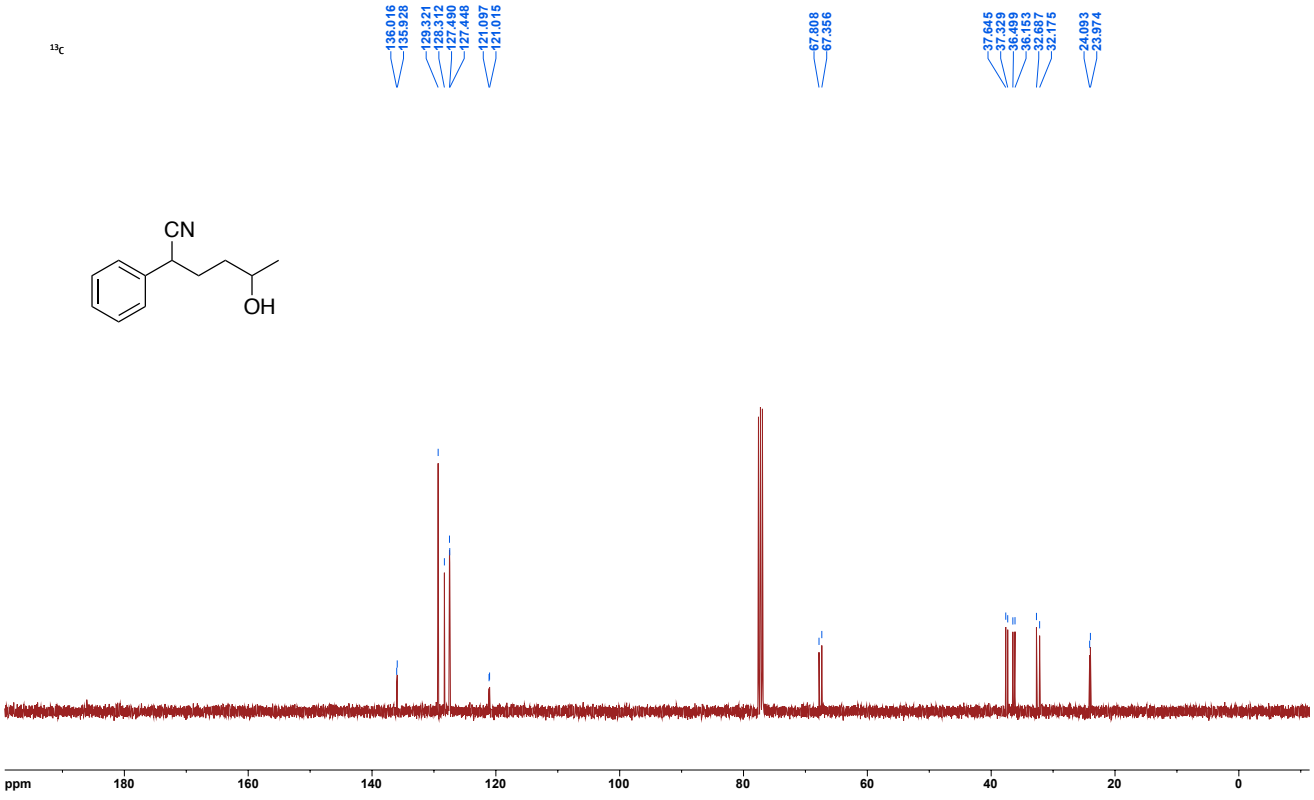


Figure 4.11 ^{1}H NMR spectrum of 5-hydroxy-2,2-diphenylhexanenitrile **4.4i:**

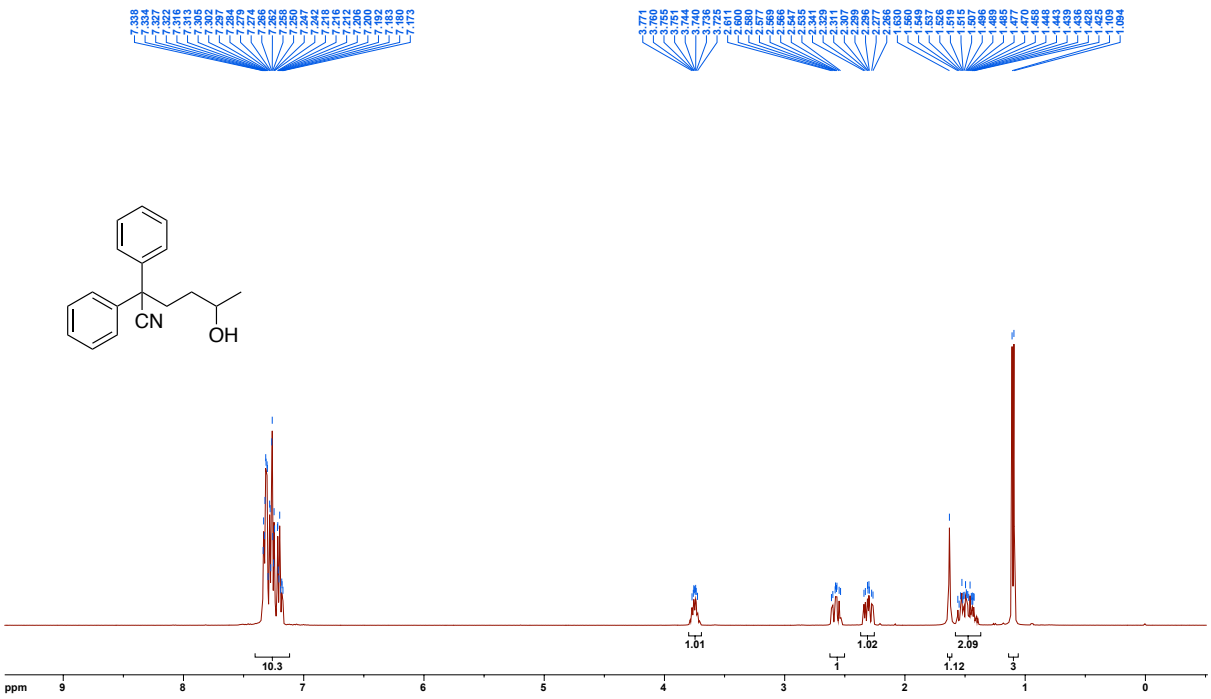


Figure 4.12 ^{13}C NMR spectrum of 5-hydroxy-2,2-diphenylhexanenitrile **4.4i:**

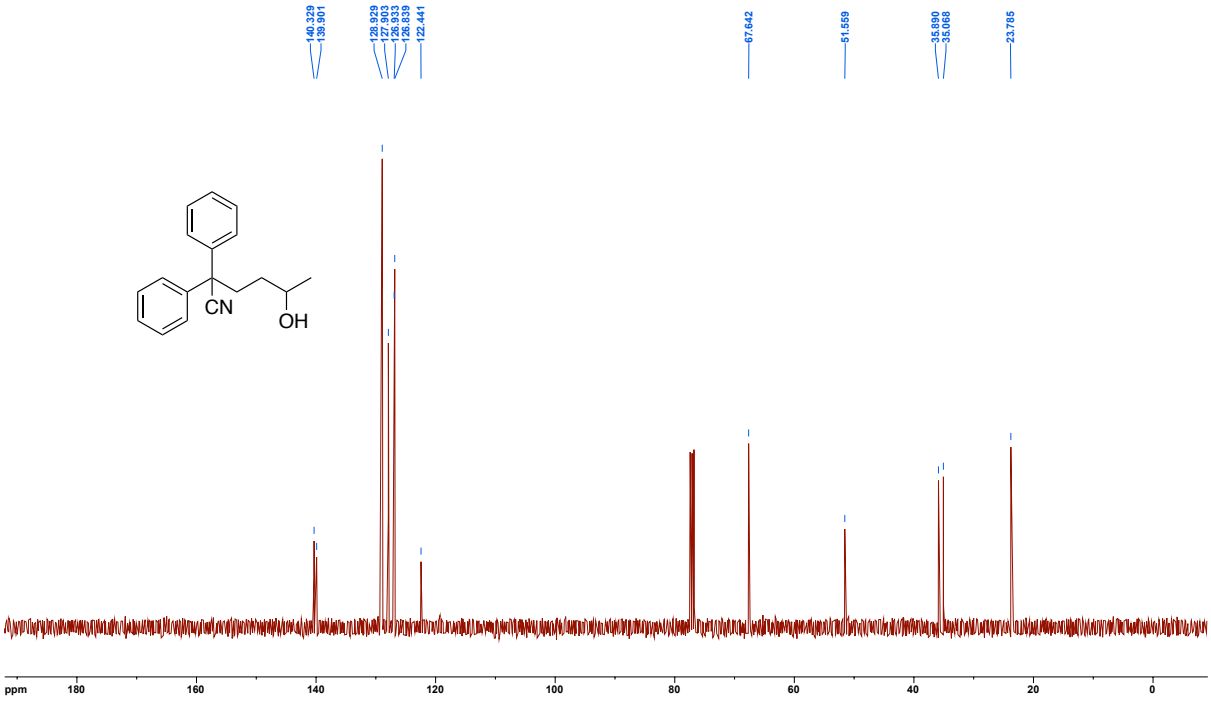


Figure 4.13 [1]H NMR spectrum of 2-(3,5-bis(trifluoromethyl)phenyl)-5-hydroxy-2-(3-hydroxyoctyl)decanenitrile **4.4aa:**

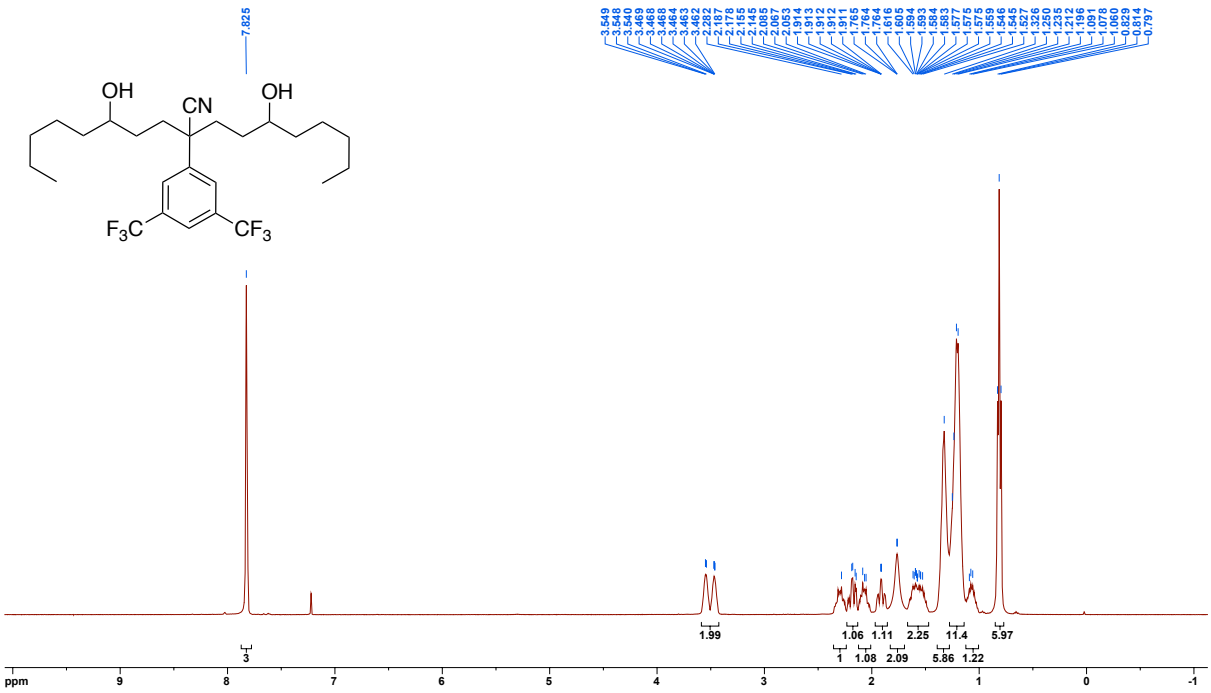


Figure 4.14 [13]C NMR spectrum of 2-(3,5-bis(trifluoromethyl)phenyl)-5-hydroxy-2-(3-hydroxyoctyl)decanenitrile **4.4aa:**

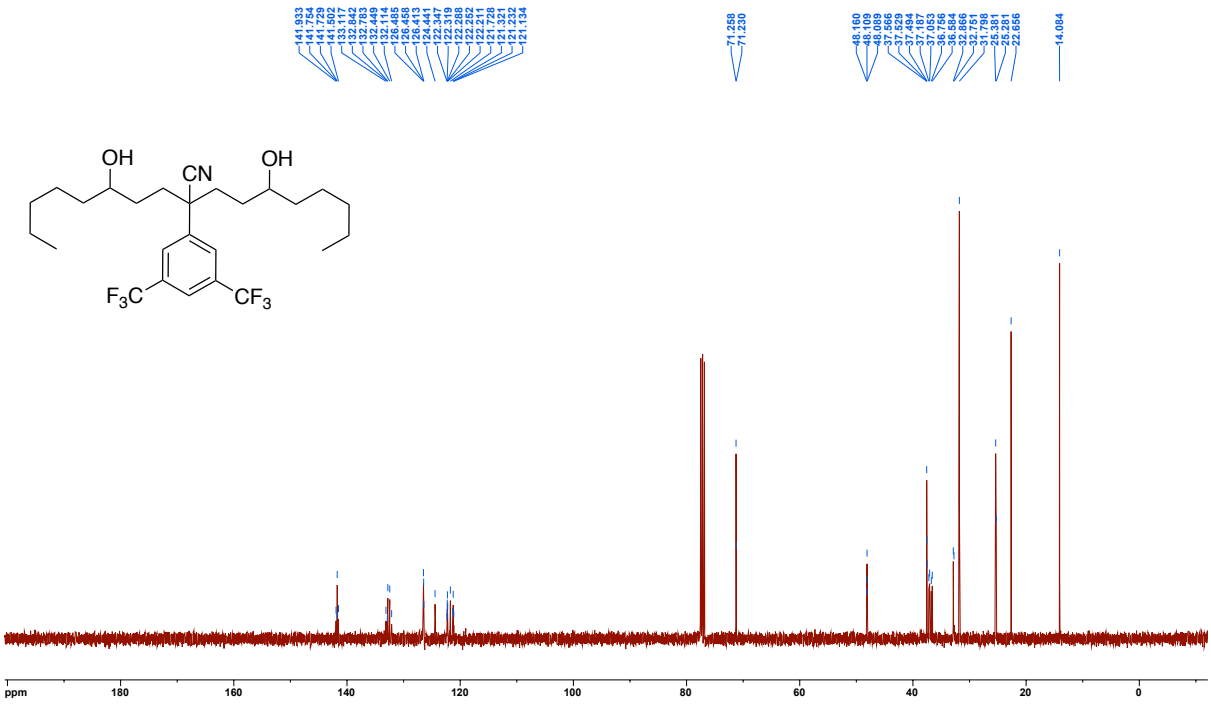


Figure 4.15 ^{1}H NMR spectrum of 5-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-2-phenylpentanenitrile **4.5d:**

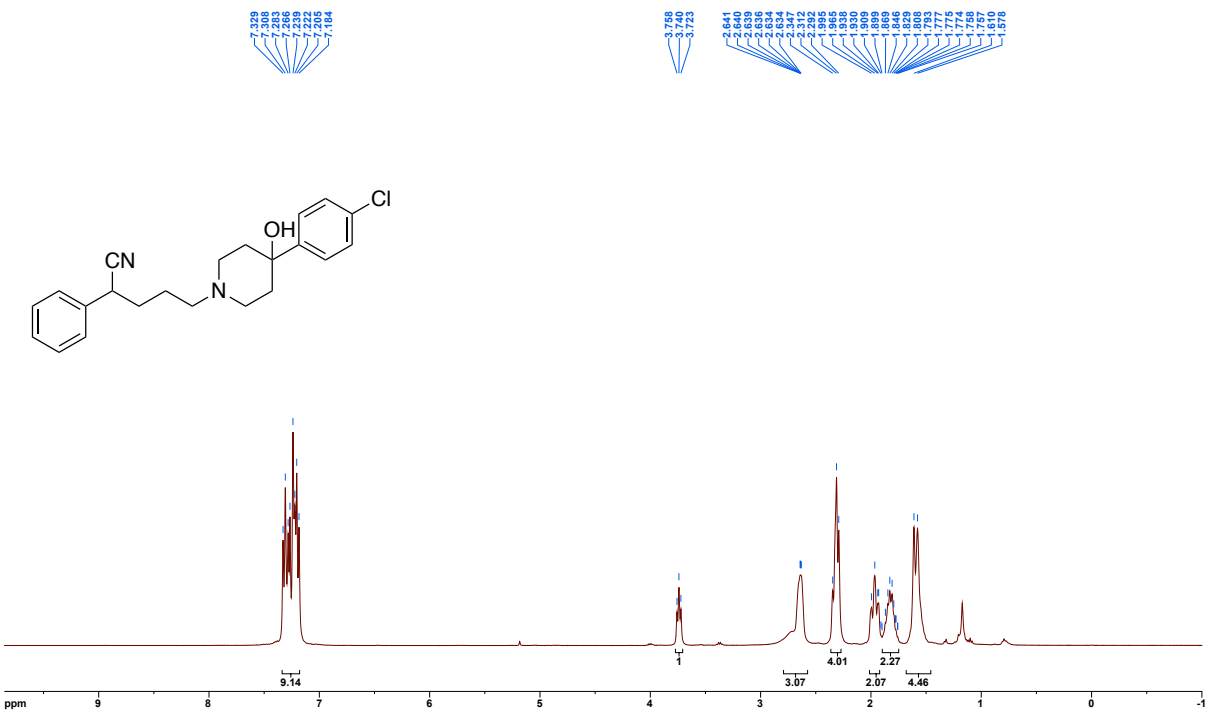


Figure 4.16 ^{13}C NMR spectrum of 5-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-2-phenylpentanenitrile **4.5d:**

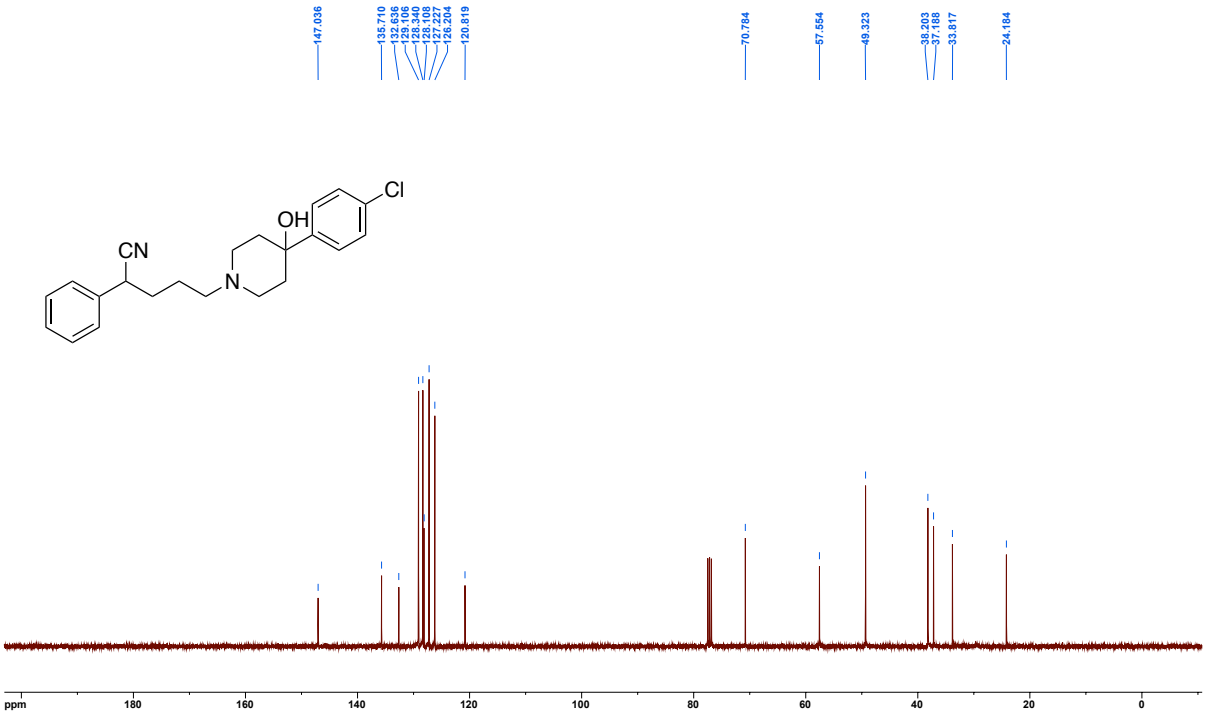


Figure 4.17 ^{1}H NMR spectrum of 2-(3-((3-methoxyphenethyl)(methyl)amino)propyl)-2-(3-methoxyphenyl)hexanenitrile **4.5h:**

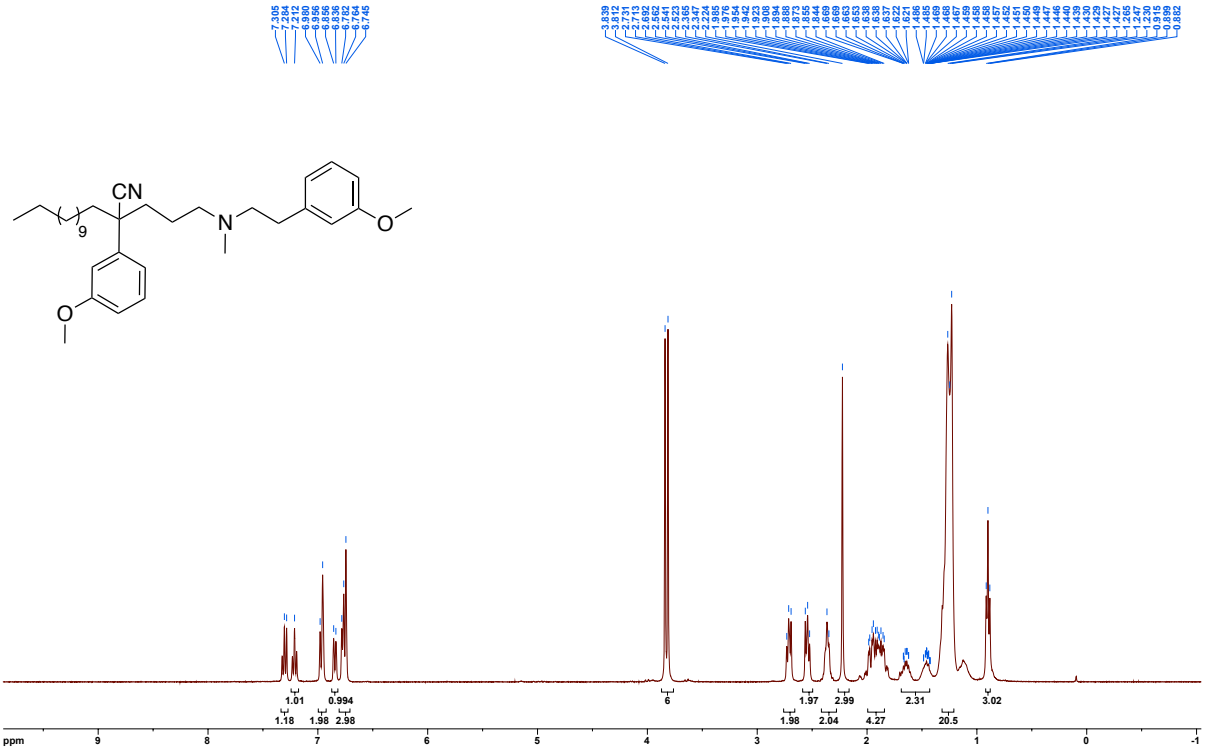


Figure 4.18 ^{13}C NMR spectrum of 2-(3-((3-methoxyphenethyl)(methyl)amino)propyl)-2-(3-methoxyphenyl)hexanenitrile **4.5h:**

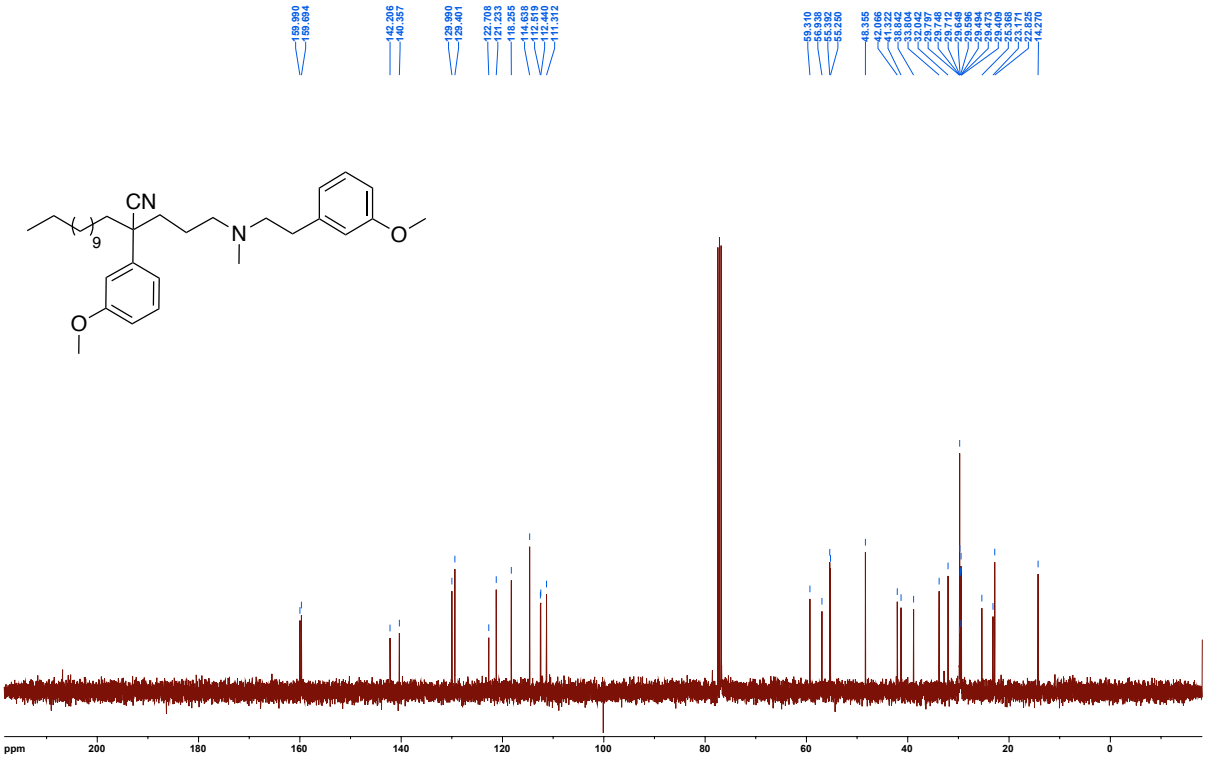


Figure 4.19 ^{1}H NMR spectrum of 4-methyl-3-phenyltetrahydro-2H-pyran-2-one **4.5o:**

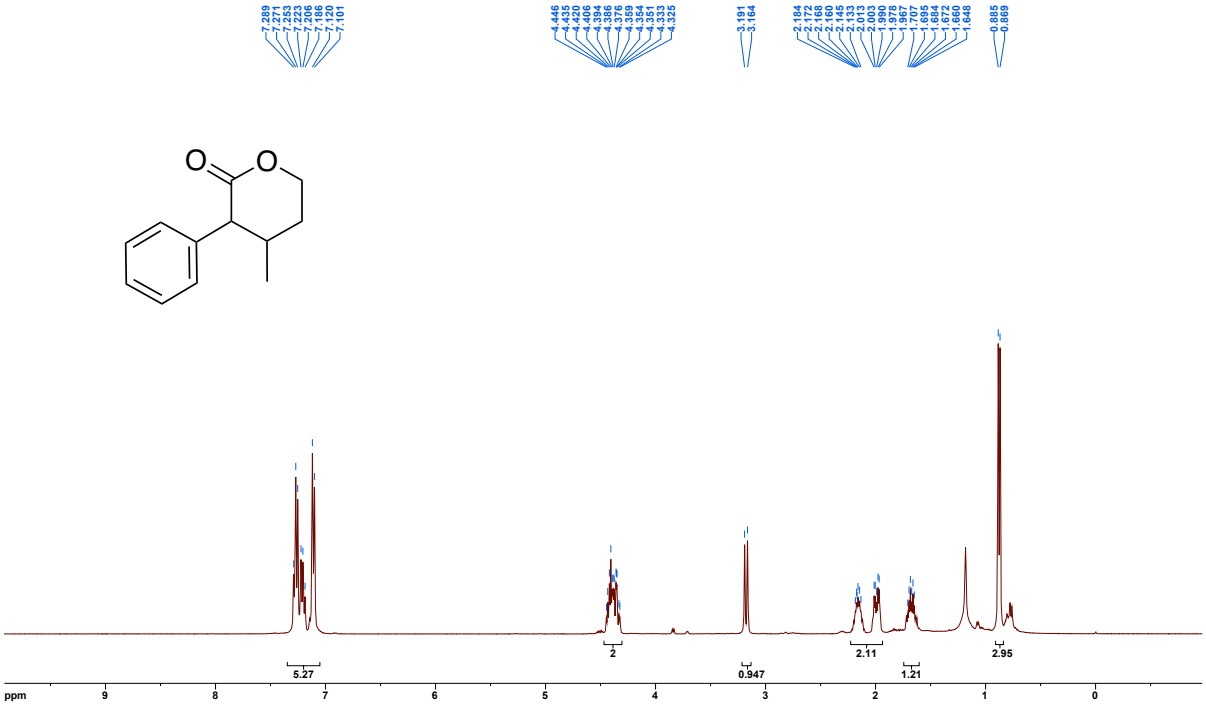
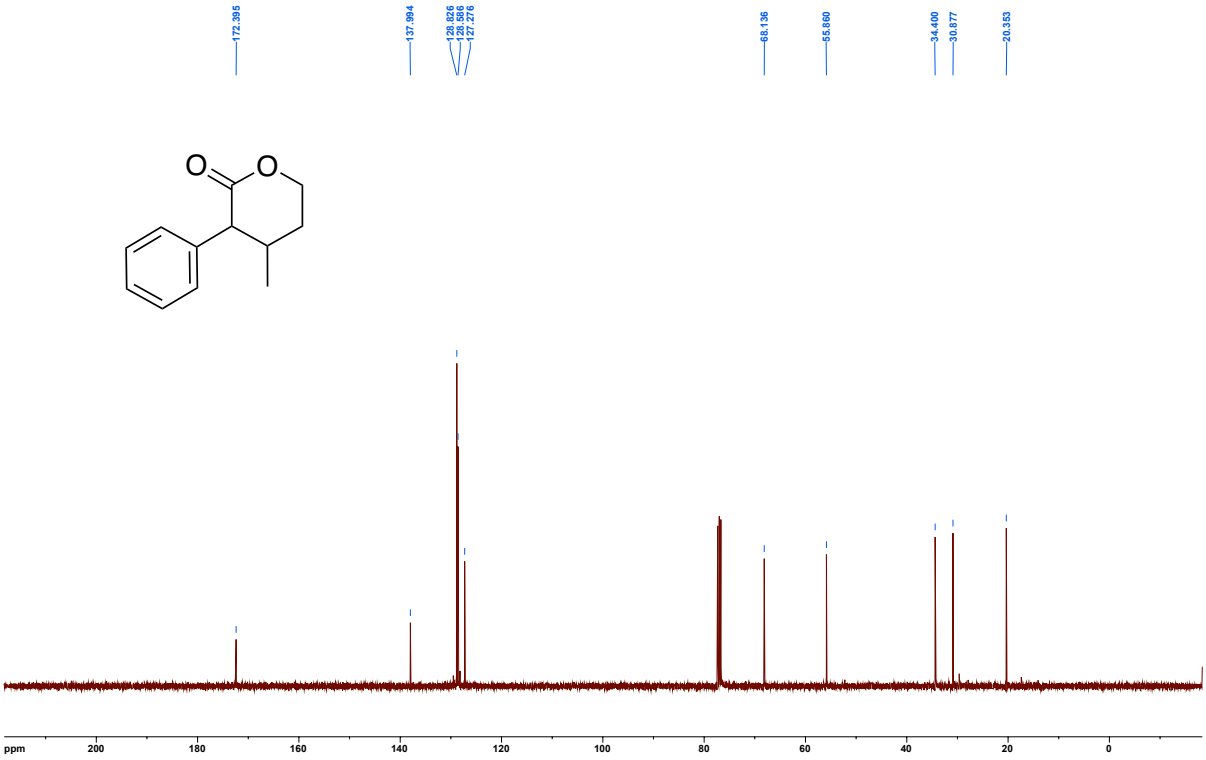


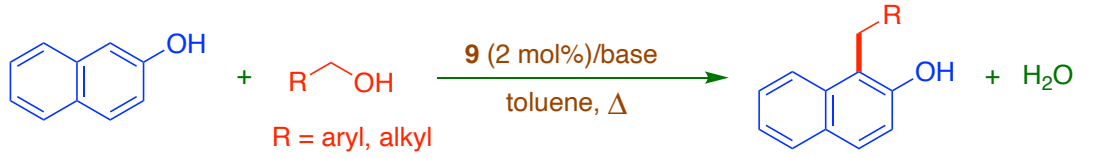
Figure 4.20 ^{13}C NMR spectrum of 4-methyl-3-phenyltetrahydro-2H-pyran-2-one **4.5o:**



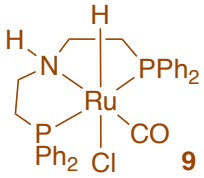
CHAPTER-5

Ruthenium-Catalyzed Selective α-Alkylation of β-Naphthols using Primary Alcohols: Elucidating the Influence of Base and Water

5.1 ABSTRACT



- Alcohols: low cost, industrial feedstock
- Alcohols as direct alkylating reagent
- Good scope of aryl and alkyl alcohols
- Exclusive ortho selectivity
- Water as a green by-product
- DFT studies



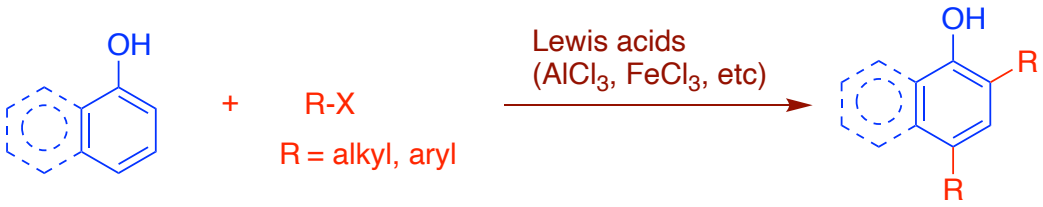
Functionalized arenes and arenols have diverse applications in chemical synthesis and material chemistry. Selective functionalization of arenols is a topic of prime interest. In particular, direct alkylation of arenols using alcohols is a challenging task. In this report, a ruthenium pincer catalyzed direct α-alkylation of β-naphthol using primary alcohols as alkylating reagents is reported. Notably, aryl and heteroaryl methanols and linear and branched aliphatic alcohols underwent selective alkylation reactions, in which water is the only byproduct. Notably, catalytically derived α-alkyl-β-naphthol products displayed high absorbance, emissive properties, and quantum yields (up to 93.2%). Dearomative bromination on α-alkyl-β-naphthol is demonstrated as a synthetic application. Mechanistic studies indicate that the reaction involves an aldehyde intermediate. DFT studies support this finding and further reveal that a stoichiometric amount of base is required to make the aldol condensation as well as elementary steps required for regeneration of catalytically active species. In situ-generated water molecule from the aldol condensation reaction plays an important role in the regeneration of an active catalyst.

5.2 INTRODUCTION

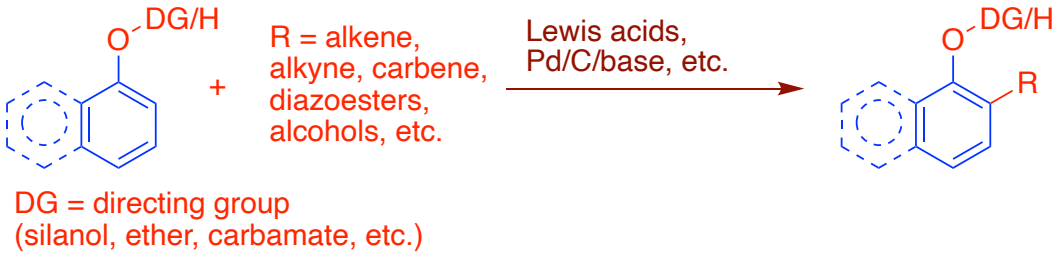
Selective construction of C–C bonds with aromatic compounds is an important strategy for further functionalization. Catalytic site-selective C–C bond formation with arenes, in particular with arenols, is challenging.[1] Lewis acid catalyzed Friedel-Crafts alkylation is employed in organic synthesis for the selective alkylation of arenols (**Scheme 5.1a**).[2] Different transition metal-catalyzed and Lewis acid mediated reactions have been developed to overcome the limitations of Friedel-Crafts alkylation.[3,4] Selective ortho C–H activation of arenols is often attained by tailoring the hydroxyl functionality with directing group linkers (**Scheme 5.1b**).[5] Among the arenols, β-naphthols have widespread applications as fungicides, antimicrobial agents, antiseptics, dyes, and antioxidants.[6] β-Naphthol serves as a biomarker for livestock and humans to establish exposure to pesticides.[7]

Scheme 5.1 Strategies for Site Selective C-C Bond Formation of Arenols

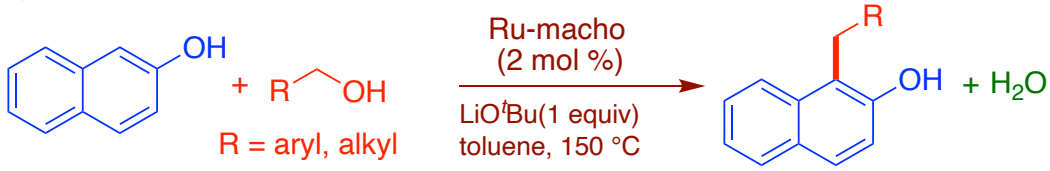
a) Friedel-Crafts alkylation:



b) Known methods:



c) This Work:



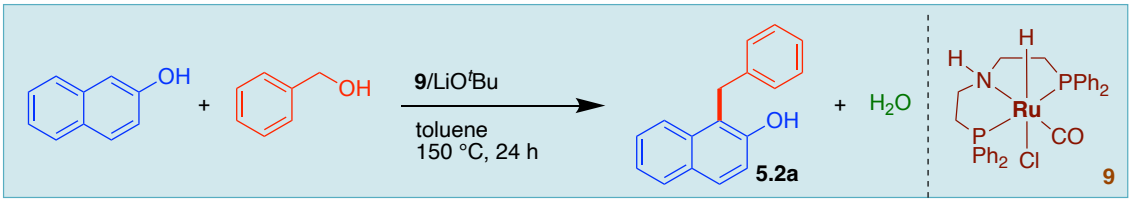
Functionalization of β-naphthol has resulted in diverse applications and gained significance, as exemplified by the synthesis of the nonsteroidal anti-inflammatory drug naproxen.[8] Reaction with alkyl halides using ionic liquid[9] and elongated synthetic procedures involving Mannich bases and their subsequent deamination have been reported[10] for the α-alkylation and α-benzylation of β-naphthols with limited substrate scope. Borrowing hydrogen strategy has emerged as a pivotal tool for the construction of C-C bond using alcohols as alkylating reagents.[11] Alcohols are bio-renewable, abundant, cheap and readily available industrial feedstock.[12] On the contrary, selective catalytic C-C bond formation reaction of β-naphthol is elusive owing to its aromaticity, and hence remains underexplored. Ortho-selective aminomethylation of β-naphthol using methanol as a C1 source has been reported.[13] Our group reported Ru-macho (**9**) catalyzed alkylation and alkenylation reactions using alcohols,[14] cross-coupling of secondary alcohols,[15] and conjugate addition of nitriles with allylic alcohols.[16] Herein, we report the catalytic site-selective α-alkylation of β-naphthols using both benzylic and aliphatic primary alcohols (**Scheme 5.1c**).

5.3 RESULTS AND DISCUSSION

Site-selective alkylation of β-naphthols began from testing the Ru-macho (**9**, 1 mol %) catalyzed reaction of benzyl alcohol using a base, LiO^{t}Bu (20 mol %) in toluene for 24 h, which delivered the anticipated 1-benzyl-2-naphthol product (**5.2a**) in 63% yield (entry 1, **Table 5.1**). Reaction performed using 1equiv of base and 1.2 equiv of benzyl alcohol at lower temperature provided diminished yield (39%, entry 2, **Table 5.1**). A similar reaction at 150 °C enhanced the product yield (entry 3, **Table 5.1**). The use of increased catalyst loading (**9**, 2 mol %) resulted in 77% of the isolated product **5.2a** (entry 4, **Table 5.1**). Further variations in the amount of base and benzyl alcohol equivalents provided the product in lower yields (entries

5,6, **Table 5.1**). Next, different bases were tested, which provided the anticipated product **5.2a** in trace amounts

Table 5.1. Optimization of reaction condition.[a]



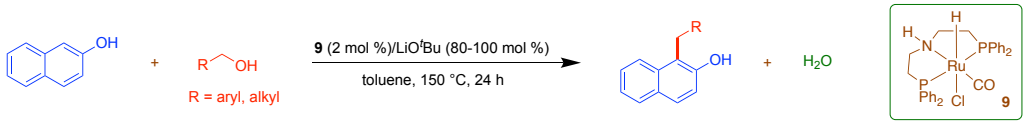
Entry	Cat. (mol %)	Base (mol %)	Alcohol (equiv)	Yield[b] (%)
1	1	LiO^{t}Bu (20)	1.5	63
2	1	LiO^{t}Bu (100)	1.2	39
3	1	LiO^{t}Bu (100)	1.2	53
4	**2**	**LiO^{t}Bu (100)**	**1.2**	**77**
5	2	LiO^{t}Bu (20)	1.5	43
6	2	LiO^{t}Bu (20)	1.2	60
7[d]	2	KO^{t}Bu (100)	1.2	<1
8[d]	2	NaO^{t}Bu (100)	1.2	<1
9[d]	2	NaOH (100)	1.2	12
10	-	LiO^{t}Bu (100)	1.2	00

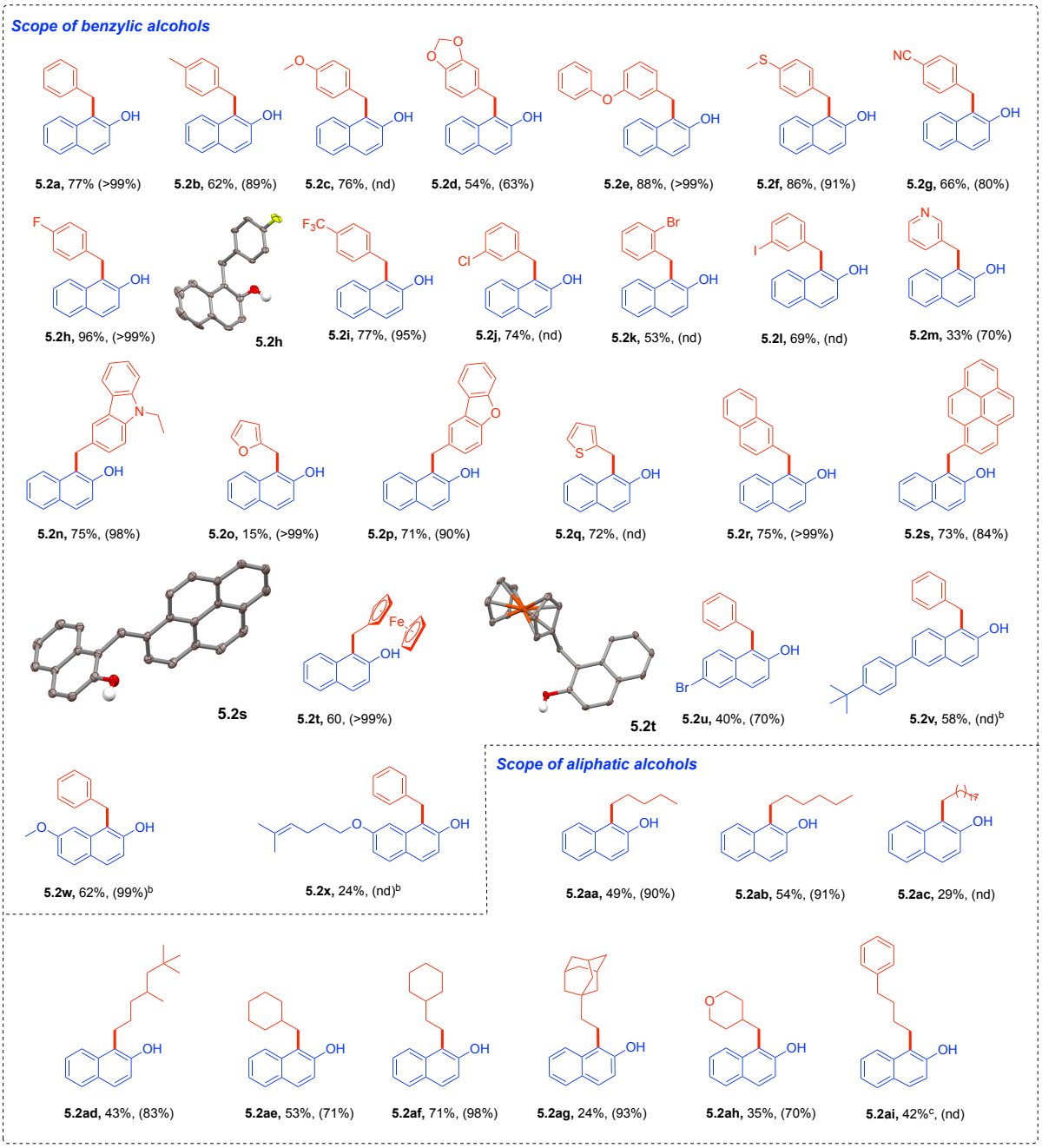
a) Reaction conditions: β-naphthol (0.5 mmol), alcohol, catalyst **9** (mol %), and base (mol %) in toluene (2 mL) were heated at 150 °C in a sealed pressure tube for 24 h. b) Yield corresponds to isolated pure product after column chromatography. c) Reaction performed at 135 °C. d) ^{1}H NMR yield obtained from crude reaction mixture using mesitylene as an internal standard.

along with the major formation of dehydrogenative self-coupled ester, and benzyl benzoate in 40 and 35% yield, respectively (entries 7,8, **Table 5.1**). The use of hydroxide bases such as NaOH delivered the compound **5.2a** in 12% yield and benzyl benzoate ester (30%, entry 9, **Table 5.1**). No product formation was observed in the control experiment performed in the absence of catalyst **9** (entry 10, **Table 5.1**).

The scope of direct α-alkylation of β-naphthol was further investigated by employing the optimized conditions (**Scheme 5.2**). Benzyl alcohols bearing electron-donating substitutions such as methyl, alkoxy, aryloxy, and 4-thio methyl groups afforded the corresponding 1-substituted-2-naphthols (**5.2b-5.2f**) in moderate to good yields. Electron-withdrawing groups like cyano, trifluoromethyl, and halogen substitutions on benzylic alcohols were tolerated (**5.2g-5.2l**). Different heteroaryl alcohols participated in the catalytic alkylation reactions. The use of pyridine-3-methanol and 2-furfuryl alcohol provided the corresponding products **5.2m** and **5.2o**, respectively, in poor yields. However, when (9-ethyl-9H-carbazol-3-yl)methanol, dibenzo[b,d]furan-2-ylmethanol and thiophene methanol were employed, the corresponding heteroarylmethyl-2-naphthol products **5.2n**, **5.2p** and **5.2q** were obtained in good yields. Polyaryl alcohols such as 2-naphthalene methanol, pyrene methanol, and ferrocene methanol delivered α-alkylation products **5.2r-5.2t** in good yields. Upon reaction of substituted 2-naphthols such as 6-bromo-2-naphthol and 6-(4-(tert-butyl)phenyl)naphthalen-2-ol with benzyl alcohol, products **5.2u-5.2v** were obtained in 40 and 58% yield, respectively. 7-Methoxy substituted 2-naphthol reacted with benzyl alcohol, which provided the corresponding product **5.2w**. When 7-((4-methylpent-3-en-1-yl)oxy)naphthalen-2-ol reacted

Scheme 5.2 Selective α-Alkylation of β-naphthols Using Primary Alcohols





[a]Reaction conditions: β-naphthol (0.5 mmol), alcohol (0.6 and 1.0 mmol for benzylic and aliphatic alcohols, respectively), catalyst **9** (2 mol %), base (1 and 0.8 equiv for benzylic and aliphatic alcohols, respectively) and toluene (2 mL) were heated at 150 °C in a pressure tube for 24 h. Reported yields correspond to pure isolated products after column chromatography.

Conversions of β-naphthols were calculated by GC using mesitylene as an internal standard and presented within parentheses. [b]Reactions were done in 0.25mmol scale. [c]3 mol % of catalyst **9** was used.

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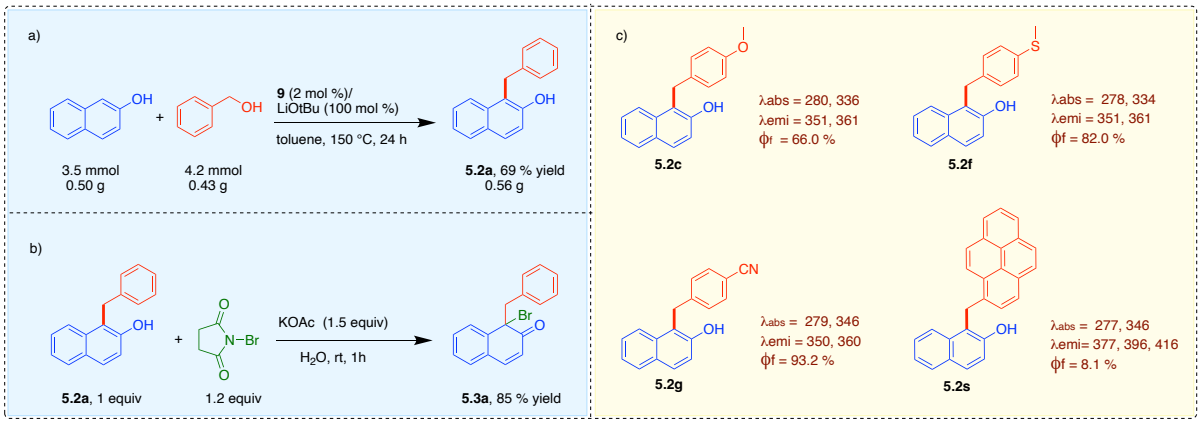
with benzyl alcohol, product **5.2x** was obtained, in which the alkene functionality remained unaffected. Representatively, the single-crystal X-ray analyses of products **5.2h**, **5.2s** and **5.2t** were performed,[17] which corroborated their assigned structure and confirmed the selective alkylation at the α-position of β-naphthol. Next, the scope of aliphatic alcohols was investigated with slight modifications in the experimental conditions. Different unactivated linear aliphatic alcohols like pentanol, hexanol, and octadecanol were reacted with β-naphthol, and their corresponding 1-alkyl-2-naphthols **5.2aa**-**5.2ac** were obtained in moderate to good yields. Further, branched aliphatic alcohol 4,6,6-trimethylheptan-1-ol and unactivated cyclic aliphatic alcohols such as 2- cyclohexymethanol, 2-cyclohexylethanol, and 2-adamantyl ethanol provided the α-alkylated products **5.2ad**-**5.2ag**. (Tetrahydro-2H-pyran-4-yl)methanol and 4-phenyl-1-butanol provided the respective 1-alkyl-2-naphthols **5.2ah**-**5.2ai** in moderate yields. Further, to demonstrate the synthetic utility and applicability of these α-alkylated β-naphthols, a scaled-up synthesis was performed, which resulted in a 69% yield of product **5.2a** (**Scheme 5.3a**). Upon reaction of isolated compound **5.2a** with N-bromo succinimide under mild basic conditions in water, the dearomative brominated product **5.3a** was obtained in very good yield (**Scheme 5.3b**).[17]

The obtained α-alkylated β-naphthol derivatives appeared to be highly emissive in the solution phase. Thus, UV-visible spectroscopic and fluorescence studies were carried out in the THF solvent at 10^{-4} M concentration of compounds **5.2c, 5.2f, 5.2g** and 10^{-5} M concentration of compound **5.2s** (**Scheme 5.3c**). The obtained values for absorbance and emission maxima were found to be in a range of 277-416 nm and 325-450 nm, respectively (Figure **5.1a** and **5.1b**).

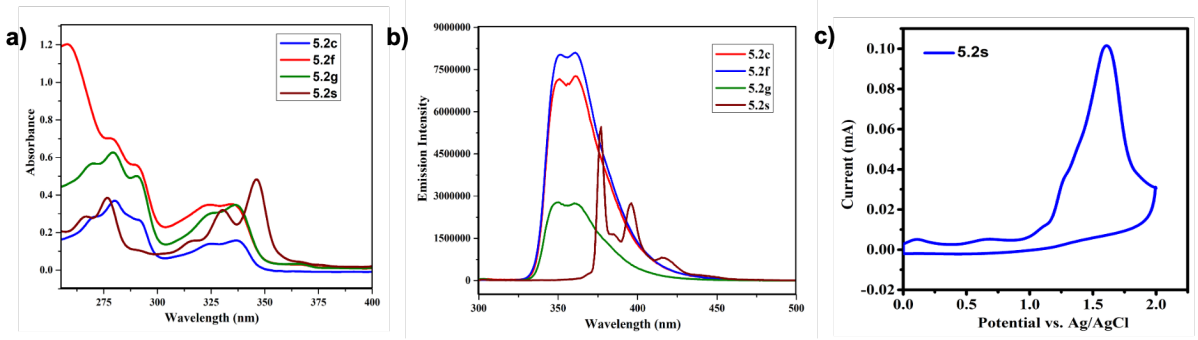
Next, the absolute quantum yield of the products **5.2c, 5.2f, 5.2g** and **5.2s** was calculated using the integration sphere method in THF solvent (Scheme 3c). Notably, products **5.2c, 5.2f** and **5.2g** provided a high quantum yield of 66-93.2%, whereas compound **5.2s** yielded only 8.1 %. The electrochemical behaviour of product **5.2s** was studied. Cyclic voltammetry analysis revealed the oxidation potential of **5.2s** at 1.6 V vs. Ag/AgCl electrode (**Figure 5.1c**) at a scan rate of 30 mV/s^{-1}.

Scheme 5.3 Scaled-up synthesis, synthetic application and photophysical properties of α-alkyl β-naphthols



[a]Reaction conditions: β-naphthol (0.5 mmol), alcohol (0.6 and 1.0 mmol for benzylic and aliphatic alcohols, respectively), catalyst **9** (2 mol %), base (1 and 0.8 equiv for benzylic and aliphatic alcohols, respectively) and toluene (2 mL) were heated at 150 °C in a pressure tube for 24 h. Reported yields correspond to pure isolated products after column chromatography. Conversions of β-naphthols were calculated by GC using mesitylene as an internal standard and presented within parentheses. [b]Reactions were done in 0.25mmol scale. [c]3 mol % of catalyst **9** was used.

Figure 5.1 (a) UV-visible spectra and (b) fluorescence spectra (c) Cyclic voltammogram

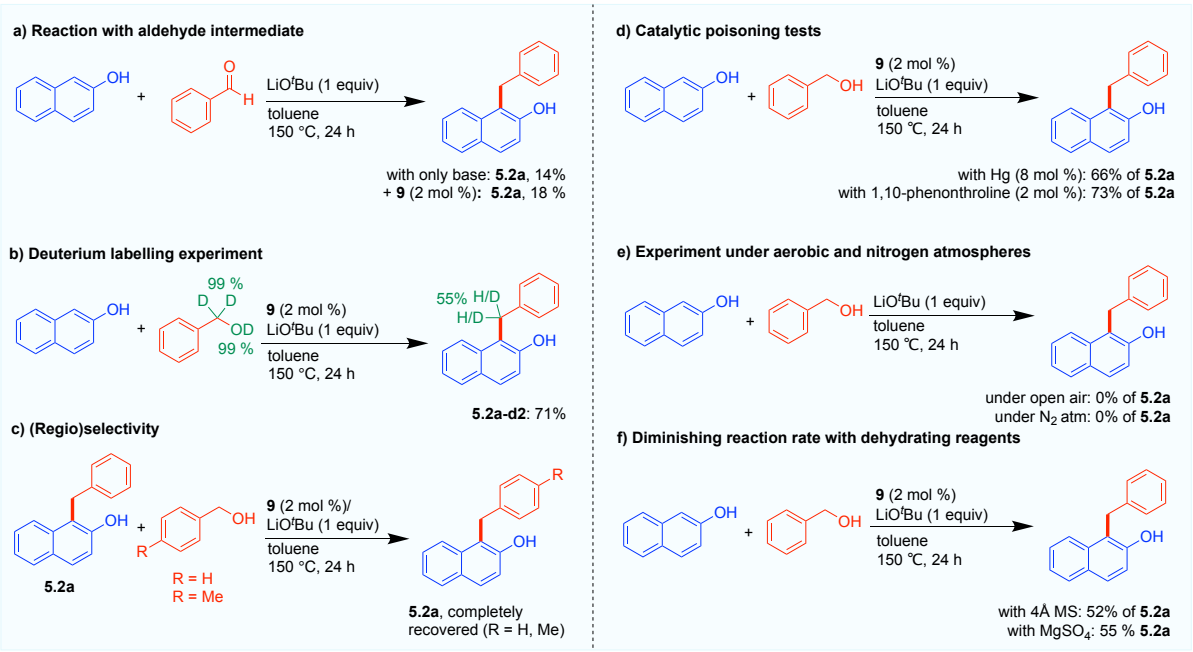


Reaction conditions: fluorescence spectra of products 5.2c, 5.2f, 5.2g recorded in THF at $10^{-}4$ M and 5.2s in THF at $10^{-}5$ M, Cyclic voltammogram of product 5.2s in CH_3CN using tetrabutylammonium hexafluorophosphate(V) (NBu_4PF_6) as an electrolyte.

Different reactions were performed to decipher the catalytic pathways (**Scheme 5.4**). The reaction of benzaldehyde with β-naphthol in the presence and absence of catalyst **9** resulted in the formation of product **5.2a** in 18 and 14% yield, respectively, indicating that catalytic α–alkylation reaction of β-naphthol proceeds via aldehyde intermediacy (**Scheme 5.4a**). An experiment performed using benzyl alcohol-d_3 revealed that 55% deuterium atoms retained at the methylene carbon of the *ortho*-substituted 2-naphthol product **5.2-d2** (**Scheme 5.4b**), which further indicates the oxidation of alcohol to aldehyde and its subsequent reaction with β-naphthol. To test the selectivity observed in this alkylation strategy, catalytic reactions were carried out independently between the isolated compound **5.2a,** with benzyl alcohol and 4-methyl benzyl alcohol under the standard condition, which resulted in the complete recovery of **5.2a** in both experiments, which confirmed chemo- and regioselectivity in this catalytic alkylation (**Scheme 5.4c**). Homogeneity of the catalyst was tested on a reaction between β-naphthol and benzyl alcohol in the presence of mercury (4 equiv) and 1,10-phenanthroline (1 equiv relative to the catalyst loading) in which product **5.2a** was isolated in 66 and 73% yield, respectively (**Scheme 5.4d**). These experiments indicate that the reaction follows a

homogeneous pathway involving molecular intermediates, and there is no decomposition of the catalyst leading to the formation of any nanoparticles during the catalysis. To further prove the integrity of catalyst **9**, the catalytic reaction between β-naphthol and benzyl alcohol was performed under standard conditions for 24 h. The resulting reaction mixture was subjected to ^{31}P NMR analysis, which revealed the presence of a characteristic signal at δ 53.0 ppm, which corresponds to the ^{31}P NMR spectrum of catalyst **9**[8] (**Figure 5.14 and 5.15),** and other signals at δ 54.0 and 54.5 ppm, which represent the intermediates formed from catalyst **9** during catalysis. Notably, no ^{31}P NMR signal for the free ligand (δ-20.90 ppm) was observed.[19] These observations clearly rule out the decomposition of the catalyst, involvement of any nanoparticle formation, and heterogeneous pathway.

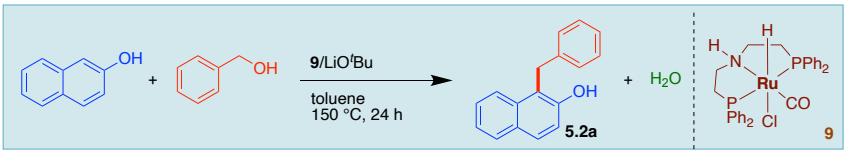
Scheme 5.4 Mechanistic Studies for Selective α-Alkylation of β-naphthols Using Primary Alcohols

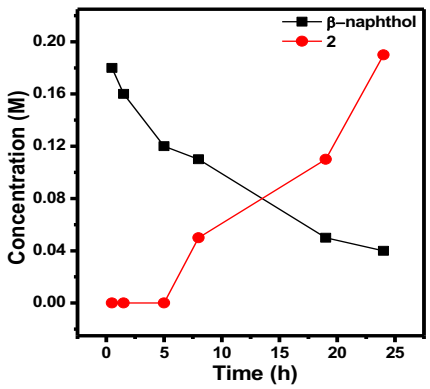


A reaction performed under an open atmosphere using LiO^{t}Bu (1 equiv), β-naphthol, and benzyl alcohol (in the absence of a catalyst **9**) failed to provide the desired alkylation product.

A similar experiment under the nitrogen atmosphere also failed. In both experiments, starting materials were fully recovered (**Scheme 5.4e**). These experiments further confirm the crucial role of catalyst **9**in the α-alkylation of β-naphthols. As the in situ formed byproduct water facilitates hydride transfer during the hydrogenation reaction, two experiments between β-naphthol and benzyl alcohol were carried out under the standard condition with added dehydrating agents such as molecular sieves (4Å) and anhydrous magnesium sulfate (**Scheme 5.4f**). The alkylation product **5.2a** was obtained in diminished yields (52 and 55%, respectively) in both experiments, which indicates that in situ formed water assists in catalysis. Upon monitoring the reaction progress in a catalytic reaction of β-naphthol and benzyl alcohol using GC, it was observed that the reaction rate increased over time (**Figure 5.2**), which further indicates that the byproduct water facilitates the catalysis.

Figure 5.2 Kinetic profile diagram: monitoring of the reaction progress by GC. Concentration of b-naphthol (black line) and product **5.2a** (red line) in the catalytic α-alkylation of β-naphthol using benzyl alcohol.



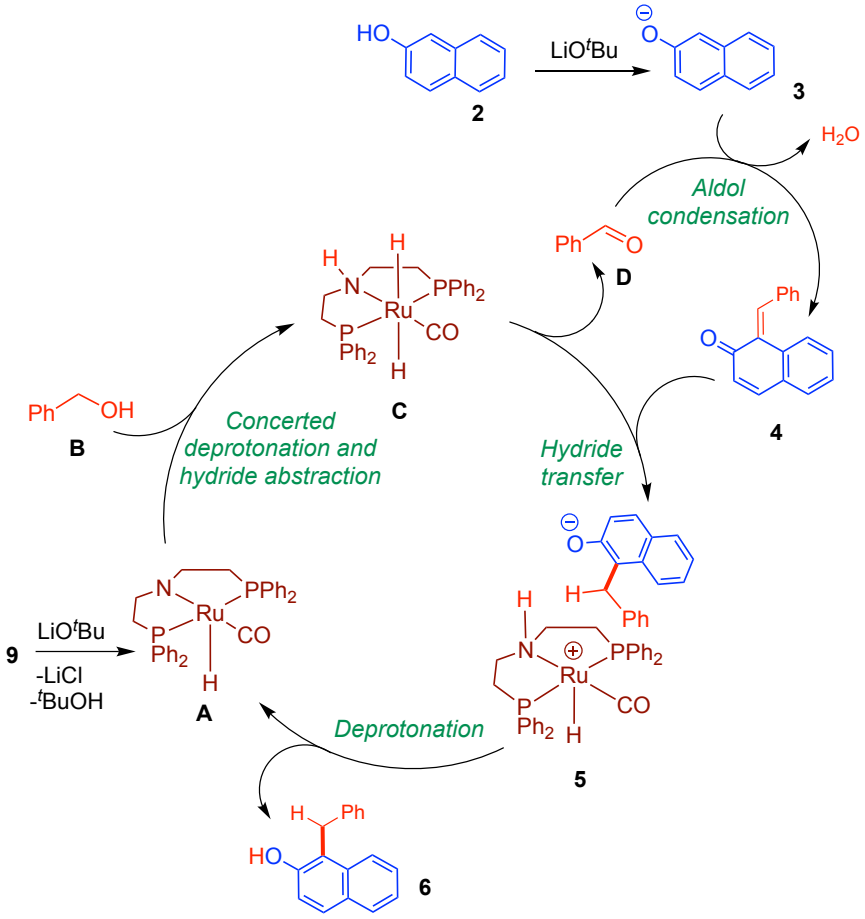


Further, a catalytic reaction between β-naphthol and benzyl alcohol together with molecular sieves (4Å) was interrupted after 18 h, and the reaction mixture was subjected to ^{1}H NMR analysis, which revealed the presence of characteristic doublet signals at δ 6.20 ppm, J = 12 Hz, and δ6.65 ppm, J = 16 Hz (**Figure 5.16**) correspond to alkene protons of the condensation product of β-naphthol and benzaldehyde (intermediate **4**, **Scheme 5.5**); the presence of intermediate **4** in the reaction mixture was also confirmed from the mass analysis (*m/z* = 255.0522 amu).

In order to get further insights into the mechanism, DFT studies were conducted at the PBE0-D3(BJ)/Def2-TZVP,SDD(Ru)+ SMD(toluene)//B3LYP-D3(BJ)/6-31G(d),SDD(Ru) level of theory.[20] The plausible catalytic cycle and detailed Gibbs free energy profile diagram are provided in **Scheme 5.5** and **Scheme 5.6.** The catalytic cycle involves three key steps – Deprotonation and hydride abstraction from benzyl alcohol to afford benzaldehyde, aldol condensation of the benzaldehyde with β-naphthoxide, formation of the α-alkylated product by the hydride and proton transfer from Ru-dihydride complex **C** (**Scheme 5.5**). The reaction begins with the deprotonation and hydride abstraction from benzyl alcohol **B** by the catalytically active ruthenium complex **A**[16,21] via a concerted transition state **TS1** (**Scheme 5.6**). This results in the generation of Ru-dihydride complex **C** and benzaldehyde **D**. Thereafter, benzaldehyde undergoes aldol condensation with the protonated LiO^{t}Bu and LiO^{t}Bu – coordinated β-naphthoxide **E** via a sequence of steps. Initial nucleophilic addition of β-naphthoxide on benzaldehyde generates the aldol precursor, alkoxide **im3,** through **TS2**. Then the transfer of a proton from the protonated LiO^{t}Bu to the alkoxide ion in **im3** results in the formation of aldol product **im4** via **TS3**. The coordinated LiO^{t}Bu then abstracts a proton from the α-carbon of the carbonyl group in **im4,** affords a carbanionic intermediate **im5** through **TS4**. Afterward, a stepwise water elimination occurs from **im5** where the hydroxyl group abstracted by Li combines with the proton in the protonated LiO^{t}Bu and generates water after

traversing **TS5** and **TS6**. All these elementary steps in aldol condensation, which result in the formation of α,β-unsaturated carbonyl complex **im7**, are made feasible by the active participation of the LiO^{t}Bu and the protonated LiO^{t}Bu. Afterward, regeneration of the active catalyst from complex **C** happens through a stepwise hydride transfer and deprotonation mechanism. The water which is generated during the aldol condensation step plays a prominent role in these steps, without which the pathway is found to be energetically unfavorable. The water molecule stabilizes the hydride transfer transition state (**TS7**) by 9.7 kcal mol^{-1}, through multiple hydrogen bonds (blue region) and π-π interactions (green region), as depicted in the non-covalent interaction (NCI) plot (**Figure 5.3**), which is found to be absent in the corresponding transition state **TS7a** without any water molecule, where only π-π interactions are present (green region). A stepwise mechanism with the direct involvement of water operates in the final deprotonation step to be catalytic regeneration. The hydroxyl group, which is generated by the LiO^{t}Bu assists deprotonation of water (via **TS8**), abstracts the N-H proton of ruthenium complex in **im11**, and leads to the regeneration of active ruthenium catalyst **A**. The overall barrier for this reaction pathway is 22.5 kcal mol (with respect to the stable intermediate **im5**), which corresponds to the hydroxyl abstraction (**TS5**) during the aldol condensation step. From our studies, the aldol reaction step in the absence of base is proved to be energetically unfavorable. The mechanism has proved to be more feasible with the involvement of two molecules of LiO^{t}Bu rather than one molecule. Other possible pathways from the stable intermediate **im2a**, concerted water elimination from **im5**, and concerted proton transfer pathway between N-H proton of ruthenium complex and naphthoxide, with the assistance of water, from **im9** were also considered but proved to be unfavorable.

Scheme 5.5 Plausible Catalytic Cycle for the α-Alkylation of β-naphthol



Scheme 5.6 Computed Gibbs free energy profile diagram for the α-alkylation of β-Naphthol in kcal mol^{-1} at the PBE0-D3(BJ)/Def2-TZVP,SDD(Ru)+SMD(toluene)// B3LYP-D3(BJ)/6-31G (d),SDD(Ru) level of theory

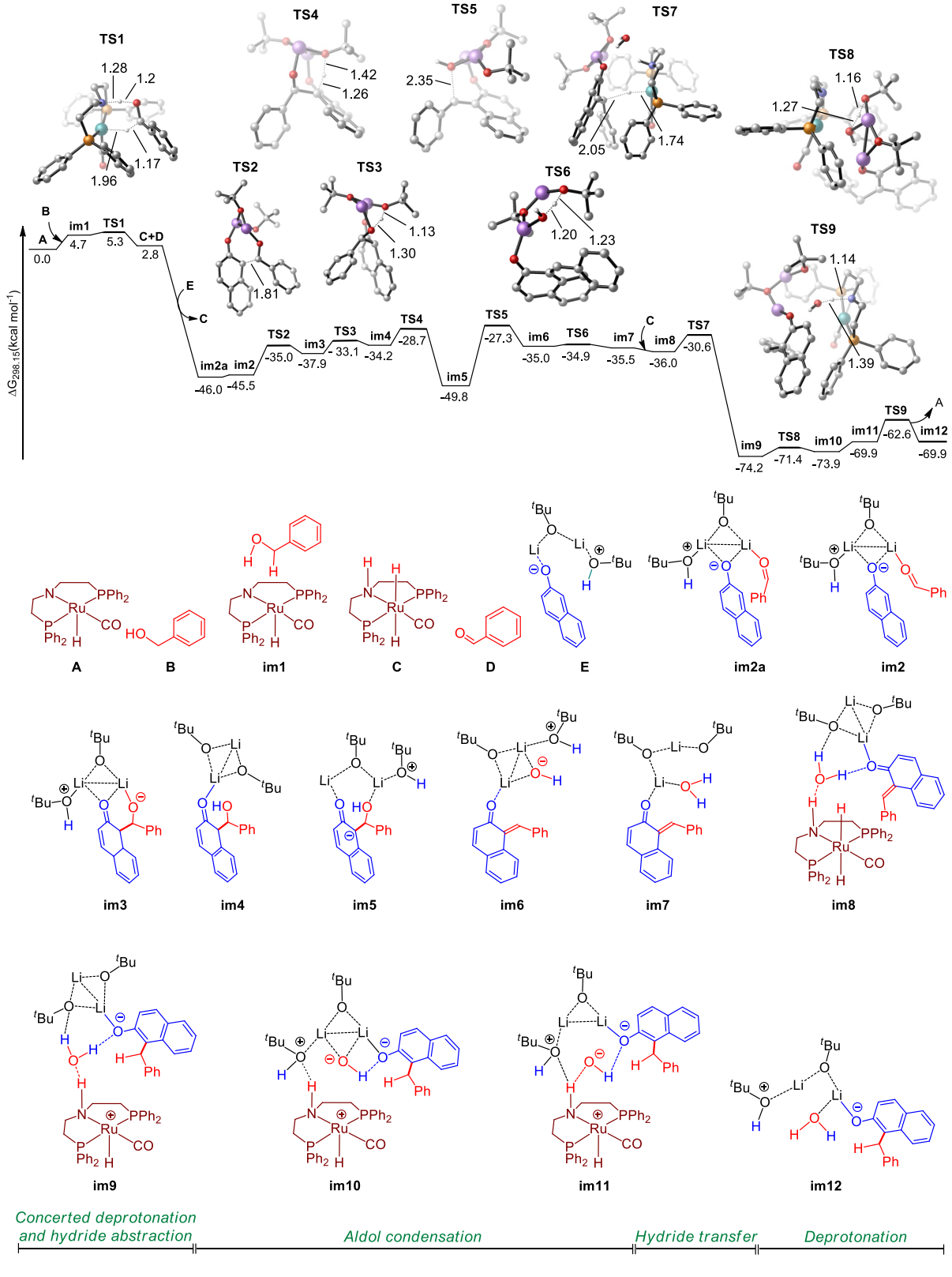
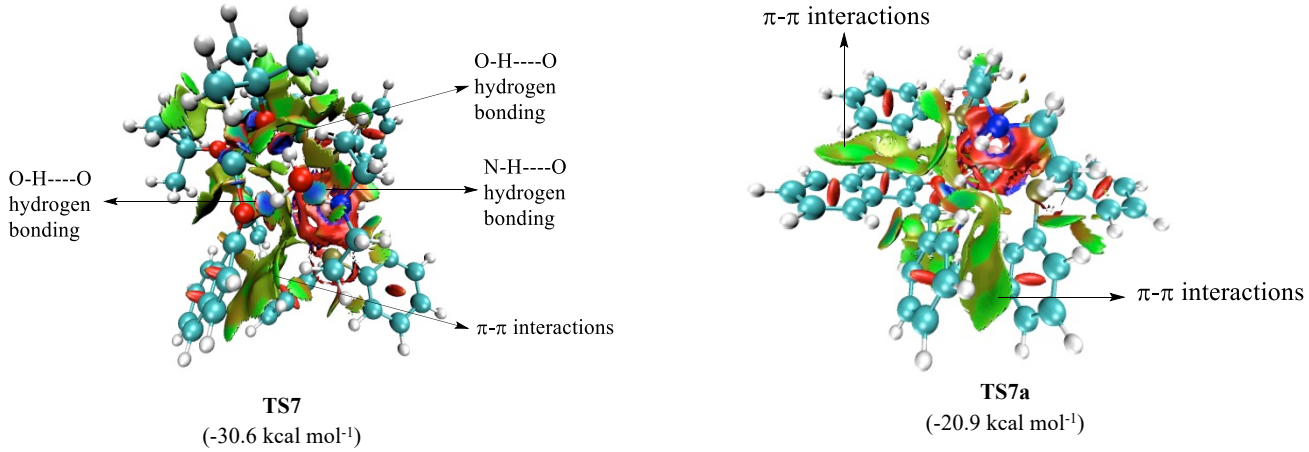


Figure 5.3 NCI plot for the hydride transfer transition state in the presence of water (TS7) and in the absence of water (TS7a). Energy in parenthesis are Gibbs free energy in kcal mol^{-1} with respect to the separated reactants.



5.4 CONCLUSIONS

In summary, Ru-macho catalyzed selective α-alkylation of β-naphthols using primary arylmethanols and linear aliphatic alcohols as alkylating reagents is reported. Remarkably, water is the only byproduct observed in the reaction making this catalytic transformation environmentally benign. High absorbance and emissive properties, as well as high quantum yields, were observed for the representative 1-alkyl-2-naphthol products. Mechanistic investigation revealed that the catalysis proceeds via aldehyde intermediates. The in situ formed aldehyde undergoes concomitant condensation with dearomatized β-naphthol to deliver the α-alkylation products. DFT studies supported these findings and proved that the reaction proceeds via three steps: concerted deprotonation and hydride abstraction from benzyl alcohol to afford benzaldehyde, aldol condensation of the benzaldehyde with β-naphthoxide, and stepwise hydride transfer and deprotonation from the Ru-dihydride complex, to generate catalytically active intermediate and α-alkylated products. The base employed in the reaction

medium played a key role in making the aldol condensation and catalytic regeneration step feasible. Further, the water molecule produced during the aldol condensation step makes a remarkable contribution towards the regeneration of the catalyst. Overall, an efficient and environmentally benign selective alkylation of β-naphthol is attained using alcohols as direct green alkylating reagents, which contributes towards sustainable development.

5.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-Macho [Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}ruthenium(II)] (**9**) was purchased from Sigma-Aldrich and stored inside glove box. Chemicals (naphthols and primary alcohols) were purchased from Acros, Sigma-Aldrich, Alfa-aesar, and Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were recorded using Waters XEVO G2-XS QTOF mass spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, and $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz) and JEOL-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS, δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm) and ^{31}P NMR chemical shifts are reported in ppm and referenced to an external 85% solution of phosphoric acid. Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of

doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (dept-135) NMR techniques. UV – Visible spectra were recorded on JASCO V-730 UV/Visible spectrophotometer. Fluorescence spectra and quantum yield were measured using Edinburgh specrofluorimeter instrument FS5. For the measurement of absolute quantum yield, the concentration of the 1-alkyl-2-naphthol compounds was such as to give an absorbance of around 0.1 at excitation wavelength. Absolute total quantum yields were measured using an integrating sphere (Edinburgh instrument FS5) mounted in SC-30 compartment of the spectrofluorimeter, with data processing by software supplied by Edinburgh instrument FS5. Cyclic voltammetry was performed with conventional three electrode system consisted of a Glassy carbon working electrode, a Pt wire as a secondary electrode, a Ag wire as a reference electrode. The voltammogram were recorded in a solution of CH_3CN containing (NBu_4PF_6) (0.1 M) as a supporting electrolyte.

GC method: GC data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard mesitylene was calculated from the average of three independent GC runs.

General optimization procedure for the site selective α-alkylation of β-naphthol using primary alcohols:

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.005-0.01 mmol), base (0.1-0.50 mmol), β-naphthol (0.5 mmol), benzyl alcohol (0.6-0.75 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further, the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using

dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yields were calculated for isolated pure products.

General procedure for the site selective *α*-alkylation of *β*-naphthols using aryl methyl alcohols:

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzyl alcohol (0.6 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. To the reaction mixture, 0.5 mmol of internal standard (mesitylene) was added and the conversion of *β*-naphthols was calculated using GC analysis. The resulting residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yields were calculated for isolated pure products.

General procedure for the site selective *α*-alkylation of *β*-naphthols using aliphatic primary alcohols:

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.4 mmol, 80 mol %), β-naphthol (0.5 mmol), aliphatic alcohol (1 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further, the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous sodium

sulfate, filtered, and concentrated. To the reaction mixture, 0.5 mmol of internal standard (mesitylene) was added and the conversion of *β*-naphthol was calculated using GC analysis. The resulting residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98)mixture as the eluent. Yields were calculated for isolated pure products.

Experimental procedure for scalable synthesis of 1-benzylnaphthalen-2-ol (5.2a, Scheme 5.3a):

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.07 mmol, 2 mol %), base (3.5 mmol, 100 mol %) , β-naphthol (3.5 mmol, 0.5 g), benzyl alcohol (4.2 mmol, 0.43 g), and toluene (5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further, the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yields were calculated for isolated pure product.

Experimental procedure for synthesis α-bromo ketone (5.3a, Scheme 5.3b):

To a 8 mL scintillation vial equipped with a magnetic stirrer was charged with 1-benzylnaphthalen-2-ol (**5.2a**, 0.25 mmol), NBS (0.24 mmol), and KOAc (0.3 mmol) in H_2O (1.5 mL). Then the mixture was stirred at room temperature for 1 h. Upon completion, the reaction mixture was extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure product.

Experimental procedures for mechanistic studies:

Catalytic reaction of β-naphthol with benzaldehyde (Scheme 5.4a):

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzaldehyde (0.6 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure product **5.2a**.

Reaction of β-naphthol with benzaldehyde using base (Scheme 5.4a):

A pressure tube (25 mL) was equipped with a stir bar, base (0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzaldehyde (0.6 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure product.

Deuterium labelling experiment (Scheme 5.4b): A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzyl alcohol-d3 (0.6 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath

temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure products.

Attempted reaction of compound 2 with benzyl alcohol and 4-methyl benzyl alcohol (Scheme 5.4c):

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), 1-benzylnaphthalen-2-ol (**5.2a**, 0.5 mmol), benzyl alcohol (0.6 mmol) (or 4-methyl benzyl alcohol, 0.6 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate mixture as the eluent. Yield was calculated for isolated pure products.

Catalyst poisoning experiments (Scheme 5.4d):

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzyl alcohol (0.6 mmol), mercury (8 mol %) (or 1,10-phenanthroline, 2 mol %), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted using dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The

resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure product **5.2a**.

Experiments under aerobic and nitrogen atmospheres in basic condition (Scheme 5.4e):

A Schlenk flask (25 mL) was equipped with a stir bar, base (LiO^{t}Bu, 0.5 mmol, 100 mol %), β-naphthol (0.5 mmol), benzyl alcohol (0.6 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The Schlenk flask was taken out of the glove box and heated at 150 °C (oil bath temperature) under open aerobic or nitrogen atmosphere conditions with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted crude reaction mixture was analysed by ^{1}H NMR spectroscopy.

Diminishing reaction rates with dehydrating reagents (Scheme 5.4f):

A pressure tube (25 mL) was equipped with a stir bar, catalyst **9** (0.01 mmol, 2 mol %), base (0.5 mmol, 100 mol %), benzyl alcohol (0.6 mmol), dehydrating reagents, molecular sieves, 4Å) (or anhydrous magnesium sulfate, 0.5 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The sealed tube was taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for 24 h. Further the solvent was evaporated, the reaction was quenched using 2M HCl (2 mL), and extracted by dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The resulted residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as the eluent. Yield was calculated for isolated pure products.

Procedure for kinetic experiments for the site selective α-alkylation of β-naphthols using primary alcohols:

Six different pressure tubes (25 mL) were equipped each with a stir bar, catalyst **9** (0.005 mmol, 2 mol %), base (0.25 mmol, 100 mol %), β-naphthol (0.25 mmol), benzyl alcohol (0.3 mmol), mesitylene (0.25 mmol), and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flasks were taken out of the glove box and heated at 150 °C (oil bath temperature) with stirring for indicated time intervals. The reaction progress was monitored by GC at 0.5, 1.5, 5, 8, 19 and 24 h period of time. The consumption of β-naphthol was corroborated with increasing concentration of α-alkylated β-naphthol product **5.2a** (**Figure 5.2**).

XRD DATA

Crystals of products **5.2h, 5.2s,** and **5.2t** were obtained after slow evaporation of DCM, layered by hexane at room temperature. Crystals suited for single crystal X-Ray diffraction measurements were mounted on a glass fiber. Geometry and intensity data were collected with a Bruker SMART D8 goniometer equipped with an APEXCCD detector and with an Incoatecmicrosource (Cu-Kα radiation, λ = 1.54184 Å, multilayer optics). The temperature was controlled using an Oxford Cryostream 700 instrument. Intensities were integrated with SAINT+ and corrected for absorption with SADABS. The structures were solved by direct methods and refined on F2 with SHELXL-97 using Olex-2 software.

Crystal data of 1-(4-fluorobenzyl)naphthalen-2-ol (5.2h) : $C_{17}H_{13}FO$, White, crystal dimension : 0.12 x 0.12 x 0.12 mm^{-1}, M = 252.27, monoclinic with space group Pbca, a = 9.6913(3) Å, b = 11.0500(4) Å, c = 22.9895(8) Å, α = 90°, β = 90° , γ = 90°, V = 2461.92(15) $Å^3$, Z = 8 F(000) = 1056.0, μ-(MoKα) = 0.093 mm^{-1}, 2θmax = 66.234, ρcalcd= 1.361 g/cm^3, T =100 K, min/max transmission factors = 0.647/1.000, 19297 Reflections collected 3046 unique (R1, 0.0456(5284)), $WR2$ = 0.1310(5781) (all data). Residual electron density max/min = 0.66/-0.59e.$Å^{-3}$. The structure has been deposited at the CCDC and can be

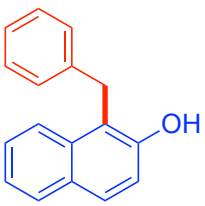
retrieved using the deposit number **CCDC** 2245597

Crystal data of 1-(pyren-1-ylmethyl)naphthalen-2-ol (5.2s): $C_{27}H_{18}O$, Green, crystal dimension : 0.1 x 0.1 x 0.1 mm^3, M = 358.41, orthorhombic with space group P 2_1 2_1 2_1 , a = 8.9320(4)Å, b = 10.3376(5)Å, c = 18.7295(10)Å, α = 90°, β = 90° , γ = 90°, V = 1729.40(15)$Å^3$, Z = 4 F(000) =752.0, μ-(MoKα) = 0.082 mm^{-1}, 2θmax = 61.104, ρcalcd= 1.377 g/cm^3, T =100 K, min/max transmission factors = 0.617/1.000, 19297 Reflections collected 4156 unique ($R1$ = 0.0389(3511)), $WR2$ = 0.0980(4156) (all data). Residual electron density max/min = 0.21/-0.18e.$Å^{-3}$. The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC** 2245598

Crystal data of 1-ferrocene-yl)naphthalen-2-ol (5.2t): $C_{24}H_{24}FeO_2$, brown, crystal dimension : 0.13 x 0.1 3x 0.13 mm^3, M = 400.28, monoclinic with space group P $2_1/n$, a = 11.1072(3) Å, b = 15.2691(4) Å, c = 11.6465(3)Å, α = 90°, β = 102.946(2)° , γ = 90°, V = 1925.00(9)$Å^3$, Z = 4 F(000) =840.0, μ-(MoKα) = 6.396 mm^{-1}, 2θmax = 61.104, ρcalcd= 1.381 g/cm^3, T =101(1) K, min/max transmission factors = 0.241/1.000, 14147 Reflections collected 4004 unique ($R1$ = 0.0603(3609)), $WR2$ = 0.1644(4004) (all data). Residual electron density max/min = 0.83/-1.39e.$Å^{-3}$. The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC** 2245599

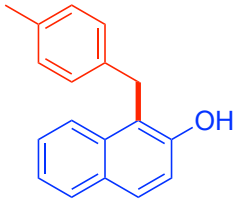
Spectral data:

1-Benzylnaphthalen-2-ol (5.2a): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. m. p 108 °C, Yield: 90 mg, 77%. IR (DCM; cm^{-1}): 3053, 1710, 1420, 1263, 895, 731, 703. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83 (dd, J_1 = 8.5 Hz, J_2 = 0.8 Hz, 1H), 7.70 (dt, J_1 = 8.1 Hz, J_2 = 0.7 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.35 (ddd, J_1 = 8.5 Hz , J_2 = 6.9 Hz , J_3 = 1.5 Hz, 1H), 7.24 (ddd, J_1 = 8.1 Hz , J_2 = 6.9 Hz , J_3 = 1.2 Hz, 1H), 7.17-7.08 (m, 5H), 7.00 (d, J = 8.8 Hz, 1H), 4.95 (s, 1H), 4.37 (s, 2H). $^{13}C\{^1H\}$ NMR (101



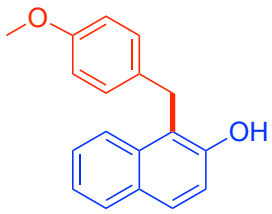
MHz, $CDCl_3$): δ 151.31, 140.11, 133.79, 129.60, 128.70, 128.67, 128.64, 128.33, 126.81, 126.25, 123.48, 123.36, 118.30, 118.01, 30.81. HRMS (ESI) m/z calcd for $C_{17}H_{14}O$ $(M+H)^+$: 234.1045, found: 234.1048.

1-(4-Methylbenzyl)naphthalen-2-ol (5.2b): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. yellow oil. Yield: 77 mg, 62%. IR



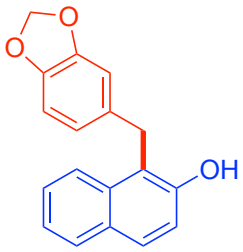
(DCM; cm^{-1}): 3052, 1711, 1510, 1263, 1025, 731. ^1H NMR (400 MHz; $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 1H), 7.72—7.70 (m, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.35 (ddd, J_1 = 8.5 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz, 1H), 7.25 (ddd, J_1 = 8.0 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.03—6.96 (m, 5H), 5.00 (s, 1H), 4.33 (s, 2H), 2.20 (s, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.34, 136.89, 135.81, 133.79, 129.60, 129.44, 128.66, 128.56, 128.20, 126.78, 123.46, 123.32, 118.47, 118.05, 30.41, 21.12. HRMS (ESI) m/z calcd for $C_{18}H_{16}O$ $(M+H)^+$: 248.1201, found: 248.1179.

1-(4-Methoxybenzyl)naphthalen-2-ol (5.2c): Purified by silica-gel column chromatography

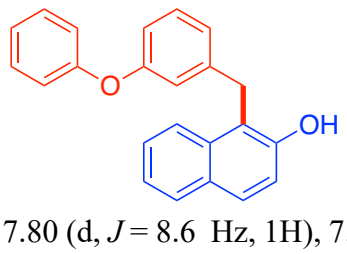


using an ethyl acetate/hexane (4:96) mixture as the eluent. Yellow solid. m. p, 111 °C, Yield: 100 mg, 76%. IR (DCM; cm^{-1}):3057, 2960, 1509, 1261, 1010, 799,734. ^1H NMR (400 MHz; $CDCl_3$): δ 7.85 (dd, J_1 = 8.5 Hz, J_2 = 0.6 Hz, 1H), 7.72 (dt, J_1 = 8.1 Hz, J_2 = 0.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.36 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.28-7.26 (m, 1H), 7.07-7.02 (m, 3H), 6.73-6.70 (m, 2H), 5.02 (s, 1H), 4.32 (s, 2H), 3.67 (s, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 158.11, 151.31, 133.74, 132.01, 129.60, 129.26, 128.68, 128.57, 126.78, 123.44, 123.33, 118.60, 118.05, 114.18, 55.38, 29.93. HRMS (ESI) m/z calcd for $C_{18}H_{16}O_2Na(M+Na)^+$: 287.1048, found: 287.1005

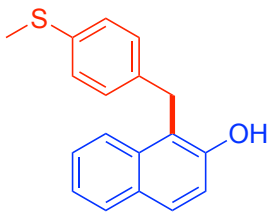
1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)naphthalen-2-ol (5.2d): Purified by silica-gel column chromatography using an ethyl acetate/hexane (10:90) mixture as an eluent. White solid. m. p 118 °C, Yield: 75 mg, 54%. IR (DCM; cm^{-1}): 3467, 3055, 2908, 1629, 1487, 1436, 1355, 1263, 1093, 1039, 988, 923, 807, 732. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.36 (ddd, J_1 = 8.5 Hz , J_2 = 6.9 Hz, 1.4 Hz, 1H), 7.24 (ddd, J_1 = 8.0 Hz , J_2 = 6.9 Hz , J_3 = 1.1 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.61 (s, 3H), 5.78 (s, 2H), 5.11 (s, 1H), 4.27 (s, 2H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 151.29, 147.97, 145.98, 134.02, 133.70, 129.59, 128.69, 128.67, 126.83, 125.53, 123.36, 121.08, 118.43, 118.00, 108.93, 108.37, 100.93, 30.46. HRMS (ESI) m/z calcd for $C_{18}H_{14}O_3(M+H)^+$: 278.0943, found: 278.0964.



1-(3-Phenoxybenzyl)naphthalen-2-ol (5.2e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colourless oil. Yield: 143 mg, 88%. IR (DCM; cm^{-1}): 3054, 2950, 2252, 1718, 1245, 903, 724, 648. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.37-7.33 (m, 1H), 7.26-7.16 (m, 3H), 7.08 (t, J = 7.8 Hz, 1H), 6.98 (dt, J_1 = 8.1 Hz , J_2 = 3.7 Hz, 2H), 6.86 (t, J = 8.0 Hz, 4H), 6.68 (t, J = 4.5 Hz, 1H), 4.34 (s, 2H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 157.46, 157.27, 151.24, 142.53, 133.73, 129.85, 129.64, 128.79, 128.76, 126.92, 126.70, 123.48, 123.42, 123.27, 119.21, 119.18, 118.97, 118.94, 118.87, 118.06, 117.96, 116.45, 30.72. HRMS (ESI) m/z calcd for $C_{23}H_{18}O_2(M+H)^+$: 326.1307, found: 326.1332.

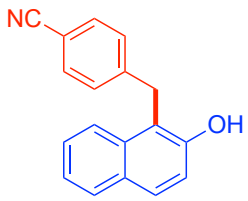


1-(4-(Methylthio)benzyl)naphthalen-2-ol (5.2f): Purified by silica-gel column chromatography using an ethyl acetate/hexane (7:93) mixture as the eluent. White solid. m. p 118-120 °C, Yield: 120 mg, 86%. IR (DCM; cm^{-1}): 3052, 2380, 1715, 1263, 731. ^{1}H NMR (400 MHz; $CDCl_3$): δ

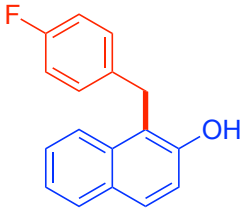


7.82 (d, J = 8.8 Hz, 1H), 7.73-7.71 (m, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.37-7.35 (m, 1H), 7.27 (dd, J_1 = 8.2 Hz, J_2 = 1.1 Hz, 1H), 7.07-7.03 (m, 5H), 5.01 (s, 1H), 4.34 (s, 2H), 2.35 (s, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.21, 137.25, 135.74, 133.67, 129.53, 128.82, 128.65, 127.30, 126.80, 123.38, 118.12, 117.91, 30.21, 16.29. HRMS (ESI) m/z calcd for $C_{18}H_{17}OS(M+H)^+$: 281.1000, found: 281.0966.

4-((2-Hydroxynaphthalen-1-yl)methyl)benzonitrile (5.2g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (7:93) mixture as the eluent. White solid. m. p 128°C, Yield: 85 mg, 66%. IR (DCM; cm^{-1}): 3052, 2253, 1707, 1503, 1359, 1263, 905, 726, 648. ^1H NMR (400 MHz; $CDCl_3$): δ 7.74-7.69 (m, 2H), 7.65 (d, J = 8.9 Hz, 1H), 7.43-7.40 (m, 2H), 7.36 (ddd, J_1 = 8.4 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz, 1H), 7.28-7.23 (m, 3H), 7.05 (d, J = 8.8 Hz, 1H), 5.52 (s, 1H), 4.43 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.39, 146.85, 133.54, 132.34, 129.51, 129.22, 129.07, 128.85, 127.06, 123.47, 123.02, 119.27, 117.80, 117.09, 109.53, 30.97. HRMS (ESI) m/z calcd for $C_{18}H_{14}NO(M+H)^+$: 260.1075, found: 260.1089.

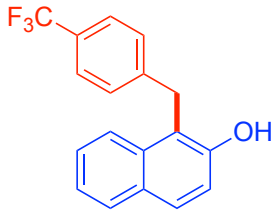


1-(4-Fluorobenzyl)naphthalen-2-ol (5.2h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. White solid. 110-115 °C, Yield: 121 mg, 96%. IR (DCM; cm^{-1}): 3054, 2306, 1702, 1507, 1263, 732. ^1H NMR (400 MHz; $CDCl_3$): δ 7.79 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.36 (ddd, J_1 = 8.4 Hz, J_2 = 6.9 Hz, J_3 = 1.4 Hz, 1H), 7.25 (ddd, J_1 = 8.0 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.09-7.06 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.85-6.81 (m, 2H), 4.93 (s, 1H), 4.33 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 162.68, 160.26, 151.14, 136.01, 135.88, 135.85, 133.67, 129.98, 129.74, 129.66, 129.63, 128.83, 128.77, 128.75, 126.92, 126.66, 123.76, 123.49, 123.45, 123.34, 118.29, 117.92, 115.49, 115.28, 29.97. HRMS (ESI) m/z calcd for $C_{17}H_{14}FO(M+H)^+$: 253.1029, found:

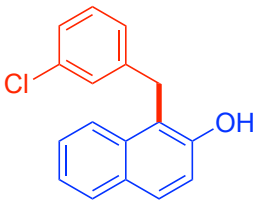


253.1037.

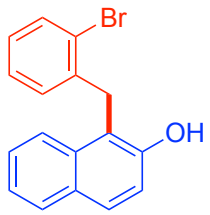
1-(4-(Trifluoromethyl)benzyl)naphthalen-2-ol (5.2i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Reddish solid. m. p 122-123°C, Yield: 116 mg, 77%. I IR (DCM; cm^{-1}): 2924, 1677, 1616,1513, 1454,1757,1323, 1264, 1163, 1121, 1066, 1018, 990, 812, 733, 699, 599. ^1H NMR (400 MHz; $CDCl_3$): δ 7.83 (dd, J_1 = 13.7, J_2 = 8.3 Hz, 2H), 7.72 (d, J = 8.8 Hz, 1H), 7.50—7.44 (m, 3H), 7.34 (dd, J_1 = 16.5 Hz, J_2 = 8.2 Hz, 3H), 7.09 (d, J = 8.8 Hz, 1H), 5.15 (s, 1H), 4.51 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.16, 144.79, 133.66, 129.63, 128.98, 127.07, 125.49, 125.46, 123.54, 123.25, 117.81, 117.66, 30.62. HRMS (ESI) m/z calcd for $C_{18}H_{14}F_3O(M+H)^+$: 303.0997, found: 303.0952.



1-(3-Chlorobenzyl)naphthalen-2-ol (5.2j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Brown oil. Yield: 99 mg, 74%. IR (DCM; cm^{-1}): 3061, 2924, 1661, 1594, 1472, 1355, 1268, 1072, 987, 849, 743. ^1H NMR (400 MHz; $CDCl_3$): δ 7.71 (dd, J_1 = 23.3, J_2 = 8.3 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.33 (dd, J_1 = 8.4 Hz, J_2 = 7.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.11 (d, J = 6.7 Hz, 1H), 7.03-6.93 (m, 4H), 5.05 (s, 1H), 4.31 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.14, 142.61, 134.40, 133.64, 129.79, 129.59, 128.88, 128.74, 128.71, 128.46, 126.97, 126.55, 126.35, 123.46, 123.28, 117.85, 117.71, 30.47. HRMS (ESI) m/z calcd for $C_{17}H_{13}ClO(M+H)^+$: 268.0655, found: 268.0654.

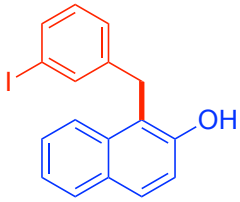


1-(2-Bromobenzyl)naphthalen-2-ol (5.2k): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Brown oil. Yield: 83 mg, 53%. IR (DCM; cm^{-1}): 3059, 2922, 2853, 1914, 1626, 1465, 1266, 1143, 1025, 813, 746. ^1H NMR (400 MHz; $CDCl_3$): δ 7.74-7.61 (m, 3H), 7.56-7.53 (m, 1H), 7.33 (ddd, J_1 = 8.4 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz,

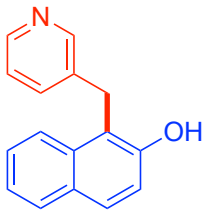


1H), 7.25 (ddd, J_1 = 8.0 Hz, J_2 = 6.8 Hz , J_3 = 1.2 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.97-6.92 (m, 2H), 6.59-6.56 (m, 1H), 4.95 (s, 1H), 4.40 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.61, 138.99, 133.82, 132.67, 129.60, 129.29, 129.06, 128.68, 127.88, 127.70, 127.04, 124.95, 123.54, 123.48, 117.90, 116.87, 31.28. HRMS (ESI) m/z calcd for $C_{17}H_{13}BrO(M)^+$: 312.0150, found: 312.0128.

1-(3-Iodobenzyl)naphthalen-2-ol (5.2l): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Yellow solid. m. p 120-125 °C, Yield: 124 mg, 69%. IR (DCM; cm^{-1}): 3052, 1702, 1561, 1419, 1263, 731, 702. ^1H NMR (400 MHz; $CDCl_3$): δ 7.76-7.69 (m, 2H), 7.58 (t, J = 17.4 Hz, 2H), 7.40-7.33 (m, 2H), 7.26-7.22 (m, 1H), 7.04-6.95 (m, 2H), 6.83 (t, J = 7.8 Hz, 1H), 5.02 (s, 1H), 4.29 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.11, 142.96, 142.94, 137.30, 135.25, 133.60, 130.30, 129.57, 128.88, 128.73, 127.58, 126.98, 123.46, 123.28, 117.84, 117.66, 94.86, 30.35. HRMS (ESI) m/z calcd for $C_{17}H_{14}IO(M+H)^+$: 361.0089, found: 361.0076.

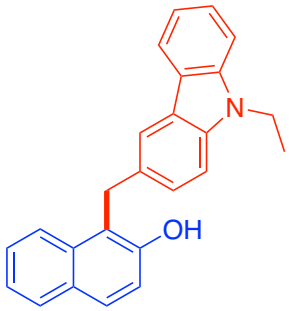


1-(Pyridin-3-ylmethyl)naphthalen-2-ol (5.2m): Purified by silica-gel column chromatography using an ethyl acetate/hexane (20:80) mixture as the eluent. White solid. m. p 125-130 °C, Yield: 39 mg, 33%. IR (DCM; cm^{-1}): 3646, 2923, 2592, 1625, 1778, 1508,1434, 1354, 1330, 1271, 1252, 997, 806, 751, 734, 705. ^1H NMR (400 MHz; DMSO-d_6): δ 9.89 (s, 1H), 8.54 (d, J = 1.5 Hz, 1H), 8.33 (dd, J_1 = 4.6 Hz, J_2 = 1.2 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.76 (dd, J_1 = 28.4 Hz, J_2 = 8.2 Hz, 2H), 7.55 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1H), 7.43-7.41 (m, 1H), 7.29-7.21 (m, 3H), 4.37 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 157.86, 154.59, 151.97, 142.13, 140.86, 138.22, 133.64, 133.46, 133.35, 131.62, 128.65, 127.89, 127.61, 123.32, 122.25, 32.38. HRMS (ESI) m/z calcd for $C_{16}H_{14}NO(M+H)^+$: 236.1075, found: 236.1048.



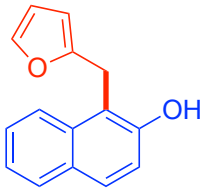
1-((9-Ethyl-9*H*-carbazol-3-yl)methyl)naphthalen-2-ol (5.2n): Purified by silica-gel column

chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. m. p



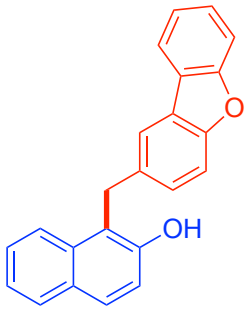
150 °C, Yield: 129 mg, 74%. IR (DCM; cm^{-1}): 3408, 2974, 1626, 1598, 1481, 1334, 1233, 1149, 986, 740. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.95-7.83 (m, 3H), 7.71-7.58 (m, 2H), 7.32 (dd, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 2H), 7.24-7.18 (m, 3H), 7.13-6.99 (m, 3H), 5.15 (s, 1H), 4.51 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$): δ 151.61, 140.31, 138.86, 133.89, 130.14, 129.67, 128.70, 128.59, 126.79, 126.14, 125.71, 123.59, 123.33, 122.78, 120.64, 119.91, 119.05, 118.71, 118.27, 108.80, 108.53, 37.61, 30.94, 13.93. HRMS (ESI) m/z calcd for $C_{25}H_{22}NO(M+H)^+$: 352.1701, found: 352.1730.

1-(Furan-2-ylmethyl)naphthalen-2-ol (5.2o): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Brown oil. Yield: 17 mg, 15%. IR



(DCM; cm^{-1}): 3054, 2252, 1712, 1372, 1265, 732. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.91 (d, J = 8.6 Hz, 1H), 7.73-7.63 (m, 2H), 7.43-7.41 (m, 1H), 7.30-7.25 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 6.18 (dd, J_1 = 3.0 Hz , J_2 = 2.0 Hz, 1H), 5.89-5.88 (m, 1H), 5.33 (s, 1H), 4.35 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.83, 151.40, 141.45, 133.38, 129.61, 128.93, 128.70, 126.85, 123.46, 123.12, 118.29, 116.05, 110.55, 106.03, 24.20. HRMS (ESI) m/z calcd for $C_{15}H_{12}O_2Na(M+Na)^+$: 247.0735, found: 247.0730.

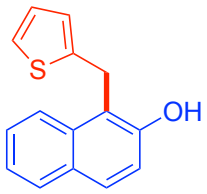
1-(Dibenzo[b,d]furan-2-ylmethyl)naphthalen-2-ol (5.2p): Purified by silica-gel column



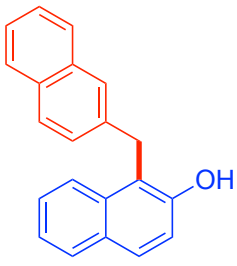
chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. m. p 128-130°C, Yield: 115 mg, 71%. IR (DCM; cm^{-1}): 3262, 3052, 1627, 1598, 1582, 1509, 1450, 1403, 1264, 1196, 1169, 1118, 957, 842, 811, 737, 478. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.90-7.88 (m, 1H), 7.75-7.72 (m, 2H), 7.66-7.64 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H),

7.38-7.33 (m, 2H), 7.31-7.29 (m, 1H), 7.25 (ddd, J_1 = 8.0 Hz, J_2 = 6.8 Hz, J_3 = 1.1 Hz, 2H), 7.19-7.16 (m, 1H), 7.03 (dd, J_1 = 18.6 Hz, J_2 = 8.8 Hz, 1H), 5.07 (s, 1H), 4.51 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 156.62, 155.01, 129.69, 128.75, 127.58, 127.14, 126.93, 126.64, 124.27, 123.73, 123.44, 122.64, 120.85, 120.09, 118.08, 111.71, 30.73. HRMS (ESI) m/z calcd for $C_{23}H_{17}O_2(M+H)^+$: 325.1229, found: 325.1261.

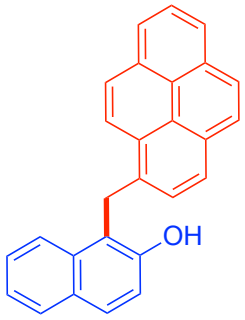
1-(Thiophen-2-ylmethyl)naphthalen-2-ol (5.2q): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. Brown liquid. Yield: 86 mg, 72%. IR (DCM; cm^{-1}): 3368,3053, 2923, 1697, 1626, 1597, 1513, 1435, 1352, 1262, 1142, 1057, 981, 809, 733, 696. ^1H NMR (400 MHz; $CDCl_3$): δ 7.85 (d, J = 8.6 Hz, 1H), 7.60 (dd, J_1 = 45.5 Hz, J_2 = 8.4 Hz, 2H), 7.34 (dd, J_1 = 8.1 Hz, J_2 = 7.3 Hz, 1H), 7.21 (dd, J_1 = 7.8 Hz, J_2 = 7.0 Hz, 1H), 6.93 (dd, J_1 = 20.0 Hz, J_2 = 7.0 Hz, 2H), 6.73 (t, J = 4.3 Hz, 1H), 6.65 (t, J = 1.7 Hz, 1H), 5.22 (s, 1H), 4.46 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150.95, 143.46, 133.28, 129.55, 128.85, 128.68, 126.88, 124.85, 123.72, 123.43, 123.18, 118.35, 117.99, 25.47. HRMS (ESI) m/z calcd for $C_{15}H_{12}OS$ $(M)^+$: 240.0609, found: 240.0600.



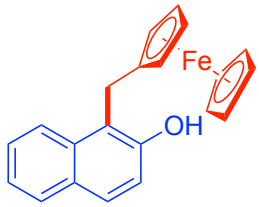
1-(Naphthalen-2-ylmethyl)naphthalen-2-ol (5.2r): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. m. p 125-126 °C, Yield: 121 mg, 75%. IR (DCM; cm^{-1}): 3052, 1708, 1506, 1263, 731. ^1H NMR (400 MHz; $CDCl_3$): δ 8.01 (d, J = 8.5 Hz, 1H), 7.87-7.70 (m, 5H), 7.62 (s, 1H), 7.50-7.37 (m, 5H), 7.15 (dd, J_1 = 13.8 Hz, J_2 = 8.8 Hz, 1H), 5.18-5.17 (m, 1H), 4.65 (s, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.35, 137.61, 133.77, 133.65, 132.19, 129.87, 129.57, 128.69, 128.61, 128.28, 127.80, 127.60, 127.06, 126.79, 126.55, 126.40, 126.21, 125.98, 125.35, 123.65, 123.43, 123.33, 118.05, 117.97, 117.76, 109.52, 30.99. HRMS (ESI) m/z calcd for $C_{21}H_{16}O(M+H)^+$: 284.1201, found: 284.1226.



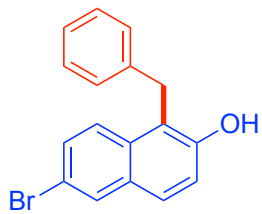
1-((3,8-Dihydropyren-4-yl)methyl)naphthalen-2-ol (5.2s): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. Yellow solid. m. p 220 °C, Yield: 130 mg, 73%. IR (DCM; cm^{-1}): 3053, 1712, 1263, 731. ^{1}H NMR (400 MHz; DMSO-d_6): δ 9.87 (s, 1H), 8.80 (d, J = 9.3 Hz, 1H), 8.35-8.27 (m, 3H), 8.11-8.00 (m, 4H), 7.86-7.82 (m, 2H), 7.66-7.64 (m, 1H), 7.39-7.23 (m, 4H), 5.11 (s, 2H). $^{13}C\{^{1}H\}$NMR (101 MHz, DMSO-d_6): δ 153.73, 135.61, 134.25, 131.39, 130.93, 129.47, 128.89, 128.87, 128.77, 128.67, 127.86, 127.85, 126.93, 126.73, 126.61, 125.97, 125.48, 125.38, 125.24, 124.57, 124.55, 123.86, 123.50, 122.82, 118.72, 117.39, 27.73. HRMS (ESI) m/z calcd for $C_{27}H_{18}ONa(M+Na)^{+}$: 381.1255, found: 381.1240.



1-(Ferrocene-2-ylmethyl)naphthalen-2-ol (5.2t): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Brown oil. Yield: mg, 60%. IR (DCM; cm^{-1}): 3053, 2956, 2929, 2868, 1783, 1667, 1460, 1279, 1063, 874, 744. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.08-6.94 (m, 6H), 5.14 (s, 1H), 4.66-4.05 (m, 11H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 150.52, 132.99, 129.20, 128.53, 128.12, 126.33, 123.27, 123.05, 119.24, 117.67, 72.16, 72.11, 72.05, 72.03, 72.00, 71.96, 70.91, 70.88, 70.85, 69.60, 69.56, 69.51, 69.50, 68.68, 68.56, 68.40, 68.34, 67.96, 67.21, 24.59. HRMS (ESI) m/z calcd for $C_{21}H_{18}FeO(M+H)^{+}$: 342.0676, found: 342.0652.

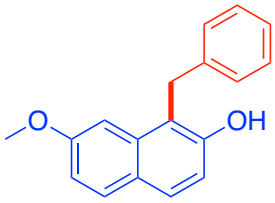


1-Benzyl-6-bromonaphthalen-2-ol (5.2u): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. m. p 118°C, Yield: 63 mg, 40%. IR (DCM; cm^{-1}): 3053, 2974, 1709, 1496, 1419, 1359, 1263, 731, 702. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.41 (dd, J_1 = 9.1 Hz, J_2 = 2.1 Hz, 1H), 7.20-7.04 (m, 6H), 5.05 (s, 1H), 4.35 (s, 2H).



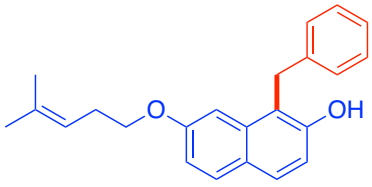
$^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 151.60, 139.74, 132.36, 130.78, 130.54, 130.01, 128.78, 128.25, 127.73, 126.41, 125.40, 119.11, 118.68, 117.15, 30.79. HRMS (ESI) m/z calcd for $C_{17}H_{14}BrO(M+H)^+$: 314.0228, found: 314.0233.

1-Benzyl-6-(4-(tert-butyl)phenyl)naphthalen-2-ol (5.2v): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 38 mg, 58%. IR (DCM; cm^{-1}): 3094, 2957, 1601, 1494, 1360, 1200, 990, 825. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.85 (s, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.14 (q, *J* = 3.5 Hz, 4H), 7.00 (d, *J* = 8.7 Hz, 3H), 4.36 (s, 2H), 1.28 (s, 9H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 151.33, 150.23, 140.11, 138.14, 135.89, 132.85, 129.88, 128.90, 128.74, 128.70, 128.35, 128.33, 126.92, 126.44, 126.29, 126.27, 125.91, 123.98, 118.38, 118.27, 34.67, 31.52, 30.88. HRMS (ESI) m/z calcd for $C_{27}H_{27}O(M+H)^+$: 367.2062, found: 367.2039.



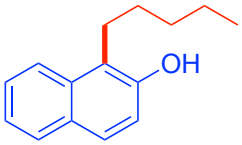
1-Benzyl-7-methoxynaphthalen-2-ol (5.2w): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 41 mg, 62%. IR (DCM; cm^{-1}): 2926, 1628, 1514, 1493, 1384, 1263, 830, 792, 613. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (dd, *J* = 27.8, 8.8 Hz, 2H), 7.16 (d, *J* = 4.3 Hz, 4H), 7.09 (d, *J* = 4.3 Hz, 2H), 6.93—6.85 (m, 2H), 5.08 (d, *J* = 0.2 Hz, 1H), 4.33 (s, 2H), 3.73 (s, 3H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 158.44, 151.84, 140.28, 135.09, 130.17, 128.68, 128.35, 128.30, 126.19, 124.95, 117.58, 115.52, 115.38, 102.68, 55.30, 31.10. HRMS (ESI) m/z calcd for $C_{18}H_{17}O(M+H)^+$: 265.1229, found:265.1263.

1-Benzyl-7-((4-methylpent-3-en-1-yl)oxy)naphthalen-2-ol (5.2x): Purified by silica-gel column chromatography using an ethyl acetate/hexane (15:85) mixture as an eluent. Viscous brown oil. Yield: 20 mg, 24%. IR (DCM; cm^{-1}): 3045, 2924, 1626, 1514, 1453, 1381, 1276, 829. ^{1}H NMR (400 MHz;



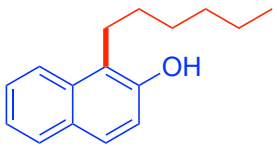
$CDCl_3$): δ 7.56 (dd, *J* = 27.2, 8.8 Hz, 2H), 7.18—7.09 (m, 6H), 6.93—6.86 (m, 2H), 5.14 (t, *J* = 6.6 Hz, 1H), 4.31 (s, 2H), 3.87 (t, *J* = 7.1 Hz, 2H), 2.40 (q, *J* = 7.0 Hz, 2H), 1.66 (s, 3H), 1.57 (s, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 157.87, 151.88, 140.30, 135.13, 134.58, 130.11, 128.67, 128.36, 128.27, 126.18, 124.89, 119.71, 117.48, 115.88, 115.33, 103.49, 67.66, 31.06, 28.27, 25.92, 18.02. HRMS (ESI) m/z calcd for $C_{23}H_{25}O_2(M+H)^+$: 333.1855, found: 333.1830.

1-Pentylnaphthalen-2-ol (5.2aa)[1]: Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colourless liquid.



Yield: 52 mg, 49%. IR (DCM; cm^{-1}): 3055, 2928, 1673, 1263, 732. ^1H NMR (400 MHz; $CDCl_3$): δ 7.96 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.51 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.36 (ddd, J_1 = 8.0 Hz, J_2 = 6.9 Hz, J_3 = 1.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.03 (t, *J* = 0.3 Hz, 1H), 3.05 (t, *J* = 7.9 Hz, 2H), 1.74-1.66 (m, 3H), 1.53-1.39 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150.40, 133. 28, 129.50, 128.69, 127.63, 126. 37, 123.32, 123.11, 120.46, 117.73, 99.99, 32.24, 29.62, 25.17, 22.76, 14.18. HRMS (ESI) m/z calcd for $C_{15}H_{18}ONa(M+Na)^+$: 237.1255, found: 237.1241.

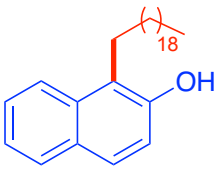
1-Pentylnaphthalen-2-ol (5.2ab)[1]: Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Colourless liquid.



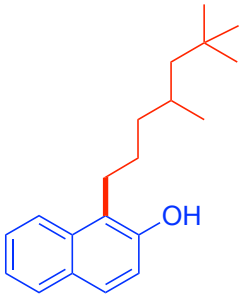
Yield: 58 mg, 54%. IR (DCM; cm^{-1}): 3063, 2925, 2857, 1719, 1679, 1510, 1459, 1271, 1109, 814, 749, 712. ^1H NMR (400 MHz; $CDCl_3$) δ 7.95 (d, J = 8.6 Hz, 1H), 7.80 (dt, J_1 = 8.1 Hz, J_2 = 0.6 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.51 (ddd, J_1 = 8.5 Hz, J_2 = 6.9, 1.5 Hz, 1H), 7.35 (ddd, J_1 = 8.1 Hz, J_2 = 6.9 Hz, J_3 = 1.2 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 1H), 3.05 (dd, J_1 = 9.0 Hz, J_2 = 6.8 Hz, 2H), 1.73-1.65 (m, 3H), 1.53-1.47 (m, 2H), 1.37 (dt, J_1 = 7.2 Hz, J_2 = 3.7 Hz, 3H), 0.94-0.91 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 150.32, 133.19, 129.44, 128.59, 127.52, 126.27, 123.03, 122.98,

120.36, 117.64, 31.83, 29.83, 29.70, 25.15, 22.69, 14.13. HRMS (ESI) m/z calcd for $C_{16}H_{20}O(M)^+$: 228.1514, found: 228.1514.

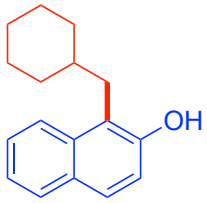
1-Octadecylnaphthalen-2-ol (5.2ac): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colourless liquid. Yield: 57 mg, 29%. IR (DCM; cm^{-1}): 3059, 2917, 2850, 1699, 1621, 1511, 1463, 1267, 1200, 114, 742. ^1H NMR (400 MHz; $CDCl_3$): δ 7.95 (d, J = 8.6 Hz, 1H), 7.81-7.79 (m, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.51 (ddd, J_1 = 8.5 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz, 1H), 7.36 (ddd, J_1 = 8.1 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 4.99 (s, 1H), 3.05 (t, J = 7.9 Hz, 2H), 1.71-1.65 (m, 3H), 1.52-1.49 (m, 2H), 1.40-1.34 (m, 32H), 0.92 (dd, J_1 = 8.2 Hz, J_2 = 5.4 Hz, 3H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150.32, 133.20, 129.45, 128.60, 127.52, 126.27, 123.04, 122.99, 120.37, 117.64, 31.95, 30.05, 29.87, 29.73, 29.71, 29.69, 29.65, 29.39, 25.16, 22.72, 14.14. HRMS (ESI) m/z calcd for $C_{28}H_{45}O(M+H)^+$: 397.3470, found: 397.3490.



1-(4,6,6-Trimethylheptyl)naphthalen-2-ol (5.2ad): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colourless liquid. Yield: 62 mg, 43%. IR (DCM; cm^{-1}): 3055, 2924, 2854, 1712, 1626, 1443, 1266, 1111, 813, 740. ^1H NMR (400 MHz; $CDCl_3$): δ 7.91 (d, J = 8.9 Hz, 1H), 7.78-7.75 (m, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.48 (td, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.32 (td, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 4.99 (s, 1H), 3.01 (ddd, J_1 = 11.1 Hz, J_2 = 8.2 Hz, J_3 = 5.9 Hz, 2H), 1.66 (s, 2H), 1.61 (d, J = 5.4 Hz, 1H), 1.37 (dd, J_1 = 14.0 Hz, J_2 = 3.7 Hz, 1H), 1.26 (m, 5H), 0.93 (s, 9H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150.23, 133.19, 128.69, 127.52, 126.39, 122.95, 120.79, 117.72, 51.23, 39.39, 31.20, 20.20, 20.15, 23.09, 22.75. HRMS (ESI) m/z calcd for $C_{20}H_{28}ONa$ (M+Na): 307.2038, found: 307.2054.

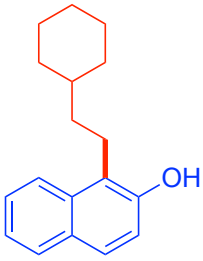


1-(Cyclohexylmethyl)naphthalen-2-ol (5.2ae): Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as the eluent.



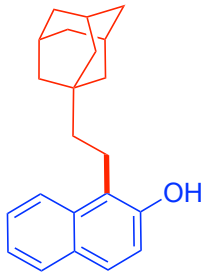
Yellow liquid. Yield: 63 mg, 53%. IR (DCM; cm^{-1}): 3052, 2925, 1711, 1420, 1263, 731, 703. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.28 (td, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.86 (s, 1H), 2.87 (d, J = 6.9 Hz, 2H), 1.71 (dd, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 2H), 1.65 (t, J = 3.0 Hz, 2H), 1.58-1.54 (m, 2H), 1.14-1.08 (m, 5H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 151.11, 133.82, 129.57, 128.70, 127. 76, 126.25, 123.62, 123.07, 119.03, 117.76, 39.00, 33.79, 32.96, 26.52. HRMS (ESI) m/z calcd for $C_{17}H_{20}O(M+H)^+$: 241.1592, found: 241.1537.

1-(2-Cyclohexylethyl)naphthalen-2-ol (5.2af): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent.

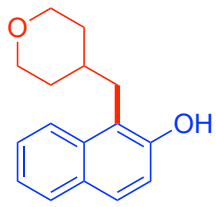


Colourless liquid. Yield: 91 mg, 71%. IR (DCM; cm^{-1}): 3052, 2307, 1713, 1507, 1263, 731. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.81 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.39-7.35 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 5.02 (s, 1H), 2.94-2.90 (m, 2H), 1.78 (d, J = 12.7 Hz, 2H), 1.66-1.57 (m, 3H), 1.42 (dt, J_1 = 10.4 Hz, J_2 = 6.7 Hz, 2H), 1.33 (dd, J_1 = 6.9 Hz, J_2 = 3.5 Hz, 1H), 1.20-1.07 (m, 3H), 0.96-0.90 (m, 2H). $^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$): δ 150.27, 133.23, 129.59, 128.72, 127.54, 126.40, 123.10, 123.05, 120.92, 117.78, 38.36, 37.53, 33.46, 26.84, 26.51, 22.67. HRMS (ESI) m/z calcd for $C_{18}H_{23}O(M+H)^+$:255.1749, found: 255.1750.

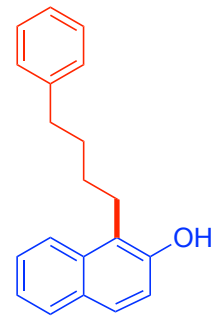
1-(2-((3r,5r,7r)-Adamantan-1-yl)ethyl)naphthalen-2-ol (5.2ag): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as the eluent. Colourless liquid. Yield: 64 mg, 60%. IR (DCM; cm^{-1}): 3059, 2900, 2846, 2670, 1678, 1564, 1450, 1348, 1238, 1124, 1069, 980, 808, 740. ^1H NMR (400 MHz; $CDCl_3$): δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.49-7.45 (m, 1H), 7.33-7.31 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 4.85 (d, *J* = 1.1 Hz, 1H), 2.99-2.95 (m, 2H), 2.03 (d, *J* = 6.5 Hz, 3H), 1.78-1.68 (m, 12H), 1.39-1.35 (m, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150. 17, 128.71, 127.46, 126.39, 123.07, 122.88, 117.72, 44.10, 42.34, 37.36, 28.87, 18.23. HRMS (ESI) m/z calcd for $C_{22}H_{27}O(M+H)^+$: 307.2062, found: 307.2075.



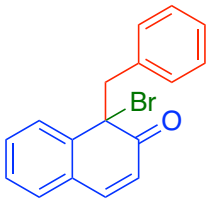
1-((Tetrahydro-2H-pyran-4-yl)methyl)naphthalen-2-ol (5.2ah): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Yellow Solid. m. p 150-155°C, Yield: 64 mg, 60%. IR (DCM; cm^{-1}): 3055, 2924, 2854, 1712, 1626, 1512, 1443, 1266, 1111, 1085, 978, 813, 740. ^1H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.41-7.37 (m, 1H), 7.24 (td, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 5.53 (s, 1H)3.90—3.86 (m, 2H), 3.24 (td, J_1 = 11.2 Hz, J_2 = 3.3 Hz, 2H), 2.94 (d, *J* = 7.3 Hz, 2H), 1.88 (td, J_1 = 7.1 Hz, J_2 = 3.4 Hz, 1H), 1.50 (ddd, J_1 = 12.7 Hz, J_2 = 9.0 Hz, J_3 = 3.9 Hz, 4H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 151.38, 128.79, 127.95, 126.41, 123.35, 123.08, 118.35, 117.71, 68.28, 36.10, 33.32, 32.02. HRMS (ESI) m/z calcd for $C_{16}H_{19}O_2(M+H)^+$:243.1385, found: 243.1400.



1-(4-Phenylbutyl)naphthalen-2-ol (5.2ai): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Colorless liquid. Yield: 64 mg, 60%. IR (DCM; cm^{-1}): 3025, 2925, 2855, 1777, 1675, 1563, 1465, 1278, 1191, 945, 750. ^1H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.41-7.37 (m, 1H), 7.27-7.08 (m, 7H), 6.96 (d, J = 8.8 Hz, 1H), 4.80 (s, 1H), 2.98 (t, J = 7.7 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.76-1.61 (m, 4H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 150.49, 142.69, 133.33, 129.59, 128.75, 128.58, 128.52, 128.45, 127.76, 126.47, 125.84, 123.17, 120.30, 117.79, 35.98, 31.69, 29.50, 25,00. HRMS (ESI) m/z calcd for $C_{20}H_{20}O(M+H)^+$: 276.1514, found: 276.1519.



1-Benzyl-1-bromonaphthalen-2(1H)-one (5.3a)[2]: Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Colorless liquid. Yield: 66 mg, 85%. ^1H NMR (400 MHz; $CDCl_3$): δ 7.87 (d, J = 7.9 Hz, 1H), 7.42 (td, J_1 = 7.7 Hz, J_2 =1.3 Hz, 1H), 7.26 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.15—7.10 (m, 2H), 7.01—6.93 (m, 3H), 6.70 (dt, J_1 =8.0 Hz, J_2 = 2.0 Hz, 2H), 6.10 (d, J = 9.9 Hz, 1H), 4.01 (dd, J_1 =144.4 Hz, J_2 = 13.4 Hz, 2H). $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 193.85, 144.87, 141.26, 135.13, 130.53, 130.27, 130.20, 129.81, 129.11, 128.25, 127.03, 124.43, 60.59, 47.11.



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^{1}H and ^{13}C NMR Spectra of 1-alkyl-2-naphthol derivatives:

Figure 5.4 ^{1}H NMR spectrum of 1-benzylnaphthalen-2-ol **5.2a**:

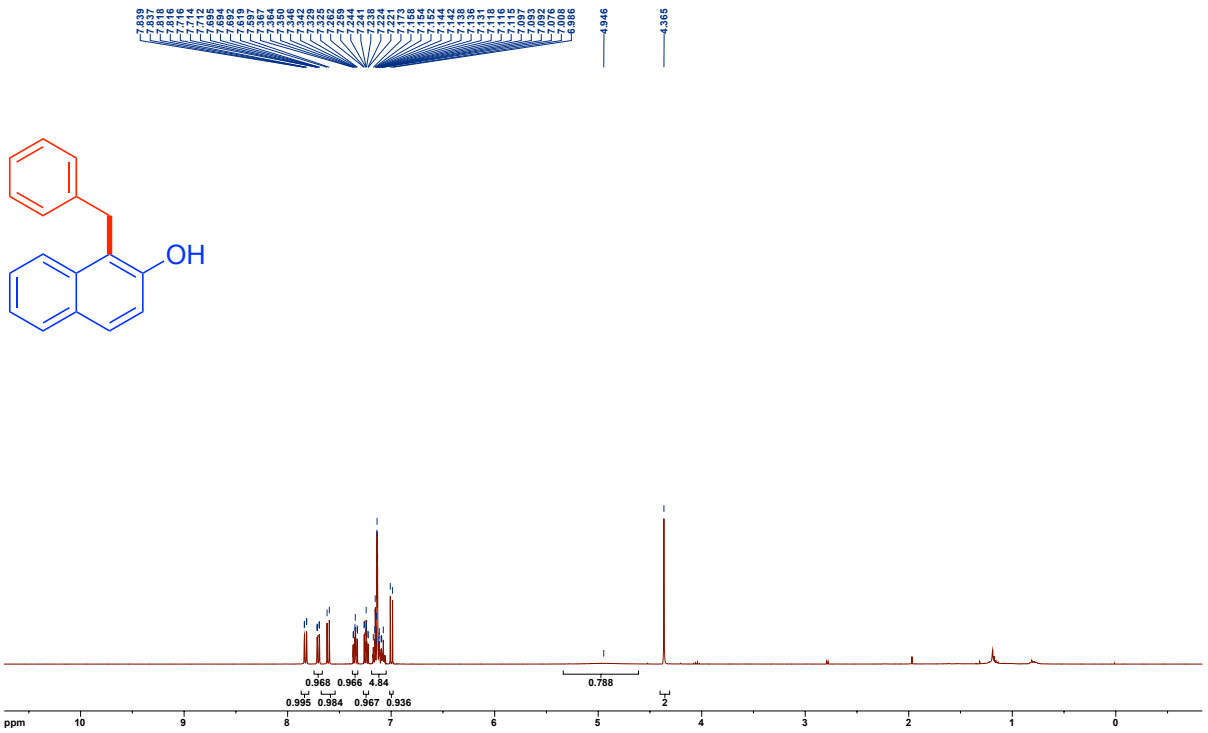


Figure 5.5 ^{13}C NMR spectrum of 1-benzylnaphthalen-2-ol **5.2a**:

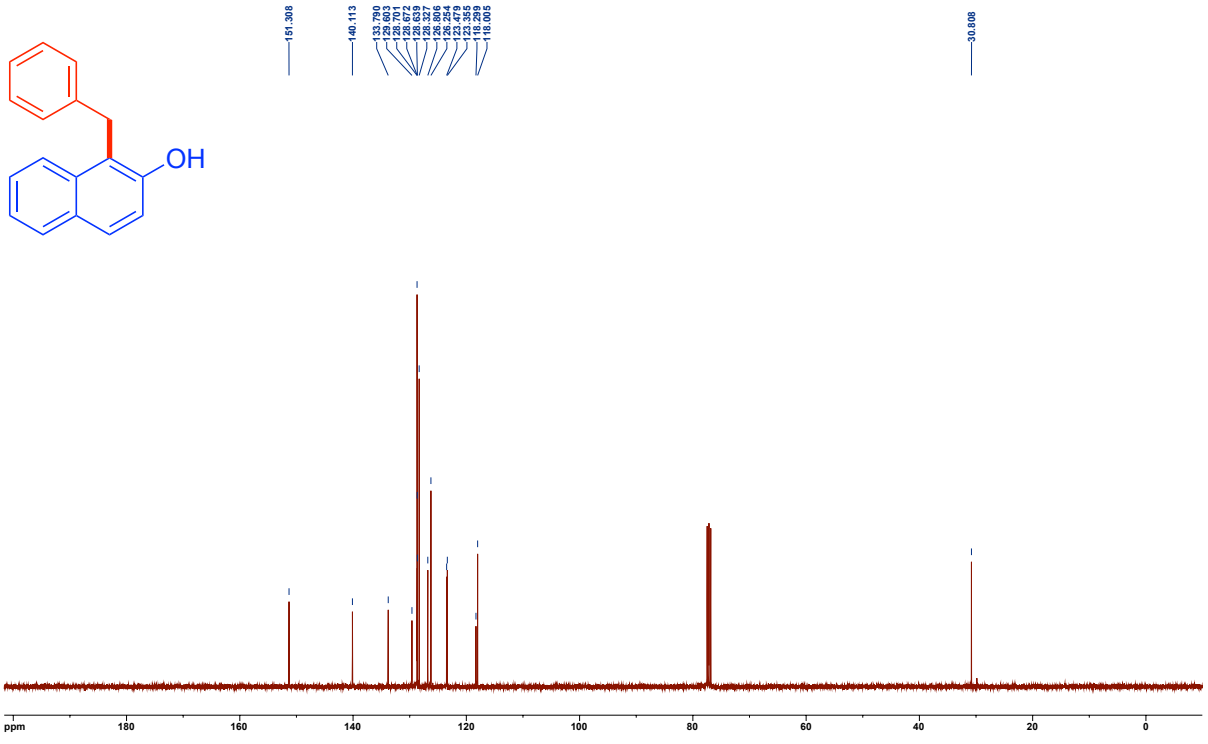


Figure 5.6 ^{1}H NMR spectrum of 1-((9-ethyl-9*H*-carbazol-3-yl)methyl)naphthalen-2-ol **5.2n**:

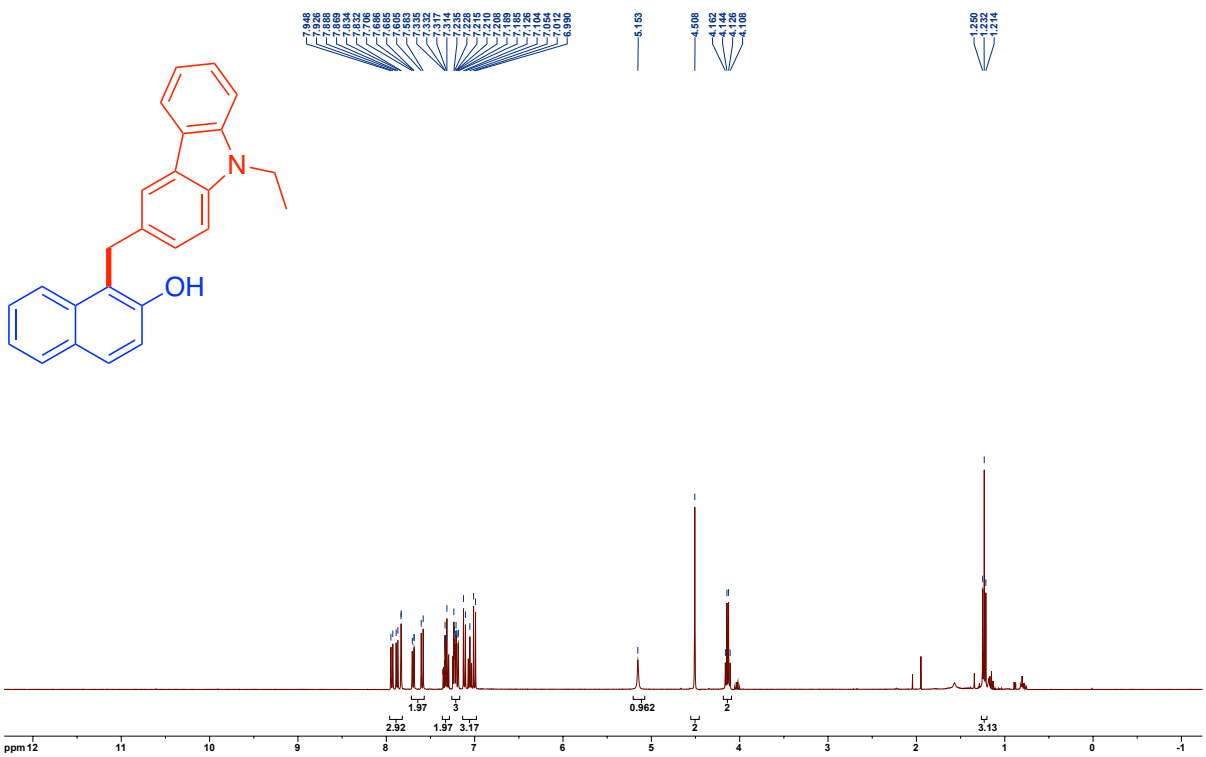


Figure 5.7 ^{13}CNMR spectrum of 1-((9-ethyl-9*H*-carbazol-3-yl)methyl)naphthalen-2-ol **5.2n**:

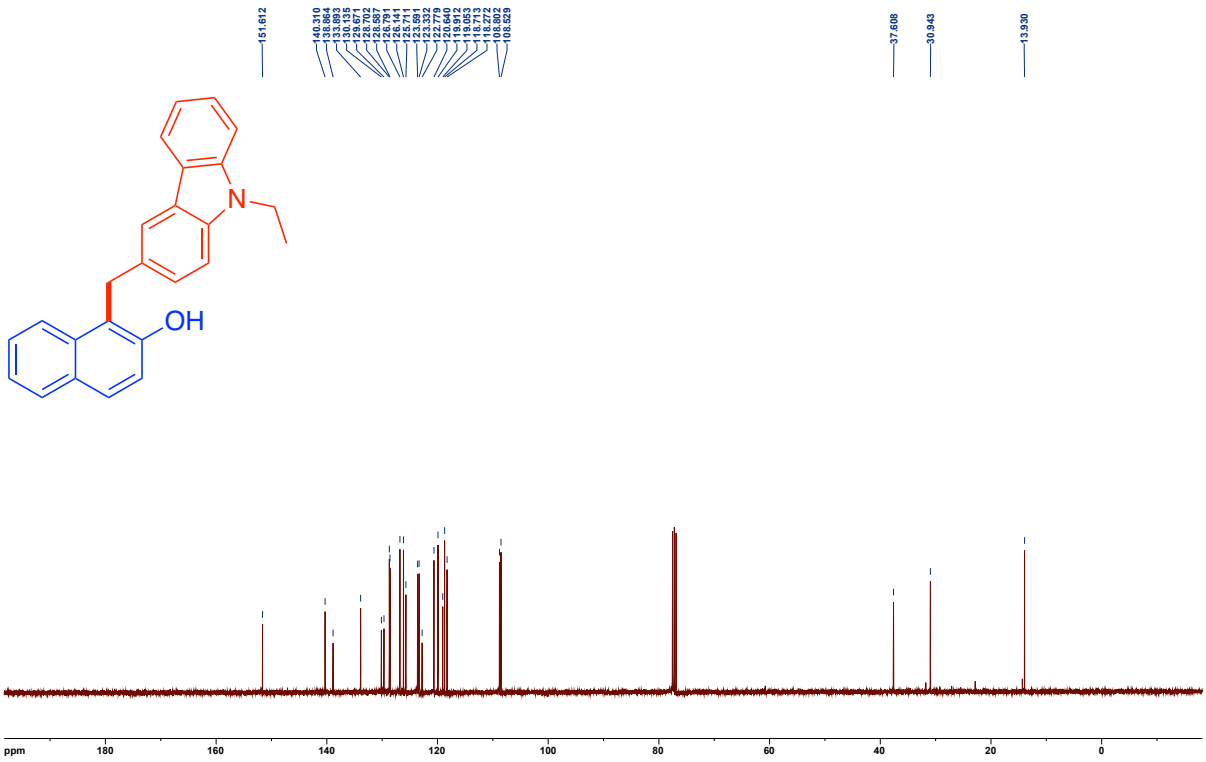


Figure 5.8 ^{1}H NMR spectrum of 1-benzyl-6-bromonaphthalen-2-ol **5.2u**:

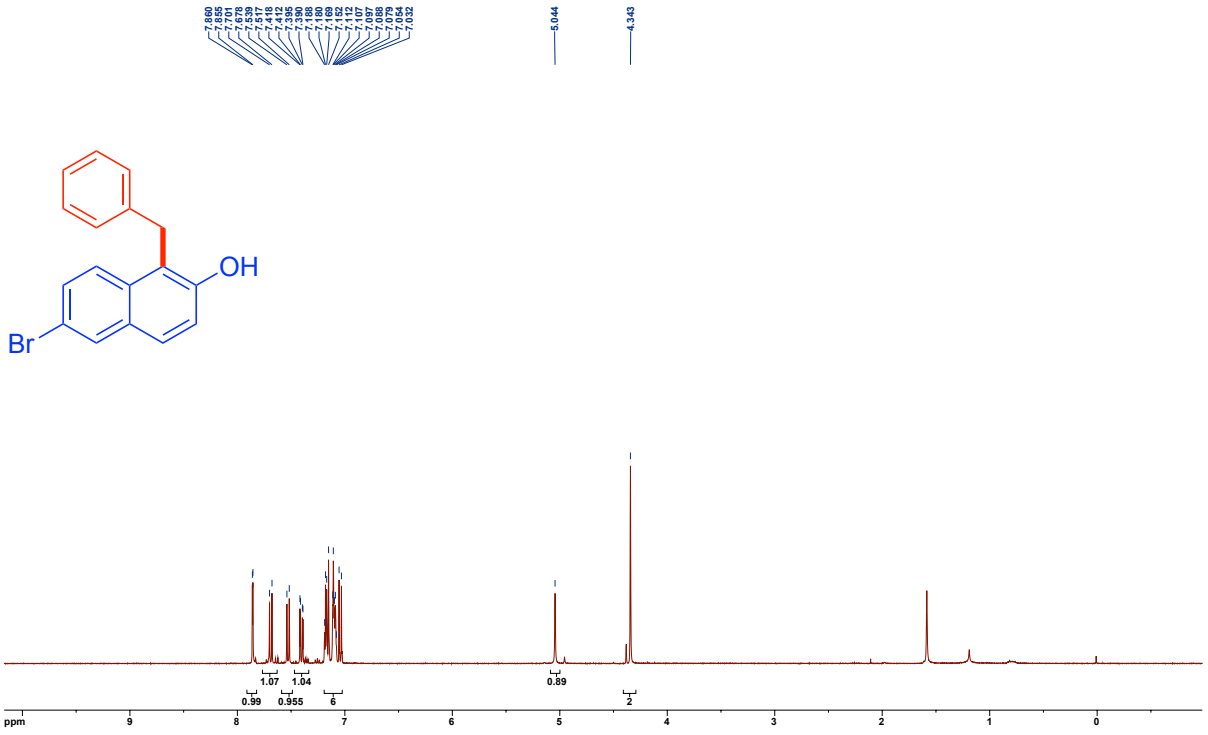


Figure 5.9 ^{13}C NMR spectrum of 1-benzyl-6-bromonaphthalen-2-ol **5.2u**:

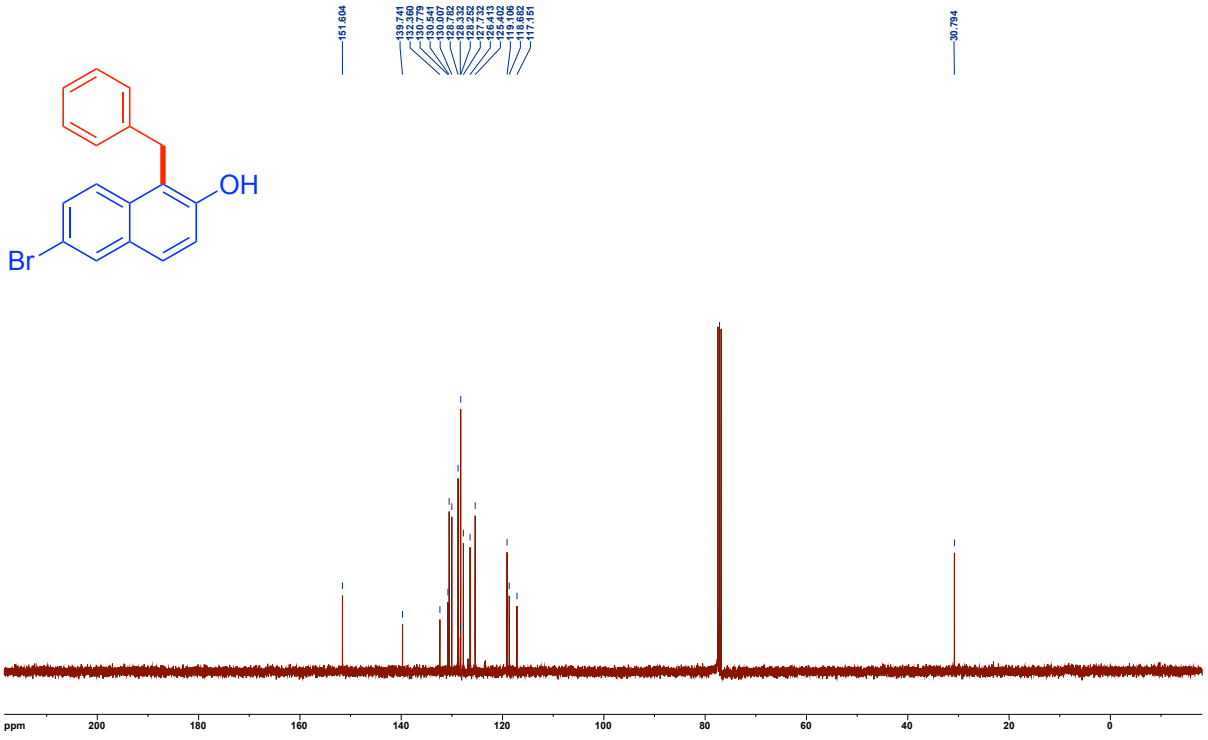


Figure 5.10 ^{1}H NMR spectrum of 1-hexylnaphthalen-2-ol **5.2aa**:

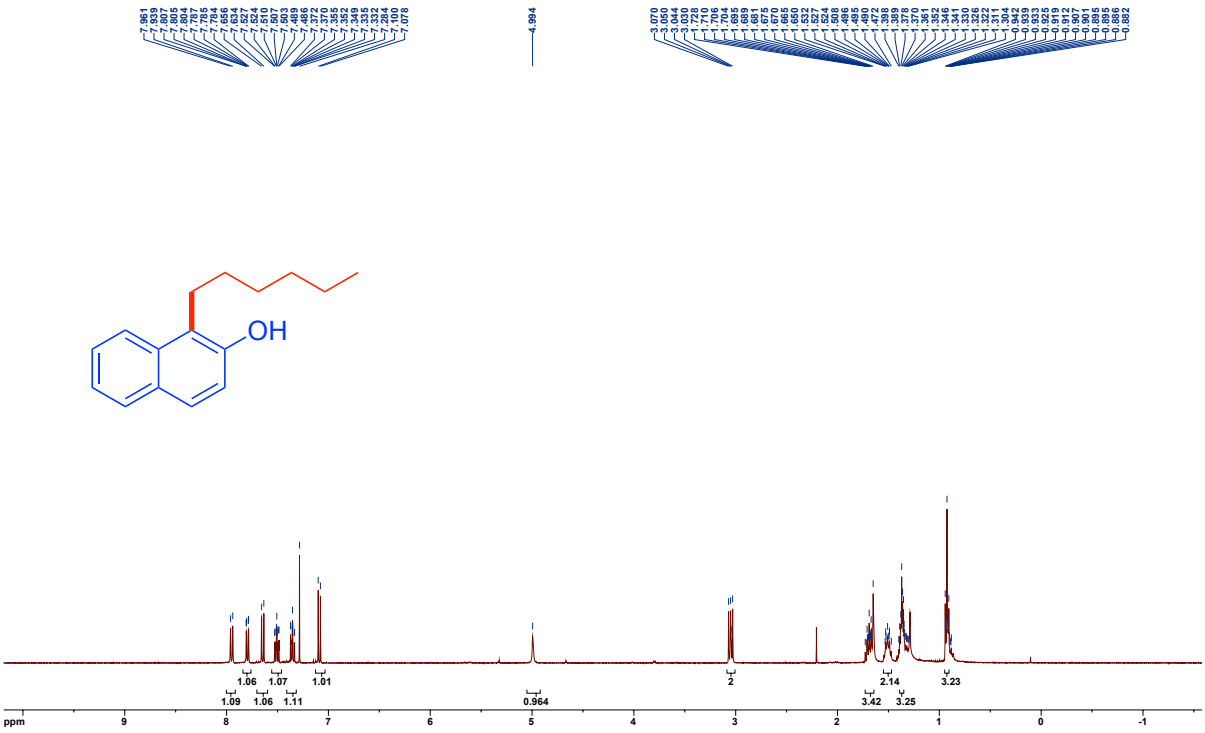


Figure 5.11 ^{13}C NMR spectrum of 1-hexylnaphthalen-2-ol **5.2aa**:

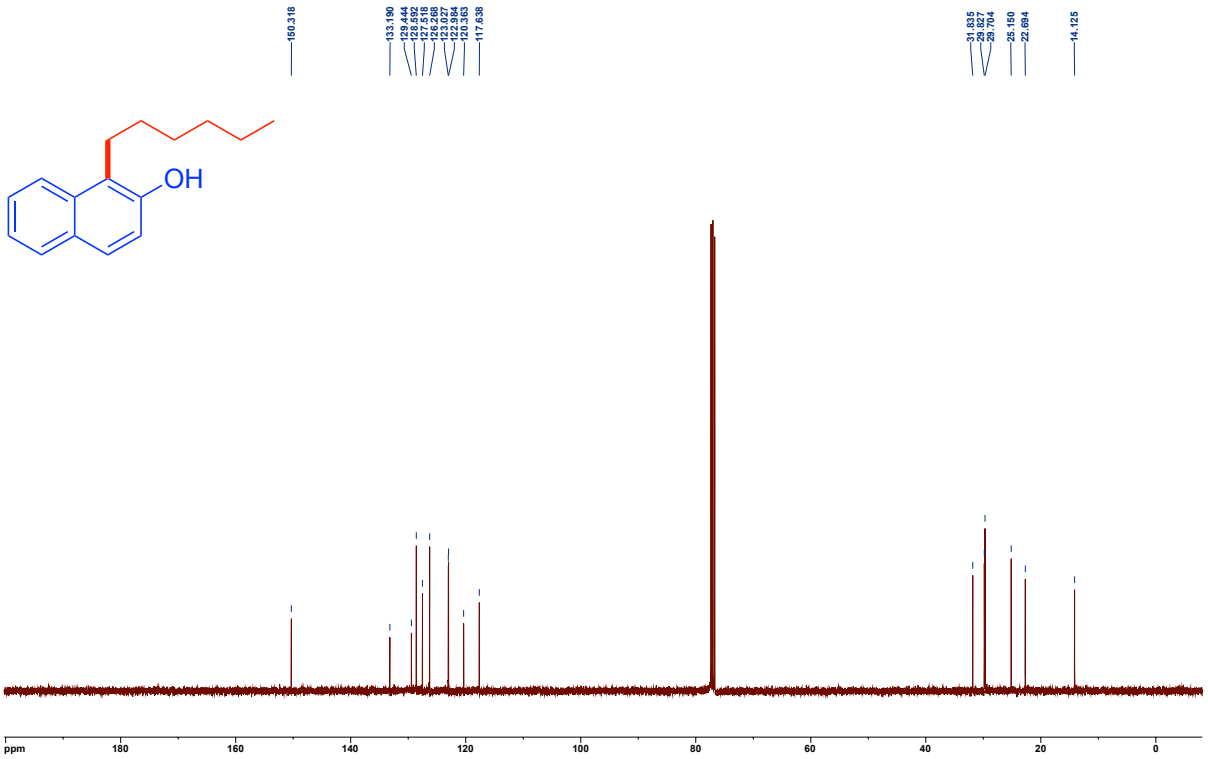


Figure 5.12 ^{1}H NMR spectrum of **5.2a-d2**:

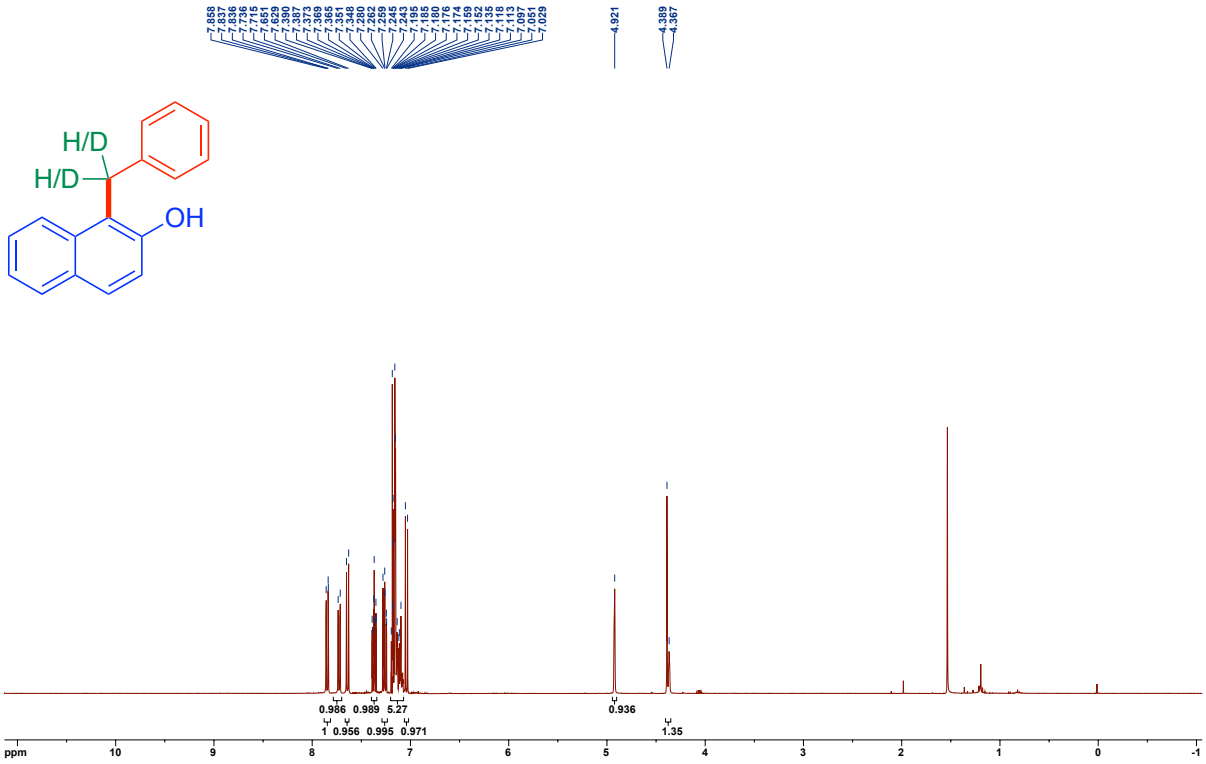


Figure 5.13 ^{13}C NMR spectrum of **5.2a-d2**:

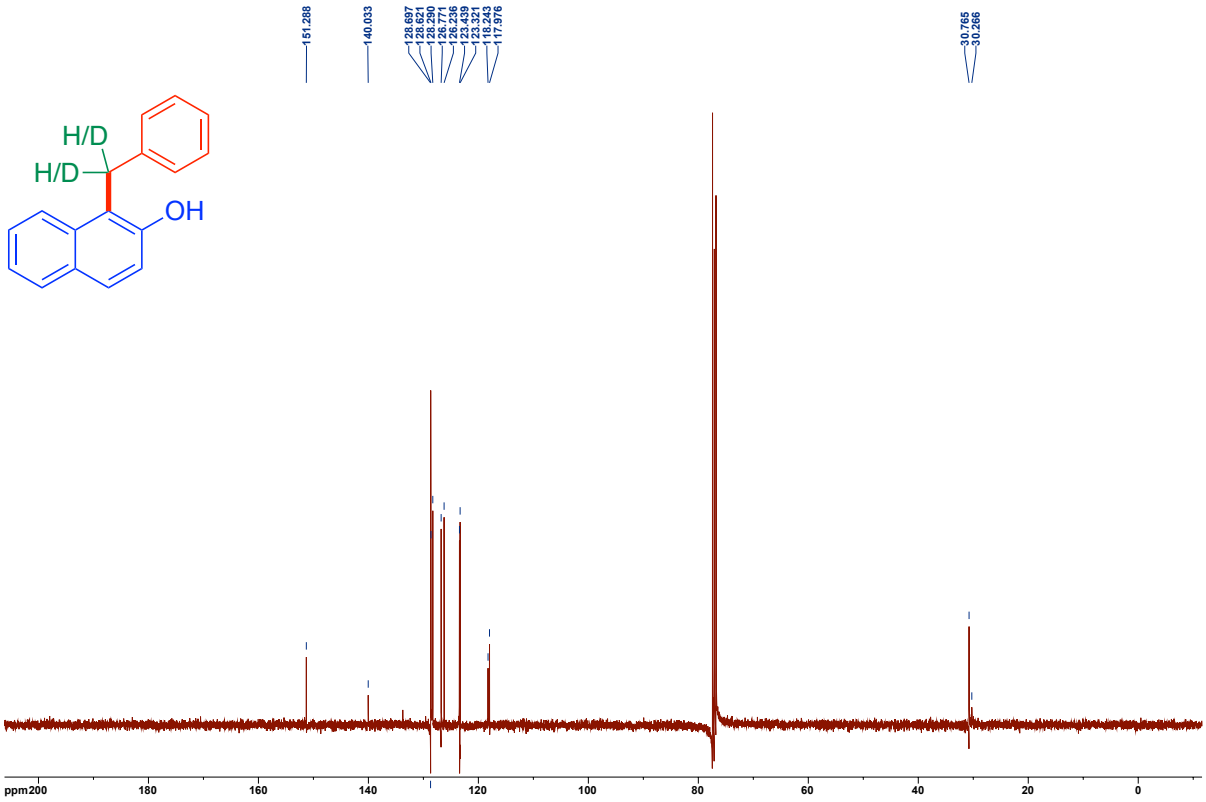


Figure 5.14 $^{31}P\{^{1}H\}$ NMR spectrum of Ru-MACHO catalyst **9** :

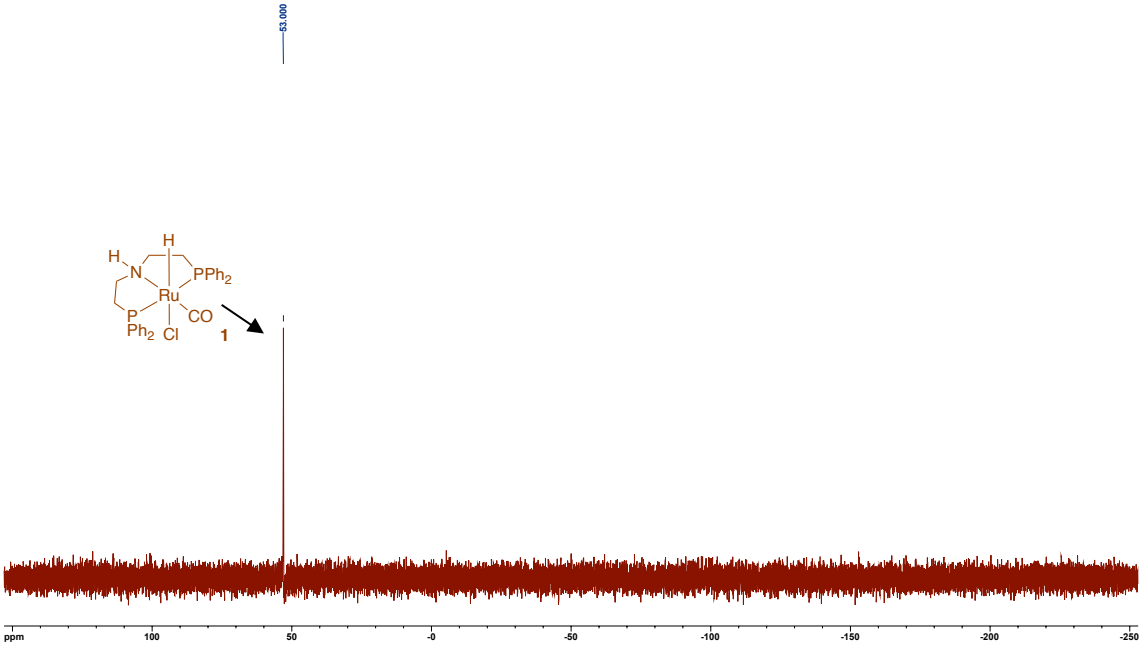


Figure 5.15 $^{31}P\{^{1}H\}$ NMR spectrum of crude reaction mixture: *signals correspond to molecular intermediates formed from catalyst* ***9****, and there is no free PNP ligand present.*

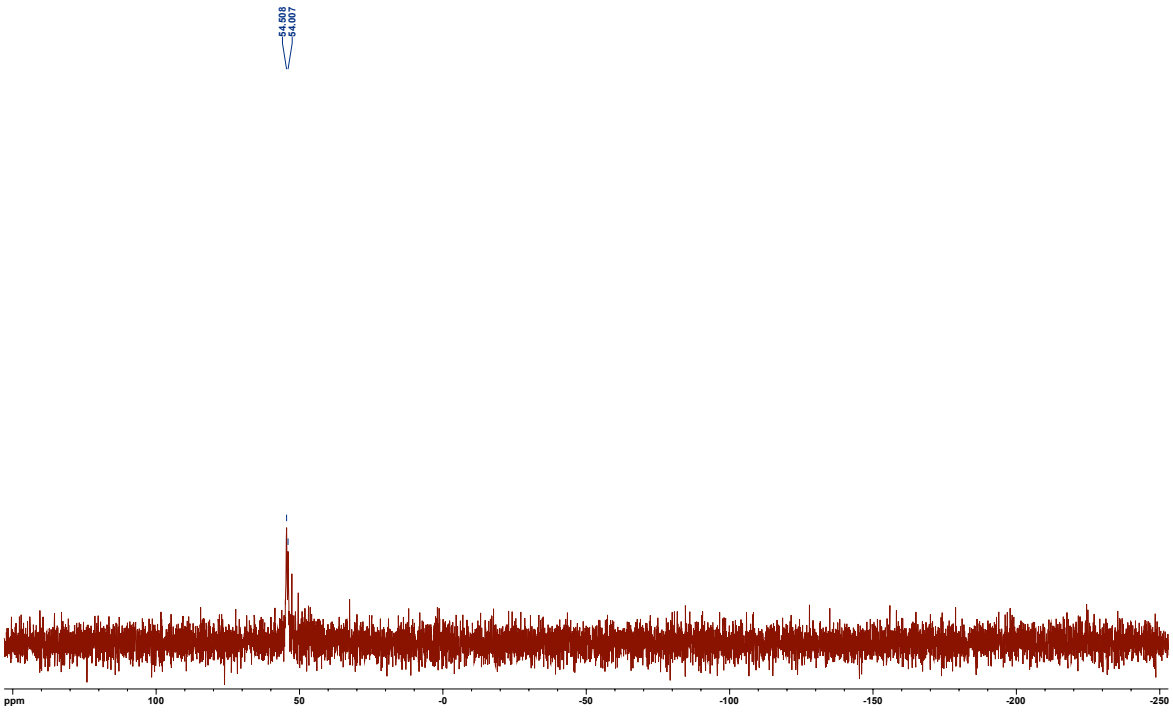
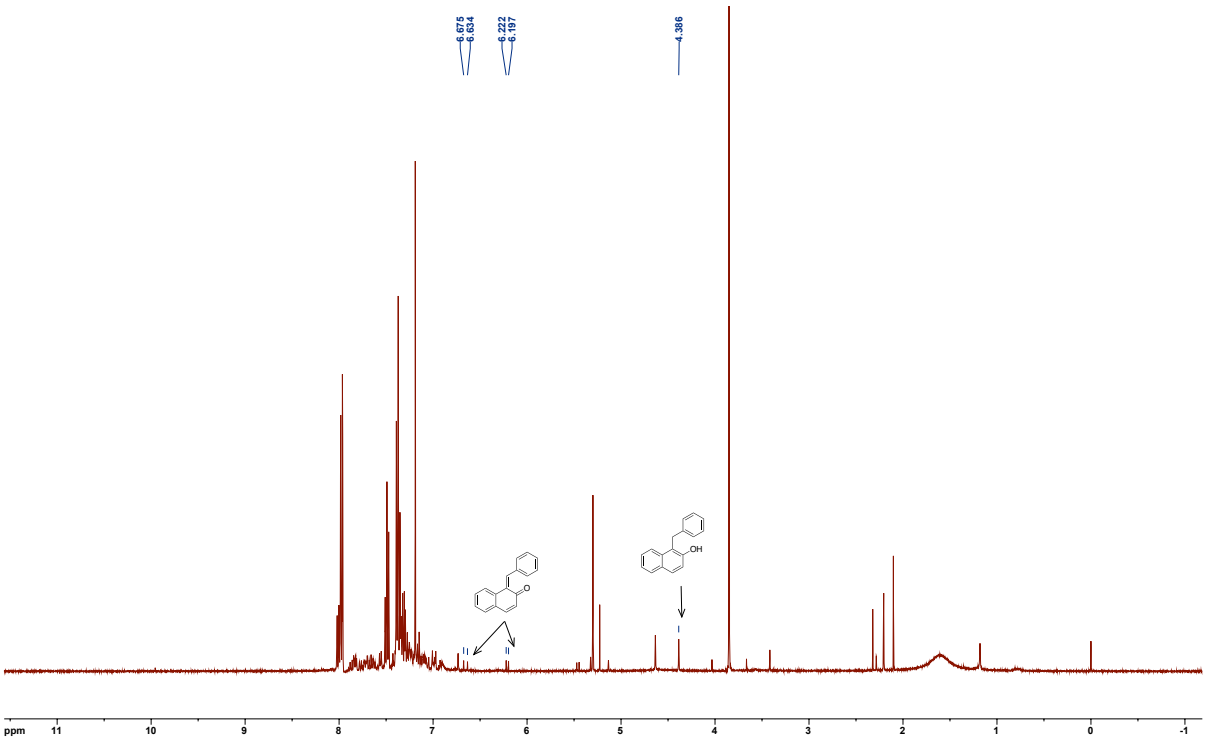


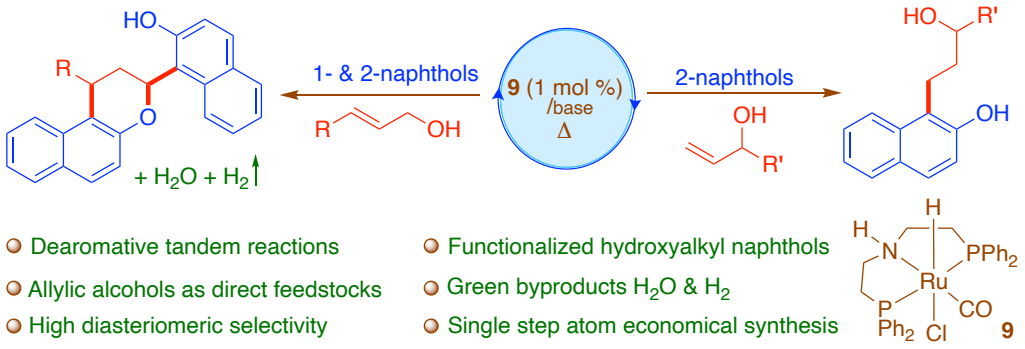
Figure 5.16 ^{1}H NMR spectrum of intermediate **4** obtained from crude reaction mixture at 18 h



CHAPTER 6

Synthesis of Functionalized Benzo[*f*]chromanes and Hydroxyalkyl Naphthols: Catalytic Coupling of Naphthols and Allylic Alcohols

6.1 ABSTRACT

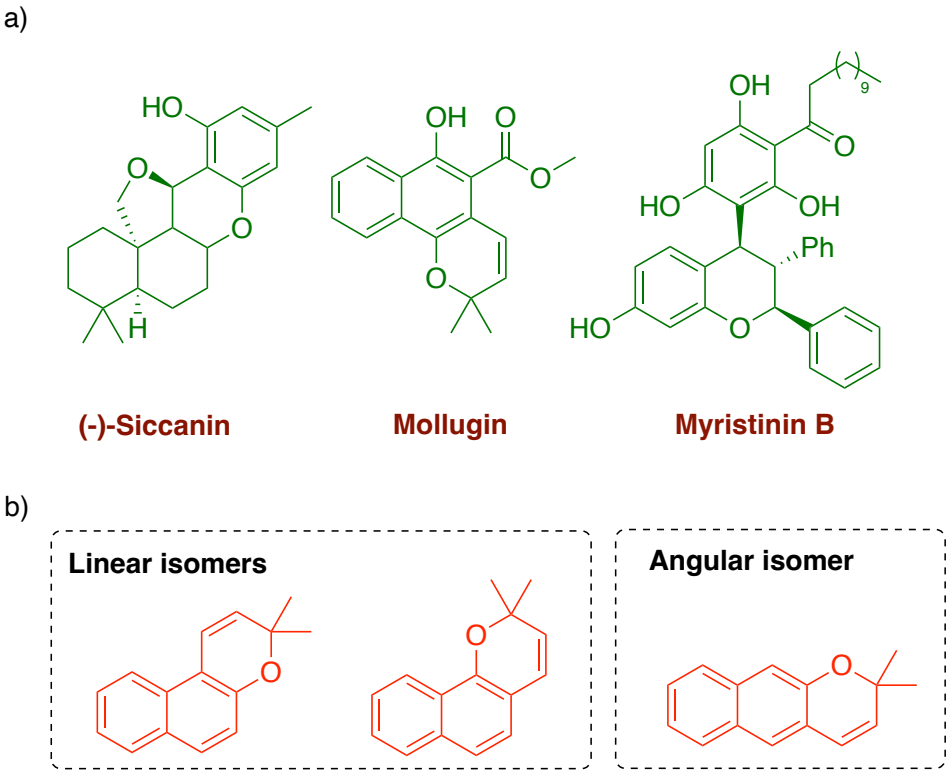


Catalytic dearomatization of arenols is an uphill task that can serve as a powerful method to construct C-C bonds with unsaturated coupling partners. Herein, a simple and efficient strategy for coupling naphthols with allylic alcohols is reported. A single Ru(II) pincer catalyzed coupling of naphthols with primary allylic alcohols led to the formation of benzo(f)chromanes, whereas the use of secondary alcohols delivered the hydroxyalkyl naphthols. Broad substrate scope and good functional group tolerance are demonstrated. Notably, a high diastereoselectivity is attained on chromanes. Hydroxyalkyl naphthols are synthetically transformed into spiroethers, and dearomative bromination is achieved on chromanes. Mechanistic studies revealed the involvement of tandem reactions, a formal O-H bond activation of allylic alcohols by an active catalyst via amine-amide metal-ligand cooperation provided α,β-unsaturated carbonyl intermediates, which further underwent 1,4 conjugate addition with dearomatized naphthols. One of the crucial intermediates, naphthyl radical, is elucidated by EPR studies and trapped using a radical scavenger. Liberated hydrogen and water molecules are the only byproducts in these transformations.

6.2 INTRODUCTION

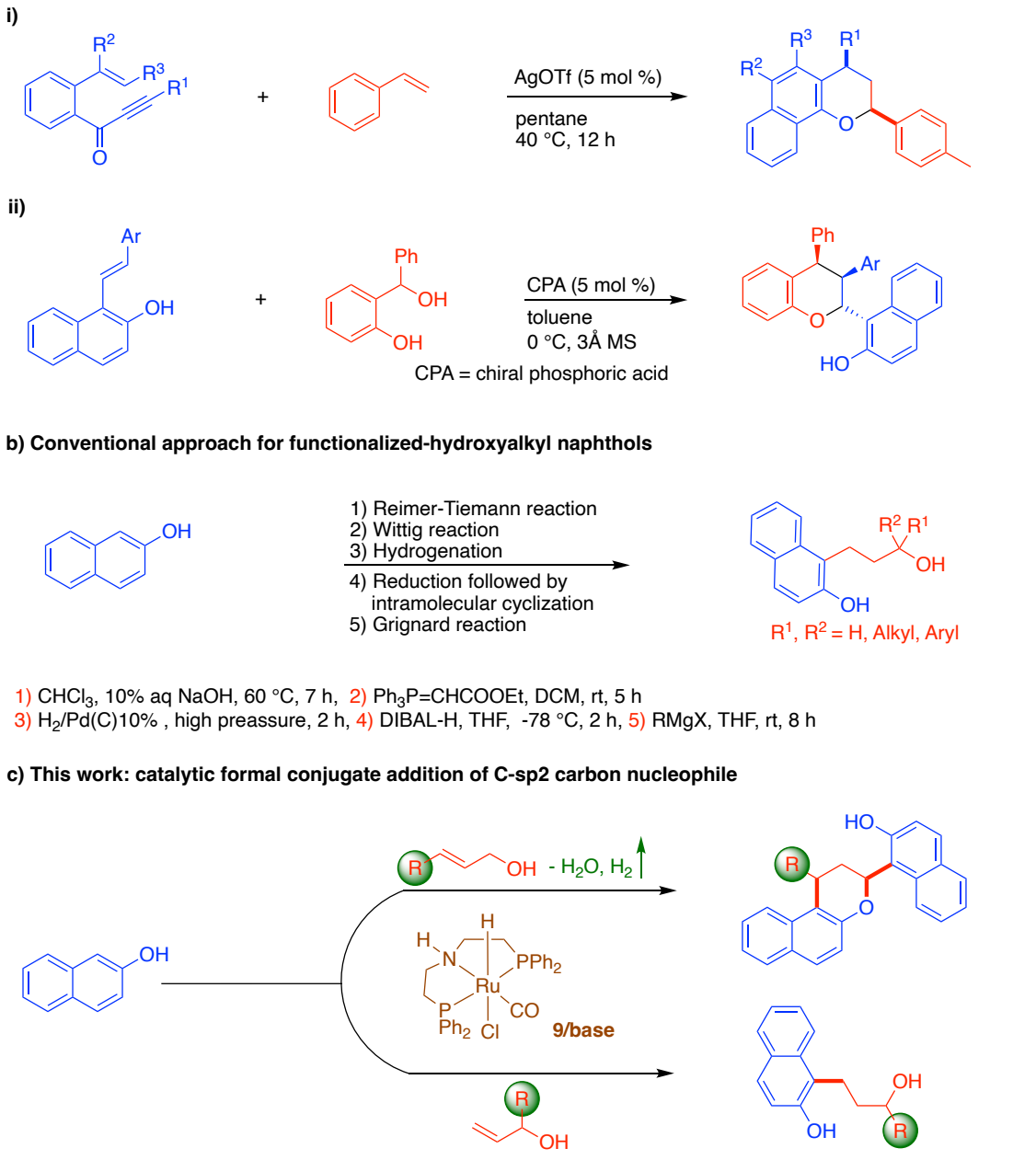
Onset from the development of Michael addition reactions,[1] conjugate addition reaction in organic synthesis is undisputed, and various elegant approaches have been engendered for the addition of carbon nucleophiles to unsaturated functional motifs.[2] Construction of C-C bonds on arenols through dearomatized transient nucleophilic species with electrophiles is an important reaction, which has diverse application in synthesis of valuable building blocks.[3] Chromanes are important scaffolds in heterocycles with widespread natural occurrence and applications in diverse fields.[4] Of particular interest is the class of benzo[*f*]chromanes or dihydronaphthopyrans, which possess vital advantages among bioactive and pharmaceutically related molecules (Figure 6.1a).[5,6] These compounds serve as indispensable and ideal targets in drug discovery.[7,8]In addition, the angularly fused naphthopyran derivatives show better photochromic properties than the linear fused motifs (Figure 6.1b).[9]

Figure 6.1. Representative Examples of Naturally Occurring Chromanes and their Skeletal Arrangements.



Synthetic strategies towards chromane derivatives involve the reaction of *ortho*-quinone methides with alkenes, organocatalyzed asymmetric reactions, and Michael addition reactions.[10,11] Lewis acid mediated intramolecular cyclization of enynones with alkenes is reported to deliver benzo[*h*]chromane derivatives (**Scheme 6.1a-i**).[12] Using a chiral phosphoric acid, asymmetric [4+2] cycloaddition of functionalized 2-naphthol derivatives with ortho-substituted phenols was attained exploring the reactivity of in situ generated *ortho*-quinone methides (**Scheme 6.1a-ii**).[13] Recently, Ramasastry reported the palladium catalyzed formal [3+3] heteroannulation strategies for the synthesis of benzo[*f*]chromenes.[14] Functionalized hydroxyalkyl naphthol derivatives are found to be serving as the essential starting materials in the synthesis of dearomative spiro-ether and spiro-amidation reactions.[15] Conventional methods towards the hydroxyalkyl naphthols require elongated and multistep synthesis (**Scheme 6.1b**),[15] involving harsh conditions and tedious procedures. Notably, there is no catalytic method known for the synthesis of hydroxyalkyl naphthols. Thus, catalytic synthesis of hydroxyalkyl naphthols scaffolds using readily available starting materials is highly desirable. Our group has developed catalytic protocols based on borrowing hydrogen and acceptorless dehydrogenation strategies using alcohols and allylic alcohols.[16-18] Recently, ruthenium catalyzed selective α-alkylation of β-naphthols using primary alcohols was attained.[19] In continuation, catalytic coupling of allylic alcohols with naphthols was envisaged leading to the dearomative conjugate addition reactions. A single pincer catalyst, upon reaction with naphthols and primary allylic alcohols, delivered functionalized benzo[*f*]chromanes or dihydronaphthopyrans, and with secondary allylic alcohols produced hydroxyalkyl naphthols (**Scheme 6.1c**).

Scheme 6.1. Synthetic Methods for Chromane Derivatives and Hydroxyalkyl Naphthols

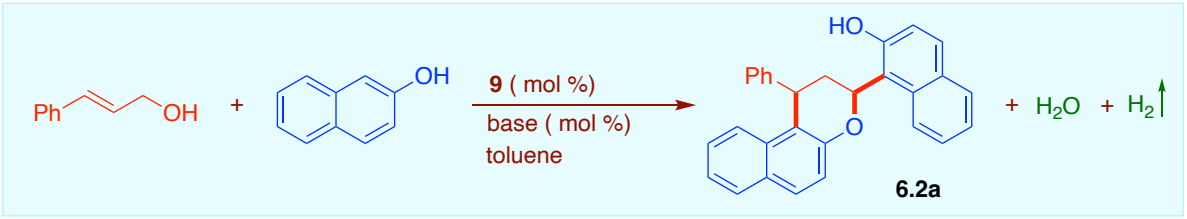


6.3 RESULTS AND DISCUSSION

At the outset, the reaction of 2-naphthol (2 equiv, 1 mmol) with cinnamyl alcohol (1 equiv, 0.5 mmol) in the presence of catalyst **9** (1 mol %) with a base NaOH (20 mol %) at 100 °C was tested, which provided the chromane product in 60 % yield after 24 h (entry 1, **Table 6.1**). When a similar reaction was carried out using a higher amount of base, yield of the product

diminished to 53 % (entry 2, **Table 6.1**). Hence, a reaction was performed using increased catalyst loading of **9** (2 mol %), temperature (135 °C), and reaction time (36 h), which delivered the desired chromane product in 67% yield (entry 3, **Table 6.1**). Further, the experiments employing higher amounts of base (30 and 40 mol %) produced the products in 70 and 80% yield, respectively (entries 4 and 5, **Table 6.1**). Catalytic reactions carried out using stronger alkoxide bases were found to be ineffective (entries 6-8, **Table 6.1**). A control reaction was performed in the absence of catalyst **9** and using base alone, which resulted in no formation of the chromane product, which indicates the necessity of the catalyst for this transformation (entry 9, **Table 6.1**).

Table 6.1. Optimization Studies for Reaction of 2-Naphthol with Cinnamyl Alcohol[a]



entry	cat (mol %)	base (mol %)	temp (°C)	time (h)	yield (%)[b]
1	1	NaOH (20)	100	24	60
2	1	NaOH (30)	100	24	53
3	2	NaOH (20)	135	36	67
4	1	NaOH (30)	135	36	70
5	**1**	NaOH (40)	**135**	**36**	**80**
6	1	LiO^{t}Bu (40)	135	36	70
7	1	LiO^{t}Bu (50)	135	36	60
8	1	KO^{t}Bu (20)	135	36	28
9	-	NaOH (20)	135	36	--

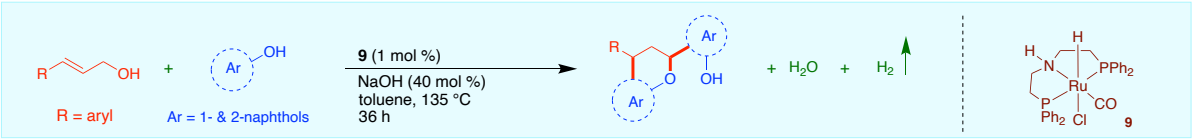
[a]Reaction condition: cinnamyl alcohol (1 equiv, 0.5 mmol), 2-naphthol (2 equiv, 1 mmol), catalyst **9** and base in toluene were refluxed at an indicated temperature and time under nitrogen

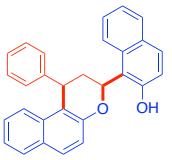
atmosphere. Catalyst and base loading are taken relative to limiting reagent cinnamyl alcohol loading. [b]Yield corresponds to isolated pure products after column chromatography.

Having optimized the experimental condition, the synthetic scope for functionalized benzo[*f*]chromanes was explored by employing diverse allylic alcohols (**Scheme 6.2**). Cinnamyl alcohol with electron-donating alkyl substituents provided the corresponding chromane derivatives **6.2b** and **6.2c** in 68 and 86% yield, respectively, with high diastereomeric ratios. Methoxy, methylenedioxy, aryloxy substituted cinnamyl alcohols provided respective products **6.2d-6.2h** in moderate to good yields. Notably, reactive functional groups such as cyano (**6.2i**), N,N-dimethyl amine (**6.2j**), carbamate (**6.2k**) and sulfonate (**6.2l**) on aryl ring of cinnamyl alcohol were tolerated. Cinnamyl alcohols bearing electron withdrawing groups such as halides (**6.2m-6.2o**) and trifluoromethyl (**6.2p**) groups provided the anticipated products in good yields. 2-Napthyl and 2-pyrene containing chromanes **6.2q** and **6.2r** were obtained from polyaryl allylic alcohols. Remarkably, furan and thiophene containing heteroaryl allylic alcohols were catalytically converted to the corresponding products **6.2s-6.2u**.

The scope of different naphthols was investigated. 1-Naphthol reacted with cinnamyl alcohol to deliver the desired product **6.2aa** in moderate yield with the d.r ratio of 50:50. β-Naphthol bearing substitutions such as (4-*tert*-butyl)phenyl at the 7-position reacted to deliver the product **6.2ab**. Methoxy and terpenyloxy substituents at the 7-position of β-naphthol were also tolerated (**6.2ac** and **6.2ad**). Notably, the C=C double in terpenyl unit is retained in product **6.2ad**. 6-Bromo-2-naphthol provided the chromane derivative **6.2ae** in good yield. While good diastereoselectivity was observed in all products, diminished selectivity displayed by **6.2u, 6.2aa and 6.2ab** perhaps attributable to the electronic effects of cinnamyl alcohol and naphthol derivatives employed in these reactions.

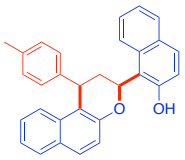
Scheme 6.2. Catalytic Coupling of Naphthols with Diverse Primary Allylic Alcohols[a]



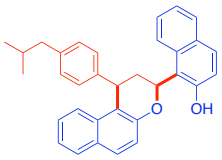


6.2a, 80%, d.r = 87:13

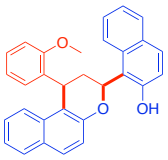
6.2a



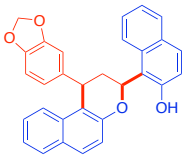
6.2b, 68%, d.r = 86:14



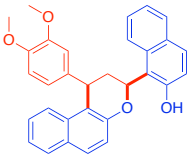
6.2c, 86% , d.r = 88:12



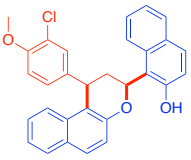
6.2d, 70% , d.r = 90:10



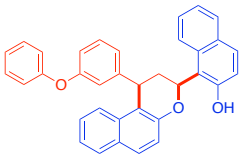
6.2e, 72% , d.r = 84:16



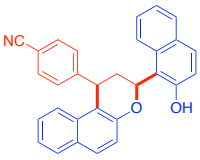
6.2f, 71% , d.r = 87:13



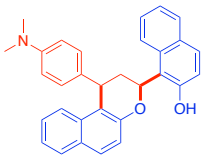
6.2g, 40% , d.r = 89:11



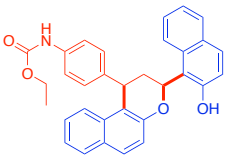
6.2h, 60% , d.r = 88:12



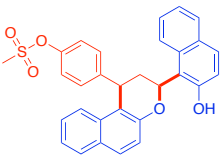
6.2i, 47% , d.r = 80:20



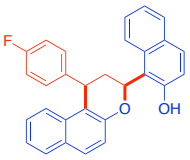
6.2j, 80% , d.r = nc



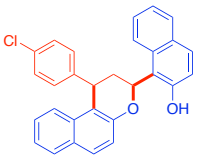
6.2k, 40% , d.r = 83:17



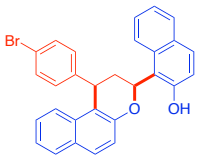
6.2l, 20% , d.r = nc



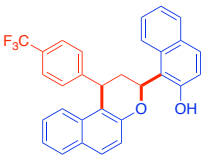
6.2m, 60% , d.r = 89:11



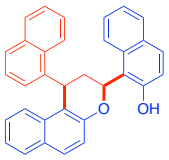
6.2n, 65% , d.r = 87:13



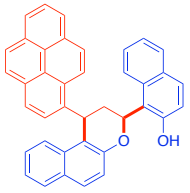
6.2o, 70% , d.r = 87:13



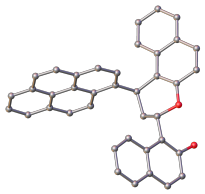
6.2p, 48% , d.r = 84:16



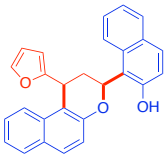
6.2q, 78% , d.r = 90:10



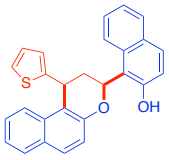
6.2r, 67% , d.r = nd



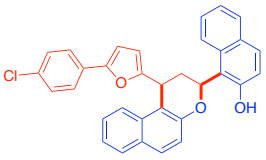
6.2r



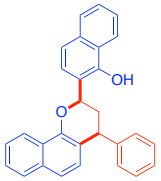
6.2s, 61% , d.r = 84:16



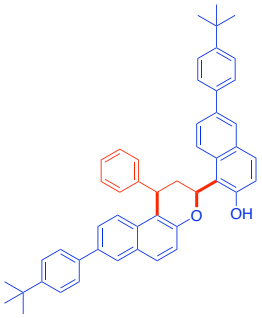
6.2t, 75% , d.r = 90:10



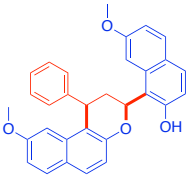
6.2u, 68% , d.r = 50:50



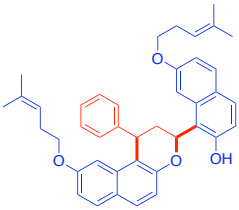
6.2aa, 48%[b] , d.r = 50:50



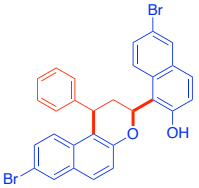
6.2ab, 67% , d.r = 54:46



6.2ac, 69% , d.r = 85:15



6.2ad, 58% , d.r = 82:18



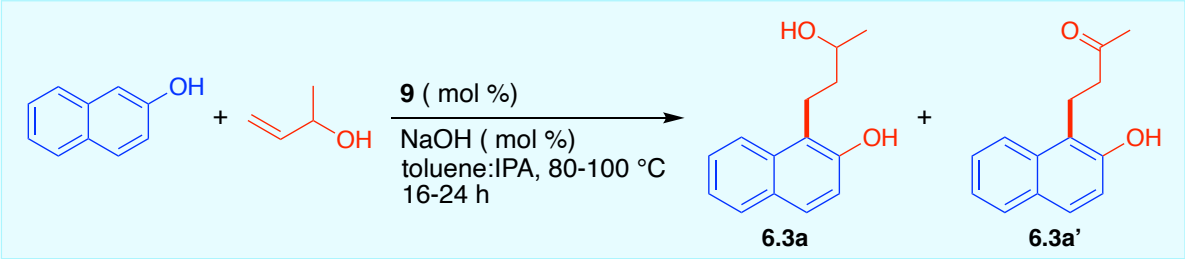
6.2ae, 81% , d.r = 88:12

[a]Reaction condition: primary allylic alcohol (1 equiv, 0.5 mmol), naphthol (2 equiv, 1 mmol), catalyst **9** (1 mol %), NaOH (40 mol %), toluene were charged in a Schlenk tube, and refluxed at 135 ℃ under nitrogen atmosphere for 36 h. d.r ratio was calculated from ^{1}H NMR analysis of crude reaction mixture. Yields were calculated for isolated pure products. [b]Reaction performed at 100℃ under nitrogen atmosphere for 24 h.

The catalytic coupling of secondary allylic alcohols with β-naphthols was investigated next, in which chromane formation was not observed. Preparatory studies revealed that ruthenium pincer **9** catalyzed reaction leads to different products when secondary allylic alcohol was employed. Notably, the hydroxyalkyl or ketoalkyl functionalization at the α-position of β-naphthol was observed (**Table 6.2**). Presumably, the conjugate addition of transient carbon nucleophile resulted from dearomatization of β-naphthol with in situ generated vinylmethyl ketone from secondary allylic alcohol led to the formation of 1-ketoalkyl-β-naphthol, and further catalytic hydrogenation of carbonyl motif produced 1-hydroxyalkyl- β-naphthol. A catalytic reaction was performed using NaOH (20 mol %) as a base at 100 °C for 16 h, which resulted in 23% hydroxylalkyl product **6.3a** and a major amount of keto functionalized β-naphthol **6.3a'** in 53% (entry 1, **Table 6.2**). This observation can be attributed to the challenging hydrogenation of keto functionality as compared with the aldehyde.[18c] Hence, the optimization was directed towards attaining the arduous hydroxylalkyl product **6.3a** by employing a transfer hydrogenation strategy using isopropanol as the additional hydrogen source. Upon performing a catalytic reaction in 1:1 toluene and isopropanol medium, the desired hydroxyalkyl product **6.3a** was obtained in 75% yield (entry 2, **Table 6.2**). The use of higher amount of base (30 and 40 mol %) provided the product **6.3a** in 77 and 80% yield, respectively, with very good selectivity and diminished formation of ketoalkyl compound **6.3a'**

(entries 3 and 4, **Table 6.2**). Control experiments were carried out using base alone and, in the absence of catalyst **9**, failed to provide the desired results (entry 5, **Table 6.2**).

Table 6.2. Optimization for Reaction of 2-Naphthol with Secondary Allylic Alcohol[a]



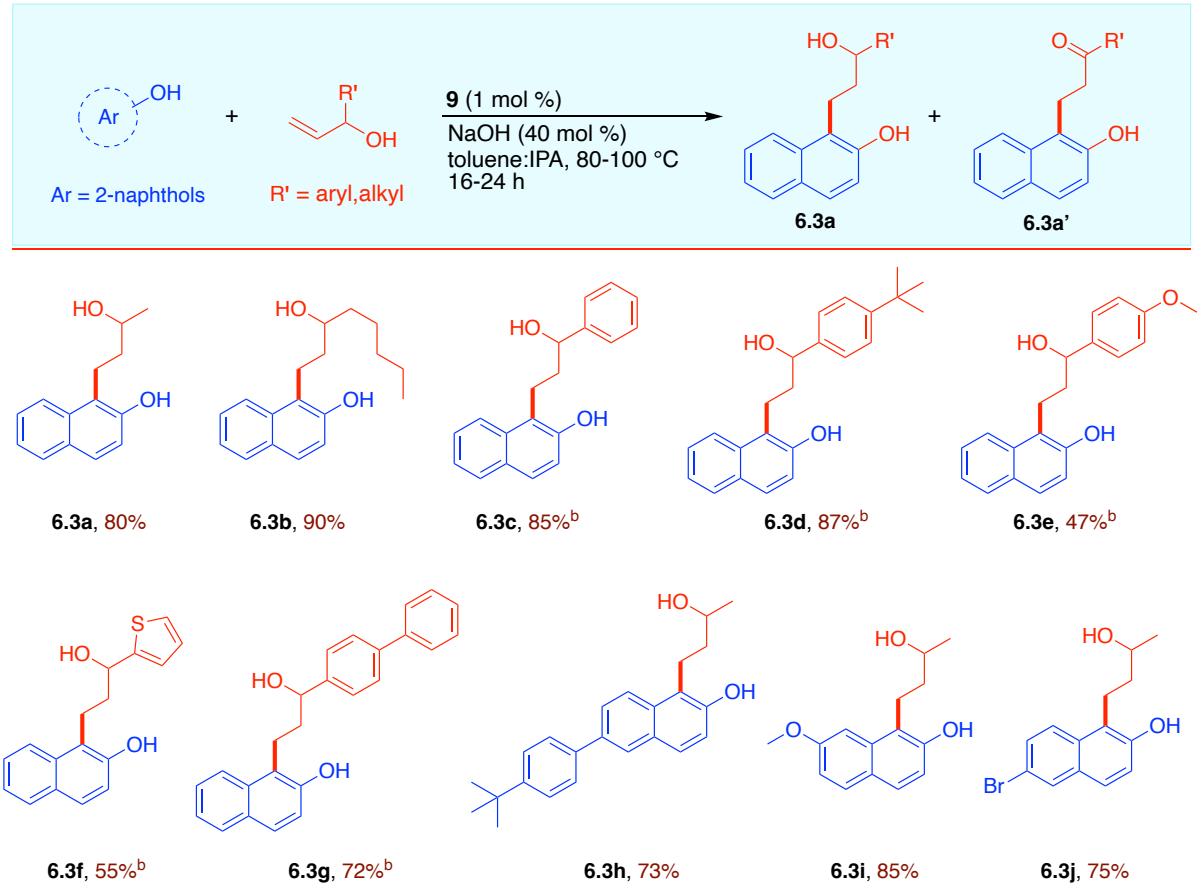
entry	base (mol %)	time(h)	yield(%)	
			6.3	**6.3a'**
1 [b]	20	16	23	53
2	20	16	75	14
3	30	16	77	10
4	**40**	**16**	**80**	**8**
5[c]	40	24	-	-

[a]Reaction condition: 2-naphthol (0.5 mmol, 1equiv), 3-buten-2-ol (1 mmol, 2 equiv), catalyst **9**, base, and toluene:IPA (1:1, 2 mL) were heated at 100 °C under nitrogen flow for indicated time. IPA = isopropyl alcohol. Yields were calculated for isolated pure products. [b]Reaction performed using toluene (2 mL) alone as a solvent. [c]Reaction performed in the absence of catalyst **9**.

With the optimized condition in hand, different secondary allylic alcohols were reacted with naphthol derivatives, which delivered the corresponding hydroxyalkyl functionalized naphthols (**Scheme 6.3**). When 1-octen-3-ol was reacted with 2-naphthol, product **6.3b** was obtained in excellent yield. Different aryl, heteroaryl, and biphenyl-substituted secondary

allylic alcohols were amenable to this reaction, which provided the corresponding products **6.3c-6.3g** in 47-87% yield. Electron-donating and electron-withdrawing substituents on 2-naphthol were tolerated and their representative reaction with 3-butene-2-ol delivered the respective products **6.3h-6.3j** with good yields. The corresponding keto product was formed in minor amounts (5-8%) in all the reactions. As far as we know, there is no catalytic method known for the synthesis of these α-(hydroxyalkyl)- β-naphthols bearing hydroxy functionality.

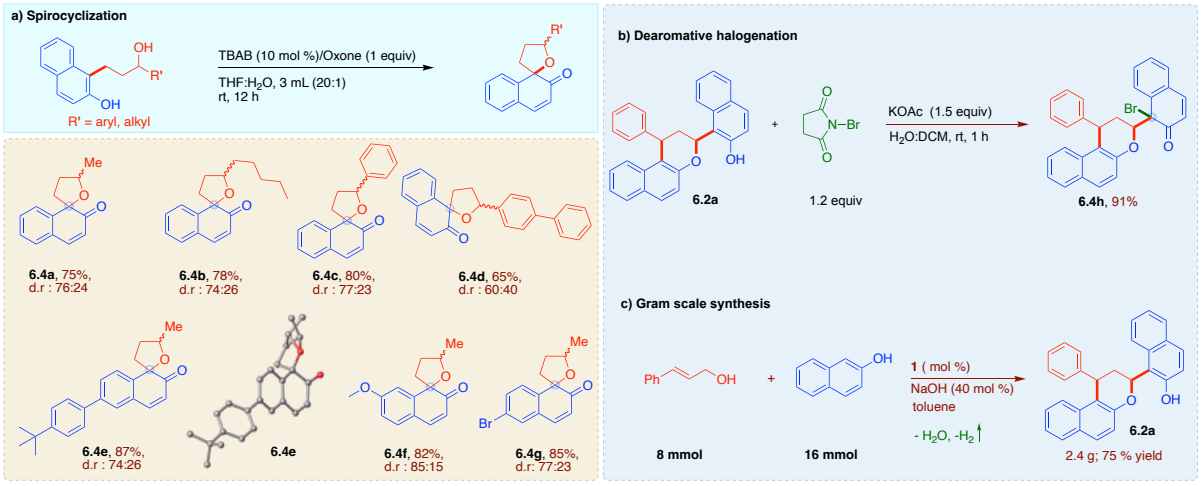
Scheme 6.3. Catalytic Synthesis of (α-Hydroxyalkyl)-2-Naphthols



[a]Reaction condition: b-naphthol (1 equiv, 0.5 mmol), allylic alcohol (2 equiv, 1 mmol), catalyst **9** (1 mol %), NaOH (40 mol %), toluene:IPA (1:1; 2 mL) were added in a Schlenk tube and heated at 100 °C under nitrogen atmosphere for 16 h. Yields correspond to pure isolated products. [b]Reaction was performed at 80 °C for 24 h.

The hydroxyalkyl naphthols were transformed into spiroethers, which resulted in dearomatization of phenolic ring of β-naphthols (**Scheme 6.4a**).[15b] Hydroxyalkyl naphthols bearing both alkyl and aryl substitutions underwent dearomative cyclization providing their corresponding spiroethers **6.4a-6.4g** in moderate to good yields. The spiroether structure of **6.4e** is unequivocally corroborated by the single-crystal X-ray analysis. In order to elaborate the synthetic utility of chromane, the reaction of product **6.2a** in presence of N-bromosuccinamide under mild basic condition was carried out, which provided the dearomative halogenated product **6.4h** in very good yield (**Scheme 6.4b**).[19] In order to demonstrate the practicality of this method, a gram-scale synthesis was performed which delivered the chromane product **6.2a** in 75% isolated yield (**Scheme 6.4c**).

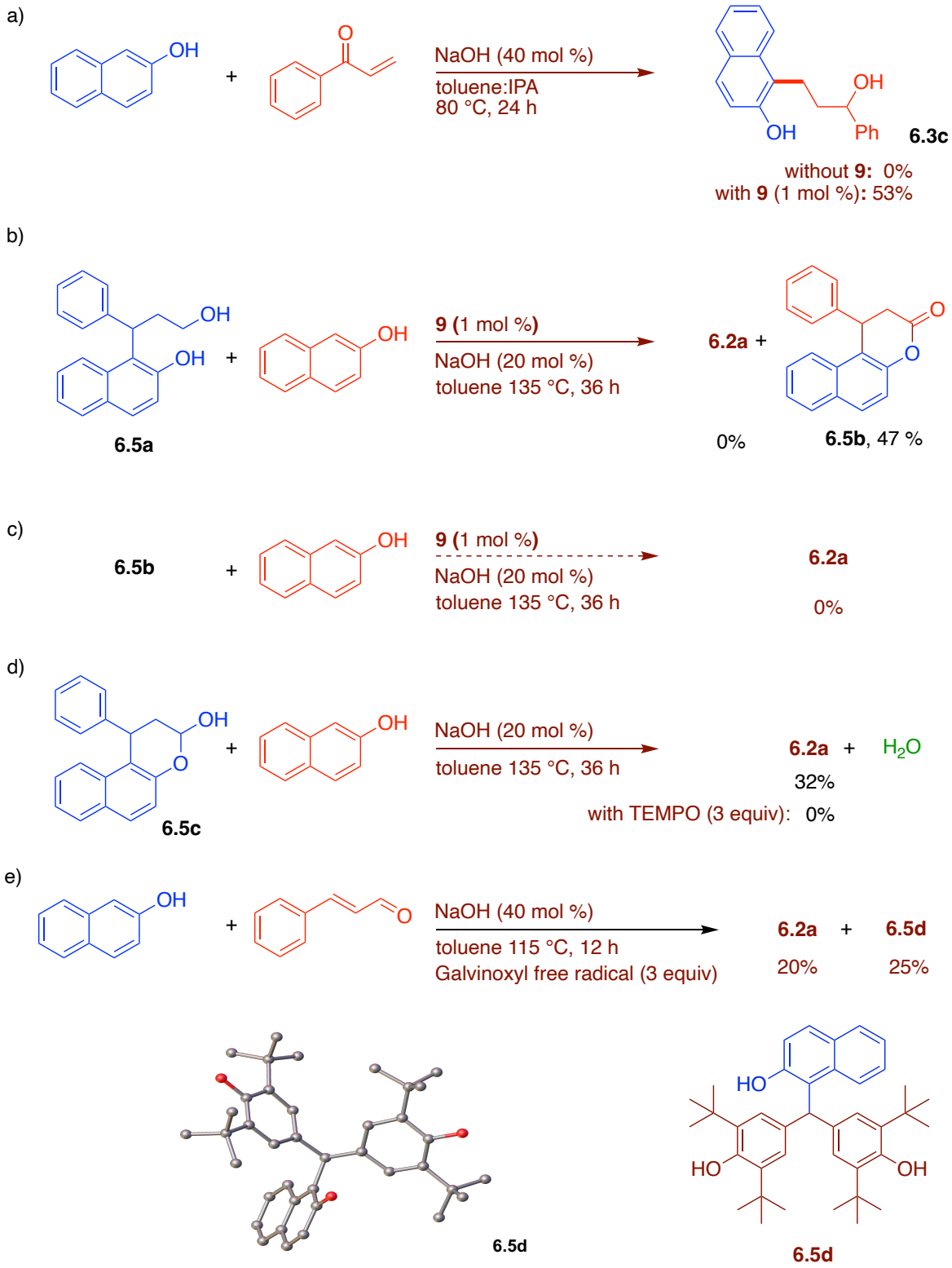
Scheme 6.4. Synthesis of Spiroethers from Hydroxyalkyl Naphthols, Dearomative Bromination of Chromane[a] and Gram Scale Synthesis



[a]Reaction condition: α-(hydroxyalkyl)-β-naphthols (0.1 mmol, 1 equiv), TBAB (10 mol %), and oxone (1 equiv) were stirred in a 25 mL round bottom flask under nitrogen atmosphere in THF:H_2O (3 mL) in 20:1 ratio for 12 h at room temperature. d.r ratio was calculated from ^1H NMR analysis of crude reaction mixture. [b]Yields were calculated for isolated pure products.

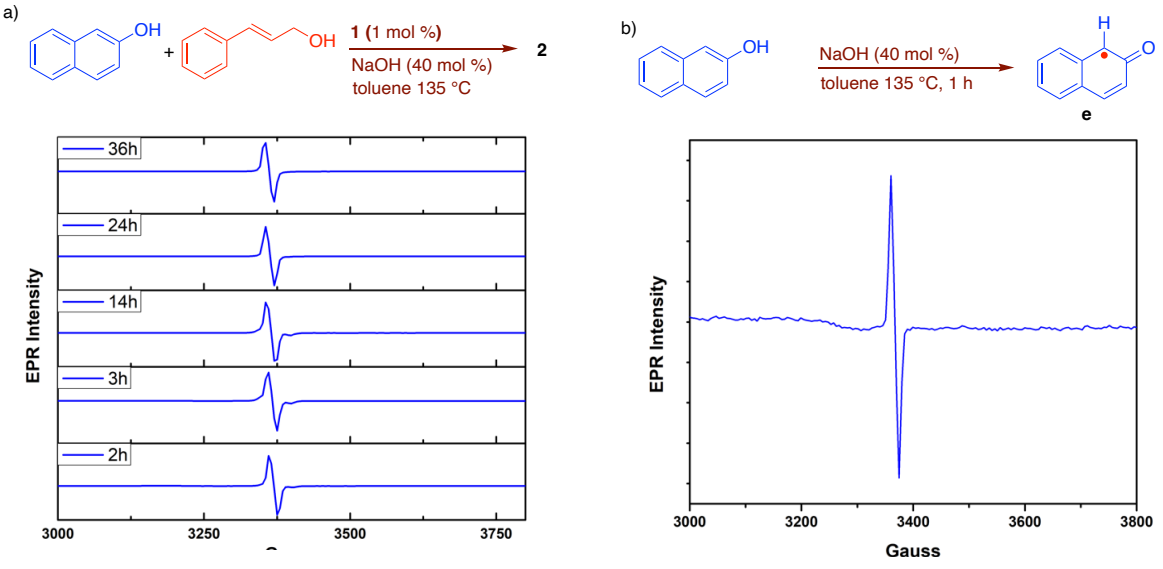
Experiments were performed to understand the mechanistic pathways of ruthenium catalyzed coupling of β-naphthols and allylic alcohols (**Scheme 6.5**). Under basic conditions, catalyst **9** is known to undergo dehydrohalogenation reaction leading to the formation of Ru(II) coordinatively unsaturated intermediate,[20] which can dehydrogenate alcohols to corresponding carbonyl compounds.[21] Hence, reaction of β-naphthol with phenylvinyl ketone was performed with and without catalyst **9**. While reaction with base alone produced no product, catalytic reaction under standard conditions provided 53% of the anticipated product **6.3c** (**Scheme 6.5a**). These experiments confirm the involvement of carbonyl intermediate in the reactions and the role of catalyst in the dehydrogenation, C-C bond formation, and transfer hydrogenation from isopropanol. Experiments were performed to identify the other possible intermediates. Upon dehydrogenation by a catalyst, allylic aldehydes are generated from allylic alcohols, which are anticipated to undergo conjugate addition by carbon nucleophiles produced in situ from β-naphthols. Hence, one of the expected intermediates **6.5a** was prepared independently and subjected to catalysis with β-naphthol under standard conditions for chromane synthesis, which failed to provide the desired product **6.2a**, and led to the formation of lactone **6.5b** via intramolecular cyclization (**Scheme 6.5b**). Lactone **6.5b** was reacted with β-naphthol under standard conditions, which also failed to provide the desired product **6.2a** (**Scheme 6.5c**). Hemiacetal **6.5c** was prepared from lactone **6.5b**, and reacted with β-naphthol under basic conditions in which the anticipated product **6.2a** was obtained in 32% yield (**Scheme 6.5d**). However, the same reaction failed to provide product **6.2a**, when performed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) radical scavenger. This experiment confirms the involvement of radical pathways involved in the reaction. Different attempts were undertaken to trap the radical intermediate. The reaction of β-naphthol, cinnamaldehyde, and the base was carried out at a slightly lower temperature for 12 h together

Scheme 6.5. Mechanistic Studies: Reaction with Possible in situ Formed Intermediates, Radical Trapping Experiments, and Single crystal X-ray Structure of Trapped Naphthyl Radical; Elipsoids Drawn at 50% Probability.



with a radical trapping agent, galvinoxyl free radical (3 equiv), which resulted in the formation of desired product **6.2a** (20%), along with a radical trapped species **6.5d** in 25% yield (**Scheme 6.5e**). Compound **6.5d** was isolated and characterized by NMR analyses, and its structure was corroborated by single-crystal X-ray analysis. EPR experiments were performed to elucidate the radical species involved in these transformations (**Figure 6.2**). The catalytic reaction of β-naphthol and cinnamyl alcohol under standard conditions was subjected to EPR measurements at different time intervals in which an EPR signal at 3365 G appeared and persisted throughout the reaction period (**Figure 6.2a**). Notably, the reaction of β-naphthol with sodium hydroxide base after 1 h produced the same EPR signal at 3365 G, indicating that β-naphthol generates the radical species under basic conditions (**Figure 6.2b**).

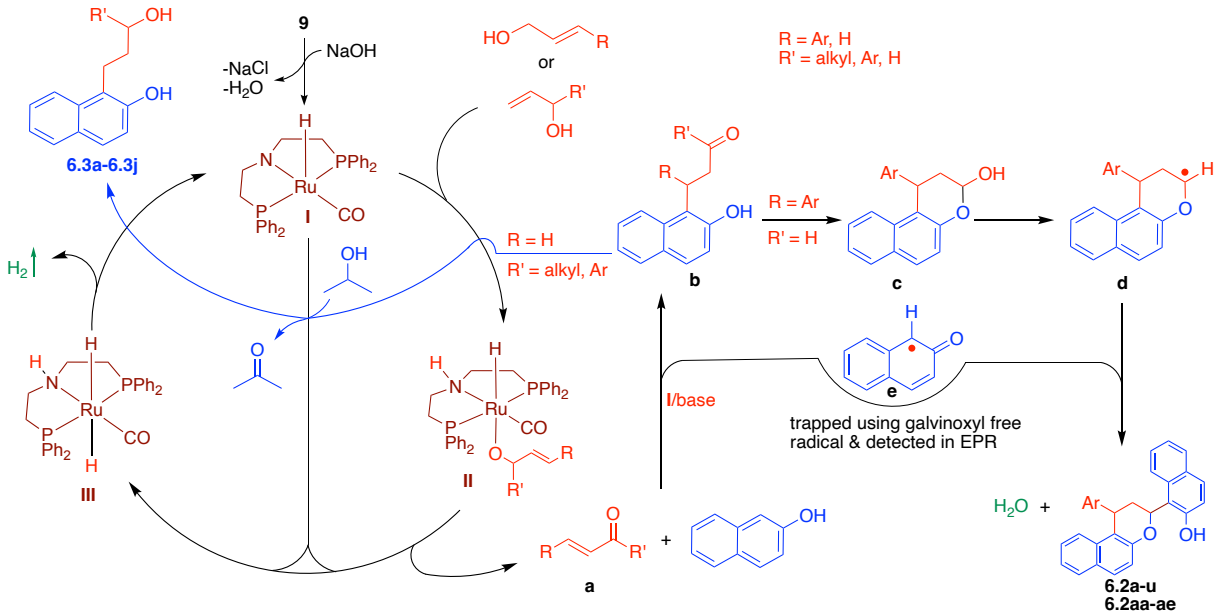
Figure 6.2. EPR studies: a) EPR monitoring studies. b) EPR signal of naphthyl radical.



Based on the experimental observation, a plausible catalytic cycle for the synthesis of functionalized chromanes and hydroxy-functionalized naphthols directly from naphthols and allylic alcohols is presented in **Scheme 6.6**. Catalyst **9** undergoes a dehydrohalogenation reaction in the presence of a base, resulting in the formation of active species **I**. The active

species **I** reacts with allylic alcohols resulting in the formal O-H activation via metal-ligand cooperation to generate the alkoxy intermediate **II**. Upon β-hydride elimination or other mechanistic pathways, vinylcarboxaldehyde (R' = H) or vinylketone (R' = alkyl, aryl) intermediates '**a**' are generated from **II**, which results in the formation of Ru-dihydride intermediate **III**. β-Naphthol reacts with base and in situ produce the transient dearomatized intermediate, which further reacts with a base to generate the carbon nucleophile that undergoes 1,4-conjugate addition reaction with α,β-unsaturated carbonyl compound '**a**' leading to the formation of intermediate "**b**". When "**b**" contains a terminal carboxaldehyde functionality (R' = H), an intramolecular cyclization occurs to produce the hemiacetal '**c**'. Hemiacetal intermediate '**c**' under basic conditions generates the radical species '**d**'. Another equivalent of β-naphthol reacts with base and produces the naphthyl radical '**e**', which was verified from an independent reaction (Figure 2b). The radical combination of '**d**' and '**e**' delivered the desired chromane products (**6.2a-u&6.2aa-ae**). Notably, the reaction of hemiacetal **6.5c** with β-naphthol under basic conditions resulted in the formation of the chromane product **6.2a** (**Scheme 6.5d**). Ru-dihydride intermediate **III** can liberate molecular hydrogen and regenerate the catalytically active intermediate **I**. When secondary allylic alcohols were employed, the in situ formed ketone intermediate '**b**' is hydrogenated by Ru-dihydride **III** to deliver the hydroxyalkyl functionalized β-naphthols **6.3a-6.3j**. Selective hydrogenation of keto-functionality to secondary alcohols is ensured by the transfer hydrogenation from isopropanol, which is also facilitated by the same catalytic system.

Scheme 6.6. Plausible Catalytic Cycles for the Cross-Coupling of β-Naphthol with Primary and Secondary Alcohols



6.4 CONCLUSIONS

In conclusion, we have demonstrated the facile conjugate addition of naphthols with allylic alcohol to afford valuable chromane and functionalized hydroxyalkyl naphthol derivatives. A wide range of allylic alcohols and naphthols participated with excellent functional group compatibility. The use of primary allylic alcohols provided the chromane derivates, while employing secondary allylic alcohols delivered the hydroxyalkyl naphthol derivatives. Mechanistic studies revealed the involvement of tandem reactions: catalytic dehydrogenation of allylic alcohols produced α,β-unsaturated carbonyl compounds, which underwent 1,4-conjugate addition with dearomatized β-naphthol under basic conditions. When the addition product is an aldehyde, intramolecular cyclization and further radical coupling with β-naphthol resulted in chromane products. Given the tandem sequence involved in these reactions with the construction of two C-C and one C-O bond with the formation of a pyran ring, the higher yields of products obtained and observed high selectivity are remarkable. If the 1,4-conjugate addition

leads to ketone intermediates, catalytic hydrogenation facilitated by transfer hydrogenation provided the hydroxyalkyl naphthol products. The naphthyl radical involved in the reaction was elucidated by EPR studies and structural characterization of a trapped radical compound. Hydroxyalkyl naphthols are synthetically transformed to spiroethers *via* dearomative cyclization reaction, and also selective dearomative bromination is demonstrated on a chromane product. Liberated molecular hydrogen and water are the only byproducts, or there is no byproduct in these reactions, which makes these protocols attractive and sustainable. Overall, these transformations represent a significant advancement in catalysis by delivering these important scaffolds directly from simple feedstock chemicals in a waste-free and environmentally benign manner.

6.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under inert atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Catalyst Ru-MACHO [Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl) ethyl]amino}ethyl]amino}ruthenium(II)] (**9**) was purchased from Sigma-Aldrich and stored inside glove box. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, and TCI Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded at Bruker AV- 400 (^1H at 400 MHz, ^{13}C at 100.6 MHz). ^1H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS, δ 0.00 ppm), and ^{13}C $\{^1H\}$ NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm).

Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Room tempertature EPR spectra were obtained using a Bruker EMX (E073) system.

Experimental Procedure for the Synthesis of Starting Materials

a) General Procedure for the Synthesis of Cinnamyl Alcohols Derivatives:

To a round-bottom flask (50 mL) charged with a magnetic stir bar, cinnamic acid derivative (1 mmol, 1 equiv) was dissolved in THF (10 mL), and then triethyl amine (1 mmol, 1 equiv) was added under nitrogen atmosphere. The reaction mixture cooled to -7 °C, and $ClCO_2Et$ (1 mmol, 1 equiv) was slowly added. The resulted reaction mixture was stirred for 1 h at -7 °C and brought to room temperature. Further, the reaction mixture was filtered, and the filtrate was transferred to another oven-dried round bottom flask. $NaBH_4$ (3 mmol, 3 equiv) in MeOH (10 mL) was added drop by drop at 0 °C. The reaction mixture was further stirred at room temperature for 8-12 h, and the solvent was removed under reduced pressure. The resulted residue was dissolved in water (10 mL), and extracted using ethyl acetate (10 mL × 3). The collected organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure using a rotavapor. The residue obtained was purified by silica-gel column chromatography using an ethyl acetate/hexane (15:85) mixture as an eluent, which provided the corresponding cinnamyl alcohol derivatives.[22]

b) **General Procedure for the Synthesis of Secondary Allylic Alcohols:**

In a round bottom flask, aldehyde (1 mmol, 1 equiv) was taken with freshly prepared anhydrous THF, and allowed to stir at 0 °C for 5 min under nitrogen atmosphere. Vinyl magnesium bromide in 1M THF solution (1 mmol, 1 mL, 1 equiv) was added dropwise, and allowed to stir for 4 h. Aqueous ammonium chloride solution was added to the reaction mixture (for

quenching), and extracted using ethyl acetate (10 mL × 3). The collected organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure using a rotavapor. The residue obtained was purified by silica-gel column chromatography using an ethyl acetate/hexane (10:90) as an eluent, which provided the corresponding allylic secondary alcohol derivatives.[23]

c) **Experimental Procedure for Synthesis of 1-(3-Hydroxy-1-phenylpropyl)naphthalen-2-ol (6.5a):**

To a round bottom flask, 1-phenyl-1,2-dihydro-3H-benzo[f]chromen-3-one (1 mmol, 1 equiv) was taken, and dissolved in dry THF (4 mL) at 0 °C was added lithium aluminium hydride (4 mmol, 4 equiv). The reaction was stirred at 0 °C for 1 h and then quenched with 5% aqueous HCl solution (2 mL). The organic layer was extracted using ethyl acetate (2×2 mL). The combined organic layers were washed with brine, dried over magnesium sulphate. The solvents were removed under reduced pressure using a rotavapor and the residue was purified by silica gel column chromatography using an ethyl acetate/hexane as an eluent.

d) **Experimental Procedure for Synthesis of 1-Phenyl-2,3-dihydro-1H-benzo[f]chromen-3-ol (6.5c)** [24]**:**

To a solution of (1-phenyl-1,2-dihydro-3H-benzo[f]chromen-3-one, 0.2 mmol, 1 equiv) in dichloromethane (5 mL) at -78 °C was added diisobutylaluminum hydride (1.5 M in toluene, 0.15 mL, 0.2 mmol). The reaction mixture was stirred at -78 °C for 2 h and then poured into an aqueous solution of potassium sodium tartrate (5 mL). After stirring at room temperature for 2 h, the aqueous layer was extracted using dichloromethane (2×5 mL). The combined organic layers were washed with brine, dried over magnesium sulphate. The solvents were removed under reduced pressure using a rotavapor and the residue was purified by silica gel column chromatography using an ethyl acetate/hexane as an eluent.

General Optimization Procedure for the Catalytic Synthesis of Benzo(*f*)chromanes:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005-0.01 mmol), base (0.01-0.25 mmol), cinnamyl alcohol (0.5 mmol, 62 μL), β-naphthol (1 mmol, 144 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 100 - 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 24-36 h. The completion of the reaction was monitored using TLC. After cooling to room temperature, the solvent was evaporated under reduced pressure using a rotavapor and the resulted residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

General Optimization Procedure for the Catalytic Synthesis of Hydroxy Functionalized β-Naphthols :

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol), base (0.01-0.20 mmol), β-naphthol (0.5 mmol, 72 mg), 3-buten-2-ol (1 mmol, 82.5 μL), and solvent (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 80-100 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 16-24 h. The completion of the reaction was monitored using TLC. After cooling to room temperature, the solvent was evaporated under reduced pressure using a rotavapor and the resulted residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

General Procedure for the Catalytic Synthesis of Benzo(*f*)chromanes: A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3 mg), NaOH (0.20 mmol, 8 mg), primary allylic alcohol (0.5 mmol), β-naphthol (1 mmol), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 135 °C (oil bath temperature) with stirring in an open

system under a flow of nitrogen for 36 h. The completion of the reaction was monitored using TLC. After cooling to room temperature, the solvent was evaporated under reduced pressure using a rotavapor. Further, d.r ratio was calculated from the ^{1}H NMR analysis of crude reaction mixture. The resulted residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

General Procedure for the Catalytic Synthesis of Hydroxy Functionalized β-Naphthols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3 mg), NaOH (0.20 mmol, 8 mg), β-naphthol (0.5 mmol), secondary allylic alcohol (1 mmol), and toluene:IPA (1:1, 2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 100 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 16-24 h. The completion of the reaction was monitored using TLC. After cooling to room temperature, the solvent was evaporated under reduced pressure using a rotavapor and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

Experimental procedure for gram-scale synthesis of Product 6.2a:

A Schlenk flask (50 mL) was equipped with a stir bar, catalyst **9** (0.08 mmol, 48.5 mg), NaOH (16 mmol, 256 mg), primary allylic alcohol (8 mmol, 1.07 mL), β-naphthol (16 mmol, 2.3 g), and toluene (6 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 36 h. Further, the solvent was evaporated and the reaction was quenched by water (0.5 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulted residue was purified by column chromatography over

silica gel (100–200 mesh) using an hexane/ethyl acetate mixture as the eluent. Yields were calculated for isolated pure products.

Experimental Procedures for Synthetic Transformations

General Procedure for Synthesis of Spiro Furanone Derivatives (6.3a-6.3j)[15b]

A round bottom flask was equipped with a stir bar, hydroxy alkyl naphthol (0.1 mmol, 1equiv), TBAB (10 mol %, 3.2 mg), and oxone (1 equiv, 30.7 mg) dissolved in THF:H_2O (3 mL) in a ratio of 20:1. The reaction was stirred at room temperature for 12 h under nitrogen atmosphere. The organic layer was separated, and extracted twice with dichloromethane (2×2 mL), and washed with brine solution, dried over anhydrous sodium sulfate. The combined organic layers were washed with brine, dried over magnesium sulphate. The solvents were removed under reduced pressure using a rotavapor and the residue was purified by silica gel column chromatography using an ethyl acetate/hexane as an eluent.

Experimental Procedure for Synthesis of Dearomative Halogenated Product (6.4h)[9]**:**

An 8 mL scintillation vial equipped with a magnetic stir bar was charged with phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol (**6.2a**, 0.25 mmol, 100 mg), N-bromosuccinamide (0.3 mmol, 53.1 mg), and potassium acetate (0.375 mmol, 36.7 mg) in DCM:H_2O (2 mL, 1:1). Then the reaction mixture was stirred at room temperature for 1 h and upon completion, extracted using dichloromethane (3 × 3 mL). The combined organic layers were washed with brine, dried over magnesium sulphate. The solvents were removed under reduced pressure using a rotavapor and the residue was purified by column chromatography over silica gel (100–200 mesh) using an hexane/ethyl acetate (2:98) mixture as an eluent. Yield was calculated for isolated pure product.

Experimental Procedure for Mechanistic Studies: Reaction with Possible in situ Formed Intermediates and Radical Trapping Experiments (Scheme 6.5):

Reaction of 1-Phenylprop-2-en-1-one with β-Naphthol in Absence of Catalyst (Scheme 6.5a, without Catalyst 9):

A Schlenk flask (25 mL) was equipped with a stir bar, NaOH (0.20 mmol, 8 mg), β-naphthol (0.5 mmol, 72 mg), 1-phenylprop-2-en-1-one (0.5 mmol, 66 mg), and toluene:IPA (2 mL, 1:1) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 80 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 24 h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. The expected product **6.3c** was not observed.

Reaction of 1-Phenylprop-2-en-1-one with β-Naphthol in Presence of Catalyst 9 (Scheme 6.5a):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3 mg), NaOH (0.20 mmol, 8 mg), β-naphthol (0.5 mmol, 72 mg), 1-phenylprop-2-en-1-one (0.5 mmol, 66 mg), and toluene:IPA (2 mL, 1:1) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 80 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 24 h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. The expected product **6.3c** was obtained in 53% isolated yield.

Reaction of 1-(3-Hydroxy-1-phenylpropyl)naphthalen-2-ol (6.5a) with β-Naphthol in Presence of Catalyst 9 (Scheme 6.5b):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3mg), NaOH

(0.10 mmol, 4 mg), β-naphthol (0.5 mmol, 72 mg), 1-(3-hydroxy-1-phenylpropyl)naphthalen-2-ol (**6.5a**, 0.5 mmol, 139 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 36 h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. The expected product **2** was not obtained.

Reaction of 1-Phenyl-1,2-dihydro-3*H*-benzo[*f*]chromen-3-one (6.5b) with β-Naphthol in Presence of Catalyst 9 (Scheme 6.5c):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3 mg), NaOH (0.10 mmol, 4 mg), β-naphthol (0.5 mmol, 72 mg), 1-phenyl-1,2-dihydro-3H-benzo[*f*]chromen-3-one (**6.5c**, 0.5 mmol, 137 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 36 h. Both TLC and ^{1}H NMR analyses of the reaction mixture confirmed the absence of anticipated product **6.2a**.

Reaction of 1-Phenyl-2,3-dihydro-1H-benzo[*f*]chromen-3-ol (6.5c) with β-Naphthol in Absence of Catalyst 9 (Scheme 6.5d):

A Schlenk flask (25 mL) was equipped with a stir bar, NaOH (0.10 mmol, 4 mg), β-naphthol (0.5 mmol, 72 mg), 1-phenyl-2,3-dihydro-1H-benzo[*f*]chromen-3-ol (**6.5c**, 0.5 mmol, 138 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 36 h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an

eluent. The expected product **6.2a** was isolated 32% yield.

Reaction in Absence of Catalyst 9 and with Presence of TEMPO (Scheme 6.5d):

A Schlenk flask (25 mL) was equipped with a stir bar, NaOH (0.10 mmol, 4 mg), β-naphthol (0.5 mmol, 72 mg), 1-phenyl-2,3-dihydro-1H-benzo[*f*]chromen-3-ol (**6.5c**, 0.5 mmol, 138 mg), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1.5 mmol, 234 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 36 h. Both TLC and ^{1}H NMR analyses of the reaction mixture confirmed the absence of anticipated product **6.2a**.

Reaction of β-Naphthol with Cinnamyl aldehyde in Presence of Galvinoxyl Free Radical (Scheme 6.5e):

A Schlenk flask (25 mL) was equipped with a stir bar, NaOH (0.20 mmol, 8 mg), cinnamyl aldehyde (0.5 mmol, 63 μL), β-naphthol (1 mmol, 144 mg), galvinoxyl free radical (1.5 mmol, 631 mg), and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 115 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 12 h. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography over silica-gel (100-200 mesh) using an ethyl acetate/hexane mixture as an eluent. The expected product **6.2a** was isolated in 20% yield together with trapped naphthyl radical compound (**6.5d**) in 25% isolated yield.

Procedure for EPR Studies:

Reaction of β-Naphthol with Cinnamyl Alcohol in Presence of Catalyst 9 for Time Profile Experiment (Figure 6.2a):

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **9** (0.005 mmol, 3 mg), NaOH (0.20 mmol, 8 mg), primary allylic alcohol (0.5 mmol, 64 μL), β-naphthol (1 mmol, 144 mg),

and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen. The aliquots were taken out at various intervals of time (2 h, 3 h, 14 h, 24 h, 36 h), and subjected to EPR measurements.

Reaction of β-Naphthol in Presence of Base (Figure 6.2b):

A Schlenk flask (25 mL) was equipped with a stir bar, NaOH (0.20 mmol, 8 mg), β-naphthol (1 mmol, 144 mg) and toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the reaction mixture was heated at 135 °C (oil bath temperature) with stirring in an open system under a flow of nitrogen for 1 h. The reaction was cooled and aliquots was subjected to EPR analysis.

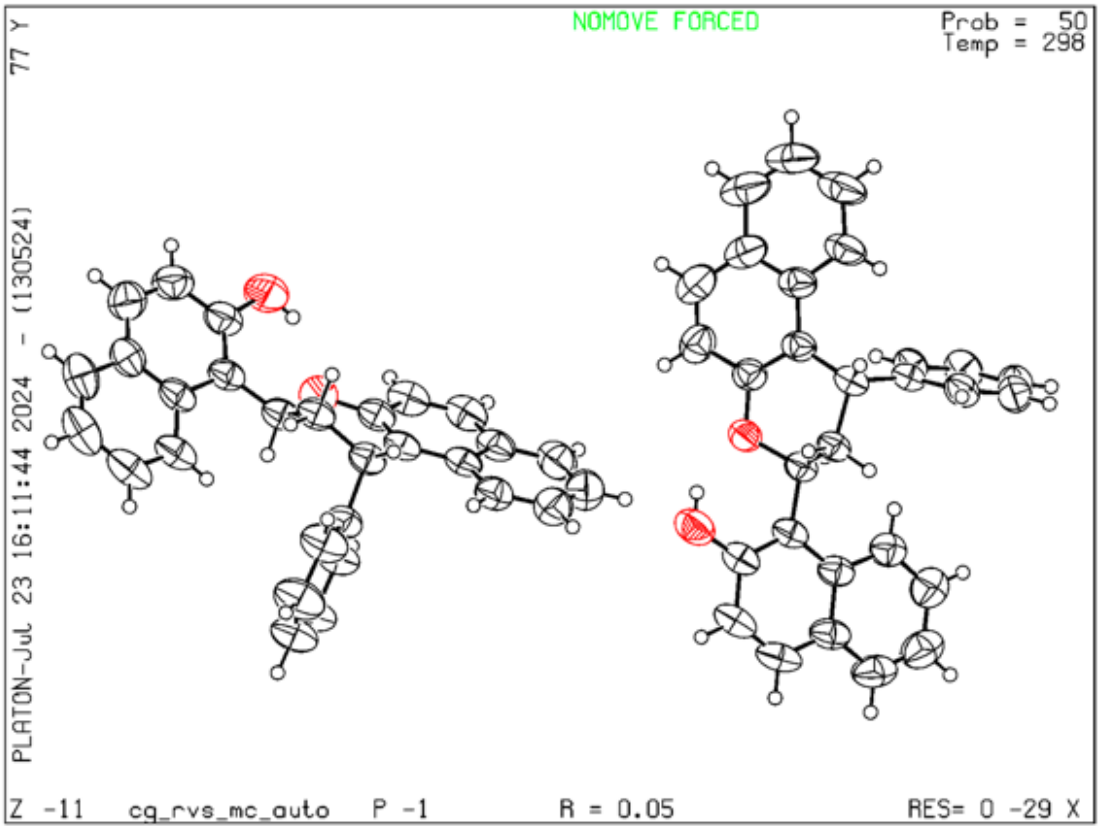
XRD Data

Crystals of products **6.2a**, **6.2r**, **6.4e** and **6.5d** was obtained after slow evaporation of DCM, layered by hexane at room temperature. Crystals suited for single-crystal X-Ray diffraction measurements were mounted on a glass fiber. Geometry and intensity data were collected with a Bruker SMART D8 goniometer equipped with an APEXCCD detector and with an Incoatecmicrosource (Cu- Kα radiation, λ = 1.54184 Å, multilayer optics). The temperature was controlled using an Oxford Cryostream 700 instrument. Intensities were integrated with SAINT+ and corrected for absorption with SADABS. The structures were solved by direct methods and refined on F2 with SHELXL-97 using Olex-2 software.

Crystal Data of 1-(1-Phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl) naphthalen-2-ol (6.2a):

$C_{29}H_{22}O_2$, Clear light white, crystal dimension: 0.12 x 0.10 x 0.09 mm^3, M = 402.46, triclinic, P-1, a = 9.87978(16) Å, b = 11.5837(2) Å, c = 19.0109(3) Å, α = 94.9415(13)°, β = 96.5662(13)°, γ= 101.0619(14)°, V = 2108.18(6) $Å^3$, T = 298.18(16) K, min/max transmission factors = Z = 4, F (000) = 848.0, μ(Cu Kα) = 0.613 mm^{-1}, 40896 Reflections measured, 8622 unique (R_{int} =0.0469) which were used in all calculations. The final *WR2* was 0.1383 (all data) and R1 was 0.0473 (I >= 2σ(I)). The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC 2379791**.

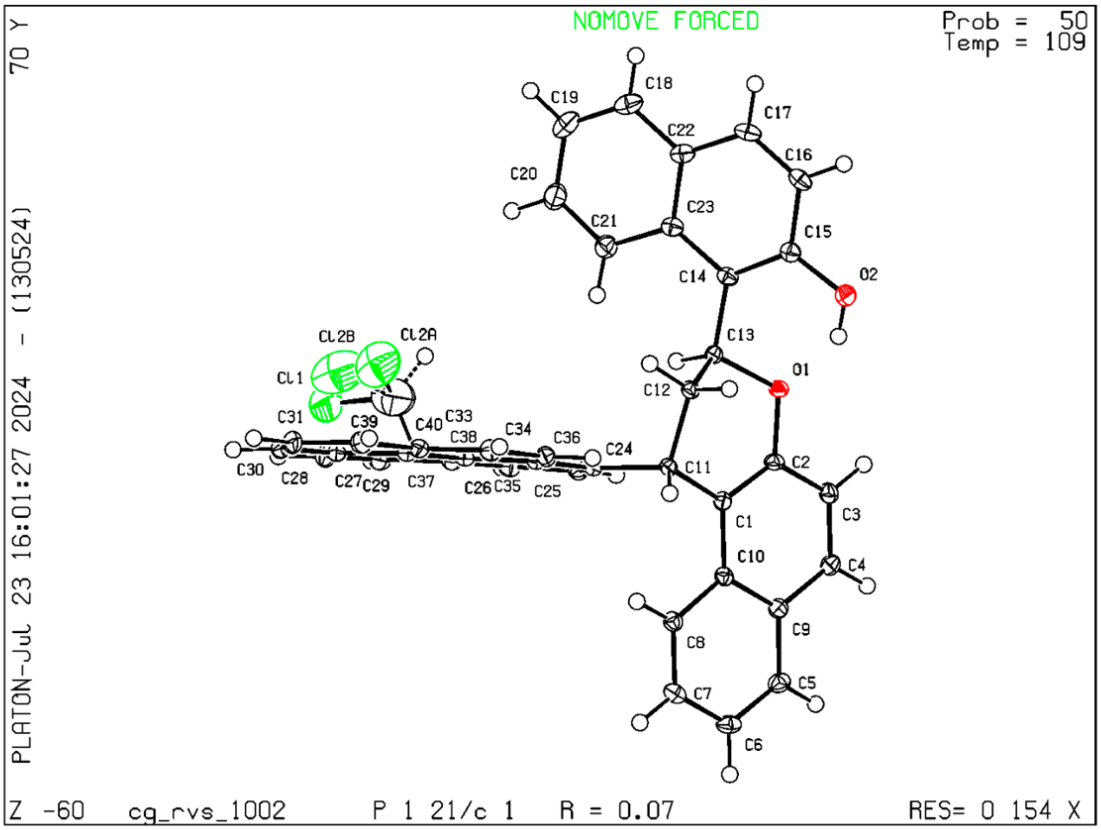
Figure 6.3. Thermal Ellipsoid Diagram of 6.2a Drawn with 50% Probability.



Crystal Data of 1-(1-(Pyren-1-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2r):

$C_{40}H_{27}Cl_2O_2$, brown, crystal dimension: 0.28 x 0.26 x 0.24 mm^3, M = 610.51, P $2_1/c$, a = 8.3723(10) Å, b = 24.8099(3) Å, c = 14.46150(10) Å, $\alpha = 90°$, $\beta = 103.399(1)°$, $\gamma = 90°$, V = 2922.12(5) $Å^3$, T = 109 K, min/max transmission factors = 0.687/1.000, Z = 4, F (000) = 1268.0, μ(Cu Kα) = 2.286 mm^{-1}, 58140 Reflections measured, 6028 unique (R_{int} = 0.0421) which were used in all calculations. The final *WR2* was 0.1921 (all data) and R1 was 0.0683 (I= > 2σ(I)). The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC 2379792**.

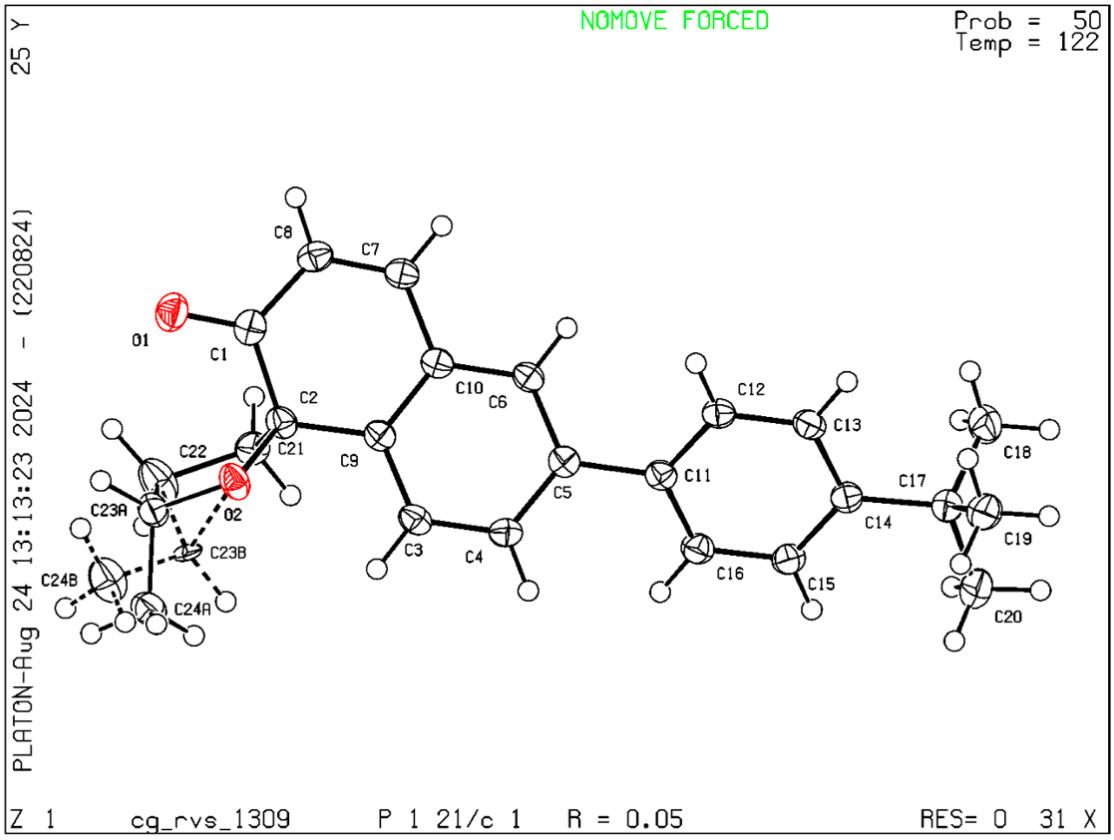
Figure 6.4. Thermal Ellipsoid Diagram of 6.2r Drawn with 50% Probability.



Crystal Data of 6'-(4-(*tert*-Butyl)phenyl)-5-methyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (6.4e):

$C_{24}H_{26}O_2$, Clear light white, crystal dimension: 0.3 x 0.26 x 0.15 mm^3, M = 346.45, monoclinic, P-2_1/c, a = 14.7410(5) Å, b = 12.0287(3) Å, c = 10.8042(3) Å, $\alpha = 90°$, $\beta = 98.516(3)$, $\gamma = 90°$, V = 1894.63(10) $Å^3$, T = 122.45K, min/max transmission factors = Z = 4, F (000) = 744.0, μ(Cu Kα) = 0.587 mm^{-1}, 14003 Reflections measured, 3928 unique (R_{int} = 0.0431) which were used in all calculations. The final *WR2* was 0.1256 (all data) and R1 was 0.0508 (I >= 2σ(I)). The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC 2379793**.

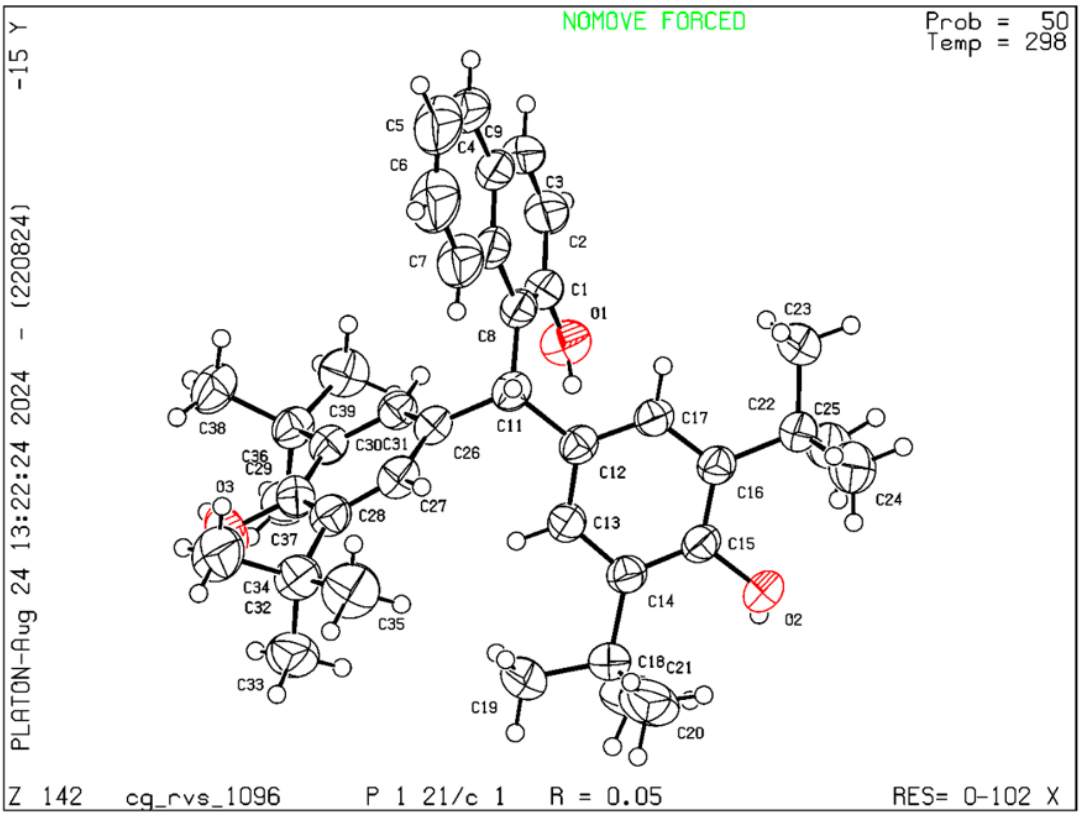
Figure 6.5. Thermal Ellipsoid Diagram of 6.4e Drawn with 50% Probability.



Crystal Data of 4,4'-((2-Hydroxynaphthalen-1-yl)methylene)bis(2,6-di-*tert*-butylphenol) (6.5d):

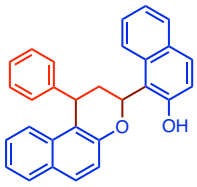
$C_{39}H_{50}O_3$, white, crystal dimension: 0.28 x 0.26 x 0.24 mm^3, M = 566.79, monoclinic, $P2_1/c$, a = 10.7351(2) Å, b = 27.2890(6) Å, c = 11.7130(3) Å, $\alpha = 90°$, $\beta = 94.438(2)$, $\gamma = 90°$, V = 3421.04(13) $Å^3$, T = 298.07K, min/max transmission factors = Z = 4, F (000) = 1232.0, μ(Cu Kα) = 0.520 mm^{-1}, 26326 Reflections measured, 7073 unique (R_{int} = 0.0420) which were used in all calculations. The final *WR2* was 0.1531 (all data) and R1 was 0.0573 (I >= 2σ(I)). The structure has been deposited at the CCDC and can be retrieved using the deposit number **CCDC 2379794**.

Figure 6.6. Thermal Ellipsoid Diagram of 6.5d Drawn with 50% Probability.



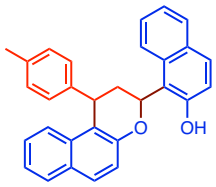
Spectral Data:

1-(1-Phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl) naphthalen-2-ol (6.2a): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 161 mg, 80%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 87:13, as determined by a comparison of the following signals: δ 5.02 (dd, J_1 = 10.9 Hz, J_1 = 8.1 Hz, 1H)-minor product, 4.90 (d, J = 5.0Hz, 1H)- major product. IR (DCM; cm^{-1}): 3054, 2985, 1423, 1264, 895, 740. ^{1}H NMR (400 MHz $CDCl_3$): δ 8.30 (s, 1H), 7.76-7.53 (m, 5H), 7.32-6.98 (m, 11H), 6.48 (d, J = 8.6 Hz, 1H), 6.00-5.97 (m, 1H), 4.80 (d, J = 4.6 Hz, 1H), 2.77-2.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.74, 151.89, 145.29, 132.99, 130.92, 130.20, 130.17, 129.64, 128.93, 128.89, 128.72, 128.70, 127.06, 126.95, 126.89, 124.20, 123.73, 123.09, 120.36, 119.86, 118.74, 115.69, 114.08, 72.88, 38.45, 36.48. HRMS (ESI) m/z calcd for $C_{29}H_{22}O_2$ $(M)^+$: 402.1620 found: 402.1601.

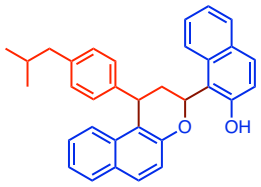
1-(1-(p-Tolyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2b): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 141 mg, 68%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 86:14, as determined by a comparison of the following signals: δ 4.95 (t, J = 9.5 Hz, 1H)-major product, 4.88 (d, J = 4.6 Hz, 1H)-minor product. IR (DCM; cm^{-1}): 3411, 3054, 2985, 2305, 1620, 1512, 1423, 1264, 895, 745. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.31 (s, 1H), 7.73-7.52 (m, 5H), 7.26-6.86 (m, 11H), 6.50 (d, J = 8.6 Hz, 1H), 5.97 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 4.5 Hz, 1H), 2.71-2.63 (m, 1H), 2.31 (d, J = 20.1 Hz, 4H), 1.17 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.75, 151.82, 142.24, 136.44, 133.07, 130.97, 130.16, 129.53, 128.97, 128.92, 128.69, 128.58, 127.03, 126.83, 124.16, 123.76, 123.06, 120.49, 119.88, 118.73, 115.99, 114.20, 72.97, 38.07, 36.54, 21.24.

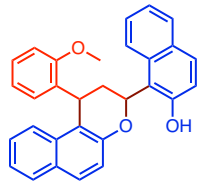
HRMS (ESI) m/z calcd for $C_{30}H_{24}O_2$ $(M)^+$: 416.1776 found: 416.1767.

1-(1-(4-Isobutylphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol (6.2c):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (1:99) mixture as an eluent. White solid. Yield: 197 mg, 86%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 88:12, as determined by a comparison of the following signals: δ 6.14 (d, J = 11.7 Hz, 1H)-major product, 5.99 (d, J = 13.8 Hz, 1H)-minor product. IR (DCM; cm^{-1}): 3410, 3053, 2956, 2868, 1621, 1599, 1513, 1465, 1402, 1352, 1265, 1227, 1145, 1097, 1062, 1022, 962, 896, 815, 739, 601. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.32 (d, J = 1.6 Hz, 1H), 7.75-7.55 (m, 5H), 7.29-7.05 (m, 9H), 6.95-6.91 (m, 1H), 6.50 (d, J = 8.6 Hz, 1H), 5.98 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 4.0 Hz, 1H), 2.73-2.32 (m, 4H), 1.87-1.80 (m, 1H), 0.89-0.77 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.81, 151.82, 142.63, 140.32, 133.07, 130.96, 130.17, 129.60, 129.53, 128.97, 128.93, 128.69, 128.42, 127.02, 126.72, 124.16, 123.79, 123.07, 120.38, 119.89, 118.72, 115.98, 114.17, 72.92, 45.15, 38.12, 36.58, 30.53, 22.81, 22.54, 22.46. HRMS (ESI) m/z calcd for $C_{33}H_{31}O_2$ $(M+H)^+$: 459.2324 found: 459.2324.

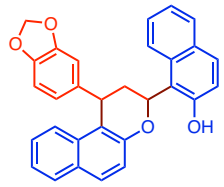
1-(1-(2-Methoxyphenyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2d):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 151 mg, 70%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 90:10, as determined by a comparison of the following signals: δ 5.42 (d, J = 9.0 Hz,)-minor product, 5.24 (d, J = 4.6 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2305, 1599, 1423, 1264, 895, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.52 (d, J = 16.6 Hz, 1H), 7.88-7.60 (m, 5H), 7.41-7.19 (m, 6H), 7.15-7.07 (m, 2H), 6.95-6.87 (m, 2H), 6.64 (dd, J = 12.7, 8.7 Hz, 1H), 6.15 (t, J = 11.3 Hz, 1H), 5.26 (dd, J = 10.6, 5.1 Hz, 1H), 3.94 (d, J = 5.7 Hz, 3H), 2.77-2.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.41, 153.75, 132.91, 130.97, 130.98, 130.38, 130.15, 130.04, 129.35,

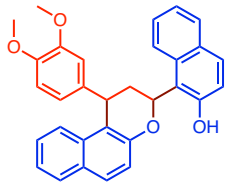
128.88, 128.62, 128.16, 126.95, 126.76, 124.11, 123.77, 123.00, 120.49, 120.43, 119.88, 118.77, 116.18, 114.34, 110.35, 73.53, 55.53, 33.65, 32.73. HRMS (ESI) m/z calcd for $C_{30}H_{24}O_2$ $(M)^+$: 433.1804 found: 433.1779.

1-(1-(Benzo[d][1,3]dioxol-5-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol



(6.2e): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 160 mg, 72%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 84:16, as determined by a comparison of the following signals: δ 6.03 (d, J = 7.7 Hz, 2H)-major product, 5.90-5.87 (m, 2H)-minor product. IR (DCM; cm^{-1}): 3405, 3055, 2983, 2894, 1620, 1599, 1483, 1437, 1401, 1349, 1316, 1262, 1231, 1146, 1102, 1041, 993, 963, 935, 896, 862, 816, 738, 626. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.29 (s, 1H), 7.78-6.64 (m, 16H), 6.05 (d, J = 11.0 Hz, 1H), 5.93 (dd, J_1 = 8.5 Hz, J_2 =1.3 Hz, 2H), 4.72 (d, J = 4.7 Hz, 1H), 2.71 (ddd, J_1 = 14.1 Hz, J_2 =12.0 Hz, J_3 =5.2 Hz, 1H), 2.36 (d, J = 14.2 Hz,1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.77, 151.74, 148.12, 146.44, 139.38, 132.95, 130.94, 130.23, 130.16, 129.70, 129.01, 128.99, 128.73, 127.07, 126.98, 124.21, 123.67, 123.12, 121.94, 120.43, 119.91, 118.72, 115.79, 114.13, 109.22, 108.57, 101.27, 72.82, 38.08, 36.45. HRMS (ESI) m/z calcd for $C_{30}H_{22}O_2$ $(M)^+$: 446.1518 found: 446.1537.

1-(1-(3,4-Dimethoxyphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol



(**6.2f**): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:99) mixture as an eluent. White solid. Yield: 164 mg, 71%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 87:13, as determined by a comparison of the following signals: δ 4.93 (d, J = 9.9 Hz, 1H)-minor product, 4.85 (d, J = 4.3 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2305, 1599, 1423, 1264, 895, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.26 (s, 1H), 7.68-7.50 (m, 5H), 7.24-6.99 (m, 6H), 6.76 (s, 1H), 6.62 (dd, J_1 = 11.2 Hz, J_1 =8.8 Hz, 2H), 6.49 (d, J = 8.2 Hz,

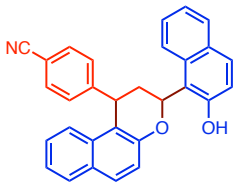
1H), 5.97 (d, J = 11.7 Hz, 1H), 4.63 (d, J = 4.4 Hz, 1H), 3.65 (dd, J = 46.8, 23.8 Hz, 6H), 2.61-2.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.71, 151.65, 149.36, 147.90, 137.71, 133.01, 130.90, 130.14, 130.04, 129.54, 128.92, 128.90, 128.64, 126.95, 124.11, 123.67, 123.10, 121.19, 120.39, 119.84, 118.64, 115.84, 114.12, 111.43, 111.15, 72.91, 56.05, 56.00, 37.91, 36.26.

1-(1-(3-Chloro-4-methoxyphenyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:99) mixture as an eluent. White solid. Yield: 93 mg, 40%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 89:11, as determined by a comparison of the following signals: δ 4.91 (d, J = 0.5 Hz, 1H)-minor product, 4.76 (d, J = 8.5 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2305, 1423, 1264, 1064, 895, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.36 (s, 1H), 7.87-7.74 (m, 4H), 7.62 (t, J = 4.5 Hz, 1H), 7.42-7.06 (m, 7H), 6.84 (dd, J_1 = 75.2, J_2 = 8.5 Hz, 2H), 6.08 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 4.3 Hz, 1H), 3.92 (d, J = 51.1 Hz, 3H), 2.47 (d, J = 14.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9, 153.7, 151.7, 139.3, 138.3, 132.8, 130.9, 130.3, 130.2, 130.1, 129.8, 129.6, 129.0, 128.7, 128.0, 127.1, 127.0, 126.2, 124.2, 124.1, 123.5, 123.1, 122.9, 120.7, 120.2, 119.9, 119.8, 119.1, 118.7, 115.1, 113.9, 112.1, 72.7, 56.3, 56.1, 37.2, 36.1. HRMS (ESI) m/z calcd for $C_{30}H_{23}ClO_3$ $(M)^+$: 466.1336 found: 466.1354.

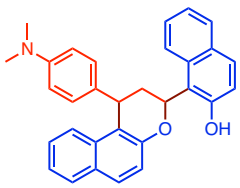
1-(1-(3-Phenoxyphenyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 148 mg, 60%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 88:12, as determined by a comparison of the following signals: δ 4.95 (dd, J_1 = 10.8 Hz, J_2 = 8.2 Hz, 1H)-minor product, 4.85 (d, J = 4.9 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2305, 1423, 1264, 1064, 895, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.33-8.28 (m, 1H),

7.79-7.65 (m, 4H), 7.59-7.55 (m, 1H), 7.41-7.26 (m, 3H), 7.24-7.17 (m, 5H), 7.15-7.09 (m, 2H), 7.01-6.87 (m, 6H), 6.75-6.67 (m, 1H), 6.27-6.03 (m, 1H), 4.80-4.78 (m, 1H), 2.80-2.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.59, 157.34, 153.81, 151.89, 147.65, 132.90, 130.95, 130.28, 130.22, 130.21, 129.89, 129.80, 129.07, 129.01, 128.79, 127.10, 126.93, 124.25, 123.82, 123.62, 123.30, 123.17, 120.30, 119.95, 119.59, 118.74, 118.58, 117.58, 115.32, 114.01, 72.85, 38.37, 36.36. HRMS (ESI) m/z calcd for $C_{35}H_{26}O_3$ $(M)^+$: 494.1882 found: 494.1876.

4-(3-(2-Hydroxynaphthalen-1-yl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)benzonitrile-methane (6.2i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 107 mg, 47%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 80:20, as determined by a comparison of the following signals: δ 4.91 (d, J = 0.5 Hz, 1H)-major product, 4.76 (d, J = 8.5 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2559, 1422, 1265, 895, 740. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.11 (s, 1H), 7.78 (d, J = 9.1 Hz, 2H), 7.64 (q, J = 8.5 Hz, 4H), 7.39-7.16 (m, 8H), 7.07 (t, J = 7.7 Hz, 2H), 6.49 (d, J = 8.6 Hz, 1H), 5.88 (d, J = 11.1 Hz, 1H), 4.84 (d, J = 5.2 Hz, 1H), 2.86-2.79 (m, 1H), 2.35 (d, J = 14.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.79, 152.11, 150.87, 132.80, 132.54, 130.79, 130.52, 130.31, 130.26, 129.53, 129.18, 129.03, 129.01, 127.41, 127.10, 124.49, 123.30, 123.12, 119.92, 119.79, 118.84, 114.03, 113.59, 111.03, 72.42, 38.55, 35.85. HRMS (ESI) m/z calcd for $C_{30}H_{21}NO_2$ $(M)^+$: 427.1572 found: 427.1600.



1-(1-(4-(Dimethylamino)phenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol (6.2j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 178 mg, 80%. IR (DCM; cm^{-1}): 3407, 3054, 2984, 1616, 1517, 1425, 1350, 1264, 1228, 1061, 895, 817, 739. ^{1}H NMR (400 MHz): δ 8.35 (s, 1 H), 7.70-7.56 (m, 6H), 7.24-6.95



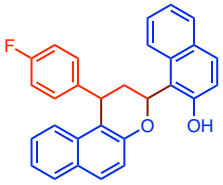
(m, 9H), 6.61 (dd, J = 21.0, 8.7 Hz, 3H), 5.98 (d, J = 10.8 Hz, 1H), 4.65 (d, J = 4.2 Hz, 1H), 2.81 (d, J = 47.7 Hz, 6H), 2.66-2.58 (m, 1H), 2.33-2.30 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6, 153.5, 149.5, 133.3, 131.0, 130.0, 129.8, 129.8, 129.3, 128.9, 128.8, 128.5, 127.8, 126.8, 126.5, 126.4, 124.0, 123.9, 123.0, 120.7, 119.8, 118.6, 116.4, 114.4, 113.2, 73.0, 41.0, 40.9, 37.4, 36.6. HRMS (ESI) m/z calcd for $C_{31}H_{28}NO_2$ $(M+H)^+$: 446.2120 found: 446.21

Ethyl(4-(3-(2-hydroxynaphthalen-1-yl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)phenyl)carbamate (6.2k): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 178 mg, 80%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 83:17, as determined by a comparison of the following signals: δ 4.95 (t, J = 9.5 Hz,)-minor product, 4.85 (d, J = 4.9 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3341, 3053, 2984, 2359, 1733, 1596, 1516, 1264, 1212, 895, 743. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.40 (s, 1H), 7.88-7.83 (m, 2H), 7.76-7.72 (m, 2H), 7.64-7.60 (m, 1H), 7.44-7.32 (m, 4H), 7.27-7.14 (m, 4H), 6.69 (d, J = 7.8 Hz, 2H), 6.09 (d, J = 11.5 Hz, 1H), 4.86 (d, J = 4.7 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.86-2.46 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.60, 151.66, 136.67, 132.81, 130.79, 130.09, 130.03, 129.53, 129.20, 128.83, 128.82, 128.59, 126.94, 126.91, 124.09, 123.58, 123.00, 120.25, 119.73, 118.61, 115.58, 113.98, 72.75, 37.65, 36.25, 14.60. HRMS (ESI) m/z calcd for $C_{32}H_{27}NO_4$ $(M)^+$: 489.1940 found: 489.1973.

4-(3-(2-Hydroxynaphthalen-1-yl)-2,3-dihydro-1H-benzo[f]chromen-1-yl)phenyl methanesulfonate (6.2l): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 50 mg, 20%. IR (DCM; cm^{-1}): 3365, 3324, 2923, 1620, 1597, 1496, 1466, 1401, 1366, 1327, 1271, 1220, 1173, 1147, 1098, 962, 862, 741. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.33-8.30 (m, 1H), 7.89-7.86 (m, 2H), 7.74 (dd, J = 9.9, 4.9 Hz, 2H), 7.61-7.59 (m,

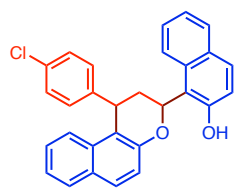
1H), 7.45-7.39 (m, 2H), 7.38-7.33 (m, 5H), 7.28-7.25 (m, 2H), 7.20-7.15 (m, 2H), 6.55 (d, J = 8.5 Hz, 1H), 6.04-6.01 (m, 1H), 4.94 (d, J = 4.4 Hz, 1H), 3.22 (s, 3H), 2.90-2.83 (m, 1H), 2.45 (d, J = 14.3 Hz, 1H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 153.72, 152.01, 147.98, 144.83, 132.73, 130.80, 130.37, 130.25, 130.21, 130.02, 129.04, 128.97, 128.89, 127.31, 127.10, 124.39, 123.46, 123.31, 122.63, 120.02, 119.83, 118.82, 114.93, 113.68, 72.64, 37.94, 37.72, 36.39, 27.77. HRMS (ESI) m/z calcd for $C_{30}H_{24}O_5S$ $(M)^+$: 496.1344 found: 496.1327.

1-(1-(4-Fluorophenyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2m):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 126 mg, 60%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 89:11, as determined by a comparison of the following signals: δ 4.96 (t, J = 9.5 Hz, 1H)-minor product, 4.85 (d, J = 4.7 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2306, 1423, 1264, 895, 739.^{1}H NMR (400 MHz; $CDCl_3$): δ 8.22 (s, 1H), 7.64 (dt, J_1 = 42.9, J_2 = 8.7 Hz, 4H), 7.44-7.43 (m, 1H), 7.25-6.92 (m, 9H), 6.50 (d, J = 8.5 Hz, 1H), 5.89 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 4.5 Hz, 1H), 2.69-2.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.03, 160.59, 153.83, 153.78, 151.85, 141.03, 140.99, 133.73, 132.82, 130.87, 130.35, 130.30, 130.23, 130.20, 130.15, 129.83, 129.58, 129.20, 129.03, 128.98, 128.81, 128.76, 128.06, 127.13, 126.99, 126.95, 126.85, 126.38, 124.29, 124.14, 123.55, 123.32, 123.17, 120.73, 120.15, 120.03, 119.90, 119.19, 118.78, 115.98, 115.86, 115.77, 115.65, 115.43, 115.36, 114.31, 113.94, 112.46, 112.33, 72.66, 37.68, 36.40. ^{19}F-NMR (377 MHz, $CDCl_3$): δ -115.86, -116.49. HRMS (ESI) m/z calcd for $C_{29}H_{21}FO_2$ $(M)^+$: 420.1526 found: 420.1540.

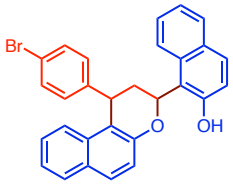
1-(1-(4-Chlorophenyl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2n):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 142 mg, 65%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of

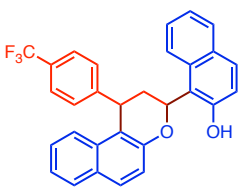
87:13, as determined by a comparison of the following signals: δ 4.98 (t, J = 9.6 Hz, 1H)-minor product, 4.88-4.87 (m, 1H)-major product. IR (DCM; cm^{-1}): 3415, 3054, 2985, 2684, 2306, 1602, 1423, 1264, 895, 738. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.23 (s, 1H), 7.81-7.65 (m, 4H), 7.50-7.07 (m, 11H), 6.58 (d, J = 8.5 Hz, 1H), 5.98-5.95 (m, 1H), 4.80-4.79 (m, 1H), 2.77 (ddd, J = 14.3, 12.0, 5.5 Hz, 1H), 2.37 (dt, J = 14.3, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.79, 151.94, 143.85, 132.84, 132.80, 130.89, 130.35, 130.22, 130.07, 129.92, 129.08, 129.06, 129.01, 128.85, 127.21, 127.06, 124.34, 123.49, 123.21, 120.15, 119.91, 118.79, 115.12, 113.90, 72.70, 37.88, 36.25, 36.21. HRMS (ESI) m/z calcd for $C_{29}H_{22}ClO_2$ $(M+H)^+$: 438.1308 found: 438.1330.

1-(1-(4-Bromophenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol(6.2o):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (3:97) mixture as an eluent. White solid. Yield: 169 mg, 70%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 87:13, as determined by a comparison of the following signals: δ 6.08 (d, J = 11.7 Hz, 1H)-major product, 5.96 (d, J = 14.8 Hz, 1H)-minor product. IR (DCM; cm^{-1}): ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.23 (d, J = 44.4 Hz, 1H), 7.76-7.60 (m, 4H), 7.46-7.33 (m, 3H), 7.30-7.14 (m, 4H), 7.07 (q, J = 8.6 Hz, 3H), 6.69 (dd, J = 126.8, 8.5 Hz, 1H), 6.00-5.90 (m, 1H), 4.86-4.71 (m, 1H), 2.76-2.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.73, 151.91, 144.35, 132.74, 132.00, 130.84, 130.41, 130.33, 130.17, 129.90, 129.03, 128.97, 128.83, 127.19, 127.05, 124.32, 123.46, 123.19, 120.86, 120.13, 119.87, 118.77, 115.00, 113.85, 72.65, 37.91, 36.16. HRMS (ESI) m/z calcd for $C_{29}H_{21}BrO_2$ $(M+H)^+$: 480.0725 found: 480.0745.

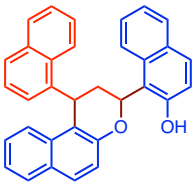
1-(1-(4-(Trifluoromethyl)phenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol



(6.2p): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 114 mg, 48%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of

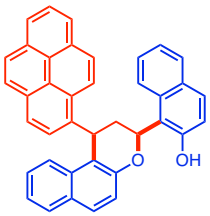
84:16, as determined by a comparison of the following signals: δ 6.14 (d, *J* = 12.2 Hz, 1H)-minor product, 6.03-6.00 (m,1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 1421, 1325, 1265, 1125, 1065, 895, 740. ^{1}H NMR (400 MHz): δ 8.19 (s, 1H), 7.82-7.79 (m, 2H), 7.68-7.60 (m, 4H), 7.48 (d, *J* = 9.8 Hz, 1H), 7.37-7.26 (m, 5H), 7.19-7.16 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 8.7 Hz, 1H), 5.95-5.92 (m, 1H), 4.89 (d, *J* = 5.2 Hz, 1H), 2.86-2.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.90, 153.62, 153.50, 151.98, 149.39, 140.09, 132.58, 130.67, 130.28, 130.12, 129.98, 129.13, 129.00, 128.96, 128.86, 128.80, 127.38, 127.19, 126.85, 125.79, 125.75, 124.30, 123.23, 123.11, 119.82, 119.76, 118.70, 114.50, 113.54, 72.49, 38.27, 36.09. HRMS (ESI) m/z calcd for $C_{29}H_{22}F_3O_2$ $(M+H)^+$: 471.1572 found: 471.1594.

1-(1-(Naphthalen-1-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2q):



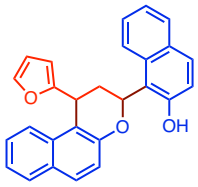
Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 178 mg, 78%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 90:10, as determined by a comparison of the following signals: δ 5.83 (d, *J* = 1.3 Hz, 1H)-minor product, 5.68 (d, *J* = 5.1 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2306, 1423, 1264, 895, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.29-8.27 (m, 2H), 7.95 (dd, *J* = 6.4, 3.2 Hz, 1H), 7.78 (dt, *J* = 9.0, 4.5 Hz, 3H), 7.59-7.48 (m, 4H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.30-7.24 (m, 3H), 7.19-7.14 (m, 1H), 7.08-6.99 (m, 3H), 6.70-6.66 (m, 1H), 6.20 (d, *J* = 8.7 Hz, 1H), 6.11 (d, *J* = 11.0 Hz, 1H), 5.57 (d, *J* = 5.5 Hz, 1H), 2.88-2.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.79, 152.40, 140.63, 134.46, 132.89, 130.80, 130.44, 130.32, 130.17, 129.66, 129.56, 128.86, 128.79, 128.74, 127.84, 127.49, 127.08, 126.90, 126.73, 126.08, 125.41, 124.23, 123.72, 122.97, 122.78, 120.12, 119.82, 118.72, 116.04, 114.01, 73.42, 34.88, 34.29. HRMS (ESI) m/z calcd for $C_{33}H_{24}O_2$ $(M)^+$: 452.1776 found: 452.1757.

1-(1-(Pyren-1-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2r):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 176 mg, 67%. IR (DCM; cm^{-1}): 3942, 369, 3054, 2985, 2305, 1602, 1423, 1265, 895, 752. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.64-8.63 (m, 1H), 8.41-7.28 (m, 15H), 7.18-7.17 (m, 2H), 6.93 (t, *J* = 10.3 Hz, 1H), 6.42-6.28 (m, 2H), 6.15-5.95 (m, 2H), 3.13-3.10 (m, 1H), 2.70 (dd, *J* = 7.5, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, CDCl3): δ 153.80, 152.48, 138.66, 132.94, 131.62, 130.97, 130.76, 130.51, 130.43, 130.20, 129.78, 128.78, 128.71, 128.65, 127.76, 127.68, 127.44, 127.23, 127.10, 126.75, 126.28, 125.65, 125.58, 125.45, 125.25, 124.83, 124.24, 123.76, 122.87, 122.17, 119.88, 119.78, 118.81, 116.16, 114.08, 73.28, 35.47, 35.35. HRMS (ESI) m/z calcd for $C_{39}H_{26}O_2$ $(M)^+$: 527.2011 found: 527.2040.

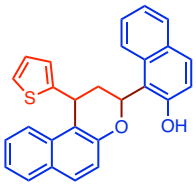
1-(1-(Furan-2-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2s): Purified



by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 119 mg, 61%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 84:16, as determined by a comparison of the following signals: δ 5.00 (d, *J* = 6.3 Hz, 1H)-minor product, 4.92 (d, *J* = 4.0 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3417, 3054, 2985, 2306, 1622, 1599, 1513, 1424, 1264, 1228, 1144, 1063, 1008, 964, 895, 816, 743. ^{1}H NMR (400 MHz): δ 8.20 (s, 1H), 8.20 (s, 1H), 7.73-7.62 (m, 5H), 7.73-7.62 (m, 5H), 7.43-7.07 (m, 7H), 7.43-7.07 (m, 7H), 6.94 (t, *J* = 4.6 Hz, 1H), 6.94 (t, *J* = 4.6 Hz, 1H), 6.27 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.27 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.09-6.06 (m, 1H), 6.09-6.06 (m, 1H), 5.81-5.80 (m, 1H), 5.81-5.80 (m, 1H), 4.77 (d, *J* = 4.2 Hz, 1H), 4.77 (d, *J* = 4.2 Hz, 1H), 2.62-2.49 (m, 2H), 2.62-2.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.11, 153.75, 151.53, 141.91, 132.99, 131.01, 130.26, 130.01, 129.83, 129.04, 129.01, 128.71, 127.09, 127.07, 124.26, 123.20, 123.15, 120.55, 119.89, 118.78, 114.13, 114.11, 110.79, 109.16, 73.69, 32.75, 32.50. HRMS (ESI) m/z calcd for $C_{27}H_{20}O_3$

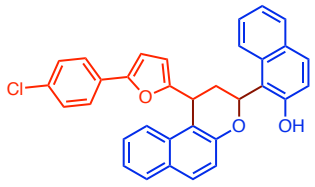
$(M)^+$: 392.1412 found: 392.1402.

1-(1-(Thiophen-2-yl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol (6.2t):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 153 mg, 75%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 90:10, as determined by a comparison of the following signals: δ 5.32 (t, *J* = 9.6 Hz,1H)-minor product, 5.13-5.12 (m, 1H)-major product. IR (DCM; cm^{-1}): 3411, 3054, 2984, 1620, 1598, 1514, 1463, 1403, 1349, 1265, 1227, 1146, 1059, 1027, 1027, 959, 895, 816, 740, 602. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.20 (s, 1H), 7.77-7.64 (m, 5H), 7.37-7.08 (m, 7H), 6.93-6.87 (m, 2H), 6.69 (d, *J* = 3.5 Hz, 1H), 6.18 (dd, *J* = 11.8, 1.2 Hz, 1H), 5.01 (d, *J* = 4.6 Hz, 1H), 2.76-2.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.85, 151.29, 149.06, 132.92, 131.04, 130.32, 130.11, 129.97, 129.04, 128.99, 128.75, 127.20, 127.13, 127.04, 126.77, 124.66, 124.29, 123.44, 123.22, 120.59, 119.91, 118.76, 115.99, 114.05, 73.19, 36.73, 34.09. HRMS (ESI) m/z calcd for $C_{27}H_{21}O_2S$ $(M+H)^+$: 409.1262 found: 409.1228.

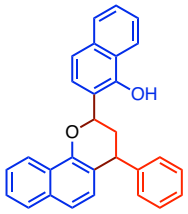
1-(1-(5-(4-Chlorophenyl)furan-2-yl)-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2u):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 170 mg, 68%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 50:50, as determined by a comparison of the following signals: δ 6.11 (d, *J* = 24.0 Hz, 1H)-minor product and 5.94 (d, *J* = 2.7 Hz, 1H)-major product. ^{1}H NMR (400 MHz): δ 1H NMR (700 MHz; CDCl3) δ 8.27 (s, 1H), 7.81-6.91 (m, 13H), 6.56 (d, J = 3.2 Hz, 1H), 6.13 (d, J = 11.6 Hz, 1H), 5.89 (d, J = 2.7 Hz, 1H), 4.89 (d, J = 4.2 Hz, 1H), 2.86-2.60 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.66, 153.75, 152.39, 151.53, 133.15, 133.02, 130.98, 130.32, 130.04, 130.02, 129.35, 129.17, 129.13, 129.02, 128.79, 127.22, 127.13, 125.04, 124.38, 123.28, 123.18, 120.42, 119.92, 118.85, 113.95, 113.94, 112.05, 106.63, 73.98, 32.90,

32.29. HRMS (ESI) m/z calcd for $C_{33}H_{24}ClO_3$ $(M+H)^+$: 503.1414 found: 503.1439.

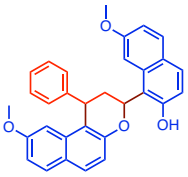
2-(4-Phenyl-3,4-dihydro-2H-benzo[h]chromen-2-yl)naphthalen-1-ol (6.2aa): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. Viscous oil. Yield: 96 mg, 48%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 50:50, as determined by a comparison of the following signals: δ 4.62-4.57 (m, 1H)-minor product and 4.53 (dd, J_1 = 5.6 Hz, J_2 = 0.4 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3425, 3056, 2923, 1622, 1576, 1502, 1453, 1386, 1301, 1260, 1203, 1149, 1099, 1022, 965, 808, 704. ^{1}H NMR (400 MHz; CDCl3) δ 8.29-8.17 (m, 2H), 8.08 (d, J = 43.2 Hz, 1H), 7.78-7.68 (m, 2H), 7.48-7.06 (m, 11H), 6.87 (d, J = 8.5 Hz, 1H), 5.61-5.37 (m, 1H), 4.50-4.40 (m, 1H), 2.81-2.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.04, 150.86, 148.98, 148.89, 145.97, 144.24, 134.28, 134.21, 133.70, 133.39, 128.86, 128.84, 128.67, 128.61, 128.54, 127.83, 127.74, 127.44, 127.40, 127.02, 126.75, 126.69, 126.64, 126.59, 126.49, 126.26, 126.23, 125.59, 125.55, 125.49, 125.14, 125.04, 124.63, 124.58, 122.26, 122.23, 121.64, 121.48, 121.26, 121.21, 120.14, 120.02, 119.84, 117.72, 117.60, 117.38, 80.41, 75.63, 43.32, 40.68, 39.29, 37.08, 34.76, 31.67, 27.00, 25.37, 22.75, 20.80. HRMS (ESI) m/z calcd for $C_{29}H_{22}O_2Na$ $(M+Na)^+$: 425.1518 found: 425.1491.

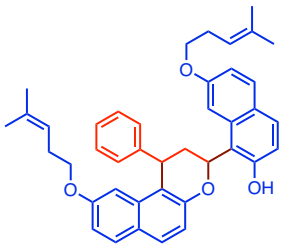
6-(4-(Tert-butyl)phenyl)-1-(8-(4-(tert-butyl)phenyl)-1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2ab): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 119 mg, 61%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 54:46, as determined by a comparison of the following signals: δ 6.18 (dd, J_1 = 29.1 Hz, J_2 = 11.7 Hz,1H)-minor product, 6.08 (dd, J_1 = 29.0 Hz, J_2 = 11.7 Hz 1H)-major product. IR (DCM; cm^{-1}): 3942, 3688, 3414, 3054, 2984, 2684, 2305, 1711, 1603, 1499, 1423, 1264, 1063, 961, 895, 738. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.44-8.30 (m, 1H), 8.08-7.90 (m, 3H), 7.81-7.60 (m, 7H), 7.55-7.50 (m, 4H), 7.39 (dddd, J = 23.7, 18.9, 10.1, 5.0 Hz, 8H), 7.23 (ddt, J = 7.1, 3.9, 1.8 Hz,

2H), 6.68-6.42 (m, 1H), 6.13 (t, J = 12.5 Hz, 1H), 4.93-4.85 (m, 1H), 2.88-2.83 (m, 1H), 2.55-2.50 (m, 1H), 1.43 (d, J = 1.6 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.93, 153.64, 153.57, 152.12, 150.31, 150.19, 145.23, 144.90, 137.84, 137.71, 136.65, 135.62, 135.57, 131.96, 130.45, 130.17, 129.88, 129.85, 129.83, 129.78, 129.20, 128.92, 128.86, 128.66, 128.53, 127.06, 126.92, 126.85, 126.74, 126.57, 126.51, 126.39, 126.34, 126.20, 125.86, 125.78, 125.45, 124.13, 124.11, 120.80, 120.72, 120.14, 119.86, 119.01, 118.88, 117.92, 115.94, 115.56, 114.01, 113.80, 72.90, 72.69, 38.42, 38.32, 36.52, 36.35, 34.58, 31.42. HRMS (ESI) m/z calcd for $C_{49}H_{46}O_2$ $(M)^+$: 666.3498 found: 666.3452.

7-Methoxy-1-(9-methoxy-1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol (6.2ac): 

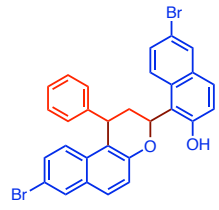
Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 143 mg, 62%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 85:15, as determined by a comparison of the following signals: δ 4.83 (t, J = 5.5 Hz, J_2 = 7.9 Hz,1H)-minor product, 4.76 (d, J = 5.3 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3054, 2985, 2306, 1622, 1424, 1265, 895, 739 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.38 (s, 1H), 7.64-7.48 (m, 4H), 7.26-7.07 (m, 6H), 6.94-6.89 (m, 2H), 6.77-6.70 (m, 2H), 5.99-5.96 (m, 2H), 4.66 (d, J = 5.2 Hz, 1H), 3.24 (d, J = 202.4 Hz, 6H), 2.78-2.35 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.48, 158.35, 154.46, 152.30, 145.73, 130.29, 130.09, 129.80, 129.16, 129.02, 128.56, 126.65, 125.31, 123.99, 117.14, 116.04, 115.99, 115.92, 114.56, 113.21, 103.21, 98.39, 72.70, 54.95, 54.49, 38.78, 35.75. HRMS (ESI) m/z calcd for $C_{31}H_{26}O_4$ $(M)^+$: 462.1831 found: 462.1843.

7-((4-Methylpent-3-en-1-yl)oxy)-1-(9-((4-methylpent-3-en-1-yl)oxy)-1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2-ol (6.2ad): Purified by silica-gel column



chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 119 mg, 61%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 82:18, as determined by a comparison of the following signals: δ 3.41 (t, *J* = 6.7 Hz,1H)-minor product, 3.30 (q, *J* = 7.6 Hz, 1H)-major product. IR (DCM; cm^{-1}): 3364, 3057, 2921, 2358, 1891, 1621, 1515, 1450, 1384, 1348, 1264, 1224, 1139, 1103, 1065, 1029, 891, 833, 739, 704, 632, 602. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.74 (d, *J* = 7.7 Hz, 1H), 8.44 (d, *J* = 31.8 Hz, 1H), 8.06-8.02 (m, 1H), 7.95-7.77 (m, 3H), 7.73-7.59 (m, 6H), 7.55-7.34 (m, 11H), 7.26-7.15 (m, 2H), 6.79-6.64 (m, 1H), 6.13 (d, *J* = 11.3 Hz, 1H), 4.95 (d, *J* = 4.6 Hz, 1H), 2.90-2.51 (m, 2H), 1.61-1.36 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.03, 157.68, 154.45, 152.22, 145.65, 134.38, 134.09, 133.64, 132.08, 130.21, 130.02, 129.80, 129.11, 128.89, 128.54, 126.74, 125.24, 123.99, 120.60, 119.55, 117.01, 116.38, 116.28, 115.95, 114.52, 113.29, 104.04, 99.22, 72.53, 67.35, 66.97, 38.67, 35.72, 28.08, 27.84, 25.85, 25.79, 17.97, 17.90. HRMS (ESI) m/z calcd for $C_{41}H_{43}O_4$ $(M+H)^+$: 599.3162 found: 599.3175.

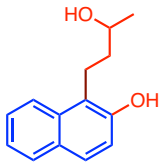
6-Bromo-1-(8-bromo-1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl) naphthalen-2-ol



(6.2ae): Purified by silica-gel column chromatography using an ethyl acetate/hexane (2:98) mixture as an eluent. White solid. Yield: 119 mg, 61%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 88:12, as determined by a comparison of the following signals: δ 5.99 (d, *J* = 5.4 Hz,1H)-minor product, 5.95-5.92 (m, 1H)-major product. IR (DCM; cm^{-1}): 3417, 3054, 2984, 1590, 1498, 1424, 1391, 1264, 1230, 1150, 1071, 958, 892, 810, 740. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.24 (s, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 9.1 Hz, 1H), 7.37-7.25 (m, 4H), 7.20-7.16 (m, 2H),

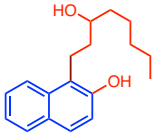
7.11-7.04 (m, 2H), 6.30 (d, J = 9.2 Hz, 1H), 5.93-5.90 (m, 1H), 4.78 (d, J = 4.8 Hz, 1H), 2.78-2.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.95, 152.05, 144.86, 131.54, 131.43, 130.79, 130.69, 130.35, 130.19, 130.05, 129.40, 129.37, 129.06, 128.79, 128.57, 127.25, 125.52, 122.07, 121.05, 119.85, 118.11, 116.80, 115.98, 114.14, 72.83, 38.36, 36.53. HRMS (ESI) m/z calcd for $C_{29}H_{20}Br_2O_2$ $(M)^+$: 560.9830 found: 560.9811.

1-(3-Hydroxybutyl)naphthalen-2-ol (6.3a): Purified by silica-gel column chromatography



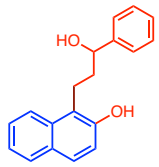
using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 86 mg, 80%. IR (DCM; cm^{-1}): 3421, 3151, 3066, 2926, 2890, 1509, 1460, 1440, 1317, 1262, 1239, 1130, 987, 916, 813. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.41 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.28-7.24 (m, 1H), 7.10 (d, J = 8.8 Hz, 1H), 3.66-3.62 (m, 1H), 3.19-3.13 (m, 2H), 1.92-1.68 (m, 3H), 1.14 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.50, 133.39, 129.64, 128.87, 128.22, 126.44, 123.08, 122.81, 119.07, 118.56, 66.90, 37.61, 23.92, 21.01. HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2$ $(M)^+$: 216.1150 found: 216.1161.

1-(3-Hydroxyoctyl)naphthalen-2-ol (6.3b): Purified by silica-gel column chromatography



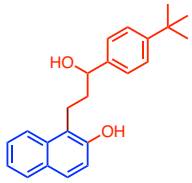
using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 121 mg, 90%. IR (DCM; cm^{-1}): 3343, 3270, 2946, 2920, 2852, 1514, 1462, 1444, 1367, 1264, 1227, 1173, 1127, 1072, 960, 922, 807, 739. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.16 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.51 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.38-7.34 (m, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.54 (dd, J = 7.5, 2.8 Hz, 1H), 3.26 (dq, J = 9.6, 4.8 Hz, 2H), 2.60 (s, 1H), 2.05-1.82 (m, 2H), 1.51-1.18 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.45, 133.37, 129.58, 128.80, 128.13, 126.37, 123.00, 122.77, 119.05, 70.92, 37.87, 35.86, 31.92, 25.41, 22.63, 20.86, 14.07. HRMS (ESI) m/z calcd for $C_{18}H_{24}O_2$ $(M)^+$: 272.1776 found: 272.1795.

1-(3-Hydroxy-3-phenylpropyl)naphthalen-2-ol (6.3c): Purified by silica-gel column



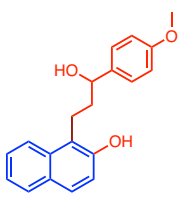
chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 118 mg, 85%. IR (DCM; cm^{-1}): 3377, 3144, 3064, 3029, 2964, 1512, 1442, 1358, 1340, 1232, 1051, 949, 807, 746, 696. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.97 (s, 1H), 7.73 (dd, *J* = 22.0, 8.2 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.36 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.26-7.04 (m, 7H), 4.45 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.28-3.13 (m, 2H), 2.10-2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.28, 143.76, 133.38, 129.62, 128.79, 128.63, 128.29, 127.95, 126.46, 125.89, 123.10, 122.77, 118.81, 118.28, 73.02, 38.01, 21.22. HRMS (ESI) m/z calcd for $C_{19}H_{18}O_2$ $(M)^+$: 278.1307 found: 278.1273.

1-(3-(4-(*tert*-Butyl)phenyl)-3-hydroxypropyl)naphthalen-2-ol (6.3d): Purified by silica-gel



column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 146 mg, 87%. IR (DCM; cm^{-1}): 3291, 2958, 2866, 1621, 1598, 1513, 1463, 1396, 1265, 1222, 1066, 968, 810, 744. ^{1}HNMR (400 MHz; $CDCl_3$): δ 7.71 (dd, *J* = 21.3, 8.3 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.34 (td, *J* = 6.6, 1.6 Hz, 1H), 7.25-7.18 (m, 3H), 7.05 (dd, *J* = 8.5, 6.3 Hz, 3H), 4.42 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.28-3.13 (m, 2H), 2.14-1.97 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.41, 152.38, 151.01, 140.67, 133.40, 129.58, 128.77, 128.24, 126.40, 125.71, 125.53, 123.06, 122.79, 118.92, 118.27, 72.79, 37.80, 34.62, 31.42, 21.30. HRMS (ESI) m/z calcd for $C_{23}H_{26}O_2Na$ $(M+Na)^+$: 357.1830 found: 357.1827.

1-(3-Hydroxy-3-(4-methoxyphenyl)propyl)naphthalen-2-ol (6.3e): Purified by silica-gel



column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 72 mg, 47%. IR (DCM; cm^{-1}): 3402, 2923, 1667, 1611, 1611, 1511, 1462, 1440, 1394, 1302, 1234, 1173, 1062, 1028, 973, 812, 753. (400 MHz; $CDCl_3$): δ 7.72 (td, *J* = 14.9, 8.3 Hz, 2H), 7.56 (t, *J* = 10.2 Hz, 1H), 7.42-7.36

(m, 1H), 7.32-7.28 (m, 2H), 7.26-7.24 (m, 1H), 7.13-7.04 (m, 2H), 6.77 (dd, J = 56.4, 8.7 Hz, 2H), 5.11 (s, 1H), 4.97-4.37 (m, 1H), 3.69 (d, J = 27.3 Hz, 3H), 3.26-3.04 (m, 2H), 2.28-2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.22, 159.12, 152.70, 152.39, 135.67, 133.56, 133.22, 132.94, 129.37, 128.88, 128.59, 128.35, 128.06, 127.65, 127.40, 127.05, 126.26, 126.23, 123.18, 122.84, 122.58, 121.89, 119.15, 118.80, 118.03, 113.86, 113.77, 113.49, 76.67, 72.33, 55.24, 55.16, 37.58, 29.44, 21.78, 21.12. HRMS (ESI) m/z calcd for $C_{20}H_{20}O_3$ $(M)^+$: 308.1412 found: 308.1391.

1-(3-Hydroxy-3-(thiophen-2-yl)propyl)naphthalen-2-ol (6.3f): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. Brown solid. Yield: 78 mg, 55%. IR (DCM; cm^{-1}): 3372, 3218, 3104, 3070, 2921, 2851, 1631, 1513, 1441, 1358, 1414, 1331, 1265, 1232, 1177, 1071, 944, 850, 810, 747. 1H NMR (400 MHz; CDCl3): δ 7.76 (dd, J_1 = 34.8, J_2 = 8.6 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.39 (td, J_1 = 7.7, J_2 =1.5 Hz, 1H), 7.28-7.24 (m, 1H), 7.17-7.08 (m, 2H), 6.83 (dd, J_1 =4.9, J_2 =2.9 Hz, 2H), 4.73 (dd, J_1 = 10.5, J_2 =3.6 Hz, 1H), 3.31-3.20 (m, 2H), 3.00 (s, 1H), 2.32-2.16 (m, 2H). ^{13}C NMR (101 MHz, CDCl3): δ 152.22, 147.15, 133.26, 129.52, 128.73, 128.32, 126.72, 126.44, 125.03, 124.44, 123.07, 122.66, 118.77, 117.74, 68.47, 37.85, 21.04. HRMS (ESI) m/z calcd for $C_{17}H_{17}O_2S$ $(M+H)^+$: 285.0949 found: 285.0874.

1-(3-([1,1'-Biphenyl]-4-yl)-3-hydroxypropyl)naphthalen-2-ol (6.3g): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 127 mg, 72%. IR (DCM; cm^{-1}): 3399, 3194, 3052, 3027, 2926, 2519, 2374, 1513, 1486, 1263, 1237, 1059, 1004, 945, 832, 809, 761, 741. ^{1}H NMR (400 MHz; CD_3OD): δ 7.83 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 7.9, 0.3 Hz, 1H), 7.64-7.59 (m, 5H), 7.49-7.25 (m, 7H), 7.12 (d, J = 8.8 Hz, 1H), 4.76 (s, 1H), 3.26-3.05 (m, 2H), 2.17-2.02 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD): δ 151.84, 144.08,

140.87, 139.99, 133.37, 129.06, 128.41, 128.07, 127.01, 126.80, 126.49, 126.45, 126.27, 125.63, 122.32, 122.00, 119.35, 117.35, 73.42, 38.56, 20.97. HRMS (ESI) m/z calcd for $C_{25}H_{22}O_2$ $(M)^+$: 354.1620 found: 354.1595.

6-(4-(*tert*-Butyl)phenyl)-1-(3-hydroxybutyl)naphthalen-2-ol (6.3h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 189 mg, 73%. IR (DCM; cm^{-1}): 3459, 3179, 2954, 2863, 1500, 1461, 1436, 1359, 1264, 1202, 989, 918, 817. ^1H NMR (400 MHz; $CDCl_3$): δ 7.71 (dd, *J* = 21.3, 8.3 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.34 (td, *J* = 6.6, 1.6 Hz, 1H), 7.25-7.18 (m, 3H), 7.05 (dd, *J* = 8.5, 6.3 Hz, 3H), 4.42 (dd, *J* = 10.9, 3.1 Hz, 1H), 3.28-3.13 (m, 2H), 2.14-1.97 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.41, 152.38, 151.01, 140.67, 133.40, 129.58, 128.77, 128.24, 126.40, 125.71, 125.53, 123.06, 122.79, 118.92, 118.27, 72.79, 37.80, 34.62, 31.42, 21.30. HRMS (ESI) m/z calcd for $C_{24}H_{28}O_2$ $(M)^+$: 348.2089 found: 348.2118.

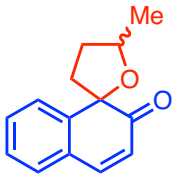
1-(3-Hydroxybutyl)-7-methoxynaphthalen-2-ol (6.3i): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 189 mg, 63%. IR (DCM; cm^{-1}): 3351, 2957, 2930, 2827, 1624, 1509, 1458, 1354, 1227, 1213, 1189, 1132, 1028, 944, 829, 801. ^1H NMR (400 MHz; $CDCl_3$): δ 7.57 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.92 (dt, *J* = 8.5, 4.1 Hz, 2H), 5.51 (s, 1H), 3.83 (s, 3H), 3.61 (ddd, *J* = 10.0, 6.5, 3.3 Hz, 1H), 3.20-2.98 (m, 2H), 1.85-1.71 (m, 2H), 1.10 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.25, 152.61, 134.56, 130.33, 127.82, 124.90, 117.80, 116.14, 114.89, 102.24, 66.73, 55.39, 37.24, 23.40, 21.04. HRMS (ESI) m/z calcd for $C_{15}H_{18}O_3$ $(M)^+$: 246.1256 found: 246.1221.

6-Bromo-1-(3-hydroxybutyl)naphthalen-2-ol (6.3j): Purified by silica-gel column chromatography using an ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 110 mg, 75%. IR (DCM; cm^{-1}): 3399, 3139, 2964, 2900,

2776, 2736, 1581, 1499, 1451, 1351, 1238, 1206, 1059, 990, 916, 809, 780. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.94 (d, J = 2.1 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.59-7.53 (m, 2H), 7.20 (d, J = 8.8 Hz, 1H), 3.73-3.67 (m, 1H), 3.28-3.14 (m, 2H), 1.97-1.82 (m, 2H), 1.24 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.98, 130.94, 129.82, 129.71, 128.60, 126.33, 123.67, 119.32, 117.84, 115.77, 65.87, 36.51, 23.01, 20.01. $C_{14}H_{15}BrO_2$ $(M)^+$: 294.0255 found: 294.0268.

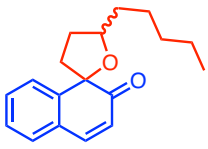
Spectral Data for Synthetic Transformations:

5-Methyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (6.4a)[4]: Purified by



silica-gel column chromatography using an ethyl acetate/hexane (10:80) mixture as an eluent. Viscous oil. Yield: 15 mg, 75%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 76:24, as determined by a comparison of the following signals: ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.63-4.52 (m, 1H)-major product, 4.16 (dt, J_1 = 15.9 Hz, J_2 = 7.2 Hz)-minor product. ^{1}H NMR (400 MHz) δ 7.57 (t, J = 8.8 Hz, 1H), 7.39-7.23 (m, 4H), 6.07 (d, J = 9.9 Hz, 1H), 4.70-4.65 (m, 1H), 2.50-2.36 (m, 1H), 2.202.00 (m, 1H), 1.93-1.80 (m, 1H), 1.71-1.62 (m, 1H), 1.50 (dd, J_1= 21.1Hz, J_2 = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3, 202.9, 145.5, 144.7, 144.3, 130.2, 129.2, 129.0, 127.8, 127.7, 125.6, 124.1, 88.7, 88.2, 79.8, 78.9, 41.4, 40.7, 32.0, 21.0, 20.9.

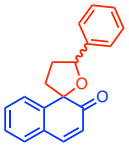
5-Pentyl-4,5-dihydro-2'H,3H-spiro[furan-2,1'-naphthalen]-2'-one (6.4b)[4]: Purified by



silica- gel column chromatography using an ethyl acetate/hexane (10:80) mixture as an eluent. Viscous oil. Yield: 21 mg, 78%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 74:26, as determined by a comparison of the following signals: δ ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.55 (quintet, J = 6.7 Hz, 1H)-major product, 4.50-4.46 (m, 1H)-minor product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.52 (d, J = 7.8 Hz,

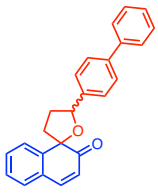
1H), 7.33-7.17 (m, 4H), 6.01 (d, J = 9.9 Hz, 1H), 4.52-4.40 (m, 1H), 2.41-2.29 (m, 1H), 2.14-1.94 (m, 1H), 1.89-1.69 (m, 2H), 1.69-1.23 (m, 8H), 0.86-0.78 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3, 203.0, 145.6, 144.6, 144.2, 130.3, 130.2, 129.7, 129.6, 129.1, 129.0, 127.8, 127.7, 125.5, 124.1, 124.1, 88.3, 87.9, 84.2, 83.0, 41.1, 40.3, 36.0, 35.5, 32.1, 30.2, 29.9, 26.3, 26.1, 22.8, 22.7, 14.2, 14.1.

5-Phenyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (6.4c): Purified by



silica-gel column chromatography using an ethyl acetate/hexane (10:80) mixture as an eluent. Viscous oil. Yield: 22 mg, 80%. ^{1}H NMR analysis of the crude reaction mixture showed a d. r. of 74:26, as determined by a comparison of the following signals: ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.63 (t, J = 7.2 Hz, 1H)-major product, 5.47 (dd, J_1 = 10.0 Hz, J_2 = 5.3 Hz, 1H)-minor product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.77-7.19 (m, 10H), 6.06 (d, J = 9.9 Hz, 1H), 5.58-5.37 (m, 1H), 3.57-2.40 (m, 2H), 2.23-1.95 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9, 202.6, 146.2, 145.0, 144.9, 144.4, 141.8, 130.4, 130.3, 129.7, 128.5, 128.4, 128.0, 127.6, 126.1, 125.8, 125.6, 124.1, 124.0, 88.2, 87.6, 85.7, 83.7, 41.5, 40.6, 33.5, 32.9.

5-([1,1'-Biphenyl]-4-yl)-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (6.4d):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (20:80) mixture as an eluent. Viscous oil. Yield: 23 mg, 65%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 60:40, as determined by a comparison of the following signals: ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.74-5.70 (m, 1H)-major product, 5.55 (dd, J_1 = 9.4, J_2 =6.0 Hz, 1H)-minor product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.99-7.83 (m, 1H), 7.71-7.52 (m, 7H), 7.45-7.21 (m, 7H), 6.09 (d, J = 9.9 Hz, 1H), 5.64-5.45 (m, 1H), 2.55-2.48 (m, 2H), 2.13-2.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9, 202.6, 146.0, 144.9, 144.9, 144.4, 141.1, 140.9, 140.8, 140.6, 140.4, 130.4, 130.3, 129.6, 129.5, 129.2, 129.1, 128.8, 128.7, 127.9, 127.8, 127.3, 127.2, 127.2, 127.1, 127.1, 126.5, 125.7, 125.6, 124.0,

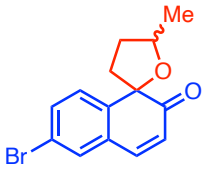
124.0, 88.2, 87.6, 85.4, 83.4, 41.5, 40.6, 33.4, 32.8.

6'-(4-(*tert*-Butyl)phenyl)-5-methyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (**6.4e**): Purified by silica-gel column chromatography using an ethyl acetate/hexane (10:80) mixture as an eluent. Yellow solid. Yield: 30 mg, 87%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 74:26, as determined by a comparison of the following signals: δ ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.27-2.20 (m, 1H)-major product, 2.12-2.07 (m, 1H)-minor product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.69-7.40 (m, 8H), 6.16 (d, J = 9.9 Hz, 1H), 4.74 (dd, J_1 = 13.6 Hz, J_2 =6.1 Hz, 1H), 2.46 (dt, J_1 = 12.6 Hz, J_2 =7.8 Hz, 1H), 2.26-2.21 (m, 1H), 2.00 (ddd, J_1 = 12.7 Hz, J_2 = 7.8 Hz, J_3 =5.0 Hz, 1H), 1.79-1.72 (m, 1H), 1.59-1.54 (m, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.2, 202.9, 150.9, 150.9, 144.8, 144.6, 144.4, 143.9, 140.8, 140.7, 137.1, 130.1, 129.9, 128.8, 128.6, 127.7, 127.5, 126.7, 126.1, 126.0, 125.9, 125.9, 124.4, 88.5, 88.0, 79.8, 78.9, 40.7, 34.7, 32.2, 31.4, 21.1.

7'-Methoxy-5-methyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (**6.4f**): Purified by silica-gel column chromatography using an ethyl acetate/hexane (10:80) mixture as eluent. Viscous oil. Yield: 20 mg, 82%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 85:15, as determined by a comparison of the following signals: ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.72-4.63 (m, 1H)-major product, 4.61 (t, J = 5.0 Hz, 1H)-minor product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.23 (t, J = 9.6 Hz, 1H), 7.16-7.06 (m, 2H), 6.71 (dt, J_1 = 8.2 Hz, J_2 =3.3 Hz, 1H), 5.90 (d, J = 9.8 Hz, 1H), 4.66-4.61 (m, 1H), 3.79 (s, 3H), 2.34 (dt, J_1 = 12.6 Hz, J_2 =7.8 Hz, 1H), 2.13-2.06 (m, 1H), 1.84 (td, J_1 = 8.2 Hz, J_2 =4.5 Hz, 1H), 1.66-1.59 (m, 1H), 1.45 (dd, J_1 = 22.8 Hz, J_2 =6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.27, 202.94, 161.69, 161.50, 148.67, 148.08, 144.62, 144.17, 130.94, 130.77, 123.03, 122.90, 121.56, 112.67, 112.33, 112.21, 111.66, 88.89, 88.35, 79.96, 79.03, 55.58, 55.49, 41.77, 41.02, 31.95, 31.44, 21.17,

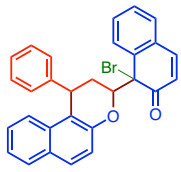
20.93.

6'-Bromo-5-methyl-4,5-dihydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-2'-one (6.4g):



Purified by silica-gel column chromatography using an ethyl acetate/hexane (10:80) mixture as an eluent. Viscous oil. Yield: 25 mg, 85%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 77:23, as determined by a comparison of the following signals: ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.52-2.47 (m, 1H)-minor product, 2.42 (dt, J_1 = 12.7 Hz, J_2 = 7.7 Hz, 1H)-major product. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.53-7.41 (m, 3H), 7.28 (dd, J_1 = 11.3 Hz, J_2 = 7.3 Hz, 1H), 6.14 (d, J = 9.9 Hz, 1H), 4.70 (dd, J = 13.6 Hz, J_2 = 6.2 Hz, 1H), 2.42 (dt, J_1 = 12.7 Hz, J_2 = 7.7 Hz, 1H), 2.22-2.17 (m, 1H), 1.93-1.65 (m, 3H), 1.52 (dd, J_1 = 24.0 Hz, J_2 = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2, 201.9, 144.8, 144.1, 142.9, 142.5, 132.8, 132.7, 131.5, 131.4, 131.4, 131.3, 127.2, 127.2, 125.2, 125.2, 121.5, 121.3, 88.3, 87.8, 79.8, 78.9, 41.1, 40.4, 31.9, 31.2, 20.9, 20.7.

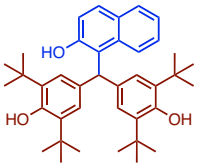
1-Bromo-1-(1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2(1*H*)-one



(6.4h): Purified by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 109 mg, 91%. ^{1}H NMR (400 MHz): δ 8.08 (d, J = 7.6 Hz, 1H), 7.66-7.49 (m, 2H), 7.37-7.06 (m, 11H), 6.96-6.86 (m, 2H), 6.16 (dd, J_1 = 45.0 Hz, J_2 = 9.9 Hz, 1H), 4.79-4.51 (m, 2H), 1.99-1.82 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$): δ 192.47, 152.41, 145.32, 144.19, 139.51, 132.59, 131.47, 130.65, 129.73, 129.47, 129.24, 129.19, 129.13, 128.74, 128.49, 128.31, 128.15, 126.77, 126.74, 124.07, 123.55, 123.09, 118.81, 114.51, 76.68, 61.64, 37.38, 31.42.

Spectral Data for Trapped Naphthyl Radical:

4,4'-((2-Hydroxynaphthalen-1-yl)methylene)bis(2,6-di-*tert*-butylphenol) (6.5d): Purified



by silica-gel column chromatography using an ethyl acetate/hexane (5:95) mixture as an eluent. White solid. Yield: 71 mg, 98%. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.16-8.08 (m, 1H), 7.82-7.80 (m, 1H), 7.74 (t, J = 7.3 Hz, 1H),

7.51-7.47 (m, 1H), 7.37-7.34 (m, 1H), 7.10-7.05 (m, 5H), 5.50 (d, J = 0.3 Hz, 1H), 5.17 (s, 2H), 1.36 (s, 36H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 152.6, 136.3, 133.6, 132.3, 129.5, 129.1, 128.6, 126.5, 125.5, 122.9, 122.8, 120.8, 119.9, 48.2, 34.2, 30.2, 30.0.

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^{1}H and ^{13}C NMR Spectras:

Figure 6.7 ^{1}H NMR spectrum of 1-(1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl) **6.2a**:

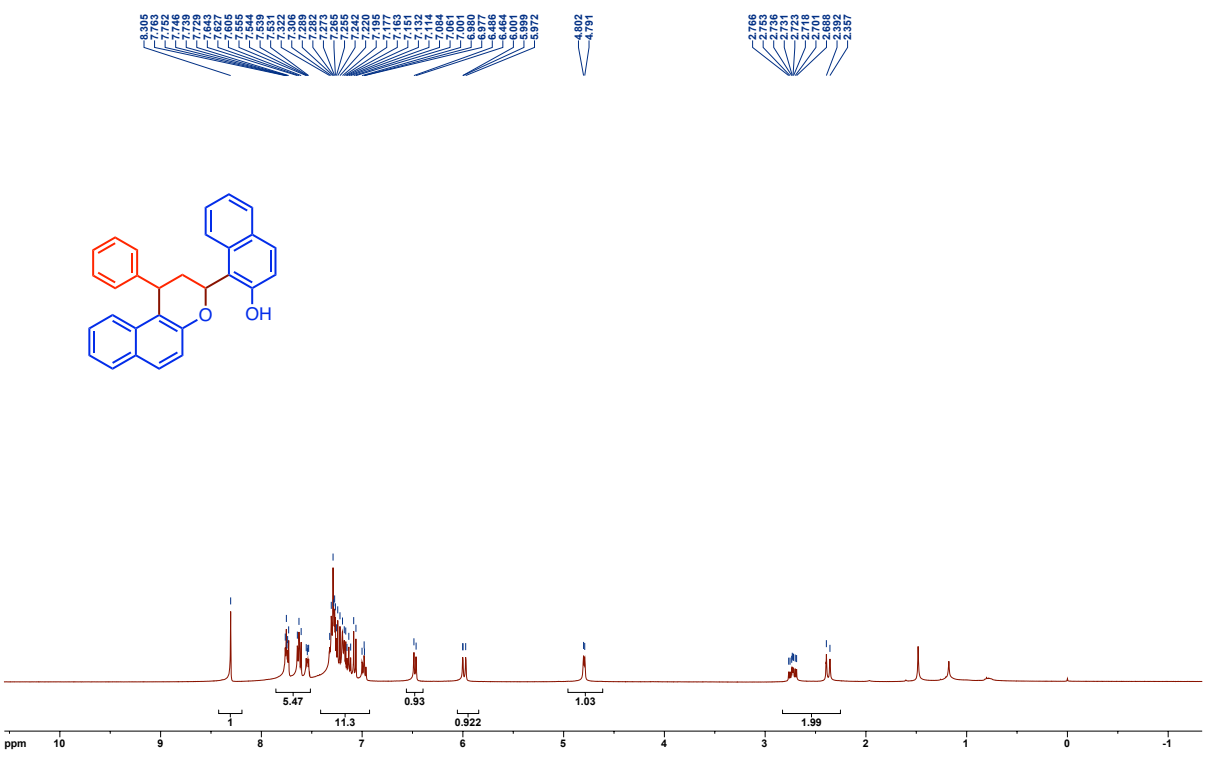


Figure 6.8 ^{13}C NMR spectrum of 1-(1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl) **6.2a**:

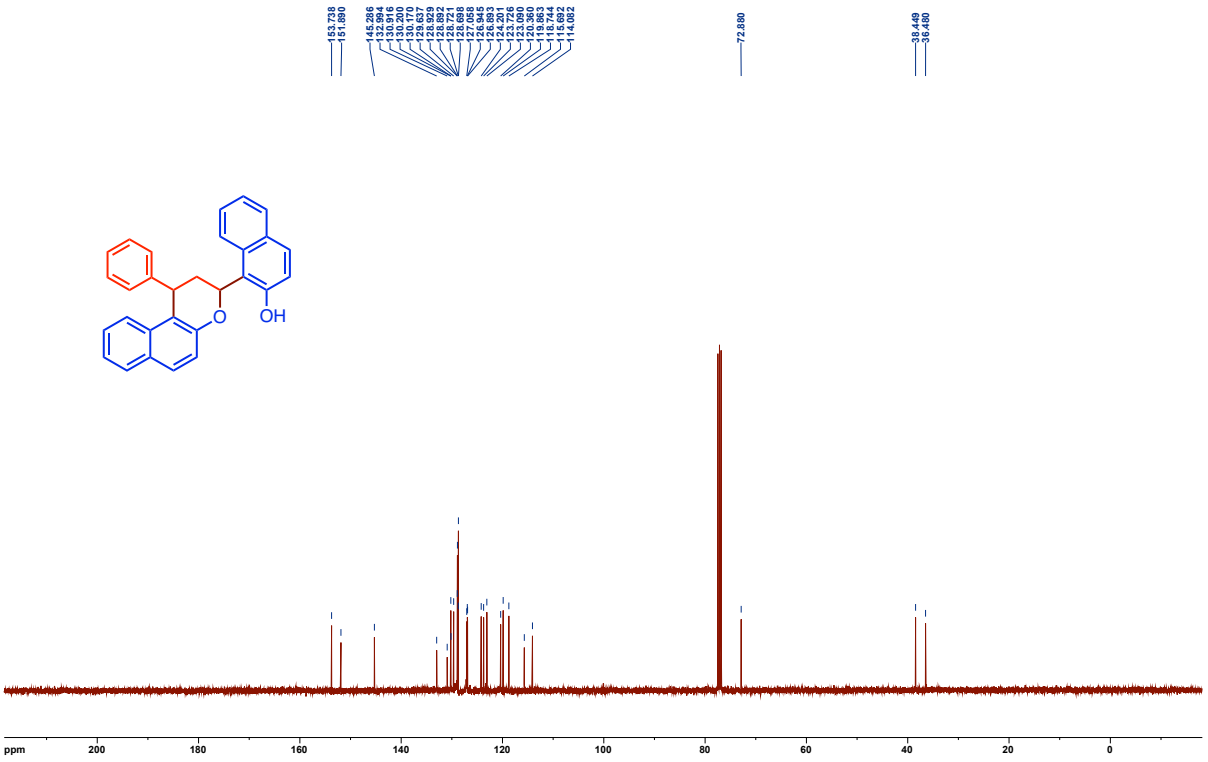


Figure 6.9 ^{1}H NMR spectrum of 7-methoxy-1-(9-methoxy-1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol **6.2ac:**

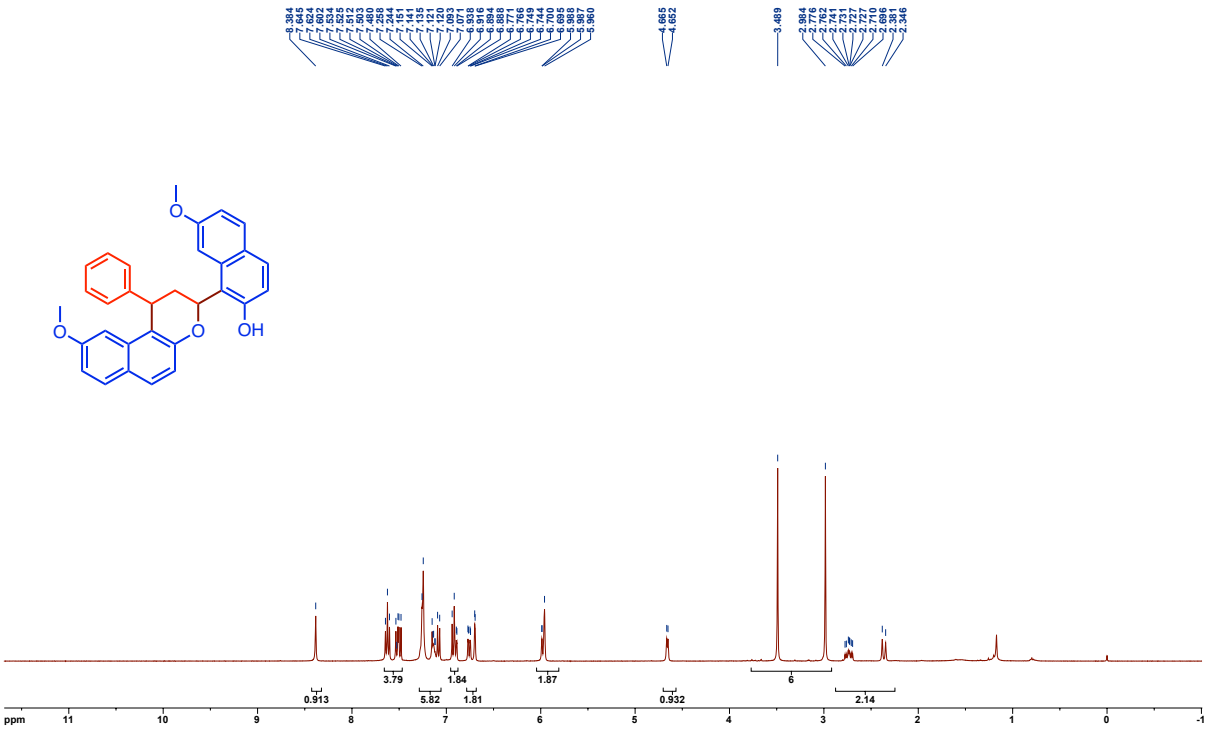


Figure 6.10 ^{13}C NMR spectrum of 7-methoxy-1-(9-methoxy-1-phenyl-2,3-dihydro-1H-benzo[f]chromen-3-yl)naphthalen-2-ol **6.2ac:**

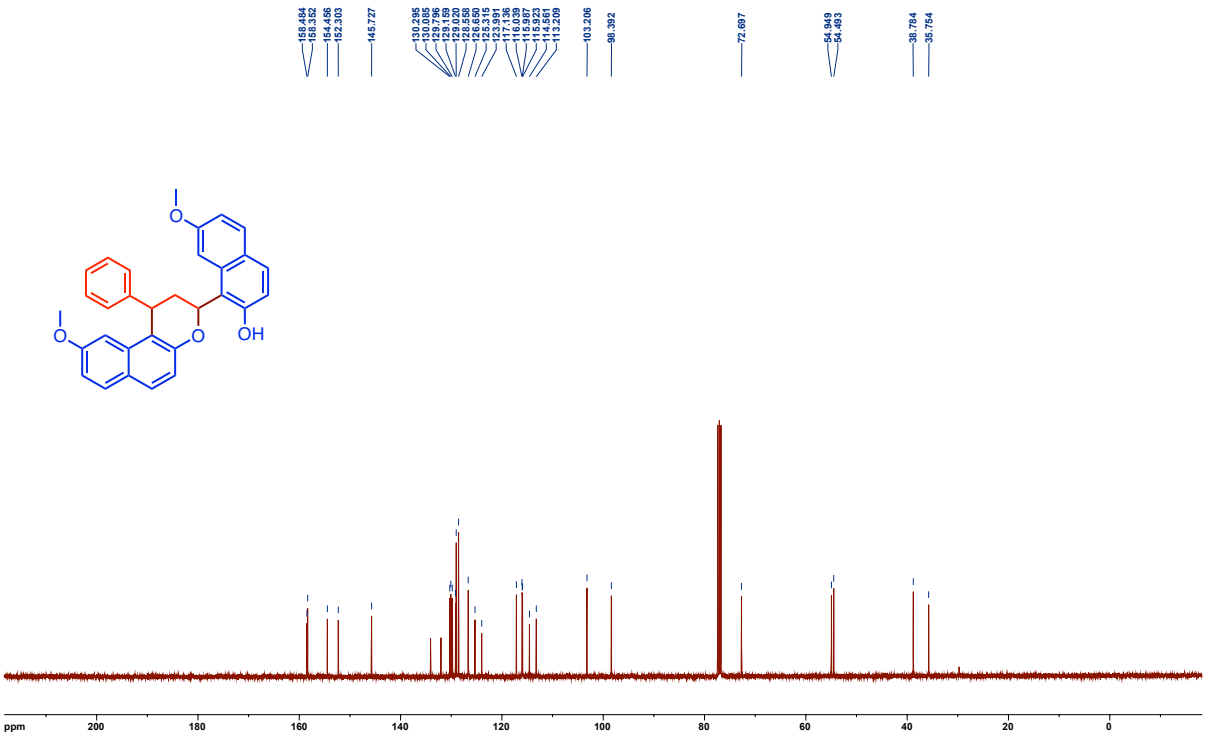


Figure 6.11 ^{1}H NMR spectrum of 1-(3-hydroxybutyl)naphthalen-2-ol **6.3a**:

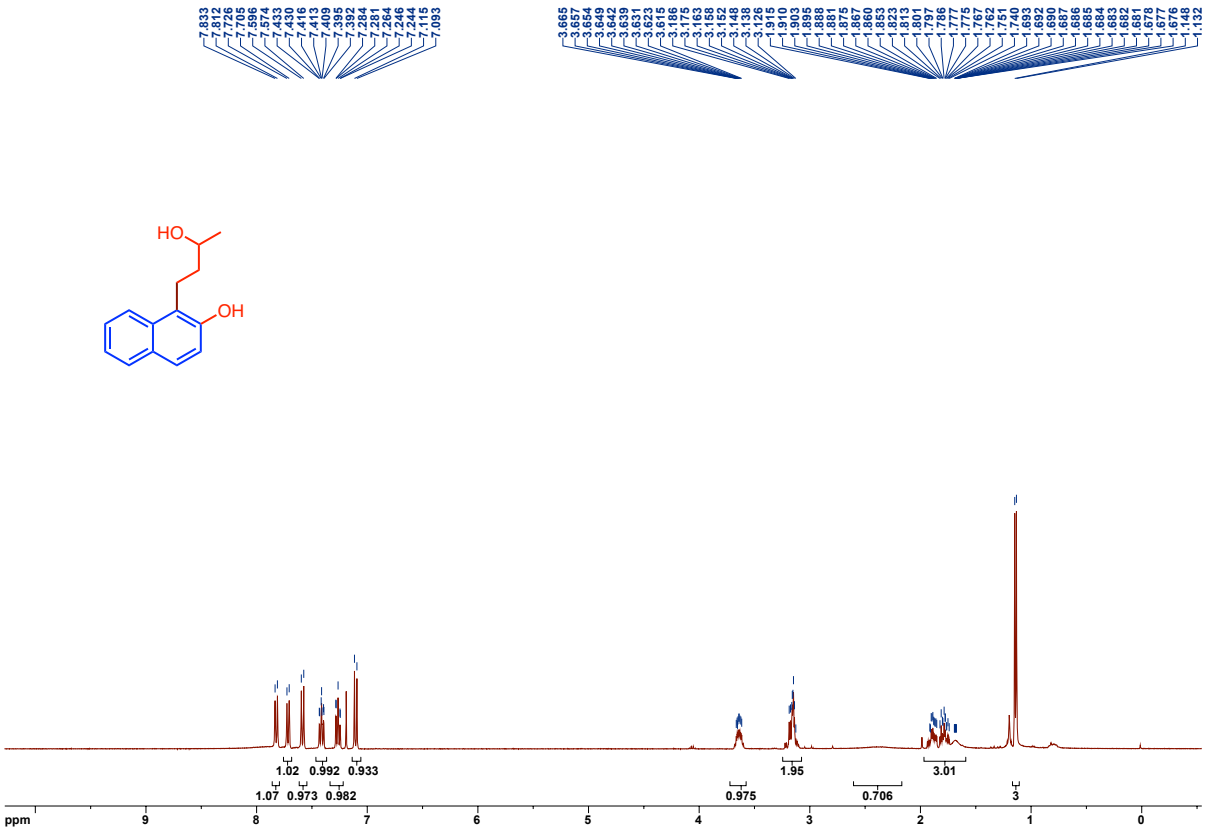


Figure 6.12 ^{13}C NMR spectrum of 1-(3-hydroxybutyl)naphthalen-2-ol **6.3a**:

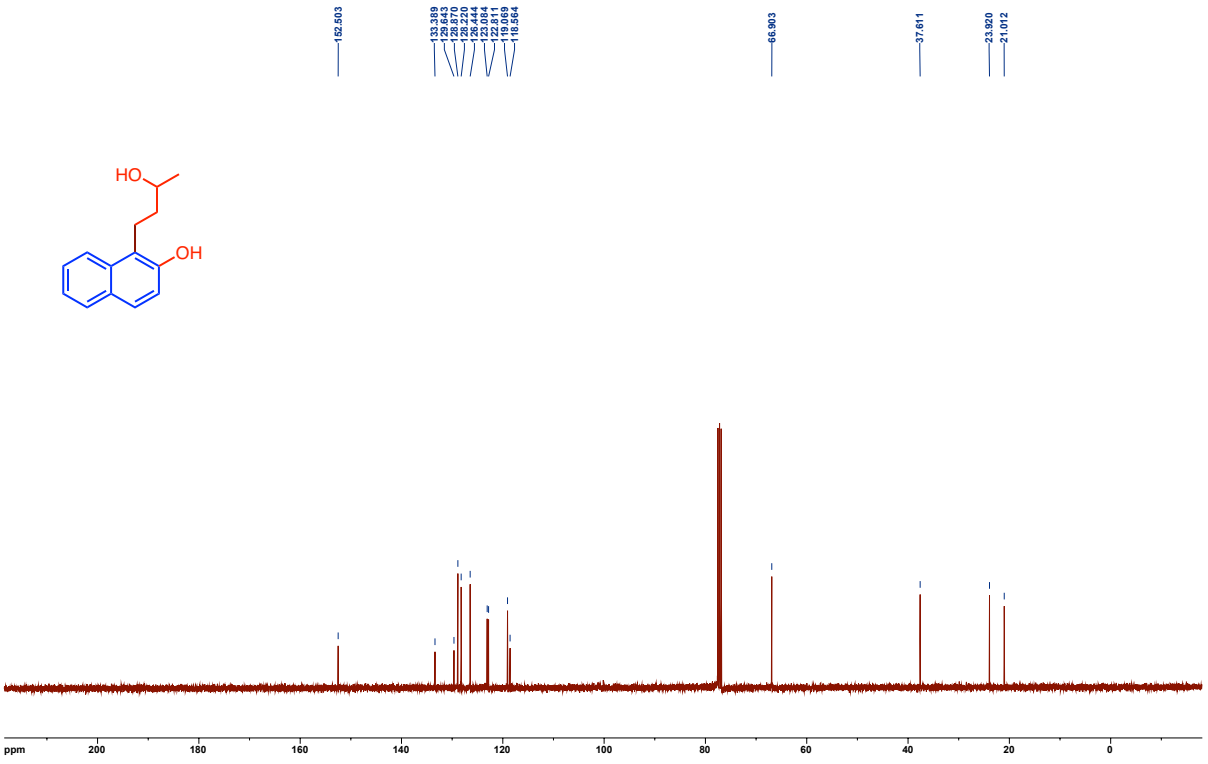


Figure 6.13 ^{1}H NMR spectrum of 5-methyl-4,5-dihydro-2'H,3H-spiro[furan-2,1'-naphthalen]-2'-one **6.4a:**

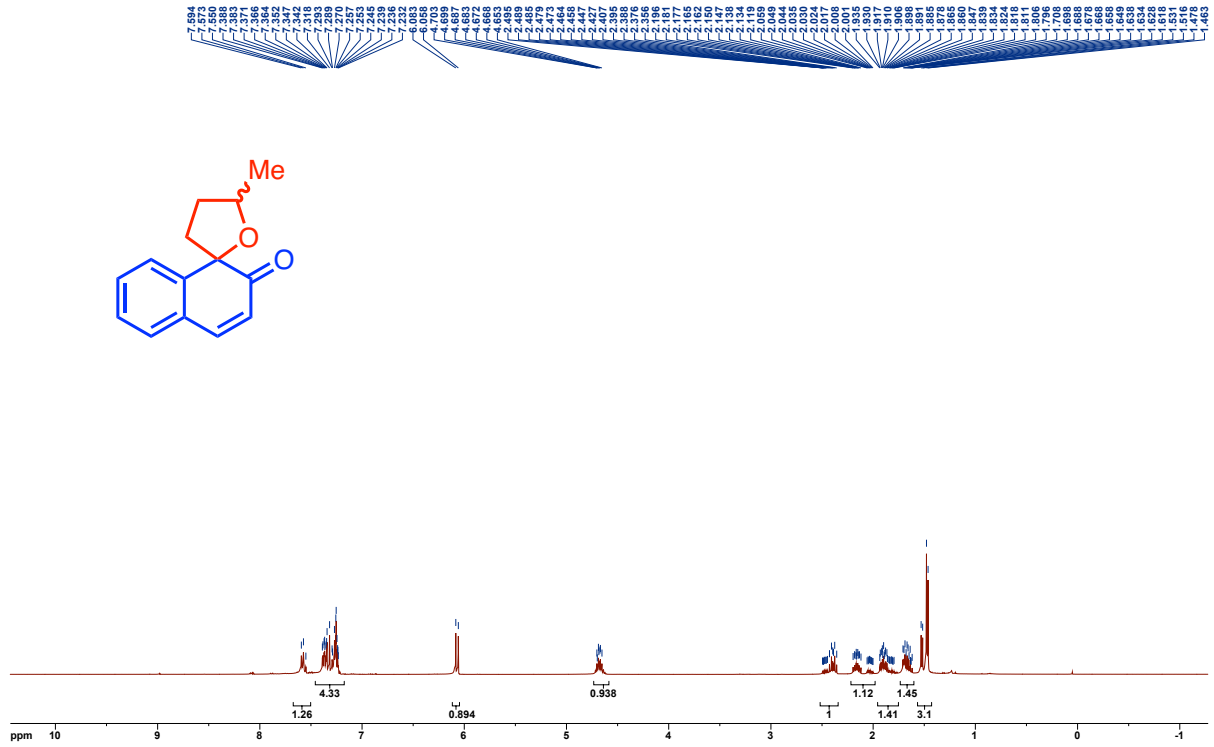


Figure 6.14 ^{13}C NMR spectrum of 5-methyl-4,5-dihydro-2'H,3H-spiro[furan-2,1'-naphthalen]-2'-one **6.4a:**

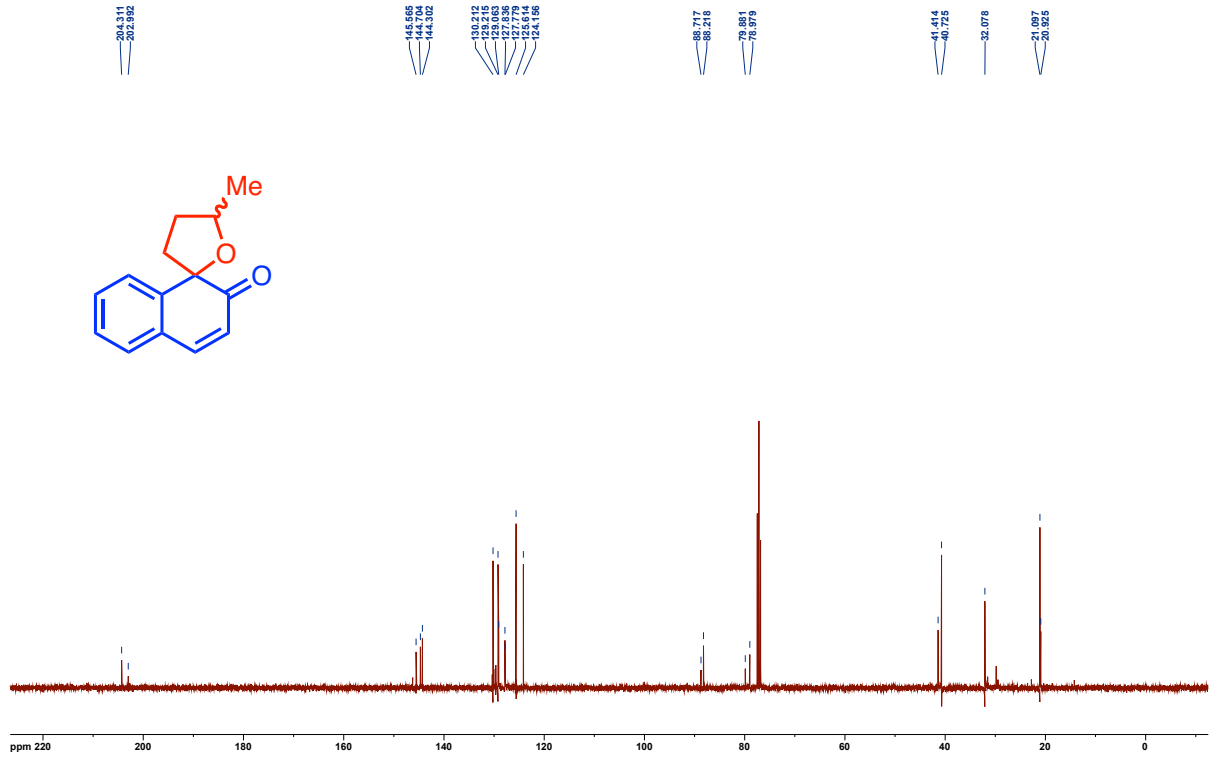


Figure 6.15 ^{1}H NMR spectrum 1-bromo-1-(1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2(1*H*)-one **6.4h:**

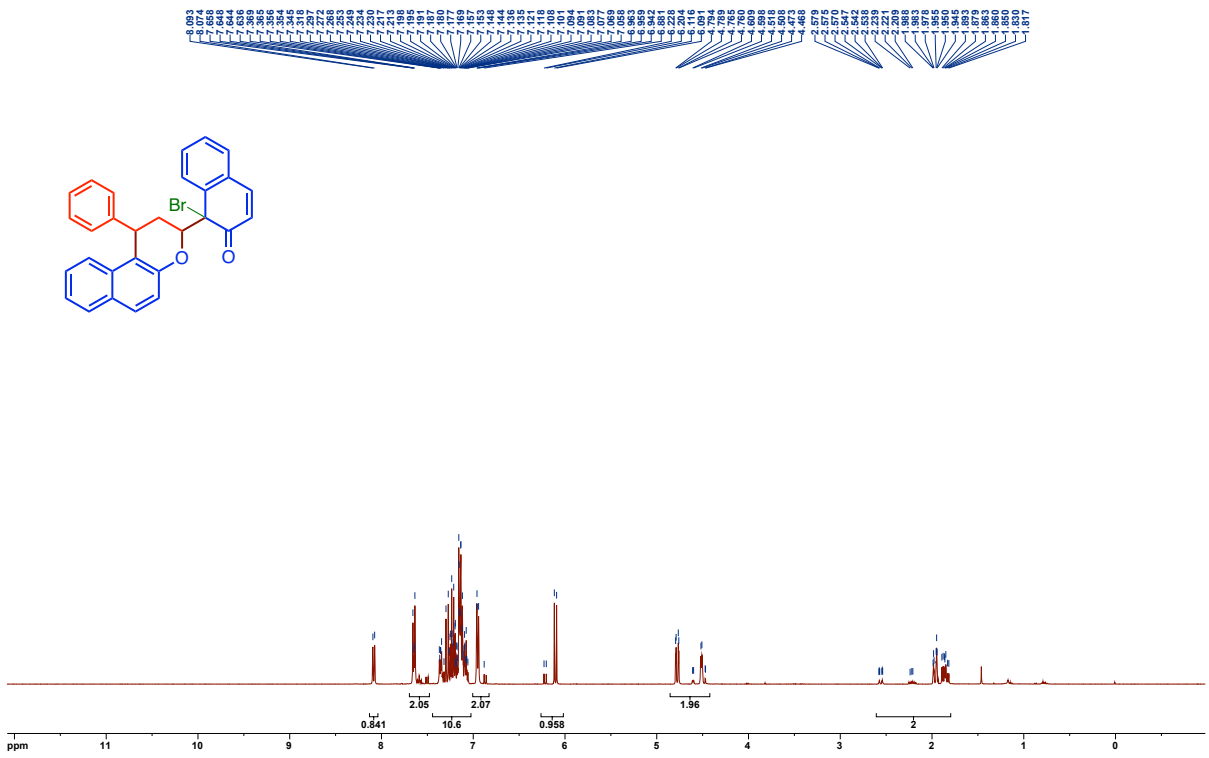


Figure 6.16 ^{13}C NMR spectrum of 1-bromo-1-(1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)naphthalen-2(1*H*)-one **6.4h**:

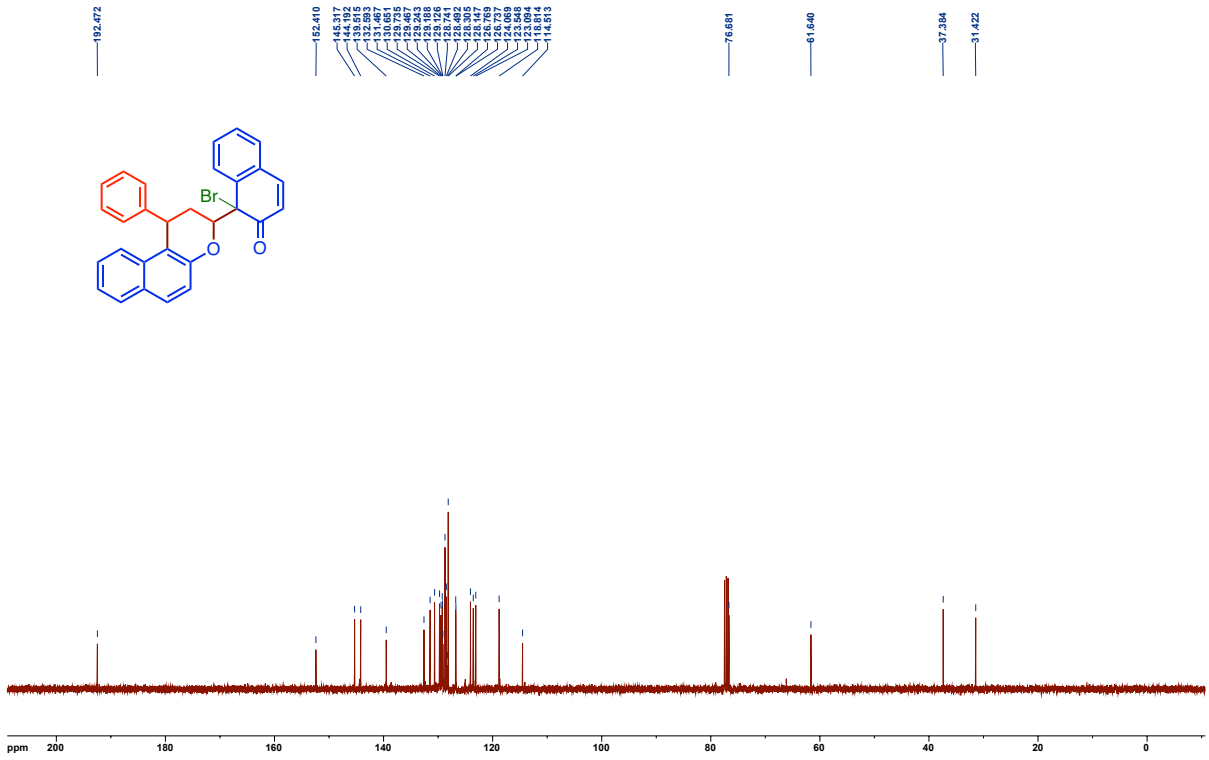


Figure 6.17 ^{1}H NMR spectrum of 4,4'-((2-hydroxynaphthalen-1-yl)methylene)bis(2,6-di-tert-butylphenol) **6.5d**:

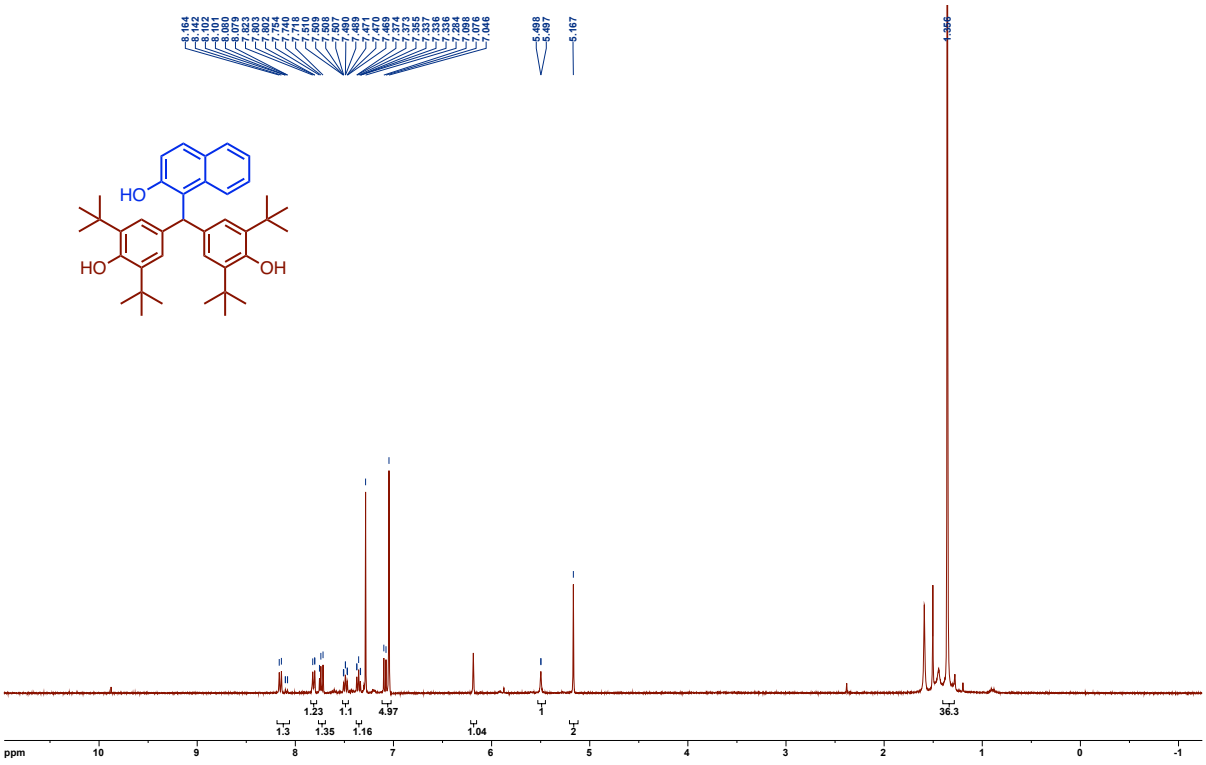
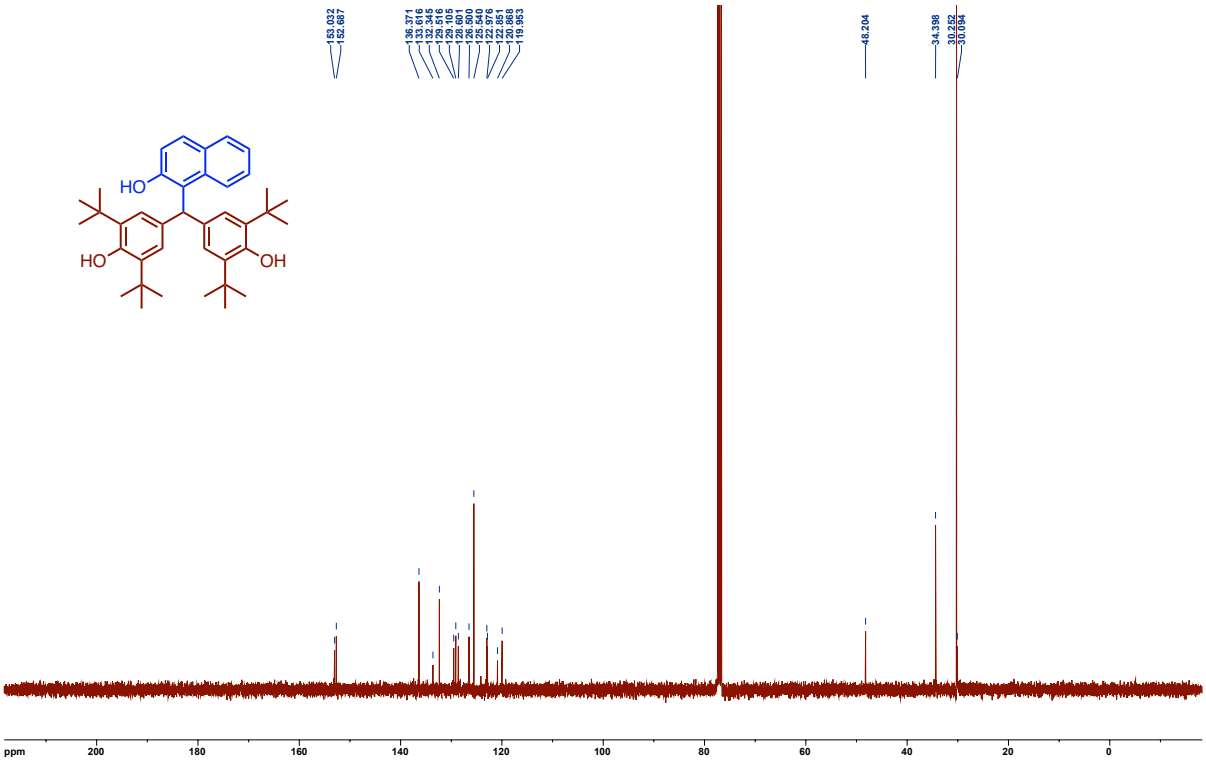


Figure 6.18 ^{13}C NMR spectrum of 4,4'-((2-hydroxynaphthalen-1-yl)methylene)bis(2,6-di-tert-butylphenol) **6.5d**:



CHAPTER-7

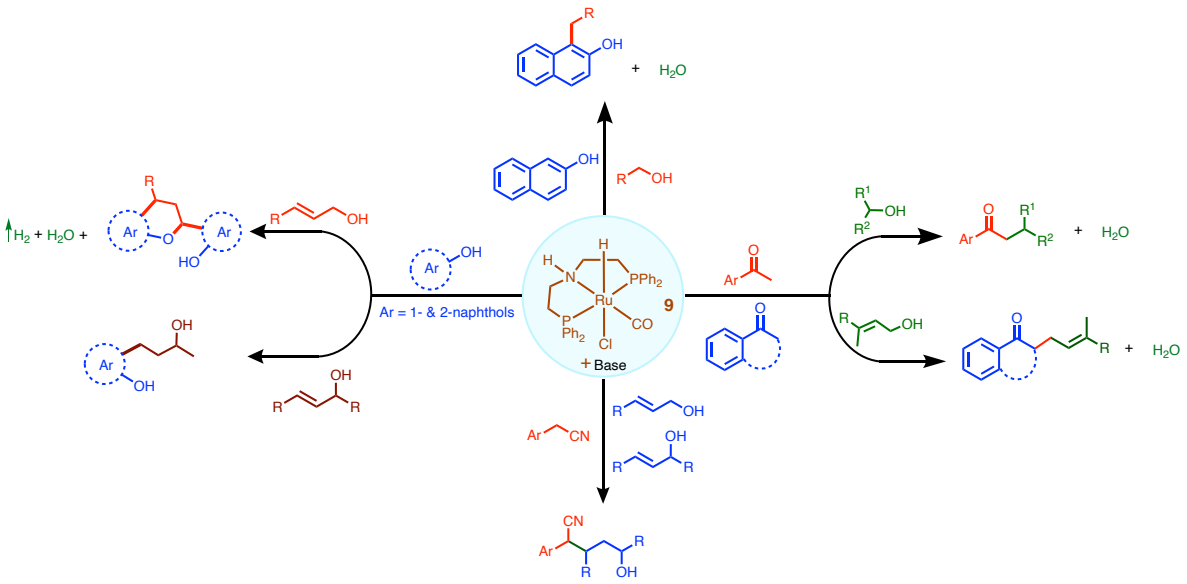
CONCLUSIONS

The development of catalytic methods to activate inert chemical bonds in small molecules remains a highly sought-after goal. Over the past few decades, chemists have devoted significant efforts to employ modern methodologies that are grounded in sustainable principles. Modern organometallic compounds, particularly those involving transition metals, have seen considerable progress and offered significant advantages over previously reported fundamental organic transformations. Notably, in the past two decades, pincer complexes have evolved into preferred catalysts in many catalytic processes.

The tridentate nature of pincer ligands, which typically enforce a meridional coordination geometry with metal precursors imparts unique stability and reactivity to these complexes, overcoming some of the limitations associated with simpler transition-metal-containing organometallic catalysts. Consequently, pincer complexes are now widely employed in a range of applications from the production of basic commodity chemicals to the synthesis of industrially important feedstocks. Among these, ruthenium-based pincer complexes have emerged as dominant catalysts due to their remarkable reactivity and preference for certain challenging reactions. This thesis explores several C–C bond-forming reactions involving key organic molecules such as ketones, nitriles, and arenols, using alcohols as alkylating agents. Alcohols, which are abundant and can be derived from lignocellulosic biomass, align with green chemistry principles, offering a sustainable alternative. Furthermore, the methodology outlined in this thesis generates minimal waste and provides high atom economy, making it a more sustainable and environmentally friendly approach compared to traditional C–C bond formation methods.

This thesis presents a simple and efficient approach for C–C bond formation at both sp^3 and sp^2 carbon centers, employing the pincer catalyst **9** (Scheme 7.1). The research demonstrates that amine-amide metal-ligand cooperation is crucial for the catalytic cycle, maintaining the metal in its +2 oxidation state throughout the process. These findings contribute to the advancement of fundamental C–C bond formation reactions, offering insights that could inspire future developments in sustainable catalytic processes. These strategies hold great potential for addressing fundamental synthetic challenges and making practical contributions to a wide range of applications.

Scheme 7.1 Catalytic C-C Bond Formation Reactions Developed Using Alcohols



Chapter 1 provides an overview of the unique reactivity observed in pincer complexes, specifically the phenomenon of metal-ligand cooperation. It includes a classification of tridentate ligands and a comprehensive list of related complexes from the literature. The chapter also discusses several C–C bond-forming reactions catalyzed by systems that operate through acceptorless dehydrogenative coupling and borrowing hydrogen strategies. Building on these methodologies, Chapters 2-6 focus on the application of the pincer catalyst **9** in various C-C bond-forming reactions. These chapters present catalytic cycles established through

experimental mechanistic studies. Wherever necessary catalytic cycles are predicted from DFT calculations.

Chapter 2 describes the α-alkylation of ketones using secondary alcohols towards the synthesis of β-disubstituted ketones using the pincer catalyst **9**. A variety of ketones, including challenging acetophenones, can be alkylated with secondary alcohols using only a catalytic amount of base. This approach avoids the use of stoichiometric base or the need for highly substituted ketones, which is a common requirement in previously reported methods. Mechanistic studies using sterically hindered alcohols revealed the formation of an α,β-unsaturated ketone intermediate, which undergoes hydrogenation to form the final β-disubstituted ketone product. The reaction follows first-order kinetics, and the only byproduct is the water molecule.

Chapter 3 presents the catalytic α-prenylation of ketones using prenols.. The pincer catalyst **9** efficiently carries out prenylation in a variety of cyclic ketones, including tetralone and indanone, as well as challenging acetophenones. Other prenols, such as phytol, geraniol, and farnesol, were also used as direct alkylating reagents. The resulting α-prenylated acetophenones were synthetically transformed into useful products. Mechanistic studies suggest that the Ru complex facilitates O-H activation of prenols, generating prenal as a reactive intermediate. This intermediate undergoes condensation, leading to the formation of the desired α-prenylated product with the formation of water as an only byproduct. The catalyst maintains a metal oxidation state of +2 throughout the catalytic cycle due to amine-amide metal-ligand cooperation.

In Chapter 4, an unprecedented formal conjugate addition of nitriles to allylic alcohols is demonstrated. A variety of aryl methyl nitriles undergo conjugate addition with primary and secondary allylic alcohols leading to the formation of δ-hydroxynitriles using the pincer catalyst **9**. This methodology has synthetic applicability for the preparation of pharmaceutically

relevant molecules. Notably, the reaction produces no byproducts, making it an atom-economical process. Deuterium labeling studies highlight the role of the catalyst in the oxidation of allylic alcohols, the conjugate addition, and the hydrogenation of δ-ketonitriles, resulting in the formation of the δ-hydroxynitriles. DFT calculations further support the dual role of the base, which activates the catalyst for the oxidation of allylic alcohols through a nearly barrierless, exergonic process and also in conjugate addition of nitriles with the in situ formed α,β-unsaturated intermediate.

Chapter 5 reports the site-selective α-alkylation of β-naphthols using the pincer catalyst **9**. A diverse range of primary alcohols, including arylmethanols and challenging aliphatic alcohols, were successfully alkylated at the α-position of β-naphthol. Preliminary mechanistic studies and theoretical calculations provide insight into the reaction mechanism. The liberated water molecule is the only byproduct and also helps in the regeneration of the active catalyst.

Chapter 6 introduces a simple method for the synthesis of benzo(f)chromanes and 1-hydroxyalkyl-2-naphthol using the pincer catalyst **9**. A single catalyst enables the formation of benzo(f)chromanes when primary allylic alcohols are used, and 1-hydroxyalkyl-2-naphthol when secondary allylic alcohols are employed. A variety of naphthols and diverse allylic alcohols were employed to obtain the chromane and hydroxy-alkyl products. Remarkably, water and molecular hydrogen are the only byproducts. Mechanistic studies reveal that tandem reactions, including O-H bond activation of allylic alcohols and a 1,4-conjugate addition to dearomatized naphthols, are involved. EPR studies detected the formation of a naphthyl radical, which was trapped using a radical scavenger.